Visible-Light Photocatalysis and Studies Towards the Total Synthesis of Sandresolide A

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

Dedicated to my beloved parents

"Research is to see what everybody else has seen, and to think what nobody else has thought"

-Albert Szent-Gyorgyi
1937 Nobel Prize for Medicine

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Abbreviations

abs	absolute	MeCN	acetonitril
AIBN	azo-isobutyronitrile	MLCT	metal-to-ligand charg transfer
Boc	tert-butyloxycarbonyl	min	minute
BuLi	*n-butyl lithium*	MS	molecular sieve
Cat.	catalytic	MV	methyl viologen
CI	chemical ionization	NMR	nuclear magnetic resonance
dr	diastereomeric ratio	NOE	nuclear Overhauser effect
DBU	1,8-Diazabicyclo[4.4.0] undec-7-ene	Nu	nucleophile
DEAD	diethylazodicarboxylate	$^1O_2$	singlet oxygen
DIPEA	di-isopropyl ethyl amine	$^3O_2$	triplet oxygen
DMN	dimethoxy naphthalene	Ph	phenyl
DMF	dimethyl formamide	Pg	protecting group
DMS	dimethyl sulfide	PCC	pyridinium chlorochromate
ee	enantiomeric excess	PET	photon electron transfer
equiv.	equivalents	RCM	ring closing metathesis
ES	excited state	rt	room temperature
Et	ethyl	RB	rose bengal
EY	eosin Y	SAR	structure-activity relationship
h	hour	SET	single electron transfer
HAT	histone-acetyl-transferase	SOMO	singly occupied molecular orbital
HPLC	high pressure liquid chromatography	TBDMS	*tert-butyldimethylsily*
		TBAF	tetrabutylammonium fluoride
HRMS	high resolution mass spectrometry	TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
		^{t}*Bu*	*tert-butyl*
HWE	Horner-Wadsworth-Emmons	TES	triethylsilyl
^{i}*Pr*	*iso-propyl*	THF	tetrahydrofuran
IR	infra red	TMS	trimethylsilyl
LAH	lithium aluminium hydride	Tf	trifluormethanesulfonate
LED	light-emitting diode	Ts	tosyl
m-CPBA	*m-chloroperbenzoic acid*	quant	quantitative
Me	methyl	UV	ultraviolet

Part I
Visible Light Photocatalysis

1. Introduction

1.1 Basic concept of photochemistry

Every chemical reaction occurs only when a molecule is provided the necessary activation energy. A simple example is the combustions of hydrocarbons into carbon dioxide and water. In this reaction, the activation energy is provided in the form of heat or a spark. When activation energy is provided in the form of light then the reaction is known as photochemical reaction. Photochemistry, a sub-discipline of chemistry, is the study of the interactions between atoms or molecules with light. In our day-to-day life many important processes involve photochemistry. The foremost example is photosynthesis, in which most plants use the sunlight to convert carbon dioxide and water into glucose and release oxygen as a side product. Not only plants but human also rely on photochemistry for the formation of vitamin D with sunlight. Often medicine bottles are made with darkened glass or labeled with 'keep away from light', which is necessary to prevent the drugs from photodegradation.

Light is another form of electromagnetic radiation, a source of energy. The Grotthuss-Draper law states that only the light that is absorbed by a system or molecule can bring about a photochemical change or photochemical reaction. Materials such as dye or phosphorus must be able to absorb light at optical frequencies. The Stark-Einstein law says that every photon that is absorbed will cause a chemical or physical reaction. The Franck-Condon principle says that the heavy atom nuclei do not change their positions, this leads to an initial geometry of the excited state which is usually not the energy minimum. During excitation the electron spin remains unchanged. Spin inversion during excitation is forbidden by quantum mechanics and therefore unlikely.

Right after the excitation several things may happen. (1) Vibronic relaxation brings the molecule quickly into the new energy minimum structure for the excited state. Energy is released into the solvent. (2) Intersystem crossing leads to triplet states by spin inversion. Again, the new energy minimum is reached by vibrational relaxation. (3) Emission of light and return to the ground state (luminescence, fluorescence, phosphorescence). (4) Quenching of the exited state: energy is transferred to another molecule. Usually diffusion controlled dynamic quenching by collision is observed. (5) Radiation less

deactivation. Molecule goes back to ground state by vibrational (thermal) deactivation (no light emission). The energy goes to the solvent/environment of molecule.

At the molecular level there are many reasons that make photochemistry interesting. 1) The excited states are rich in energy. Therefore, the reactions that may occur can be highly endothermic in the ground state. Using the equation $E = h\nu$ we can correlate light of a wavelength of 350 nm with an energy of 343 kJ/mol. 2) In the excited state antibonding orbitals are occupied. This may allow reactions that are not possible for electronic reasons in the ground state. 3) Photochemical reaction can include singlet and triplet states, while thermal reactions usually only show singlet states. In photochemical reaction intermediates may be formed which are not accessible at thermal conditions. But for all those things to happen the most important criteria are that a molecule must absorb the photon and there should be a proper source of light to provide the photon of particular energy it requires to excite.

A molecule absorbs visible and/or ultraviolet light, which introduces energy to recognize or break most covalent bonds. The equation $E = hc/\lambda$ tells us that longer wavelength visible light (400-800 nm) is less energetic than light in the accessible shorter wavelength (200-400 nm) near ultraviolet region (Fig. 1).

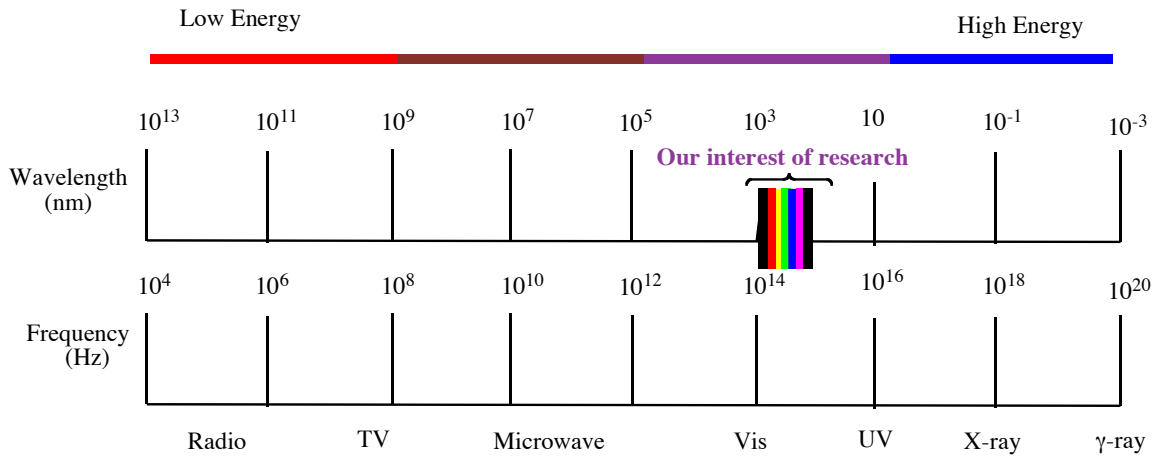


Fig. 1: Energy and wavelength relationship of light (self drawn).

Consequently, ultraviolet light is most often used to effect photochemical change. It is also important to construct lamps and reaction vessels from glass that is transparent to the desired wavelength so that the light reaches to the targeted functional group without

being blocked by the medium, the reactor. Quartz is used for both, reactor as well as lamp (cut off < 170 nm) otherwise filter of pyrex (cut off < 275 nm), corex (cut off < 260 nm) or vycor (cut off < 220 nm) is necessary to remove unwanted wavelengths.

Reactant molecule is elevated to excited state by directly absorbing photon from the light source. If the reactant molecule is not able to absorb the required photon or if the required light source of certain wavelength is not available then a photosensitizer is employed, which absorbs the photon and transfer the energy to the reactant. This process in known as photosensitization. In general inorganic metal complexes and organic dyes are employed as photosensitizers. The reverse process is called quenching when a photoexcited state is deactivated by a chemical compound.

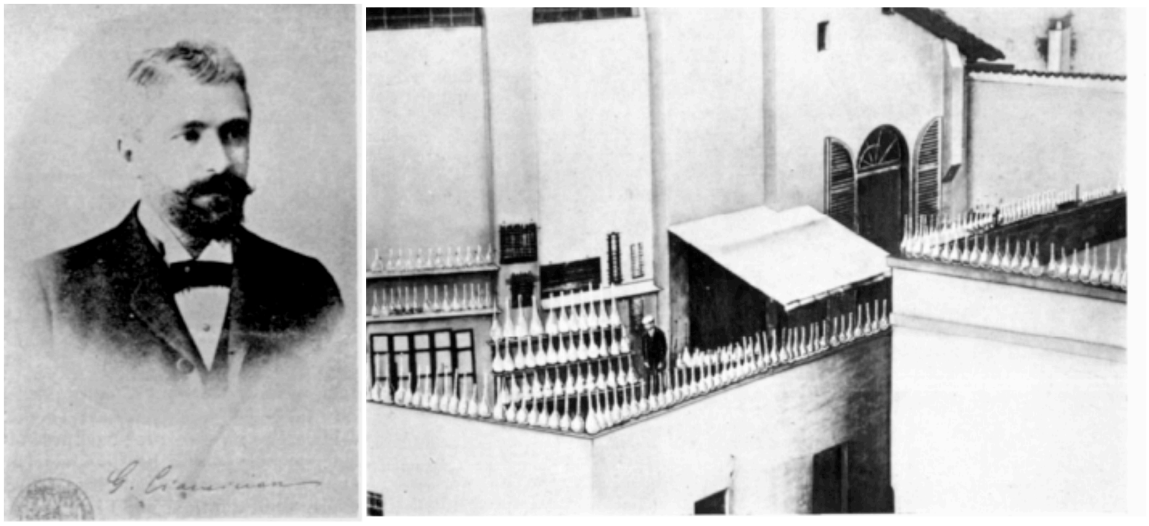
1.2 Historical background

Inspired by the ability of plants to make use of solar energy, Giacomo Ciamician (professor of chemistry at the university of Bologna, Italy from 1889-1922) was the first scientist to investigate the photochemical reaction in a systematic way. He is known as the father of photochemistry. He clearly understood the importance of sunlight, as apparent by the following words: *"there is another agent that has a profound effect on the processes of organisms and that deserves to be deeply investigated: that is light"*.[1a-b]

He realized that chemistry is a central science that permeates many other field of knowledge, and that can play an essential role in solving the four greatest problems of humanity: food, health, energy and environment. Specifically, his thought on the energy problem are very close to those discussed in present days. He strongly recommended to replace fossil fuels (i.e., coal) with the energy that the earth receives from the sun everyday. In particular, he forecasted the production of fuels by means of artificial photochemical reactions (artificial photosynthesis), which is still one of the most important goals of current research in the field of chemistry.

Considering the secret of complex chemistry of plants resides in the use of light, he undertook to study in a systematic way what he called "the chemical action of light". He not only published many important results, but also he enjoyed very much working with light. He joked about the unexpected behavior of some photochemical reactions- " *In ordinary….chemistry the reactions take place in some definite way, but the*

photochemical reactions often furnish surprises…..".[1b] During his researches Ciamician met also an experimental difficulty. In order to perform photochemical experiments, a suitable light source is essential. Nowadays scientists are engaged in this research field by using powerful halogen, mercury and tungsten lamps with light filters that allow the selection of almost monochromatic light beams or LEDs. In most cases, also continuous or pulsed laser sources are now routine equipment in photochemical laboratories. At the beginning of the last century, however, halogen, mercury, LED and laser light sources were not yet available and the light emitted by the tungsten lamps was too faint and too "red" to induce photochemical reactions. Since the sun was the only convenient light source for his photochemical experiments, the balconies of the institute where Ciamician worked were the most suitable place for his laboratory (Fig. 2), and he was quite happy



a b

Fig. 2: (a) Prof. Giacomo Ciamician (1857-1922), (b) Giacomo Ciamician surveys his collection of tubes and flasks exposed to the sun on the balcony of his institute[1a] (Images are taken from ref. 1a with the permission of Prof. M. Venturi and Prof. V. Balzani, Bologna, Italy; authors of ref 1a).

about that: *"Whoever saw Ciamician in his laboratory balcony, where hundreds of bottles and glass pipes containing various substances and mixtures were exposed to the sun rays, and heard him speaking of his results and projects, can say how happy he was. But only who worked with him can know how much work he had to do, how much*

patience he had to have, how able he had to be, how much nose he had to have, ... to isolate and characterize the products of very complex reactions ..."[1b]

1.3 Visible light an indefinitely renewable source for chemical reactions

Fossil fuels supply energy for transportation, industrial manufacturing, heating of buildings, and the production of electricity. Thus consumption of fossil fuels generates urgent and serious problems such as global climate variation, environmental pollution and natural sources depletion. However, the reserves of coal, oil, and natural gas are limited; in fact, they are called nonrenewable energy resources, because once the supplies that are available are used up, they cannot be replaced. It is predicted that at the current rate of energy consumption, available reserves of oil and natural gas will be greatly decreased during the twenty-first century. Coal is more plentiful, but its use can contribute to environmental problems such as global warming (an increase in Earth's temperature over time). Because of growing energy demands in developing nations as well as the energy needs of industrialized societies, it will become increasingly necessary to turn to alternative sources of energy in the future. Conserving energy and using it more efficiently are additional ways of addressing the energy problem. Giacomo noticed that the enormous quantity of energy that the earth received from the sun, in comparison with the part that is being stored by the plants in the geological periods, is largely wasted. The exploitation of solar light first of all involved the best use of cultivable lands in order to afford both food and (renewable) starting materials for the chemical industry. The conversion of solar energy could be improved by modern agriculture to afford enough food for mankind. Furthermore, plants could be used as a chemical laboratory. As for non-cultivable land, such as that exposed to a high amount of solar energy like the Sahara desert (which receives daily solar energy equivalent to five times the annual production of coal), suitable photochemical plants could be set up for the production of simple compounds such as ozone or sulfur trioxide (to be used as reagents), for organic synthesis or for producing electrical energy by batteries based on photochemical processes. The Earth receives 174 petawatts (1 petawatt = 10^{15} watts) of incoming solar radiation at the upper atmosphere. Approximately 30% is reflected back to space while the rest is absorbed by clouds, oceans and land masses. The spectrum of solar light at the Earth's

surface is mostly spread across the visible and near infrared ranges with a small part in the near ultraviolet (Fig. 3). Therefore, the use of visible light as a promoter in synthesis is very appealing because of its natural vast abundance. Apart from that handling visible light (compare to UV light) is very easy and safe and it can be potentially applied on an industrial scale.

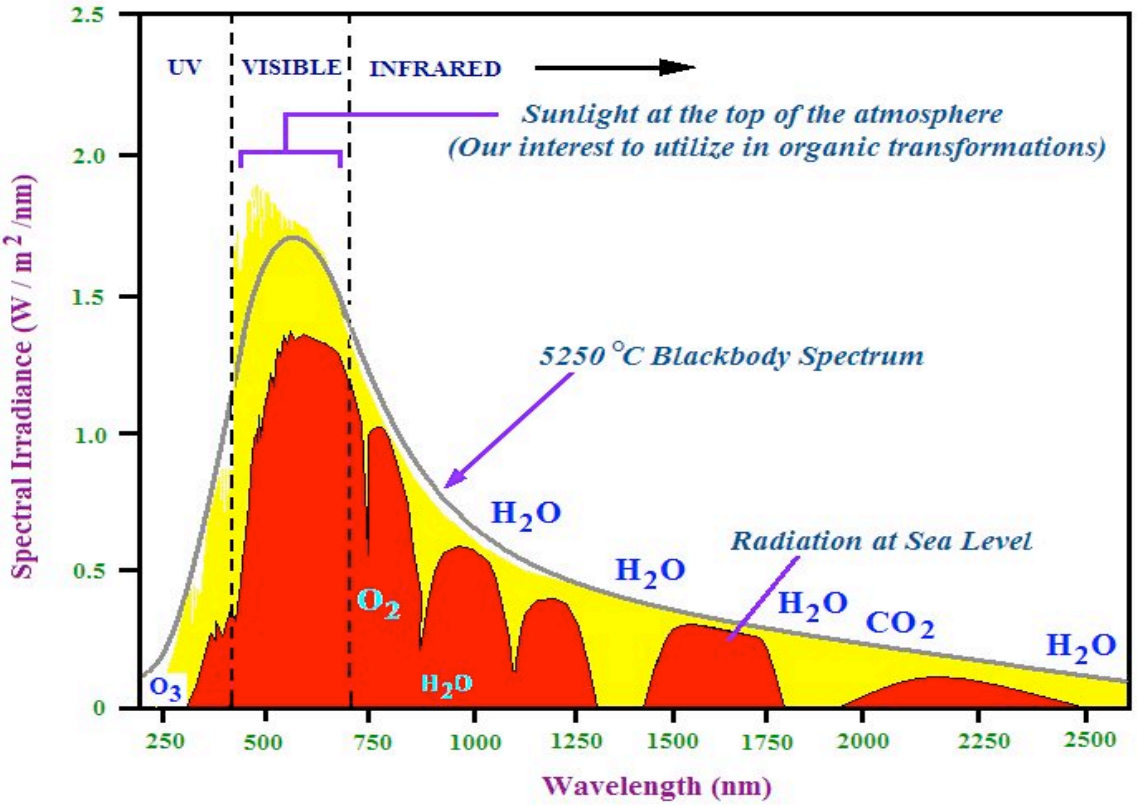
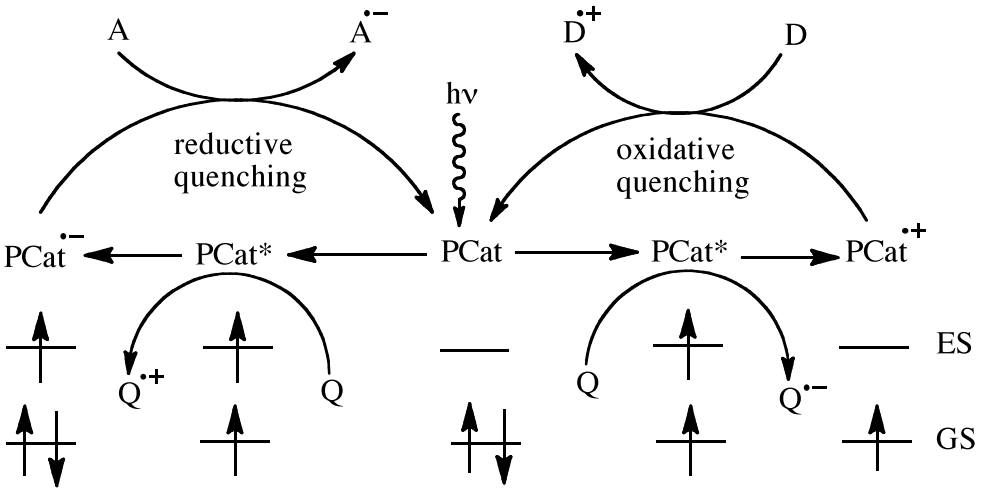


Fig. 3: Solar radiation spectrum (self drawn).

1.4 Recent advancement in visible light photocatalysis

Necessity is the mother of invention. The increasing need for more economical synthetic methods and sustainable processes can be seen as a key driving force for new inventions that inspires the creative rethinking of known concepts, which lead to the development of novel chemistry. The infinitely available, easily handled and environmentally friendly visible light makes it attractive for chemists to promote it for green chemical reactions. One obstacle is the requirement for specialized photoreactors to generate high intensity UV light or to concentrate natural sunlight.[2] Thus it is particularly important to develop efficient method for the utilization of visible light to perform chemical reactions.

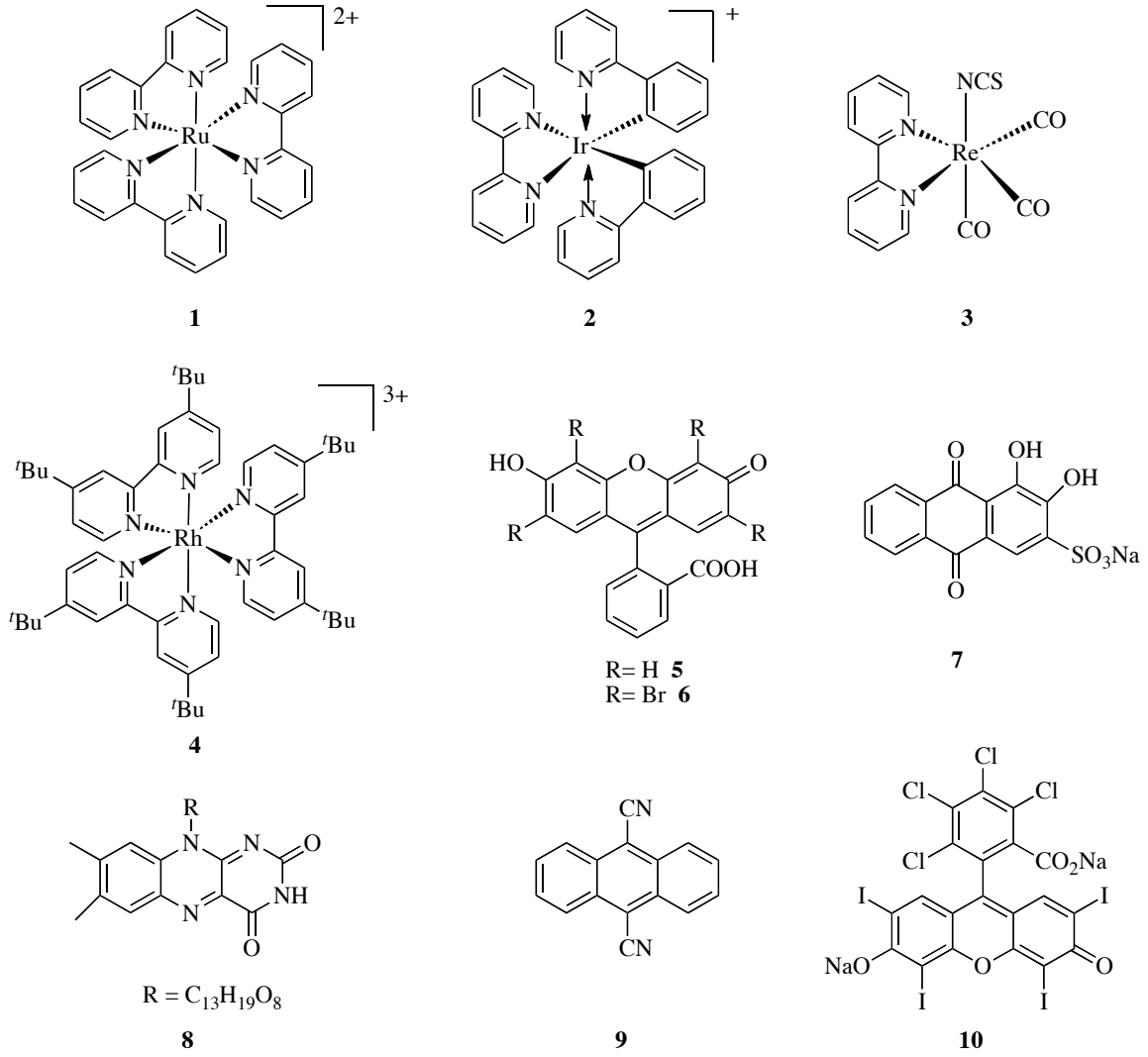
However, the lack of visible light absorption by many organic molecules has limited the potential application of photochemical reactions. One major approach to address this barrier and to develop new efficient processes using visible light is the use of photosensitizers and photocatalysts by utilizing their electron/energy transfer processes to sensitize organic molecules to carry out required photochemical reactions[3]. Photoredox catalysis relies on the general property of excited states to be both more easily reduced as well as more easily oxidized than their corresponding ground states, and so the photocatalyst can serve either as an electron donor or an electron acceptor to be regenerated in the catalytic cycle (Scheme 1). Photo-excitation of a photocatalyst (PCat) by an appropriate wavelength gives an excited species with higher energy electron (PCat*), which may be converted to a radical cation ($PCat^{\cdot+}$) by donating an electron to the quencher (Q).



Scheme 1. Photoredox catalysis by oxidative and reductive pathways with the electronic state of the catalyst. PCat = photocatalyst, Q = quencher, D = donor, A = acceptor, GS and ES = ground state and excited state of photocatalyst respectively.

The quencher upon 1e-reduction results in a stable anionic radical ($Q^{\cdot-}$), which undergoes reductive transformations. For completing the photocatalytic cycle, the cationic radical species of the photocatalyst ($PCat^{\cdot+}$) accepts an electron from the donor molecule (D) and comes back to the ground state and get ready for next cycle (oxidative quenching) . The

oxidative transformation occurs when the reverse process takes place, in which the photoexcited catalyst (PCat*) accepts an electron from the quencher and then donates the same to an accepter molecule (A) with return to the ground state and completion of the catalytic cycle (reductive quenching). Depending upon the nature of the quencher, i.e. donor or acceptor, it is possible to use the photocatalyst both in oxidative as well as in reductive pathways.



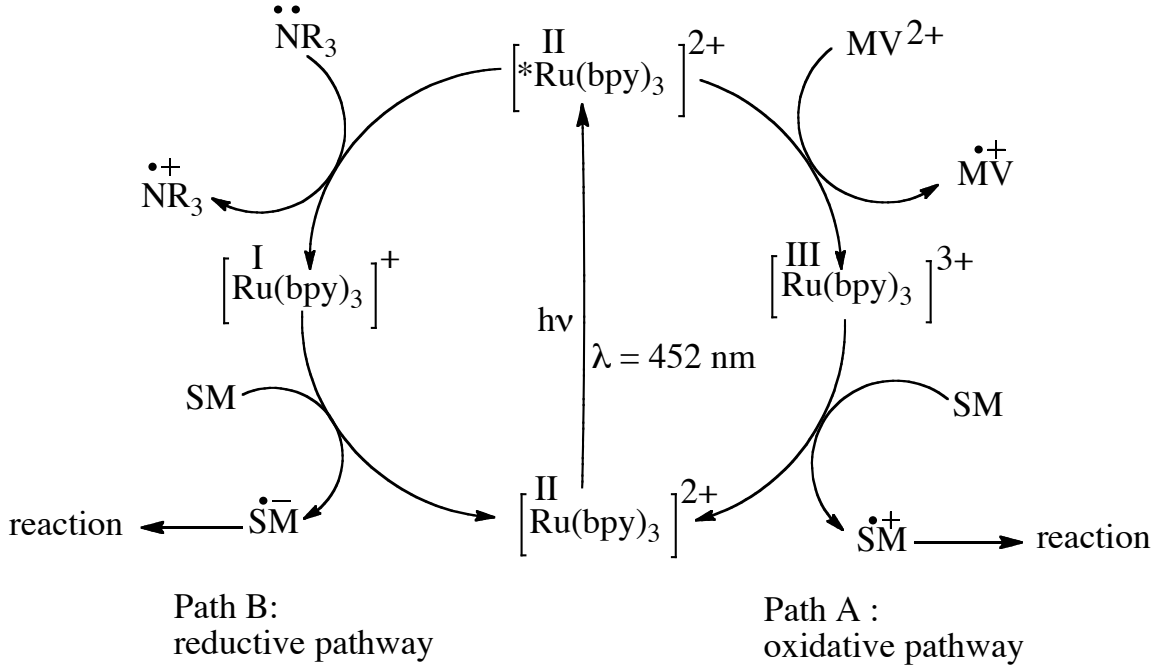
Scheme 2: Inorganic and organic photoredox catalysts.

A number of inorganic compounds such as TiO_2, CdS, $Ru(bpy)_3Cl_2$ (**1**), $Ir(ppy)_2(dtbbpy)PF_6$ (**2**), $Re(bpy)(CO)_3SCN$ (**3**), $Rh\{4,4'(^tBu)_2bpy\}_3$ (**4**) are used as visible light photocatalysts. Besides inorganic compounds, organic compounds are also

used as visible light photocatalyst, a few of these are fluorescein (**5**), eosin Y (**6**), alizarin red S (**7**), flavin (**8**), 9,10-dicyanoanthracene (**9**), rose bengal (**10**) etc (Scheme 2).

$Ru(bpy)_3Cl_2$ as photocatalyst

Current research has focused on the use of the widely applicable and greatly studied organometallic ruthenium (II) polypyridine complexes (e.g., $[Ru(bpy)_3]^{2+}$), which are superior photoredox catalysts not only because of their absorbance in the visible range (λ_{max} = 452 nm), but also because of their unique properties in terms of chemical stability, excited-state lifetimes (originating from metal-to-ligand charge-transfer (MLCT)), and their favorable redox potentials in the excited state that can be tuned by the adjacent ligands.[4] Moreover, $Ru(bpy)_3Cl_2$ can readily accept a photon from a variety of light sources to populate the $*[Ru(bpy)_3]^{2+}$ metal-to-ligand charge transfer (MLCT) excited state (Scheme 3). $*[Ru(bpy)_3]^{2+}$ can function as a reductant or an oxidant depending upon the conditions employed and the proper selection of the quencher (Scheme 3).

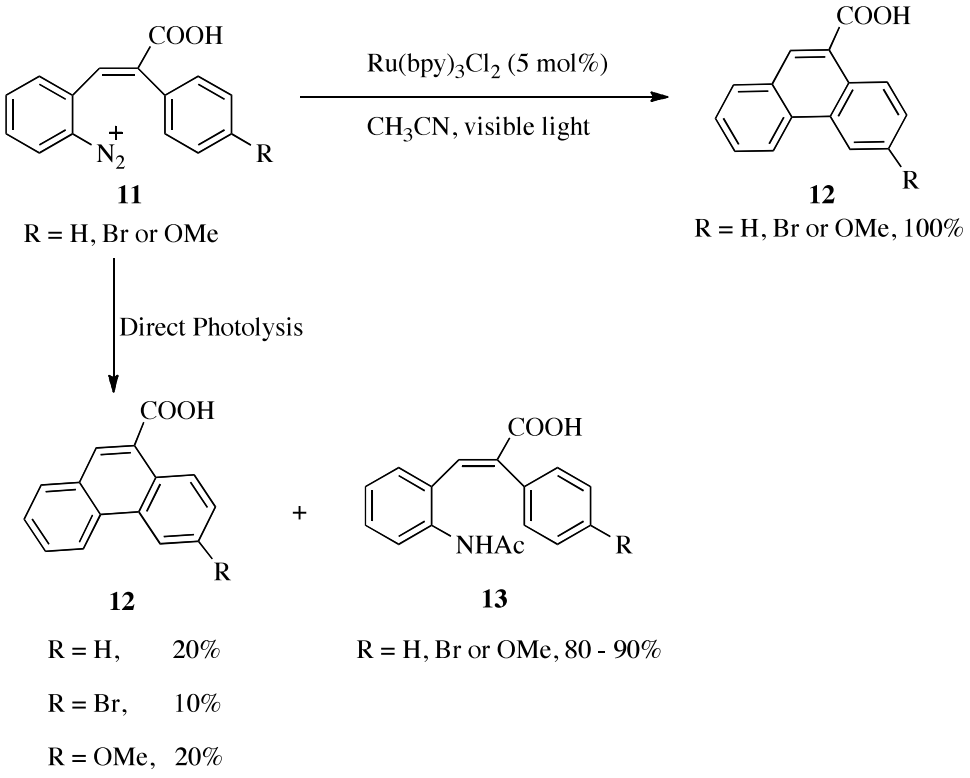


Scheme 3: Reductive and oxidative photocatalytic cycles of $Ru(bpy)_3Cl_2$.

Oxidative quenching of $*[Ru(bpy)_3]^{2+}$ by $S_2O_8^{2-}$, Ar-NO_2, or methyl viologen (MV^{2+})

provides $[Ru(bpy)_3]^{3+}$, a strong oxidant (+1.29 V *vs*. SCE = Standard Calomel Electrode, in CH_3CN), which can easily oxidized reactant molecules to their radical cations (SM to SM^{+}) (Path A, oxidative quenching). While the interaction of $*[Ru(bpy)_3]^{2+}$ with reductive quenchers (e.g., tertiary amine (NR_3), oxalate, xanthate, ascorbate) generates $[Ru(bpy)_3]^{+}$, a strong reducing agent (-1.33 V *vs*. SCE in CH_3CN), which is able to transform reactants to their radical anions (SM to SM^{-}) (Path B, reductive quenching).[5]

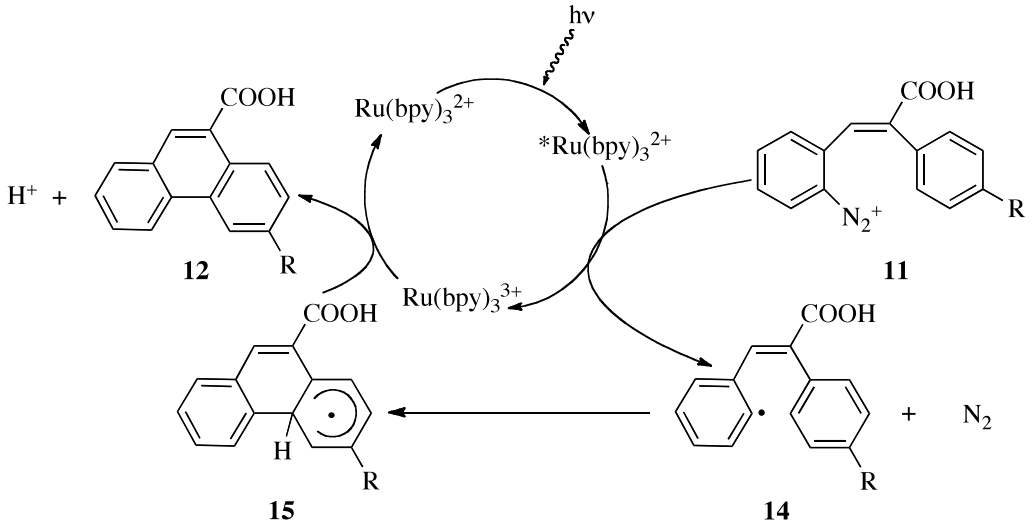
In spite of the excellent photoredox properties and their ease of preparation from commercially available precursors, tris(bipyridine) ruthenium complexes have been paid very little attention from synthetic organic chemists. In 1984, Cano-Yelo and Deronzier reported one of the first examples, representing a photocatalytic Pschorr reaction for the synthesis of phenanthrene and substituted phenanthrenes (Scheme 4).[6] The Pschorr reaction involves an intramolecular arylation upon reduction of a diazonium salt by a reducing agent, electrochemical reduction, or simple heating.[7]



Scheme 4: Photocatalytic Pschor reaction.

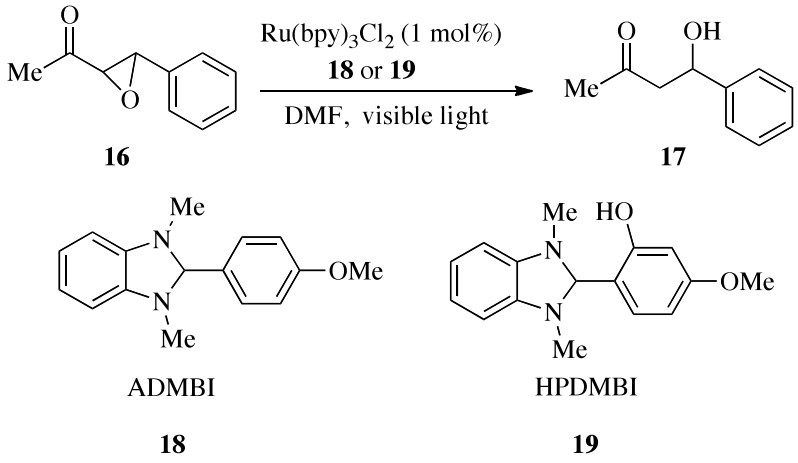
As the starting material **11** was used for the photocatalytic Pschorr reaction; visible light irradiation of **11** in the presence of $Ru(bpy)_3^{2+}$ in acetonitrile produced phenanthrene

carboxylic acid **12** in quantitative yield. The proposed mechanism of this reaction is outlined in Scheme 5. Excitation of $[Ru(bpy)_3]^{2+}$ by visible light generates $*[Ru(bpy)_3]^{2+}$ $\{Ru(bpy)_3^{3+}/ *Ru(bpy)_3^{2+} = -0.86$ V *vs*. SCE$\}$ which transfers an electron to **11** ($E1/2 = -0.1$ V *vs*. SCE in CH_3CN) to produce the aryl radical **14**. Intramolecular radical arylation furnishes radical **15** which undergoes oxidation by $[Ru(bpy)_3]^{3+}$ and subsequent deprotonation to give **12** while regenerating the catalyst $[Ru(bpy)_3]^{2+}$.



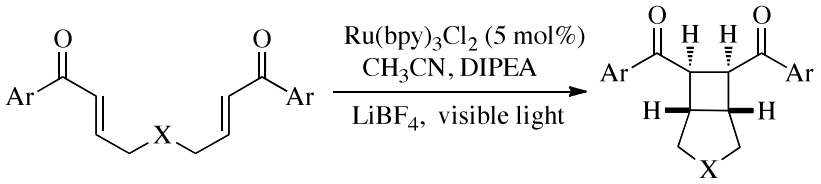
Scheme 5: Mechanism of Pschorr reaction.

In 2006, Hasegawa and *et al*. reported the photocatalytic reductive opening of Cα–O bonds of ketoepoxides to afford β-hydroxy ketones.[8] They used *N,N*-dimethylbenzimidazolines (Scheme 6, compound **18** or **19**) as sacrificial electron and hydrogen atom donors. The low oxidation potentials of ADMBI **18** (+0.28 V *vs*. SCE) and HPDMBI **19** (+0.30 V *vs*. SCE) suggest that the reaction is occurring *via* reductive quenching of $*[Ru(bpy)_3]^{2+}$ to $[Ru(bpy)_3]^{+}$. Protonation of the ketone allows single electron transfer from $[Ru(bpy)_3]^{+}$ to the π*-orbital of the carbonyl group of **16**. Subsequent opening of the epoxide and hydrogen atom abstraction affords the observed β-hydroxy ketone **17**. Although only moderate yields and conversion was achieved, this reaction demonstrates the potential of $[Ru(bpy)_3]^{+}$ as a useful reducing agent.



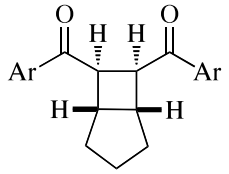
Scheme 6: Ring opening of epoxide by reductive photocatalysis.

Pioneering studies by Krische *et al*. demonstrated that bis-enones could undergo copper- and cobalt-mediated single electron transfer to initiate formal [2+2] cycloaddition reactions.[9] Inspired by this work, in 2008, Yoon and co-workers applied Ru-based photoredox catalysis with visible light to generate the required radical anion intermediate from the corresponding aryl enones.[10] The electron donor diisopropylethylamine (DIPEA) was used to generate the reductive Ru^{+} species. Upon irradiation with simple visible-light sources or sunlight, symmetrical and unsymmetrical substrates that possess at least one aryl enone moiety undergo efficient cyclization with high to excellent diastereoselectivity (Scheme 7). Aryl enones with either electron-donating or electron-withdrawing substituents are suitable reaction partners, while a variety of α,β-unsaturated carbonyl compounds can serve as Michael-type acceptors; even quaternary centers can be formed in the case of α-substituted derivatives (Scheme 7, **25**). In contrast to the intramolecular reaction, in which the *cis* (meso) isomer is formed preferentially, the intermolecular dimerization affords the all-*trans* (rac) cyclobutane moieties. $LiBF_4$ turned out to be crucial for the reaction to proceed; playing a dual role; the Li salt not only improves the solubility of the reactants in the CH_3CN, but possibly also serves as a Lewis acid to facilitate the single electron transfer (SET) activation of the enone.

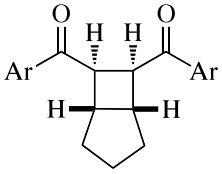


20 **21**

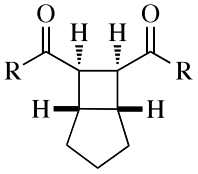
Intramolecular



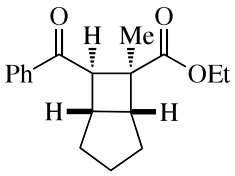
22
(Ar = p-$MeOC_6H_4$)
98% , 10:1 dr



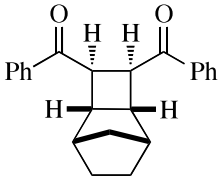
23
(Ar = p-ClC_6H_4)
96% , >10:1 dr



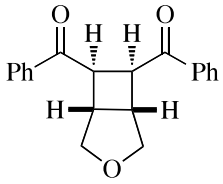
24
(R = 2-furyl)
89% , > 10:1 dr



25
84% , 10:1 dr

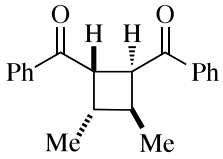


26
54%, 6:1 dr

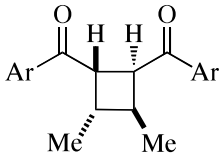


27
90%, 5:1 dr

Intermolecular



28
82%, > 5:1 dr

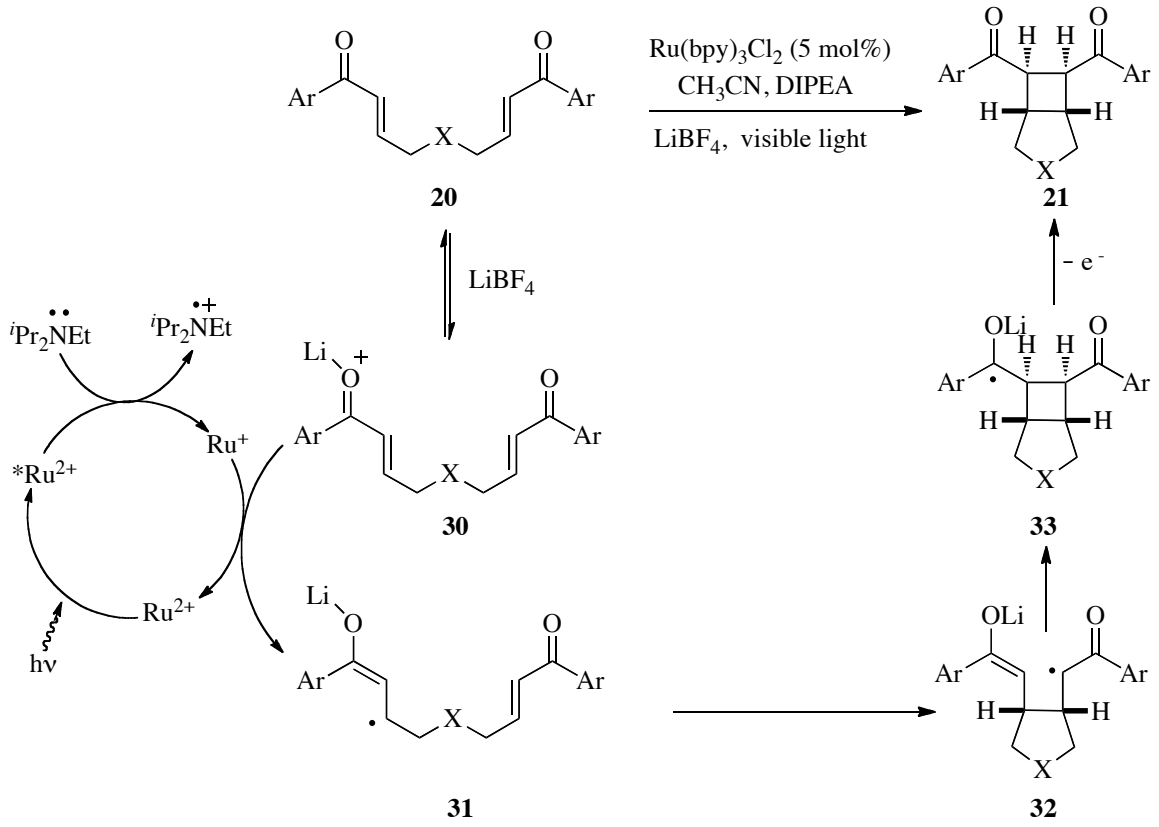


29
(Ar = p-ClC_6H_4)
93% > 10:1 dr

Scheme 7: Visible light photocatalysed [2+2] cycloaddition of enones.

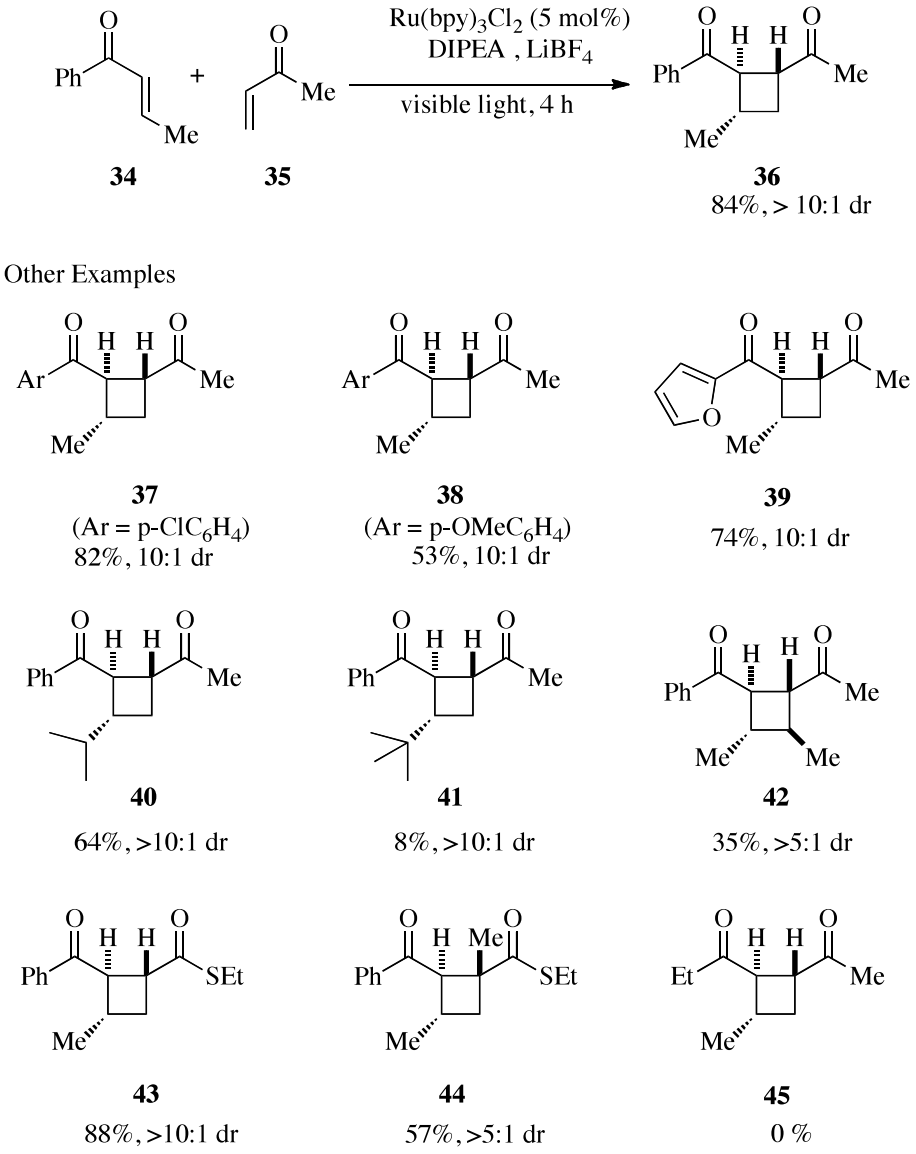
The authors proposed that excitation of $[Ru(bpy)_3]^{2+}$ by visible light generates the photoexcited state $*[Ru(bpy)_3]^{2+}$, which is followed by single electron transfer from DIPEA forming $[Ru(bpy)_3]^{+}$, a strong reductant (-1.33 V *vs*. SCE). A single electron reduction of lithium coordinated enone **31** produces the radical **32**, eventually leading to the cyclobutane product **21** (Scheme 8). Presumably, an intramolecular 1,4-addition of radical in **31** to α, β-unsaturated carbonyl moiety takes place, followed by radical

cyclization, furnishing the cyclobutane radical **33**. Oxidation of **33** can be achieved either by excited $*[Ru(bpy)_3]^{2+}$ or by the DIPEA radical cation and produces the cyclobutane **21** along with $[Ru(bpy)_3]^{+}$ or DIPEA.



Scheme 8: Proposed mechanism for photocatalysed [2+2] cycloaddition reaction.

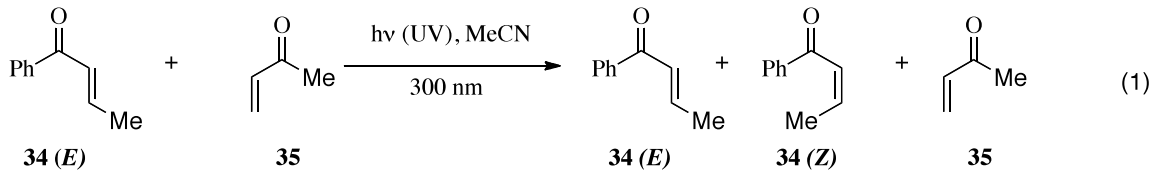
After successfully achieving the homodimarization of aryl enones Yoon *et al*. reported a highly diastereoselective cross intermolecular [2+2] cycloaddition of acyclic enones under comparable reaction conditions.[11] To overcome the major undesired pathway of homodimerization of the aryl enone, the authors had to select more reactive Michael acceptors as the second reaction component (Scheme 9). A mixture of methyl vinyl ketone **35** and aryl enone **34** (2.5:1), $[Ru(bpy)_3]^{2+}$ (5 mol%), $^{i}Pr_2NEt$, and $LiBF_4$ was subjected to visible light irradiation for 4 h and provided the cross [2+2]-cycloadduct **36** (84%, >10:1 dr) in a highly chemoselective fashion. Only trace amounts of homo-coupled product derived from **34** were observed. Both electron-rich and poor substrates are compatible under these conditions.



Scheme 9: Intermolecular [2+2] cycloaddition of enones.

Variation of the substituents at the β-position was possible; however the reaction was sensitive to steric bulk. Substitution at the β-position with primary and secondary alkyl groups proceeded smoothly, whereas *tert*-butyl substitution provided a very low yield of **41**. α, β-Unsaturated thioesters proved to be very good Michael acceptor partners to provide good yields of hetero-coupled product. Formation of quaternary centers also proceeded smoothly with reasonably good yield and diastereoselectivity (**44**, 57%, dr 5:1). On the basis of the previous results, as expected, the reaction between two alkyl enones did not provide any of the cycloaddition products **45**. Interestingly, irradiation of

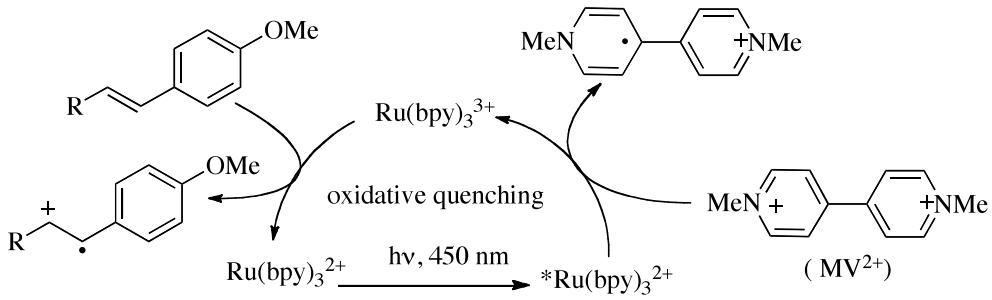
34 and **35** with UV light did not provide any cycloaddition products, it causes predominantly photochemical *E/Z* isomerization of the substrates (eqn 1).



34 (*E*) **35** **34 (*E*)** **34 (*Z*)** **35**

The important feature of Yoon's reactions was the selective excitation of photocatalyst ($Ru(bpy)_3Cl_2$) and not the enones. These visible light mediated intra- and intermolecular cycloaddition reactions were very effective with respect to their chemoselectivity, diastereoselectivity and yield. The major drawback of these methods was the requirement of an alkene that was sufficiently electron deficient to undergo efficient one-electron reduction by $Ru(bpy)_3^{2+}$, in fact, electron rich olefins (e. g. styrene) do not react under the reaction conditions mentioned.

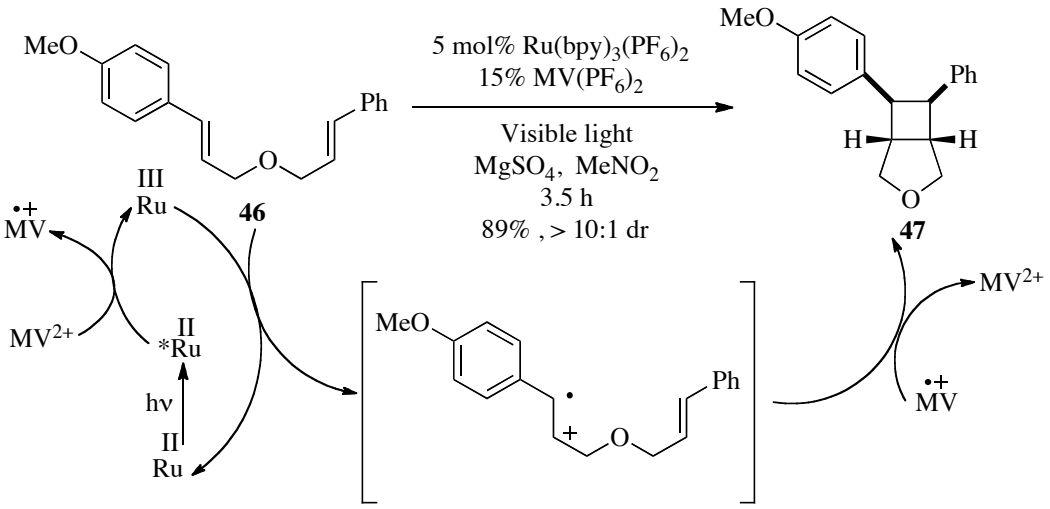
To overcome the above mentioned disadvantage, the Yoon group designed a complementary method for photooxidative electron transfer catalysis that could engage electron-rich olefins in productive [2+2]-cycloadditions.[12] Utilizing the oxidative quenching cycle of $Ru(bpy)_3^{2+}$ (Scheme 10) they were able to perform intramolecular [2+2]-cycloaddition reactions of a variety of styrene derivatives. It seemed logical that the photogenerated $Ru(bpy)_3^{3+}$ complex generated upon visible light irradiation of $Ru(bpy)_3^{2+}$ in the presence of methyl viologen (MV^{2+}) should also oxidize electron-rich styrene, affording a radical cation that undergoes subsequent a [2+2]-cycloaddition reaction. Bis(styrene) **46** (Scheme 11) underwent efficient intramolecular cycloaddition upon irradiation in the presence of 5 mol % $[Ru(bpy)_3]^{2+}$ and 15 mol % MV^{2+}, affording cyclobutane **47** in 89% yield with excellent diastereoselectivity. In contrast, no cycloaddition product was observed upon irradiation of **46** with UV light under conventional methods. In this study it was also reported that the above-mentioned reaction works very well in $MeNO_2$ rather than in MeCN, DMF and DMSO.



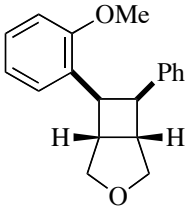
Scheme 10: Oxidative quenching cycle.

Addition of $MgSO_4$ gave slightly higher and reproducible yields. Both electron rich and electron poor styrenes reacted smoothly with the photogenerated radical cation. From the [2+2] cycloaddition product it was very clear that at least one styrene must bear an electron donating substituent at the *para* or *ortho* position (**47** and **48**), *meta* substituted and unsubstitured styrenes were most likely not electron rich enough to undergo one-electron oxidation to afford the key radical cation intermediate. Substituents at the α-position of the styrene are tolerated (**52**), which enables access to all-carbon quaternary stereocenters on the cyclobutane framework. In contrast, β-substituents significantly retard the rate of reaction. The identity of the tether seems to be critical; both oxygen and nitrogen-containing tethers gave good yields (**55**).

The authors also reported that the irradiation of isomeric bis(styrene) with visible light in the presence of $Ru(bpy)_3^{2+}$ and MV^{2+} always gave the same *cis* diastereomer as the major cycloaddition product. Compounds **57** and **58**, (*E,Z*)-bis(styrenes) isomeric to the (*E,E*)-substrate **46** (Scheme 12) were irradiated separately under the above standard conditions. In all cases, the major product observed was the same *cis* diasteromer being obtained from the cycloaddition of **46**, indicating that the stereochemical integrity of the olefins is lost in the course of the reaction.



Few more examples



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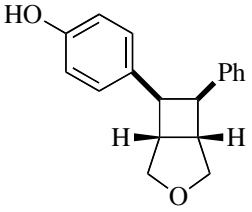

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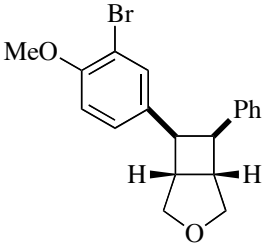

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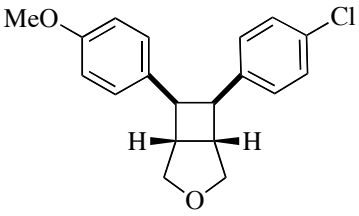
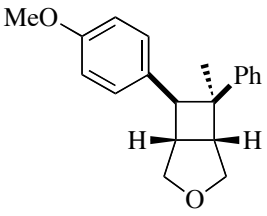


51, 92%



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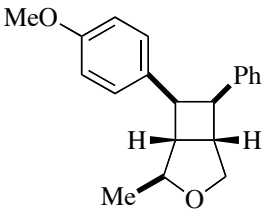

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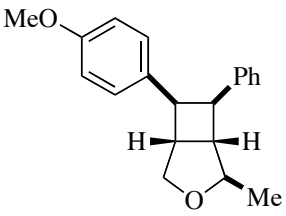

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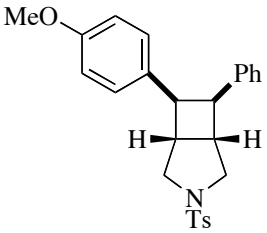

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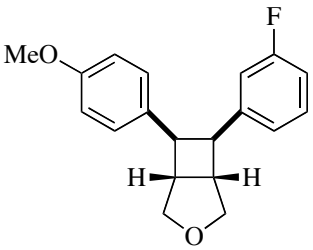
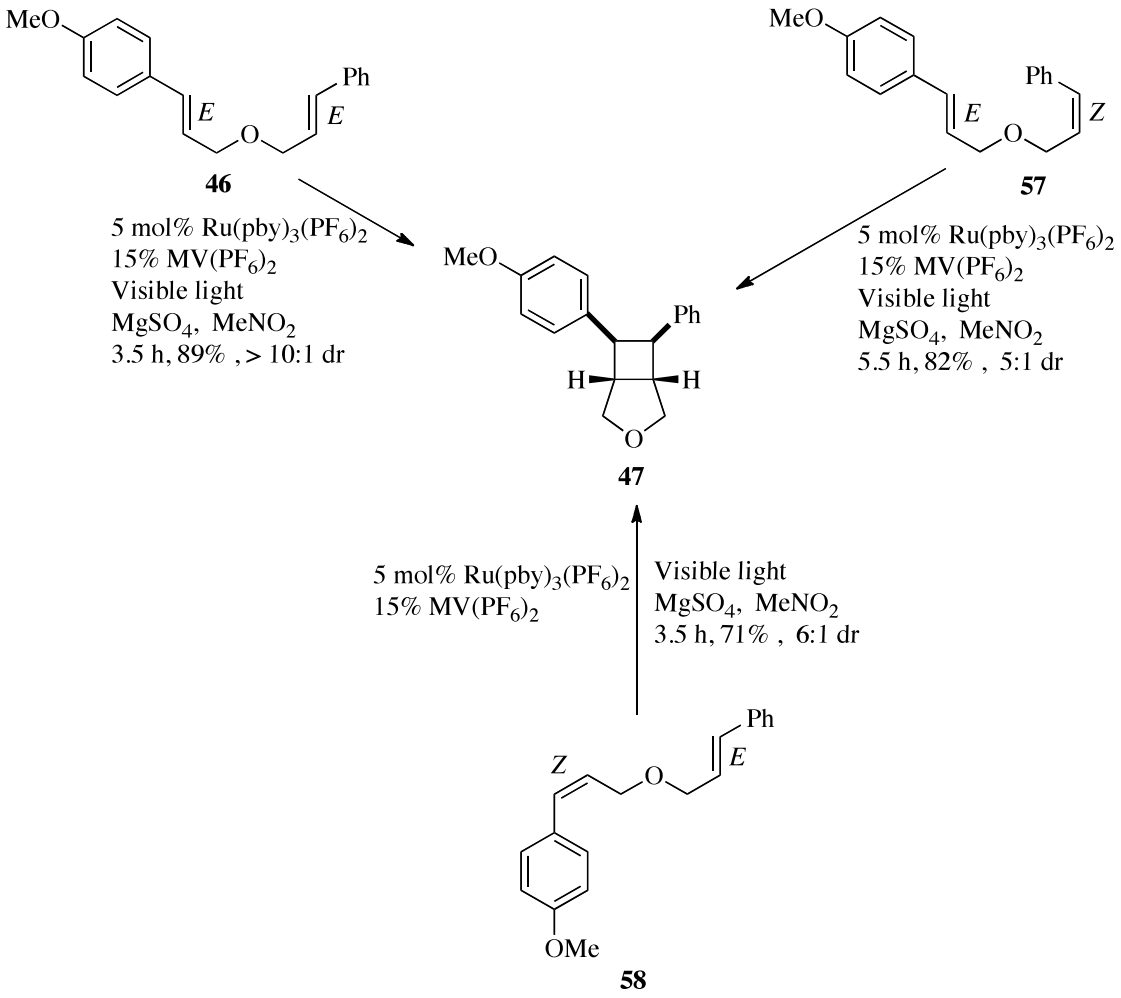


56, 78%

Scheme 11: Photooxidative [2+2] cycloaddition.

For better understanding they monitored the cycloaddition of **57** by GC. During the course of the reaction, **57** underwent isomerization to **46** at a rate competitive with that of cycloaddition.

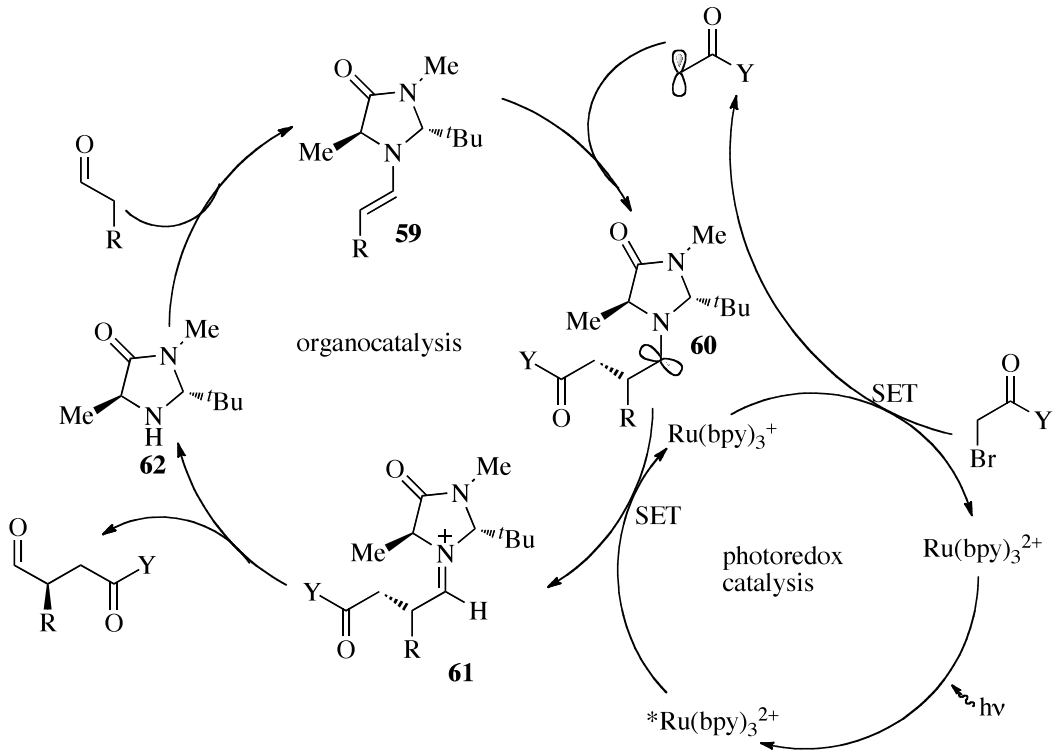


Scheme 12: Stereoconvergent [2+2] cycloaddition.

As the reaction proceeds, the ratio of *cis*-**57** to the isomeric *trans* cycloadduct increases from 1:1 at 30 min to 5:1 upon completion of the reaction. This allows the conclusion that the [2+2]-cycloaddition step is itself stereospecific, as predicted from previous theoretical and experimental studies of radical cation cyclobutanations,[13] but that the rate of the cycloaddition is relatively slow compared to the rate of olefin isomerization.

Merging photoredox catalysis with organocatalysis, Macmillan *et al*. reported[14] the asymmetric α-alkylation of aldehydes. The combination of Ru-mediated photoredox

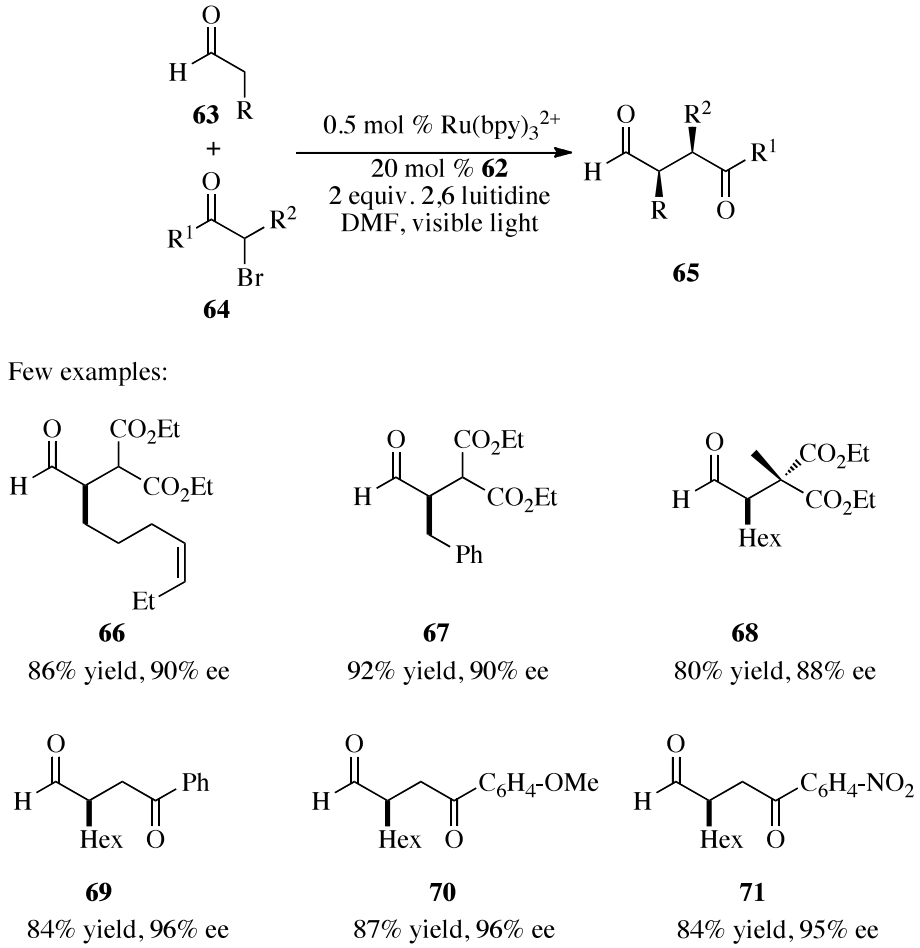
catalysis with a SOMO-type aminocatalysis (SOMO: singly occupied molecular orbital) provided a catalytic recycling system for the photocatalyst where both its oxidation and reduction steps were productive.



Scheme 13: The combination of photoredox catalysis and organocatalysis.

Not only does the cooperative interaction of the two catalytic cycles (photoredox and organocatalytic) yield α-alkylated aldehydes with high enantioselectivities in a previously elusive reaction, but also a sacrificial electron donor was not needed. In fact, the alkyl radicals, which were photocatalytically derived from the corresponding activated halides, were directly trapped by the electron-rich enamine species (Scheme 13). The resulting α-amino radical was in turn oxidized by the photoexcited $*[Ru(bpy)_3]^{2+}$ providing the reductive Ru^+ species for the dehalogenation. The α-alkylation method proceeded under mild conditions and also required only a standard energy-saving light bulb as a light source. The chiral imidazolidinone catalyst allows for the effective enantiofacial differentiation for the radical attack of the enamine, but will not react with the sterically more hindered α-substituted products, and potential product

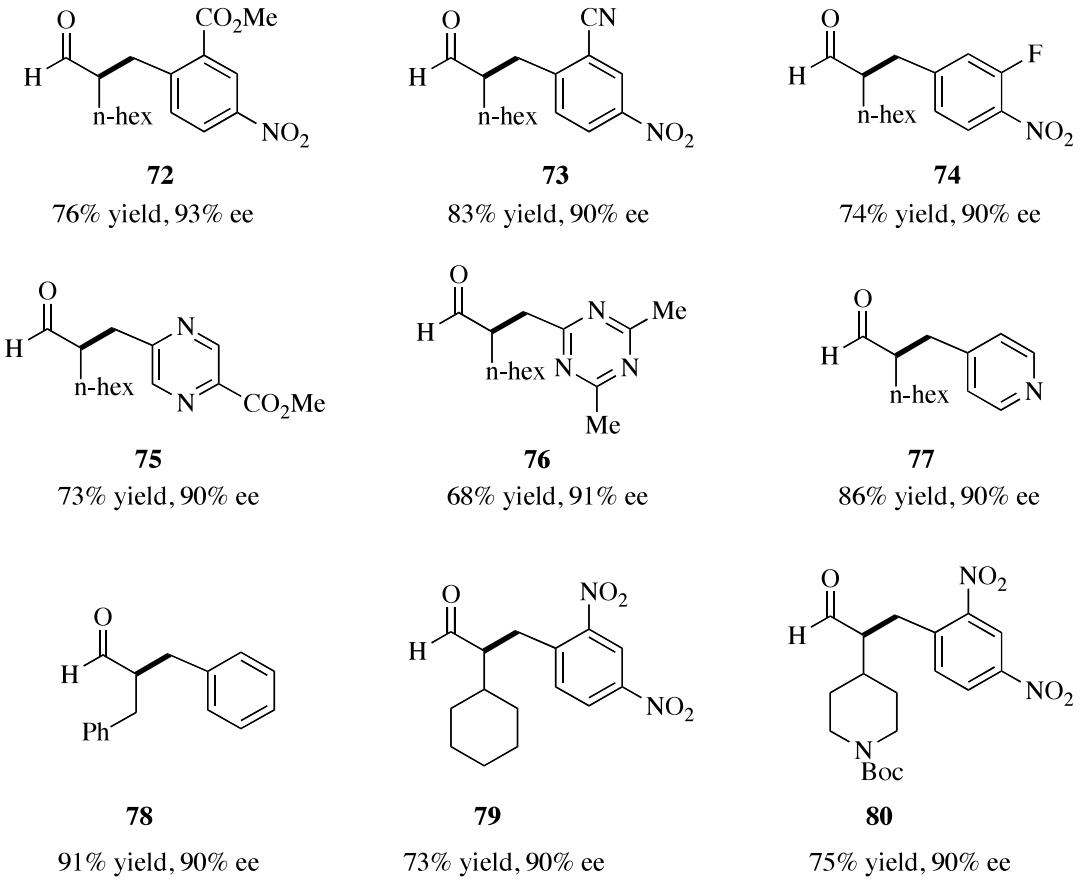
racemization by enamine formation was avoided. Broad ranges of α-alkylation products were accessible from aliphatic aldehydes in good to excellent yields with high enantioselectivities (Scheme 14).



