N-HETEROCYCLIC CARBENES:

FROM DESIGN TO SYNTHESIS AND THEIR APPLICATION AS

NUCLEOPHILIC CATALYSTS

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Dedicated to My Deceased Brother:

Jamie Ross Struble

I love and miss you everyday.

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I will be the first to admit that I have not always been a model graduate student. Sometimes letting my emotions get me in trouble or simply not knowing how to pick my battles and keep my mouth shut; missing "deadlines" whether real or fictitious; or not showing up to work by 9am, 9:30am or finally 10am on most days. However, not to sound arrogant by any means, I thank myself. I did it: the all nighters, the seven-day work week, the sleeping in lab, staying until 4am on Saturday nights while my friends were out drinking, the chain-smoking, the brief alcoholism, the excessive abuse of caffeine, the pain and suffering of a failing project, the excitement of being the first to make a catalyst, the heartbreak from the death of family and friends, the misery of an

angry boss, the misery from feeling lazy or tired, the bitterness, the constant moving, all the writing, reading and proofreading....I endured and stayed focused on my goal. I did it ! (...well presuming this thesis gets accepted...)

ABSTRACT

N-HETEROCYCLIC CARBENES:

FROM DESIGN TO SYNTHESIS AND THEIR APPLICATION AS NUCLEOPHILIC

CATALYSTS

Justin Robert Struble

Jeffrey W. Bode

Our group has pioneered novel internal redox process of aldehydes possessing an internal *α*-reducible functionality mediated by N-heterocyclic carbenes (NHCs). Two discrete discoveries have been crucial to the success of our program. The first has been the identification of reaction parameters intimately related to the fate of the putative reactive intermediates to exquisitely allow access to a single reaction outcome (e.g. NHC-enolate vs homoenolate). The second, and more crucial, has been the development of new *N*-mesityl substituted triazolium and imidazolium salts that serve as precursors to the N-heterocyclic carbene nucleophilic catalyst. Our achiral and chiral, bicyclic *N*-mesityl triazolium salts have shown unprecedented reactivity and selectivity in a variety of conceptually new transformations. As such we have been the first to disclose highly enantioselective intermolecular annulations providing access to stereochemically rich heterocycles. Moreover, the synthesis of a novel *N*-mesityl aminoindanol-derived imidazolium salt allowed for the first time the investigation into the inherent reactivity differences that exist between two classes of NHCs (triazolium vs. imidazolium). Current efforts toward catalyst development via a combinatorial approach promise the opportunity to discover new enantioselective NHC-catalyzed processes.

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LIST OF ABBREVIATIONS

Abbreviation	Name	Chemical Structure
[α]	optical rotation	
Ac	acetyl	
Ad	adamantyl	
anisyl	4-methoxyphenyl	
aq	aqueous	
Ar	aryl	
Bn	benzyl	
br	broad	
c	concentration	
°C	degrees Celsius	
calcd	calculated	
cat	catalyst	
Cbz	benzyloxycarbonyl	
cm⁻¹	inverse centimeters	
CN	cyano	
Cy	cyclohexyl	
d	day	
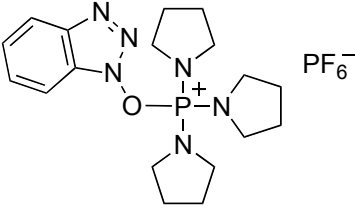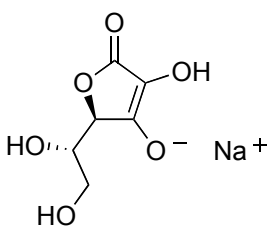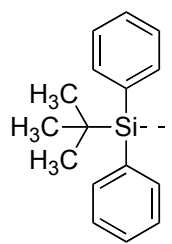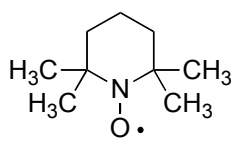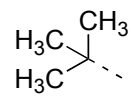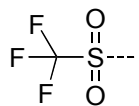
Abbreviation	Name	Chemical Structure
d	doublet	
δ	chemical shift	
DABCO	1,4-diazabicyclo[2.2.2]octane	
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	
DCC	dicyclohexylcarbodiimide	
(DHQ)₂PHAL	*bis*(dihydroquinino)phthalazine	
DIPEA	*N,N*-diisopropylethylamine	
DMP	Dess-Martin periodinane 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one	
DMAP	*N,N*-4-dimethylaminopyridine	
DMDO	dimethyl dioxirane	
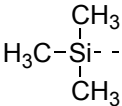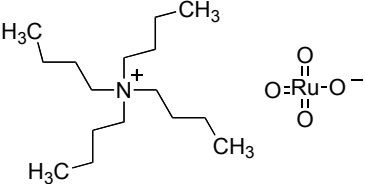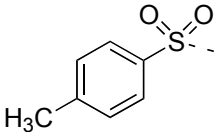
Abbreviation	Name	Chemical Structure
DMF	*N*,*N*-dimethylformamide	
DMM	dimethoxymethane	
DMSO	dimethylsulfoxide	
dr	diastereomeric ratio	
EDCI	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride	
EDTA	ethylenediamine tetraacetic acid	
ee	enantiomeric excess	
EI	electron impact ionization	
equiv	equivalents	
Et	ethyl	
Et₂O	diethyl ether	
EtOAc	ethyl acetate	
ESI	electrospray ionization	
EWG	electron-withdrawing group	

Abbreviation	Name	Chemical Structure
g	gram	
h	hour	
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate	
HBTU	*O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate	
HOAt	1-hydroxy-7-azabenzotriazole	
HOBt	1-hydroxybenzotriazole	
HPLC	high-pressure liquid chromatography	
HRMS	high resolution mass spectrometry	
Hz	hertz	
IBX	2-iodoxybenzoic acid	
IR	infrared spectrum	
J	coupling constant	
KHMDS	potassium *bis*(trimethylsilyl)amide	
L	liter	

Abbreviation	Name	Chemical Structure
M	Molar or Molarity	
M⁺	molecular ion	
m	multiplet	
m	meta	
*m*CPBA	*meta* chloroperoxybenzoic acid	
Me	methyl	H_3C-
mes	mesityl 2,4,6-trimethylphenyl	
mg	milligram	
min	minutes	
mL	milliliter	
mmol	millimole	
mol	mole	
mol%	mole percent	
mp	melting point	
MS	mass spectrometry	
N	normal or normality	
NaIO₄	sodium periodate	
naphth	napthyl	
NHC	N-heterocyclic carbene	

Abbreviation	Name	Chemical Structure
NMM	*N*-methylmorpholine	
NMR	nuclear magnetic resonance	
o	ortho	
OsO$_4$	osmium tetroxide	
Oxone®	potassium peroxymonosulfate	
p	para	
p-Tol	*para*-tolyl	
Pd/C	palladium on carbon	
i-Pr	isopropyl	
Ph	phenyl	
PhH	benzene	
PhCl	chlorobenzene	
PhMe	toluene	
PMB	4-methoxybenzyl	
ppm	parts per million	

Abbreviation	Name	Chemical Structure
PTLC	preparative thin-layer chromatography	
PyBOP	(Benzotriazol-1-yloxy) tripyrrolidinophosphonium hexafluorophosphate	
SFC	supercritical fluid chromatography	
sodium ascorbate	(+)-L-Sodium ascorbate	
t	tert	
t~r~	retention time	
TBDPS	*tert*-butyldiphenylsilyl	
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical	
t-Bu	*tert*-butyl	
Tf	trifluoromethanesulfonyl	

Abbreviation	Name	Chemical Structure
THF	tetrahydrofuran	
TLC	thin-layer chromatography	
TMS	trimethylsilyl	
TPAP	tetra-*n*-propylammonium perruthenate	
Ts	tosyl	
ν	wavenumber	

List of Publications

1. He, M.; Struble, J. R.; Bode, J. W. "Highly Enantioselective Azadiene Diels-Alder Reactions Catalyzed by Chiral N-Heterocyclic Carbenes." *J. Am. Chem. Soc.* **2006**, *128* (26), 8418–8420.

2. Struble, J. R.; Kaeobamrung, J.; Bode, J. W. "Synthesis of an *N*-Mesityl Substituted Chiral Imidazolium Salt for NHC-Catalyzed Reactions." *Org. Lett.* **2008**, *10* (5), 957–960.

3. Struble, J. R.; Bode, J. W. "A Modular Synthesis of Chiral Aminoindanol-Derived Imidazolium Salts." *Tetrahedron* **2008**, *64* (29), 6961–6972.

4. Struble, J. R.; Bode, J. W. "Formal Synthesis of Salinosporamide A via NHC-Catalyzed Intramolecular Lactonization" *Tetrahedron* **2009**, *65* (26), 4957–4967*.*

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Chapter 1: History of N-Heterocyclic Carbenes (NHCs) as Nucleophilic Catalysts

1.1 Introduction

Over the past two decades N-heterocyclic carbenes (NHCs) have received increasing attention due to their storied role as ligands for transition metal complexes and, more recently, their remarkable properties as catalysts in their own right. For transition-metal-mediated processes they act as surrogates for phosphine ligands due their well-documented σ-donating abilities.[1–3] Perhaps even more impressive is their ever-growing use as nucleophilic organocatalysts that promote a variety of umpolung or "charge reversal" processes.[4–7] Beside their facile reactivity and selectivity, NHCs are also touted as environmentally safe whereby they tend to exhibit little to no toxicity and the reaction conditions in which they are used are often very mild.
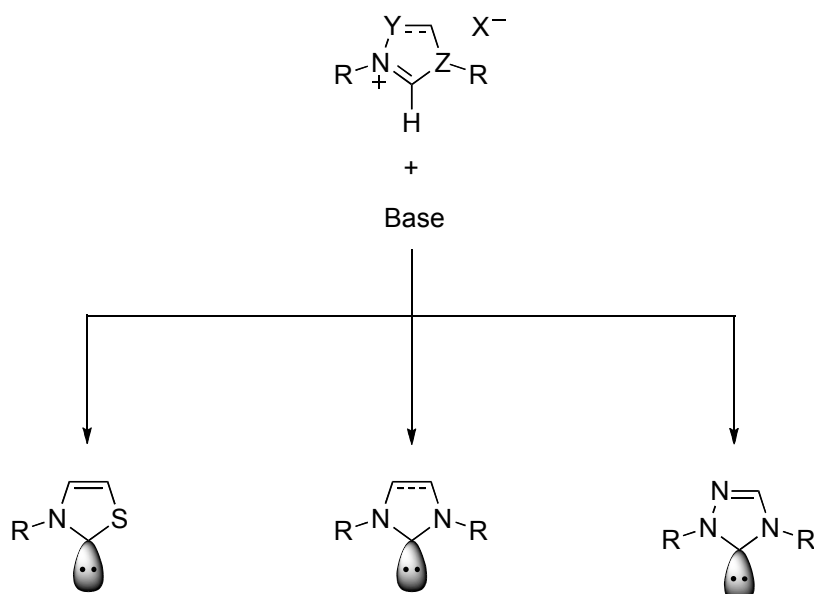
Figure 1. General classes of N-heterocyclic carbenes employed as nucleophilic catalysts.

In general there are three types of NHCs used in small molecule catalysis; all of which are most commonly derived from their bench-stable parent salts upon deprotonation of the C-2 proton with a suitable base (Figure 1). The three types stem from the difference in the heteroatomic ring. Thiazolium salts bear a sulfur atom (Y = C, Z = S) in the parent heterocycle; imidazolium salts are imidazole derivatives whereby two nitrogen atoms flank the C-2 center and can be fully saturated at the C-4 and C-5 positions (Y = C, Z = N); and triazolium salts, which are derivatives of 1,2,4-triazoles (Y = N, Z = N) containing three nitrogen atoms in the carbene heterocycle. Although N-heterocyclic carbenes possess the common features of all carbenes as neutral, six-electron, bivalent species they are particularly stable compared to the classical carbenes discovered at the turn of the 19th century by Buchner and Curtius[8] and Staudinger and Kupfer[9] due to the presence of the heteroatoms adjacent to the singlet carbene center.

1.2   Reactions of Acyl Anion Equivalents: The Benzoin and Stetter Reaction

1.2.1 Reactions of Acyl Anion Equivalents: The Benzoin Condensation

Discovered in 1832 by Liebig and Wöhler,[10] the benzoin reaction is one of the oldest reactions in organic chemistry. Classically, the reaction was catalyzed by the cyanide ion that causes the self condensation of an aryl aldehyde to produce an α-hydroxyketone (Scheme 1). In 1903, Lapworth proposed a mechanism whereby addition of hydrogen cyanide across the carbonyl of benzaldehyde followed by deprotonation resulted in an anion of inverted nucleophilic reactivity which he termed an "active aldehyde".[11] The catalytically generated "active aldehyde" has since been renamed as an "acyl anion equivalent" and represents an umpolung of the aldehyde C-1 position from an electrophile to a nucleophile ($a_1 \rightarrow d_1$).[12]
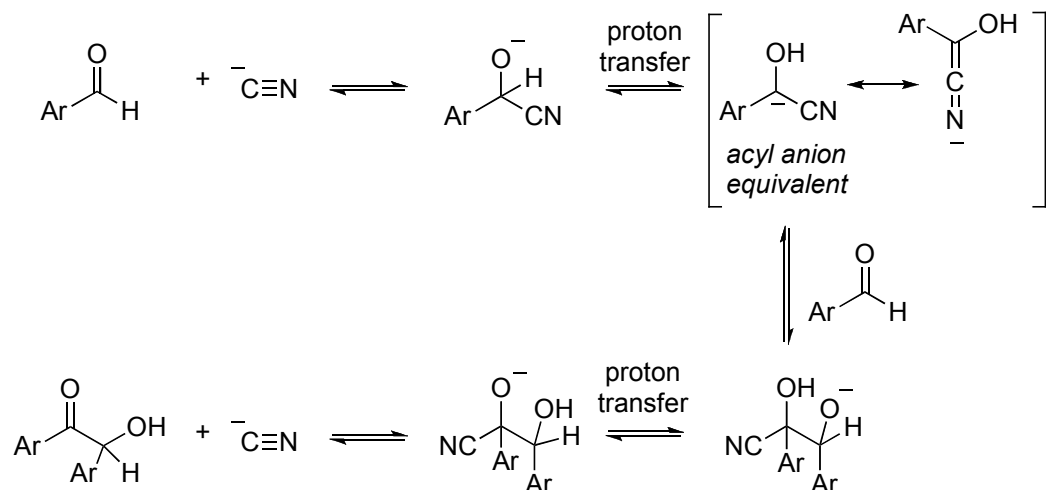
Scheme 1. Cyanide catalyzed benzoin condensation.
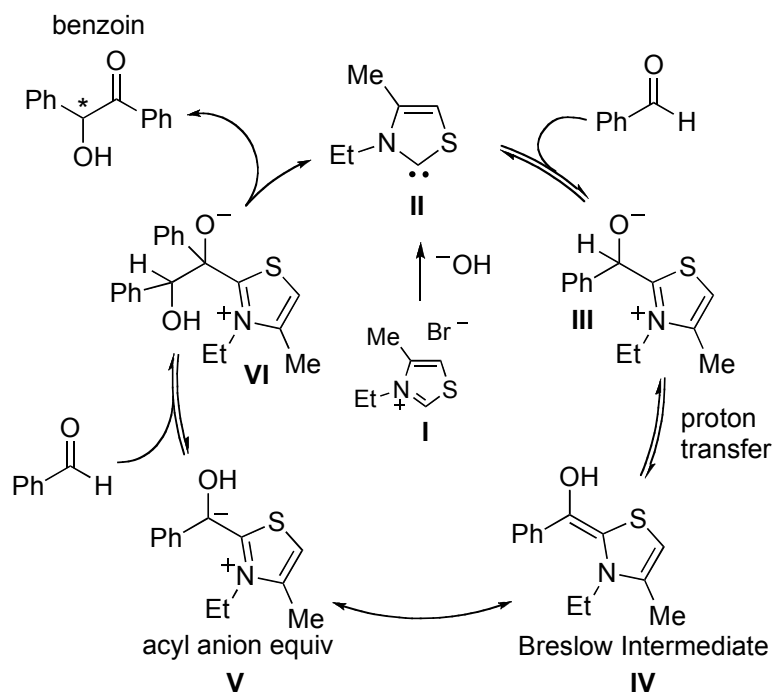
Scheme 2. Breslow's proposed mechanism for the thiazolium-catalyzed benzoin condensation.

In 1943, Ukai et al. found that the vitamin B1 enzyme cofactor thiamine, a naturally occurring thiazolium salt, catalyzed the benzoin self-condensation of benzaldehyde.[13] Shortly thereafter, in his seminal 1958 report, Breslow proposed that the C-2 conjugate

base of the thiazolium ring acts as a nucleophilic ylide (a mesomeric structure to the carbene) to activate the aldehyde in analogous manner to cyanide.[14] The overall catalytic process is presented in Scheme 2. Deprotonation of thiazolium salt **I** yields the free carbene **II** that undergoes nucleophilic attack on benzaldehyde. A proton transfer event produces **IV** (the Breslow intermediate), a resonance form of **V** (the acyl anion equivalent) that undergoes nucleophilic attack on a second equivalent of benzaldehyde. A subsequent proton transfer event yields **VI**, this intermediate collapses to produce the *α*-hydroxyketone benzoin and regenerate the nucleophilic carbene catalyst **II**.
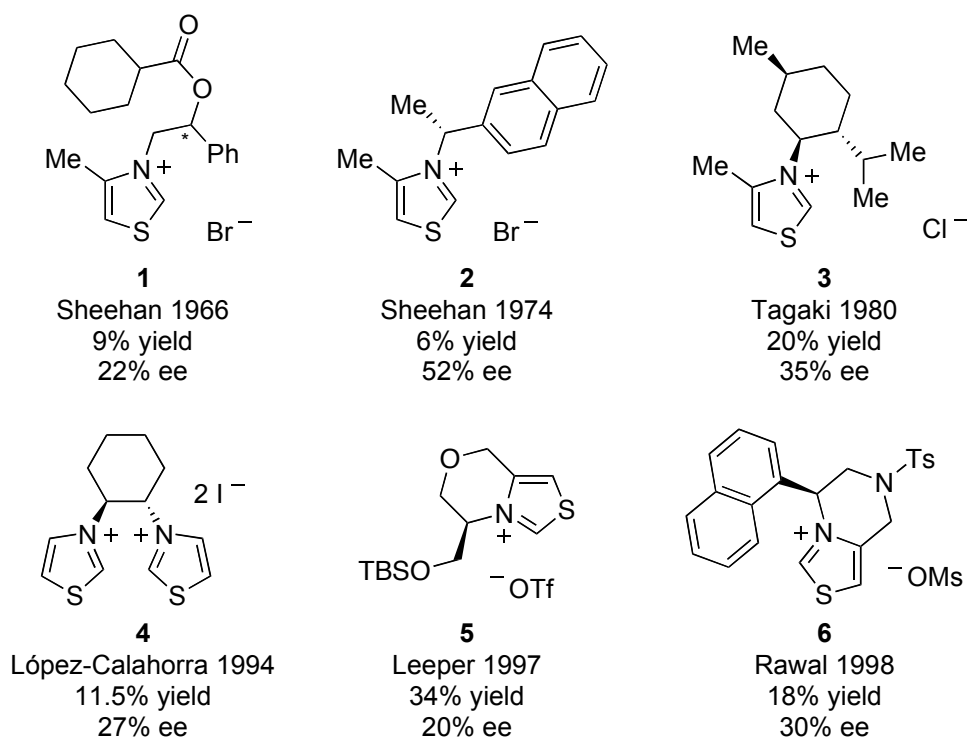
Figure 2. Selected chiral thiazolium salts for the asymmetric benzoin condensation.

In addition to the formation of a new C–C bond, the benzoin reaction creates a new stereogenic center. Naturally, this caused an explosion of interest in the synthesis of chiral heteroazolium salts to render the benzoin reaction enantioselective. In 1966, Sheehan was the first to validate this concept when he reported an asymmetric benzoin

condensation, albeit with low yield and enantioselectivity (22% ee), using chiral thiazolium salt **1** (Figure 2).[15] In 1974, he introduced a modified precatalyst **2** that offered improved enantioselectivity (52%) but with a meager yield of only 6%.[16] Since these initial reports, many research groups have focused on the production of chiral thiazolium salts for improving the efficiency and selectivity of the asymmetric benzoin condensation. Notable contributions are summarized in Figure 2.[17–20]

Before 1997, the chiral thiazolium catalysts possessed a free degree of rotation in the chiral element adjacent to the reactive site. Leeper and co-workers[19] as well as Rawal[20] were the first to present the rational design of chiral thiazolium salts with a rigid backbone that they hypothesized would restrict the degrees of free rotation during the C–C bond-forming event and thus lead to enhanced selectivity. Although their initial designs fell short of achieving high enantioselectivity (See Figure 2 **5** and **6**), this thinking laid the groundwork for subsequent heteroazolium NHC catalyst design.
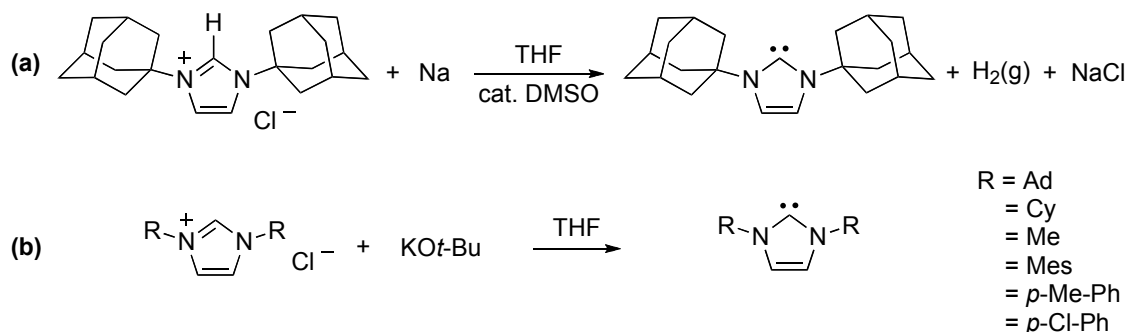
Scheme 3. Arduengo's isolation of free imidazolium-derived carbenes.

With that in mind, the field of asymmetric benzoin heteroazolium catalysis underwent a resurgence when two events unfolded. The first was the isolation and characterization of a stable heteroazolium-derived carbene (often termed Wanzlik carbenes after his pioneering research in the area)[21, 22] by Arduengo in 1991 (Scheme 3a).[23] He later went on to isolate and fully characterize several imidazolium-derived

carbenes with less bulky substituents (Scheme 3b).[24] These reports presented solid evidence that the previously implicated carbenes in NHC-promoted processes were real.
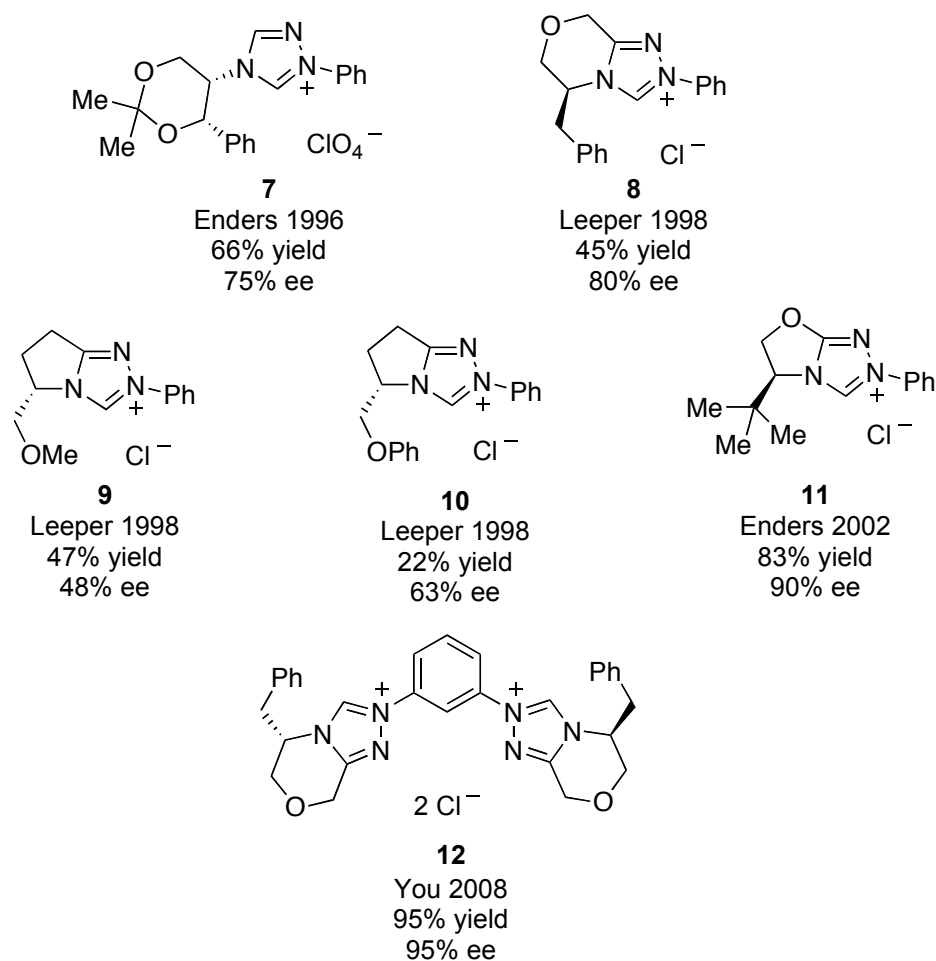
Figure 3. Selected chiral triazolium NHC catalysts for the asymmetric benzoin condensation.

The second event was Enders' synthesis of a chiral triazolium-derived NHC in 1996 that was capable of catalyzing the asymmetric benzoin condensation thus opening up the possibility to include an extra degree of chirality compared to the thiazolium counterpart.[25] This work was followed by several groups in the next decade designing and synthesizing chiral triazolium salts that led to the vast improvement in efficiency and selectivity in the benzoin reaction. Recent identification of bistriazolium NHC **12** currently stands as the state of the art for asymmetric benzoin condensation (Figure 3).[26–28]
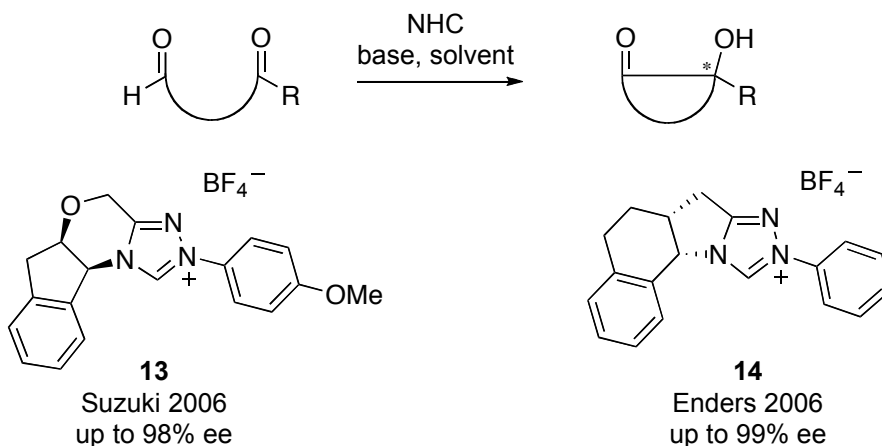
Figure 4. Intramolecular aldehyde-ketone crossed benzoin.

In 2003, Suzuki, Hachisu and Bode reported the first crossed-benzoin reaction between a ketone and an aldehyde for the preparation of preanthraquinones using a thiazolium NHC catalyst.[29] They followed up in 2006 with an asymmetric variant employing a chiral triazolium salt **13** derived from *cis*-1,2-aminoindanol.[30] In contemporaneous work, Enders and co-workers published an asymmetric version of the intramolecular crossed-benzoin reaction utilizing a novel chiral triazolium NHC catalyst **14** to produce 5- and 6-membered acyloins in moderate to high yield and enantioselectivity (Figure 4).[31, 32]

1.2.2 Reactions of Acyl Anion Equivalents: The Stetter Reaction

In the early 1970s Stetter developed a logical extension of the benzoin reaction by employing a Michael acceptor as the electrophilic partner for the acyl anion addition to provide 1,4-dicarbonyl derivatives (Scheme 4).[33, 34] As with the benzoin condensation the first Stetter addition was catalyzed by the cyanide ion and was then extended to thiazolium salts shortly thereafter in 1976.[35, 36]
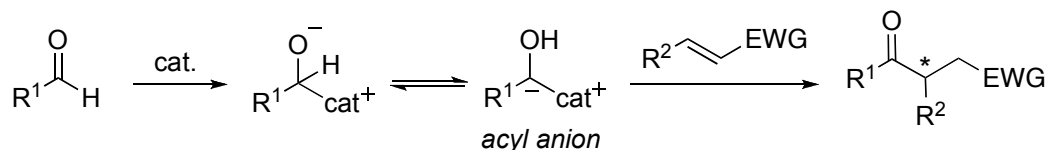
Scheme 4. The Stetter reaction.

A possible detriment in the intermolecular Stetter reaction is for the donor aldehyde to undergo a self-benzoin condensation instead of the 1,4-addition. In 2004, Scheidt and co-workers[37] developed a strategy that employs acylsilanes as precursors to acyl anion equivalents.[38–40] Using a thiazolium catalyst in the presence of an acylsilane and a conjugate acceptor smoothly afforded the corresponding Sila-Stetter adducts in good yield (Scheme 5).
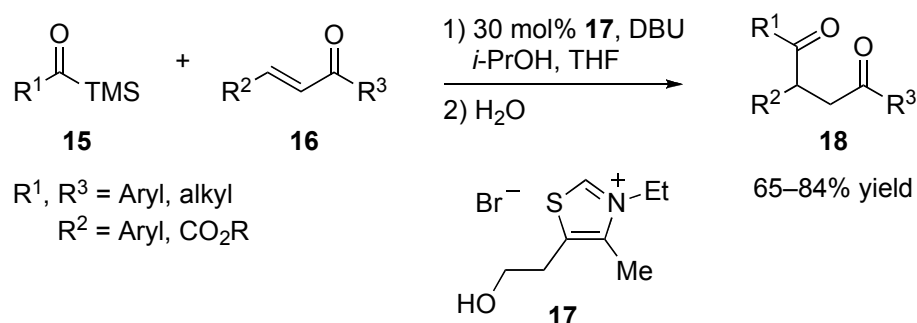
Scheme 5. Thiazolium catalyzed Sila-Stetter reaction.

In the postulated catalytic cycle the carbene catalyst **I**, formed *in situ* via deprotonation by base, undergoes nucleophilic addition to the acylsilane **15**. A subsequent 1,2-silyl migration (Brook rearrangement) affords **II** and **III** that undergoes desilylation in the presence of DBU and alcoholic solvent (*i*-PrOH) to afford the Breslow intermediate **IV**. A 1,4-addition to the Michael acceptor **16** and collapse of the tetrahedral intermediate **V** expels the carbene catalyst **I** and the Stetter product **17** (Figure 5). In subsequent reports, Scheidt and co-workers extended this concept employing a one-pot process for the production of furans and pyrroles[41] as well as acyl anion addition to *N-*

phophinoylimines[42] and toward the direct acylation of nitroalkenes[43] in the presence of a thiourea and a fluoride source.
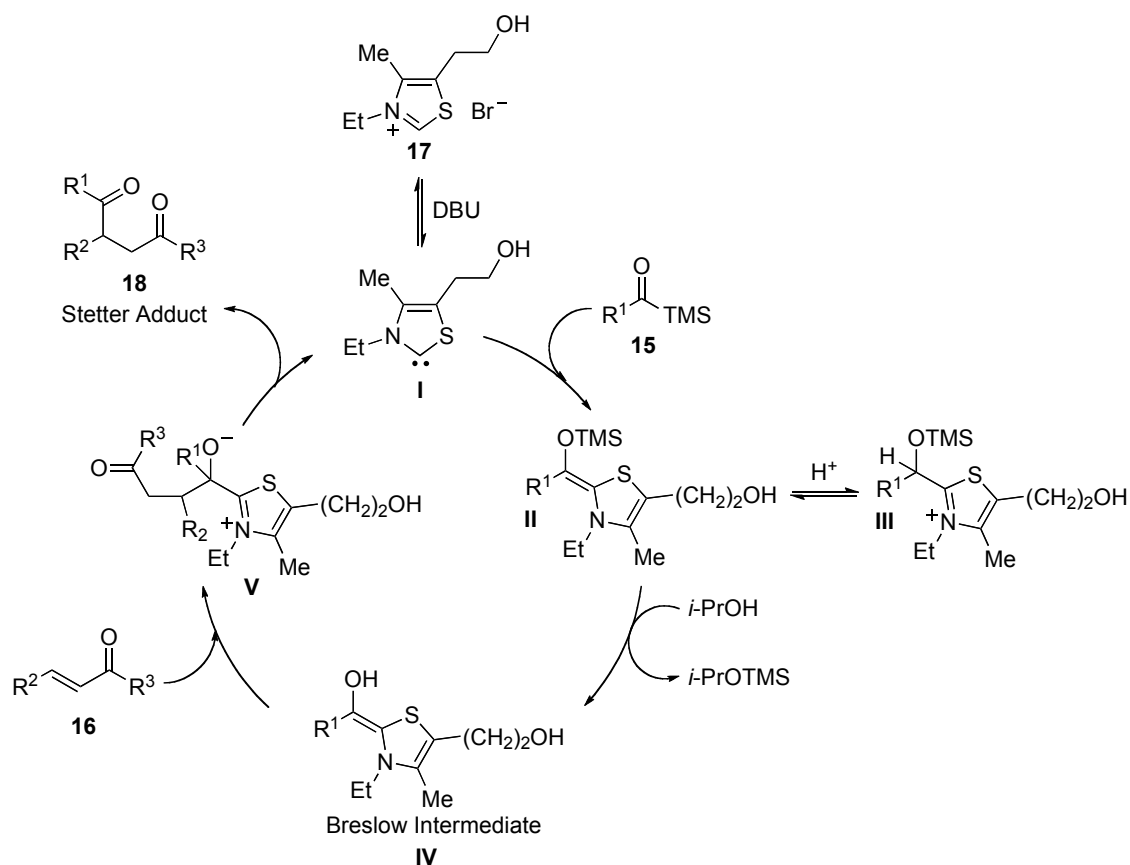
Figure 5. Mechanistic proposal for the Sila-Stetter reaction.
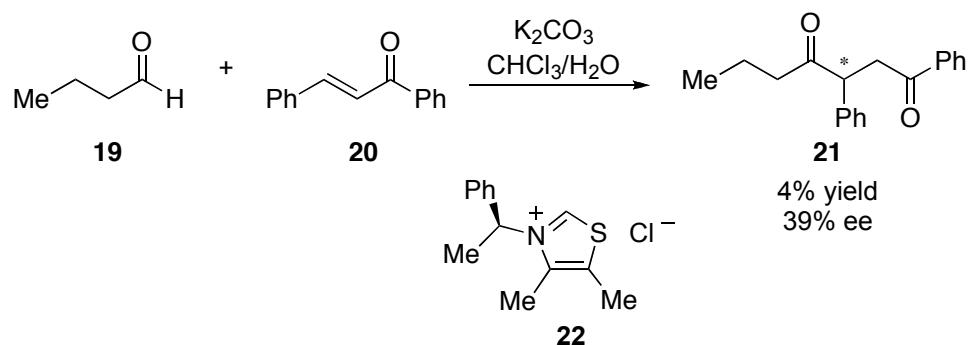
Scheme 6. The first asymmetric Stetter reaction.

Although the Stetter reaction offered great promise for the synthesis of optically active 1,4-dicarbonyl derivatives, it laid much less explored for the greater part of two decades. In 2002, Enders and co-workers reported the first asymmetric intermolecular Stetter reaction between *n*-butanal and chalcone using chiral thiazolium catalyst **22**, albeit only as a footnote in a review possibly due to the poor yield and moderate selectivity (Scheme 6).[44, 45] More recently Enders and Han communicated an enantioselective intermolecular Stetter addition between 2-furyl-aldehydes and arylidenemalonates. Enantioselectivities of up to 76% (up to 99% after one recrystalization) were achieved using *N*-benzyl chiral triazolium catalyst **26** derived from pyroglutamic acid (Scheme 7).
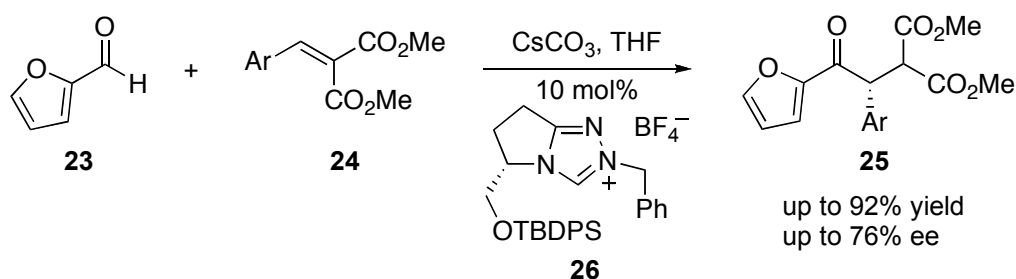
Scheme 7. Highly asymmetric intermolecular Stetter reaction reported by Enders.
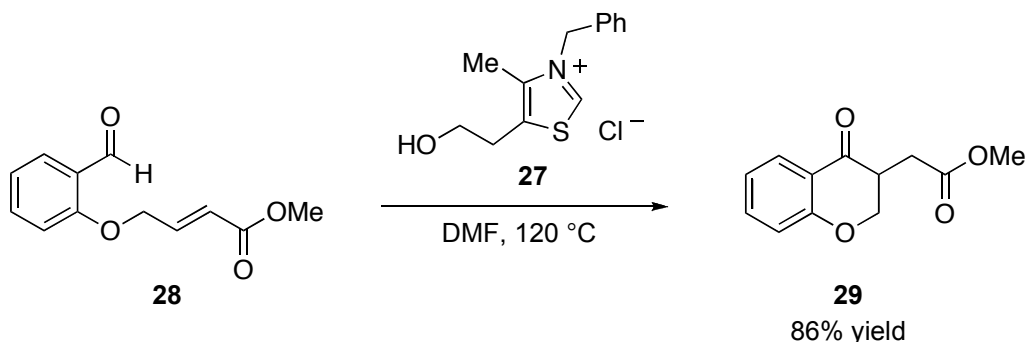
Scheme 8. First detailed study of the intramolecular Stetter reaction reported by Ciganek.

The intramolecular Stetter reaction has received considerably more attention than the intermolecular variant. Starting in 1995, Ciganek reported an interesting

intramolecular version of the Stetter reaction to provide benzo-annulated furanones and pyranones using the achiral thiazolium salt **27**.[46] The transformation of **28** to benzannulated pyranone **29** has become the test for catalyst efficiency and selectivity in the intramolecular Stetter reaction (Scheme 8). Enders was the first to disclose an asymmetric variant of this transformation employing the same chiral triazolium precatalyst **7** (See Figure 3) that was used to promote the asymmetric benzoin condensation.[47]
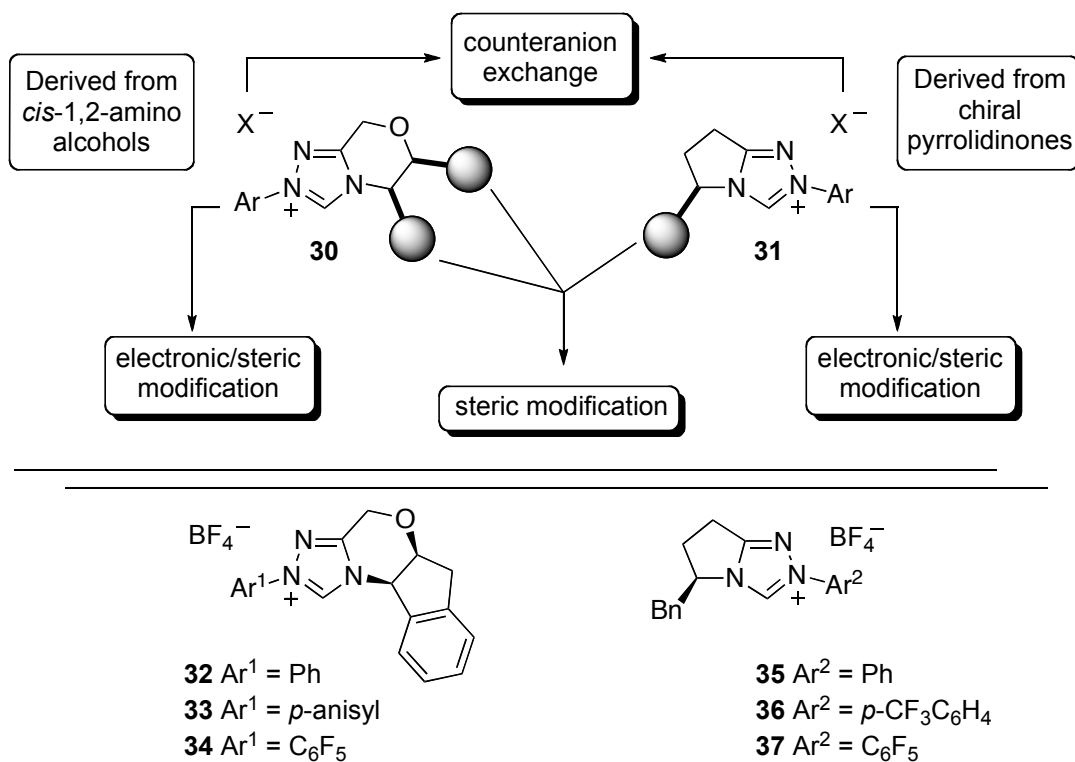
Figure 6. Rovis' approach to chiral catalyst design for the asymmetric intramolecular Stetter reaction.

Beside a few scattered reports for the asymmetric intramolecular Stetter reaction, the research program developed by Rovis and co-workers has emerged at the forefront of this transformation. Since 2002, they have disclosed several reports regarding highly enantioselective intramolecular Stetter additions, and their body of work has recently

been nicely reviewed.[45] The success of their program has been a direct result of their systematic studies of two chiral bicyclic triazolium scaffolds: **31** derived from chiral pyrrolidinones and **32** derived from chiral 1,2-cis-amino alcohols (Figure 6).[45] These studies originate from the pioneering work of Knight and Leeper who were the first to report these chiral motifs for use in the asymmetric benzoin condensation.[26] Rovis' subsequent investigation of these motifs has led to the identification of superior catalysts of two general classes that efficiently catalyze the intramolecular Stetter reaction with high levels of enantioselectivity for a variety of tethered electrophiles. The first class are triazolium salts **32**–**34** derived from aminoindanol; the second are triazolium salts **35**–**37** derived from a chiral pyrrolidinone that ultimately is traced back to L-phenylalanine.

$X = C, NR^2, O, S$
$EWG = –CO_2R, CO(SR),$
  $COR, CO(NR_2),$
  $CN, PO(OEt)_2, PO(Ph)_2$

up to 99% ee
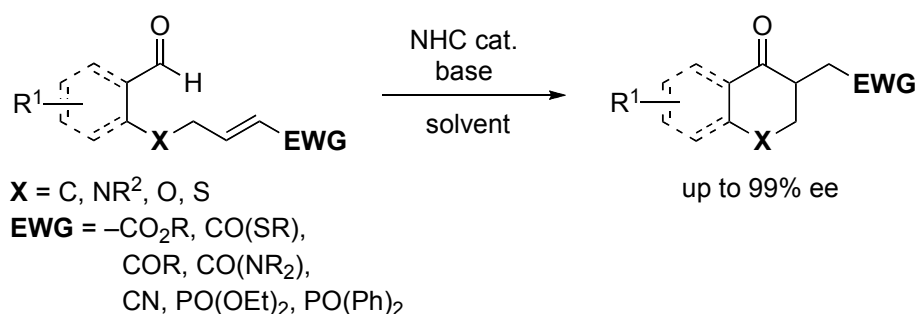
Scheme 9. Rovis' systematic study of aromatic substrates in the intramolecular Stetter reaction.

The two catalyst scaffolds provided complementary reactivity and selectivity when it came to substrates that were unsatisfactory in either reactivity or selectivity. In general the aminoindanol motif often led to a higher degree of selectivity whereas the phenylalanine-derived motif was on average more reactive.[45] Thus, Rovis and co-workers were able to probe systematically the various effects of the substrate in the asymmetric intramolecular Stetter reaction. They began investigating aromatic substrates and probing the effects of different tethers and and tether lengths, substitution of the aromatic ring, and type of electron-withdrawing-group (Scheme 9). They found

that carbon, nitrogen, sulfur and oxygen were all well tolerated in the tether and that 5 and 6-membered rings formed smoothy while seven-membered rings were often unsuccessful. The aromatic backbone tolerated electron-donating and electron-releasing groups as long as the position was not *ortho* to the aldehyde. Finally, this method was also extended to the production of all carbon quaternary stereocenters often in high yield (11–96%) and enantioselectivity (82–99%).[48]
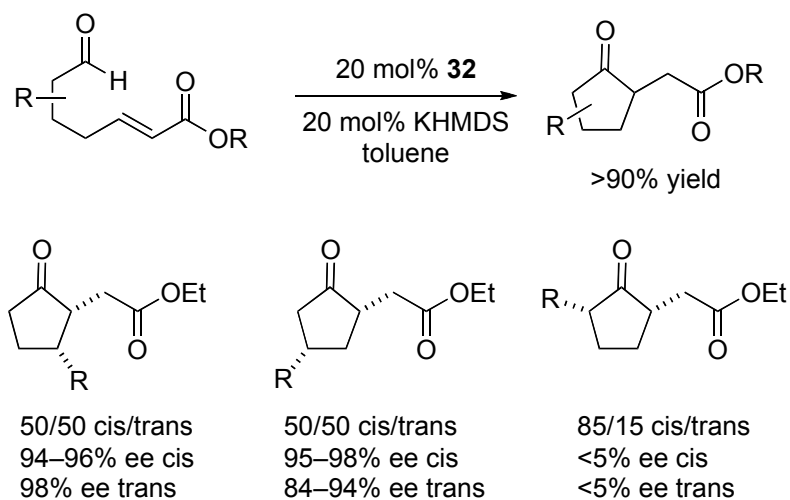
Scheme 10. Effects of preexisting stereocenters in the intramolecular Stetter reaction.

Next they extended the scope of the intramolecular Stetter reaction to aliphatic substrates utilizing NHC precatalysts **34** and **35**, affording good yields and enantiomeric excesses of up to 99% even for cases that produced a quaternary stereocenter. This led them to probe the effect of preexisting stereocenters on the cyclization event to produce chiral disubstituted-cyclopentanones (Scheme 10).[49] Interestingly no diastereoselectivity was observed upon cyclization when the preexisting stereocenter was at the 3- or 4-position; however, high levels of enantioselectivity for both the *cis* and *trans* isomer were achieved. Conversely, when the preexisting stereocenter was at the 2-position (alpha to the aldehyde) then good levels of diastereoselectivity were observed but no

enantioselectivity suggesting that the substrate stereocenter overrides the catalyst selectivity preference.

Scheme 11. Asymmetric intermolecular Stetter addition of glyoxamides to alkylidenemalonates.

Finally, Rovis and co-workers turned their sights back toward the asymmetric intermolecular Stetter reaction and in 2008 disclosed the Stetter reaction between glyoxamides **38** and alkylidenemalonates **39** (Scheme 11).[50] The *N*-pentafluorophenyl phenylalanine-derived NHC precatalyst **37** provided the proper balance for promoting the addition with excellent yields and enantioselectivities. Noteworthy is that the authors have demonstrated that the Stetter products could be converted to *γ*-lactones with three contiguous stereocenters as a single diastereomer with 90% ee. Very recently, Rovis and co-workers have disclosed two subsequent highly diastereo- and enantioselective intermolecular Stetter reactions.[51, 52] With the aforementioned set of NHC precatalysts, it is likely that a general asymmetric Stetter reaction will someday soon come to fruition.

1.3 NHC-Promoted Transesterifications

Early contributions to the NHC-promoted esterification were reported in 1994 by the Smith research group.[53] The transfer of an alkoxycarbonyl from 2-alkoxycarbonyl-imidazolium salts to benzyl alcohol was carried out in the presence of DABCO. However, several limitations existed; notably the alkoxycarbonyl unit was transferred directly from a preformed stoichiometric amount of the 2-alkoxyimidazolium salts (Scheme 12).
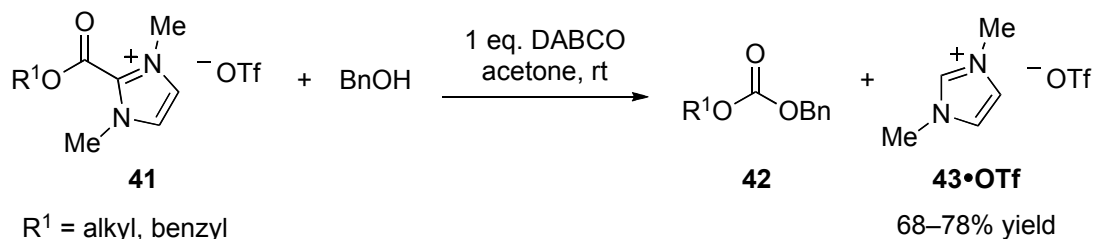
Scheme 12. NHC-mediated transesterification developed by Smith and Bakhtiar.

In 2002, the research groups of Nolan[54] and Hedrick[55] concurrently reported the first NHC-catalyzed transesterification reactions using substoichiometric amounts of an N-heterocyclic carbene catalyst (Scheme 13). In the case of Nolan and co-workers, as little as 0.5 mol% catalyst loading of either IMes (**44**) or ICy (**45**) could efficiently promote an acyl transfer from vinylacetate to primary alcohols under mild conditions. The work of Hedrick and co-workers expanded the scope of the reaction to secondary alcohols by employing the NHC **43** and benzoylacetate as the acetylating agent. An interesting application to arise from this process was the production of several polyesters. In 2004, Nolan followed up on his initial report and expanded the scope of the NHC-promoted transesterification to a variety of secondary alcohols including aliphatic, cyclic and aromatic by using NHC **45** in the presence of methyl- or ethyl acetate and molecular sieves to drive the equilibrium reaction.[56] A limited number of tertiary alcohols participated in the transesterification albeit under prolonged reaction times and high catalyst loadings.
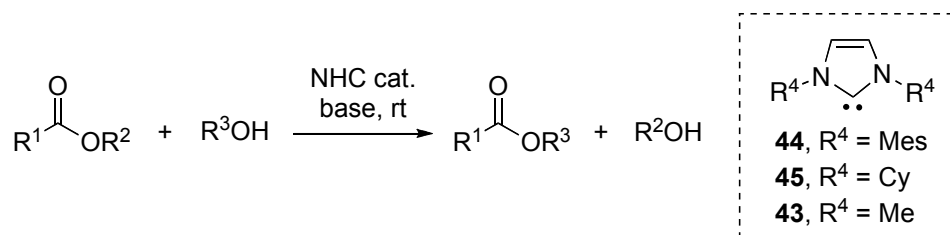
Scheme 13. NHC-promoted transesterification reactions developed by Nolan and co-workers and Hedrick and co-workers.

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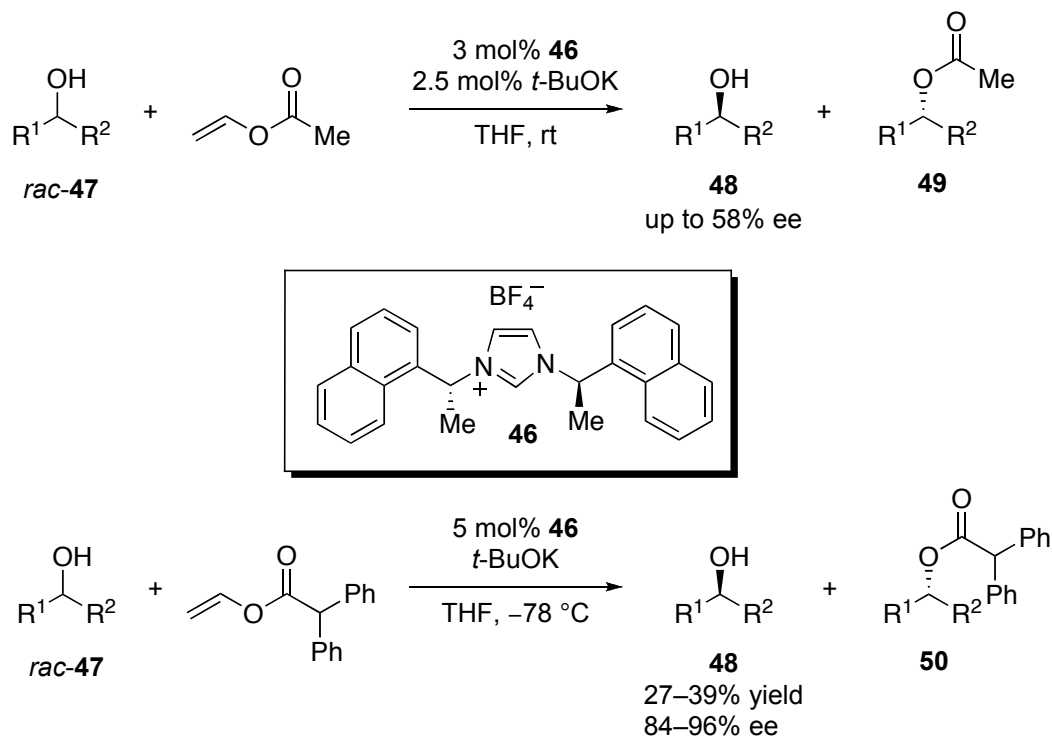
Scheme 14. NHC-catalyzed kinetic resolution of secondary alcohols by Suzuki (Top) and Maruoka (Bottom)

An interesting extension of this method came from the groups of Suzuki[57, 58] and Maruoka[59] whereby a C_2-symmetric chiral imidazolium salt **46** was used to promote the kinetic resolution of chiral secondary alcohols. The initial report from Suzuki et al. produced up to 58% ee using vinyl acetate as the acetylating agent and later 68% with vinyl propionate. Maruoka et al. found that by employing the preformed free carbene of **46**, formed by deprotonation with *t*-BuOK, and the more sterically demanding vinyl diphenyl acetate led to improved enantiomeric excesses of up to 96% (Scheme 14). However, it should be noted that in 2004 Rovis and co-workers disclosed the kinetic resolution of racemic ethyl lactate and racemic hydrobenzoin using a catalytically generated activated carboxylate from an *α*-bromoaldehyde and a chiral bicyclic triazolium salt (vida infra).[60]

1.4 Internal Redox Reactions of α-Functionalized Aldehydes

1.4.1 Activated Carboxylates

An activated carboxylate refers to a carbonyl-derived species that is more susceptible to nucleophilic attack than a free carboxylic acid. Examples of classical activated carboxylates include, but are not limited to, thioesters, acyl cyanides, acid halides, acid anhydrides, and activated esters of carboxylic acids formed from common peptide coupling reagents such as HOBt or HATU. However, NHCs can act as potent reagents for transforming an aldehyde possessing an internal, α-reducible functional group into an activated carboxylate poised for nucleophilic displacement. This basic process is outlined in Scheme 15. The nucleophilic carbene, either preformed or formed *in situ* in the presence of base, undergoes nucleophilic attack on the aldehyde, giving rise to a tetrahedral intermediate that upon proton transfer renders the Breslow intermediate. Internal displacement of the reducible functional group X yields an NHC-enol intermediate that tautomerizes to the activated carboxylate.
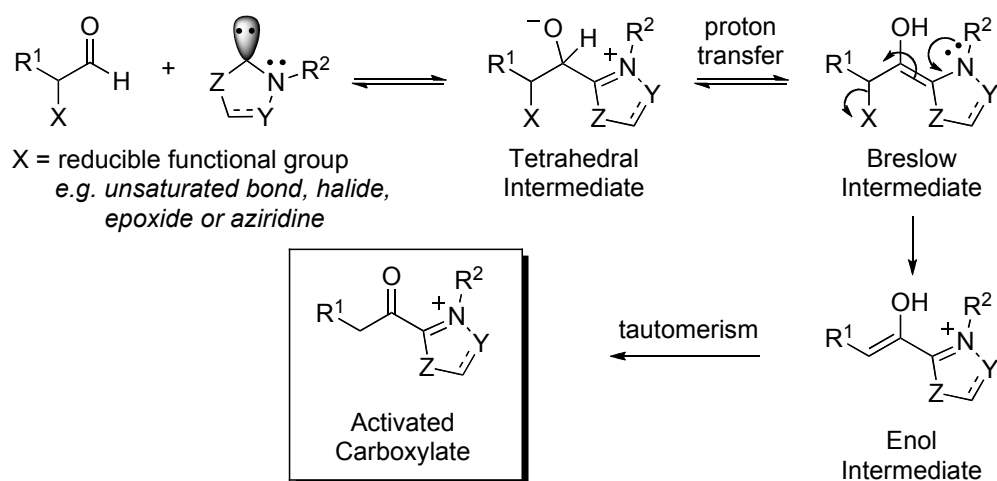
Scheme 15. NHC-promoted formation of activated carboxylates from aldehydes possessing an internal α-reducible functional group.

In 2004, Ken Chow from our group successfully applied this concept to the stereoselective synthesis of *β*-hydroxyesters from chiral *α,β*-epoxyaldehydes employing thiazolium NHC precatalyst **51** (Scheme 16).[61] In the same report our group disclosed the redox esterification of chiral *N*-tosylaziridinyl aldehydes. The postulated catalytic cycle is presented as follows (Figure 7). Deprotonation of thiazolium precatalyst **51** yields the free carbene **I** which undergoes nucleophilic attack on the epoxyaldehyde **55** leading to the tetrahedral intermediate **II**. A proton transfer event forms the Breslow intermediate **III**. Internal opening of the epoxide followed by a second proton transfer event affords NHC-enolate **V**. Alcohol-mediated tautomerization renders the activated carboxylate **VI** which undergoes nucleophilic attack by the resultant alkoxide to turnover the carbene catalyst and expel the *β*-hydroxyester **56**.
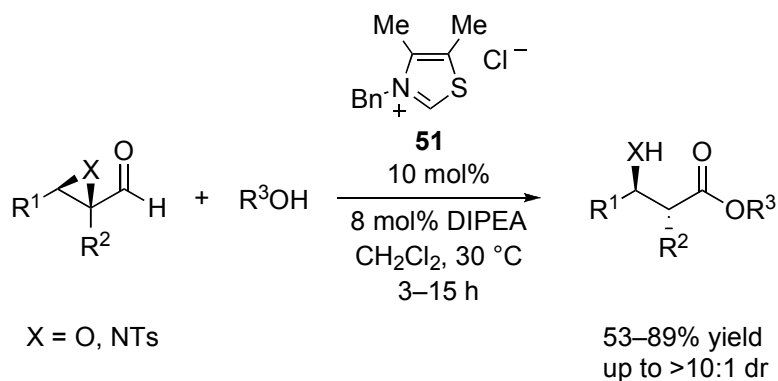
Scheme 16. NHC-catalyzed redox esterification of *α,β*-epoxyaldehydes and *α,β*-*N*-tosylaziridinyl aldehydes with thiazolium **51**.
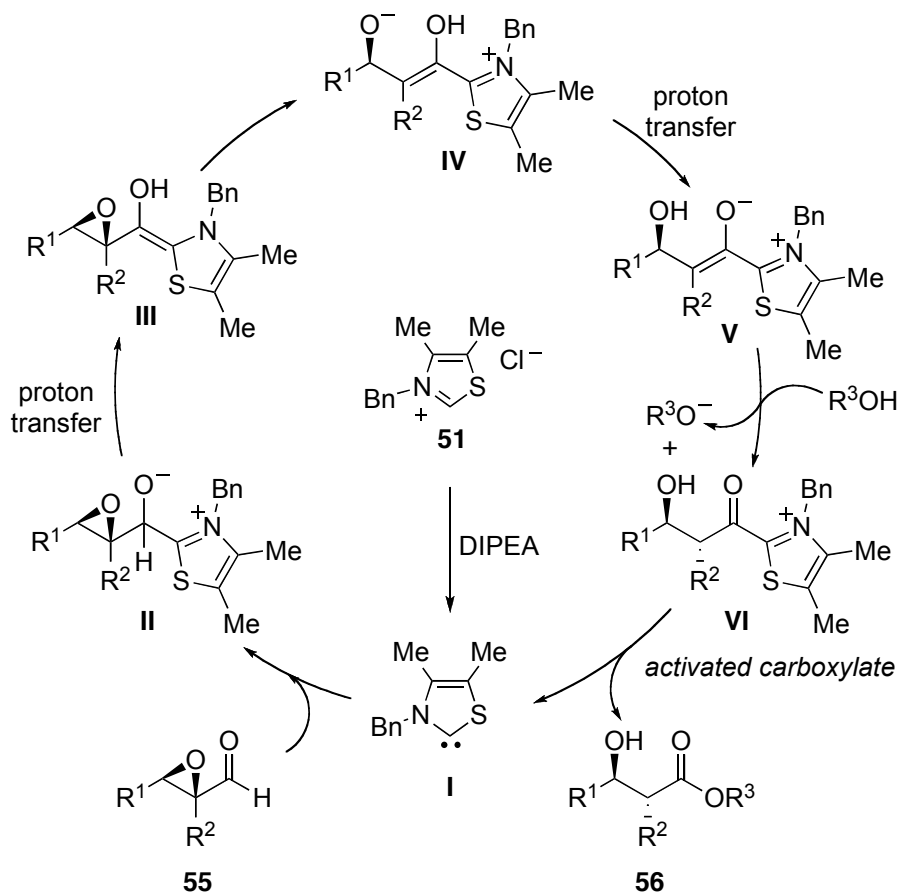
Figure 7. Postulated catalytic cycle proposed by Bode for the NHC-catalyzed redox esterification of α,β-epoxyaldehydes.

Around the same time Rovis and co-workers communicated the redox esterification of α-haloaldehydes under mild conditions in good yield utilizing triazolium NHC-precatalyst **35•Cl** (Scheme 17).[60] It is noteworthy that the use of chiral triazolium salt **57** exemplified the desymmetrization of a *meso*-diol in 75% yield and 83% ee, suggesting that the chiral NHC catalyst was intimately involved in the bond-forming event. In 2005, Rovis et al. extended this method to redox esterification of α,α-dichloroaldehydes with phenols employing the chiral aminoindanol-derived triazolium salt **34** to produce highly enantiomerically enriched α-chloroesters (up to 93%) in good yield.[62]

Scheme 17. Redox esterification of α-haloaldehydes reported by Rovis.

An impressive extension of this reaction reported by Dr. Stephanie Sohn from our group is the ring-opening esterification of formylcyclopropanes.[63] The internal reducible functional group is a C–C bond and both alcohols and thiols are viable nucleophiles. In the case where chiral trisubstituted formylcyclopropanes **61** are employed, acyclic β-substituted carbonyl derivatives **62** are obtained (Scheme 18).

Scheme 18. NHC-mediated reductive opening of formylcyclopropanes

In related processes, Sohn reported the amidation of aldehydes with an α-reducible functional group (Scheme 19).[64] She found that a stoichiometric amount of imidazole

was essential to overcoming imine formation between the starting aldehyde and the amine nucleophile. The reaction was optimized for the use of formylcyclopropanes and further exemplified by use of α-chloroaldehydes and enals as aldehyde substrates. Both primary, including O-protected (L)-phenylalanine, and secondary amines were smoothly acylated. Current efforts are underway in our group to exploit this reaction as a means for the kinetic resolution of racemic amines. In parallel studies, Rovis and co-workers have documented a similar redox amidation of aldehydes bearing an α-reducible bond.[65] They employed α,α-dichloraldehydes, α,β-unsaturated aldehydes, α,β-epoxyaldehydes and α,β-aziridinylaldehydes as substrates and HOAt as the stoichiometric acyl transfer reagent.
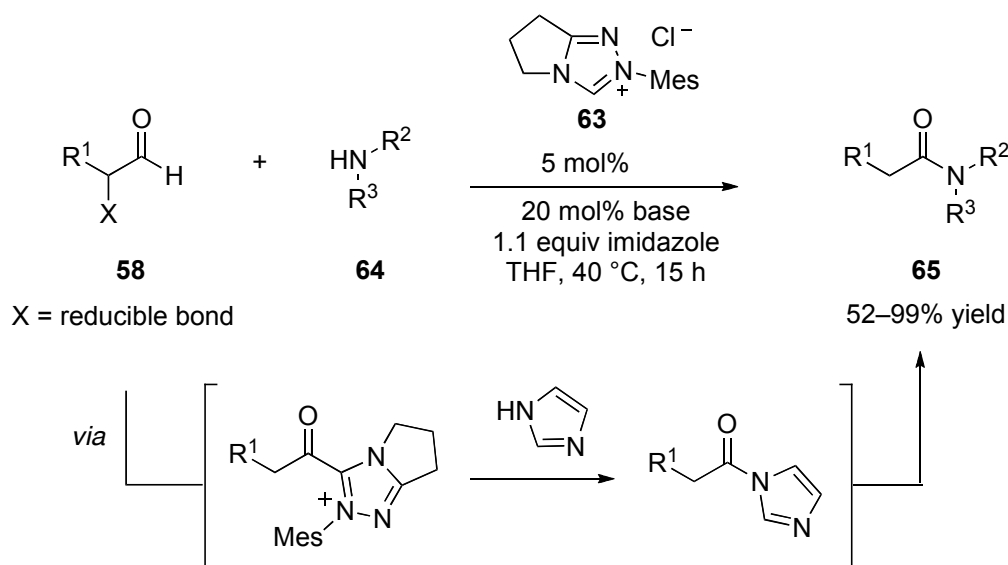
Scheme 19. NHC-promoted amidation of aldehydes with an internal reducible bond reported by Sohn and Bode.

It is well-known that thiazolium salts catalyze the oxidation of aldehydes to esters.[66] In the presence of a suitable NHC catalyst, the initially formed 1,2-adduct can be oxidized directly to the activated carboxylate, which upon nucleophilic displacement of the bound catalyst by an alcohol affords the ester. Significant contributions have been

reported by Shinkai,[67] Diederich,[68, 69] and Higashiura,[70, 71] using a combination of thiazolium-derived NHC-catalysts and Fe(III) salts as the stoichiometric oxidant. In recent years, the Scheidt group has expanded on this tandem oxidation/NHC-redox esterification process. Initial reports focused on the *in situ* oxidation of allylic, benzylic and propargylic alcohols to the corresponding α,β-unsaturated aldehyde using MnO_2.[72] The authors noted the sensitivity of the reaction toward azolium catalysts; specifically a triazolium catalyst was necessary to provide faster and more complete reaction conversion. Subsequently, they have greatly expanded the scope of this process to include aliphatic alcohols as well aliphatic and α,β-unsaturated aldehydes.[73, 74] Very recently, Studer and co-workers reported the NHC-catalyzed oxidation of aldehydes using two equivalents of TEMPO and a stoichiometric amount of DBU at room temperature to afford TEMPO esters that could be readily transesterified.[75] Again, a triazolium salt was identified as a superior precatalyst compared to either thiazolium or imidazolium salts. Notably, this process eliminates the need for a metal-based oxidant, employs as little as 0.5 mol % of the precatalyst, and allows the recovery and recycling of the TEMPO oxidant.

1.4.2 Catalytically Generated Homoenolates

N-Heterocyclic carbenes have also been shown to be effective catalysts for promoting an $a_3 \rightarrow d_3$ umpolung of the β-carbon of an α,β-unsaturated aldehydes. These reactive intermediates are termed homoenolate equivalents and undergo nucleophilic additions to a variety of electrophiles. Seminal reports on this transformation appeared simultaneously in 2004 by our group[76] and the group of Glorius.[77] In both cases the imidazolium NHC precatalyst IMesCl (**44•Cl**) was employed to convert an enal into a conjugate donor that efficiently underwent nucleophilic addition to a carbonyl acceptor. We reported the *cis*-diastereoselective (up to 5:1 *cis*:*trans*) formation of γ-butyrolactones

between enals and aromatic aldehydes while Glorius and co-workers found aryl, trifluoromethyl ketones to be sufficient electrophiles leading to *γ*-butyrolactones bearing a quaternary center with a *cis*-preference for the Ar and R^1 groups of approximately 2:1 (Scheme 20). In a follow-up report in 2008, Glorius and co-workers reported that use of a thiazolium NHC led to a diastereomeric preference of up to 10:1 for the *trans*-diastereomer.[78] Recently You and co-workers presented a diastereoselective synthesis *γ*-butyrolactones using a novel camphor-derived triazolium NHC catalyst and *α*-ketoesters as the electrophilic partner.[79]

Scheme 20. First reports of NHC-catalytically generated homoenolates by Bode and Glorius.

Dr. Ming He in our group extended the synthetic utility of this reaction by using *N*-sulfonyl aldimines as electrophiles to form *γ*-butyrolactams in moderate to good diastereoselectivity and good yield.[80] Interestingly, we found that homoenolate additions worked well in the presence of a protic solvent; in either *t*-BuOH (*γ*-butyrolactams) or a 10:1 THF:*t*-BuOH solution (*γ*-butyrolactones). In 2008, Dr. Michael Rommel in our laboratory discovered that the novel bicyclic triazolium salt **63**, first identified in our

group, efficiently catalyzed the addition of enals to cyclic ketimines with catalyst loadings of as little as 0.5 mol % (Scheme 21).[81] This method was tolerant of a variety functional groups on both the aldehyde and imine partners. In addition to aromatic and hetoaromatic enals, aliphatic aldehydes including acrolein successfully participated in the homoenolate addition. As for the cyclic ketimines, aliphatic, aromatic and heteroaromatic were all equally tolerated. In this report, we not only demonstrated that an enantioselective variant was achievable (6:1 dr, 73% ee, and 91% yield) but also that the cyclic sulfonyl group could be reductively cleaved to unveil a γ-butyrolactam bearing a quaternary stereocenter.
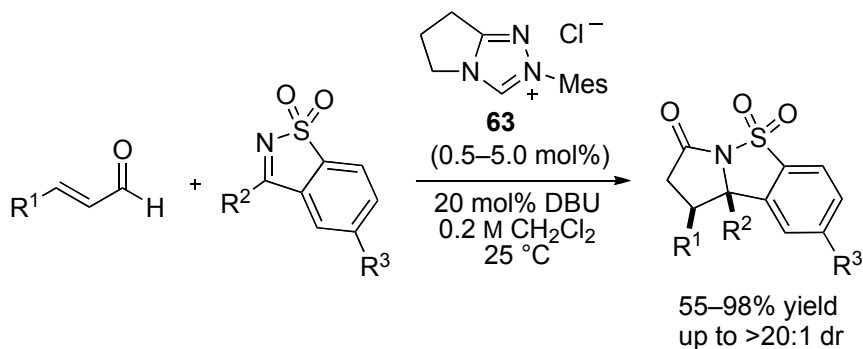
Scheme 21. Homoenolate additions to cyclic ketimines with low catalyst loading.

In less than 5 years since the initial reports of catalytically generated homoenolate equivalents, an explosion of interesting chemical transformations have appeared utilizing different electrophilic partners and an extensive review of this field appeared in 2008 by Nair and co-workers.[82] Notable contributions from Nair's group include the addition of homoenolates to chalcones[83] and acyclic dienones to form 3,4-trans-disubstituted aryl- and styrenyl-cyclopentenes, respectively; to tropone[84] to afford bicyclic δ-lactones; to 1,2-diketones,[85, 86] isatin and to aryldibenzylidene cyclopentanones[87] to produce spiro-annulated adducts. It is worth noting that all the homoenolate additions reported by Nair and co-workers occurred in the presence of imidazolium NHC IMes.
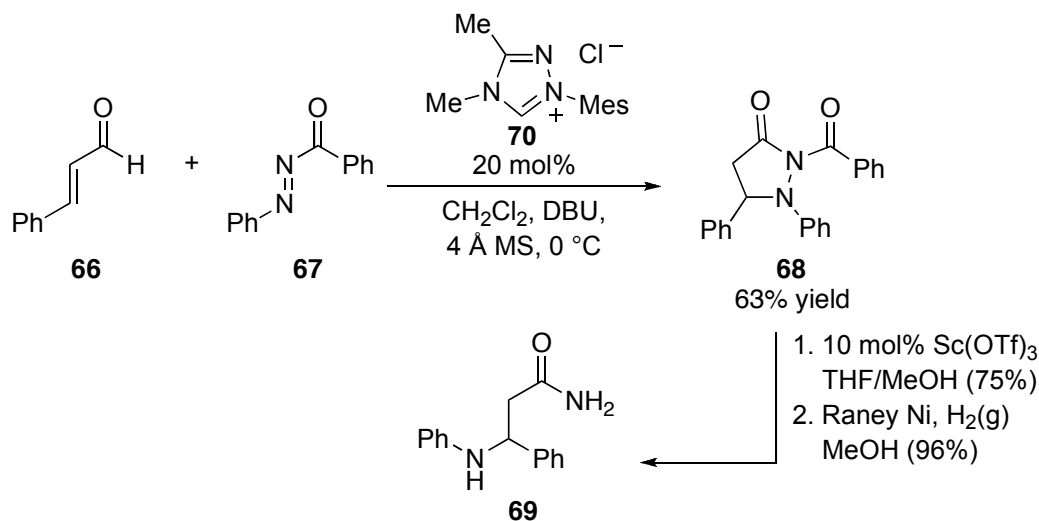
Scheme 22. Example of the direct amination of an NHC-generated homoeneolate reported by Scheidt.

Scheidt and co-workers have also reported significant progress in the area of NHC-enolate additions. They have recently discovered that 1,3-dipoles such as azomethine ylides[88] and *N*-phenyl nitrones[89] participate in formal [3+3] cycloaddition reactions with NHC-enolates to afford pyridazinones and *γ*-amino esters, respectively, with excellent diastereoselectivities. Furthermore, their group has realized the electrophilic amination of NHC-enolates via a formal [3+2] cycloaddition between the catalytically-generated homoenolate and acyl aryldiazenes **67** to afford a pyrazolidinone **68** as a single regioisomer.[90] The cycloadduct **68** was shown to be converted to a *β*-aminoamide **69** upon treatment with Sm(OTf)₃ in THF/MeOH followed by Raney Nickel reduction (Scheme 22). In a related process, Ying and co-workers recently reported a formyl [3+2] annulation between nitrosobenzene and an NHC-enolate derived from imidazolium precatalyst **70** and enals.[91] The intermediate cycloadduct **71** was immediately subjected to acidic methanol to afford *β*-amino ester **72** via an acid catalyzed esterification followed by a Bamberger-type rearrangement (Scheme 23).
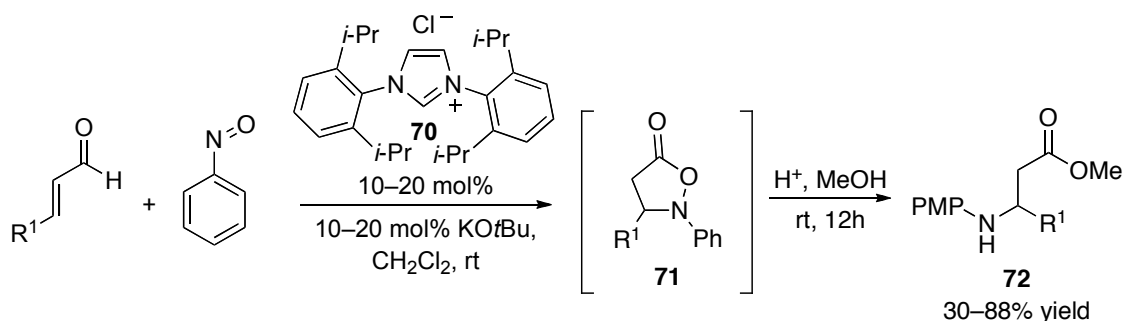
Scheme 23. NHC-catalyzed amination of enals.

1.4.3 Protonation of the Homoenolate: Nucleophilic Trapping of Activated Carboxylates

During the course of our studies into the catalytic generation of homoeneolates, we made the following discovery. When NHCs generated *in situ* by deprotonation with base were allowed to react with enals **73** to produce intermediate homoenolates, the fate of the homoenolate was intimately tied to the strength of the base as well as the type of NHC used (imidazolium vs. triazolium). When an imidazolium salt such as IMesCl was used in the presence of the strong base, C–C bond formation was preferred, giving rise to the γ-lactone dimer **74**. However, when a weaker tertiary amine base was employed along side the newly discovered *N*-mesityl bicyclic triazolium precatalyst **63•BF₄**, then protonation of the homoenolate occurred followed by nucleophilic trapping of the requisite activated carboxylate to afford the reduced ester **75** (Scheme 24).[92] Under optimized conditions, primary and secondary alcohols underwent esterification with a variety of enals in good to excellent yield (63–99%). At about the same time in 2005, Scheidt and Chan independently communicated a similar solution toward protonation of the catalytically generated homoenolates, promoted by *in situ* formed NHCs derived from benzimidazolium salts, by using excess phenol as an added proton source. Although this related process nicely achieved the desired protonation event, their

conditions required 5 equivalents of alcohol, added phenol, and elevated reaction temperatures.
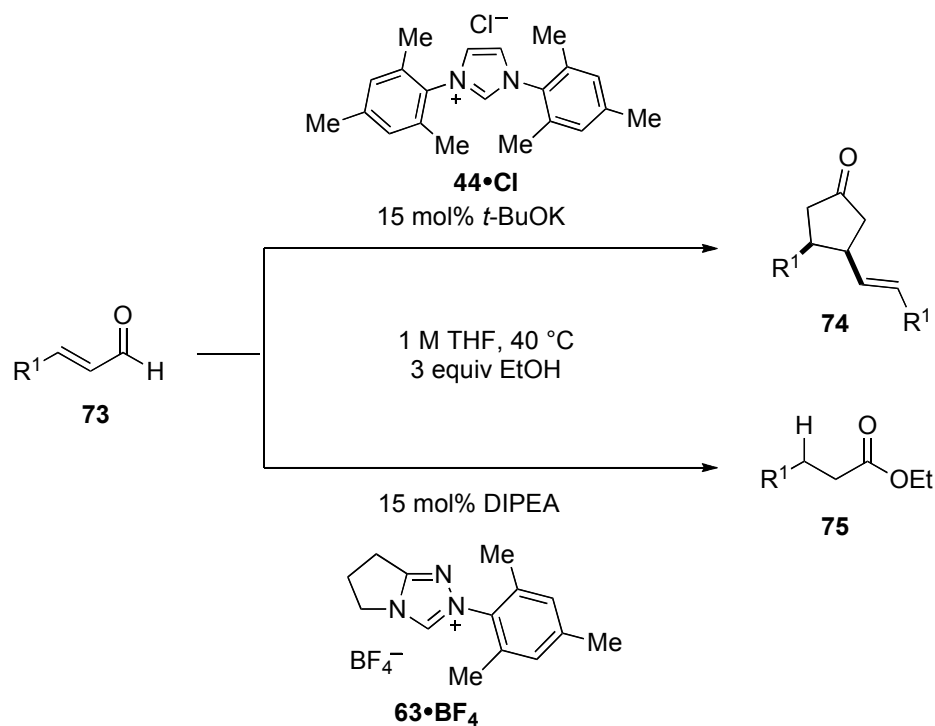
Scheme 24. The effect of base and catalyst type on the fate of catalytically generated homoenolates.

Discovery of the protonation of NHC-homoenolates has greatly expanded the synthetic utility of NHC-promoted internal redox reactions. In 2006, Zeitler developed an analogous extension of this method for the stereoselective preparation of (*E*)-configured α,β-unsaturated esters from propargylic aldehydes.[93] It is noteworthy that the sterically demanding imidazolium salt IMesCl was again found to be the most effective precatalyst but also that weak tertiary amine bases (DIPEA, DMAP, imidazole) were crucial to the success of the reaction. This underlies our initial observation that a sufficiently acidic conjugate acid is likely responsible for the protonation of the catalytically generated homoenolate. These related processes are outlined in Figure 8. Nucleophilic addition of the N-heterocyclic carbene to either an enal or alkynal leads to the Breslow intermediate

which is in resonance with the homoenolate equivalent. Protonation at the *β*-position by the conjugate acid of the weak tertiary amine base gives rise to an NHC-enol that undergoes tautomerism to the activated carboxylate. Nucleophilic attack by an alcohol releases the catalyst and affords the acylated nucleophile.
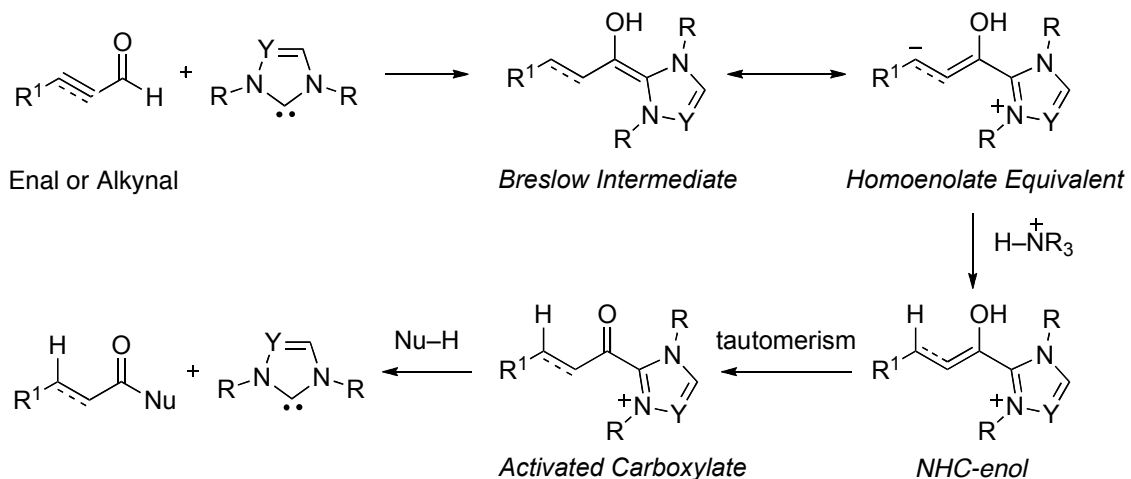
Figure 8. Nucleophilic trapping of activated carboxylates generated from protonation of NHC-homoenolates derived from enals and alkynals.

1.5 Conclusion

Since their initial use as organocatalysts for the benzoin and Stetter reactions, NHCs have witnessed an explosion in their scope as nucleophilic catalysts for a variety of conceptually new organic transformations. As new catalyst manifolds are developed, it is likely that new substrate types and electrophiles that are currently unreactive in already reported transformations will be utilized, thus expanding the horizon of the types of chemistry that will be achievable by these interesting small molecule catalysts. Similarly, the ever-expanding advent of new chiral scaffolds will likely render known reactions enantioselective in the upcoming years.

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Chapter 2: Design and Synthesis of *N*-Mesityl Triazolium Salts for NHC-Catalyzed Redox Reactions

2.1 State of the Art Syntheses for Triazolium Salts

2.1.1 Syntheses of Achiral Triazolium Salts

There are two general methods for the syntheses of 1,4-disubstituted triazolium triazolium salts and 1,3,4-trisubstituted triazolium salts.[1-3] The first method begins from the bisformyl hydrazine **78** (derived from an alkyl- or arylhydrazine that has been formylated via a mixed anhydride) which is condensed with acetic anhydride in the presence of perchloric acid. The intermediate oxadiazolinium **79** is then subjected to a ring-opening ring-closing (RORC) reaction with an appropriate amine to afford the 1,4-disubstituted triazolium salt **80** (Scheme 25). The 1,3,4-trisubstituted triazolium salts can be synthesized by starting from an acylhydrazine and then performing the subsequent aforementioned chemical transformations. The second, and perhaps more often utilized, method for the preparation of 1,4-disubstituted triazolium salts and 1,3,4-trisubstituted triazolium salts is a one-pot procedure outlined in Scheme 26. Condensation between an *in situ* prepared imidoyl chloride **82** and an *N*-substituted, *N*-formylhydrazine **83** followed by cyclization and anion exchange affords the desired triazolium salt **84**.

R^1 = alkyl or aryl
R^2 = alky or aryl
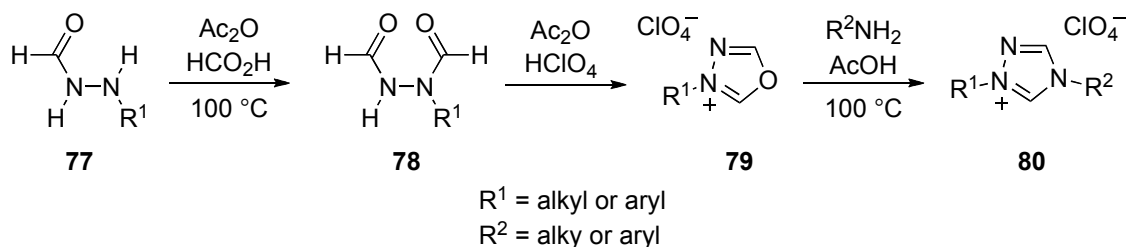
Scheme 25. A general synthesis of of 1,4-disubstituted triazolium salts.

R[1] = alkyl, aryl or H
R[2] = alky or aryl
R[3] = alky or aryl

Scheme 26. A general synthesis of 1,4-disubstituted and 1,3,4-trisubstituted triazolium salts.

A notable utilization of the latter method is Enders preparation of 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene (**85**), an unusually stable free carbene that can be stored for prolonged periods of time.[4] The free carbene can be obtained by treatment of its parent triazolium salt with a methanolic solution of sodium methoxide followed by *α*-elimination in vacuo of the resultant C-2 ether to afford the free carbene. Enders and co-workers have shown that this free carbene can undergo a wide variety of electrophilic additions: additions to alcohols, thiols, and amines to yield the corresponding insertion products (Figure 9, path **a**); to molecular oxygen, sulfur, and selenium to form the triazolinone, -thione, and -selenone (Figure 9, path **b**); to heterocumulenes such as phenylisocyanates and carbon disulfide to produce the corresponding betaines (Figure 9, path **c**); and to doubly activated double bonds such as fumaric and maleic esters, nitriles, maleic imides and nitro olefins to afford the open-chain allylic adducts (Figure 9 path **d**). Furthermore, it can also add to transition metals to form metal-ligand complexes (Figure 9, path **e**) and even be used as a nucleophilic NHC catalyst for the formation of acyl anion equivalents that can undergo benzoin condensations (Figure 9, path **f**).[5]
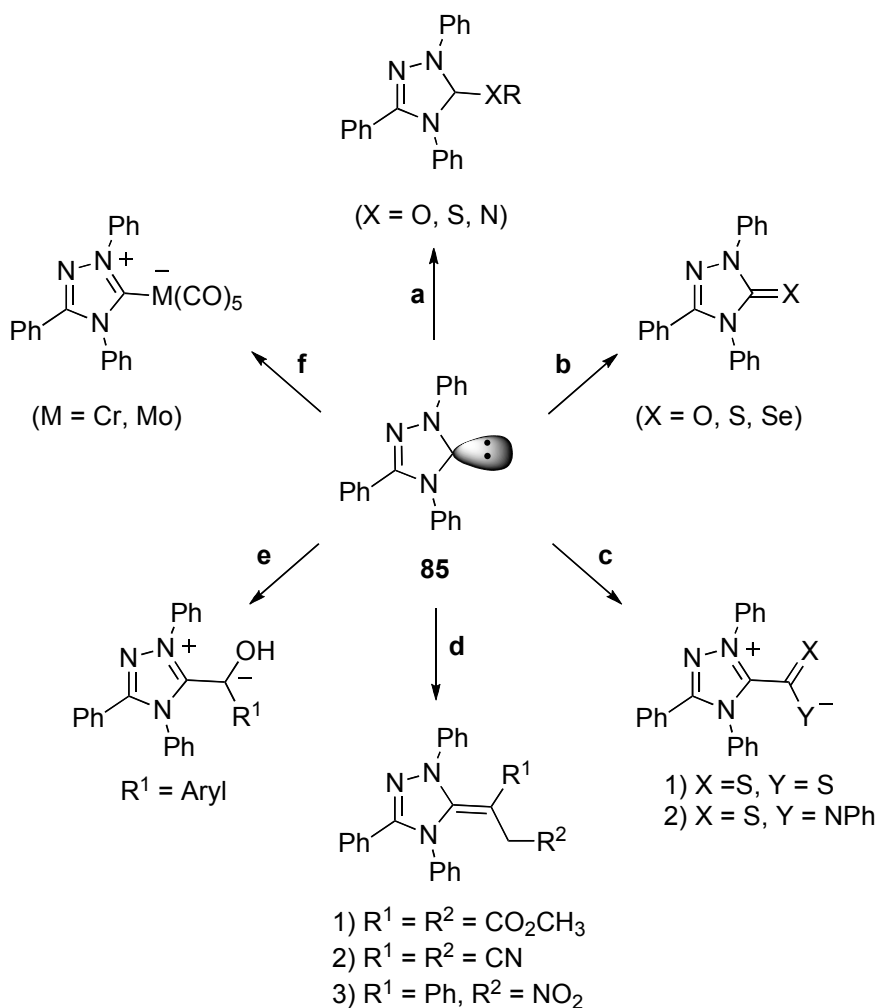
Figure 9. Electrophilic additions of Enders' free carbene **85**.

While 1,4-disubstituted triazolium salts and 1,3,4-trisubstituted triazolium salts have been used as competent NHC precatalysts for a variety of transformations (See Chapter 1 and the references therein), by far the most widely used achiral triazolium salts employed are those based on a bicyclic motif. In 2005, Rovis and co-workers[6] disclosed an elegant synthesis of bicyclic triazolium salts derived from 2-pyrrolidinone based on the modification of Leeper's work (Scheme 27).[7] Starting with *O*-methylation of 2-pyrrolidinone with dimethyl sulfate followed by condensation with phenylhydrazine, treatment with base, and reacidification with HCl provided the intermediate hydrochloride

salt **88**. Final treatment with trimethyl orthoformate in MeOH afforded the bicyclic *N*-phenyl triazolium salt **57**.
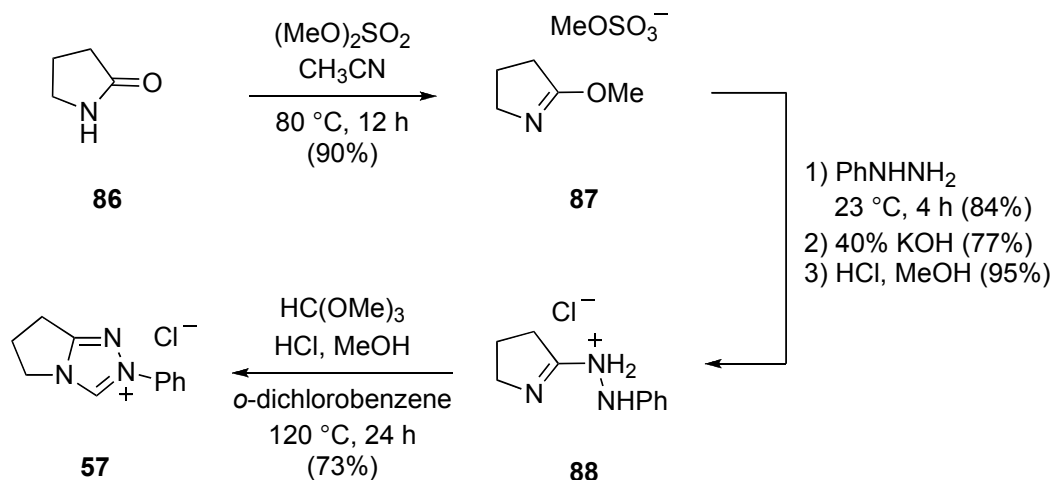
Scheme 27. Rovis' linear synthesis of bicyclic *N*-phenyl triazolium salt **57**.

In the same report the authors disclosed a modified one-pot synthesis of the bicyclic triazolium salts (Scheme 28). Meerwein methylation of 2-pyrrolidinone followed by condensation with pentafluorophenylhydrazine followed by removal of solvent provided the hydrazinium salt **89** in excellent yield. Final ring closure by treatment with neat triethyl orthoformate at elevated temperature smoothly provided the *N*-pentafluorophenyl bicyclic triazolium salt **90** in good yield.
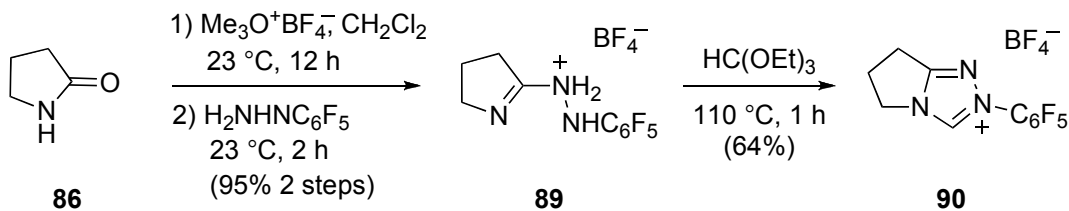
Scheme 28. Rovis' one-pot protocol for the production of bicyclic triazolium salts.

2.1.2 Syntheses of Chiral Triazolium Salts

The two most commonly employed scaffolds utilized for chiral triazolium salts are again bicyclic in nature. The first class is based on chiral 2-pyrrolidinones whereby the chiral element resides at the 3 position (Figure 10a). The chiral lactams employed as the starting material are conveniently prepared from either an amino acid or pyroglutamic acid. The second class is derived from cis-1,2-aminoalcohols (Figure 10b). The cis-1,2-aminoalcohols are often derived from *α*-amino acids as well.
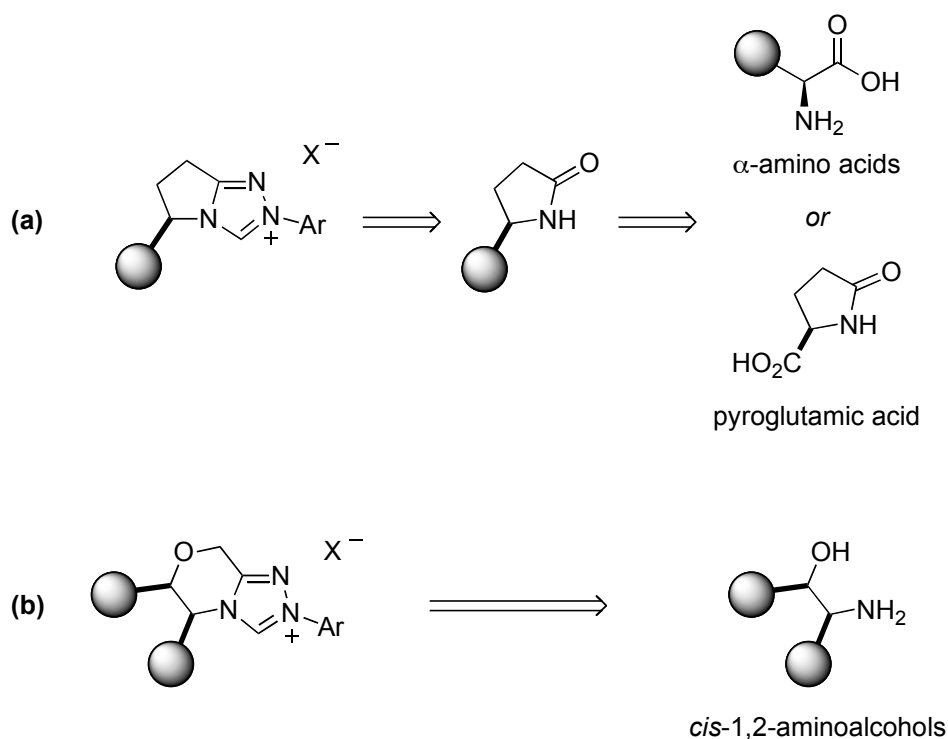
Figure 10. Common motifs for chiral triazolium salts.

In 1998, in the search for a catalyst capable of stereoinduction in the benzoin condensation, Knight and Leeper introduced the first chiral bicyclic triazolium salt **91** (Scheme 29).[7] Starting from morpholinone **92,** synthesized from phenylalanol, Meerwein methylation followed by liberation of the resultant salt with base provided the free iminoether **93**. Condensation with phenylhydrazine hydrochloride and subsequent ring

closure of **94** with trimethyl orthoformate afforded the desired chiral triazolium salt **91**. In the same report Knight and Leeper disclosed the synthesis of two triazolium salts derived from (L)-pyroglutamic acid employing the same aforementioned three step process (Figure 11, **95** and **96**). Shortly thereafter, Enders expanded the utility of this latter process and communicated the synthesis of NHC triazolium precatalysts **97**–**98**[8] and **99**–**102**[9] for enantioselective benzoin condensations utilizing a procedure similar to Rovis.
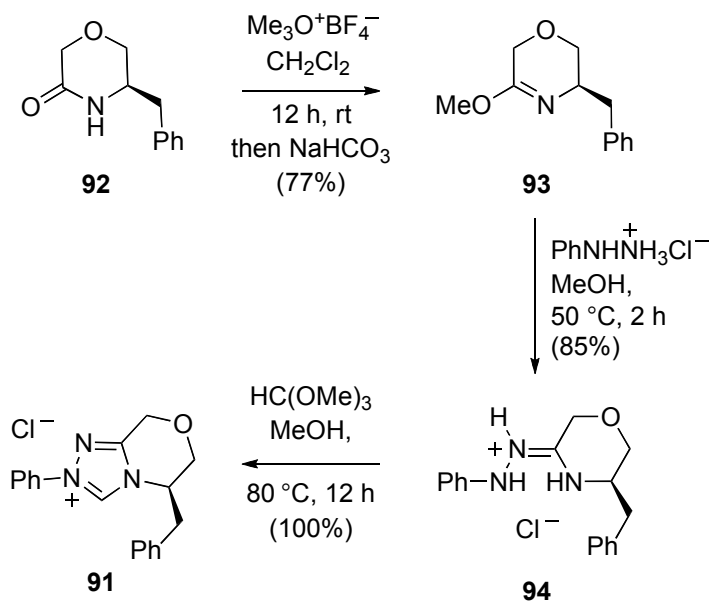
Scheme 29. First reported synthesis of a chiral bicyclic triazolium NHC precatalyst by Leeper.

Knight and Leeper 1998	Enders 2006	Enders 2008	Enders 2008
95, R^1 = Me	**97**, R^1 = TIPS	**99**, R^1 = TBS, R^2 = Ph	**102**
96, R^1 = Ph	**98**, R^1 = TBS	**100**, R^1 = TMS, R^2 = Me	
		101, R^1 = TMS, R^2 = Ph	
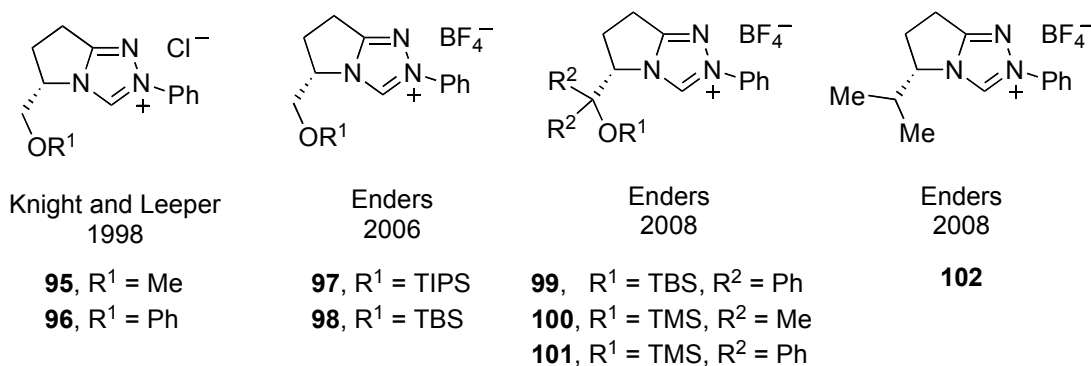
Figure 11. Chiral bicyclic triazolium salts derived from (L)-pyroglutamic acid.

Rovis and co-workers rejuvenated the *cis*-aminoalcohol scaffold with their syntheses of several triazolium salts derived from *cis*-1,2-aminoindanol for use in the asymmetric Stetter reaction.[6, 10] They employed their one-pot protocol identified for the synthesis of bicyclic triazolium salts (see Scheme 28) to afford various *N*-substituted aminoindanol-derived triazolium salts in good yield (Figure 12). NHC catalysts based off this scaffold have emerged as some of the most efficient and selective for a variety of NHC-promoted internal redox processes (See Chapter 1 and vide infra).

32, Ar = Ph
33, Ar = *p*-anisyl
34, Ar = C$_6$F$_5$

103

104
cis-1,2-aminoindanol
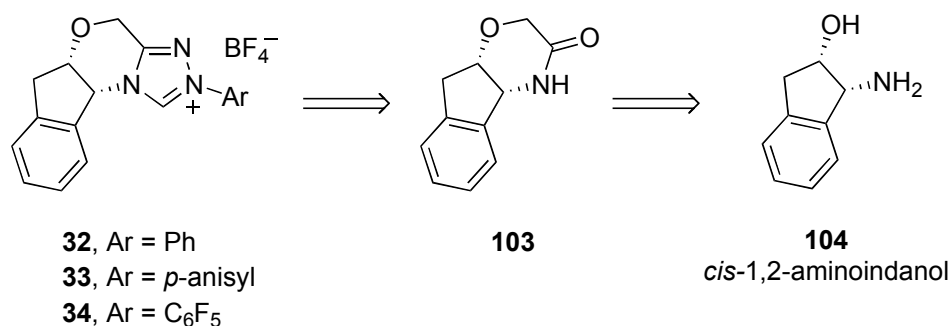
Figure 12. Aminoindanol-derived chiral triazolium salts reported by Rovis.

2.2 Synthesis of a Novel *N*-Mesityl Substituted Achiral Triazolium Salt for NHC-Promoted Redox Reactions: RMesCl

The first NHC-promoted process investigated by our group was the redox esterification of enals.[11] Dr. Stephanie Sohn, in the course of her studies, found that essential to the success of this reaction was the identification of conditions that allowed the protonation of the intermediate homoenolate leading to an activated carboxylate poised for nucleophilic displacement by an alcohol. A screening of reaction parameters led to the discovery of the necessity to employ the weak tertiary amine base. A screening of NHC precatalysts showed thiazolium salts to be incompetent for the desired

transformation. Imidazolium salt **44•Cl** offered improved efficiency, but tended to produce the unsaturated carboxylic acid as a byproduct, an outcome that we attributed to the slow turnover of the catalyst-bound activated carboxylate. Although triazolium salt **57**, previously described by Rovis, was unproductive, the *p*-methoxyphenyl analogue **106** was effective, but with a limited range of substrates. Further studies on catalyst syntheses identified *N*-mesityl triazolium precatalyst **63•BF₄** as uniquely active, effecting redox esterifications of enals overnight with as little as 2 mol% of the salt (Scheme 30).
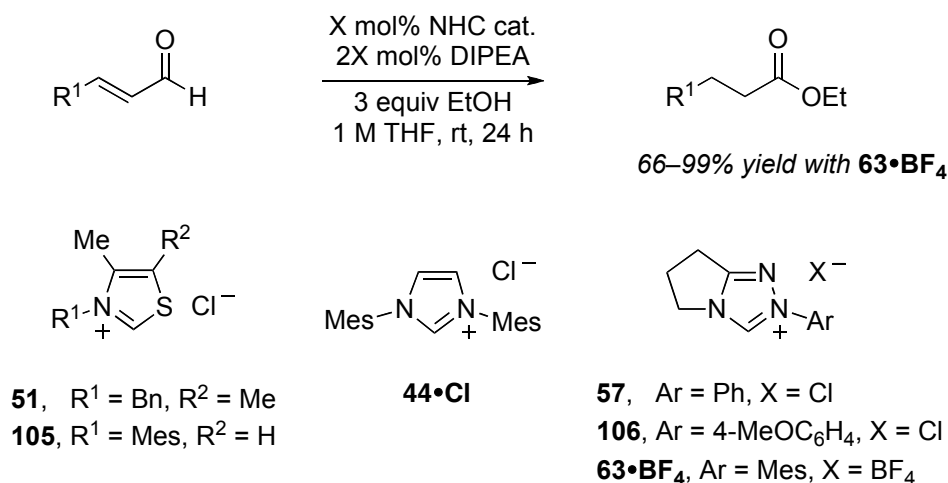
Scheme 30. Screening of azolium salts for the NHC-catalyzed redox esterification of enals.

Although this result was exciting, our progress in this area was stymied by the unreliability for the production of NHC precatalyst **63•BF₄**. Rovis has described a concise, high-yielding synthesis of a number of achiral bicyclic triazolium salts salts (see Schemes 27 and 28).[6] While we have found these protocols to be very effective for the synthesis of triazolium salts bearing simple aromatic groups, we obtained capricious outcomes when attempting to apply these procedures to the preparation of the *N*-mesityl substituted variant. We traced much of our difficulties to the low purity and poor stability of 2-mesitylhydrazine,[12] the key condensation partner for the production of the amidrazone intermediate. We found that 2-mesitylhydrazine decomposed readily in air

and use of the crude hydrazine in the condensation led to intractable oils. To circumvent this problem, we adopted the protocol originally reported by Knight and Leeper (See Scheme 29),[7] in which the neutral iminoether was allowed to react with the arylhydrazine hydrochloride salt.
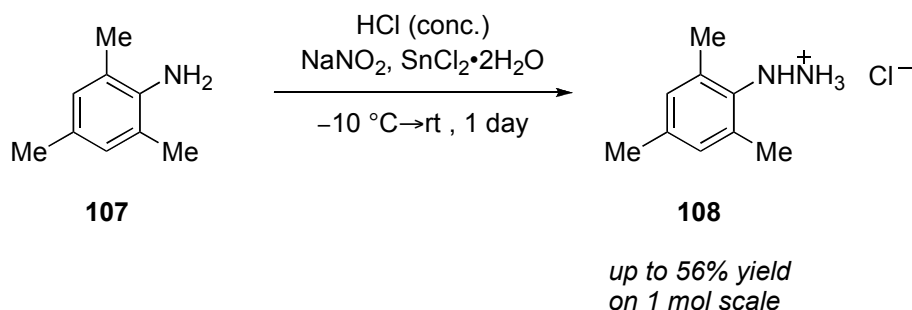
Scheme 31. Preparative scale preparation of 2-mesitylhydrazinium hydrochloride **108**.

This approach required a reliable and scaleable synthesis of 2-mesitylhydrazinium hydrochloride **108**. After arduous experimentation, we found that a refined Sandmeyer approach from the corresponding aniline **107** was the most efficient route (Scheme 31).[13] Critical to the success of this reaction on scale was the vigilant monitoring of the internal reaction temperature during the diazonium formation and reduction steps. When internal reaction temperatures rose above 5 °C, decreased yields of <20% were observed. The careful, drop-wise additions of the sodium nitrite and stannous chloride solutions as well as maintaining a cold external bath of −10 °C were crucial to the outcome of the reaction. Although the isolated yield of this particular hydrazinium is moderate (typically in the range of 36–56%), this procedure is robust and reproducible on a preparative scale of up to 1 mole.

The synthesis of the desired bicyclic *N*-mesityl triazolium salt commenced from 2-pyrrolidinone (Scheme 32). Methylation was executed using dimethyl sulfate, and liberation of the free base upon treatment with NaHCO₃ provided the iminoether **109**, which was used without further purification. The condensation of 2-mesitylhydrazinium

hydrochloride **108** and the iminoether **109** was carried out under the conditions reported by Leeper.[7] Final ring closure with triethyl orthoformate in the presence of a stoichiometric amount of anhydrous HCl at elevated temperature afforded the desired triazolium salt **63,** which we have conveniently coined RMesCl. The synthesis is highly reliable and can be performed to give up to 10 g of **63** in a single synthetic run.
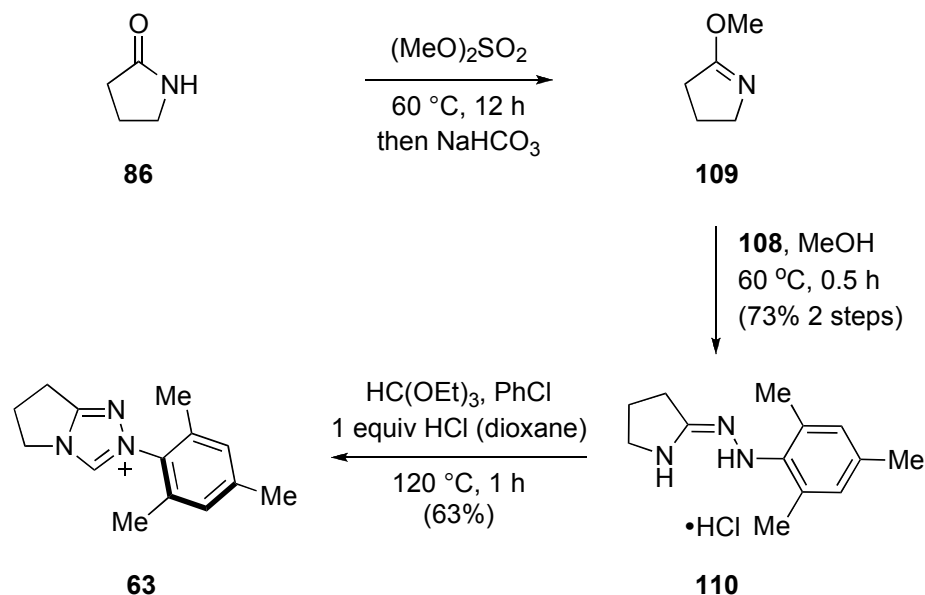
Scheme 32. Synthesis of *N*-mesityl triazolium salt **63** (**RMesCl**).

The most challenging aspect of the synthesis of the *N*-mesityl substituted triazolium salt **63** was the ring-closing reaction with triethyl orthoformate. After considerable experimentation, we found two important factors that led to clean, high-yielding reactions for the production of *N*-mesityl substituted triazolium salts. First, it was essential to add an equivalent of anhydrous HCl to the reaction mixture. Second, and most critically, we found that extended reaction times were detrimental to the isolation of the desired triazolium salts. In contrast to prior protocols that employed longer reactions times (>12 hours), reaction periods of 1–2 hours were generally preferred. Qualitatively, the progress of the reaction could be followed by the solubilization of the starting

amidrazone hydrochloride; when a clear solution had formed the reaction was generally complete.

Since it's inception, we have documented the profound reactivity of *N*-mesityl triazolium salt **63**. The access to this NHC precatalyst has allowed our group to identify many conceptually new NHC-promoted redox processes that only **63** efficiently catalyzes.

2.3   Synthesis of an Aminoindanol-Derived *N*-Mesityl Triazolium Salt for Enantioselective NHC-Promoted Annulations

2.3.1 Identification of an NHC-Promoted Azadiene Inverse Electron Demand Diels-Alder Reaction

In a continuing effort to develop new carbon–carbon bond forming reactions between catalytically generated homoenolates from NHCs and enals (Figure 13), we reasoned that protonation or trapping of the formal homoenolate **II** should lead to formation of an enol **III** or enolate **IV** intermediate poised for carbon-carbon bond formation and subsequent catalyst expulsion. However, an unexpected obstacle was the reluctance of protonation at the *β*-position of the Breslow intermediate **I**, or its resonance homoenolate **II**, when generated from an imidazolium catalyst even in protic solvents at elevated temperatures. To address this we designed triazolium NHC precatalyst **63**, which in conjunction with a weak tertiary amine base provided the desired protonation event (vide supra).
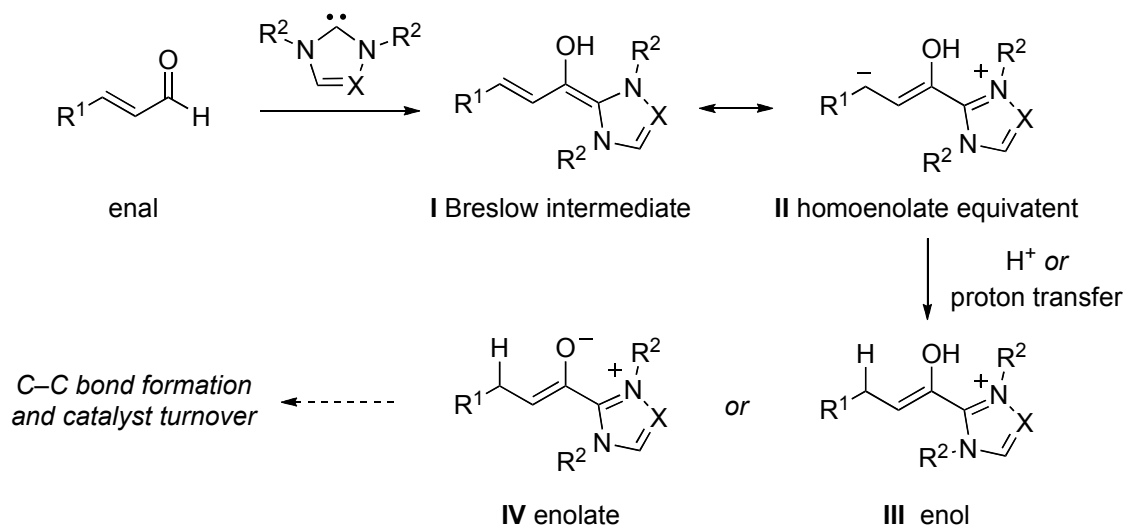
Figure 13. Proposed catalytically generated NHC-enolate formation.

Yet, efforts to trap these postulated NHC-enolates were frustrated by the tendency of the nucleophilic carbene to react with an added electrophile in preference to the enal. When a more electrophilic enal, ethyl *trans*-4-oxo-butenoate (**111**), was chosen as the coupling partner with *N*-sulfonyl aldimines (**112**) in conjunction with an imidazolium-derived carbene (**44•Cl**), preferential formation of γ-butyrolactams (**113**) was observed (Scheme 33). However, when our hindered *N*-mesityl triazolium precatalyst **63** was used, a new product had formed. Elucidation by single crystal X-ray analysis revealed the new product to be a dihydropyridinone (**114**) formed via a Diels-Alder reaction between the *N*-sulfonylimine and a catalytically generated enolate. After optimization of the reaction conditions, we discovered that the reaction proceeds under extremely mild conditions. Naturally, we then turned our attention to developing an enantioselective version of this newly discovered LUMO$_{diene}$-controlled Diels-Alder cycloaddition. To this end, we screened several aminoindanol-derived chiral triazolium catalysts that proved to be either unreactive or produce the desired dihydropyridinone in only modest yields and enantioselectivities. Postulating that once again a more hindered triazolium catalyst may

be needed, we turned our sights toward developing and synthesizing a chiral *N*-mesityl triazolium NHC precatalyst.
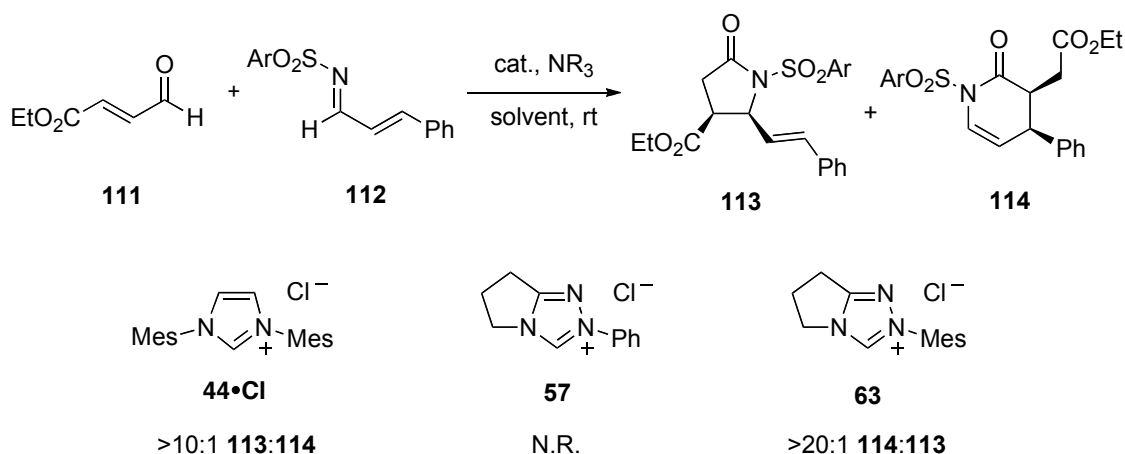
Scheme 33. Precatalyst screening for the NHC-promoted azadiene Diels-Alder reaction.

2.3.2 Synthesis of an N-Mesityl Substituted Aminoindanol-Derived Triazolium Salt

Due to Rovis' success with the aminoindanol motif as an effective chiral motif for stereoinduction in the asymmetric intramolecular Stetter reaction (see Chapter 1), we sought to apply this privileged scaffold toward the production of an *N*-mesityl variant in the hopes that we might render our newly discovered NHC-promoted azadiene Diels-Alder reaction enantioselective. Armed with the knowledge that the condensation of 2-mesityl hydrazinium hydrochloride and an appropriate iminoether occurs readily at slightly elevated temperatures (see Scheme 32), we reasoned that the same method could be applied to the condensation of activated morpholinone **115** described by Rovis (Scheme 34). Methylation of morpholinone *ent*•**103** with Meerwein's salt and subsequent treatment with aqueous sodium bicarbonate afforded iminoether **115**. Initial attempts to condense iminoether **115** with 2-mesityl hydrazinium hydrochloride **108** under neutral conditions failed to yield the desired amidrazone hydrochloride **116**. Prolonged reaction

times improved the conversion but not to useable levels. Often solvolysis of **116** would occur affording morpholinone **ent•103** as a major product. Empirically, we found the necessity to employ a catalytic amount of anhydrous HCl and a prolonged reaction period of 2 days to afford the desired amidrazone hydrochloride in good yield. Finally, treatment of **116** with excess triethylorthoformate and an equimolar amount of anhydrous HCl in chlorobenzene provided smooth conversion to the crude precatalyst **117**, which was recrystallized from toluene and isolated as a white powder in 64% yield. Again it should be stressed that prolonged exposure to heating caused decomposition of the triazolium salt and that the added stoichiometric amount of anhydrous HCl was crucial to the success of the reaction. Impressively, we optimized the procedure to forego any chromatography and the production of either enantiomer could be achieved on a >20g scale.
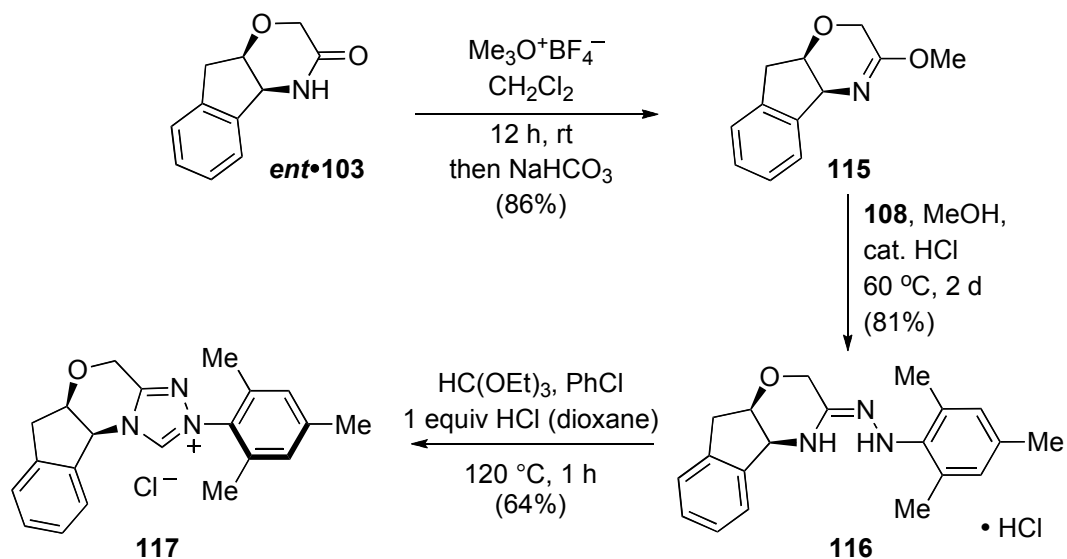
Scheme 34. Concise and scalable synthesis an *N*-mesityl substituted aminoindanol-derived triazolium salt.

With the new chiral triazolium precatalyst **117** in hand, we tested its efficacy in the NHC-promoted azadiene Diels-Alder reaction against other chiral triazolium precatalysts

possessing different substitution of the *N*-aryl group (Scheme 35). The *p*-methoxy derivative **33** reported by Rovis[6] was found to be completely ineffective. Although *o*-tolyl derivative **118** provided the dihydropyridinone **114** with excellent diastereo- and enantioselectivity, the yield was only modest. To our delight our new *N*-mesityl derivative **117** not only provided the dihydropyridinone **114** in excellent yield but also as a single stereoisomer.
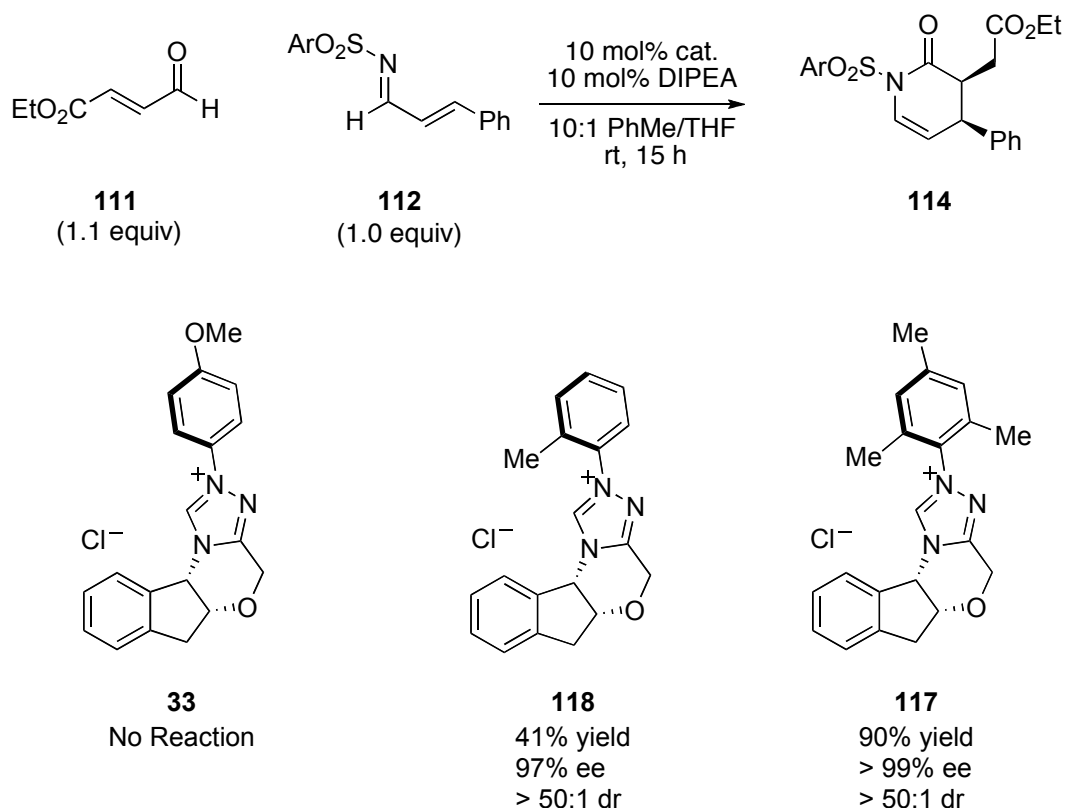
Scheme 35. Screening of chiral aminoindanol-derived triazolium salts for the enantioselective azadiene Diels-Alder reaction.

