Asymetric Oxidation Reactions Catalyzed by Chiral Substituted Polymers / Nanoclusters; Synthesis of 6-(dimethylamino)-2-phenylisoindolin-1-one Derivative.

by

Bo Hao

B.S., Xiamen University, 2011

AN ABSTRACT OF A DISSERTATION

submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

Department of Chemistry
College of Arts and Sciences

KANSAS STATE UNIVERSITY
Manhattan, Kansas

2018

Abstract

The discovery of new methodologies to advance the fields of synthetic organic, nanoclusters, and polymer chemistry is critical in the asymmetric synthesis of organic compounds. Particularly, catalytic asymmetric oxidation reactions are economic. The oxidation reactions provide chiral molecules and additional functionality onto the molecules for functional group manipulation. New kinds of polymers, namely chiral-substituted poly-*N*-vinylpyrrolidinones (CSPVPs), stabilize the bimetallic nanoclusters such as Pd/Au or Cu/Au and induce chirality. These chiral polymers wrap around the nanometer-sized (~3 nm) bimetallic nanoclusters and catalyze a number of enantioselective oxidation reactions using oxygen or hydrogen peroxide as the oxidant. Cycloalkanediols were asymmetrically oxidized by 1 atm of oxygen gas to yield the corresponding hydroxyl ketone under the catalysis of Pd/Au (3:1) – CSPVP nanoclusters. Alkenes were oxidized by Pd/Au (3:1)-CSPVP nanoclusters under 2 atmospheric of oxygen in water to give the syn-dihydroxylated products in high chemical and excellent optical yields. Various cycloalkanes underwent regio- and enantio-selective C-H oxidation with Cu/Au (3:1)-CSPVP and 30% hydrogen peroxide to produce the corresponding chiral oxo-molecules in very good to excellent chemical and optical yields. We further discovered an enantioselective desymmetrization of α,α -dialkenyl-alkanols and α,α -dialkenyl-amino acid ethyl esters to give chiral disubstituted lactones and lactams, respectively. A number of medium-sized natural products and drugs were also oxidized regioselectively to give the corresponding mono-oxygenated products. A broad-spectrum predictive C-H oxidation of complex molecules is possible. Chapter 1 mainly discussed the synthesis and characterization of the new classes of chiral substituted PVP and bimetallic nanoclusters. Chapter 2 focus on various kind of oxidation reactions by the catalysis of CSPVP stabilized bimetallic nanoclusters.

Among various bioluminescence assays, firefly luciferase based bioluminescence assays are popular due to their high specific activity, low background noise and ease of use. However, it has been found that some aromatic carboxylic acid substantially inhibited the firefly luciferase reporter enzyme’s activity. In order to study firefly luciferase inhibition and the proteins associated with inhibition mechanism, we designed two 6-(dimethylamino)-2-phenylisoindolin-1-one derivatives as probe molecules. The synthesis of one probe molecule is discussed in Chapter 3 and the further investigation of its inhibitory activity on firefly luciferase is being conducted by our collaborator, Dr. Madoka Nakagomi at Itsuu Foundation, Japan.

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Approved by:

Major Professor
Dr. Duy H. Hua

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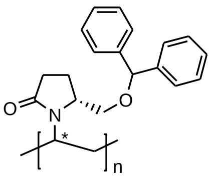

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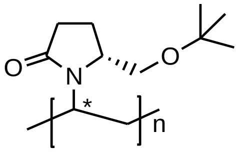

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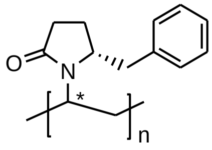

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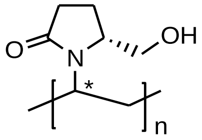

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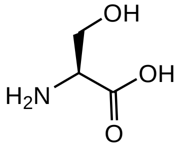

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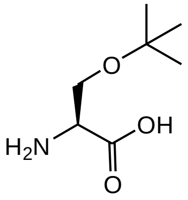

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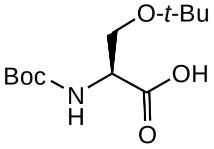

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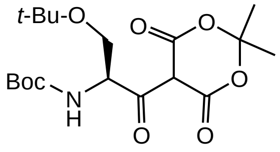

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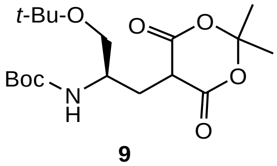

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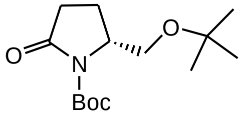

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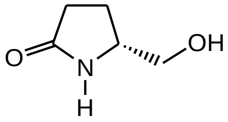

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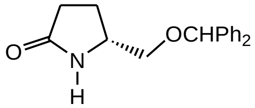

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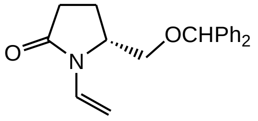

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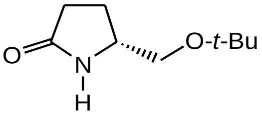

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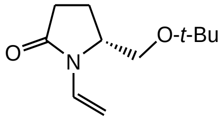

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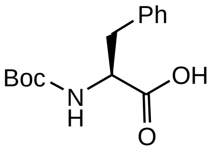

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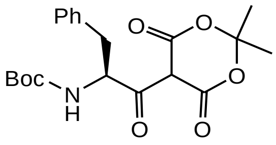
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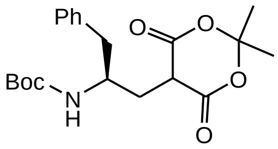
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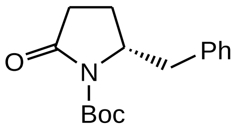
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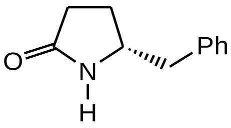
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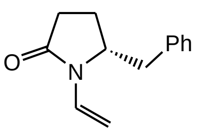
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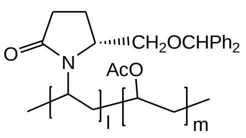
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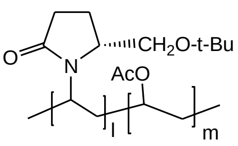
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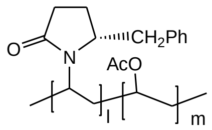
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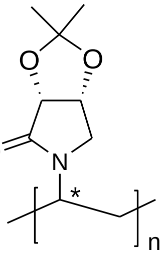
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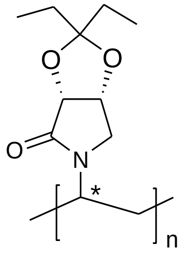
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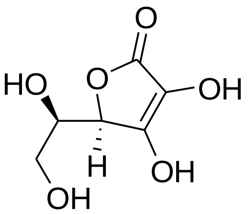
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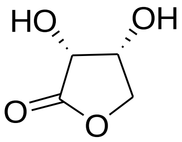
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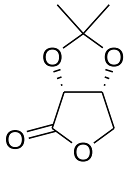
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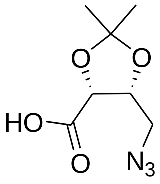
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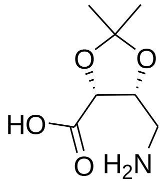
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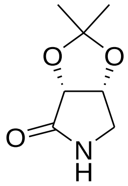
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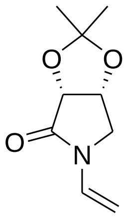
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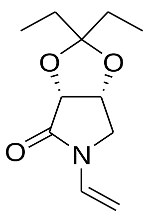
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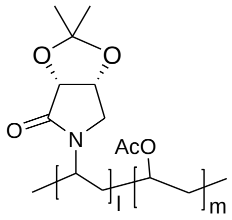
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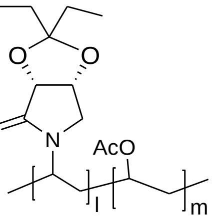
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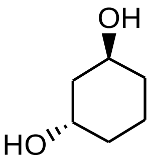
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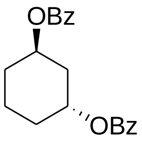
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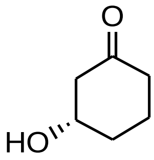
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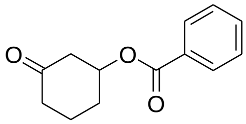
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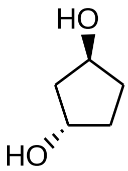
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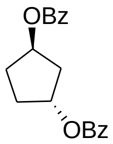
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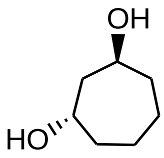
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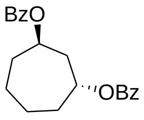
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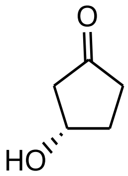
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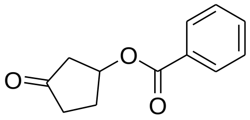
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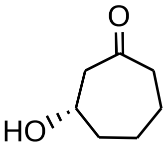
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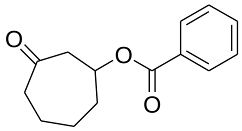
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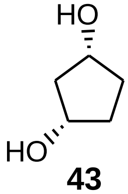
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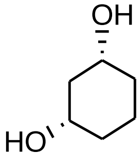
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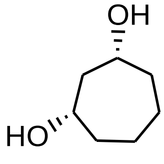
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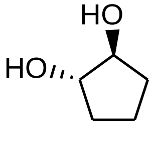
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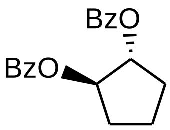

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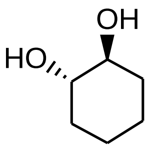

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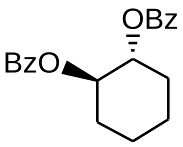

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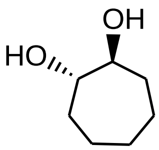

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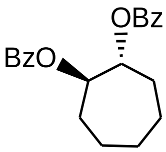

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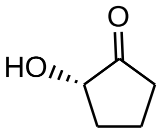

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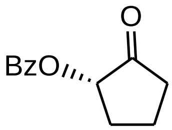

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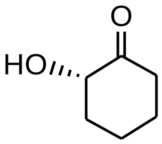
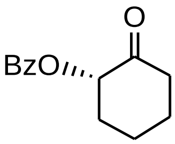
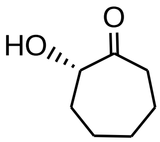


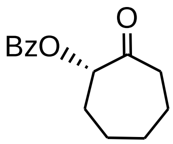
(S)-**50**



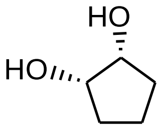
(S)-**50A**



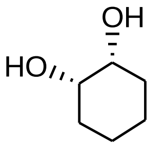
(*S*)-**51**



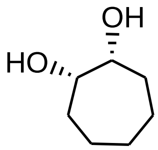
(*S*)-**51A**



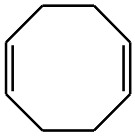
52



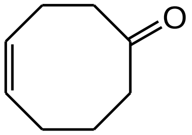
53



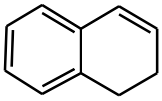
54



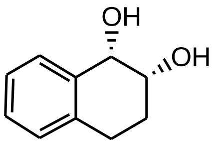
55



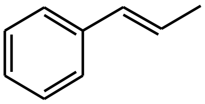
56



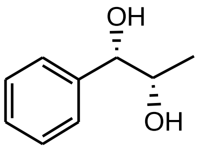
57



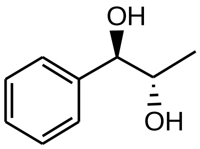
(1*S*,2*R*)-58

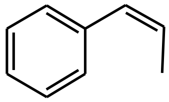


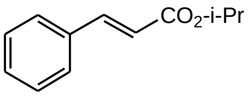
59

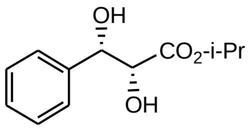


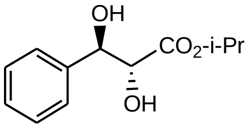
(1*S*,2*S*)-60

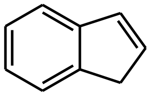

(1*R*,2*S*)-61

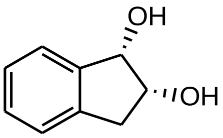

62

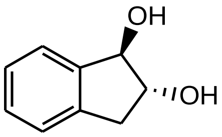

63

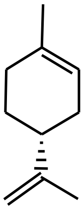

(2*R*,3*S*)-64

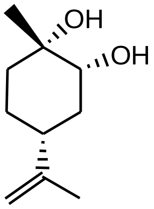

(2*R*,3*R*)-65

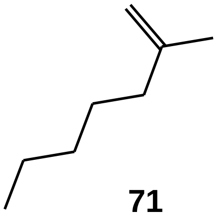

66

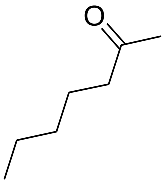

(1*S*,2*R*)-67

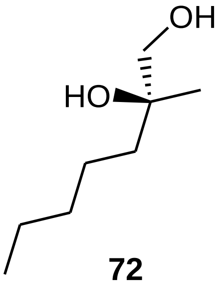

(1*R*,2R)-68

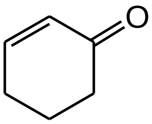

(*R*)-69

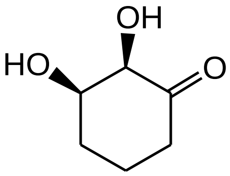

(1*S*,2*R*,4*R*)-70

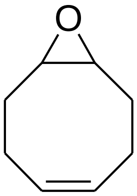

71

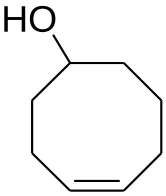

71A

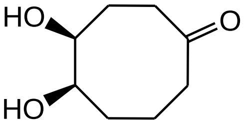

72

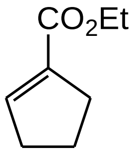

73

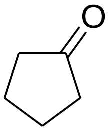

(2*R*,3*R*)-74

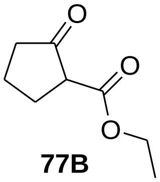

75

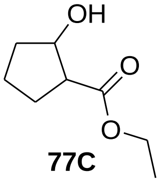

75A

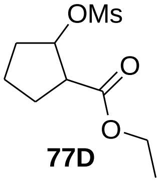

(4*S*,5*R*)-76

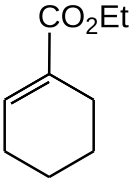

77


77A


77B


77C


77D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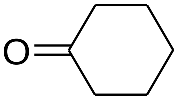
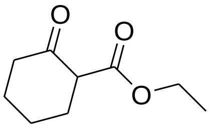
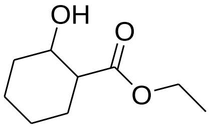

78A


78B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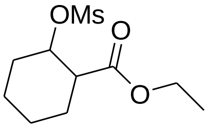
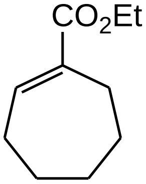

78D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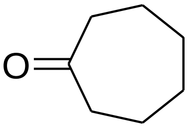
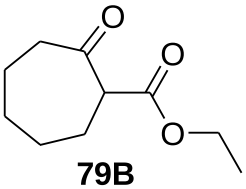
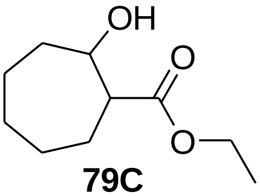
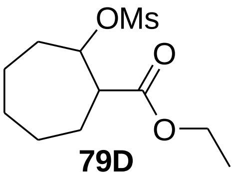
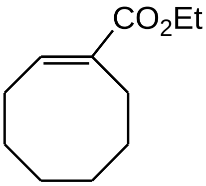

79A


79B


79C



79D



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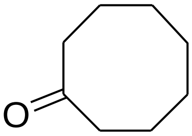
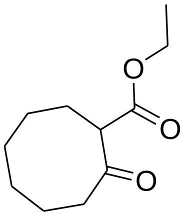
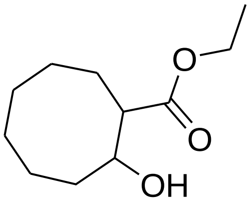


80A



80B



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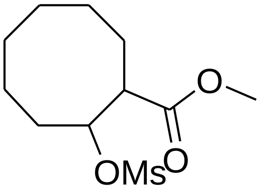
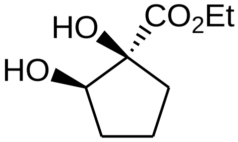
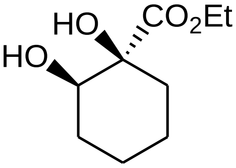


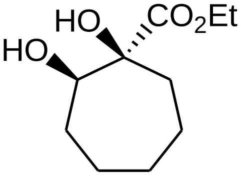
80D



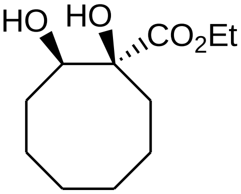
(*1S,2R*)-81



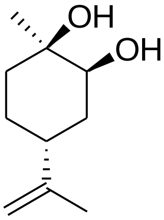
(*1S,2R*)-82



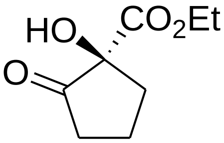
(*1S,2R*)-83



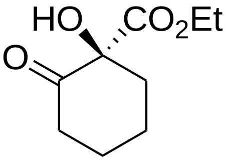
(*1S,2R*)-84



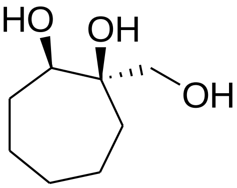
(1R,2S,4R)-85



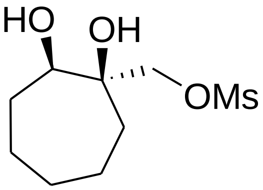
(*S*)-86



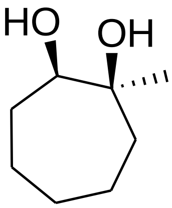
(*S*)-87



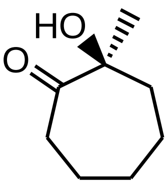
88



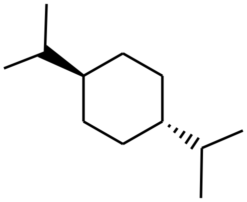
89



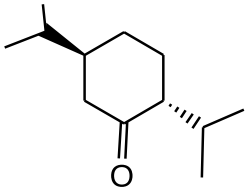
90



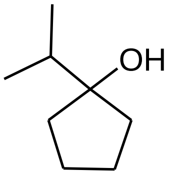
91



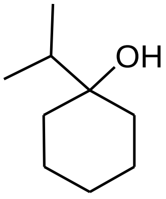
92



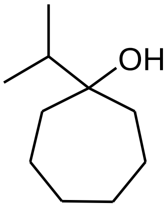
(2*R*,5*S*)-**93**



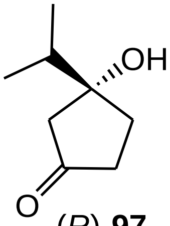
94



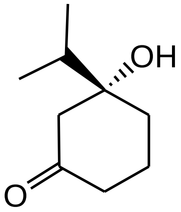
95



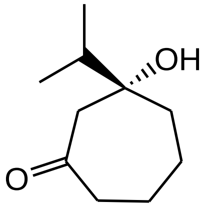
96



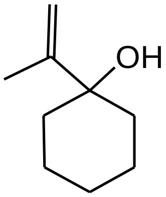
(*R*)-**97**



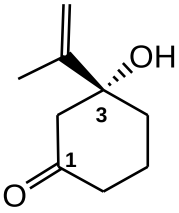
(*R*)-**98**



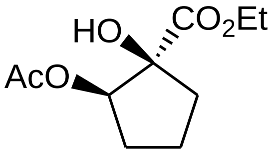
(*R*)-**99**



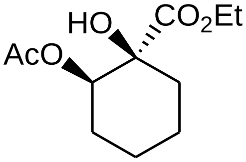
100



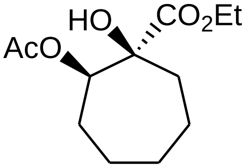
(*R*)-**101**



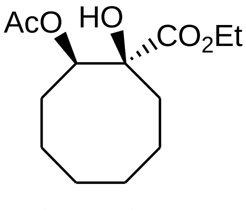
(1*S*,2*R*)-**102**



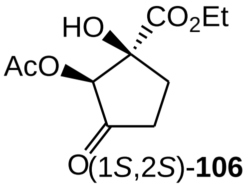
(1*S*,2*R*)-**103**



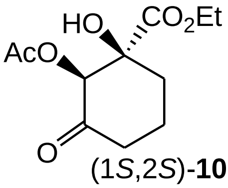
(1*S*,2*R*)-**104**



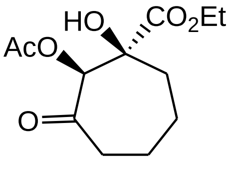
(1*S*,2*R*)-**105**



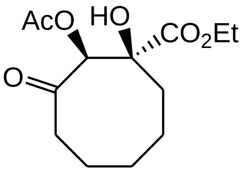
(1*S*,2*S*)-**106**



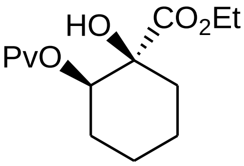
(1*S*,2*S*)-**107**



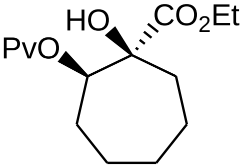
(1*S*,2*S*)-**108**



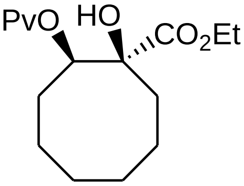
(1*S*,2*S*)-**109**



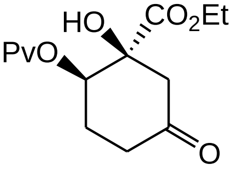
(1*S*,2*R*)-**110**



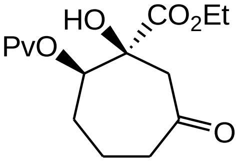
(1*S*,2*R*)-**111**



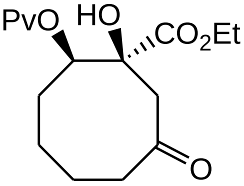
(1*S*,2*R*)-**112**



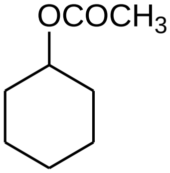
(1*S*,2*R*)-**113**



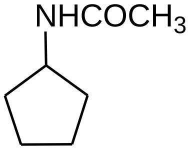
(1*S*,2*R*)-**114**



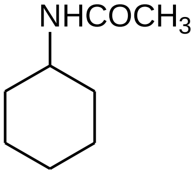
(1*S*,2*R*)-**115**



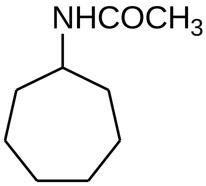
116



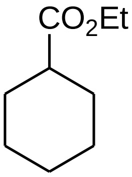
117



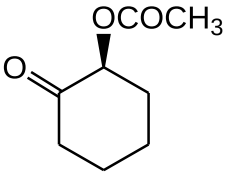
118



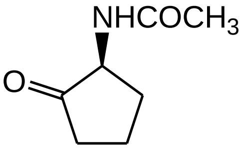
119



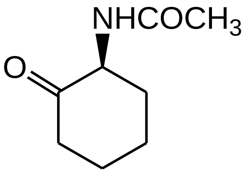
120



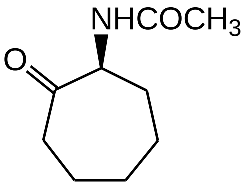
(*S*)-**121**



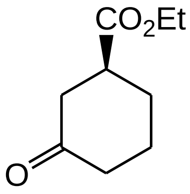
(*S*)-**122**



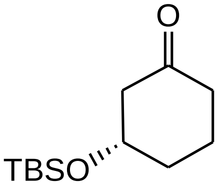
(*S*)-**123**



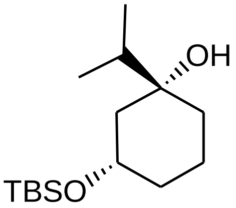
(*S*)-**124**



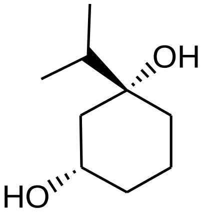
(*S*)-**125**



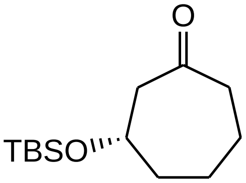
(S)-**126**



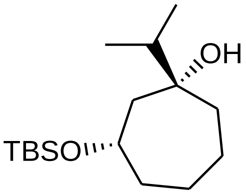
(1*R*,3*S*)-**127**



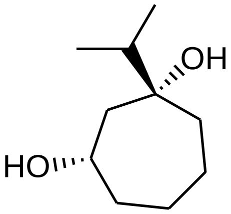
(1*R*,3*S*)-**128**



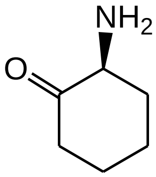
(S)-**129**



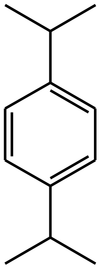
(1*R*,3*S*)-**130**



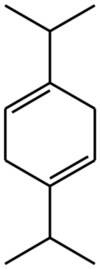
(1*R*,3*S*)-**131**



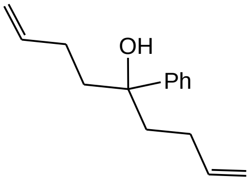
(S)-**132**



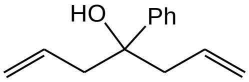
133



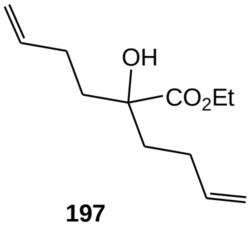
134



195



196



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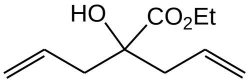

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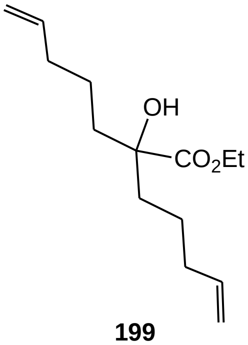

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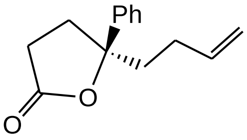
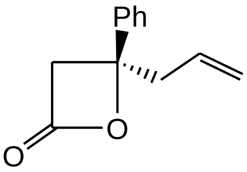
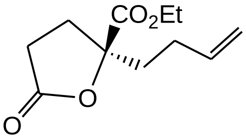


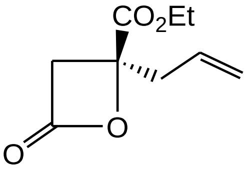
(S)-200



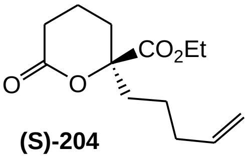
(S)-201



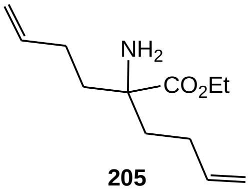
(S)-202



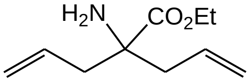
(S)-203



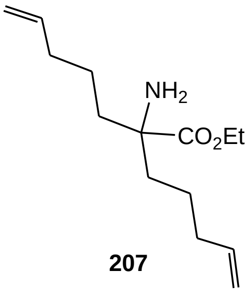
(S)-204



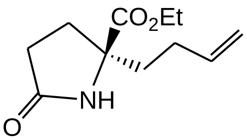
205



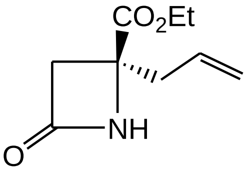
206



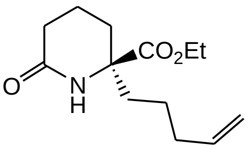
207



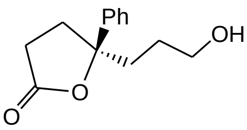
(S)-208



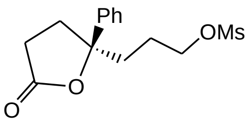
(S)-209



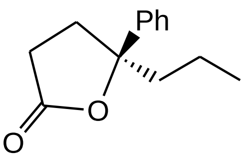
(S)-210



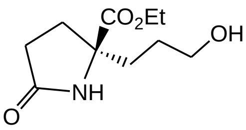
(*S*)-211



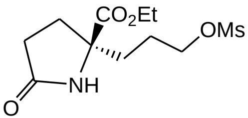
(*S*)-212

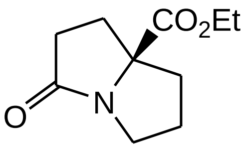


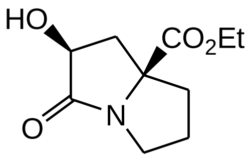
(*S*)-213

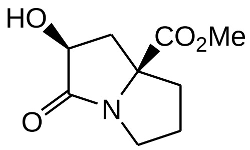


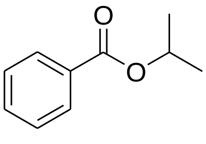
(*S*)-214

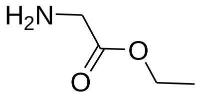

(*S*)-215

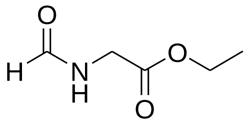

(*S*)-216


(2*S*,7a*S*)-217


(2*S*,7a*S*)-218


221


222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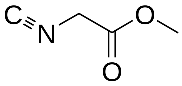
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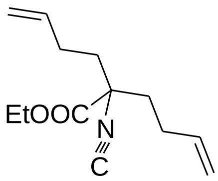
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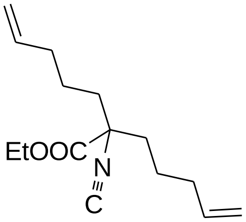
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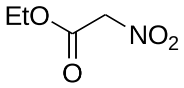
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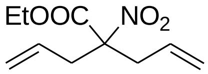
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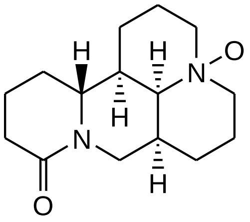
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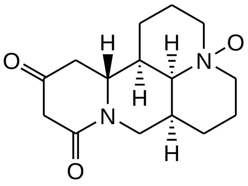
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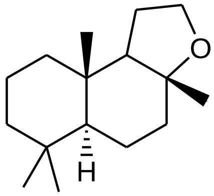
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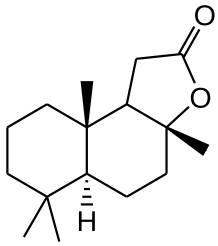
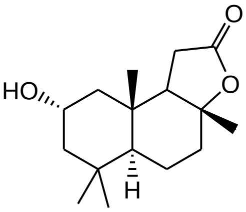

232



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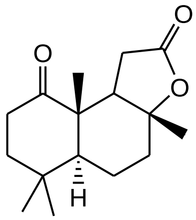

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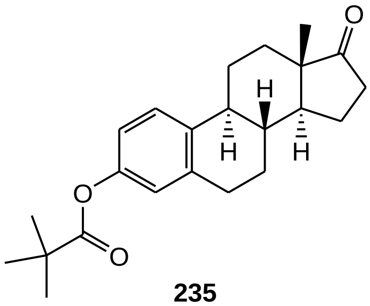

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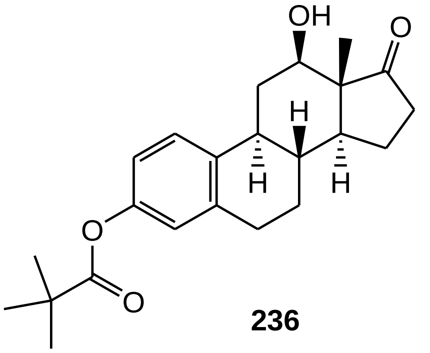

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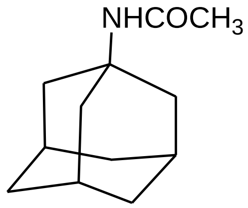

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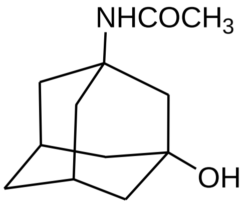

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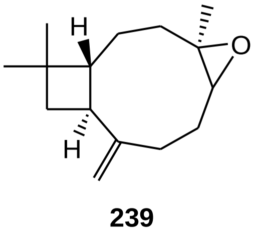

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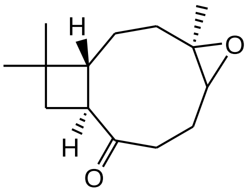

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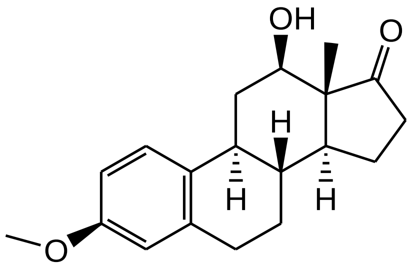

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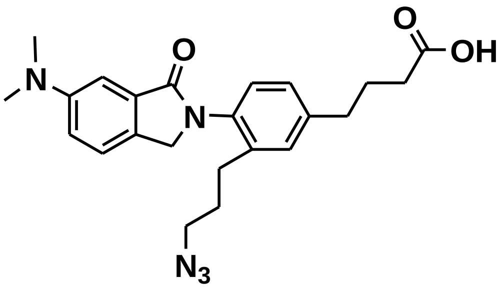

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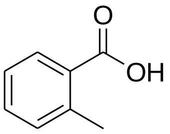

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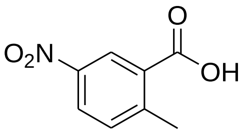

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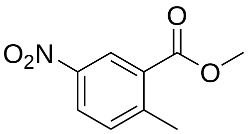

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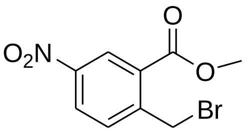

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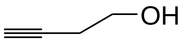

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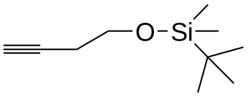

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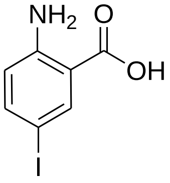

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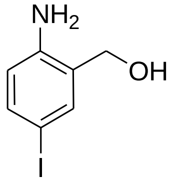

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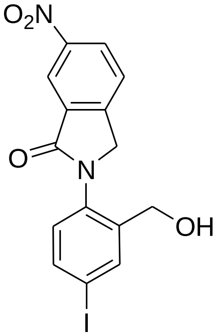

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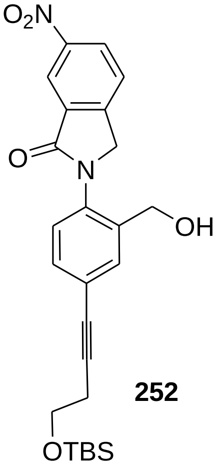

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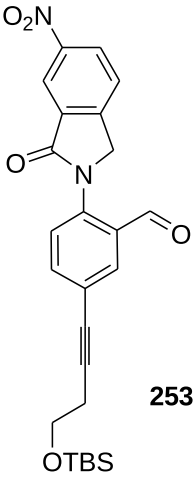

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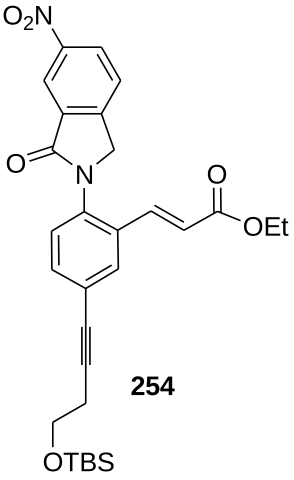

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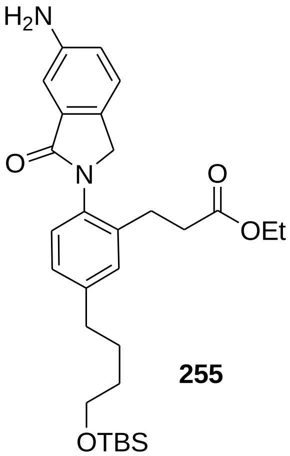

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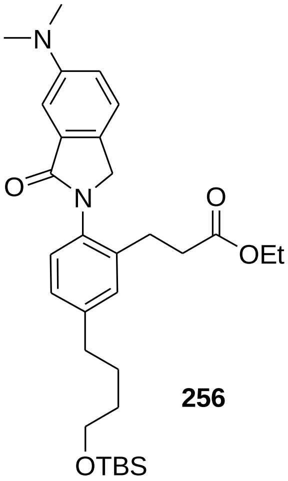

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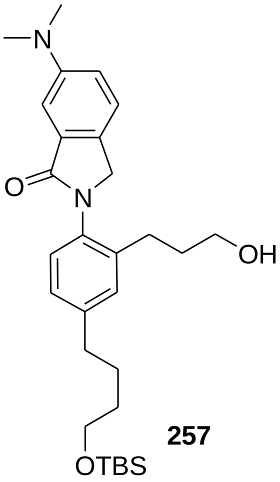

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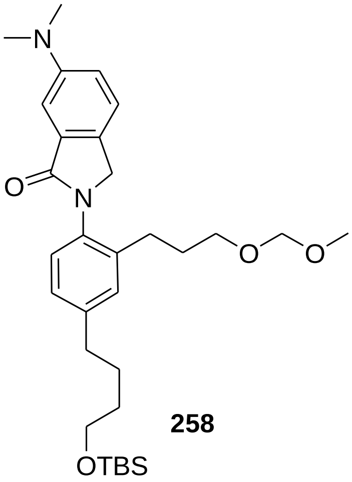

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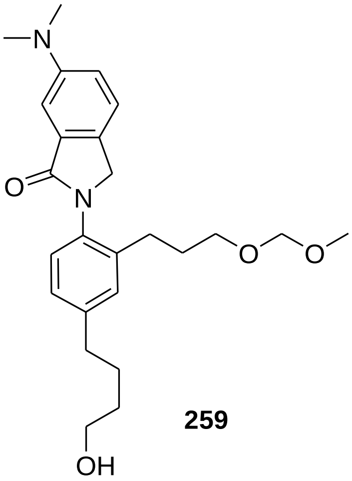

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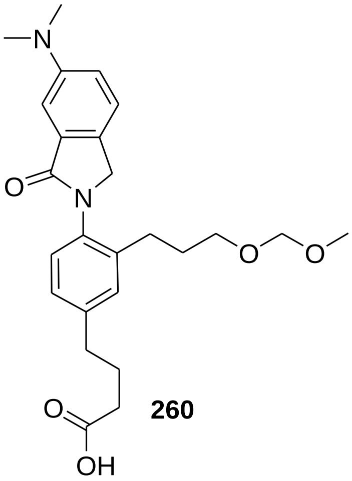

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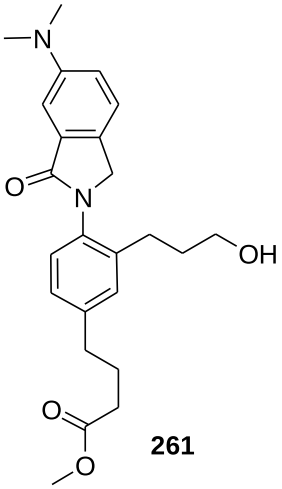

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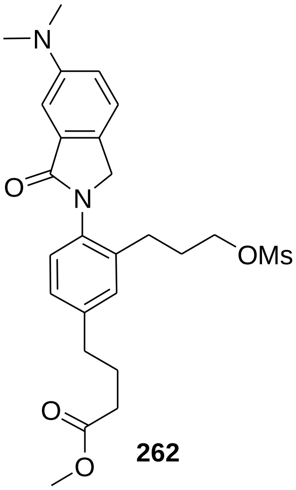

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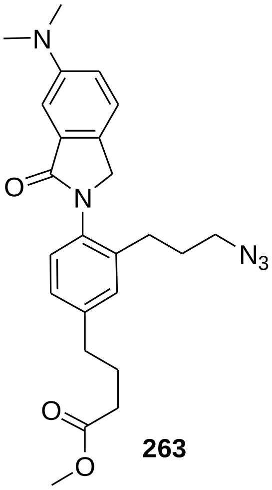

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δ	delta, chemical shift
ee	enantiomeric excess

List of Abbreviations

PVP	Poly-*N*-vinyl-pyrolidinone
PAMAM	Poly(amidoamine)
THF	Tetrahydrofuran
CSPVP	Chiral substituted poly-*N*-vinyl-pyrolidinone
AIBN	Azobis(isobutyronitrile)
NVP	*N*-vinylpyrrolidone
DMF	Dimethylfomaide
DP	Degree of polymerization
GPC	Gel Permeation Chromatography
DLS	Dynamic Light Scattering
AFM	Atomic Force Microscopy
NMR	Nuclear magnetic resonance
TEM	Transition electron microscopy
XPS	X-ray photoelectron spectroscopy
CD	Circular dichroism
TON	Turnover Number
DCM	Dichloromethane
EA	Ethyl Acetate
HTS	High throughput screening
ATP	Adenosine triphosphate
D-LH$_2$	D-isomer of firefly luciferin
AMP	Adenylate
Co-A	Coenzyme A
NBS	N-Bromosuccinimide
TBSCl	*Tert*-Butyldimethylsilyl chloride
EtOH	Ethanol
PCC	Pyridinium chlorochromate
DIBAl-H	Diisobutylaluminium hydride

MOMCl	Chloromethyl methyl ether
DIPEA	*N*,*N*-Diisopropylethylamine
IBX	2-Iodoxybenzoic acid

Acknowledgements

First of all, many thanks go to my advisor Dr. Duy H. Hua and his wife Mrs. Sadami Hua. It is really my honor to have a chance to work in the Hua's group. From here, I got systematic training of how to be a qualified synthetic chemist. Dr. Hua is the one who told me never give up. Except all of the synthetic techniques, he also taught me the importance to be a reliable and responsible person. Mrs. Sadami Hua is a super-nice lady who always cares about the group members and shares delicious home-made cookies with us.

Then, I would like to thank all my committee members, Dr. Stefan H. Bossmann, Dr. Ping Li and Dr. Wenjun Ma for their generous suggestions, helps and dedications during my Ph. D. study. Really appreciate it.

I would like to give my thanks to my labmates in the Hua group, Dr. Jianyu Lu, Dr. Serkan Koldas, Dr. Sahani Weerasekara, Dr. Man Zhang, Dr. Medha J. Gunaratna, Dr. Huafang Fan, Dr. Fei Ma, Mr. Zongbo Tong, Mr. Kyle Apley, Ms. Sarah Seiwald, Mr. Vu Nguyen, Mr. Eric Carlson and Mr. Alex Meier for their excellent teamwork in different projects. Thank all my collaborates and friends for providing analytical instrument for different analysis.

Thank K-State Chemistry Department for all of the technique support. Thank the department faculties and staff, Mr. Jim Hodgson, Dr. Leila Maurmann, Dr. Simon Sham, Mr. Ron Jackson, Mr. Tobe Eggers, Dr. Tingting Liu, Ms. Mary Dooley and Ms. Kimberly Ross and others for their kind help in my five years.

Dedication

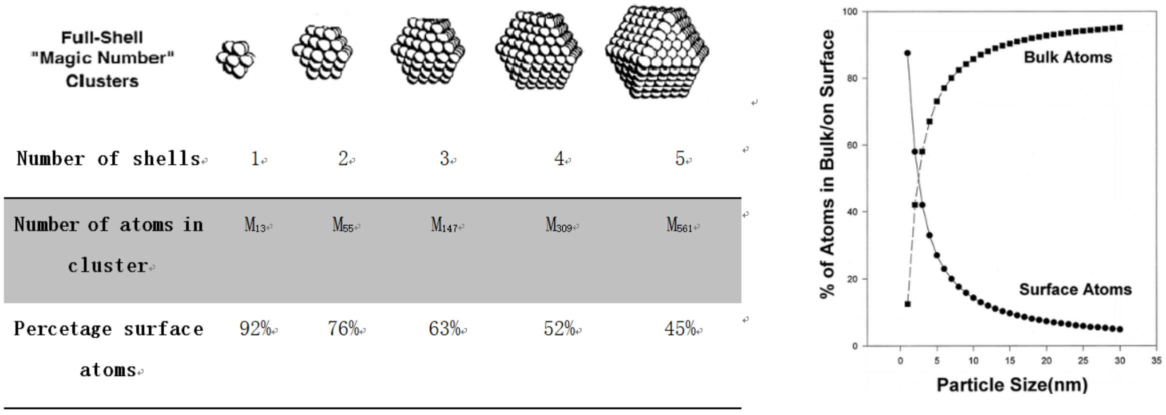
My beloved wife, Jiawei Gong, and my parents: Mr. Jianmin Hao and Mrs. Lianqing Chu. They are the ones who always stand by my side and encourage me all the time during my Ph.D. study. Thank all my friends in and outside the United States for their companion and friendship in my five years abroad study.

Chapter 1 - Synthesis and Characterization of Chiral Substituted Poly-*N*-vinylpyrrolidones and Bimetallic Nanoclusters

(Partial of the results and discussions in this chapter was published[1] and adapted with permission of *Journal of the American Chemical Society*. Copyright © 2016 American Chemical Society.)

1.1 Background and Significance

Catalyst is considered as a chemical compound capable of directing and accelerating reactions while remaining unaltered at the end of the reactions. There are many types of catalysts used in the industry or specific reactions, including transition metal salts,[2] organic molecules,[3] enzymes,[4] organometallic compounds,[5] etc. They can be divided into groups as heterogeneous, homogeneous and biological.[6] Beside the biological catalyst, the homogeneous catalysts mostly have higher catalytic activity since it can dissolve in the solvent and contact with the substrates directly. However, they often decompose rapidly during the reaction conditions.



Full-Shell "Magic Number" Clusters					
Number of shells	1	2	3	4	5
Number of atoms in cluster	M_{13}	M_{55}	M_{147}	M_{309}	M_{561}
Percetage surface atoms	92%	76%	63%	52%	45%

Figure 1. Inverse Relationship Between the Total Number of Atoms in Full Shell Clusters and the Percentage of Surface Atoms.

Transition metal nanoclusters gain great interest recently due to their unique chemical and physical properties result from their nano-dimensions.[7] Metal clusters have a geometry rule which is designed full-shell or magic number clusters. The number of atoms increases while the percentage of the surface atoms reduced. (**Figure 1**[8])

Transition metal nanoclusters are nearly monodispersed particles and generally are less than 4 nm in diameter. They have generated great attentions over the past decade. Nanoclusters also have notable potential as new type of catalysts and they also have high activity and selectivity than standard metal catalysts. Without stabilizing material, the metal nanoclusters likely aggregate, due to their high surface area to volume ratio. To overcome aggregation and provide high nanoclusters stability, polymer-stabilized metal nanoclusters have been used.[9]

Polymer science, which focuses on primarily synthetic polymers, becomes a hot research area in the recent years. Developing methods for the synthesis of polymer with specific functional is critical on both research and industry purpose. Polymer-stabilized chiral catalysts and reagents have received considerable attention in regard to organic synthesis of optically active compounds.[1] The use of polymer-stabilized catalysts has become one of the essential techniques in organic synthesis. [10-12] From the point of view of green chemistry, the polymer-stabilized chiral catalysis method provides a clean and safe alternative method of asymmetric processes. Not only their practical aspect but also the particular microenvironment they may create in a polymer network will make them attractive for utilization in organic reactions, especially in stereoselective synthesis. Chiral polymer synthesis that is directed toward chiral catalysts must be developed. In this case, the polymer, which will be used for the stabilization of bimetallic nanoclusters as asymmetric catalyst, need to induce a stereogenic center on the polymers.

Most polymeric support materials used for the chiral catalyst have been crosslinked polystyrene derivatives, mainly because of their easy preparation and introduction of functional groups on the side chain of the polymer.[13, 14] Each polymer support would provide a specific microenvironment for the reaction if they can be precisely designed.

Alloying has been serving as an effective method for modifying the catalytic properties of transition-metal surfaces. Supported bimetallic clusters regularly exhibit catalytic properties superior to those of their single-metal counterparts.[15-17] For this reason, they have attracted great interest in recent years [16, 18]. Due to the high ratio of surface area and volume, different kinds of supporting materials are needed, including inorganic oxides, carbon,[19] organic ligands,[20] organic polymers,[10] etc. However, the use of chiral polymers as supporting material and chiral inducers has not been developed. Herein, poly-*N*-vinylpyrrolidinone, which is so called PVP as abbreviate, have been focused and chiral substituted PVP was designed and synthesized. Normally, PVP is a polymeric fine chemical obtained from its monomer, *N*-vinylpyrolidinone (NVP), by free radical polymerization in laboratory. It is soluble in water with a very high solubility, and also soluble in most of the organic solvent, such as alcohols, carboxylic acids, halogen alkanes, esters, ketones and THF. Moreover, PVP is relatively stable under high temperature and no significant changes under 250 ^{o}C.

1.2 Synthesis of Chiral Substituted Poly-*N*-vinylpyrrolidinone

Poly-*N*-vinylpyrrolidinone, as a chain polymeric material, has two ways to induce the chirality including side-chain chirality and main-chain chirality[21].(**Figure 2**) Since there are only two carbon the backbone of PVP in each unit and polymerization with the radical mechanism, it is difficult to control the chirality on the main-chain of PVP. Making a chiral substituted

N-vinylpyrrolidinone, as the monomer of chiral substituted PVP, becomes important and sufficient. In particular, with the successful synthesis of CSPVP, we realized the tacticity of CSPVP is not randomly assembled in certain cases. I will discuss it later.[22]

Figure 2. Polymer Having a Side-chain Chiral Ligand or Main-chain Chiral Ligand.

On the five-membered pyrrolidinone ring, there are three secondary carbons which can induce the stereogenic center. Base on that, we designed and synthesized two classes of CSPVPs. One is the 5-substituted chiral polymer, and the other one is the 3,4-disubstituted chiral polymer. (**Figure 3**)

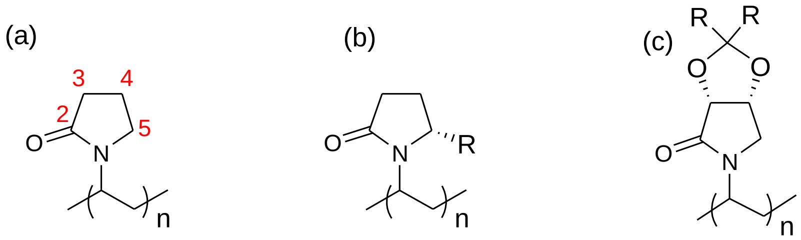


Figure 3. (a) PVP (b) 5-substituted Chiral PVP (c) 3,4-disubstituted Chiral PVP.

1.2.1 Synthesis of 5-Substituted Chiral PVP

We synthesized four 5-substituted chiral PVPs **1** – **4** from cheap optically pure amino acids. (**Table 1**) The synthetic procedure can be divided into two parts, the synthesis of the corresponding monomer and polymerization.

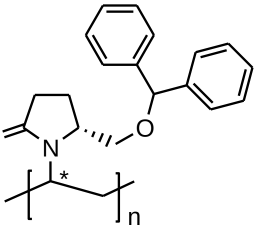
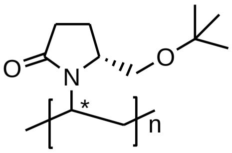
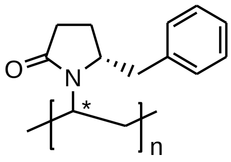
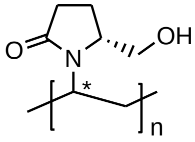
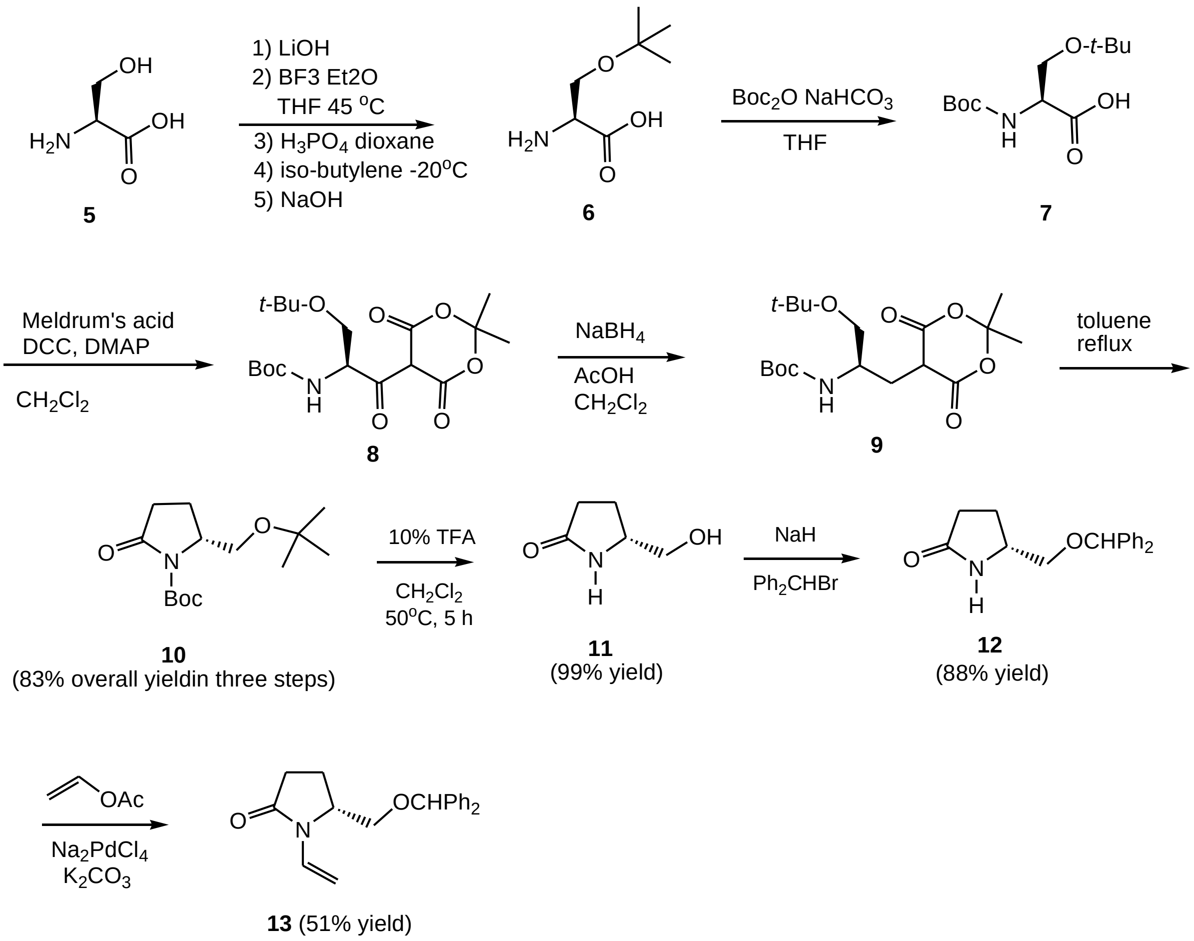
			
1 MW 106,000	**2** MW 68,000	**3** MW 76,000	**4** MW 56,500

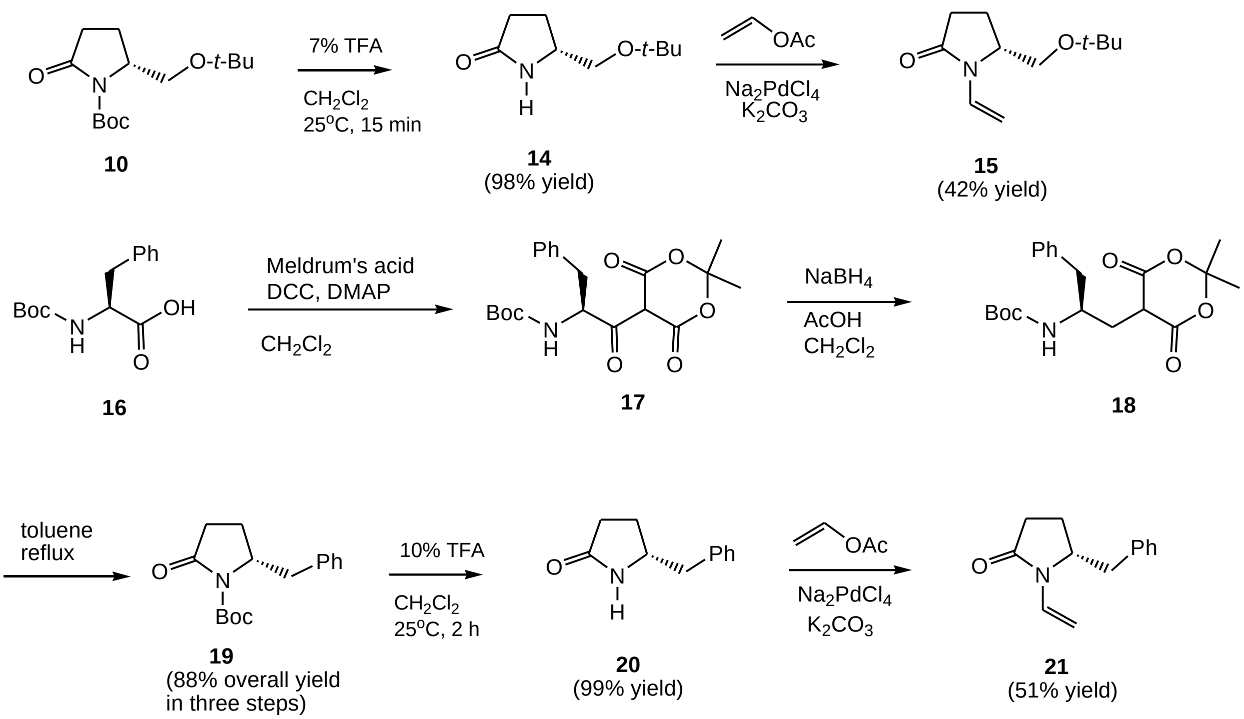
Table 1. 5-Substituted Chiral PVP 1 – 4.

The synthetic route for the monomer of CSPVP **1** is shown in **Scheme 1**. Chiral compounds **11** were made from L-amino acids by following a reported procedure.[23-26] *N*-Boc-*O*-*t*-butyl L-serine **7** is commercially available material or made from L-serine **5**. L-serine was basified with LiOH, complexed with BF_3•EtO_2 to protect both amino group and carboxylic acid, followed with protecting the hydroxyl group by isobutylene and removed boron complex with NaOH to afford *O*-*tert*-butyl L-serine (**6**). The amino group in compound **6** was protected by Boc_2O in the presence of base to give compound **7**. Compound **7** was coupled with Meldrum's acid with coupling reagent DCC and DMAP, followed by reduction of the ketone function with sodium borohydride, cyclization under heat, and removal of both the Boc group and *O*-*tert*-butyl group with trifluoroacetic acid (TFA) in CH_2Cl_2 under 50 ^{o}C to give compound **11**. Consequently, (*R*)-5-benzhydryloxymethyl-2-pyrrolidinone (**12**) was synthesized from the alkylation of compound **11** with sodium hydride and benzhydryl bromide. *N*-Vinylation of **12** with Na_2PdCl_4, K_2CO_3 and vinyl acetate[27] under anhydrous condition gave corresponding *N*-vinylpyrrolidinones **13** with 51% yield.



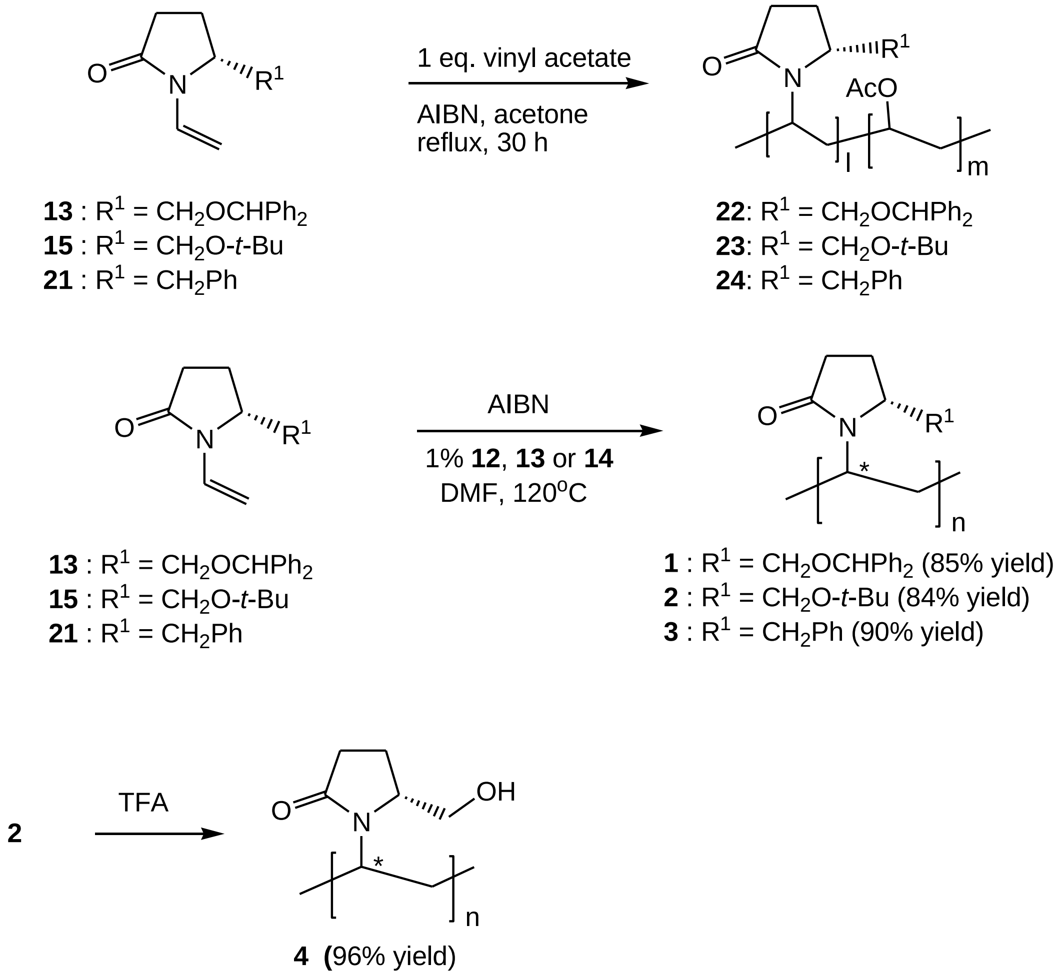
Scheme 1. Synthesis of *N*-vinyl-5-benzhydryloxymethylpyrrolidinone (13).

Notably, if compound **10** with 10% TFA in methylene chloride being refluxed under 50 °C for 5 hours, both the Boc group and *O*-*tert*-butyl group were removed. However, under room temperature for 2 hours, only Boc group in compound **10** was removed by 10% TFA in methylene chloride to give compound **14**. Compound **15** was obtained by the *N*-vinylation of compound **14** with vinyl acetate by the catalysis of Na_2PdCl_4 under base condition.[27] Moreover, the synthesis of compound **21**, as the monomer of CSPVP **3**, can be made with similar method from Boc-phenylaniline. (**Scheme 2**)



Scheme 2. Synthesis of *N*-vinyl-5-substituted pyrrolidinone 15 & 21.

The preparation of poly-*N*-vinyl-5-substituted pyrrolidinone **1 - 3** were carried out by dispersion polymerization with *N*-vinyl-5-substituted pyrrolidinone (CSNVP) **13**, **15**, **21**, as initial monomer, poly(*N*-vinyl-5-substituted pyrrolidone-*co*-vinyl acetate) **22 - 24** as dispersant, and 2, 2′-azobisisobutyronitrile (AIBN) as initiator.[28] (**Scheme 3**) The copolymerization process of CSNVP **13**, **15**, **21** and 1 equiv of vinyl acetate with a free radical initiator for both vinyl compounds were refluxed in acetone to give corresponding copolymer. After the formation of copolymer, hexane was added to precipitate the polar polymer from acetone. For the polymerization of CSNVP, Zhai’s group prepared polyvinylpyrrolidone (PVP) microspheres in ethyl acetate by dispersion polymerization with NVP as initial monomer, poly(*N*-vinylpyrrolidone-*co*-vinyl acetate) (P (NVP-*co*-VAc)) as dispersant, and AIBN as free radical initiator.[28] Since the monomer, *N*-vinyl-5-substituted pyrrolidinone, is much more bulky than normal NVP, the connection of the free radical on the vinyl carbon becomes much more difficult and needs higher energy to form the backbone of polymer. High temperature and high concentration of the monomer was conducted in the polymerization step. Polymerization of **13**, **15**, **21** separately with a catalytic amount of AIBN and in the presence of 1% of respective copolymer **22** − **24** in DMF at 120 ℃ for 7 days gave polymers **1** − **3**. CSPVP is soluble in DMF and diethyl ether is also needed to isolate CSPVP from solvent. Polymer **4** was prepared through the removal of the *tert*-butyl group of polymer **15** with 10% TFA in dichloromethane. All the four CSPVPs are white solid and gradually become sticky after exposing in the air with the absorption of moisture.



Scheme 3. Polymerization for 5-substituted Chiral PVP.

The modification of CSPVP, such as the step from CSPVP **2** to CSPVP **4,** provides a sufficient method to get new CSPVP containing different functional group with different size and properties. I have also tried to synthesize CSPVP **1** from CSPVP **4** by treatment CSPVP **1** with NaH and benzhydryl bromide. Under a very harsh reaction condition, only 92% of the units were reacted and remained 8% of hydroxyl group on the new polymers. It is because the bulky group is difficult to connect onto the limited space in the polymers in some certain tacticity of CSPVP. It also gives side evidence that the 5-substituted chiral PVP, at least CSPVP **4** is atactic. It can also be confirmed by ^{13}C NMR which shows many sets of signal on the similar carbon from different units. Both *R*- and *S*-stereochemistry (labelled * in **Table 1**) are likely presented in the stereogenic center in the polymer alkane backbone, and they are not identifiable. Presumably, this stereogenic center of the polymers can be isotactic, atactic, and syndiotactic. [29]

1.2.2 Synthesis of 3,4-Disubstituted Chiral PVP

With the experience from the successful synthesis of 5-substituted chiral PVP, a new class of CSPVP was designed, due to the hypothesis that in the bimetallic CSPVP nanoclusters, the substituent on the pyrrolidinone ring controls the stereochemical outcome of the reactions, resulting in asymmetric oxidations. Two new polymers **25** & **26** (**Table 2**) are derived from D-isoascorbic acid (**27**), an inexpensive starting material comparing with chiral amino acids especially the unnatural amino acids.

The synthesis of polymer **25** & **26** was achieved from the corresponding monomer **33** & **34**. Chiral compound **32** was made from D-isoascorbic acid by following a reported procedure.[22, 30, 31] (**Scheme 4**) D-Isoascorbic acid (**27**) was oxidative cleaved by 30% hydrogen peroxide and sodium carbonate. Acetonide formation was carried out by the coupling of compound **28** with acetone under the catalysis of anhydrous $CuSO_4$. Compound **29** was treated with sodium azide in *N*,*N*-dimethylformamide (DMF) at 100°C to open the lactone ring with S_N2-type mechanism, followed by the reduction of the azido function with hydrogen and Pd/C in methanol and yielded very polar compound **31**. After heating compound **31** under high vacuum and heat (120 °C), compound **32** is formed and sublimated by using a sublimator. Vinylation of chiral lactam **32** with vinyl acetate (distilled), potassium carbonate and catalytic amount of freshly prepared Na_2PdCl_4 at 50°C gave *N*-vinyllactam **33** in an 80% yield.[27] Compare with 5-substituted pyrolidinone, the yield of vinylation significantly increased, may due to the steric hinderance effect in **1** - **4**. The nitrogen in compound **33** is on a much opener site for an easier, faster vinylation and avoiding the side products.

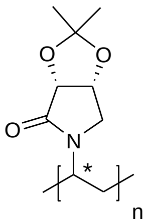
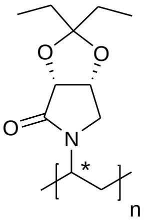
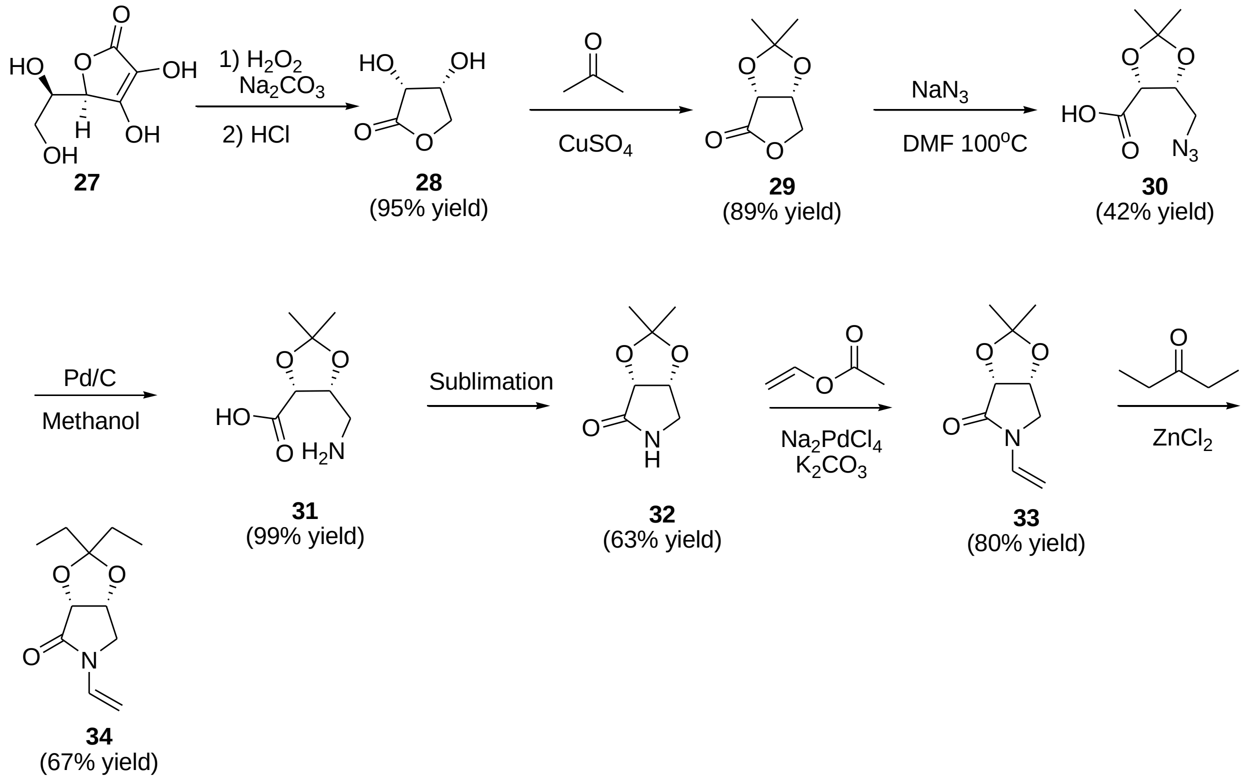
	
25 MW 75,000	**26** MW 92,000

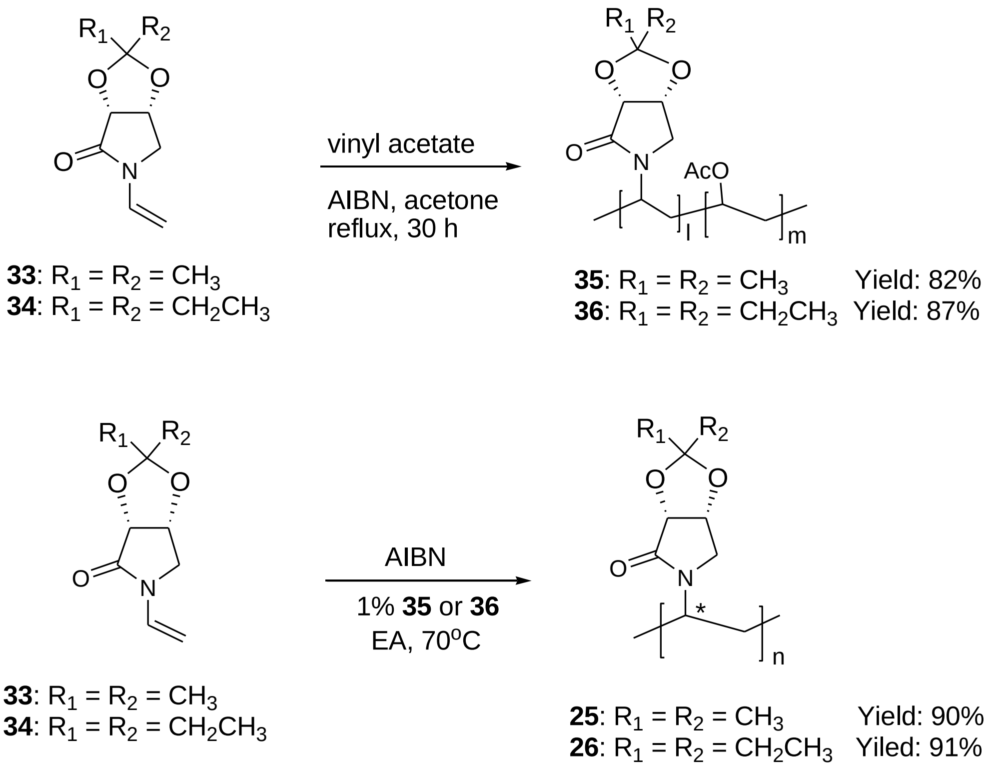
Table 2. 3,4-Disubstituted Chiral PVP 25 & 26

To get compound **34**, similar procedure was done by using 3-pentanone instead of acetone to give (*3aR,6aR*)-2,2-diethyl-dihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one. After the azidation, reduction and sublimation, a new pyrrolidinone analog with diethyl group was obtained and became difficult for the vinylation without clear reason. Therefore, a new ketal exchange reaction was discovered by dissolving compound **33** in 3-pentanone with adding zinc chloride under 65 °C to distill off the produced acetone for 40 hours to yield 67% of the desired product **34**.



Scheme 4. Synthesis of *N*-vinyl-3,4-disubstituted pyrrolidinone 33 & 34.

Similar to CSPVP **1–4**, CSPVP **25 & 26** were prepared separately in about 90% yield by heating *N*-vinyl pyrrolidinone derivatives **33** & **34**, 1% of respective copolymer **35** & **36** and a catalytic amount of azobisisobutyronitrile (AIBN) in ethyl acetate at 70 ^{o}C for 2 days. The polymerization conditions are milder and reactions time are significantly dropped, comparing with CSPVP **1–4**, may also due to the size of the CSNVP.



33: $R_1 = R_2 = CH_3$
34: $R_1 = R_2 = CH_2CH_3$

35: $R_1 = R_2 = CH_3$ Yield: 82%
36: $R_1 = R_2 = CH_2CH_3$ Yield: 87%

33: $R_1 = R_2 = CH_3$
34: $R_1 = R_2 = CH_2CH_3$

25: $R_1 = R_2 = CH_3$ Yield: 90%
26: $R_1 = R_2 = CH_2CH_3$ Yiled: 91%

Scheme 5. Polymerization for 2,3-Disubstituted Chiral PVP 25 & 26.

1.2.3 Characterization of Chiral Substituted PVP

All the CSPVPs are water soluble and their molecular weights were determined by gel permeation chromatography with CSPVP water solution in Dr. Shi's Lab in Grain Science, KSU. (**Figure 4**) TSKgel GMHxl column was used and THF as eluent solvent with a flow rate of 1 mL/min. The molecule weight (Mw) was shown in **Table 1** and **Table 2**. Base on the calculation, the degree of polymerization for CSPVP **1**, **2**, **3**, **25**, **26** are 345, 345, 378, 409, 436, respectively, which means the method for polymerization is constant. Because the relatively difficulty for the polymerization, degree of polymerization (DP) of CSPVP **1**–**3** are smaller than CSPVP **25** & **26**.

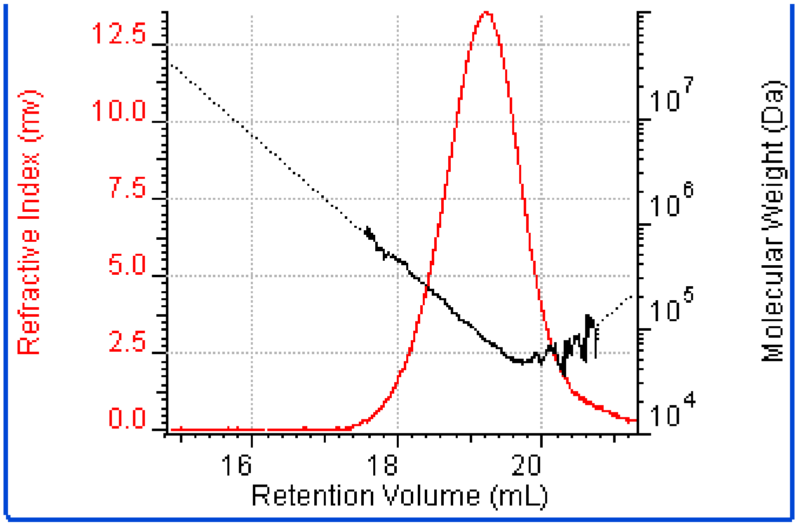


Figure 4. Gel Permeation Chromatography Chart of CSPVP 1.

The polydispersity index is used as a measure of the broadness of a molecular weight distribution of a polymer, and is defined by: Polydispersity index (PI) = Mw / Mn. The number average molecular weight, abbreviate as Mn, is the statistical average molecular weight of all the polymer chains in the sample, and the weight average molecular weight, shown as Mw, is quoted for a molecular weight distribution. There is an equal weight of molecules on either side of Mw in the distribution. The larger the polydispersity index, the broader the molecular weight. A monodisperse polymer where all the chain lengths are equal has an Mw/Mn = 1. Base on the results from GPC, the polydispersity index for CSPVPs are around 1.05 to 1.1.(**Table 3**) The result suggested the size of CSPVPs are uniform from the dispersion polymerization method[28] and may give constant results on the catalytic activity of the bimetallic-CSPVP nanoclusters.

	CSPVP **1**	CSPVP **25**	CSPVP **26**
Mw	106,184	75,245	91,988
Mn	100,602	68,185	85,232
Polydispersity Index	1.055	1.104	1.079

Table 3. Polydispersity Index of CSPVP 1, 25 & 26.

The average sizes, size distribution were also studied by dynamic light scattering (DLS). In **Figure 5**, Panel A and C are the autocorrelation function over time of **1** & **26** in H_2O (deionized) solution with concentration of 0.12 mol/L, respectively, Panel B and D are size distribution graph of **1** & **26** in H_2O solution with concentration of 0.12 mol/L. DLS graphs of **1** showed a major ensemble of 12–20 nm sizes particles with an average size of 18.6 nm along with a few 152 nm-sized particles, suggesting that different shapes and few large aggregates were presented in the aqueous solution. Similarily, DLS graphs of **26**, taken on ZetaPALS zeta potential analyzer, showed a major ensemble of 11–18 nm sizes particles with an average size of 14.6 nm along with a few 158 nm-sized particles. The size of polymer particle is also in a narrow band which fit the result of polydispersity from GPC analysis.

From the image of atomic force microscopy (AFM) obtained from Nanoscope IIIa SPM atomic force microscope, the size of the polymer can also be measured.(**Figure 6**) In panel A and C, AFM image of CSPVP **1 & 26** are shown and indicated the shapes and sizes of the polymers. Panel B and D measure the height (Y axis) and width (X axis) of polymer **1 & 26**. On the mica, the CSPVPs appeared unshaped with a diameter of ~15–30 nm and a height of 1 nm.

The NMR spectrum is difficult to analysis for the polymers since the signals in ^1H NMR are broad and ^{13}C NMR is complex unless the polymer is regularly assembled. The ^1H & ^{13}C NMR of commercially available PVP, CSPVP **1** – **3** are all difficult to analyze which means the stereogenic center on the polymers backbone can be isotactic, atactic, and syndiotactic.[29] Fortunately, it likely has lesser effect on the asymmetric oxidation reactions which will discuss later. However, based on the ^{13}C NMR spectra of polymers **25** and **26**, they likely adapted syndiotactic or isotactic stereochemistry in the polymer backbone. For example, the ^{13}C NMR spectrum of polymer **25** shows only 12 signals having δ values (in ppm) of 160.9 (C=O), 113.5

(O-C-O), 74.7 (C-O), 73.0 (C-O), 48.8 (C-N), 47.7 (C-N), 43.0 (CH_2), 42.7 (CH-N), 29.2 (CH_2), 28.5 (CH_2), 8.4 (CH_3) and 7.0 (CH_3), the simplicity of signal patents suggest the polymer was regularly assembled during polymertization. The exactly tacticity will be studied and confirmed.

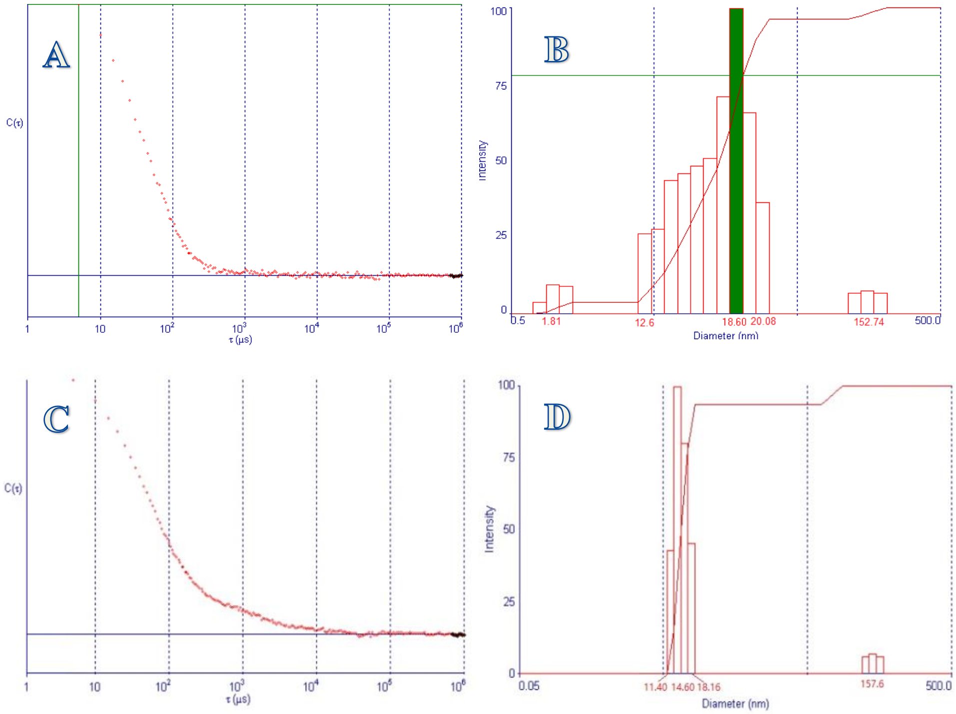


Figure 5. Dynamic Light Scattering Studies of CSPVP 1 (A & B) & 26 (C & D).

Since the purpose of making the different functionalized CSPVP is used for inducing a chiral environment on the asymmetric synthesis, the catalyst, CSPVP stabilized bimetallic nanoclusters was synthesized.

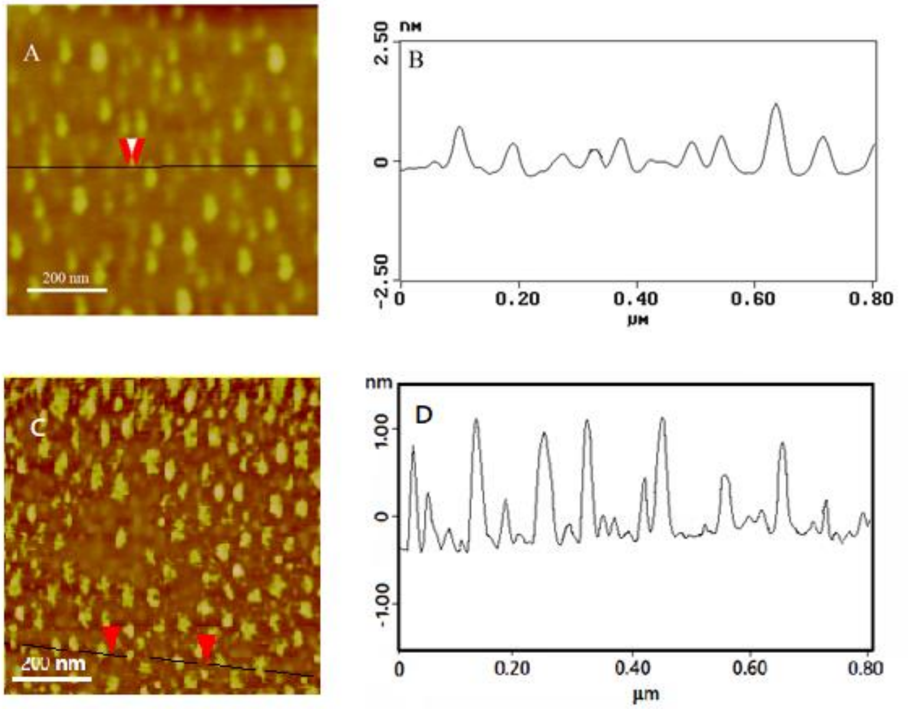


Figure 6. A Representative Atomic Force Microscopy Image and Measurement of Particle Height for CSPVP 1 (A & B) & 26 (C & D).

1.3 Synthesis and Characterization of CSPVP Stabilized Bimetallic Nanoclusters

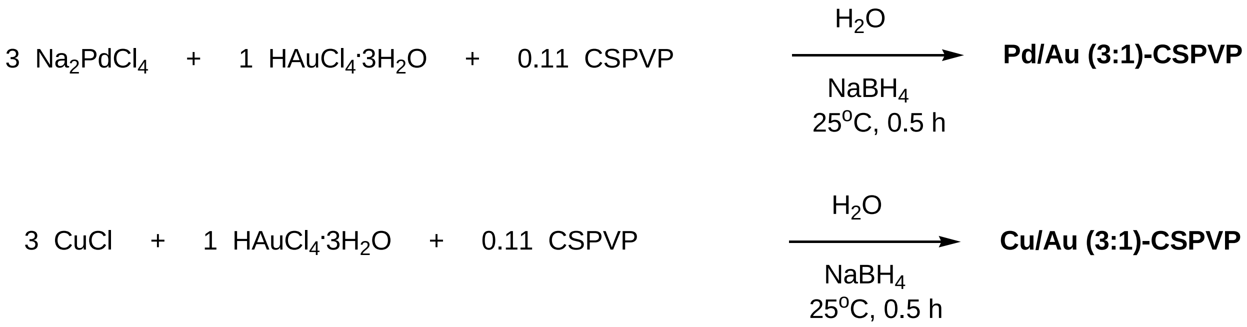
Various of nanoclusters for different purpose have been made by number of methods including molecular beams, chemical reduction, thermal decomposition, ion implantation, electrochemical synthesis, radiolysis, sonochemical synthesis, and biosynthesis.[32] We have synthesized various bimetallic nanoclusters including Pd/Au and Cu/Au, using the chemical reduction method[10] in the presence of various of CSPVPs. We used gold due to its high catalytic activity and synergistic electronic effects, which will enhance the catalytic activity of Pd and Cu.[10-12, 33-35]

1.3.1 Synthesis of Pd/Au-CSPVP Nanoclusters and Cu/Au-CSPVP Nanoclusters

In the bimetallic nanoclusters, both the valences of two metals are 0, which means the high valence metal salt need to be reduced in the solution. For example[10], a solution of Na_2PdCl_4 (3 equiv.), $HAuCl_4$ (1 equiv.), and CSPVP **1** (0.11 equiv.) in deionized water was well mixed to give a yellow solution. To it, 40 equiv. of $NaBH_4$ were added under ice bath and stirred under room temperature for 30 min (**Scheme 6**) to give a light brown to dark grey solution depending on the concentrations. After adding $NaBH_4$, Pd(II) in Na_2PdCl_4 and Au(III) in $HAuCl_4$ were reduced to Pd(0) and Au(0), respectively. The color of the solution changes to black immediately to indicate the formation of Pd/Au-CSPVP nanoclusters. Because the presence of CSPVP as supporting material, Pd(0) and Au(0) do not aggregate due to the metal atom or nanocluster complex with the carbonyl of CSPVP. Different from the bulky metal (0), the high solubility of CSPVP stabilized bimetallic nanoclusters in water makes the nano-size metal as a homogeneous dispersion without precipitate. Without CSPVP, Pd and Au will form black precipitate after adding $NaBH_4$, suggesting CSPVP is nessecary for the formation of nanoclusters.

Theoritically, only 9 equiv. of hydride are needed for the reduction of Pd (II) (3 equiv.) and Au (III) (1 equiv.). Therefore, for certain reaction, especially C-H oxidation, only 8 equiv. of $NaBH_4$ was added to avoid the large excess $NaBH_4$ influencing the reaction outcome.

Similarly, Cu/Au-CSPVP nanoclusters were synthesized using the chemical reduction method. $CuCl_2$ is a good Cu source which has a high solubility in water, easily storage and relatively stability. However, the Cu/Au-CSPVP nanoclusters made from Cu (II) are not stable due to the precipitation. Therefore, CuCl was used for preparing the Cu/Au-CSPVP nanoclusters. Notably, CuCl can be slowly oxidized by $HAuCl_4$ to give $CuCl_2$. To avoid it, CSPVP (0.11 equiv.), $HAuCl_4$ (1 equiv.) and $NaBH_4$ (40 equiv.) were added into 0 ^oC CuCl (3 equiv.) in deionized water solution in sequence to give a dark brown solution. The solution was stirred under room temperature for 30 minutes and Cu/Au-CSPVP nanoclusters solution was ready to use for the asymmetric catalytic reactions. (**Scheme 6**)



$$3\ \mathrm{Na_2PdCl_4} + 1\ \mathrm{HAuCl_4{\cdot}3H_2O} + 0.11\ \mathrm{CSPVP} \xrightarrow[\mathrm{NaBH_4},\ 25^{o}\mathrm{C},\ 0.5\ \mathrm{h}]{\mathrm{H_2O}} \textbf{Pd/Au (3:1)-CSPVP}$$

$$3\ \mathrm{CuCl} + 1\ \mathrm{HAuCl_4{\cdot}3H_2O} + 0.11\ \mathrm{CSPVP} \xrightarrow[\mathrm{NaBH_4},\ 25^{o}\mathrm{C},\ 0.5\ \mathrm{h}]{\mathrm{H_2O}} \textbf{Cu/Au (3:1)-CSPVP}$$

Scheme 6. The Synthesis of Pd/Au-CSPVP Nanoclusters and Cu/Au-CSPVP Nanoclusters.

For the CSPVP stabilized bimetallic nanocluster catalyzed oxidation reaction, the nanoclusters catalyst solution was used directly into the reaction. But for the characterization of nanoclusters, the crude nanocluster solution was filtered through a Vivaspin 20 centrifugal filter device (3,000 MWCO), washed with deionized water twice to remove low MW inorganic materials, and lyophilized to give a powder. The resulting nanoclusters was dissolved in water to certain concentration and subjected to analysis.

1.3.2 Characterization of Pd/Au-CSPVP Nanoclusters and Cu/Au-CSPVP Nanoclusters

It has been reported the carbonyl in the amide group in PVP was coordinated with the surface of Pd in the nanoclusters.[36, 37] Because of the chelation, the amide C=O have greater character of ${}^{\delta-}$O-C=N${}^{\delta+}$ which give the pyrolidinone ring at 1648 cm^{-1} of polymer **26** in IR spectrum shifted to 1643.5 cm^{-1} for Cu/Au (3:1)-**26** and 1641.9 cm^{-1} for Pd/Au (3:1)-**26**. The shift of Cu/Au (3:1)-**26** suggests the similar chelation for Cu and CSPVP. **(Figure 7)**

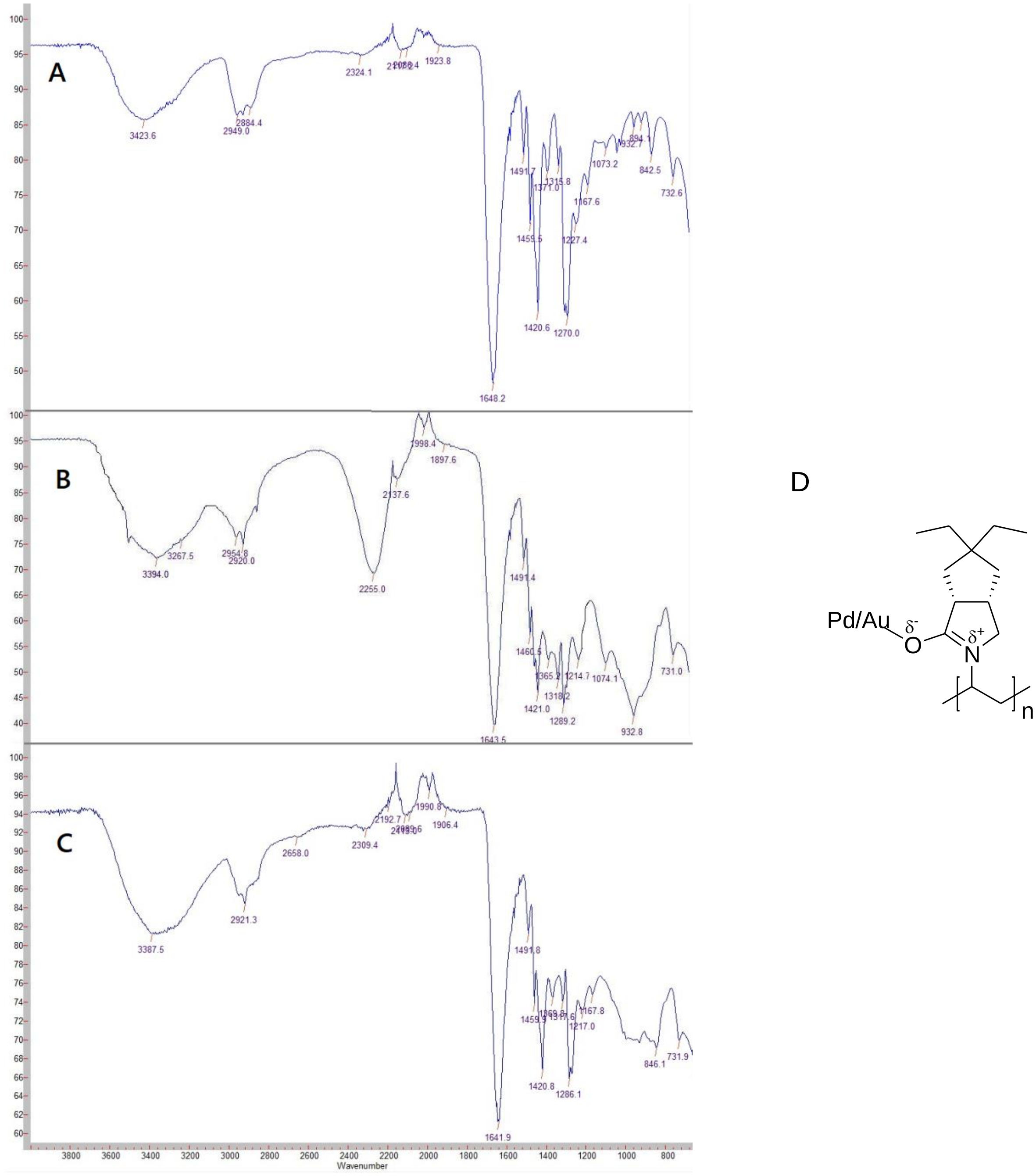


Figure 7. IR Spectra for (A) CSPVP-26, (B) Cu:Au-CSPVP26 (C) Pd:Au-CSPVP26 (D) Pd/Au Complex with CSPVP.

As a nanomaterial, several kinds of microscopy or size distribution analysis were conducted including atomic force microscopy (AFM), transition electron microscopy (TEM) and dynamic light scattering (DLS). In AFM images obtained from Nanoscope IIIa SPM atomic force microscope, (**Figure 8**) 50-100 nm in diameters and ~ 5 nm in heights of spherical particles were found for both Pd/Au-CSPVP**26** and Cu/Au-CSPVP**26**, as example. And in DLS which was taken on ZetaPALS zeta potential analyzer, (**Figure 9**) 90-120 nm sized nanoparticles were revealed in Pd/Au-CSPVP**26** and Cu/Au-CSPVP**26** water solutions with a concentration of 4.36 mol/L Pd/Au (3:1) or Cu/Au (3:1) and 0.12 mol/L CSPVP**26**, suggesting the size of polymer **26** wrapped particles was ~7.5 times larger than polymer **26** alone (14.6 nm shown in **Figure 5**), and the measured sizes of the particles from AFM and DLS were similar. Small amount of 12 – 14 nm size particles shown in DLS may indicate the free CSPVP which was not chelate with metals.

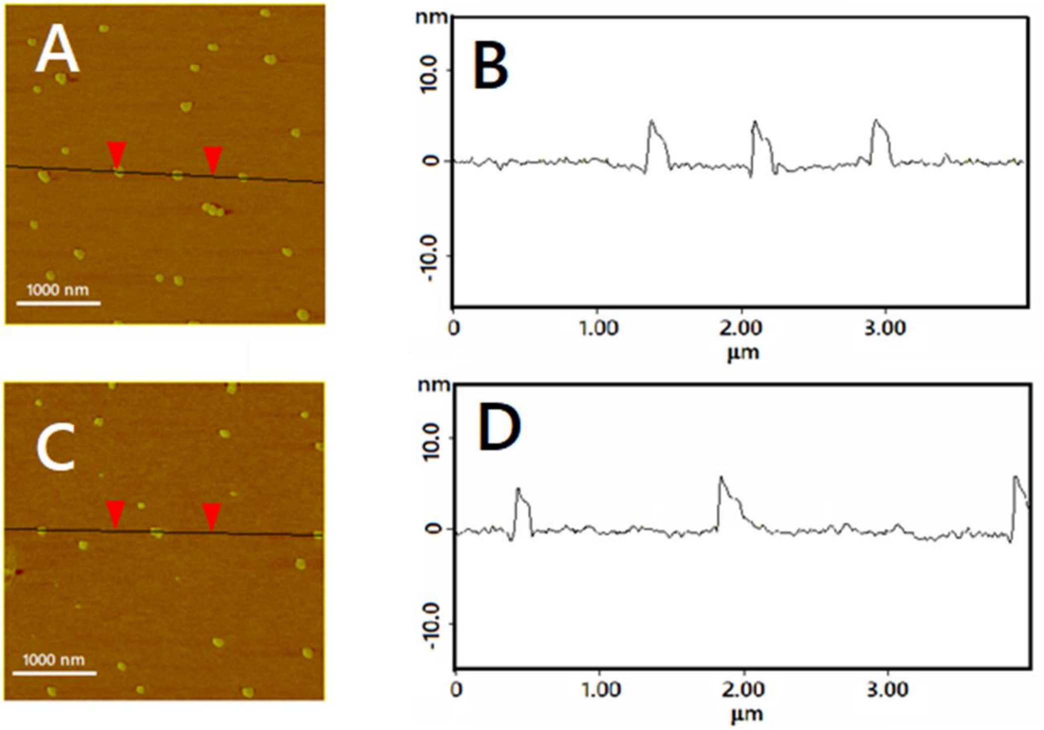


Figure 8. A Representative Atomic Force Microscopy Image and Measurement of Particle Height for Pd:Au-CSPVP26 (Panel A & B) and Cu:Au-CSPVP26 (Panel C & D).

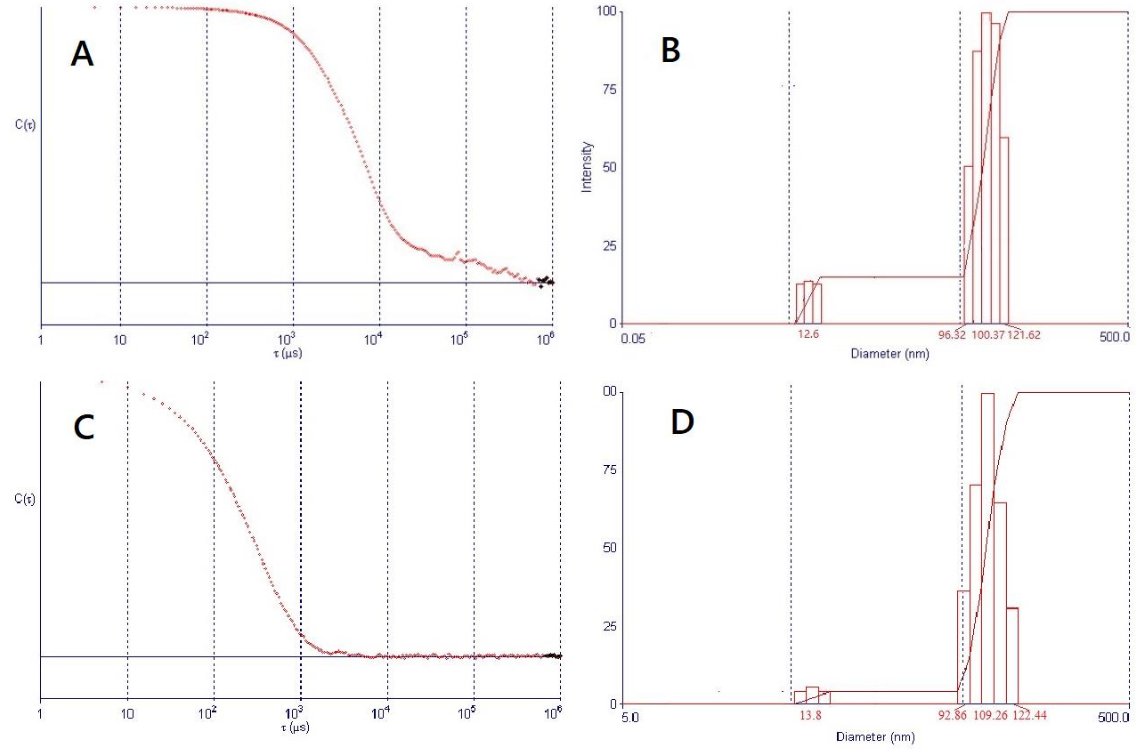


Figure 9. Dynamic Light Scattering Results for Pd:Au-CSPVP26 (Panel A & B), Cu:Au-CSPVP26 (Panel C & D).

TEM images, which is taken on FEI CM100 TEM instrument, revealed average diameters of 3.32 ± 1.08 nm and 3.41 ± 1.13 nm for Pd/Au (3:1)-**26** and Cu/Au (3:1)-**26**, respectively. The nano-sizes (3–4 nm) of the nanoclusters are similar to those reported for Pd/Au using PVP as a stabilizer.[10, 36] The approximate total numbers of metal atoms and molecules of polymer in a spherical nanocluster can be calculated utilizing the magic-cluster sizes $N_{total} = 1/3(10n^3-15n^2+11n-3)$, where n is the number of layers of shell in the metallic nanoparticles with face-centered cubic close-packed structure.[38] Since the average sizes of Pd/Au (3:1)-**26** and Cu/Au (3:1)-**26** nanoclusters are 3.32 and 3.41 nm, respectively (from TEM), utilizing the aforementioned equation there are respectively ~727 and 923 atoms of Pd/Au (3:1) and Cu/Au

(3:1) in a nanocluster, and each nanoclusters are stabilized by approximately 20 and 25 polymers, respectively. The calculation is shown below:

For Pd/Au (3:1)-2:

(diameters for Au and Pd are 0.288 and 0.275, respectively.)

Diameter d = (3 x 0.275 + 0.288) / 4 = 0.278

Nanocluster diameter: 11.9d = 3.32 nm (the diameter of Pd/Au is obtained from TEM)

The shell number: n = 6.5

The number of atoms in a 3.32nm nanocluster: N = 1/3[10n3 – 15n2 + 11n – 3] = 727 atoms

Mole of metals in each nanocluster: 1.21 x 10^{-21} mol

Mole of CSPVP in each nanocluster: 1.21 x 10-21 x 0.11 / 4 = 3.3 x 10^{-23} mol

Number of CSPVP in each nanocluster: 3.3 x 10-23 x N_A (Avogadro number) = 3.3 x 10-23 x 6.022 x 1023 = 20.0

For Cu/Au (3:1)-2:

(diameters for Au and Cu are 0.288 and 0.256, respectively.)

Diameter d = (3 x 0.256 + 0.288) / 4 = 0.264

Nanocluster diameter: 12.9d = 3.41 nm (the diameter of Cu/Au is obtained from TEM)

The shell number: n = 7

The number of atoms in a 3.41 nm nanocluster: N = 1/3[10n3 – 15n2 + 11n – 3] = 923 atoms

Mole of metal in each nanocluster: 1.53 x 10^{-21}

Mole of CSPVP in each nanocluster: 1.53 x 10-21 x 0.11 / 4 = 4.22 x 10^{-23}

Number of CSPVP in each nanocluster: 5.3 x 10-23 x 6.022 x 1023 = 25.4

Because of the numbers and extended structure of the chiral polymer, the sizes of the bimetallic nanocluster/polymer found by AFM and DLS are much larger than bimetallic nanoclusters found in TEM (the polymer cannot be observed by TEM).

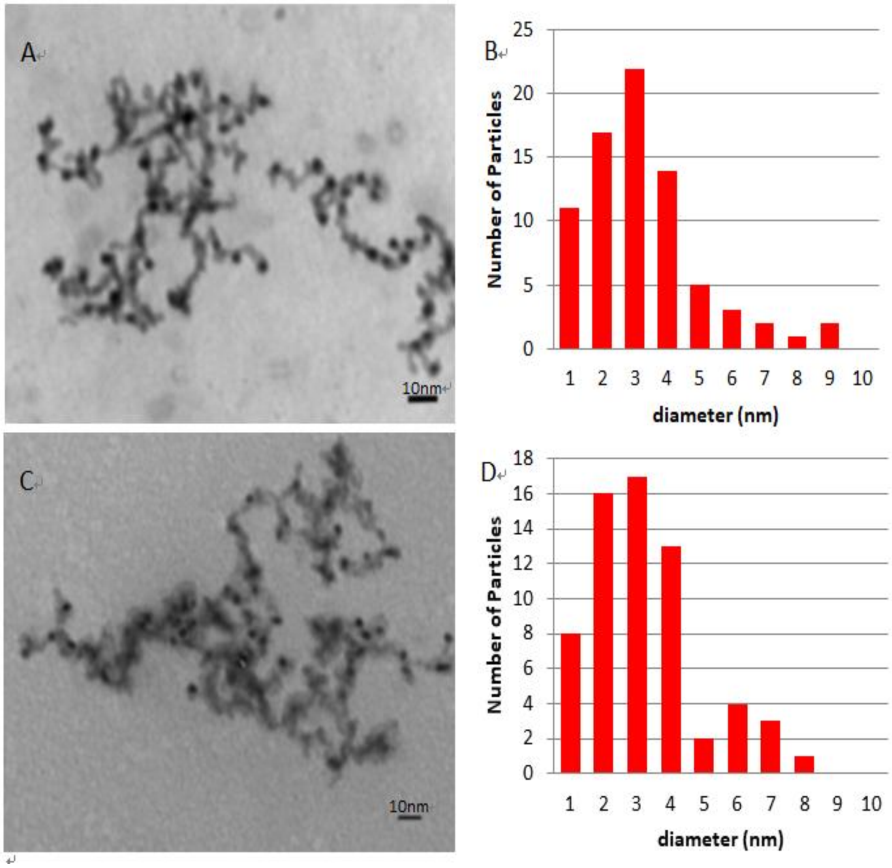


Figure 10. Representative TEM Image and Measurement of the Diameter for Pd:Au-CSPVP26 (Panel A & B), Cu:Au-CSPVP26 (Panel C & D).

Moreover, the elemental analysis including inductively coupled plasma-mass spectrometry (ICP-MS) were carried out. Results of the ICP-MS, taken on NexION® 300D, showed a ratio of 2.985 ± 0.172 of Pd and Au in the Pd/Au (3:1)-**26** sample, and a ratio of 3.148 ± 0.432 of Cu and Au in the Cu/Au (3:1)-**26** sample. This is in agreement of the 3:1 ratio of the two metals used in the preparation of nanoclusters. To digest the metallic samples, the following method is used. To a solution of 10 mg of Pd/Au (3:1)-**26** or Cu/Au (3:1)-**26** in 100 μL of deionized water was added 2 mL of aqua regia solution at 70 °C under sonication for 3 h, and the solution was cooled to 25 °C, diluted to 1 mL with a 1% HNO_3 / 2% HCl solution. The resulting solution was diluted to certain concentration for the ICP-MS analysis.

In wdie-scan XPS spectrum of the Pd/Au-**1** and Cu/Au-**1,**(Panel A & C) major elements of the polymer, carbon (C 1s at 284.6 eV), oxygen (O 1s at 530.6 eV), and nitrogen (N 1s at 398.6 eV) are shown. Panel B & C showed the binding energy of two maximums at 84.1 eV and 335.1 eV derived from $4f_{7/2}$ Au and $3d_{5/2}$ Pd, respectively in Pd/Au-**1** sample. Similarly, 932.7 eV derived from $2p_{3/2}$ Cu is also appeared in Cu/Au-**1** sample in Panel F.[36] X-ray photoelectron spectroscopy (XPS) study was performed on a PHI 5400 XPS system. (**Figure 11**)

The UV-vis spectrum of Pd/Au-**26** and Cu-Au-**26** were also obtained from Agilent Cary 100 UV-Vis Spectrophotometer. (**Figure 12**) It is clearly shows the presence of strong signal at 303 nm in the nanoclusters which is very weak in the CSPVP**26** alone.

In order to study the chirality of CSPVP stabilized bimetallic nanoclusters, circular dichroism (CD) was taken on Jasco J-815 Circular Dichroism (CD) Spectropolarimeter. (**Figure 13**) For the CSPVP**26** in water solution with a concentration of 0.011 mM alone, there is only a slight negative band on 520 nm. But after forming the bimetallic nanoclusters, they exhibit positive CD band at 280 nm and strong band at 500 nm, which is similar like the reported chiral polymers and chiral Au nanoclusters.[36, 39, 40] The strong optical absorptions are not from CSPVP**26** or metals. It has been reported the (R)-Au_{38} and (S)-Au_{38} nanoclusters presented mirror-imaged CD spectra with similar optical absorption but on opposite sign. It illustrated the chirality of nanoclusters can be performed by CD spectra. The presence of strong optical absorption in Pd/Au-**26** and Cu/Au-**26** indicate the nanoclusters solution is a chiral environment.

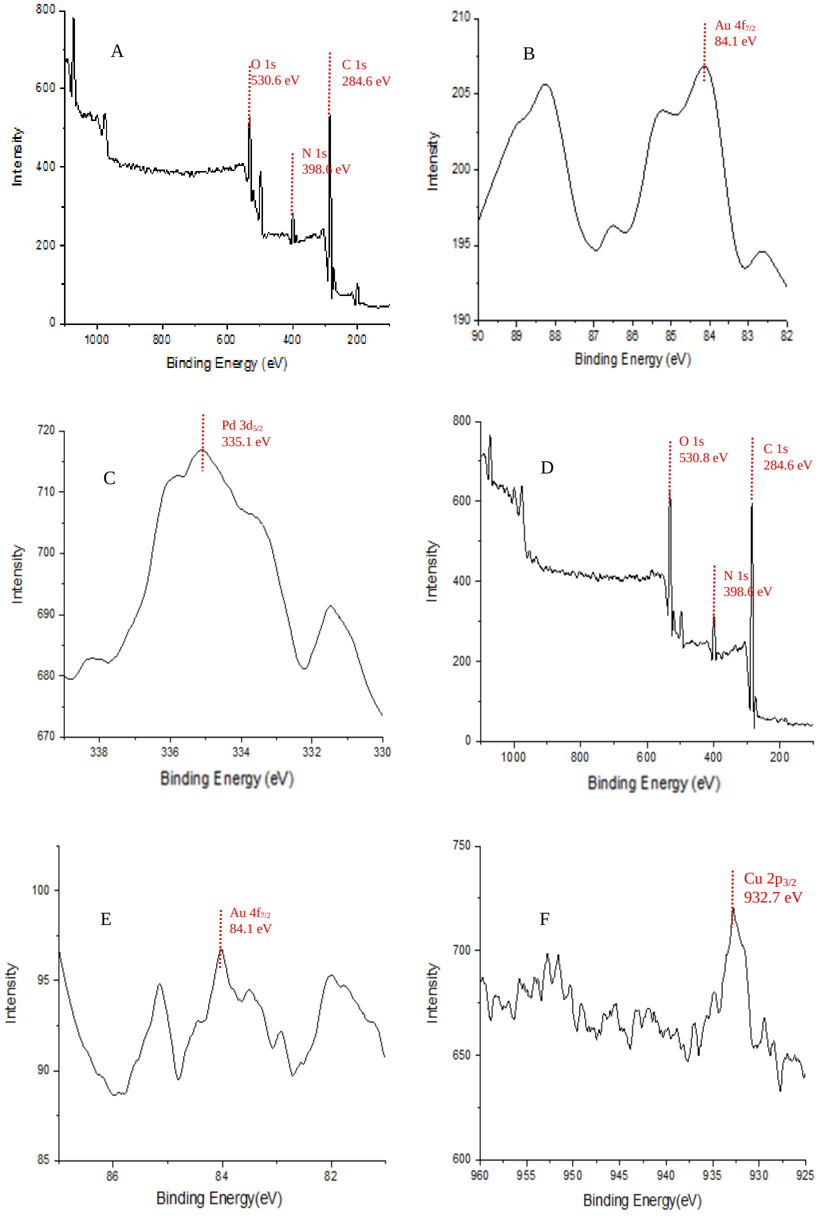


Figure 11. **X-ray photoelectron spectroscopy Results for Pd:Au-CSPVP1 (Panel A, B & C), Cu:Au-CSPVP1 (Panel D, E & F).**

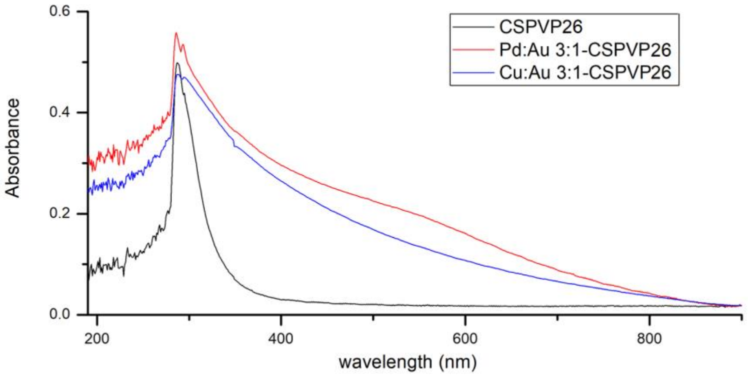


Figure 12 Representative UV-Vis spectra of CSPVP26, Pd:Au-CSPVP26 & Cu:Au-CSPVP26

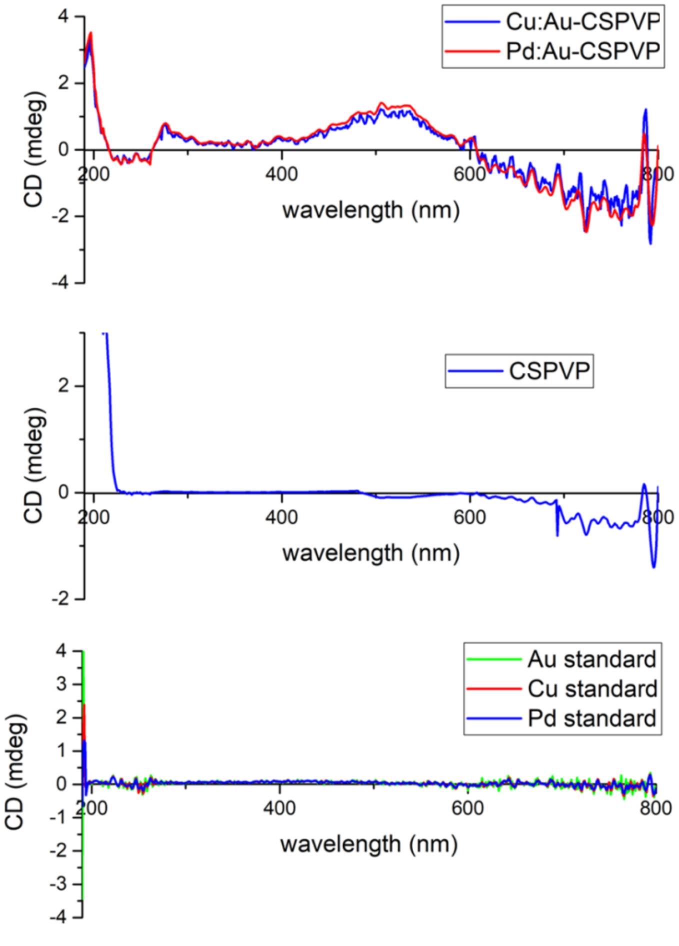


Figure 13. Representative CD spectra of Cu:Au-CSPVP26 & Pd:Au-CSPVP26 (top panel), CSPVP 26 (middle panel), and Au, Cu, and Pd standard solution as controls.

1.4 Conclusion

In this chapter, the synthesis of two classes of new polymers, namely chiral-substituted poly-N-vinylpyrrolidinones (CSPVPs) were discussed. From the characterization results, the CSPVPs are uniform. They were used for the stabilization of the bimetallic nanoclusters such as Pd/Au or Cu/Au and inducted of chirality into the nanomaterial. The size, component and other physical / chemical properties of the bimetallic nanoclusters (~3.5 nm), which are wrapped around by chiral polymers, were also studied and discussed.

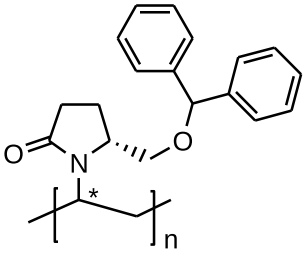
1.5 Synthetic Experimental Procedures

1.5.1 General

^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were measured from a solution in $CDCl_3$ unless otherwise mentioned. The chemical shift data for each signal on ^{1}H NMR are given in units of δ relative to TMS ($\delta = 0$) or $CHCl_3$ ($\delta = 7.26$) in ppm. For ^{13}C NMR spectra, the chemical shifts are recorded relative to $CDCl_3$ ($\delta = 77.0$). Low-resolution mass spectra were taken from an API 2000-triple quadrupole ESI-MS/MS mass spectrometer. High-resolution mass spectra were obtained using a Waters LCT Premier time of flight mass spectrometer. IR spectra were measured directly in solid form from Agilent Cary 630 FTIR. UV-Vis spectra were obtained from Agilent Cary 100 UV-Vis Spectrophotometer. Optical Rotation were measured by Bodenseewerk Perkin-Elmer & Co Gmbh Ueberlingen.

1.5.2 Representative Synthesis

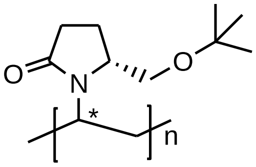
Poly[(5*R*)-5-(benzhydryloxymethyl)-1-vinylpyrrolidin-2-one] (1). (BH7-041)



1

To a hot (120°C) solution of 1.2 mg (1% by weight) of copolymer **24** in 0.5 mL of DMF under argon, were added 120 mg (0.43 mmol) of compound **13** and 0.28 mg (1.7 μmol) of AIBN. The solution was stirred for 6 days at 120°C (until no monomer **13** was found by NMR spectrum of an aliquot from the reaction solution), cooled to 25°C, and diluted with diethyl ether. The precipitate was collected by filtration, dried under vacuum to give 102 mg (84% yield) of polymer **1** as a white solid. The average molecular weight of polymer **1**, 106,000, was determined by gel permeation chromatography using TSKgel GMHxl column and THF as solvent with a flow rate of 1 mL/min. ^{1}H NMR δ 7.3–6.8 (m, 6 H, Ph), 6.6–6.3 (m, 4 H, Ph), 3.8–3.76 (m, 1 H), 3.4–3.0 (m, 3 H), 2.45–1.0 (m, 7 H). ^{13}C NMR δ 176.1–175.4, 145.5–144.5, 128.6–124.3, 72.4–69.1, 69.0–67.2, 45.9–41.5, 40.6–39.3, 37.3–34.4, 32.2–34.6, 19.0–18.5. IR (neat) ν 3050, 2954, 2890, 1650 (s), 1462, 1441, 1423, 1290.

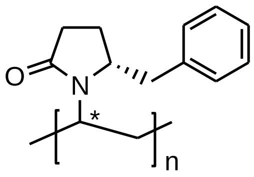
Poly[(5*R*)-5-(*tert*-butoxymethyl)-1-vinylpyrrolidin-2-one] (2). (BH4-048)



2

To a solution of 90 mg (0.45 mmol) of monomer **15** and 2 mg of copolymer **22** in 0.2 mL of ethyl acetate under argon was added a solution of 0.3 mg of AIBN in 0.1 mL of ethyl acetate. The solution was heated to reflux for 14 h, cooled to 25°C, diluted with diethyl ether, and filtered to collect the white solid. The solid was dried under vacuum to give 76 mg (83% yield) of polymer **2**. The average molecular weight of polymer **2** was 68,000, which was determined by gel permeation chromatography using TSKgel GMHxl column and THF as solvent with a flow rate of 1 mL/min. ^{1}H NMR δ 4.0–3.0 (m, 4 H), 2.5–1.4 (bm, 6 H), 1.71 (bs, 9 H, *t*-Bu). The polymer was used in the subsequent catalytic asymmetric oxidation reactions without further purification.

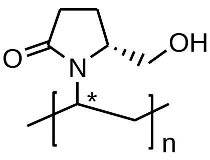
Poly[(5*R*)-5-(benzyl)-1-vinylpyrrolidin-2-one] (3). (BH1-046)



3

To a solution of 0.30 g (1.5 mmol) of monomer **21** and 3 mg of copolymer **23** in 0.6 mL of ethyl acetate under argon was added a solution of 1 mg of AIBN in 0.1 mL of ethyl acetate. The solution was heated to reflux for 6 h, cooled to 25°C, diluted with diethyl ether, and filtered to collect the white solid. The solid was dried under vacuum to give 0.27 g (89% yield) of polymer **3**. The average molecular weight of polymer **3** was 76,000, which was determined by gel permeation chromatography using TSKgel GMHxl column and THF as solvent with a flow rate of 1 mL/min. ^{1}H NMR δ 7.25–6.25 (m, 5 H, Ph), 4.0–3.0 (m, 4 H), 2.5–1.2 (m, 6 H); ^{13}C NMR δ 175.8-174.8, 145.2-144.9, 139.8-135.0, 45.3-41.3, 30.5-30.2, 19.8-18.6. The polymer was used in the subsequent catalytic asymmetric oxidation reactions without further purification.

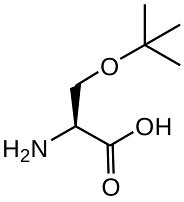
Poly[(5*R*)-5-(hydroxymethyl)-1-vinylpyrrolidin-2-one] (4). (BH4-076)



4

A solution of 0.20 g (3 μmol) of polymer **2** and 34 mg (0.3 mmol) of trifluoroacetic acid in 0.2 mL of CH_2Cl_2 was stirred at 25^{o}C for 2 h, and concentrated to dryness to give 0.14 g (96% yield) of polymer **4**. The average molecular weight of polymer **4** was 56,480, which was determined by gel permeation chromatography using TSKgel GMHxl column and THF as solvent with a flow rate of 1 mL/min. ^{1}H NMR δ 4.1–2.8 (m, 4 H), 2.5–1.25 (m, 7 H). The polymer was used in the subsequent catalytic asymmetric oxidation reactions without further purification.

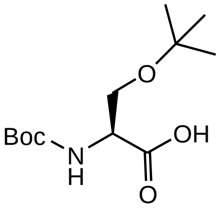
(S)-2-Amino-3-tert-butoxypropanoic acid (6) (BH4-039)



6

A solution of 0.5 g (4.7 mmol) of L-serine and 0.197 g (4.7 mmol) of LiOH•H_2O IN 3 mL of deionized water was stirred for 1 hour, concentrated to give white solid as serine mono lithium salt and dissolved in 7.05 mL of anhydrous THF. To it, 2.82 mL of BF_3•Et_2O was dropwise added, stirred under Ar at room temperature overnight and 45 ^{o}C for 2 hours to give a gray solution. The resulting solution was concentrate under vacuum and the residue was dissolved in 14.7 mL of dioxane in a seal tube. To it, 0.21 mL of 85% H_3PO_4 was added and cooled to -20^{o}C followed by 20 mL of isobutylene (by introducing the gas directly) into the sealed tube reactor and react under room temperature for 2.5 hours, evaporated all the isobutylene, added 1N NaOH solution to pH = 10, concentrated under vacuum to give 3.1g crude product as white solids. This mixture (containing **6** and other inorganic salts) was used in the following step without further purification.

(S)-3-*tert*-Butoxy-2-(tert-butoxycarbonyl)propanoic acid (7) (BH4-043)

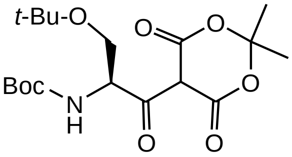


7

To a solution of 3.1g of crude material *t*-Bu-serine (**6**) in 10 mL of 1:1 THF/H_2O solution, 3 eq of $NaHCO_3$ and 1.2 eq of Boc_2O were added at 0 ^oC under ice bath and stirred overnight under room temperature, extracted with 3 x 10 mL diethyl ether. The combined organic layer was acidified with concentrated citric acid to pH = 4-5, extracted with 3 x 10 mL dichloromethane, washed with brine, dried over anhydrous sodium sulfate, concentrate to give desired product. The NMR data is the same as the commercially available compound.

(*S*)-*tert*-Butyl
3-*tert*-butoxy-1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-1-oxopropan-2-ylcarbamate (8).

(BH7-030)



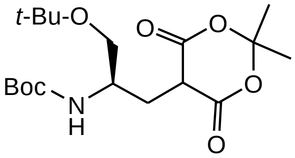
8

A solution of 4.0 g (15.3 mmol) of *N*-Boc-*O*-*tert*-butyl-L-serine (**7**), 3.3 g (23 mmol) of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione), and 2.8 g (22.9 mmol) of 4-(dimethylamino)pyridine (DMAP) in 80 mL of dichloromethane under argon was cooled to 0^oC over an ice-water bath. To it, a solution of 3.47 g (16.8 mmol) of

N,N'-dicyclohexylcarbodiimide (DCC) in 20 mL of dichloromethane was added dropwise. The mixture was stirred for 12 hours under argon and the precipitated (*N*,*N*'-dicyclohexylurea) was removed by filtration. The filtrate was washed with 50 mL of 5% HCl, and then water, dried (anhydrous Na_2SO_4), and concentrated to dryness leaving 5.83 g of compound **8** as a white solid. This compound was used in the following step without further purification. ^{1}H NMR δ 5.67–5.63 (m, 1 H), 5.49–5.47 (m, 1 H), 3.74–3.70 (m, 2 H), 3.62 (s, 1 H, NH), 1.76 (s, 3 H), 1.73 (s, 3 H), 1.46 (s, 9 H), 1.26 (s, 9 H). ^{13}C NMR δ 206.8, 172.7, 152.3, 105.9, 79.0, 75.0, 62.0, 60.6, 59.9, 30.0 (3 C), 28.4 (3 C), 25.6 (2 C). MS (ESI, MeOH): *m/z* = 388.7 ($[M + H]^+$).

(*R*)-*tert*-Butyl 3-*tert*-butoxy-1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)propan-2-ylcarbamate (9).

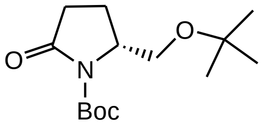
(BH7-031)



9

To a cold (0°C) solution of 5.80 g (15.2 mmol) of compound **8** in 150 mL of dichloromethane under argon were added 5.51 g (91.8 mmol) of acetic acid and 1.51 g (39.8 mmol) of $NaBH_4$. The solution was stirred at 0°C for three hours and at 25°C for 12 hours, diluted with 30 mL of water, the dichloromethane layer was separated, and the water layer was extracted with dichloromethane three times. The combined organic layers were washed with water and brine, dried (anhydrous Na_2SO_4), concentrated to give a yellow oil, which was crystallized from diethyl ether to give 5.27 g of compound **9** as a white solid. ^{1}H NMR δ 5.08–5.09 (m, 1 H), 4.08–4.00 (m, 1 H), 3.62 (s, 1 H, NH), 3.45–3.41 (m, 2 H), 2.5–2.45 (m, 1 H), 2.16–2.01 (m, 1 H), 1.80 (s, 3 H), 1.72 (s, 3 H), 1.40 (s, 9 H), 1.05 (s, 9 H); ^{13}C NMR δ 208.0, 174.6, 151.0, 105.7, 79.3, 74.7, 69.8, 49.6, 47.1, 31.9, 28.4, 25.7. MS (ESI, MeOH): *m/z* = 374.0 ($[M + H]^+$), 299.9.

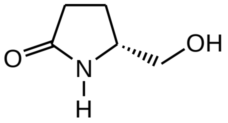
(*R*)-N-(*tert*-Butoxycarbonyl)-5-(*tert*-butoxymethyl)-pyrrolidin-2-one (10). (BH7-032)



10

A solution of 5.26 g (14.10 mmol) of compound **9** in 40 mL of toluene under argon was heated to reflux for 6 hours, cooled to 25^{o}C, concentrated under vacuum, and column chromatographed on silica gel using hexane and ethyl acetate (4:1) as eluent to give 3.44 g (83% overall yield in three steps) of compound **10** as a yellow oil. $[\alpha]_D^{22}$ = +80.7 (c 1.0, CHCl$_3$); ^{1}H NMR δ 4.09–4.07 (m, 1 H), 3.52 (dd, J = 10, 4 Hz, 1 H), 3.31 (dd, J = 10, 1.6 Hz, 1 H), 2.56 (dt, J = 17.6, 9.6 Hz, 1 H), 2.20 (dd, J = 17.6, 9.2 Hz, 1 H), 2.05–1.84 (m, 2 H), 1.40 (s, 9 H), 1.02 (s, 9 H). ^{13}C NMR δ 175.3, 150.1, 82.6, 73.2, 62.9, 58.0, 32.5, 28.2, 27.5, 21.7. MS (ESI, MeOH): *m/z* = 294.1 ([M + Na]$^+$), 272.0 ([M+ H]$^+$), 194.1, 172.1, 116.0. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{14}H_{26}NO_4$: 272.1862; found: 272.1887.

(*R*)-5-(Hydroxymethyl)pyrrolidin-2-one (11). (BH7-033)

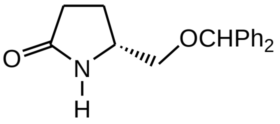


11

A solution of 1.0 g (3.6 mmol) of compound **10** in 5 mL of 10% trifluoroacetic acid in dichloromethane was stirred at 50^{o}C for 5 hours, cooled to 25^{o}C, and diluted with dichloromethane. The solution was washed with an aqueous solution of NaHCO$_3$, then water and brine, dried (MgSO$_4$), concentrated to give 0.42 g (99% yield) of compound **11** as a brown oil. This material was used in the subsequent step without further purification. $[\alpha]_D^{22}$ = -60.2 (c 1.0, CHCl$_3$); ^{1}H NMR δ 6.7–6.6 (bs, 1 H, NH), 4.46 (dd, J = 11.2, 4 Hz, 1 H), 4.21 (dd, J = 11.2, 7.2 Hz, 1 H), 4.15–4.04 (m, 1 H), 2.54–2.32 (m, 4 H, CH$_2$ and OH), 1.98–1.87 (m, 1 H);

^{13}C NMR δ 181.6, 65.2, 57.5, 30.3, 22.3; MS (ESI, MeOH): *m/z* = 116.0 ($[M + H]^+$, 100%), 98.1. HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_5H_9NO_2Na^+$: 138.0531 found: 138.0537.

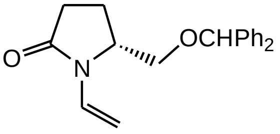
(*R*)-5-(Benzhydryloxymethyl)pyrrolidin-2-one (12). (BH7-043)



12

To a cold (0°C) solution of 0.43 g (3.74 mmol) of compound **11** in 1 mL distilled THF under argon, was added 0.15 g (3.74 mmol) of NaH (60% in mineral oil; NaH was washed twice with dried diethyl ether). The mixture was stirred at 0°C for 30 minutes and added 1.11 g (4.48 mmol) of bromodiphenylmethane. The mixture was stirred at 50°C for 12 hours, diluted with 1 mL of H_2O, and the organic THF layer was separated and concentrated under vacuum and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as an eluent to give 0.93 g (88% yield) of compound **12** as a brown oil. $[\alpha]_D^{22}$ = -63.2 (c 1.0, $CHCl_3$); ^{1}H NMR δ 7.4–7.2 (m, 10 H, Ar), 6.06–5.98 (bs, 1 H, NH), 5.35 (s, 1 H), 3.95–3.88 (m, 1 H, CHN), 3.48 (dd, J = 9.6, 3.6 Hz, 1 H, CHO), 3.36 (dd, J = 9.6, 8 Hz, 1 H, CHO), 2.41–2.27 (m, 2 H, $CH_2C{=}O$), 2.24–2.14 (m, 1 H), 1.79–1.68 (m, 1 H); ^{13}C NMR δ 178.1, 141.8 (2 C), 128.7 (4 C), 127.9 (2 C), 127.1 (4 C), 84.1, 73.0, 54.1, 29.9, 23.4; MS (ESI, MeOH): *m/z* = 304.1 ($[M + Na]^+$), 194.0, 167.1. HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{18}H_{19}NO_2Na^+$: 304.1313; found: 304.1320.

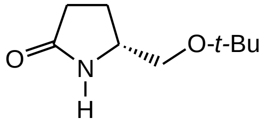
(*R*)-5-(Benzhydryloxymethyl)-1-vinylpyrrolidin-2-one (13). (BH7-048)



13

To a solution of 1.20 g (4.27 mmol) of compound **12** in 50 mL of vinyl acetate under argon, were added 4.0 g of 3 Å molecular sieves, 27 mg (0.34 mmol) of Na_2PdCl_4, and 1.06 g (7.69 mmol) of K_2CO_3. The mixture was stirred at 50°C under argon for 28 hours, cooled to 25°C, filtered, concentrated under vacuum, and column chromatographed on silica gel using a mixture of hexane and diethyl ether (1:1) as an eluent to give 0.67 g (51% yield) of pure compound **13** as a brown oil. $[\alpha]_D^{22}$ = +24.6 (c 1.0, $CHCl_3$); ^1H NMR δ 7.35–7.20 (m, 10 H), 6.98 (dd, J = 16.4, 9.2 Hz, 1 H, CH=), 5.31 (s, 1 H), 4.38 (d, J = 9.2 Hz, 1 H, $=CH_2$), 4.34 (d, J = 16.4 Hz, 1 H, $=CH_2$), 4.13–4.08 (m, 1 H), 3.68 (dd, J = 9.2, 4.8 Hz, 1 H), 3.52 (dd, J = 9.2, 2.8 Hz, 1 H), 2.70 (dt, J = 17, 10 Hz, 1 H), 2.42–2.34 (m, 1 H), 2.20–2.11 (m, 2 H); ^{13}C NMR δ 178.8, 142.5, 138.1, 128.7 (4 C), 127.9 (2 C), 127.1 (4 C), 96.8, 84.2, 73.6, 54.0, 30.2, 23.7. MS (ESI, MeOH): *m/z* = 330.1 ($[M + Na]^+$). HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{20}H_{21}NO_2Na^+$: 330.1470; found: 330.1490.

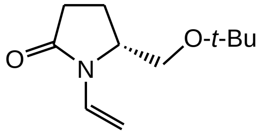
(*R*)-5-(*t*-Butyloxymethyl)pyrrolidin-2-one (14). (BH4-057)



14

A solution of 10.2 g (37.5 mmol) of compound **10** in 100 mL of 7% trifluoroacetic acid (TFA) in dichloromethane was stirred at 25°C for 15 minutes and then diluted with 30 mL of saturated $NaHCO_3$. The mixture was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with water, and brine, dried ($MgSO_4$), concentrated to give 6.28 g (98% yield) of compound **14** as a brown oil. This material was used in the subsequent step without further purification. $[\alpha]_D^{22}$ = -10.8 (c 1.0, $CHCl_3$); ^1H NMR δ 7.8–7.72 (bs, 1 H, NH), 3.94–3.86 (m, 1 H, CHN), 3.43 (dd, J = 9.0, 3.2 Hz, 1 H, CH_2O), 3.25 (dd, J = 9.0, 8.0 Hz, 1 H, CH_2O), 2.61–2.45 (m, 2 H, $CH_2C=O$), 2.28–2.18 (m, 1 H), 1.86–1.75 (m, 1 H), 1.18 (s, 9 H); ^{13}C NMR δ 175.5, 74.4, 65.2, 59.7, 32.4, 28.0 (3 C), 22.5. MS (ESI, MeOH): *m/z* = 194.1 ([M + Na]$^+$; 100%), 172.3. HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_9H_{17}NO_2Na^+$: 194.1157; found: 194.1172.

(*R*)-5-(*t*-Butyloxymethyl)-1-vinylpyrrolidin-2-one (15). (BH4-058)

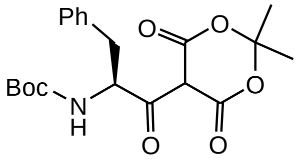


15

To a solution of 2.0 g (11.6 mmol) of compound **14** in 35 mL of vinyl acetate under argon, were added 4.0 g of 3 Å molecular sieves, 0.27 g (0.9 mmol) of Na_2PdCl_4, and 2.25 g (16.3 mmol) of K_2CO_3. The mixture was stirred at 50°C under argon for 14 hours, cooled to 25°C, filtered, concentrated under vacuum, and column chromatographed on silica gel using a mixture of hexane and ethyl acetate (1:2) as an eluent to give 0.96 g (42% yield) of pure compound **15** as a yellow oil. $[\alpha]_D^{22}$ = +9.6 (c 1.0, $CHCl_3$); ^{1}H NMR δ 7.0 (dd, J = 16, 9 Hz, 1H, CH=), 4.45 (d, J = 9 Hz, 1 H, =CH_2), 4.44 (d, J = 16 Hz, 1 H, =CH_2), 4.06–4.00 (m, 1 H, CHN), 3.52 (dd, J = 9.2, 4.8 Hz, 1 H, CH_2O), 3.41 (dd, J = 9.2, 2.8 Hz, 1 H, CH_2O), 2.64 (dt, J = 17.2, 10.8 Hz, 1 H), 2.35–2.26 (m, 1 H), 2.14–2.05 (m, 2 H), 1.13 (s, 9 H); ^{13}C NMR δ 175.3, 139.7, 93.1, 74.6, 63.5, 58.8, 32.4, 28.2 (3 X), 20.8. MS (ESI, MeOH): *m/z* = 220.2 ([M + Na]$^+$), 198.2 (M+H$^+$), 187.1. HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{11}H_{19}NO_2Na^+$: 220.1313; found: 220.1333.

(*S*)-*tert*-Butyl 1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-1-oxo-3-phenylpropan-2-ylcarbamate (17).

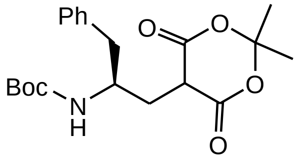
(BH1-042)



17

A solution of 1.33 g (5.0 mmol) of Boc-L-phenylalanine, 1.08 g (7.5 mmol) of Meldrum's acid, and 0.95 g (7.5 mmol) of 4-(dimethylamino)pyridine (DMAP) in 70 mL of dichloromethane under argon was cooled to 0^{o}C over an ice-water bath. To it, a solution of 1.13 (5.5 mmol) g of *N,N'*-dicyclohexylcarbodiimide (DCC) in 15 mL of dichloromethane was added dropwise. The mixture was stirred for 12 hours under argon and the precipitated (*N*,*N*'-dicyclohexylurea) was removed by filtration. The filtrate was washed with 5% HCl twice, and then water, dried (anhydrous Na_2SO_4), and concentrated to dryness leaving 1.90 g of **17** as white solid. This compound was used in the following step without further purification. ^{1}H NMR δ 7.3 -7.15 (m, 5 H), 4.5–4.4 (m, 1 H), 4.3–4.2 (m, 1 H), 3.9–3.8 (m, 1 H), 2.8–2.7 (m, 2 H), 1.7 (s, 3 H), 1.65 (s, 3 H); ^{13}C NMR δ 207.5, 170.8, 153.1, 135.8, 129.6 (2 C), 128.9 (2 C), 127.4, 105.7, 80.3, 62.7, 60.3, 33.8, 28.4, 26.8.

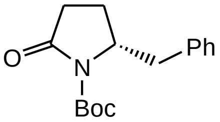
(*R*)-*tert*-Butyl 1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3-phenylpropan-2-ylcarbamate (18). (BH1-043)



18

To a cold (0^{o}C) solution of 1.90 g (4.85 mmol) of compound **17** in 25 mL of dichloromethane under argon were added 1.75 g (29.1 mmol) of acetic acid and 0.48 g (12.6 mmol) of $NaBH_4$. The solution was stirred at 0^{o}C for three hours and at 25^{o}C for 12 hours, diluted with 30 mL of water, the dichloromethane layer was separated, and the water layer was extracted with dichloromethane three times. The combined organic layers were washed with water and brine, dried ($MgSO_4$), concentrated to give 1.78 g of compound **18** as a white solid. This compound was used in the subsequent step without further purification. ^{1}H NMR δ 7.35–7.19 (m, 5 H), 4.48–4.43 (m, 1 H), 4.24–4.20 (m, 1 H), 3.92–3.90 (m, 1 H), 2.88–2.83 (m, 2 H), 2.31–2.11 (m, 2 H), 1.81 (s, 3 H), 1.77 (s, 3 H), 1.25 (s, 9 H); ^{13}C NMR δ 174.7, 150.2, 137.3, 129.6 (2 C), 129.0 (2 C), 127.1, 83.2, 59.2, 39.7, 31.3, 28.3 (3 C), 21.8.[41] MS (ESI, MeOH): *m/z* = 400.2 ($[M + Na]^+$).

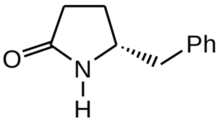
(*R*)-*N*-(*tert*-Butoxycarbonyl)-5-benzylpyrrolidin-2-one (19). (BH1-029)



19

A solution of 0.35 g (0.93 mmol) of compound **18** in 20 mL of toluene under argon was heated to reflux for 4 hours, cooled to 25°C, concentrated, and column chromatographed on silica gel using hexane and ethyl acetate (4:1) as eluent to give 0.23 g (88% overall yield in three steps) of compound **19** as a yellow oil. The material was used in the subsequent step without purification. $[\alpha]_D^{22}$ = +48.7 (c 1.5, $CHCl_3$); Lit.[41] +48.5 (c 1.50, $CHCl_3$). ^{1}H NMR δ 7.34–7.29 (m, 2 H), 7.28–7.24 (m, 1 H), 7.20–7.17 (m, 2 H), 4.39–4.34 (m, 1 H, CHN), 3.13 (dd, J = 13.5, 4 Hz, 1 H), 2.73 (dd, J = 13.5, 9.6 Hz, 1 H), 2.35–2.27 (m, 2 H), 2.20–1.90 (m, 1 H), 1.85–1.76 (m, 1 H), 1.57 (s, 9 H); ^{13}C NMR δ 174.8, 150.1, 137.3, 129.6 (2 C), 129.0 (2 C), 127.1, 83.3, 59.3, 39.7, 31.3, 28.4 (3 C), 21.8. MS (ESI, MeOH): *m/z* = 298.1 ($[M + Na]^+$).

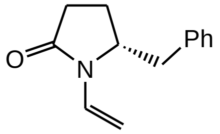
(*R*)-5-Benzylpyrrolidin-2-one (20). (BH2-053)



20

A solution of 1.0 g (12.9 mmol) of compound **19** in 5 mL of 10% trifluoroacetic acid in dichloromethane was stirred at 25°C for 2 hours, diluted with dichloromethane, and washed with an 10% aqueous solution of $NaHCO_3$, then water and brine, dried ($MgSO_4$), concentrated to give 0.61 g (96% yield) of compound **20** as a brown oil. This material was used in the subsequent step without further purification. $[\alpha]_D^{22}$ = +39.7 (c 1.19, EtOH); Lit.[41] +39.6 (c 1.19, EtOH). ^{1}H NMR δ 7.33–7.12 (m, 5 H), 5.95–5.90 (bs, 1 H, NH), 3.92–3.83 (m, 1 H, CHN), 2.83 (dd, J = 13.4, 5.6 Hz, 1 H), 2.72 (dd, J = 13.4, 7.6 Hz, 1 H), 2.34–2.20 (m, 3 H), 1.89–1.80 (m, 1 H); ^{13}C NMR δ 178.1, 137.8, 129.3 (2 C), 129.2 (2 C), 127.1, 55.9, 43.2, 30.3, 27.2; MS (ESI, MeOH): *m/z* = 198.1 ($[M + Na]^+$).

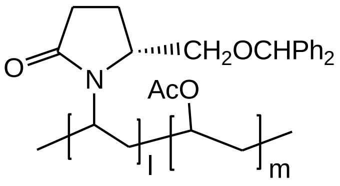
(*R*)-5-(Benzyl)-1-vinylpyrrolidin-2-one (21). (BH2-059)



21

To a solution of 0.60 g (3.42 mmol) of compound **20** in 30 mL of vinyl acetate under argon, were added 2.0 g of 3 Å molecular sieves, 88 mg (0.30 mmol) of Na_2PdCl_4, and 0.86 g (6.2 mmol) of K_2CO_3. The mixture was stirred at 50°C under argon for 28 hours, cooled to 25°C, filtered, concentrated under vacuum, and column chromatographed on silica gel using a mixture of hexane and diethyl ether (1:1) as an eluent to give 0.46 g (67% yield) of pure compound **21** as a yellow oil. $[\alpha]_D^{22}$ = +38.3 (c 1.0, $CHCl_3$); ^{1}H NMR δ 7.34–7.23 (m, 3 H), 7.18–7.14 (m, 2 H), 7.08 (dd, J = 16.4, 9.6 Hz, 1 H, =CH), 4.63 (d, J = 16.4 Hz, 1 H, $=CH_2$), 4.60 (d, J = 9.6 Hz, 1 H, $=CH_2$), 4.22- 4.17 (m, 1 H, CHN), 3.00 (dd, J = 14, 3 Hz, 1 H), 2.81 (dd, J = 14, 8 Hz, 1 H), 2.24–2.17 (m, 1 H), 2.10–1.91 (m, 3 H); ^{13}C NMR δ 173.7, 137.1, 129.7, 128.9 (2 C), 128.4, 127.1 (2 C), 95.3, 57.0, 36.6, 30.1, 22.8; MS (ESI, MeOH): *m/z* = 224.1 ($[M + Na]^+$), 202.0 ($M+H^+$; 100%). HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{13}H_{15}NONa$: 224.1051; found: 224.1076.

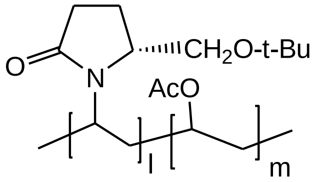
Copolymer 22 from (*R*)-5-(benzhydryloxymethyl)-1-vinylpyrrolidin-2-one (13) and vinylacetate. (BH7-040)



22

To a solution of 93 mg (0.33 mmol) of compound **13** and 28 mg (0.33 mmol) of vinyl acetate in 0.15 mL of acetone under argon, was added 10 mg (0.066 mmol) of AIBN, and the solution was stirred under reflux for 30 h. The solution was cooled to 25°C, diluted with hexane, and stirred for 10 min. The white precipitate was collected by filtration, dried under vacuum to give 0.106 g (88% yield) of copolymer **22** as a white solid. ^{1}H NMR δ 7.50–6.3 (m, 11 H, Ph & CH), 3.6–1.0 (m, 16 H).

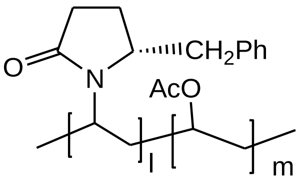
Copolymer 23 from (*R*)-5-(*tert*-butoxymethyl)-1-vinylpyrrolidin-2-one (15) and vinylacetate. (BH3-035)



23

From 30 mg (0.15 mmol) of **15**, 13 mg (0.15 mmol) of vinyl acetate and 0.25 mg of AIBN, copolymer **23**, 39 mg (90% yield), was obtained. ^{1}H NMR δ 4.90–2.75 (m, 5 H), 2.70–0.80 (m, 20 H).

Copolymer 24 from (*R*)-5-benzyl-1-vinylpyrrolidin-2-one (21) and vinylacetate. (BH1-045)

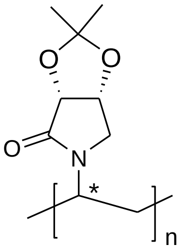


24

From 50 mg (0.25 mmol) of monomer **21**, 21.4 mg (0.25 mmol) of vinyl acetate and 0.7 mg of AIBN, copolymer **24**, 65 mg (91% yield), was obtained. ^{1}H NMR δ 7.20–6.80 (m, 3 H), 6.75–6.30 (m, 2 H), 3.50–3.00 (m, 3 H), 2.5–1.1 (m, 13 H).

Poly[(3a*R*,6a*R*)-2,2-dimethyl-5-vinyl-dihydro-3a*H*-[1,3]dioxolo[4,5-c]pyrrol-4(5*H*)-one] (25).

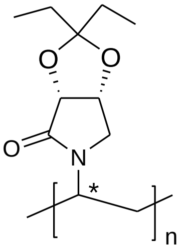
(BH9-043)



25

To a solution of 0.3 mg (0.2% by weight) of copolymer **35** in 0.5 mL of ethyl acetate under argon, were added 70 mg (0.38 mmol) of compound **33** and 0.3 mg (2 μmol) of AIBN. The solution was stirred for 2 days at 70°C (until no monomer **33** was detected by NMR spectrum of an aliquot from the reaction solution), cooled to 25°C, and diluted with hexane. The precipitate was collected by filtration, dried under vacuum to give 63 mg (90% yield) of polymer **25** as a white solid. The average molecular weight of polymer **25**, 75,000 (n = 410), was determined by gel permeation chromatography using TSKgel GMHxl column and water as solvent with a flow rate of 1 mL/min. $[\alpha]_D^{22}$ = -74.3 (c 1.6, H_2O); ^{1}H NMR δ 4.7–4.3 (m, 2 H, CHO), 3.8–3.0 (m, 3 H, CHN, CH_2N), 1.6–1.1 (8 H, CH_2, 2 CH_3); ^{13}C NMR δ 161.0, 113.0, 74.7, 72.1, 48.7, 47.8, 46.1, 45.6, 27.2, 25.9. IR (neat) ν 3020, 2940, 2143, 1648 (s), 1420, 1285, 1169, 1024, 830.

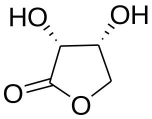
Poly[(3a*R*,6a*R*)-2,2-diethyl-5-vinyl-dihydro-3a*H*-[1,3]dioxolo[4,5-c]pyrrol-4(5*H*)-one] (26). (BH10-016)



26

To a solution of 0.4 mg (0.2% by weight) of copolymer **36** in 0.8 mL of ethyl acetate under argon, were added 0.18 g (0.99 mmol) of compound **34** and 0.72 mg (4 μmol) of AIBN. The solution was stirred for 2 days at 70°C (until no monomer **34** was detected by NMR spectrum of an aliquot from the reaction solution), cooled to 25°C, and diluted with hexane. The precipitate was collected by filtration, dried under vacuum to give 0.16 g (91% yield) of polymer **26** as a white solid. The average molecular weight of polymer **26**, 92,000 (n = 436), was determined by gel permeation chromatography using TSKgel GMHxl column and water as solvent with a flow rate of 1 mL/min. $[\alpha]_D^{22}$ = -138.9 (c 1.8, H_2O); ^{1}H NMR δ 4.7–4.6 (m, 2 H, CHO), 3.7–3.0 (m, 3 H, CHN, CH_2N), 1.6–1.3 (6 H, CH_2), 0.9–0.6 (m, 6 H, CH_3); ^{13}C NMR δ 160.9, 113.5, 74.7, 73.0, 48.8, 47.7, 43.0, 42.7, 29.2, 28.5, 8.4, 7.0. IR (neat) ν 3423, 2949, 2884, 1648 (s), 1460, 1420, 1270, 842; UV-Vis 299 nm (ε = 45090 L mol^{-1}cm^{-1}).

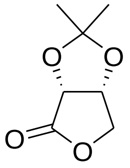
(3*R*,4*R*)-3,4-Dihydroxy-dihydrofuran-2(3H)-one (28). (BH11-084)



28

To a cold (0 °C) solution of 17.6 g (0.1 mol) of *D*-isoascorbic acid (**27**) in 250 mL of H_2O, 21.2 g (0.2 mol) of Na_2CO_3 and 22.7 g (0.2 mol) of 30% H_2O_2 were added dropwise, the solution was stirred at 0 °C for 10 minutes and 42 °C for 30 minutes. To the reaction solution, 4.0 g of activated charcoal was added in portion over 10 minutes, and the mixture was stirred at 80 °C for 30 minutes, filtered through Celite during hot and washed the filter cake with 50 mL of H_2O. The filtrate was carefully acidified with 6 *N* HCl until pH 1, concentrated on a rotary evaporator and then under vacuum to give 36.9 g of solid. The crude products were purified by adding 200 mL of ethyl acetate and heating to reflux for 10 minutes. The hot solution was filtered and the filtrate containing the desired product was saved. The extraction of the product from the solid was repeated by refluxing in 200 mL of ethyl acetate and filtered. Both filtrates were combined, cool over an ice-water bath, and the crystallized white solid was collected by filtration to give 11.0 g (94 % yield) of the titled compound. $[\alpha]_D^{22}$ = -73.2 (c 0.5, H_2O), Lit[22] $[\alpha]_D^{22}$ = -72.8 (c 0.498, H_2O); ^{1}H NMR (DMSO-d6) δ 5.75 (dd, *J* = 7.2, 3.2 Hz, 1 H, OH), 5.34 (s, 1 H, OH), 4.39–4.34 (m, 1 H), 4.26 (dt, *J* = 10, 3.2 Hz, 1 H), 4.24–4.19 (m, 1 H), 4.03 (dd, *J* = 10, 3.2 Hz 1 H); ^{13}C NMR (DMSO-d6) δ 177.1, 72.5, 70.1, 69.0; MS (ESI, MeOH): m/z = 141.4 ($[M + Na]^+$), 72.4.

(2*R*,3*R*)-*O*-Isopropylidene-D-erythronolactone (29). (BH9-145)

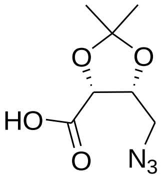


29

To a solution of 1.6 g (13.6 mmol) of **28** in 25 mL of anhydrous acetone under argon, 4.5 g (28.5 mmol) of $CuSO_4$ was added. The mixture was stirred for 36 hours and the precipitated inorganic salt was removed by filtration over a pad of Celite. The filtrate was concentrated to dryness leaving 2.32 g of yellow solid. The crude product was column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as an eluent to give 1.90 g (89% yield) of the titled compound as a pale yellow solid. $[\alpha]_D^{22}$ = -114.64 (c 1.5, acetone), Lit[42]. $[\alpha]_D^{20}$ = +116.3 (c 1.5, acetone); ^{1}H NMR δ 4.85 (bs, 1 H), 4.72 (bs, 1 H), 4.39 (bs, 2 H), 1.42

(s, 3 H), 1.34 (s, 3 H); ^{13}C NMR δ 174.8, 113.9, 75.8, 74.8, 70.5, 26.9, 25.6; MS (ESI, MeOH): m/z = 181.3 ($[M + Na]^+$), 95.6.

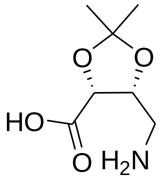
(2*R*,3*R*)-4-Azido-4-deoxy-2,3-*O*-isopropylidene-D-erythronic acid (30). (BH9-147)



30

A solution of 1.90 g (12.0 mmol) of **29** and 2.73 g (42.1 mmol) of NaN_3 in 12 mL of distilled DMF was heated to 110 °C under argon for 24 hours. The reaction solution was diluted with 500 mL of diethyl ether, 10 mL of H_2O and 20% aqueous HCl to pH 2, and extracted with 40 mL of ethyl acetate four times. The combined extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as an eluent to give 1.03 g (42% yield) of the titled compound as a pale yellow solid. The major by-product was azido((4R,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanone. $[\alpha]^{22}_{D}$ (c 0.47, acetone); Lit.[30] +72 (c 0.47, acetone); ^{1}H NMR δ 9.52–9.0 (bs, 1 H, OH), 4.67 (d, *J* = 7.2 Hz, 1 H), 4.60–4.56 (m, 1 H), 3.60 (dd, *J* = 13.2, 3.2 Hz, 1 H), 3.40 (dd, *J* = 13.2, 6 Hz, 1 H), 1.63 (s, 3 H), 1.42 (s, 3 H); ^{13}C NMR δ 172.2, 112.2, 73.8, 70.8, 52.0, 27.1, 26.2; MS (ESI, MeOH): m/z = 224.1 ($[M + Na]^+$), 143.6, 85.6.

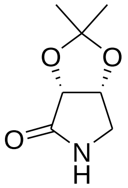
(2*R*,3*R*)-4-Amino-4-deoxy-2,3-*O*-isopropylidene-D-erythronic acid (31). (BH9-151)



31

To a solution of 1.01 g (5.0 mmol) of **30** in 100 mL of methanol, 50 mg of 10% Pd/C was added, and the mixture was shake under 2 atm. of hydrogen gas for 4 hours in a hydrogenator. The mixture was removed from the hydrogenator, filtered through a pad of Celite, the filtrated was concentrated to dryness leaving 0.86 g (99% yield) of the titled compound as a pale yellow solid. $[\alpha]_D^{22}$ = +91.6 (c 1.0, 60% aqueous acetone), Lit[30] $[\alpha]_D^{20}$ = +92 (c 1.02, 60% aqueous acetone); ^{1}H NMR (DMSO-d6) δ 4.39 (d, *J* = 7.2 Hz, 1 H), 4.31–4.24 (m, 1 H), 2.76 (t, *J* = 8 Hz, 2 H), 1.39 (s, 3 H), 1.23 (s, 3 H); MS (ESI, MeOH): m/z = 176.1 ($[M + H]^+$), 198.1 ($[M + Na]^+$).

(2*R*,3*R*)-4-Amino-4-deoxy-2,3-*O*-isopropylidene-*D*-erythronolactam (32). (BH9-031)

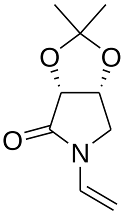


32

An amount of 0.16 g (0.93 mmol) of **31** was placed in a sublimator and heated to 160–170 °C/0.5 mm Hg under vacuum, and 92 mg (63% yield) of **32** was obtained as white solid. This material was used in the subsequent step without further purification. $[\alpha]^{22}_D$ = -60.3(c 0.78, MeOH); Lit[30]. -59 (c 0.78, MeOH); ^{1}H NMR δ 6.31 (bs, 1 H, NH), 4.79 (t, *J* = 5.2 Hz, 1 H), 4.58 (d, *J* = 6 Hz, 1 H), 3.59 (dd, J = 11, 4.8 Hz, 1 H), 3.49 (d, J = 11 Hz, 1 H), 1.49 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR δ 174.4, 113.0, 76.7, 74.9, 46.0, 27.2, 25.8; MS (ESI, MeOH): m/z = 158.4 ($[M + H]^+$).

(2*R*,3*R*)-4-Amino-4-deoxy-2,3-*O*-isopropylidene-*N*-vinyl-D-erythronolactam (33).

(BH9-035)

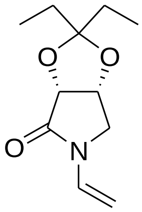


33

To a solution of 90 mg (0.57 mmol) of compound **32** in 10 mL of vinyl acetate under argon, were added 1.0 g of 3 Å molecular sieves, 13 mg (0.046 mmol) of Na_2PdCl_4, and 0.14 g (1.03 mmol) of K_2CO_3. The mixture was stirred at 50°C for 14 hours, cooled to 25°C, filtered through Celite, concentrated under vacuum, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as an eluent to give 84 mg (80% yield) of **33** as a yellow oil. $[\alpha]_D$ -20.1(c 1.0, $CHCl_3$); ^{1}H NMR δ 7.05 (dd, *J* = 16.0, 9.2 Hz, 1 H, CH=), 4.82–4.79 (m, 1 H), 4.70 (d, *J* = 6.4 Hz, 1 H), 4.53 (d, *J* = 9.2 Hz, 1 H, $=CH_2$), 4.48 (d, *J* = 16 Hz, 1 H, $=CH_2$), 3.62 (d, *J* = 2.8 Hz, 2 H), 1.39 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR δ 169.4, 129.2, 113.0, 96.7, 78.1, 72.1, 48.7, 27.2, 25.9; MS (ESI, MeOH): m/z = 184.0 ($[M + H]^+$). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_9H_{14}NO_3^+$: 184.0974 found: 184.0952.

(3a*R*,6a*R*)-5-Vinyl-2,2-diethyl-dihydro-3a*H*-[1,3]dioxolo[4,5-c]pyrrol-4(5*H*)-one (34).

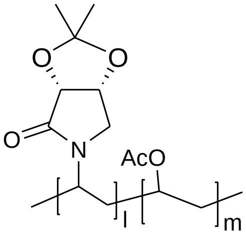
(BH10-011)



34

A mixture of 0.25 g (1.37 mmol) of compound **33**, 5 mg of $ZnCl_2$ (0.04 mmol) and 7 mL of 3-pentanone was placed in a distillation apparatus equipped with a short distill head and heated to 65 °C to remove the by-product acetone over 40 hours. The resulting mixture was diethyl ether, filtered through Celite, and washed with a small amount of diethyl ether. The filtrate was concentrated under vacuum and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as an eluent to give 192 mg (67% yield) of **34** as a yellow oil. $[\alpha]_D$ -43.2 (c 1.0, $CHCl_3$); ^{1}H NMR δ 7.07 (dd, *J* = 16.0, 9.2 Hz, 1 H, CH=), 4.84–4.81 (m, 1 H), 4.72 (d, *J* = 6.4 Hz, 1 H), 4.55 (d, *J* = 9.2 Hz, 1 H, $=CH_2$), 4.49 (d, *J* = 16 Hz, 1 H, $=CH_2$), 3.64 (d, *J* = 2.8 Hz, 2 H), 1.70 (q, *J* = 7.2 Hz, 2 H), 1.65 (q, *J* = 7.2 Hz, 2 H), 0.91 (t, *J* = 6 Hz, 6 H); ^{13}C NMR δ 169.3, 128.8, 115.5, 96.6, 78.0, 71.9, 48.6, 30.0, 29.6, 8.4, 7.6. MS (ESI, MeOH): m/z = 212.2 ($[M + H]^+$) 234.3 ($[M + Na]^+$). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{11}H_{18}NO_3^+$: 212.1287 found: 212.1269.

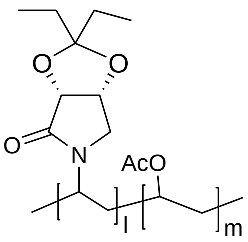
Poly(3,4-disubstituted *N*-vinyl pyrrolidinone-co-vinyl acetate) [P(DVP-co-VAc)] 35 from compound 33 and vinyl acetate. (BH9-042)



35

To a solution of 10 mg (55 μmol) of *N*-vinylpyrrolidinone 33 and 4.7 mg (55 μmol) of vinyl acetate in 20 μL of acetone under argon, was added 0.1 mg (0.6 μmol) of azobisisobutyronitrile (AIBN), and the solution was stirred under reflux for 30 h. The solution was cooled to 25°C, diluted with hexane, and stirred for 10 min. The white precipitate was collected by filtration, dried under vacuum to give 12 mg (82% yield) of copolymer **35** as a white solid. ^{1}H NMR δ 4.90–2.75 (m, 5 H), 2.70–0.80 (m, 22 H).

Poly(3,4-disubstituted *N*-vinyl pyrrolidinone-co-vinyl acetate) [P(DVP-co-VAc)] 36 from compound 34 and vinyl acetate. (BH10-15)



36

To a solution of 15 mg (55 μmol) of compound **34** and 4.7 mg (55 μmol) of vinyl acetate in 20 μL of acetone under argon, was added 0.1 mg (0.6 μmol) of AIBN, and the solution was stirred under reflux for 30 h. The solution was cooled to 25°C, diluted with hexane, and stirred for 10 min. The white precipitate was collected by filtration, dried under vacuum to give 17.2 mg (87% yield) of copolymer **36** as a white solid. ^{1}H NMR δ 4.90–2.75 (m, 5 H), 2.70–0.80 (m, 26 H).

Chapter 2 - Asymmetric Oxidation Reactions and Late Stage Oxidation Reactions Catalyzed by Bimetallic Nanoclusters

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Organic transformation reactions using bimetallic nanoclusters[15] in the oxidation of alcohols,[10, 43, 44] formic acid oxidation,[45] aldehyde oxidation,[46] C-H oxidation,[36] Ullmann coupling,[47] Suzuki coupling reaction,[48] tandem oxidation-Michael addition reaction,[49] have been reported. However, these reports do not include studies of enantio- or stereo-selectivity.

Catalytic asymmetric oxidation is challenging and the results can have a great impact to the chemistry community. With the catalysis of CSPVP stabilized bimetallic nanoclusters, several kinds of the oxidation reaction, including alcohol oxidations, alkene dihydroxylations, alkane C-H oxidations, oxidative ring closing of dienes and late-stage oxidations of complex molecules are all investigated and discussed in this chapter.

2.1 Selective Asymmetric Oxidation Reactions of Alcohols.

2.1.1 Background and Significance

Oxidation of alcohols to their respective aldehyde or ketone is a useful and fundamental organic reaction. Many methods have been developed by inducing stoichiometric amount of oxidants, which may produce large amount of highly polluted and toxic waste, such as bromate[50], permanganate[51] or chromate[52]. Recently, transition metal nanoparticle–catalyzed aerobic alcohol oxidation with high catalytic activity and selectivity has been investigated. [10, 44]

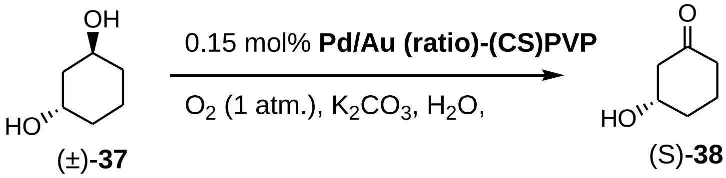
Alcohol can be selectively oxidized to ketone or aldehyde in the presence of other functional groups.

Although desymmetrization of meso diols and diol derivatives using various organic reagents and enzymes have appeared,[53-55] reports on the enantioselective oxidation of a mixture of racemic diols *via* kinetic resolution are limited, with the exception of oxidation of racemic benzylic vicinal diols.[56] Hence, asymmetric oxidation of racemic diols by kinetic resolution or meso diols using bimetallic nanoclusters with chiral stabilizer may give high catalytic activity, regio- and enantioselectivity.

2.1.2 Results and Discussions

With the general idea, (±)-*trans*-1,3-cyclohexanediol (**37**) was used to study the reaction conditions and possible products. (±)-*trans*-1,3-cyclohexanediol was prepared by the seperation of mixture of *cis* & *trans*-1,3-cyclohexanediol by adding $CuCl_2$. *cis*-1,3-Cyclohexanediol was precipitated in diethyl ether due to the formation of complex with Cu^{2+} and *trans*-1,3-cyclohexanediol remained in diethyl ether. Ammonia acetone solution was used to destroyed the *cis*-1,3-cyclohexanediol/Cu^{2+} complex and yield pure *cis*-1,3-cyclohexanediol (**44**).

For instance, treatment of (±)-**37** with 0.2 mol% Pd/Au–CSPVP **3** (the amount of catalyst is based on the total moles of Pd and Au) and 0.3 equiv of K_2CO_3 in water under 1 atmospheric oxygen to yield (*S*)-3-hydroxycyclohexanone (**38**). After screening different ratios of Pd versus Au such as 1:0, 9:1, 3:1, 1:1, 0:1 of the bimetallic nanoclusters, Pd/Au (3:1)-CSPVP appears to provide the highest catalytic activity and chemical yields in the aerobic catalytic asymmetric oxidation of (±)-*trans*-cyclohexanediol (**37**).(**Table 4**, entries 1–5) Higher temperature was needed when using palladium without gold and the reaction gave lower enantioselectivity. However, gold nanaclusters cannot catalyze the oxidation reaction even under 100 ^{o}C which indicate palladium is the real catalyst in the reaction and gold can improve the catalytic reactivity. Another control experiment was conducted by using normal PVP (MW = 40,000) instead of CSPVP, which gave achiral product. It is also an evidence which shows the chiral environment was induced from CSPVP.(**Table 4**, entry 6)



entry	PVP	Pd:Au	reaction time	Temperature(^{o}C)	% yield	% ee
1	**3**	1:0	14 days	80	42	64
2	**3**	9:1	14 days	60	44	83
3	**3**	3:1	7 days	60	47	88
4	**3**	1:1	7 days	60	38	82
5	**3**	0:1		no reaction under 100 ^{o}C		
6	achiral	3:1	7 days	60	46	0

Table 4. Reaction Condition Studies for the Oxidation of (±)-*trans*-cyclohexanediol(37).

After understanding the best ratio of Pd/Au, the reaction condition was consistently used for the oxidation of (±)-*trans*-cycloalkanediols to give the similar and comparable results. The first generation of polymer **1** – **4** were tested in the same reaction condition. 0.2 mol% of Pd/Au (3:1)-CSPVP **1** – **4** and 0.3 equiv. of K_2CO_3 in water under 1 atmospheric oxygen at 60 ^{o}C for 7 days was used for the oxidation of (±)-*trans*-1,3-cyclohexanediols (**37**) and gave 46–49% chemical yields and 70–99% ee of (*S*)-3-hydroxycyclohexanone (**38**) along with the recovered

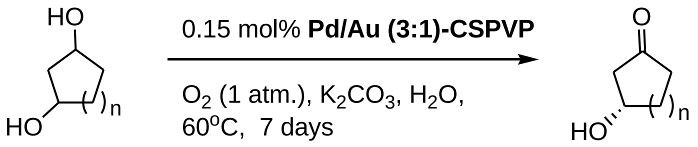
(*R*,*R*)-**37** (**Table 5**, entries 1–4). It appears CSPVP**1** gives the best enantioselectivity due to the bulkiest C5-substituent group. It is also another provement thet the enantioselective oxidation was because of the appearance of CSPVP. Therefore, Pd:Au(3:1)-CSPVP**1** was locked to be the catalyst of diol oxidation reactions.