Scheme 14: Asymmetric α-alkylation of aldehyde.

In a very recent extension of this merger of enamine and organometallic photoredox catalysis, MacMillan and coworkers have reported a visible-light-mediated, conceptually new approach to enantioselective α-benzylation of aldehydes.[15] Irradiation of the catalytic system promoted the reductive generation of electrophilic benzyl radicals and their subsequent addition to the electron-rich enamine, which was formed by a cooperative aminocatalytic cycle. Good results were obtained by using the Ir-based complex *fac*-Ir(ppy)$_3^+$ (ppy = 2-phenylpyridine) in catalytic amount. The asymmetric

formation of the pharmaceutically important α-benzyl compounds proceeds at room temperature in high yields and enantioselectivity. A broad range of electron-deficient aryl and heteroaryl methylene bromides are well tolerated for this benzylation reaction (Scheme 15).

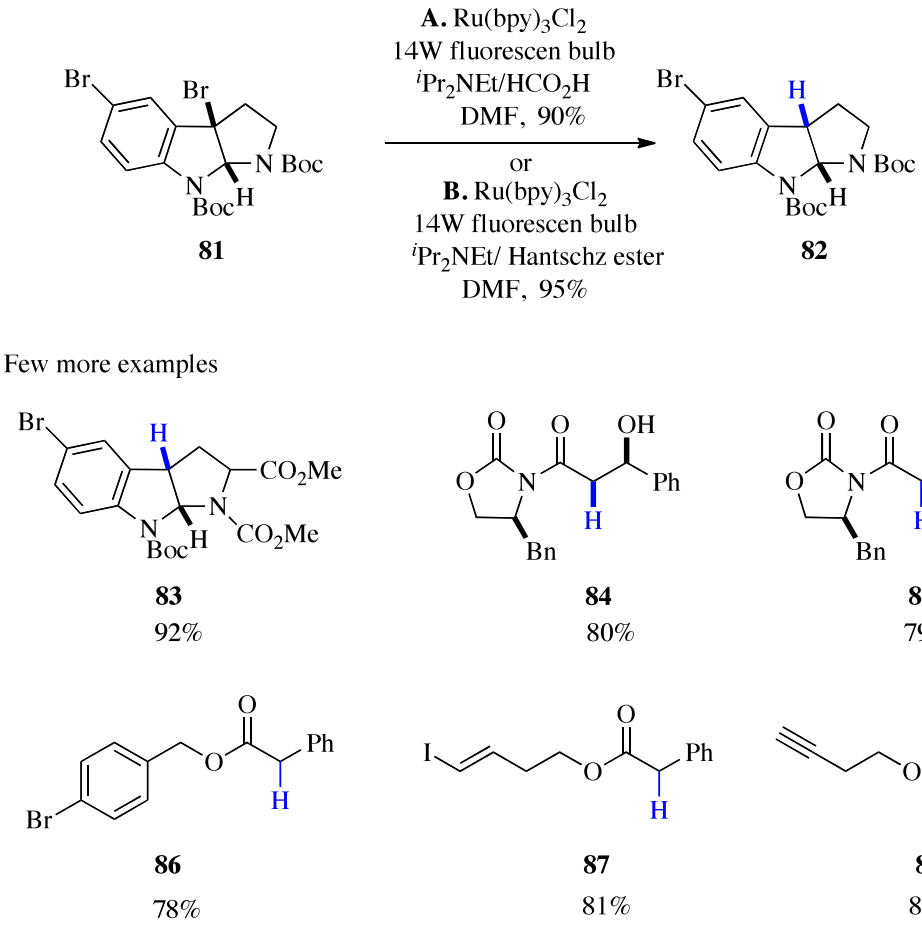


Scheme 15: Asymmetric α-benzylation of aldehyde.

MacMillan's approach not only demonstrates the power of photoredox chemistry, but also illustrates the great possibilities that appear from the combination of different concepts.

Photoredox-mediated reductive dehalogenation was first reported by Fukuzumi for α-haloacetophenones and it has been further developed by Stephenson and co-workers into a synthetically useful transformation.[16] Halogens α-to a carbonyl, electron withdrawing or aryl group could be selectively reduced under these conditions. Conceptually, this

reaction also proceeds *via* reductive quenching of photoexcited $*[Ru(bpy)_3]^{2+}$ to $[Ru(bpy)_3]^{+}$ and subsequent electron transfer to C–X bond α-to an electron-withdrawing group, followed by hydrogen abstraction. For this transformation, the authors have described two set of reaction conditions in DMF (Scheme 16): **A**. $Ru(bpy)_3Cl_2$ (1.0 mol%), $^{i}Pr_2NEt$ (10 equiv.) and HCO_2H (10 equiv.); or **B**. $Ru(bpy)_3Cl_2$ (1.0 mol%), $^{i}Pr_2NEt$ (2.0 equiv.) and Hantzsch ester (1.1 equiv.).

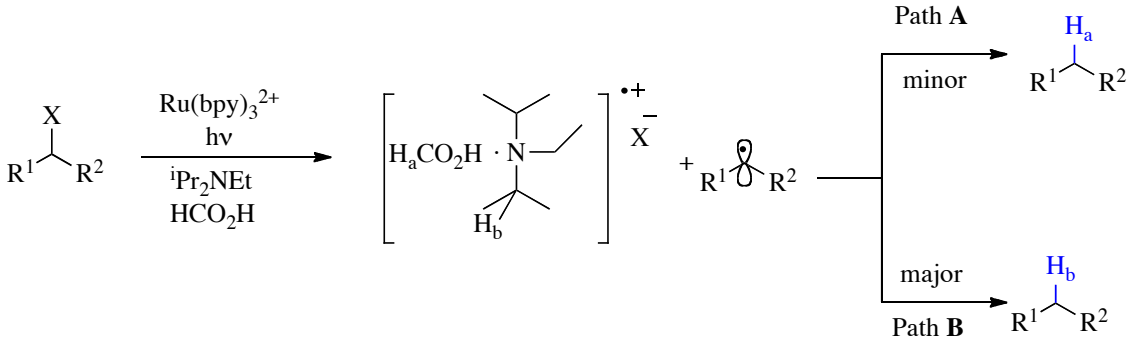


Scheme 16: Reductive dehalogenation using photoredox catalysis.

Both conditions provided reductive dehalogenation in excellent yields and could be chosen based on the specific substrate. In particular, condition **B** was utilized for less activated halogen substrates for which the S_N2 substitution of the formate ion was competitive with the reductive dehalogenation when using conditions **A**.

Isotopic labeling experiments revealed that $^{i}Pr_2NEt$ was the major source of the hydrogen

atom which quenches the alkyl radical. Based on these observations, they proposed the mechanism shown in Scheme 17. Reductive quenching of visible light excited $*[Ru(bpy)_3]^{2+}$ to $Ru(bpy)_3^{+}$ by $^{i}Pr_2NEt{\cdot}HCO_2H$ and subsequent electron transfer to cleave the C–X bond α-to an electron withdrawing group generates the alkyl radical. Reduction of this radical could be achieved *via* two pathways: (a) hydrogen abstraction from formic acid (H_a, minor); or (b) hydrogen abstraction from $^{i}Pr_2NEt$ (H_b, major).



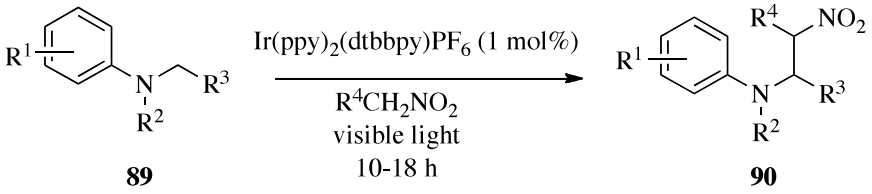
Scheme 17: Plausible mechanism for the reductive dehalogenation.

Although the reductive dehalogenation using photoredox catalysis at this stage is only limited to activated halogen compounds, it should be possible to be extended to the reduction of unactivated halogen substrates by modifying redox potentials of the photocatalysts. Furthermore, photocatalytic generation of a radical by the reduction of a C–X bond has great potential as an alternative for C–C bond forming reactions *via* the chemistry of alkyl free-radicals.

Another conceptual attempt was made by Stephenson and co-workers was that the iminium ion generated under photoredox conditions could be intercepted with an appropriate nucleophile.[17] Preliminary studies indicated that simple nucleophiles such as CH_3OH could trap the iminium ion generated from *N*-aryltetrahydroisoquinolines **89** in the presence of $Ir(ppy)_2(dtbbpy)PF_6$ (1 mol%) under visible light irradiation. Simply switching the solvent from CH_3OH to CH_3NO_2 provided the aza-Henry products in excellent yields for a variety of substrates (Scheme 18). Although the reaction is much slower, *N*-phenylpyrrolidine was also a competent substrate in this reaction (**99**, 27% yield, 40% conversion after 72 h).

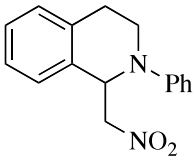
Both light and a photocatalyst were found to be necessary for the efficient conversion to

the aza-Henry products, while the exclusion of oxygen from the reaction resulted in a diminished rate. On the basis of luminescence quenching experiments, the following mechanism was proposed (Scheme 19), the radical cation of the amine **100** was formed upon visible light excitation of the Ir^{3+} catalyst and reductive quenching.

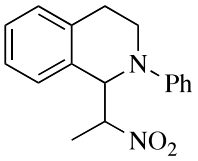


89 **90**

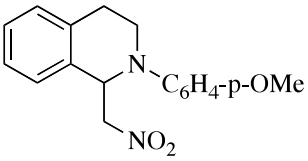
Few more examples



91, 92%



92, 96%



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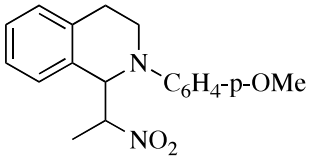

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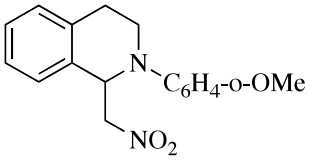

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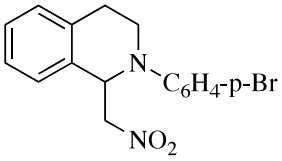
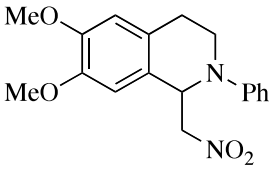
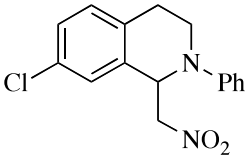


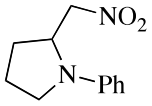
96, 93%



97, 92%



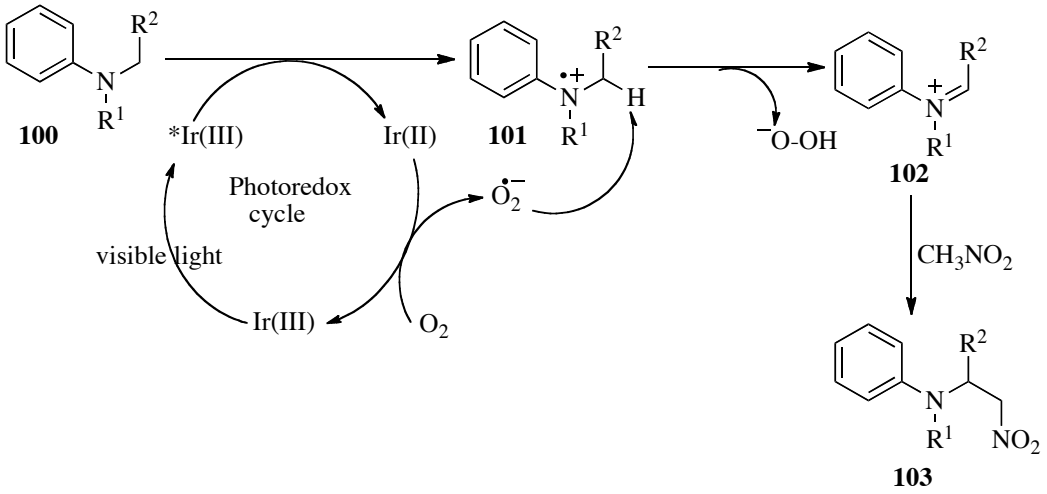
98, 95%



99, 27%

Scheme 18: Oxidative aza-Henry reactions using photoredox catalyis.

While the mechanism for catalyst turnover was not clear at this time, the authors proposed that adventitious oxygen likely played a critical role in the reaction. The corresponding radical anion may abstract a hydrogen atom from the trialkylammonium radical cation to form the desired iminium ion. Nucleophilic attack of nitromethane onto the iminium provides the observed product **103**.



Scheme 19: Proposed mechanism of the aza-Henry reaction.

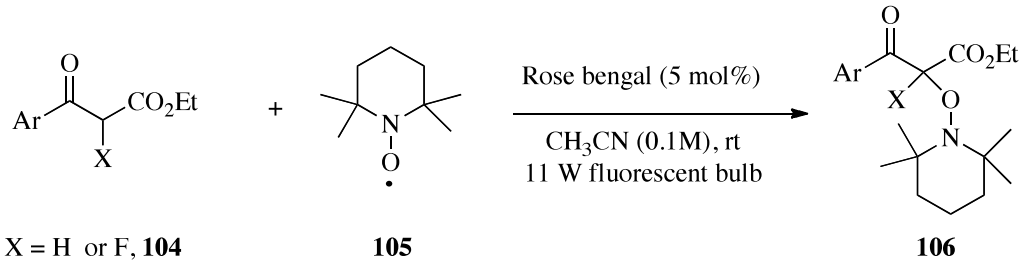
The dual reactivity (oxidative and reductive quenching) of the photoexcited state of catalysts such as $[Ru(bpy)_3]^{2+}$ or Ir^{3+} and their applications in organic synthesis discussed here provide an introduction to photoredox catalysis as it has been utilized in organic synthesis. Recent reports by MacMillan, Yoon and Stephenson showed the utility of reductive as well as oxidative quenching of $*[Ru(bpy)_3]^{2+}$ or $*Ir^{3+}$ and its application to various synthetic transformations. Yoon's formal [2+2]-cycloadditions of enones represent 'visible light' as a reagent for chemical reactions. MacMillan's photoredox organocatalysis demonstrates the control of facial selectivity in radical mediated asymmetric alkylations. Finally, Stephenson's work on photoredox catalysis provides a tin-free, environmental friendly method to access free radical intermediates for reductive dehalogenation. These recent developments in photoredox catalysis provide early attempts into the broad potential of these methods to mediate a variety of useful chemical transformations.

Organic Dyes as Photocatalyst

Organic dyes, which are more environments friendly, cheaper and easier to prepare, present a practical alternative to inorganic photocatalysts. In fact, several industrial pilot studies have been conducted with organic dyes as photocatalyst.[18] Organic dyes as

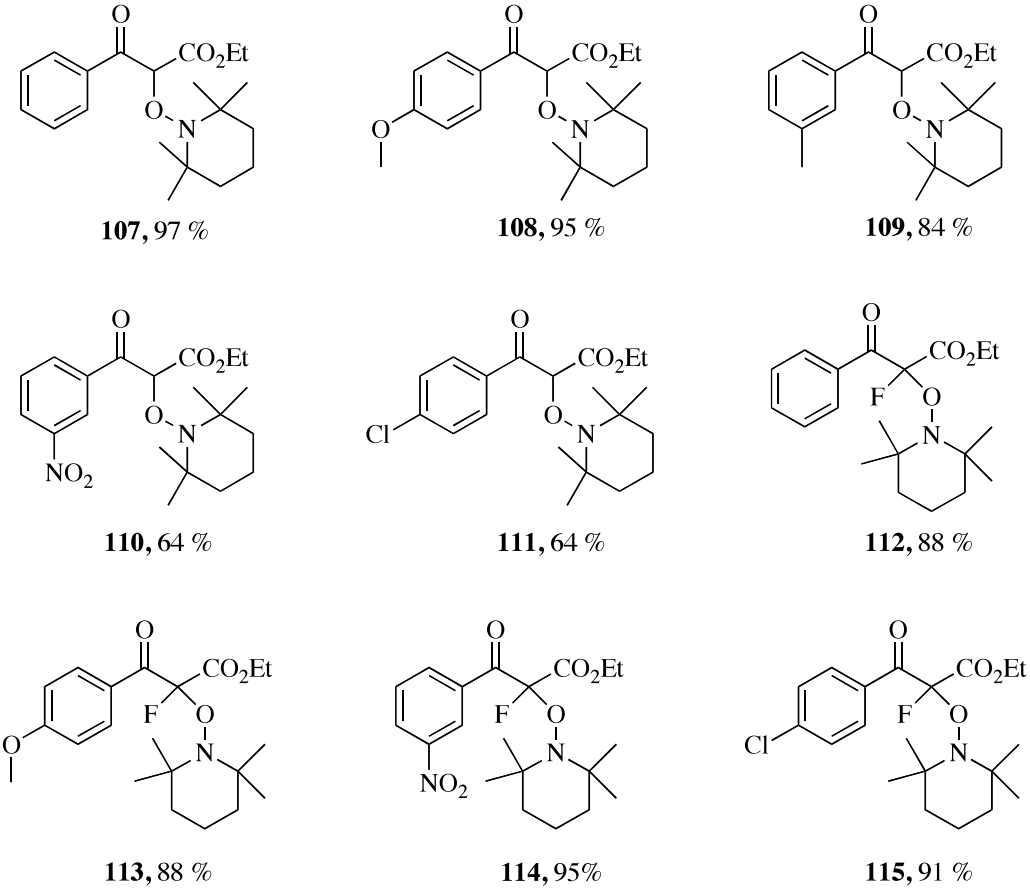
photocatalysts can also be used in conjunction with ultraviolet light from 419 nm Rayonet lamps. However, the high cost and toxicity of the ruthenium and iridium salts as well as their limited availability in the future are the practical imitation to these metal-based methods. Therefore, the use of organic dyes as photocatalyst in combination with visible light is one of special interest to study.

Recently, Choon-Hong *et al.* reported[19] the use of Rose Bengal (**10**), an organic dye, as a visible light photocatalyst to investigate novel α-oxyamination reactions between 1,3-dicarbonyl compounds and a free radical (TEMPO). Compounds that are difficult to obtain such as quaternary fluorinated compounds were synthesized using this method. This visible light photocatalytic reaction was also performed in water. Rose Bengal (RB), which has a strong absorption band in the range of 500–600 nm, was efficient in catalyzing the α-oxyamination reaction between β-ketoester **104** and TEMPO **105** to give the product **106** (Scheme 20). There is a great effect of solvent on the reactivity of this reaction where the optimized condition showed that acetonitrile was the best solvent for the photocatalysis reaction. Although $[Ru(bpy)_3]^{2+}$ gave very low conversion to the product but using Rose Bengal, very good conversion and yield were obtained. Electron deficient aromatic compounds showed faster reaction rate than electron rich aromatic compounds, while alkyl ketone ester did not give any products. Using the same methodology a variety of α-fluoro α-hydroxy acid derivatives were synthesized with high yield.



X = H or F, **104** **105** **106**

Few more examples :



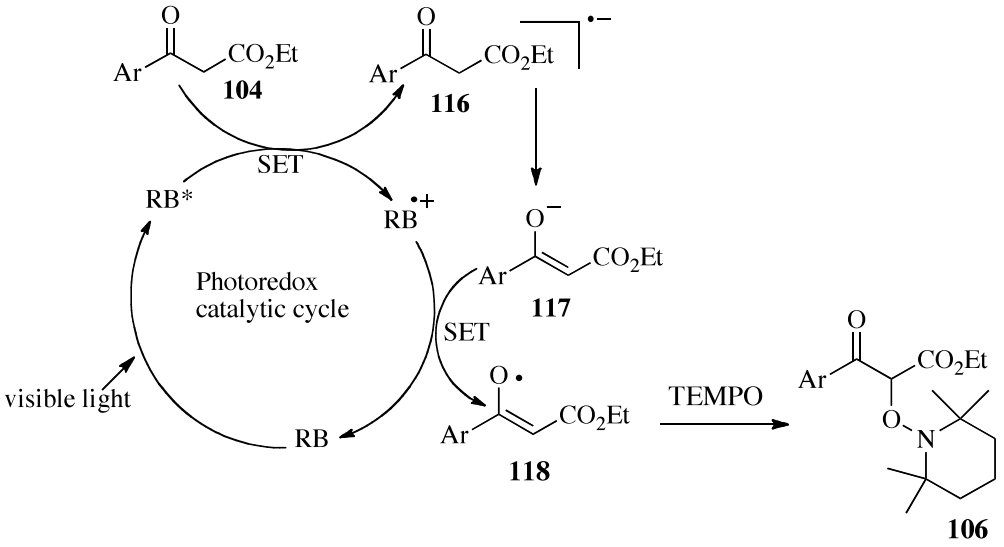
107, 97 % **108,** 95 % **109,** 84 %

110, 64 % **111,** 64 % **112,** 88 %

113, 88 % **114,** 95% **115,** 91 %

Scheme 20: Visible light mediated α-oxyamination reaction.

As Rose Bengal is well known as a sensitizer for singlet oxygen production, control experiments were conducted in a glove box to verify the role of oxygen. It was clearly shown that oxygen was not essential for the visible light driven α-oxyamination reaction. Based on that result, they proposed a mechanism for the α-oxyamination reactions (Scheme 21).



Scheme 21: Proposed mechanism for α-oxyamination reaction.

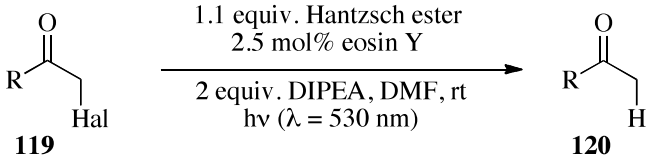
Photoexcitation by visible light, Rose Bengal (RB) accepts a photon from the visible light to form RB*. As a reductant, it transfers an electron to the substrate **104** *via* a single electron transfer process (SET). Rose Bengal was recycled *via* another SET process from the electron rich intermediate **117**. The radical **118** was coupled with free radical TEMPO to give the product **106**. Thus, this method was applied to the synthesis of a variety of α-hydroxy acid derivatives with excellent yields and also to the synthesis of quaternary α-fluorinated α-hydroxy acid derivatives.

Zeitler *et al*. reported[20] a versatile metal-free, purely organic photoredox catalysis by utilizing green light, the most abundant part of solar energy. They demonstrated the successful application of simple, inexpensive organic dyes as effective photocatalysts for the cooperative organocatalytic asymmetric intermolecular α-alkylation of aldehydes. They observed that classic organic dyes show striking similarities to the widely employed organometallic ruthenium- and iridium-containing photosensitizers. To achieve this desired transformation they investigated the conditions reported by Stephenson and co-workers for the photocatalytic dehalogenation of activated benzylic halides in the presence of $[Ru(bpy)_3]^{2+}$. Upon irradiation with green light from high-power LEDs with an emission of λ = 530 nm, they found that among the dyes, eosin Y was the best organic photocatalyst for their subsequent studies and using the same they performed dehalogenations of a varieties of aromatic halogen compounds (Table 1). Electron-

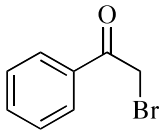
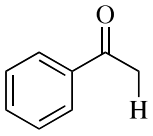
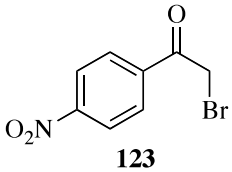
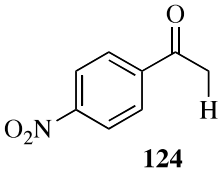
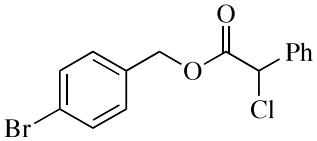
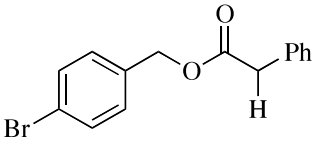
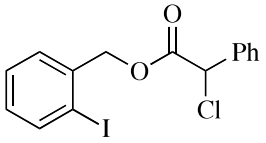
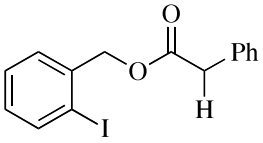
withdrawing substituents (Table 1, entry 2), polar functional groups such as esters were well tolerated in that conditions and exclusive chemoselectivity for α-activated substrates over aryl halides was observed for the defunctionalization (Table 1, entries 3 and 4). In all cases the obtained yields of the isolated products were equal or better than those for the reported transition-metal-catalyzed counterpart proving the effectiveness of their operationally simple, inexpensive conditions.

Next they applied the organic dyes as photoredox catalysts in the asymmetric organocatalytic C–C bond formations developed by MacMillan *et al.* The transformations (Scheme 22) were found to be both high-yielding and enantioselective when a combination of eosin Y (**6**) and MacMillan's imidazolidinone catalyst were applied.

Table 1: Photocatalytic reductive dehalogenation using eosin Y

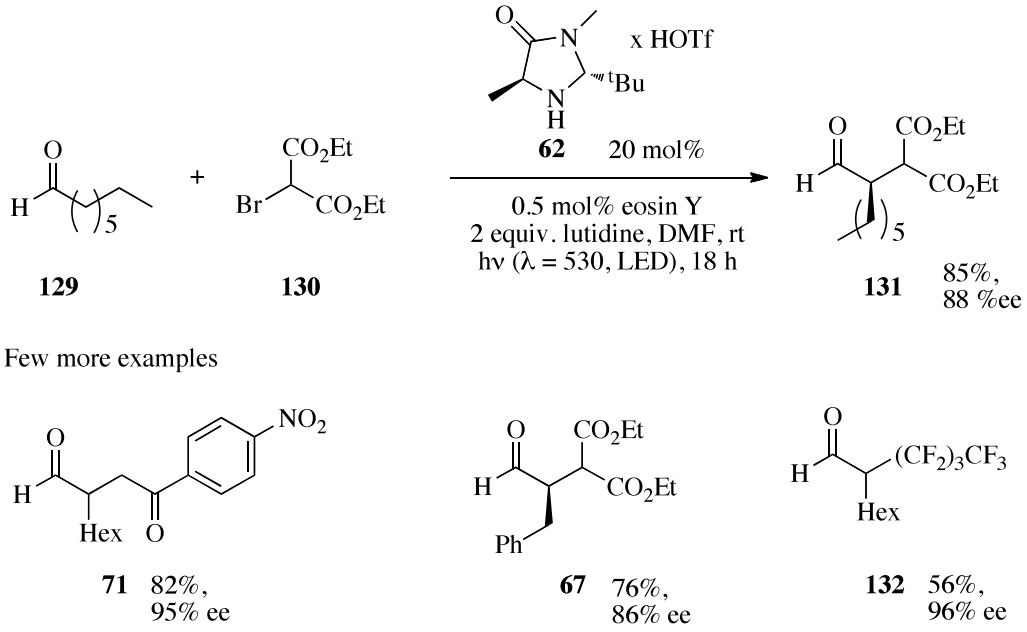


119 **120**

entry	substrate	product	yield (%)
1	 **121**	 **122**	100
2	 **123**	 **124**	83
3	 **125**	 **126**	78
4	 **127**	 **128**	89

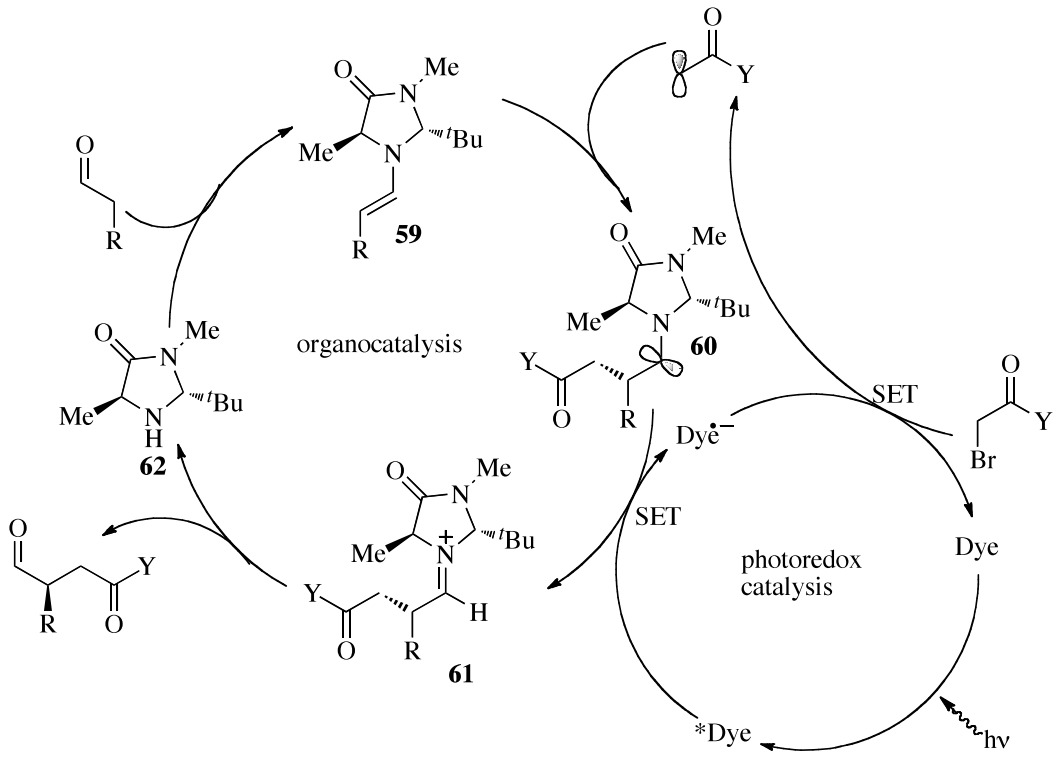
Even though the organic-dye-sensitized conditions required longer reaction times, but it did not give any product racemization. Performing the reaction under direct sunlight led to faster conversion with a slight lowering in enantioselectivity, most probably because of the increased reaction temperature.

From a mechanistic point of view they proposed that eosin Y acts as a photoredox catalyst after its excitation with visible light and population of its more stable triplet state finally enabling single-electron transfer (Scheme 23).

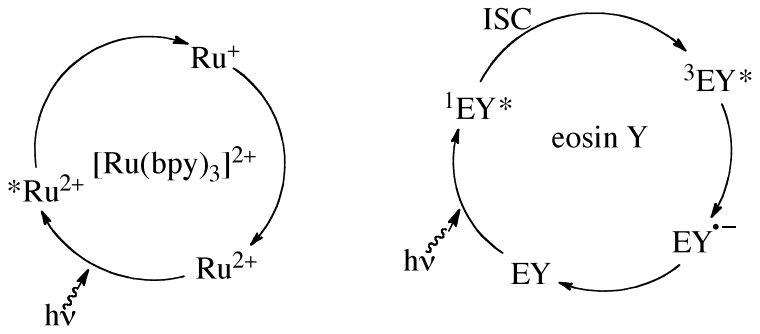


Scheme 22: Organocatalytic enantioselective α-alkylation using eosin Y as photocatalyst.

Similar to the chemistry of $*Ru^{2+}$ both reductive and oxidative quenching are known for excited eosin Y $^3EY*$. As all the results were comparable to those of MacMillan *et al.* they presume that eosin Y acts as a reductant relying on the sacrificial oxidation of a catalytic amount of the enamine as the initial electron reservoir to furnish the electron-deficient alkyl radical by means of SET with an alkyl halide. Addition of this radical to the electron-rich olefin of the enamine that is simultaneously generated within the organocatalytic cycle merges both activation pathways. In the catalytic cycle the subsequent oxidation of the amino radical to the iminium species provides the electron for the reductive quenching of the dye's excited state $^3EY*$.



Photochemical steps of the metal catalyst and organic dye



Scheme 23: Proposed mechanism with organic dye.

Conclusion:

The dual reactivity of the photoexcited state of catalysts such as $[Ru(bpy)_3]^{2+}$ and their applications in organic synthesis discussed above, provide an introduction to photoredox catalysis as it has been utilized in organic synthesis. Recent efforts by Yoon, MacMillan and Stephenson demonstrate the utility of reductive quenching of $*[Ru(bpy)_3]^{2+}$ and its application to various synthetic transformations. Stephenson's work on photoredox

catalysis provides a tin-free, environmental friendly method to access free radical intermediates for reductive dehalogenation and the mild generation of reactive iminium intermediates *via* C–H activation. On the other hand recent efforts by Tan and Zeitler demonstrate the use of organic dyes as photocatalyst, an alternative of metal free phtocatalysis using visible light makes the organic synthesis more economic and environmentally benign catalyst. Above all, use of visible light in organic synthesis makes photoredox catalysis as an attractive and 'green' alternative for chemical synthesis. These recent developments in photoredox catalysis provide an early glimpse into the broad potential of these methods to mediate a variety of useful chemical transformations.

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2. Aim of the work

2.1 Development and application of new catalytic system for organic transformation in presence of visible light

The aim of this work was to develop new chemical transformations going through radical intermediates, which are liberated by photoredox catalysis in the presence of visible light. MacMillan and Stephenson have focused on the use of photoredox catalyst $Ru(bpy)_3Cl_2$ to promote enantioselective alkylations of aldehydes[1] or reductive dehalogenations,[2] respectively, starting from acyl bromides or tertiary benzyl halides. In all of these cases, photoexcited $*Ru^{2+}$ receives an electron from a sacrificial electron donor such as a tertiary amine, which in turn transfers that electron to a substrate. Applying those conditions to a variety of primary acyl bromides, we noticed however their undesired direct reaction with the tertiary amine by a nucleophilic substitution, thus greatly reducing the yield of the desired radical processes. In the search for an alternative photocatalytic system we came across the combination of 1,5-dimethoxynaphthalene (DMN) as a primary and ascorbic acid as a sacrificial electron donor,[3] being applied by Pandey *et al*.[4] for the cyclization of aldehydes and ketones onto tethered α,β-unsaturated esters. We studied here that these reagents in combination with $Ru(bpy)_3Cl_2$ form an excellent photocatalytic system allowing the visible light mediated reductive debromination of vicinal dibromides as well as α-halocarbonyl compounds in high yields.[5]

2.2 Photocatalytic oxygenation of cyclic enamines and enol ethers

Last few decades, increasing attention has been drawn to β-and γ-amino acids and their derivaties as an important constituents of natural products and as valuable intermediates for the preparation of peptidomimetics[6] and β-and γ-lactums.[7] Abundant methods are known for the synthesis of α-amino acids,[8] there are considerably fewer routes to the β-and higher amino acid analogs.[9] Reiser *et al*. reported[10] a general approach to both β-and γ-amino esters and amino aldehydes by ozonolysis of 2,3-dihydropyrrols and 1,2,3,4-tetrahydropyridines. However, alternative of ozonolysis for this process is highly

desirable due to huge energy demand of the process, toxicity of ozone and safety risk. We developed an alternative method for oxidative ring opening of cyclic enamines and enol ethers by using singlet oxygen, generated by photocatalyst $Ru(bpy)_3Cl_2$ in the presence of visible light, to the corresponding acyclic amino aldehyde derivatives. This method is also applicable for oxidative ring opening of cyclic enol ethers to their formyl protected aldol and homoaldol products.

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3. Visible Light mediated reductive dehalogenation of α-halo ketones

3.1 Reduction of Carbon–Halogen bond

Taking into account the general resistance to degradation of organic halogenated materials, many efficient methods and techniques have been developed to properly treat this type of compounds.[1] Inactivation by oxidative methods and incineration[2] generally causes the production of some harmful chemicals. Reductive methods can be considered as an alternative to oxidation by incineration. Among them, electrochemical,[3] photochemical,[4] ultrasonic,[5] microbial,[6] and radiolytic and thermal[7] reductive methods have been reported.

In this regard, chemical methods have been by far the most studied ones.[8] The chemical reduction of organic halides involving the replacement of halogen by hydrogen is the so called hydrogenolysis of the carbon-halogen bond or hydrodehalogenation reaction. The great importance of this reaction draws attention from all chemists, and organic chemists in particular, due to its importance for organic synthesis. The large variety of reducing systems developed to date practically guarantees the existence of a specific reagent for a given substrate, to successfully carry out this type of transformation. Therefore, the method of choice will depend mainly on the characteristics of the substrate i.e., the nature of the carbon-halogen bond involved, hybridization at the halogen-bearing carbon, substituent effects, and the presence of other halogens or functional groups.

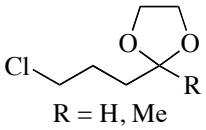
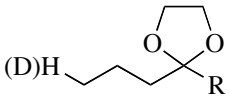
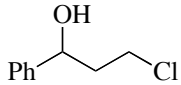
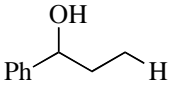
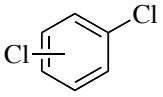
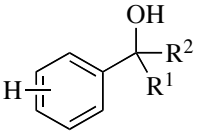
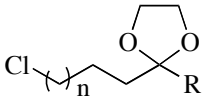
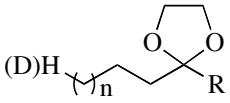
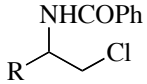
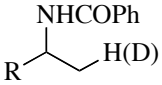
The most important chemical methods[8] to accomplish the hydrodehalogenation of organic halides are catalytic hydrogenation,[9a] reduction with metals or low-valent metal compounds,[9b] reduction with metal hydrides,[9c-d] and reduction with some strong nucleophilic neutral or anionic species.[9e] A few metal- or low-valent metal compound-mediated processes are discussed below.

3.2 Metal mediated dehalogenation

Both alkali and alkaline-earth metals in the zero valent state are well-known reducing agents of the carbon-halogen bond. One of the simplest ways to achieve the halogen-hydrogen interchange in an organic halide is using lithium as an electron source followed

by the addition of a proton source. In the past few years, Yus *et al*. have developed a methodology based on the use of lithium powder and a catalytic amount of an arene (naphthalene) or 4,4'-di-tert-butylbiphenyl (DTBB), which has been applied to the generation of very reactive organolithium intermediates under very mild reaction conditions, either from halogenated or nonhalogenated materials.[10] Thus, the lithiation reaction under these conditions (alternatively stoichiometric lithium naphthalenide was used in some cases) applied to a series of alkyl, aryl, vinyl, and benzyl chlorides or to an alkyl bromide, followed by the addition of water or deuterium oxide, led to the corresponding reduced products (Table 2).[11]

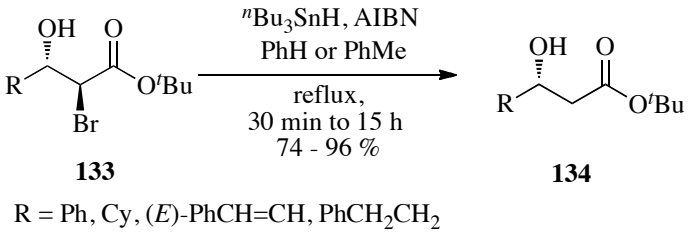
Table 2: Reduction of organic halides with Li-naphthalene.

starting material	condition	product	yield(%)[ref]
 R = H, Me	Li, $C_{10}H_8$, -78 °C		80-90[11a,b]
	i) ^{n}BuLi, -78 °C ii) Li, $C_{10}H_8$		89[11c]
	i) Li, $C_{10}H_8$, -78 °C ii) R^1COR^2		63-96[11d]
 R = H, Et, Ph n = 2, 3	Li, $C_{10}H_8$ (4-8 %), -78 °C		73-92[11f]
 R = Et, Ph	i) ^{n}BuLi, -78 °C ii) Li, $C_{10}H_8$		84-91[11g,h]

Organotin hydrides are certainly the most frequently used organotin compounds in the laboratory, which have proved to be capable and versatile reagents for both radical generation and kinetically controlled radical trapping.[12] By far, the most used tin hydride is tri-*n*-butyltin hydride (TBTH), with applications in many fields of synthesis including

the replacement of halogen by hydrogen. The system TBTH-AIBN is the most utilized for radical-promoted hydrodehalogenation of organic halides. For instance, in the early 1990s Lin *et al*. applied it to the efficient dechlorination of 2'- chloro-3'-O-imidazolycarbonyl and 2'-chloro-3'-O- acetyl nucleosides to give the corresponding 2'-deoxynucleosides in 97 % and 96 % yield, respectively.[13]

anti-α-Bromo β-hydroxy esters **133**, which were synthesized by Corey *et al*., are useful precursors of acetate aldols **134**, obtained in good yields by debromination with TBTH-AIBN in benzene or toluene under refluxing condition. In general, shorter reaction times and better yields were observed with toluene in comparison to benzene (Scheme 25).[14]



133 **134**

R = Ph, Cy, (*E*)-PhCH=CH, PhCH$_2$CH$_2$

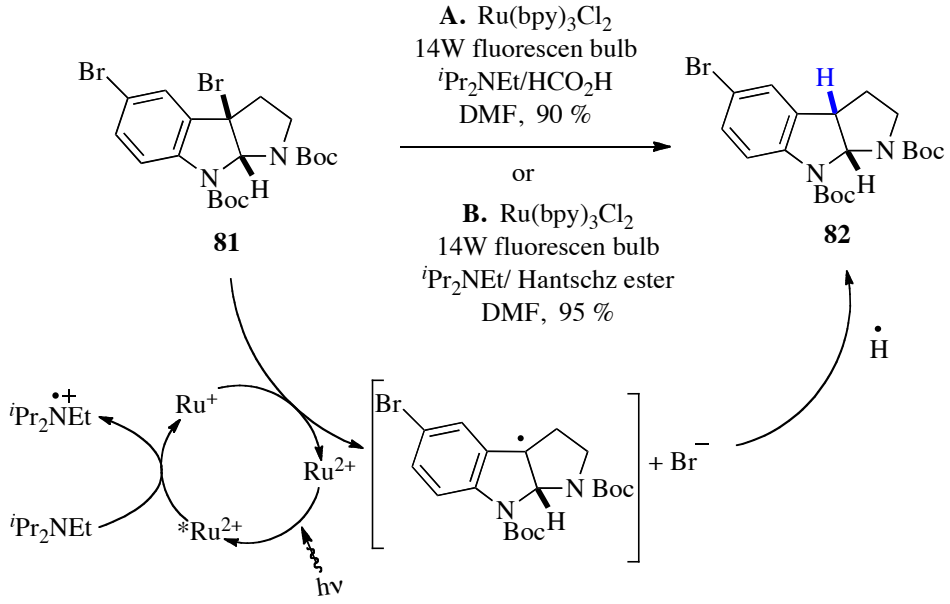
Scheme 25: Dehalogenation of *anti*-α-bromo-β-hydroxy esters.

There are wide varieties of tin hydrides known in literature, which show good performance for the dehalogenation of bromides, iodides, and α-halocarbonyl compounds. However, the necessity to employ stoichiometric amounts of these strongly reducing agents might cause problems of selectivity and functional group compatibility. Moreover, the toxicity of the widely used organotin compounds makes the development of more sustainable alternatives desirable.

3.3 Visible light promoted dehalogenation

To overcome the disadvantage of using reagents that are toxic, hazardous and difficult to purify (*cf*. ^{n}Bu$_3$SnH/AIBN) for dehalogenations, Stephenson *et al*. reported[15] a conceptually new methodology for the tin-free reductive dehalogenation reaction promoted by visible light in the presence of a catalytic amount of photocatalyst, Ru(bpy)$_3$Cl$_2$. They showed dehalogenation of a variety of compounds by utilizing the reductive quenching property of photoexcited *Ru(bpy)$_3^{2+}$ to Ru(bpy)$_3^{+}$ and subsequent

electron transfer to carbon-halogen bond α-to an electron-withdrawing group, followed by proton abstraction. The visible light mediated reductive cleavage of α-activated carbon–halogen bonds proceeds under mild conditions by a radical mechanism and tolerates a number of different hydrogen sources. When a tenfold excess of $^{i}Pr_2NEt$ was used, the tertiary amine plays a dual role, sacrificially donating an electron to form the Ru reductant and allowing hydrogen- atom transfer from the amine radical cation.[16] However, if the amine-based formation of a radical is less feasible, formic acid can serve as a hydrogen source, as was shown by isotope labeling experiments. Alternatively, Hantzsch ester derivatives can act as highly efficient hydrogen sources, providing high yields of products in comparable reaction times (Scheme 5). Here Hantzsch esters offer the advantage to avoid competitive S_N2-type side reactions of the formate ion.

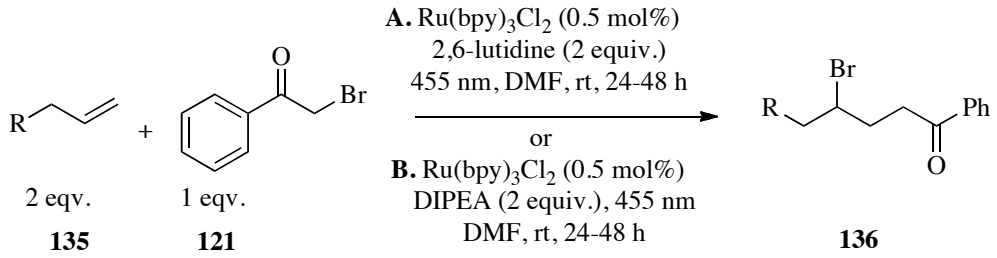


Scheme 26: Tin-free photoredox catalytic reductive dehalogenation.

3.4 Development of $Ru(bpy)_3Cl_2$-Dimethoxynaphthalene-Ascorbic acid combination for dehalogenation

Recently, our group has focused on the use of renewable and sustainable materials for organic transformation. Realizing the practical advantage of visible light as an "infinitely available" promoter for chemical transformation and inspired by the work of MacMillan[17]

and Stephenson,[15] we focused our research to develop new chemical transformations going through radical intermediates. We wanted to utilize alkyl and vinyl bromides as radical precursors being liberated by photoredox catalysis in the presence of visible light. The idea was to trap an alkyl radical, which was generated by photoredox catalysis in the presence of visible light, by an alkene. Since the 2-bromoacetophenone (**121)** generates an alkyl radical very smoothly with $Ru(bpy)_3^{2+}$ in the presence of visible light (as reported by MacMillan[17]), we used the same to trap the alkyl radical with 1-octene or with allyl benzene. Applying identical conditions reported by MacMillan[17] and Stephenson[15], we observed a negligible amount of addition product **136** (Scheme 27).

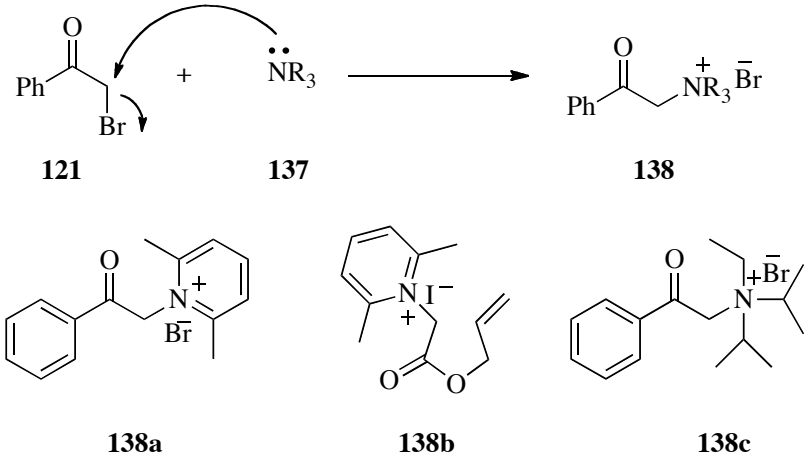


entry	alkene	halide	product	isolated yield (%)
1	C_5H_{11} **135a**	**121**	C_5H_{11}, O, Ph, Br **136a**	7
2	Ph **135b**	**121**	Ph, O, Ph, Br **136b**	10
3	I, O, O **135c**	.....	No cyclized product	-----

Scheme 27: Addition of alkyl halide to alkene mediated by visible light.

In both cases only one regioisomeric product was obtained (entry 1 and 2, Scheme 27). Surprisingly, we noticed that there was no starting material (alkyl halide **121**, used in 1

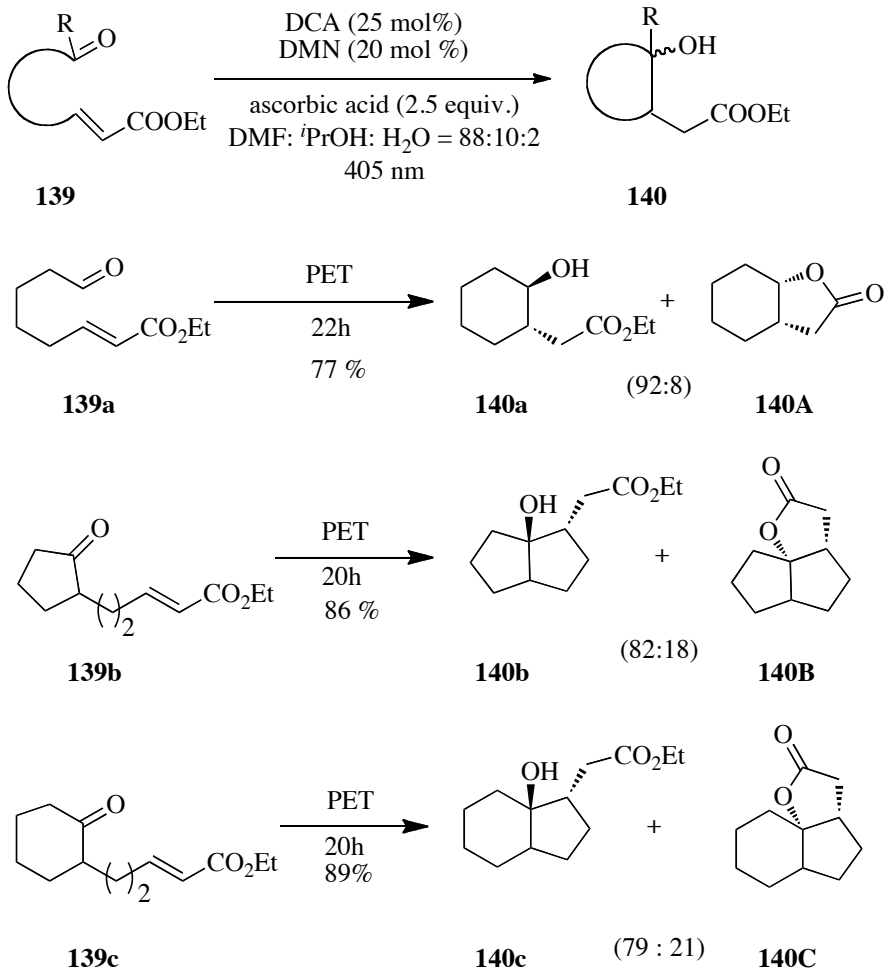
equiv.) remaining at the end of the reaction. Low yield of the product and at the same time total consumption of starting material prompted us to investigate the mass balance of the reaction. In further investigation we observed that tertiary amine (DIPEA or 2,6-lutidine), which was used as sacrificial electron donor, underwent nucleophilic substitution reaction with the halide and resulted in the formation of undesired quaternary ammonium salt of the corresponding amine (Scheme 28), thus greatly reducing the yield of the desired radical process. We performed the reaction with several tertiary amines that are relatively less nucleophilic and more sterically hindered around the nitrogen centre to prevent nuclophilic attack to the halide. Nevertheless, in all cases we ended up with the undesired quaternary salt. Therefore, it was necessary to find a sacrificial electron donor that had more or less no nucleophilicity under the above reaction conditions.



Scheme 28: Formation of ammonium salt.

In search of an alternative photocatalytic system we came across the combination of 1,5-dimethoxynaphthalene (DMN) as a primary and ascorbic acid as secondary and sacrificial electron donor, as applied by Pandey *et al*.[18] for the cyclization of aldehydes and ketones onto the tethered α, β-unsaturated ester by employing 9,10-dicyanoanthracene (DCA) as a visible light harvesting electron acceptor (Scheme 29). We applied this sacrificial electron donor combination (DMN and ascorbic acid) with $Ru(bpy)_3^{2+}$ for our reaction conditions in the presence of visible light. The reactions (Scheme 27) were again performed with this new photocatalytic system using DMF alone

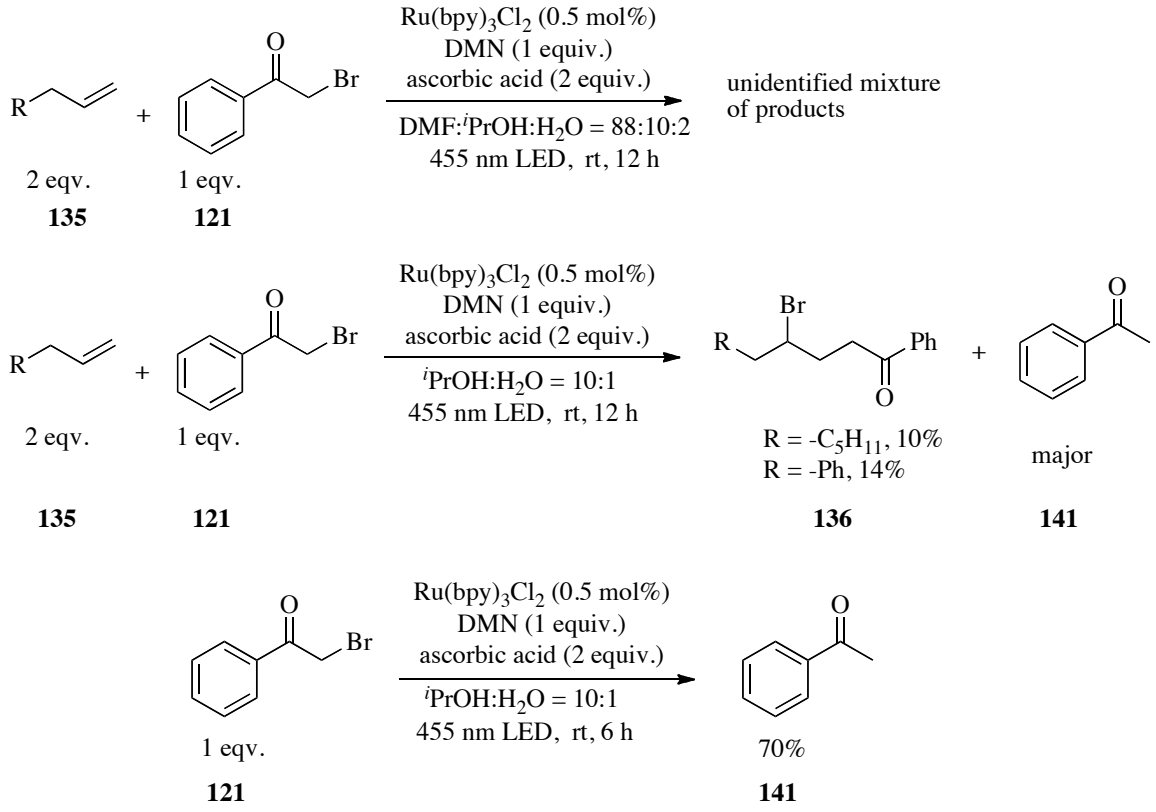
and DMF : ^{i}PrOH : H_2O = 88 : 10 : 2 mixture (as reported by Pandey *et al*.[18]) as solvent. In both cases, reactions were not clean and gave unidentified mixture of products. Subsequently, we performed the reactions in isopropanol-water mixture (10:1), nevertheless, the desired addition product was observed only in very low yield as compared to the previous case.



Scheme 29: Cyclization of aldehyde and ketones to their tethered α, β-unsaturated ester reported by Pandey *et al*.[18] (PET = Photoinduced Electron Transfer).

In addition to the desired product, one major side product was formed which was found to be the reduced product originating from the alkyl halide (Scheme 30). With this result, we came to the conclusion that in the reaction medium the alkyl radical was generated by the new photocatalytic system and it abstracted a proton more rapidly from a solvent

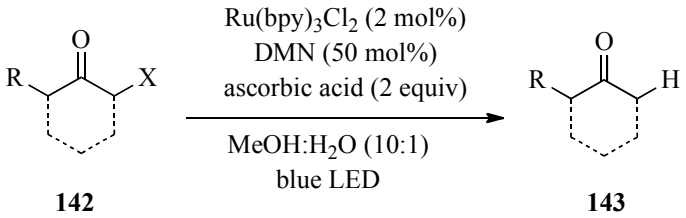
molecule or from ascorbic acid than trapping by the alkene which was present in the reaction mixture. We verified that reaction pathway in the absence of alkene to check whether it gave complete conversion to the reduced product. Indeed, **121** was completely converted to acetophenone within a few hours with good yield (Scheme 30). At the time of our study, there had only been one report from Stephenson group,[15] for the dehalogenation of an alkyl halide using visible light in which they used tertiary amine as electron donor. With this result in hand, we decided to apply our photocatalytic combination ($Ru(bpy)_3^{2+}$, DMN and ascorbic acid) to reductive dehalogenation of alkyl halides.



Scheme 30: Reaction with new photocatalytic system leads to dehlogenated product.

3.5 Dehalogenation of aromatic and cyclic aliphatic α-halo carbonyl compounds

The new catalytic system, which we developed, was applied for the dehalogentaion of aromatic and cyclic aliphatic α-halo carbonyl compounds.

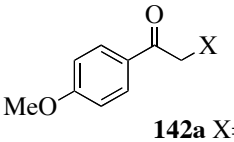
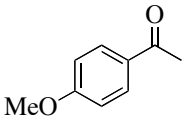
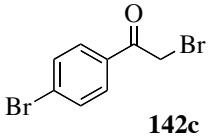
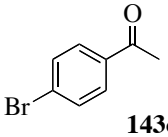
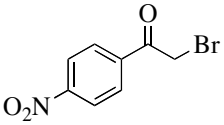
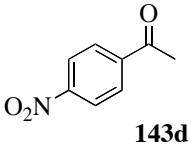
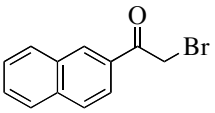
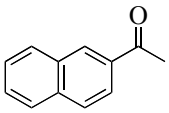


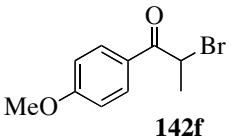
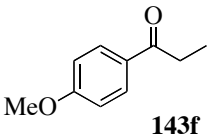
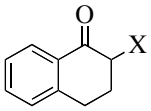
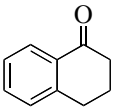
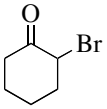
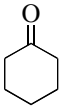
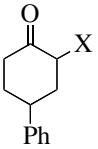
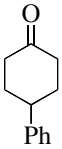
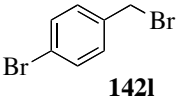
142 **143**

Scheme 31: Photocatalytic reductive dehalogenation of α-halocarbonyl compounds.

Irradiation of α-halo carbonyl compound **142** by blue LED (455 ± 10 nm) with $Ru(bpy)_3Cl_2$ in the presence of DMN and ascorbic acid smoothly gave rise to corresponding dehalogenated compound **143** (Scheme 31). Reaction conditions for the dehalogenation were optimized using 2-bromo-1-(4-methoxyphenyl)ethanone **142a** (Table 3, entry1) as model substrate.

Table 3: Photocatalyzed reductive dehalogenation of α-haloketones[a].

entry	substrate	product	time (h)	isolated yield[b] (%)
1	 **142a** X=Br **142b** X=Cl	 **143a**	5 40 15	93 90[c] 81
2	 **142c**	 **143c**	5	89
3	 **142d**	 **143d**	24	72
4	 **142e**	 **143e**	12	84

entry	substrate	product	time (h)	isolated yield[b] (%)
5	 **142f**	 **143f**	24	54
6	 **142g** X= Br **142h** X=Cl	 **143g**	24 36	71 82
7	 **142i**	 **143i**	24	50
8	 **142j** X= Br **142k** X= Cl	 **143j**	18 24	75 63
9	 **142l**	NR[d]	48	-----

[a]Reaction conditions: organohalide (1.0 equiv), $Ru(bpy)_3Cl_2$ (2 mol%), DMN (50 mol%), ascorbic acid (2 equiv), $MeOH/H_2O$ = 10:1, blue LED. [b]Isolated yield after purification by chromatography on SiO_2, [c]10 mol% DMN was employed, [d]NR = no reaction.

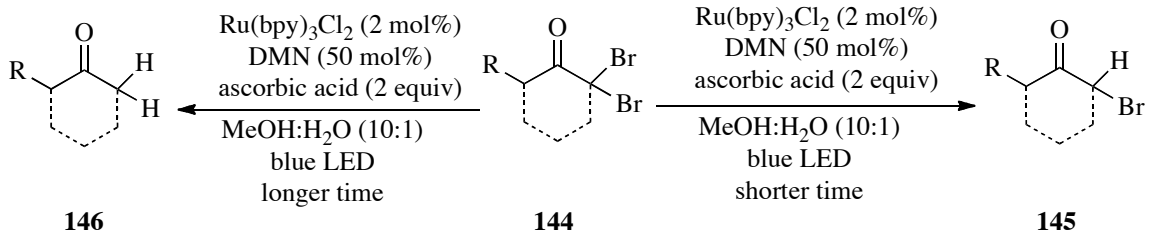
Optimization of reaction conditions revealed that a methanol-water mixture (10:1) was the best choice of solvent for the process, employing 2 mol% of ruthenium catalyst and 50 mol% of DMN. The reaction proceeded well in acetonitrile or only methanol, although with considerably longer reaction times (24 h instead of 5 h for full conversion), while DMF resulted in an unclean reaction with the formation of a number of unidentified side products. A control experiment excluding $Ru(bpy)_3Cl_2$ gave a very negligible amount of **143a** whereas decreasing the amount of DMN (10 mol%) required 40 h to complete the reaction. For this process we also observed that a carbonyl group next to halogen was necessary for successful dehalogentaion, which was confirmed when

142l was subjected to the same conditions for dehalogenation. Even after 48 h the starting material was intact (Table 3, entry 9). Both primary and secondary α-bromocarbonyl compounds can be reduced in high yield (Table 3, entries 1-8) under the reaction conditions. This protocol was also amenable to the corresponding α-chlorocarbonyl compounds. However, longer reaction times were necessary to achieve good conversion (Table 3, entries 1, 6 and 8). Good functional group tolerance, notably for those that could in principle also undergo reduction such as aromatic nitro or bromo moieties (Table 3, entries 2, 3) was observed.

3.6 Selective mono-debromination of α,α-dibromo compounds

The selective debromination of α-bromoketones is a useful transformation in organic synthesis and remains a challenging problem because of the presence of more than one reducible groups. The problem becomes more complicated in α,α-dibromoketones particularly when selective debromination of one bromo group is required. Although a number of methods have been reported for the debromination of α-bromocarbonyl compounds using a variety of reagents, only one procedure is known[19] for monodebromination of *gem*-α,α-dibromoketones. This provoked us to find a suitable method for this challenging transformation.

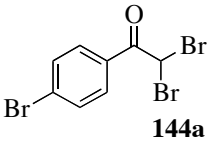
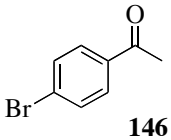
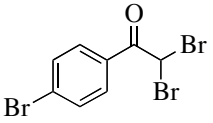
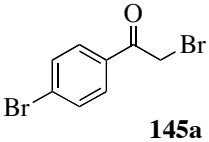
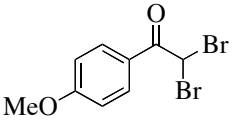
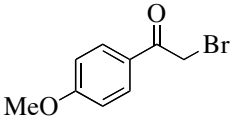
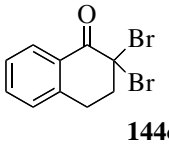
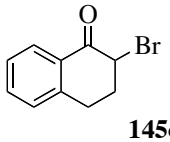
In this regard, the protocol, which we developed for the reduction of acyl halides, was applied for selective debromination of α, α-dibromo to their corresponding monobromo ketones. By proper control of reaction time, the selective photocatalytic reduction of α, α-dibromoketones to either monobromo ketones or to the doubly debrominated parent ketones became possible (Scheme 32). The reaction conditions were the same as for debromination of α-halocarbonyl compounds except that for selective monodebromination the reaction was stopped (confirmed by TLC) when the doubly debrominated product just started to form (Table 4).



Scheme 32: Selective monodebromination of α, α-dibromocarbonyl compounds.

A good functional group tolerance, such as aromatic bromo (that could in principle undergo reduction) was observed (Table 4, entry 1, 2). But selective monodechlorination did not work well with this protocol.

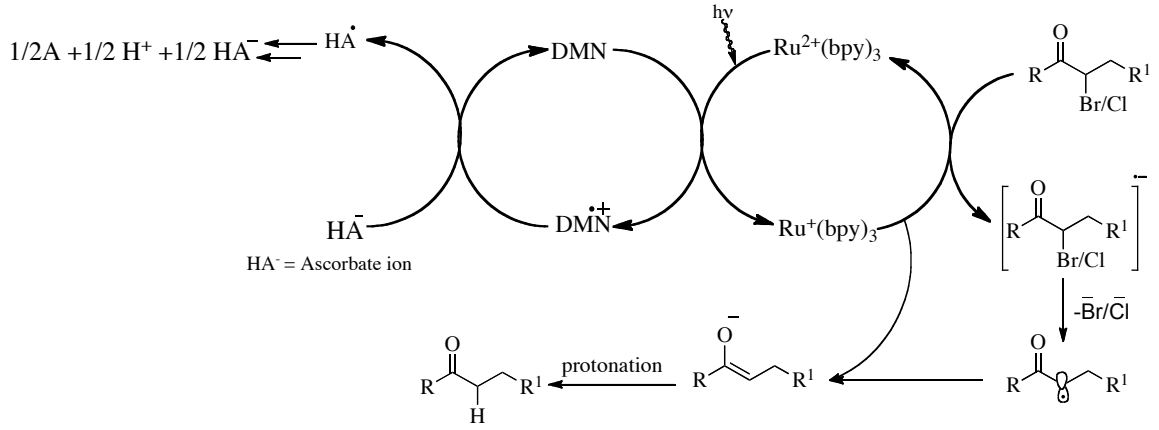
Table 4: Photocatalysed selective debromination of dibromo compounds[a].

Entry	Substrate	Product	Time (h)	Isolated yield[b] (%)
1	 **144a**	 **146**	9	71
2	 **144a**	 **145a**	0.5	88[c]
3	 **144b**	 **145b**	2	70[c]
4	 **144c**	 **145c**	0.5	54[c]

[a]Reaction conditions: organohalide (1.0 equiv), $Ru(bpy)_3Cl_2$ (2 mol%), DMN (50 mol%), ascorbic acid (2 equiv), $MeOH/H_2O$ = 10:1, blue LED. [b]Isolated yield after purification by chromatography on SiO_2, [c]The reaction was stopped (TLC monitoring) when 2-fold debrominated product just started to form.

3.7 Proposed mechanism

Mechanistically, we proposed that the dehalogenation involves the activation of the substrate to form a radical intermediate by transferring one electron from Ru(I) (Scheme 33) following literature precedent. It is well established that Ru(II) readily accepts a photon from a variety of light sources (here from blue LED) to populate the activated *Ru(II) metal-to-ligand charge transfer excited state. DMN acting as the primary donor, transfers an electron to initiate the catalytic cycle by generating a Ru(I) complex. As Ru(I) is a potent reductant, it is able to transfer a single electron to the α-halocarbonyl substrate, thus furnishing a radical anion that rapidly eliminates a halide. The resulting α-acyl radical then can be further reduced by the photocatalyst to give an enolate that ultimately undergoes protonation to give the dehalogenated product.



Scheme 33: Mechanistic proposal for photocatalytic dehalogenation.

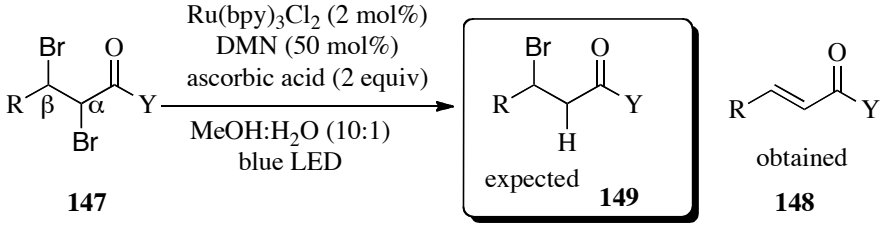
Conclusion:

In conclusion, we have developed a conceptually new photocatalytic system with visible light to drive sequential electron transfer processes for reductive dehalogenation of monobromides or chlorides to their dehalogenated counterparts and *gem*-dibromides to monobromides selectively. As a key structural feature, a carbonyl group positioned alpha to one halogen atom is required for the success of this transformation.

4. Debromination of *vic*-dibromides to alkene by visible light

4.1 Protection-deprotection of olefins by bromination-debromination

To expand the scope of our work, we wanted to apply our photocatalytic combination to more competitive substrates. We planned to dehalogenate the halogen which is α-to the carbonyl in the presence of halogen β-to the carbonyl, e.g., compound **147** contains two bromine atoms: one is α-to the carbonyl and the other is β-to the carbonyl. We wanted to selectively dehalogenate the α-bromine (Scheme 34), as our photocatalytic combination works only when there is a carbonyl next to the halogen. For this purpose we irradiated vicinal dibromocarbonyl compounds **147** by a blue LED (455 ± 10 nm) with $Ru(bpy)_3Cl_2$ in the presence of DMN and ascorbic acid. Although from the irradiation we expected α-dehalogenated product **149,** in reality we obtained α, β-unsaturated carbonyl compound **148** in good yields. We utilize this methodology for the deprotection of bromine to get olefins.



Scheme 34: Photocatalyzed reductive debromination of vicinal dibromides.