Table 1. NHC-catalyzed, enantioselective azadiene Diels-Alder reaction.[a]
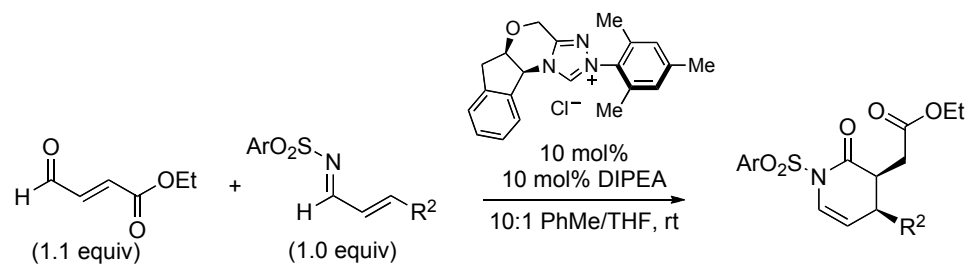
Entry	R^2	Product	yield (%)[b]	ee (%)[d]
1	Ph		90	99 (*S*, *S*)
2[c]	Ph		90	99 (*R*, *R*)
3	MeO–C$_6$H$_4$		81	99 (*S*, *S*)
4	Me(C=O)–C$_6$H$_4$		55	99 (*S*, *S*)
5	(2-furyl)		71	99 (*S*, *S*)
6	*n*-Pr		88	99 (*S*, *S*)

[a] Ar = 4-MeOC$_6$H$_4$. All reactions were performed at 0.05 M for 23–48 h. In all cases only a single
   diastereomer was detected in unpurified reaction mixtures by ^{1}H NMR or HPLC analysis
[b] Isolated yield after chromatography.
[c] 10 mol % **ent-117** was used as catalyst.
[d] Determined by HPLC analysis.

Our NHC-catalyzed annulation proceeds under exceptionally mild conditions. Simply stirring nearly an equimolar ratio of the enal and imine substrates in the presence of 10 mol % of precatalyst **117** and 10 mol % DIPEA at ambient temperature for 23–48 h followed by removal of the solvent and purification by chromatography provided the *cis*-3,4-dihydropyridinones in good to excellent yield and excellent enantioselectivity (97–99% ee) as a single diastereomer (>50:1) with a preference for the *cis* isomer. This process tolerated a full range of *α,β*-unsaturated imines including both electron-rich and electron-deficient cinnamaldehyde derivatives as well as heterocyclic and aliphatic aldehydes (Table 1).

Table 2. Variation of the enal substrate in the NHC-catalyzed Diels-Alder reaction.[a]

Entry	R²	Product	yield (%)[b]	ee (%)[d]
1	Ph		70	97 (*S, S*)
2[c]	Ph		51	99 (*S, S*)
3	*n*-Pr		71	98 (*S, S*)
4			52	98 (*S, S*)

[a] Ar = 4-MeOC$_6$H$_4$. All reactions were performed at 0.05 M for 23–48 h. In all cases only a single diastereomer was detected in unpurified reaction mixtures by ^{1}H NMR or HPLC analysis
[b] Isolated yield after chromatography.
[c] An additional 1.0 equiv of enal was added after 15 h.
[d] Determined by HPLC analysis.

This process was further amenable to changes in the enal substrate (Table 2). The synthetically attractive *tert*-butyl ester readily participated in the annulation providing the dihydropyridinone adduct in excellent yield and enatioselectivity (Table 2, entry 1). Methyl and phenyl ketones also readily participated Diels-Alder reaction (Table 2, entries 2–5) affording the desired products with exceptional enantioselectivity (>98% ee).

Our azadiene Diels-Alder process was the first highly enantioselective NHC-promoted intermolecular annulation reported. The exceptional diastereoselectivity (>50:1) is rationalized by the high preference for the *endo* transition state that not only benefits from secondary orbital overlap but is accentuated by the *trans* periplanar relationship of the nitrogen lone pair of the *N*-sulfonylimine and the C–O σ bond of the NHC-enolate, providing additional stabilization by means of a transition-state anomeric effect.[14, 15] Furthermore, we have postulated that protonation of the Breslow intermediate can only occur in a fully conjugated, extended arrangement that necessarily leads to the (Z)-enolate or (Z)-enol arrangement.[11] The *cis*-diastereoselectivity would arise from this (Z)-enolate geometry of the dienophile provided by the sterically demanding *N*-mesityl group of the bound NHC catalyst. The absolute stereochemistry is believed to be a result of the induced facial bias by the bulky aminoindanol backbone. The model shown in Figure 14 rationalizes the observed relative and absolute stereochemistry of the products.
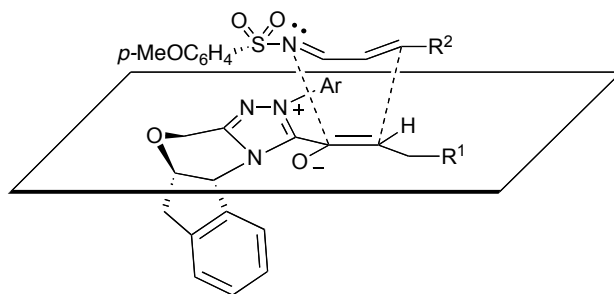
Figure 14. Stereochemical model for the observed stereoselectivity in the NHC-promote LUMO$_{diene}$-controlled inverse electron demand Diels-Alder reaction.

2.4 Discovery of New Redox Processes Preferentially Promoted by *N*-Mesityl Substituted Triazolium Salts

2.4.1 Extension of the NHC-Promoted Hetero Diels-Alder Reaction

Access to *N*-mesityl aminoindanol-derived triazolium salt **117** has allowed our group to discover a plethora of novel NHC-promoted redox processes. We first were able to extend the utility of the NHC-catalyzed hetero Diels-Alder process to include an oxodiene Diels-Alder variant. Critical to the success of this process was the identification of new substrates capable of forming NHC-enolates as unactivated enals tend to undergo dimerization reactions.
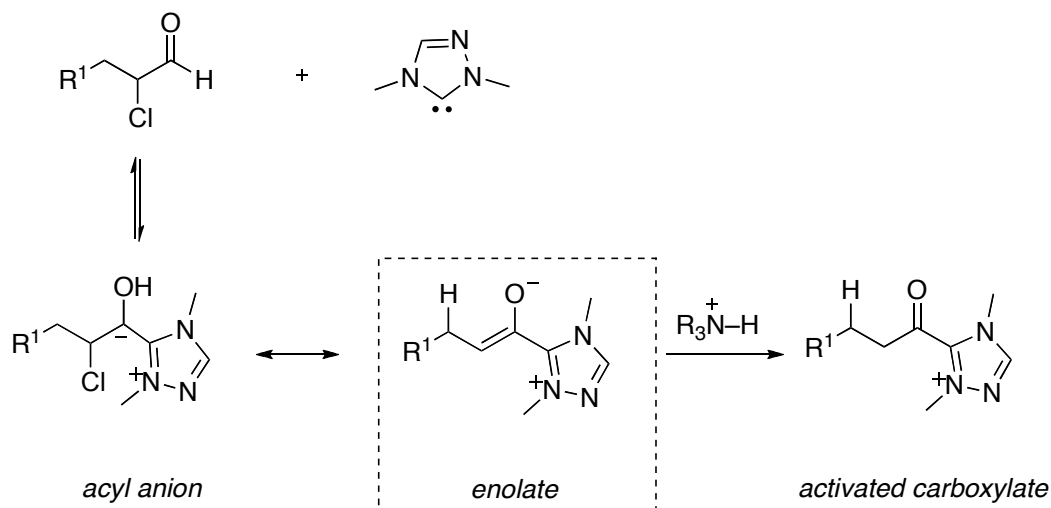
Figure 15. Recognition of the intermediate NHC-enolate *en route* to the activated carboxylate.

In 2005, Rovis et al. reported the enantioselective protonation of catalytically generated chiral enolates as an approach to the synthesis of *α*-chloroesters.[16] The chiral NHC-enolates were formed via a reaction between a chiral triazolium-derived NHC catalyst and *α,α*-dichloroaldehydes. In a previous report, *α*-chloroaldehydes were utilized to access activated carboxylates for NHC-promoted redox esterifications.[17] A proposed

intermediate in the catalytic pathway to the activated carboxylate is an NHC-enol or NHC-enolate (Figure 15). We surmised that racemic α-chloroaldehydes could serve as suitable substrates for the generation of chiral enolates foregoing the dimerization pitfalls previously encountered when enals were employed.
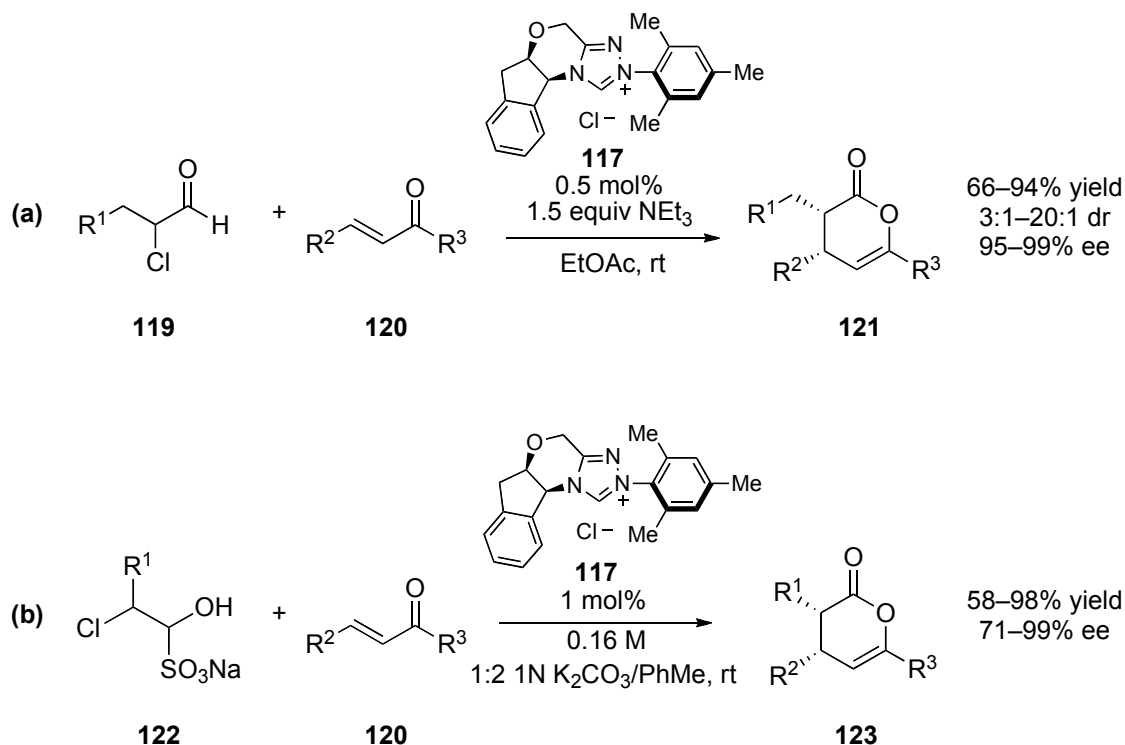
Scheme 36. Enantioselective 1-oxodiene hetero Diels-Alder reaction with low catalyst loading.

Using our recently synthesized chiral triazolium salt Dr. He from our group realized the highly enantioselective NHC-promoted 1-oxodiene Diels-Alder process between *α*-chloroaldehydes **119** and chalcones **120** to afford nonracemic 3,4,6-trisubstituted dihydropyran-2-ones (Scheme 36a).[18] Particularly noteworthy is that this highly enantioselective process proceeded in the presence of only 0.5 mol % of precatalyst **117**. Yet, the greatest detriment to this process was the need for the *α*-chloroaldehydes

as they had to be freshly prepared prior to use due to their sensitivity. To circumvent this issue, Dr. He subsequently reported the use of *α*-chloroaldehyde bisulfite salts **122** as bench stable precursors to *α*-chloroaldehydes for the enantioselective oxodiene Diels-Alder reaction (Scheme 36b).[19] Again the requirement of only 1 mol % of **117** to promote the oxodiene Diels-Alder reaction in excellent yield and superb diastereo- and enantioselectivity is a testament to the unprecedented efficiency and selectivity of our *N*-mesityl aminoindanol-derived precatalyst.

2.4.2 NHC-Promoted Benzoin-Oxy-Cope Reactions

In 2006, the Nair research group reported a highly diastereoselective annulation between catalytically generated homoenolate equivalents and chalcones promoted by imidazolium salt **44•Cl** to produce *trans*-1,3,4-trisubstituted triarylcyclopentenes as a single diastereomer (Scheme 37). The postulated mechanism is exemplified in Figure 16. The mechanism begins with a homoenolate-Michael addition by the Breslow intermediate onto the chalcone leading to an NHC-enol that subsequently undergoes keto-aldol addition. Finally, *β*-lactonization via nucleophilic displacement of the catalyst followed by decarboxylation turns over the catalytic cycle and affords the cyclopentene adduct.

R[1] = Aryl, Me   R[2] = Aryl, Me   55–88% yield
R[3] = Aryl
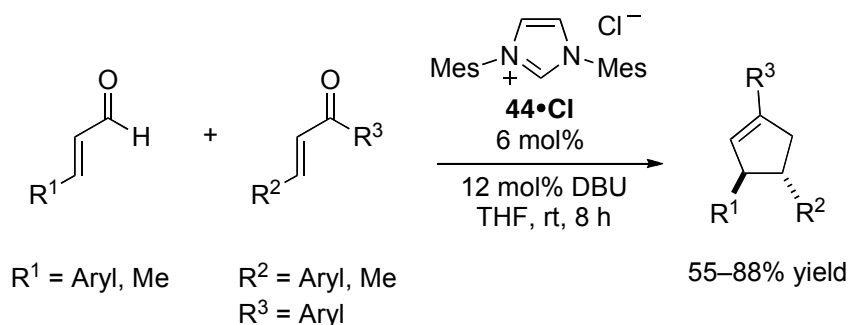
Scheme 37. Diastereoselective synthesis of *trans*-1,3,4-cyclopentenes reported by Nair.
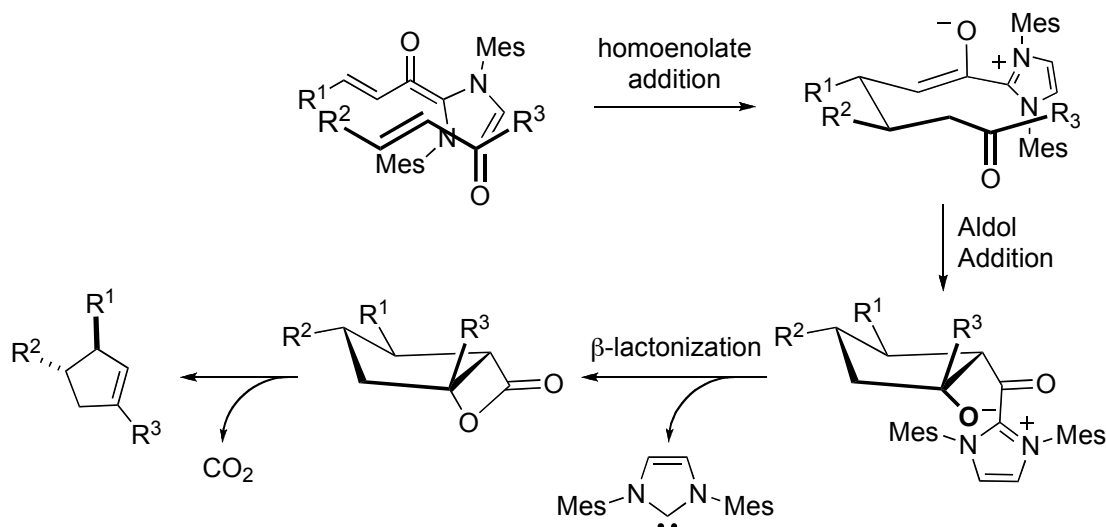
Figure 16. Mechanistic hypothesis for Nair's NHC-promoted cyclopentene reaction.

During the course of our investigations into the NHC-promoted Diels-Alder annula-

tions we observed an interesting by-product, a 1,3,4-cyclopentene similar to the products

reported by Nair. Recognizing that a catalytically generated homoenolate might be

involved in the formation of cyclopentenes via addition to chalcones, we surmised that

our chiral *N*-mesityl triazolium salt might allow us to render this process enantioselective.

Pei-Chen Chiang from our group found that under optimized conditions precatalyst **117**

was highly effective for the enantioselective construction of 1,3,4-cyclopentenes from

enals and electron-deficient chalcones (Scheme 38).[20] Contrary to Nair's findings, a

preference for the *cis*-diastereomer was observed in all cases examined. Further

investigation into the reaction mechanism implicated a benzoin–oxy-Cope process

instead of an initial homoenolate addition (Figure 17). We postulate that a keto-crossed-

benzoin addition of the Breslow intermediate to the chalcone sets a boat transition state

for an oxy-Cope rearrangement leading to an NHC-enolate intermediate similar to the

one reported by Nair. Congruent with Nair's proposal, intramolecular aldol addition

followed by *β*-lactonization and subsequent decarboxylation affords the *cis*-1,3,4-cyclopentene adduct.
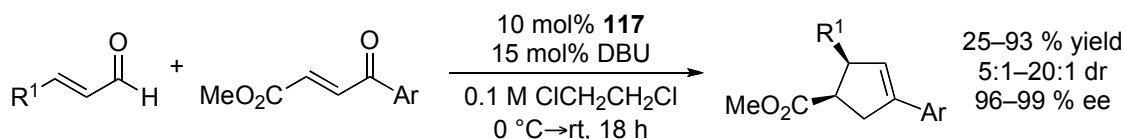
Scheme 38. Enantioselective cyclopentene annulation reported by Chiang and Bode.
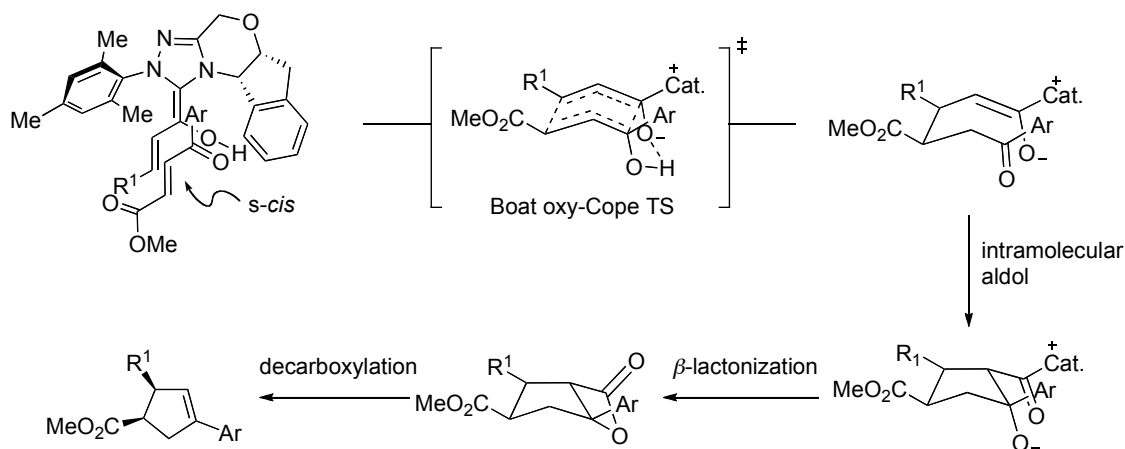
Figure 17. Mechanistic proposal for the triazolium-derived NHC-mediated annulation between enals and chalcones.

Armed with this mechanistic insight and the unprecedentedly reactive and selective precatalyst **117** Dr. Ming He was able to realize the enantioselective, NHC-catalyzed bicyclo-*β*-lactam formation via direct annulations of enals and unsaturated *N*-sulfonyl ketimines (Scheme 39).[21] Mechanistically speaking, we believe that this highly stereoselective annulation is analogous to the aforementioned benzoin–oxy-Cope formation of *cis*-1,3,4-cyclopentenes. A NHC-mediated aza-benzoin–oxy-Cope process and subsequent tautomerization leads to the chiral NHC-enolate. An intramolecular Mannich reaction followed by *β*-lactam formation affords the bicyclic-*β*-lactam adducts (Figure 18).
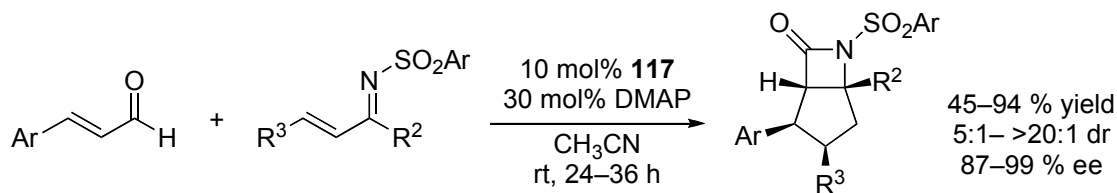
Scheme 39. Highly enantioselective, bicyclo-β-lactam formation via direct annulations of enals and unsaturated *N*-sulfonyl ketimines catalyzed by **117**.
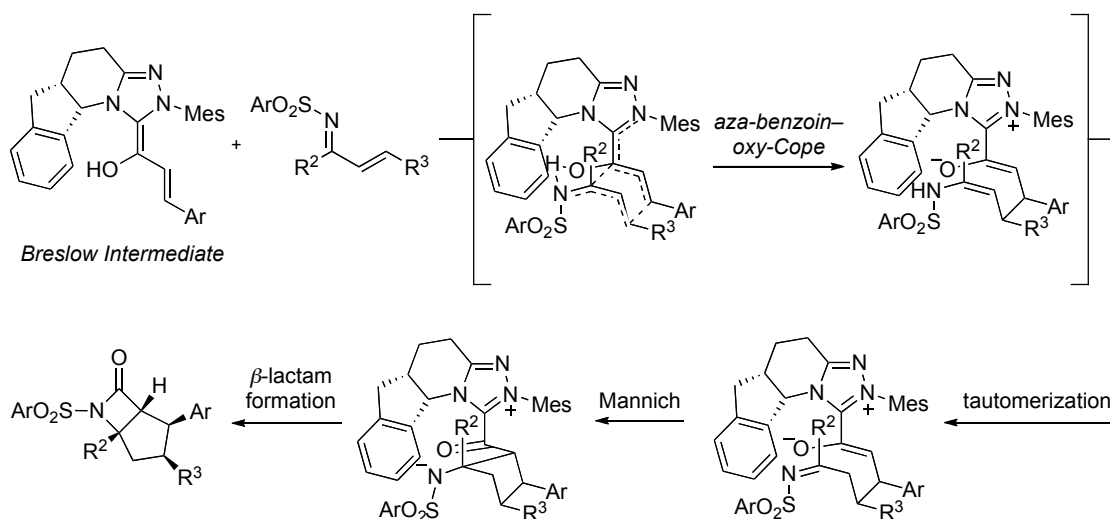
Figure 18. Mechanistic proposal for the triazolium-derived NHC-mediated annulation between enals and *N*-sulfonyl ketimines.

2.5 Development of a Modular Platform for the Synthesis of Chiral *N*-Mesityl Triazolium Salts

2.5.1 Identification of a Platform with a Suitable Functional Handle

We reported the first *N*-mesityl substituted triazolium salt (**63**) in 2005 for the redox esterification of enals,[11] which we have conveniently named RMesCl. Our protocol for the synthesis of *N*-mesityl substituted bicyclic triazolium salts is not limited to the production of RMesCl (**63**) or the aminoindanol-derived precatlyst **117**. Our group has

also found these protocols to be directly applicable to other classes of *N*-mesityl substituted triazolium NHC precatalysts (Figure 19). Pei-Chen Chiang from our group has demonstrated that this procedure was amenable to *N*-mesityl substituted triazolium salts based on bicyclic scaffolds of increasing ring size (**124–125**),[22] the chiral bicyclic scaffold derived from *α*-amino acids popularized by Rovis (**126–128**),[6, 22] and the achiral morpholinone precatalyst **129**. We have further utilized our synthetic process to prepare the chiral the morpholinone-derived bicyclic precatalysts (**130–131**) first reported by Scheidt and co-workers.[23, 24]
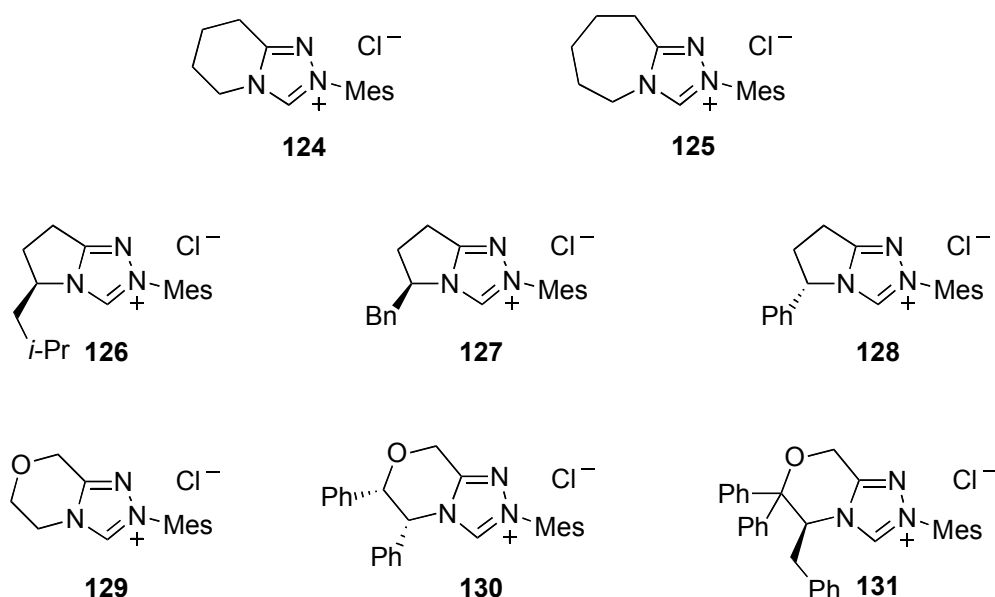
Figure 19. Examples of *N*-mesityl substituted triazolium salts prepared by our reported method.

Our anticipation that the synthesis of novel *N*-mesityl substituted triazolium NHCs by our method will facilitate the discovery of new NHC-promoted processes and offer the possibility to render such processes enantioselective have led us to investigate a combinatorial approach toward the rapid access of chiral triazolium salts. We decided that there were three prerequisites for this approach. First, both enantiomers of the catalyst must be easily accessible. Second was the need to identify a functional group

that can be easily manipulated into a variety of functional groups under mild conditions. Third, and possibly most critically, was that the functional group manipulation should occur after the triazolium ring system has been built. By doing so we would possibly avoid the most difficult synthetic step in the sequence, the final ring closure to the triazolium salt.

2.5.2 Synthesis of the Platform Based on an Azide Functional Handle

To execute this strategy we identified chiral azide **132** derived from (L)-pyroglutamic acid[25] as a viable precursor on which to build this platform (Figure 20). More specifically, we have already shown that chiral 2-pyrrolidinones serve as substrates for the synthesis of chiral bicyclic *N*-mesityl triazolium salts (vide supra). Furthermore, azides are precursors to a variety of transformations such as the [3+2] Hüisgen cycloaddition to form 1,2,3-triazoles and reduction to the amine which can act as a functional handle itself.

133   **132**   (L)-Pyroglutamic acid
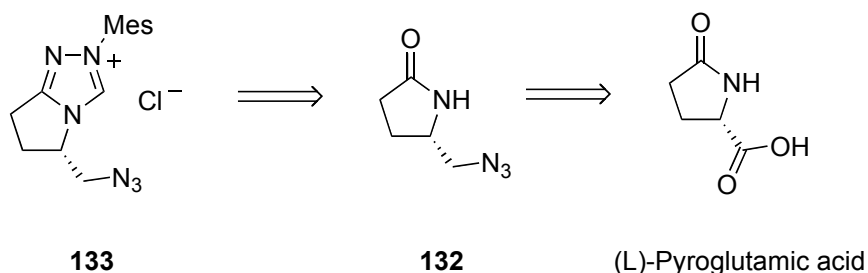
Figure 20. Retrosynthetic approach for the modular synthesis of chiral *N*-mesityl triazolium salts.

The synthesis of triazolium salt **133** was readily achieved in three steps from azide **132**. Meerwein methylation followed by condensation of the free iminoether with 2-mesitylhydrazinium hydrochloride (**108**) provided the crude amidrazone **134**.

Subsequent ring closure under our conditions optimized for the syntheses of *N*-mesityl triazolium salts provided the desired salt **133** in 32% overall yield (Scheme 40).
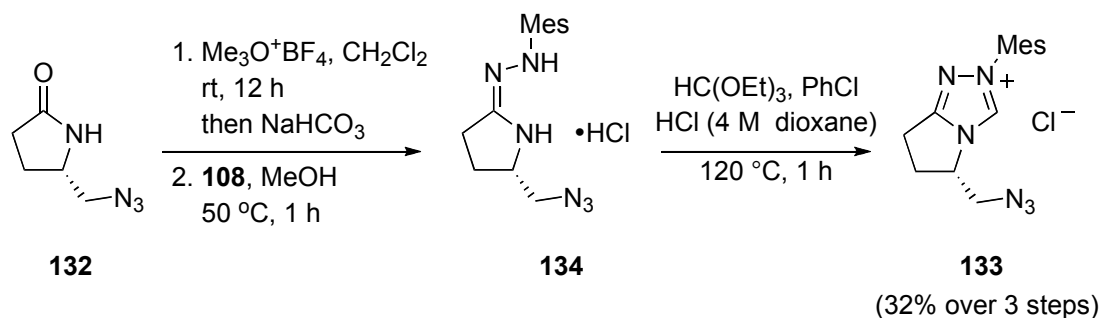
Scheme 40. Synthesis of triazolium salt **133** possessing an azide functional handle.

2.5.3 Derivatization of Triazolium Salt **133**

With our triazolium platform in hand, we explored some functional group transformations of the azide. We initially explored a Cu(I) promoted [3+2] Hüisgen cycloaddition to access 1,2,3-triazole-functionalized triazolium salts since this would open the possibility to attenuate rapidly the steric bulk of the chiral arm. Employing conditions similar to those reported by Sharpless,[26] cycloaddition between the azide of the triazolium salt **133** and phenyl acetylene (**135**) readily occurred to afford the desired triazole-functionalized triazolium salt **136** (Scheme 41). The modest isolated yield reflects the difficulty in isolation of the triazole salt.
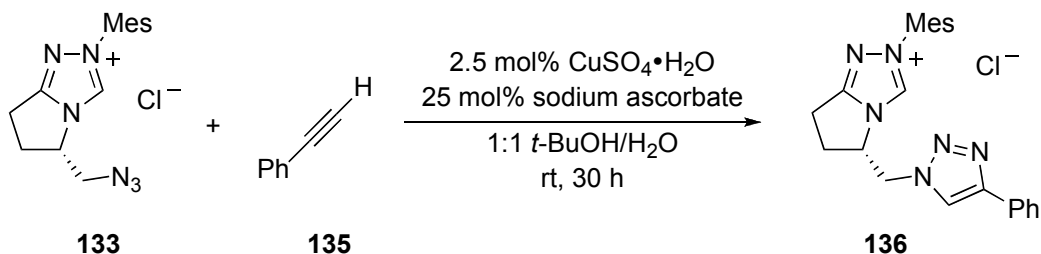
Scheme 41. [3+2] Hüisgen cycloaddition between azide **133** and phenylacetylene.

We next chose to reduce the azide to the primary amine as this had the potential to open up avenues for further derivatization. We were delighted to find that reduction with zinc metal under mild aqueous acidic conditions smoothly afforded the reduced triazolium salt in good yield after one hour (Scheme 42). Currently it is unclear as to whether the reduced product exists as the free amine triazolium salt **137a** or the free carbene **137b**. The latter is supported by ^{1}H NMR due to the absence of the C-2 proton in the region of 9.0–12 ppm and the presence of a singlet upfield with an integration of three protons. However, this result might reflect a deprotonation that occurs in solution.
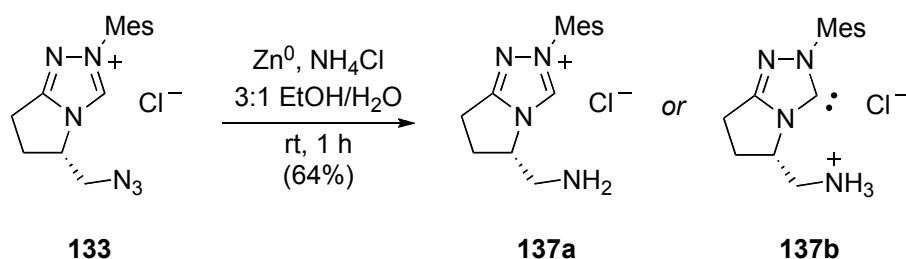
Scheme 42. Reduction of azide triazolium salt **133**.

With the amine-functionalized triazolium salt in hand, we surmised that this could provide access to a thiourea derivative. We chose two commercially available isothiocyanates with which to treat the amine. We were pleased to find that when triazolium salt **137** was treated with either isocyanate **138** or **139** in DMF at 40 °C overnight, considerable conversion to the thiourea adducts **140** and **141** was observed by ^{1}H NMR and LRES MS ESI[+] (Scheme 43). However, difficulty in purification precluded isolation of the pure thiourea derivatives. Interestingly, the reaction between triazolium **137** and the *p*-nitrophenyl isothiocyanate afforded a bis-adduct from the addition of both the amine and the carbene. This result lends credence to our previous observation that **137** may exist as a free carbene in solution. Although these studies are currently in their

infancy, we anticipate the syntheses of thiourea-functionalized triazolium salts in the near future.
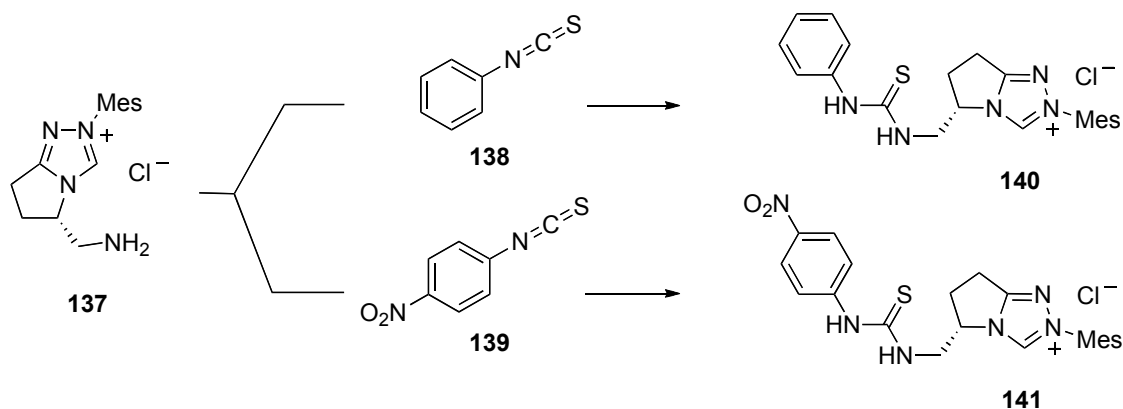
Scheme 43. Initial investigation into thiourea-functionalized chiral triazolium salts.

2.6 Conclusion

We have described the synthesis of the first *N*-mesityl substituted triazolium salt **63** (RMesCl) in 2005 for the redox esterification of enals. Since this initial report we have extended our method to the production of a chiral *N*-mesityl aminoindanol-derived triazolium salt **117** that has shown its unprecedented reactivity and selectivity in a variety of NHC-mediated redox processes including the first reported NHC-catalyzed Diels-Alder and benzoin–oxy-Cope reactions. The utility of our method has been exemplified by the syntheses of several novel *N*-mesityl bicyclic triazolium salts in our group. Furthermore, we have identified a modular platform for the combinatorial approach toward the production of a variety of chiral triazolium salts. Initial investigations show great potential to access a wide range of new chiral *N*-mesityl triazolium salts. We anticipate that our unique *N*-mesityl triazolium salts will allow the identification of new NHC-promoted processes and offer a possible solution toward rendering such processes enantioselective.

2.7 References

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Chapter 3: A Modular Synthesis of Chiral Aminoindanol-Derived Imidazolium Salts

3.1 Introduction

Over the past two decades N-heterocyclic carbenes (NHCs) have received increasing attention due to their storied role as ligands for transition metal complexes[1-7] and, more recently, their remarkable properties as catalysts in their own right.[8-12] As an increasing number of processes catalyzed by either NHCs or their transition metal complexes are reported, interest in developing highly enantioselective variants through the design and synthesis of chiral NHCs continues to grow.[13-15] To this end, important advances have been made by Grubbs,[16] Hoveyda,[17] Glorius,[13, 18] Montgomery,[19] and many others in the preparation and application of novel, chiral imidazolium-derived NHCs for catalytic applications (Figure 21).

142

143

144

144
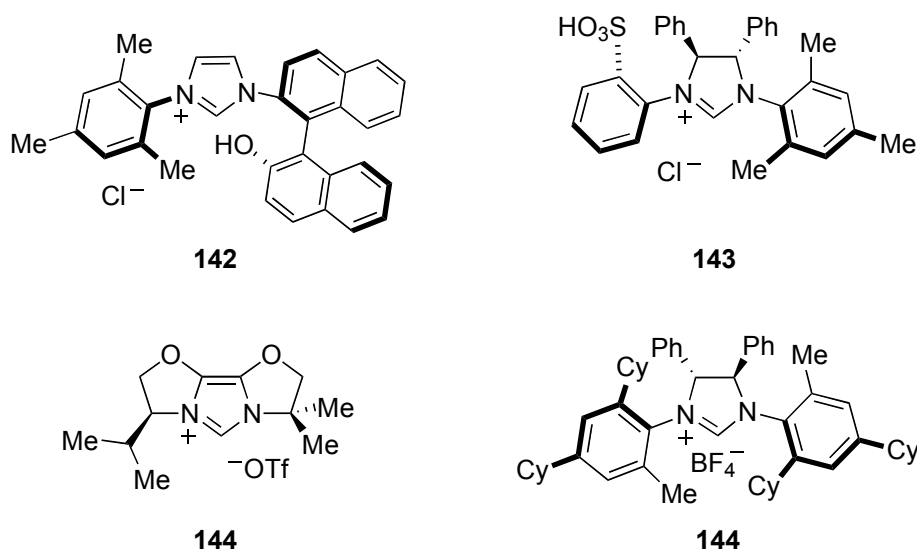
Figure 21. Selected examples of chiral imidazolium salts as NHC-precursors.

In our own studies, we have pioneered the development of novel NHC-catalyzed redox processes of α-functionalized aldehydes, resulting in conceptually new approaches to ester[20-22] and amide[23] formation and the development of a new generation of highly selective annulation reactions from simple starting materials.[24-31] We have documented that these novel NHC-catalyzed reactions appear to fall into two discrete categories: those catalyzed by *imidazolium*-derived NHCs and those promoted by *triazolium*-derived NHCs.[32] For example, our group[24] and that of Glorius,[33] have independently documented the *imidazolium*-derived NHC catalyzed generation of homoenolate equivalents from enals. These species undergo nucleophilic additions to aldehydes, activated ketones, imines, and enones to give stereochemically rich annulation products under exceptionally mild and simple reaction conditions (Figure 22).
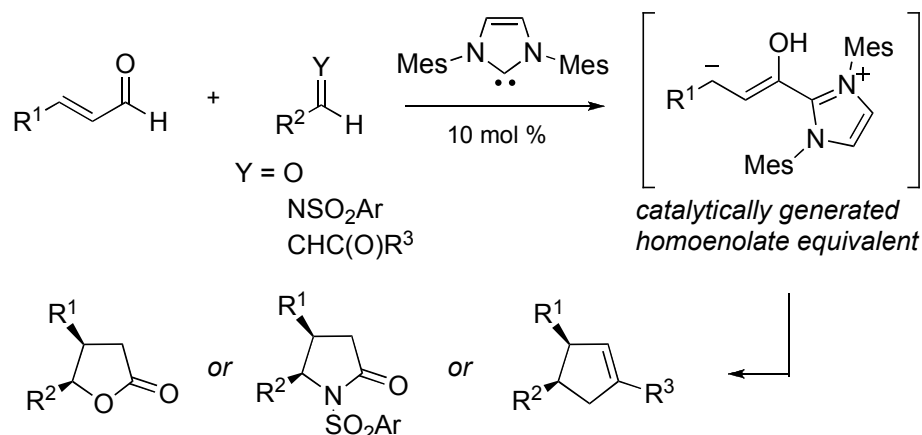
Figure 22. NHC-promoted annulations of catalytically generated homoenolates with various electrophiles.

The use of a simple organic molecule as a catalyst raises the promise of developing enantioselective variants of these annulations through the design and synthesis of chiral NHC catalysts. Indeed, chiral *triazolium*-derived NHCs have been employed as highly selective catalysts for benzoin and intramolecular Stetter

reactions.[34, 35] Our group has also reported a number of novel annulation processes that employ chiral *N*-mesityl substituted aminoindanol-derived *triazolium* precatalyst **117** for highly enantioselective annulations for inverse electron demand hetero-Diels-Alder reactions and benzoin–oxy-Cope reactions (Figure 23).[26-29, 31] In almost all cases, the NHC catalyst **117** affords the expected products in good yields and outstanding enantioselectivities.

117
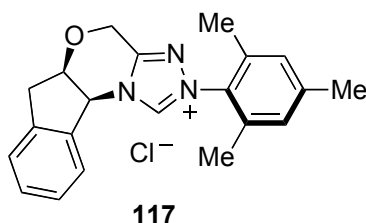
Figure 23. *N*-Mesityl substituted aminoindanol-derived triazolium NHC precatalyst.

In contrast, with the exception of a few instances,[30, 36] the use of **117** or other *triazolium*-derived NHCs uniformly fails to provide products arising from NHC-catalyzed generation of homoenolates. The lack of reactivity of the triazolium salts, coupled with the relative difficulty in preparing chiral imidazolium salts that promote homoenolate-based annulations of enals has stymied the development of enantioselective variants of these promising annulation reactions.

In seeking to address this, we have developed a practical synthesis of chiral imidazolium-derived NHC precatalysts built onto the chiral aminoindanol backbone that has proved so successful for enantioselective NHC-catalyzed reactions. In this chapter, we document these studies in detail, including the application of this synthetic route to diverse chiral *N*-substituted imidazolium salts and their preparation on a multi-gram scale.

3.2 Synthetic Routes Toward Imidazolium Salts

3.2.1 Most Commonly Employed Synthetic Preparations of Imidazolium Salts

The most easily accessible imidazolium salts are derived from imidazole. For *N,N'*-symmetrically substituted imidazolium salts with an unsaturated backbone (Scheme 44a), a single-pot procedure is employed whereby an appropriate amine is condensed with glyoxal (R^1 = H) or a 1,2-diketone in the presence of formaldehyde and a mineral acid. The *N,N'*-unsymmetrically substituted imidazolium salts (Scheme 44b) are readily prepared in analogous manner by first condensation of an amine and ammonium chloride with glyoxal (R^1 = H) or a 1,2-diketone in the presence of formaldehyde followed by alkylation of the intermediate imidazole. An orthoformate route allows the conversion of 1,2-diamines, obtainable from a Pd-catalyzed Buchwald coupling, directly to the imidazolium salt (Scheme 44c).[2, 37] This is the preferred route for the preparation of imidazolium salts with a saturated, often chiral, backbone. Furthermore, both *N,N'*-symmetrical and *N,N'*-unsymmetrical derivatives are accessible via this method.
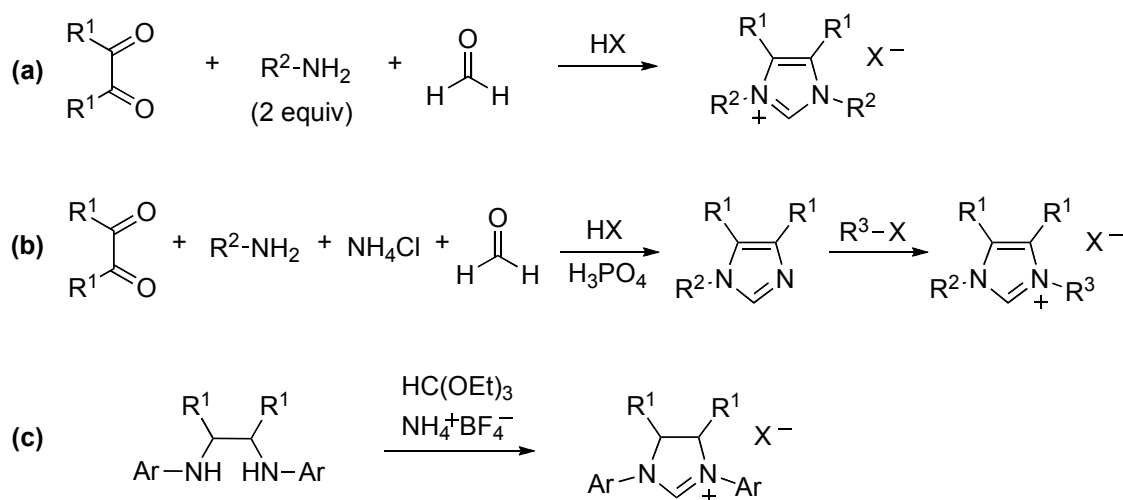
Scheme 44. Most common preparations of imidazolium salts.

3.2.1 Recent Progress in the Synthesis of Imidazolium Salts

Subsequent to our work, Glorius and co-workers have recently disclosed a modular one-pot synthesis of both symmetrical and unsymmetrical imidazolium salts (Scheme 45).[38] This procedure is an improvement of Fürstner's recent report (vide infra). In the key step, formamidines and α-halo ketones are coupled to afford imidazolinium intermediates that are readily dehydrated to yield to corresponding imidazolium salt.

X = Cl, Br
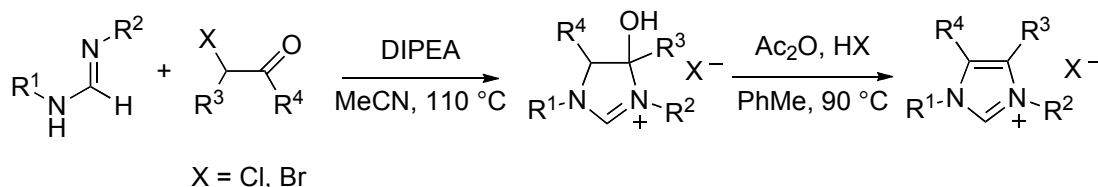
Scheme 45. Glorius' modular synthesis of imidazolium salts.

A postliminary report from Gilbertson and Prasad has addressed the synthesis of imidazolium salts with an unsaturated backbone. Their synthesis featured a one-pot process from *N*-(2-iodoethyl)arylamine salts and primary amines (Scheme 46). The authors note the ready, gram-scale accessibility of the *N*-(2-iodoethyl)arylamine salts from commercially available 2-iodoethanol. Nucleophilic coupling of the salt and amine leads to the 1,2-diamine which can be closed under standard conditions, triethyl ortho-formate and formic acid, to provide the desired imidazolium salt. This procedure complements previous strategies that require the 1,2-diamine production via a bisimine reduction, exhaustive bisamide reduction or Pd-catalyzed couplings. In this manner nearly thirty imidazolium salts (symmetrical, unsymmetrical, and chiral) were prepared.
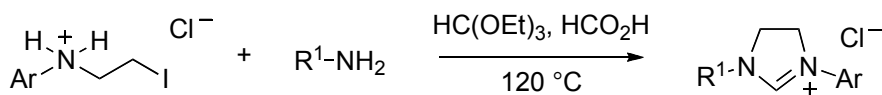
Scheme 46. Gilberston's synthesis of saturated imidazolium salts.

3.3 Synthesis of a *N*-Mesityl Substituted Aminoindanol-Derived Imidazolium Salt

3.3.1 Retrosynthetic Analysis

The intense interest in the development and understanding of N-heterocyclic carbenes and their complexes have led to a number of notable advances in their preparation.[37, 39, 40] Unfortunately, in our hands we were generally unable to extend these routes to the preparation of our desired, chiral bicyclic imidazolium salts. During the course of these efforts, Fürstner[41] reported a new synthetic entry into unsymmetrically *N,N'*-disubstituted imidazolium salts based on a heterocyclic interconversion strategy (Scheme 47). This elegant procedure hinges on a three-step, one-pot protocol to prepare diverse imidazolium salts from *N*-formyl amino ketones or aldehydes. We reasoned that chiral aminoindanol-derived imidazolium salts such as **145** could be similarly accessed from intermediates **146** and **147**, a retrosynthetic analysis that considerably simplifies access to this highly desired class of NHC-precursors. We further postulated that the diastereomeric formyl ketones **146** and **147** could be derived from diastereomeric epoxides **148** and **149** by intramolecular cyclization and oxidation. In turn, **148** and **149** would be obtained from readily available chiral aminoindanol **104** by *N*-formylation, alkylation, and epoxidation (Scheme 48).

R^3 = H, alkyl
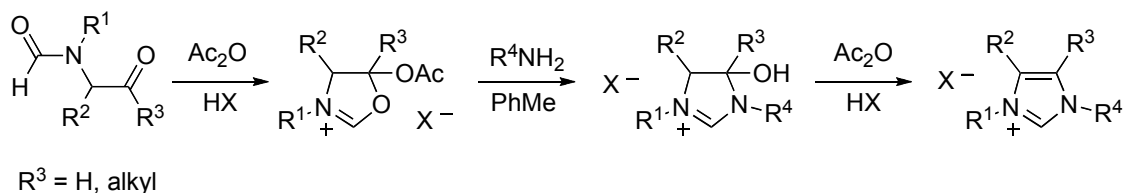
Scheme 47. Fürstner's synthetic route to unsymmetrically substituted imidazolium salts.
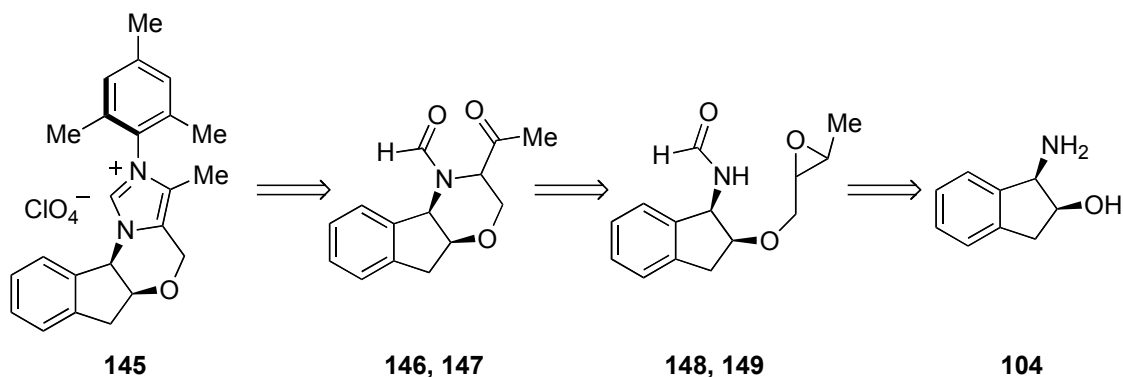
Scheme 48. Retrosynthetic approach toward the synthesis of a *N*-mesityl aminoindanol-dervied imidazolium salt.

3.3.2 Alkylation Strategy

We began our studies with a literature procedure for the *N*-formylation of (1*R*, 2*S*)-(+)-1-amino-2-indanol, **104**.[42] We initially surmised that the *N*-fomylated amide **150** would be reluctant to undergo alkylation, making possible selective *O*-alkylation in the subsequent step. This *O*-alkylation, however, proved to be difficult, and yields greater than 40% were never consistently achieved even after several attempts to optimize the reaction parameters. In many cases, competing *N*-alkylation of the formamide reduced the isolated yields of the desired product. In contrast, excellent overall yields of the desired *N*-formyl, *O*-crotylated product **151** were achieved simply by switching the order of the steps and performing the *O*-alkylation directly on unprotected aminoindanol (Scheme 49).
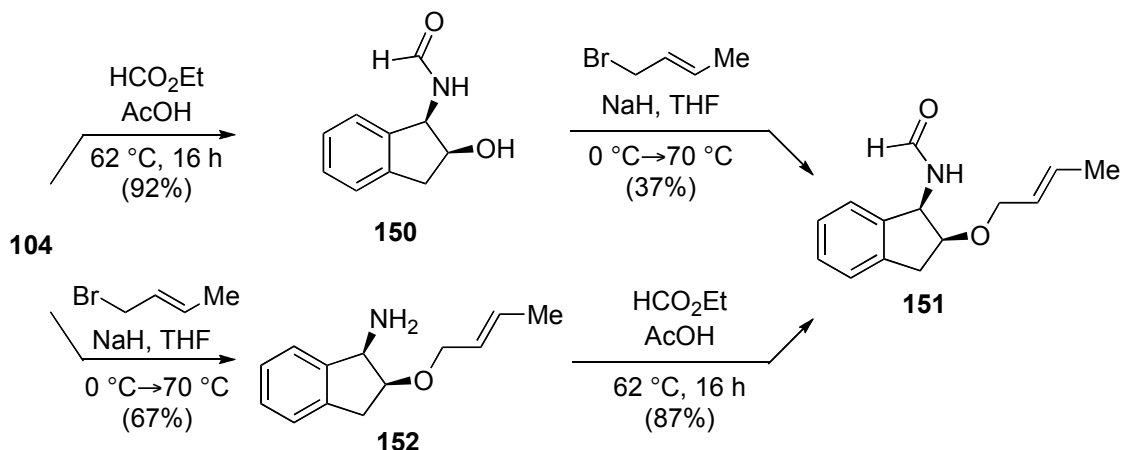
Scheme 49. Chemoselective alkylation and formylation of 1,2-aminoindanol.

3.3.3 Epoxidation and Cyclization

With **151** in hand we were pleased to find that epoxidation occurred readily under a variety of straightforward conditions. Treatment of the alkene with excess *m*CPBA (~3 equivalents) in CH_2Cl_2 overnight provided **148** and **149** in nearly quantitative yield, as a 1:1 mixture of diastereomers. The only drawback to this method was purification of the epoxide, which required the removal of excess peracid and the acid byproduct, and led to the formation of colored impurities that proved difficult to remove upon scale-up. We therefore turned to epoxidation via the *in situ* generation of dimethyldioxirane (DMDO).[43] This epoxidation was clean and scalable, but afforded slightly lower conversions than *m*CPBA. Nevertheless, this approach proved to be the method of choice for preparative scale synthesis of diastereomeric mixture of the epoxides **148** and **149** (Scheme 50)

Early attempts to induce a 6-*exo*-tet ring closure onto the epoxide under basic conditions (NaH or KHMDS) were stymied by low yields and decomposition. A single precedent for this ring closure employed 10 equivalents of NaH in DMF.[44] Indeed, ring closure ensued under these conditions, but yields were only moderate (~50%) and

purification and characterization of **152** and **153** proved difficult due to the resultant mixture of diastereomers and amide rotamers.
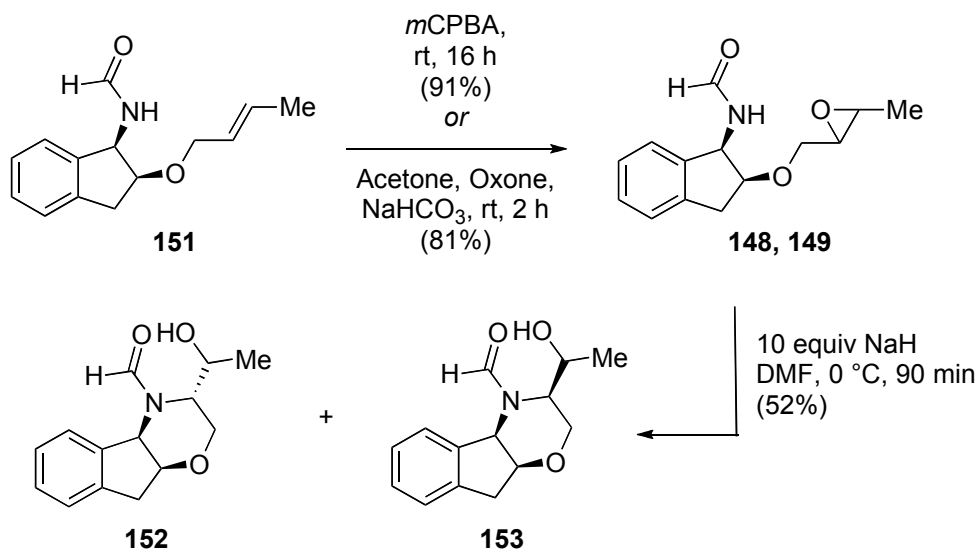
Scheme 50. Epoxidation and intramolecular epoxide opening.

We sought to improve the overall yield of the cyclization through the stereo-selective synthesis of a single epoxide diastereomer via a Shi epoxidation (Scheme 51).[45] Since the D-fructose derived Shi catalyst was more readily prepared than its enantiomer, we explored this hypothesis by using the two enantiomers of aminoindanol -derived formyl olefins, **151** and **ent-151**, and a single enantiomer of the Shi catalyst **154**. When formyl olefin **151**, derived from (1*R*, 2*S*)-(+)-*cis*-1-amino-2-indanol, **104**, was employed, the epoxidation was quite efficient (~90% yield) but the diastereoselectivity was only moderate (5:1). However, a single diastereomer of the epoxide **148** was obtained after one recrystallization from hexanes/EtOAc. In evaluating the modest yield and product mixture of the cyclization, we were cognizant of the fact that the two diastereomeric epoxides **148** and **149** could potentially undergo ring formation at different rates, possibly leading to complications or by-products.

When the other formyl olefin, *ent*-**151**, derived from the opposite enantiomer of aminoindanol was used as the starting material, the epoxidation also proceeded cleanly to afford *ent*-**149** as a 5:1 mixture of diastereomers, and again a single diastereomer could be obtained after one recrystallization from hexanes/EtOAc. This diastereomer also cyclized cleanly in the presence of sodium hydride to afford **156** in 76% yield. Although yields of the morpholine products were consistently higher when pure diastereomers were employed in the ring-closing step, there does not appear to be a significant rate difference in the cyclization of the two diastereomeric epoxides. Despite the different stereochemistry, both diastereomers proved amenable to the subsequent steps and gave the identical imidazolium salts as the final product. These observations, coupled with other findings on the conversion of ketones **146** and **147** to the final product ,led to our decision to stay with the lower yielding, but operationally simpler, achiral epoxidation and ring closure shown in Scheme 50 for further studies.
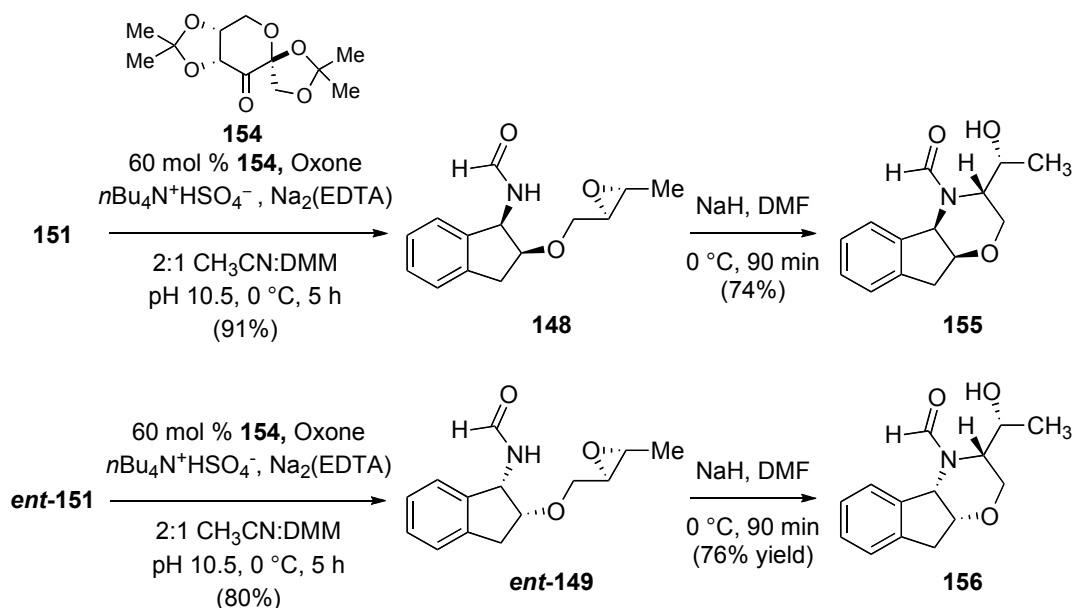
Scheme 51. Stereoselective synthesis of morpholines **155** and **156** by Shi epoxidation.

3.3.4 Oxidation

An early route to the chiral imidazolium salts began with allylation, rather than crotylation of aminoindanol **104**. While epoxidation and cyclization proceeded cleanly, we encountered serious difficulties in obtaining the *N*-formyl aldehyde via oxidation of cyclization product **157**. Oxidation of the primary alcohol using standard protocols (TEMPO, TPAP, IBX, SO$_3$·pyridine, DMP) yielded little or none of the desired aldehyde but rather numerous byproducts and returned starting material, with the major side product identified as over-oxidized morpholinone **158** (Scheme 52).
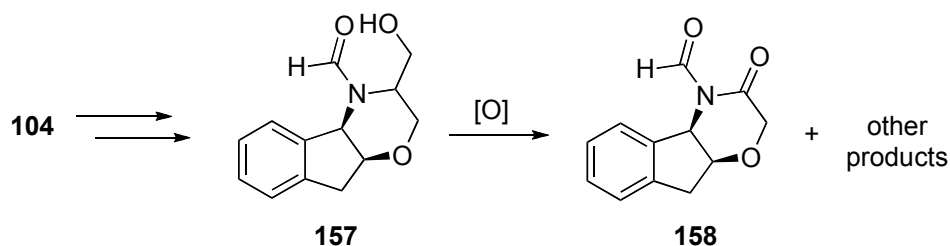
Scheme 52. Unexpected oxidative cleavage of *N*-formyl amino alcohol **157**.

To circumvent this unexpected difficulty, we elected to introduce the crotyl group during alkylation, which would subsequently lead to a secondary alcohol poised for oxidation to the ketone. We were pleased to find that Dess-Martin periodinane (DMP) gave smooth conversion to the ketone in high yield. Further studies, particularly for larger scale preparation of ketones **146** and **147**, also identified Swern oxidation conditions that also afforded the ketone in good yield on a 10-gram scale. Under the Swern conditions, we found the *N*-formyl ketones to be sensitive toward epimerization, affording **146** as the major diastereomer (Scheme 53).
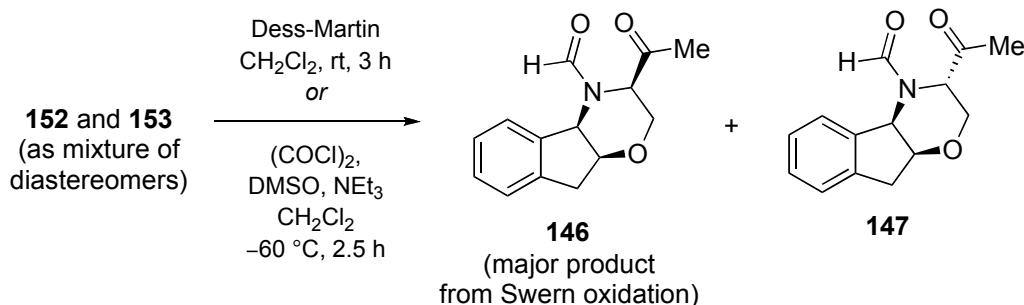
Scheme 53. Oxidation of secondary alcohols **152** and **153**.

3.3.5 Oxazolinium Formation and Conversion to N-Substituted Imidazolium Salts

Ketone intermediates **146** and **147** are the key precursors to Fürstner's heterocyclic interconversion strategy for the synthesis of imidazolium salts from an oxazolinium intermediate. Although Fürstner had demonstrated a remarkably diverse range of compounds prepared with this strategy, he reported no examples of the use of sterically hindered anilines with ketone-derived amino carbonyls.[41] Initial attempts to form the oxazolinium salt **159** by treatment of the *N*-formyl ketones with Ac$_2$O and aqueous or anhydrous acids HCl and HBF$_4$ proved unsuccessful. Reactions performed at low temperature returned only starting material; upon heating, deprotection of the *N*-formyl group was observed. When HClO$_4$ was employed, a trace amount of product was observed by mass spectrometric analysis of the crude reaction mixture. From this initial hint, we quickly discerned that the oxazolinium adduct was heat sensitive. Thus, treatment of the formyl ketone with HClO$_4$ in Ac$_2$O was carried out at 0 °C to prevent deformylation. Furthermore, the oxazolinium salt could not be handled or stored for an extended period of time. Once triturated from the reaction mixture, residual solvent was removed *in vacuo* at room temperature since even a gentle warming of the solution upon rotary evaporation bath caused decomposition. We further found that analytically cleaner reactions occurred when diastereomers **146** and **147** were taken on separately through

the modified Fürstner protocol, although the identical final product and similar yields were obtained in each case. These important modifications led to a robust and reliable procedure for the preparation of **145**, which served as the key starting material for a modular synthesis of diverse *N*-substituted NHCs (Scheme 54).
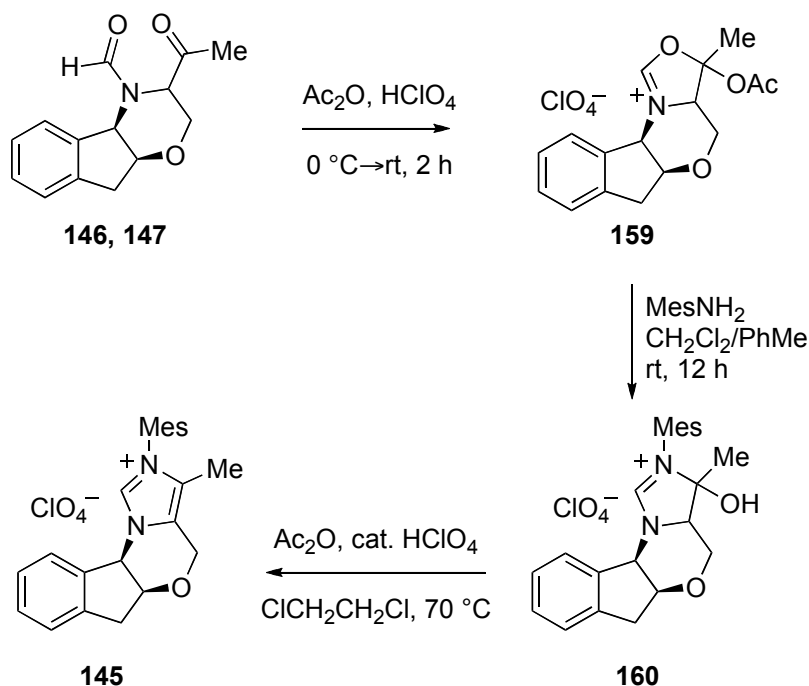
Scheme 54. Heterocyclic interconversion and elimination for the synthesis of imidazolium salts.

Acetal **159** was allowed to react with a variety of amines giving rise to the aminal intermediate **160** (*e.g.*, with 2,4,6-trimethylanilne) as a set of diastereomers. Although in several cases the aminal could be isolated, purification was difficult and most of the aminal intermediates were used directly for the elimination step without purification. Furthermore, the diastereomers could not be separated, but this was without consequence as the offending stereogenic center was destroyed upon acid elimination to give the imidazolium salt. We also improved upon Fürstner's heterogeneous protocol, which used toluene as the solvent, for a homogeneous one with CH₂Cl₂/toluene that often allowed a cleaner rearrangement to the aminal intermediate.

The acid catalyzed acylation/elimination strategy originally outlined by Fürstner typically led to decomposition and only trace amounts of the desired imidazolium salt in our hands. We found that by dramatically reducing the equivalents of Ac_2O a cleaner reaction occurred, a finding mirrored by Fürstner in a recent application of this method.[46] Still, in several cases, purification of the imidazolium salt was hindered by an intractable oil formed in the reaction. During the optimization of the reaction for large-scale production of **145**, we discovered that changing from a heterogeneous protocol (toluene) to a homogeneous one (1,2-dichloroethane) provided cleaner elimination, allowing for easier purification of the imidazolium salt. Furthermore, under these conditions the reaction could be readily monitored by ^{1}H NMR of an aliquot from the reaction.

These conditions proved (*vide infra)* reliable for a broad range of amines, allowing access to a diverse set of *N*-substituted imidazolium salts that can be used as precursors to N-heterocyclic carbene ligands and catalysts.

3.3.6 Preparative Scale Production of N-Mesityl Imidazolium Salt 145

Given our success of utilizing the *N*-mesityl substituted, aminoindanol-derived triazolium salt **117** for highly enantioselective annulation reactions, we were particularly interested in undertaking a systematic survey of the differences between the imidazolium and triazolium salts of otherwise identical structure. In anticipation of these studies, we applied our optimized route to the synthesis of the aminoindanol derived NHC-precursors to a preparative scale synthesis of **145**. Beginning with (1*R*, 2*S*)-(+)-*cis*-1-amino-2-indanol, each step up to the oxazolinium intermediate can be performed on >8 gram scale. The final three-step sequence was performed on a 5 g scale to produce ~4.5 g of **145** in 51% yield from the formyl ketone intermediates **146** and **147** (Scheme

55). The structure of this compound was confirmed by single crystal X-ray diffraction (Figure 24).
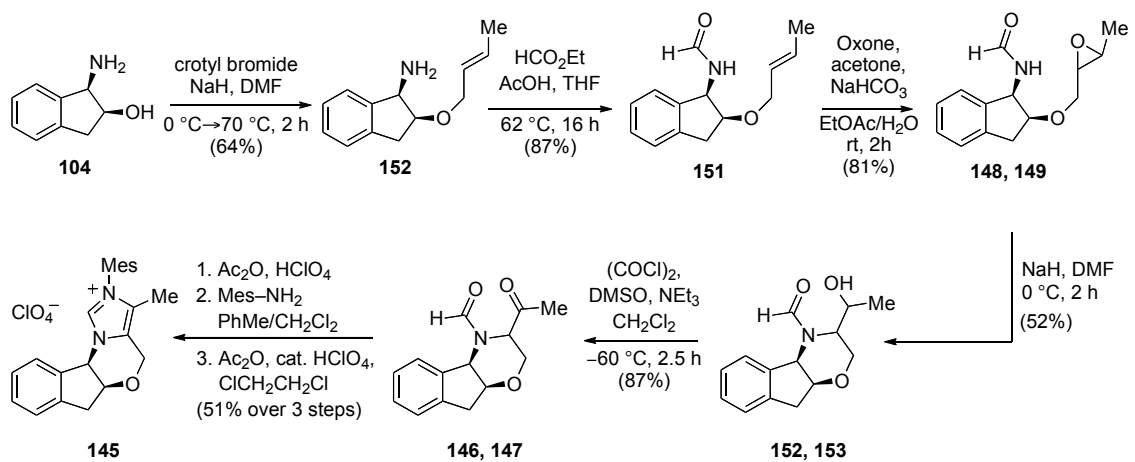
Scheme 55. Preparative scale synthesis of *N*-mesityl substituted imidazolium salt **145**.
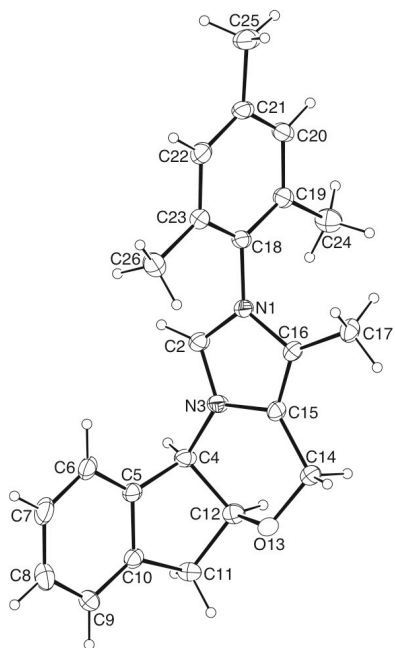
Figure 24. ORTEP plot of *N*-mesityl substituted imidazolium salt **145**. Anion omitted for clarity.

Table 3. *N*-Substituted chiral aminoindanol-derived imidazolium salts prepared from common acetal intermediate **159**.

159

RNH₂, PhMe
or
RNH₂, PhMe/CH₂Cl₂
rt, 3–16 h

Ac₂O, cat. HClO₄
PhMe or ClCH₂CH₂Cl
70–80 °C, 0.25–20 h

145, 161–173

145, 78% yield

161, 51% yield

162, 70% yield

163, 61% yield

164, 35% yield

165, 48% yield

166, 35% yield

167, 75% yield

168, 63% yield

169, 53% yield

170, 50% yield

171, 20% yield

172, 22% yield

173, 69% yield
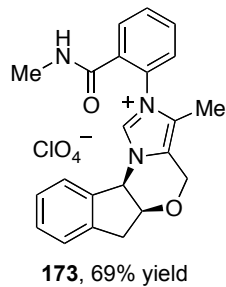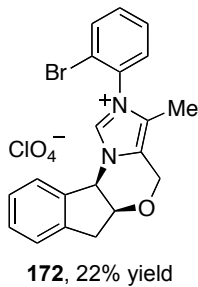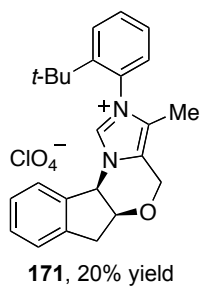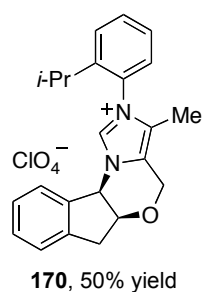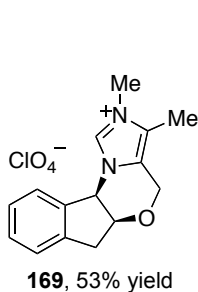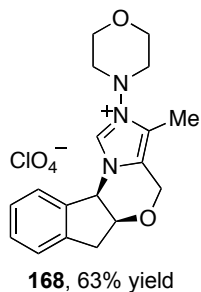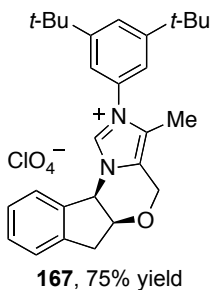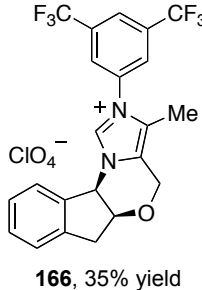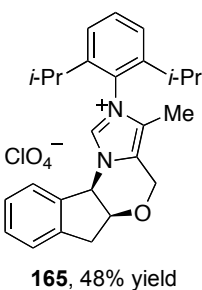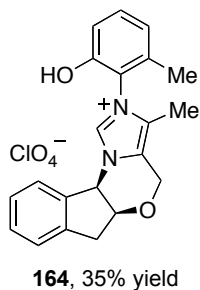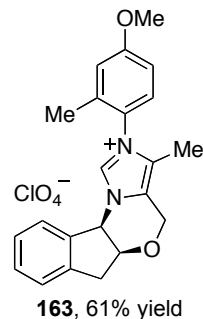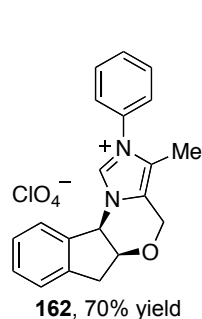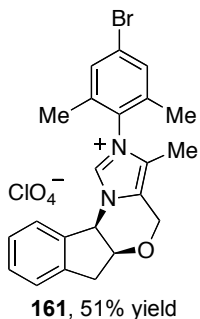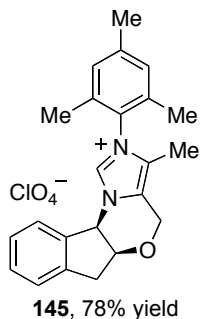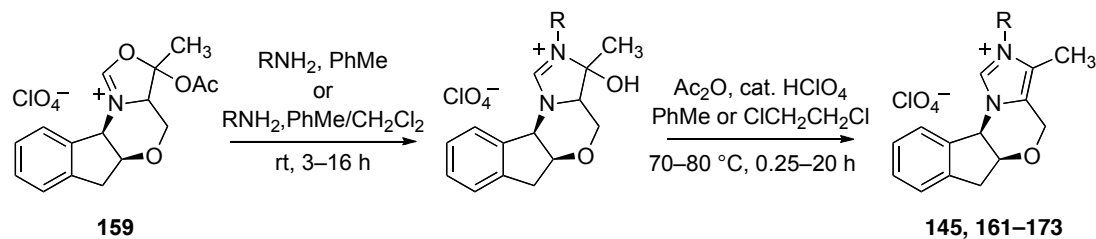
3.4 Synthesis of Other *N*-Substituted Chiral Imidazolium Salts

An important consideration in any catalyst or ligand design strategy is the ability to rapidly access structural derivatives that may enhance reactivity or selectivity in a catalytic reaction. A major attraction of the Fürstner method, and our implementation of it to prepare chiral amino alcohol-derived imidazolium salts, is the ability to introduce a wide range of *N*-substituents at the final stage of the synthesis simply by choice of the appropriate amine.

In preliminary studies, we have confirmed that this modular approach to chiral imidazolium salts is indeed viable and provides access to diverse *N*-substituents (Table 3). Indeed both hindered and unhindered anilines work well in the reaction, making possible the preparation of **145**, **161–167**, and 1**70–173**. Unprotected functional groups including phenols and amides do not significantly suppress the heterocyclic interconversion. Alkylamines are also excellent reaction partners, allowing, for example, the synthesis of *N*-Me substituted imidazolium **169**. Even hydrazines are viable, providing access to *N*-morpholino imidazolium **168**.

3.5 Conclusion

In summary, we have developed a modular, scaleable route to the preparation of chiral aminoindanol-derived imidazolium salts, which will find use as precursors to N-heterocyclic carbene catalysts and ligands. Our eight-step route takes advantage of a chemoselective alkylation, intramolecular epoxide-opening, and a modification of the Fürstner imidazolium synthesis to achieve a robust, scaleable method for the preparation of *N*-aryl, *N*-alkyl, and *N*-amino imidazolium salts. We have recently established that precatalysts such as **145** can serve as catalysts for enantioselective

NHC-catalyzed homoenolate additions of enals to aldehydes, imines, and enones (Chapter 4). We anticipate that the facile access to diverse and complex imidazolium salts will facilitate our own ongoing studies aimed at improving the reactivity and selectivity of these novel annulation reactions. Furthermore, our studies provide one of the first practical routes to chiral, bicyclic imidazolium salts that may find use as novel ligands for transition metal-mediated reactions and NHC-catalyzed transformations.

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Chapter 4:   Observed Differences in the Reactivity of Triazolium and Imidazolium NHC-Precatalysts of Nearly Identical Structure

4.1   Introduction

N-Heterocyclic carbenes derived from azolium salts are remarkable and versatile catalysts for a wide range of organic transformations.[1-5] The classical benzoin and Stetter reactions of simple aldehydes are catalyzed by thiazolium and triazolium-derived carbenes.[6-8] More recently, an extensive array of new processes operating via reactive intermediates catalytically generated by internal redox reactions of α-functionalized aldehydes have been discovered.[3, 9, 10] Successful developments from our laboratory
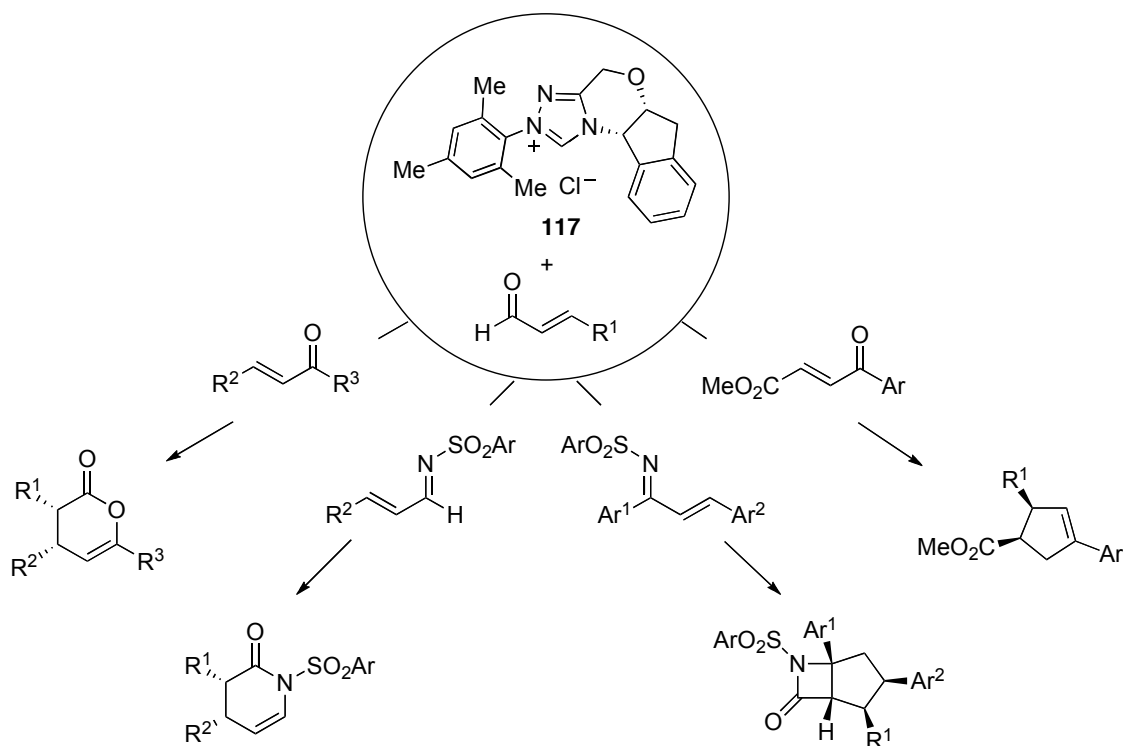
Figure 25. Selected stereoselective annulations promoted by NHC-precatlyst **117** recently reported by our group.

include enantioselective triazolium-catalyzed annulations affording *cis*-disubstituted dihydropyranones[11, 12] and dihydropyridinones,[13] cyclopentenes,[14] and bicyclic *β*-lactams,[15] all with exceptional levels of diastereo- and enantioselectivity employing our *N*-mesityl aminoindanol derived triazolium catalyst (Figure 25). We and Glorius have also documented diastereoselective annulations of enals and aldehydes to afford *γ*-butyrolactones using imidazolium catalysts;[16-18] and our group has also disclosed the diastereoselective annulations of enals and *N*-sulfonyl aldimines to afford *γ*-lactams.[19]

The starting materials for many of these annulation processes are similar or identical, but the reaction outcomes differ dramatically by the choice of imidazolium vs triazolium NHC precatalysts. These disparate results have led to considerable confusion over the difference between the imidazolium and triazolilum precatalysts. Direct comparisons between the reactivity and mechanistic pathways of these two classes have been precluded by the use of structurally different catalyst classes in each case. We sought to explore systematically whether an inherent reactivity difference existed between a NHC catalyst derived from imidazolium or triazolium salts of nearly identical structure.

ent-117   145
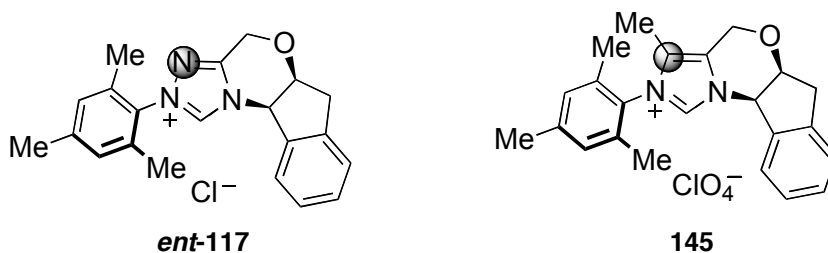
Figure 26. *N*-Mesityl aminoindanol-derived triazolium salt *ent*-**117** and imidazolium salt **145** of nearly identical stucture.

To address these important issues we designed and synthesized the chiral imidazolium salt **145** (see Chapter 3), which corresponds to the *N*-mesityl aminoindanol-derived triazolium salt *ent*-**117** that has served as the most reactive and selective

precatalyst in numerous annulation processes. The successful synthesis of **145** allowed us for the first time to directly compare these two catalyst classes, which differ only by a single atom distal from the reactive center. The distinct reactivity profiles of these two catalyst classes provided valuable insight into the mechanistic differences and the challenges associated with developing enantioselective variants.
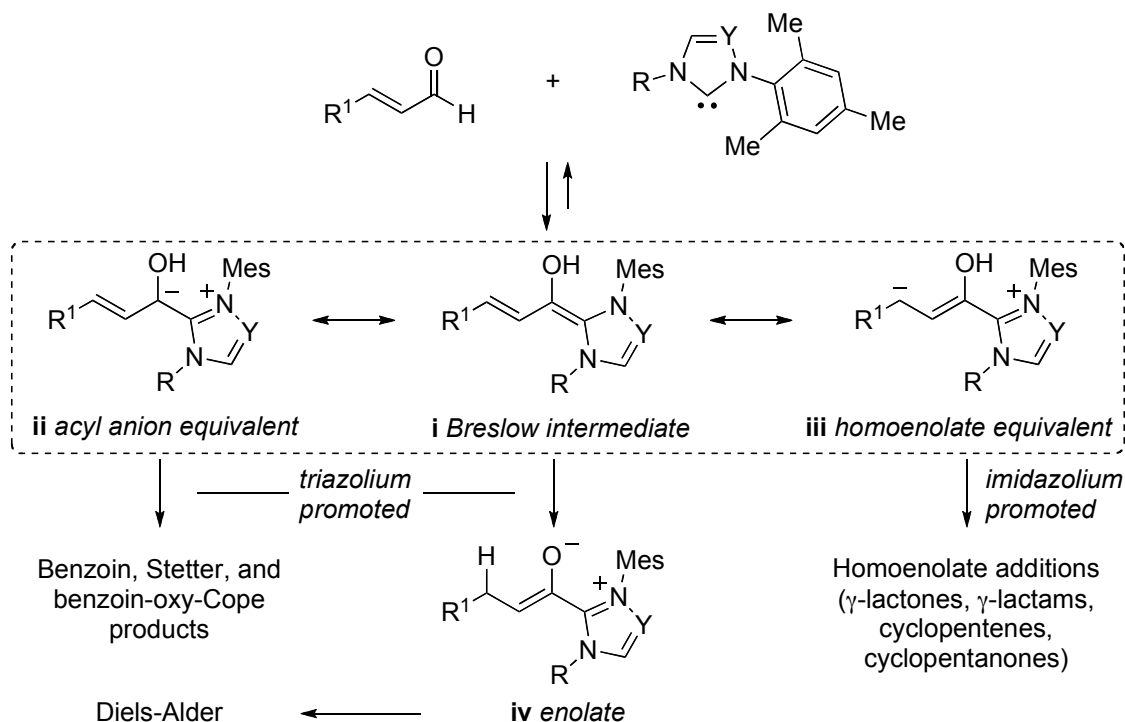
Scheme 56. Reactive intermediates catalytically generated by NHC-promoted redox reactions of α,β-unsaturated aldehydes.

The basis of the novel annulation reactions of α,β-unsaturated aldehydes and electrophiles is the catalytic generation of unique reactive intermediates by internal redox reactions promoted by the association of an *N*-heterocyclic carbene and the enal (Scheme 56). Depending on the structure of the catalyst and the facility of proton-transfer events, the initially formed Breslow intermediate **i** can ultimately serve as acyl anion equivalent **ii**, homoenolate equivalent **iii**, or enolate **iv**. In the latter two cases, the aldehyde is simultaneously oxidized to the carboxylic acid oxidation state. We have

97

observed that the fate of the Breslow intermediate under identical reaction parameters is intimately controlled not by the steric demands of the catalyst but rather by the choice of imidazolium vs triazolium-derived NHCs.

At the outset of our studies, we sought to address two recurring issues in our development of novel, NHC-catalyzed reactions. First, numerous annulation processes were promoted exclusively by one catalyst type (imidazolium or triazolium) but not the other. Even in the few instances where a given transformation is promoted by either catalyst class, such as cyclopentene-forming annulations, we and Nair have demonstrated that different mechanisms may be operating.[14, 20] Second, although highly enantioselective *triazolium*-catalyzed processes have been achieved for diverse reaction types, no examples of highly selective *imidazolium*-catalyzed processes have been documented.

4.2 NHC-Promoted Redox Reactions Preferentially Promoted by Triazolium Salt *ent*-117•ClO₄

With chiral imidazolium precatalyst **145** in hand, we undertook a systematic comparison of *imidazolium* vs *triazolium* precatalysts in reactions known to be catalyzed by *N*-heterocyclic carbenes. Our previous studies employed triazolium salt ***ent*-117** as the precatalyst, but our corresponding imidazolium salt was most easily prepared and handled as the perchlorate salt. To avoid any concern over counterion effects, we prepared and employed the perchlorate variant triazolium ***ent*-117•ClO₄** for comparison by simple anion exchange with $LiClO_4$. All the reactions surveyed were run under identical conditions according to known published procedures with no attempts to optimize conversion or selectivity.

(a) Aza-diene Diels-Alder reaction

With *imidazolium* **145** as catalyst:	no reaction
With *triazolium* **ent-117•ClO₄** as catalyst:	76% yield, >50:1 dr, >99% ee

(b) Oxo-diene Diels-Alder reaction

With *imidazolium* **145** as catalyst:	no reaction
With *triazolium* **ent-117•ClO₄** as catalyst:	95% yield, >20:1 dr, >99% ee
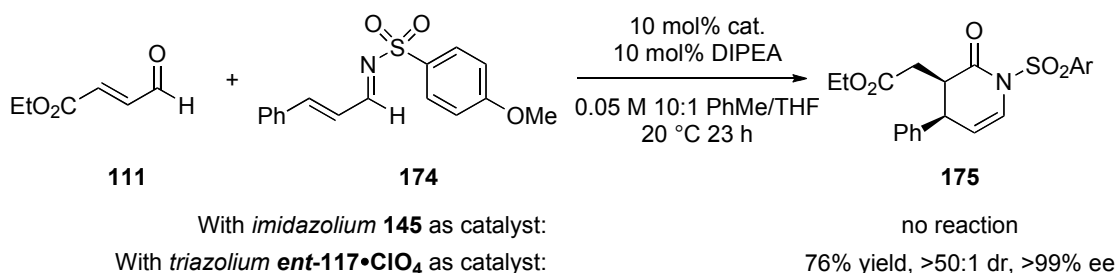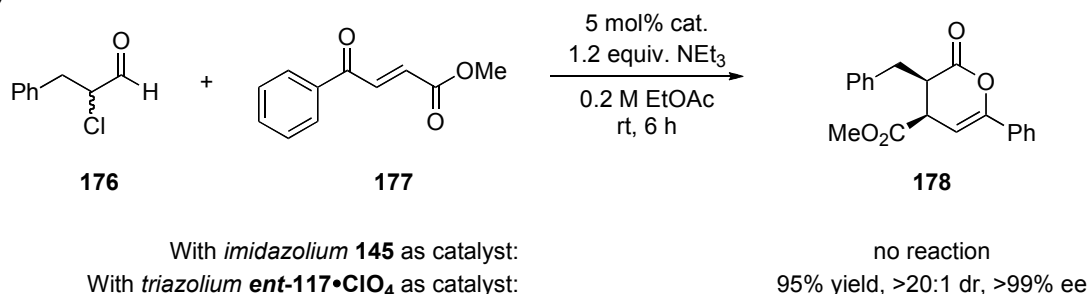
(c) Cyclopentene-forming benzoin-oxy-Cope reaction

With *imidazolium* **145** as catalyst:	10% yield, 1.6:1 dr, 99% ee
With *triazolium* **ent-117•ClO₄** as catalyst:	84% yield, 7:1 dr, 99% ee
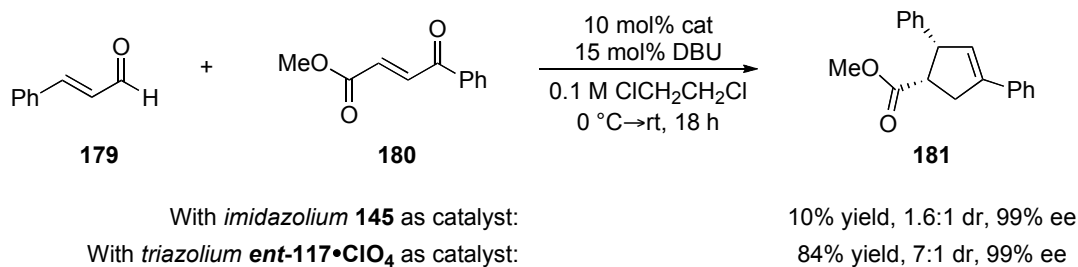
(d) Bicyclo β-lactam formation via aza-benzoin-oxy–Cope

With *imidazolium* **145** as catalyst:	5% yield, 96% ee
With *triazolium* **ent-117•ClO₄** as catalyst:	84% yield, 7:1 dr, 99% ee
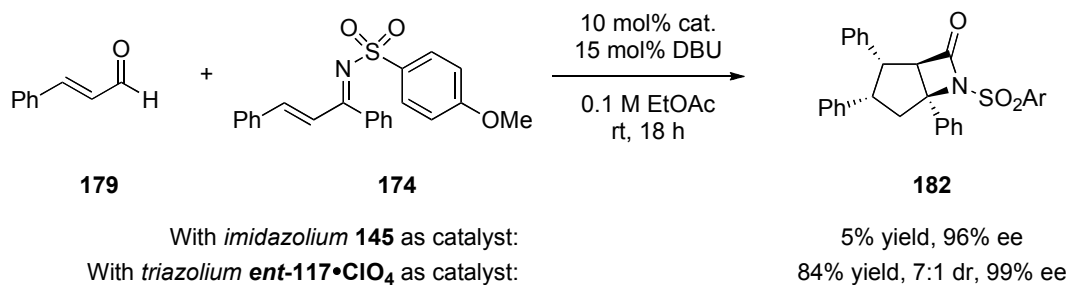
Scheme 57. Reactions preferentially catalyzed by triazolium precatalyst **ent-117•ClO₄**.

As we anticipated from our results using achiral imidazolium salts, precatalyst **145** was ineffective for NHC-catalyzed inverse electron-demand Diels−Alder processes; only unreacted starting material was observed. This was true regardless of how the key catalyst-bound enolate was generated, either via redox reactions of electron-deficient enals[13] (Scheme 57a) or α-chloroaldehydes (Scheme 57b).[11] Imidazolium salt **145** also proved unreactive in our recently disclosed annulation of enals and electron-deficient enones[14] (Scheme 57c) or *N*-sulfonyl ketimines[15] (Scheme 57d), processes that we believe proceed via a benzoin−oxy-Cope reaction; yet as previously reported precatlyst ***ent*-117•ClO₄** allowed for the formation of the cyclopentene and β-lactam products in excellect enantio- and diastereoselectivity.

(a) Intramolecular Stetter Reaction

With *imidazolium* **145** as catalyst: no reaction
With *triazolium* ***ent*-117•ClO₄** as catalyst: 94% yield, 98% ee
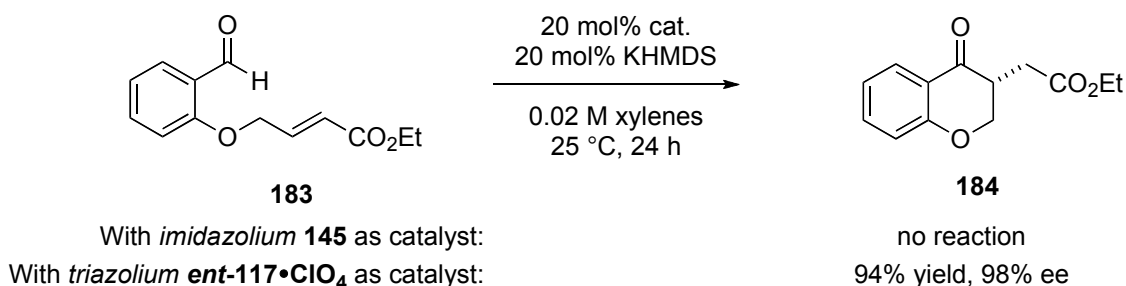
(b) Intermolecular benzoin dimerization

With *imidazolium* **145** as catalyst: 11% yield
With *triazolium* ***ent*-117•ClO₄** as catalyst: 83% yield
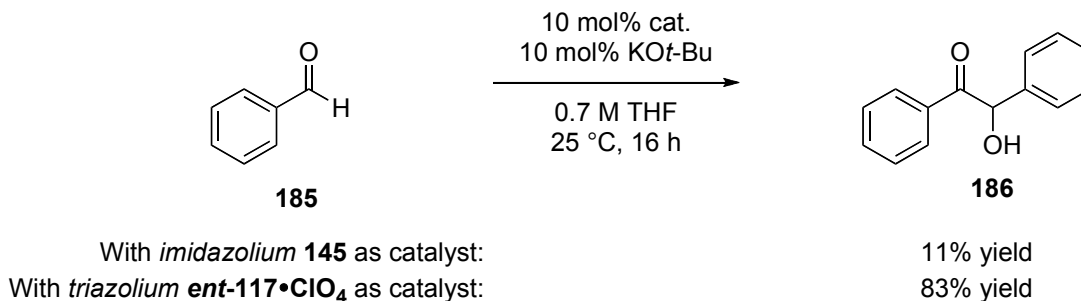
Scheme 58. Reactions preferentially catalyzed by triazolium precatalyst ***ent*-117•ClO₄**.

Interestingly, triazolium precatalyst ***ent*-117•ClO$_4$**, but not its imidazolium counterpart, was highly effective for intramolecular Stetter[21, 28] (Scheme 58a) and intermolecular benzoin reactions[22] (Scheme 58b). Although the benzoin and Stetter reactions are well-known to be catalyzed by other triazolium-derived NHCs, this was the first time the *N*-mesityl substituted variant had been employed. These results strongly suggest that the lack of benzoin products observed when *N*-mesityl substituted imidazolium-derived NHCs are employed stem from the properties of the imidazolium ring rather than steric restrictions of the *N*-mesityl moeity. Of particular note is that our *N*-mesityl triazolium salt rivals other state-of-the-art catalysts generally employed for the asymmetric Stetter reaction in both efficiency and selectivity.[8]

4.3 NHC-Promoted Redox Reactions Preferentially Promoted by Imidazolium Salt 145

In contrast, NHC-catalyzed annulation process that we and others have postulated to occur via catalytically generated homoenolate equivalents operate preferentially with imidazolium-derived precatalysts. The three reactions shown in Scheme X have all been reported to proceed in good yields in the presence of catalytic amounts of of the commercially available achiral imidazolium salt IMesCl. Although these processes work well with this catalyst, only a single report by Glorius of an enantioselective variant had appeared prior to our work, who obtained a maximum of 25% ee for a related annulation.[18] Despite the high reactivity of triazolium-derived carbenes for the processes shown in Schemes 57 and 58, ***ent*-117•ClO$_4$** and related triazolium salts were almost ineffective for the reactions shown in Scheme 59. The difference in reactivity between the annulations shown in Scheme 59a and Scheme 59b is particularly striking.

The cyclopentanone-forming annulation shown in Scheme 59c was recently reported by Nair and co-workers,[28] who suggest that it proceeds via the intermediacy of

a catalytically generated homoenolate. In support of this hypothesis, triazolium *ent-*
117•ClO₄, which is typically a poor catalyst for homoenolate-based annulations, is
almost unreactive. In contrast, imidazolium **145** effects the expected transformation in
85% ee, the highest level of enantioselectivity yet reported for any transformation
catalyzed by a chiral imidazolium-derived NHC at the time of our report.

(a) γ-Butyrolactone-forming annulation

With *imidazolium* **145** as catalyst:

55% yield, 1.4:1 dr
32% ee (*cis*), 34% ee (*trans*)

With *triazolium* ***ent-*117•ClO₄** as catalyst:

14% yield, 1.3:1 dr
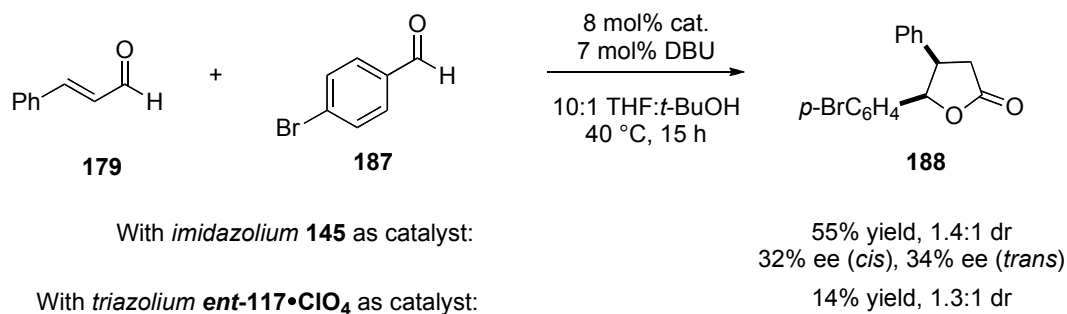
(b) γ-Lactam-forming annulation

With *imidazolium* **145** as catalyst:
With *triazolium* ***ent-*117•ClO₄** as catalyst:

25% yield, 10:1 dr, 24% ee
trace aza-benzoin product

(c) Cyclopentanone-forming annulation

With *imidazolium* **145** as catalyst:
With *triazolium* ***ent-*117•ClO₄** as catalyst:

34% yield, >10:1 dr, 85% ee
10% yield , ~5:1 dr, 92% ee
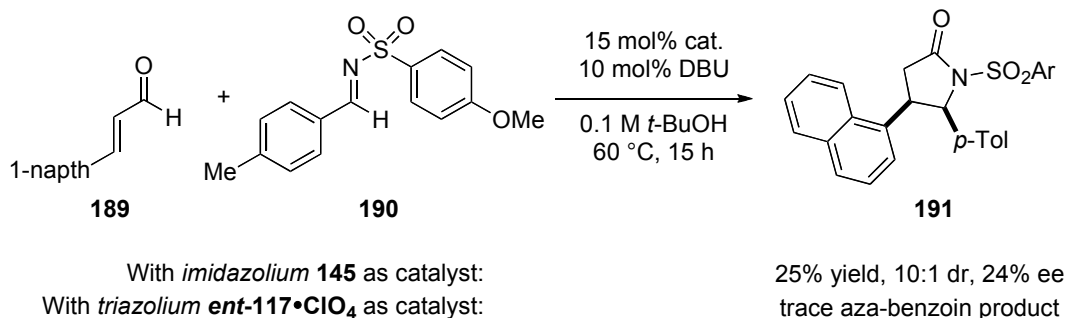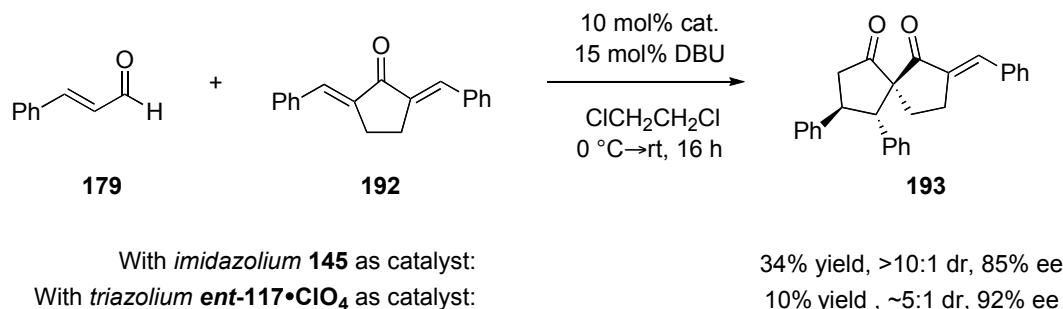
Scheme 59. Reactions preferentially catalyzed by imidazolium precatalyst **145**.

4.4 Conclusion

The results of the catalyst comparison confirmed, for the first time, that profound reactivity differences exist between the two classes of NHC-precatalysts. Of nine discrete reaction types screened, six processes were promoted almost exclusively by the triazolium precatalyst **ent-117•ClO₄** (Schemes 57 and 58). Another three processes, all of which invoke catalytically generated homoenolates as the putative reactive intermediates, were preferentially promoted by the imidazolium salt **145** (Scheme 59).

4.5 References

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Chapter 5: Formal Synthesis of Salinosporamide A via NHC-Catalyzed Intramolecular Lactonization

5.1 Introduction

Over the past decade, significant advances have been achieved in reactions catalyzed by N-heterocyclic carbenes (NHCs).[1-8] Conceptually new reaction pathways have been identified, making possible the production of stereochemically rich heterocycles from simple, readily available starting materials under exceptionally mild reaction conditions. An intriguing feature of these reactions is the often exquisite control over competing reaction pathways. For example, α,β-unsaturated enals can react as either homoenolate or ester enolate equivalents (Figure 27). In intermolecular annulation reactions, we have been successful in achieving complete control over these reaction pathways through careful choice of catalysts and reaction conditions.[9, 10]
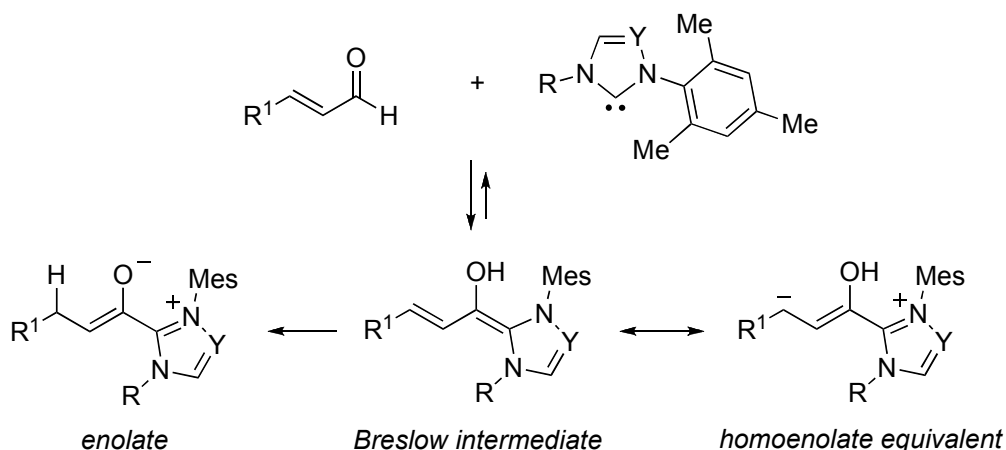
Figure 27. Catalytically generated intermediates from the reaction of NHCs and enals.

To further explore the ability of catalyst design to dictate the reaction outcome, we examined the more challenging case of selective enolate versus homoenolate reactivity

in a densely functionalized substrate that would lead to synthetically valuable bicyclic products. These studies originate from our recent discovery that α,β-unsaturated aldehydes undergo reactions with N-heterocyclic carbenes, leading to the catalytic generation of homoenolates or enolates via internal redox processes.[11] We have applied the generation of homoenolates to the formation of γ-butyrolactones[11] and γ-lactams.[12] We have disclosed that enals and α-chloroaldehydes serve as precursors to ester enolate equivalents for highly enantioselective inverse-electron demand Diels-Alder reactions.[13, 14] Building on these studies, Scheidt has reported intramolecular variants of both the homoenolate and enolate pathways and has alluded to competition between these two reaction manifolds in cyclization reactions.[15-17]

We recognized that an intramolecular cyclization of **194** via the homoenolate pathway would provide a concise entry into the salinosporamide class of natural products (Figure 28). Salinosporamide A[18-25] is a secondary metabolite of the marine actinomycete bacteria of salinospora strain CNB-392. It is a potent inhibitor of the 20S proteasome and has attracted much attention because of its impressive in vitro cytotoxic activity against many tumor cell lines. To execute this synthesis, however, we needed to identify catalysts and reaction conditions that would react selectively via the desired homoenolate pathway.
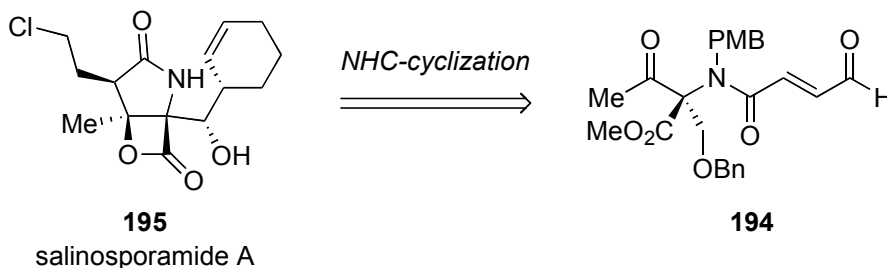
Figure 28. Proposed entry into the synthesis of salinosporamide A.

5.2 Development of a Novel NHC-Catalyzed Intramolecular Cyclization-Lactonization

5.2.1 Initial Attempts Toward a General NHC-promoted Intramolecular Cyclization-Lactonization

At the outset of our studies, we sought to develop a general strategy toward the formation of *cis*-fused *γ*-lactam-*γ*-lactone adducts via an NHC-promoted intramolecular homoenolate addition of an enal to a tethered ketone followed by lactonization of the resulting alkoxide on the subsequently formed activated carboxylate (Figure 29). Toward this end, enal **196** was synthesized by the coupling of aminoketone **197**[26] with carboxylic acid **198** (Scheme 60). However, when **196** was allowed to react with either commercially available imidazolium precatalyst IMesCl (**44•Cl**) or our achiral *N*-mesityl triazolium precatalyst RMesCl (**63**) in THF at 40 °C in the presence of DBU, the desired product **199** was not observed, rather the *N*-substituted succinimide **200** was obtained exclusively (Scheme 60). We suspect that succinimide **200** results from an NHC-catalyzed redox generation of an activated carboxylate and subsequent *N*-acylation of the tethered amide.
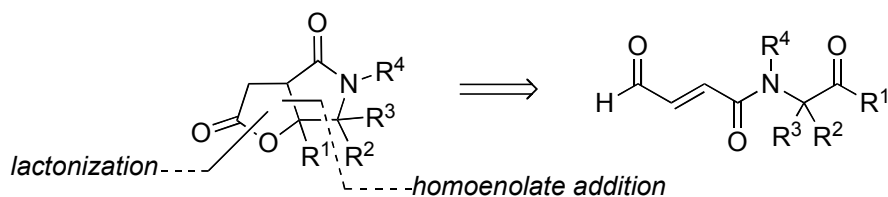
Figure 29. Retrosynthetic strategy toward the formation of *γ*-lactam-*γ*-lactone adducts.

Scheme 60.

1. HBTU, DIPEA
   CH$_2$Cl$_2$, rt, 20 h
   (67%)

2. 2N HCl(aq)
   (quant.)

197   **198**   **196**

20 mol% NHC
20 mol% DBU

THF, 40 °C, 12 h

196   **199**   **200**

not observed   *quant.*

NHCs

Me   Me

Cl$^-$

Me   Me   Me   Me

44•Cl
IMesCl

Me

Cl$^-$

Me   Me

63
RMesCl
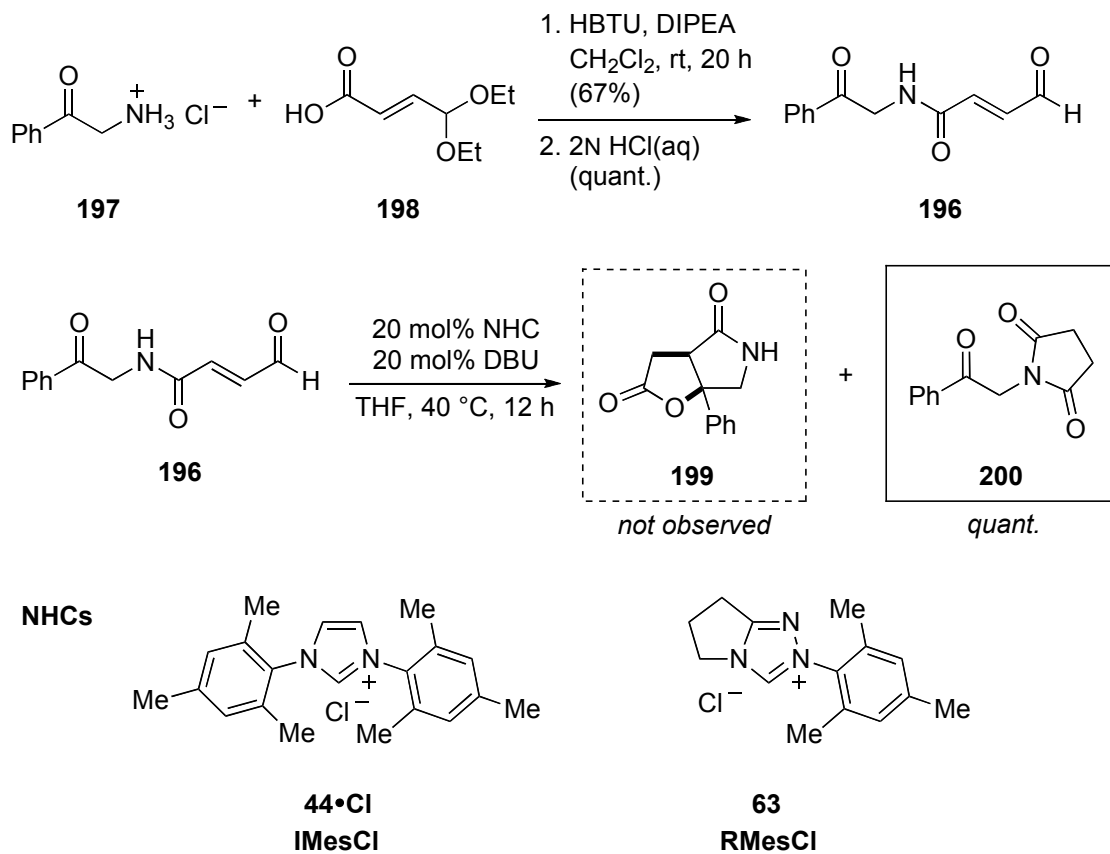
Scheme 60. Initial attempts at a general NHC-catalyzed intramolecular cyclization.

5.2.2 Further Investigations into the NHC-promoted Intramolecular Cyclization

At this point we recognized the need to employ a protecting group on the amide. The benzyl protecting group was chosen based on ease of the preparation of the amine coupling partner as well as the potential for its facile removal by catalytic hydrogenation. Subsequently, *N*-benzyl protected phenyl ketone **201** was synthesized from 2-bromoacetophenone and subsequently coupled with acid **198** using EDCI. Deprotection of the acetal using aqueous hydrochloric acid afforded the aldehyde **202** (Scheme 61). We subjected the aldehyde to NHC-precatalyst RMesCl with DBU in THF at 40 °C and were pleased to find the desired product, albeit in low yield and as a complex mixture.

Careful analysis of the reaction mixture revealed that in addition to the desired γ-lactam-γ-lactone product **203**, 6-membered lactam **204** was also formed. A plausible catalytic cycle is presented in Figure 30.
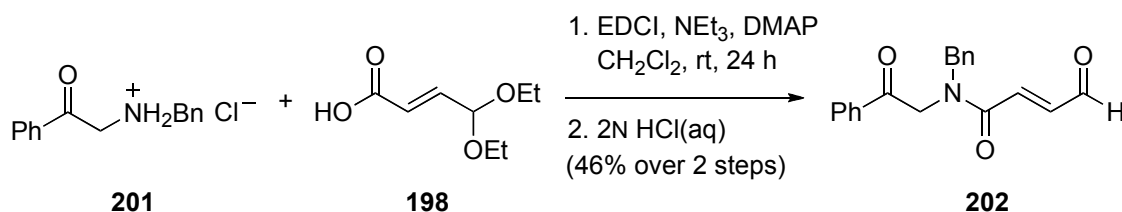
Scheme 61. Synthesis of *N*-benzyl protected substrate **202.**

Deprotonation of the precatalyst provides the active NHC catalyst **I** that undergoes nucleophilc attack on the enal **202** to provide the initial tetrahedral intermediate **II**. A proton transfer event leads to the Breslow intermediate **III**, the fate of which is intimately related to the strength of base and reaction conditions employed. A resonance structure of the Breslow intermediate is the homoenolate equivalent **IV**; this can participate in an intramolecular nucleophilic addition to the tethered ketone followed by lactonization via the resultant activated carboxylate **VI** to turn the catalyst over and produce the desired lactam **203** (pathway **A**). Protonation of the homoenolate **IV**, however, generates an NHC-enolate **VII** that can undergo an intramolecular keto-aldol addition affording alkoxide intermediate **VIII**. Lactonization would then result in expulsion of the catalyst and formation β-lactone **205**, which readily undergoes decarboxylation[16, 27, 28] to afford δ-lactam **204** (pathway **B**). From the reaction mixture, we also isolated **206**, which we believe arises from a base-catalyzed olefin isomerization, followed by an intramolecular aldol addition (aldol pathway **C**). We corroborated pathway **C** by subjecting aldehyde **202** to DBU in THF at 40 °C; complete conversion to the α-pyridone **206** was observed (Scheme 62).
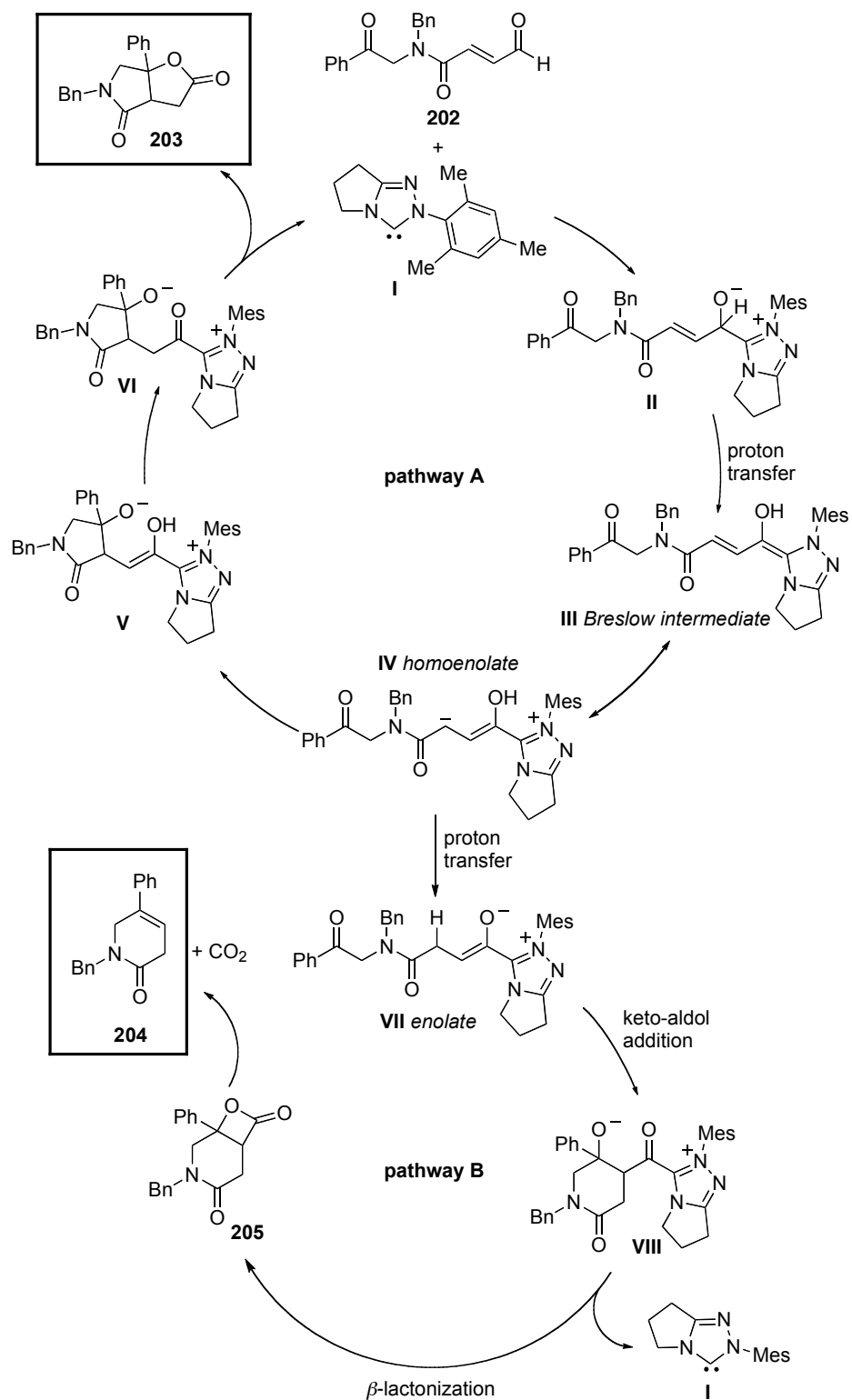
Figure 30. Postulated catalytic cycle for NHC-promoted pathways **A** and **B**.
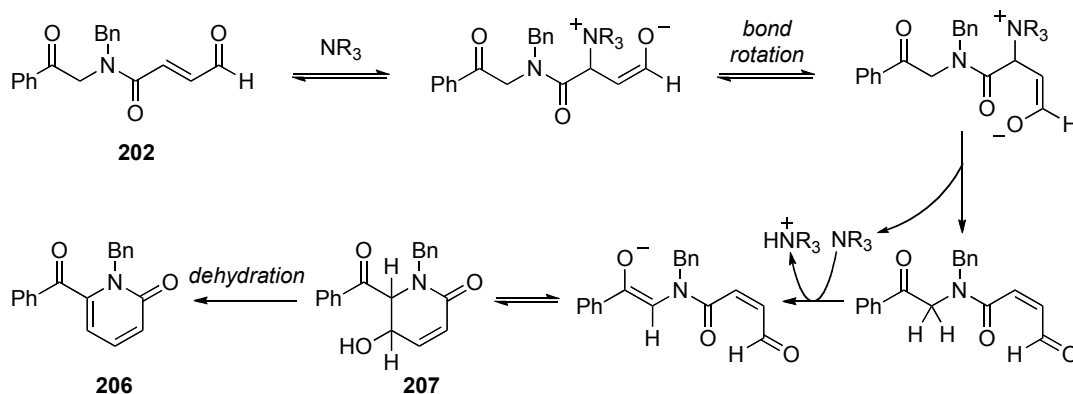
Scheme 62. Base-catalyzed intramolecular aldol pathway **C**.

Optimization was carried out in an attempt to bias the formation of the desired *γ*-lactam-*γ*-lactone, which arises from pathway **A**. The most pertinent results are summarized in Table 4. When imidazolium catalyst IMesCl (**44•Cl**) was used in conjunction with the strong tertiary amine base DBU, the intramolecular aldol pathway **C** predominated (entry 1). However, when a weaker tertiary amine base was employed, pathway **C** was completely suppressed but the formation of products arising from the enolate pathway **B** increased (entry 3). We attribute this to the facile protonation of the homoenolate by the conjugate acid of weak tertiary amine bases such as triethylamine. Use of our triazolium catalyst RMesCl (**63**) yielded products of all three pathways with pathway **B** dominating when DBU was used (entry 2), and pathway **A** and **B** dominating when the weaker amine base triethylamine was used (entry 4). We further discovered that of the chiral triazolium NHC-precatalysts tested, pathway **C** could be suppressed when catalyst **130**, reported by Scheidt and co-workers,[15, 16] was used along with either a strong base under dilution (entry 5), a bulky tertiary amine base in a chlorinated solvent (entry 6), or a strong base in *t*-BuOH (entry 7). However, we could never bias the product distribution to favor the desired *γ*-lactam-*γ*-lactone product in greater than 50% yield. Perhaps even more problematic was the inability to isolate the desired bicyclic product. Multiple

attempts to purify the reaction mixtures by recrystalization, column chromatography or preparative HPLC were all met with failure.