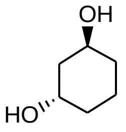
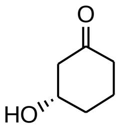
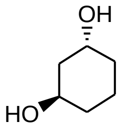
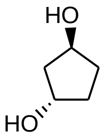
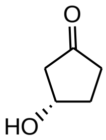
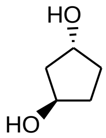
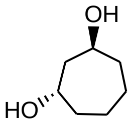
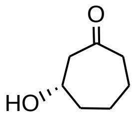
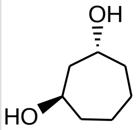
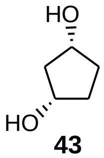
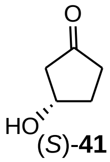
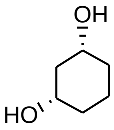
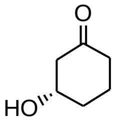
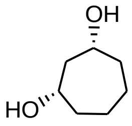
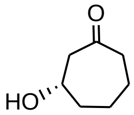
Through kinetic resolution, two enantiomers react with different reaction rates in a chemical reaction with a chiral catalyst, resulting in an enatioencriched sample of the less reactive enantiomer. In the oxidation of (±)-*trans*-1,3-cyclohexanediols (**37**), 50% of diols was recovered with 92% ee, which means at least 96% of (*R*,*R*)-**37** was not oxidized in 7 days. With the kinetic resolution of Pd:Au(3:1)-CSPVP**1,** (*S*,*S*)-**37** was oxidaized much faster than (*R*,*R*)-**37**. Therefore, stopping the reaction before half of the starting material reacted was needed to get optical pure (*S*)-**38**. Since the reactions were difficult to stop at exactly half point and partial of (*S*,*S*)-**37** remained in the recovered enriched (*R*,*R*)-**37**, the enantiomeric excess of the recovered (*R*,*R*)-**37** was related to the experiment operation and have potential to increase. It also provides an effective way to separate the racemic **37** to (*R*,*R*)-**37** from (*S*,*S*)-**37.** Moreover, hydroxyl ketone (*S*)-**38** did not undergo oxidation, revealing an electron-withdrawing ketone group impeded further oxidation.

Using 0.2 mol% of Pd/Au (3:1)-**1**, other five- and seven-membered cycloalkanes, such as 1,3-*trans*-cycloalkanediols (±)-**39,** (±)-**40** and *trans*-1,2-cycloalkanediols (±)-**46**–(±)-**48**, were similarly oxidized to give excellent chemical and optical yields. Results are presented in **Table 5** (entries 5 and 6, and entries 10–12). *trans*-(±)-**39** and *trans*-(±)-**40** were obtained with Cu^{2+} complex method similar like *trans*-(±)-**37**. *trans*-(±)-**46**–(±)-**48** were separated from mixture of *cis* and *trans* mixture by column chromatography on silica gel. Meanwhile, *cis*-**43–45** and **52**–**54** were isolated for oxidation study.

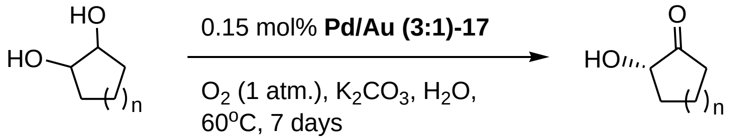
When the amounts of catalysts were increased to 0.40 mol% (double) or 0.80 mol% (quadruple) of Pd/Au (3:1)-**1**, the oxidation of (±)-**37** were respectively completed in 6 and 5 days, with chemical yields of 47% (99% ee) and 49% (99% ee) of (*S*)-**38**. Hence, an increase of the amounts of catalyst shortens the reaction time. The recyclability of the Pd/Au (3:1)-**1** catalyst was also examined. Hence, the catalyst, recovered from the oxidation reaction of (±)-**37**, was reused under similar reaction conditions for a second time, and 39% yield (99% ee) of (S)-**38** was isolated. The catalyst was further recycled for a third time but only 18% yield (98% ee) of (S)-**38** was obtained, showing the catalyst can be reused albeit with lower catalytic activities. The turnover number (TON) of the catalytic oxidation reaction after three cycles is > 706.

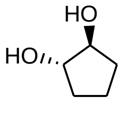
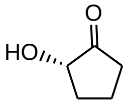
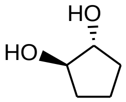
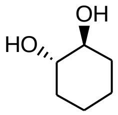
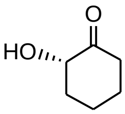
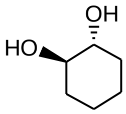
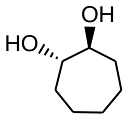
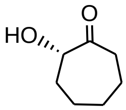
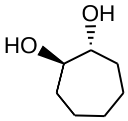
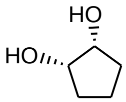
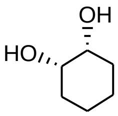
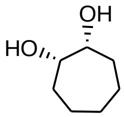
The meso 1,3 and 1,2-*cis*-cycloalkanediols do not undergo oxidation reaction under similar reaction conditions as those of *trans*-diols. It may due to the fact that *cis*-diols form stable complexes with the nanoparticles.[57] However, under elevated pressure of oxygen (30 psi.) and temperature (120^{o}C), the reactions took place in 3 days to give 89–97% yields in 90–92% ee of the oxidized (*S*)-hydroxyl ketones (**Table 5**, entries 7–9 and entries 13–15). The higher reaction temperature (120^{o}C) lowered slightly the optical yields comparing with those obtained from *trans*-cycloalkanediols. This oxidative desymmetrization of meso-diols is synthetically useful, since it provides the chiral hydroxyketones without the recovery of starting diols. Importantly, both *trans*- and *cis*-diols gave only the (S)-hydroxy ketones. No changes in reaction rate and chemical and optical yields in the oxidation reaction of meso-**53** were found when doubling the amount of **1** but maintaining the amount of Pd/Au (3:1).



entry	substrate	**CSPVP**	product	% yield$^{(a)}$	% ee	recovered diol	% yield$^{(b)}$	% ee
1	 (±)-**37**	**1**	 (S)-**38**	49	99	 (*R*,*R*)-**37**	50	92
2	(±)-**37**	**2**	(S)-**38**	46	83	(*R*,*R*)-**37**	52	79
3	(±)-**37**	**3**	(S)-**38**	46.5	88	(*R*,*R*)-**37**	52	81
4	(±)-**37**	**4**	(S)-**38**	46	70	(*R*,*R*)-**37**	51	65
5	 (±)-**39**	**1**	 (*S*)-**41**	48	99	 (*R*,*R*)-**39**	53	91
6	 (±)-**40**	**1**	 (*S*)-**42**	46	99	 (*R*,*R*)-**40**	53	85
7$^{(c)}$	 **43**	**1**	 (*S*)-**41**	97	90	-	-	-
8$^{(c)}$	 **44**	**1**	 (S)-**38**	89	91	-	-	-
9$^{(c)}$	 **45**	**1**	 (*S*)-**42**	94.5	92	-	-	-

(to be continued)

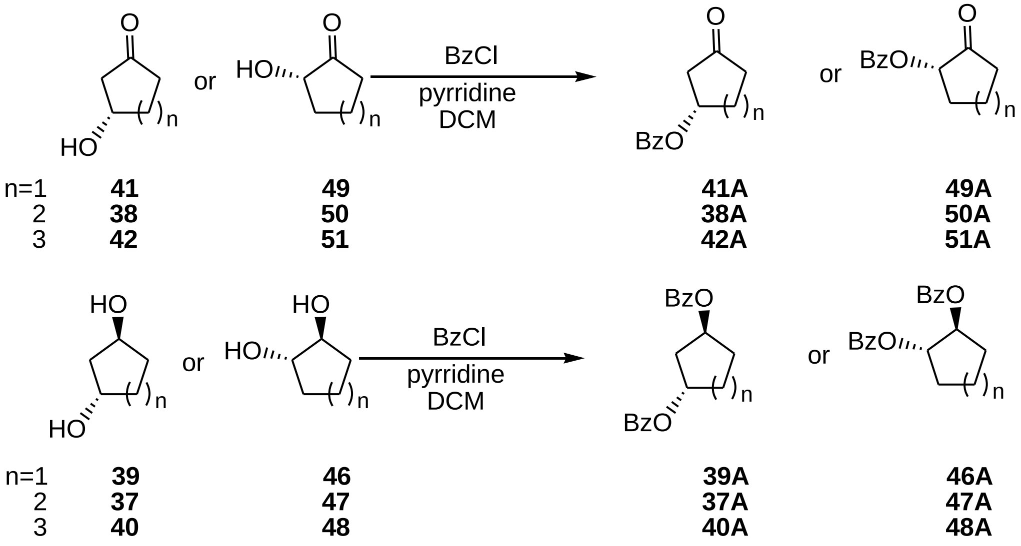


entry	substrate	**CSPVP**	product	% yield[(a)]	% ee	recovered diol	% yield[(b)]	% ee
10	 (±)-**46**	**1**	 (*S*)-**49**	47	99	 (*R*,*R*)-**46**	50	88
11	 (±)-**47**	**1**	 (S)-**50**	44.5	99	 (*R*,*R*)-**47**	50	87
12	 (±)-**48**	**1**	 (*S*)-**51**	46.5	99	 (*R*,*R*)-**48**	54	88
13[(c)]	 **52**	**1**	(*S*)-**49**	94	91	-	-	-
14[(c)]	 **53**	**1**	(S)-**50**	96.5	92	-	-	-
15[(c)]	 **54**	**1**	(*S*)-**51**	94	91	-	-	-

(a) Isolated yields were based on starting racemic or meso-diols. (b) Percent recoveries were based on recovered unreacted starting diols. (c) Reactions were carried out at 120°C under 30 psi. of oxygen for 3 days.

Table 5. Results of Catalytic Asymmetric Oxidation of 1,3 and 1,2-Cycloalkanediols.

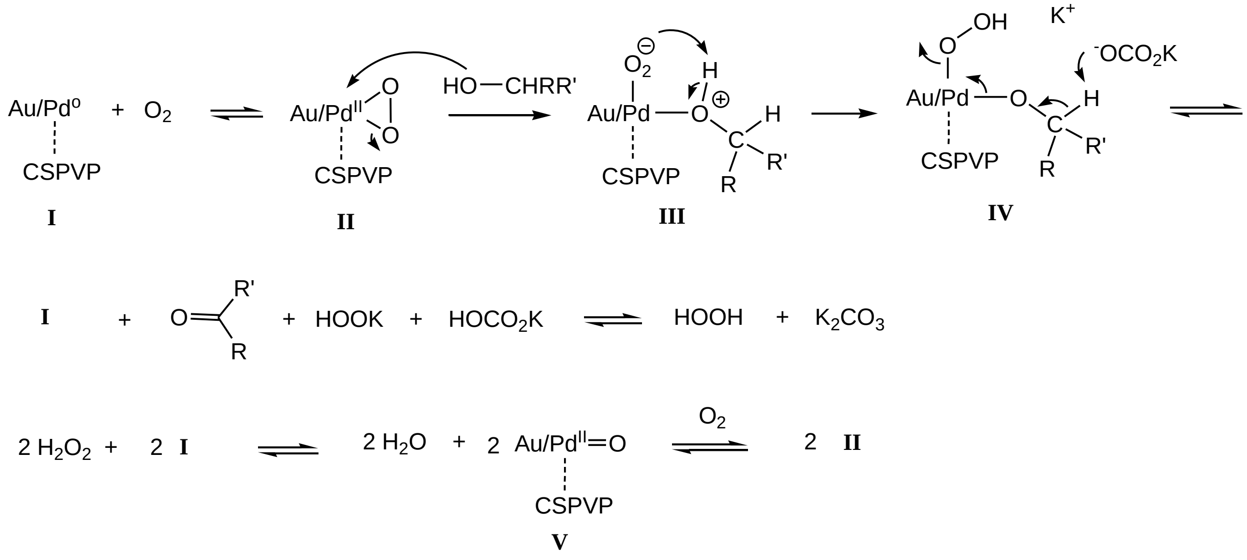
The absolute configurations of (*S*)-**38**, (*S*)-**41** and (*S*)-**49**–(*S*)-**51** were determined by comparison of the sign of the reported specific rotations.[58-61] The specific rotation of (*S*)-**42** has not been reported previously and its absolute configuration was assumed based on the retention time of its benzoate derivative in HPLC/chiral column. Optical purities were measured through HPLC/chiral column of their benzoyl derivatives, which were synthesized by the treatment of the hydroxyl ketones with benzoyl chloride and pyridine. In all cases, PVP was used in place of CSPVP under similar reaction conditions to provide the racemic products for HPLC/chiral column analyses. The absolute configurations and optical purities of the unreacted diols (*R*,*R*)-**37,** (*R*,*R*)-**39**, (*R*,*R*)-**40** and (*R*,*R*)-**46**–(*R*,*R*)-**48** were similarly determined by comparison of the sign of the reported specific rotations[62, 63] and through HPLC/chiral column of their dibenzoate derivatives obtained from the reactions of the diols with benzoyl chloride and pyridine. (**Scheme 7**)



Scheme 7. Benzoylation of (*S*)-Hydroxycycloalkanones and Dibenzoylation of Recovered (*R*,*R*)-Cycloalkanediols.

Dr. Hua has proposed the mechanism for the oxidation of diols.[1] (**Scheme 8)** It has been reported a η^2-peroxido Pd^{II} (peroxopalladium) species **II**[64] formed with the oxidation of Pd(0).[65] Then the hydroxyl group in diols attacks Pd(II), open the three membered ring and gives complex **III**, which undergoes proton transfer to give **IV**. Finally, the base, K_2CO_3, removes the C-1 proton and gives the corresponding ketone, **I** and H_2O_2. Oxidation of **I** with H_2O_2 gives **II** and go into next catalytic circle.[66] The exact mechanism for the enantioselectivity is not clear.

Nanoclusters Pd/Au-CSPVP provides excellent enantioselectivities (91–99% ee) in the oxidation of diols, and results of the enantioselectivity from the oxidation of *trans*-diols are comparable to those reported using enzymes.[67, 68]



Scheme 8. Proposed Mechanism for the Asymmetric Catalytic Oxidation of Racemic and Meso 1,3-Cycloalkanediols and 1,2-Cycloalkanediols.

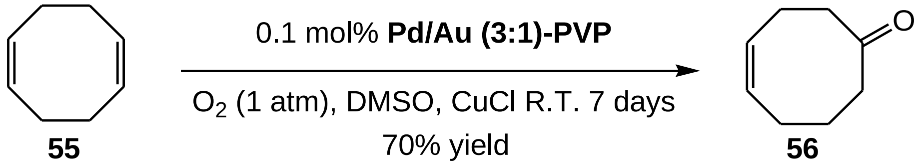
2.2 Asymmetric Dihydroxylation of Alkenes.

2.2.1 Background and Significance

The development of catalytic reaction of alkene transformed the chemical industry and gave various ways for the organic synthesis. For example, the Nobel Prize in chemistry 2001 was divided to Professor Knowles, Noyori and Sharpless for their work on chirally catalyzed hydrogenation or dihydroxylation reactions. Dihydroxylation is the process by which an alkene is converted into a vicinal diol. Although there are many routes to accomplish this oxidation, the most common and direct processes use a high-oxidation-state transition metal, such as Prevost *anti*-Dihydroxylation[69], Upjohn *syn*-Dihydroxylation[70] and *syn*-Woodward Dihydroxylation[71], catalytic asymmetric *syn*-dihydroxylation reactions were majorly conducted by the Sharpless asymmetric dihydroxylation process.[72] However, the use of toxic and volatile osmium tetraoxide catalyst makes the reaction purification difficult. Moreover, the enantioselective dihydroxylation of some *Z*-1,2-disubstituted alkenes and alkenes containing stereogenic centers using Sharpless method gave lower enantioselectivity.[72] Therefore, Other asymmetric dihydroxylation reactions with osmium-free catalysts[73] including palladium-catalyzed difunctionalization of alkenes,[74] RuO_4,[75] $KMnO_4$,[76] and iron complexes[77] have also been investigated. Until now, Asymmetric dihydroxylation of alkenes using bimetallic nanoparticles and chiral polymers have not been discovered. Pd/Au(3:1)-CSPVP catalyst without osmium dihydroxylated alkenes with similar or higher enantioaselectivity compare with sharpless method.

2.2.2 Results and Discussions

Although no dihydroxylation of alkenes took place at 1 atmospheric of oxygen with Pd:Au(3:1)-PVP nanoclusters, but with the co-catalyst CuCl, (no reaction without CuCl) the corresponding ketone (**56**) was isolated from the oxidation of cyclooctadiene (**55**) with 70% yield in DMSO. The dihydroxylation product was not detected. (**Scheme 9**)



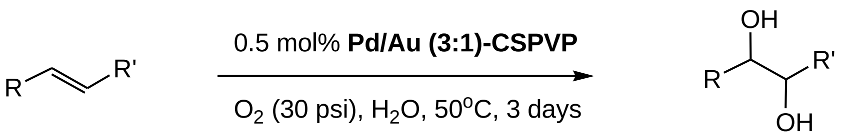
Scheme 9. Oxidation of Cyclooctadiene.

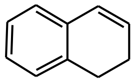
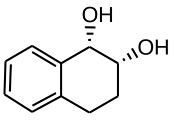
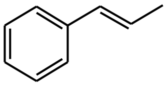
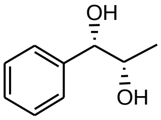
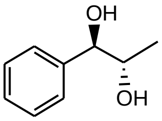
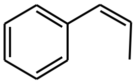
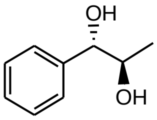
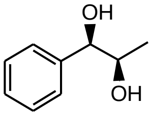
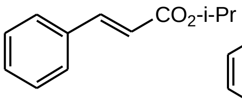
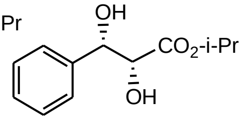
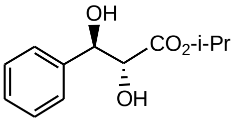
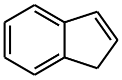
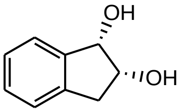
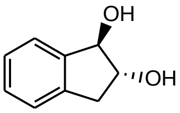
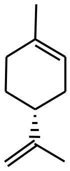
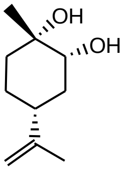
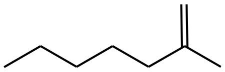
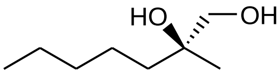
However, various alkenes were readily oxidized at 30 psi. of oxygen in excellent to good chemical yields and excellent optical yields. Results of the oxidation are summarized in **Table 6**. For example, treatment of 1,2-dihydronaphthalene (**57**) with 0.5 mol% of Pd/Au (3:1)-**1** in water at 25^{o}C under 30 psi. of oxygen for 3 days gave (1*S*,2*R*)-**58** in 86% yield and 99% ee (**Table 6**, entry 1). Only a single product was isolated in the reaction. The Sharpless dihydroxylation of **57** using DP-PHAL gave 56% ee of (1*R*,2*S*)- **58**.[78] Other disubstituted alkenes including *trans*- and *cis*-β-methylstyrene (**59** and **62**, respectively; **Table 6**, entries 2 and 3) also underwent oxidation reactions at 25^{o}C. In the oxidation of *trans*-**59**, the *syn*-adduct (1*S*,2*S*)-**60** was isolated in 87% yield and 99% ee along with a small amount of *anti*-adduct (1*R*,2*S*)-**61** in 6% yield and 97% ee. Similarly, in the oxidation of *cis*-**62**, the *syn*-adduct (1*S*,2*R*)-**61** was isolated in 90% yield and 98% ee as well as 8% yield of anti-adduct (1*R*,2*R*)-**60** in 98% ee. However, only syn-addut (1*S*,2*R*)-**58** was isolated when 0.3 equiv of K_2CO_3 was added to the oxidation reaction of **57** at 25^{o}C. The disubstituted alkenes without aromatic ring were also examined, for example, cyclohex-2-enone (**73**) and cyclooct-4-enone (**75**), were oxidized under similar condition except at 50 ^{o}C to (2R,3*R*)-**74** (86% yield) and (4S,5*R*)-**76** (85% yield), respectively. (**Table 6**, entries 9 and 10) The increase of reaction temperature indicates the aryl group, as a electron-donating group, increased the activity for the oxidation reaction. The higher ee value (99%), the oxidation of **73** and **75** gave, indicate the enantioselectivity of

CSPVP**26** is better than CSPVP**1** even the reaction temperature are higher. Notably, the dihydroxylation takes place from the *re* face of the alkenes (in regarding to C1 of **57**, **59**, **62**, **73** and **75**).

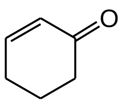
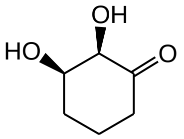
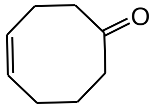
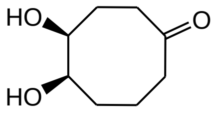
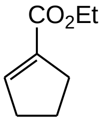
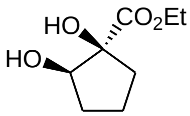
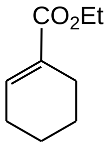
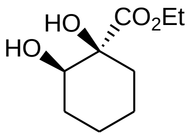
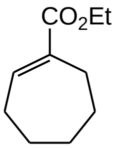
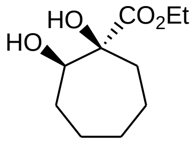
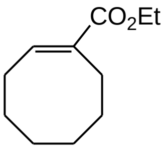
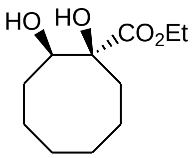
The oxidation of alkenes containing an electron-withdrawing group such as *trans*-cinnamic acid ester **63** and indene (**66**) only proceeded at 50^{o}C giving the *syn*-adducts (2*R*,3*S*)-**64** (82% yield; 99% ee) and (1*S*,2*R*)-**67** (67% yield; 93% ee), respectively, as the major products. The respective *anti*-adducts, (2*R*,3*R*)-**65** (3% yield; 97% ee) and (1*R*,2*R*)-**68** (11% yield; 94% ee) were also isolated as minor products. (**Table 6**, entries 4 and 5) Since (1*R*,2*R*)-**68** was obtained in 11% yield, *anti*-adduct was tried to improve as a major product. As expected, in the presence of 0.3 equiv of K_2CO_3 at 70^{o}C for 5 h, (1*R*,2*R*)-**68** was isolated in 59% yield and 91% ee. (**Table 6**, entries 6)

Trisubstituted alkenes such as (*R*)-(+)-limonene (**69**), containing a stereogenic center, also underwent stereoselective oxidation at 25^{o}C to give a single stereoisomer (1*S*,2*R*,4*R*)-**70**. (**Table 6**, entries 7) The formation of (1*S*,2*R*,4*R*)-**70** from the dihydroxylation reaction of limonene is remarkable, since the dihydroxyl functions were delivered from the same side of the bulky isopropenyl group. The cyclic trisubstituted alkene reacted preferentially compared to the acyclic terminal disubstituted olefin group, suggesting electron-donating groups such as alkyl and aryl enhance the reactivity towards the nanoclusters.



entry	CSPVP	substrate	product(s)	% yield(s)	% ee
1(a)	**1**	 **57**	 **(1*S*,2*R*)-58**	86	99
2(a)	**1**	 **59**	 **(1*S*,2*S*)-60**  **(1*R*,2*S*)-61**	87 , 6	99 , 97
3(a)	**1**	 **62**	 **(1*S*,2*R*)-61**  **(1*R*,2*R*)-60**	90 , 8	98 , 98
4	**1**	 **63**	 **(2*R*,3*S*)-64**  **(2*R*,3*R*)-65**	82 , 3	99 , 97
5	**1**	 **66**	 **(1*S*,2*R*)-67**  **(1*R*,2R)-68**	67 , 11	93 , 94
6(b)	**1**	**66**	**(1*S*,2*R*)-67** **(1*R*,2R)-68**	5 , 59	89 , 91
7	**1**	 **(*R*)-69**	 **(1*S*,2*R*,4*R*)-70**	92	-
8(c)	**26**	 **71**	 **72**	73	97

(To be continued)

entry	CSPVP	substrate	product(s)	% yield(s)	% ee
9	**26**	 **73**	 **(2*R*,3*R*)-74**	86	99
10	**26**	 **56**	 **(4*S*,5*R*)-76**	85	99
11	**26**	 **77**	 **(*1S,2R*)-81**	77	99
12	**26**	 **78**	 **(*1S,2R*)-82**	83	99
13	**26**	 **79**	 **(*1S,2R*)-83**	85	99
14	**26**	 **80**	 **(*1S,2R*)-84**	81	99

(a) Reactions were conducted at 25^{o}C for 3 days; (b) reactions were conducted at 70^{o}C for 5 h in the presence of 0.3 equiv K_2CO_3; (c) 5% mol of Pd:Au-CSPVP nanoclusters was used.

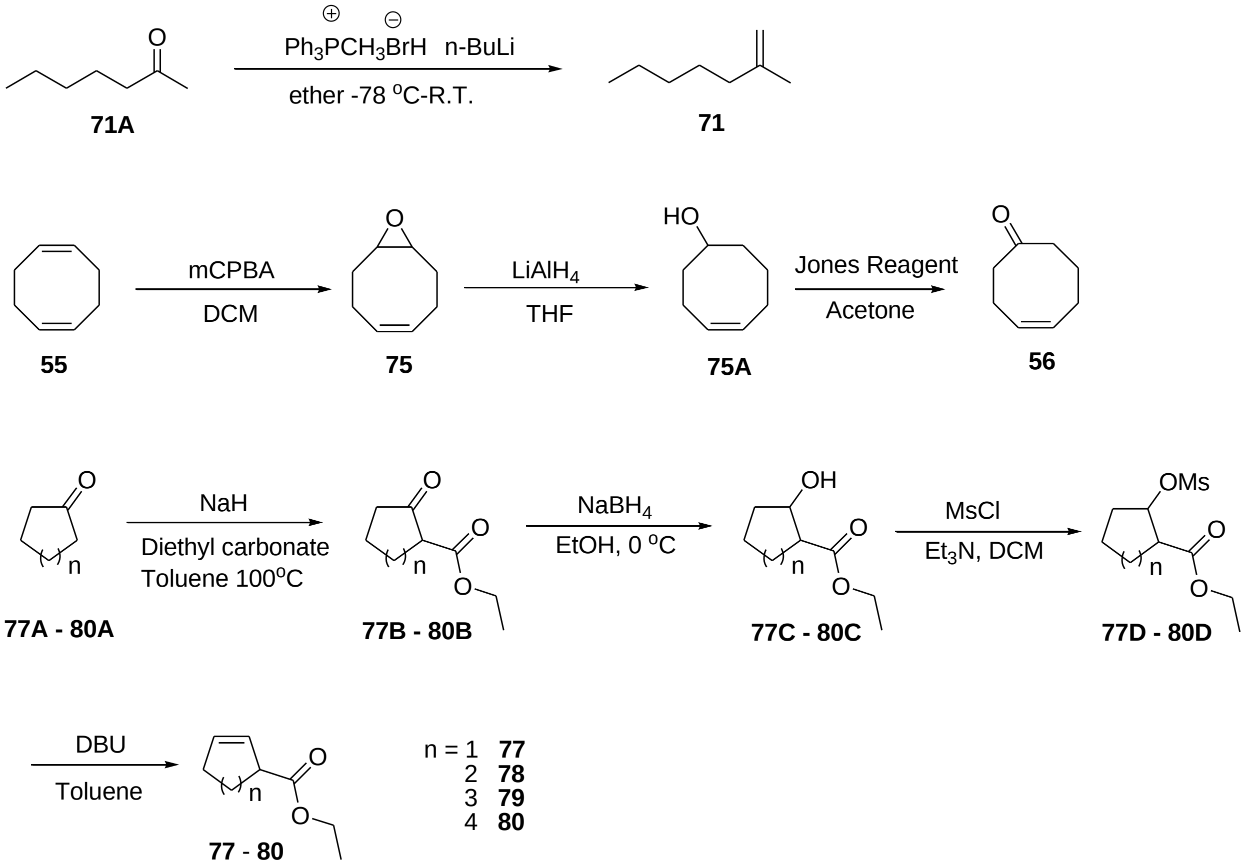
Table 6. Results of Catalytic Asymmetric Dihydroxylation of Alkenes.

However, the terminal disubstituted olefin group can also be oxidized by increasing the amount of the catalyst. With 5 % of Pd/Au(3:1)-CSPVP**26**, 2-methylhept-1-ene (**71**) were oxidized to (*S*)-2-methylheptane-1,2-diol (**72**) with 73% chemical and 97% optical yield. (**Table 6**, entries 8)

Molecule (+)-(*R*)-**71** has previously been obtained from an improved Sharpless oxidation in a 85% yield and 86% ee.[79, 80] The successful oxidation of **71** expanded the scope of the oxidation method.

The oxidation of trisubstituted alkenes containing an electron-withdrawing group, ethyl cycloalk-1-enecarboxylate (**77** – **80**) were also oxidized at 50^{o}C and gave the *syn*-adducts (1*S*,2*R*)-**81 – 84** with 77 – 81% yield and ~99% ee. (**Table 6**, entries 11–14)

The substrates were commercially available if not mentioned below. Compound **71** was made by Wittig Reaction from 2-heptanone (**71A**). With the epoxidation of cyclooctadiene (**55**) with mCPBA in methylene chloride, reduction with $LiAlH_4$ in THF and oxidation of alcohol with Jones Reagent, cyclooct-4-enone (**56**) was obtained. Compound **77**–**80** were made from cycloalkanone **77A**–**80A**, respectively. The compounds **77A**–**80A** were treated with NaH and diethyl carbonate in toluene, reduced the ketone with $NaBH_4$, protected the resulting alcohol with MsCl-Et_3N and eliminate to give **77**–**80** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The preparation of the substrates was conducted by Dr. Man Zhang and Mr. Kyle Apley. (**Scheme 10**)

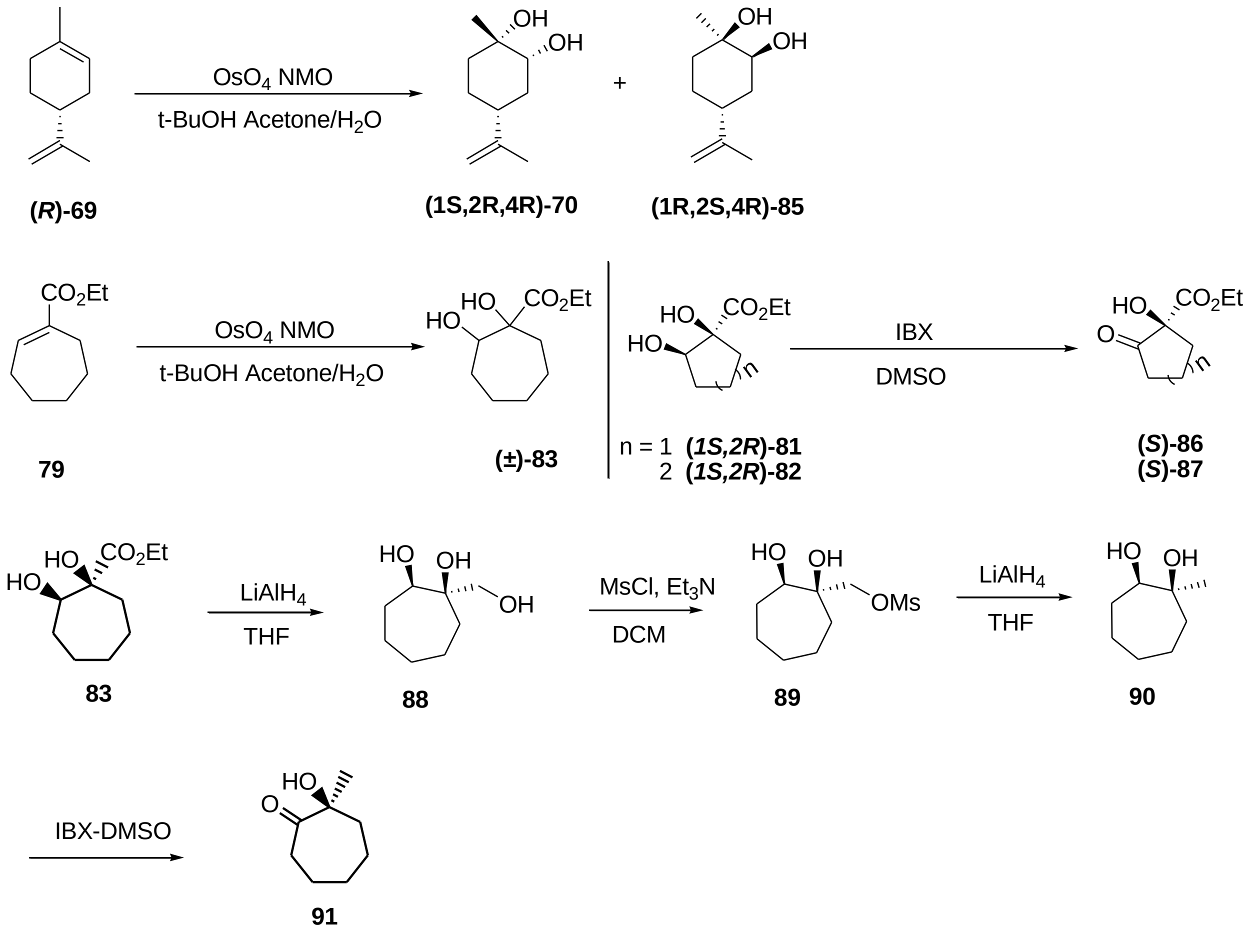


Scheme 10. The Preparation of the Substrates for Dihydroxylation Reactions.

The absolute configurations were determined by comparing the sign and specific rotations of the respective reported molecules.[67, 68, 81, 82] To determine the stereochemistry of **70** (which has not been reported previously), we independently prepared (1*S*,2*R*,4*R*)-**70** and its (1*R*,2*S*,4*R*)-diastereomer (**85**)[83] by the reaction of (*R*)-**69** with OsO_4 (catalytic amount)-NMO in t-BuOH-H_2O followed by silica gel column chromatography. The *syn*-stereochemistry of the products were confirmed independently by oxidizing **79** with OsO_4-NMO in t-BuOH-H_2O to give (±)-**83**, whose ^{1}H NMR spectrum was identical to that of (-)-**83**. The absolute configuration of **81** and **82** were deduced by oxidation with IBX-DMSO to the corresponding (-)-(1*S*)-1-hydroxy-2-oxocycloalkanecarboxylic ethyl esters (**86** and **87**, respectively), whose specific rotations are similar to those reported (+)-(*1R*)-isomers but possessing opposite sign.[84]

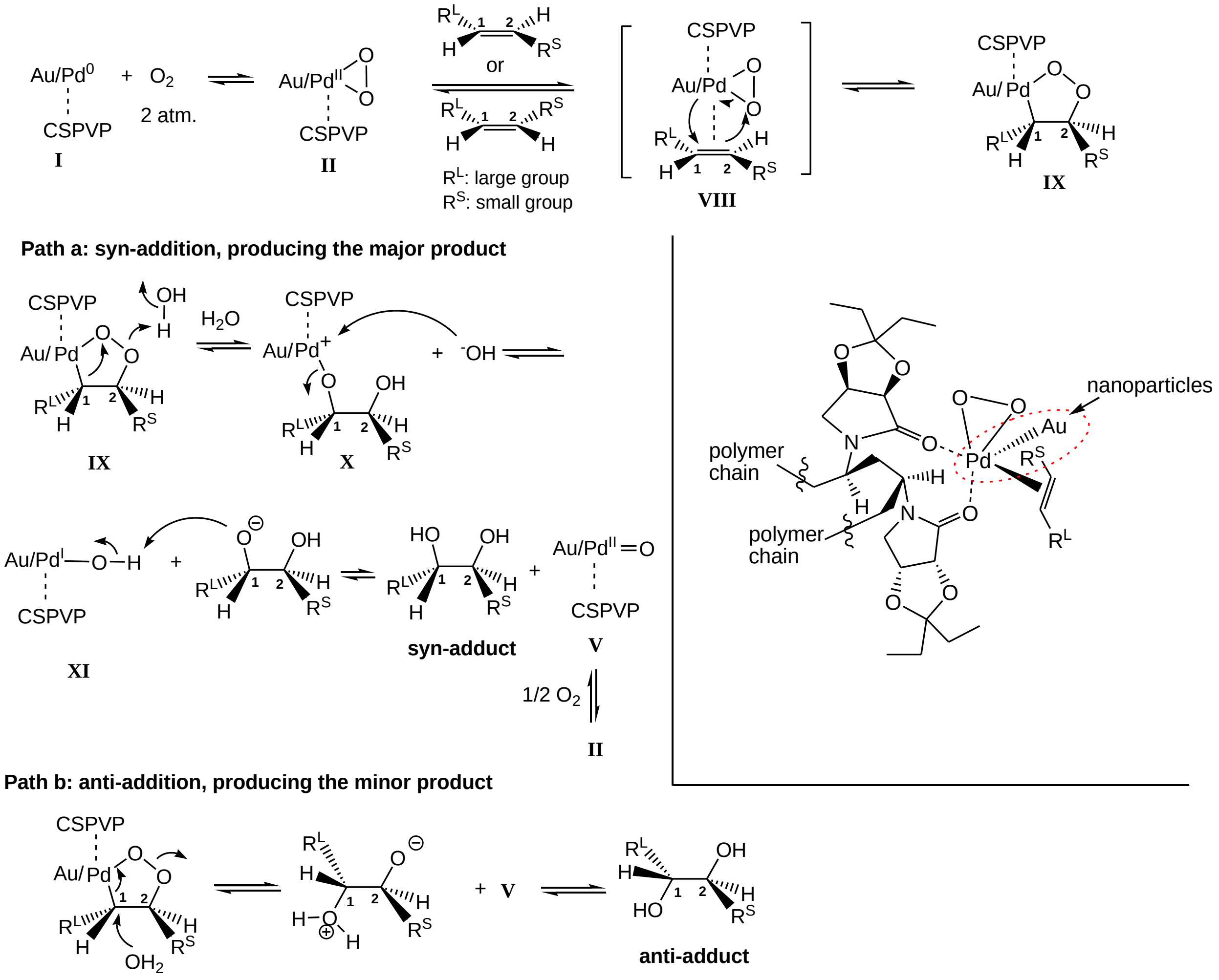
The C1-absolute stereochemistry of (-)-**83** was established by converting it to the known compound, (2*S*)-2-hydroxy-2-methylcycloheptanone (**91**). [85] Molecule **83** was reduced by $LiAlH_4$ to give corresponding triol and mesylated the primary alcohol with MsCl/Et_3N to give **89**. Molecule **89** was reduced with $LiAlH_4$ and oxidized the secondary alcohol with IBX/DMSO to give **91**. The highest reported % ee's of the dihydroxylation products of **59**, **62**, **63** (the ethyl ester analog), **66**, **71** and **73** from Sharpless asymmetric dihydroxylation reactions are 98,[86] 81,[87] 99,[82], 89,[88] 86[79] and 99,[89] respectively. Optical purities of all dihydroxylated molecules were measured using HPLC/chiral column. Hence, the Pd/Au-CSPVP provided higher or similar enantiomeric selectivities in the catalytic asymmetric dihydroxylation reactions.

Dr. Hua has also proposed the mechanism for the dihydroxylation of alkenes.[1] Similar to that described in **Scheme 8**, Pd(0) was oxidized to η^2-peroxido Pd(II) (peroxopalladium) species **II** and complexed with C=C in alkenes. Through intermediate **VIII**, metallo-1,2-dioxolane **IX**[65] was formed. Carbon-1 of **IX** undergoes a 1,2-alkyl shift from Pd to oxygen (path a) leading to intermediate **X**, which hydrolyzes to give the *syn*-adducts. In some case, the 1,2-alkyl shift takes place rapidly and only the *syn*-adducts were found. In other investigated alkenes, in addition to major path a, water attacks C1 of intermediate **IX** from the backside, path b, providing *anti*-addition diols as the minor products. (**Scheme 12)**



Scheme 11. Confirmation of the Absolutely Configurations of the Dihydroxylation Products.

The asymmetric aerobic oxidation of alkenes by Pd/Au-CSPVP at ambient temperature or 50°C provided excellent chemical and optical yields of the *syn*-dihydroxylated products and in certain cases where higher temperature (such as 70°C) is required, an addition of a weak base such as K_2CO_3 afforded *anti*-dihydroxylated molecules as the major products.



Scheme 12. Proposed Mechanism and Stereo- and Regio-chemistry of the Enantioselective Oxidation of Alkenes.

2.3 Selective C-H Asymmetric Oxidation Reactions of Cycloalkanes.

2.1.1 Background and Significance

C-H oxidation has a long history and an ongoing presence in research at the forefront of chemistry and interrelated fields. In a single molecule, even medium-size organic molecules, so many different C-H bond can be oxidized. The active C-H oxidative sites normally have weaker

C-H bond dissociation energy and other effect, such as electronic effect, steric effect, conjugation and hyperconjugation, etc. [90] Therefore, the active C-H oxidation sites are normally on aromatic ring,[91] benzylic[92] or allylic[93] position. Regio- and enantioselective C-H oxidation of cycloalkanes is one of the most challenging transformations in organic synthesis. In general, directing groups such as hydroxyl group, ester or amide are needed for the regioselectivity. Although various of different catalyst such as iron complexes,[94-96] gold reagents,[97] and others[90, 98-100] in C-H oxidation have been reported, no research on the use of bimetallic nanoclusters and chiral supports in the catalytic enantio- and region-selective C-H oxidation appears. C-H oxidation is a highly atom-economic process, and regioselective catalytic asymmetric C-H oxidation would provide a powerful tool for organic synthesis. To explore the scope of the oxidation reactions, a more challenging catalytic asymmetric C-H oxidation was investigated.

2.1.2 Results and Discussions

Since the Pd:Au(3:1)-CSPVP did not work well for the C-H oxidation, different bimetallic nanoclusters have been investigate for the C-H oxidation including Fe:Au(3:1)-CSPVP and Cu:Au(3:1)-CSPVP. Both Fe:Au(3:1)-CSPVP and Cu:Au(3:1)-CSPVP have the catalytic activity on the C-H oxidation of isopropylcyclohexane to yield 3-isopropylcyclohexanone. However, Fe:Au(3:1)-CSPVP nanoclusters are not stable at high temperature, forming the black precipitate which is magnetic. Therefore, instead of using Pd:Au (3:1)-CSPVP nanoclusters, Cu:Au (3:1)-CSPVP nanoclusters was used for the C-H oxidation of the cycloalkanes.

Under oxygen atmosphere (30 psi.), no C-H oxidation product was detected, making the stronger oxidizer (hydrogen peroxide) necessary for the oxidation reactions. After making the crude Cu:Au(3:1)-CSPVP solution, the substrate was added into it followed with 30% H_2O_2. The remaining $NaBH_4$ was also quanched by H_2O_2 with the formation of hydrogen gas. Since the organic substrates are difficult to dissolve in water, acetonitrile was added slowly into the reaction system until the entire substrate dissolving after heating to 50 ^oC. Too much acetonitrile (>1/2 by volumn by experience) may produce black precipitate after heating for several hours which means the nanoclusters decomposition.

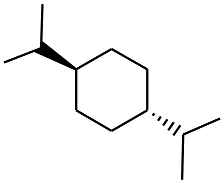
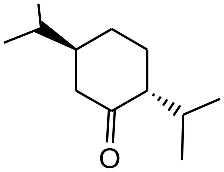
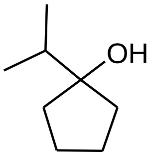
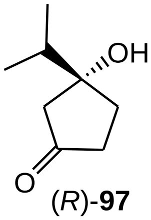
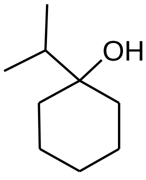
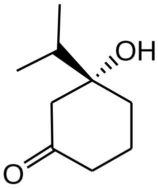
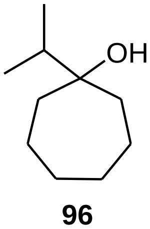
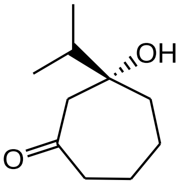
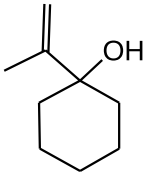
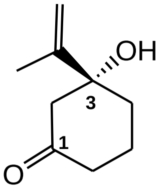
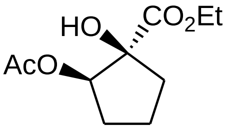
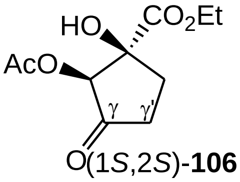
Results of the catalytic asymmetric C-H oxidation reactions of various substituted achiral cycloalkanes using 1 mol% Cu/Au (3:1)-**CSPVP** and H_2O_2 at 50^{o}C are summarized in **Table 7**. The products are chiral molecule obtained from the desymmetrization process of the achiral substrates. For example, oxidation of meso-*trans*-1,4-diisopropylcyclohexane (**92**) gave an 87% yield of (2*R*,5*S*)-**93**. (**Table 7**, entry 1) There are four C-H bond positions which has potenssial to be oxidized. The four methyls on isopropyl group, two methine C-H's on isopropyl group, two methine C-H's on cyclohexanone ring and four methylene groups on the ring. It appears the four methine C-H's, which have weaker bond dissociation energies,[90] and four sterically less hindered methyls were not oxidized. Moreover, the four methylene group was selectively oxidize two of them to give a chiral product with 81% ee. The Cu:Au(3:1)-CSPVP**1** performed both region- and enantioselectivity on the catalytic oxidation reaction of **92**. The specific rotation and ^{1}H and ^{13}C NMR spectral data of (2*R*,5*S*)-**93** were in agreement with those of the reported compound synthesized from (*S*)-perillaldehyde.[101]

Similarily, 1-isopropylcycloalkanols **94–96** and 1-isopropenylcyclohexanol (**100**) were conducted to be oxidized with the catalysis of Cu:Au(3:1)-CSPVP**1** and yield corresponding ketone (*R*)-**97**–(*R*)-**99**, and (*R*)-**101**, respectively (**Table 7**, entries 2–5). The hydroxyl group is the directing group in the reaction and only γ position away from hydroxyl group were oxidized to give both region- and enantioselectivity. Notebly, the -C=CH_2 of **100**，which is more active than the alkane moiety, was not oxidized at 50°C under H_2O_2 with the Cu:Au (3:1)-CSPVP nanoclusters,

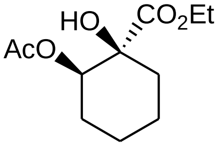
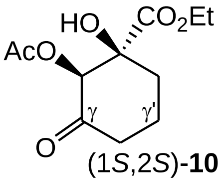
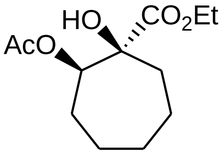
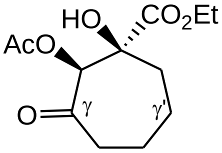
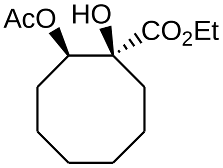
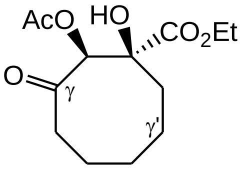
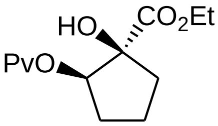
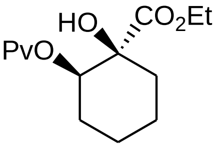
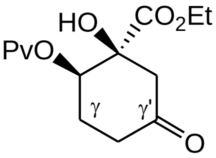
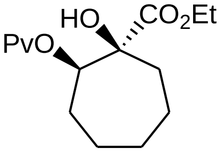
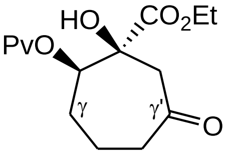
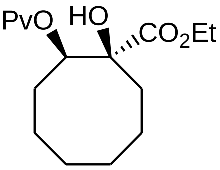
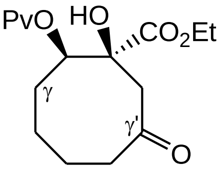
The regiochemistry of (*R*)-**97**–(*R*)-**99**, and (*R*)-**101** were analyzed by 2D COSY spectroscopy. In the COSY spectrum of (*R*)-**97**, the signal at δ 2.41–2.30 ppm assigned for C2-hydrogens has no correlation with other protons, while the signals at ~2.25 and 2.05 ppm assigned for C5 hydrogens show correlation with C4 hydrogens at 2.01 and 1.60 ppm. Similar correlations were found in the 2D COSY spectra of (*R*)-**98**, (*R*)-**99**, and (*R*)-**101**. Moreover, (*R*)-**98** and (*R*)-**99** were independently synthesized from (*S*)-**38** and (*S*)-**42**, respectively, by silylation of the C3-hydroxyl group followed by addition reaction with isopropylmagnesium bromide,[102] removal of the silicon protecting group, and oxidation with IBX-DMSO.(**Scheme 13**) Their NMR spectra and specific rotations were similar to those obtained from the C-H oxidations. The products indicated the chelation of nanoclusters and the *tert*-hydroxy group directed asymmetric oxidation at γ-carbon away from C-OH group of cycloalkanes.

More directing group effect, such as alcohol, ester, and amide, were studied. Compounds **102 – 105** were designed and investigated due to the presence of acetoxy, hydroxyl and ethyl ester group. Oxidation of **102** – **105** with 1 mol% Cu/Au (3:1)-**26** and H_2O_2 at 50°C gave exclusively C3-oxo products **106** – **109** (76–83% yields), respectively.(**Table 7**, entries 6 – 9) Compare with the oxidation results from **94** – **96**, the active C-H bonds for the Cu/Au (3:1)-CSPVP catalytic oxidation of **102 – 105** should be γ'- carbon which are not in agreement with the real results. The oxidation took place at the γ-carbon away from C-OH group of cycloalkanes. It indicated the directing group in **102** – **105** were acetoxy group, which directed the oxidation on the γ-carbon away from C=O of acetoxy group. With the appearance of C=O, the directing effect of hydroxyl group was override, indicated the directing effect of C=O was stronger than hydroxyl group.

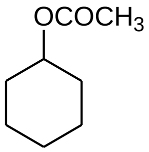
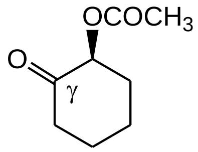
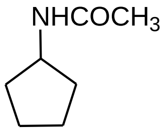
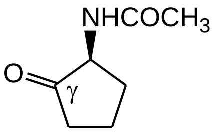
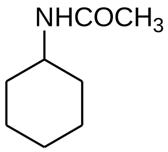
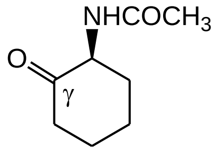
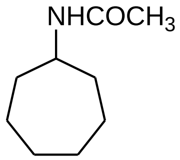
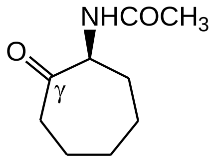
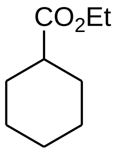
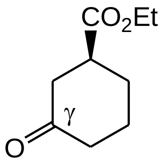
Cyclic alkanes $\xrightarrow[\text{30\% } H_2O_2\text{, } CH_3CN\text{, } 50^oC\text{, 7 days}]{\text{5 mol\% } \textbf{Cu/Au (3:1)-CSPVP}}$ Chiral oxidized cyclic alkanes

entry	CSPVP	substrate	product	% yield	% ee
1(a)	**1**	 **92**	 (2*R*,5*S*)-**93**	87	81
2(a)	**1**	 **94**	 (*R*)-**97**	91	92
3(a)	**1**	 **95**	 (*R*)-**98**	98	91
4(a)	**1**	 **96**	 (*R*)-**99**	89	93
5(a)	**1**	 **100**	 (*R*)-**101**	98	93
6(a)	**26**	 (1*S*,2*R*)-**102**	 (1*S*,2*S*)-**106**	83	-

(To be continued)

entry	CSPVP	substrate	product	% yield	% ee
7 (a)	**26**	 (1*S*,2*R*)-**103**	 (1*S*,2*S*)-**107**	83%	-
8 (a)	**26**	 (1*S*,2*R*)-**104**	 (1*S*,2*S*)-**108**	76%	-
9 (a)	**26**	 (1*S*,2*R*)-**105**	 (1*S*,2*S*)-**109**	83%	-
10 (a)	**26**	 (1*S*,2*R*)-**81A**	No product detected		
11	**26**	 (1*S*,2*R*)-**110**	 (1*S*,2*R*)-**113**	83%	-
12	**26**	 (1*S*,2*R*)-**111**	 (1*S*,2*R*)-**114**	88%	-
13	**26**	 (1*S*,2*R*)-**112**	 (1*S*,2*R*)-**115**	88%	-

(To be continued)

entry	CSPVP	substrate	product	% yield	% ee
14	**26**	 **116**	 (*S*)-**121**	94	94
15	**26**	 **117**	 (*S*)-**122**	76	92
16	**26**	 **118**	 (*S*)-**123**	72	93
17	**26**	 **119**	 (*S*)-**124**	84	93
18	**26**	 **120**	 (*S*)-**125**	88	92

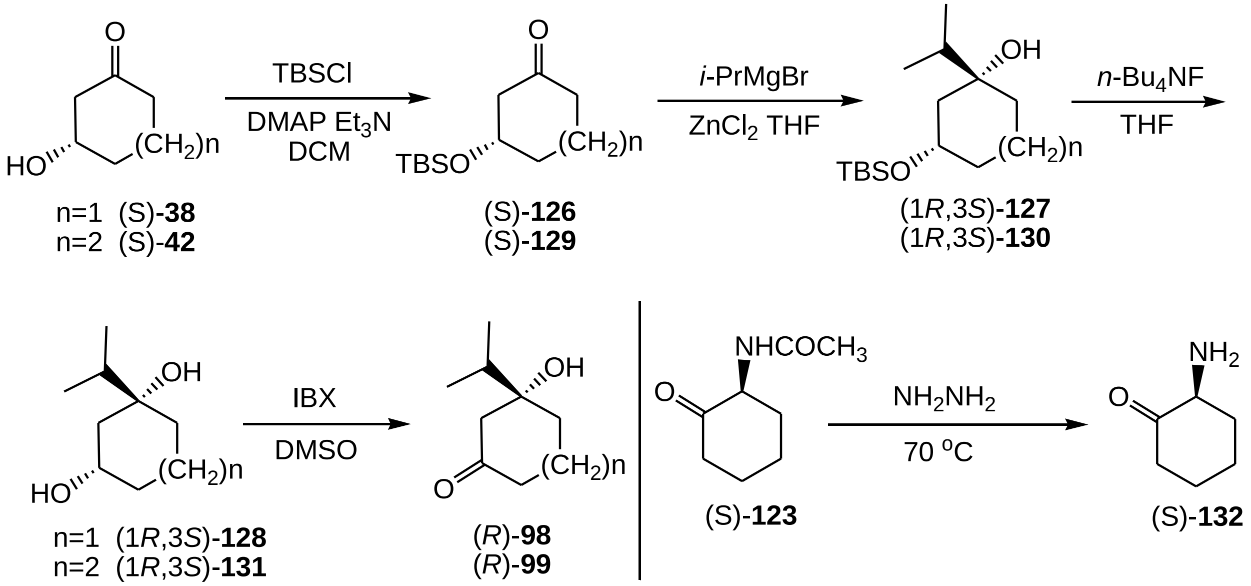
(a) 1% mol of Cu:Au-CSPVP nanoclusters was used.

Table 7. Results of Catalytic Asymmetric C-H Oxidation of Cycloalkanes.

After changing the acetoxy group to pivaloyl group, the oxidation took place at the γ'- carbon of the C1-hydroxyl group, which was in agreement of the hydroxyl directing effect. For example, oxidation of compounds **110–112** gave only **113–115**, respectively, in 83–90% yields.(**Table 7**, entries 11–13) Because the bulky *tert*-butyl moiety blocks the chelation of C=O in PvO with nanoclusters, allowing the OH group to chelate and direct the oxidation. The regiochemistry of **113–115** were revealed by their 1H and 2D COSY NMR spectra. Notably, no desired oxidation product was isolate from the treatment of monopivaloyl (PvO) analog of (*1S*,*2R*)-Ethyl 1,2-dihydroxycyclopentanecarboxylate (**81A**) even heating to 100 ^{o}C with seal tube. (**Table 7**, entries 10) It may due to the crowed environment on the five-membered ring which prevented the active C-H bond oxidation.

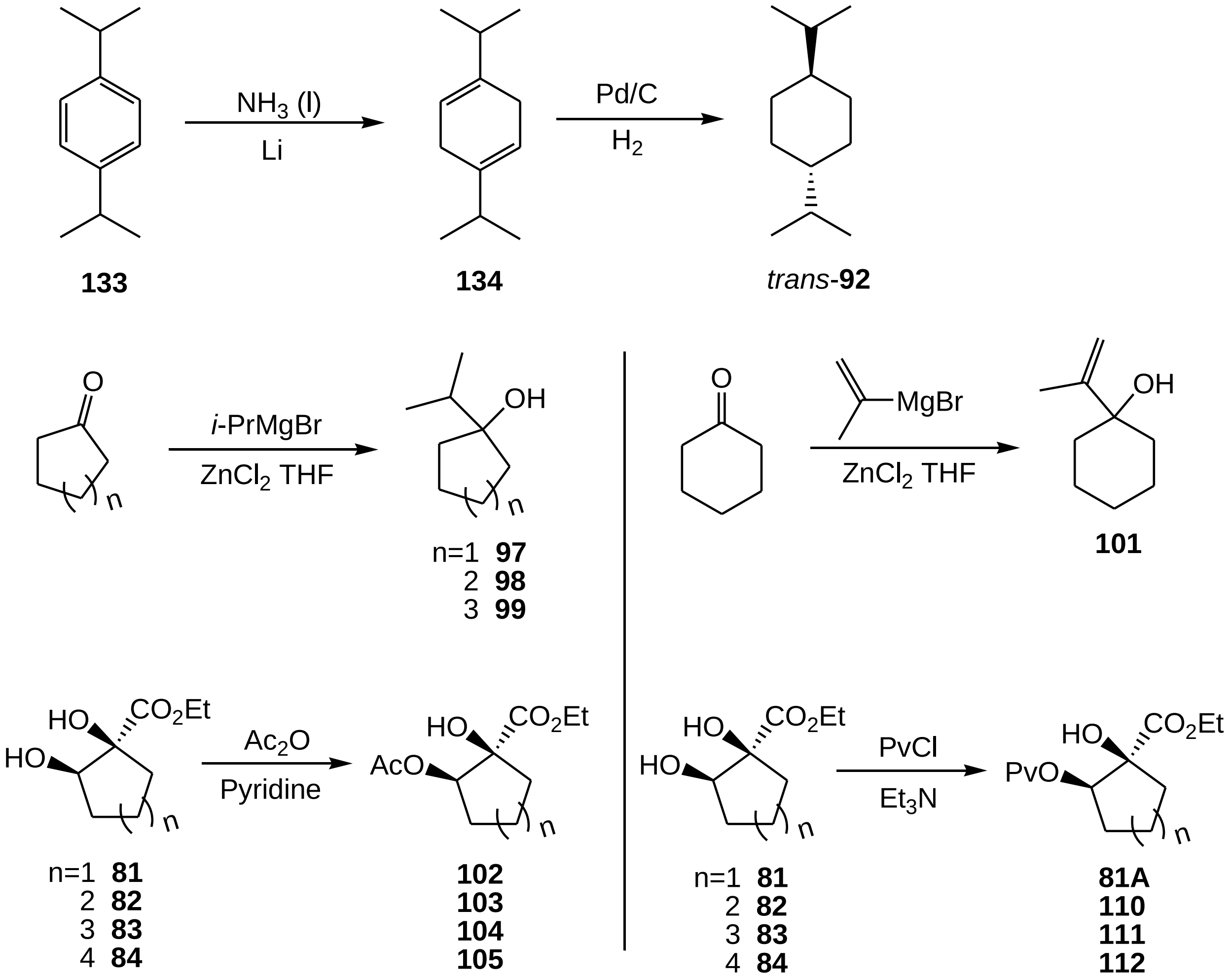
This functional-group directing effect provides guidance for desymmetrized C-H oxidation. Hence, monofunctionalized cyclohexanes **116** – **120** were oxidized readily to give respective (S)-**121** – (S)-**125** in excellent chemical (72–94%) and optical (92–94% ee) yields (**Table 7**, entries 14–18). Notebly, in order to study the effect of borane in the catalyst solution, molecular weight cut off membrane was used to remove all the inorganic small molecules including borane. The remaining solution was used directly to conduct the C-H oxidation of **120** to **125** and gave similar results as the crude catalyst solution with 87% yield and 92% ee. The acetoxy, acetamide, and ethyl ester functions apparently directed the oxidation at the γ-carbon away from C=O group on the ring. From the above results, the aptitude of directive oxidation can be summarized as followed: CH_3CO_2 ~ CH_3CONH > OH > CO_2Et.

The NMR spectra of **121**, **123–125** were identical to those reported.[103-105] The sign of specific rotation of (*S*)-**121**, is opposite to that reported (*R*)-**121**.[103] Compound (*S*)-**123** was converted to 2-(*S*)-aminocyclohexanone (**132**) by the treatment with 85% hydrazine at 70^{o}C, (**Scheme 13**) and the sign of specific rotation of the resulting amine, $[\alpha]_D^{22} = -71.3$ (c 0.5, $CHCl_3$), is opposite to that of reported 2-(*R*)-aminocyclohexanone.[103] The absolutely configuration of **122** and **124** were assumed based on the oxidation result of **118** to (*S*)-**123**. Absolute configuration of (*S*)-**125**, $[\alpha]_D^{22} = +2.62$ (c 1.61, MeOH), was similar to that reported.[105]



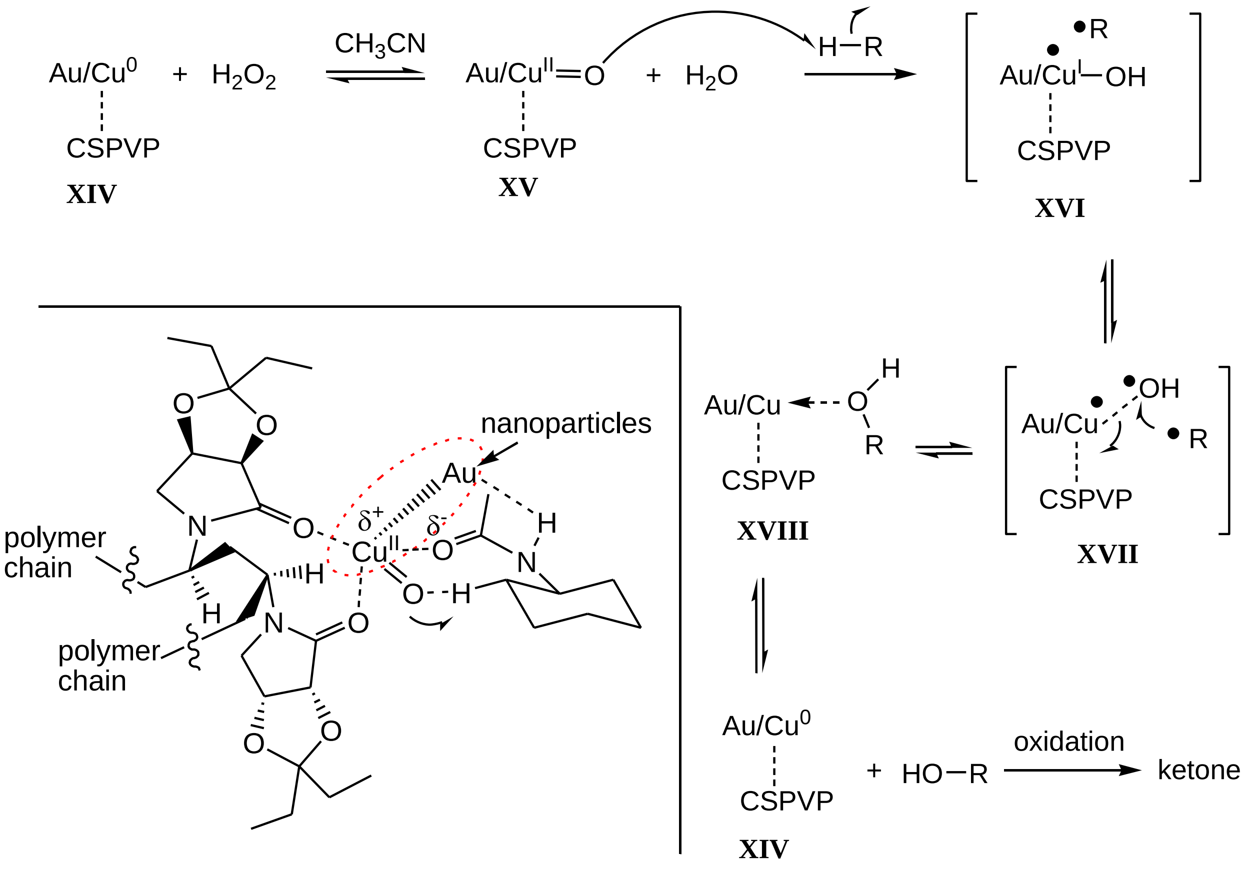
Scheme 13. The Synthesized Molecules for Confirming the Absolutely Configurations of the Cycloalkanes Oxidation Products.

Trans-**92** was made by Birch Reduction by Li-NH$_3$ from 1,4-diisopropylbenzene (**133**). Compounds **94** – **96** and **100** were made from the addition reactions of isopropylmagnesium bromide or isopropenylmagnesium bromide with cycloalkanones in the presence of 0.2 equiv of ZnCl$_2$ in THF at 0°C, respectively.[102] Alcohols **81** – **84** were mono-acetylated with acetic anhydride (Ac$_2$O) and pyridine to give 89–95% yields of **102** – **105** and mono-pivaloylated with pivaloyl chloride and Et$_3$N to give 85–88% yields of **110** – **112**. Compounds **116** – **120** were simply esterificated or acetylated from cyclic alcohol or amine, respectively.(**Scheme 14**) Dr. Man Zhang and Mr. Kyle Apley helped to prepare the substrates **94** – **96** and **116** – **120**.



Scheme 14. The Preparation of the Substrates for Cycloalkane C-H Oxidation Reactions

Dr. Hua has also proposed the mechanism for the Cu/Au-CSPVP catalytic C-H oxidation reactions based on the previously suggested mechanism of copper complexes bearing trispyrazolylborate ligands.[1, 106] (**Scheme 15)** Cu^0/Au **XIV** first reacts with H_2O_2 to give copper(II) oxo complex **XV**, which activated the C-H bond by pulling a hydrogen atom from the substrate to produce hydroxyl copper(I) radical and cycloalkyl radical complex **XVI**. Cycloalkyl radical and hydroxyl radical then form a C-O bond to yield alcohol and regenerates XIV. The alcohols were further oxidized under the reaction conditions to give ketones. Cu(II) complexed with the directing group and O in Cu(II)=O formed hydrogen bonding with the H on the active site, constructed a six (hydroxyl group as directing group) or seven-membered ring (carbonyl as directing group) transition state.



Scheme 15. Proposed Mechanism of the Enantioselective Catalytic Oxidation of Alkanes.

Various substituted cycloalkanes were oxidized by Cu/Au-CSPVP and H_2O_2 to furnish chiral cycloalkanones. With the presence of various directing group, the regio-selective C-H oxidation was achieved with high chemical yield. Moreover, the desymmetrization of 1,4-disubstituted cyclohexane or monosubstituted cycloalkanes expanded the scope of the asymmetric oxidation catalyzed by CSPVP stabilized bimetallic nanoclusters and gave application prospects for the oxidation of complex compounds.

2.4 Asymmetric Oxidative Ring-Closing Reaction of Dienes.

2.1.1 Background and Significance

After the discovery of C-H oxidation on the cyclic compounds, acyclic substrates have also been investigated. Unfortunately, the acyclic compounds, such as heptan-4-yl acetate or *N*-(heptan-4-yl)acetamide, cannot be oxidized with the similar condition. However, based on the directing effect of OH group, 5-methylnona-1,8-dien-5-ol was conduct for the oxidation reaction and the desymmetrized ring-closing product γ-Lactone was isolated without other C-H oxidation products.(discovered by Dr. Man Zhang in Hua's laboratory) γ-Lactones or lactams are part of the important core structural in many research fields such as pharmaceutical chemistry, natural products, perfumes and food additives.[107, 108] Different kinds of catalysts with different catalytic mechanisms have been reported for the formation of chiral lactone or lactam, such as gold,[109] rhodium,[110] titanium,[111] palladium,[112] and chiral phosphoric acid[113]. Various copper catalyzed oxidative ring-closing reaction has been reported, such as arylation, [114-116] lactone formation[107] or lactam formation[117]. However, the use of bimetallic NCs and chiral supports in the asymmetric oxidative ring-closing reaction for making lactone or lactam has not been reported. The development of the new methodology gives an efficient and fast route for the synthesis and functionalization of lactone or lactam with a stereogenic center on the γ position.

2.1.2 Results and Discussions

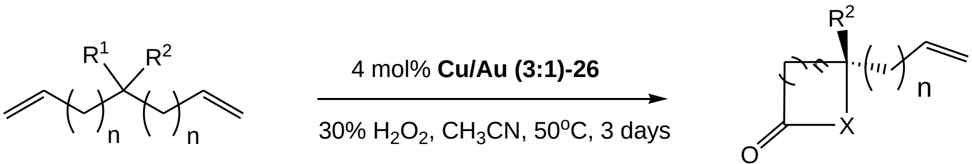
Base on Dr. Man Zhang's discovery of the γ-Lactone formation, the reaction condition was optimized for getting desirable results with better chemical and optical yield. For example, compound **197** was added into 4 mol% of Cu/Au(3:1)-**26** in water, (crude nanocluster solution), followed with adding 30% H_2O_2, heating to 50 ^oC and adding mimimum amount of CH_3CN to dissolve the substrate. Notebly, because of the appearance of ester group in the substrates, 40 equiv. of $NaBH_4$ (compare with 1 equiv. of $HAuCl_4$, 100 equiv. of substrates) will be a significant amount which will hydrolysis the ester group. Therefore, the amount of $NaBH_4$ was cutted to 10 equiv. (compare with 1 equiv. of $HAuCl_4$, 100 equiv. of substrates) for the oxidative ring-closing reaction.

The results for the oxidative ring-closing reaction were summarized in **Table 8**. For example, treatment of **195** with 4 mol% Cu/Au (3:1)-**26** and 30% H_2O_2 in CH_3CN-H_2O at 50^{o}C gave (*S*)-**200** in 71% yield and 96% ee. (**Table 8**, entry 1) Instead of using CSPVP**26**, CSPVP**25** and CSPVP**1** were also used to investigate the enantioselectivity of 5-monosubstituted polymers and 3,4-disubstituted polymers. With CSPVP **25** or CSPVP**1**, 95% or 90% ee product were obtained respectively, indicating CSPVP**26** gave the highest enantioselectivity among the three polymers. Other analogs with phenyl group or ethyl ester group such as **196** – **199** were conducted with similar condition to yield similarly catalytic asymmetric oxidative ring closing reaction product **201**–**204**, respectively. (**Table 8**, entries 2 – 5) With this method, highly stained four-membered ring lactone **201** and **203** were produced although the yield is lower because of the formation of polymers.

Not only γ-lactone, γ-lactam **208** – **210** were also produced with similar reaction condition from the amino ester analog **205** – **207**, respectively, in good chemical (64-93%) and excellent optical (92-95% ee) yields. (**Table 8**, entries 6 – 8)

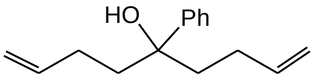
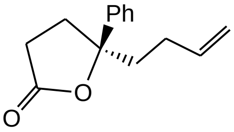
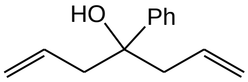
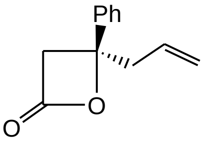
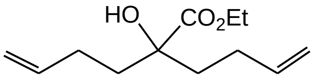
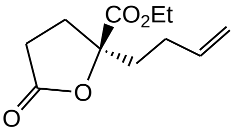
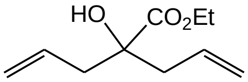
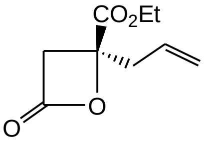
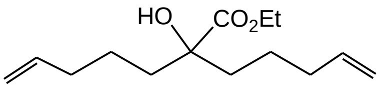
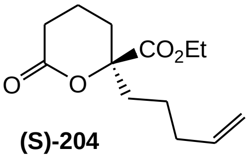
The absolute configuration of (*S*)-**200** was determined by converting it to (-)-(*S*)-5-phenyl-5-propyl-dihydrofuran-2-one (**213**) with $[\alpha]_D^{22}$ = -42.1 (c 0.02, MeOH), and the optical rotation agrees to that reported.[118] Molecule (*S*)-**200** was ozonolysized with O_3 in methylene chloride and reduced with $NaBH_4$ to give corresponding alcohol **211**. Then the alcohol **211** was mesylated by MsCl in the presence of Et_3N and reduced to remove OMs with $NaBH_4$ and gave known compound (*S*)-**213**.[119] The absolute configuration of (*S*)-**208** was determined by conversion into a previously reported pyrrolizidinone (**218**) with similar reported optical rotation.[120] Molecule (*S*)-**208** was ozonolysized with O_3 in methylene chloride and educed with $NaBH_4$ to give corresponding alcohol **214**. The alcohol **214** was mesylated by MsCl in the presence of Et_3N to give a good leaving group OMs in compound **215**. After the treatment of **215** with NaH, N^- in the lactam ring attacked the CH_2OMs and gave cyclized product **216**. Molecule **216** was treated with LDA to form enolate and hydroxylated by MoOPH[121] (57% yield along with 8% of the α-OH isomer). Finally, ethyl ester (**217**) was tranfered to methyl ester **218**. (**Scheme 16**)

Compounds **195–199** were maily prepared by Kyle Apley and they were made by the Grignard Reaction from isopropyl benzoate or diethyl oxalate with corresponding alkenyl magnesium bromide, respectively. Compounds **205** and **207** were prepared from glycine ethyl ester (**222**) by the sequence: (i) treatment with ethyl formate to give **223**,[122] (ii) isocyano product (**224**) formation with $POCl_3$-Et_3N,[122] (iii) alkylation with NaH and corresponding alkenyl bromide, (iv) hydrolysis of isocyano group to give desired products. Compound **206** were synthesized by treatment of ethyl 2-nitroacetate (**227**) with 1-propenyl acetate followed the reduction with Zn/AcOH. (**Scheme 17**)



R^1 = OH or NH_2
R^2 = Ph or CO_2Et
n = 1 - 3

X = O or NH
R^2 = Ph or CO_2Et
n = 1 - 3

entry	substrate	product	% yield	% ee
1	 **195**	 **(S)-200**	71	96
2	 **196**	 **(S)-201**	44	92
3	 **197**	 **(S)-202**	84	93
4	 **198**	 **(S)-203**	33	93
5	 **199**	 **(S)-204**	83	93

(To be continued)

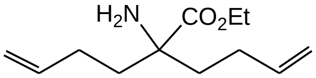
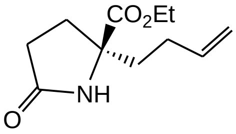
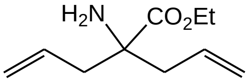
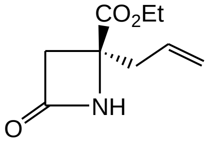
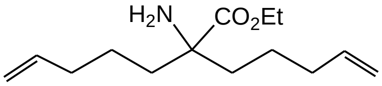
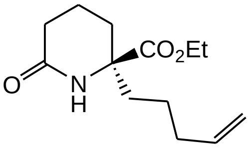
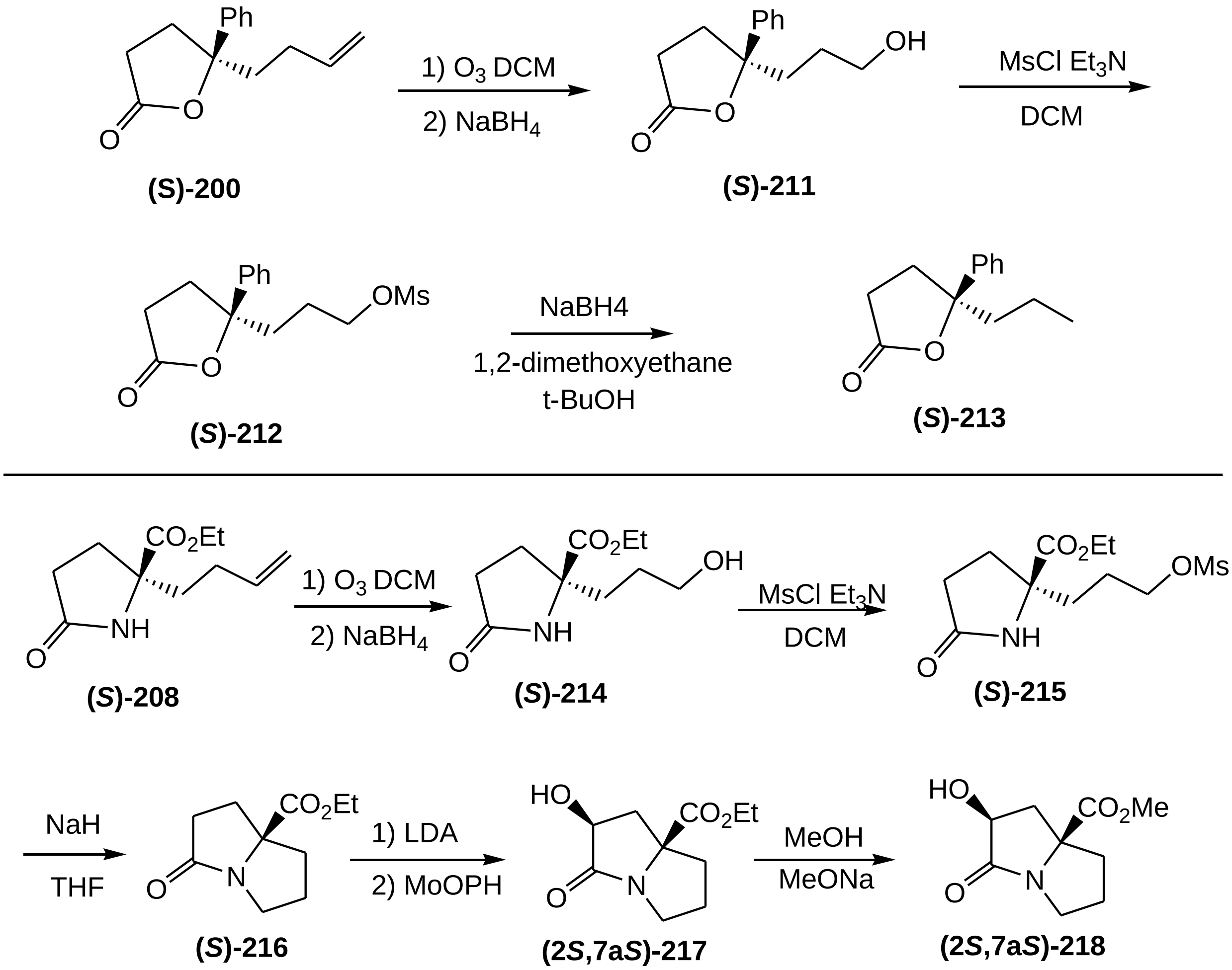
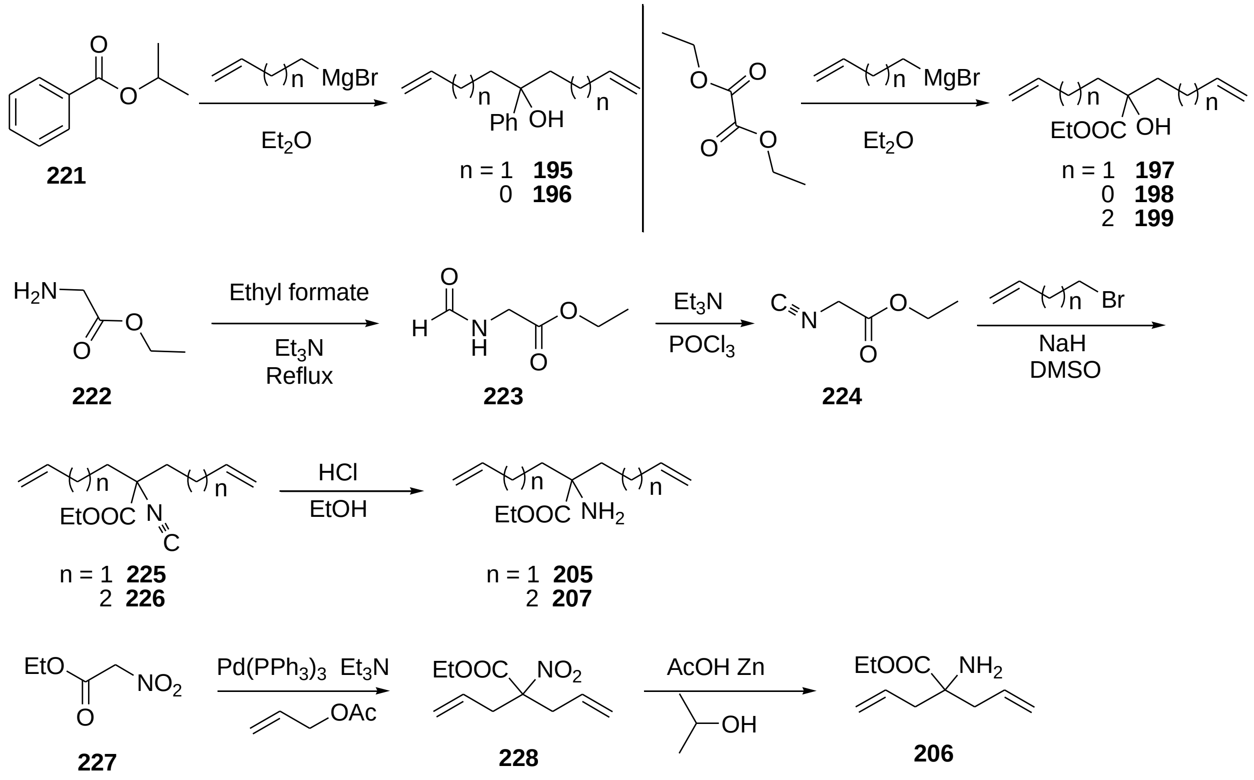
entry	substrate	product	% yield	% ee
6	 **205**	 **(S)-208**	84	95
7	 **206**	 **(S)-209**	64	92
8	 **207**	 **(S)-210**	93	94

Table 8. **Results of Catalytic Oxidative Ring-Closing Reactions.**



Scheme 16. Syntheses of Known Molecules for Confirming the Absolutely Configurations of the Oxidative Ring-Closing Products.

A mechanism for the formation of lactones and lactams is proposed (**Scheme 19**), Similarily, Cu^0/Au **XIV** first reacts with H_2O_2 to give copper(II) oxo complex **XV**, which subtracts a hydrogen atom from OH or NH_2 in the substrates, gives hydroxyl copper(I) radical and a oxygen or nitrogen radical intermediate **XIX**. The two radicals then form a Cu-O(N) bond and the C=C in substrates is oxidized by hydroxyl copper to give corresponding alcohol **XXI** and Cu^0/Au **XIV**. After removing a molecule of formaldehyde from **XXI**, intermediate **XXII** is attacked by water and give **XXIII** which is further oxidized to corresponding lactone or lactam.

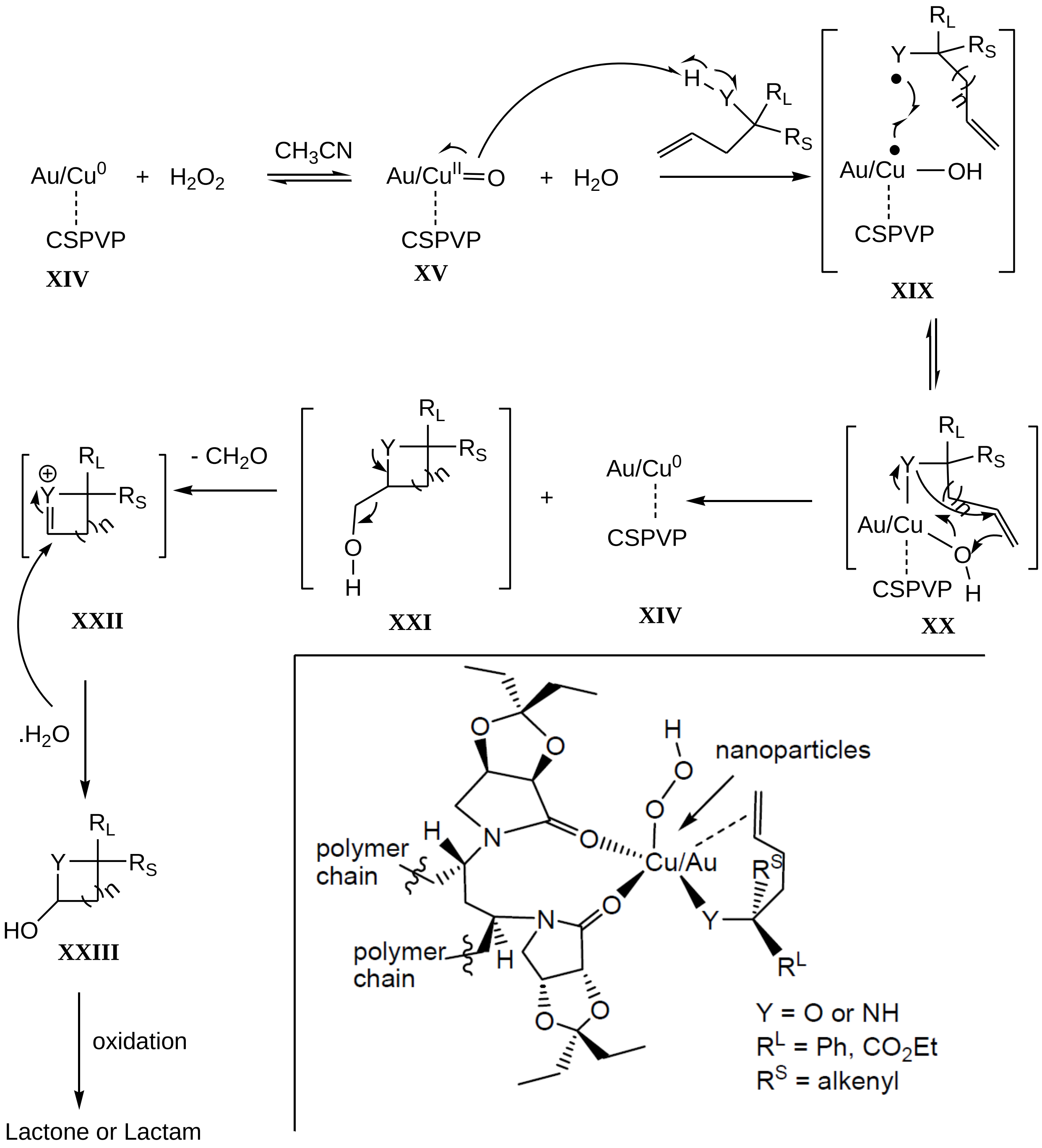


Scheme 17. Preparations of the Substrates for Oxidative Ring-Closing Reactions

2.5 Selective Late-stage C-H Oxidation of Complex Molecules.

2.1.1 Background and Significance

Among the frontier challenges in chemistry in the twenty-first century are the interconnected goals of increasing synthetic efficiency and diversity in the construction of complex molecules. The selective and efficient modification of complex molecules, such as nature products and bioactive compounds, with disparate functional groups is a long-standing challenge that has been solved gradually by using catalysts to perform relatively pure transformations. The straightforward step(s), which is so-called “late-stage” functionalization, provide various analogs with similar scaffold without doing intricate total synthesis. Due to the size of the molecule, more active sites can be converted in single molecule and selective transformation is important.

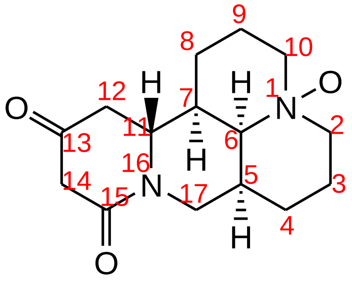


Scheme 18. Proposed Mechanism of the Enantioselective Ring Closing Reaction for Dienes.

However, most of the reported C-H oxidation[123] and halogenation[124] often take place at the allylic C-H, or benzylic C-H bond due to a lower bond dissociation energy comparing with that of unactivated CH_2 and CH_3 bonds. The "late-stage" aliphatic C-H alkylation,[125, 126] C-H azidation,[127] and C-H oxidation[128-130] have been investigated in recent years and newly installed functional groups can be further converted into various functionalities, building up a molecule library for testing the bioactivity or drug mechanism study.

2.1.2 Results and Discussions

With the successful C-H oxidations of small size cycloalkanes, medium to large size molecule or nature products were also oxidized to their corresponding analogs. Due to the oxidation difficulty and valuable products, more catalyst (5 mol % – 30 mol %) were used and several substrates gave positive results. For example, oxymatrine (**229**) is one of quinolizidine alkaloid compounds extracted from a Chinese herb called *Sophora Flavescens* and can be used for the protection of cardiovascular system.[131] With the catalysis of 30 mol % Cu/Au(3:1)-**26** in CH_3CN and H_2O_2, single oxidative product **230** was isolate with 60% yield and recover 33% of **229**. (**Table 9**, Entry 1) Cu/Au-**26** catalyzed reaction has highly selectivity with the directing effect by the carbonyl on C-15, β-carbon away from C=O. The structure was determined by comparing the ^{13}C NMR with reported compound.[132] No C-H oxidation of oxymetrine has been reported previously except microorganism catalyzed oxidation of **230**, giving 10 products with hydroxyl or oxo group on C-12, C-13, C-14.[132] COSY study has been taken. Base on the assignment of oxymatrine which was reported[133] and the COSY of the product, the ^{1}H NMR assignment was shown below. (**Figure 14**)

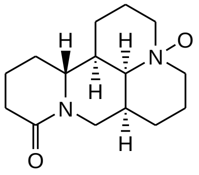
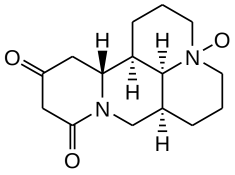
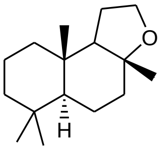
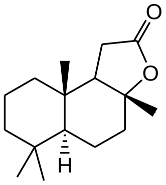
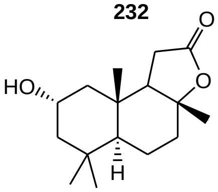
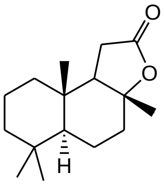
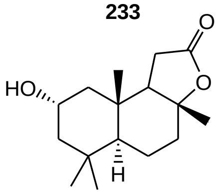
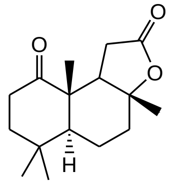


δ	intergration	assignment
5.15-5.09	1	11CH
4.41	1	17CH
4.20	1	17CH
3.50-3.25	2	14CH$_2$
3.22-3.02	5	2CH$_2$, 6CH, 10CH$_2$
2.82-2.60	2	3CH, 9CH
2.48-2.37	1	12CH
2.32	1	12CH
2.10-2.04	1	8CH
1.89-1.48	7	3CH, 4CH$_2$, 5CH, 7CH, 8CH, 9CH

Figure 14 COSY Study and ^{1}H NMR Assignment for 13-Oxo-oxymatrine *N*-oxide (230)

A medium-sized natural product, ambroxide (**231**), also underwent regioselective oxidation with 5 mol % of Cu/Au(3:1)-**26** to give sclareolide (**232**) with 74% yield and (2*S*)-2-hydroxysclareolide (**233**) with 6% yield. (**Table 9**, Entry 2) The oxygen in **231** activated α-C for C-H oxidation and gave lactone, as reported.[134, 135] However, unlike reported iron complex,[134] sclareolide (**232**) was further oxidized to (2*S*)-2-hydroxysclareolide (**233**) in 38% yield and 3% yield of 1-oxosclareolide (**234**) along with 46% recovery of **232**, in a separate experiment. (**Table 9**, Entry 3) Notably, the C2 – equatorial hydroxyl function of **233** does not undergo further oxidation, likely due to steric hindrance (C2-axial-H is shielded by C15-β- and C16-methyls).[136] ^{1}H and ^{13}C NMR spectral data of **233** and **234** are identical to those reported.[96, 136]

$$\text{complex molecule} \xrightarrow[\text{30\% H}_2\text{O}_2\text{, CH}_3\text{CN, 50}^{\text{o}}\text{C, 7 days}]{\textbf{Cu/Au (3:1)-CSPVP}}$$

entry	substrate	product(s)	% yield(s)	% recover
1	 **229**	 **230**	60	33
2	 **231**	 **232**	74	3
		 **233**	6	
3	 **232**	 **233**	38	46
		 **234**	3	

(To be continued)

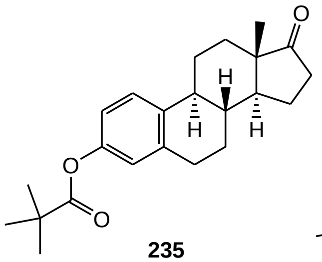
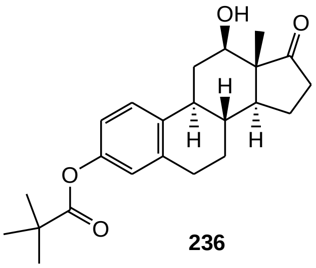
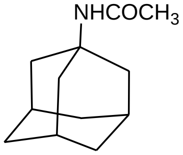
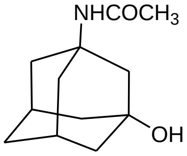
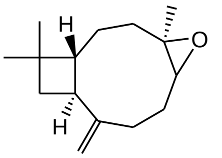
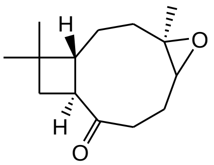
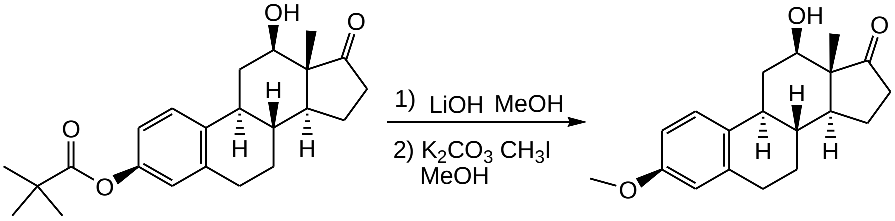
entry	substrate	product(s)	% yield(s)	% recover
4	 **235**	 **236**	58	15
5	 **237**	 **238**	74	13
6	 **239**	 **240**	67	17

Table 9. Results of Late-stage C-H Oxidation for Complex Molecules.

Steroid type of compound was also selectively oxidized. For example, estrone is an estrogenic hormone and has been discontinued for medical use with the superseding by its derivatives.[137] With 5 mol % of Cu/Au(3:1)-**26** in CH_3CN/H_2O_2, 58% yield of 12β-hydroxyl estrone derivative (**236**) was isolated from pivaloyl ester of estrone (**235**) with 15% recovery yield. (**Table 9**, Entry 4) The activated C-12 was directed by the carbonyl group which is β-carbon away. Copper catalyzed C-H oxidation of estrone derivatives with 12β-hydroxyl product has been reported and the conversion from ketone to imine as a directing group for copper is necessary.[138] The structure of **236** was determined by comparison of the reported 12β-hydroxyl estrone derivative **241**[138] after the convertion of pivaloyl ester to methoxy group by hydrolysis with LiOH/MeOH and methylation with CH_3I. (**Scheme 20**)

Amantadine has been approved for use as an anti-viral and an anti-parkinsonian medical by FDA. *N*-Acetylamantadine (**237**) was oxidized at the δ-carbon (away from C=O) to give **238** in 74% yield with the catalysis of 5 mol % Cu/Au(3:1)-**26**. (**Table 9**, Entry 5) The oxidation took place at C3 (δ-carbon) of **237**, which may due to ring strain of adamantane structure.[139] (**Table 9**, Entry 5) The ^{1}H and ^{13}C NMR data of **238** are identical to those reported.[140]

To my surprise, caryophyllene oxide (**239**) was also oxidized, but not similar C-H oxidation. The terminal C=C was oxidized to C=O and gave kobusone (**240**) with 67% yield by the catalysis of 5 mol % Cu/Au(3:1)-**26**. The ^{1}H and ^{13}C NMR data of **240** are identical to those reported.[141] The synthesis of kobusone has been reported from caryophyllene oxide in 2 steps (47% overall yield), as reported.[141]



236

241

Scheme 19. The Synthetic Route for the Confirmation of the C-H Oxidation Product.

In summary, the oxidation produced ketone function (in some cases, the hydroxyl group), which can be converted into amines, amides, or oxime for possible enhancement of bioactivity or for biological mechanistic study. Importantly, there are few methods in the literature can produce the proposed oxidized products in merely one step. Even though the oxidations of complex molecules with the catalysis of Cu/Au-CSPVP are not predictable for now, but it still gives a chance for the late-stage modification and provides various value products.

2.6 Conclusion

In this chapter, several of oxidation reactions were discussed. Cycloalkanediols were asymmetric oxidized by 1 atm of oxygen gas to yield corresponding hydroxyl ketone under the catalysis of Pd/Au(3:1)–CSPVP nanoclusters. Alkenes were oxidized by Pd/Au(3:1)-CSPVP nanoclusters under 2 atmospheric of oxygen in water to give the syn-dihydroxylated products in high chemical and excellent optical yields. Various cycloalkanes underwent regio- and enantio-selective C-H oxidation with Cu/Au(3:1)-CSPVP and 30% hydrogen peroxide to produce the corresponding chiral oxo-molecules in very good to excellent chemical and optical yields. An enantioselective desymmetrization of α,α-dialkenyl-alkanols and α,α-dialkenyl–amino acid ethyl esters to give chiral disubstituted lactones and lactams, respectively. A number of medium-sized natural products and drugs were also oxidized regioselectively to give the corresponding mono-oxygenated products. A broad-spectrum predictive C-H oxidation of complex molecules is possible.

2.7 Synthetic Experimental Procedures

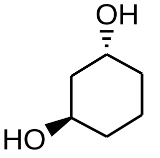
2.6.1 General

^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were measured from a solution in $CDCl_3$ unless otherwise mentioned. The chemical shift data for each signal on ^{1}H NMR are given in units of δ relative to TMS (δ = 0 ppm) or $CHCl_3$ (δ = 7.26 ppm). For ^{13}C NMR spectra, the chemical shifts are recorded relative to $CDCl_3$ (δ = 77.0 ppm). Low-resolution mass spectra were taken from an API 2000-triple quadrupole ESI-MS/MS mass spectrometer. High-resolution mass spectra were obtained using a LCT Premier time of flight mass spectrometer from Waters. IR spectra were measured directly in solid form from Agilent Cary

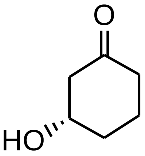
630 FTIR. Optical Rotation were measured by Bodenseewerk Perkin-Elmer & Co Gmbh Ueberlingen. Optical purities of various oxidized products were determined by HPLC using chiral column, Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries, Exton, PA.

2.6.2 Procedures and Analysis Results for Oxidation of *trans*-Cycloalkanediols.

(*R*,*R*)- *trans*-1,3-Cyclohexanediol (37) & (*S*)-3-hydroxycyclohexanone (38) (BH7-056)



(*R*,*R*)-**37**

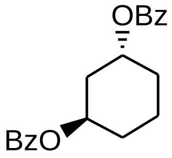


(S)-**38**

To a solution of 4.8 mL of Pd/Au (3:1)-**1** (2.1 μmol of Pd/0.7 μmol of Au-0.08 μmol of **1**) in H_2O, were added 0.16 g (1.39 mmol) of racemic *trans*-1,3-cyclohexanediol (**37**) and 68 mg (0.42 mmol) K_2CO_3 under 1 atmospheric pressure of O_2 (a balloon was used). The solution was stirred at 60 °C for 7 days and the reaction progress was monitored by ^{1}H NMR until about a half of the diol was consumed. The reaction solution was cooled to 25°C, diluted with water, and extracted three times with dichloromethane (20 mL each). The combined extracts were dried (anhydrous Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of ethyl acetate and diethyl ether (3:7) as an eluent to give 78 mg [97.5% yield based on reacted (*S*,*S*)-**37**] of (*S*)-3-hydroxycyclohexanone (**38**) in 99% ee and 81 mg (50% recovery based on racemic diol) of (*R*,*R*)-**37** in 92% ee. (*S*)-**38**: $[\alpha]_D^{22} = +45.2$ (c 0.8, $CHCl_3$); Lit.[58] +37.3 (c 0.80, $CHCl_3$; 82% ee). ^{1}H NMR δ 4.13–4.07 (m, 1 H, CHO), 3.30 (bs, 1 H, OH), 2.56 (dd, J = 14, 4.4 Hz, 1 H, $CH_2C=O$), 2.33 (dd, J = 14, 8 Hz, 1 H, $CH_2C=O$), 2.24 (t, J = 7 Hz, 2 H, $CH_2C=O$), 2.05–1.87 (m, 2 H), 1.75–1.56 (m, 2 H); ^{13}C NMR δ 210.9, 69.8, 50.6, 41.1, 32.9, 20.9. MS (ESI, MeOH): *m/z* = 137.1 ($[M + Na]^+$). The % ee's of the hydroxyketones and diols were determined by subjecting the benzoate derivatives to HPLC using chiral column

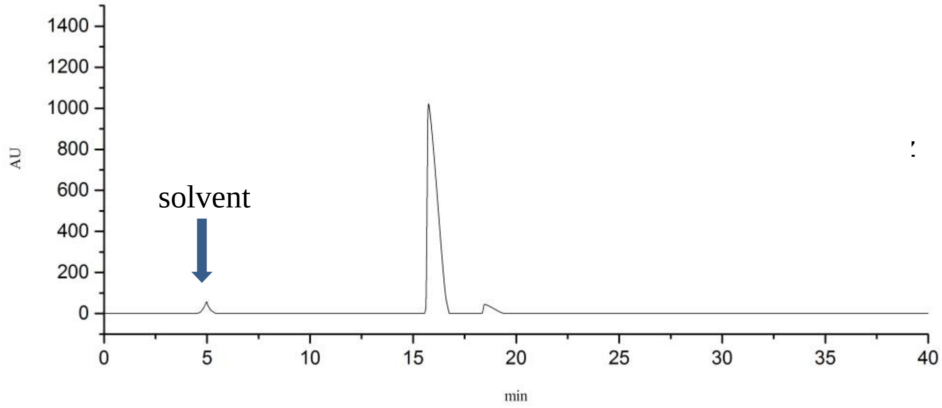
[Chiralpak AD(-H) column, size: 0.46 cm x 25 cm]. (*R*,*R*)-**37**: NMR spectra were identical to the authentic *trans*-1,3-cyclohexanediol. $[\alpha]_D^{22}$ = +3.18 (c 2.0, CH_2Cl_2); Lit.[63] -3.5 (c 2.0, CH_2Cl_2). The % ee was determined from the HPLC/chiral column of the benzoate derivative (*R*,*R*)-**37A & (***S*)-**38A**.

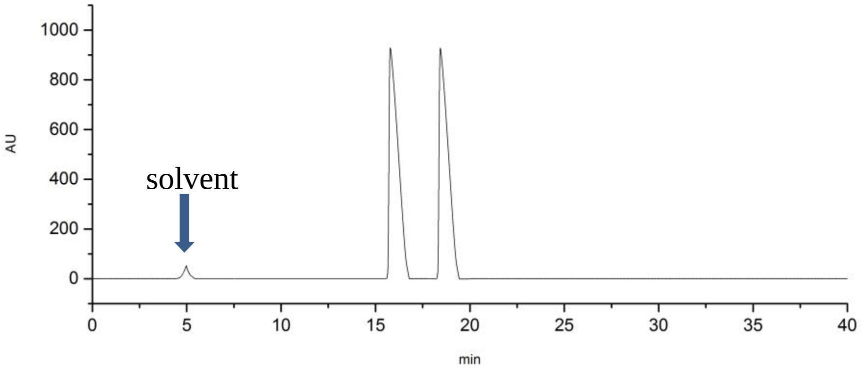
(*R*,*R*)-1,3-Di(phenylcarbonyloxy)cyclohexane (37A). (BH8-015)



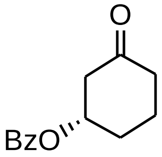
(*R,R*)-**37A**

A solution of 10 mg (86 μmol) of (*R*,*R*)-**37**, 24 mg (0.17 mmol) of benzoyl chloride in 0.1 mL of pyridine and 0.3 mL of dichloromethane was stirred at 25°C for 8 h under argon. The solution was diluted with 1 mL of water, concentrated to dryness, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 17 mg (61% yield) of (*R*,*R*)-**37A** in 92% ee. ^{1}H NMR δ 8.06 (d, J = 8 Hz, 4 H), 7.56 (t, J = 8 Hz, 2 H), 7.45 (t, J = 8 Hz, 4 H), 5.47–5.45 (m, 2 H), 2.15–2.12 (m, 2 H), 1.94–1.91 (m, 2 H), 1.90–1.60 (m, 4 H); ^{13}C NMR δ 166.0 (2 C), 133.1 (2 C), 130.8 (2 C), 129.8 (4 C), 128.6 (4 C), 70.8 (2 C), 36.1, 30.6 (2 C), 19.7. MS (ESI, MeOH): *m/z* = 347.2 ($[M + Na]^+$). The % ee of this compound was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane:*i*-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 15.7 min (*R,R* enantiomer, major), t_R = 18.6 min (*S*,*S* enantiomer, minor). The racemic *trans*-dibenzoate **37A** were similarly prepared for HPLC/chiral column study from the corresponding racemic *trans*-diols.



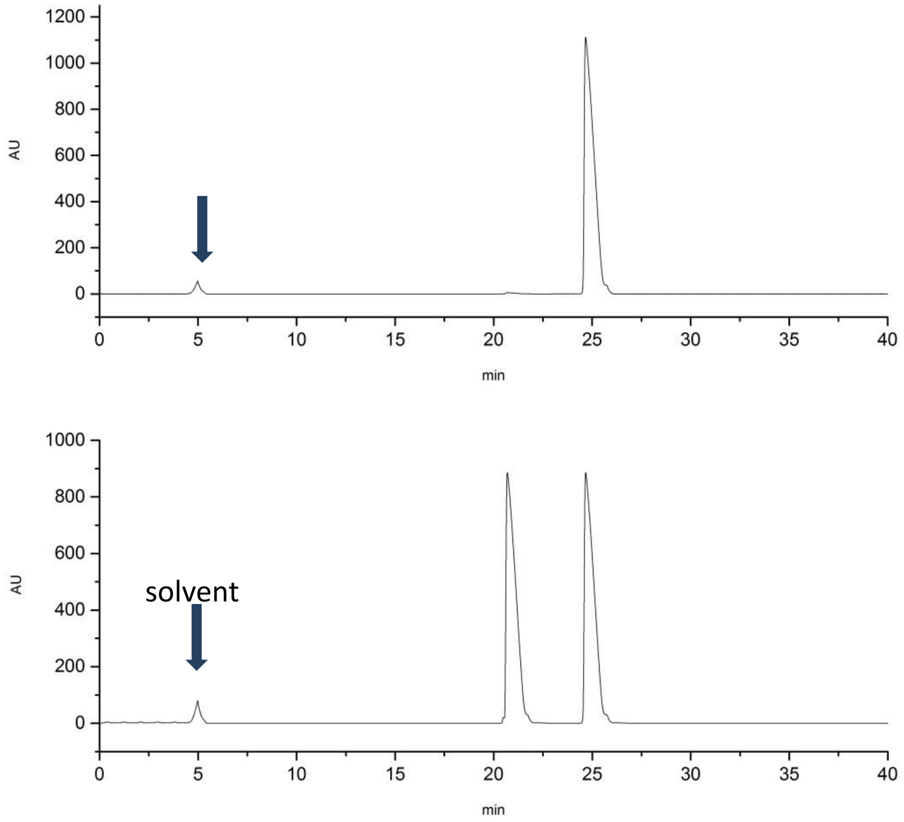


(*S*)-3-Oxocyclohexyl benzoate (38A). (BH7-073)

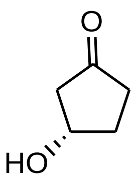


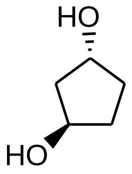
(S)-**38A**

To a solution of 50 mg (0.44 mmol) of (*S*)-**38** in 1.5 mL of dichloromethane under argon at 0^{o}C, was added 0.1 mL of pyridine and 0.12 g (0.85 mmol) of benzoyl chloride. The reaction solution was stirred at 0^{o}C for 1 h, diluted with water, and extracted with CH_2Cl_2 twice. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of ethyl acetate and hexane (1:2) as an eluent to give 88 mg (92% yield) of (*S*)-**38A** in 99% ee. ^{1}H NMR δ 8.00 (d, J = 7.6 Hz, 2 H), 7.56 (t, J = 7.6 Hz 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 5.55–5.50 (m, 1 H, CHO), 2.75 (dd, J = 14.8, 4 Hz, 1 H), 2.66 (dd, J = 14.8, 5.6 Hz, 1 H), 2.50–2.40 (m, 2 H), 2.17–2.2.0 (m, 3 H), 1.97–1.85 (m, 1 H); ^{13}C NMR δ 208.4, 165.7, 133.4, 129.8, 128.7, 128.6, 72.4, 46.8, 41.3, 29.6, 21.1. MS (ESI, MeOH): *m/z* = 241.1 ([M + Na]$^+$). The % ee of this compound was determined by HPLC using chiral column, Chiralpak AD(-H) column, n-hexane-i-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 21 min (*R* enantiomer, minor), t_R = 25 min (*S* enantiomer, major).



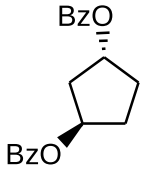
(*S*)-3-Hydroxycyclopentanone (41) & (*R*,*R*)-cyclopentanediol (39) (BH7-067)


(*S*)-**41**


(*R*,*R*)-**39**

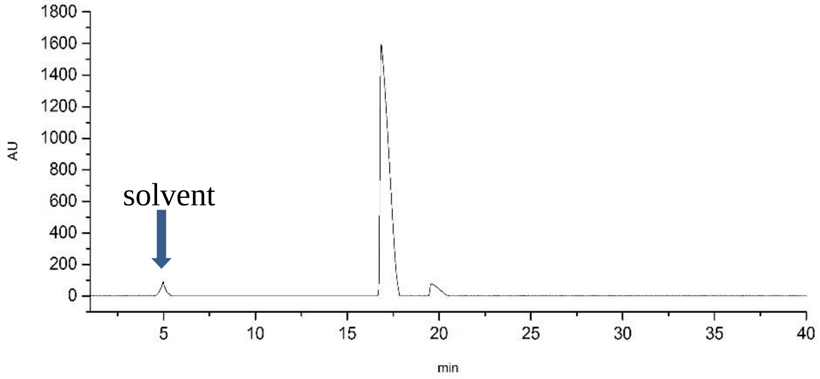
From 15 mg (0.147 mmol) of (±)-cyclopentanediol (**39**), 0.48 mL of Pd/Au (3:1)-**1** (0.22 μmol of Pd/0.07 μmol of Au-0.008 μmol of **1**) in H_2O, 6.8 mg (96% yield based on reacted diols **39**; 99% ee) of (*S*)-**41** and 8.0 mg (53% recovery of (*R*,*R*)-**39** in 91% ee. Compound (*S*)-**41**: $[\alpha]_D^{22}$ = -33.8 (c 0.6, CH_2Cl_2); Lit.[59] -18.3 (c 0.50, CH_2Cl_2; for S-configuration, 83% ee). ^1H NMR δ 4.63–4.60 (m, 1 H, CHO), 2.52–2.36 (m, 2 H), 2.28–2.12 (m, 3 H), 2.10–2.00 (m, 1 H), 1.85–1.87 (bs, 1 H, OH); ^{13}C NMR δ 218.0, 69.9, 47.9, 35.8, 32.3. MS (ESI, MeOH): *m/z* = 123.0 ($[M + Na]^+$). (*R*,*R*)-**39**: The NMR spectra were identical to those of the authentic 1,3-*trans*-cyclopentanediol. $[\alpha]_D^{22}$ = +17.3 (c 1.0, $CHCl_3$). The % ee was determined from the HPLC/chiral column of the benzoate derivative (*R*,*R*)-**39A &** (*S*)-**41A**.

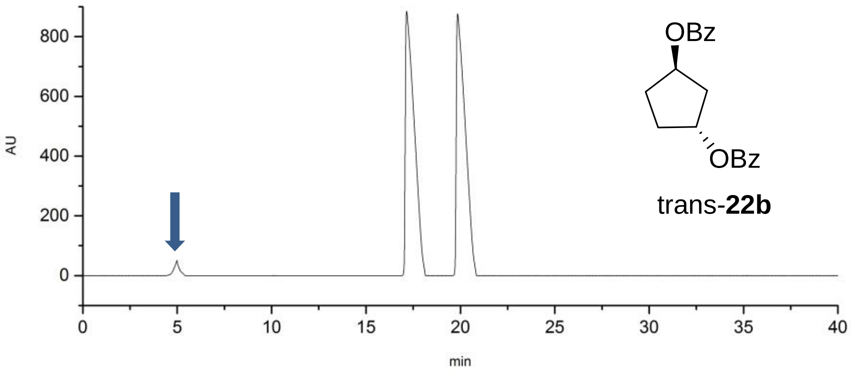
(*R*,*R*)-1,3-Diphenylcarbonyloxycyclopentane (39A). (BH8-021)



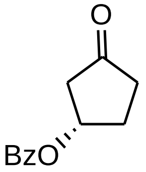
(*R*,*R*)-**39A**

From 15 mg (0.147 mmol) of (R,R)-19 and 82 mg (0.59 mmol) of benzoyl chloride in 0.2 mL of pyridine and 0.5 mL of dichloromethane, 26 mg (57% yield) of (*R*,*R*)-**39A** in 91% ee. ^1H NMR δ 8.06 (d, J = 8.5 Hz, 4 H), 7.56 (t, J = 8.5 Hz, 2 H), 7.45 (t, J = 8.5 Hz, 4 H), 5.49–5.44 (m, 2 H), 2.16–2.13 (m, 2 H), 1.94–1.86 (m, 4 H); ^{13}C NMR δ 166.6 (2 C), 133.1 (2 C), 130.8 (2 C), 129.8 (4 C), 128.6 (4 C), 71.5 (2 C), 39.7, 24.5 (2 C). MS (ESI, MeOH): *m/z* = 332.8 ($[M + Na]^+$),. The % ee of this compound was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane:*i*-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 16.8 min (*R,R* enantiomer, major), t_R = 19.6 min (*S,S* enantiomer, minor). The racemic *trans*-dibenzoate **39A** were similarly prepared for HPLC/chiral column study from the corresponding racemic *trans*-diols.



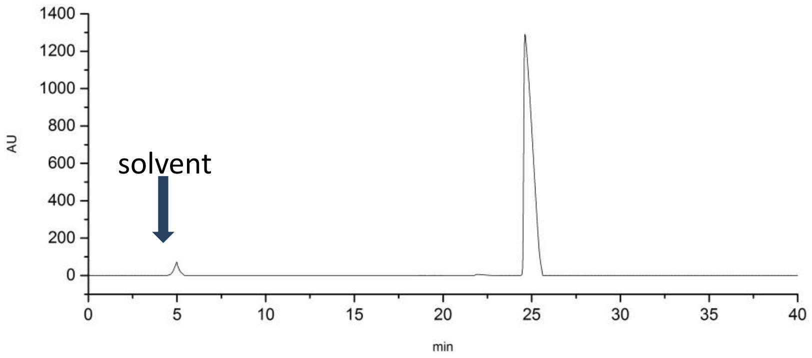


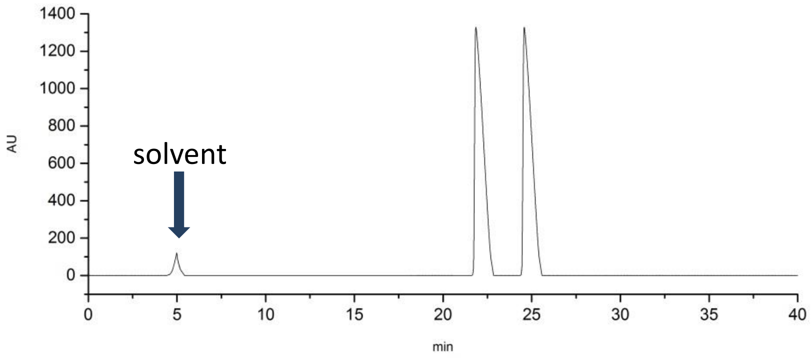
(*S*)-3-Oxocyclopentyl benzoate (41A). (BH7-075)



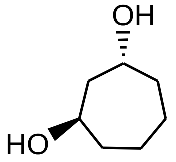
(*S*)-**41A**

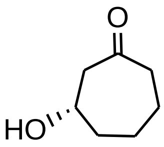
From 6.8 mg (68 μmol) of (*S*)-**41** and 19 mg (0.14 mmol) of benzoyl chloride and 0.1 mL of pyridine in 1 mL of dichloromethane, 13 mg (94% yield) of (*S*)-**41A** in 99% ee. ^{1}H NMR δ 8.09–8.07 (m, 2 H), 7.59–7.46 (m, 1 H), 7.45–7.42 (m, 2 H), 5.49–5.44 (m, 1 H), 2.73–2.68 (m, 1 H), 2.55–2.51 (m, 1 H), 2.37–2.25 (m, 4 H); ^{13}C NMR δ 215.8, 165.7, 133.4, 129.8, 128.7, 128.6, 72.5, 44.4, 35.6, 29.2. MS (ESI, MeOH): *m/z* = 227.2 ([M + Na]$^+$). The % ee of this compound was determined by HPLC using chiral column, Chiralpak AD(-H) column, n-hexane/i-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 22 min (*R* enantiomer, minor), t_R = 24.5 min (*S* enantiomer, major).





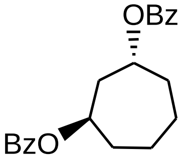
(*R*,*R*)-Cycloheptanediol (40) & (*S*)-3-Hydroxycycloheptanone (42). (BH7-104)


(*R*,*R*)-**40**


(*S*)-**42**

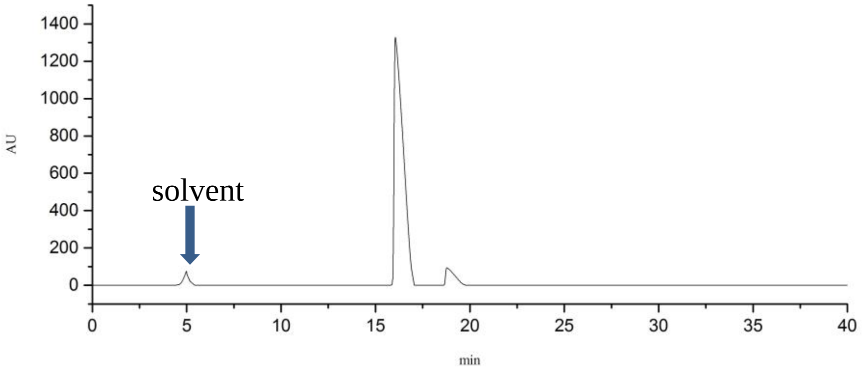
From 30 mg (0.23 mmol) of (±)-cycloheptanediol (**40**), 0.8 mL of Pd/Au (3:1)-**1** (0.35 μmol of Pd/0.12 μmol of Au-0.013 μmol of **1**) in H_2O, 13.4 mg (92% yield based on reacted diols **40**; 99% ee) of (*S*)-**42** and 15.8 mg (53% recovery) of (*R*,*R*)-**40**. Compound (*S*)-**42**: $[\alpha]_D^{22}$ = +16.4 (c 0.8, CH_2Cl_2). ^1H NMR[60] δ 4.13–4.06 (m, 1 H, CHO), 2.84–2.74 (m, 2 H), 2.54–2.40 (m, 2 H), 1.94–1.70 (m, 6 H), 1.65–1.55 (m, 1 H); ^{13}C NMR δ 212.4, 67.7, 51.8, 44.5, 39.0, 24.5, 23.9. MS (ESI, MeOH): *m/z* = 151.1 ([M + Na]$^+$). (*R*,*R*)-**40**: The NMR spectra were identical to those of authentic 1,3-*trans*-cycloheptanediol. $[\alpha]_D^{22}$ = +16.9 (c 1.0, $CHCl_3$). The % ee was determined from the HPLC/chiral column of the benzoate derivative (*R*,*R*)-**40A &** (*S*)-**42A**.

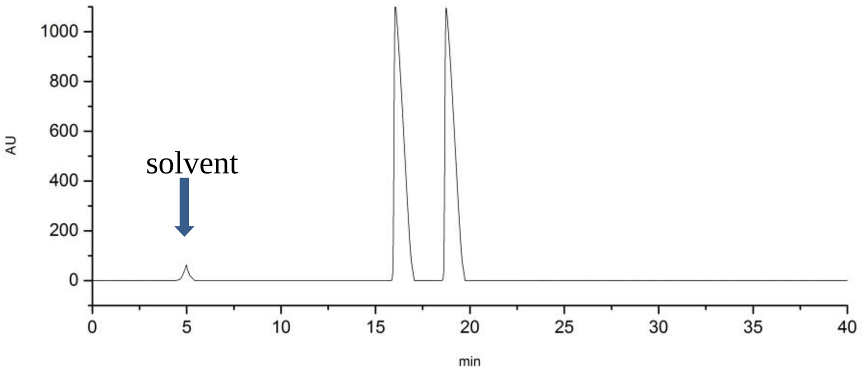
(*R*,*R*)-1,3-(Diphenylcarbonyloxy)cycloheptane (40A). (BH8-020)



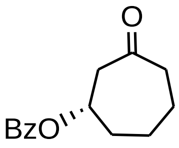
(*R*,*R*)-**40A**

From 15 mg (0.12 mmol) of (*R*,*R*)-**40** and 64 mg (0.46 mmol) of benzoyl chloride in 0.2 mL of pyridine and 0.5 mL of dichloromethane, 22 mg (56% yield) of (*R*,*R*)-**40A** in 85% ee. ^{1}H NMR δ 8.06 (d, J = 8 Hz, 4 H), 7.56 (t, J = 8 Hz, 2 H), 7.45 (t, J = 8 Hz, 4 H), 5.49–5.44 (m, 2 H), 2.13 (t, J = 6 Hz, 2 H), 2.02–1.88 (m, 4 H), 1.87–1.74 (m, 4 H); ^{13}C NMR δ 166.5 (2 C), 133.1 (2 C), 130.8 (2 C), 129.8 (4 C), 128.6 (4 C), 70.9 (2 C), 36.3, 29.1 (2 C), 24.1 (2 C). MS (ESI, MeOH): *m/z* = 361.4 ([M + Na]$^+$), 249.1, 217.3, 123.1, 102.2. The % ee of this compound was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane:*i*-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 16.1 min (*R*,*R* enantiomer, major), t_R = 18.8 min (*S*,*S* enantiomer, minor).The racemic *trans*-dibenzoate **40A** were similarly prepared for HPLC/chiral column study from the corresponding racemic *trans*-diols.





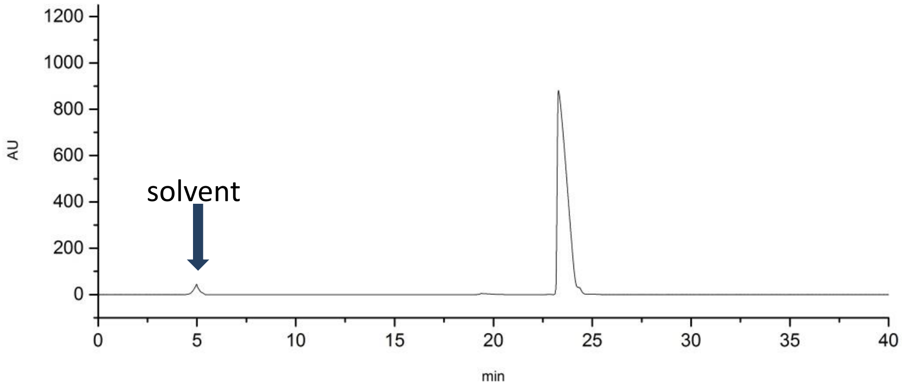
(*S*)-3-Oxocycloheptyl benzoate (42A). (BH7-107)

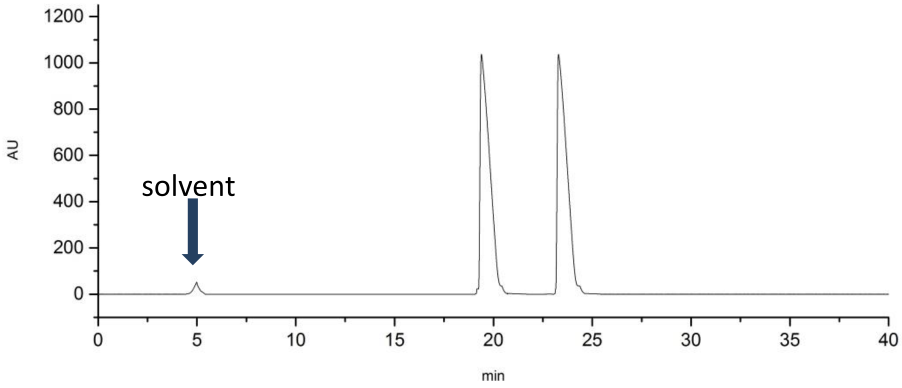


(*S*)-**42A**

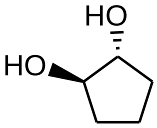
From 10 mg (0.078 mmol) of (*S*)-**42**, 22 mg (0.16 mmol) of benzoyl chloride and 0.1 mL of pyridine in 0.5 mL of dichloromethane, 18 mg (98% yield) of (*S*)-**42A** (99% ee) was obtained. ^{1}H NMR δ 8.00 (d J = 7.6 Hz, 2 H), 7.56 (t, J = 7.6 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 5.54–5.50 (m, 1 H), 2.86 (dd, J = 12, 4.4 Hz, 1 H), 2.81 (dd, J = 12, 8 Hz, 1 H), 2.47–2.40 (m, 2 H), 2.32–2.25 (m, 2 H), 2.15–2.05 (m, 3 H), 1.96–1.86 (m, 1 H); ^{13}C NMR δ 208.2, 165.7, 133.7, 129.8 (2 C), 129.0, 128.6 (2 C), 72.4, 46.8, 40.8, 29.1, 21.8, 21.0. MS (ESI, MeOH): *m/z* = 255.1 ([M + Na]$^+$). The % ee of this compound was determined by HPLC using chiral column, Chiralpak

AD(-H) column, n-hexane/i-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 19 min (*R* enantiomer, minor), t_R = 23 min (*S* enantiomer, major).

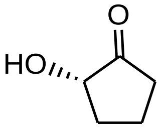




(*R*,*R*)- 1,2-Cyclopentanediol (46) & (*S*)-2-hydroxycyclopentanone (49) (BH7-102)



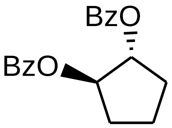
(*R*,*R*)-**46**



(*S*)-**49**

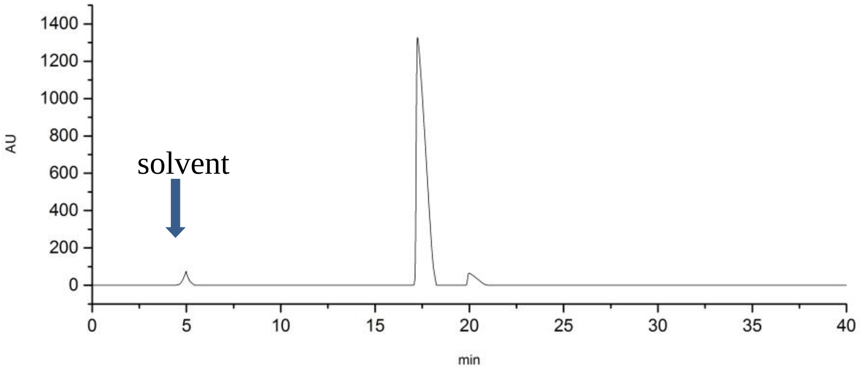
From 30 mg (0.29 mmol) of (±)-**46**, 1.0 mL of Pd/Au (3:1)-**1** (0.438 μmol of Pd/0.146 μmol of Au-0.017 μmol of **1**) in H_2O, 14 mg (94% yield; based on reacted (*S*,*S*)-**46**) of (*S*)-**49** (99% ee) and 15 mg (50% recovery) of (*R*,*R*)-**46**. The % ee of (*S*)-**49** was determined by HPLC/chiral of benzoate derivative (*S*)-**49A**. Compound (*S*)-**49**: $[\alpha]_D^{22}$ = +40.6 (c 1.0, $CHCl_3$); Lit.[61] -37.4 (c 1.0, $CHCl_3$) for (*R*)-configuration (>99% ee). ^{1}H NMR δ 4.10 (dd, J = 12, 5 Hz, 1 H, CHO), 3.65–3.55 (bs, 1 H, OH), 2.50–2.34 (m, 2 H), 2.27–2.10 (m, 2 H), 1.86–1.60 (m, 2 H); ^{13}C NMR δ 211.9, 75.1, 40.5, 37.6, 26.3. MS (ESI, MeOH): *m/z* = 123.0 (M+Na$^+$). (*R*,*R*)-**46**: The NMR spectra were identical to those of the authentic 1,2-*trans*-cyclopentanediol. $[\alpha]_D^{22}$ = -19.9 (c 1.1, $CHCl_3$); Lit.[62] -21.3 (c 1.1, $CHCl_3$) for (*R*,*R*)-configuration (>99% ee).

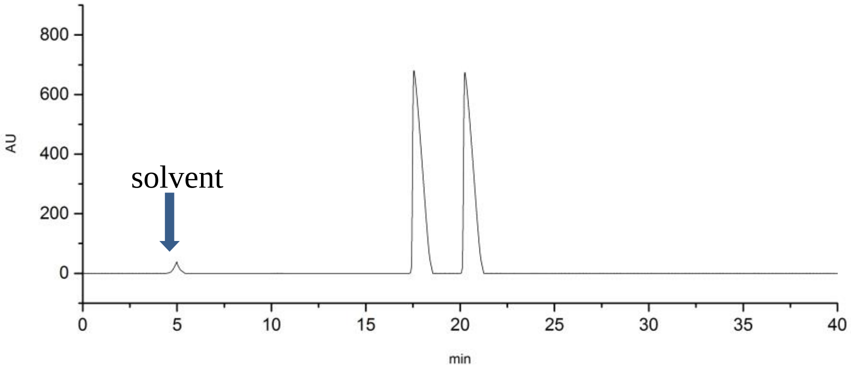
(*R*,*R*)-1,2-(Diphenylcarbonyloxy)cyclopentane (46A). (reaction was taken by Dr. Man Zhang. HPLC was taken by me)



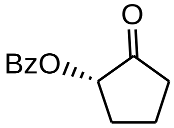
(*R*,*R*)-**46A**

From 14 mg (0.14 mmol) of (*R*,*R*)-**46**, 58 mg (0.41 mmol) of benzoyl chloride in 0.1 mL of pyridine and 2 mL of dichloromethane, gave 29 mg (67% yield) of (*R*,*R*)-**46A**. ^{1}H NMR δ 8.04–8.00 (m, 4 H), 7.58–7.53 (m, 2 H), 7.46–7.38 (m, 4 H), 5.50 (t, J = 4 Hz, 2 H, CHO), 2.36–2.29 (m, 2 H), 2.00–1.80 (m, 4 H); ^{13}C NMR δ 166.2, 133.3, 130.3, 129.9 (4 C), 128.6 (4 C), 79.7, 30.8, 21.9. MS (ESI, MeOH): *m/z* = 333.0 (M+Na$^+$), 265.3, 189.1, 105.2. The % ee (88%) of (*R*,*R*)-**46A** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 17.3 min (*R*,*R* enantiomer, major), t_R = 20.0 min (*S*,*S* enantiomer, minor). The racemic *trans*-dibenzoate **46A** were similarly prepared for HPLC/chiral column study from the corresponding racemic *trans*-diols.



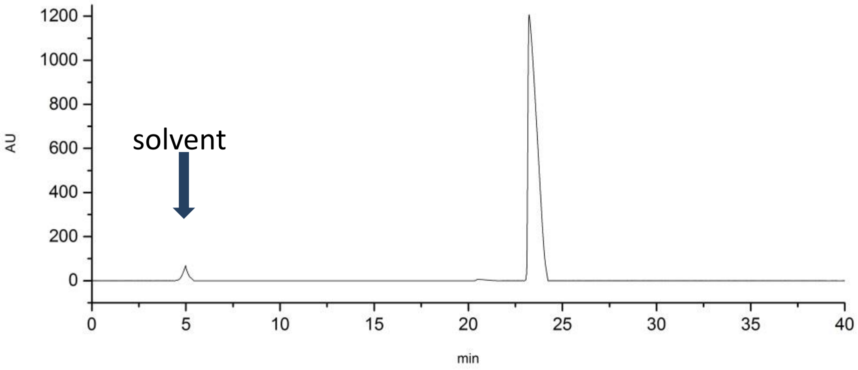


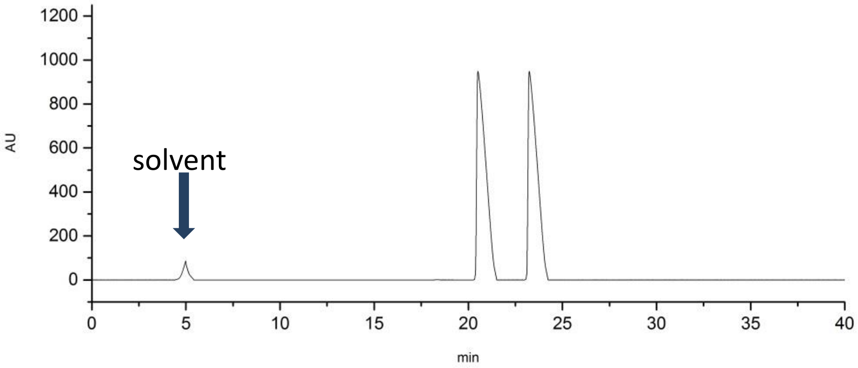
(*S*)-2-Oxocyclopentyl benzoate (49A). (BH7-113)



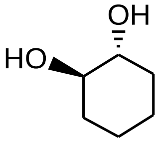
(*S*)-**49A**

From 10 mg (0.1 mmol) of (*S*)-**49** and 28 mg (0.2 mmol) of benzoyl chloride in 0.1 mL of pyridine and 0.5 mL of dichloromethane, 16.8 mg (82% yield) of (*S*)-**49A** in 99% ee was obtained. ^{1}H NMR δ 8.08 (d, J = 7.6 Hz, 2 H), 7.57 (t, J = 7.6 Hz, 1 H), 7.45 (t, J = 7.6 Hz, 2 H), 5.46 (dd, J = 9, 3 Hz, 1 H), 2.75–2.65 (m, 1 H), 2.55–2.45 (m, 1 H), 2.17–2.08 (m, 1), 1.95–1.85 (m, 3 H); ^{13}C NMR δ 204.6, 169.2, 133.4, 130.1 (2 C), 129.9, 128.6 (2 C), 77.2, 39.9, 31.2, 21.4. MS (ESI, MeOH): *m/z* = 227.2 (M+Na$^+$). The % ee of this compound was determined by HPLC using chiral column, Chiralpak AD(-H) column, n-hexane/i-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 20.5 min (*R* enantiomer, minor), t_R = 23.3 min (*S* enantiomer, major).

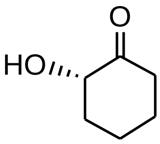




(*R*,*R*)-1,2-Cyclohexanediol (47) & (*S*)-2-hydroxycyclohexanone (50) (BH7-061)



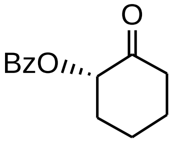
(*R*,*R*)-**47**



(S)-**50**

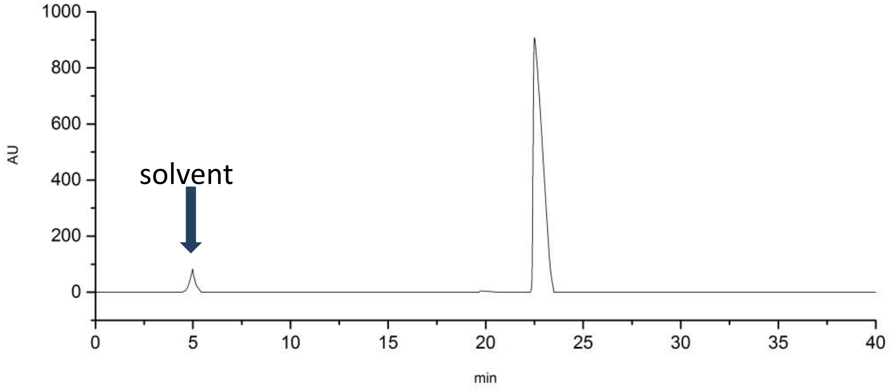
From 161 mg (1.39 mmol) of (±)-**47**, 4.8 mL of Pd/Au (3:1)-**1** (2.1 μmol of Pd/0.7 μmol of Au-0.08 μmol of **1**) in H_2O, 72 mg (89% yield; based on reacted (*S*,*S*)-**47**) of (*S*)-**50** (99% ee) and 80 mg (50% recovery) of (*R*,*R*)-**47**. Compound (*S*)-**50**: $[\alpha]_D^{22}$ = -20.7 (c 0.65, $CHCl_3$); Lit.[67] +20.6 (c 1.0, $CHCl_3$) for (*R*)-**50** (>99.0% ee). ^1H NMR δ 4.11 (dd, J = 12, 7 Hz, 1 H, CHO), 3.70–3.55 (bs, 1 H, OH), 2.60–2.30 (m, 3 H), 2.15–1.45 (m, 5 H); ^{13}C NMR δ 211.7, 75.6, 39.7, 36.9, 27.8, 23.6. MS (ESI, MeOH): *m/z* = 115.1 ($M+H^+$). (*R*,*R*)-**47**: $[\alpha]_D^{22}$ = -34.7 (c 1.0, H_2O); Lit.[61] +37.1 (c 1.0, H_2O) for (*S*,*S*)-**29** (>99.0% ee).

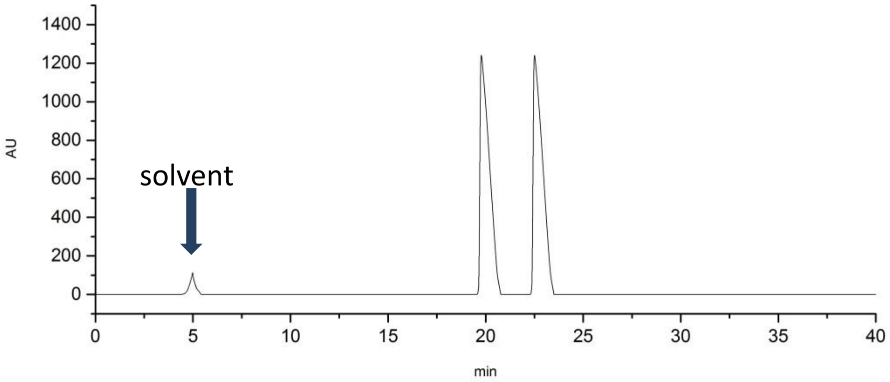
(S)-2-Oxocyclohexyl benzoate (50A). (BH7-078)



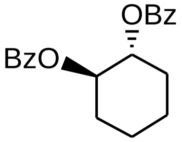
(S)-**50A**

From 50 mg (0.44 mmol) of (*S*)-**50** and 0.122 mg (0.87 mmol) of benzoyl chloride in 0.1 mL of pyridine and 1.5 mL of dichloromethane, 66 mg (69% yield) of (*S*)-**50A** (99% ee). ^{1}H NMR δ 8.08 (d, J = 8 Hz, 2 H), 7.56 (t, J = 8 Hz, 1 H), 7.45 (t, J = 8 Hz, 2 H), 5.41 (dd, J = 12, 7 Hz, 1 H), 2.60–2.40 (m, 3 H), 2.18–1.64 (m, 5 H); ^{13}C NMR δ 204.7, 169.2, 133.3, 130.1 (2 C), 129.9, 128.6 (2 C), 77.2, 40.7, 33.4, 27.4, 24.0. MS (ESI, MeOH): *m/z* = 241.4 (M+Na^{+}). The % ee of this compound was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 20 min (*R* enantiomer, minor), t_R = 22.5 min (*S* enantiomer, major).



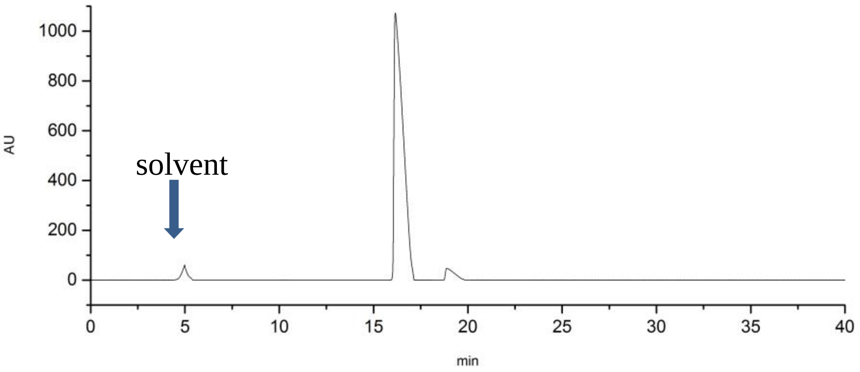


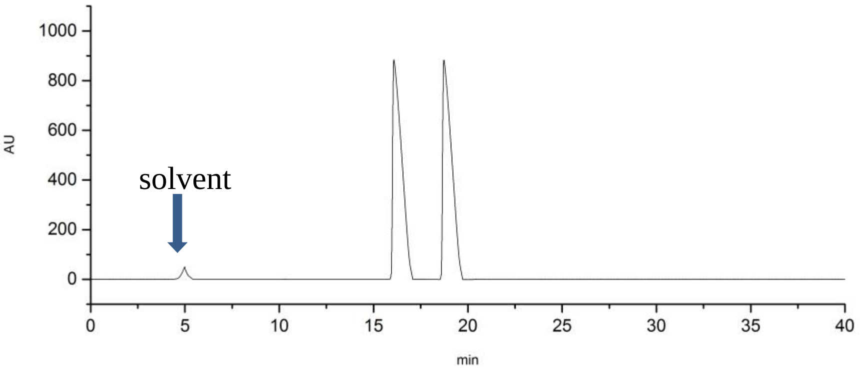
(*R*,*R*)-1,2-Di(phenylcarbonyloxy)cyclohexane (47A). (BH8-015)



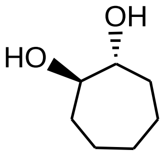
(*R*,*R*)-**47A**

From 20 mg (0.17 mmol) of (*R*,*R*)-**47** and 49 mg (0.34 mmol) of benzoyl chloride in 0.2 mL of pyridine and 0.6 mL of dichloromethane, 51 mg (85% yield) of (*R*,*R*)-**47A** was isolated after silica gel column chromatography. ^{1}H NMR δ 7.94 (d, J = 7.5 Hz, 4 H), 7.46 (t, J = 7.5 Hz, 2 H), 7.33 (t, J = 7.5 Hz, 4 H), 5.41–5.35 (m, 2 H), 2.27–2.23 (m, 1 H), 2.12–2.06 (m, 1 H), 1.90–1.77 (m, 3 H), 1.63–1.49 (m, 3 H); ^{13}C NMR δ 166.2 (2 C), 133.1 (2 C), 129.9 (2 C), 129.1 (4 C), 128.6 (4 C), 74.5 (2 C), 30.4 (2 C), 23.6 (2 C). MS (ESI, MeOH): *m/z* = 347.2 (M+Na$^+$), 243.2, 123.1, 102.1. The % ee (87%) of (*R*,*R*)-**47A** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 16.2 min (*R*,*R* enantiomer, major), t_R = 18.9 min (*S*,*S* enantiomer, minor). The racemic *trans*-dibenzoate **47A** were similarly prepared for HPLC/chiral column study from the corresponding racemic *trans*-diols.

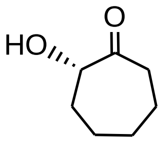




(*R*,*R*)-1,2-Cycloheptanediol (48) & (*S*)-2-hydroxycycloheptanone (51) (BH7-108)



(*R*,*R*)-**48**

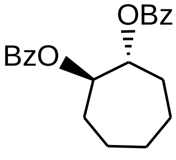


(*S*)-**51**

From 30 mg (0.23 mmol) of (±)-cycloheptanediol (**48**), 0.8 mL of Pd/Au (3:1)-**1** (0.35 μmol of Pd/0.12 μmol of Au-0.013 μmol of **1**) in H_2O, 13.5 mg (93% yield based on reacted diols (*S*,*S*)-**48**; 99% ee) of (*S*)-**51** and 16.3 mg (54% recovery) of (*R*,*R*)-**48** (88% ee). The % ee was determined by HPLC/chiral column of benzoate derivative (*S*)-**51A**. Compound (*S*)-**51**: $[\alpha]_D^{22}$ = -143.9 (c 0.8, $CHCl_3$); Lit.[61] -86.4 (c 1.0, $CHCl_3$) for (*R*)-**51** (>99.0% ee). ^{1}H NMR δ 4.31–4.26 (m, 1 H), 3.83–3.75 (bs, 1 H, OH), 2.71–2.61 (m, 1 H), 2.46 (ddd, J = 17, 11, 4 Hz, 1 H), 2.08–1.55 (m, 7 H), 1.40–1.30 (m, 1 H); ^{13}C NMR δ 213.3, 77.20, 39.9, 33.5, 29.4, 26.5, 23.6.

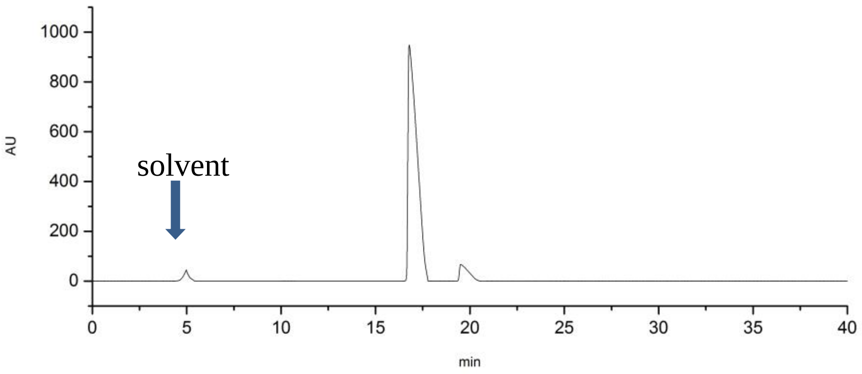
MS (ESI, MeOH): *m/z* = 129.2 (M+H$^+$). (*R*,*R*)-**48**: The NMR spectra were identical to those of the authentic 1,2-*trans*-cycloheptanediol. $[\alpha]_D^{22}$ = -4.9 (c 0.7, $CHCl_3$); Lit.[61] +10.7 (c 1.0, $CHCl_3$) for (*S*,*S*)-**48** (>99.0% ee).

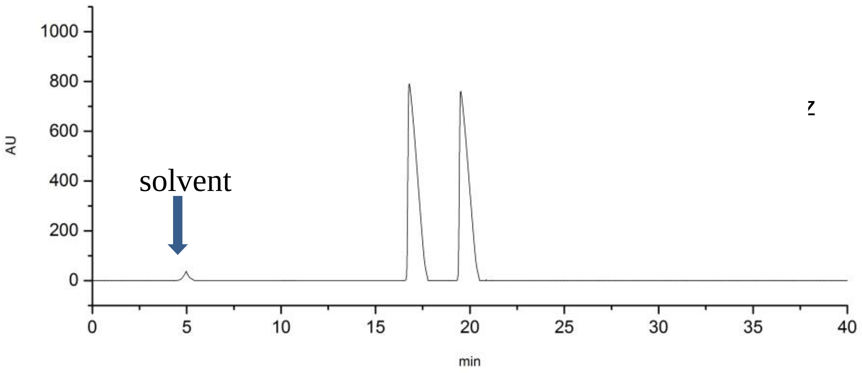
(*R*,*R*)-1,2-Di(phenylcarbonyloxy)cycloheptane (48A). (reaction was taken by Dr. Man Zhang. HPLC was taken by me)



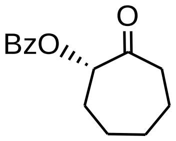
(*R*,*R*)-**48A**

From 10 mg (0.077 mmol) of (*R*,*R*)-**48** and 32 mg (0.23 mmol) of benzoyl chloride in 61 μL of pyridine and 2 mL of dichloromethane, 23 mg (90% yield) of (*R*,*R*)-**48A** was isolated after silica gel column chromatography. ^{1}H NMR δ 7.97 (d, J = 7 Hz, 4 H), 7.49 (t, J = 7 Hz, 2 H), 7.38–7.34 (m, 4 H), 5.42–5.40 (m, 2 H, CHO), 2.20–2.00 (m, 2 H), 1.88–1.75 (m, 4 H), 1.75–1.60 (m, 4 H); ^{13}C NMR δ 166.3, 133.1, 130.5, 129.8 (4 C), 128.5 (4 C), 77.6, 30.7, 28.5, 23.1. MS (ESI, MeOH): *m/z* = 361.3 ([M + Na]$^+$). The % ee (88%) of (*R*,*R*)-**48A** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 16.8 min (*R*,*R* enantiomer, major), t_R = 19.5 min (*S*,*S* enantiomer, minor). The racemic *trans*-dibenzoate **48A** were similarly prepared for HPLC/chiral column study from the corresponding racemic *trans*-diols.



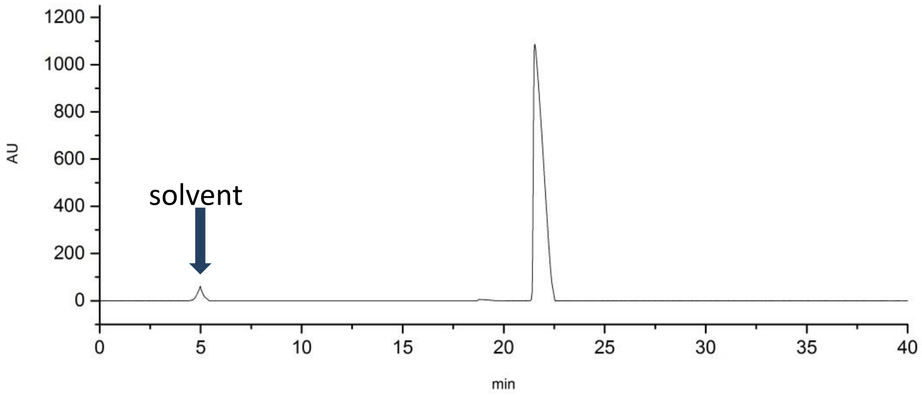


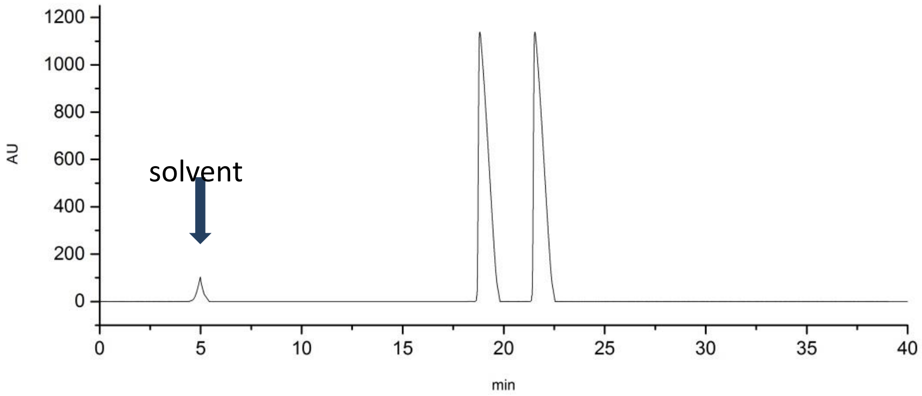
(*S*)-2-Oxocycloheptyl benzoate (51A). (BH7-118)



(*S*)-**51A**

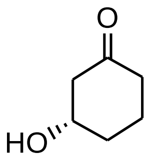
From 10 mg (78 μmol) of (*S*)-**51** and 22 mg (0.16 mmol) of benzoyl chloride in 0.1 mL of pyridine and 0.5 mL of dichloromethane, 17.6 mg (97% yield) of (*S*)-**51A** (99% ee) was obtained. ^{1}H NMR δ 8.08 (d, J = 8 Hz, 2 H), 7.57 (d, J = 8 Hz, 1 H), 7.45 (t, J = 8 Hz, 2 H), 2.75–2.65 (m, 1 H), 2.55–2.45 (m, 1 H), 2.16–2.10 (m, 1 H), 2.0–1.65 (m, 6 H), 1.51–1.40 (m, 1 H); ^{13}C NMR δ 207.4, 165.1, 133.4, 130.1 (2 C), 129.9, 128.6 (2 C), 79.9, 40.8, 30.8, 27.3, 26.1, 22.0. MS (ESI, MeOH): *m/z* = 255.1 ([M + Na]$^+$). The % ee of this compound was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 19 min (*R* enantiomer, minor), t_R = 21.5 min (*S* enantiomer, major).





2.6.3 Procedures and Analysis Results for Oxidation of *cis*-Cycloalkanediols.

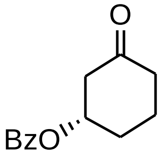
(*S*)-3-Hydroxycyclohexanone (38) (BH7-053)



(S)-**38**

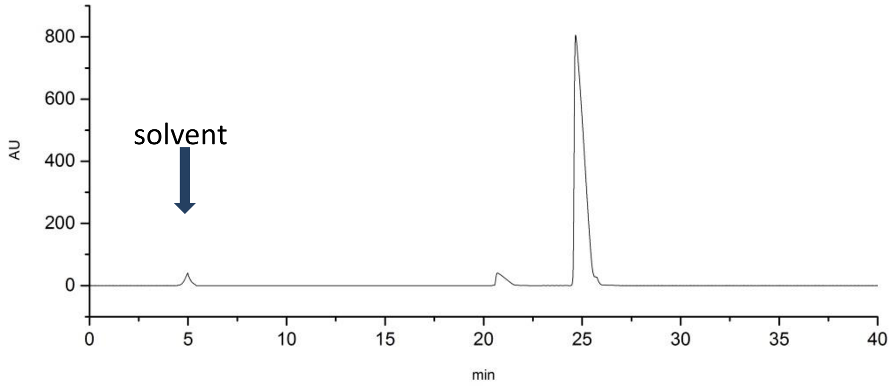
To a solution of 4.8 mL of Pd/Au (3:1)-**1** (2.1 μmol of Pd/0.7 μmol of Au-0.08 μmol of **1**) in H_2O, were added 16 mL of deionized H_2O, 0.16 g (1.39 mmol; 662 equivalents based on Pd mole atoms) of racemic meso-*cis*-1,3-cyclohexanediol (**44**) and 68 mg (0.42 mmol) K_2CO_3. The solution was transferred into a high pressure apparatus (Parr Pressure Reactor), stirred at 120^{o}C under 30 psi O_2 for 3 days. The stirring was stopped and reactor was cooled to 25^{o}C. The solution was extracted three times with dichloromethane (20 mL each) and the combined extracts were washed with water and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of ethyl acetate and hexane (1:1) as an eluent to give 0.141 g (89% yield) of (*S*)-**38** in 91% ee (determined by HPLC/chiral column of the benzoate derivative (*S*)-3**8A**). (*S*)-**38**: $[\alpha]_D^{22}$ = +40.1 (c 0.8, $CHCl_3$).; Lit.[58] for (*S*)-**38**: +37.3 (c 0.80, $CHCl_3$; 82% ee). ^{1}H and ^{13}C NMR spectra were identical to those of (*S*)-**38** obtained from the oxidation of *trans*-1,3-cyclohexanediol.

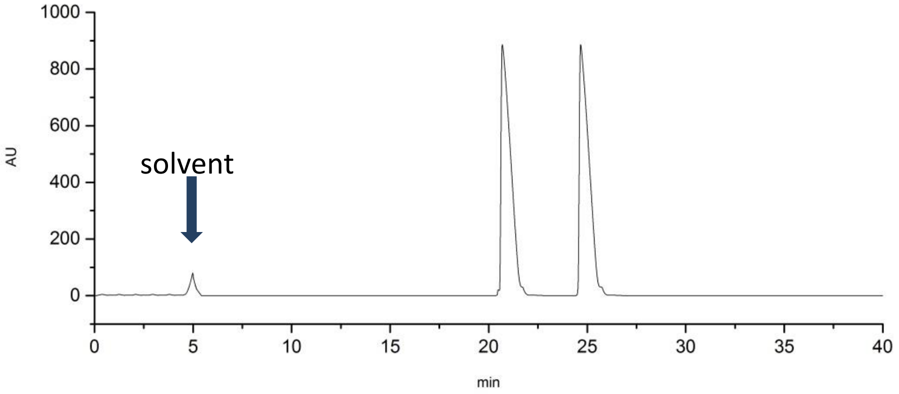
(*S*)-3-Oxocyclohexyl benzoate (38A). (BH7-071)



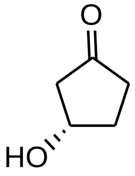
(S)-**38A**

From 0.1 g (0.87 mmol) of (*S*)-**38** and 0.24 g (1.74 mmol) of benzoyl chloride in 0.2 mL of pyridine and 3 mL of dichloromethane, 0.174 g (92% yield) of (*S*)-**38A** (91% ee) was obtained. The % ee of (*S*)-**38a** was determined by HPLC using chiral column, Chiralpak AD(-H) column, n-hexane/i-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 21 min (*R* enantiomer, minor), t_R = 25 min (*S* enantiomer, major).





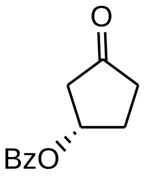
(*S*)-3-Hydroxycyclopentanone (41) (BH7-069)



(*S*)-**41**

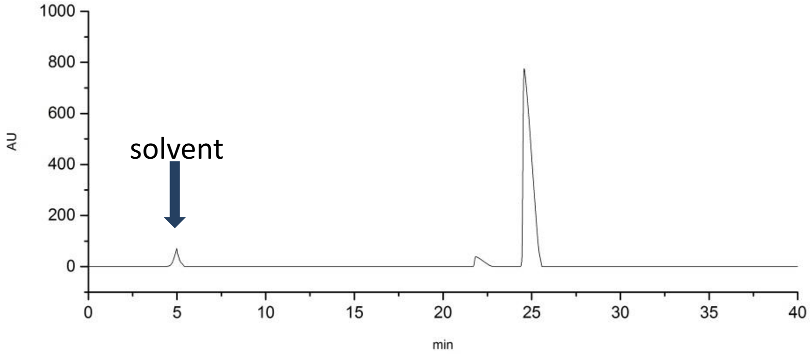
From 30 mg (0.29 mmol) of **43**, 1.0 mL of Pd/Au (3:1)-**1** (0.438 μmol of Pd/0.146 μmol of Au-0.017 μmol of **1**) in H_2O at 120°C and 30 psi of O_2 for 3 days, 28.3 mg (97% yield) of (*S*)-**41** in 90% ee (determined by HPLC/chiral column of the benzoate derivative (*S*)-**41A**) was isolated. (*S*)-**41**: $[\alpha]_D^{22}$ = -29.9 (c 0.6, CH_2Cl_2), Lit.[59] -18.3 (c 0.50, CH_2Cl_2; for S-configuration, 83% ee). ^{1}H and ^{13}C NMR spectra were identical to those of (*S*)-**41** obtained from the oxidation of *trans*-1,3-cyclopentanediol.

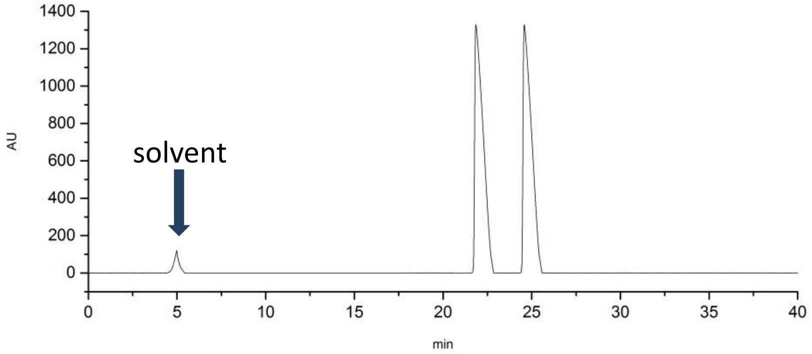
(*S*)-3-Oxocyclopentyl benzoate (41A). (BH7-076)



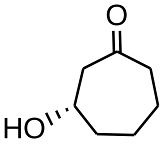
(*S*)-**41A**

From 20 mg (0.20 mmol) of (*S*)-**41** and 56 mg (0.40 mmol) of benzoyl chloride in 0.1 mL of pyridine and 1 mL of dichloromethane, 29 mg (71% yield) of (*S*)-**41A** (90% ee) was obtained. The % ee (90%) of compound (*S*)-**41A** was determined by HPLC using chiral column, Chiralpak AD(-H) column, n-hexane/i-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 21.8 min (*R* enantiomer, minor), t_R = 24.5 min (*S* enantiomer, major).





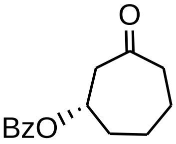
(*S*)-3-Hydroxycycloheptanone (42). (BH7-080)



(*S*)-**42**

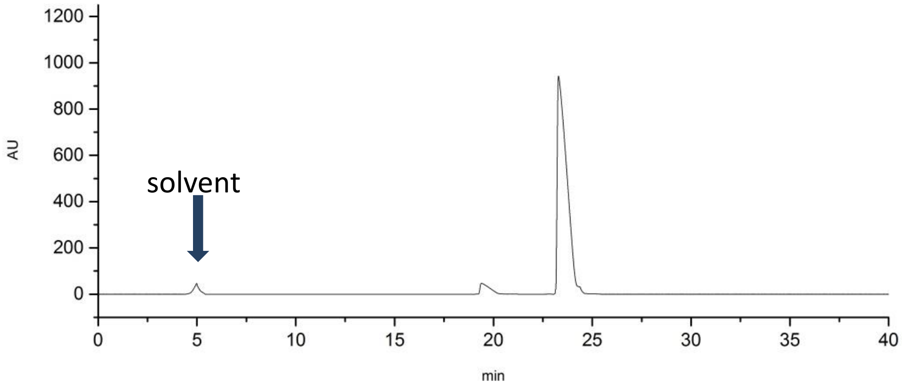
From 30 mg (0.23 mmol) of **45**, 0.79 mL of Pd/Au (3:1)-**1** (0.347 μmol of Pd/0.116 μmol of Au-0.013 μmol of **1**) in H_2O at 120°C and 30 psi of O_2 for 3 days, 28 mg (94.5% yield) of (*S*)-**42** in 92% ee (determined by HPLC/chiral column of the benzoate derivative (*S*)-**42A**) was isolated. $[\alpha]_D^{22}$ = +15.2 (c 0.8, $CHCl_3$). ^1H and ^{13}C NMR spectra were identical to those of (*S*)-**42** obtained from the oxidation of *trans*-1,3-cycloheptanediol.

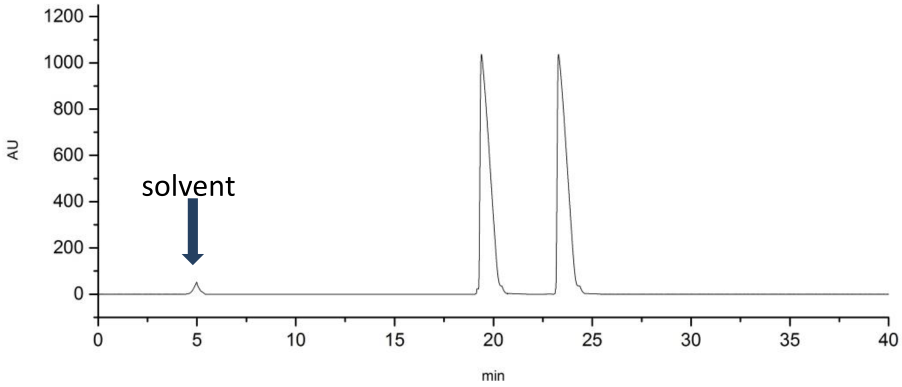
(*S*)-3-Oxocycloheptyl benzoate (42A). (BH7-106)



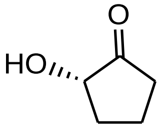
(*S*)-**42A**

From 25 mg (0.20 mmol) of (*S*)-**42** and 55 g (0.39 mmol) of benzoyl chloride in 0.1 mL of pyridine and 1 mL of dichloromethane, 44 mg (97% yield) of (*S*)-**42A** (92% ee) was obtained. ^1H and ^{13}C NMR spectra were identical to those of (*S*)-**42A** as described above.The % ee of this compound was determined by HPLC using chiral column, Chiralpak AD(-H) column, n-hexane/i-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 19 min (*R* enantiomer, minor), t_R = 23 min (*S* enantiomer, major).





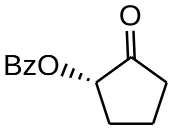
(*S*)-2-Hydroxycyclopentanone (49) (BH7-065)



(*S*)-**49**

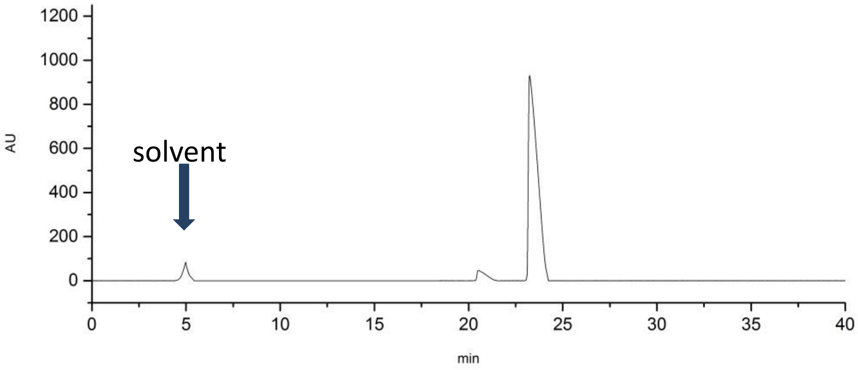
From 60 mg (0.588 mmol) of **52**, 2 mL of Pd/Au (3:1)-**1** (0.89 μmol of Pd/0.296 μmol of Au-0.034 μmol of **1**) in H_2O at 120°C and 30 psi of O_2 for 3 days, 55.4 mg (94.2% yield) of (*S*)-**49** in 91% ee (determined by HPLC/chiral column of the benzoate derivative (*S*)-**49A**). $[\alpha]_D^{22}$ = +38.4 (c 1.0, $CHCl_3$); Lit.[61] -37.4 (c 1.0, $CHCl_3$) for (*R*)-configuration (>99% ee). ^{1}H and ^{13}C NMR spectra were identical to those of (*S*)-**49** obtained from the oxidation of *trans*-1,2-cyclopentanediol.

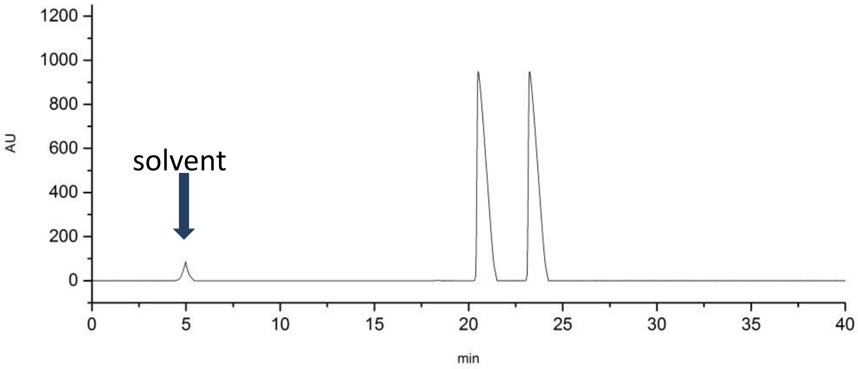
(*S*)-2-Oxocyclopentyl benzoate (49A). (BH7-112)



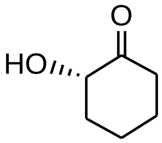
(*S*)-**49A**

From 40 mg (0.40 mmol) of (*S*)-**49** and 0.112 g (0.80 mmol) of benzoyl chloride in 0.3 mL of pyridine and 1.5 mL of dichloromethane, 80 mg (98% yield) of (*S*)-**49A** (91% ee) was obtained. ^{1}H and ^{13}C NMR spectra were identical to those of (*S*)-**49A** as described above. The % ee of this compound was determined by HPLC using chiral column, Chiralpak AD(-H) column, n-hexane/i-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 20.5 min (*R* enantiomer, minor), t_R = 23.3 min (*S* enantiomer, major).





