The Development Of New Organocatalysts and New Organocatalytic Cascade Reactions

By

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ABSTRACT

The Development Of New Organocatalysts and Organocatalytic Cascade Reactions

By Patrick Gordon McGarraugh

Advisor: Professor Stacey Brenner-Moyer

Abstract: Organocatalysis is the use of small organic molecules to catalyze chemical reactions. They are generally cheaper, less toxic, and easier to handle on a laboratory and industrial scale than more traditional metal–based catalysts. This dissertation discusses the development of new organocatalysts and organocatalytic methods for the asymmetric synthesis of useful small molecules. The research conducted has specifically focused on the use of chiral diarylprolinol silyl ether organocatlysts and their ability to catalyze a variety of useful cascade reactions through iminium and enamine catalysis. Cascade reactions are useful in that a great deal of molecular complexity may be generated in a one–pot process using simple, readily available building blocks. Herein, is provided a comprehensive background on the use of diarylprolinol silyl ethers in the catalysis of iminium–initiated cascade reactions. The research conducted has focused on three main topics: 1.) The development of a novel class of bifunctional bissulfonamide organocatalysts for the asymmetric conjugate addition of dicarbonyls to nitroolefins. 2.) The use of diarylprolinol silyl ether organocatalysts to catalyze a novel Michael-Michael cascade reaction which generates fused carbocycles. 3.) The discovery and development of a novel organocascade kinetic resolution reaction using diarylprolinol silyl ether organocatalysts, which can be used for the synthesis of chiral 2,6-disubstituted tetrahydropyrans and chiral 2,5-disubstituted tetrahydrofurans.

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LIST OF SYMBOLS AND ABBREVIATIONS

Å	angstrom
$[\alpha]_D$	optical rotation
Ac	acetyl
AcO	acetate
AcOH	acetic acid
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
c	concentration
°C	degree Celsius
^{13}C NMR	carbon-13 nuclear magnetic resonance
calcd	calculated
Cbz	carboxybenzyl
$CDCl_3$	deuterated chloroform
CD_2Cl_2	deuterated dichloromethane
CD_3CN	deuterated acetonitrile
Conv	Conversion
CSA	camphorsulfonic acid
δ	nuclear magnetic shift

d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DKR	dynamic kinetic resolution
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
E^+	electrophile
ee	enantiomeric excess
epi	epimer
equiv	equivalents
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
Et_2O	diethyl ether

Et_3N	triethylamine
EWG	electron withdrawing group
FT-IR	Fourier transform infrared spectroscopy
g	gram
h	hour
^{1}H NMR	proton nuclear magnetic resonance
hfc	3-(heptafluoropropylhydroxymethylene)-camphorate
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resonance mass spectrometry
Hz	Hertz
*i*Pr	*iso*-propyl
*i*PrOH	*iso*-propyl alcohol
IR	infrared
J	coupling constant
kcal	kilocalorie
L	liter
LRMS	low resonance mass spectrometry
m	multiplet
M	molar
M^+	positively charged mass
M^-	negatively charged mass
mM	millimolar

MBH	Morita–Baylis–Hillman
MCR	multi-component reaction
Me	methyl
MeCN	acetonitrile
MeO	methoxy
MeOH	methanol
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
mol	mole
mol %	mole percent
MS	molecular sieves
MTBD	9-methyl-2,3,4,6,7,8-hexahydropyrimido[1,2-a]pyrimidine
NaOAc	sodium acetate
*n*BuLi	*n*-butyl lithium
Nf	nonaflate
NFSI	*N*-fluorobenzenesulfonimide
NMO	*N*-Methylmorpholine-*N*-oxide
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu^-	nucleophile

obsd	observed
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
pH	potential of hydrogen
$PhCO_2H$	benzoic acid
pK_a	ionization constant
PMB	*para*-methoxybenzyl
PNB	*para*-nitrobenzoate
ppm	parts per million
rac	racemic
rt	room temperature
s	singlet
t	triplet
TBAF	tetra-*N*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
*t*Bu	*tert*-butyl
*t*BuLi	*tert*-butyl lithium
Temp.	temperature
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl
TS	transition state
TSes	transition states
TsO	tosylate
UV	ultraviolet
µL	microliter
wt.%	weight percent

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Chapter 1.

Introduction To Organocatalysis

1.1 Organocatalysis

Developing sustainable, environmentally friendly methods to carry out chemical transformations is of the utmost importance in preserving our planet and its people. Therefore, reducing the amount of contaminants produced by a chemical process is invaluable in developing new methods in organic synthesis. Catalysis is one technique employed by organic chemists to do this. A catalyst is able to accelerate a chemical reaction in only small amounts by lowering the activation energy required for a reaction to occur. This reduces the amount of energy required for a process, and because catalysts are only used in sub-stoichiometric amounts, they can reduce the amount of waste generated by a process.

Historically, most catalysts have consisted of one or more heavy metal atoms. Catalysts of this type have been used in a number of extremely important chemical reactions in the laboratory and on an industrial scale. While catalysts of this type have led to tremendous breakthroughs in the synthesis of many useful compounds, they do have their drawbacks. Metal catalysts can be very costly, toxic in only trace amounts, and difficult to handle (e.g., air and water sensitive).

Organocatalysis is the use of small organic molecules to catalyze a chemical reaction.[1] Catalysts of this type consist only of carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorous and other non–metal elements. Organocatalysts are advantageous when compared to metal catalysts for a variety of reasons. They are generally much cheaper to make as compared to metal catalysts, because they are derived from simple, readily available organic molecules. They

are generally not air or water sensitive, making them much easier to handle on a laboratory and an industrial scale. Most importantly, they are generally less toxic than metal catalysts. This becomes important in the synthesis of pharmaceuticals, when the target molecule being made must be free from trace metal contamination. Organocatalysts thus represent a "green" alternative to metal catalysts in organic synthesis, and more specifically, the synthesis of biologically active molecules.

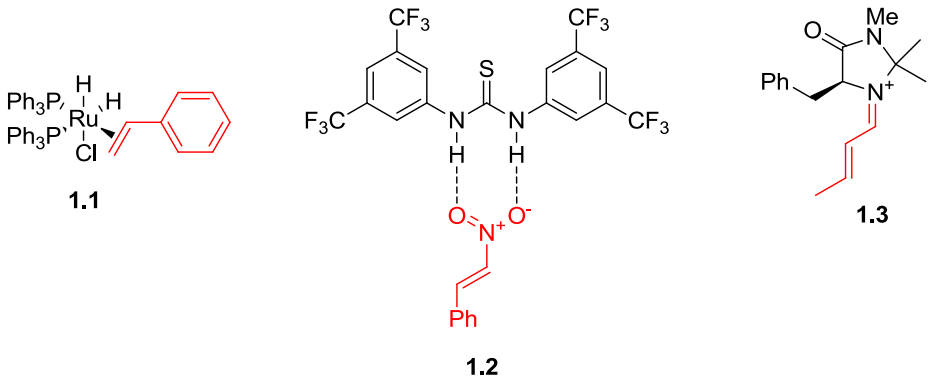
The last fifteen years have seen a huge flux in the amount of research being conducted in the field of asymmetric organocatalysis.[1] Several hundred papers each year describe the development of new organocatalysts and new organocatalytic methods for the synthesis of important synthetic intermediates and biologically active compounds.[1] Although the field is still relatively young, especially when compared to metal catalysis, many asymmetric organocatalytic methods are establishing themselves as extremely powerful tools for the synthesis of relevant molecular scaffolds.

The research described in this dissertation focuses on the development of new asymmetric organocatalysts and organocatalytic methods. The goal of this research has been to not only use these new catalysts and methods for the generation of synthetically useful molecular scaffolds, but also to investigate the mechanisms through which these organocatalytic processes operate. A thorough understanding of how known organocatalysts work could lead to the discovery of potentially more efficient and useful catalysts and catalytic methods in the future.

1.2 Types of Organocatalysts

Metal catalysts generally interact with a potential substrate through coordination of the substrate to an empty position on the metal atom (complex **1.1** in **Figure 1.1**).[2] Different organocatalysts, on the other hand, can operate in different ways.

Figure 1.1 Different Types of Catalyst Activated Complexes



Hydrogen bonding organocatalysts operate by donation of non-covalent hydrogen bonds to the substrate (complex **1.2** in **Figure 1.1**).[3] This hydrogen bond donation withdraws electron density from the substrate molecule, making it more susceptible to nucleophilic attack. Once the nucleophilic attack on the substrate molecule has taken place, the hydrogen bond donating catalyst can go on to activate another molecule of the substrate.

Many organocatalysts operate by covalently bonding with the substrate molecule to form a reactive species (complex **1.3** in **Figure 1.1**).[4] This high energy reactive species undergoes a chemical reaction, and then the catalyst is released from the product so it is free to form the reactive species with another substrate molecule.

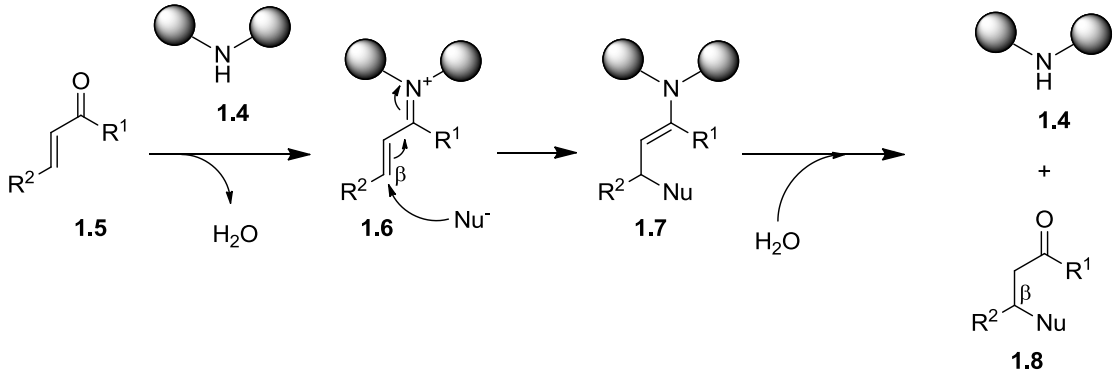
Covalently bonding organocatalysts generally contain a secondary, or a primary, amine functionality. They are generally used to activate carbonyl containing compounds such as

ketones and aldehydes. There are two main modes of activation through which these amine organocatalysts activate aldehydes and ketones: "iminium catalysis" and "enamine catalysis".