Bromination-debromination sequences are widely used in organic synthesis for the protection-deprotection of olefins. Although functionalization of olefins by simple bromination generally proceeds smoothly and stereospecifically in high yields, reversing the process to the parent olefin *via* a debromination step is more challenging. There are a number of reagents known for this transformation,[20] however, the necessity to employ stoichiometric amounts of strongly reducing agents might cause problems of selectivity and functional group compatibility. Moreover, the toxicity of some reagents such as the

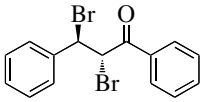
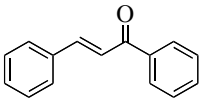
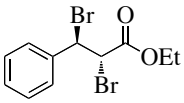
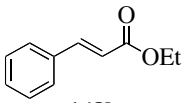
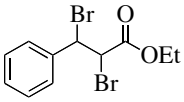
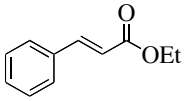
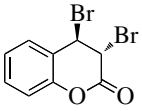
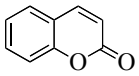
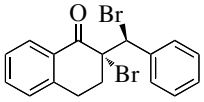
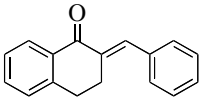
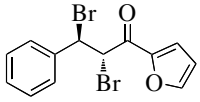
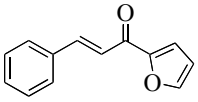
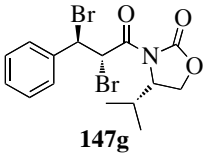
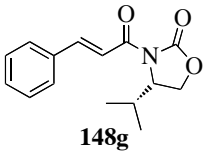
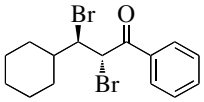
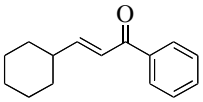
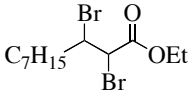
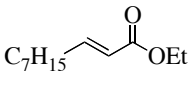
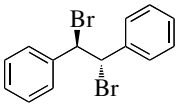
widely used organotin compounds makes the development of environmentally friendly catalytic alternatives desirable. However, our visible light mediated mild photocatalytic combination gave reductive debromination of vicinal dibromides to α, β-unsaturated compounds in high yields.

4.2 Debromination of *vic*-dibromide leading to disubstituted alkene

A representative range of disubstitued *vic*-dibromides **147** underwent debromination by this procedure to provide the corresponding alkenes **148** (Table 5), with quantum yields ranging between 0.01 and 0.02. The same optimized reaction conditions as mentioned before were employed. Reducing the amount of DMN was possible (from 50 mol% to 25 mol%) but resulted in slower conversion of the substrate (*cf* entries 1 and 2). However, DMN could be recovered at the end of the reaction and reused, making the employment of higher amounts more practical but nevertheless economically acceptable. A carbonyl substituent, e.g., a ketone, ester, lactone or oxazolidinone, adjacent to the bromide was required for the debromination to take place (entries 1-9), e.g., no reaction took place with 1,2-dibromo-1,2-diphenylethane (entry 10). Moreover, alkyl substituted dibromides reacted sluggishly in most cases (Table 5, entries 8,9). Only (*E*)-configurated disubstituted alkenes were obtained from acyclic precursors in all cases, even when a 43:57 mixture of *erythro* and *threo vic*-dibromide **147c** (Table 5, entry 3) was subjected to the above conditions. The cyclic dibromide **147d** also underwent debromination smoothly (Table 5, entry 4), giving rise to the (*Z*)-configurated alkene **148d** predetermined by the ring size of the cycle.

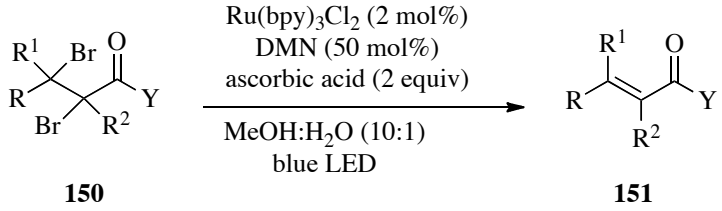
Using **147a** (Table 5, entry 1) as a representative substrate, a series of control experiments were performed. Exclusion of any one of the reaction components ($(Ru(bpy)_3Cl_2)$, DMN or ascorbic acid) yielded only a negligible amount of the product, even after 48 h.

Table 5: Reductive debromination of *vic* dibromocarbonyl compounds leading to disubstituted alkene.

entry	substrate	product	time (h)	isolated yield (%)
1	 **147a**	 **148a**	8 36	92 83[c]
2	 **147b**	 **148b**	8 36	88 74[c]
3[d]	 **147c**	 **148b**	12	73
4	 **147d**	 **148d**	5	92
5	 **147e**	 **148e**	8	75
6	 **147f**	 **148f**	24	26[e]
7	 **147g**	 **148g**	5	89
8	 **147h**	 **148h**	36	28[e]
9	 **147i**	 **148i**	24	26[e]
10	 **147j**	-----	24	NR[f]

4.3 Trisubstituted alkene by reductive debromination of *vic*-dibromo compounds

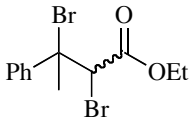
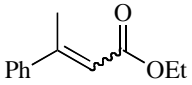
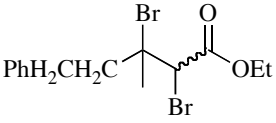
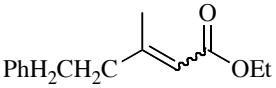
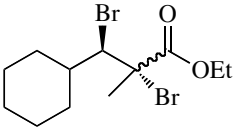
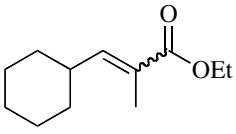
Dibromocarbonyl compounds leading to trisubstituted alkenes after dehalogenation were also employed utilizing the same photocatalytic combination. In all the cases yields were good but the *E*/*Z*-selectivity in debrominations of compounds that gave rise to trisubstituted alkenes (Scheme 35, Table 6) seemed to be governed by the relative stability

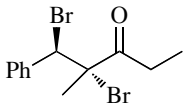
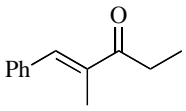
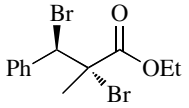
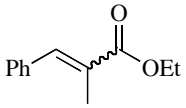


Scheme 35: Photocatalytic vicinal debromination leads to trisubstituted alkene.

of the products, allowing in some cases the conversion of stereomixtures of dibromides to one geometrically pure alkene (Table 6, entry 1 and 3), but might also lead to *E*/*Z*-mixtures of alkenes despite starting from diastereomerically pure dibromide (Table 6, entry 5). Moreover, alkyl-substituted dibromides reacted sluggishly which leads to lower conversion to product (Table 6, entries 2 and 3).

Table 6: Reductive debromination of vicinal dibromides leading to trisubstituted alkene[a].

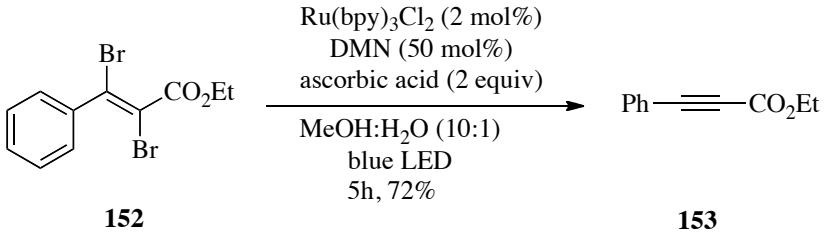
Entry	Substrate	Product	Time (h)	Isolated yield[b] (%)
1	 **150a**: *erythro:threo*=67:33	 **151a**: *E:Z*=95:5	12	70
2	 **150b**: *erythro:threo*=80:20	 **151b**: *E:Z*=84:16	24	65[c]
3	 **150c**: *erythro:threo*=52:48	 **151c**: *E:Z*=95:5	24	27[c]

Entry	Substrate	Product	Time (h)	Isolated yield[b] (%)
4	 **150d***: erythro:threo*=100:0	 **151d**: *E:Z*=100:0	24	75[c]
5	 **150e**: *erythro:threo*=100:0	 **151e**: *E:Z*=75:25	24	65[c]

[a]Reaction conditions: organohalide (1.0 equiv), $Ru(bpy)_3Cl_2$ (2 mol%), DMN (50 mol%), ascorbic acid (2 equiv), $MeOH/H_2O$ = 10:1, blue LED. [b]Isolated yield after purification by chromatography on SiO_2, [c]4 mol% of $Ru(bpy)_3Cl_2$ was employed

4.4 Photocatalysed debromination leads to alkyne

The synthesis of an alkyne from the corresponding *vic*-dibromoalkene was also achieved successfully utilizing the same reaction conditions as previously applied for the debromination of the *vic*-dibromoalkanes (Scheme 36). Thus, treatment of (*E*)-ethyl 2,3-dibromo-3-phenylacrylate **152** in the previously reported reaction condition gave ethyl 3-phenylpropiolate **153** in good yield.



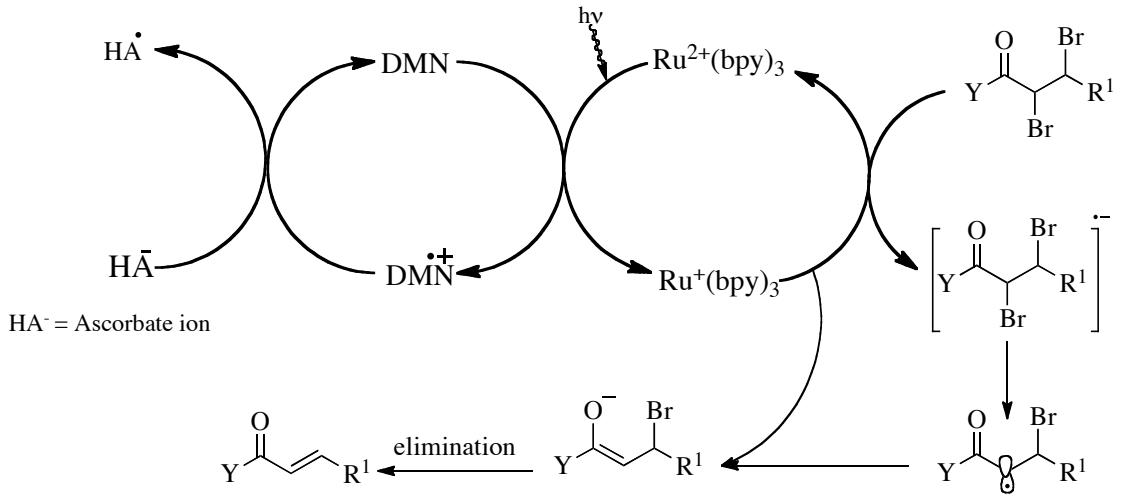
152 **153**

Scheme 36: Photocatalytic reductive debromination of a *vic*-dibromoalkene.

4.5 Mechanistic explanation

We propose a similar mechanism that was already put forward for the dehalogenation of α-halocarbonyl compounds. The excited *Ru(II) accepts an electron from the primary electron donor DMN to generate a Ru(I) complex. As Ru(I) is potent reductant, it

transfers a single electron to the *vic*-dibromide substrate which furnishes a radical anion and rapidly eliminates a bromide. The resulting α-acyl radical again accepts an electron from the photocatalyst and gives an enolate, which eliminates the other bromide and leads to the α, β-unsaturated carbonyl compound (Scheme 37). We also observed that E2-type *anti*-elimination does not occurs for the disubstituted *vic*-dibromides (Table 5, entry 3, even when we started with a mixture of *erythro* and *threo* dibromides, we ended up with only *E*-isomer in the product). For trisubstituted substrate the elimination also proceed by the same type of mechanism where a stable radical or anion intermediate breaks down to the alkenes according to their thermodynamic stability (Table 6, entry 5, although we started with diastereomerically pure dibromides but we ended up with *E*/*Z* mixture of products).



Scheme 37: Mechanistic proposal for debromination of *vic*-dibromides.

Conclusion

In conclusion, we have developed a conceptually new photocatalytic system with visible light to drive sequential electron transfer processes for reductive debromination of vicinal dibromides to (*E*)-alkenes and alkynes, *gem*-dibromides to monobromides, and monobromides or chlorides to their dehalogenated counterparts. As a key structural feature, an α-carbonyl group to one halogen atom is required for the success of the

transformation. The photosystem is also highlighted by its chemoselectivity, resulting in reduced products in high yields under mild reaction conditions.

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5. Efficient Photocatalytic oxygenation of cyclic enamines and enol ethers

5.1 Singlet Oxygen ($^1O_2$)

Molecular oxygen is one of the most important substances on the earth. Oxygen comprises 21% of the atmosphere, 89 % of seawater by weight, and at least 47 % of the Earth's crust. Almost all living organisms utilize oxygen for energy generation and respiration. In the 1840s Michael Faraday discovered that oxygen is attracted to a magnet. Almost a century later, in 1925, Robert Mulliken explained why oxygen is magnetic using quantum theory. His analysis showed that molecular oxygen has two unpaired electrons in its lowest energy state, which is known as triplet ground state of oxygen. Singlet oxygen ($^1O_2$) is a higher energy state molecular oxygen species. Singlet oxygen ($^1O_2$) was first observed in 1924 and then defined as a more reactive form of oxygen. The main method of production of $^1O_2$ is by photosensitization reactions. In 1931, Kautsky (from Heidelberg University, Germany) first proposed that $^1O_2$ might be a reaction intermediate in dye-sensitized photo-oxygenation.[1] Following this suggestion, many studies have showed that $^1O_2$ is an important and versatile reagent for oxidation reactions including cycloaddition reactions to produce endoperoxides and ene reactions to provide allylic hydroperoxides. It has been also demonstrated that $^1O_2$ can react with many kinds of biological molecules such as DNA, proteins and lipids.[2] Since oxygen is ubiquitous and efficiently quenches electronically excited states, $^1O_2$ is likely to be formed following irradiation in numerous ways and involved in various chemical and biological processes as well as in several disease processes. Therefore, better understanding of its chemical and physical nature is important and interesting area of study till date.

5.2 Electronic structures and the lifetime of singlet oxygen

Molecular orbital theory can explain the electronic structure of molecular oxygen. The lowest electronic state of oxygen is a triplet ground state ($^3\Sigma_g^-$) with two unpaired electrons distributed in the highest occupied orbitals. Rearrangement of the electron spins within these two degenerate orbitals result in two possible singlet excited states (Table 7). The $^1\Delta_g$ state has an energy only 23 kcal above that of the ground state; both electrons are

paired in a single orbital, leaving the other vacant. This state might be expected to undergo two-electron reactions. The higher energy singlet state ($^1\Sigma_g^+$) comes from the spin pairing electrons in different orbitals and might be expected to undergo one-electron free-radical reactions. In both forms of $^1O_2$, the spin restriction is removed so that the oxidizing ability is greatly increased. The $^1\Sigma_g^+$ state has a much shorter lifetime than $^1\Delta_g$ state because $^1\Sigma_g^+$ is more reactive than the $^1\Delta_g$ form. It decays to $^1\Delta_g$ state before chemical reactions can occur. The different energy states of two excited states of molecular oxygen are summarized in Table 7 and the molecular orbital picture is shown in fig 4.

Table 7: Different energy state of molecular oxygen.

State of the oxygen molecule	Occupancy of highest orbitals	Energy above ground state
Second excited state ($^1\Sigma_g^+$)	↑ ↓	37 kcal/mol
First excited state ($^1\Delta_g$)	↑↓	23 kcal/mol
Ground state ($^3\Sigma_g^-$)	↑ ↑	

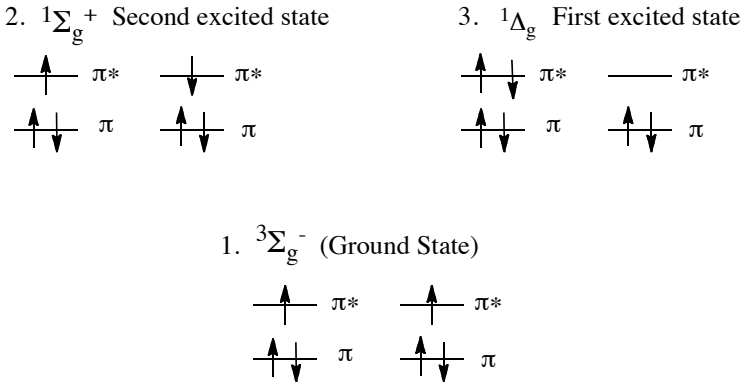


Fig. 4. Molecular orbital of singlet oxygen.

5.3 Generation of singlet oxygen

Both physical and chemical methods can generate singlet oxygen. One of the most important methods is photosensitization. Photosensitization refers to light-activated process that requires the presence of a light-absorbing substance, the photosensitizer, that initiate a physical, chemical, or biological process in a non-absorbing substrate. The

photosensitizer absorbs light from suitable light source and populates the singlet excited state which converts to metastable triplet state *via* Inter System Crossing (ISC). The pathway in which the photosensitizer triplet state reacts first with a substrate other than molecular oxygen is termed *Type I*. In the alternative *Type II* pathway, the photosensitizer triplet state reacts first with molecular oxygen and generates $^1O_2$, which reacts with substrate and leads to the product formation (Fig. 5), while the photosensitizer returns to the ground state. The commonly used photosensitizers are rose bengal **10**, eosin, methylene blue, tetraphenylporphyrin and its derivatives, C_{60} etc.

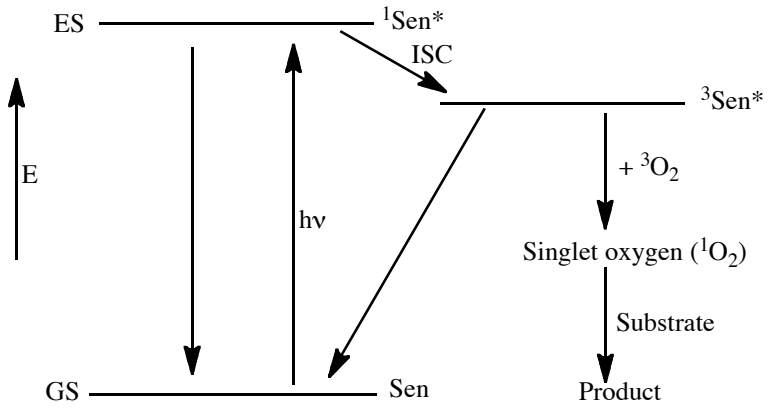


Fig. 5. *Type II* pathway to produce $^1O_2$ (GS = Ground State, ES = Excited State, Sen = Sensitizer, ISC = Inter System Crossing).

There are several chemical methods which can generate $^1O_2$. One of the biologically significant reactions is hydrogen peroxide and hypochlorite ion reaction, because OCl^- can be formed by the enzyme myeloperoxidase during phagocytosis according to $OCl^- + H_2O_2 \rightarrow {}^1O_2 + Cl^- + H_2O$. Other chemical methods include the thermolysis of endoperoxides of some aromatic hydrocarbons and some organic ozonides.

5.4 Quenching of singlet oxygen

Quenching of singlet oxygen involves the deactivation of the excited state of molecule. Deactivation can be accomplished by either physical or chemical quenching. Physical quenching leads only to the deactivation of singlet oxygen to its ground state with no oxygen consumption or product formation. In chemical quenching, by contrast, singlet

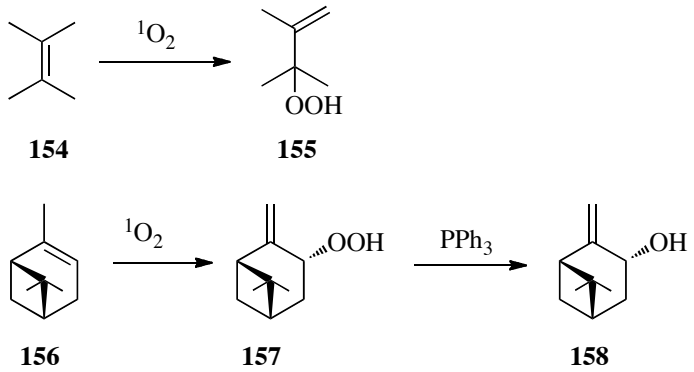
oxygen reacts with quencher R to produce RO_2. Two major mechanisms of $^1O_2$ quenching are known, namely energy transfer and charge transfer quenching. Energy transfer quenching is the reverse of reaction by which singlet oxygen is formed. It involves formation of triplet quencher and ground state oxygen ($^1O_2 + Q \rightarrow {}^3O_2 + {}^*Q$). Charge transfer quenching involves the interaction between the electron-deficient $^1O_2$ molecule and electron donors (substrate molecules) to form a charge transfer complex, which leads to different chemical reactions.

5.5 Reactions of singlet oxygen

The most important reactions of singlet oxygen involve its reactions with carbon-carbon double bonds, which are present in many biological molecules, such as carotene, chlorophyll, and unsaturated fatty acids.

(a) Alder-ene reaction (Schenck reaction)

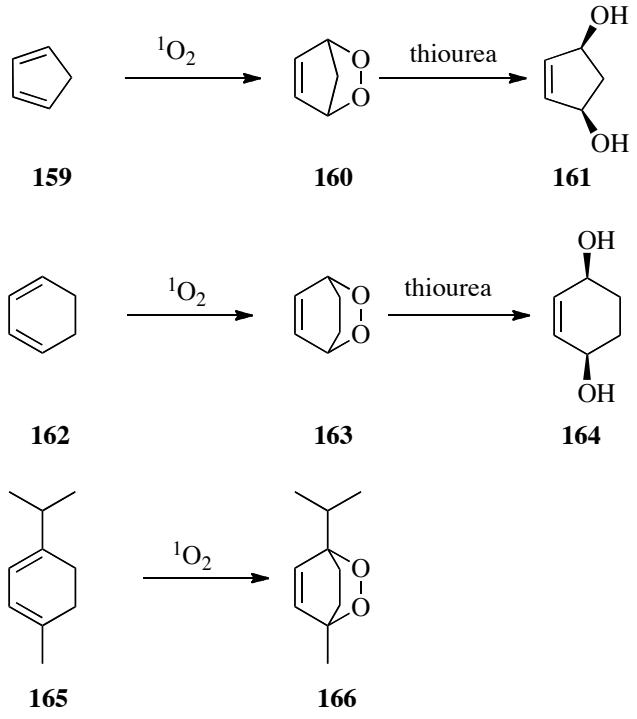
In this reaction, oxygen adds stereospecifically to the alkyl substituted olefins to form allylic hydroperoxides with migration of the double bond. The resulting allylic hydroperoxides can be easily converted into α, β-unsaturated carbonyl compounds and allyl alcohols.[3,4] A variety of mechanisms have been proposed to explain the products observed in this reaction. The cis-alkene is more reactive than trans isomer. A few ene reactions are shown below (Scheme 38).



Scheme 38: Singlet oxygen mediated ene reactions.

(b) [4+2] Cycloaddition reaction

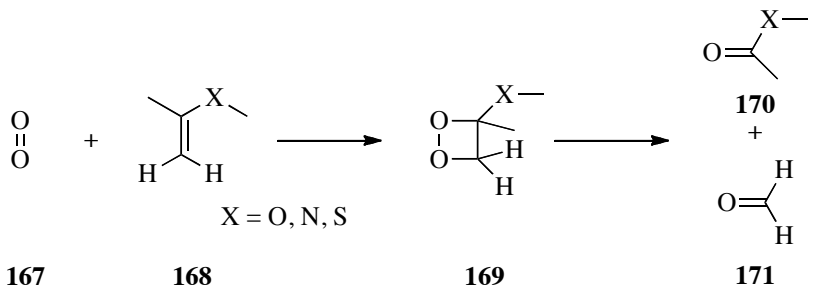
Singlet oxygen can react as a good dienophile with dienes such as *cis* dienes or aromatic hydrocarbons to yield endoperoxides, which can be reduced by thiourea to give corresponding diols. This reaction is similar to the well-known Diels-Alder reaction.[3] The initially formed endoperoxides may undergo fragmentation back to reactants or rearrange to products through the homolytic fission of the oxygen-oxygen bond. The concerted character of this addition reaction has been indicated based on experimental observations. Few examples are shown below (Scheme 39).



Scheme 39: [4+2] reaction with singlet oxygen as dinophile

(c) Reaction with electron rich system

Singlet oxygen can also react with electron rich systems, in which carbon-carbon double bonds have adjacent electron donating atoms (oxygen, nitrogen, sulfur). In these reactions, an oxetane type adduct is formed. When these dioxetanes are unstable they decompose to give carbonyl compounds (Scheme 40). Decomposition of dioxetane is sometimes accompanied by chemiluminiscence.

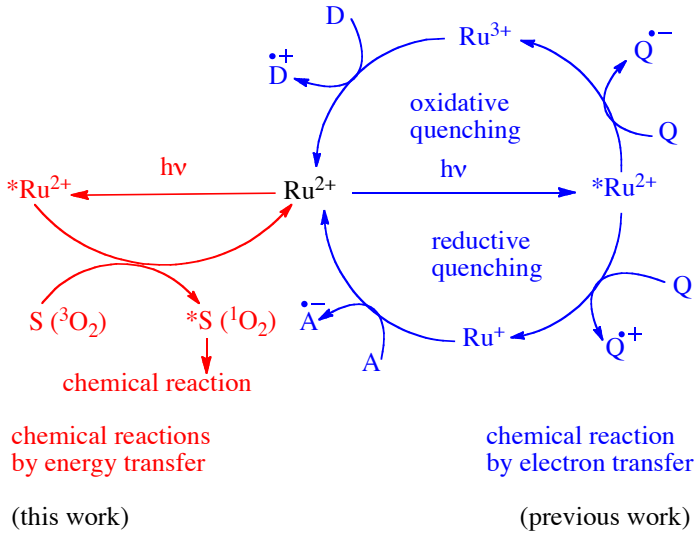


Scheme 40: Reaction of singlet oxygen with electron rich system.

5.6 $Ru(bpy)_3Cl_2$ complex as sensitizer for singlet oxygen generation

Visible-light sensitization is an attractive means to initiate organic reactions[5] because of the lack of absorbance of visible light by organic compounds. This means that the side reactions often associated with the use of high-energy UV light are minimized. Photocatalysts such as $Ru(bpy)_3Cl_2$ (bpy = 2,2'-bipyridine) offer a means to selectively functionalize organic molecules; however, their use in initiating chemical reactions relevant to organic chemistry is very limited.[6] Tuning the excited state property of the photocatalyst, it is possible to design organic transformations by transferring electron or energy from the higher energy state catalyst to the substrate molecules (Scheme 41). Electron transfer from excited photocatalyst to substrate molecules occurs by oxidative and reductive quenching pathways, which have been discussed broadly in the previous part of this thesis. Organic reactions mediated by energy transfer from excited photocatalyst are discussed in this part.

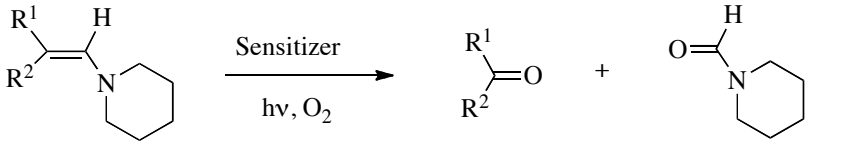
The excited photocatalyst, usually in the triplet state, reacts with triplet oxygen to give singlet oxygen. Singlet oxygen is a highly reactive species that has shown to be efficiently photosensitized by a large number of compounds, most of which have been organic compounds.[7,8] Sometimes inorganic complexes are more effective in this purpose rather than organic compounds. One of the best example is $Ru(bpy)_3Cl_2$.[9,10] The complex ion tris(2,2'-bipyridine) ruthenium(II) $[Ru(bpy)_3]^{2+}$ is known to be a good singlet oxygen photo-sensitizer due to both its relatively strong absorption in the visible region of the spectrum and long lived triplet metal to ligand charge transfer state ^{3}MLCT, making its excited state susceptible to quench by oxygen in normal organic solvents.[11-16]



Scheme 41: Photocatalysis by electron transfer and energy transfer pathways. Q = quencher, D = donor, A = acceptor, S = substrate molecule.

5.7 Oxygenation of cyclic enamines and enol ethers

Singlet molecular oxygen production by photocatalyst $Ru(bpy)_3Cl_2$, had been studied widely, but the application of $^1O_2$, produced particularly by this catalyst in the presence of visible light, has not been truly studied for organic transformations. In accord with our interest to develop new chemical transformations going through radical intermediates, we wanted to utilize cyclic enamines as radical precursors being liberated by photoredox catalysis. In the course of the reaction, we observed oxidative cleavage of enamine double bond to the corresponding carbonyl derivatives in the presence of molecular oxygen and catalytic amount of photocatalyst $Ru(bpy)_3Cl_2$ promoted by visible light. Enamins are known to be excellent substrates for dye-sensitized photooxygentaion; the C-C double bond is cleaved to give a ketone or aldehyde and an amide[17] (Scheme 42). With this literature evidence, we planned to oxygenate cyclic enamines to obtain synthetically useful amino acid derivatives.



168a-c **171a-c** **170a-c**

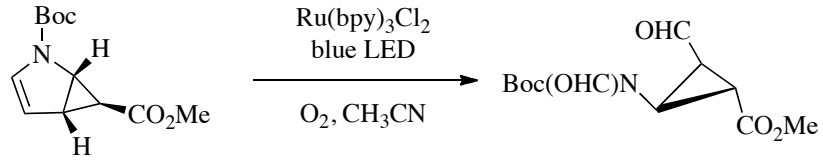
168a $R^1 = R^2 = CH_3$
168b $R^1 = R^2 = Ph$
168c $R^1 = Ph, R^2 = H$

96 - 100 %

Scheme 42: Photooxygenation of enamines.[17]

Our preliminary studies focused on the oxidative cleavage of enamine double bond of **172a**. Initial success was obtained upon subjecting **172a** to irradiation by a blue LED lamp (λ = 455 ± 10 nm) with $Ru(bpy)_3Cl_2$ (2 mol%) in open air using CH_3CN as solvent for 24 h. These conditions provided 56 % isolated yield of the product **173a**, with remaining unidentified side products. Subsequent optimization revealed that the presence of oxygen accelerate the oxidation by reduction of reaction time with diminish side products. In addition, lowering of catalyst loading (0.5 mol %) was possible for the oxidation with prolonging the reaction time (Table 8).

Table 8: Optimization of the oxidative cleavage of enamine double bond of **172a**



172a **173a**

entry	conditions	yield(%)[a]
1	open air, $Ru(bpy)_3Cl_2$ (5 mol%), 24 h	56
2	open air, $Ru(bpy)_3Cl_2$ (2 mol%), 24 h	52
3	O_2 bubble, $Ru(bpy)_3Cl_2$ (2 mol%), 30 min	72
4	O_2 bubble, $Ru(bpy)_3Cl_2$ (0.5 mol%), 6 h	65

[a]Isolated yield after purification by chromatography on SiO_2

Using **172a** as representative substrate, different solvents were also evaluated in this oxidation reaction (Table 9). The screening of solvents revealed that CH_3CN was the best choice of solvent for this reaction. The reaction proceeds smoothly within 30 min without significant formation of side products. Chloroform was also a good alternative for the reaction, whereas due to the longer reaction time we preferred CH_3CN. In other solvents such as MeOH, DMF gave the desire product with considerably longer reaction time and more unidentified spots in TLC.

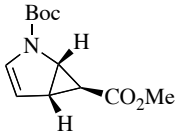
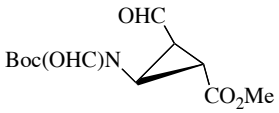
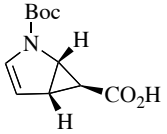
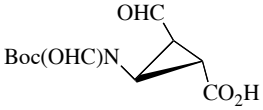
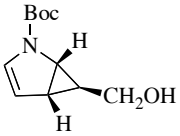
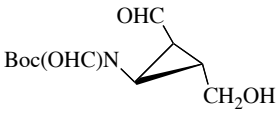
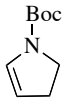
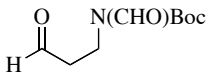
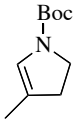
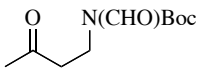
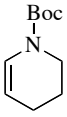
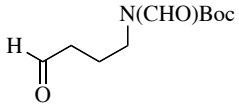
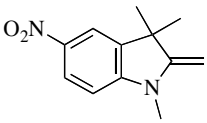
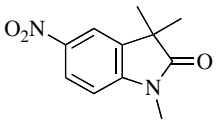
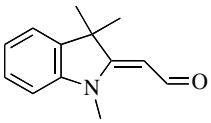
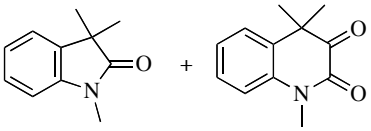
Table 9: Screening of different solvents in the photooxidation reaction

entry	solvent	Time (h)	yield(%)[a]
1	DMF	2.0	42
2	$CHCl_3$	3.0	70
3	MeOH	4.0	48
4	CH_3CN	0.5	72

[a]Isolated yield after purification by chromatography on SiO_2

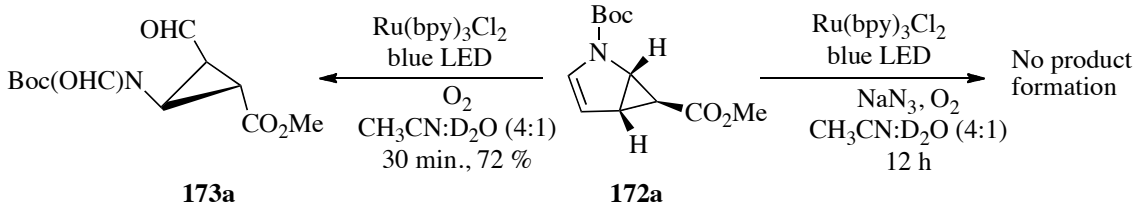
The scope of this process was illustrated by the examples detailed in Table 10. Utilizing our optimized conditions, we were able to successfully oxidize different types of cyclic enamines in the presence of other functional groups such as carboxylic acid (entry 2), free hydroxyl (entry 3) and nitro (entry 7). Many cyclopropyl substituted amino acids, especially cyclopropanecarboxylic acid, display important biological properties; consequently their syntheses have been widely studied.[18] The strategy described here provided the diastereoselective access to 2-aminocyclopropanecarboxylic acid derivatives **173a-c** from readily available starting materials **172a-c**. Different types of *N*-formyl aldehydes obtained in good yields from cyclic enamines (entry 4 and 6) whereas in similar fashion *N*-formyl ketone **173e** was obtained from substituted enamine in excellent yield (entry 5, 7 and 8). A ring expansion product **173h'** was observed in case of compound **172h** along with the desired product. Furthermore, these reactions were highlighted with their excellent yield in almost all the cases with shorter reaction time. The reactions were also independent of the protection group present at the nitrogen atom.

Table 10: Oxidative cleavage of cyclic enamines[a]

entry	substrate	product	time (h)	yield[b]
1	 **172a**	 **173a**	0.5	72
2	 **172b**	 **173b**	1.0	89
3	 **172c**	 **173c**	1.0	85
4	 **172d**	 **173d**	2.5	81
5	 **172e**	 **173e**	4.0	93
6	 **172f**	 **173f**	3.5	94
7	 **172g**	 **173g**	3.0	72
8	 **172h**	 **173h** + **173h'**	5.0	35 + 26

[a]Reaction conditions: cyclic enamine (1.0 equiv.), $Ru(bpy)_3Cl_2$ (2 mol %), O_2, CH_3CN, blue LED. [b]Isolated yield after purification by chromatography on SiO_2

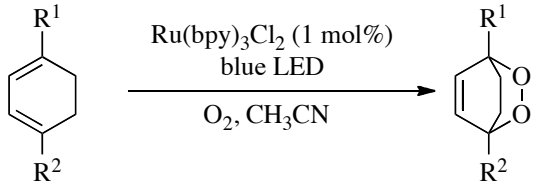
Throughout our investigations, we conducted a series of control experiments using **172a** as a representative substrate. Exclusion of any of the reaction components, including visible light, $Ru(bpy)_3Cl_2$ did not afford any oxidized product **173a** even after 24 h. The necessity of singlet oxygen was also examined by adding NaN_3 in the reaction mixture during the oxidation of **172a** by above conditions. The azide ion is a strong physical quencher of singlet molecular oxygen and is frequently employed to show involvement of $^1O_2$ in oxidation processes.[19] To prove the crucial role of singlet oxygen in this reaction, **172a** was subjected to irradiation in CH_3CN-D_2O mixture (4:1, D_2O was employed to dissolve sodium azide. Singlet oxygen has also longer life time in D_2O compared to H_2O) by a blue LED with $Ru(bpy)_3Cl_2$ in the presence of one equivalent of sodium azide. There was no formation of **173a** even after 12 h, while in the absence of NaN_3 in the same solvent condition gave the desire aldehyde **173a** in 30 min (Scheme 43). Singlet oxygen, generated by the sensitization of the catalyst, was immediately quenched by azide ion present in the reaction mixture and therefore, no product formation was observed. This directly indicated the necessity of singlet oxygen in the above oxidation process.

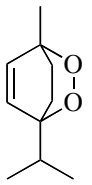


Scheme 43: Quenching of singlet oxygen by azide ion.

To further support the generation of singlet oxygen in our reaction conditions, we performed literature reported [4+2]-cycloaddition of singlet oxygen with cyclodienes[20-21] in our reaction conditions. Treatment of cyclodienes **162** and **165** with blue LED in the presence of catalytic amount of $Ru(bpy)_3Cl_2$ gave endoperoxides **163** and **166** in good yields, which were isolated in room temperature. This directly indicates the generation of singlet oxygen in our reaction conditions.

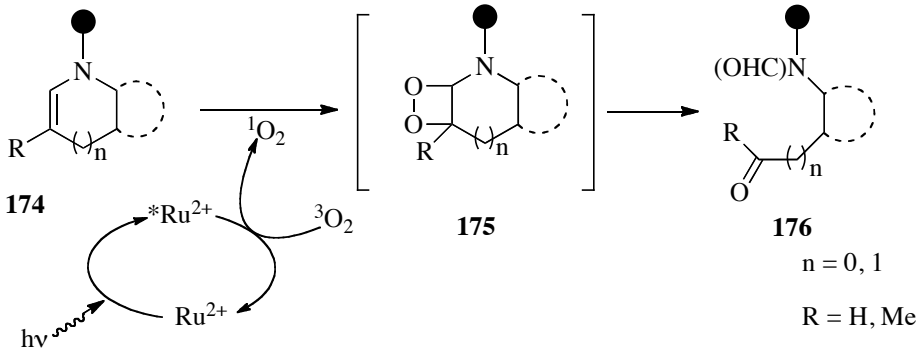
Table 11: Visible light promoted [4+2] cycloaddition of singlet oxygen catalyzed by $Ru(bpy)_3Cl_2$



entry	substrate	product	time (h)	yield[a] (%)
1	$R^1 = R^2 = H$		1.0	62
	162	**163**		
2	R^1 = Me, $R^2 = {}^i$Pr		1.0	65
	165	**166**		

[a]Isolated yield after purification by chromatography on SiO_2

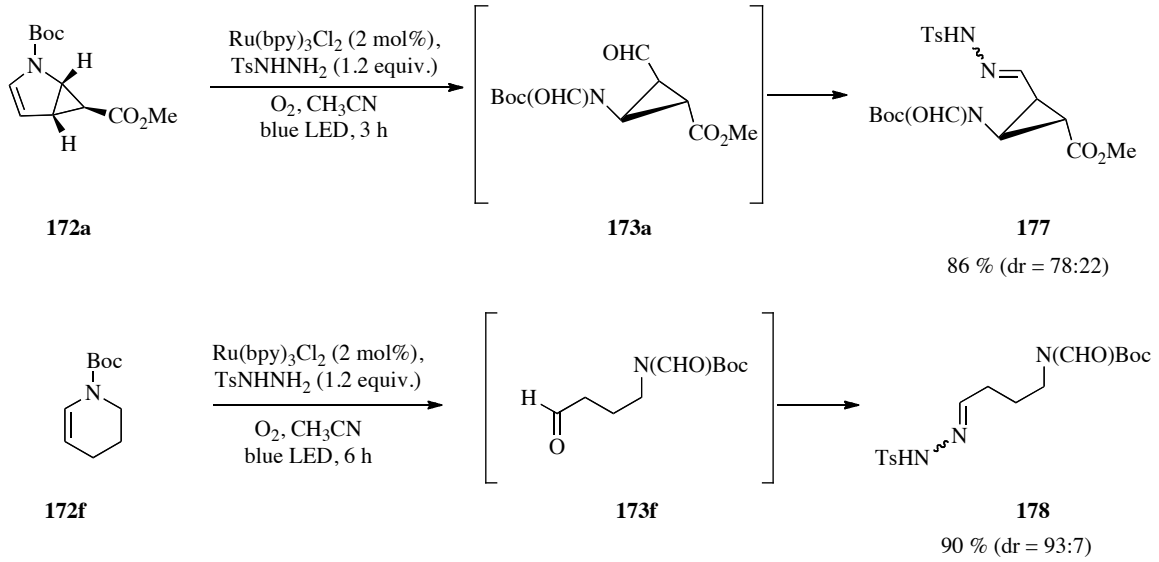
Accordingly, we proposed a mechanism wherein the photoexcited *Ru(II) undergoes energy transfer leading to singlet oxygen production. The enamines add to singlet oxygen in [2+2]-cycloaddition fashion and produce unstable 1,2 dioxetanes intermediates **175**, which decomposed quantitatively into the corresponding carbonyl fragments and resulting the desired products (Scheme 44).



Scheme 44: Proposed mechanism of photooxidation of enamines.

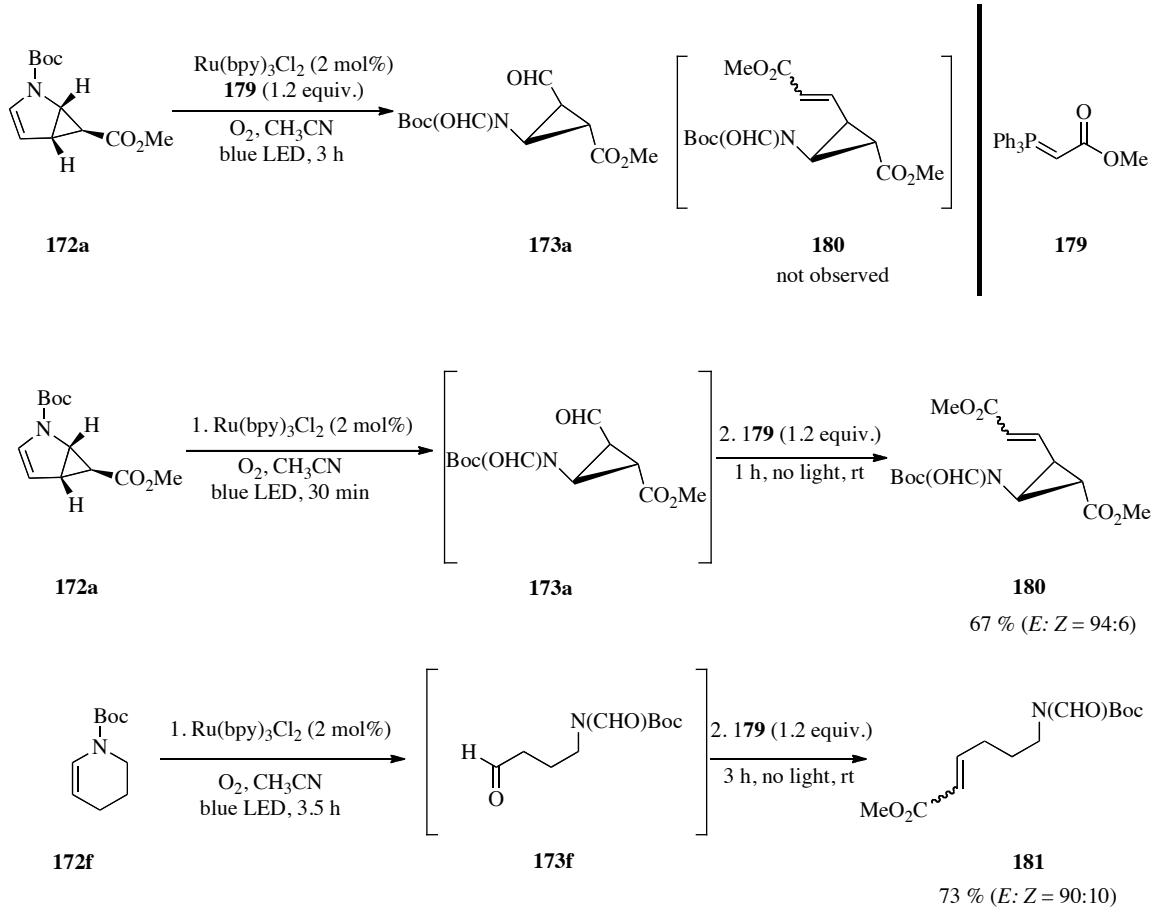
Last few years, increasing attention has been drawn to β-and γ-aminoacids and their derivatives as important constituents of natural products and as valuable intermediates, e.g., for the preparation of peptidomimetics,[22] and β- and γ-lactums.[23] However, while abundant methods are known for the synthesis of α-amino acids,[24] there are considerably fewer routes to β- and higher amino acid analogs.[25] Moreover, the corresponding amino aldehydes are often more difficult to obtain because of their tendency to undergo subsequent condensation reactions. One general approach to β- and γ-amino esters and amino aldehydes by ozonolysis of 2,3-dihydropyrroles and 1,2,3,4-tetrahydropyridines which was reported by Reiser *et al*.,[26] whereas the use of hazardous ozone in the laboratory is the practical disadvantage of that method. In this context our visible light mediated operationally simple and mild reaction conditions provided amino aldehydes or ketones. The products obtained are fully protected at nitrogen, allowing further derivatization of the aldehyde or the ketone group. This is especially advantageous for the cyclopropyl amino acid derivatives, which seem to be extremely prone to ring opening in the unprotected stage.[27] The *N*-Boc group can be selectively removed by treatment with mild acid and provides the free amino group. The oxidative cleavage of cyclic enamine by this method leading to products, e.g., **173a-c**, which preserved the relative and absolute stereochemistry of the starting material.

We expected that the protected amino aldehyde or ketone products generated in this method will be further derivatized for the generation of new intermediates. To highlight this possibility, we have applied our photo oxidative products to the synthesis of the precursor of useful reactions. As illustrated above, exposure of compound **172a** and tosyl-hydrazine to our oxidative protocol directly afforded **177** in 86% isolated yield in one pot (Scheme 45). The presence of tosyl-hydrazine did not affect the oxidation of the enamine in the same reaction mixture. Oxidation of **172a** by the above method first generated compound **173a**, which subsequently underwent hydrazone formation and resulting compound **177**. In the similar fashion compound **172f** yielded acyclic hydrazone **178**. These hydrazones can be used as precursors of Bamford-Stevens and Shapiro reactions, which furnish substituted alkenes at the end.



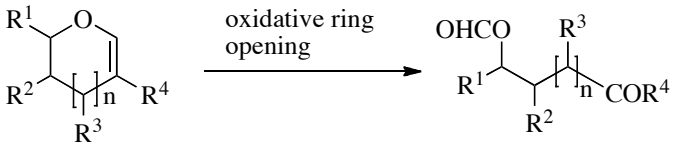
Scheme 45: One pot synthesis of hydrazones from cyclic enamines.

To further expand upon this methodology, we wanted to examine the possibility of two consecutive reactions in one pot using photo oxidation reactions. Irradiation of **172a** with $Ru(bpy)_3Cl_2$ in the presence of oxygen and Wittig salt **179**, we expected *N*-formyl alkene **180** as an end product. After 30 min irradiation by blue LED, we observed complete conversion of **172a** to the corresponding amino aldehyde **173a**, but no amino alkene **180** was observed. The stirring was continued for additional 5 h in absence of light, but the product **180** was not formed. In another set of reaction, **172a** was exposed 30 min to light from blue LED in the presence of $Ru(bpy)_3Cl_2$ and oxygen for complete conversion to **173a** and then Wittig salt **179** was added to the reaction mixture and stirring was continued for another 1 h in absence of light. This reaction conditions resulted amino alkene **180** as diastereomeric mixture (*trans:cis* = 96:4) in 67 % yield (Scheme 46). With this observation we concluded the decomposition of Wittig salt in the presence of light or oxygen and therefore no olefination product was formed. Thus, by sequential addition of Wittig salt to the photo oxidation product of **172a,** we were able to isolate the amino alkene **180** in good yield. Similar sequential addition of Wittig salt **179** to the oxidation product of **172f** afforded **181** in good yield.



Scheme 46: Synthesis of alkene starting from cyclic enamine *via* photo oxidation reaction.

The scope of the above photo-oxygenation mediated by visible light was further explored with substituted cyclic enol ethers. We envisioned substituted cyclic enol ethers as direct precursor to aldol and homoaldol products. Therefore, the oxidative ring opening of these cyclic enol ethers should lead to access of aldol and homoaldol products (Scheme 47).

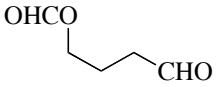
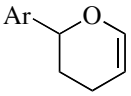
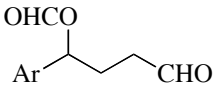


Scheme 47: Oxidative ring opening leads to aldol (n = 0) and homoaldol (n = 1) products.

One of the well-known methods for this type of oxidative ring opening is ozonolysis,[28] but alternatives to ozonolysis are highly recommended due to huge energy demand of the

process, toxicity of ozone, and safety risks. By applying our mild reaction conditions, we were able to cleave cyclic enol ethers to their formyloxy aldehydes. Treatment of 3,4-dihydro-2H-pyran **182a** under identical photo-oxygenation reaction conditions resulted in homoaldol product **183a** in 68 % yield. Following the same protocol **183b** was obtained from the substituted pyran **182b**.

Table 12: Oxidative ring opening of cyclic enol ethers leading to homoaldol products[a]

entry	substrate	product	time (h)	yield[b] (%)
1	 **182a**	 **183a**	3.0	68
2	 Ar = -C_6H_4-p-OMe **182b**	 **183b**	3.5	60

[a]Reaction conditions: enol ether(1.0 equiv.), $Ru(bpy)_3Cl_2$ (1 mol %), O_2, CH_3CN, blue LED. [b]Isolated yield after purification by chromatography on SiO_2

The strategy described here to prepare formyl-protected homoaldol compounds should be useful because of mild reaction conditions under which the products were obtained. The cleavage of cyclic enol ethers afforded free aldehyde functionality, which can be further derivatized to useful intermediates. Nevertheless, the formyl group can selectively be removed by using secondary amines. Further substrate scope of this type of enol ethers is currently under study.

5.8 Conclusion:

In conclusion, we have developed a photocatalytic method with visible light to drive sequential energy transfer processes for oxidative ring opening of cyclic enamines and enol ethers to their amino aldehyde and formyloxy aldehyde respectively. This methodology represents a potential means for accessing a variety of β- and higher amino

acid analogs staring from cyclic enamines. The method also leads to synthetically useful homoaldol products starting from cyclic enol ethers, which are difficult to obtain by other means. The protocol is highlighted by its chemoselectivity affording the oxidized compounds in high yields and mild reaction conditions. The reactions are operationally very simple and can eliminate the use of hazardous, toxic ozone for the oxidative ring opening of cyclic enamines and enol ethers.

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Part II

Studies Towards the total synthesis of Sandresolide A

6. Introduction

6.1 Importance of natural product synthesis

Natural products (NPs) play a dominant role in the discovery of leads for the development of drugs. Natural products are bioactive secondary metabolites those are isolated from all kingdoms of life and have proven to be a powerful source of disease modulating drugs throughout the history of medicinal chemistry and pharmaceutical drug development.[1] For many centuries medical treatment were entirely of natural origin and composed of herbs, animal products, and inorganic materials. Those effective treatments were subsequently recorded and documented leading to the early herbals. The knowledge of drugs grew from these records to provide a scientific description of natural materials used in medicine[2] which is known as pharmacognosy. With the improvement of the chemical tools and techniques, the active constituents were isolated from plants, structurally characterized, and in due course many were synthesized in the laboratory. Few cases more active or better-tolerated drugs were produced by chemical modifications or by synthesis of analogues of the active principles. In a recent review, Newman, Cragg and Snader analyzed the number of NP-derived drugs present in the total drug launches from 1981 to 2002 and found that NPs were a significant source of these new drugs, especially in the oncological and antihypertensive therapeutic areas.[3] In addition to providing many new drug leads, NPs and NP-derived drugs were well represented in the top 35 worldwide selling ethical drugs in 2000, 2001 and 2002.[4] A few natural products derived medicinal compounds are shown in Fig 6., which have been used as drugs for different diseases.

There are various motives for natural product synthesis. Perhaps one wants to improve the knowledge of chemical reactivity and further exploit chemical properties of the molecule. One may also check for the correctness of the structure. If the compound has medical importance, one may hope that the synthetic compound will be less expensive or more easily accessible than the natural product. It can also be desirable to modify some details of the molecular structure. An antibiotic substance of medical importance is often first isolated from a microorganism, perhaps in amounts of few milligrams or a gram. There ought to be exist a number of related compounds with similar effects; they may be

more or less potent, some may have undesirable secondary effects. If it is possible to synthesize the compounds in laboratory, it will be possible to modify the details of the structure and to find the most effective remedies. Nature produces molecules having lot of complexity there by proves that nature is the uncontested master of science and fine arts, whereas chemists try to synthesize those molecules in the laboratory and want to be superior than nature, sometimes.

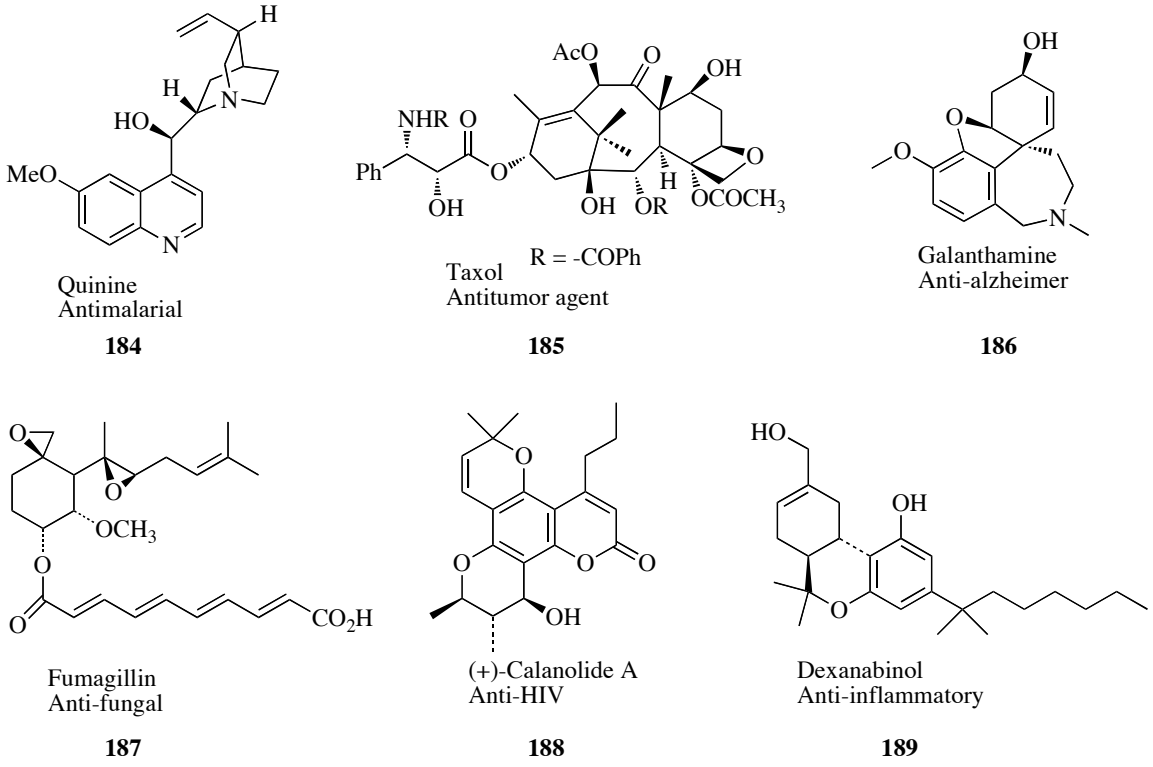


Fig. 6: Medicinally important natural products.

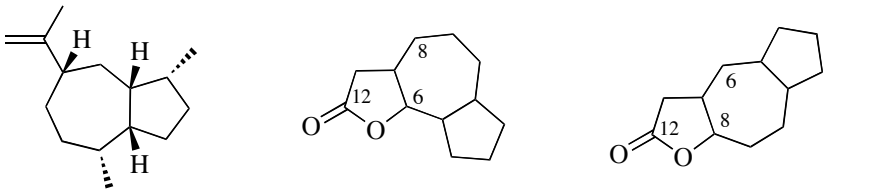
6.2 Total synthesis and drug discovery are synergistic and complementary

Total synthesis of natural products attracted chemists from beginning of twentieth century, whereas its greatest contribution to the drug discovery and development was realized in the later years.[5] The evolution of drug discovery and development process closely relates with that of total synthesis. The two disciplines must be considered in unity, for they are very synergistic and complementary. Academic research focuses on organic and natural product synthesis, which provides highly relevant basic knowledge

and training to researchers wishing to pursue the science of drug discovery and development process. Application of this knowledge to the pharmaceutical industry leads to the discovery of new drugs and benefits the society. Medicinal and combinatorial chemists have so many tools at their disposal today in their quests for huge number of novel and diverse small molecules. This is primarily the result of the contributions of total synthesis and of organic synthesis as a whole. Advancement in molecular biology facilitates drug discovery today by allowing the elucidation of the human genome and proteome, with the progress in total synthesis, which enables the construction of the molecules needed to bind and modulate the function of disease-associated biological targets. A handful of past and current "miracle drugs" from plants can easily illustrate the importance of total synthesis of natural products in drug discovery, from Quinine to Taxol, from Aspirin to the birth control pill. The development of powerful and highly selective methodologies those have control of reactions in chemo-, regio-, stereo-, and enantio-selectivity extended the frontiers of total synthesis to near the feasible limit.

6.3 γ-Butyrolactone based natural products: Guaianolides

The synthesis of natural products possessing bioactivity is a fascinating subject which has excited the synthetic organic chemists world ever since. Of all the well known natural products, about 10% carry a γ- butyrolactone moiety either as a characteristic structural element or even as a central unit. The utility of these structural subunits is enhanced by the ease of construction and functionalization of this lactone ring system. Sesquiterpenes and diterpenes, having a wide variety of both well-known and rare carbon skeletons, are the most common gorgonian and soft coral metabolites.[6] Guaianolides, consisting of tricyclic 5,7,5-ring system, represent one of the largest subgroup of naturally occurring sesquiterpene lactones exhibiting significant biological activity.[7,8] As the name itself indicates, the core structure of the guaianolides is derived from Guaiane, a natural product with a *cis*-fused 5,7-bicyclic hydroazulene ring system **190** (Fig. 7). The guaianolide skeleton along with the 5,7-bicyclic hydroazulene ring system often contains a third ring, a γ-lactone, fused to the seven membered ring. Guaianolides exist in two forms namely, guaian-6,12-olides and guaian-8,12-olides **191** and **192** respectively (Fig. 7).



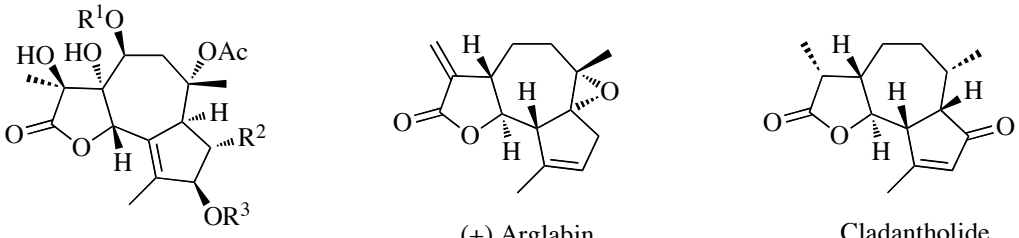
guaiane **190**

Guaian-6,12-olide
Angular guaianolides **191**

Guaian-8,12-olide
Linear guaianolides **192**

Fig. 7: Skeleton of Guaianolides.

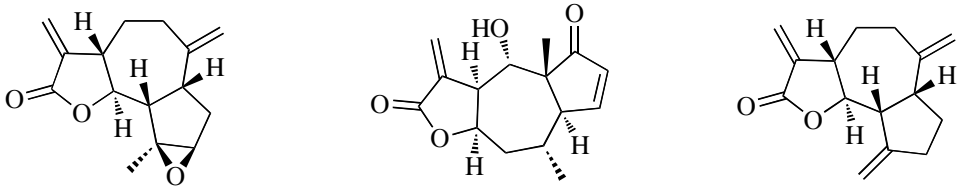
These two classes differ in their site of annulation relative to the γ-butyrolactone motif and can simply be termed as angular and linear guaianolides respectively.



Thapsigargines **193**

(+) Arglabin **194**

Cladantholide **195**



Estafiatin **196**

Helenalin **197**

Dehydrocostus
Lactone **198**

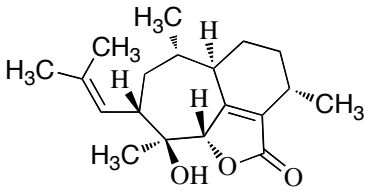
Fig. 8: Structurally diverse guaianolides.

The γ-butyrolactone ring is *trans*-annulated in approximately 85% of all known guaianolides, while in few guaianolides, the hydroazulene core is also *cis*-fused in the 5,7,5-tricyclic carbon skeleton.[9] Along with the structural diversity, guaianolides exhibit a broad range of biological activity and stimulate the development of research in their total synthesis. Some guaianolides have been reported to possess high antitumor, antihistosomal, anthelminthic, contraceptive, root-growth stimulatory and germination

inhibitory activities.[10] The representative members shown above (Fig. 8) exemplify the structural diversity found within this class of compounds. (+)-Arglabin (**194**), another prominent member of guaianolides, was isolated from *Artemisia glabella*[11] and shows promising antitumor activity and cytotoxicity against different tumor cell lines (Human tumor cell lines IC_{50}= 0.9-5.0 μg/ml)[12] and the first total synthesis of (+)-Arglabin was recently reported from our group.[13]

6.4 Sandresolide A, γ-butyrolactone based diterpene

Sesquiterpenes and diterpenes having a wide variety of well-known and rare carbon skeletons are the most common gorgonian and soft coral metabolites. Among Carribbean gorgonians, members of the genus *Pseudopterogorgia* are profilic in nature, with 15 known species, of which about six species have been chemically investigated. It was from the same *Pseudopterogorgia elisabethae* that the pseudopterosins, a family of anti-inflammatory amphilectane-based diterpene glycosides, were first reported in 1986 and since that time several related compounds such as the *seco*-pseudopterosine, the elisabethins, the elisabatins pseudopteroxazile and *seco*-pseudopterazole have been described. Sandresolide A (**199**),[14] (Fig. 9) a *nor*-diterpene lactone was isolated from *Pseudopterogorgia elisabethae* collected near San Andres Island, possessing powerful anti-inflammatory activity. Pharmacological studies of Sandrasolide A (**199**) have shown that it is a chemically novel anti-inflammatory and analgesic agent, but shows acute toxicity in the range of 300 mg/kg in mice. Moreover, it appears that the mechanism of action is distinct from that of the cyclooxygenase inhibiting anti-inflammatory agents, making this compound especially fascinating from a biological point of view. One of the interesting features is that it has a different skeleton compared to linear and angular guaianolides, whilst it can be synthesized starting from the same building block γ-butyro-lactone.



199

Fig.9: Chemical structure of Sandresolide A.

6.5 Conclusion

The chemistry of natural products attracts chemists because it's fascinating nature and its useful discipline in organic chemistry. More or less complicated and useful substances are constantly discovered and investigated. For the determination of the structure, the architecture of the molecule, we have today very powerful tools. The chemists of the twentieth century would have been greatly amazed if they had heard of the methods now at hand. However, one cannot say that the work is easier; the steadily improving methods make it possible to deal with more and more difficult problems and the ability of nature to build up complicated substances has, as it seems, no limits.

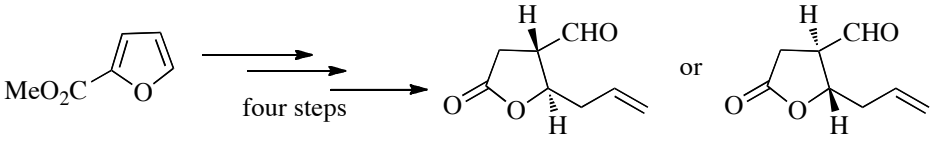
The search for new synthetic ways towards the diterpenes and sesquiterpenes did not only result in new total synthesis of complex and biologically active natural products, but also contributed to the development of a wide range of new and modern chemistry. The diverse bioactivity of diterpenes and sesquiterpenes makes them attractive synthetic targets since the availability of these compounds from natural sources is very limited. As there are more and more members of the diterpenes and sesquiterpenes family discovered, full evaluation of their biological activity and their synthesis is still of current interest.

7. Aim of the work

7.1 Development of 5-6-7 new ring system starting from simple aromatic compounds

γ-Butyrolactones are very common structural units found in about 10% of all naturally occurring organic compounds. They occur in a wide variety of structural patterns such as mono-, di- and trisubstituted monocyclic forms. They are also present as part of more complex structures, e.g., in bicyclic and tricyclic ring systems. A broad range of biological activities like strong antibiotic, antihelminthic, antifungal, antitumor, antiviral, anti-inflamatory and cytostatic properties etc. are exhibited by this class of compounds. Consequently, they have been recognized as interesting lead structures for developing new drugs.

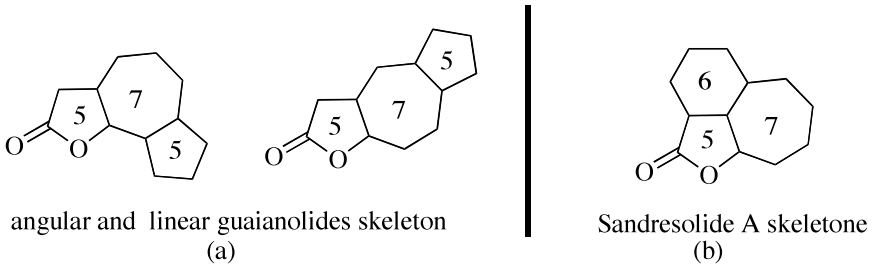
Most of the substituted γ-butyrolactones are found only as single enantiomer and the physiological activities are often dependent on the enantiomeric purity and absolute configuration of the butyrolactones. Reiser *et al*. have developed[15] a methodology to make enantiomerically pure γ-butyrolactone moiety starting from inexpensive furoic ester in few steps (Scheme 48). The application of this methodology was successfully shown in the total synthesis of several guaianolides (e.g., total synthesis of (+)-Arglabin[13]) that consists of 5-7-5 fused angular or linear ring systems (Fig. 10, a).



200 **201** **202**

Scheme 48: Synthesis of γ-butyrolactone by Reiser *et al*.

Utilizing the γ-butyrolactone moiety as central basic unit, we wanted to build a different type of fused ring system, which was not reported previously by Reiser and co-workers. With this interest, we found that Sandresolide A, a diterpene that contains a novel 5-6-7 fused ring system, different from other guaianolides (Fig. 10, b).



angular and linear guaianolides skeleton
(a)

Sandresolide A skeletone
(b)

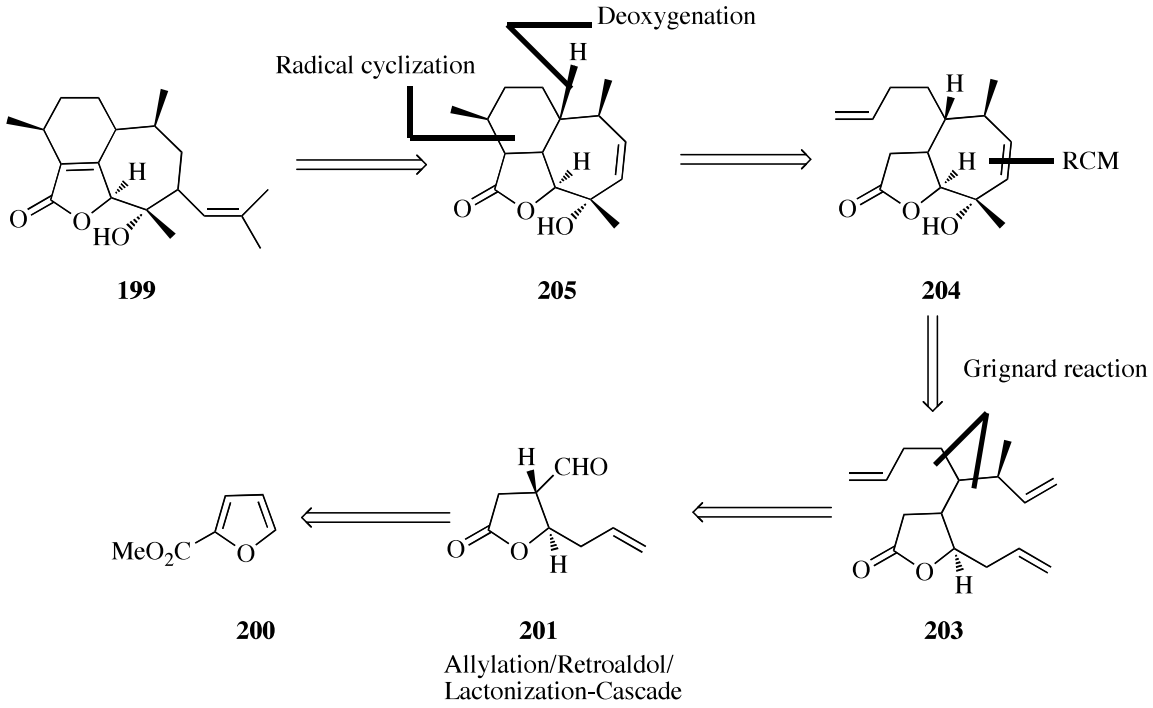
Fig. 10: Different natural products skeleton having γ-lactone moiety

The tricyclic 5-6-7 fused ring system was planned to synthesize utilizing the same methodology applied for the synthesis of guaianolides. Not only by its structural appeal but Sandresolide A also has good biological activity (such as anti-inflammatory agent) and its total synthesis was also not reported so far. All these factors prompted us to aim for the total synthesis of Sandrasolide A, which was chosen as one of my PhD research topic.

8. Progress towards the total synthesis of Sandresolide A

8.1 Retrosynthetic Strategy

The general retrosynthetic strategy shown below (Scheme 49) gives the outline to achieve the target molecule Sandersolide A (**199**). Retrosynthesis of the natural product **199** suggested that it could be obtained from the precursor **201** *via* Grignard reaction followed by a combination of ring closing metathesis (RCM) and radical cyclization, subsequent functionalization of the tricyclic ring. The precursor **201** can be readily obtained from inexpensive furoic ester **200** by a synthetic route that has been established by Reiser *et al.* involving an enantioselective cyclopropanation of **200** followed by a retroaldol/lactonization sequence.[15]



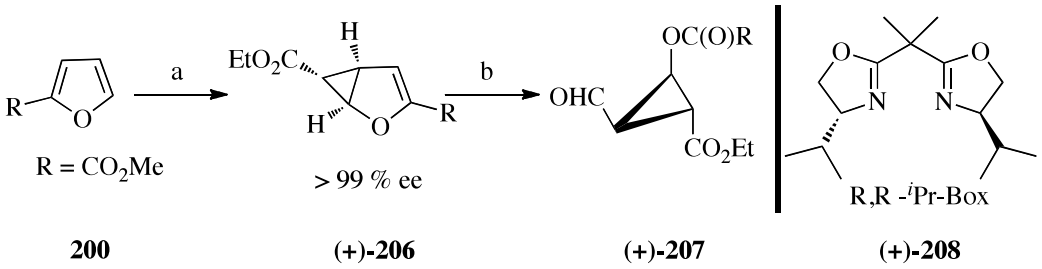
199 **205** **204** **200** **201** **203**

Scheme 49: Retrosynthetic approach towards the total synthesis of Sandresolide A.