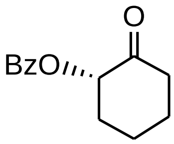
(*S*)-2-Hydroxycyclohexanone (50) (BH7-058)



(S)-**50**

From 0.161 g (1.39 mmol; 662 equivalents based on Pd mole atoms) of **53**, 4.8 mL of Pd/Au (3:1)-**1** (2.1 μmol of Pd/0.7 μmol of Au-0.08 μmol of **1**) in H_2O at 120°C and 30 psi of O_2 for 4 days, 0.142 g (96.5% yield) of (*S*)-**50** in 92% ee [determined by HPLC/chiral column of the benzoate derivative (*S*)-**50A**] was isolated. (*S*)-**50**: $[\alpha]_D^{22}$ = -18.8 (c 0.65, $CHCl_3$); Lit.[67] +20.6 (c 1.0, $CHCl_3$) for (*R*)-**50** (>99.0% ee). ^{1}H and ^{13}C NMR spectra were identical to those of (*S*)-**50** obtained from the oxidation of *trans*-1,2-cyclohexanediol.

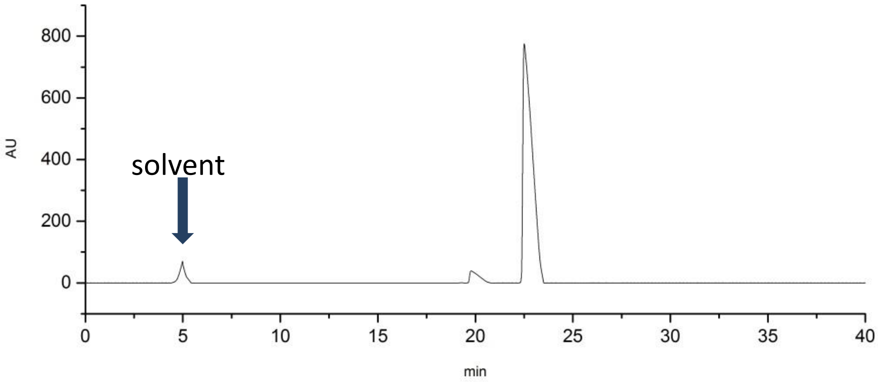
(S)-2-Oxocyclohexyl benzoate (50A). (BH7-077)

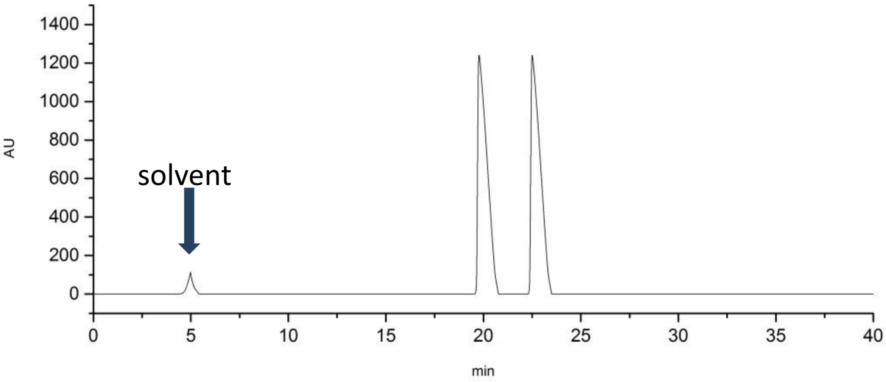


(S)-**50A**

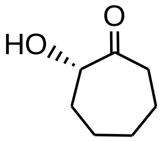
From 0.10 g (0.87 mmol) of (*S*)-**50** and 0.245 g (1.74 mmol) of benzoyl chloride in 0.2 mL of pyridine and 3 mL of dichloromethane, 0.169 g (89% yield) of (*S*)-**50A** (92% ee) was obtained. ^{1}H and ^{13}C NMR spectra were identical to those of (*S*)-**50A** as described above.

The % ee of this compound was determined by HPLC using chiral column, Chiralpak AD(-H) column, n-hexane/i-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 20 min (*R* enantiomer, minor), t_R = 22.5 min (*S* enantiomer, major).





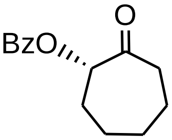
(*S*)-2-Hydroxycycloheptanone (51) (BH7-110)



(*S*)-**51**

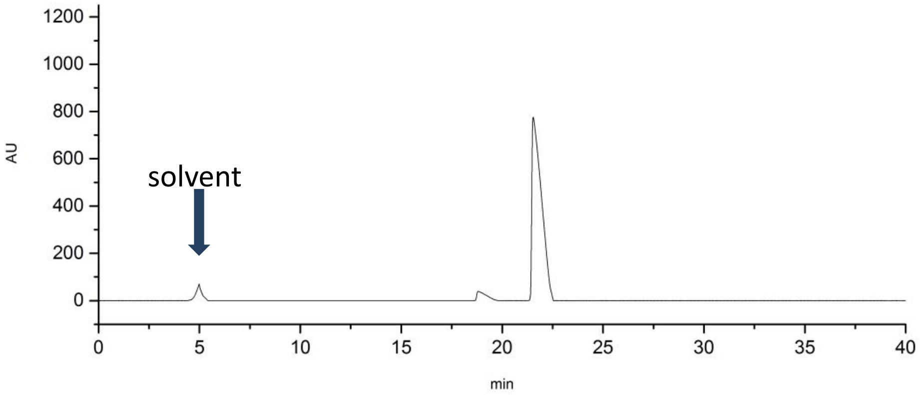
From 30 mg (0.23 mmol) of **54**, 0.79 mL of Pd/Au (3:1)-**1** (0.347 µmol of Pd/0.116 µmol of Au-0.013 µmol of **1**) in H_2O at 120°C and 30 psi of O_2 for 3 days, 27.6 mg (94% yield) of (*S*)-**51** in 91% ee (determined by HPLC/chiral column of the benzoate derivative (*S*)-**51A**). (*S*)-**51**: $[\alpha]_D^{22}$ = -130.6 (c 1.0, $CHCl_3$). Lit.[61] -86.4 (c 1.0, $CHCl_3$) for (*R*)-**51** (>99.0% ee). ^{1}H and ^{13}C NMR spectra were identical to those of (*S*)-**51** obtained from the oxidation of *trans*-1,2-cycloheptanediol.

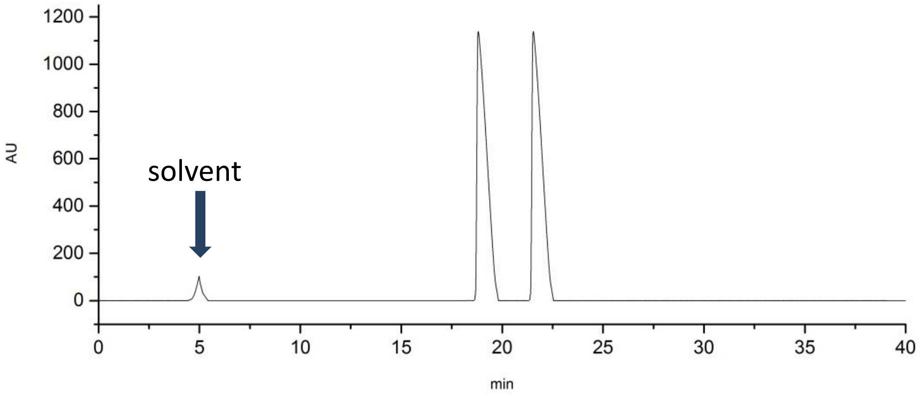
(S)-2-Oxocycloheptyl benzoate (51A). (add notebook #)



(*S*)-**51A**

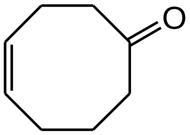
From 20 mg (0.156 mmol) of (*S*)-**51** and 44 mg (0.31 mmol) of benzoyl chloride in 0.2 mL of pyridine and 1 mL of dichloromethane, 35 mg (97% yield) of (*S*)-**51A** (91% ee) was obtained. ^{1}H and ^{13}C NMR spectra were identical to those of (*S*)-**51A** as described above. The % ee of this compound was determined by HPLC using chiral column, Chiralpak AD(-H) column, n-hexane/i-PrOH = 90:10, flow rate: 0.5 mL/min; t_R = 19 min (*R* enantiomer, minor), t_R = 21.5 min (*S* enantiomer, major).





2.6.4 Procedures and Analysis Results for Dihydroxylation of Alkenes.

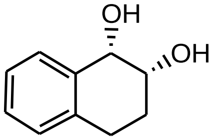
(Z)-cyclooct-4-enone(56) (BH1-071)



56

To a 0 °C solution of 23 μmol of Na_2PdCl_4, 7 μmol of $HAuCl_4$ and 0.8 μmol of PVP in 1.5 mL DMSO, 20 mg (20 μmol) of $NaCNBH_3$ was added and stirred for 30 minutes to give Pd:Au(3:1)-PVP nanoclusters DMSO solution. To it, 5 mL of DMF, 31 mg (312 mmol) of CuCl was added and stirred for 30 minutes under 1 atmospheric of O_2 to give a dark green solution. To it, 0.033 g (0.313 mmol) of cyclooctadiene **55** was added and reacted under 1 atmospheric of O_2 for 7 days, extracted with 3 x 20 mL of diethyl ether, washed combined organic layer with 5 mL water, dried over Na_2SO_4, concentrated under vacuum and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as eluents to give 27 mg (69.6% yield) of **56**. ^{1}H NMR[142] δ 5.74–5.63 (m, 2H), 2.52–2.42 (m, 6H), 2.33–2.08 (m,2H), 1.63–1.56 (m, 2H); ^{13}C NMR δ 215.0, 130.9, 130.4, 47.4, 40.5, 26.5, 24.1, 22.0; MS (ESI, MeOH): *m/z* = 125.1 ($[M + H]^+$).

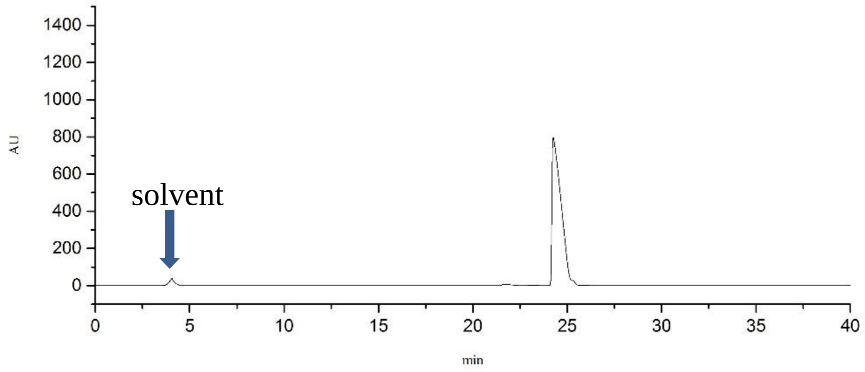
(1*S*,2*R*)-1,2,3,4-Tetrahydronaphthalene-1,2-diol (58) (BH7-051)

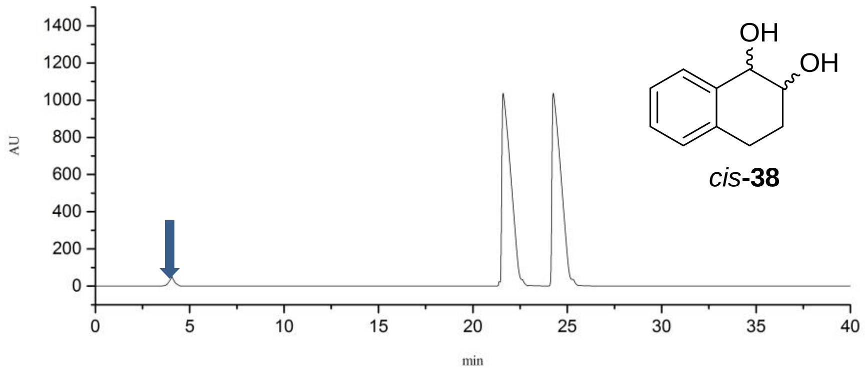


(1*S*,2*R*)-58

To an aqueous solution of 6.6 mL of Pd/Au (3:1)-**1** (2.9 μmol of Pd/0.96 μmol of Au-0.10 μmol of **1**) in a Parr pressure reactor, were added 14 mL of deionized H_2O and 0.10 g (0.77 mmol) of 1,2-dihydronaphthalene (**57**). The apparatus was charged at 30 psi of O_2 and stirred at 25°C for

3 days. The solution was then maintained under normal atmosphere, extracted with ethyl acetate three times (20 mL each), and the combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 89 mg (86% yield) of (1*S*,2*R*)-**58** in 99% ee. The optical purity was determined using HPLC-chiral column. $[\alpha]_D^{22}$ = +35.0 (c 0.74, $CHCl_3$). Lit.[67] +35 (c 0.74, $CHCl_3$; >98% ee). ^1H NMR δ 7.44–7.41 (m, 1 H), 7.26–7.20 (m, 2 H), 7.13–7.11 (m, 1 H), 4.68 (d, J = 3.6 Hz, 1 H), 4.02–3.98 (m, 1 H), 3.00–2.92 (m, 1 H), 2.82–2.78 (m, 1 H), 2.53–2.45 (bs, 2 H, OH), 2.07–2.00 (m, 1 H), 2.00–1.87 (m, 1 H); ^{13}C NMR δ 136.6, 136.4, 130.1, 128.8, 128.4, 126.7, 70.2, 69.8, 27.1, 26.5. MS (ESI, MeOH): *m/z* = 165.1 ($[M + H]^+$). The % ee of this compound was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 85:15, flow rate: 0.5 mL/min; t_R = 21.6 min (1*S*,2*R* enantiomer, minor), t_R = 24.2 min (1*R*,2*S* enantiomer, major).

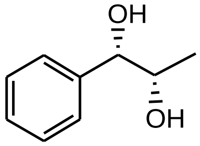




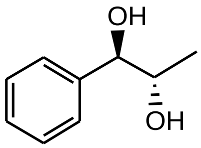
cis-**38**

(1*S*,2*S*)-1-Phenylpropane-1,2-diol (60) and (1*R*,2*S*)-1-phenylpropane-1,2-diol (61)

(BH7-044)

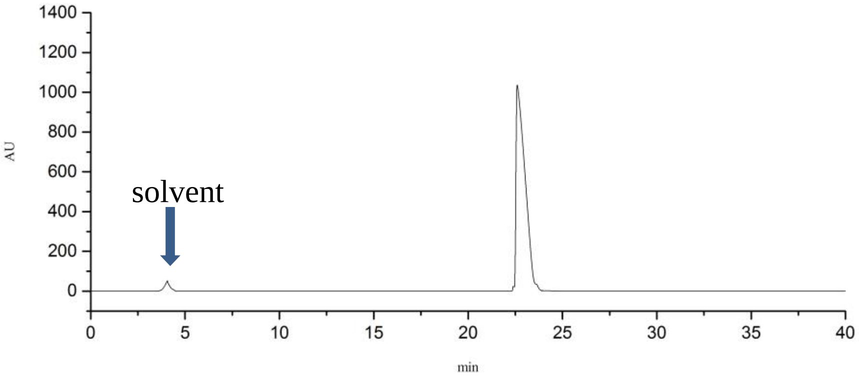


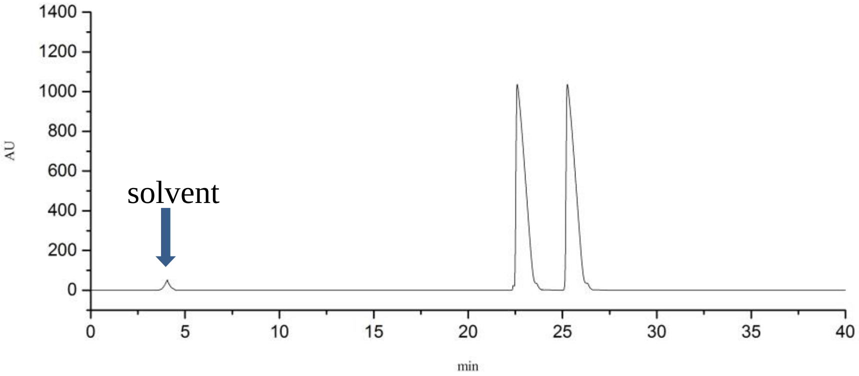
(1*S*,2*S*)-60



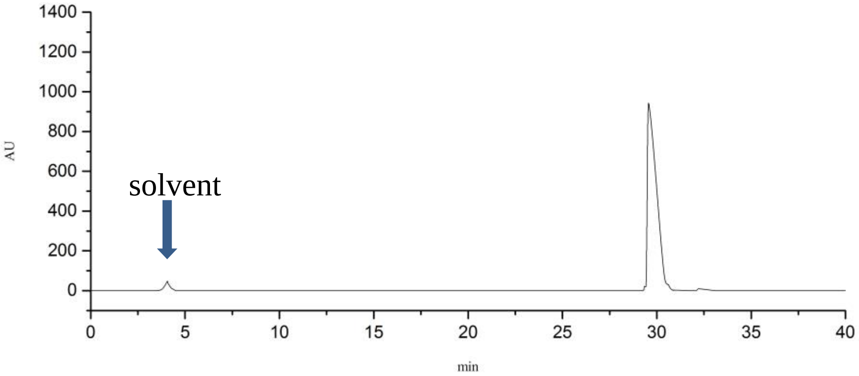
(1*R*,2*S*)-61

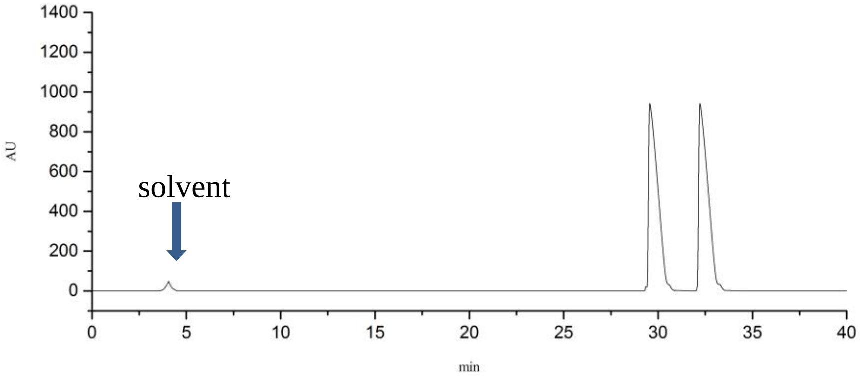
From Pd/Au (3:1)-**1** (7.9 µmol of Pd/2.65 µmol of Au-0.29 µmol of **1**) and 0.25 g (2.1 mmol) of *trans*-β-methylstyrene (**59**) in 30 mL of deionized water, after stirring at 25°C under 30 psi of O_2 in a Parr pressure reactor for 3 days, 0.281 g (87% yield) of (1*S*,2*S*)-**60** (99% ee) and 19 mg (6% yield) of (1*R*,2*S*)-**61** (97% ee) along with 13 mg of **59** (5% recovery) were obtained after column chromatography. The optical purity was determined using HPLC/chiral column as described above. (1*S*,2*S*)-**60**: $[\alpha]_D^{22}$ = +51.7 (c 1.9, $CHCl_3$). Lit.[68] +54.3 (c 1.9, $CHCl_3$). ^1H NMR δ 7.45–7.24 (m, 5 H), 4.37 (d, J = 8 Hz, 1 H), 3.86 (pent, J = 6.5 Hz, 1 H), 2.30–2.15 (bs, 1 H, OH), 1.75–1.60 (bs, 1 H, OH), 1.07 (d, J = 6.5 Hz, 3 H, Me); ^{13}C NMR δ 142.3, 129.9 (2 C), 128.6, 126.7 (2 C), 79.9, 72.4, 18.1. MS (ESI, MeOH): *m/z* = 175.1 ($[M + Na]^+$). Compound (1*R*,2*S*)-**61**: $[\alpha]_D^{22}$ = -37.3 (c 2.52, $CHCl_3$). Lit.[68] -29.9 (c 2.52, $CHCl_3$). ^1H NMR δ 7.36–7.27 (m, 5 H), 4.68 (d, J = 4.4 Hz, 1 H), 4.03–4.00 (m, 1 H), 2.15–1.80 (bs, 1 H, OH), 1.75–1.50 (bs, 1 H, OH), 1.05 (d, J = 6 Hz, 3 H, Me); ^{13}C NMR δ 140.4, 128.2 (2 C), 127.9, 126.7 (2 C), 77.5, 71.4, 17.5. MS (ESI, MeOH): *m/z* = 174.9 ($[M + Na]^+$). The % ee (99%) of (1*S*,2*S*)-**60** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 85:15, flow rate: 0.5 mL/min; t_R = 22.6 min (1*S*,2*S* enantiomer, major), t_R = 25.8 min (1*R*,2*R* enantiomer, minor).





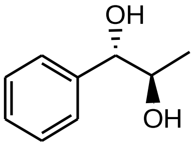
The % ee (97%) of (1*R*,2*S*)-**61** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 85:15, flow rate: 0.5 mL/min; t_R = 29.6 min (1*R*,2*S* enantiomer, major), t_R = 32.2 min (1*S*,2*R* enantiomer, minor).



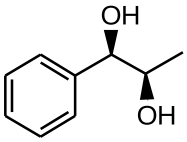


(1*S*,2*R*)-1-Phenylpropane-1,2-diol (61) and (1*R*,2*R*)-1-phenylpropane-1,2-diol (60)

(BH8-026)

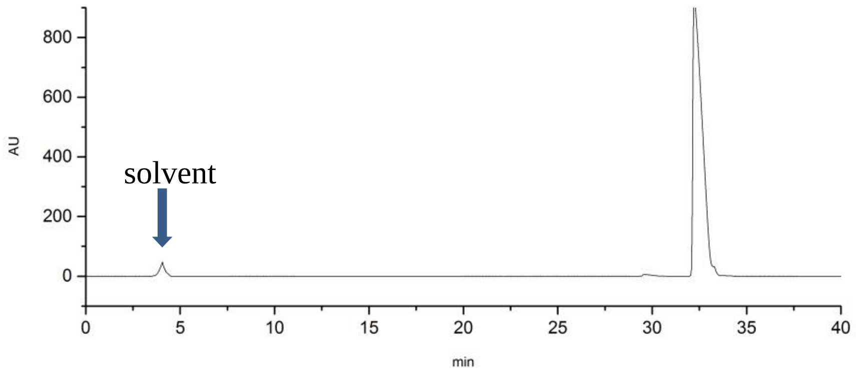


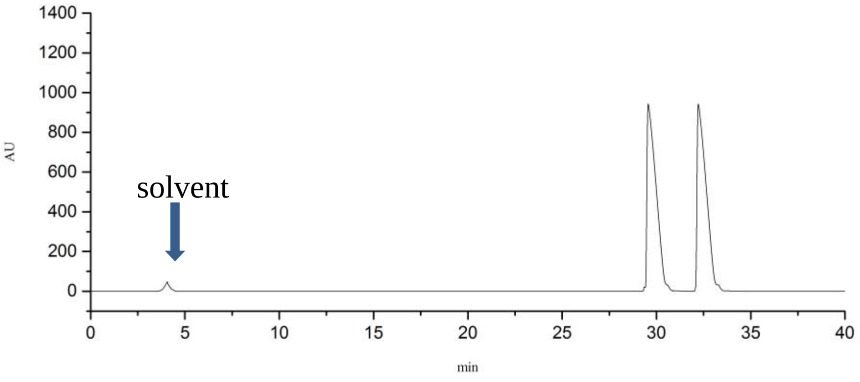
(1*S*,2*R*)-61



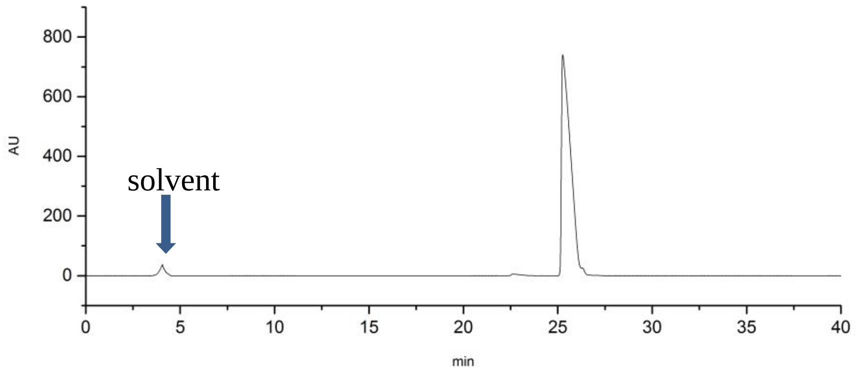
(1*R*,2*R*)-60

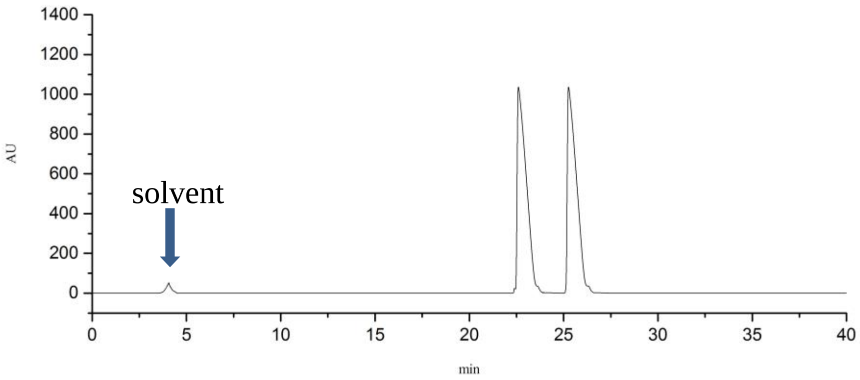
From Pd/Au (3:1)-**1** (7.94 μmol of Pd/2.65 μmol of Au-0.29 μmol of **1**) and 0.25 g (2.1 mmol) of *cis*-β-methylstyrene (**62**) in 30 mL of deionized water, after stirring at 25°C under 30 psi of O_2 in a Parr pressure reactor for 3 days, 0.291 g (90% yield) of (1*S*,2*R*)-**61** (98% ee) and 26 mg (8% yield) of (1*R*,2*R*)-**60** (98% ee) were obtained after column chromatography. (1*S*,2*R*)-**61**: $[\alpha]_D^{22}$ = +37.1 (c 2.52, $CHCl_3$). Lit.[68] +36.1 (c 2.52, $CHCl_3$). ^1H and ^{13}C NMR spectra were identical to those of compound (1*R*,2*S*)-**61**. The % ee (98%) of (1*S*,2*R*)-**61A** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 85:15, flow rate: 0.5 mL/min; t_R = 29.6 min (1*R*,2*R* enantiomer, minor), t_R = 32.2 min (1*S*,2*R* enantiomer, major).



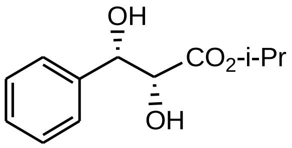


(1*R*,2*R*)-**60**: $[\alpha]_D^{22}$ = -51.8 (c 1.9, $CHCl_3$). Lit.[68] -51.3 (c 3.5, $CHCl_3$). ^{1}H and ^{13}C NMR spectra were identical to those of (1*S*,2*S*)-**60**. The % ee (98%) of (1*R*,2*R*)-**60** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 85:15, flow rate: 0.5 mL/min; t_R = 22.6 min (1*S*,2*S* enantiomer, minor), t_R = 25.8 min (1*R*,2*R* enantiomer, major).

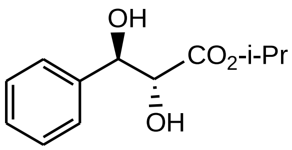




(2*R*,3*S*)-Isopropyl 2,3-dihydroxy-3-phenylpropanoate (64) and (2*R*,3*R*)-isopropyl 2,3-dihydroxy-3-phenylpropanoate (65) (BH7-116)

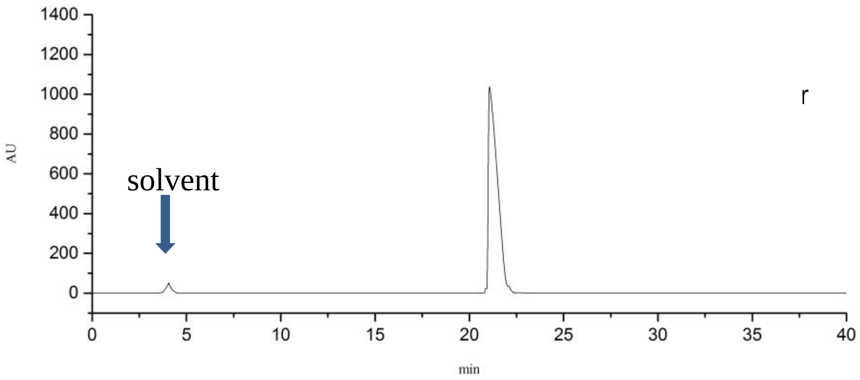


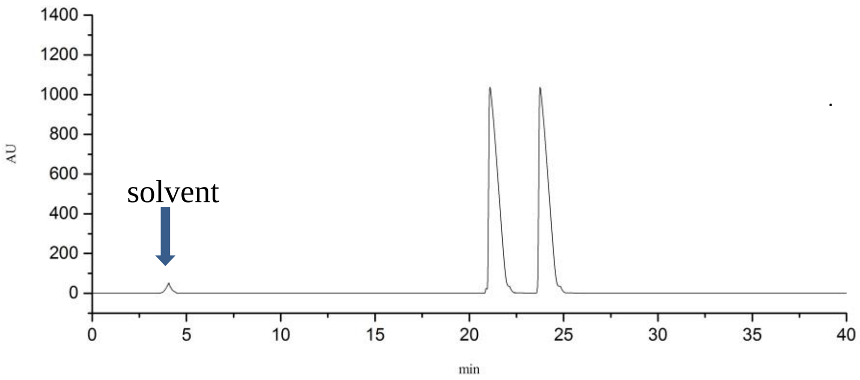
(2*R*,3*S*)-64



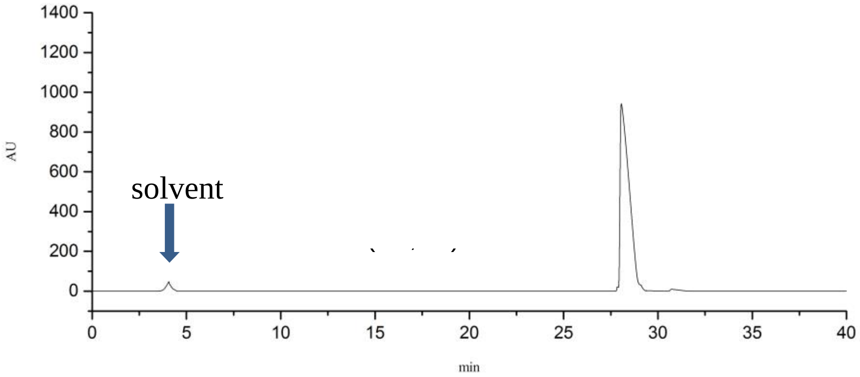
(2*R*,3*R*)-65

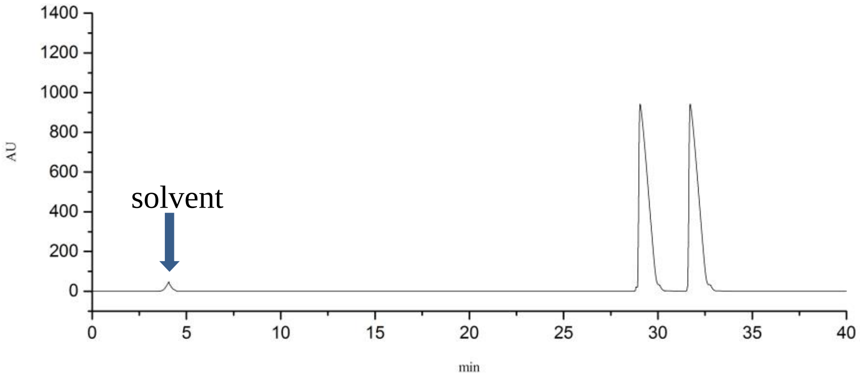
From Pd/Au (3:1)-**1** (1.97 μmol of Pd/0.66 μmol of Au-0.073 μmol of **1**) and 0.10 g (0.52 mmol) of *trans*-isoproyl 3-phenylpropenoate (**63**) in 20 mL of deionized water, after stirring at 50°C under 30 psi of O_2 in a Parr pressure reactor for 3 days, 96 mg (82% yield) of (2*R*,3*S*)-**64** (99% ee) and 3.7 mg (3% yield) of (2*R*,3*R*)-**65** (97% ee) were obtained after column chromatography. The optical purity was determined using HPLC/chiral column as described above. (2*R*,3*S*)-**64**: $[\alpha]_D^{22}$ = +9.7 (c 0.15, $CHCl_3$). Lit.[81] +10.6 (c 1.02, $CHCl_3$; >99%). ^{1}H NMR δ 7.40–7.36 (m, 3 H), 7.34–7.32 (m, 2 H), 5.16 (hept, J = 6 Hz, 1 H), 5.01 (d, J = 6 Hz, 1H), 4.36 (d, J = 6 Hz, 1 H), 2.70–2.48 (bs, 2 H, OH), 1.31 (d, J = 6 Hz, 3 H); ^{13}C NMR δ 166.8, 144.6, 130.3, 129.1 (2 C), 128.2 (2 C), 86.1, 74.2, 67.9, 22.2. MS (ESI, MeOH): *m/z* = 225.0 ($[M + H]^+$). The % ee (99%) of (2*R*,3*S*)-**64** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 85:15, flow rate: 0.5 mL/min; t_R = 21.1 min (2*R*,3*S* enantiomer, major), t_R = 25.8 min (2*S*,3*R* enantiomer, minor).



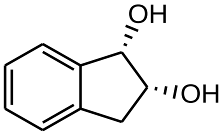


(2*R*,3*R*)**-65**: $[\alpha]_D^{22}$ = +7.3 (c 0.15, $CHCl_3$). ^{1}H NMR δ 7.40–7.35 (m, 3 H), 7.34–7.31 (m, 2 H), 5.14 (hept, J = 6 Hz, 1 H), 5.06 (d, J = 6.8 Hz, 1H), 4.38 (d, J = 5.2 Hz, 1 H), 2.25–2.00 (bs, 2 H, OH), 1.31 (d, J = 6 Hz, 3 H); ^{13}C NMR δ 169.4, 145.4, 131.3, 130.0 (2 C), 129.2 (2 C), 87.4, 75.1, 69.1, 23.1. MS (ESI, MeOH): *m/z* = 225.0 ($[M + H]^+$, 100%). The % ee (97%) of (2*R*,3*R*)-**65** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 85:15, flow rate: 0.5 mL/min; t_R = 28.1 min (2*R*,3*R* enantiomer, major), t_R = 32.0 min (2*S*,3*S* enantiomer, minor).

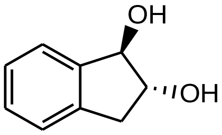




(1*S*,2*R*)-2,3-Dihydro-1H-indene-1,2-diol (67) and (1*R*,2*R*)-2,3-dihydro-1H-indene-1,2-diol (68). (BH7-084)

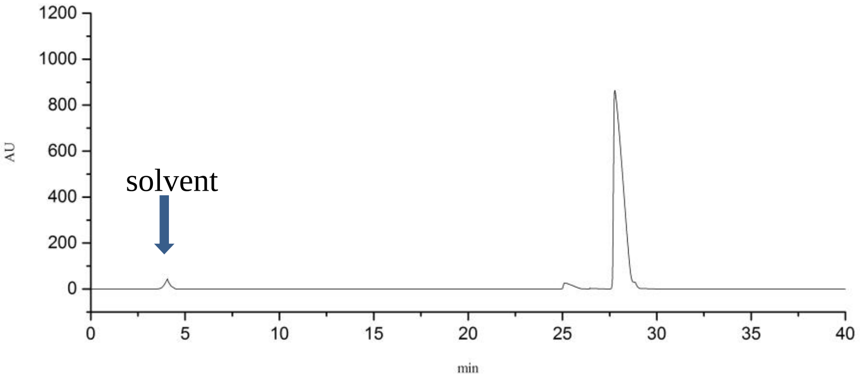


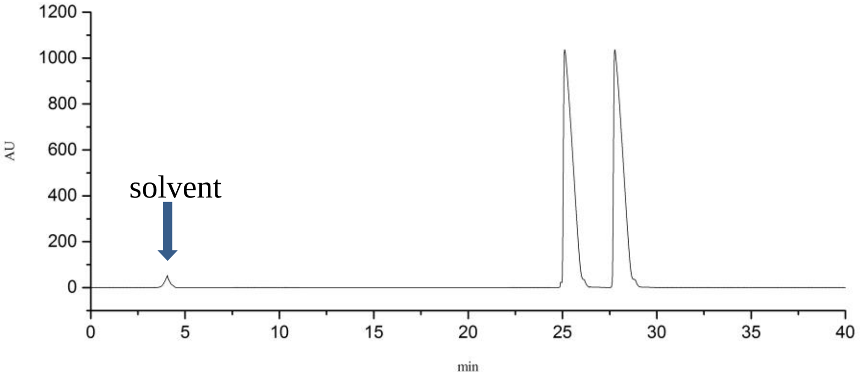
(1*S*,2*R*)-67



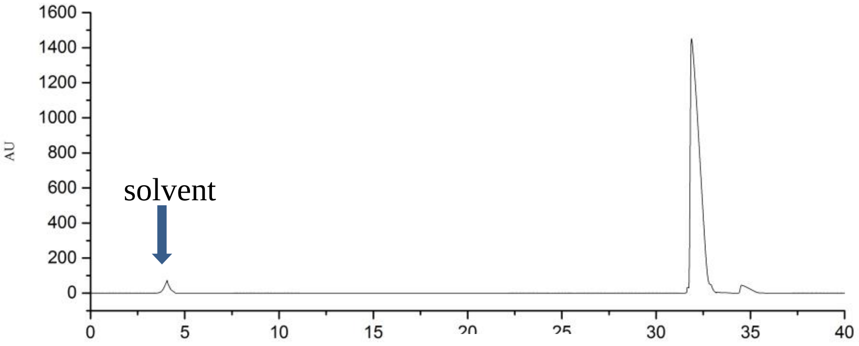
(1*R*,2R)-68

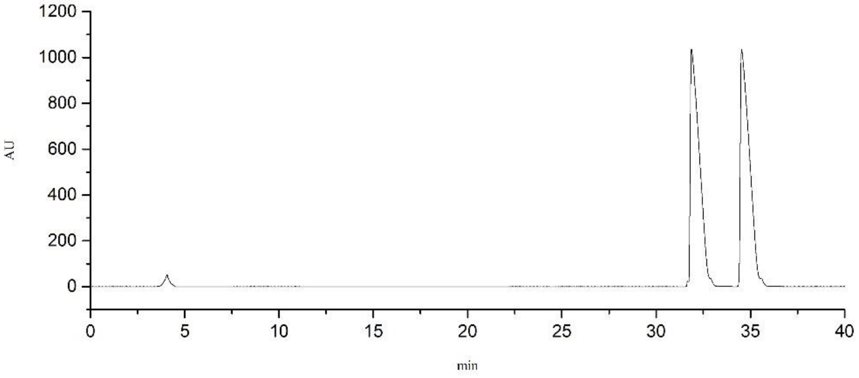
From Pd/Au (3:1)-**1** (19.3 μmol of Pd/6.7 μmol of Au-0.74 μmol of **1**) and 0.30 g (2.59 mmol) of indene (**66**) in 20 mL of deionized water, after stirring at 50^{o}C under 30 psi of O_2 in a Parr pressure reactor for 2 days, 0.261 g (67% yield) of (1*S*,2*R*)-**67** (93% ee) and 44 mg (11% yield) of (1*R*,2*R*)-**68** (94% ee) were obtained after column chromatography. The optical purity was determined using HPLC/chiral column. Compound (1*S*,2*R*)-**67**: $[\alpha]_D^{22}$ = -46.9 (c 1.14, $CHCl_3$). Lit.[67] -48.0 (c 1.14, $CHCl_3$). ^{1}H NMR δ 7.45–7.42 (m, 1 H), 7.31–7.20 (m, 3 H), 5.03–5.02 (m, 1 H, CH-O), 4.54–4.52 (m, 1 H, CH-O), 3.14 (dd, J = 16, 6 Hz, 1 H), 2.96 (dd, J = 16, 4 Hz, 1 H), 2.50–2.25 (bs, 2 H, OH); ^{13}C NMR δ 142.2, 140.2, 129.0, 127.4, 125.6, 125.3, 76.2, 73.7, 38.9. MS (ESI, MeOH): *m/z* = 173.1 ($[M + Na]^+$). Compound (1*R*,2*R*)-**67**: $[\alpha]_D^{22}$ = -28.8 (c 0.675, EtOH). Lit.[82] +30.5 (c 0.675, EtOH). ^{1}H NMR δ 7.40–7.36 (m, 1 H), 7.28–7.18 (m, 3 H), 5.02–5.01 (m, 1 H), 4.40–4.38 (m, 1 H), 3.28 (dd, J = 16, 7.6 Hz, 1 H), 2.83 (dd, J = 16, 8 Hz, 1 H), 2.10–2.09 (m, 1 H, OH), 2.05–2.02 (m, 1 H, OH); ^{13}C NMR δ 141.8, 141.3, 130.1, 128.9, 128.3, 126.6, 73.0, 72.4, 37.5 MS (ESI, MeOH): *m/z* = 151.1 ($[M + H]^+$). The % ee (93%) of (1*S*,2*R*)-**67** compound was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 85:15, flow rate: 0.5 mL/min; t_R = 25.0 min (1*R*,2*S* enantiomer, minor), t_R = 27.8 min (1*S*,2*R* enantiomer, major).



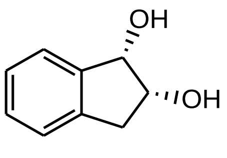


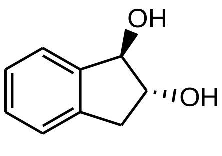
The % ee (94%) of compound (1*R*,2*R*)-**68** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 85:15, flow rate: 0.5 mL/min; t_R = 31.5 min (1*R*,2*R* enantiomer, major), t_R = 35 min (1*S*,2*S* enantiomer, minor).





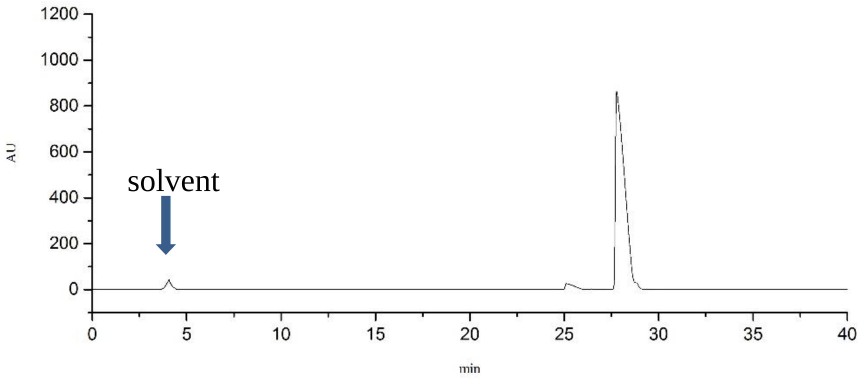
(1*S*,2*R*)-2,3-Dihydro-1H-indene-1,2-diol (46) and (1*R*,2*R*)-2,3-dihydro-1H-indene-1,2-diol (47) (BH7-063)

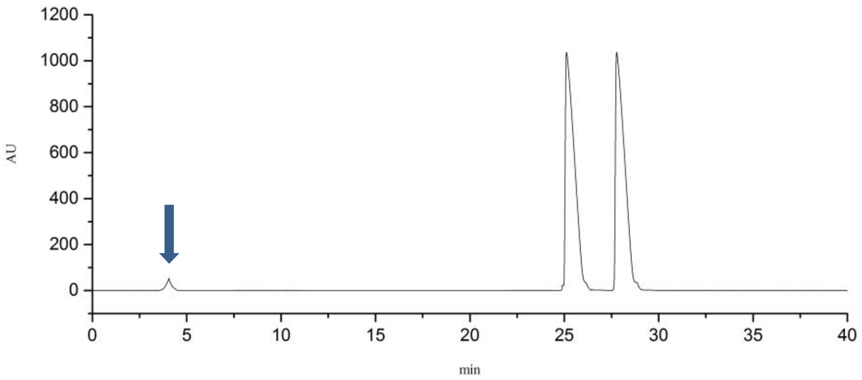

(1*S*,2*R*)-67


(1*R*,2R)-68

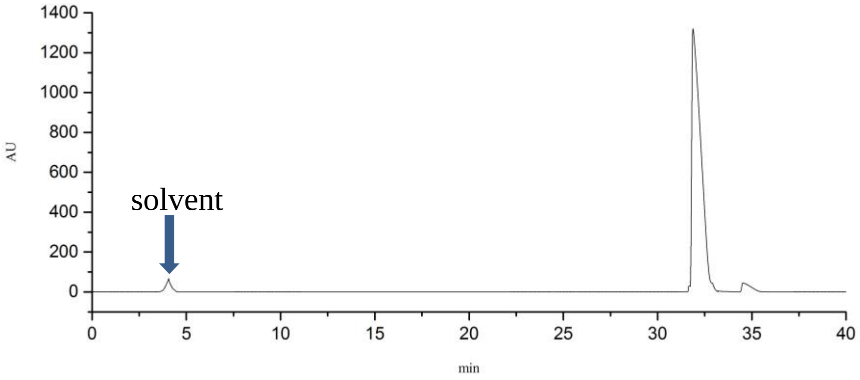
To an aqueous solution of 15 mL of Pd/Au (3:1)-**1** (6.5 μmol of Pd/2.2 μmol of Au-0.24 μmol of **1**) in a Parr pressure reactor, were added 5 mL of deionized H_2O, 77 mg (0.56 mmol) of K_2CO_3, and 0.20 g (1.75 mmol) of indene (**66**). The apparatus was charged at 30 psi of O_2 and stirred at

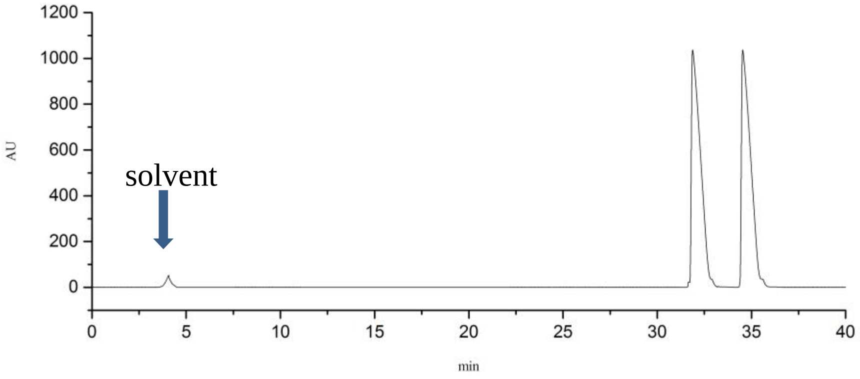
70^{o}C for 5 hours. The solution was then maintained under normal atmosphere, extracted with ethyl acetate three times (20 mL each), and the combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 0.117 g (59% yield based on recovered **66**) of (1*R*,2*R*)-**68** in 91% ee and 10 mg (5% yield based on recovered **66**) of (1*S*,2*R*)-**67** in 89% ee, along with 47 mg (23.5% recovery) of **66**. (1*R*,2*R*)-**68**: $[\alpha]_D^{22}$ = -27.7 (c 1.14, $CHCl_3$). Lit.[82] +30.5 (c 0.675, EtOH). (1*S*,2*R*)-**67**: $[\alpha]_D^{22}$ = -44.9 (c 1.14, $CHCl_3$). Lit.[81] -48.0 (c 1.14, $CHCl_3$). ^{1}H NMR and ^{13}C NMR spectra of **67** and **68** were identical to those described above. No hydroxyindanones were detected. The % ee (89%) of (1*S*,2*R*)-**67** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 85:15, flow rate: 0.5 mL/min; t_R = 25.0 min (1*R*,2*S* enantiomer, minor), t_R = 27.8 min (1*S*,2*R* enantiomer, major).



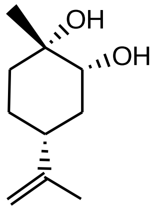


The % ee (91%) of (1*R*,2*R*)-**68** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 85:15, flow rate: 0.5 mL/min; t_R = 31.5 min (1*R*,2*R* enantiomer, major), t_R = 34.6 min (1*S*,2*S* enantiomer, minor).





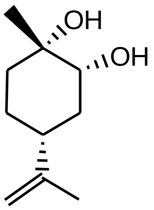
(1*S*,2*R*,4*R*)-1-Methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diol (70) (BH8-030)



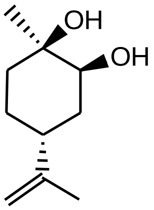
(1*S*,2*R*,4*R*)-70

From Pd/Au (3:1)-**1** (2.86 μmol of Pd/0.99 μmol of Au-0.11 μmol of **1**) and 52 mg (0.39 mmol) of (*R*)-(+)-limonene (**69**) in 20 mL of deionized water, after stirring at 25°C under 30 psi of O_2 in a Parr pressure reactor for 3 days, 61 mg (92% yield) of (1*S*,2*R*,4*R*)-**70** was obtained as a single stereoisomer after column chromatography. No other stereoisomers were detected. $[\alpha]_D^{22}$ = +22.6 (c 0.5, $CHCl_3$). ^{1}H NMR δ 4.74 (s, 2 H), 3.92 (s, 1 H), 2.32–2.23 (m, 1 H), 2.18–2.09 (m, 1 H), 2.03–1.94 (m, 1 H), 1.88–1.64 (m, 4 H), 1.73 (s, 3 H), 1.63 (s, 3 H), 1.64–1.58 (bs, 2 H, OH); ^{13}C NMR δ 149.3, 109.3, 74.4, 71.7, 37.5, 35.6, 33.9, 29.4, 27.0, 21.1. MS (ESI, MeOH): *m/z* = 171.0 ($[M + H]^+$). HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{10}H_{18}NO_2Na^+$: 193.1199; found: 193.1197.

(1*S*,2*R*,4*R*)-1-Methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diol (70) and (1*R*,2*S*,4*R*)-1-Methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diol (85) (BH8-038)



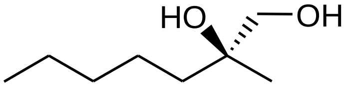
(1*S*,2*R*,4*R*)-70



(1*R*,2*S*,4*R*)-85

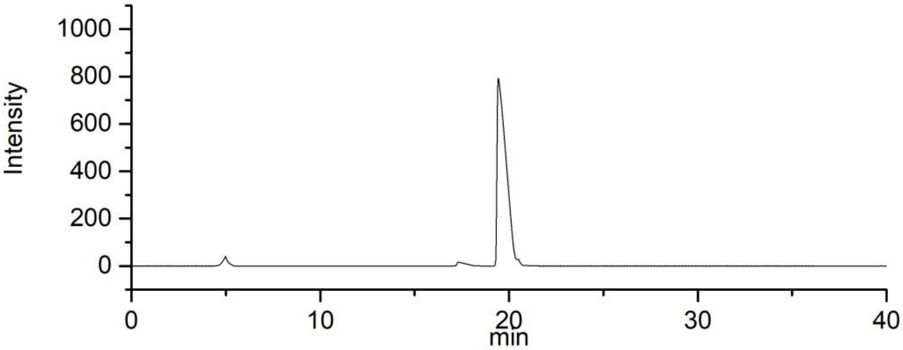
A solution of 0.20 g (1.47 mmol) of (*R*)-(+)-limonene (**69**), 7.5 mg (29 μmol) of OsO_4, and 0.21 g (1.76 mmol) of *N*-methylmorpholine *N*-oxide (NMO) in 2 mL of *t*-BuOH, 7 mL of acetone and 2.5 mL of water was stirred 0^oC for 30 min and 25^oC for 14 h. The reaction mixture was filtered through Celite and concentrated on a rotary evaporator to remove acetone and t-BuOH, diluted with water (20 mL), and extracted three times with dichloromethane (20 mL each). The combined extract was washed with brine, dried (anhydrous Na_2SO_4), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ether as eluent to give 27 mg (11% yield) of (1*S*,2*R*,4*R*)-**70** and 0.118 g (47% yield) of (1*R*,2*S*,4*R*)-**85**[83] along with 46 mg (23% recovery) of (*R*)-limonene. (1*S*,2*R*,4*R*)-**70**: $[\alpha]_D^{22}$ = +22.6 (c 0.5, $CHCl_3$). ^{1}H and ^{13}C NMR spectra were identical to those of compound **70** obtained from the catalytic asymmetric dihydroxylation reaction described above. (1*R*,2*S*,4*R*)-**85**: $[\alpha]_D^{22}$ = +41.8 (c 1.0, MeOH); Lit.[81] +42 (c 1.0, MeOH). ^{1}H NMR δ 4.72–4.69 (m, 2 H), 3.67–3.64 (m, 1 H), 2.38–2.30 (bs, 1 H, OH), 1.93–1.78 (m, 3 H), 1.74–1.67 (m, 1 H), 1.71 (s, 3 H, Me), 1.55–1.50 (m, 1 H), 1.42 (s, 1 H, OH), 1.34–1.25 (m, 2 H), 1.25 (s, 3 H, Me); ^{13}C NMR δ 148.9, 108.7, 73.5, 71.2, 37.2, 33.6, 33.3, 26.1, 25.7, 20.6.

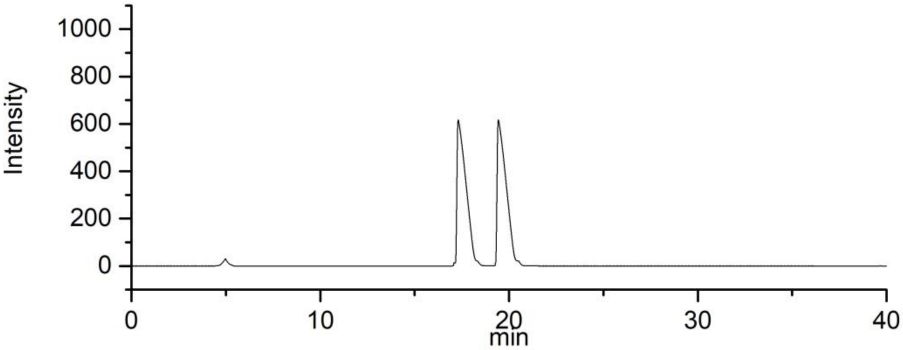
(S)-2-Methylheptane-1,2-diol (72) (BH10-143)



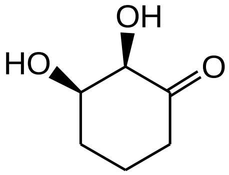
72

To an aqueous solution of 2 mL of Pd/Au (3:1)-**2** (10 μmol of Pd, 3.3 μmol of Au, and 0.16 μmol of **26**) in a Parr pressure reactor, were added 18 mL of deionized H_2O and 30 mg (0.27 mmol) of 2-methylhept-1-ene (**71**). The apparatus was maintained under 30 psi of O_2, stirred at 50 ^{o}C for 3 days, vented to normal atmosphere, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 28.6 mg (73.4% yield) of **(S)-72** in 97% ee. $[\alpha]_D^{22}$ = -2.28 (c 1.2, $CHCl_3$), Lit.[80] +2.3 (c 1.21, $CHCl_3$; 97% ee, *R*-configuration); ^{1}H NMR δ 3.46 (dd, *J* = 11.2, 3.6 Hz, 1H), 1.48-1.45 (m, 2H), 1.35-1.30 (m, 6H), 1.16 (s, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 73.2, 69.8, 38.7, 32.5, 23.5, 23.0, 22.3, 14.2; MS (ESI, MeOH): m/z = 147.3 ($[M + H]^+$). The % *ee* (97%) of (*S*)-**72** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 85:15, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 17.8 min (*R* enantiomer, minor), t_R = 19.9 min (*S* enantiomer, major).





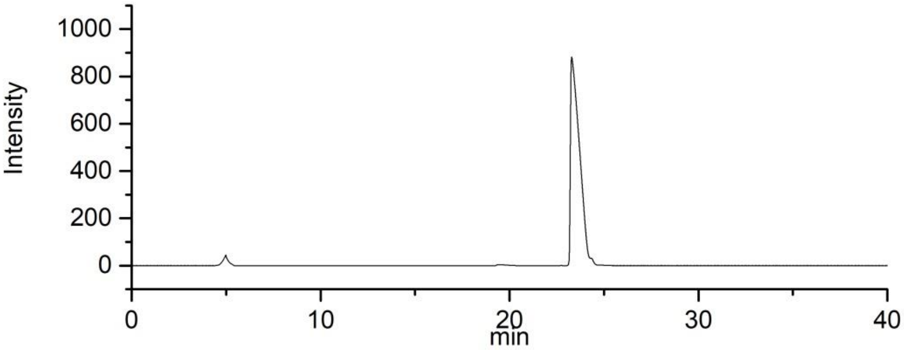
(*2R,3R*)-2,3-Dihydroxycyclohexanone (74) (BH10-071)

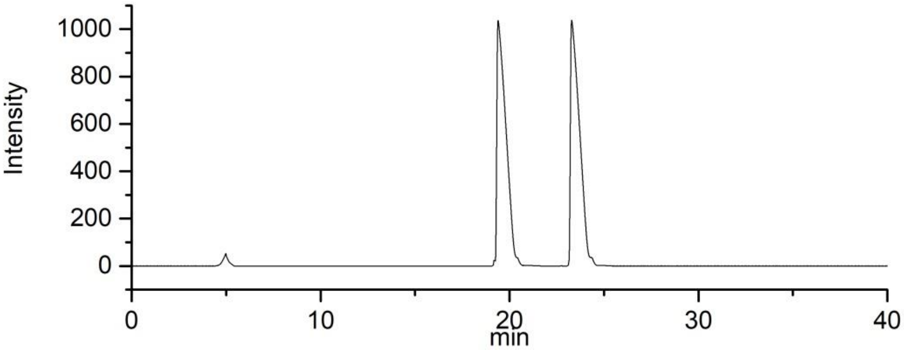


(2*R*,3*R*)-74

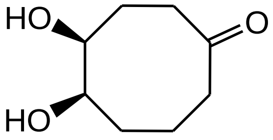
To an aqueous solution of 2 mL of Pd/Au (3:1)-**26** (0.84 μmol of Pd, 0.27 μmol of Au, and 0.03 μmol of **26**) in a Parr pressure reactor were added 18 mL of deionized H_2O and 21 mg (0.21 mmol) of cyclohex-2-enone (**73**). The apparatus was maintained under 30 psi of O_2, stirred at 50 ^oC for 3 days, vented to normal atmosphere, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 24 mg (86% yield) of **(**2*R*,3*R***)-74** in 99% ee. $[\alpha]_D^{22}$ = -13.8 (c 0.6, $CHCl_3$); Lit. [89] +1.48 (neat, l = 2 dm; for 2*S*,3*S* configuration). ^1H NMR δ 4.41(d, *J* =

3.2, 1H), 4.21 (dd, *J* = 6, 2.8 Hz, 1H), 3.92 (b, 1H), 2.59–2.52 (m, 2H), 2.36 (td, *J* = 14.8, 1.6 Hz, 1H), 2.17–2.04 (m, 2H), 1.95–1.82 (m, 2H); ^{13}C NMR δ 210.1, 82.6, 72.3, 38.0, 31.0, 18.9; MS (ESI, MeOH): m/z = 267.1 ([M + Na]$^+$). The % *ee* (99%) of (*2R,3R*)-**74** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 85:15, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 19.6 min (*2S,3S* enantiomer, minor), t_R = 23.8 min (*2R,3R* enantiomer, major)



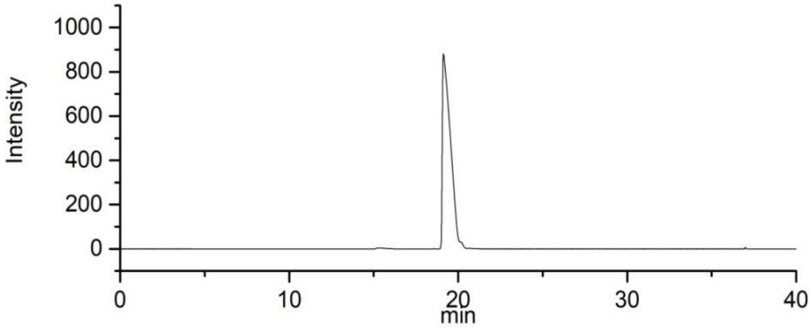


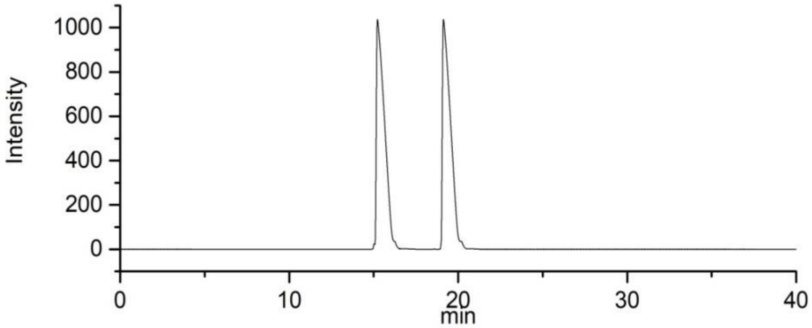
(4*S*,5*R*)-4,5-dihydroxycyclooctanone (76) (BH10-091)



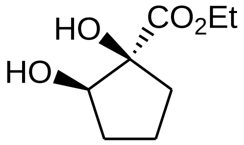
(4S,*5R*)-76

To an aqueous solution of 2 mL of Pd/Au (3:1)-**26** (0.75 μmol of Pd, 0.25 μmol of Au, and 0.014 μmol of **26**) in a Parr pressure reactor, were added 18 mL of deionized H_2O and 25 mg (0.2 mmol) of (Z)-cyclooct-4-enone (**56**). The apparatus was maintained under 30 psi of O_2, stirred at 50 °C for 3 days, vented to normal atmosphere, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 26.8 mg (85% yield) of (4*S*,5*R*)-**76** in 99% ee. $[\alpha]_D^{22}$ = -16.4 (c 0.5, $CHCl_3$); ^1H NMR δ 3.78 (d, *J* = 7.8, 1H), 3.39–3.36 (m, 1H), 2.51–2.29 (m, 4H), 2.02–1.97 (b, 1H), 1.85–1.52 (m, 5H), 1.40–1.25 (m, 2H), 1.35–1.25 (m, 2H); ^{13}C NMR δ 211.6, 79.3, 78.3, 42.2, 33.5, 32.2, 26.5, 17.5; MS (ESI, MeOH): m/z = 181.1 ($[M + Na]^+$). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_8H_{15}O_3^+$: 159.1021, found: 159.1023. The % *ee* (99%) of (*4S,5R*)-**21** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 85:15, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 15.7 min (*4R,5S* enantiomer, minor), t_R = 19.4 min (*4S,5R* enantiomer, major).



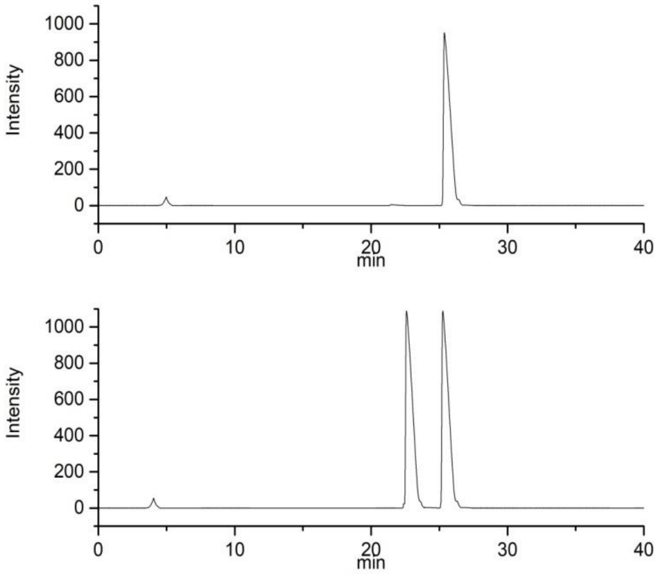


(*1S,2R*)-Ethyl 1,2-dihydroxycyclopentanecarboxylate (81). (BH10-062)

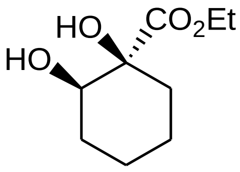


(*1S,2R*)-81

To an aqueous solution of 2 mL of Pd/Au (3:1)-**26** (0.84 μmol of Pd/0.27 μmol of Au-0.0295 μmol of **26**) in a Parr pressure reactor were added 18 mL of deionized H_2O and 0.03 g (0.214 mmol) of ethyl cyclopent-1-enecarboxylate (**77**). The apparatus was maintained under 30 psi of O_2, stirred at 50 ^oC for 3 days, vented to normal atmosphere, and extracted three times with ethyl acetate (20 mL each). The combined extracts were washed with water, and brine, dried ($MgSO_4$), and concentrated to dryness. The crude product was column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as eluents to give 28.3 mg (77% yield) of (1*S*,2*R*)-**81** in 99% ee. $[\alpha]_D$ = -36.8 (1.0, $CHCl_3$); ^1H NMR δ 4.26 (q, *J* = 7.2 Hz, 2H), 4.04 (t, J = 8.8 Hz, 1H), 3.12 (b, 1H), 2.64 (b, 1H), 2.20 – 2.16 (m, 1H), 2.14 – 2.03 (m, 1H),1.93–1.80 (m, 2H), 1.73–1.58 (m, 2H), 1.30 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 176.4, 79.1, 75.9, 62.0, 33.4, 27.5, 25.6, 14.0; MS (ESI, MeOH): m/z = 197.3 ([M + Na]$^+$) HRMS-ESI: m/z [M + H]$^+$ calcd for $C_8H_{15}O_4^+$: 175.0970, found: 175.0962. The % *ee* (99%) of (*1S,2R*)-**81** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 85:15, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 22.6 min (*1R,2S* enantiomer, minor), t_R = 25.3 min (*1S,2R* enantiomer, major).

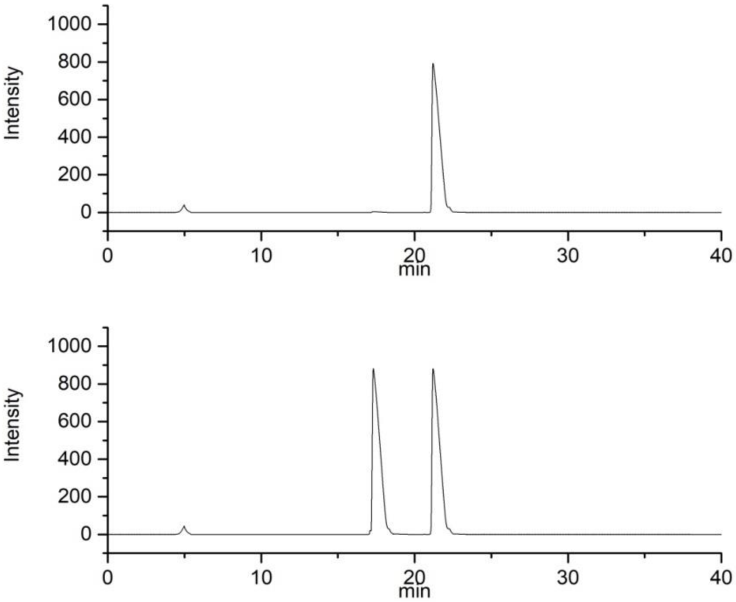


(1*S*,2*R*)-Ethyl 1,2-dihydroxycyclohexanecarboxylate (82). (BH9-069)

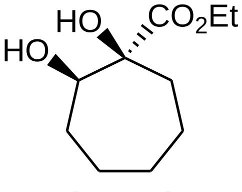


(*1S,2R*)-82

To an aqueous solution of 2 mL of Pd/Au (3:1)-**26** (2.44 μmol of Pd, 0.81 μmol of Au, and 0.09 μmol of **26**) in a Parr pressure reactor were added 18 mL of deionized H_2O and 0.1 g (0.65 mmol) of ethyl cyclohex-1-enecarboxylate (**78**). The apparatus was maintained under 30 psi of O_2, stirred at 50 ^oC for 3 days, vented to normal atmosphere, and extracted with ethyl acetate three times (20 mL each). The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 102 mg (83% yield) of (1*S*,2*R*)-**82** in 99% ee. $[\alpha]_D^{22}$ = -29.6 (c 1.0, $CHCl_3$); ^{1}H NMR δ 4.29 (q, *J* = 6.8 Hz, 2H), 3.92 (t, J = 9.6 Hz, 1H), 3.48 (b, 1H), 2.22 (d, 1H), 1.93–1.42 (m, 8H), 1.30 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 177.9, 79.1, 73.8, 60.8, 33.2, 28.5, 22.4, 20.3, 14.4; MS (ESI, MeOH): m/z = 211.2 ([M + Na]$^+$). HRMS-ESI: m/z [M + H]$^+$ calcd for $C_9H_{17}O_4^+$: 189.1127, found: 189.1129. The % *ee* (99%) of (*1S,2R*)-**82** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 85:15, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 17.6 min (*1R,2S* enantiomer, minor), t_R = 22.3 min (*1S,2R* enantiomer, major).



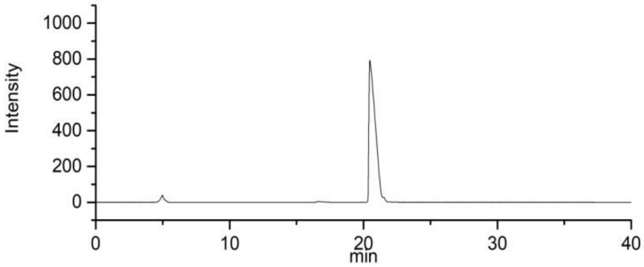
(*1S*,*2R*)-Ethyl 1,2-dihydroxycycloheptanecarboxylate (83). (BH9-025)

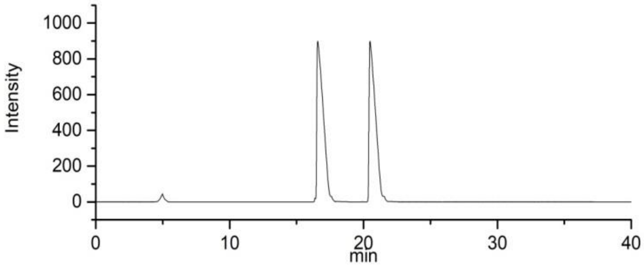


(*1S*,*2R*)-83

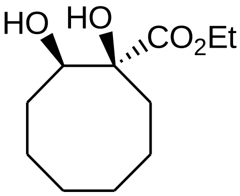
To an aqueous solution of 2 mL of Pd/Au (3:1)-**26** (1.12 μmol of Pd, 0.37 μmol of Au, and 0.041 μmol of **26**) in a Parr pressure reactor, were added 18 mL of deionized H_2O and 50 mg (0.30

mmol) of ethyl cyclohept-1-enecarboxylate (**79**). The apparatus was maintained at 30 psi of O_2, stirred at 50 ^{o}C for 3 days, vented to normal atmosphere, and extracted with ethyl acetate three times (20 mL each). The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 51 mg (85% yield) of (1*S*,2*R*)-**83** in 99% ee. $[\alpha]_D^{22}$ = -71.6 (c 1.0, $CHCl_3$); ^{1}H NMR δ 4.27 (q, *J* = 5.2 Hz, 1 H), 3.72 (t, *J* = 4.8 Hz, 1 H), 3.48 (b, 1 H), 2.24 (d, *J* = 9.6 Hz, 1H), 1.85 – 1.39 (m, 9 H,), 1.30 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 177.2, 78.8, 76.4, 62.3, 35.2, 32.2, 27.6, 23.2, 20.8, 14.4. MS (ESI, MeOH): m/z = 225.3 ([M + Na]$^+$). HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{10}H_{18}O_4^+$: 203.1283 found: 203.1279; The % *ee* (99%) of (*1S*,*2R*)-**83** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 85:15, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 16.2 min (*1R*,*2S* enantiomer, minor), t_R = 20.6 min (*1S*,*2R* enantiomer, major).



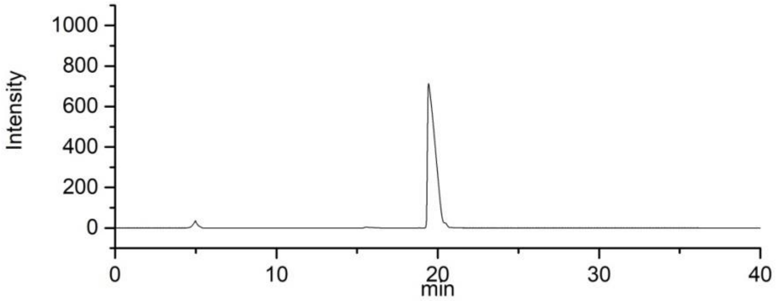


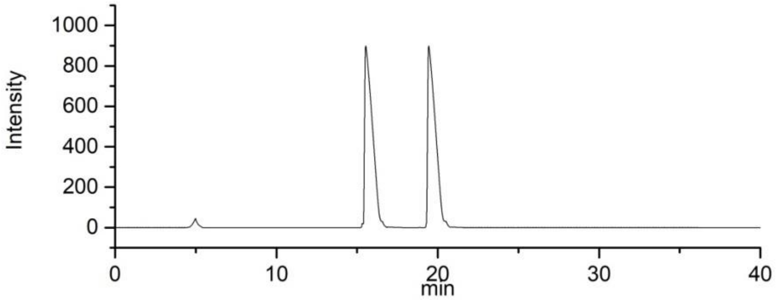
(1*S*,2*R*)-Ethyl 1,2-dihydroxycyclooctanecarboxylate (84). (BH10-083)



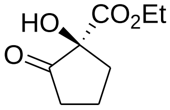
(*1S,2R*)-84

To an aqueous solution of 2 mL of Pd/Au (3:1)-**26** (1.53 μmol of Pd, 0.51 μmol of Au, and 0.056 μmol of **26**) in a Parr pressure reactor, were added 18 mL of deionized H_2O and 74 mg (0.41 mmol) of ethyl cyclooct-1-enecarboxylate (**80**). The apparatus was maintained under 30 psi of O_2, stirred at 50 ^{o}C for 3 days, vented to normal atmosphere, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 72.3 mg (81% yield) of (1*S*,2*R*)-**84** in 99% ee. $[\alpha]_D^{22}$ = -16.2 (c 1.0, $CHCl_3$); ^{1}H NMR δ 4.29 (q, *J* = 6.8 Hz, 2H), 3.12 (t, J = 9.6 Hz, 1H), 3.51 (b, 1H), 2.25 (d, 1H), 2.08 (m, 1H), 1.93–1.42 (m, 12H), 1.30 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 176.9, 79.4, 73.8, 62.2, 33.5, 31.2, 27.4, 26.5, 24.7, 21.2, 14.3; MS (ESI, MeOH): m/z = 239.4 ([M + Na]$^+$); HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{11}H_{21}O_4^+$: 217.1440, found: 217.1429; The % *ee* (99%) of (*1S*,*2R*)-**84** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 85:15, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 15.3 min (*1R,2S* enantiomer, minor), t_R = 20.0 min (*1S,2R* enantiomer, major).





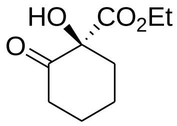
(S)-Ethyl 1-hydroxy-2-oxocyclopentanecarboxylate (86) (BH10-139)



(*S*)-86

To a solution of 17.4 mg (0.1 mmol) (*1S*,*2R*)-ethyl 1,2-dihydroxycyclopentanecarboxylate in 1 mL DMSO, 56 mg (0.2 mmol) of IBX was added and stirred at room temperature for 10 hours. The resulting solution was diluted with 2 mL water, extracted with 3 x 10 mL ethyl acetate, washed with brine, dried over Na_2SO_4, concentrated under vacuum and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 12.1 mg (70% yield) of the titled compound. $[\alpha]_D$ -14.6 (0.2, $CHCl_3$); Lit.[84] $[\alpha]_D$ +12 (1.0, $CHCl_3$ for R configuration); ^{1}H NMR δ 4.19−4.14 (q, *J* = 7.2 Hz, 2H), 3.84 (b, 1H), 2.44−2.34 (m, 3H), 2.09−1.98 (m, 3H), 1.24 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 213.5, 171.5, 79.9, 62.4, 35.8, 34.8, 18.8, 13.8. MS (ESI, MeOH): 173.1([M + H]$^+$).

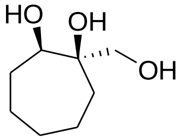
Ethyl 1-hydroxy-2-oxocyclohexanecarboxylate (87) (BH10-137)



(*S*)-87

To a solution of 18.8 mg (0.1 mmol) (1S,2R)-ethyl 1,2-dihydroxycyclopentanecarboxylate in 1 mL DMSO, 56 mg (0.2 mmol) of IBX was added and stirred at room temperature for 10 hours. The resulting solution was diluted with 2 mL water, extracted with 3 x 10 mL ethyl acetate, washed with brine, dried over Na_2SO_4, concentrated under vacuum and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 11.6 mg (61% yield) of the titled compound. $[\alpha]_D$ -126.8 (0.1, $CHCl_3$); Lit.[84] $[\alpha]_D$ +134 (1.0, $CHCl_3$ for R configuration); ^1H NMR δ 4.33 (s, 1H), 4.21 (q, J = 7.2 Hz, 2H), 2.68−2.49 (m, 3H), 2.06−1.97(m, 1H), 1.86−1.76 (m, 2H), 1.73−1.59 (m, 2H), 1.27 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 207.4, 170.1, 80.7, 62.1, 39.0, 37.7, 27.1, 22.0, 14.1. MS (ESI, MeOH): 187.1([M + H]$^+$).

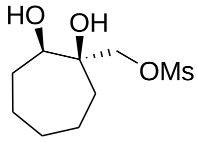
(*1R,2R*)-1-(Hydroxymethyl)cycloheptane-1,2-diol (88) (BH9-044)



88

To a cold (0 °C) solution of 18 mg (0.09 mmol) of (1*S*,2*R*)-**83** in 1 mL of THF under argon was added 5.1 mg (0.13 mmol) of $LiAlH_4$. The mixture was warmed to room temperature, stirred for 2 hours, and added 2 g of $Na_2SO_4{\bullet}10\ H_2O$ and one drop of CH_3COOH. The resulting solution was filtered through Celite, washed with 20 mL of methylene chloride, and concentrated under vacuum to give 14.1 mg of compound **88**. This material was used in the subsequent step without further purification. $[\alpha]_D^{22}$ = -22.3 (c 0.2, $CHCl_3$); ^1H NMR δ 3.96 (t, J = 9.6 Hz, 1H), 3.58 (m, 2H), 2.88 (b, 1H), 2.62 (b, 1H), 1.91–1.46 (m, 10H); ^{13}C NMR δ 81.4, 71.9, 65.8, 32.6, 29.3, 28.5, 25.9, 22.8; MS (ESI, MeOH): m/z = 161.2 ([M + H]$^+$).

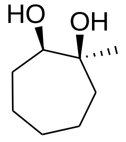
[(1*R*,2*R*)-1,2-Dihydroxycycloheptyl]methyl methanesulfonate (89) (BH9-045)



89

To a solution of 12 mg (0.075 mmol) of (1*R*,2*R*)-**88** in 4 mL of distilled methylene chloride under argon were added 7.5 mg (0.075 mmol) of Et_3N and 8.5 mg (0.075 mmol) of methanesulfonyl chloride (MsCl). It was stirred for 5 hours, diluted with 5 mL of H_2O, and extracted with 10 mL of CH_2Cl_2 twice. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of diethyl ether and hexane in a ratio of 6:1 as an eluent to give 11 mg (60% yield) of (*1R,2R*)-**89**. $[\alpha]_D^{22}$ = -80.7 (c 0.1, $CHCl_3$); ^{1}H NMR δ 4.06 (t, J = 9.6 Hz, 1H), 3.92 (m, 2H), 2.91 (s, 3H), 2.45 (b, 1H), 2.03 (d, 1H), 1.86–1.46 (m, 10H); ^{13}C NMR δ 78.9, 76.4, 69.2, 37.9, 35.5, 31.4, 27.6, 22.9, 20.6; MS (ESI, MeOH): m/z = 261.1 ($[M + Na]^+$).

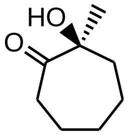
(*1S*,*2R*)-1-Methylcycloheptane-1,2-diol (90) (BH9-051)



90

To a cold (0 °C) solution of 9.8 mg (0.041 mmol) of (*1R,2R*)-**89** in 1 mL of distilled THF under argon was added 1.56 mg (0.041 mmol) of $LiAlH_4$. The mixture was warmed to room temperature and stirred for 6 hours, diluted with 1 mL of water and 0.5 mL of HCl, and extracted twice with 10 mL each of ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give (*1S,2R*)-**90**. This material was used in the subsequent step without further purification. ^{1}H NMR δ 3.91 (t, *J* = 9.2 Hz, 1H), 3.39 (b, 1H), 2.23 (d, 1H), 1.88–1.42 (m, 10H), 1.30 (s, 3H); ^{13}C NMR δ 80.6, 73.6, 32.5, 28.5, 27.0, 24.7, 22.6, 20.5; MS (ESI, MeOH): m/z = 183.4 ([M + K]$^+$).

(*S*)-2-Hydroxy-2-methylcycloheptanone (91) (BH9-053)

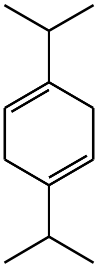


91

To a solution of 14 mg (0.048 mmol) of 2-iodoxybenzoic acid (IBX) in 1 mL of DMSO under argon was added 6.3 mg (0.044 mmol) of (*1S*,*2R*)-**90**. The solution was stirred for 8 hours, dilute with 20 mL of CH_2Cl_2, and washed three times with 5 mL each of H_2O. The combined organic layer was dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as an eluent to give 5.2 mg (83% yield) of (*S*)-**91**. $[\alpha]_D^{22}$ = -71.2 (c = 0.24, $CHCl_3$); Lit.[85] -71 (c 0.24, $CHCl_3$; *S*-configuration); ^{1}H NMR δ 3.42 (b, 1 H), 2.73 – 2.67 (m, 1 H), 2.55–2.48 (m,1 H), 2.16–2.10 (m, 1 H), 1.99 ‒ 1.60 (m, 6 H,), 1.23 (s, 3 H); ^{13}C NMR δ 216.3, 89.2, 36.9, 33.5, 31.4, 27.2, 25.9, 21.3. MS (ESI, MeOH): m/z = 165.3 ([M + Na]$^+$).

2.6.5 Procedures and Analysis Results for Oxidation of Cycloalkanes.

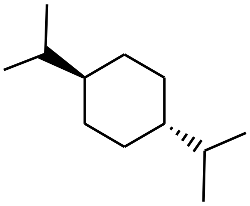
1,4-Diisopropyl-1,4-cyclohexadiene (134) (BH4-110)



134

To a cold (-78^{o}C) solution of 40 mL of liquid NH_3 under argon was added 0.86 g (0.12 mol) of lithium wire, and the resulting blue solution was stirred at -35^{o}C for 1 h. To it, a solution of 4.0 g (24.7 mmol) of 1,4-diisopropylbenzene in 5.4 g of *t*-BuOH was added, and the solution was stirred for 6 h at -35^{o}C under argon. The reaction solution was diluted with aqueous NH_4Cl (10 mL), extracted twice with diethyl ether, and the combined extract was washed with water, brine, and dried ($MgSO_4$). The solvents were removed by distillation under normal pressure, and residue was column chromatographed on silica gel using hexane as eluent to give 2.81 g (70% yield) of 1,4-diisopropyl-1,4-cyclohexadiene (**134**) along with 0.96 g (24% recovery) of 1,4-diisopropylbenzene. ^{1}H NMR δ 5.46 (s, 2 H, =CH), 2.64 (s, 4 H, CH_2), 2.19 (hept, J = 7 Hz, 2 H), 1.01 (d, J = 7 Hz, 12 H); ^{13}C NMR δ 140.9, 116.4, 34.7, 27.8, 21.5. MS (ESI, MeOH): *m/z* = 165.0 ($[M + H]^+$).

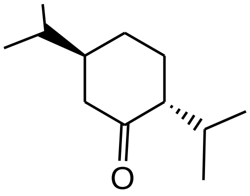
***trans*-1,4-Diisopropylcyclohexane (92)** (BH4-112)



92

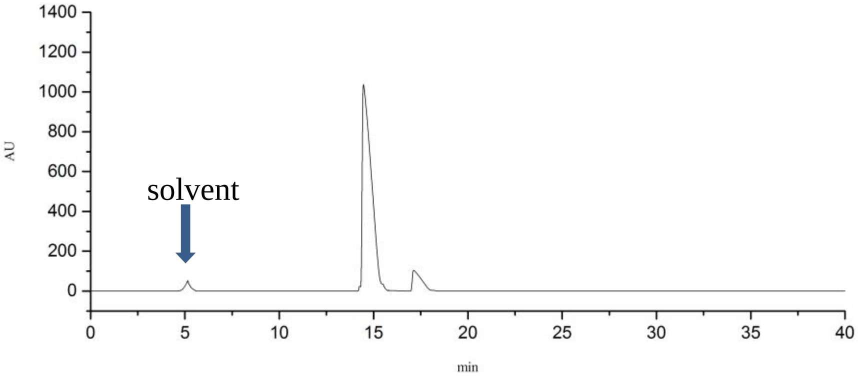
A mixture of 2.0 g (12.2 mmol) of 1,4-diisopropyl-1,4-cyclohexadiene and 0.14 g of 10% Pd/C in 30 mL of ethyl acetate in a bottle was shaken under 30 psi of H_2 on a Parr hydrogenator for 16 h and then maintained under normal pressure. The mixture was filtered through Celite, and the filtrate was concentrated by distillation under normal pressure and column chromatographed on silica gel using pentane as solvent to give 1.3 g (65% yield) of pure **92** along with 0.50 g of **92** and **134** (2:1). Compound **92**: ^{1}H NMR δ 1.73–1.68 (m, 2 H), 1.59–1.05 (m, 7 H), 0.95–0.90 (m, 3 H), 0.84 (d, J = 7.2 Hz, 12 H); ^{13}C NMR δ 42.6, 30.2, 26.7, 20.1. MS (ESI, MeOH): *m/z* = 207.0 ($[M + K]^+$).

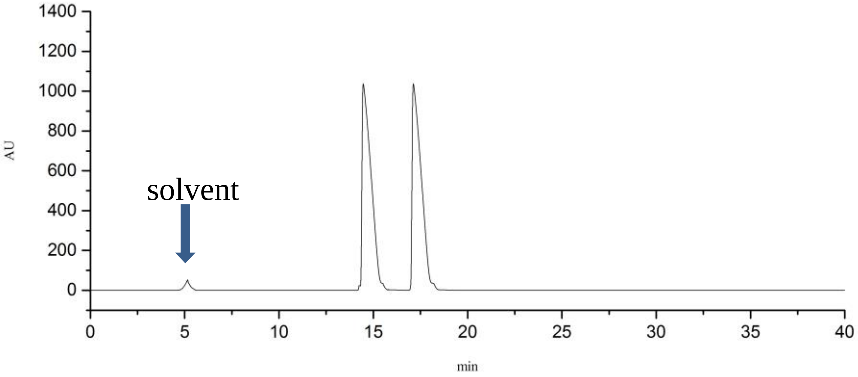
(2*R*,5*S*)-2,5-Diisopropylcyclohexanone (93) (BH7-100)



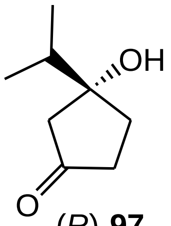
(2*R*,5*S*)-**93**

To a solution of 2 mL of Cu/Au (3:1)-**1** (4.46 μmol of Cu/1.49 μmol of Au-0.16 μmol of **1**) were added 3 mL of acetonitrile, 0.10 g (0.60 mmol) of **92** and 3 mL of 30% H_2O_2, and the resulting solution was stirred at 50°C for 7 days. The solution was cooled to 25°C and extracted three times with diethyl ether (15 mL each). The combined extracts were washed with water and then brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as eluents to give 94 mg (87% yield) of (2*R*,5*S*)-**93** in 81% ee along with 7 mg (7% recovery) of **92**. The optical purity was determined using HPLC/chiral column. Compound (2*R*,5*S*)-**93**: $[\alpha]_D^{22}$ = +12.1 (c 1.5, $CHCl_3$). Lit.[101] +14 (c 1.51, $CHCl_3$). ^{1}H NMR δ 2.38 (ddd, J = 12, 3.4, 2.2 Hz, 1 H), 2.13–2.05 (m, 1 H), 1.83–1.52 (m, 3 H), 1.43–0.85 (m, 5 H), 1.01 (d, J = 7 Hz, 6 H), 0.84 (d, J = 7 Hz, 6 H); ^{13}C NMR δ 213.0, 56.2, 46.5, 32.6, 28.8, 27.9, 25.9, 21.2, 19.6 (2 C), 18.6 (2 C). MS (ESI, MeOH): *m/z* = 205.1 ($[M + Na]^+$; 100%), 139.0. The % ee (81%) of (1*R*,5*S*)-**93** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, detected at 220 nm wavelength; t_R = 14.5 min (2*R*,5*S* enantiomer, major), t_R = 17.2 min (2*S*,5*R* enantiomer, minor).





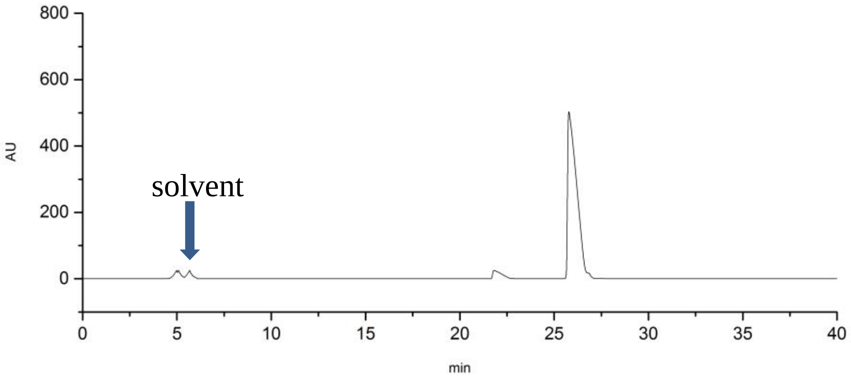
(*R*)-3-Hydroxy-3-isopropylcyclopentanone (97). (BH7-091)

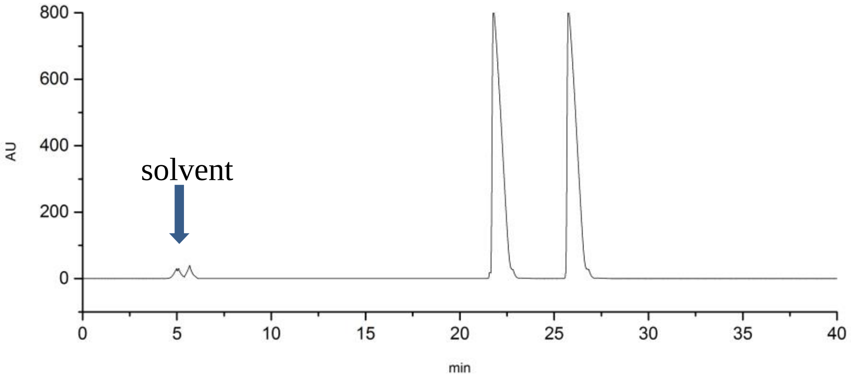


(*R*)-**97**

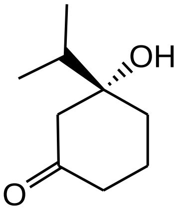
From 90 mg (0.70 mmol) of 1-isopropylcyclopentanol (**94**), 2.4 mL of Cu/Au (3:1)-**1** (5.27 μmol of Cu/1.75 μmol of Au-0.19 μmol of **1**), 2 mL of H_2O_2, and 1 mL of CH_3CN stirring at 50°C for 7 days, 91 mg (91% yield) of (*R*)-**97** in 92% ee. $[\alpha]_D^{22}$ = +13.7 (c 0.20, $CHCl_3$). ^{1}H NMR δ 2.41–2.30 (m, 2 H, C2 Hs), 2.30–2.17 (m, 1 H, C5 H), 2.07–1.80 (m, 4 H, C5 H, C4 Hs, & C$\underline{H}$Me$_2$), 1.72–1.60 (m, 2 H, C4 H & OH), 1.02 (d, J = 7 Hz, 6 H). The proton NMR assignments were derived from 2D COSY spectrum. ^{13}C NMR δ 205.9, 73.3, 53.6, 42.4, 32.5, 22.0, 16.7. MS (ESI, MeOH): *m/z* = 143.0 ([M + H]$^+$),. HRMS-Hexane Atmospheric

Pressure Chemical Ionization (HAPCI): *m/z* $[M]^+$ calcd for $C_8H_{14}O_2$: 142.0994; found: 142.0049. The % ee (92%) of (*R*)-**97** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, detected at 220 nm wavelength; t_R = 23.5 min (*S* enantiomer, minor), t_R = 27.5 min (*R* enantiomer, major).





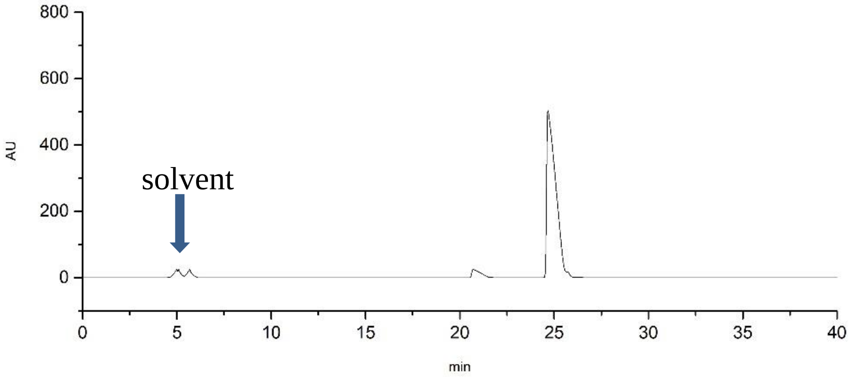
(*R*)-3-Hydroxy-3-isopropylcyclohexanone (98) (BH7-098)

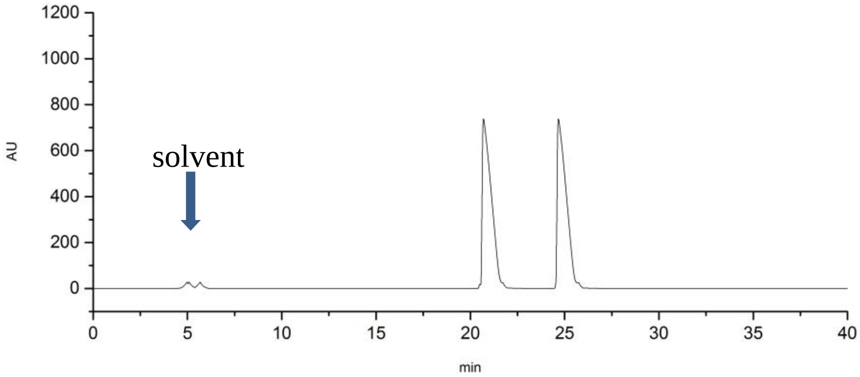


(*R*)-**98**

From 0.10 g (0.70 mmol) of 1-isopropylcyclohexanol (**95**), 2.4 mL of Cu/Au (3:1)-**1** (5.27 μmol of Cu/1.75 μmol of Au-0.19 μmol of **1**), 2 mL of H_2O_2, and 1 mL of CH_3CN stirring at 50°C for

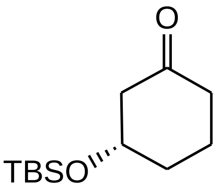
7 days, 0.107 g (98% yield) of (*R*)-**98** in 91.4% ee. $[\alpha]_D^{22}$ = +6.1 (c 0.20, $CHCl_3$). ^{1}H NMR δ 2.45–2.40 (m, 2 H), 2.15–2.10 (m, 2 H), 1.96–1.88 (m, 2 H), 1.77–1.60 (m, 4 H), 0.88 (d, J = 6.8 Hz, 6 H). The proton NMR assignments were derived from 2D COSY spectrum. ^{13}C NMR δ 205.1, 73.2, 54.2, 42.4, 34.3, 29.3, 23.7, 17.5. MS (ESI, MeOH): *m/z* = 157.3 ([M + H]$^+$). HRMS-Hexane Atmospheric Pressure Chemical Ionization (HAPCI): *m/z* [M+H]$^+$ calcd for $C_9H_{17}O_2$: 157.1229; found: 157.1221. The % ee (91.4%) of (*R*)-**56** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, detected at 220 nm wavelength; t_R = 20.8 min (*S* enantiomer, minor), t_R = 24.7 min (*R* enantiomer, major).





Alternate synthetic route for (*R*)-98 to determine the absolutely configuration

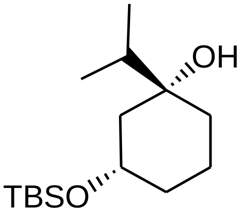
(*S*)-3-(*t*-Butyldimethylsilyloxy)cyclohexanone (126) (BH8-034)



(S)-**126**

To a solution of 40 mg (0.35 mmol) of (*S*)-3-hydroxycyclohexanone (**38**), 4 mg (0.036 mmol) of 4-dimethylaminopyridine, and 0.10 g (1.0 mmol) of trimethylamine in 3 mL of dichloromethane at 0°C under argon, was added 77 mg (0.51 mmol) of *t*-butyldimethylsilyl chloride. The solution was stirred for 4 h, diluted with 10 mL of water, and extracted three times with ethyl acetate (10 mL each). The combined extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel to give 28 mg (35% yield) of (*S*)-3-(*t*-butyldimethylsilyloxy)cyclohexanone (**126**) and 17 mg (49% yield) of 2-cyclohexenone along with 4 mg (10% recovery) of starting 3-hydroxyketone **38**. ^{1}H NMR δ 4.17–4.12 (m, 1 H), 2.62 (dd, J = 14, 4 Hz, 1 H), 2.36 (dd, J = 14, 7.5 Hz, 1 H), 2.28 (t, J = 6.5 Hz, 2 H), 2.15–2.00 (m, 2 H), 1.82–1.65 (m, 2 H), 1.00 (s, 9 H), 0.38 (s, 6 H).

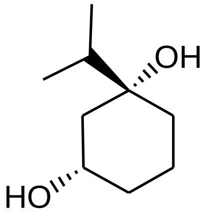
(1*R*,3*S*)-3-(*t*-Butyldimethylsilyloxy)-1-isopropylcyclohexanone (127) (BH10-040)



(1*R*,3*S*)-**127**

To a mixture of 1.7 mg (13 μmol) of anhydrous $ZnCl_2$ in 2 mL of dry THF under argon at 25°C, was added a solution of 0.18 mmol of isopropylmagnesium bromide in 1 mL of THF, and the solution was stirred for 1 h and then cooled to 0°C. To it, was added a solution of 28 mg (0.12 mmol) of (*S*)-**126** in 0.5 mL of THF via cannula under argon and the resulting solution was stirred at 0°C for 4 h. The solution was diluted with aqueous NH_4Cl and water (10 mL), extracted three times with ethyl acetate (20 mL each), and the combined extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluent to give 23 mg (70% yield) of (1*R*,3*S*)-3-(*t*-butyldimethylsilyloxy)-1-isopropylcyclohexanone (**127**). No other stereoisomer was found. ^{1}H NMR δ 4.37 (m, 1 H), 1.96–1.50 (m, 8 H), 1.32–1.24 (m, 2 H), 0.97 (s, 9 H), 0.91 (d, J = 7 Hz, 6 H), 0.36 (s, 6 H); ^{13}C NMR δ 73.3, 66.2, 37.5, 35.6, 33.1, 26.2, 23.9 (3 C), 20.9, 18.6, 16.9 (2 C), -1.15 (2 C).

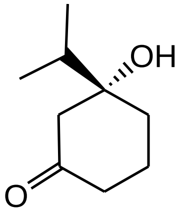
(1*R*,3*S*)-1-Isopropyl-1,3-cyclohexanediol (128) (BH8-046)



(1*R*,3*S*)-**128**

A solution of 14 mg (52 μmol) of the above (1*R*,3*S*)-**127** and 0.10 mL (0.10 mmol) of *n*-Bu_4NF (1 M in THF) in 0.5 mL of THF was stirred under argon at 0°C for 1 h and then at 25°C for 1.5 h. The solution was diluted with water (10 mL), and extracted three times with diethyl ether (10 mL each). The combined extract was washed with brine, dried ($MgSO_4$), and concentrated under vacuum to give 8.7 mg of (1*R*,3*S*)-1-isopropyl-1,3-cyclohexanediol, which was used immediately in the following reaction without further purification.

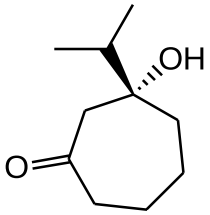
(*R*)-3-Hydroxy-3-isopropylcyclohexanone (98) (BH8-046)



(*R*)-**98**

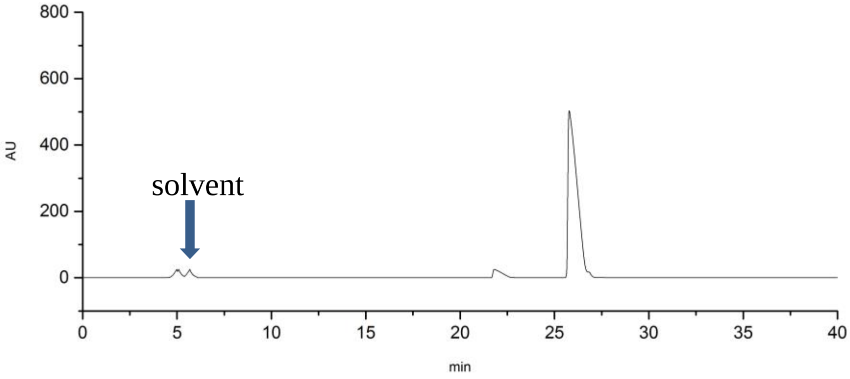
To a solution of **128** in 0.5 mL of DMSO was added 16 mg (57 μmol) of IBX under argon at 25°C. The resulting mixture was stirred for 14 h, filtered to remove white solid, and rinsed with 20 mL of diethyl ether. The ether filtrate was washed three times with water (10 mL each), dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of hexane and ethyl acetate (1:2) as eluent to give 7.6 mg (95% yield) of (*R*)-3-hydroxy-3-isopropylcyclohexanone (**98**). $[\alpha]_D^{22}$ = +6.4 (c 0.20, $CHCl_3$). ^1H and ^{13}C NMR spectra were identical those of (*R*)**-98** synthesized from the Pd/Au-**1** catalytic oxidation reaction.

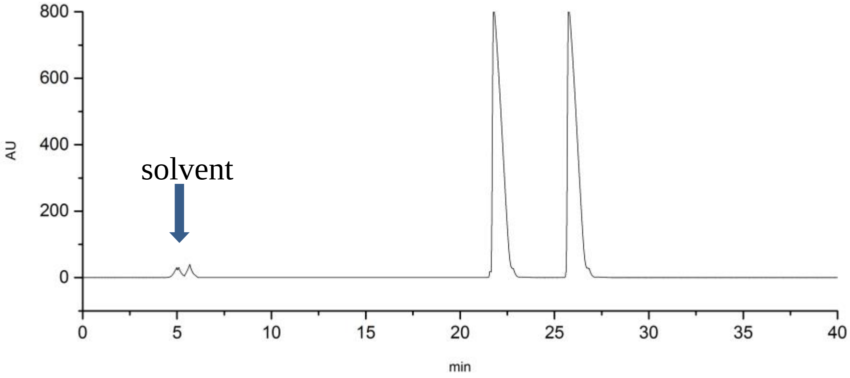
(*R*)-3-Hydroxy-3-isopropylcycloheptanone (99). (BH7-096)



(*R*)-**99**

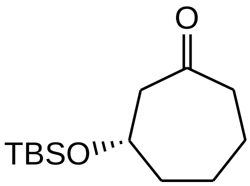
From 42 mg (0.27 mmol) of 1-isopropylcycloheptanol (**96**), 0.92 mL of Cu/Au (3:1)-**1** (2.0 μmol of Cu/0.65 μmol of Au-0.074 μmol of **1**), 1 mL of H_2O_2, and 1 mL of CH_3CN stirring at 50°C for 7 days, 41 mg (89% yield) of (*R*)-**99** in 93% ee. $[\alpha]_D^{22}$ = +23.8 (c 0.20, $CHCl_3$). ^1H NMR δ 2.35 (d, J = 2 Hz, 2 H, C2 Hs), 2.16–2.18 (m, 2 H, C7 Hs), 1.97–1.93 (m, 2 H, C6 Hs), 1.90–1.83 (m, 1 H, C$\underline{H}$Me$_2$), 1.75–1.70 (m, 1 H, C4 H), 1.67–1.58 (m, 3 H, C5 Hs & C4 H), 1.30–1.20 (bs, 1 H, OH), 0.86 (d, J = 8 Hz, 6 H). The proton NMR assignments were derived from 2D COSY spectrum. ^{13}C NMR δ 206.1, 74.4, 52.8, 41.6, 37.4, 33.9, 27.0, 21.0, 17.1 (2 C). MS (ESI, MeOH): *m/z* = 171.1 ($[M + H]^+$). HRMS-Hexane Atmospheric Pressure Chemical Ionization (HAPCI): *m/z* $[M+H]^+$ calcd for $C_{10}H_{19}O_2$: 171.1385; found: 171.1381. The % ee (93%) of (*R*)-**99** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, detected at 220 nm wavelength; t_R = 21.7 min (*S* enantiomer, minor), t_R = 25.8 min (*R* enantiomer, major).





Alternate synthetic route for (*R*)-99 to determine the absolutely configuration

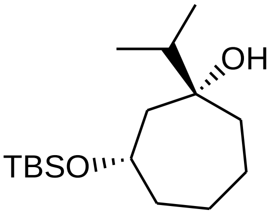
(*S*)-3-(*t*-Butyldimethylsilyloxy)cycloheptanone (129) (BH8-044)



(S)-**129**

To a solution of 15 mg (0.12 mmol) of (*S*)-3-hydroxycycloheptanone (**42**), 1.5 mg (0.012 mmol) of 4-dimethylaminopyridine, and 35 mg (0.35 mmol) of trimethylamine in 1 mL of dichloromethane at 0^{o}C under argon, was added 25 mg (0.17 mmol) of *t*-butyldimethylsilyl chloride. The solution was stirred for 8 h, diluted with 10 mL of water, and extracted three times with ethyl acetate (10 mL each). The combined extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel to give 19 mg (76% yield) of (*S*)-3-(*t*-butyldimethylsilyloxy)cycloheptanone and 3.2 mg (25% yield) of 2-cycloheptenone. The silyloxycycloheptanone was used in the following step without purification. (*S*)-3-(*t*-Butyldimethylsilyloxy)cycloheptanone: ^{1}H NMR δ 4.12–4.10 (m, 1 H), 2.85–2.75 (m, 2 H), 2.55–2.40 (m, 2 H), 1.95–1.55 (m, 6 H), 0.98 (s, 9 H), 0.37 (s, 6 H).

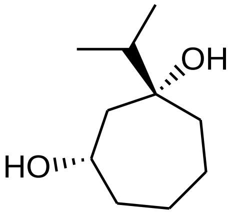
(1*R*,3*S*)-3-(*t*-Butyldimethylsilyloxy)-1-isopropylcycloheptanone (**130**) (BH8-048)



(1*R*,3*S*)-**130**

To a mixture of 1.1 mg (8 μmol) of anhydrous $ZnCl_2$ in 0.5 mL of dry THF under argon at 25°C, was added a solution of 0.12 mmol of isopropylmagnesium bromide in 0.2 mL of THF, and the solution was stirred for 1 h and then cooled to 0°C. To it, was added a solution of 19 mg (0.078 mmol) of (*S*)-3-(*t*-butyldimethylsilyloxy)cycloheptanone in 0.2 mL of THF via cannula under argon and the resulting solution was stirred at 0°C for 3 h. The solution was diluted with aqueous NH_4Cl and water (10 mL), extracted three times with ethyl acetate (10 mL each), and the combined extract was washed with brine, dried (anh. Na_2SO_4), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluent to give 14 mg (62% yield) of (1*R*,3*S*)-3-(*t*-butyldimethylsilyloxy)-1-isopropylcycloheptanone (**130**). No other stereoisomer was found. ^{1}H NMR δ 4.42–4.35 (m, 1 H), 2.02–1.50 (m, 9 H), 1.35–1.20 (m, 3 H), 0.97 (s, 9 H), 0.91 (d, J = 7 Hz, 6 H), 0.36 (s, 6 H); ^{13}C NMR δ 75.6, 70.9, 35.0, 33.1, 30.6, 29.6, 25.8 (3 C), 25.5, 24.3, 20.0, 17.2 (2 C), -1.6 (2 C).

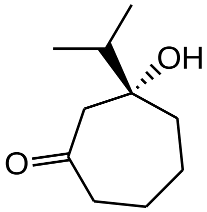
(1*R*,3*S*)-1-Isopropyl-1,3-cycloheptanediol (131) (BH8-050)



(1*R*,3*S*)-**131**

A solution of 7 mg (24 μmol) of the above (1*R*,3*S*)-**130** and 48 μL (48 μmol) of *n*-Bu_4NF (1 M in THF) in 0.5 mL of THF was stirred under argon at 25°C for 2 h. The solution was diluted with water (10 mL), and extracted three times with diethyl ether (10 mL each). The combined extract was washed with brine, dried ($MgSO_4$), and concentrated under vacuum to give 4.2 mg of (1*R*,3*S*)-1-isopropyl-1,3-cycloheptanediol, which was used immediately in the following reaction without further purification.

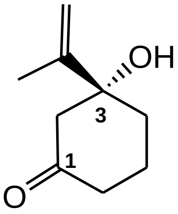
(*R*)-3-Hydroxy-3-isopropylcycloheptanone (99) (BH8-050)



(*R*)-**99**

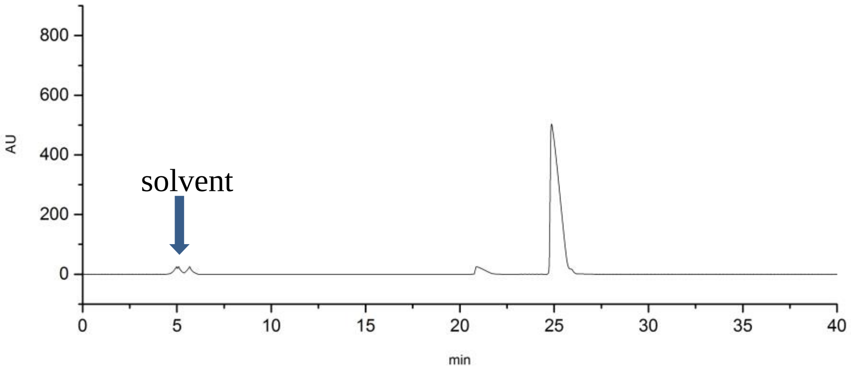
To a solution of **131** in 0.5 mL of DMSO was added 8 mg (26 μmol) of IBX under argon at 25°C. The resulting mixture was stirred for 14 h, filtered to remove white solid, and rinsed with 10 mL of diethyl ether. The ether filtrate was washed three times with water (10 mL each), dried (anh. Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane and ethyl acetate (1:2) as eluent to give 4.0 mg (96% yield) of (*R*)-3-hydroxy-3-isopropylcycloheptanone (**99**). $[\alpha]_D^{22} = +25.9$ (c 0.20, $CHCl_3$). ^1H and ^{13}C NMR spectra were identical those of **99** synthesized by the oxidation reaction from 1-isopropyl-1-cycloheptanol with Pd/Au-**1** catalyst.

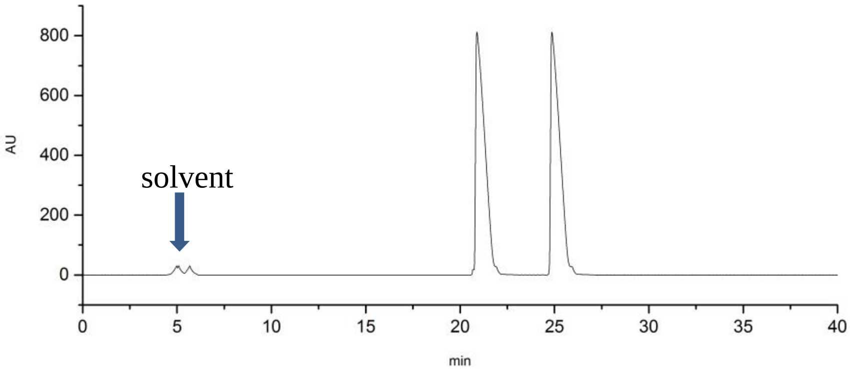
(*R*)-3-Hydroxy-3-(isopropenyl)cyclohexanone (101) (BH8-024)



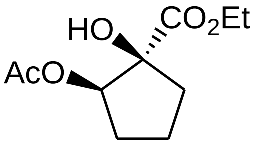
(*R*)-**101**

From 70 mg (0.50 mmol) of 1-isopropenylcyclohexanol (**100**), 1.7 mL of Cu/Au (3:1)-**1** (3.75 μmol of Cu/1.25 μmol of Au-0.13 μmol of **1**), 1.5 mL of H_2O_2, and 1.5 mL of CH_3CN stirring at 50°C for 8 days, 76 mg (98% yield) of (*R*)-**101** in 93% ee. $[\alpha]_D^{22}$ = +17.3 (c 1.0, $CHCl_3$). ^1H NMR δ 5.07 (d, J = 0.8 Hz, 1 H, =CH), 4.95 (d, J = 0.8 Hz, 1 H, =CH), 2.35–2.32 (m, 2 H, C2 Hs), 2.16–2.15 (m, 2 H, C6 Hs), 2.00–1.95 (m, 2 H, C4 Hs), 1.85 (s, 3 H), 1.85–1.7 (m, 2 H, C5 Hs), 1.7–1.55 (bs, 1 H, OH). The proton NMR assignments were derived from 2D COSY spectrum. ^{13}C NMR δ 209.5, 152.2, 109.2, 76.1, 52.9, 40.8, 38.8, 23.0, 17.8. MS (ESI, MeOH): *m/z* = 177.1 ($[M + Na]^+$). HRMS-hexane Atmospheric Pressure Chemical Ionization (HAPCI): *m/z* $[M+H]^+$ calcd for $C_9H_{15}O_2$: 155.1072; found: 155.1088. The % ee (93%) of (*R*)-**101** was determined by HPLC using chiral column, Chiralpak AD(-H) column, *n*-hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, detected at 220 nm wavelength; t_R = 20.8 min (*S* enantiomer, minor), t_R = 24.9 min (*R* enantiomer, major).





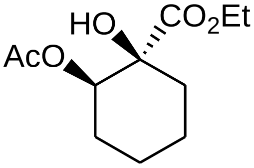
(1*S*,2*R*)-Ethyl 2-acetoxy-1-hydroxycyclopentanecarboxylate (102) (BH10-068)



(1*S*,2*R*)-**102**

A solution of 20 mg (0.12 mmol) of (1*S*,2*R*)-**81**, 12 mg (0.11 mmol) of acetic anhydride and 9.1 mg (0.11 mmol) of pyridine in 1 mL of CH_2Cl_2 was stirred under argon for 12 hours, acidified with 1*N* HCl to pH 5, and extracted twice with 10 mL each of CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as an eluent to give 24 mg (96% yield) of **(1*S*,2*R*)-102**. $[\alpha]^{22}_D = +125.6$ (0.2, $CHCl_3$); ^1H NMR δ 5.09 (dd, *J* = 11.2, 2.4 Hz, 1H), 4.22 (q *J* = 7.2 Hz, 2H), 3.50 (bs, 1H), 1.98 (s, 3H), 1.86–1.55 (m, 6H), 1.27 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 175.4, 170.2, 78.5, 78.0, 62.2, 28.7, 23.9, 21.0, 17.9, 14.3; MS (ESI, MeOH): m/z = 239.1 ($[M + Na]^+$). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{10}H_{17}O_5^+$: 217.1076, found: 217.1080.

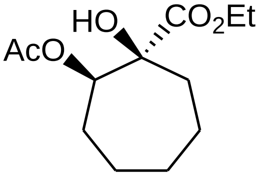
(1*S*,2*R*)-Ethyl 2-acetoxy-1-hydroxycyclohexanecarboxylate (103) (BH10-030)



(1*S*,2*R*)-**103**

To a solution of 50 mg (0.27 mmol) of (1*S*,2*R*)-**82** in 2 mL of CH_2Cl_2 under argon were added 27 mg (0.27 mmol) of acetic anhydride and 21 mg (0.27 mmol) of pyridine. The solution was stirred for 6 hours, acidified with 1*N* HCl to pH 5, and extracted twice with 10 mL each of CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as an eluent to give 26 mg (42% yield) of (1*S*,2*R*)-**103** and 19 mg (38% recovery) of (1*S*,2*R*)-**82** . $[\alpha]^{22}_D$ = +28.4 (0.2, $CHCl_3$); ^1H NMR δ 5.08 (dd, *J* = 11.2, 2.4 Hz, 1H), 4.19 (q *J* = 7.2 Hz, 2H), 2.85 (b, 1H), 1.98 (s, 3H), 1.78–1.55 (m, 8H), 1.25 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 176.0, 170.3, 79.1, 78.3, 62.2, 36.2, 29.4, 28.7, 20.9, 19.8, 14.2; MS (ESI, MeOH): m/z = 231.4 ($[M + H]^+$). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{11}H_{19}O_5^+$: 231.1232, found: 231.1235.

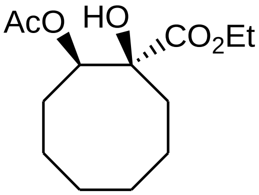
(*1S,2R*)-Ethyl 2-acetoxy-1-hydroxycycloheptanecarboxylate (104) (BH9-034)



(1*S*,2*R*)-**104**

To a solution of 48 mg (0.24 mmol) of (1*S*,2*R*)-**83** in 2 mL of CH_2Cl_2, 24 mg (0.24 mmol) of acetic anhydride and 18 mg (0.24 mmol) of pyridine were added. The reaction was stirred under argon for 3 hours, acidified with 1*N* HCl to pH 5, and extracted with 10 mL of CH_2Cl_2 twice. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ether as an eluent to give 26 mg (45% yield) of (1*S*,2*R*)-**104** and 24 mg (50% recovery) of (1*S*,2*R*)-**83**. $[\alpha]^{22}_{D}$ = +48.6 (0.5, $CHCl_3$); ^{1}H NMR δ 5.07 (dd, *J* = 11.2, 2.4 Hz, 1H), 4.20 (q *J* = 7.2 Hz, 2H), 3.25 (b, 1H), 1.98 (s, 3H), 1.94–1.55 (m, 10H), 1.25 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 175.9, 169.9, 78.6, 78.0, 62.3, 35.6, 28.6, 27.3, 23.3, 21.4, 21.2, 14.3; MS (ESI, MeOH): m/z = 267.1 ([M + Na]$^+$). HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{12}H_{21}O_5^+$: 245.1389, found: 245.1392.

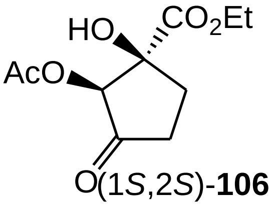
***(1S,2R)*-Ethyl 2-acetoxy-1-hydroxycyclooctanecarboxylate (105)** (BH10-159)



(1*S*,2*R*)-**105**

To a solution of 20 mg (0.093 mmol) of (1*S*,2*R*)-**84** in 1 mL of CH_2Cl_2, 9.48 mg (0.093 mmol) of acetic anhydride and 7.4 mg (0.093 mmol) of pyridine were added. The reaction was stirred under argon for 5 hours, acidified with 1*N* HCl to pH 5, and extracted three times with 10 mL of CH_2Cl_2 each. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ether as an eluent to give 17.6 mg (74% yield) of (1*S*,2*R*)-**105**. $[\alpha]^{22}_{D}$ = +16.2 (0.1, $CHCl_3$); ^{1}H NMR δ 5.03 (d, *J* = 10.8 Hz, 1H), 4.20 (q *J* = 7.2 Hz, 2H), 2.41 (b, 1H), 1.98 (s, 3H), 1.90–1.55 (m, 12H), 1.25 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 175.4, 170.9, 78.6, 77.8, 62.3, 30.4, 28.9, 28.6, 26.1, 23.8, 21.0, 18.4, 14.1; MS (ESI, MeOH): m/z = 281.1 ([M + Na]$^+$).]; HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{13}H_{23}O_5^+$: 259.1546, found: 259.1550.

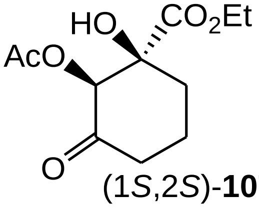
(*1S,2S*)-Ethyl 2-acetoxy-1-hydroxy-3-oxocyclopentanecarboxylate (106) (BH10-082)



(1*S*,2*S*)-**106**

To an aqueous solution of 3 mL of Cu/Au (3:1)-**26** (0.69 μmol of Cu, 0.23 μmol of Au, and 0.025 μmol of **26**), were added 1 mL of 30% H_2O_2, 2 mL of CH_3CN and 20 mg (0.092 mmol) of (*1S,2R*)-**102**. The resulting solution was stired at 50°C for 3 days, cooled to 25°C, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 17.7 mg (83% yield) of (*1S,2S*)-**106**. $[\alpha]^{22}_{D}$ = +134.2 (0.2, $CHCl_3$); ^1H NMR δ 5.21 (s, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 2.52–2.48 (m, 2H), 1.96 (s, 3H), 1.95–1.86 (m, 2H) 1.24 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 212.0, 177.1, 173.1, 100.2, 76.4, 62.2, 27.6, 20.5, 17.6, 14.2; MS (ESI, MeOH): m/z = 231.1 ($[M + H]^+$); HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{10}H_{15}O_6^+$: 231.0869, found: 231.0870.

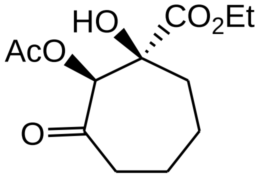
(*1S,2S*)-Ethyl 2-acetoxy-1-hydroxy-3-oxocyclohexanecarboxylate (107) (BH10-037)



(1*S*,2*S*)-**107**

To an aqueous solution of 3 mL of Cu/Au (3:1)-**26** (0.82 μmol of Cu, 0.27 μmol of Au, and 0.030 μmol of **26**), were added 1 mL of 30% H_2O_2, 2 mL of CH_3CN and 25 mg (0.109 mmol) of (*1S,2R*)-**103**. The resulting solution was stired at 50°C for 3 days, cooled to 25°C, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 22 mg (83% yield) of (*1S,2S*)-**107**. $[\alpha]^{22}_{D}$ = +20.2 (0.1, $CHCl_3$); ^1H NMR δ 5.10 (s, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.81 (b, 1H), 2.52–2.48 (m, 2H), 1.96 (s, 3H), 1.90–1.72 (m, 4H) 1.24 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 212.0, 177.2, 173.0, 100.0, 76.3, 62.4, 32.1, 27.9, 23.5, 20.7, 14.2; MS (ESI, MeOH): m/z = 267.1 ([M + Na]$^+$). HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{11}H_{17}O_6^+$: 245.1025, found: 245.1031.

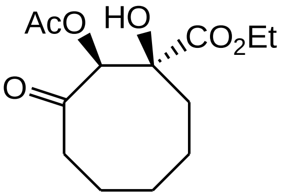
(*1S,2S*)-Ethyl 2-acetoxy-1-hydroxy-3-oxocycloheptanecarboxylate (108). (BH9-040)



(1*S*,2*S*)-**108**

To an aqueous solution of 3 mL of Cu/Au (3:1)-**26** (0.80 μmol of Cu, 0.26 μmol of Au, and 0.029 μmol of **26**), were added 1 mL of 30% H_2O_2, 2 mL of CH_3CN and 26 mg (0.107 mmol) of (*1S,2R*)-**104**. The resulting solution was stirred at 50°C for 3 days, cooled to 25°C, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 21 mg (76% yield) of (*1S,2S*)-**108**. $[\alpha]^{22}_{D}$ = +18.6 (0.1, $CHCl_3$); ^{1}H NMR δ 5.22 (s, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.48 (b, 1H), 2.52–2.48 (m, 2H), 1.96 (s, 3H), 1.78–1.54 (m, 6H) 1.24 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 211.2, 177.5, 172.4, 100.0, 76.5, 61.4, 32.1, 30.6, 25.6, 24.5, 20.7, 14.2; MS (ESI, MeOH): m/z = 281.1 ([M + Na]$^+$). HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{12}H_{19}O_6^+$: 259.1182, found: 259.1176.

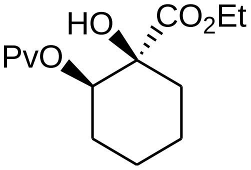
(*1S,2S*)-Ethyl 2-acetoxy-1-hydroxy-3-oxocyclooctanecarboxylate (109) (BH11-015)



(1*S*,2*S*)-**109**

To an aqueous solution of 3 mL of Cu/Au (3:1)-**26** (0.43 μmol of Cu, 0.15 μmol of Au, and 0.016 μmol of **26**), were added 1 mL of 30% H_2O_2, 2 mL of CH_3CN and 15 mg (0.058 mmol) of (*1S,2R*)-**105**. The resulting solution was stirred at 50°C for 4 days, cooled to 25°C, and extracted three times with 20 mL each of methylene chloride. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 13.2 mg (83% yield) of (*1S,2S*)-**109** and recover 0.8 mg (5.3% yield) of (*1S,2R*)-**105**. $[\alpha]^{22}_{D}$ = +43.8 (0.1, $CHCl_3$); ^{1}H NMR δ 5.12 (s, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.51–2.47 (m, 2H), 1.96 (s, 3H), 1.90–1.48 (m, 8H) 1.24 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 211.8, 177.5, 173.7, 100.2, 76.4, 62.2, 34.4, 32.2, 26.8, 25.3, 23.7, 21.3, 14.2; MS (ESI, MeOH): m/z = 295.1 ($[M + Na]^+$). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{13}H_{21}O_6^+$: 273.1138, found: 273.1133.

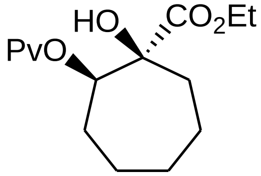
(*1S,2R*)-Ethyl 1-hydroxy-2-(pivaloyloxy)cyclohexanecarboxylate (110) (BH10-140)



(1*S*,2*R*)-**110**

To a solution of 50 mg (0.27 mmol) of (1*S*,2*R*)-**82** in 2 mL of CH_2Cl_2 under argon were added 32 mg (0.27 mmol) of pivaloyl chloride and 21.3 mg (0.27 mmol) of pyridine. The solution was stirred for 10 hours, acidified with 1*N* HCl to pH 5, and extracted twice with 20 mL each of CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as an eluent to give 57 mg (80% yield) of (1*S*,2*R*)-**110**. $[\alpha]^{22}_D$ =+21.2 (0.4, $CHCl_3$); ^{1}H NMR δ 5.02 (d, *J* = 10.6 Hz, 1H), 4.26 (q, *J* = 6.8 Hz, 2H), 2.01–1.54 (m, 8H), 1.31 (t, *J* = 6.8 Hz, 3H), 1.26 (s, 9H); ^{13}C NMR δ 177.0, 172.6, 79.5, 79.1, 62.2, 38.9, 31.8, 28.5, 27.5, 22.8, 19.5, 14.4; MS (ESI, MeOH): m/z = 273.1 ($[M + H]^+$). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{14}H_{25}O_5^+$: 273.1702, found: 273.1700.

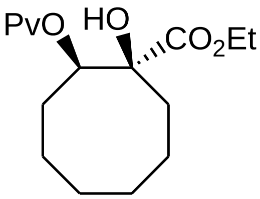
(*1S,2R*)-Ethyl 1-hydroxy-2-(pivaloyloxy)cycloheptanecarboxylate (111) (BH9-057)



(1*S*,2*R*)-**111**

To a solution of 80 mg (0.396 mmol) of (1*S*,2*R*)-**83** in 3 mL of CH_2Cl_2 under argon were added 48 mg (0.396 mmol) of pivaloyl chloride and 31.3 mg (0.396 mmol) of pyridine. The solution was stirred for 15 hours, acidified with 1*N* HCl to pH 5, and extracted twice with 20 mL each of CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as an eluent to give 39 mg (34% yield) of (1*S*,2*R*)-**111** and 42 mg (52% recovery) of (1*S*,2*R*)-**83**. $[\alpha]^{22}_D$ = +14.6 (0.5, $CHCl_3$); ^{1}H NMR δ 5.04 (d, *J* = 10.6 Hz, 1H), 4.26 (q, *J* = 6.8 Hz, 2H), 3.49 (bs, 1H), 1.92–1.42 (m, 10H), 1.31 (t, *J* = 6.8 Hz, 3H), 1.26 (s, 9H); ^{13}C NMR δ 176.9, 172.6, 79.4, 79.3, 62.2, 38.7, 32.1, 28.9, 27.3, 26.4, 24.7, 21.1, 14.2; MS (ESI, MeOH): m/z = 287.1 ($[M + H]^+$). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{15}H_{27}O_5^+$: 287.1859, found: 287.1864.

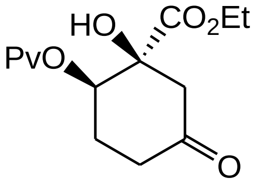
(*1S,2R*)-Ethyl 1-hydroxy-2-(pivaloyloxy)cyclooctanecarboxylate (112) (BH10-141)



(1*S*,2*R*)-**112**

To a solution of 40 mg (0.185 mmol) of (1*S*,2*R*)-**84** in 2 mL of CH_2Cl_2 under argon were added 22 mg (0.185 mmol) of pivaloyl chloride and 14.6 mg (0.185 mmol) of pyridine. The solution was stirred for 10 hours, acidified with 1*N* HCl to pH 5, and extracted twice with 20 mL each of CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as an eluent to give 51 mgheld) of (1*S*,2*R*)-**112**. $[\alpha]^{22}_{D}$ = +67.3 (0.2, $CHCl_3$); ^{1}H NMR δ 5.04 (d, *J* = 10.6 Hz, 1H), 4.23 (q, *J* = 6.8 Hz, 2H), 2.78 (bs, 1H), 1.86–1.44 (m, 12H), 1.31 (t, *J* = 6.8 Hz, 3H), 1.26 (s, 9H); ^{13}C NMR δ 176.5, 172.2, 79.5, 79.0, 62.2, 39.1, 31.8, 30.0, 29.3, 28.5, 25.5, 22.9, 17.1, 14.4; MS (ESI, MeOH): m/z = 315.7 ($[M + H]^+$). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{16}H_{29}O_5^+$: 315.2015, found: 315.2017.

(*1S,2R*)-Ethyl 1-hydroxy-5-oxo-2-(pivaloyloxy)cyclohexanecarboxylate (113) (BH11-023)

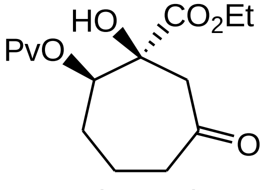


(1*S*,2*R*)-**113**

To an aqueous solution of 6 mL of Cu/Au (3:1)-**26** (2.05 μmol of Cu, 0.69 μmol of Au, and 0.075 μmol of **26**), were added 1 mL of 30% H_2O_2, 2 mL of CH_3CN and 15 mg (0.055 mmol) of (*1S*,*2R*)-**110**. The resulting solution was stirred at 50°C for 6 days, cooled to 25°C, and extracted three times with 20 mL each of methylene chloride. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 13.1 mg (83%

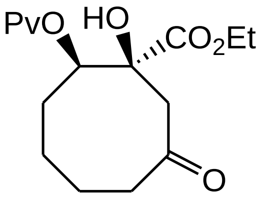
yield) of (*1S,2S*)-**113** and recover 1.1 mg (7.2% yield) of (*1S*,*2R*)-**110**. $[\alpha]^{22}_{D}$ = +61.3 (0.5, $CHCl_3$); ^1H NMR δ 4.25 (q, *J* = 6.8 Hz, 2H, CH_2O), 3.62 – 3.60 (m, 1H, CHOPv), 2.71 (dd, *J* = 7.2, 1.6 Hz, 1H, CHC=O), 2.59 (dd, *J* = 7.2, 1.6 Hz, 1H, CHC=O), 2.40 – 2.32 (m, 1H), 2.28–2.22 (m, 1H), 2.04 – 2.00 (m, 2H), 1.51 (s, 9H), 1.31 (t, *J* = 6.8 Hz, 3H); The proton NMR assignments were derived from 2D COSY spectrum; ^{13}C NMR δ 211.4, 176.9, 174.3, 80.6, 79.3, 62.2, 47.5, 38.8, 33.2, 26.4, 21.4, 14.4; MS (ESI, MeOH): m/z = 309.4 ($[M + H]^+$); HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{14}H_{23}O_6^+$: 287.1495, found: 287.1501.

(*1S,2R*)-Ethyl 1-hydroxy-6-oxo-2-(pivaloyloxy)cycloheptanecarboxylate (114) (BH9-059)


(1*S*,2*R*)-**114**

To an aqueous solution of 6 mL of Cu/Au (3:1)-**26** (2.50 μmol of Cu, 0.83 μmol of Au, and 0.09 μmol of **26**), were added 1 mL of 30% H_2O_2, 2 mL of CH_3CN and 20 mg (0.066 mmol) of (*1S*,*2R*)-**111**. The resulting solution was stirred at 50°C for 7 days, cooled to 25°C, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 18.3 mg (87.5% yield) of (*1S*,*2S*)-**113** and recover 1.3 mg (6.5% yield) of (*1S*,*2R*)-**111**. $[\alpha]^{22}_{D}$ = +16.4 (0.5, $CHCl_3$); ^1H NMR δ 4.25 (q, *J* = 6.8 Hz, 2H, CH_2O), 3.82 – 3.83 (m, 1H, CHOPv), 2.81 (d, *J* = 7.2 Hz, 1H, CHC=O), 2.60 (d, *J* = 7.2, 1.6 Hz, 1H, CHC=O), 2.37 – 2.35 (m, 2H), 1.96 – 1.62 (m, 4H), 1.51 (s, 9H), 1.31 (t, *J* = 6.8 Hz, 3H); The proton NMR assignments were derived from 2D COSY spectrum; ^{13}C NMR δ 210.4, 176.9, 173.1, 80.2, 79.3, 62.1, 46.5, 43.5, 38.7, 27.4, 26.5 21.2, 14.0; MS (ESI, MeOH): m/z = 323.4 ($[M + Na]^+$). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{15}H_{25}O_6^+$: 301.1651, found: 301.1651.

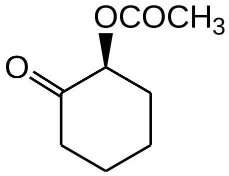
(*1S,2R*)-Ethyl 1-hydroxy-7-oxo-2-(pivaloyloxy)cyclooctanecarboxylate (115) (BH11-025)



(1*S*,2*R*)-**115**

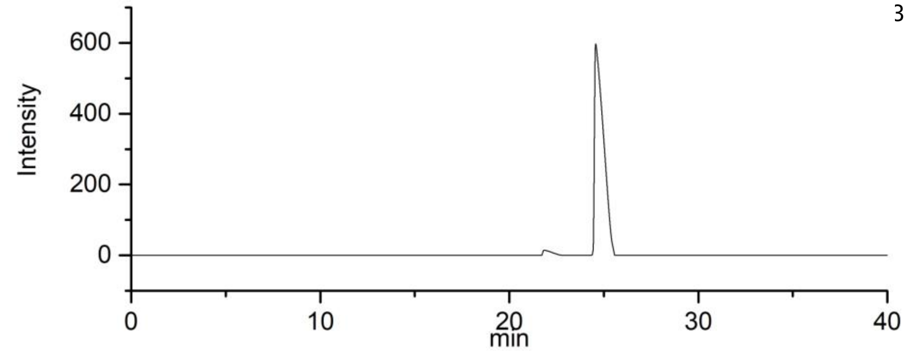
To an aqueous solution of 6 mL of Cu/Au (3:1)-**26** (1.9 μmol of Cu, 0.63 μmol of Au, and 0.069 μmol of **26**), were added 1 mL of 30% H_2O_2, 2 mL of CH_3CN and 15 mg (0.05 mmol) of (*1S,2R*)-**112**. The resulting solution was stirred at 50°C for 7 days, cooled to 25°C, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 14.1 mg (90% yield) of (*1S,2S*)-**115**. $[\alpha]^{22}_{D}$ = +21.7 (0.7, $CHCl_3$); ^{1}H NMR δ 4.40 (bs, 1H, OH), 4.24 (q, *J* = 6.8 Hz, 2H, CH_2O), 3.76 – 3.74 (m, 1H), 2.73 (dd, *J* = 7.2, 1.6 Hz, 1H), 2.61 (dd, *J* = 7.2, 1.2 Hz, 1H), 2.46–2.23 (m, 3H), 2.10–1.96 (m, 2H), 1.76-1.72 (m, 3H), 1.51 (s, 9H), 1.31 (t, *J* = 6.8 Hz, 3H); The proton NMR assignments were derived from 2D COSY spectrum; ^{13}C NMR δ 210.2, 176.9, 172.9, 80.6, 79.1, 62.1, 41.6, 40.6, 38.7, 33.5, 27.4, 24.7, 21.2, 14.3; MS (ESI, MeOH): m/z = 337.7 ($[M + Na]^+$); HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{16}H_{27}O_6^+$: 315.1808, found: 315.1807.

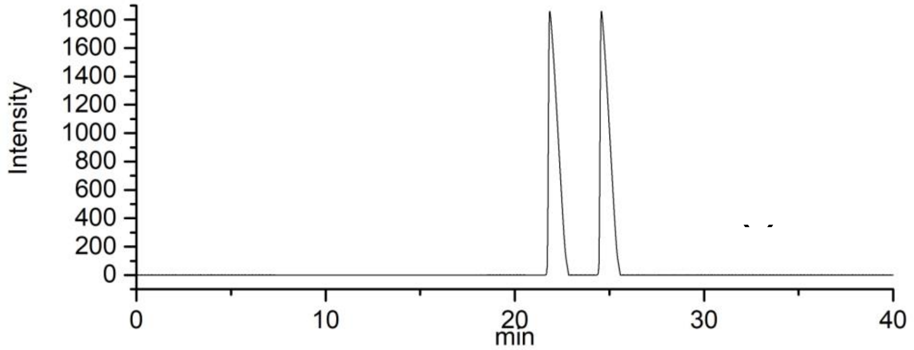
(*S*)-2-Oxocyclohexyl acetate (121) (BH10-135)



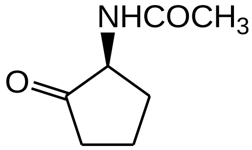
(*S*)-**121**

To an aqueous solution of 5 mL of Cu/Au (3:1)-**26** (7.0 μmol of Cu, 2.3 μmol of Au, and 0.132 μmol of **26**), were added 1 mL of 30% H_2O_2, 2 mL of CH_3CN and 30 mg (0.188 mmol) of **116**. The resulting solution was stirred at 50°C for 7 days, cooled to 25°C, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 30.7 mg (94% yield) of (*S*)-**121**. $[\alpha]_D^{22}$ = -80.4 (c 1.2, MeOH); Lit.[103] $[\alpha]_D^{22}$ = +75.8 (c 1.2, MeOH for 88% *ee* R configuration); ^{1}H NMR : δ5.17 (dd, *J* = 11.2, 6.0 Hz, 1H), 2.35–2.54 (m, 3H), 2.16 (s, 3H), 1.78–1.89 (m, 3H), 1.66-1.76 (m, 2H); ^{13}C NMR : δ = 204.2, 170.3, 76.3, 40.1, 32.7, 26.9, 23.2, 20.1; MS (ESI, MeOH): m/z = 179.5 ($[M + Na]^+$); The % *ee* (94%) of (*S*)-**121** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 95:5, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 21.9 min (*R* enantiomer, minor), t_R = 25.0 min (*S* enantiomer, major).



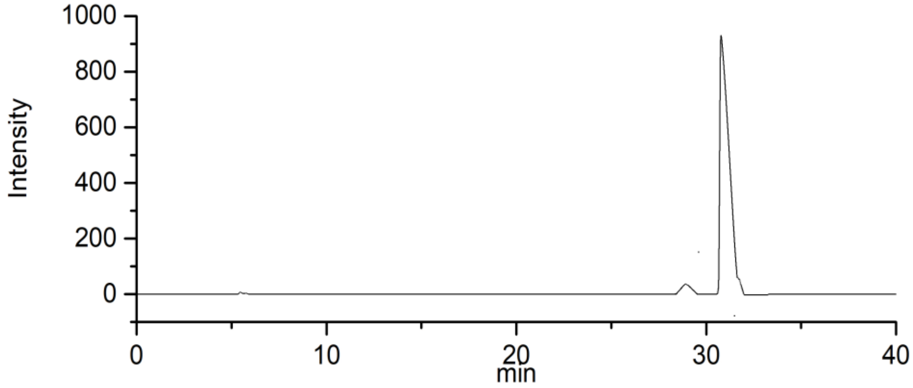


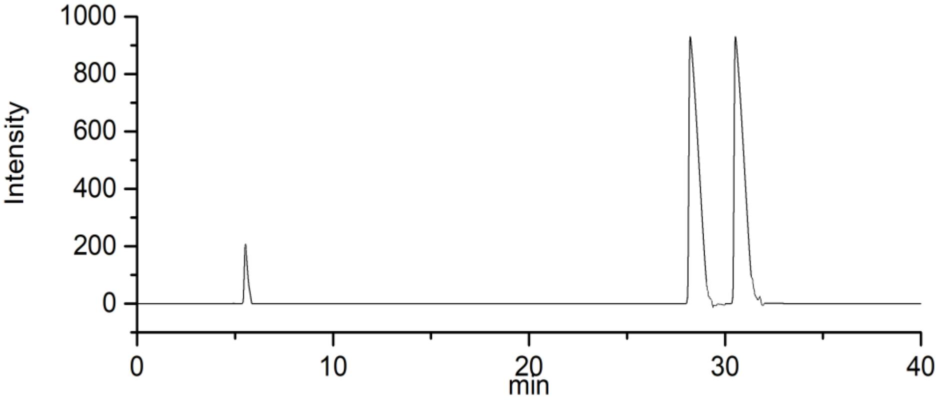
(*S*)-*N*-(2-Oxocyclopentyl)acetamide (122) (BH12-095)



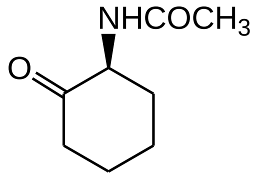
(*S*)-**122**

To an aqueous solution of 6 mL of Cu/Au (3:1)-**26** (6.7 μmol of Cu, 2.2 μmol of Au, and 0.132 μmol of **26**), were added 0.5 mL of 30% H_2O_2, 2 mL of CH_3CN and 22.5 mg (0.178 mmol) of **117**. The resulting solution was stirred at 50^{o}C for 7 days, cooled to 25^{o}C, and extracted three times with 10 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 17.5 mg (76% yield) of (*S*)-**122** and recover 3.8 mg (16.9% yield) of **117**. $[\alpha]_D^{22}$ = -41.6 (c 0.2, $CHCl_3$); ^{1}H NMR δ 4.62–4.51 (m, 1H), 4.11 (bs, 1H, NH), 2.68–2.48 (m, 2H), 2.10 (s, 3H), 2.04–1.75 (m, 4H); ^{13}C NMR δ 210.2, 170.5, 60.5, 32.3, 23.3, 14.2, 12.9; HRMS-ESI: m/z [M + H]+ calcd for $C_7H_{12}NO_2^+$: 142.0868, found: 142.0861. The % ee (92%) of (*S*)-**122** was determined by HPCL using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/i-PrOH = 95:5, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 28.6 min (R enantiomer, minor), t_R = 31.0 min (S enantiomer, major).



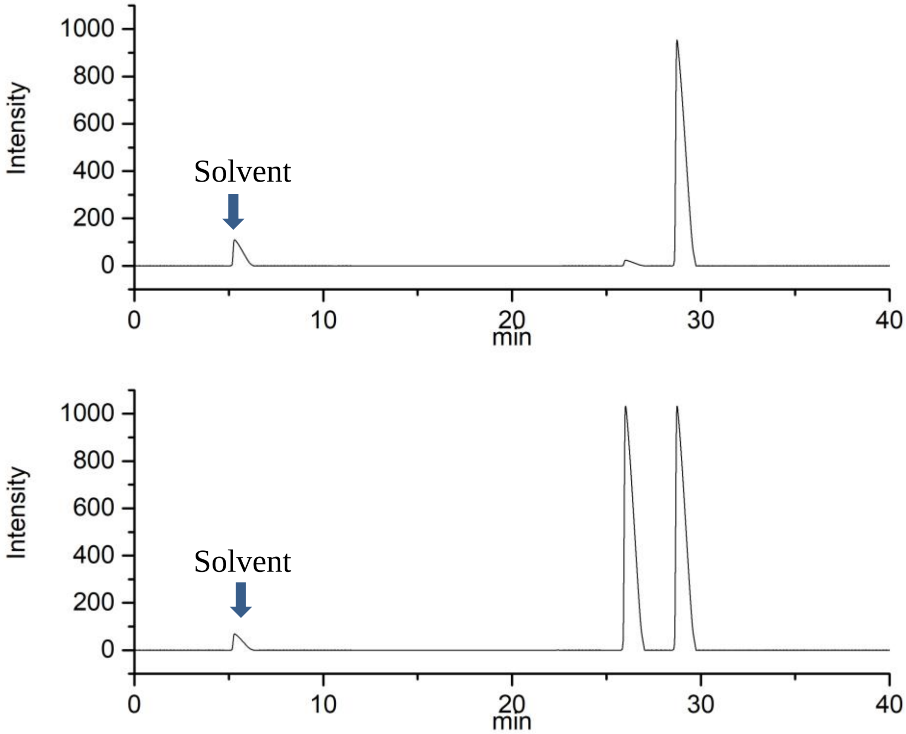


(*S*)-*N*-(2-Oxocyclohexyl)acetamide (123) (BH10-099)

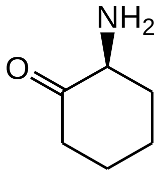


(*S*)-**123**

To an aqueous solution of 6 mL of Cu/Au (3:1)-**26** (13.4 μmol of Cu, 4.5 μmol of Au, and 0.263 μmol of **26**), were added 1 mL of 30% H_2O_2, 4 mL of CH_3CN and 50 mg (0.357 mmol) of **118**. The resulting solution was stirred at 50°C for 7 days, cooled to 25°C, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 39.2 mg (72% yield) of (*S*)-**123** and recover 8.6 mg (17.2% yield) of **118**. $[\alpha]_D^{22}$ = -62.4 (c 0.5, $CHCl_3$); ^1H NMR[104] δ 5.90 (bs, 1H, NH), 4.51-4.44 (m, 1H), 2.70–2.35 (m, 3H), 2.19-2.11 (m, 1H), 2.02 (s, 3H), 1.95- 1.79 (m, 2H), 1.75-1.66 (m, 1H), 1.35-1.26 (m, 1H); ^{13}C NMR δ 209.9, 171.4, 60.0, 43.0, 37.4, 30.0, 25.4, 25.0; The % *ee* (93%) of (*S*)-**123** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 95:5, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 26.1 min (*R* enantiomer, minor), t_R = 29.5 min (*S* enantiomer, major).



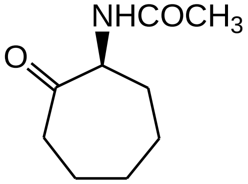
(*S*)-2-Aminocyclohexanone (132) (BH10-133)



(S)-**132**

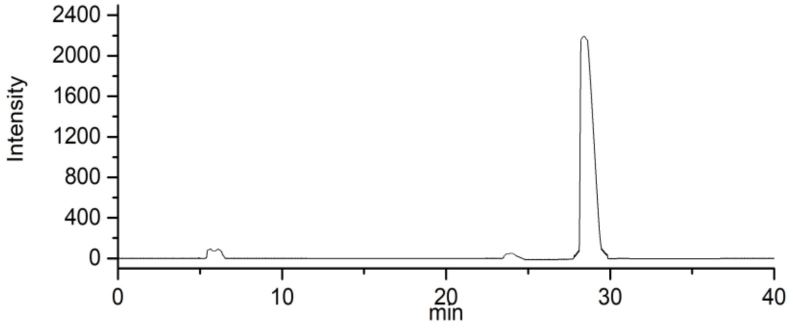
A solution of 15.5 mg (0.1 mmol) of **123** in 1 mL of hydrazine was heated to 70 °C under argon for 12 hours until no starting material remaining. The resulting solution was purified by column chromatography on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 11.4 mg (99% yield) of (*S*)-**132**. $[\alpha]_D^{22}$ = -71.3 (c 0.5, $CHCl_3$) Lit.[103] $[\alpha]_D^{22}$ = +68.1 (c 0.5, $CHCl_3$ for *R* configuration); ^{1}H NMR : δ 3.35–3.27 (m, 1H), 2.40–2.12 (m, 3H), 1.96–1.50 (m, 5H); ^{13}C NMR : δ209.3, 57.7, 38.7, 27.6, 26.7, 20.8; MS (ESI, MeOH): m/z = 114 ($[M + H]^+$).

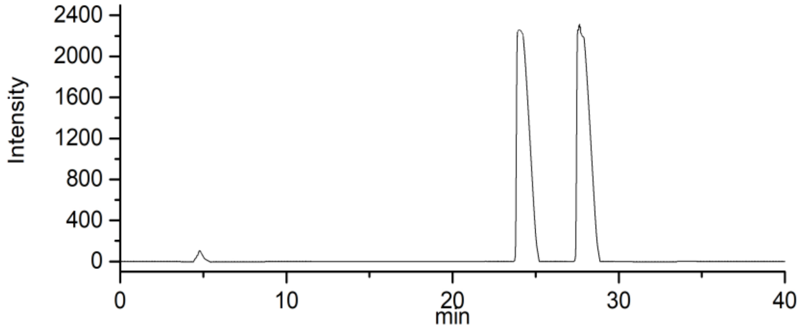
(*S*)-*N*-(2-Oxocycloheptyl)acetamide (124) (BH12-097)



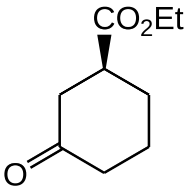
(*S*)-**124**

To an aqueous solution of 3 mL of Cu/Au (3:1)-**26** (6.7 μmol of Cu, 2.2 μmol of Au, and 0.132 μmol of **26**), were added 0.5 mL of 30% H_2O_2, 2 mL of CH_3CN and 27.5 mg (0.178 mmol) of **119**. The resulting solution was stirred at 50°C for 7 days, cooled to 25°C, and extracted three times with 10 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 25.6 mg (84% yield) of (*S*)-**124** and recover 2 mg (7.3% yield) of **119**. $[\alpha]_D^{22}$ = -127.2 (c 0.2, $CHCl_3$); ^{1}H NMR[104] : δ 6.25 (br, 1H), 4.69-4.59 (m, 1H), 2.71–2.41 (m, 2H), 2.14-2.05 (m, 1H), 2.02 (s, 3H), 1.95-1.67 (m, 5H), 1.50-1.41 (m, 1H), 1.35-1.25 (m, 1H); ^{13}C NMR δ 210.4, 169.5, 59.0, 41.6, 32.9, 29.1, 27.6, 23.4, 23.2. The % ee (93%) of (*S*)-**124** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/i-PrOH = 95:5, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 24.2 min (R enantiomer, minor), t_R = 28.0 min (S enantiomer, major).



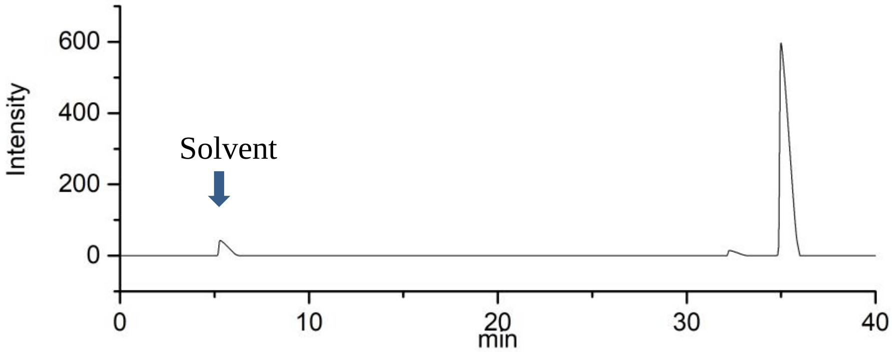


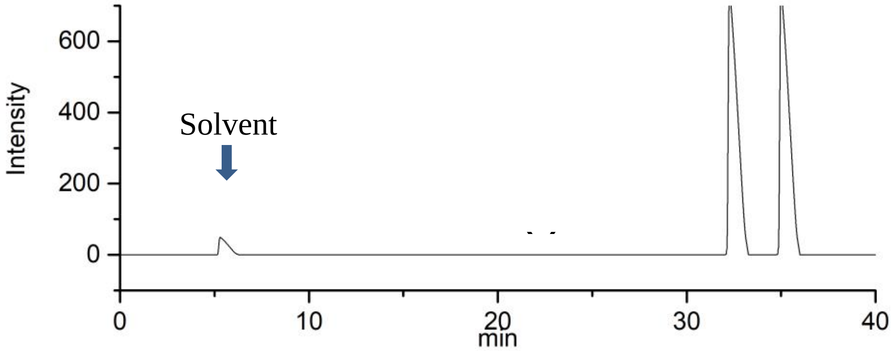
(*S*)-Ethyl 3-oxocyclohexanecarboxylate (125) (BH10-122)



(*S*)-**125**

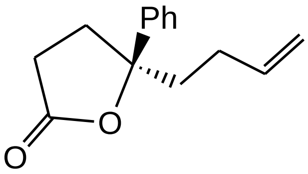
To an aqueous solution of 8 mL of Cu/Au (3:1)-**26** (20.5 μmol of Cu, 6.8 μmol of Au, and 0.383 μmol of **26**), were added 1 mL of 30% H_2O_2, 3 mL of CH_3CN and 80 mg (0.548 mmol) of **120**. The resulting solution was stirred at 50°C for 7 days, cooled to 25°C, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 76.9 mg (88% yield) of (*S*)-**125**. $[\alpha]_D^{22}$ = +2.62 (c 1.61, MeOH) Lit.[105] $[\alpha]_D^{22}$ = +2.7 (c 1.6, MeOH, 96% *ee*) The % *ee* (93%) of (*S*)-**46** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 95:5, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 32.4 min (*R* enantiomer, minor), t_R = 35.2 min (*S* enantiomer, major); ^{1}H NMR : δ 4.15 (q, *J* = 7.2 Hz, 2H), 3.79–3.77 (m, 1H), 2.60–2.58 (m, 2H), 2.78–2.25 (m, 2H), 2.14–2.05 (m, 2H), 1.89–1.78 (m, 2H), 1.25 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 209.3, 173.7, 61.1, 43.2, 43.1, 40.9, 27.6, 24.3, 14.3; MS (ESI, MeOH): m/z = 193.2 ($[M + Na]^+$).





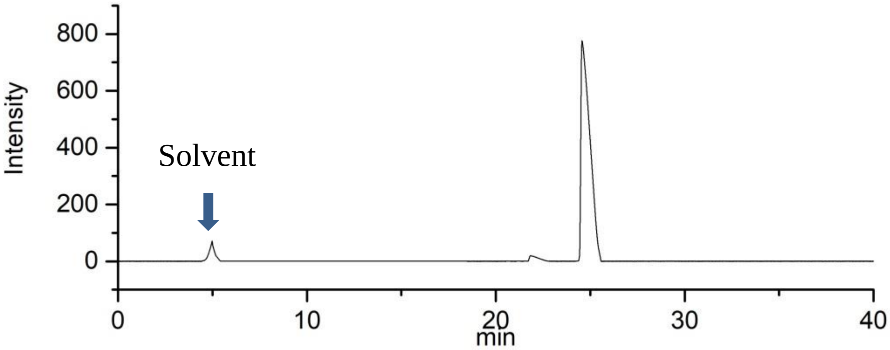
2.6.6 Procedures and Analysis Results for Oxidative Ring Closing Reaction of Dienes.

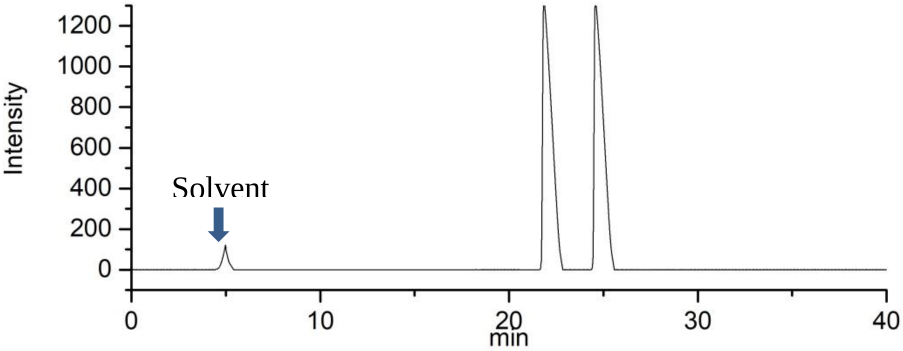
(*S*)-5-(3-Butenyl)-5-phenyl-dihydrofuran-2(3H)-one (200) (BH10-021)



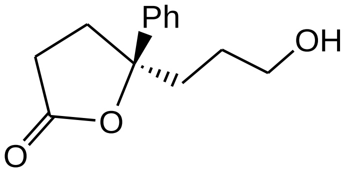
(S)-200

To an aqueous solution of 3 mL of Cu/Au (3:1)-**26** (3.7 μmol of Cu, 1.2 μmol of Au, and 0.13 μmol of **26**), were added 1 mL of 30% H_2O_2, 2 mL of CH_3CN and 25 mg (0.116 mmol) of 5-phenylnona-1,8-dien-5-ol (**195**). The resulting solution was stirred at 50°C for 3 days, cooled to 25°C, and extracted three times with 10 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 35.3 mg (71% yield) of **(S)-200** in 96% ee. $[\alpha]_D^{22}$ = -14.6 (0.3, $CHCl_3$); ^{1}H NMR δ 7.39–7.22 (m, 5H), 5.84–5.74 (m, 1H), 4.95 (d, *J* = 16.4 Hz, 1H), 4.92 (d, *J* = 9.6 Hz, 1H), 2.53 (m, 2H), 2.14–1.79 (m, 6H); ^{13}C NMR δ 175.2, 142.3, 138.9, 127.2, 126.2, 125.1, 115.4, 92.2, 40.1, 34.4, 32.2, 28.1; MS (ESI, MeOH): m/z = 217.1 ($[M + H]^+$); HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{14}H_{17}O_2^+$: 217.1229, found: 217.1227. The % *ee* (96%) of (*S*)-**200** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 95:5, flow rate 0.5 mL/min, detected at 254 nm wavelength; t_R = 22.2 min (*R* enantiomer, minor), t_R = 25.0 min (*S* enantiomer, major).





(S)-5-(3-Hydroxypropyl)-5-phenyl-dihydrofuran-2(3H)-one (211) (BH11-056)

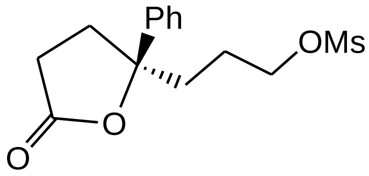


(*S*)-211

To 6 mL of methylene chloride, ozone was bubbled into it under -78 ^{o}C for 3 minutes and gave a blue solution. To it, 19 mg of **200** (0.0879 mmol) was added and stir for 5 minutes under -78 ^{o}C until no starting material remaining. After the ozone evaporates, 6.7 mg (0.176 mmol) of $NaBH_4$ was added, the mixture was warmed up to room temperature and stirred for 1 hour under Ar. The reaction was quenched by 2 mL of sat. NH_4Cl solution and extracted three times with 20 mL each of methylene chloride. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 13 mg (67% yield) of **211**. $[\alpha]_D^{22}$ = -143.1

(0.05, $CHCl_3$); ^1H NMR δ 7.32–7.20 (m, 5H), 3.79 (t, *J* = 8.8 Hz, 1H), 2.25–2.19 (m, 2H), 2.10–1.52 (m, 7H); ^{13}C NMR δ 175.1, 142.3, 127.2, 126.2, 125.1, 92.2, 34.3, 33.0, 28.6, 28.0; MS (ESI, MeOH): m/z = 243.4 ($[M + Na]^+$).

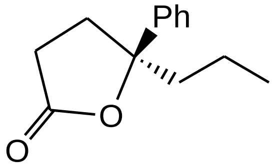
(S)-3-(5-Oxo-2-phenyl-tetrahydrofuran-2-yl)propyl methanesulfonate (212) (BH11-062)



(*S*)-212

To a mixture of **211** (13 mg, 0.059 mmol) and dry triethylamine (6.6 mg, 0.065 mmol) in 1 mL of dry dichloromethane under argon, methanesulfonyl chloride (15.4 mg, 0.135 mmol) was added dropwise at 0°C. The reaction mixture was stirred for 8 hours at room temperature, quenched with 0.5 mL of water and extracted with methylene chloride (3 x 10 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum to give 17 mg (96.5% yield) **212**. The residue was used in the subsequent step without further purification. ^1H NMR δ 7.32–7.20 (m, 5H), 4.13–4.02 (m, 2H), 2.95 (s, 3H), 2.25–2.19 (m, 2H), 2.07–1.52 (m, 6H); ^{13}C NMR δ 175.4, 142.3, 127.1, 125.7, 124.6, 91.9, 71.7, 35.7, 32.9, 27.66, 26.8, 21.6; MS (ESI, MeOH): m/z = 299.1 ($[M + H]^+$).

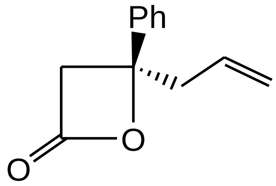
(S)-5-Phenyl-5-propyl-dihydrofuran-2(3H)-one (213) (BH11-063)



(*S*)-213

To a mixture of **212** (17 mg, 0.057 mmol) and *t*-BuOH (21 mg, 0.285 mmol) in 1 mL 1,2-dimethoxyethane, $NaBH_4$ (6.4 mg, 0.171 mmol) was added at 0°C. The reaction solution was stirred for 30 minutes at room temperature, heated to reflux overnight, quenched with 15 mL of water and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 8.4 mg (72% yield) **213**. $[\alpha]_D^{22}$ = -42.1 (c 0.02, MeOH), Lit.[118] -33.0 (c 0.01, MeOH for (S)-**58C** with 74%ee); ^{1}H NMR δ 7.32–7.20 (m, 5H), 2.55–2.33 (m, 4H), 1.91–1.81 (m, 2H), 1.34–1.25 (m, 1H) 1.08–1.01 (m, 1H), 0.79 (t, J = 7.2 Hz); ^{13}C NMR δ 177.3, 143.5, 128.7, 127.7, 125.0, 90.0, 45.1, 35.5, 29.1, 17.6, 14.3; MS (ESI, MeOH): m/z = 205.3 ([M + H]$^+$).

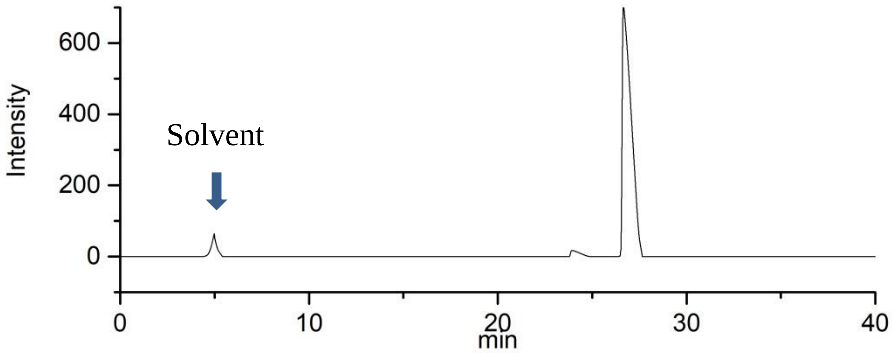
(*S*)-4-Allyl-4-phenyloxetan-2-one (201) (BH10-053)

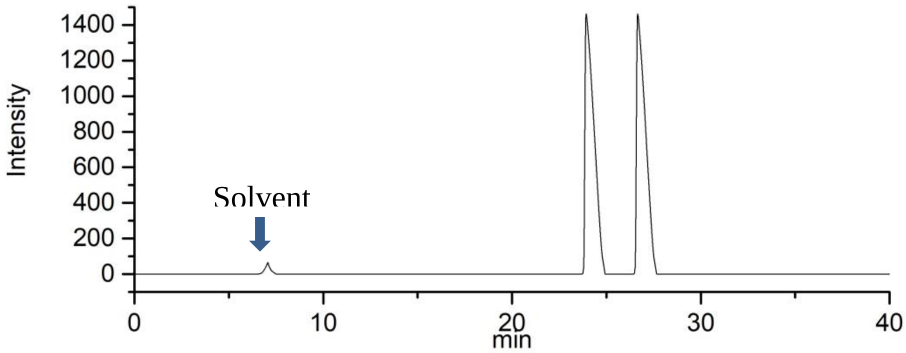


(S)-201

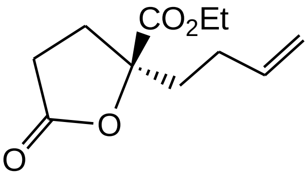
To an aqueous solution of 3 mL of Cu/Au (3:1)-**26** (3.9 μmol of Cu, 1.3 μmol of Au, and 0.073 μmol of **26**), were added 1 mL of 30% H_2O_2, 8 mL of CH_3CN 15 mL of water and 25 mg (0.133 mmol) of 4-phenylhepta-1,6-dien-4-ol (**196**). The resulting solution was heated to 60°C for 6 days, cooled to 25°C, and extracted three times with 10 mL each of methylene chloride. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 10.9 mg (44% yield) of **(S)-201** in 92% ee and 7.3 mg (29% recovery) of **196**. $[\alpha]_D^{22}$ = -16.8 (0.2, $CHCl_3$); ^{1}H NMR δ 7.43–7.22 (m, 5H), 5.66–5.56 (m, 1H), 5.06 (d, *J* = 12 Hz, 1H), 4.98 (d, *J* = 4.8 Hz, 1H), 3.70 (d, *J* = 12.8 Hz, 1H), 3.48 (d, *J* = 12.8 Hz, 1H), 2.70 (dd, *J* = 14, 6.4 Hz, 1H), 2.52 (dd, *J* = 14, 6.4 Hz, 1H); ^{13}C NMR δ 174.9, 142.9, 138.9, 127.3, 126.3, 125.2, 115.5, 92.8, 43.7, 37.6; MS (ESI, MeOH): m/z = 189.1 ([M + H]$^+$); HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{12}H_{13}O_2^+$: 189.0916, found: 189.0918.

The % *ee* (92%) of (*S*)-**201** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 95:5, flow rate 0.5 mL/min, detected at 254 nm wavelength; t_R = 24.3 min (*R* enantiomer, minor), t_R = 27.0 min (*S* enantiomer, major).



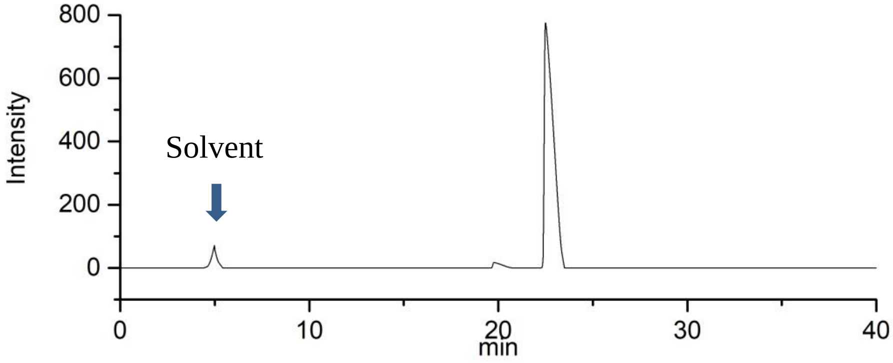


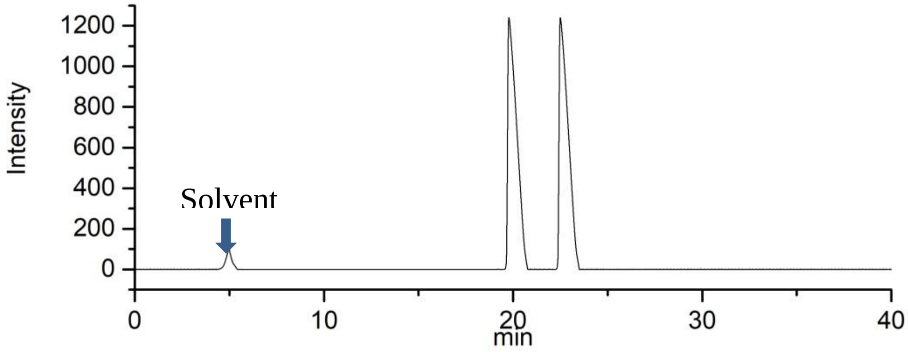
(S)-Ethyl 2-(but-3-enyl)-5-oxo-tetrahydrofuran-2-carboxylate (202). (BH11-051)



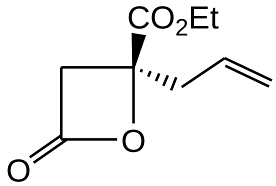
(S)-202

To an aqueous solution of 5 mL of Cu/Au (3:1)-**26** (2.9 µmol of Cu, 1.0 µmol of Au, and 0.11 µmol of **26**), were added 1 mL of 30% H_2O_2, 5 mL of CH_3CN and 20 mg (0.095 mmol) of ethyl 2-(but-3-enyl)-2-hydroxyhex-5-enoate (**197**). The resulting solution was heated to 50 ^oC for 3 days, and extracted three times with 10 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 16.7 mg (84% yield) of **(S)-202** in 93% ee and recovered 0.6 mg (3% yield). $[\alpha]_D^{22}$ = +35.7 (0.4, $CHCl_3$); ^{1}H NMR δ 5.85 – 5.75 (m, 1H), 5.03 (d, *J* = 17.2 Hz, 1H), 4.98 (dd, *J* = 12, 6 Hz, 1H), 4.21 (q, *J* = 6.8 Hz, 2H), 2.59 (m, *J* = 9.2, 6.4 Hz, 2H), 2.25–1.63 (m, 6H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 177.4, 174.9, 138.9, 115.4, 97.6, 61.5, 40.1, 34.4, 30.2, 23.8, 14.9; MS (ESI, MeOH): m/z = 234.0 ($[M + Na]^+$). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{11}H_{17}O_4^+$: 213.1127, found: 213.1127. The % *ee* (93%) of (*S*)-**202** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 90:10, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 20.0 min (*R* enantiomer, minor), t_R = 23.1 min (*S* enantiomer, major).