1.3 Iminium Catalysis

In iminium catalysis, an amine catalyst of type **1.4** and an α,β-unsaturated carbonyl compound of type **1.5** condense to form an iminium ion of type **1.6**. This condensation is accompanied by the release of water (**Scheme 1.1**). The iminium ion formed is a highly reactive species which is susceptible to conjugate addition at the β-position. This conjugate addition can be an *inter*molecular or *intra*molecular process.

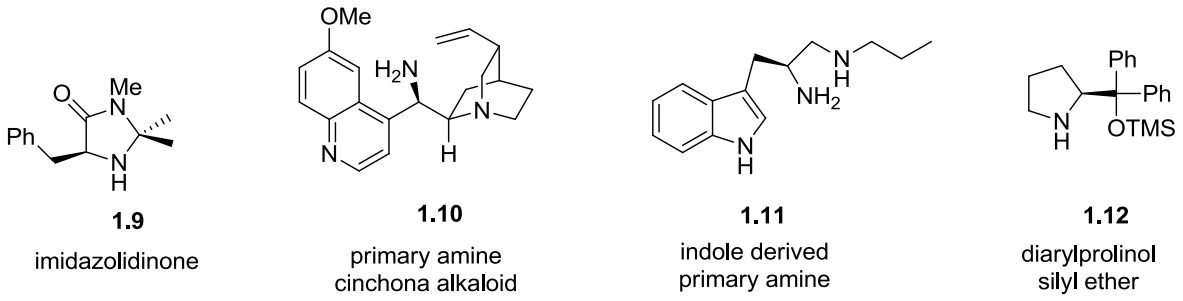
Scheme 1.1 Iminium Catalysis



Once the conjugate addition occurs with a nucleophile (Nu^-), the resulting enamine **1.7** is hydrolyzed to give β-functionalized carbonyl compounds of type **1.8**. The amine catalyst, which becomes free after hydrolysis, can now activate another substrate molecule. This type of catalysis can be made asymmetric by using a chiral amine catalyst which will direct from which face the nucleophile attacks the reactive species. Many different chiral iminium forming organocatalysts have been developed and used in a variety of asymmetric conjugate additions[5]

and cycloaddition reactions.[4] A few important iminium–forming catalysts (**1.9**–**1.12**)[4,6-8] are shown in **Figure 1.2**.

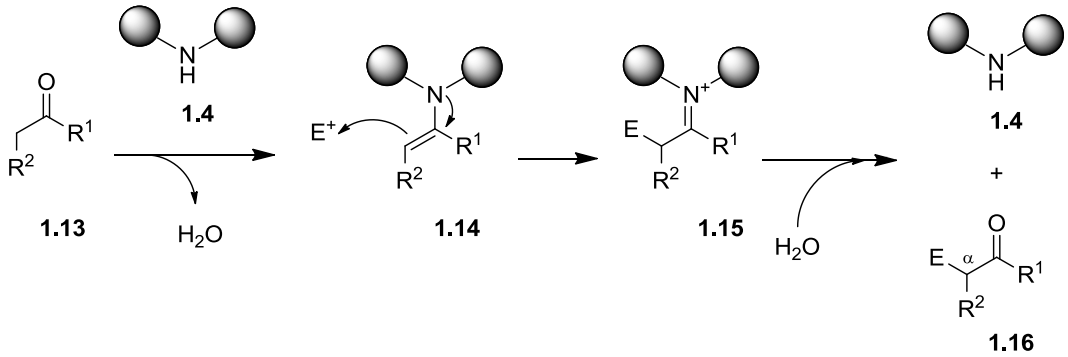
Figure 1.2 Iminium–Forming Catalysts



1.4 Enamine Catalysis

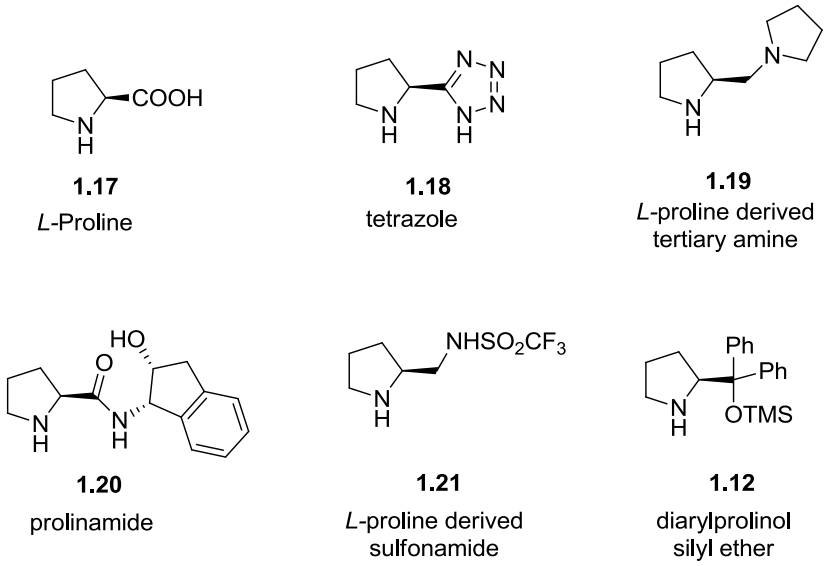
In enamine catalysis, an amine catalyst of type **1.4** and a saturated carbonyl compound of type **1.13** condense to form an enamine species of type **1.14**. This condensation is accompanied with the release of water into the reaction mixture. The enamine which is formed can now act as a nucleophile and react with an electrophile (E^+) via an *inter*molecular or *intra*molecular reaction.

Scheme 1.2 Enamine Catalysis



Once this reaction occurs, the resulting iminium ion **1.15** is hydrolyzed to give α-functionalized products of type **1.16**. The catalyst, which is also released, is free to activate another molecule of the substrate. This type of catalysis can also be made asymmetric by using a chiral amine catalyst which will direct the approach of the electrophile toward the enamine.[9] Some of these chiral enamine–forming catalysts (**1.17**–**1.21** and **1.12**)[10-15] are depicted in **Figure 1.3**.

Figure 1.3 Enamine–Forming Catalysts



1.5 Diarylprolinol Silyl Ether Organocatalysts

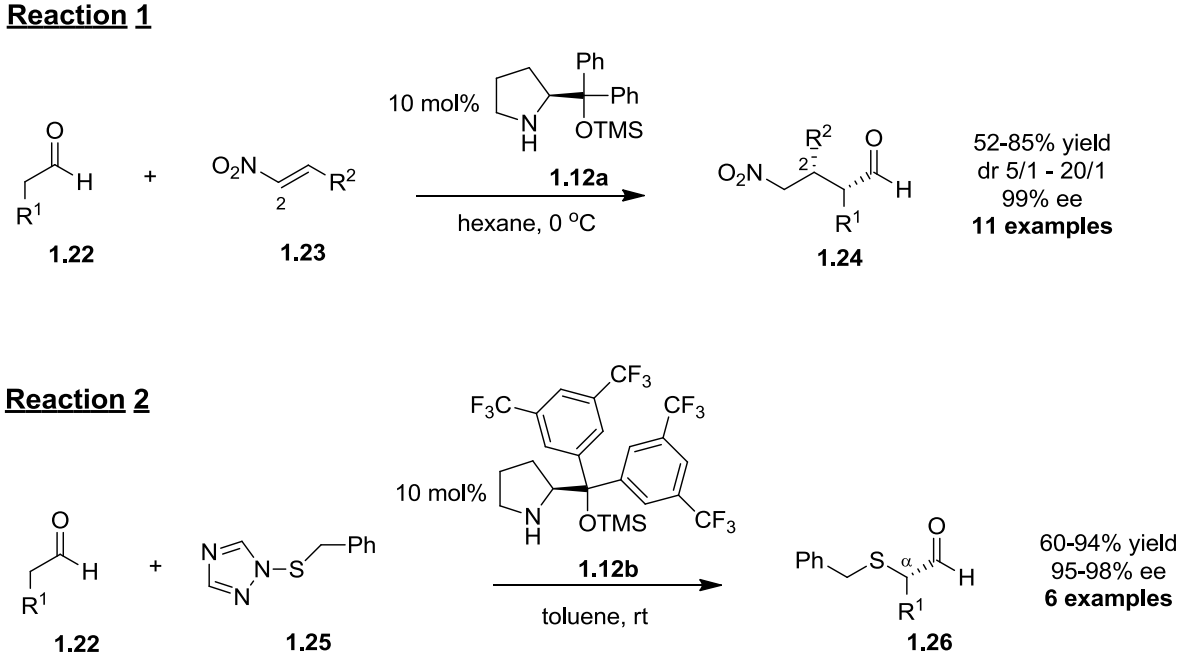
Iminium–forming catalysts and enamine–forming catalysts both possess a similar amine functionality. Interestingly, it is rare when an organocatalyst is effective at catalyzing both iminium– and enamine–type reactions in good conversion with high selectivity. However, diarylprolinol silyl ethers, such as **1.12**, have proven to be extremely efficient asymmetric

catalysts for a variety of enamine– *and* iminium–catalyzed transformations involving aldehydes.[16]