8.2 Synthesis of Cyclopropylcarbaldehyde 207

Cyclopropanes are an important class of compounds because of their occurrence in numerous natural products, drugs and also because of their value as synthetic building blocks in organic synthesis. Highly functionalized 1,2,3-trisubstituted

cyclopropylcarbaldehyde **207** was synthesized in enantiomerically pure form in a two step sequence starting from methyl-2-furoate (**200**) (Scheme 50).[16-18] Thus upon a Cu(I)-mediated asymmetric, regio and diastereoselective cyclopropanation of methyl-2-furoate (**200**) using ethyl diazoacetate in the presence of chiral ligand (*R,R*)-^{i}Pr-Box (+)-**208** resulted in cyclopropanated adduct (+)-**206** with high enantioselectivity of 85-90 % *ee*, which was improved to >99 % *ee* upon recrystallization. The ozonolysis of the unreacted double bond under standard conditions followed by reductive workup afforded enantiomerically pure cyclopropylcarbaldehyde (+)-**207** in good yield. The whole sequence can be scaled up to 50-100 g with out significant drop in enantiomeric excess of products.



Scheme 50: Conditions: a) (i) ethyl diazoacetate (2.67 eq.), $Cu(OTf)_2$ (0.66 mol%), (*R,R*)-^{i}Pr-box (+)-**208** (0.84 mol %), $PhNHNH_2$ (0.70 mol %), CH_2Cl_2, 0 °C, 40 %, 85-90 % *ee*; (ii) recrystallization (pentane) >99 % *ee*, 32 %. b) (i) O_3, CH_2Cl_2, –78 °C(ii) dimethylsulfide (4 eq.), 22 h, –78 °C to rt, 90 %.

The stereochemical outcome and high enantioselectivities of the cyclopropanated product during asymmetric cyclopropanation depends on the stereochemistry of the bis(oxazoline)-ligand (BOX) **208** used in the reaction (Fig. 11).

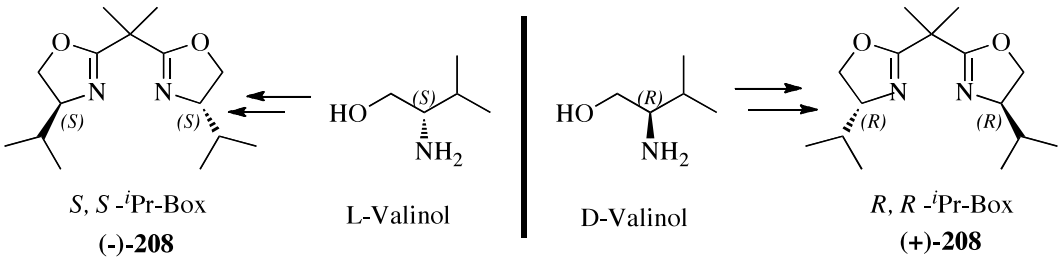
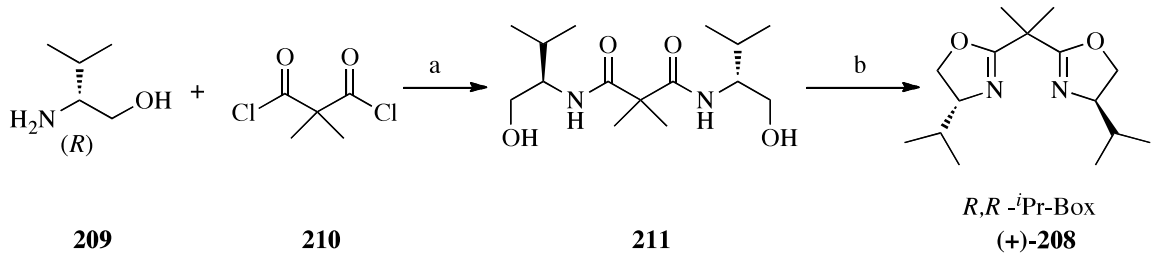


Fig. 11: Two enantiomers of BOX-ligand

The use of other enantiomer of BOX ligand, i.e. (-)-**208** in the above sequence gives rise to the synthesis of (-)-**207**. Thus with the choice of appropriate chiral ligand, the synthesis of either of the enantiomers of cyclopropylcarbaldehyde **207** can be achieved. Both enantiomers of the chiral BOX-ligand **208** were prepared from D or L- valinol **209** derived from the corresponding amino acids by sodium borohydride reduction and iodine (Scheme 51). The regio, diastereo, and high enantio-selectivities observed during the cyclopropanation step can be explained by applying the models suggested by Pfaltz[19] and Andersson[20] for the asymmetric



Scheme 51: Synthesis of chiral BOX-ligand. Conditions: a) valinol (2.0 eq.), NEt_3 (2.5 eq.), CH_2Cl_2, 0 °C-rt, 70 min, 81 %; b) DMAP (10 mol %), NEt_3 (4.0 eq.), TsCl (2.0 eq.), CH_2Cl_2, rt, 27 h, 85 %.

cyclopropanation of alkenes. The reactive complex **212** involved in the reaction can be accessed by reacting partner **200** in two ways (Fig. 12). Out of the two possible approaches, an approach from the right side is more favored, since an attack from left side shows strong repulsive interaction between **200** and ^{i}Pr group of the ligand (+)-**208**. In the subsequent cyclopropanation, the less substituted and presumably more electron rich double bond of **200** is attacked.

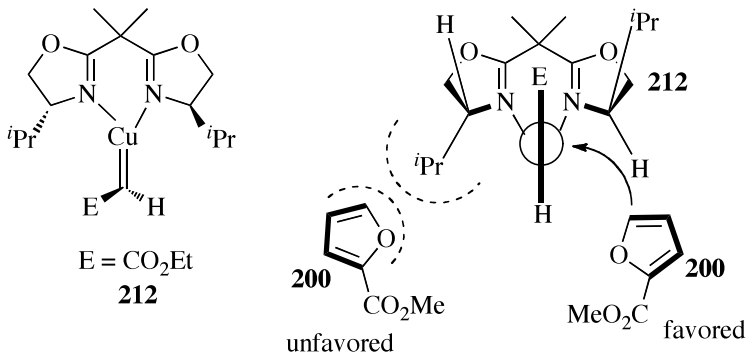
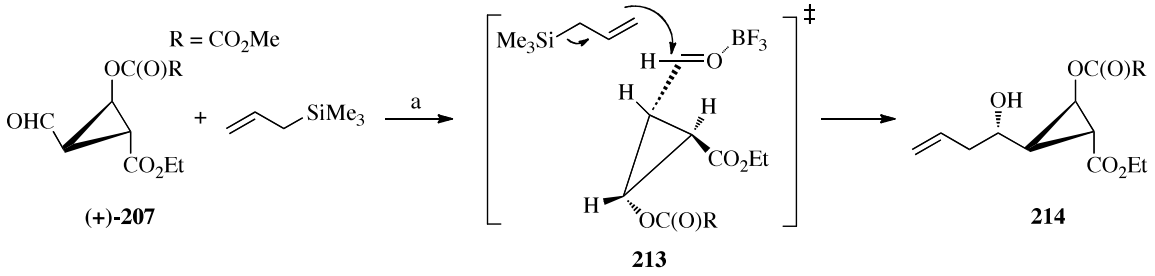


Fig. 12: Model for asymmetric cyclopropanation showing the observed selectivity (reprinted from ref. 21)

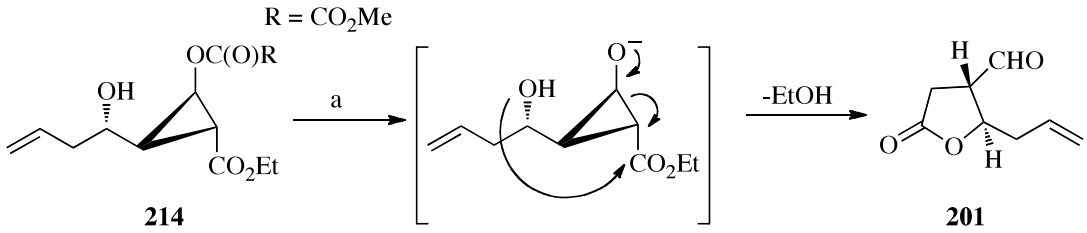
8.3 Synthesis of *trans*-4, 5-disubstituted γ-butyrolactone

Having synthesized the key intermediate cyclopropylcarbaldehyde (+)-**207** the next step was addition of allylsilane to cyclopropylcarbaldehyde (+)-**207**. The stereocontrol addition on a cyclopropyl-substituted carbonyl compound such as **207** can be explained by analyzing the conformational preferences and applying the Felkin-Anh-model[22] in combination with the Curtin-Hammett-principle.[23] Thus, Borontrifluoride mediated addition of allylsilane to cyclopropylcarbaldehyde (+)-**207** proceeded with excellent double stereocontrol, in which the attack of the allylsilane takes place in accordance with Felkin-Anh paradigm (Scheme 52). The stereochemical outcome of this reaction can be demonstrated by the proposed transition state **213**. In this case, the nucleophile attacks the *s-cis*-conformation of the carbonyl group in *anti*-orientation leading to the experimentally observed *anti*-Felkin-Anh-product **214**.



Scheme 52. Conditions: a) $BF_3 \cdot OEt_2$ (1.1 eq.), CH_2Cl_2, -78 °C, 16 h, 80 % (crude).

Without purification, the adduct **214** was directly subjected to base which results in the saponification of the labile oxalic ester group. As a result, the now unmasked donor-acceptor cyclopropane[24] undergoes a cascade of ring opening (retroaldol) and lactonization to afford **201** as single stereoisomer (Scheme 53).



Scheme 53. Retroaldol-lactonization. Conditions: a) $Ba(OH)_2 \cdot 8H_2O$ (0.55 eq.), MeOH, rt, 2 h, 50 % (over two steps).

9. Construction of 5-6 bicyclic fused ring

We envisioned that for the total synthesis of Sandresolide A **199**, we needed to first construct the tricyclic core **217** (Fig. 13), which on functionalization should give the required target molecule. Keeping this in mind our first target was to build up the tricyclic core **217**. We visualized that, starting from γ-lactone **201,** there are two alternative ways to make the tricyclic core **217** (Fig. 13).

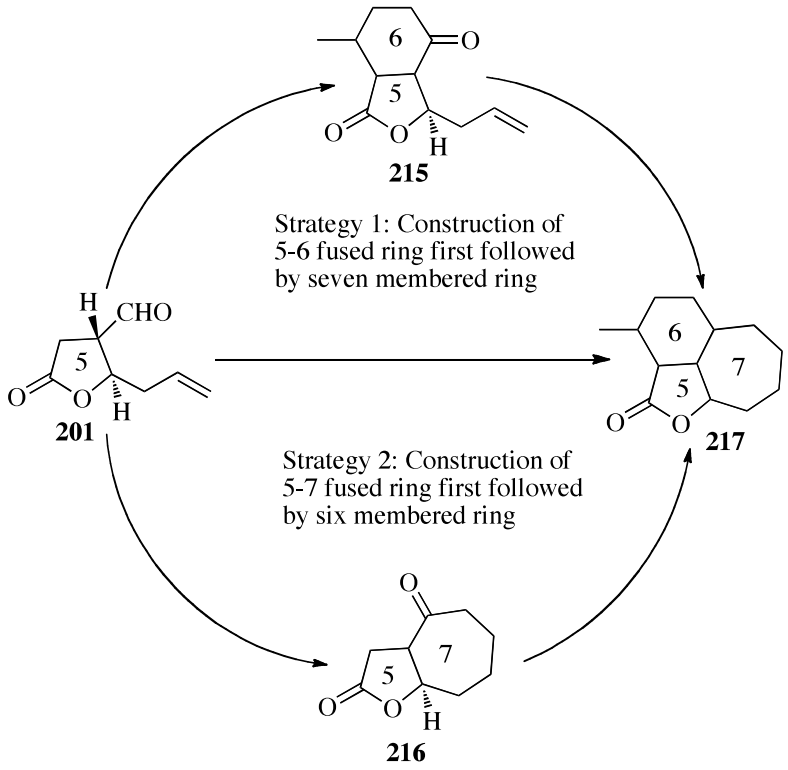


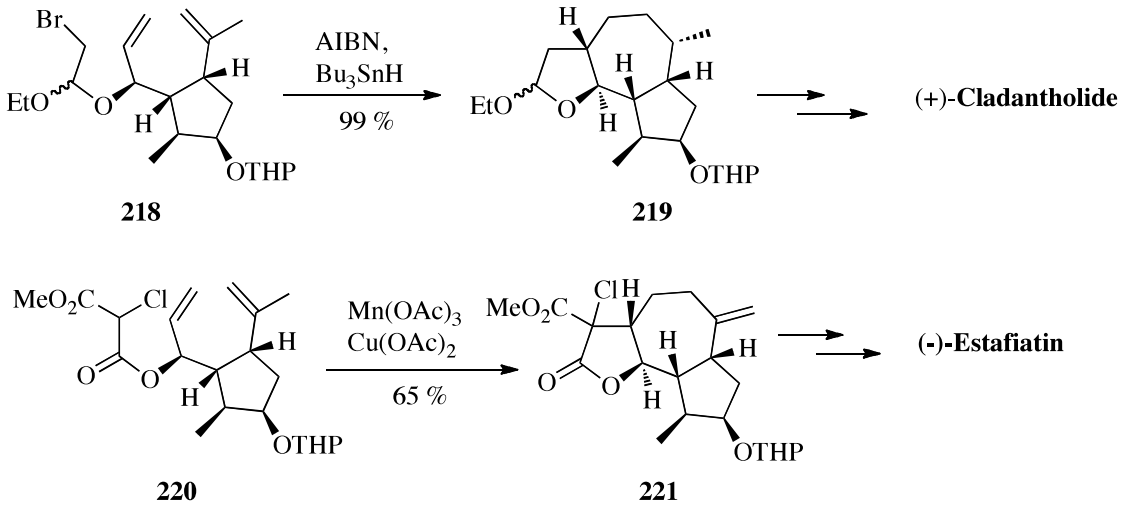
Fig. 13: Different strategies for making tricyclic core.

It should be possible to make first 5-6 fused bicyclic ring **215,** followed by the construction of seven membered ring to end up with **217**. On the other hand, it should also be feasible to construct first 5-7 fused bicyclic ring **216,** followed by the construction of sixmembered ring to get tricyclic core **217** (Fig. 13). Although the later strategy is well known from our group i.e., the construction of 5-7 fused ring *via* RCM for the synthesis of guaianolides, we envisioned that the first strategy involving construction of 5-6 fused ring system **215** from γ-lactone **201** would be a challenging task. Also this would lead to the development of a new methodology for the construction of 5-6-7 fused system

starting from γ-lactone **201**. Therefore, we proceeded for the construction of 5-6 fused system **215**.

9.1 Radical Cyclization Approach

Over the past few decades, radical cyclization has emerged as a powerful carbon-carbon bond-forming reaction that is widely used in organic synthesis. It has been utilized to a greater extent for the synthesis of complex organic molecules and natural products, especially the formation of polycyclic ring *via* cascade radical cyclization[25] is very interesting, atom economic and economically favorable process in organic synthesis. The radical cyclization approach was successfully utilized in the total synthesis of guainolides (+)-Cladantholide, (-)Estafiatin as shown below (Scheme 54).



Scheme 54: Radical cascade reactions for total synthesis of natural products.

Having such literature precedence, we wanted to apply radical cyclization approach to construct the six membered ring fused with γ-butyrolactone. Thus it was envisioned to perform a radical cyclization, installation of a butene side arm in **201** was necessary to yield **222** as shown in Fig. 14.

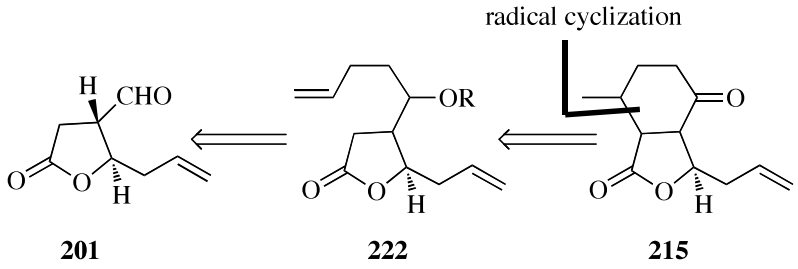
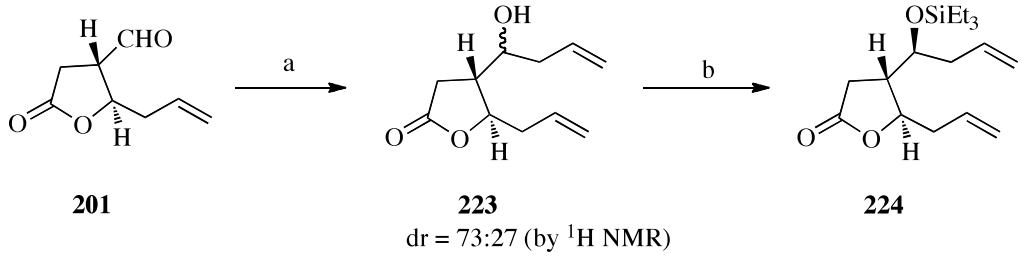


Fig. 14: Retrosynthesis for making 5-6 fused ring.

To investigate the practical feasibility of such radical cyclization, we did a model study by installing a one carbon less allyl side arm in **201** (Scheme 55) by Lewis acid mediated allyl TMS addition followed by the silyl protection of the free hydroxyl group in **223** to yield **224**.



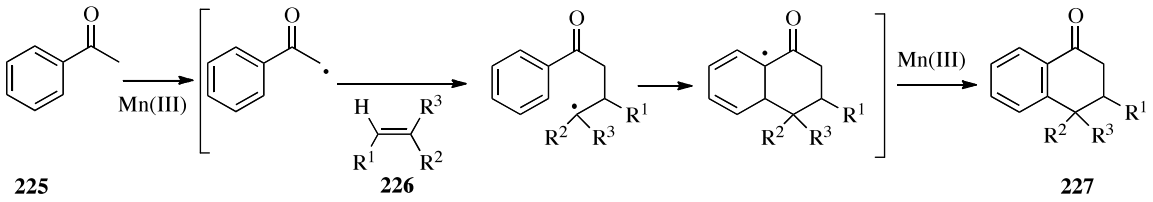
Scheme 55: Allylation and protection of γ-butyrolactone. Conditions: a) $BF_3.OEt_2$, allyl TMS, -78 °C, 24 h, 82 %. b) (i) Et_3N, TESCl, rt, 24 h (ii) separation, 75 %

Having the model substrate compound **224** in hand, we proceed for the radical cyclization which is described below.

9.1.1 High-Valent Transition Metal-Promoted Radical Cyclization Approach

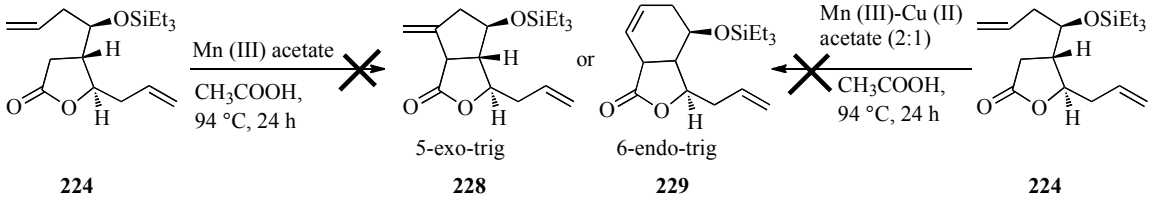
It is well reported in literature that ketones, esters, and aldehydes are very easily oxidized by high-valent transition metals, such as Mn (III), Fe (III), Co (II), and Cu (II) acetate, to give α-oxoalkyl radicals that can add to olefins to form a variety of interesting products. For example substituted α-tetralones **227** have been synthesized by Mn (III)- promoted addition of aromatic methyl ketone **225** to various olefins **226** (Scheme 56).[26] It is also

known that Mn (III) – Cu (II) combination also works great for this type of radical reactions.[26-28]



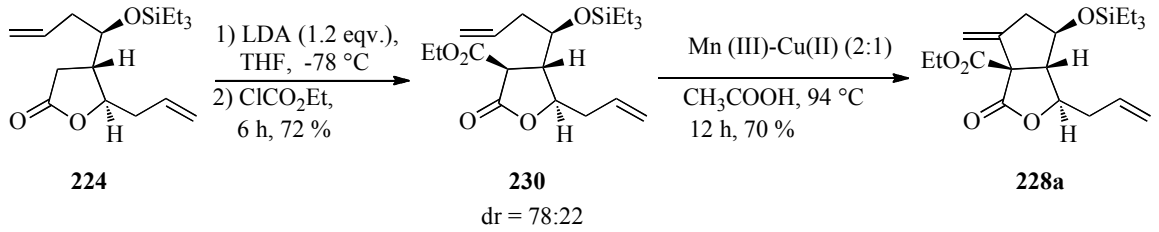
Scheme 56: Transition metal mediated radical cyclization.

Having this literature evidence, we treated compound **224**, with two equivalent of Mn (III) acetate in acetic acid at 94 °C (Scheme 57). Upon monitoring the reaction, there was no expected 5-exo-trig product formation even after 24 h. The same reaction when performed with identical reaction conditions employing a Mn (III) – Cu (II) acetate combination (Mn / Cu = 2:1 equiv.) instead of Mn (III) alone there was no expected 6-endo-trig product formation observed, only starting material was recovered.



Scheme 57: Approach towards cyclization using transition metal.

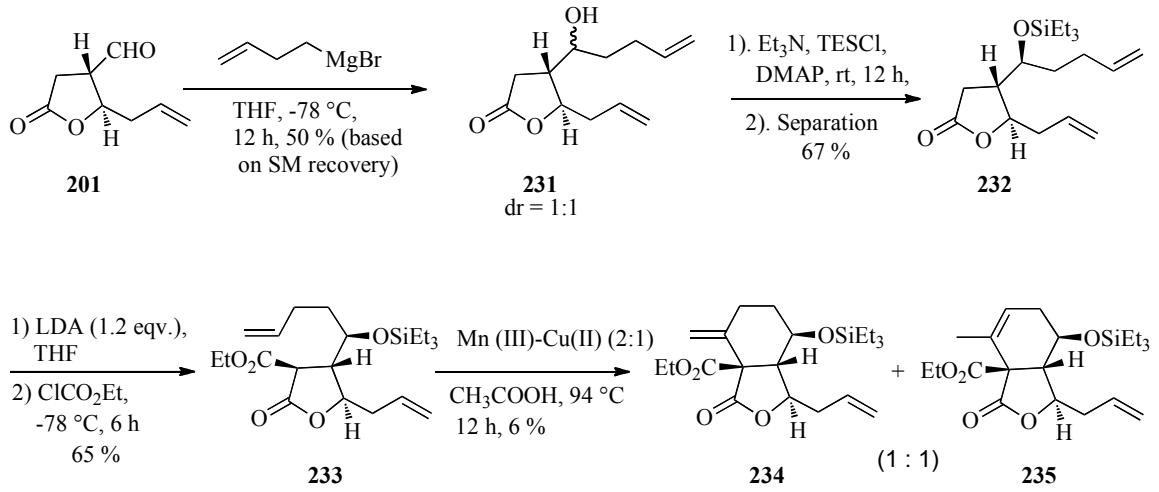
With this observation, it was thought that the α-position of lactone carbonyl was not so activated to be oxidized by the metal. To make this position easily oxidizable, we introduced an electron withdrawing ester group that can be easily removed by decarbalkoxylation[29] and then performed metal promoted radical cyclization (Scheme 58). Interestingly with this approach we obtained only 5-exo-trig cyclized product **228a** in good yield. There was no 6-endo-trig cyclized product (similar to **229)** obtained although both are possible according to Baldwin's rule.



224 **230** dr = 78:22 **228a**

Scheme 58: Radical cyclization leads to 5-exo-trig product.

After getting the success of doing cyclization in the model substrate we were confident enough to make the desire cyclized product **215**. For this purpose we introduced a homoallyl side chain and subsequent protection of the hydroxyl group gave compound **232** (Scheme 59). Introduction of an ester group α-to the lactone carbonyl afforded compound **233**, which was subjected to cyclization using the standard conditions applied during the case of model study. Interestingly, in the cyclization conditions, we obtained desired product **234** in combination with its regioisomer **235** as non-separable mixture in 1:1 ratio but in very low yield (Scheme 59). By applying different reaction conditions, we were not able to improve the yield significantly, as well as, the separation problems associated with **234** and **235** led us to think alternative way for cyclization.

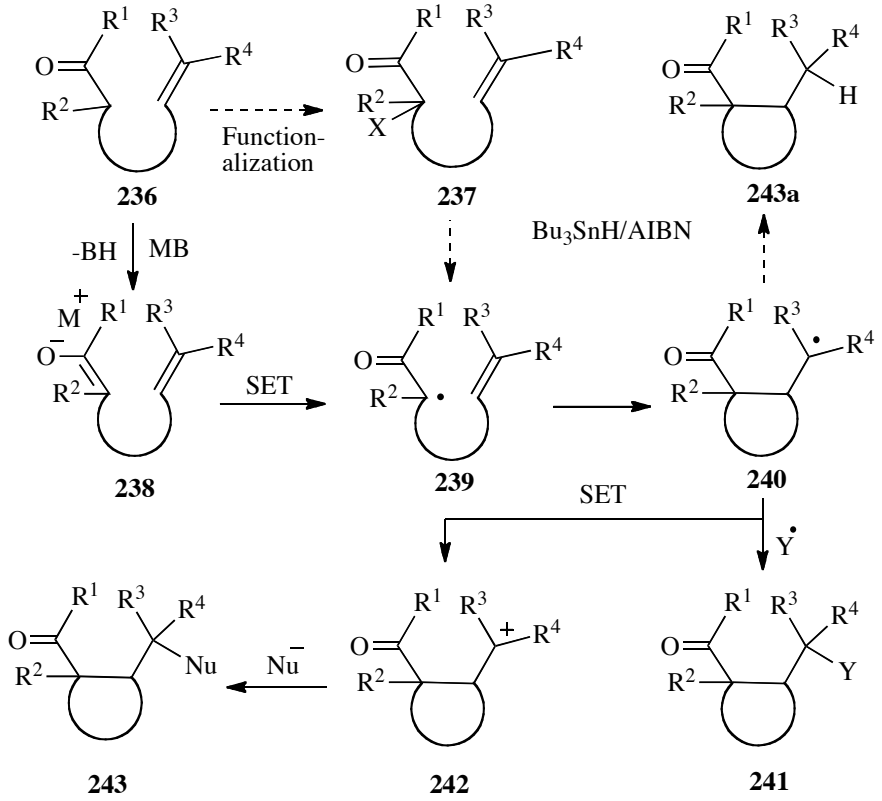


201 **231** dr = 1:1 **232** **233** **234** (1 : 1) **235**

Scheme 59: Construction of six membered ring *via* radical cyclization.

9.1.2 Oxidative Radical Cyclization Approach

Our next approach for cyclization was oxidative radical cyclization, which involves very interesting chemistry. An oxidative radical cyclization is a single electron transfer (SET) oxidation of ester enolates, which can undergo cyclization with olefins intramolecularly to generate an intermediate, which further can produce a variety of compounds depending upon the use of trapping reagent (Scheme 60). The anionic precursor **238** is simply generated by deprotonation of **236**.

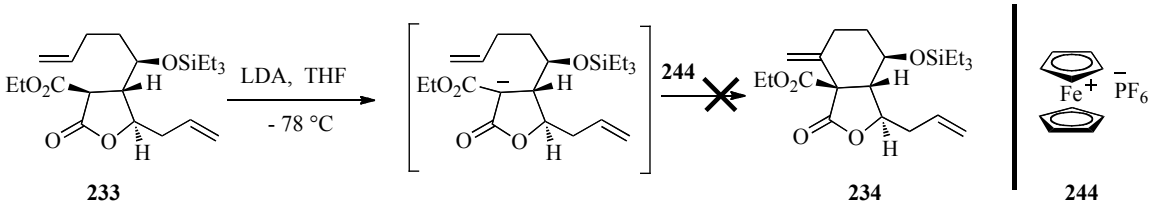


Scheme 60: Variation in oxidative radical cyclization

In contrast, traditional Bu_3SnH-mediated radical chain reaction require precursor **237** that often originate from functionalization of **236** or **238**. Slow reaction rate of **239** to **240**, which may not propagate chain reactions, especially at low temperatures and are not of particular concern in processes starting from **238**. Finally, in contrast to radical chain reactions, removal of ultimate radical **240** can be achieved either by trapping with external reagents **Y** to form **241** or by further SET oxidation to produce a carbenium ion

242, which may react with nucleophiles to give **243**. Opportunities for the synthesis of diversely functionalized products are hence much broader than those offered by tin hydride reactions.

Impressed by this chemistry, we treated the lithium enolate of compound **233** for radical 6-*exo* cyclization. We thought that SET oxidation of **233**-enolate should give an α-carbonyl radical and that will undergo cyclization. But in reality, treatment of compound **233** with strong base like LDA, and ferrocinium hexafluoro complex **244** (as SET oxidant, reported by Jahn *et al.*[30]), did not bring any successful transformation (Scheme 61).



233 **234** **244**

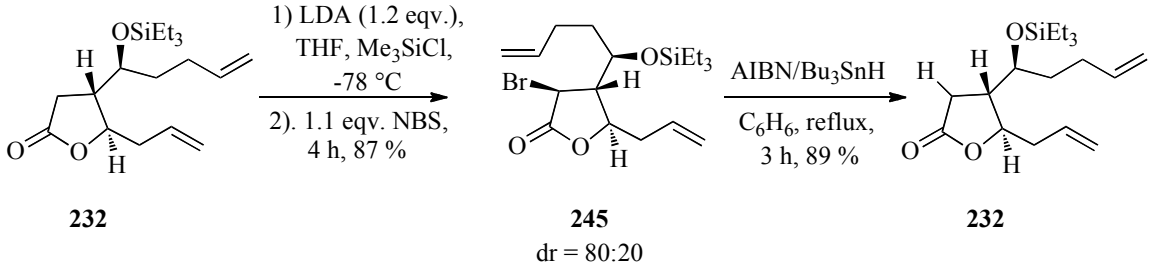
Scheme 61: oxidative radical cyclization approach.

Changing the reaction conditions such as altering base from LDA to LHMDS, SET oxidant from ferrocinium complex to Cu (II)-2-ethylhexanoate[31] and varying temperature did not show any reactivity; all the time starting material was recovered. Based on these observations we concluded that the radical α-to the carbonyl group is not generating in substrate **233** by this method. With this conclusion we thought of doing the cyclization with conventional AIBN/Bu_3SnH method.

9.1.3 Conventional AIBN/Bu_3SnH Approach for Cyclization

Getting almost negative results by applying the above two modern methods, we decided to proceed for the cyclization with conventional AIBN/Bu_3SnH. Starting from halogenated compounds, AIBN/Bu_3SnH mediated cyclization is very well known and quite old but effective chemistry as shown before in Scheme 54 (page- 89). For this intention we started from compound **232**. Bromination of compound **232** (Scheme 62) with NBS selectively gave α-bromo carbonyl compound **245** (neither allylic bromination nor double bond bromination was observed, which is not ruled out theoretically possible

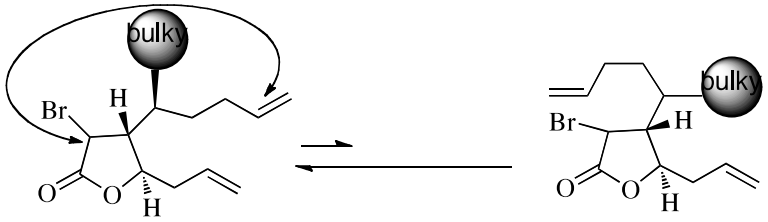
because of two allylic side chains are present in compound **232**). Treatment of compound **245** with AIBN/Bu_3SnH in benzene as solvent at refluxing condition unfortunately did not give the cyclized product **234**, rather gave the dehalogenated product **232** (Scheme 62).



232 **245** dr = 80:20 **232**

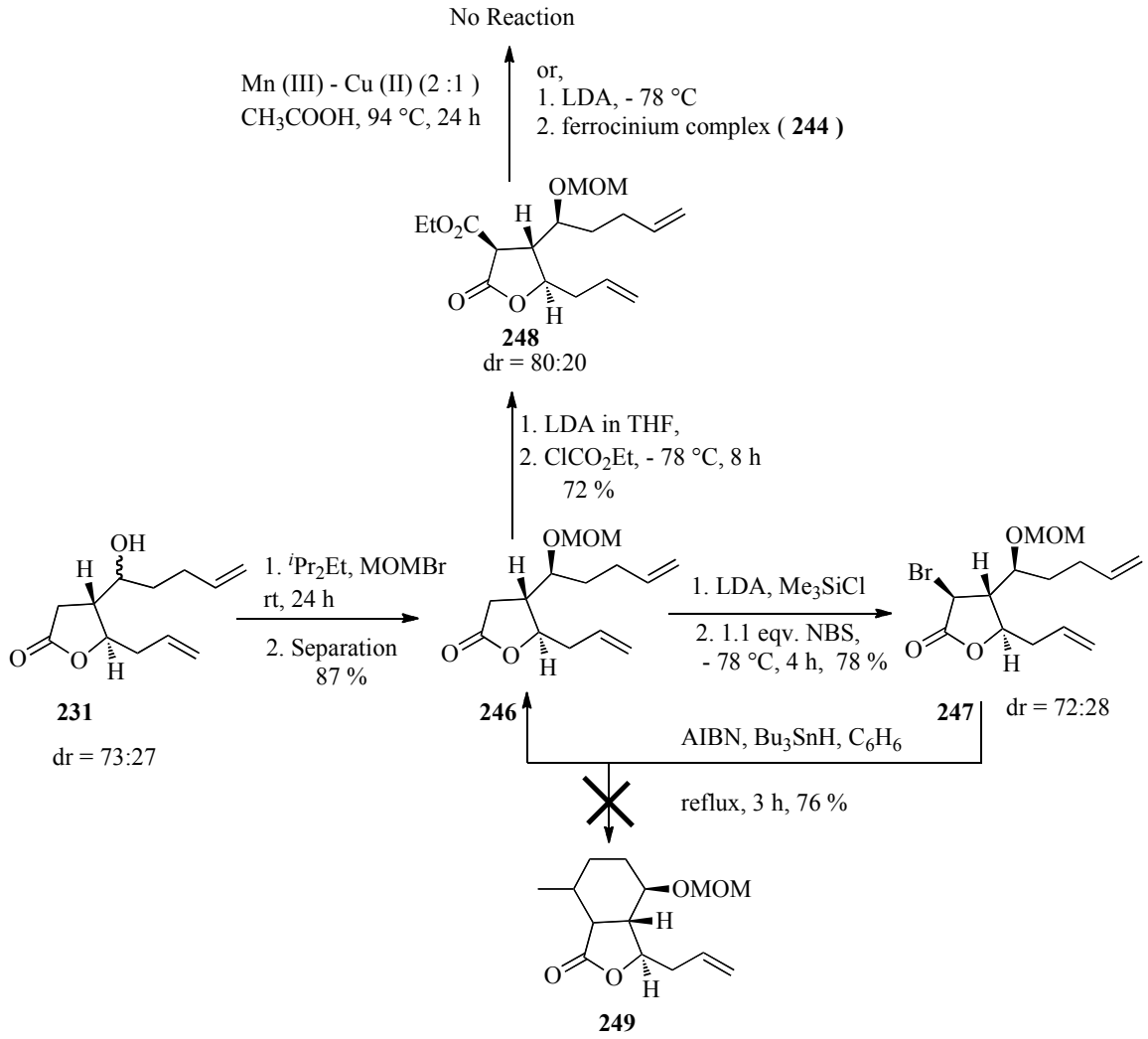
Scheme 62: AIBN/Bu_3SnH approach for cyclization

Failure in the methods forced us to find the problem for cyclization in molecular level. We realized that, for making six membered ring by radical cyclization, it is necessary for the double bond to be in the close proximity of the radical center. From all these observations, we came into conclusion that probably the large size protecting group – $OSiEt_3$, oriented in such a way that it was hindering the double bond to come closer to the radical center generated by the above applied methods (Fig. 15). Therefore, we thought that it is necessary to replace the bulky protecting group with a small protecting or better to say linear protecting group. Therefore, we changed bulky protecting group to a linear protecting group –MOM and carried out the same AIBN/Bu_3SnH reaction (Scheme 63). But, unfortunately in this case also we observed dehalogenated product **246**.



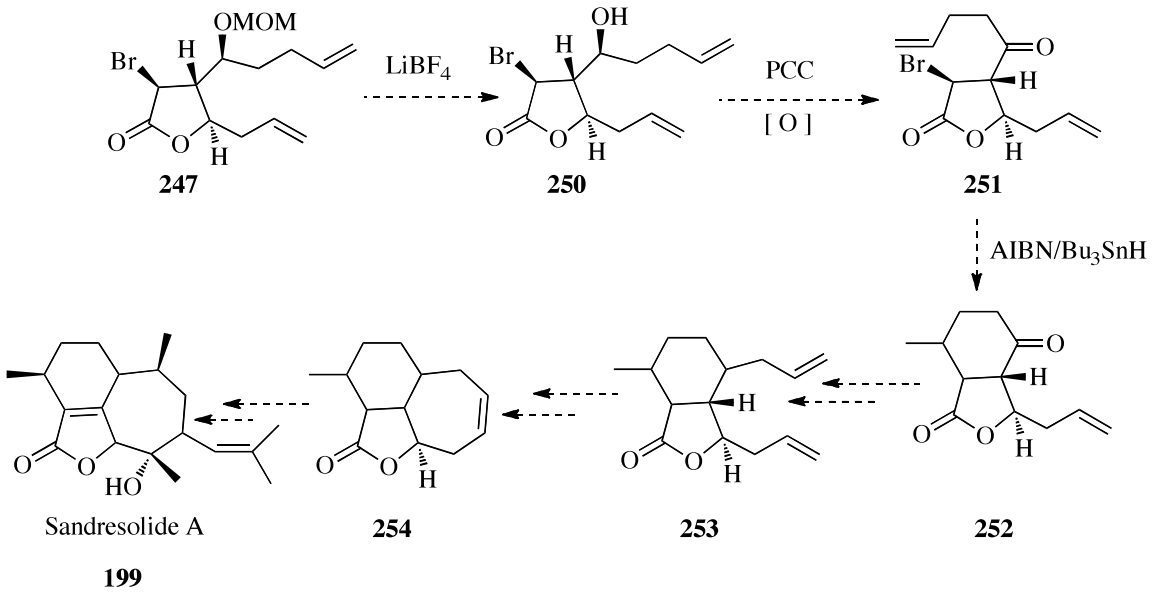
245 **245**

Fig. 15: Bulkiness may be the cause of non-cyclization.



Scheme 63: Approach for cyclization using different protecting group.

Taking the above observations into consideration, we concluded that, -MOM was also not a suitable protecting group to facile the cyclization. Therefore, we decided to remove the protecting group completely. So the future perspective for the radical cyclization was to deprotect the protecting group and obtain **250** (Scheme 64). Now PCC oxidation of **250** should give the oxidized product **251**, which should undergo cyclization by AIBN/Bu_3SnH method to produce **252**. Further allylation and followed by RCM should give the tricyclic core **254**, which on functionalization should give the target molecule **199**. These approaches are currently under investigation.



Scheme 64: Future plans towards the synthesis Sandresolid A.

9.2 Conclusion:

Anybody can draw a picture, but pictures painted by famous painters such as van Gogh, Monet, and Picasso are praised as "art". At the present time, anyone may be able to synthesize natural products, even those having complicated structure by advanced organic chemistry. Hence, "art" is much more essential to be introduced into the organic synthesis. That is the significance of the total synthesis and development of bioactive compounds. For the total synthesis of Sandresolide A, we took the risk to apply completely new and sophisticated approaches to develop new chemistry, new methodologies. Although the chemistry in paper does not work well all the time in flask, but it is sometimes necessary to go beyond the known route to develop new chemistry, new methodology irrespective of risk of failure. Albeit our new approaches got failed, we were daring enough to take the risk and wanted to develop new chemistry. But, our new approach should lead to the total synthesis of Sandresolide A, as there is no royal road to success in total synthesis and development of useful bioactive compounds, steady efforts are the only way to achieve that goal.

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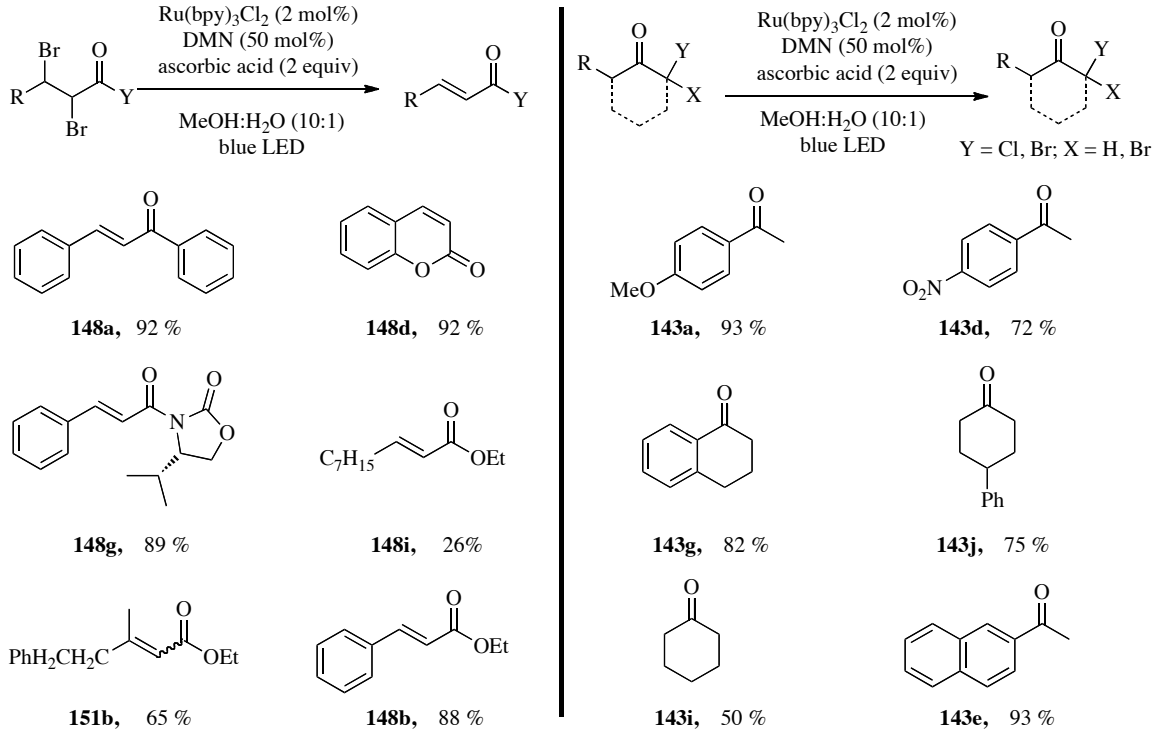
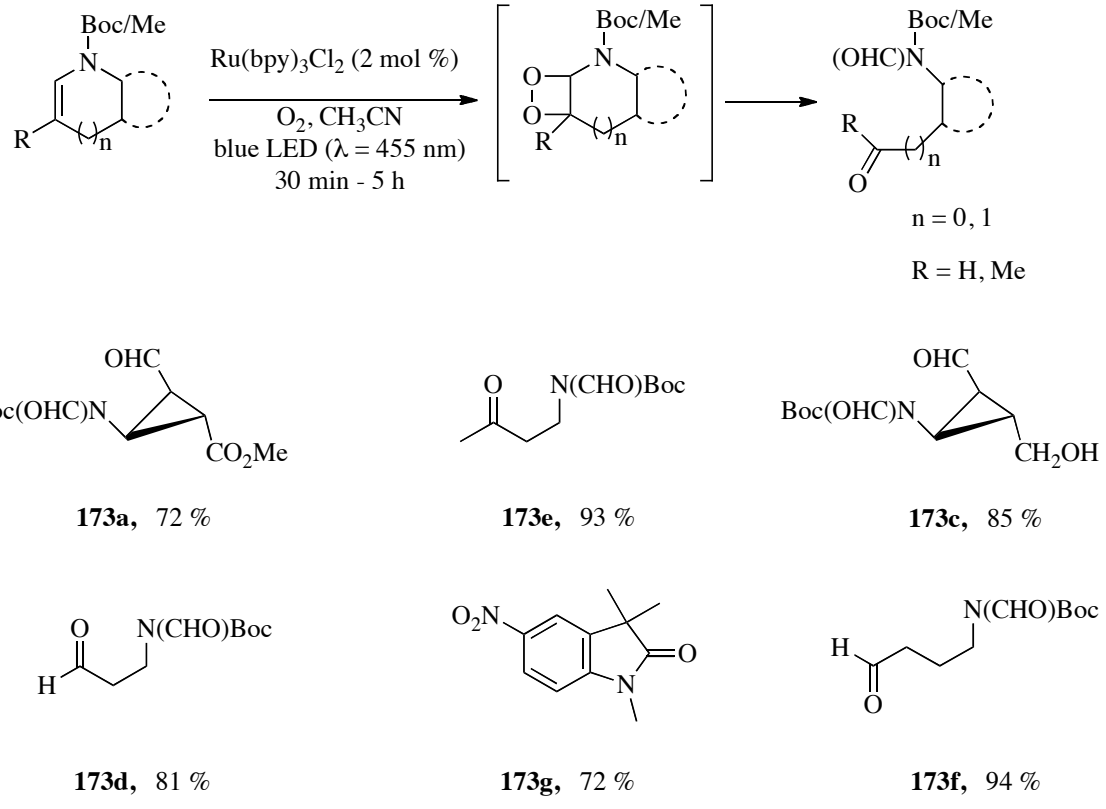
Summary

Photocatalysis with visible light is undoubtedly one of the emerging strategies to meet the increasing demand for more sustainable processes. This thesis describes the use of visible light as a promoter for organic transformations. Most of the organic molecules are unable to absorb light in the visible region. Keeping this in mind, we utilized $Ru(bpy)_3Cl_2$ complex as photosensitizer. We developed ''$Ru(bpy)_3Cl_2$, 1,5-dimethoxynaphthalene-ascorbic acid'', a new photocatalytic combination for reduction of carbon-halogen bonds. This conceptually new photocatalytic system with visible light is very efficient to drive sequential electron transfer processes for reductive debromination of vicinal dibromo carbonyl compounds to (*E*)-alkenes and alkynes, *gem*-dibromides to monobromides, and monobromides or chlorides to their dehalogenated counterparts (Scheme 65). As a key structural feature, a carbonyl group positioned α-to one halogen atom is required for the success of the transformation. The photosystem is also highlighted by its chemoselectivity, resulting in reduced products in high yields under mild reaction conditions.



Scheme 65: Reductive dehalogenation of vicinal dibromo and α-halo carbonyl compounds.

Singlet oxygen ($^1O_2$) is a higher energy state molecular oxygen. It is quite well known as a reaction intermediate for cycloaddition reactions to produce endoperoxides and ene reactions to provide allylic hydroperoxides. This highly reactive singlet oxygen has shown to be efficiently photosensitized by a large number of compounds, most of which have been organic compounds. We utilized $Ru(bpy)_3Cl_2$ complex as a singlet oxygen generator in presence of visible light and performed oxidative cleavage of cyclic enamines and enol ethers. β-And γ-aminoacids and their derivatives are very important constituents of natural products and as a valuable intermediates for the preparation of peptidomimetics. Applying our methodology we successfully performed oxidative ring opening of cyclic enamines, which lead to β-and higher amino acid analogs (Scheme 66). The oxidative cleavage of enamines by this method leads to products, which preserved the relative and absolute stereochemistry of starting material. This methodology can also be utilized as an alternative of hazardous ozone to perform this type of oxidative cleavage.

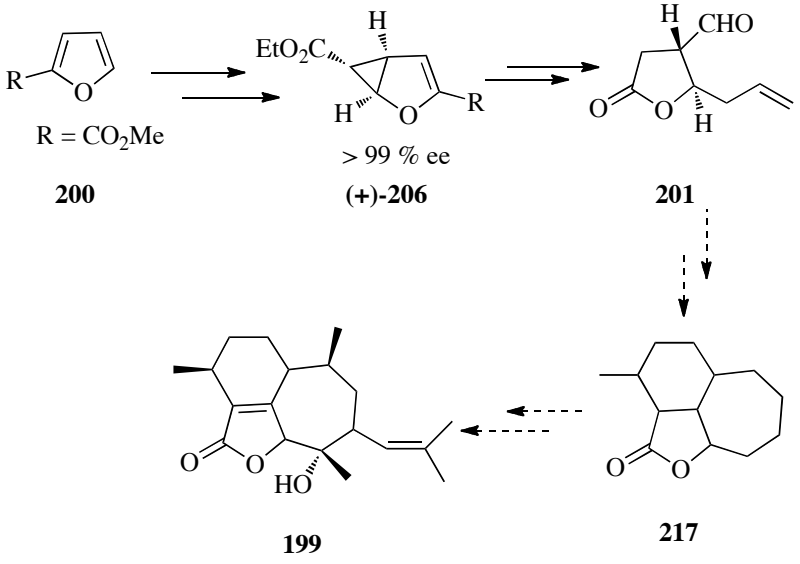


Scheme 66: Oxidative cleavage of cyclic enamines.

This thesis also describes the studies towards the synthesis of natural product Sandresolide A (**199**), a *nor*-diterpene lactone. Every natural product type isolated from the seemingly limitless chemical diversity in nature provides a unique set of research opportunities deriving from its distinctive three-dimensional architecture and biological properties. Diterpene and sesquiterpene lactones exhibit a broad range of biological activity along with the structural diversity and stimulate the development of research in their total synthesis. The essence of total synthesis lies in how readily available starting materials can be converted to complex molecular architectures through controlled, efficient and logically orchestrated carbon-carbon and carbon-heteroatom bond connectivities.

With our synthetic approach we showed how simple aromatic starting materials could be converted to chiral building blocks such as *anti*-disubstituted γ-butyro-lactones that are key structural motifs of guaianolides and can also be utilized as central basic unit to build different types of ring system other than guauanolides.

Starting from furoic ester **200** we tried to synthesize the natural product Sandresolide A where *trans*-4,5-disubstituted γ-butyro lactone (**201**) served as a central building block of the molecule (Scheme 67).



Scheme 67: Studied towards the synthesis of Sandresolide A.

11. Experimental part

11.1 General information

^{1}H NMR-Spectra were recorded on Bruker Avance 300, Bruker Avance 400, Bruker Avance 600, Varian Inova 600, Bruker DRX-400 with a H/C/P/F QNP gradient probe and Bruker Avance 500 with a dual carbon/proton CPDUL cryoprobe. The chemical shift δ is given in [ppm], calibration was set on chloroform-d_1 (7.26 ppm) or tetramethylsilane (0.00 ppm) as internal standard. The spectra were evaluated in 1st order and the coupling constants are given in Hertz [Hz]. The following abbreviations for the spin multiplicity were used: s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, m = multiplet, dt = doublet of a triplet, dd = double doublet, ddd = doublet of a double doublet, sept = septet. The used deuterated solvents are given separately.

^{13}C NMR-Spectra were recorded on Bruker Avance 300, Bruker Avance 400, Bruker Avance 600, Varian Inova, Bruker DRX-400 with a H/C/P/F QNP gradient probe and Bruker Avance 500 with a dual carbon/proton CPDUL cryoprobe. The chemical shift δ is given in [ppm], calibration was set on chloroform-d_1 (77.16 ppm), or tetramethylsilane (0.00 ppm) as internal standard. The multiplicity of the signals were detected by DEPT 135 and 90 (DEPT = distortionless enhancement by polarization transfer)

Masspectrometry was performed on Varian MAT 311A, Finnigan MAT 95, Thermoquest Finnigan TSQ 7000, Nermag quadrupoles, VG ZAB high-resolution double-focusing and VG Autospec-Q tandem hybrid with EBEqQ configuration. The percentage set in brackets gives the peak intensity related to the basic peak (I = 100%). High resolution mass spectrometry (HRMS): The molecular formula was proven by the calculated precise mass.

Elemental analysis was prepared by the micro analytic section of the University of Regensburg using a Vario EL III or Mikro-Rapid CHN (Heraeus).

Thin layer chromatography (TLC) was prepared on TLC-aluminium sheets (Merck, silica gel 60 F_{254}, 0.2 mm). Detection in UV-light l = 254 nm, staining with I_2, Mostain, molybdatophosphoric-acid (5% in ethanol), $KMnO_4$ solution or vanillin-sulfuric acid.

Column chromatography was performed in glass columns (G2 or G3). As a stationary phase silica gel Merck-Geduran 60 (0.063-0.200 mm) or flash silica gel Merck 60 (0.040-0.063 mm) was used.

Solvents: Abs. solvents were prepared according to usual lab procedures or taken from the MB-SPS solvent purification system. Ethylacetate, hexanes (40-60 °C) and dichloromethane were purified by distillation before use. Further solvents and reagents were of p.a. quality.

Reactions with oxygen- and moisture sensitive reactants were performed in oven dried and in vacuo heated reaction flasks under a pre-dried inert gas (nitrogen or argon) atmosphere. For cooling to temperatures < -40 °C a cryostat Haake EK 90 or dry ice/*iso*-propanol mixture was used.

11.2 Dehalogenation of *vicinal* dibromo, α-halo and α,α-dibromo carbonyl compounds

General Procedure for the preparation of α-bromo/α,α'-dibromo carbonyl compounds:

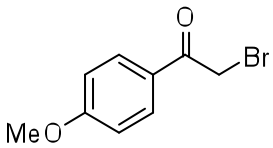
General Procedure A[1] (GP-A):

To a stirred solution of the corresponding ketone (1 mmol) in $CHCl_3$ (3.0 mL) was added dropwise 2.0 mL (4.0 mL for dibromination) of bromine solution (0.55 M in chloroform) at 0 °C and after complete addition the reaction mixture brought into room temperature. The stirring was continued at room temperature for another 1h and then gently heated at 65 °C. Completion of the reaction was determined by checking TLC. After completion of the reaction, reaction mixture brought to room temperature and a saturated solution of $Na_2S_2O_3$ was added to quench the unreacted bromine and stirring continued for another 30 min. The reaction mixture was extracted with $CHCl_3$ (2 x 5.0 mL) and the combined organic layers washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Depending upon the substrate the desire compound was obtained by crystallization (EA/PE) or by column chromatography.

General Procedure B[2] (GP-B):

Ketone (1 mmol) N-halosuccinimide (NBS/ NCS, 1 mmol) were triturated together with p-toluenesulfonic acid (PTSA, 0.1 mmol) in a porcelain mortar for 20 min. The reaction mixture was then heated to 80 °C for 2 h, turning into a dense paste. Water was then added (5.0 mL) followed by extraction with diethyl ether (20.0 mL). The organic phase was washed with water (10.0 mL), dried over Na_2SO_4 and solvent evaporated under reduced pressure. Depending upon the substrate the desire compound was obtained by crystallization (EA/PE) or by column chromatography.

2-Bromo-1-(4-methoxyphenyl)ethanone (142a) (GP-A)[3]

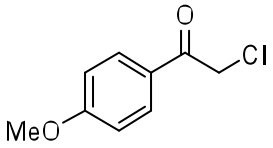


According to the general procedure (GP-A), 1-(4-methoxyphenyl) ethanone (0.16 g, 1.01 mmol) and 2.05 mL of bromine solution (0.55 M in chloroform) afforded **142a** (0.17 g, 0.75 mmol, 75 %) as crystalline solid after crystallization from EA/PE. R_f(EtOAc/hexane 1:9): 0.24.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 3.91 (s, 3H), 4.45 (s, 3H), 6.95 (d, *J* = 9.05 Hz, 2H), 7.97 (d, *J* = 8.78 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 30.7, 55.6, 114.1, 126.9, 131.4, 164.1, 189.9.

2-Chloro-1-(4-methoxyphenyl)ethanone (142b) (GP-B)[4]

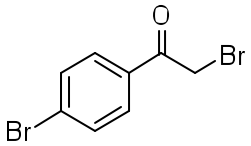


According to the general procedure (GP-B), 1-(4-methoxyphenyl) ethanone (0.52 g, 3.46 mmol) and NCS (0.44 g, 3.33 mmol) afforded **142b** (0.45 g, 2.49 mmol, 75 %) as crystalline solid after crystallization from EA/PE. R_f(EtOAc/hexane 1:9): 0.30.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 3.89 (s, 3H), 4.66 (s, 2H), 6.95 (d, *J* = 9.05 Hz, 2H), 7.93 (d, *J* = 9.05 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 45.7, 55.6, 114.1, 127.2, 130.9, 164.1, 189.6.

2-Bromo-1(4-bromophenyl)ethanone (142c) (GP-A)[5]

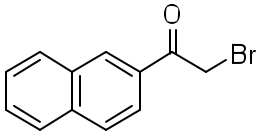


According to the general procedure (GP-A), 1-(4-bromophenyl) ethanone (0.48 g, 2.41 mmol) and 5.10 mL of bromine solution (0.55 M in chloroform) afforded **142c** (0.57 g, 2.06 mmol, 82 %) as crystalline solid after crystallization from EA/PE. R_f(EtOAc/hexane 1:9): 0.47.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 4.4 (s, 2H), 7.65 (d, *J* = 8.78 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 30.3, 129.3, 130.4, 132.2, 133.3, 190.4.

2-Bromo-1-(naphthalen-2-yl)ethanone (142e) (GP-A)[6]

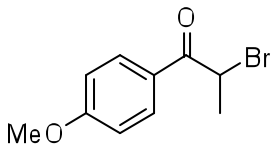


According to the general procedure (GP-A), 1-(naphthalen-2-yl)-ethanone (1.01 g, 5.94 mmol) and 11.80 mL of bromine solution (0.55 M in chloroform) afforded **142e** (1.03 g, 4.17 mmol, 71 %) as crystalline solid after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.43.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 4.59 (s, 2H), 7.53-7.69 (m, 2H), 7.84-8.08 (m, 4H), 8.52 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 30.9, 124.2, 127.1, 127.9, 128.8, 129.0, 129.7, 131.0, 131.3, 135.9, 191.3.

2-Bromo-1-(4-methoxyphenyl)propan-1-one (142f) (GP-A)[7]

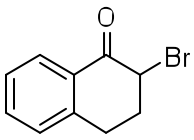


According to the general procedure (GP-A), 1-(4-methoxyphenyl)-propan-1-one (0.59 g, 3.59 mmol) and 7.30 mL of bromine solution (0.55 M in chloroform) afforded **142f** (0.64 g, 2.67 mmol, 73 %) as white solid after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.42.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 1.89 (d, *J* = 6.8 Hz, 3H); 3.88 (s, 3H); 5.27 (q, *J* = 6.8 Hz, 1H); 6.96 (dd, 2.4, 8.8 Hz, 2H); 8.02 (dd, *J* = 2.4, 8.8 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 20.2, 41.4, 55.5, 113.9, 126.8, 131.3, 163.9, 192.0.

2-Bromo-3,4-dihydronaphthalen-1(2H)-one (142g) (GP-B)[8]



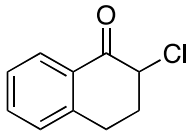
According to the general procedure (GP-B), 3,4-dihydronaphthalene-1(2H)-one (0.49 g, 3.35 mmol) and NBS (0.61 g, 3.44 mmol) afforded

142g (0.44 g, 1.95 mmol, 57 %) as gummy oil after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.39.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 2.35-2.58 (m, 2H), 2.83- 2.95 (m, 1H), 3.22-3.49 (m, 1H), 4.71 (t, *J* = 4.39 Hz, 1H), 7.21-7.37 (m, 2H), 7.45-7.55 (m, 1H), 8.11 (dd, *J* = 1.37, 7.95 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 26.1, 31.9, 50.6, 127.1, 128.6, 128.8, 129.9, 134.2, 143.0, 190.5.

2-Chloro-3,4-dihydronaphthalen-1(2H)-one (142h) (GP-B)[9]



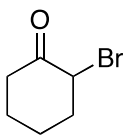
According to the general procedure (GP-B), 3,4-dihydronaphthalene-1(2H)-one (0.98 g, 6.71 mmol) and NCS (0.91 g, 6.84 mmol) afforded **142h** (0.79 g, 4.45 mmol, 65 %) as yellowish oil after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.41.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 2.36-2.67 (m, 2H), 2.90- 3.06 (m, 1H), 3.18-3.33 (m, 1H), 4.57-4.67 (m, 1H), 7.22-7.38 (m, 2H), 7.45-7.58 (m, 1H), 8.08 (d, *J* = 7.95 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 26.3, 32.4, 59.8, 127.1, 128.5, 128.7, 130.4, 134.1, 143.1, 190.8.

MS (EI, 70 eV): m/z = 90.1 (37.22), 118.0 (100), 145.1 (11.00), 180.5 (39.40) [M+].

2-Bromocyclohexanone (142i) (GP-B)[10]



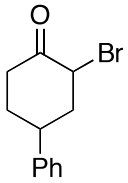
According to the general procedure (GP-B), cyclohexanone (1.99 g, 20.31 mmol) and NBS (3.63 g, 20.41 mmol) afforded **142i** (2.34 g, 13.26 mmol, 65 %) as brown oil after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.66.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 1.61-2.11 (m, 4H), 2.12-2.41 (m, 3H), 2.90-3.33 (m, 1H), 4.39-4.49 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 22.1, 27.6, 36.7, 37.9, 53.4, 203.5.

MS (EI, 70 eV): m/z = 97.1(100), 132.0(15.49), 176.0(29.52) [M+].

2-Bromo, 4-phenylcyclohexanone (142j) (GP-B)[10]



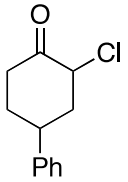
According to the general procedure (GP-B), 4-phenylcyclohexanone (0.51 g, 2.93 mmol) and NBS (0.51 g, 2.87 mmol) upon refluxation in CCl_4 (12 h) afforded **142j** (0.54 g, 2.15 mmol, 75 %) as white crystalline solid (mp 112-116 °C; lit. 115-116 °C) after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.47.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 1.85-2.05 (m, 1H), 2.17-2.30 (m, 1H), 2.35-2.50 (m, 3H), 3.25-3.41 (m, 1H), 3.45-3.60 (m, 1H), 4.40-4.47 (m, 1H), 7.20-7.40 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 33.6, 35.6, 37.2, 41.9, 50.8, 126.9, 128.8, 143.3, 203.9.

MS (EI, 70 eV): m/z =117.1 (100), 173.1 (32.79), 252.0 (68.19) [M+].

2-Chloro, 4-phenylcyclohexanone (142k) (GP-B)



According to the general procedure (GP-B), 4-phenylcyclohexanone (0.49 g, 2.81 mmol) and NCS (0.38 g, 2.87 mmol) upon refluxation in CCl_4 (12 h) afforded **142k** (0.20 g, 1.02 mmol, 35 %) as white crystalline solid after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.46.

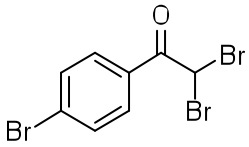
^{1}H NMR (300 MHz, $CDCl_3$), δ = 1.85-2.07 (m, 1H), 2.13-2.51 (m, 4H), 3.09-3.28 (m, 1H), 3.42-3.62 (m, 1H), 4.29-4.34 (m, 1H), 7.20-7.39 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 33.7, 35.9, 36.6, 40.5, 59.9, 126.9, 128.8, 143.2, 204.3.

MS (EI, 70 eV): m/z =104.1(100), 153.1(43.06), 208.1(49.82) [M+].

HRMS (EI, 70 eV): Calcd for $C_{12}H_{13}ClO$ $[M]^+$: 208.0655, found: 208.0658.

2,2-Dibromo-1-(4-bromophenyl)ethanone (144a) (GP-A)[11]

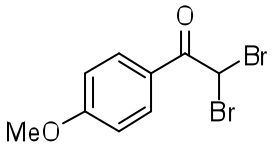


According to the general procedure (GP-A), 1-(4-bromophenyl)-ethanone (0.52 g, 2.61 mmol) 9.20 mL of bromine solution (0.55 M in chloroform) afforded **144a** (0.76 g, 2.11 mmol, 84 %) as crystalline solid after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.62.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 6.6 (s, 1H), 7.65 (d, *J* = 8.78 Hz, 2H), 7.98 (d, *J* = 8.50 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 39.2, 129.5, 129.9, 131.2, 132.3, 185.1.

2,2-Dibromo-1-(4-methoxyphenyl)ethanone (144b) (GP-A)[12]

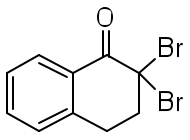


According to the general procedure (GP-A), 1-(4-methoxyphenyl)-ethanone (0.42 g, 2.80 mmol) and 10.20 mL of bromine solution (0.55 M in chloroform) afforded **144b** (0.62 g, 2.01 mmol, 72 %) as crystalline solid after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.30.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 3.90 (s, 3H), 6.66 (s, 1H), 6.97 (d, *J* = 8.78 Hz, 2H), 8.08 (d, *J* = 9.05 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 39.8, 55.6, 114.2, 123.3, 132.2, 164.5.

2,2-Dibromo-3,4-dihydronaphthalen-1(2H)-one (144c) (GP-B)[11]



According to the general procedure (GP-B), 3, 4-dihydronaphthalene-1(2H)-one (0.48 g, 3.28 mmol) and NBS (1.21 g, 6.84 mmol) afforded

144c (0.47 g, 1.54 mmol, 45 %) as colorless gummy oil after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.48.

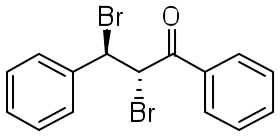
^{1}H NMR (300 MHz, $CDCl_3$), δ = 2.95-3.18 (m, 4H), 7.20-7.43 (m, 2H), 7.46-7.60 (m, 1H), 8.11- 8.24 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 29.3, 45.8, 67.3, 127.3, 127.6, 128.6, 129.4, 130.1, 134.4, 142.1, 184.2.

General procedure for preparation of vicinal dibromides:[13]

To a solution or suspension of the corresponding chalcone (1.53 mmol) in 8.0 mL of $CHCl_3$ was added dropwise 3.0 mL of bromine solution (0.56 M in chloroform) at 0 °C. The mixture was stirred at room temperature until the reaction was completed (monitored by TLC). After completion of the reaction a saturated solution of $Na_2S_2O_3$ was added to quench the unreacted bromine and stirring continued for another 30 min. The reaction mixture was extracted with $CHCl_3$ (2x 8.0 mL) and the combined organic layers were washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Depending upon the substrate the desired compound was obtained by crystallization (EA/PE) or by column chromatography.

(*2S, 3R*)-2, 3-dibromo-1,3-diphenylpropan-1-one (147a)[14]

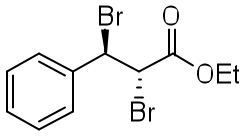


According to the general procedure, (*E*)-1,3-diphenylprop-2-en-1-one (0.32 g, 1.53 mmol) and 3.10 mL of bromine solution (0.56 M in chloroform) afforded **147a** (0.46 g, 1.12 mmol, 82%) as white solid after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.46

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.65 (d, *J* = 11.4 Hz, 1H), 5.83 (d, *J* = 11.4 Hz, 1H), 7.34-7.49 (m, 3H), 7.51-7.61 (m, 4H), 7.63-7.71 (m, 1H), 8.10 (d, *J* = 8.4 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.8, 49.8, 128.4, 128.9, 128.9, 129.0, 129.3, 134.2, 134.4, 138.2, 191.2.

(*2S, 3R*)-ethyl 2,3-dibromo-3-phenylpropanoate (147b)[15]



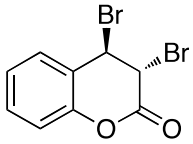
According to the general procedure, ethyl cinnamate (1.99 g, 11.31 mmol) and 22.30 mL of bromine solution (0.56 M in chloroform) afforded **147b** (3.35 g, 9.97 mmol, 88%) as white crystalline solid after crystallization from EA/PE mixture. R_f (EtOAc/hexane 1:9): 0.59

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (t, *J* = 7.13 Hz, 3H), 4.36 (q, *J* = 7.13 Hz, 2H), 4.83 (d, *J* = 11.8 Hz, 1H), 5.35 (d, *J* = 11.8 Hz, 1H), 7.30-7.65 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 47.0, 50.7, 62.7, 128.1, 128.9, 129.4, 137.7, 167.8.

MS (EI, 70 eV): m/z = 77.1 (42.09), 103.1 (100), 183.0 (29.65), 225 (59.95), 335.8 (2.26) [M+].

3,4-Dibromochroman-2-one (147d)[16]



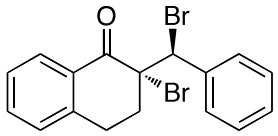
According to the general procedure, 2H-chromen-2-one (0.51 g, 3.49 mmol) and 6.70 mL of bromine solution (0.56 M in chloroform) afforded **147d** (0.96 g, 3.15 mmol, 92 %) as light yellow solid after crystallization from EA/PE mixture. R_f (EtOAc/hexane 1:9): 0.33.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.96 (d, *J* = 2.74 Hz, 1H), 5.35 (d, *J* = 2.74 Hz, 1H), 7.14-7.29 (m, 2H), 7.36- 7.52 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.3, 43.7, 117.7, 119.9, 125.6, 128.7, 131.6, 150.4, 160.7.

MS (EI, 70 eV): m/z = 118.0 (100), 146.0 (76.33), 225.0 (35.64), 303.8 (6.25) [M+].

(*R*)-2-bromo-2-((*S*)-bromo(phenyl)methyl)-3,4-dihydronaphthalen-1(2H)-one (147e)[17]



According to the general procedure, (*E*)-2-benzylidene-3,4-dihydro naphthalen-1(2H)-one (0.39 g, 1.66 mmol) and 3.40 mL

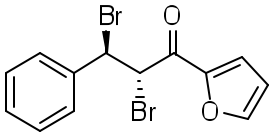
of bromine solution (0.56 M in chloroform) afforded **147e** (0.52 g, 1.33 mmol, 78 %) as light pink solid (mp 152-154 °C; lit. 153-154 °C) after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.48.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42-2.52 (m, 1H), 2.93-3.27 (m, 3H), 6.2 (s, 1H), 7.25-7.65 (m, 8H), 8.25 (d, *J* = 7.68 Hz, 1H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 26.2, 30.7, 55.4, 68.8, 127.3, 127.8, 128.7, 128.9, 129.4, 129.8, 131.1, 134.3, 136.2, 142.5, 188.6.