Table 4. NHC-Catalyzed cyclization-lactonization of substrate **202**.
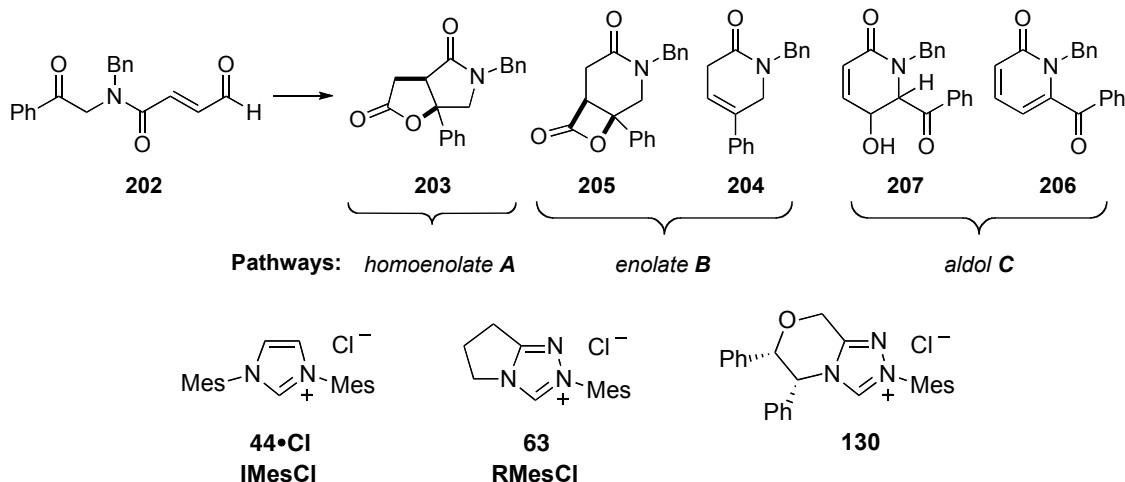
Entry	Catalyst (mol%)	Base (mol%)	Solvent (conc.)	Temp. (°C)	A : B : C [a]
1	IMesCl (20)	DBU (15)	THF (0.1M)	40	9 : 0 : 91
2	RMesCl (20)	DBU (15)	THF (0.1M)	40	25 : 25 : 50
3	IMesCl (20)	NEt$_3$ (15)	THF (0.1M)	40	55 : 45 : 0
4	RMesCl (20)	NEt$_3$ (15)	THF (0.1M)	40	42 : 42 : 16
5	**130** (15)	DBU (10)	10:1 THF:t-BuOH (0.02M)	40	50 : 50 : 0
6	**130** (15)	DIPEA (100)	CH$_2$Cl$_2$ (0.1M)	40	50 : 50 : 0
7	**130** (15)	DBU (10)	t-BuOH (0.1M)	40	50 : 42 : 8
8	**130** (15)	DBU (10)	t-BuOH (0.1M)	60	58 : 42 : 0
9	**130** (15)	NEt$_3$ (10)	t-BuOH (0.1M)	60	62 : 38 : 0
10	**130** (15)	DBU (10)	t-BuOH (0.1M)	80	58 : 42 : 0

All reactions listed proceeded with 100% conversion; isolated yields were not determined.
[a] Product pathway ratios were determined from ^{1}H NMR analysis of unpurified reaction mixtures.

From our results we hypothesized that there may exist a rotational barrier for the two rotamers of tertiary amide. As such, one rotamer might undergo intramolecular cyclization by the homoenolate faster than the other. The rate of this rotation might be in competition with the rate of protonation of the homoenolate that leads to the NHC-enolate which cyclizes to form the products of pathway **B**. To test this hypothesis, we subjected **202** to our optimized conditions at 60 °C and indeed a more favorable product

distribution was achieved (entries 8 and 9). However, further increase of the reaction temperature did not improve the ratio of desired product (entry 10).
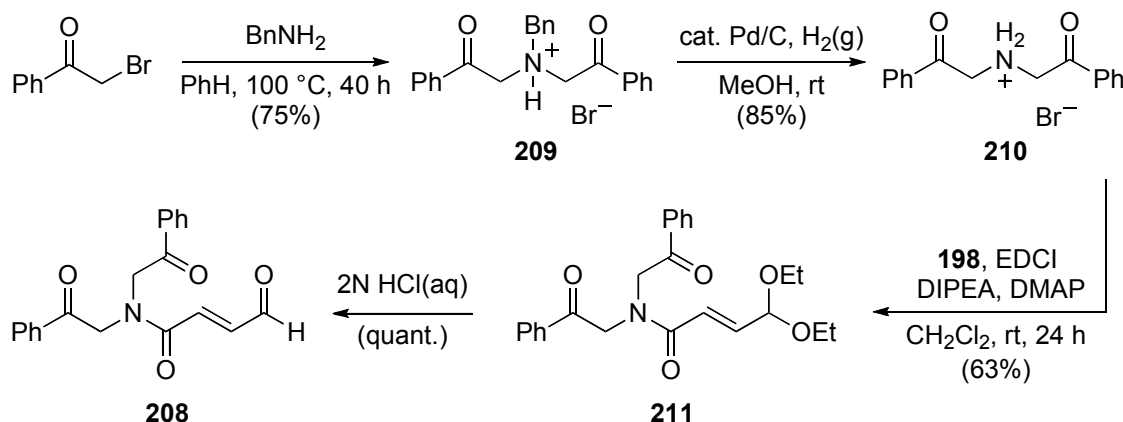
Scheme 63. Synthesis of symmetrical enal **208**.

Similarly, we reasoned that a symmetrical tertiary amide would obviate the need for elevated temperatures to bias the homoenolate pathway **A**. Aldehyde **208** was synthesized to probe our initial hypothesis further (Scheme 63). The symmetrical bisketone **210** was synthesized in two steps from 2-bromoacetophenone and subsequently coupled with acid **198** using EDCI. Deprotection of the diethyl acetal (**211**) with aqueous hydrochloric acid furnished the symmetrical α,β-unsaturated aldehyde **208**.

Initially triazolium catalysts were identified as superior to imidazolium catalysts for obtaining the desired γ-lactam-γ-lactone product **212** (Table 5, entries 1–3). Further optimization identified 10:1 THF:*t*-BuOH as the most suitable solvent system and RMesCl the best precatalyst for biasing pathway **A** (entries 4–13). It should be noted that strong bases DBU and *t*-BuOK (entries 4, 5 and 7) as well as the weaker but bulkier tertiary amine base DIPEA (entry 6) helped to suppress pathway **C**. Lowering the temperature initially suppressed pathway **C** (entries 4 and 5) but further cooling suppressed pathway **B** while enhancing pathway **C** (entry 8), suggesting that protonation of the homoenolate was faster than intramolecular cyclization. Dilution favored pathway

A (entries 9–13), whereas raising the amount of base tended to favor pathway **C** for the strong base DBU (entry 11) but pathway **B** for the weaker base DIPEA (entry 12). The optimum conditions identified employed DBU at lower loading than the catalyst, moderate heating (40 °C), and dilute conditions (0.01 M), resulting in a 3:1 ratio of annulation products **A**:**B** (entry 13). Although we demonstrated that the symmetrical substrate did provide an improved ratio of the desired product, again difficulty in purification precluded ready access to the desired bicycle **212**.

Table 5. NHC-Catalyzed cyclization-lactonization of substrate **208**.
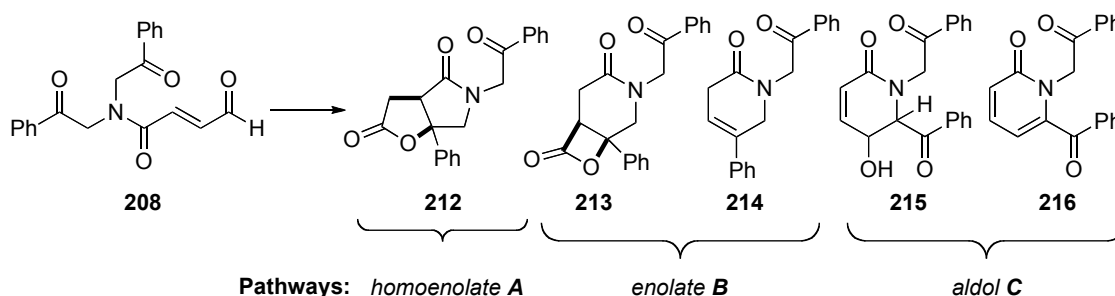
Entry	Catalyst (mol%)	Base (mol%)	Solvent (conc.)	Temp. (°C)	A : B : C [a]
1	RMesCl (15)	DBU (10)	t-BuOH (0.10M)	60	50 : 17 : 33
2	IMesCl (15)	DBU (10)	t-BuOH (0.10M)	60	10 : 14 : 76
3	**130** (15)	DBU (10)	t-BuOH (0.10M)	60	66 : 17 : 17
4	RMesCl (15)	DBU (10)	10:1 THF:t-BuOH (0.10M)	60	40 : 60 : 0
5	RMesCl (15)	DBU (10)	10:1 THF:t-BuOH (0.10M)	40	43 : 57 : 0
6	RMesCl (15)	DIPEA (10)	10:1 THF:t-BuOH (0.10M)	40	45 : 55 : 0
7	RMesCl (15)	t-BuOK (10)	10:1 THF:t-BuOH (0.10M)	40	34 : 33 : 33
8	RMesCl (15)	DBU (10)	10:1 THF:t-BuOH (0.10M)	20	13 : 0 : 87
9	RMesCl (15)	DBU (10)	10:1 THF:t-BuOH (0.05M)	40	66 : 17 : 17
10	RMesCl (15)	DIPEA (10)	10:1 THF:t-BuOH (0.05M)	40	50 : 50 : <1
11	RMesCl (15)	DBU (50)	10:1 THF:t-BuOH (0.05M)	40	9 : <1 : 91
12	RMesCl (15)	DIPEA (50)	10:1 THF:t-BuOH (0.05M)	40	50 : 50 : 0
13	RMesCl (15)	DBU (10)	10:1 THF:t-BuOH (0.01M)	40	75 : 25 : <1

All reactions listed proceeded with 100% conversion; isolated yields were not determined.
[a] Product pathway ratios were determined from ^{1}H NMR analysis of unpurified reaction mixtures.

Of the two competing undesired pathways (**B** and **C**), pathway **C** was the easier to address. By blocking the *α*-position of the ketone, we could effectively eliminate pathway **C** since no enolizable hydrogens would exist. Also, there would be no concern for the

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use of either a strong base or an excess (compared to the precatalyst) of base. For this purpose, the geminal dimethyl substrate **217** was designed and synthesized (Scheme 64). Starting from Cbz-AIB, the acid was converted to the Weinreb amide **218** using DCC. *N*-Alkylation was carried out in DMF with NaH and benzyl bromide providing **219** in quantitative yield. Formation of methyl ketone **220** was achieved using MeMgBr in Et$_2$O, and the benzyl carbamate was subsequently removed by catalytic hydrogenation in acidic media to afford **221**. Amide formation with acid **198** proved most efficient via the isobutyl mixed anhydride at elevated temperature; standard coupling reagents such as HBTU, HATU, and EDCI were ineffective. Finally, deprotection of the diethyl acetal **222** afforded the desired aldehyde **217** in moderate yield due to its sensitivity to silica gel purification.
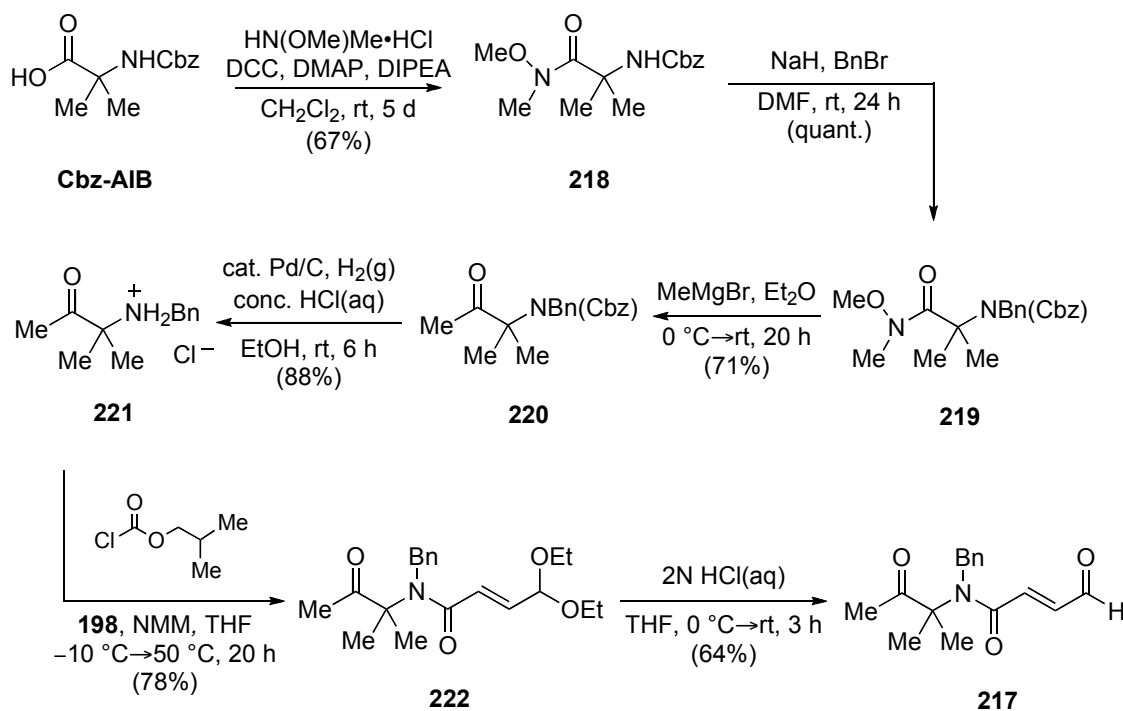

Scheme 64. Synthesis of *gem*-dimethyl substrate **217**.

When aldehyde **217** was allowed to react in the presence of 15 mol % of RMesCl, 10 mol % of DBU at 0.05 M in 10:1 THF:*t*-BuOH for 20 h, we only observed the desired

γ-lactam-*γ*-lactone **223**. Furthermore, we identified that IMesCl was an even more effective catalyst for the desired transformation, providing the desired lactam in 79% isolated yield (Table 6, entry 1). We briefly screened several chiral precatalysts. Our triazolium *N*-mesityl aminoindanol-derived precatalyst ***ent*-117** provided the desired product in 75% yield but only 5% ee (entry 2). Our structurally related imidazolium *N*-mesityl aminoindanol-derived precatalyst **145** provided **223** in a reduced 50% yield and 9% ee (entry 3). Two chiral *N*-mesityl triazolium precatalysts, **130** and **131**, developed by Scheidt,[15, 29] proved just as effective with a slight increase in enantiomeric excess (entries 4 and 5). By employing precatalyst **131** and reducing the temperature to –20 °C, we obtained the *γ*-lactam-*γ*-lactone **223** with an enantiomeric excess of 40%.

Table 6. NHC-Catalyzed cyclization-lactonization of substrate **217**.
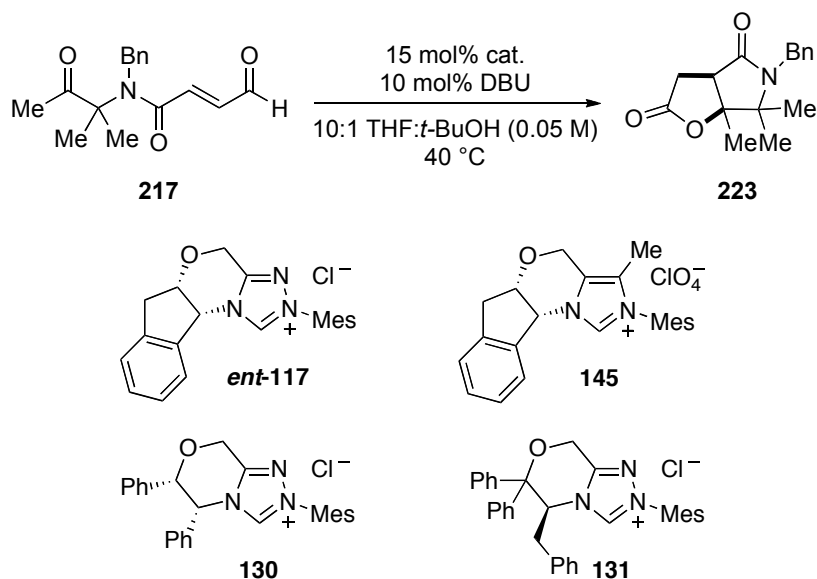
Entry	Catalyst	Yield	%ee[a]
1	IMesCl	79%	*NA*
2	***ent*-117**	75%	5
3	**145**	50	9
4	**130**	78	9
5	**131**	73	23 (40)[b]

[a] Determined by Chiral SFC analysis. [b] Performed at –20 °C.

5.3   Formal Synthesis of Salinosporamide A

5.3.1 Retrosynthetic Analysis

Encouraged by our results we sought to apply our method to streamlining the previously reported synthesis of salinosporamide A. During the course of our investigation, Lam and co-workers reported a formal synthesis of salinosporamide A via a nickel-catalyzed reductive aldol cyclization-lactonization strategy to construct **224**.[25] In parallel studies, we had identified intermediate **224** as a target for our NHC-promoted intramolecular cyclization-lactonization strategy for a formal synthesis of salinosporamide A (Figure 31).
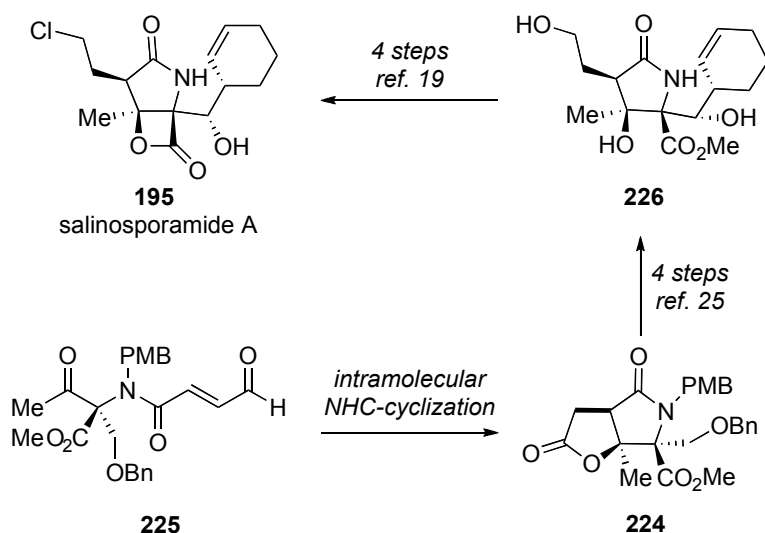
Figure 31. Proposed formal synthesis of salinosporamide A from aldehyde **225** employing our intramolecular NHC-cyclization.

Our retrosynthetic plan is outlined in Figure 32. Lactam **224** would be obtained from the NHC catalyzed cyclization-lactonization of aldehyde **225,** which in turn would be synthesized in an analogous manner to our previous aldehyde substrates via amide bond formation between acid **198** and amine **227** followed by a deprotection-oxidation

sequence. The synthesis of **227** from L-threonine has previously been reported by Corey in his synthesis of salinosporamide A.[19]
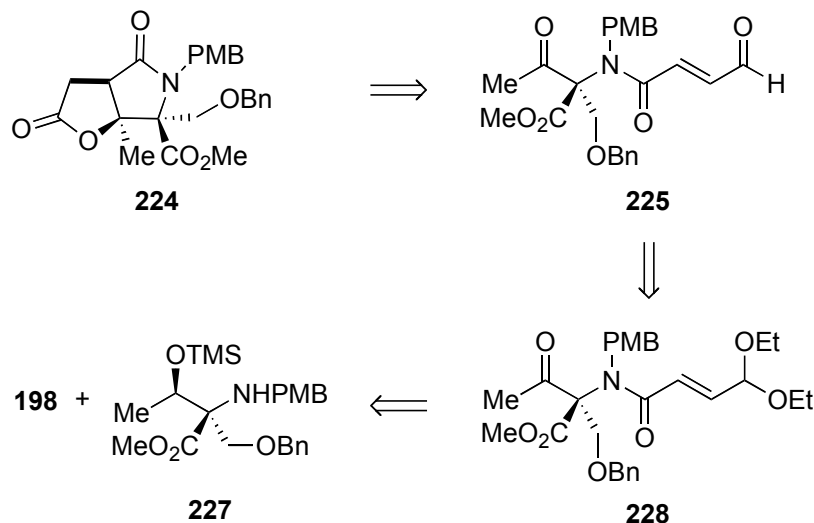
Figure 32. Retrosynthetic analysis for intermediate γ-lactam **224.**

5.3.2 Synthesis of Key Substrate 225

Attempted amide formation between acid **198** and amine **227** did not appreciably proceed in the presence of coupling reagents HBTU, HATU, PyBop or EDCI. Instead, either a trace amount of the desired amide, decomposition of the amine, deprotection of the silyl group, or no reaction was observed under a variety of conditions. We attempted the amide bond formation via the mixed anhydride of acid **198**. Neither the isobutyl, isopropenyl, nor 2,4,6-trichlorophenyl mixed anhydride provided any of the desired amide. Formation of the amide via the 2,3,4,5,6-pentafluorophenyl ester derivative of **198** also proved unsuccessful. Attempts to acylate amine **227** via an acid chloride formed by means of the Vilsmeier reagent and acid **198** yielded trace amounts of the desired product in certain cases, but often returned starting material and deprotected

alcohol accompanied by decomposition of the acid chloride. After numerous attempts to couple amine **227** and acid **198** had failed, we revised our synthesis of aldehyde **225**.

We instead accessed aldehyde **225** from amine **227** by first using a three-step sequence of *N*-acylation with sorbyl chloride, silyl ether cleavage under aqueous acidic conditions, and Dess-Martin[29] oxidation to afford ketone **229** in 60% overall yield. Next we performed a regioselective Sharpless dihydroxylation[30] at the *γ,δ*-position of **229** using a procedure similar to one reported by Zhang and O'Doherty[31] to access diol **230** as a single diastereomer in moderate yield. Finally cleavage of the diol was smoothly accomplished with sodium periodate in quantitative yield (Scheme 65).
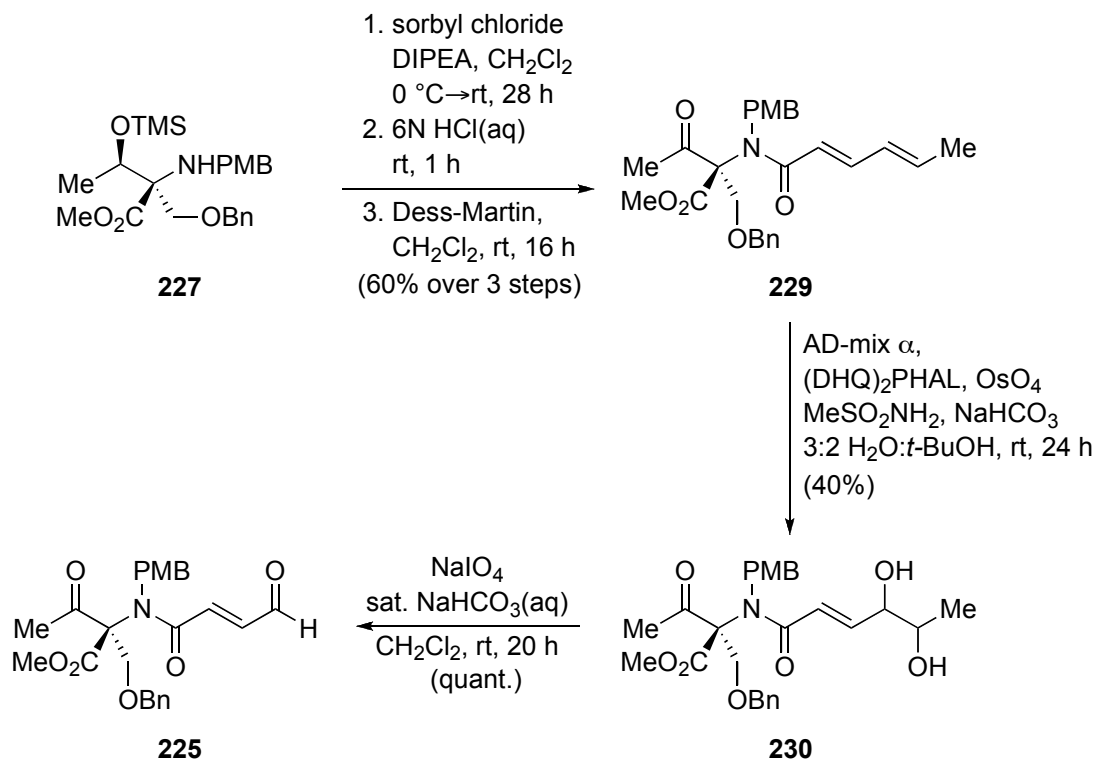

Scheme 65. Synthesis of key enal substrate **225** for NHC-catalyzed intramolecular cyclization.

5.3.3 Formal Synthesis of Salinosporamide A

Having successfully synthesized key intermediate **225**, we subjected the enal to our previously optimized conditions for cyclization of substrate **217**. When **225** was allowed to react with 15 mol % IMesCl and 10 mol % DBU in 10:1 THF:*t*-BuOH at 40 °C a complete conversion to the *γ*-lactam-*γ*-lactone products **231** and **232** was observed (Table 7, entry 1). Although the isolated yield was good (75%), the diastereomeric ratio was only 3:1 in favor of the undesired diastereomer. We therefore sought to bias the stereochemical outcome through the use of chiral catalyst. We employed our *N*-mesityl aminoindanol derived chiral triazolium catalyst **117** (entry 2); the diastereomeric ratio decreased to 1.1:1 still in favor of the undesired diastereomer but with increased yield (84%). Interestingly, the use of the enantiomeric precatalyst **ent-117** provided nearly an identical outcome (entry 3). Triazolium salts, **130** and **131**, which had previously led to higher enantiomeric ratios with substrate **225**, gave slightly higher diastereomeric ratios: 1.7:1 and 1.5:1, respectively, but again in favor of the undesired diastereomer (entry 4– 5). Therefore, choice of the appropriate catalyst, **117**, did indeed influence the strong substrate control over the diastereoslective homoenolate addition to the ketone whereby a 1:1.1 ratio of desired:undersired lactam is our best result (see entry 2). Our NHC-catalyzed intramolecular cyclization-lactonization of enal **225** provided lactams **231** and **232** in excellent yield and represents a formal synthesis of salinospoaramide A.

Table 7. NHC-Catalyzed cyclization-lactonization of substrate **225**.[a] Formal synthesis of salinosporamide A.
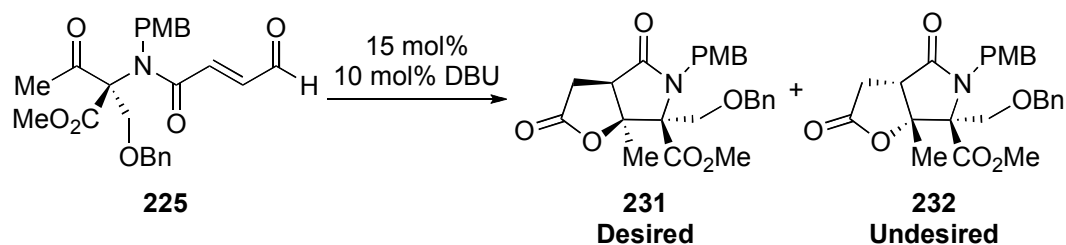
Entry	Catalyst	Yield[b] (%)	dr[c] (desired/undesired)
1	IMesCl	75	1:3
2	**117**	88	1:1.1
3	*ent*-**117**	84	1:1.2
4	**130**	93	1:1.7
5	**131**	77	1:1.5

[a] Reactions were performed at 0.05 M in 10:1 THF:*t*-BuOH at 40 °C for 3 h.

[b] Combined isolated yield of both diastereomers.

[c] Determined from ^{1}H NMR of unpurified reaction mixtures.

5.4 Conclusion

We have presented an NHC-catalyzed intramolecular cyclization-lactonization of enals to ketones tethered by an amide bond, producing densely functionalized γ-lactam-γ-lactone adducts. In the course of these studies we have documented reaction parameters that can preferentially favor the formation of one catalytically generated reactive intermediate over another (NHC-enolate vs. homoenolate). Furthermore, to demonstrate the utility of this method, we accomplished a formal synthesis of salinosporamide A, a potent 20S proteasome inhibitor, via intermediates reported by Corey and by Lam. The attraction of our synthesis is the use of a NHC-promoted intramolecular cyclization-lactonization strategy to construct the carbocyclic core of salinosporamide A whereby a carbon-nitrogen, carbon-oxygen, and carbon-carbon bond are all formed in a single catalytic step.

5.5 References

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Chapter 6: Experimental Procedures

6.1 General Methods

All reactions utilizing air- or moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry Nitrogen. Dichloromethane, 1,2-dichloroethane, xylenes and chlorobenzene were distilled over CaH_2. t-BuOH was distilled from Na^0. Toluene, THF, MeOH, DMF, DMSO and EtOAc were dried by passage over activated alumina under Ar atmosphere. Benzaldehyde and $trans$-cinnamaldehyde were purified by distillation prior to use. 2,4,6-trimethylaniline was fractionally distilled under reduced pressure from Zn^0 (granular). 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was distilled from KOH. Triethylamine (NEt_3) and N,N'-diisopropylethylamine (DIPEA) were distilled from CaH_2. Acetic anhydride was shaken over P_2O_5, filtered, shaken over K_2CO_3, filtered, and fractionally distilled. Perchloric acid was purchased from Fisher Scientific as 60 or 70 wt % solutions in water. Other reagents were used without further purification. Thin layer chromatography (TLC) was performed on Merck precoated plates (silica gel 60 F254, Art 5715, 0.25 mm) and were visualized by fluorescence quenching under UV light or by staining with phosphomolybdic acid, potassium permanganate, or cerium sulfate solutions. Silica-gel preparative thin-layer chromatography (PTLC) was performed using plates prepared from Merck Kieselgel 60 PF254 (Art 7747). Column chromatography was performed on E. Merck Silica Gel 60 (230–400 Mesh) using a forced flow of 0.1–0.5 bar. ^1H NMR and ^{13}C NMR were measured on a Varian Unity 400 spectrometer or on a Bruker Avance II 500 MHz, 125 MHz respectively. The peaks labeled with an asterisks (*) indicate peaks of either the minor diastereomer ($trans$-), amide rotamers, or atropisomers where appropriate. Chemical shifts are expressed in parts per million (PPM) downfield from residual solvent peaks and coupling constants

are reported as Hertz (Hz).   Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared (IR) spectra were recorded on a JASCO FT/IR-430 spectrophotometer and are reported as wavenumbers (cm^{-1}). Optical rotations were acquired using a JASCO DIP-370 polarimeter operating at the sodium D line with a 100 mm path length cell and are reported as follows: $[\alpha]^T$ (concentration (g/mL x 100), solvent).

6.2 HPLC Conditions

Column, Diacel Chiralpak AS-H, (4.6 x 250mm) Eluent: hexanes/*i*-PrOH. Flow Rate 1.0 mL/min. Detection: 254 nm. Column, Diacel Chiralpak AD-H, (4.6 x 250mm) Eluent: hexanes/*i*-PrOH. Flow Rate 1.0 mL/min. Detection: 254 nm.

6.3 SFC Conditions

Column, Diacel Chiralpak AS-H, (4.6 x 250mm) Eluent: *i*-PrOH in CO_2, MeOH in CO_2. Flow Rate 2.0 mL/min. Detection: 254 nm. Column, Diacel Chiralpak AD-H, (4.6 x 250mm) Eluent: *i*-PrOH in CO_2. Flow Rate 2.0 mL/min. Detection: 254 nm. Column, (R,R)-Whelk-01 (4.6 x 250mm) Eluent: *i*-PrOH in CO_2. Flow Rate 2.0 mL/min. Detection: 254 nm.

6.4 Experimental Procedures

107 → **108**
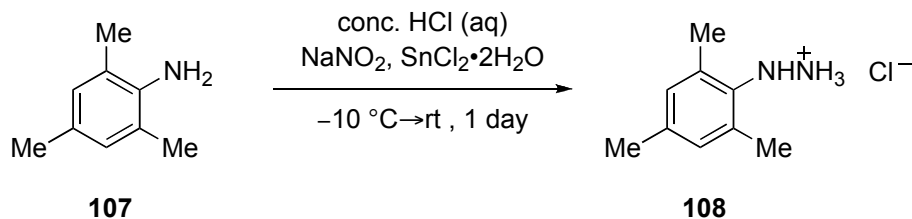
2-Mesitylhydrazinium chloride (108)

A 3-neck 1-L round-bottomed flask was charged with a magnetic stir bar and placed in a −10 °C MeOH bath. The flask was charged with conc. aq HCl (26.5 mL) and H_2O. The center neck of the reaction vessel was equipped with a 60-mL pressure-equalizing addition funnel and charged with 2,4,6-trimethylaniline (15.0 mL, 107 mmol, 1.00 equiv), which was added drop-wise over a period of approximately 5 min resulting in a thick white slurry and stirring was continued for an additional 15 min. The reaction vessel was equipped with a thermometer to monitor the internal temperature of the reaction. The addition funnel was charged with a freshly prepared solution of $NaNO_2$ (7.38 g, 107 mmol, 1.00 equiv) in H_2O (12 mL) and added drop-wise so as to maintain an internal temperature of < 5 °C. The addition funnel was washed with H_2O (5 mL) and stirring was continued for an additional 30 min. The addition funnel was charged with a solution of $SnCl_2 \cdot 2H_2O$ (60.4 g, 268 mmol, 2.50 equiv) in 1:1 concd HCl/H_2O and added drop-wise over 4 h maintaining an internal reaction temperature of < 5 °C. The addition funnel and thermometer were removed and the thick heterogeneous orange mixture was stirred at 0 °C for 1 h before being allowed to warm to ambient temperature. Vigorous stirring was maintained for an additional 16 h. The mixture was cooled to 0 °C. The orange precipitate was collected by suction filtration and the reaction vessel washed with brine (5 x 50 mL) that was poured over the collected solid with each wash. The orange solid

was transferred to a 1-L round-bottomed flask and Et_2O (300 mL) and a magnetic stir bar were added. The heterogeneous mixture was placed in an ice/brine bath and the flask was equipped with a pressure-equalizing addition funnel charged with aq 10 M NaOH (200 mL) that was added over approximately 30 min. An additional 100 mL of H_2O was added and stirring was maintained for an additional 1 h before the biphasic mixture was allowed to warm to ambient temperature and transferred to a separatory funnel. The organic layer was separated and the aqueous phase extracted with Et_2O (2 x 200 mL). The organic fractions were combined and washed with brine (250 mL), dried over Na_2SO_4, and filtered into a dry 1-L round-bottomed flask charged with a magnetic stir bar. The drying agent was washed with Et_2O (3 x 30 mL). The orange solution was placed under an atmosphere of $N_2(g)$ and immersed in an ice/brine bath. A solution of HCl (4 M in 1,4-dioxane, 27.0 mL, 108 mmol) was added via syringe over 15 min inducing a white precipitate. Stirring was maintained for 30 min and then allowed to warm to ambient temperature. The pale orange precipitate was collected by suction filtration and washed with Et_2O (50 mL). The crude solid was transferred to a 200-mL round-bottomed flask and the residual volatiles removed under reduced pressure. The crude solid was suspended in a solution of 200 proof $EtOH/Et_2O$ (5:1, 60 mL) and placed in a sonicating bath for 30 min. The pale orange solid was collected by suction filtration, and washed with a solution of 200 proof $EtOH/Et_2O$ (1:1, 3 x 30 mL). The filtrate was concentrated under reduced pressure to produce an orange crystalline solid which was suspended in a solution of 200 proof $EtOH/Et_2O$ (1:1, 15 mL) and placed in a sonicating bath for 5 min; the pale orange solid was collected by suction filtration and washed with a solution of 200 proof $EtOH/Et_2O$ (1:1, 3 x 5 mL). The collected solids were combined and the residual volatiles removed under reduced pressure to afford the title compound (7.28 g, 36.4 %) as a pale orange powder. ^{1}H NMR (500 MHz, d6-DMSO) δ: 9.40 (variable bs, 3H), 6.88 (s, 2H), 6.61 (bs, 1H), 2.32 (s, 6H), 2.20 (s, 3H); ^{13}C NMR

(125 MHz, d_6-DMSO) δ: 137.9, 136.2, 134.9, 129.1, 20.45, 17.8; IR (KBr) ν 3294, 3002, 2964, 2911, 2680, 1564, 1513, 1481, 852, 825, 753 cm^{-1}; HRMS (ESI) calcd for $C_9H_{15}N_2^+$ [M]$^+$ 151.1230, found 134.0921 [M – NH$_3$]$^+$.
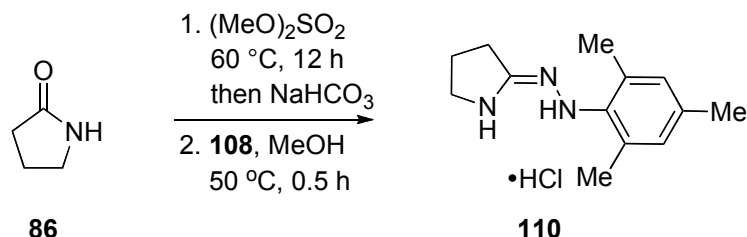
(Z)-2-(2-mesitylhydrazono)pyrrolidine hydrochloride (110)

An oven-dried 100-mL round-bottomed flask was charged with 2-pyrrolidinone and dimethyl sulfate. The neat mixture was stirred at 60 °C for 16 h under an atmosphere of N$_2$(g). The mixture was allowed to cool to ambient temperature, diluted with CH$_2$Cl$_2$ (20 mL) and slowly quenched over 3 hours by the addition of sat aq NaHCO$_3$ (30 mL). Once effervescence had ceased, the biphasic mixture was transferred to a separatory funnel and diluted with CH$_2$Cl$_2$ (80 mL) and sat aq NaHCO$_3$ (70 mL). The organic phase was separated and the aqueous phase extracted with CH$_2$Cl$_2$ (50 mL). The combined organic fractions were dried over Na$_2$SO$_4$, filtered and carefully concentrated under reduced pressure (~450 mbar) at ambient temperature to afford the crude iminoether. To a flame-dried 200-mL round-bottomed flask was weighed the crude iminoether (5.70 g, 57.5 mmol, 1.1 equiv) by passage through a plug of Na$_2$SO$_4$; MeOH (80 mL) and 2-mesitylhydrazinium hydrochloride **108** were added. The reaction vessel was equipped with a water-jacketed condenser and the orange solution stirred at 50 °C under an atmosphere of N$_2$(g) for 0.5 h. The solution was allowed to cool to ambient temperature and the solvent removed under reduced pressure to afford a crude orange solid. The crude solid was suspended in EtOAc (130 mL) and stirred vigorously under reflux until a

free-flowing light orange precipitate was observed. The precipitate was collected by suction filtration and washed with EtOAc to afford the title compound as a pale-orange solid (9.60 g, 73%). ^{1}H NMR (500 MHz, d$_6$-DMSO) δ 11.16 (bs, 1H), 10.08 (s, 1H), 7.17 (s, 1H), 6.84 (s, 2H), 3.63–3.59 (t, 2H, J = 7.2 Hz), 2.83 (t, 2H, J = 7.9 Hz), 2.19 (s, 9H), 2.14 (t, 2H, J = 7.4 Hz); ^{13}C NMR (125 MHz, d$_6$-DMSO) δ 167.7, 138.6, 133.6, 130.9, 129.3, 46.8, 28.4, 20.8, 20.3, 17.9; IR (KBr) ν 3436, 3217, 2959, 2908, 1687, 1480, 1306, 1229, 853 cm^{-1}; HRMS (ESI) calcd for C$_{13}$H$_{20}$N$_3^+$ [M]$^+$ 218.1652, found 218.1646 [M]$^+$.
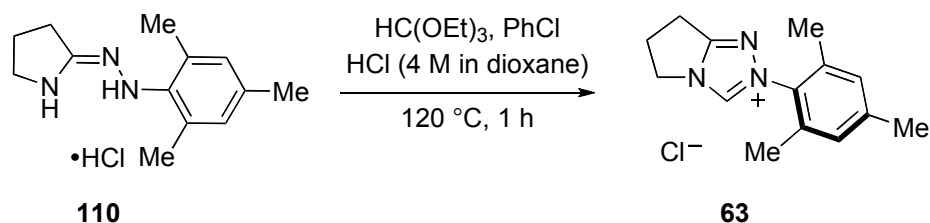
2-Mesityl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium chloride (63)

An oven-dried 350-mL sealed tube was charged with a magnetic stir bar, **110** (9.3 g, 37 mmol, 1.0 equiv), triethylorthoformate (50 mL, 370 mmol, 10 equiv), chlorobenzene (38 mL) and anhydrous HCl (4 M in 1,4-dioxane, 9.2 mL, 37 mmol, 1.0 equiv). The reaction vessel was purged with N$_2$(g), sealed, and placed in an oil bath. The suspension was stirred at 120 °C until all of starting material **110** had dissolved (*ca.* 1 h). The tan-colored solution was allowed to cool to ambient temperature, transferred to a 250-mL round-bottomed, and concentrated under reduced pressure to afford a crude brown foam. Recrystalization from toluene afforded the title compound (6.5 g, 67%) as a white powder. ^{1}H NMR (500 MHz, CDCl$_3$) δ 11.19 (s, 1H), 6.95 (s, 2H), 4.87 (t, 2H, J = 7.4 Hz), 3.21 (t, 2H, J = 7.8 Hz), 2.89–2.85 (m, 2H), 2.32 (s, 3H), 2.08 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 162.4, 143.0, 142.0, 135.1, 132.0, 129.8, 48.6, 27.0, 22.2, 21.3, 17.8; IR

(thin film) ν 2975, 1590, 1447, 1387, 1200, 974 cm⁻¹; HRMS (ESI) calcd for $C_{14}H_{18}N_3^+$ [M]⁺ 228.1495, found 228.1489 [M]⁺.
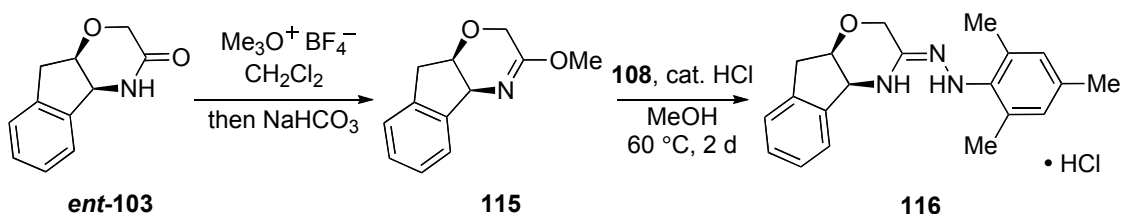
(Z)-2-Mesityl-1-((4aS,9aR)-4,4a,9,9a-tetrahydroindeno[2,1b][1,4]oxazin-3(2H)-ylid-ene)hydrazinium chloride (116)

A flame-dried 500-mL round-bottomed flask was charged with a magnetic stir bar, (4aS,9aR)-4,4a,9,9a-tetrahydroindeno[2,1-*b*][1,4]oxazin-3(2*H*)-one (**ent-103**)[1] (7.00 g, 37.0 mmol, 1.00 equiv), CH₂Cl₂ (185 mL) and trimethyloxonium tetrafluoroborate (6.57 g, 44.4 mmol, 1.20 equiv). The tan solution was stirred at ambient temperature under an atmosphere of N₂(g) or 16 h. The solution was cooled to 0 °C and quenched by the slow, portion-wise addition of sat aq NaHCO₃ (150 mL) over a period of 1.5 h; stirring was maintained for an additional 1 h. The biphasic solution was transferred to a separatory funnel, the organic phase separated, and the aqueous phase extracted with CH₂Cl₂ (3 x 100 mL). The combined organic fractions were dried over Na₂SO₄, filtered, and concentrated to afford the crude iminoether **115** (6.48 g, 86%) as a brown solid which was used without further purification. A flame-dried 500-mL round-bottomed flask was charged with a magnetic stir bar, 2-mesitylhydrazinium chloride (**108**) (6.44 g, 34.4 mmol, 1.00 equiv) and MeOH (138 mL) resulting in a light red/orange solution. To this solution was added (**115**) (7.00 g, 34.4 mmol, 1.00 equiv) and the stirred at ambient temperature until a deep red homogeneous solution was obtained (*ca.* 5 min). A catalytic amount of anhydrous HCl (4 M in 1,4-dioxane, 0.86 mL, 0.10 mmol) was added, the

reaction flask equipped with a water–jacketed condenser and the solution stirred at 60 °C under an atmosphere of N_2(g) for 48 h. The reaction was allowed to cool to ambient temperature and the concentrated under reduced pressure to afford a crude orange solid. The crude material was suspended in EtOAc (125 mL) and stirred vigorously in a at 90 °C under an atmosphere of N_2(g) for 30 min causing a light yellow precipitate to form. The suspension was allowed to cool to ambient temperature with vigorous stirring and immersed in an ice/water bath at 0 °C with vigorous stirring. The precipitate was collected by suction filtration and washed with EtOAc (3 x 20 mL) affording the title compound (10.0 g 81.3%) as a light yellow powder. ^{1}H NMR (500 MHz, d_6-DMSO) δ 11.29 (s, 1H), 11.06 (d, 1H, J= 3.1 Hz), 7.71–7.69 (m, 1H), 7.31–7.28 (m, 3H), 7.11 (s, 1H), 6.87 (s, 2H), 5.00 (t, 1H, J = 3.6 Hz), 4.72 (t, H, J = 4.4 Hz), 4.61 (d, 1H, J = 16.7 Hz), 4.52 (d, 1H, J = 16.7 Hz), 3.29 (dd, 1H, J = 16.9 Hz, 4.7 Hz), 2.97 (d, 1H, J = 16.9 Hz), 2.22 (s, 6H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 159.3, 140.2, 139.7, 138.3, 134.9, 133.8, 131.2, 129.4, 129.1, 128.2, 126.7, 124.9, 124.8, 77.0, 62.0, 60.1, 56.1, 37.1, 20.4 17.9; IR (KBr) ν 3294, 3119, 2997, 2966, 2951, 2918, 2731, 2692, 1676, 1514, 1483, 1335, 739 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{24}N_3O^+$ [M]$^+$ 322.1914, found 322.1912 [M]$^+$.
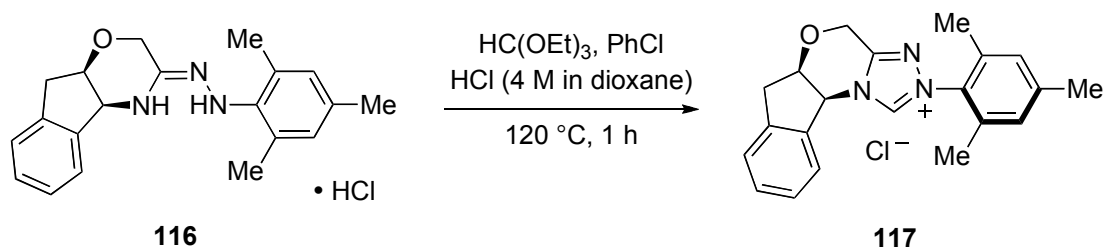
(5a*R*,10b*S*)-5a,10b-Dihydro-2-(2,4,6-trimethylphenyl)-4*H*,6*H*-indeno[2,1-b]-1,2,4-tria zolo[4,3-d]-1,4-oxazinium chloride (117)

An oven-dried 350-mL sealed tube was charged with a magnetic stir bar, **116** (9.00 g, 25.1 mmol, 1.00 equiv), triethylorthoformate (33.4 mL, 201 mmol, 8.0 equiv), chlorobenzene (25.5 mL) and anhydrous HCl (4 M in 1,4-dioxane, 6.28 mL, 25.1 mmol, 1.00 equiv). The reaction vessel was purged with $N_2(g)$, sealed, and placed in an oil bath. The suspension was stirred at 120 °C until all of starting material **116** had dissolved (*ca.* 1 h). The tan-colored solution was allowed to cool to ambient temperature, transferred to a 250-mL round-bottomed flask, and concentrated under reduced pressure to afford a crude brown foam. Recrystallization from toluene afforded the title compound (5.86 g, 63.5%) as a white powder. ^{1}H NMR (500 MHz, d_6-DMSO) δ: 11.28 (bs, 1H), 7.64 (s, 1H), 7.45–7.33 (m, 5H), 7.21 (s, 2H), 6.11 (s, 1H), 5.26 (d, 1H, *J* = 16.0 Hz), 5.08 (d, 1H, *J* = 16.0 Hz), 4.99 (t, 1H, *J* = 4.4 Hz), 3.50 (dd, 1H, *J* = 16.9, 4.8 Hz), 3.16 (d, 1H, *J* = 17.0 Hz), 2.37 (s, 3H), 2.12 (s, 6H); ^{13}C NMR (125 MHz, d_6-DMSO) δ: 150.2, 144.5, 141.5, 140.7, 136.1, 134.8, 131.2, 129.4, 127.3, 125.5, 123.9, 76.9, 61.2, 59.8, 37.0, 20.7, 17.0; IR (KBr) ν 2923, 2853, 1581, 1460, 1223, 1099 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{22}N_3O^+$ [M]$^+$ 332.1757, found 332.1760 [M]$^+$; [α]$_D^{20}$ = −129.4 (c 1.00, EtOH); Anal. Calcd for $C_{21}H_{22}ClN_3O$: C, 68.56; H, 6.03; N, 11.42. Found: C, 68.28; H, 6.20; N, 11.26.
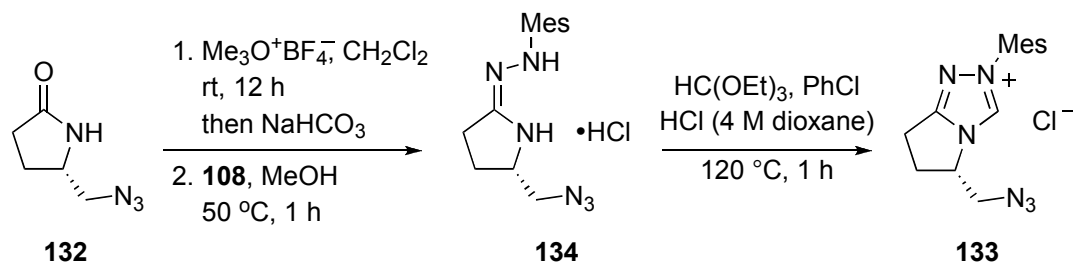
(*S*)-5-(Azidomethyl)-2-mesityl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium chloride (133)

A flame-dried 1-L round-bottomed flask was charged with a magnetic stir bar, **132**[2] (6.0 g, 43 mmol, 1.0 equiv), CH$_2$Cl$_2$ (300 mL) and trimethyloxonium tetrafluoroborate (7.0 g, 47 mmol, 1.1 equiv). The tan solution was stirred at ambient temperature under an atmosphere of N$_2$(g) for 17 h. The solution was cooled to 0 °C and quenched by the slow, portion-wise addition of sat aq NaHCO$_3$ (300 mL) over a period of 1.5 h; stirring was maintained for an additional 1 h. The biphasic solution was transferred to a separatory funnel, the organic phase separated, dried over Na$_2$SO$_4$, filtered, and concentrated to afford the crude iminoether (5.6 g, 85%) as a brown oil which was used without further purification. A flame-dried 500-mL round-bottomed flask was charged with the crude iminoether (5.5 g, 35 mmol, 1.0 equiv), a magnetic stir bar, 2-mesitylhydrazinium chloride (**108**) (6.6 g, 35 mmol, 1.0 equiv) and MeOH (140 mL) resulting in a deep red-orange solution that was stirred at 50 °C under an atmosphere of N$_2$(g) for 1 h. The reaction was allowed to cool to ambient temperature and the concentrated under reduced pressure to afford **134** as a crude orange solid. The crude material was suspended in EtOAc and placed in a sonicating bath. The light orange precipitate (recovered 2-mesitylhydrazinium hydrochloride **108**) was removed by suction filtration. The filtrate was concentrated under reduced pressure to afford crude **134** (8.7 g, 79%) as an orange foam. To the round-bottomed flask charged with crude **134** was added triethylorthoformate (38 mL, 280 mmol, 10 equiv), chlorobenzene (28 mL) and

anhydrous HCl (4 M in 1,4-dioxane, 7.0 mL, 28 mmol, 1.0 equiv). The reaction vessel was equipped with a water-jacketed condensor and stirred at 100 °C for 50 min under an atmosphere of N_2(g). The brown solution was allowed to cool to ambient temperature and concentrated under reduced pressure. The crude brown solid was purified by flash column chromatography (gradient, CH_2Cl_2/acetone, 10:1→5:1→2:1→1:1) to give the title compound (4.45 g, 50%) as a tan powder. ^{1}H NMR (500 MHz, d_6-DMSO) δ 10.77 (bd, 1H,), 7.16 (s, 2H), 5.03 (bs, 1H), 4.18–4.12 (bm, 1H), 3.95–3.94 (bm, 1H), 3.34–3.18 (m, 3H), 2.96–2.89 (m, 1H), 2.37 (s, 3H), 2.08 (s, 6H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 162.7, 141.8, 141.2, 134.8,131.9, 129.3, 59.5, 52.0, 30.0, 21.3, 20.7, 16.9; IR (KBr) ν 2919, 2108, 1586, 1442, 1388, 1331, 1290, 1037, 854 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}N_6^+$ [M]$^+$ 283.1666, found 283.1671 [M]$^+$.
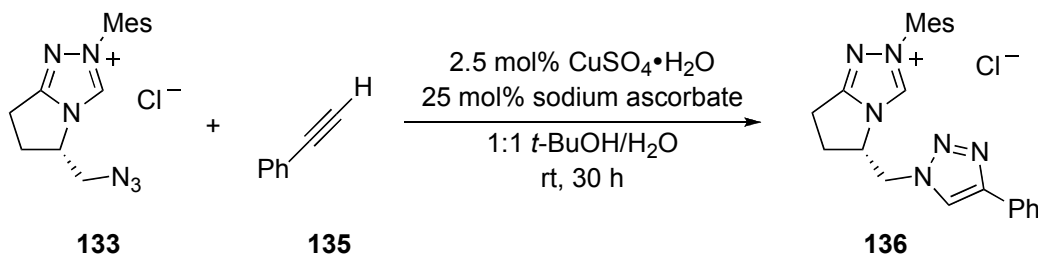
(S)-2-Mesityl-5-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium chloride (136)

An oven-dried 10-mL round-bottomed flask was charged **133** (0.25 g, 0.78 mmol, 1.0 equiv) and 1:1 t-BuOH/H_2O (3.1 mL). The reaction vessel was purged with N_2(g) and freshly prepared solutions of (+)-L-sodium ascorbate (1.0 M in Millipore H_2O, 0.19 mL, 0.19 mmol, 0.25 equiv) and $CuSO_4$ •5H_2O (0.30 M in Millipore H_2O, 0.0065 mL, 0.0019 mmol, 0.025 equiv) were added via syringe through a septum. Phenylacetylene **135** (0.094 mL, 0.86 mmol, 1.1 equiv) was added and the solution stirred at ambient temperature for 30 h. Removal of solvent under reduced pressure provided the crude

residue which was dissolved in H_2O (10 mL), transferred to a separatory funnel and extracted with $CHCl_3$ (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude solid was suspended in EtOAc and placed in a sonicating bath for approximately 10 min. The resultant precipitate was collected by suction filtration and washed with EtOAc to afford the title compound (0.18 g, 55%) as a tan powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.47 (s, 1H), 8.58 (s, 1H), 7.79 (d, 2H, J = 7.0 Hz), 7.40–7.30 (m, 5H), 6.92 (s, 2H), 5.95 (bd, 1H, J = 14.5 Hz), 5.04 (d, 1H, J = 14.0 Hz), 3.20–3.06 (m, 2H), 2.89–2.82 (m, 2H), 2.30 (s, 3H), 1.96 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 147.8, 142.9, 142.2, 135.0, 131.9, 129.9, 129.7, 129.0, 158.5, 125.8, 122.9, 60.0, 51.7, 30.8, 21.6, 21.8, 17.6; IR (thin film) ν 3053, 2976, 1587, 1440, 1386, 1203, 1040, 855 cm^{-1}; HRMS (ESI) calcd HRMS (ESI) calcd for $C_{23}H_{25}N_6^+$ [M]$^+$ 385.2135, found 385.2125 [M]$^+$.
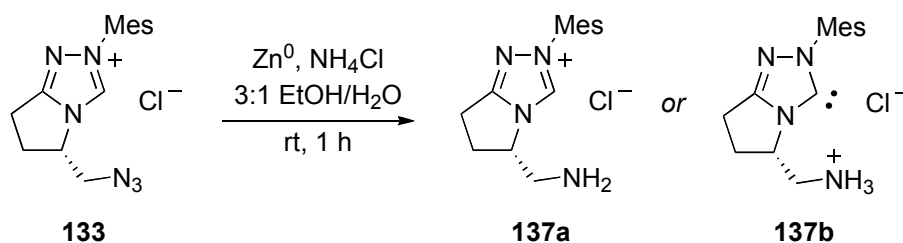
(S)-5-(Aminomethyl)-2-mesityl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium chloride (137a)

To a solution of **133** (3.18 g, 9.97 mmol, 1.00 equiv) in 200 proof EtOH/H_2O (3:1, 10 mL) was added NH_4Cl (0.847 g, 13.0 mmol, 1.30 equiv) and Zn^0 powder (1.39 g, 25.9 mmol, 2.3 equiv); vigorous stirring was maintained for 1 h at ambient temperature. DMSO (10 mL) was added and the insoluble solids were removed by suction filtration and washed with DMSO (5 mL). A magnetic stir bar was added to the filtrate and Et_2O (100 mL) was added with vigorous stirring resulting in the formation of an oil. In order to induce

precipitation, 200 proof EtOH (20 mL) was added with vigorous stirring. The heterogeneous mixture was placed in a sonicating bath until all traces of the initially formed oil had dissolved. The resultant precipitate was collected by suction filtration and washed with EtOAc affording the title compound (1.85 g, 63.6%) as a white powder. ^{1}H NMR (500 MHz, d$_6$-DMSO) δ 7.05 (s, 2H), 4.60 (q, 1H, J = 8.5 Hz), 3.36–3.14 (m, 2H), 3.06 (dd, 1H, J = 16.5, 9.0 Hz), 2.752–2.713 (m, 2H), 2.40–2.34 (shoulder m, 1H), 2.32 (s, 3H), 2.08 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (125 MHz, d$_6$-DMSO) δ 172.9, 160.0, 139.4, 135.4, 134.9, 128.7, 128.6, 57.0, 44.8, 31.7, 30.7, 21.2, 20.7, 17.2, 17.0; IR (KBr) ν 3434, 3330, 3252, 3049, 2992, 1588, 1402, 1234, 1134, 1023, cm^{-1}; HRMS (ESI) calcd for C$_{15}$H$_{21}$N$_4^+$ [M]$^+$ 257.1761, found 257.1746 [M]$^+$.
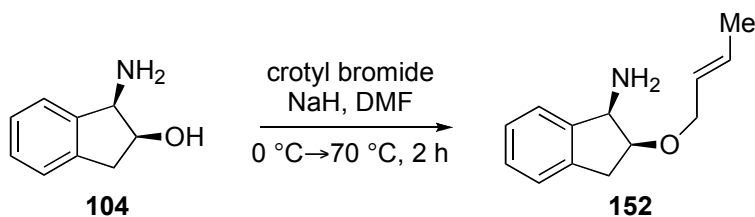
(1R,2S)-2-((E)-But-2-enyloxy)-2,3-dihydro-1H-inden-1-amine (152)

A flame-dried 500-mL round-bottomed flask equipped with a magnetic stir bar was charged with NaH (60 % oil dispersion, 960 mg, 24 mmol, 1.2 equiv). The NaH was washed with anhydrous pentane (1 x 50 mL) and the pentane removed via syringe. The flask was charged with THF (200 mL) and cooled to 0 °C. (1R, 2S)-(+)-1-amino-2-indanol **104** (3.0 g, 20 mmol, 1.0 equiv) was added in two portions 10 min apart. The suspension was stirred until H$_2$(g) evolution had ceased. The flask was equipped with a water-jacketed condenser and heated to 70 °C under N$_2$(g). A solution (66 v/v% in THF) of *trans*-crotyl bromide (85% purity, 2.7 mL, 22 mmol, 1.1 equiv) was added drop-wise over 90 min. The resulting blueish-purple solution was stirred for an additional 40 min at

which time it had turned light tan in color. The mixture was cooled to 0 °C and quenched

by the drop-wise addition of sat aq NH$_4$Cl. The resulting suspension was poured into a

separatory funnel and brine (250 mL) was added. The organic phase was separated and

the aqueous phase extracted with EtOAc (2 x 150 mL). The organic phases were com-

bined and dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The

resulting oil was dissolved in Et$_2$O (200 mL) and treated with HCl (4 M in 1,4-dioxane,

5.0 mL) at 0 °C. The white precipitate was collected by vacuum filtration and washed

with excess Et$_2$O to afford the HCl salt of compound **152** which was freebased with 1 N

NaOH and extracted with Et$_2$O. Concentration of the ethereal phase yielded the title

compound as a colorless oil (2.6 g, 64%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.38–7.36 (m,

1H), 7.22–7.19 (m, 3H), 5.76–5.71 (m, 1H), 5.64–5.59 (m, 1H), 4.27 (d, 1H, J = 5.4 Hz),

4.13 (dd, 1H, J = 10.8, 5.4 Hz), 4.08–4.0 (m, 2H), 3.02–2.98 (m, 1H), 1.72 (dd, 3H, J =

6.4, 1.4 Hz), 1.59 (br s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 144.9, 140.0, 129.6, 127.8,

127.0, 125.2, 124.5, 81.3, 70.6, 65.2, 58.4, 36.0, 17.9; IR (thin film) ν 3378, 3022, 2914,

2857, 1587, 1458, 1342, 1105, 966 cm^{-1}, HRMS (ESI) calcd for C$_{13}$H$_{18}$NO$_2$ [M]$^+$

203.1310, found 204.1403 [M+H]$^+$.
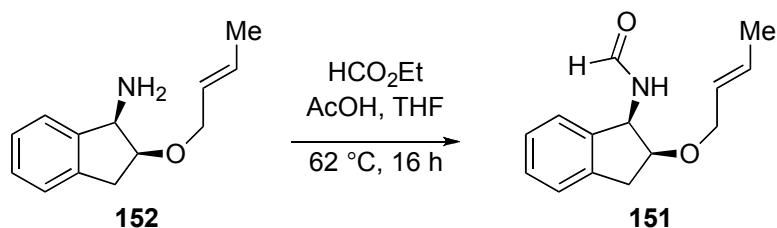
_N_-((1_R_,2_S_)-2-((_E_)-But-2-enyloxy)-2,3-dihydro-1_H_-inden-1-yl)formamide (151)

A 0.50 M solution of (1_R_,2_S_)-2-((_E_)-but-2-enyloxy)-2,3-dihydro-1_H_-inden-1-amine **152**

(5.2 g, 26 mmol, 1.00 equiv) in THF (50 mL) was treated with ethyl formate (16 mL, 200

mmol, 7.90 equiv) and catalytic glacial acetic acid (0.070 mL, 1.3 mmol, 0.05 equiv). The

flask was equipped with a water-jacketed condenser and the solution stirred in an oil bath operating with an external temperature of 62 °C under N_2(g) for 15 h. The solution was concentrated under reduced pressure and the resulting crude solid recrystallized from a 70:30 mixture of hexanes/EtOAc and collected by suction filtration in two crops to afford **151** as a white solid (5.2 g , 87%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.38 (s, 1H), 7.33–7.20 (m, 4H), 6.38 (bs, 1H), 5.73–5.58 (m, 1H), 5.57–5.51 (m, 2H), 4.32–4.30 (m, 1H), 4.05–4.01 (m, 1H), 3.96–3.92 (m, 1H), 3.08–3.0 (m, 2H), 1.70 (d, 2H, J = 6.3 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 161.3, 141.3, 139.8, 130.3, 128.4, 127.3, 127.3, 125.2, 124.8, 79.4, 70.6, 54.5, 36.7,18.0; IR (thin film) ν 3071, 3025, 2919, 2856, 1652, 1448, 1400 cm^{-1}; m.p. 69–72 °C; HRMS (ESI) calcd for $C_{14}H_{17}NO_2$ [M]$^+$ 231.1259, found 232.1434 [M+H]$^+$, 254.1153 [M+Na]$^+$.
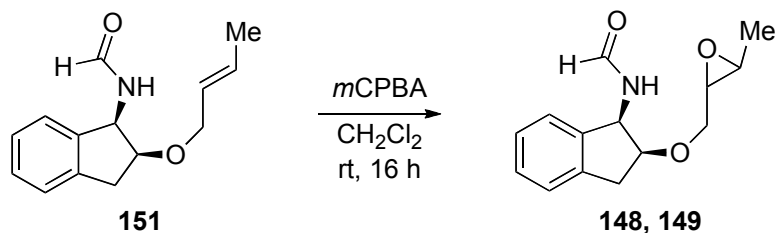
_N_-((1_R_,2_S_)-2-((3-methyloxiran-2-yl)methoxy)-2,3-dihydro-1_H_-inden-1-yl)formamide (148, 149)

To a 0.088 M solution of _N_-((1_R_,2_S_)-2-((_E_)-but-2-enyloxy)-2,3-dihydro-1_H_-inden-1-yl) formamide **151** (5.2 g, 22 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (250 mL) was added _m_CPBA (70–75 % purity, 28 g, 80 mmol, 4.0 equiv). The solution was stirred at ambient temperature until the starting material was consumed as visualized by TLC (_ca_. 12 h). The solution was diluted with CH$_2$Cl$_2$ (500 mL), washed with H$_2$O (1 x 1.0 L), 1 N NaOH(aq) (1 x 1.0 L), and again with H$_2$O (1 x 1.0 L). The organic phase was dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to a yellow oil which was purified by flash

column chromatography (gradient, hexanes/EtOAc, 1:1→1:1.5) to yield compounds **148** and **149** as a white solid as a 1:1 mixture of diastereomers (5.1 g, 91%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.34 (s, 1H), 7.30–7.19 (m, 4H), 6.56 (d, 1H), 5.61–5.56 (m, 1H), 4.34–4.27 (m, 1H), 3.81–3.78 (m, 1H), 3.58 (dd, 2H, J = 11.6, 5.2 Hz), 3.11–3.02 (m, 2H), 2.93–2.83 (m, 2H), 1.31–1.27 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.5, 141.0, 139.7, 128.3, 127.3, 125.2, 124.6, 81.4, 69.9, 58.1, 54.7, 52.2, 37.1, 17.4; IR (thin film) ν 3307, 3030, 2990, 2924, 2859, 1684, 1497, 1384, 1119, 1084 cm^{-1}; m.p. 77–79 °C; HRMS (ESI) calcd for C$_{14}$H$_{17}$NO$_3$ [M]$^+$ 247.1208, found 248.1370 [M+H]$^+$, 270.1107 [M+Na]$^+$.

151   **148, 149**
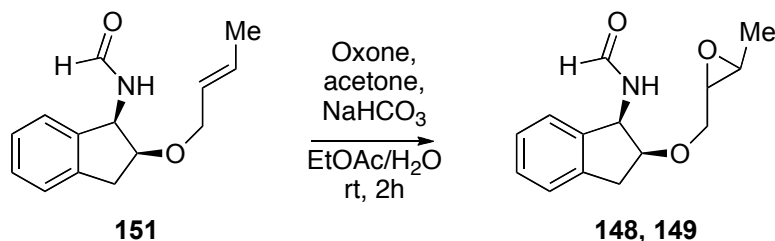
N-((1R,2S)-2-((3-Methyloxiran-2-yl)methoxy)-2,3-dihydro-1H-inden-1-yl)formamide (148, 149)

To a vigorously stirred mixture of NaHCO$_3$ (14.5 g, 171 mmol, 5.00 equiv), water (260 mL), EtOAc (170 mL), N-((1R,2S)-2-((E)-but-2-enyloxy)-2,3-dihydro-1H-inden-1-yl)form-amide **151** (8.00 g, 34.5 mmol, 1.00 equiv), and acetone (25.5 mL, 345 mmol, 10.0 equiv) in a 1-L round-bottomed flask was added dropwise a 0.235 M solution of Oxone® (42.5 g, 69.0 mmol, 2.00 equiv) in H$_2$O (250 mL) over 1 h. The biphasic mixture was stirred an additional 1 h at ambient temperature. The organic phase was separated and the aqueous phase extracted with EtOAc (500 mL). The combined organic phases were washed with brine (500 mL), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column

chromatography (gradient, hexanes/EtOAc, 50:50→40:60→30:70→20:80) to yield **148** and **149** as a white solid and as a 1:1 mixture of diastereomers (6.45 g, 81%).
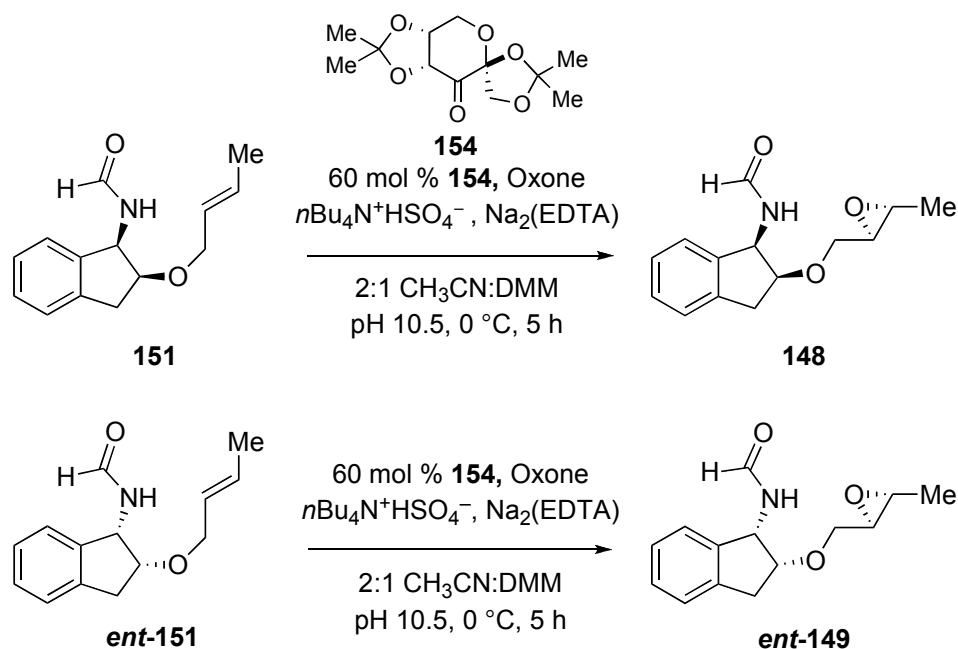
Representative Procedure for Shi Epoxidation:

N-((1R,2S)-2-(((2R,3R)-3-Methyloxiran-2-yl)methoxy)-2,3-dihydro-1H-inden-1-yl)for-mamide (148).

A 500-mL round-bottomed flask was charged with magnetic stir bar, N-((1R,2S)-2-((E)-but-2-enyloxy)-2,3-dihydro-1H-inden-1-yl)formamide **151** (2.31 g, 10.0 mmol, 1.0 eqiuv), the Shi catalyst derived from D-fructose **154** (0.775 g, 3.00 mmol, 0.300 equiv), tetrabutylammonium hydrogen sulfate (0.153 g, 0.450 mmol, 0.450 equiv), pH 10.5 buffer (100 mL) comprised of 0.050 M aqueous solution of $Na_2B_4O_7$ in a 0.40 mM aqueous solution of $Na_2(EDTA)$, and a mixture of CH_3CN/dimethoxymethane (1:2, 150 mL) and cooled to 0 °C. A solution of Oxone® (10.1 g, 16.5 mmol, 1.65 equiv) in 0.40 mM $Na_2(EDTA)$ (70 mL) was added via syringe pump over 2.5 h; simultaneously a

1.0 M solution of K_2CO_3 (70 mL) was added in small portions. After half of the addition was complete another portion of Shi catalyst (0.775 g, 3.00 mmol, 0.300 equiv) was added. Once the addition was complete, the biphasic mixture was allowed to stir at 0 °C for an additional 2.5 h. Water was added (500 mL) and the mixture was extracted with CH_2Cl_2 (4 x 150 mL). The combined organic phases were washed with H_2O (1 x 150 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a colorless oil. Purification by flash column chromatography (gradient, hexanes/acetone, 3:1→2:1→1:1) afforded **148** and **149** as a white solid and as a 5:1 mixture of diastereomers (2.24 g, 91%). Recrystallization (hexanes/EtOAc, 1:1) afforded diastereomerically pure **148**. Epoxide **ent-149** was prepared in an analogous manner from formamide **ent-151** (80%).

148: ^1H NMR (500 MHz, d_4-methanol) δ 8.25 (s, 1H), 7.25–7.19 (m, 4H), 5.47 (d, 1H, J = 5.4 Hz), 4.32 (dd, 1H, J = 9.9, 4.4 Hz), 3.81 (dd, 1H, J = 11.6, 2.8 Hz), 3.47 (dd, 1H, J = 11.6, 5.8 Hz), 3.07 (d, 2H, J = 4.4 Hz), 2.92–2.88 (m, 2H), 1.27 (d, 3H, J = 5.2 Hz); ^{13}C NMR (125 MHz, d_4-methanol) δ 163.8, 142.1, 141.4, 129.2, 128.0, 126.0, 125.2, 82.4, 71.2, 59.3, 55.7, 53.3, 37.5, 37.5, 17.4; IR (thin film) ν 322.66, 3059, 2997, 2919, 2868, 1653, 1544, 1382, 1082, 864, 727 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{17}NO_3$ $[M]^+$ 247.1208, found 248.1282 (M+H), 270.1097 (M+Na).

ent-149: ^1H NMR (500 MHz, d_4-methanol) δ 8.25 (s, 1H), 7.25–7.20 (m, 4H), 5.48 (d, 1H, J = 5.4 Hz), 4.33 (dd, 1H, J = 9.8, 4.4 Hz), 3.80 (dd, 1H, J = 11.5, 3.1 Hz), 3.45 (dd, 1H, J = 11.5, 6.0 Hz), 3.06 (d, 2H, J = 4.3 Hz), 2.94–2.87 (m, 2H), 1.28 (d, 3H, J = 5.2 Hz); ^{13}C NMR (125 MHz, d_4-methanol) δ 163.8, 142.1, 141.4, 129.2, 128.0, 126.0, 125.2, 82.2, 71.1, 59.2, 55.7, 53.3, 37.4, 17.4; IR (thin film) ν 3260, 3048, 2919, 2868, 1650, 1544, 1382, 1082, 858, 727 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{17}NO_3$ $[M]^+$ 247.1208, found 248.1247 $[M+H]^+$, 270.1104 $[M+Na]^+$.

148, 149 → NaH, DMF, 0 °C, 2 h → **152, 153**
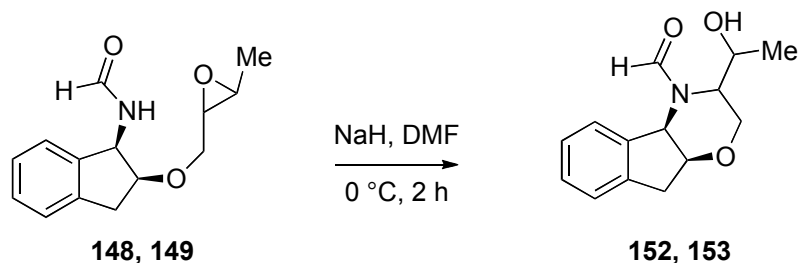
(4a*R*,9a*S*)-3-(1-hydroxyethyl)-2,3,9,9a-tetrahydroindeno[2,1-*b*][1,4]oxazine-4(4a*H*)-carbaldehyde (152, 153)

A flame-dried 1-L round-bottomed flask equipped with a magnetic stir bar was charged with NaH (60% oil dispersion, 15.2 g, 380 mmol, 10.0 equiv). The NaH was washed with anhydrous pentane (120 mL), and the pentane removed via syringe. The flask was charged with DMF (500 mL) and cooled to 0 °C. A 1.0 M solution of **148** and **149** (9.90 g, 40.0 mmol, 1.00 equiv) in DMF (40 mL) was added drop-wise over 80 min and stirred for an additional 30 min during which time it had turned blue in color. The mixture was slowly quenched with ice-cold sat aq NH₄Cl. The majority of DMF was removed under reduced pressure and the resultant oil diluted with EtOAc (400 mL) and H₂O (300 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (2 x 300 mL). The combined organic phases were washed with brine (2 x 500 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to a red oil which was purified by flash column chromatography (gradient, CH₂Cl₂/acetone, 6:1→4:1→2:1) to yield compounds **152** and **153** as an inseparable complex mixture of diastereomers and amide rotamers as an orange solid (5.0 g, 52%). IR (thin film) ν 3408, 3071, 3046, 3024, 2975, 2911, 1651, 1410, 1273, 1106, 1077 cm⁻¹; HRMS (ESI) calcd for $C_{14}H_{17}NO_3$ [M]⁺ 247.1208, found 248.1208 [M+H]⁺.

146
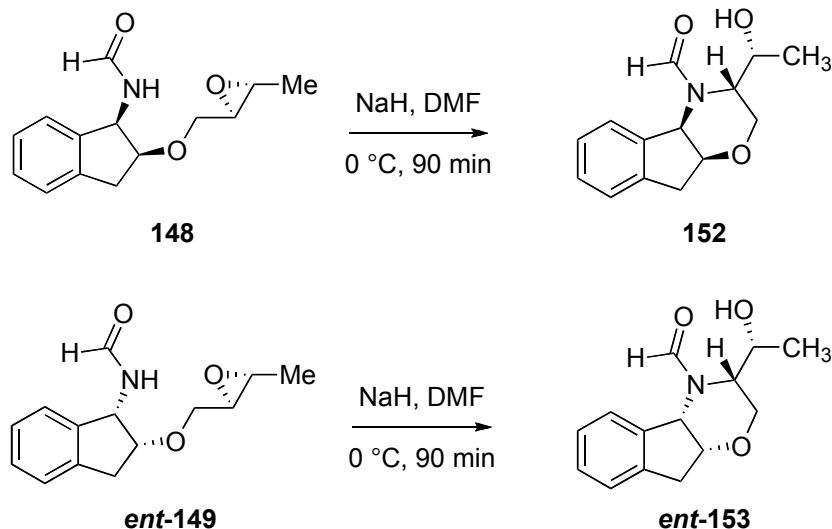
(3S,4aR,9aS)-3-((R)-1-Hydroxyethyl)-2,3,9,9a-tetrahydroindeno[2,1-b][1,4]oxazine-4 (4aH)-carbaldehyde (152)

A flame-dried 50-mL round-bottomed flask equipped with a magnetic stir bar was charged with NaH (60% oil dispersion, 1.23 g, 30.8 mmol, 10.0 equiv). The NaH was washed with anhydrous pentane (7.0 mL). The flask was charged with DMF (38.0 mL) and cooled to 0 °C. A 0.16 M solution of *N*-((1*R*,2*S*)-2-((3-methyloxiran-2-yl)methoxy)-2,3-dihydro- 1*H*-inden-1-yl)formamide **148** (762 mg, 3.08 mmol, 1.00 equiv) in DMF (28 mL) was added drop-wise over 75 min. The mixture was stirred for an additional 25 min during which time it had turned blue in color. The mixture was slowly poured over ice-cold sat aq NH₄Cl (250 mL). Brine was added (1.0 L) and the solution was extracted with EtOAc (5 x 100 mL). The combined organic phases were washed with brine (2 x 1 L), dried over MgSO₄, filtered, and concentrated under reduced pressure to a yellow oil which was purified by flash column chromatography (gradient, CH₂Cl₂/acetone, 8:1→4:1→2:1→1:1) to yield **152** as a white solid as a ~3:1 mixture of rotamers (564 mg, 74%). Alcohol *ent*-**153** was prepared as ~1.5:1 mixture of rotamers in an analogous manner from epoxide *ent*-**149** (76%).

147

152: ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.84* (s, 1H), 8.21 (s, 1H), 7.34–7.20 (m, 4H), 7.34–7.10* (m, 4H), 5.87* (d, 1H, J = 3.9 Hz), 4.92 (d, 1H, J = 4.5 Hz), 4.53–4.47 (m, 2H), 4.53–4.47* (m, 2H), 4.46* (dd, 1H, J = 4.6, 1.5 Hz); 4.21 (d, 1H, J = 5.7 Hz), 3.89 (dd, 1H, J = 12.0, 3.3 Hz), 3.85* (d, 1H, J = 2.5 Hz), 3.74 (dd, 1H, J = 12.0, 9.0 Hz), 3.63* (dd, 1H, J = 11.5, 10.9 Hz), 3.57–3.54 (m, 1H), 3.25–3.22* (m, 1H), 3.07–3.04 (m, 12H), 2.95* (d, 1H, J = 2.6 Hz), 2.51* (d, 1H, 3.9 Hz), 1.78* (s, 1H), 1.31* (d, 3H, J = 6.5 Hz), 1.23 (d, 3H, J = 6.8 Hz); ^{13}C NMR (500 MHz, CDCl$_3$) δ 163.4, 162.0, 141.1, 141.0, 138.8, 137.2, 129.2, 128.0, 127.5, 127.1, 126.1, 125.6, 124.2, 123.4, 78.0, 77.7, 65.5, 65.2, 64.4, 64.3, 61.9, 58.9, 57.4, 56.4, 38.5, 37.1, 21.2, 19.5; IR (thin film) ν 3422, 2975, 2908, 1639, 1273, 1105, 1074, 1032, 738 cm^{-1}; HRMS (ESI) calcd for C$_{14}$H$_{17}$NO$_3$ [M]$^+$ 247.1208, found 248.1325 (M+H).

ent-**153**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.40* (s, 1H), 8.33 (s, 1H), 7.31–7.15* (m, 4H), 7.31–7.15 (m, 4H), 5.56 (d, 1H, J = 4.5 Hz), 4.82* (d, 1H, 4.3 Hz), 4.37* (t, 1H, J = 4.3 Hz), 4.33–4.29* (m, 1H), 4.33–4.29 (m, 1H), 4.25 (d, 1H, J = 12.0 Hz), 4.02* (dd, 1H, J = 9.2, 2.8 Hz), 3.53 (dd, 1H, J = 12.0, 2.9 Hz), 3.48–3.40* (m, 2H), 3.48–3.40 (m, 2H), 3.15–3.09* (m, 2H), 3.15–3.09 (m, 2H), 3.06–2.99 (m, 1H), 2.13 (d, 1H, J = 4.9 Hz), 1.82* (d, 1H, J = 5.5 Hz), 1.19* (d, 3H, J = 6.0 Hz), 1.17 (d, 3H, J = 6.2 Hz); ^{13}C NMR (500 MHz, CDCl$_3$) δ 163.8, 163.6, 140.1, 140.1, 139.9, 128.7, 128.1, 127.2, 127.0, 125.7, 125.3, 124.4, 123.6, 78.0, 77.8, 65.6, 64.9, 64.6, 64.4, 60.4, 59.3, 55.7, 53.7, 38.4, 38.2, 20.9, 20.4; IR (thin film) ν 3417, 2980, 2913, 1659, 1412, 1269, 1110, 1077, 1032, 912, 727 cm^{-1}; HRMS (ESI) calcd for C$_{14}$H$_{17}$NO$_3$ [M]$^+$ 247.1208, found 248.1316 [M+H]$^+$.

152, 153 → Dess-Martin, CH$_2$Cl$_2$, rt, 3 h → **146** + **147**
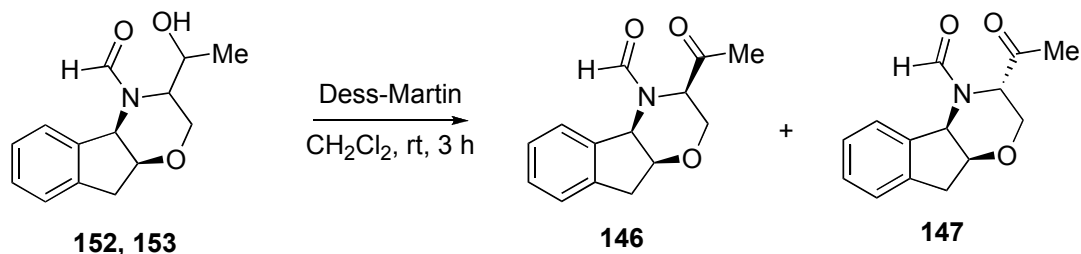
(4a*R*,9a*S*)-3-Acetyl-2,3,9,9a-tetrahydroindeno[2,1-*b*][1,4]oxazine-4(4a*H*)-carb-aldehyde (146, 147)

A 0.50 M solution of **152** and **153** (3.73 g, 15.1 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (30.0 mL) was added to a suspension of Dess-Martin periodinane (8.40 g, 22.5 mmol, 1.50 equiv) in CH$_2$Cl$_2$ (115 mL). The solution was stirred at ambient temperature until all the starting material was consumed as visualized by TLC (*ca*. 3 h). The solution was diluted with CH$_2$Cl$_2$, washed with 1N NaOH (1 x 150 mL), H$_2$O (2 x 225 mL), and brine (150 mL). The solution was filtered through Celite, dried over Na$_2$SO$_4$, and concentrated under reduced pressure to afford a crude solid which was purified by flash column chromatography (hexanes/acetone, 3:2) to give the ketones as a set of diastereomer **146** and its amide rotamer and diastereomer **147** as tan solid (3.25 g, 88%). The diastereomers could be separated by flash column chromatography.

146: ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.37 (s, 1H), 7.30–7.20 (m, 4H), 5.05 (d, 1H, *J* = 4.6 Hz), 4.58 (q, 1H, *J* = 4.5 Hz), 4.30 (dd, 1H, *J* = 7.4, 4.3 Hz), 3.90 (dd, 1H, *J* = 4.3, 12.0 Hz), 3.78 (dd, 1H, *J* = 12.0, 7.4 Hz), 3.12 (d, 2H, *J* = 4.0 Hz), 1.61 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 203.0, 163.5, 140.7, 138.6, 129.3, 127.6, 126.1, 124.1, 77.8, 64.4, 59.0, 58.0, 36.9, 28.4; IR (thin film) ν 3074, 3018, 2908, 2864, 1721, 1675, 1400, 1218 cm^{-1}; m.p. 174–176 °C; HRMS (ESI) calcd for C$_{14}$H$_{15}$NO$_3$ [M]$^+$ 245.1052, found 246.1096 [M+H]$^+$, 268.0970 [M+Na]$^+$.

147: ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.57 (s, 1H), 8.39* (s, 1H), 7.34–7.18 (m, 4H), 7.32–7.18* (m, 4H), 5.58* (d, 1H, *J* = 4.1 Hz), 4.96 (d, 1H, *J* = 4.2 Hz), 4.71 (d, 1H, *J* = 3.3

Hz), 4.44* (d, 1H, J = 3.4 Hz), 4.42–4.40 (m, 2H), 4.32* (t, 1H, J = 4.5 Hz), 3.83–3.78*

(m, 2H), 3.61 (dd, 1H, J = 12.2, 4.0 Hz), 3.13–3.12* (m, 1H), 3.10–3.09 (m, 1H), 3.02 (d,

1H, J = 16.9 Hz), 2.98* (d, 1H, J =16.9 Hz), 2.08 (s, 3H), 2.00* (s, 3H); IR (thin film) ν

2906, 1724, 1673, 1460, 1402, 1357, 1105, 1044 cm^{-1}; ^{13}C NMR (500 MHz, CDCl$_3$) δ

204.8, 203.1, 164.7, 163.7, 140.1, 140.0, 138.3, 138.1, 128.5, 128.1, 126.9, 126.8,

126.6, 126.5, 125.5, 125.0, 124.9, 78.2, 78.1, 65.3, 64.2, 65.3, 64.2, 60.2, 56.6, 56.2,

38.3, 38.1, 27.3, 27.3; HRMS (ESI) calcd for C$_{14}$H$_{15}$NO$_3$ [M]$^+$ 245.1052, found 246.1113

(M+H), 268.0951 (M+Na).
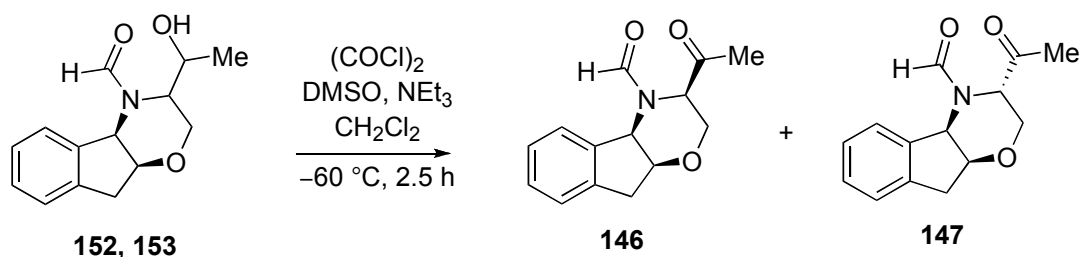
(4aR,9aS)-3-Acetyl-2,3,9,9a-tetrahydroindeno[2,1-b][1,4]oxazine-4(4aH)-carbalde-

hyde (146, 147)

To a 0.256 M solution of oxalyl chloride (6.70 mL, 76.8 mmol, 2.50 equiv) in CH$_2$Cl$_2$ (300

mL) cooled to –60 °C, was slowly added a 1.50 M solution of DMSO (13.6 mL, 192

mmol, 5.00 equiv) in CH$_2$Cl$_2$ (128 mL). Next, a 1.00 M solution of (4aR,9aS)-3-

(1-hydroxyethyl)-2,3,9,9a-tetrahydroindeno[2,1-b][1,4]oxazine-4(4aH)-carbaldehyde

(9.50 g, 38.4   mmol, 1.00 equiv) in CH$_2$Cl$_2$ (38.4 mL) was added portion-wise over 30

min. The solution was allowed to warm to –20 °C and stirred 1 h. The solution was

cooled to –60 °C, NEt$_3$ (53.2 mL, 384, mmol, 10.0 equiv) was added drop-wise over 30

min, and stirring was continued for 30 min before allowing the solution to warm to

ambient temperature. A white precipitate was collected and the filtrate washed with H$_2$O

(2 x 500 mL). The combined aqueous phases were extracted with CH$_2$Cl$_2$ (2 x 500 mL);

the combined organic phases were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient, CH$_2$Cl$_2$/acetone, 20:1→10:1→5:1→2:1) to yield a mixture of **146** and **147** as white solids (8.2 g, 87%).

146, 147   Ac$_2$O, HClO$_4$ 0 °C→rt, 2 h   **159**
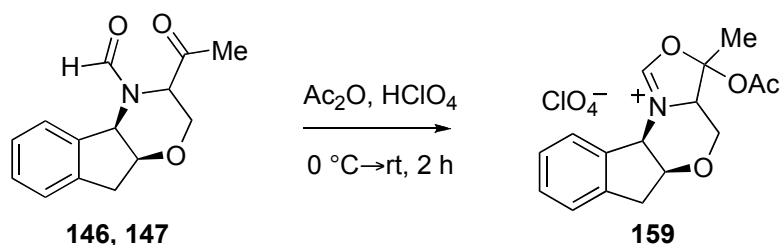
Conversion of *N*-Formyl Ketones 146 or 147 to Oxazolinium Salt 159.

To an oven-dried 25-mL round-bottomed flask equipped with a magnetic stir bar and charged with a mixture of ketones **146** and **147** (245 mg, 1.00 mmol, 1.00 equiv) was added Ac$_2$O (1.5 mL, 16 mmol, 16 equiv). The mixture was cooled to 0 °C and HClO$_4$ (70%, 0.10 mL, 1.2 mmol, 1.2 equiv; or 60%, 0.12 mL, 1.2 mmol, 1.2 equiv) was added drop-wise over 20 min. The light brown solution was allowed to warm to ambient temperature and stirred for 2–3 h. The solution was twice triturated with Et$_2$O and the supernatant decanted each time. Residual solvent was removed from the resulting white solid under reduced pressure at ambient temperature to afford the crude oxazolinium salt **159** as a tan foam (388 mg, quant.), which was immediately used in the subsequent conversion to the imidazolium salts.
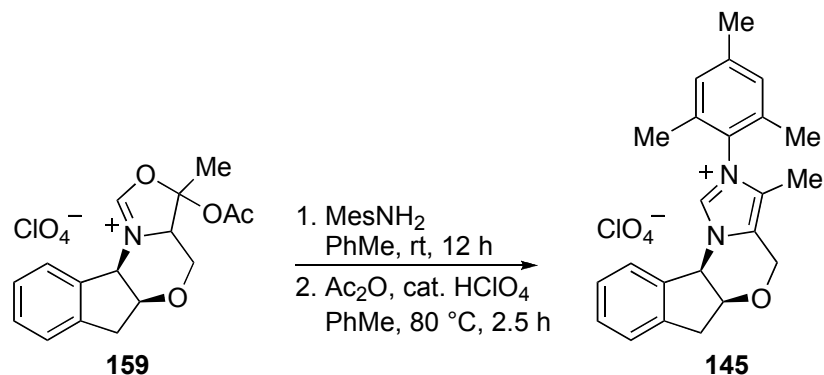
Preparation of *N*-Mesityl substituted imidazolium salt (145)

To a round-bottomed flask charged with a magnetic stir bar and oxazolinium salt **159** (700 mg, 1.8 mmol, 1.0 equiv) was added toluene (10 mL) and 2,4,6-trimethyl aniline (0.38 mL, 2.7 mmol, 1.5 equiv). The heterogeneous mixture was stirred at ambient temperature for 3 h. The solvent was decanted and the precipitate washed with Et₂O (2 x 10 mL). Residual solvent was removed under reduced pressure to afford the aminal intermediate as a light white solid and as a mixture of diastereomers (835 mg, quant.). A mixture of the aminal intermediate (98 mg, 0.21 mmol, 1.0 equiv) in toluene (1.0 mL) was treated with Ac₂O (0.40 μL, 0.42 mmol, 2.0 equiv) and HClO₄ (70%, 7.0 μL, 0.082 mmol, 0.20 equiv) and stirred at 80 °C for 2.5 h. The solution was allowed to cool to ambient temperature and concentrated under reduced pressure. The crude solid was suspended in Et₂O and placed in a sonicating bath. Once the precipitate had become white it was collected by suction filtration and washed with EtOAc to yield **145** (73 mg, 78% over 3 steps). ^{1}H NMR (500 MHz, d₆-acetone) δ 9.71 (s, 1H), 7.64 (d, 1H, *J* = 7.6 Hz), 7.44 (d, 2H, *J* = 7.4 Hz), 7.40 (t, 1H, *J* = 7.4 Hz), 7.22 (s, 2H), 6.10 (d, 1H, *J* = 4.0 Hz), 5.11 (d, 1H, *J* = 15.0 Hz), 5.06 (t, 1H, *J* = 4.5 Hz), 4.98 (d, 1H, *J* = 15.0 Hz), 3.49 (dd, 1H, *J* = 17.0, 4.8 Hz), 3.23 (d, 1H, *J* = 17.0 Hz), 2.40 (s, 3H), 2.14 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, d₆-acetone) δ 141.9, 141.5, 137.8, 136.0, 135.9, 135.2, 130.3, 130.2, 129.8, 129.6, 127.8, 126.2, 125.8, 125.2, 124.0, 78.0, 61.4, 60.0,

38.0, 20.8, 17.1, 7.6; IR (thin film) ν 3122, 3047, 2925, 2860, 1539, 1461, 1214, 1097 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{25}N_2O^+$ [M]$^+$ 345.1961, found 345.1931 [M]$^+$; $[\alpha]_D^{20}$ = −134.0 (c 0.55, CH_2Cl_2).

1. Ac$_2$O, HClO$_4$
2. Mes–NH$_2$
   PhMe/CH$_2$Cl$_2$
   rt, 12h

3. Ac$_2$O, cat. HClO$_4$
   ClCH$_2$CH$_2$Cl
   70 °C, 6 h

146, 147

145
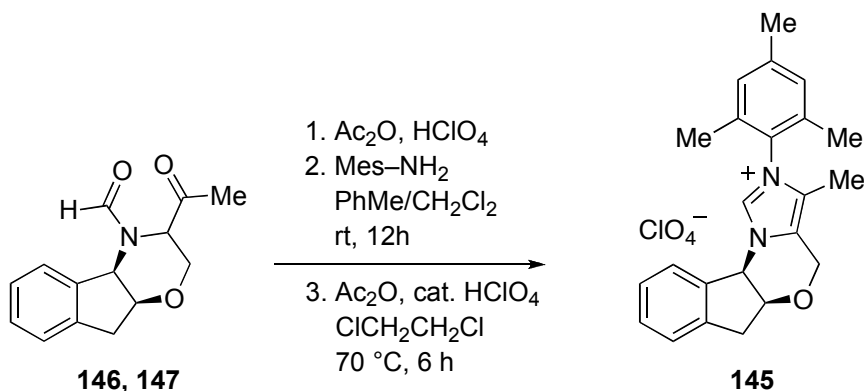
Procedure for Multi-Gram Synthesis of *N*-Mesityl substituted imidazolium salt (145)

To an oven-dried 100-mL Schlenk flask equipped with a magnetic stir bar and charged with ketones **146** and **147** (5.0 g, 20 mmol, 1.0 equiv) was added Ac$_2$O (30 mL, 326 mmol, 16 equiv). The mixture was cooled to 0 °C and HClO$_4$ (60 %, 2.6 mL, 25 mmol, 1.2 equiv.) was added drop-wise over 20 min. The brown solution was allowed to warm to ambient temperature and then stirred for 2 h. The solution was twice triturated with Et$_2$O and the supernatant decanted each time. The resulting white solid was dried under reduced pressure, dissolved in a minimal amount of CH$_2$Cl$_2$ before 1 volume equivalent of toluene was added. Next, 2,4,6-trimethyl aniline (32 mL, 31 mmol, 1.5 equiv) was added and the solution stirred overnight. The brown solution was concentrated under reduced pressure to an oil. The oil was dissolved in a minimal amount of CH$_2$Cl$_2$ and triturated with Et$_2$O in a sonicating bath. The white precipitate was collected by suction filtration and washed with excess Et$_2$O to give the aminal intermediate as a white solid

and as a mixture of diastereomers (5.9 g, 63 %). This white solid (5.9 g, 13 mmol, 1.0 equiv) was transferred to an oven-dried 200 mL round-bottomed flask equipped with a magnetic stir bar and dissolved in 85 mL of 1,2-dichloroethane (0.15 M). Next, Ac$_2$O (2.4 mL, 25 mmol, 2.0 equiv) and HClO$_4$ (60 %, 0.26 mL, 2.5 mmol, 0.20 equiv) were added and the solution stirred at 70 °C. The reaction was monitored by ^{1}H NMR analysis of aliquots from the reaction. After 4 h, another 0.26 mL of HClO$_4$ was added in order to drive the reaction to completion. The reaction was complete as indicated from NMR after an additional 2 h of stirring. The solution was allowed to cool to ambient temperature and concentrated under reduced pressure. The resulting oil was dissolved in a minimal amount of CH$_2$Cl$_2$ and triturated with Et$_2$O in a sonicating bath. The precipitate was collected by suction filtration to afford **145** as a white crystalline solid (4.6 g, 81%; 51% over three steps).
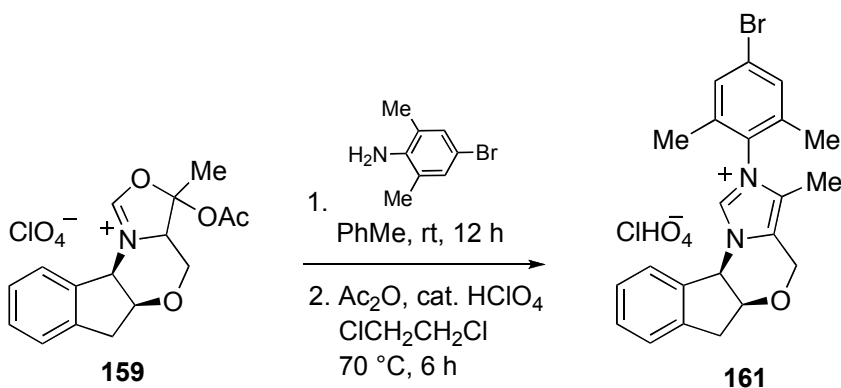
Preparation of *N*-2,6-dimethyl-4-bromophenyl substituted imidazolium salt (161)

To a round-bottomed flask charged with a magnetic stir bar and oxazolinium salt **159** (388 mg, 1.00 mmol, 1.00 equiv) was added toluene (10 mL) and 4-bromo-2,6-dimethyl aniline (300 mg, 1.50 mmol, 1.50 equiv). The heterogeneous mixture was stirred at ambient temperature for 13 h. The precipitate was collected by suction filtration and washed with Et$_2$O to afford the crude aminal intermediate as a white powder and as a

mixture of diastereomers (300 mg, 57%). A 0.25 M solution of the aminal intermediate

(200 mg, 0.38 mmol, 1.0 equiv) in 1,2-dichloroethane (1.5 mL) was treated with Ac_2O

(0.070 mL, 0.76 mmol, 2.0 equiv) and $HClO_4$ (70%, 6.0 µL, 0.080 mmol, 0.20 equiv) and

stirred at 70 °C for 3 h. The solution was allowed to cool to ambient temperature and a

precipitate collected by suction filtration and washed with 1,2-dichloroethane to afford

161 as a yellow solid (170 mg, 89%; 51% over 3 steps). ^1H NMR (400 MHz, d_6-acetone)

δ 9.78 (s, 1H), 7.65–7.63 (m, 3H), 7.44 (d, 1H, J = 7.4 Hz), 7.40 (t, 1H, J = 7.3 Hz), 7.33

(t, 1H, J = 7.4 Hz), 6.10 (d, 1H, J = 3.7 Hz), 5.13 (d, 1H, J = 15.0 Hz), 5.06 (t, 1H, J = 4.3

Hz), 4.98 (d, 1H, J = 15.0 Hz), 3.49 (dd, 1H, J = 16.9, 4.8 Hz), 3.23 (d, 1H, J = 17.0 Hz),

2.21 (s, 3H), 2.13 (s, 6H); ^{13}C NMR (100 MHz, d_6-acetone) δ 141.8, 139.4, 138.1, 132.8,

132.6, 131.9,130.1, 128.2, 126.5, 125.9, 125.8, 125.4, 124.3, 78.3, 61.8, 60.3, 38.3,

17.4, 7.9; IR (thin film) ν 3115, 3042, 2913, 2852, 1533, 1460, 1203, 1099, 858, 747

cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{24}BrN_2O^+$ $[M]^+$ 409.0910, found 409.0914 $[M]^+$; $[\alpha]_D^{20}$ =

−109.8 (c 0.25, CH_2Cl_2).
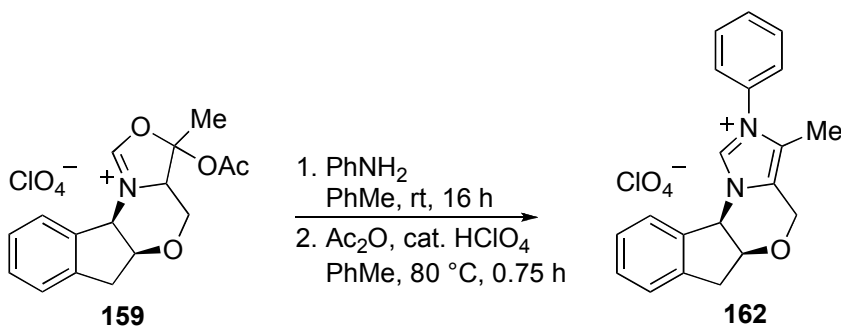
Preparation of *N*-Phenyl substituted imidazolium salt (162)

To a round-bottomed flask charged with a magnetic stir bar and oxazolinium salt **159**

(388 mg, 1.00 mmol, 1.00 equiv) was added toluene (5.0 mL) and aniline (0.13 mL, 1.5

mmol, 1.5 equiv). The heterogeneous mixture was stirred at ambient temperature for 16

h. The solution was decanted, the remaining oil washed with Et$_2$O (2 x 10 mL), and excess solvent removed under reduced pressure to afford the crude aminal intermediate as a brown foam and as a mixture of diastereomers (420 mg, quant crude yield). A suspension of the aminal intermediate (420 mg, 1.0 mmol, 1.0 equiv) in toluene (4.0 mL) was treated with Ac$_2$O (0.19 mL, 2.0 mmol, 2.0 equiv) and HClO$_4$ (70%, 17 μL, 0.20 mmol, 0.20 equiv). The mixture was stirred at 80 °C for 45 min. After allowing the reaction to cool to ambient temperature the supernatant was decanted, the excess solvent removed under reduced pressure, and the resulting residue triturated with Et$_2$O in a sonicating bath to afford 135 mg of **162** as a brown solid. The filtrate was then purified by flash column chromatography (gradient, CH$_2$Cl$_2$/acetone, 19:1→9:1) to afford another 145 mg of **162** as an off-white powder (230 mg, 70% over 3 steps). ^{1}H NMR (500 MHz, d$_6$-acetone) δ 9.77 (s, 1H), 7.79–7.72 (m, 5H), 7.67 (d, 1H, J = 7.6 Hz), 7.41 (d, 1H, J = 7.4 Hz), 7.38 (t, 1H, J = 7.4 Hz), 7.30 (t, 1H, J = 7.4 Hz), 5.99 (d, 1H, J = 4.1 Hz), 5.08 (d, 1H, J = 15.1 Hz), 4.99 (t, 1H, J = 4.5 Hz), 4.95 (d, 1H, J = 15.0 Hz), 3.47 (dd, 1H, J = 16.9, 4.8 Hz), 3.21 (d, 1H, J = 16.9 Hz), 2.23 (s, 3H); ^{13}C NMR (125 MHz, d$_6$-acetone) δ 141.7, 137.8, 135.6, 134.5, 131.7, 131.0, 130.0, 127.9, 127.4, 126.3, 126.1, 125.0, 124.7, 78.3, 61.5, 60.2, 38.2, 8.6; IR (thin film) ν 3121, 3059, 2928, 1545, 1460, 1217, 1094, 774 cm^{-1}; HRMS (ESI) calcd for C$_{20}$H$_{19}$N$_2$O$^+$ [M]$^+$ 303.1492, found 303.1502 [M]$^+$; [α]$_D^{20}$ = −177.4 (c 0.19, CH$_2$Cl$_2$).
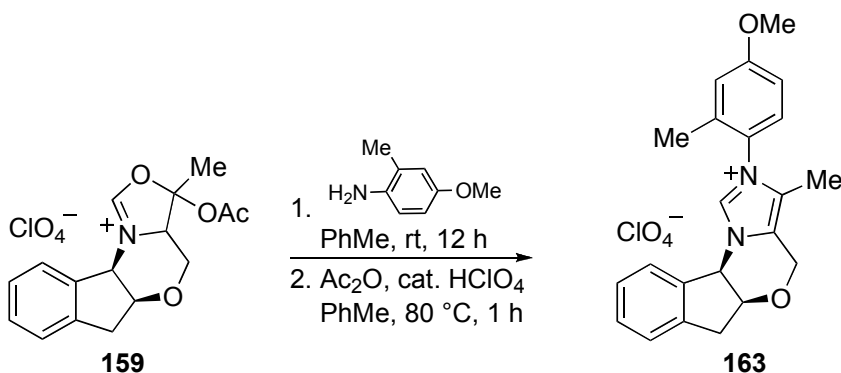
Preparation of *N*-2-methyl-4-methoxyphenyl substituted imidazolium salt (163)

To a round-bottomed flask charged with a magnetic stir bar and oxazolinium salt **159** (388 mg, 1.00 mmol, 1.00 equiv) was added toluene (5.0 mL) and 4-methoxy-2-methylaniline (0.20 mL, 1.5 mmol, 1.5 equiv). The heterogeneous mixture was stirred at ambient temperature for 12 h. The supernatant was decanted, the crude oil washed with Et₂O (2 x 10 mL), and residual solvent removed under reduced pressure to afford the crude aminal intermediate as a light purple solid and as mixture of diastereomers (430 mg, 92% yield). A suspension of the crude aminal intermediate (430 mg, 0.92 mmol, 1.0 equiv) in toluene (4.0 mL) was treated with Ac₂O (0.18 mL, 1.8 mmol, 2.0 equiv) and HClO₄ (70%, 16 μL, 0.18 mmol, 0.20 equiv). The mixture was stirred at 80 °C for 1 h. After allowing the reaction to cool to ambient temperature, the reaction was concentrated under reduced pressure to a brown solid. This solid was suspended in Et₂O, at which time had turned into an oil, in a sonicating bath while methanol was drop-wise added as needed until the oil began to precipitate as a light purple powder. This precipitate was collected by suction filtration and the purification process repeated on the filtrate to afford a second crop of **163** as a light purple solid and as a 1:1 mixture of atropisomers (370 mg, 66%; 61% over 3 steps). ¹H NMR (500 MHz, d₆-acetone) δ 9.71 (d, 1H, *J* = 10 Hz), 7.63 (d, 1H, *J* = 7.6 Hz), 7.56 (d, 1H, *J* = 8.4 Hz), 7.44–7.38 (m, 2H), 7.32 (s, 1H), 7.12 (d, 1H, *J* = 2.4 Hz), 7.05 (dd, 1H, *J* = 8.6, 2.4 Hz), 6.04 (s, 1H), 5.09 (d, 1H, *J* = 14.9 Hz),

5.03 (s, 1H), 4.95 (d, 1H, J = 4.6 Hz), 3.91 (s, 3H), 3.48 (d, 1H, J =16.9 Hz), 3.23 (d, 1H,

J = 17.0 Hz), 2.20 (d, 3H, J = 12.0 Hz), 2.12 (s, 3H); ^{13}C NMR (125 MHz, d$_6$-acetone) δ

162.4, 141.8, 137.9, 136.0, 130.0, 129.9, 128.0, 126.7, 126.4, 125.9, 125.0, 124.8,

124.4, 117.3, 113.6, 78.3, 61.5, 60.2, 56.1, 38.3, 17.5, 8.2; IR (thin film) ν 3126, 3053,

2930, 1544, 1502, 1463, 1217, 1094, 734 cm^{-1}; HRMS (ESI) calcd $C_{22}H_{23}N_2O_2^+$ [M]$^+$

347.1754, found 347.1768 [M]$^+$; [α]$_D^{20}$ = −147.5 (c 0.28, CH_2Cl_2).
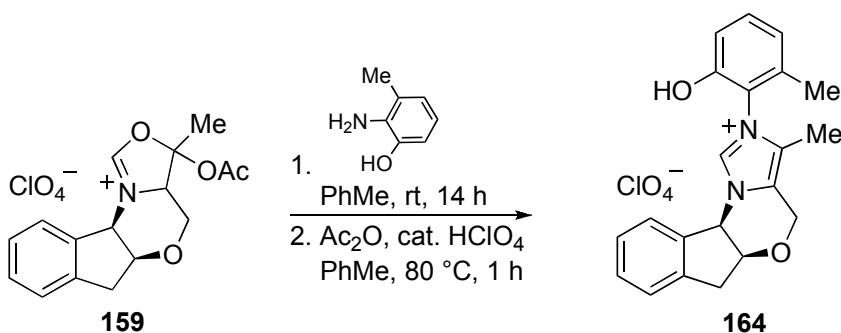
Preparation of *N*-2-hydroxy-6-methylphenyl substituted imidazolium salt (164)

To a round-bottomed flask charged with a magnetic stir bar and oxazolinium salt **159**

(388 mg, 1.00 mmol, 1.00 equiv) was added toluene (5.0 mL) and 2-hydroxy-6-

methylaniline (185 mg, 1.50 mmol, 1.50 equiv). The heterogeneous mixture was stirred

at ambient temperature for 14 h. The solution was triturated with Et$_2$O, the supernatant

was decanted, and residual solvent removed under reduced pressure to afford a mixture

of the crude aminal intermediate and parent aniline as a brown solid (482 mg, quant

crude yield). A suspension of the crude aminal intermediate (450 mg, 1.0 mmol, 1.0

equiv) in toluene (4.0 mL) was treated with Ac$_2$O (0.12 mL, 1.2 mmol, 1.2 equiv) and

HClO$_4$ (70%, 17 μL, 0.20 mmol, 0.20 equiv). The mixture was stirred at 80 °C for 1 h.

After allowing the reaction to cool to ambient temperature, the supernatant was

decanted, the residual solvent removed under reduced pressure, and the product

precipitated from CH_2Cl_2. The precipitate was collected by suction filtration to afford **164** as a light grey powder and as a 4:1 mixture of atropisomers (150 mg, 35% over 3 steps). ^1H NMR (500 MHz, d_6-acetone) δ 9.74* (s, 1H), 9.72 (s, 1H), 9.48 (bs, 1H, OH), 9.43* (bs, 1H, OH), 7.64* (d, 1H, J = 7.5 Hz), 7.58 (d, 1H, J = 7.6 Hz), 7.45–7.41 (m, 3H), 7.41–7.34* (m, 3H), 7.30 (t, 1H, J = 7.4 Hz), 7.09* (d, 1H, J = 8.6 Hz), 7.08 (d, 1H, J = 8.2 Hz), 7.03 (d, 1H, J = 7.6 Hz), 6.11* (d, 1H, J = 4.1 Hz), 6.08 (d, 1H, J = 4.1 Hz), 5.12 (d, 1H, J = 15.0 Hz), 5.12–5.09* (m, 2H), 5.06 (t, 1H, J = 4.5 Hz), 4.97* (d, 1H, J = 15.0 Hz), 4.96 (d, 1H, J = 14.9 Hz), 3.53–3.50* (m, 1H), 3.49 (dd, 1H, J = 16.9, 4.9 Hz), 3.24* (d, 1H, J = 16.9 Hz), 3.22 (d, 1H, J = 16.9 Hz), 2.21 (s, 3H), 2.15* (s, 3H), 2.11* (s, 3H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, d_6-acetone) δ 153.9, 153.8, 141.8, 138.0, 137.8, 136.4, 133.0, 132.9, 132.8, 130.1, 130.0, 128.2, 128.0, 126.6, 126.5, 126.4, 124.8, 124.5, 124.3, 122.9, 120.8, 115.3, 115.2, 78.3, 61.6, 60.2, 38.3, 17.3, 7.9; IR (KBr pellet) ν 3350, 3132, 3053, 2924, 1592, 1544, 1477, 1298, 1105, 951, 738, 624 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_2^+$ [M]$^+$ 333.1598, found 333.1607 [M]$^+$; $[α]_D^{20}$ = −129.6 (c 0.22, MeOH).
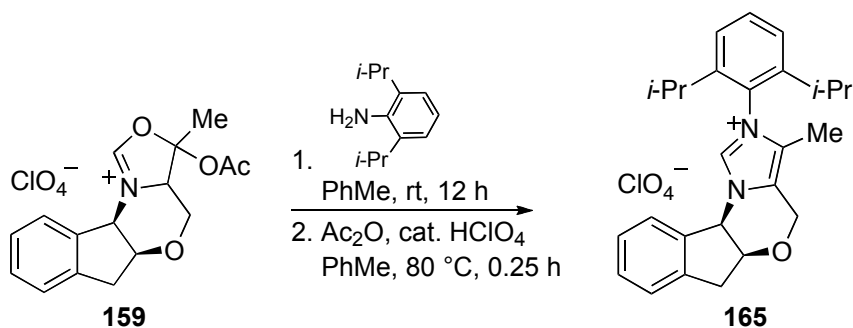
Preparation of *N*-2,6-diisopropylphenyl substituted imidazolium salt (165)

To a round-bottomed flask charged with a magnetic stir bar and oxazolinium salt **159** (388 mg, 1.00 mmol, 1.00 equiv) was added toluene (10 mL) and 2,6-diisopropylaniline

(0.28 mL, 1.5 mmol, 1.5 equiv). The heterogeneous mixture was stirred at ambient temperature for 12 h. Et_2O was added, the supernatant decanted, and the resultant oil concentrated under reduced pressure to afford the crude aminal intermediate as a light yellow foam and as a mixture of diastereomers (360 mg, 71%). A suspension of the aminal intermediate (360 mg, 0.71 mmol, 1.0 equiv) in toluene (3.0 mL) was treated with Ac_2O (0.13 mL, 1.4 mmol, 2.0 equiv) and $HClO_4$ (70%, 12 μL, 0.14 mmol, 0.20 equiv) and stirred at 80 °C for 15 min. The solution was allowed to cool to ambient temperature, concentrated under reduced pressure, and the residue purified by flash column chromatography (gradient, CH_2Cl_2/MeOH, 98:2→95:5) to give **165** as a yellow foam (235 mg, 68%; 48% over 3 steps). ^1H NMR (500 MHz, d_6-acetone) δ 9.93 (s, 1H), 7.72–7.69 (t, 1 H, J = 7.8 Hz), 7.57–7.52 (m, 3H), 7.46 (d, 1H, J = 7.4 Hz), 7.40 (t, 1H, J = 7.4 Hz), 7.33 (t, 1H, J = 7.4 Hz), 6.10 (d, 1H, J = 4.0 Hz), 5.11 (d, 1H, J = 15.0 Hz), 5.07 (t, 1H, J = 4.4 Hz), 4.98 (d, 1H, J = 15.0 Hz), 3.49 (dd, 1H, J = 16.9, 4.8 Hz), 3.23 (d, 1H, J = 16.9 Hz), 2.80 (d, 1H, J = 16.9 Hz), 2.64 (septet, 1H, J = 6.8 Hz), 2.26 (septet, 1H, J = 6.8 Hz), 2.10 (s, 3H), 1.26 (dd, 6H, J = 10.0, 6.8 Hz), 1.21 (dd, 6H, J = 6.8, 2.5 Hz); ^{13}C NMR (125 MHz, d_6-acetone) δ 147.1, 146.9, 142.0, 138.2, 135.8, 133.0, 130.2, 129.1, 128.0, 126.9, 126.6, 126.0, 125.8, 125.8, 124.1, 123.7, 78.3, 61.8, 60.3, 38.4, 25.3, 25.2, 23.4, 23.2, 8.3; IR (thin film) ν 3116, 3045, 2965, 2929, 2871, 1538, 1462, 1202, 1099, 733, 624 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{32}N_2O^+$ [M]$^+$ 387.2431, found 387.2446 [M]$^+$; $[α]_D^{20}$ = −94.5 (c 0.22, CH_2Cl_2).

159 → **166**
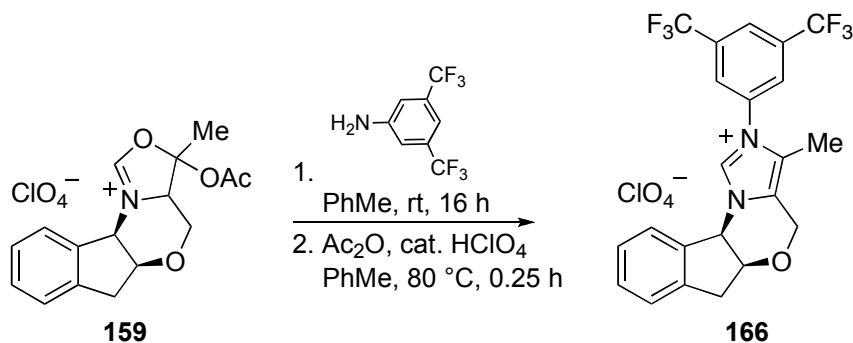
Preparation of *N*-3,5-bis(trifluoromethyl)phenyl substituted imidazolium salt (166)

To a round-bottomed flask charged with a magnetic stir bar and oxazolinium salt **159** (388 mg, 1.00 mmol, 1.00 equiv) was added toluene (10 mL) and 3,5-bis(trifluoromethyl)aniline (0.23 mL, 1.5 mmol, 1.5 equiv). The heterogeneous mixture was stirred at ambient temperature for 16 h. The supernatant was decanted, the crude oil washed with Et$_2$O (1 x 10 mL), and residual solvent removed under reduced pressure to afford the crude aminal intermediate as a yellow solid and a mixture of diastereomers (560 mg, quant. crude yield). A suspension of the crude aminal intermediate (560 mg, 1.0 mmol, 1.0 equiv) in toluene (4.0 mL) was treated with Ac$_2$O (0.19 mL, 2.0 mmol, 2.0 equiv) and HClO$_4$ (70%, 17 µL, 0.20 mmol, 0.20 equiv). The mixture was stirred at 80 °C for 15 min. After allowing the reaction to cool to ambient temperature, the supernatant was decanted, residual solvent removed under reduced pressure, and the resulting residue suspended in a mixture of Et$_2$O/EtOAc (2:1, 7 mL) and sonicated until precipitation had occurred. The imidazolium salt **166** was collected by suction filtration as a white solid (190 mg, 35% over 3 steps). ^{1}H NMR (500 MHz, d$_6$-acetone) δ 10.00 (s, 1H), 8.60 (s, 2H), 8.47 (s, 1H), 7.63 (d, 1H J = 7.7 Hz), 7.43 (d, 1H, J = 7.5 Hz), 7.39 (t, 1H, J = 7.4 Hz), 7.29 (t, 1H, J = 7.4 Hz), 6.04 (d, 1H, J = 4.1 Hz), 5.13 (d, 1H, J = 15.1 Hz), 5.02 (t, 1H, J = 4.3 Hz), 4.95 (d, 1H, J = 15.1 Hz), 3.50 (dd, 1H, J = 17.0, 4.8 Hz), 3.23 (d, 1H, J = 17.0 Hz), 2.34 (s, 3H); ^{13}C NMR (125 MHz, d$_6$-acetone) δ 141.8, 137.6, 136.7, 136.3,

134.0, 133.7, 130.2, 129.3, 127.9, 126.7, 126.4, 125.0, 125.0, 78.4, 61.7, 60.2, 38.3, 8.6; IR (thin film) ν 3148, 3058, 2937, 1543, 1368, 1280, 1105, 1076, 905, 604 cm^{-1}; HRMS (ESI) calcd for C$_{22}$H$_{17}$F$_6$N$_2$O$^+$ [M]$^+$ 439.1240, found 439.1246 [M]$^+$; [α]$_D^{20}$ = −141.9 (c 0.15, CH$_2$Cl$_2$).
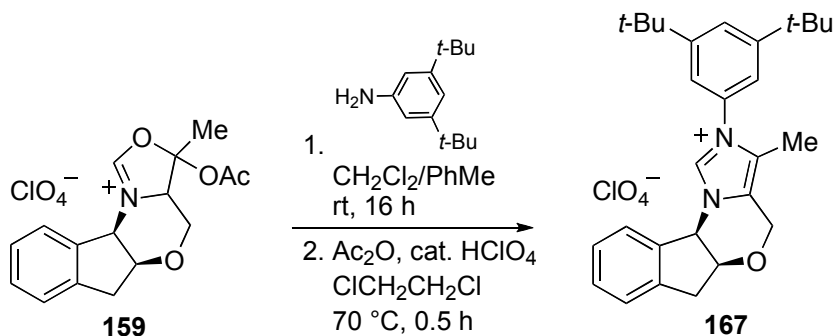
Preparation of *N*-3,5-di-*tert*-butylphenyl substituted imidazolium salt (167)

To a solution of oxazolinium salt **159** (388 mg, 1.00 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (3.0 mL) was added toluene (10 mL) and 3,5-di-*tert*-butylaniline (0.23 mL, 1.5 mmol, 1.5 equiv). The solution was stirred at ambient temperature for 16 h during which a white solid had precipitated. The precipitate was collected by suction filtration and washed with Et$_2$O to afford the aminal intermediate as a white powder and as a mixture of diastereomers (420 mg, 79% yield). A 0.25 M solution of the aminal intermediate (420 mg, 0.79 mmol, 1.0 equiv) in 1,2-dichloroethane (3.1 mL) was treated with Ac$_2$O (0.15 mL, 1.6 mmol, 2.0 equiv) and HClO$_4$ (70%, 14 μL, 0.16 mmol, 0.20 equiv) and stirred at 70 °C for 30 min. After allowing the solution to cool to ambient temperature, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (CH$_2$Cl$_2$/MeOH, 30:1) to afford **167** as a light yellow foam (385 mg, 95%; 75% over 3 steps). ^{1}H NMR (500 MHz, d$_6$-acetone) δ 9.75 (s, 1H), 7.80 (t, 1H, *J* = 1.7 Hz), 7.65–7.63 (m, 3H), 7.41 (d, 1H, *J* = 7.4 Hz), 7.35 (t, 1H, *J* = 7.3 Hz), 7.29 (t, 1H, *J* = 7.4 Hz), 5.97

(s, 1H, J = 4.2 Hz), 5.06 (d, 1H, J = 15.0 Hz), 4.96 (t, 1H, J = 4.4 Hz), 4.90 (d, 1H, J = 15.0 Hz), 3.46 (dd, 1H, J = 16.9 Hz, 4.9 Hz), 3.20 (d, 1H, J = 16.9 Hz), 2.23 (s, 3H), 1.41 (s, 18H); ^{13}C NMR (125 MHz, d$_6$-acetone) δ 154.0, 141.6, 137.8, 135.5, 134.2, 129.9, 127.8, 126.2, 126.0, 125.3, 124.9, 124.5, 121.6, 78.2, 61.3, 60.1, 38.1, 35.8, 31.4, 8.7; IR (thin film) ν 3126, 3053, 2952, 2868, 1608, 1597, 1538, 1477, 1365, 1248, 1096, 733, 624 cm^{-1}; HRMS (ESI) calcd for C$_{28}$H$_{35}$N$_2$O$^+$ [M]$^+$ 415.2744, found 415.2742 [M]$^+$; $[\alpha]_D^{20}$ = −133.7 (c 0.25, CH$_2$Cl$_2$).
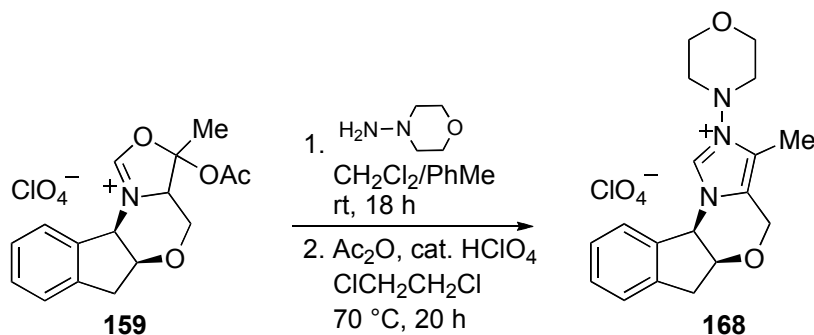
Preparation of *N*-Morpholino substituted imidazolium salt (168)

To a solution of oxazolinium salt **159** (388 mg, 1.00 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (5.0 mL) was added toluene (5.0 mL) and 4-aminomorpholine (0.15 mL, 1.5 mmol, 1.5 equiv). The heterogeneous mixture was stirred at ambient temperature for 18 h. Et$_2$O was added to the mixture causing an oil to form. The supernatant was decanted, the oil was dissolved in a minimal amount of CH$_2$Cl$_2$ (~5 mL) and triturated with Et$_2$O, the super-natant decanted, and residual solvent removed under reduced pressure to afford the crude aminal intermediate as a light yellow solid and as a mixture of diastereomers (360 mg, 84%). A 0.25 M solution of the aminal intermediate (360 mg, 0.84 mmol, 1.0 equiv) in 1,2-dichloroethane (3.4 mL) was treated with Ac$_2$O (0.15 mL, 1.6 mmol, 2.0 equiv) and HClO$_4$ (70%, 7.0 μL, 0.080 mmol, 0.10 equiv) and stirred at 70 °C for 20 h. After allowing

the solution to cool to ambient temperature, the solvent was removed under reduced

pressure, and the residue purified by flash column chromatography (gradient, CH_2Cl_2/

MeOH, 95:5→90:10) to afford **168** as a yellow solid (260 mg, 75 %, 63 % over 3 steps).