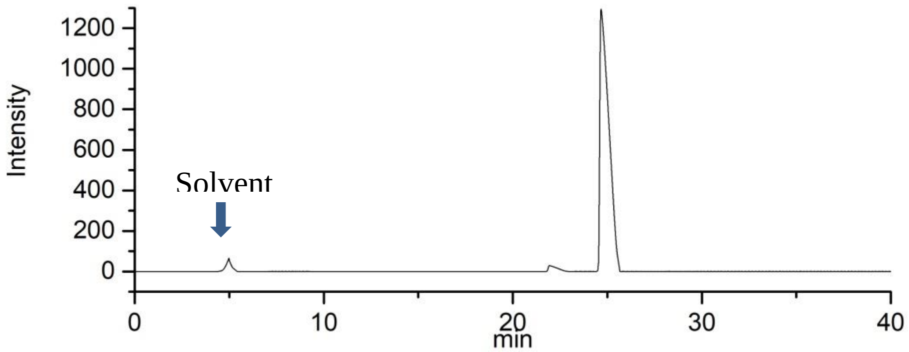


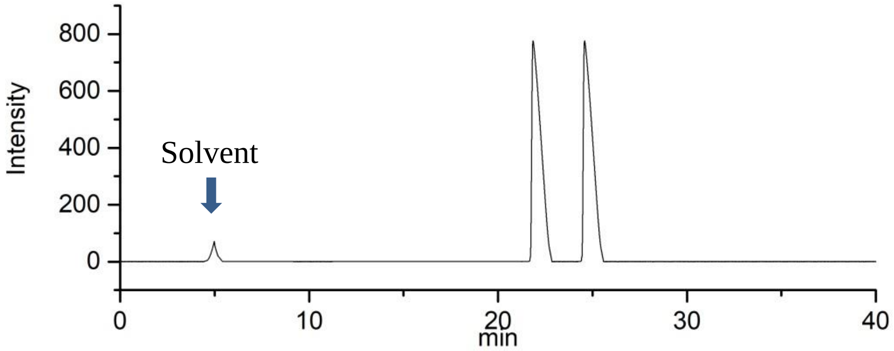
(S)-Ethyl 2-allyl-4-oxooxetane-2-carboxylate (203) (BH11-013)



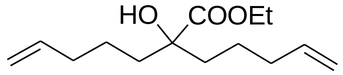
(S)-203

To an aqueous solution of 3 mL of Cu/Au (3:1)-**26** (3.4 μmol of Cu, 1.4 μmol of Au, and 0.13 μmol of **26**), were added 2 mL of 30% H_2O_2, 3 mL of CH_3CN and 20 mg (0.115 mmol) of ethyl 2-allyl-2-hydroxypent-4-enoate (**198**). The resulting solution was stirred to 50°C for 7 days, and extracted three times with 15 mL each of methylene chloride. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 6.2 mg (33% yield) of **(S)-203** in 93% ee and 1 mg (5% recovery) of **198**. $[\alpha]_D^{22}$ = +28.9 (0.3, $CHCl_3$); ^{1}H NMR δ 5.83 – 5.73 (m, 1H), 5.11 (d, *J* = 14.4 Hz, 1H), 5.10 (d, *J* = 11.2 Hz, 1H), 4.21 (q, *J* = 6.8 Hz, 2H), 3.70 (d, *J* = 12.8 Hz, 1H), 3.49 (d, *J* = 12.8 Hz, 1H), 2.52–2.40 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 176.9, 173.3, 137.7, 115.3, 86.6, 61.4, 40.2, 25.8, 14.8; MS (ESI, MeOH): m/z = 207.2 ($[M + Na]^+$); HRMS-ESI: m/z $[M + H]^+$ calcd for $C_9H_{13}O_4^+$: 185.0814, found: 185.0811. The % *ee* (93%) of (*S*)-**203** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 90:10, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 22.3 min (*R* enantiomer, minor), t_R = 25.1 min (*S* enantiomer, major).





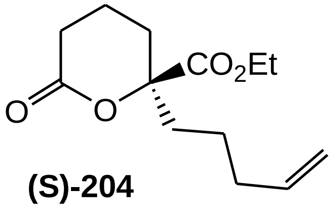
Ethyl 2-hydroxy-2-(pent-4-enyl)hept-6-enoate.(199) (BH11-045)



199

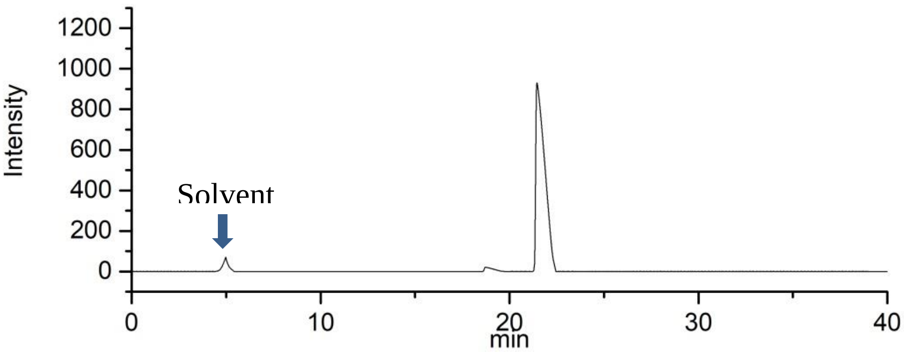
To a suspension of 70.88 mg (2.95 mmol) Mg in 5 mL anhydrous THF, 100 mg (0.671 mmol) of 5-bromopent-1-ene was added and heated with heat gun to initiate the reaction. To it, 300 mg (2.031 mmol) of 5-bromopent-1-ene was added and heated to 50 ^{o}C under argon until no Mg remaining. 111.1 mg (1.61 mmol) of diethyl oxalate in 5 mL of anhydrous THF was dropwise cannulated into the Grignard reagent under -78 ^{o}C, stirred at room temperature for 3 hours, quenched with sat. NH_4Cl solution, extracted three times of 30 mL each of methylene chloride and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as an eluent to give 112 mg (35% yield) of the titled compound. ^{1}H NMR δ 5.74 (m, 2H), 4.96 (dd, *J* = 17.2 1.6 Hz, 2H), 4.92 (d, *J* = 9.6 Hz, 2H), 4.14 (q, *J* = 6.8 Hz, 2H), 2.04 – 1.98 (m, 4H), 1.75 – 1.35 (m, 8H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 177.5, 138.4, 114.8, 79.6, 61.0, 43.0, 35.8, 24.2, 14.5; MS (ESI, MeOH): m/z = 267.1 ([M + Na]+).

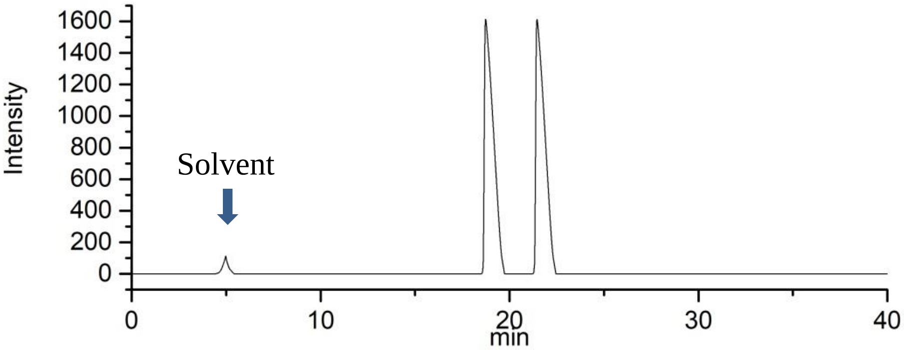
(S)-ethyl 6-oxo-2-(pent-4-enyl)-tetrahydro-2H-pyran-2-carboxylate (204). (BH11-049)



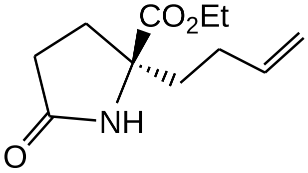
(S)-204

To an aqueous solution of 3 mL of Cu/Au (3:1)-**26** (4.8 μmol of Cu, 1.6 μmol of Au, and 0.17 μmol of **26**), were added 2 mL of 30% H_2O_2, 4 mL of CH_3CN and 40 mg (0.0845 mmol) of ethyl 2-hydroxy-2-(pent-4-enyl)hept-6-enoate (**199**). The resulting solution was heated to 50 ^{o}C for 6 days, and extracted three times with 25 mL each of methylene chloride. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 33 mg (83% yield) of **(S)-204** in 93% ee and recovered 2 mg (6% yield) of **199**. $[\alpha]_D^{22}$ = +17.5 (0.3, $CHCl_3$); ^{1}H NMR δ 5.84–5.74 (m, 1H), 4.95 (d, *J* = 16.4 Hz, 1H), 4.92 (d, *J* = 9.6 Hz, 1H), 4.21 (q, *J* = 6.8 Hz, 2H), 2.50 (t, 8.0 Hz, 2H), 2.18–1.40 (m, 10H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 177.7, 174.7, 138.9, 115.4, 89.0, 61.4, 37.5, 34.4, 32.9, 29.3, 24.9, 23.8, 14.8; MS (ESI, MeOH): m/z = 235.0 ([M + Na]$^+$). HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{13}H_{21}O_4^+$: 241.1440, found: 241.1440. The % *ee* (93%) of (*S*)-**204** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 90:10, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 18.6 min (*R* enantiomer, minor), t_R = 22.0 min (*S* enantiomer, major).





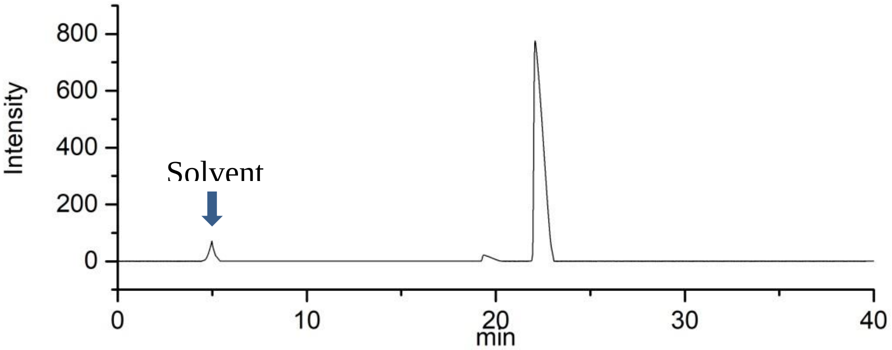
(*S*)-Ethyl 2-(but-3-enyl)-5-oxopyrrolidine-2-carboxylate (208). (BH10-051)

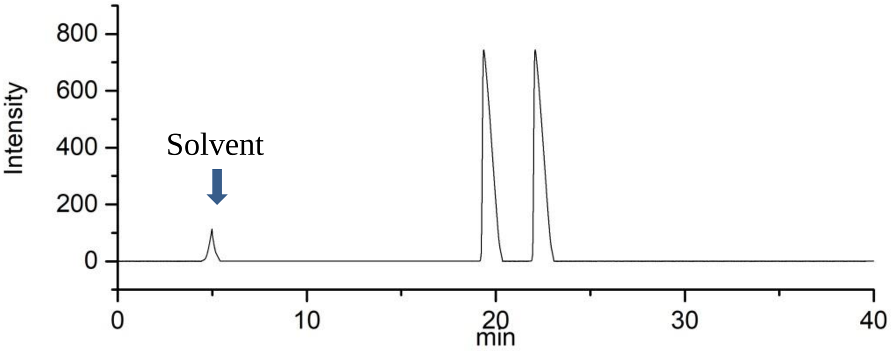


(S)-208

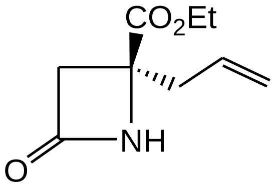
To an aqueous solution of 15 mL of Cu/Au (3:1)-**26** (21.3 μmol of Cu, 7.1 μmol of Au, and 0.7 μmol of **26**), were added 5 mL of 30% H_2O_2, 5 mL of CH_3CN and 150 mg (0.711 mmol) of ethyl 2-amino-2-(but-3-enyl)hex-5-enoate (**205**). The resulting solution was stirred to 50°C for 3 days, cooled to room temperature, and extracted three times with 40 mL each of methylene chloride. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 126 mg (84% yield) of **(S)-208** in 95% ee. $[\alpha]_D^{22}$ = +18.6 (0.2, $CHCl_3$); ^1H NMR δ 8.18 (bs, NH), 5.83–5.71 (m, 1H), 5.10 (d, *J* = 17.2 Hz, 1H), 4.95 (d, *J* =

9.2 Hz, 1H), 4.24 (q, *J* = 6.8 Hz, 2H), 2.62 (t, J = 8.4 Hz, 1H), 2.21–1.64 (m, 6H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 176.9, 173.5, 138.1, 115.3, 61.6, 27.0 ,40.1, 36.7, 33.4, 23.2, 14.8; MS (ESI, MeOH): m/z = 234.6 ([M + Na]$^+$). HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{11}H_{18}NO_3^+$: 212.1287, found: 212.1288. The % *ee* (95%) of (*S*)-**208** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 90:10, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 19.6 min (*R* enantiomer, minor), t_R = 22.2 min (*S* enantiomer, major).



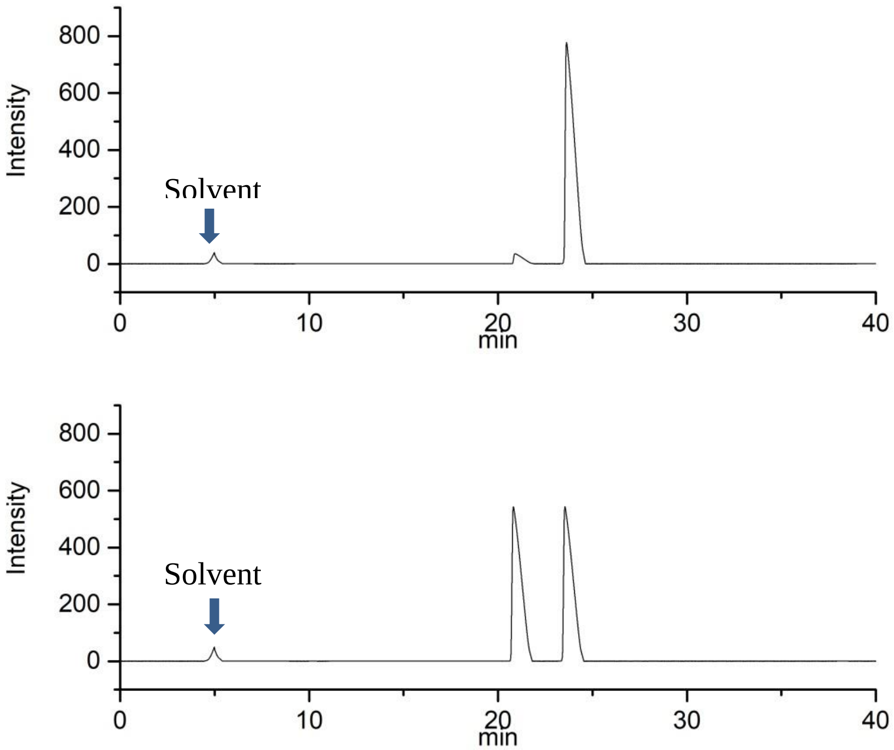


(S)-Ethyl 2-allyl-4-oxoazetidine-2-carboxylate (209). (BH11-060)

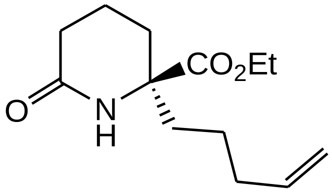


(S)-209

To an aqueous solution of 2 mL of Cu/Au (3:1)-**26** (3.2 μmol of Cu, 1.0 μmol of Au, and 0.06 μmol of **26**), were added 1 mL of 30% H_2O_2, 2 mL of CH_3CN and 20 mg (0.1093 mmol) of ethyl 2-allyl-2-aminopent-4-enoate (**206**). The resulting solution was heated to 50 °C for 7 days, and extracted three times with 20 mL each of methylene chloride. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 12.8 mg (64% yield) of **(S)-209** in 92% ee. $[\alpha]_D^{22}$ = +33.7 (0.2, $CHCl_3$); ^{1}H NMR δ 7.28 (bs, 1H), 5.80–5.70 (m, 1H), 5.16 (d, *J* = 19.2 Hz, 1H), 5.15 (d, *J* = 10.8 Hz, 1H), 4.21 (q, *J* = 6.8 Hz, 2H), 3.21–3.12 (m, 2H), 2.62–2.45 (m, 1H), 2.31–2.28 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 177.0, 173.3, 137.7, 115.3, 61.8, 57.0, 38.4, 24.3, 14.0; MS (ESI, MeOH): m/z = 206.2 ($[M + Na]^+$). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_9H_{14}NO_3^+$: 184.0974, found: 184.0963. The % *ee* (92%) of (*S*)-**209** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 90:10, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 20.9 min (*R* enantiomer, minor), t_R = 24.1 min (*S* enantiomer, major).



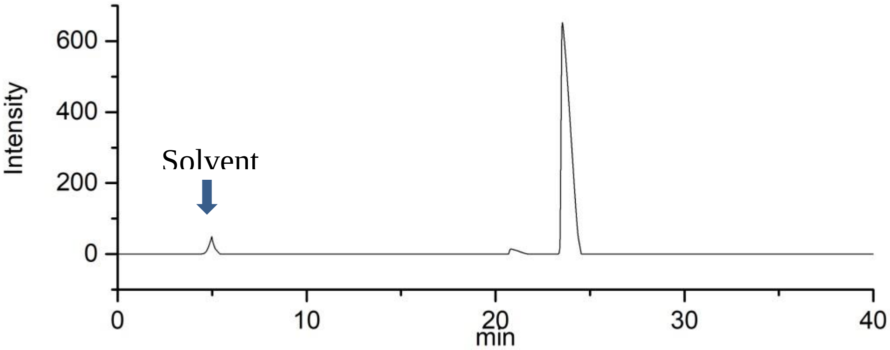
(*S*)-Ethyl 6-oxo-2-(pent-4-enyl)piperidine-2-carboxylate (210) (BH11-037)

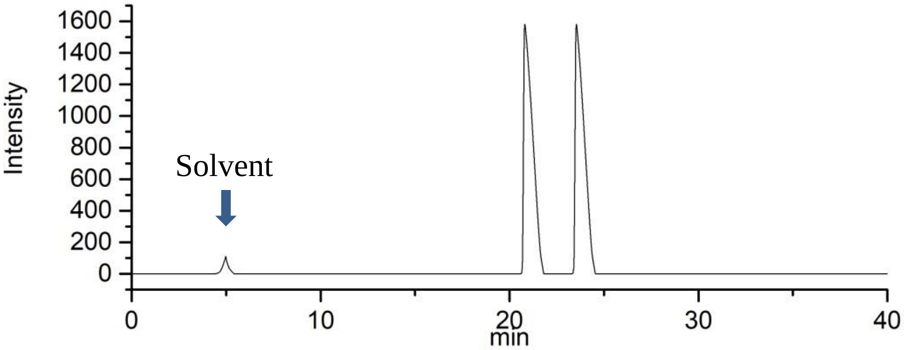


(S)-210

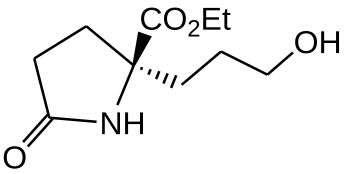
To an aqueous solution of 2 mL of Cu/Au (3:1)-**26** (2.5 μmol of Cu, 0.8 μmol of Au, and 0.046 μmol of **26**), were added 1 mL of 30% H_2O_2, 5 mL of CH_3CN and 20 mg (0.0845 mmol) ethyl 2-amino-2-(pent-4-enyl)hept-6-enoate (**207**). The resulting solution was stirred at 50°C for 5 days, cooled to room temperature, and extracted three times with 15 mL each of methylene chloride. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 18.6 mg (93% yield) of **(*S*)-210** in 94% ee. $[\alpha]_D^{22}$ = +48.7 (0.5,

$CHCl_3$); ^1H NMR δ 5.79 – 5.69 (m, 1H), 4.96 (d, *J* = 17.2 Hz, 1H), 4.92 (d, *J* = 10.0 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.32 (td, *J* = 10.2, 2.4 Hz, 2H) 1.77–1.37 (m, 10H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 177.9, 172.4, 138.9, 116.4, 61.4, 56.5, 39.0, 34.4, 31.1, 27.0, 23.5, 22.8, 14.8; MS (ESI, MeOH): m/z = 262.2 ($[M + Na]^+$). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{13}H_{22}NO_3{}^+$: 240.1660, found: 240.1651. The % *ee* (94%) of (*S*)-**210** was determined by HPLC using chiral column, Chiralpak AD(-H) column [Chiralpak AD(-H) column, size: 0.46 cm x 25 cm, from Daicel Chemical Industries], n-hexane/*i*-PrOH = 90:10, flow rate 0.5 mL/min, detected at 220 nm wavelength; t_R = 21.2 min (*R* enantiomer, minor), t_R = 24.5 min (*S* enantiomer, major).





(S)-Ethyl 2-(3-hydroxypropyl)-5-oxopyrrolidine-2-carboxylate (214) (BH11-019)

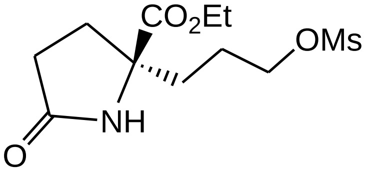


(*S*)-214

To a solution of 12 mL of methylene chloride under argon at -78^{o}C, ozone was bubbled into it for 3 minutes while the argon was turned off, to give a blue solution. To it, 35 mg of **208** (0.167 mmol) was added and stirred for 15 minutes at -78 ^{o}C (until no starting material remaining). The remaining ozone was evaporated by introducing argon into the system for 10 minutes. To it, 12.6 mg (0.33 mmol) of $NaBH_4$ and 0.5 mL of methanol were added, and the solution was warmed up to room temperature and stirred for 1 hour. The reaction was quenched by 2 mL of saturated aqueous NH_4Cl solution and extracted three times with 40 mL each of methylene chloride. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 26.2 mg (75% yield) of **214**. $[\alpha]_D^{22}$ = +31.7 (0.05, $CHCl_3$); ^{1}H NMR δ 4.29 (q, *J* = 7.2 Hz, 2H), 3.53–3.61 (m, 2H), 2.55–2.45 (m, 1H), 2.25–1.62 (m, 8H), 1.32 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 177.0, 173.4, 65.8, 62.6, 61.6, 35.0, 29.6, 27.2, 24.1, 14.8; MS (ESI, MeOH): m/z = 216.3 ($[M + H]^+$).

(*S*)-Ethyl 2-(3-(methylsulfonyloxy)propyl)-5-oxopyrrolidine-2-carboxylate (215)

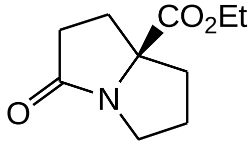
(BH11-021)



(*S*)-215

To a cold (0^{o}C) solution of **214** (26 mg, 0.123 mmol) and triethylamine (13.6 mg, 0.135 mmol) in 2 mL of dichloromethane under argon was added methanesulfonyl chloride (15.4 mg, 0.135 mmol) dropwise. The reaction solution was stirred for 8 hours at room temperature, diluted with 0.5 mL of water and extracted with methylene chloride (3 x 10 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator and then under vacuum to give 29 mg (80.4% yield) **215**. The residue was used in the subsequent step without further purification. $[\alpha]_D^{22}$ = +131.6 (0.1, $CHCl_3$); ^{1}H NMR δ 4.22 (q, *J* = 7.2 Hz, 2H), 3.96–3.85 (m, 2H), 2.95 (s, 3H), 2.53–2.45 (m, 1H), 2.22–1.64 (m, 8H), 1.32 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 177.0, 173.4, 70.0, 65.9, 61.6, 37.9, 35.0, 29.9, 26.1, 20.5, 14.9; MS (ESI, MeOH): m/z = 316.3 ($[M + Na]^+$).

(*S*)-Ethyl 3-oxo-hexahydro-1*H*-pyrrolizine-7a-carboxylate (216) (BH11-027)

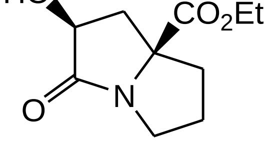


(*S*)-216

To a cold (0°C) solution of 29 mg (0.099 mmol) of **215** in 2 mL distilled THF under argon was added NaH (2.5 mg, 0.104 mmol), and the solution was stirred at room temperature for 3 hour, quenched with 0.5 mL of water, and extracted with methylene chloride (3 x 10 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, concentrated under vacuum, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 16 mg (78% yield) of **216.** $[\alpha]_D^{22}$ = -41.6 (0.05, $CHCl_3$); ^{1}H NMR δ 4.20 (q, *J* = 7.2 Hz, 2H), 3.61–3.48 (m, 2H), 2.55 (dd, *J* = 4.8, 1.2 Hz, 1H), 2.38 (d, *J* = 4.4 Hz, 1H), 2.25–1.80 (m, 6H), 1.30 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 175.4, 173.4, 67.7, 61.6, 43.2, 42.4, 32.2, 27.2, 20.0, 14.8; MS (ESI, MeOH): m/z = 220.1 ($[M + Na]^+$).

(2*S*,7a*S*)-Ethyl 2-hydroxy-3-oxo-hexahydro-1H-pyrrolizine-7a-carboxylate (217)

(BH11-053)

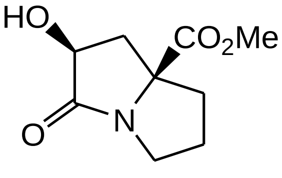


(2*S*,7a*S*)-217

To a cold (-78°C) solution of 0.11 mL (1.05 mmol) of diisopropylamine in 5 mL distilled THF under argon was added 1 mL of *n*-BuLi (1M in hexanes). The resulting solution was warmed up to room temperature and stirred for 1 hour to give a LDA solution. To a cold (-78°C) solution of **216** (19 mg, 0.096 mmol) in 1 mL of distilled THF under argon, 0.6 mL of LDA solution was added dropwise and stirred at room temperature for 30 minutes. To 62.5 mg (0.144 mmol) of MoOPH at -30°C under argon was added the above anion solution via cannula, and the solution was stirred for 40 minutes, warmed to room temperature, diluted with 2 mL of saturated aqueous Na_2SO_3 solution, and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, concentrated to dryness, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 11.7 mg (57% yield) of **(2*S*,7a*S*)-217** and 1.6 mg (7.8% yied) of **(2*R*,7a*S*)-217.** $[\alpha]_D^{22}$ = -8.9 (c 0.88, $CHCl_3$), ^1H NMR δ 5.91 (b, 1H), 4.41 (d, *J* = 6.8, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.64 (d, *J* = 10.0 Hz, 1H), 3.28 (dd, *J* = 10.4, 2.0 Hz, 1H), 2.54 (d, *J* = 12.8 Hz, 1H), 2.32 (d, *J* = 12.8 Hz, 1H), 2.26 (d, *J* = 11.2 Hz, 1H), 2.14-1.98 (m, 2H), 1.62 (m, 1H), 1.24 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 174.4, 173.7, 74.1, 72.2, 61.6, 41.0, 39.9, 36.0, 25.5, 14.9; m/z = 236.1 ($[M + Na]^+$).

(2*S*,7a*S*)-Methyl 2-hydroxy-3-oxo-hexahydro-1H-pyrrolizine-7a-carboxylate (218)

(BH11-067)

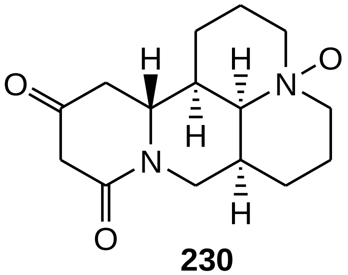


(2*S*,7a*S*)-218

To a solution of (11.5 mg,0.054 mmol) **217** (11.5 mg, 0.054 mmol) in 2 mL of distilled MeOH under argon was added 1 mg of MeONa, and the solution was stirred at room temperature for 8 hours, concentrated on a rotary evaporator, and diluted with 20 mL of methylene chloride. The solution was washed with 5 mL of water, and 5 mL of brine, dried over anhydrous sodium sulfate, concentrated under vacuum, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 4.2 mg (37% yield) of **218** and 4.8 mg (41% recovery) of **217**. Compound **218**: $[\alpha]_D^{22}$ = -10.2 (c 0.88, $CHCl_3$), Lit.[120] -10.2 (c 0.88, $CHCl_3$); ^{1}H NMR δ 4.95 (bs, 1H), 4.37 (d, *J* = 6.8, 1H), 3.76 (s, 3H), 3.64 (dt, *J* = 10.4, 1.2 Hz, 1H), 3.28 (dd, *J* = 10.4, 2.0 Hz, 1H), 2.54 (d, *J* = 12.8 Hz, 1H), 2.35 (d, *J* = 12.8 Hz, 1H), 2.23 (d, *J* = 11.2 Hz, 1H), 2.14-2.00 (m, 2H), 1.63-1.61 (m, 1H); ^{13}C NMR δ 174.4, 173.8, 74.1, 72.2, 52.8, 41.2, 39.8, 36.0, 25.5; m/z = 222.1 ($[M + Na]^+$).

2.6.7 Procedures and Analysis Results for Late-stage C-H Oxidation of Complex Molecules.

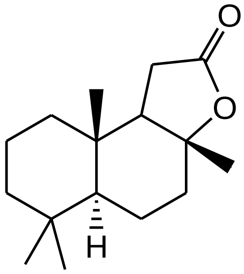
13-Oxo-oxymatrine *N*-oxide (230) (BH11-088)



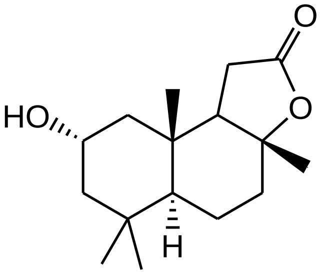
230

To an aqueous solution of 6 mL of Cu/Au (3:1)-**26** (41.6 μmol of Cu, 13.9 μmol of Au, and 0.76 μmol of **26**), were added 3 mL of 30% H_2O_2, 4 mL of CH_3CN and 49 mg (0.185 mmol) of oximatrine *N*-oxide (**229**). The resulting solution was stirred at 80°C for 7 days, cooled to 25°C, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 31 mg (60% yield) of **230** and recover 16.3 mg (33.3% yield) of **229**. $[\alpha]_D^{22}$ = + 14.6 (c 0.2, MeOH); ^{1}H NMR δ 5.15 – 5.09 (m, 1H), 4.41 (dd, *J* = 12, 5.2 Hz, 1H), 4.20 (t, *J* = 12.4 Hz, 1H), 3.50–3.25 (m, 2H), 3.22–3.02 (m, 5H), 2.82–2.60 (m, 2H), 2.48–2.37(m, 1H), 2.32 (t, *J* = 4.8 Hz, 1H), 2.10–2.04 (m, 1H), 1.89–1.48 (m, 7H); ^{13}C NMR[132] δ 210.1, 169.1, 69.1, 68.3, 66.6, 52.3, 45.2, 43.3, 42.0, 41.5, 34.5, 26.0, 24.4, 17.3, 17.0; MS (ESI, MeOH): m/z = 301.4 ($[M + Na]^+$). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{15}H_{23}N_2O_3^+$: 279.1709, found: 279.1714. The ^{13}C NMR data is in agreement with that reported[132] and the structure was further verified by NMR 2D COSY experiment.

Sclareolide (232) & (*2S*)-2-Hydroxysclareolide (233). (BH11-086)



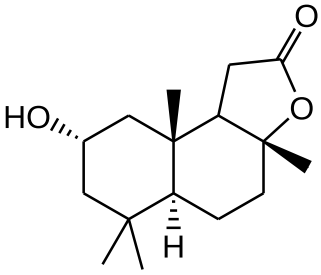
232



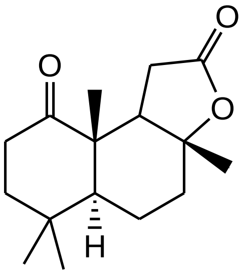
233

To an aqueous solution of 8 mL of Cu/Au (3:1)-**26** (15.9 μmol of Cu, 5.3 μmol of Au, and 0.30 μmol of **26**), were added 2 mL of 30% H_2O_2, 4 mL of CH_3CN and 100 mg (0.423 mmol) of ambroxide **231**. The resulting solution was stirred at 80 °C for 5 days, cooled to 25°C, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 78.3 mg (73.9% yield) of **232**, 6.7 mg (5.9% yield) of **233** and recover 3.2 mg (3.2% yield) of **231**. **232:** ^{1}H NMR δ 3.39 (dd, *J* = 14.2, 1.2 Hz, 1H), 2.16 (dd, J = 16.4, 6.8 Hz, 1 H), 2.06 (dt, J = 12, 3.2 Hz, 1 H), 1.95 (dd, J = 14.4, 6.4 Hz, 1 H), 1.89–1.83 (m, 1 H), 1.71–1.62 (m, 2 H), 1.47–1.33 (m, 2 H), 1.32 (s, 3 H), 1.22–1.13 (m, 1 H), 1.058 (dd, J = 13, 3 Hz, 1 H), 0.89 (s, 3 H), 0.86 (s, 3 H), 0.82 (s, 3 H); ^{13}C NMR δ 86.6, 59.3, 56.8, 42.4, 39.7, 38.9, 36.3, 33.4, 33.3, 28.9, 21.8, 21.1, 20.8, 18.3, 15.3; MS (ESI, MeOH): *m/z* = 251.2 ($M+H^+$). **233**: $[\alpha]_D^{22}$ = +78 (c 0.1, MeOH). Lit.[136] -100 (c 0.006, MeOH). ^{1}H NMR δ 4.03–3.94 (m, 1 H), 2.42 (t, J = 14.4 Hz, 1 H), 2.27 (dd, J = 16.4, 6.4 Hz, 1 H), 2.10 (dt, J = 12, 3.2 Hz, 1 H), 2.01 (dd, J = 14.4, 6.4 Hz, 1 H), 1.94–1.80 (m, 3 H), 1.74–1.66 (m, 1 H), 1.40–1.35 (m, 1 H), 1.33 (s, 3 H), 1.28–1.25 (m, 1 H), 1.17 (t, J = 11.6 Hz, 1 H), 1.08 (dd, J = 13, 3 Hz, 1 H), 0.96 (s, 3 H), 0.95 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR δ 176.0, 86.0, 64.4, 58.9, 56.3, 51.6, 48.4, 38.5, 37.5, 34.7, 33.2, 28.7, 21.9, 21.7, 20.1, 16.2; MS (ESI, MeOH): *m/z* = 289.4 ([M + Na]$^+$).

(2*S*)-2-Hydroxysclareolide (233) & 1-Oxosclareolide (234) (BH8-098)



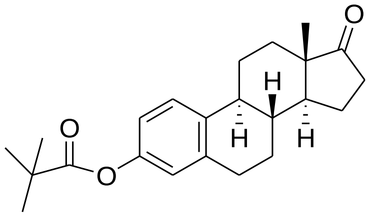
233



234

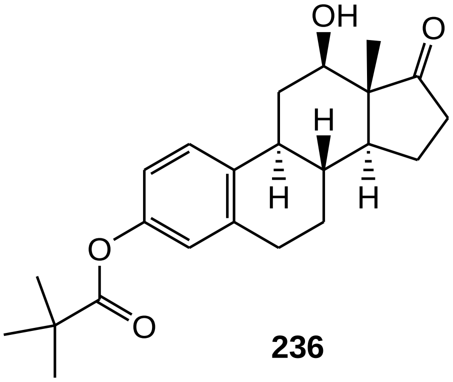
To a solution of 12 mL of Cu/Au (3:1)-**1** (24 μmol of Cu/8.0 μmol of Au-0.88 μmol of **1**) in H_2O (as described above) were added 12 mL of acetonitrile, 100 mg (0.40 mmol) of (+)-sclareolide (**232**) and 1.5 mL of 30% H_2O_2, and the resulting solution was stirred at 60^{o}C for 6 days. The solution was cooled to 25^{o}C, diluted with water, and extracted three times with diethyl ether (20 mL each). The combined extracts were washed with water and then brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate, followed by dichloromethane and methanol as eluents to give 40 mg (37.5% yield) of **233** and 3.3 mg (3% yield) of **234** along with 46 mg (46% recovery) of **232** and 10 mg of unidenficable polymers. The NMR data of **233** is the same as the one synthesis from **231**. **234**: ^{1}H NMR δ 2.96 (dd, J = 17, 7 Hz, 1 H), 2.68 (ddd, J = 16, 8.8, 6.4 Hz, 1 H), 2.53 (dd, J = 16.8, 14.4 Hz, 1 H), 2.29 (ddd, J = 15.6, 8.8, 5.2 Hz, 1 H), 2.15 (dd, J = 14.4, 6.4 Hz, 1 H), 2.10–2.05 (m, 1 H), 1.94–1.80 (m, 2 H), 1.70–1.60 (m, 2 H), 1.35 (s, 3 H), 1.19 (s, 3 H), 1.05 (s, 3 H), 1.04–0.96 (m, 1 H), 1.02 (s, 3 H), 0.91–0.86 (m, 1 H). MS (ESI, MeOH): *m/z* = 287.3 ([M + Na]$^+$).

Estrone pivalate (235) (BH12-062)



To a solution of 100 mg (0.37 mmol) of estrone in 3 mL of CH_2Cl_2 under argon were added 44 mg (0.37 mmol) of pivaloyl chloride and 29.2 mg (0.37 mmol) of pyridine. The solution was stirred for 10 hours, acidified with 1N HCl to pH 5, and extracted three times with 20 mL each of CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as an eluent to give 117 mg (89% yield) of the titled compound. $[\alpha]_D^{22} = +97$ (c 0.1, $CHCl_3$); ^{1}H NMR[143] δ 7.28 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.79 (s, 1H), 2.94 – 2.88 (m, 2H), 2.53 – 2.30 (m, 3H), 2.16 – 1.89 (m, 4H), 1.67 – 1.38 (m, 6H), 1.35 (s, 9H), 0.91 (s, 3H); ^{13}C NMR δ 177.0, 172.6, 79.5, 79.1, 62.2, 38.9, 31.8, 28.5, 27.5, 22.8, 19.5, 14.4.

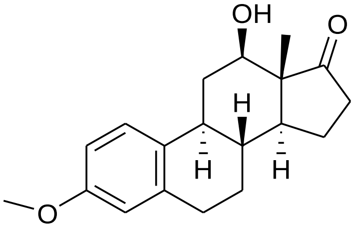
12β-hydroxy estrone pivalate (236) (BH12-105)



236

To an aqueous solution of 5 mL of Cu/Au (3:1)-**26** (7.5 μmol of Cu, 2.5 μmol of Au, and 0.28 μmol of **26**), were added 3 mL of 30% H_2O_2, 2 mL of CH_3CN and 70.8 mg (0.2 mmol) of **235**. The resulting solution was stirred at 50°C for 7 days, cooled to 25°C, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 42.6 mg (58.2% yield) of **236** and recover 10.9 mg (15.4% yield) of **235**. $[\alpha]_D^{22} = -5.6$ (c 0.1, $CHCl_3$); ^{1}H NMR δ 7.25 (dd, *J* = 9.6, 2.0 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 3.98 (dd, *J* = 10.8, 3.6 Hz, 1H), 2.94–2.87 (m, 2H), 2.59–2.46 (m, 2H), 2.41–2.30 (m, 1H), 2.20–1.98 (m, 3H), 1.78 – 1.72 (m, 1H), 1.63–1.35 (m, 5H), 1.36 (s, 9H), 0.98 (s, 3H); ^{13}C NMR δ 222.0, 174.1, 149.3, 136.0, 131.2, 126.0, 117.9, 116.9, 72.9, 52.1, 48.5, 42.8, 38.6, 36.6, 35.8, 32.6, 29.6, 27.0, 21.1, 9.4. HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{23}H_{31}O_4^+$: 371.2222, found: 371.2209.

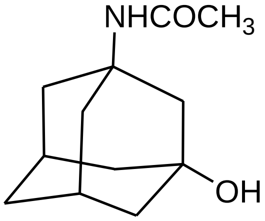
12β-Hydroxy-3-methoxy-estra-1.3.5(10)-triene-17-one (241). (BH12-107)



241

To a solution of 18.5 mg (0.05 mmol) of **236** in 1 mL MeOH, add 3.6 mg (0.15 mmol) of LiOH. The resulting solution was stirred at room temperature for 6 hours until no starting material remaining, concentrated under vacuum and dissolve with 10 mL methylene chloride, adjusted the pH to 2 with HCl and extracted 2 times with each 10 mL methylene chloride. The combined organic solution was concentrated under vacuum. To the residue, 2 mL of MeOH, 6.9 mg (0.05mmol) of K_2CO_3, 7.1 mg (0.05 mmol) of CH_3I was added and heated to reflux for 6 hours. After cooling down, the solution was concentrated under vacuum, dissolve with 10 mL methylene chloride & 5 mL of water, extract 2 times with each 10 mL methylene chloride. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 10.1 mg (67.6% yield) of **241.** $[\alpha]_D^{22} = - 40.2$ (c 0.1, $CHCl_3$); ^1H NMR[138] δ 7.16 (dd, J = 8.8, 2.0 Hz, 1H), 6.71 (dd, J = 8.6, 2.8 Hz, 1H), 6.63 (d, J = 2.7 Hz, 1H), 3.98 (dd, J = 10.8, 3.6 Hz, 1H), 3.78 (s, 3H), 2.96–2.87 (m, 2H), 2.59–2.46 (m, 2H), 2.41–2.30 (m, 1H), 2.20–1.98 (m, 3H), 1.78 – 1.72 (m, 1H), 1.63–1.35 (m, 5H), 0.98 (s, 3H); ^{13}C NMR δ 222.8, 157.9, 137.7, 131.3, 126.2, 114.2, 111.7, 72.8, 55.5, 52.3, 48.5, 42.4, 37.4, 36.0, 33.3, 29.7, 26.4, 21.6, 8.5.

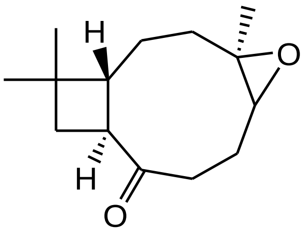
***N*-3-hydroxyadamantan-1-yl acetamide (238)** (BH11-029)



238

To an aqueous solution of 4 mL of Cu/Au (3:1)-**26** (9.7 μmol of Cu, 3.2 μmol of Au, and 0.18 μmol of **26**), were added 2 mL of 30% H_2O_2, 4 mL of CH_3CN and 50 mg (0.259 mmol) of **237**. The resulting solution was stirred at 50°C for 7 days, cooled to 25°C, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 32.1 mg (74% yield) of **238** and recover 6.4 mg (12.8% yield) of **237**. ^1H NMR[140] δ 5.25–5.17 (bs, 1H), 2.29–2.22 (m, 2H), 2.03–1.95 (m, 2H), 1.95–1.88 (m, 7H), 1.72–1.67 (m, 4H), 1.58–1.53 (m, 2H); ^{13}C NMR δ 169.8, 69.6, 54.8, 49.5, 44.5, 40.8, 35.3, 31.0, 25.0.

Kobusone (240) (BH10-080)



240

To an aqueous solution of 3 mL of Cu/Au (3:1)-**26** (8.5 μmol of Cu, 2.9 μmol of Au, and 0.31 μmol of **26**), were added 2 mL of 30% H_2O_2, 2 mL of CH_3CN and 50 mg (0.23 mmol) of **239**. The resulting solution was stirred at 80°C for 4 days, cooled to 25°C, and extracted three times with 20 mL each of ethyl acetate. The combined extracts were washed with water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluents to give 34.0 mg (67.4% yield) of **240** and recover 8.7 mg (17.4% yield) of **239**. $[\alpha]_D^{22} = - 131.6$ (c 0.2, $CHCl_3$); ^1H NMR [141] δ 3.01–3.09 (m, 1H), 2.67 (dd, *J* = 4.0, 8.0 Hz, 1H), 2.58-2.49 (m, 2H), 2.42-2.33 (m, 1H), 2.13 (dt, *J* = 2.4, 8.0 Hz,1H), 2.07-2.03 (m, 1H), 1.94-1.90 (m, 1H), 1.66-1.60 (m, 2H), 1.54-1.46 (m, 1H), 1.46-1.38 (m, 1H), 1.29 (s, 3H), 1.02 (s, 6H), 0.93 (td, *J* = 10.8, 3.2 Hz, 1H), ^{13}C NMR δ 214.6, 61.9, 59.2, 52.8, 51.6, 39.2, 37.9, 35.5, 34.7, 29.6, 26.7, 25.0, 22.4, 16.4; MS (ESI, MeOH): m/z = 245.3 ($[M + Na]^+$).

Chapter 3 - Synthesis of 6-(Dimethylamino)-2-phenylisoindolin-1-one derivative.

3.1 Background and Significance

Bioluminescence is the production and emission of light by a living organism. It is a form of chemiluminescence. Bioluminescence occurs widely in marine vertebrates and invertebrates, as well as in some fungi, microorganisms including some bioluminescent bacteria and terrestrial invertebrates such as fireflies. [144] Bioluminescence is widely used in high throughput screening (HTS) as a light based detection method to assay biological activities of molecules, proteins or genes against a defined set of enzymes or receptor targets.[145] In a general sense, the principal chemical reaction in bioluminescence involves some light-emitting molecule and an enzyme, generally called the luciferin and the luciferase, respectively. Luciferase is a generic term for the class of oxidative enzymes that produce bioluminescence, and is usually distinguished from a photo protein. The luciferase requires other cofactors such as calcium or magnesium ions, and sometimes also the energy-carrying molecule adenosine triphosphate (ATP). [144] Hence firefly luciferase is used as a sensor of the ATP content in cells as a measure of cell viability, and in biochemical assays to measure ATP-dependent enzyme reactions such as kinases.[146] Besides that, firefly luciferase has been commonly used as a reporter in cells expressing a luciferase gene or its enzymatic activity under the control of a promoter of interest to assess its transcriptional activity.[147, 148] However, it has been found that some molecules can directly inhibit firefly reporter enzyme in cells, independently from promoter-specific transcriptional activity.[149] In contrast, some inhibitors have found to form stable firefly enzyme-inhibitor complexes which are more resistant to degradation than the free firefly enzyme.[150, 151] This leads to a reporter enzyme accumulation and signal activation in cells, independent of effects on transcription/translation.[150, 151] These phenomena give rise to false results in cell-based HTS assays.[150] Therefore, to avoid these misleading activities, study of firefly luciferase inhibitors and their mechanisms of inhibition are highly relevant.

Crystal structure of firefly luciferase has shown two distinct domains, a large N-terminal domain (residues 1−436) and a small C-terminal domain (residues 440−550), separated by a wide cleft.[152] It is suggested that, seven residues (Gly200, Lys206, Glu344, Asp422, Arg437, Gly446 and Glu455) play a crucial role in the binding of ATP and in adenylate formation.[152] Hence, the active site of luciferase is proposed to locate on the surface of both domains facing each other across a large cleft.[152] Further, it is believed that upon substrate binding, the two domains move together to form the active center.[152] Site-directed mutation studies have shown that Lys529 is crucial for effective substrate orientation and for transition state stabilization which lead to efficient adenylate formation.[153] (**Figure 15**)

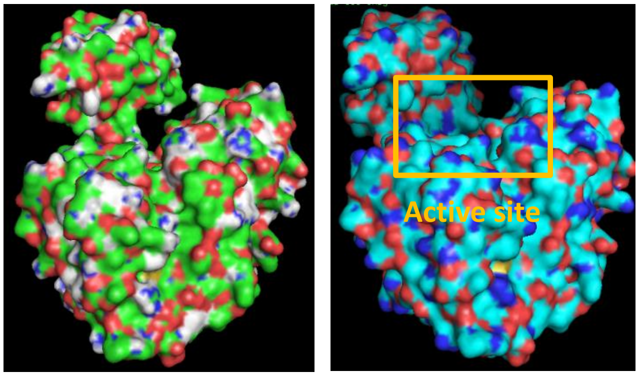


Figure 15. Surface view of (a) firefly luciferase without its substrate (Protein Data Bank accession number 1LCI) [152] (b) firefly luciferase in complex with bromoform (Protein Data Bank accession number 1BA3).[154]

Natural substrate of luciferase enzyme is the D-isomer of firefly luciferin (D-LH_2) which is chemically defined as (*S*)-2-(6'-hydroxy-2'-benzothiazolyl)-2-thiazoline-4-carboxylic acid (**Figure 16**).[155] The bioluminescent chemical reaction catalyzed by luciferase is a two-step process.[146, 155] In the first step of the bioluminescent reaction, D-luciferyl-adenylate (D-LH_2-AMP) intermediate is formed by the reaction of D-luciferin (D-LH_2) and ATP in the presence of Mg^{2+}.[146, 155] Oxidation of luciferyl-adenylate (D-LH_2-AMP) intermediate with molecular oxygen in the following step produces AMP, oxyluciferin and light.[146, 155] (**Scheme 20**, eq 1–2)

It is reported that the primary structure of firefly luciferase has a high sequence similarity to a long-chain acyl-CoA synthetase.[156] Therefore, besides the light emitting reactions, firefly luciferase catalyzes fatty acyl-CoA synthesis as well.[157] First, long-chain fatty acids are adenylated in the presence of ATP and Mg^{2+}, and the subsequent step is the thioesterification with CoA.[157, 158] (**Scheme 20**, eq 3–4) It is suggested that luciferase catalyzes the adenylation of fatty acids via carboxylic acid moiety in a mechanism similar to the adenylation step of the bioluminescence reaction of luciferase.[159] As reported, long chain fatty acids (C12-C20) can be a competitive inhibitors of firefly luciferase against luciferin in micromolar concentration level.[158, 160]

$$\text{luciferase + D-luciferin + ATP-Mg}^{2+} \rightleftharpoons \text{luciferase.D-luciferyl-AMP + PPi-Mg}^{2+} \quad (1)$$

$$\text{luciferase.D-luciferyl-AMP} + O_2 \longrightarrow \text{luciferase + AMP} + CO_2 + \text{oxyluciferin} + h\nu \quad (2)$$

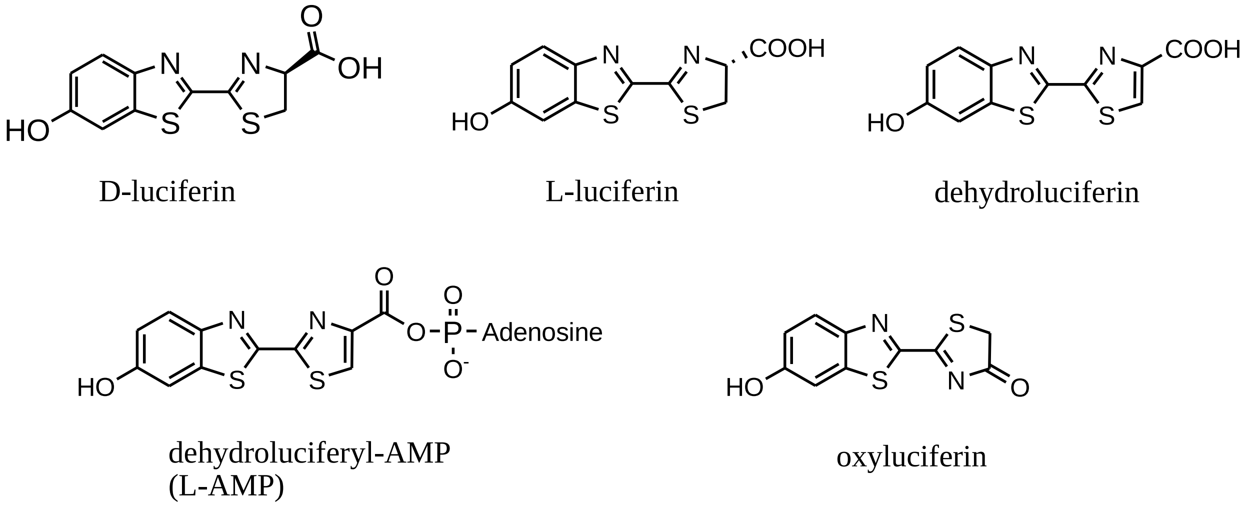
$$\text{luciferase + fatty acid + ATP-Mg}^{2+} \rightleftharpoons \text{luciferase.fatty acyl-AMP + PPi-Mg}^{2+} \quad (3)$$

$$\text{luciferase.fatty acyl-AMP + CoA} \rightleftharpoons \text{fatty acyl-CoA + AMP + luciferase} \quad (4)$$

$$\text{luciferase.dehydroluciferyl-AMP + CoA} \longrightarrow \text{luciferase + AMP + luciferyl-CoA} \quad (5)$$

Scheme 20. Luciferase Catalyzed Reactions.

Common inhibitors that inhibit firefly luciferase activity are found to be substrates related compounds, intermediates or products of the luciferase catalyzed reaction and fatty acids.[155] Substrates related compounds such as L-luciferin, dehydroluciferin, intermediates such as dehydroluciferyl-adenylate (L-AMP), and products such as pyrophosphate (PPi) and oxyluciferin were found to inhibit bioluminescent light emission in a competitive or noncompetitive manner.[161-165] However, coenzyme A (CoA) was found to prevent this inhibition by reacting with dehydroluciferyl-adenylate (L-AMP).[166] CoA reaction with L-AMP results free luciferase and luciferyl-CoA (L-CoA) which is found to be a weaker inhibitor in the bioluminescence reaction.[160, 166] (**Scheme 20**, eq 5)



D-luciferin

L-luciferin

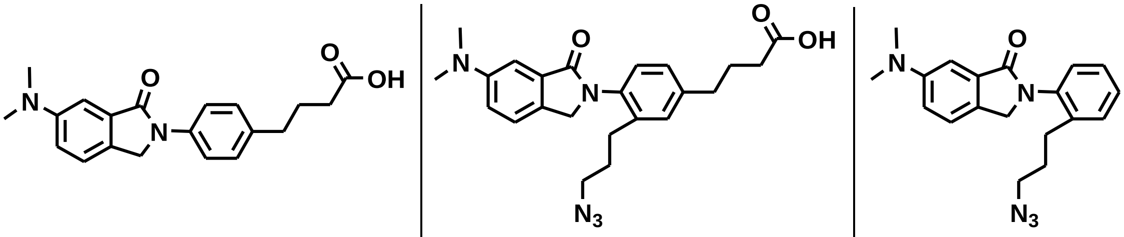
dehydroluciferin

dehydroluciferyl-AMP
(L-AMP)

oxyluciferin

Figure 16. Structure of D-luciferin and Firefly Luciferase Inhibitors.

Nakagomi and coworkers have reported an aromatic carboxylic acid, F-53 which inhibits the enzymatic activity of firefly luciferase by covalently binding to a regulatory lysine residue (Lys529) *via* an amide bond formation.[167] Based on experimental results, they proposed that the carboxylic acid of F-53 is first activated to its CoA-thioester derivative by luciferase via its acyl-CoA synthetase activity.[167] This F-53-CoA derivative is proposed to inactivate luciferase *via* acylation of Lys-529 by an unknown cellular acetyltransferase.[167] With knowledge of above mentioned results, our research efforts focused on synthesizing two analogous probes of F-53 possessing ortho 3-azidopropyl substituent on the phenyl ring with (**242**) and without (**243**) butyric acid group (**Scheme 21**). We hypothesized that compound **242** acts on luciferase by competing for the binding site of the luciferin substrate which is involved in the light emission. Therefore, these two probe molecules will be used to study the mechanism of luciferase inhibition further for understanding the effects of carboxylic acid-containing drugs.



F-53 **242** **242A**

Scheme 21. Structure of F-53, 242 and 242A.

3.2 Synthetic Route and Discussions

Before the synthesis of compound **242**, similar compounds **F-53** and **242A** were successfully made by Dr. Ai Ito in Research Foundation ITSUU Laboratory and Dr. Medha Gunaratna in Dr. Hua's Lab, respectively. With the general idea of the multi-step synthetic routes for **F-53** and **242A**, the synthesis of **242** was designed. However, due to the side chain on the phenyl ring, the synthesis of **242** becomes more complicated. Base on the retrosynthetic analysis, **242** can be disconnected into three parts, the isoindolinone, the aniline derivative and δ-side chain. (**Figure 17**) The final synthetic route to obtain **242** was shown in **Scheme 22**.

For the first part, O-toluic acid, **243** in conc. sulfuric acid was treated with a solution of potassium nitrate in conc. sulfuric acid following a reported procedure.[168] (**Scheme 22**) In this reaction, potassium nitrate reacts with sulfuric acid to form nitric acid and potassium bisulfate. Sulfuric acid being a stronger acid than nitric acid facilitates generation of NO^{2+} in situ. Importantly, to avoid the formation of di-nitrated product, potassium nitrate in conc. sulfuric acid should be added dropwise to keep the nitronium ion concentration low and the reaction should be carried out at 0 ^{o}C to slow down the reaction. During workup, since mixing concentrated sulfuric acid with water gives off much heat, reaction mixture should be added to ice rather than water. The resulting product was a mixture of 2-methyl-5-nitrobenzoic acid, **244** (85%) and 2-methyl-3-nitrobenzoic acid (15%). The compound can be purified by recrystallization through 2:1 ether: dichloromethane.

Since both products are very polar and they both have very similar Rf values, the mixture was directly treated with thionyl chloride in methanol.[169] Reaction mixture was refluxed to give a mixture of corresponding methyl esters **245** and its isomer in a quantitative yield. Resultant compound, **245** was able to purify using hexane *via* recrystallization. Benzylic bromination of compound **245** using *N*-bromosuccinimide and a radical initiator, benzoyl peroxide afforded compound **246**,[168] as a key precursor for **242**.

The para-side chain synthesis was start from 3-butyn-1-ol (**247**). Because of the active hydroxyl group, TBS protection of alcohol was needed. With the presence of imidazole as a base in methylene chloride, TBSCl was added into **247** to yield **248**.[170]

2-Amino-5-iodobenzoric acid (**249**), as a cheap amino acid, was used as the substrate for the aniline derivative part of **242**. Firstly, the carboxylic acid was reduced by $LiAlH_4$ in THF to give corresponding alcohol **250**. The coupling of **250** with **246** in EtOH at reflux temperature for 24 h resulted its condensation product **251**.[167] Low temperature and less reaction times resulted uncyclized product. From the appearance of uncyclized by-product, the amino group attack Br with a S_N2 reaction was much faster than the amidation. The isolated uncyclized product was cyclized again in reflux ethanol to give **251**. At the same time, the alcohol on ortho position was also attacked the Br to give ether type product in ~10% yield.

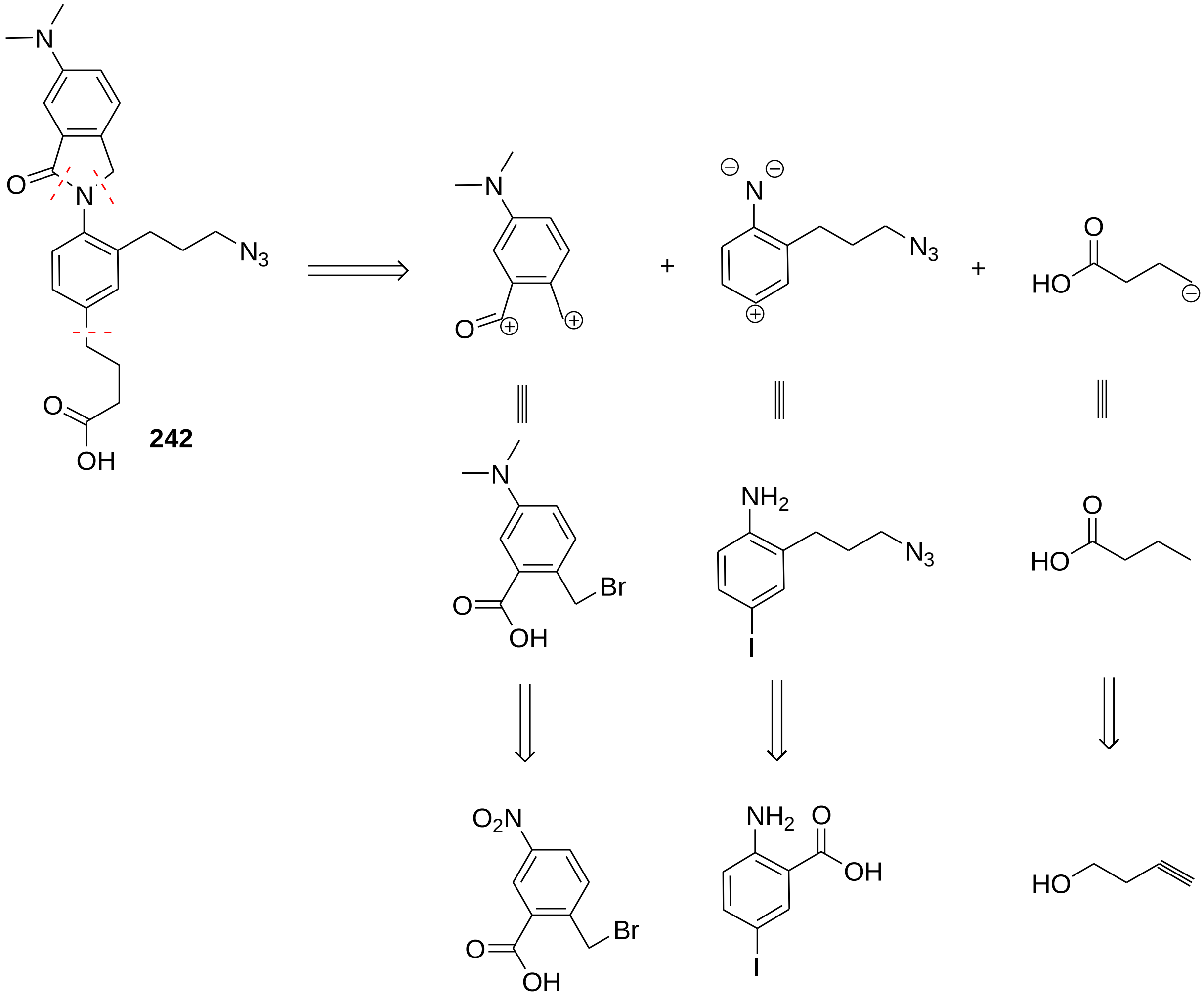
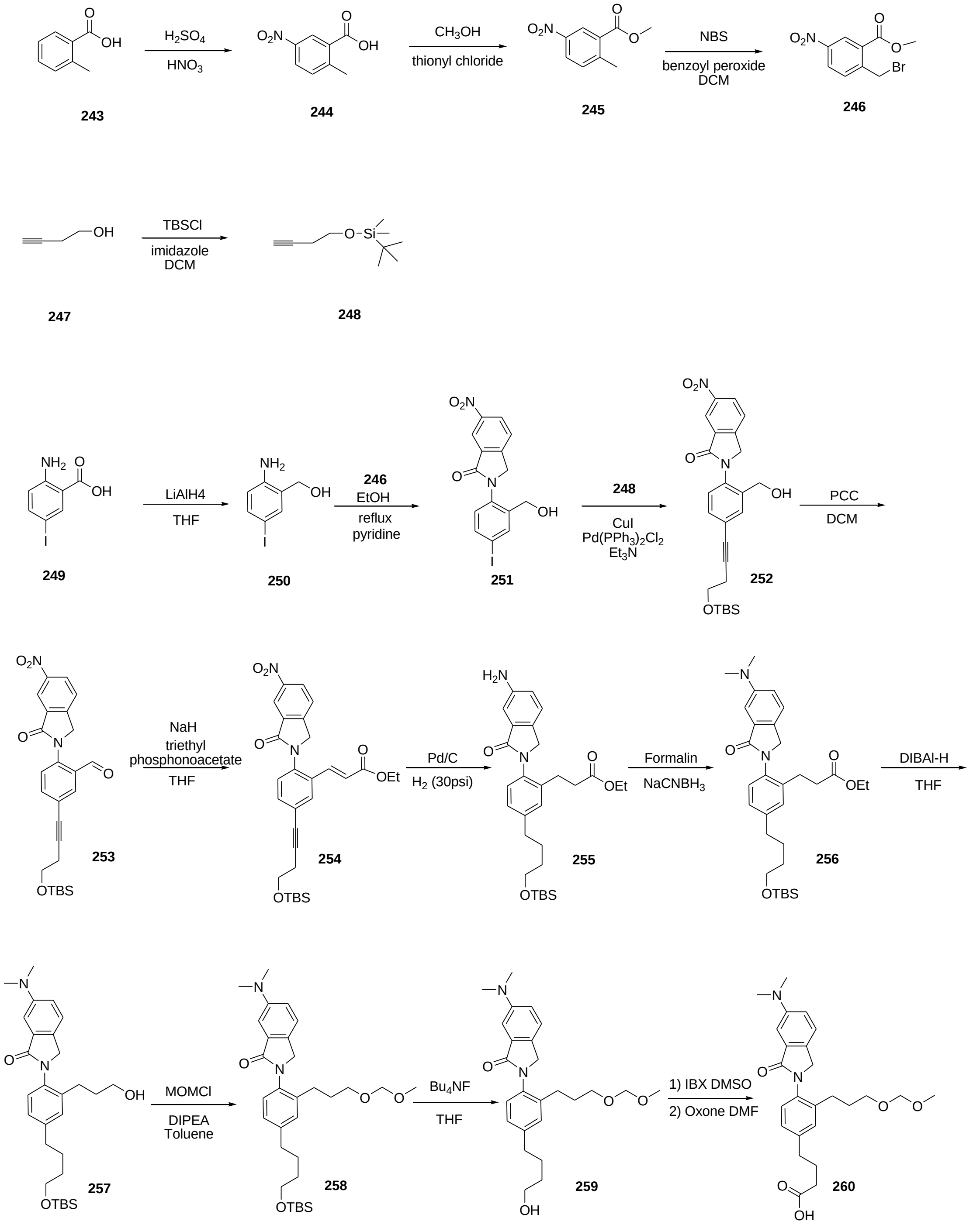
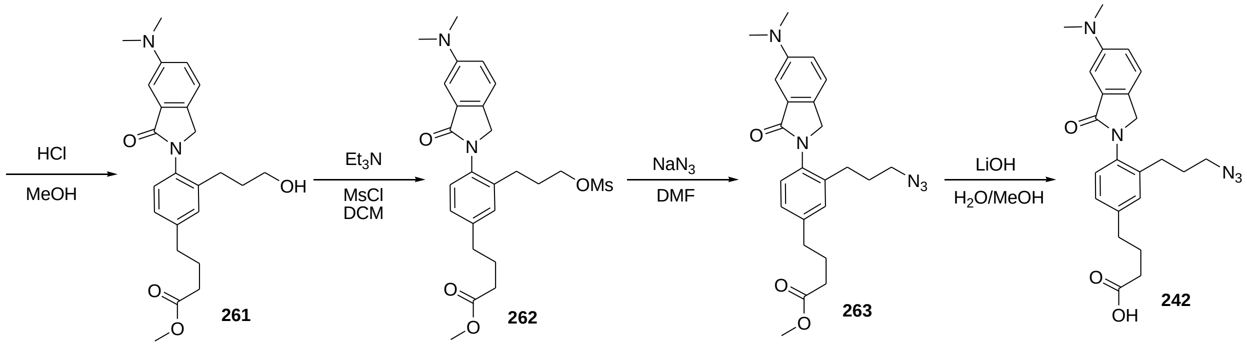


Figure 17. Synthons and Synthetic Equivalents of 242.

The connection between **251** and **248** was constructed by Sonogashira Reaction, coupling the benzyl iodide and C-C triple bond. The Suzuki Coupling was tried with both pinacol-borane and catechol-borane, the alkenylboron was not easy to make and yield of the reaction was not consistence (32–68% yield). Therefore, a milder route, Sonogashira Coupling was carried out with the catalysis of $Pd(PPh_3)_2Cl_2$ and cuprous iodide as a co-catalyst in trimethylamine as solvent. The reaction was needed to be done in a dry box and gave only desired organic product **252** in a quantitative yield.



(To be continued)



Scheme 22. The Synthetic Route for Compound 242.

Compound **252** was oxidized by PCC at room temperature in dry methylene chloride and gave quantitative yield of corresponding aldehyde **253**. The work up process was the key to the reaction since large amount of sticky PCC may cover the product and make a lower yield. After the filter through Celite, the sonication of Celite in methylene chloride was necessary, even though partial PCC was dissolve back into the solution. The adding of molecular sieve into the reaction was also helpful to avoid the sticky PCC. Compound **253** was finally purified by chromatography column.

With the optimized Horner-Wadsworth-Emmons reaction, **253** was reacted with stabilized phosphorus ylide (phosphonate carbanion) and leaded to **254** with *E*-selectivity. Sodium Hydride was used to make the phosphorus ylide with triethylphosphonoacetate.[171] The product **254** was hydrogenated with the catalysis of Pd/C to reduce C-C double bond, and C-C triple bond and NO_2 group at the same time. Reductive methylation of aryl amino group of compound **255** was achieved using formaldehyde and sodium cyanoborohydride by reductive amination to obtain *N*, *N*-dimethyl product **256**, followed with the reduction of ester group to alcohol with DIBAl-H with 95% yield.

Compound **257** was protected with MOMCl with DIPEA as an amine and remove TBS protecting group with TBAF in THF for the preparation of functionalization on para-side chain.

The terminal alcohol was oxidized to carboxylic acid (**260**) with two steps, (1) oxidation to aldehyde with IBX/DMSO and (2) oxidation to carboxylic acid with oxone.[172] To avoid the mesylation of the carboxylic acid, the methyl ester was made with HCl/MeOH. At the same time, MOM was removed in the same reaction to give **261**. The hydroxyl group of compound **261** was mesylated using MsCl/Et_3N and followed by the azidation with sodium azide to give compound **263** in a quantitative yield. Finally, the methyl ester was hydrolysis with LiOH and yield the final product **242**.

3.3 Future Work

Both probe molecules **242** and **243** were sent to Dr. Madoka Nakagomi's lab for biology studies. They will be used for identifying target protein(s) in the firefly luciferase inhibition through click chemistry. Probe molecule **242** consists of three elements which are important in the activity-based protein profiling studies, (1) a reactive carboxylic group that can covalently reacts with a residue in the active site of the target enzyme (2) a spacer for selectivity and (3) an azide group that can undergo Cu(I)-catalyzed [3+2] dipolar cycloaddition with an alkyne bearing a fluorescent detection tag.[173-175] Probe molecule **243**, which does not have a butyric acid group will be used as the negative control.

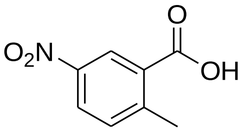
3.4 Synthetic Experimental Procedures

3.4.1 General

^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were measured from a solution in $CDCl_3$ unless otherwise mentioned. The chemical shift data for each signal on ^{1}H NMR are given in units of δ relative to TMS ($\delta = 0$) or $CHCl_3$ ($\delta = 7.26$). For ^{13}C NMR spectra, the chemical shifts are recorded relative to $CDCl_3$ ($\delta = 77.0$). Low-resolution mass spectra were taken from an API 2000-triple quadrupole ESI-MS/MS mass spectrometer. High-resolution mass spectra were obtained using a Waters LCT Premier time of flight mass spectrometer. IR spectra were measured directly in solid form from Agilent Cary 630 FTIR. Chemicals were purchased from Fisher Scientific Co., Aldrich Chemical Co., Chem-Impex International, and VWR International.

3.4.2 Representative Synthesis

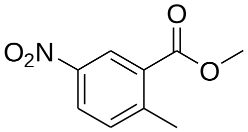
2-Methyl-5-nitrobenzoic acid (**244**) (BH12-021)



244

To a solution of **243** (15 g, 110.17 mmol) in conc. sulfuric acid (90 mL), a solution of potassium nitrate (15 g, 143.22 mmol) in conc. sulfuric acid (90 mL) was added dropwise over 1 h at 0 °C. The reaction mixture was added to a 100 g of ice chips and stirred vigorously until all ice melted. The resulting precipitate was re-dissolved in diethyl ether. The ether layer was washed with water and dried with anhydrous sodium sulfate. The solution was concentrated under vacuum to obtain 18.62 g (93.2% yield) of a mixture of compound **244** (85%) and 2-methyl-3-nitrobenzoic acid (15%) as a white solid. The compound can be purified by recrystallization through 2:1 ether: dichloromethane. ^{1}H NMR[168] δ ppm 8.95 (s, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 7.50 (m, 1H), 2.80 (s, 3H); ^{13}C NMR δ ppm 166.7, 146.8, 145.2, 132.5, 131.2, 126.1, 125.2, 20.9.

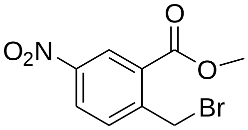
2-Methyl-5-nitrobenzoic acid methyl ester (**245**). (BH12-022)



245

To a mixture of **244** (85%) and 2-methyl-3-nitrobenzoic acid (15%) (9.05 g, 50 mmol) in methanol (120 mL), thionyl chloride (7.26 mL, 100 mmol) was added dropwise at 0 ^{o}C and it was allowed to reflux for 4 h at 70 ^{o}C. The solution was concentrated under vacuum, then re-dissolved in ethyl acetate (150 mL). A solution of saturated sodium bicarbonate (70 mL) was added to adjust the pH to 8. The product was extracted from the aqueous layer using ethyl acetate twice. The combined organic layer was washed with brine (70 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum and recrystallized with hexane to obtain 8.3 g (99% yield based on **244**) of compound **245** as a white solid; mp. 66~67 ^{o}C; ^{1}H NMR[176] δ ppm 8.78 (d, *J* = 2.73 Hz, 1H), 8.25 (dd, *J* = 2.54, 8.40 Hz, 1H), 7.44 (d, *J* = 8.20 Hz, 1H), 3.96 (s, 3H), 2.73 (s, 3H); ^{13}C NMR δ ppm 165.8, 147.8, 145.9, 132.7, 130.4, 126.0, 125.6, 52.3, 21.8.

Methyl 2-(bromomethyl)-5-nitrobenzoate (**246**) (BH12-023)

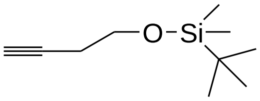


246

A mixture of **245** (12.6 g, 40 mmol) and *N*-bromosuccinimide (18.4 g, 44 mmol) in dichloroethane (200 mL), in the presence of a catalytic amount of benzoyl peroxide (780 mg) was refluxed for 15 h under argon. The reaction mixture was neutralized with saturated sodium bicarbonate and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexanes: ethyl acetate = 9:1) to obtain 10.90 g

(62.1% yield) of compound **246** as a white solid; mp. 77~78 °C; ^{1}H NMR[177] δ 8.82 (d, *J* = 1.95 Hz, 1H), 8.34 (dd, *J* = 8.40, 1.95 Hz, 1H), 7.69 (d, *J* = 8.59 Hz, 1H), 5.01 (s, 2H), 4.02 (s, 3H); ^{13}C NMR δ ppm 165.0, 147.4, 146.1, 133.0, 130.3, 126.9, 126.4, 53.0, 29.3.

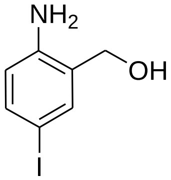
3-(tert-Butyldimethylsiloxy)-1-butyne (**248**) (BH12-026)



248

To a solution of **247** (2.8 g, 40 mmol) in 200 mL anhydrous methylene chloride, imidazole (5.8 g, 80 mmol) and TBSCl (9.68 g, 60 mmol) were added and stirred under argon at room temperature overnight. The reaction solution was washed with water (2 x 50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and concentrate under rotary evaporator and vacuum. The residue was purified by silica gel column chromatography (hexanes: ethyl acetate = 5:1) to obtain 6.9 g (96.5% yield) of compound **248** as a colorless oil. ^{1}H NMR[178] δ 3.74 (t, *J* = 7.2 Hz, 2H), 2.39 (m, 2H), 1.96 (s, 1H), 0.10 (s, 9H), 0.07 (s, 6H); ^{13}C NMR δ ppm 82.0, 70.1, 61.8, 26.1, 24.3, 18.6, -5.4.

(2-Amino-5-iodophenyl)methanol (**250**) **(**BH12-013**)**

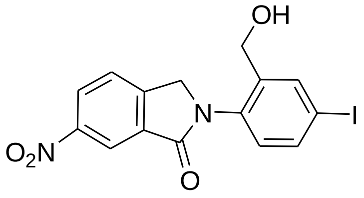


250

To a cold (0 °C) solution of 3 g (11.4 mmol) of 2-amino-5-iodobenzoic acid (**249**) in 100 mL of dry THF, 0.44 g (11.4 mmol) of $LiAlH_4$ was added in portion over 20 minutes and the reaction mixture was stirred at room temperature for 3 hours to give a yellow solution. Progress of the reaction is monitored by TLC until no starting material remains. To it, H_2O (3 mL) and 10%

aqueous NaOH solution (3 mL) were added to the solution, filtered to remove Al(OH)$_3$ and washed with of ethyl acetate (3 x 50 mL). The filtrate was concentrated and the residue was purified by silica gel column chromatography using a gradient mixture of hexane and diethyl ether as an eluent to give 1.96 g (70% yield) of the titled compound as a light yellow solid; mp. 181~183 ^{o}C; ^{1}H NMR[179] δ 7.40–7.35 (m, 2H), 6.48 (d, *J* = 8 Hz, 1H), 4.61 (d, *J* = 2.8 Hz, 2H), 4.21 (broad, 1H); ^{13}C NMR δ ppm 147.2, 138.0, 136.4, 128.6, 117.5, 76.6, 62.0.

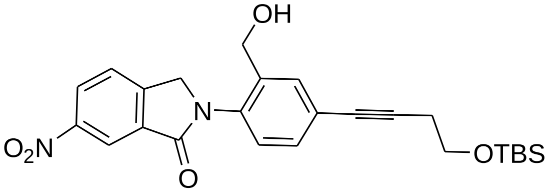
2-(2-(Hydroxymethyl)-4-iodophenyl)-6-nitroisoindolin-1-one (**251**) (BH12-024)



251

To a solution of **250** (4 g, 16 mmol) and **246** (4.37 g, 16 mmol) in absolute ethanol (200 mL) under argon, dry pyridine (1.64 g, 20.8 mmol) was added. The reaction mixture was refluxed at 80 ^{o}C for 30 h. After cooling to room temperature, the reaction was neutralized with saturated sodium bicarbonate. The reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with saturated sodium chloride (100 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum and the residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 1:1) to obtain 1.92 g (52% yield) of compound **251** as a yellow oil. ^{1}H NMR δ 8.80 (s, 1H), 8.49 (dd, *J* = 2.15, 8.40 Hz, 1H), 7.68 (d, *J* = 8.59 Hz, 1H), 7.32–7.42 (m, 3H), 4.62 (m, 4H); ^{13}C NMR δ ppm 166.7, 151.8, 148.6, 139.2, 134.2, 130.9, 129.3, 128.1, 128.0, 126.4, 124.9, 119.8, 88.6, 61.2, 53.1. HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{15}H_{12}IN_2O_4$: 410.9842 found: 410.9839.

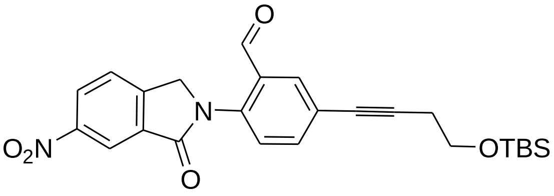
2-(4-(4-(tert-Butyldimethylsilyloxy)but-1-ynyl)-2-(hydroxymethyl)phenyl)-6-nitroisoindolin-1-one (252) (BH12-029)



252

To a yellow solution of **251** (1.9 g, 2.5 mmol) in 200 mL triethylamine, CuI (17.6 mg, 0.09 mmol) and bis(triphenylphosphine)palladium chloride (64.9 mg, 0.09 mmol) were added under nitrogen in a dry box. The reaction mixture was stirred under argon for 20 minutes and (but-3-ynyloxy)(tert-butyl)dimethylsilane (**248**) (937 mg, 5.097 mmol) was added into it to give a green solution. The solution was stirred under nitrogen at room temperature overnight, concentrated under vacuum, and re-dissolve in 100 mL of ethyl acetate and 50 mL of H_2O. The mixture was extracted with ethyl acetate (2 x 100 mL) and the combined organic layer was washed with saturated sodium chloride (50 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum and the residue was purified by silica gel column chromatography (hexanes: ethyl acetate = 1:1) to obtain 1.87 g (86.6% yield) of compound **252** as a yellow oil. ^{1}H NMR δ 8.80 (s, 1H), 8.50 (dd, *J* = 2.15, 8.40 Hz, 1H),7.87 (d, *J* = 4 Hz, 1H) 7.60 (d, *J* = 8 Hz, 1H), 7.31 (d, *J* = 4.4 Hz, 1H), 7.14 (s, 1H), 4.62 (m, 4H), 3.79 (t, *J* = 7.2 Hz, 2H), 2.59 (t, *J* = 4.8 Hz, 2H), 0.90 (s, 9H), 0.09 (s, 6H) ; ^{13}C NMR δ ppm 166.4, 153.2, 140.3, 137.2, 135.6, 133.1, 129.8, 128.1, 127.3, 125.4, 123.0, 120.8, 118.1, 116.0, 82.4, 63.6, 61.2, 54.3, 27.6, 24.0, 19.0 (3C), -5.1(2C). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{25}H_{31}N_2O_5Si$: 467.2002 found: 467.2013.

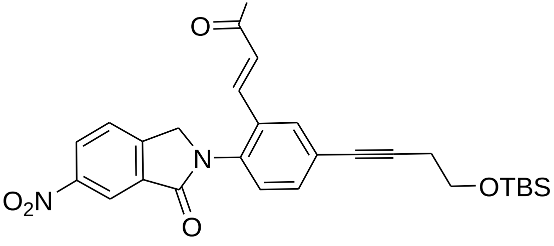
5-(4-(tert-Butyldimethylsilyloxy)but-1-ynyl)-2-(6-nitro-1-oxoisoindolin-2-yl)benzaldehyde (253). (BH12-031)



253

To a solution of **252** (1.9 g, 4.07 mmol) in 50 mL anhydrous methylene chloride under argon, activated 4 Å molecular sieve (2 g) and pyridinium chlorochromate (1.05 g, 4.88 mmol) were added and stirred at room temperature for 3 hours to give a dark green solution. The solution was filtered through Celite and washed with 100 mL of methylene chloride. The filtrate was concentrated under an evaporator and vacuum and purified by silica gel column chromatography (hexanes:ethyl acetate = 1:1) to obtain 1.82 g (96% yield) of compound **253** as a yellow oil. ^{1}H NMR δ 10.36 (s, 1H), 8.80 (s, 1H), 8.49 (dd, *J* = 2.15, 8.40 Hz, 1H), 8.38 (d, *J* =4.8 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.62 (s, 1H), 7.40 (d, *J* = 4.0 Hz 1H), 4.62 (s, 2H), 3.79 (t, *J* = 7.2 Hz, 2H), 2.60 (t, *J* = 4.8 Hz, 2H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR δ ppm 195.0, 162.1, 153.1, 141.9, 139.6, 139.2, 132.1, 131.4, 128.6, 120.3, 118.6, 117.6, 114.2, 102.6, 88.2, 81.2, 61.8, 60.4, 26.0, 24.0, 18.8 (3C), -5.1 (2C). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{25}H_{29}N_2O_5Si$: 465.1846 found: 465.1862.

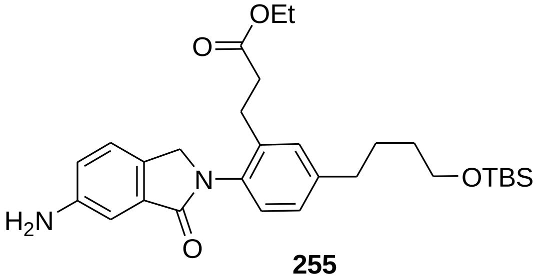
Ethyl-3-(5-(4-(tert-butyldimethylsilyloxy)but-1-ynyl)-2-(6-nitro-1-oxoisoindolin-2-yl)phenyl)acrylate (**254**) (BH12-033)



254

To a cold (0°C) solution of triethyl phosphonoacetate (878 mg, 3.92 mmol) in 30 mL anhydrous THF under argon, NaH (98 mg, 3.92 mmol) was added in portion and the solution was stirred at room temperature for 2 hours to give a colorless solution. To it, a solution of **253** (1.82 g, 3.92 mmol) in 30 mL THF was added via cannula and stirred under argon at room temperature for another 2 hours. The reaction was quenched by 2 mL of H_2O and extracted three times with 50 mL each of methylene chloride. The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated under vacuum, and purified by silica gel column chromatography (hexanes:ethyl acetate = 1:2) to obtain 2.0 g (96% yield) of compound **254** as a yellow oil. ^{1}H NMR δ 8.80 (s, 1H), 8.49 (dd, *J* = 2.15, 8.40 Hz, 1H), 7.70 (m, 2H), 7.51 (s, 1H), 7.33 (d, *J* = 8.0 Hz 1H), 6.67 (s, 1H), 6.35 (d, *J* = 8 Hz, 1H), 4.62 (s, 2H), 4.23 (q, *J* = 6.8, 2H), 3.78 (t, *J* = 7.2 Hz, 2H), 2.58 (t, *J* = 4.8 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR δ ppm 167.5, 163.2, 152.4, 138.9, 137.1, 134.2, 133.2, 130.8, 129.6, 125.8, 124.3, 122.6, 121.4, 116.8, 114.8, 111.0, 88.2, 81.6, 61.8, 60.6, 34.8, 27.2, 25.0, 23.9, 19.0 (3C), -5.0 (2C). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{29}H_{35}N_2O_6Si$: 535.2264 found: 535.2259.

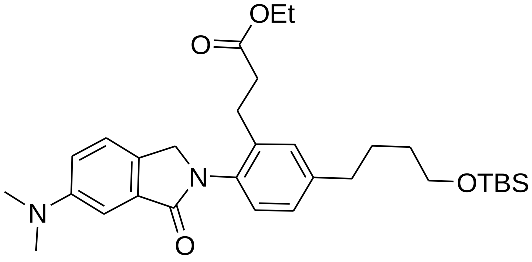
Ethyl-3-(2-(6-amino-1-oxoisoindolin-2-yl)-5-(4-(tert-butyldimethylsilyloxy)butyl)phenyl)propanoate (255). (BH12-035)



255

To a solution of **254** (2.0 g, 3.76 mmol) in 30 mL of ethyl acetate, 50 mg of 10% palladium/carbon was added and shake under 30 psi hydrogen gas overnight. The reaction mixture was filtered through Celite and concentrated under vacuum to give 1.91 g (99% yield) of compound **255** as a yellow oil. This molecule was used in the subsequent step without purification. ^{1}H NMR δ 7.30–6.90 (m, 6H), 4.62 (s, 2H), 4.20 (q, *J* = 6.8, 2H), 3.64 (t, *J* = 7.2 Hz, 2H), 2.89 (m, 2H), 2.62 (m, 4H), 1.70–1.55 (m, 4H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR δ ppm 168.0, 165.0, 147.6, 138.4, 136.1, 131.4, 130.6, 128.4, 128.0, 127.2, 124.0, 119.6, 116.2, 109.8, 63.0, 61.2, 34.0, 31.2, 29.9, 28.6, 27.4, 26.6, 25.4, 24.8, 18.0 (3C), -5.4 (2C). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{29}H_{43}N_2O_4Si$: 511.2992 found: 511.3001 .

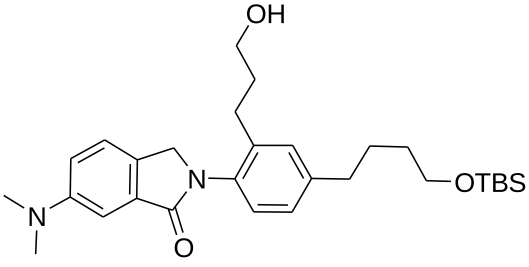
Ethyl 3-(5-(4-(tert-butyldimethylsilyloxy)butyl)-2-(6-(dimethylamino)-1-oxoisoindolin-2-yl)phenyl)propanoate (**256**). (BH12-045)



256

To a solution of **255** (1.91 g, 3.76 mmol) in MeOH, formalin (37% W/W, 6.11 g, 37.6 mmol) and sodium cyanoborohydride (1.42 g, 22.5 mmol) were added, and the solution was stirred for 24 h at room temperature. The reaction solution was neutralized with saturated sodium bicarbonate and extracted with ethyl acetate three times. The combined organic layer was washed with saturated sodium chloride (70 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 1:1) to obtain 1.92 g (94.9% yield) of compound **256** as a yellow oil. ^{1}H NMR δ 7.35–6.90 (m, 6H), 4.58 (s, 2H), 4.20 (q, *J* = 6.8, 2H), 3.61 (t, *J* = 7.2 Hz, 2H), 2.99 (s, 6H), 2.82 (m, 2H), 2.58 (m, 4H), 1.70–1.55 (m, 4H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ ppm 168.2, 165.0, 148.2, 140.1, 138.2, 132.3, 131.9, 129.8, 129.6, 126.7, 120.9, 115.6, 113.0, 106.4, 62.8, 60.1, 41.8(2C), 34.6, 32.0, 29.6, 27.3, 26.9, 26.1, 25.8, 24.9, 18.0 (3C), -5.2 (2C). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{31}H_{47}N_2O_4Si$: 539.3305 found: 539.3305.

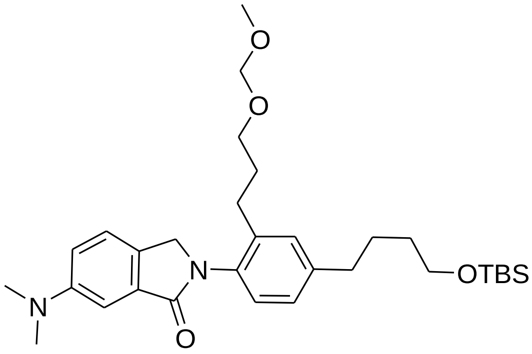
2-(4-(4-(tert-Butyldimethylsilyloxy)butyl)-2-(3-hydroxypropyl)phenyl)-6-(dimethylamino)isoindolin-1-one (257) (BH12-047)



257

To a cold (-78 °C) solution of **256** (1.92 g, 3.5 mmol) in 40 mL anhydrous THF under argon, 9 mL (9 mmol) of diisobutylaluminum hydride (1M in toluene) solution was added dropwise. After adding, the reaction was stirred at -30 °C for 2 hours until no starting material remained, quenched with 2 mL of H_2O, filtered and extracted the filtrate three times with ethyl acetate (60 mL each). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrate under vacuum. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 1:2) to obtain 1.68 g (95% yield) of compound **257** as a yellow oil. ^{1}H NMR δ 7.35–6.90 (m, *6*H), 4.60 (s, 2H), 3.61 (m, 4H), 2.99 (s, 6H), 2.69 (t, *J* = 6.4 Hz, 2H), 2.55 (t, *J* = 8.4 Hz, 2H), 1.86 (m, 2H), 1.70–1.40 (m, 4H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR δ ppm 168.8, 149.8, 139.1, 136.5, 131.6, 129.0, 128.7, 128.2, 127.9, 126.5, 122.2, 116.0, 105.1, 63.8, 60.1, 53.8, 50.4, 39.8 (2C), 37.5, 35.2, 28.4, 27.3, 26.2, 18.4 (3C), -5.1 (2C). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{29}H_{45}N_2O_3Si$: 497.3199 found: 497.3221.

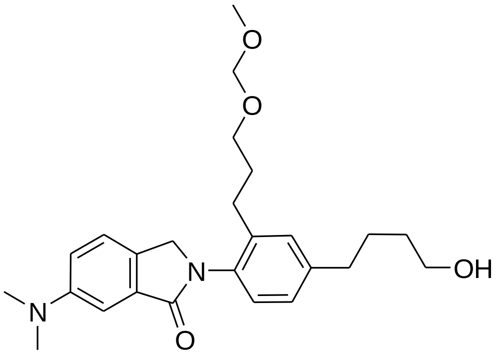
2-(4-(4-(tert-Butyldimethylsilyloxy)butyl)-2-(3-(methoxymethoxy)propyl)phenyl)-6-(dimethylamino)isoindolin-1-one (258) (BH12-051)



258

To a solution of **257** (1.68 g, 3.38 mmol) in 100 mL anhydrous methylene chloride under argon, *N,N*-diisopropylethylamine (1.09 g, 8.45 mmol) and chloromethyl methyl ether (0.544 g, 6.76 mmol) were added. The reaction was reflux for 12 hours, diluted with 100 mL methylene chloride, washed with 10% citric acid (50 mL), saturated $NaHCO_3$ solution (50 mL), and brine (50 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 1:1) to obtain 1.70 g (93% yield) of compound **258** as a yellow oil. ^{1}H NMR δ 7.35–6.90 (m, *6*H), 5.22 (s, 2H), 4.57 (s, 2H), 3.97 (t, *J* = 6.4 Hz, 2H), 3.61 (m, 5H), 2.99 (s, 6H), 2.59 (m, 4H), 1.90–1.55 (m, 6H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR δ ppm 168.7, 149.7, 139.1, 136.5, 131.9, 129.1, 128.8, 128.3, 127.9, 126.5, 122.2, 116.1, 105.1, 99.9, 63.8, 62.1, 60.6, 53.8, 50.4, 39.8 (2C), 35.1, 32.2, 28.4, 27.3, 26.2, 18.5 (3C), -4.9 (2C). HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{31}H_{49}N_2O_4Si$: 541.3462 found: 541.3459.

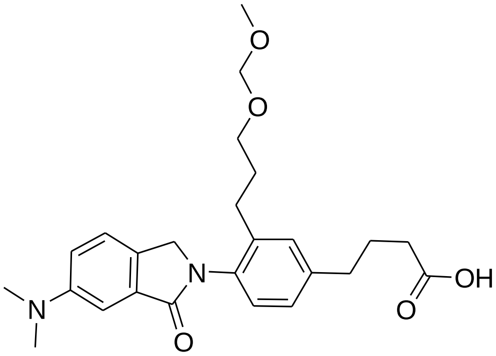
6-(Dimethylamino)-2-(4-(4-hydroxybutyl)-2-(3-(methoxymethoxy)propyl)phenyl)isoindolin-1-one (**259**). (BH12-055)



259

To a solution of **258** (1.70 g, 3.18 mmol) in 20 mL THF under argon, 3.18 mL of 1M tetra-*n*-butylammonium fluoride THF solution was added. The reaction was stirred under room temperature for 4 hours until no starting material remained, washed with water (2 x 20 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to obtain 1.34 g (99% yield) of compound **259** as a yellow oil. This material was used in the subsequent step without further purification. ^{1}H NMR δ 7.35–6.90 (m, *6*H), 5.23 (s, 2H), 4.60 (s, 2H), 3.97 (t, *J* = 6.4 Hz, 2H), 3.61 (m, 5H), 2.99 (s, 6H), 2.58 (m, 4H), 1.88–1.56 (m, 6H); ^{13}C NMR δ ppm 169.9, 151.5, 140.1, 137.5, 133.2, 129.9, 129.5, 128.7, 128.2, 127.5, 123.2, 117.1, 106.3, 99.9, 63.8, 62.1, 53.8, 50.2, 41.0 (2C), 36.4, 35.1, 31.6, 28.8, 25.1. HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{25}H_{35}N_2O_4$: 427.2597 found: 427.2612.

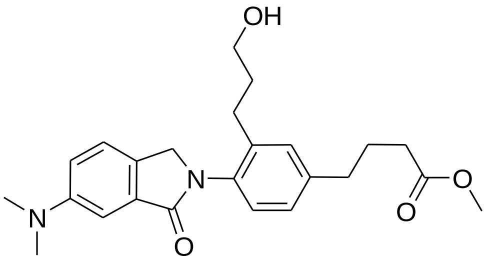
4-(4-(6-(Dimethylamino)-1-oxoisoindolin-2-yl)-3-(3-(methoxymethoxy)propyl)phenyl)butanoic acid (**260**). (BH12-058)



260

To a solution of **259** (1.065 g, 2.5 mmol) in 20 mL DMSO under argon, IBX (1.05 g, 3.75 mmol) was added and stirred at room temperature overnight. To it, 200 mL of ethyl acetate was added and washed with water (3 x 50 mL). The organic layer was concentrated and the residue was re-dissolved with 30 mL of DMF. To it, oxone (0.57 g, 3.75 mmol) was added and stirred for 6 hours. The solution was basified with 100 mL of saturated $NaHCO_3$, washed with 50 mL of methylene chloride, acidified 10% HCl until pH = 4, and extracted with ethyl acetate (4 x 100 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum to obtain 0.711 g (64.6% yield) of compound **260** as a pale yellow solid. This material was used in the subsequent step without further purification. mp. 191~192 ^{o}C; ^{1}H NMR δ 7.35–6.90 (m, 6H), 5.21 (s, 2H), 4.60 (s, 2H), 3.97 (t, *J* = 6.4 Hz, 2H), 3.61 (s, 3H), 2.99 (s, 6H), 2.58 (m, 4H), 2.39 (t, *J* = 6.4 Hz, 2H), 1.88 (m, 2H) 1.54 (m, 2H); ^{13}C NMR δ ppm 176.3, 169.6, 151.3, 140.2, 137.6, 132.6, 129.9, 129.6, 129.1, 128.6, 127.5, 123.1, 117.1, 106.7, 99.8, 62.0, 53.8, 50.2, 40.8 (2C), 37.8, 33.2, 31.2, 27.0, 25.1. HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{25}H_{32}N_2O_5$: 440.2311 found: 440.2317.

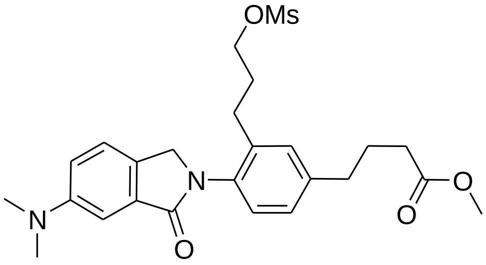
Methyl-4-(4-(6-(dimethylamino)-1-oxoisoindolin-2-yl)-3-(3-hydroxypropyl)phenyl)butanoate (261). (BH12-064)



261

To a solution of **260** (0.711 g, 1.61 mmol) in 20 mL of MeOH, 2 mL of conc. HCl is added and stirred for 24 hours. To it, 50 mL of saturated $NaHCO_3$ solution was added, and concentrated under vacuum to remove MeOH. The residue was extracted with ethyl acetate (4 x 50 mL) and the combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 1:1) to obtain 0.584 g (88% yield) of compound **261** as a yellow oil. ^{1}H NMR δ 7.35–6.90 (m, 6H), 4.57 (s, 2H), 3.71 (s, 3H), 3.61 (t, *J* = 6 Hz, 2H), 2.99 (s, 6H), 2.58 (m, 4H), 2.39 (t, *J* = 6.4 Hz, 2H), 1.88 (m, 2H) 1.54 (m, 2H); ^{13}C NMR δ ppm 174.8, 169.8, 151.1, 140.1, 137.6, 132.5, 129.9, 129.6, 129.2, 128.4, 127.5, 123.1, 117.1, 106.6, 61.4, 53.8, 51.2, 40.8 (2C), 37.8, 32.2, 31.8, 27.1, 25.1. HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{24}H_{31}N_2O_4$: 411.2284 found: 411.2279.

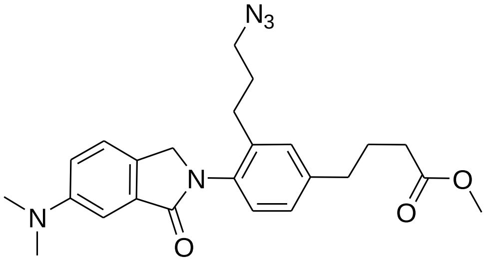
Methyl-4-(4-(6-(dimethylamino)-1-oxoisoindolin-2-yl)-3-(3-(methylsulfonyloxy)propyl)phenyl)butanoate (**262**) (BH12-078)



262

To a mixture of **261** (0.6 g, 1.467 mmol) and dry triethylamine (306 µL, 2.19 mmol) in 20 mL of dry dichloromethane under argon, methanesulfonyl chloride (0.251 g, 2.19 mmol) was added dropwise at 0°C. The reaction mixture was stirred for 8 hours at room temperature, quenched with 5 mL of water, and extracted with methylene chloride (3 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 1:1) to obtain 0.713 g (99% yield) of compound **262** as a yellow oil. ^{1}H NMR δ 7.35–6.90 (m, 6H), 4.61 (s, 2H), 4.31 (t, *J* = 6.4 Hz, 2 H), 3.72 (s, 3H), 3.07 (s, 3H), 2.99 (s, 6H), 2.58 (m, 4H), 2.40 (t, *J* = 6.4 Hz, 2H), 1.88 (m, 2H) 1.60 (m, 2H); ^{13}C NMR δ ppm 174.8, 169.8, 151.2, 140.1, 137.6, 132.4, 130.2, 129.6, 128.6, 128.2, 127.5, 123.0, 117.1, 106.4, 68.2, 53.8, 51.2, 41.2 (2C), 37.6, 32.2, 31.8, 31.4, 27.0, 25.3. HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{25}H_{33}N_2O_6S$: 489.2059 found: 489.2023.

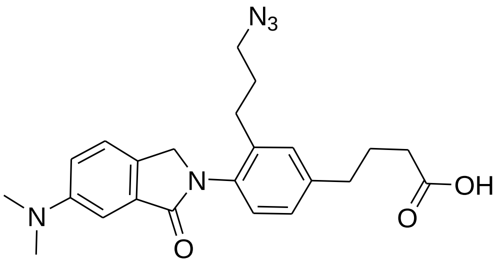
Methyl-4-(3-(3-azidopropyl)-4-(6-(dimethylamino)-1-oxoisoindolin-2-yl)phenyl)butanoate (263) (BH12-082)



263

To a solution of **262** (0.713 g, 1.46 mmol) in 30 mL of dry DMF under argon, NaN_3 (379 mg, 5.83 mmol) was added. The reaction mixture was stirred at room temperature for 18 hours. To it, $NaHCO_3$ solution (10 mL) was added and extracted with methylene chloride (3 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 1:1) to obtain 0.617 g (97.2% yield) of compound **263** as a yellow oil. ^1H NMR δ 7.35–6.90 (m, 6H), 4.61 (s, 2H), 3.70 (s, 3H), 3.25 (t, *J* = 6.0 Hz, 2H), 3.01 (s, 6H), 2.58 (m, 4H), 2.38 (t, *J* = 6.4 Hz, 2H), 1.88 (m, 2H) 1.59 (m, 2H); ^{13}C NMR δ ppm 176.2, 169.9, 151.6, 140.8, 138.1, 134.6, 132.8, 131.1, 130.6, 130.2, 129.8, 126.0, 115.2, 105.0, 53.8, 53.4, 50.9, 40.6 (2C), 35.0, 32.4, 31.8, 29.3, 28.7. HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{24}H_{30}N_5O_3$: 436.2349 found: 436.2361.

4-(3-(3-Azidopropyl)-4-(6-(dimethylamino)-1-oxoisoindolin-2-yl)phenyl)butanoic acid (242). (BH12-090)



242

To a solution of **263** (0.617 g, 1.42 mmol) in 30 mL of MeOH, 2 mL of 10% aqueous LiOH solution was added and stirred at room temperature for 6 hours. The resulting solution was concentrated under vacuum to remove MeOH and washed with 50 mL of methylene chloride. The aqueous layer was acidified with 10% aqueous HCl until pH = 4, concentrated under vacuum and purified by a short column chromatography to obtain 0.532 g (89% yield) of compound **242** as a light yellow solid; mp. 183~186 ^{o}C; ^{1}H NMR δ 7.35–6.95 (m, 6H), 4.62 (s, 2H), 3.24 (t, *J* = 6.0 Hz, 2H), 3.02 (s, 6H), 2.58 (m, 4H), 2.39 (t, *J* = 8.0 Hz, 2H), 1.90 (m, 2H) 1.59 (m, 2H); ^{13}C NMR δ ppm 178.2, 169.1, 150.6, 139.2, 137.6, 133.4, 129.8, 129.2, 128.7, 128.3, 127.6, 124.3, 117.5, 106.4, 53.6, 50.9, 40.8 (2C), 35.0, 32.4, 31.8, 29.5, 28.9; HRMS-ESI: m/z [M + H]$^{+}$ calcd for $C_{23}H_{28}N_5O_3$: 422.2192 found: 422.2187.

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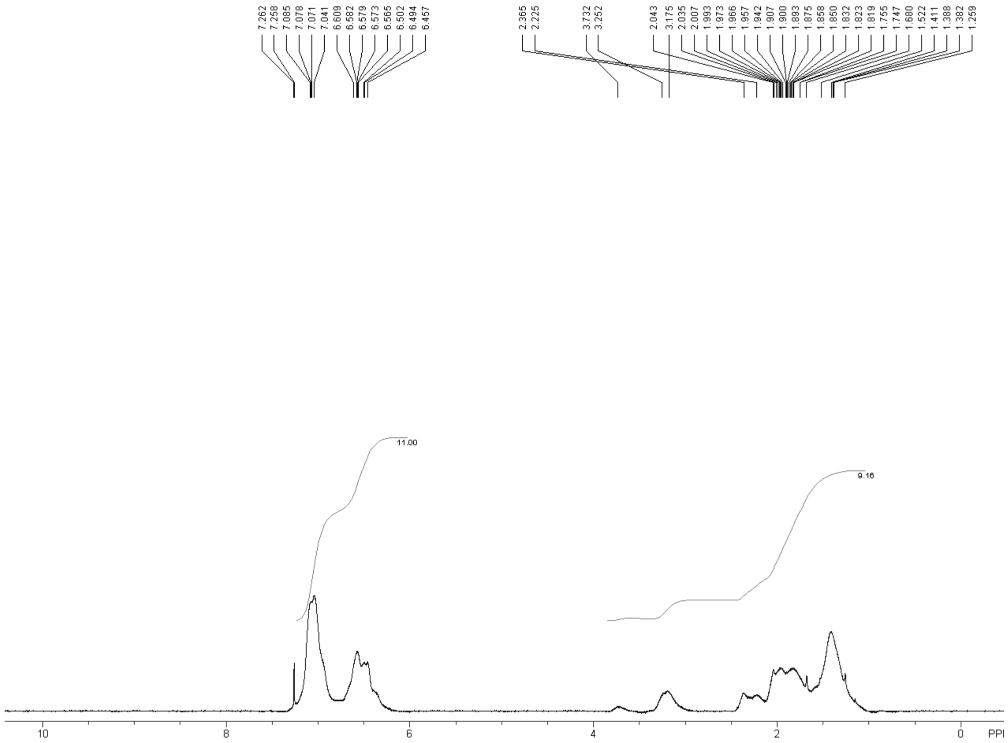
Appendix A. ^{1}H-NMR, ^{13}C NMR and Mass Spectrum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6.457
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2.225
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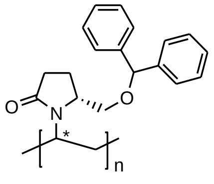
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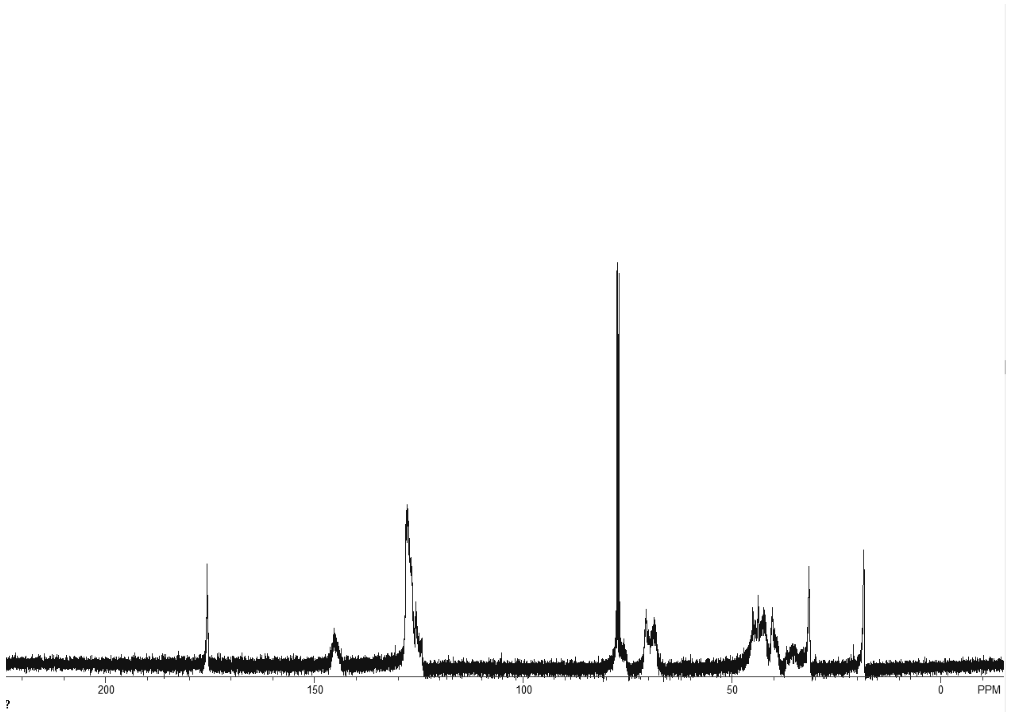
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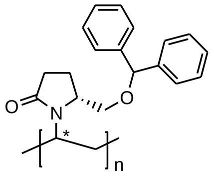
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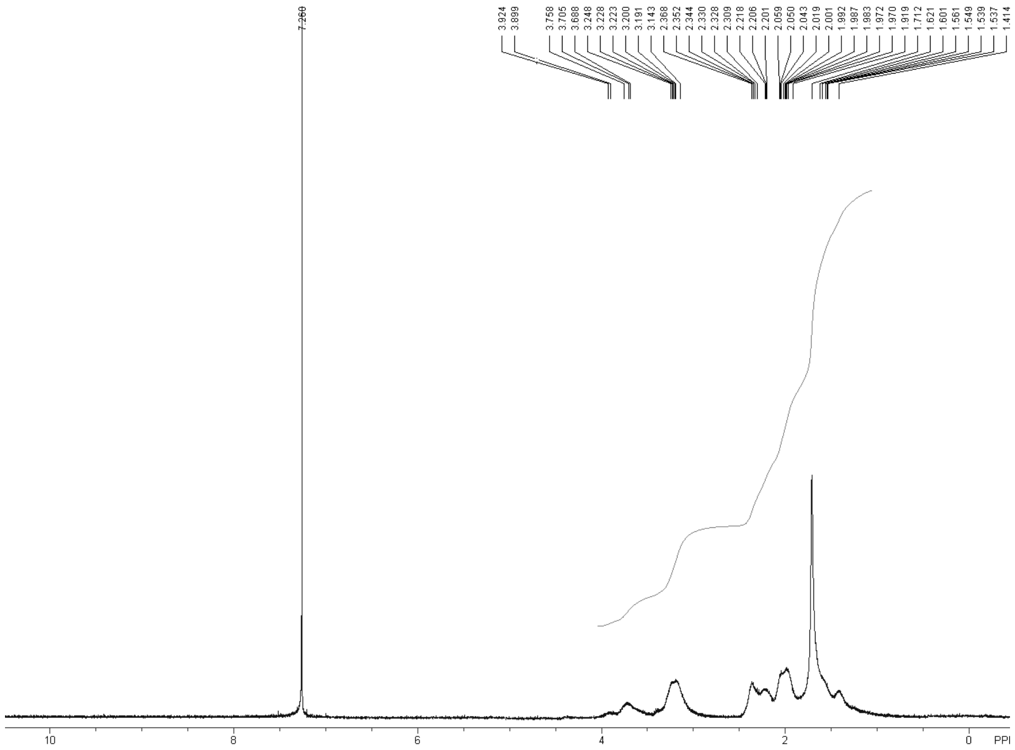

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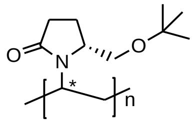

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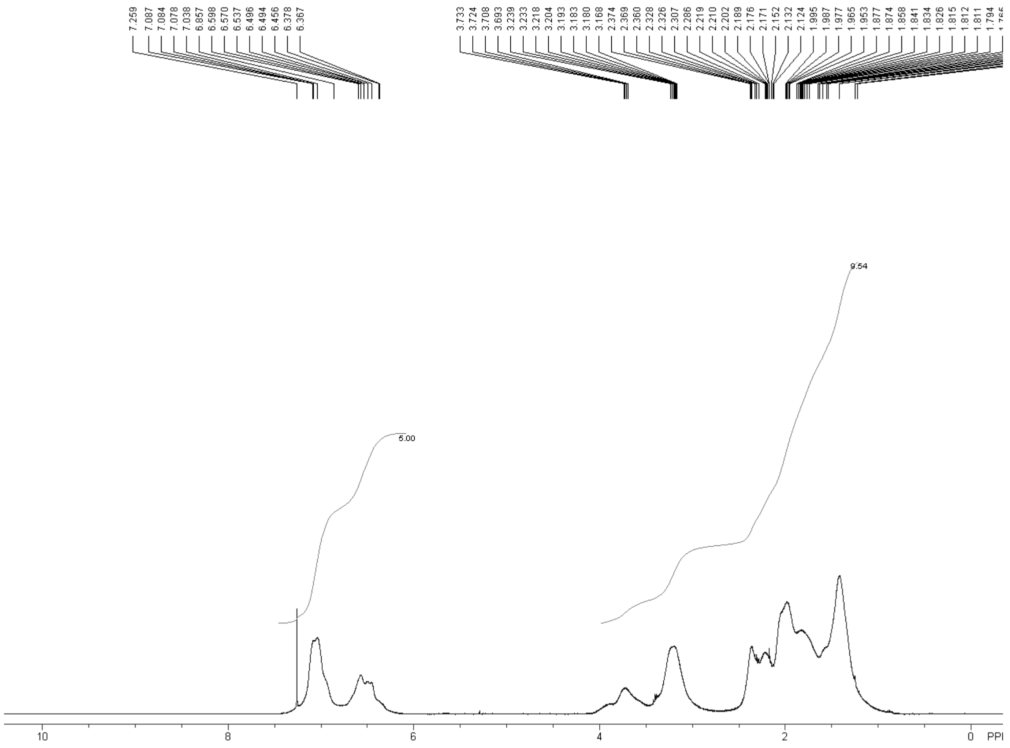

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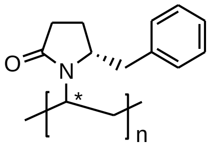

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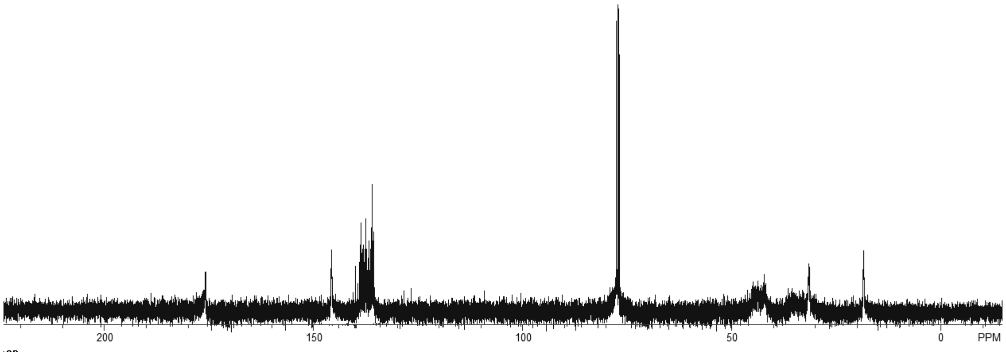
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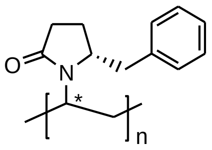
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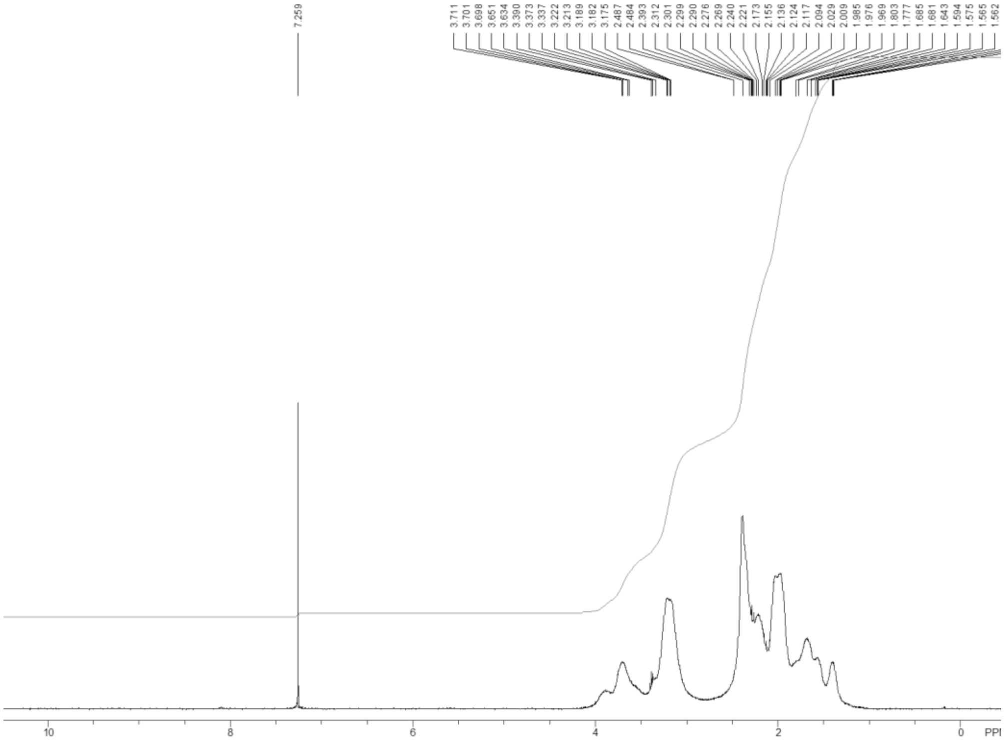
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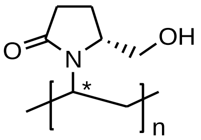
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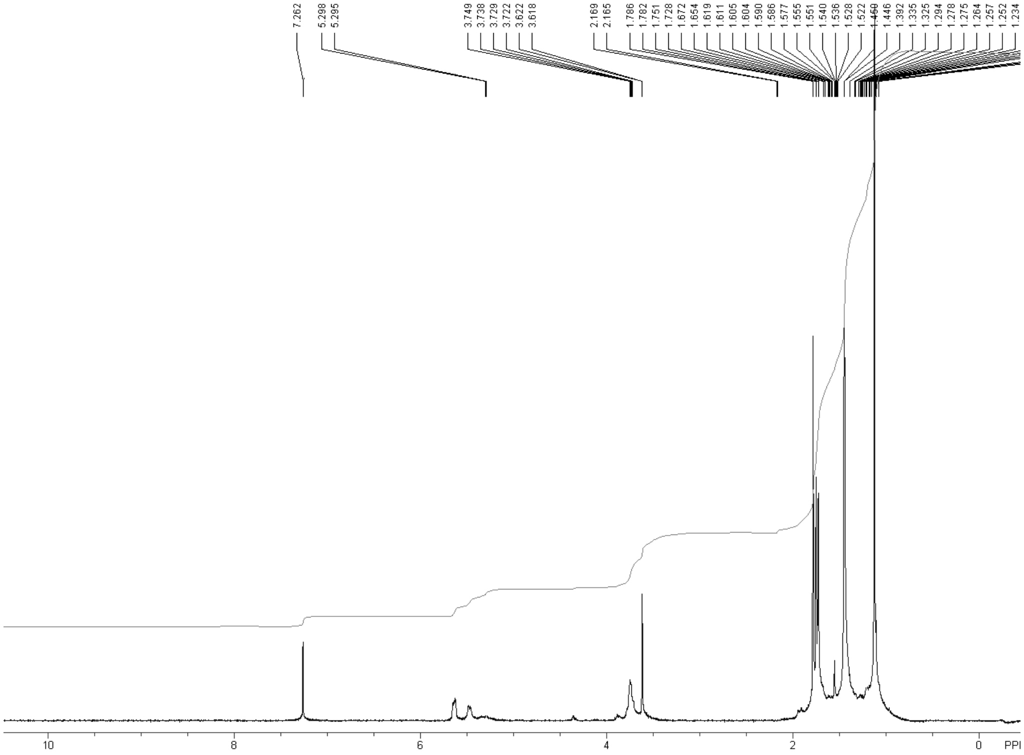
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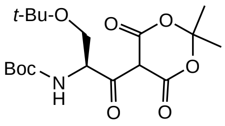
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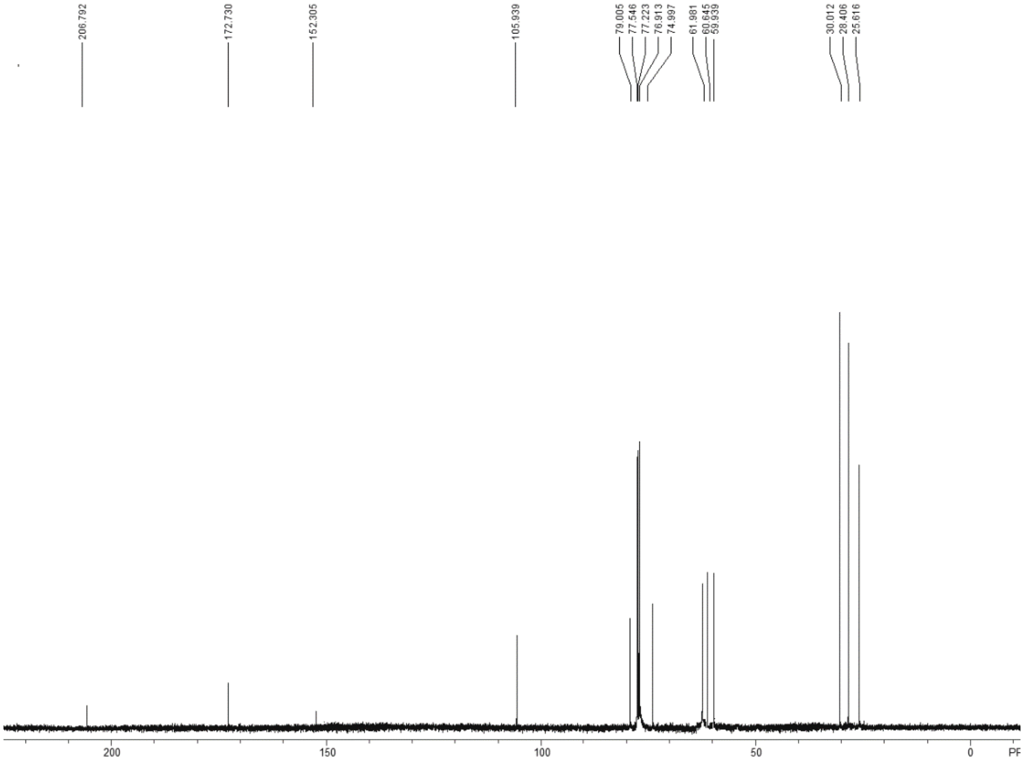
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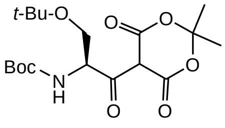
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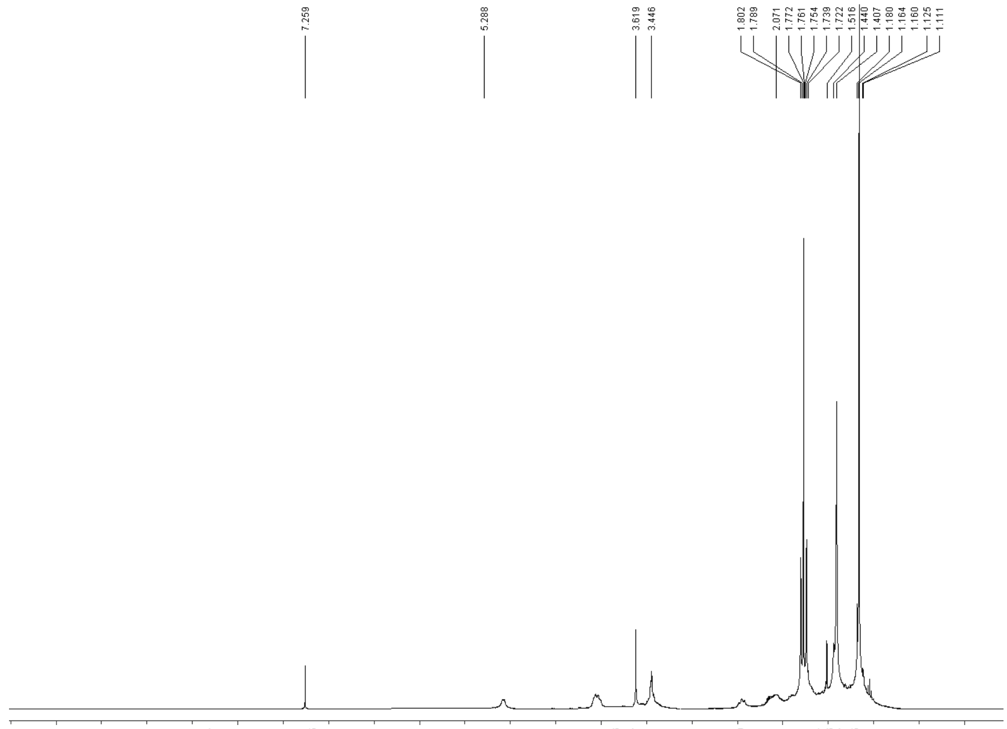
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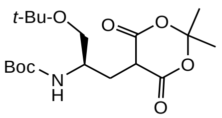
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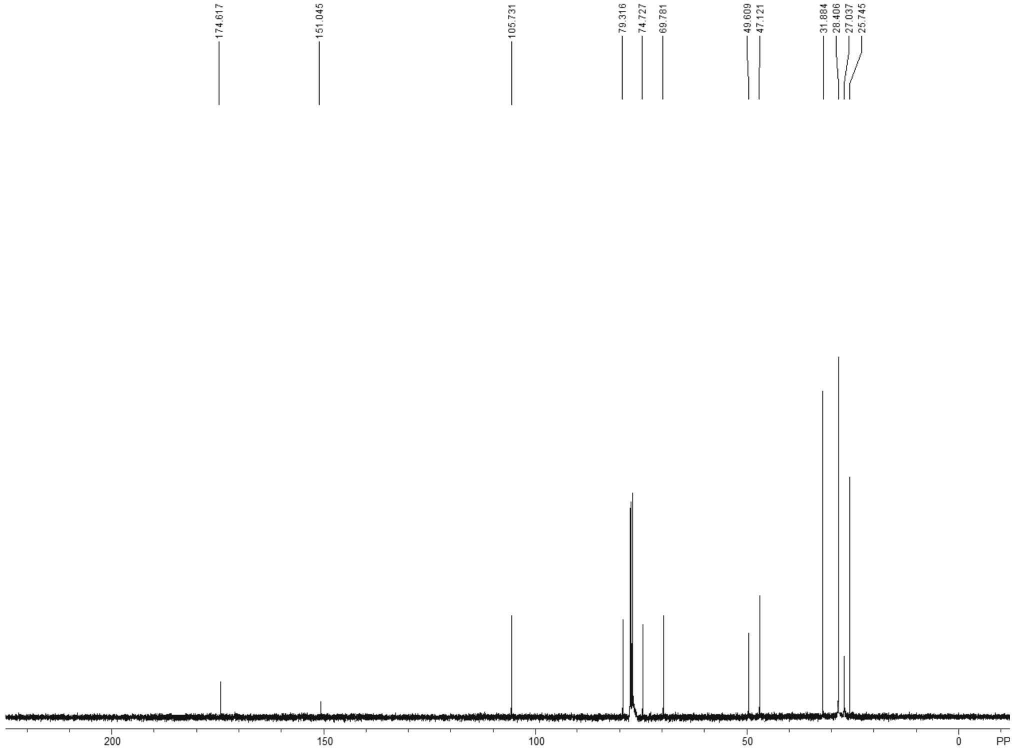
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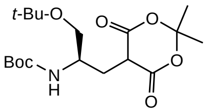
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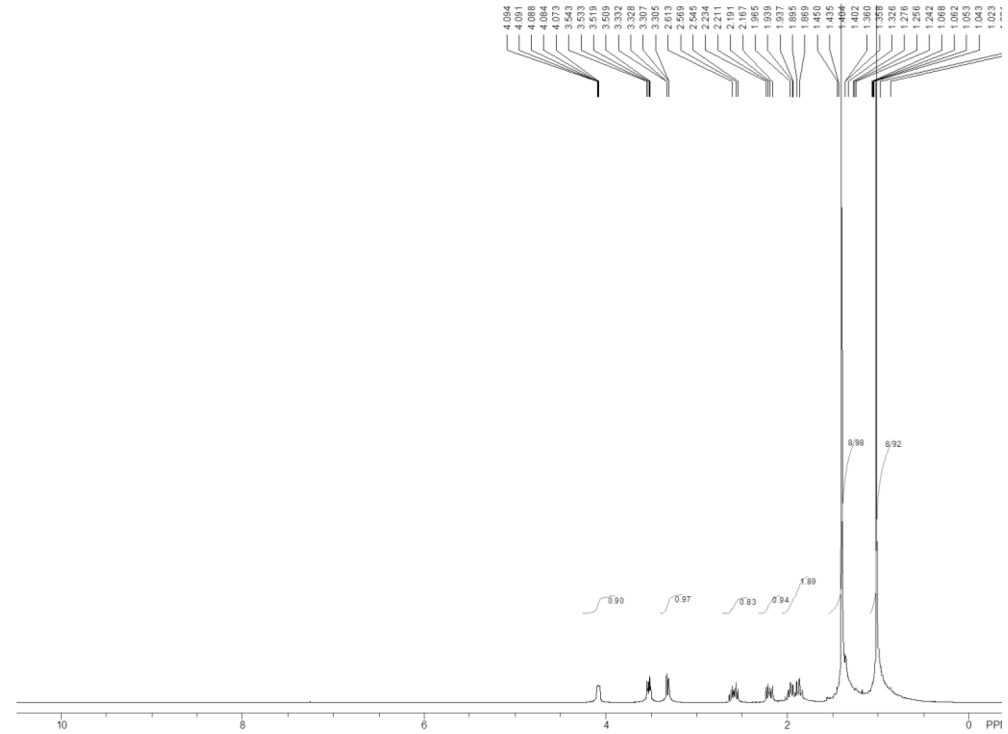
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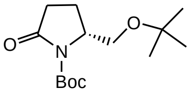
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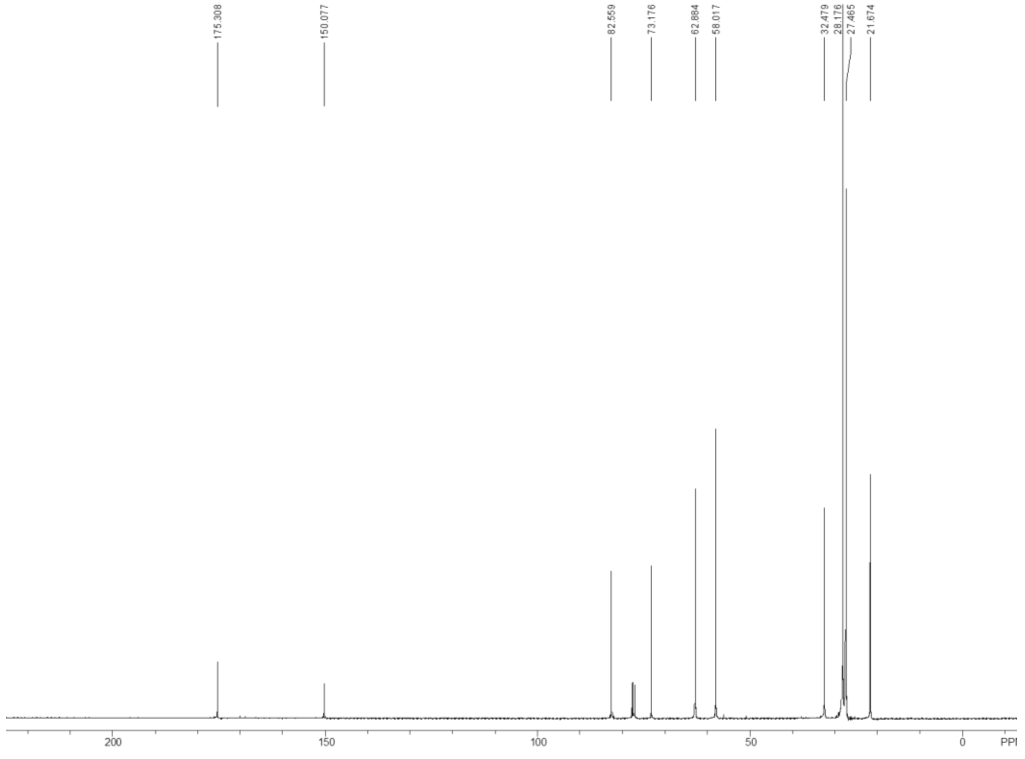
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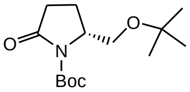
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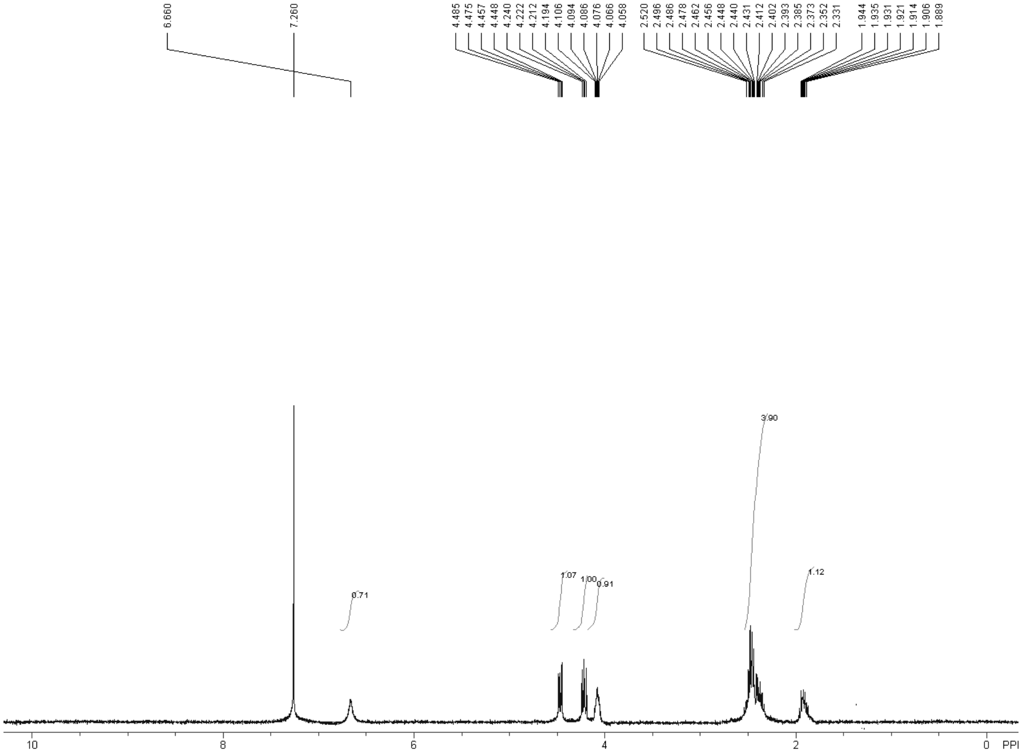
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2.331
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1.935
1.931
1.921
1.914
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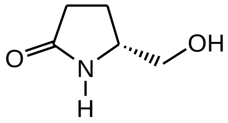
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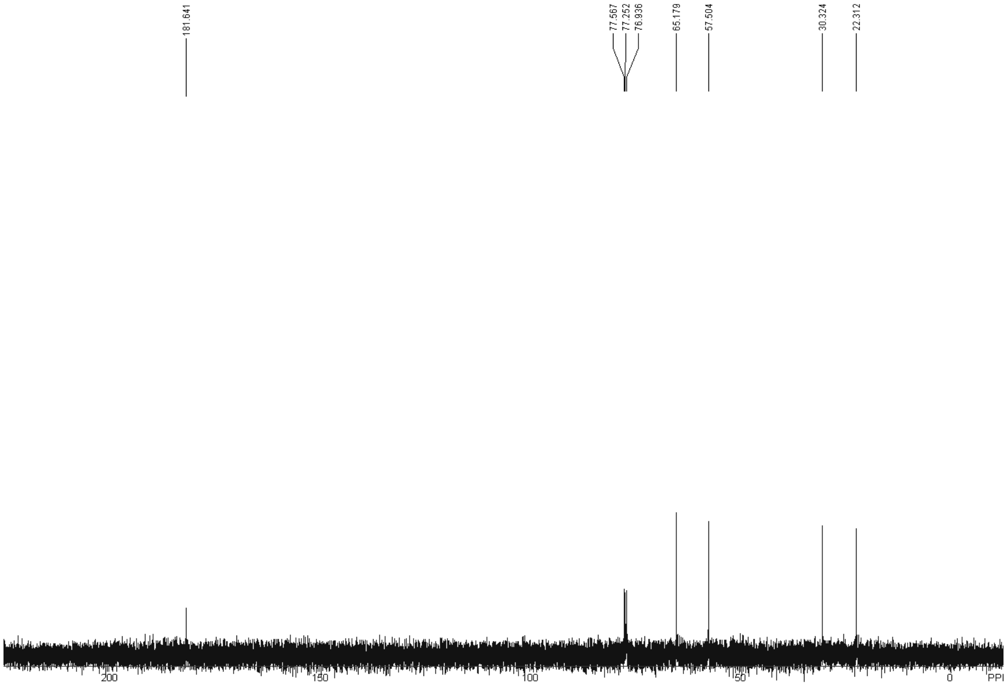
H
OH

11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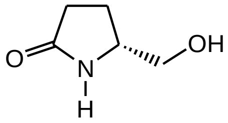
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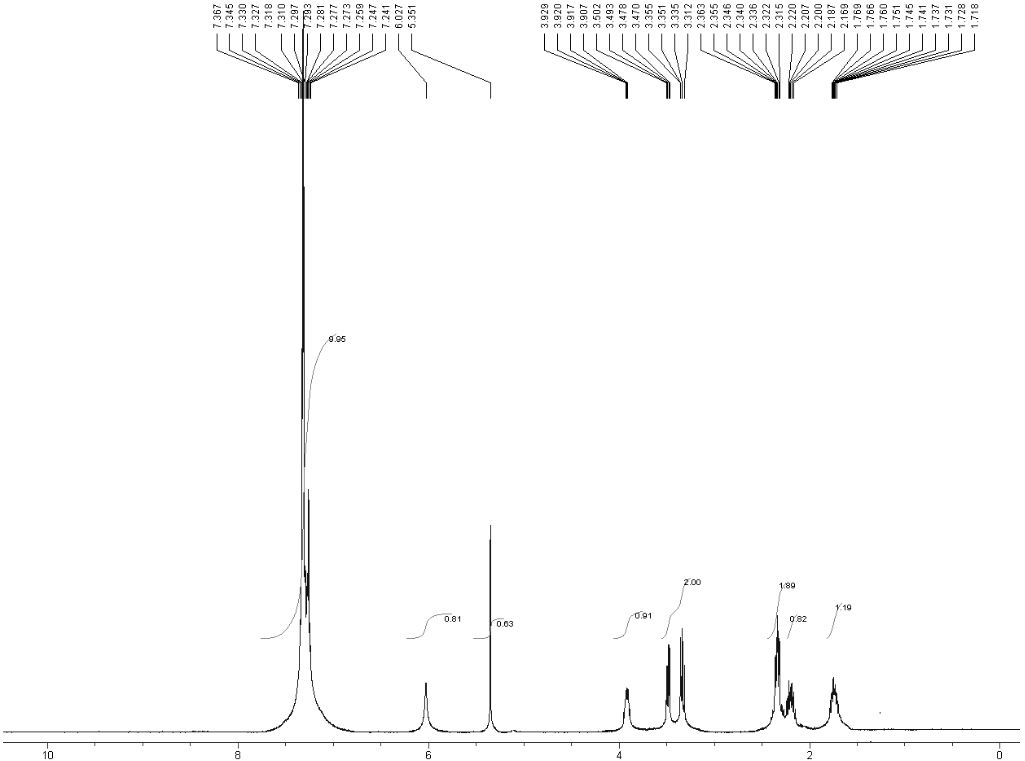
H
OH

11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3.920
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3.335
3.312
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2.220
2.207
2.200
2.187
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1.751
1.745
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1.737
1.731
1.728
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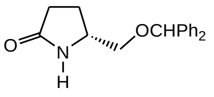
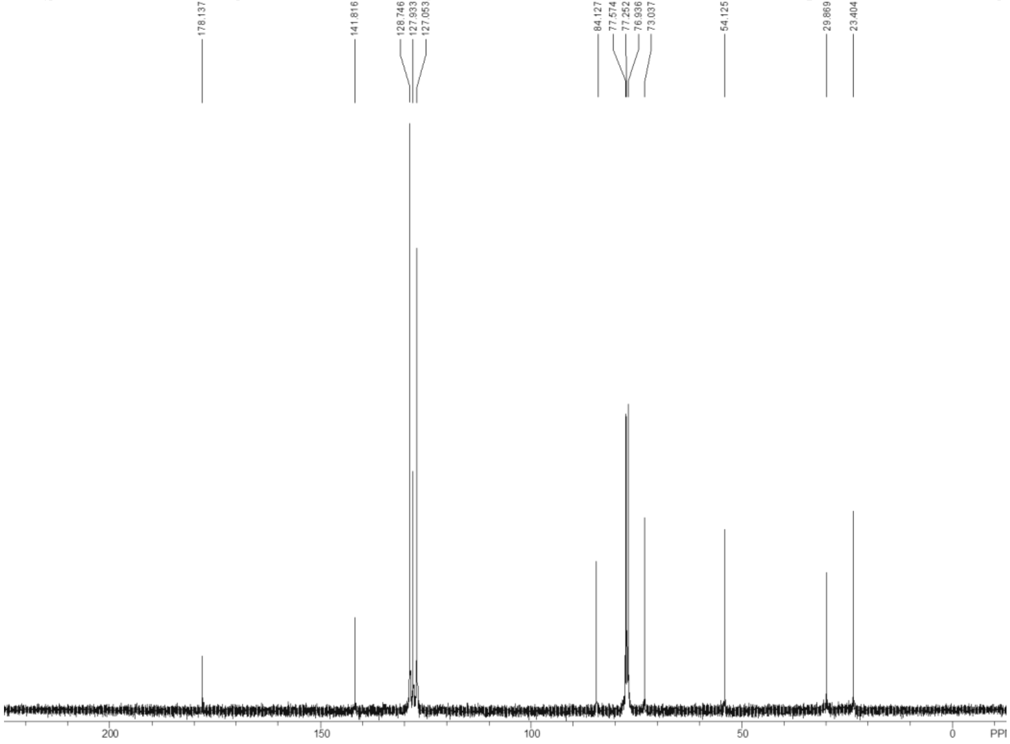

O
N
H
OCHPh$_2$

12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54.125
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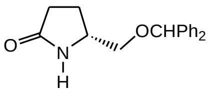
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H
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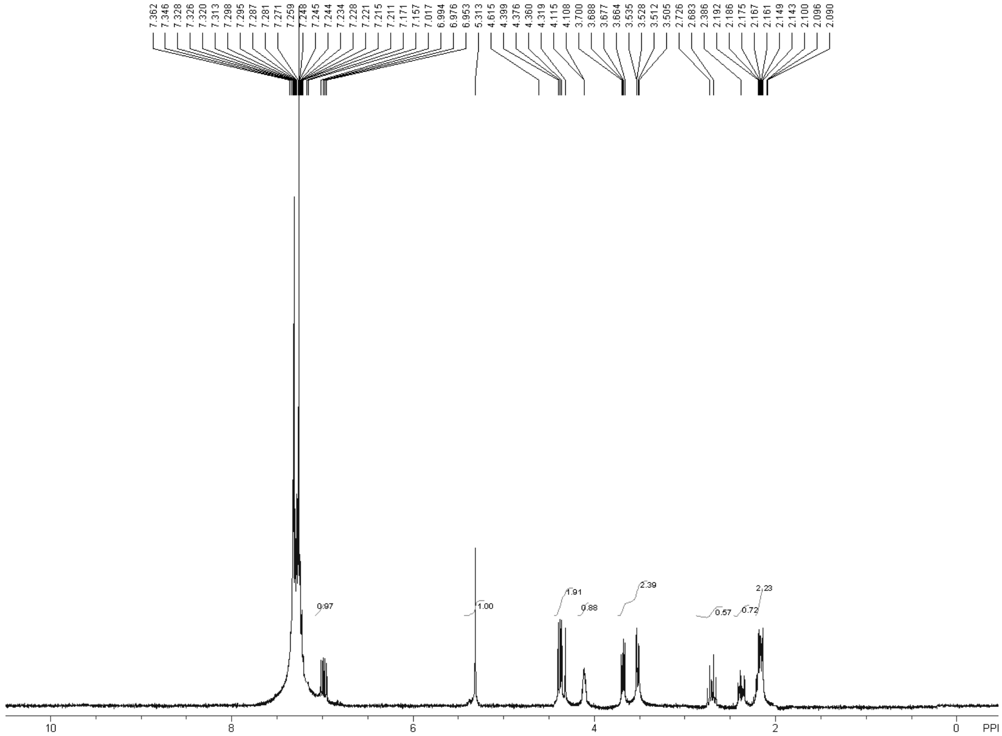
12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7.245
7.244
7.234
7.228
7.221
7.215
7.211
7.171
7.157
7.017
6.994
6.976
6.953
5.313
4.615
4.399
4.376
4.360
4.319
4.115
4.108
3.700
3.688
3.677
3.664
3.535
3.528
3.512
3.505
2.726
2.683
2.386
2.192
2.186
2.175
2.167
2.161
2.149
2.143
2.100
2.096
2.090
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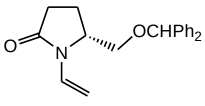
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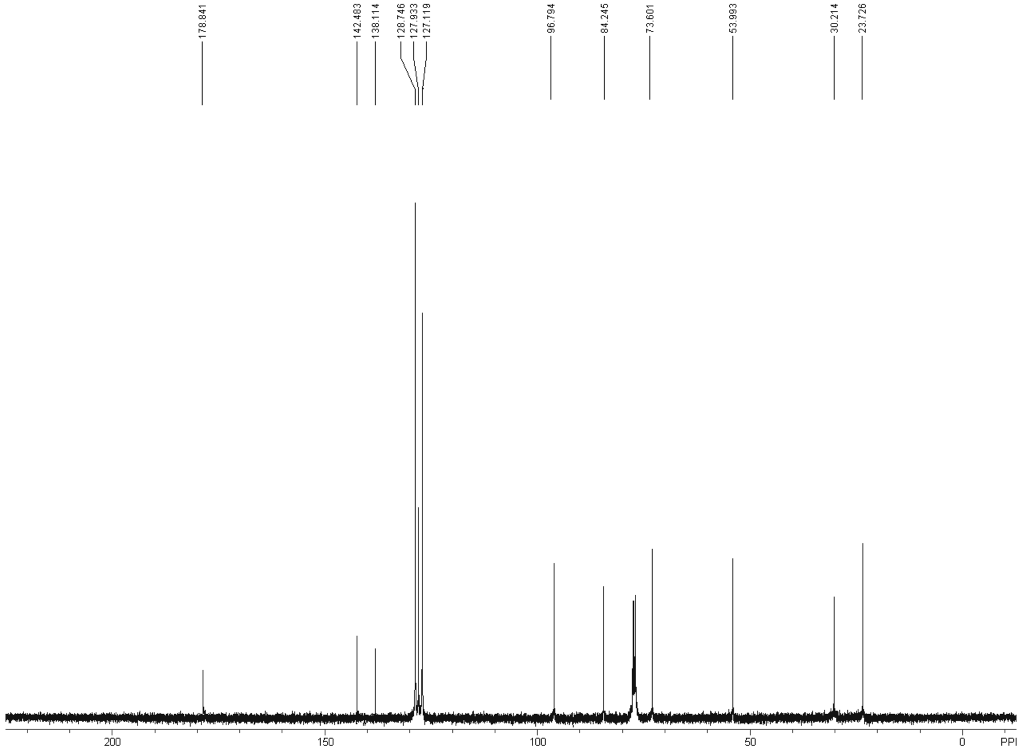
OCHPh2

13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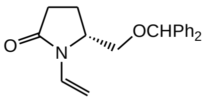
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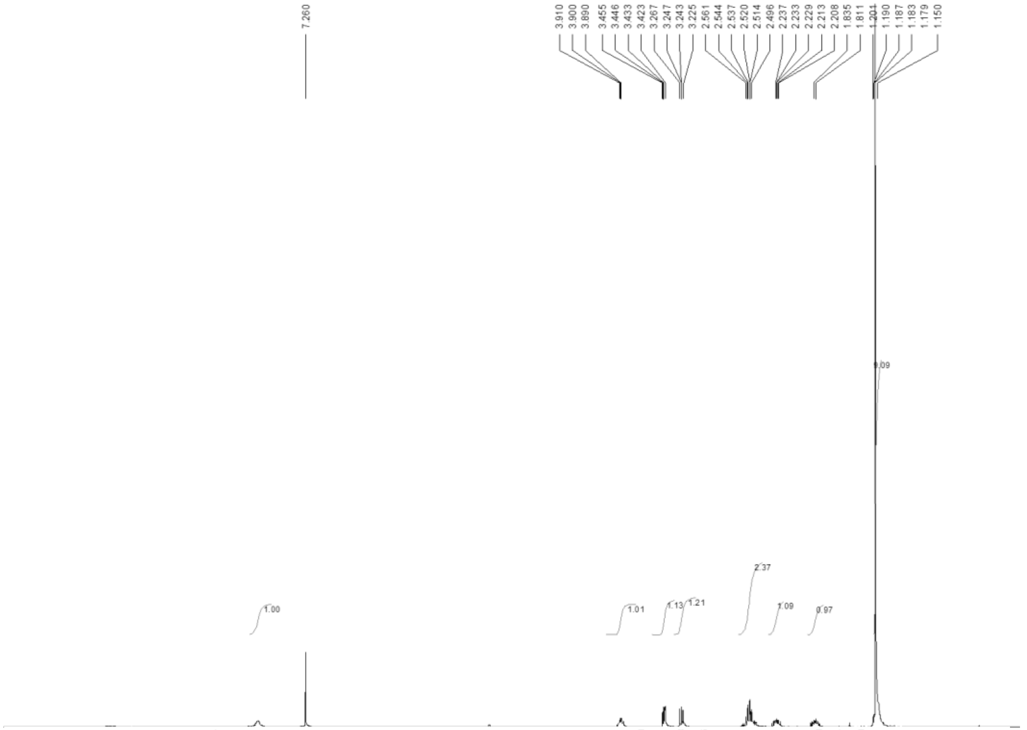
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3.900
3.890
3.455
3.446
3.433
3.423
3.267
3.247
3.243
3.225
2.561
2.544
2.537
2.520
2.514
2.496
2.237
2.233
2.229
2.213
2.208
1.835
1.811
1.201
1.190
1.187
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1.01
1.13
1.21
2.37
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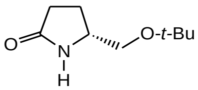
0.97
9.09
PP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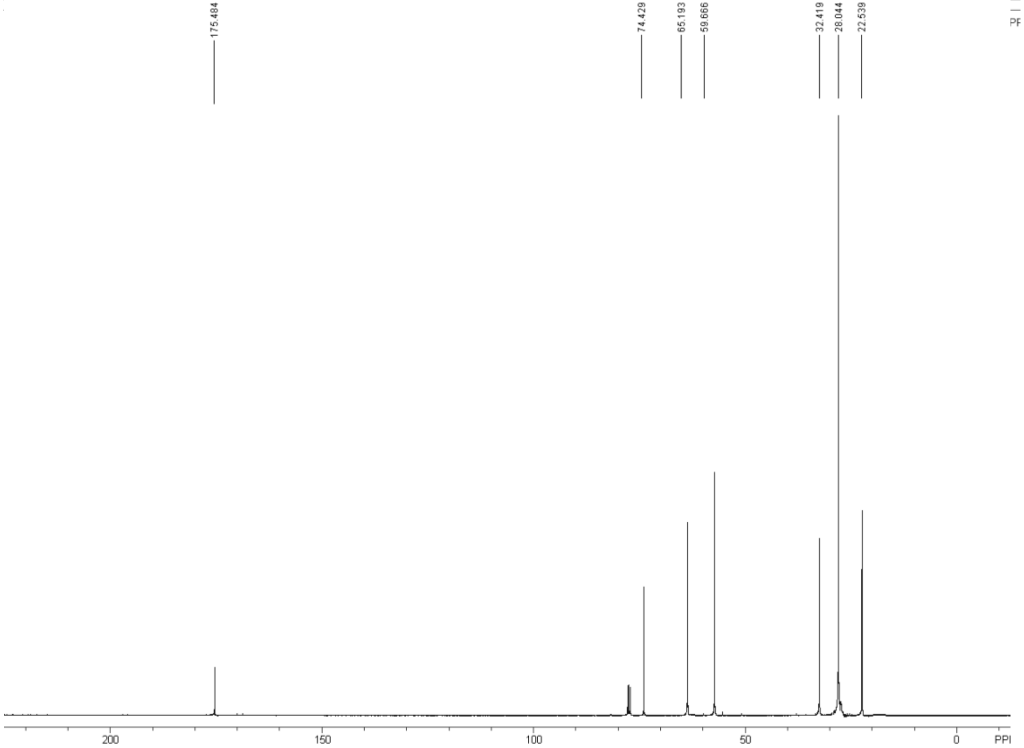
N
H
O-*t*-Bu

14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22.539
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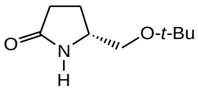
0
PP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N
H
O-*t*-Bu

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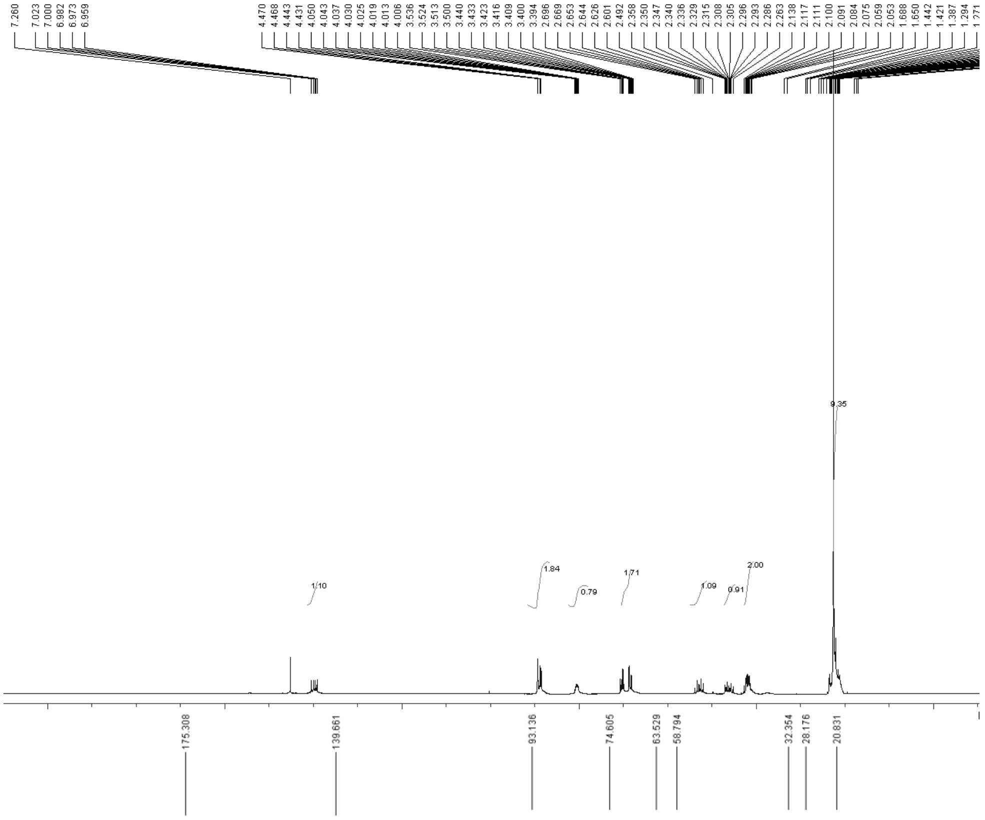
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4.037
4.030
4.025
4.019
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4.006
3.536
3.524
3.513
3.500
3.440
3.433
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3.394
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2.293
2.286
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2.100
2.091
2.084
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1.294
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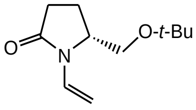
20.831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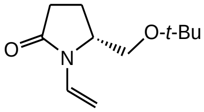
N
O-t-Bu

15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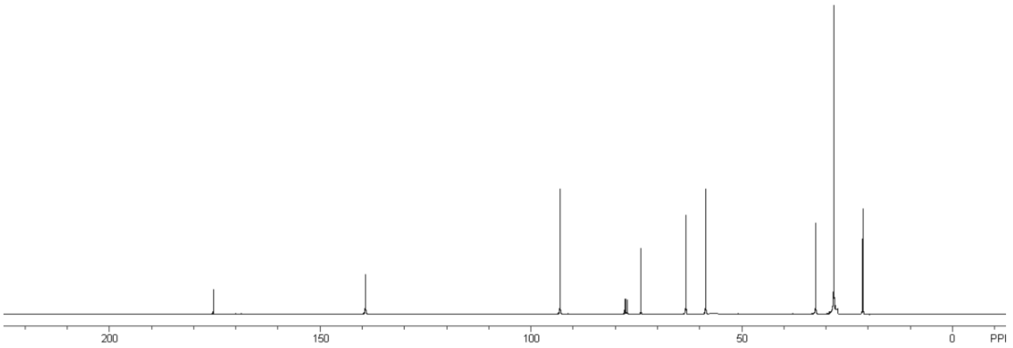
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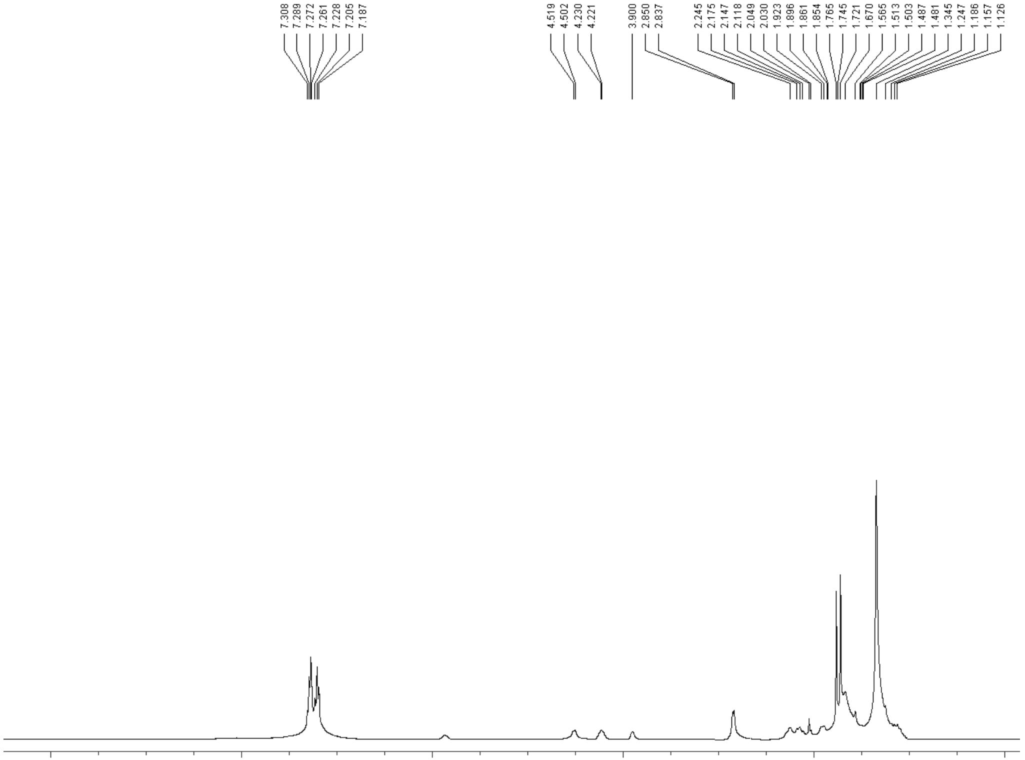
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4.230
4.221
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2.850
2.837
2.245
2.175
2.147
2.118
2.049
2.030
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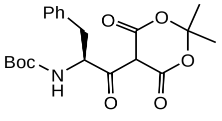
1.126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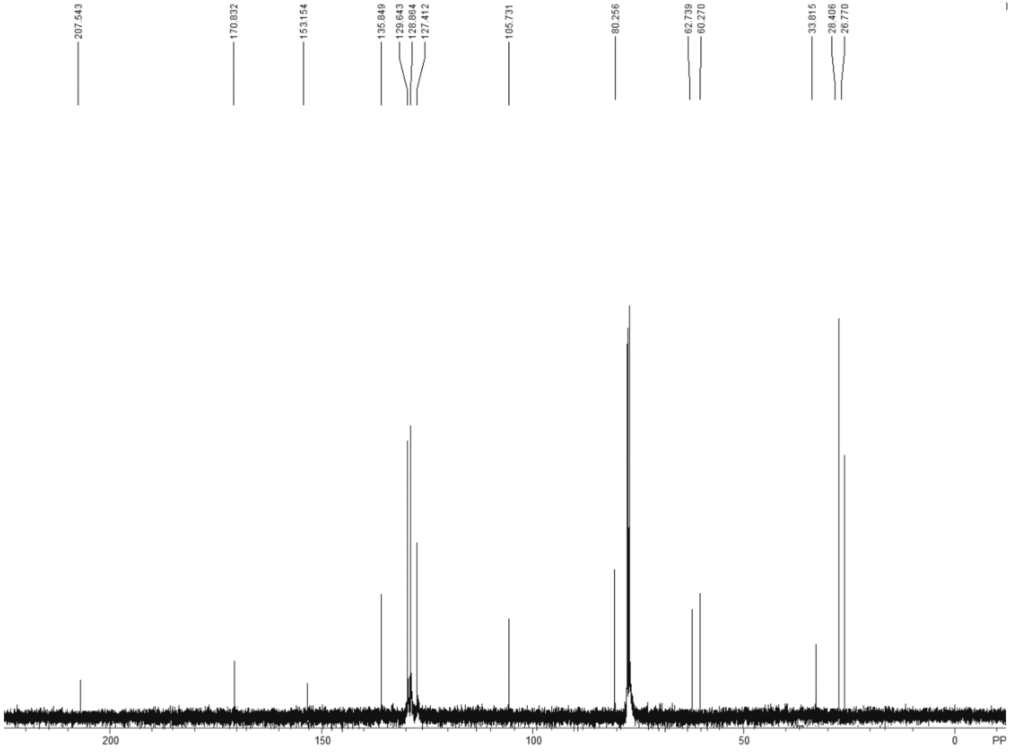
Boc
N
H
O
O
O
O

17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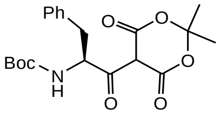
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Boc
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O

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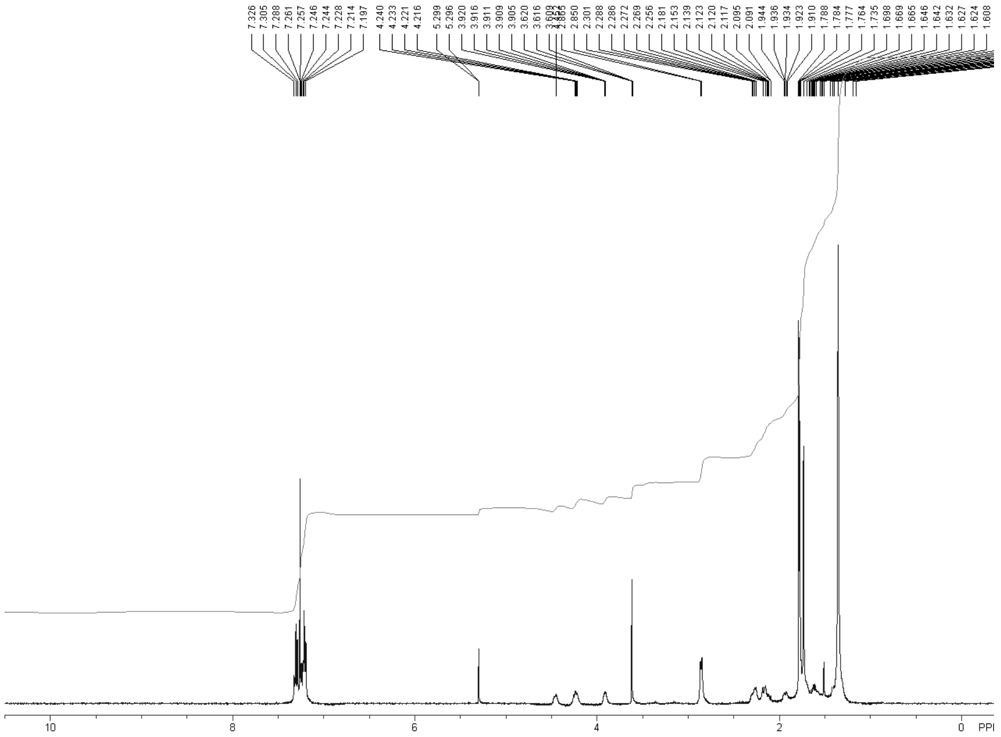
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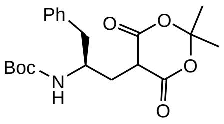
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Boc
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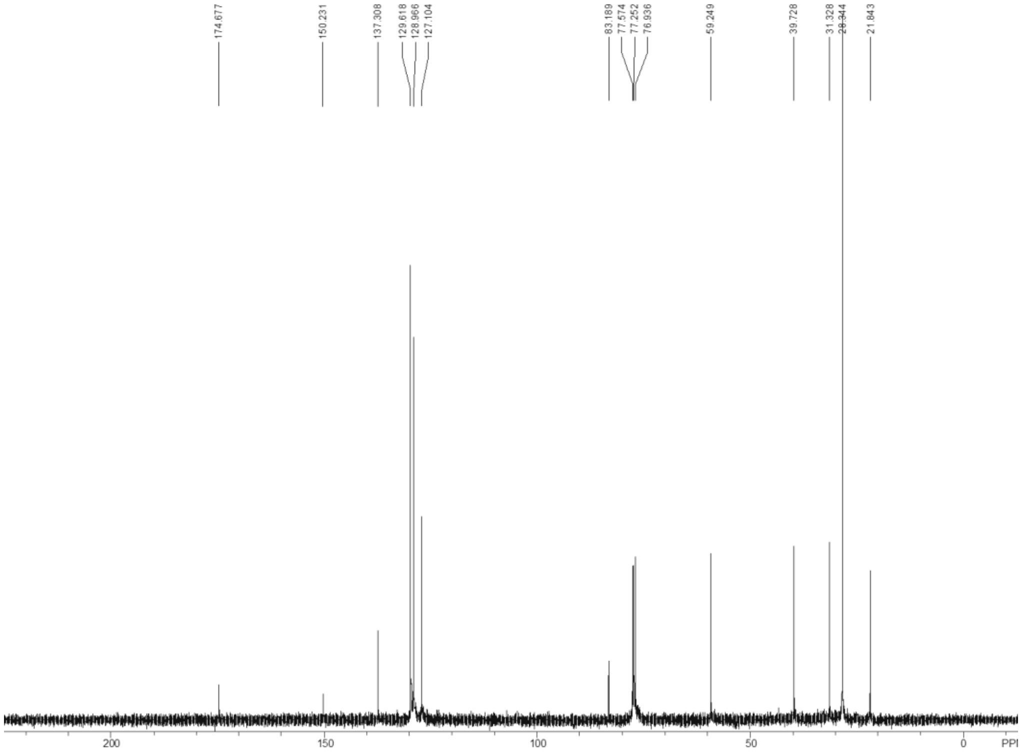
O