MS (EI, 70 eV): m/z = 233.1 (100), 313.0 (4.16), 393.9 (0.15) [M+].

(*2S,3R*)-2,3-dibromo-1-(furan-2-yl)-3-phenylpropan-1-one (147f)[18]



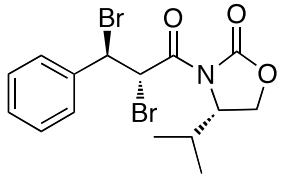
According to the general procedure, (*E*)-1-(furan-2-yl)-3-phenylprop-2-en-1-one (0.81 g, 4.09 mmol) and 8.05 mL of bromine solution (0.56 M in chloroform) afforded **147f** (1.21 g, 3.35 mmol, 82 %) as light yellow solid after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.34.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.57 (d, *J* = 11.80 Hz, 1H), 5.74 (d, *J* = 11.80 Hz, 1H), 6.64- 6.72 (m, 1H), 7.35-7.60 (m, 6H), 7.70-7.79 (m, 1H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 47.1, 49.1, 113.3, 119.8, 128.3, 128.9, 129.3, 138.1, 147.6, 150.3, 180.1.

MS (EI, 70 eV): m/z = 95.0 (100), 197.1 (86.18), 277.0 (9.71), 357.9 (0.15) [M+].

(*S*)-3-((*2S, 3R*)-2,3-dibromo-3-phenylpropanoyl)-4-isopropyloxazolidin-2-one (147g)[19]



According to the general procedure, (*S*)-3-cinnamoyl-4-isopropyloxazolidin-2-one (1.19 g, 4.63 mmol) and 9.10 mL of

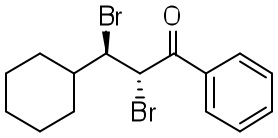
bromine solution (0.56 M in chloroform) afforded **147g** (1.72 g, 4.07 mmol, 88 %) as light yellow solid after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.27.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88-1.02 (m, 6H), 2.40-2.60 (m, 1H), 4.20-4.47 (m, 2H), 4.50-4.65 (m, 1H), 5.51 (d, *J* = 11.52 Hz, 1H), 6.58 (d, *J* = 11.52 Hz, 1H), 7.26-7.60 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8, 17.8, 28.0, 43.4, 50.2, 58.6, 63.5, 128.4, 128.9, 129.4, 137.5, 153.2, 167.2.

MS (EI, 70 eV): m/z = 260.2 (35.79), 277.1 (100), 279.2 (75.78), 437.0 (6.60) [MNH_4^+].

(*2R,3S*)-2,3-dibromo-3-cyclohexyl-1-phenylpropan-1-one (147h)



According to the general procedure, (*E*)-3-cyclohexyl-1-phenylprop-2-en-1-one (0.54 g, 2.52 mmol) and 4.90 mL of bromine solution (0.56 M in chloroform) afforded **147h** (0.83 g, 2.22 mmol, 88 %) as white solid after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.63.

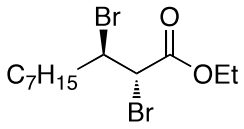
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11-1.95 (m, 10H), 2.00-2. 22 (m, 1H), 4.72 (dd, *J* = 2.19, 11.25 Hz, 1H), 5.52 (d, *J* = 11.25 Hz, 1H), 7.46-7.55 (m, 2H), 7.59-7.66 (m, 1H), 7.95-8.08(m, 2H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 25.5, 26.0, 26.07, 26.13, 32.0, 39.6, 45.4, 59.1, 128.8, 128.9, 133.9, 134.6, 191.3.

MS (EI, 70 eV): m/z = 105.0 (100), 213.1 (1.99), 292.1 [M-HBr].

Elemental Analysis: Anal. Calcd for $C_{15}H_{18}Br_2O$: C, 48.16; H, 4.85. Found: C, 48.59; H, 4.94.

Ethyl 2,3-dibromodecanoate (147i)



According to the general procedure, (*E*)-ethyl dec-2-enoate (0.78 g, 4.02 mmol) and 7.90 mL of bromine solution (0.56 M in chloroform) afforded **147i** (1.18 g, 3.31 mmol, 82 %) as gummy oil after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.70.

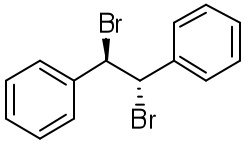
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.72 Hz, 3H), 1.21-1.67 (m, 13H), 1.74-1.88 (m, 1H), 2.15-2.30 (m, 1H), 4.28 (q, *J* = 7.13 Hz, 2H), 4.36-4.40 (m, 2H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 13.8, 14.1, 22.6, 26.2, 28.7, 29.0, 31.7, 35.1, 48.1, 52.9, 62.3, 167.9.

MS (EI, 70 eV): m/z = 216.3 (100), 233.3 (11.01), 374.0 (41.02) [MNH_4^+].

HRMS (EI, 70 eV): Calcd for $C_{12}H_{22}Br_2O_2$ $[M+H]^+$: 357.0065, found: 357.0029.

(*1R,2S*)-1,2-dibromo-1,2-diphenylethane (147j)[14]

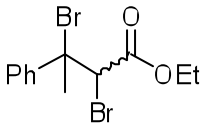


According to the general procedure, (*E*)-1,2-diphenylethene (2.11 g, 11.72 mmol) and 21.80 mL of bromine solution (0.56 M in chloroform) afforded **147j** (3.62 g, 10.66 mmol, 96 %) as white solid after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.69.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.52 (s, 2H), 7.12-7.32 (m, 10H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 59.1, 128.2, 128.6, 137.8.

Ethyl 2,3-dibromo-3-phenylbutanoate (*erythro*:*threo* = 67:33) (150a)



According to the the general procedure, (*E*)-ethyl 3-phenylbut-2-enoate (1.01 g, 5.31 mmol) and 10.40 mL of bromine solution (0.56 M in

chloroform) afforded **150a** (1.25 g, 3.57 mmol, 68 %) as colorless oil after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.60.

^{1}H NMR (*erythro* compound) (300 MHz, $CDCl_3$): δ = 1.37 (t, *J* = 7.13 Hz, 3H), 2.55 (s, 3H), 4.30-4.37 (m, 2H), 5.08 (s, 1H), 7.30-7.40 (m, 3H), 7.57-7.67 (m, 2H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 13.8, 25.4, 54.0, 62.3, 65.7, 126.6, 128.4, 142.5, 167.5.

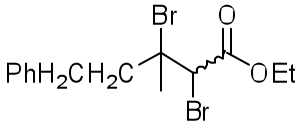
^{1}H NMR (*threo* compound) (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.13 Hz, 3H), 2.55 (s, 3H), 3.86 (q, *J* = 7.04 Hz, 2H), 5.11 (s, 1H), 7.30-7.40 (m, 3H), 7.57-7.67 (m, 2H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 13.5, 27.8, 57.8, 61.8, 68.9, 127.1, 128.9, 140.5, 166.5.

MS (EI, 70 eV): m/z = 191.2 (41.45), 208.2 (100), 286.1 (2.85) [M-HBr], 368.0 (10.02) [MNH_4^+].

HRMS (EI, 70 eV): Calcd for $C_{12}H_{14}Br_2O_2$ $[M-H]^+$: 346.9283, found: 346.9284

Ethyl 2,3-dibromo-3-methyl-5-phenylpentanoate (*erythro*:*threo* = 80:20) (150b)



According to the the general procedure, ethyl 3-methyl-5-phenylpent-2-enoate (0.49 g, 2.24 mmol) and 4.50 mL of bromine solution (0.56 M in chloroform) afforded **150b** (0.67 g, 1.78 mmol, 78 %) as colorless oil after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.66.

^{1}H NMR (*erythro* compound) (300 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.13 Hz, 3H), 2.10 (s, 3H), 2.20-2.30 (m, 2H), 2.80-2.90 (m, 2H), 4.24-4.32 (m, 2H), 4.70 (s, 1H), 7.17-7.36 (m, 5H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 13.9, 26.7, 31.7, 46.0, 51.9, 62.2, 66.8, 126.2, 128.5, 140.6, 167.5.

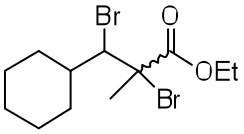
^{1}H NMR (*threo* compound) (300 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.13 Hz, 3H), 2.00 (s, 3H), 2.20-2.30 (m, 2H), 2.80-2.90 (m, 2H), 4.24-4.32 (m, 2H), 4.74 (s, 1H), 7.17-7.36 (m, 5H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 13.9, 29.8, 32.5, 41.3, 55.5, 62.2, 67.6, 126.2, 128.5, 141.0, 167.4.

MS (EI, 70 eV): m/z = 91.1 (100), 131.1 (28.72), 217.2 (15.40), 299.1 (5.21), 376.0 (1.20) [M^+].

HRMS (EI, 70 eV): Calcd for $C_{14}H_{18}Br_2O_2$, [M^+]: 375.9674, found: 375.9667.

(*2S,3R*)-ethyl 2,3-dibromo-3-cyclohexyl-2-methylpropanoate (*erythro*:*threo*= 52:48) (150c)



According to the general procedure, (*E*)-ethyl 3-cyclohexyl-2-methylacrylate (0.74 g, 3.77 mmol) and 7.40 mL of bromine solution (0.56 M in chloroform) afforded **150c** (1.02 g, 2.80 mmol, 75 %) as colorless oil after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.81.

^{1}H NMR (*erythro* compound) (300 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.13 Hz, 3H), 1.00-2.20 (m, 11H), 1.99 (s, 3H), 4.20-4.32 (m, 2H), 4.54 (d, *J* = 3.63 Hz, 1H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 13.8, 23.6, 25.8, 26.1, 31.9, 33.7, 39.4, 42.8, 62.5, 64.9, 68.9, 169.2.

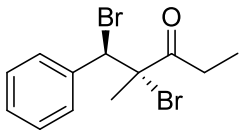
^{1}H NMR (*threo* compound) (300 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.13 Hz, 3H), 1.00-2.20 (m, 11H), 2.02 (s, 3H), 4.20-4.32 (m, 2H), 4.59 (d, *J* = 1.64 Hz, 1H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 13.8, 23.6, 25.8, 26.1, 31.9, 33.7, 39.4, 42.8, 62.5, 64.9, 68.9, 169.3.

MS (EI, 70 eV): m/z = 197.3 (16.27), 214.2 (100), 231.2 (5.99), 374.1 (20.84) [MNH_4+].

Elemental Analysis: Anal. Calcd for $C_{12}H_{20}Br_2O_2$: C, 40.47; H, 5.66. Found: C, 40.69; H, 5.73.

(*1R,2S*)-1,2-dibromo-2-methyl-1-phenylpentan-3-one (150d)



According to the general procedure, (*E*)-2-methyl-1-phenylpent-1-en-3-one (0.61 g, 3.50 mmol) and 6.80 mL of bromine solution (0.56 M in chloroform) afforded **150d** (0.79 g, 2.39 mmol, 70 %) as colorless oil after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.57.

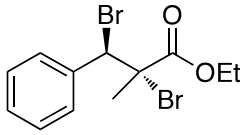
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.13 Hz, 3H), 2.01 (s, 3H), 2.75-3.10 (m, 2H), 5.68 (s, 1H), 7.30-7.40 (m, 3H), 7.47-7.59 (m, 2H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 8.7, 21.6, 29.4, 56.5, 68.8, 127.9, 129.0, 130.9, 135.5, 202.6.

MS (EI, 70 eV): m/z = 175.1 (100), 192.2 (98.01), 349.9 (21.43) [MNH_4^+].

HRMS (EI, 70 eV): Calcd for $C_{12}H_{14}Br_2O$, [M^+]: 331.9412, found: 331.9410.

(*2S,3R*)-ethyl 2,3-dibromo-2-methyl-3-phenylpropanoate (150e)



According to the general procedure, ethyl 2-methyl-3-phenylacrylate (0.81 g, 4.26 mmol) and 8.30 mL of bromine solution (0.56 M in chloroform) afforded **150e** (0.82 g, 2.43 mmol, 72 %) as colorless oil after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.40.

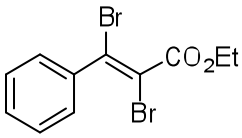
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (t, *J* = 7.13 Hz, 3H), 2.06 (s, 3H), 4.30-4.40 (m, 2H), 5.77 (s, 1H), 7.32-7.40 (m, 3H), 7.50-7.58 (m, 2H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 13.9, 22.1, 57.3, 61.8, 62.8, 127.7, 129.0, 130.9, 135.5, 169.3.

MS (EI, 70 eV): m/z = 191.2 (21.78), 208.2 (100), 286.1 (3.19) [M-HBr], 366 (96.9) [MNH_4+].

HRMS (EI, 70 eV): Calcd for $C_{12}H_{14}Br_2O_2$, [M^+]: 347.9361, found: 347.9355.

(*E*)-ethyl 2,3-dibromo-3-phenylacrylate (152)[14]



According to the general procedure, ethyl 3-phenylpropiolate (1.22 g, 7.01 mmol) and 13.70 mL of bromine solution (0.56 M in chloroform) afforded **152** (0.74 g, 2.24 mmol, 32 %) as gummy oil after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.58.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (t, *J* = 7.13 Hz, 3H), 4.39 (q, *J* = 7.13 Hz, 2H), 7.35-7.49 (m, 5H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 13.4, 62.8, 107.6, 121.5, 128.1, 128.3, 128.4, 128.7, 129.7, 138.2, 164.0.

MS (EI, 70 eV): m/z = 102.1 (100), 182.0 (47.31), 227 (67.10), 253.0 (68.31), 288.9 (38.81), 331.9 (38.64) [M+].

General procedure for the Photoredox catalyzed reduction of halides:

An oven dried 10 mL vial equipped with a plastic septum and magnetic stir bar was charged with tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), the corresponding halide (0.173 mmol, 1.0 equiv), 1,5-dimethoxynaphthalene (0.087 mmol, 0.5 equiv) and ascorbic acid (0.348 mmol, 2 equiv). The flask was purged with a stream of nitrogen and 1.0 mL of solvent (MeOH: H_2O = 10:1) was added. The resultant mixture was degassed for 10 min by nitrogen sparging and placed at a distance of ~ 0.5 -1.0 cm from a blue LED lamp.[20] After the reaction was completed (as judged by TLC analysis), the mixture was diluted with 3.0 mL of methanol and directly concentrated in vacuo. The residue was purified by chromatography on silica gel, using PE/ EA as the solvent

system. 1,5-Dimethoxynaphthalene (DMN) was re-isolated during the column purification [R_f(EtOAc/hexane 1:9): 0.63].

Determination of Quantum Yield:

Quantum yield was determined by the laboratory apparatus reported by Riedle *et al*.[21] In a typical experimental setup, light from a blue LED was passed through a reference cuvette containing 2.0 mL of solvent (MeOH:H_2O = 10:1) and the transmitted radient power P_{ref} was noted by a solar cell. Then the reference cuvette was exchanged with the sample cuvette containing **147a** (0.271 mmol, 1 equiv), tris(2,2´-bipyridyl) ruthenium (II) chloride hexahydrate (0.004 g, 2 mol%), 1,5-dimethoxynaphthalene (0.025 g, 0.135 mmol, 0.5 equiv) and ascorbic acid (0.093 g, 0.542 mmol, 2 eqiv) in 2.0 mL of solvent (MeOH:H_2O = 10:1) and the timer was started. After 30 min, transmitted power, P_{sample} was noted in the same solar cell and the sample was taken to the chemical analysis to measure the final product concentration. Conversion to the product **148a** was determined by the crude NMR of the sample and the quantum yield was determined by the following equation:

$$Q.Y. = \frac{N_{prod}}{N_{ph,\,abs}} = \frac{C_{prod}.V.N_A.h.c}{P_{abs}.t.\lambda}$$

Here, N_{prod} and C_{prod} are the number of molecules and the according concentration of product species. $N_{ph,\,abs}$ is the number of photons absorbed. V is the sample volume, N_A, h and c are natural constants, P_{abs} is the absorbed optical power, t is the illumination time and λ is the wavelength of the blue LED.

Therefore,

C_{prod} = 18 mmol/l (13% conversion)

V = 2.0 mL

$N_A = 6.022 \times 10^{23}\ mol^{-1}$

$P_{abs} = (P_{ref} - P_{sample}) = 371\ mW$

$h = 6.626 \times 10^{-34}\ Js$

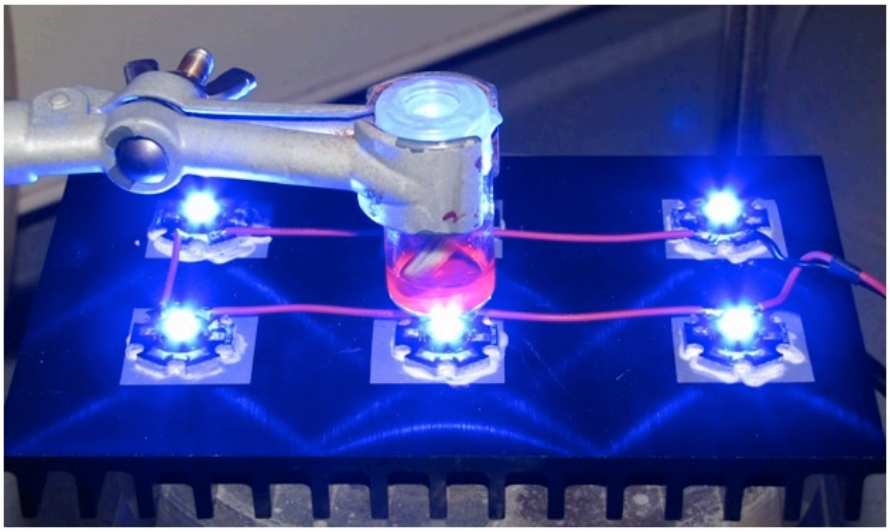
$c = 2.998 \times 10^{8}\ m/s$

$t = 30\ min = 1800\ s$

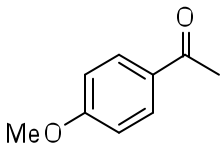
$\lambda = 460\ nm$

Quantum yield = 0.014

Reaction Apparatus



1-(4-methoxyphenyl) ethanone (143a)[22]

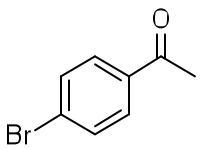


According to the general procedure, **142a** (0.102 g, 0.44 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded 1**43a** (0.06 g, 0.41 mmol, 93 %) as white solid after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.25.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 2.52 (s, 3H), 3.83 (s, 3H), 6.91 (d, *J* = 9.05 Hz, 2H), 7.91 (d, *J* = 9.05 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 26.3, 55.4, 113.6, 130.3, 130.8, 163.4, 196.8.

1-(4-bromophenyl) ethanone (143c)[22]

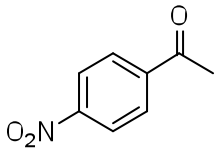


According to the general procedure, **142c** (0.101 g, 0.36 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **143c** (0.064 g, 0.32 mmol, 89 %) as white solid after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.38.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 2.59 (s, 3H), 7.61 (d, *J* = 8.78 Hz, 2H), 7.82 (d, *J* = 8.78 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 26.5, 128.3, 129.8, 131.9, 135.8, 197.0.

1-(4-nitrophenyl)ethanone (143d)[22]

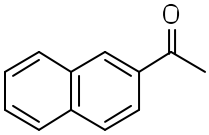


According to the general procedure, **142d** (0.148 g, 0.61 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **143d** (0.073 g, 0.44 mmol, 72 %) as white solid after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.31.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 2.69 (s, 3H), 8.08-8.15 (d, *J* = 8.78 Hz, 2H), 8.29-8.35 (d, *J* = 9.05 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 27.0, 123.9, 129.3, 141.3, 196.3.

1-(naphthalen-2-yl)ethanone (143e)[22]

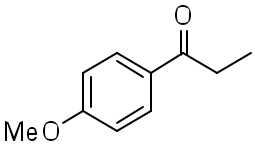


According to the general procedure, **142e** (0.152 g, 0.60 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **143e** (0.086 g, 0.51 mmol, 84 %) as white solid after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.35.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 2.79 (s, 3H), 7.51-7.70 (m, 2H), 7.83-8.12 (m, 4H), 8.48 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 26.7, 123.9, 126.8, 127.8, 128.4, 128.5, 129.5, 130.2, 197.7.

1-(4-methoxyphenyl)propan-1-one (143f)[22]

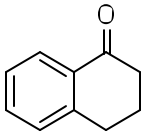


According to the general procedure, **142f** (0.098 g, 0.41 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **143f** (0.037 g, 0.22 mmol, 54 %) as white solid after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.32.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 1.21 (t, *J* = 7.40 Hz, 3H), 2.95 (q, *J* = 7.31 Hz, 2H), 3.86 (s, 3H), 6.93 (d, *J* = 9.05 Hz, 2H), 7.95 (d, *J* = 9.05 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 8.4, 31.4, 55.4, 113.6, 130.0, 130.2, 163.3, 199.5.

3,4-Dihydronaphthalen-1(2H)-one (143g)[23]



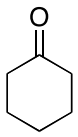
According to the general procedure, **142g** (0.079 g, 0.36 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-

dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **143g** (0.037 g, 0.25 mmol, 71 %) as gummy oil after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.33.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 2.07-2.21 (m, 2H), 2.66 (t, *J* = 6.99 Hz, 2H), 2.97 (t, *J* = 6.17 Hz, 2H), 7.21-7.35 (m, 2H), 7.41-7.52 (m, 1H), 8.03 (dd, *J* = 1.09 Hz, 7.68 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 23.3, 29.7, 39.2, 126.2, 126.6, 127.5, 132.6, 133.4, 144.5, 198.4.

Cyclohexanone (143i) [24]

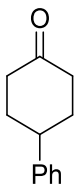


According to the general procedure, **142i** (0.101 g, 0.56 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **143i** (0.028 g, 0.28 mmol, 50 %) as yellowish oil after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.36.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 1.59-1.71 (m, 2H), 1.72-1.87 (m, 4H), 2.21-2.32 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 24.7, 26.9, 42.1, 212.0.

4-Phenylcyclohexanone (143j)[25]



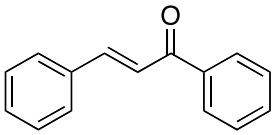
According to the general procedure, **142j** (0.075 g, 0.29 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **143j** (0.039 g, 0.22 mmol, 75 %) as white solid after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.28.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 1.85-2.05 (m, 2H), 2.15-2.30 (m, 2H), 2.45-2.57 (m, 4H), 2.95-3.10 (m, 1H), 7.15-7.40 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 33.9, 41.4, 42.8, 126.6, 128.6, 144.8, 211.2.

MS (EI, 70 eV): m/z =104.1 (89.14), 119.1 (63.97), 174.1 (100) [M+].

(*E*)-1,3-diphenylprop-2-en-1-one (148a)[26]

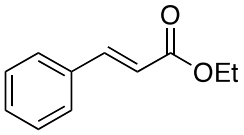


According to the general procedure, **147a** (0.064 g, 0.17 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **148a** (0.033 g, 0.16 mmol, 92 %) as pale yellow solid after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.41.

^{1}H NMR (300 MHz; $CDCl_3$), δ = 7.36-7.70 (m, 9H), 7.84 (d, *J* = 15.6 Hz, 1H), 7.98-8.10 (m, 2H).

^{13}C NMR (75 MHz; $CDCl_3$), δ = 122.1, 128.5, 128.5, 128.6, 128.9, 130.5, 132.8, 134.9, 138.2, 144.8, 190.6.

Ethyl (*E*)-cinnamate (148b)[26]

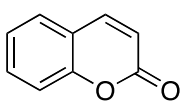


According to the general procedure, **147b** (0.11 g, 0.29 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **148b** (0.046 g, 0.26 mmol, 88 %) as gummy oil after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.51.

^{1}H NMR (300 MHz, $CDCl_3$), δ = 1.33 (t, *J* = 7.2 Hz, 3H), 4.26 (q, *J* = 7.2, 2H), 6.43 (d, *J* = 16 Hz, 1H), 7.34-7.39 (m, 3H), 7.46-7.53 (m, 2H), 7.68 (d, *J* = 16 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$), δ = 14.3, 60.5, 118.3, 128.0, 128.9, 130.2, 134.4, 144.6, 167.0.

2H-chromen-2-one (148d)[27]

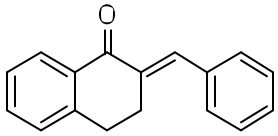


According to the general procedure, **147d** (0.10 g, 0.33 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxy naphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **148d** (0.044 g, 0.30 mmol, 92 %) as yellow solid after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.16.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.42 (d, *J* = 9.87 Hz, 1H), 7.21-7.35 (m, 2H), 7.46- 7.56 (m, 2H), 7.72 (d, *J* = 9.87, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 116.7, 116.9, 118.8, 124.4, 127.8, 131.8, 143.4, 154.0, 160.8.

(*E*)-2-benzylidene-3,4-dihydronaphthalen-1(2H)-one (148e)[28]



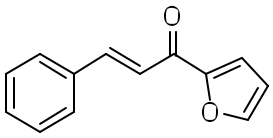
According to the general procedure, **147e** (0.20 g, 0.50 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **148e** (0.089 g, 0.38 mmol, 75 %) as white solid after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.41.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.95 (t, *J* = 6.27 Hz, 2H), 3.14 (t, *J* = 6.27 Hz, 2H), 7.23-7.52 (m, 8H), 7.89(s, 1H), 8.14 (d, *J* = 7.68, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 120.0, 121.3, 129.1, 129.8, 130.7, 135.3, 135.4, 159.3, 162.8.

MS (EI, 70 eV): m/z = 233.1 (100), 234.1 (55.48) [M+].

(*E*)-1-(furan-2-yl)-3-phenylprop-2-en-1-one (148f)[29]



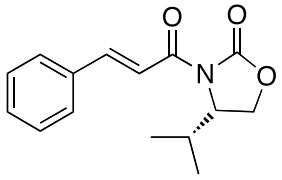
According to the general procedure, **147f** (0.071 g, 0.20 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **148f** (0.01 g, 0.052 mmol, 26 %) as white solid after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.22.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.59-6.61 (m, 1H), 7.32-7.49 (m, 5H), 7.62-7.70 (m, 3H), 7.88 (d, *J* = 15.64 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.5, 117.5, 121.1, 128.5, 128.9, 130.6, 134.7, 144.0, 146.5, 153.7, 178.0.

MS (EI, 70 eV): m/z = 77.1 (27.63), 103.1 (27.39), 141.0 (35.24), 197.1 (100), 198.1 (72.91) [M+].

(*S*)-3-cinnamoyl-4-isopropyloxazolidin-2-one (148g)[30]



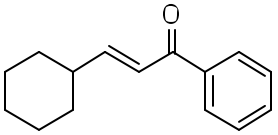
According to the general procedure, **147g** (0.06 g, 0.14 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **148g** (0.033 g, 0.13 mmol, 89 %) as white solid after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.12.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 7.12 Hz, 3H), 0.96 (d, *J* = 7.12 Hz, 3H), 2.38-2.52 (m, 1H), 4.11-4.37 (m, 2H), 4.51-4.60 (m, 1H), 7.32-7.50 (m, 3H), 7.53-7.70 (m, 2H), 7.83 (d, *J* = 15.7 Hz, 1H), 7.96 (d, *J* = 15.7 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 18.0, 28.5, 58.6, 63.4, 117.1, 128.6, 128.9, 130.6, 134.6, 146.2, 154.2, 165.2.

MS (EI, 70 eV): m/z = 147.1 (15.45), 260.2 (31.55) [MH^+], 277.1 (100) [MNH_4^+].

(*E*)-3-cyclohexyl-1-phenylprop-2-en-1-one (148h)[29]



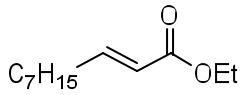
According to the general procedure, **147h** (0.049 g, 0.13 mmol), tris(2,2´-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **148h** (0.008 g, 0.04 mmol, 28 %) as yellow oil after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.53.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12-1.42 (m, 5H), 1.61-1.91 (m, 5H), 2.17-2.33 (m, 1H), 6.82 (d, *J* = 15.6 Hz, 1H), 7.01 (dd, *J* = 15.6, 6.6 Hz, 1H), 7.40-7.58 (m, 3H), 7.92 (d, *J* = 6.9 Hz, 2H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 25.7, 25.9, 31.8, 41.0, 123.4, 128.4, 128.5, 132.5, 138.2, 154.9, 191.4.

MS (EI, 70 eV): m/z = 77.0 (28.75), 105.0 (100), 157.1 (6.07), 214.1 (28.58) [M+].

(*E*)-ethyl dec-2-enoate (148i)[31]



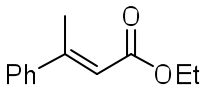
According to the general procedure, **147i** (0.112 g, 0.31 mmol), tris(2,2´-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **148i** (0.016 g, 0.08 mmol, 26 %) as gummy colorless oil after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.56.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.72 Hz, 3H), 1.13-1.65 (m, 13H), 2.11-2.25 (m, 2H), 4.17 (q, *J* = 7.13 Hz, 2H), 5.80 (d, *J* = 15.64 Hz, 1H), 6.90-7.03 (m, 1H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 14.0, 14.2, 22.6, 28.0, 29.0, 29.1, 31.7, 32.2, 60.1, 121.2, 149.5, 166.8.

MS (EI, 70 eV): m/z = 55.1 (100), 101.1 (90.63), 153.2 (61.84), 198.2 (2.95) [M+].

(*E*)-ethyl 3-phenylbut-2-enoate (151a)[32]



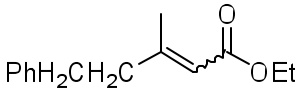
According to the general procedure, **150a** (0.094 g, 0.27 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxy naphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **151a** (0.036 g, 0.19 mmol, 70 %) as yellow oil after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.48.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.13 Hz, 3H), 2.58 (s, 3H), 4.22 (q, *J* = 7.13 Hz, 2H), 6.14 (s, 1H), 7.32-7.55 (m, 5H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 14.3, 17.9, 59.8, 117.2, 126.3, 128.4, 128.9, 142.2, 155.6, 166.9.

MS (EI, 70 eV): m/z = 191.2 (44.35) [MH+], 208.1 (100) [MNH_4+].

Ethyl 3-methyl-5-phenylpent-2-enoate (*E*:*Z* = 84:16) (151b)[33]



According to the general procedure, **150b** (0.088 g, 0.23 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **151b** (0.033 g, 0.15 mmol, 65 %) as yellow oil (*E/Z* mixture) after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.46.

^{1}H NMR (*E*-isomer) (300 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.13 Hz, 3H), 2.21 (s, 3H), 2.40-2.48 (m, 2H), 2.74-2.84 (m, 2H), 4.15 (q, *J* = 7.13 Hz, 2H), 5.69 (s, 1H), 7.13-7.35 (m, 5H).

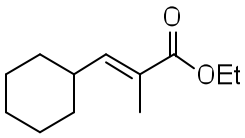
^{13}C NMR (75MHz, $CDCl_3$): δ = 14.3, 18.9, 33.9, 42.7, 59.5, 116.0, 126.1, 128.2, 128.4, 141.1, 158.9, 166.8.

^{1}H NMR (*Z*-isomer) (300 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.13 Hz, 3H), 1.88 (s, 3H), 2.40-2.48 (m, 2H), 2.74-2.84 (m, 2H), 4.15 (q, *J* = 7.13 Hz, 2H), 5.69 (s, 1H), 7.13-7.35 (m, 5H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 14.3, 18.9, 33.9, 42.7, 59.5, 116.0, 126.1, 128.2, 128.4, 141.1, 158.9, 166.8.

MS (EI, 70 eV): m/z = 91.1 (100), 144.2 (22.65), 173.1 (9.47), 218.2 (1.87) [M+].

(*E*)-ethyl 3-cyclohexyl-2-methylacrylate (151c)[32]



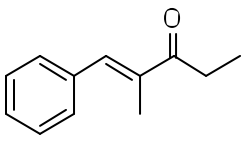
According to the general procedure, **150c** (0.13 g, 0.34 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **151c** (0.019 g, 0.09 mmol, 27 %) as gummy oil after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.76.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11-1.78 (m, 10H), 1.28 (t, *J* = 7.13 Hz, 3H), 1.84 (s, 3H), 2.23-2.39 (m, 1H), 4.18 (q, *J* = 7.13 Hz, 2H), 6.58 (d, *J* = 8.23 Hz, 1H).

^{13}C NMR (75MHz, $CDCl_3$): δ =12.4, 14.3, 25.6, 25.9, 31.9, 37.7, 60.4, 147.3, 168.2.

MS (EI, 70 eV): m/z = 197.2 (25.78) [MH+], 214.3 (100) [MNH_4+].

(*E*)-2-methyl-1-phenylpent-1-en-3-one (151d)[28]



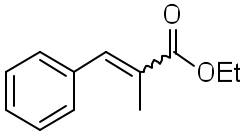
According to the general procedure, **150d** (0.08 g, 0.24 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **151d** (0.032 g, 0.18 mmol, 75 %) as colorless oil after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.42.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.27 Hz, 3H), 2.09 (s, 3H), 2.84 (q, *J* = 7.27 Hz, 2H), 7.30-7.45 (m, 5H), 7.53 (s, 1H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 8.8, 13.2, 30.8, 128.5, 129.7, 136.0, 137.2, 138.2. 203.0.

MS (EI, 70 eV): m/z = 145.1 (5.11), 175.1 (100) [MH+], 192.2 (90.75) [MNH_4+].

Ethyl 2-methyl-3-phenylacrylate (*E*:*Z* = 75:25) ((151e)[32]



According to the general procedure, **150e** (0.064 g, 0.19 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **151e** (0.023 g, 0.12 mmol, 65 %) as colorless oil (*E/Z* mixture) after column purification on silica gel. R_f(EtOAc/hexane 1:9): 0.34.

^{1}H NMR (*E*-isomer) (300 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.13 Hz, 3H), 2.12 (s, 3H), 4.28 (q, *J* = 7.13 Hz, 2H), 7.29-7.43 (m, 5H), 7.70 (s, 1H).

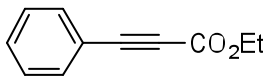
^{13}C NMR (75MHz, $CDCl_3$): δ = 14.0, 14.3, 128.2, 128.3, 128.6, 129.6, 135.9, 138.6, 168.7.

^{1}H NMR (*Z*-isomer) (300 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.13 Hz, 3H), 2.12 (s, 3H), 4.18 (q, *J* = 7.13 Hz, 2H), 6.71 (s, 3H), 7.29-7.43 (m, 5H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 13.6, 21.3, 60.5, 127.4, 127.9, 128.0, 134.2, 168.7.

MS (EI, 70 eV): m/z = 191.2 (43.49) [MH+], 208.1 (100) [MNH_4+].

Ethyl 3-phenylpropiolate (153)[34]



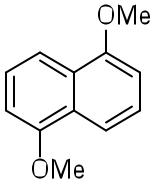
According to the general procedure, **152** (0.08 g, 0.24 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), 1,5-dimethoxynaphthalene (0.5 equiv) and ascorbic acid (2 equiv) afforded **153** (0.03 g, 0.17 mmol, 72 %) as gummy colorless oil after column purification on silica gel. R_f (EtOAc/hexane 1:9): 0.50.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.13 Hz, 3H), 4.30 (q, *J* = 7.13 Hz, 2H), 7.30-7.50 (m, 3H), 7.55 - 7.65 (m, 2H).

^{13}C NMR (75MHz, $CDCl_3$): δ = 14.1, 62.1, 80.7, 86.0, 119.6, 128.5, 130.6, 133.0, 154.1.

MS (EI, 70 eV): m/z = 102.1 (65.32), 129.0 (100), 174.0 (16.37) [M+].

1, 5-Dimethoxynaphthalene (Isolated after reaction)



^{1}H NMR (300 MHz; $CDCl_3$), δ = 3.98 (s, 6H); 6.85 (d, *J* = 7.47 Hz, 2H), 7.36 (t, *J* = 8.09 Hz, 2H), 7.84 (d, *J* = 8.72 Hz, 2H).

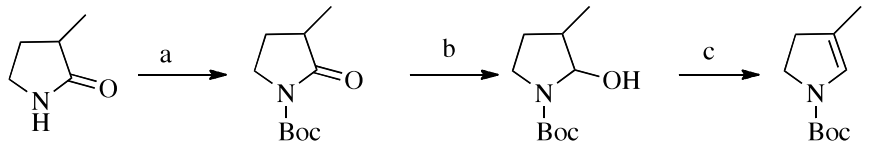
^{13}C NMR (75 MHz; $CDCl_3$), δ = 55.5, 104.5, 114.1, 125.1, 126.6, 155.2.

R_f (EtOAc/hexane 1:9): 0.63

11.3 Photo oxygenation of cyclic enamines and enol ethers

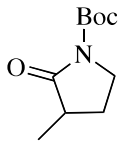
***tert*-Butyl 4-methyl-2,3-dihydro-1H-pyrrole-1-carboxylate (172e)[35]**

Compound **172e** was prepared in three steps starting from commercially available 3-methyl-2-pyrrolidinone **172E**, according to the following procedure.

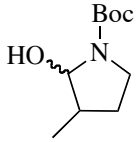


172E **172E'** **172E''** **172e**

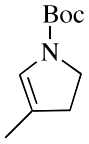
Scheme and conditions: (a) $(Boc)_2O$ (1.2 equiv.), DMAP (0.15 equiv.), CH_3CN, rt, over night, 82 %. (b) DIBAL-H, THF, -78 °C, 3h, 92 % (crude). (c) (i) TFAA (1 equiv.), toluene, 0 °C; (ii) 2,6-lutidine, 0 °C to rt, over night; (iii) reflux, 20 min, 63 %.



In a 100 mL flask di-*tert*-butyl dicarbonate, $(Boc)_2O$ (5.28 g, 24.24 mmol) and 4-(dimethylamino)pyridine, DMAP (0.37 g, 3.01 mmol) were added to 3-methyl-2-pyrrolidinone, **172E** (2.0 g, 20.20 mmol) in acetonitrile (30 mL) under nitrogen. The mixture was stirred at room temperature for over night. Evaporation of the solvent under reduced pressure and subsequent column chromatography on SiO_2 afforded 3.32 g (82 %) of **172E'** as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.15 (d, *J* = 6.86 Hz, 3H), 1.45 (s, 3H), 1.51-1.69 (m, 1H), 2.08-2.22 (m, 1H), 2.41-2.56 (m, 1H), 3.45-3.56 (m, 1H), 3.65-3.75 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 15.36, 26.38, 27.99, 38.57, 44.29, 82.61, 150.40, 176.59.



To a solution of **172E'** (1.0 g, 5.03 mmol) in 7 mL of THF at -78 °C was slowly added DIBAL-H (1 M solution in hexane, 7.02 mL, 7.03 mmol) and stirred for 6 h. The reaction mixture was quenched with saturated NH_4Cl (10.0 mL) and allowed to reach room temperature. Further the mixture was treated with 10 % Na_2CO_3 (10.0 mL) and 20 mL CH_2Cl_2, stirred for 10 min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrate in vacuo. The product **172E"** (0.92 g, 92 %) was directly used for next step without further purification.



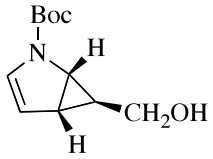
To a stirred solution of the crude product **172E"** (0.92g, 4.57 mmol), 2,6-lutidine (10.66 mL, 91.54 mmol), and toluene (80 mL) at 0 °C under N_2, was added 1 equiv of $(CF_3CO)_2O$, stirred for 6 h at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred overnight. The mixture was refluxed for 30 min, cooled to room temperature. To the mixture was added saturated $NaHCO_3$ (40.0 mL) and stirred for 1 h. The organic layer was separated and the aqueous layer extracted with hexane. The combined toluene/hexane extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 to afford **172e** as colorless oil (0.57g, 63%).

R_f (hexane/ ethylacetate 70: 30) = 0.76

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.41 (s, 9H), 1.70 (s, 3H), 2.36-2.55 (m, 2H), 3.57-3.75 (m, 2H), 6.11 (6.23) (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.63, 28.47, 33.17, 45.27, 79.64, 118.23, 124.15, 151.4.

MS (EI, 70 eV): m/z (%) = 128.1 (20.11), 145.1 (100), 184.1 (76.63) [MH+], 201.2 (7.35) [MNH_4+].

(*1S,5S,6S*)-*tert*-Butyl 6-(hydroxymethyl)-2-azabicyclo[3.1.0]hex-3-ene-2-carboxylate (172c)



An oven-dried, 50 mL flask was flushed with dry nitrogen and charged with lithium aluminum hydride (35 mg, 0.87 mmol) in 5 mL THF. A solution of **172a** (0.30 g, 1.25 mmol) in 3 mL of THF was added dropwise at 0 °C and was stirred further for additional 2 h at room temperature. After completion of the reaction (monitored by TLC), 5 mL water was added slowly to destroy the excess hydride. The organic layer, combined with two ethyl acetate extracts of the aqueous layer, was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography on silica gel to afford **172c** (0.15 g, 57 %) as gummy oil.

R_f (hexane/ ethylacetate 70: 30) = 0.15.

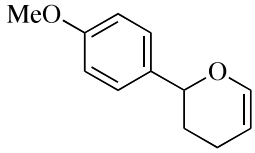
^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.55-0.65 (m, 1H), 1.46 (s, 9H), 2.06-2.27 (m, 1H), 3.30-3.87 (m, 3H), 5.05-5.35 (m, 1H), 6.29 (d, *J* = 3.56 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 23.99, 25.23, 28.33, 39.91, 63.09, 81.19, 111.14, 128.39, 151.84.

IR (neat) = 3375, 1700, 1591, 1414, 1392, 1367, 1135, 761 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 173.0 (100), 194.0 (8.56), 212.0 (12.95) $[MH]^+$, 229.1 (61.31) $[MNH_4]^+$.

HRMS (EI, 70 eV): Calcd for $C_{11}H_{17}NO_3$ [M^+]: 211.1208, found: 211.1209.

2-(4-Methoxyphenyl)-3,4-dihydro-2H-pyran (182b)[36]



According to the literature procedure,[37] an oven-dried schlenk flask was evacuated and filled with nitrogen were added 4-iodoanisole (0.502 g, 2.14 mmol), 3,4-dihydro-2*H*-pyran (2.18 mL, 25.64 mmol), K_2CO_3 (0.442 g, 3.20 mmol), DMF (6 mL) and palladium

(II) acetate (0.024 mg, 0.107 mmol). The mixture was stirred at 115 °C for 72 h, allowed to cool to room temperature. EtOAc (20 mL) was added to the reaction mixture, and then the reaction mixture was washed with H_2O (3 × 10 mL). The organic layer was dried over Na_2SO_4. After filtration, solvent was evaporated and purified by column chromatography (hexanes–EtOAc, 19:1), to afford 2-(4-methoxy-phenyl)-3,4-dihydro-2*H*-pyran **182b** (0.305 g, 75%) as colorless oil.

R_f (hexane/ ethylacetate 70: 30) = 0.59

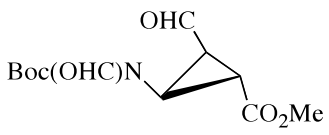
^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.83-2.11 (m, 3H), 2.17-2.37 (m, 1H), 3.82 (s, 3H), 4.72-4.82 (m, 2H), 6.54 (d, *J* = 5.48 Hz, 1H), 6.83-6.97 (m, 2H), 7.25-7.37 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 20.48, 30.19, 55.30, 76.63, 100.58, 113.81, 127.28, 134.20, 144.33, 159.14.

MS (EI, 70 eV): m/z (%) = 119.0 (20.99), 134.1 (100), 190.1 (21.98)$[M]^+$.

General procedure for the Photo-oxidation of cyclic enamines and enol ethers:

An oven dried 10 mL round bottom flask equipped with a plastic septum and magnetic stir bar was charged with tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), the corresponding cyclic enamine/enol ethers (0.209 mmol, 1.0 equiv) and 1 mL of CH_3CN. The resultant mixture was bubbled for 3 min by oxygen sparging and placed at a distance of ~ 0.5 -1.0 cm from a blue LED lamp[20] with an oxygen balloon. After the reaction was completed (judged by TLC analysis), the mixture was directly concentrated in vacuo. The residue was purified by chromatography on silica gel, using PE/ EA or PE/acetone as the solvent system.

(1*R*,2*S*)-Methyl 2-(*N*-(*tert*-butoxycarbonyl)formamido)-3-formylcyclopropanecarboxylate (173a)[38]



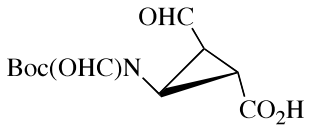
According to the general procedure, **172a** (0.05 g, 0.209 mmol), tris(2,2′- bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%) afforded **173a** (0.041 g, 0.15 mmol, 72 %) in 30 min as colorless oil after column purification on silica gel.

R_f (hexane/ EtOAc 5:1) = 0.19.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.52 (s, 9H), 2.75 (dd, *J* = 6.0, 4.8 Hz, 1H), 2.96 (ddd, *J* = 8.2, 6.0, 2.3 Hz, 1H), 3.21 (dd, *J* = 7.92, 4.8 Hz, 1H), 3.75 (s, 3H), 9.07 (s, 1H), 9.54 (d, *J* = 2.46 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.78, 27.88, 34.94, 36.66, 52.62, 85.40, 151.90, 163.40, 170.01, 193.10.

MS (EI, 70 eV): m/z (%) = 189.1 (7.61), 272.1 (1.12) [MH+], 289.1 (100) [MNH_4+].

(*1R,2S*)-2-(N-(*tert*-butoxycarbonyl)formamido)-3-formylcyclopropanecarboxylic acid (173b)



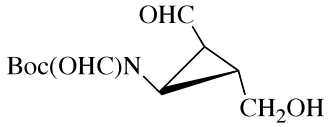
According to the general procedure, **172b** (0.051 g, 0.226 mmol), tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%) afforded **173b** (0.052 g, 0.202 mmol, 89 %) in 1 h as colorless oil after column purification on silica gel.

R_f(hexane/ EtOAc 30:70) = 0.15.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.54 (s, 9H). 2.75 (dd, *J* = 4.66, 5.76 Hz, 1H), 3.05-2.96 (m, 1H), 3.23 (dd, *J* = 4.66, 7.95 Hz, 1H), 9.09 (s, 1H), 9.56 (d, *J* = 2.46 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.90, 28.37, 35.11, 36.75, 85.64, 151.84, 163.49, 174.35, 192.93.

MS (CI, NH_3): m/z (%) = 57.1 (100), 112.0 (25.58), 157 (23.69), 240.1 (0.58), 257 (0.90) [M^+].

***tert*-Butyl formyl((1S,3S)-2-formyl-3-(hydroxymethyl)cyclopropyl)carbamate (173c)**



According to the general procedure, **172c** (0.071 g, 0.331 mmol), tris(2,2′- bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%) afforded **173c** (0.068 g, 0.279 mmol, 85 %) in 1 h as colorless oil after column purification on silica gel.

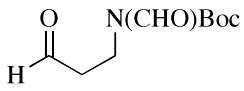
R_f(hexane/ EtOAc 1:1) = 0.31.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.52 (s, 9H), 2.20-2.30 (m, 1H), 2.41-2.49 (m, 1H), 2.60 (bs, 1H), 2.82 (dd, *J* = 5.48, 7.68 Hz, 1H), 3.50 (dd, *J* = 7.68, 10.97 Hz, 1H), 3.85-4.00 (d *J* = 10.42 Hz, 1H), 9.12 (s, 1H), 9.45 (d, *J* = 3.01 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.96, 30.05, 32.40, 35.91, 62.07, 85.42, 152.20, 164.17, 195.61.

IR (neat) = 3455, 1741, 1699, 1370, 1290, 1157, 849 cm^{-1}.

HRMS (EI, 70 eV): Calcd for $C_{11}H_{18}NO_5$ [MH^+]: 244.1185, found: 244.1186.

tert-Butyl formyl(3-oxopropyl)carbamate (173d)



According to the general procedure, **172d** (0.05 g, 0.295 mmol), tris(2,2´- bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%) afforded **173d** (0.048 g, 0.238 mmol, 81 %) in 2.5 h as colorless oil after column purification on silica gel.

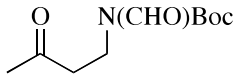
R_f(hexane/ EtOAc 80:20): = 0.31.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.54 (s, 9H), 2.67 (dt, *J* = 1.64, 6.86 Hz, 2H), 3.95 (t, *J* = 6.99 Hz, 2H), 9.13 (s, 1H), 9.76(t, *J* = 1.78 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 26.99, 33.49, 41.63, 83.67, 161.83, 198.75.

IR (neat) = 1740, 1722, 1686, 1341, 1153, 776 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 57.1 (100), 100.0(1.21), 133.0(0.99).

tert-Butyl formyl(3-oxobutyl)carbamate (173e)



According to the general procedure, **172e** (0.093 g, 0.508 mmol), tris(2,2´- bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%) afforded **173e** (0.102 g, 0.474 mmol, 93 %) in 4 h as colorless oil after column purification on silica gel.

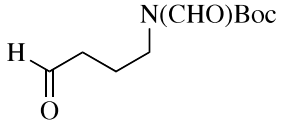
R_f(hexane/ EtOAc 70:30) = 0.53.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.55 (s, 9H), 2.15 (s, 3H), 2.68 (t, *J* = 7.54 Hz, 2H), 3.85 (t, *J* = 7.54 Hz, 2H), 9.12 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.04, 29.99, 35.82, 41.78, 84.39, 162.89, 206.17.

MS (EI, 70 eV): m/z (%) = 116.0 (41.76), 133.0 (100), 216.1 (18.99) [MH^+], 233.1 (94.11) [MNH_4+].

HRMS (EI, 70 eV): Calcd for $C_{10}H_{17}NO_4$ [M^+]: 215.1158, found: 215.1162.

tert-Butyl formyl(4-oxobutyl)carbamate (173f)



According to the general procedure, **172f** (0.01 g, 0.546 mmol), tris(2,2´- bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%) afforded **173f** (0.111 g, 0.516 mmol, 94 %) in 3.5 h as colorless

oil after column purification on silica gel.

R_f(hexane/ EtOAc 70:30) = 0.63.

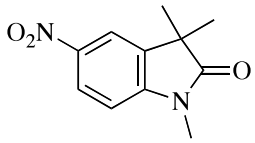
^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.55 (s, 9H). 1.81-1.93 (m, 2H), 2.43-2.50 (m, 2H), 3.63 (t, *J* = 6.99 Hz, 2H), 9.16 (s, 1H), 9.77 (t, *J* = 1.09 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 20.79, 28.04, 39.70, 41.02, 84.27, 152.36, 163.12, 201.05.

IR (neat): 1736, 1687, 1344, 1153, 1072, cm^{-1}.

MS (EI, 70 eV): m/z (%) = 57.1 (100), 159.1 (2.86) [M^+- C_4H_8].

HRMS (EI, 70 eV): Calcd for $C_{10}H_{17}NO_4$ [MH^+]: 216.1236, found: 216.1239.

1,3,3-Trimethyl-5-nitroindolin-2-one (173g)[39]



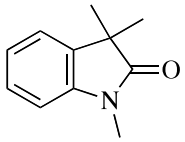
According to the general procedure, **172g** (0.05 g, 0.229 mmol), tris(2,2´- bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%) afforded **173g** (0.036 g, 0.164 mmol, 72 %) in 3 h as yellowish oil after column purification on silica gel.

R_f(hexane/ EtOAc 70:30) = 0.42

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.43 (S, 6H), 3.29 (S, 3H), 6.92 (d, *J* = 8.78 Hz, 1H), 8.10 (d, *J* = 2.46 Hz, 1H), 8.26 (dd, *J* = 2.19, 8.78 Hz, 1H). - ^{13}C NMR (75 MHz, $CDCl_3$) δ = 24.18, 26.66, 44.23, 107.57, 118.33, 125.20, 136.48, 148.38, 181.27.

MS (EI, 70 eV): m/z (%) = 130.0 (20.00), 159.0 (25.50), 190.0 (10.24), 205.0 (64.20), 220.0 (100) [$M]^+$

1,3,3-Trimethylindolin-2-one (173h)[40]



According to the general procedure, **172h** (0.102 g, 0.507 mmol), tris(2,2´- bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%) afforded **173h** (0.031 g, 0.177 mmol, 35 %) in 5 h as colorless oil after column purification on silica gel.

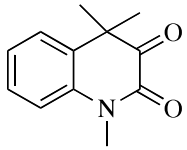
R_f(hexane/ EtOAc 70:30) = 0.64.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.34 (s, 6H), 3.19 (s, 3H), 6.83 (d, *J* = 7.68 Hz, 1H), 7.04 (t, *J* = 7.40 Hz, 1H), 7.16-7.25 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 24.39, 26.21, 44.18, 108.01, 122.26, 122.47, 127.66, 135.92, 142.47, 181.32.

IR (neat) = 2968, 1707, 1613, 1493, 1472, 1382, 1348, 1124, 755 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 117.0 (12.03), 160.1 (100), 175.1 (73.92)[M^+].

1,4,4-Trimethylquinoline-2,3-(1H,4H)-dione (173h')[41]



According to the general procedure, **172h** (0.102 g, 0.507 mmol), tris(2,2´- bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%) afforded **173h'** (0.027 g, 0.133 mmol, 26 %) in 5 h as colorless oil after column purification on silica gel.

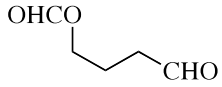
R_f(hexane/ EtOAc 70:30) = 0.33.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.53 (s, 6H), 3.52 (s, 3H), 7.10 (d, *J* = 8.23 Hz, 1H), 7.16 (t, *J* = 7.54 Hz, 1H), 7.32-7.40 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 23.9, 30.16, 48.35, 115.63, 124.47, 124.68, 127.55, 128.57, 130.71, 156.95, 195.47.

IR (neat) = 1739, 1677, 1607, 1459, 1369, 755 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 160.1 (100), 175.1 (24.30), 203.1 (15.17) [M^+].

4-Oxobutyl formate (183a)[42]

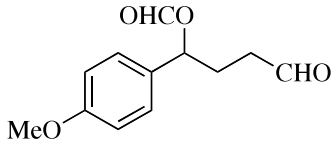


According to the general procedure, **182a** (0.12 g, 1.07 mmol), tris(2,2´- bipyridyl)ruthenium(II)chloride hexahydrate (1 mol%) afforded **183a** (0.084 g, 0.724 mmol, 68 %) in 3 h as colorless oil after column purification on silica gel.

R_f(hexane/ EtOAc 70:30) = 0.37.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.95-2.06 (m, 2H), 2.57 (t, *J* = 7.13 Hz, 2H), 4.20 (t, *J* = 6.72 Hz, 2H), 8.04 (s, 1H), 9.80 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.12, 40.26, 62.85, 160.87, 200.89.

1-(4-Methoxyphenyl)-4-oxobutyl formate (183b)



According to the general procedure, **182b** (0.05 g, 0.263 mmol), tris(2,2´- bipyridyl)ruthenium(II)chloride hexahydrate (1 mol%) afforded **183b** (0.035 g, 0.157 mmol, 60 %) in 3.5 h as colorless oil after column purification on silica gel.

R_f(hexane/ EtOAc 1:1) = 0.70.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.98-2.34 (m, 3H), 2.43-2.49 (m, 1H), 3.80 (s, 3H), 5.84 (t, *J* = 6.84 Hz, 1H), 6.86-6.91 (m, 2H), 7.25-7.30 (m, 2H), 8.07 (s, 1H), 9.74 (t, *J* = 1.09 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.29, 39.91, 55.31, 74.61, 114.07, 127.97, 130.98, 159.70, 160.28, 200.74.

MS (EI, 70 eV): m/z (%) = 77.0 (17.25), 109.0 (21.39), 121.0 (22.49), 137.0 (59.07), 178.0 (100), 222.0 (14.80)[M^+].

HRMS (EI, 70 eV): Calcd for $C_{12}H_{14}O_4$ [M^+]: 222.0892, found: 222.0887.

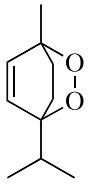
2,3-Dioxabicyclo[2.2.2]oct-5-ene (163)[43]

According to the general procedure, **162** (0.16 g, 2.01 mmol), tris(2,2´-bipyridyl)ruthenium(II)chloride hexahydrate (1 mol%) afforded **163** (0.141 g, 0.125 mmol, 62 %) in 1 h as colorless oil after column purification on silica gel.

R_f(hexane/ EtOAc 70:30) = 0.64.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.43-1.51 (m, 2H), 2.20-2.33 (m, 2H), 4.60-4.70 (m, 2H), 6.67 (dd, *J* = 3.29, 4.39 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.61, 70.87, 132.20.

1-Isopropyl-4-methyl-2,3-dioxabicyclo[2.2.2]oct-5-ene (166)[44]



According to the general procedure, **165** (0.501 g, 3.67 mmol), tris(2,2´-bipyridyl)ruthenium(II)chloride hexahydrate (1 mol%) afforded **166** (0.408 g, 2.42 mmol, 65 %) in 1 h as colorless oil after column purification on silica gel.

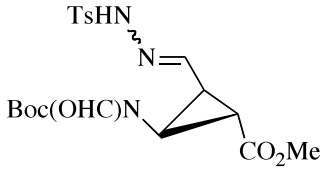
R_f(hexane/ EtOAc 70:30) = 0.54.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.99 (d, *J* = 7.13 Hz, 6H), 1.37 (s, 3H), 1.51 (d, *J* = 9.60 Hz), 1.85-2.06 (m, 3H), 6.40 (d, *J* = 8.78 Hz, 1H), 6.49 (d, *J* = 8.78 Hz, 1H). - ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.17, 17.25, 21.41, 25.60, 29.50, 32.13, 74.38, 79.80, 133.04, 136.39.

General procedure for one pot hydrazone formation *via* Photo-oxidation of cyclic enamines:

An oven dried 10 mL round bottom flask equipped with a plastic septum and magnetic stir bar was charged with tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), the corresponding cyclic enamine (0.209 mmol, 1.0 equiv.), tosyl-hydrazine (0.251 mmol, 1.2 equiv.) and 1 mL of CH_3CN. The resultant mixture was bubbled for 3 min by oxygen sparging and placed at a distance of ~ 0.5 -1.0 cm from a blue LED lamp[20] with an oxygen balloon. After the full conversion of cyclic enamine to corresponding aldehyde (judged by TLC analysis), the light was switched off and stirring was continued until the full consumption of aldehyde (monitored by TLC). The crude mixture was directly concentrated in vacuo. The residue was purified by chromatography on silica gel, using PE/ EA as the solvent system.

(*1S,2R*)-Methyl-2-(N-(tert-butoxycarbonyl)formamido)-3-((2-tosylhydrazono) methyl)cyclopropanecarboxylate (177)



According to the general procedure, **172a** (0.05 g, 0.209 mmol), tris(2,2′- bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%) and tosyl-hydrazine (0.046 g, 0.251 mmol) were irradiated 30 min with blue LED followed by 2.5 h stirring at room temperature in absence of light afforded **177** (0.079 g, 0.179 mmol, 86 %, dr = 78:22) as colorless oil after column purification on silica gel.

R_f(hexane/ EtOAc 70:30) = 0.19.

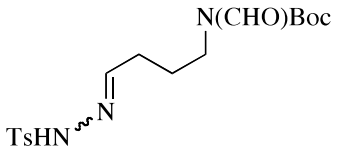
Major isomer, ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.47 (s, 9H), 2.43 (s, 3H), 2.48 (dd, *J* = 4.39, 6.03 Hz, 1H), 2.51-2.60 (m, 1H), 3.08 (dd, *J* = 4.39, 7.68 Hz, 1H), 3.73 (s, 3H), 6.99 (d, *J* = 5.48 Hz, 1H), 7.31 (d, *J* = 7.95 Hz, 2H), 7.73 (d, *J* = 8.23 Hz, 2H), 8.03 (s, 1H), 8.81 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.63, 26.58, 27.81, 28.63, 36.39, 52.45, 85.03, 127.84, 129.47, 135.10, 143.99, 144.34, 152.16, 163.59, 170.83.

Minor isomer, ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.42 (s, 9H), 2.41(s, 3H), 2.35 (dd, *J* = 4.66, 6.03 Hz, 1H), 2.62-2.72 (m, 1H), 3.17 (dd, *J* = 4.11, 7.68 Hz, 1H), 3.75 (s, 3H), 6.32 (d, *J* = 6.86 Hz, 1H), 7.31 (d, *J* = 7.95 Hz, 2H), 7.87 (d, *J* = 8.23 Hz, 2H), 8.51 (s, 1H), 8.93 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.63, 26.58, 27.81, 28.63, 36.39, 52.45, 85.03, 128.86, 129.76, 135.10, 143.99, 144.34, 152.16, 163.59, 170.83.

IR (neat) = 1732, 1707, 1284, 1159, 731 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 439.9 (51.69) [MH^+], 456.9 (77.97), [MNH_4^+].

***tert*-Butyl formyl(4-(2-tosylhydrazono)butyl)carbamate (178)**



According to the general procedure, **172f** (0.05 g, 0.273 mmol), tris(2,2´- bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%) and tosyl-hydrazine (0.061 g, 0.327 mmol) were irradiated 3.5 h with blue LED followed by 2.5 h stirring at room temperature in absence of light afforded **178** (0.094 g, 0.245 mmol, 90 %, dr = 93:7) as colorless oil after column purification on silica gel.

R_f(hexane/ EtOAc 1:1) = 0.51.

Major isomer, ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.52 (s, 9H), 1.61-1.75 (m, 2H), 2.15-2.25 (m, 2H), 2.41 (s, 3H), 3.51 (t, *J* = 7.27 Hz, 2H), 7.17 (t, *J* = 5.07 Hz, 1H), 7.27-7.34 (m, 2H), 7.76-7.84 (m, 2H), 7.86 (s, 1H), 9.12 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.60, 24.68, 28.04, 29.64, 39.67, 84.22, 127.96, 129.63, 135.26, 144.13, 151.04, 163.02.

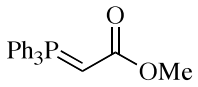
Minor isomer, ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.54 (s, 9H), 1.80-1.91 (m, 2H), 2.05-2.13 (m, 2H), 2.42 (s, 3H), 3.62 (t, *J* = 6.99 Hz, 2H), 6.69 (t, *J* = 5.35 Hz, 1H), 7.27-7.34 (m, 2H), 7.76-7.84 (m, 2H), 8.04 (s, 1H), 9.17 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.60, 24.68, 28.04, 29.64, 39.67, 84.22, 127.96, 129.63, 135.26, 144.13, 151.04, 163.02.

IR (neat) = 1737, 1686, 1342, 1147, 569 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 383.9 [MH+], 400.9 [MNH_4^+].

Preparation of Wittig Salt

Methyl 2-(triphenylphosphoranylidene)acetate (179)[45]



A solution of methyl bromoacetate (4.0 g, 26.14 mmol) in 10 mL of ethyl acetate was added to a solution of 8.21 g (31.37 mmol) of triphenylphosphane in 50 mL of ethyl acetate. After stirring overnight, the white precipitate was filtered off, washed with diethyl ether and dried in vacuo at 40 °C for 4 h. The crude precipitate was dissolved in 150 mL of dichloromethane and 2 equiv. (2.05 g, 51.25 mmol) of NaOH in 100 mL water was added to it and vigorously shaken in a separatory funnel. The water layer was washed with dichloromethane (2 x 20 mL). The combined dichloromethane layers were dried with Na_2SO_4 and the solvent was

evaporated to yield 8.65 g (25.74 mmol, 98%) of the two rotameric forms of **179** as a white solid.

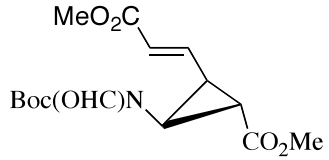
^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.90 (25 %) + 3.56 (75 %) (s, 3H), 7.42-7.84 (m, 15H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 30.60, 49.81, 127.18, 128.43, 131.96, 132.16, 133.25, 171.31.

General procedure for one pot alkene formation *via* Photo-oxidation of cyclic enamines:

An oven dried 10 mL round bottom flask equipped with a plastic septum and magnetic stir bar was charged with tris(2,2′-bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%), the corresponding cyclic enamine (0.209 mmol, 1.0 equiv) and 1 mL of CH_3CN. The resultant mixture was bubbled for 3 min by oxygen sparging and placed at a distance of ~ 0.5 -1.0 cm from a blue LED lamp[20] with an oxygen balloon. After the reaction was completed (as judged by TLC analysis), the light was stitched off and the flask was flushed with nitrogen. Then Wittig salt **179** (0.250 mmol, 1.2 equiv) was added to it and stirring was continued at room temperature until the full consumption of aldehyde (monitored by TLC). After completion of the reaction, 5 mL hexane and 2 mL water were added to it. Organic layer was separated and the aqueous layer was again extracted with hexane (3 x 8 mL) and the combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel, using PE/EA as the solvent system.

(*1S,2R*)-Methyl-2-(N-(tert-butoxycarbonyl)formamido)-3-((*E*)-3-methoxy-3-oxoprop-1-en-1-yl)cyclopropanecarboxylate (180)



According to the general procedure, **172a** (0.05 g, 0.209 mmol), tris(2,2′- bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%) and 1 mL of CH_3CN were irradiated 30 min and followed by addition of Wittig salt **179** (0.084 g, 0.251 mmol) in absence of light afforded **180** (0.046g, 0.140 mmol, 67 %, *trans:cis* = 94:6) as white solid.

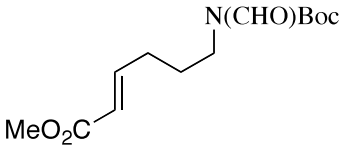
R_f(hexane/ EtOAc 70:30) = 0.38.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.51(s, 9H), 2.26 (dd, *J* = 4.11, 5.48 Hz, 1H), 2.49-2.59 (m, 1H), 3.23 (dd, *J* = 4.39, 7.68 Hz, 1H), 3.72 (s, 3H), 3.76 (s, 3H), 6.02 (d, *J* = 15.64 Hz, 1H), 6.40 (dd, *J* = 9.87, 15.64 Hz, 1H), 9.17 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.83, 29.38, 29.61, 36.84, 51.67, 52.56, 85.17, 123.22, 142.36, 152.22, 163.47, 166.06, 170.80.

IR (neat) = 1715, 1655, 1449, 1370, 1284, 1254, 1156 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 202.1 (3.30), 245.0 (18.55), 345.1 (100) [MNH_4^+].

(*E*)-Methyl 6-(N-(tert-butoxycarbonyl)formamido)hex-2-enoate (181)



According to the general procedure, **172f** (0.05 g, 0.273 mmol), tris(2,2′- bipyridyl)ruthenium(II)chloride hexahydrate (2 mol%) and 1 mL of CH_3CN were irradiated 3.5 h and followed by addition of Wittig salt **179** (0.109 g, 0.327 mmol) in absence of light afforded **181** (0.054 g, 73 %, *trans:cis* = 90:10) as gummy oil.

R_f(hexane/ EtOAc 80:20) = 0.63.

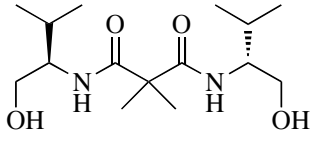
^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.54 (s, 9H), 1.63-1.76 (m, 2H), 2.14-2.26 (m, 2H), 3.60 (t, *J* = 7.27 Hz, 2H), 3.71 (s, 3H), 5.84 (dt, *J* = 15.64, 1.64 Hz, 1H), 6.86-6.99 (m, 1H), 9.15 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 26.61, 28.03, 29.40, 39.93, 51.43, 84.14, 121.55, 147.86, 152.36, 162.99, 166.87.

IR (neat) = 1724, 1686, 1437, 1343, 1146, 852 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 172.1 (8.93), 189.1 (32.86), 289.2 (100) [MNH_4^+].

11.4 Studies towards the synthesis of Sandresolide A

(*R,R*)-N,N'-Bis(1-hydroxymethyl-2-methylpropyl)-2,2-dimethyl-malonamide (211)



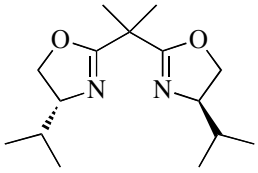
An oven dried 250 mL, 3-necked round-bottom flask equipped with a stirring bar and two 50 mL pressure-equalizing addition funnels connected to a mineral oil bubbler was purged with nitrogen and charged with (*D*)-valinol (5.13 g, 0.050 mol, 2.0

eq.). The flask was immersed in an ice bath at 0 °C and NEt_3 (17.4 mL, 0.124 mol) was added drop wise *via* the first addition funnel. 2,2-Dimethylpropanedioyl dichloride (3.3 mL, 0.25 mol, 1.0 eq.) in dry CH_2Cl_2 (25 mL) was then added drop wise over 25 min. *via* the second addition funnel. The internal temperature increases from 0 °C to 10 °C during the addition. Subsequently, the ice bath was removed and the reaction mixture was allowed to warm to rt. Stirring was continued for 45 min, resulting in a colorless precipitate that was dissolved by addition of dry CH_2Cl_2 (120 mL). After addition of aqueous HCl (1N, 30 mL), the aqueous layer was separated and extracted with CH_2Cl_2 (3x15 mL). The combined organic layers were washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford crude product as a pale yellow solid. Recrystallization of the crude product from ethyl acetate (40 mL) yielded **211** (4.30 g, 14.2 mmol, 57%) as white crystals. The mother liquor was concentrated and the residue recrystallized from ethyl acetate (10 mL) to yield a second crop of **211** (1.60 g, 5.27 mmol, 21%); the process was repeated to yield a third crop of **211** (0.440 g, 1.45 mmol, 6%, total yield: 6.40 g, 21.1 mmol, 84%).

R_f (ethylacetate:methanol 95:5) = 0.25. mp. 98-99 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.8 Hz, 6 H), 0.96 (d, *J* = 6.8 Hz, 6 H), 1.50 (s, 6 H), 1.82 (oct, *J* = 6.8 Hz, 2 H), 2.66 (bs, 2 H), 3.52 (m, 2 H), 3.69–3.86 (m, 4 H), 6.41 (d, *J* = 8.6 Hz, 2 H). ^{13}C NMR (75 MHz, CDCl3): δ = 18.8, 19.6, 23.7, 29.1, 50.2, 57.1, 63.5, 174.5.