^{1}H NMR (500 MHz, d_6-acetone) δ 10.09 (s, 1H), 7.58 (d, 1H, J = 7.7 Hz), 7.41–7.35 (m,

2H), 7.30 (t, 1H, 7.3 Hz), 5.90 (d, 1H, J = 4.1 Hz), 5.00 (d, 1H, J = 15.0 Hz), 4.95 (t, 1H,

J = 4.4 Hz), 4.82 (d, 1H, J = 15.1 Hz), 3.92 (t, 4H, J = 4.5 Hz), 3.47 (t, 4H, J = 4.5 Hz),

3.43–3.40 (m, 1H), 3.17 (d, 1H, J = 16.9 Hz), 2.35 (s, 3H); ^{13}C NMR (125 MHz, d_6-

acetone) δ 141.7, 137.7, 132.9, 130.0, 127.9, 126.4, 125.8, 124.8, 122.7, 78.3, 67.3,

61.4, 60.0, 57.2, 38.2, 7.4; IR (thin film) ν 3115, 2969, 2863, 1460, 1270, 1102, 1080,

923, 741 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}N_3O_2^+$ [M]$^+$ 312.1707, found 312.1720 [M]$^+$;

$[α]_D^{20}$ = −174.5 (c 0.20, CH_2Cl_2).
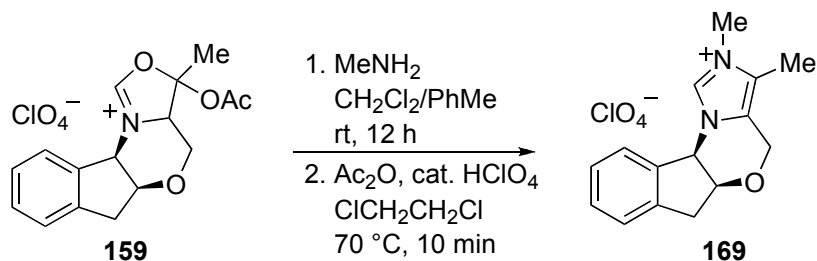
Preparation of *N*-Methyl substituted imidazolium salt (169)

To a solution of oxazolinium salt **159** (388 mg, 1.00 mmol, 1.00 equiv) in CH_2Cl_2 (5.0 mL)

was added toluene (5.0 mL) and a solution of *N*-methyl amine (2.0 M in THF, 0.75 mL,

1.5 mmol, 1.5 equiv). The heterogeneous mixture was stirred at ambient temperature for

12 h. The precipitate was collected by suction filtration and washed with Et_2O to afford

the crude aminal intermediate as a white powder and as a mixture of diastereomers (310

mg, 86 % yield). A 0.25 M solution of the aminal intermediate (300 mg, 0.83 mmol, 1.0

equiv) in 1,2-dichloroethane (3.3 mL) was treated with Ac_2O (0.16 mL, 1.7 mmol, 2.0

equiv) and HClO$_4$ (70 %, 7.0 µL, 0.080 mmol, 0.10 equiv) and stirred at 70 °C for 10 min. After allowing the solution to cool to ambient temperature, the solvent was removed under reduced pressure and the resultant residue dissolved in a minimal amount of CH$_2$Cl$_2$ and triturated with toluene. The precipitate was collected by suction filtration to afford **169** as a white powder (180 mg, 64%; 53% over 3 steps). ^{1}H NMR (400 MHz, d$_6$-acetone) δ 9.56 (s, 1H), 5.53 (d, 1H, J = 7.6 Hz), 7.41–7.30 (m, 2H), 7.28 (t, 1H, J = 7.3 Hz), 5.91 (s, 1H), 5.02 (d, 1H, J = 15.2), 4.95 (t, 1H, J = 4.5 Hz), 4.83 (d, 1H, J = 15.0 Hz), 4.06 (s, 3H), 3.43 (dd, 1H, J = 16.9, 4.9 Hz), 3.18 (d, 1H, J = 17.0 Hz), 2.36 (s, 3H); ^{13}C NMR (100 MHz, d$_6$-acetone) δ 141.6, 138.1, 135.7, 129.9, 127.9, 126.2, 126.0, 124.7, 124.0, 78.2, 61.1, 60.0, 38.1, 34.2, 7.8; IR (thin film) ν 3137, 3076, 2930, 1636, 1558, 1446, 1253, 1096, 760, 738, 624 cm^{-1}; HRMS (ESI) calcd for C$_{15}$H$_{17}$N$_2$O$^+$ [M]$^+$ 241.1335; found, 241.1338 [M]$^+$; [α]$_D^{20}$ = −163.7 (c 0.33, CH$_2$Cl$_2$).
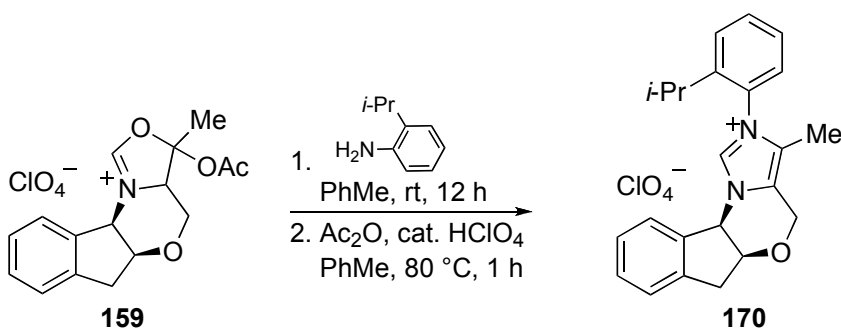
Preparation of *N*-2-isopropylphenyl substituted imidazolium salt (170)

To a round-bottomed flask charged with a magnetic stir bar and oxazolinium salt **159** (388 mg, 1.00 mmol, 1.00 equiv) was added toluene (10 mL) and 2-isopropyl aniline (0.21 mL, 1.5 mmol, 1.5 equiv). The heterogeneous mixture was stirred at ambient temperature for 12 h during which time a solid precipitated. The precipitate was suspended in EtOAc collected by suction filtration and washed with EtOAc to afford the

crude aminal intermediate as a white powder and as a mixture of diastereomers (325 mg, 71%). A mixture of the aminal intermediate (325 mg, 0.70 mmol, 1.0 equiv) in toluene (2.8 mL) was treated with Ac_2O (0.13 mL, 1.4 mmol, 2.0 equiv) and $HClO_4$ (70%, 13 µL, 0.14 mmol, 0.20 equiv) and heated at 80 °C for 1 h. The solution was decanted and the oil concentrated under reduced pressure to afford a brown foam which was dissolved in a minimal amount of EtOAc, placed in a sonicating bath and triturated with Et_2O. Isolation of the precipitate by suction filtration provided two crops of **170**, 100 mg and 120 mg respectively, as a white powder (220 mg, 71%; 50% over 3 steps) and as a 1:1 mixture of atropisomers. ^1H NMR (500 MHz, d_6-acetone) δ 9.85 (d, 1H, J = 1.6 Hz), 7.75–7.73 (m, 2H), 7.65–7.51 (m, 3H), 7.47–7.39 (m, 2H), 7.35–7.30 (m, 1H), 6.06 (dd, 1H, J = 28.6, 4.2 Hz), 5.13–5.08 (m, 1H), 5.05–5.02 (m, 1H), 4.99–4.91 (m, 1H), 3.49–3.46 (m, 1H), 3.23 (dd, 1H, J = 16.9, 2.7 Hz), 2.77* (septet, 1H, J = 6.9 Hz), 2.59 (septet, 1H, J = 6.9 Hz), 2.12 (d, 3H, J = 2.6 Hz), 1.30–1.24 (m, 6H); ^{13}C NMR (125 MHz, d_6-acetone) δ 146.8, 146.6, 142.0, 141.8, 138.1, 137.8, 136.0, 135.8, 132.9, 132.9, 131.7, 130.2, 130.1, 129.0, 128.7, 128.5, 128.5, 128.4, 128.3, 128.1, 128.0, 127.0, 126.8, 126.6, 126.4, 125.0, 124.9, 124.1, 78.3, 61.7, 61.6, 60.3, 60.2, 38.4, 38.3, 28.9, 28.6, 24.8, 24.8, 23.4, 23.0, 8.4, 8.3; IR (thin film) ν 3120, 3057, 2967, 2930, 2871, 1540, 1461, 1268, 1224, 1099, 733, 623 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{25}N_2O^+$ [M]$^+$ 345.1916, found 345.1955 [M]$^+$; $[\alpha]_D^{20}$ = −113.3 (c 0.12, CH_2Cl_2).
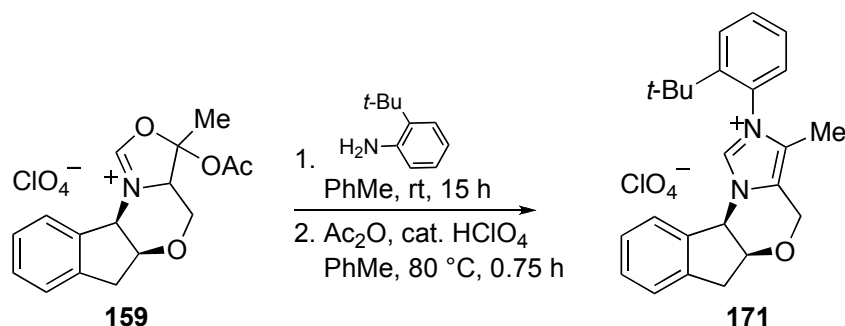
Preparation of *N*-2-*tert*-butylphenyl substituted imidazolium salt (171)

To a round-bottomed flask charged with a magnetic stir bar and oxazolinium salt **159** (388 mg, 1.00 mmol, 1.00 equiv) was added toluene (10 mL) and 2-*tert*-butylaniline (0.24 mL, 1.5 mmol, 1.5 equiv). The heterogeneous mixture was stirred at ambient temperature for 15 h. The aminal intermediate was collected by suction filtration as a tan powder and as a mixture of diastereomers (410 mg, 86%). A suspension of the aminal intermediate (410 mg, 0.86 mmol, 1.0 equiv) in toluene (3.5 mL) was treated with Ac₂O (0.16 mL, 1.7 mmol, 2.0 equiv) and HClO₄ (70%, 16 µL, 0.17 mmol, 0.20 equiv) and stirred at 80 °C for 45 min. The solution was decanted and the oil concentrated under reduced pressure to a brown foam that was dissolved in a minimal amount of EtOAc, placed in a sonicating bath and triturated with Et₂O. Isolation by suction filtration afforded **171** in 3 crops as a yellow solid and ~10:1 mixture of atropisomers (90 mg, 23%; 20% over 3 steps). ^{1}H NMR (500 MHz, d₆-acetone) δ 9.97* (s, 1H), 9.94 (s, 1H), 7.89 (dd, 1H, *J* = 8.2, 1.4 Hz), 7.71–7.68 (m, 1H), 7.68* (d, 1H, *J* = 1.5 Hz), 7.60–7.57 (m, 1H), 7.54–7.49 (m, 1H), 7.49–7.47* (m 1H), 7.46–7.41 (m, 4H), 7.40 (d, 1H, *J* = 7.4 Hz), 7.30–7.16* (m, 7H), 6.18* (d, 1H, *J* = 5.0 Hz), 6.01 (d, 1H, *J* = 4.2 Hz), 5.13 (d, 1H, *J* = 15 Hz), 5.10–5.08* (m, 2H), 5.02 (t, 1H, *J* = 4.4 Hz), 4.93 (dd, 1H, *J* = 15.0 Hz, 1.0 Hz), 3.50 (dd, 1H, *J* = 16.9, 5.0 Hz), 3.31* (dd, 1H, *J* = 16.8, 4.1 Hz), 3.24 (d, 1H, *J* = 16.9 Hz), 3.15* (d, 1H, *J* = 16.7 Hz), 2.16* (s, 3H), 2.14 (s, 3H), 1.32* (s, 9H), 1.29 (s, 9H); ^{13}C NMR (125 MHz,

d$_6$-acetone) δ 147.5, 142.0, 138.1, 137.0, 132.6, 131.7, 131.5, 131.3, 130.8, 130.2, 129.0, 128.8, 128.7, 128.1, 128.0, 127.9, 126.6, 125.0, 124.3, 78.3, 61.6, 60.1, 38.3, 36.9, 32.1, 8.92; IR (thin film) ν 3123, 3056, 2967, 1540, 1482, 1213, 1099, 733, 624 cm^{-1}; HRMS (ESI) calcd for C$_{24}$H$_{27}$N$_2$O$^+$ [M]$^+$ 359.2118; found, 359.2112 [M]$^+$; [α]$_D^{20}$ = −202.7 (c 0.073, CH$_2$Cl$_2$).
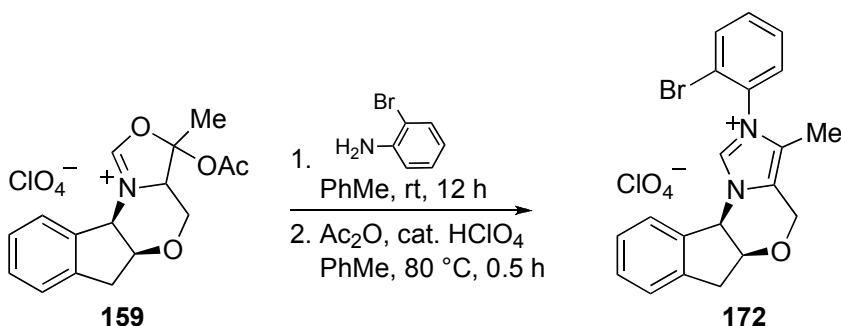
Preparation of *N*-2-bromophenyl substituted imidazolium salt (172)

To a round-bottomed flask charged with a magnetic stir bar and oxazolinium salt **159** (388 mg, 1.00 mmol, 1.00 equiv) was added toluene (10 mL) and 2-bromoaniline (0.14 mL, 1.5 mmol, 1.5 equiv). The heterogeneous mixture was stirred at ambient temperature for 12 h. The solution was concentrated under reduced pressure to a brown foam which was suspended in Et$_2$O (10 mL) and EtOAc (4 mL), placed in a sonicating bath and methanol (< 1 mL) added until a solid precipitate formed. The precipitate was collected by suction filtration to afford two crops of the crude aminal intermediate as a white solid and as a mixture of diastereomers (130 mg, 26%). A suspension of the aminal intermediate (125 mg, 0.25 mmol, 1.0 equiv) in toluene (1.0 mL) was treated with Ac$_2$O (47 µL, 0.50 mmol, 2.0 equiv) and HClO$_4$ (70%, 4.0 µL, 0.050 mmol, 0.20 equiv) and stirred at 80 °C for 30 min. The solution was concentrated under reduced pressure and the residue purified by flash column chromatography (gradient, CH$_2$Cl$_2$:MeOH,

98:2→95:5→92:8→90:10) to afford **172** as a yellow solid as a 2:1 mixture of atropisomers (100 mg, 83 % yield, 22 % over 3 steps). ^{1}H NMR (500 MHz, d$_6$-acetone) δ 9.90* (s, 1H), 9.82 (s, 1H), 8.01 (d, 1H, J = 8.0 Hz), 7.97* (d, 1H, J = 7.3 Hz), 7.79–7.70 (m, 3H), 7.66* (d, 1H, J = 7.6 Hz), 7.61 (d, 1H, J = 7.6 Hz), 7.44 (d, 1H. J = 7.4 Hz), 7.39 (t, 1h, J = 7.3 Hz), 7.32 (t, 1H, J = 7.3 Hz), 6.14* (d, 1H, J = 3.6 Hz) 6.02 (d, 1H, J = 3.8 Hz), 5.13* (d, 1H, J = 15.1 Hz), 5.12 (d, 1H, J = 15.0 Hz), 5.01* (t, 1H, J = 4.4 Hz), 5.01 (t, 1H, J = 4.4 Hz), 4.92 (d, 1H, J = 15.0 Hz), 3.50* (dd, 1H, J = 16.9, 4.7 Hz), 3.50 (dd, 1H, J = 16.9, 4.7 Hz), 3.24* (d, 1H, J = 16.9 Hz), 3.22 (d, 1H, J = 16.9 Hz), 2.17* (s, 3H), 2.14 (s, 3H); ^{13}C NMR (125 MHz, d$_6$-acetone) δ 141.8, 138.0, 136.4, 136.1, 134.9, 134.8, 134.2, 133.5, 131.1, 130.8, 130.5, 130.4, 130.1, 128.1, 128.0, 126.6, 126.5, 126.3, 125.0, 124.7, 124.3, 121.9, 78.3, 61.7, 60.2, 38.4, 38.2, 8.4, 8.3; IR (thin film) ν 3124, 3058, 2926, 1544, 1482, 1267, 1219, 1092, 736, 622 cm^{-1}; HRMS (ESI) calcd for C$_{20}$H$_{18}$BrN$_2$O$^+$ [M]$^+$ 381.0597, found 381.0607 [M]$^+$; [α]$_D^{20}$ = −84.9 (c 0.11, CH$_2$Cl$_2$).
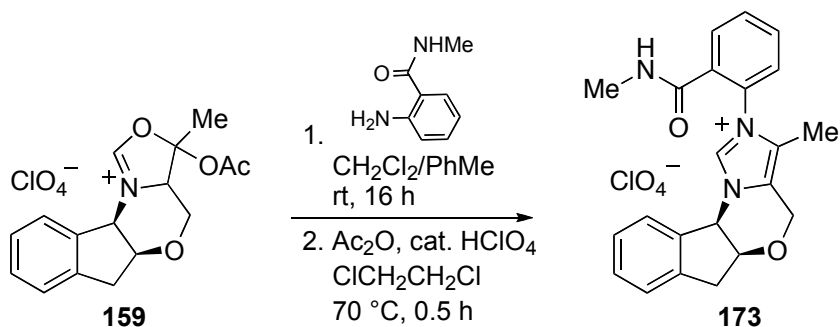
Preparation of *N*-2-(*N*-methylbenzamido) substituted imidazolium salt (173)

To a 1.0 M solution oxazolinium salt **159** (388 mg, 1.00 mmol, 1.00 equiv) in CH$_2$Cl$_2$ in a round-bottom flask charged with a magnetic stir bar was added a 1 M solution of 2-amino-*N*-methylbenzamide[3] (1.5 mL, 1.5 mmol, 1.5 equiv) in CH$_2$Cl$_2$ followed by toluene (3.0 mL). The cloudy solution was stirred at ambient temperature for 16 h. The solution

was triturated with Et₂O, the supernatant decanted, and residual solvent removed under reduced pressure to afford the crude aminal intermediate as a light tan foam and as a mixture of diastereomers (475 mg, 99%). A 0.25 M solution of the aminal intermediate (475 mg, 0.99 mmol, 1.0 equiv) in 1,2-dichloroethane (4.0 mL) was treated with Ac₂O (0.19 mL, 2.0 mmol, 2.0 equiv) and HClO₄ (70 %, 17 µL, 0.20 mmol, 0.20 equiv). The solution was stirred at 70 °C for 30 min, concentrated under reduced pressure, and the residue purified by flash column chromatography (CH₂Cl₂/MeOH, 95:5) to afford **173** as a white solid (320 mg, 70%; 69% over 3 steps). ^{1}H NMR (500 MHz, d₆-acetone) δ 9.67 (s, 1H), 7.9 (br s, 1H, NH), 7.89–7.77 (m, 4H), 7.62 (d, 1H, J = 7.6 Hz), 7.41 (d, 1H, J = 7.4 Hz), 7.38 (t, 1H, J = 7.4 Hz), 7.32 (t, 1H, J = 7.4 Hz), 5.97 (s, 1H), 5.04 (d, 1H, J = 15.0 Hz), 4.99 (br s, 1H), 4.89 (d, 1H, J = 15.0 Hz), 3.47 (dd, 1H, J = 16.9, 4.8 Hz), 3.20 (d, 1H, J = 16.9 Hz), 2.81 (d, 3H, J = 4.7 Hz), 2.10 (s, 3H); ^{13}C NMR (125 MHz, d₆-acetone) δ 166.4, 141.6, 138.1, 136.6, 135.4, 132.5, 132.4, 131.9, 129.9, 129.8, 129.6, 127.9, 127.2, 126.2, 124.8, 123.6, 78.3, 61.5, 60.1, 38.3, 26.8, 8.4; IR (thin film) ν 3362, 3128, 3061, 2931, 1662, 1604, 1545, 1217, 1099, 734, 623 cm⁻¹; HRMS (ESI) calcd for C₂₂H₂₂N₃O₂⁺ [M]⁺ 360.1707; found, 360.1711 [M]⁺; $[\alpha]_D^{20}$ = −124.9 (c 0.19, CH₂Cl₂).
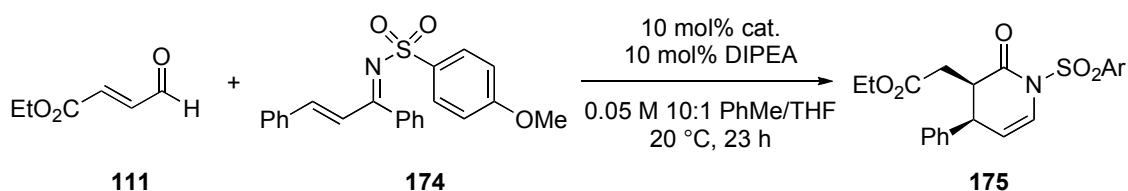
Ethyl-2-((3*S*,4*S*)-1-(4-methoxyphenylsulfonyl)-2-oxo-4-phenyl-1,2,3,4-tetra-hydropyridin-3-yl) acetate (175)

To an oven-dried 10-mL round-bottomed flask equipped with a magnetic stir bar was added *trans-N*-(4-methoxybenzenesulfonyl)-3-phenylprop-2-ene-1-imine **174** (60 mg,

0.20 mmol, 1.0 equiv), the precatalyst (10 mol %), ethyl *trans*-4-oxo-2-butenoate **111** (26.5 µL, 0.22 mmol, 1.1 equiv), and 4.0 mL of 10:1 toluene:THF (0.050 M). The flask was purged with N_2(g), *N,N*-diisopropylethylamine (DIPEA) was added (3.5 µL, 0.020 mmol, 0.10 equiv, 10 mol %) and the solution allowed to stir at 20 °C for 23 h. The reaction was concentrated under reduced pressure and the resulting mixture purified by flash column chromatography (hexanes/EtOAc, 3:1) to afford the title compound (65 mg , 76% yield from the triazolium catalyst *ent-***117•ClO4**). ^{1}H NMR (500 MHz, CDCl3) δ 8.03 (d, 2H, *J* = 8.6 Hz), 7.16–7.12 (m, 2H), 7.05–6.99 (m, 4H), 6.58 (d, 2H, *J* = 7.4 Hz), 5.59 (m, 1H), 4.18–4.08 (m, 2H), 3.92 (s, 3H), 3.65 (t, 1H, *J* = 6.8 Hz), 3.55–3.51 (m, 1H), 2.57 (dd, 1H, *J* = 17.3, 6.0 Hz), 1.94 (dd, 1H, *J* = 17.3, 7.5 Hz), 1.21 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, CDCl3) δ 171.7, 168.9, 164.4, 136.8, 131.4, 129.2, 128.9, 127.9, 127.9, 124.6, 114.3, 113.5, 60.9, 56.0, 44.1, 42.1, 31.5, 14.3; IR (thin film) ν 3086, 2982, 1720, 1594, 1496, 1454, 1406, 1367, 1264, 1132, 1091 cm^{-1}, m.p. = 111–113 °C; HRMS (ESI) calcd for $C_{22}H_{23}NO_6S$ [M]$^+$ 429.1246, found 452.1160 [M+Na]$^+$; 99% ee from the triazolium precatalyst *ent-***117•ClO4** as determined by HPLC (AS-H, 9:1 hexanes/*i*-PrOH), t_r = 34.8 min, t_r = 45.0 min; $[α]_D^{20}$ = −70.2 (c 1.0, CH_2Cl_2).
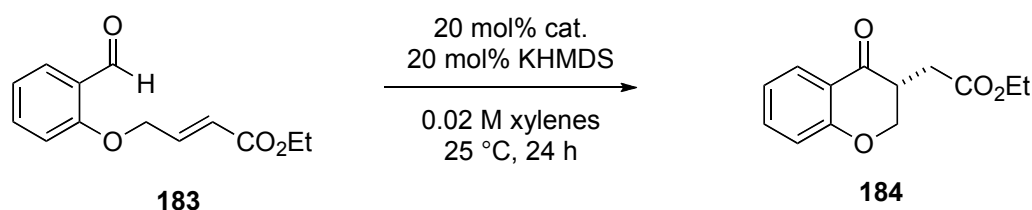
(*R*)-(4-Oxo-chroman-3-yl)-acetic acid ethyl ester (184)

An oven-dried 10-mL round-bottomed flask equipped with a stir bar was charged with the precatalyst (20 mol %) and xylenes (4.0 mL) and purged with N_2(g). A 0.50 M (toluene) solution of KHMDS (0.040 mL, 0.024 mmol, 20 mol %) was added and the mixture

allowed to stir at ambient temperature for 15 min. Next (*E*)-ethyl 4-(2-formylphenoxy)but-2-enoate **184** (28 mg, 0.12 mmol, 1.0 equiv) in 2.0 mL of xylenes (0.060 M) was added and the solution stirred at 25 °C for 24 h. The solution was immediately poured onto a column of silica gel and eluted (hexanes/*i*-PrOH, 6:1) to afford the product as a colorless oil (26.5 mg, 94% yield from triazolium catalyst ***ent*-117•ClO₄**). ^{1}H NMR (500 MHz, CDCl₃) δ 7.89 (dd, 1H, *J* = 7.9, 1.7 Hz), 7.49 (m, 1H), 7.04 (m, 1H), 6.98 (dd, 1H, *J* = 8.4, 0.6 Hz), 4.61 (dd, 1H, *J* = 11.2, 5.2 Hz), 4.30 (t, 1H, *J* = 11.2 Hz), 4.20 (m, 2H), 3.35 (m, 1H), 2.95 (dd, 1H, *J* = 17.0, 4.8 Hz), 2.42 (dd, 1H, *J* = 17.0, 8.2 Hz), 1.29 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, CDCl₃) δ 192.8, 171.6, 162.0, 136.2, 127.6, 121.7, 120.7, 118.0, 70.5, 61.2, 42.8, 30.6, 14.4; IR (thin film) ν 2987, 2929, 2850, 1734, 1690, 1606, 1301, 1214 cm^{-1}; 98% ee from chiral triazolium catalyst as determined by HPLC (AD-H column, 97:3 hexanes:*i*-PrOH, 0.5 mL/min), t_r = 27.7 min, t_r = 39.9 min; $[\alpha]_D^{20}$ = −17.0 (c 0.12, CH₂Cl₂).
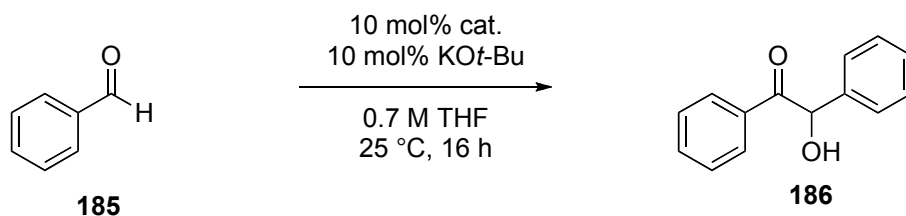
2-Hydroxy-1,2-diphenylethanone (186)

To an oven-dried 5.0-mL vial equipped with a magnetic stir bar was added the precatalyst (10 mol %). The vial was purged with N₂(g) and benzaldehyde (50 μL, 0.50 mmol, 1.0 equiv) and THF (0.35 mL) were added. The reaction mixture was allowed to stir at 25 °C for 5 min before a 1.0 M (THF) solution of potassium *tert*-butoxide (0.050 mL, 0.050 mmol, 10 mol %) was added drop-wise. The resulting solution was allowed to stir at 20 °C for 16 h. The contents of the vial were poured over water (5 mL) and

extracted with CH_2Cl_2 (2 x 5 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (hexanes/EtOAc, 5:1) to afford the title compound as a white solid (6.0 mg, 11% yield from the imidazolium precatalyst **145**; 44.0 mg, 83% yield from the triazolium precatalyst **ent-117•ClO₄**). ¹H NMR (500 MHz, CDCl₃) δ 7.93 (m, 2H), 7.55–7.52 (m, 1H), 7.42–7.39 (m, 2H), 7.36–7.28 (m, 5H), 5.96 (d, 1H, J = 6.1 Hz), 4.55 (d, 1H, J = 6.1 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 199.1, 139.21, 134.1, 133.7, 129.3, 129.3, 128.9, 128.8, 128.0, 29.9; IR (thin film) ν 3380, 2924, 2852, 1681, 1449, 1263, 1206, 1092, 1068, 977 cm⁻¹.
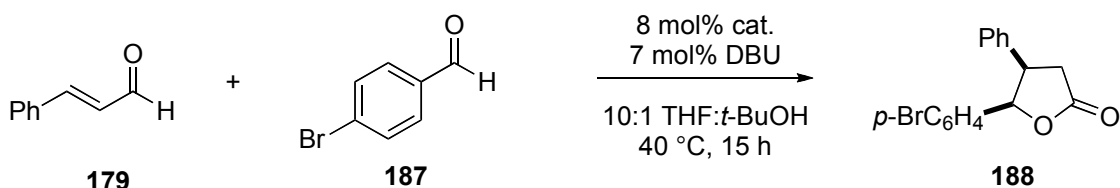
***cis*-5-(4-Bromophenyl)-4-phenyl-dihydrofuran-2(3H)-one (188)**

Into an oven-dried 5-mL vial equipped with a magnetic stir bar was added the precatalyst (8 mol %), 4-bromobenzaldehyde (92 mg, 0.50 mmol, 2.0 equiv), *trans*-cinnamaldehyde (32 µL, 0.25 mmol, 1.0 equiv), and 0.50 mL 10:1 THF: *t*-BuOH. The vial was purged with N₂(g) and DBU (2.7 µL, 0.018 mmol, 7 mol %) was added. The solution was allowed to stir at 25 °C for 15 h. The solution was concentrated under reduced pressure and the mixture purified by flash column chromatography (hexanes/EtOAc, 4:1) to afford the lactone diastereomers (55% yield from the imidazolium precatalyst **145**; 14% yield from the triazolium precatalyst **ent-117•ClO₄**). ¹H NMR (500 MHz, CDCl₃) δ 7.28–7.24 (m, shoulder, 2H), 7.15–7.14 (m, 3H), 6.84–6.82 (m, 2H), 6.78 (d, 2H, J = 8.3 Hz), 5.77 (d, 1H, J = 6.8 Hz), 4.07–4.03 (m, 1H), 3.07 (dd, 1H, J = 17.4, 8.3 Hz), 2.93 (dd, 1H, J =

17.4, 5.8 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 176.5, 136.6, 131.3, 128.7, 128.1, 127.9, 127.6, 122.1, 84.2, 46.9, 35.2; IR (thin film) ν 3064, 3033, 2927, 1784, 1594, 1491, 1173, 1072, 1010, 980, 732 cm^{-1}; HRMS (EI) calcd for C$_{16}$H$_{13}$BrO$_2$ [M]$^+$ 316.0099, found 316.0111 [M]$^+$; 32% ee from the imidazolium catalyst as determined by SFC (AD-H column, 7% *i*-PrOH in CO$_2$), t$_r$ = 14.1 min, t$_r$ = 16.7 min; [α]$_D^{20}$ = 67.0 (c 0.10, CH$_2$Cl$_2$).

trans-5-(4-Bromophenyl)-4-phenyl-dihydrofuran-2(3*H*)-one (*diast*-188)

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.48–7.45 (m, 2H), 7.38–7.31 (m, 3H), 7.18–7.16 (m, 2H), 7.05 (d, 2H, *J* = 8.4 Hz), 5.37 (d, 1H, *J* = 8.8 Hz), 3.55–3.49 (m, 1H), 3.06 (dd, 1H, *J* = 17.6, 8.4 Hz), 2.90 (dd, 1H, *J* = 17.6, 11.1 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 175.0, 137.5, 132.0, 129.4, 128.3, 127.6, 127.4, 122.9, 86.9, 51.0, 37.3, 29.9; IR (thin film) ν 3063, 3032, 2926, 1790, 1491, 1268, 1195, 1143, 1004, 699 cm^{-1}; HRMS (EI) calcd for C$_{16}$H$_{13}$BrO$_2$ [M]$^+$ 316.0099, found 316.0108 [M]$^+$; 34% ee from the imidazolium precatalyst as determined by SFC (AD-H column, 7% *i*-PrOH in CO$_2$), t$_r$ = 11.2 min, t$_r$ = 15.9 min; [α]$_D^{20}$ = −28.0 (c 0.10, CH$_2$Cl$_2$).
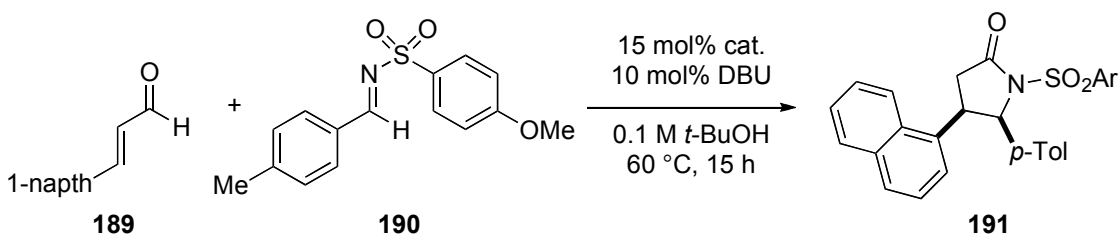
cis-1-(4-Methoxyphenylsulfonyl)-4-(naphthalen-1-yl)-5-*p*-tolylpyrrolidin-2-one (191)

To an oven-dried 5-mL vial equipped with a magnetic stir bar was added (*E*)-3-(naphthalen-1-yl)acrylaldehyde **189** (18 mg, 0.10 mmol, 1.0 equiv), (*E*)-4-methoxy-N-(4-methylbenzylidene)benzenesulfonamide **190** (29 mg, 0.10 mmol, 1.0 equiv), and the precatalyst (15 mol %) and purged with N$_2$(g). Next *t*-BuOH (1.0 mL) was added followed

by DBU (1.5 mg, 0.010 mmol, 10 mol %) and the vial again purged with N_2(g). The vial was capped and stirred at 60 °C for 15 h. The reaction mixture was concentrated under reduced pressure and taken up in 1.0 mL of THF and 1.0 mL of 1.0 M aq HCl and stirred 12 h at ambient temperature to decompose the remaining imine. The solution was adjusted to pH 12 using 10% aq NaOH. The solution was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic phases dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by PTLC (hexanes/EtOAc, 2:1) to yield the title compound as a white solid (11.5 mg, 25% yield from the imidazolium precatalyst **145**; trace lactam and azabenzoin as an inseparable mixture from the triazolium precatalyst ***ent*-117•ClO₄**). ^{1}H NMR (500 MHz, CDCl₃) δ 8.24 (d, 1H, J = 8.5 Hz), 7.84 (d, 1H, J = 8.1 Hz), 7.72 (d, 2H, J = 9.0 Hz), 7.71– 7.66 (m, 1H), 7.60 (d, 1H, J = 8.2 Hz), 7.54 (t, 1H, J = 7.5 Hz), 7.04 (t, 1H, J = 7.7 Hz), 6.86 (d, 2H, J = 9.0 Hz), 6.63–6.61 (m, 3H), 6.23 (d, 2H, J = 8.0 Hz), 5.94 (d, 1H, J = 7.7 Hz), 4.87–4.81 (m, 1H), 3.86 (s, 3H), 3.29 (dd, 1H, J = 16.9, 13.7 Hz), 2.70 (dd, 1H, J = 16.9, 7.4 Hz), 2.11 (s, 3H); ^{13}C NMR (125 MHz, CDCl₃) δ 172.7, 164.2, 137.6, 133.8, 132.2, 132.0, 131.4, 131.0, 129.4, 128.7, 128.2, 127.0, 126.4, 126.0, 125.0, 124.4, 122.9, 113.9, 66.2, 55.9, 41.1, 34.6, 21.1; IR (thin film) ν 3055, 2987, 2306, 1736, 1596, 1422, 1266, 1166, 896, 740 cm^{−1}; m.p. 200–202 °C; MS (ESI) calcd for $C_{28}H_{25}NO_4S$ [M]⁺ 471.1504, found 471.1509 [M]⁺; 20% ee from the imidazolium precatalyst **145** as determined by SFC (AS-H column, 15% MeOH in CO_2) t_r = 14.8 min, t_r = 16.2 min; $[\alpha]_D^{20}$ = −90.0 (c 0.067, CH_2Cl_2).

General Procedure for NHC-Promoted Cyclization-Lactonization Catalytic Reactions

A vial was charged with the NHC precatalyst, the substrate, and purged with $N_2(g)$. Next, the solvent was added followed by the base under an atmosphere of $N_2(g)$. The vial was sealed and stirred at the designated temperature until the starting material was consumed as indicated by TLC analysis. Finally, the solvent was removed under reduced pressure and the crude reaction mixture purified by silica gel chromatography.
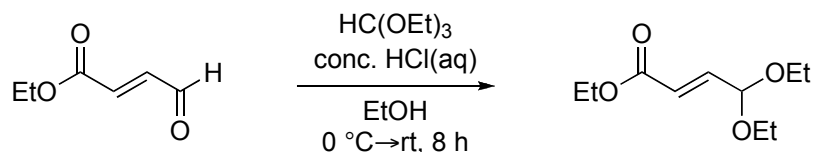
(*E*)-Ethyl 4,4-diethoxybut-2-enoate

To a 1.0 M solution of (*E*)-ethyl 4-oxobut-2-enoate (12.0 mL, 100 mmol, 1.00 equiv) in 200 proof EtOH cooled to 0 °C was added triethylorthoformate (12.8 mL, 120 mmol, 1.2 equiv) and conc. aq HCl (0.100 mL, 1.16 mmol, 0.0116 eqiuv). The solution was stirred at 0 °C for 4 h, allowed to warm to ambient temperature, and stirred until the disappearence of the starting material as indicated by TLC analysis (*ca* 4 h). The solution was concentrated under reduced pressure and the crude oil dissolved in EtOAc (150 mL). This solution was washed with H_2O (150 mL), and the aqueous layer back-extracted with EtOAc (150 mL). The combined organic fractions were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound as a clear liquid (19.5 g, 88%). ^1H NMR (500 MHz, CDCl$_3$) δ 6.80 (dd, 1H, *J* = 15.8, 4.2 Hz), 6.13 (dd, 1H, *J* = 15.8, 1.3 Hz), 5.04 (dd, 1H, *J* = 4.2, 1.3 Hz), 4.20 (q, 2H, *J* = 7.1 Hz), 3.65 (dq, 2H, *J* = 7.1, 2.3 Hz), 3.52 (dq, 2H, *J* = 7.1, 2.4 Hz), 1.29 (t, 3H, *J* =

7.1 Hz), 1.22 (t, 6H, J = 7.1 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 166.3, 143.6, 124.2, 99.2, 61.4, 60.7, 15.3, 14.3; IR (thin film) ν 2981, 2927, 2878, 1722, 1446, 1373, 1304, 1269, 1181, 1058 cm^{-1}; HRMS (ESI) calcd for C$_{10}$H$_{18}$O$_4$ [M]$^+$ 202.1205, found 225.1106 [M+Na]$^+$.
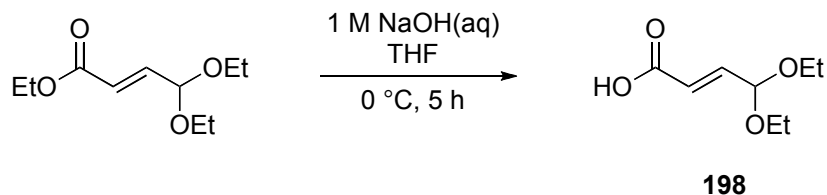
(*E*)-4,4-Diethoxybut-2-enoic acid (198)

A 1.0 M aq solution of NaOH (20 mL, 20 mmol, 1.0 equiv) was added slowly to a chilled (0 °C) 1 M solution of (*E*)-ethyl 4,4-diethoxybut-2-enoate (4.0 g, 20 mmol, 1.0 equiv) in THF (20 mL). The solution was allowed to warm to ambient temperature and stirred until the consumption of starting material was observed by TLC (*ca* 5 h). The solution was diluted with CH$_2$Cl$_2$ (100 mL) and the pH of the aqueous phase adjusted with 1N aq HCl until pH~2 was achieved. The organic layer was separated and the aqueous layer extracted with CH$_2$Cl$_2$ (100 mL). The organic layers were combined, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to afford the title compound as a yellow liquid (3.5 g, quant.). ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.92 (dd, 1H, J = 15.8, 4.0 Hz), 6.16 (dd, 1H. J = 15.8, 1.4 Hz), 5.09 (dd, 1H, J = 4.0, 1.3 Hz), 3.66 (dq, 2H, J = 7.1, 2.4 Hz), 3.54 (dq, 2H, J = 7.1, 2.4 Hz), 1.23 (t, 6H, J = 7.1 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.7, 150.5, 125.0, 103.3, 66.2, 15.1; IR (thin film) ν 3104, 2981, 2937, 2898, 1796, 1761, 1377, 1348, 1136, 1013, 929, 890, 817 cm^{-1}; HRMS (ESI) calcd for C$_8$H$_{14}$O$_4$ [M]$^+$ 174.0892, found 173.0803 [M−H]$^-$.

(*E*)-4,4-Diethoxy-*N*-(2-oxo-2-phenylethyl)but-2-enamide

N,N-Diisopropylethylamine (0.52 mL, 3.0 mmol, 3.0 equiv) was added to a solution of **198** (0.35 g, 2.0 mmol, 2.0 equiv) and HBTU (0.76 g, 2.0 mmol, 2.0 equiv) in CH_2Cl_2 (10 mL). After 10 min of stirring, 2-oxo-2-phenylethanaminium chloride[4] **197** (0.17 g, 1.0 mmol, 1.0 equiv) was added in a single portion and the solution stirred at ambient temperature for 20 h. The solution was diluted with CH_2Cl_2 (15 mL) and washed with sat aq $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were washed with sat aq NH_4Cl (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography afforded the title compound as a white solid (0.195 g, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00–7.98 (m, 2H), 7.63 (t, 1H, *J* = 7.4 Hz), 7.51 (t, 1H, *J* = 7.8 Hz), 6.78 (dd, 1H, *J* = 15.5, 3.8 Hz), 6.70 (bs, 1H), 6.28 (dd, 1H, *J* = 15.5, 1.4 Hz), 5.10 (dd, 1H, *J* = 3.8, 1.4 Hz), 4.84 (d, 2H, *J* = 4.3 Hz), 3.66 (dq, 2H, *J* = 7.1, 2.4 Hz), 3.53 (dq, 2H, *J* = 7.1, 2.4 Hz), 1.23 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.1, 165.2, 140.5, 134.4, 129.1, 128.1, 125.9, 99.2, 61.3, 46.7, 15.4; IR (thin film) ν 3311, 2976, 2873, 1678, 1638, 1377, 1058, 1003, 979 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{21}NO_4$ [M]$^+$ 291.1471, found 314.1356 [M+Na]$^+$.

(E)-4-Oxo-N-(2-oxo-2-phenylethyl)but-2-enamide (196)

A solution of (E)-4,4-diethoxy-N-(2-oxo-2-phenylethyl)but-2-enamide (0.10 g, 0.34 mmol, 1.0 equiv) in THF (4.0 mL) was treated with 2N aq HCl (1.2 mL, 2.4 mmol, 7.0 equiv) at rt and stirred until the consumption of starting material was observed by TLC (*ca* 5 min). The solution was diluted with H_2O (15 mL) and EtOAc (15 mL); the organic layer was separated, washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure affording the title compound as a light tan solid (0.074 g, quant.). ^1H NMR (500 MHz, CDCl$_3$) δ 9.79 (d, 1H, *J* = 7.4 Hz), 8.00 (dd, 2H, *J* = 8.4, 1.2 Hz), 7.66 (dt, 1H, *J* = 7.4, 1.2 Hz), 7.53 (t, 2H, *J* = 7.5 Hz), 7.02 (dd, 1H, *J* = 15.6, 7.4 Hz), 6.89 (d, 1H, *J* = 15.6 Hz), 4.89 (d, 1H, *J* = 4.3 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 193.5, 192.4, 163.4, 141.4, 138.3, 134.7, 129.2, 129.1, 128.2, 46.8; IR (thin film) ν 3316, 3060, 2922, 2848, 1695, 1675, 1670, 1540, 1358, 1230, 984 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{11}NO_3$ [M]$^+$ 217.0739, found 240.0622 [M+Na]$^+$.
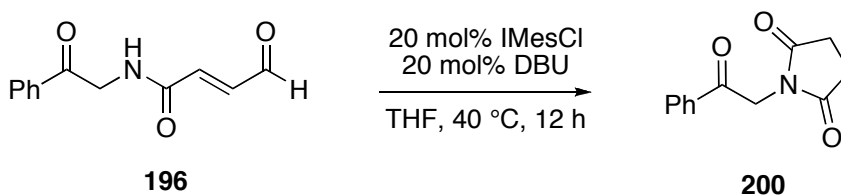
1-(2-Oxo-2-phenylethyl)pyrrolidine-2,5-dione (200)

An oven-dried vial was charged with IMesCl (0.0075 g, 0.022 mmol, 0.20 equiv) and **196** (0.023 g, 0.11 mmol, 1.0 equiv) and purged with N$_2$(g). To this mixture was added THF (1.0 mL) and DBU (3.3 μL, 0.022 mmol, 0.20 equiv). The vial was sealed, and the

reaction stirred at 40 °C for 12 h. The solution was concentrated under reduced pressure and purified by PTLC (hexanes/acetone, 2:1). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.97 (dd, 2H, J = 8.4, 1.2 Hz), 7.63 (dt, 1H, J = 7.4, 1.2 Hz), 7.52–7.49 (m, 2H), 4.95 (s, 2H), 2.87 (s, 4H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 190.3, 176.8, 134.3, 129.0, 128.3, 44.9, 28.5; HRMS (ESI) calcd for C$_{12}$H$_{11}$NO$_3$ [M]$^+$ 217.0739, found 240.0627 [M+Na]$^+$.
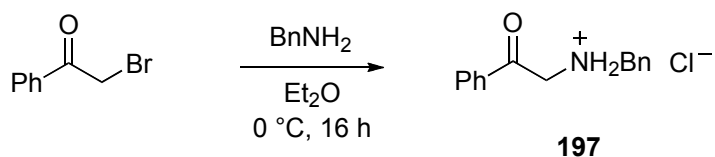
N-Benzyl-2-oxo-2-phenylethanaminium chloride (197)

A 1.0 M solution of 2-bromo-1-phenylethanone (10.0 g, 50.0 mmol, 1.00 equiv) in Et$_2$O (50.0 mL) was added to a chilled (0 °C) 2.0 M solution of benzylamine (10.9 mL, 100 mmol, 2.00 equiv) in Et$_2$O over a 10 minute period and stirred at 0 °C for 16 h. The precipitate was filtered and washed with Et$_2$O. The filtrate was cooled to 0 °C and conc. aq HCl (4.0 mL) was slowly added. The resultant orange precipitate was filtered and washed with Et$_2$O. The precipitate was sonicated in 60 mL of 1:1 Et$_2$O:EtOH (200 proof) until the solid appeared white in color. The precipitate was collected by suction filtration and washed with Et$_2$O affording crop 1 (2.80 g, 21.4%) of the title compound as a white crystalline solid. The filtrate was then concentrated and the resulting solid sonicated in a 1:1 Et$_2$O:EtOH (200 proof) solution until the solid appeared white in color. The precipitate was collected by suction filtration and washed with Et$_2$O affording crop 2 (3.70 g, 28.2%) of the title compound as a white powder. ^{1}H NMR (500 MHz, d$_6$-DMSO) δ 9.45 (bs, 2H), 8.00–7.98 (m, 2H), 7.93–7.91 (m, 1H), 7.77–7.74 (m 1H), 7.63–7.60 (m, 2H), 7.56–7.54 (m, 2H), 7.48–7.44 (m, 2H), 4.82 (s, 2H), 4.21 (s, 2H); ^{13}C NMR (125 MHz, d$_6$-DMSO) δ 192.2, 134.8, 133.7, 131.8, 130.3, 129.2, 128.8, 128.2, 128.1, 51.9, 50.2; IR (KBr) ν

2977, 2912, 2785, 2730, 2608, 2435, 1712, 1579, 1461, 1225, 742 cm⁻¹; HRMS (ESI) calcd for $C_{15}H_{16}ClNO^+$ [M]⁺ 226.1226, found 226.1223 [M]⁺.
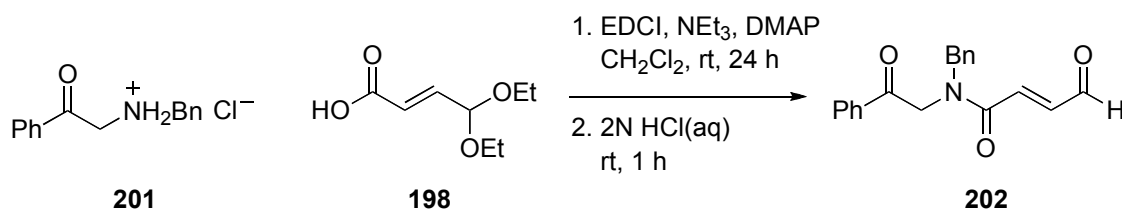
(*E*)-*N*-Benzyl-4-oxo-*N*-(2-oxo-2-phenylethyl)but-2-enamide (196)

To a solution of **198** (1.50 g, 8.61 mmol, 2.00 equiv) in CH_2Cl_2 (50.0 mL) were sequentially added **21** (1.12 g, 4.28 mmol, 1.00 equiv), EDCI (1.65 g, 8.60 mmol, 2.00 equiv), 4-dimethylaminopyridine (0.525 g, 4.30 mmol, 1.00 equiv), and triethylamine (3.00 mL, 21.5 mmol, 5.02 equiv) and the resulting brown solution stirred at ambient temperature for 24 h. The solution was diluted with CH_2Cl_2 (100 mL), washed with 1N aq HCl (2 x 75 mL) followed by sat aq NaHCO₃ (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure affording a brown foam. The foam was dissolved in THF (13 mL) and treated with 6N aq HCl (13 mL, 26 mmol, 6.0 equiv) for 1 h. After diluting the solution with CH_2Cl_2 (~70 mL) and H₂O (~50 mL) the organic phase was separated. The aqueous phase was further extracted with CH_2Cl_2 (2 x 50 mL). The organic phases were combined, dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude aldehyde as a brown solid. Sonication of the crude solid in Et₂O/EtOAc precipitated the pure aldehyde as a tan solid and as a ~3:1 mixture of amide rotamers that was collected by suction filtration and washed with Et₂O (0.60 g, 46% over 2 steps). ¹H NMR (500 MHz, CDCl₃) δ 9.73 (d, 1H, *J* = 7.5 Hz), 9.64* (d, 1H, *J* = 5.2 Hz), 7.93 (d, 2H, *J* = 7.5 Hz), 7.85* (d, 2H, *J* = 7.5 Hz), 7.60–7.22 (m, 9H), 7.65–7.22* (m, 9H), 7.03 (dd, 1H, *J* = 15.5, 7.5 Hz), 7.03* (dd, 1H, *J* = 15.5, 7.5 Hz), 6.96 (d,

1H, J = 5.5 Hz), 6.96* (d, 1H, J = 5.5 Hz), 4.87 (s, 2H), 4.78 (s, 2H), 4.76* (s, 2H), 4.72*

(s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 193.4, 192.5, 165.8, 139.9, 139.7,139.4, 138.9,

135.7, 135.2, 134.7, 134.2, 129.5, 129.4, 129.1, 129.1, 128.9, 128.6, 128.2, 128.1,

126.9, 52.8, 52.2, 50.6; IR (thin film) ν 3065, 3035, 2932, 1697, 1647, 1451, 1358,

1230, 1117, 1077, 994 cm^{-1}; HRMS (ESI) calcd for C$_{19}$H$_{17}$NO$_3$ [M]$^+$ 307.1208, found

308.1284 [M+H]$^+$.

209
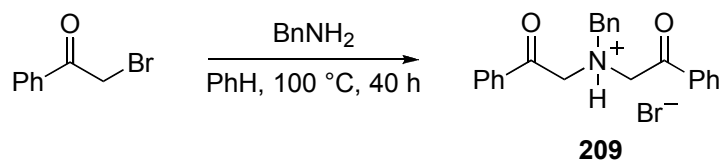
N-Benzyl-2-oxo-*N*-(2-oxo-2-phenylethyl)-2-phenylethanaminium bromide (209)

Prepared by modification of a published procedure:[5] A 2.0 M solution of benzylamine

(5.5 mL, 50 mmol, 1.0 equiv) in benzene (25 mL) was added to a 1.0 M solution of 2-

bromo-1-phenylethanone (10 g, 50 mmol, 2.0 equiv) in benzene (50 mL). The resultant

suspension was then diluted by the addition of an additional 30 mL benzene. The

suspension was heated under reflux at 100 °C for 2 days. After allowing the reaction to

cool to ambient temperature, the precipitate was collected by suction filtration and

washed with benzene (75 mL). The precipitate was suspended in MeOH (75 mL) and

placed in a sonicating bath for 30 min. The precipitate was collected by suction filtration

and washed with MeOH (25 mL). Residual solvent was removed under reduced

pressure affording the title compound as a white powder (8.0 g, 75%). ^{1}H NMR (500

MHz, d$_6$-DMSO) δ 7.88 (d, 4H, J = 7.3 Hz), 7.71 (t, 2H, J = 7.4 Hz), 7.60–7.55 (m, 6H),

7.34–7.32 (m, 3H), 5.05 (bs, 4H), 4.51 (bs, 2H); ^{13}C NMR (125 MHz, d$_6$-DMSO) δ 191.4,

134.9, 132.0, 129.9, 129.2, 128.8, 128.4, 128.1, 60.2, 60.0; IR (KBr) ν 3011, 2977,

2922, 1692, 1604, 1451, 1254, 895 cm^{-1}; HRMS (ESI) calcd for C$_{16}$H$_{22}$NO$_2{}^+$ [M]$^+$ 344.1645, found 344.1647 [M]$^+$.

209 → **210**

cat. Pd/C, H$_2$(g)

MeOH, rt, 8 h
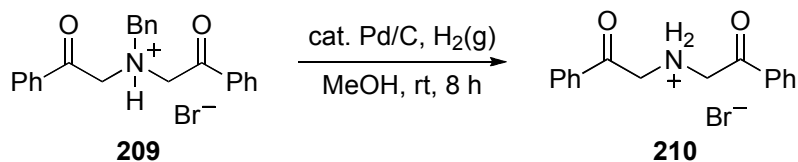
Bis(2-oxo-2-phenylethyl)ammonium bromide (210)

A 200-mL Schlenck flask was charged with 10% Pd/C (0.172 g, 0.162 mmol, 0.010 equiv of Pd). The reaction vessel was evacuated and backfilled with H$_2$(g) 10 times. MeOH (75.0 mL) was added followed by **209** (6.88 g, 16.2 mmol, 1.0 equiv). H$_2$(g) was bubbled through the suspension until all of **209** had dissolved (*ca.* 8 h). The solution was filtered through celite to remove the Pd/C, the Celite cake was washed with MeOH, and the filtrate concentrated under reduced pressure. The crude solid was recrystallized from MeOH to afford the title compound as a white solid (4.6 g, 85%). ^{1}H NMR (500 MHz, d$_6$-DMSO) δ 9.54 (bs, 2H), 8.00 (d, 4H, *J* = 7.6 Hz), 7.76 (t, 2H, *J* = 7.4 Hz), 7.62 (t, 4H, *J* = 7.7 Hz), 4.84 (s, 4H); ^{13}C NMR (125 MHz, d$_6$-DMSO) δ 192.2, 134.9, 133.6, 129.3, 128.3, 52.3; IR (KBr) ν 3001, 2912, 2814, 2716, 2588, 1687, 1599, 1554, 1368, 1259, 969 cm^{-1}; HRMS (ESI) calcd for C$_{15}$H$_{16}$NO$^+$ [M]$^+$ 226.1226, found 226.1232 [M]$^+$.

(*E*)-4,4-Diethoxy-*N,N*-bis(2-oxo-2-phenylethyl)but-2-enamide (211)

In a single portion, **210** (4.0 g, 12 mmol, 1.0 equiv) was added to a solution of **198** (4.2 g, 24 mmol, 2.0 equiv) in CH_2Cl_2 (120 mL). Next, EDCI (4.6 g, 24 mmol, 2.0 equiv), *N,N*-dimethylaminopyridine (1.5 g, 12 mmol, 1.0 equiv) and *N,N*-diisopropylethylamine (10.5 mL, 60 mmol, 5.0 equiv) were sequentially added. The brown solution was stirred for 24 h at rt. After concentration of the solution under reduced pressure, the crude material was dissolved in EtOAc (250 mL) and sequentially washed with an aq 10% citric acid solution (2 x 125 mL), H_2O (100 mL), sat aq $NaHCO_3$ (2 x 125 mL), H_2O (1 x 100 mL), and brine (1 x 100 mL). The EtOAc solution was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc, 2:1) afforded the title compound as a yellow foam (3.1 g, 63%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (m, 4H), 7.63–7.55 (m, 2H), 7.50–7.43 (m, 4H), 6.74 (dd, 1H, *J* = 15.3, 3.8 Hz), 6.38 (d, 1H, 15.3 Hz), 5.01 (s, 4H), 4.99 (d, 1H, *J* = 3.8 Hz), 3.57–3.53 (m, 2H), 3.46–3.42 (m, 2H), 1.10 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.9, 194.0, 167.2, 142.1, 135.1, 134.6, 134.3, 133.9, 129.1, 128.9, 128.2, 128.0, 122.4, 99.2, 61.2, 54.9, 52.9, 15.2; IR (thin film) ν 3063, 2976, 2927, 1697, 1658, 1449, 1346, 1229, 1117, 1059, 1004, 756 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{27}NO_5$ [M]$^+$ 409.1889, found 432.1788 [M+Na]$^+$.

(*E*)-4-Oxo-*N*,*N*-bis(2-oxo-2-phenylethyl)but-2-enamide (208)

A 0.33 M solution of **211** (3.1 g, 7.6 mmol, 1.0 equiv) in THF (23 mL) was treated with 2N

aq HCl (23 mL, 46 mmol, 6.0 equiv) and stirred vigorously for 1 h at ambient

temperature. The solution was diluted with EtOAc (125 mL), washed with brine (100

mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the

title compound as a yellow foam (2.5 g, quant). ^{1}H NMR (500 MHz, CDCl3) δ 9.66 (d, 1H,

J = 7.1 Hz), 7.99–7.95 (m, 3H), 7.66–7.60 (m, 2H), 7.54–7.46 (m, 4H), 7.02 (d, 1H, *J* =

15.7 Hz), 6.94 (dd, 1H, *J* = 15.7, 7.1 Hz), 5.05 (s, 4H); ^{13}C NMR (125 MHz, CDCl3) δ

194.1, 193.3, 192.4, 166.0, 139.0, 136.1, 134.8, 134.7, 134.2, 134.1, 129.2, 129.0,

128.1, 128.1, 55.0, 53.1; IR (thin film) v 3068, 2932, 2834, 2742, 1697, 1654, 1600,

1449, 1351, 1229, 1112, 917, 756 cm^{−1}; HRMS (ESI) calcd for $C_{20}H_{17}NO_4$ [M][+] 335.1158,

found 358.1031 [M+Na][+].
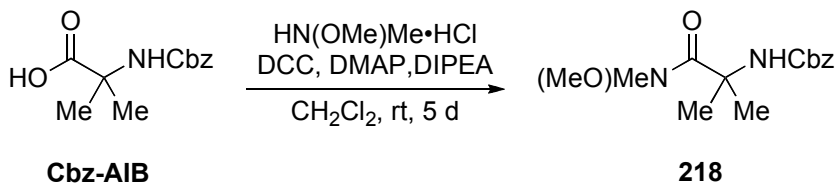
Benzyl-1-(methoxy(methyl)amino)-2-methyl-1-oxopropan-2-ylcarbamate (218)

To stirring solution of Cbz-AIB[6] (23.0 g, 96.9 mmol, 1.00 equiv) in CH_2Cl_2 (400 mL) was

sequentially added *N*,*O*-dimethyl hydroxylamine hydrochloride (11.3 g, 116 mmol, 1.20

equiv), *N,N*-dimethylaminopyridine (14.2 g, 116 mmol, 1.20 equiv), *N,N*-diisopropylethylamine (20.0 mL, 116 mmol, 1.2 equiv), and *N,N'*-dicyclohexylcarbodiimide (11.3 g, 116 mmol, 1.20 equiv). The resultant suspension was stirred for 5 days. The precipitate was filtered and the filtrate diluted with CH_2Cl_2 (400 mL). This solution was sequentially washed with an aq 10% citric acid solution (2 x 400 mL), sat aq $NaHCO_3$ (2 x 400 mL), and H_2O (2 x 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc, 3:2) afforded the title compound as white solid (18.0 g, 67 %). ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.29 (m, 5H), 5.77 (bs, 1H), 5.08 (s, 2H), 3.60 (s, 3H), 3.19 (s, 3H) 1.60 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 154.7, 136.8, 128.6, 128.2, 66.4, 60.8, 57.3, 34.0, 24.2; IR (thin film) ν 3327, 3034, 2985, 2937, 1717, 1649, 1527, 1454, 1386, 1367, 1258, 1073, 995, 746, 698 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{20}N_2O_4$ $[M]^+$ 280.1432, found 303.1311 $[M+Na]^+$.

218   **219**
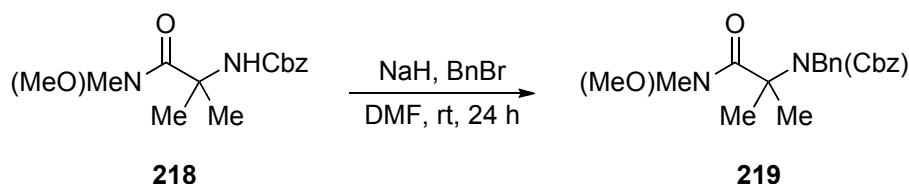
Benzyl benzyl(1-(methoxy(methyl)amino)-2-methyl-1-oxopropan-2-yl)carbamate (219)

To a stirring solution of **218** (9.16 g, 32.7 mmol, 1.00 equiv) in DMF (165 mL) cooled to 0 °C was added NaH (60% mineral oil dispersion, 1.57 g, 39.2 mmol, 1.20 equiv). After effervescence had ceased (*ca* 10–15 min), benzyl bromide (4.30 mL, 36.0 mmol, 1.10 equiv) was slowly added. The solution was allowed to warm to ambient temperature and stirred for 24 h. The solution was poured into a separatory funnel containing a solution of 1:1 sat aq NH_4Cl/brine (500 mL) and extracted with EtOAc (2 x 300 mL). The combined

organic fractions were then washed with brine (500 mL), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (gradient, hexanes/EtOAc 2:1→4:3→1:1) afforded the title compound as a white solid (12.1 g, quant). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30–7.24 (m, 10H), 5.22 (s, 3H), 4.68 (s, 2H), 3.38 (bs, 3H), 3.11 (bs, 3H), 1.43 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 175.2, 139.3, 136.5, 128.6, 128.4, 128.2, 127.5, 127.2, 67.5, 62.3, 60.0, 47.7, 33.8, 25.1; IR (thin film) ν 3033, 2990, 2939, 1697, 1665, 1401, 1356, 1228, 1095, 998 699 cm^{-1}; HRMS (ESI) calcd for C$_{21}$H$_{26}$N$_2$O$_4$ [M]$^+$ 370.1893, found 393.1798 [M+Na]$^+$.
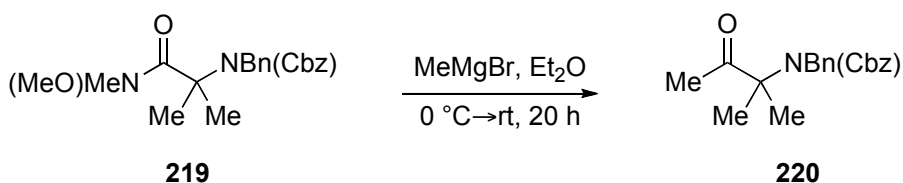
Benzyl benzyl(2-methyl-3-oxobutan-2-yl)carbamate (220)

Methyl magnesium bromide (3.0 M in Et$_2$O, 55.0 mL, 165 mmol, 5.00 equiv) was added slowly to a chilled solution (0 °C) of **219** (12.1 g, 32.7 mmol, 1.00 equiv) in Et$_2$O (165 mL). The suspension was allowed to warm to ambient temperature and stirred for 20 h. The suspension was cooled again to 0 °C and ice was carefully and slowly added over a 2 h period until the addition of more ice no longer caused gas evolution. The solution was decanted from the precipitate into a separatory funnel and diluted with EtOAc (300 mL) and H$_2$O (300 mL). The aqueous phase was removed; the organic phase was washed with brine (250 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude material was sonicated in Et$_2$O and the title compound precipitated as a white solid that was collected by suction filtration (crop 1: 5.5 g, 59%). The filtrate was concentrated and sonicated in a 3:2 solution of hexanes/Et$_2$O. Again the

title compound precipitated as a white solid and was collected by suction filtration (crop 2: 2.0 g, 19%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30–7.24 (m, 10H), 5.16 (s, 2H), 4.64 (s, 2H), 2.05 (bs, 3H), 1.26 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 207.5, 156.6, 139.4, 136.2, 128.7, 128.6, 128.3, 127.3, 127.1, 67.9, 66.9, 47.5, 34.0, 23.6, 23.1; IR (thin film) ν 3063, 2985, 2941, 1722, 1693, 1458, 1405, 1351, 1253, 1220, 1088, 741 cm^{-1}; HRMS (ESI) calcd for C$_{20}$H$_{23}$NO$_3$ [M]$^+$ 325.1678, found 348.1579 [M+Na]$^+$.

220   **221**
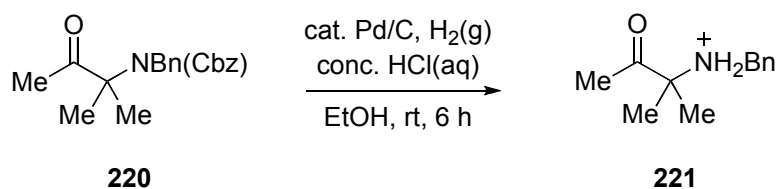
N-Benzyl-2-methyl-3-oxobutan-2-aminium chloride (221)

A 2-neck, round-bottomed flask was purged with N$_2$(g) and charged with 10% Pd/C (1.14 g, 1.08 mmol, 0.0500 equiv of Pd). The reaction vessel was evacuated and back-filled with H$_2$(g) three times before EtOH (200 proof, 100 mL) was added. Next, **220** (7.00 g, 21.5 mmol, 1.00 equiv) was added followed by conc. aq HCl (3.70 mL, 43.0 mmol, 2.00 equiv).   The heterogeneous solution was stirred at ambient temperature under an atmosphere of H$_2$(g) until the starting material was consumed as indicated by TLC analysis. Upon completion of the reaction, the solids were removed by filtration through a pad of Celite and the filter cake washed with MeOH. The filtrate was concentrated under reduced pressure to provide a crude white solid. The crude material was suspended in CH$_2$Cl$_2$ (200 mL), treated with sat aq NaHCO$_3$ and stirred at ambient temperature for 2 h. The biphasic mixture was transferred to a separatory funnel, the organic phase removed and the aqueous phase extracted with CH$_2$Cl$_2$ (100 mL). The combined organic phases were washed with brine (150 mL), dried over Na$_2$SO$_4$, filtered

and concentrated under reduced pressure providing a crude oil. The oil was subjected to high vacuum to remove any 3-amino-3-methylbutan-2-one that resulted from over hydrogenation. The remaining crude material was dissolved in Et_2O (100 mL), cooled to 0 °C, treated with anhydrous HCl (4.0 M in dioxane, 5.40 mL, 21.6 mmol), and stirred for 30 min. The resultant precipitate was collected by vacuum filtration to afford the title compound as a white solid (4.31 g, 88%). [^1]H NMR (500 MHz, $CDCl_3$) δ 9.89 (bs, 2H), 7.64 (d, 2H, J = 7.0 Hz), 7.35–7.30 (m, 3H), 3.86 (t, 2H, J = 5.9 Hz), 2.18 (s, 3H), 1.54 (s, 6H); [^13]C NMR (125 MHz, $CDCl_3$) δ 204.7, 131.4, 130.5, 129.5, 128.9, 67.4, 48.0, 24.5, 21.6; IR (thin film) ν 3424, 3034, 2917, 2855, 1720, 1547, 1453, 1133, 757, 702 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{18}NO_3$ [M]$^+$ 192.1383, found 192.1390 [M]$^+$.
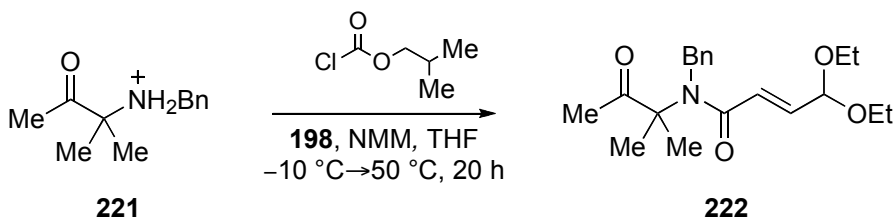
(*E*)-*N*-Benzyl-4,4-diethoxy-*N*-(2-methyl-3-oxobutan-2-yl)but-2-enamide (222)

Isobutyl chloroformate (0.52 mL, 4.0 mmol, 1.0 equiv) was added drop-wise to a solution of **198** (0.70 g, 4.0 mmol, 1.0 equiv) and *N*-methylmorpholine (2.2 mL, 20 mmol, 5.0 equiv) in THF (20 mL) at −10 °C. The resultant suspension was stirred for 20 min at −10 °C before the addition of **221** (1.1 g, 4.8 mmol, 1.2 equiv). The reaction vessel was equipped with a water-jacketed condenser and stirred at 50 °C for 20 h. The suspension was allowed to cool to ambient temperature, poured onto an aqueous 10% citric solution (50 mL) and extracted with EtOAc (75 mL). The organic extract was sequentially washed with aq 10% citric acid solution (50 mL), H_2O (30 mL), sat aq $NaHCO_3$ (2 x 50 mL), H_2O

(30 mL), and brine (30 mL). The solution was dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc, 3:2 doped with 0.5%/vol NEt$_3$) provided the title compound as a white solid (1.1 g, 78%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.40–7.35 (m, 4H), 7.31–7.28 (t, 1H, J = 6.8 Hz), 6.82 (dd, 1H, J = 15.2, 4.0 Hz), 6.45 (d, 1H, J = 15.2 Hz), 4.96 (d, 1H, J = 4.0 Hz), 4.67 (s, 2H), 3.59–3.53 (m, 2H), 3.45–3.39 (m, 2H), 2.18 (s, 3H), 1.30 (s, 6H), 1.12 (t, 6H, J = 7.0 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 206.1, 167.2, 142.9, 138.3, 129.1, 127.7, 126.3, 123.7 99.5, 66.4, 61.5, 47.8, 24.4, 22.9, 15.2; IR (thin film) ν 3034, 2980, 2931, 2883, 1717, 1663, 1619, 1410, 1351, 1121, 1053, 737 cm^{-1}; HRMS (ESI) calcd for C$_{20}$H$_{29}$NO$_4$ [M]$^+$ 347.2097, found 348.2163 [M+H]$^+$.

222   **217**
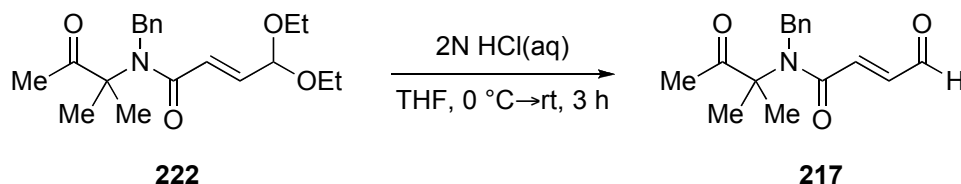
(*E*)-*N*-Benzyl-*N*-(2-methyl-3-oxobutan-2-yl)-4-oxobut-2-enamide (217)

A chilled (0 °C) solution of **222** (0.25 g, 0.72 mmol, 1.0 equiv) in THF (3.6 mL) was treated with 2N aq HCl (2.1 mL, 4.3 mmol, 6.0 equiv). The solution was slowly allowed to warm to ambient temperature. Upon completion, as observed by TLC analysis, the solution was diluted with EtOAc (25 mL), washed with brine (20 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc, 3:2 doped with 0.5%/vol NEt$_3$) provided the title compound as a white solid (0.13 g, 64%). ^{1}H NMR (500 MHz, CDCl$_3$) δ ; 9.62 (d, 1H, J = 7.0 Hz), 7.46–7.33 (m, 5H), 7.06–6.97 (m, 2H), 4.74 (s, 2H), 2.23 (s, 3H), 1.37 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 206.0, 192.3, 165.8, 140.1, 137.4, 129.4, 128.2, 126.1,

66.8, 48.0, 24.7, 23.0; IR (thin film) ν 3034, 2985, 2931, 2849, 2736, 1712, 1693, 1644, 1419, 1351, 1254, 1117, 1029, 976 cm⁻¹; HRMS (ESI) calcd for $C_{16}H_{19}NO_3$ [M]⁺ 273.1365, found 274.1440 [M+H]⁺.
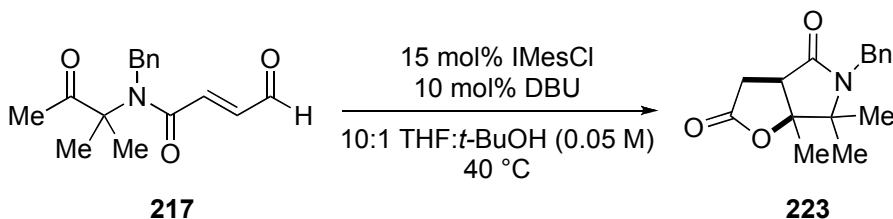
(3aR,6aR)-5-Benzyl-6,6,6a-trimethyltetrahydro-2H-furo[2,3-c]pyrrole-2,4(5H)-dione (223)

Prepared according to the general procedure for NHC-promoted cyclization-lactonization. The following procedure is representative: An oven-dried vial was charged with IMesCl (13.4 mg, 0.0393 mmol, 0.150 equiv) and **217** (72.0 mg, 0.263 mmol, 1.00 equiv). The vial was purged with N_2(g) and charged with 10:1 THF:t-BuOH (5.2 mL) and DBU (0.25 M solution in 10:1 THF: t-BuOH, 0.10 mL, 0.025 mmol, 0.10 equiv). The vial was capped and the reaction stirred at 40 °C for 4.5 h. The solvent was removed under reduced pressure and the crude solid purified by flash column chromatography (gradient, hexanes/EtOAc/i-PrOH, 49:49:2→47.5:47.5:5) affording the title compound as a white foam (57 mg, 79%). ¹H NMR (500 MHz, CDCl₃) δ 7.31–7.28 (m, 2H), 7.26–7.21 (m, 3H), 4.52 (d, 1H, J = 15.5 Hz), 4.41 (d, 1H, J = 15.5 Hz), 3.08 (dd, 1H, J = 18.0, 0.7 Hz), 3.03 (d, 1H, J = 9.0 Hz), 2.89 (dd, 1H, J = 18.0, 9.0 Hz), 1.45 (s, 3H), 1.26 (s, 3H), 1.07 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.0, 171.9, 137.9, 128.9, 127.6, 127.5, 90.2, 65.9, 46.5, 43.5, 31.7, 24.7, 20.2, 18.9; IR (thin film) ν 2976, 2937, 1780, 1693, 1410, 1268, 1229, 1200, 1122, 1083, 946 cm⁻¹; HRMS (ESI) calcd for $C_{16}H_{19}NO_3$ [M]⁺ 273.1365, found 296.1249 [M+Na]⁺.
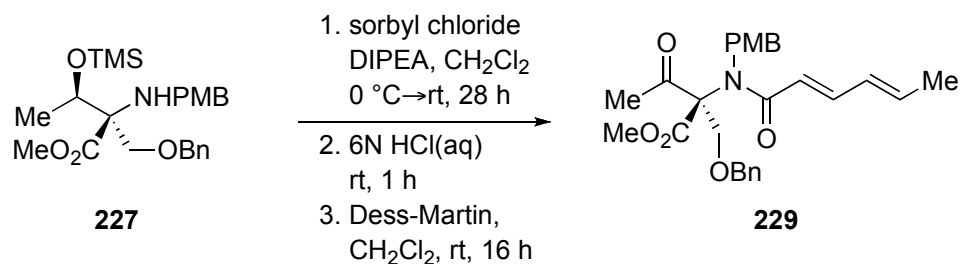
(*R*)-Methyl 2-(benzyloxymethyl)-2-((2*E*,4*E*)-*N*-(4-methoxybenzyl)hexa-2,4-dienamido)-3-oxobutanoate (229)

To a 0.50 M solution of **227**[8] (0.357 g, 0.80 mmol, 1.0 equiv) in CH_2Cl_2 (1.6 mL) cooled to 0 °C was added *N,N*-diisopropylethylamine (0.21 mL, 1.2 mmol, 1.5 equiv). Sorbyl chloride (0.125 g, 0.96 mmol, 1.2 equiv) was added drop-wise and the solution stirred at 0 °C for 0.5 h before being allowed to warm to ambient temperature. Stirring was continued for an additional 22 h. The solution was diluted with CH_2Cl_2 (20 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was dissolved in THF (4.0 mL) and treated with 6N aq HCl (1.0 mL, 6.0 mmol, 7.5 equiv) at ambient temperature for 3 h. The solution was diluted with EtOAc (25 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude orange oil was dissolved in CH_2Cl_2 (8.0 mL), Dess-Martin periodinane (0.41 g, 0.96 mmol, 1.2 equiv) was added and the suspension stirred overnight. The solvent was removed under reduced pressure and the crude material taken up in EtOAc (30 mL). The solution was washed with a 1:1 solution of sat aq $NaHCO_3$/sat aq $Na_2S_2O_3$ (20 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc, 4:1 doped with 0.1%/vol NEt_3) provided the title compound as a light yellow foam (0.225 g, 60% over 3 steps). ^{1}H NMR (500 MHz,

CDCl$_3$) δ 7.33–7.26 (m, 6H), 7.12–7.11 (m, 2H), 6.90 (d, 2H, J = 8.5 Hz), 6.11–6.05 (m, 2H), 6.02 (d, 1H, J = 14.8 Hz), 4.91 (d, 1H, J = 18.4 Hz), 4.76 (d, 1H, J = 18.4 Hz), 4.30 (d, 1H, J = 11.9 Hz), 4.26 (d, 1H, J = 11.9 Hz), 3.82 (s, 3H), 3.79–3.74 (m, 2H), 3.77 (s, 3H), 2.42 (s, 3H), 1.78 (d, 3H, J = 5.0 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.1, 169.9, 168.8, 158.8, 145.4, 139.1, 137.0, 130.9, 130.2, 128.5, 128.0, 127.6, 127.3, 117.9, 114.2, 73.8, 70.7, 55.4, 52.9, 48.9, 28.1, 18.7; IR (thin film) ν 3029, 3000, 2951, 2839, 1737, 1654, 1617, 1517, 1356, 1249, 1175, 1098, 1029, 1000 cm^{-1}; HRMS (ESI) calcd for C$_{27}$H$_{31}$NO$_6$ [M]$^+$ 465.2151, found 466.2240 [M+H]$^+$.
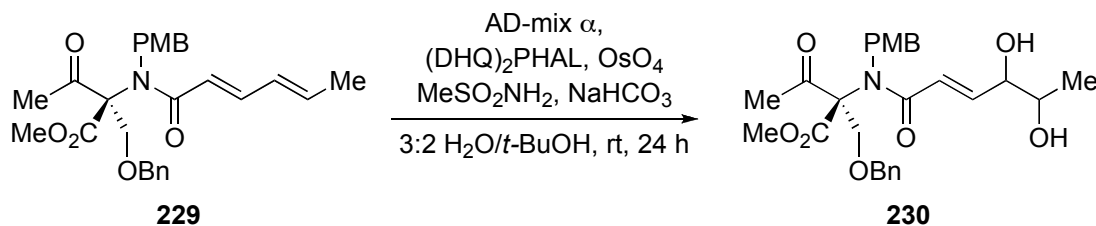
(2R)-Methyl-2-(benzyloxymethyl)-2-((E)-4,5-dihydroxy-N-(4-methoxybenzyl)hex-2-enamido)-3-oxobutanoate (230)

To a round-bottomed flask charged with **229** (0.042 g, 0.090 mmol, 1.0 equiv) was sequentially added AD-mix α (0.126 g), (DHQ)$_2$PHAL (0.0077 g, 0.0099 mmol, 0.11 equiv), NaHCO$_3$ (0.0023 g, 0.27 mmol, 3.0 equiv), MeSO$_2$NH$_2$ (0.0086 g, 0.090 mmol, 1.0 equiv) and a solution of H$_2$O/t-BuOH (5:3, 1.5 mL). The mixture was cooled to 0 °C and OsO$_4$ (4% wt in H$_2$O, 0.0023 g, 0.0090 mmol, 0.10 equiv) was added. The mixture was allowed to warm to ambient temperature and stirred vigourously for 24 h before being quenched with sat aq Na$_2$SO$_3$ (0.5 mL). The aqueous mixture was extracted with EtOAc (4 x 7 mL), the combined extracts washed with 2N aq KOH (5.0 mL) and brine (5.0 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure.

Purification by flash column chromatography (CHCl₃/MeOH, 15:1) yielded the title compound as a light tan foam (0.020 g, 44%). ^{1}H NMR (500 MHz, CDCl₃) δ 7.37–7.26 (m, 5H), 7.12–7.11 (m, 2H), 6.89 (d, 2H, J = 8.6 Hz), 6.87–6.83 (m, 1H), 6.42 (d, J = 15.0 Hz), 4.91 (d, 1H, J = 18.4 Hz), 4.79 (d, 1H, J = 18.3 Hz), 4.29 (d, 1H, J = 11.9 Hz), 4.26 (d, 1H, J = 11.9 Hz), 3.93 (bd, 1H, J = 4.1 Hz), 3.81 (s, 3H), 3.78 (s, 3H), 3.74 (s, 2H), 3.62 (bs, 1H), 2.56 (d, 1H, J = 5.0 Hz), 2.41 (s, 3H), 1.70 (bs, 1H), 1.14 (d, 3H, J = 6.3 Hz); ^{13}C NMR (125 MHz, CDCl₃) δ 198.1, 169.2, 168.6, 158.9, 146.4, 136.8, 130.5, 128.5, 128.1, 127.7, 127.3, 121.6, 114.2, 77.5, 76.0, 73.9, 70.5, 70.2, 55.4, 53.0, 49.0, 28.2, 19.1; IR (thin film) ν 3420, 3029, 2932, 2878, 1737, 1712, 1658, 1615, 1517, 1409, 1361, 1244, 1092, 824 cm⁻¹; HRMS (ESI) calcd for C₂₇H₃₃NO₈ [M]⁺ 499.2206, found 500.2278 [M+H]⁺.
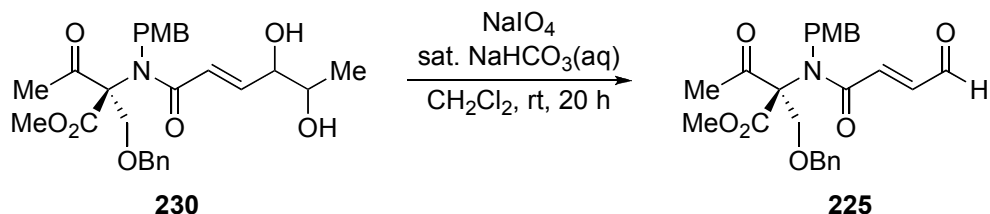
(R,E)-Methyl-2-(benzyloxymethyl)-2-(N-(4-methoxybenzyl)-4-oxobut-2-enamido)-3-oxobutanoate (225)

A solution of **230** (0.043 g, 0.086 mmol, 1.0 equiv) in CH₂Cl₂ (1.0 mL) was treated with sat aq NaHCO₃ (0.10 mL) and NaIO₄ at ambient temperature for 20 h. The heterogeneous mixture was filtered through a plug of Na₂SO₄ that was further washed with CH₂Cl₂ (15 mL). The filtrate was concentrated under reduced pressure to afford the title compound as a white foam (0.039 g, quant). ^{1}H NMR (500 MHz, CDCl₃) δ 9.56 (d, 1H, J = 7.1 Hz), 7.38–7.33 (m, 2H), 7.31–7.26 (m, 3H), 7.13–7.11 (m, 2H), 7.01–6.92 (m, 4H), 4.97 (d, 1H, J = 18.4 Hz), 4.81 (d, 1H, J = 18.6 Hz), 4.32 (d, 1H, J = 11.9 Hz), 4.28

(d, 1H, J = 11.7 Hz), 3.83 (s, 3H), 3.81 (s, 3H), 3.79 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (125

MHz, CDCl$_3$) δ 197.8, 192.4, 168.0, 167.5, 159.2, 140.2, 139.6, 136.5, 129.7, 128.6,

128.2, 127.8, 127.2, 114.5, 77.9, 74.0, 70.3, 55.5, 53.2, 49.2, 28.1; IR (thin film) ν 3006,

2953, 2922, 2834, 1742, 1694, 1651, 1513, 1412, 1357, 1248, 1110 cm^{-1}; HRMS (ESI)

calcd for C$_{25}$H$_{27}$NO$_7$ [M]$^+$ 453.1788, found 476.1665 [M+Na]$^+$.
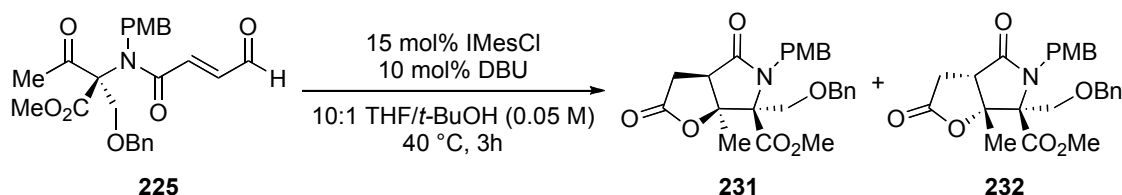
(3a*R*,6*R*,6a*S*)-Methyl 6-(benzyloxymethyl)-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydro-2*H*-furo[2,3-*c*]pyrrole-6-carboxylate (231 deisred) and (3a*S*,6*R*, 6a*R*)-Methyl 6-(benzyloxymethyl)-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydro-2*H*-furo[2,3-*c*]pyrrole-6-carboxylate (232 undesired)

Prepared according to the general procedure for the NHC-promoted cyclization-lactonization. The following procedure is representative: An oven-dried vial containing **225** (12.4 mg, 0.027 mmol, 1.0 equiv) was charged with IMesCl (1.4 mg, 0.0040 mmol, 0.15 equiv). The vial was purged with N$_2$(g) and then charged with 10:1 THF:*t*-BuOH (0.55 mL) and DBU (0.50 µL, 0.0036 mmol, 0.10 equiv). The vial was capped and the reaction stirred at 40 °C for 6 h. The solvent was removed under reduced pressure and the crude solid purified by flash column chromatography (hexanes/acetone, 3:1) to afford the mixture of diastereomers as a white film (9.3 mg, 75%).

231 desired: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.33–7.26 (m, 5H), 7.09 (d, 2H, J = 6.8 Hz), 6.78 (d, 2H, J = 8.6 Hz), 5.04 (d, 1H, J = 15.2 Hz), 4.28 (d, 1H, J = 15.2 Hz), 3.91 (d, 1H, J = 11.5 Hz), 3.83–3.80 (m, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.21 (d, 1H, J = 10.4 Hz),

3.04 (d, 1H, J = 9.3 Hz), 2.95 (d, 1H, J = 18.3 Hz), 2.80 (dd, 1H, J = 18.3, 9.6 Hz), 1.60 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 173.7, 173.1, 167.1, 159.2, 136.9, 130.2, 129.6, 128.6, 128.1, 127.5, 113.8, 88.6, 76.0, 73.0, 67.9, 55.4, 53.0, 47.7, 45.3, 30.9, 19.6; IR (thin film) ν 2956, 2922, 2853, 1790, 1761, 1702, 1614, 1512, 1454, 1400, 1249, 1181, 1131, 737 cm^{-1}; HRMS (ESI) calcd for C$_{25}$H$_{27}$NO$_7$ [M]$^+$ 453.1788, found 476.1690 [M+H]$^+$.

232 undesired: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36–7.29 (m, 3H), 7.20 (d, 2H, J = 6.8 Hz), 7.08 (d, 2H, J = 8.6 Hz), 6.78 (d, 2H, J = 8.6 Hz), 4.67 (d, 1H, J = 15.1 Hz), 4.37 (d, 1H, J = 15.1 Hz), 4.30 (d, 1H, J = 11.6 Hz), 4.25 (d, 1H, J = 11.6 Hz), 3.89 (d, 1H, J = 10.2 Hz), 3.78 (s, 3H), 3.71 (d, 1H, J = 10.0 Hz), 3.63 (s, 3H), 3.04–2.99 (m, 2H), 2.84 (dd, 1H, J = 18.4, 10.0 Hz), 1.47 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 173.6, 173.4, 169.4, 160.0, 137.3, 129.4, 129.2, 128.5, 128.0, 127.9, 86.8, 75.5, 73.8, 68.9, 55.4, 53.0, 47.2, 45.3, 31.1, 21.6; IR (thin film) ν 2951, 2927, 2853, 1790, 1746, 1702, 1610, 1512, 1439, 1249, 1127, 737 cm^{-1}; HRMS (ESI) calcd for C$_{25}$H$_{27}$NO$_7$ [M]$^+$ 453.1788, found 476.1691 [M+H]$^+$.

6.5 References

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Chapter 7:   Spectra
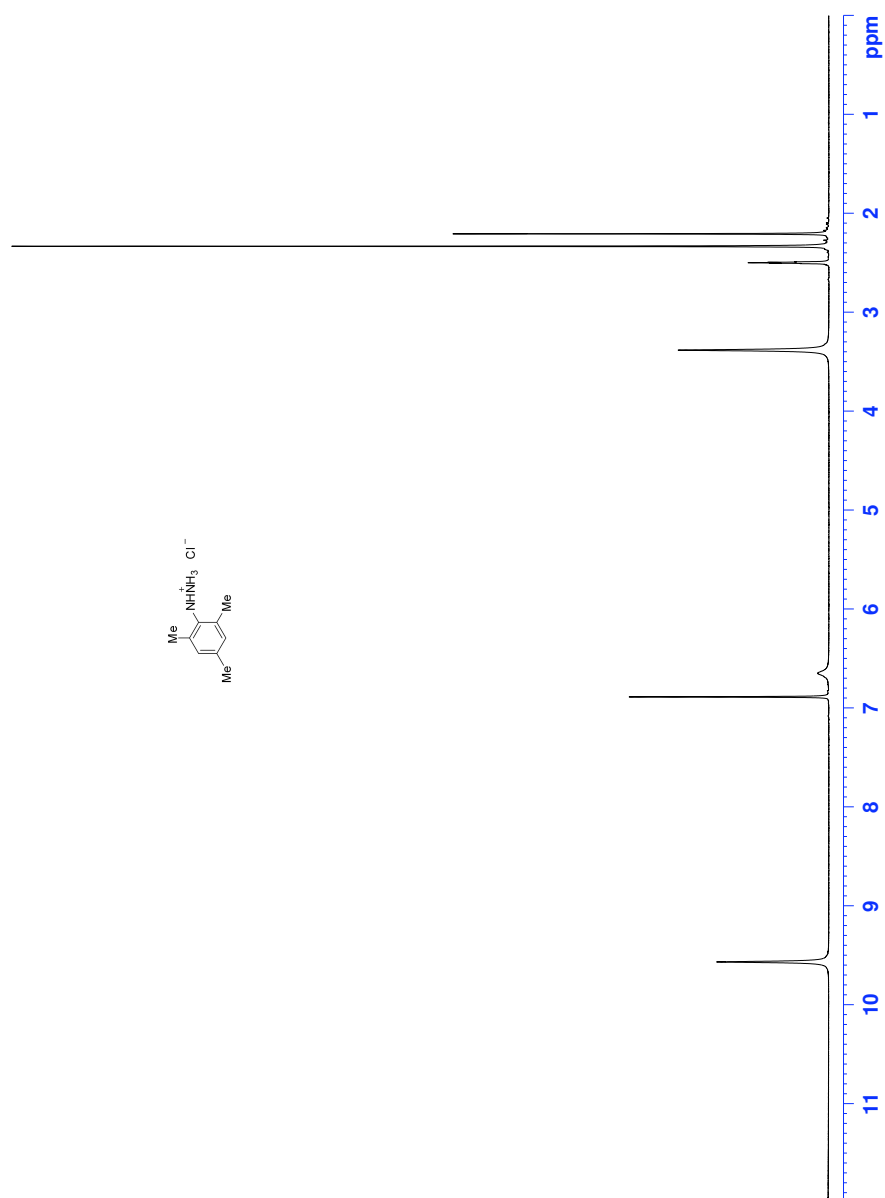
Figure 33. ^1H NMR spectrum of compound **108**.

200
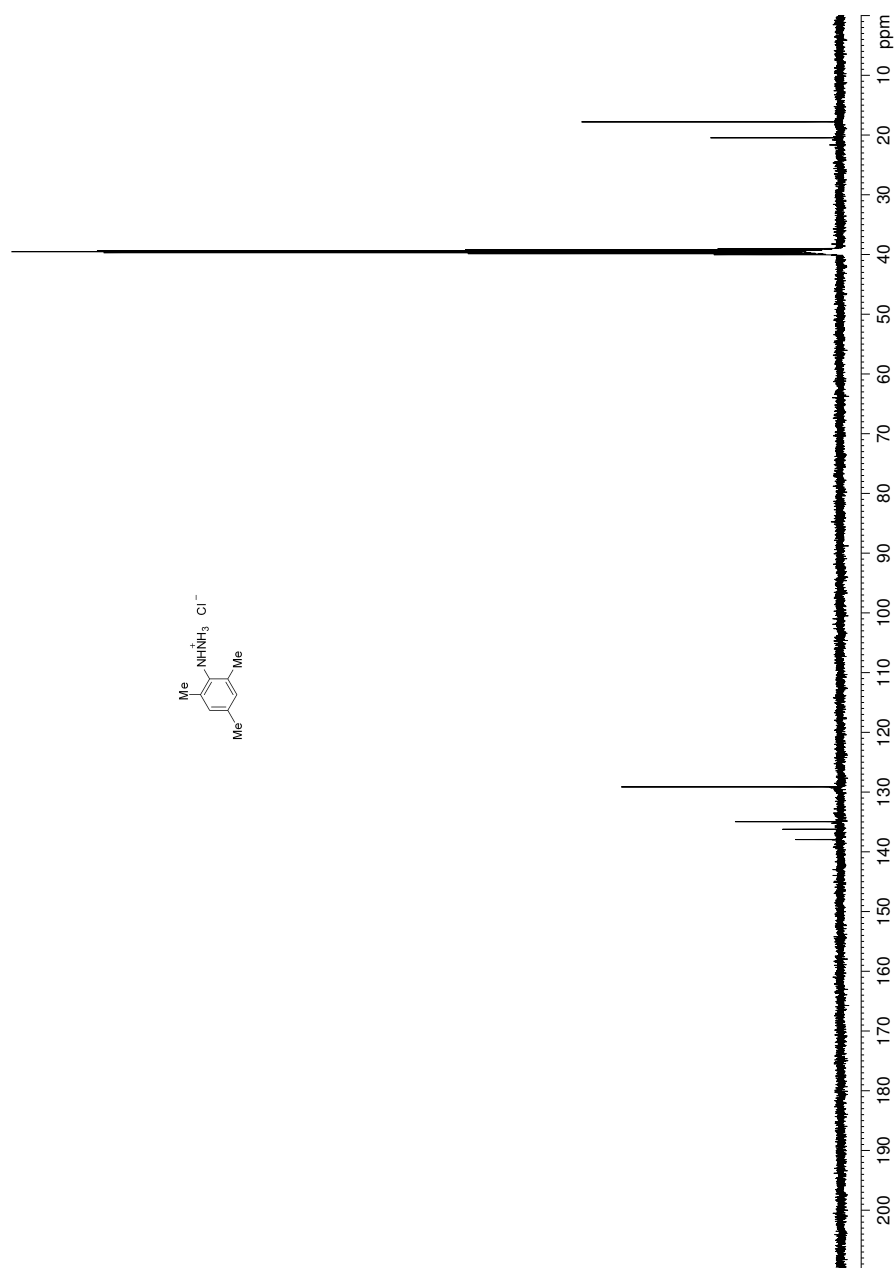
Figure 34. ^{13}C NMR spectrum of compound **108**.

201
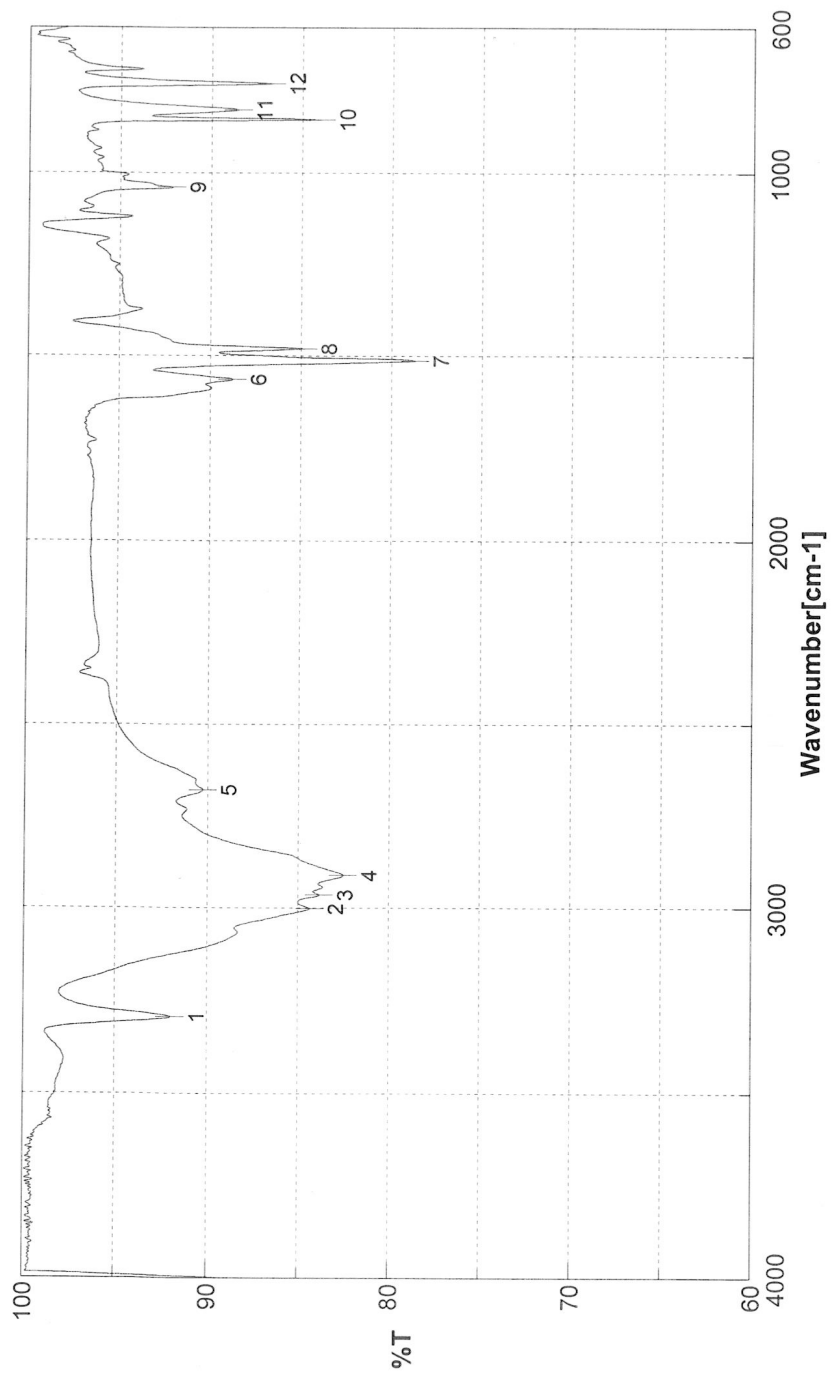
Figure 35. IR spectrum of compound **108**.
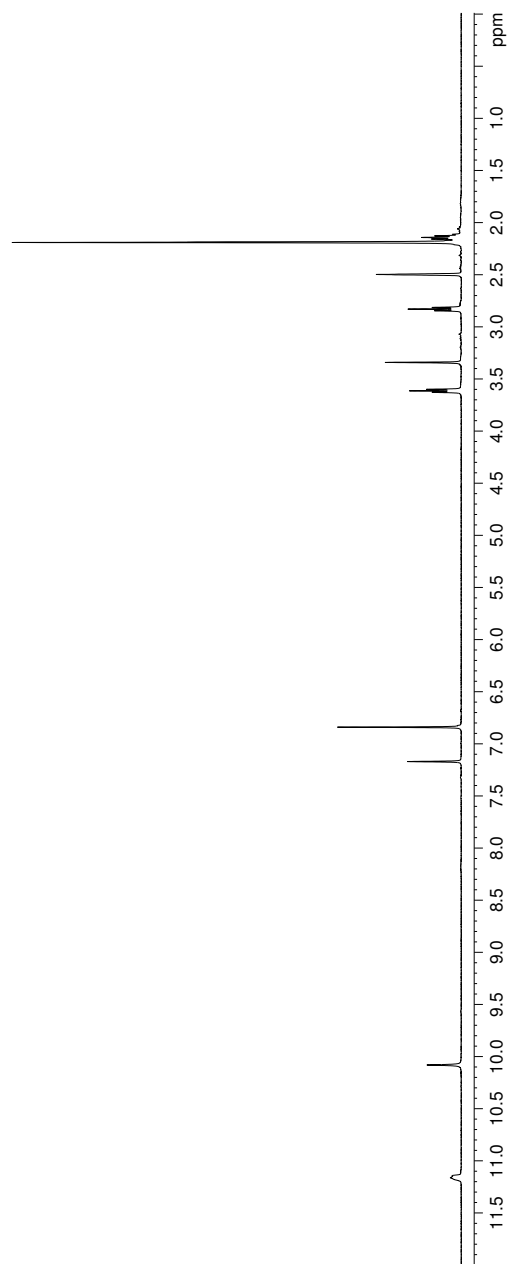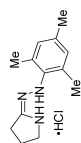
Figure 36. ^{1}H NMR spectrum of compound **110**.
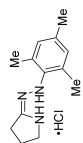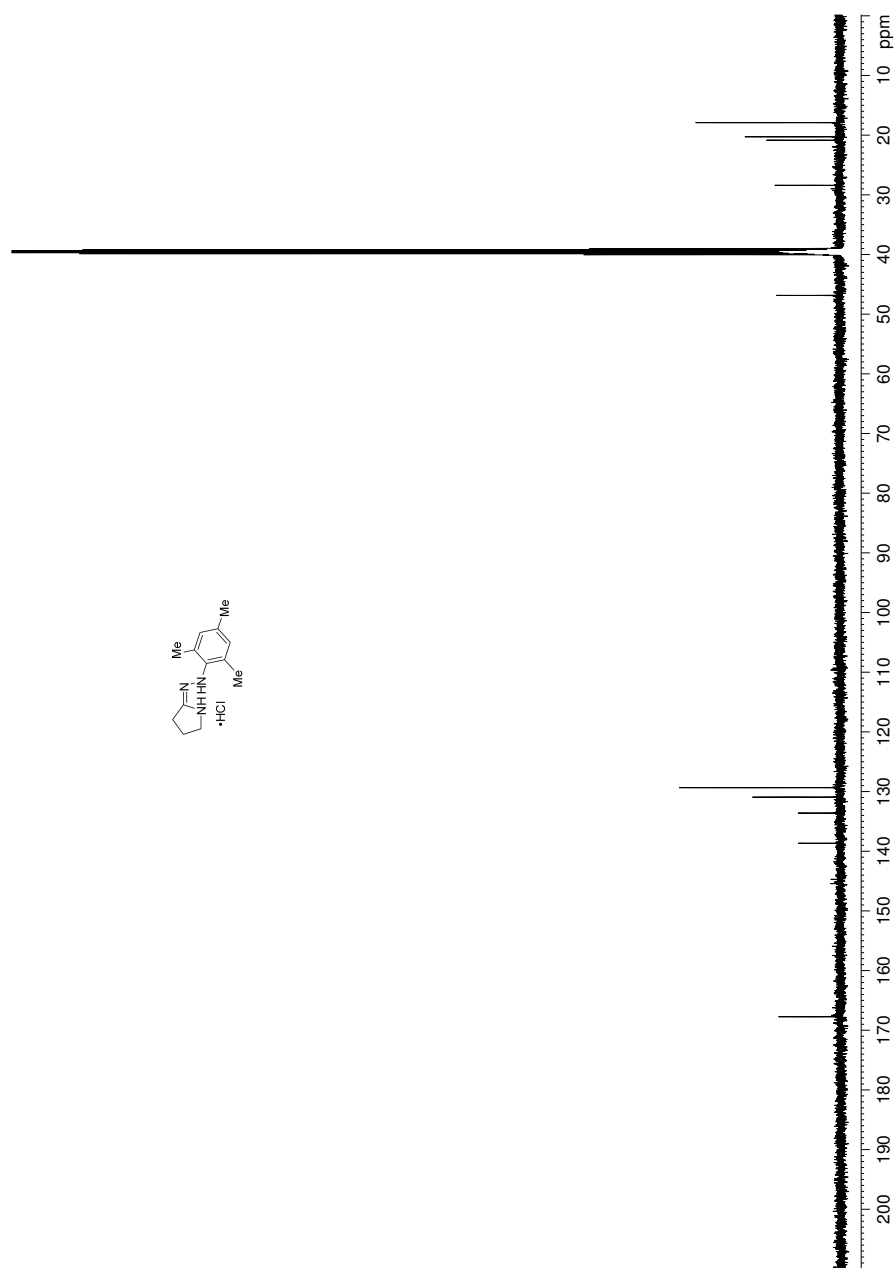
Figure 37. ^{13}C NMR spectrum of compound **100**.
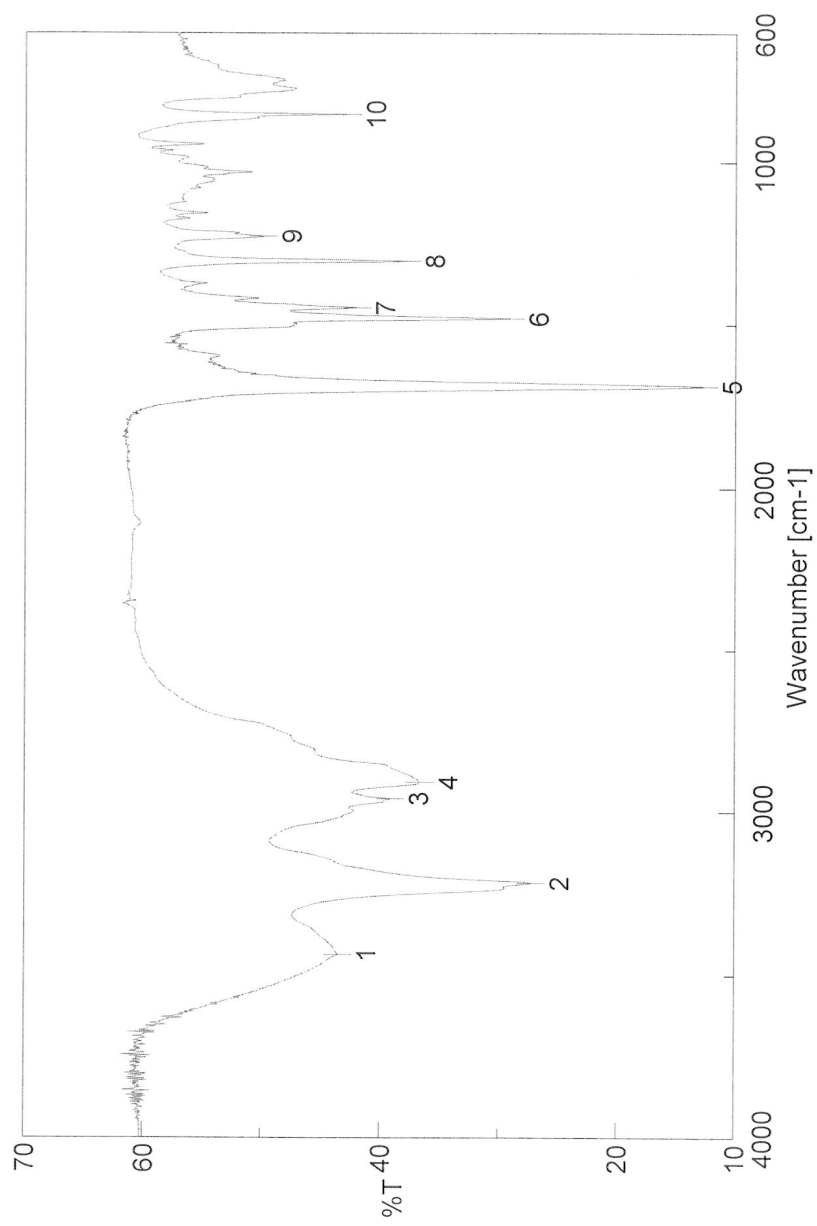
Figure 38. IR spectrum of compound **110**.
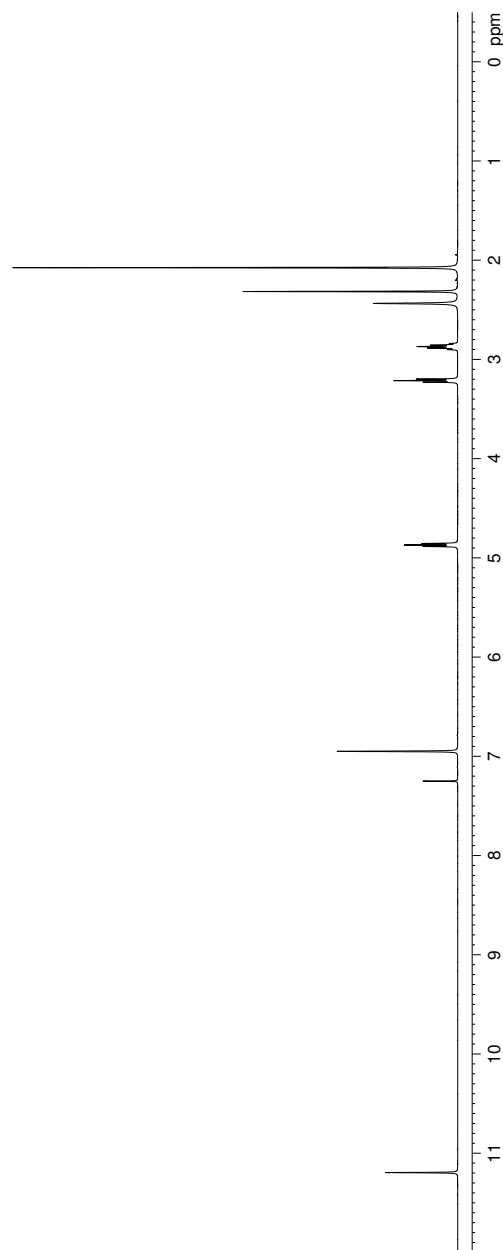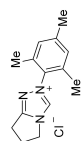
Figure 39. ^{1}H NMR spectrum of compound **61** (RMesCl).

206
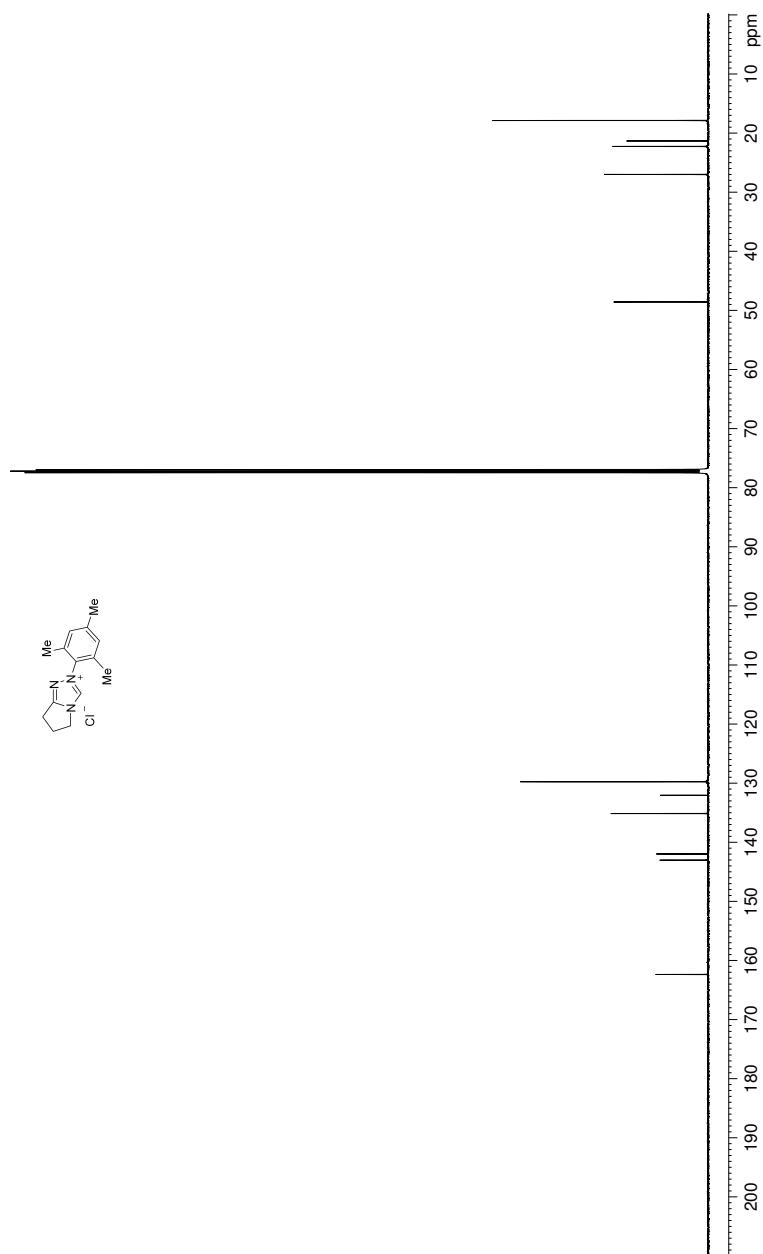
Figure 40. ^{13}C NMR spectrum of compound **61** (RMesCl).
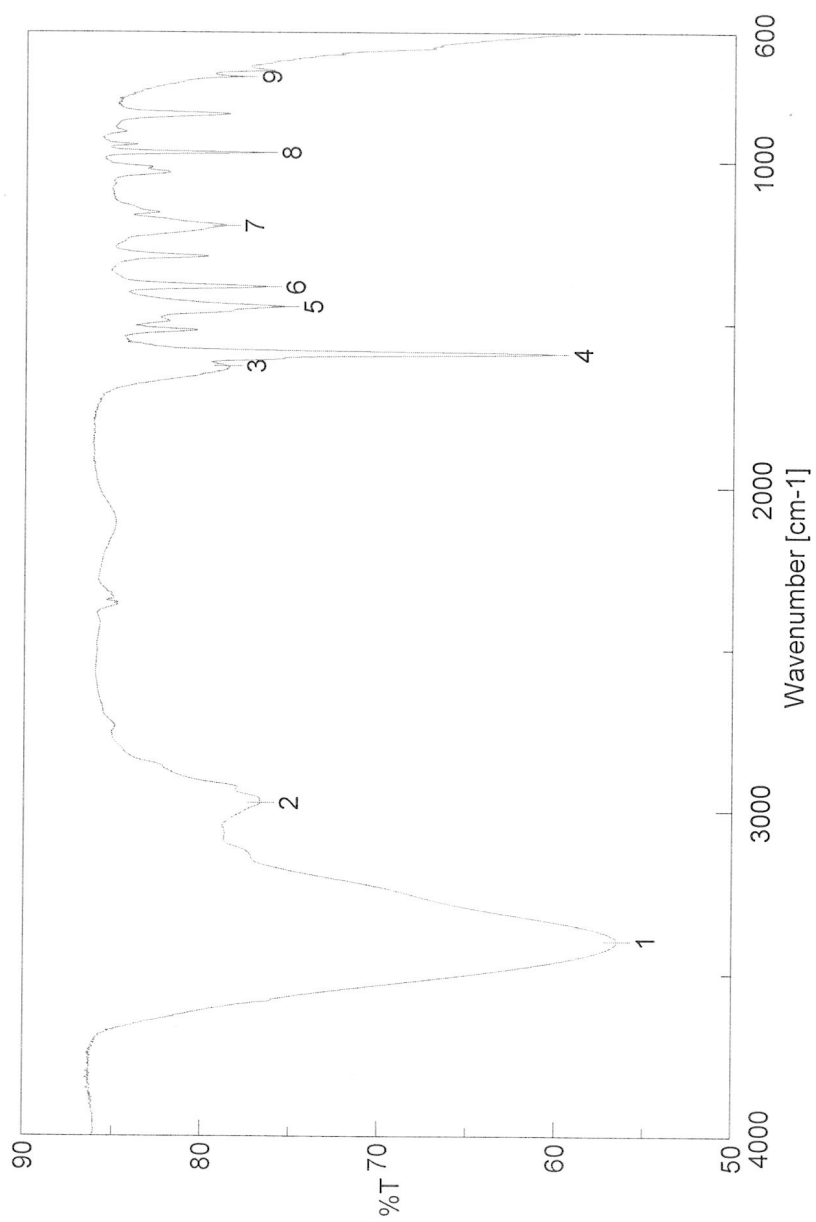
Figure 41. IR spectrum of compound **61** (RMesCl).
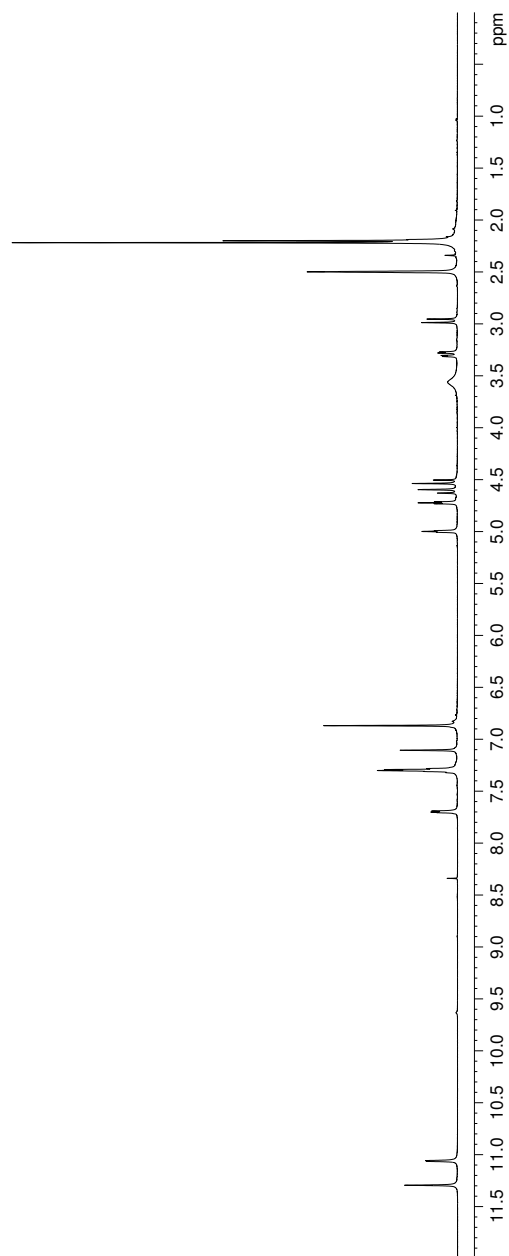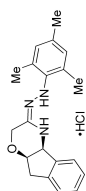
Figure 42. ^{1}H NMR spectrum of compound **116**.
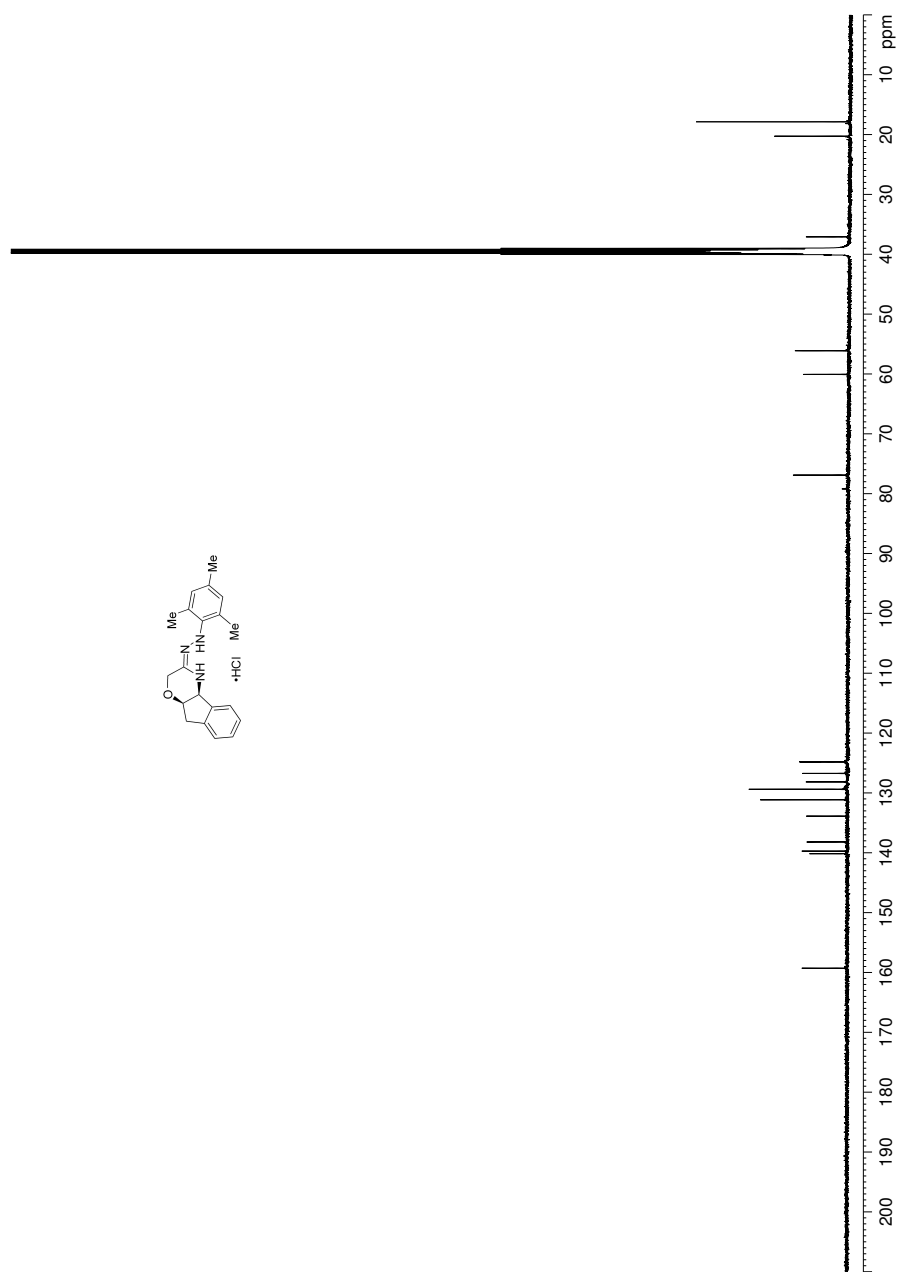
Figure 43. ^{13}C NMR spectrum of compound **116**.
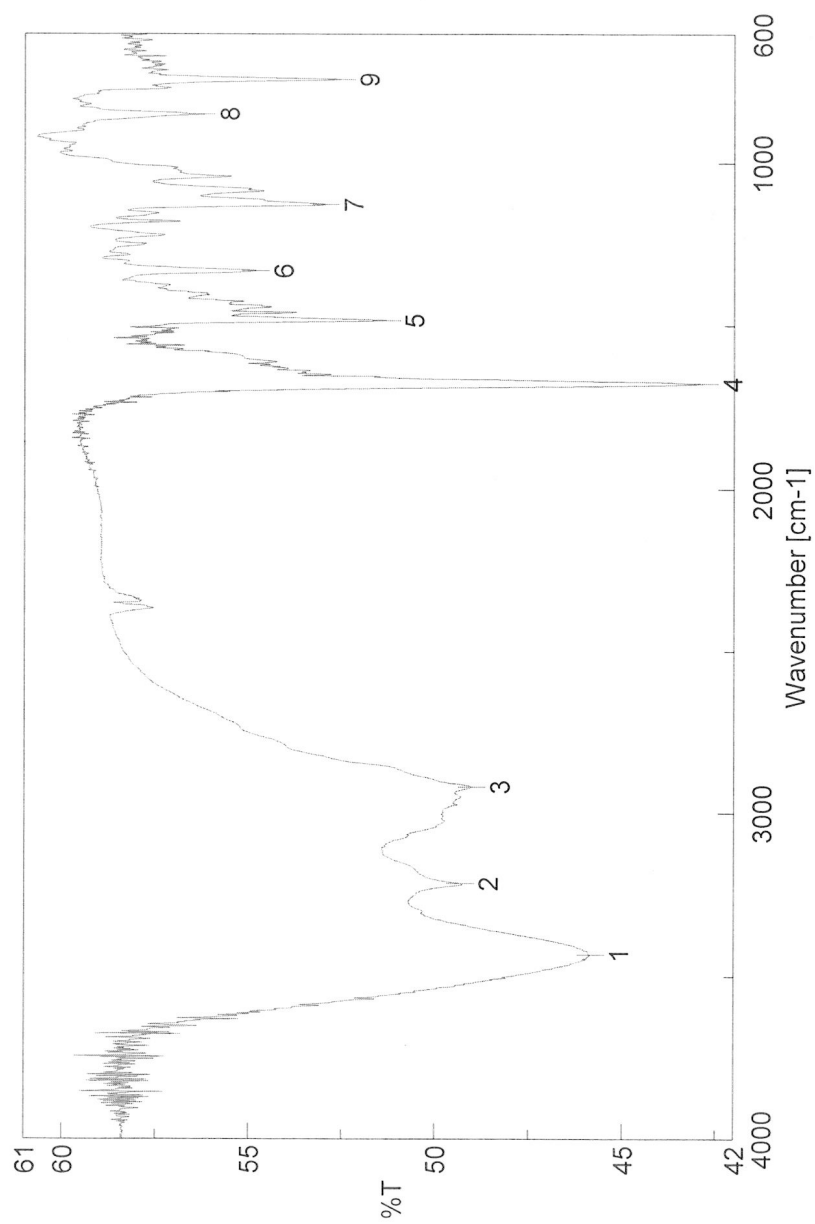
Figure 44. IR spectrum of compound **116**.