1.6 Diarylprolinol Silyl Ethers in Enamine Catalysis

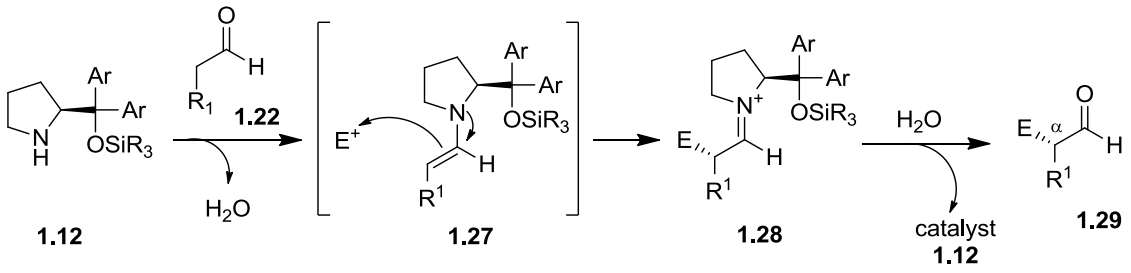
Diarylprolinol silyl ethers of type **1.12** were first independently used as enamine–forming organocatalysts by Hayashi et al.[15] and Jørgensen et al.[17] in 2005. Hayashi used catalyst **1.12a** for the addition of aliphatic aldehydes of type **1.22** to nitroolefins of type **1.23** to give products of type **1.24**, which contain two stereocenters (**Reaction 1**, **Scheme 1.3**). Jørgensen used catalyst **1.12b** for the sulfenylation of aliphatic aldehydes with **1.25** to give α-functionalized products of type **1.26** (**Reaction 2**, **Scheme 1.3**).

Scheme 1.3 Earliest Use Of Diarylprolinol Silyl Ethers as Organocatalysts



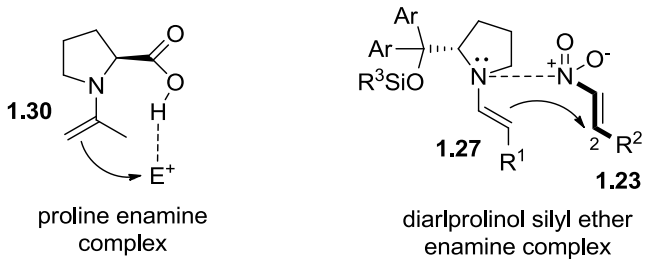
Diarylprolinol silyl ethers activate aliphatic aldehyde substrates for enamine catalysis and induce asymmetric induction via the mechanism illustrated in (**Scheme 1.4**). An enamine of type **1.27** is formed from condensation of the aldehyde (**1.22**) and the catalyst (**1.12**). The more stable *E*-enamine is exclusively formed. The C=C bond of the enamine orients itself on the side of the pyrrolidine ring opposite the bulky diaryl silyl ether substituent. The electrophile (E^+) approaches the complex from the opposite face of the bulky substituent, imparting selectivity in bond formation and giving an iminium species of type **1.28**. The catalyst is released via hydrolysis of the iminium ion giving enantioenriched, α-functionalized products of type **1.29**.

Scheme 1.4 Mechanism of Enamine Catalysis by Diarylprolinol Silyl Ethers



In Hayashi's Michael addition, the stereochemical configuration of the 2-carbon in **1.24** is set by the orientation of the approaching nitroolefin. It is suggested that a stabilizing electrostatic interaction between the nitro group and the enamine nitrogen atom is responsible for the orientation observed (**Figure 1.4**).

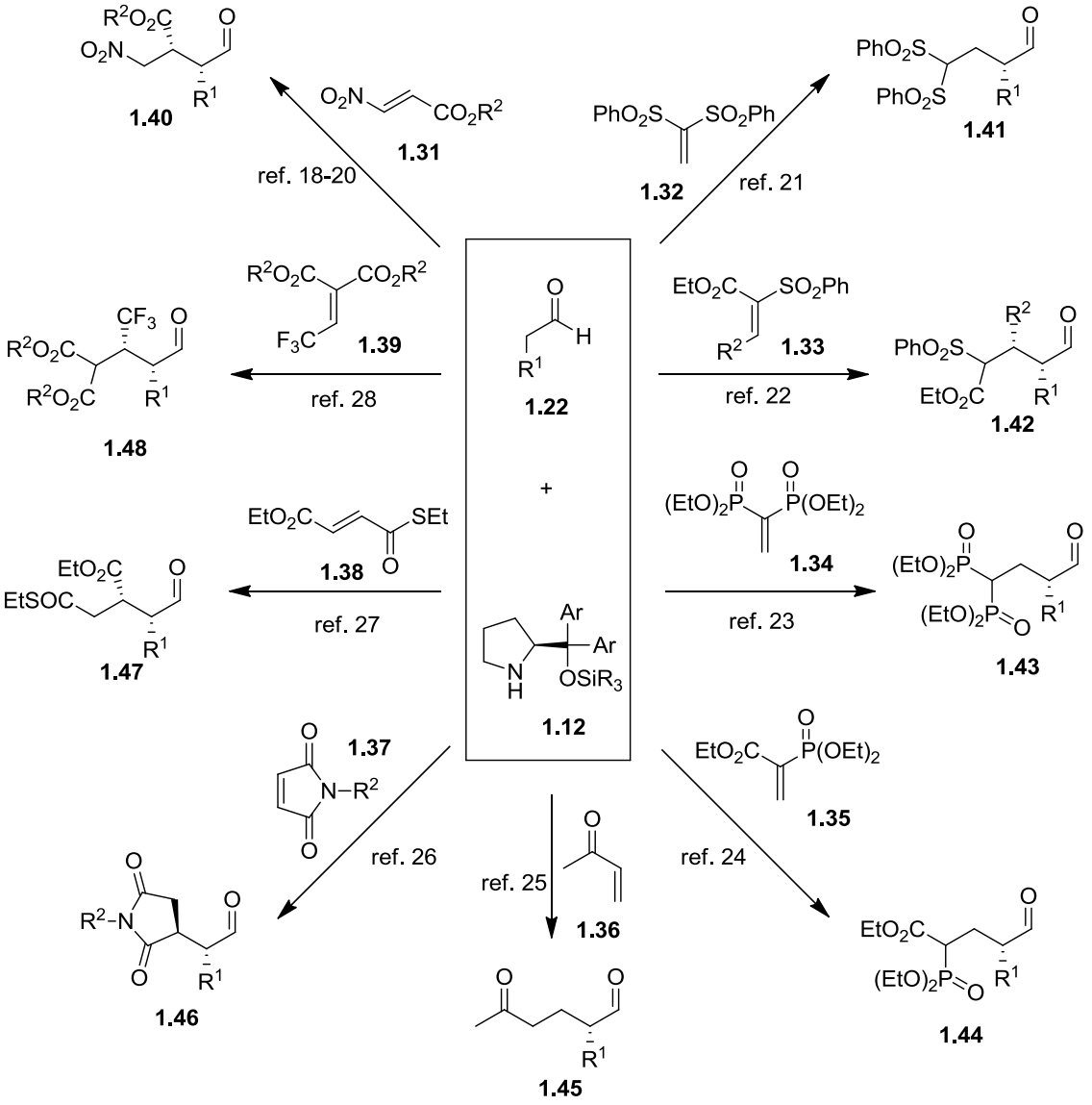
Figure 1.4 Approach of Electrophile In *L*-proline vs. Diarylprolinol Silyl Ether



First generation enamine organocatalysts such as *L*-proline direct the approach of the incoming electrophile through a hydrogen bonding interaction (**Figure 1.4**).[10] This interaction results in approach of the electrophile (E^+) from the same face as the pyrrolidine substituent, as observed in enamine complex **1.30**. However, diarylprolinol silyl ethers direct the incoming electrophile through a steric blocking interaction, promoting approach from the opposite side of the pyrrolidine substituent. In this way, two different organocatalysts can give products of a similar enamine catalyzed reaction with opposite stereochemical configurations at the α-position.