(*R,R*)-bis(4-*iso*-propyloxazoline) ((+)208)



An oven dried 500 mL, 2-necked round-bottom flask equipped with a stirring bar and a 50 mL, pressure-equalizing addition funnel connected to a mineral oil bubbler was purged with nitrogen and charged with (*R,R*)-*N,N'*-bis-(1-hydroxymethyl-2-methylpropyl)-2,2-dimethylmalon- amide **(211)** (5.5 g, 18.4 mmol), DMAP (0.204 g, 1.67 mmol) and dry CH_2Cl_2 (130 mL). The flask was immersed in a water bath at rt and NEt_3 (10.25 mL, 73.4 mmol) was added slowly *via* syringe. Subsequently, tosyl-chloride (7.10 g, 37 mmol, 2.0 eq.), dissolved in dry CH_2Cl_2 (15 mL), was added dropwise over 30 min. After completion of the addition the funnel was rinsed with dry CH_2Cl_2 (2.5 mL) and the

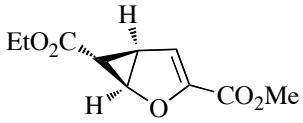
reaction mixture was stirred for an additional 27 h at rt. The reaction mixture was treated with sat. NH_4Cl (70 mL) followed by water (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3x55 mL), and the combined organic layers were dried over $MgSO_4$. The organic solution was filtered and concentrated under vacuum. The oily residue was treated with hot pentane (40 mL), stirred for 5 min and the supernatant liquid was decanted. This procedure was repeated three times and the collected pentane layers were combined and concentrated under vacuum to yield (+)-**211** (4.05 g, 15.2 mmol, 83%) as a colorless oil, which rendered solid while stored at -35 °C under a N_2-atmosphere.

An analytically pure sample for characterization purposes was obtained by Kugelrohr-distillation (95-100 °C, 0.5 mm Hg) of the crude material.

R_f(dichloromethane/methanol 9:1) = 0.25

^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.85 (d, *J* = 6.8 Hz, 6 H), 0.91 (d, *J* = 6.8 Hz, 6 H), 1.51 (s, 6 H), 1.88-1.73 (m, 2 H), 4.06-3.93 (m, 4 H), 4.26-4.15 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.3, 18.5, 24.4, 32.2, 38.5, 69.9, 71.5, 168.7.

(1*R*,2*R*,3*R*)-(+)-2- Oxalic acid 2-ethoxycarbonyl-3-formylcyclopropylester methyl ((+)-206)

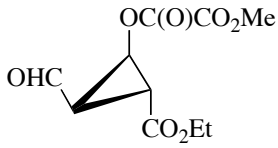


A 500 mL flask equipped with a stirring bar and a 500 mL, pressure-equalizing, addition funnel with incorporated Mariotte tube connected to a mineral oil bubbler, was purged with nitrogen and cooled to 0 °C. It was charged with $Cu(OTf)_2$ (0.227 g, 0.628 mmol, 0.66%mol), (*R,R*)-*iso*-propyl-bis(oxazoline) (+)-**211** (0.211 g, 0.799 mmol, 0.84 mol%) and dry CH_2Cl_2 (10 mL) resulting in a deep blue solution. After stirring for 10 min furan-2-carboxylic acid methyl ester **200** (12 g, 95 mmol, 1.0 eq.) was poured in and phenyl hydrazine (3 drops) was added *via* a syringe leading to a color change to red-brown which indicates the reduction of copper(II) to copper(I). This solution was stirred for 30 min and subsequently ethyldiazoacetate (215 mL solution of 10.14% mass, 0.25 mol, 2.67 eq.) in CH_2Cl_2 was added *via* the addition funnel during 5 days. On completion of addition the solution was stirred for 1 h until no gas evolution was observed any longer. The reaction mixture was passed through a pad of basic alumina, followed by CH_2Cl_2 (500 mL). The organic layers were combined and concentrated under reduced pressure to

afford yellow-brown oil. The residue was purified by fractioned distillation under reduced pressure (p = $3x10^{-2}$ mbar, b.p. = 38-44 °C) and starting material (4.78 g, 37.9 mmol, 40%) was recovered. The brown residue was purified by column chromatography (silica, 4x36 cm, hexanes: ethylacetate 9:1) to yield the desired product (+)-**206** (10.8 g, 50.90 mol, 85% *ee*, 54% yield, 89% yield based on recovered starting material) as a yellowish oil. To obtain enantiomeric pure product the oil was treated with *n*-pentane (200 mL) followed by CH_2Cl_2 (8 mL) with stirring until the solution changed from cloudy to clear. The solution was kept for 16 h at -27 °C and a small enantiomerically pure crystal was added which gave rise to colorless crystals after 6 d. The supernatant liquid was removed by filtration and the remaining crystals were dried *in vacuo* to afford (+)-**206** (6.90 g, 33.0 mmol, 34%, >99% *ee*) as colorless crystals. After concentration of the mother liquor *in vacuo* the residue was again treated with *n*-pentane (120 mL) and CH_2Cl_2 (2 mL) and set for crystallization at -27 °C for 5 d. Removal of the supernatant liquid and drying *in vacuo* afforded (+)-**206** (0.609 g, 2.87 mmol, 3%, >99% *ee*, total yield: 7.51 g, 35.39 mol, 38% yield, 62% yield based on recovered starting material) as colorless crystals.

R_f (hexanes: ethylacetate 5:1, Vanilline) = 0.16. mp. = 42 °C. – $[\alpha]^{20}_D$ = +272 (c = 1.0, CH_2Cl_2). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (dd, *J* = 2.7, 1.1 Hz, 1 H, 6-H), 1.27 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.87 (ddd, *J* = 5.3, 2.9, 2.7 Hz, 1 H, 5-H), 3.81 (s, 3 H, OCH_3), 4.16 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 4.97 (dd, *J* = 5.3, 1.1 Hz, 1 H, 1-H), 6.40 (d, *J* = 2.9 Hz, 1 H, 4-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.20 (+, CH_3), 21.43 (+, C-6), 31.97 (+, C-5), 52.26 (+, OCH_3), 61.08 (-, CH_2), 67.54 (+, C-1), 116.19 (+, C-4), 149.15 (Cquart, C-3), 159.54 (Cquart, CO), 171.78 (Cquart, CO). – IR (KBr): $\tilde{\nu}$ = 3118, 2956, 1720, 1617, 1428, 1380, 1297, 1166, 1124, 1041, 954, 831, 725 cm^{-1}.

(1*R*,2*R*,3*R*)-(-)-oxalic acid 2-ethoxycarbonyl-3-formyl-cyclopropyl ester methyl ester ((+)-207))



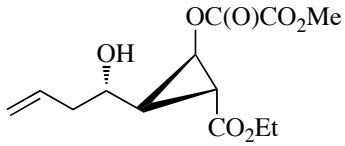
A 100 mL flask was charged with a solution of (+)-**206** (3.022 g, 14.24 mmol, 1.0 eq.) in dry CH_2Cl_2 (50 mL). The flask was equipped with a gas passing tube connected with one side to an ozone generator and with the other side to a drying tube containing KOH coated clay ending up in the hood. The solution was cooled to -78 °C

and a constant stream of oxygen containing ozone (O_2 = 150 l/h, O_3 = 7 g/h) was immersed into the solution until a deep blue color appeared (approx. 15 min). Excess of ozone was expelled by passing a constant flow of oxygen for another 10 min into the solution. The gas inlet tube was replaced by a drying tube. DMS (2.28 mL, 57 mol, 4.0 eq.) was added at -78 °C, and the reaction mixture was allowed to warm up slowly to rt and stirred for 22 h. The solution was washed with sat. $NaHCO_3$ (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with H_2O (5 mL) and the aqueous layer was extracted again with CH_2Cl_2 (5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to yield the aldehyde (3.199 g, 13.10 mmol, 92%) as a pale yellow oil which can be used without any further purification. To obtain a colorless microcrystalline solid the crude product was crystallized from Et_2O (3 mL) and stored at -35 °C for 2 weeks. The solvent was removed by a pipette and the solid was dried in vacuo to give (+)-**207** (3.124 g, 12.78 mmol) in 94% yield.

mp. = 52 °C. - $[\alpha]^{20}_D$ = + 37.5 (c = 1.0, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.2 Hz, 3 H), 2.81 (ddd, *J* = 7.2, 6.0, 4.0 Hz, 1 H), 2.93 (dd, *J* = 6.0, 3.6 Hz, 1 H), 3.92 (s, 3 H), 4.20 (q, *J* = 7.2 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 1 H), 4.83 (dd, *J* = 7.2, 3.6 Hz, 1 H), 9.47 (d, *J* = 4.0 Hz, 1 H).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (+, CH3), 26.36 (+, C-3), 34.86 (+, C-2), 54.00 (+, CO_2CH_3), 58.87 (+, C-1), 62.03 (-, CH_2), 156.59 (Cquart, CO), 156.86 (Cquart, CO), 168.13 (Cquart, CO_2Et), 192.13 (+, CHO). – IR (KBr): $\tilde{\nu}$ = 2985, 1779, 1751, 1724, 1708, 1445, 1312, 1290, 1208, 1005, 736 cm^{-1}.

(*1R,2R,3S*)-2-(ethoxycarbonyl)-3-((*S*)-1-hydroxybut-3-en-1-yl)cyclopropyl methyl oxalate (214)

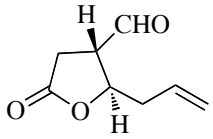


14g (57.33 mmol) of cyclopropane carbaldehyde (+)-**207** was taken in a 220 mL of anhydrous dichloromethane at -78 °C, to this 8.64 mL (68.79 mmol) of BF_3. EtO_2 was added slowly. After five minutes, 13.7 mL (86 mmol) of allyltrimethylsilane was added drop wise and the reaction was stirred for 12 h at -78 °C. Saturated $NaHCO_3$ was added to the reaction mixture and allowed to rt. The organic layer was separated and the aqueous layer

was extracted with CH_2Cl_2 (3x25 mL). The combined organic layers washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure afford the cyclopropane allylalcohol **214** in quantitative yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.0 Hz, 3H), 1.81-1.92 (m, 1H), 2.15 (dd, *J* = 6.2, 2.7 Hz, 1H), 2.31-2.51 (m, 4H), 3.70 (ddd, *J* = 7.3, 7.3, 5.4 Hz, 1H), 3.88 (s, 3H), 4.13 (q, *J* = 7.0 Hz, 2H), 4.72 (dd, *J* = 7.5, 2.8 Hz, 1H), 5.14-5.22 (m, 2H), 5.76-5.93 (m, 1H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 24.7, 31.3, 41.7, 53.8, 58.8, 61.3, 67.8, 118.8, 133.4, 157.2, 157.2, 170.6.

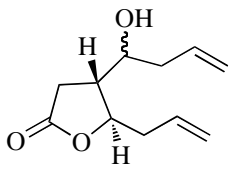
(2R,3S)-2-allyl-5-oxotetrahydrofuran-3-carbaldehyde (201)



16.4 g (61.19 mmol) of cyclopropane allylalcohol **214** was taken in 260 mL of methanol and to this 9.65 g (30.6 mmol) of $Ba(OH)_2$ in 310 mL of methanol was added drop wise at 0 °C . The reaction was stirred for 6 h and the solvent was removed under reduced pressure. The crude mixture was diluted with CH_2Cl_2 and water. The layers were separated after long time. The organic layer was taken and dried over anhydrous Na_2SO_4 and the crude product was purified by column chromatography to afford **201** in 50 % yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32-2.59 (m, 2H), 2.71 (dd, *J* = 18.2, 9.9 Hz, 1H), 2.89 (dd, *J* = 18.2, 7.5 Hz, 1H), 3.19 (m, 1H), 4.74 (dd *J* = 11.9, 6.2 Hz, 1H), 5.10- 5.27 (m, 2H), 5.75 (m, 1H), 9.69 (d, *J* = 1.2 Hz, 1H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.8, 39.2, 51.2, 78.0, 120.4, 130.9, 174.2, 197.4.

(4R,5R)-5-allyl-4-(1-hydroxybut-3-en-1-yl)dihydrofuran-2(3H)-one (223)

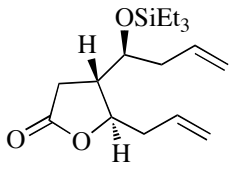


A solution of (+)-**201** (0.10 g, 0.649 mmol, 1 eq.) in CH_2Cl_2 (2 mL) was cooled down to -78 °C under N_2 atmosphere. $BF_3{\cdot}Et_2O$ (0.1 mL, 0.77 mmol) was added *via* syringe and stirred for 20 min. Trimethylallylsilane (0.11 g, 0.97 mmol) in CH_2Cl_2 (2 mL) was added subsequently *via* syringe drop wise for 5 min. The resulting brown solution was stirred for overnight at -78 °C, and then it was quenched with sat. $NaHCO_3$ (0.5 mL), allowed to warm up to room temperature. The layers were separated and the aqueous layer was again extracted with CH_2Cl_2 (5 x 2 mL). The combined organic layers were

washed with H_2O, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo* to yield **223** (0.104 g, 82%). The yellowish oil thus obtained (in 73 : 27 dr ratio) was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01-2.91 (m, 7H), 3.71-3.82 (m, 1H), 4.71 (dd, *J* = 11.9, 6.2 Hz, 1H), 5.12-5.41 (m, 4H), 5.72-6.02 (m, 2H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.75, 38.80, 40.09, 44.68, 68.59, 81.15, 119.04, 119.64, 132.21, 133.45, 176.42.

(4S,5R)-5-allyl-4-((S)-1-((triethylsilyl)oxy)but-3-en-1-yl)dihydrofuran-2(3H)-one (224)



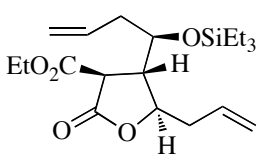
To a solution of **223** (100 mg, 0.510 mmol, 1 eq.) in CH_2Cl_2 (2 mL) was added DMAP (0.5 eq.), Et_3N (0.141 mL, 1.02 mmol, 2 eq.), followed by the drop wise addition of TESCl (0.13 mL, 0.765 mmol, 1.5 eq.) and stirred at room temperature for 36 h. The reaction mixture was quenched with H_2O and the layers were separated. The organic phase was washed with $NaHCO_3$ (1 mL), brine and dried over Na_2SO_4. The filtrate was concentrated in *vacuo* and purified by silica gel column chromatography (PE: EA= 9:1) to afford **224** (81 mg, and the another diastereomer 37 mg, overall 75%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.66 (t, *J* = 7.71, 6H), 0.91 (q, *J* = 7.71, 9H), 2.01-2.19 (m, 1H), 2.20-2.53 (m, 5H), 2.61-2.69 (m, 1H), 3.71-3.82 (m, 1H), 4.35 (dd, *J* = 11.9, 6.2 Hz, 1H), 5.12-5.21 (m, 4H), 5.72-5.92 (m, 2H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 5.11, 6.59, 28.22, 38.77, 41.00, 44.22, 70.23, 81.36, 118.19, 118.93, 132.33, 133.41, 176.61.

R_f(hexanes: ethylacetate 19:1, Vanillin) = 0.47.

HRMS (EI, 70 eV): Calcd for $C_{17}H_{30}O_3Si$ [M^+]: 310.5308, found: 310.5011.

(4S,5R)-ethyl 5-allyl-2-oxo-4-(1-((triethylsilyl)oxy)but-3-en-1-yl)tetrahydrofuran-3-carboxylate (230)



A solution of **224** (60 mg, 0.193 mmol, 1 eq.) in THF (2 mL) was cooled down to -78 °C under N_2 atmosphere. Freshly prepared LDA (1.7 eq.) was added *via* syringe and stirred for 30 min. Ethylchloroacetate (0.046 mL, 0.291 mmol) in THF (2 mL) was added subsequently *via* syringe drop wise for 5 min. The resulting solution was stirred for

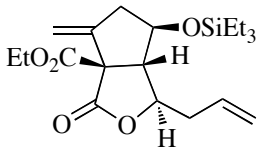
another hour at -78 °C, and then warm to rt and then it was quenched (after disappearance of starting material judged by TLC) with sat. NH_4Cl (0.5 mL). The layers were separated and the aqueous layer was again extracted with ethylacetate (5 x 2 mL). The combined organic layers were washed with H_2O, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo* to yield **230** (51 mg, 75%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.66 (t, *J* = 7.71, 6H), 0.91 (q, *J* = 7.71, 9H), 1.25 (t, *J* = 7.13 Hz, 3H), 2.01-2.19 (m, 1H), 2.20-2.31 (m, 1H), 2.39-2.48 (m, 2H), 2.80-2.90 (m, 1H), 3.71-3.82 (m, 1H), 3.84 (d, *J* = 2.4 Hz, 1H), 4.17 (q, *J* = 7.13 Hz, 2H), 4.35 (m, 1H), 4.92-5.18 (m, 4H), 5.52-5.82 (m, 2H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 5.12, 6.82, 14.04, 38.83, 40.67, 47.02, 48.21, 62.11, 70.58, 80.66, 118.76, 119.20, 132.07, 132.86, 168.56, 171.68.

R_f(hexanes: ethylacetate 9:1, Vanillin) = 0.39.

HRMS (EI, 70 eV): Calcd for $C_{20}H_{34}O_5Si$ [M^+]: 382.2176, found: 382.2123.

(1R,6aS)-ethyl 1-allyl-4-methylene-3-oxo-6-((triethylsilyl)oxy)hexahydro-1H-cyclopenta[c]furan-3a-carboxylate (228a)



To a suspension of $Mn(OAc)_3$ (58 mg, 0.219 mmol, 2 eq.) and $Cu(OAc)_2$ (22 mg, 0.109 mmol, 1eq.) in CH_3COOH (1 mL), compound **230** (34 mg, 0.109 mmol) in 1 mL of CH_3COOH was added and refluxed at 94 °C for 5h. After cooled to rt, 2 mL of water and sat. $NaHSO_3$ solution (0.5 mL) were added to it. Then the solution was extracted with CH_2Cl_2 (10x3 mL). The combined organic layers were washed with $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo* and then passed through silica gel to afford **228a** (29 mg, 70%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.66 (t, *J* = 7.71, 6H), 0.91 (q, *J* = 7.71, 9H), 1.25 (t, *J* = 7.13 Hz, 3H), 2.41-2.59 (m, 3H), 2.65-2.75 (m, 1H), 3.12-3.21 (m, 1H), 4.27 (q, *J* = 7.13 Hz, 2H), 4.35-4.41 (m, 1H), 4.72-4.78 (m, 1H), 5.12-5.22 (m, 2H), 5.27 (bs, 1H), 5.61 (bs, 1H), 5.81-5.91 (m, 1H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.74, 6.74, 39.86, 41.79, 54.97, 62.39, 71.81, 114.19, 118.91, 132.48, 142.77, 168.56, 171.68.

R_f(hexanes: ethylacetate 9:1, Vanillin) = 0.34.

HRMS (EI, 70 eV): Calcd for $C_{20}H_{32}O_5Si$ [M^+]: 380.5506, found: 380.5496.

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12. Appendix

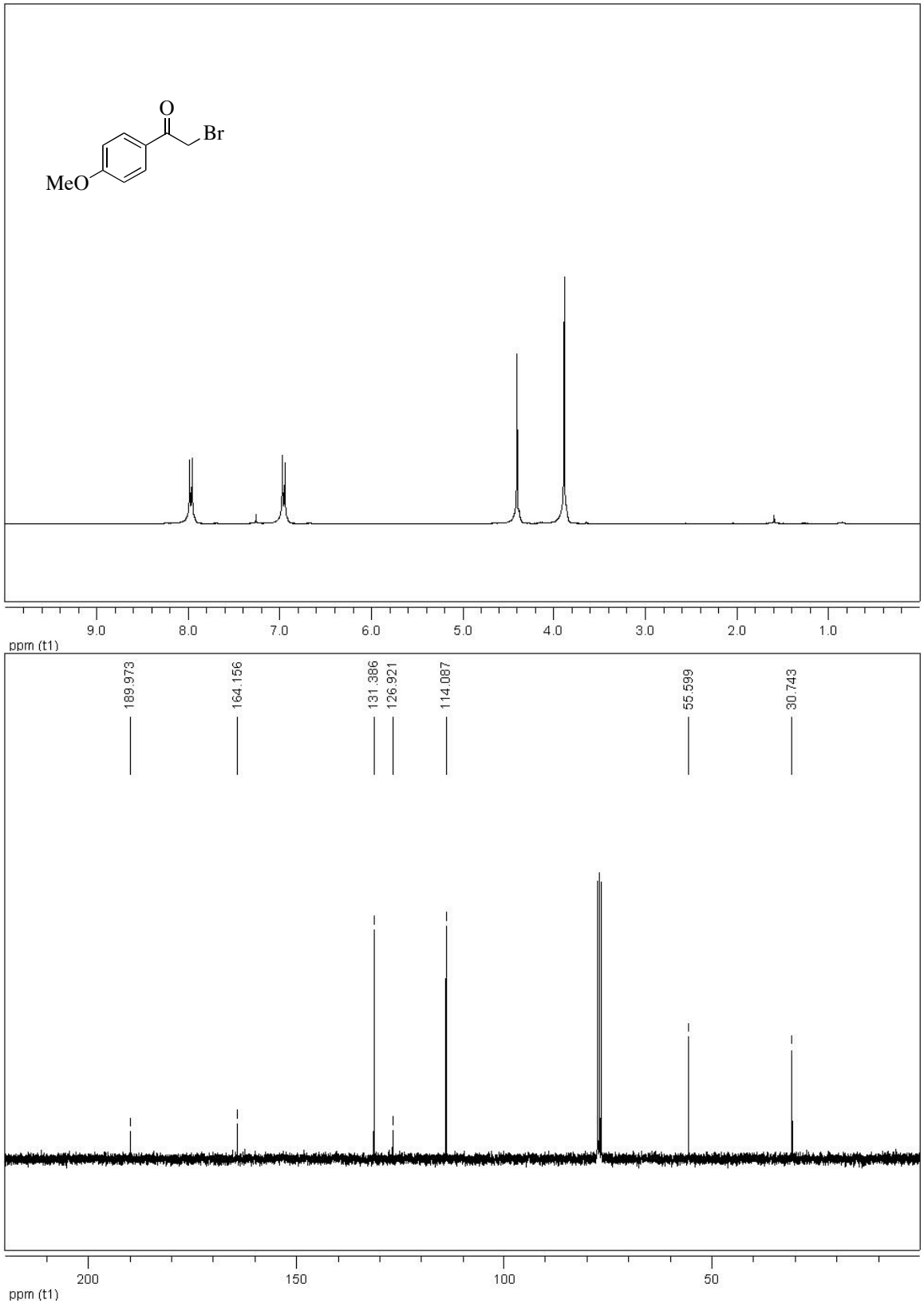
NMR-spectra

^{1}H-NMR spectra – upper image

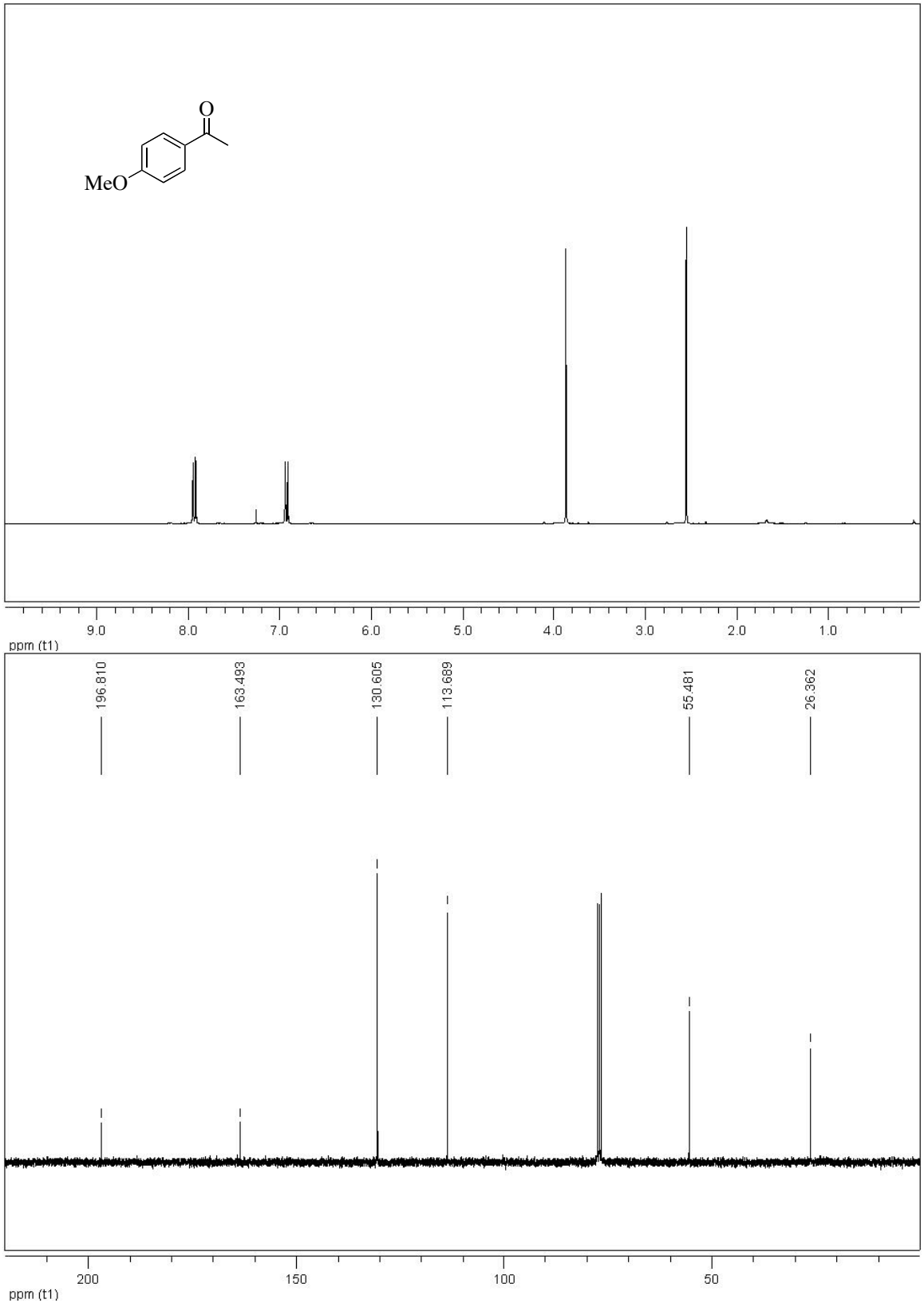
^{13}C- NMR spectra – lower image

Solvents, if not stated otherwise: $CDCl_3$

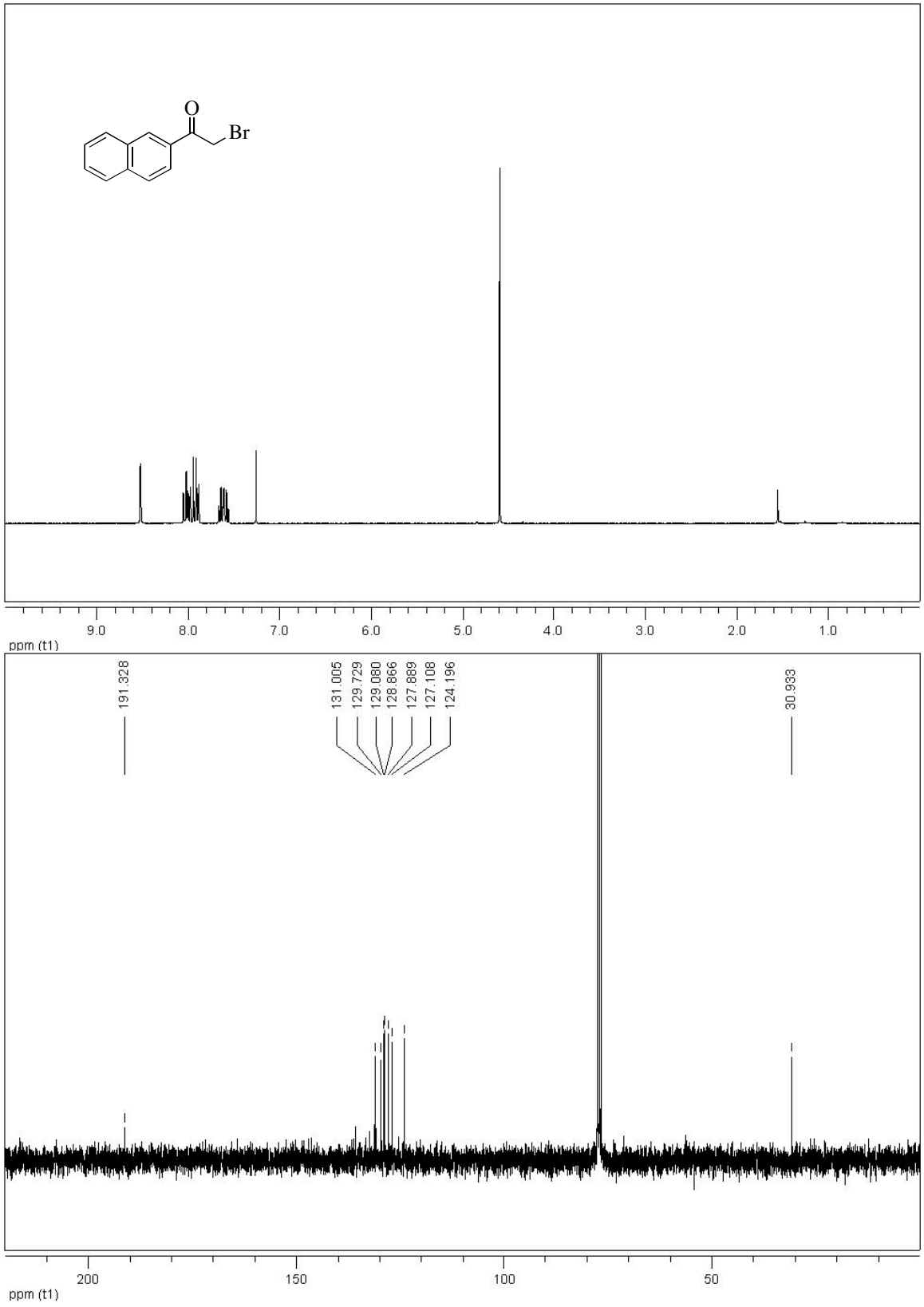
2-Bromo-1-(4-methoxyphenyl)ethanone (142a)



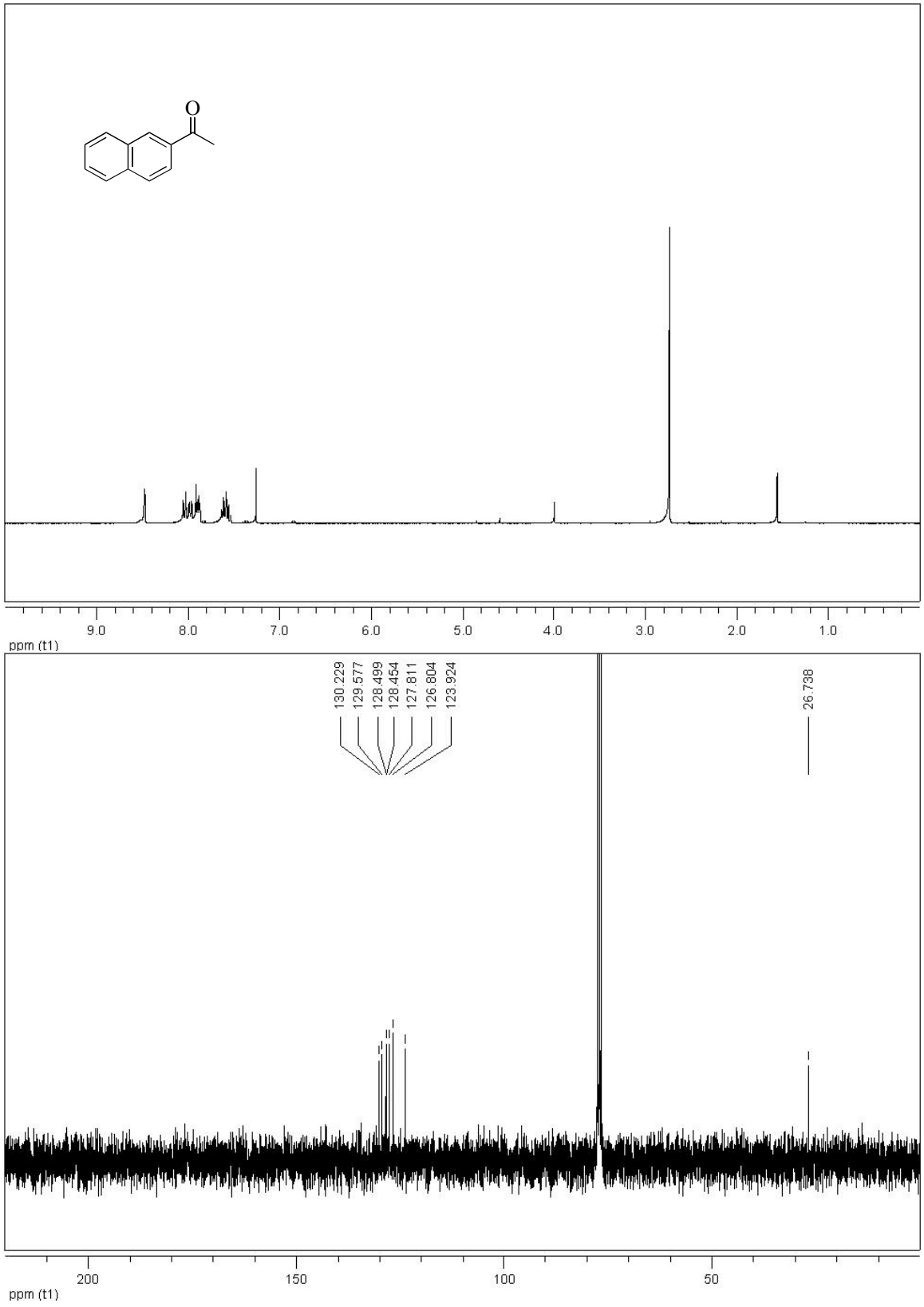
1-(4-methoxyphenyl) ethanone (143a)



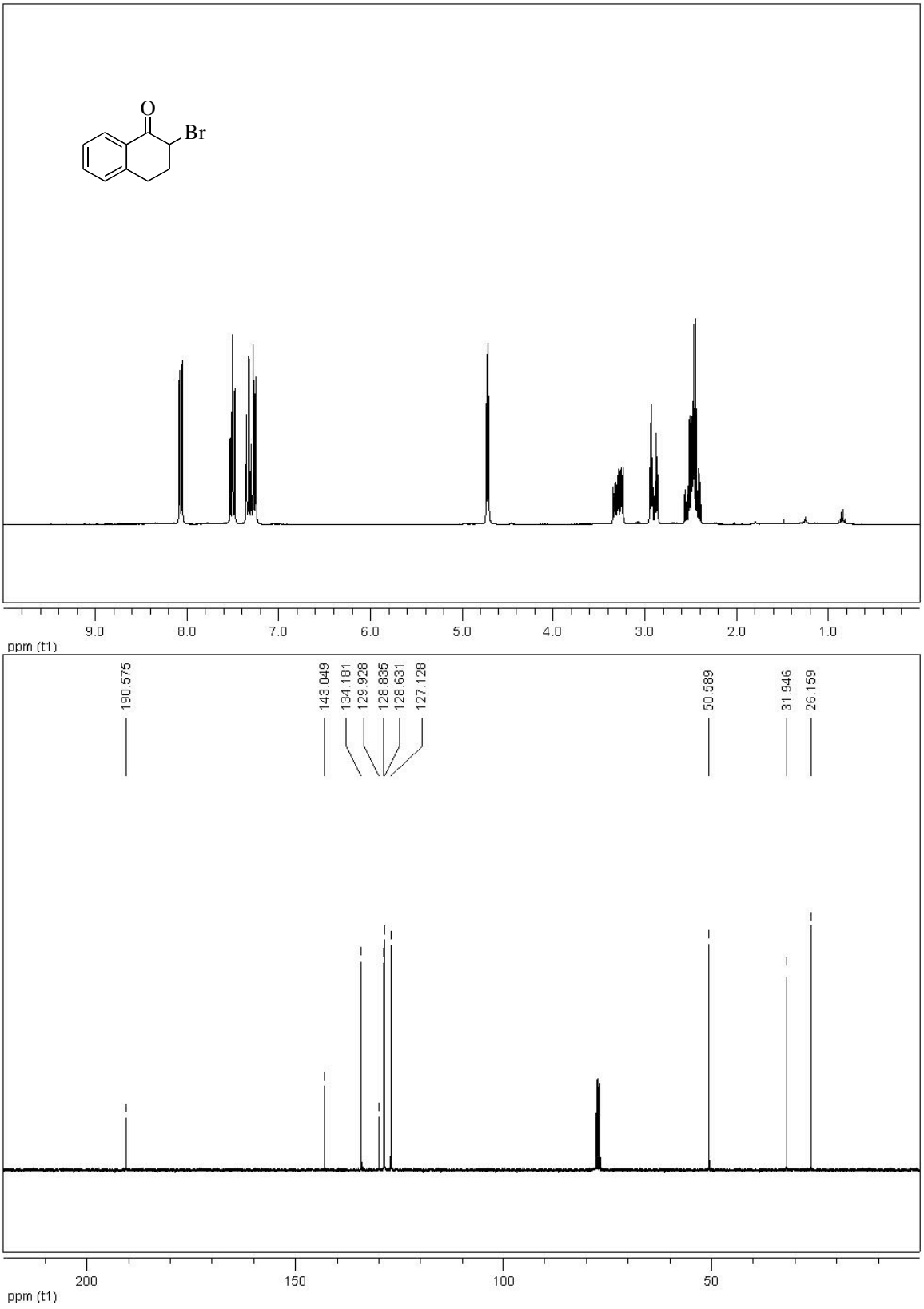
2-Bromo-1-(naphthalen-2-yl)ethanone (142e)



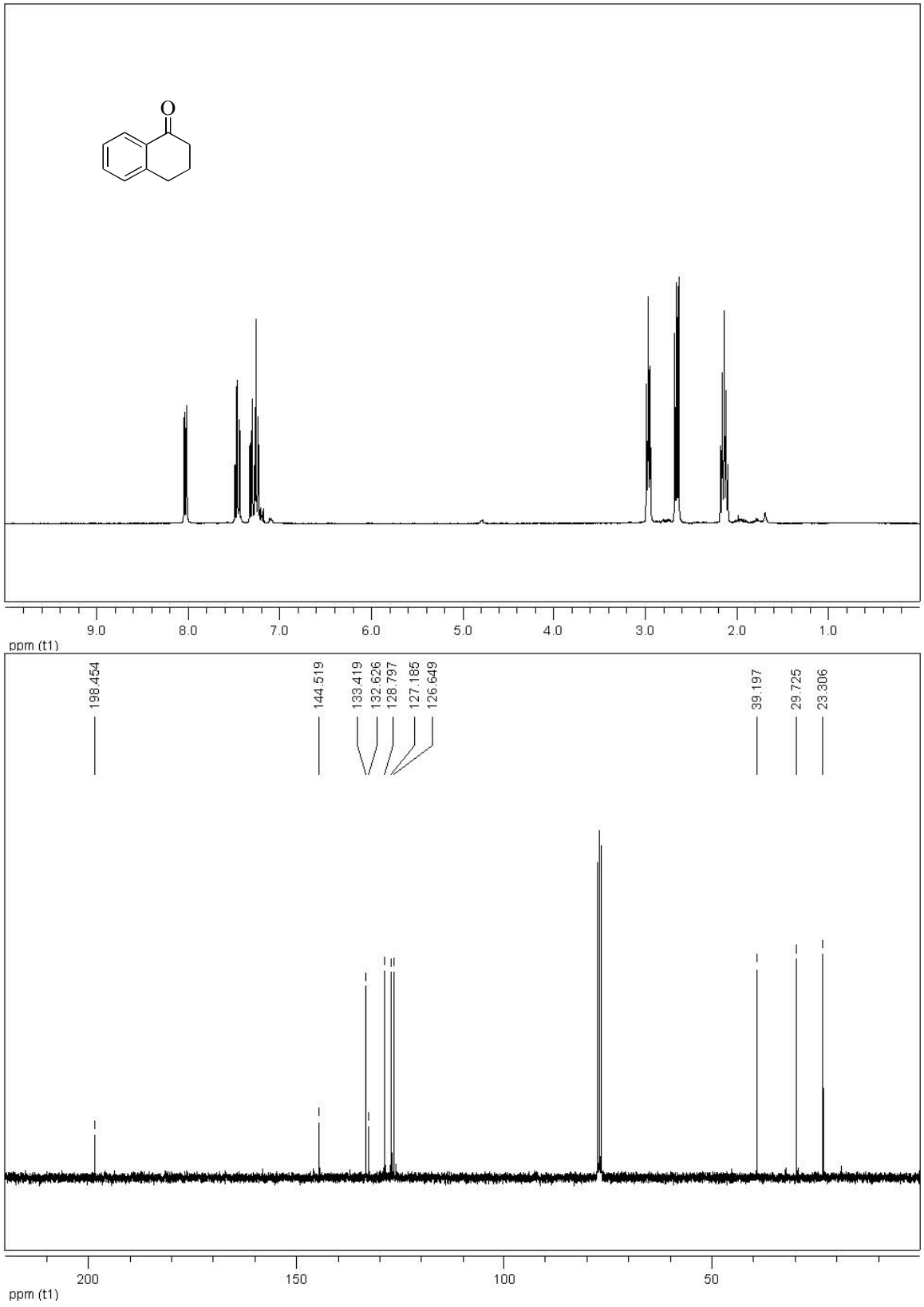
1-(naphthalen-2-yl)ethanone (143e)



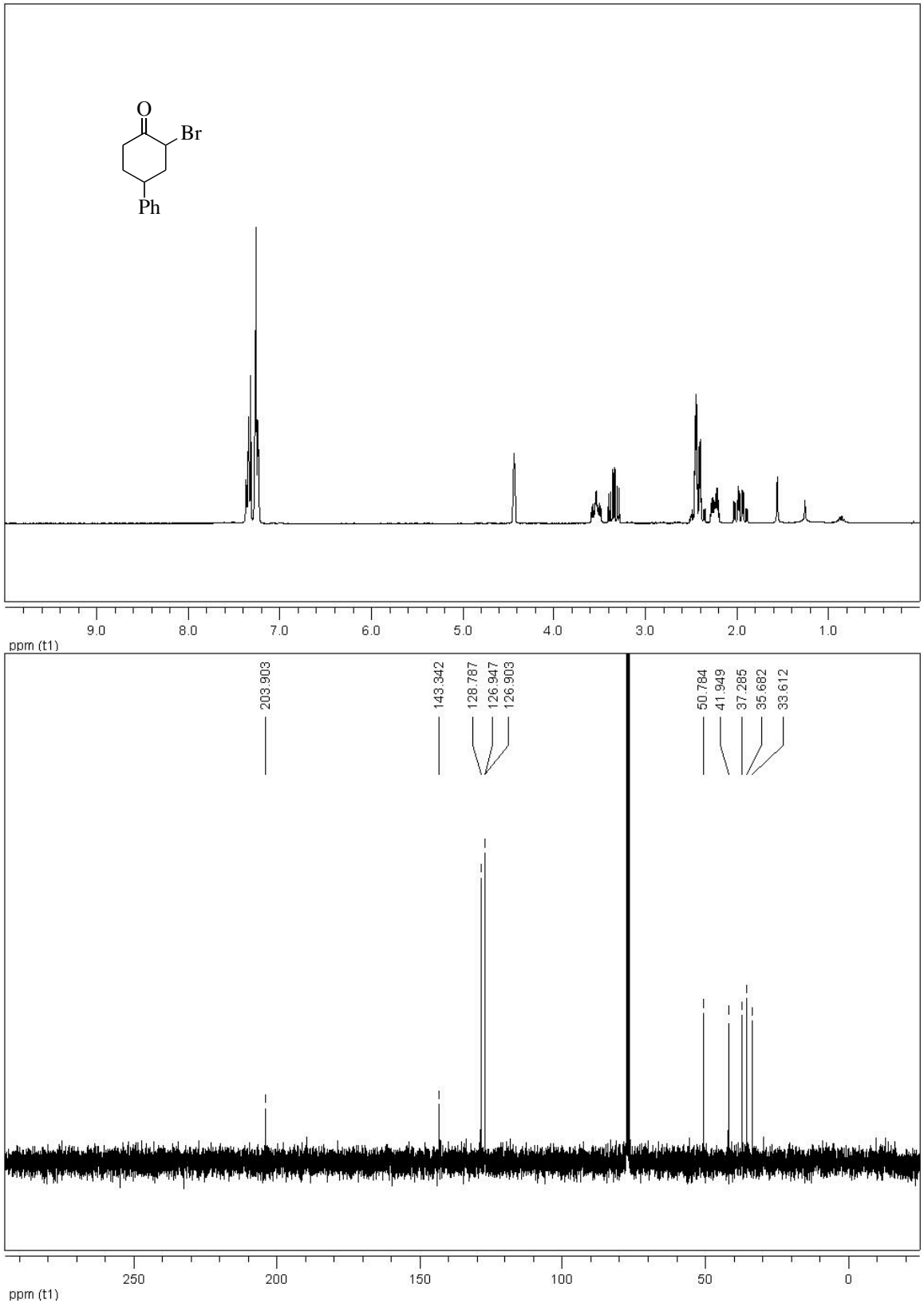
2-Bromo-3,4-dihydronaphthalen-1(2H)-one (142g)



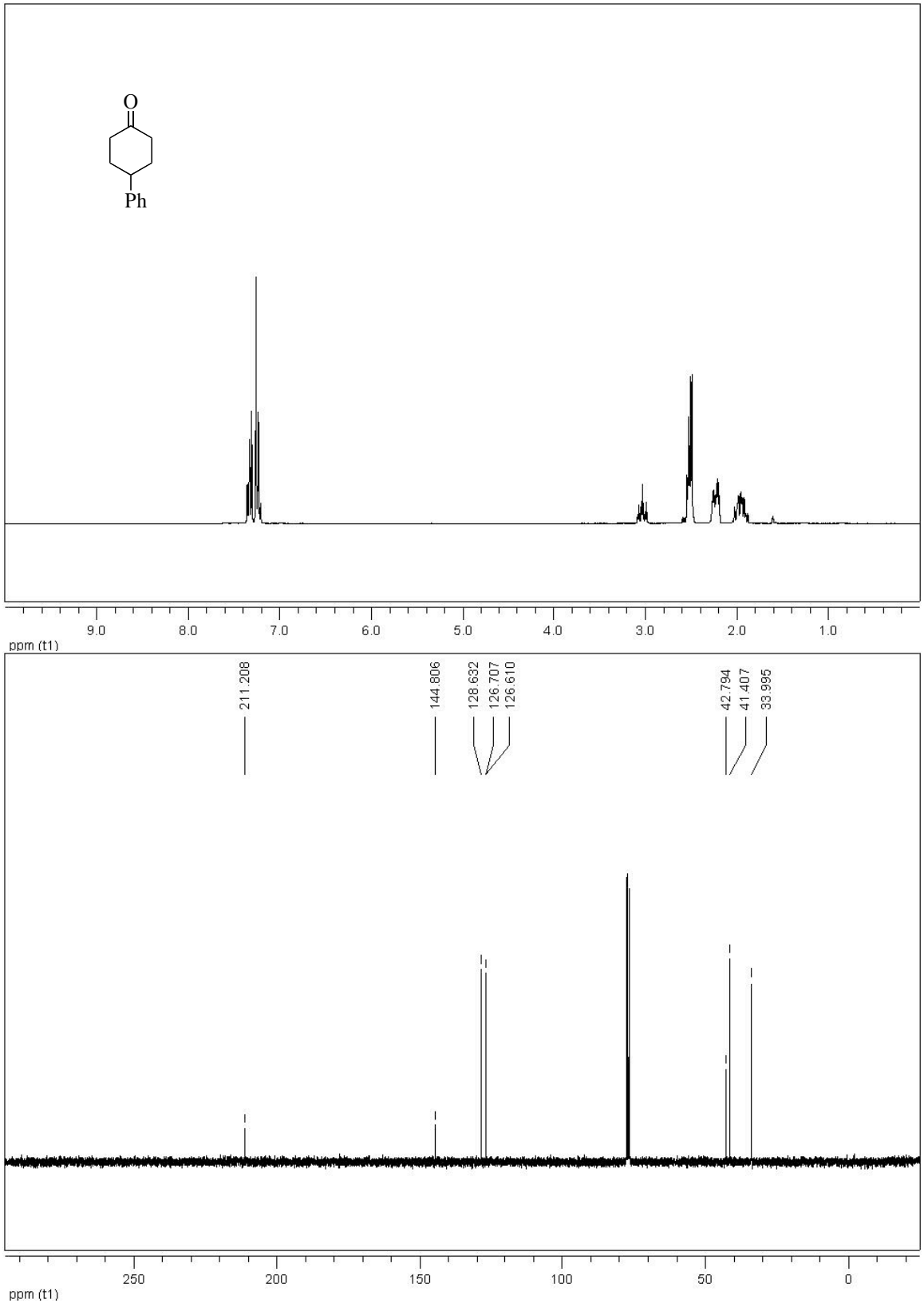
3,4-Dihydronaphthalen-1(2H)-one (143g)



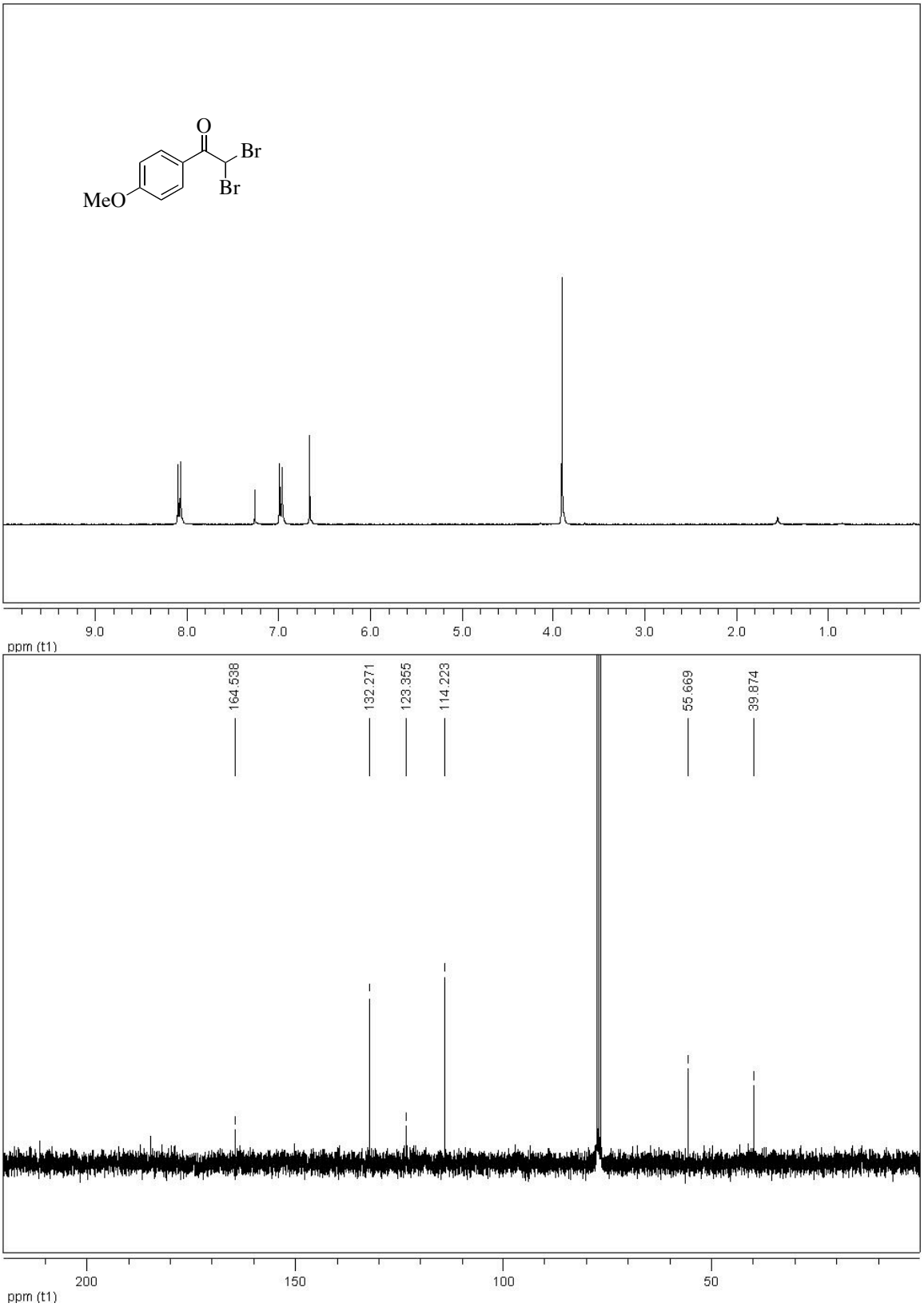
2-Bromo, 4-phenylcyclohexanone (142j)



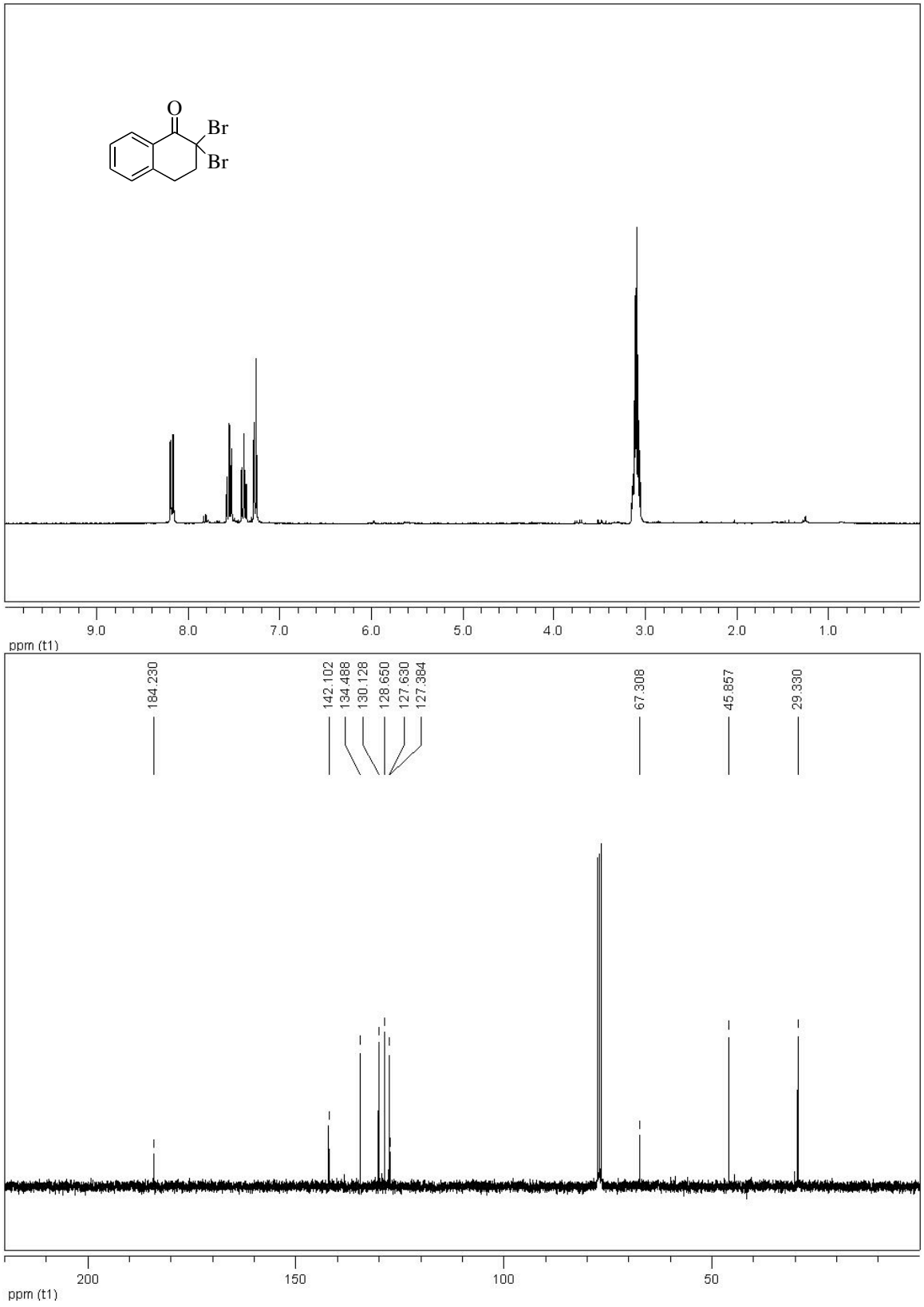
4-Phenylcyclohexanone (143j)



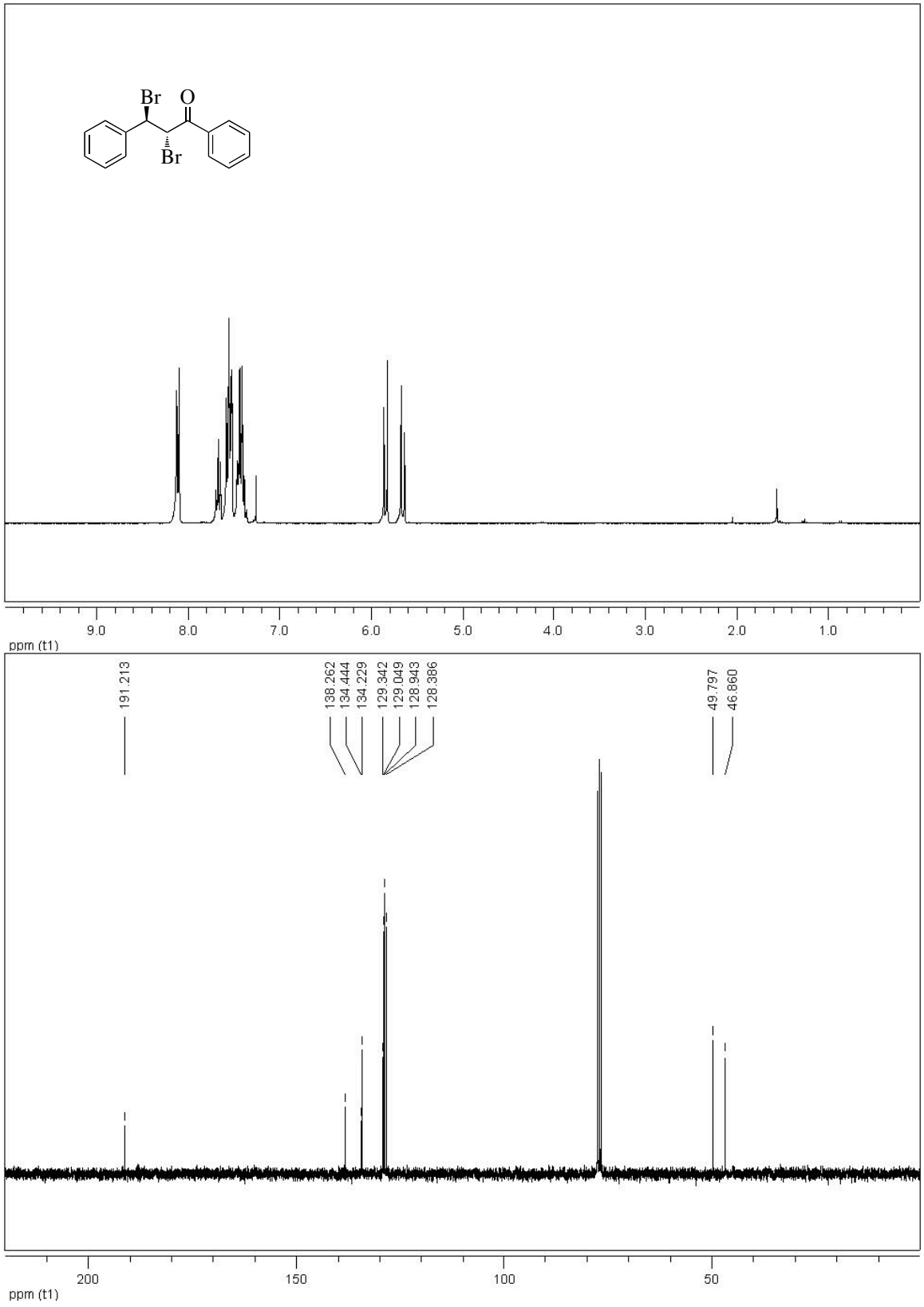
2,2-Dibromo-1-(4-methoxyphenyl)ethanone (144b)



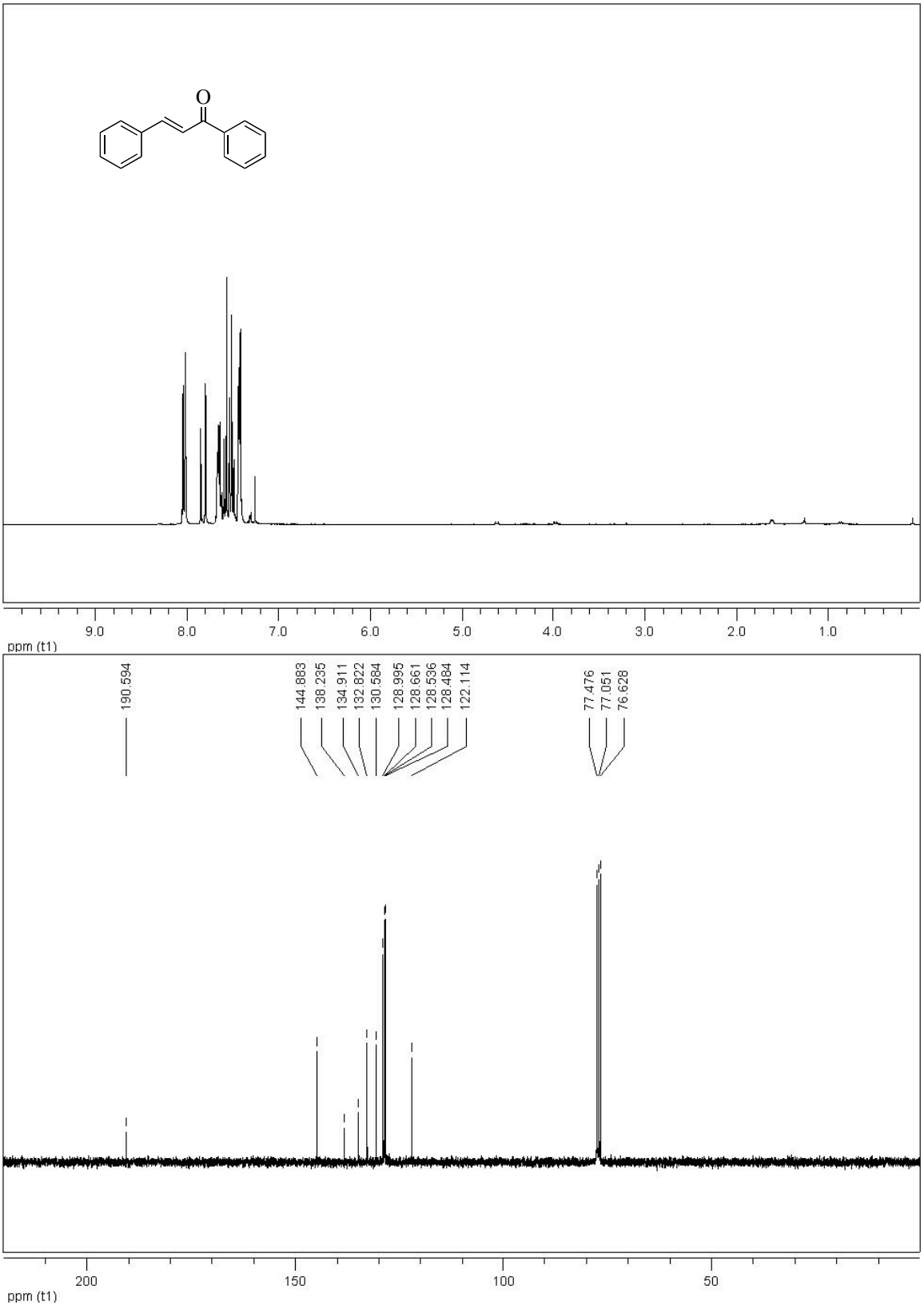
2,2-Dibromo-3,4-dihydronaphthalen-1(2H)-one (144c)



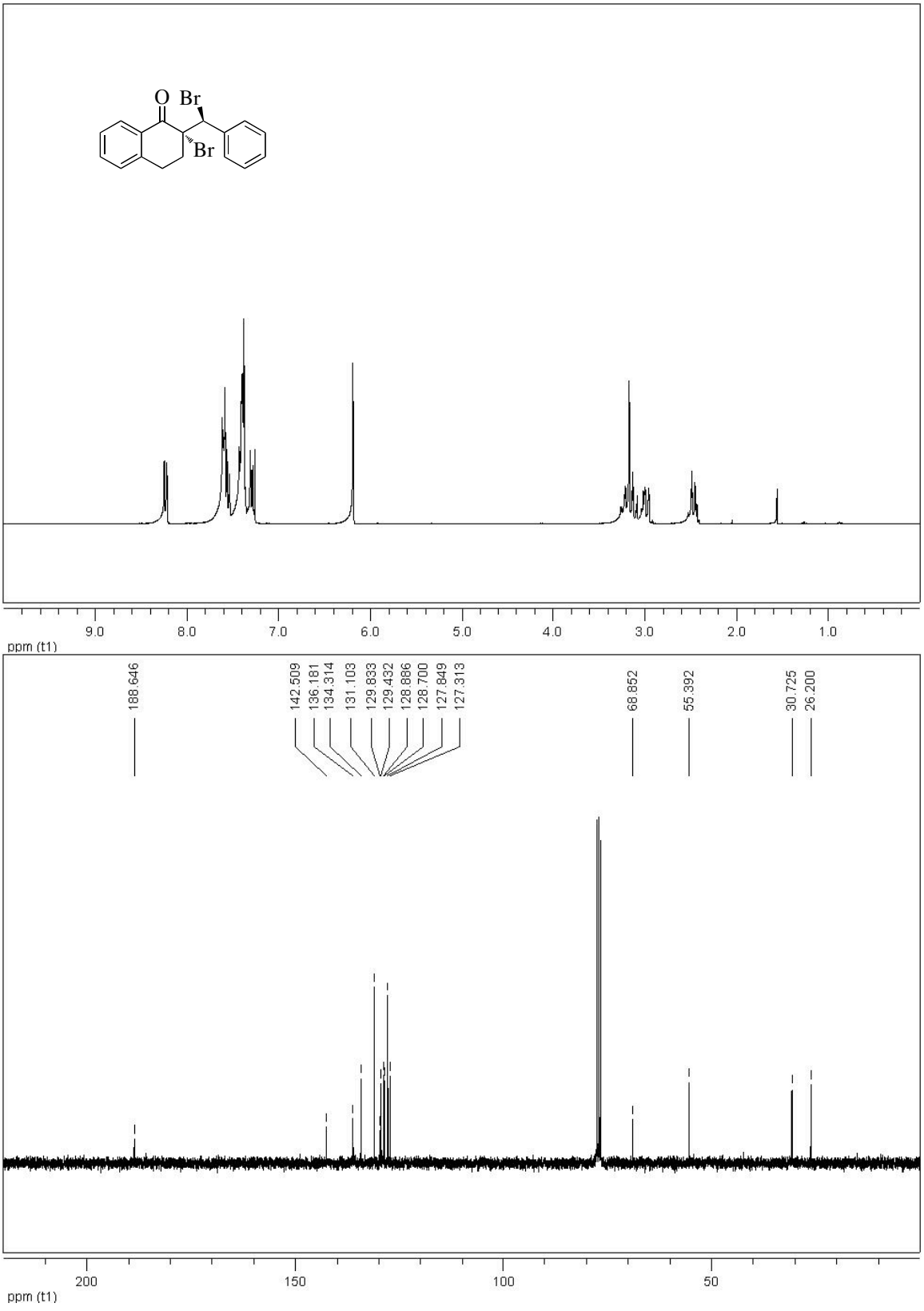
(*2S, 3R*)-2, 3-dibromo-1,3-diphenylpropan-1-one (147a)



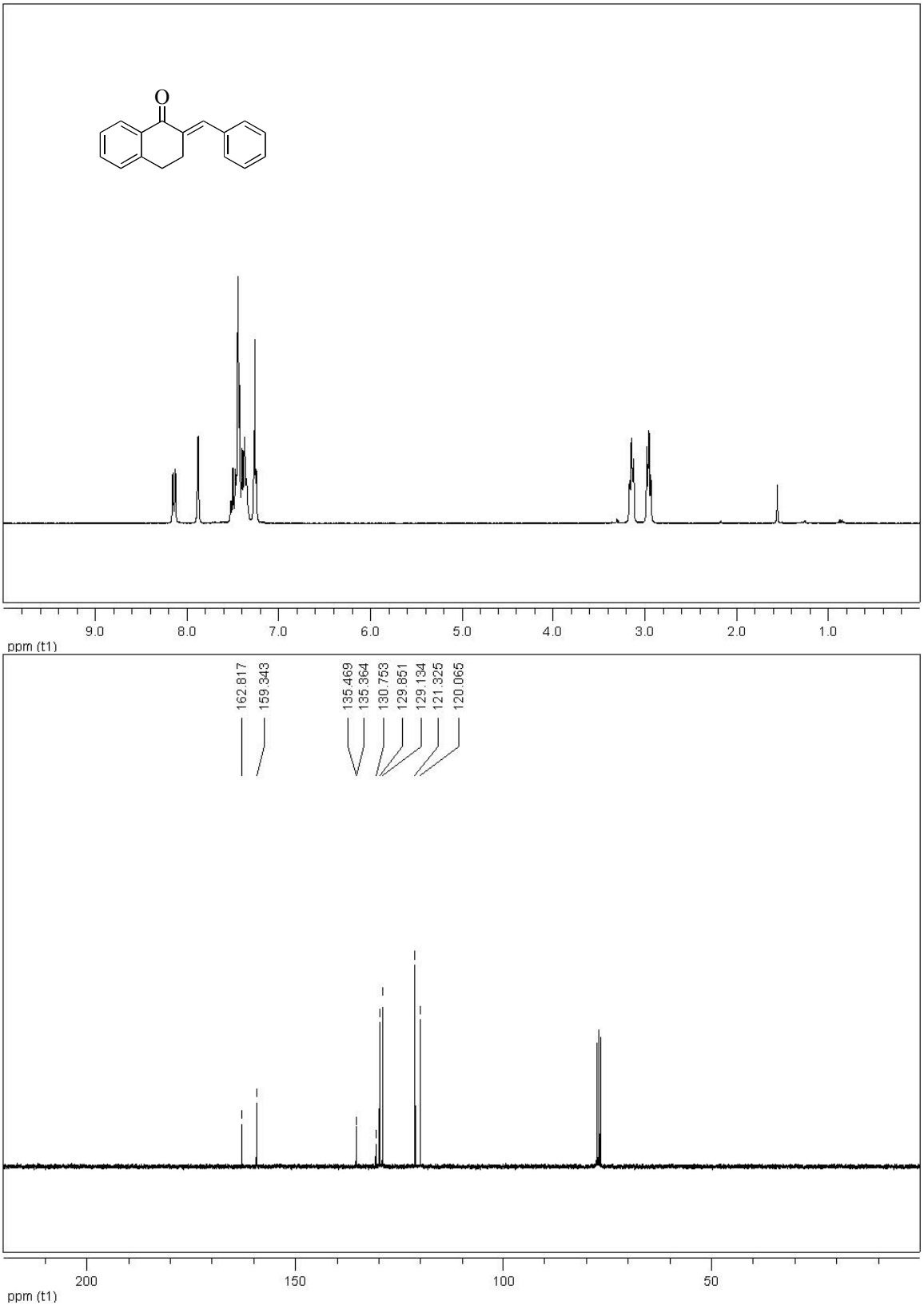
(*E*)-1,3-diphenylprop-2-en-1-one (148a)