Figure 45. ^{1}H NMR spectrum of compound **117**.

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Figure 46. ^{13}C NMR spectrum of compound **117**.

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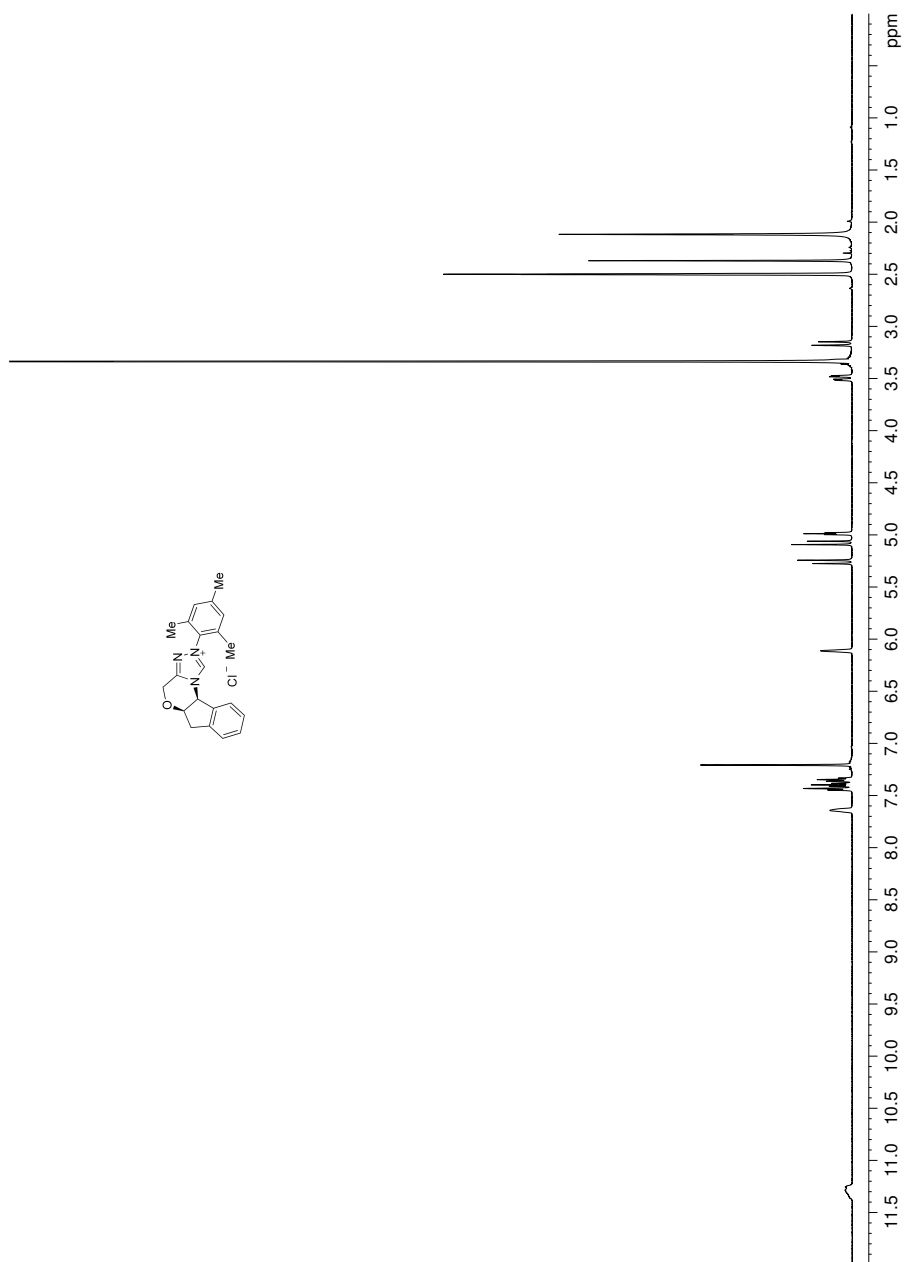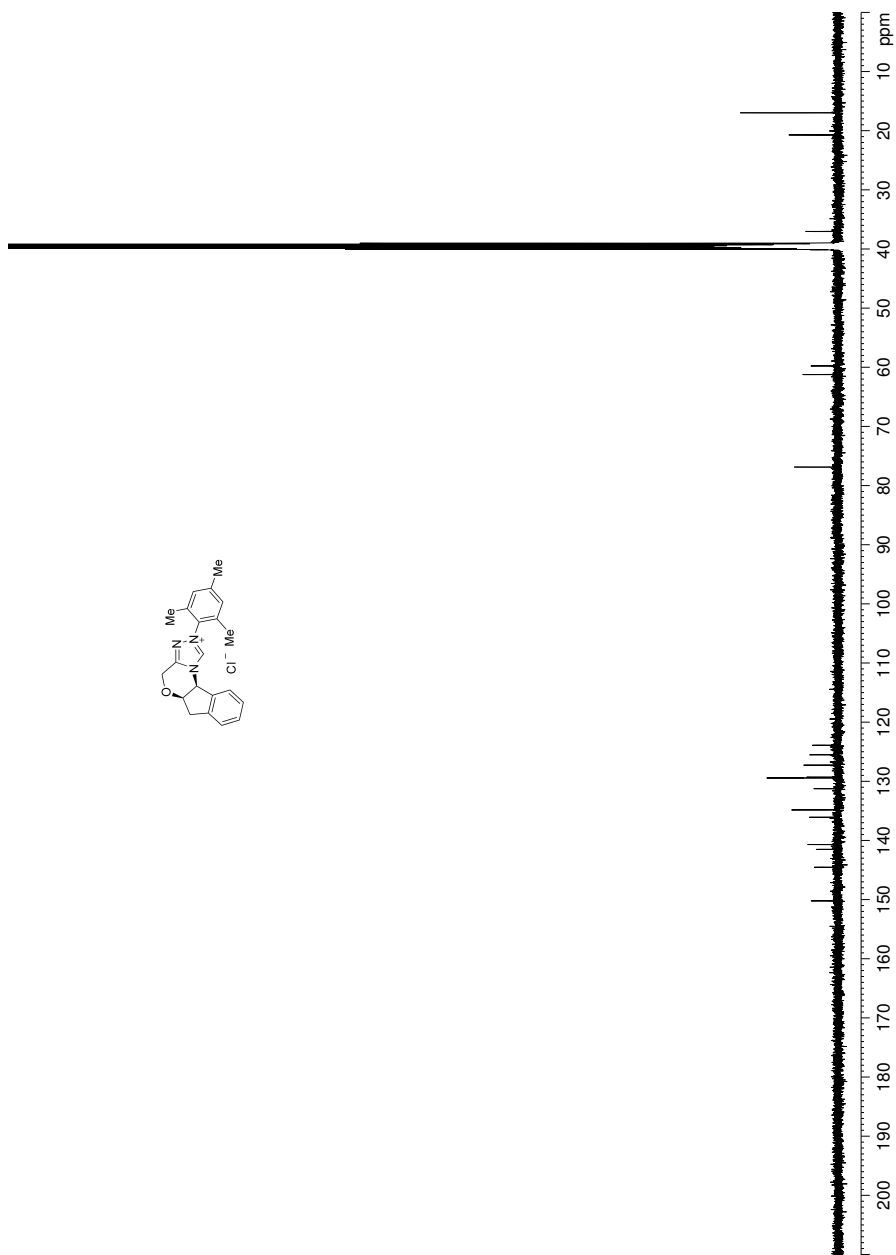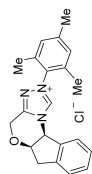
Figure 47. IR spectrum of compound **117**.
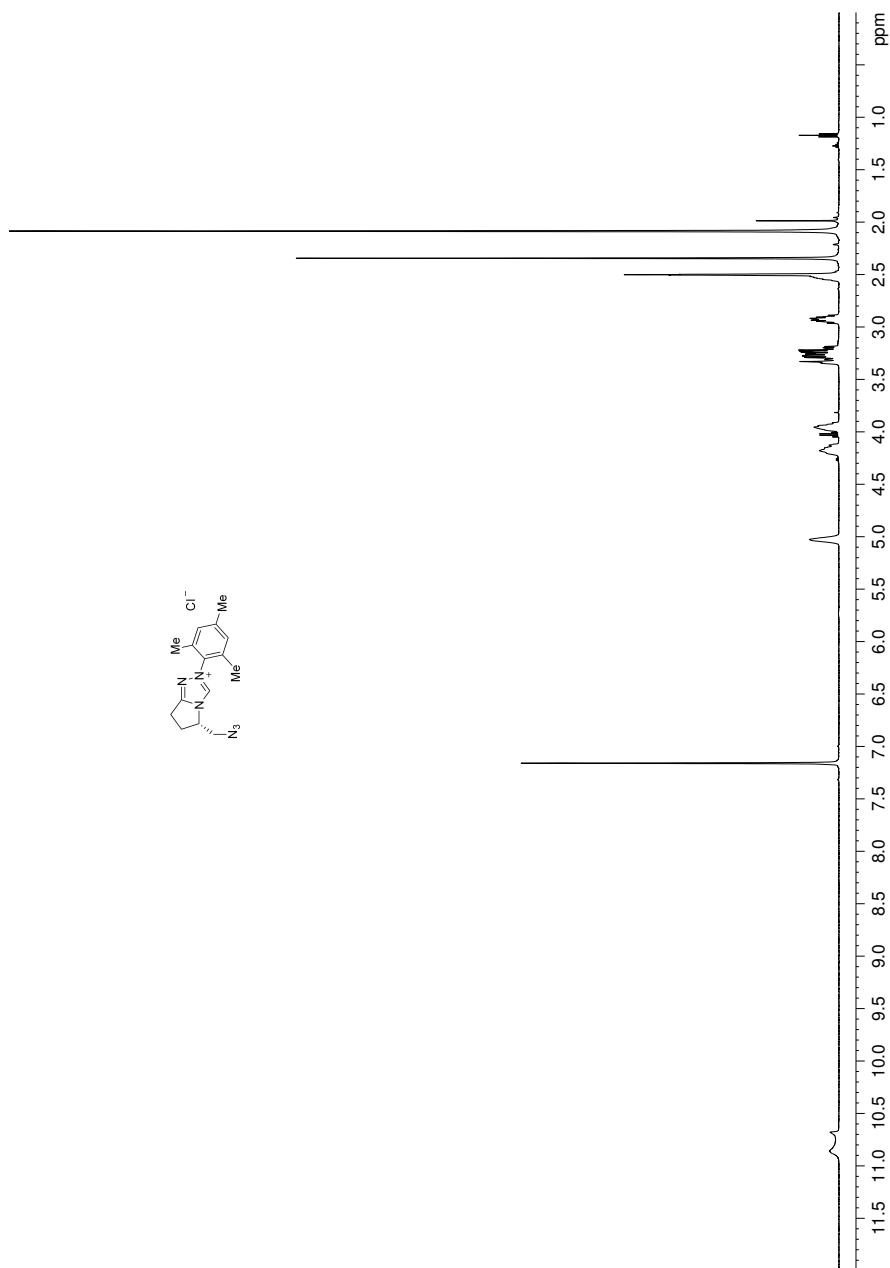
Figure 45. ^{1}H NMR spectrum of compound **133**.
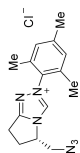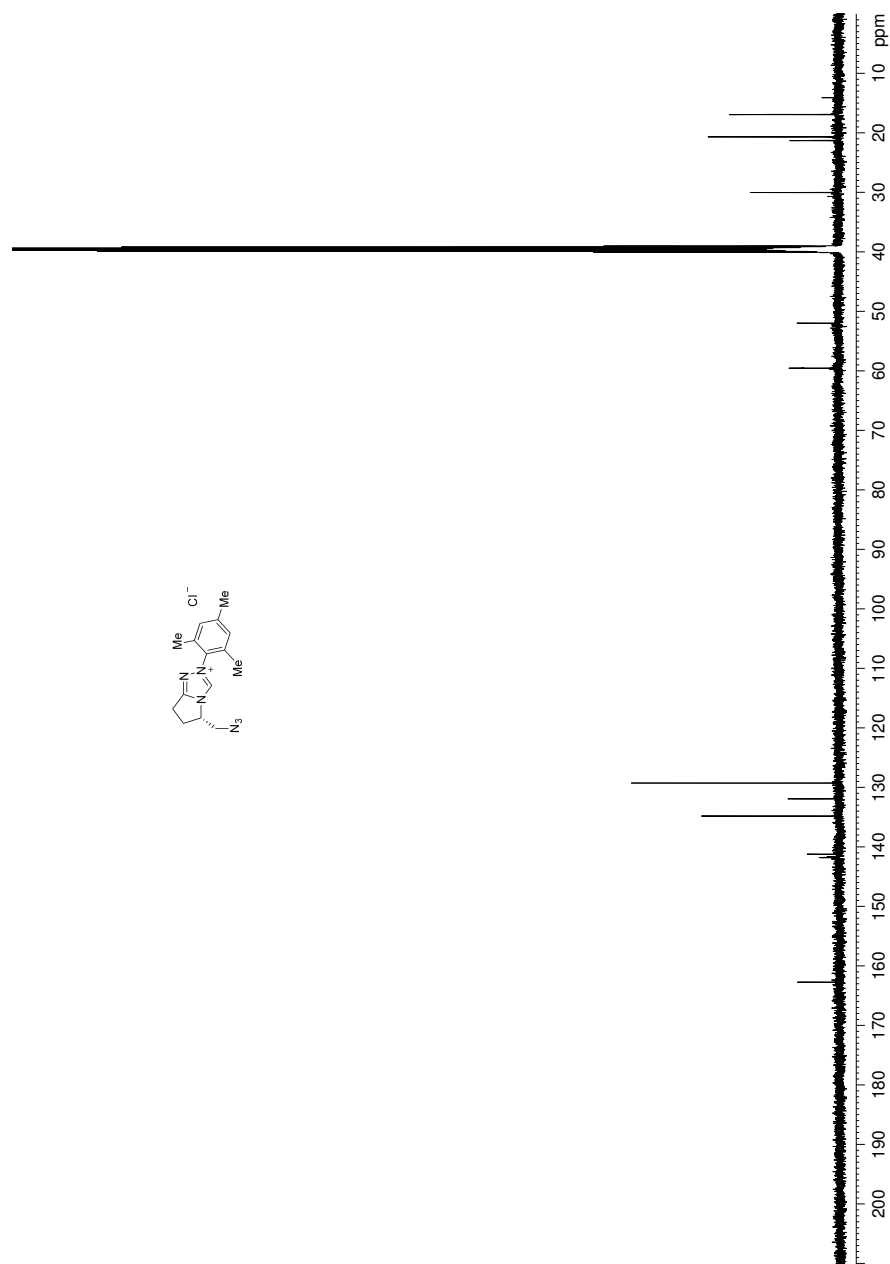
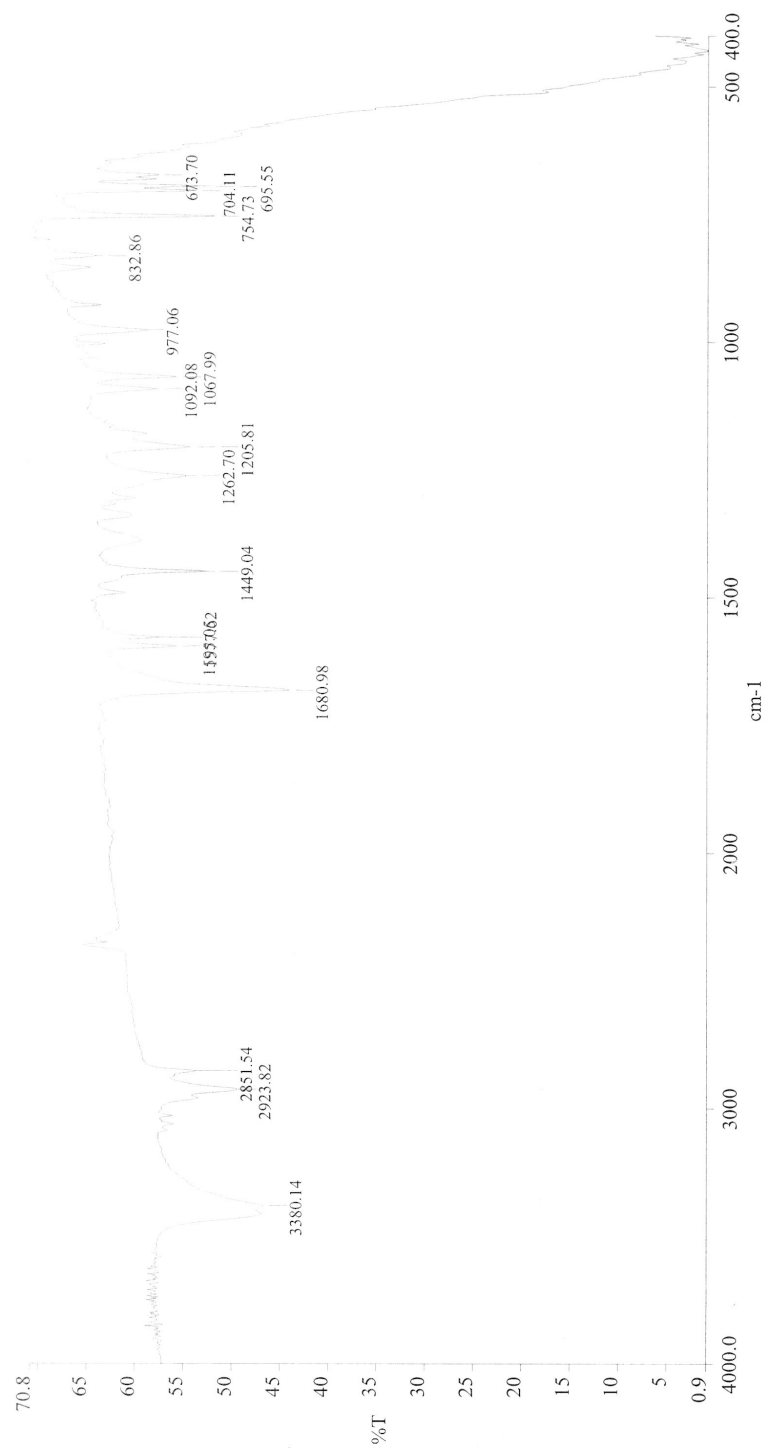**Figure 46.** ^{13}C NMR spectrum of compound **133**.
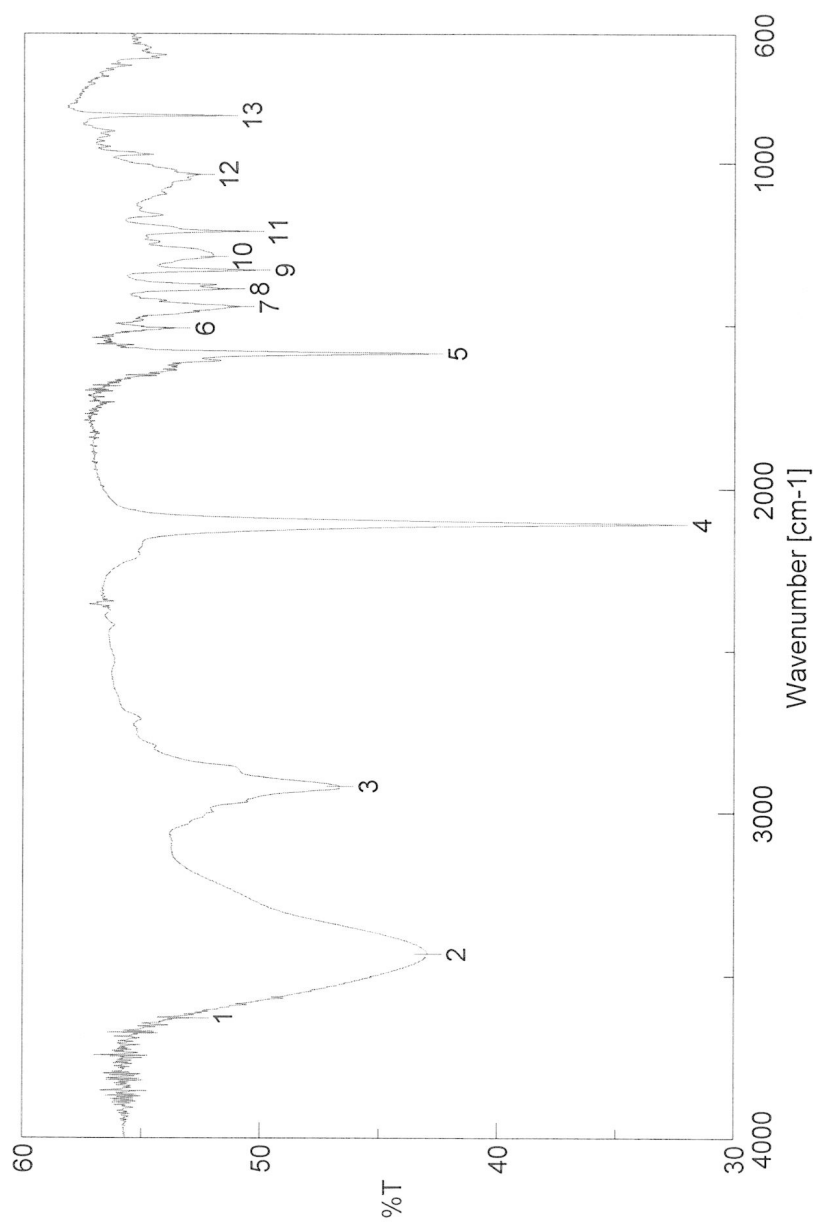
Figure 47. IR spectrum of compound **133**.
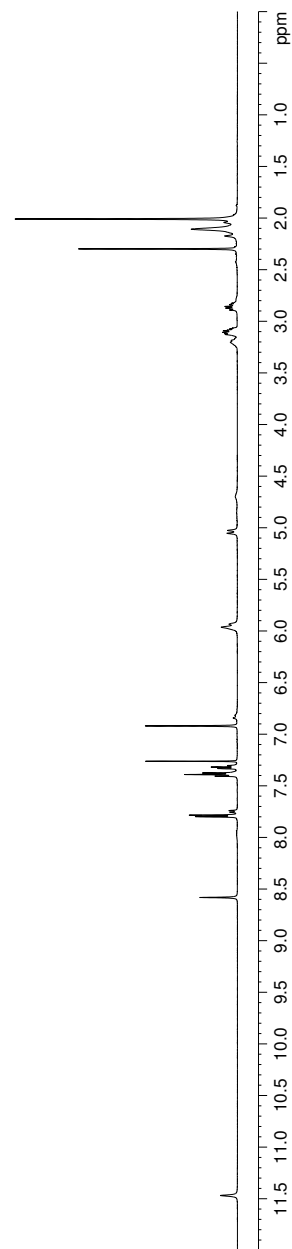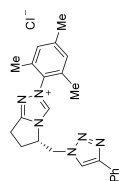
Figure 48. ^{1}H NMR spectrum of compound **136**.

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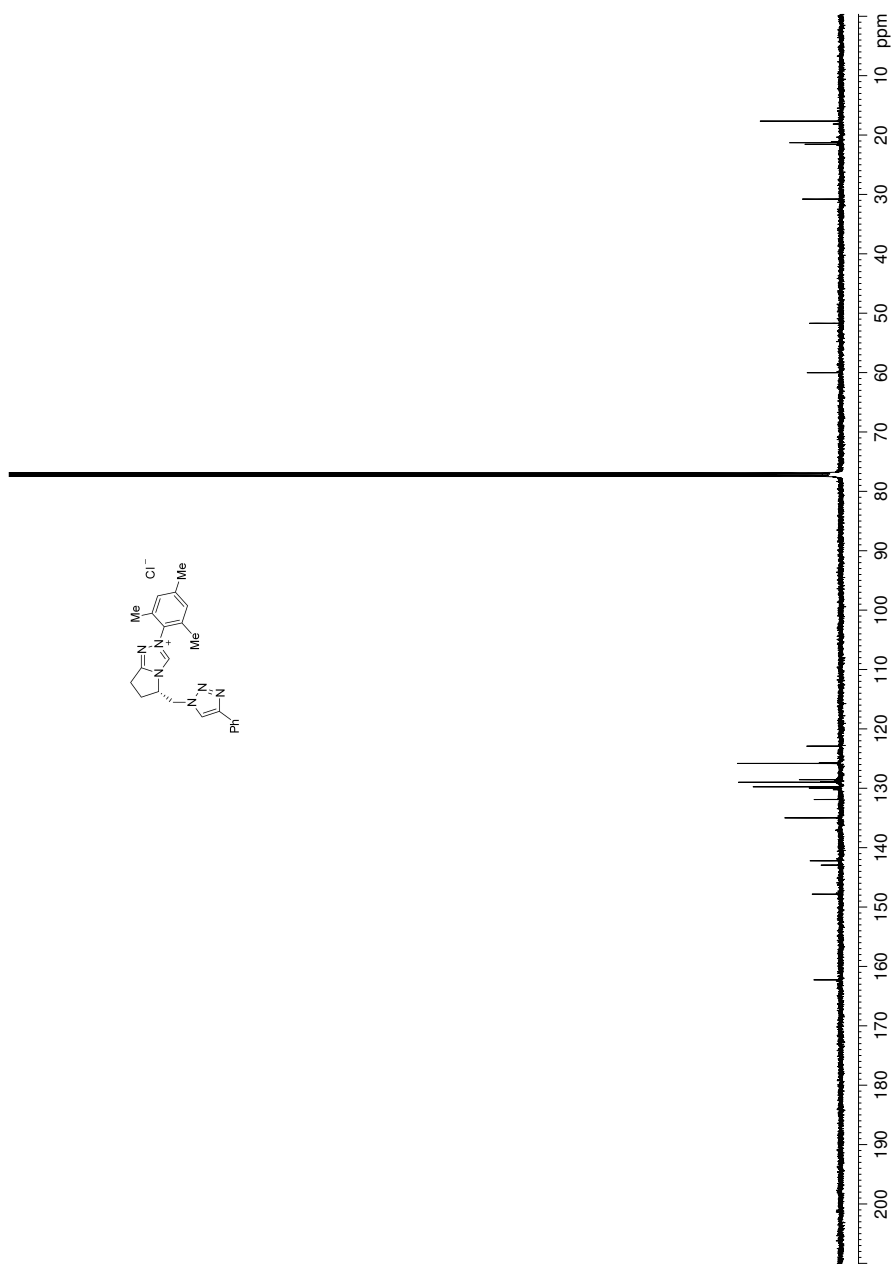
Figure 49. ^{13}C NMR spectrum of compound **136**.

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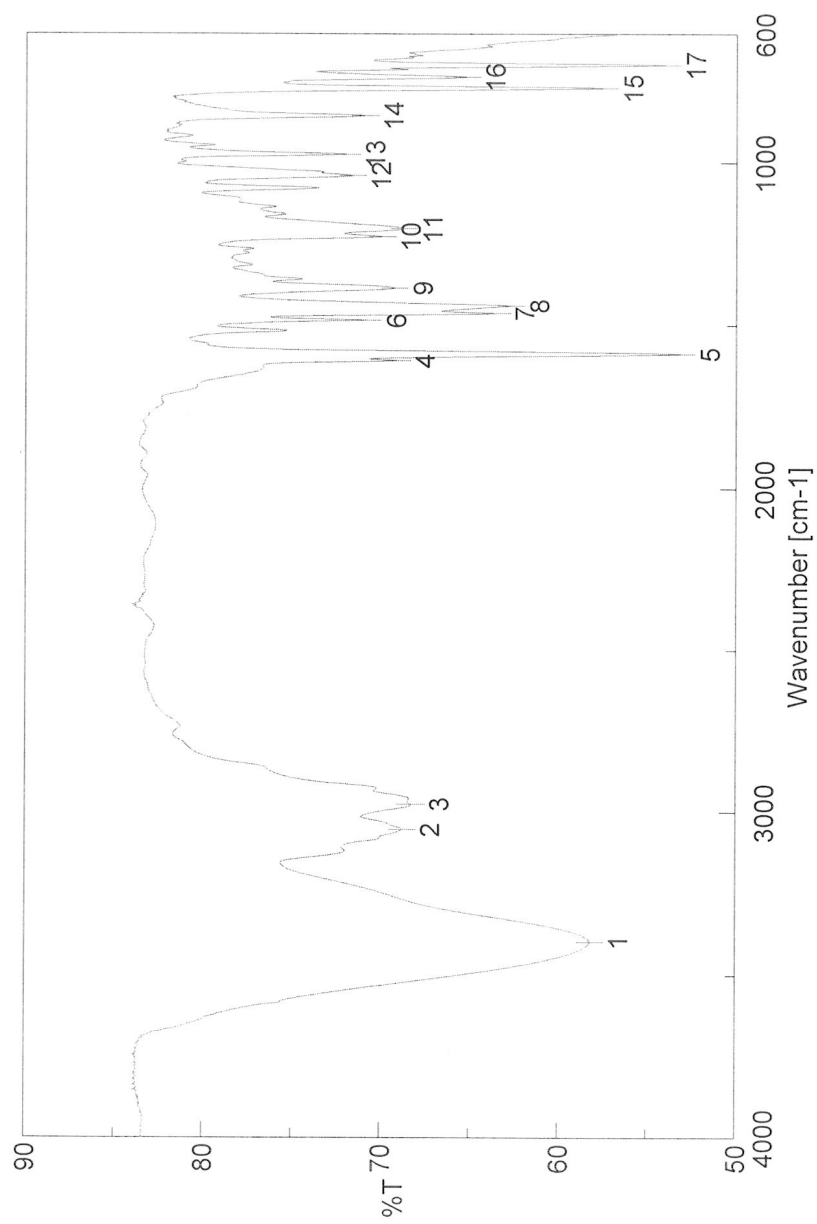
Figure 50. IR spectrum of compound **136**.
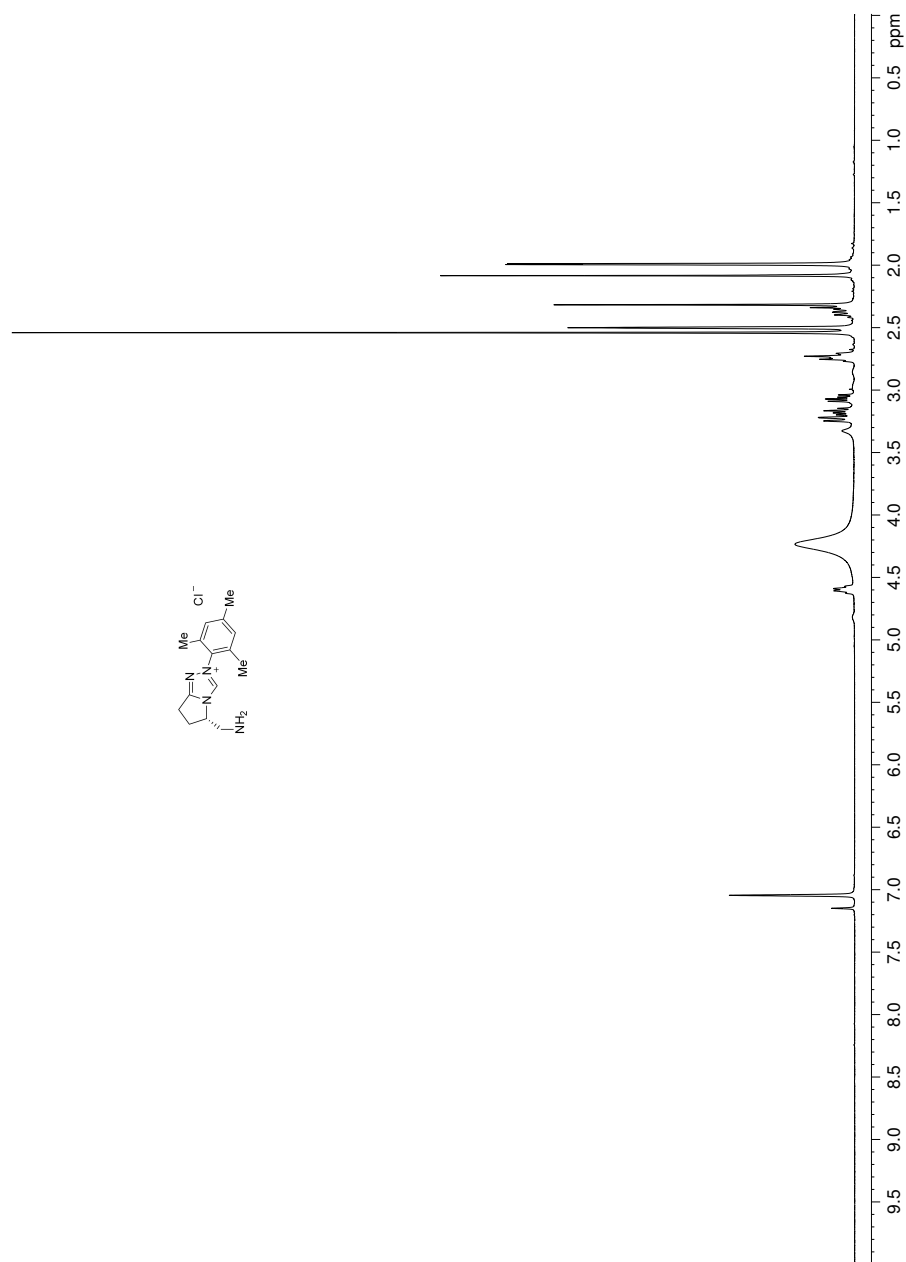
Figure 51. ¹H NMR spectrum of compound **137**.
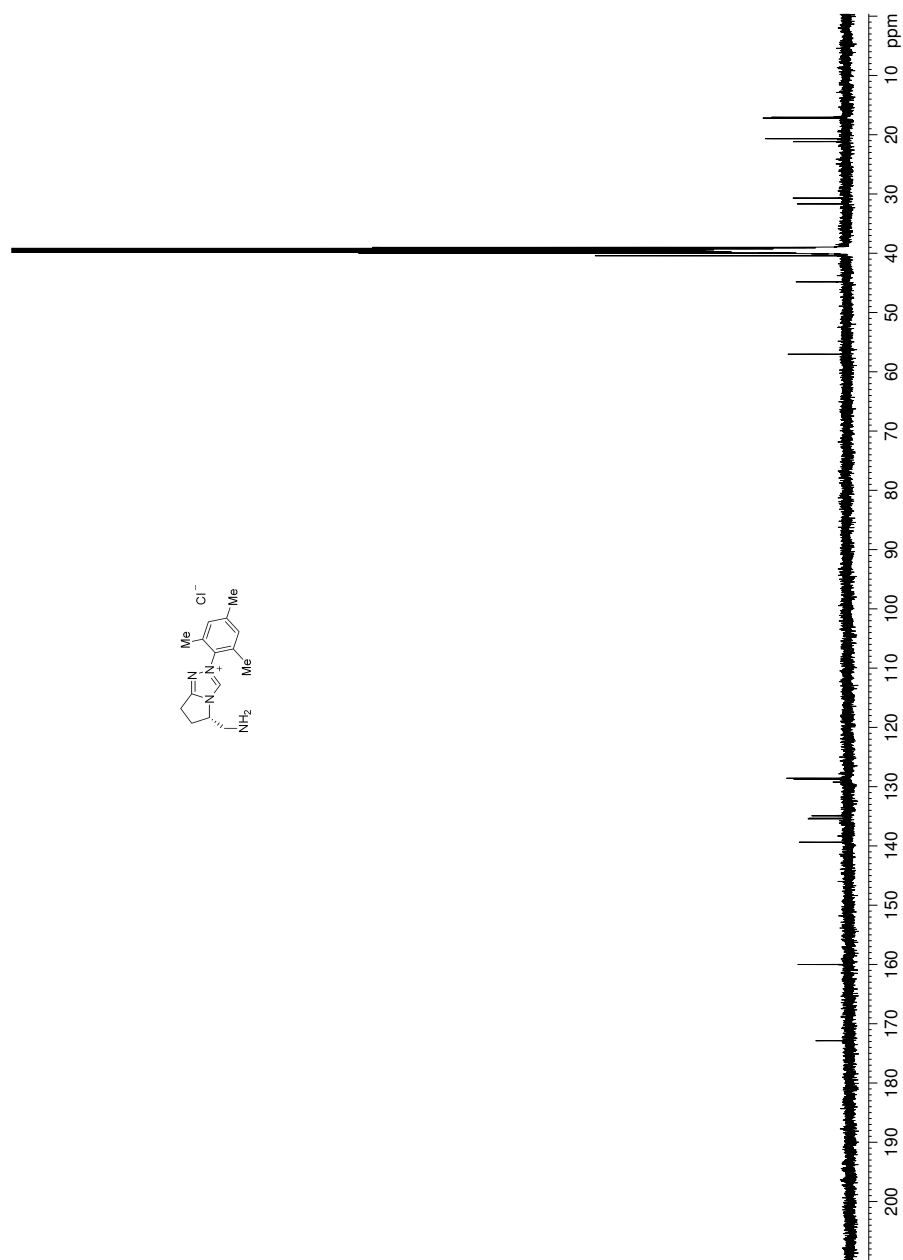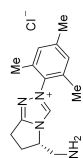
Figure 52. ^{13}C NMR spectrum of compound **137**.
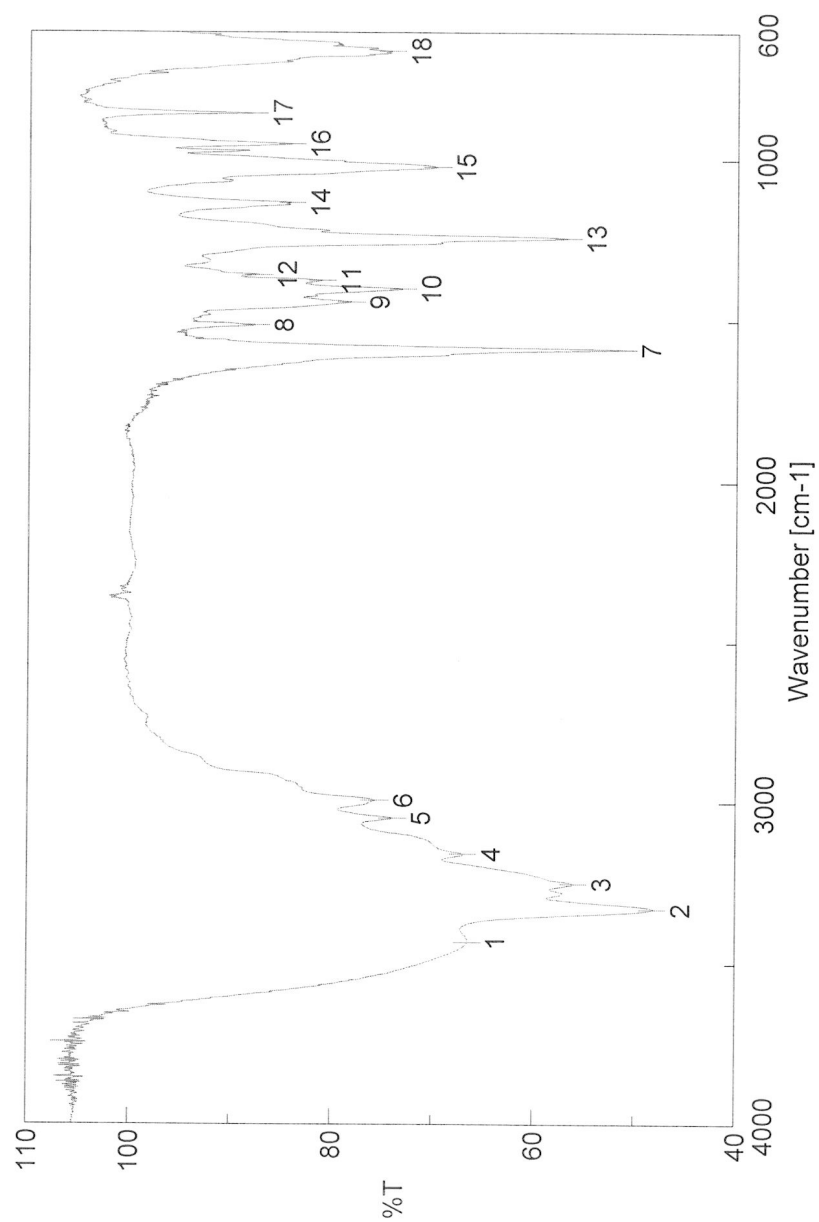
Figure 53. IR spectrum of compound **137**.
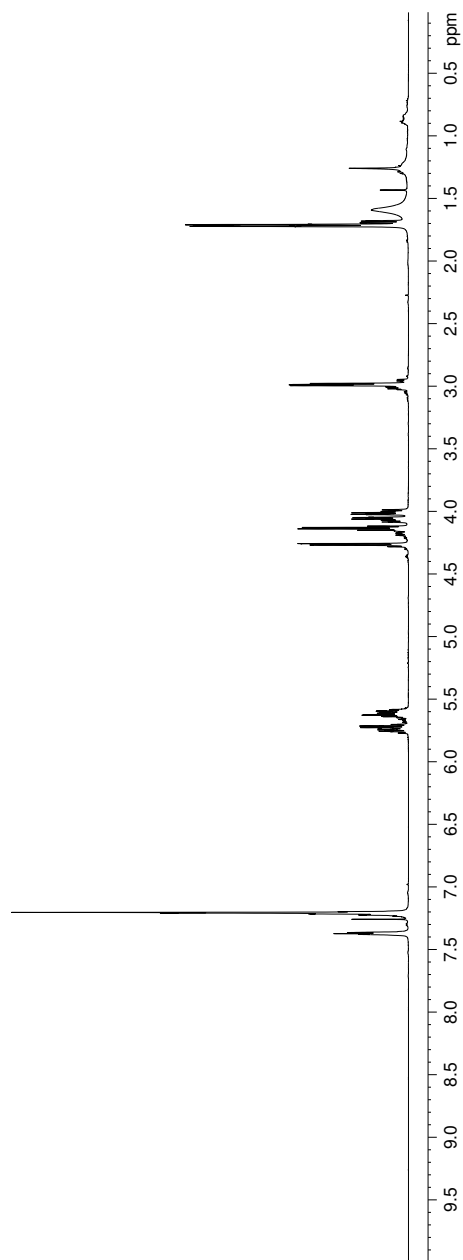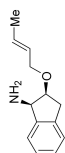
Figure 54. ^{1}H NMR spectrum of compound **152**.

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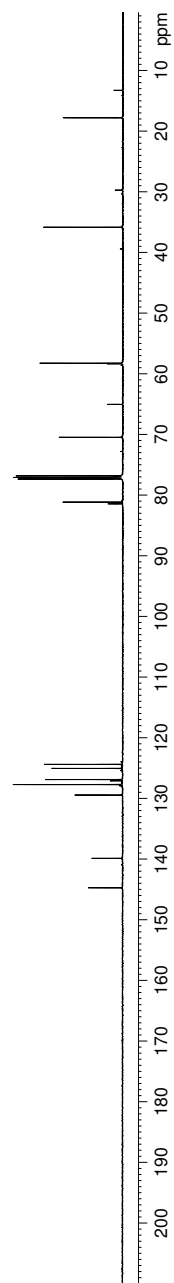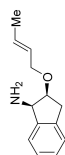
Figure 55. ^{13}C NMR spectrum of compound **152**.
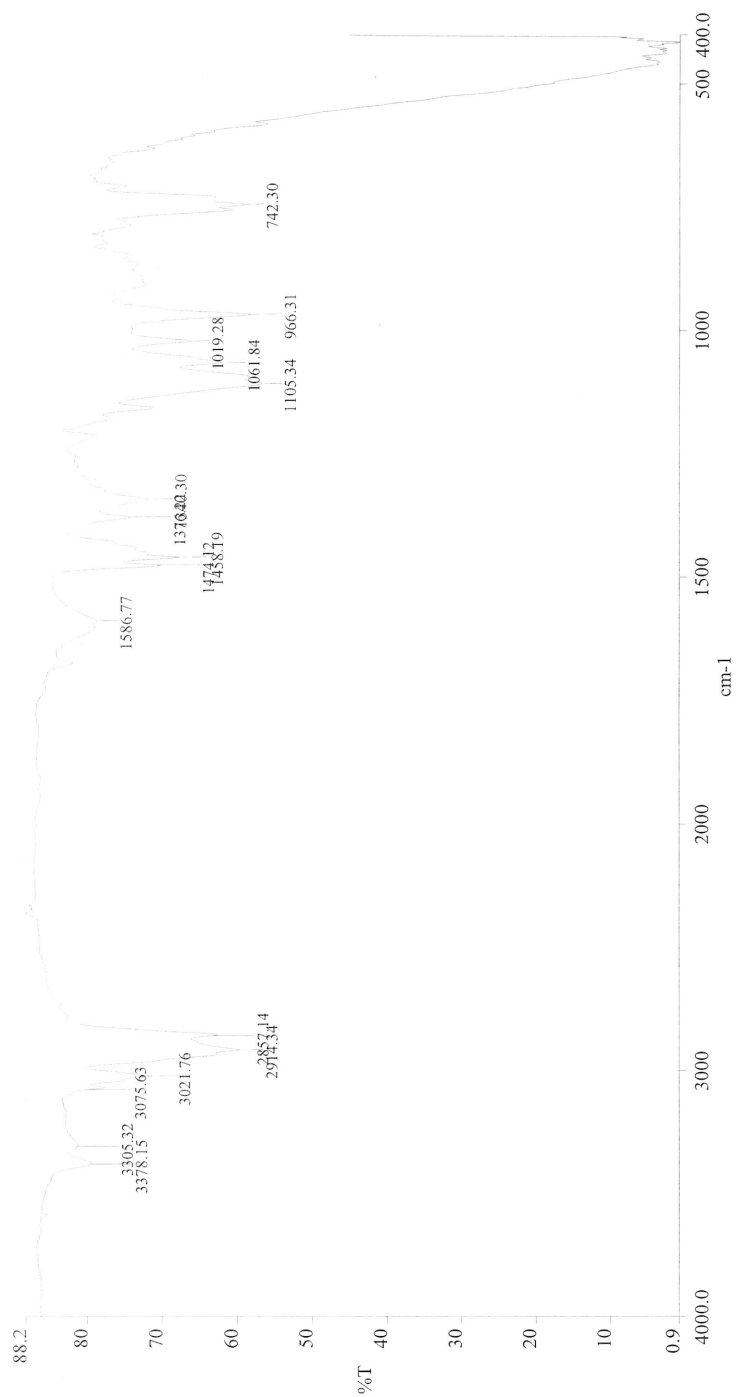
Figure 56. IR spectrum of compound **152**.

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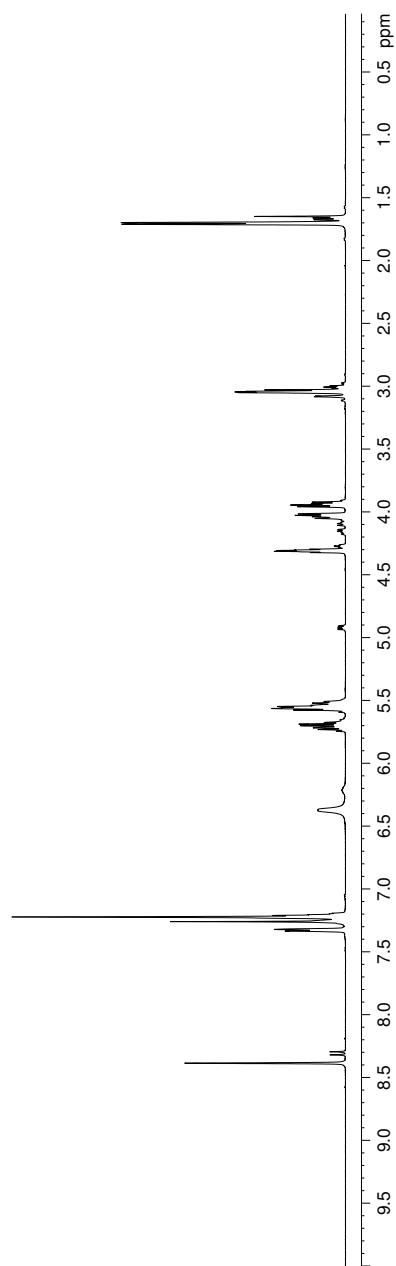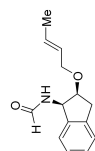
Figure 57. ^{1}H NMR spectrum of compound **151**.

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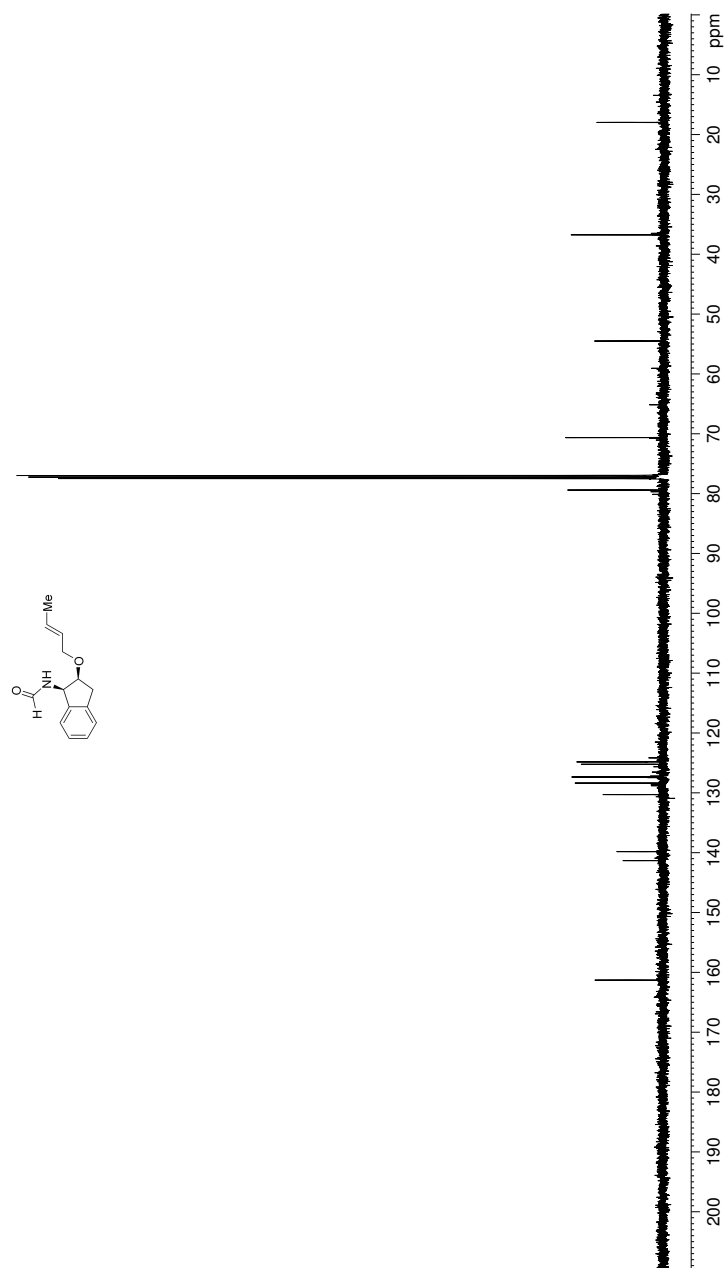
Figure 58. ^{13}C NMR spectrum of compound **151**.
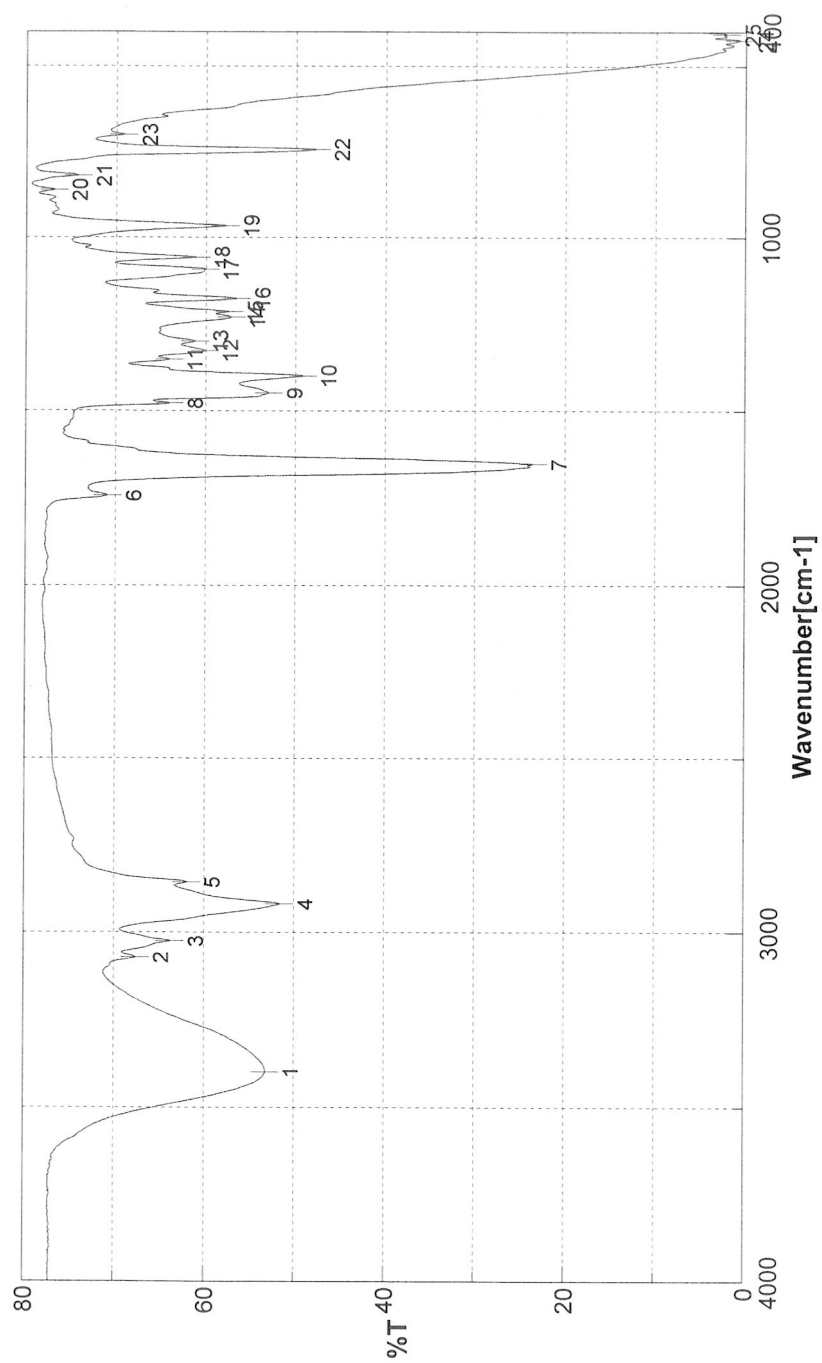
Figure 59. IR spectrum of compound **151**.
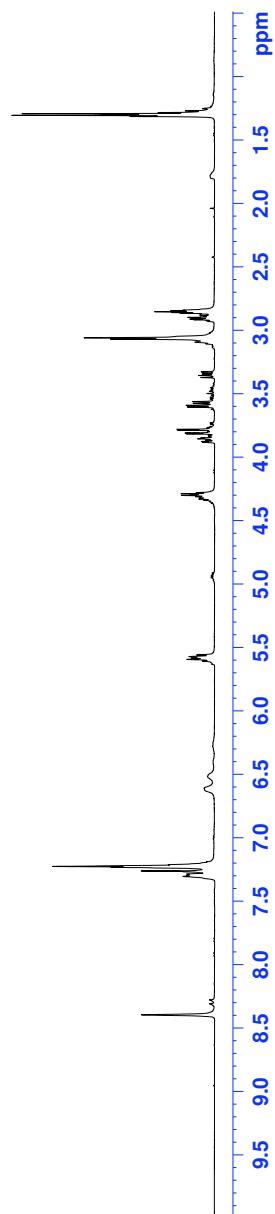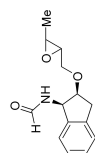
Figure 60. ¹H NMR spectrum of compound **148,149**.
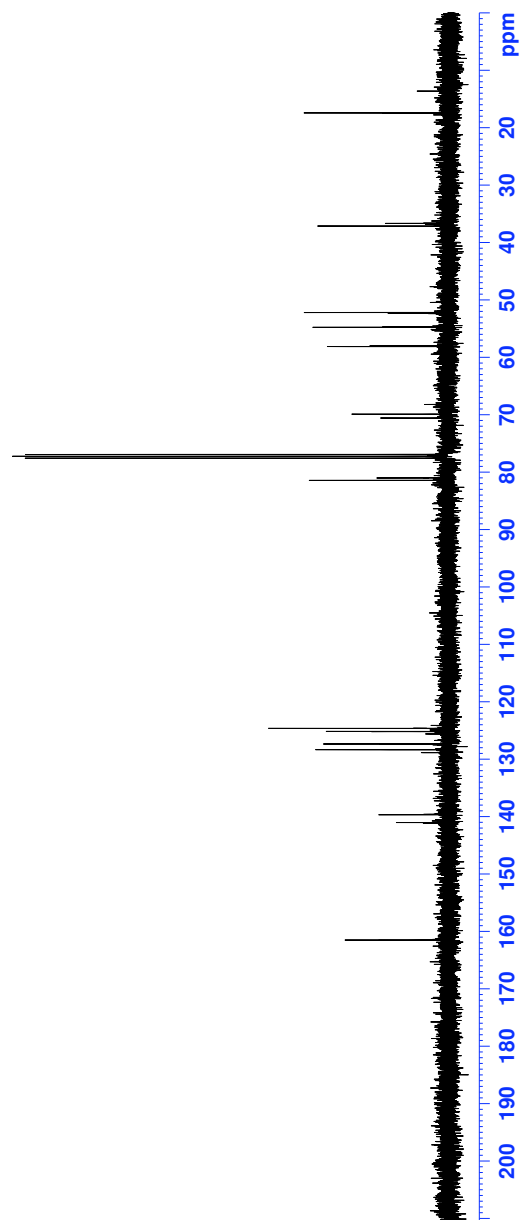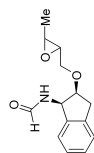
Figure 61. ^{13}C NMR spectrum of compound **148,149**.
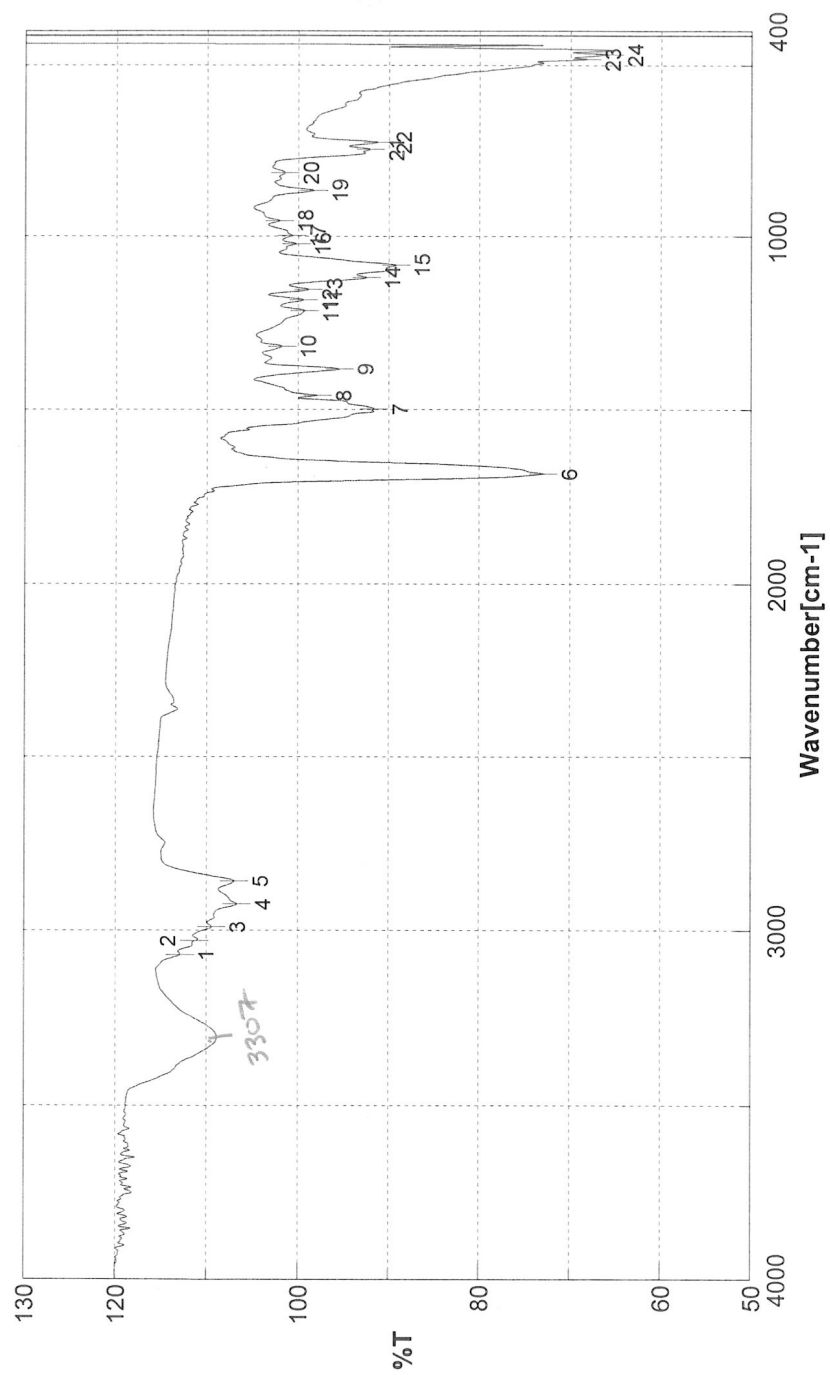
Figure 62. IR spectrum of compound **148,149**.

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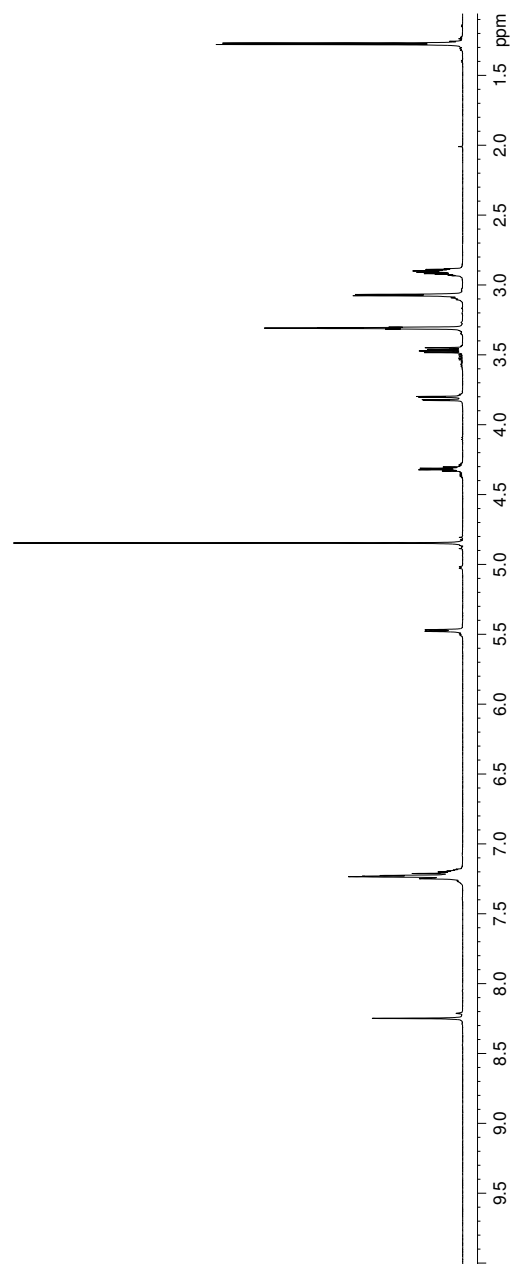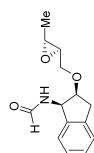
Figure 63. ¹H NMR spectrum of compound **148**.
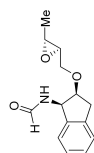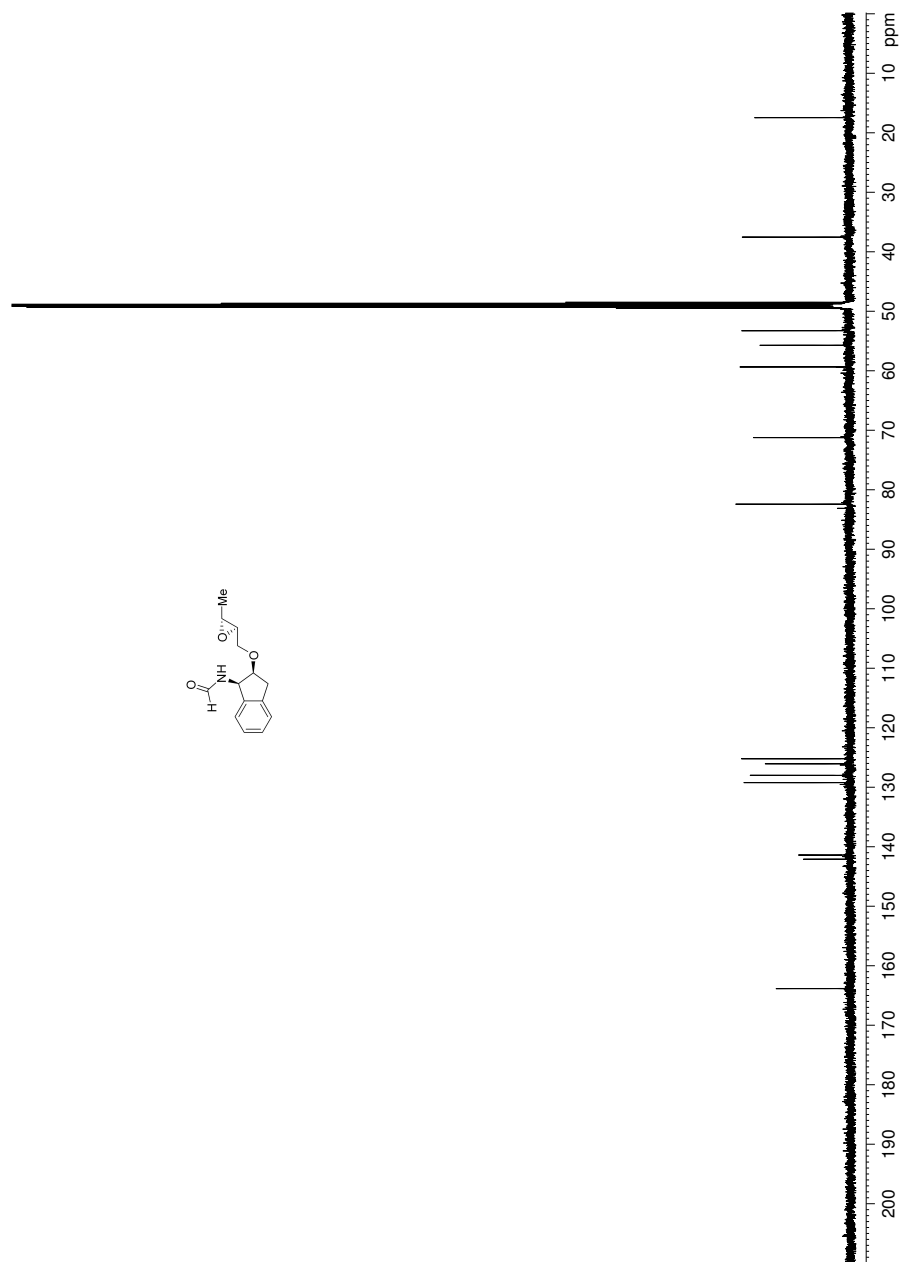
Figure 64. ^{13}C NMR spectrum of compound **148**.
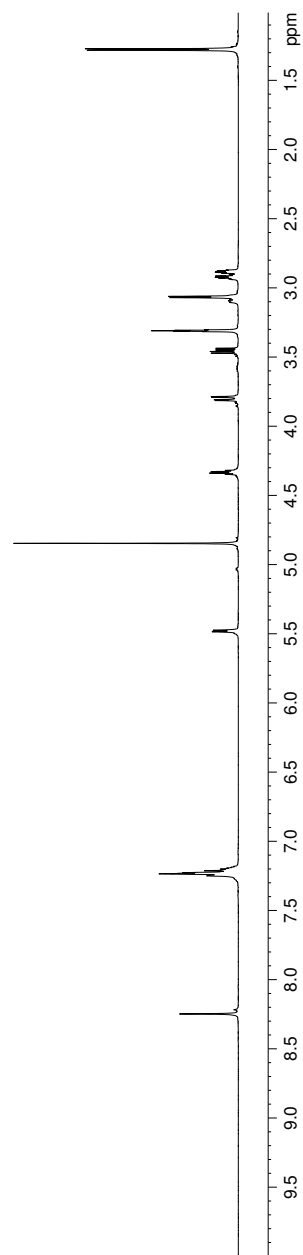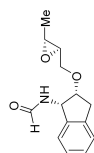
Figure 65. ¹H NMR spectrum of compound *ent*-149.

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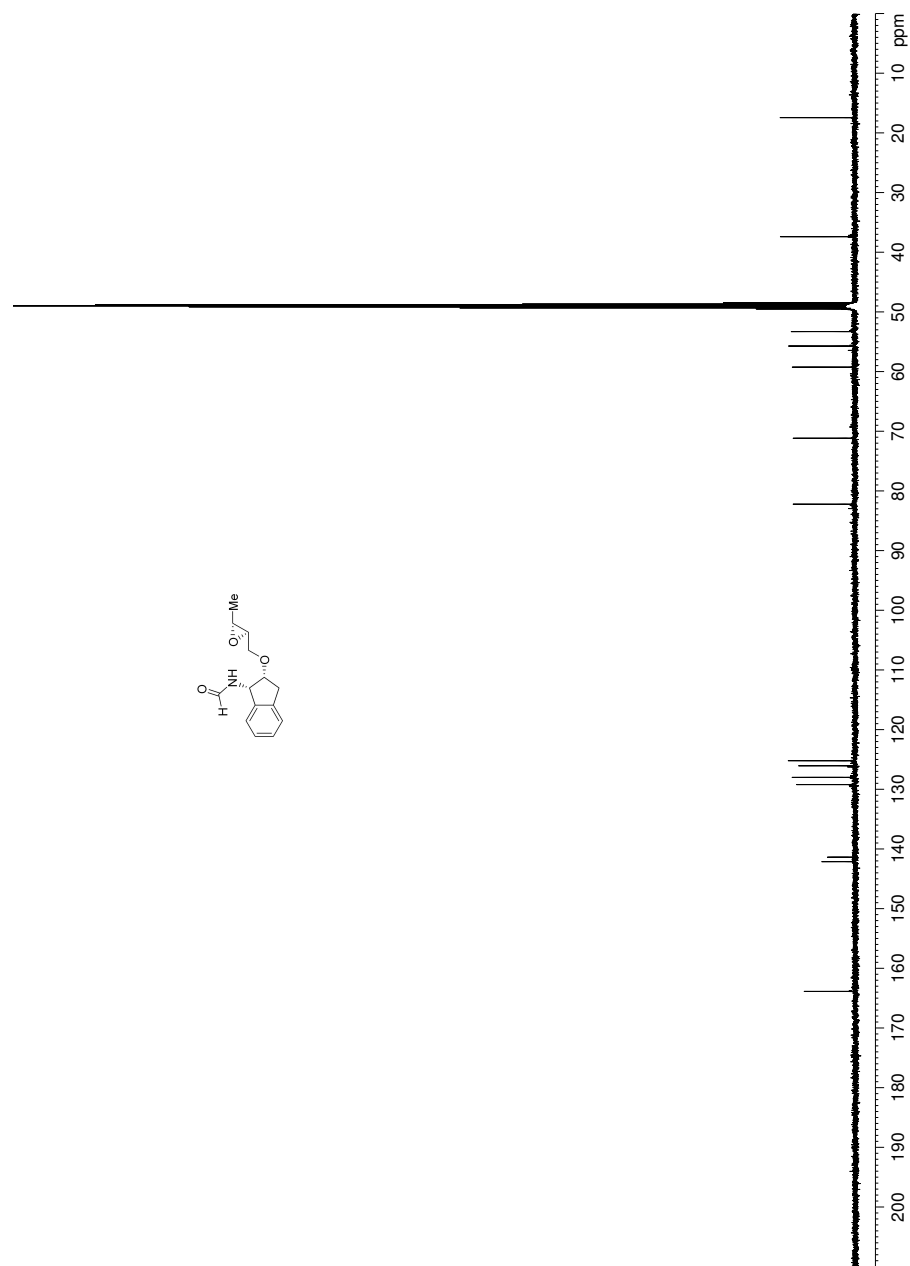
Figure 66. ^{13}C NMR spectrum of compound *ent*-149.

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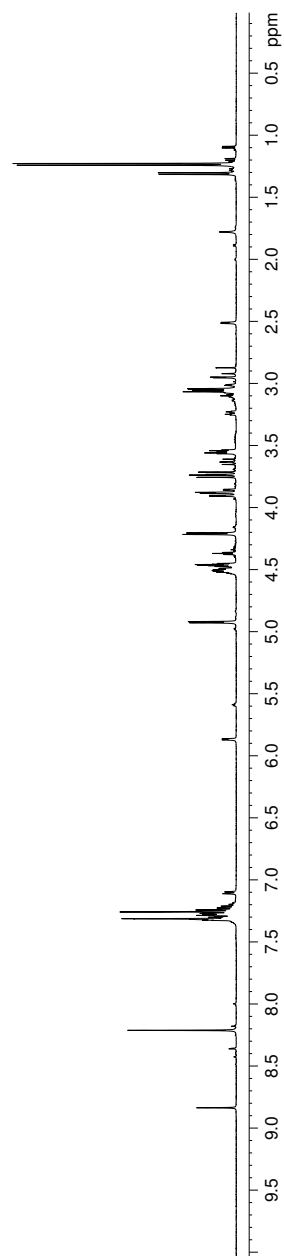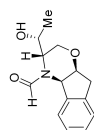
Figure 67. ^{1}H NMR spectrum of compound **152**.
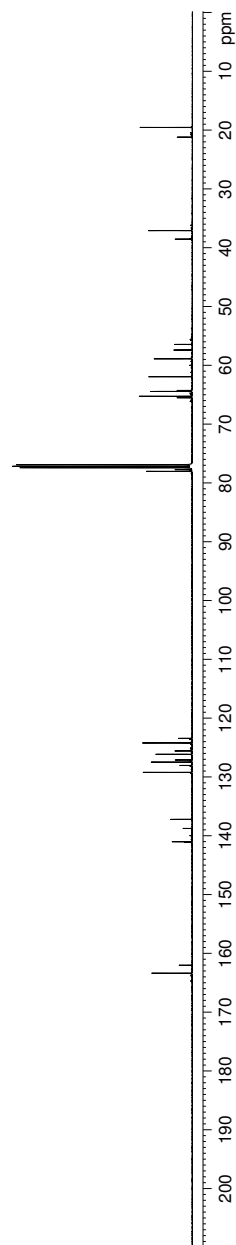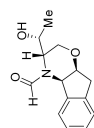
Figure 68. ^{13}C NMR spectrum of compound **152**.

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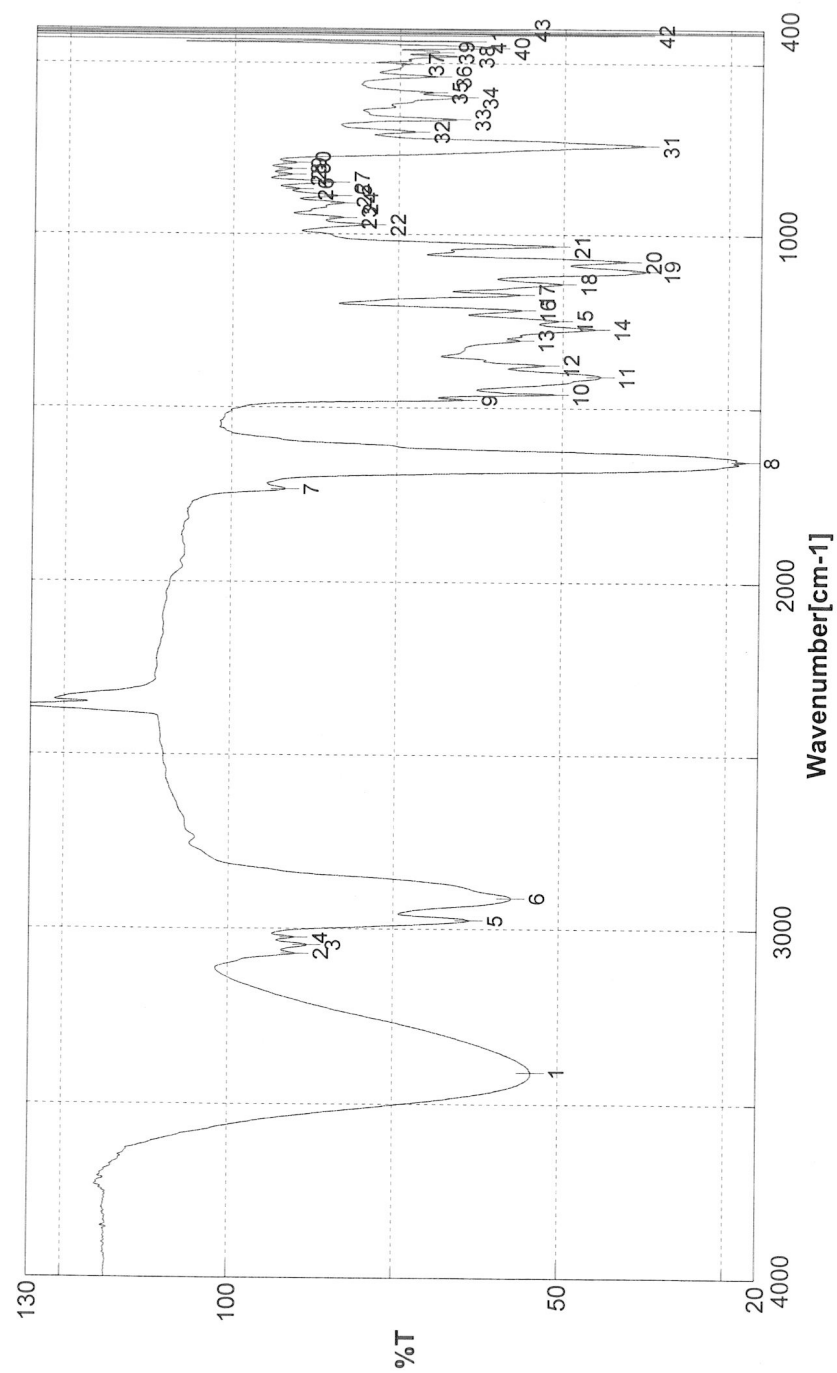
Figure 69. IR spectrum of compound **149**.
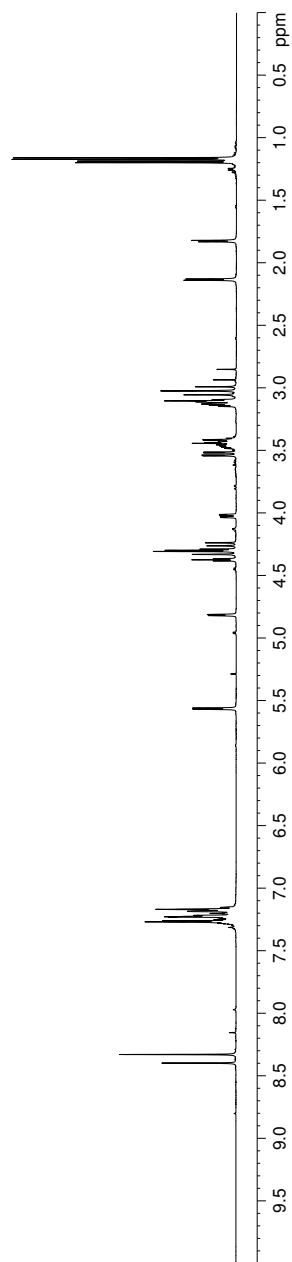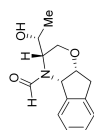
Figure 70. ^{1}H NMR spectrum of compound *ent*-**153**.

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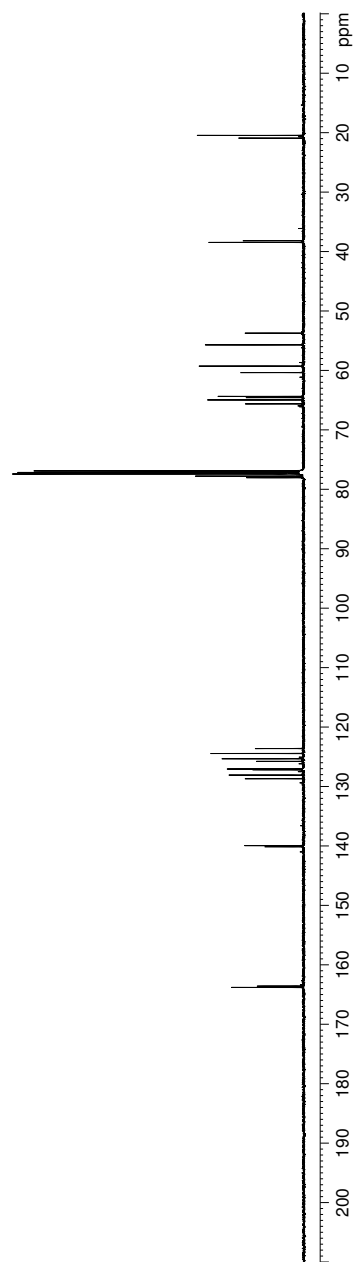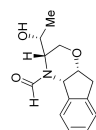
Figure 71. ^{13}C NMR spectrum of compound *ent*-**153**.

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Figure 72. IR spectrum of compound *ent*-**153**.
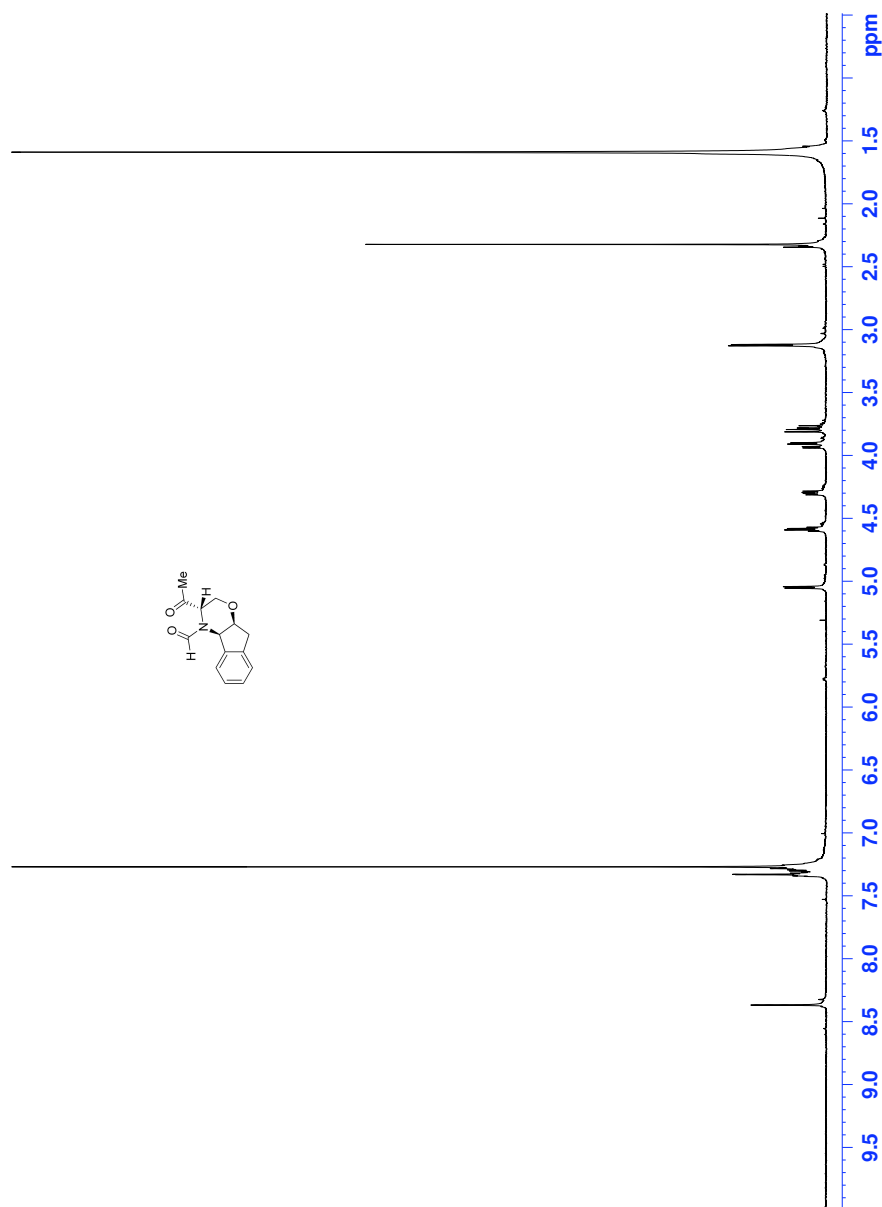
Figure 73. ^{1}H NMR spectrum of compound **147**.

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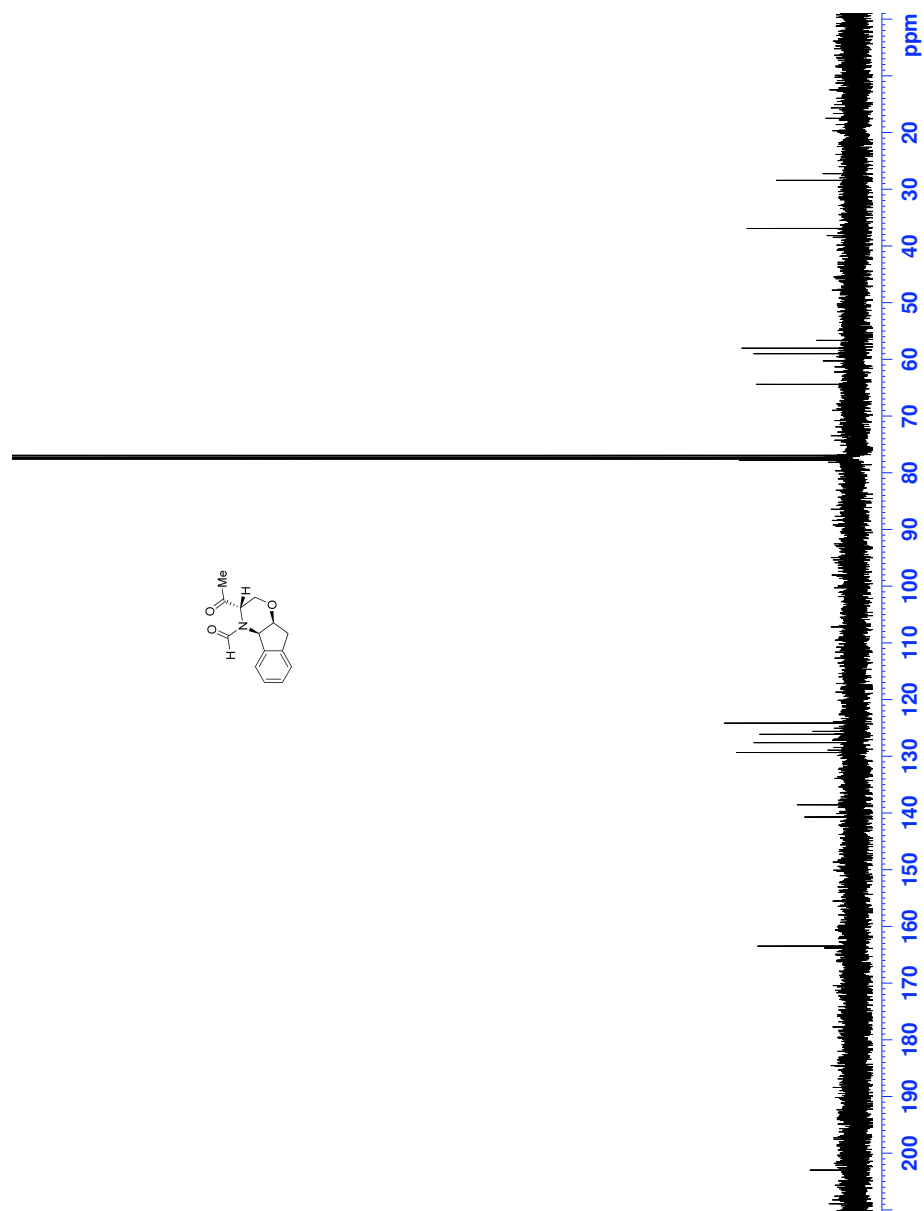
Figure 74. ^{13}C NMR spectrum of compound **147**.
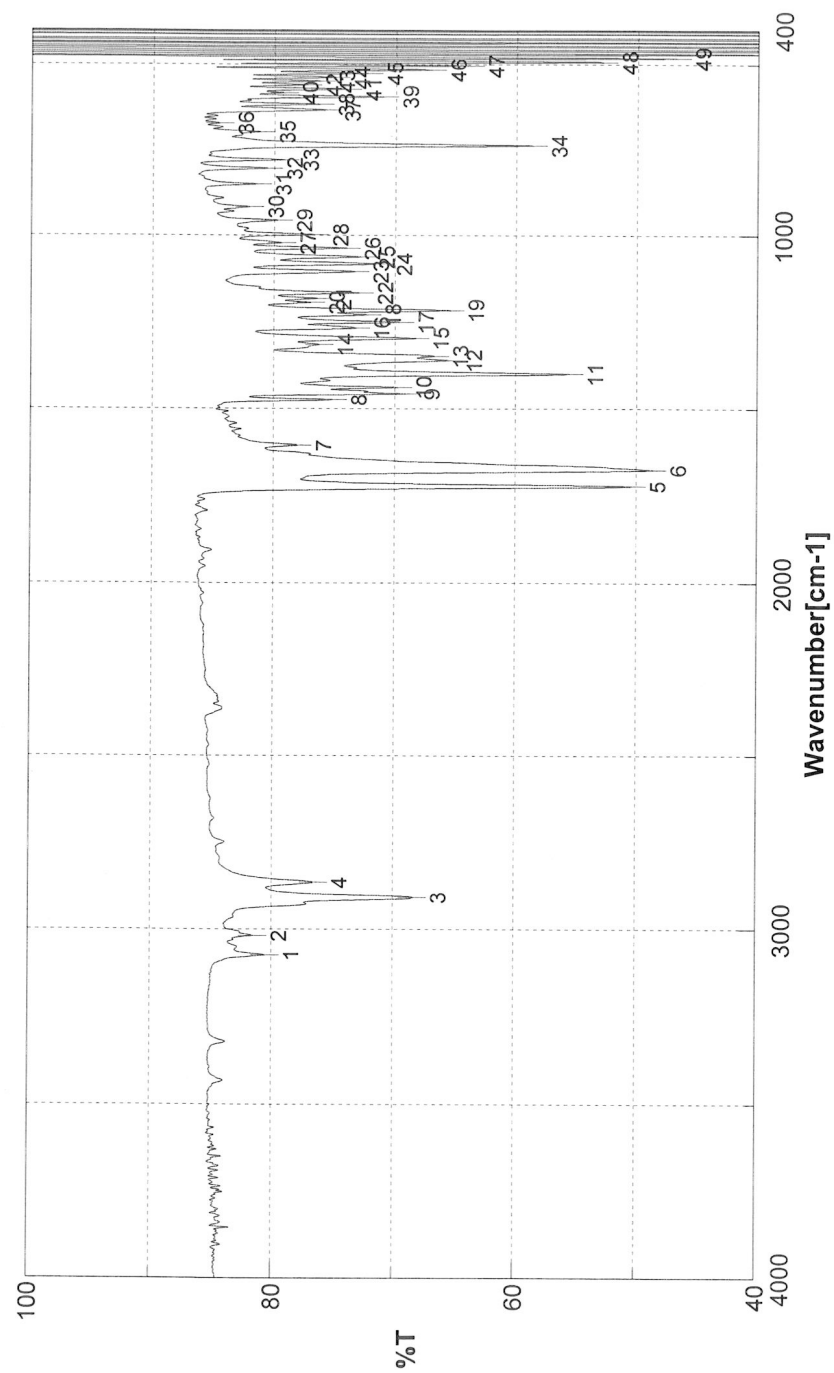
Figure 75. IR spectrum of compound **147**.
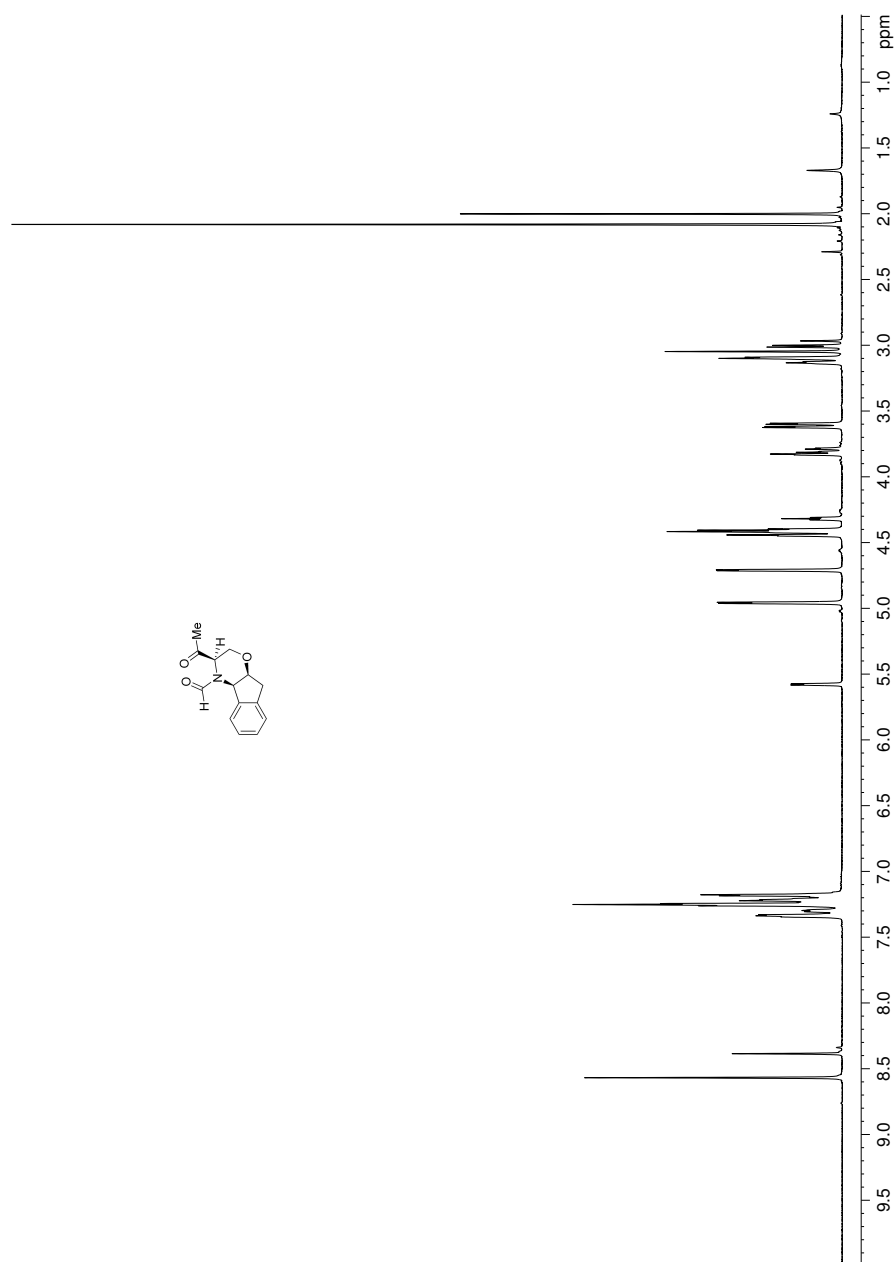
Figure 76. ^{1}H NMR spectrum of compound **146**.
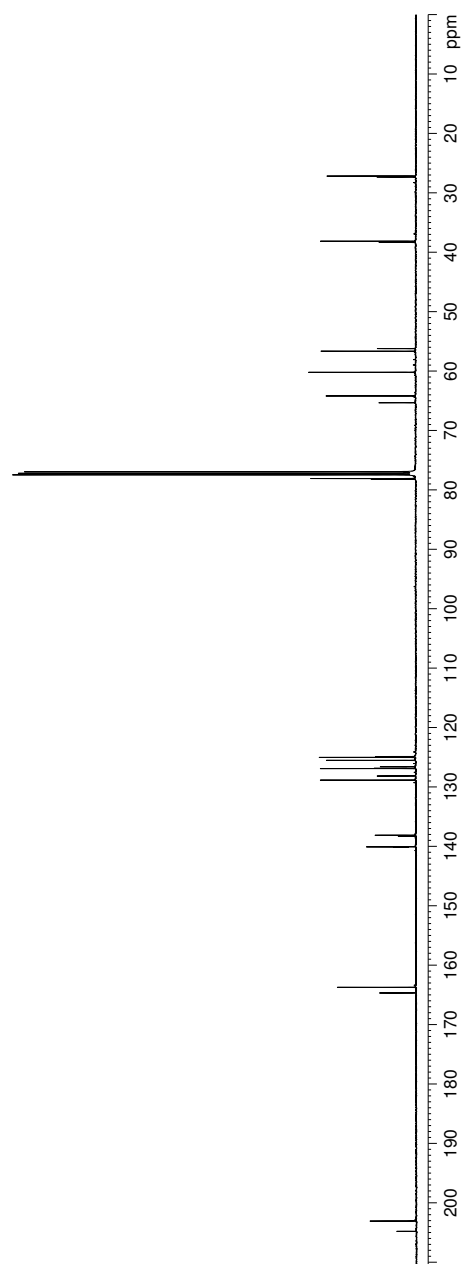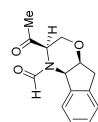
Figure 77. ^{13}C NMR spectrum of compound **146**.
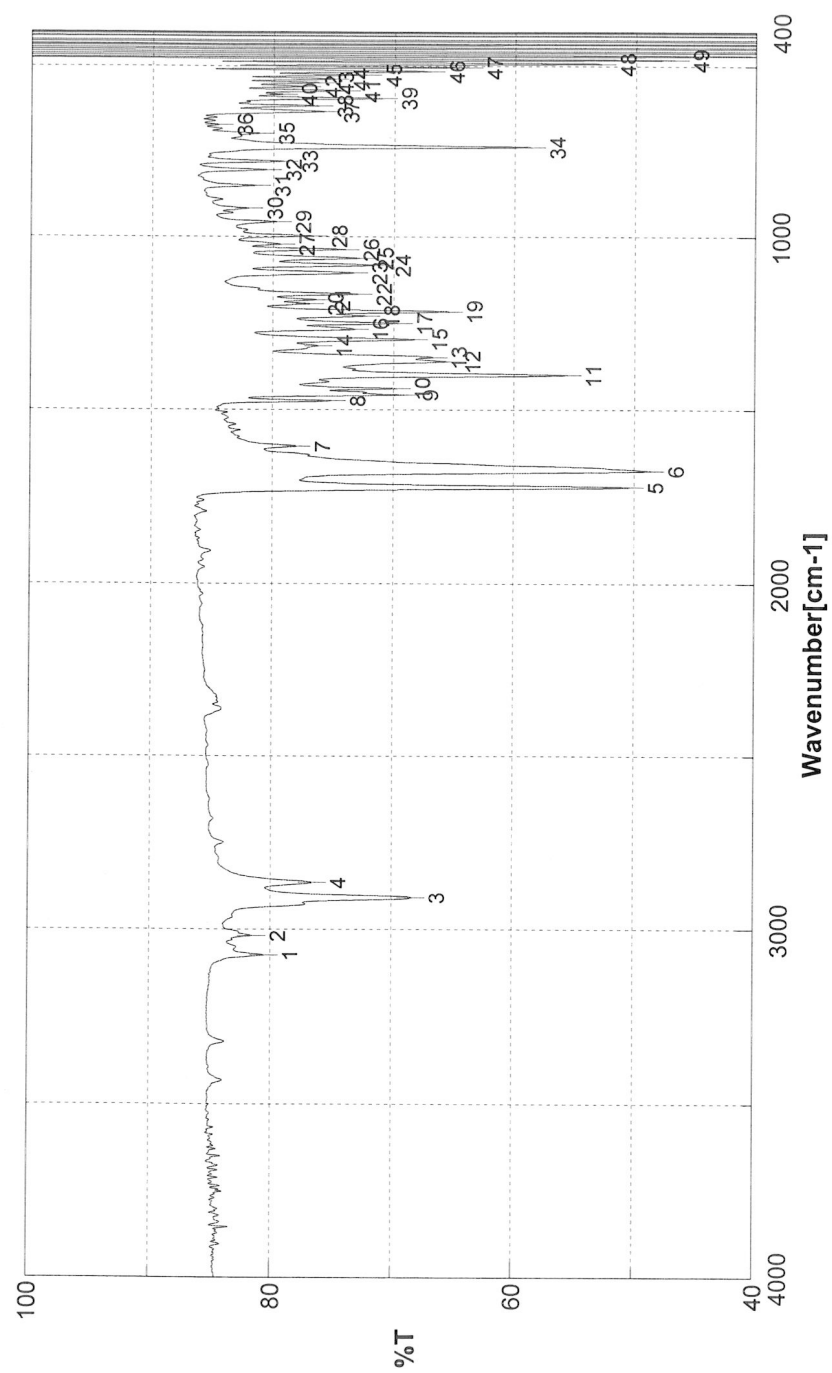
Figure 78. IR spectrum of compound **146**.
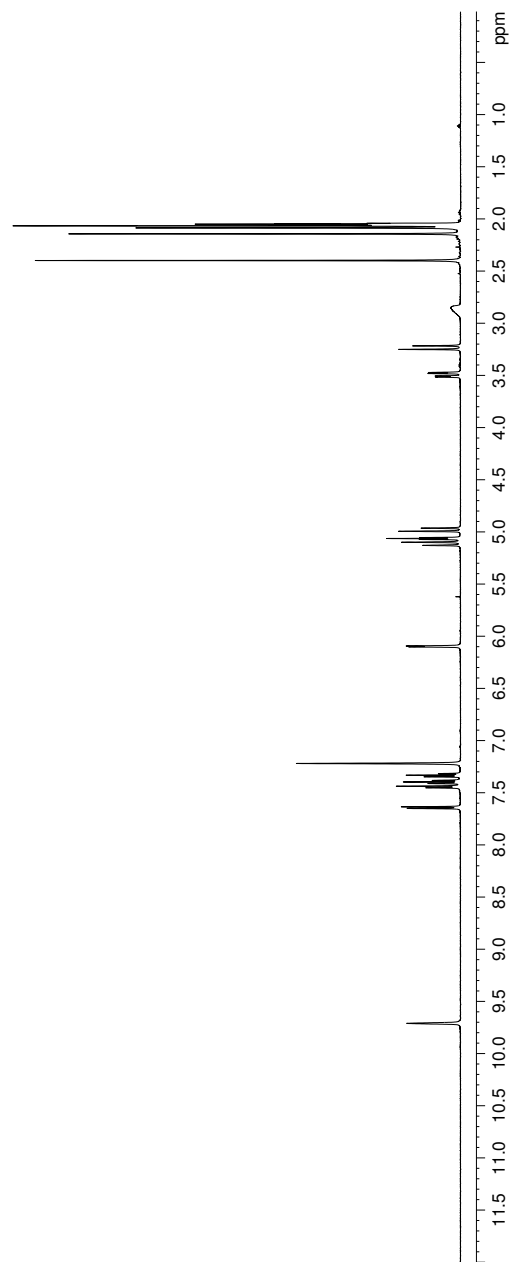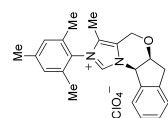
Figure 79. ^{1}H NMR spectrum of compound **145**.
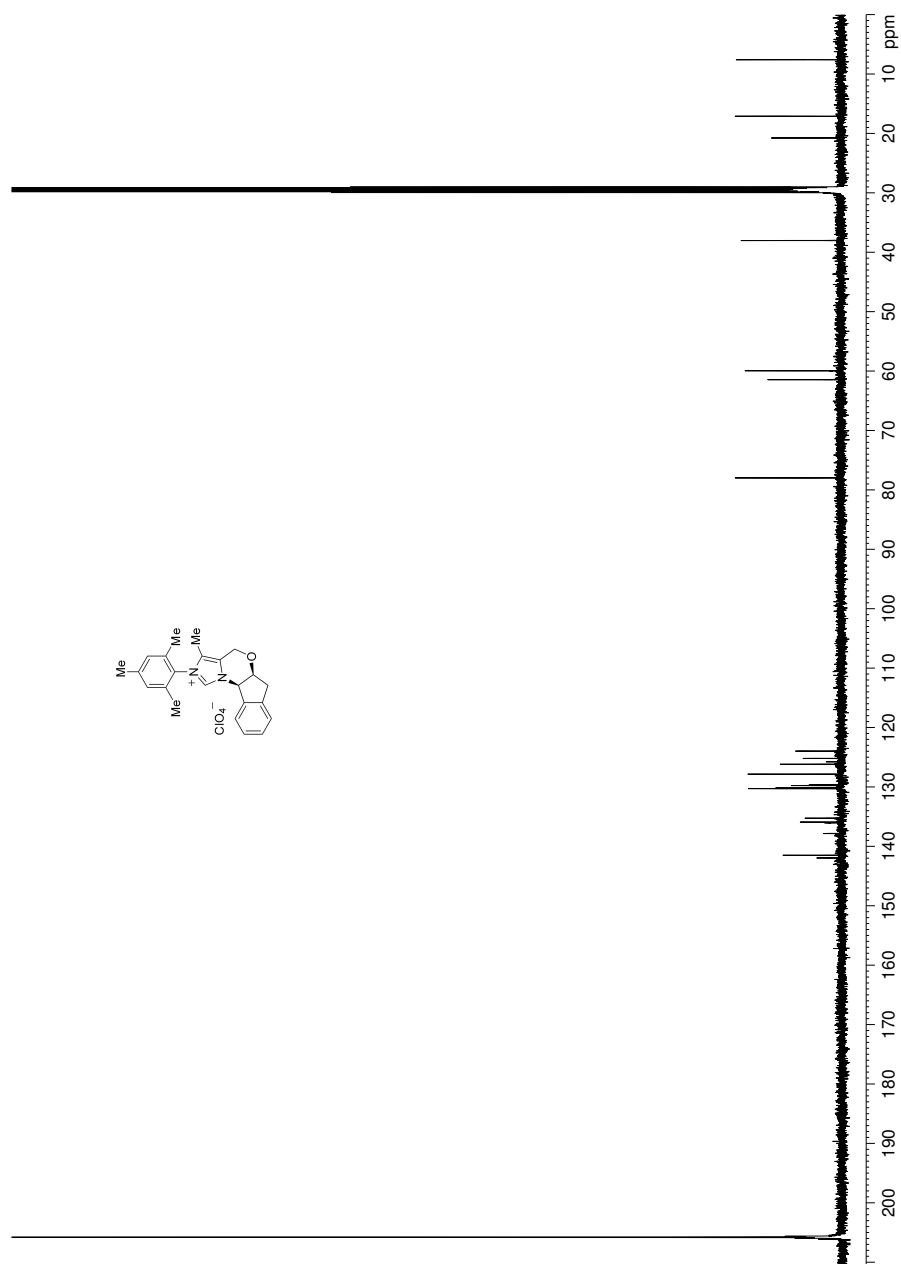
Figure 80. ^{13}C NMR spectrum of compound **145**.
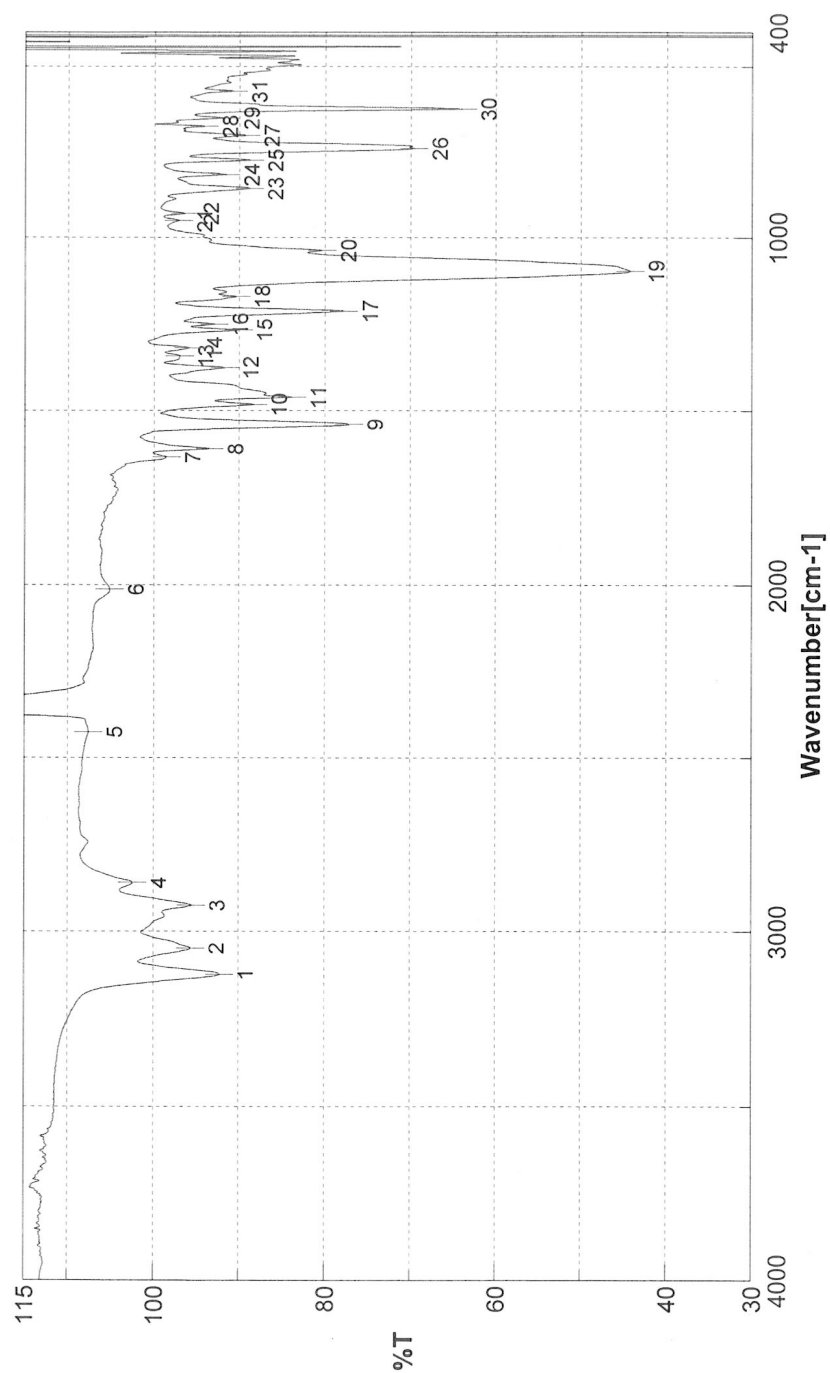
Figure 81. IR spectrum of compound **145**.

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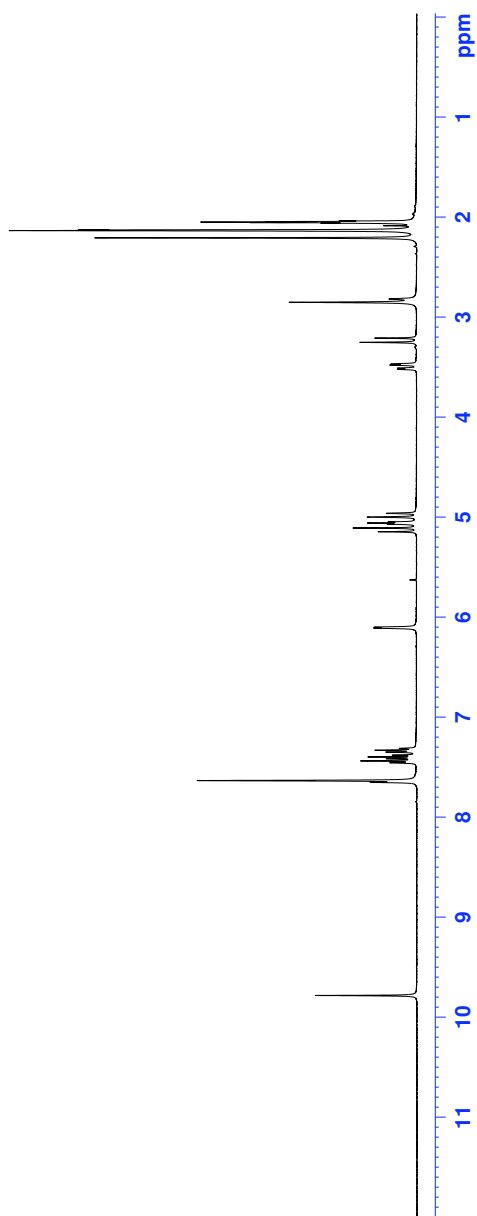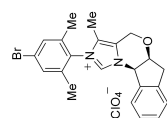
Figure 82. ¹H NMR spectrum of compound **161**.
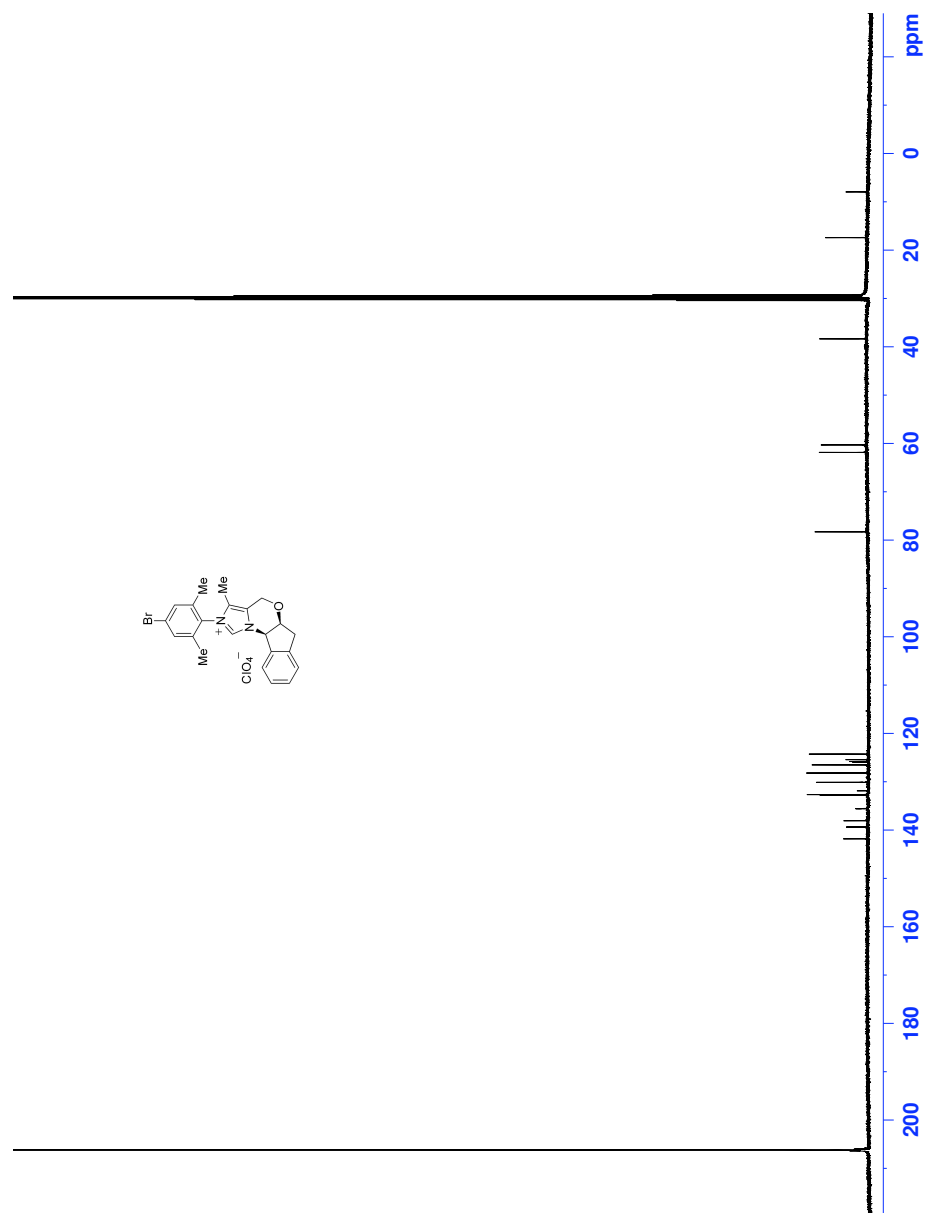
Figure 83. ^{13}C NMR spectrum of compound **161**.
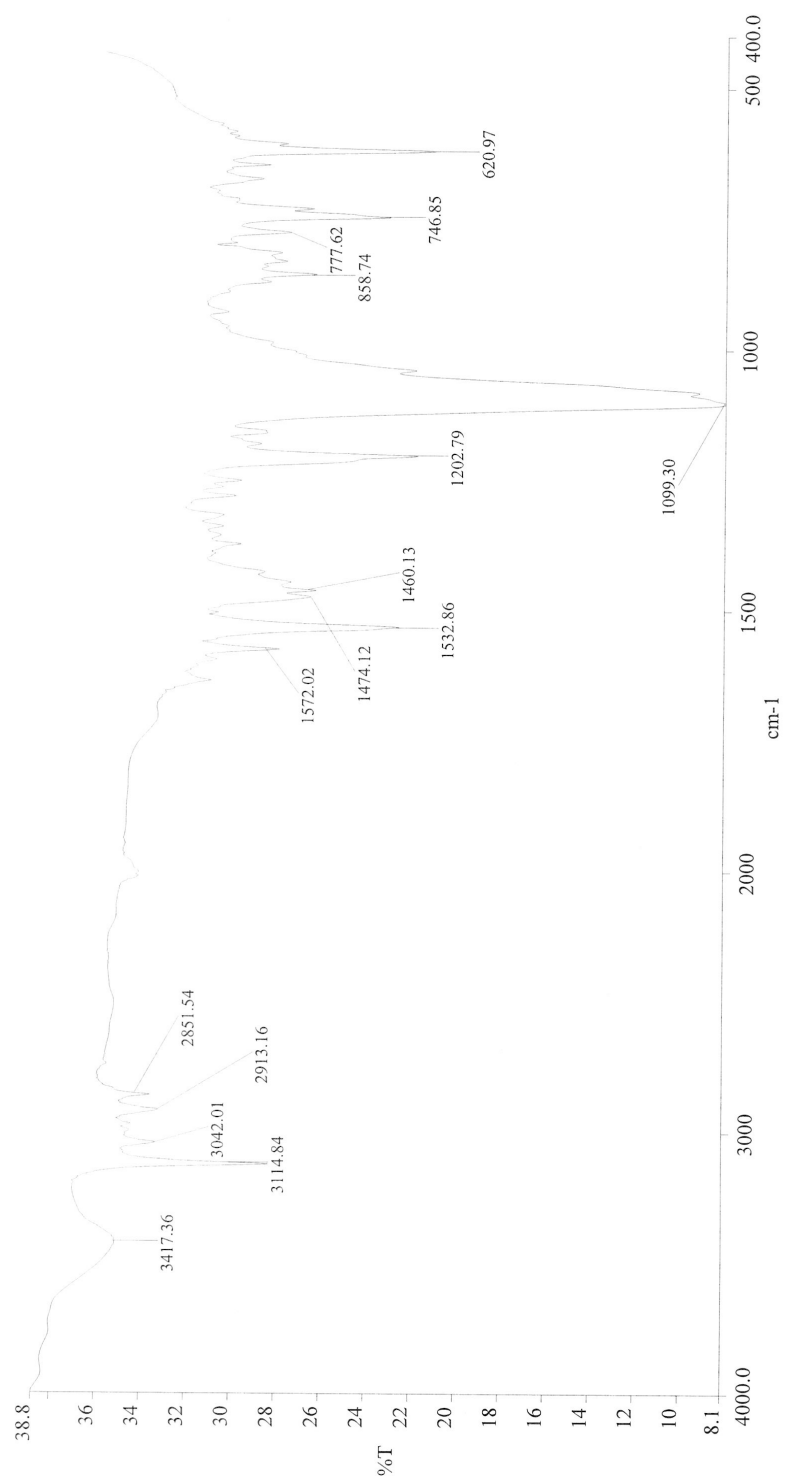
Figure 84. IR spectrum of compound **161**.