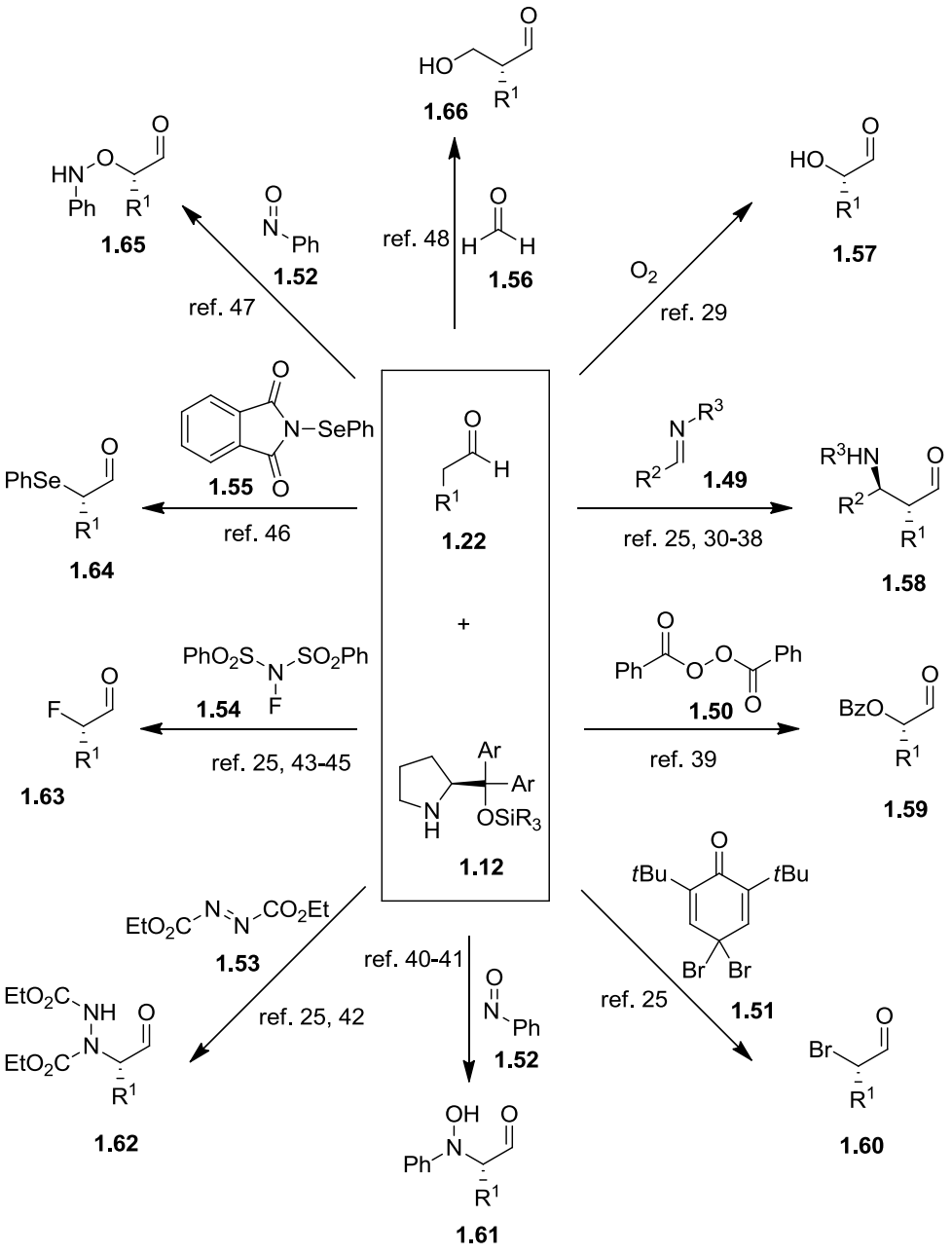
In the past six years since the first use of diarylprolinol silyl ethers as enamine–forming catalysts, there have been many reactions developed with a wide variety of electrophiles. Some of the different Michael additions that have been performed, which involve Michael acceptors **1.31**–**1.39** and products **1.40**–**1.48**, are illustrated in **Scheme 1.5**.[18-28]

Scheme 1.5 Enamine–Catalyzed Michael Additions with Diarylprolinol Silyl Ethers



In addition to the α-sulfenylation reaction described previously (**Reaction 2**, **Scheme 1.3**), other α-functionalizations have been performed with a wide array of reagents (**1.49**–**1.56**) to give many diverse products (**1.57**–**1.66**) (**Scheme 1.6**).[25,29-48]

Scheme 1.6 Enamine–Catalyzed α-Functionalizations with Diarylprolinol Silyl Ethers

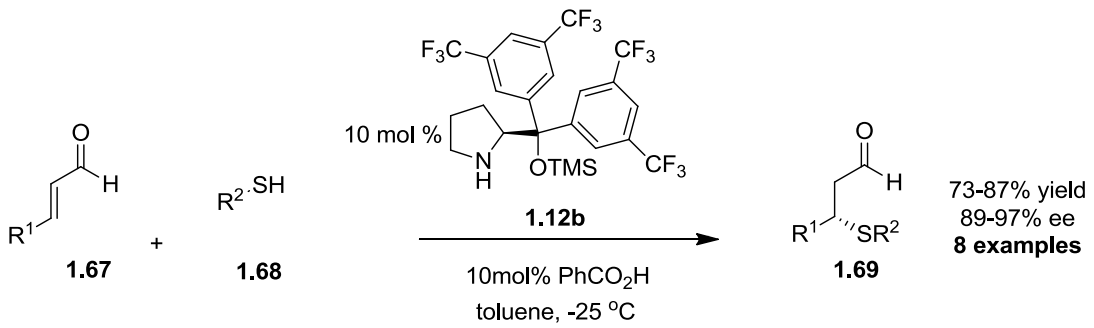


1.7 Diarylprolinol Silyl Ethers in Iminium Catalysis

One of the earliest reactions utilizing diarylprolinol silyl ethers as iminium–forming organocatalysts was reported in 2005 by Jorgensen et al.[8] Thiols of type **1.68** were added to α,β-

unsaturated aldehydes of type **1.67** in the presence of catalyst **1.12b** (**Scheme 1.7**). This reaction gave β-functionalized aldehydes of type **1.69** with outstanding selectivity.

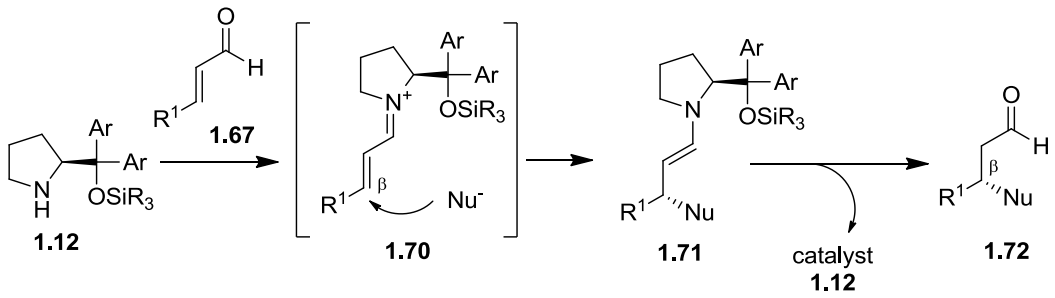
Scheme 1.7 Iminium–Catalyzed Addition of Thiols to α,β Unsaturated Aldehydes



Benzoic acid is used as a cocatalyst in this reaction in order to promote catalyst turnover. This practice of using a simple acid cocatalyst in conjunction with an asymmetric iminium–forming catalyst is quite common.

The mechanism of asymmetric induction for this type of process is illustrated in **Scheme 1.8**. The catalyst (**1.12**) condenses with α,β-unsaturated aldehyde (**1.67**) to form highly reactive conjugated iminium ions of type **1.70**. The C=C bond of the iminium ion orients itself on the side of the pyrrolidine ring opposite the bulky diaryl silyl ether substituent. Nucleophilic attack occurs at the β-position with the nucleophile (Nu^-) approaching from the opposite face of the bulky substituent. The resulting enamine of type **1.71** is hydrolyzed, releasing the catalyst and β-functionalized products of type **1.72**.

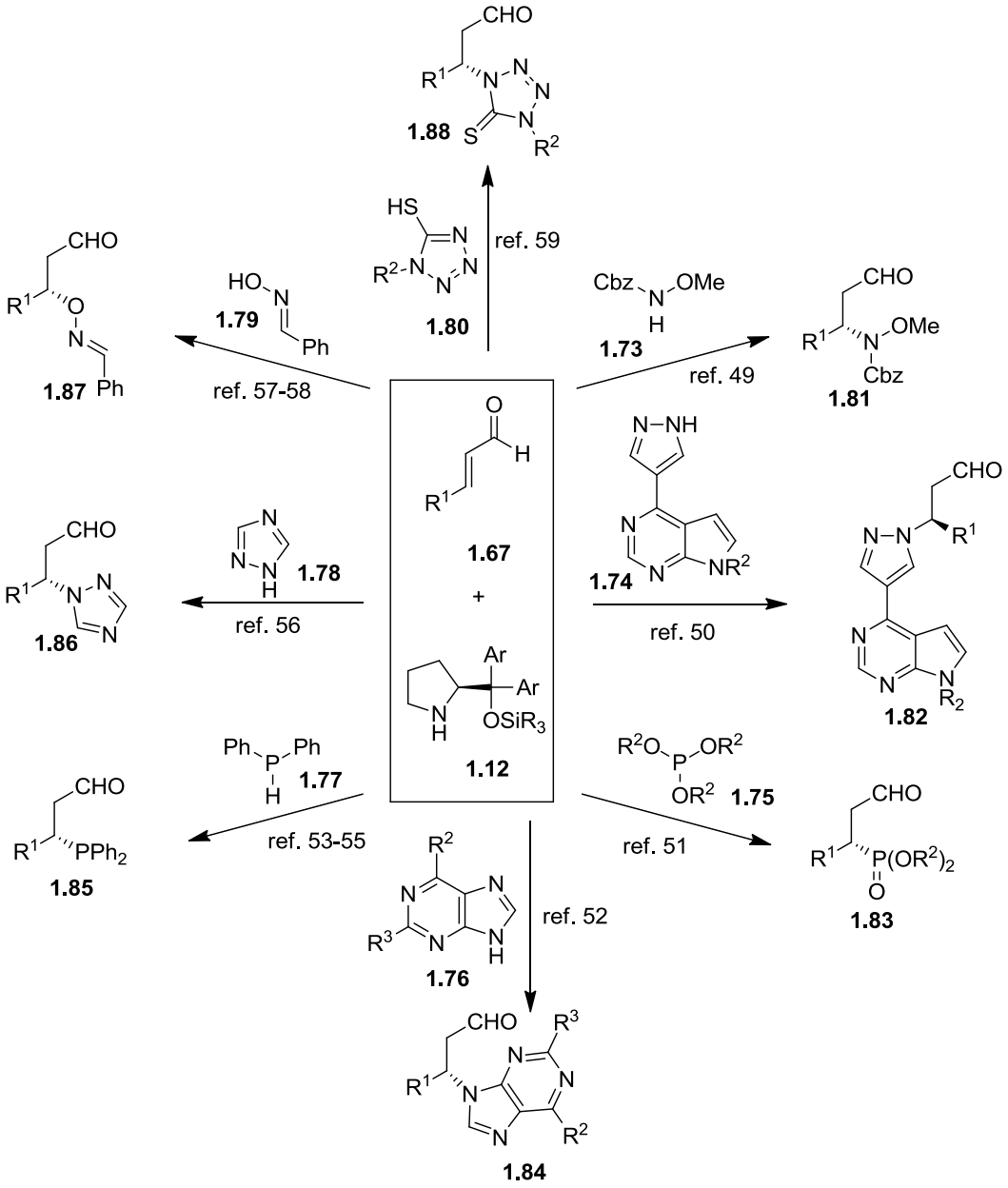
Scheme 1.8 Mechanism of Iminium Catalysis with Diarylprolinol Silyl Ethers



The process of asymmetric induction is similar to that of the enamine–catalyzed process in that the steric bulk of the silyl group serves two functions. It dictates on which side of the pyrrolidine ring the reactive center of the complex is situated, and it also blocks approach of the incoming reactant from one face forcing bond formation to occur at the less hindered face.