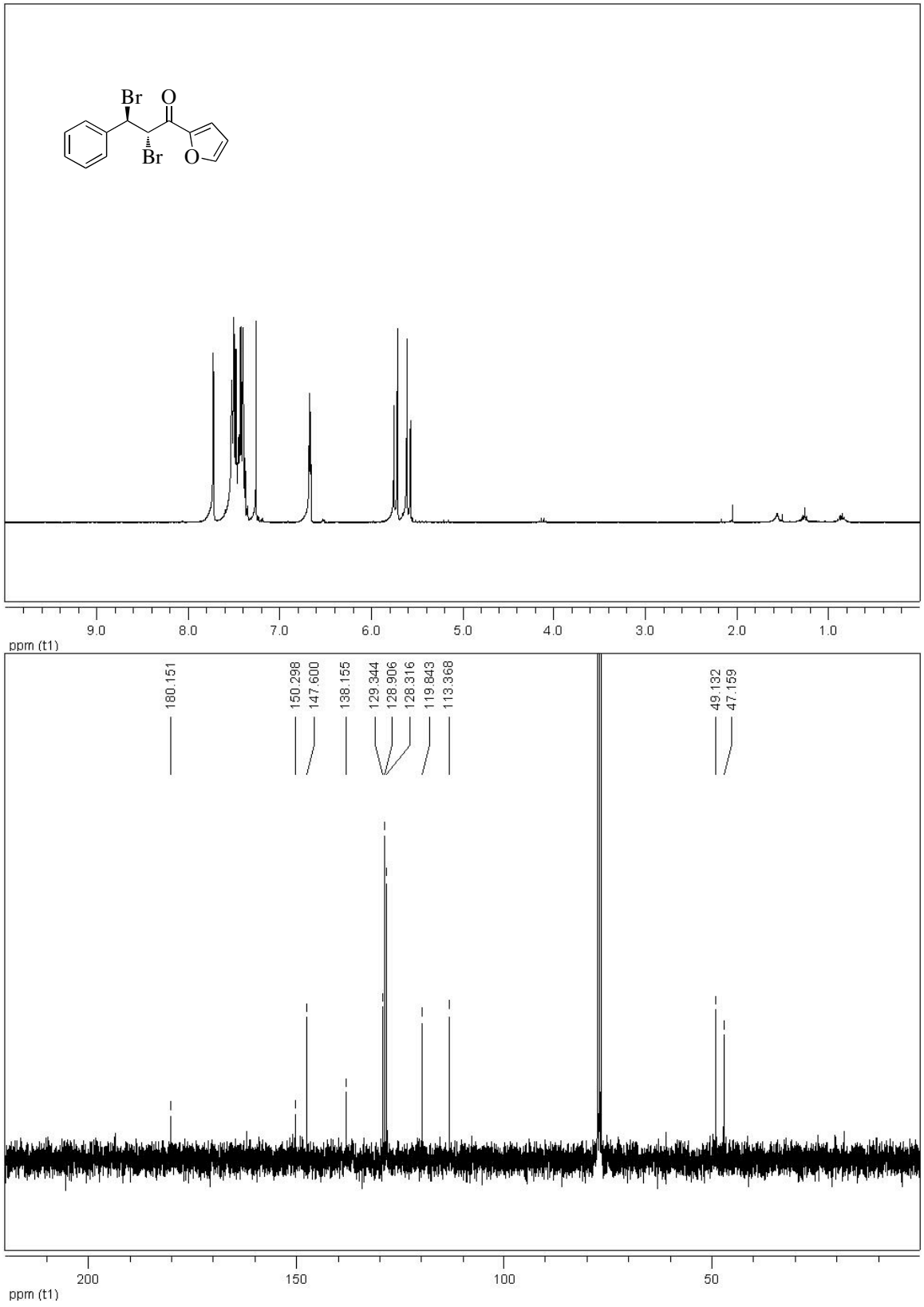
(*R*)-2-bromo-2-((*S*)-bromo(phenyl)methyl)-3,4-dihydronaphthalen-1(2H)-one (147e)



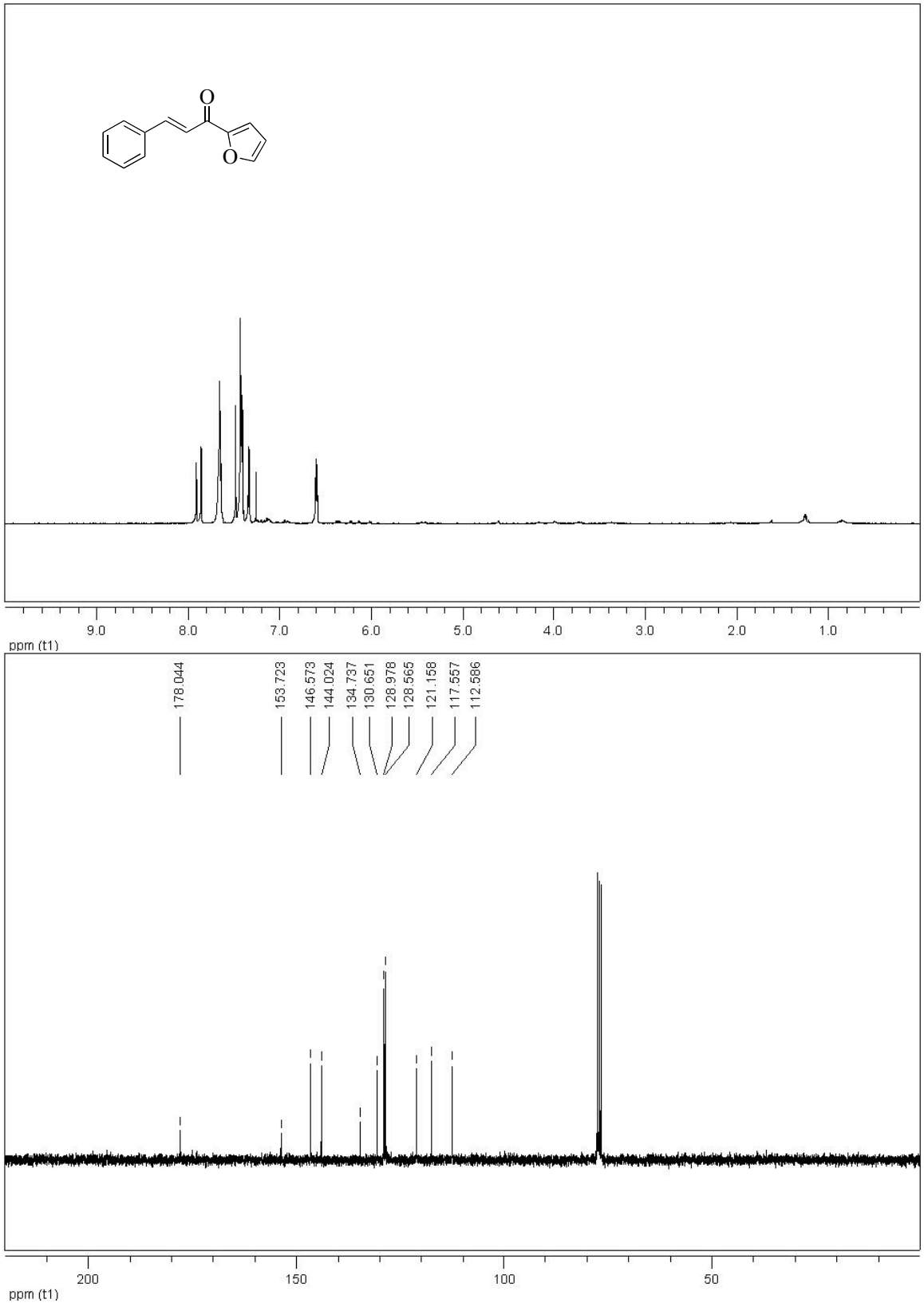
(*E*)-2-benzylidene-3,4-dihydronaphthalen-1(2H)-one (148e)



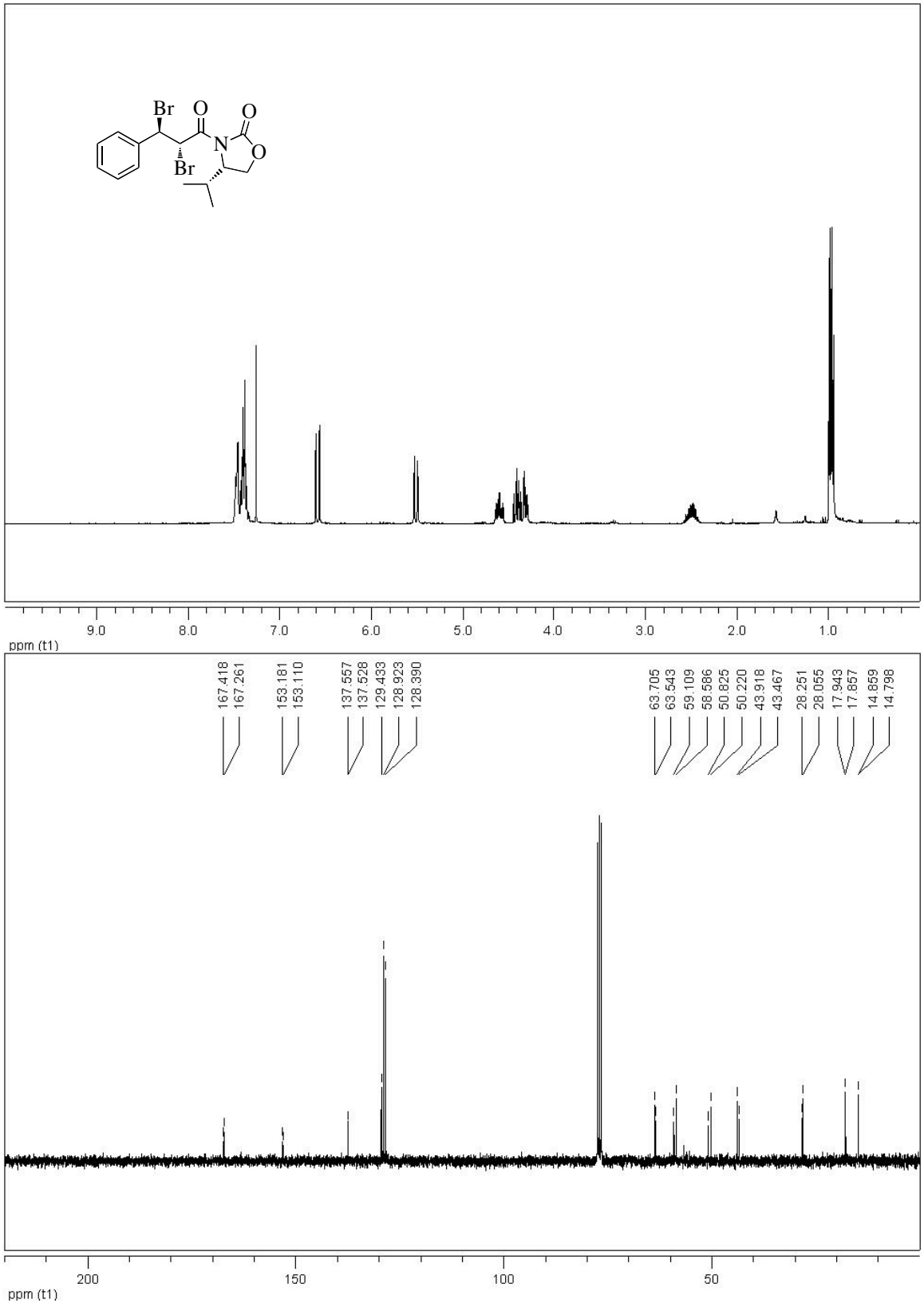
(*2S,3R*)-2,3-dibromo-1-(furan-2-yl)-3-phenylpropan-1-one (147f)



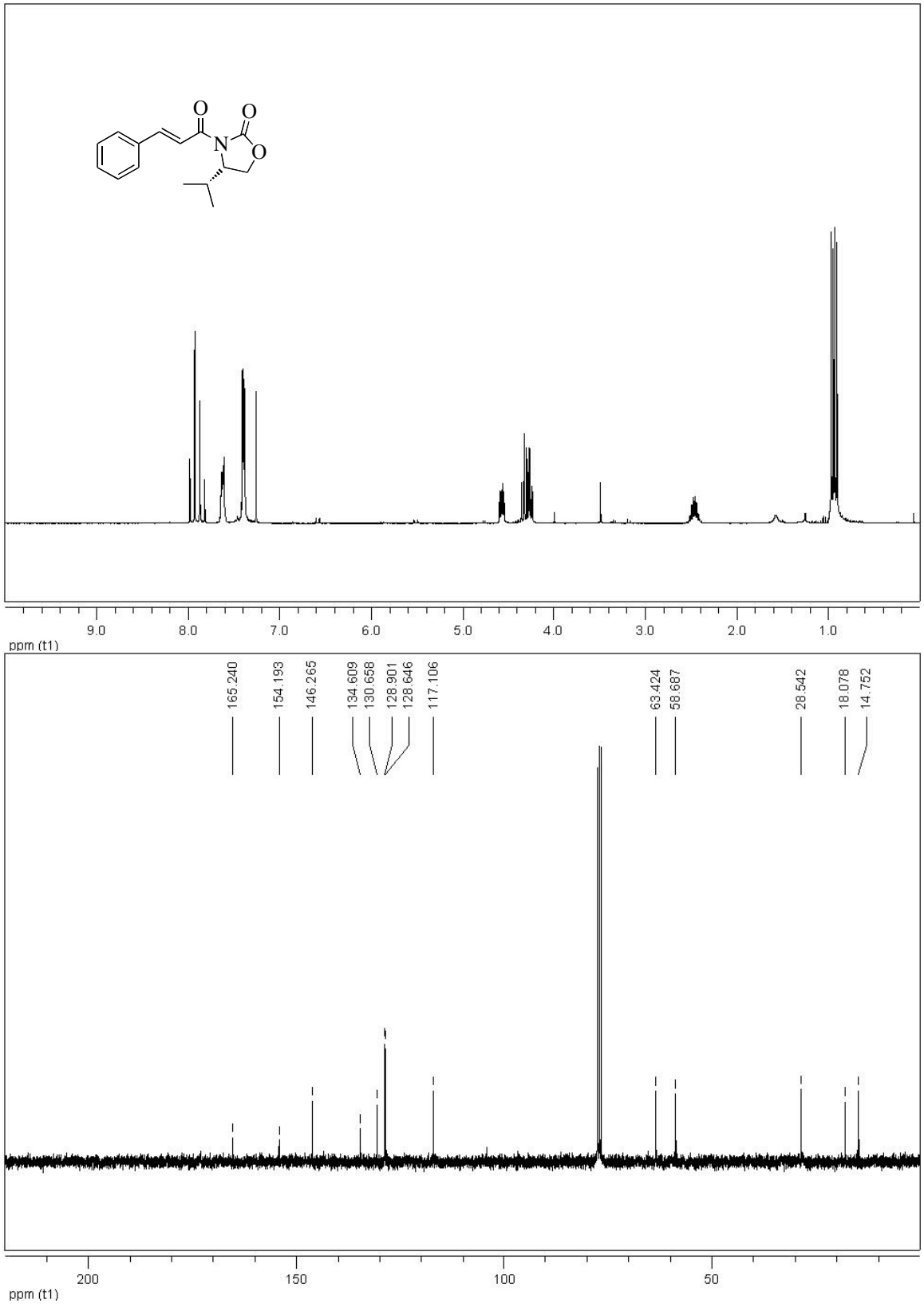
(*E*)-1-(furan-2-yl)-3-phenylprop-2-en-1-one (148f)



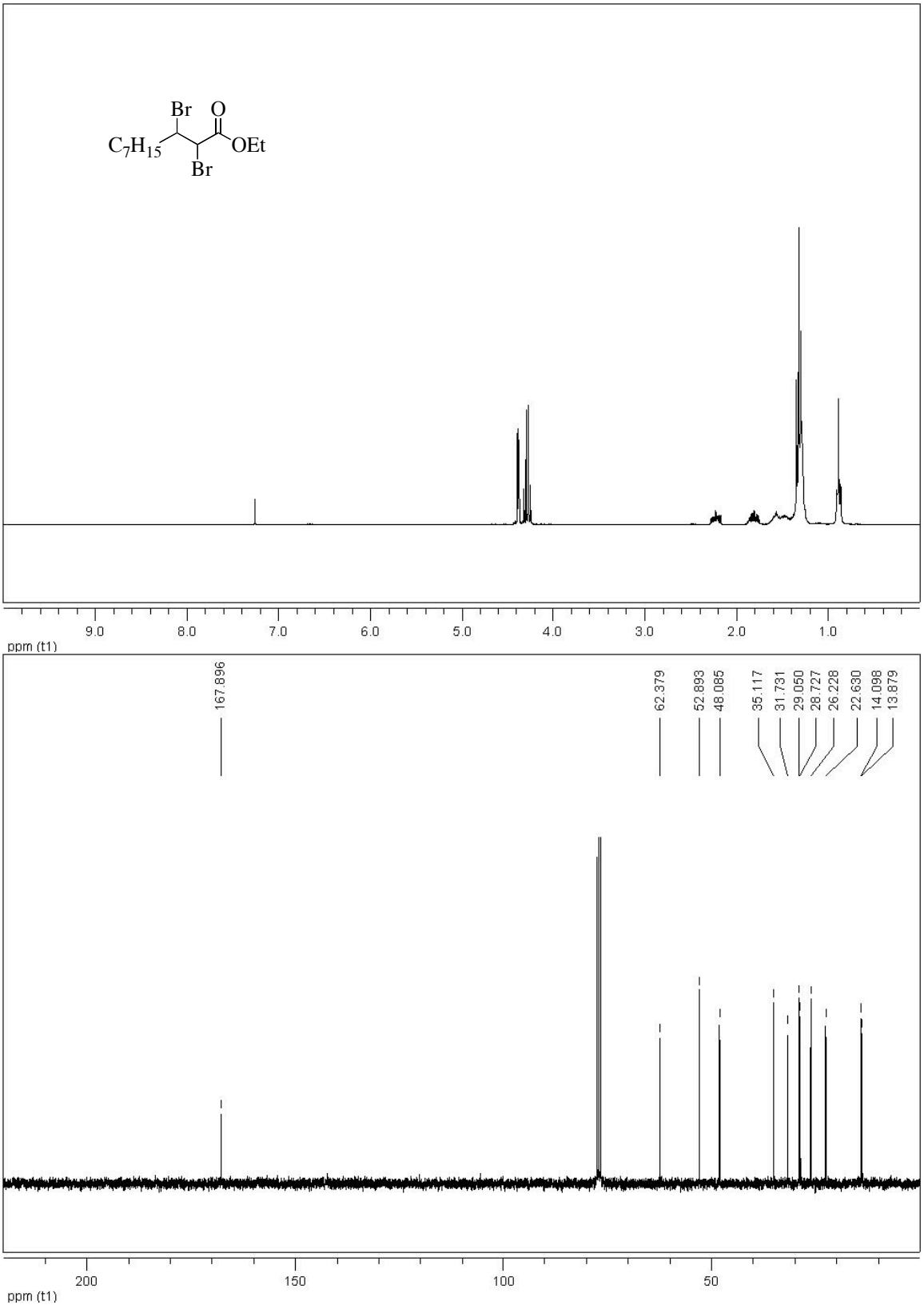
(*S*)-3-((*2S, 3R*)-2,3-dibromo-3-phenylpropanoyl)-4-isopropyloxazolidin-2-one (147g)



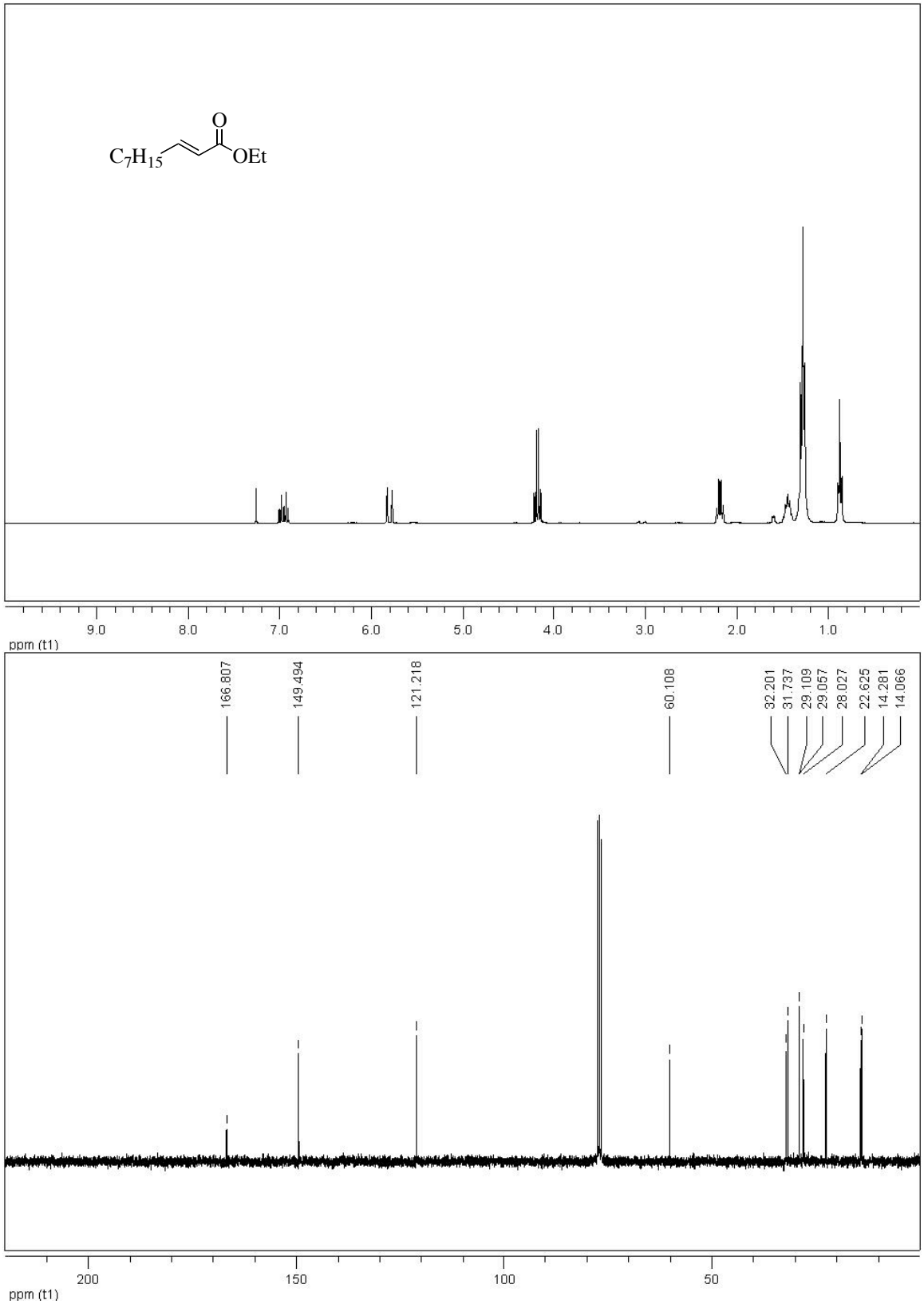
(*S*)-3-cinnamoyl-4-isopropyloxazolidin-2-one (148g)



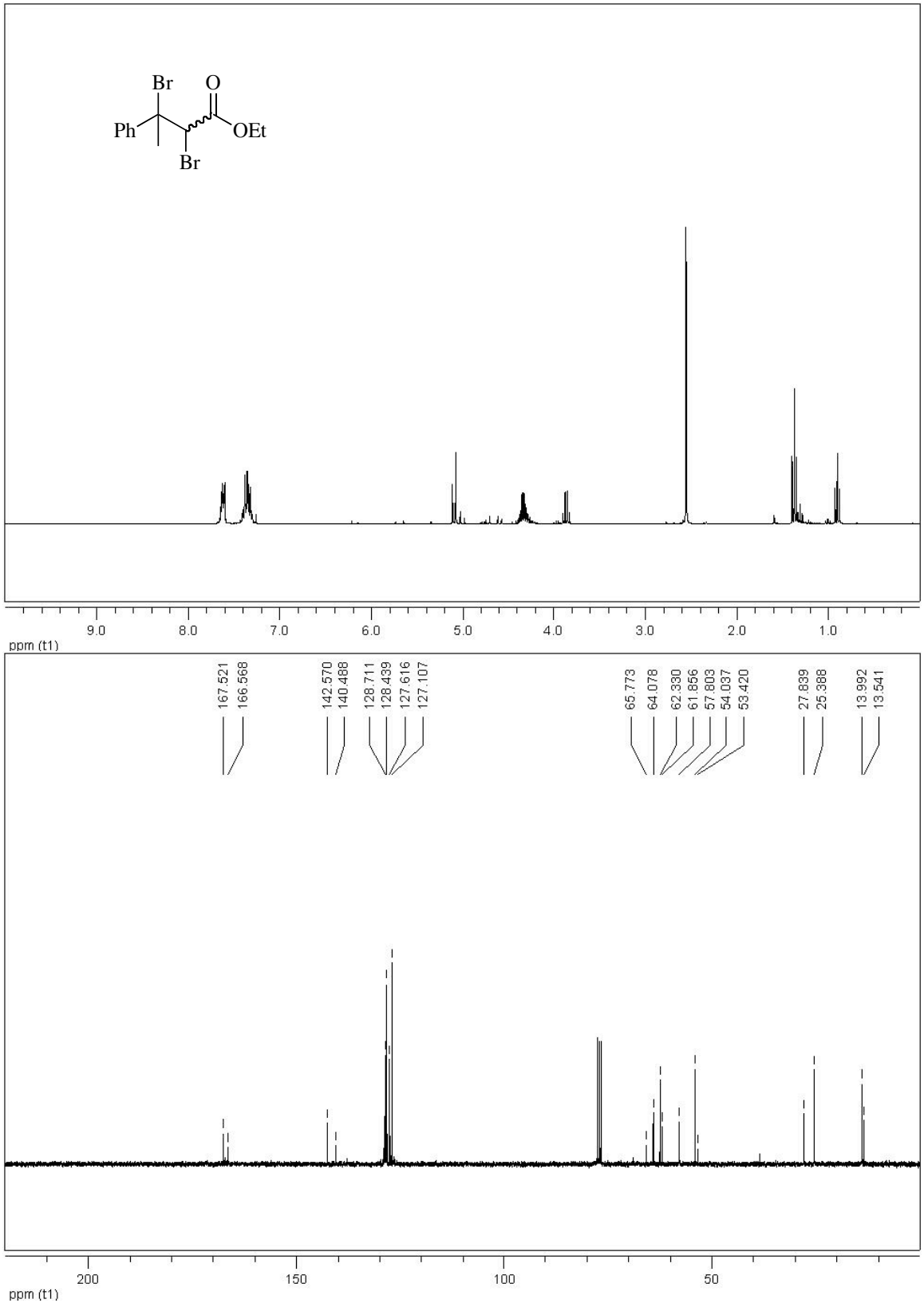
Ethyl 2,3-dibromodecanoate (147i)



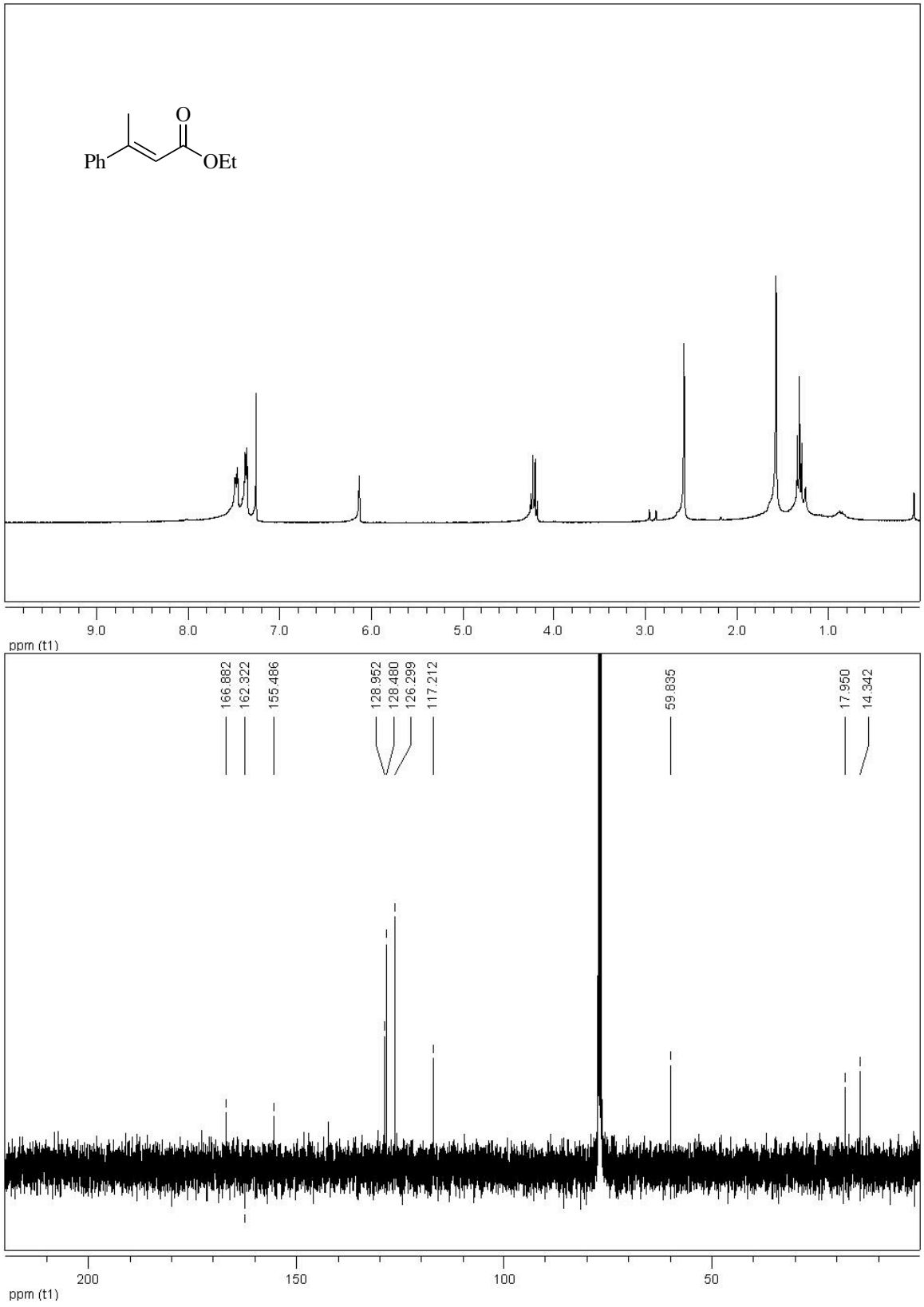
(*E*)-ethyl dec-2-enoate (148i)



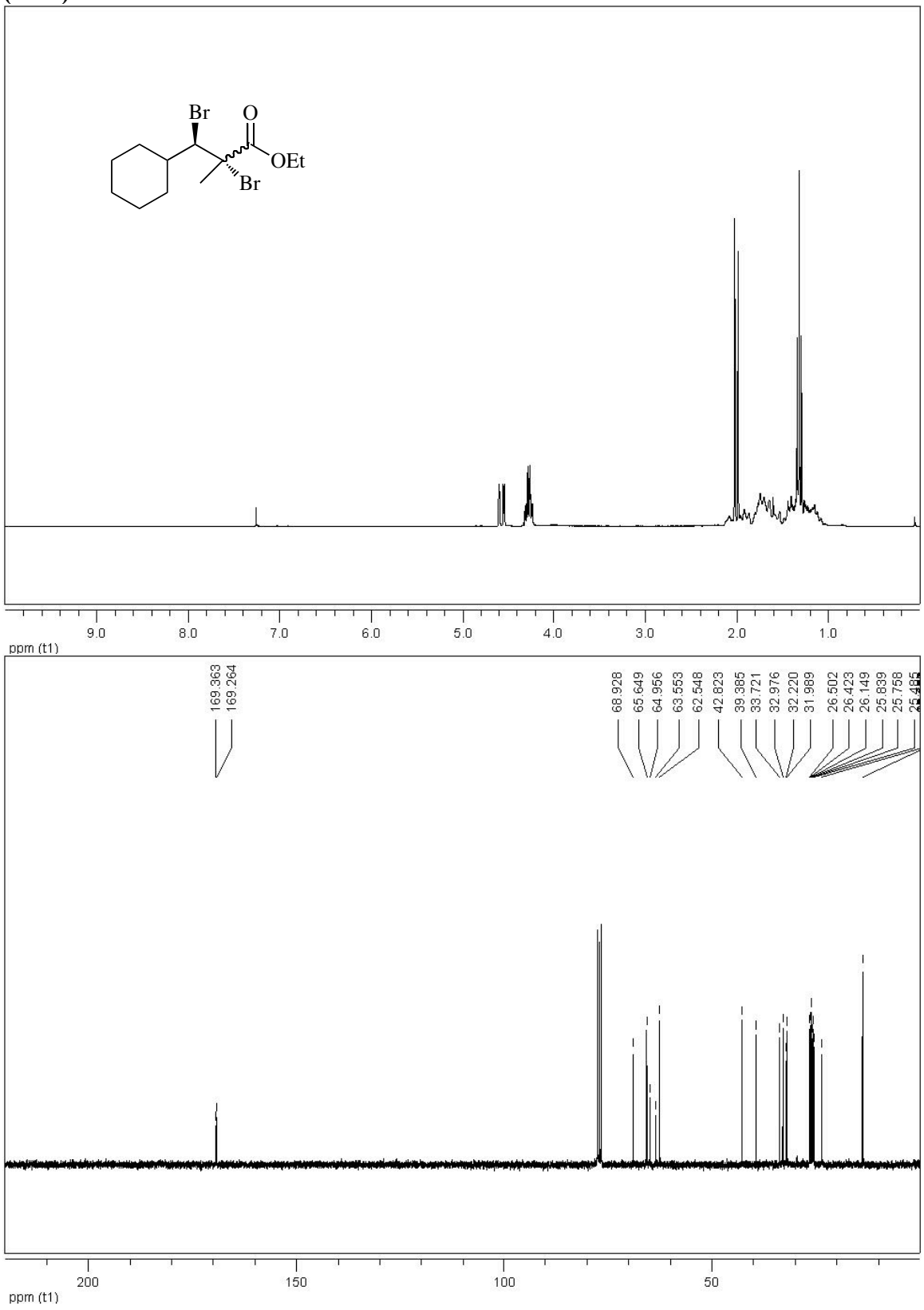
Ethyl 2,3-dibromo-3-phenylbutanoate (*erythro*:*threo* = 67:33) (150a)



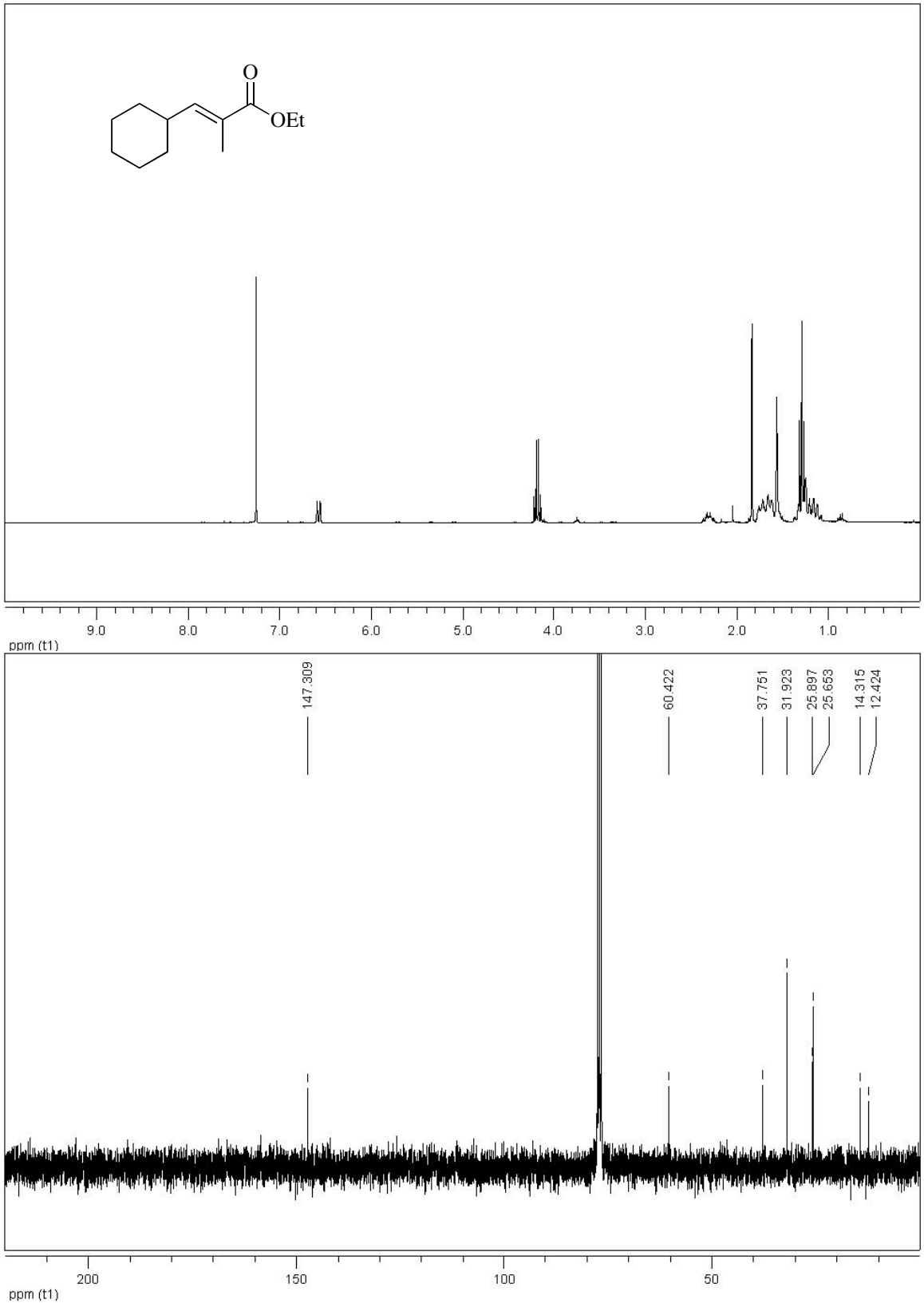
(*E*)-ethyl 3-phenylbut-2-enoate (151a)



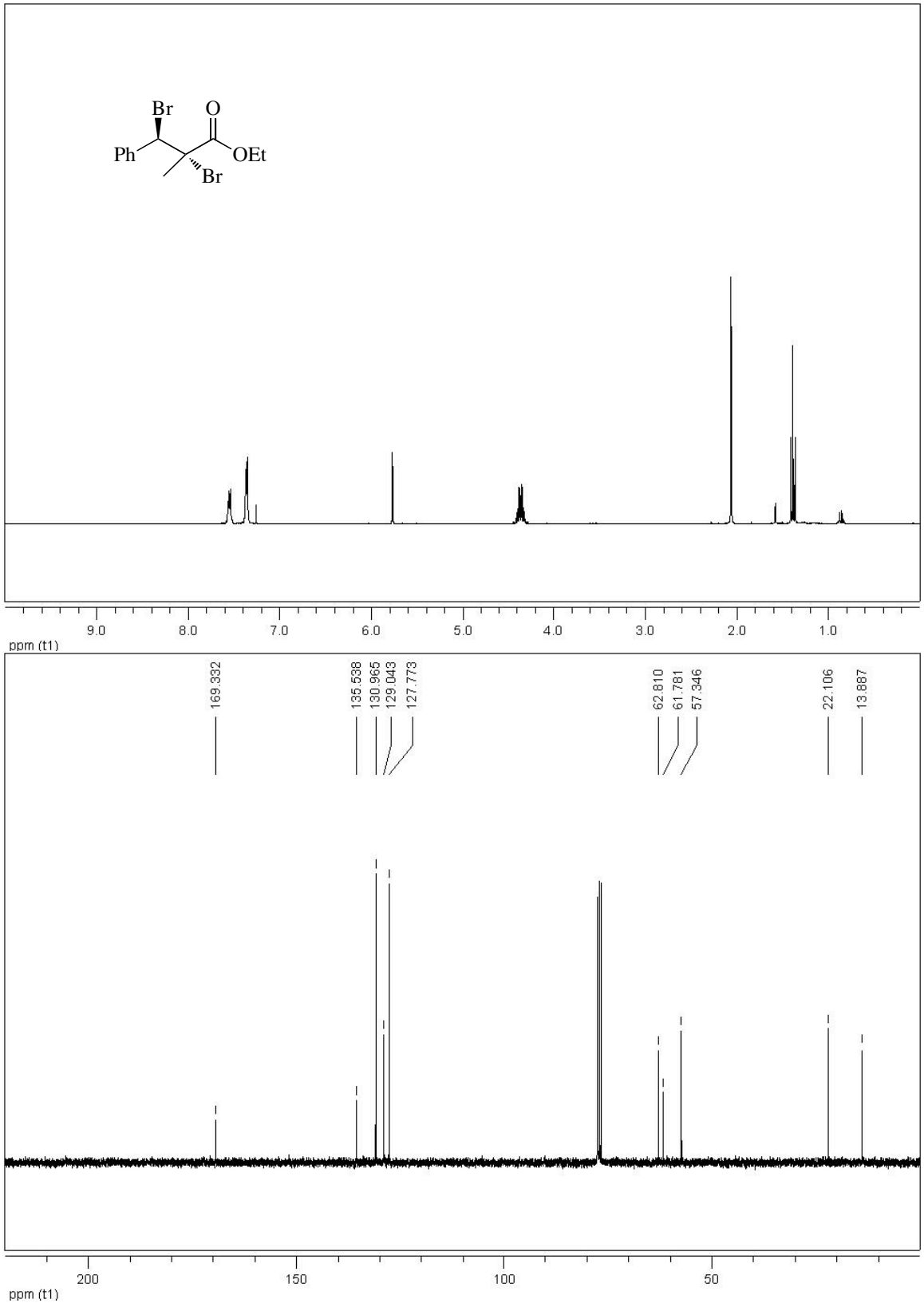
***(2S,3R*)-ethyl 2,3-dibromo-3-cyclohexyl-2-methylpropanoate (*erythro*:*threo*= 52:48) (150c)**



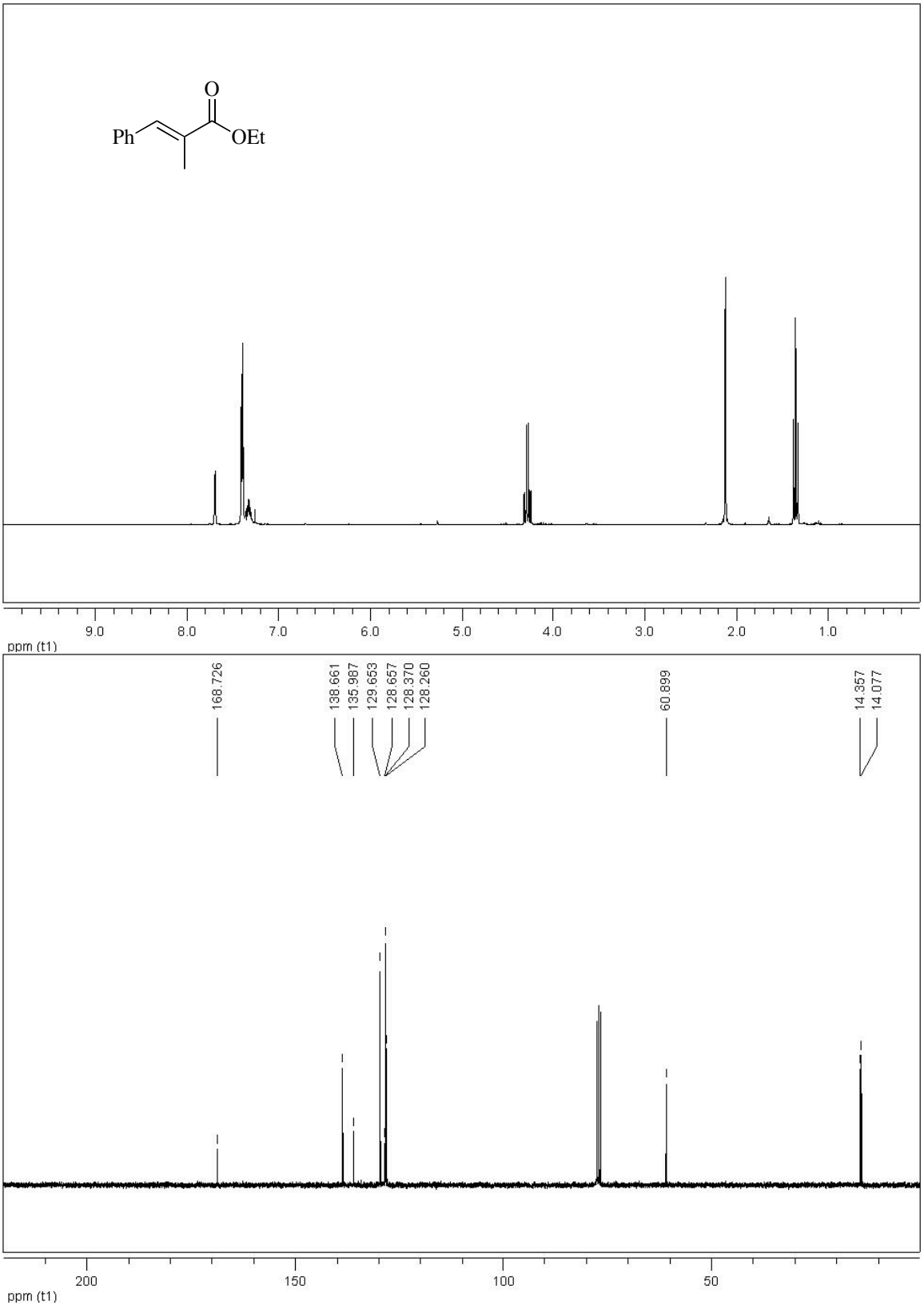
(*E*)-ethyl 3-cyclohexyl-2-methylacrylate (151c)



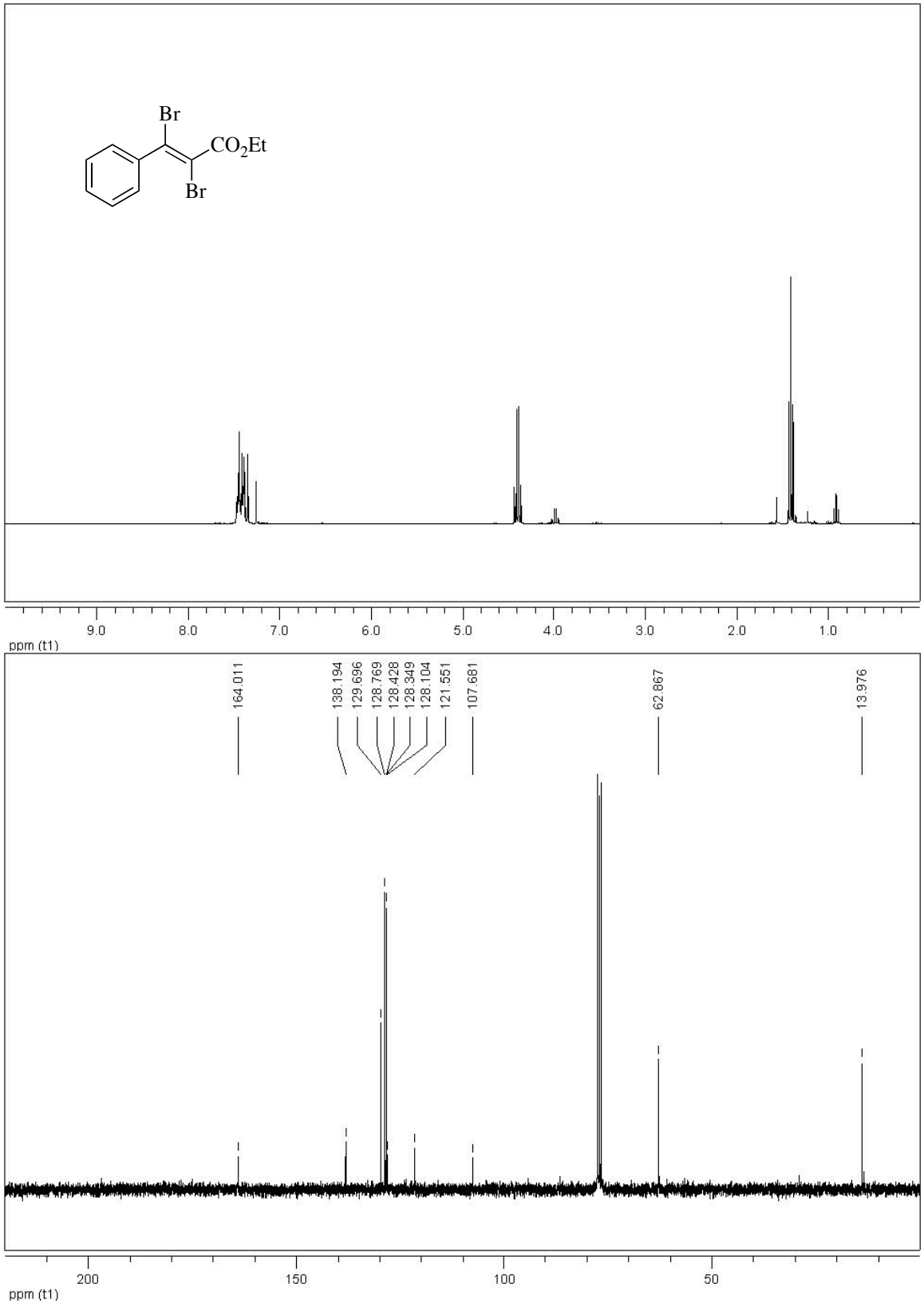
(*2S,3R*)-ethyl 2,3-dibromo-2-methyl-3-phenylpropanoate (150e)



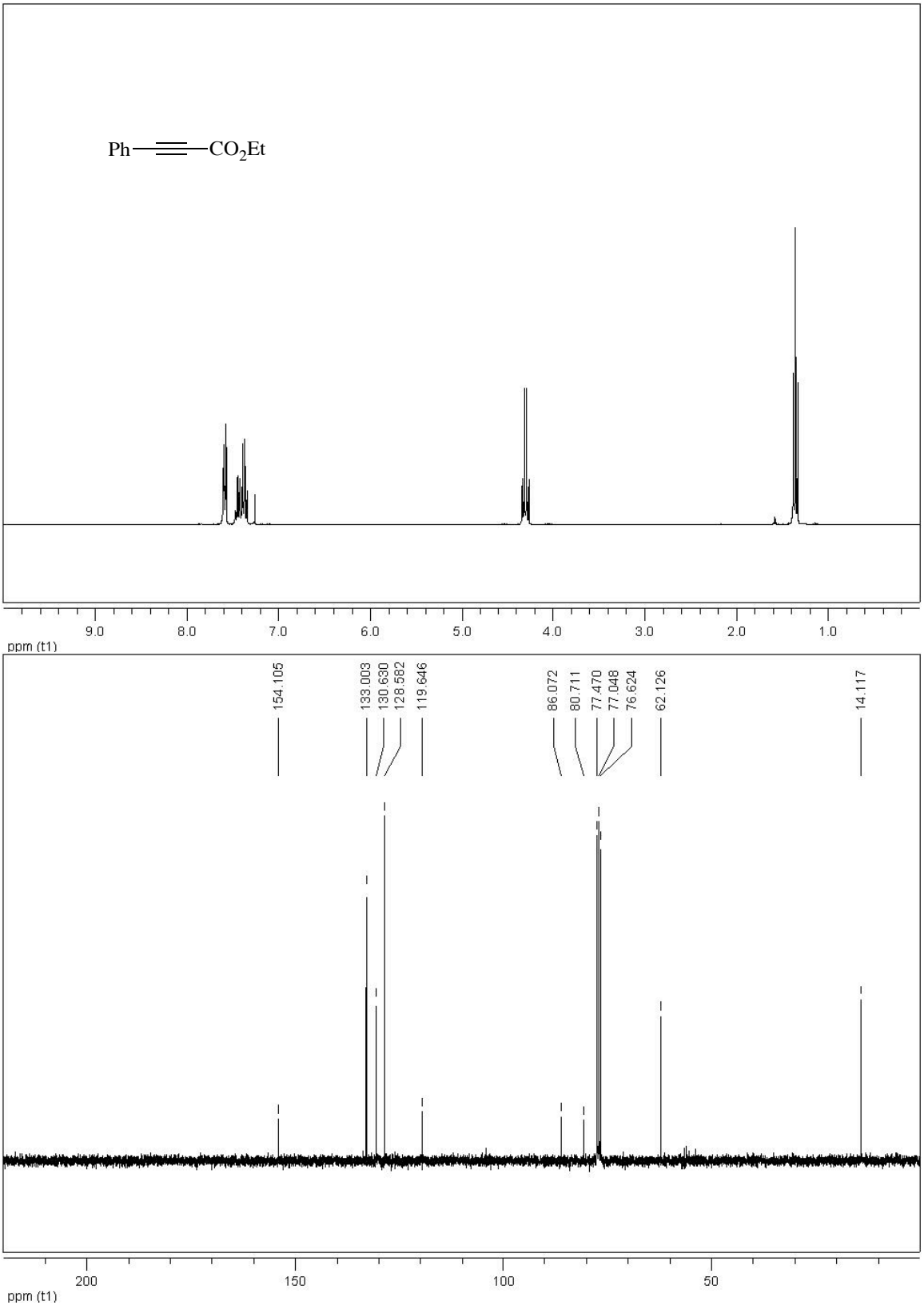
Ethyl 2-methyl-3-phenylacrylate (151e)



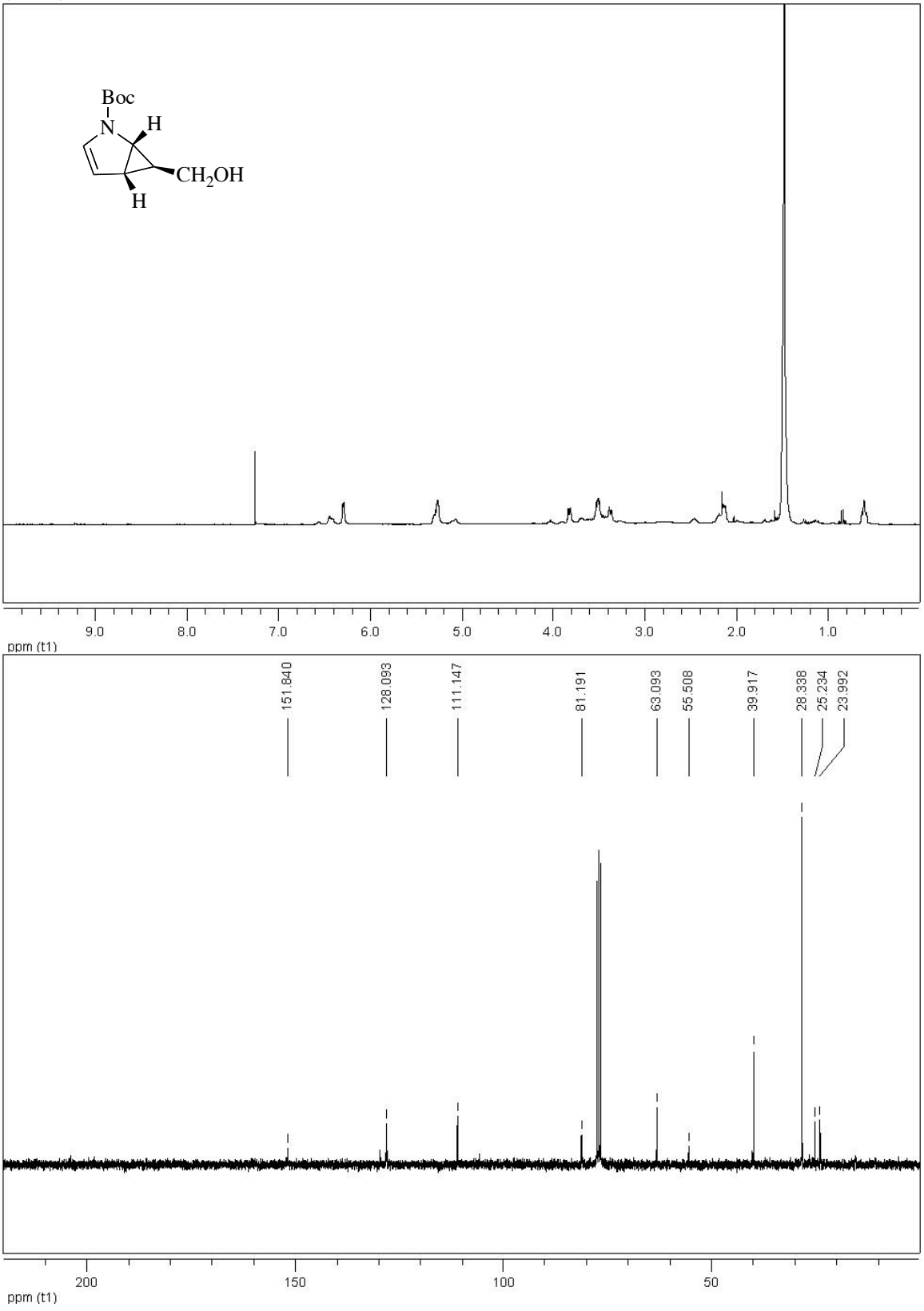
(*E*)-ethyl 2,3-dibromo-3-phenylacrylate (152)



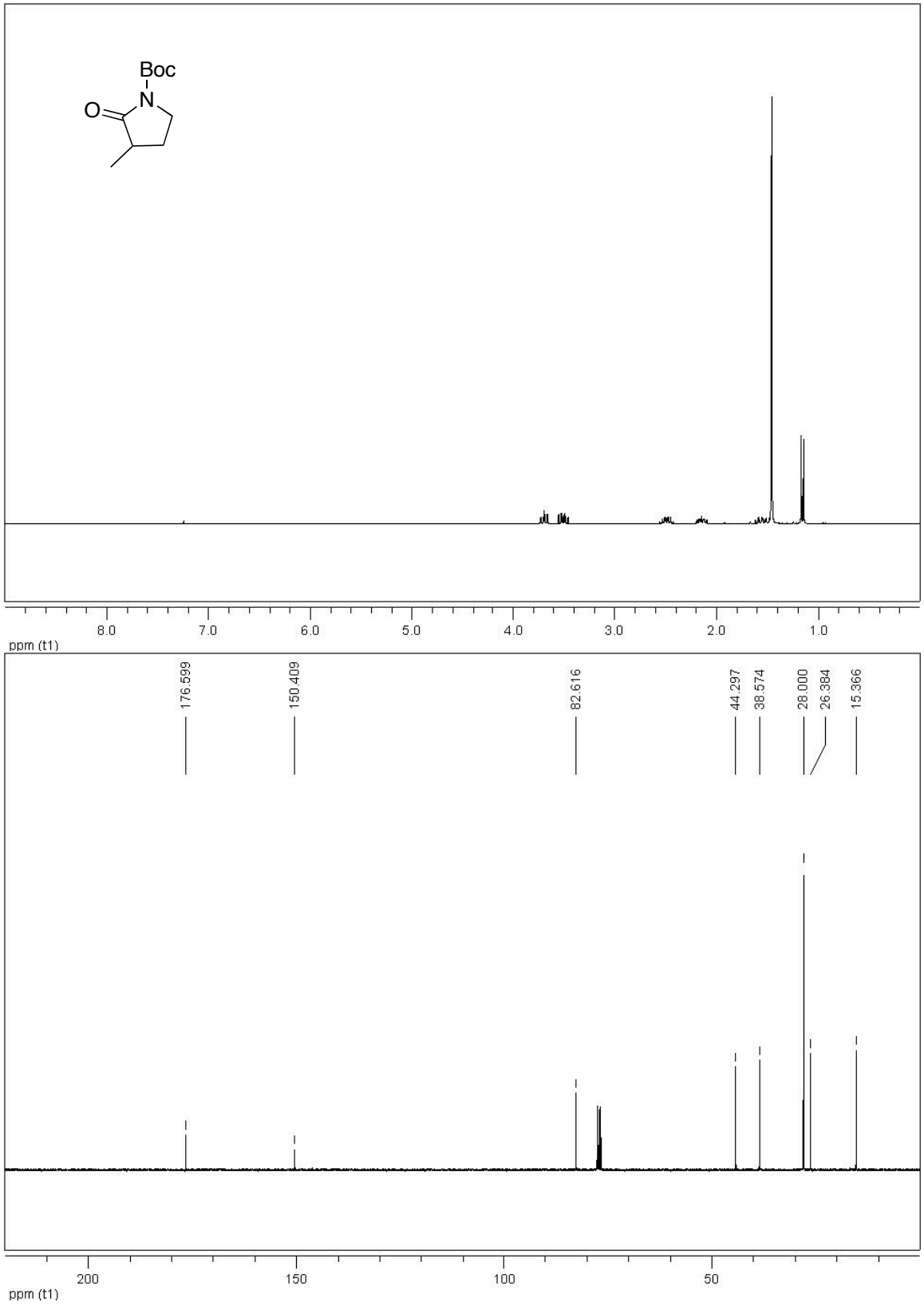
Ethyl 3-phenylpropiolate (153)



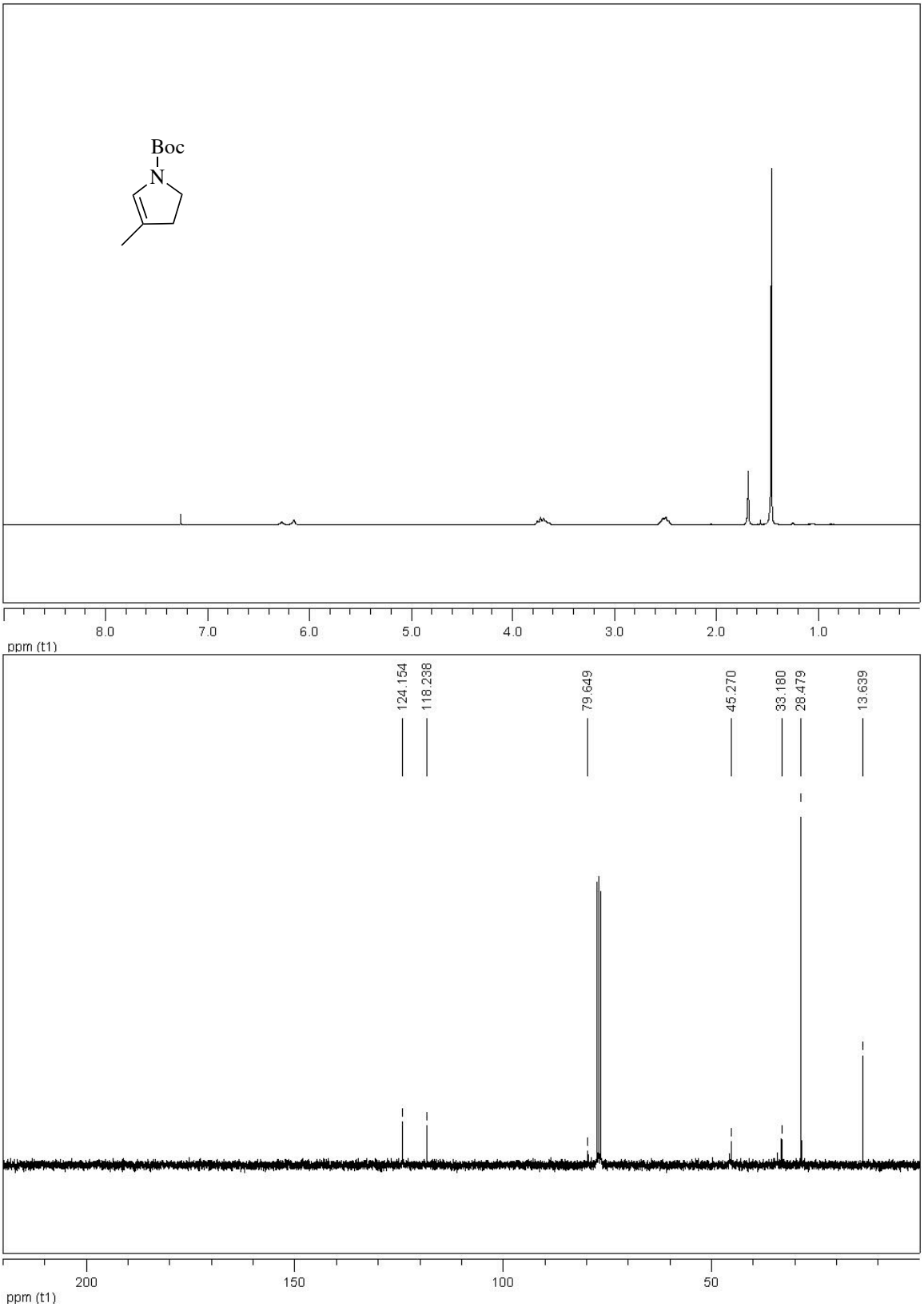
(*1S,5S,6S*)-*tert*-Butyl 6-(hydroxymethyl)-2-azabicyclo[3.1.0]hex-3-ene-2-carboxylate (172c)



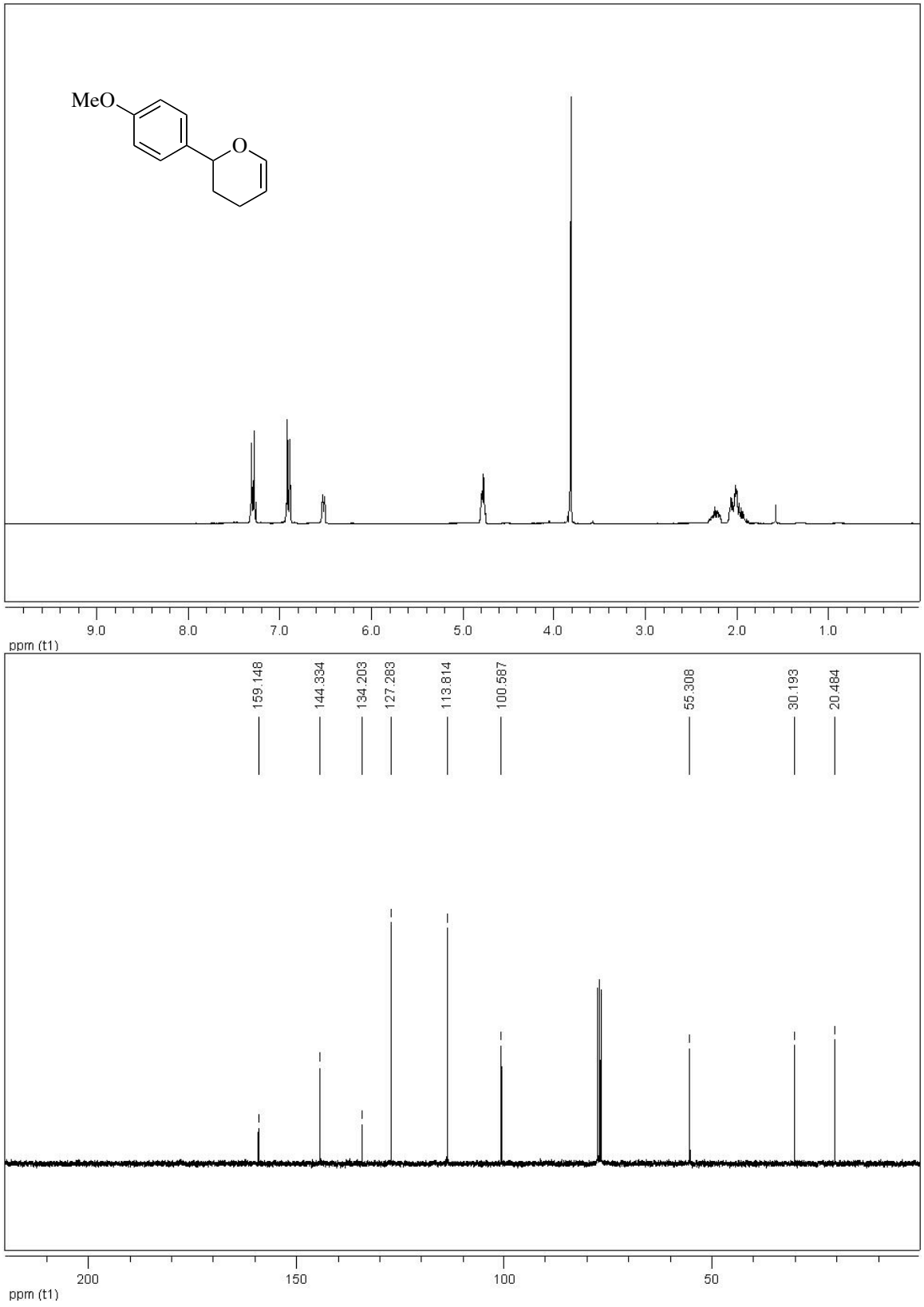
tert-Butyl 3-methyl-2-oxopyrrolidine-1-carboxylate (172E')