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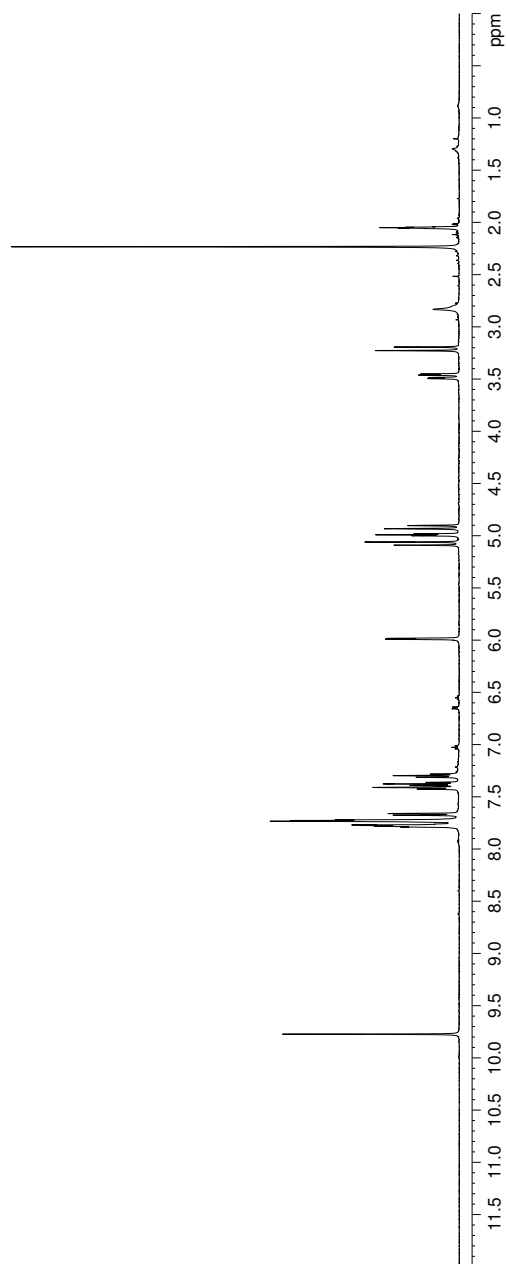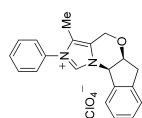
Figure 85. ^{1}H NMR spectrum of compound **162**.

255
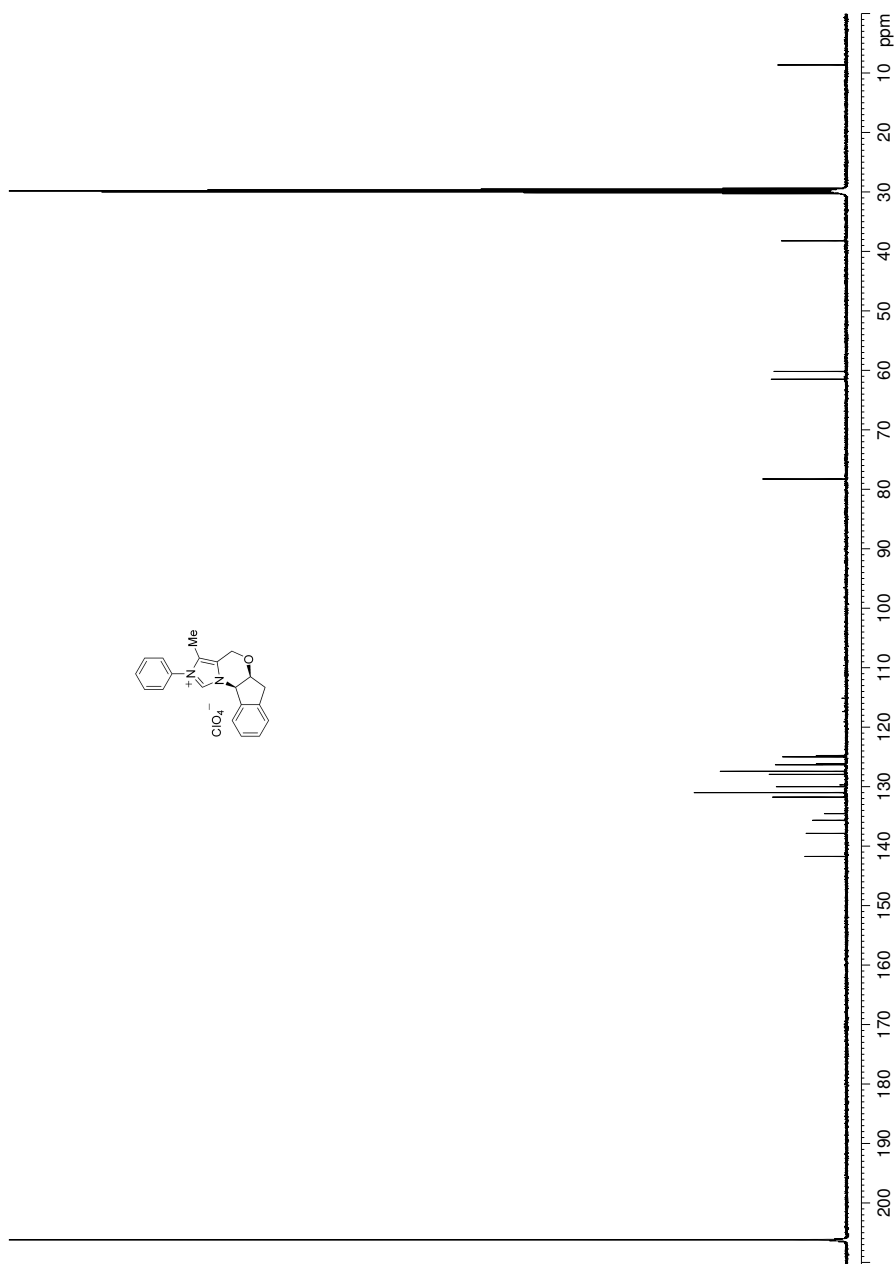
Figure 86. ^{13}C NMR spectrum of compound **162**.
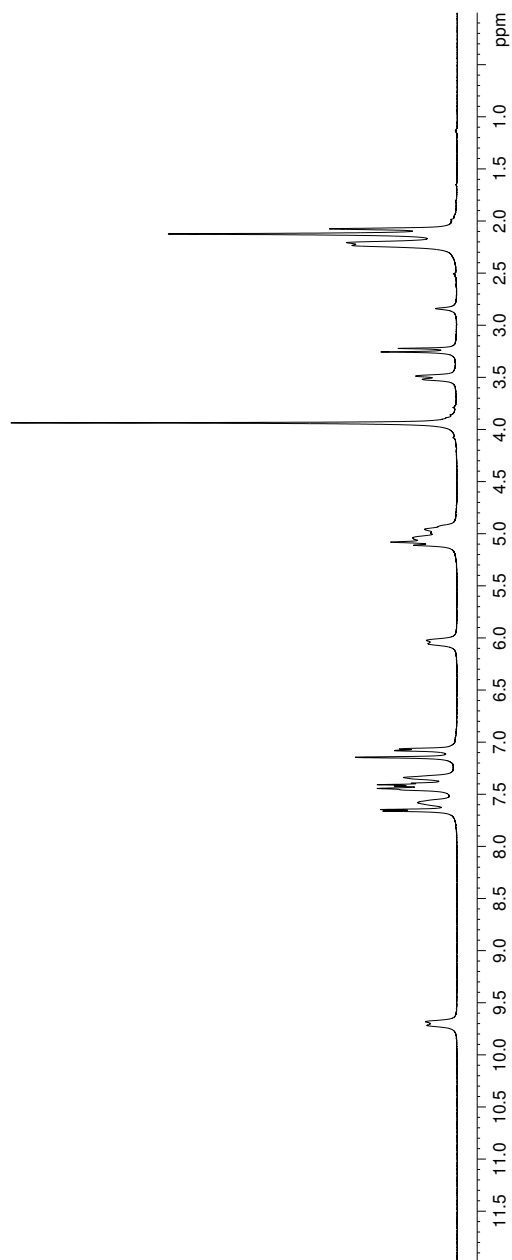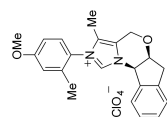
Figure 87. ^{1}H NMR spectrum of compound **163**.

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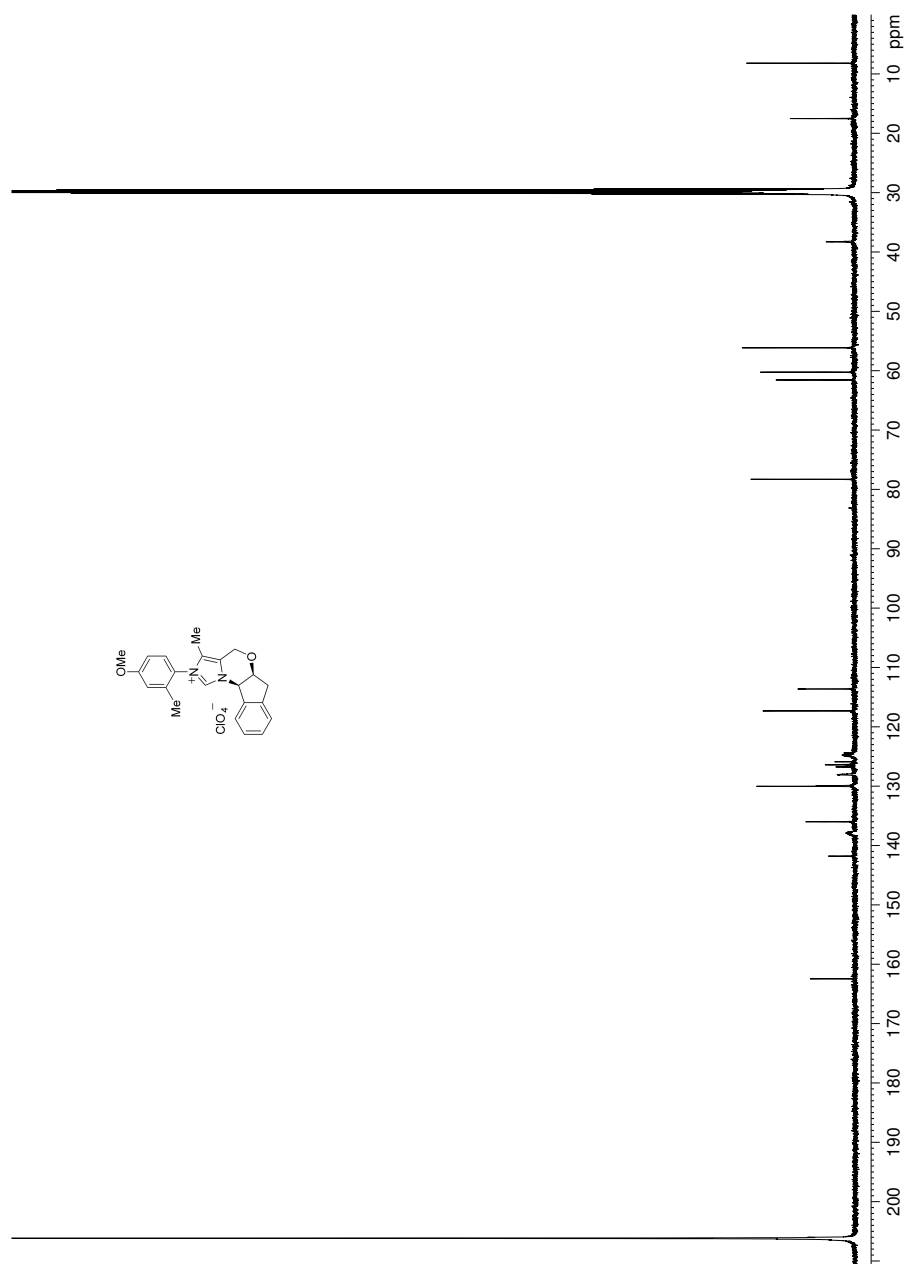
Figure 88. ^{13}C NMR spectrum of compound **163**.
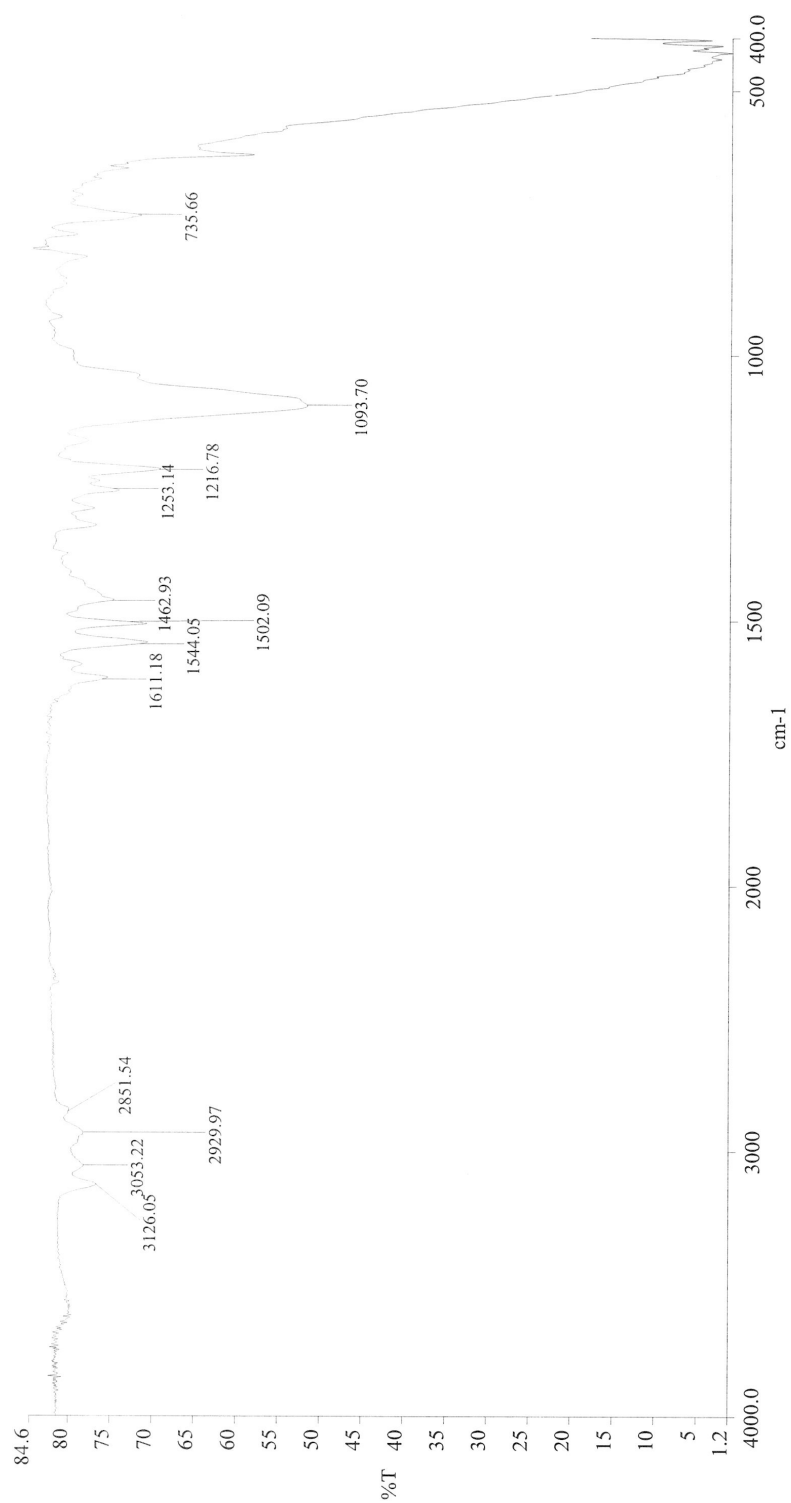
Figure 89. IR spectrum of compound **163**.

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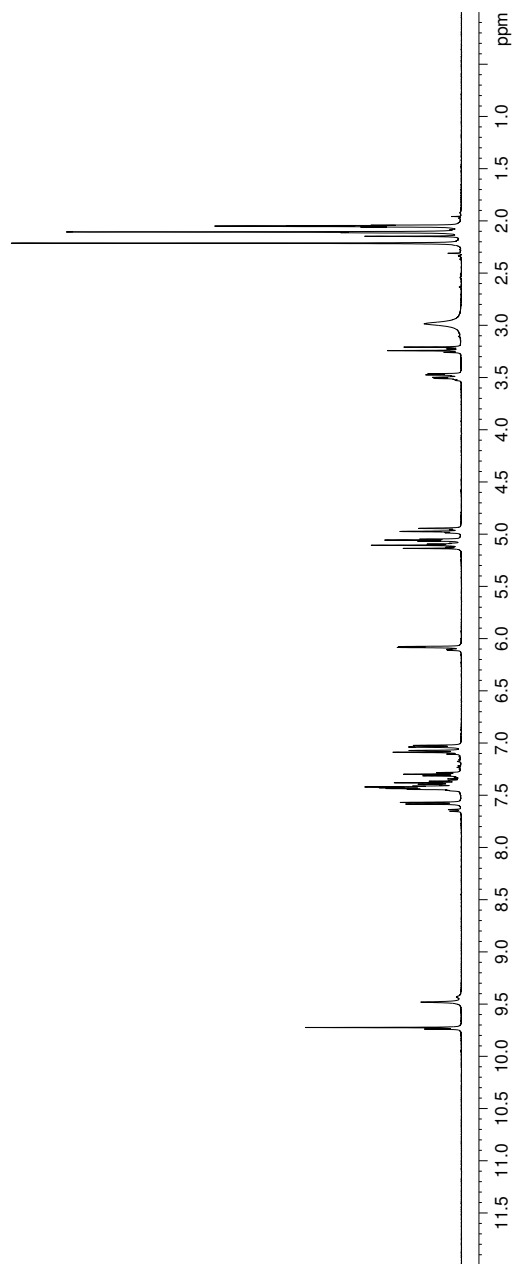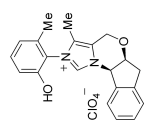
Figure 90. ¹H NMR spectrum of compound **164**.
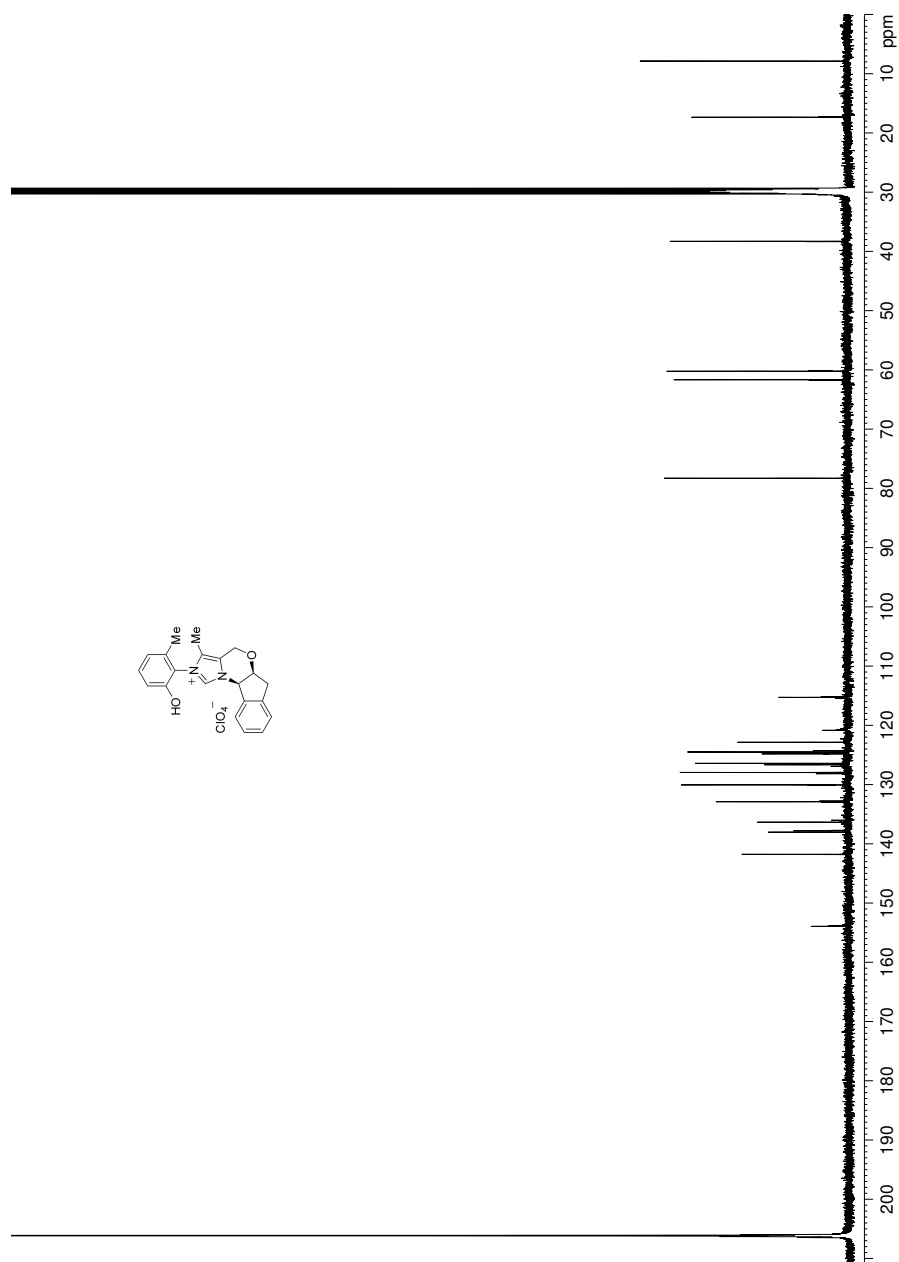
Figure 91. ^{13}C NMR spectrum of compound **164**.
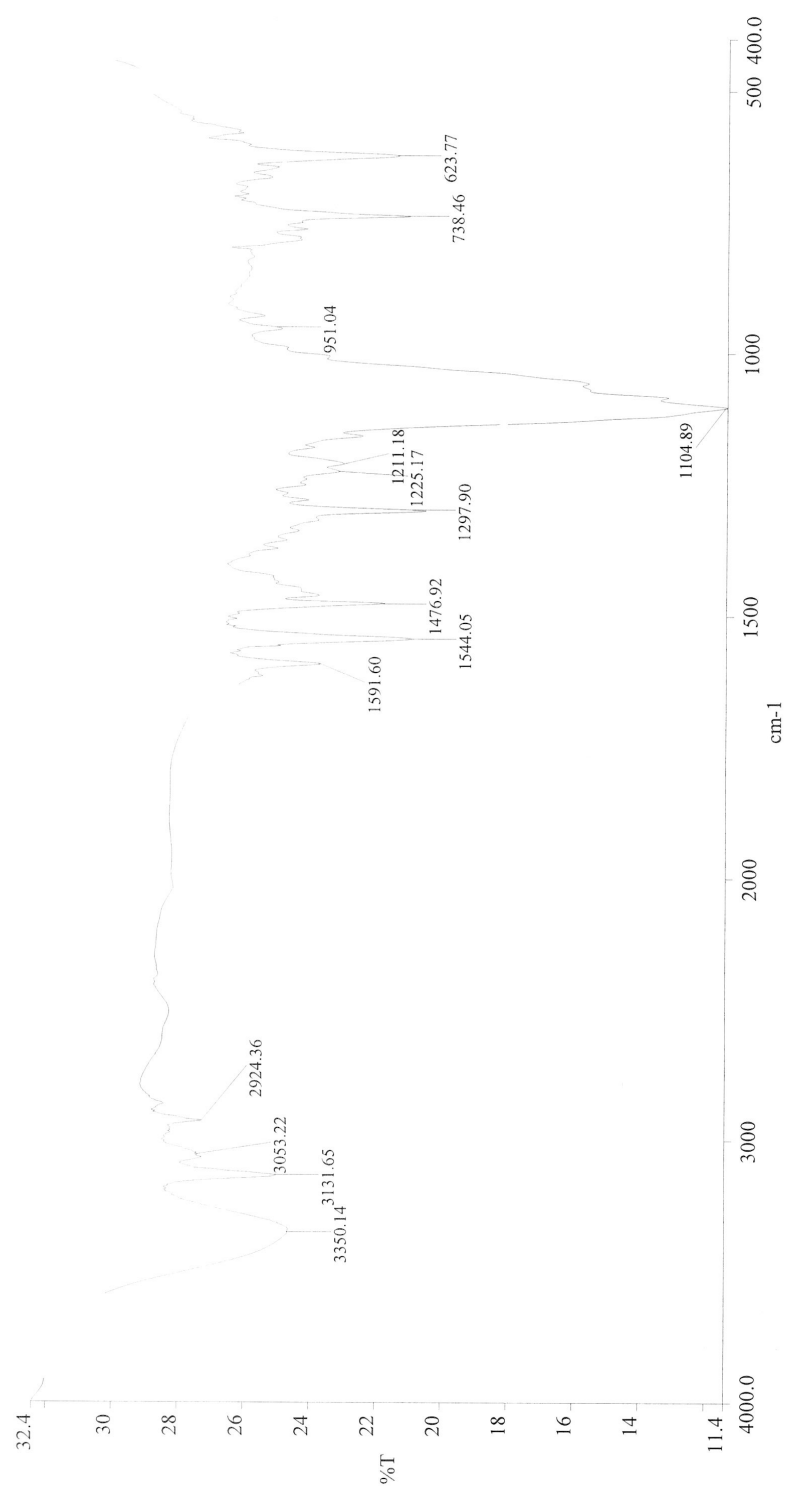
Figure 92. IR spectrum of compound **164**.
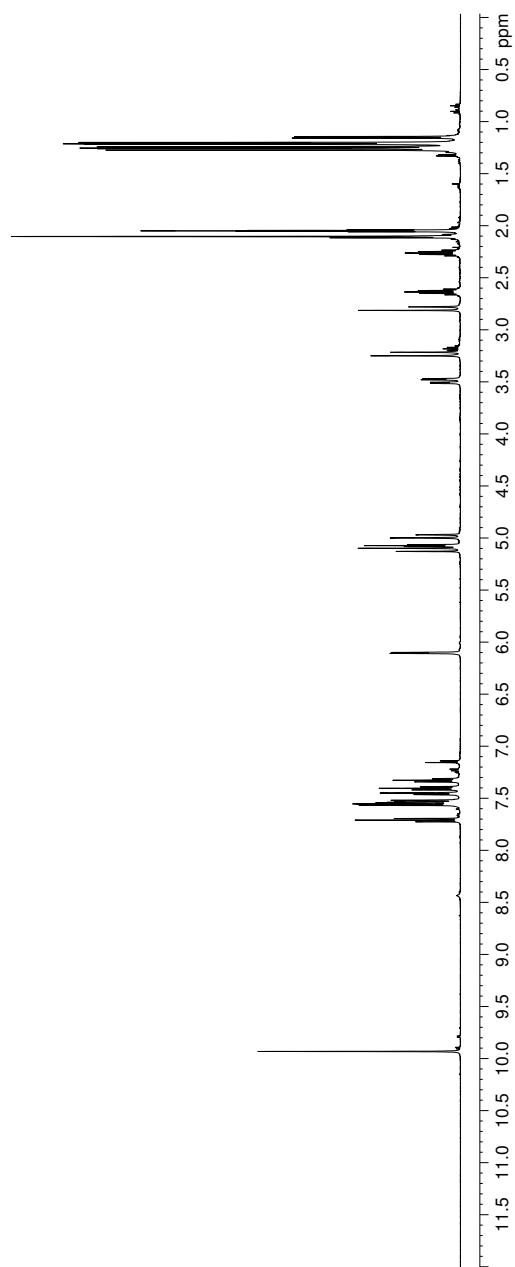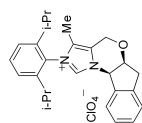
Figure 93. ^{1}H NMR spectrum of compound **165**.
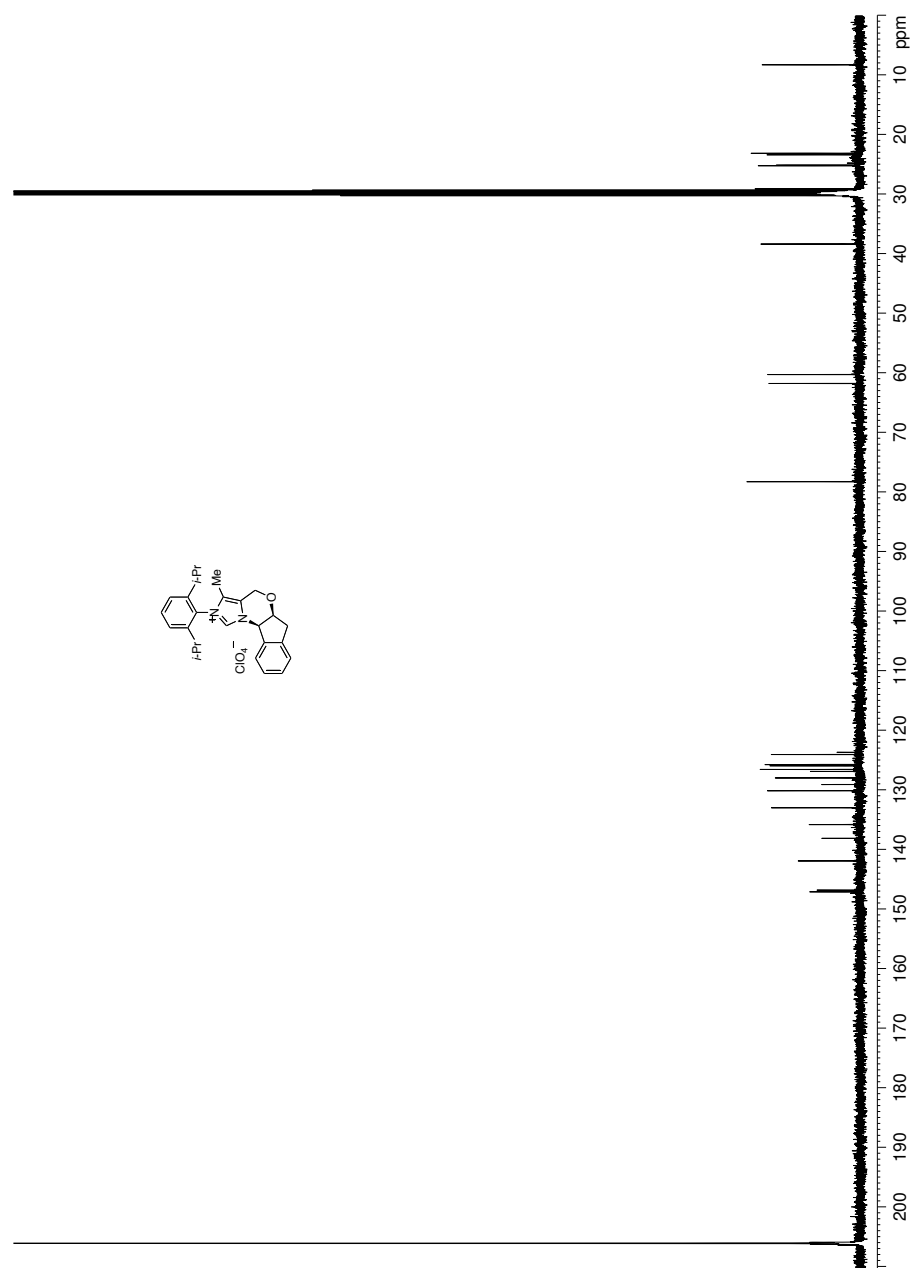
Figure 94. ^{13}C NMR spectrum of compound **165**.

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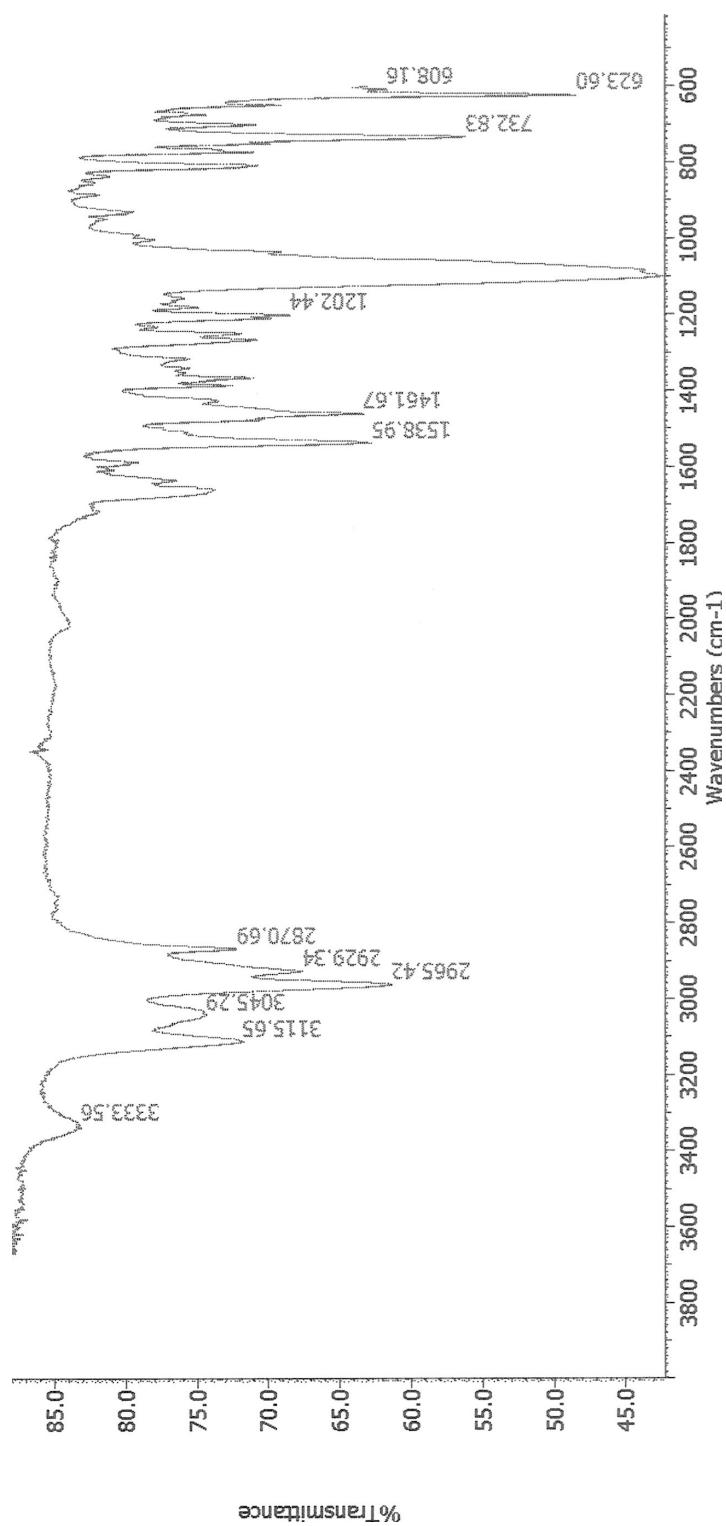
Figure 95. IR spectrum of compound **165**.
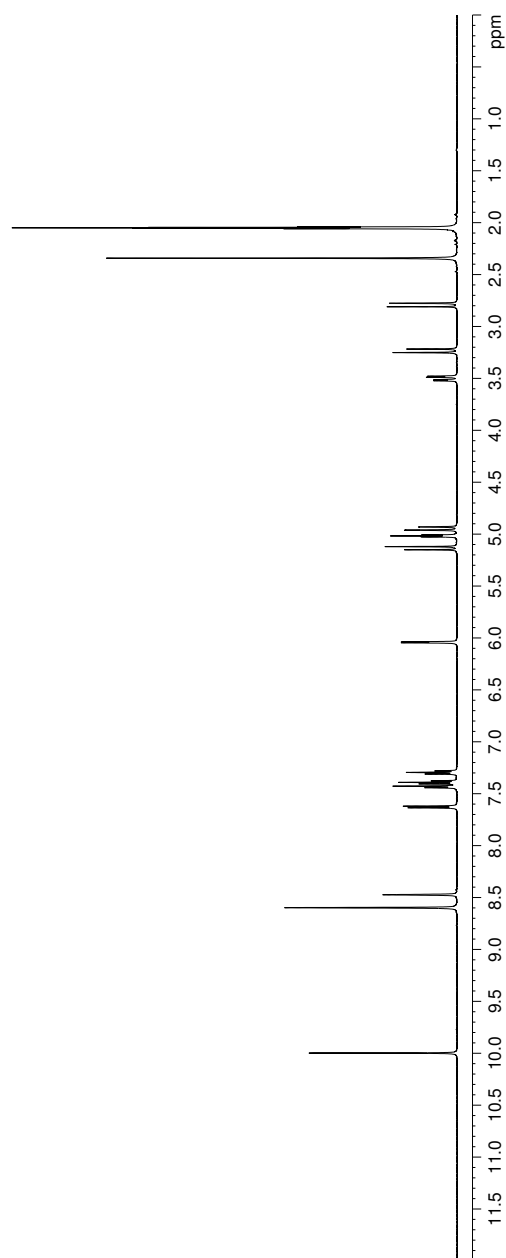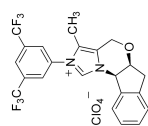
Figure 96. ¹H NMR spectrum of compound **166**.
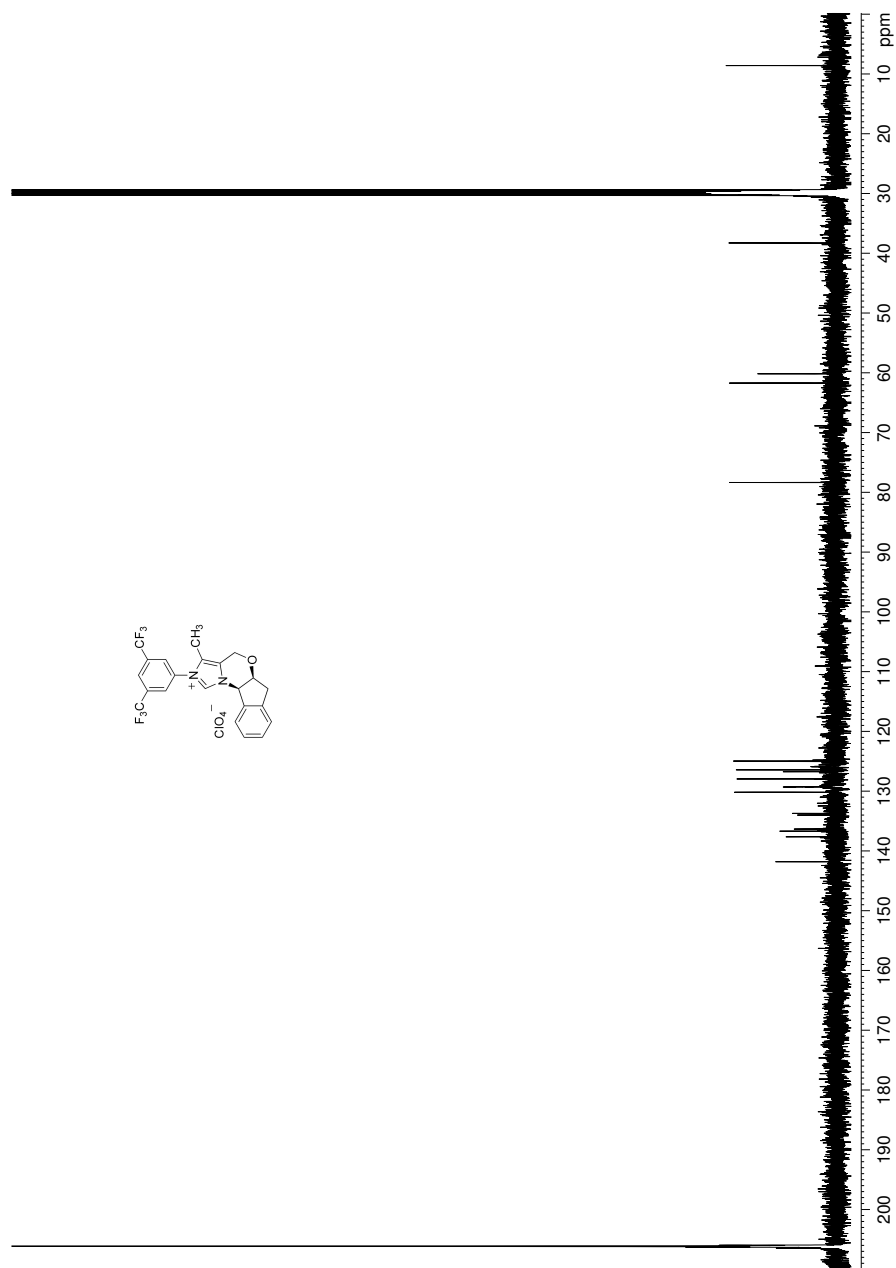
Figure 97. ^{13}C NMR spectrum of compound **166**.
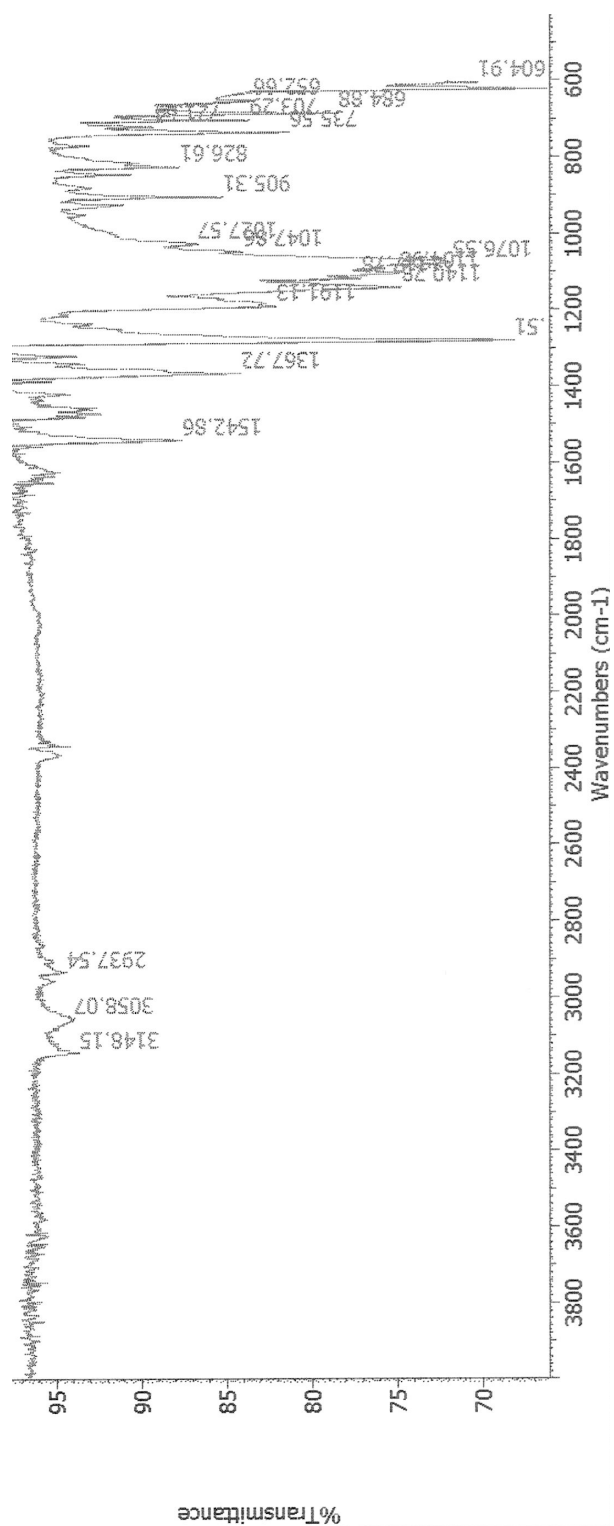
Figure 98. IR spectrum of compound **166**.
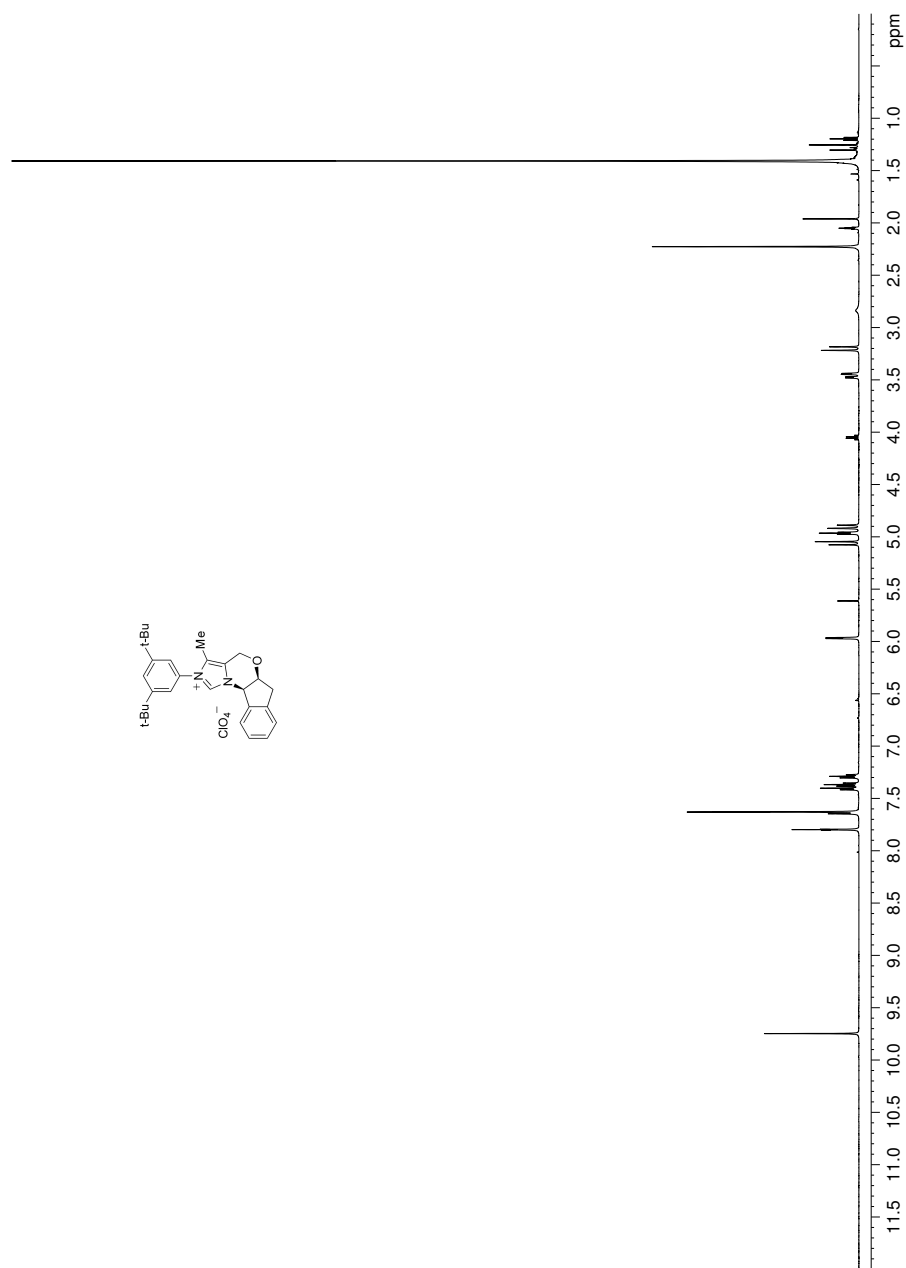
Figure 99. ^{1}H NMR spectrum of compound **167**.

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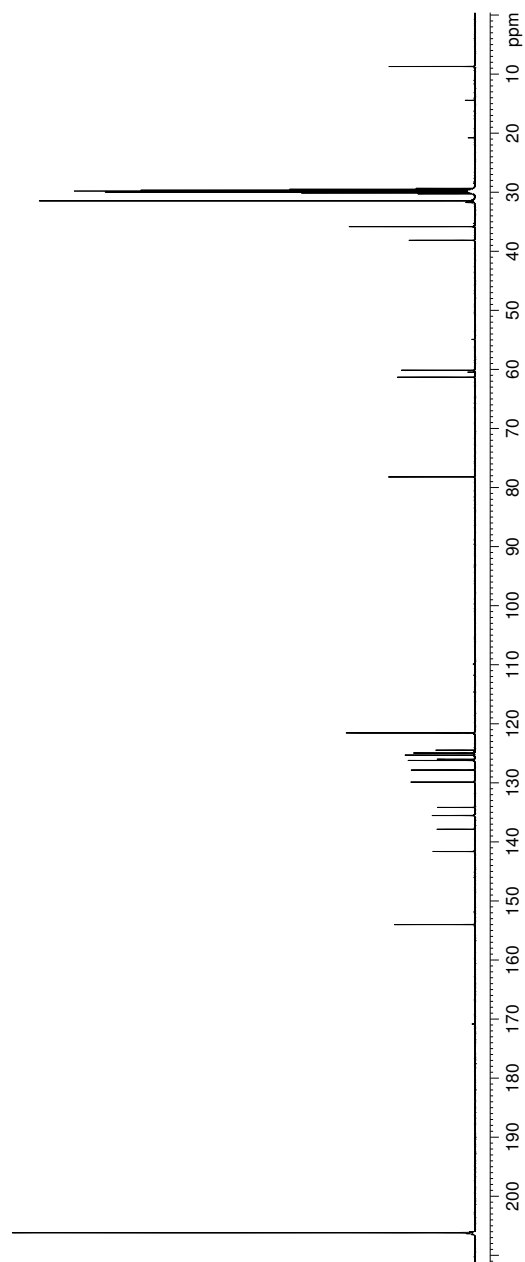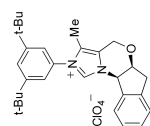
Figure 100. ^{13}C NMR spectrum of compound **167**.
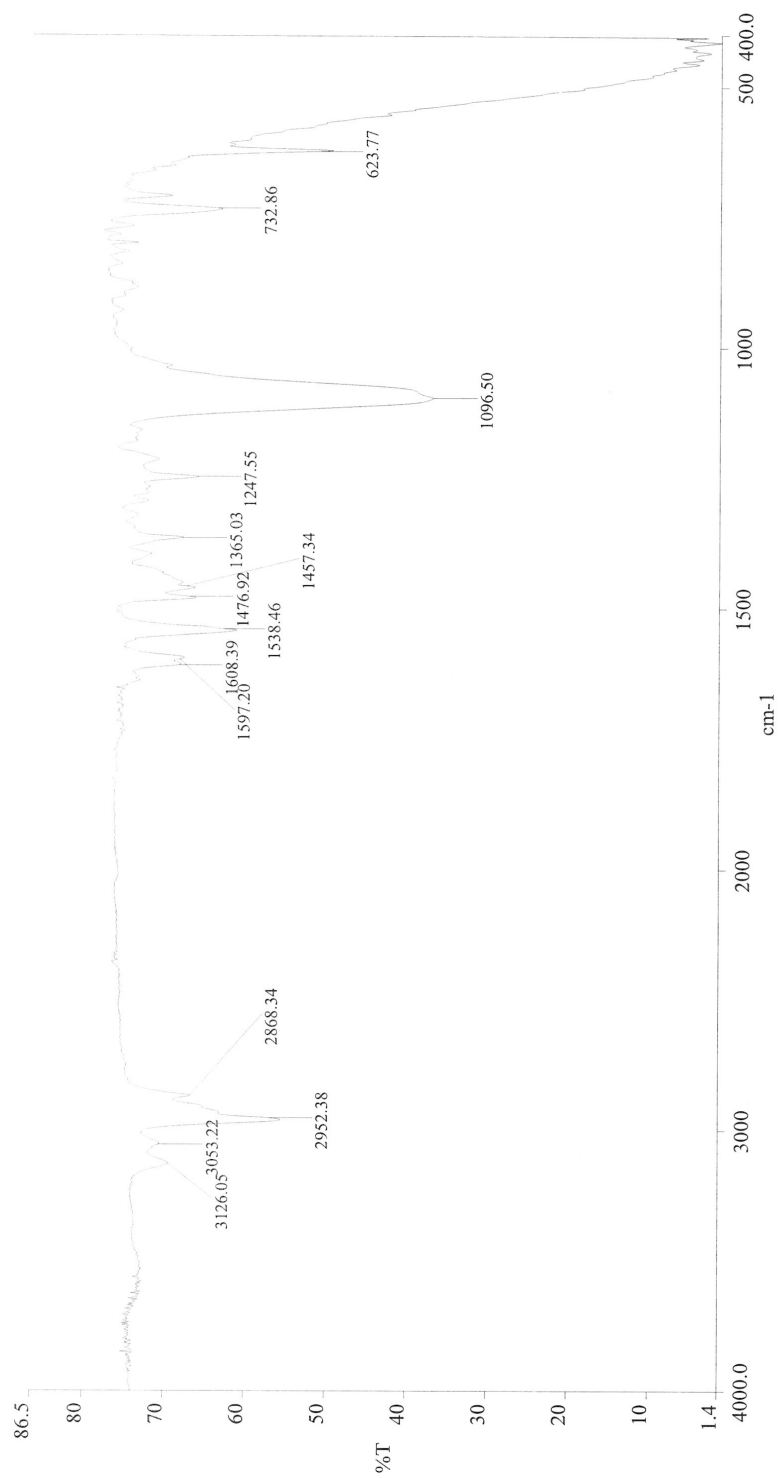
Figure 101. IR spectrum of compound **167**.

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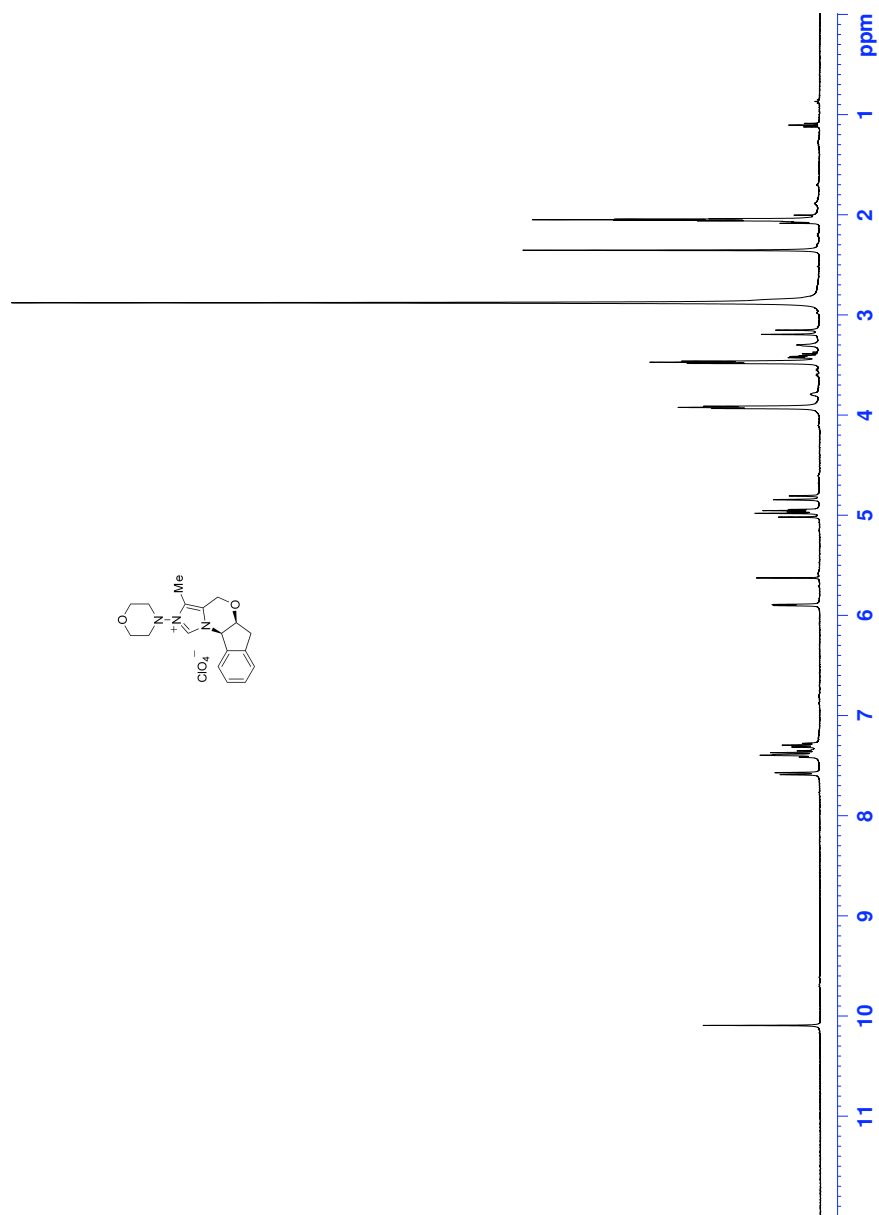
Figure 102. ¹H NMR spectrum of compound **168**.
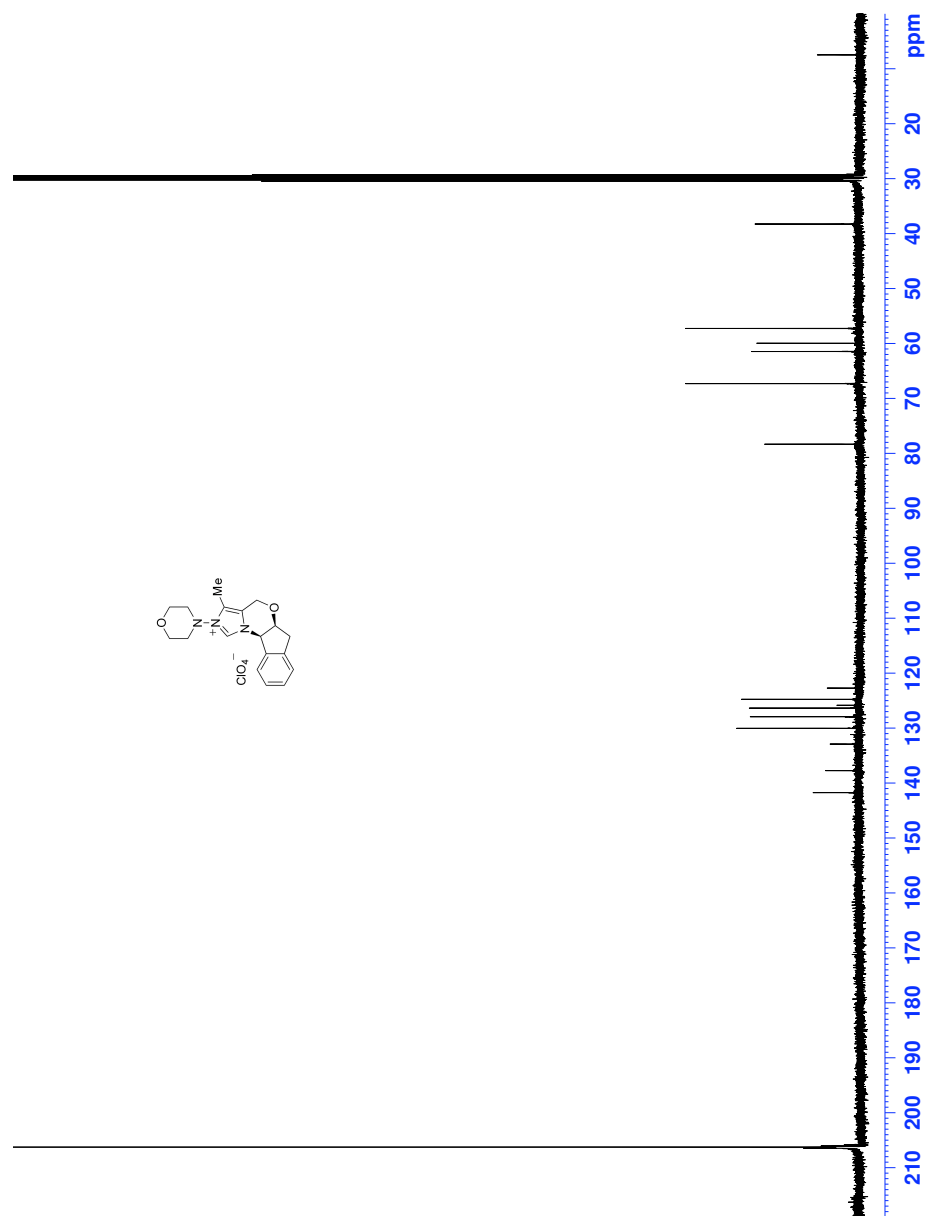
Figure 103. ^{13}C NMR spectrum of compound **168**.

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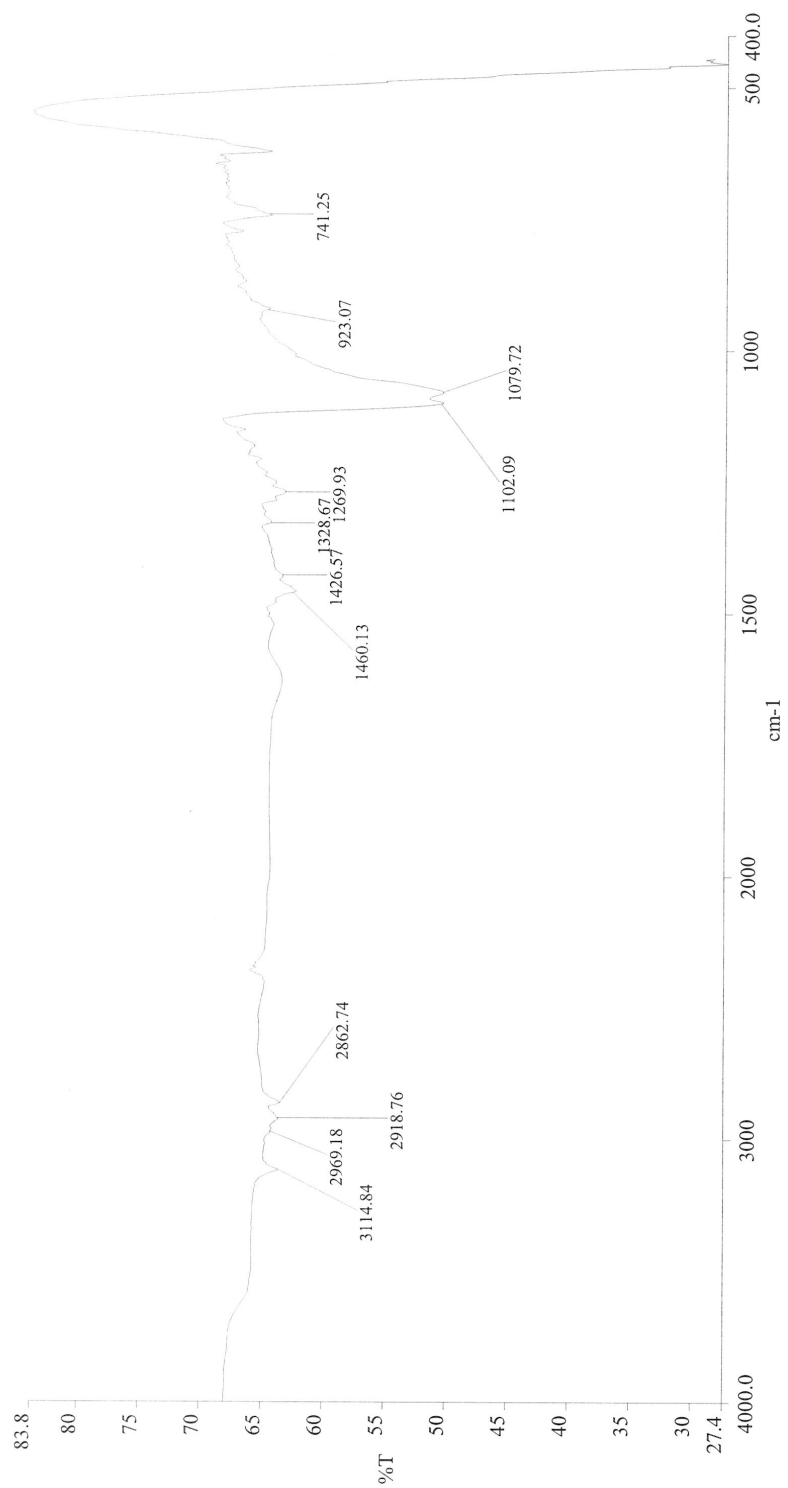
Figure 104. IR spectrum of compound **168**.
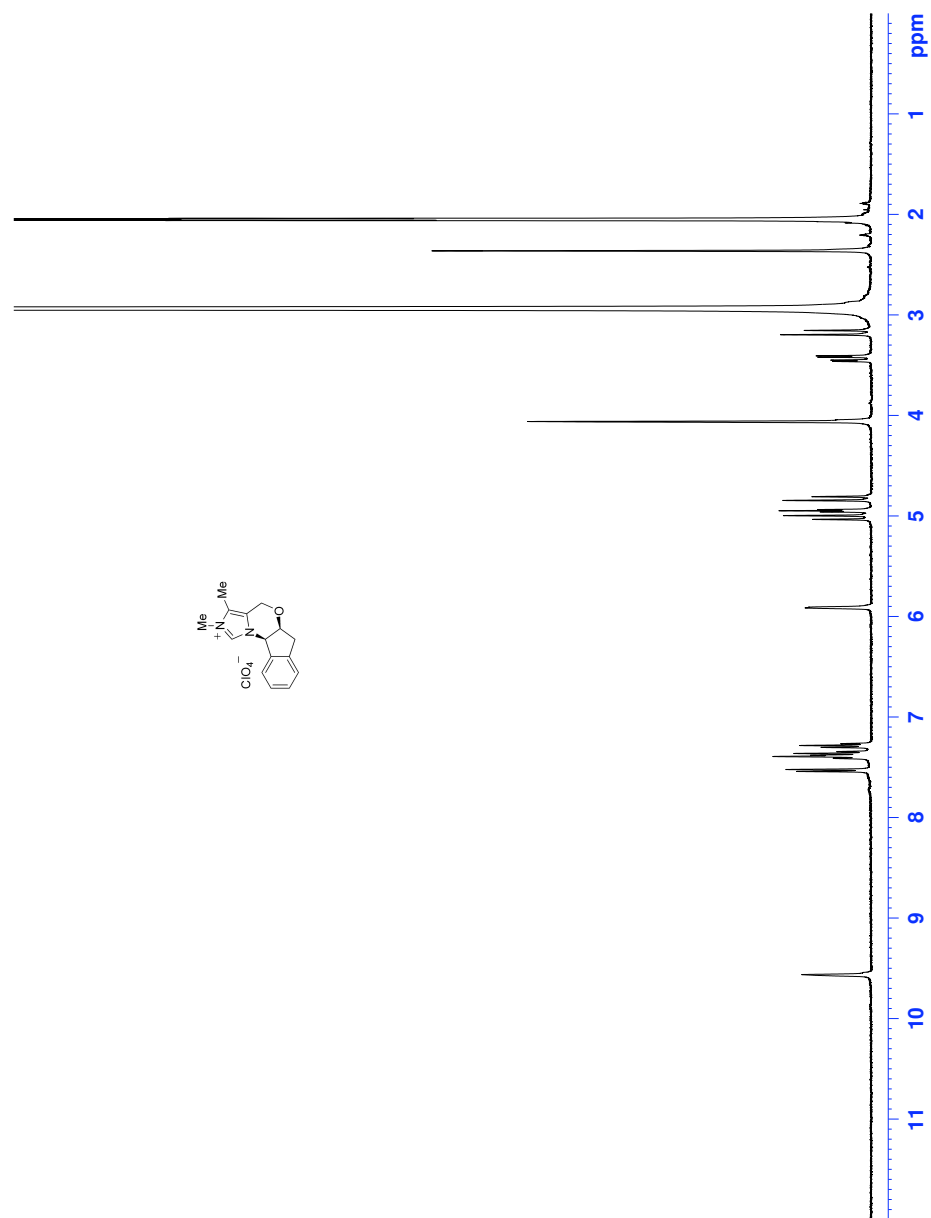
Figure 105. ¹H NMR spectrum of compound **169**.
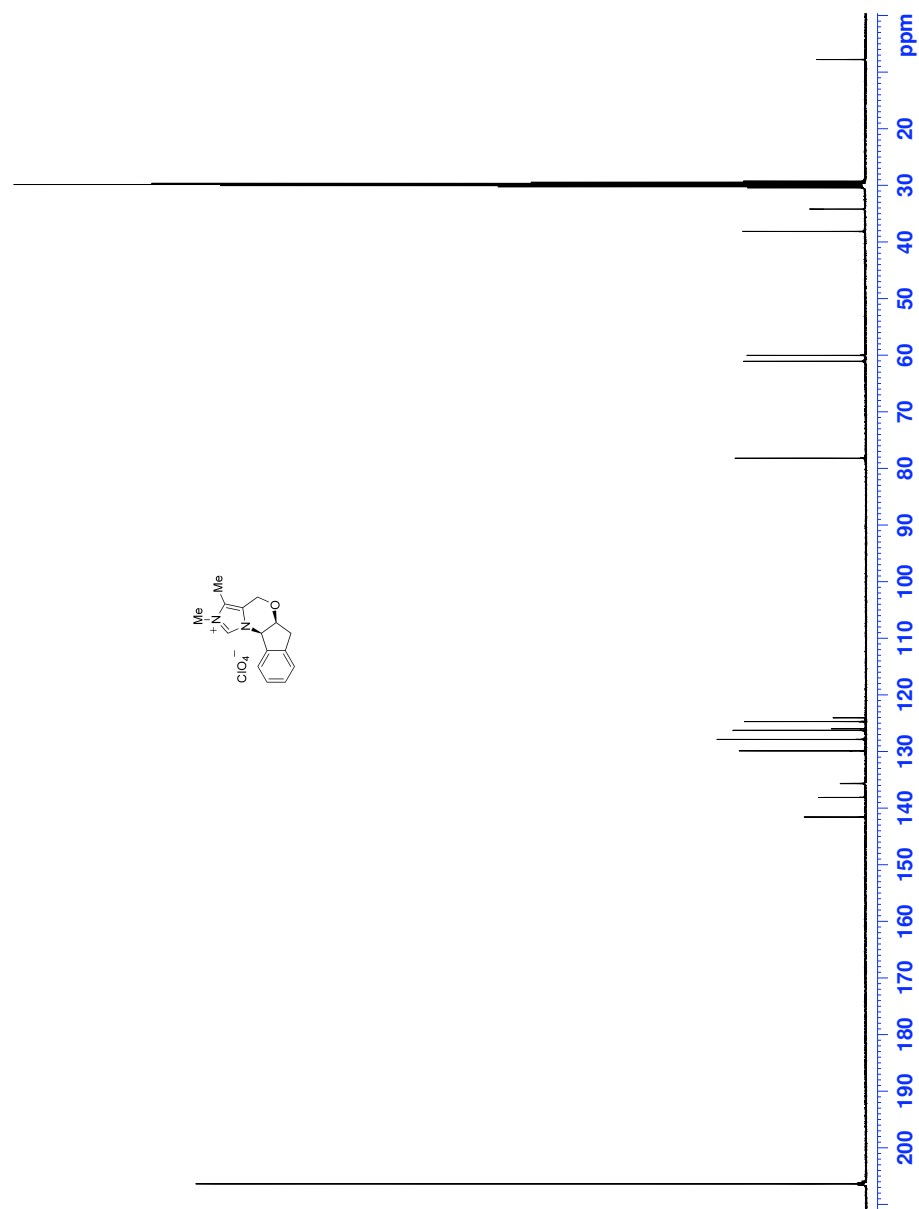
Figure 106. ^{13}C NMR spectrum of compound **169**.
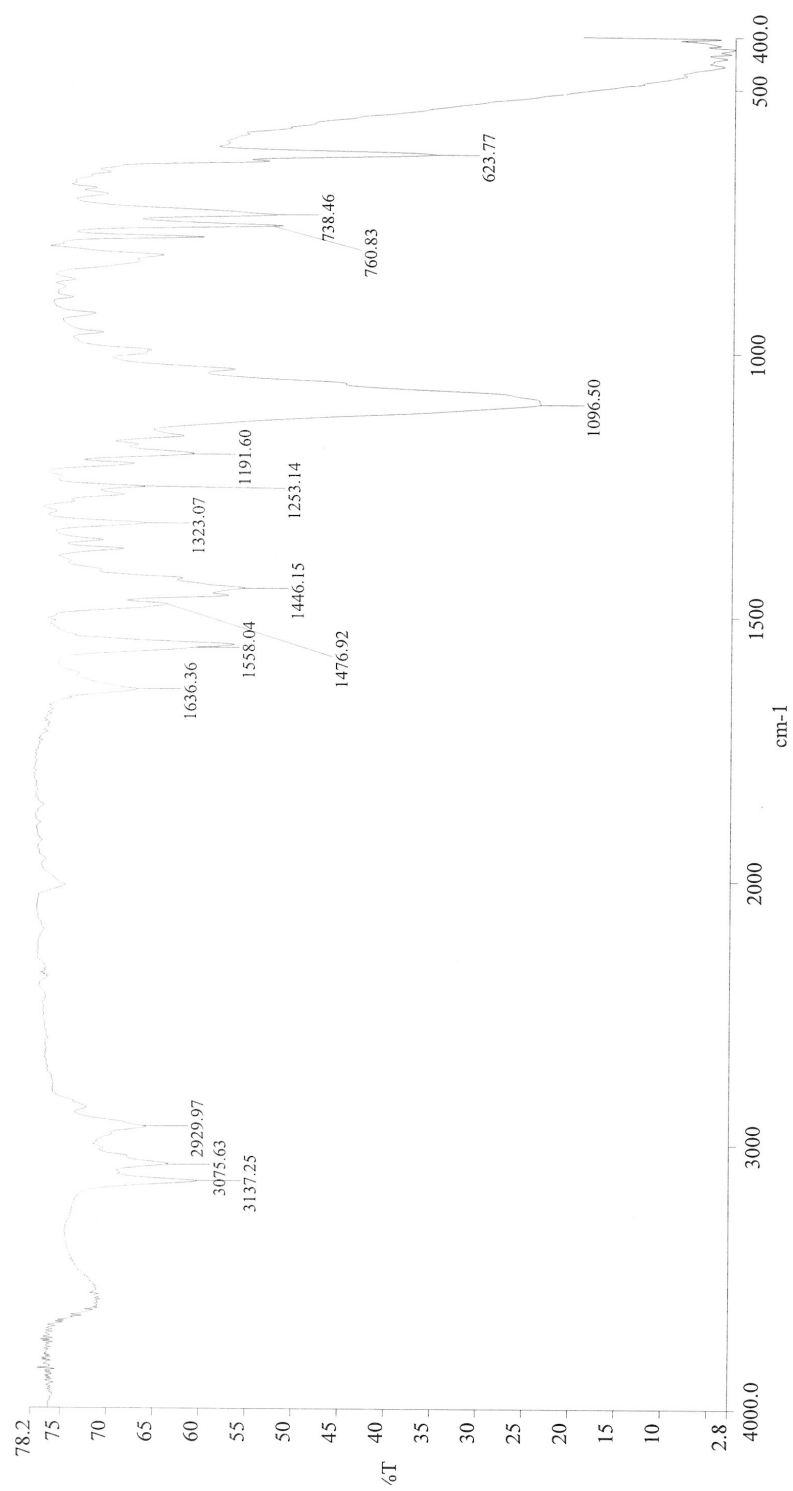
Figure 107. IR spectrum of compound **169**.

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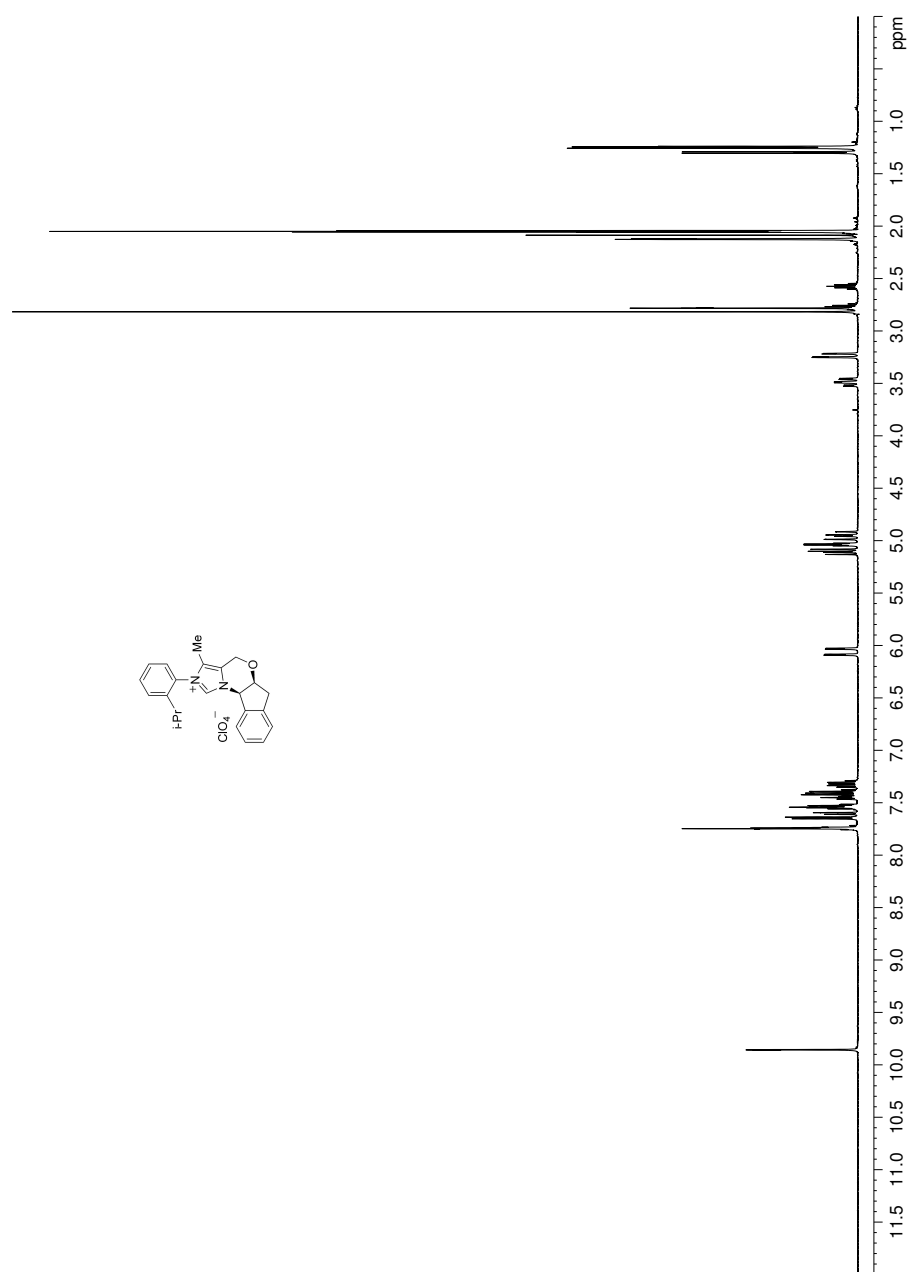
Figure 108. ¹H NMR spectrum of compound **170**.
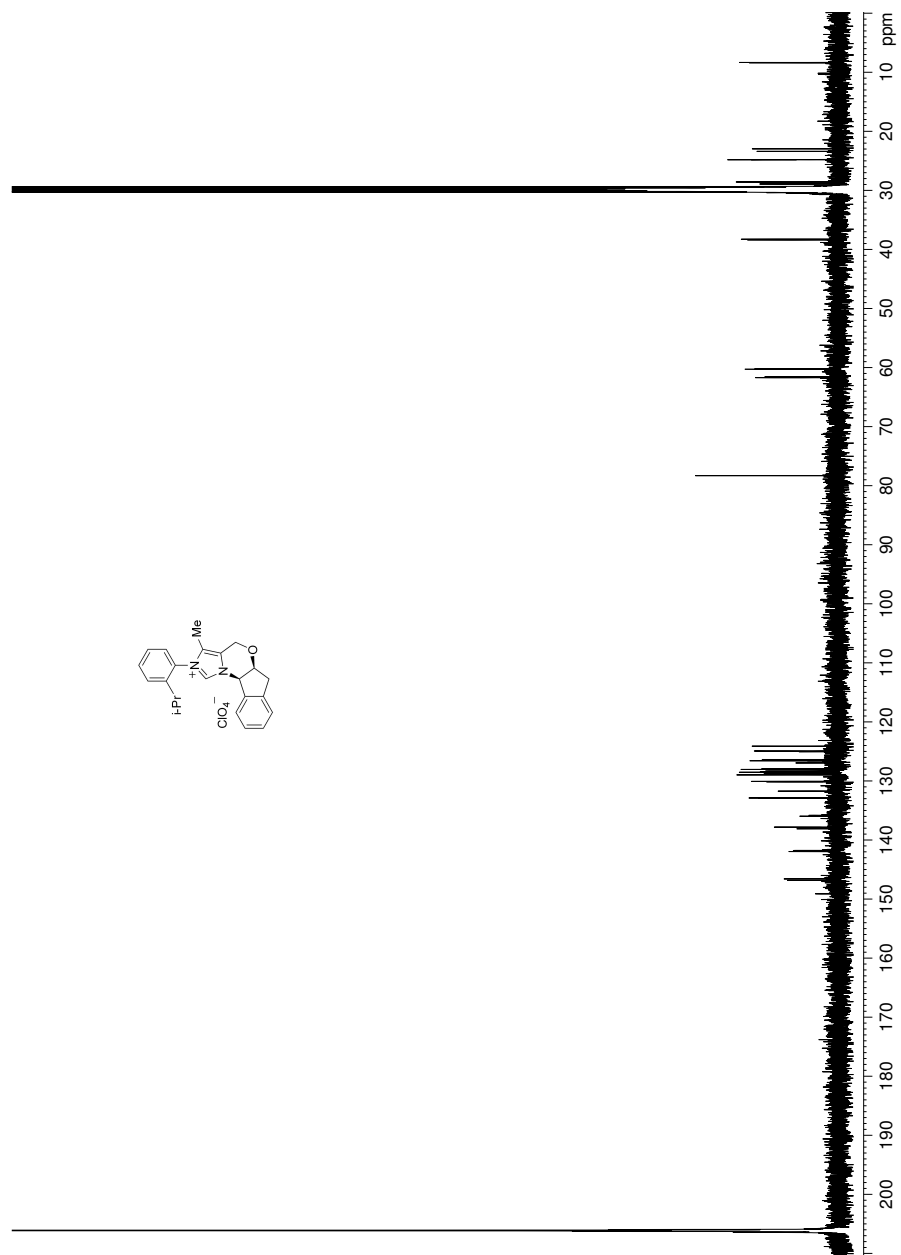
Figure 109. ^{13}C NMR spectrum of compound **170**.
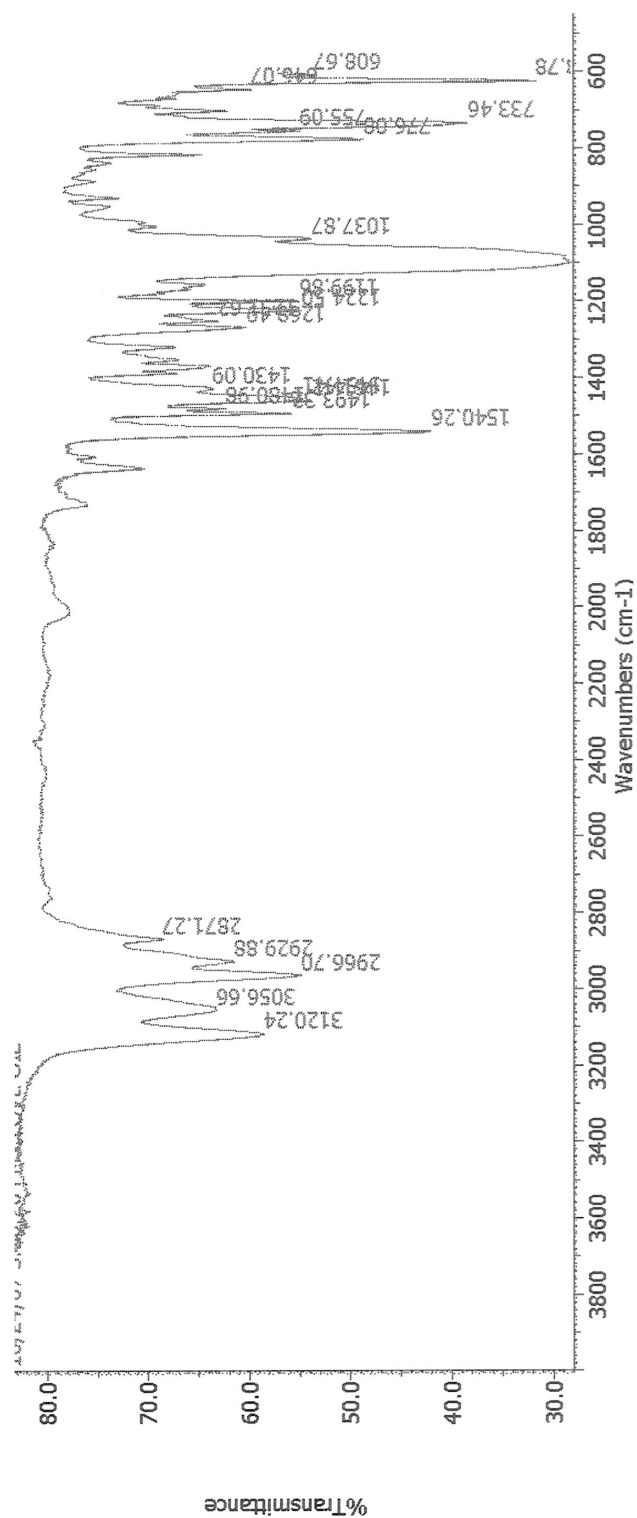
Figure 110. IR spectrum of compound **170**.
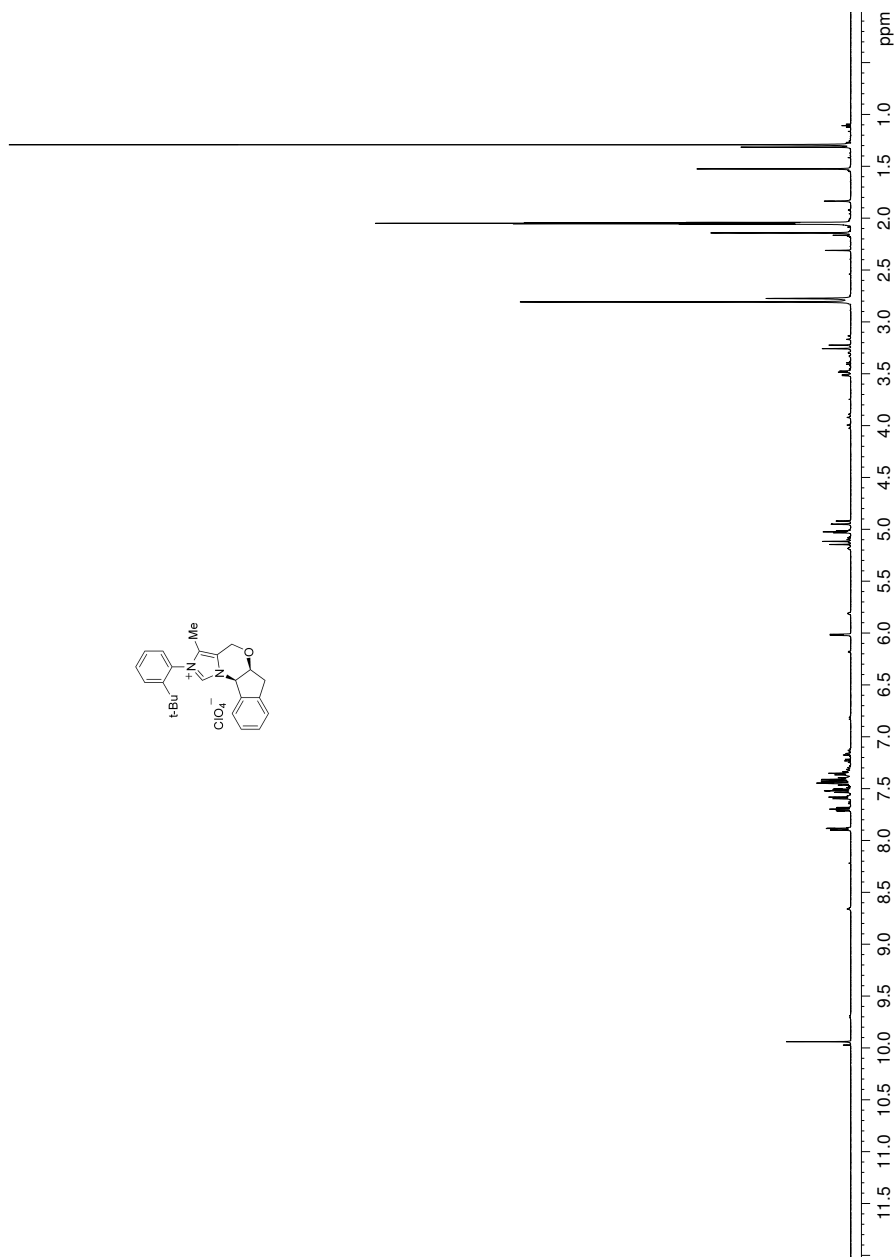
Figure 111. ^{1}H NMR spectrum of compound **171**.

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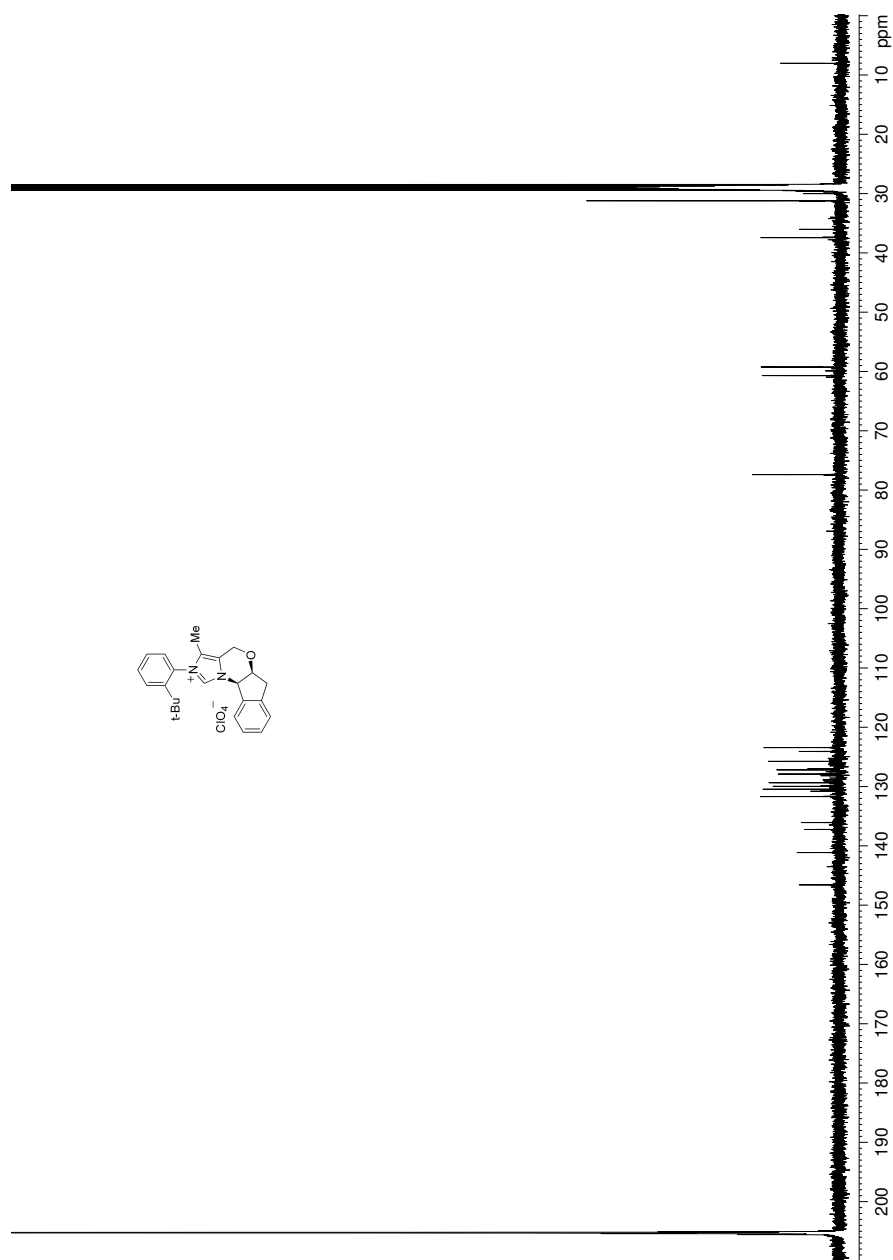
Figure 112. ^{13}C NMR spectrum of compound **171**.
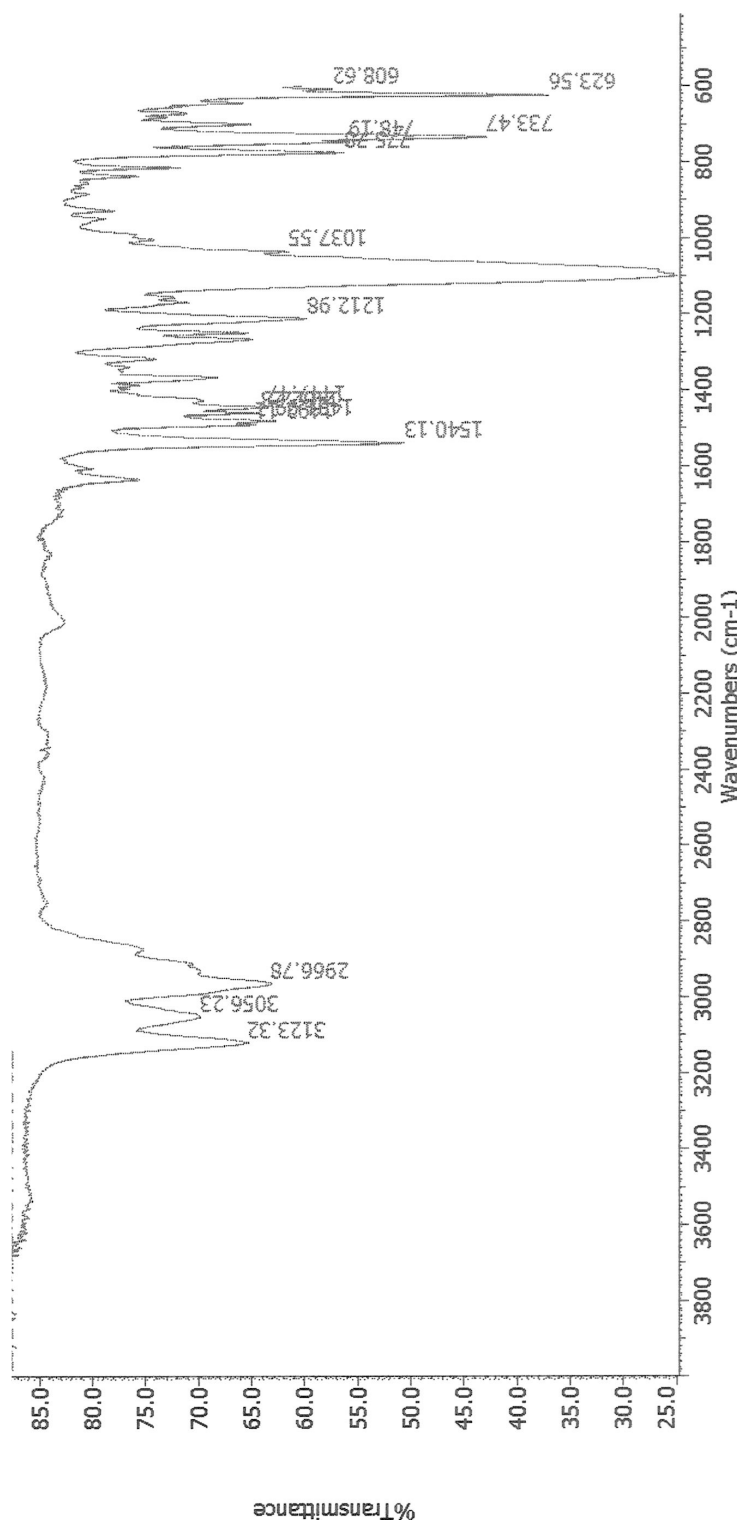
Figure 113. IR spectrum of compound **171**.

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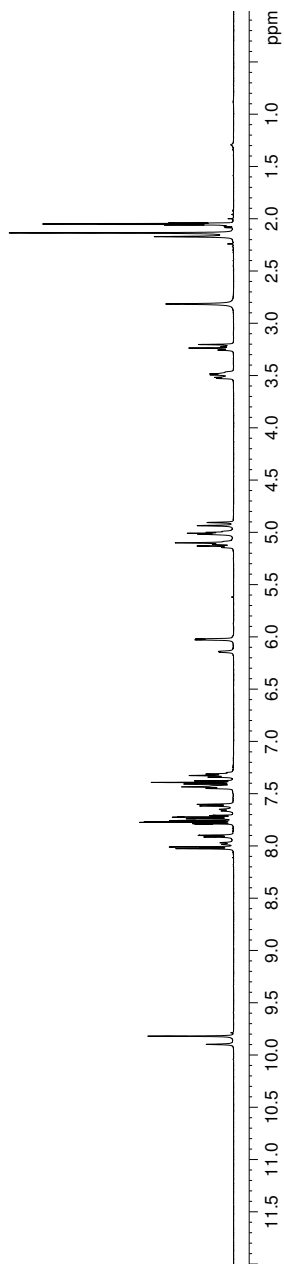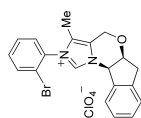
Figure 114. ^{1}H NMR spectrum of compound **172**.

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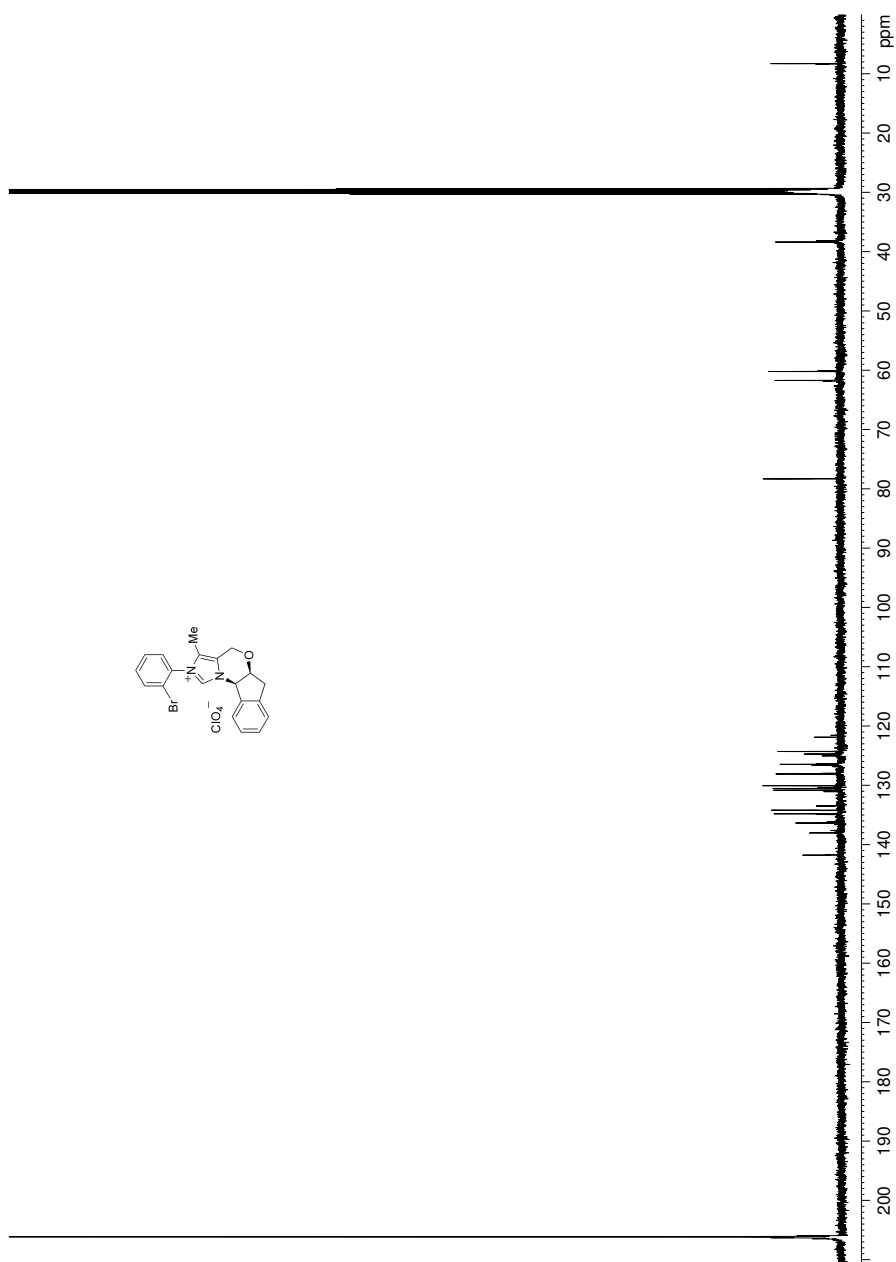
Figure 115. ^{13}C NMR spectrum of compound **172**.
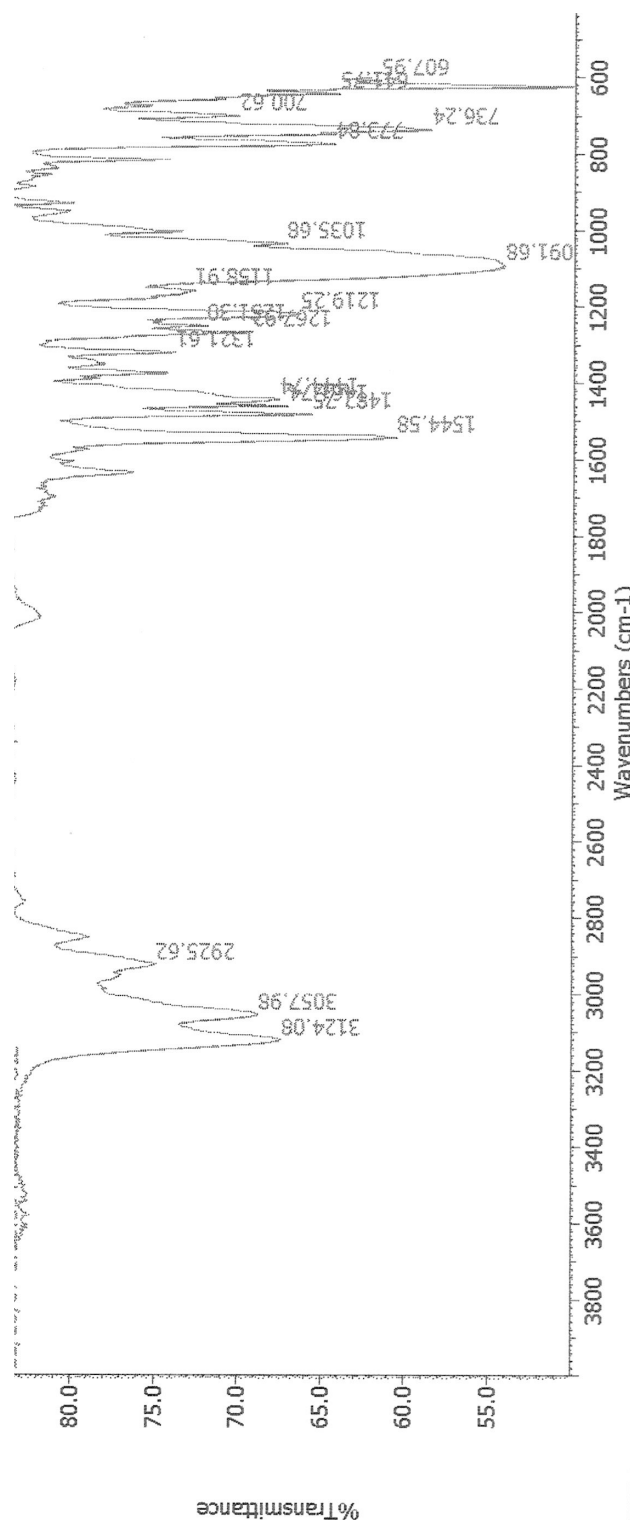
Figure 116. IR spectrum of compound **172**.

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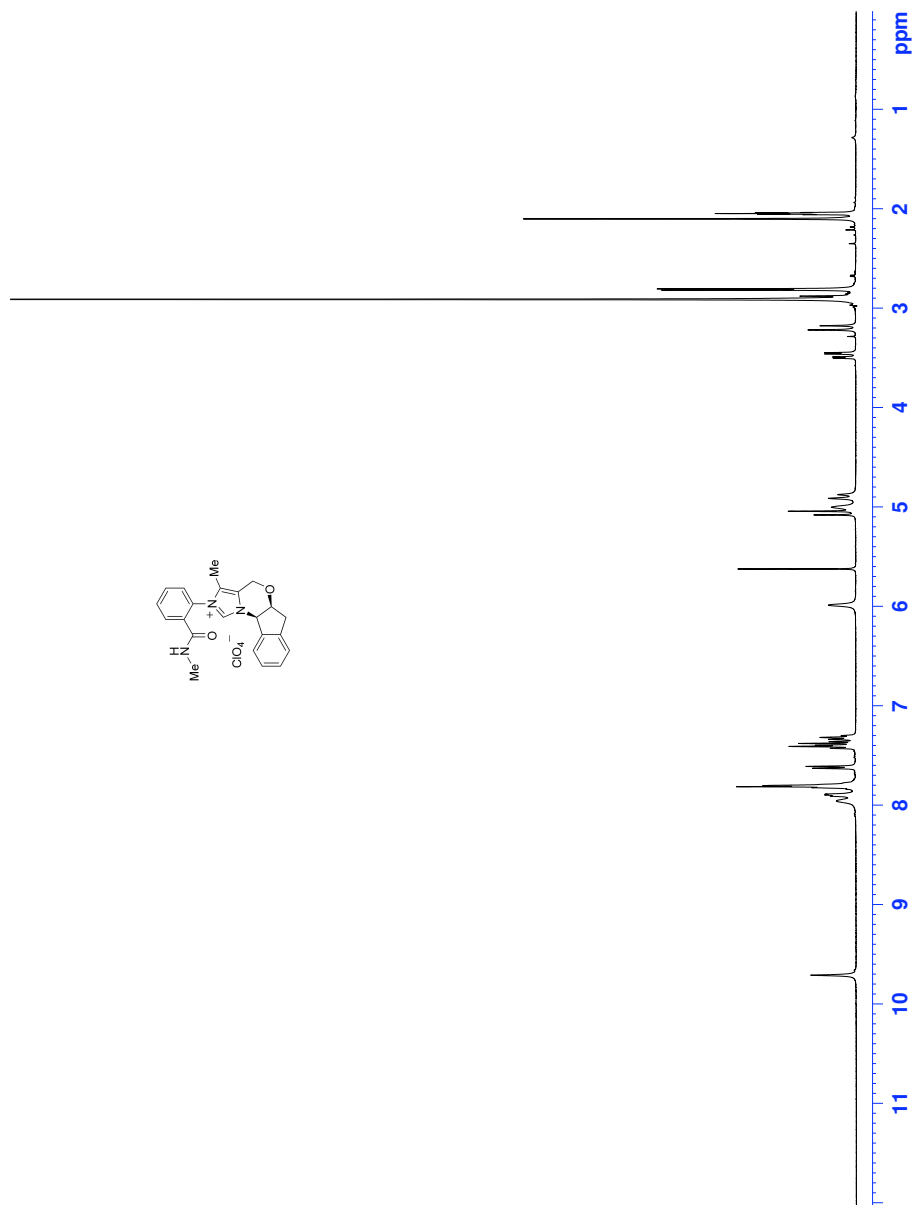
Figure 117. ¹H NMR spectrum of compound **173**.
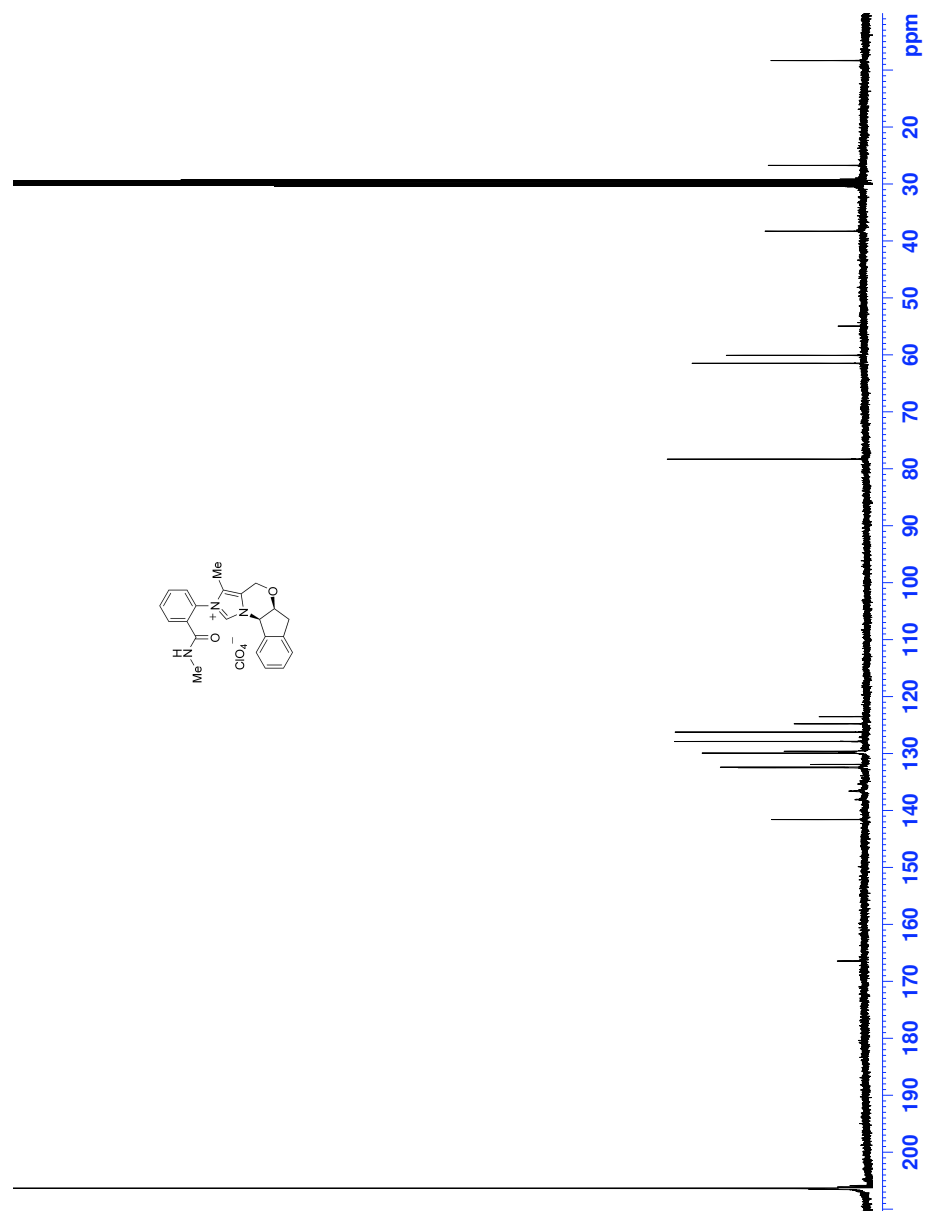
Figure 118. ^{13}C NMR spectrum of compound **173**.
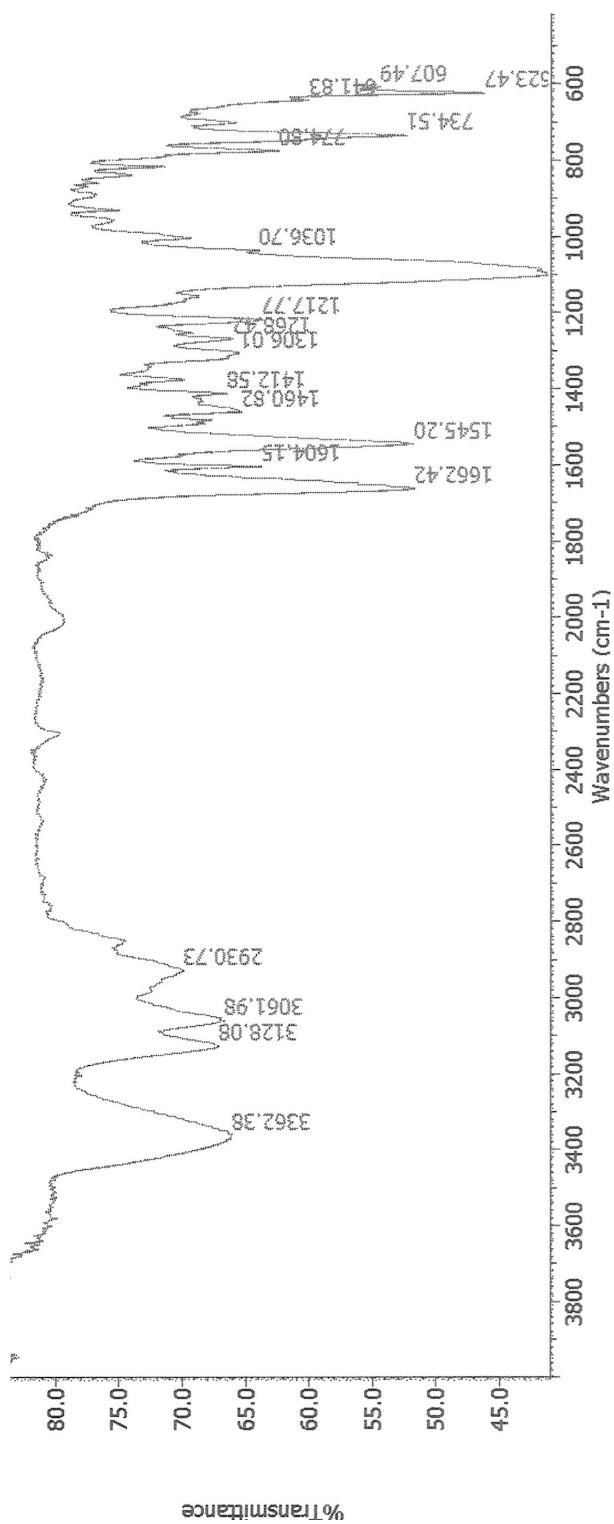
Figure 119. IR spectrum of compound **173**.
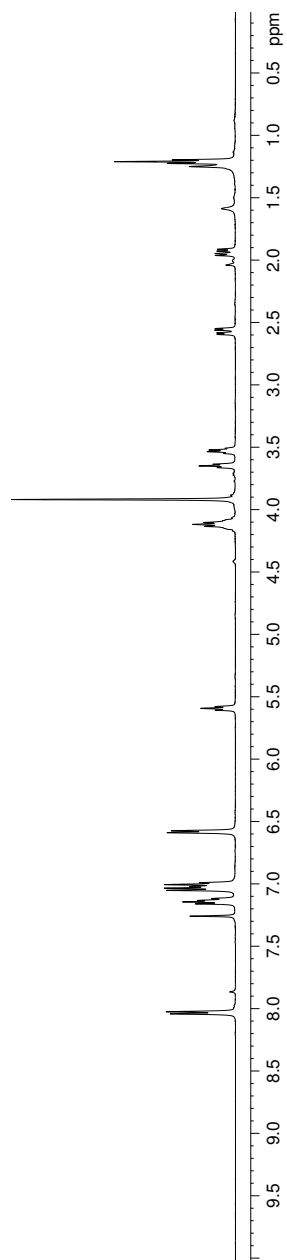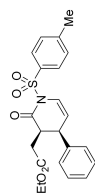
Figure 120. ^{1}H NMR spectrum of compound **175**.
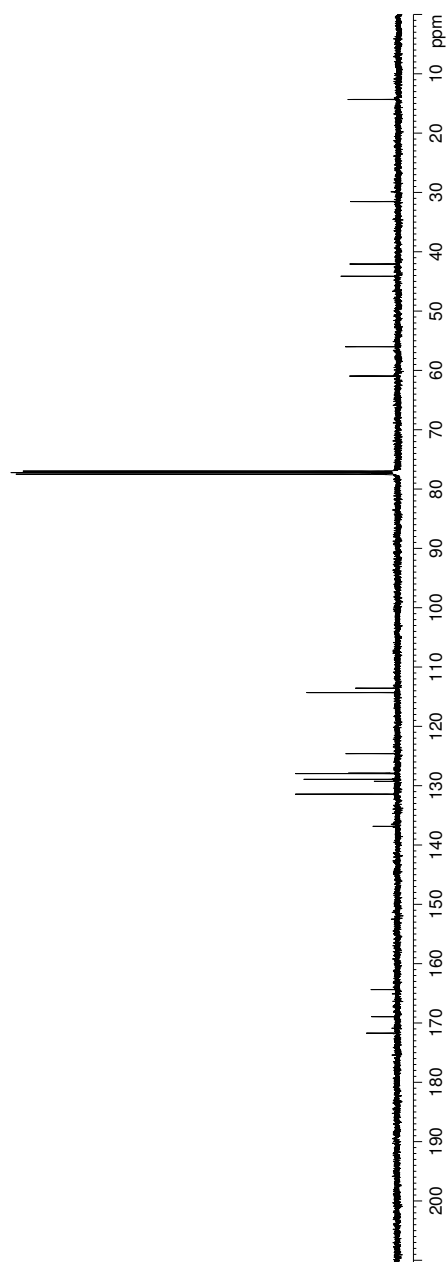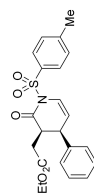
Figure 121. ^{13}C NMR spectrum of compound **175**.
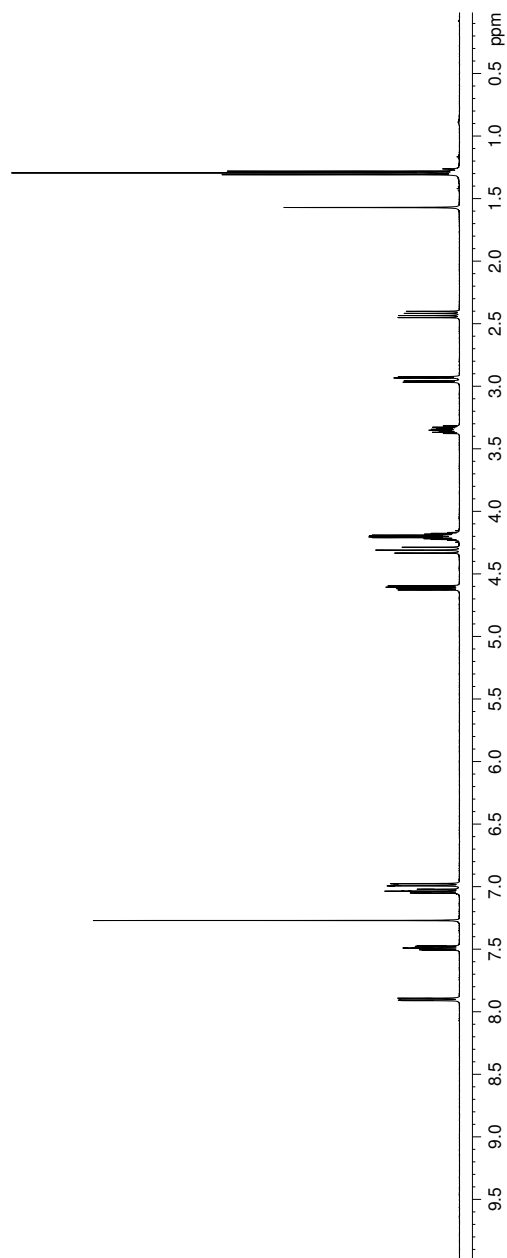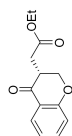
Figure 122. ^{1}H NMR spectrum of compound **184**.
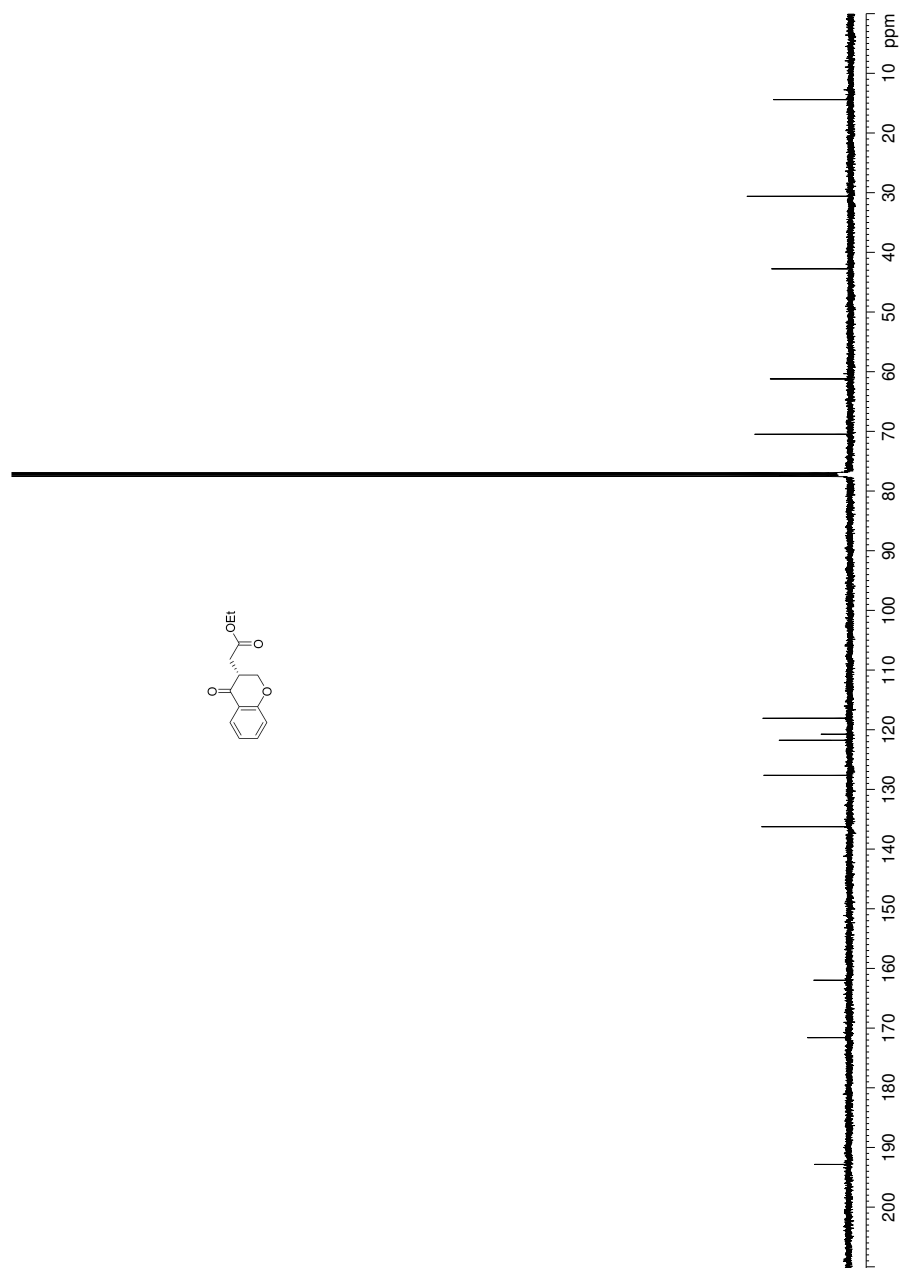
Figure 123. ^{13}C NMR spectrum of compound **184**.
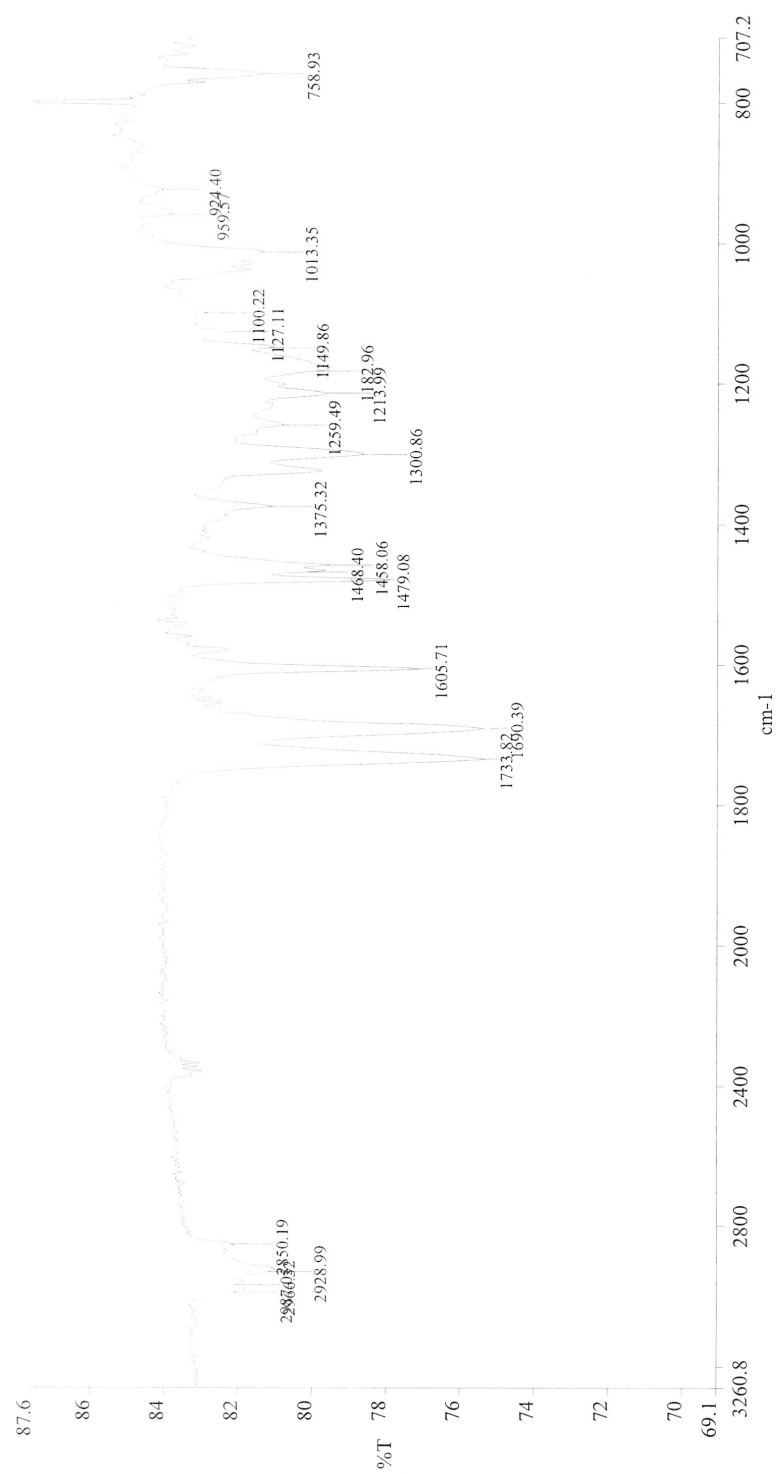
Figure 124. IR spectrum of compound **184**.
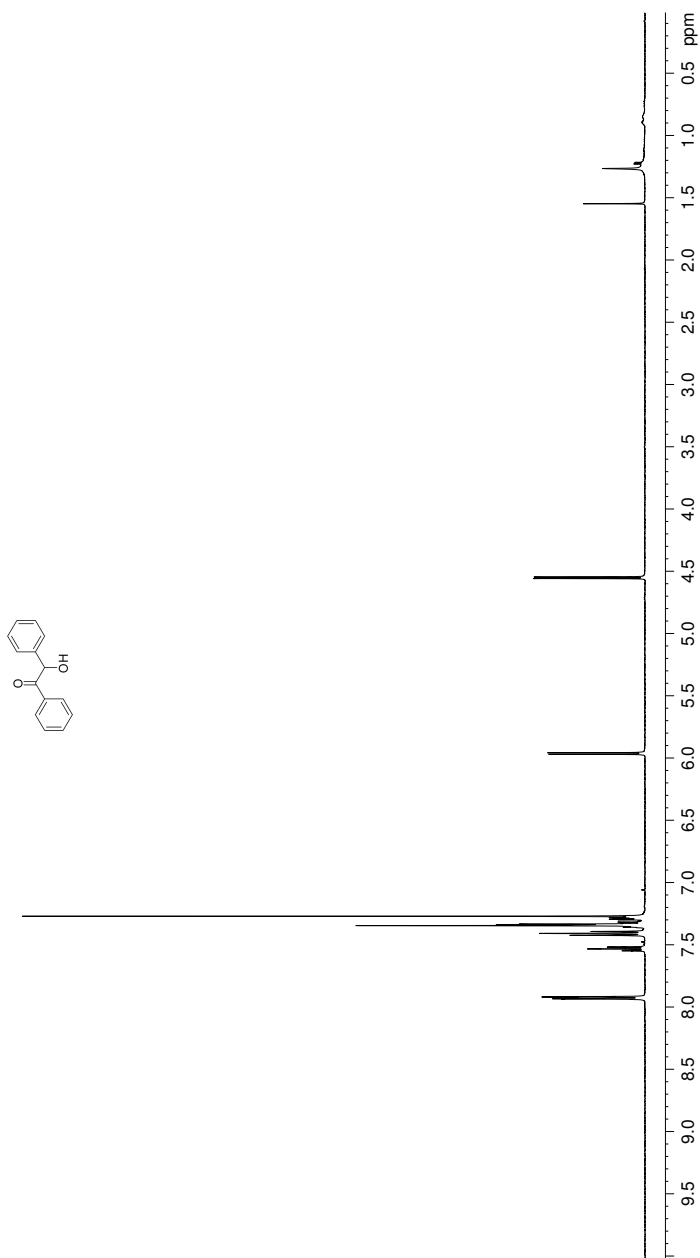
Figure 125. ^{1}H NMR spectrum of compound **186**.