18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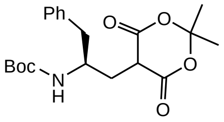
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Boc
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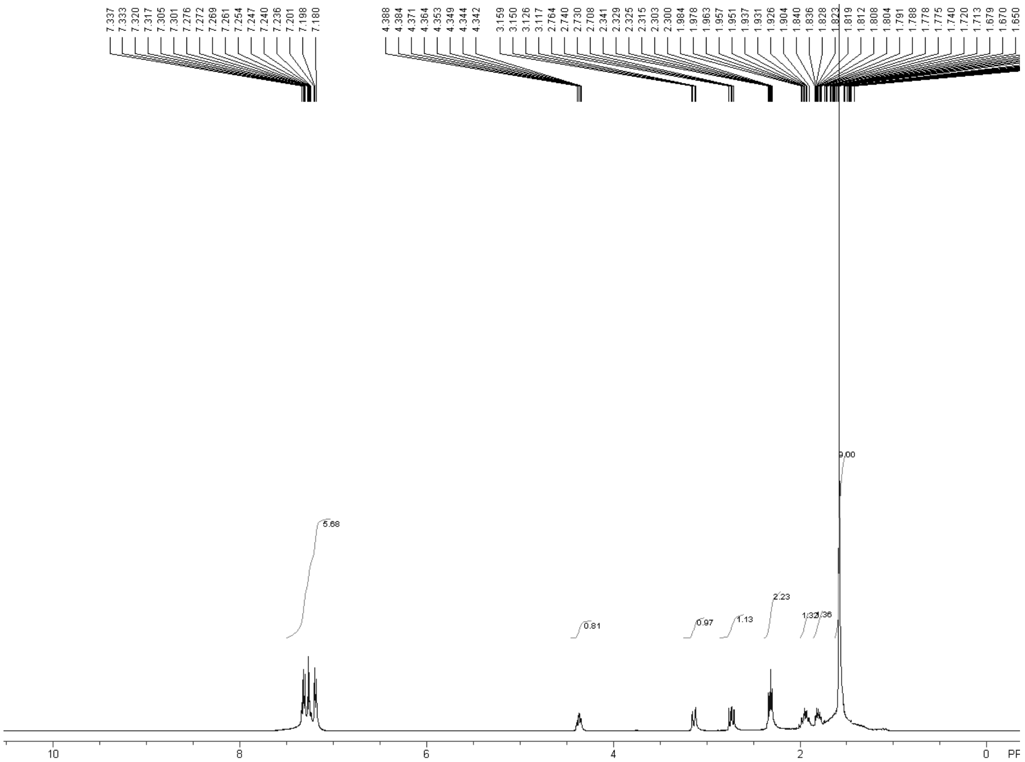
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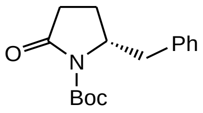
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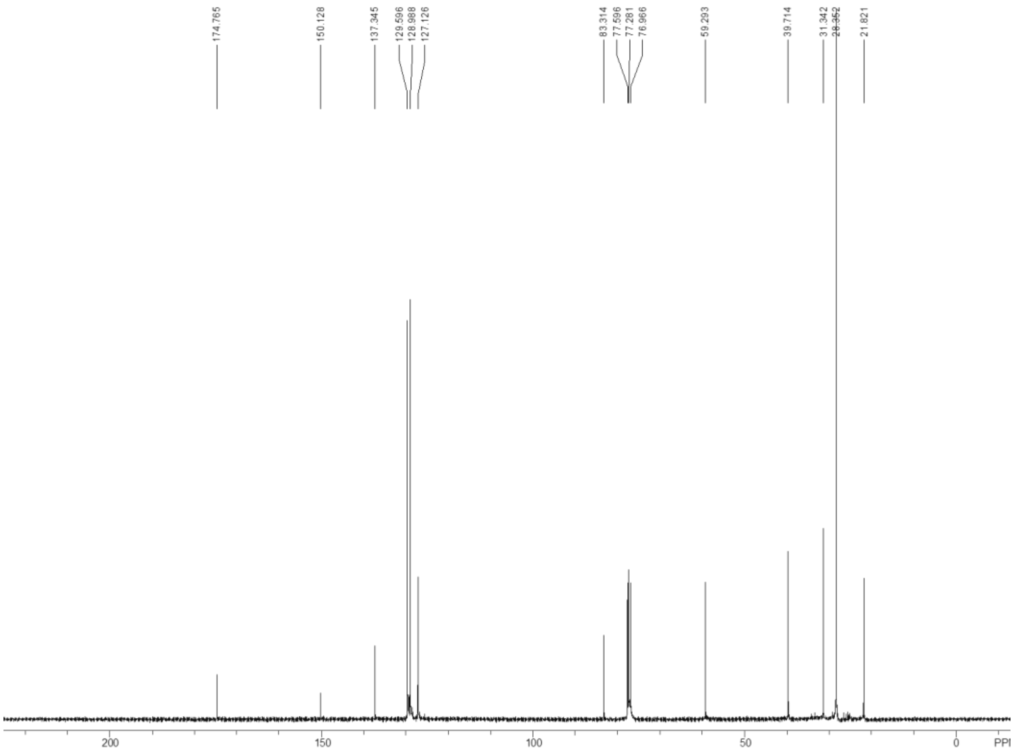
N
Boc
Ph

19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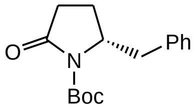
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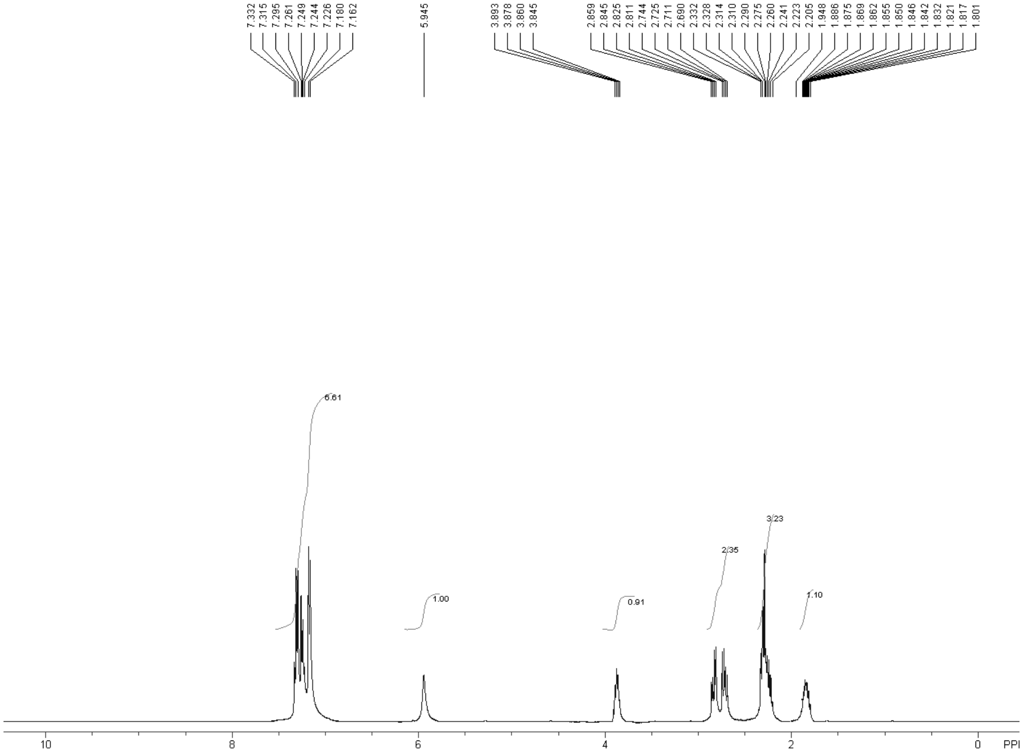
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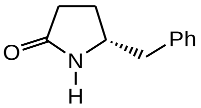
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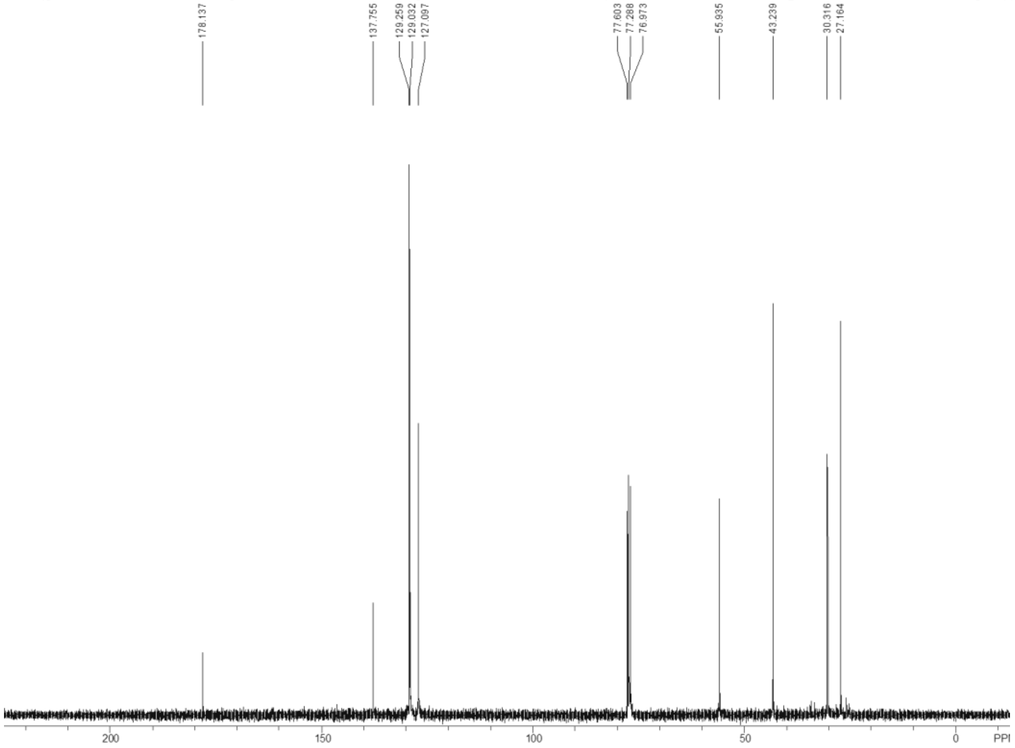
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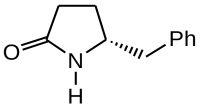
0
PPI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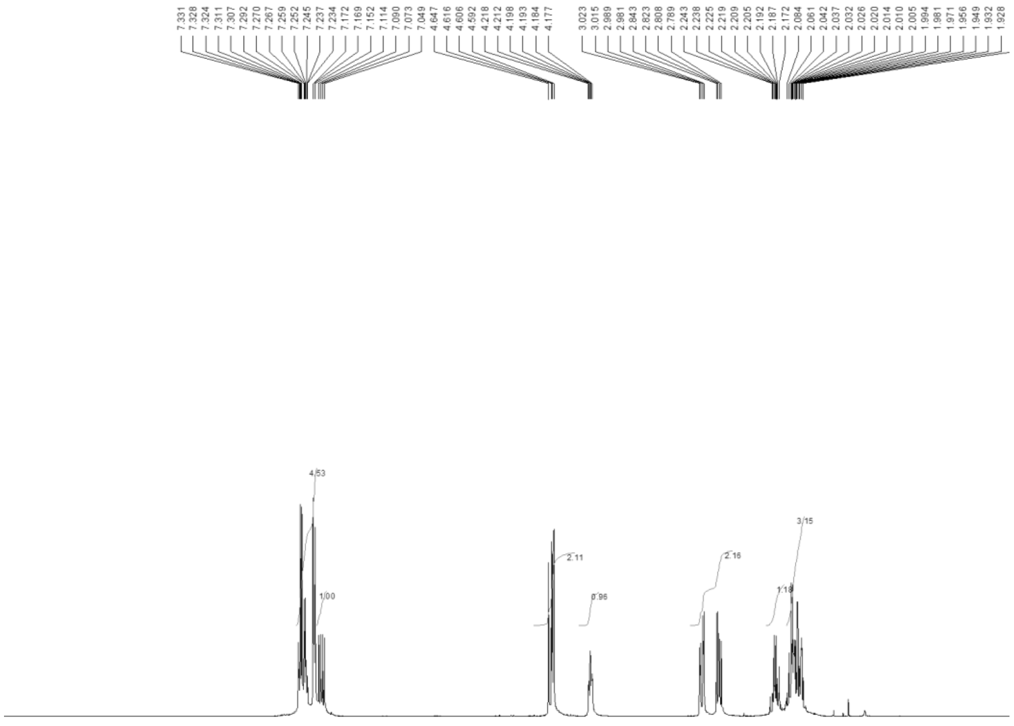
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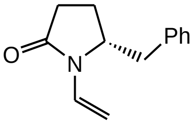
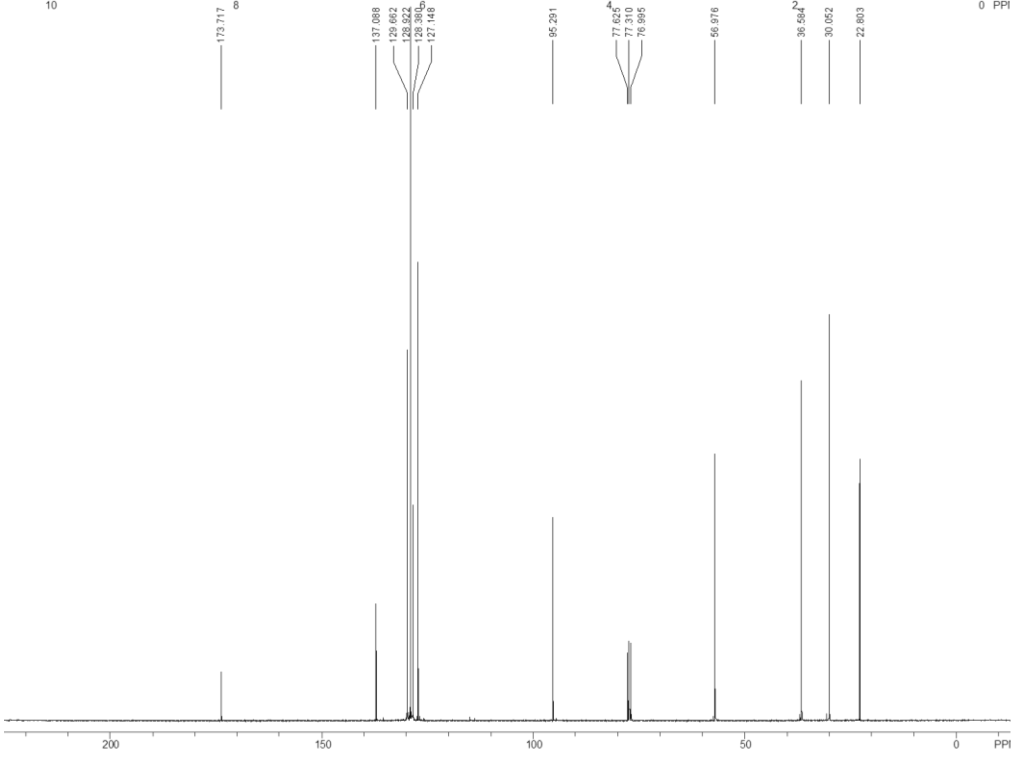


21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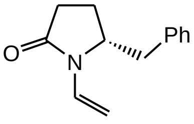
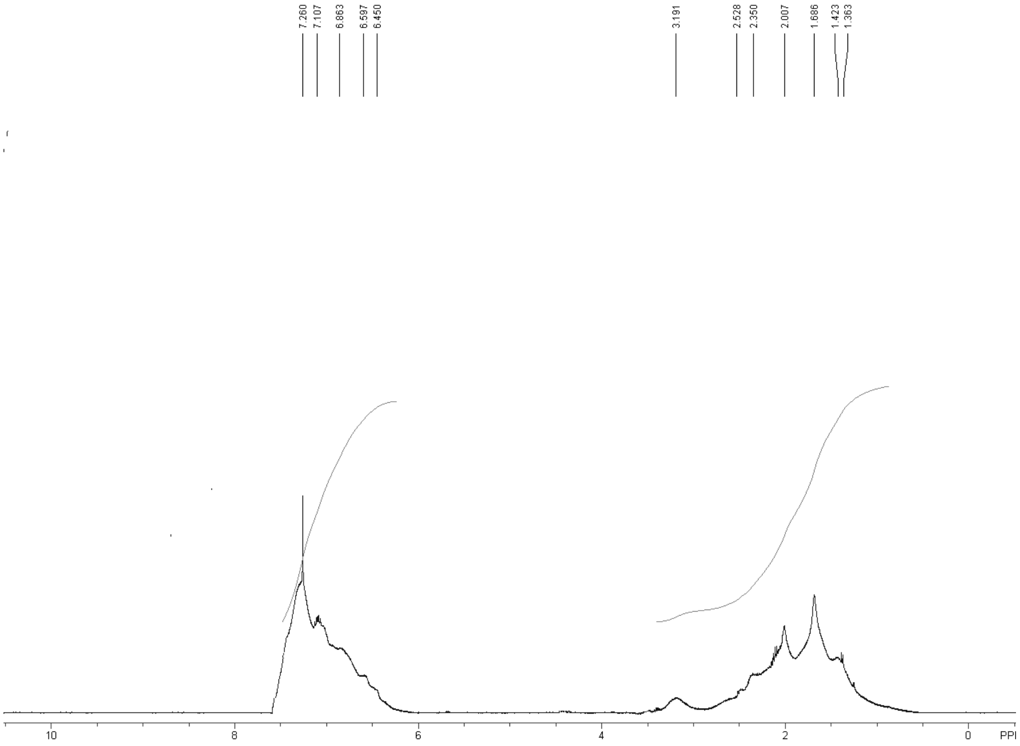
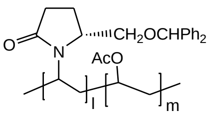
30.052
22.803
200
150
100
50
0
PPM

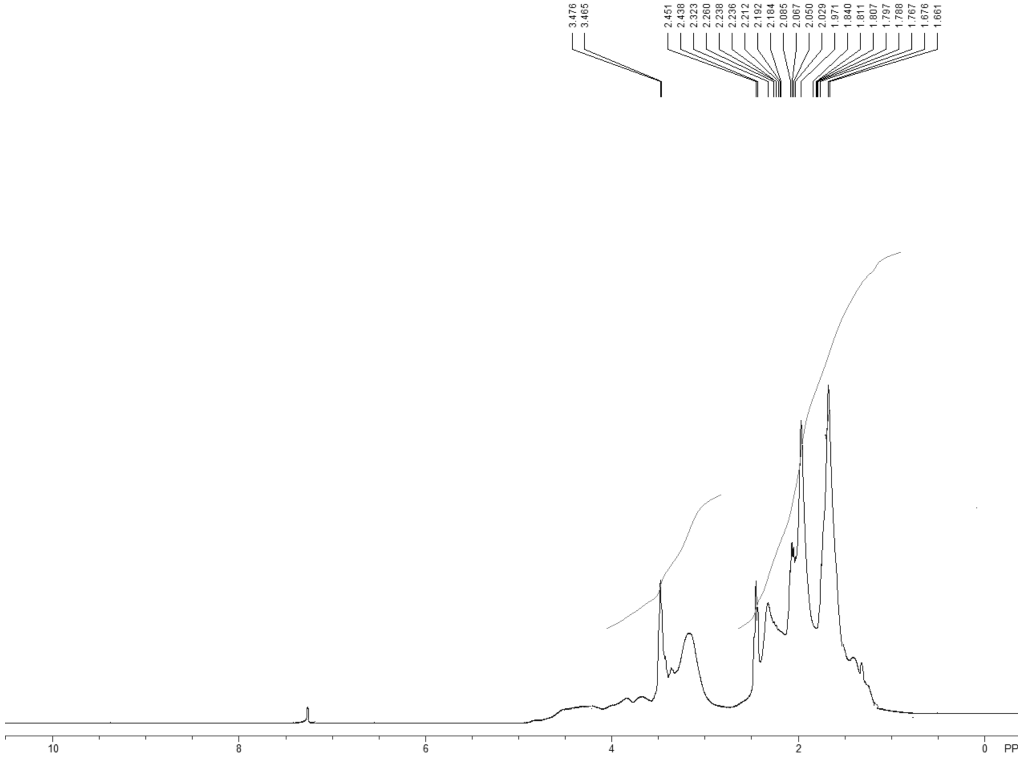


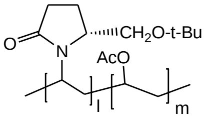
21


7.260
7.107
6.863
6.597
6.450
3.191
2.528
2.350
2.007
1.686
1.423
1.363
10
8
6
4
2
0
PPI

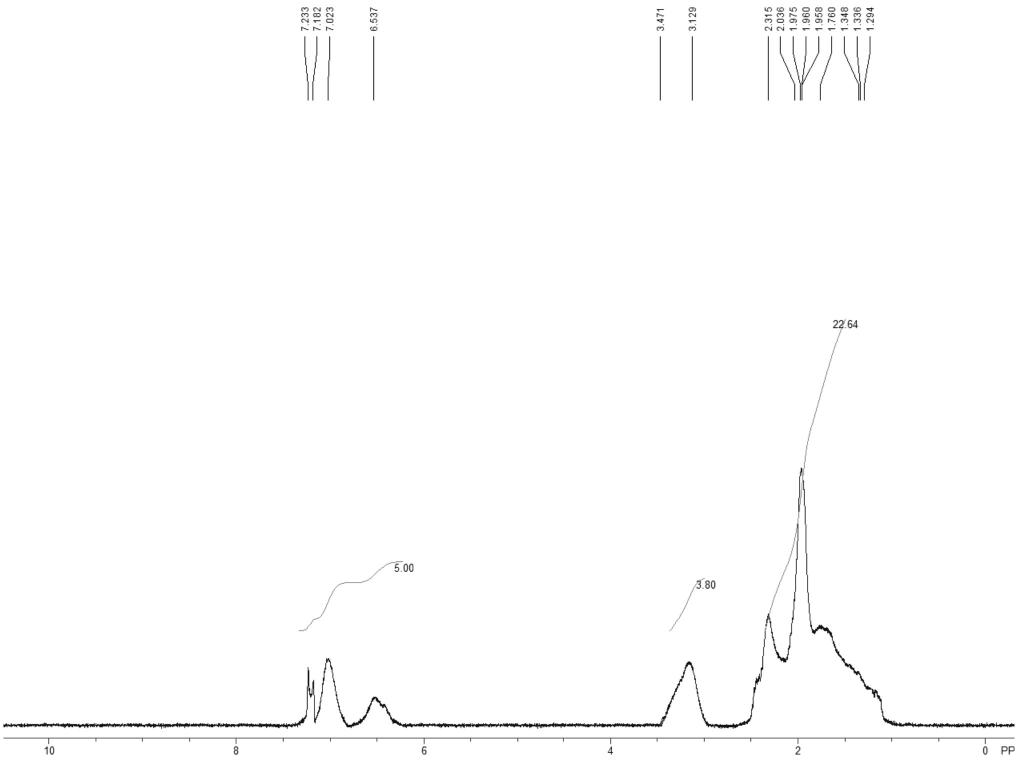

O
N
CH2OCHPh2
AcO
l
m

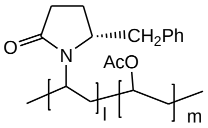
22


3.476
3.465
2.451
2.438
2.323
2.260
2.238
2.236
2.212
2.192
2.184
2.085
2.067
2.050
2.029
1.971
1.840
1.811
1.807
1.797
1.788
1.767
1.676
1.661
10
8
6
4
2
0
PP

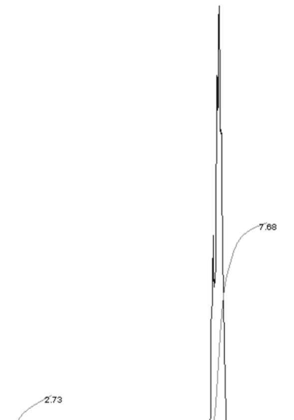

O
N
CH2O-t-Bu
AcO
l
m

23


7.233
7.182
7.023
6.537
3.471
3.129
2.315
2.036
1.975
1.960
1.958
1.760
1.348
1.336
1.294
5.00
3.80
22.64
10
8
6
4
2
0
PP


O
N
CH$_2$Ph
AcO
l
m

24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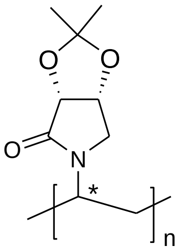
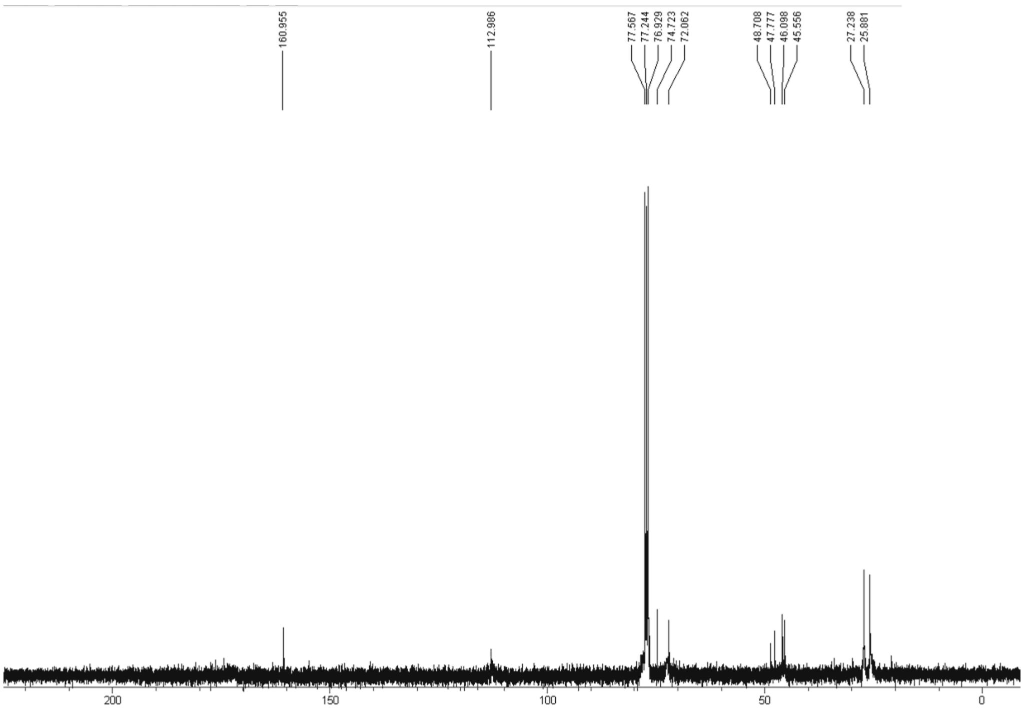
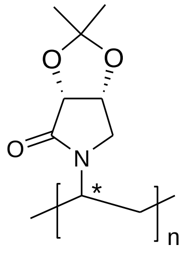
2.73
7.68
10
8
6
4
2
0

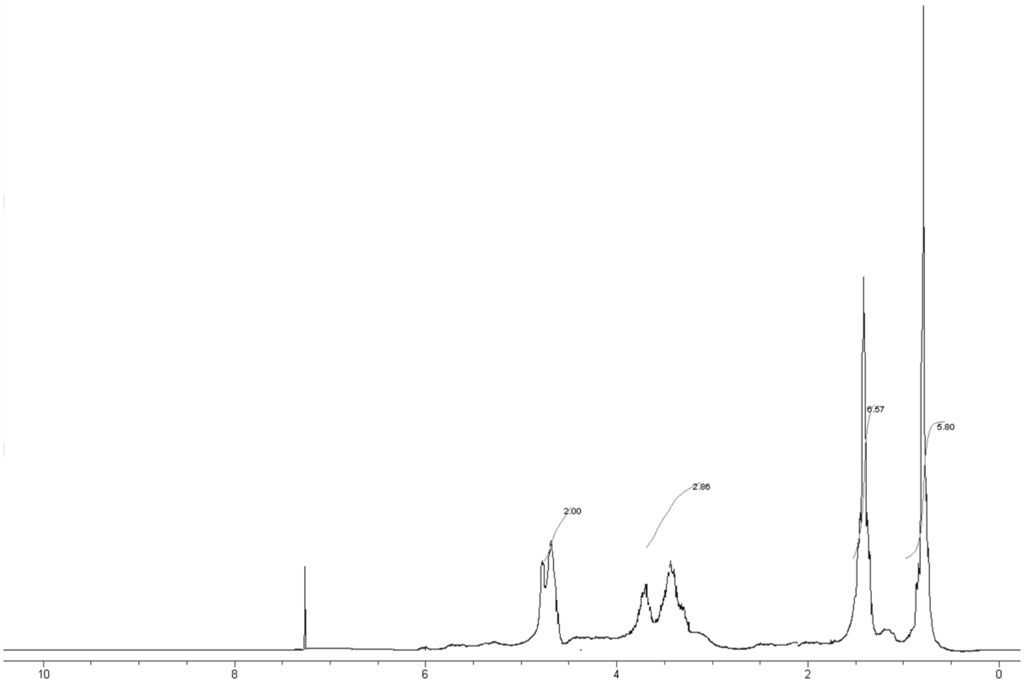

O
O
O
N
*
n

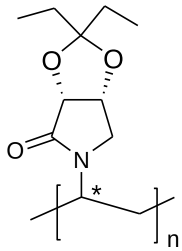
25


160.955
112.986
77.567
77.244
76.929
74.723
72.062
48.708
47.777
46.098
45.556
27.238
25.881
200
150
100
50
0

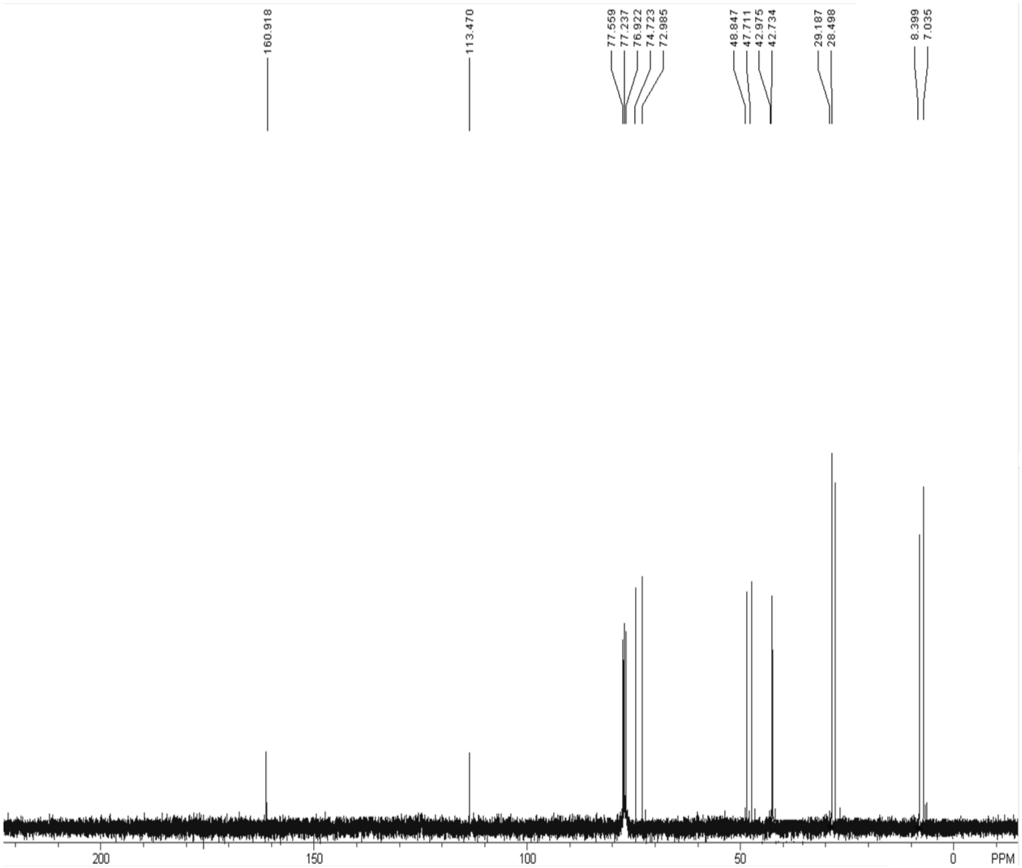

O
O
O
N
*
n

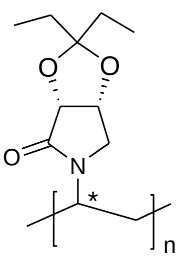
25


2.00
2.86
6.57
5.80
10
8
6
4
2
0

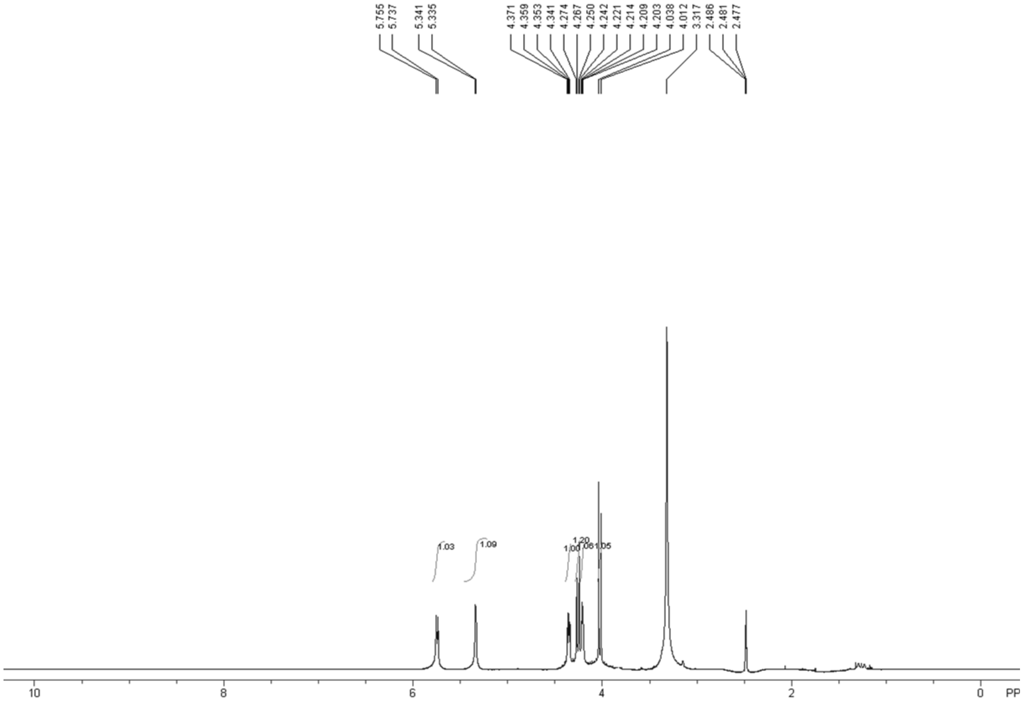

O
O
O
N
*
n

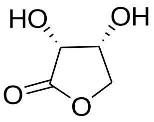
26


160.918
113.470
77.559
77.237
76.922
74.723
72.985
48.847
47.711
42.975
42.734
29.187
28.498
8.399
7.035
200
150
100
50
0
PPM

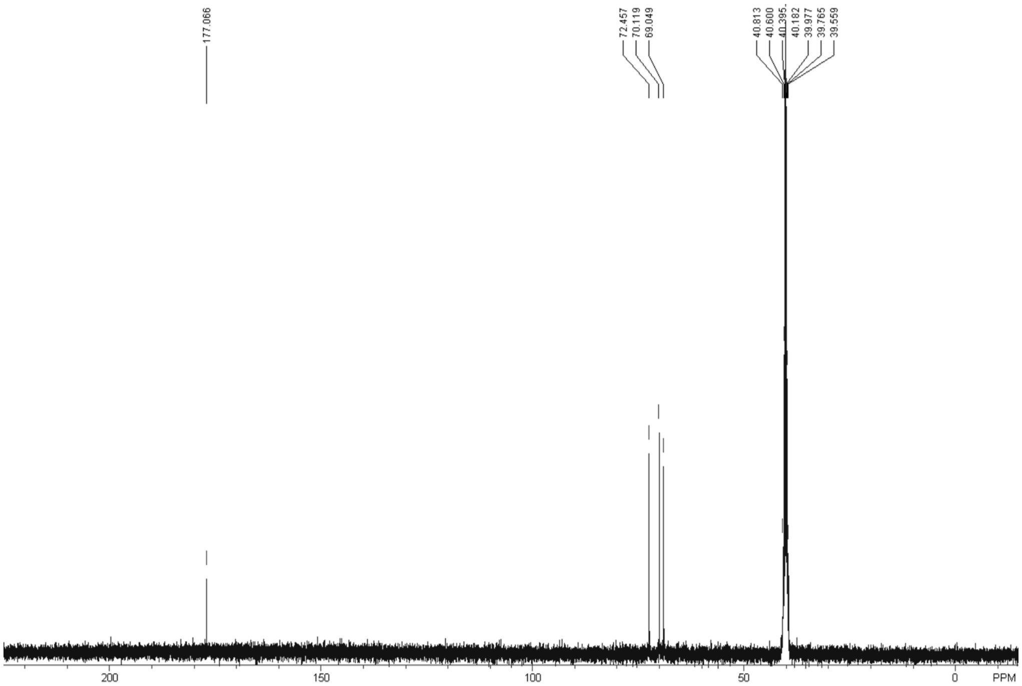


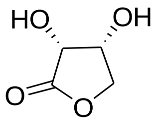
26


5.755
5.737
5.341
5.335
4.371
4.359
4.353
4.341
4.274
4.267
4.250
4.242
4.221
4.214
4.209
4.203
4.038
4.012
3.317
2.486
2.481
2.477
1.03
1.09
1.00
1.20
1.06
1.05
10
8
6
4
2
0
PP

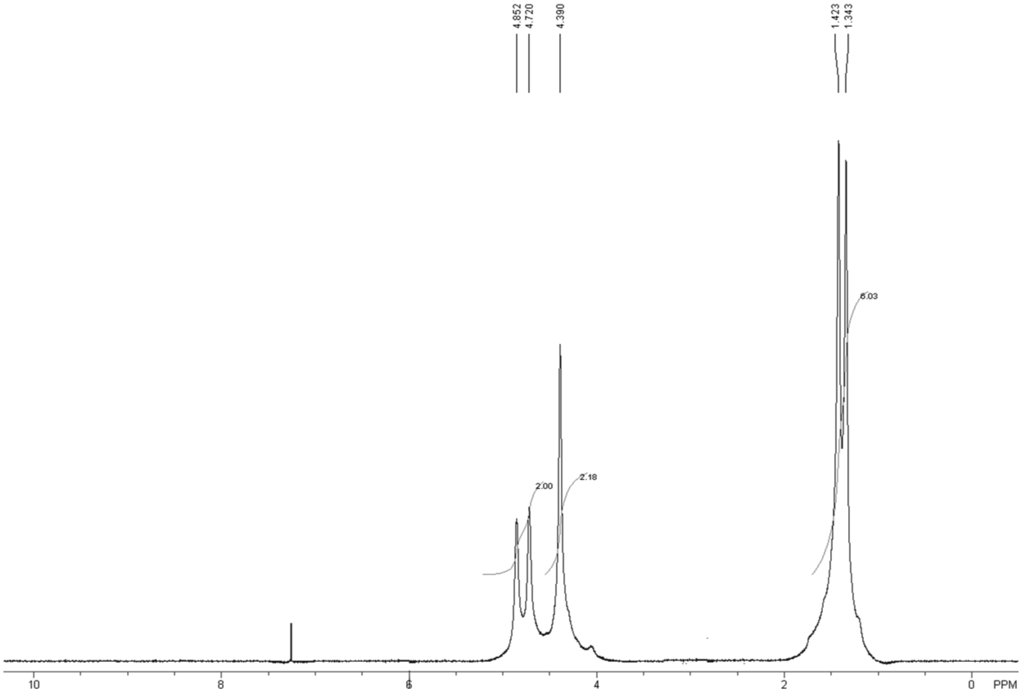


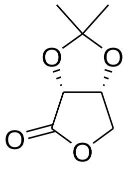
28


177.066
72.457
70.119
69.049
40.813
40.600
40.395
40.182
39.977
39.765
39.559
200
150
100
50
0
PPM

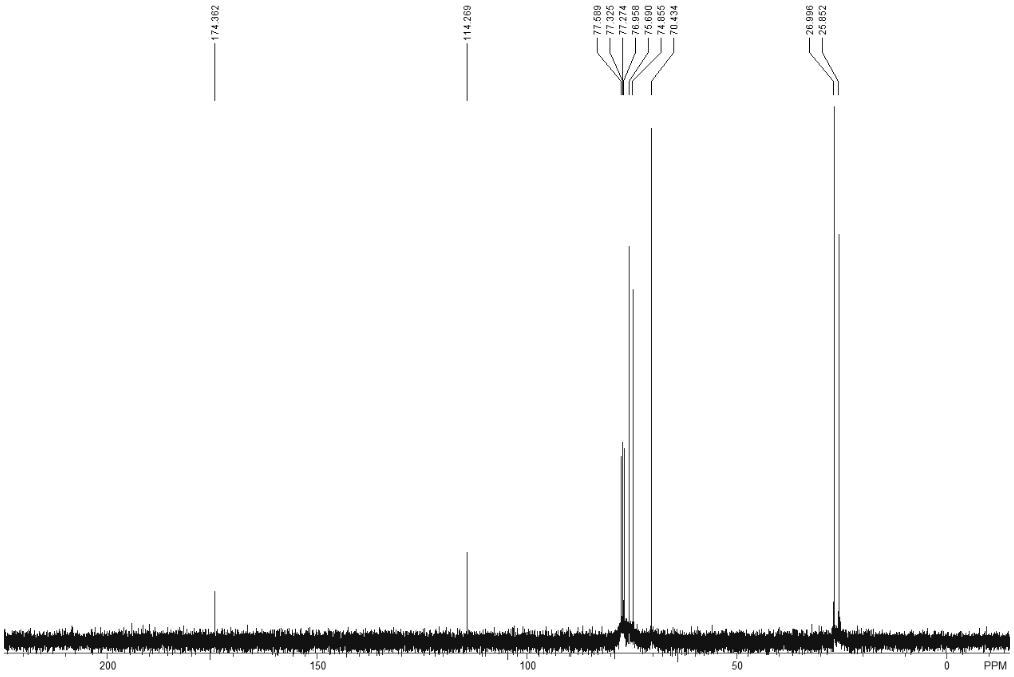


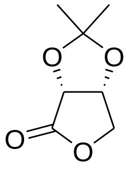
28


4.852
4.720
4.390
1.423
1.343
2.00
2.18
6.03
10
8
6
4
2
0
PPM

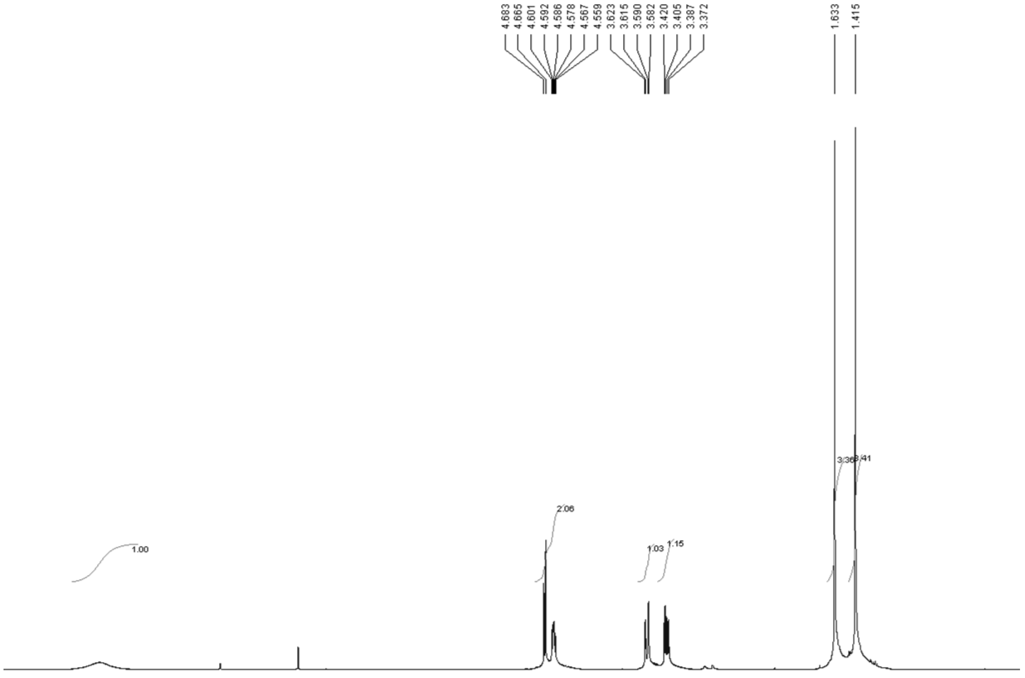


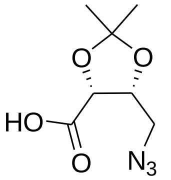
29


174.362
114.269
77.589
77.325
77.274
76.958
75.690
74.855
70.434
26.996
25.852
200
150
100
50
0
PPM

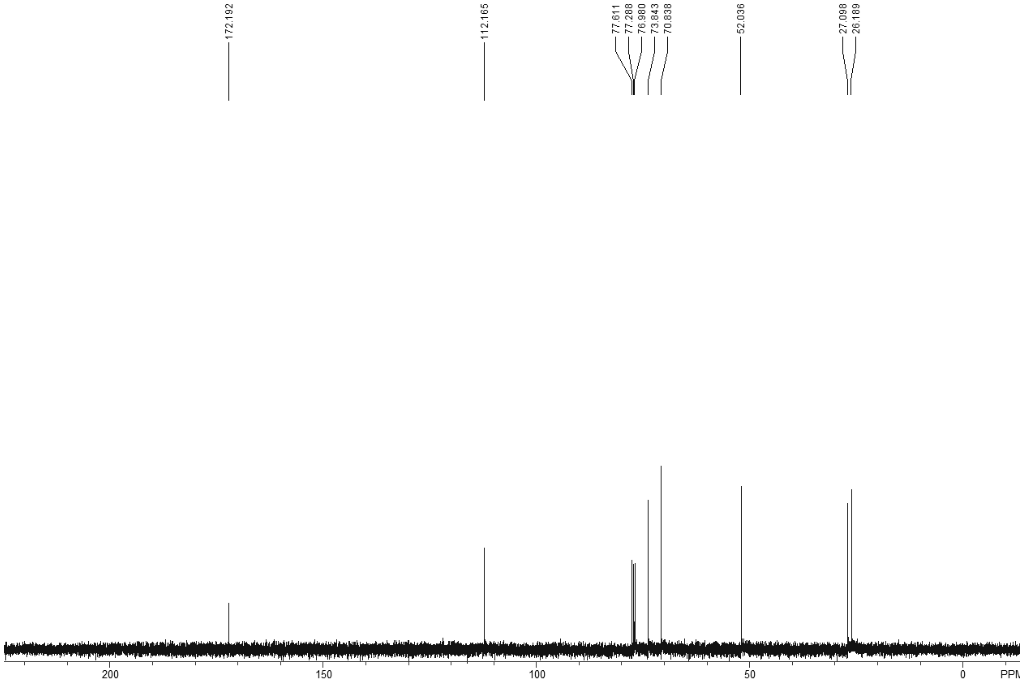

O
O
O
O

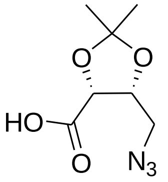
29


4.683
4.665
4.601
4.592
4.586
4.578
4.567
4.559
3.623
3.615
3.590
3.582
3.420
3.405
3.387
3.372
1.633
1.415
1.00
2.06
1.03
1.15
3.36
3.41
10
8
6
4
2
0
PF

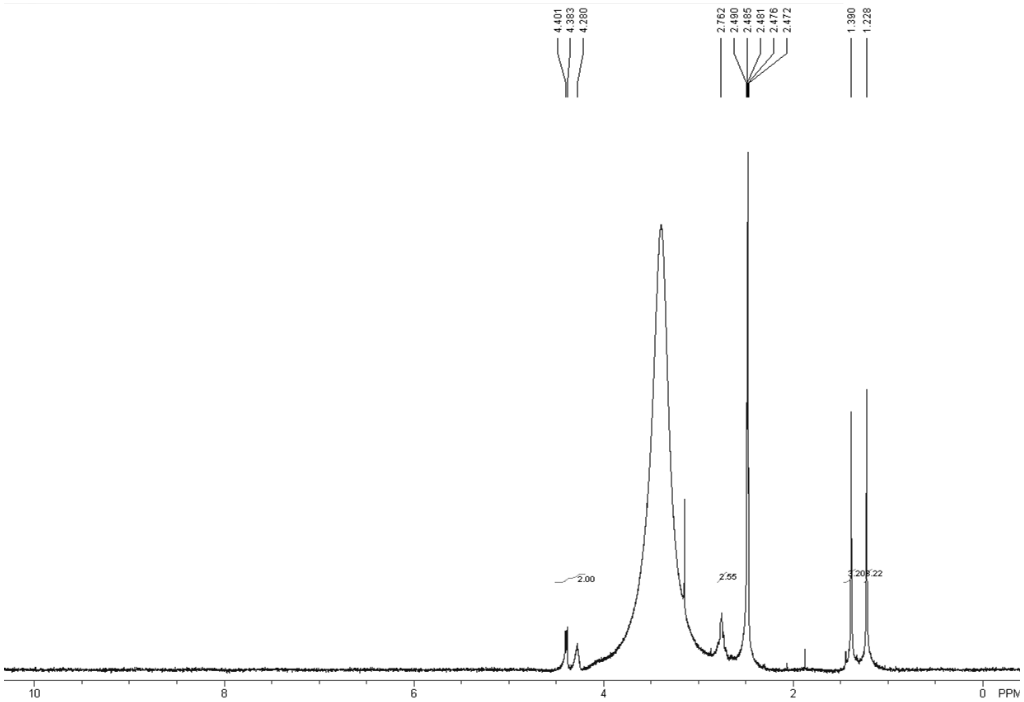

O
O
HO
O
N3

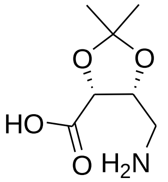
30


172.192
112.165
77.611
77.288
76.980
73.843
70.838
52.036
27.098
26.189
200
150
100
50
0
PPM

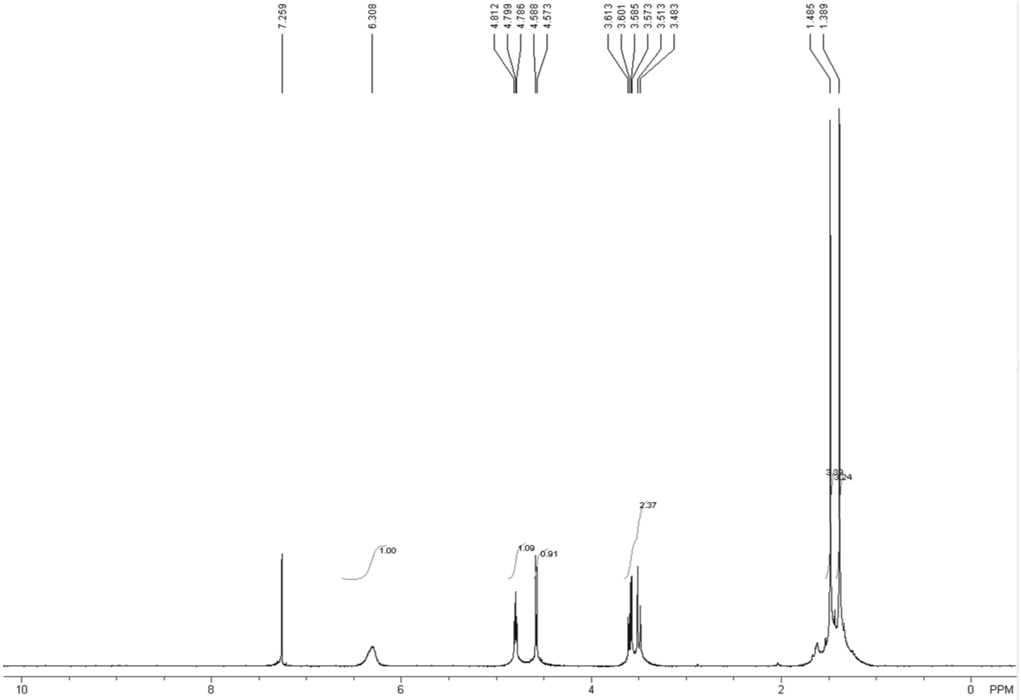

O
O
HO
O
N_3

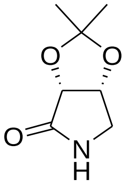
30


4.401
4.383
4.280
2.762
2.490
2.485
2.481
2.476
2.472
1.390
1.228
2.00
2.55
3.20
3.22
10
8
6
4
2
0
PPM

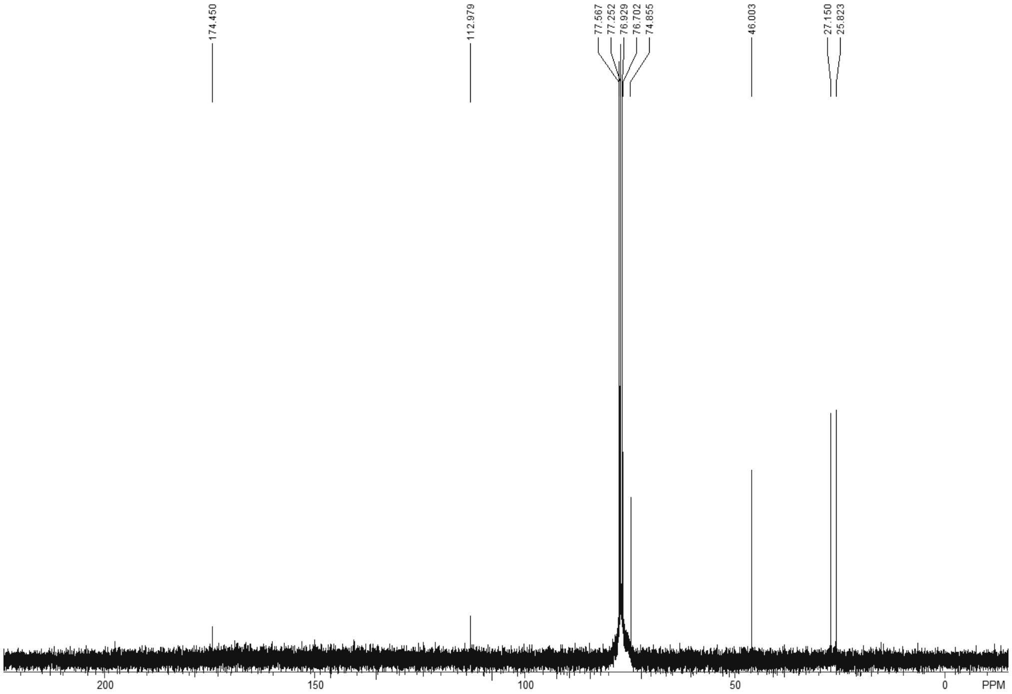

O
O
HO
O
H_2N

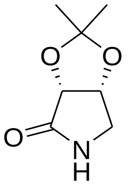
31


7.259
6.308
4.812
4.799
4.786
4.588
4.573
3.613
3.601
3.585
3.573
3.513
3.483
1.485
1.389
1.00
1.09
0.91
2.37
3.39
3.24
10
8
6
4
2
0
PPM

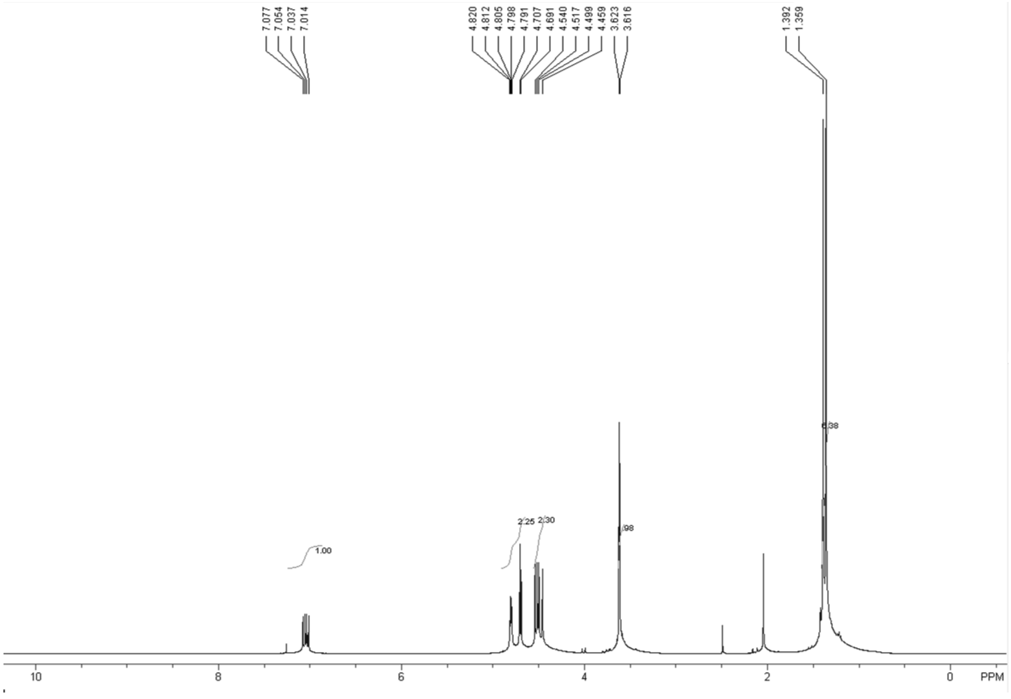

O
O
O
N
H

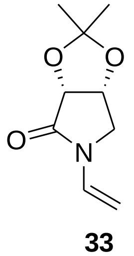
32


174.450
112.979
77.567
77.252
76.929
76.702
74.855
46.003
27.150
25.823
200
150
100
50
0
PPM

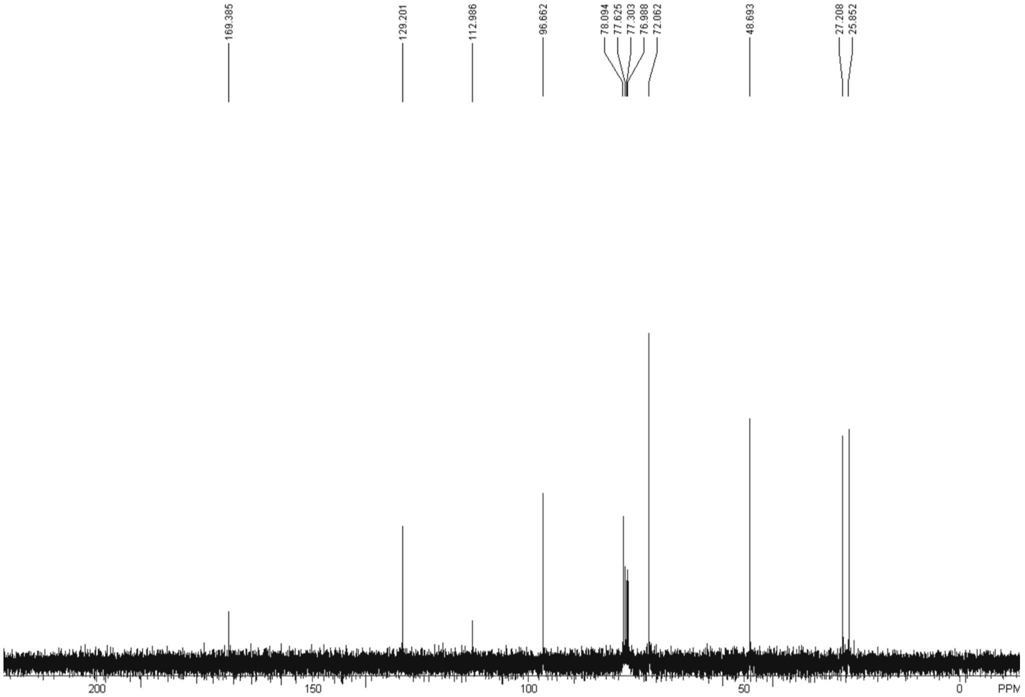

O
O
O
N
H

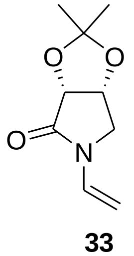
32


7.077
7.054
7.037
7.014
4.820
4.812
4.805
4.798
4.791
4.707
4.691
4.540
4.517
4.499
4.459
3.623
3.616
1.392
1.359
1.00
2.25
2.30
.98
6.38
10
8
6
4
2
0
PPM

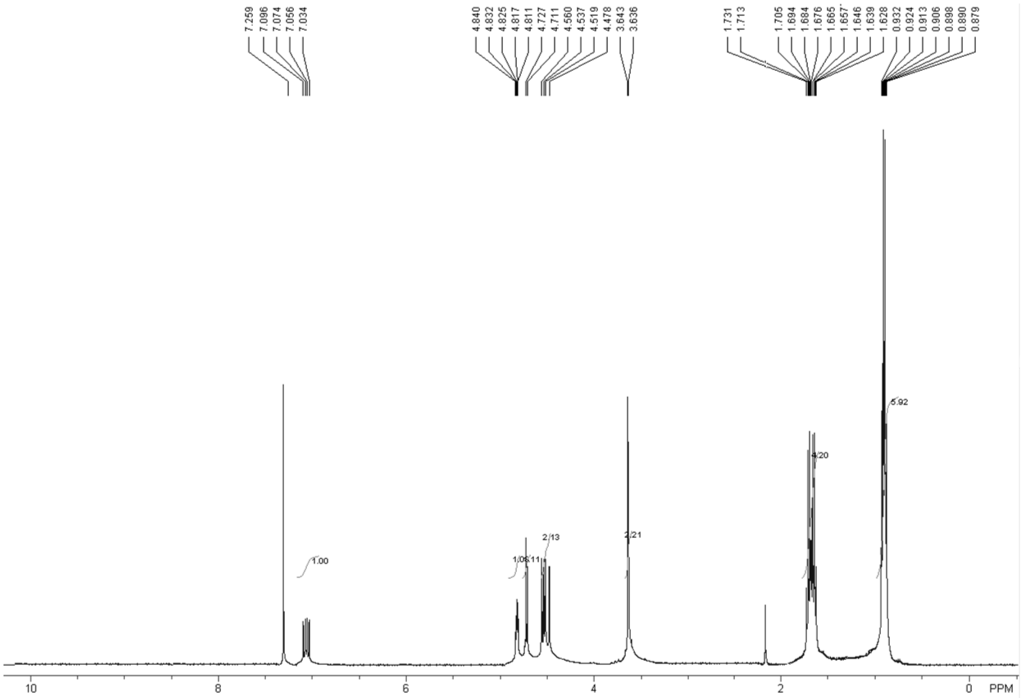

O
O
O
N

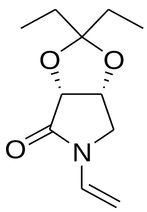
33


169.385
129.201
112.986
96.662
78.094
77.625
77.303
76.988
72.062
48.693
27.208
25.852
200
150
100
50
0
PPM

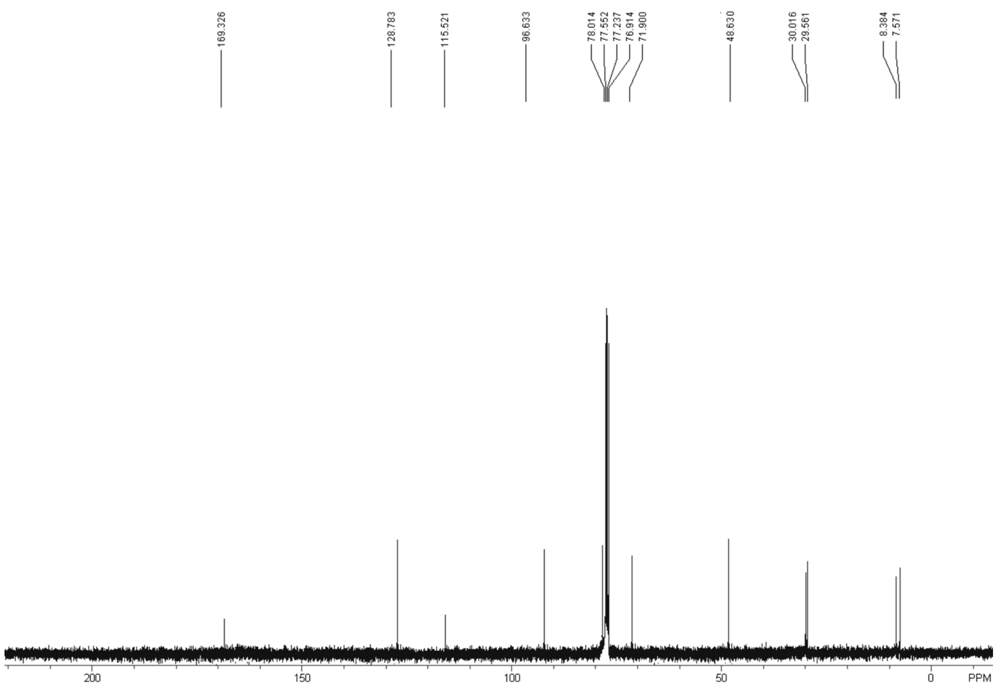

O
O
O
N

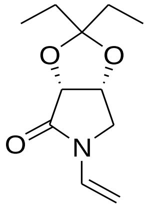
33


7.259
7.096
7.074
7.056
7.034
4.840
4.832
4.825
4.817
4.811
4.727
4.711
4.560
4.537
4.519
4.478
3.643
3.636
1.731
1.713
1.705
1.694
1.684
1.676
1.665
1.657
1.646
1.639
1.628
0.932
0.924
0.913
0.906
0.898
0.890
0.879
1.00
1.06
1.11
2.13
2.21
4.20
5.92
10
8
6
4
2
0
PPM

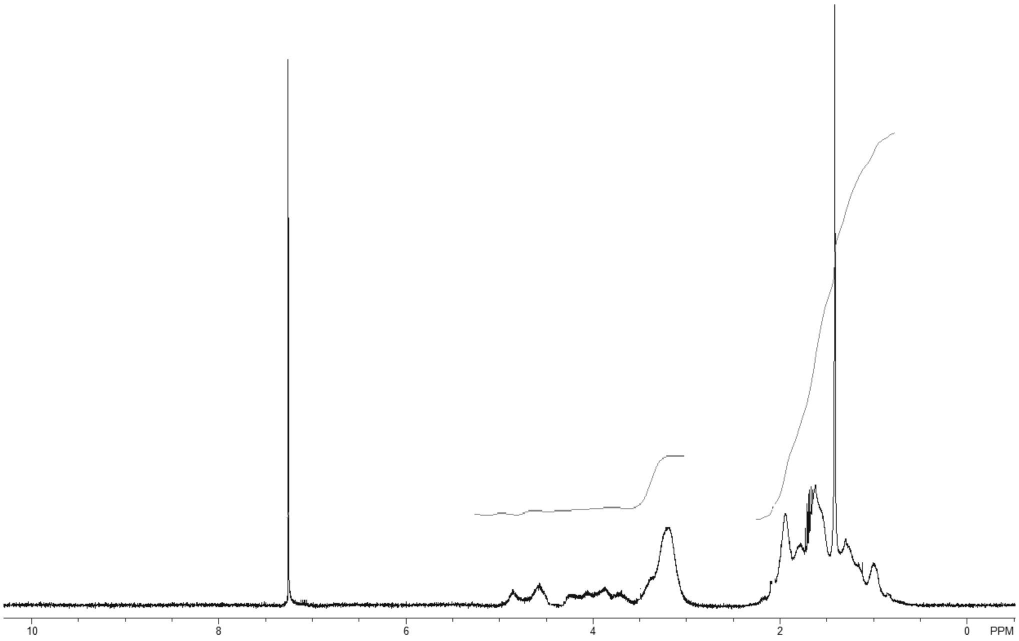

O
O
O
N

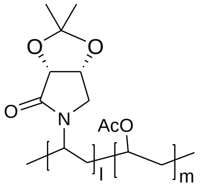
34


169.326
128.783
115.521
96.633
78.014
77.552
77.237
76.914
71.900
48.630
30.016
29.561
8.384
7.571
200
150
100
50
0
PPM

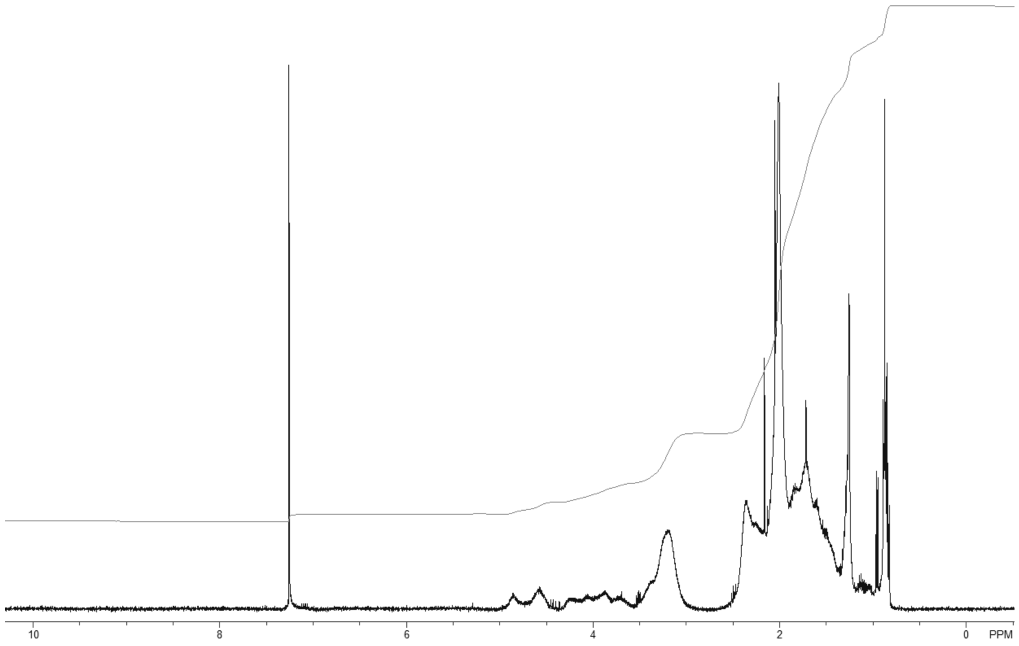

O
O
O
N

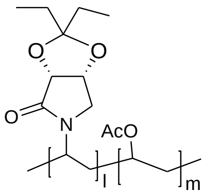
34



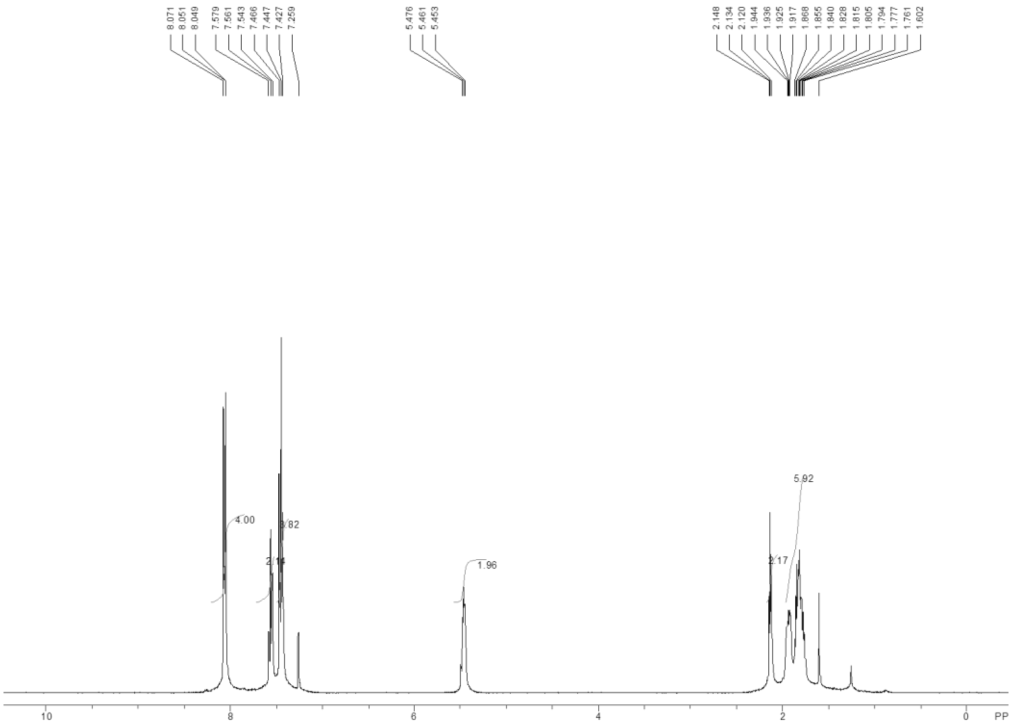


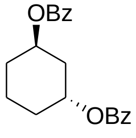
35



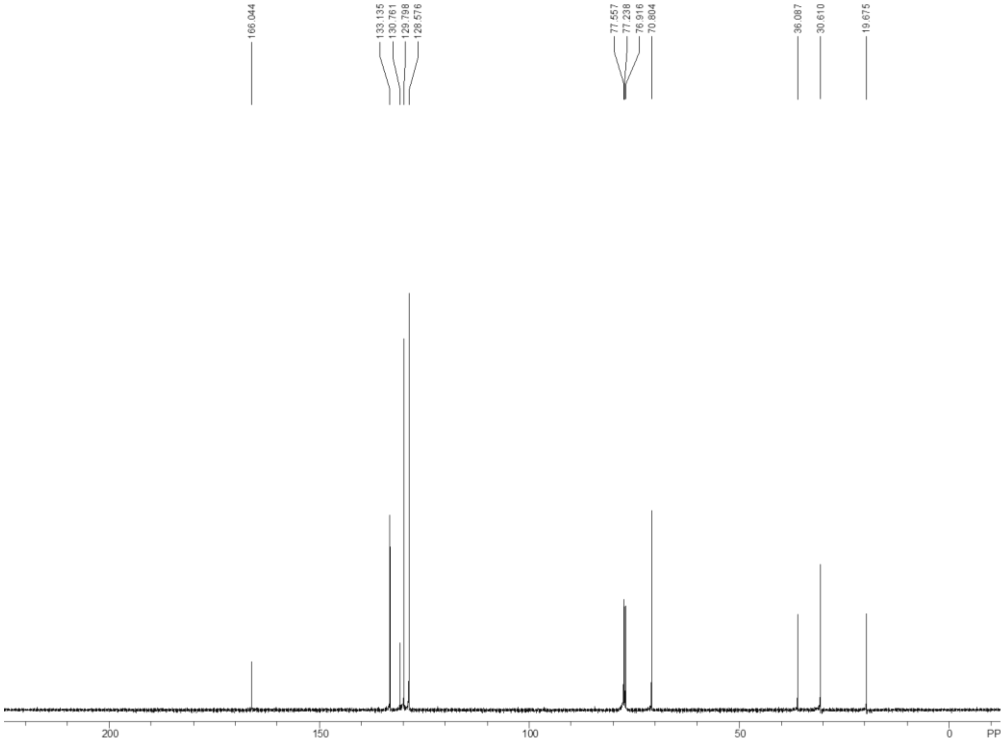


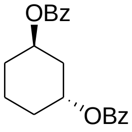
36


8.071
8.051
8.049
7.579
7.561
7.543
7.466
7.447
7.427
7.259
5.476
5.461
5.453
2.148
2.134
2.120
1.944
1.936
1.925
1.917
1.868
1.855
1.840
1.828
1.815
1.805
1.794
1.777
1.761
1.602
4.00
3.82
2.14
1.96
2.17
5.92
10
8
6
4
2
0
PP

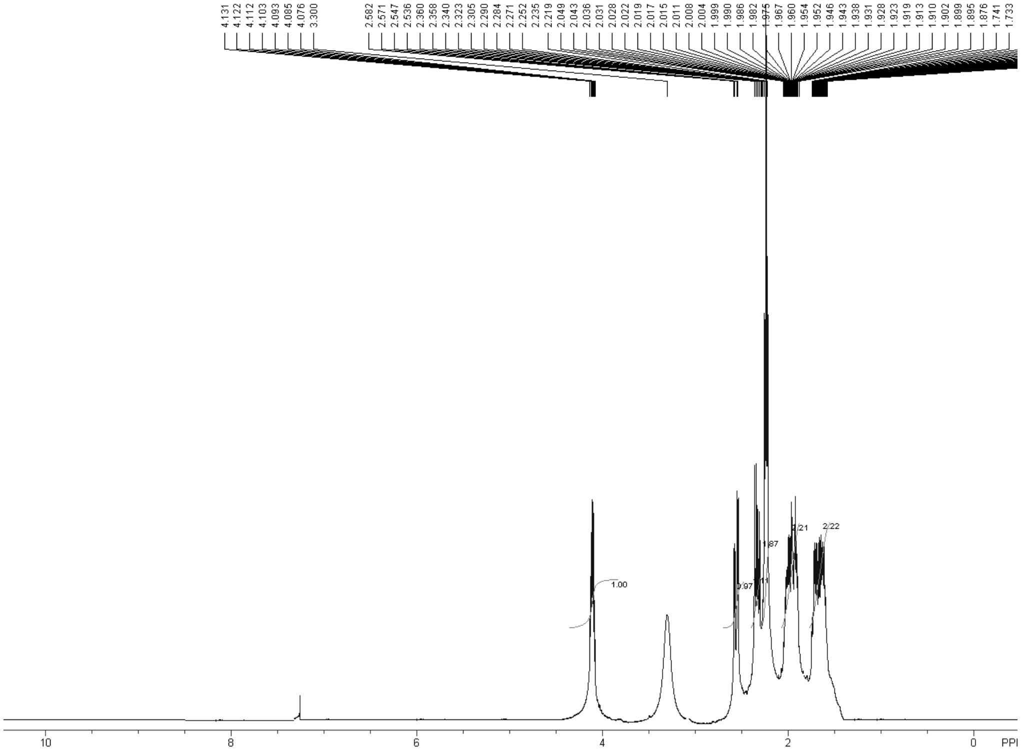

OBz
OBz

37A


166.044
133.135
130.761
129.798
128.576
77.557
77.238
76.916
70.804
36.087
30.610
19.675
200
150
100
50
0
PP


OBz
OBz

37A


4.131
4.122
4.112
4.103
4.093
4.085
4.076
3.300
2.582
2.571
2.547
2.536
2.360
2.358
2.340
2.323
2.305
2.290
2.284
2.271
2.252
2.235
2.219
2.049
2.043
2.036
2.031
2.028
2.022
2.019
2.017
2.015
2.011
2.008
2.004
1.999
1.990
1.986
1.982
1.975
1.967
1.960
1.954
1.952
1.946
1.943
1.938
1.931
1.928
1.923
1.919
1.913
1.910
1.902
1.899
1.895
1.876
1.741
1.733
1.00
0.97
1.87
2.21
2.22
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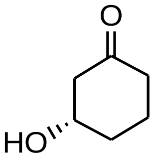
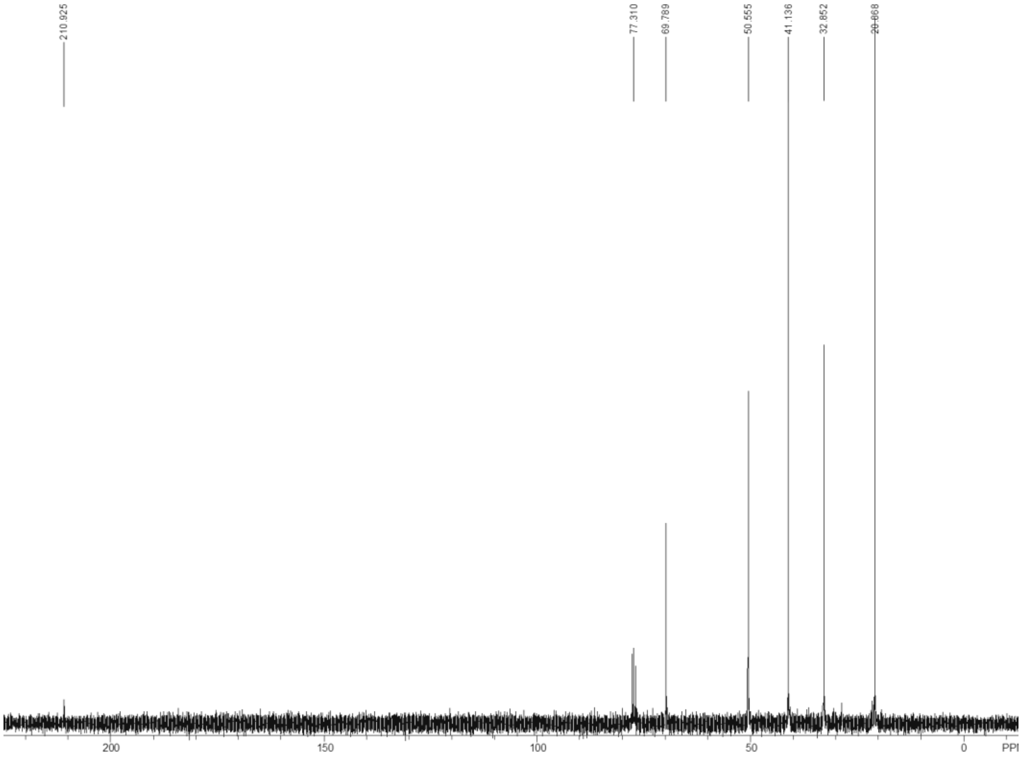
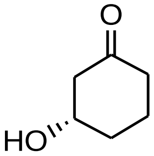
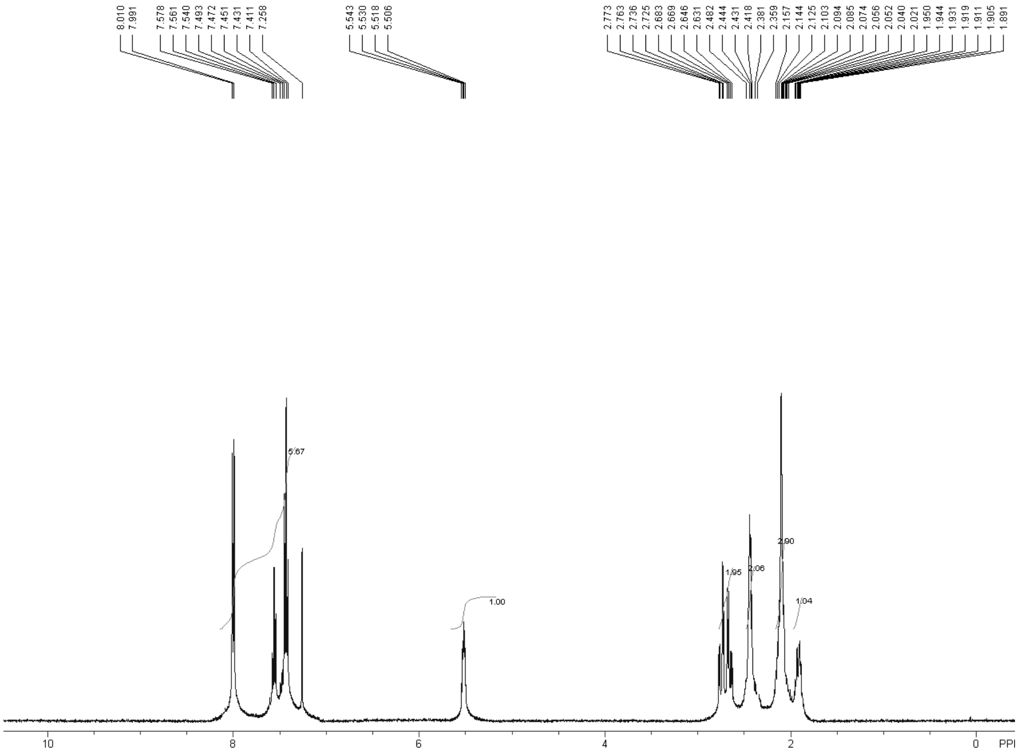
0
PPM


(S)-**38**


210.925
77.310
69.789
50.555
41.136
32.852
20.868
200
150
100
50
0
PPM


(S)-**38**


8.010
7.991
7.578
7.561
7.540
7.493
7.472
7.451
7.431
7.411
7.258
5.543
5.530
5.518
5.506
2.773
2.763
2.736
2.725
2.683
2.669
2.646
2.631
2.482
2.444
2.431
2.418
2.381
2.359
2.157
2.144
2.125
2.103
2.094
2.085
2.074
2.056
2.052
2.040
2.021
1.950
1.944
1.931
1.919
1.911
1.905
1.891
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1.00
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2.06
2.90
1.04
10
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4
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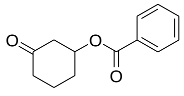
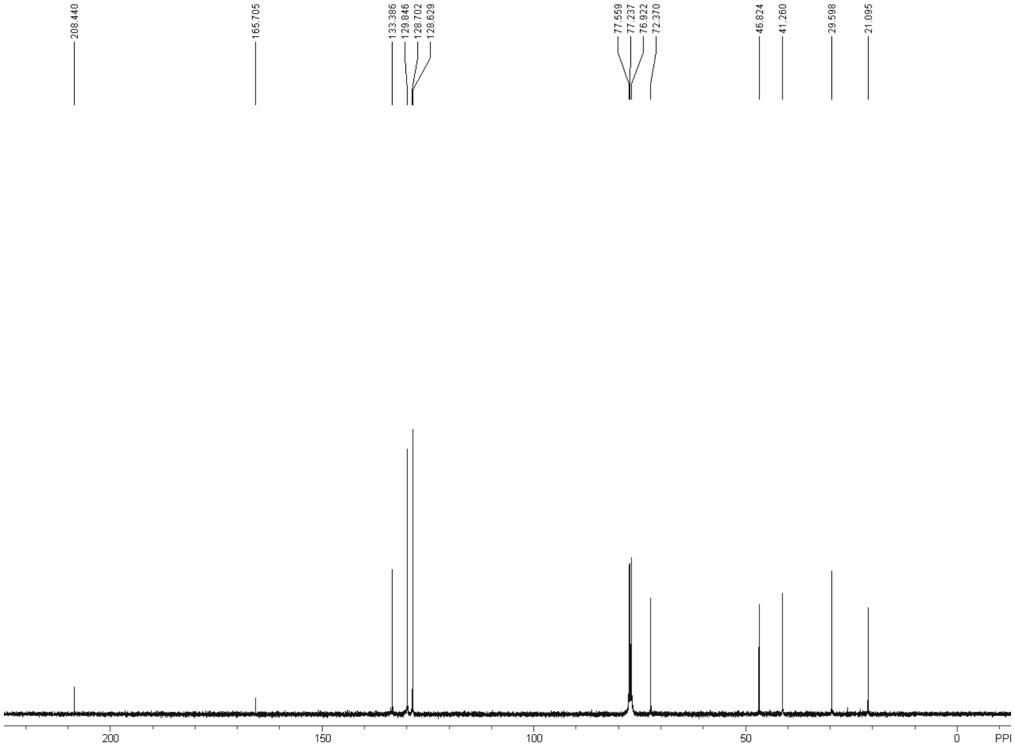
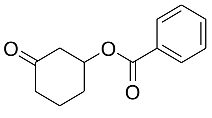
0
PPI

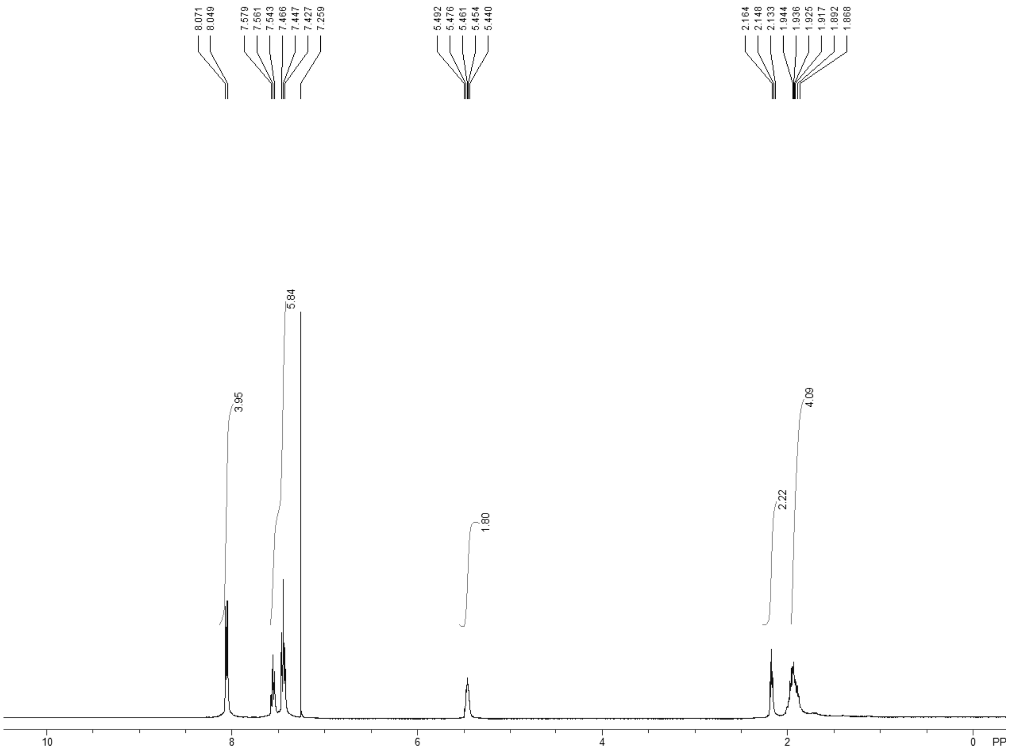

O
O
O

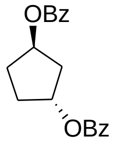
38A


208.440
165.705
133.386
129.846
128.702
128.629
77.559
77.237
76.922
72.370
46.824
41.260
29.598
21.095
200
150
100
50
0
PPI

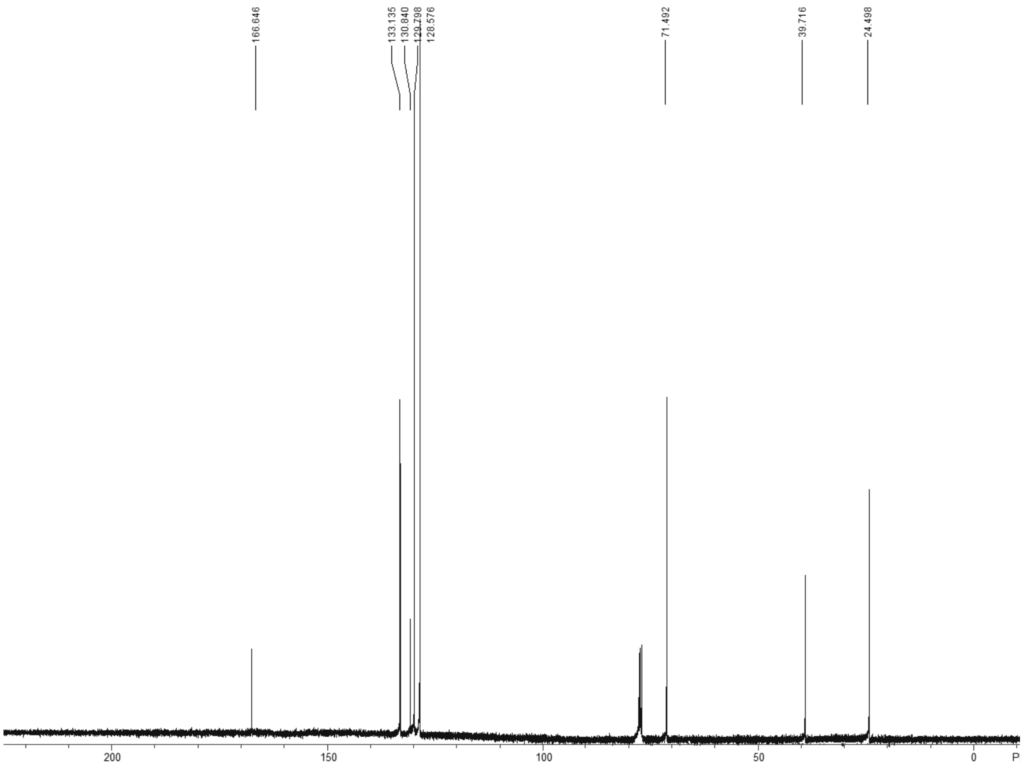

O
O
O

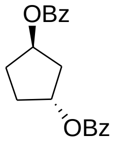
38A


8.071
8.049
7.579
7.561
7.543
7.466
7.447
7.427
7.259
5.492
5.476
5.461
5.454
5.440
2.164
2.148
2.133
1.944
1.936
1.925
1.917
1.892
1.868
3.95
5.84
1.80
2.22
4.09
10
8
6
4
2
0
PP

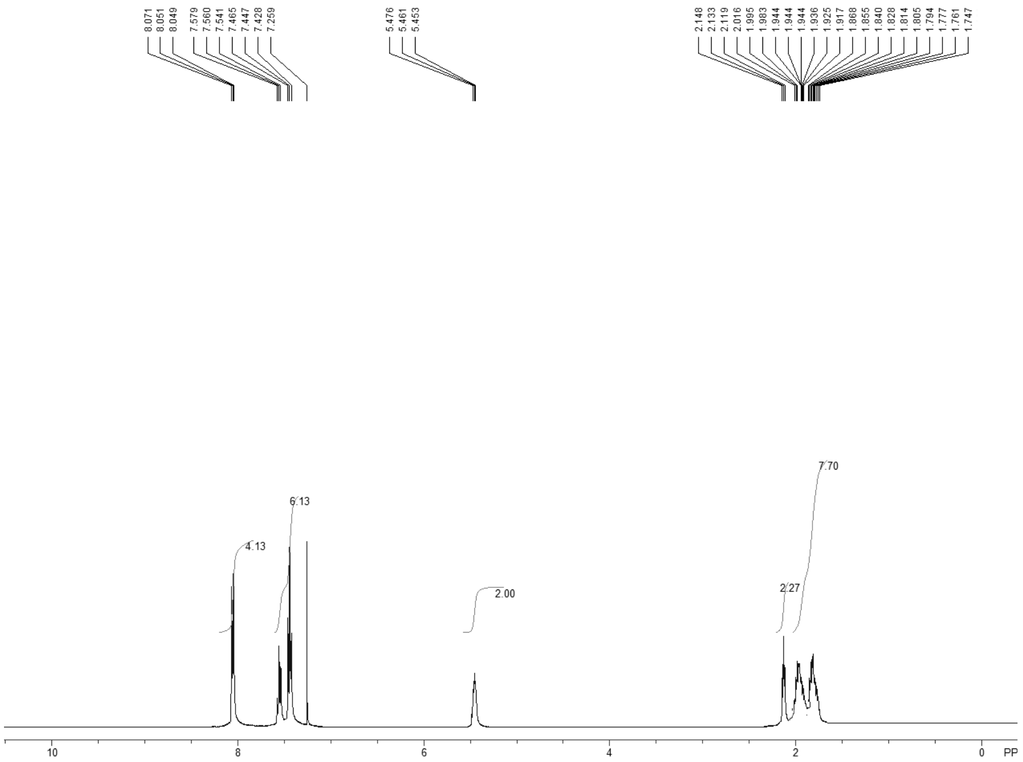

OBz
OBz

39A


166.646
133.135
130.840
129.798
128.576
71.492
39.716
24.498
200
150
100
50
0
P


OBz
OBz

39A


8.071
8.051
8.049
7.579
7.560
7.541
7.465
7.447
7.428
7.259
5.476
5.461
5.453
2.148
2.133
2.119
2.016
1.995
1.983
1.944
1.944
1.944
1.936
1.925
1.917
1.868
1.855
1.840
1.828
1.814
1.805
1.794
1.777
1.761
1.747
4.13
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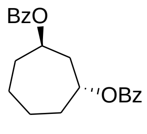
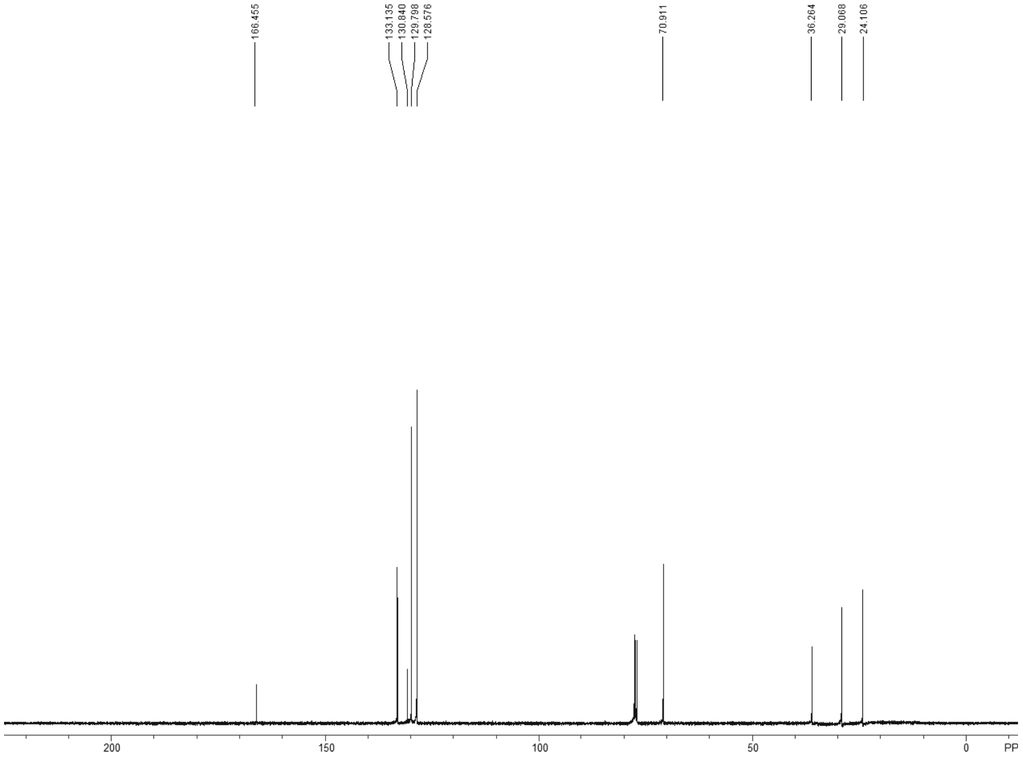
2.00
2.27
7.70
10
8
6
4
2
0
PP


BzO
OBz

40A


166.455
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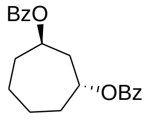
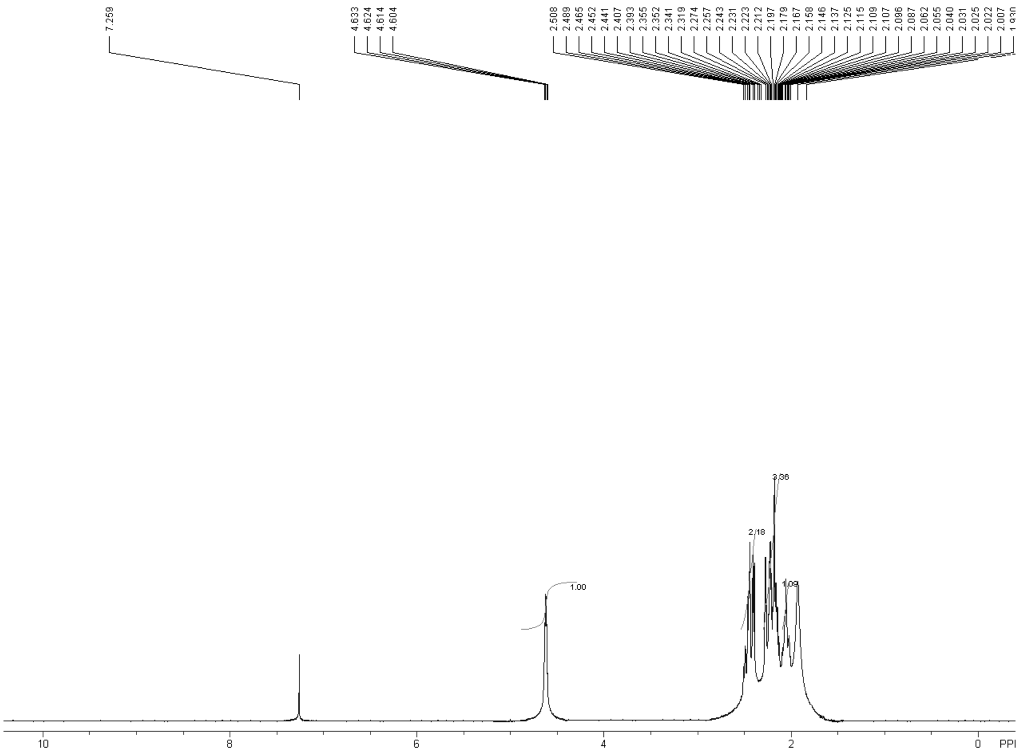
130.840
129.798
128.576
70.911
36.264
29.068
24.106
200
150
100
50
0
PP


BzO
OBz

40A


7.259
4.633
4.624
4.614
4.604
2.508
2.489
2.465
2.452
2.441
2.407
2.393
2.355
2.352
2.341
2.319
2.274
2.257
2.243
2.231
2.223
2.212
2.197
2.179
2.167
2.158
2.146
2.137
2.125
2.115
2.109
2.107
2.096
2.087
2.062
2.055
2.040
2.031
2.025
2.022
2.007
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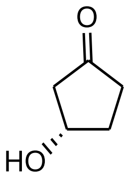
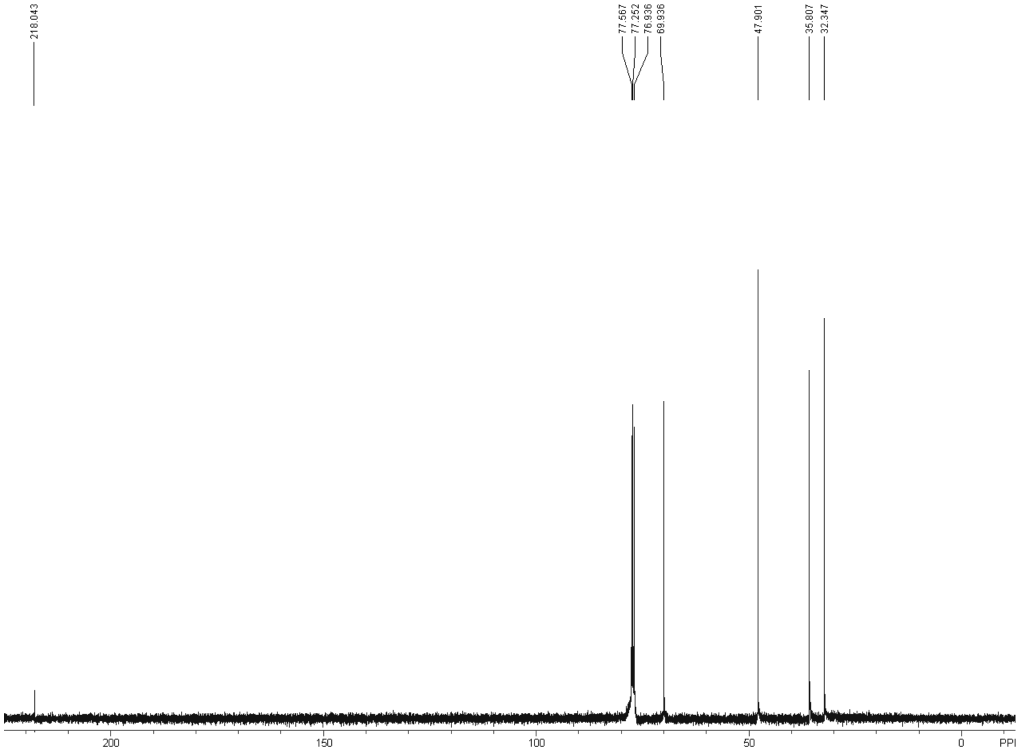
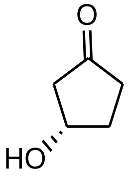
1.09
10
8
6
4
2
0

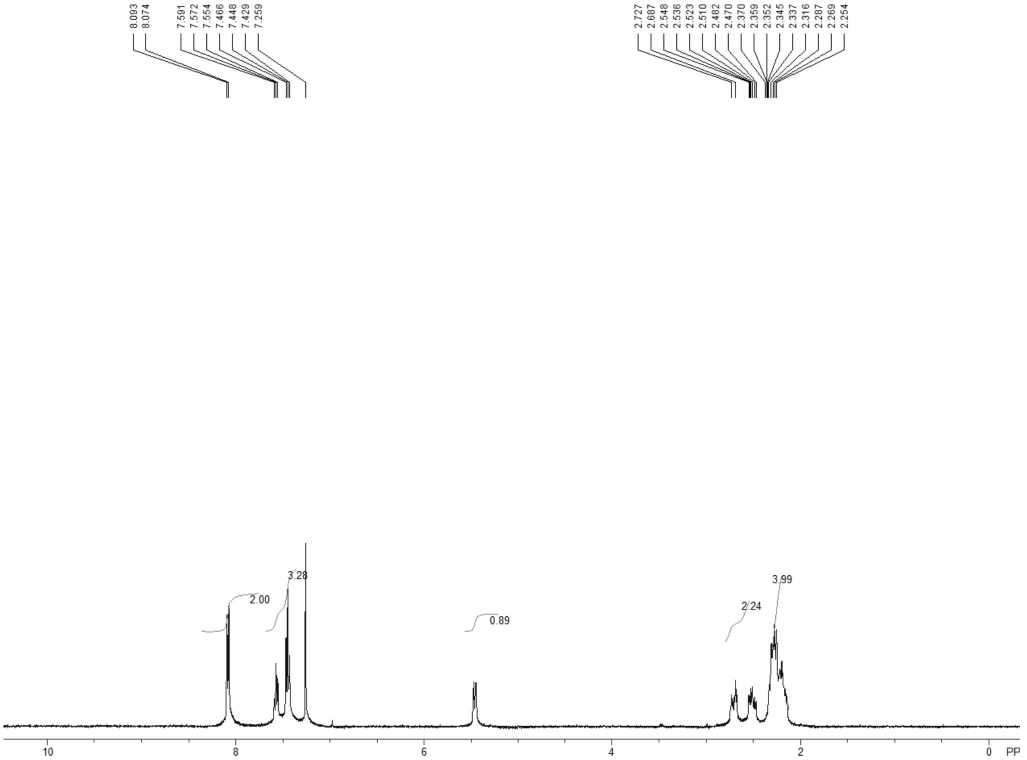

O
HO

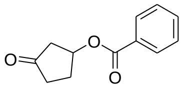
(*S*)-**41**


218.043
77.567
77.252
76.936
69.936
47.901
35.807
32.347
200
150
100
50
0

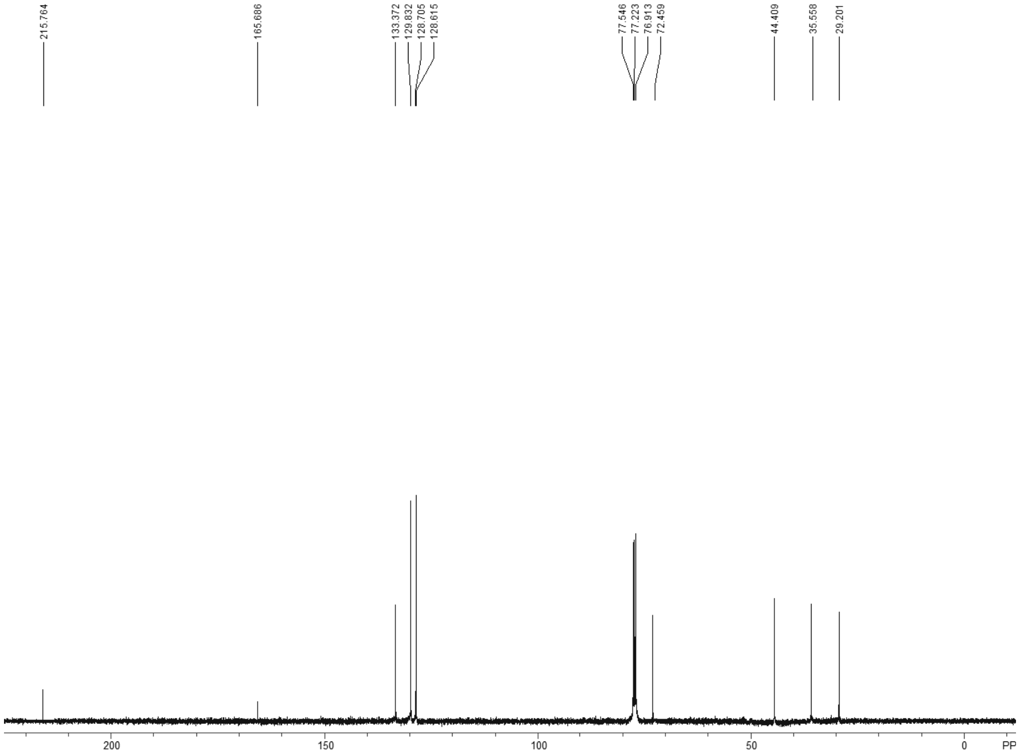

O
HO

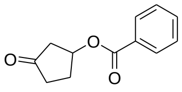
(*S*)-**41**


8.093
8.074
7.591
7.572
7.554
7.466
7.448
7.429
7.259
2.727
2.687
2.548
2.536
2.523
2.510
2.482
2.470
2.370
2.359
2.352
2.345
2.337
2.316
2.287
2.269
2.254
2.00
3.28
0.89
2.24
3.99
10
8
6
4
2
0
PP

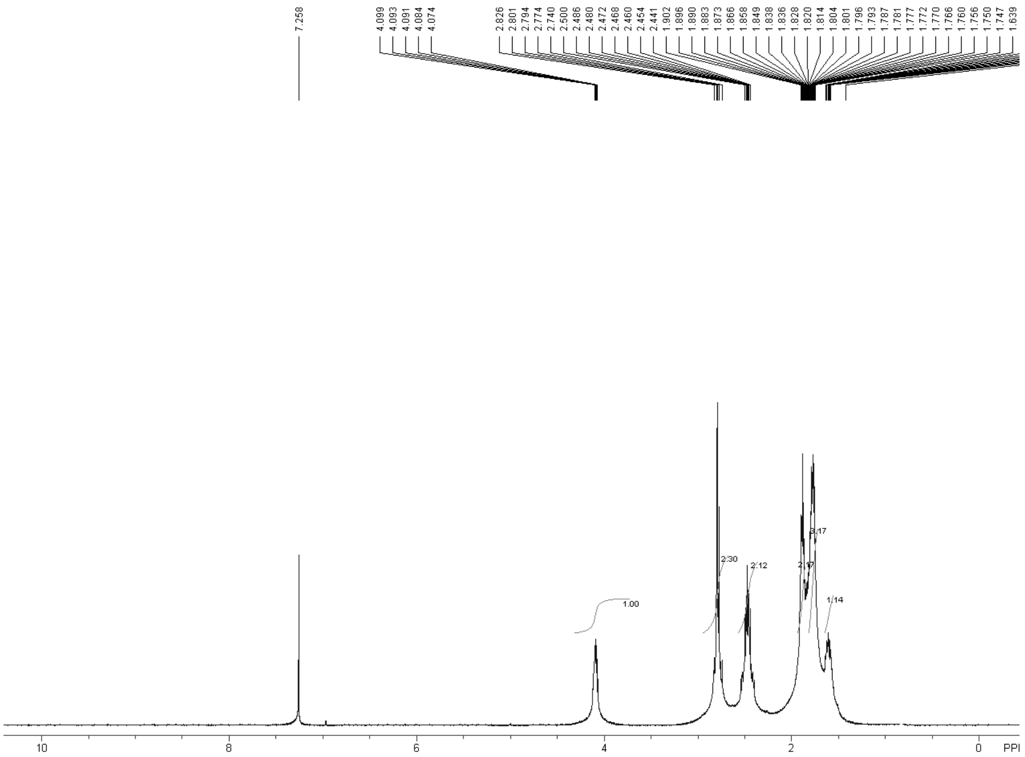


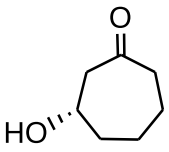
41A


215.764
165.686
133.372
129.832
128.705
128.615
77.546
77.223
76.913
72.459
44.409
35.558
29.201
200
150
100
50
0
PP

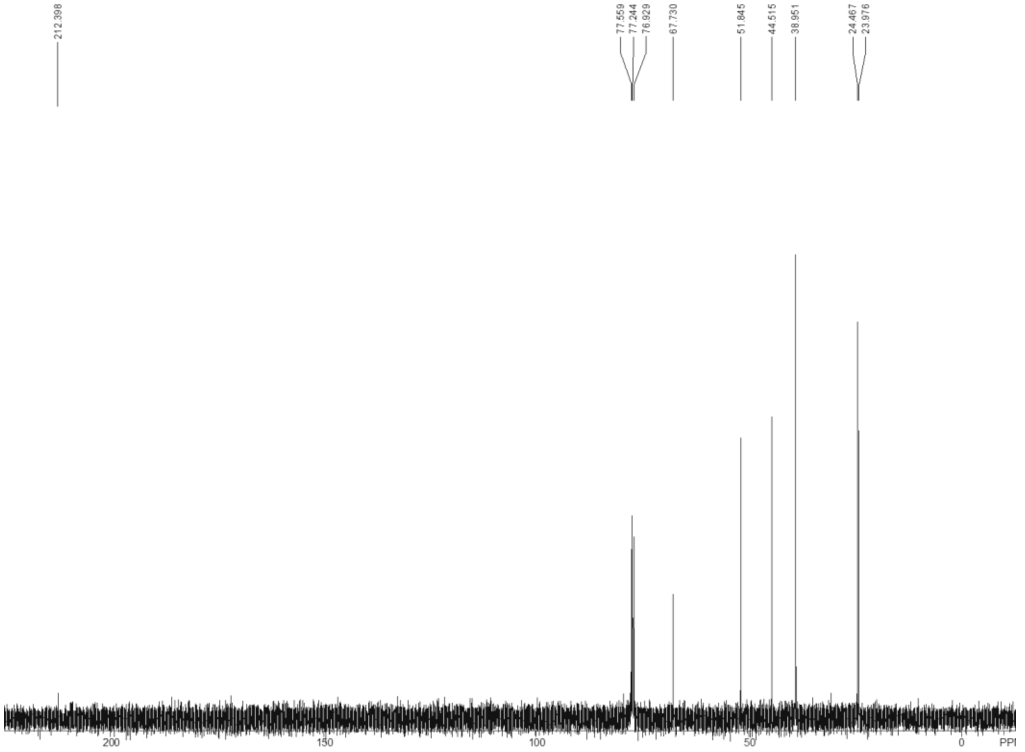


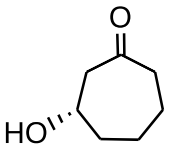
41A


7.258
4.099
4.093
4.091
4.084
4.074
2.826
2.801
2.794
2.774
2.740
2.500
2.486
2.480
2.472
2.468
2.460
2.454
2.441
1.902
1.896
1.890
1.883
1.873
1.866
1.858
1.849
1.838
1.836
1.828
1.820
1.814
1.804
1.801
1.796
1.793
1.787
1.781
1.777
1.772
1.770
1.766
1.760
1.756
1.750
1.747
1.639
1.00
2.30
2.12
2.17
2.17
1.14
10
8
6
4
2
0
PP

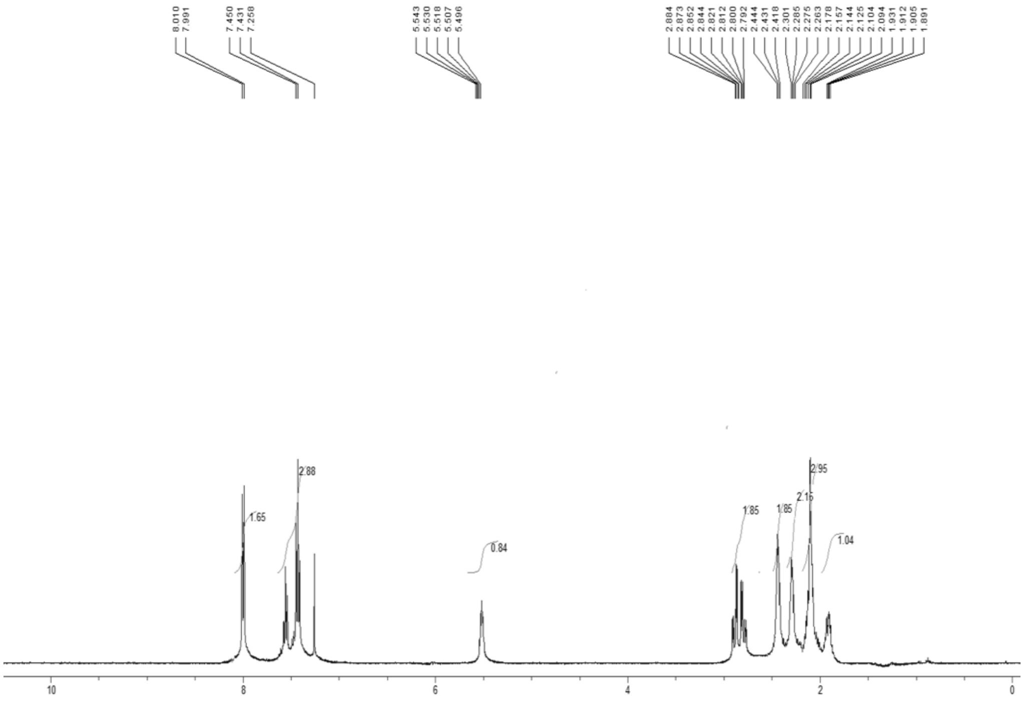

O
HO

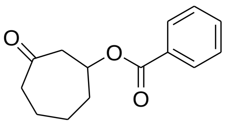
(*S*)-**42**


212.398
77.559
77.244
76.929
67.730
51.845
44.515
38.951
24.467
23.976
200
150
100
50
0
PP

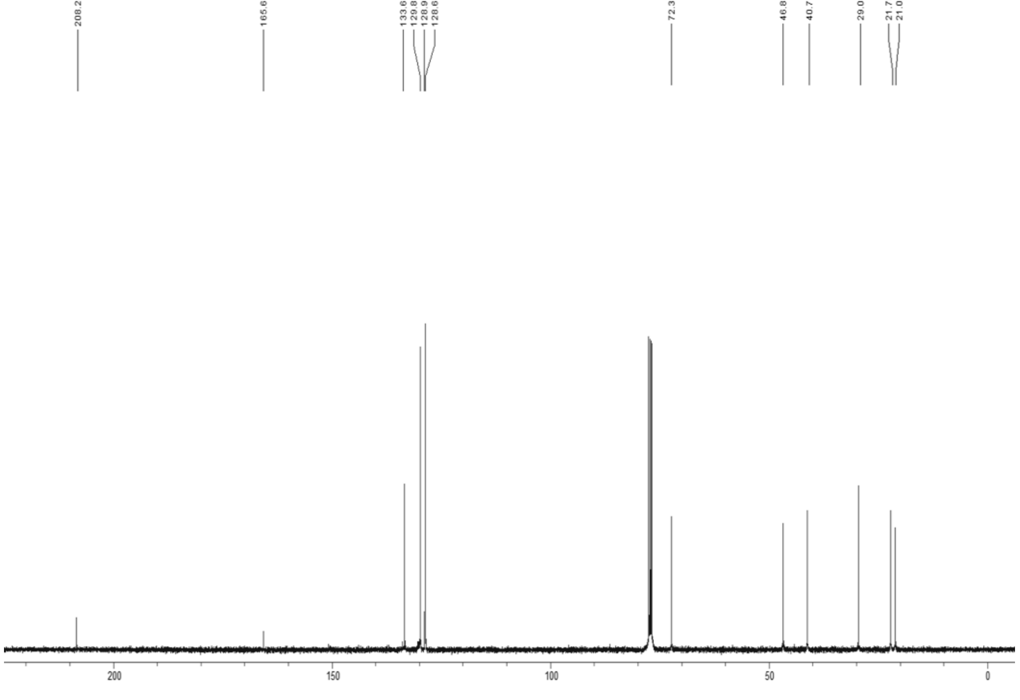

O
HO

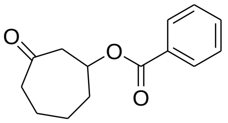
(*S*)-**42**


8.010
7.991
7.450
7.431
7.258
5.543
5.530
5.518
5.507
5.496
2.884
2.873
2.852
2.844
2.821
2.812
2.800
2.792
2.444
2.431
2.418
2.301
2.285
2.275
2.263
2.178
2.157
2.144
2.125
2.104
2.094
1.931
1.912
1.905
1.891
1.65
2.88
0.84
1.85
1.85
2.16
2.95
1.04
10
8
6
4
2
0

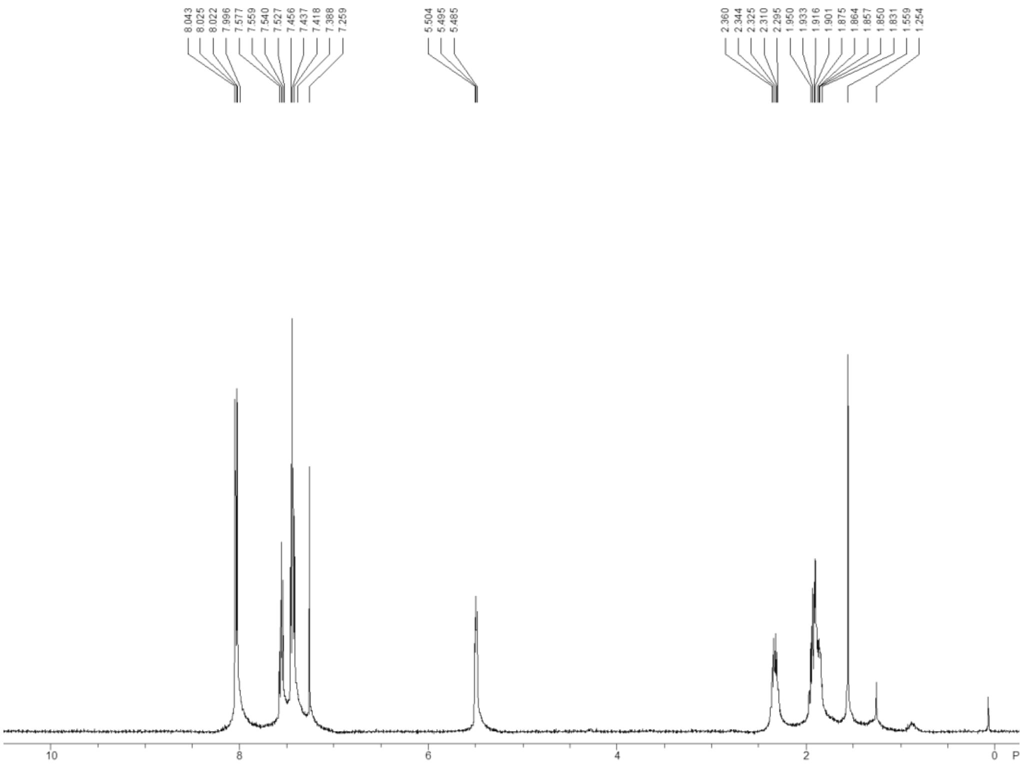


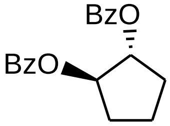
42A


208.208
165.686
133.687
129.832
128.962
128.615
72.361
46.817
40.773
29.053
21.797
21.028
200
150
100
50
0

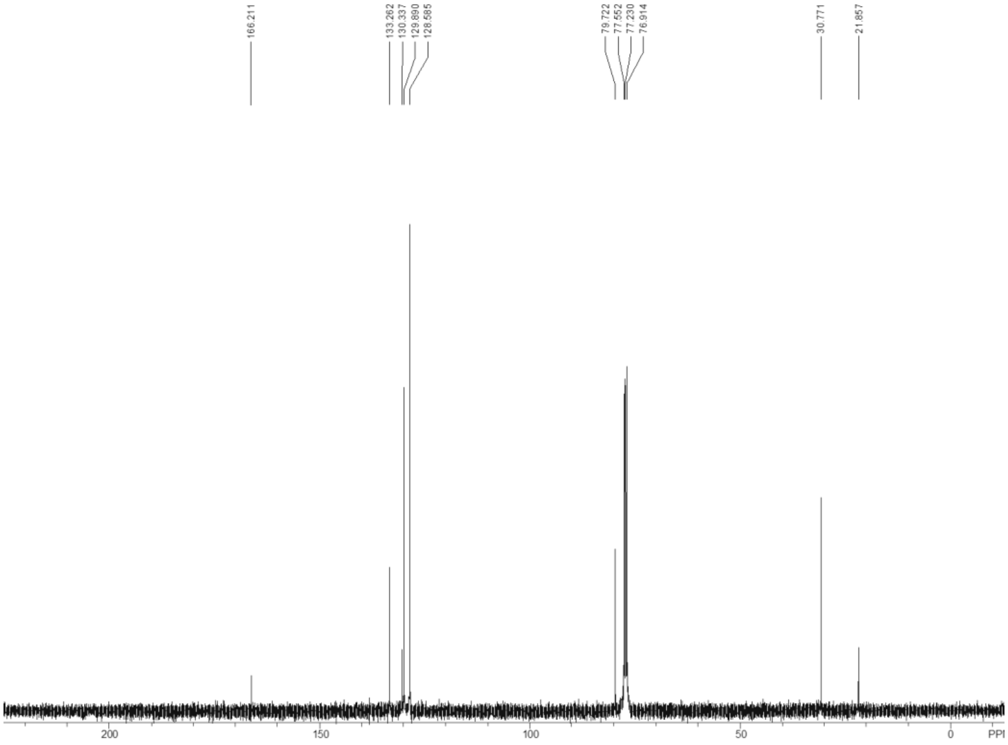


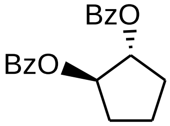
42A


8.043
8.025
8.022
7.996
7.577
7.559
7.540
7.527
7.456
7.437
7.418
7.388
7.259
5.504
5.495
5.485
2.360
2.344
2.325
2.310
2.295
1.950
1.933
1.916
1.901
1.875
1.864
1.857
1.850
1.831
1.559
1.254
10
8
6
4
2
0
P

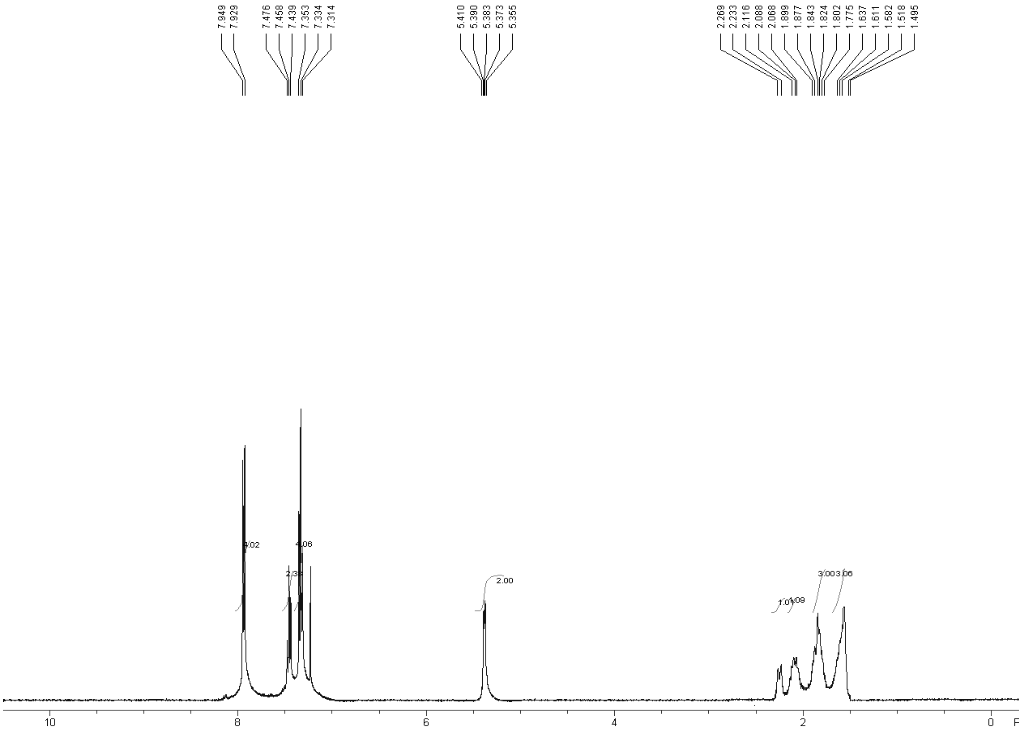

BzO
BzO

(*R*,*R*)-**46A**


166.211
133.262
130.337
129.890
128.585
79.722
77.552
77.230
76.914
30.771
21.857
200
150
100
50
0
PPI


BzO
BzO

(*R*,*R*)-**46A**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7.929
7.476
7.458
7.439
7.353
7.334
7.314
5.410
5.390
5.383
5.373
5.355
2.269
2.233
2.116
2.088
2.068
1.899
1.877
1.843
1.824
1.802
1.775
1.637
1.611
1.582
1.518
1.495
4.02
2.38
4.06
2.00
1.01
1.09
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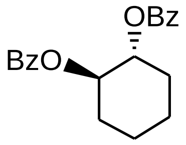
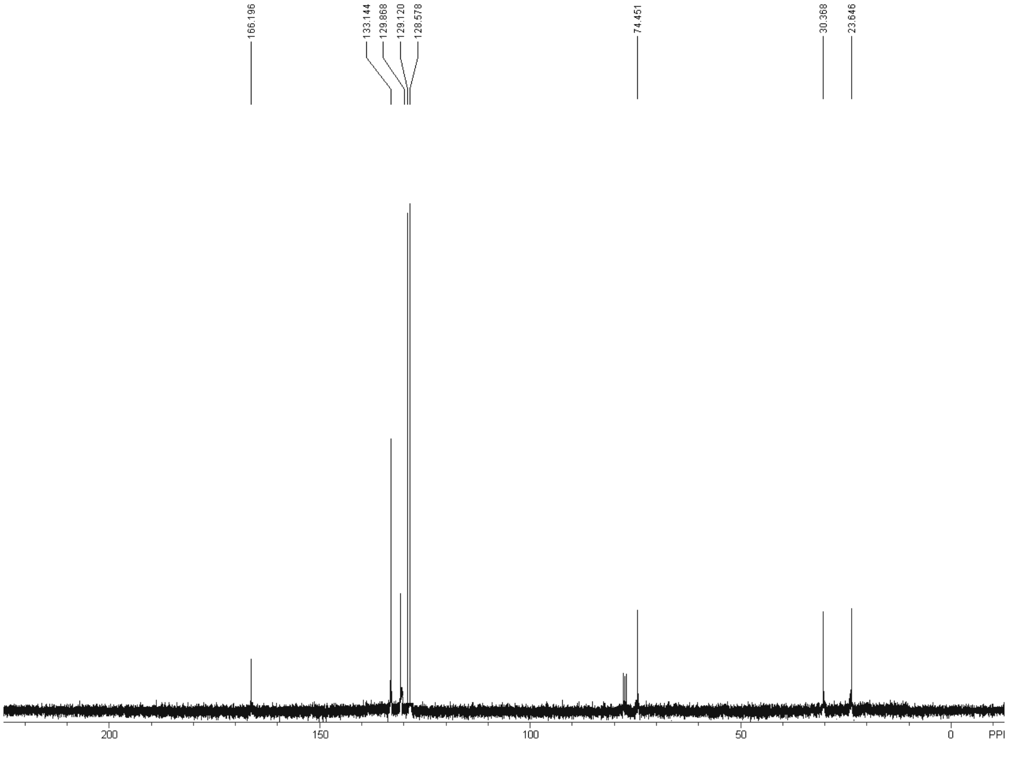
3.06
10
8
6
4
2
0


OBz
BzO

(*R*,*R*)-**47A**


166.196
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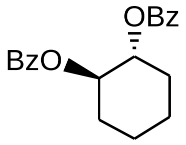
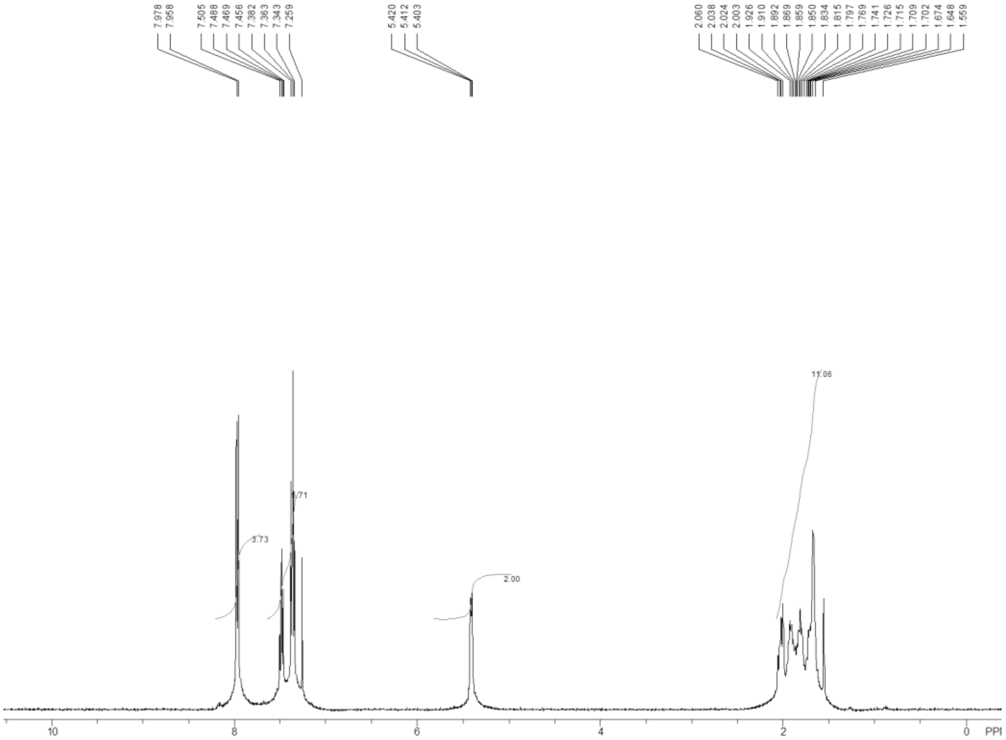
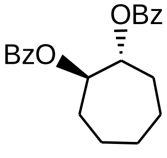
129.868
129.120
128.578
74.451
30.368
23.646
200
150
100
50
0
PPI

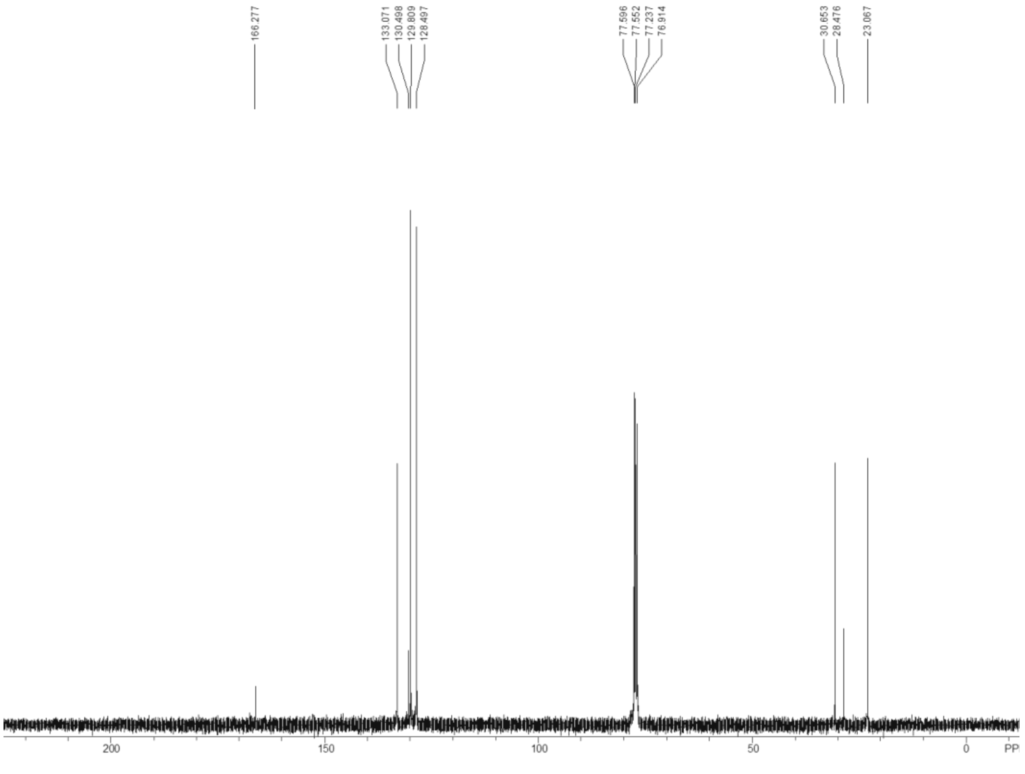

OBz
BzO

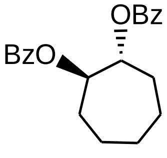
(*R*,*R*)-**47A**


7.978
7.958
7.505
7.488
7.469
7.456
7.382
7.363
7.343
7.259
5.420
5.412
5.403
2.060
2.038
2.024
2.003
1.926
1.910
1.892
1.869
1.859
1.850
1.834
1.815
1.797
1.769
1.741
1.726
1.715
1.709
1.702
1.674
1.648
1.559
3.73
5.71
2.00
11.06
10
8
6
4
2
0
PPM

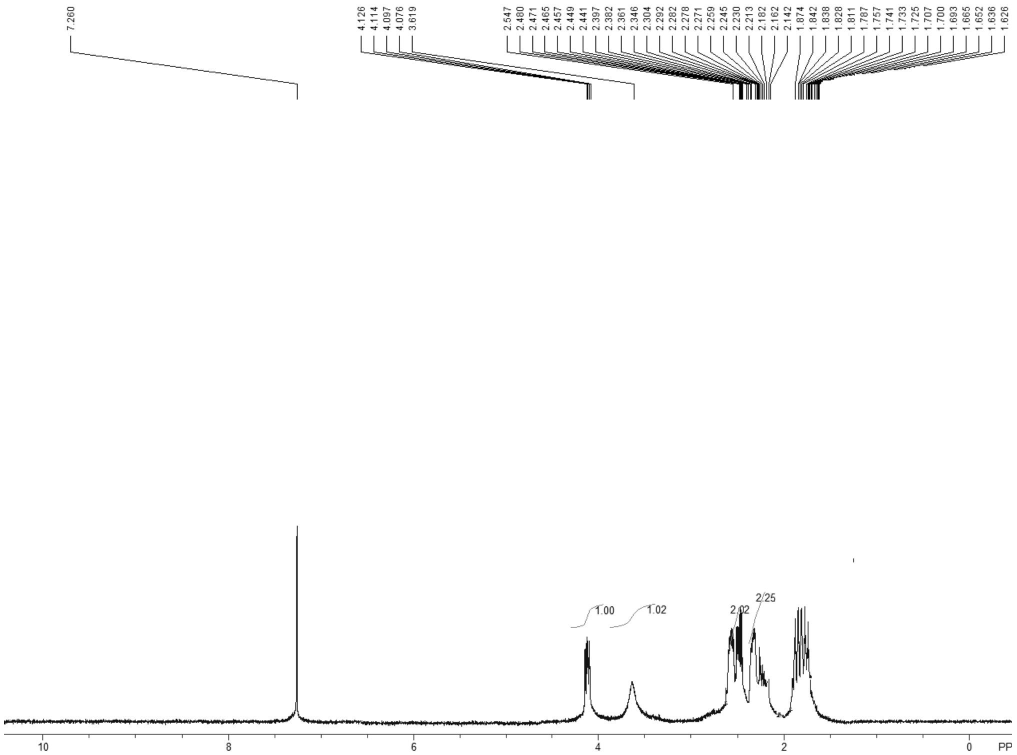

OBz
BzO

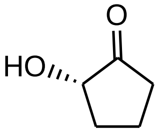
(*R*,*R*)-**48A**


166.277
133.071
130.498
129.809
128.497
77.596
77.552
77.237
76.914
30.653
28.476
23.067
200
150
100
50
0
PPM

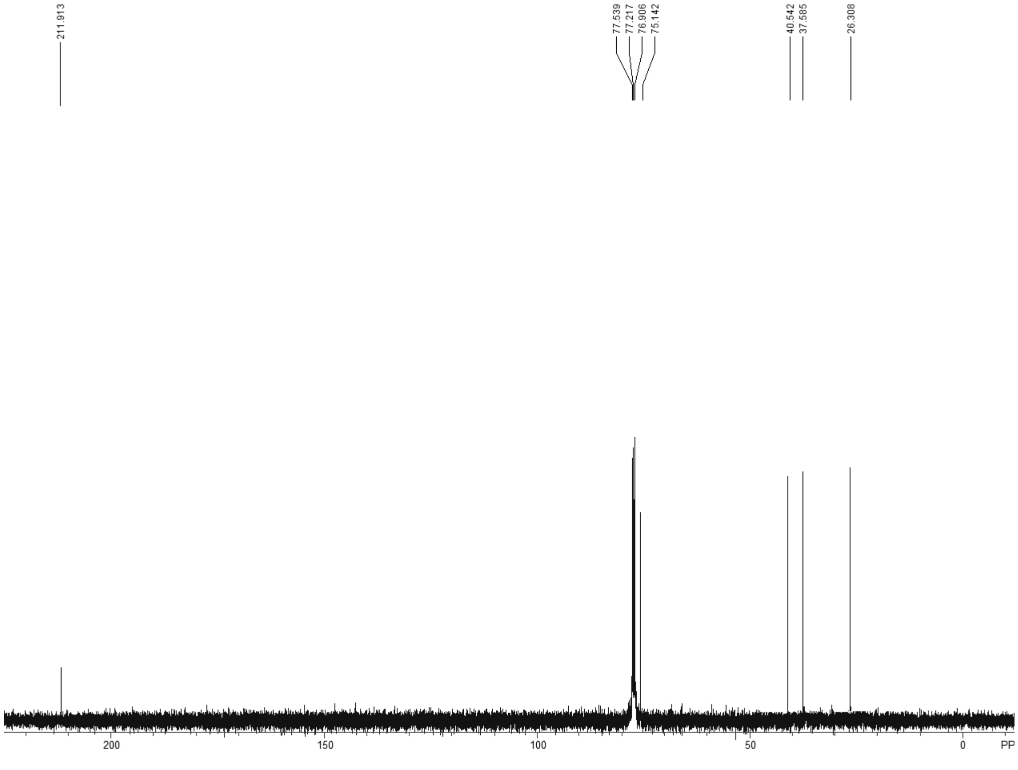

OBz
BzO

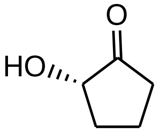
(*R*,*R*)-**48A**


7.260
4.126
4.114
4.097
4.076
3.619
2.547
2.480
2.471
2.465
2.457
2.449
2.441
2.397
2.382
2.361
2.346
2.304
2.292
2.282
2.278
2.271
2.259
2.245
2.230
2.213
2.182
2.162
2.142
1.874
1.842
1.838
1.828
1.811
1.787
1.757
1.741
1.733
1.725
1.707
1.700
1.693
1.665
1.652
1.636
1.626
1.00
1.02
2.02
2.25
10
8
6
4
2
0
PP

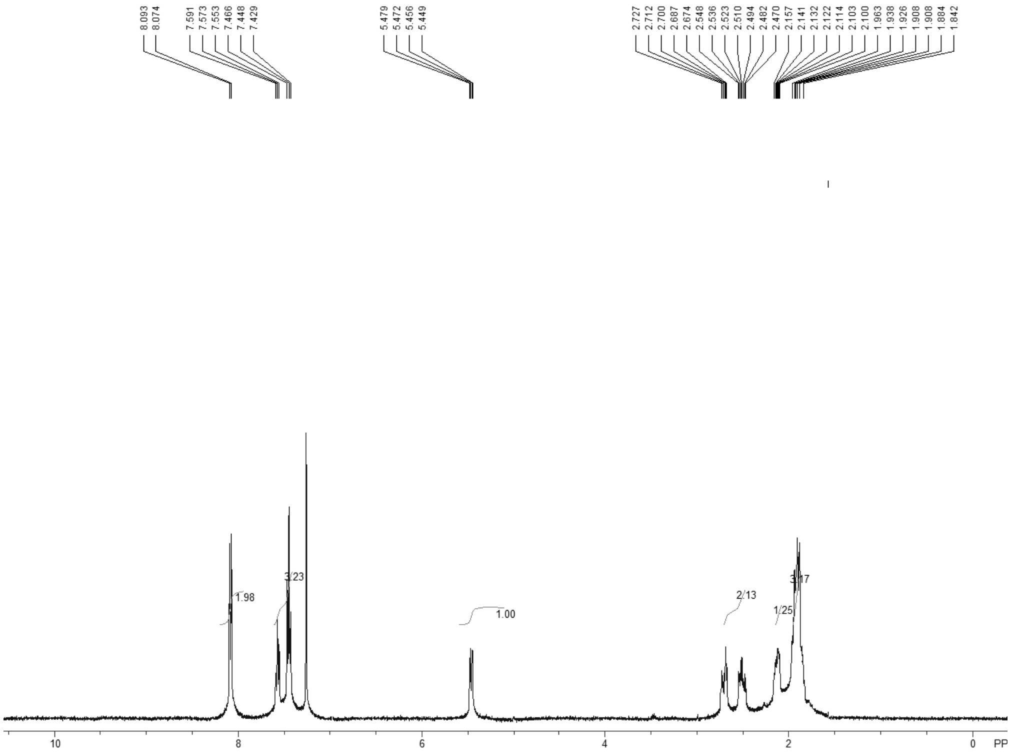

O
HO

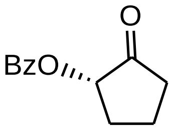
(*S*)-**49**


211.913
77.539
77.217
76.906
75.142
40.542
37.585
26.308
200
150
100
50
0
PP

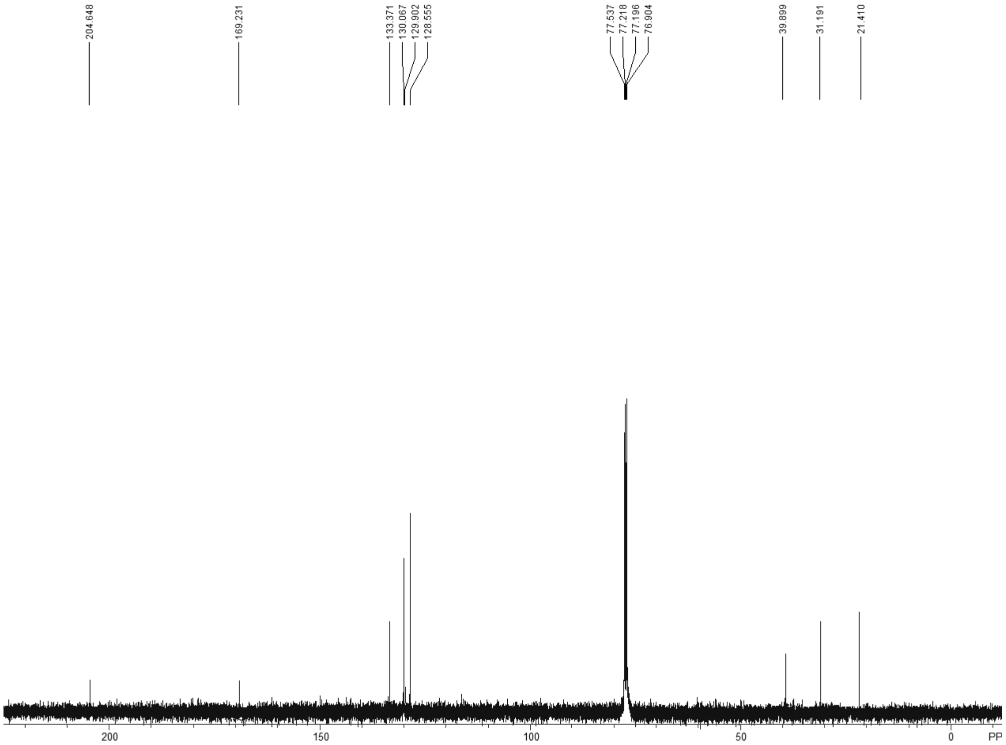

O
HO

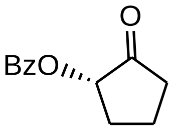
(*S*)-**49**


8.093
8.074
7.591
7.573
7.553
7.466
7.448
7.429
5.479
5.472
5.456
5.449
2.727
2.712
2.700
2.687
2.674
2.548
2.536
2.523
2.510
2.494
2.482
2.470
2.157
2.141
2.132
2.122
2.114
2.103
2.100
1.963
1.938
1.926
1.908
1.908
1.884
1.842
1.98
3.23
1.00
2.13
1.25
3.17
10
8
6
4
2
0
PP

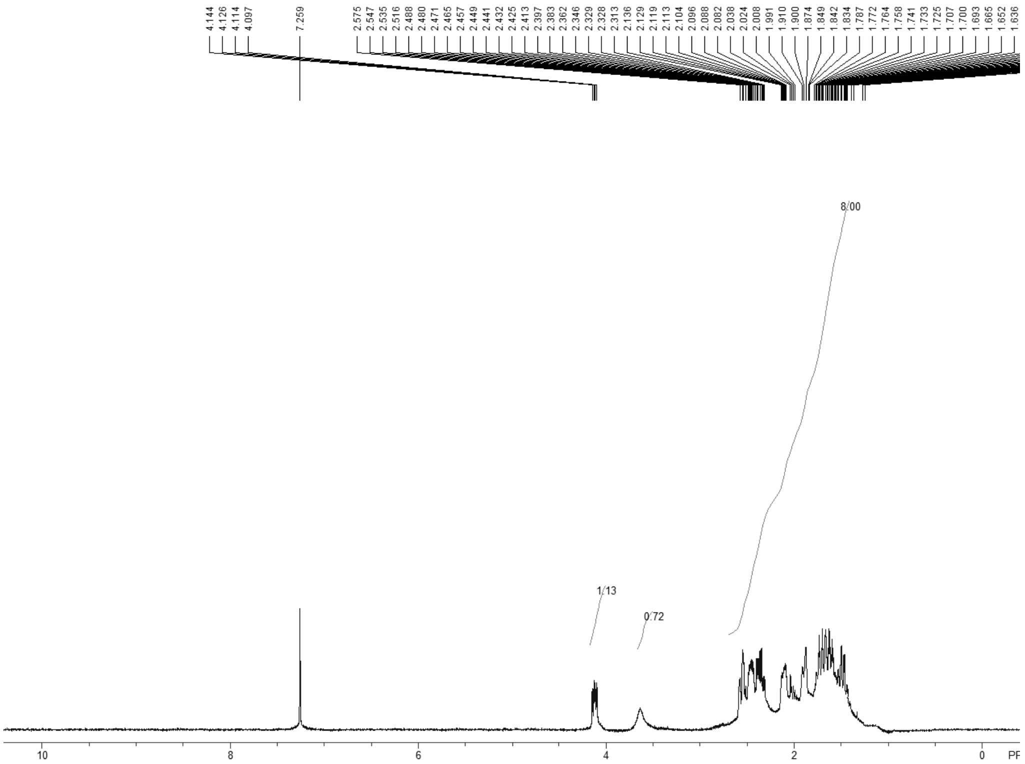

O
BzO

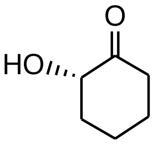
(*S*)-**49A**


204.648
169.231
133.371
130.067
129.902
128.555
77.537
77.218
77.196
76.904
39.899
31.191
21.410
200
150
100
50
0
PP

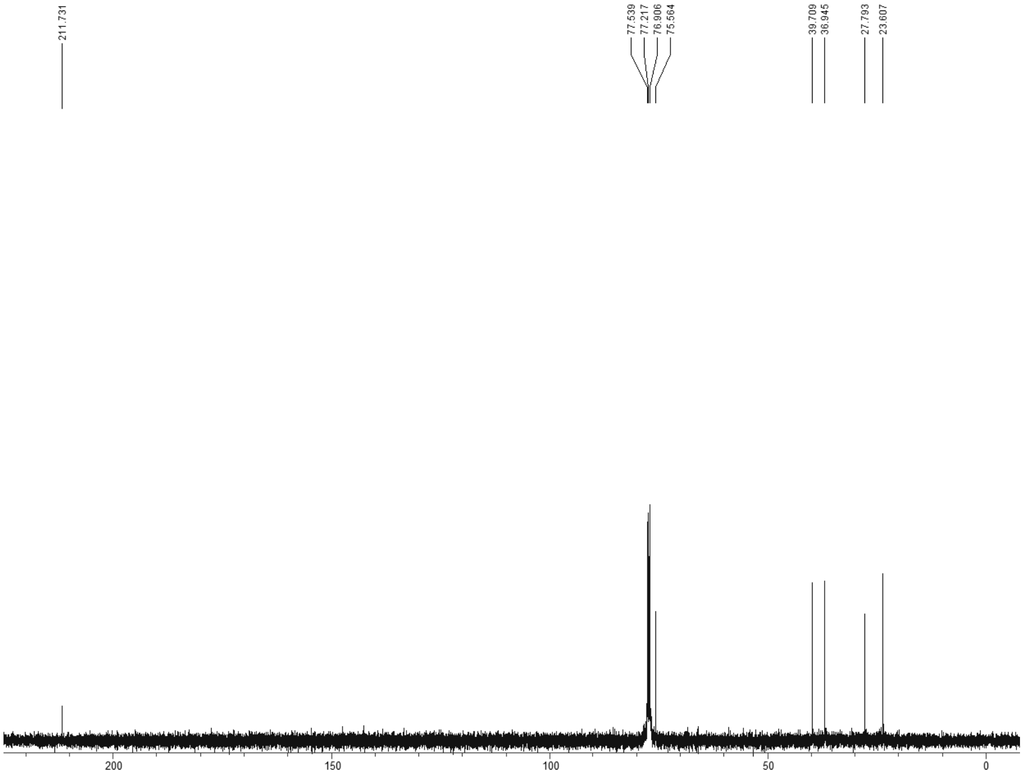

O
BzO

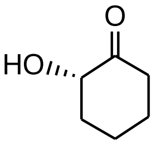
(*S*)-**49A**


4.144
4.126
4.114
4.097
7.259
2.575
2.547
2.535
2.516
2.488
2.480
2.471
2.465
2.457
2.449
2.441
2.432
2.425
2.413
2.397
2.383
2.362
2.346
2.329
2.328
2.313
2.136
2.129
2.119
2.113
2.104
2.096
2.088
2.082
2.038
2.024
2.008
1.991
1.910
1.900
1.874
1.849
1.842
1.834
1.787
1.772
1.764
1.758
1.741
1.733
1.725
1.707
1.700
1.693
1.665
1.652
1.636
8.00
1.13
0.72
10
8
6
4
2
0
PF

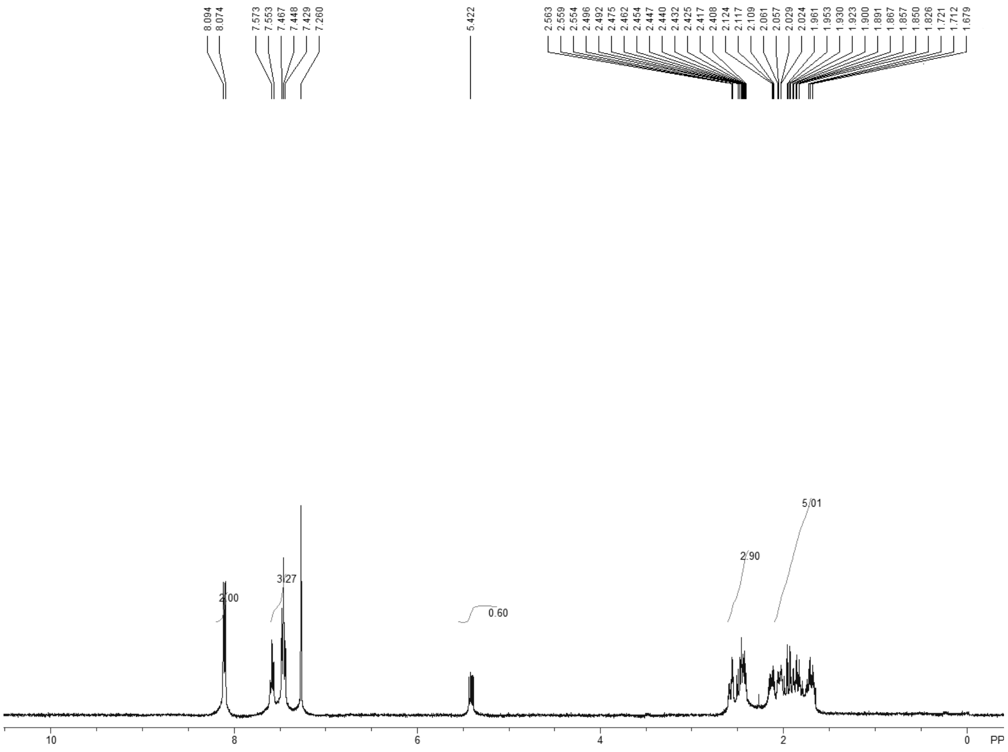

O
HO

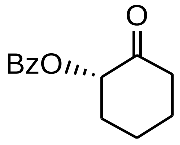
(S)-**50**


211.731
77.539
77.217
76.906
75.564
39.709
36.945
27.793
23.607
200
150
100
50
0

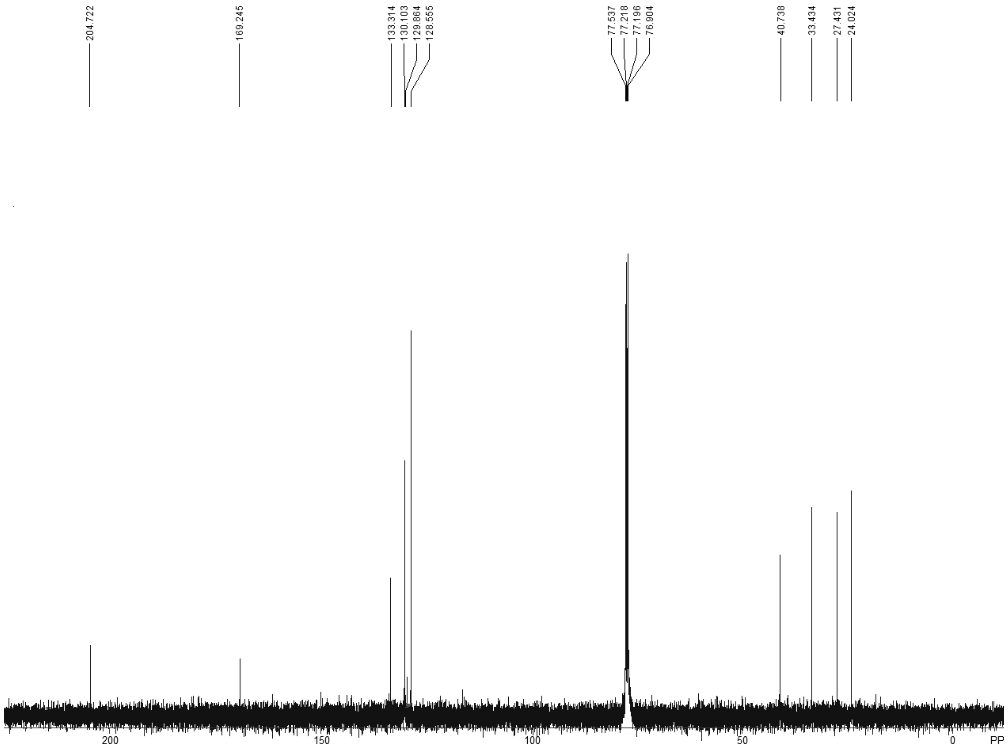

O
HO

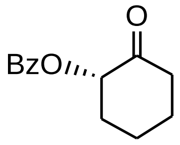
(S)-**50**


8.094
8.074
7.573
7.553
7.467
7.448
7.429
7.260
5.422
2.563
2.559
2.554
2.496
2.492
2.475
2.462
2.454
2.447
2.440
2.432
2.425
2.417
2.408
2.124
2.117
2.109
2.061
2.057
2.029
2.024
1.961
1.953
1.930
1.923
1.900
1.891
1.867
1.857
1.850
1.826
1.721
1.712
1.679
2.00
3.27
0.60
2.90
5.01
10
8
6
4
2
0
PP

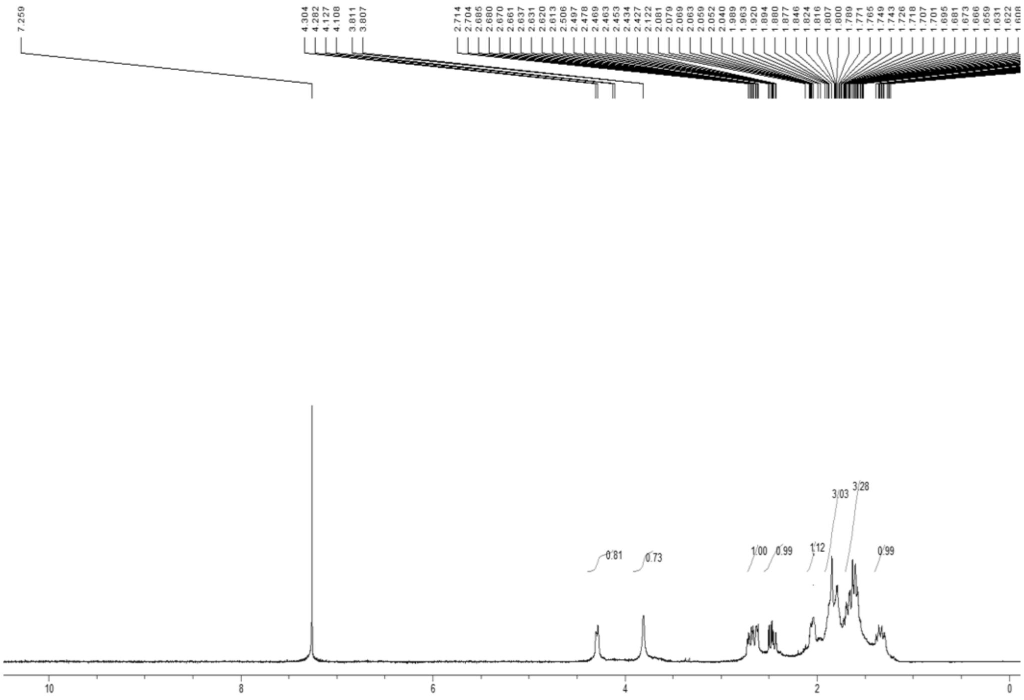

O
BzO

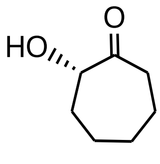
(S)-**50A**


204.722
169.245
133.314
130.103
129.864
128.555
77.537
77.218
77.196
76.904
40.738
33.434
27.431
24.024
200
150
100
50
0
PP

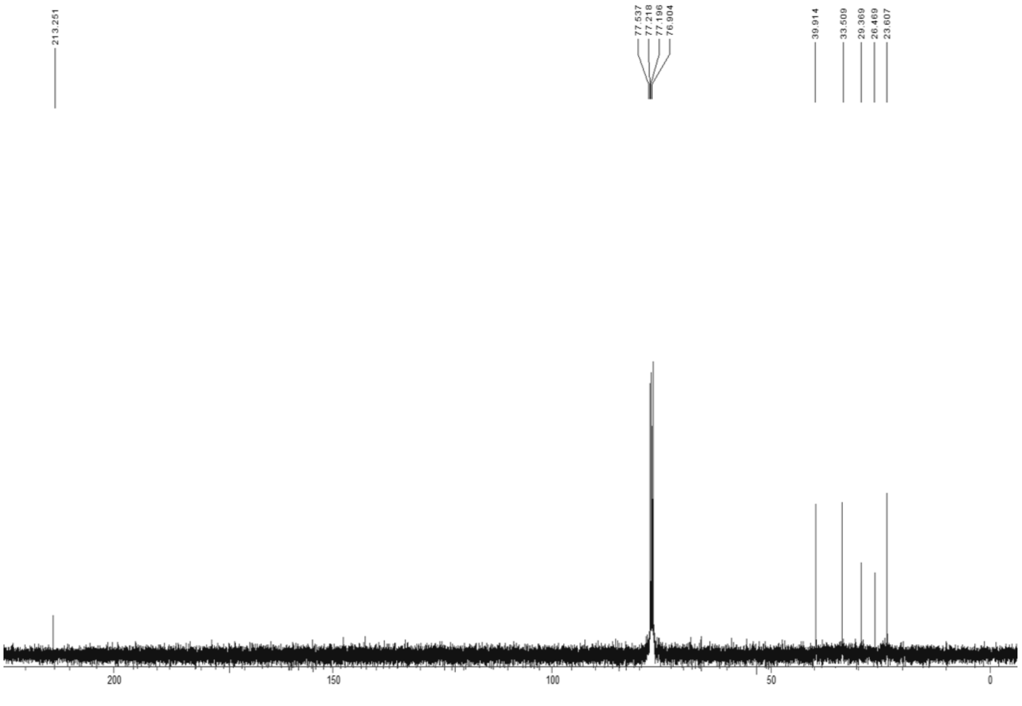

O
BzO

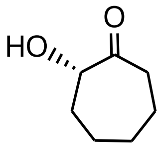
(S)-**50A**


7.259
4.304
4.282
4.127
4.108
3.811
3.807
2.714
2.704
2.685
2.680
2.670
2.661
2.637
2.631
2.620
2.613
2.506
2.497
2.478
2.469
2.463
2.453
2.434
2.427
2.122
2.081
2.079
2.069
2.063
2.059
2.052
2.040
1.989
1.963
1.920
1.894
1.880
1.877
1.846
1.824
1.816
1.807
1.800
1.789
1.771
1.765
1.749
1.743
1.726
1.718
1.707
1.701
1.695
1.681
1.673
1.666
1.659
1.631
1.622
1.608
0.81
0.73
1.00
0.99
1.12
3.03
3.28
0.99
10
8
6
4
2
0

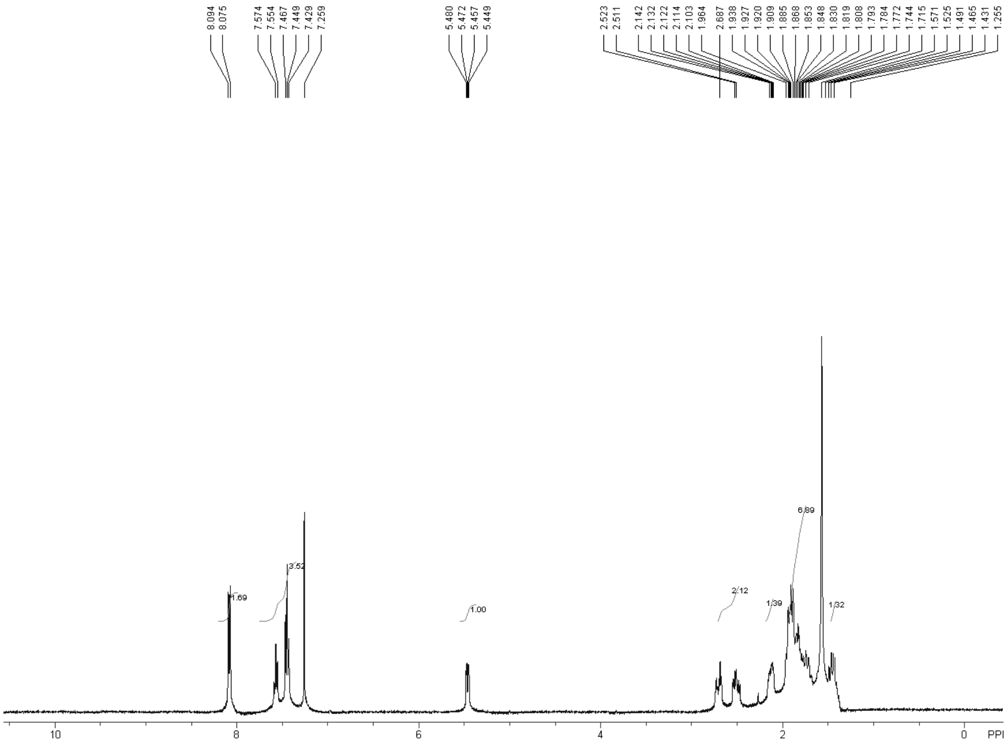

HO
O

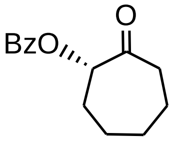
(*S*)-**51**


213.251
77.537
77.218
77.196
76.904
39.914
33.509
29.369
26.469
23.607
200
150
100
50
0

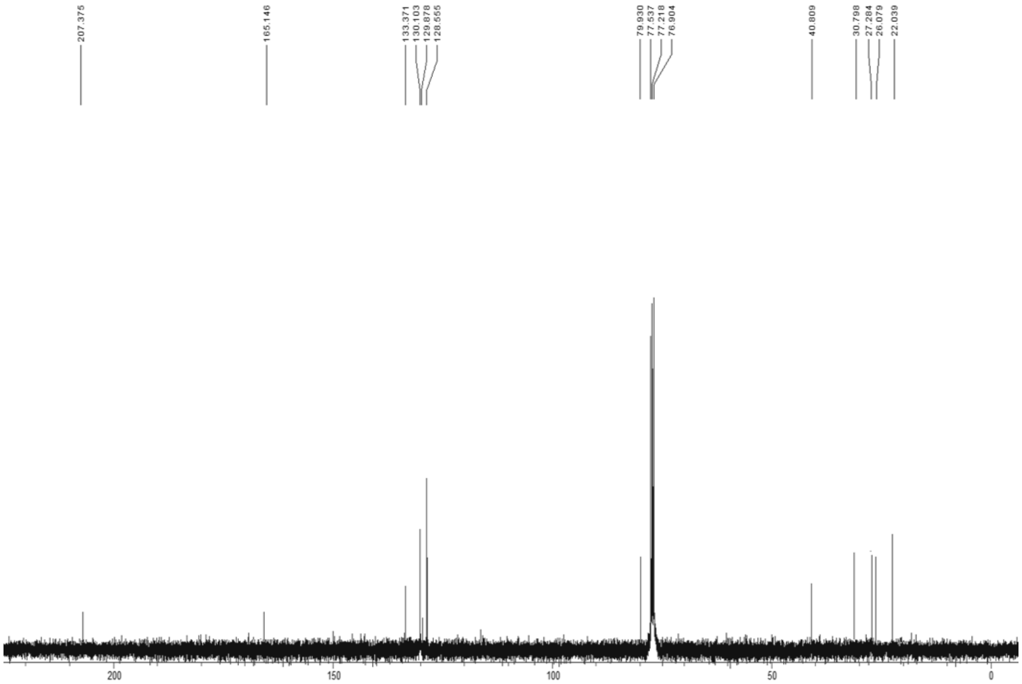

HO
O

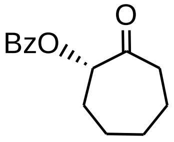
(*S*)-**51**


8.094
8.075
7.574
7.554
7.467
7.449
7.429
7.259
5.480
5.472
5.457
5.449
2.523
2.511
2.142
2.132
2.122
2.114
2.103
1.964
2.687
1.938
1.927
1.920
1.909
1.885
1.868
1.853
1.848
1.830
1.819
1.808
1.793
1.784
1.772
1.744
1.715
1.571
1.525
1.491
1.465
1.431
1.255
1.69
3.52
1.00
2.12
1.39
6.89
1.32
10
8
6
4
2
0
PPI