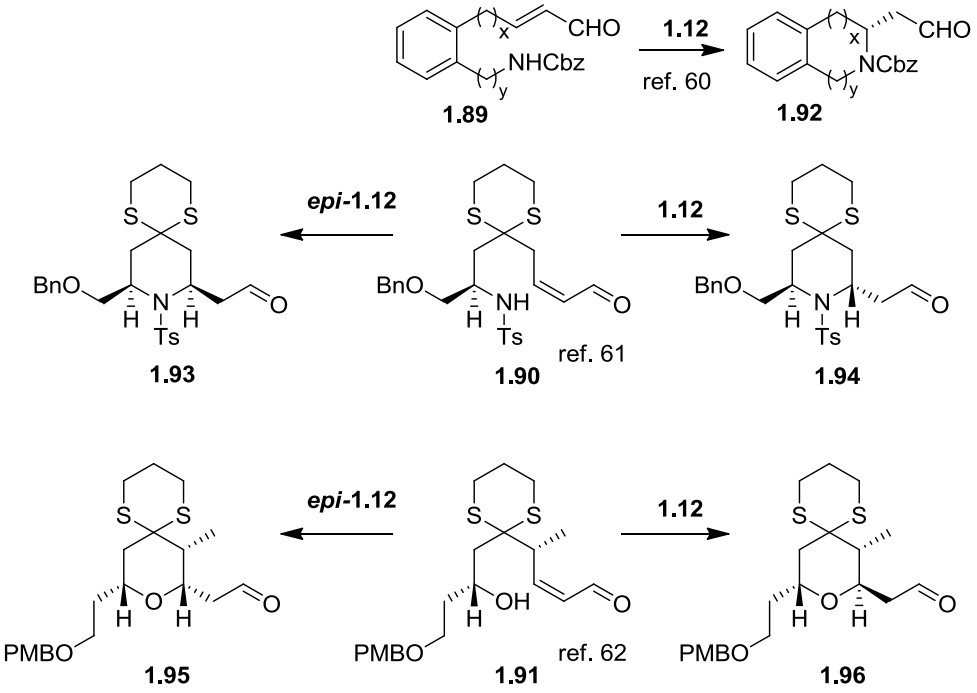
Since the initial discovery that diarylprolinol silyl ethers could participate in iminium catalysis as well as enamine catalysis, they have been used in many asymmetric reactions with a variety of Michael donors. Some examples of *inter*molecular hetero-Michael additions catalyzed by diarylprolinol silyl ethers are shown in **Scheme 1.9**.[49-59] By using Michael donors **1.73**–**1.80**, products **1.81**–**1.88** containing new C–N, C–O, and C–P bonds can be formed.

Scheme 1.9 Intermolecular Hetero-Michael Additions Catalyzed by Diarylprolinol Silyl Ethers



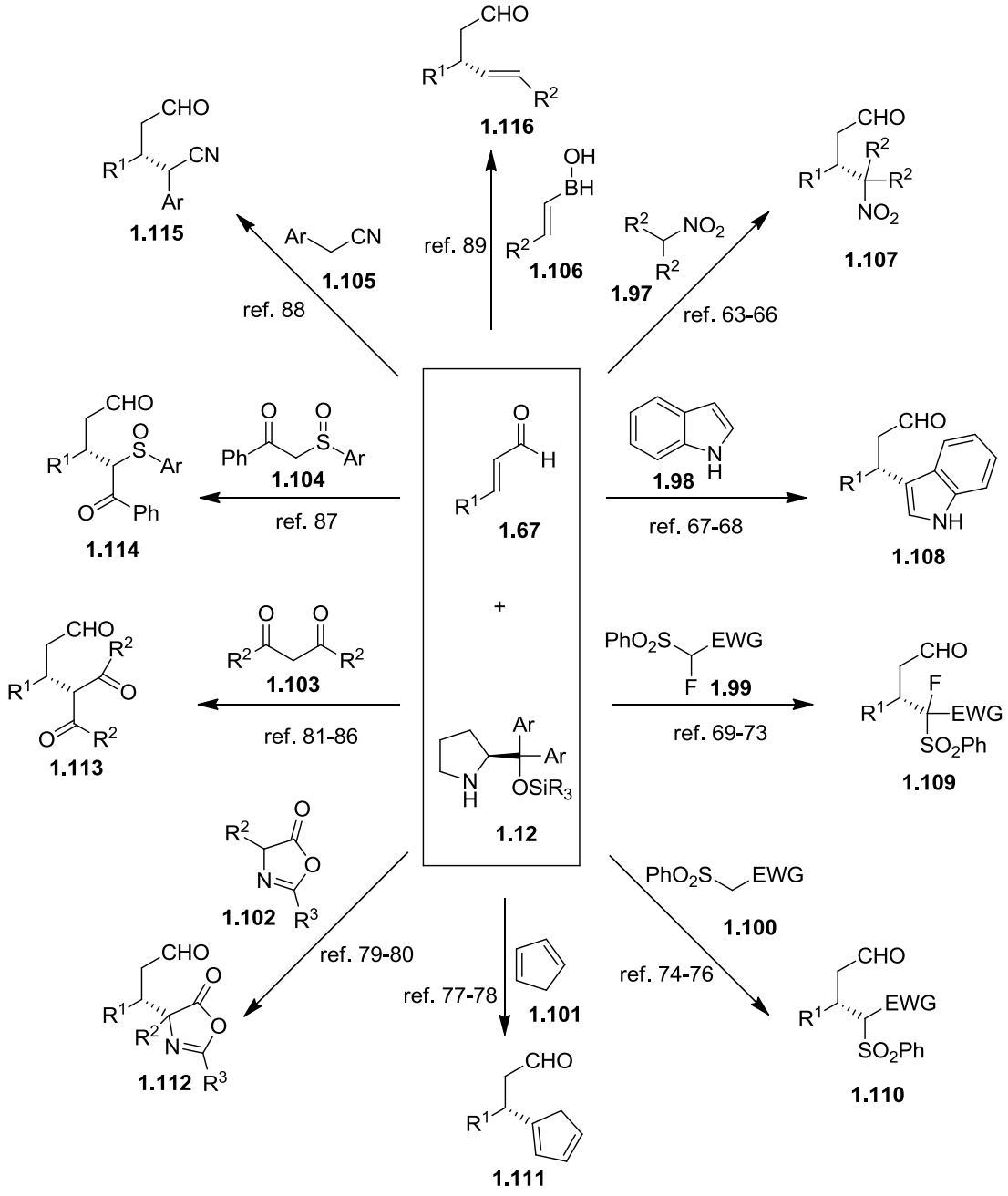
There are also a few examples of *intra*molecular hetero-Michael additions catalyzed by diarylprolinol silyl ethers (**Scheme 1.10**).[60-62] The substituted α,β-unsaturated aldehydes **1.89**–**1.91** were used to generate products **1.92**–**1.96**. Products **1.93**, **1.94**, and **1.96** were converted to valuable natural products.

Scheme 1.10 Intramolecular Hetero-Michael Additions Catalyzed by Diarylprolinol Silyl Ethers



Diarylprolinol silyl ethers have also participated in many iminium–catalyzed reactions involving carbon-centered Michael donors **1.97**–**1.106** (**Scheme 1.11**). These reactions give a variety of interesting products like **1.107**–**1.116**.[63-89] These reactions are illustrated in **Scheme 1.11**. Dicarbonyl Michael donors of type **1.103** are particularly good Michael donors for a number of different organocatalyzed conjugate additions. They have been used in conjunction with other iminium catalysts such as *L*-proline salts,[90-93] tetrazoles,[94] and chiral primary amines.[95] They have also been used extensively with hydrogen bonding organocatalysts such as quaternary ammonium salts,[96-97] cinchona alkaloids,[98-112] and bifunctional thioureas.[113-122]