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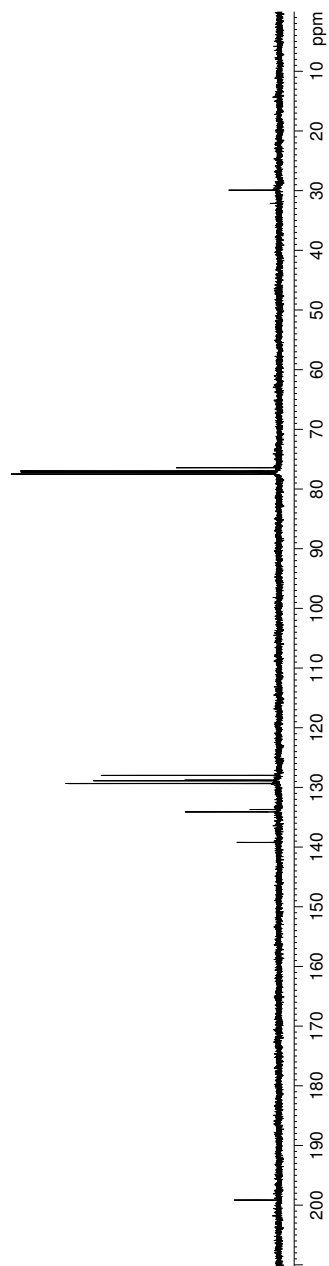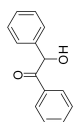
Figure 126. ^{13}C NMR spectrum of compound **186**.

Figure 127. IR spectrum of compound **186**.
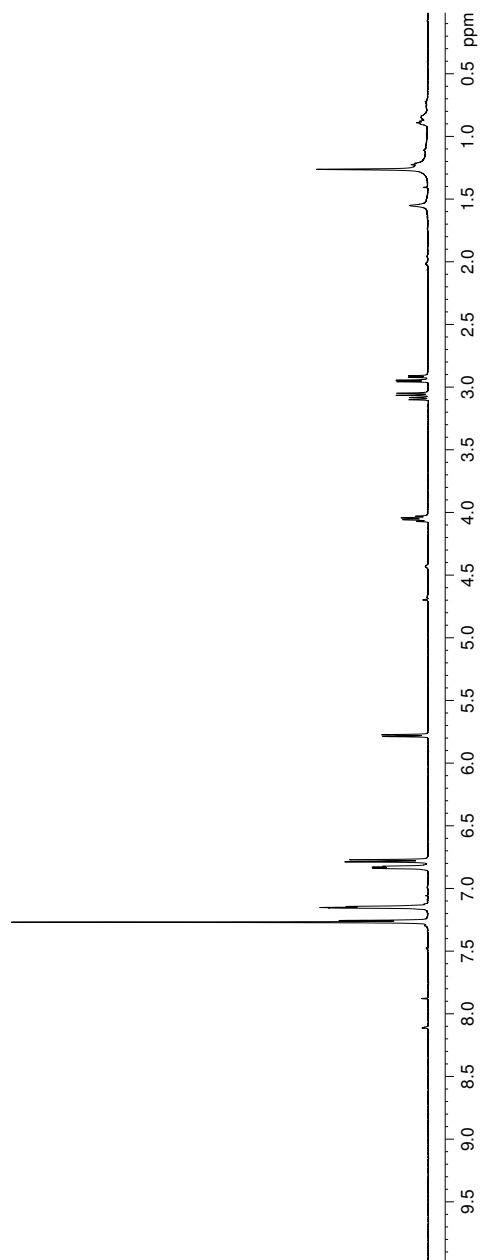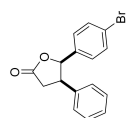
Figure 128. ^{1}H NMR spectrum of compound **188**.
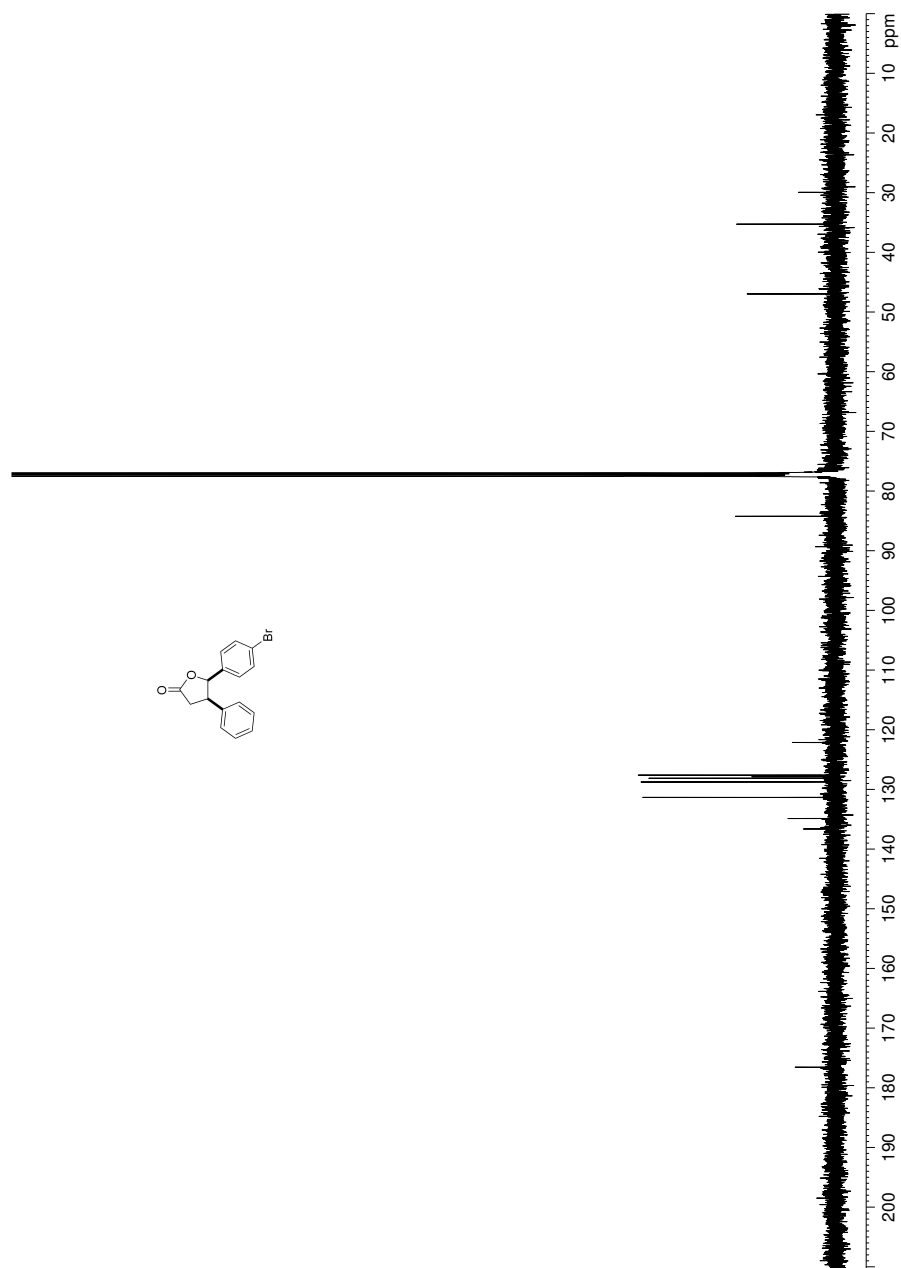
Figure 129. ^{13}C NMR spectrum of compound **188**.

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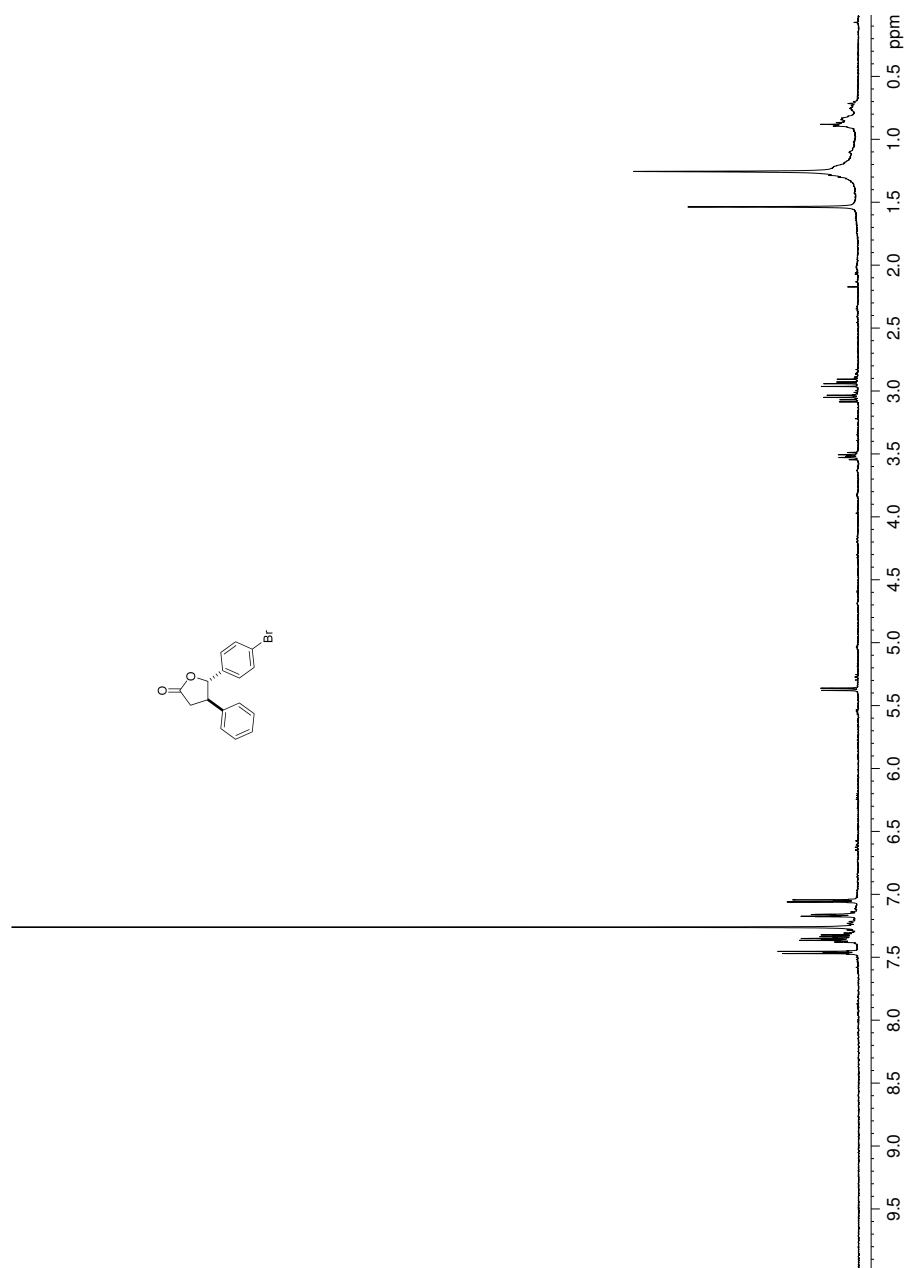
Figure 130. ^{1}H NMR spectrum of compound *diast-188*.
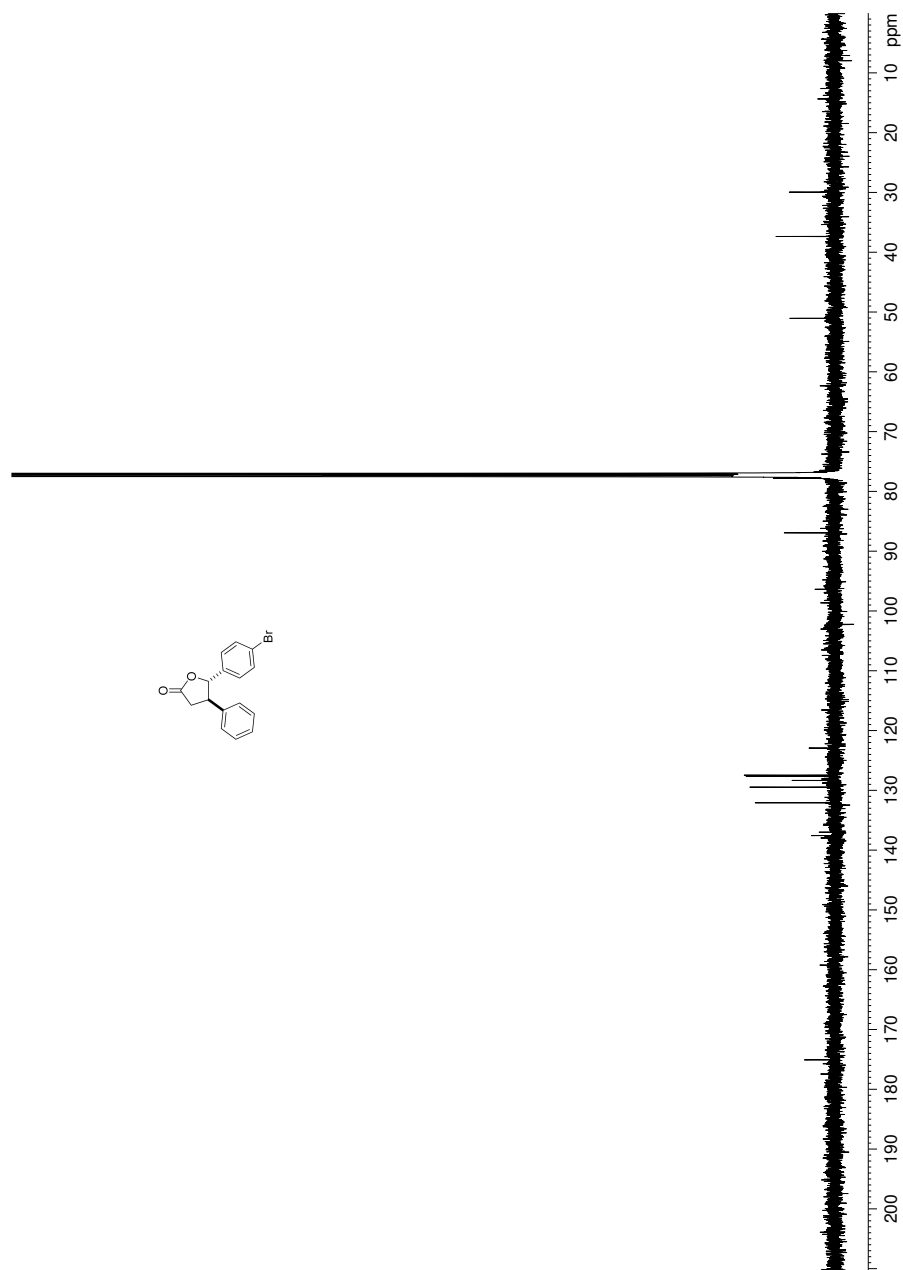
Figure 131. ^{13}C NMR spectrum of compound *diast-188*.
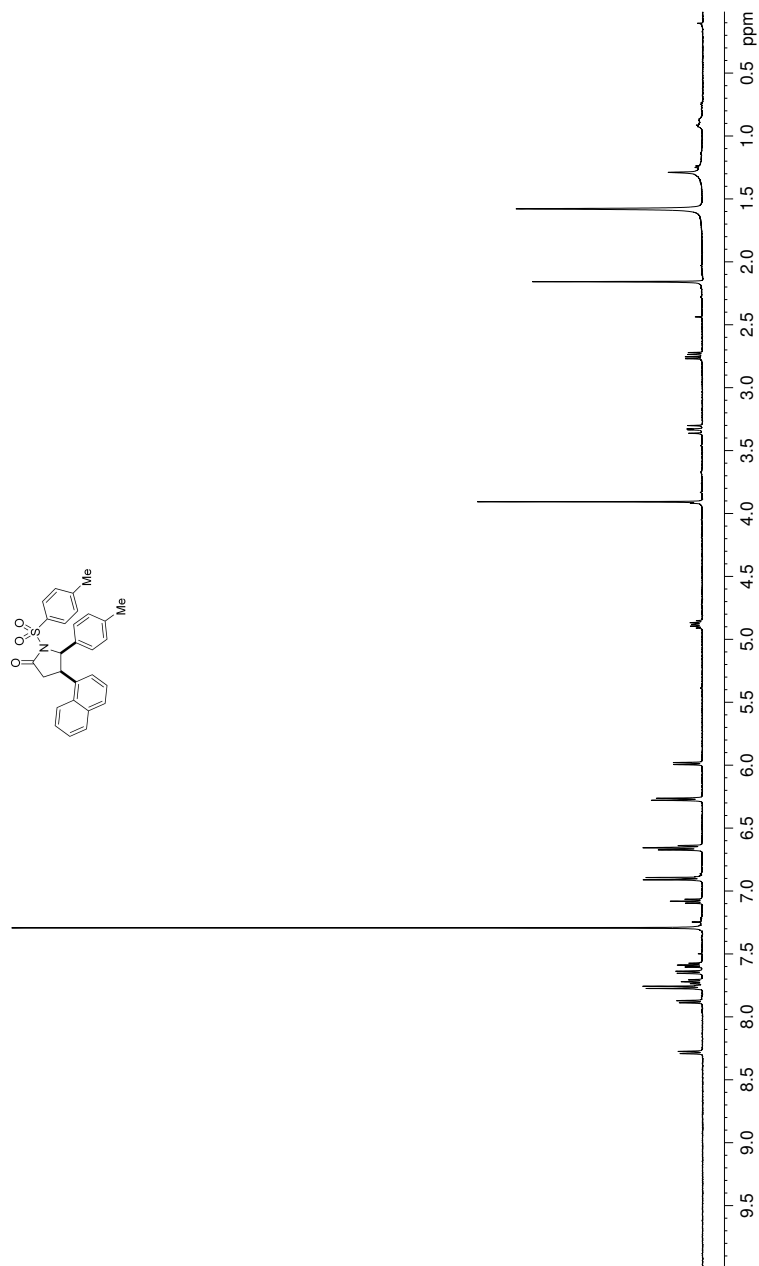
Figure 132. ^{1}H NMR spectrum of compound **191**.

Figure 131. ^{13}C NMR spectrum of compound **191**.
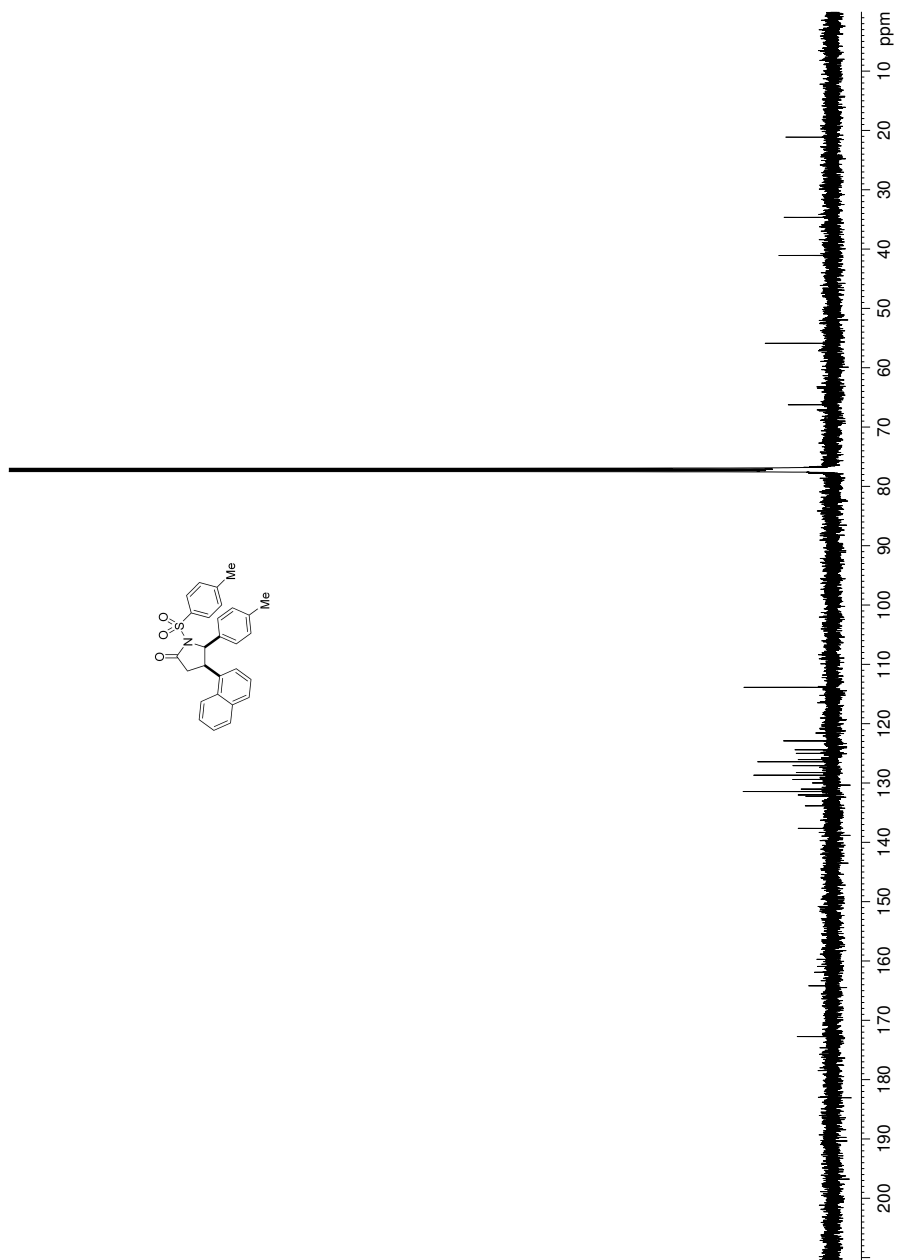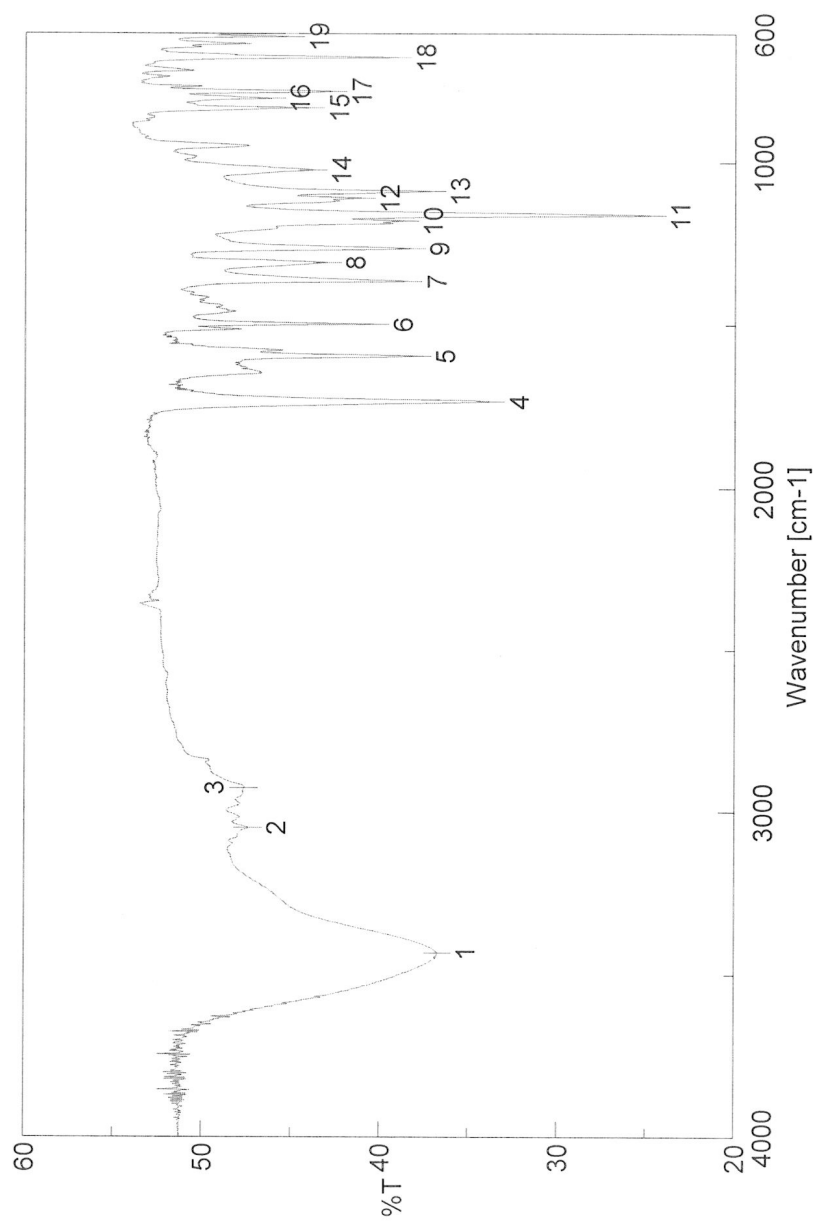
Figure 132. IR spectrum of compound **191**.
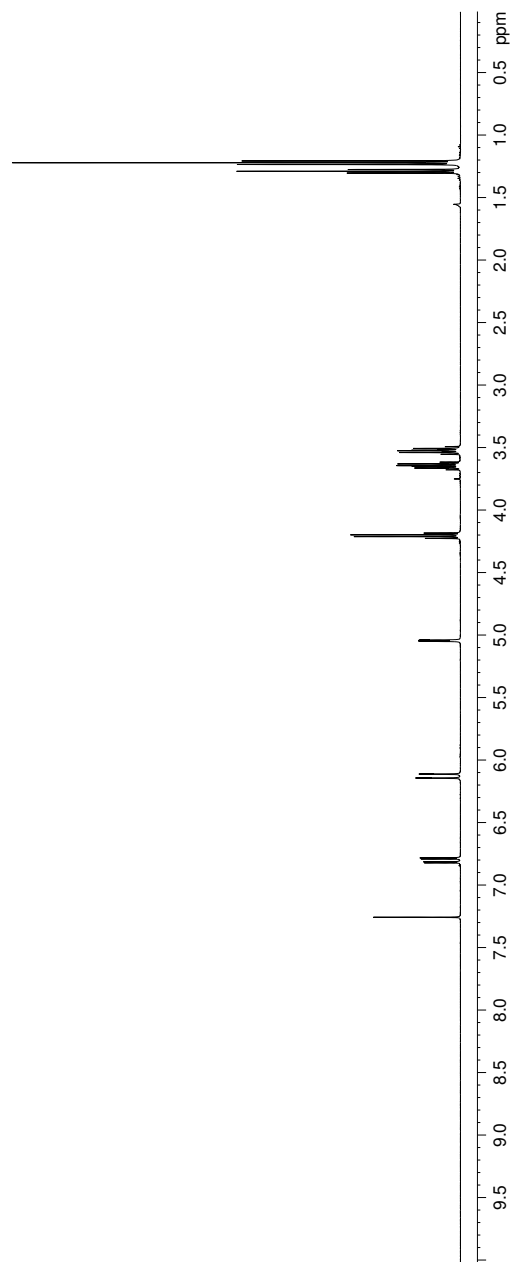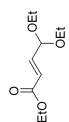
Figure 133. ¹H NMR spectrum of compound (*E*)-Ethyl 4,4-diethoxybut-2-enoate.
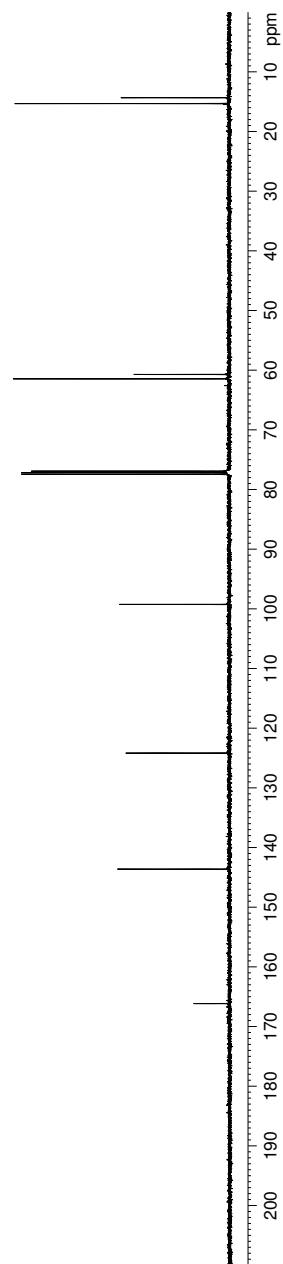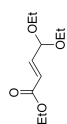
Figure 134. ^{13}C NMR spectrum of compound (*E*)-**Ethyl 4,4-diethoxybut-2-enoate.**
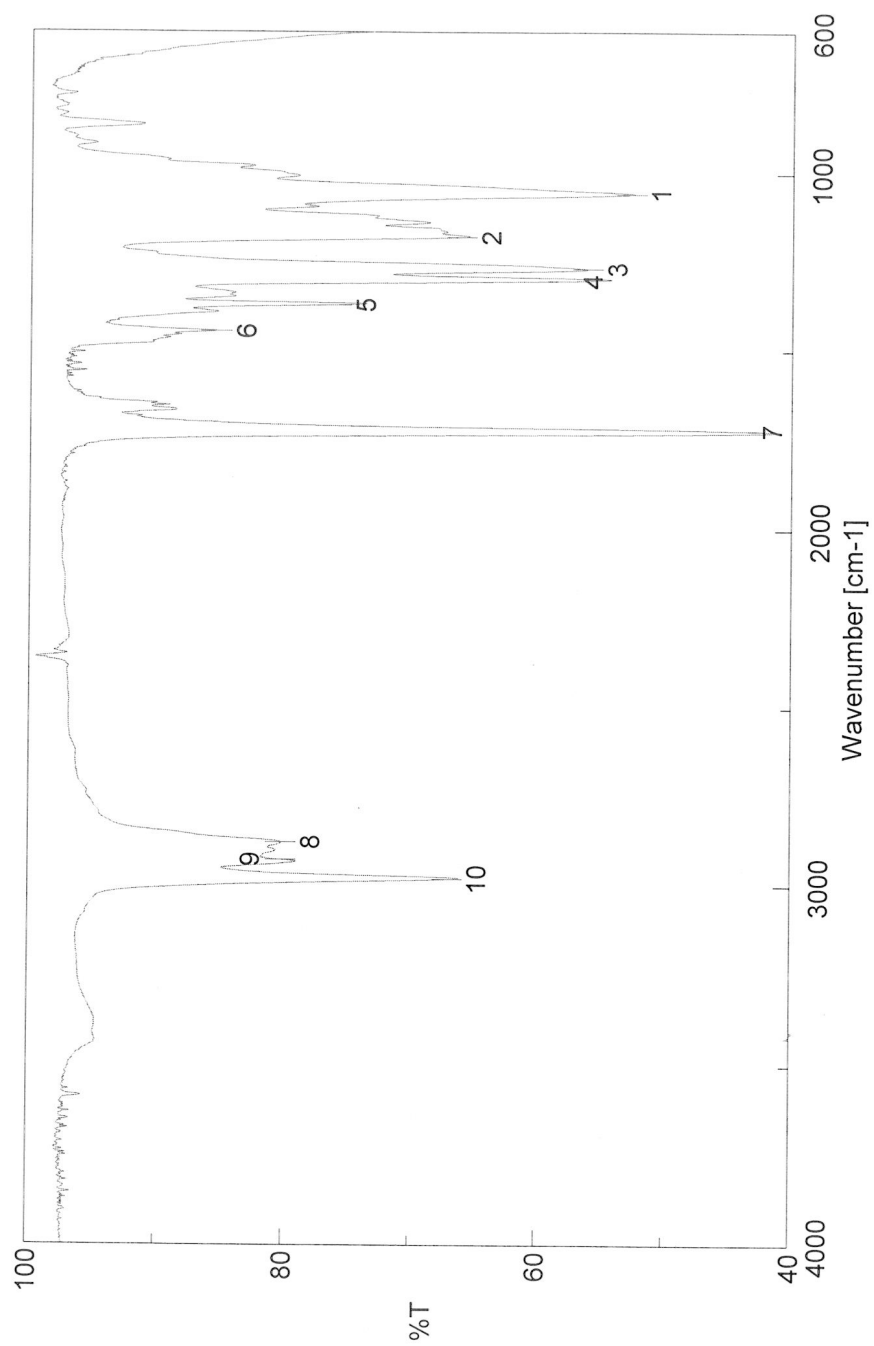
Figure 135. IR spectrum of compound (*E*)-Ethyl 4,4-diethoxybut-2-enoate.
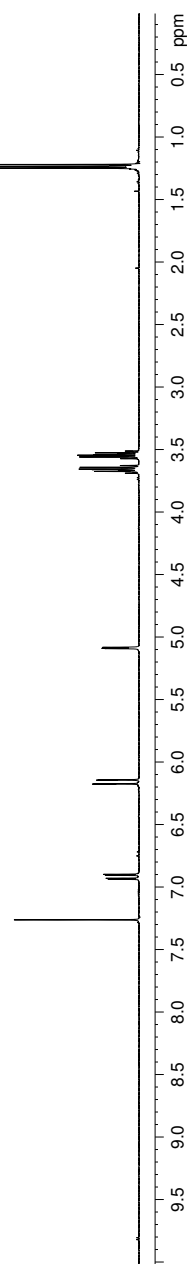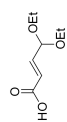
Figure 136. ¹H NMR spectrum of compound **198**.
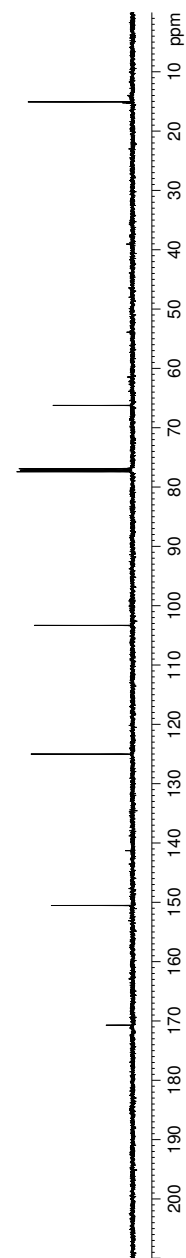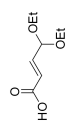
Figure 137. ^{13}C NMR spectrum of compound **198**.

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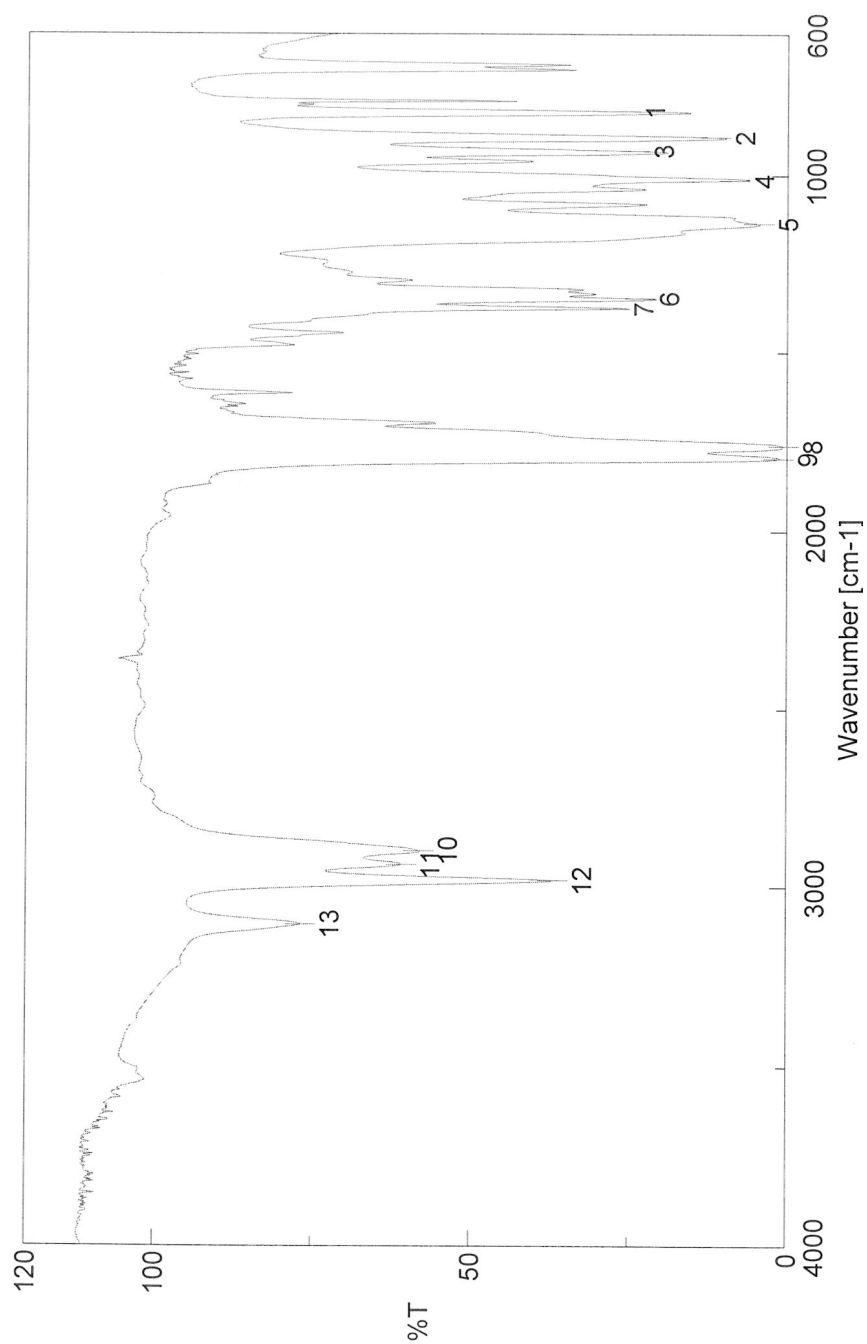
Figure 138. IR spectrum of compound **198**.
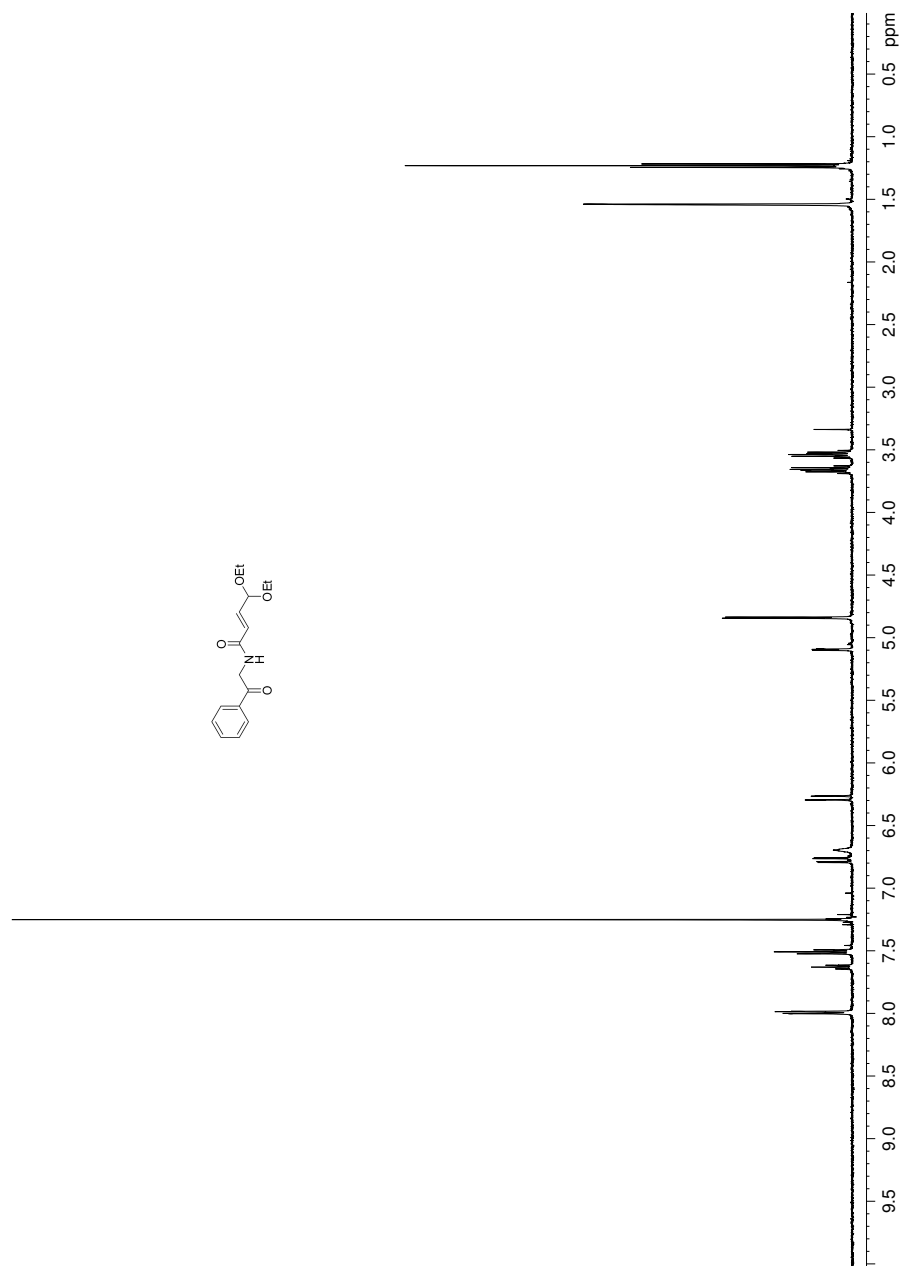
Figure 139. ^{1}H NMR spectrum of compound (**E**)-**4,4-Diethoxy-N-(2-oxo-2-phenylethyl)but-2-enamide**.

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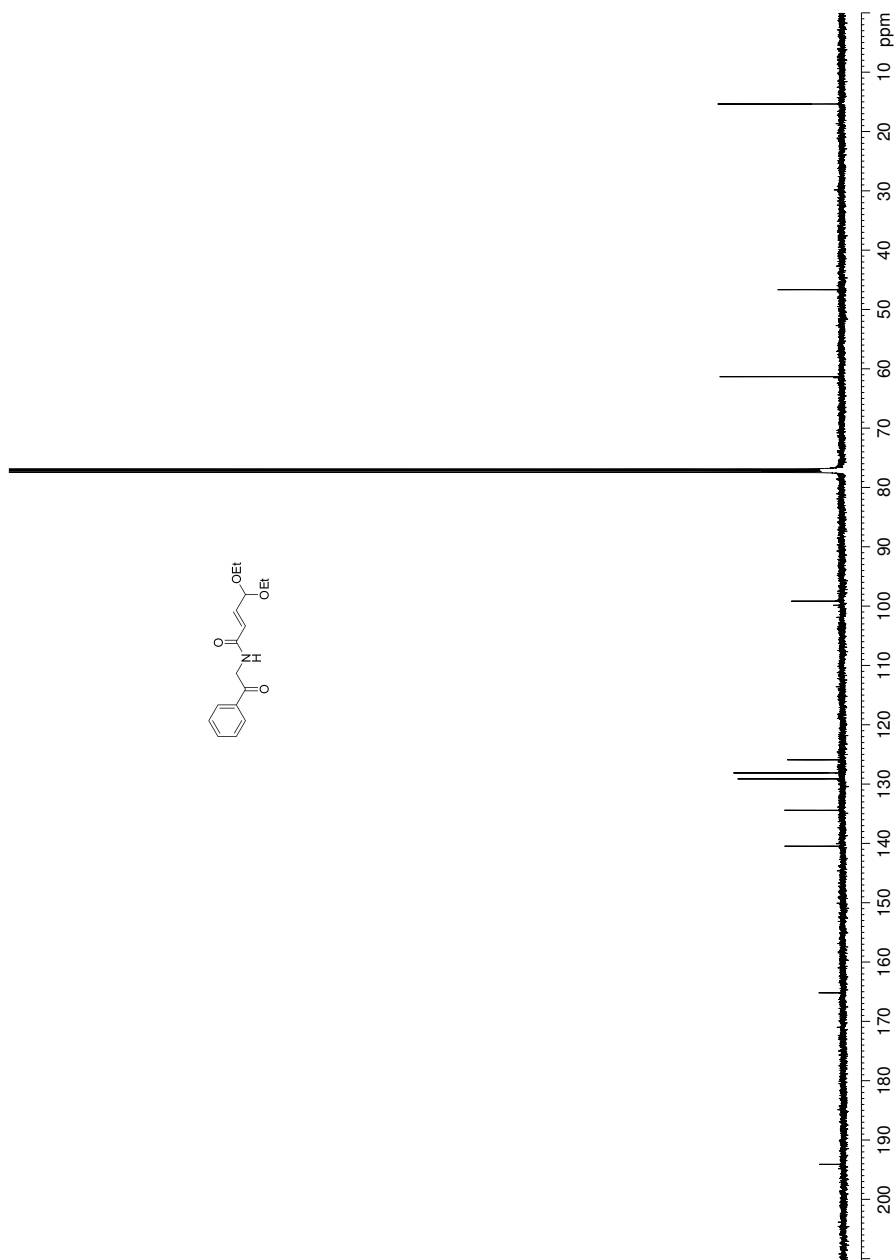
Figure 140. ^{13}C NMR spectrum of compound (**E**)-4,4-Diethoxy-**N**-(2-oxo-2-phenylethyl)but-2-enamide.
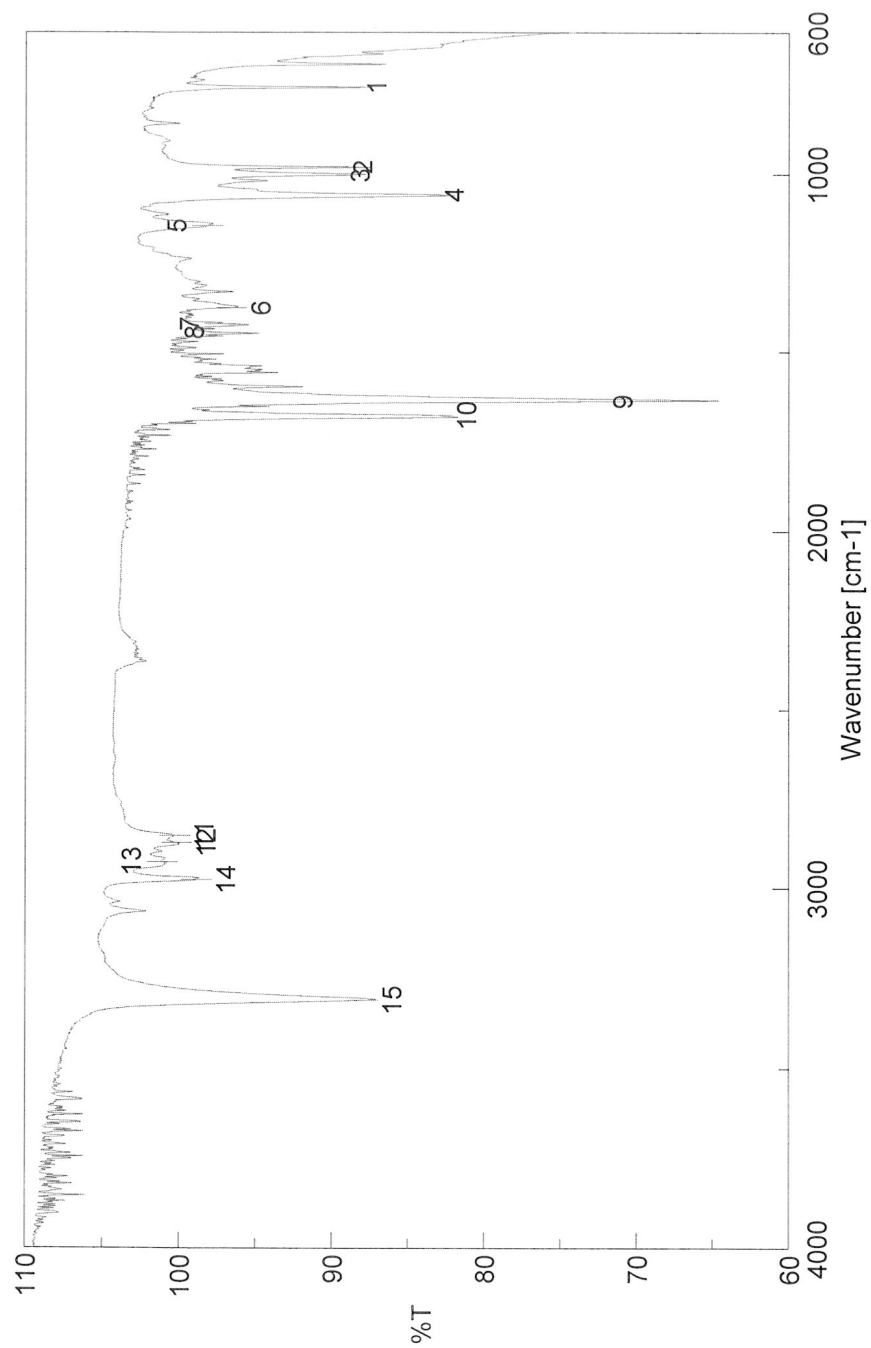
Figure 141. IR spectrum of compound (*E*)-**4,4-Diethoxy-*N*-(2-oxo-2-phenylethyl)but-2-enamide**.

313
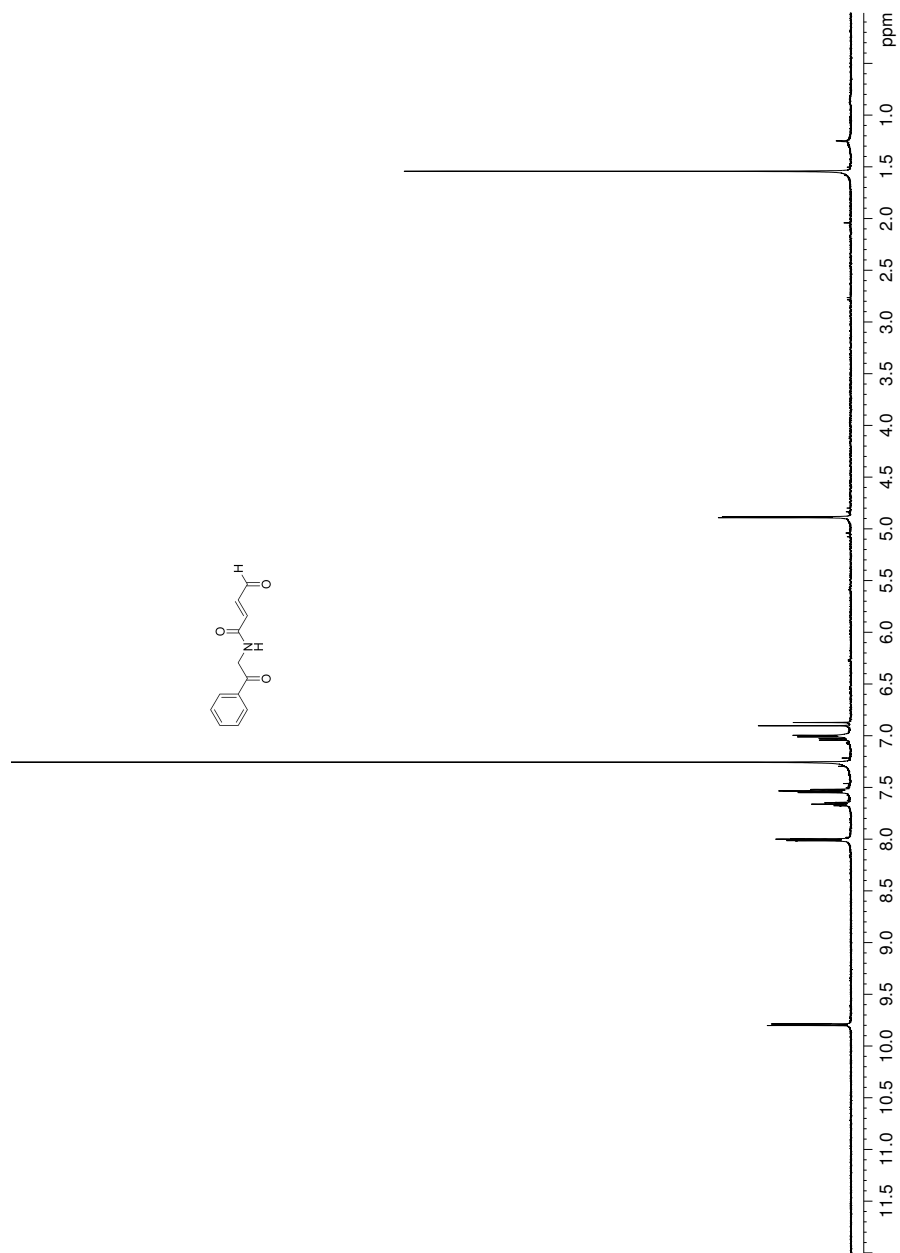
Figure 142. ^{1}H NMR spectrum of compound **196**.

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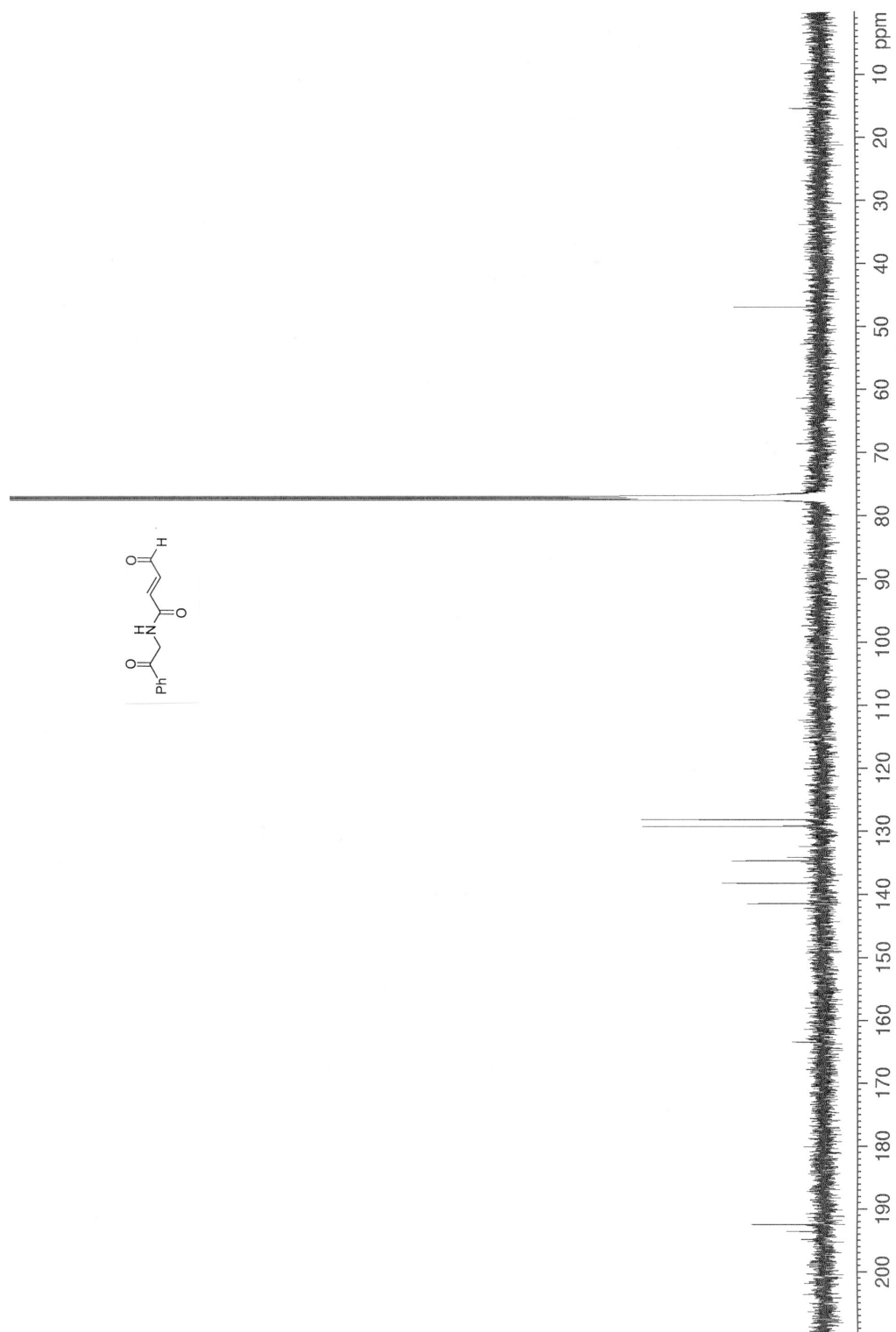
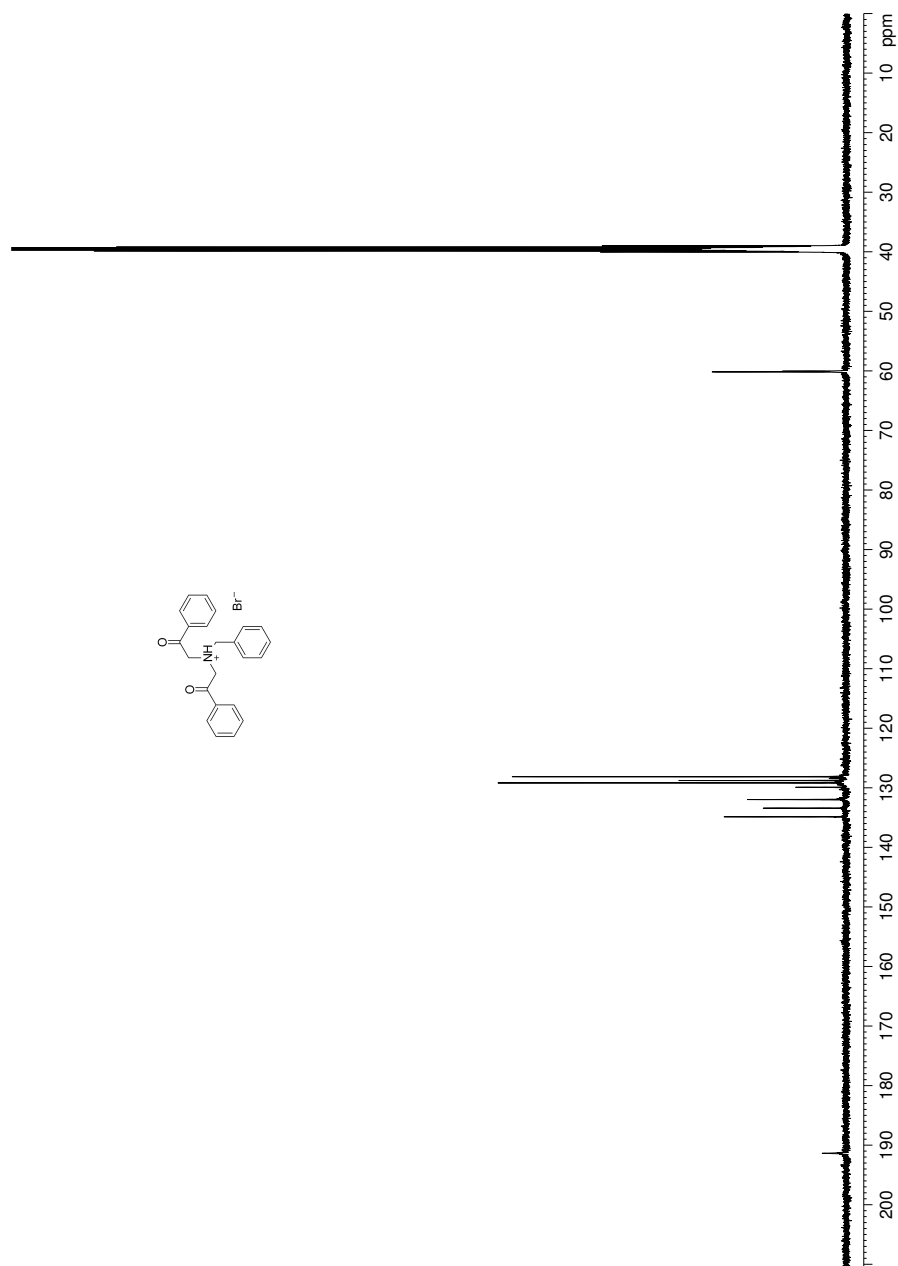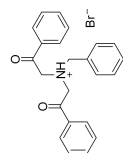Figure 143. ^{13}C NMR spectrum of compound 196.
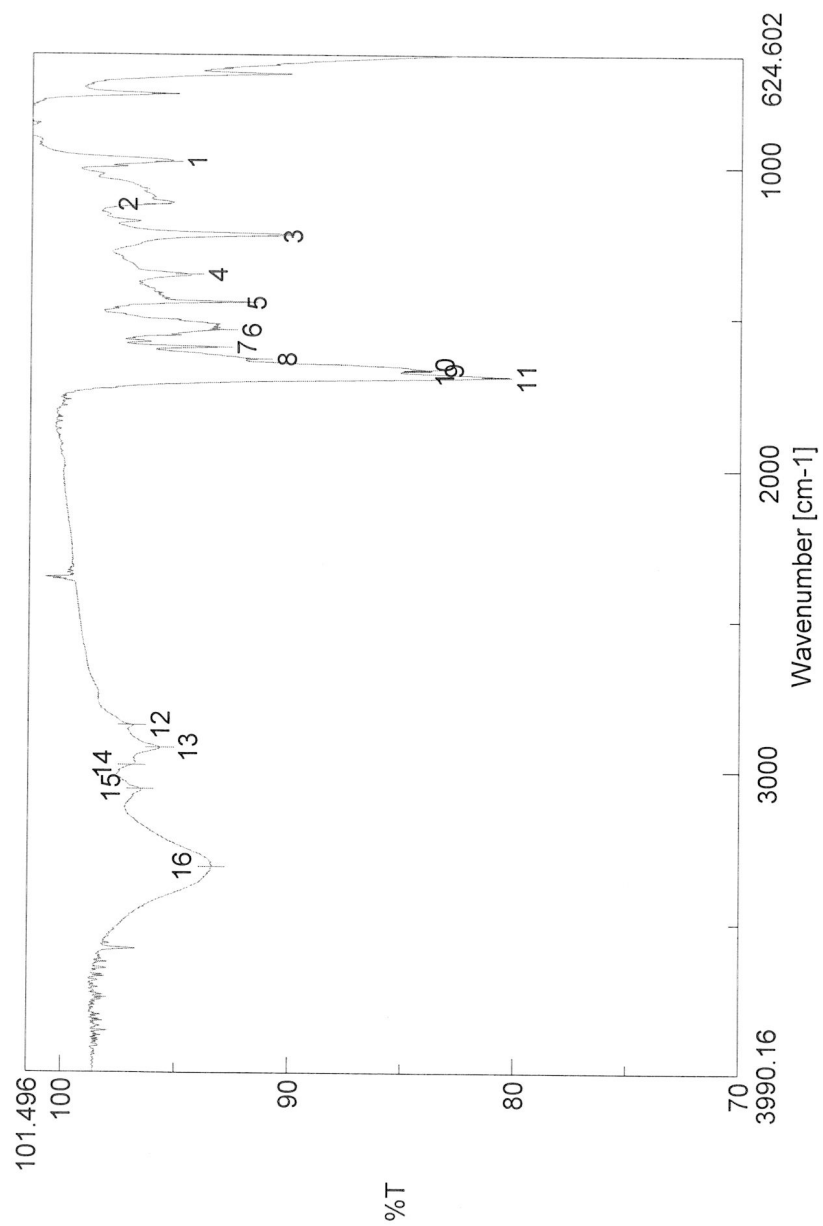
Figure 144. IR spectrum of compound **196**.
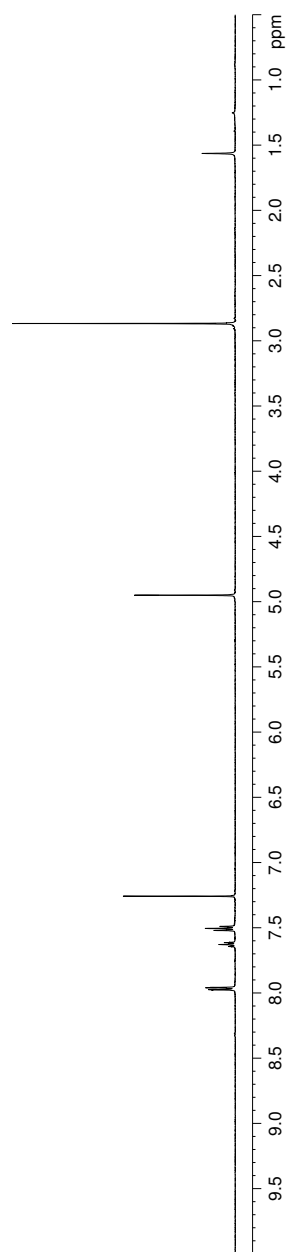
Figure 145. ^{1}H NMR spectrum of compound **200**.

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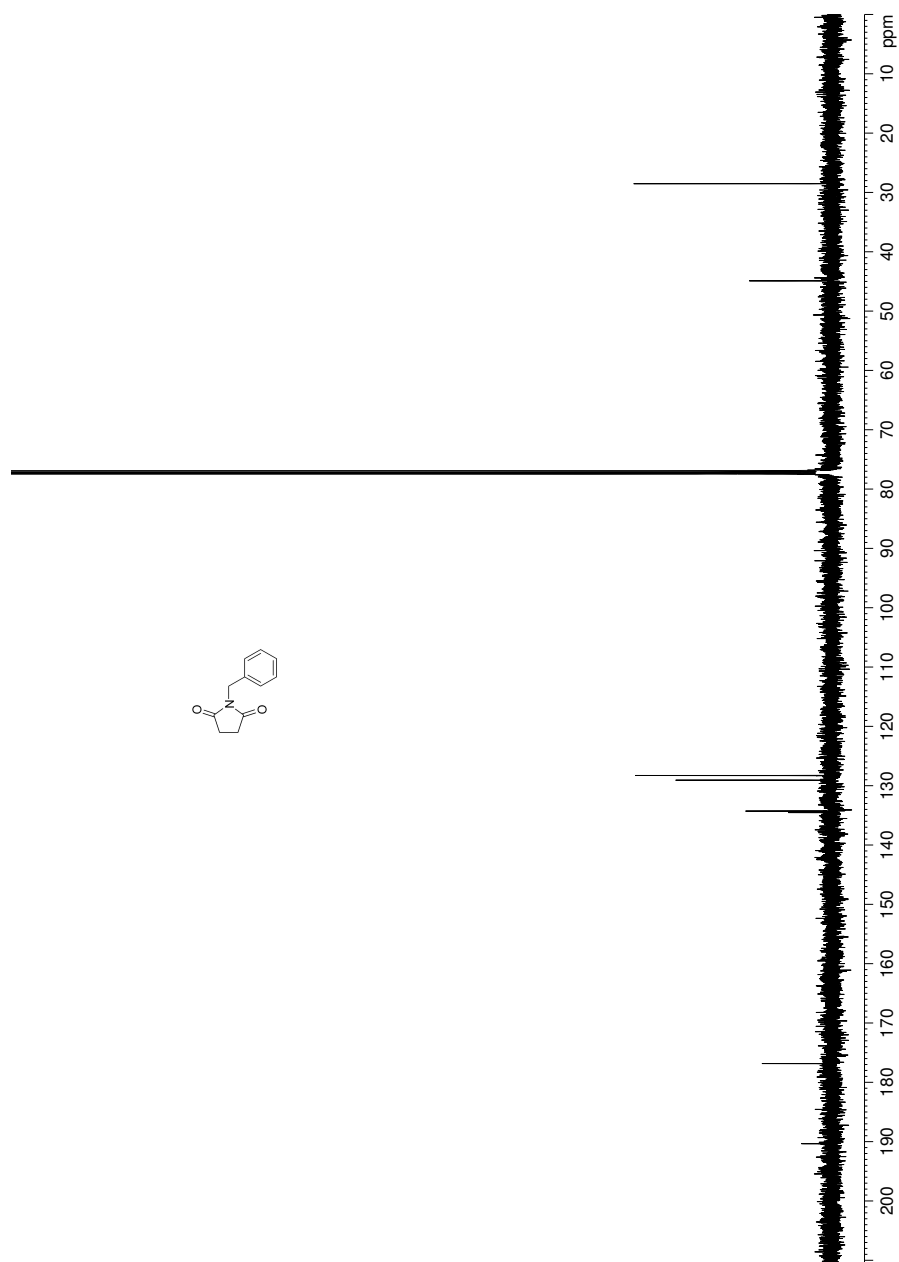
Figure 146. ^{13}C NMR spectrum of compound **200**.
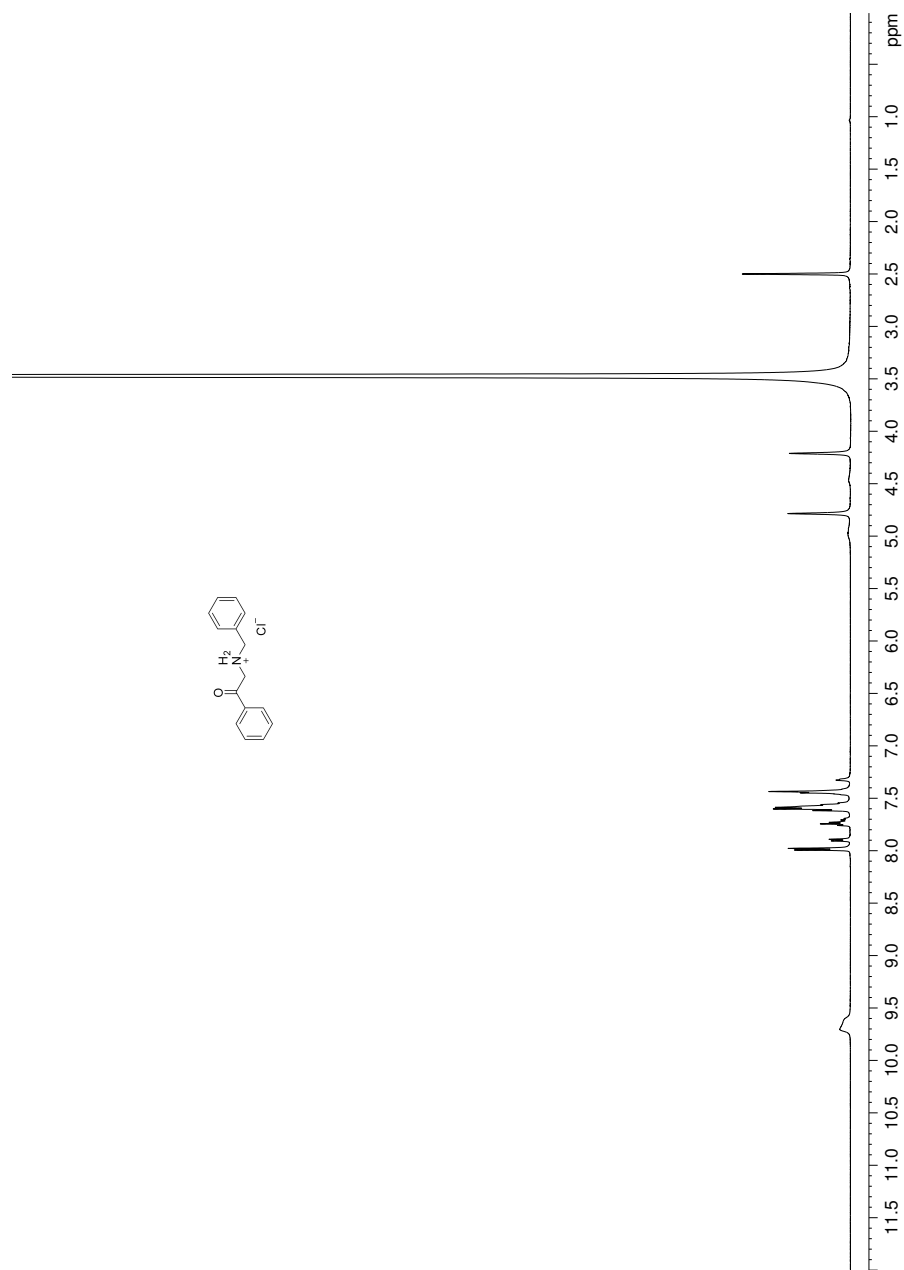
Figure 147. ¹H NMR spectrum of compound **201**.
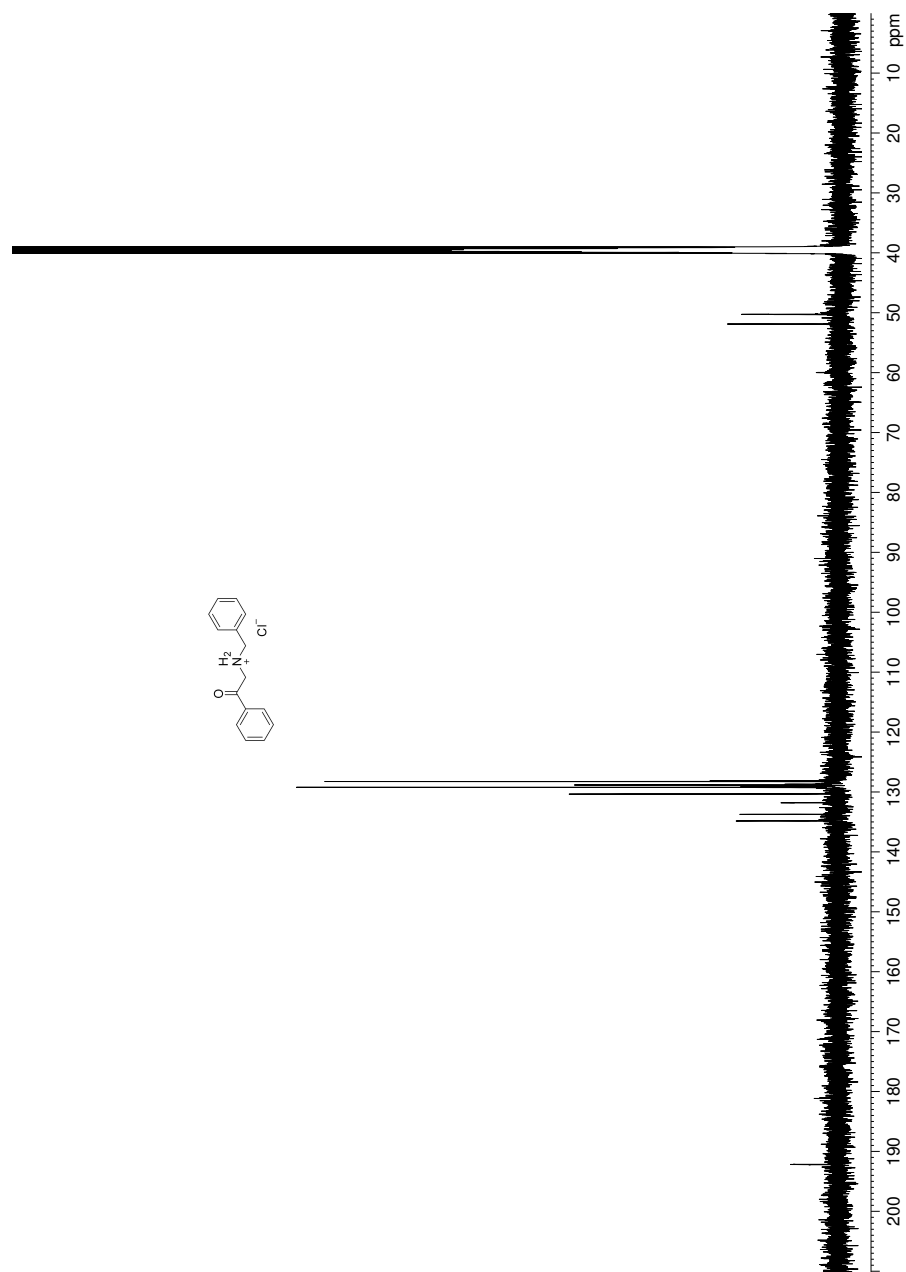
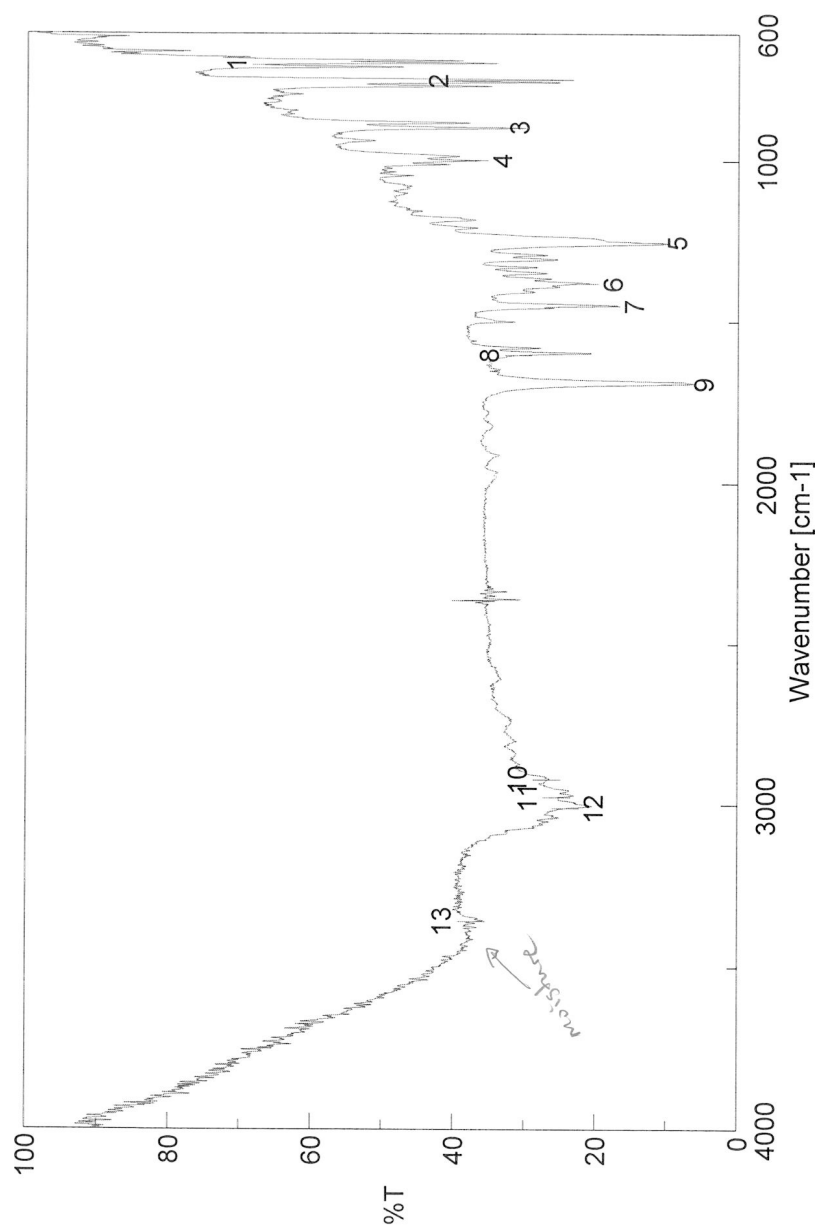**Figure 148.** ^{13}C NMR spectrum of compound **201**.
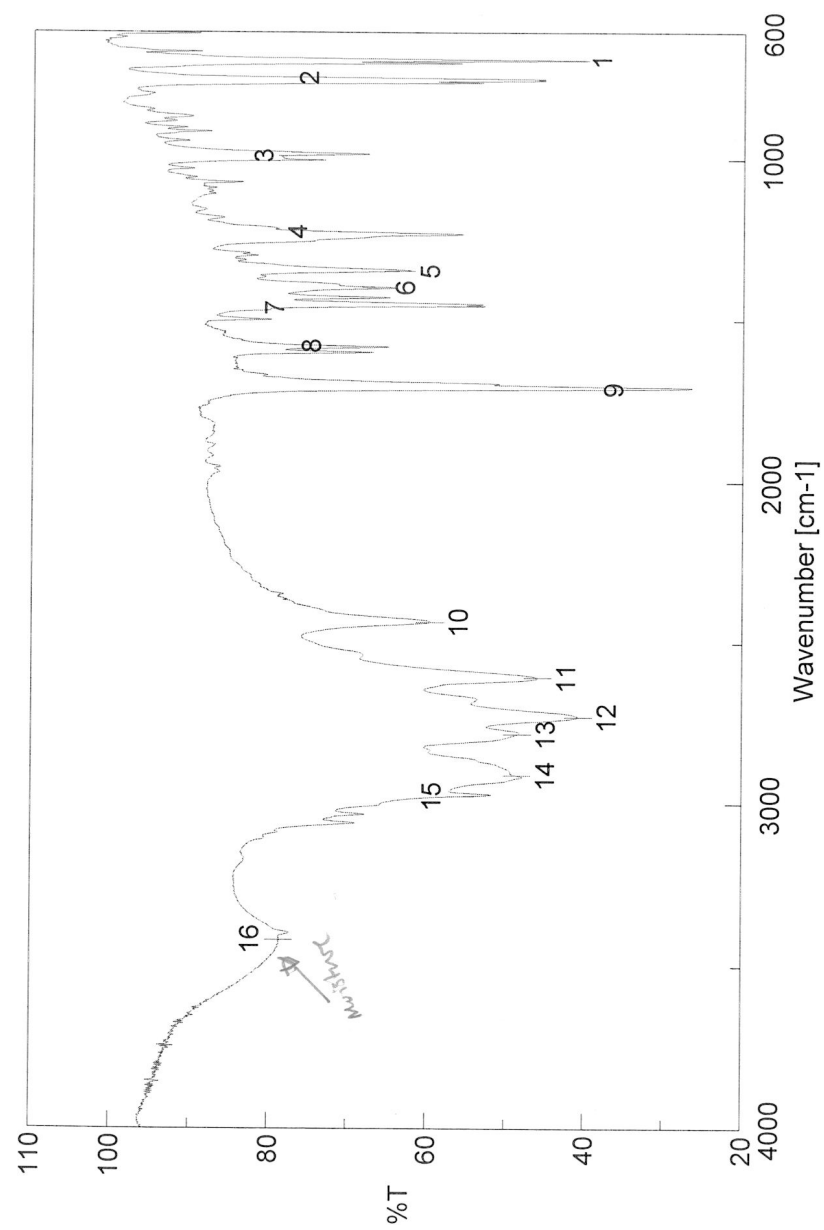
Figure 149. IR spectrum of compound **201**.

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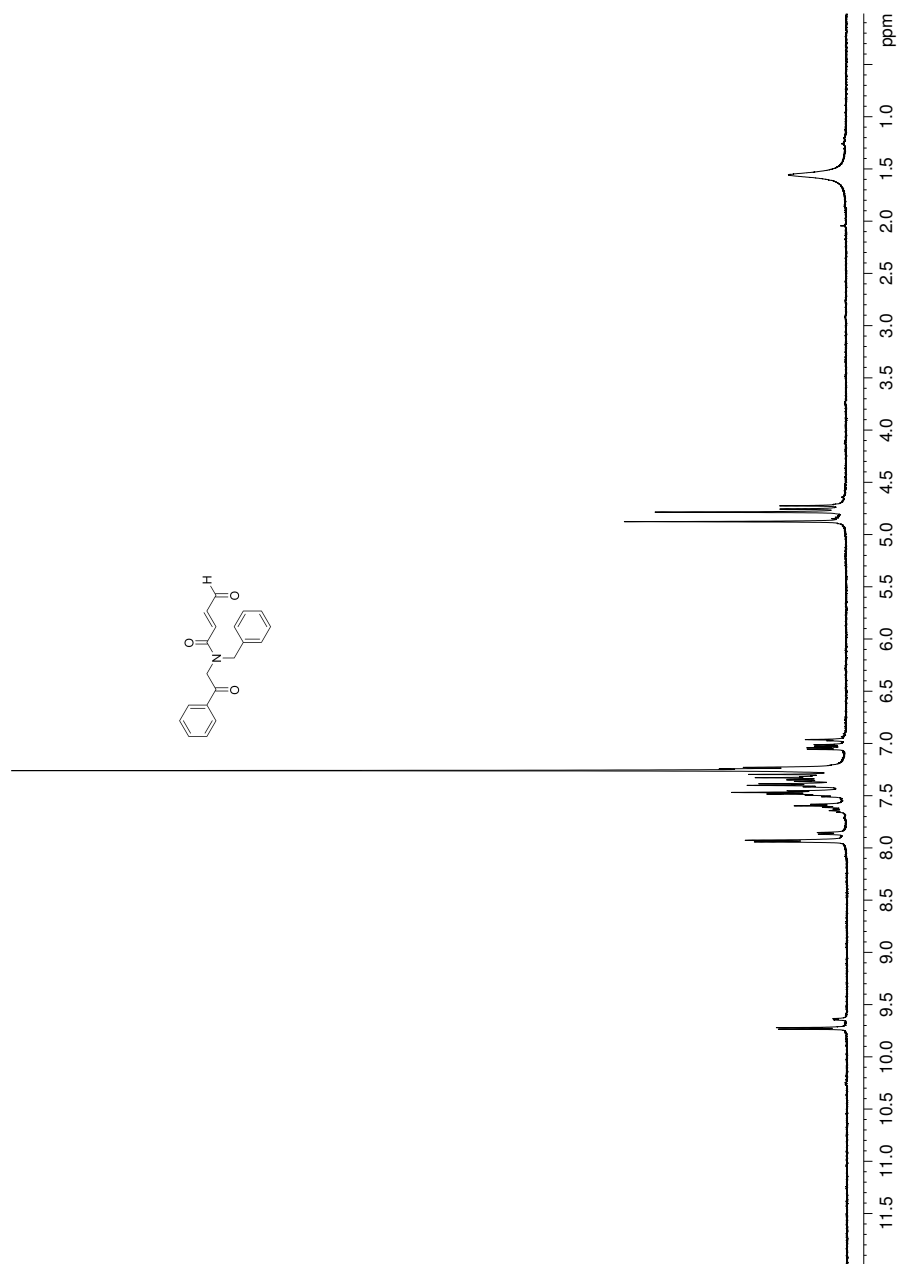
Figure 150. ^{1}H NMR spectrum of compound **202**.
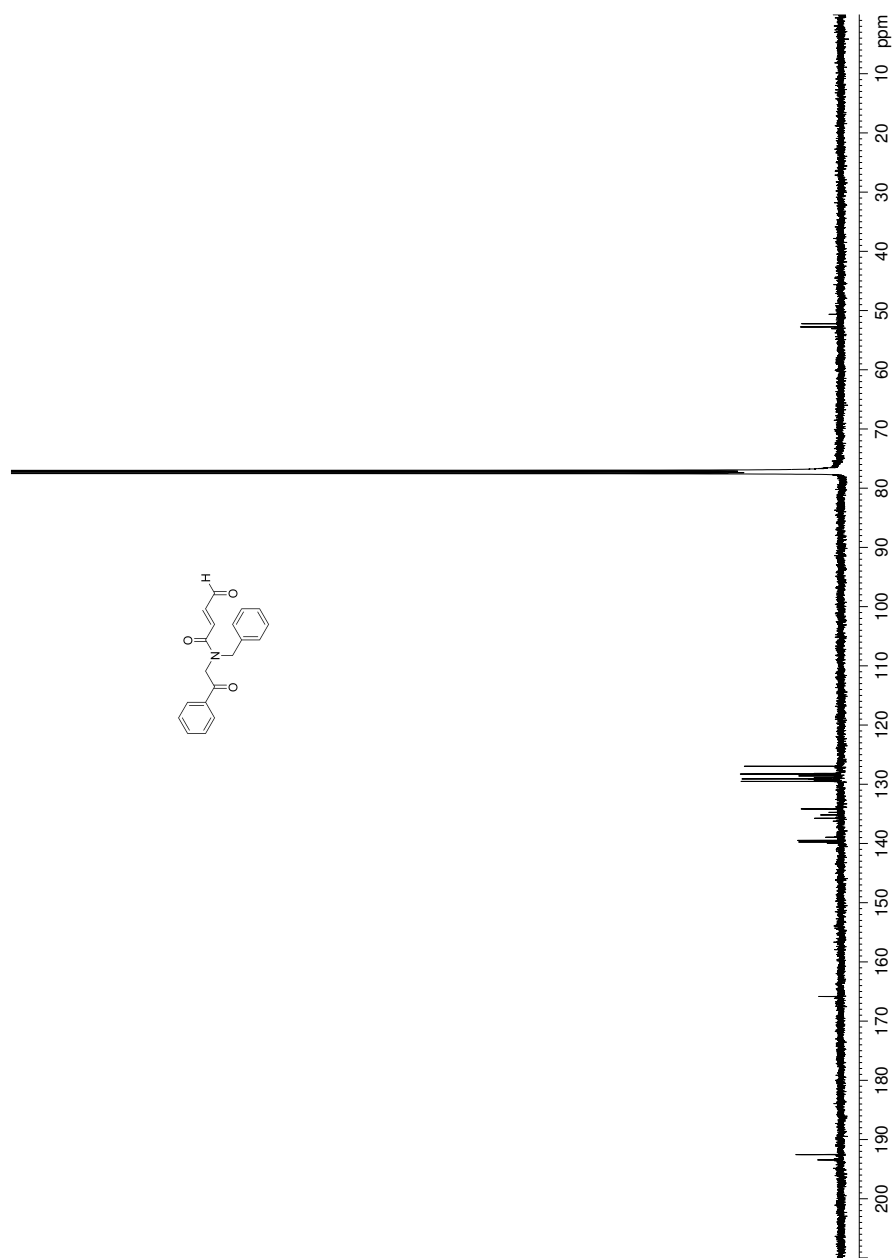
Figure 151. ^{13}C NMR spectrum of compound **202**.

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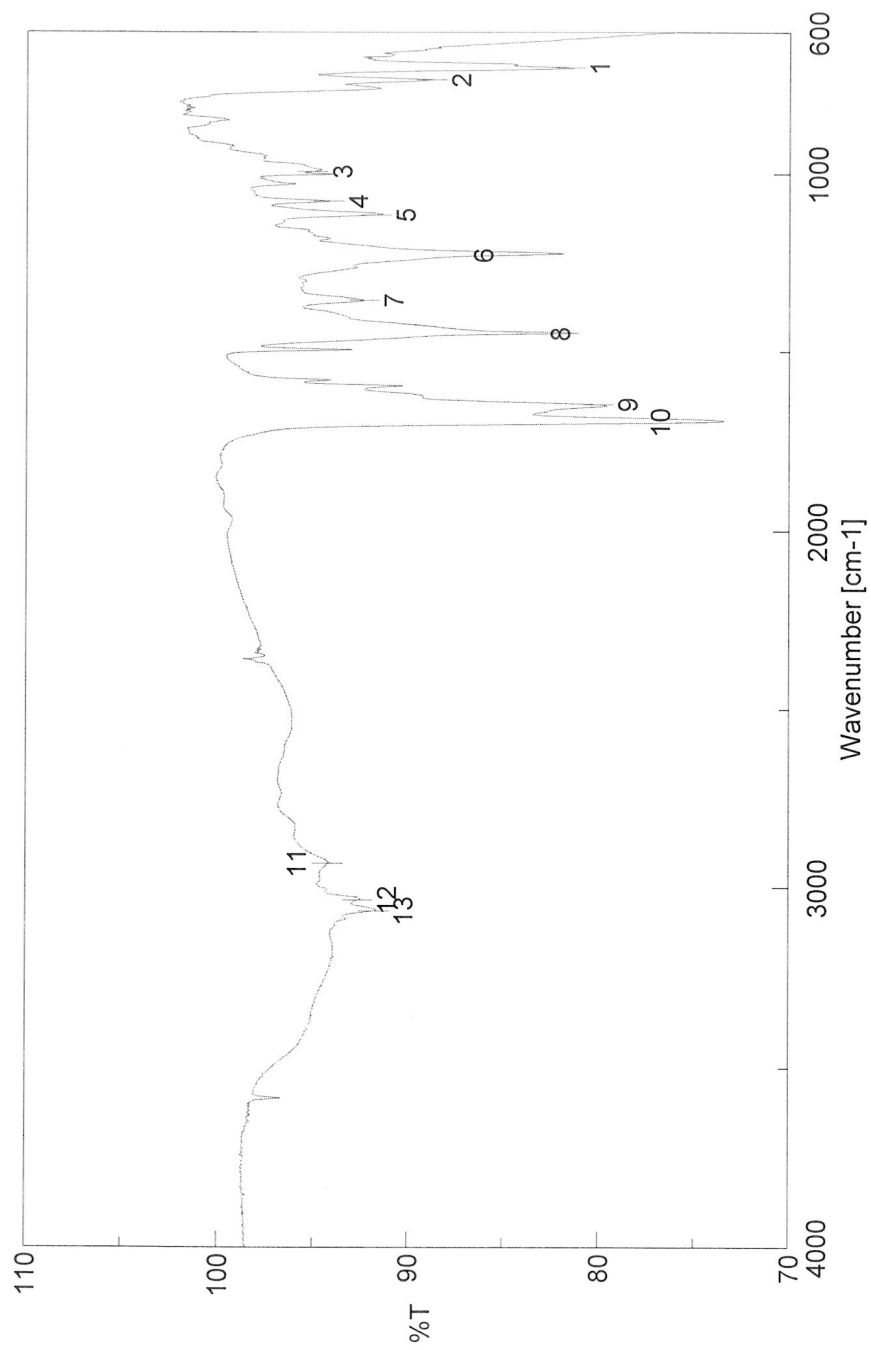
Figure 152. IR spectrum of compound **202**.

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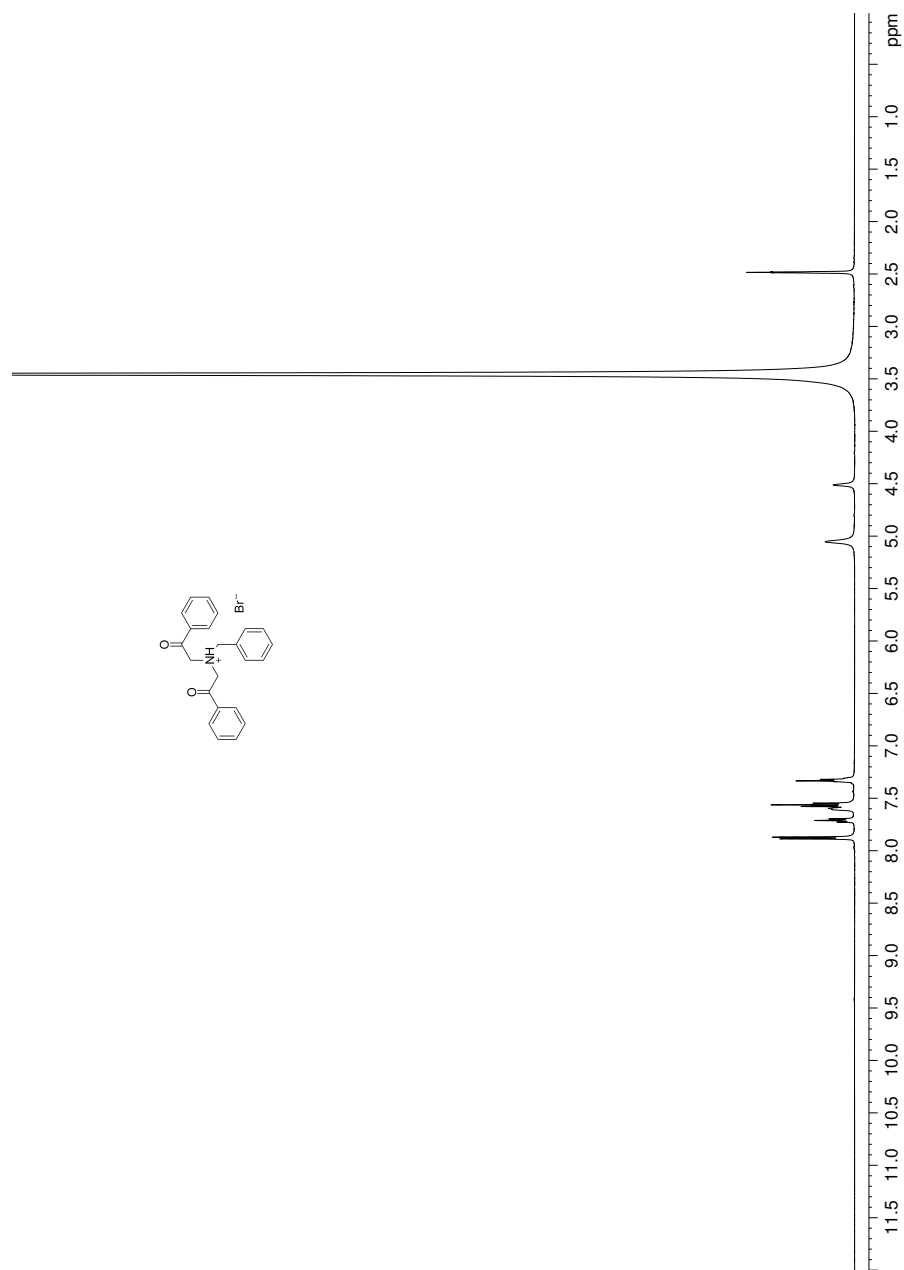
Figure 153. ^{1}H NMR spectrum of compound **209**.

Figure 154. ^{13}C NMR spectrum of compound **209**.
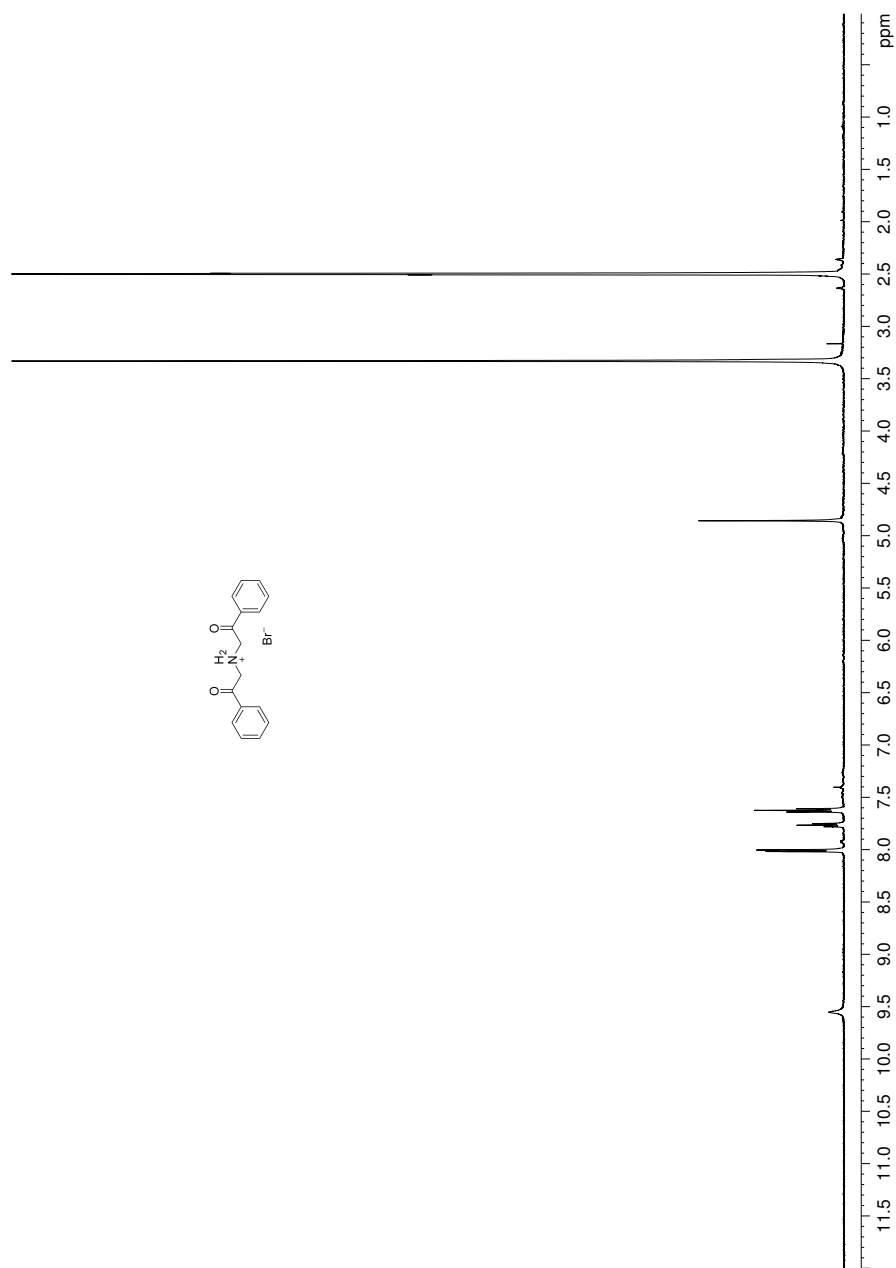
Figure 155. IR spectrum of compound **209**.

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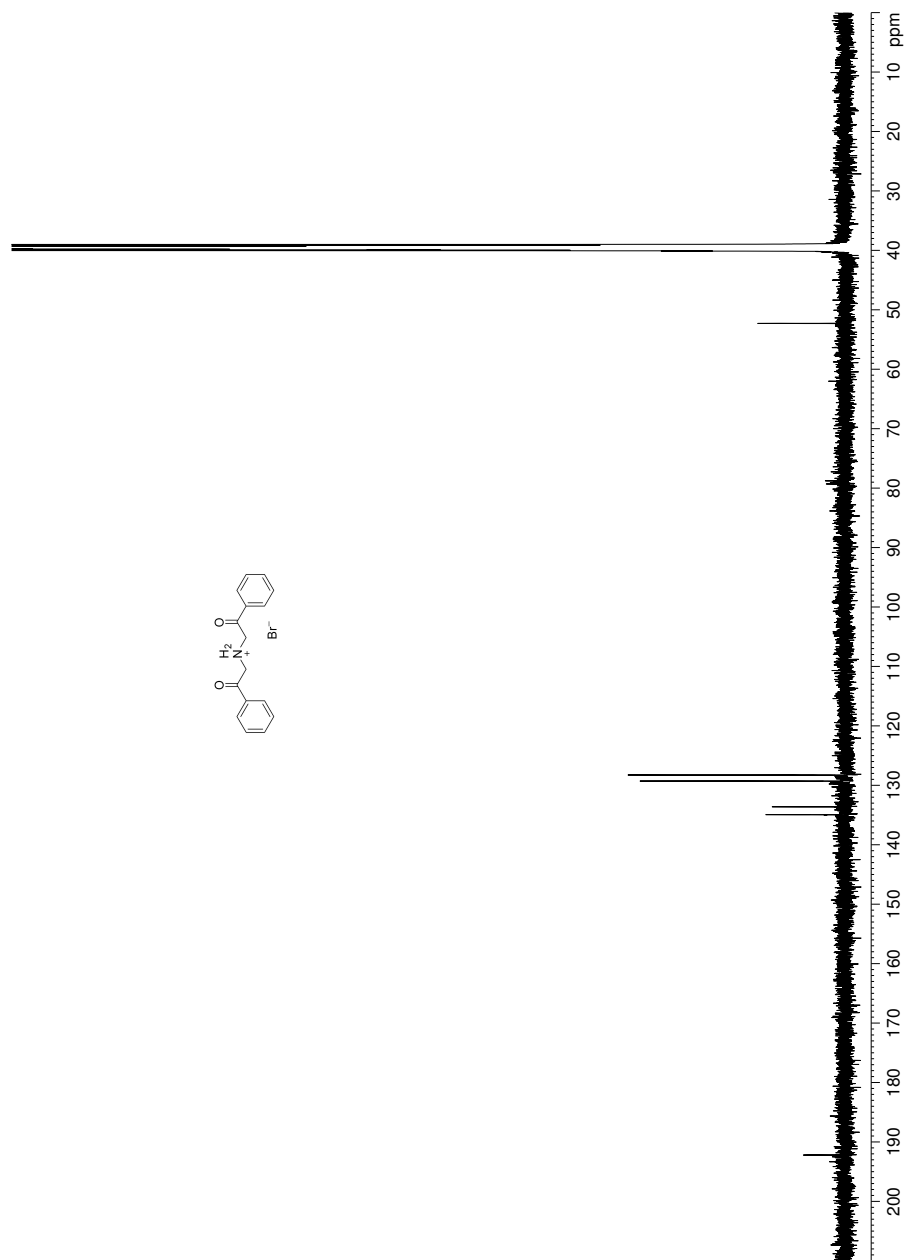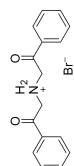
Figure 156. ¹H NMR spectrum of compound **210**.

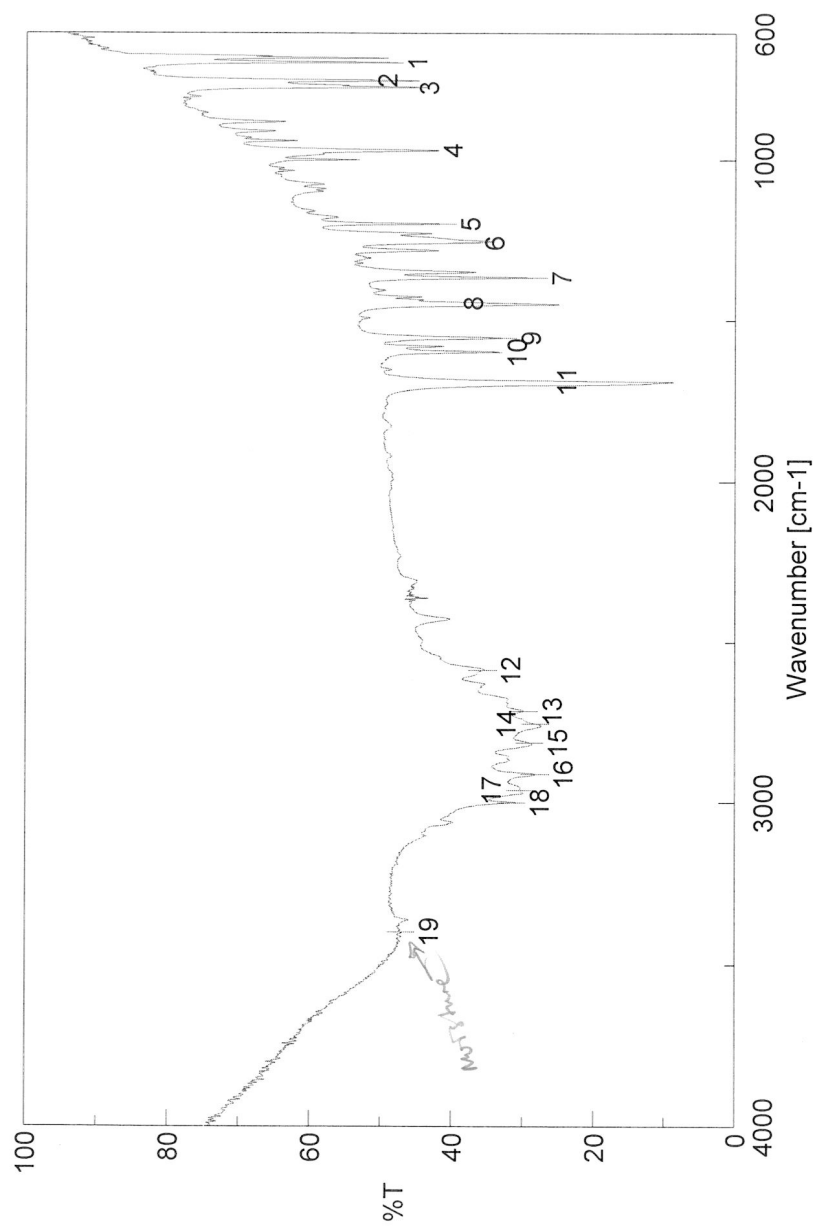**Figure 157.** ^{13}C NMR spectrum of compound **210**.

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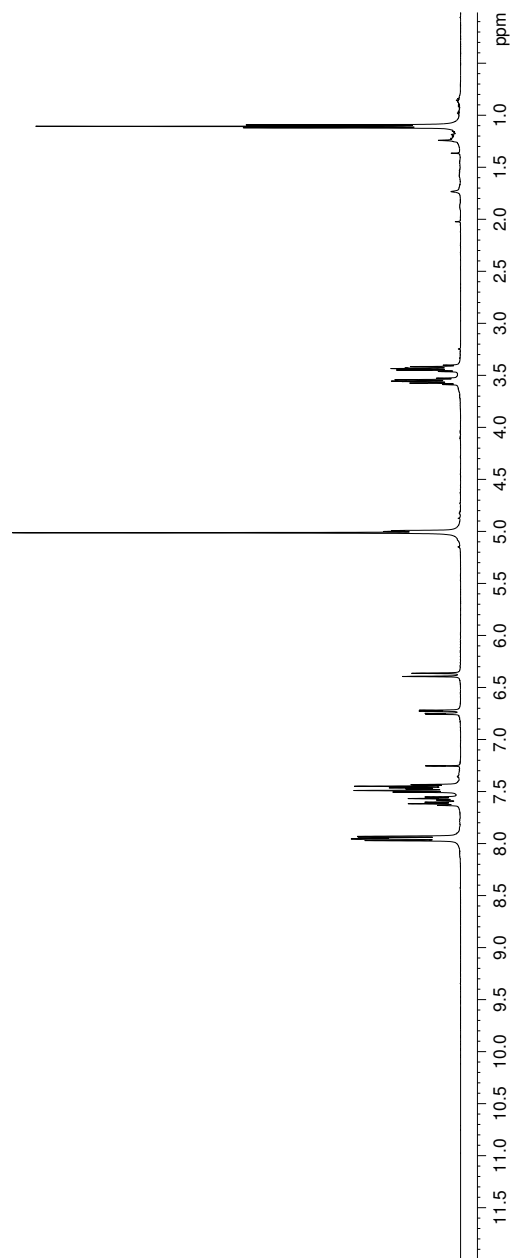**Figure 158**. IR spectrum of compound **210**.

Figure 159. ^{1}H NMR spectrum of compound **211**.

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Figure 160. ^{13}C NMR spectrum of compound **211**.

Figure 161. IR spectrum of compound **211**.

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Figure 162. ^{1}H NMR spectrum of compound **208**.

Figure 163. ^{13}C NMR spectrum of compound **208**.

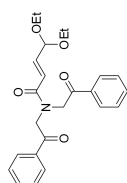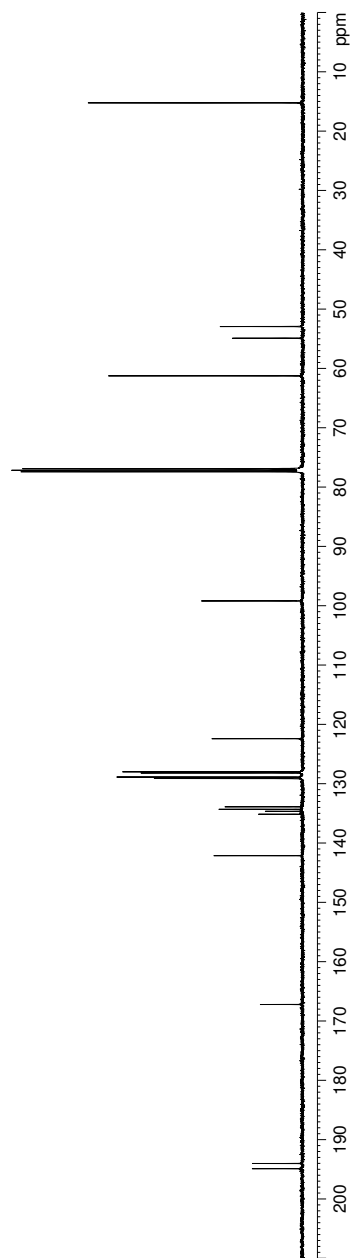**Figure 164.** IR spectrum of compound **208**.

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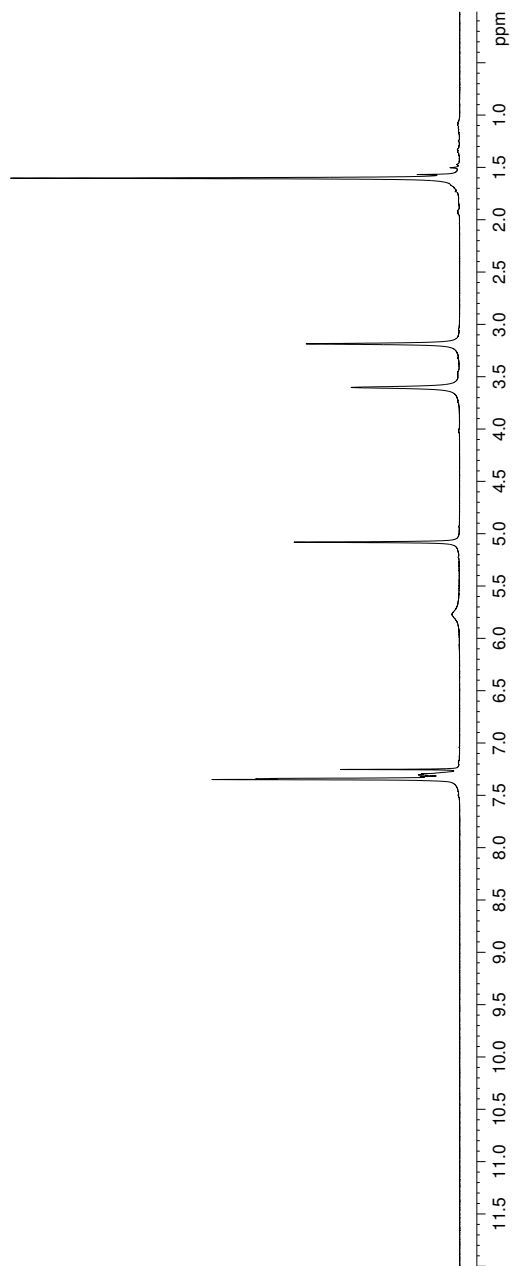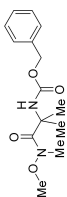
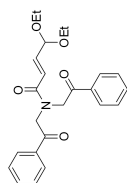**Figure 165.** ^{1}H NMR spectrum of compound **218**.

Figure 166. ^{13}C NMR spectrum of compound **218**.

Figure 167. IR spectrum of compound **218**.

Figure 168. ¹H NMR spectrum of compound **219**.