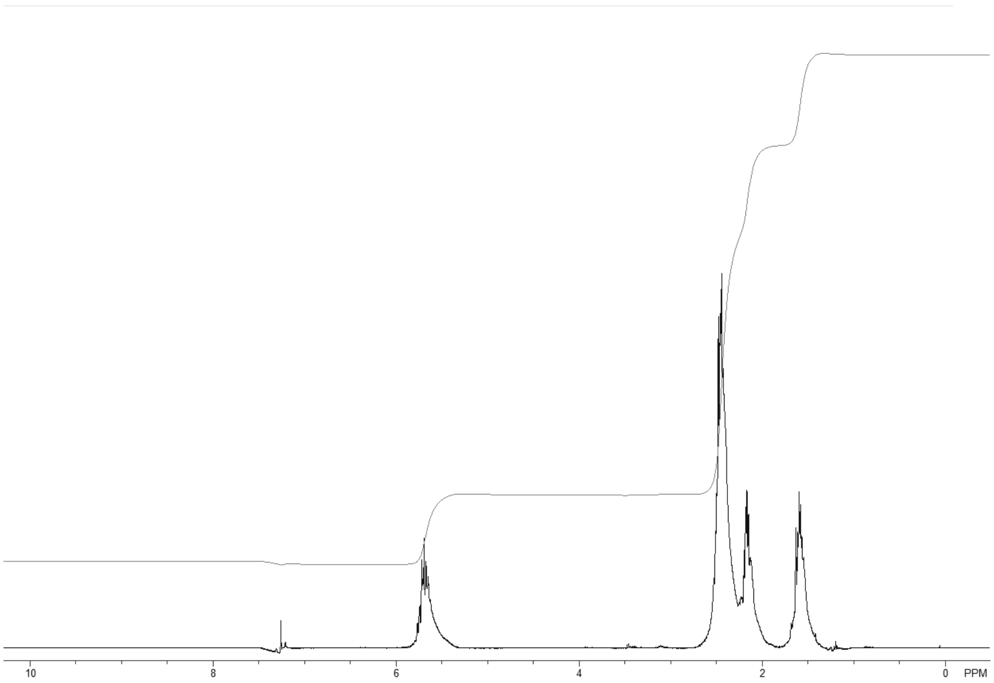

BzO
O

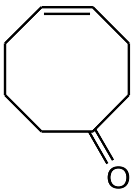
(*S*)-**51A**


207.375
165.146
133.371
130.103
129.878
128.555
79.930
77.537
77.218
76.904
40.809
30.798
27.284
26.079
22.039
200
150
100
50
0

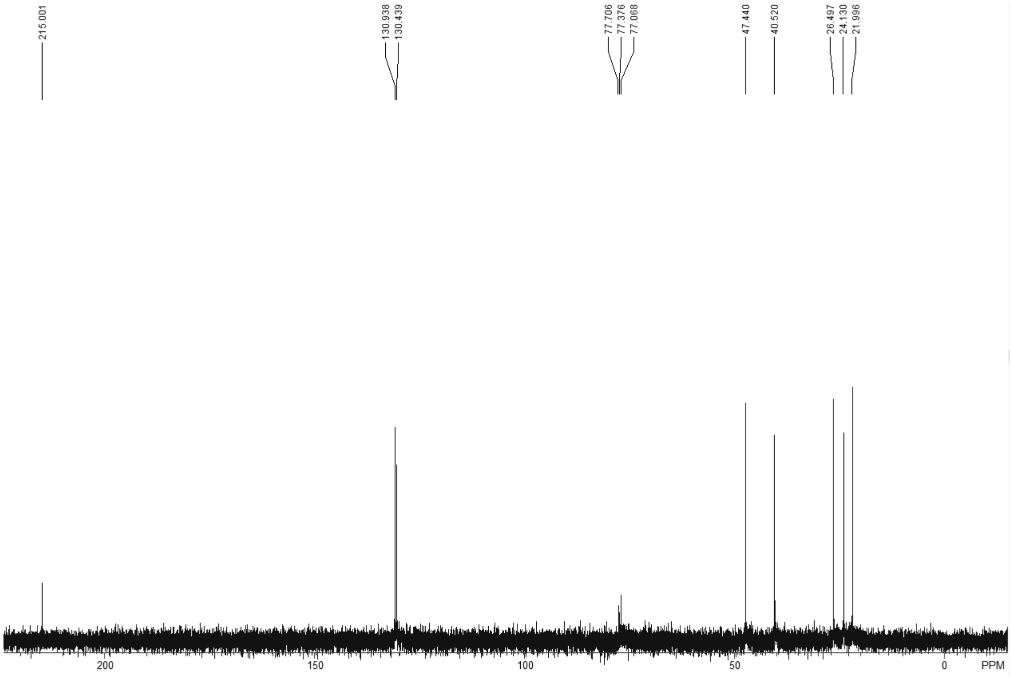

BzO
O

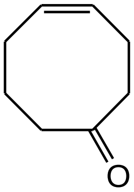
(*S*)-**51A**


10
8
6
4
2
0
PPM

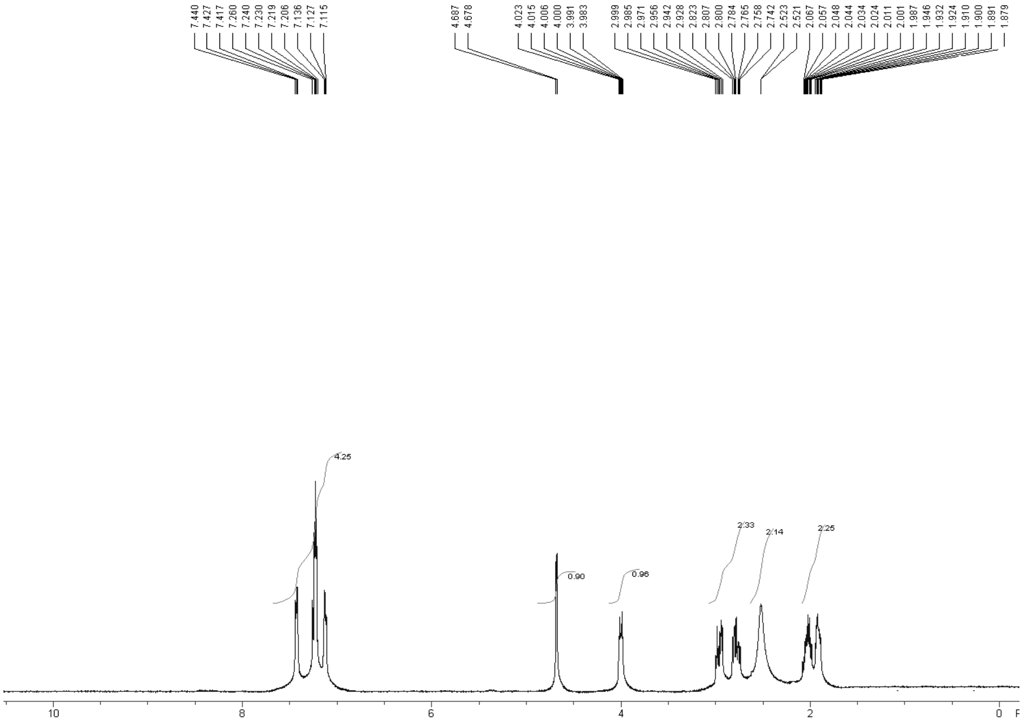

O

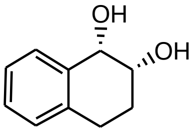
56


215.001
130.938
130.439
77.706
77.376
77.068
47.440
40.520
26.497
24.130
21.996
200
150
100
50
0
PPM

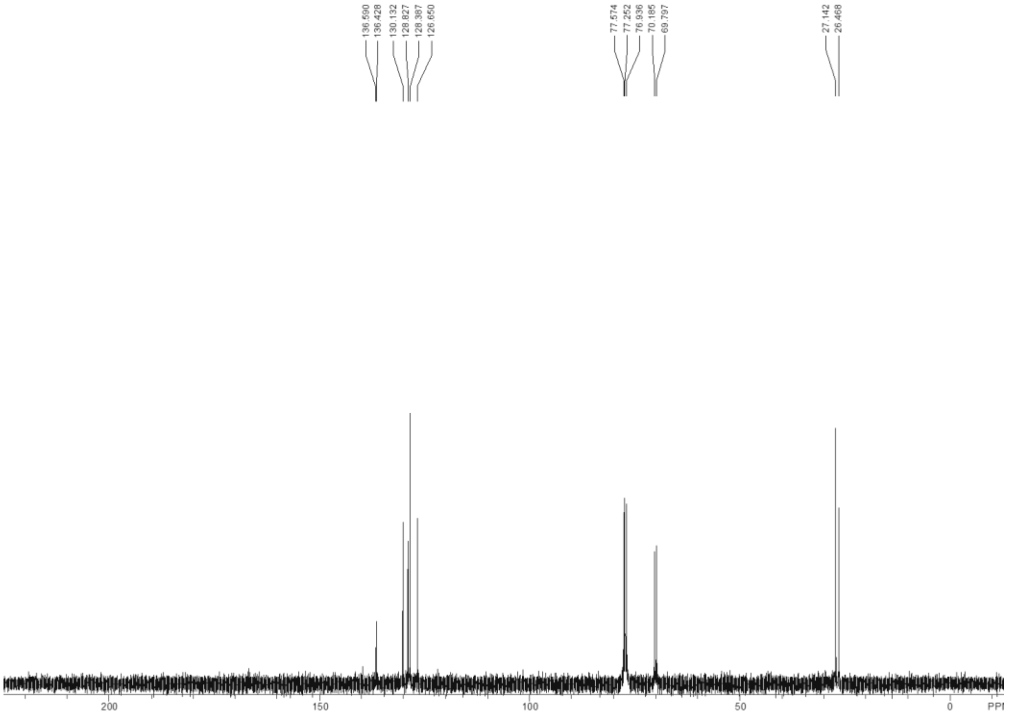

O

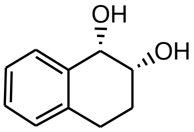
56



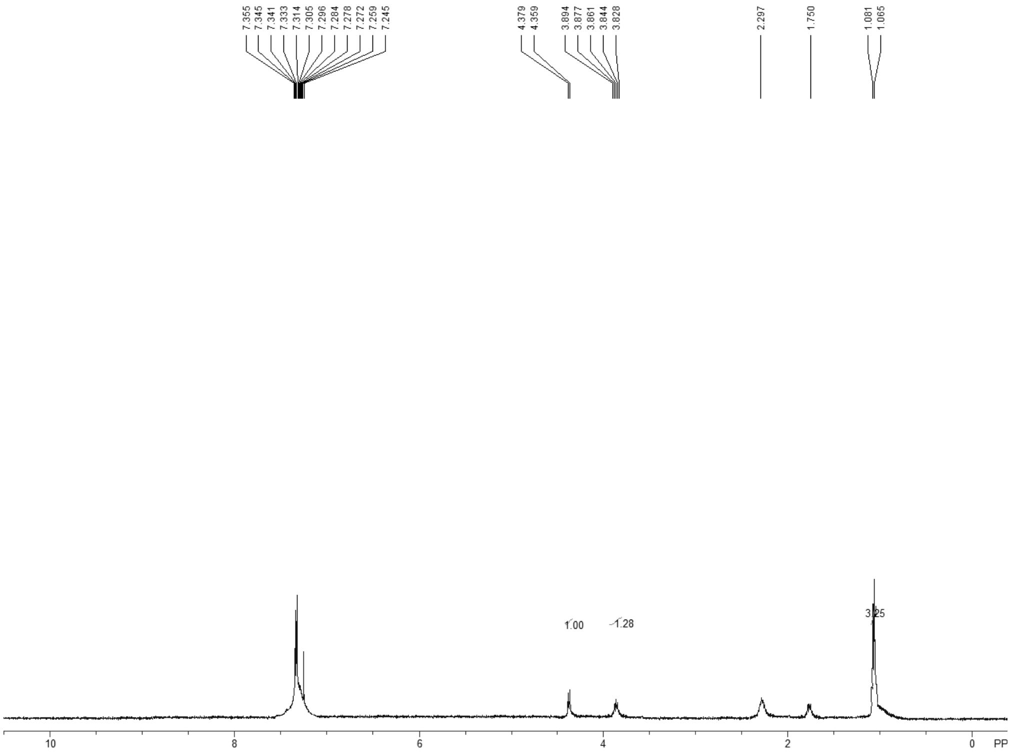


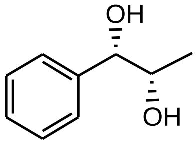
(1*S*,2*R*)-58



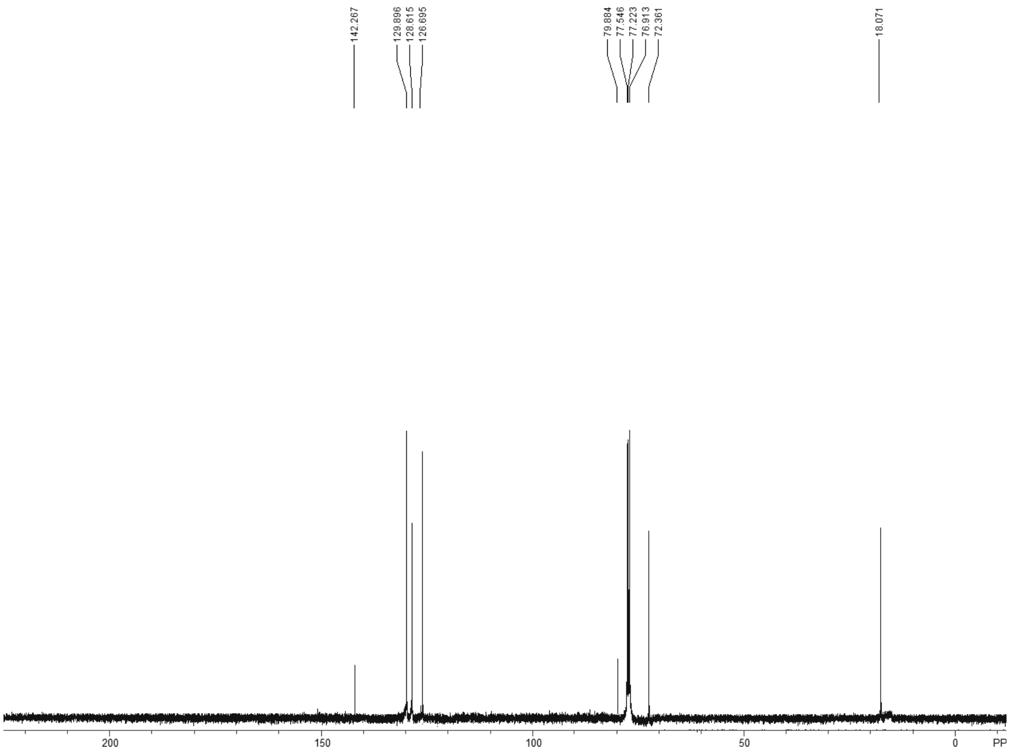


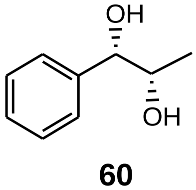
(1*S*,2*R*)-58


7.355
7.345
7.341
7.333
7.314
7.305
7.296
7.284
7.278
7.272
7.259
7.245
4.379
4.359
3.894
3.877
3.861
3.844
3.828
2.297
1.750
1.081
1.065
1.00
1.28
3.25
10
8
6
4
2
0
PP

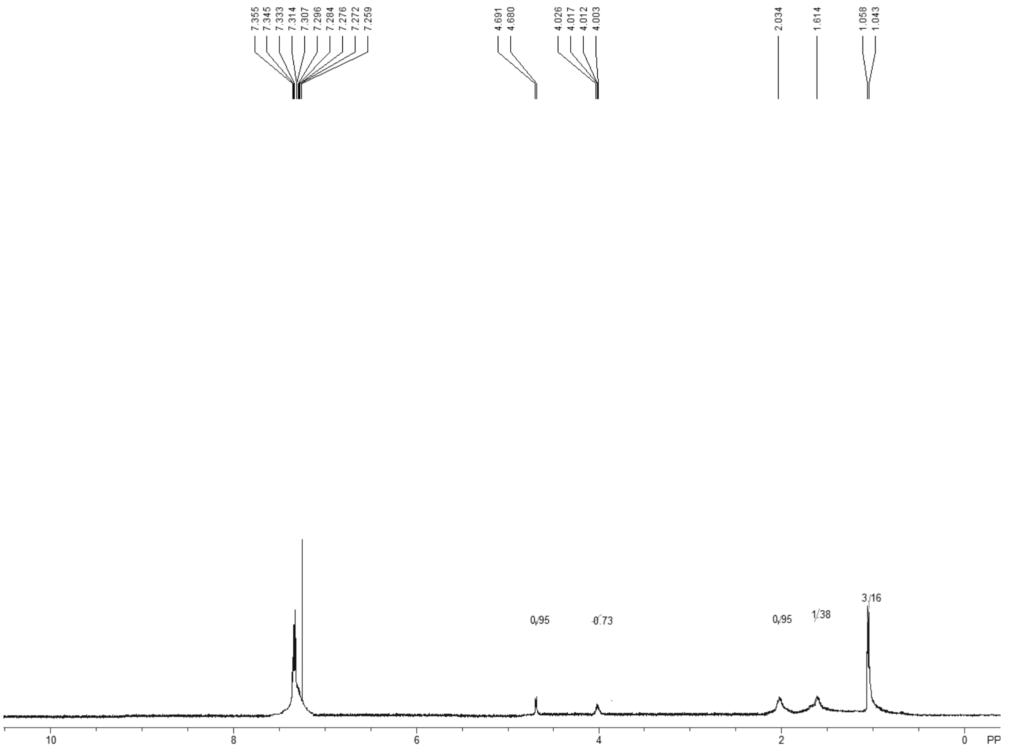

OH
OH

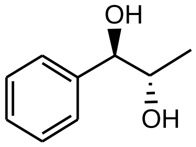
60


142.267
129.896
128.615
126.695
79.884
77.546
77.223
76.913
72.361
18.071
200
150
100
50
0
PP

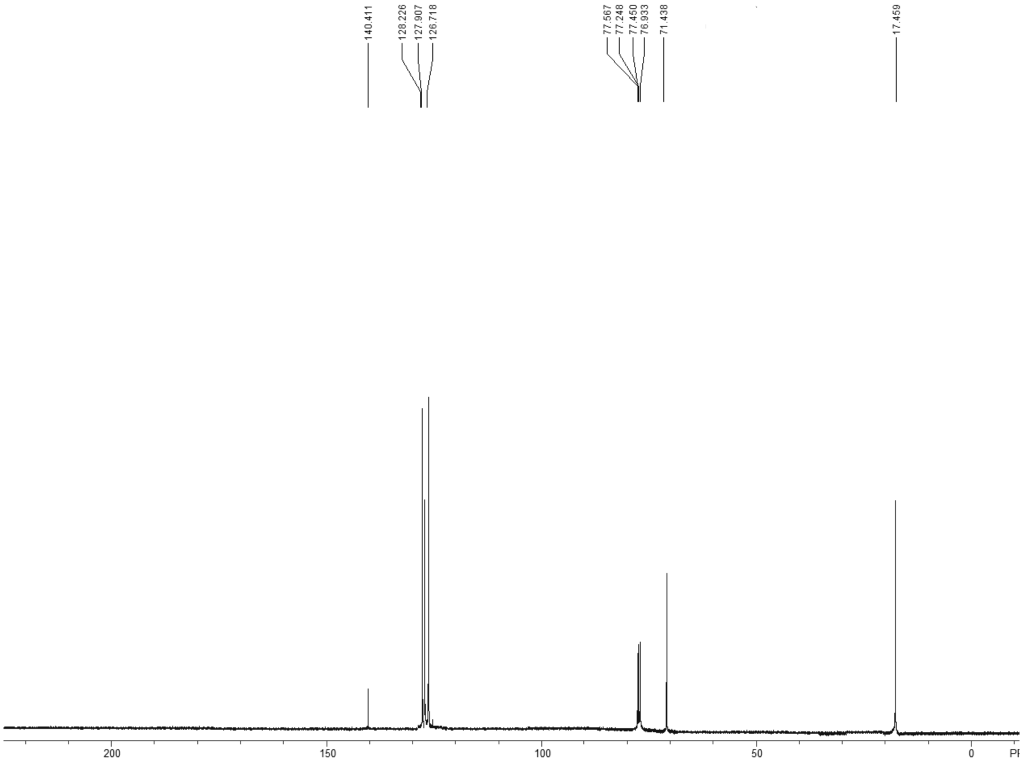

OH
OH

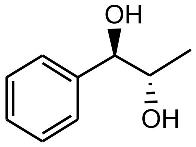
60


7.355
7.345
7.333
7.314
7.307
7.296
7.284
7.276
7.272
7.259
4.691
4.680
4.026
4.017
4.012
4.003
2.034
1.614
1.058
1.043
0.95
0.73
0.95
1.38
3.16
10
8
6
4
2
0
PP

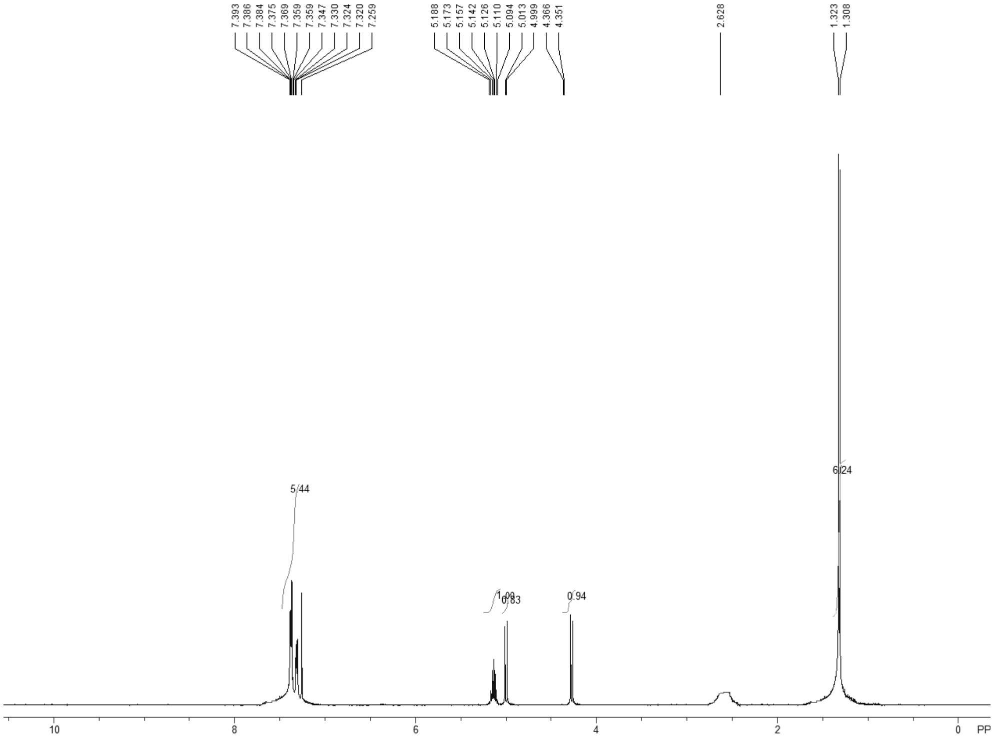

OH
OH

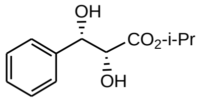
61


140.411
128.226
127.907
126.718
77.567
77.248
77.450
76.933
71.438
17.459
200
150
100
50
0
PI

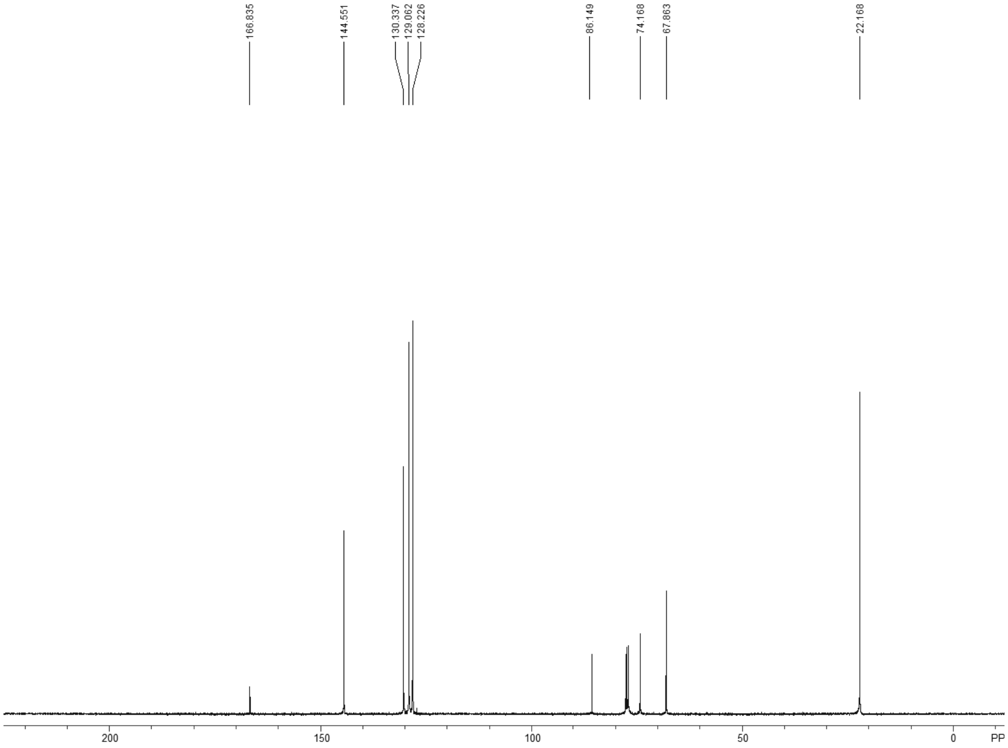

OH
OH

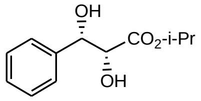
61



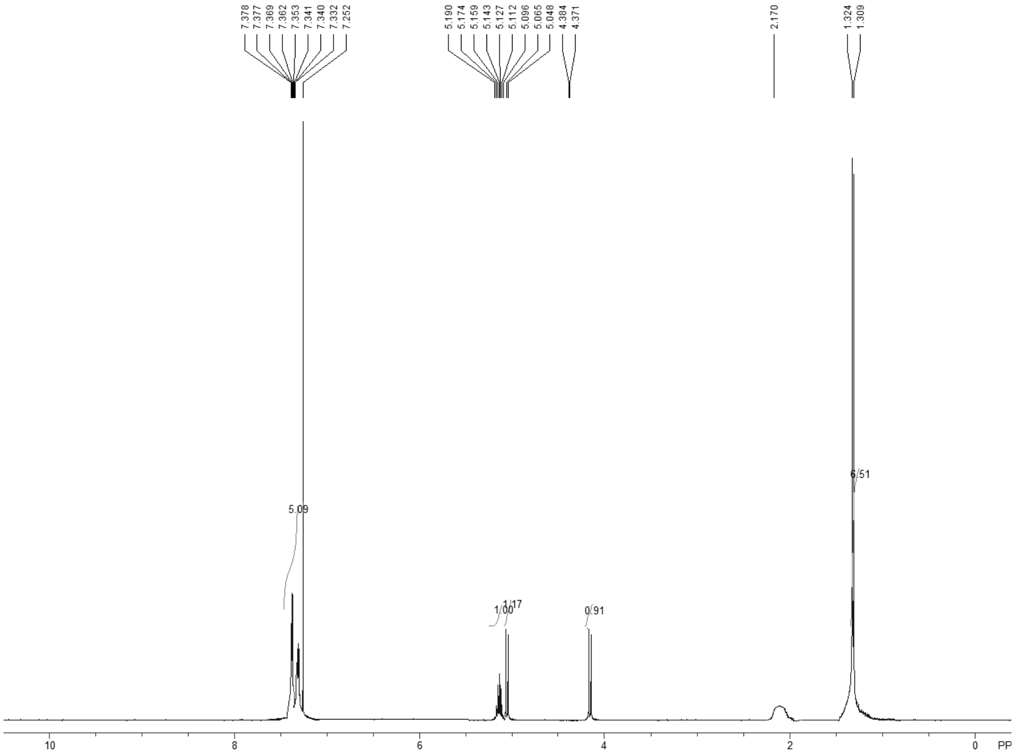


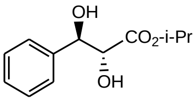
(2*R*,3*S*)-64



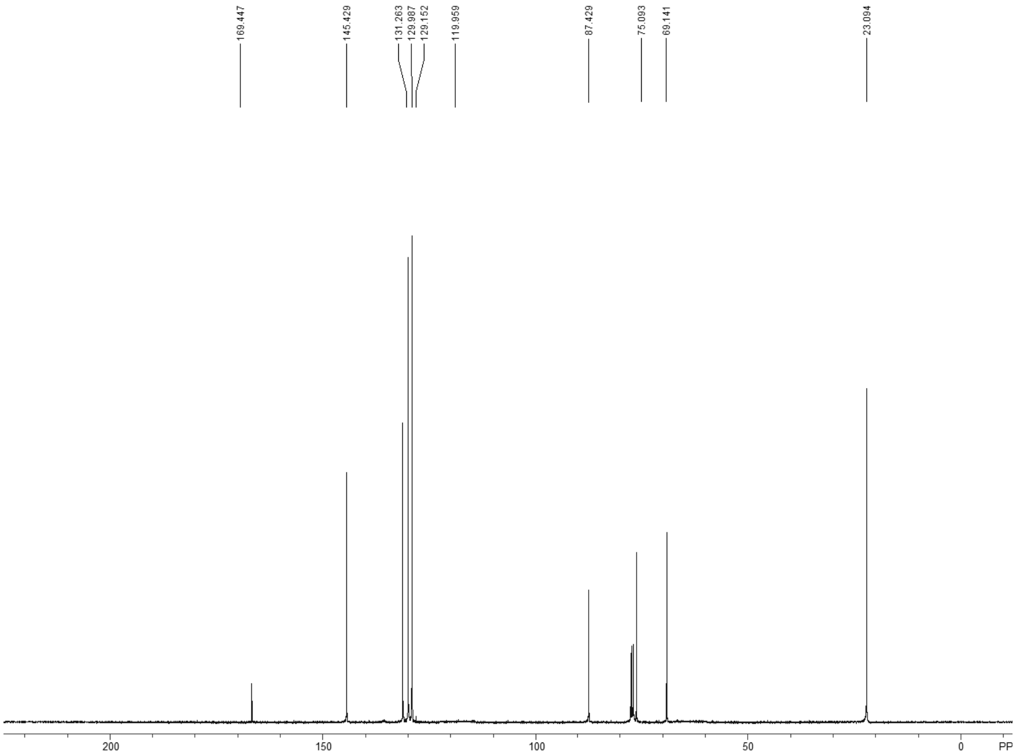


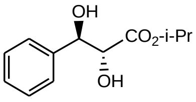
(2*R*,3*S*)-64



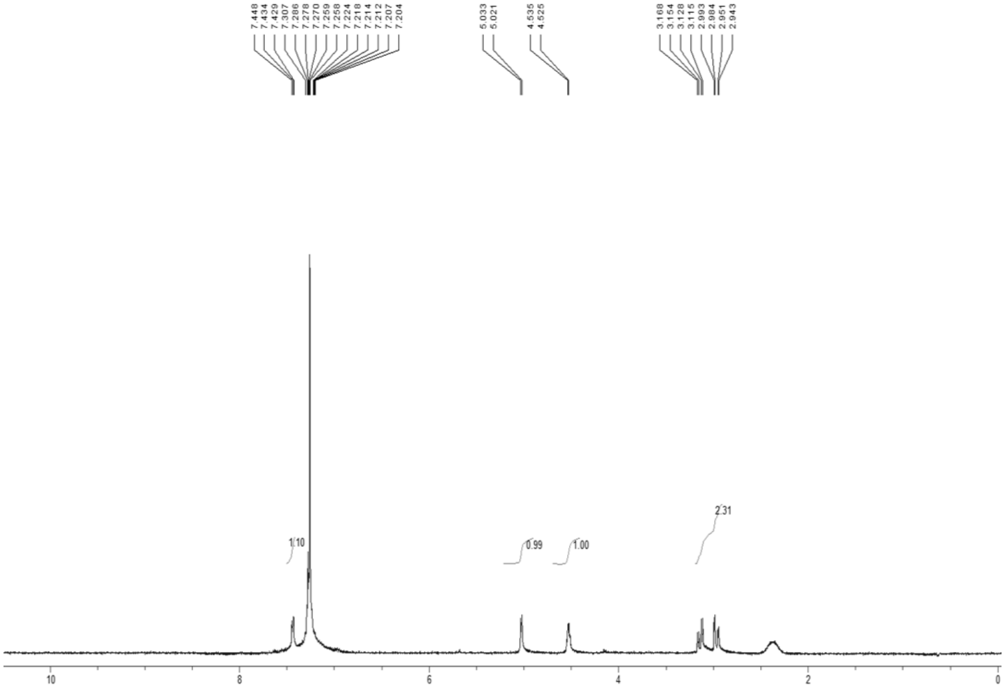


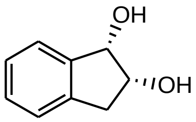
(2*R*,3*R*)-65



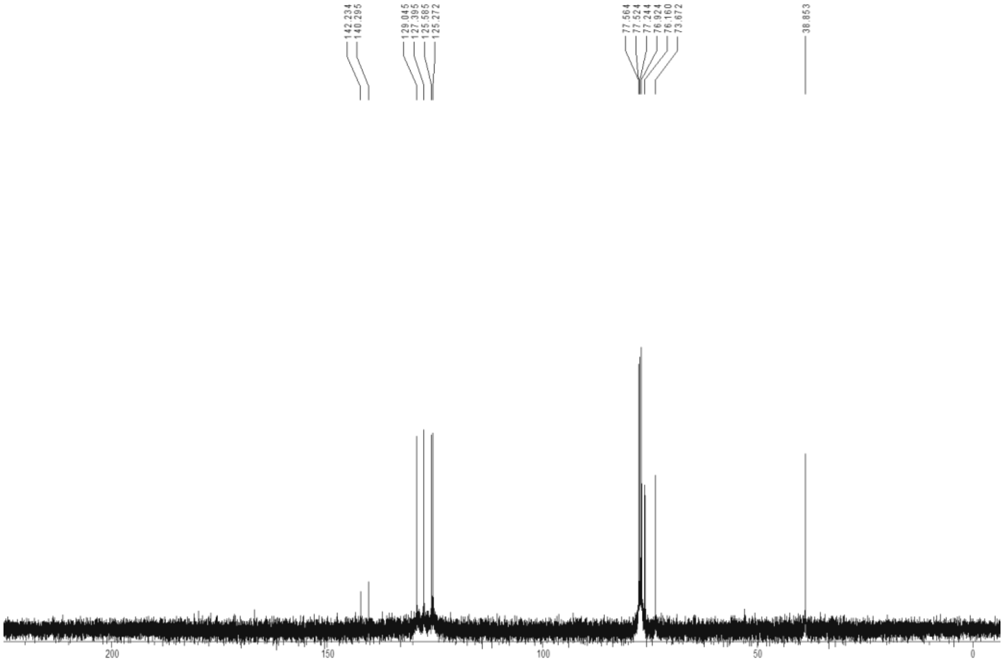


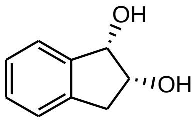
(2*R*,3*R*)-65



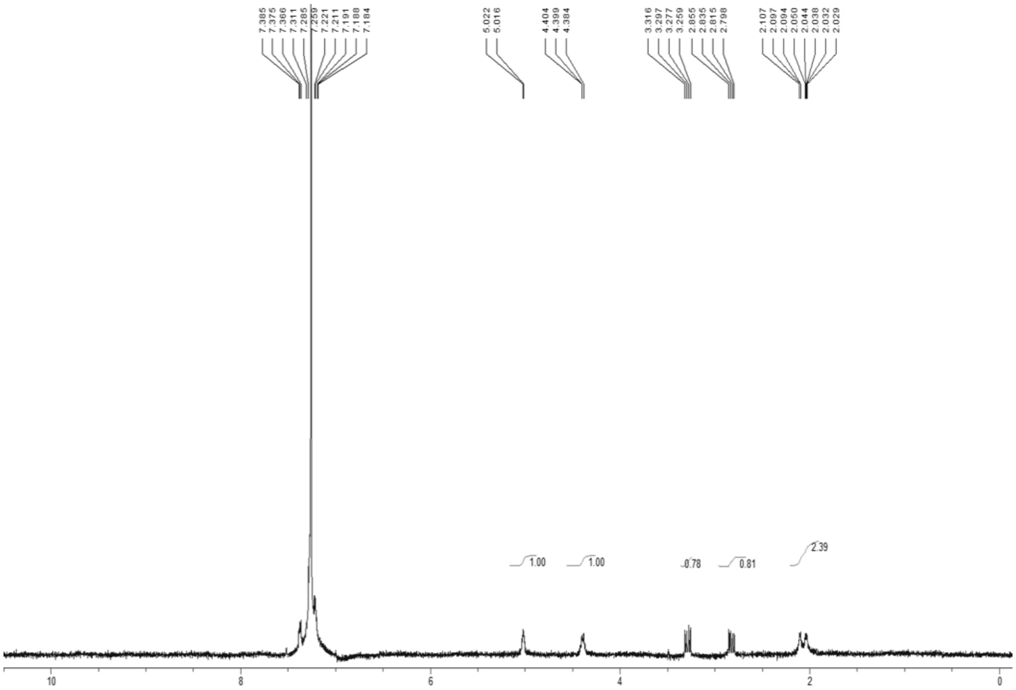


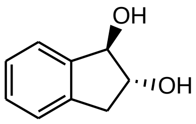
(1*S*,2*R*)-67



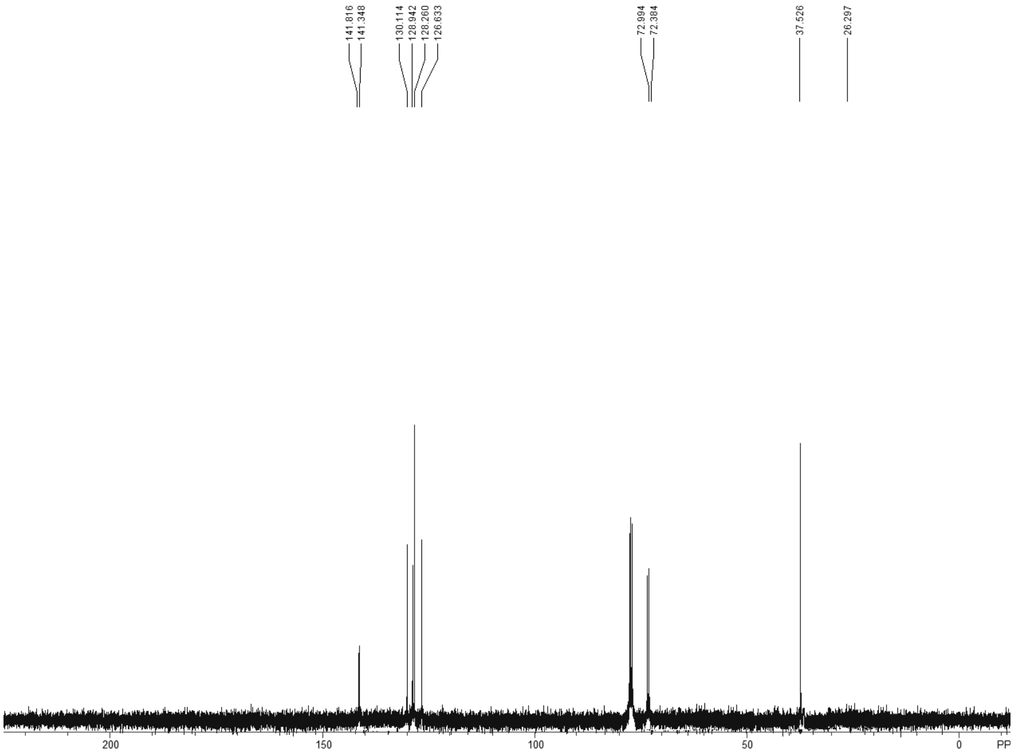


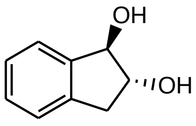
(1*S*,2*R*)-67



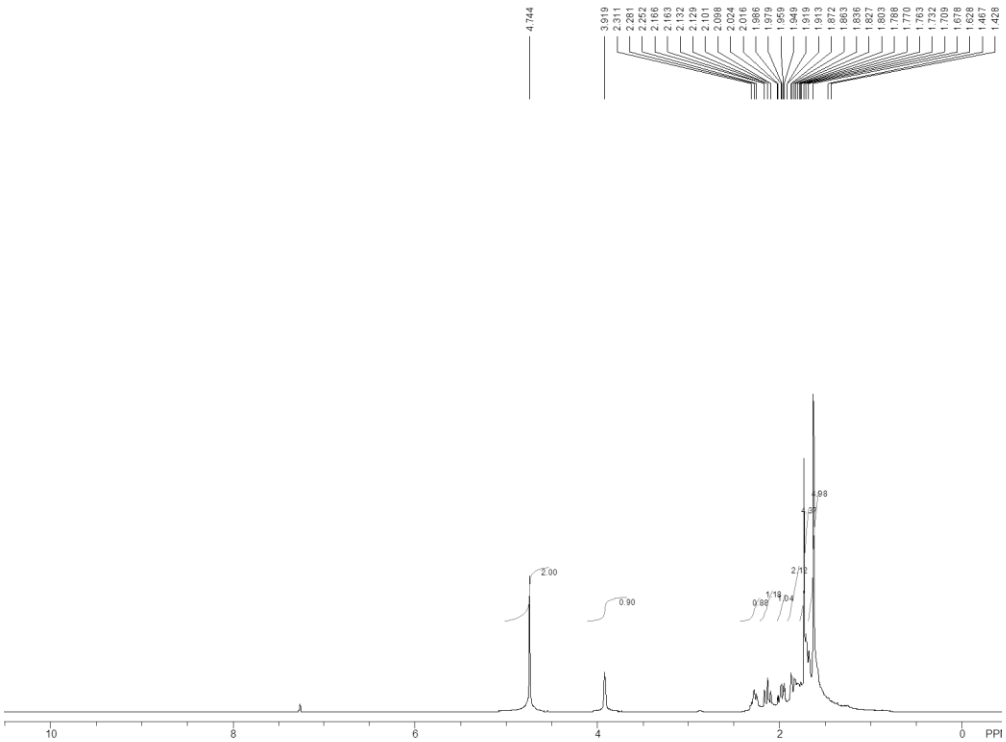


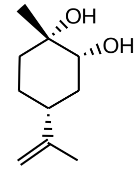
(1*R*,2R)-68



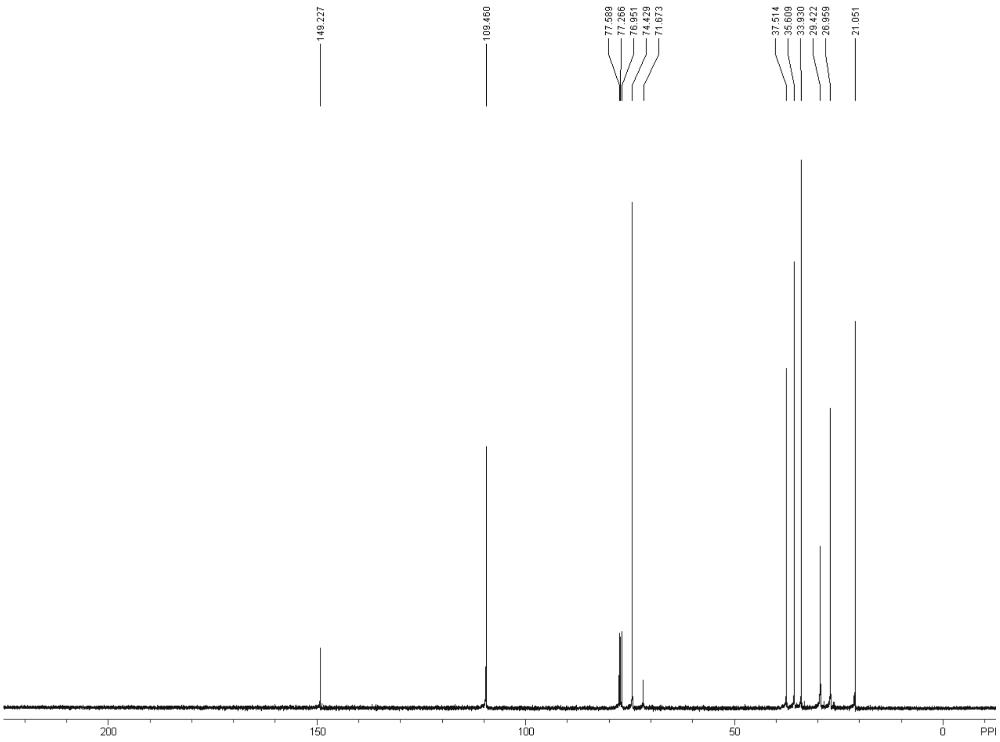


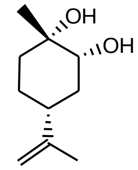
(1*R*,2R)-68



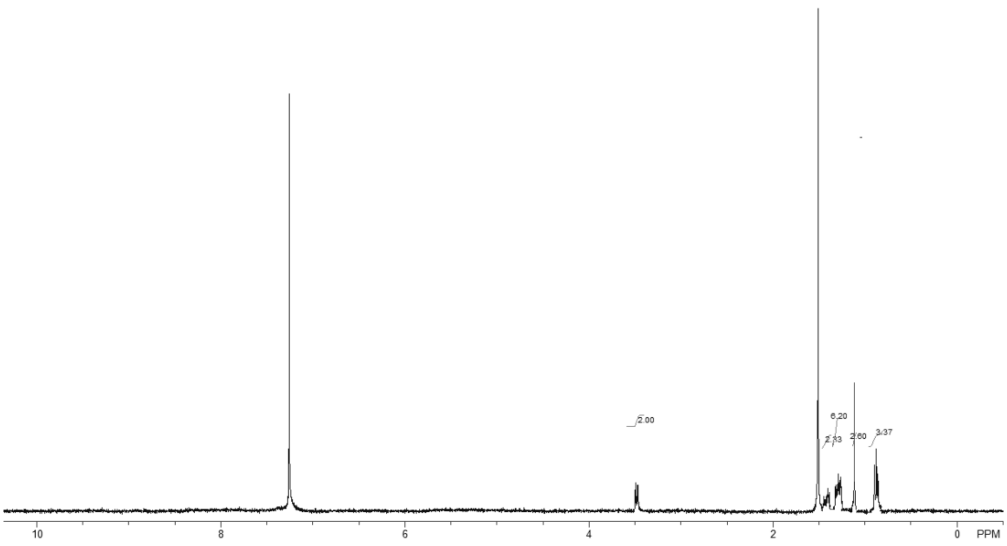


(1*S*,2*R*,4*R*)-70

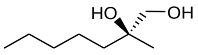




(1*S*,2*R*,4*R*)-70

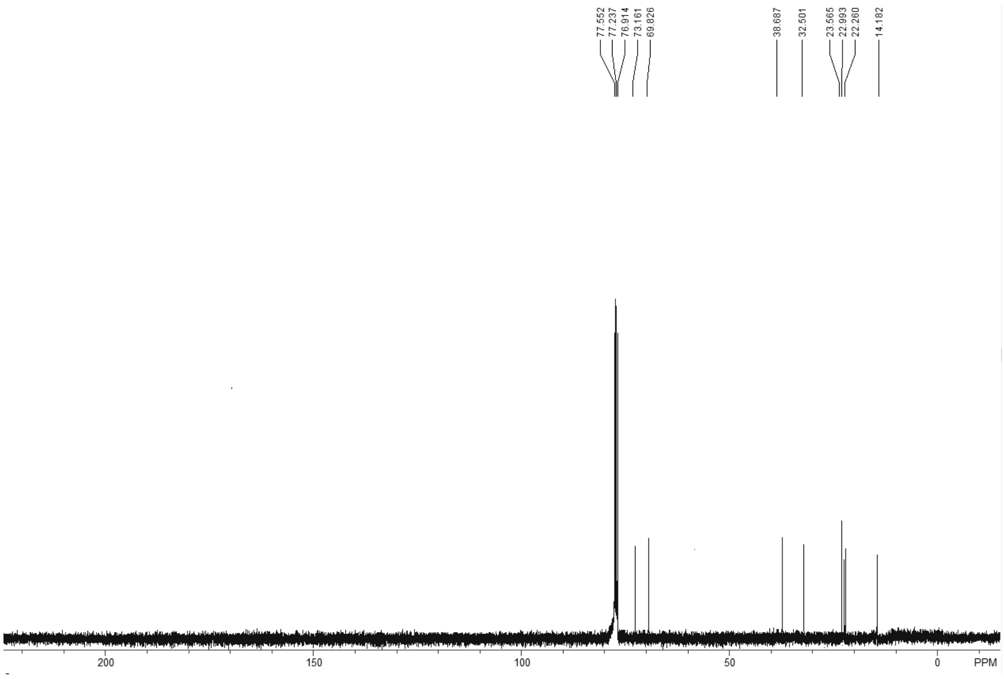


2.00
6.20
2.13
2.60
3.37
10
8
6
4
2
0
PPM

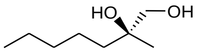


HO
OH

72

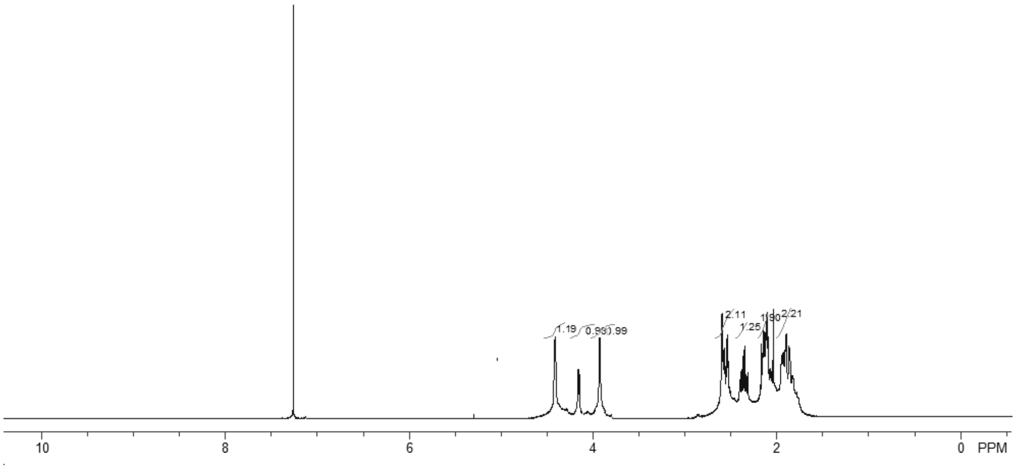


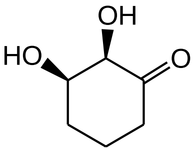
77.552
77.237
76.914
73.161
69.826
38.687
32.501
23.565
22.993
22.260
14.182
200
150
100
50
0
PPM



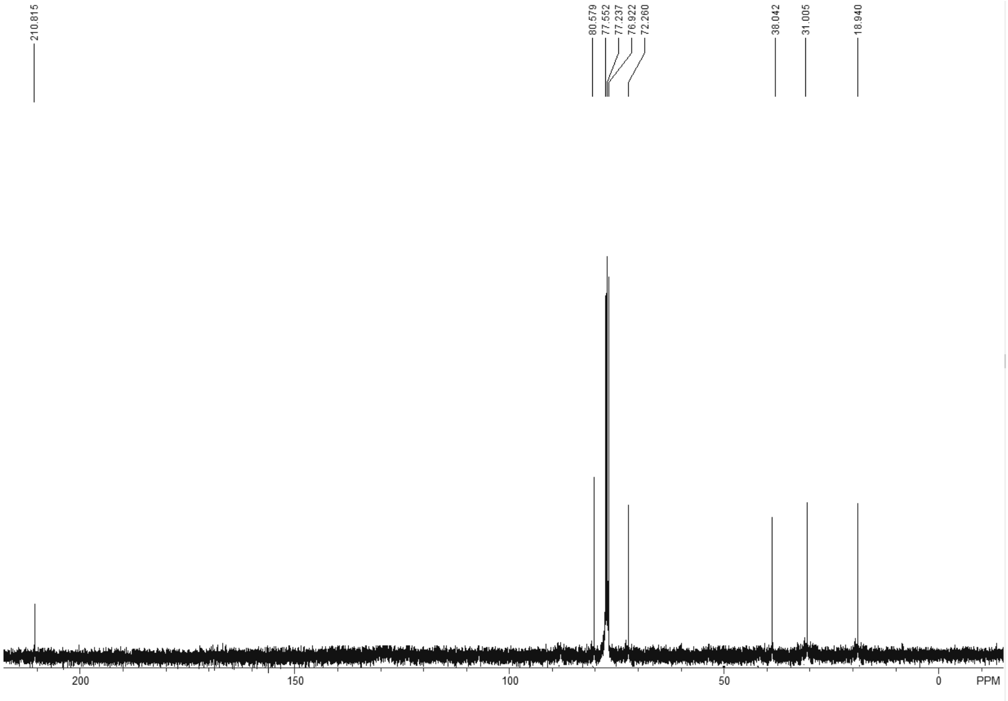
HO
OH

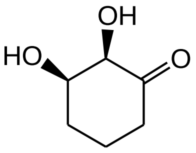
72



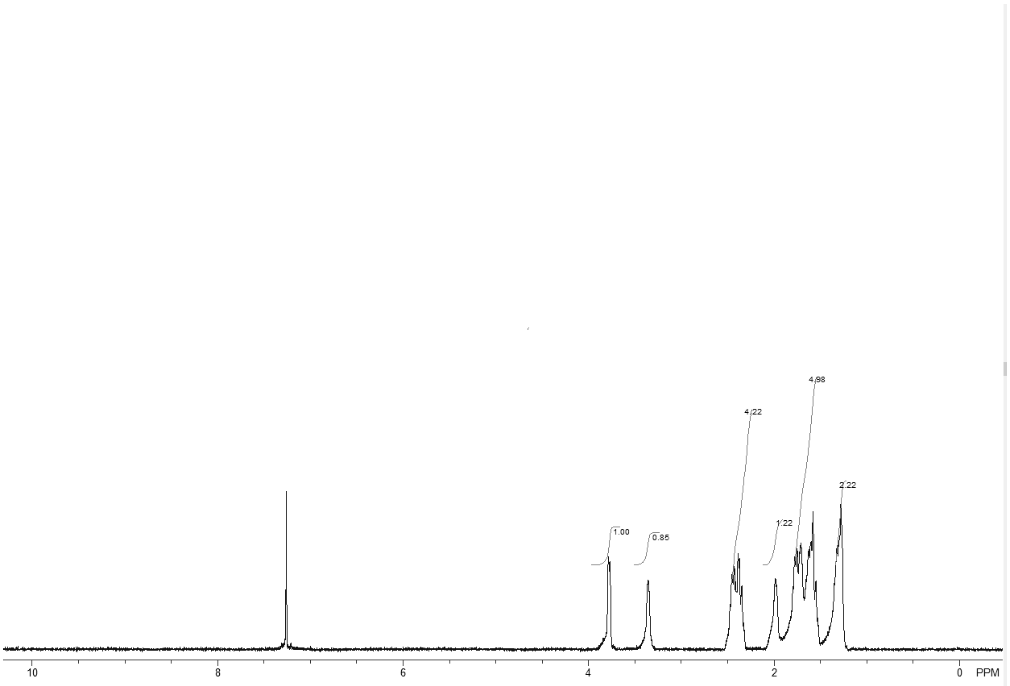


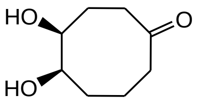
(2*R*,3*R*)-74



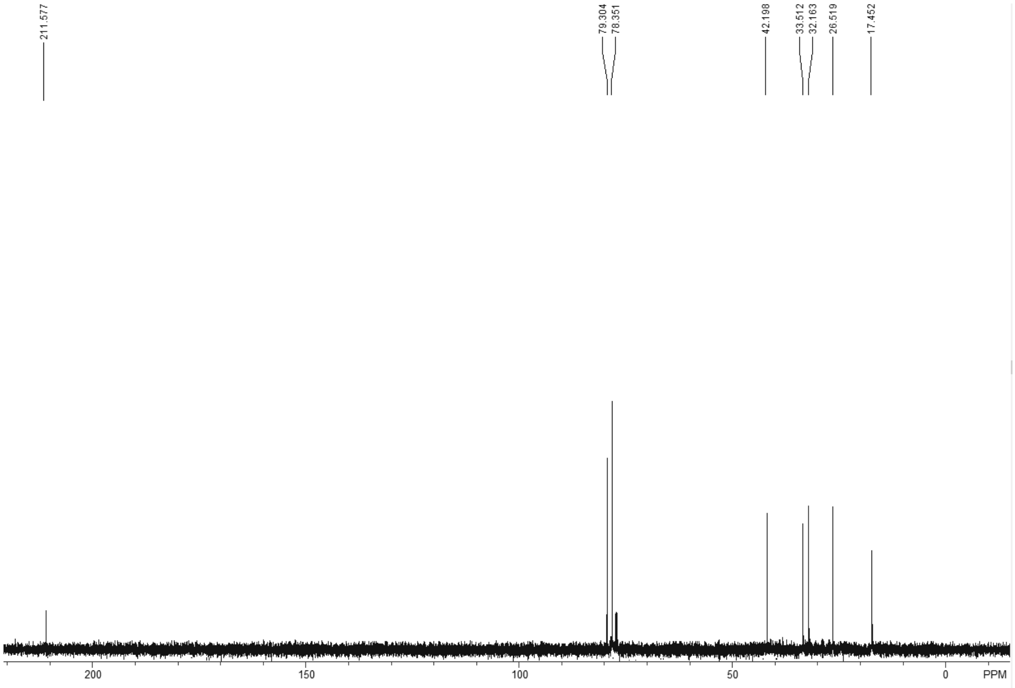


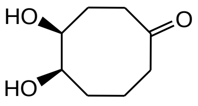
(2*R*,3*R*)-74



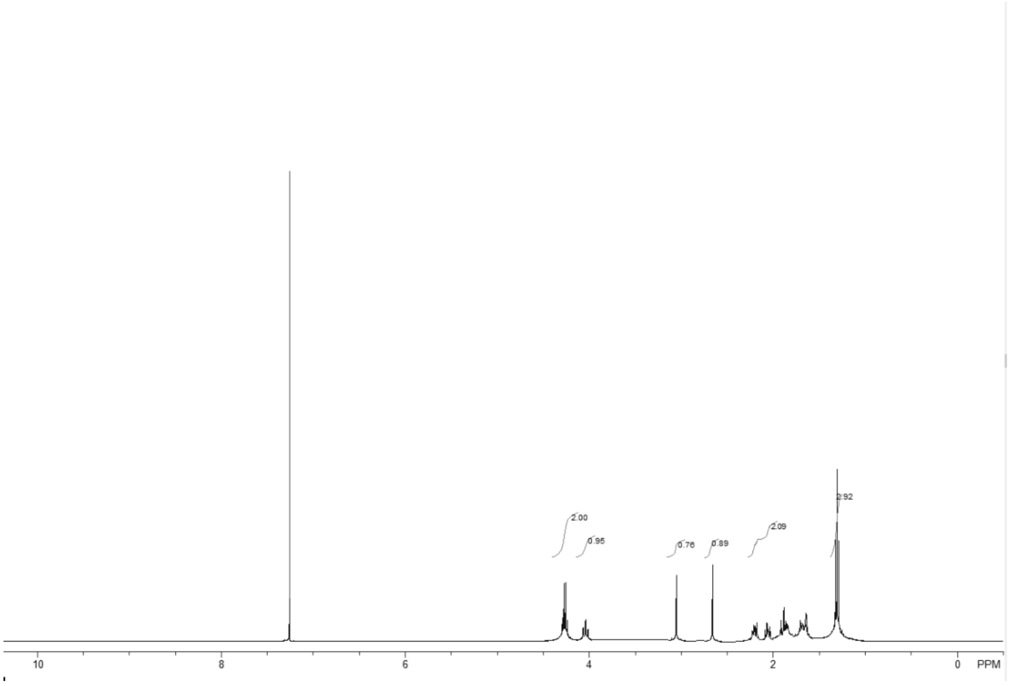


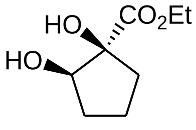
(4S,5*R*)-76



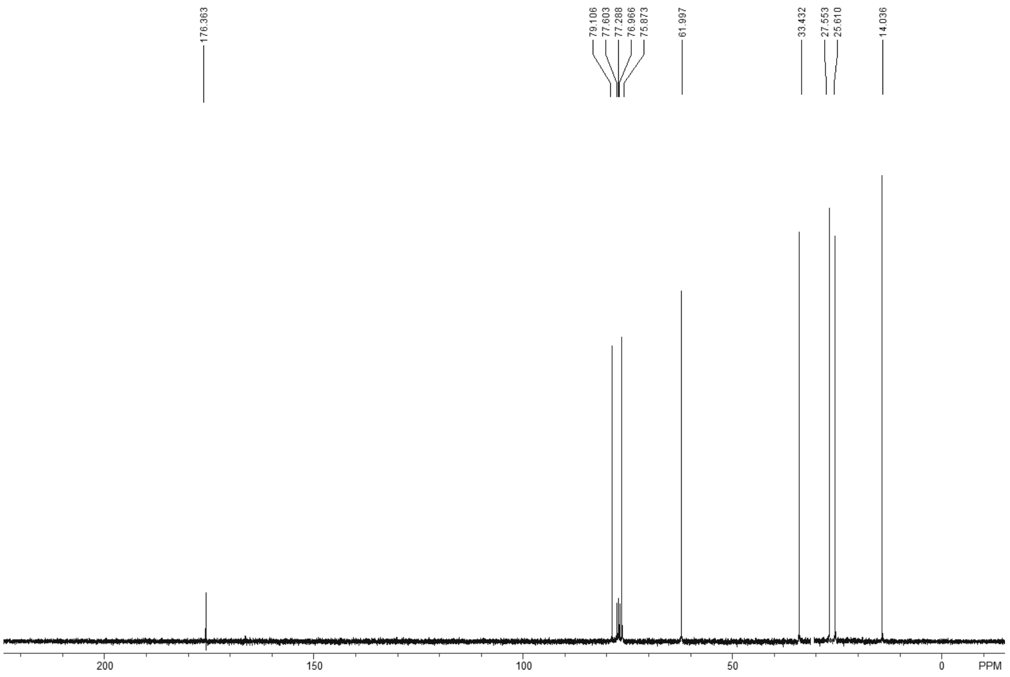


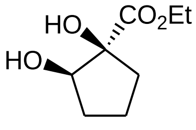
(4S,5*R*)-76



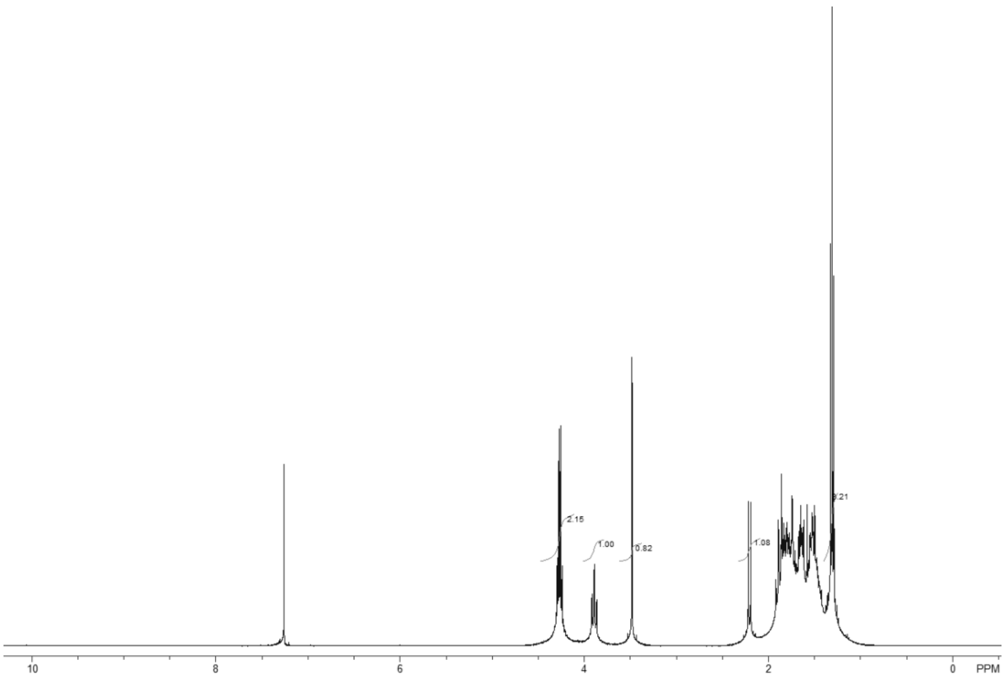


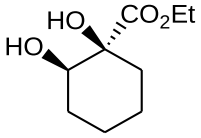
(*1S*,*2R*)-81



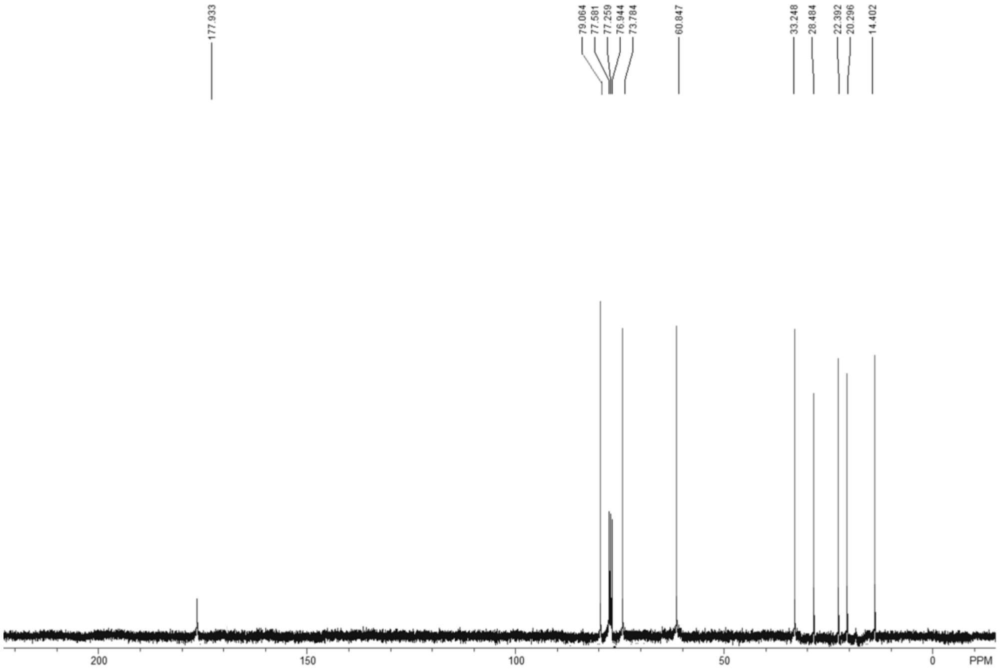


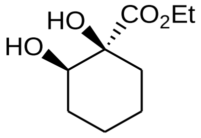
(*1S*,*2R*)-81



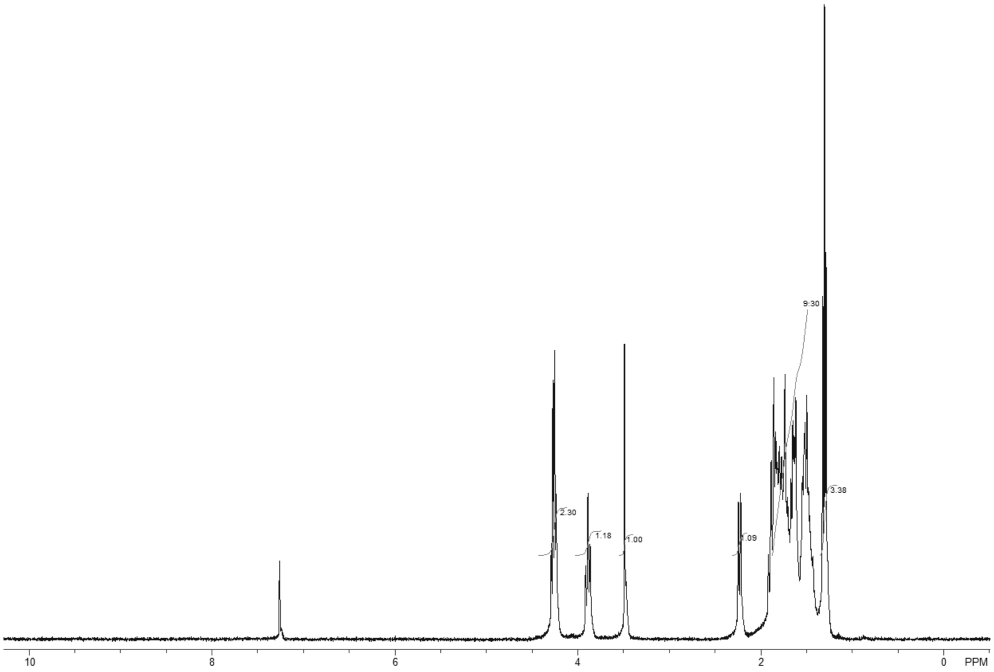


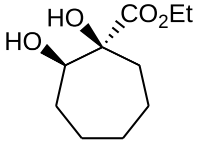
(*1S,2R*)-82



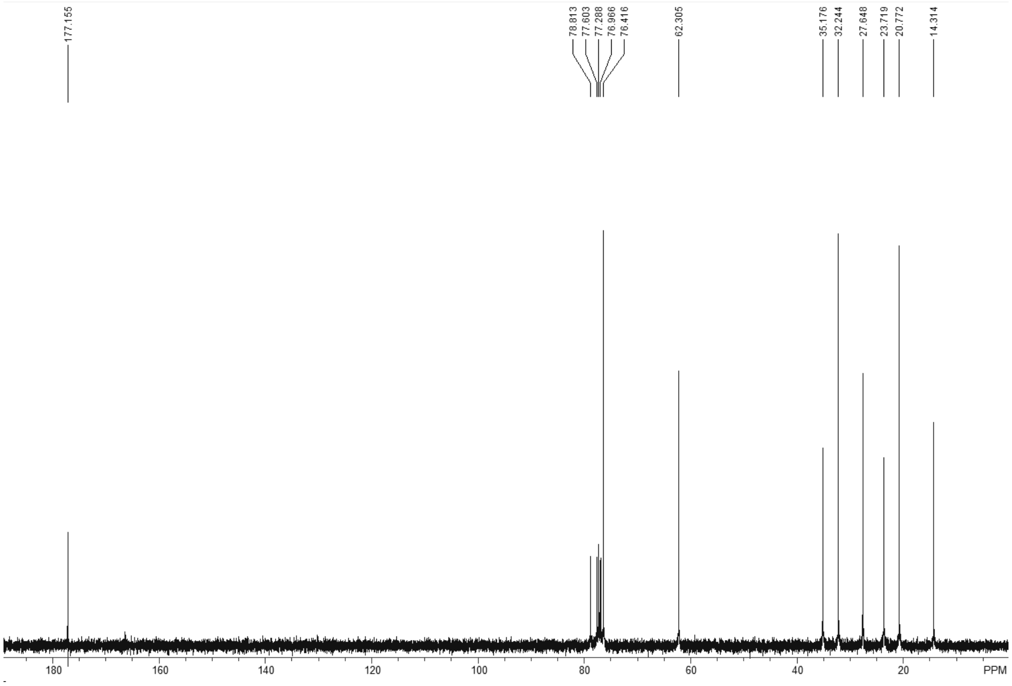


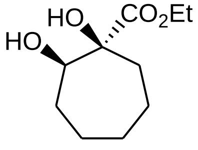
(*1S,2R*)-82



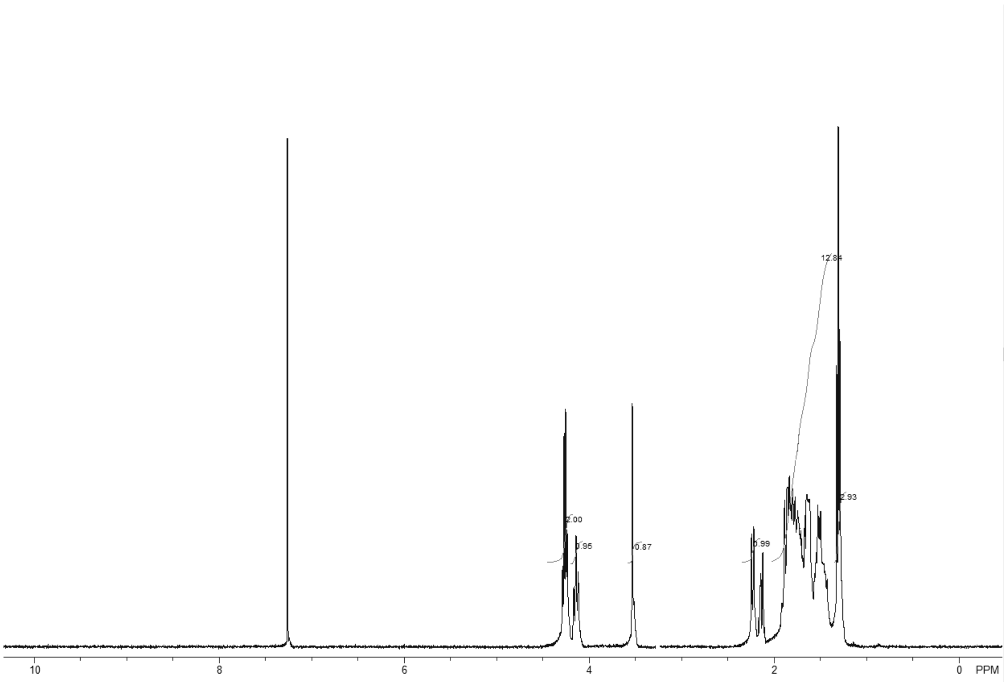


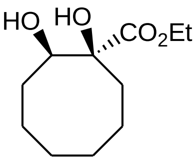
(*1S*,*2R*)-83



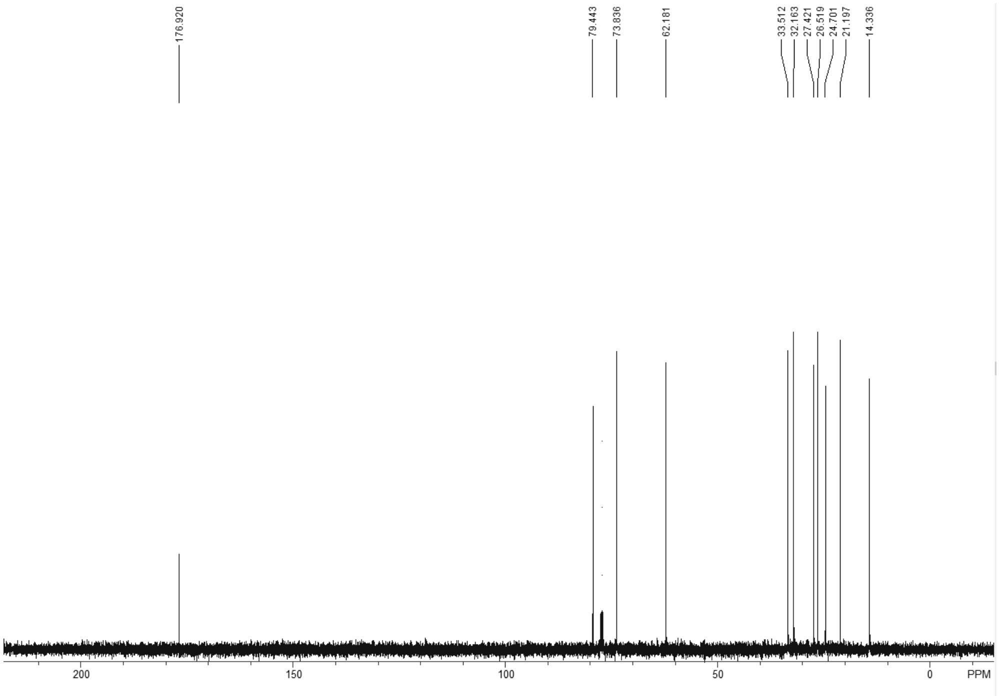


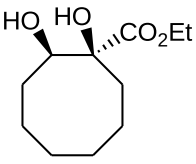
(*1S*,*2R*)-83



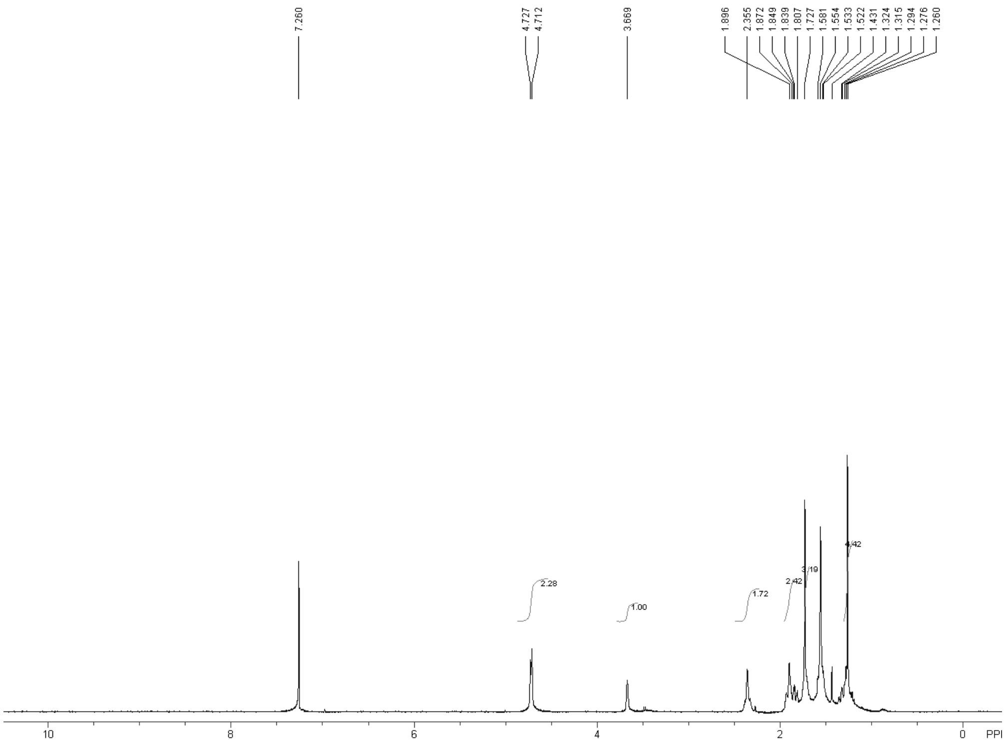


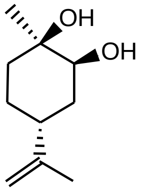
(*1S,2R*)-84



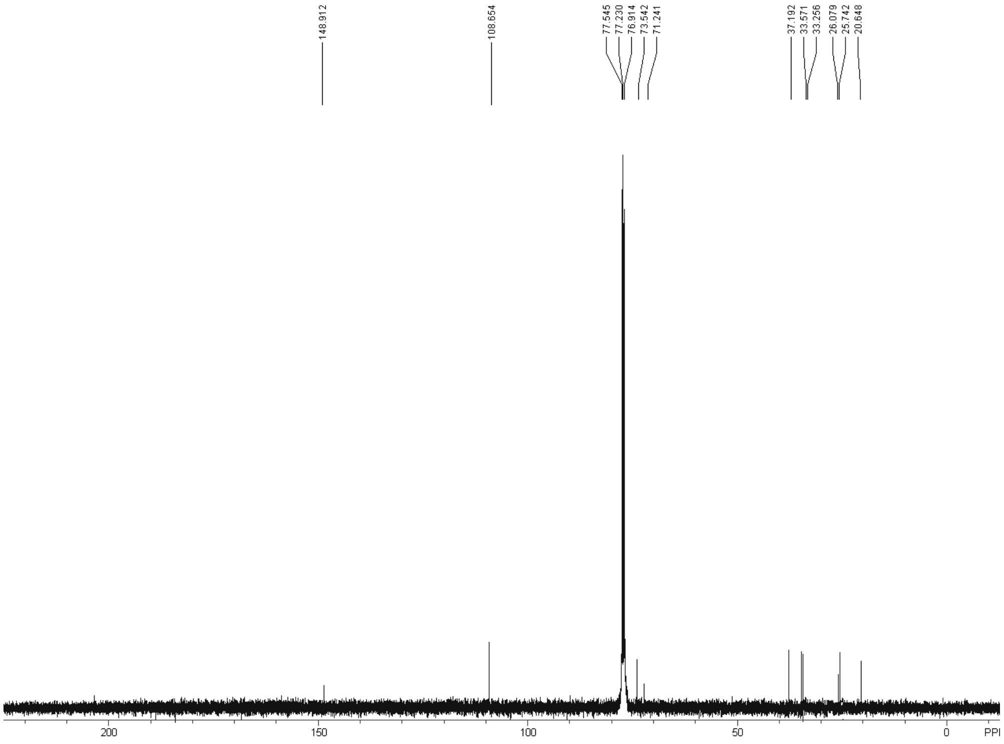


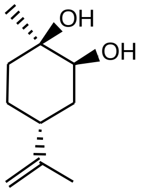
(*1S,2R*)-84



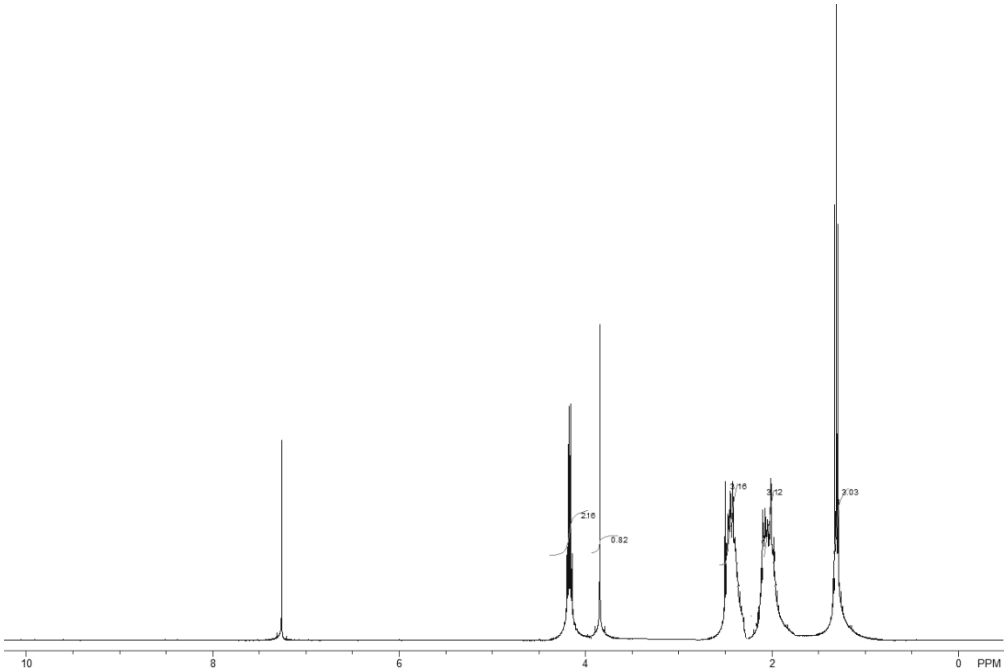


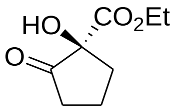
(1*R*,2*S*,4*R*)-85



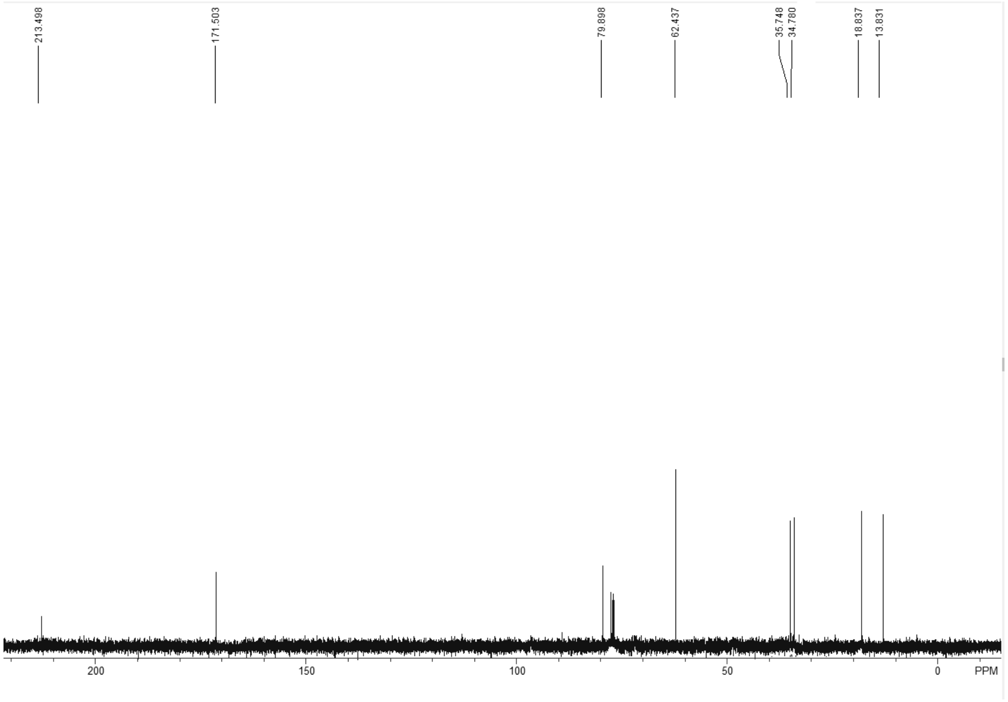


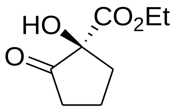
(1*R*,2*S*,4*R*)-85


2.16
0.82
3.16
3.12
3.03
10
8
6
4
2
0
PPM

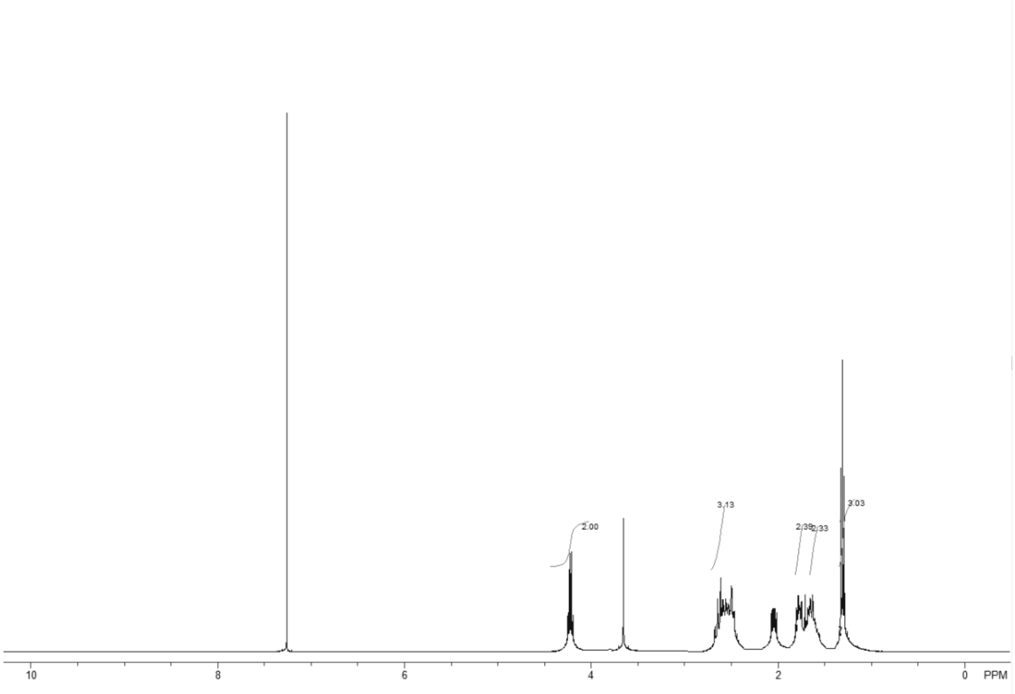

HO
CO2Et
O

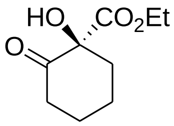
(*S*)-86


213.498
171.503
79.898
62.437
35.748
34.780
18.837
13.831
200
150
100
50
0
PPM

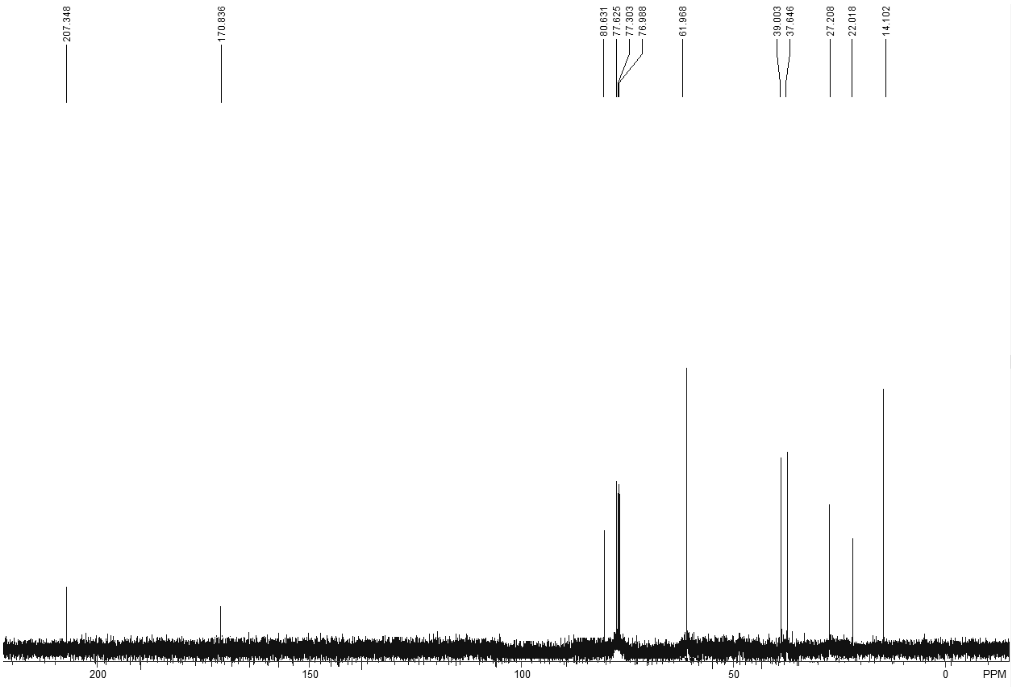

HO
CO2Et
O

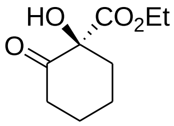
(*S*)-86


2.00
3.13
2.39
2.33
3.03
10
8
6
4
2
0
PPM

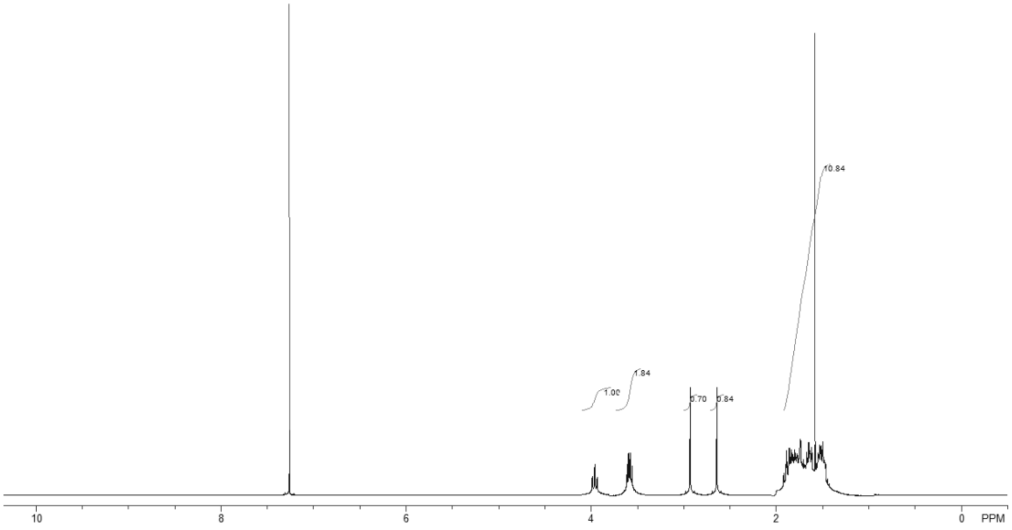

HO
CO2Et
O

(*S*)-87

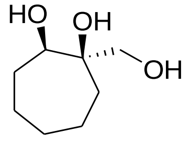

207.348
170.836
80.631
77.625
77.303
76.988
61.968
39.003
37.646
27.208
22.018
14.102
200
150
100
50
0
PPM


HO
CO2Et
O

(*S*)-87

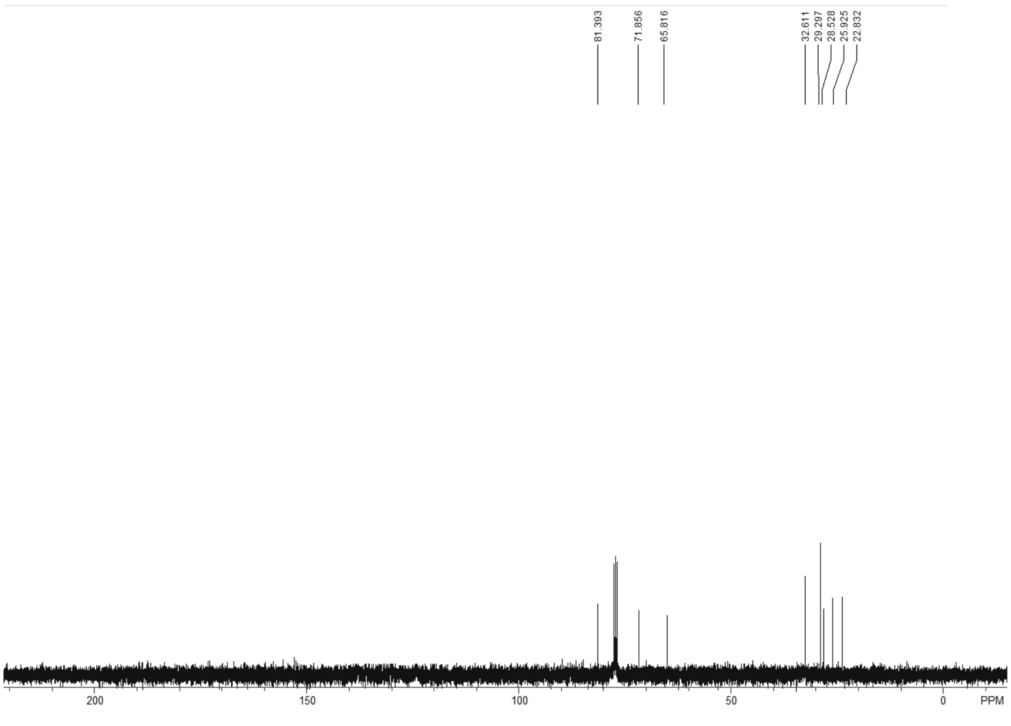


1.00
1.84
0.70
0.84
10.84
10
8
6
4
2
0
PPM

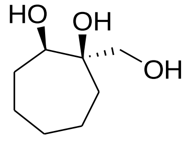


HO
OH
OH

88

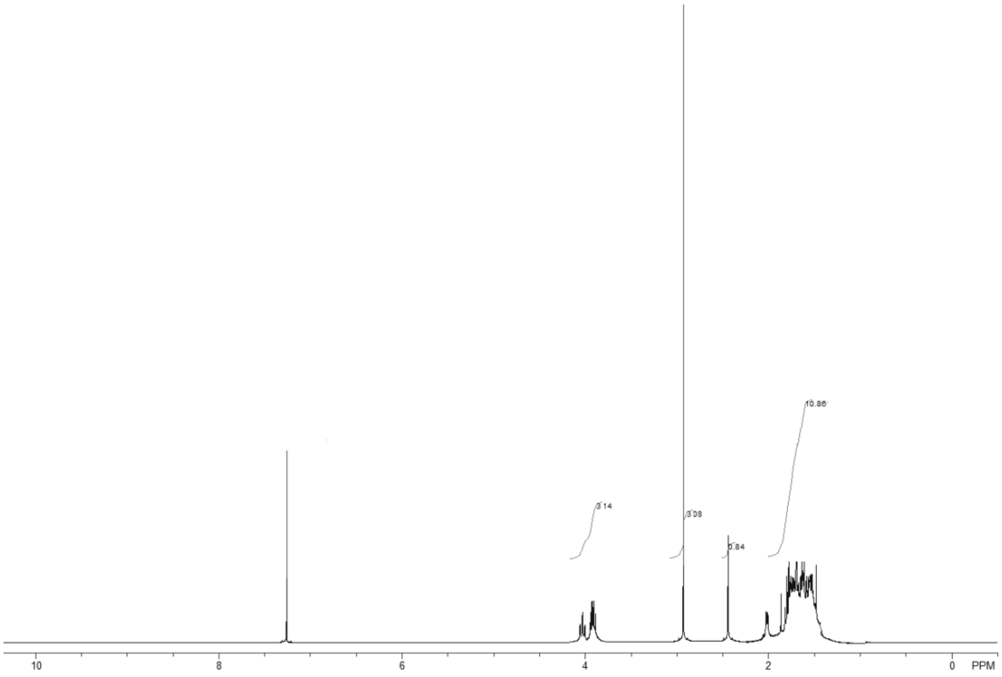


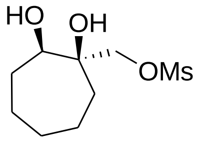
81.393
71.856
65.816
32.611
29.297
28.528
25.925
22.832
200
150
100
50
0
PPM



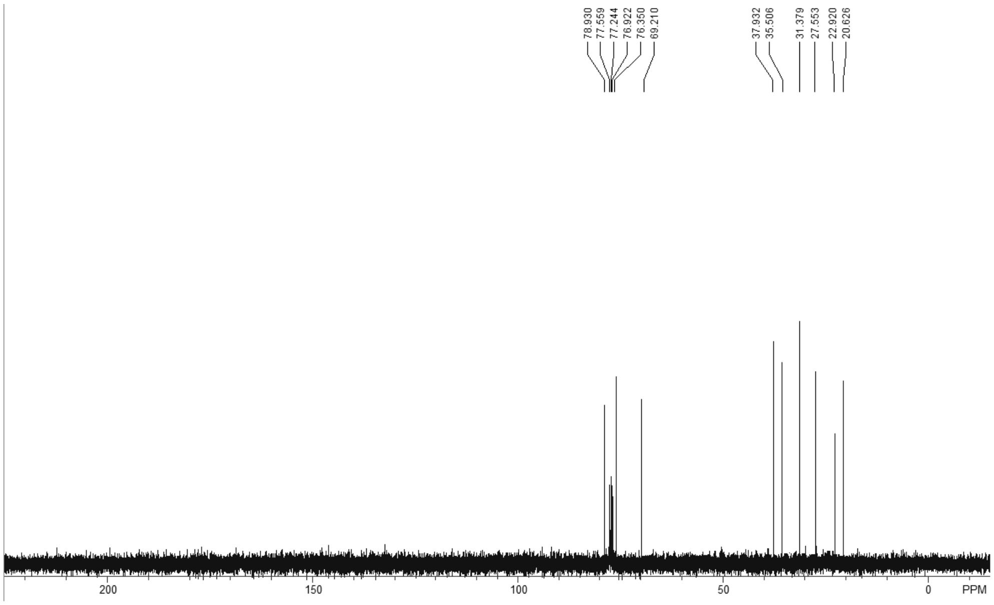
HO
OH
OH

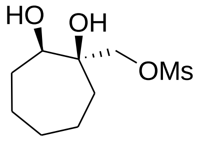
88


3.14
3.08
2.84
10.86
10
8
6
4
2
0
PPM

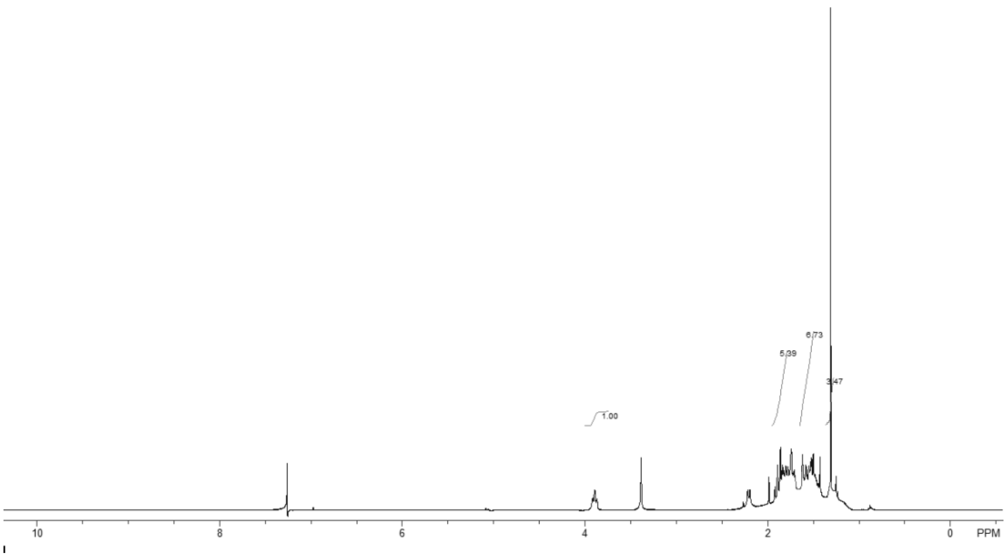

HO
OH
OMs

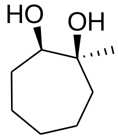
89


78.930
77.559
77.244
76.922
76.350
69.210
37.932
35.506
31.379
27.553
22.920
20.626
200
150
100
50
0
PPM

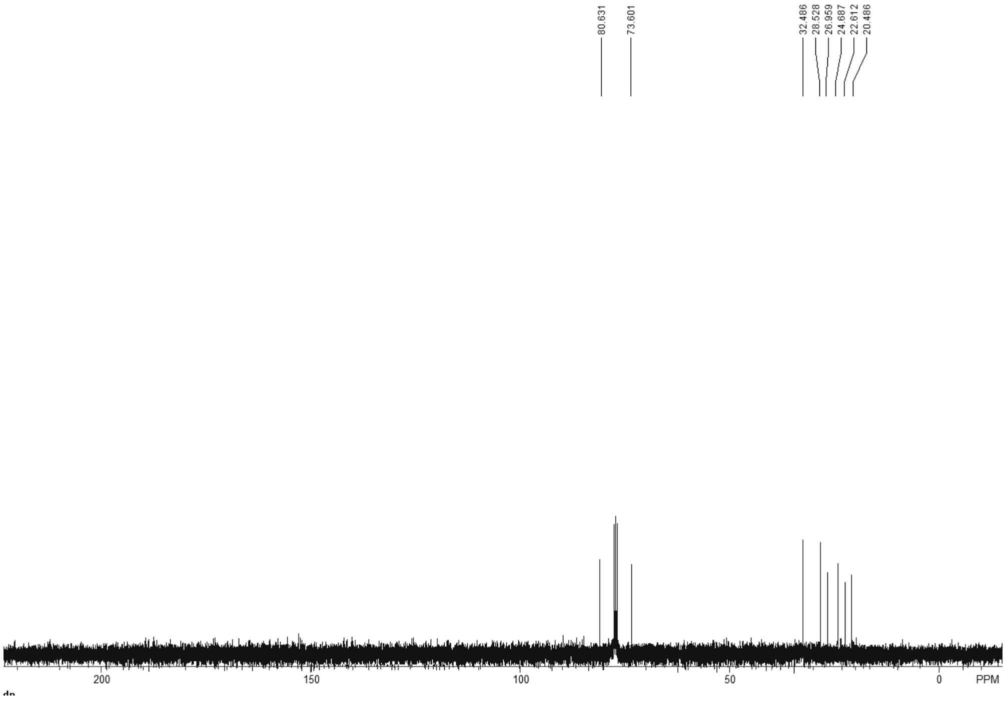

HO
OH
OMs

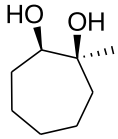
89


1.00
5.39
6.73
3.47
10
8
6
4
2
0
PPM

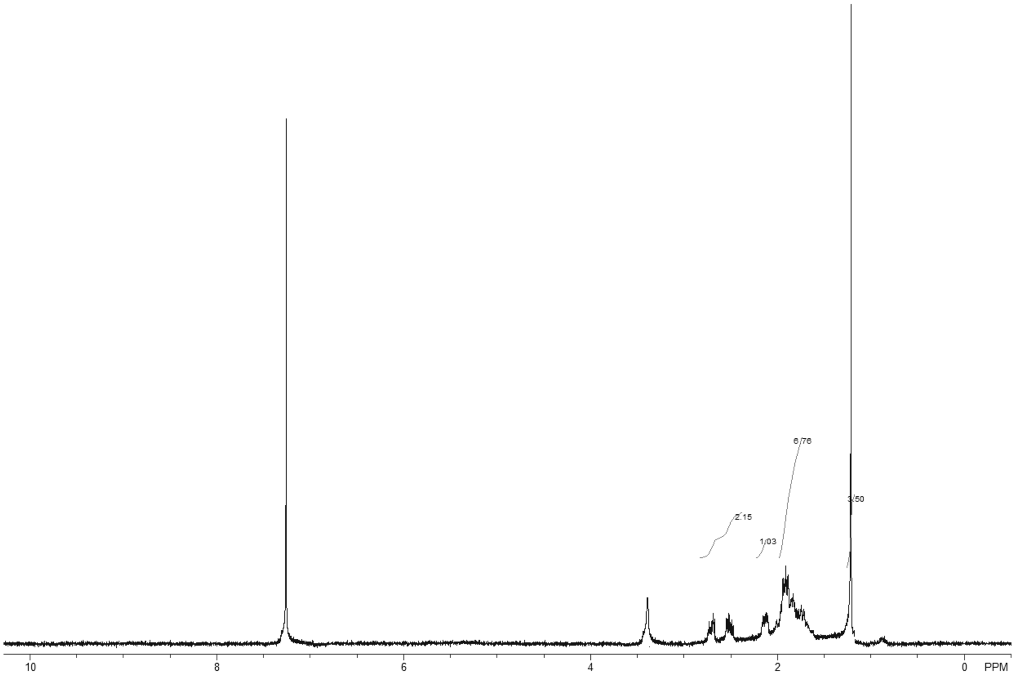

HO
OH

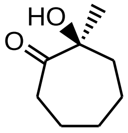
90


80.631
73.601
32.486
28.528
26.959
24.687
22.612
20.486
200
150
100
50
0
PPM

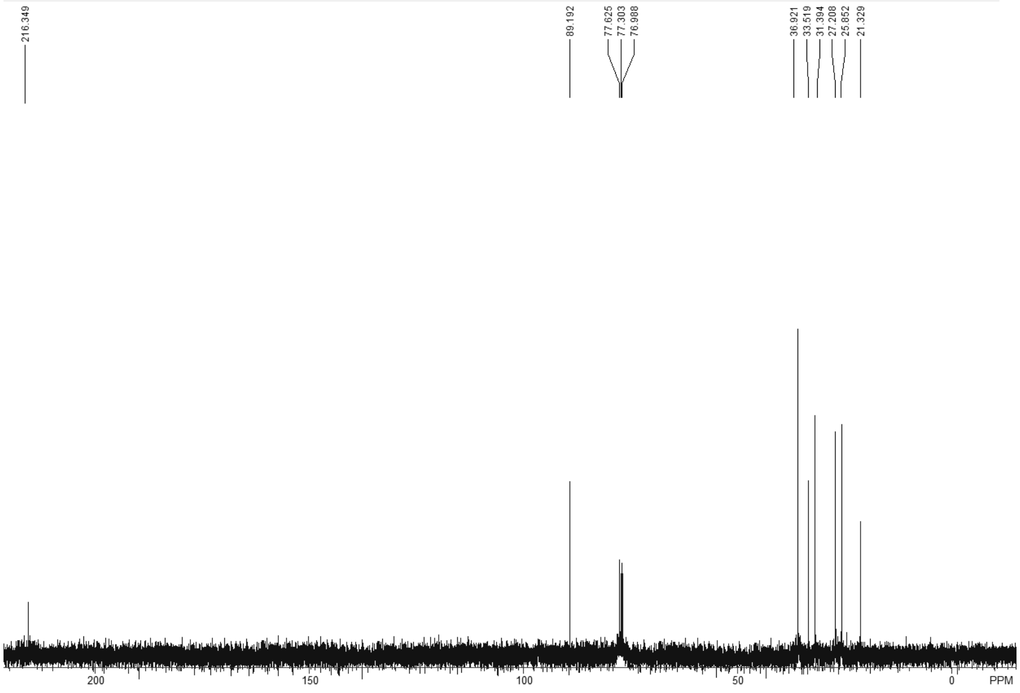

HO
OH

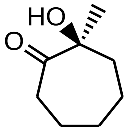
90


2.15
1.03
6.76
3.50
10
8
6
4
2
0
PPM

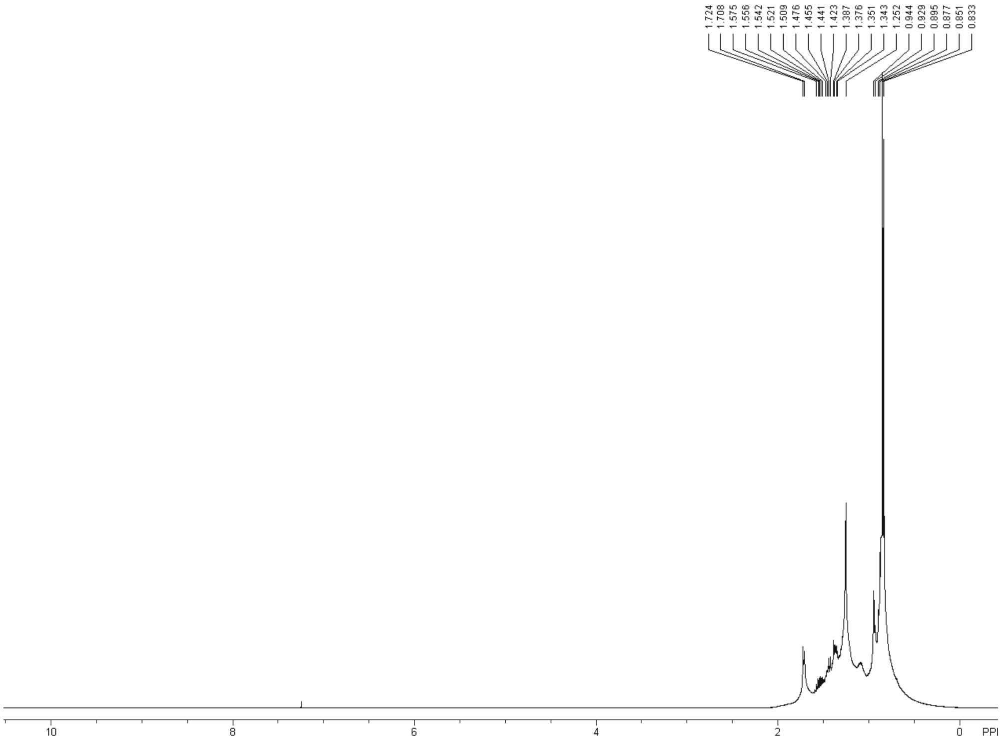

HO
O

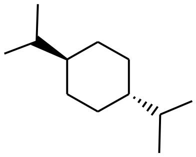
91


216.349
89.192
77.625
77.303
76.988
36.921
33.519
31.394
27.208
25.852
21.329
200
150
100
50
0
PPM

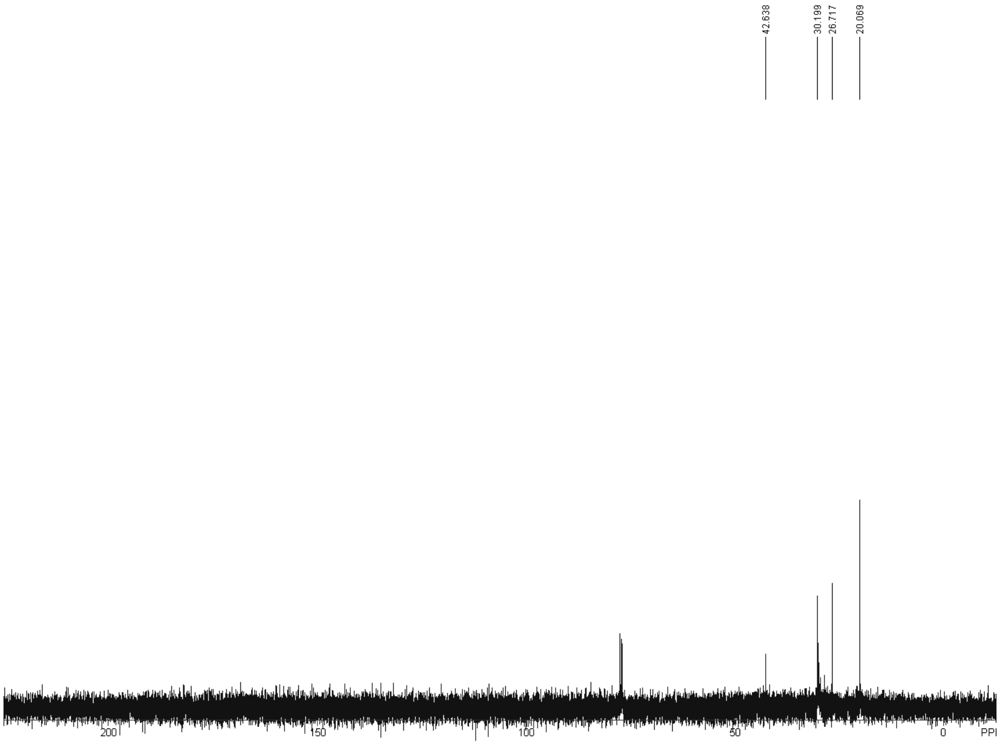

HO
O

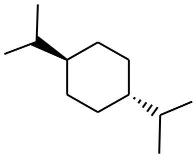
91


1.724
1.708
1.575
1.556
1.542
1.521
1.509
1.476
1.455
1.441
1.423
1.387
1.376
1.351
1.343
1.252
0.944
0.929
0.895
0.877
0.851
0.833
10
8
6
4
2
0
PP

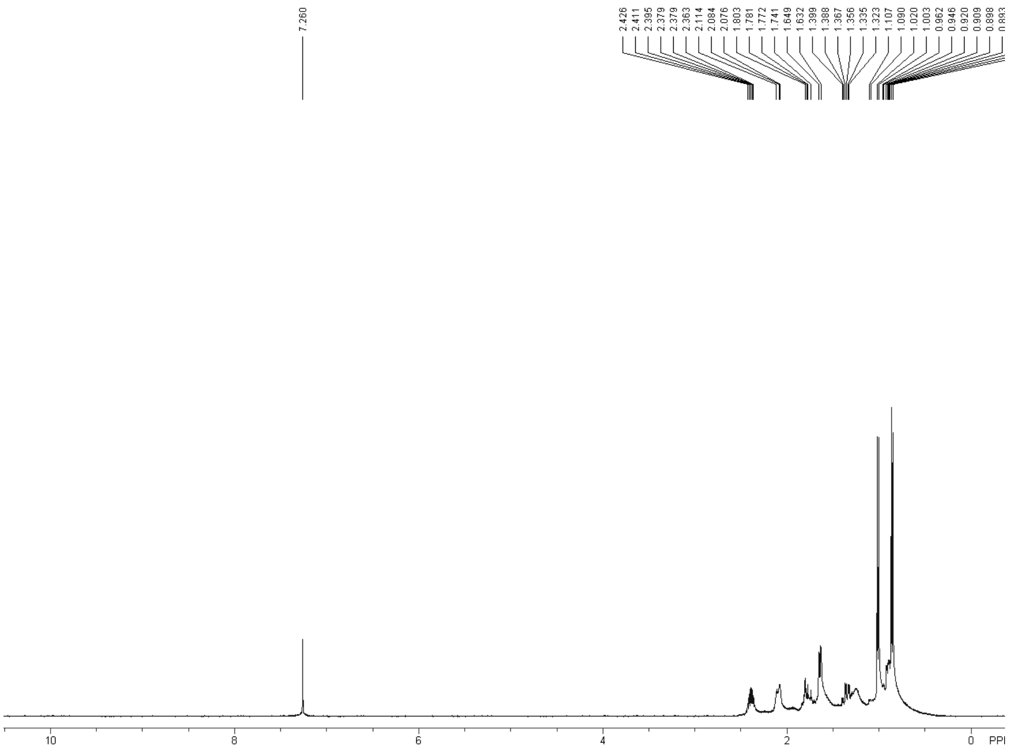


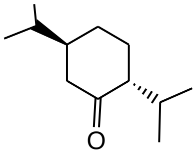
92


42.638
30.199
26.717
20.069
200
150
100
50
0
PP

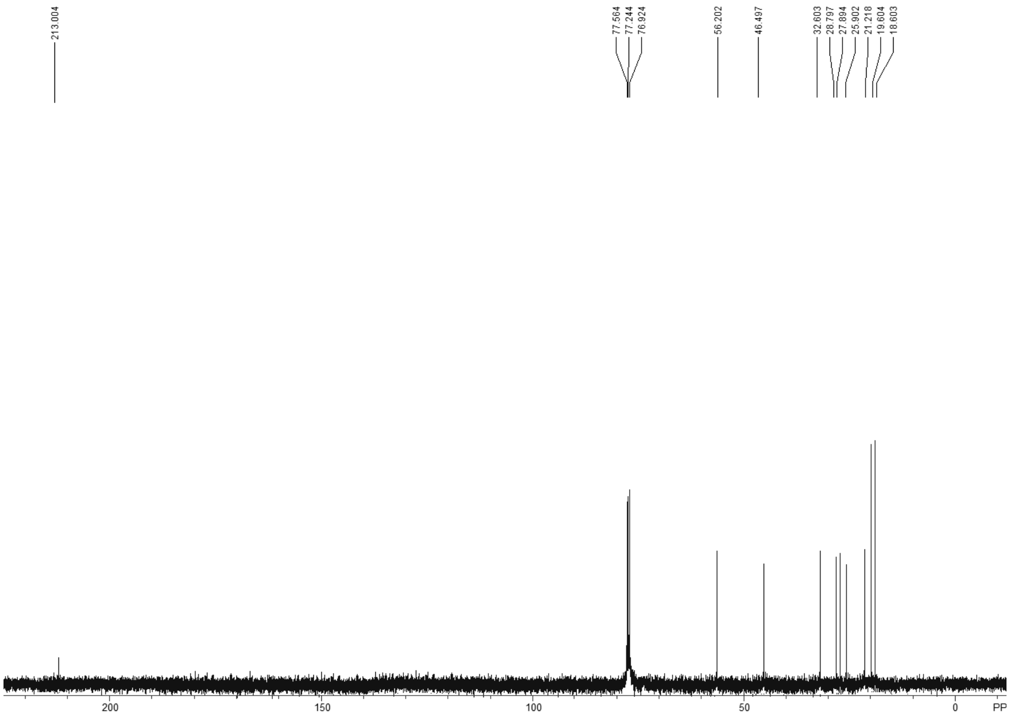


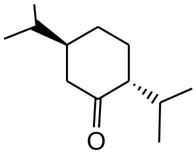
92



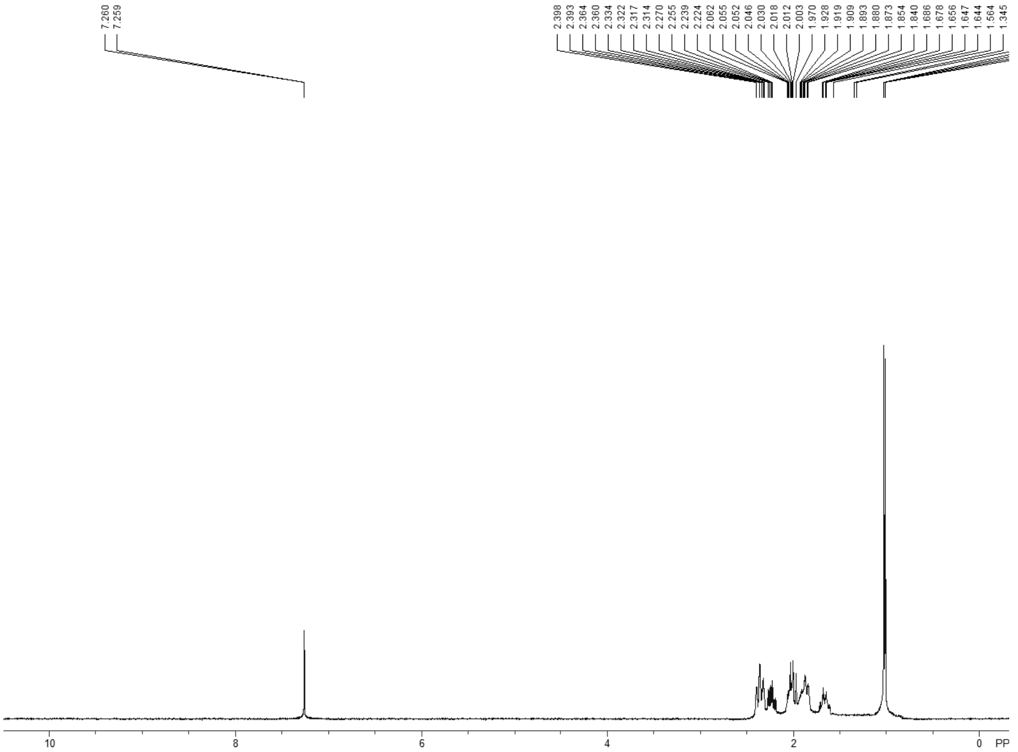


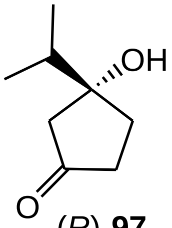
(2*R*,5*S*)-**93**



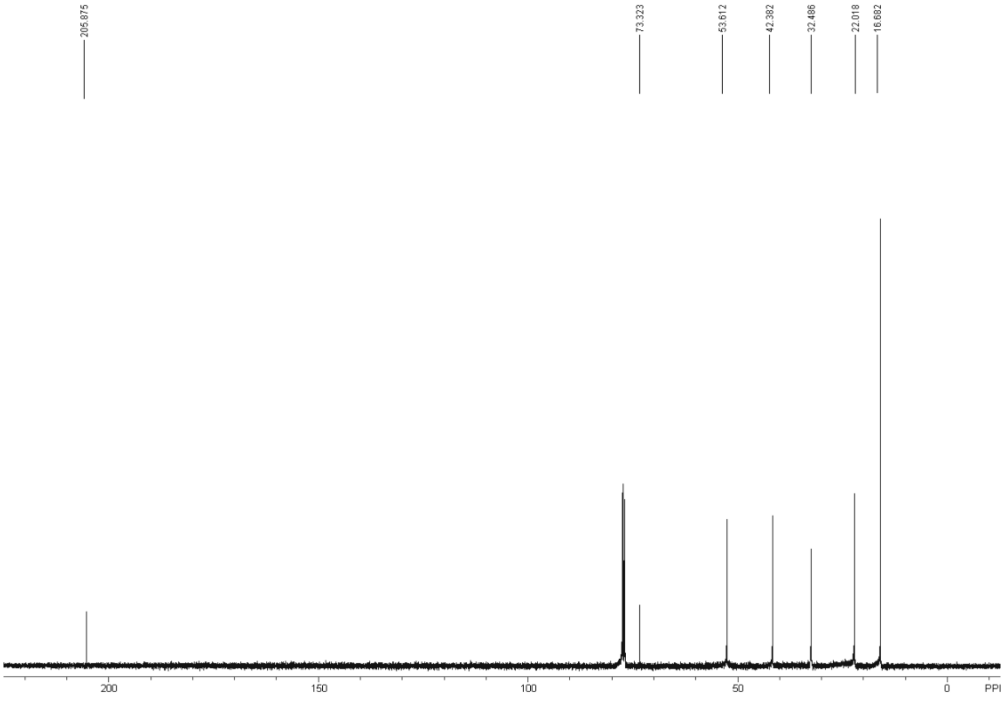


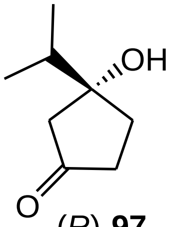
(2*R*,5*S*)-**93**


7.260
7.259
2.398
2.393
2.364
2.360
2.334
2.322
2.317
2.314
2.270
2.255
2.239
2.224
2.062
2.055
2.052
2.046
2.030
2.018
2.012
2.003
1.970
1.928
1.919
1.909
1.893
1.880
1.873
1.854
1.840
1.686
1.678
1.656
1.647
1.644
1.564
1.345
10
8
6
4
2
0
PP

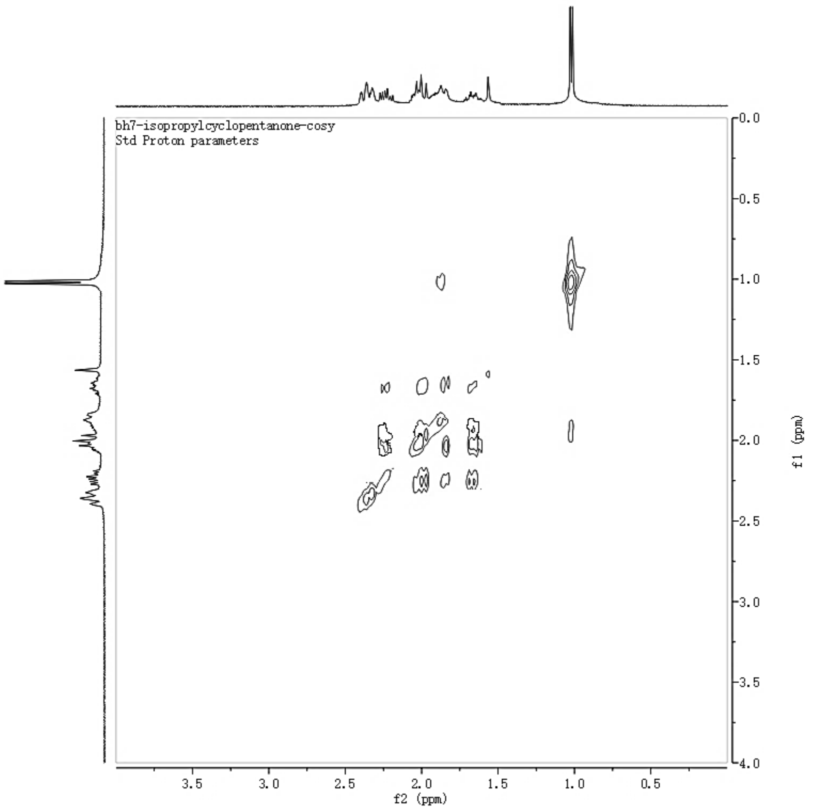

OH
O

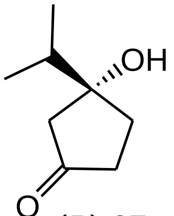
(*R*)-**97**


205.875
73.323
53.612
42.382
32.486
22.018
16.682
200
150
100
50
0
PPI

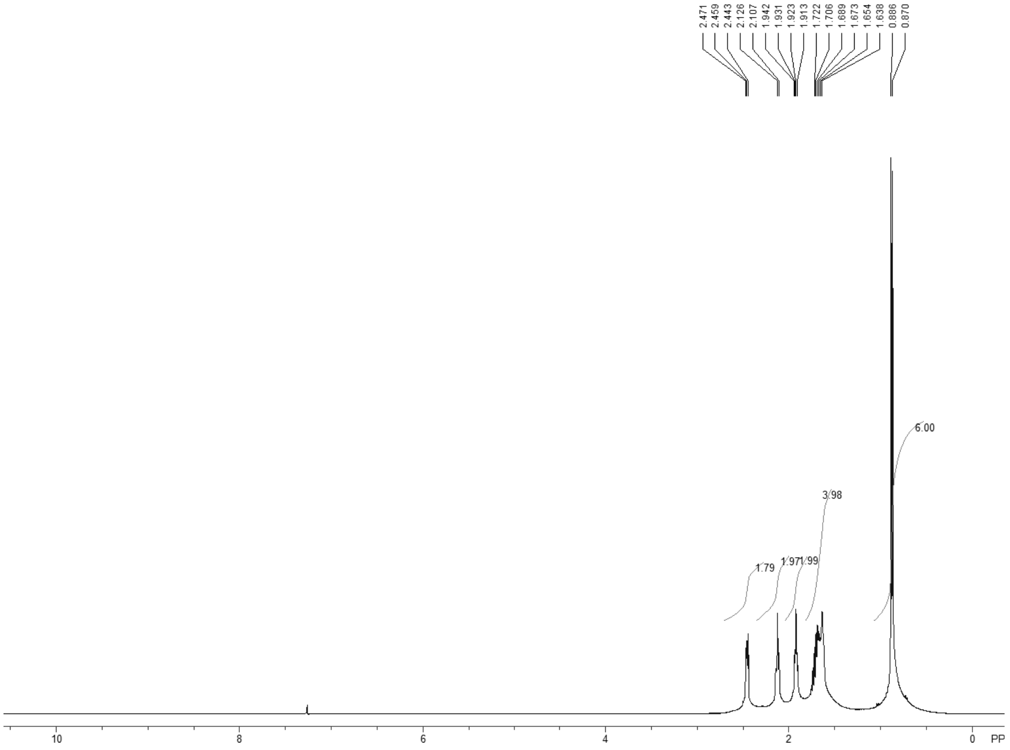

OH
O

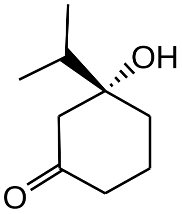
(*R*)-**97**


bh7-isopropylcyclopentanone-cosy
Std Proton parameters
f2 (ppm)
f1 (ppm)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
4.0

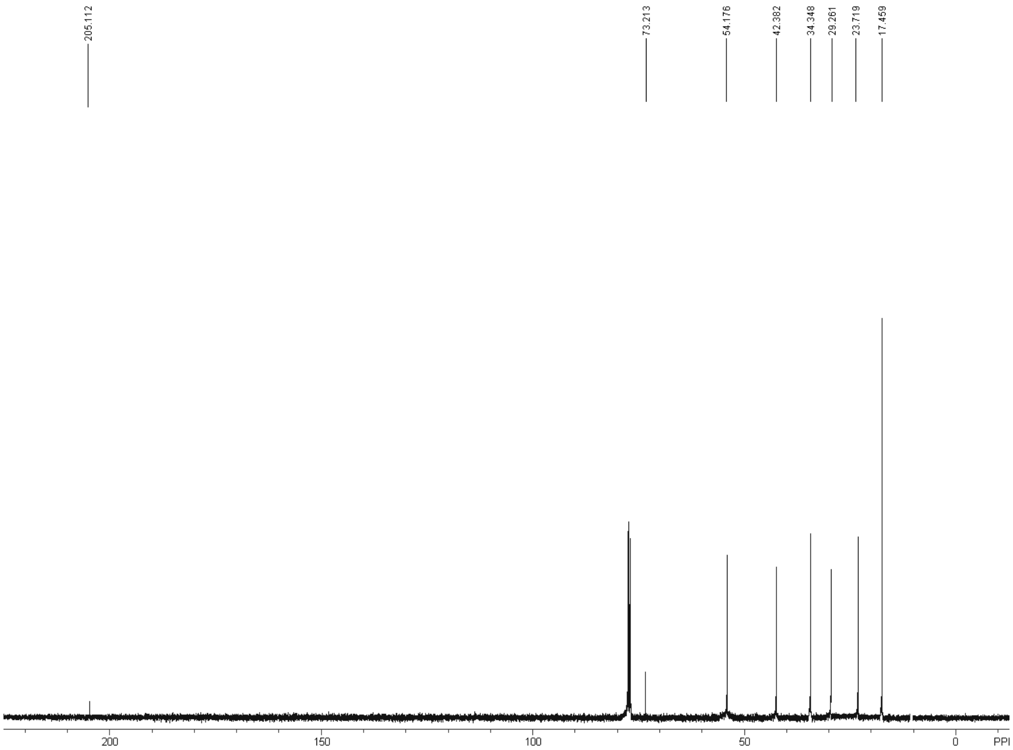


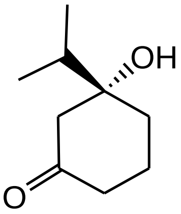
(*R*)-**97**


2.471
2.459
2.443
2.126
2.107
1.942
1.931
1.923
1.913
1.722
1.706
1.689
1.673
1.654
1.638
0.886
0.870
6.00
3.98
1.79
1.97
1.99
10
8
6
4
2
0
PP

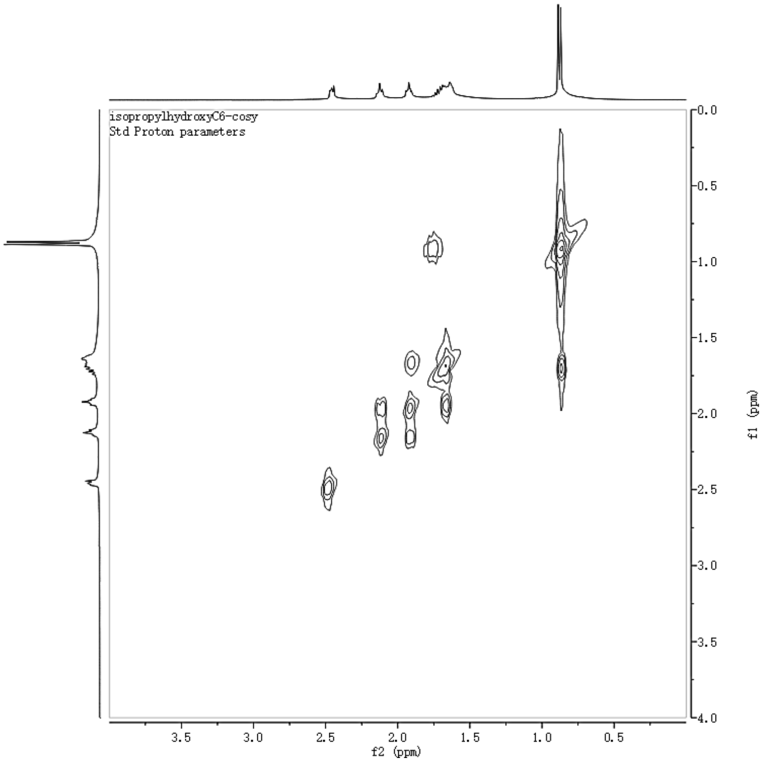


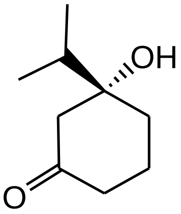
(*R*)-**98**


205.112
73.213
54.176
42.382
34.348
29.261
23.719
17.459
200
150
100
50
0
PPI

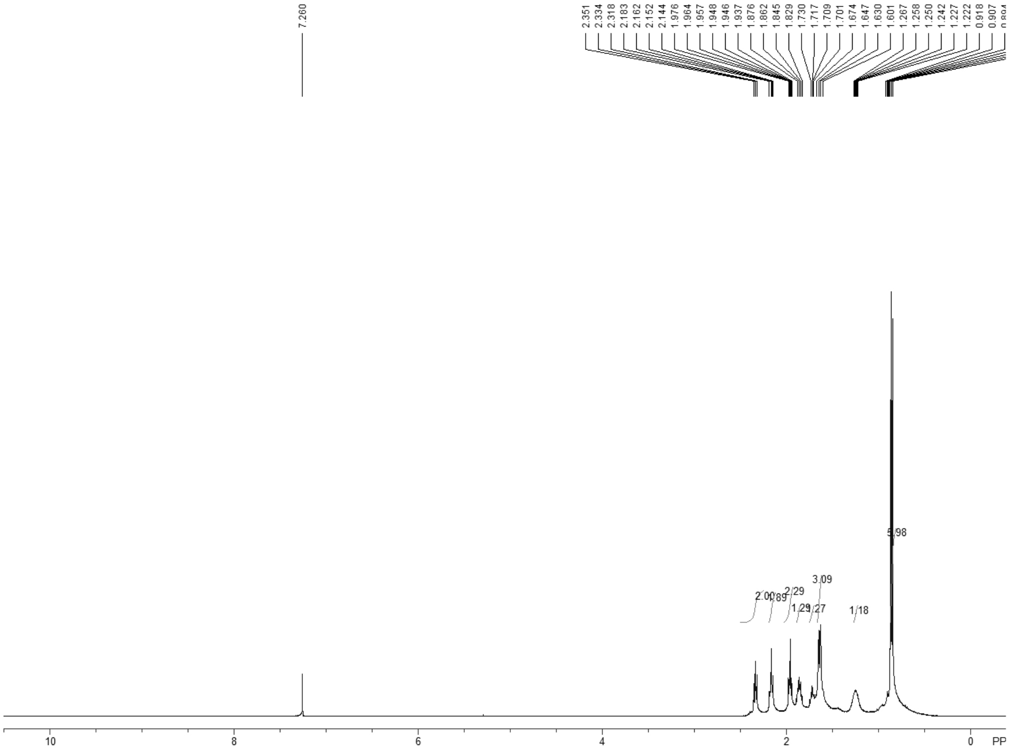

OH
O

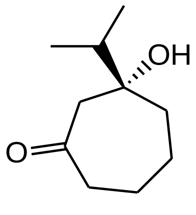
(*R*)-**98**


isopropylhydroxyC6-cosy
Std Proton parameters
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
f1 (ppm)

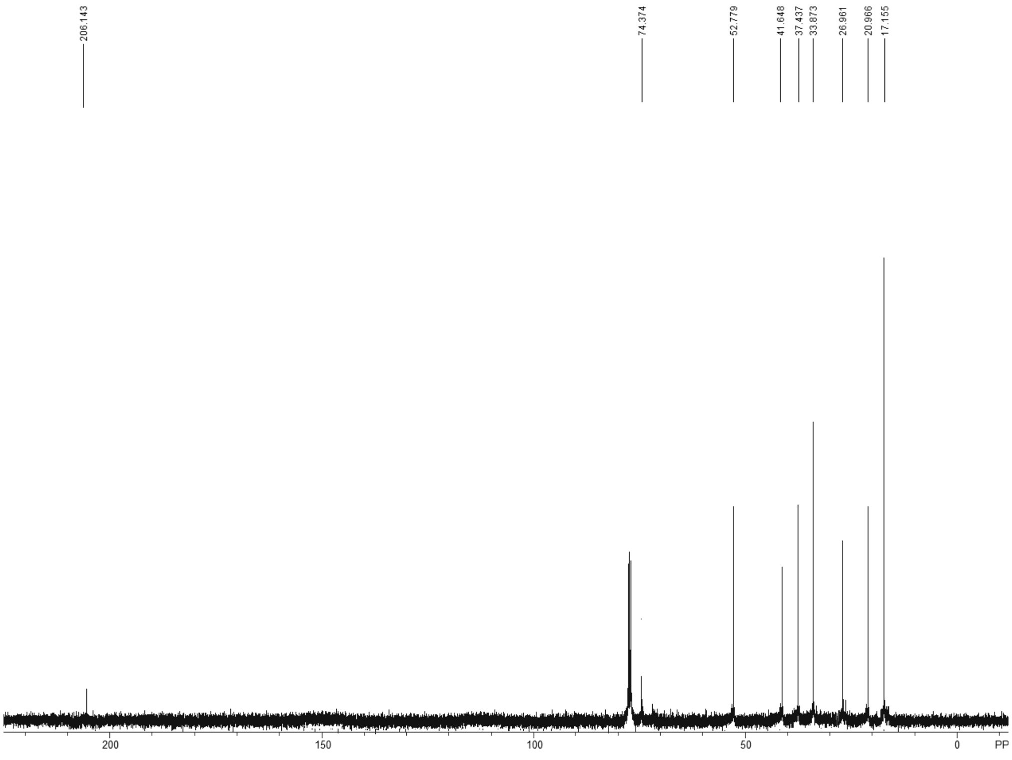

OH
O

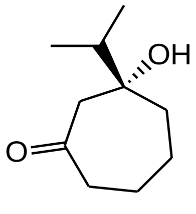
(*R*)-**98**


7.260
2.351
2.334
2.318
2.183
2.162
2.152
2.144
1.976
1.964
1.957
1.948
1.946
1.937
1.876
1.862
1.845
1.829
1.730
1.717
1.709
1.701
1.674
1.647
1.630
1.601
1.267
1.258
1.250
1.242
1.227
1.222
0.918
0.907
5.98
3.09
2.00
0.89
2.29
1.29
1.27
1.18
10
8
6
4
2
0
PP

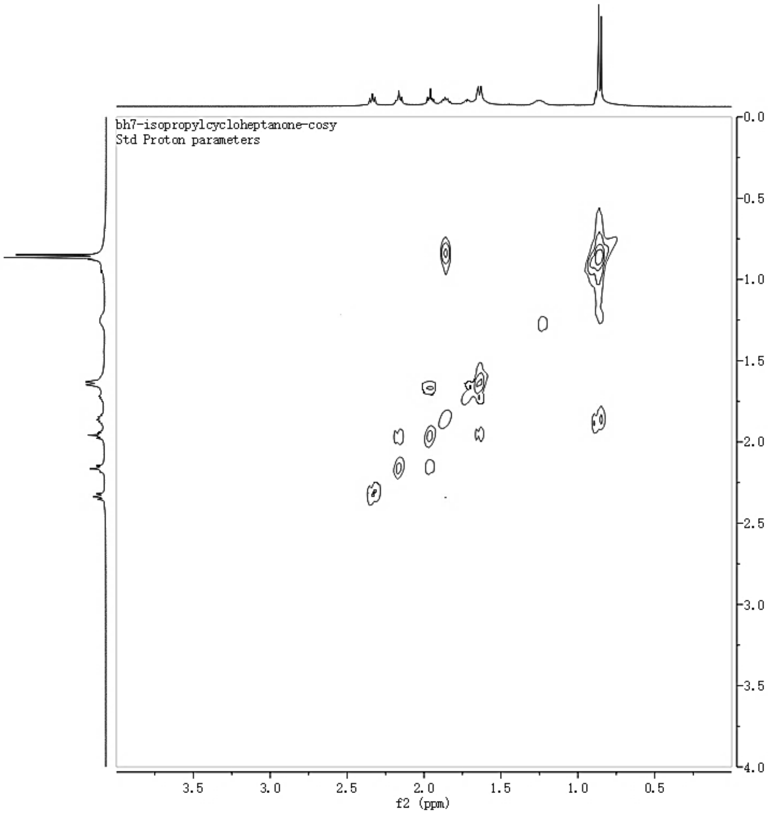

OH
O

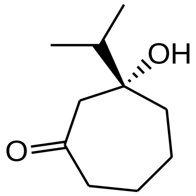
(*R*)-**99**


206.143
74.374
52.779
41.648
37.437
33.873
26.961
20.966
17.155
200
150
100
50
0
PP

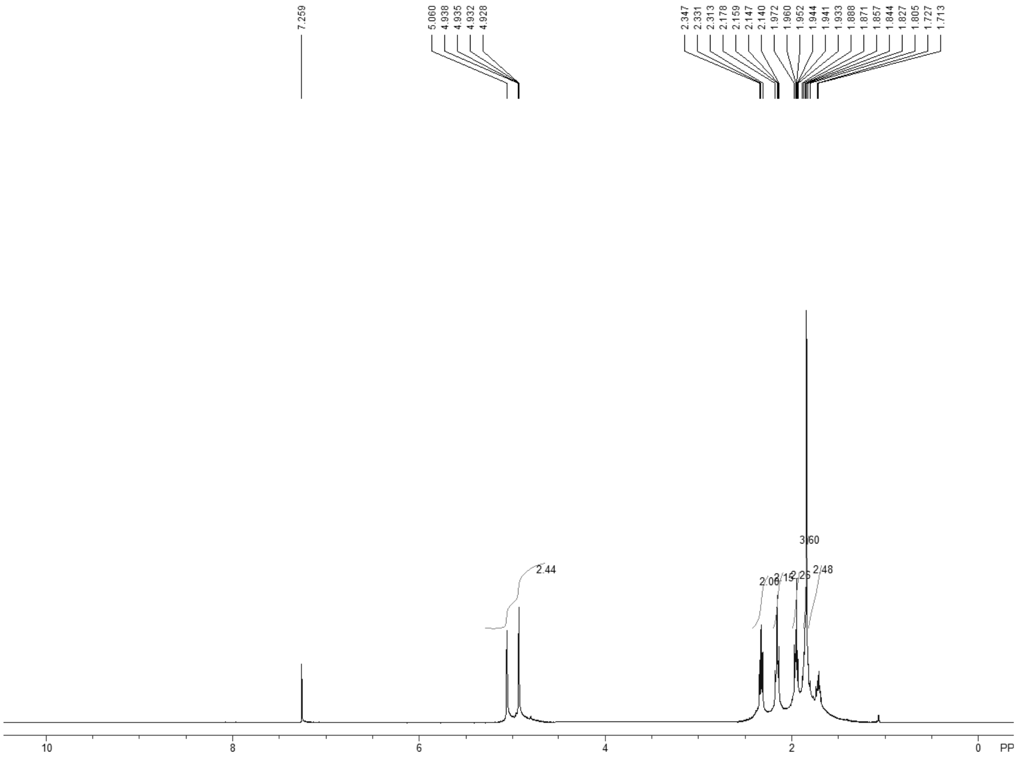

OH
O

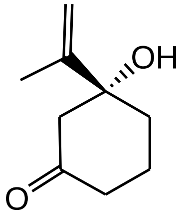
(*R*)-**99**


bh7-isopropylcycloheptanone-cosy
Std Proton parameters
f1 (ppm)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

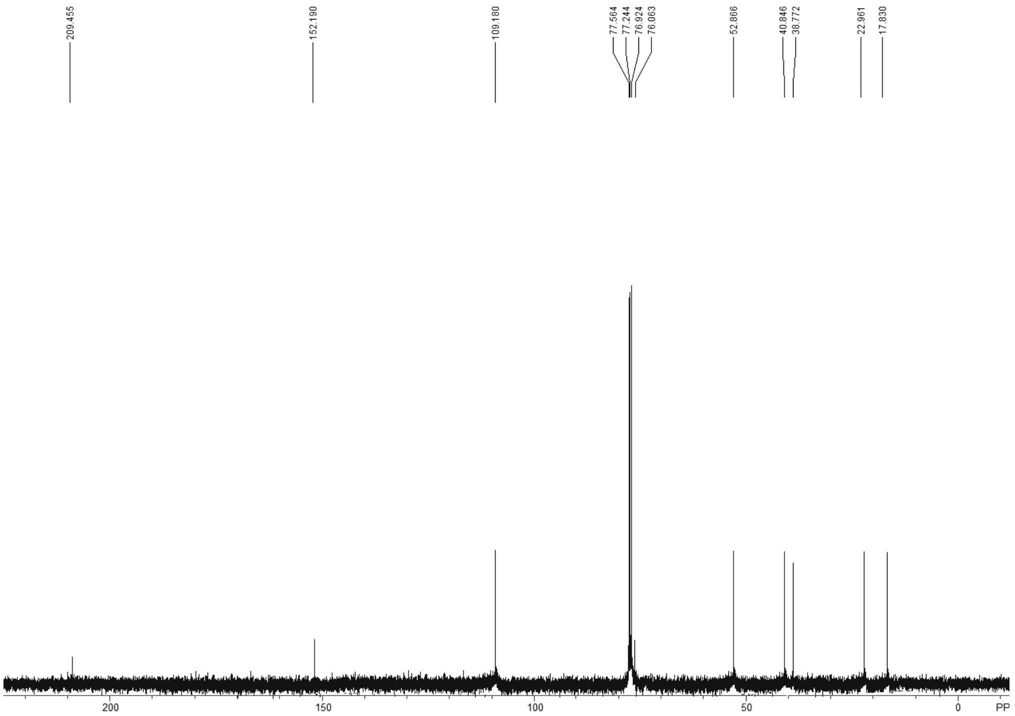

OH
O

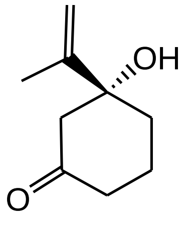
(*R*)-**99**


7.259
5.060
4.938
4.935
4.932
4.928
2.347
2.331
2.313
2.178
2.159
2.147
2.140
1.972
1.960
1.952
1.944
1.941
1.933
1.888
1.871
1.857
1.844
1.827
1.805
1.727
1.713
2.44
2.06
2.13
2.25
3.60
2.48
10
8
6
4
2
0
PP

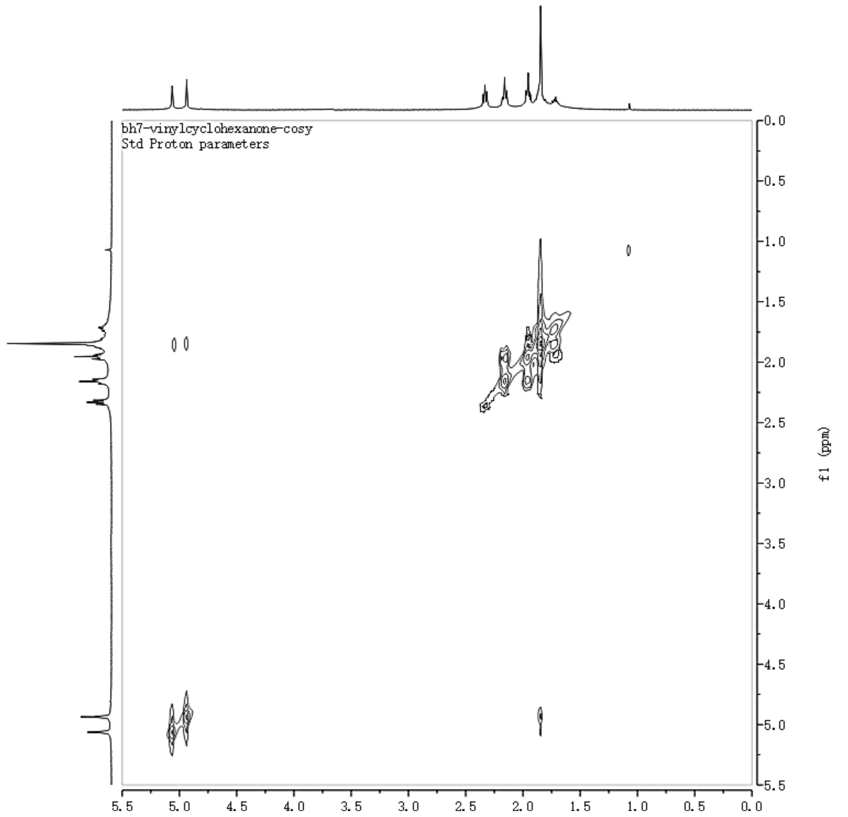

OH
O

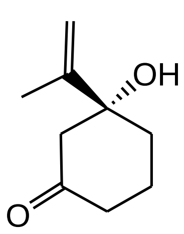
(*R*)-**101**


209.455
152.190
109.180
77.564
77.244
76.924
76.063
52.866
40.846
38.772
22.961
17.830
200
150
100
50
0
PP

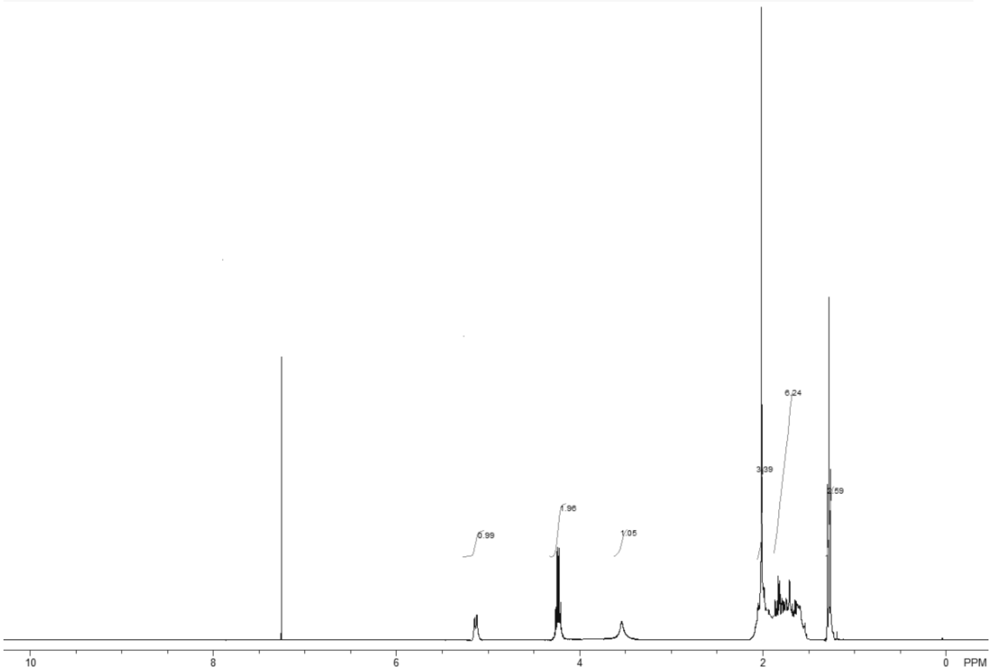

OH
O

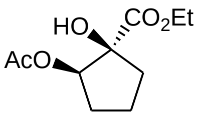
(*R*)-**101**


bh7-vinylcyclohexanone-cosy
Std Proton parameters
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