Scheme 1.11 Carbon Michael Additions Catalyzed by Diarylprolinol Silyl Ethers

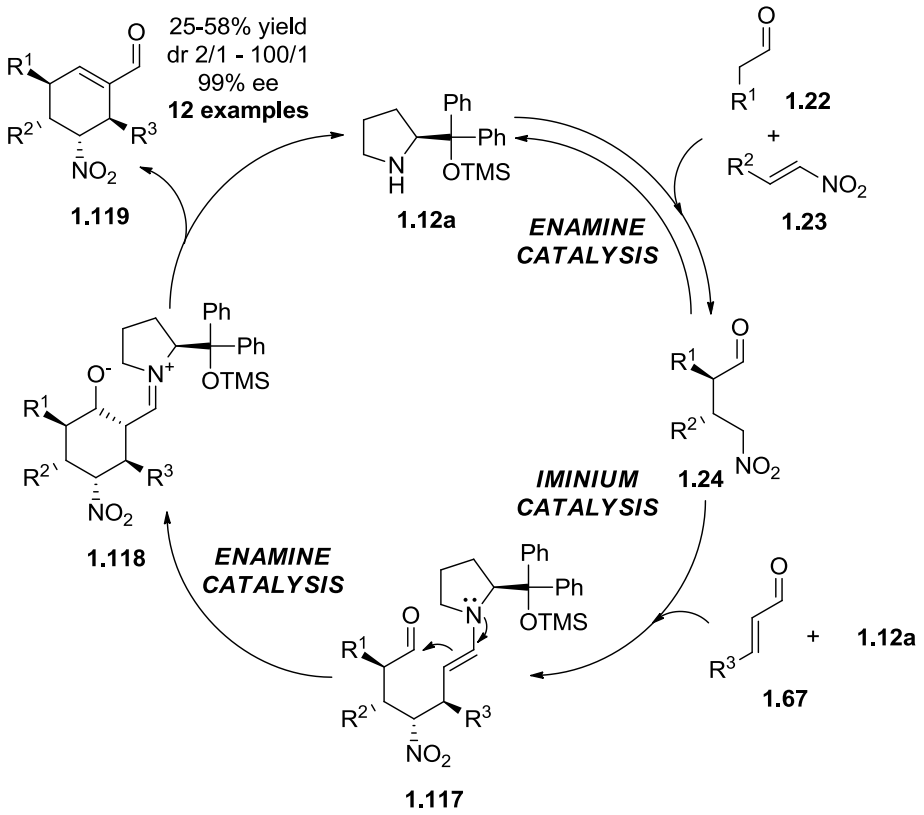


1.8 Diarylprolinol Silyl Ethers In Cascade Reactions

Organocatalytic cascade reactions have been extensively studied in the last ten years.[123] Reactions of this type are extremely useful, because multiple bonds and chiral centers are formed

in one–pot, thereby rapidly generating great molecular complexity from quite simple reactants. Due to their ability to participate in both enamine and iminium catalysis, diarylprolinol silyl ethers are extremely efficient at catalyzing cascade reactions and multi–component reactions (MCR's). An example of this type of process, involving three components reacting to form substituted cyclohexenes, was reported in *Nature* by Enders et al. in 2006.[124] The catalytic cycle for this process is illustrated in **Scheme 1.12**. Aliphatic aldehydes of type **1.22** undergo enamine catalysis in the presence of catalyst **1.12a** and Michael acceptors of type **1.23**.

Scheme 1.12 Enamine–Iminium–Enamine Triple Cascade Reaction



The resulting nitroalkanes, **1.24**, act as Michael donors to α,β-unsaturated aldehydes of type **1.67** in an iminium–catalyzed process. The resulting intermediates, **1.117**, then undergo an

enamine–catalyzed *intra*molecular aldol reaction to give iminium ions, **1.118**, which undergo hydrolysis and elimination to give cyclohexene products, **1.119**. This process gives highly complex products with four stereocenters from three incredibly simple starting materials. The catalysis sequence of this triple cascade reaction is enamine–iminium–enamine.

1.9 Diarylprolinol Silyl Ethers In Iminium–Initiated Cascade Reactions

Since the discovery of catalyst **1.12a**'s potency as a promoter of cascade reactions, diarylprolinol silyl ethers have been used in many different cascade sequences. Although the cascade reaction depicted in **Scheme 1.12** begins with an enamine–catalyzed step, most of the cascade sequences catalyzed by diarylprolinol silyl ethers begin with an iminium–catalyzed conjugate addition to an α,β-unsaturated aldehyde of type **1.67**.

One of the most common cascade sequences involving an iminium–catalyzed first step is an iminium–enamine cascade reaction (**Scheme 1.13, Reaction 1** and **2**). This type of reaction begins with a conjugate addition to an iminium ion of type **1.70**. This is immediately followed by an enamine–catalyzed reaction with an electrophile (E^+) to give the product. This type of process may involve three components (**Reaction 1**) or two components (**Reaction 2**).

In the three component reaction (**Reaction 1**, **Scheme 1.13**), the original α,β-unsaturated aldehyde is modified via two sequential intermolecular reactions involving a nucleophile (Nu^-) and a distinct electrophile (E^+) to give products of type **1.120** via intermediates of type **1.71**. The more commonly observed two component process, where the nucleophile and electrophile are tethered together, involves an *inter*molecular reaction followed by an *intra*molecular reaction to give products of type **1.122** via intermediates of type **1.121**. In both cases the stereochemical configurations at the α and β positions of the original aldehyde are both set by the steric bulk of

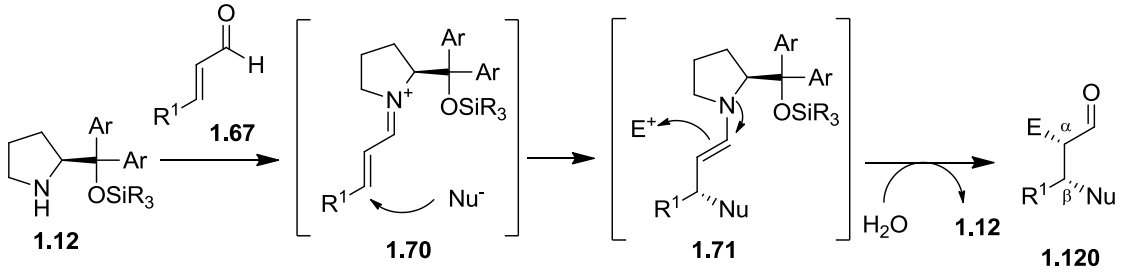
the catalyst (as shown previously in **Schemes 1.4** and **1.8**), selectively generating products of type **1.120** or type **1.122**, both with a *syn* relative configuration between the α and β substituents.

Another common iminium–initiated sequence is depicted in **Reaction 3** in **Scheme 1.13**. The initial conjugate addition, generating enamines of type **1.123**, is performed by a nucleophile tethered to another nucleophile. Catalyst release is then mediated via hydrolysis and the final step of the cascade reaction involves intramolecular nucleophilic attack to the aldehyde in intermediates of type **1.124**. This type of reaction gives products of type **1.125**. The stereochemical configuration at the β-position of the aldehyde is set by the catalyst during the first step. Any other stereocenters set during the cascade reaction are established by the original stereocenter at the β-position.

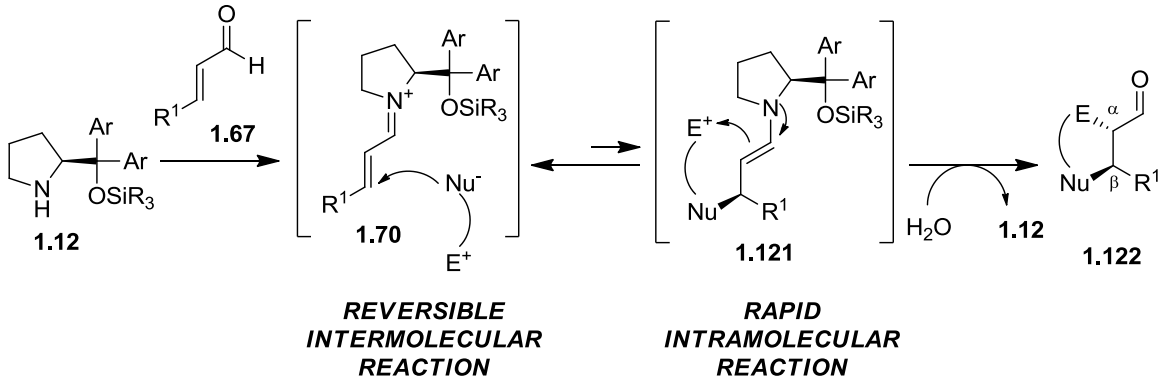
Utilizing a reaction like **Reaction 2** or **Reaction 3** can be extremely useful. A reversible *inter*molecular reaction in the first step, which forms an unstable intermediate of type **1.121** or **1.123,** can be overcome by a rapid *intra*molecular reaction in the second step, which is not reversible. Although the equilibrium of the first reaction of the cascade sequence may be shifted towards the starting materials, the reactive intermediate can be "trapped" with a rapid (intramolecular) second bond formation, which can prevent the retro–reaction from occurring.

Scheme 1.13 Three Different Iminium–Initiated Cascade Sequences

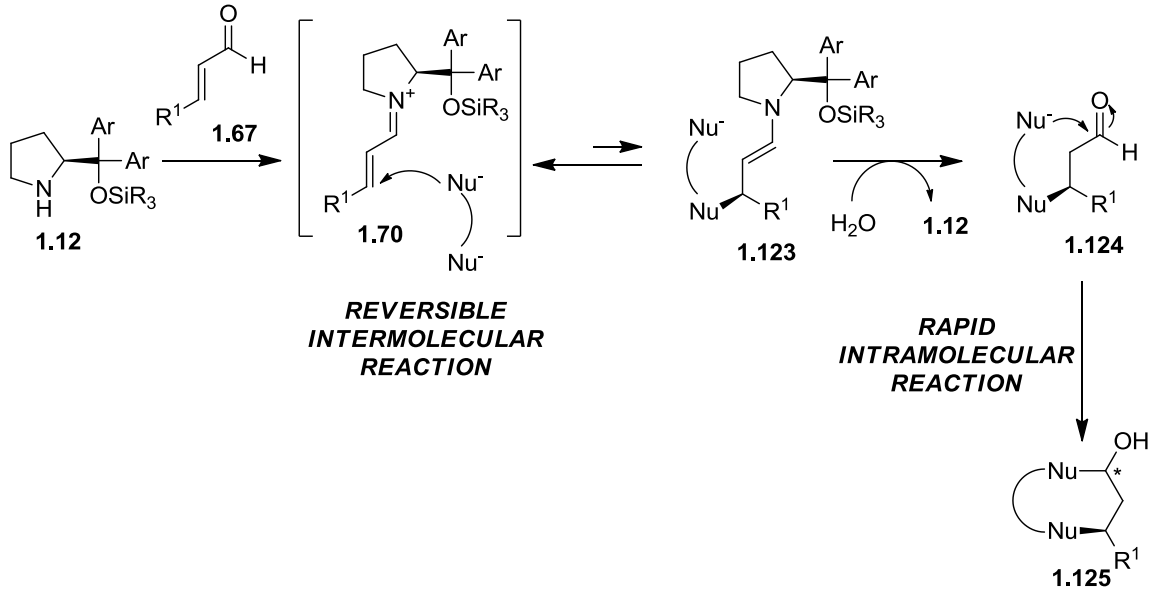
REACTION 1- 3 components, *inter*molecular-*inter*molecular



REACTION 2- 2 components, *inter*molecular-*intra*molecular



REACTION 3- 2 components, *inter*molecular-*intra*molecular



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Chapter 2.