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Figure 169. ^{13}C NMR spectrum of compound **219**.
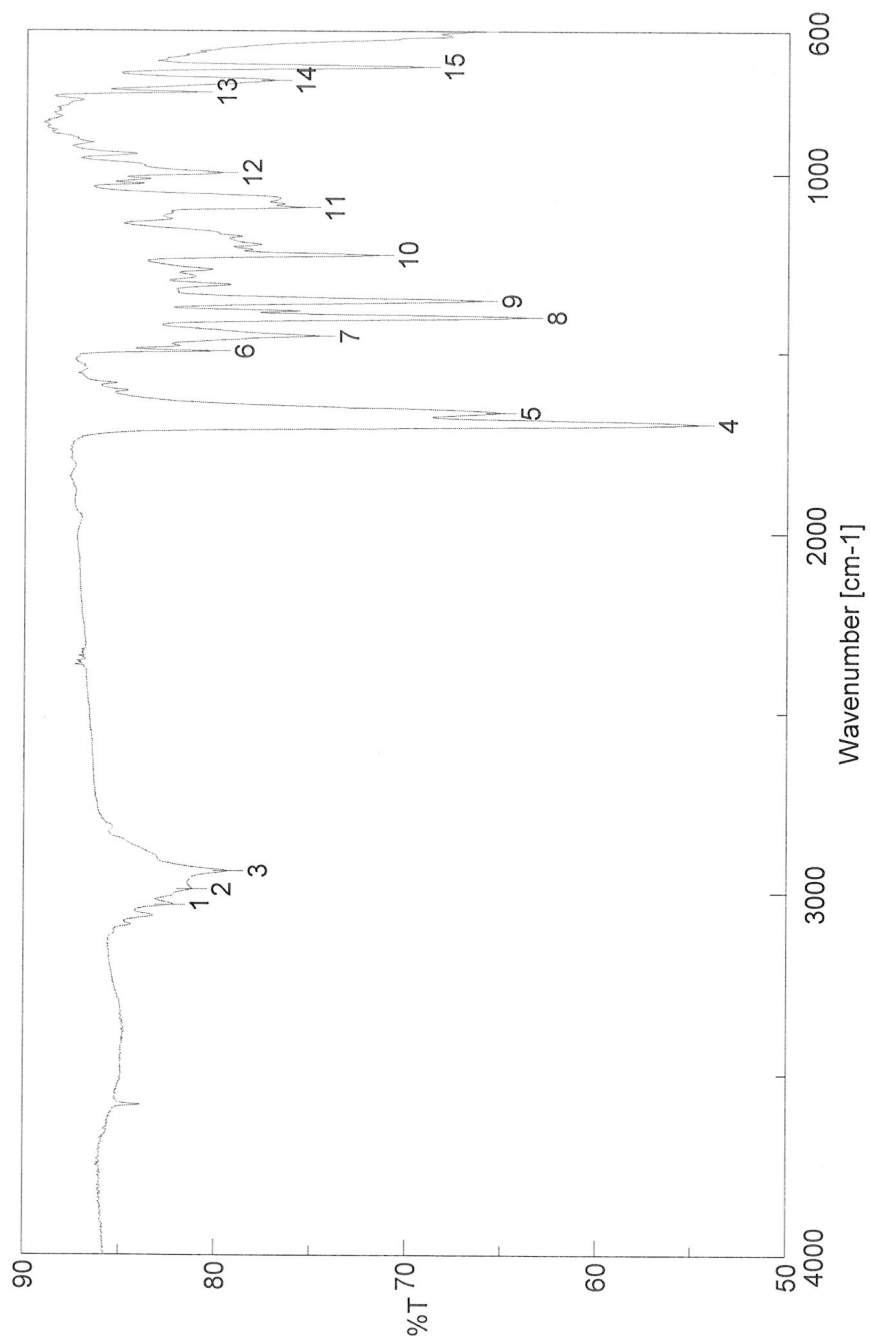
Figure 170. IR spectrum of compound **219**.

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Figure 171. ^{1}H NMR spectrum of compound **220**.
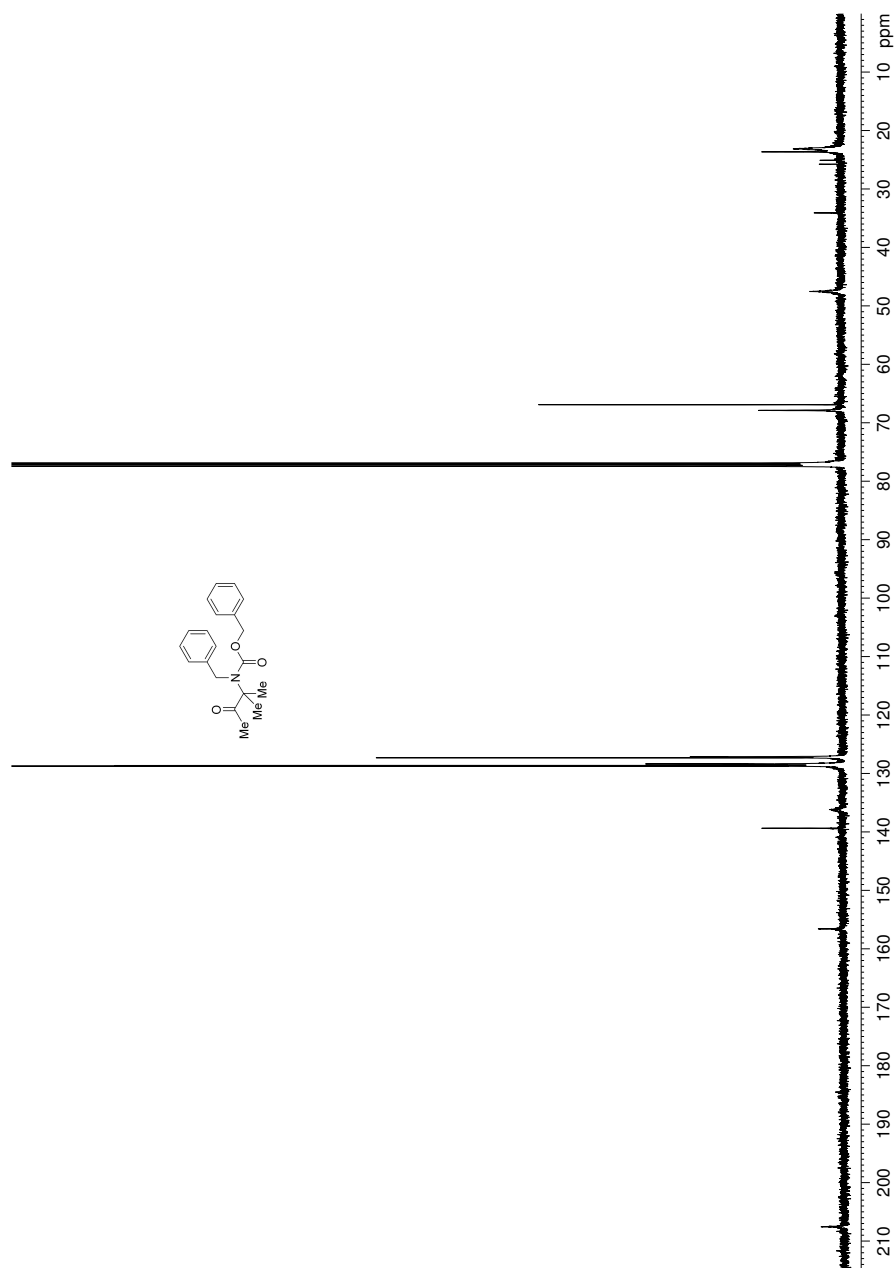
Figure 172. ^{13}C NMR spectrum of compound **220**.

Figure 173. IR spectrum of compound **220**.
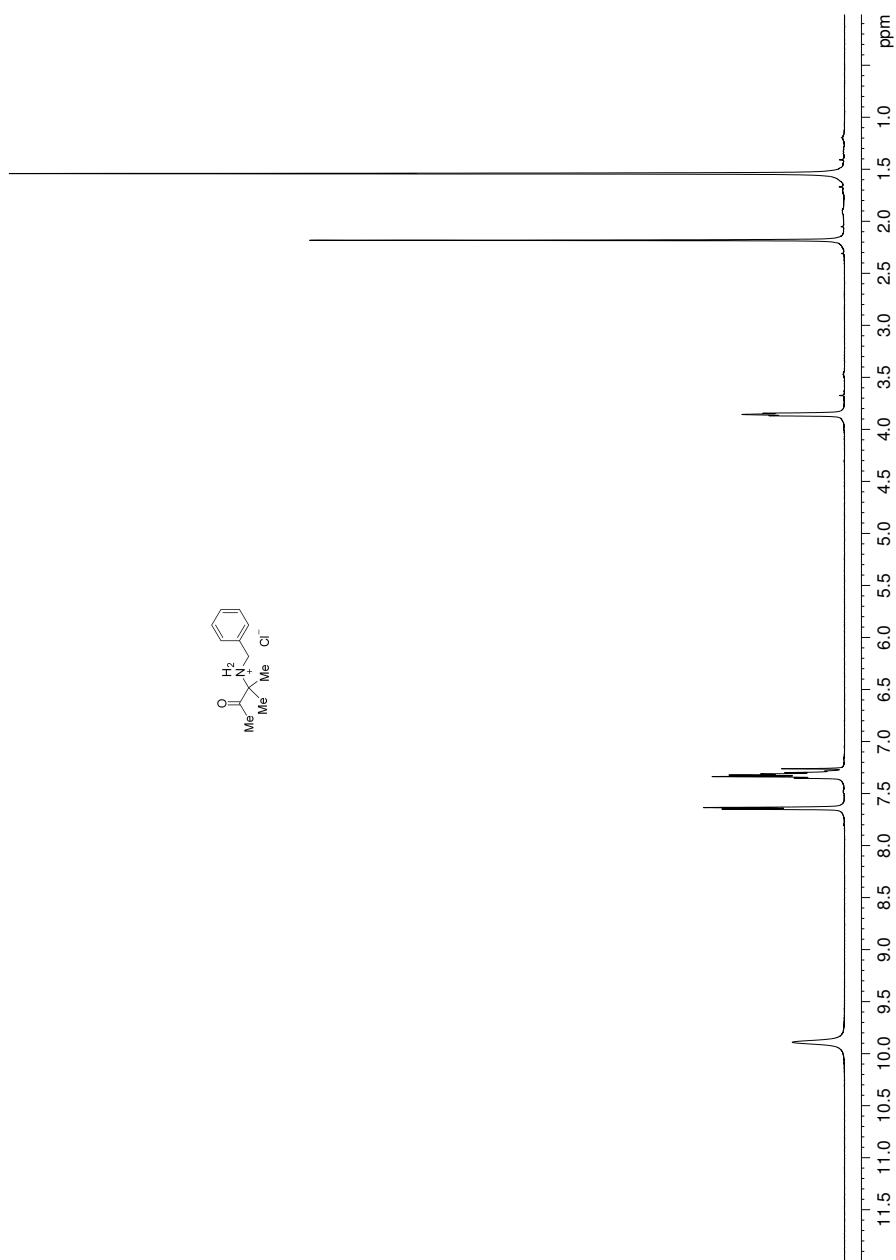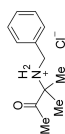
Figure 174. ^{1}H NMR spectrum of compound **221**.
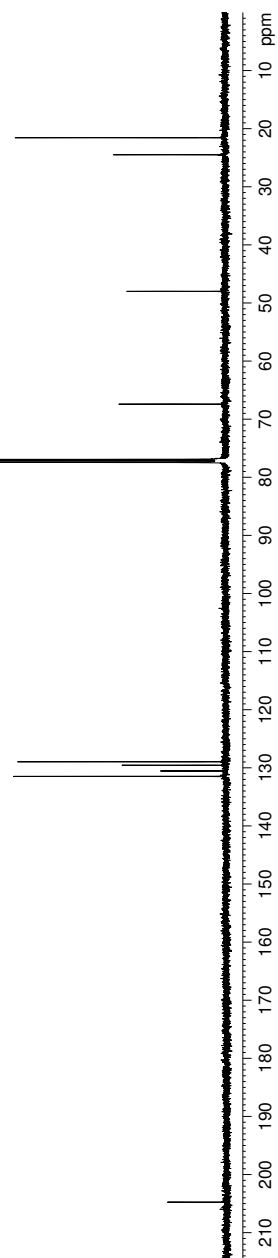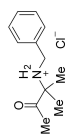
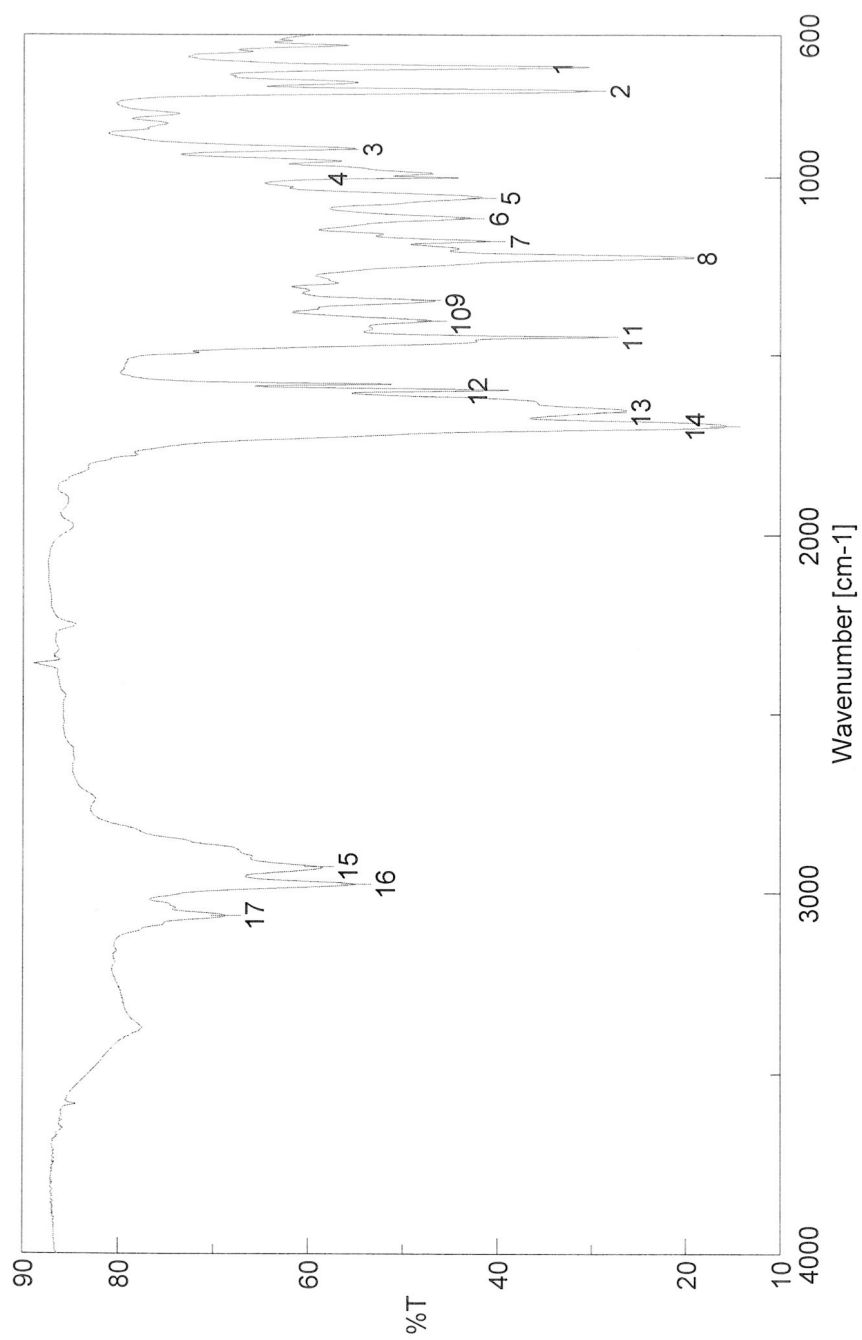**Figure 175.** ^{13}C NMR spectrum of compound **221**.
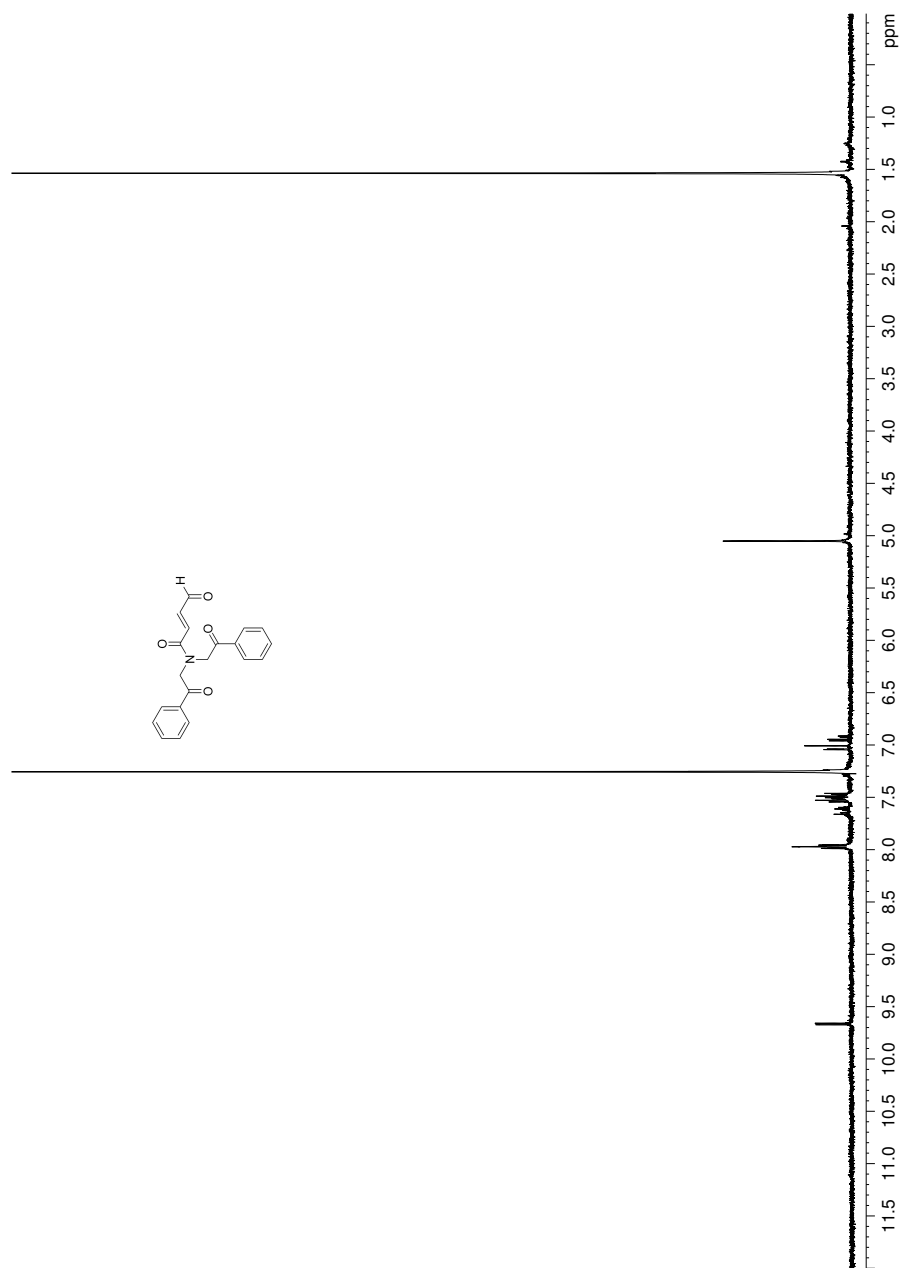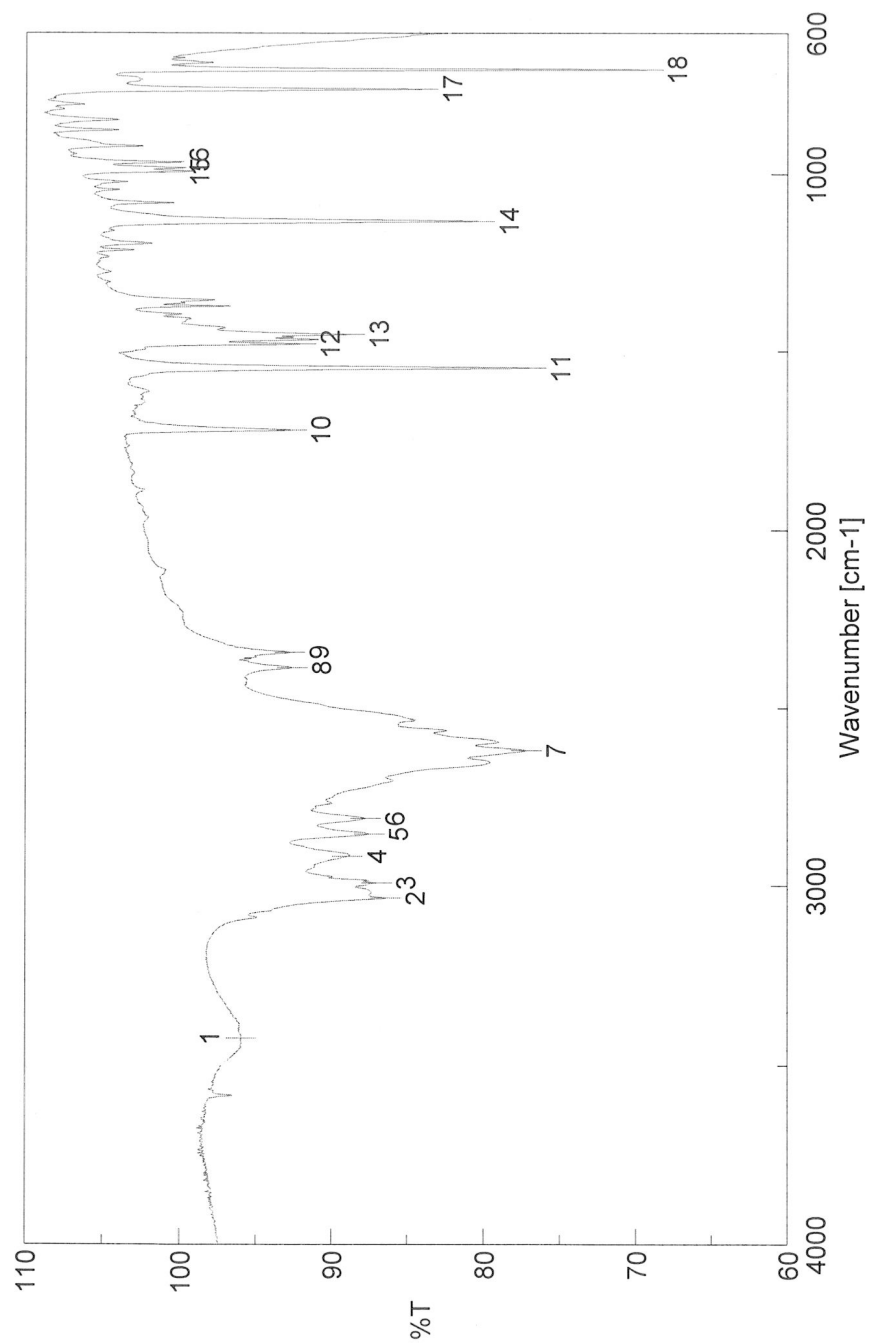
Figure 176. IR spectrum of compound **221**.
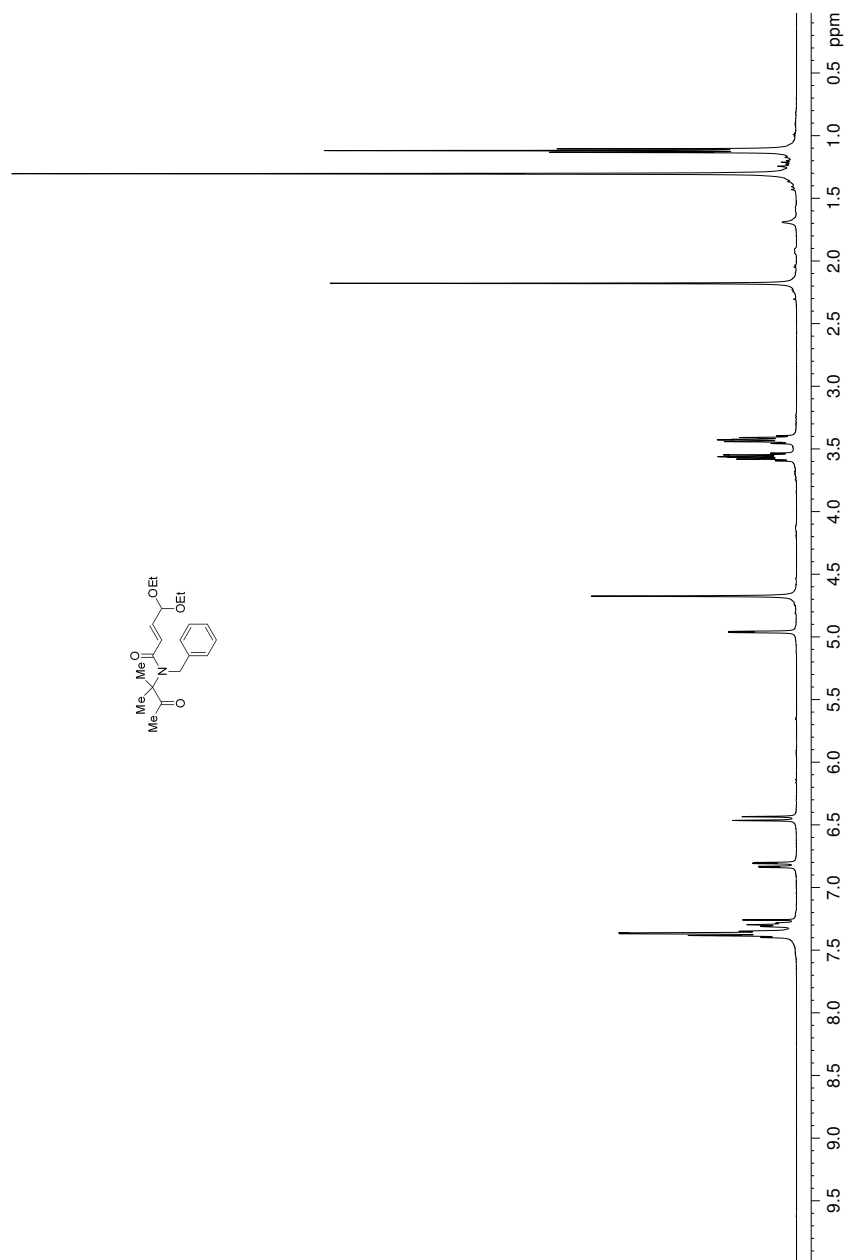
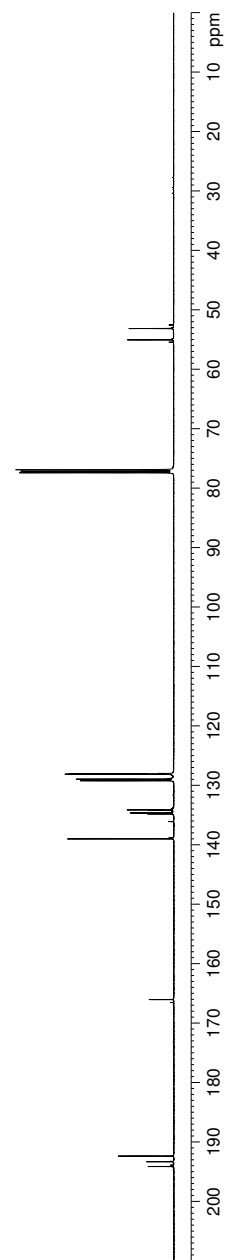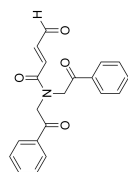**Figure 177.** ¹H NMR spectrum of compound **222**.

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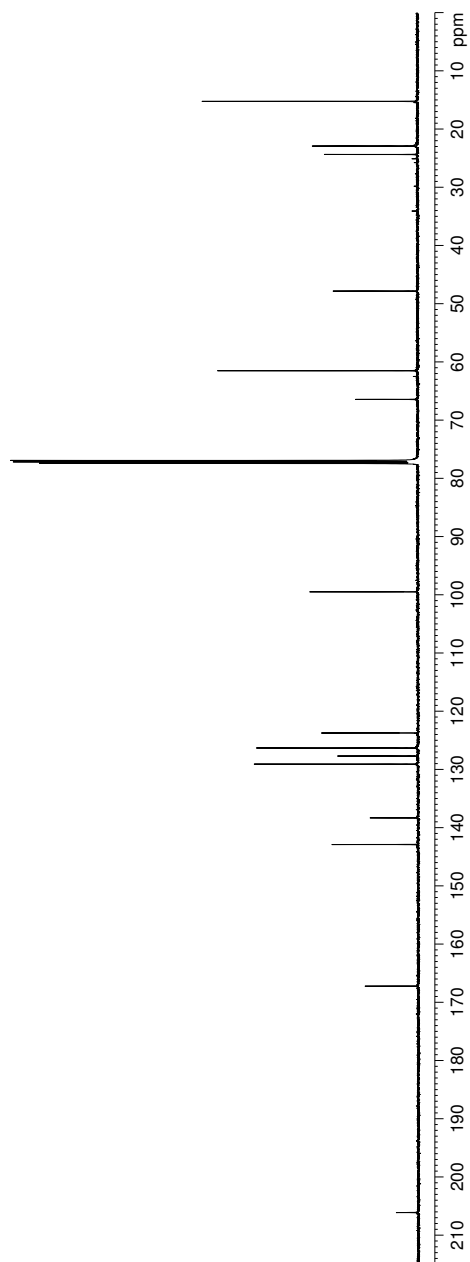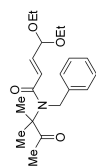
Figure 178. ^{13}C NMR spectrum of compound **222**.
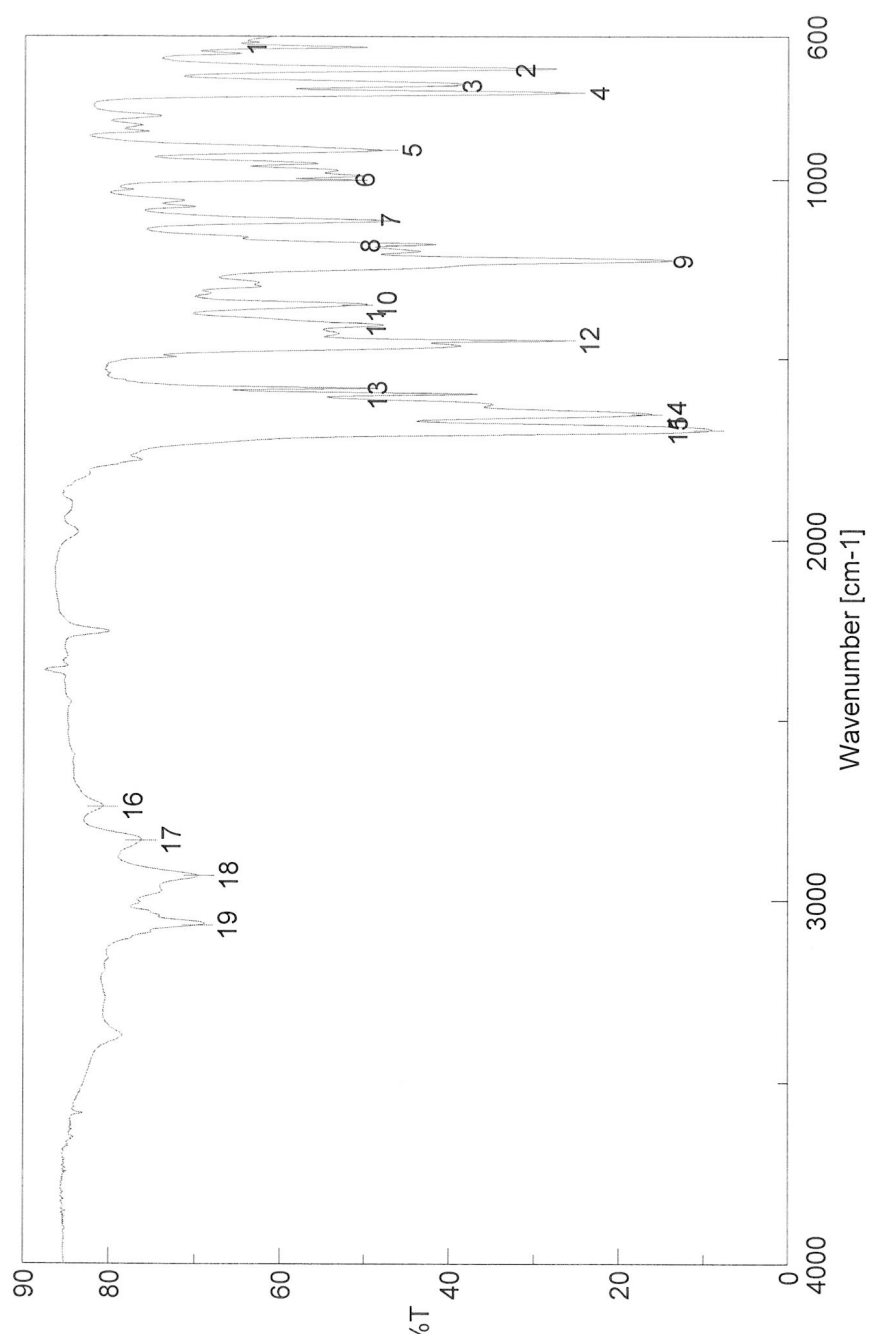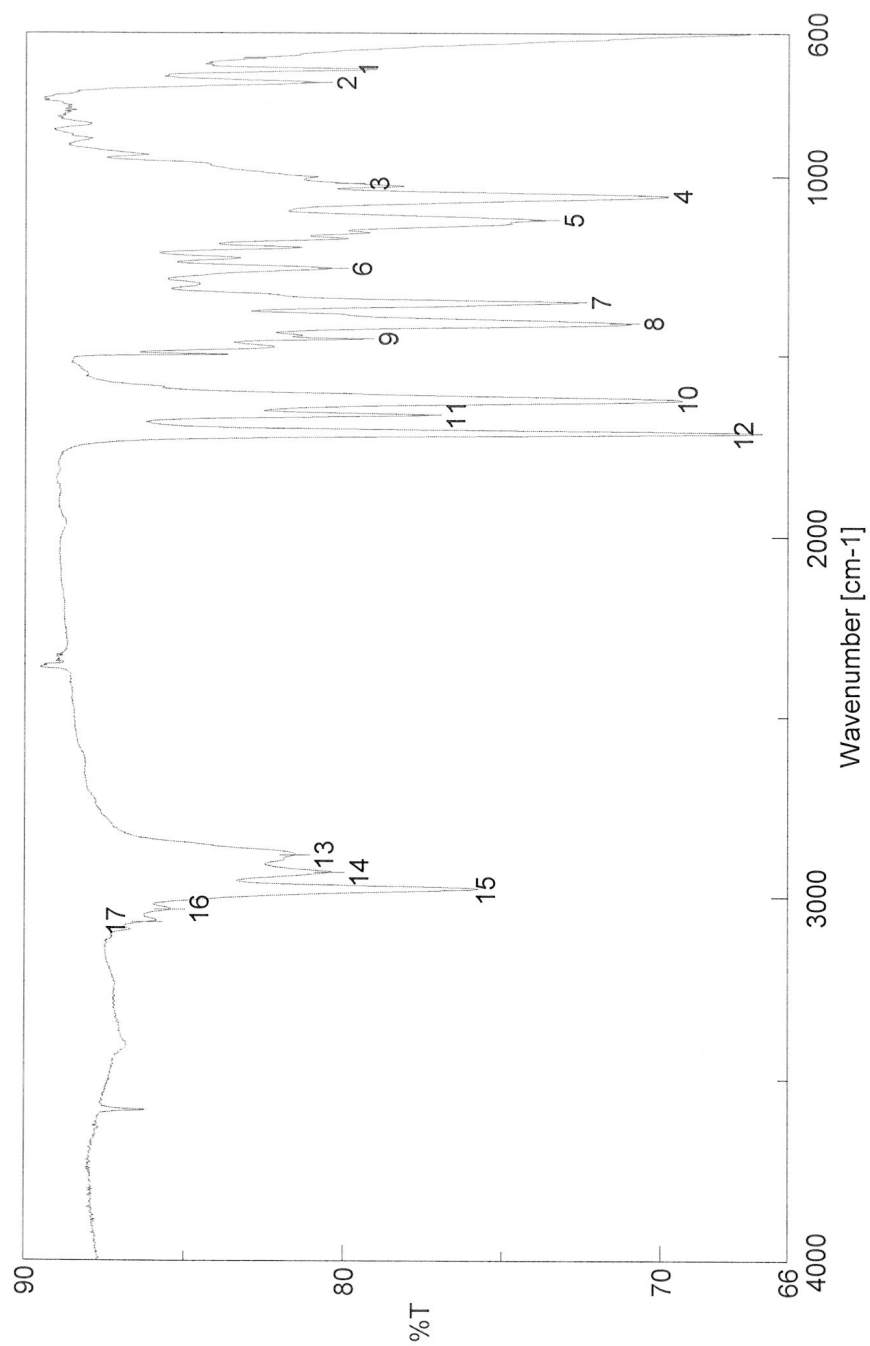
Figure 179. IR spectrum of compound **222**.
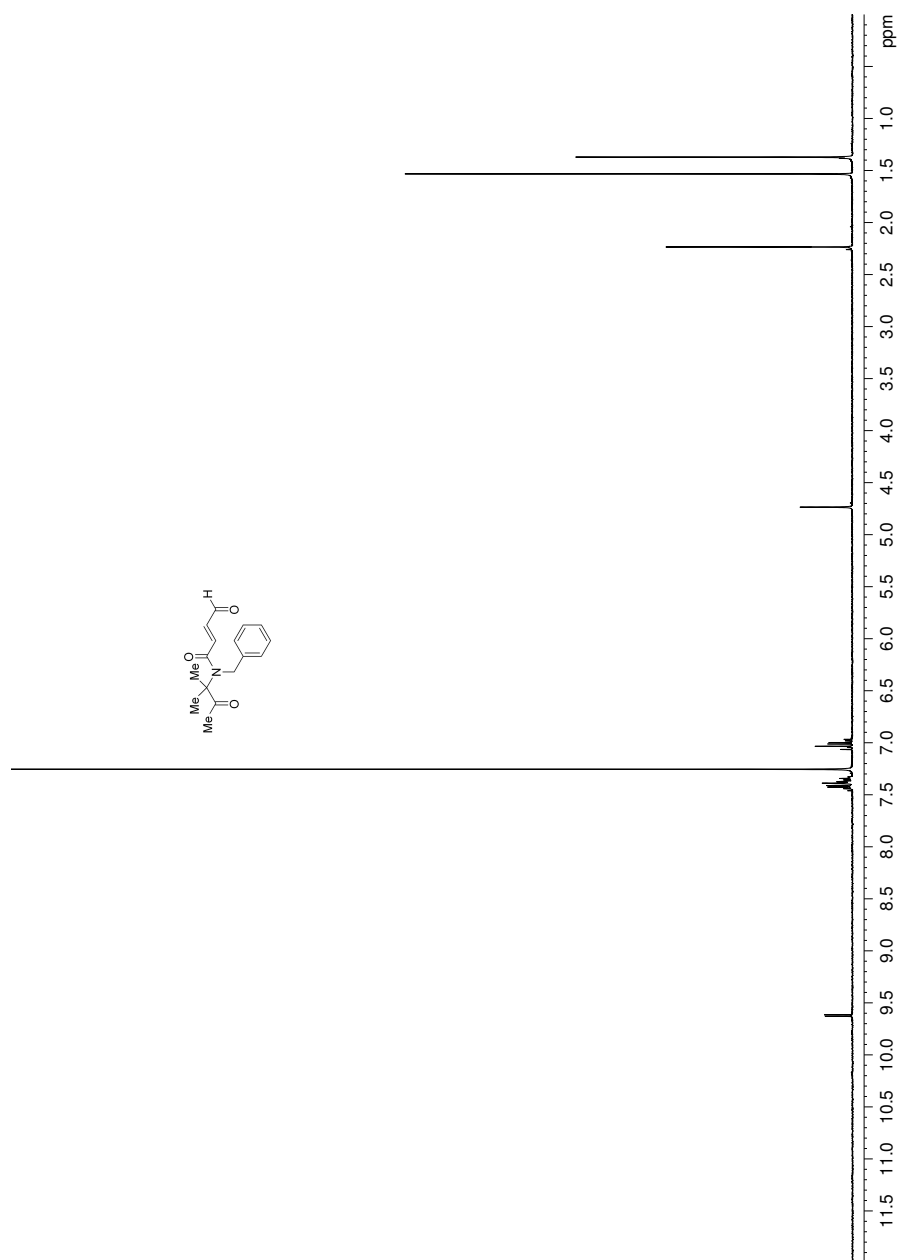
Figure 180. ^{1}H NMR spectrum of compound **217**.
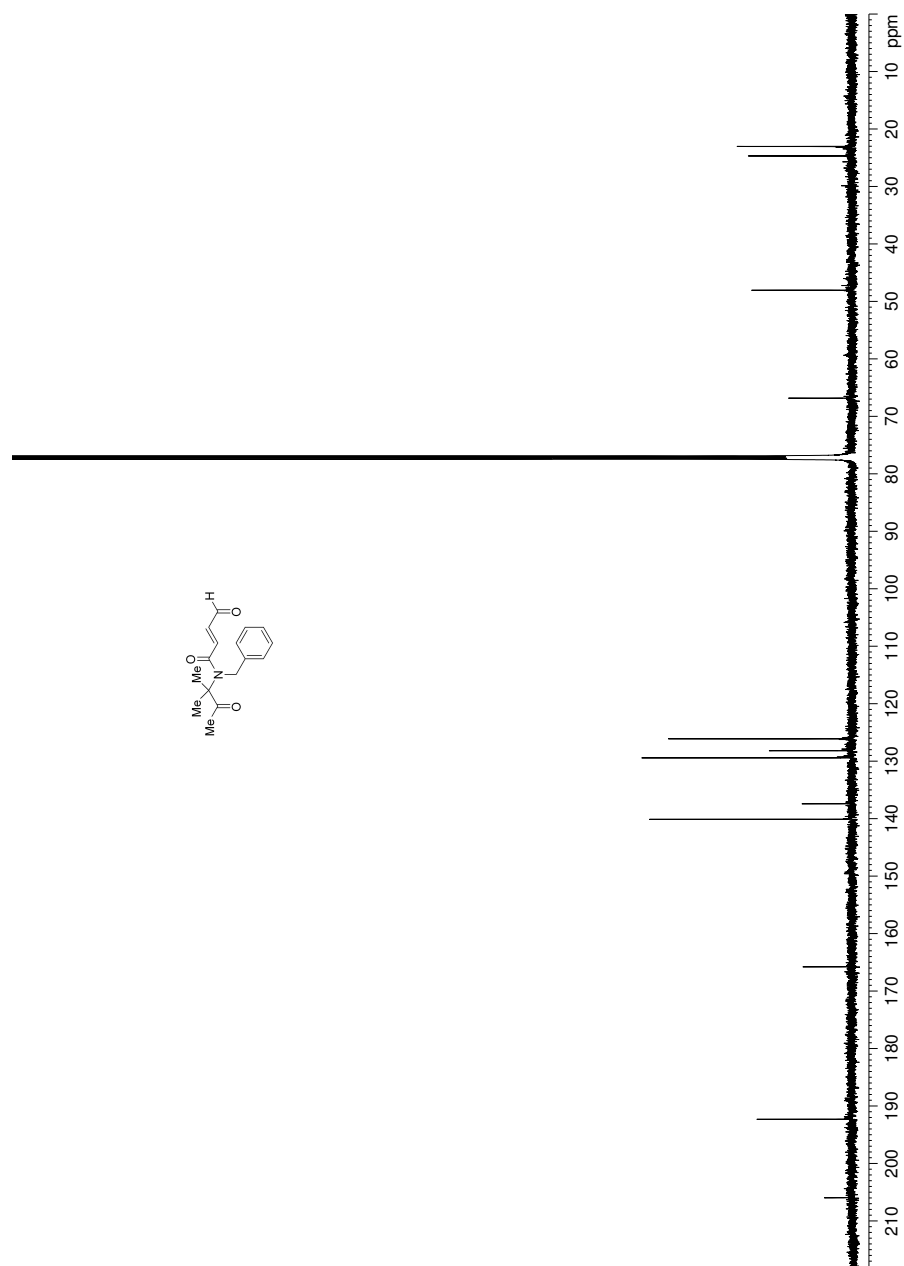
Figure 181. ^{13}C NMR spectrum of compound **217**.

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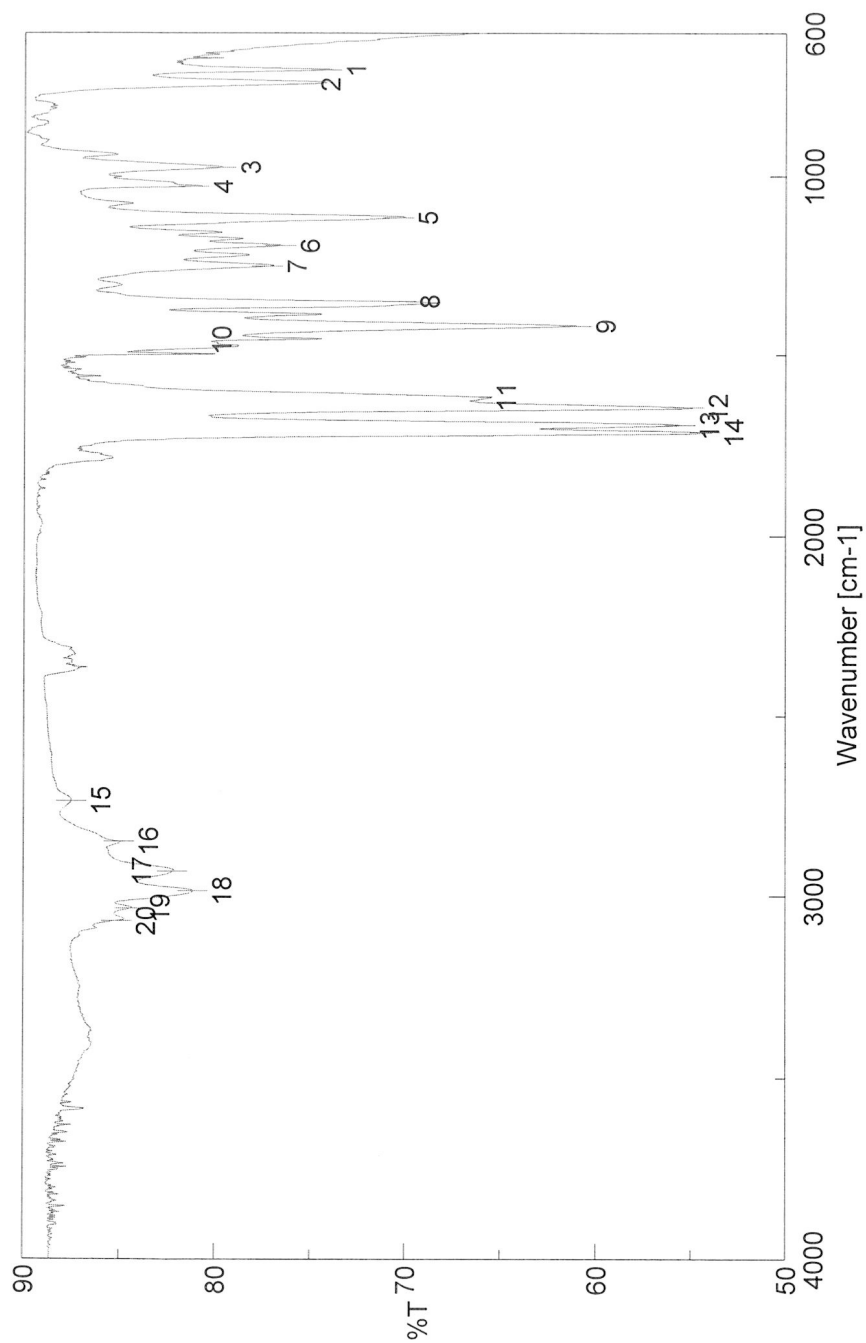
Figure 182. IR spectrum of compound **217**.

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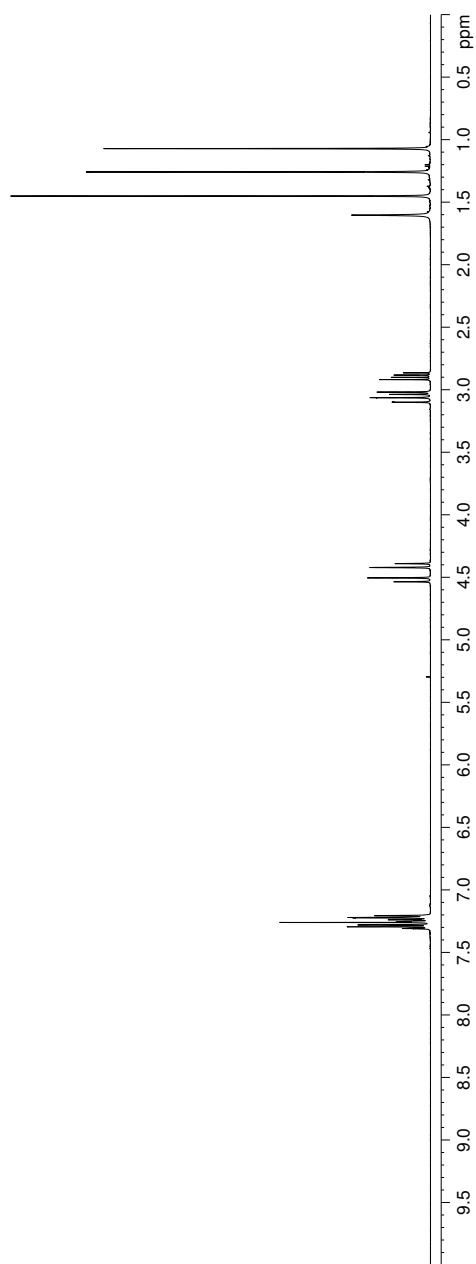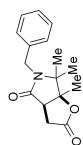
Figure 183. ^{1}H NMR spectrum of compound **223**.

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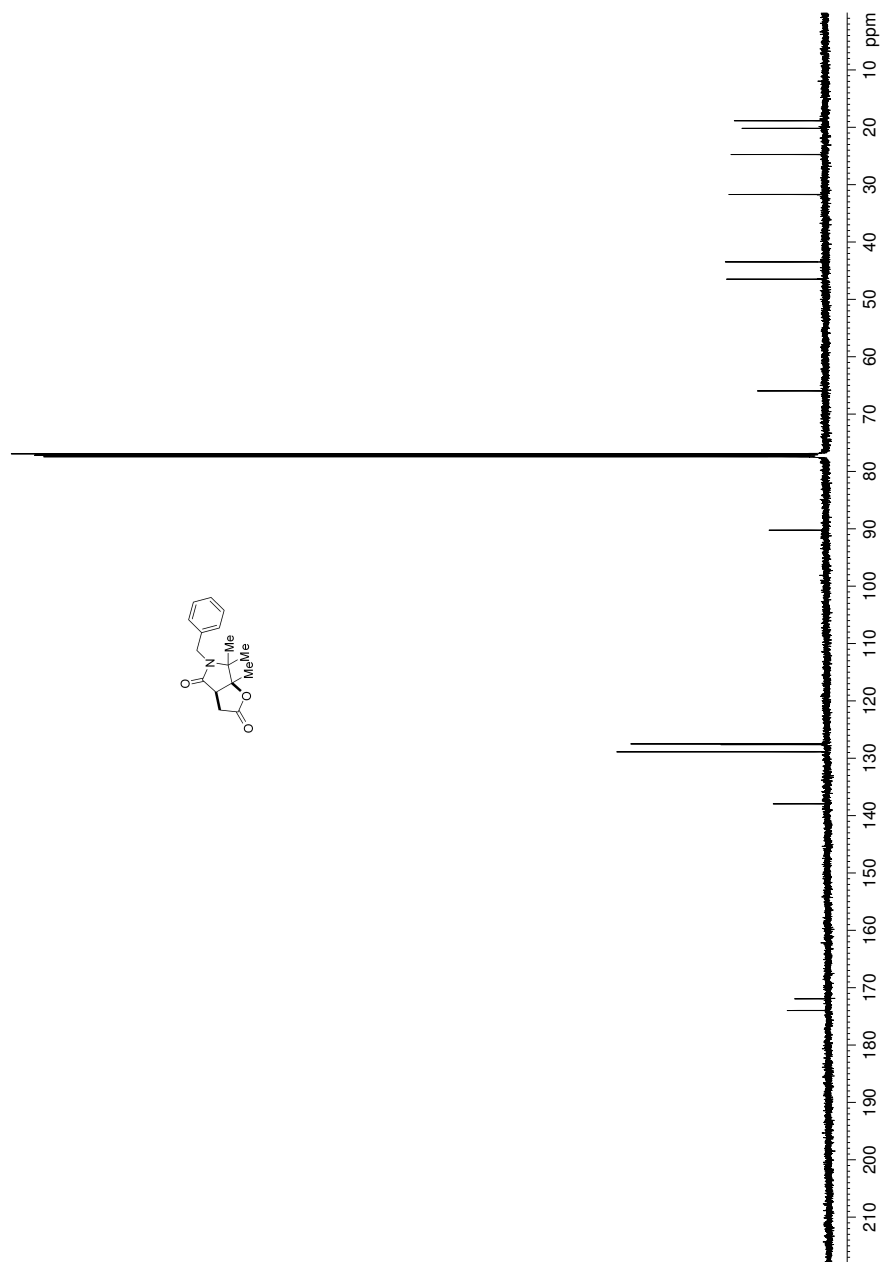
Figure 182. ^{13}C NMR spectrum of compound **223**.
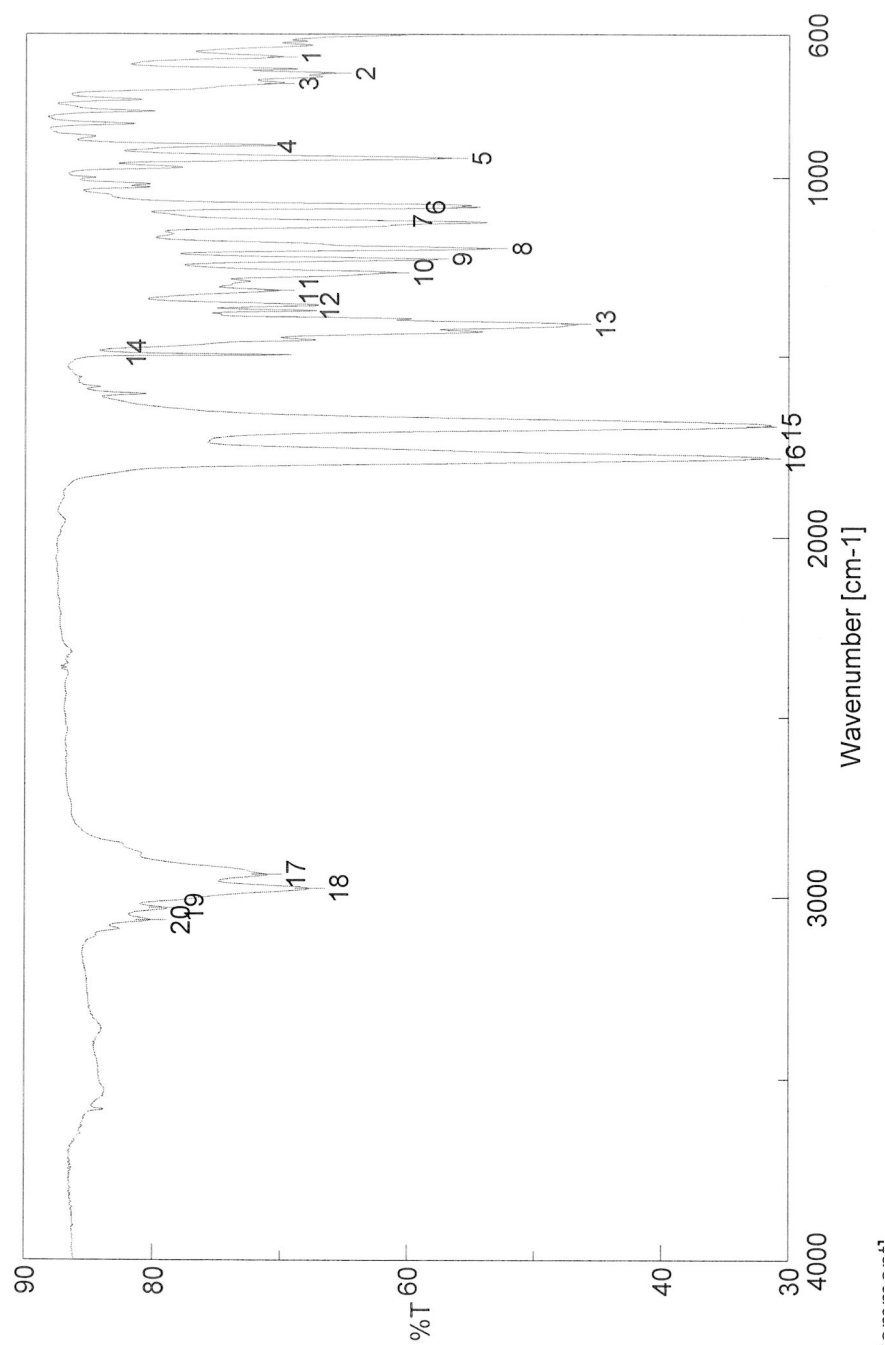
Figure 183. IR spectrum of compound **223**.
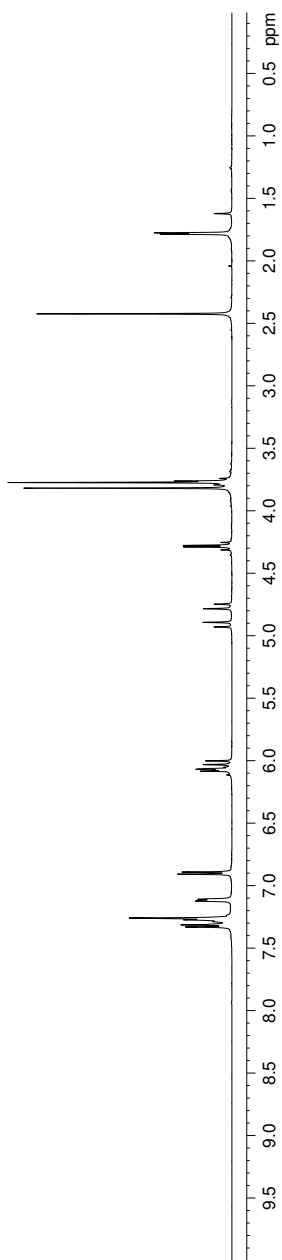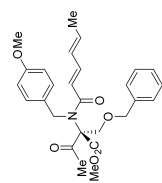
Figure 184. ¹H NMR spectrum of compound **229**.
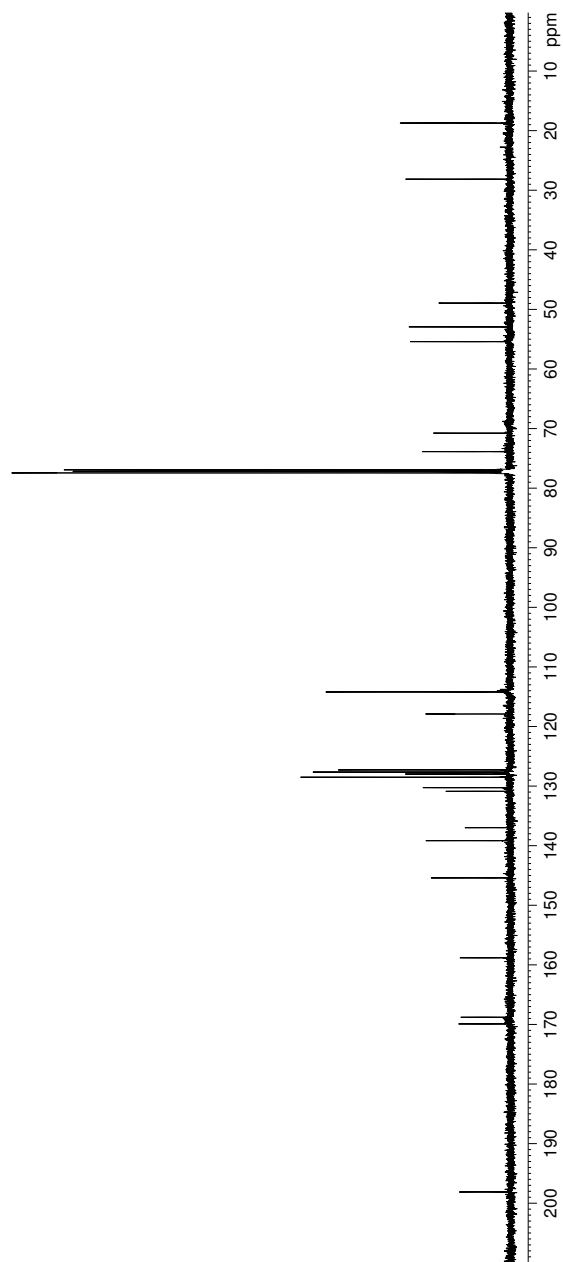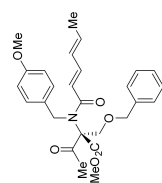
Figure 185. ^{13}C NMR spectrum of compound **229**.
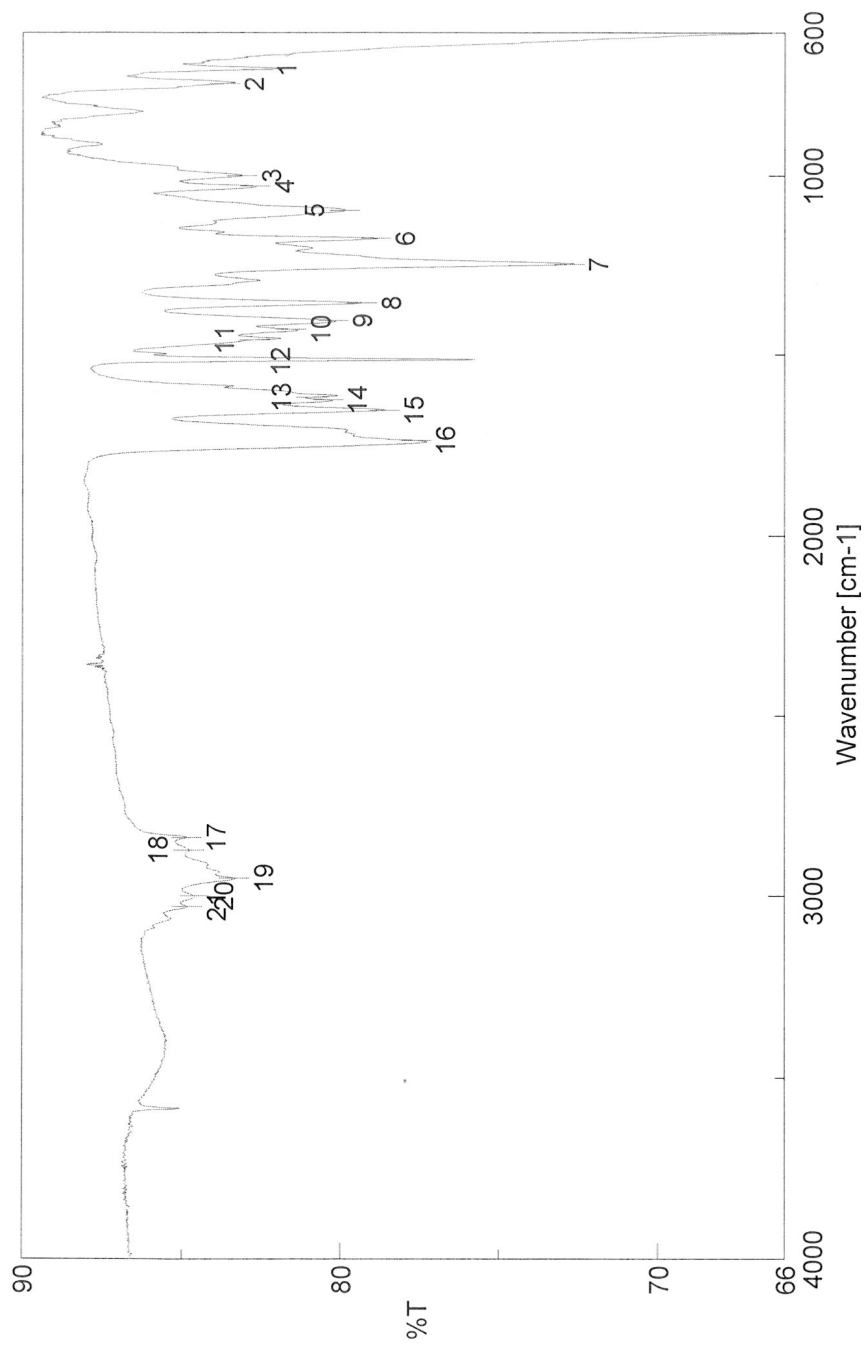
Figure 186. IR spectrum of compound **229**.
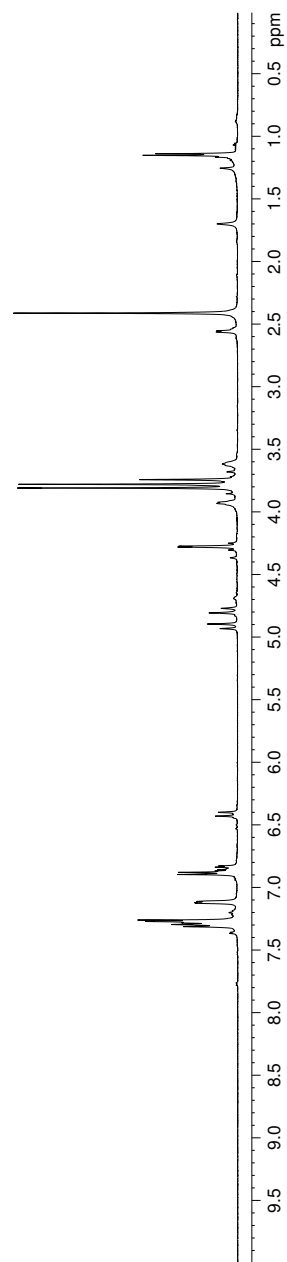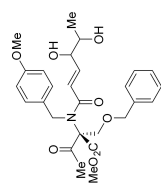
Figure 187. ¹H NMR spectrum of compound **230**.

Figure 188. ^{13}C NMR spectrum of compound **230**.

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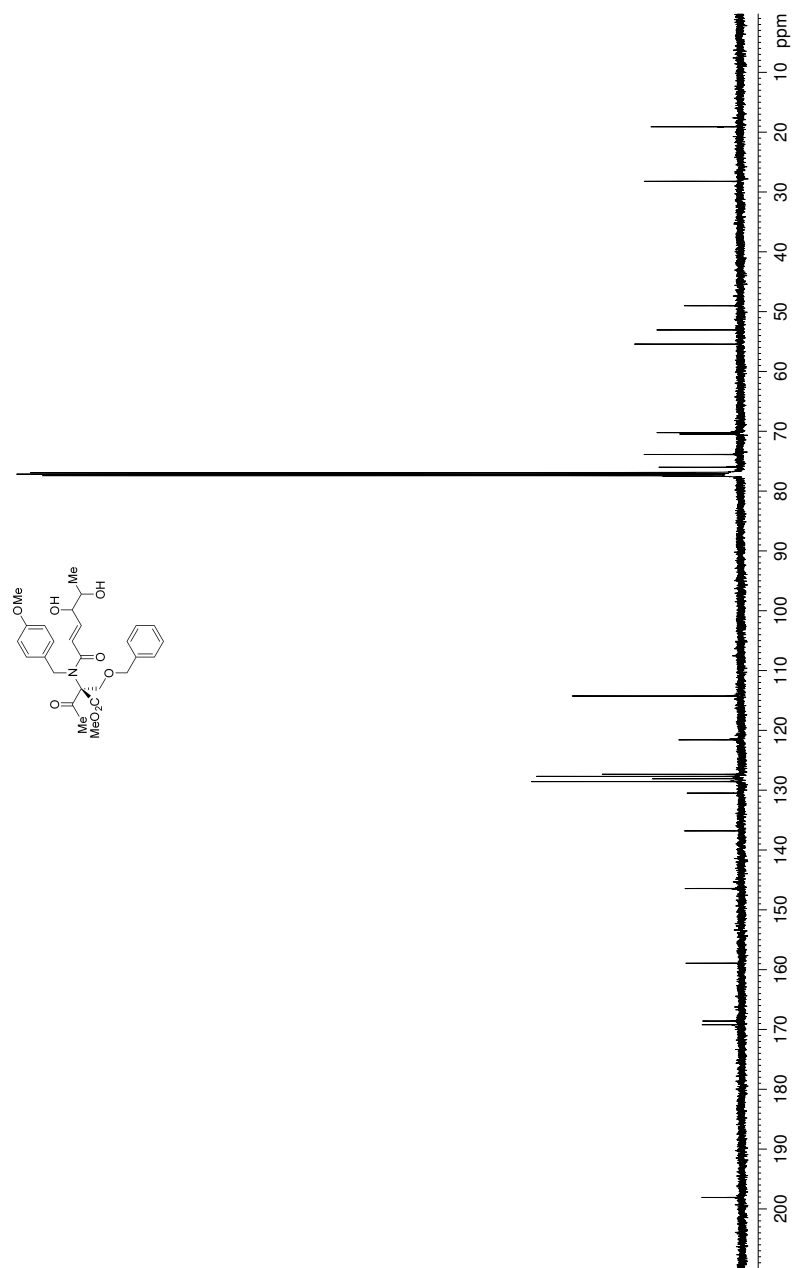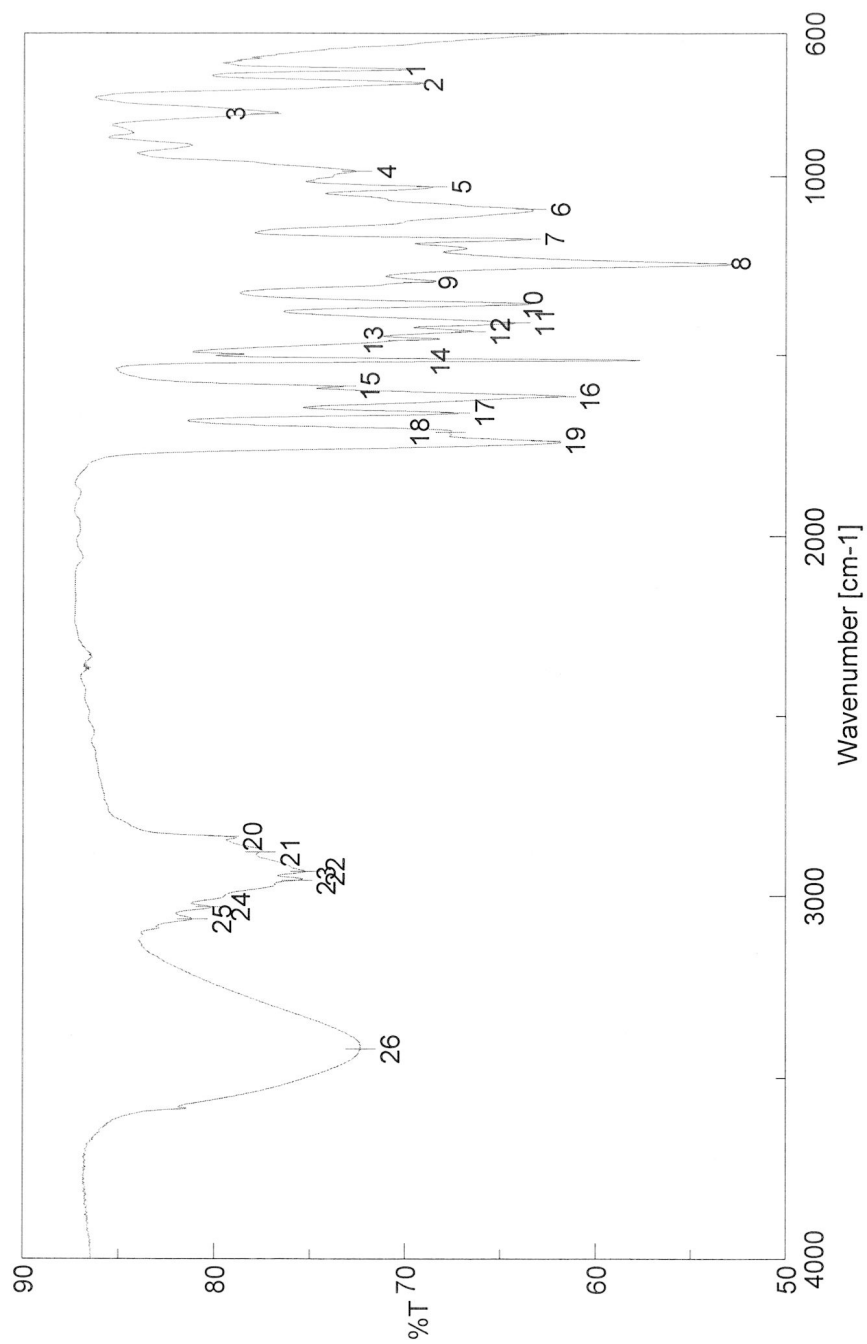
Figure 189. IR spectrum of compound **230**.
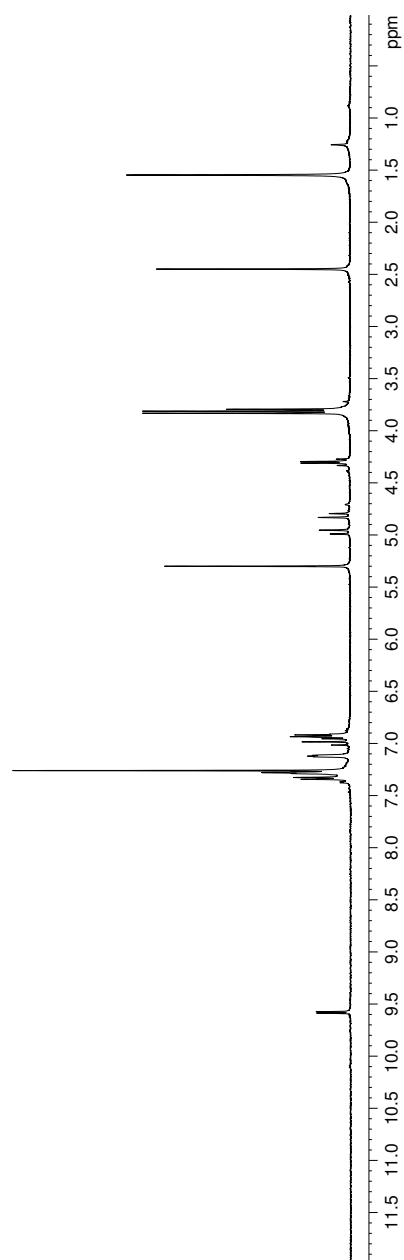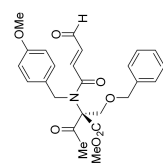
Figure 190. ¹H NMR spectrum of compound **225**.
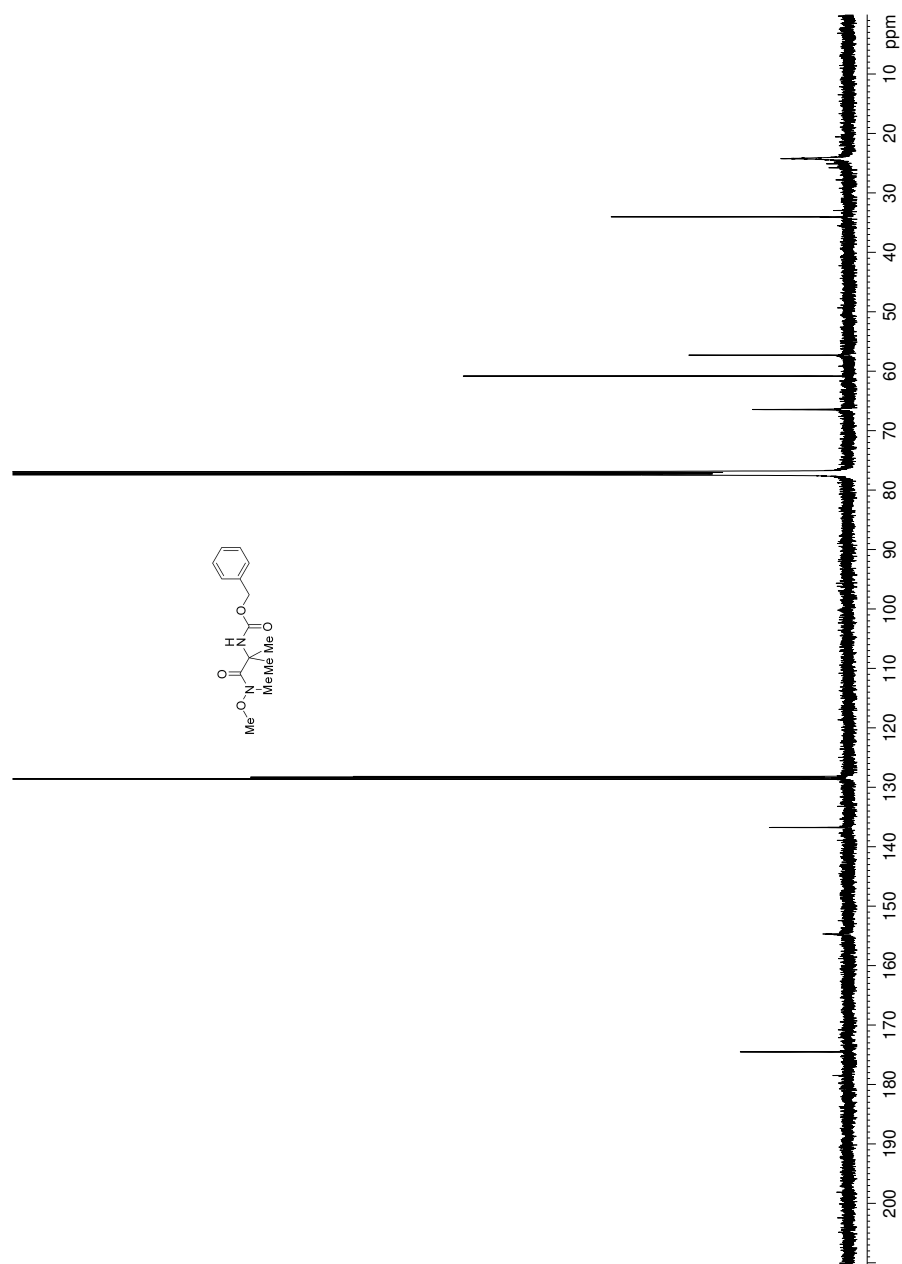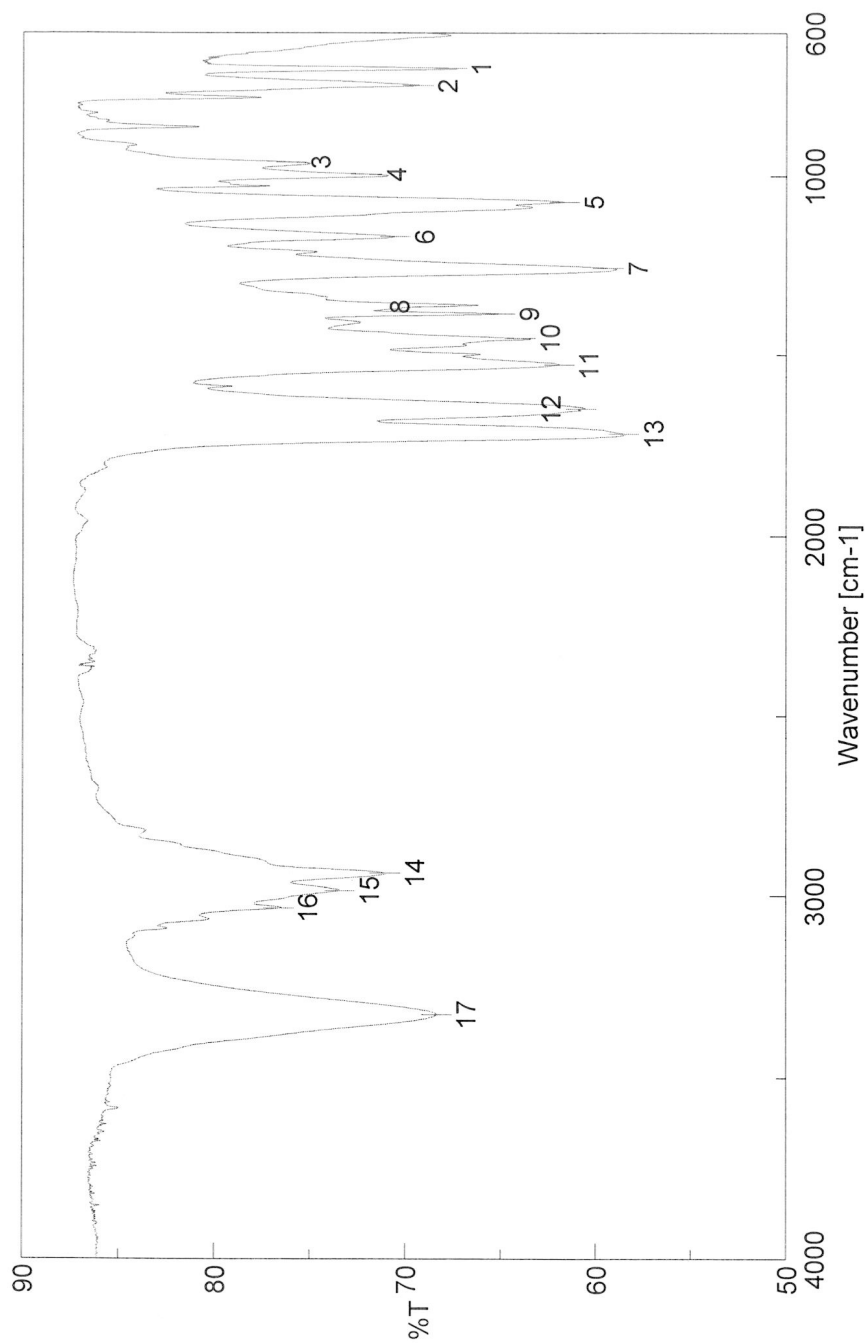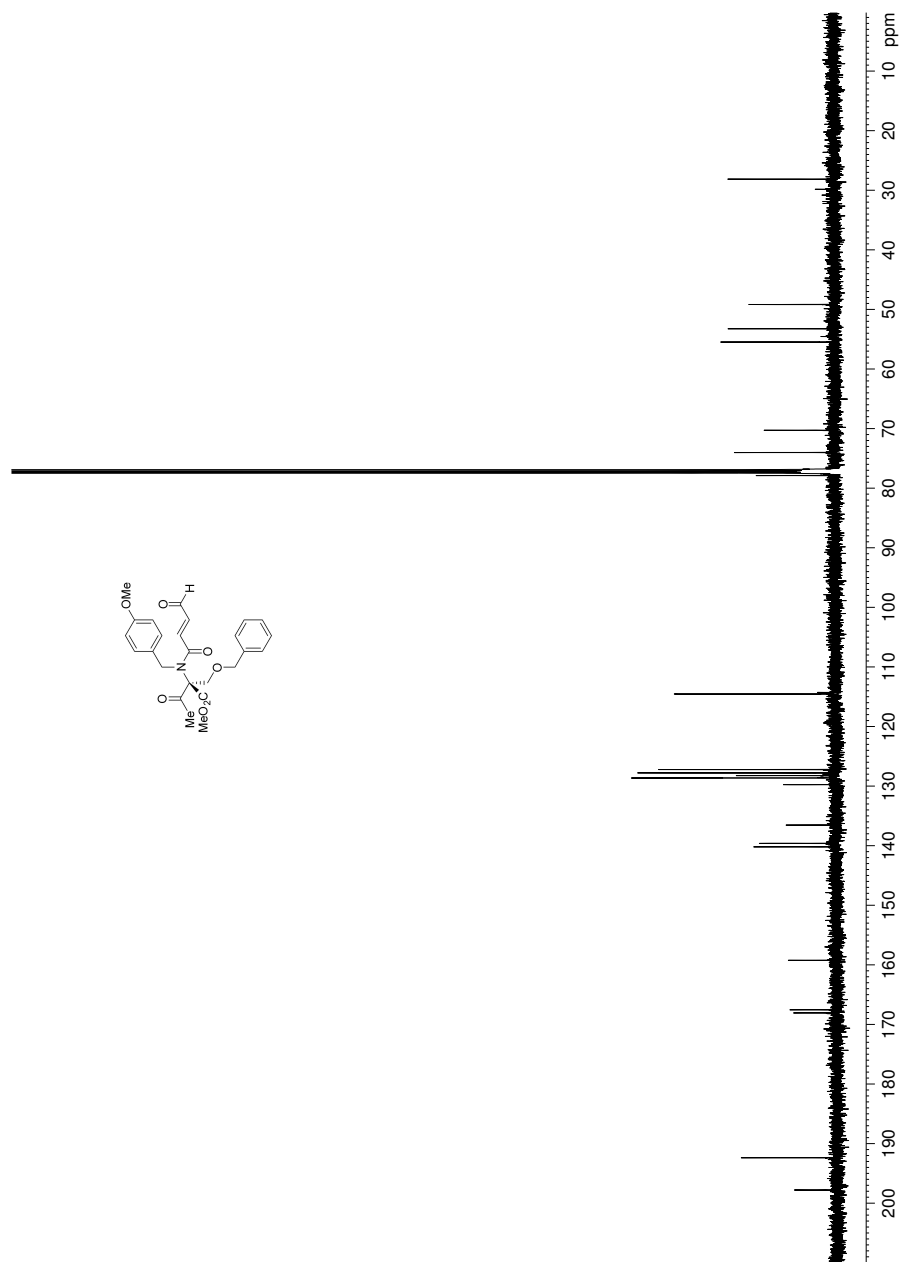
Figure 191. ^{13}C NMR spectrum of compound **225**.
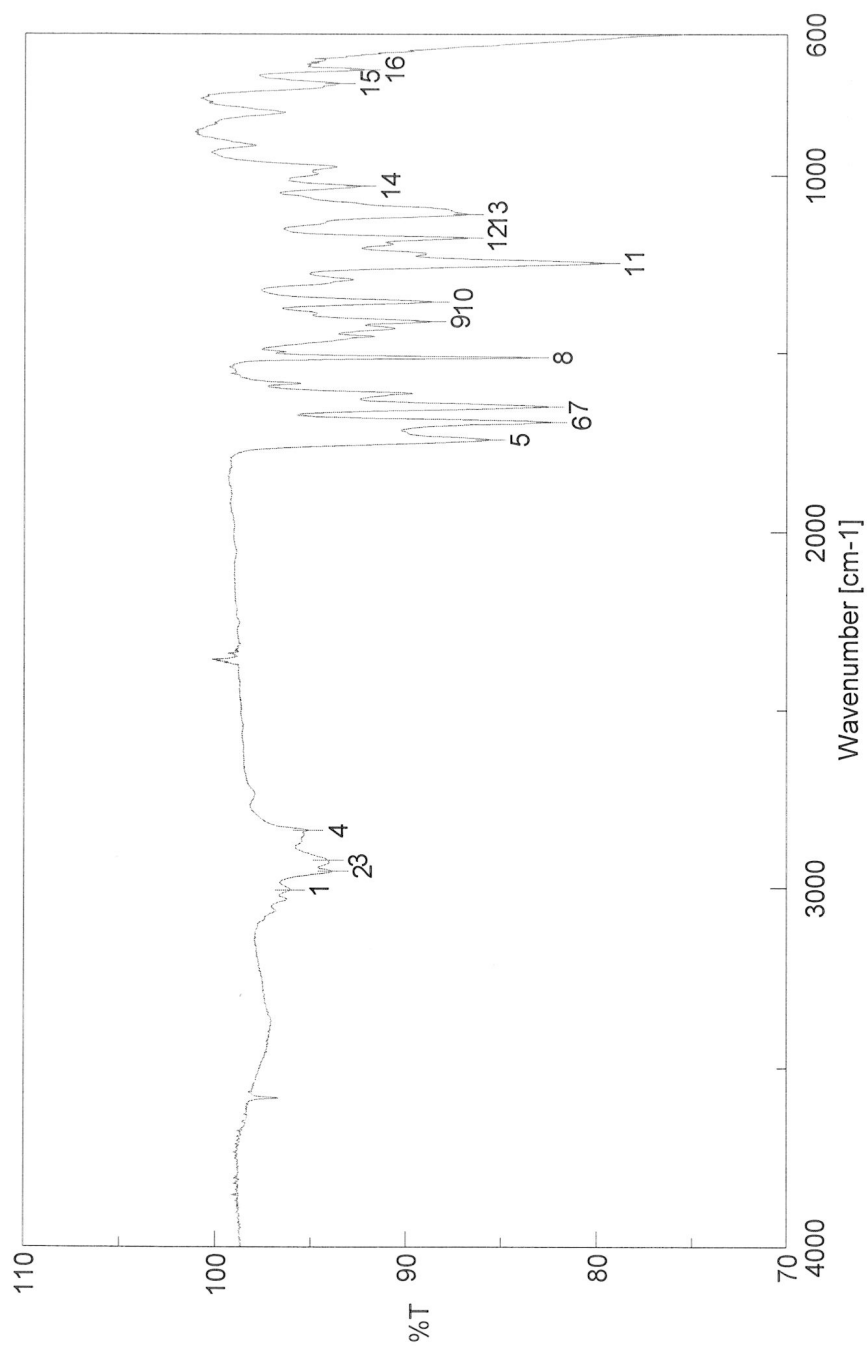
Figure 192. IR spectrum of compound **225**.

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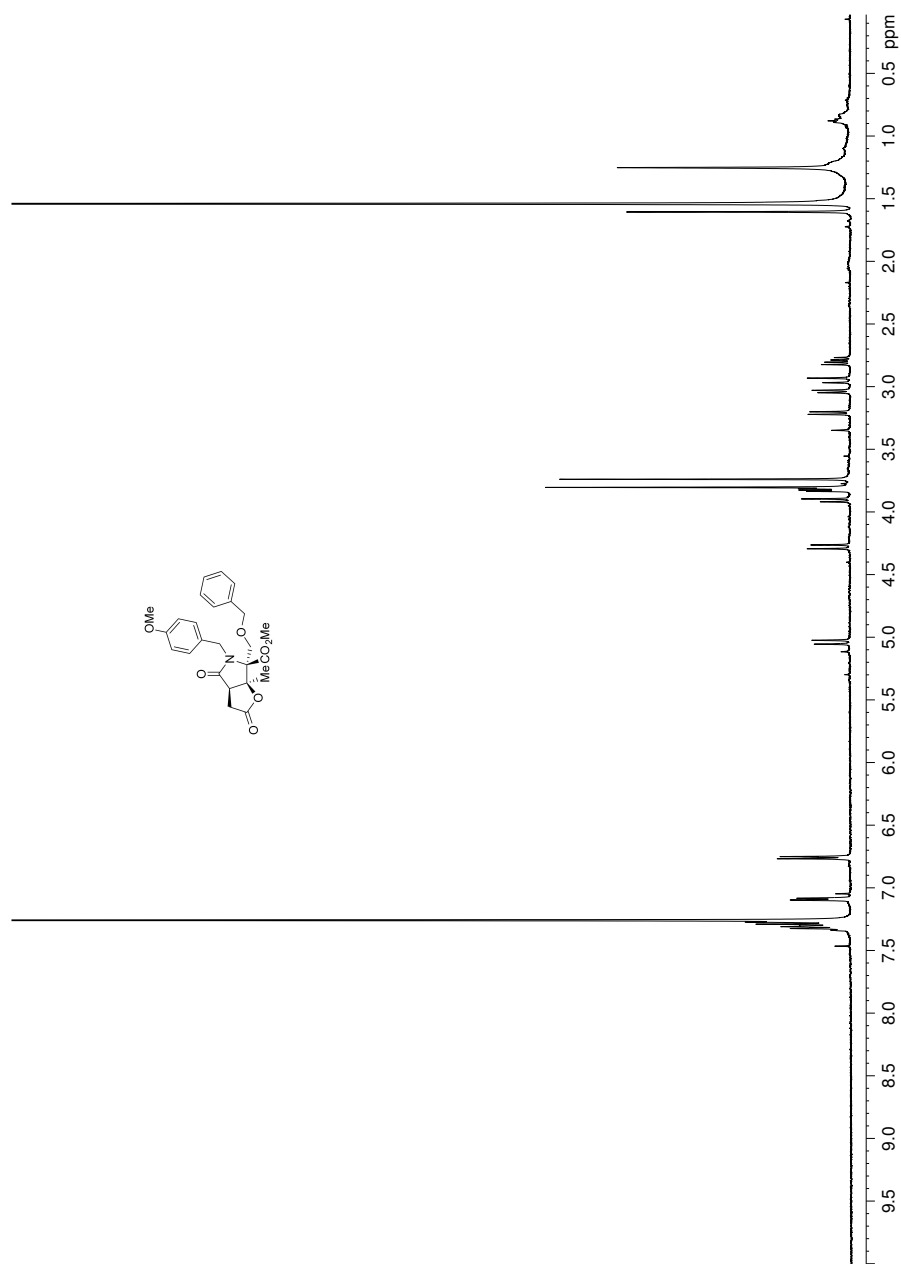
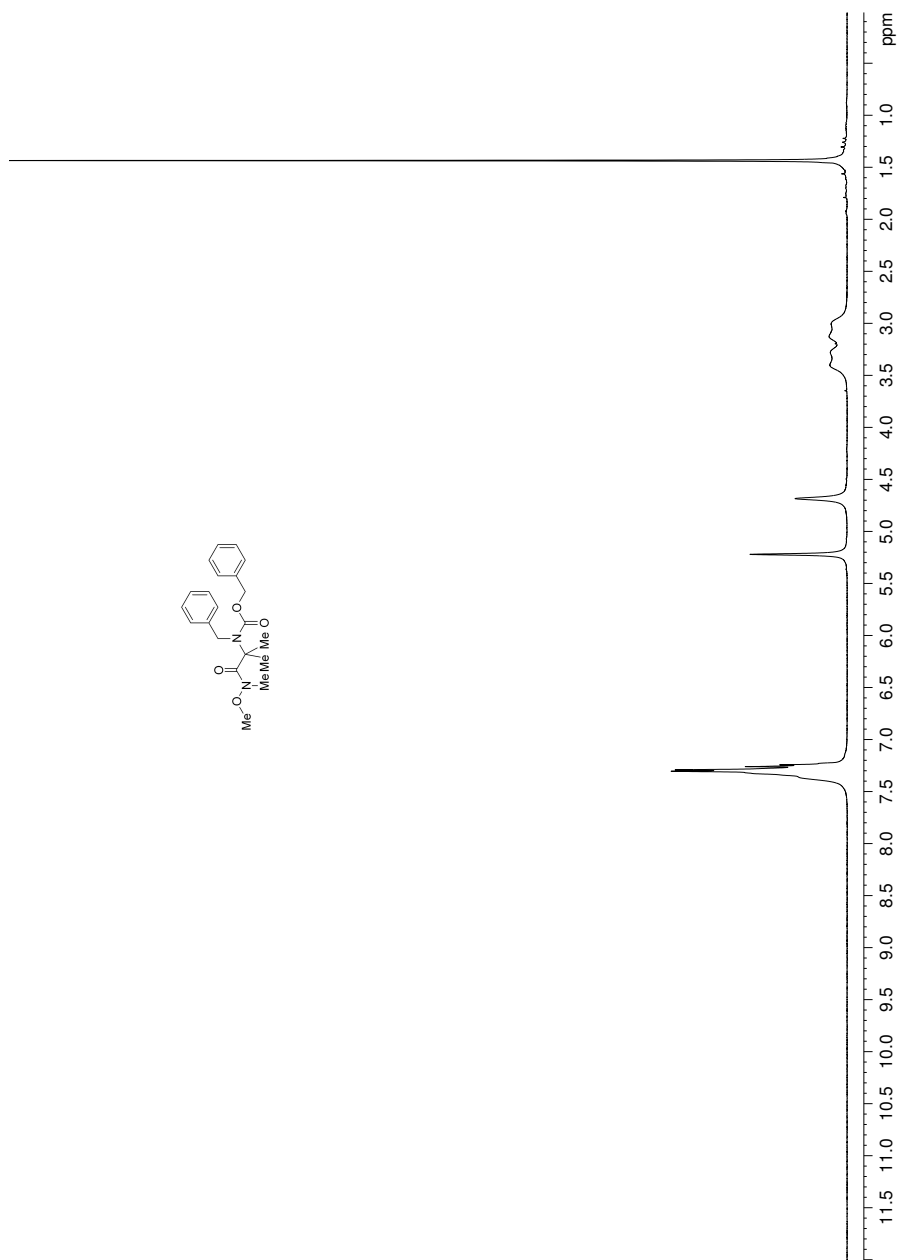**Figure 193.** ^{1}H NMR spectrum of compound **231**.
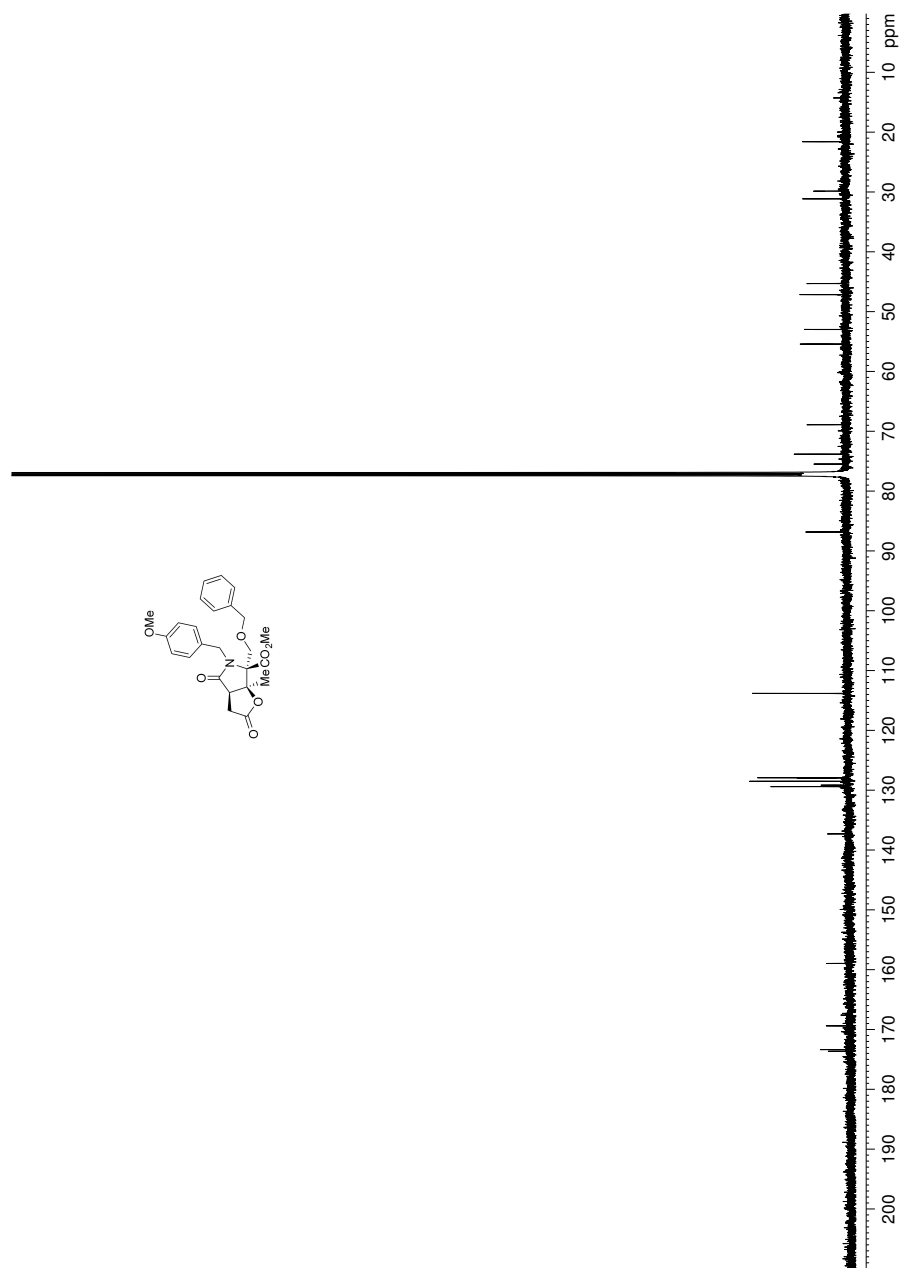
Figure 194. ^{13}C NMR spectrum of compound **231**.
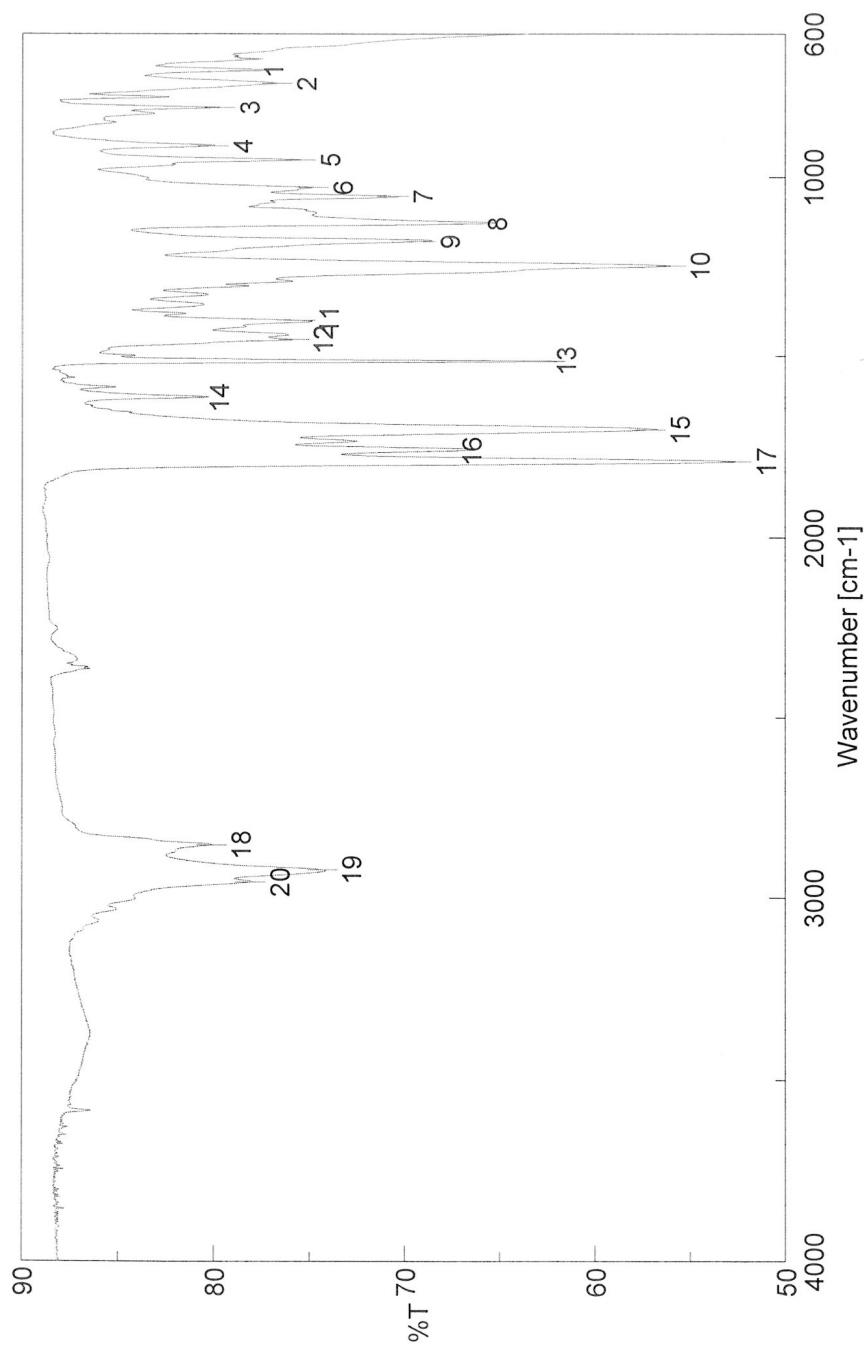
Figure 195. IR spectrum of compound **231**.

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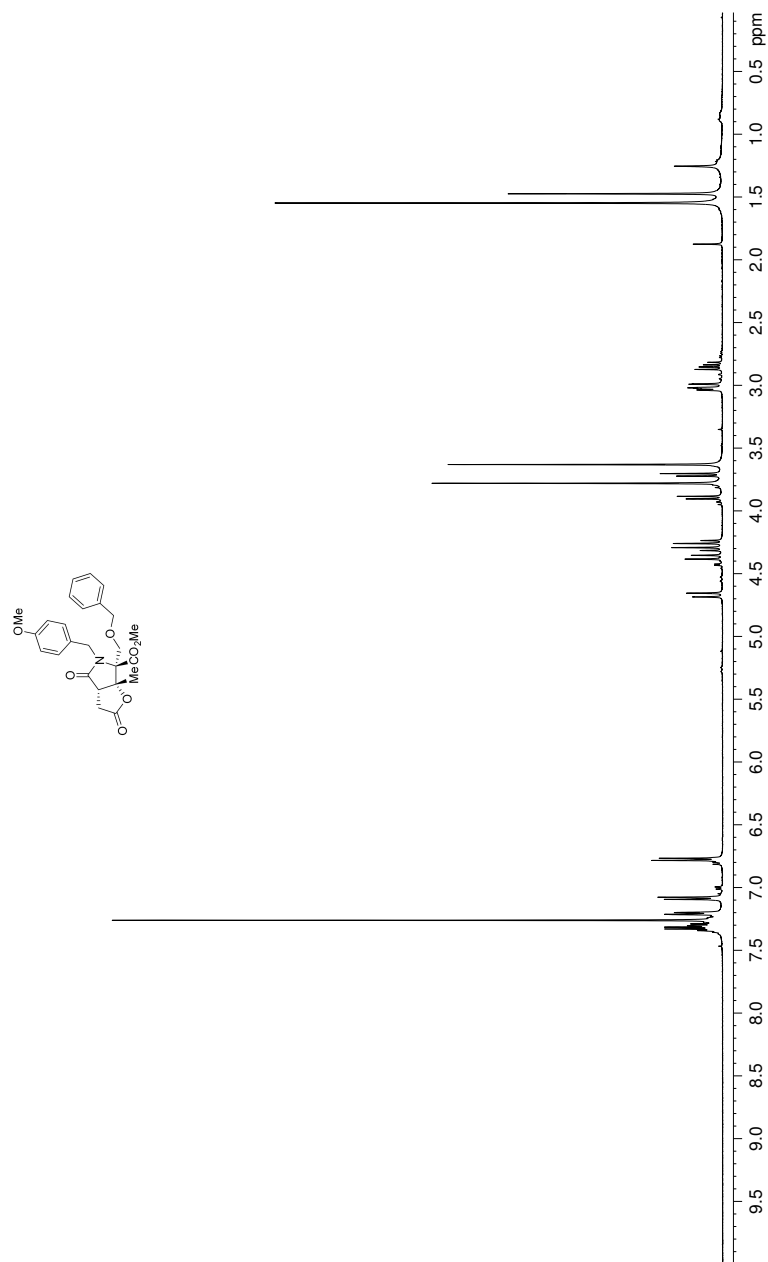
Figure 196. ^{1}H NMR spectrum of compound **232**.
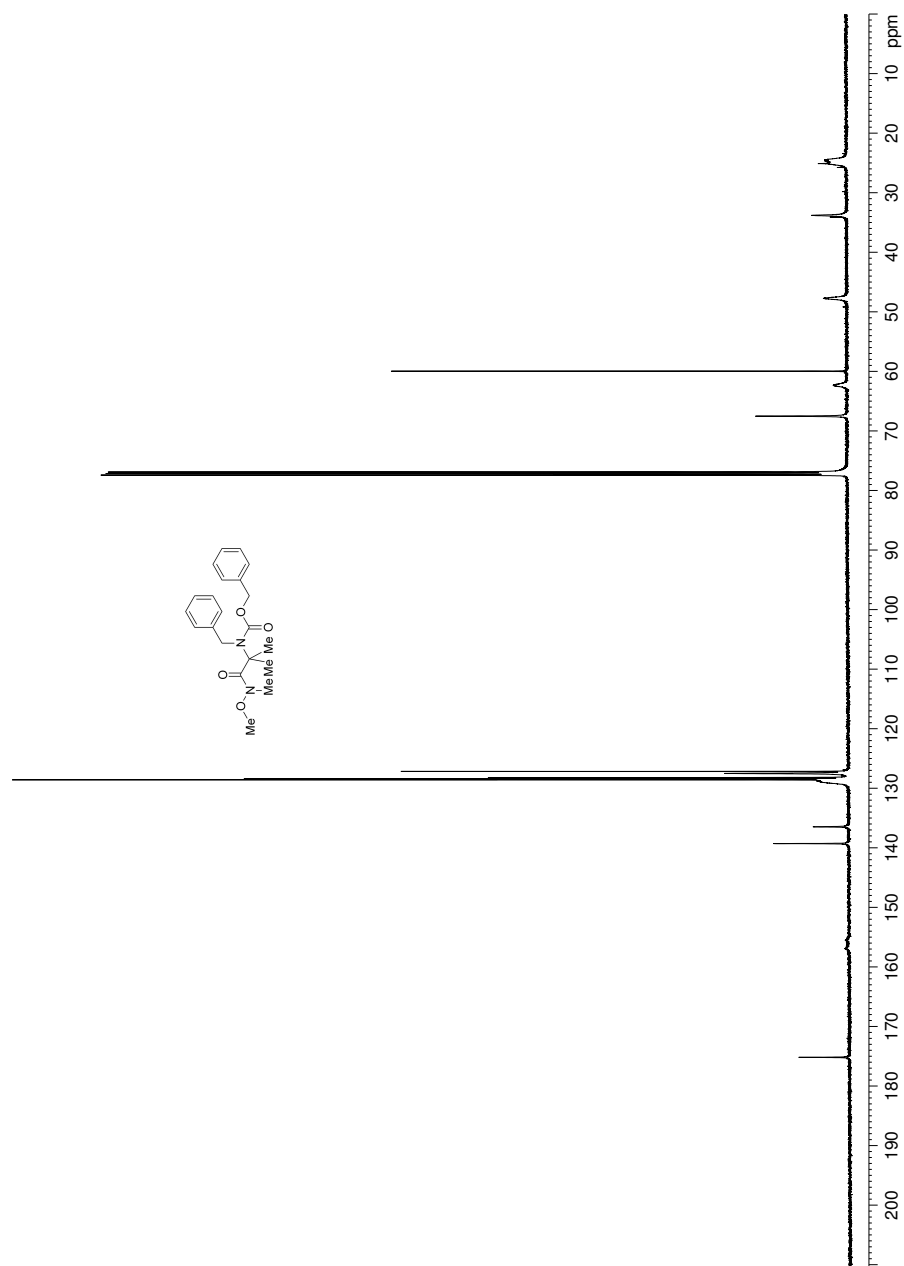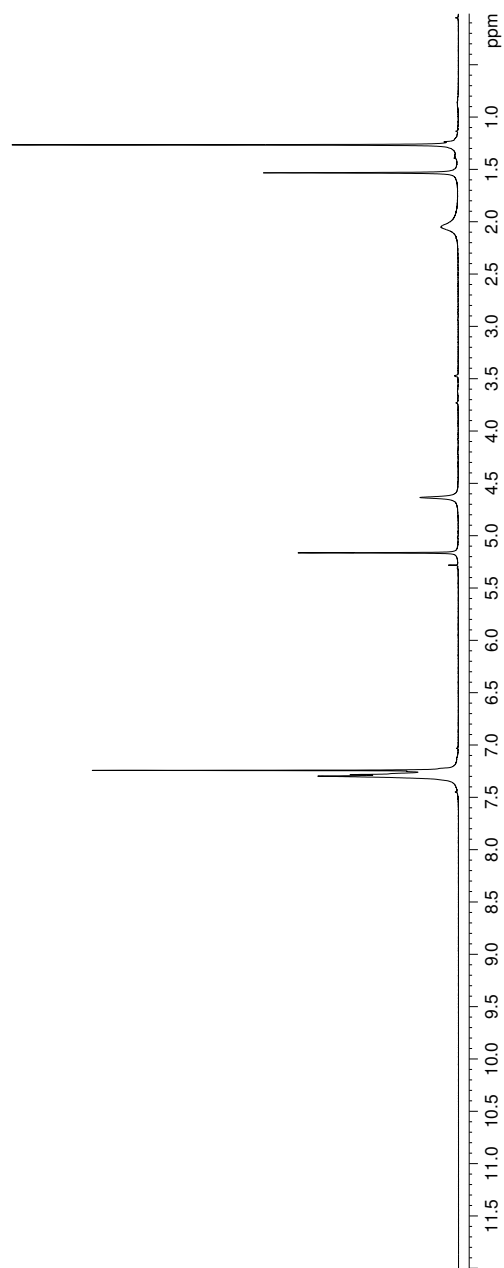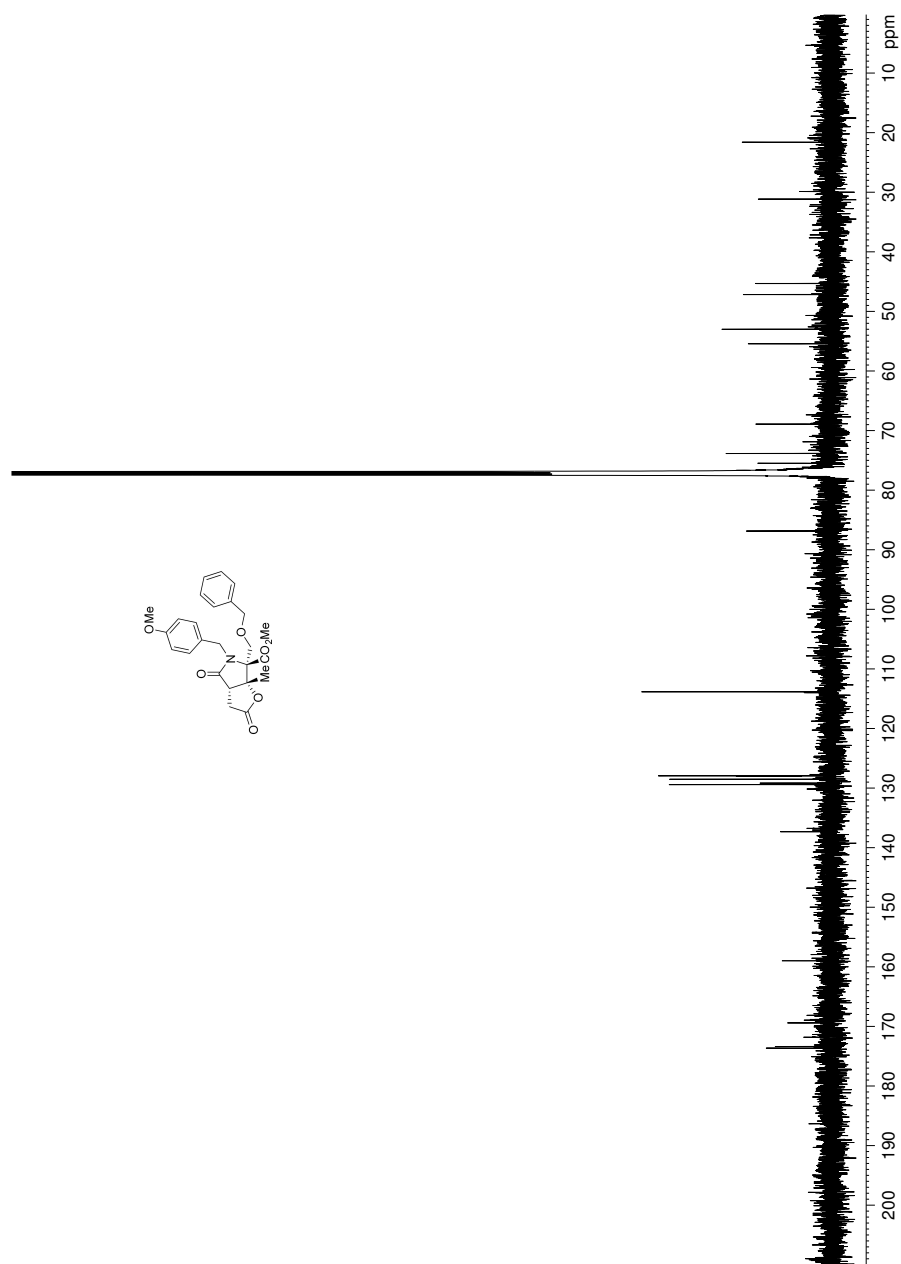
Figure 197. ^{13}C NMR spectrum of compound **232**.

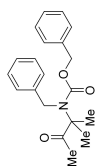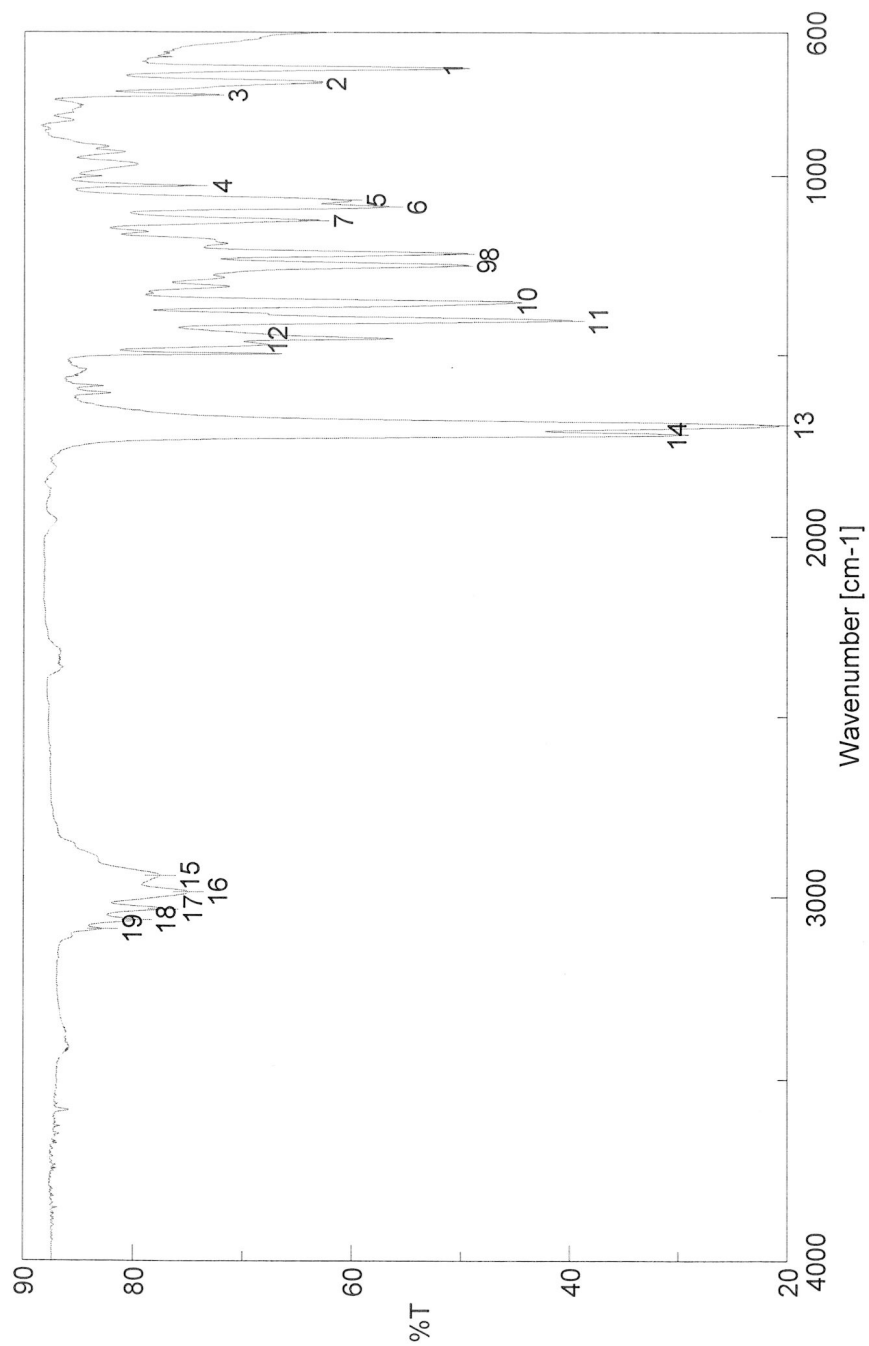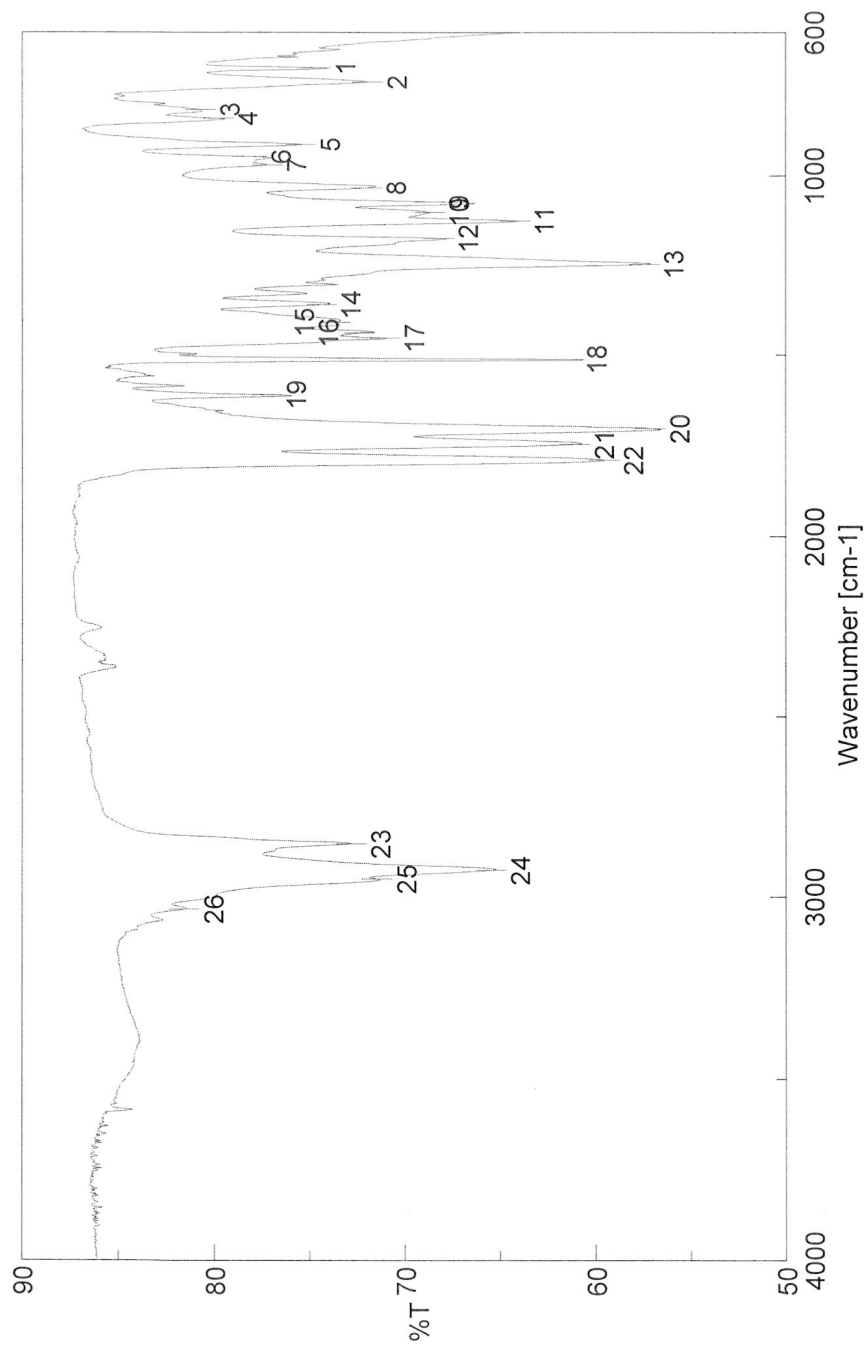**Figure 198.** IR spectrum of compound **232**.

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