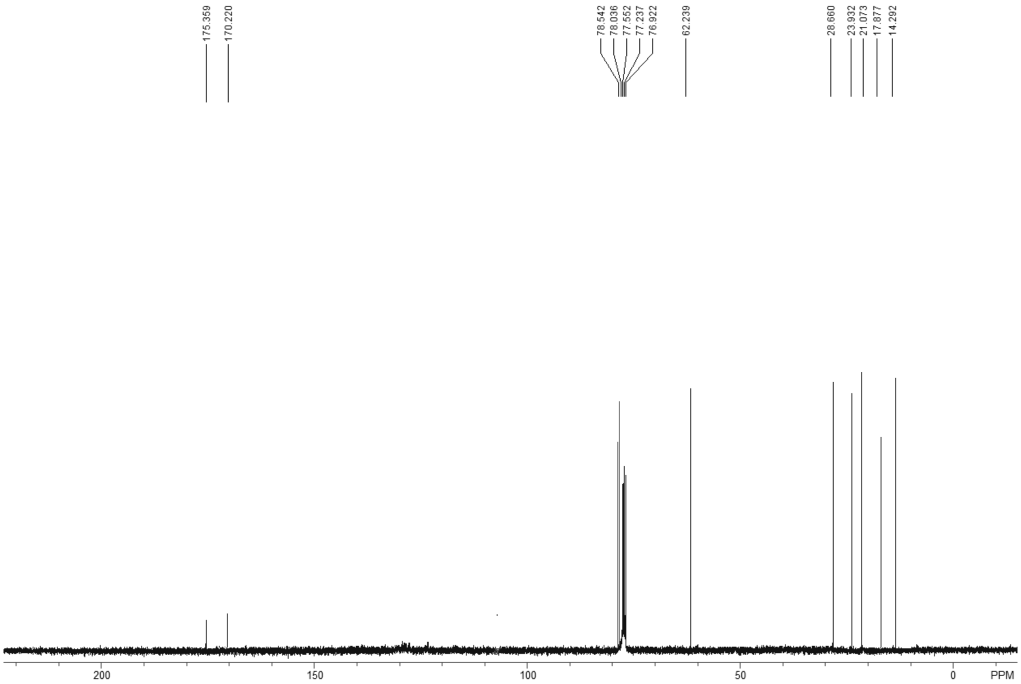

OH
O

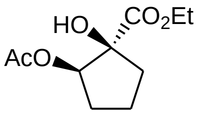
(*R*)-**101**



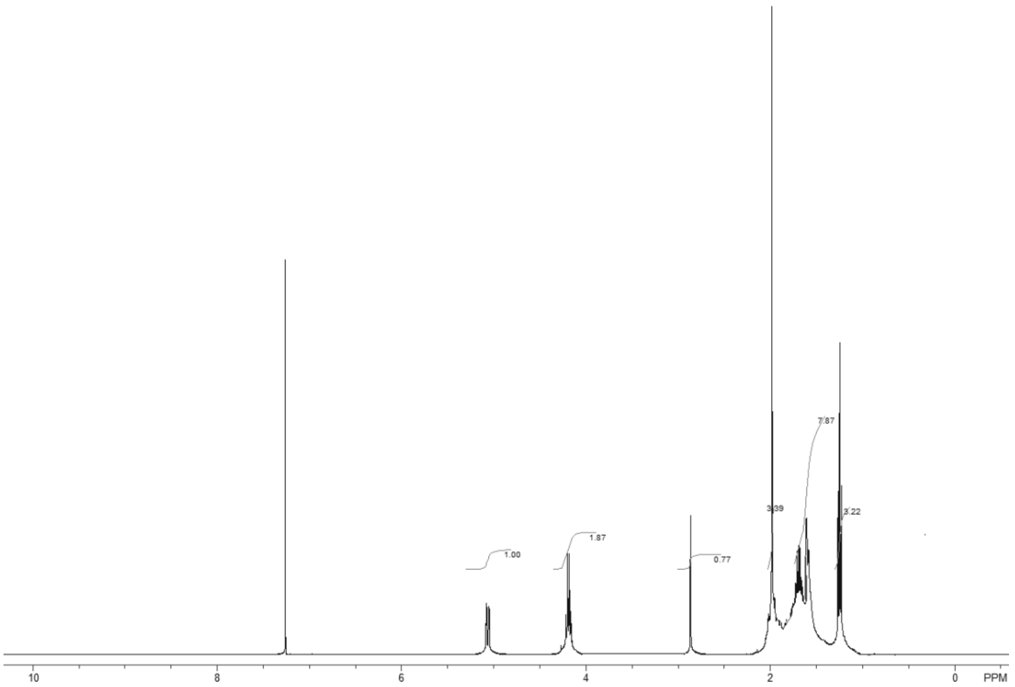


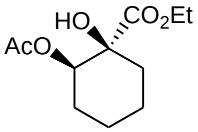
(1*S*,2*R*)-**102**



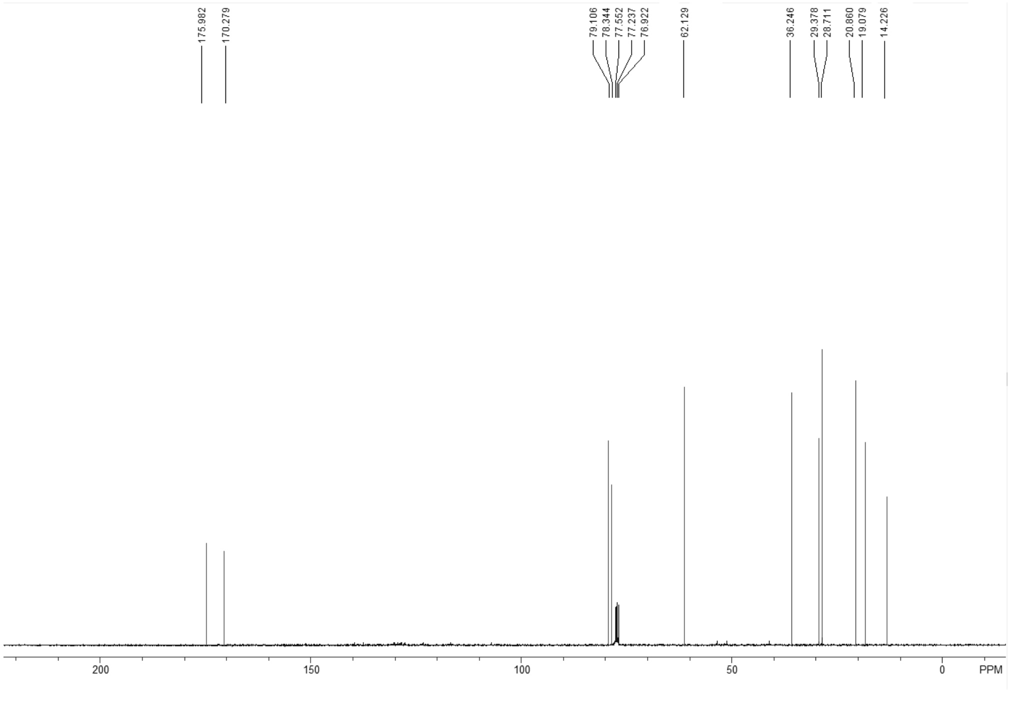


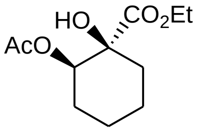
(1*S*,2*R*)-**102**



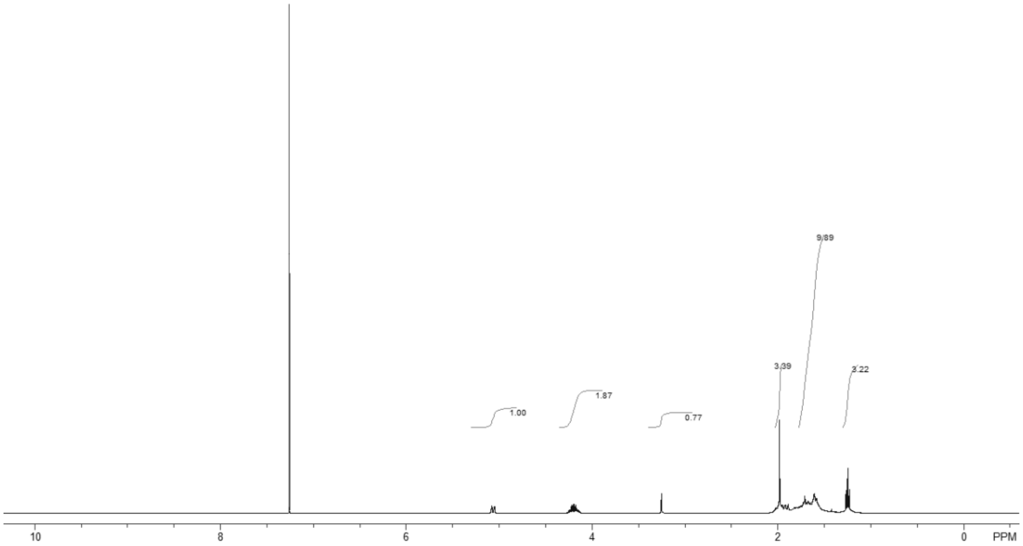


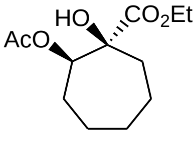
(1*S*,2*R*)-**103**



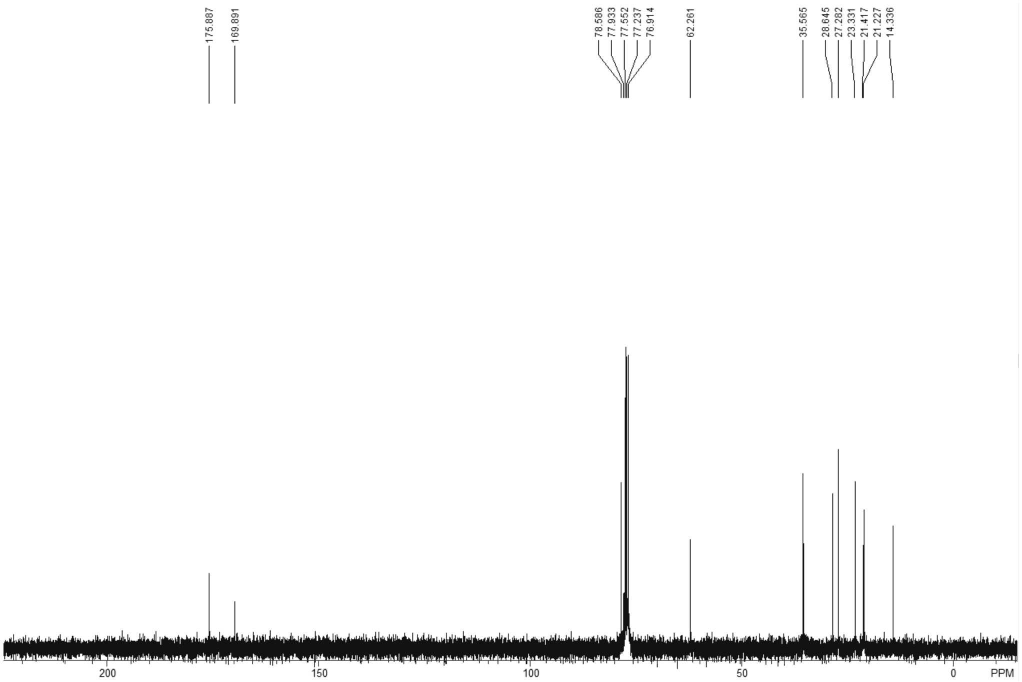


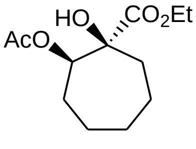
(1*S*,2*R*)-**103**



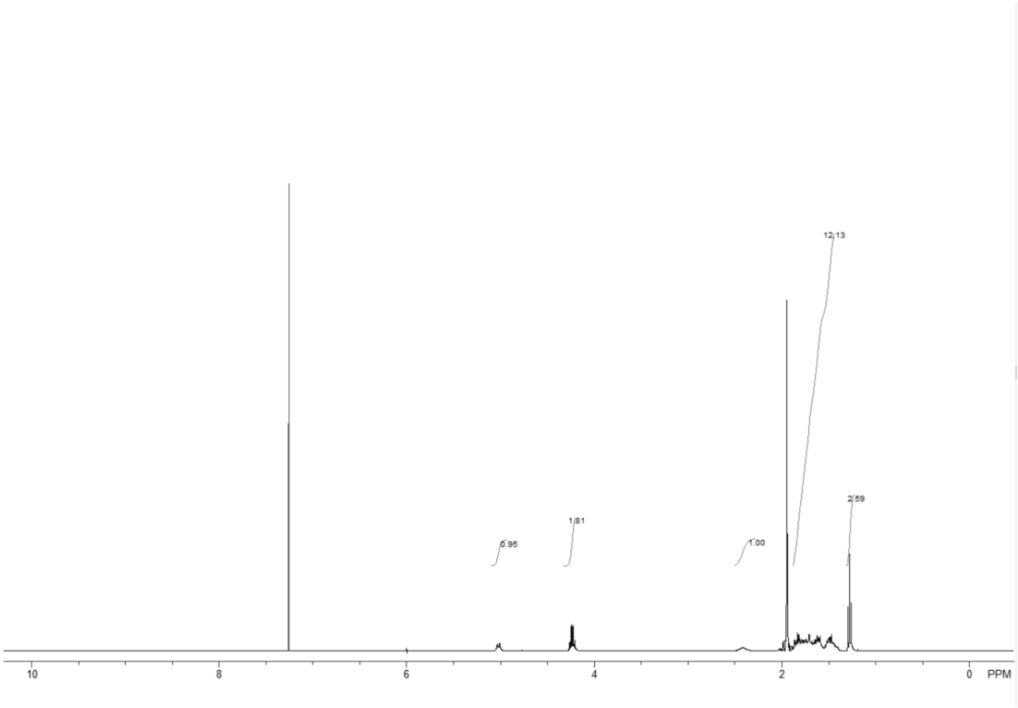


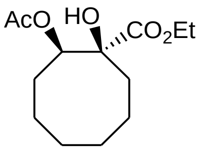
(1*S*,2*R*)-**104**



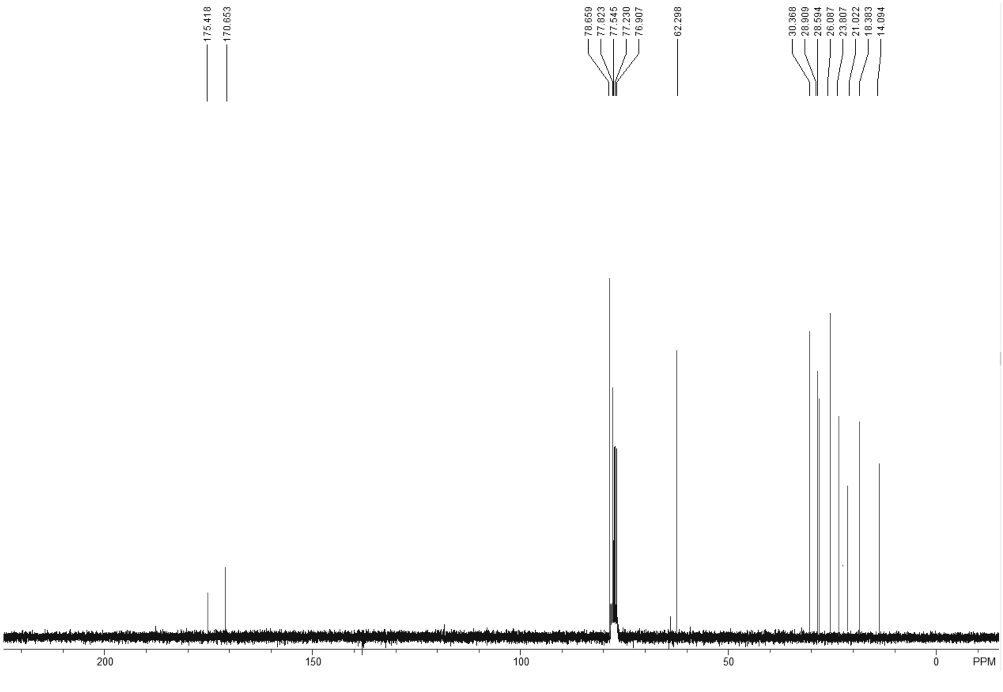


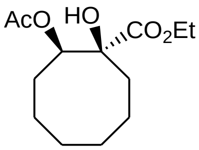
(1*S*,2*R*)-**104**



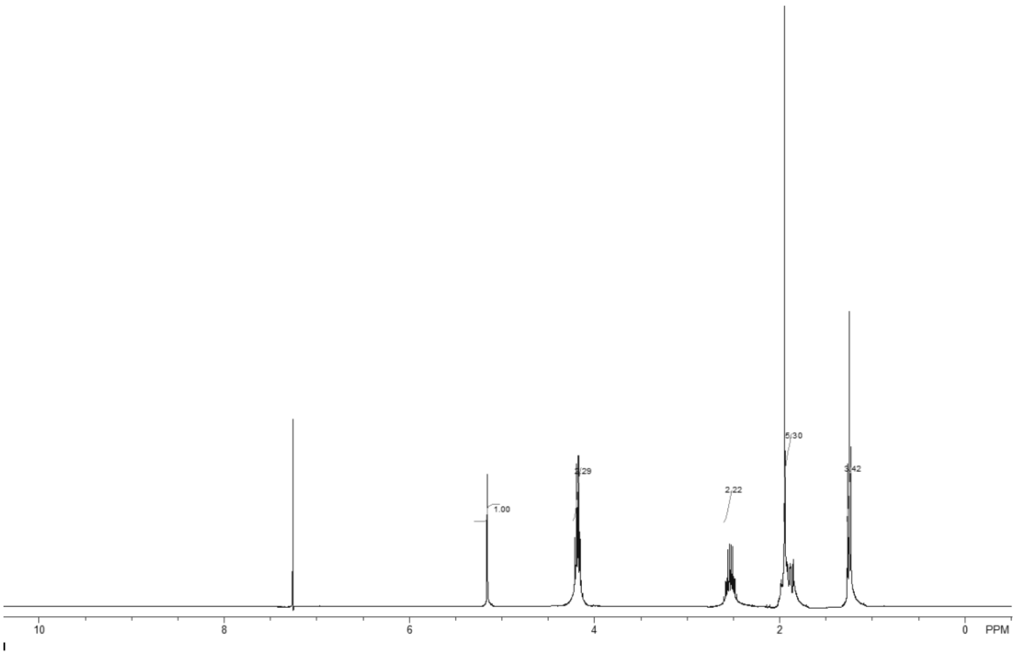


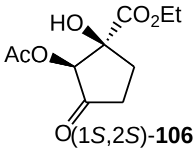
(1*S*,2*R*)-**105**



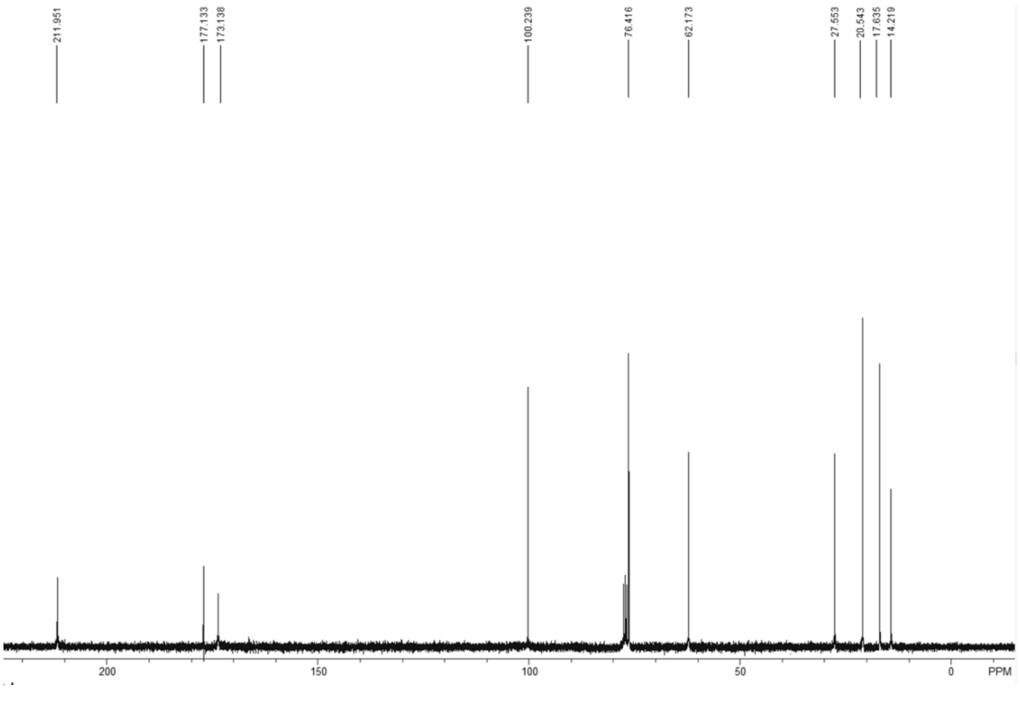


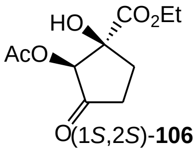
(1*S*,2*R*)-**105**



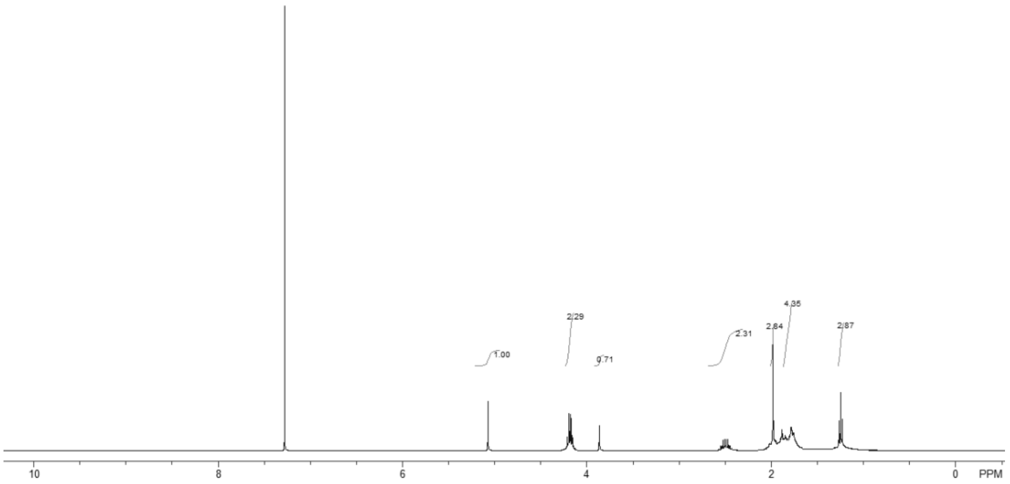


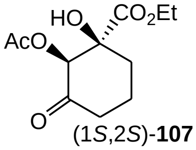
(1*S*,2*S*)-**106**



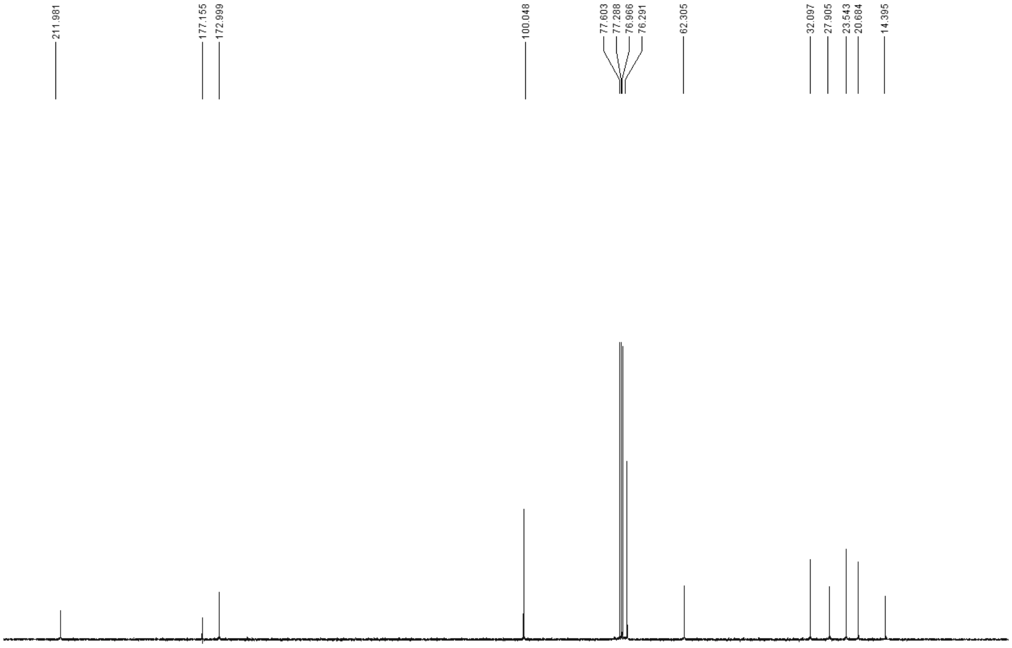


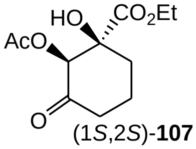
(1*S*,2*S*)-**106**



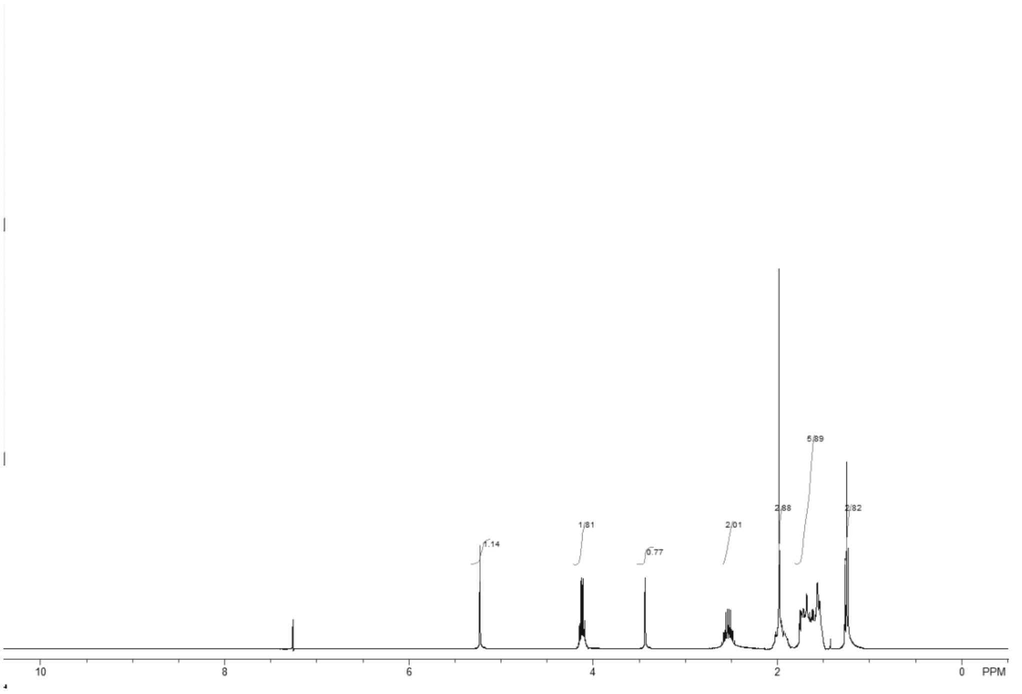


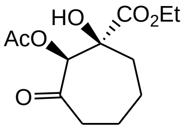
(1*S*,2*S*)-**107**



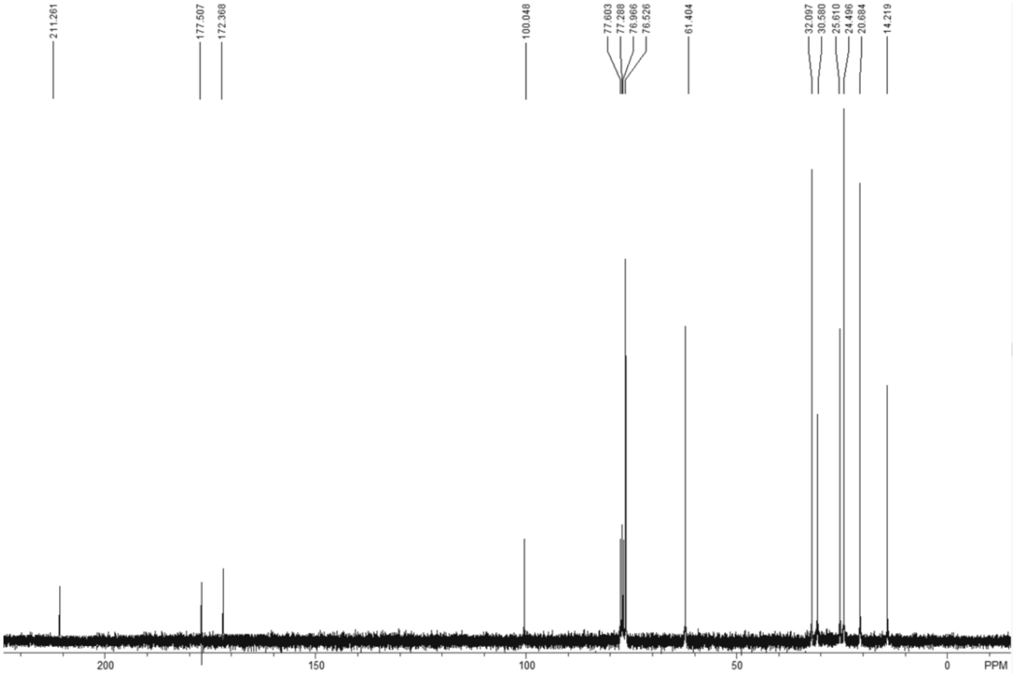


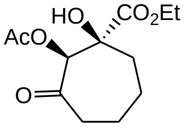
(1*S*,2*S*)-**107**



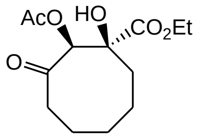


(1*S*,2*S*)-**108**

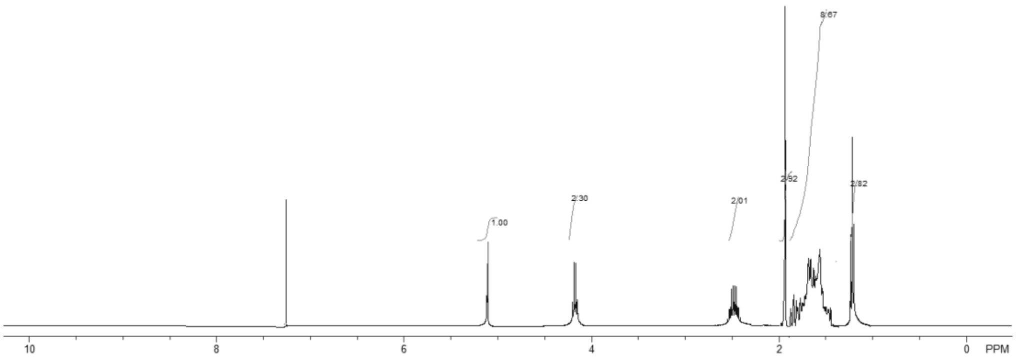


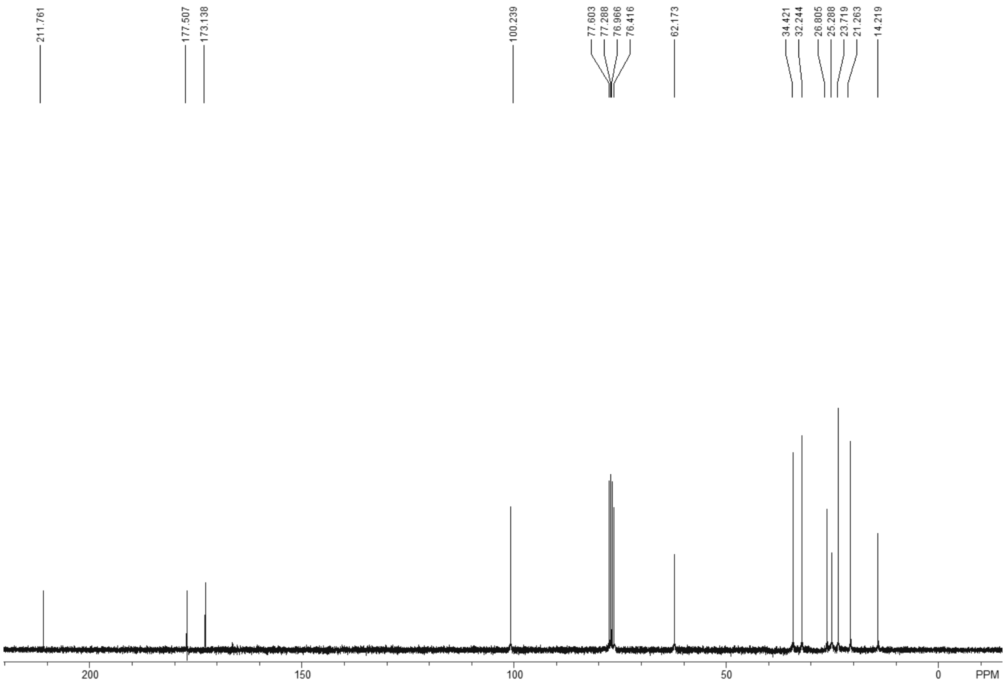


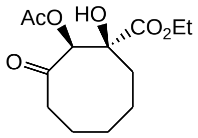
(1*S*,2*S*)-**108**



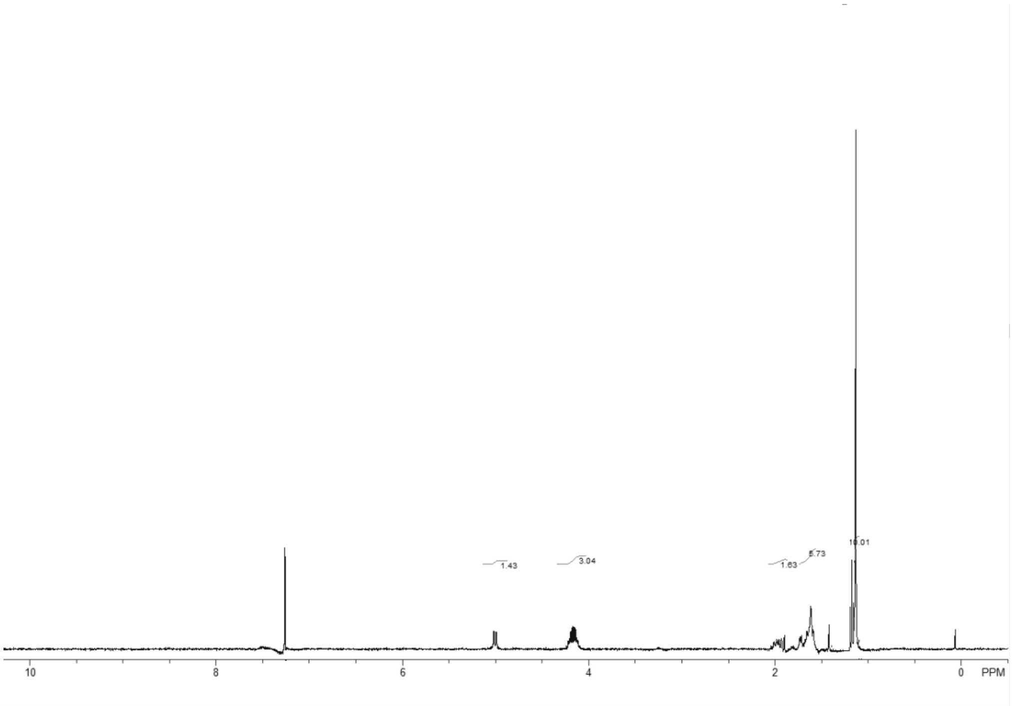
(1*S*,2*S*)-**109**

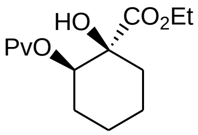




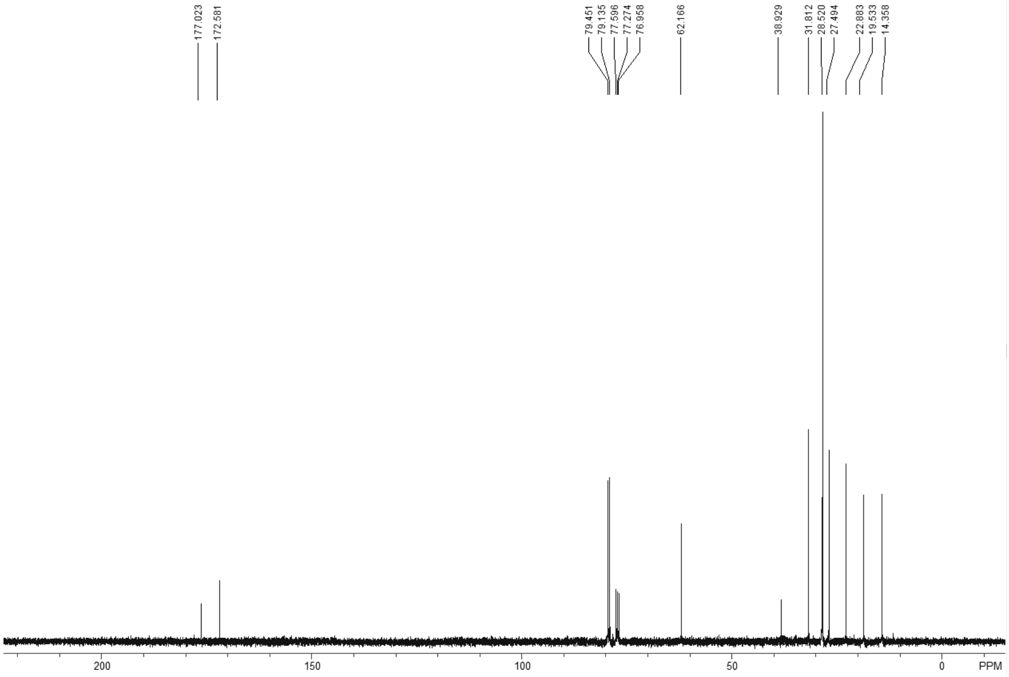


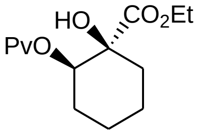
(1*S*,2*S*)-**109**



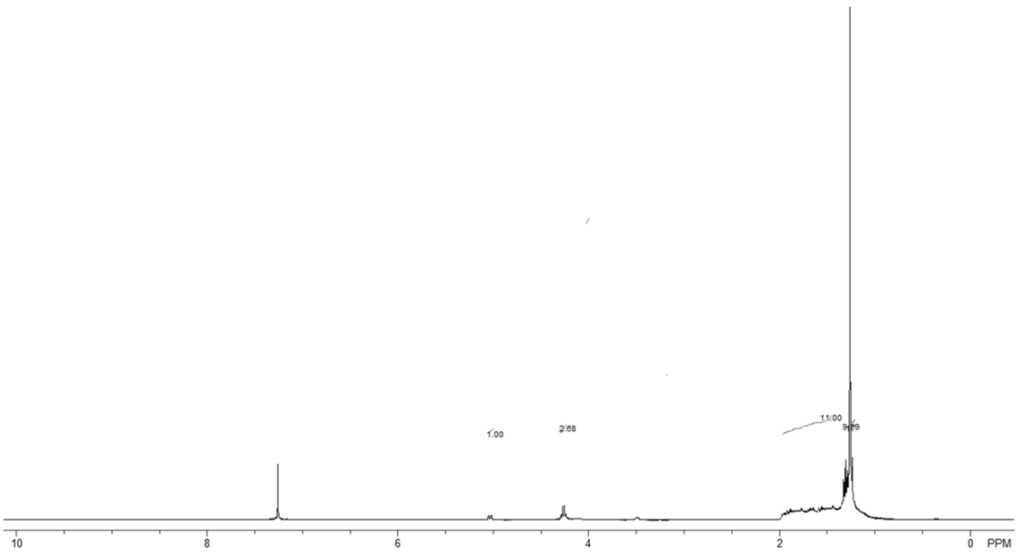


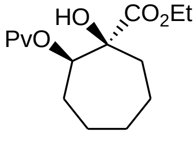
(1*S*,2*R*)-**110**



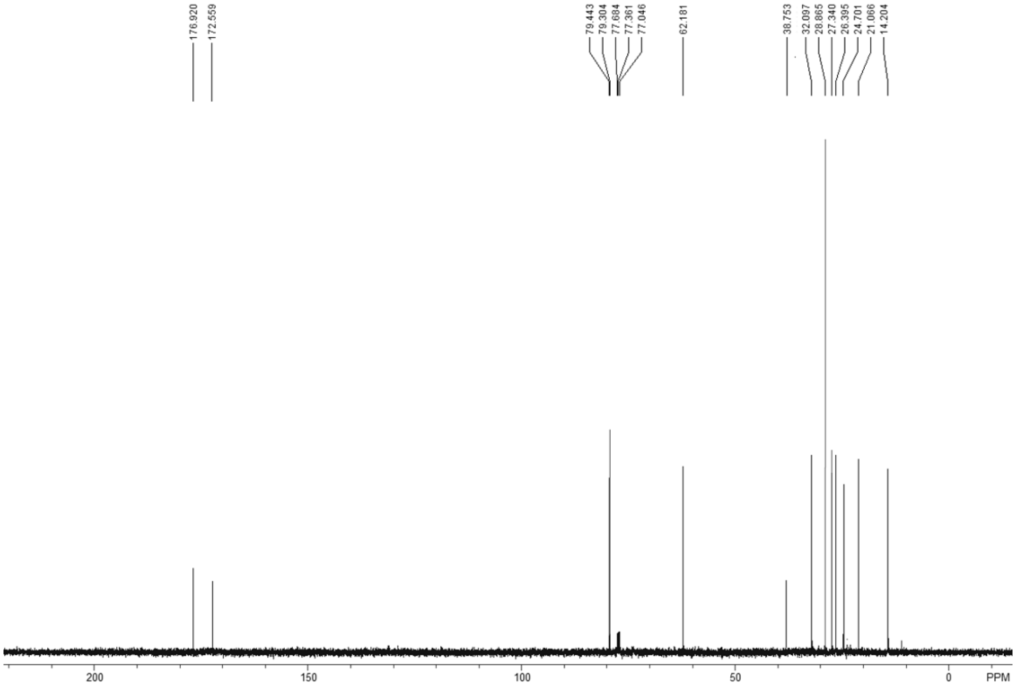


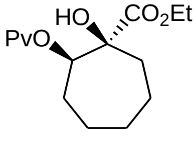
(1*S*,2*R*)-**110**



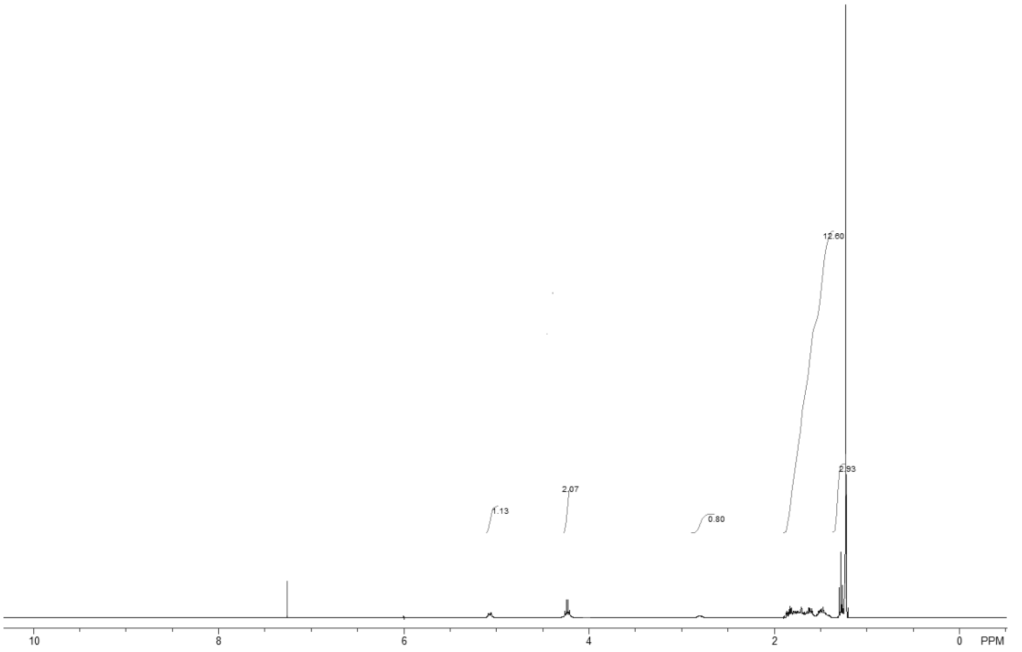


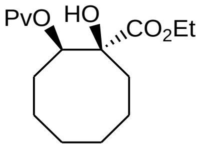
(1*S*,2*R*)-**111**



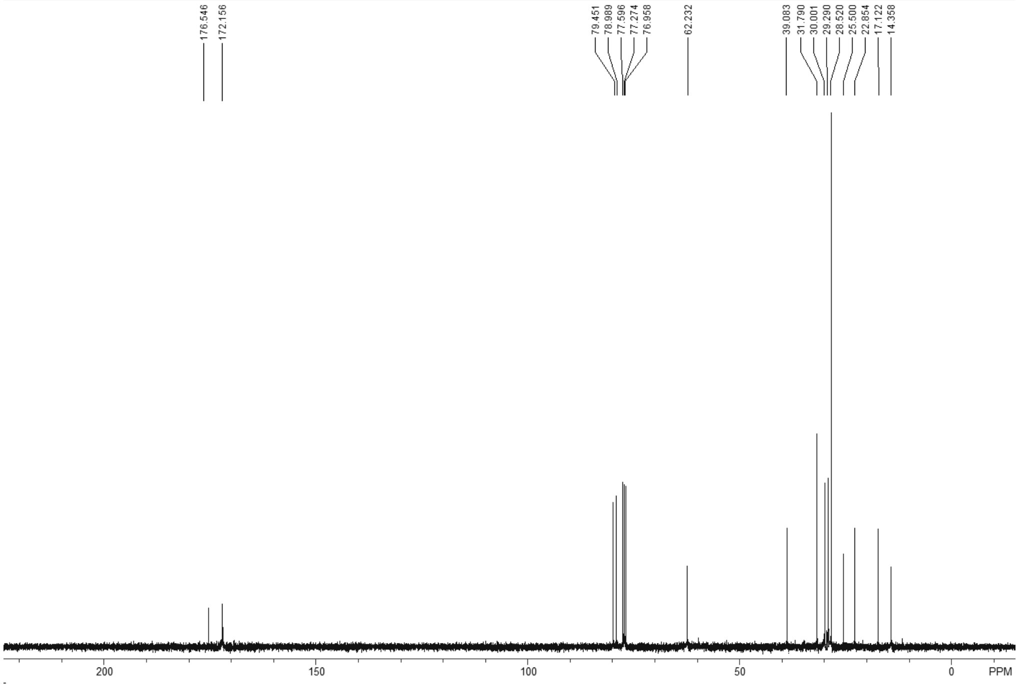


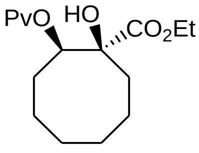
(1*S*,2*R*)-**111**



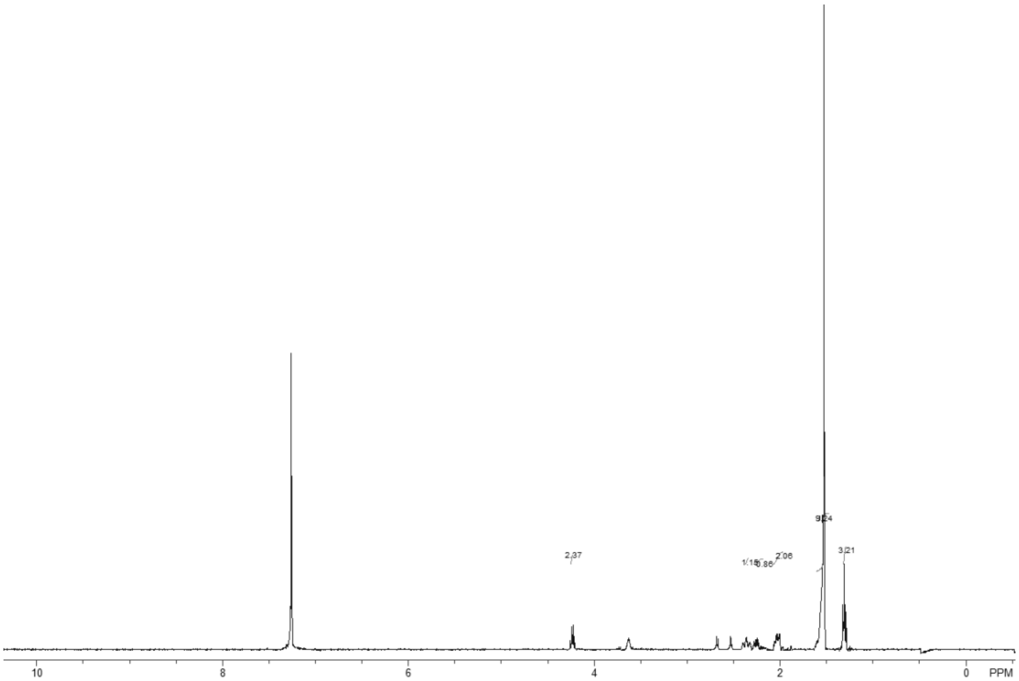


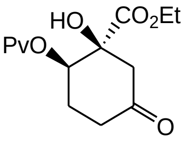
(1*S*,2*R*)-**112**



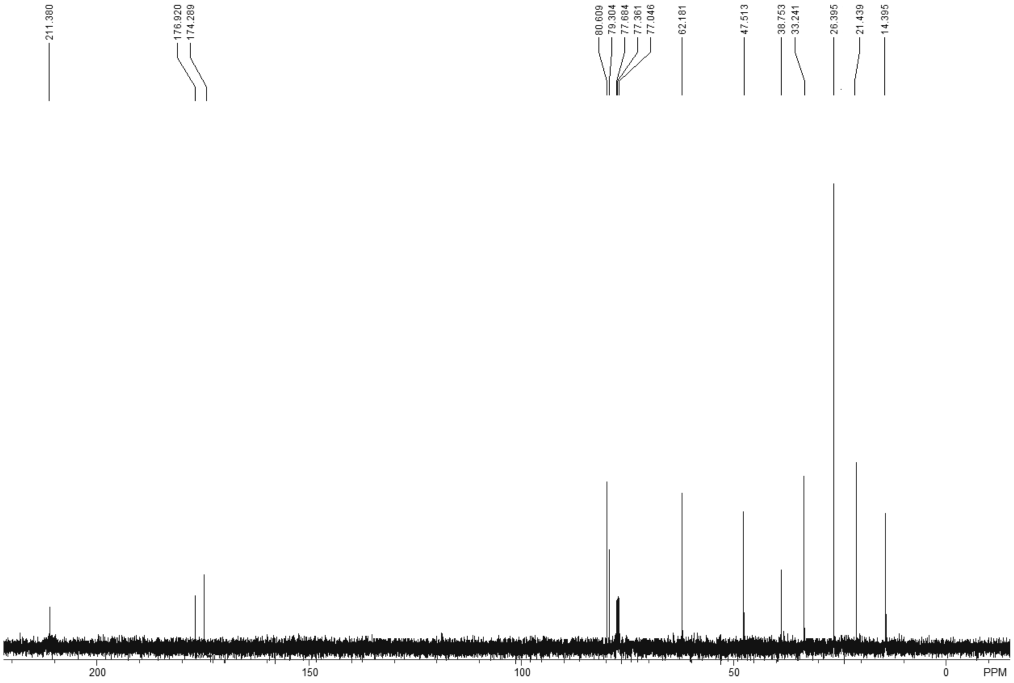


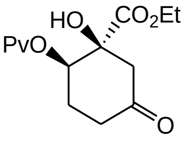
(1*S*,2*R*)-**112**



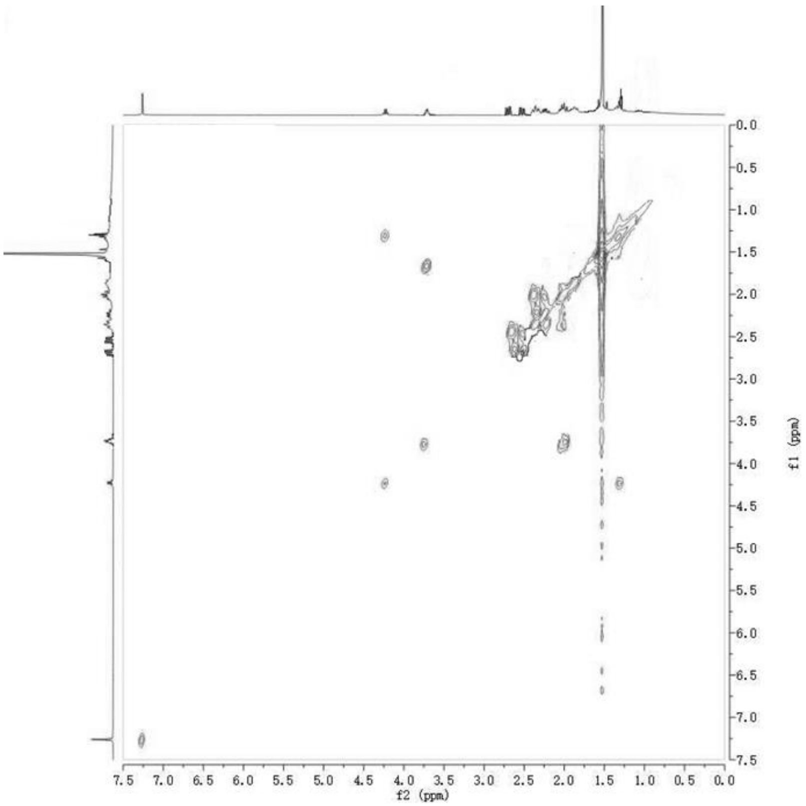


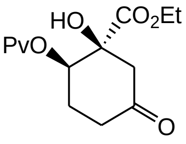
(1*S*,2*R*)-**113**



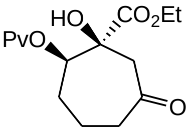


(1*S*,2*R*)-**113**

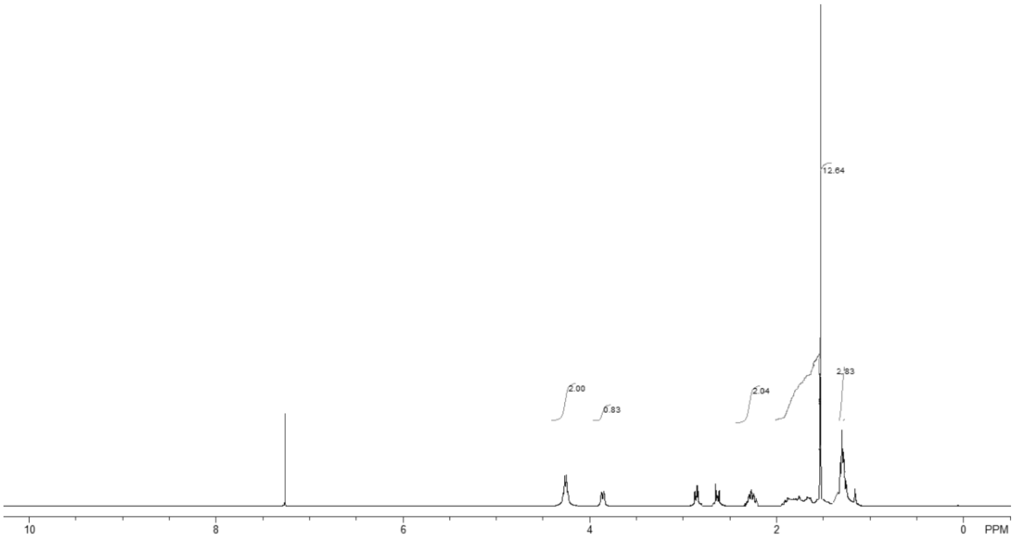


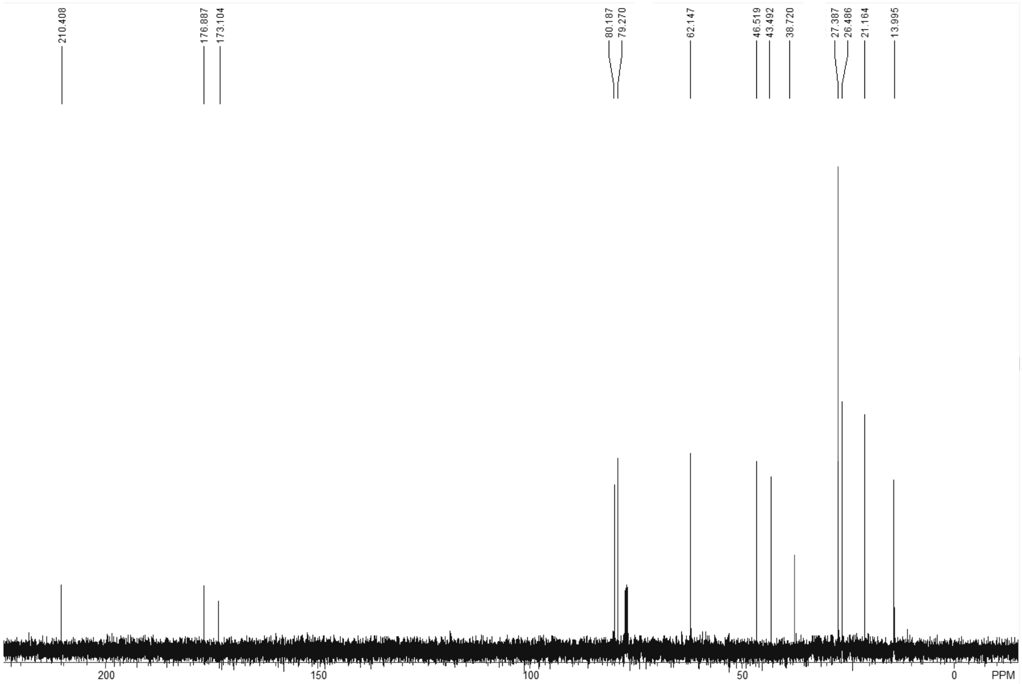


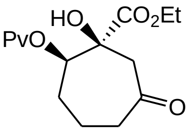
(1*S*,2*R*)-**113**



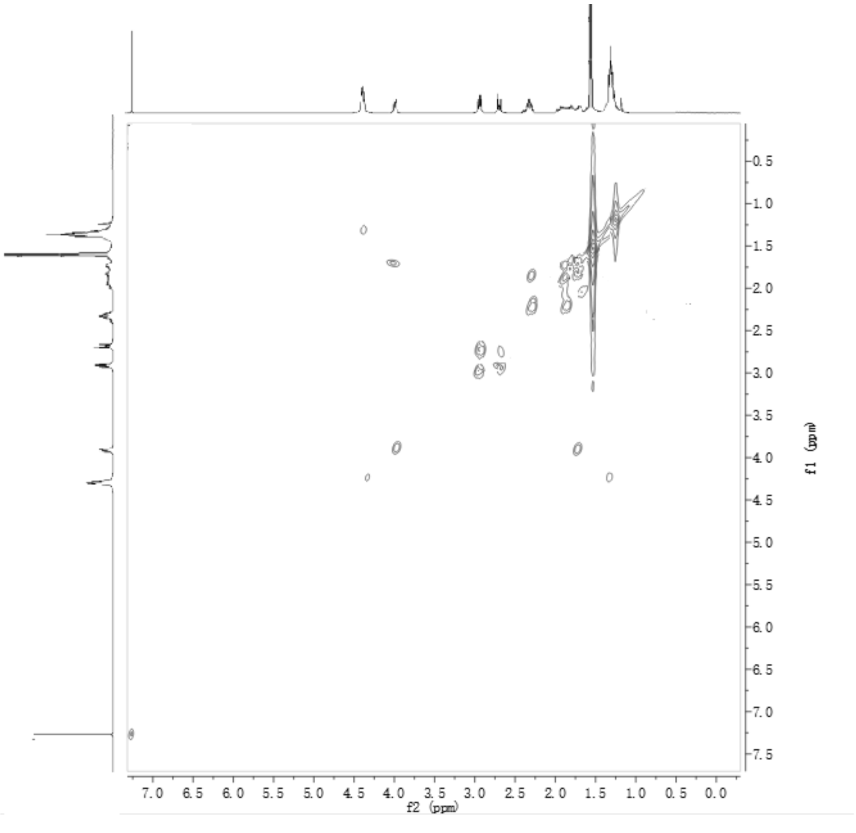
(1*S*,2*R*)-**114**

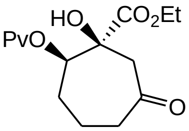




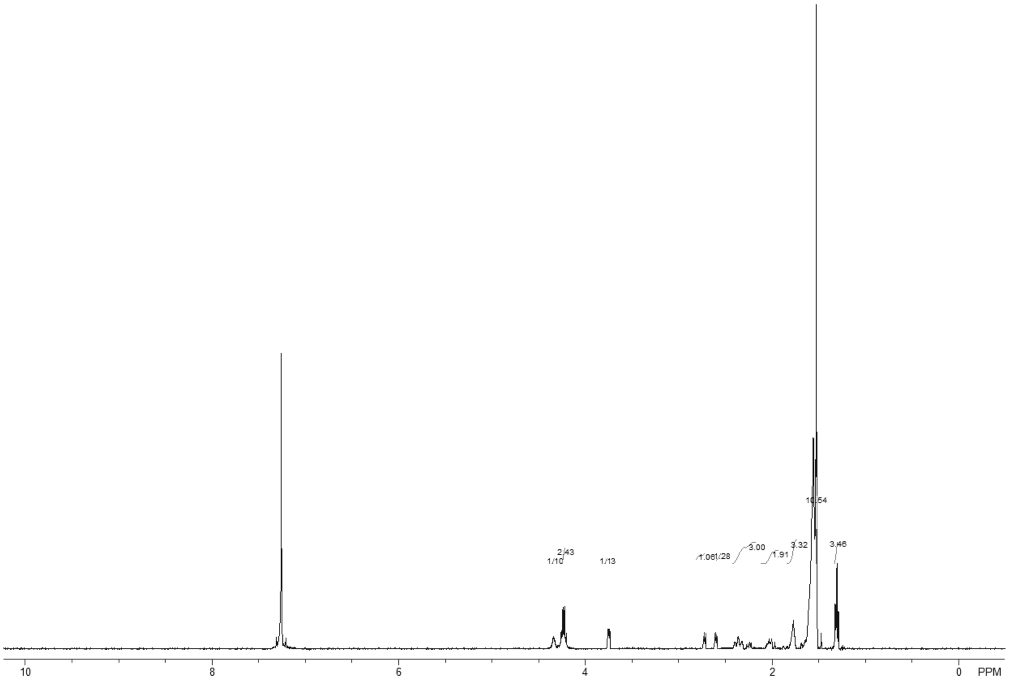


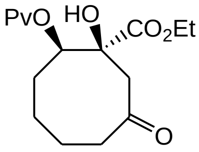
(1*S*,2*R*)-**114**



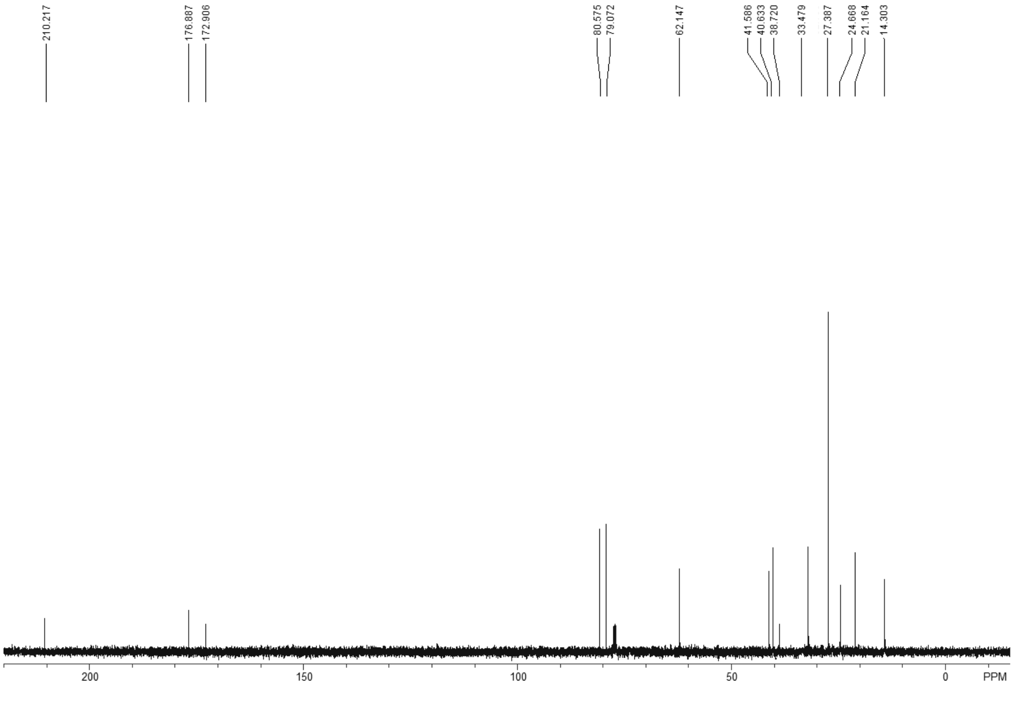


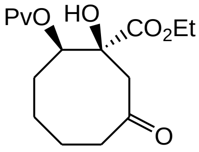
(1*S*,2*R*)-**114**



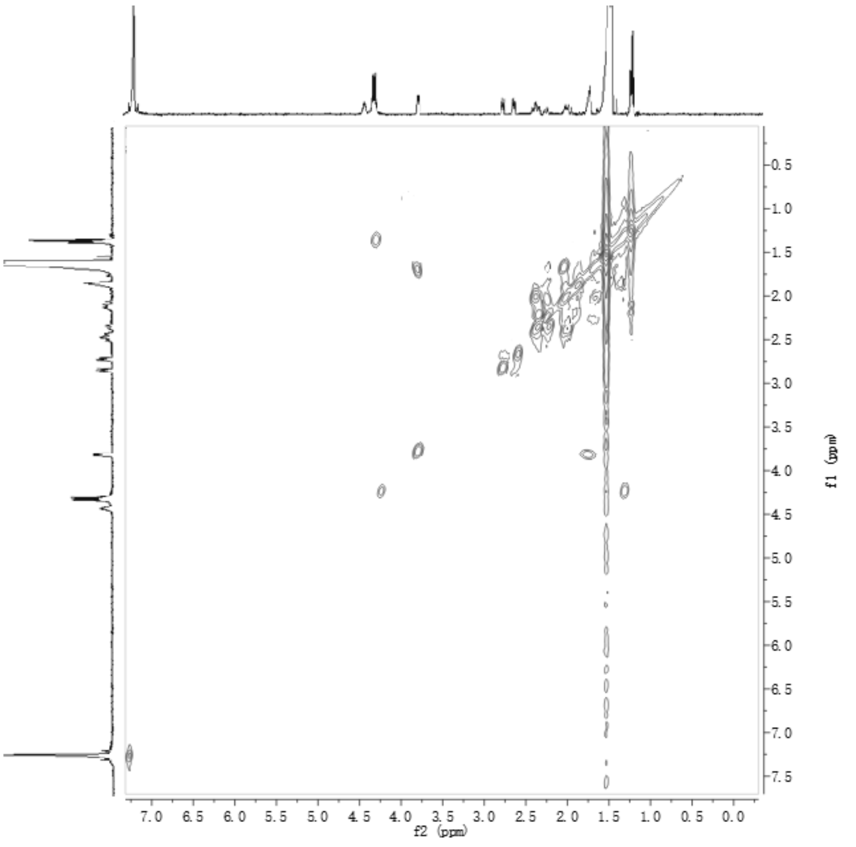


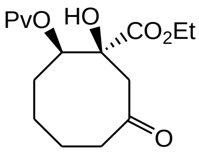
(1*S*,2*R*)-**115**



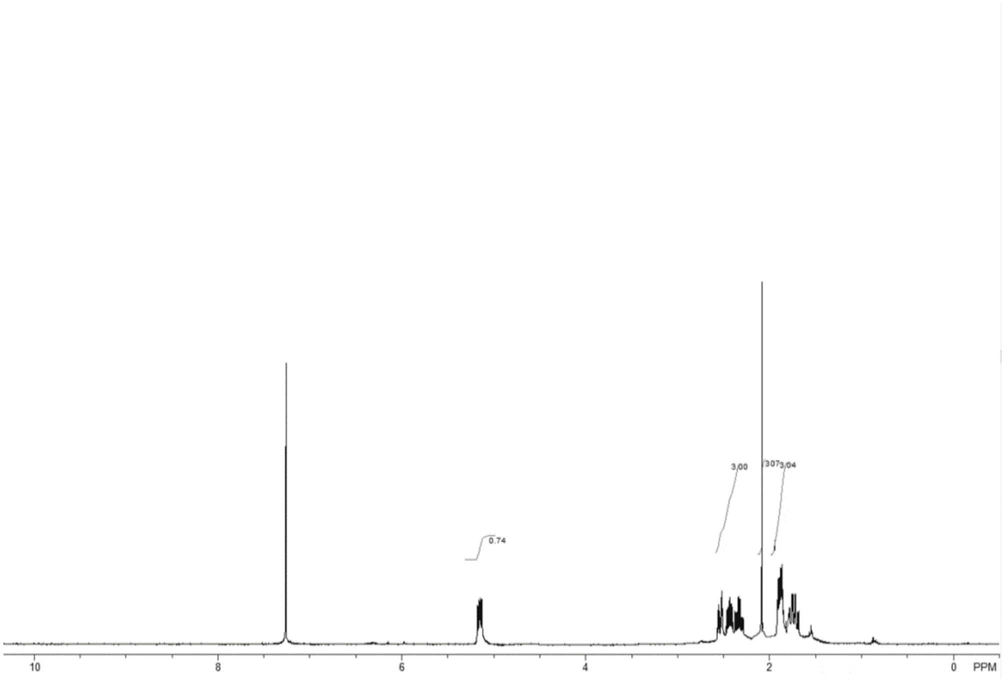


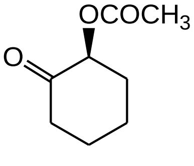
(1*S*,2*R*)-**115**



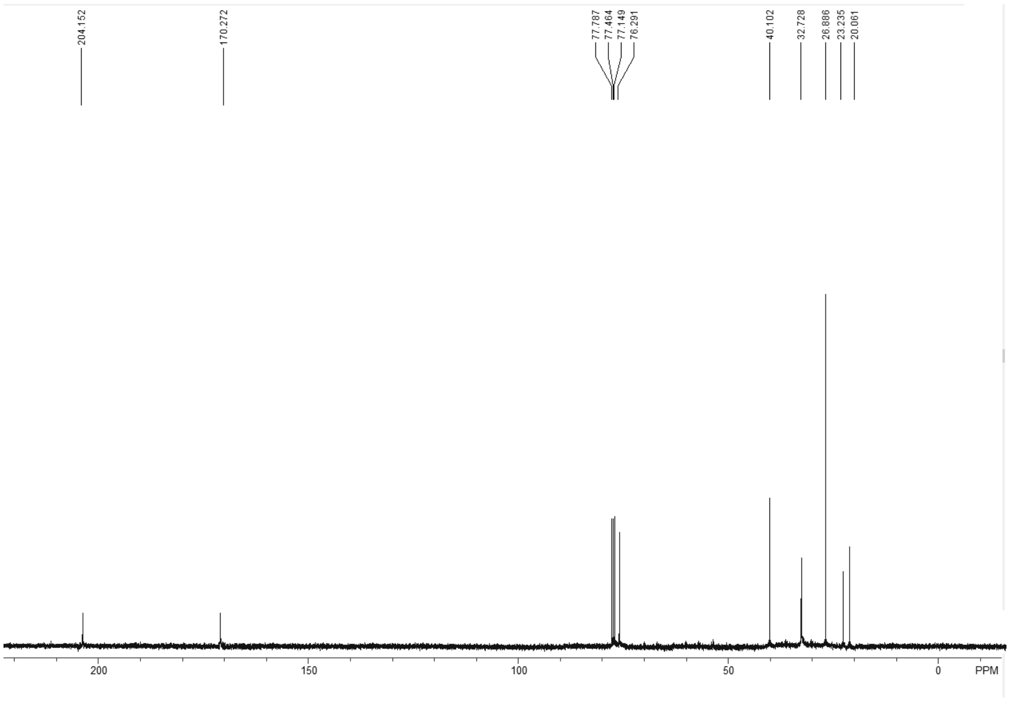


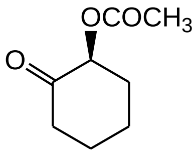
(1*S*,2*R*)-**115**



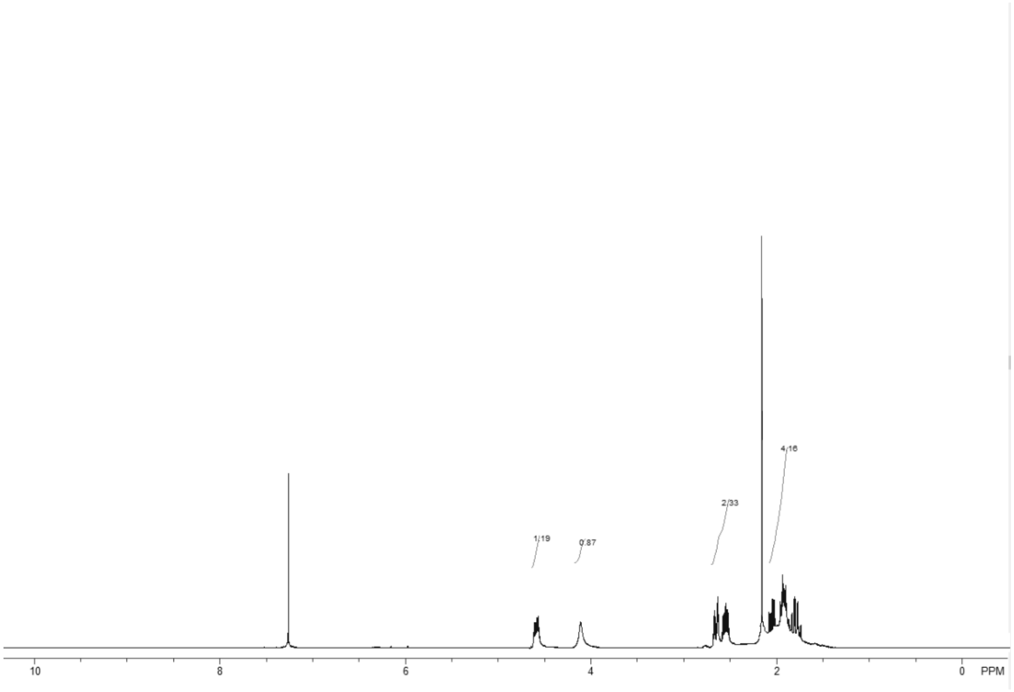


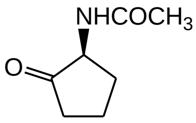
(*S*)-**121**


204.152
170.272
77.787
77.464
77.149
76.291
40.102
32.728
26.886
23.235
20.061
200
150
100
50
0
PPM

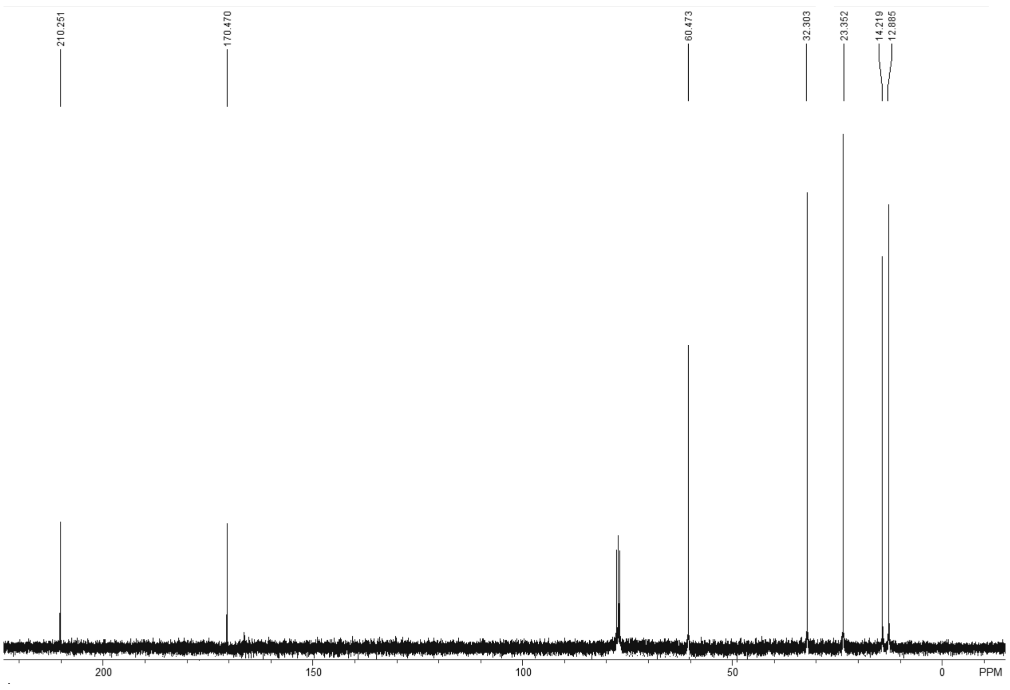

OCOCH$_3$
O

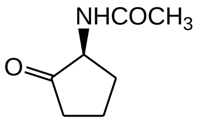
(*S*)-**121**


1.19
0.87
2.33
4.16
10
8
6
4
2
0
PPM

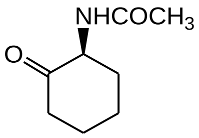

NHCOCH$_3$
O

(*S*)-**122**

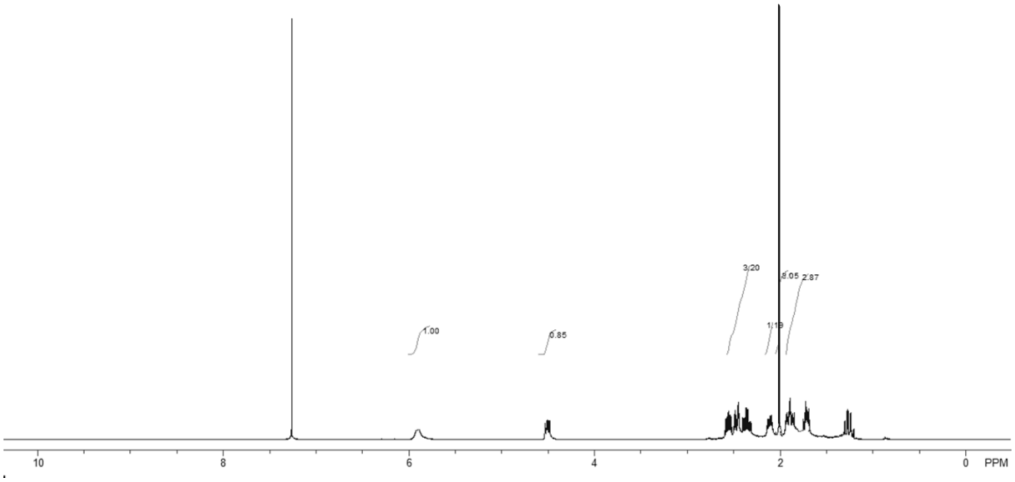

210.251
170.470
60.473
32.303
23.352
14.219
12.885
200
150
100
50
0
PPM

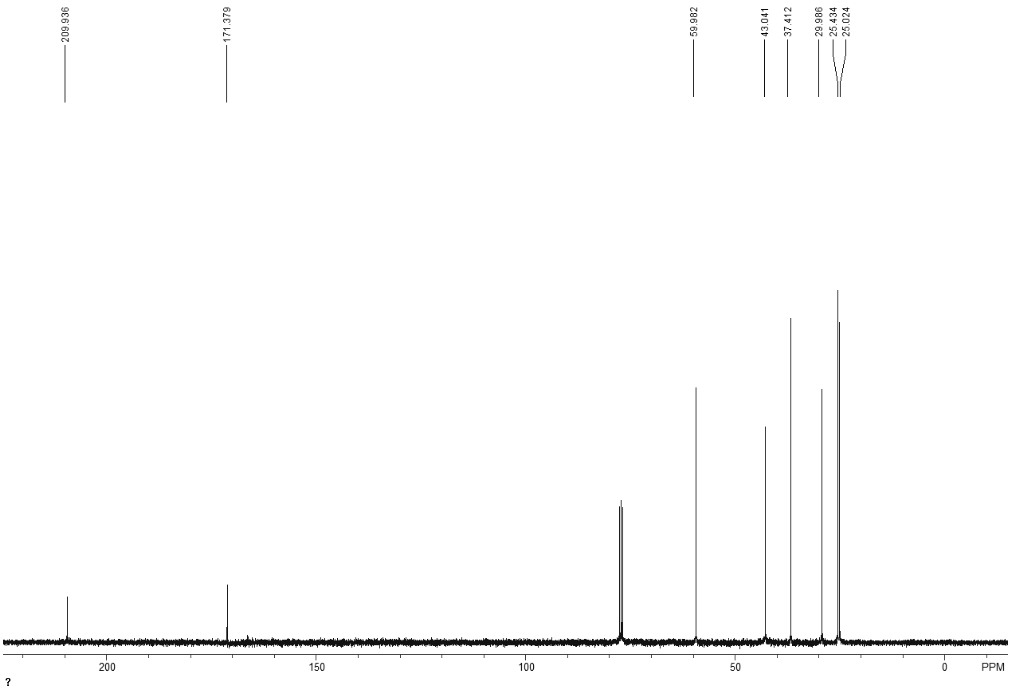

NHCOCH3
O

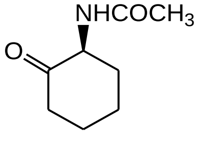
(*S*)-**122**


NHCOCH3
O

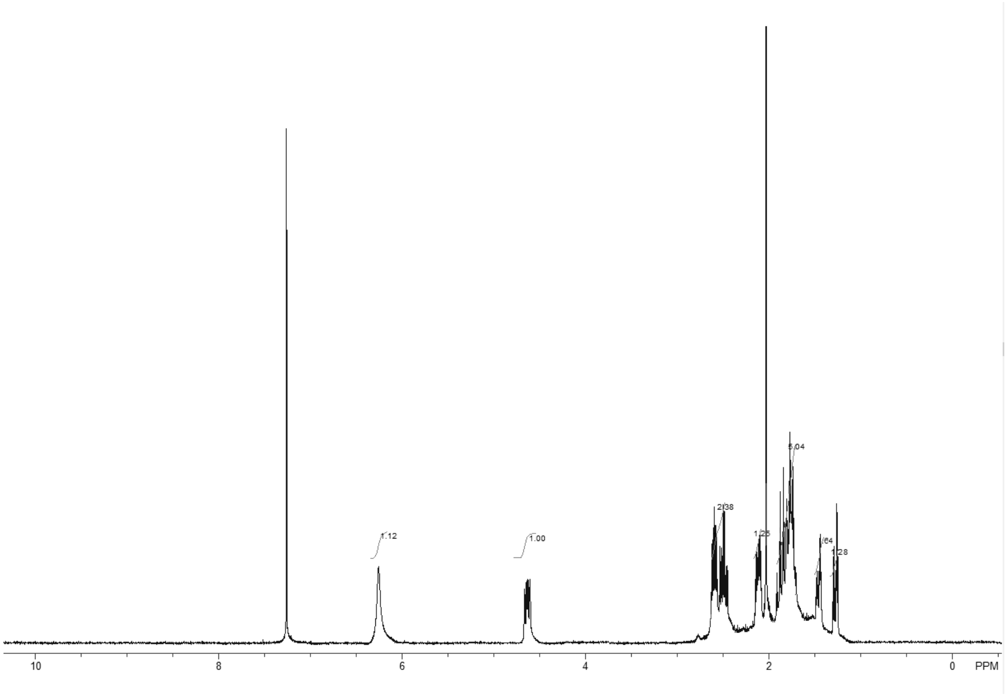
(*S*)-**123**

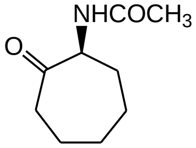

1.00
0.85
3.20
1.19
6.05
2.87
10
8
6
4
2
0
PPM


209.936
171.379
59.982
43.041
37.412
29.986
25.434
25.024
200
150
100
50
0
PPM
?

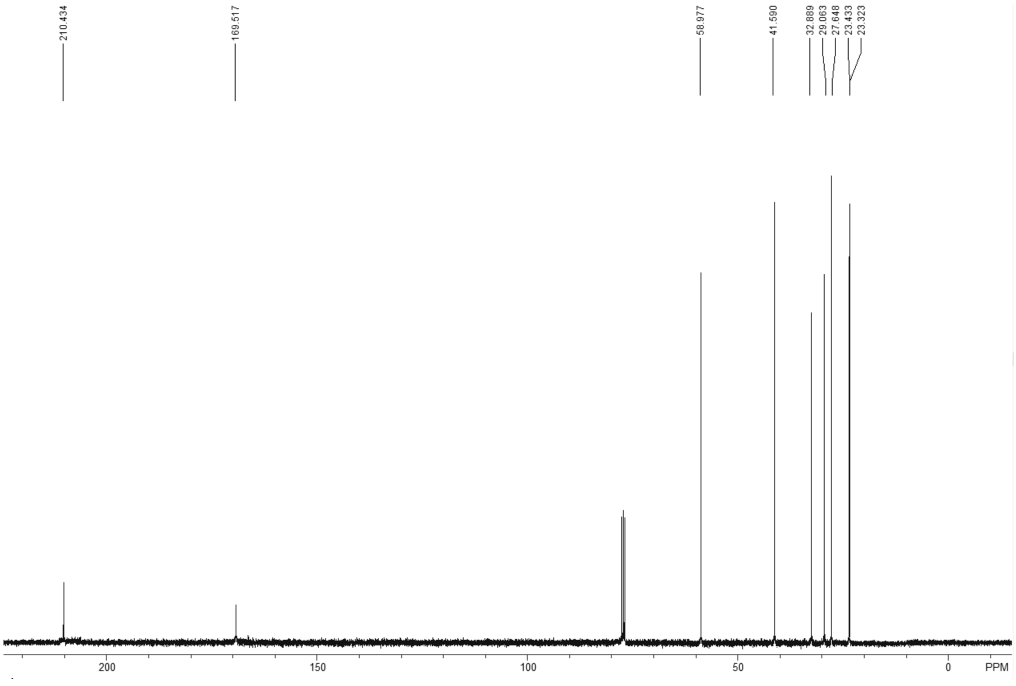

NHCOCH$_3$
O

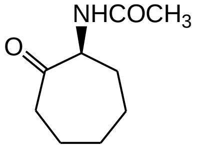
(*S*)-**123**


1.12
1.00
2.38
1.25
5.04
.64
1.28
10
8
6
4
2
0
PPM

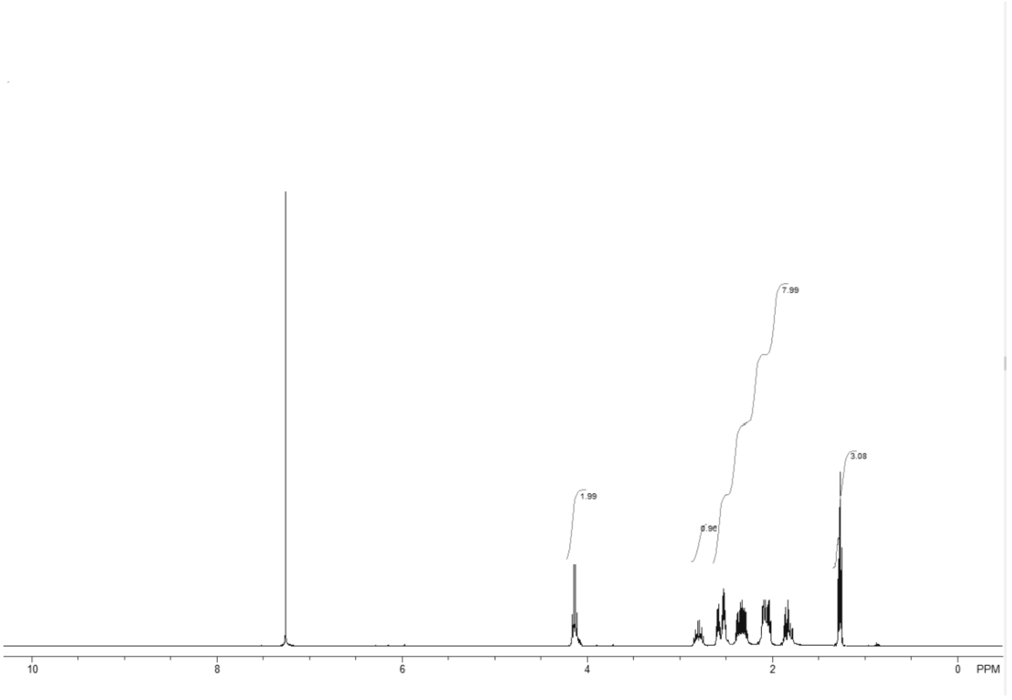

NHCOCH$_3$
O

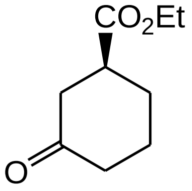
(*S*)-**124**


210.434
169.517
58.977
41.590
32.889
29.063
27.648
23.433
23.323
200
150
100
50
0
PPM

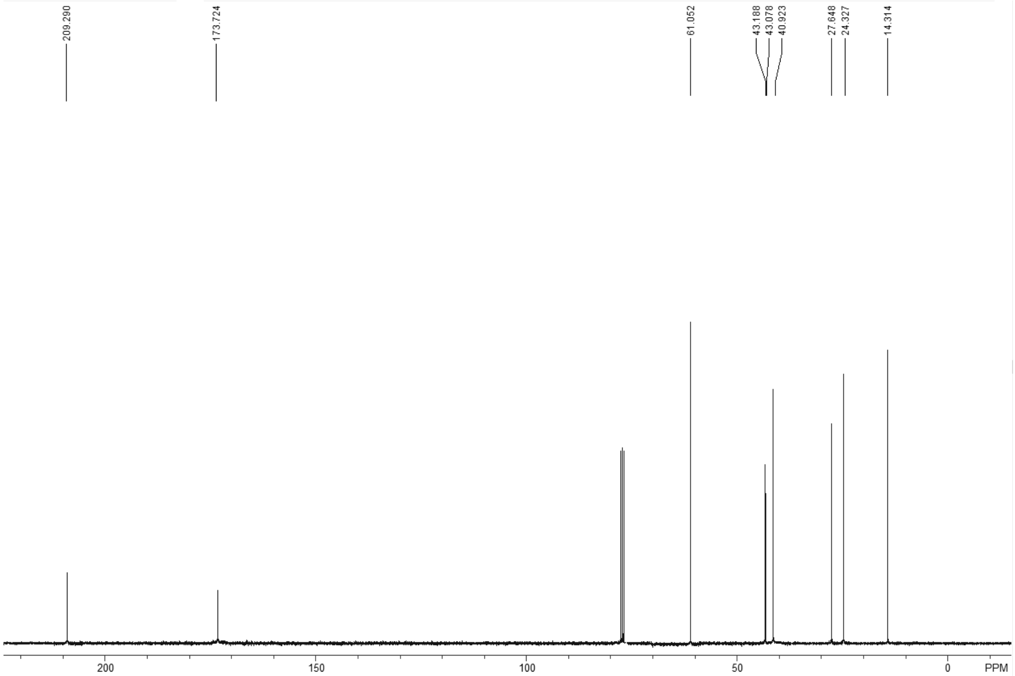

NHCOCH3
O

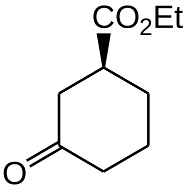
(*S*)-**124**


1.99
0.96
7.99
3.08
10
8
6
4
2
0
PPM

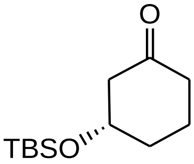

CO2Et
O

(*S*)-**125**

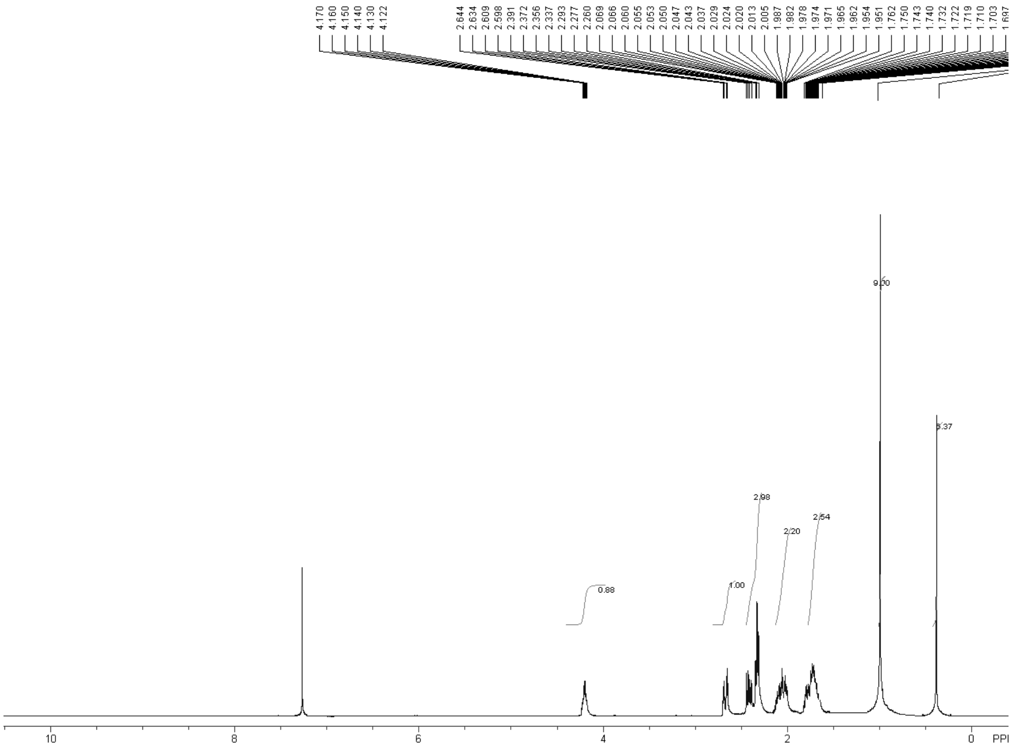

209.290
173.724
61.052
43.188
43.078
40.923
27.648
24.327
14.314
200
150
100
50
0
PPM

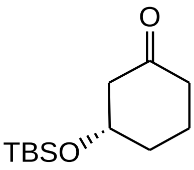

CO$_2$Et
O

(*S*)-**125**

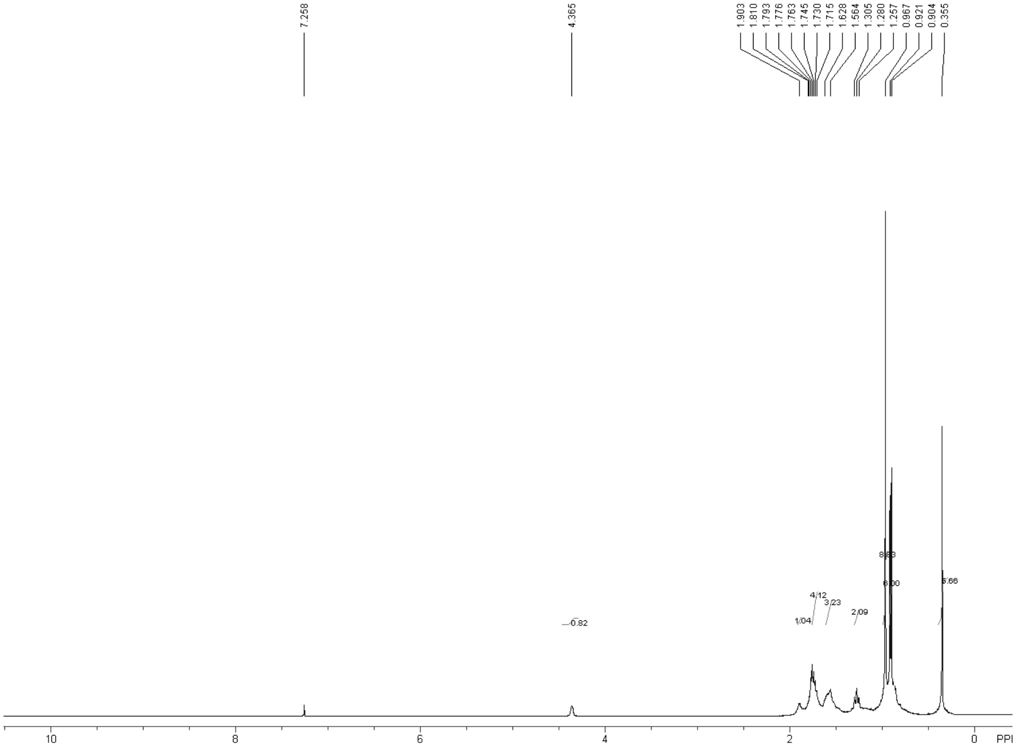

O
TBSO

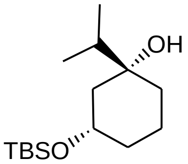
(S)-**126**



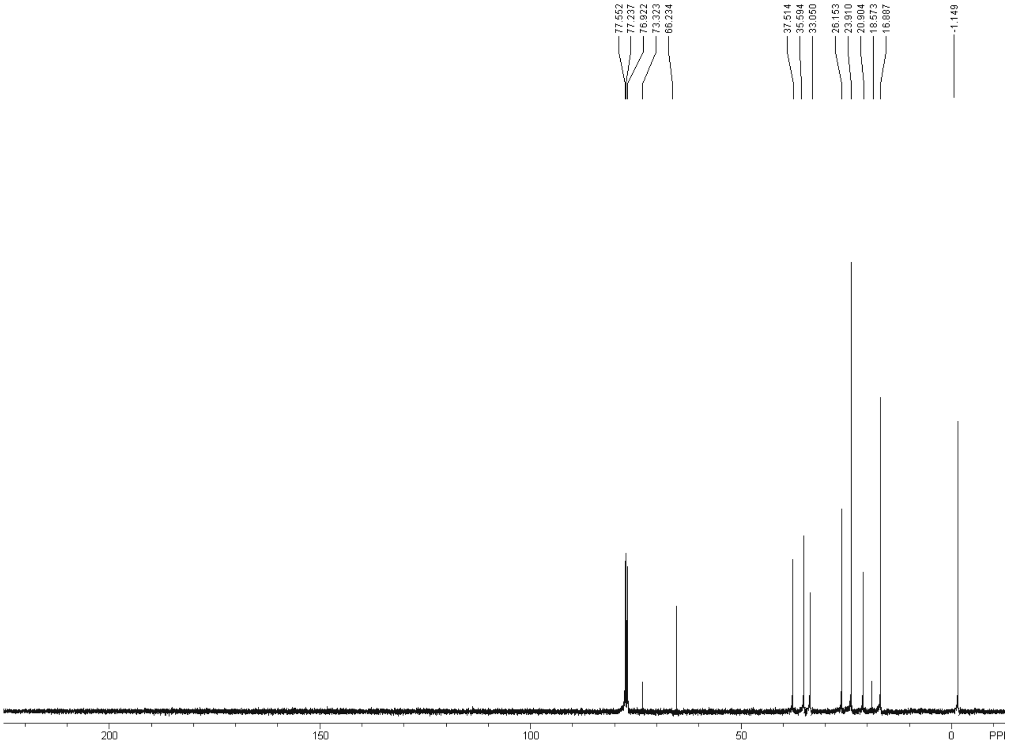


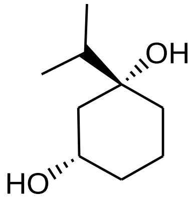
(S)-**126**



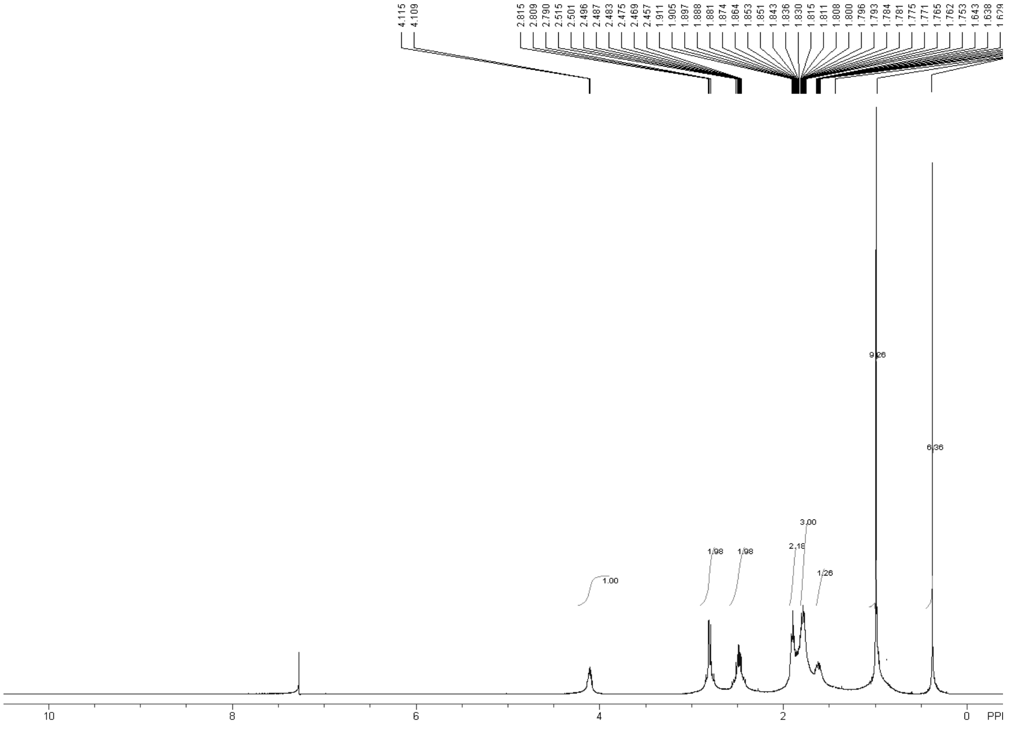


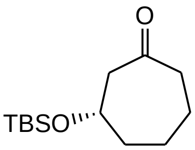
(1*R*,3*S*)-**127**



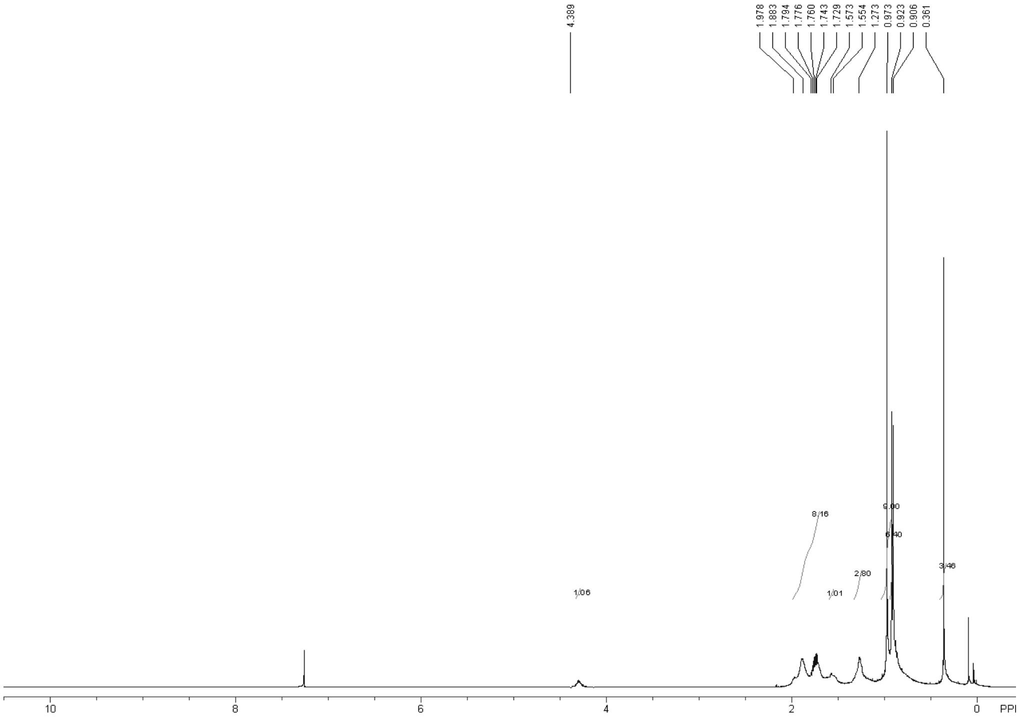


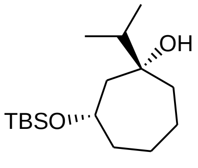
(1*R*,3*S*)-**128**



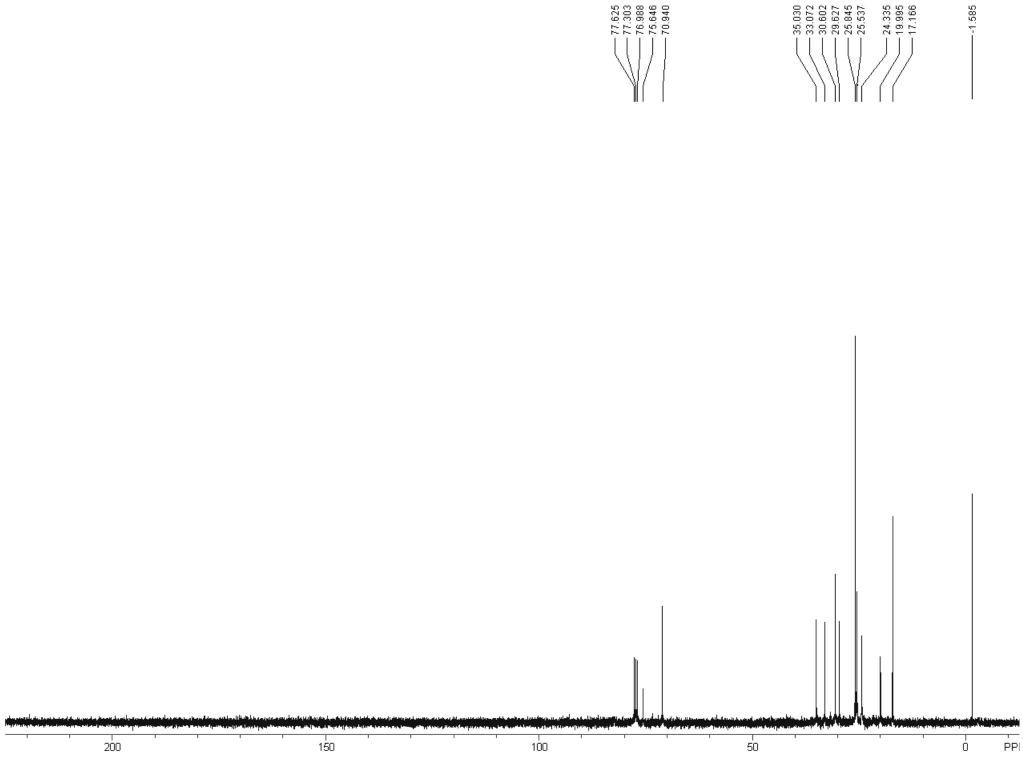


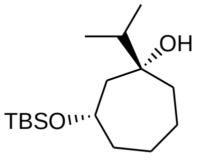
(S)-**129**



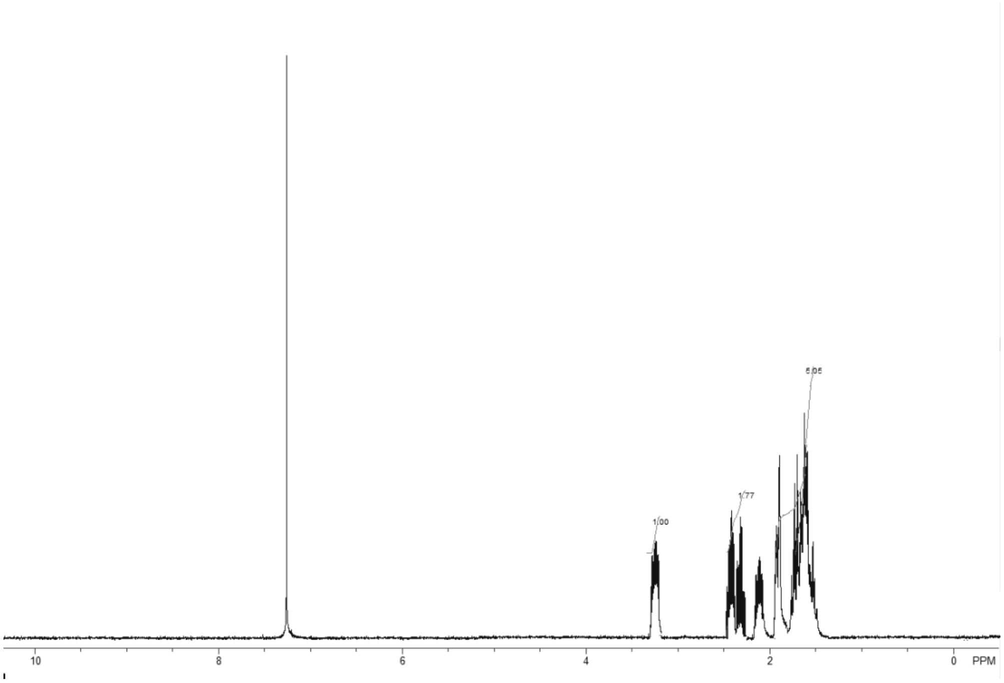


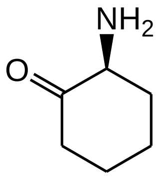
(1*R*,3*S*)-**130**



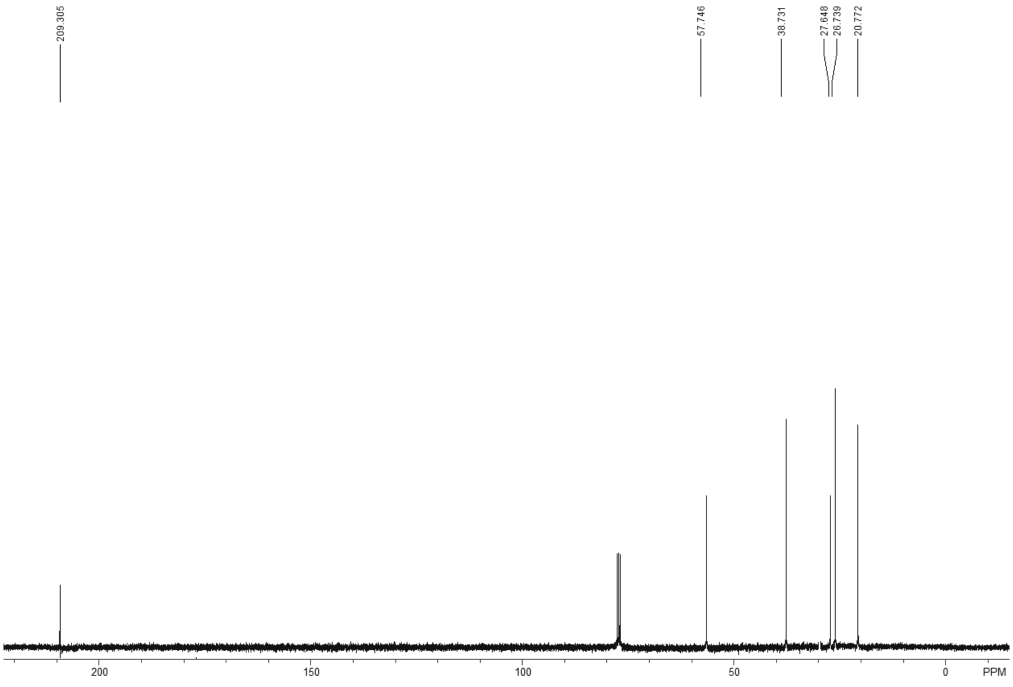


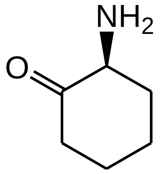
(1*R*,3*S*)-**130**


1.00
1.77
5.05
10
8
6
4
2
0
PPM

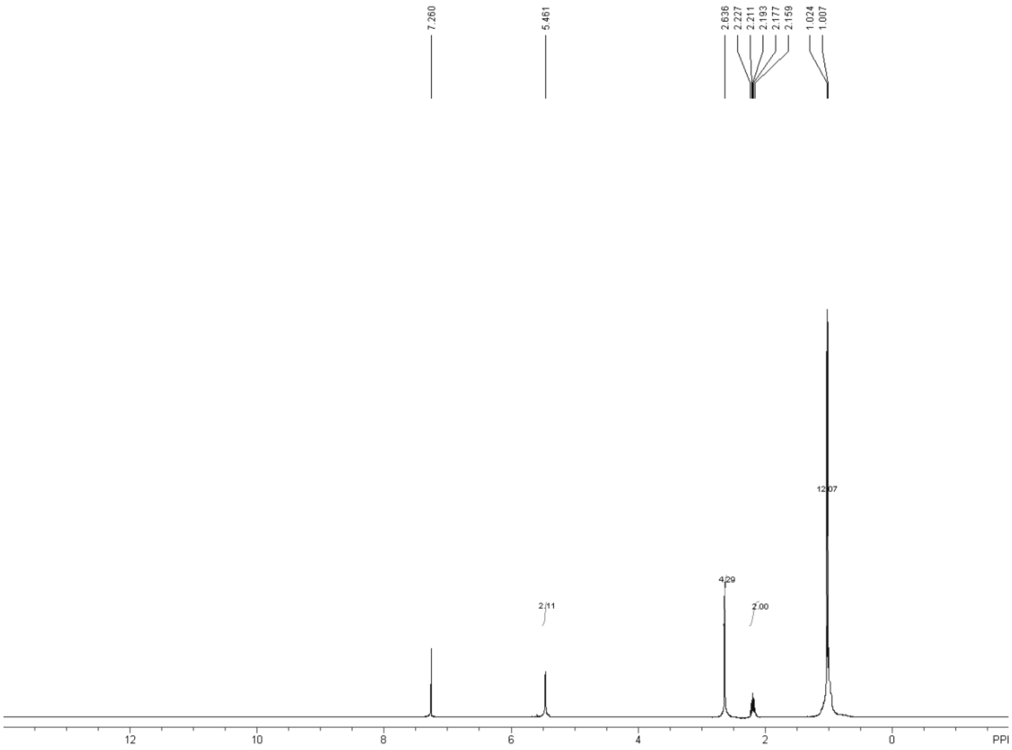

NH2
O

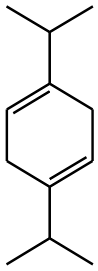
(S)-**132**


209.305
57.746
38.731
27.648
26.739
20.772
200
150
100
50
0
PPM

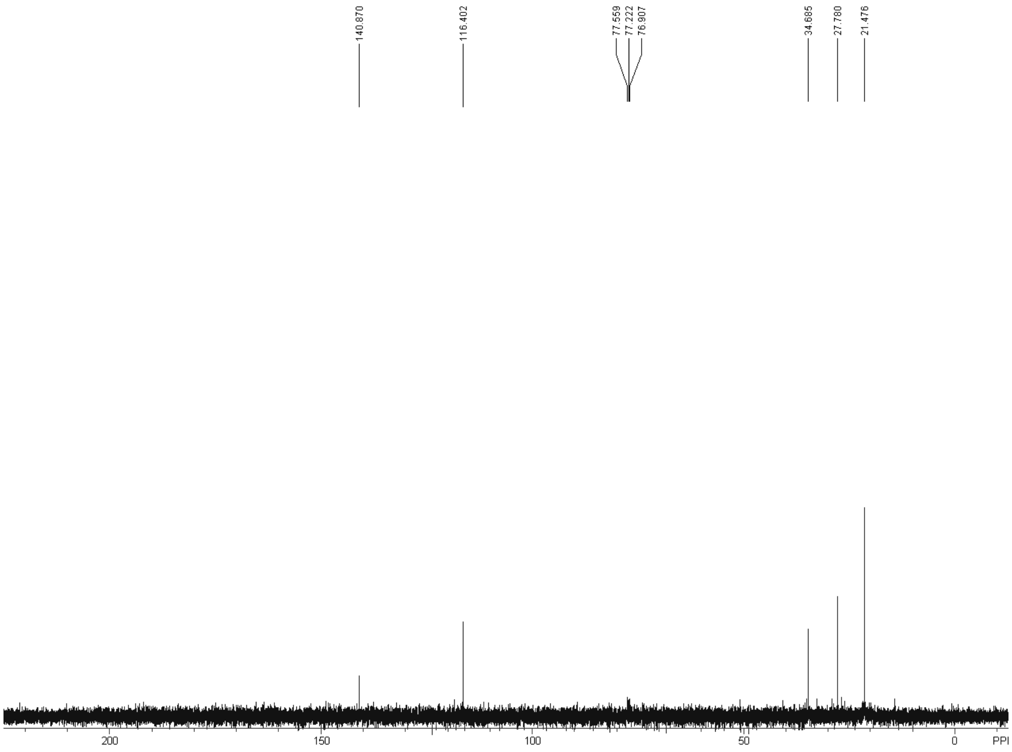

NH2
O

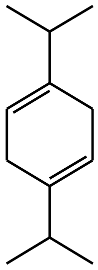
(S)-**132**


7.260
5.461
2.636
2.227
2.211
2.193
2.177
2.159
1.024
1.007
2.11
4.29
2.00
12.07
12
10
8
6
4
2
0
PPI

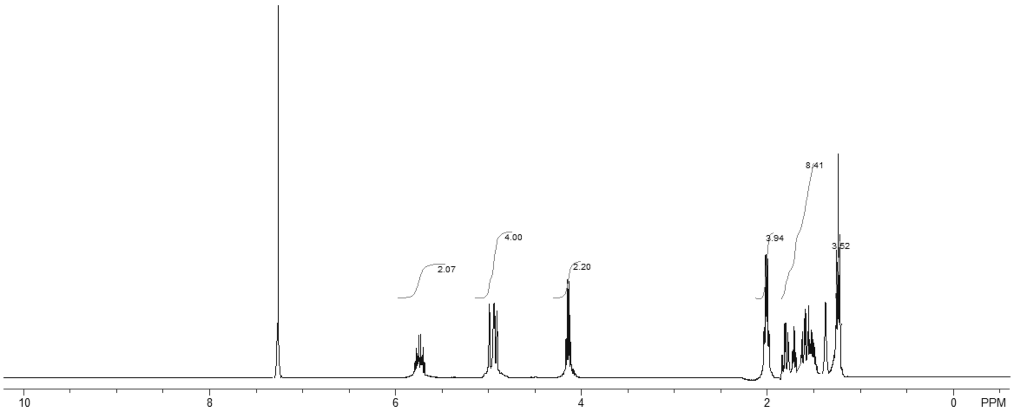


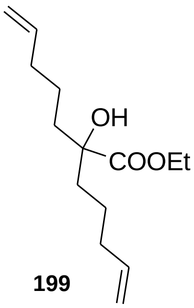
134


140.870
116.402
77.559
77.222
76.907
34.685
27.780
21.476
200
150
100
50
0
PPI

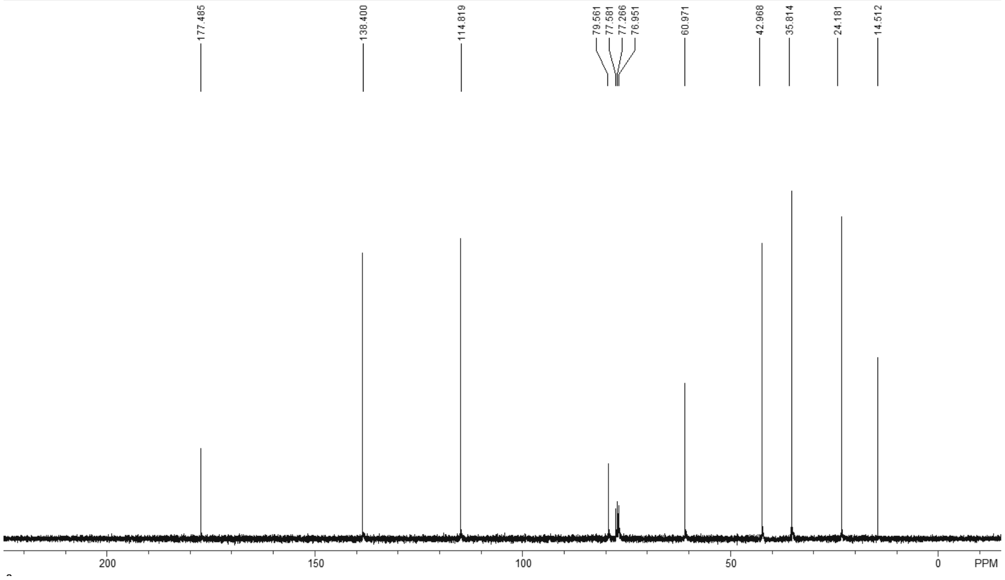


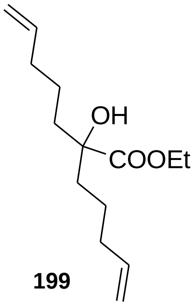
134


2.07
4.00
2.20
3.94
8.41
3.52
10
8
6
4
2
0
PPM

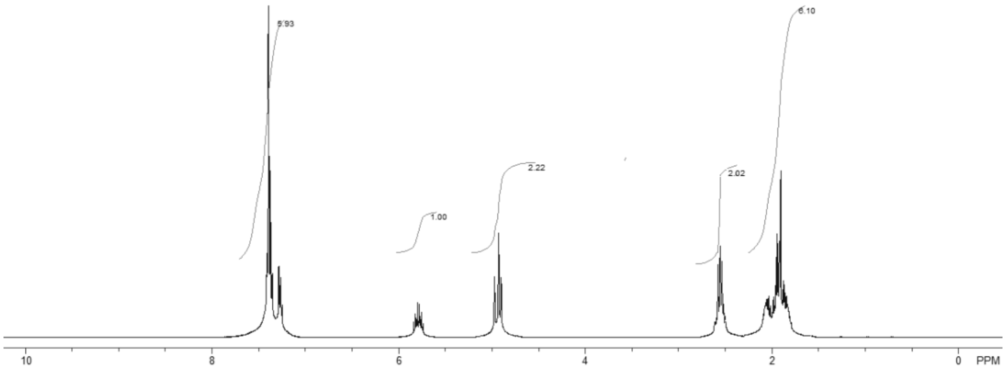

OH
COOEt

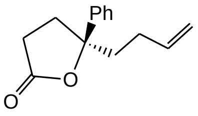
199


177.485
138.400
114.819
79.561
77.581
77.266
76.951
60.971
42.968
35.814
24.181
14.512
200
150
100
50
0
PPM

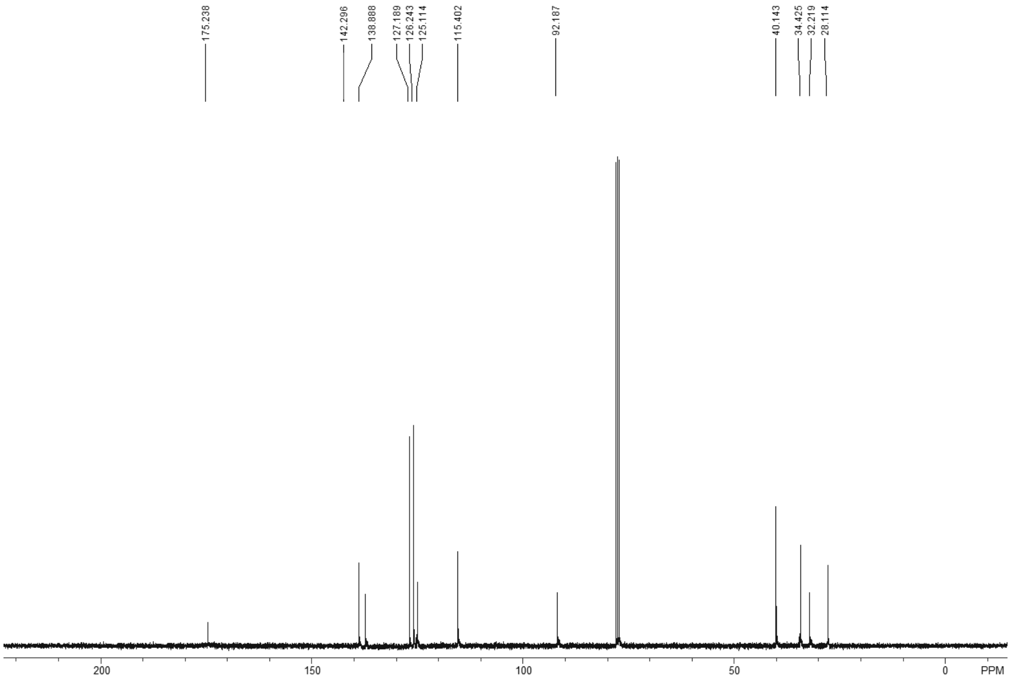

OH
COOEt

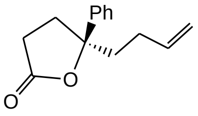
199


5.93
1.00
2.22
2.02
6.10
10
8
6
4
2
0
PPM

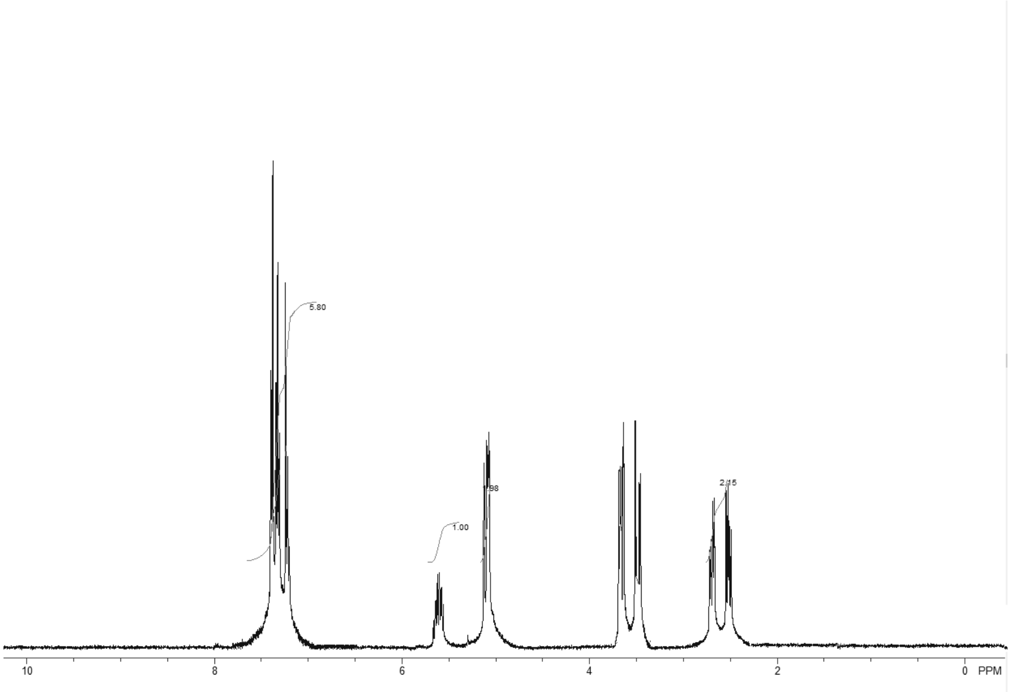

Ph
O
O

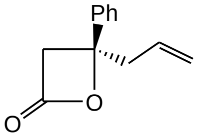
(S)-200


175.238
142.296
138.888
127.189
126.243
125.114
115.402
92.187
40.143
34.425
32.219
28.114
200
150
100
50
0
PPM

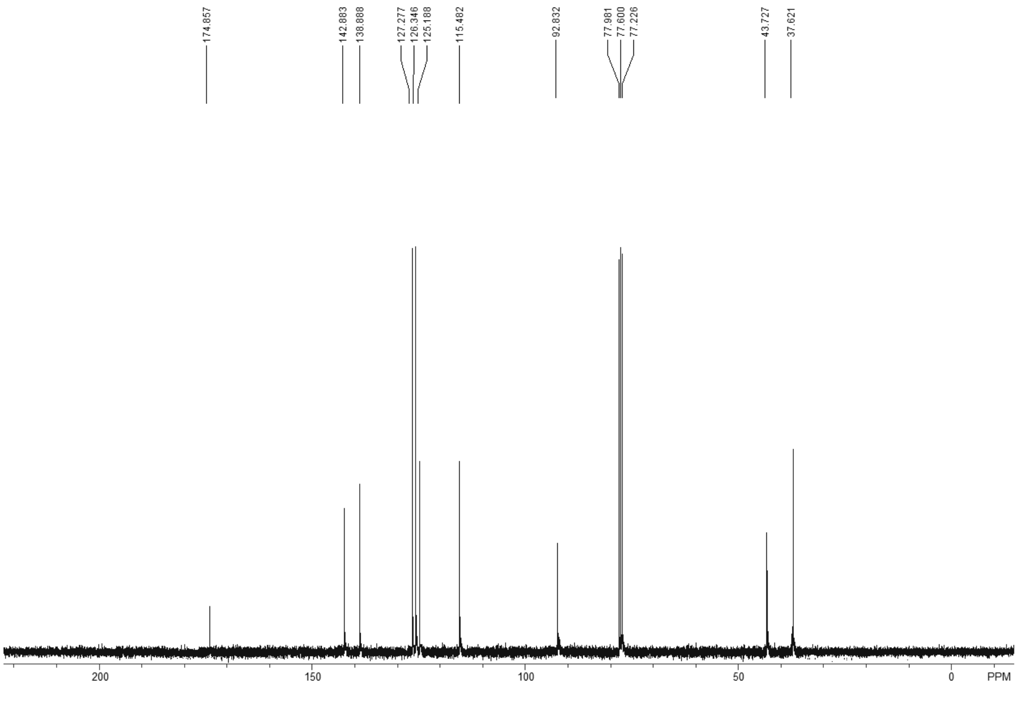

Ph
O
O

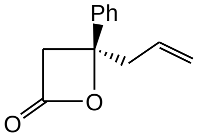
(S)-200


5.80
1.00
1.98
2.15
10
8
6
4
2
0 PPM

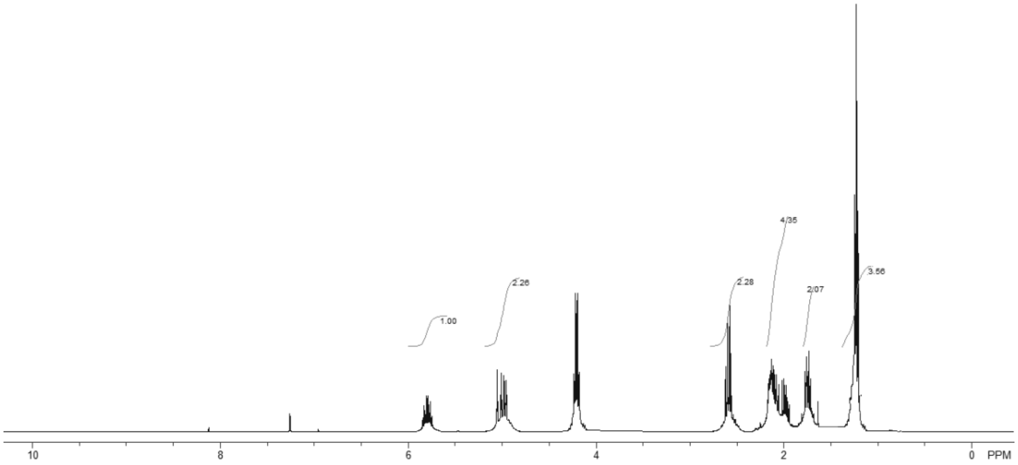


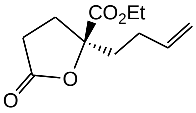
(S)-201


174.857
142.883
138.888
127.277
126.346
125.188
115.482
92.832
77.981
77.600
77.226
43.727
37.621
200
150
100
50
0
PPM

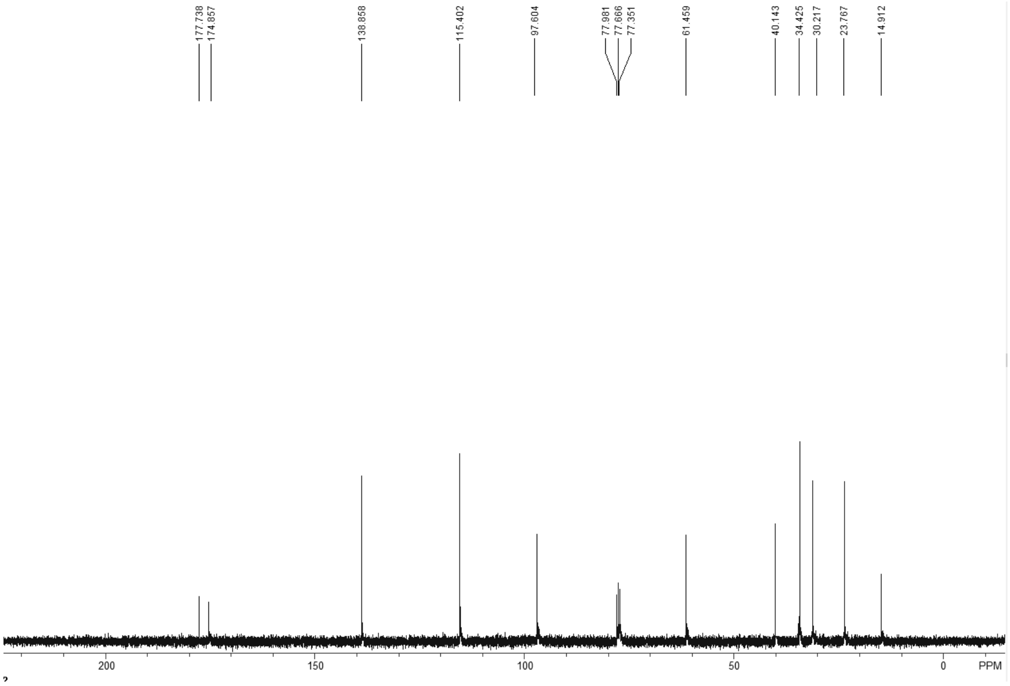


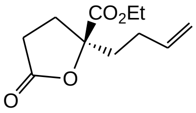
(S)-201


1.00
2.26
2.28
4.35
2.07
3.56
10
8
6
4
2
0
PPM

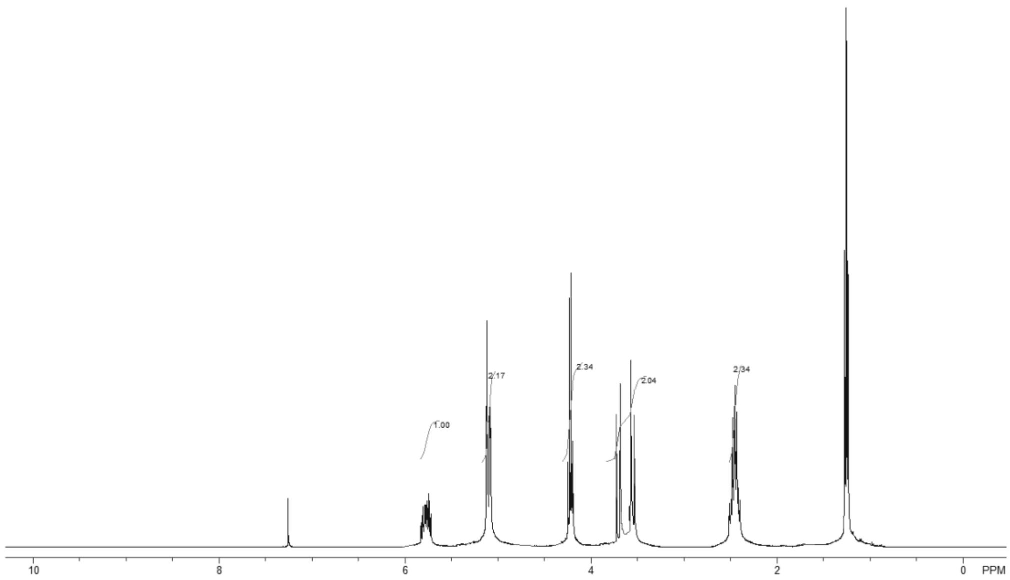


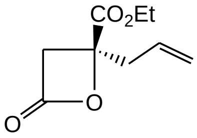
(S)-202


177.738
174.857
138.858
115.402
97.604
77.981
77.666
77.351
61.459
40.143
34.425
30.217
23.767
14.912
200
150
100
50
0
PPM

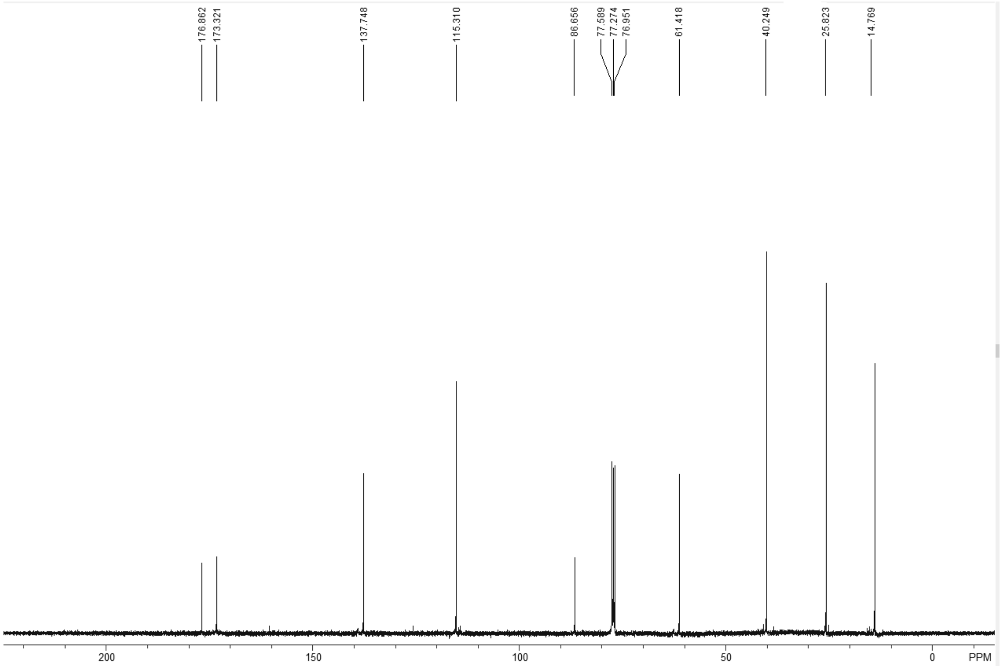


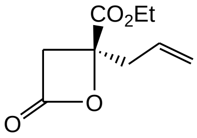
(S)-202


1.00
2.17
2.34
2.04
2.34
10
8
6
4
2
0
PPM

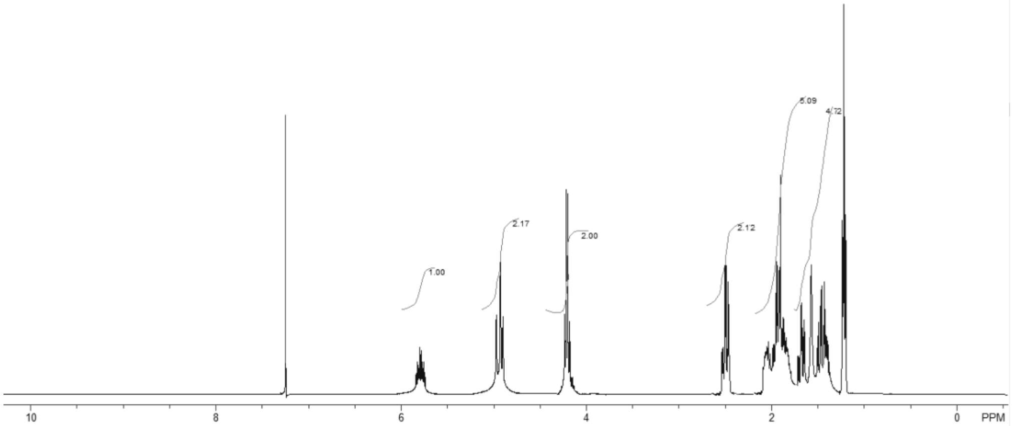

CO2Et
O
O

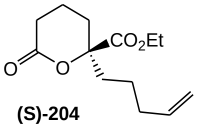
(S)-203


176.862
173.321
137.748
115.310
86.656
77.589
77.274
76.951
61.418
40.249
25.823
14.769
200
150
100
50
0
PPM

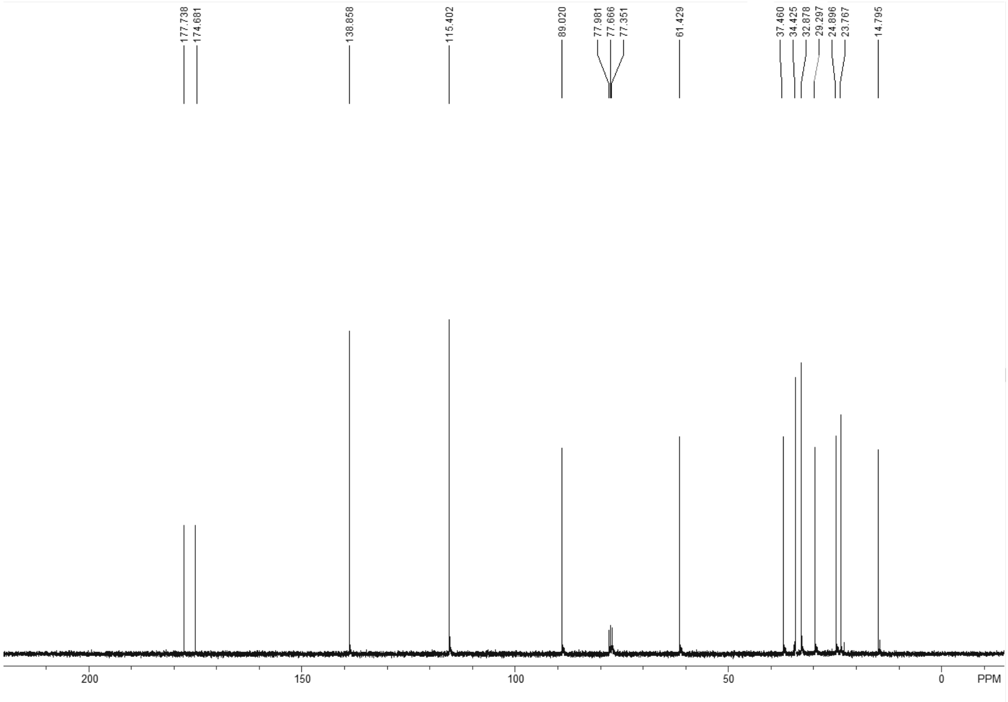

CO2Et
O
O

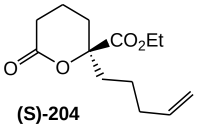
(S)-203


1.00
2.17
2.00
2.12
5.09
4.72
10
8
6
4
2
0
PPM

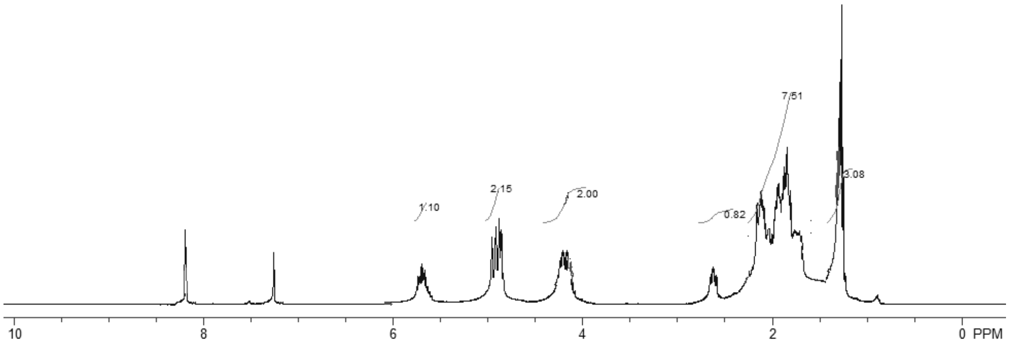

CO$_2$Et
O
O

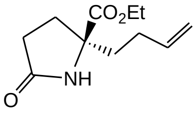
(S)-204


177.738
174.681
138.858
115.402
89.020
77.981
77.666
77.351
61.429
37.460
34.425
32.878
29.297
24.896
23.767
14.795
200
150
100
50
0
PPM

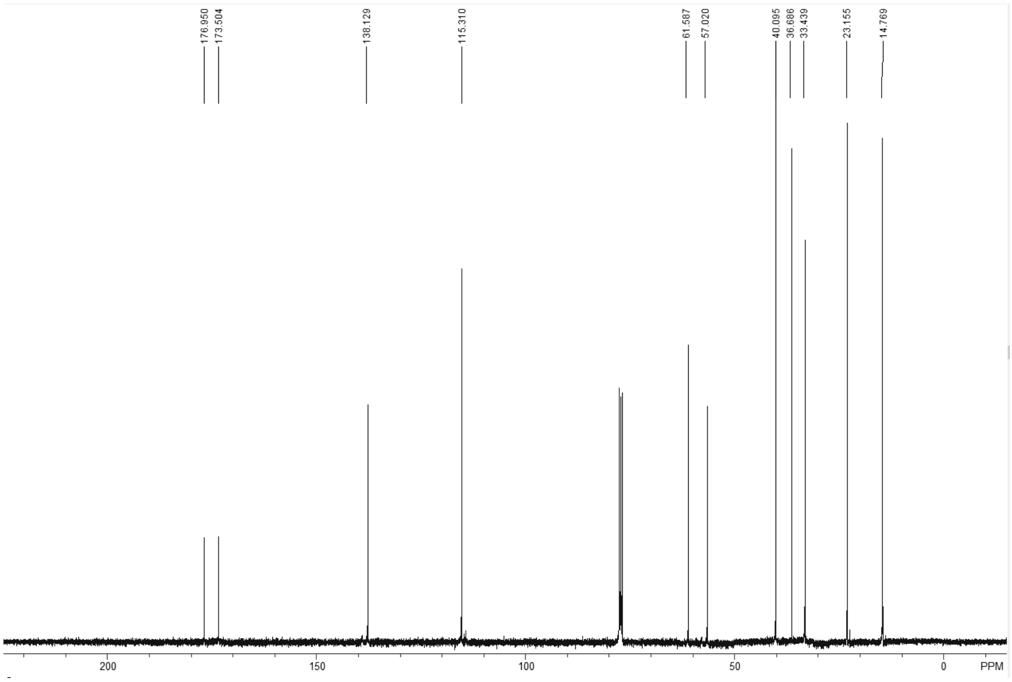

CO$_2$Et
O
O

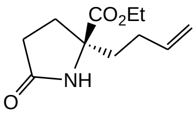
(S)-204


1.10
2.15
2.00
0.82
7.51
3.08
10
8
6
4
2
0 PPM

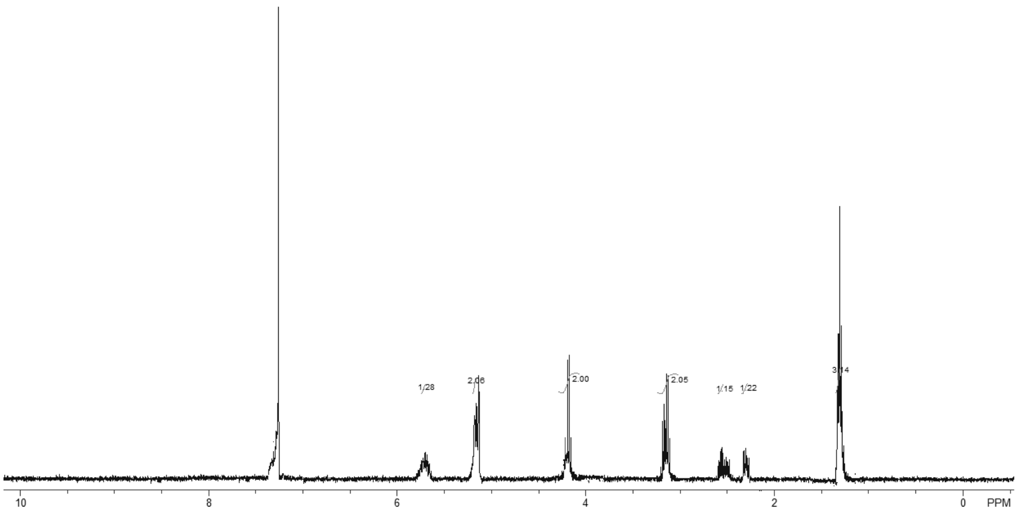

CO$_2$Et
NH
O

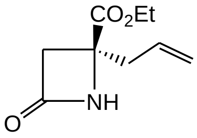
(S)-208


176.950
173.504
138.129
115.310
61.587
57.020
40.095
36.686
33.439
23.155
14.769
200
150
100
50
0
PPM

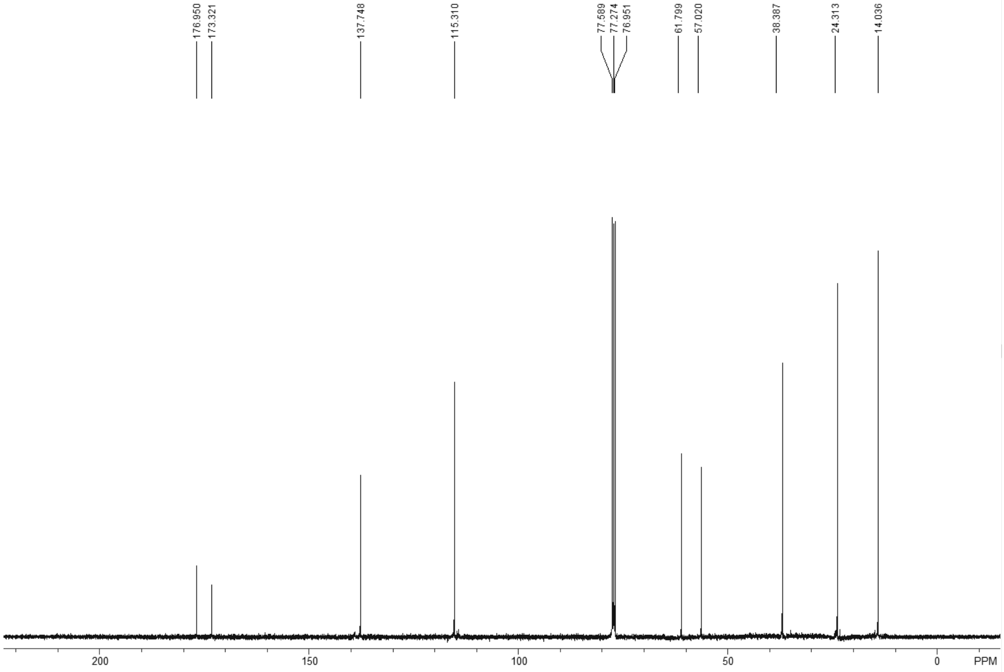

CO$_2$Et
NH
O

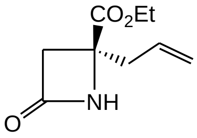
(S)-208


1.28
2.06
2.00
2.05
1.15
1.22
3.14
10
8
6
4
2
0
PPM

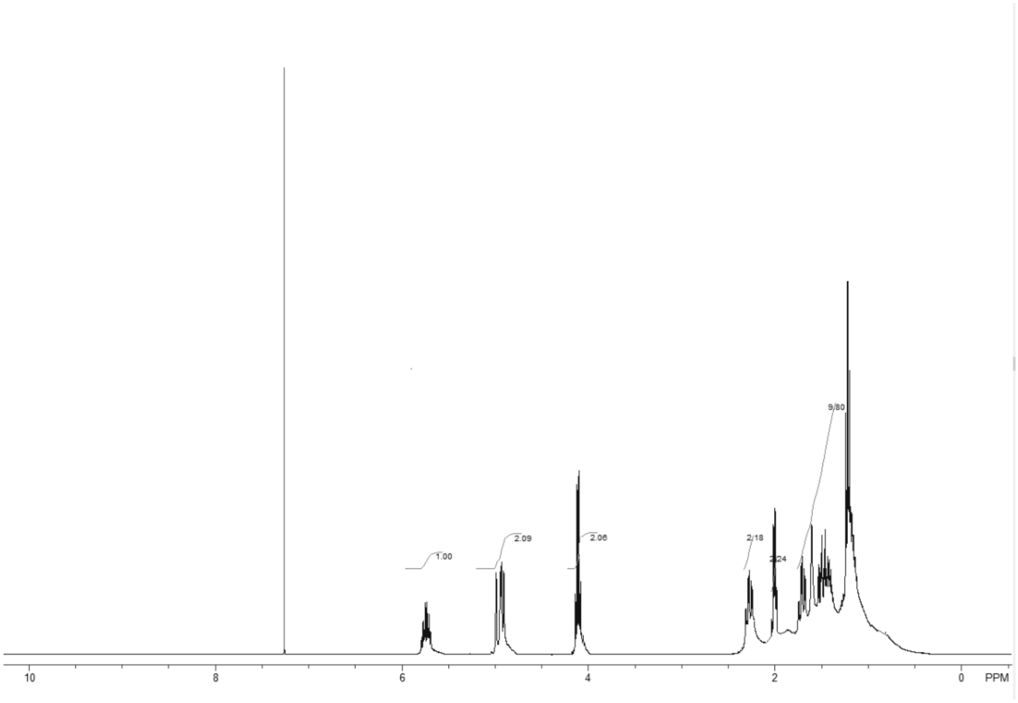

CO2Et
NH
O

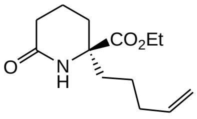
(S)-209


176.950
173.321
137.748
115.310
77.589
77.274
76.951
61.799
57.020
38.387
24.313
14.036
200
150
100
50
0
PPM

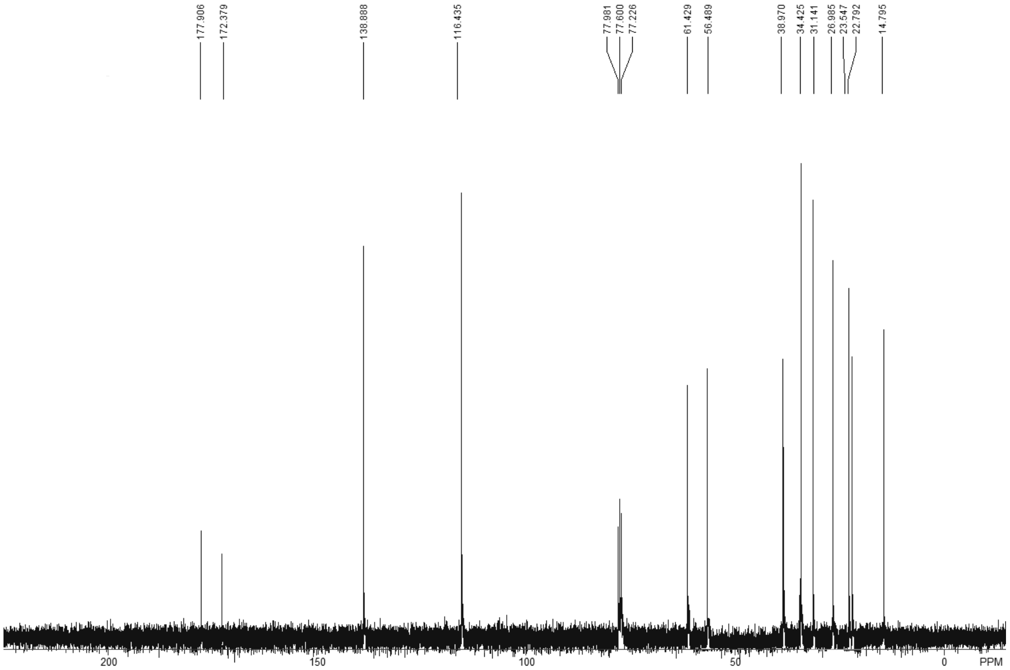

CO2Et
NH
O

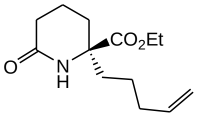
(S)-209


1.00
2.09
2.06
2.18
2.24
9.80
10
8
6
4
2
0
PPM

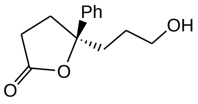

CO2Et
O
N
H

(S)-210

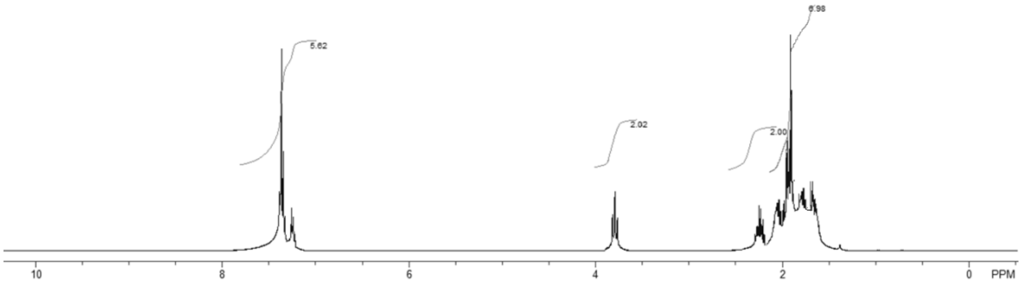

177.906
172.379
138.888
116.435
77.981
77.600
77.226
61.429
56.489
38.970
34.425
31.141
26.985
23.547
22.792
14.795
200
150
100
50
0
PPM

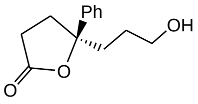

CO2Et
O
N
H

(S)-210

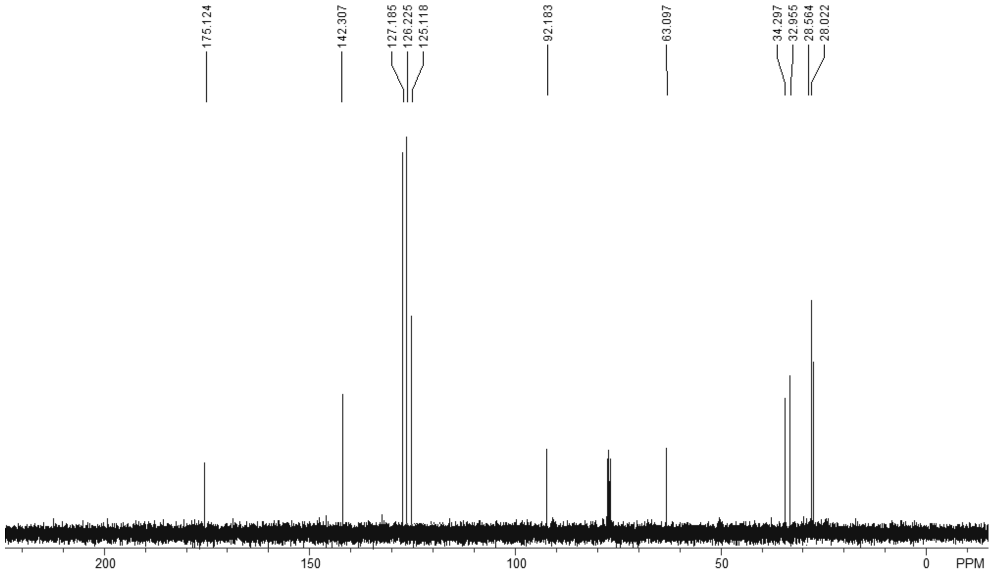

Ph
OH
O
O

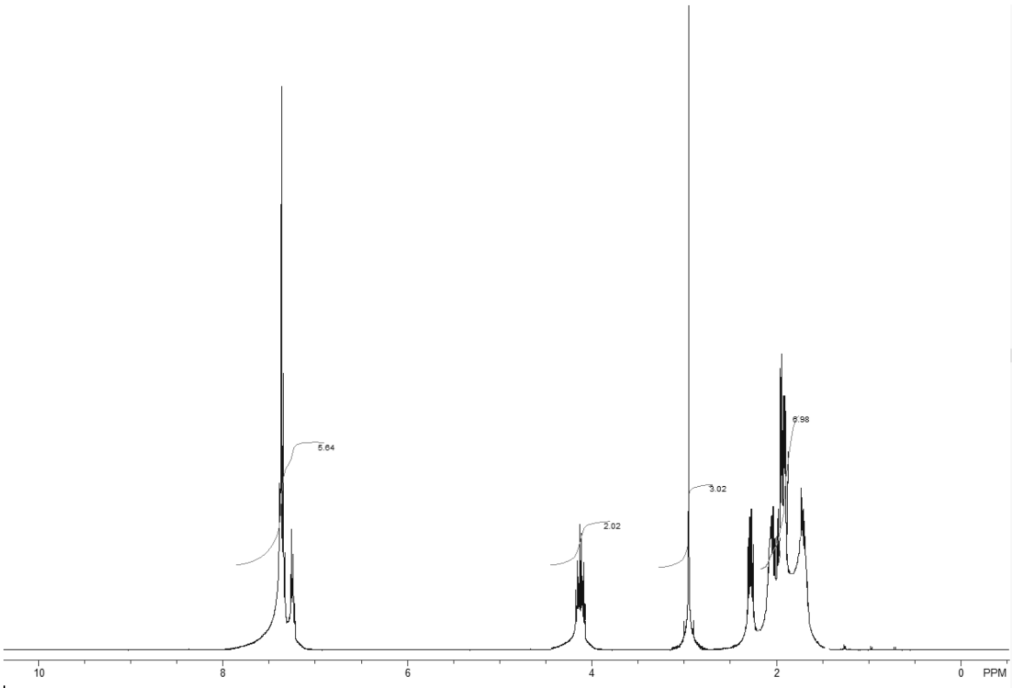
(S)-211

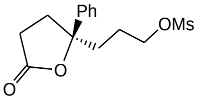

5.62
2.02
2.00
6.98
10
8
6
4
2
0
PPM


Ph
OH
O
O

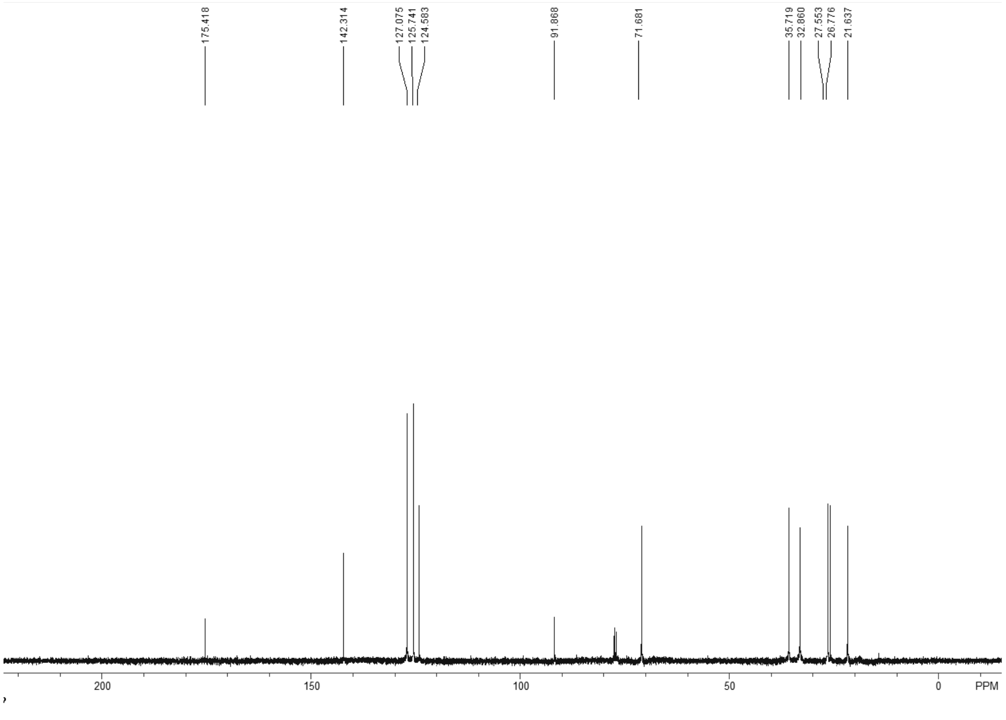
(S)-211

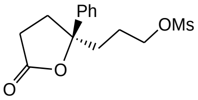

175.124
142.307
127.185
126.225
125.118
92.183
63.097
34.297
32.955
28.564
28.022
200
150
100
50
0
PPM


5.64
2.02
3.02
6.98
10
8
6
4
2
0
PPM

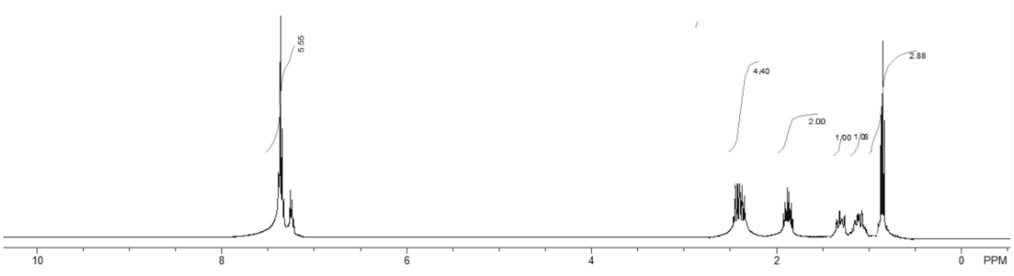

Ph
OMs
O
O

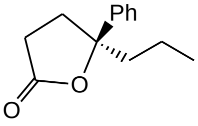
(*S*)-212


175.418
142.314
127.075
125.741
124.583
91.868
71.681
35.719
32.860
27.553
26.776
21.637
200
150
100
50
0
PPM

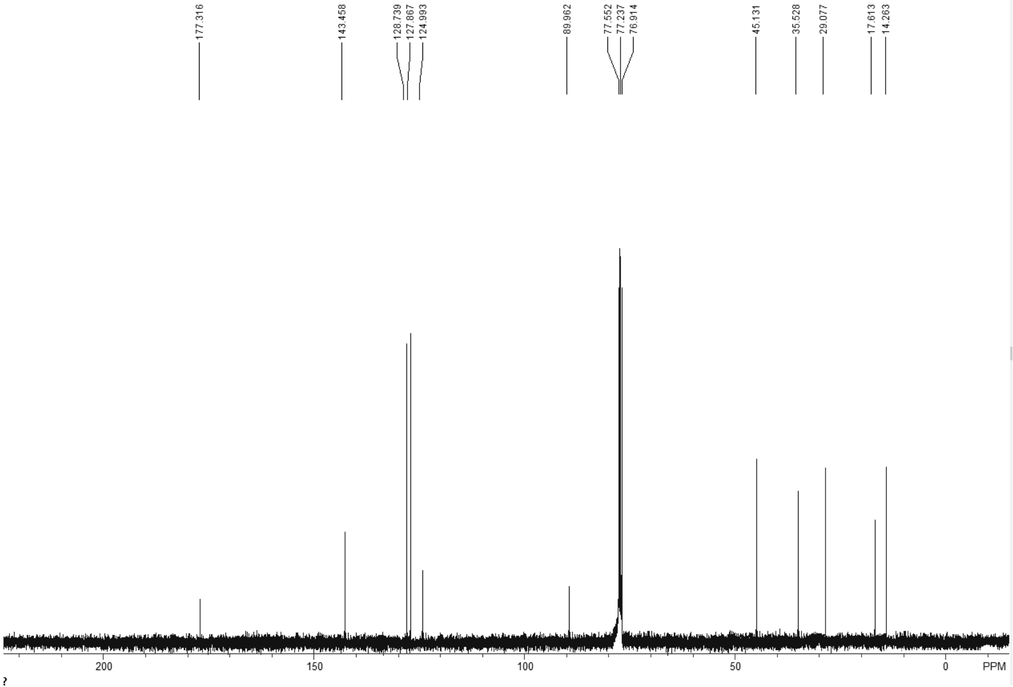

Ph
OMs
O
O

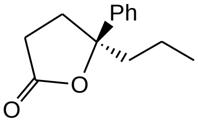
(*S*)-212


5.55
4.40
2.00
1.00
1.08
2.88
10
8
6
4
2
0
PPM

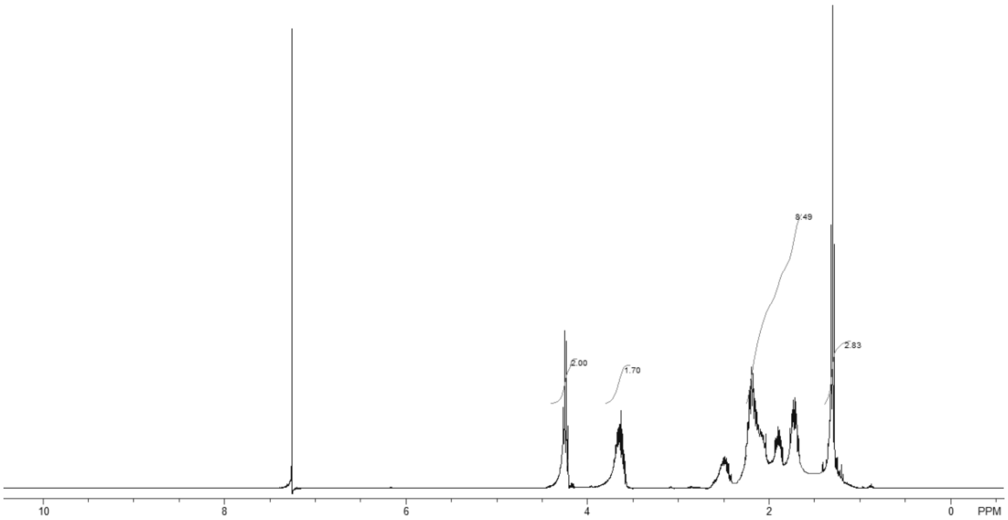

Ph
O
O

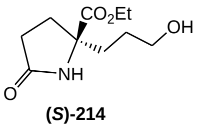
(*S*)-213


177.316
143.458
128.739
127.867
124.993
89.962
77.552
77.237
76.914
45.131
35.528
29.077
17.613
14.263
200
150
100
50
0
PPM

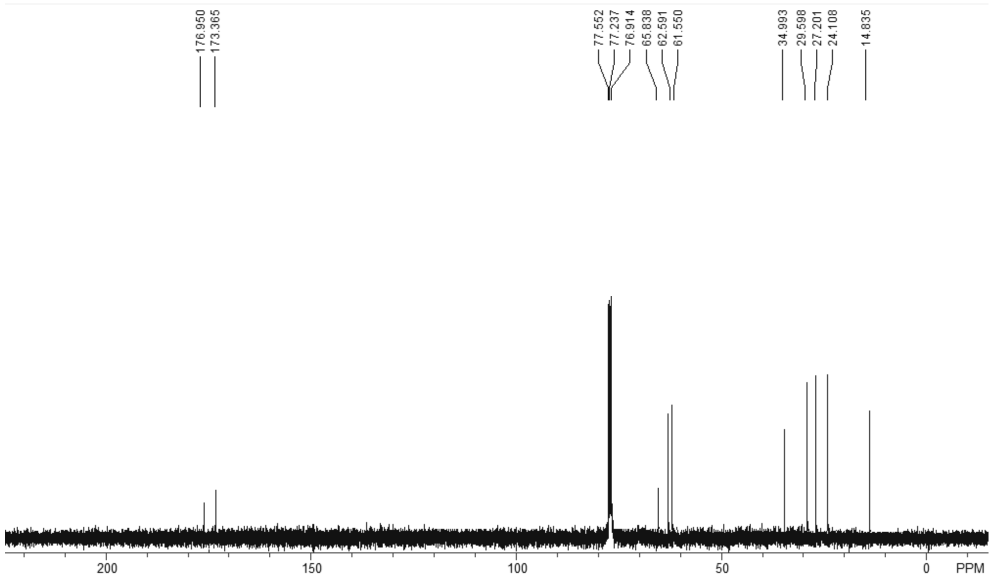

Ph
O
O

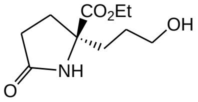
(*S*)-213


2.00
1.70
8.49
2.83
10
8
6
4
2
0
PPM

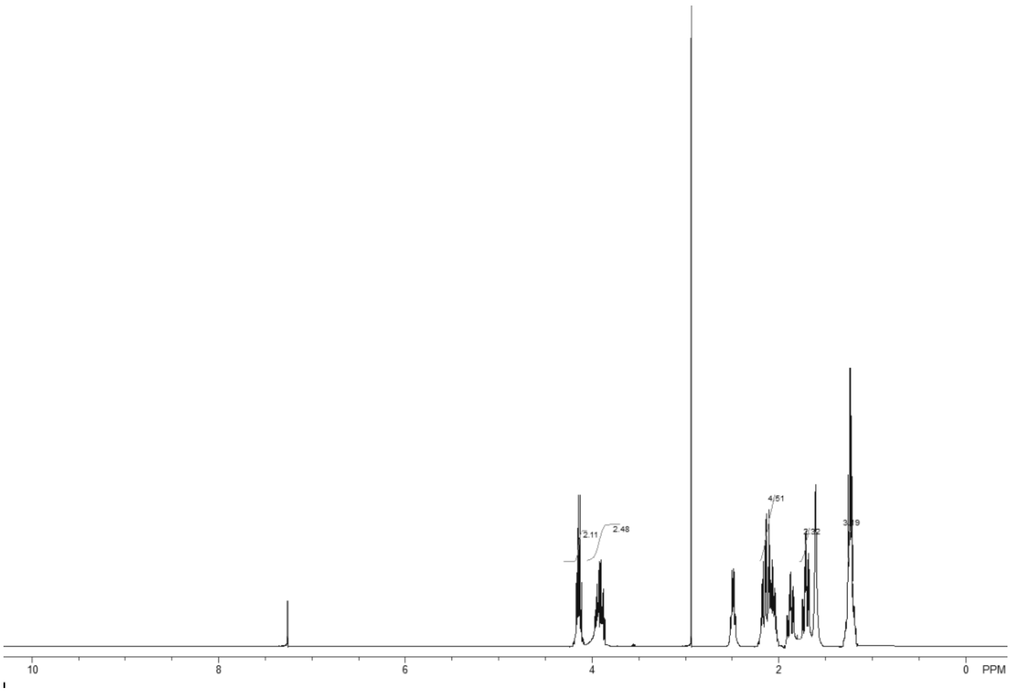

CO2Et
OH
NH
O

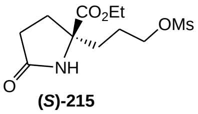
(*S*)-214


176.950
173.365
77.552
77.237
76.914
65.838
62.591
61.550
34.993
29.598
27.201
24.108
14.835
200
150
100
50
0
PPM

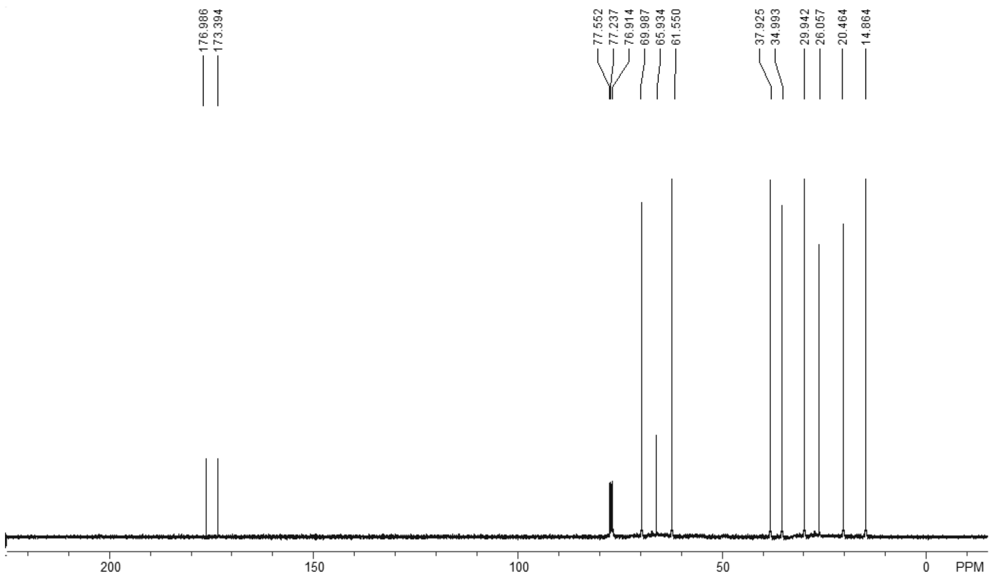

CO2Et
OH
NH
O

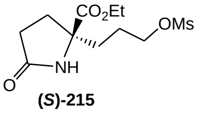
(*S*)-214


2.11
2.48
4.51
2.32
3.39
10
8
6
4
2
0
PPM

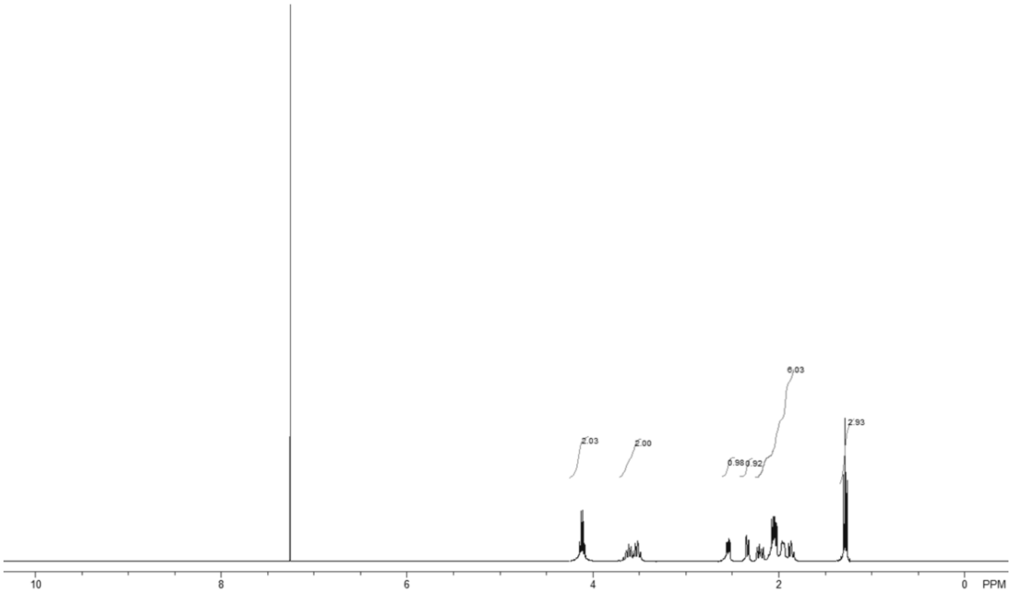

CO_2Et
OMs
NH
O

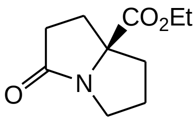
(*S*)-215


176.986
173.394
77.552
77.237
76.914
69.987
65.934
61.550
37.925
34.993
29.942
26.057
20.464
14.864
200
150
100
50
0
PPM

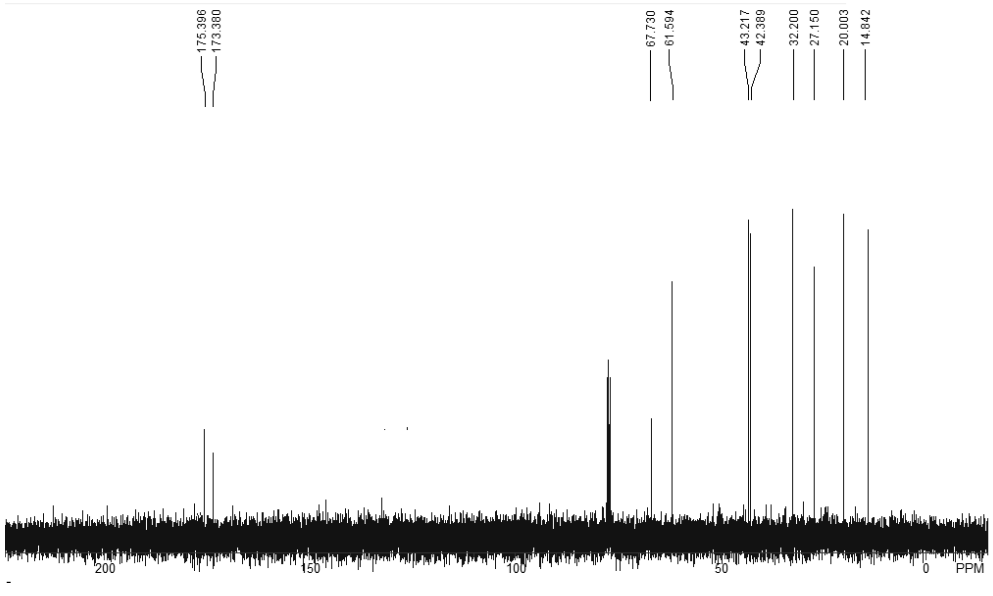

CO_2Et
OMs
NH
O

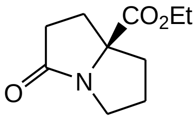
(*S*)-215


2.03
2.00
0.98
0.92
6.03
2.93
10
8
6
4
2
0
PPM

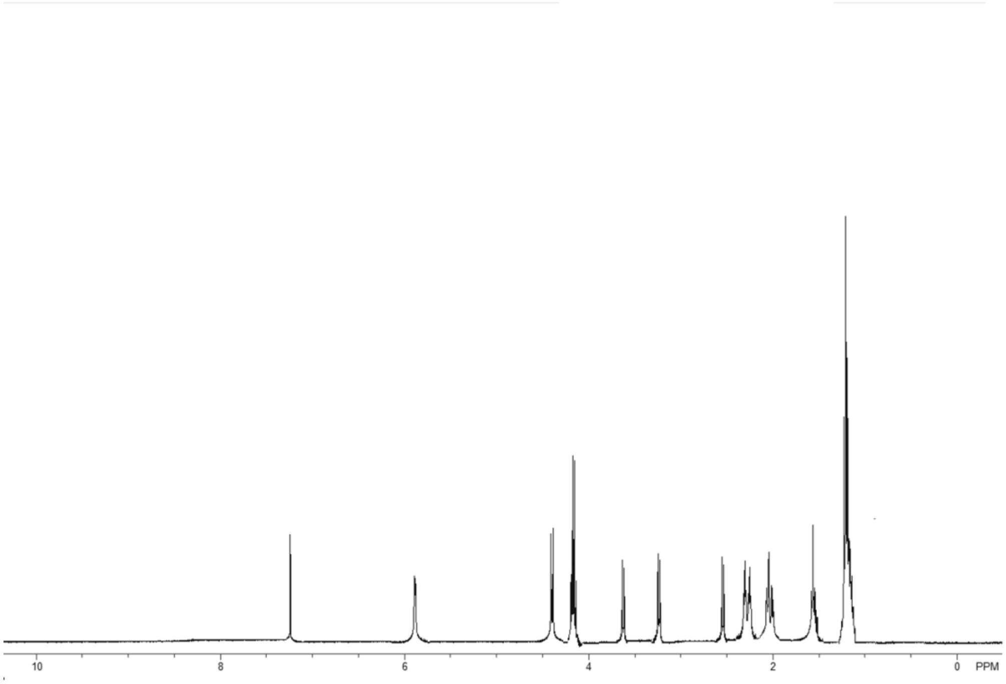

CO$_2$Et
O
N

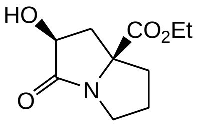
(*S*)-216


175.396
173.380
67.730
61.594
43.217
42.389
32.200
27.150
20.003
14.842
200
150
100
50
0
PPM

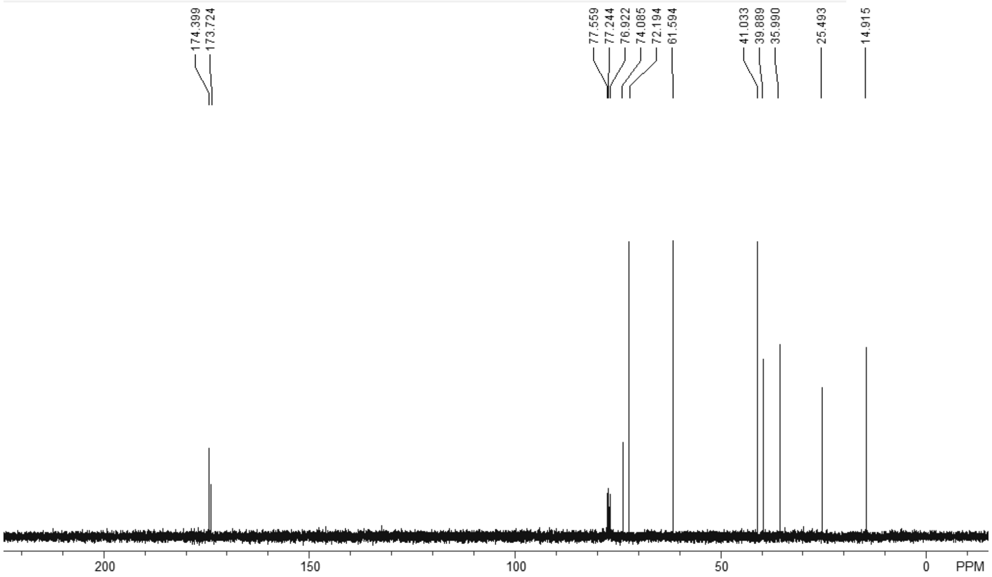

CO$_2$Et
O
N

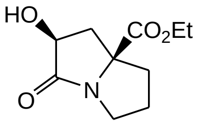
(*S*)-216



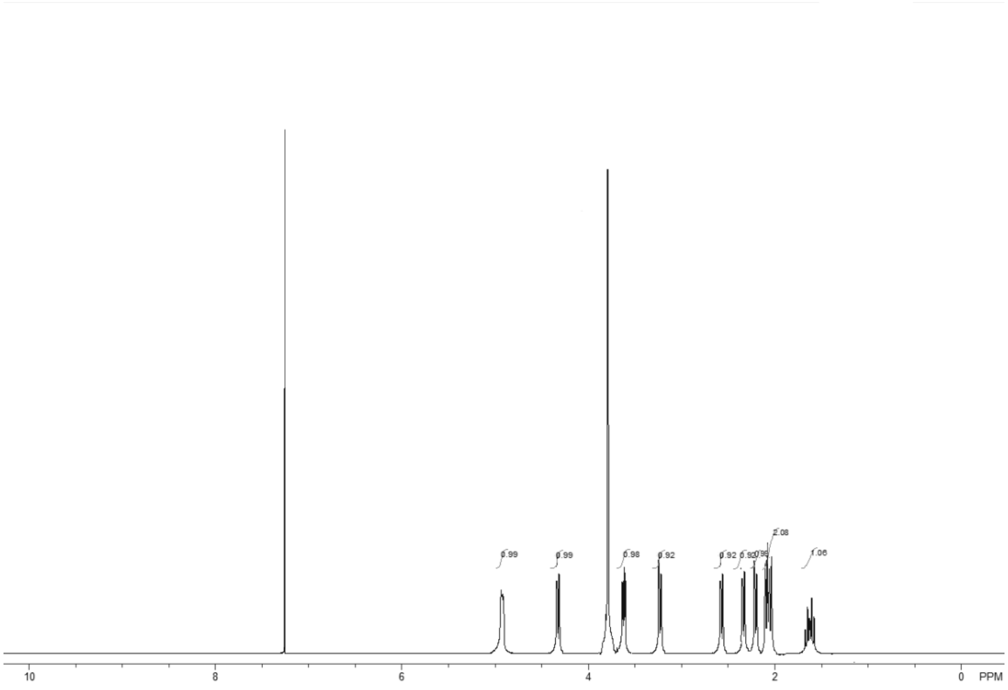


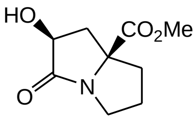
(2*S*,7a*S*)-217



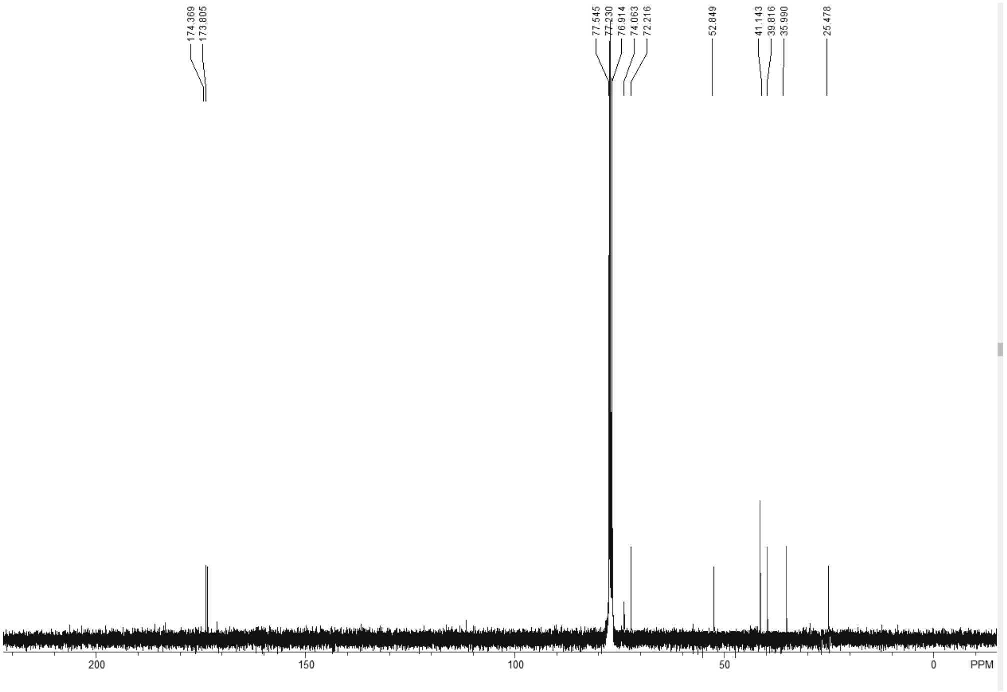


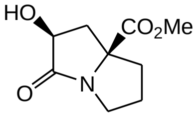
(2*S*,7a*S*)-217



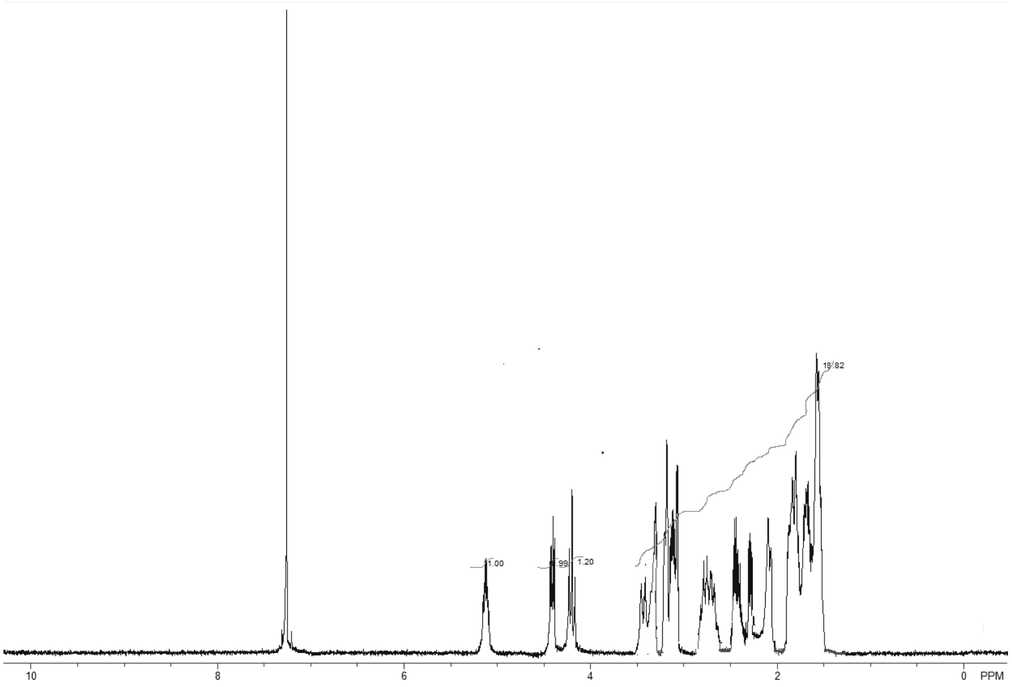


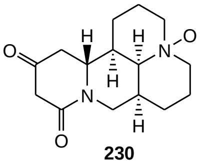
(2*S*,7a*S*)-218



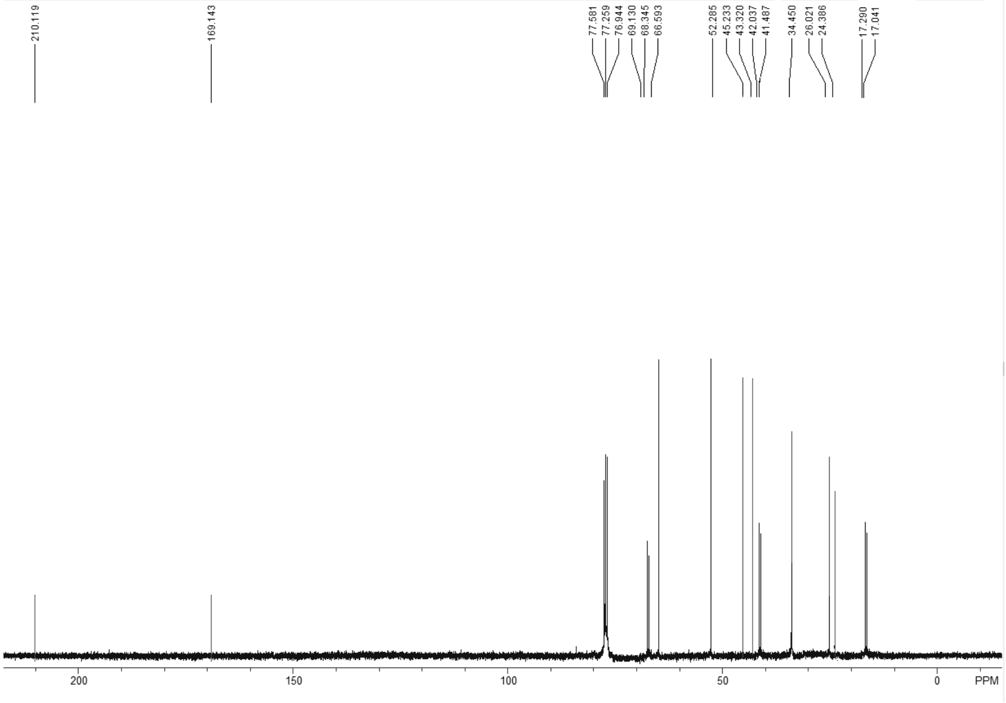


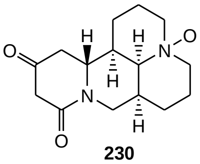
(2*S*,7a*S*)-218


1.00
1.99
1.20
19.82
10
8
6
4
2
0
PPM

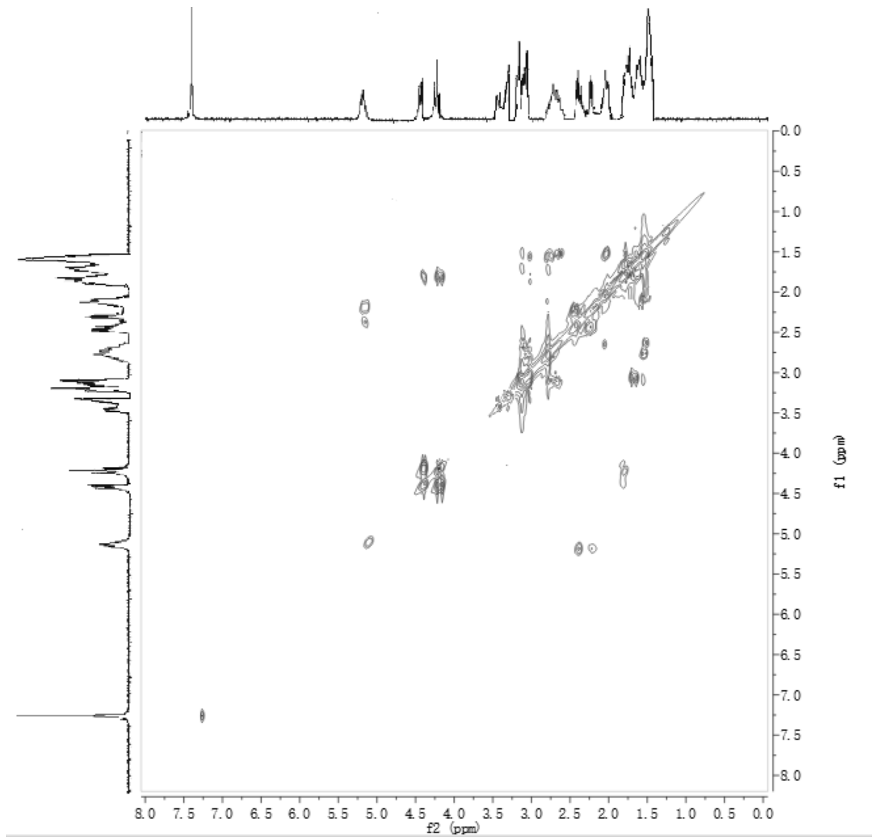

O
H
H
N
O
H
N
H
O

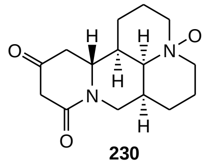
230


210.119
169.143
77.581
77.259
76.944
69.130
68.345
66.593
52.285
45.233
43.320
42.037
41.487
34.450
26.021
24.386
17.290
17.041
200
150
100
50
0
PPM