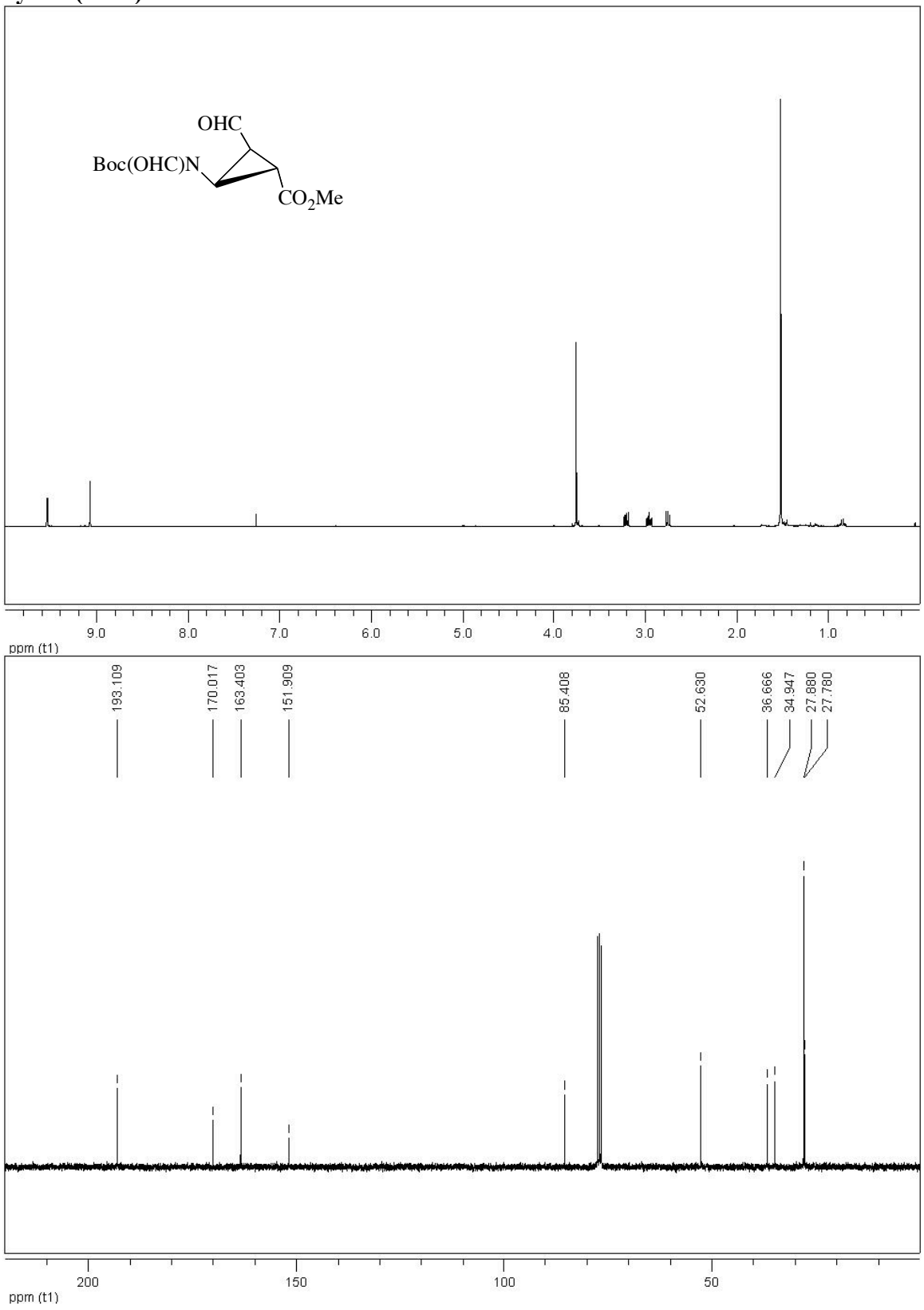
tert-Butyl 4-methyl-2,3-dihydro-1H-pyrrole-1-carboxylate (172e)



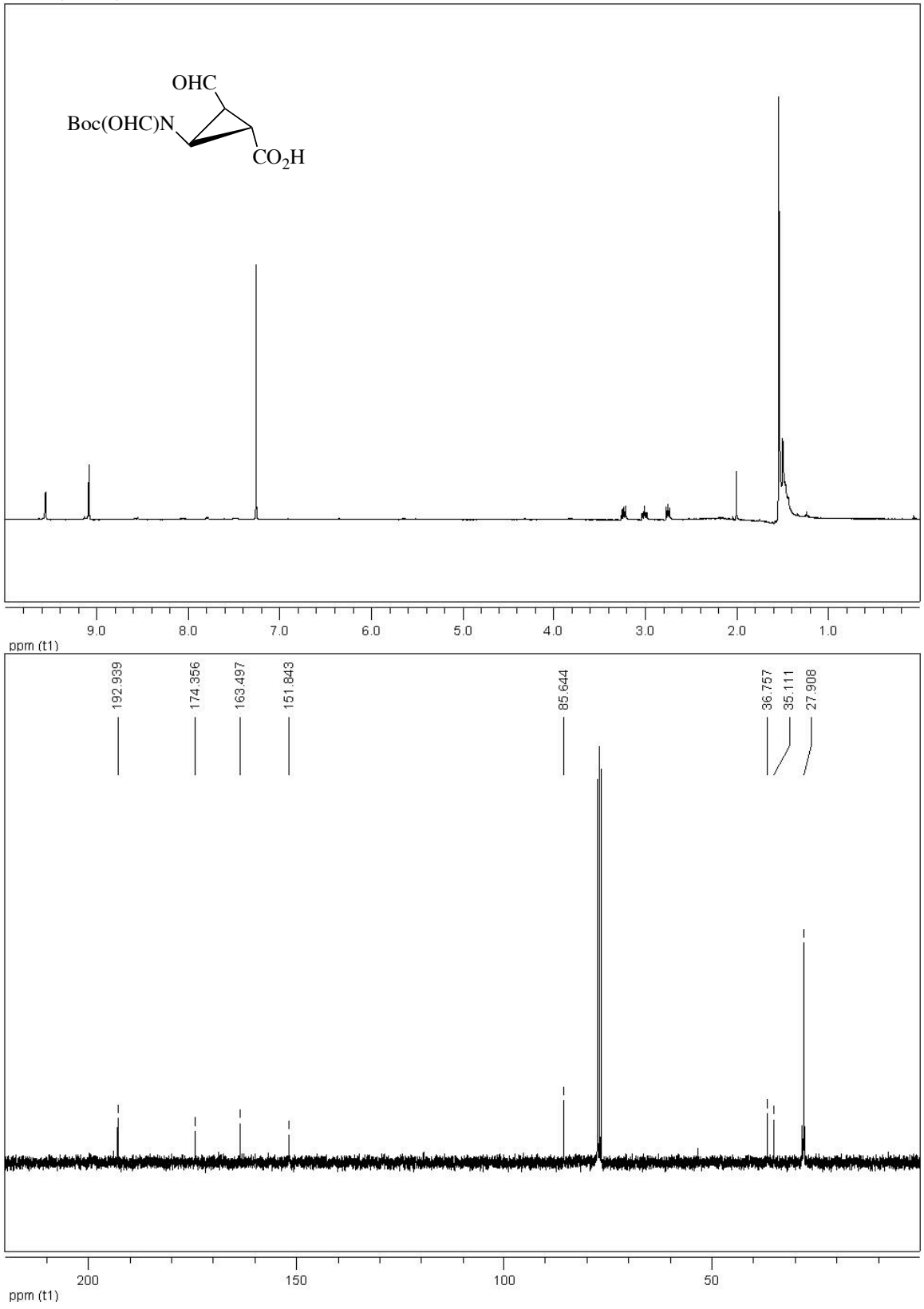
2-(4-Methoxyphenyl)-3,4-dihydro-2H-pyran (182b)



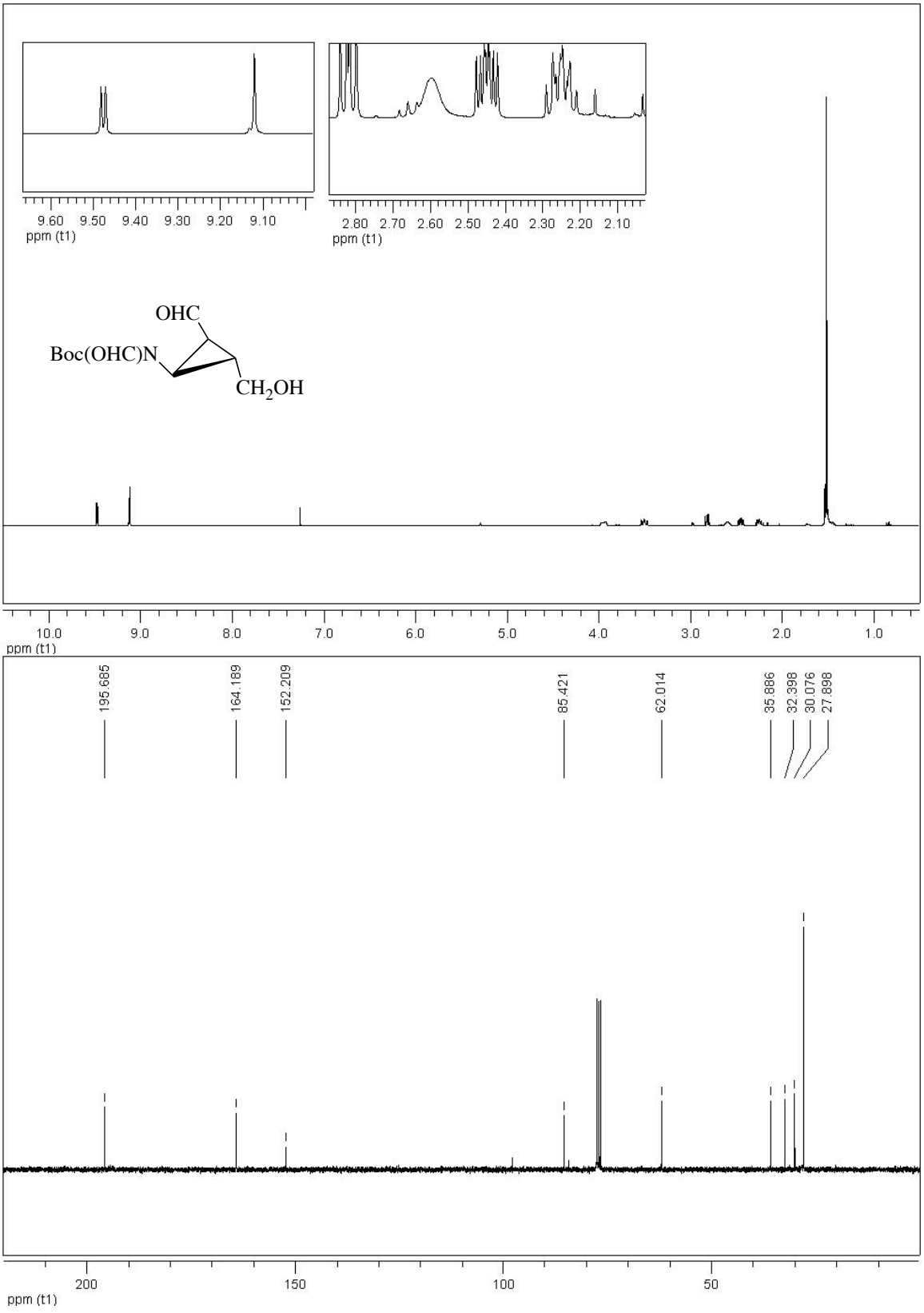
(1*R*,2*S*)-Methyl 2-(*N*-(*tert*-butoxycarbonyl)formamido)-3-formylcyclopropanecarboxylate (173a)



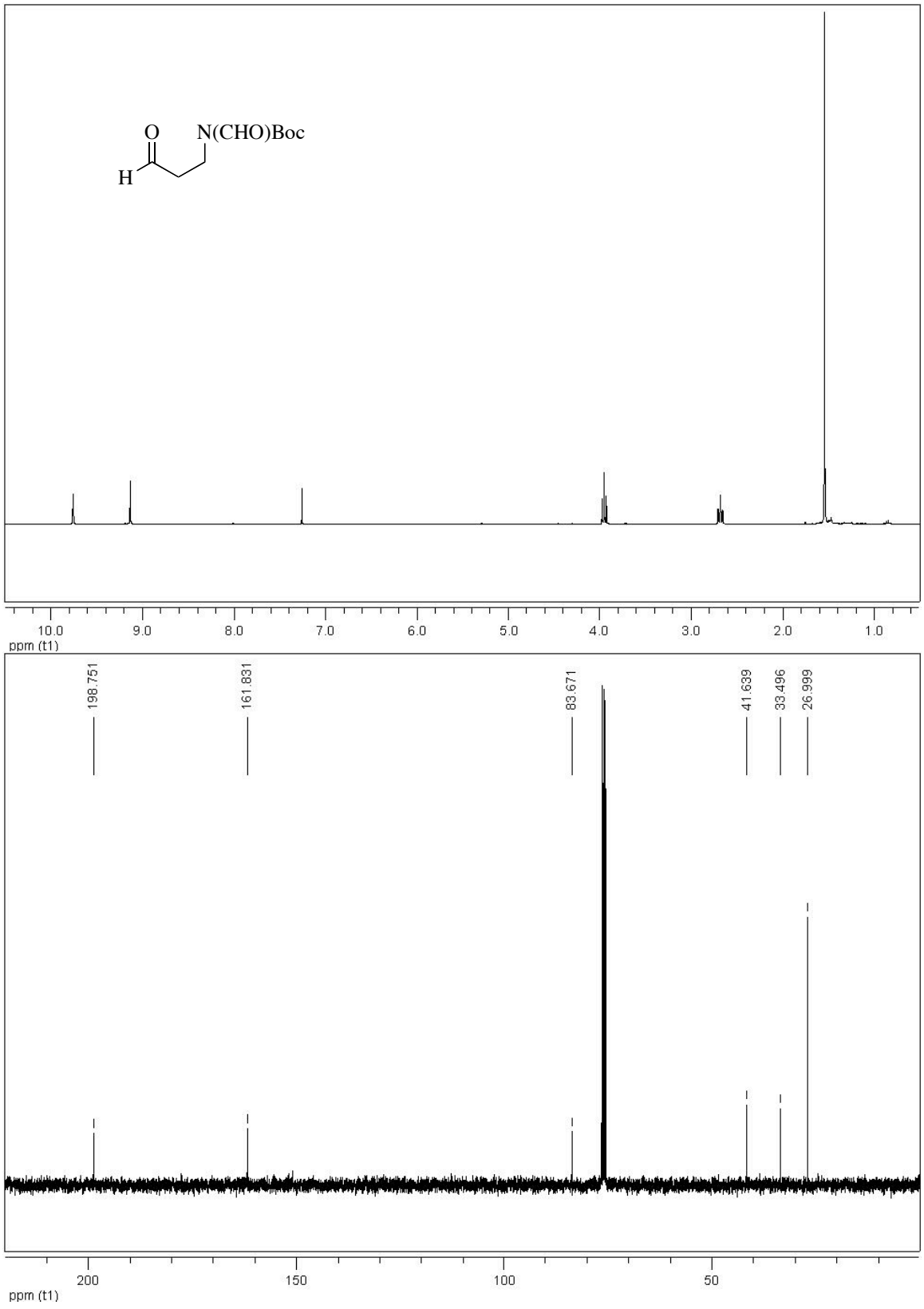
(*1R,2S*)-2-(N-(*tert*-butoxycarbonyl)formamido)-3-formylcyclopropanecarboxylic acid (173b)



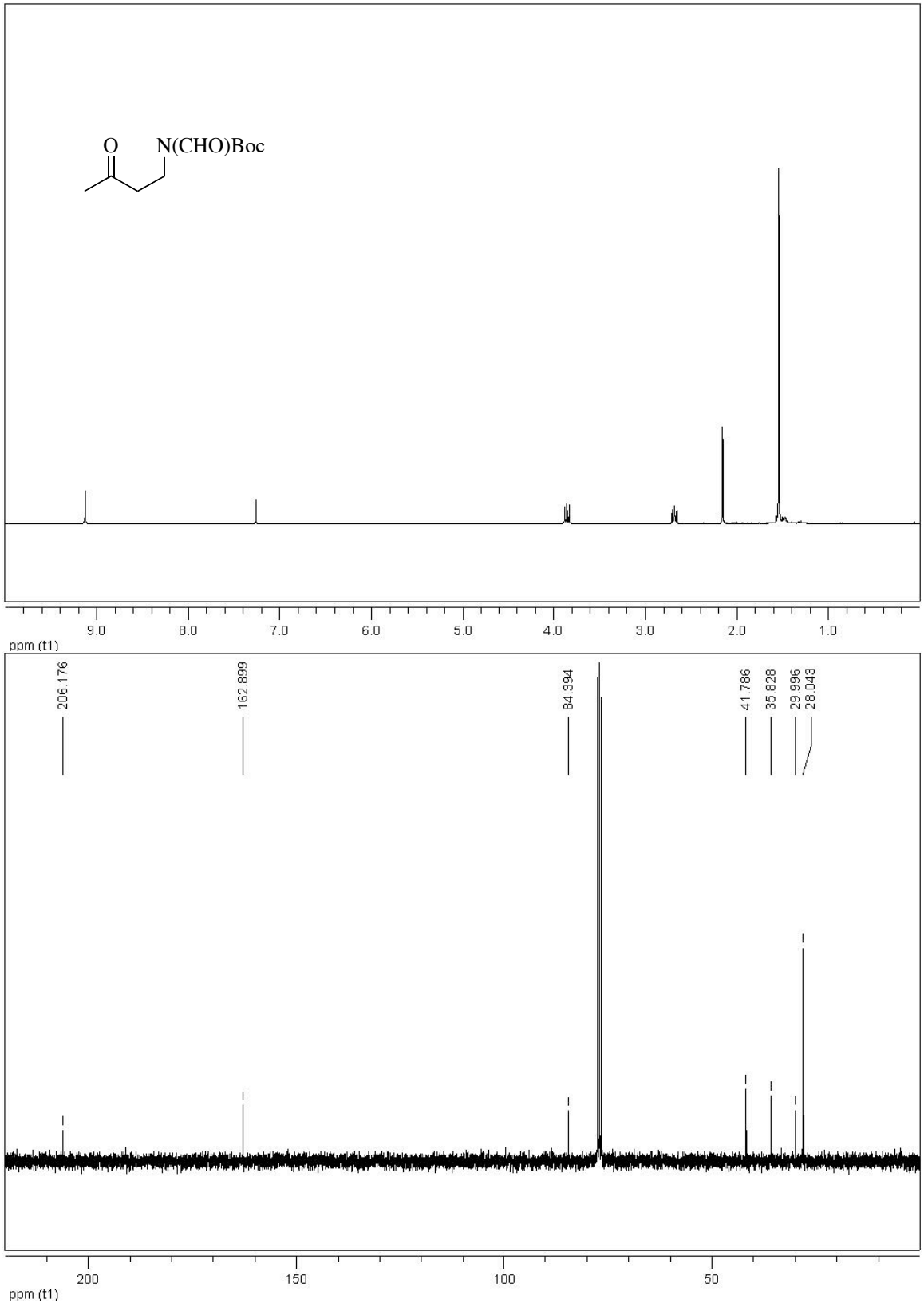
tert-Butyl formyl((1S,3S)-2-formyl-3-(hydroxymethyl)cyclopropyl)carbamate (173c)



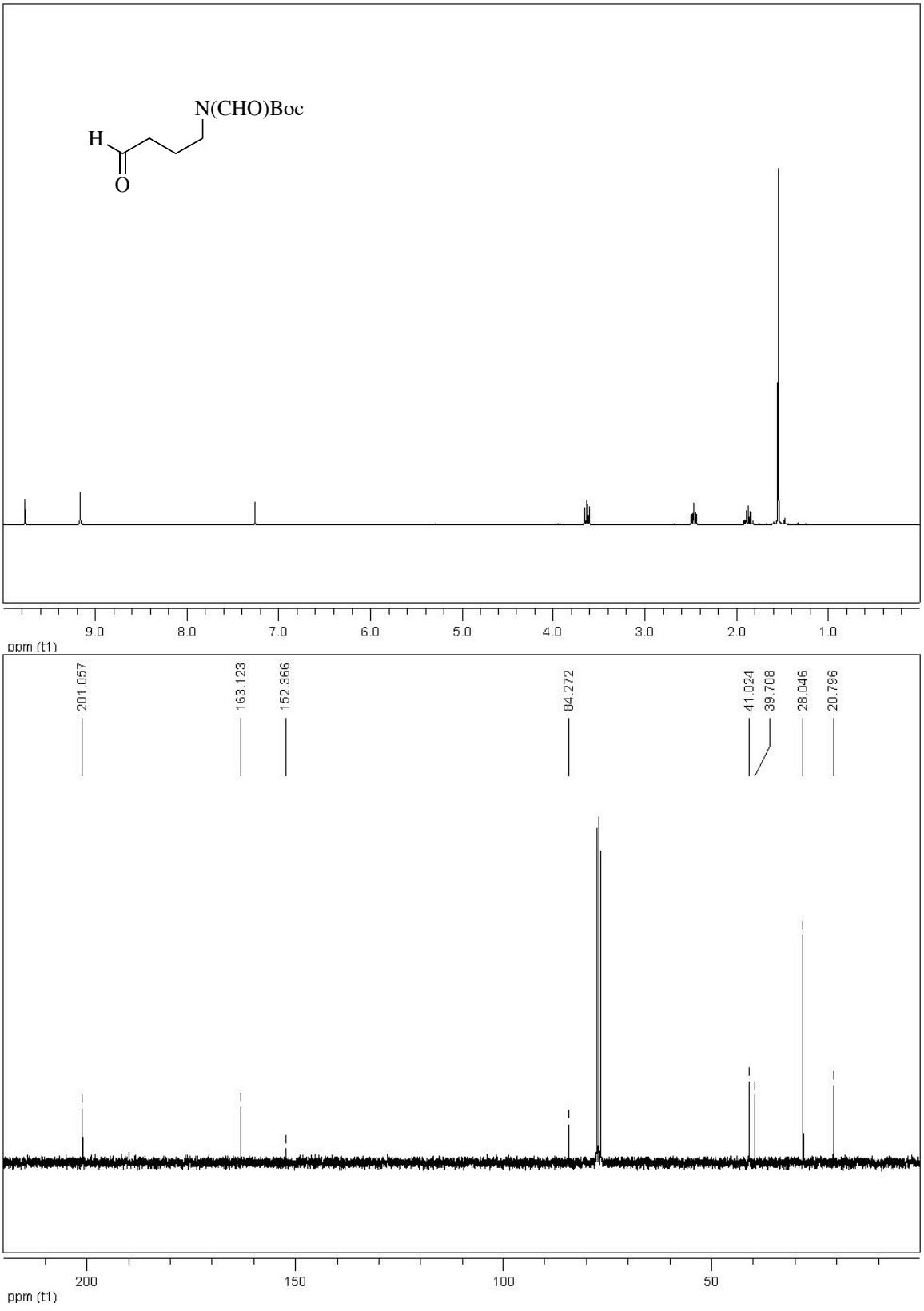
tert-Butyl formyl(3-oxopropyl)carbamate (173d)



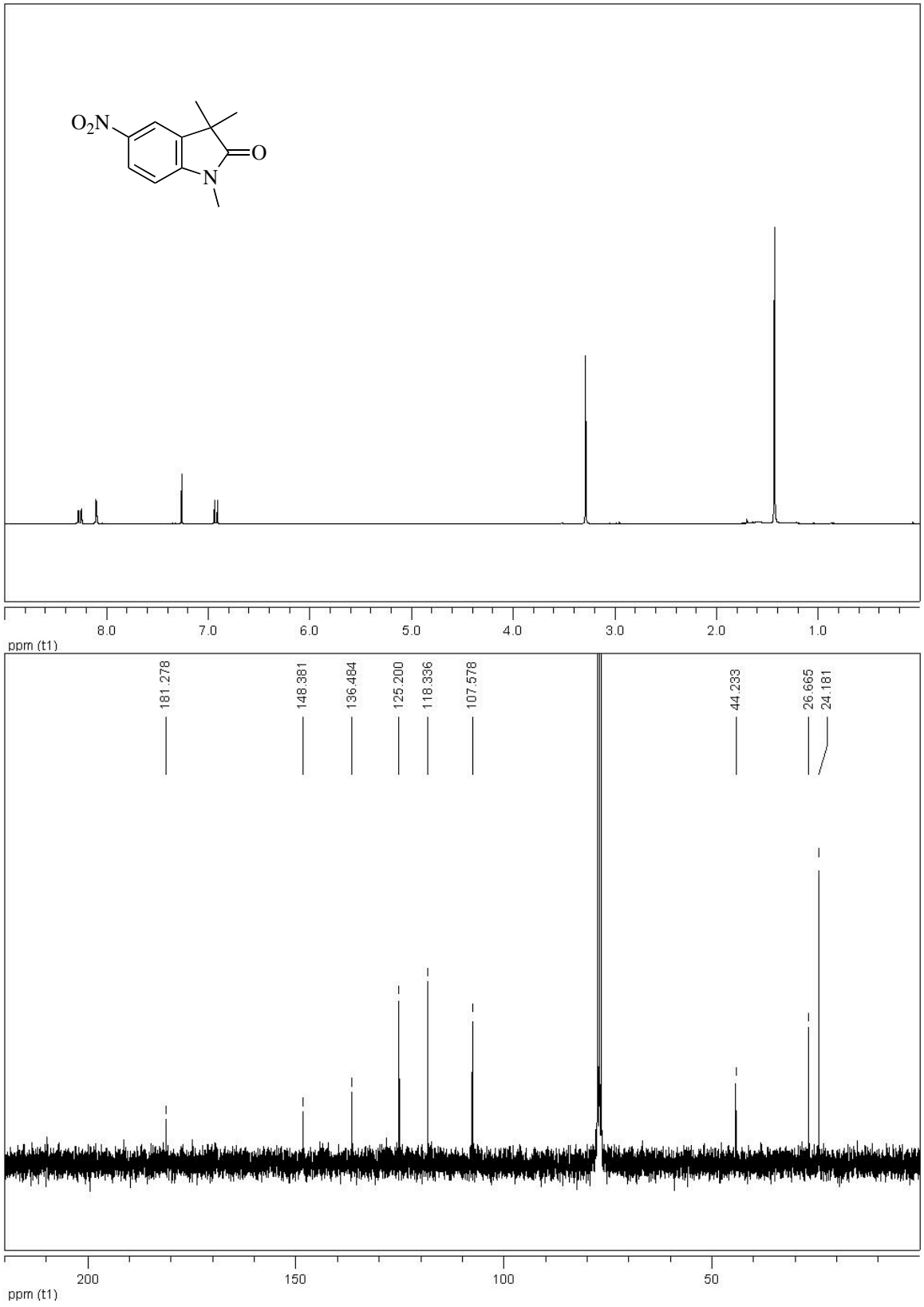
tert-Butyl formyl(3-oxobutyl)carbamate (173e)



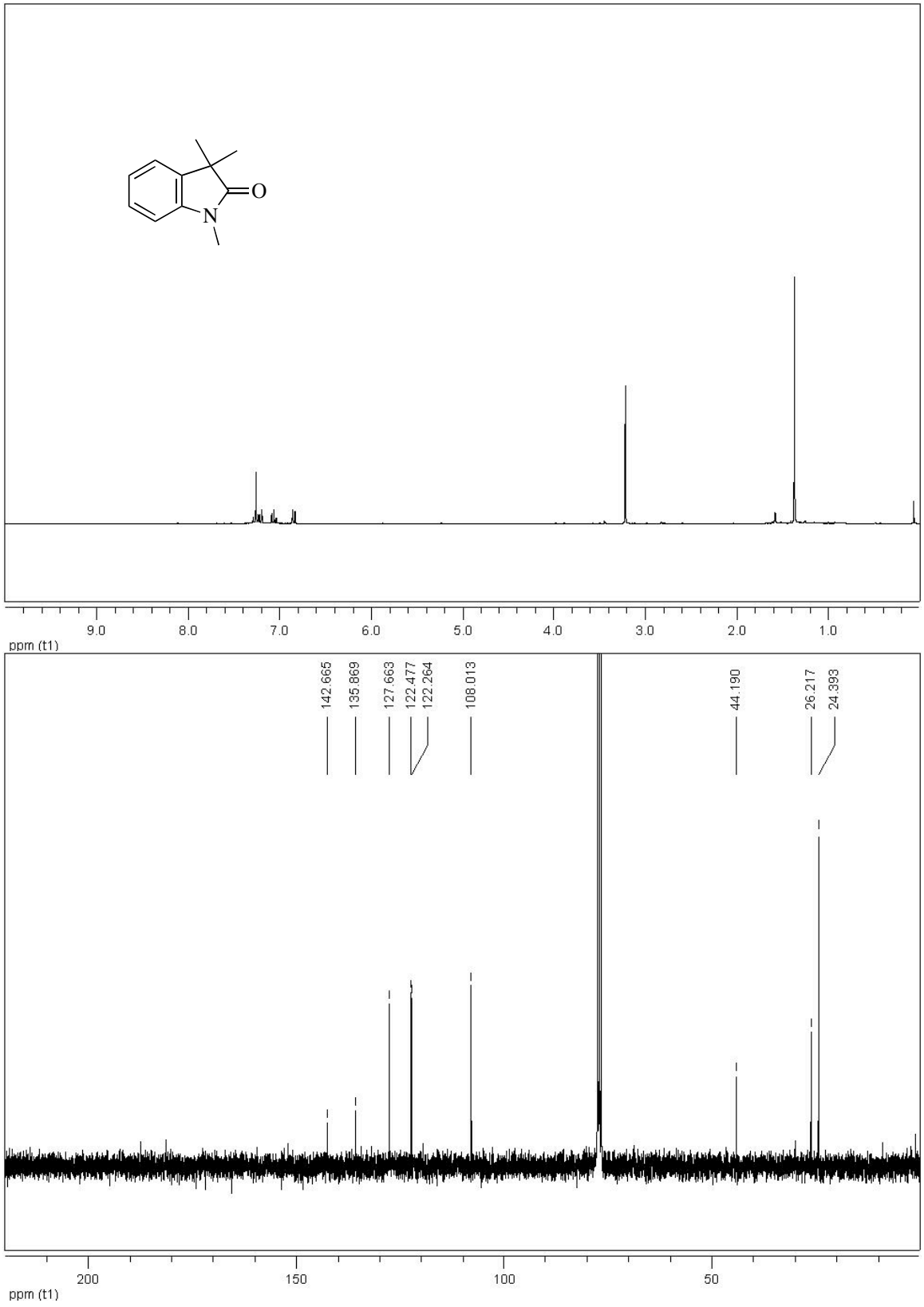
tert-Butyl formyl(4-oxobutyl)carbamate (173f)



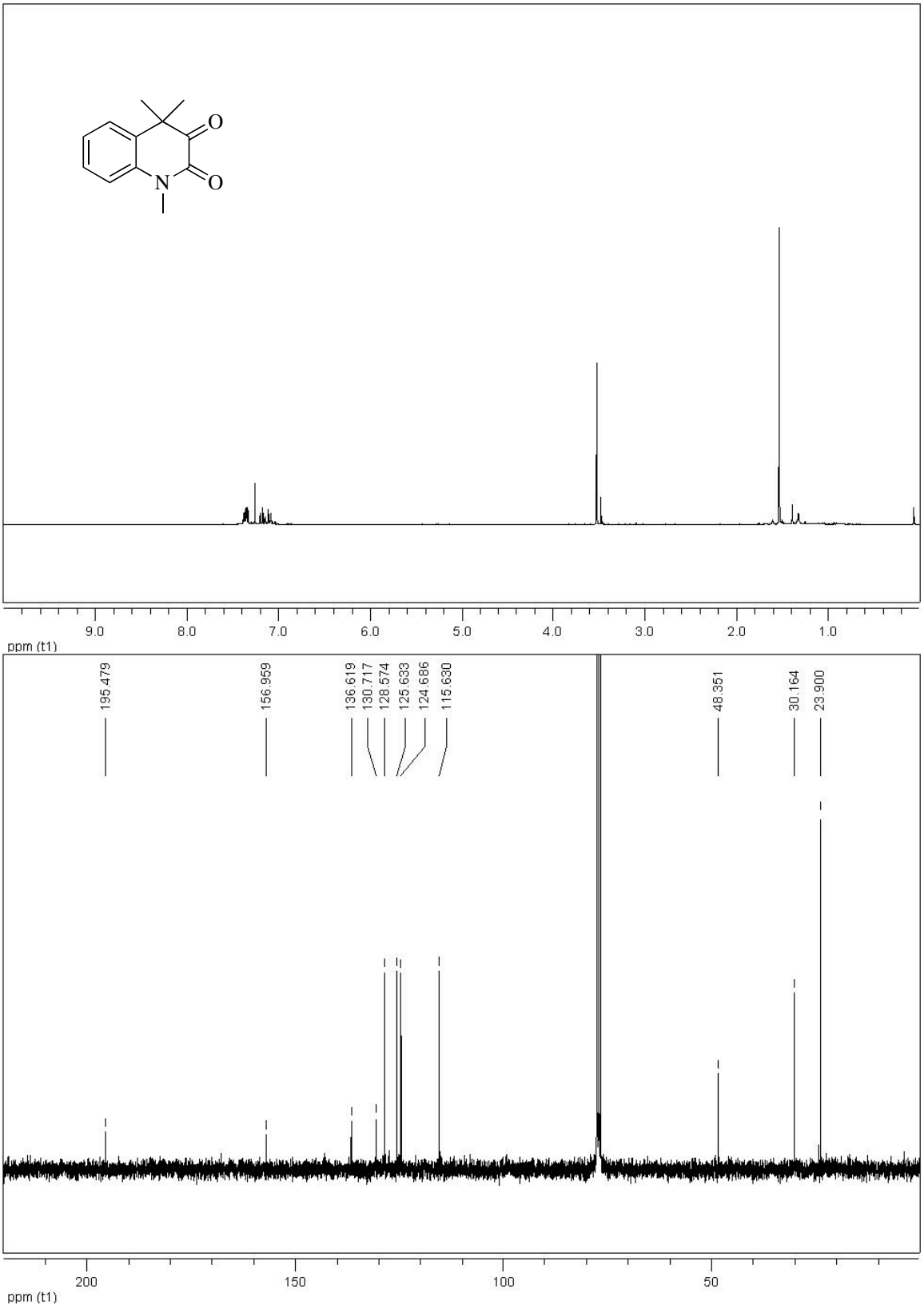
1,3,3-Trimethyl-5-nitroindolin-2-one (173g)



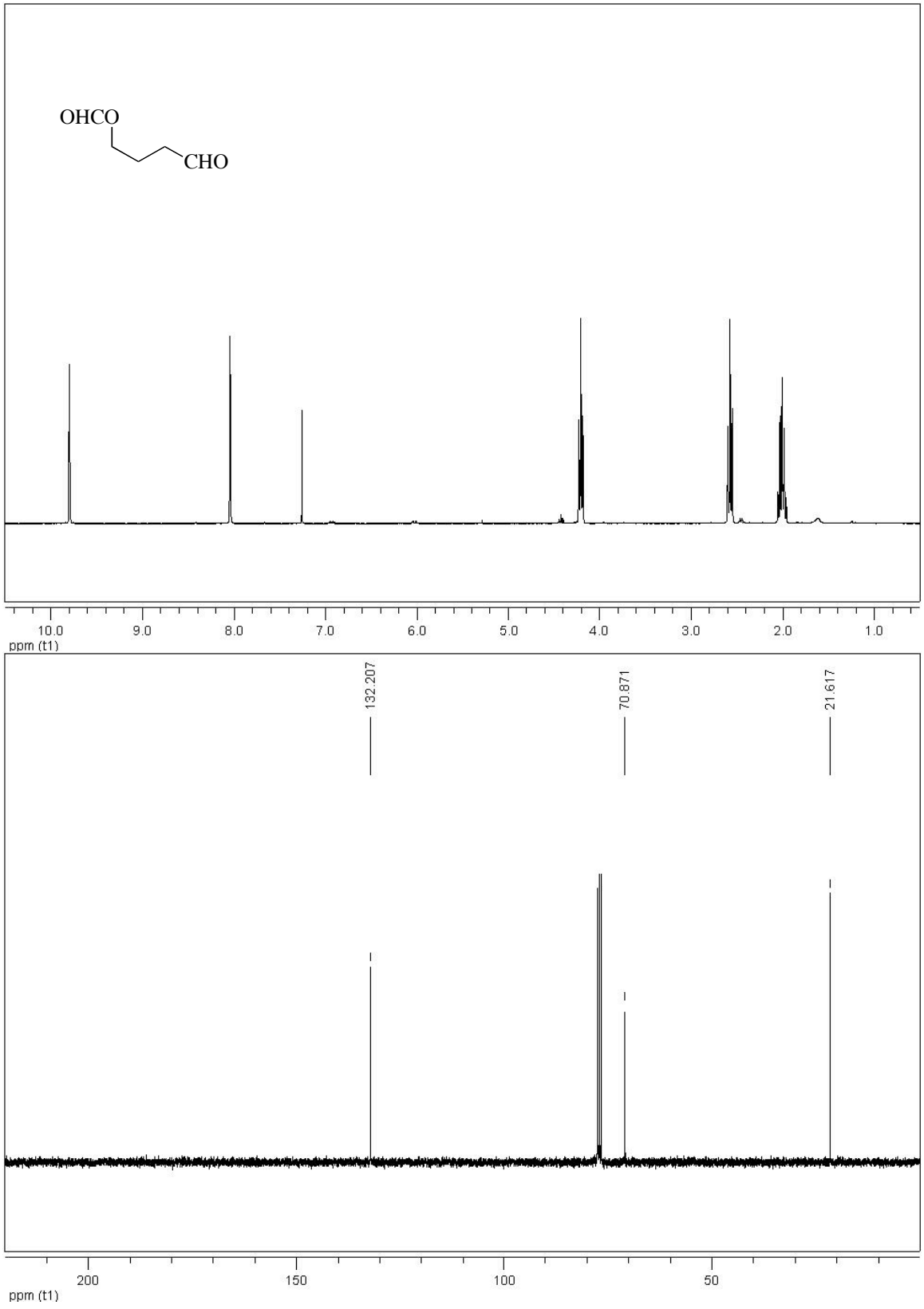
1,3,3-Trimethylindolin-2-one (173h)



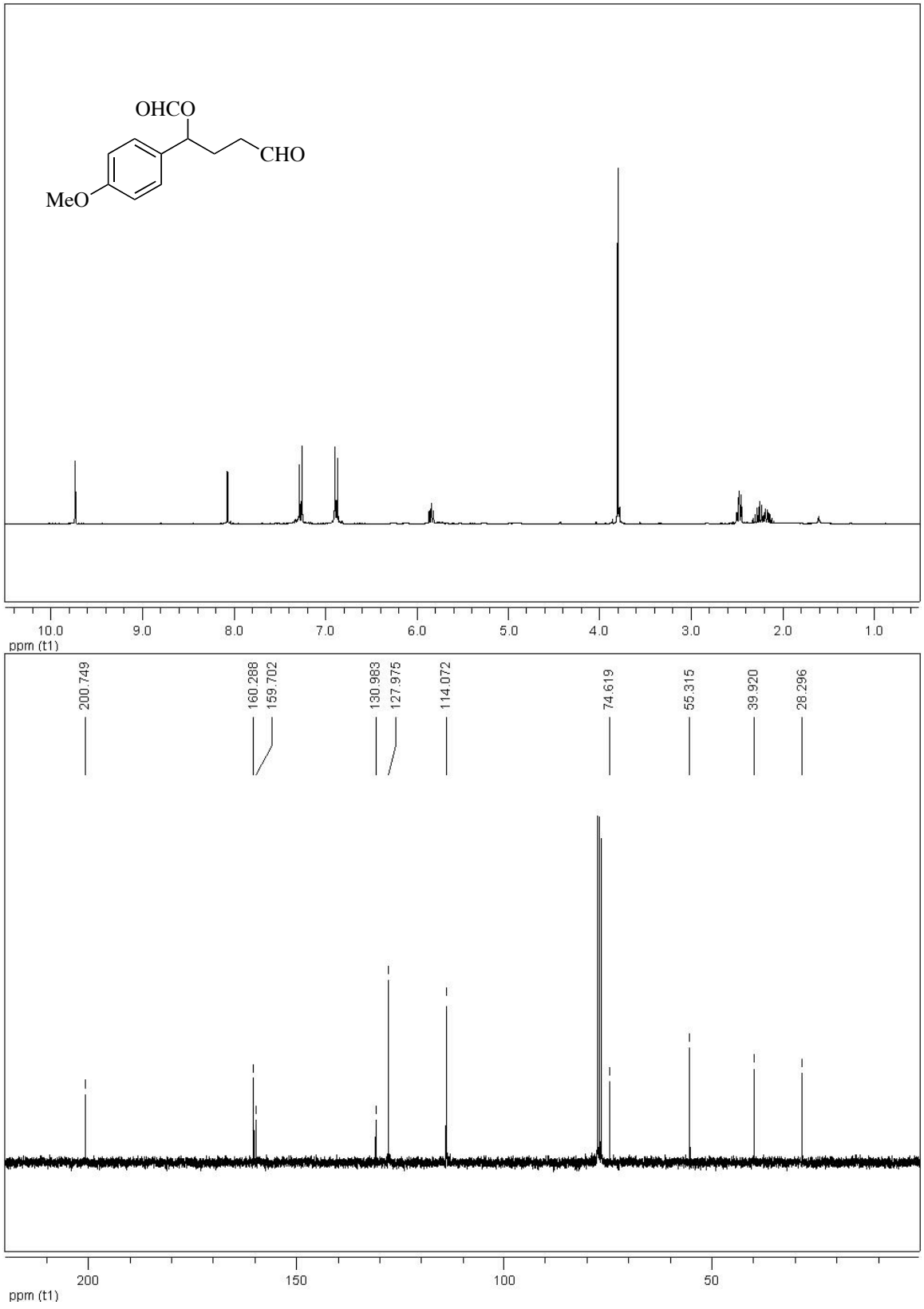
1,4,4-Trimethylquinoline-2,3-(1H,4H)-dione (173h´)



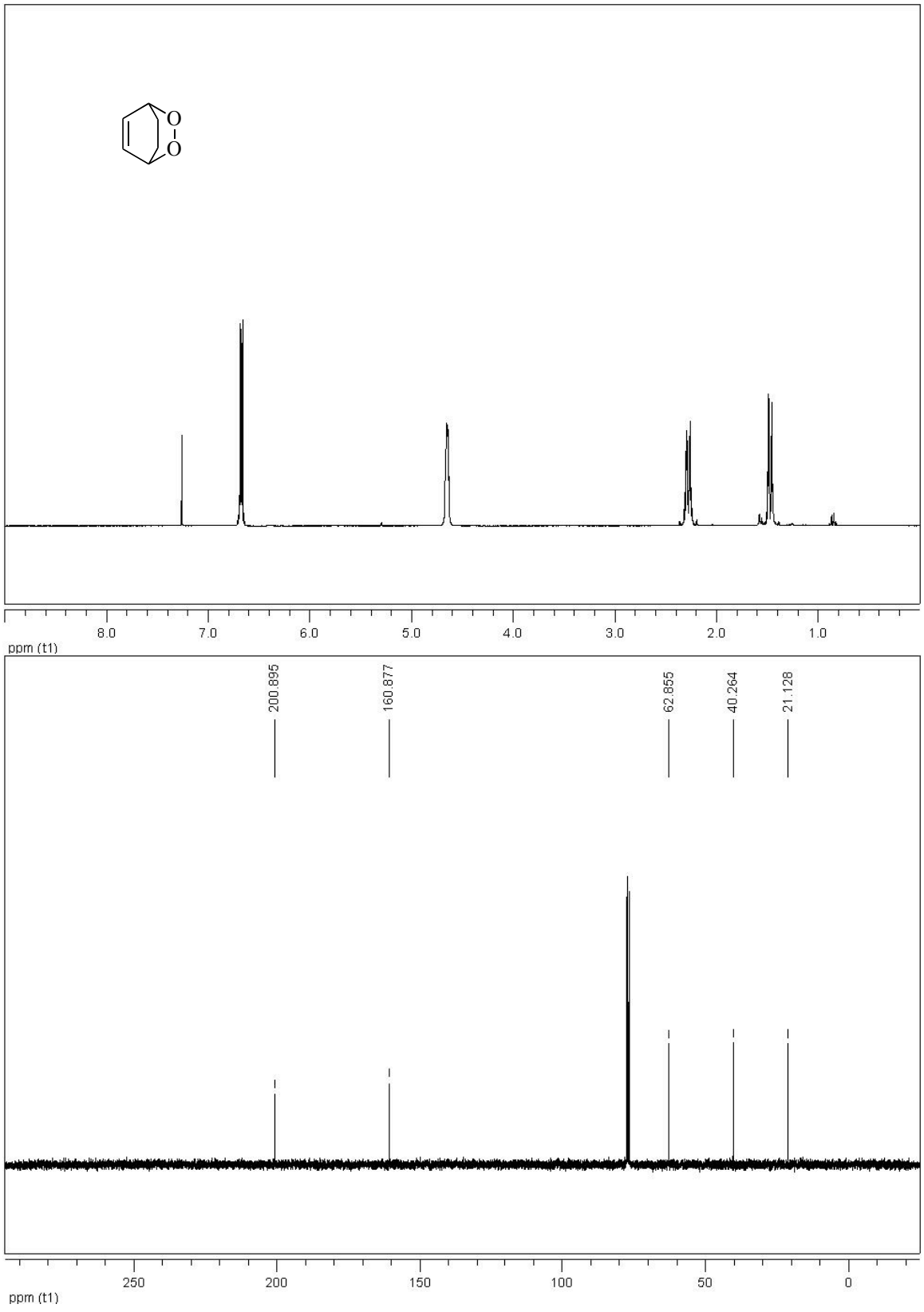
4-Oxobutyl formate (183a)



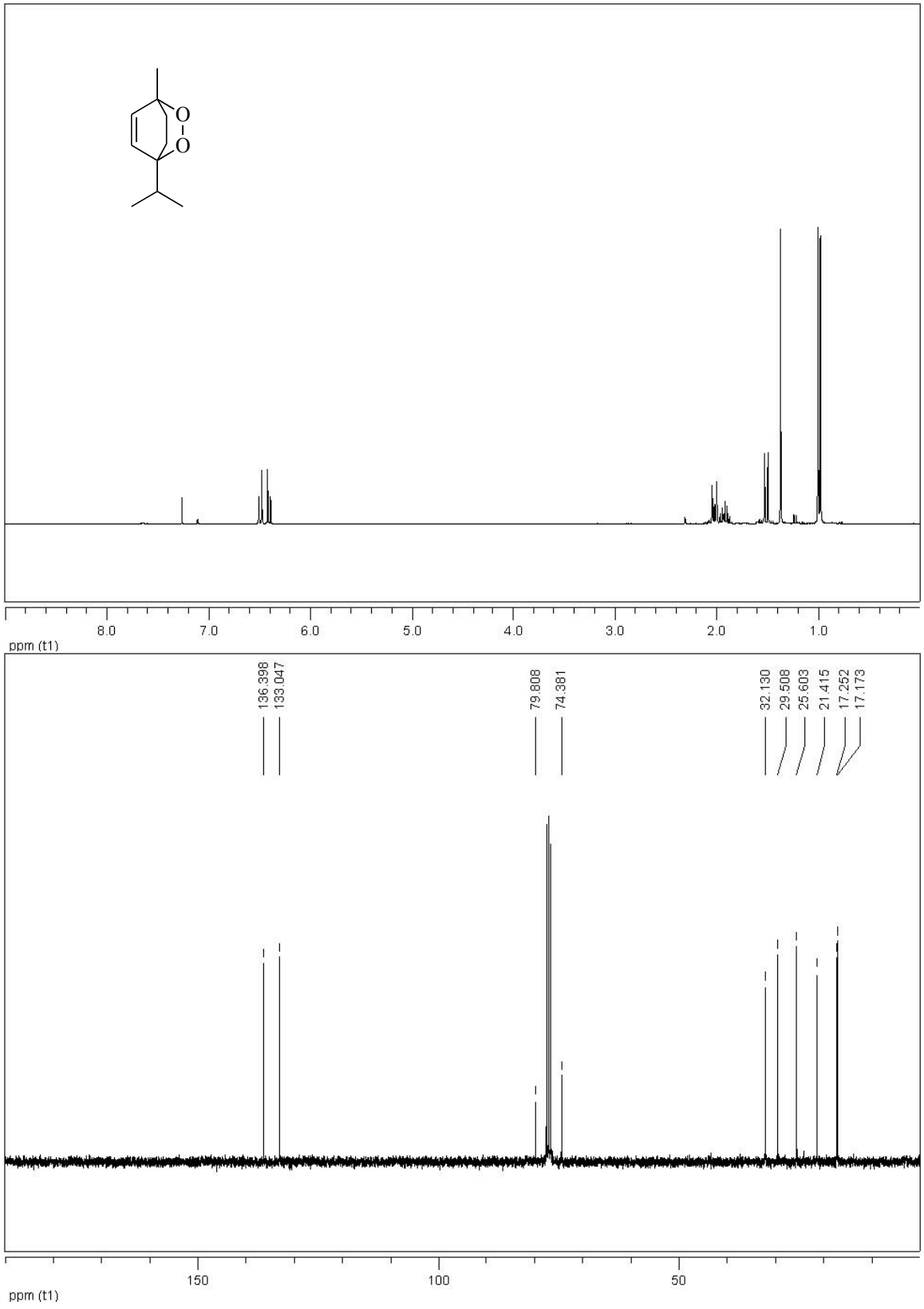
1-(4-Methoxyphenyl)-4-oxobutyl formate (183b)



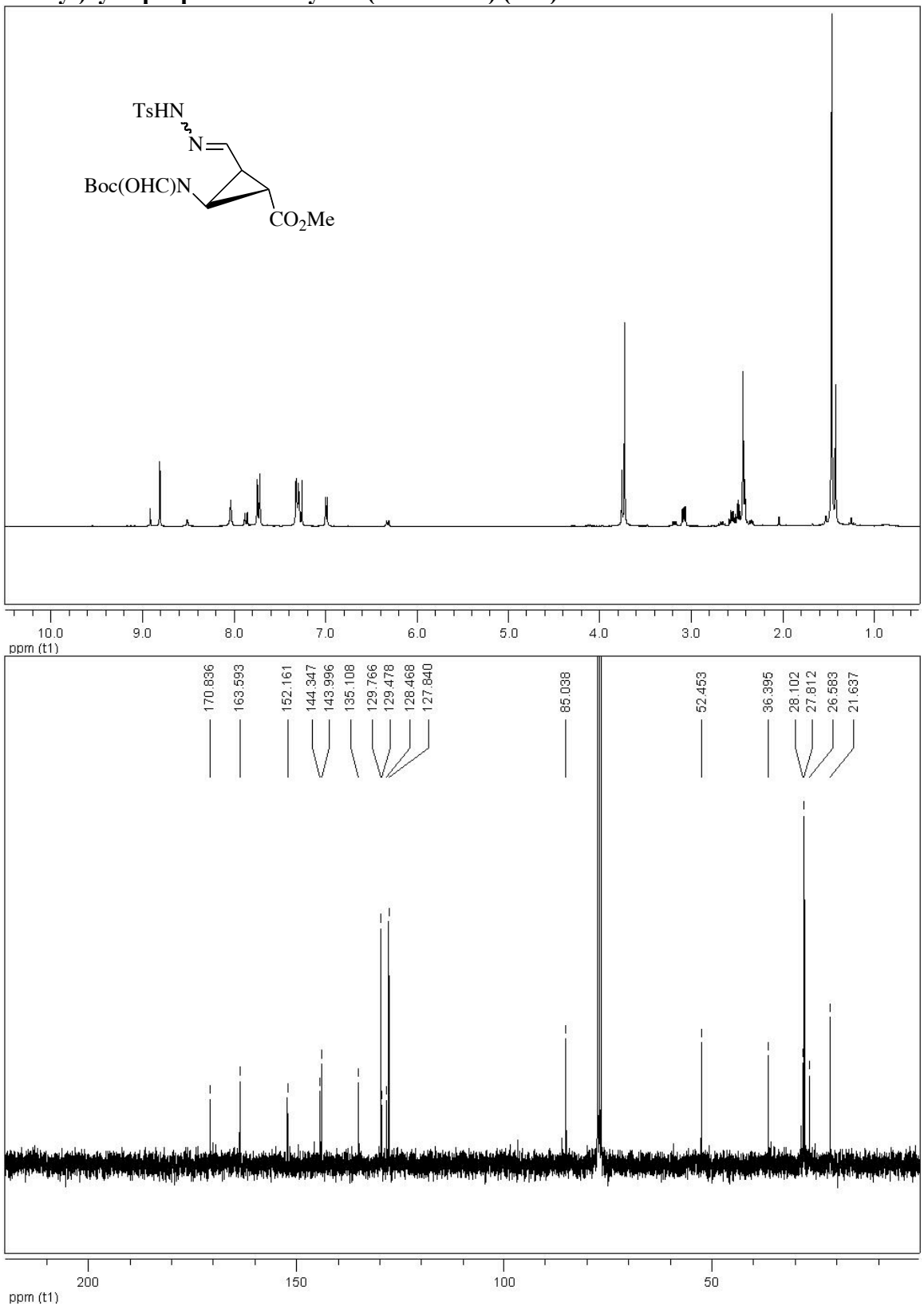
2,3-Dioxabicyclo[2.2.2]oct-5-ene (163)



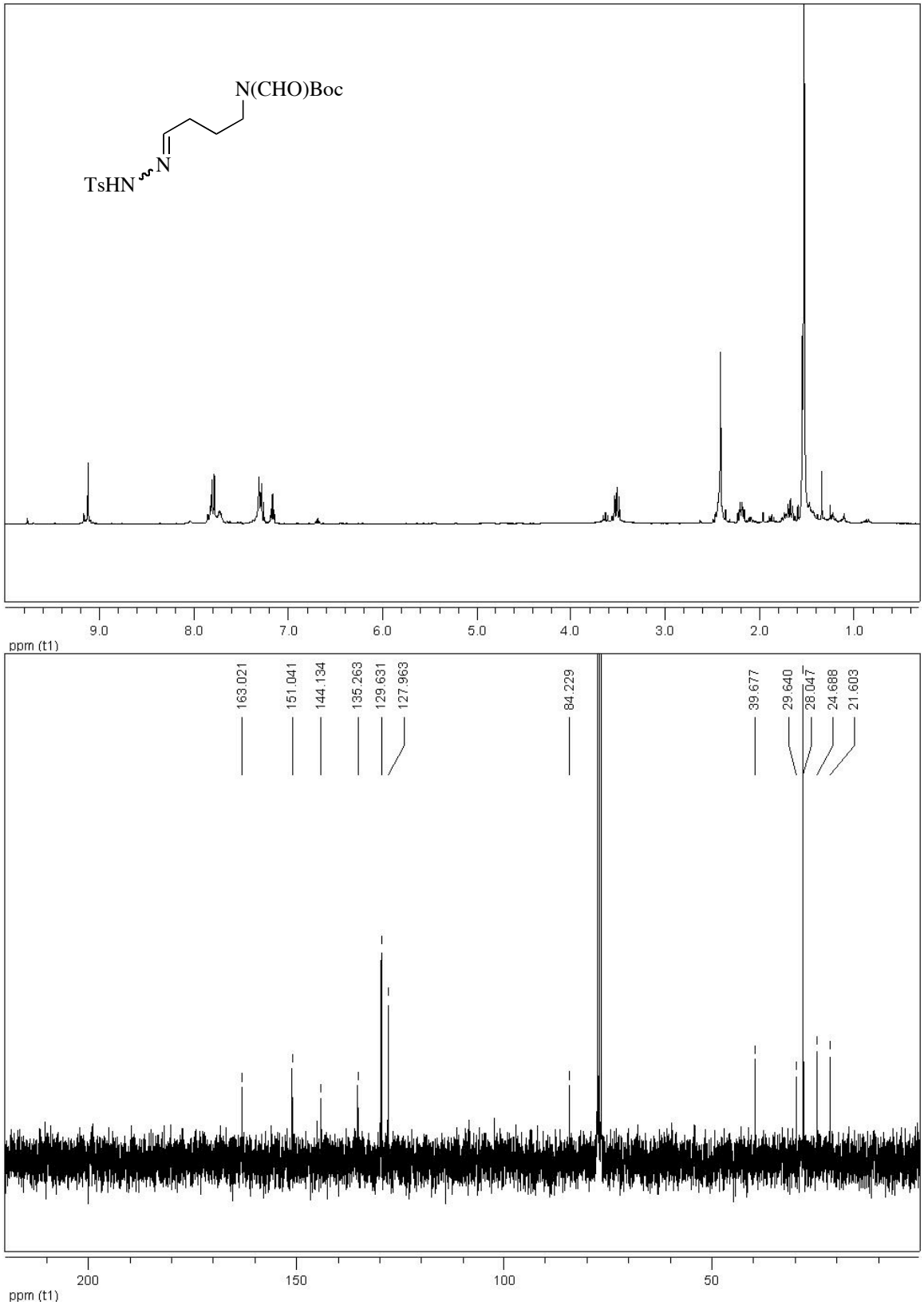
1-Isopropyl-4-methyl-2,3-dioxabicyclo[2.2.2]oct-5-ene (166)



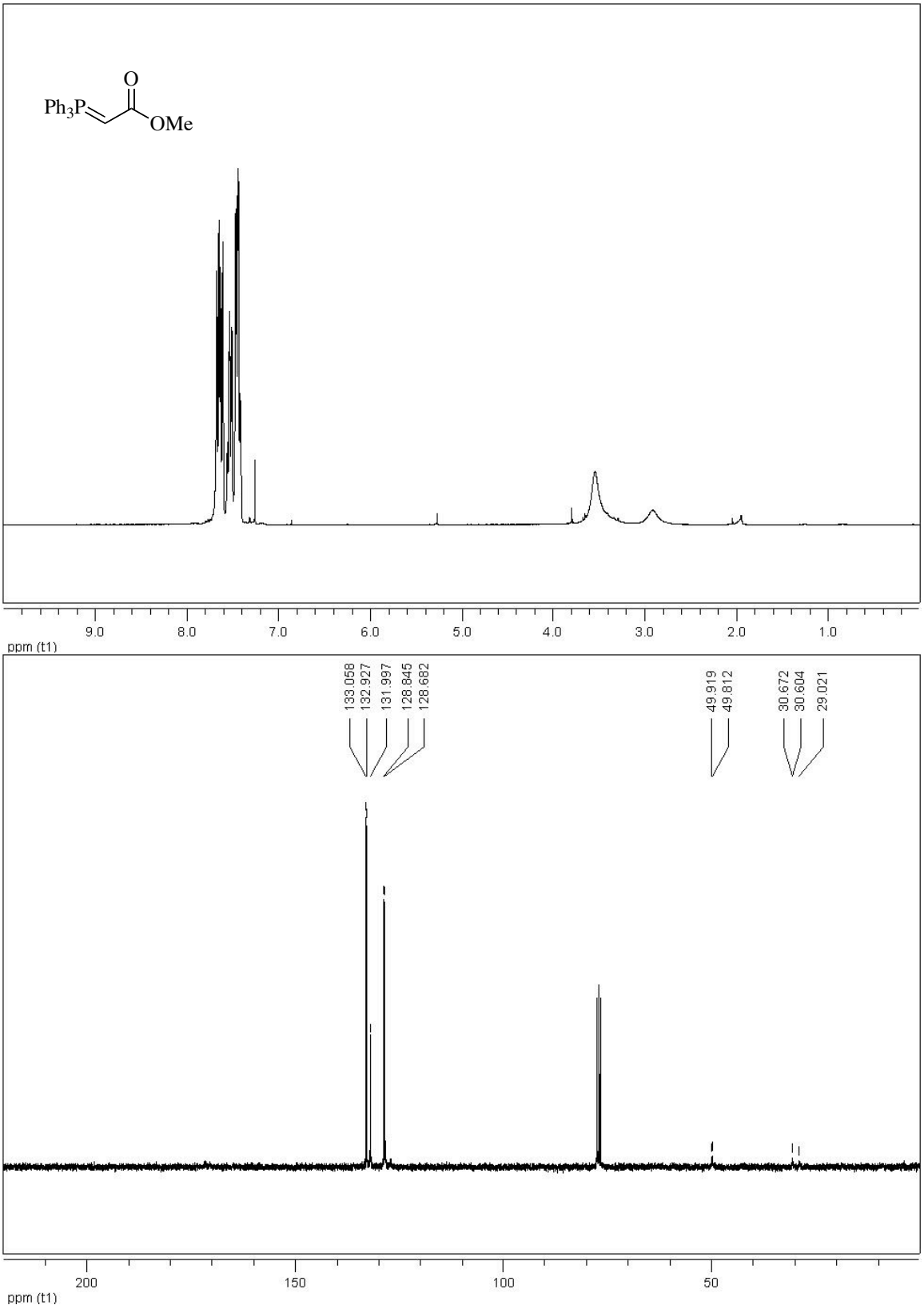
(*1S,2R*)-Methyl-2-(N-(tert-butoxycarbonyl)formamido)-3-((2-tosylhydrazono) methyl)cyclopropanecarboxylate (dr = 78:22) (177)



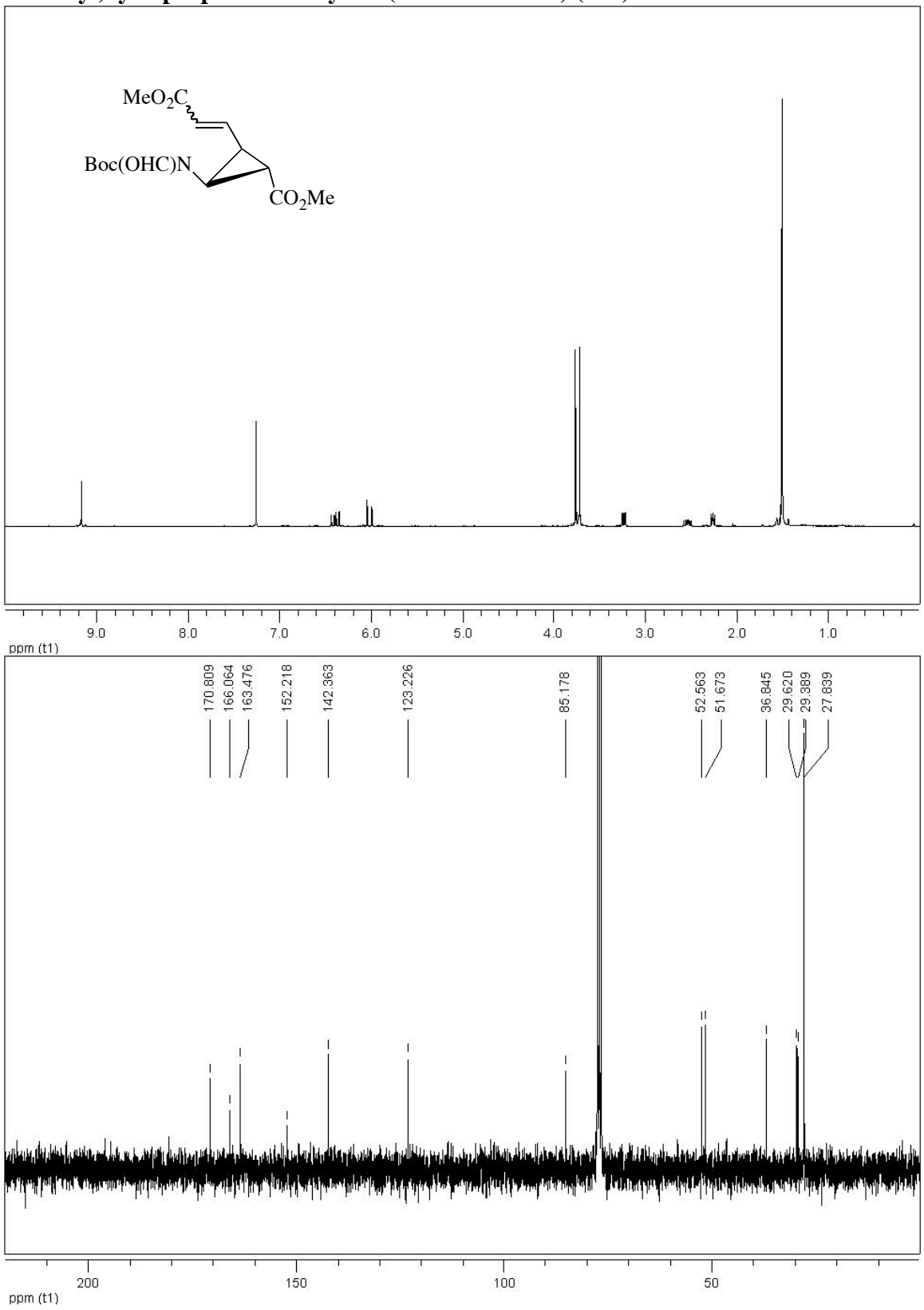
tert-Butyl formyl(4-(2-tosylhydrazono)butyl)carbamate (dr = 93:7) (178)



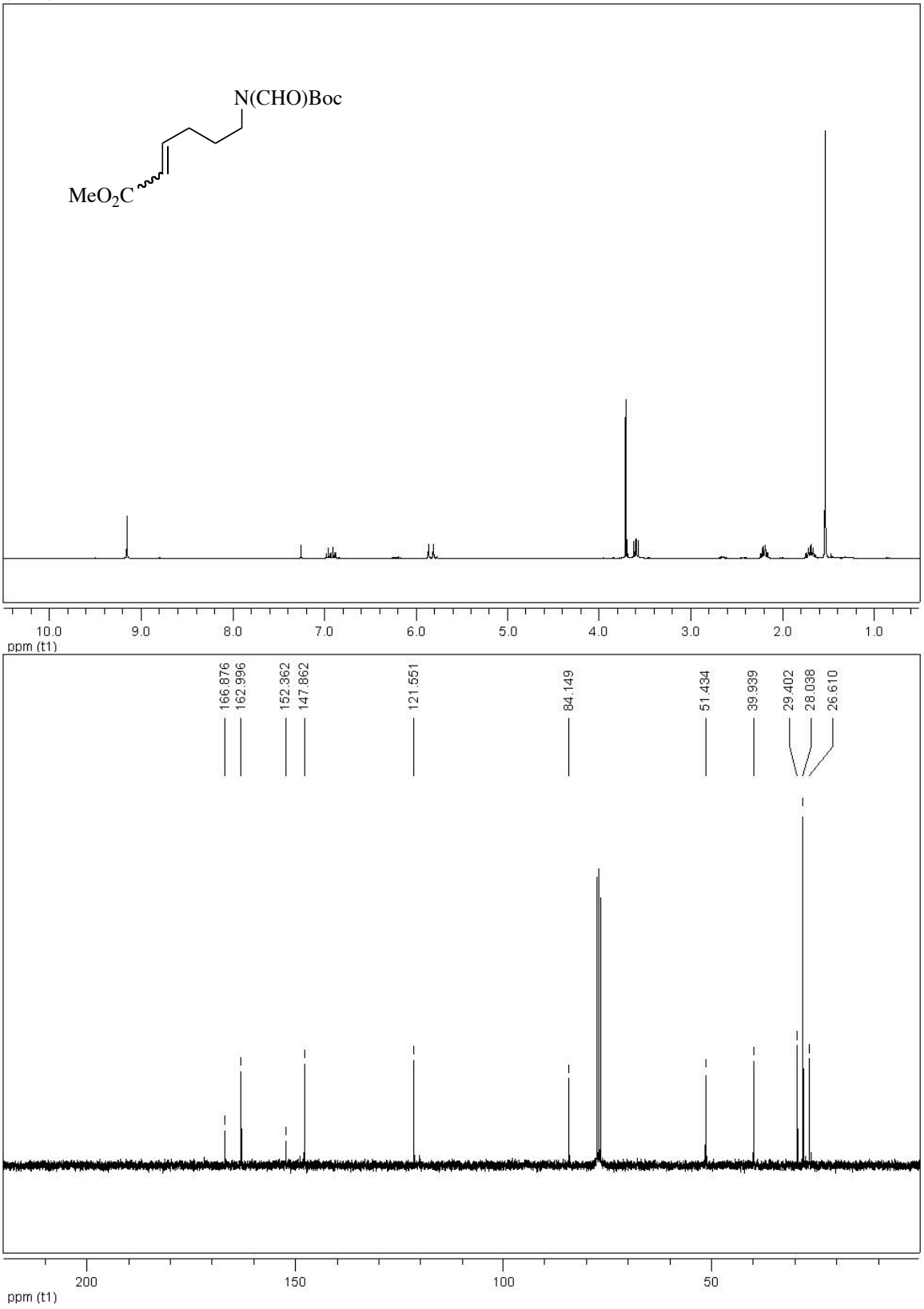
Methyl 2-(triphenylphosphoranylidene)acetate (179)



(*1S,2R*)-Methyl 2-(N-(tert-butoxycarbonyl)formamido)-3-((*E*)-3-methoxy-3-oxoprop-1-en-1-yl)cyclopropanecarboxylate (*trans:cis* = 94:6) (180)



(*E*)-Methyl 6-(N-(tert-butoxycarbonyl)formamido)hex-2-enoate (*trans:cis* = 90:10) (181)



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Marital status	Single

Education

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10/2007 - present	Pursuing Phd (organic chemistry under supervision of Prof. Dr. Oliver Reiser), Regensburg University, Germany.
07/2006	M.Sc (Organic Chemistry), Indian Institute of Technology(IIT)- Kharagpur, India.
09/2002	B.Sc (Chemistry), University of Calcutta, India.

Experience

10/2007 - present	Pursuing PhD in Synthetic Organic Chemistry as a **DAAD** fellow with Prof. Dr. Oliver Reiser, University Of Regensburg, Regensburg, Germany.
07/2006 - 05/2007	Worked as 'Junior Research Scientist' at Syngenta Biosciences Pvt. Ltd., Goa, India. Research towards the development of new agrochemicals (fungicides, herbicides and pesticides).
05/2005 - 06/2006	Project student under Prof. Dr. Sauman Hajra at the Department Of Chemistry, IIT- Kharagpur, India. Studies towards the synthesis of 'Azepine' core of (-)-Balanol.

Awards and Achievements

- National Scholarship, West Bengal Govt., India.
- Merit Scholarship, Indian Institute of Technology, Kharagpur, India
- Qualified for Graduate Aptitude Test in Engineering [GATE] – 2006.
- DAAD (Deutscher Akademischer Austausch Dienst) fellowship for doing PhD in Germany, 2007.
- Selected among young scientists worldwide to participate in the 59th Meeting of Nobel laureates, dedicated to Chemistry, Lindau, Germany, June 28th-July 3rd 2009.
- Discussion Leader Award at the 2nd INDIGO PhD Research Conference at Germany, October 3rd to 6th 2010.

Scientific Activities And Workshop

- Participant in the 59th Meeting of Nobel Laureates, dedicated to Chemistry, Lindau, Germany, June 28th - July 3rd 2009.
- Participated in the 117th BASF International Summer Course, Ludwigshafen, Germany, July 21st- July 31st, 2009.
- Attained 2nd German-Indian Symposium "Frontiers of Chemistry", Leipzig, Germany, 16-19th September, 2009 (Poster presentation).
- Active participant in the 3rd EuCheMS Chemistry Congress, Nurnberg, Germany, August 29- September 2, 2010 (Poster Presentation).
- Attained 22nd Lecture Conference of the GDCh-Division Photochemistry, Erlangen, Germany, 27-29th September 2010 (Poster presentation).
- Participated in the 2nd INDIGO PhD Research Conference and Intensive Course, Germany, 3-6th October 2010.

Publications

4. "L-Proline/$CoCl_2$ Catalyzed Highly Diastereo - and Enantioselective Direct Aldol Reactions"
Ananta Karmakar, **Tapan Maji**, Sebastian Wittmann and Oliver Reiser*, *Chem. Eur. J.* **(***Manuscript under preparation***)**

3. "Visible-Light Photoredox Catalysis: Dehalogenation of Vicinal Dibromo-, α-Halo-, and α,α-Dibromocarbonyl Compounds"
Tapan Maji, Ananta Karmakar and Oliver Reiser *, *J. Org. Chem*., **2011**, 76(2), 736-739.

2. "Iron(II)–bis(isonitrile) complexes: novel catalysts in asymmetric transfer hydrogenations of aromatic and heteroaromatic ketones",
Anu Naik, **Tapan Maji** and Oliver Reiser*, *Chem. Commun*., **2010**, 46, 4475–4477

1. "Stereoselective synthesis of (-)-chloramphenicol and (+)-thiamphenicol", Saumen Hajra,* Ananta karmakar, **Tapan Maji** and Amiya Kumar Medda. *Tetrahedron*, **2006**, 62, 8959-8965.

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