Iminium–Initiated Cascade Reactions

Catalyzed By Diarylprolinol Silyl Ethers

2.1 Carbon-Centered Michael Donors

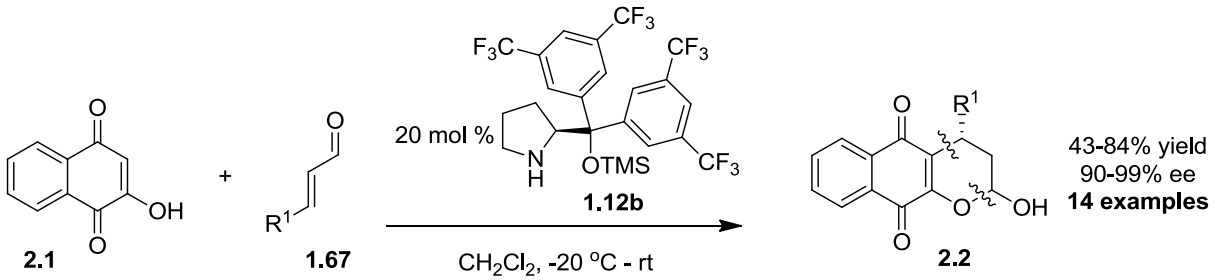
There is a great diversity of organocatalyzed conjugate additions involving carbon-centered nucleophiles,[1] and as such, a large number of carbon-centered Michael donors have been employed in diarylprolinol silyl ether catalyzed cascade reactions. The most common Michael donors employed in these iminium–initiated reactions are dicarbonyl compounds.

2.1.1 Dicarbonyl Michael Donors

2.1.1.1 Michael–Acetalization Reactions

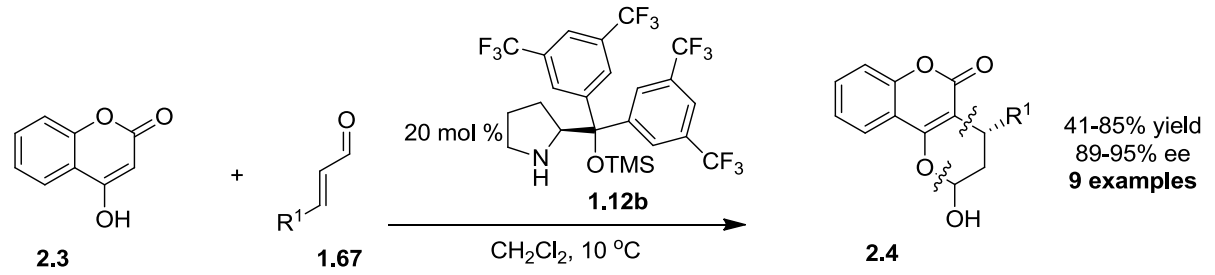
In 2008, Reuping et al.[2] presented a synthesis using a Michael–acetalization sequence. Napthoquinone **2.1** was used as the Michael donor in a reaction with α,β-unsaturated aldehydes (**1.67**) to selectively form 1,4-napthoquinone products of type **2.2** (**Scheme 2.1**). The optimal catalyst for this reaction was the trifluoromethyl-substituted diarylprolinol silyl ether **1.12b**. The product of this reaction could be converted to biologically active 1,2-pyranonapthoquinones with one additional step.

Scheme 2.1 Michael–Acetalization Cascade Reaction Gives 1,4-napthoquinones



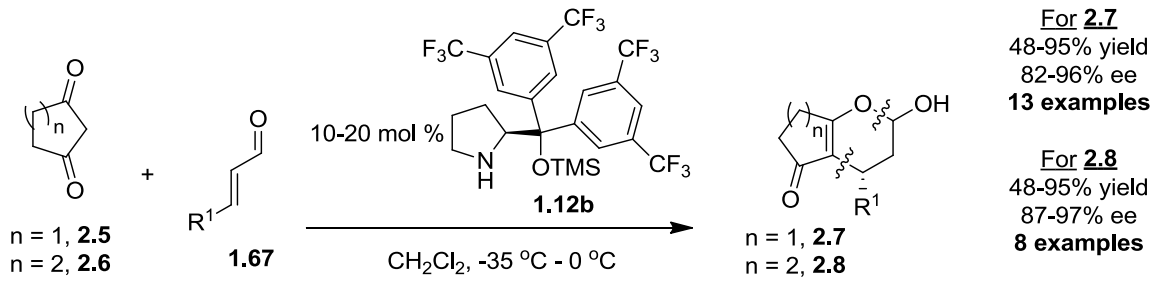
This cascade process was extended to reactions involving 4-hydroxycoumarin, **2.3**, as the Michael donor. These reactions produced chiral pyranocoumarins of type **2.4** (**Scheme 2.2**). This same method was utilized for the synthesis of chromenones and quinolinones.[3]

Scheme 2.2 Michael–Acetalization Cascade Reaction Gives Pyranocoumarins



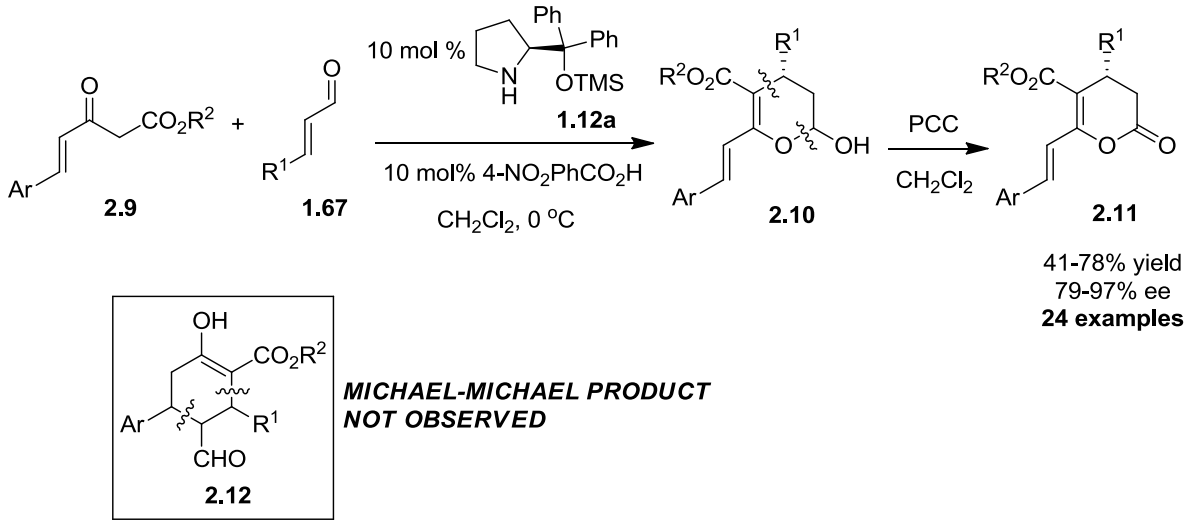
Two similar reactions were independently performed by Jørgensen et al.[4] and Reuping et al.[5] These reactions generated asymmetric products of type **2.7** and type **2.8** from 1,3-cyclopentanedione **2.5** and cyclohexane-1,3-dione **2.6** respectively. Both types of products were collected in excellent yield and excellent selectivity (**Scheme 2.3**).

Scheme 2.3 Michael–Acetalization Cascade Reaction Gives Benzopyrans and Dihydropyrans



Another Michael–acetalization cascade reaction, utilizing conjugated β-keto ester Michael donors, **2.9**, and catalyst **1.12a,** has been developed.[6] This reaction gave highly conjugated lactones of type **2.11** after PCC oxidation of the resulting hemiacetals of type **2.10** (**Scheme 2.4**). Interestingly, no Michael–Michael cascade products of type **2.12** were observed during this transformation.