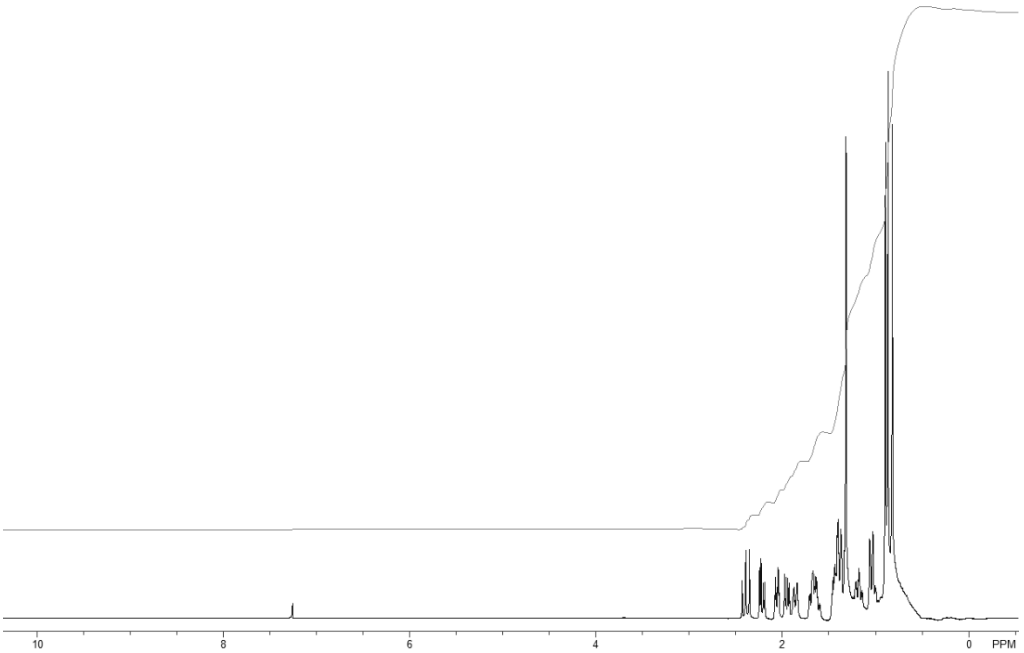

O
H
H
N
O
H
N
H
O

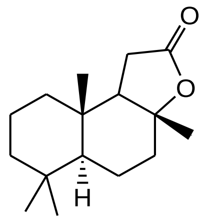
230


8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0
f1 (ppm)

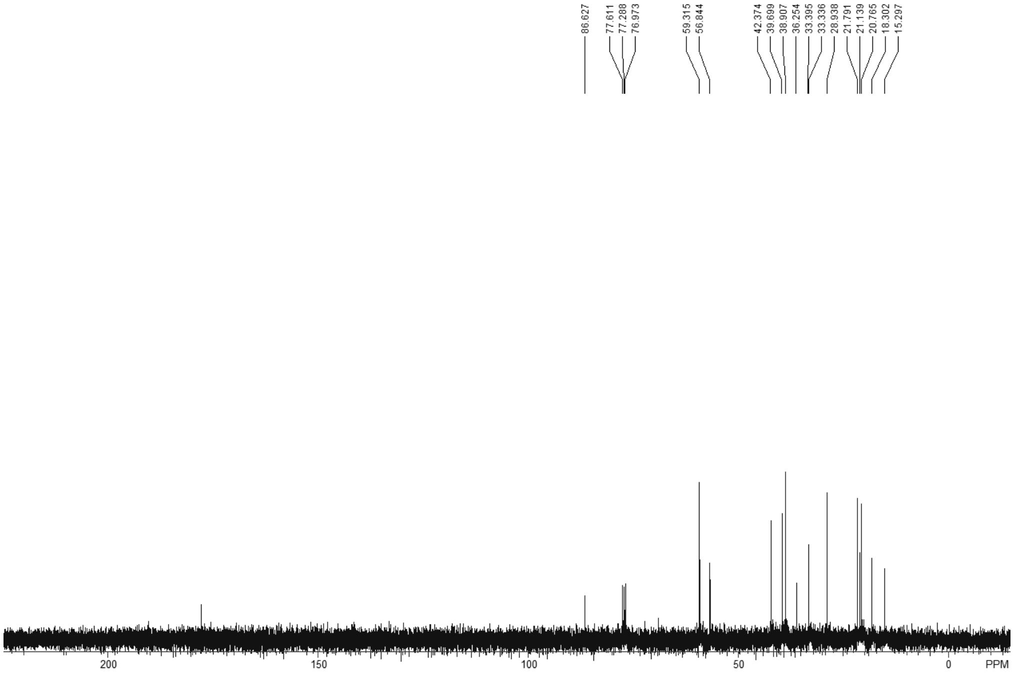

O
H
H
H
N
O
N
O
H

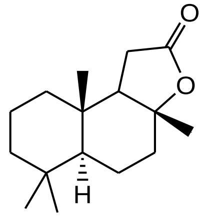
230


10
8
6
4
2
0
PPM

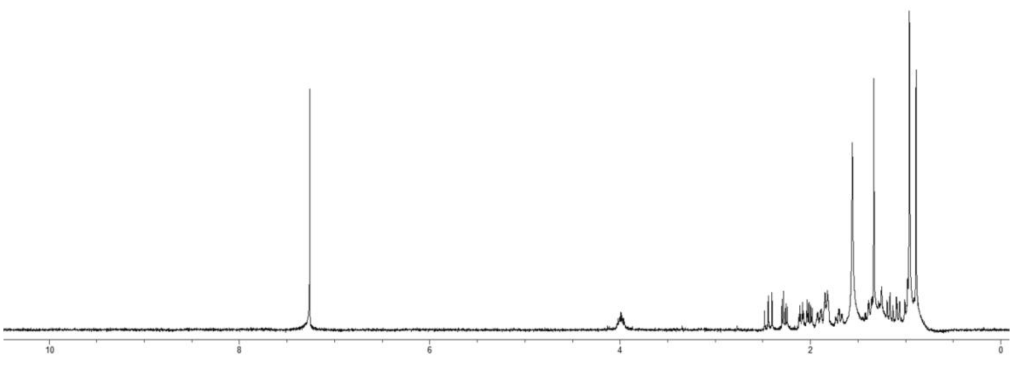

O
O
H

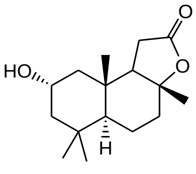
232


86.627
77.611
77.288
76.973
59.315
56.844
42.374
39.699
38.907
36.254
33.395
33.336
28.938
21.791
21.139
20.765
18.302
15.297
200
150
100
50
0
PPM

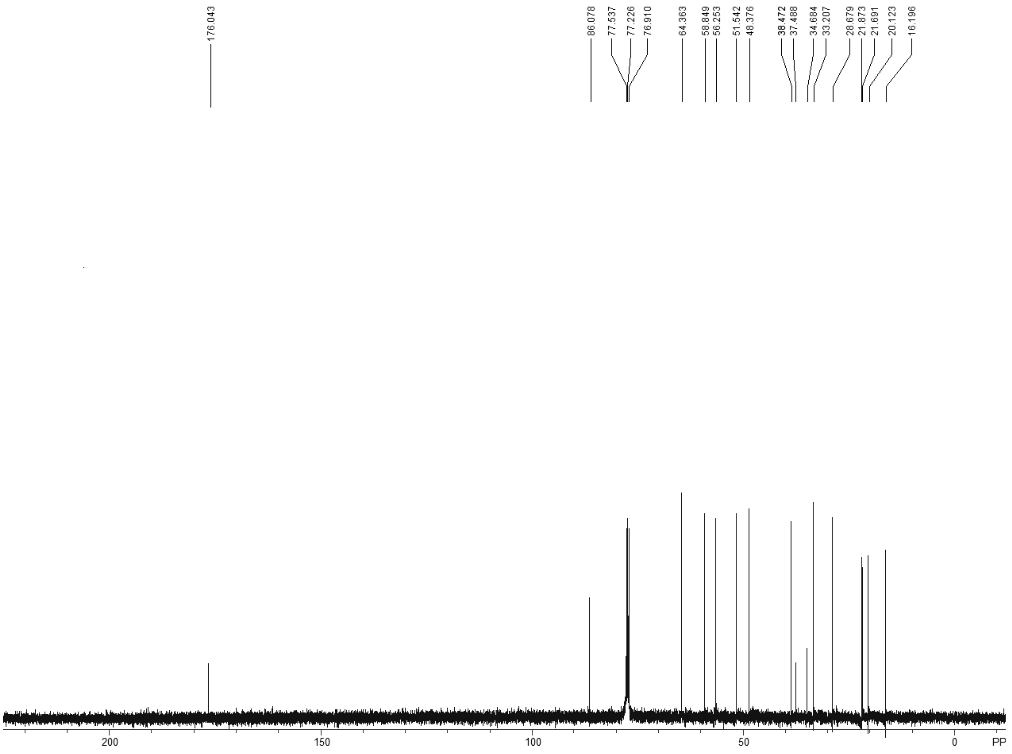

O
O
H

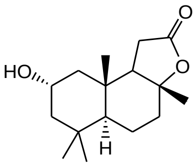
232


10
8
6
4
2
0

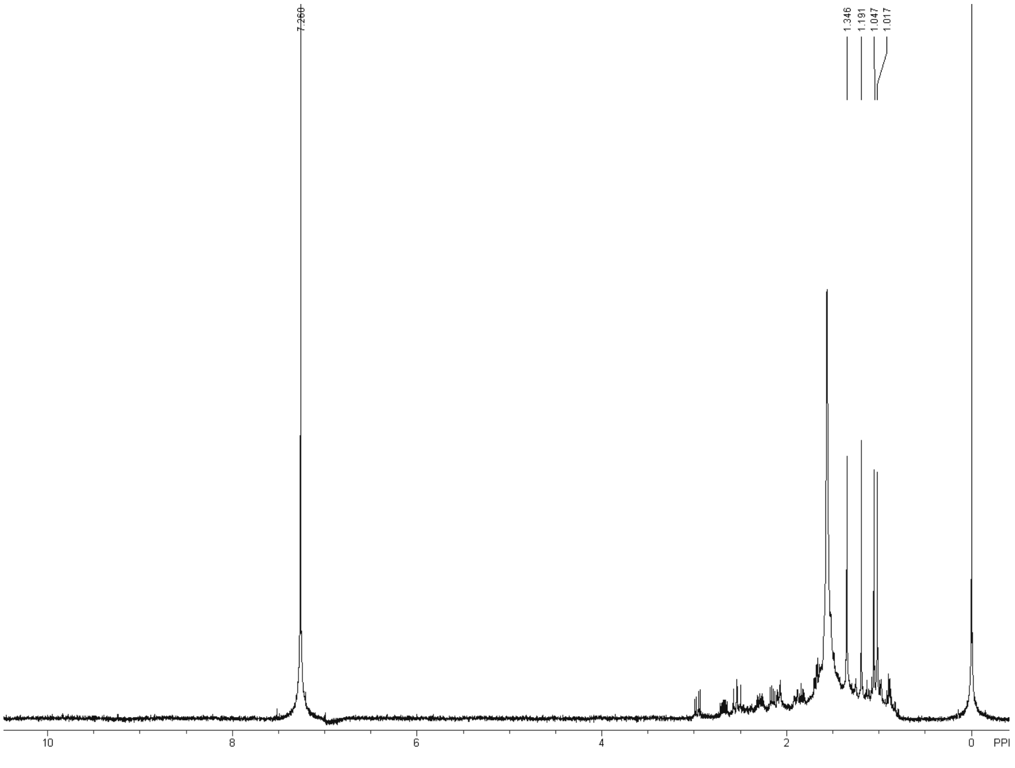

HO
O
O
H

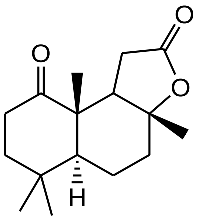
233


176.043
86.078
77.537
77.226
76.910
64.363
58.849
56.253
51.542
48.376
38.472
37.488
34.684
33.207
28.679
21.873
21.691
20.123
16.196
200
150
100
50
0
PP

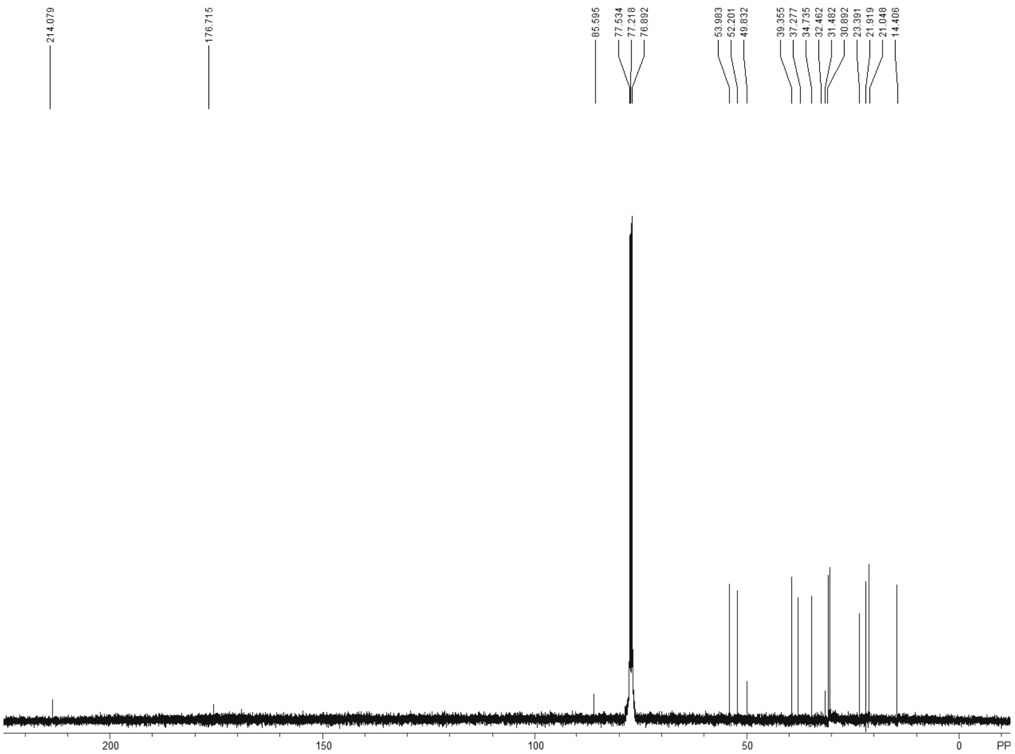

HO
O
O
H

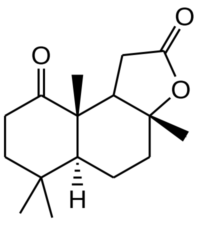
233


7.260
1.346
1.191
1.047
1.017
10
8
6
4
2
0
PP

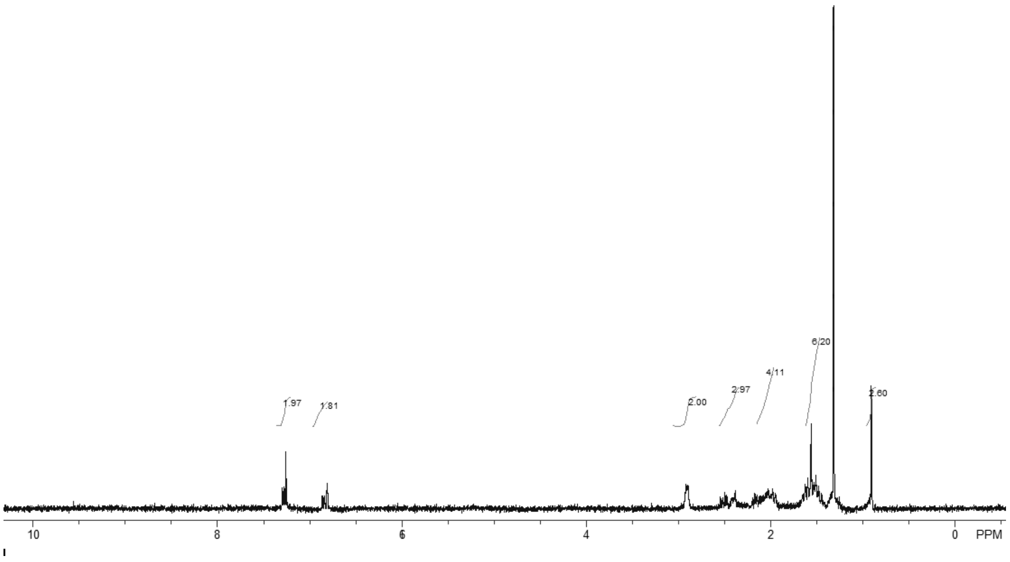

O
O
O
H

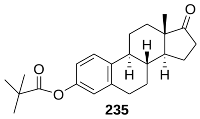
234


214.079
176.715
85.595
77.534
77.218
76.892
53.983
52.201
49.832
39.355
37.277
34.735
32.462
31.482
30.892
23.391
21.919
21.048
14.406
200
150
100
50
0
PP

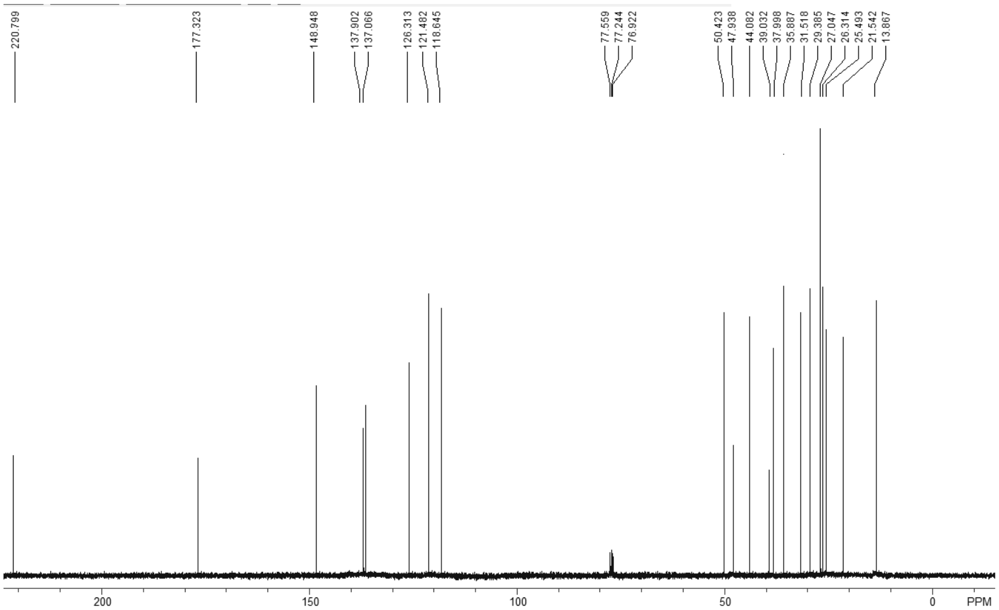

O
O
O
H

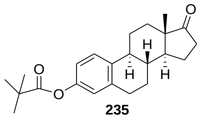
234


1.97
1.81
2.00
2.97
4.11
6.20
2.60
10
8
6
4
2
0
PPM

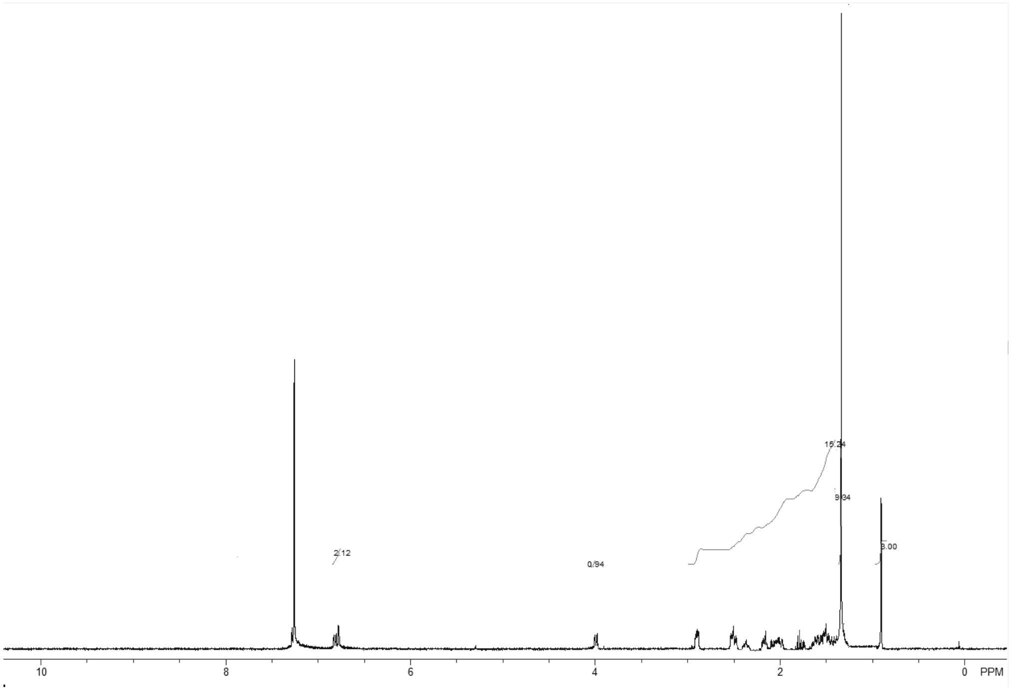

O
O
O
H
H
H

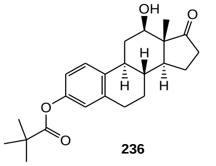
235


220.799
177.323
148.948
137.902
137.066
126.313
121.482
118.645
77.559
77.244
76.922
50.423
47.938
44.082
39.032
37.998
35.887
31.518
29.385
27.047
26.314
25.493
21.542
13.867
200
150
100
50
0
PPM

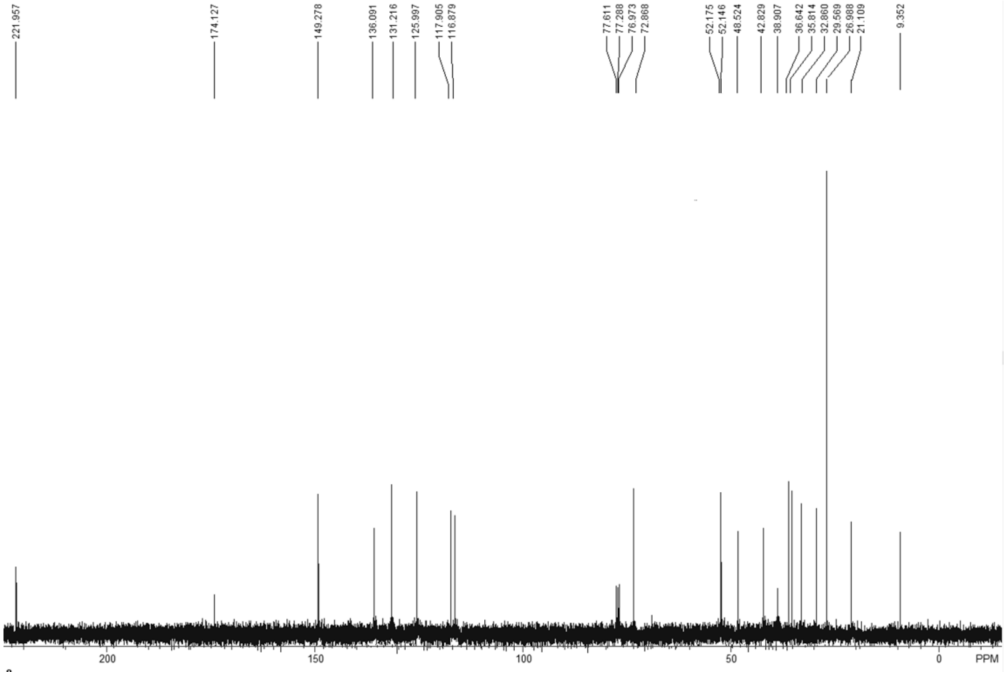

O
H
H
H
O
O

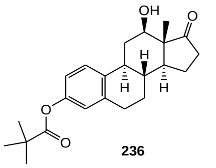
235


2.12
0.94
15.24
9.34
3.00
10
8
6
4
2
0
PPM

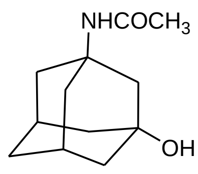

OH
O
H
H
H
O
O

236

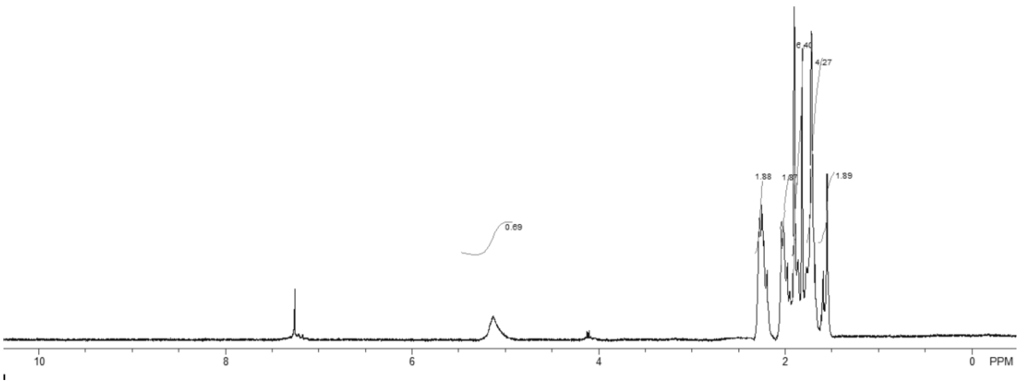

221.957
174.127
149.278
136.091
131.216
125.997
117.905
116.879
77.611
77.288
76.973
72.868
52.175
52.146
48.524
42.829
38.907
36.642
35.814
32.860
29.569
26.988
21.109
9.352
200
150
100
50
0
PPM

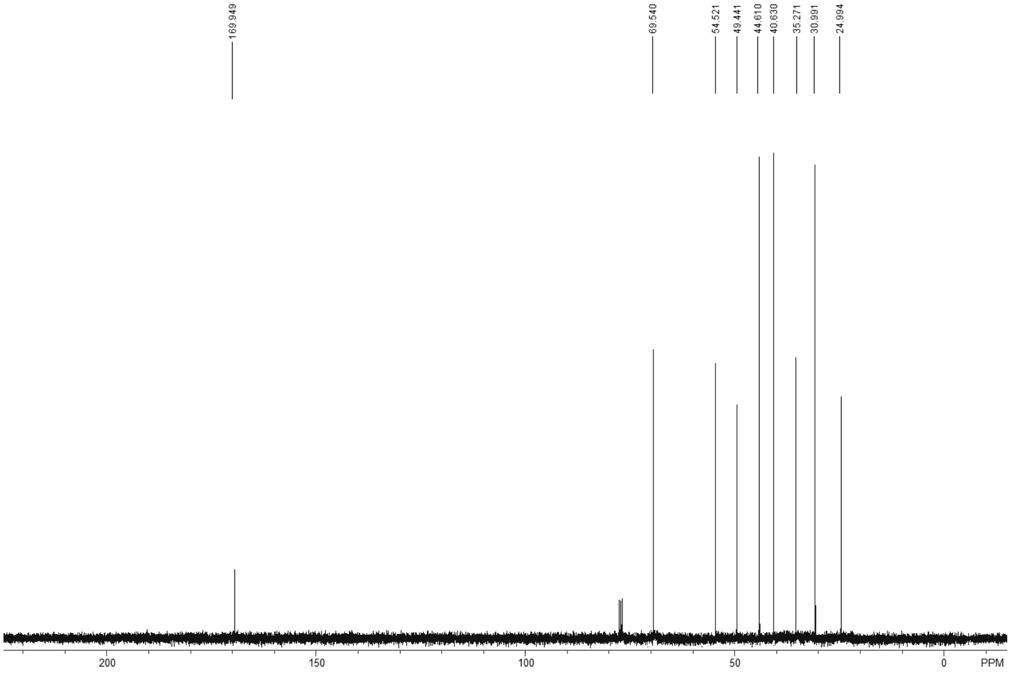

OH
O
H
H
H
O
O

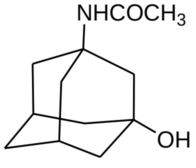
236


NHCOCH3
OH

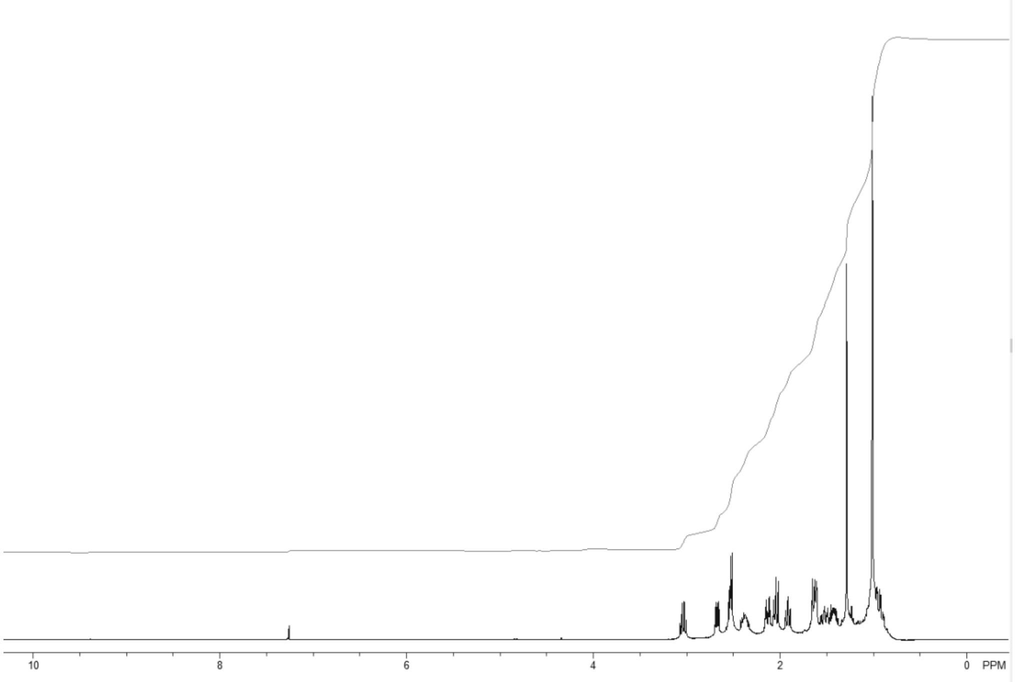
238

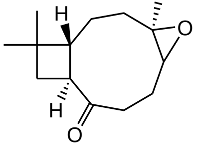

0.69
1.88
1.87
6.40
4.27
1.89
10
8
6
4
2
0
PPM


169.949
69.540
54.521
49.441
44.610
40.630
35.271
30.991
24.994
200
150
100
50
0
PPM

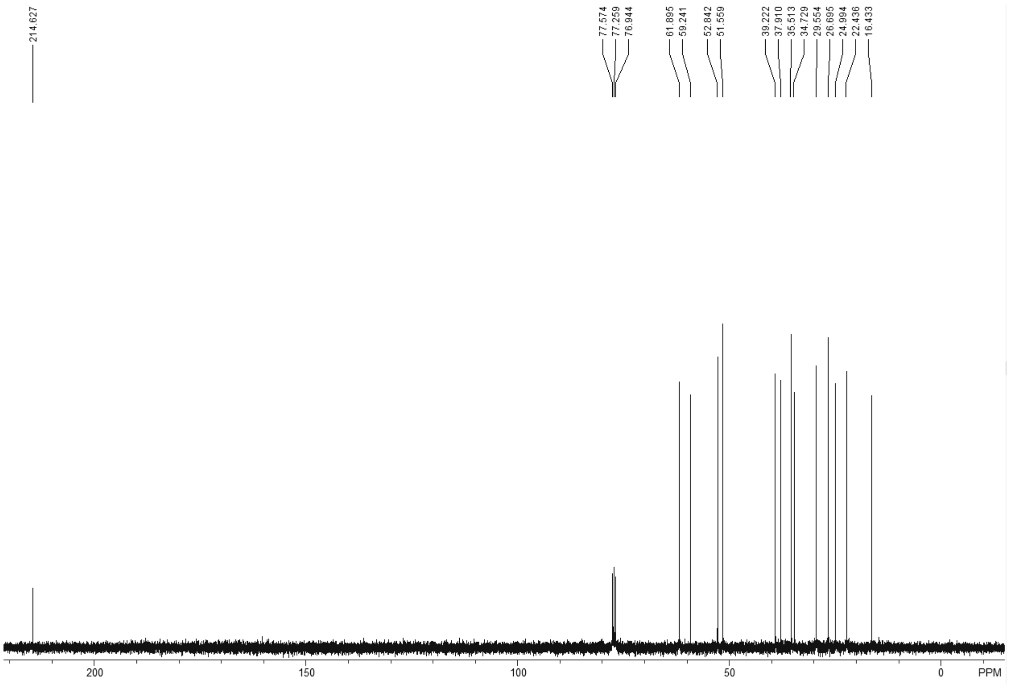

NHCOCH3
OH

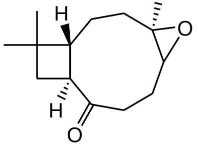
238


10
8
6
4
2
0
PPM

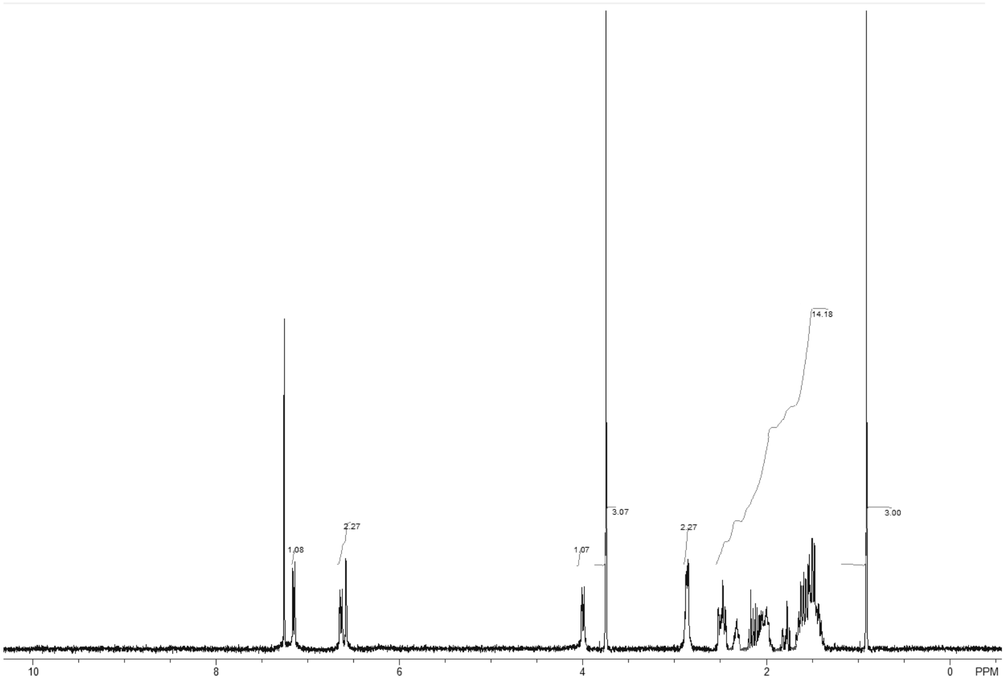

H
O
H
O

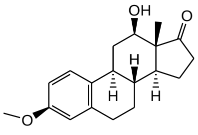
240


214.627
77.574
77.259
76.944
61.895
59.241
52.842
51.559
39.222
37.910
35.513
34.729
29.554
26.695
24.994
22.436
16.433
200
150
100
50
0
PPM

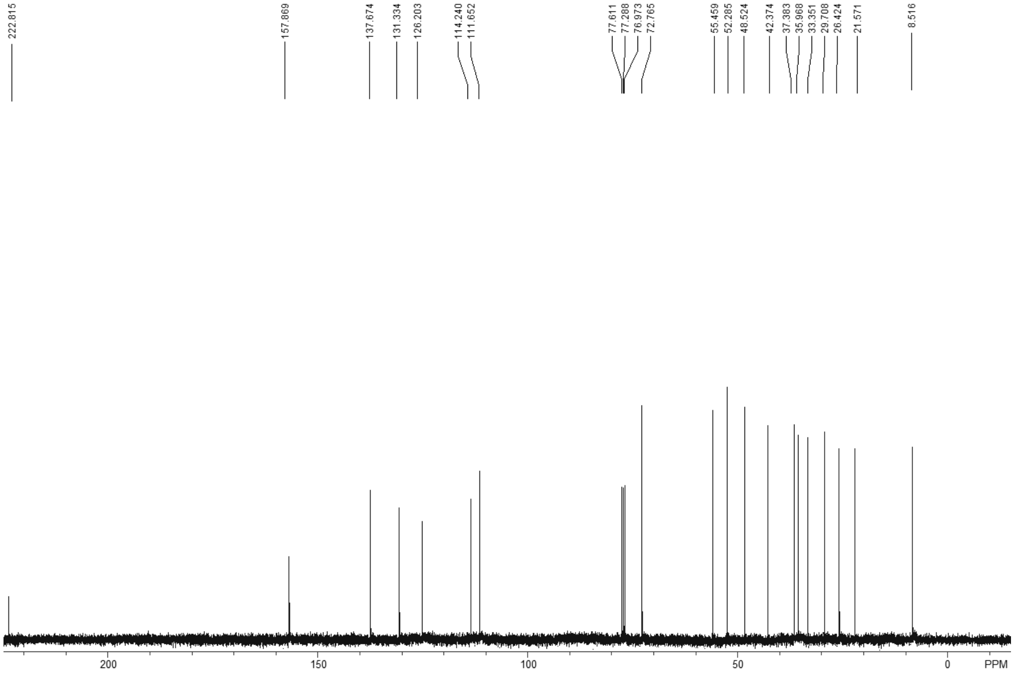

H
H
O
O

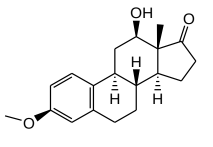
240


1.08
2.27
1.07
3.07
2.27
14.18
3.00
10
8
6
4
2
0
PPM

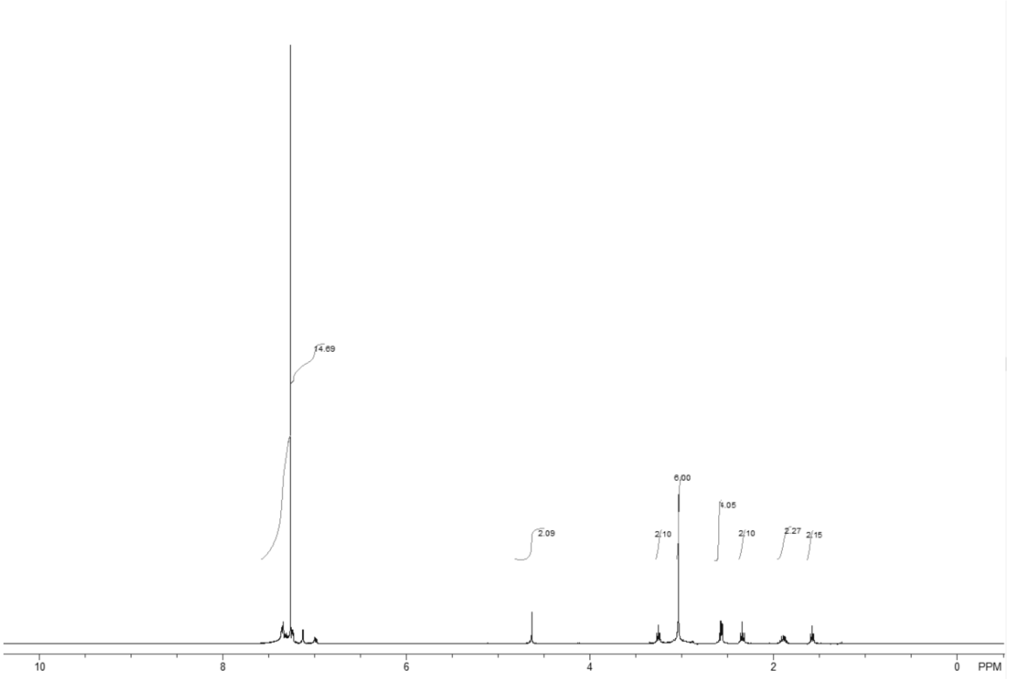

OH
O
H
H
H
O

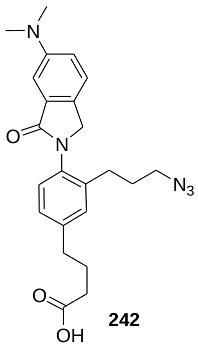
241


222.815
157.869
137.674
131.334
126.203
114.240
111.652
77.611
77.288
76.973
72.765
55.459
52.285
48.524
42.374
37.383
35.968
33.351
29.708
26.424
21.571
8.516
200
150
100
50
0
PPM

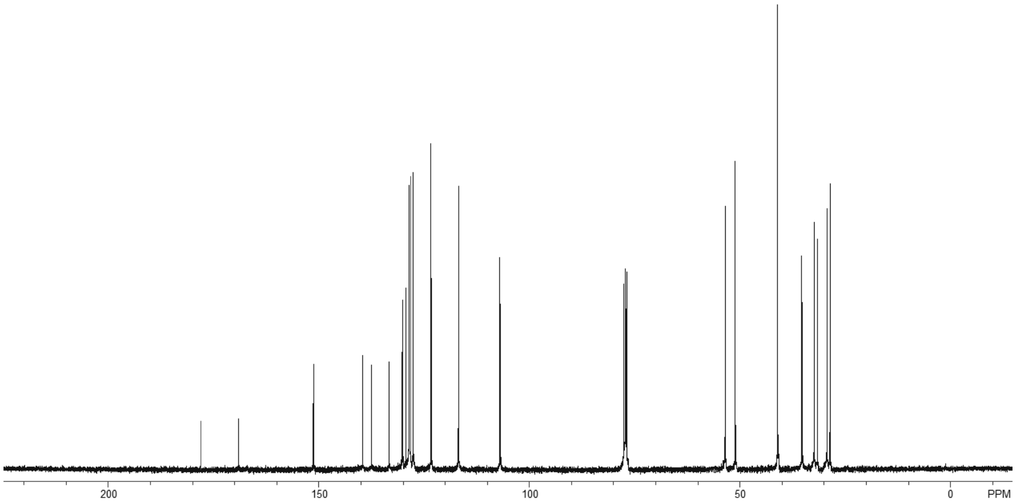

OH
O
H
H
H
O

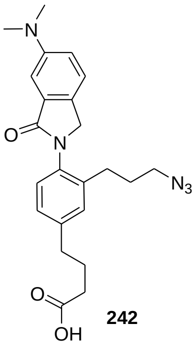
241


14.69
2.09
2.10
6.00
4.05
2.10
2.27
2.15
10
8
6
4
2
0
PPM

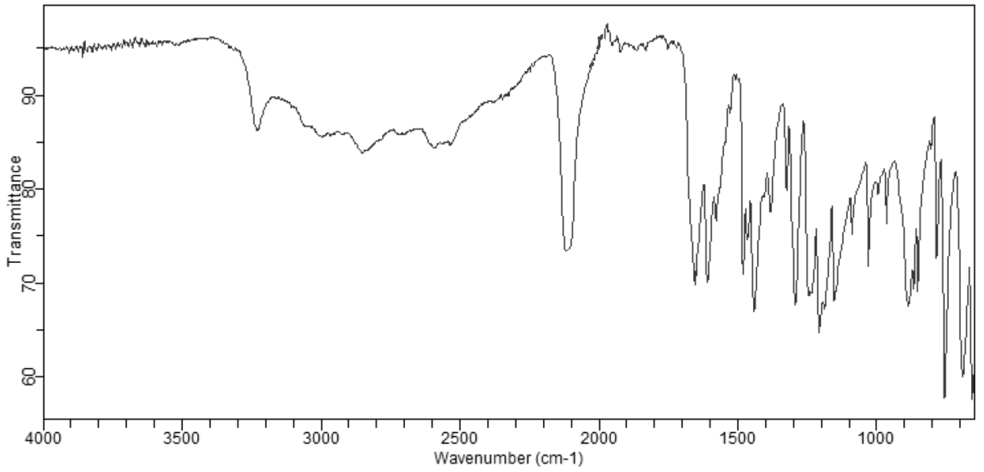

N
O
N
N3
O
OH

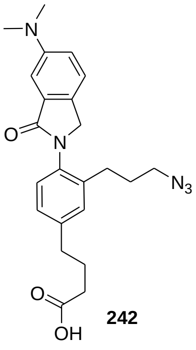
242


200
150
100
50
0
PPM

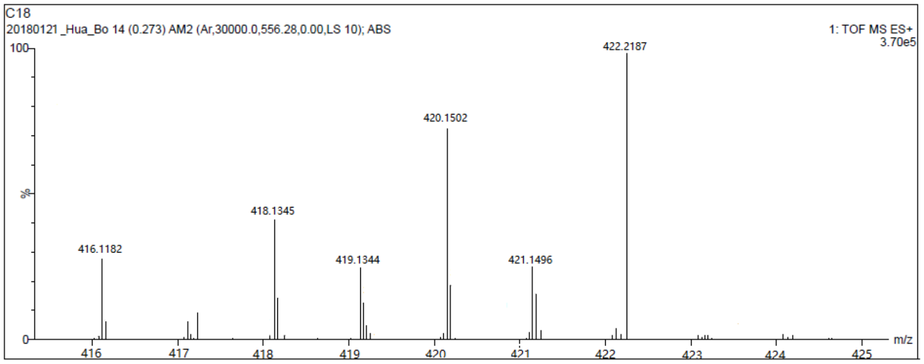

N
O
N
N3
O
OH

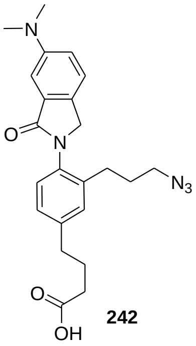
242


Transmittance
90
80
70
60
4000
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)

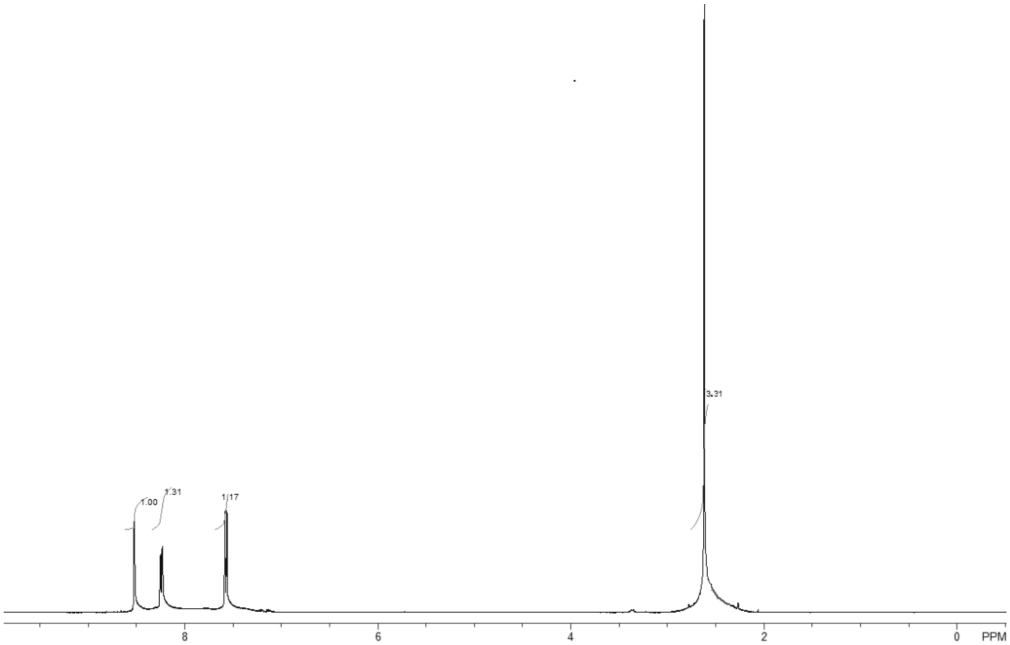

N
O
N
N3
O
OH

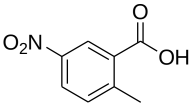
242


C18
20180121 _Hua_Bo 14 (0.273) AM2 (Ar,30000.0,556.28,0.00,LS 10); ABS
1: TOF MS ES+
3.70e5
100
%
0
422.2187
420.1502
418.1345
416.1182
419.1344
421.1496
416
417
418
419
420
421
422
423
424
425
m/z

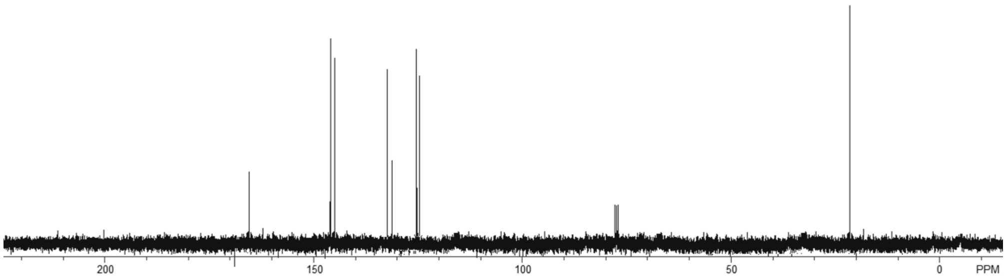

N
O
N
N$_3$
O
OH

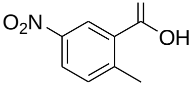
242


1.00
1.31
1.17
3.31
8
6
4
2
0
PPM

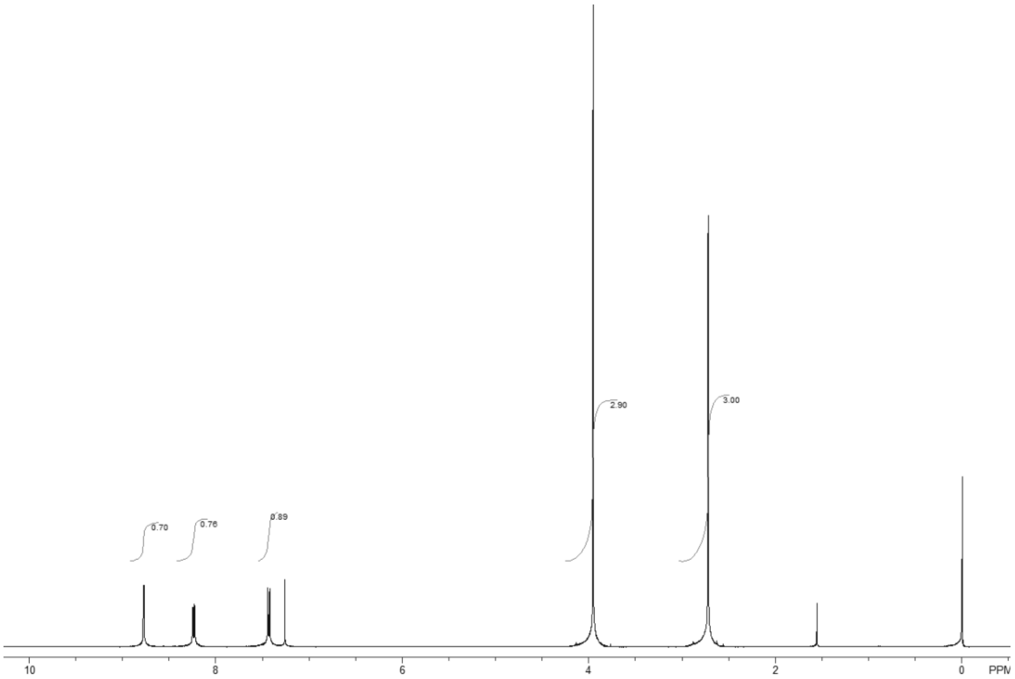

O$_2$N
O
OH

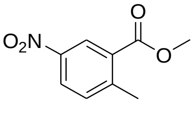
244


200
150
100
50
0
PPM

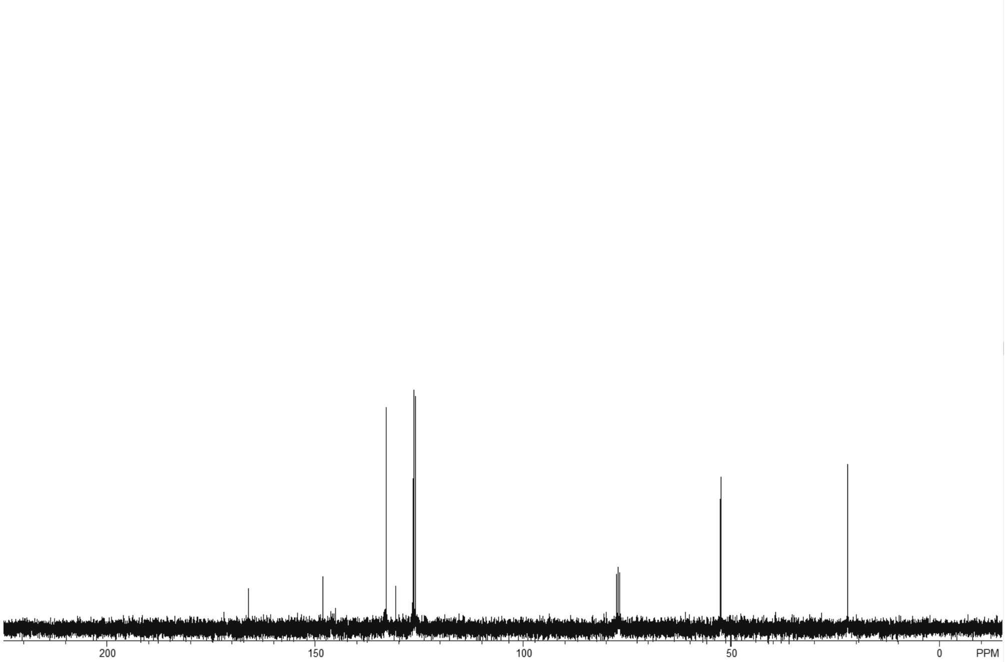

O
O$_2$N
OH

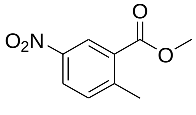
244


0.70
0.76
0.89
2.90
3.00
10
8
6
4
2
0
PPM

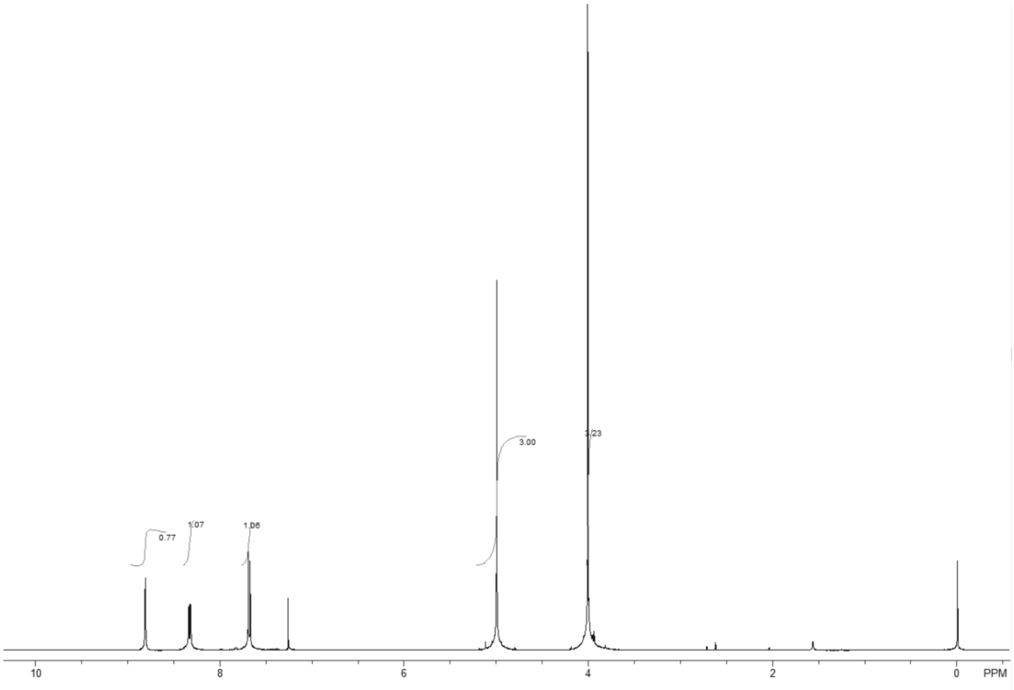

O
O$_2$N
O

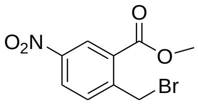
245


200
150
100
50
0
PPM

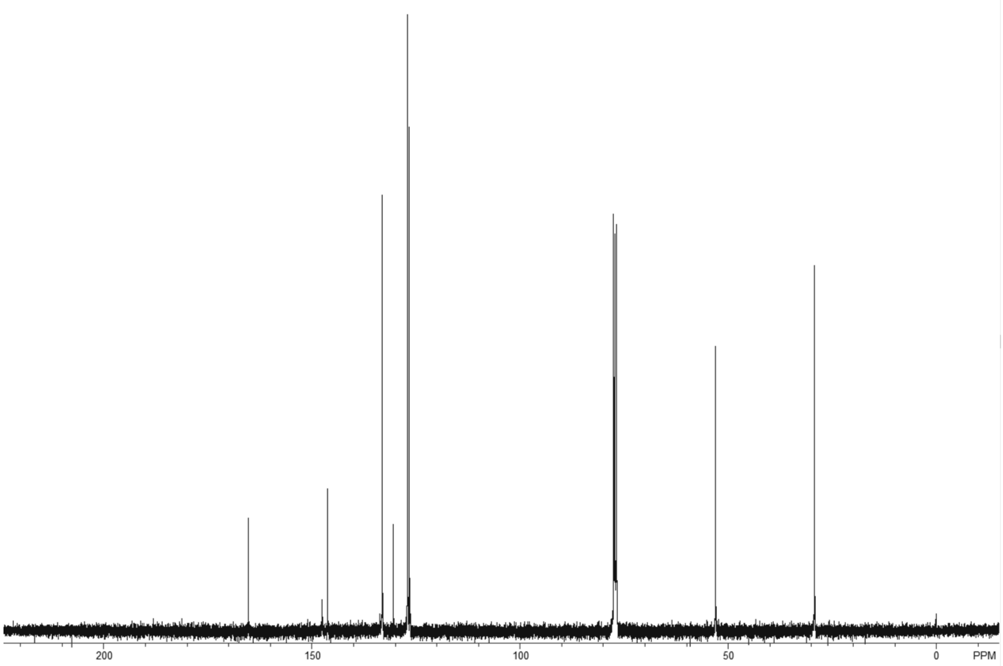

O
O_2N
O

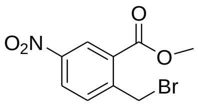
245


0.77
1.07
1.06
3.00
3.23
10
8
6
4
2
0
PPM

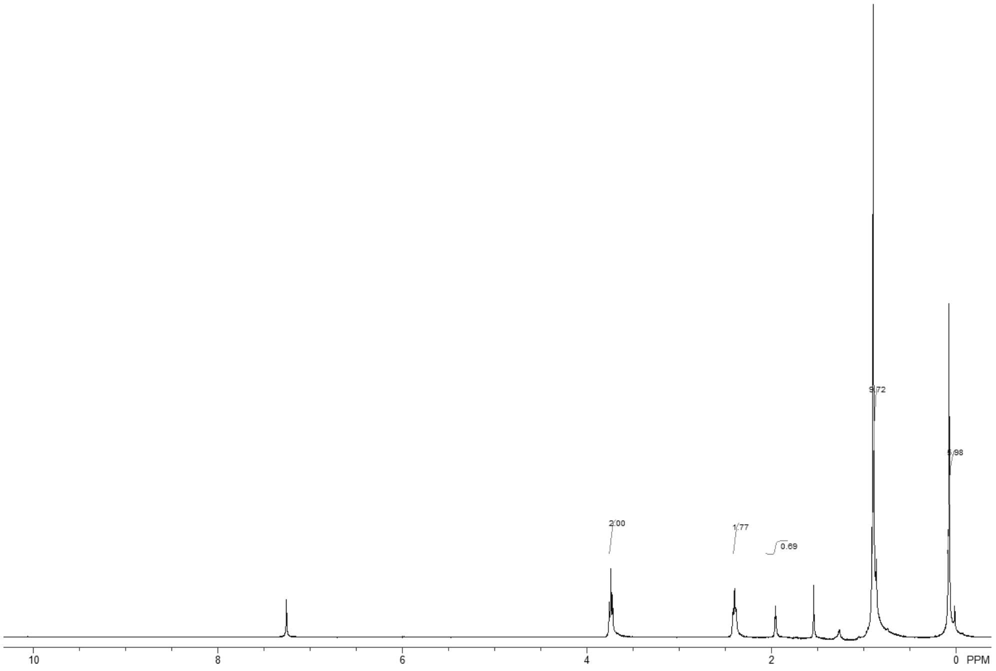

O
O_2N
O
Br

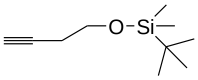
246


200
150
100
50
0
PPM

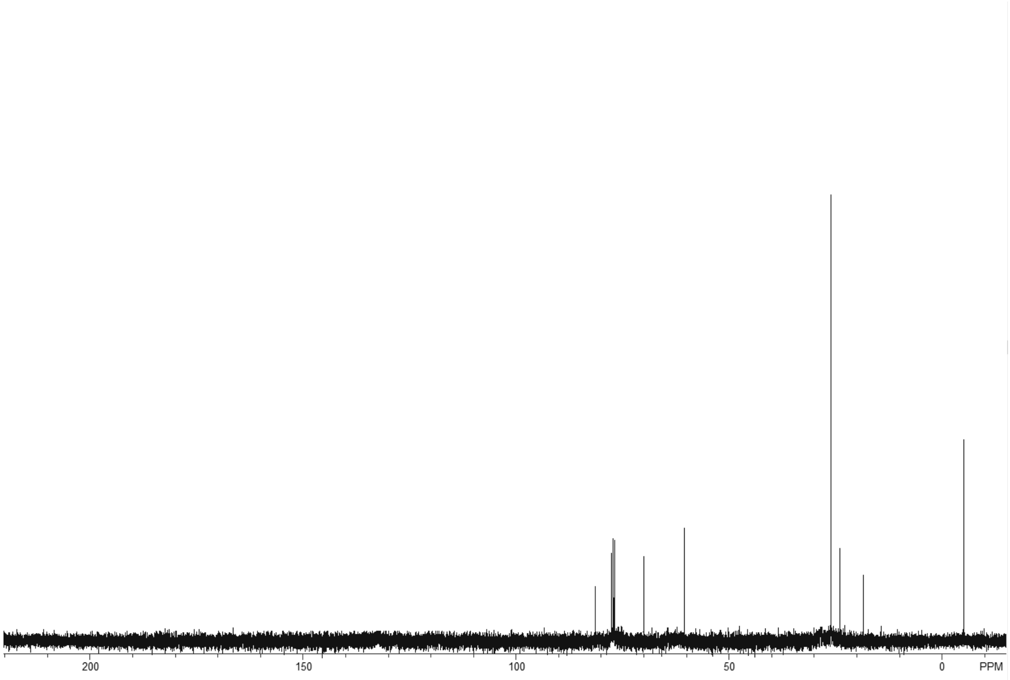

O$_2$N
O
O
Br

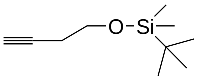
246


2.00
1.77
0.69
9.72
5.98
10
8
6
4
2
0
PPM

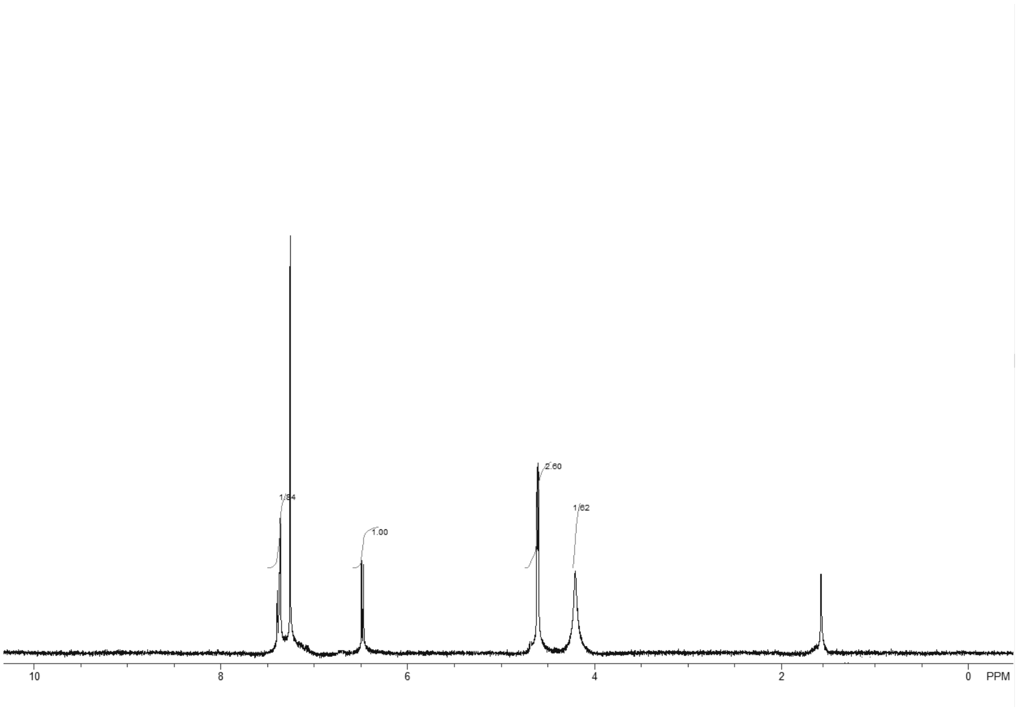

O
Si

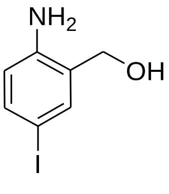
248



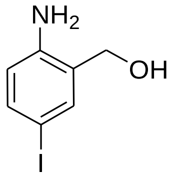


248

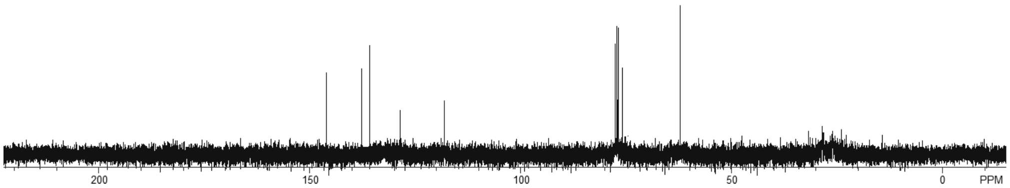


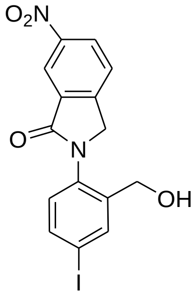


250

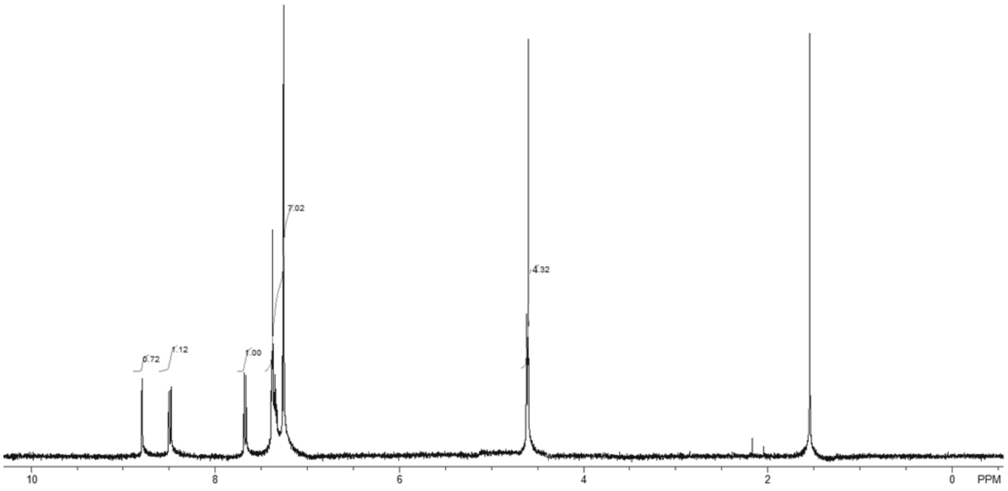


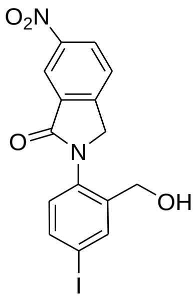
250



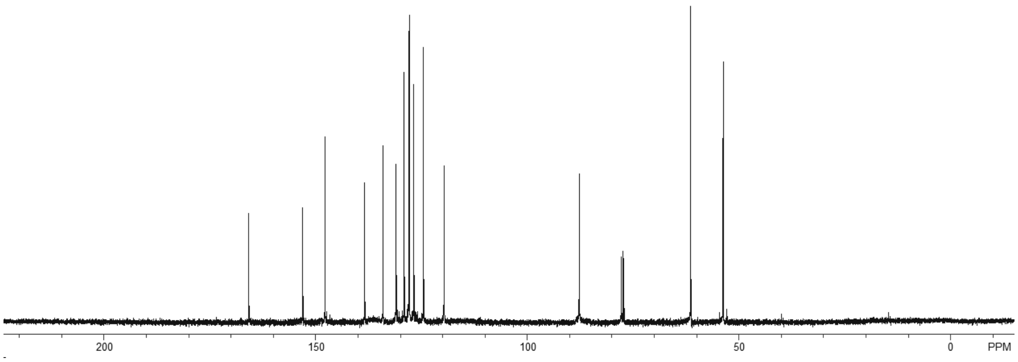


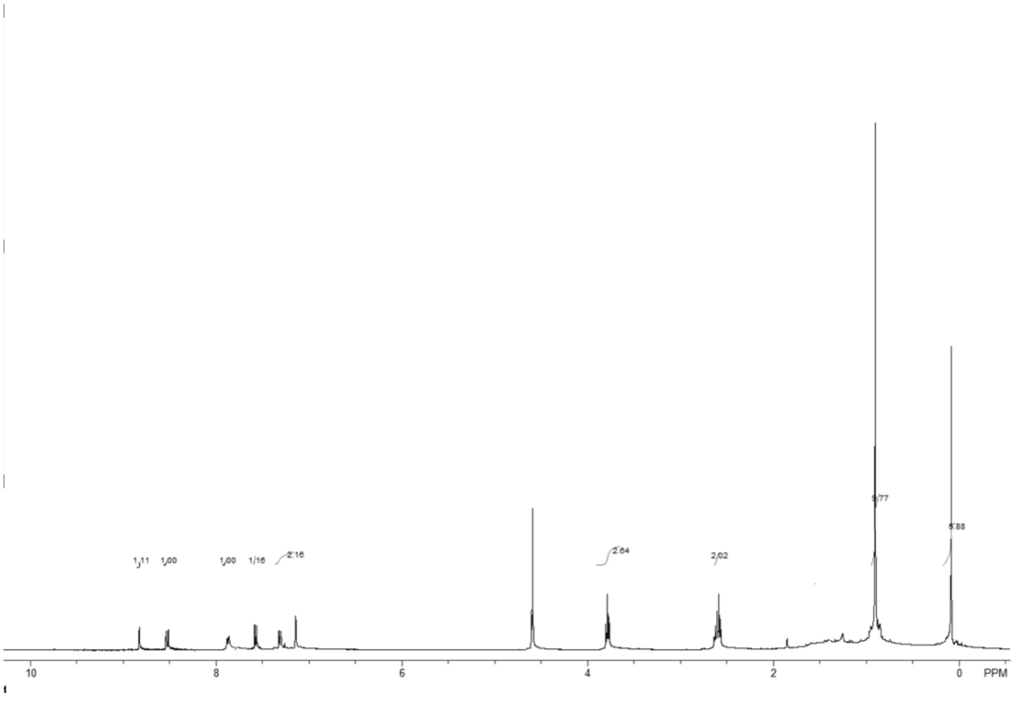
251

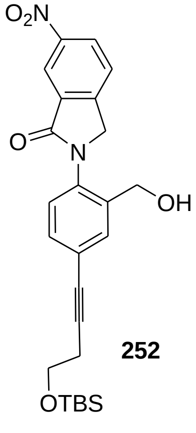



O$_2$N
O
N
OH
I

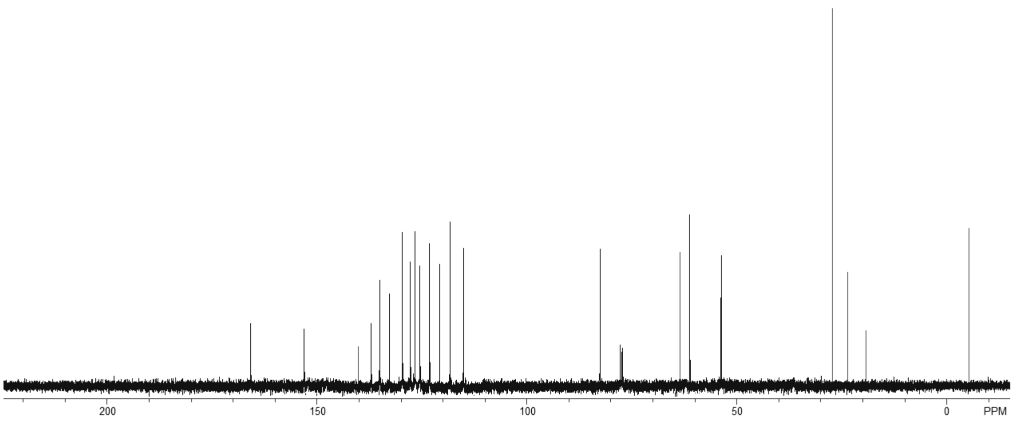
251

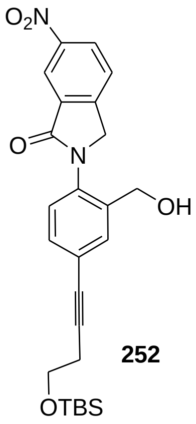

200
150
100
50
0
PPM


1.11
1.00
1.00
1.16
2.16
2.64
2.02
9.77
5.88
10
8
6
4
2
0
PPM

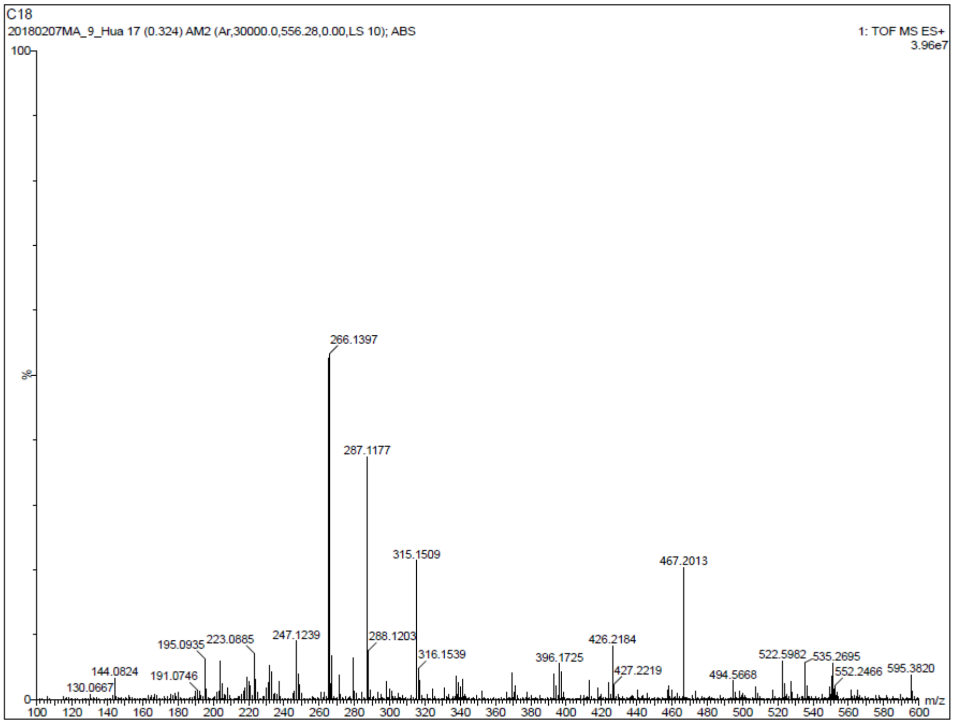

O$_2$N
O
N
OH
OTBS

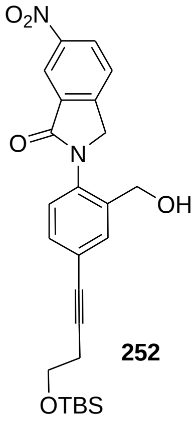
252


200
150
100
50
0
PPM

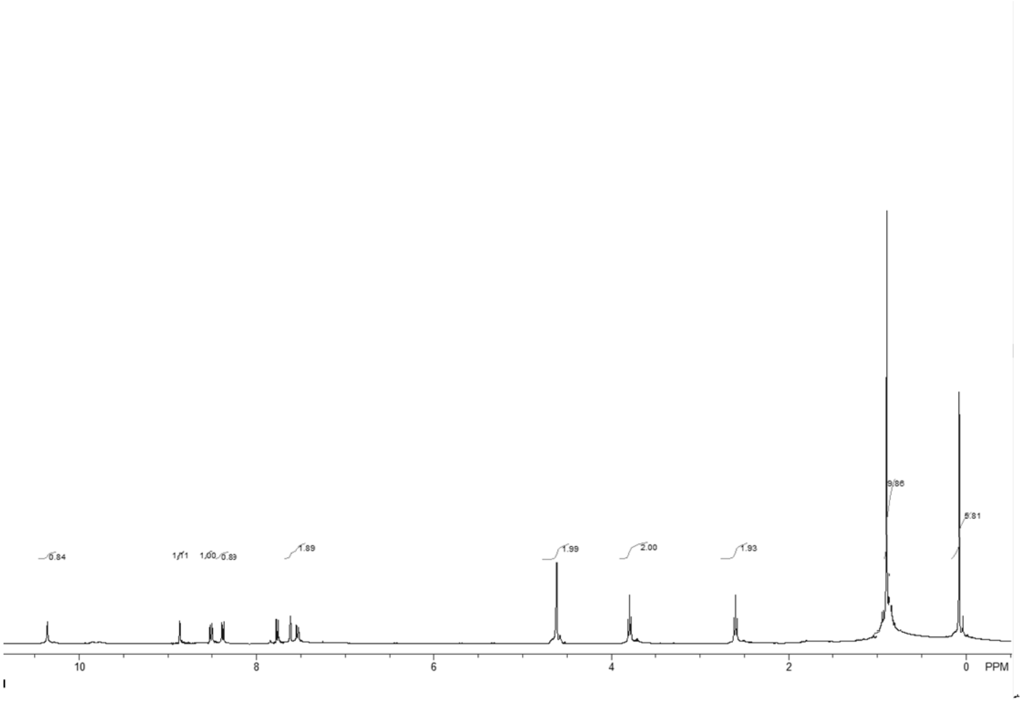

O2N
O
N
OH
OTBS

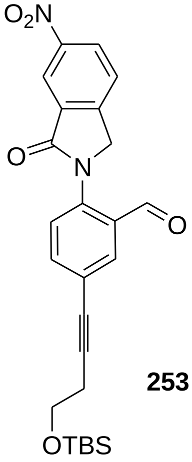
252


C18
20180207MA_9_Hua 17 (0.324) AM2 (Ar,30000.0,556.28,0.00,LS 10); ABS
1: TOF MS ES+
3.96e7
100
%
0
266.1397
287.1177
315.1509
467.2013
195.0935
223.0885
247.1239
288.1203
316.1539
426.2184
396.1725
427.2219
144.0824
191.0746
130.0667
494.5668
522.5982
535.2695
552.2466
595.3820
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480
500
520
540
560
580
600
m/z

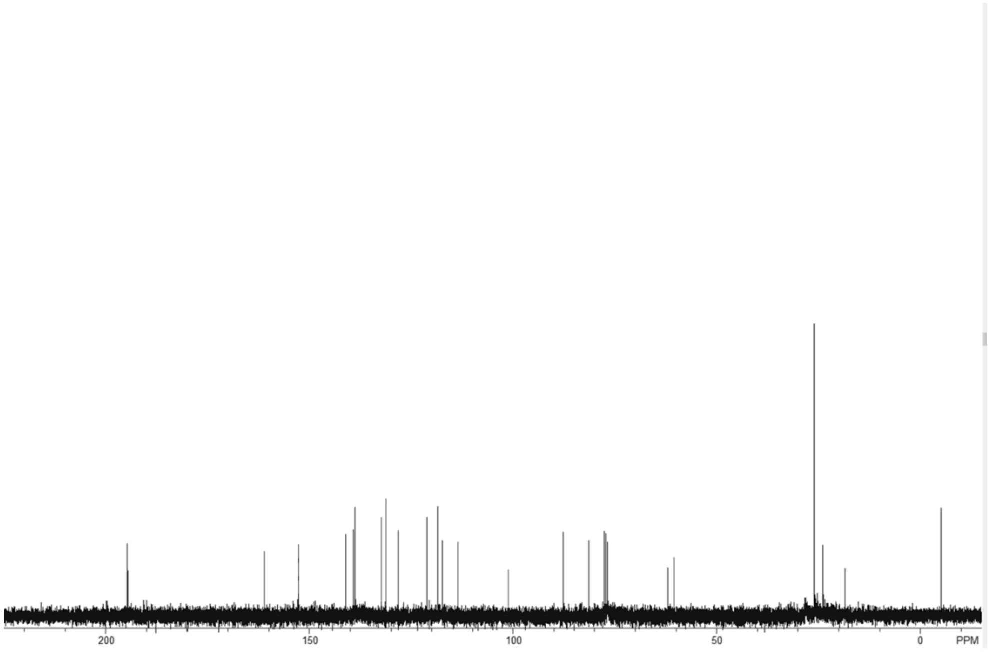

O2N
O
N
OH
OTBS

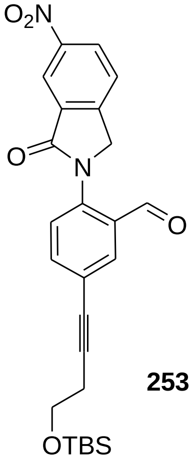
252


0.84
1.11
1.00
0.89
1.89
1.99
2.00
1.93
9.86
5.81
10
8
6
4
2
0
PPM

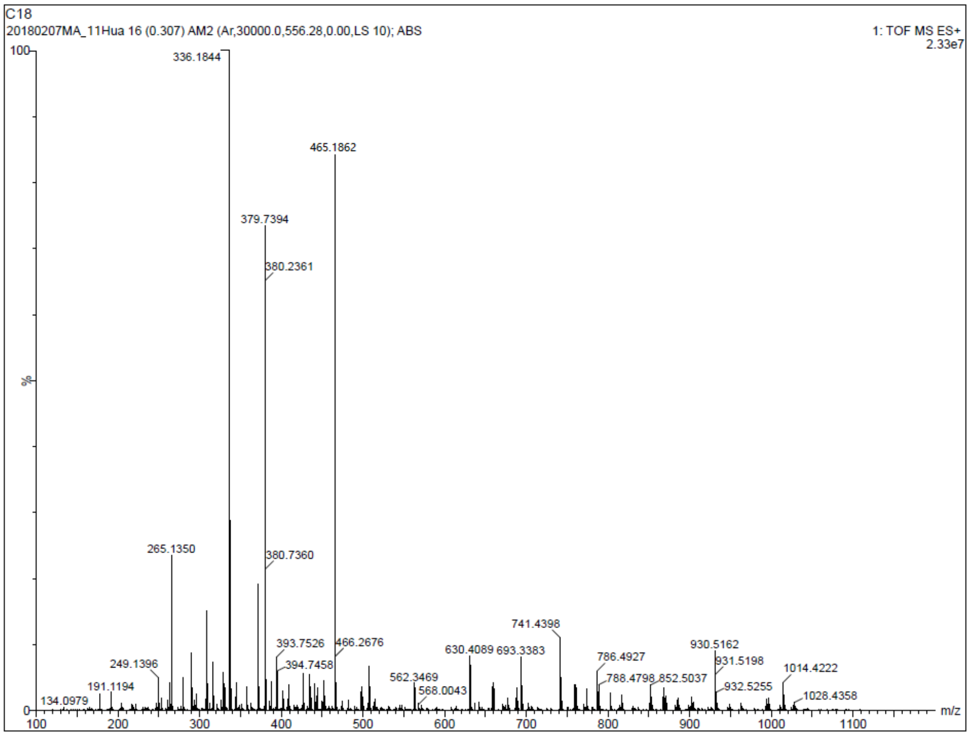

O2N
O
N
O
OTBS

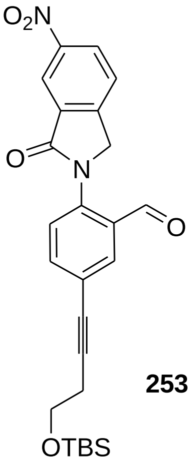
253


200
150
100
50
0
PPM

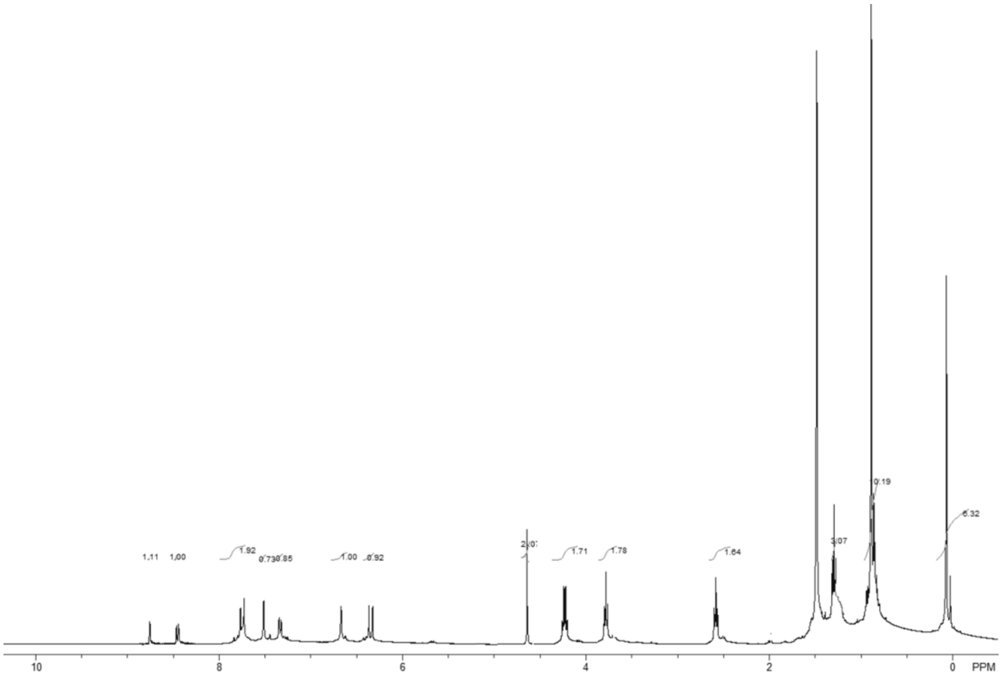

O2N
O
N
O
OTBS

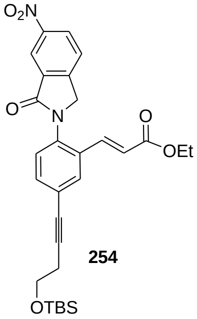
253


C18
20180207MA_11Hua 16 (0.307) AM2 (Ar,30000.0,556.28,0.00,LS 10); ABS
1: TOF MS ES+
2.33e7
100
%
0
336.1844
465.1862
379.7394
380.2361
265.1350
380.7360
249.1396
191.1194
134.0979
393.7526
394.7458
466.2676
562.3469
568.0043
630.4089
693.3383
741.4398
786.4927
788.4798
852.5037
930.5162
931.5198
932.5255
1014.4222
1028.4358
100
200
300
400
500
600
700
800
900
1000
1100
m/z

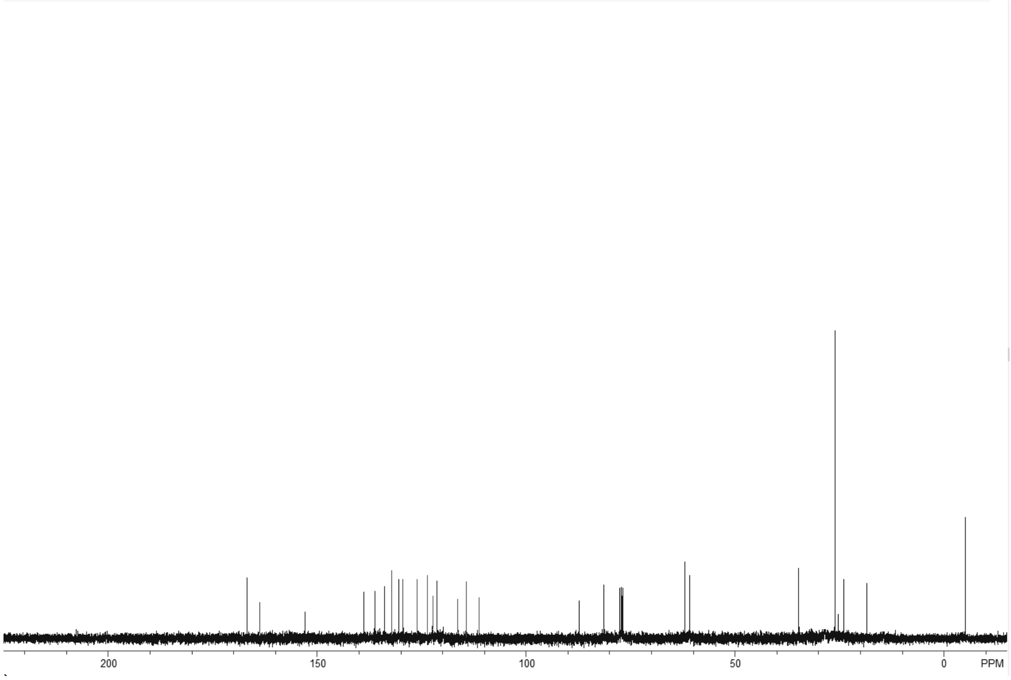

O2N
O
N
O
OTBS

253

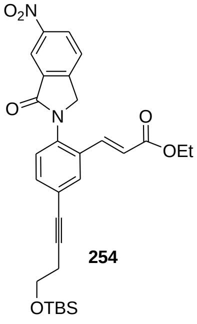

1.11
1.00
1.92
0.73
0.85
1.00
0.92
2.01
1.71
1.78
1.64
3.07
9.19
6.32
10
8
6
4
2
0
PPM


O2N
O
N
O
OEt
OTBS

254

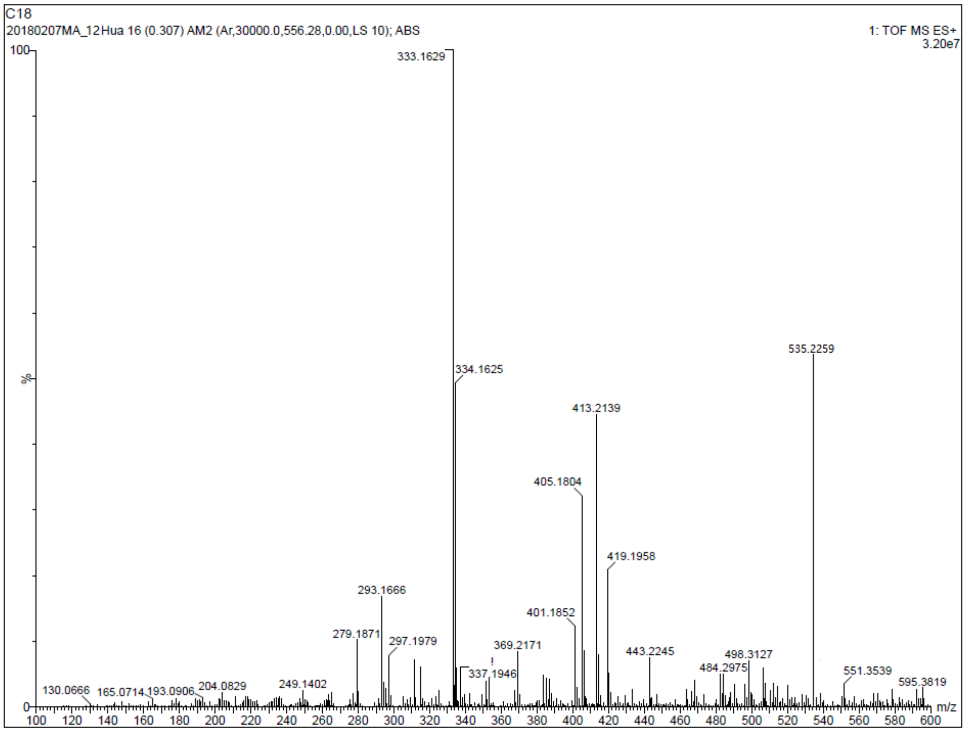


200
150
100
50
0
PPM

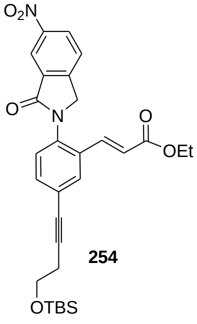


O2N
O
N
O
OEt
OTBS

254

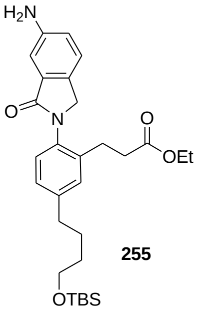


C18
20180207MA_12Hua 16 (0.307) AM2 (Ar,30000.0,556.28,0.00,LS 10); ABS
1: TOF MS ES+
3.20e7
100
%
0
333.1629
334.1625
535.2259
413.2139
405.1804
419.1958
293.1666
401.1852
279.1871
297.1979
369.2171
337.1946
443.2245
498.3127
484.2975
551.3539
595.3819
130.0666
165.0714
193.0906
204.0829
249.1402
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480
500
520
540
560
580
600
m/z

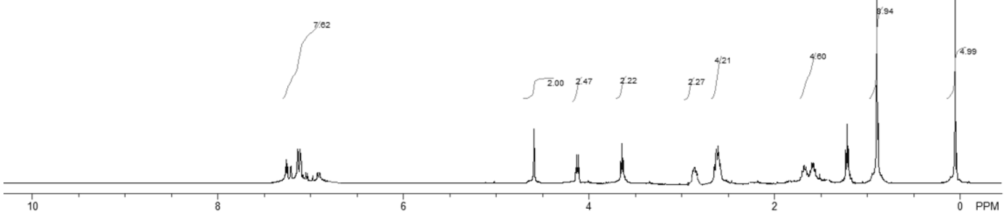


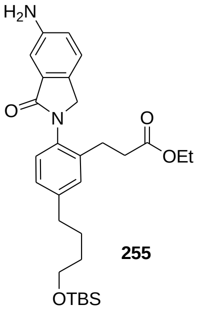
O2N
O
N
O
OEt
OTBS

254

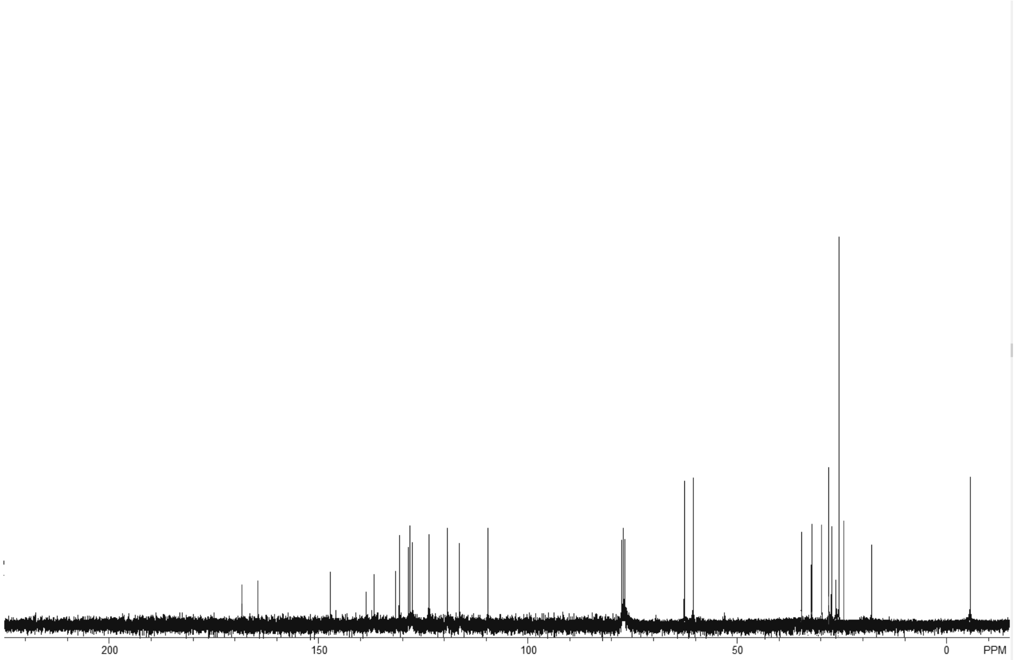

H2N
O
N
O
OEt
OTBS

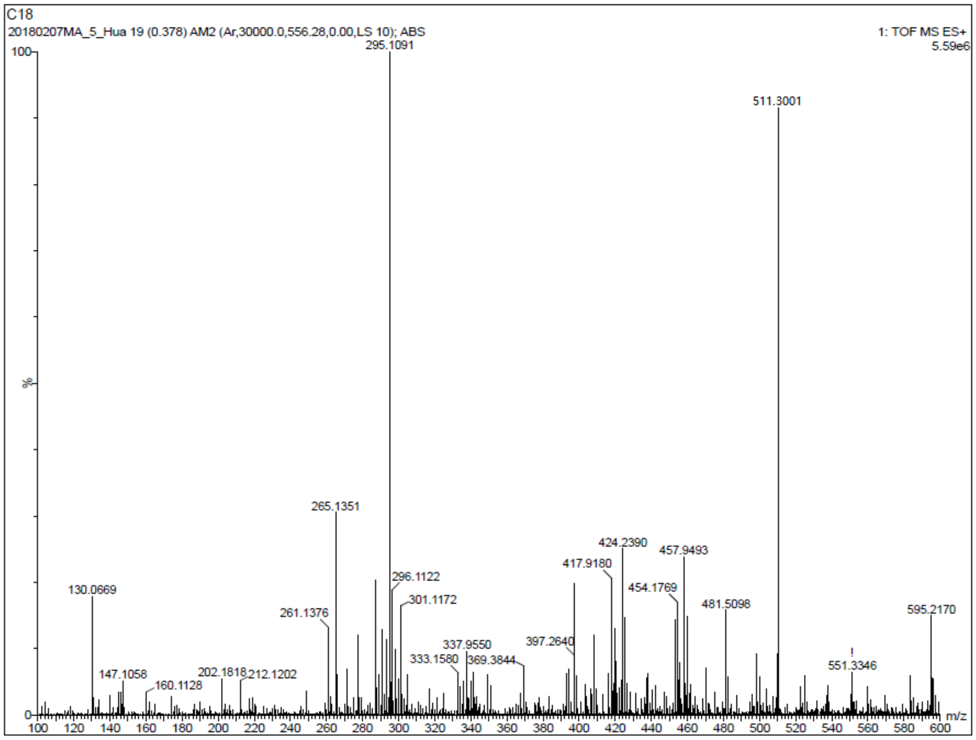
255

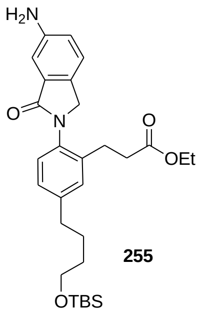

7.62
2.00
2.47
2.22
2.27
4.21
4.60
9.94
4.99
10
8
6
4
2
0
PPM


H2N
O
N
O
OEt
OTBS

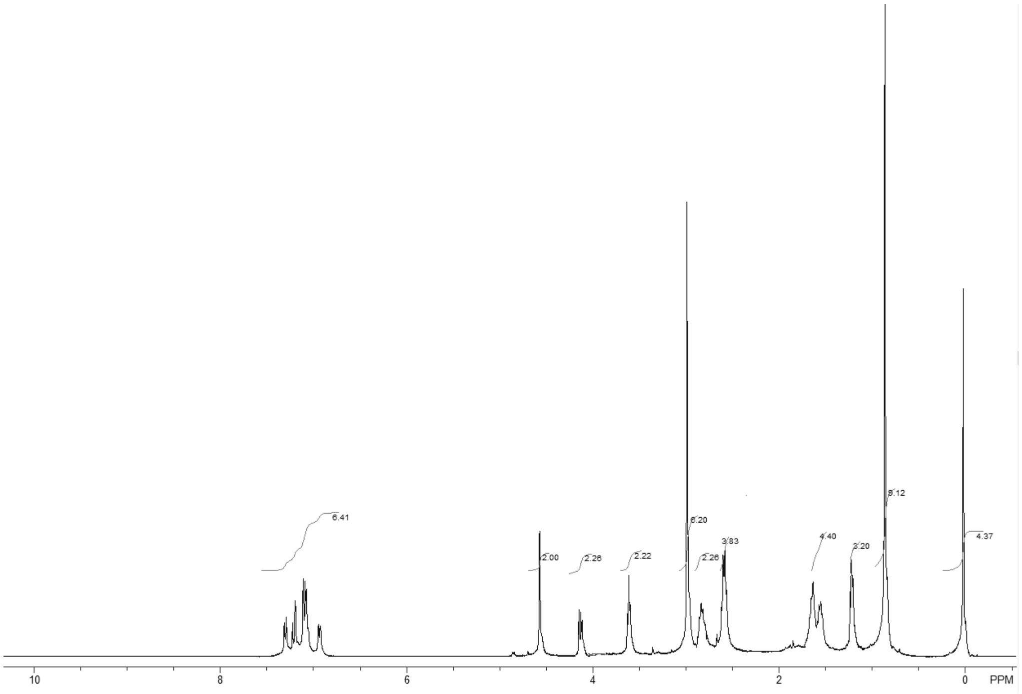
255

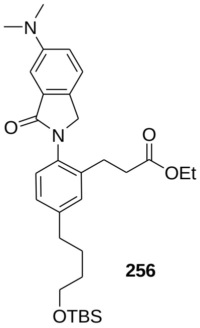

200
150
100
50
0
PPM


C18
20180207MA_5_Hua 19 (0.378) AM2 (Ar,30000.0,556.28,0.00,LS 10); ABS
1: TOF MS ES+
5.59e6
100
%
0
295.1091
511.3001
265.1351
424.2390
457.9493
417.9180
296.1122
454.1769
130.0669
301.1172
481.5098
595.2170
261.1376
337.9550
397.2640
333.1580
369.3844
551.3346
147.1058
202.1818
212.1202
160.1128
100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 580 600
m/z

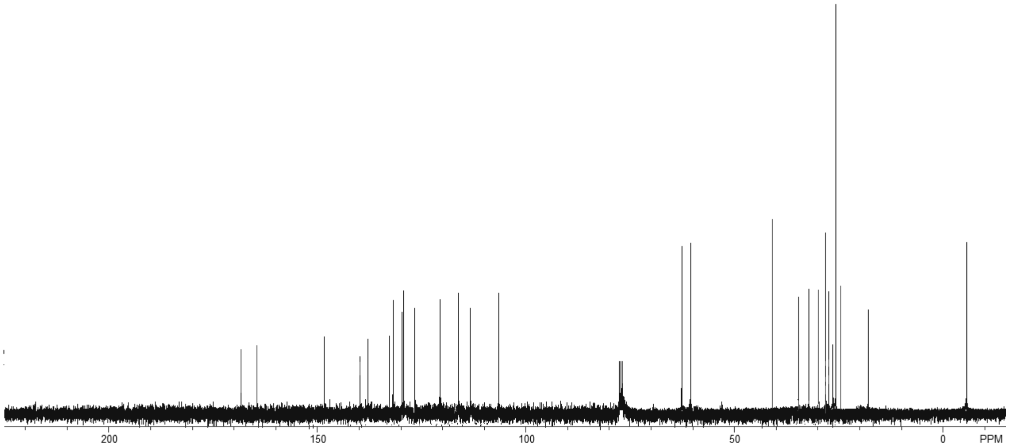

H2N
O
N
O
OEt
OTBS

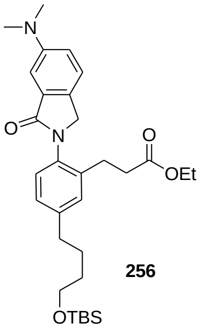
255


6.41
2.00
2.26
2.22
6.20
2.26
3.83
4.40
3.20
8.12
4.37
10
8
6
4
2
0
PPM

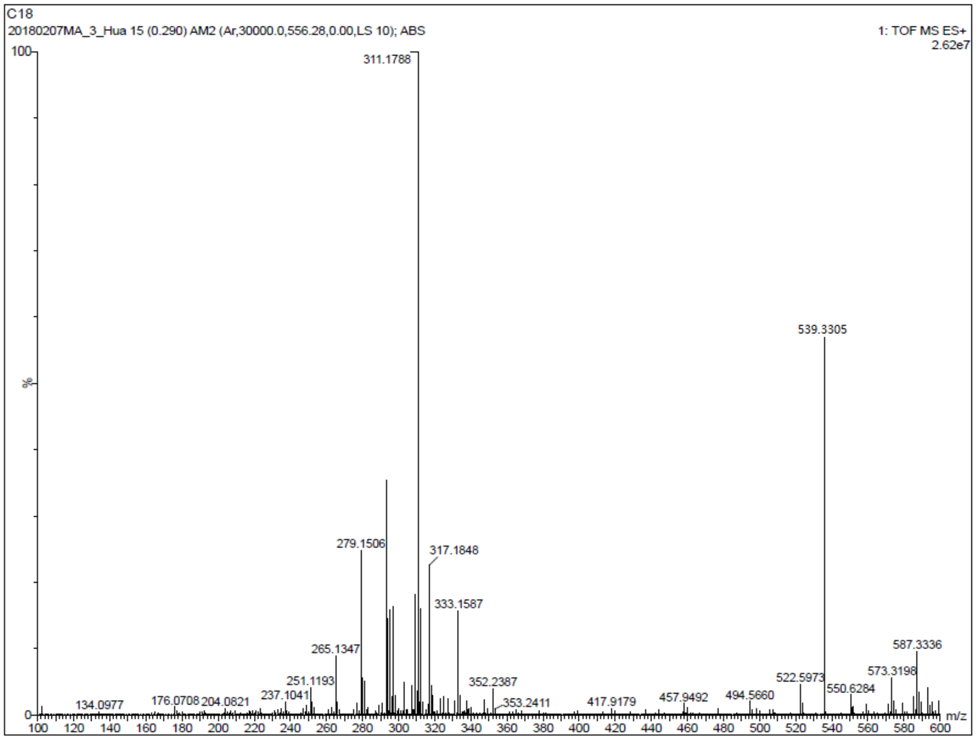

N
O
N
O
OEt
OTBS

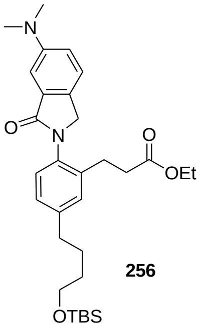
256


200
150
100
50
0
PPM

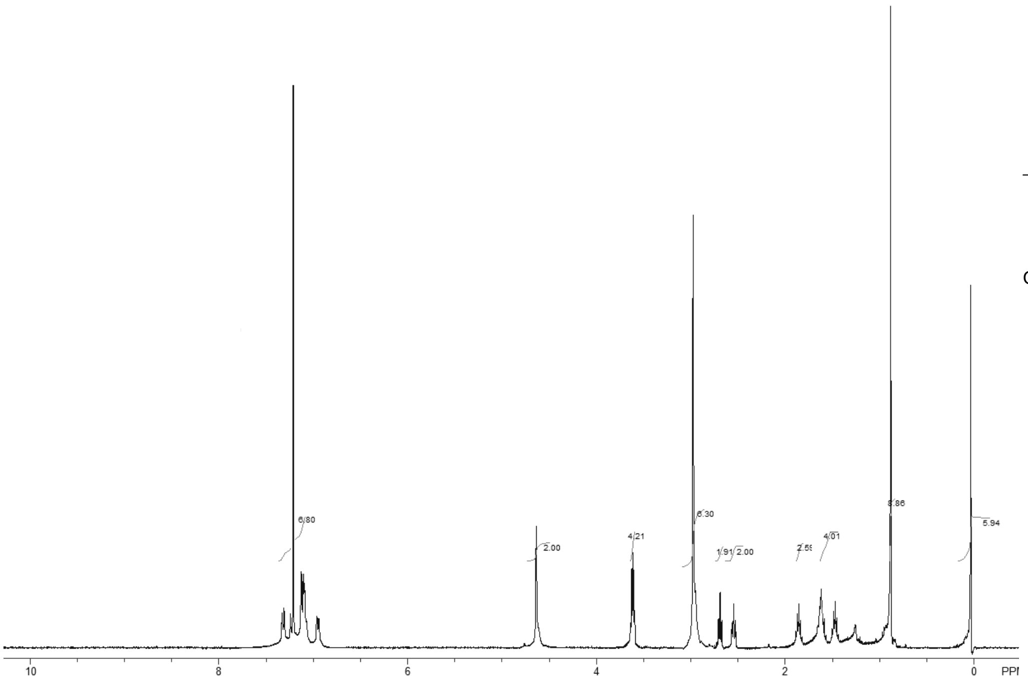

N
O
N
O
OEt
OTBS

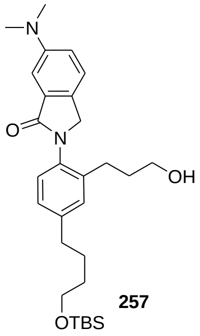
256


C18
20180207MA_3_Hua 15 (0.290) AM2 (Ar,30000.0,556.28,0.00,LS 10); ABS
1: TOF MS ES+
2.62e7
100
%
0
311.1788
539.3305
279.1506
317.1848
333.1587
265.1347
587.3336
573.3198
251.1193
352.2387
522.5973
550.6284
237.1041
134.0977
176.0708
204.0821
353.2411
417.9179
457.9492
494.5660
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480
500
520
540
560
580
600
m/z

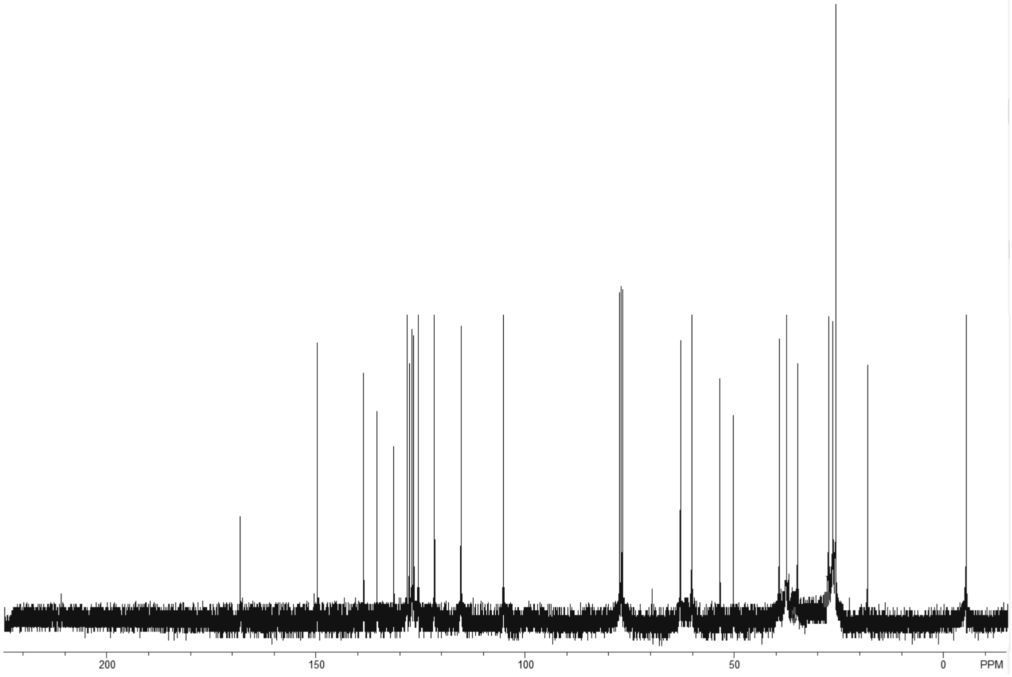

N
O
N
O
OEt
OTBS

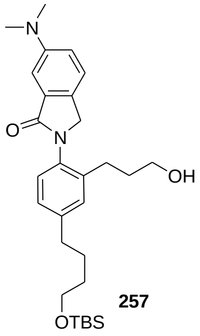
256


6.80
2.00
4.21
6.30
1.91
2.00
2.55
4.01
8.86
5.94
10
8
6
4
2
0
PPM

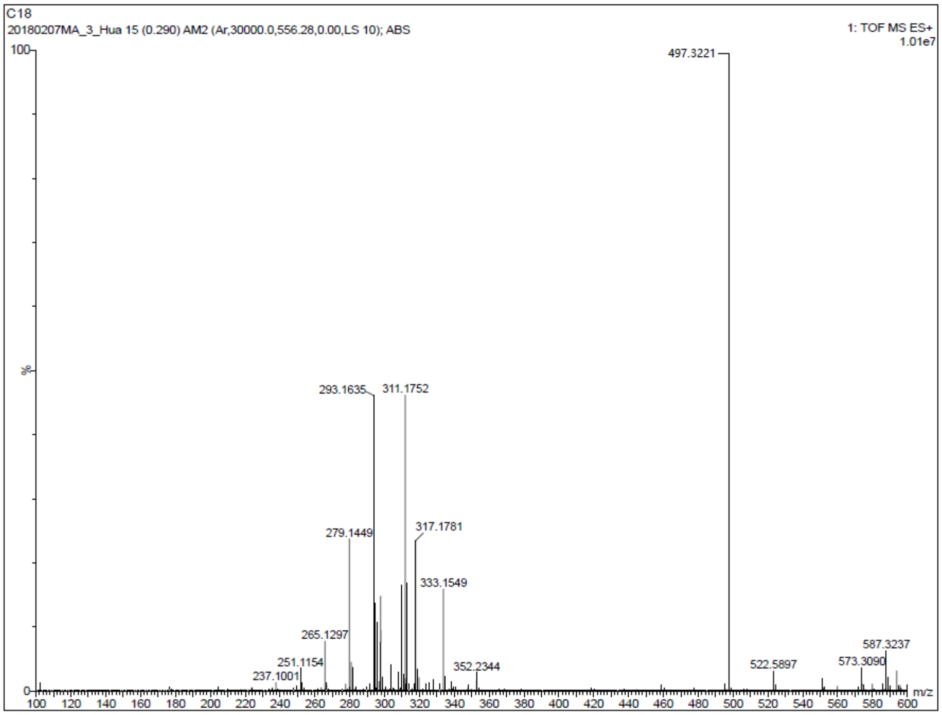

N
O
N
OH
OTBS

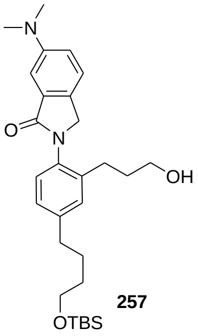
257


200
150
100
50
0
PPM

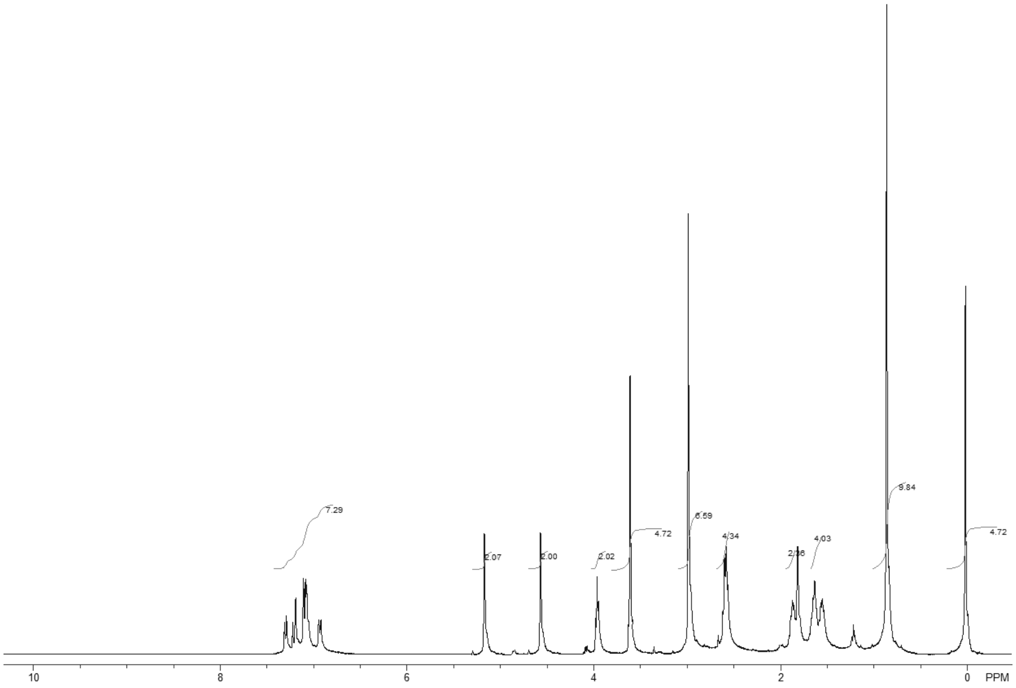

N
O
N
OH
OTBS

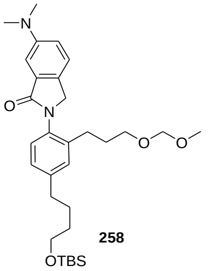
257


C18
20180207MA_3_Hua 15 (0.290) AM2 (Ar,30000.0,556.28,0.00,LS 10); ABS
1: TOF MS ES+
1.01e7
100
%
0
497.3221
293.1635
311.1752
279.1449
317.1781
333.1549
265.1297
251.1154
237.1001
352.2344
522.5897
573.3090
587.3237
m/z
100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 580 600

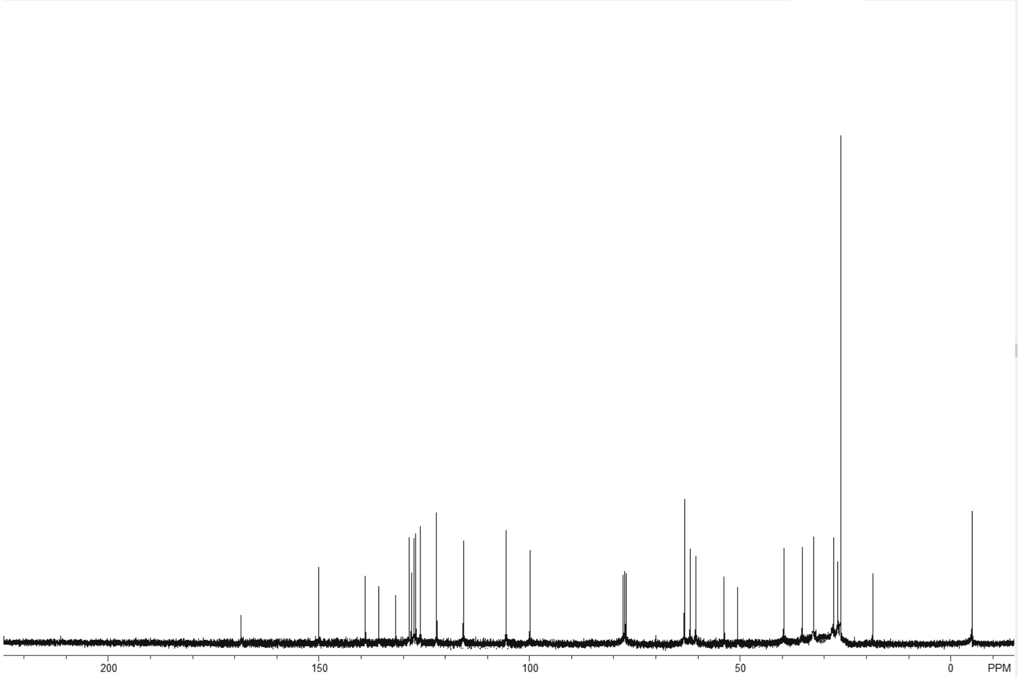

N
O
N
OH
OTBS

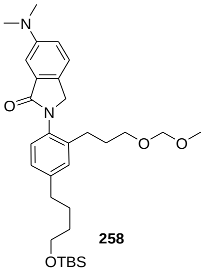
257


7.29
2.07
2.00
2.02
4.72
6.59
4.34
2.36
4.03
9.84
4.72
10
8
6
4
2
0
PPM

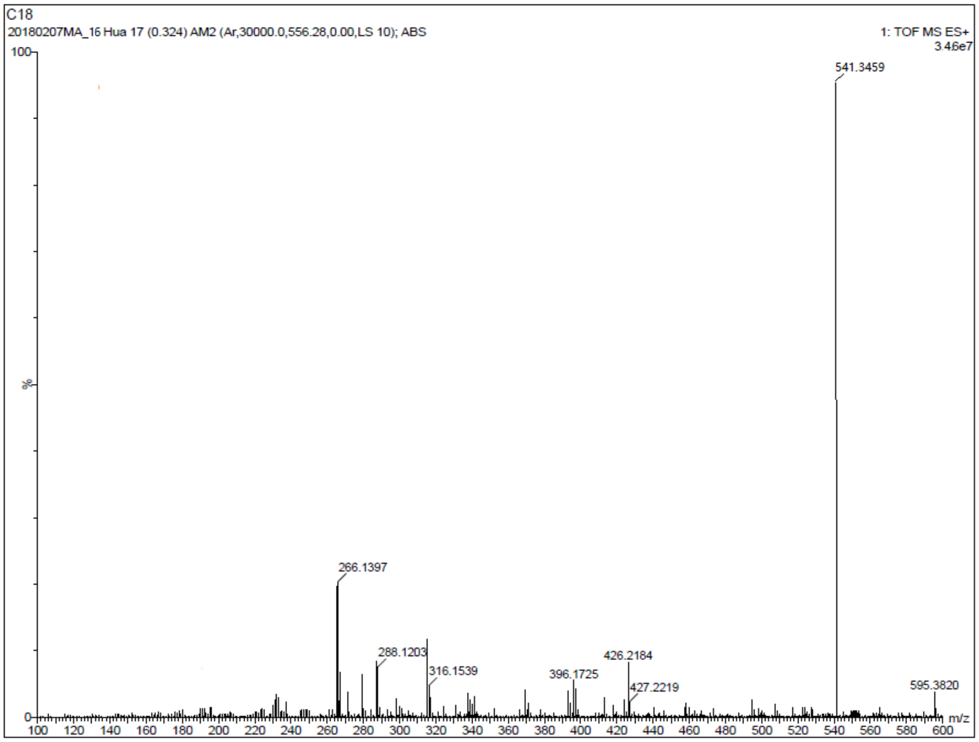

N
O
N
O
O
OTBS

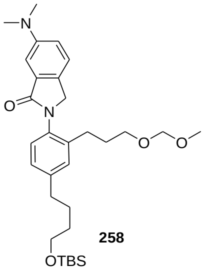
258


200
150
100
50
0
PPM

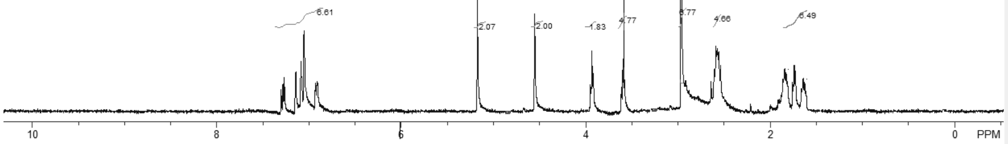

N
O
N
O
O
OTBS

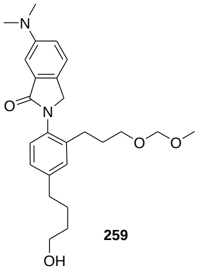
258


C18
20180207MA_16 Hua 17 (0.324) AM2 (Ar,30000.0,556.28,0.00,LS 10); ABS
1: TOF MS ES+
3.46e7
100
%
0
541.3459
266.1397
288.1203
316.1539
396.1725
426.2184
427.2219
595.3820
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480
500
520
540
560
580
600
m/z

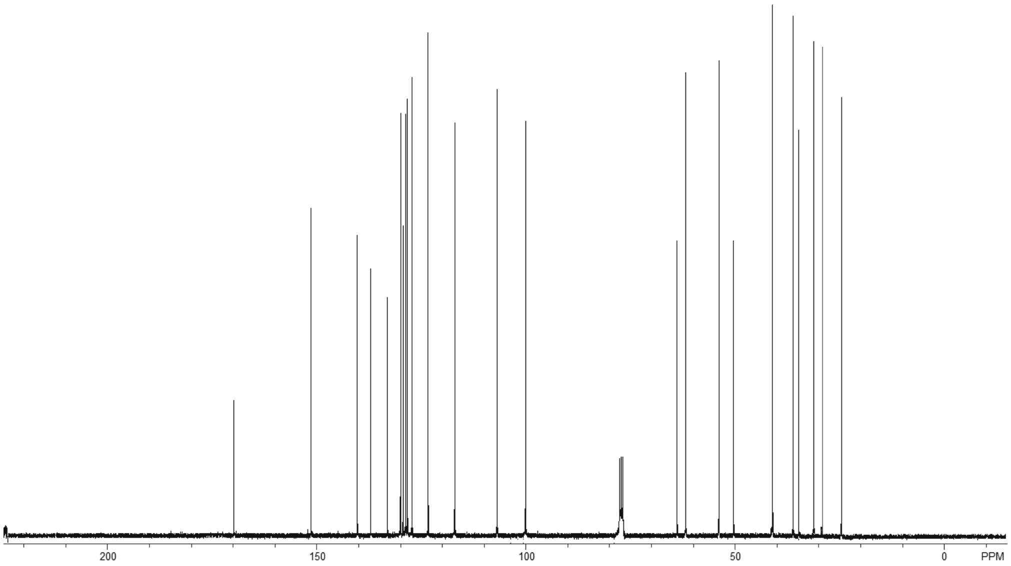

N
O
N
O
O
OTBS

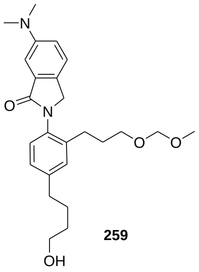
258


6.61
2.07
2.00
1.83
4.77
6.77
4.66
6.49
10
8
6
4
2
0
PPM

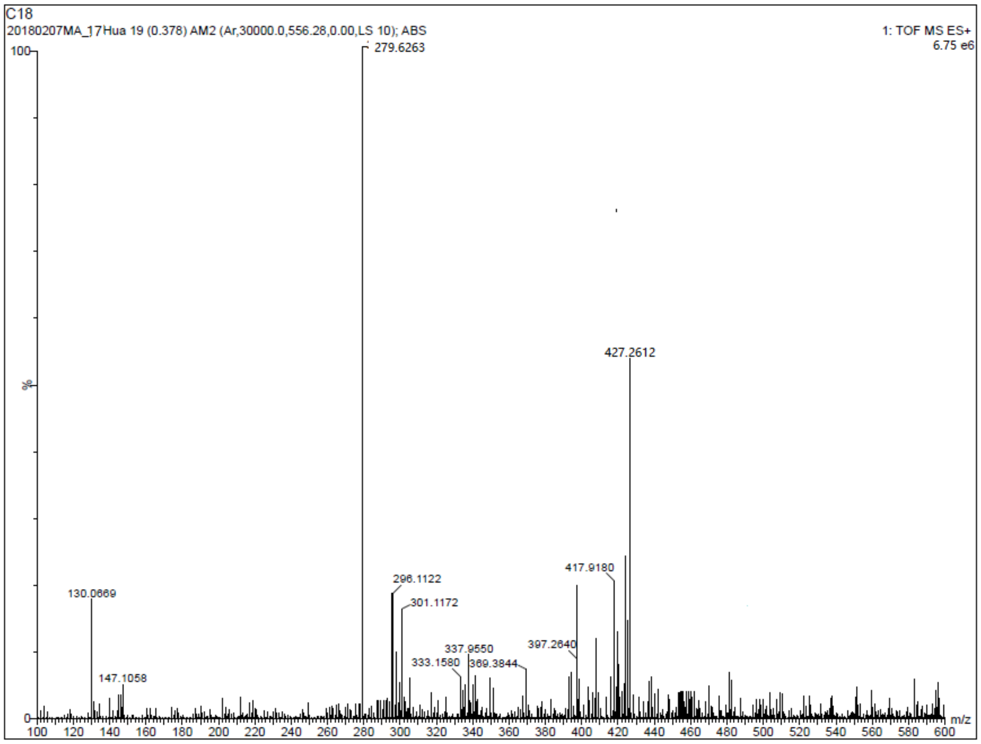

N
O
N
O
O
OH

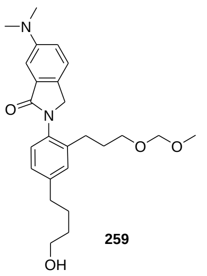
259


200
150
100
50
0
PPM

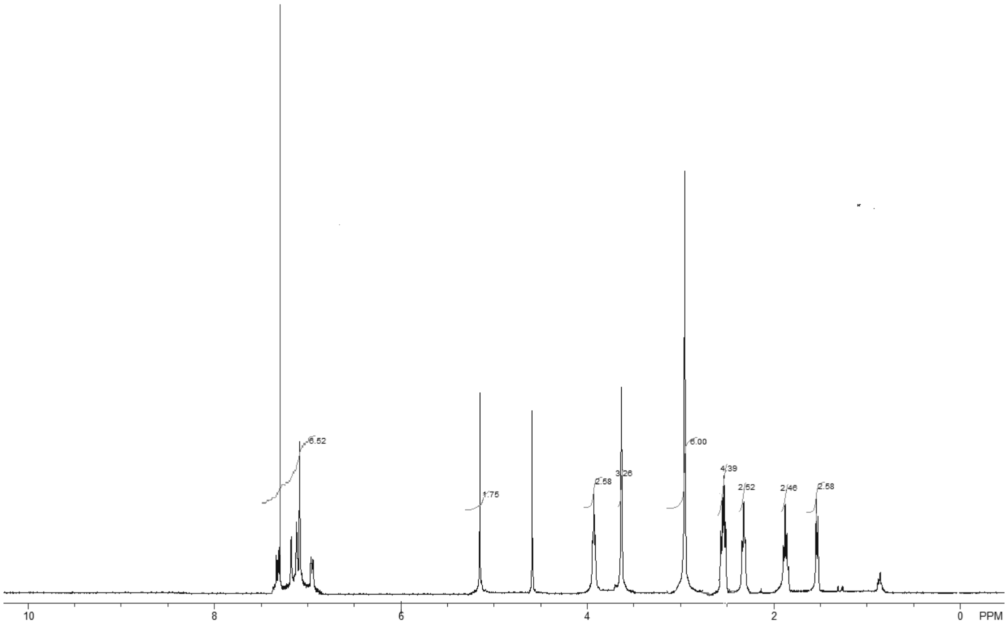

N
O
N
O
O
OH

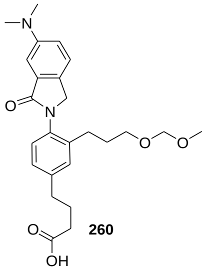
259


C18
20180207MA_17Hua 19 (0.378) AM2 (Ar,30000.0,556.28,0.00,LS 10); ABS
1: TOF MS ES+
6.75 e6
100
%
0
279.6263
427.2612
417.9180
296.1122
301.1172
130.0669
147.1058
337.9550
333.1580
369.3844
397.2640
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480
500
520
540
560
580
600
m/z

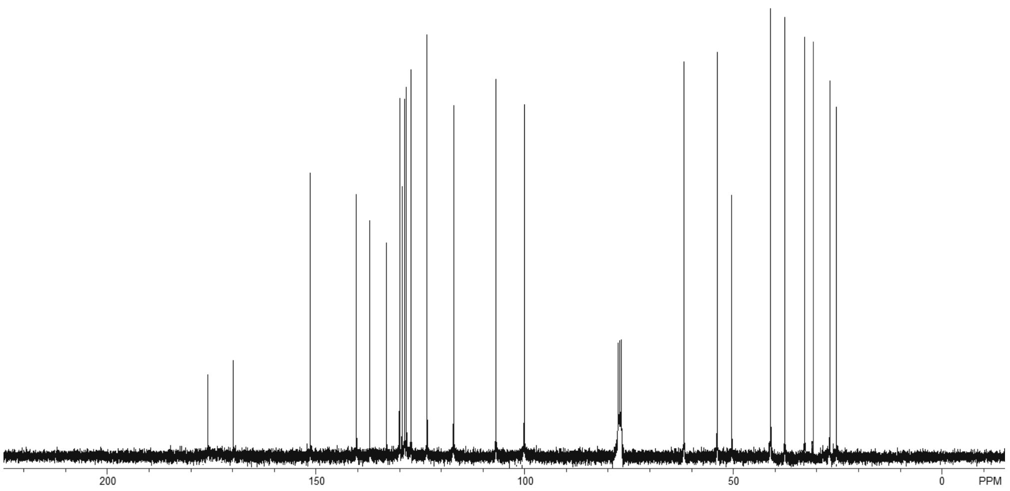

N
O
N
O
O
OH

259

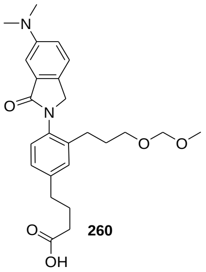

6.52
1.75
2.58
3.26
6.00
4.39
2.52
2.46
2.58
10
8
6
4
2
0
PPM


N
O
N
O
O
O
OH

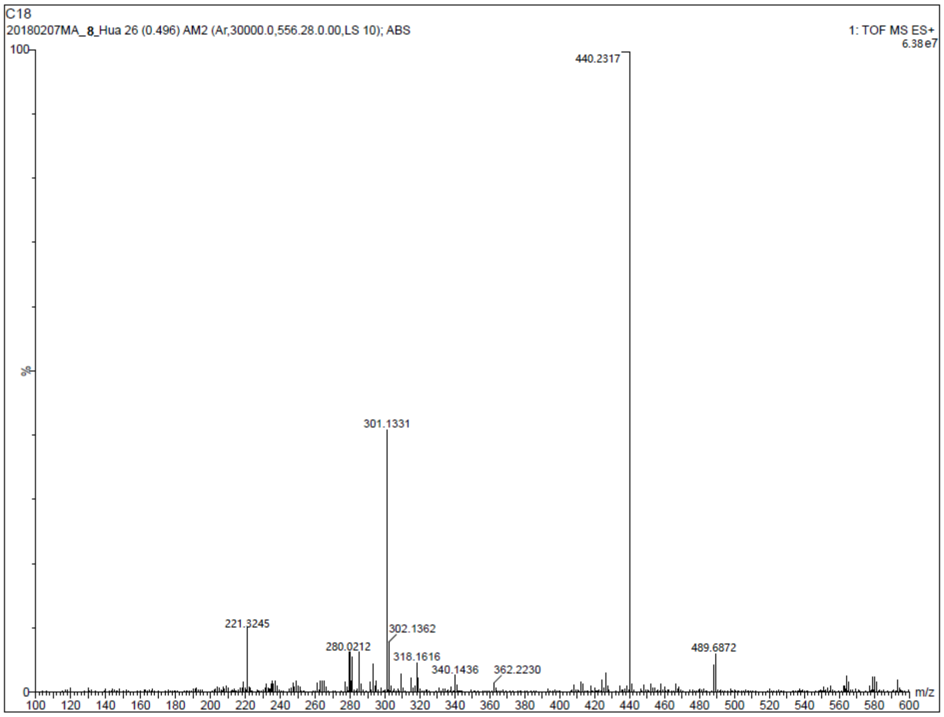
260



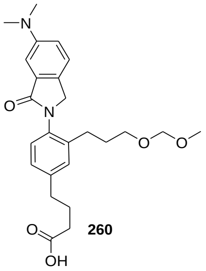
200
150
100
50
0
PPM



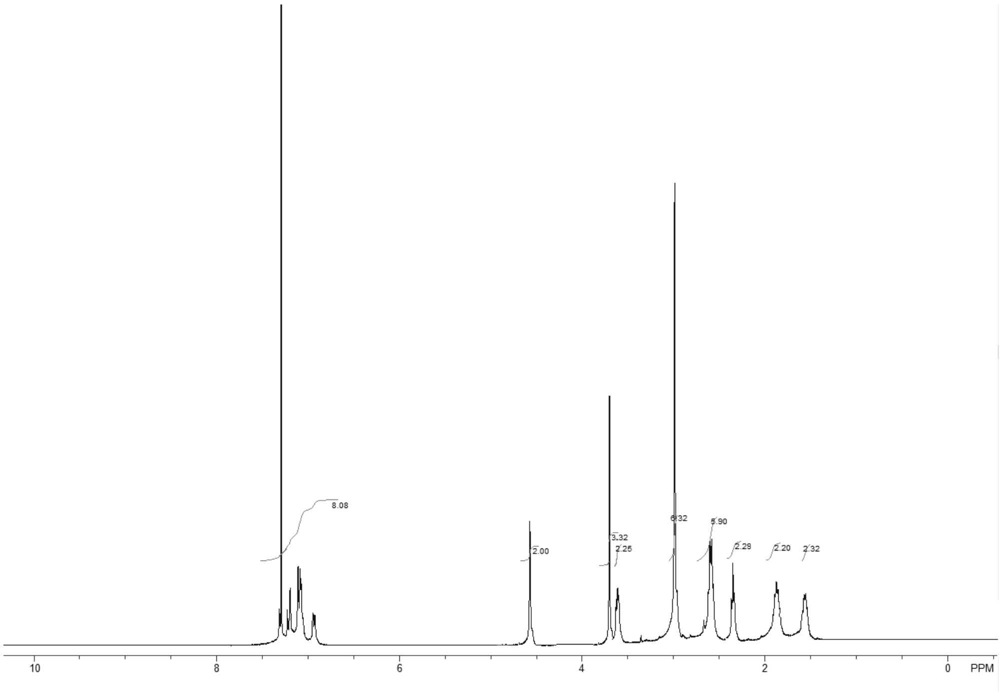
260

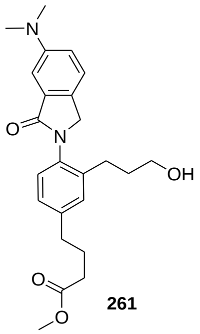


C18
20180207MA_8_Hua 26 (0.496) AM2 (Ar,30000.0,556.28.0.00,LS 10); ABS
1: TOF MS ES+
6.38e7
100
%
0
440.2317
301.1331
221.3245
280.0212
302.1362
318.1616
340.1436
362.2230
489.6872
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480
500
520
540
560
580
600
m/z

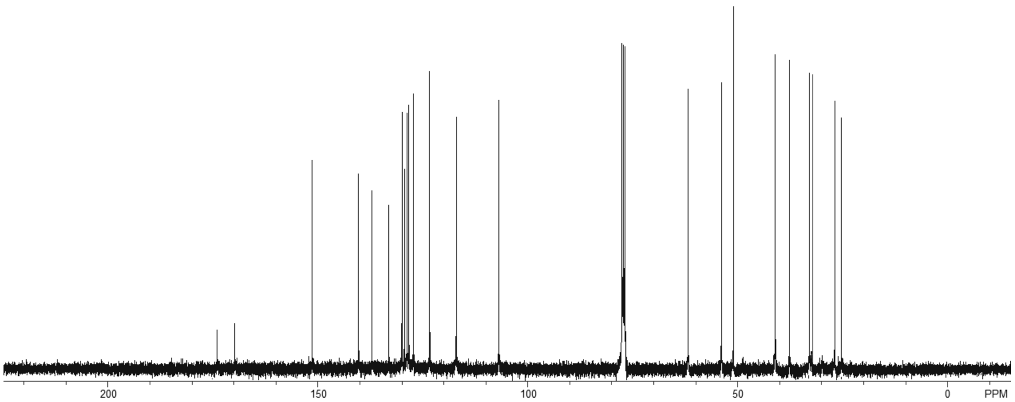


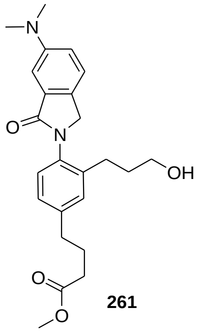
260


8.08
2.00
3.32
2.25
6.32
5.90
2.29
2.20
2.32
10
8
6
4
2
0
PPM

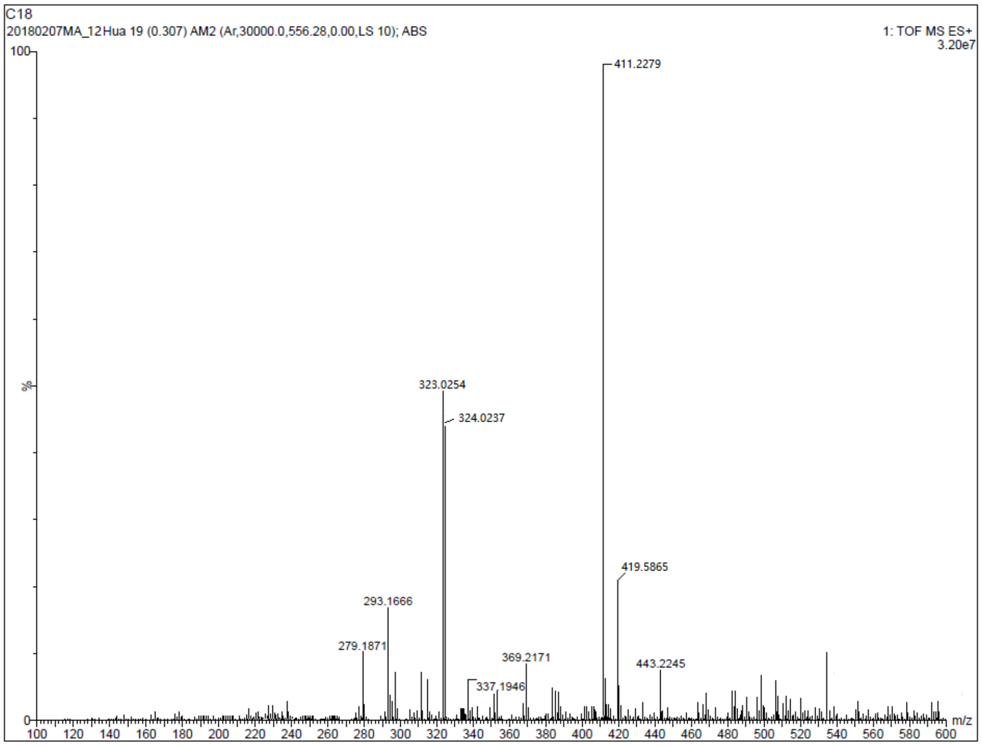

N
O
N
OH
O
O

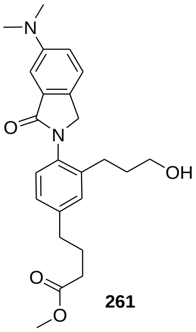
261


200
150
100
50
0
PPM

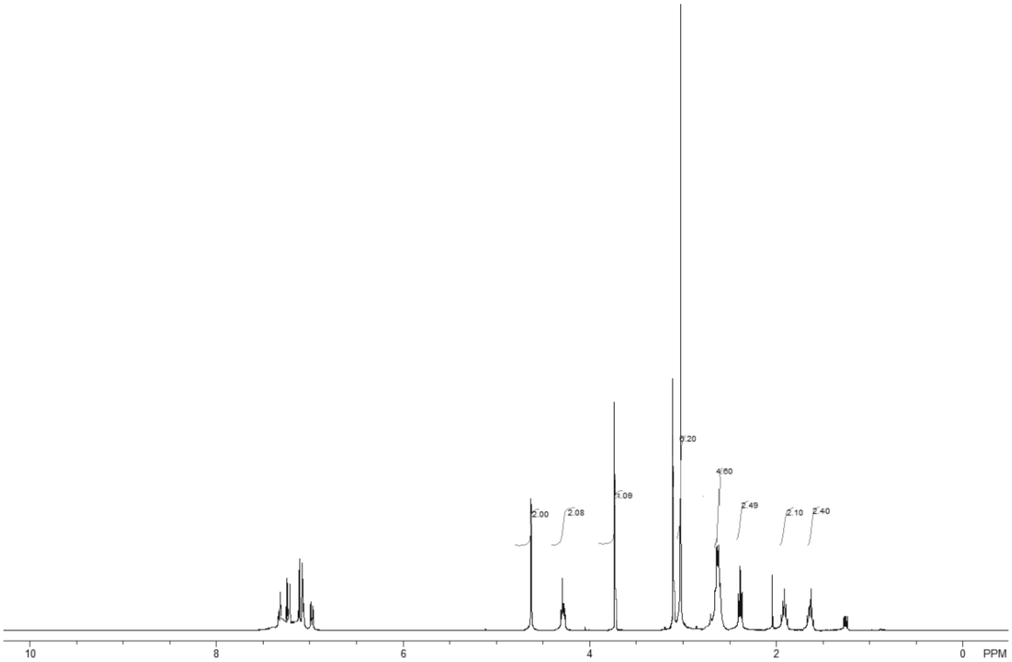

N
O
N
OH
O
O

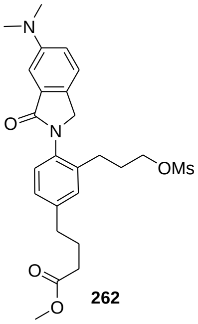
261


C18
20180207MA_12Hua 19 (0.307) AM2 (Ar,30000.0,556.28,0.00,LS 10); ABS
1: TOF MS ES+
3.20e7
100
%
0
411.2279
323.0254
324.0237
419.5865
293.1666
279.1871
369.2171
337.1946
443.2245
100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 580 600
m/z

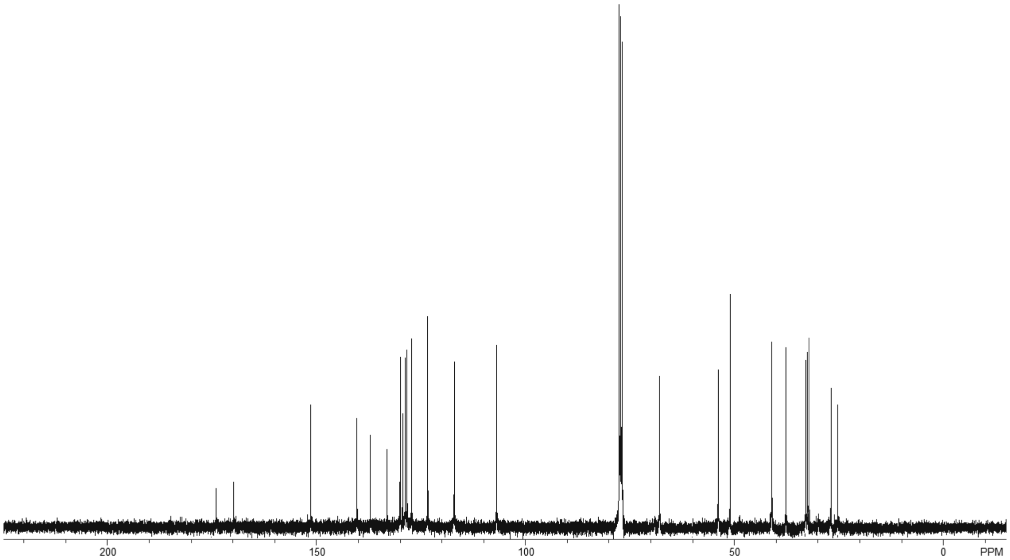

N
O
N
OH
O
O

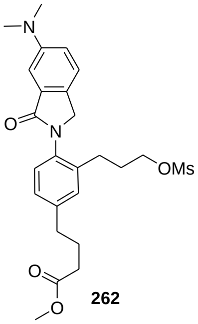
261


2.00
2.08
3.09
6.20
4.60
2.49
2.10
2.40
10
8
6
4
2
0
PPM

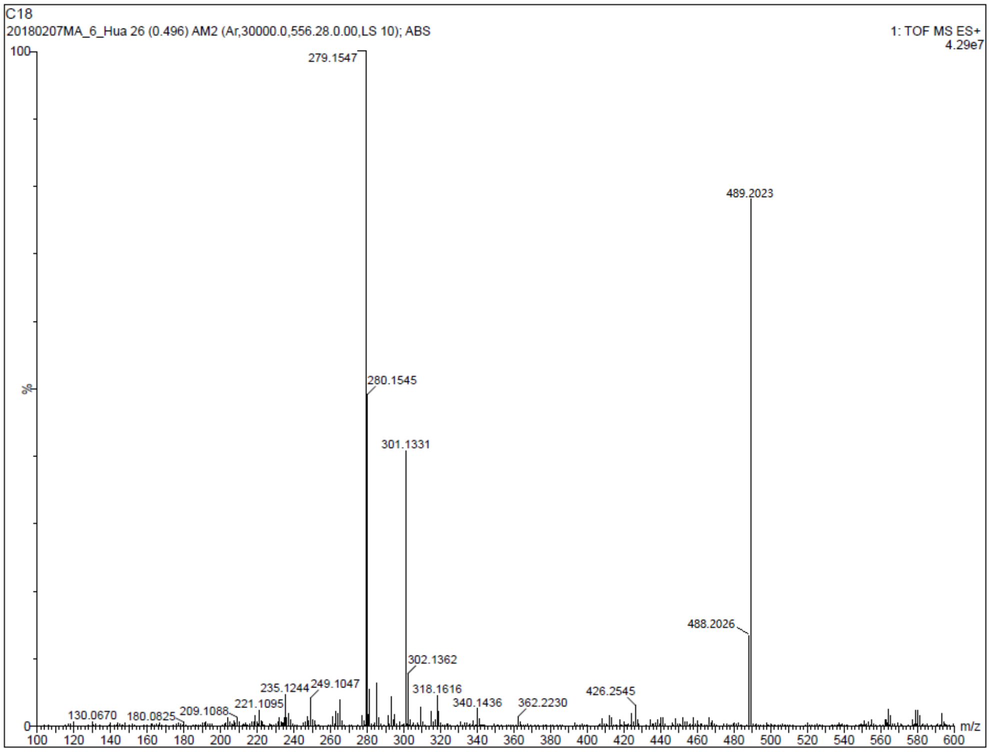

N
O
N
OMs
O
O

262


200
150
100
50
0
PPM


N
O
N
OMs
O
O

262


C18
20180207MA_6_Hua 26 (0.496) AM2 (Ar,30000.0,556.28.0.00,LS 10); ABS
1: TOF MS ES+
4.29e7
100
%
0
279.1547
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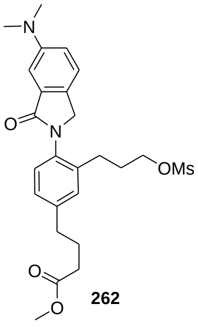
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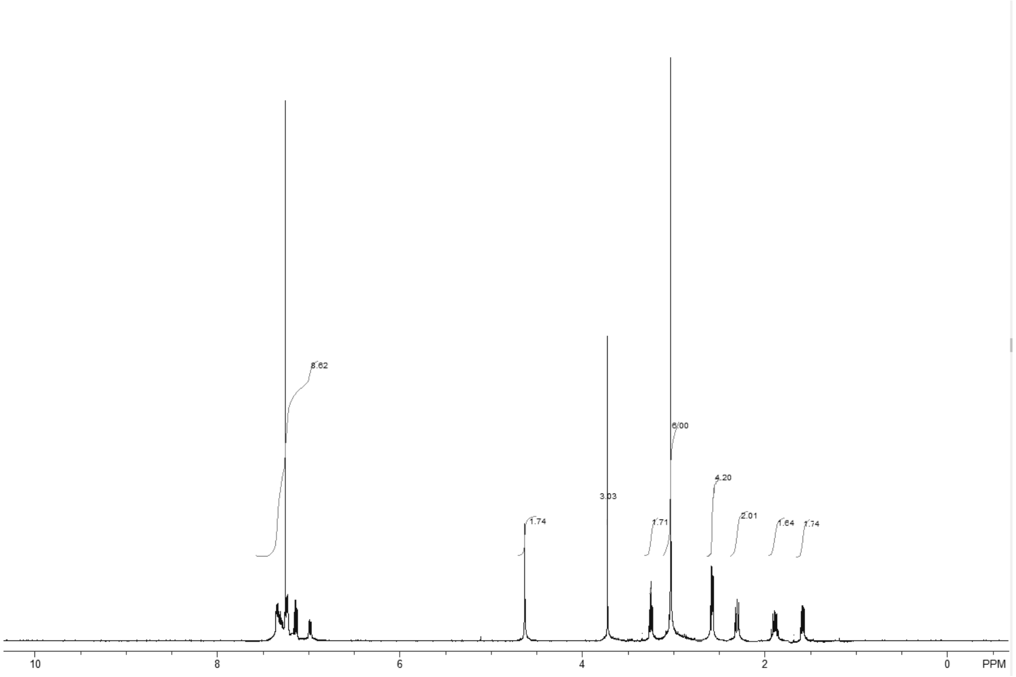
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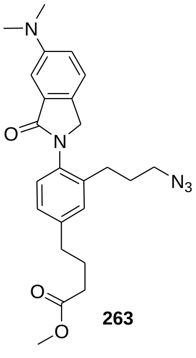
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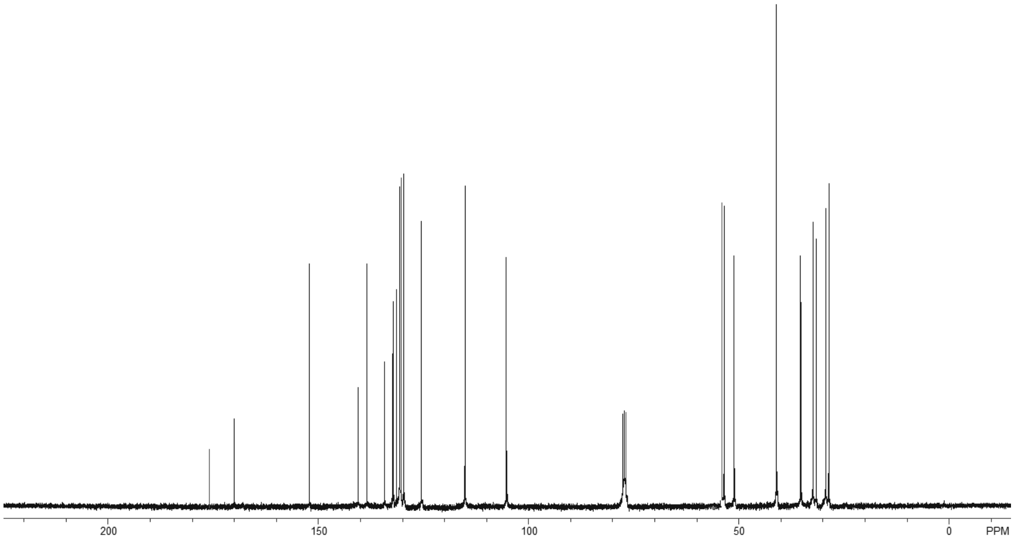
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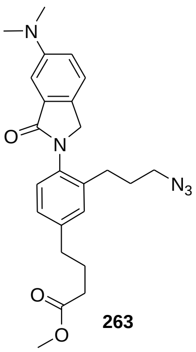
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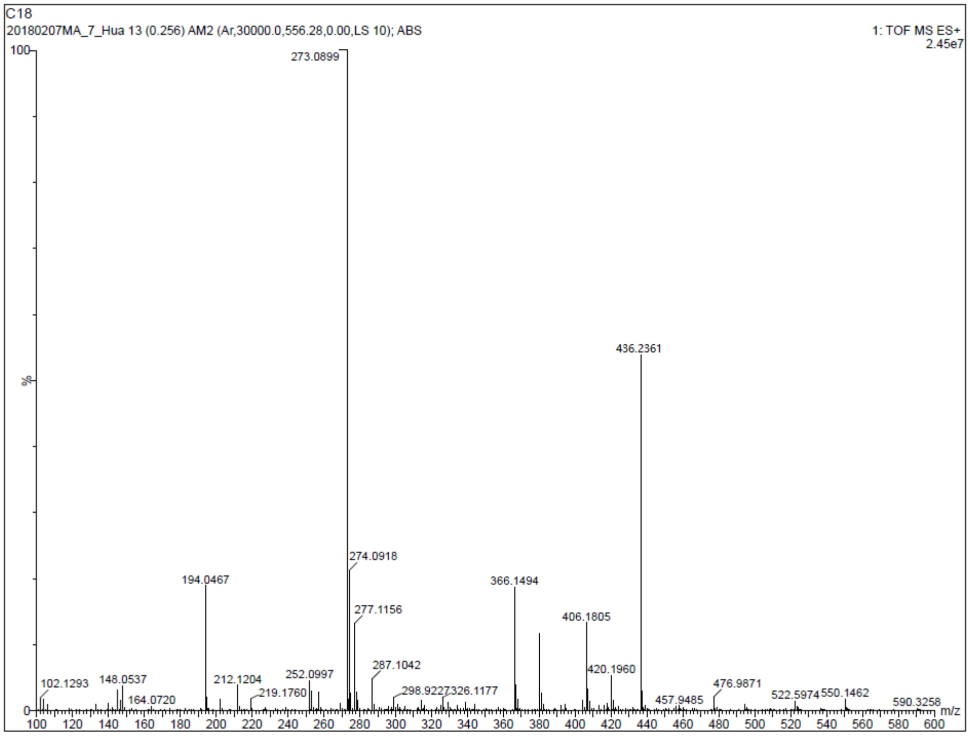
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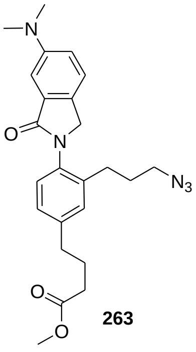
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263