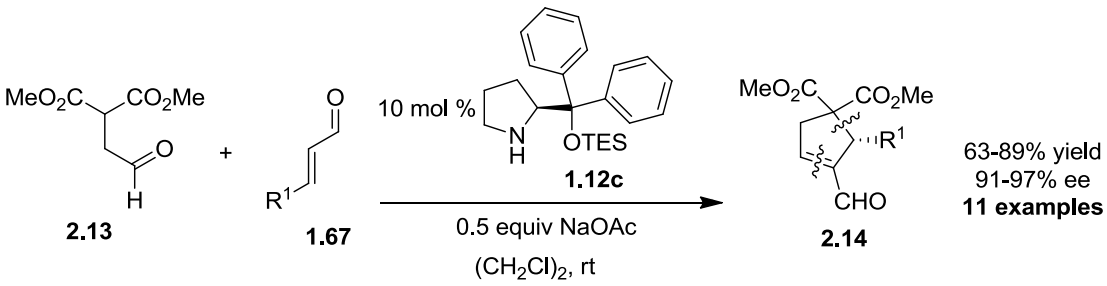
Scheme 2.4 Michael–Acetalization Cascade Reaction Gives Lactones



2.1.1.2 Michael–Aldol Reactions

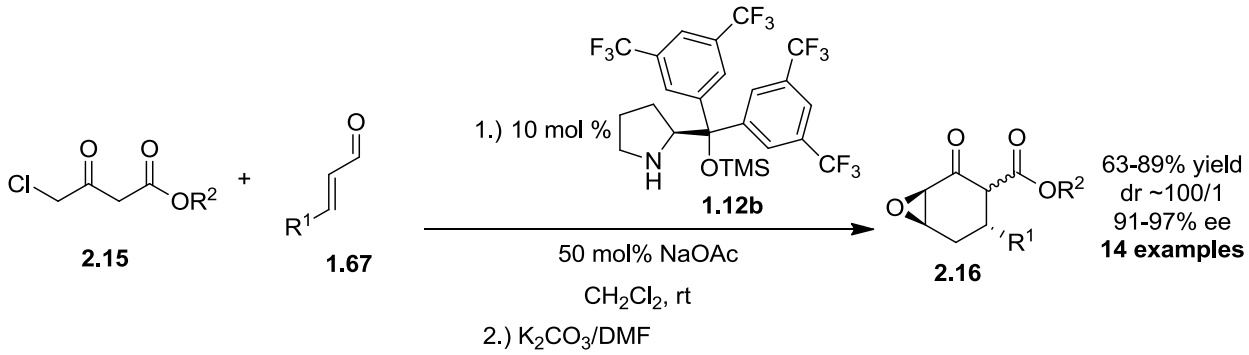
Wang and co-workers performed a synthesis of densely functionalized cyclopentanes of type **2.14** using α,β-unsaturated aldehydes (**1.67**) and Michael donor **2.13** (**Scheme 2.5**).[7] This reaction proceeded via an iminium–enamine cascade process. The optimal catalyst for the reaction was found to be the slightly bulkier TES protected prolinol **1.12c**.

Scheme 2.5 Michael–Aldol Cascade Reaction Gives Functionalized Cyclopentanes



The Jørgensen group utilized halogen–substituted Michael donors of type **2.15** in a particularly elegant Michael–aldol–alkylation cascade reaction.[8] This reaction involved an iminium–catalyzed Michael addition followed by a base catalyzed aldol–alkylation reaction which gave bicyclic epoxides of type **2.16** (**Scheme 2.6**). A similar process was used by Jørgensen et al. to generate synthetically useful substituted cyclohexenones.[9,10]

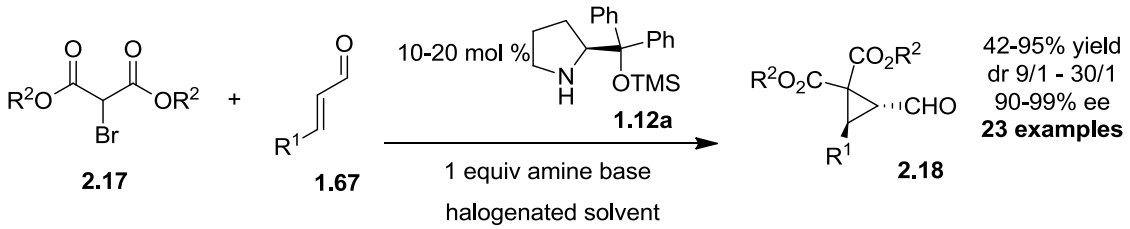
Scheme 2.6 Michael–Aldol–Alkylation Cascade Reaction



2.1.1.3 Michael–Alkylation Reactions

Most of the Michael-alkylation cascade reactions that have been developed using diarylprolinol silyl ethers have been cyclopropanation reactions using bromo–substituted dicarbonyl compounds of type **2.17**. The first reactions of this type were developed independently by Wang et al.[11] and Córdova et al.[12] In both cases the cyclopropane products, **2.18**, were collected in good yield with excellent diastereo– and enantioselectivity (**Scheme 2.7**). An equivalent of amine base was included in the reaction mixture in order to neutralize the HBr produced by the substitution reaction.

Scheme 2.7 Cyclopropanation Cascade Reaction

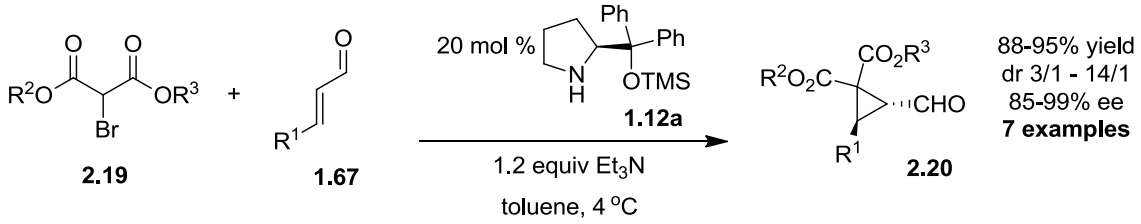


This reaction was extended to include nonsymmetrical malonates of type **2.19**. This reaction was useful because it generated products of type **2.20** with a quaternary chiral center

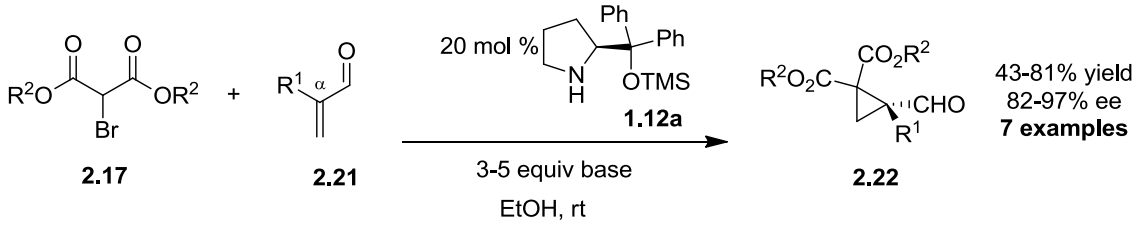
with good diastereoselectivity (**Scheme 2.8**, **Reaction 1**).[13] This organocatalyzed cyclopropanation reaction was also extended to α-branched unsaturated aldehydes, **2.21**. This reaction gave products of type **2.22**, also with a quaternary chiral center, in good yield with high selectivity (**Scheme 2.8**, **Reaction 2**).[14]

Scheme 2.8 Cyclopropanation Cascade Reactions: Quaternary Chiral Centers

Reaction 1:

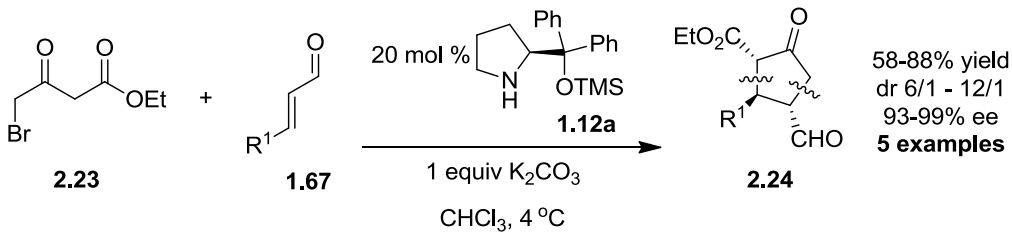


Reaction 2:



Attempts to use a Michael–alkylation cascade reaction in order to generate functionalized cyclopentanones were also successful (**Scheme 2.9**).[15] Bromo–substituted β-keto ester **2.23** was used as the Michael donor with a variety of α,β-unsaturated aldehydes (**1.67**). The products, **2.24**, that were generated contained three chiral centers and were isolated with good selectivity.

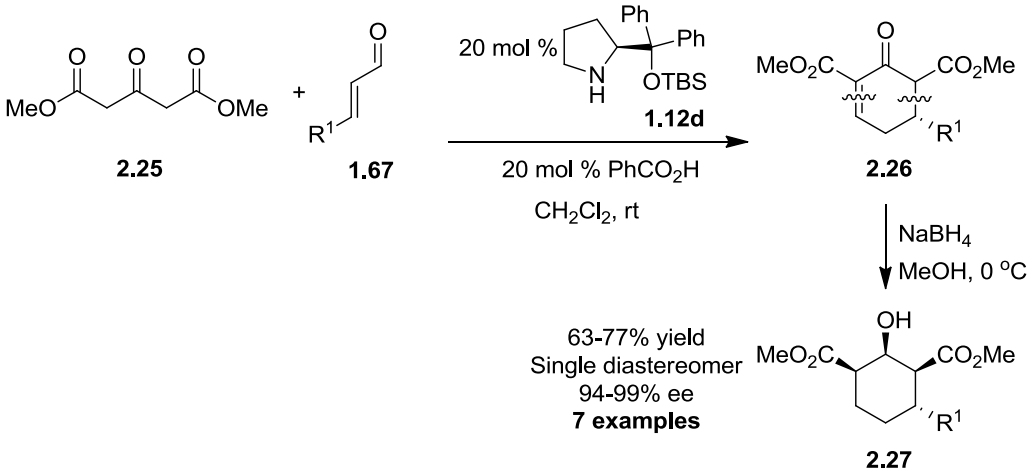
Scheme 2.9 Synthesis of Cyclopentanones Using a Michael–Alkylation Cascade



2.1.1.4 Michael–Knoevenagel Reactions

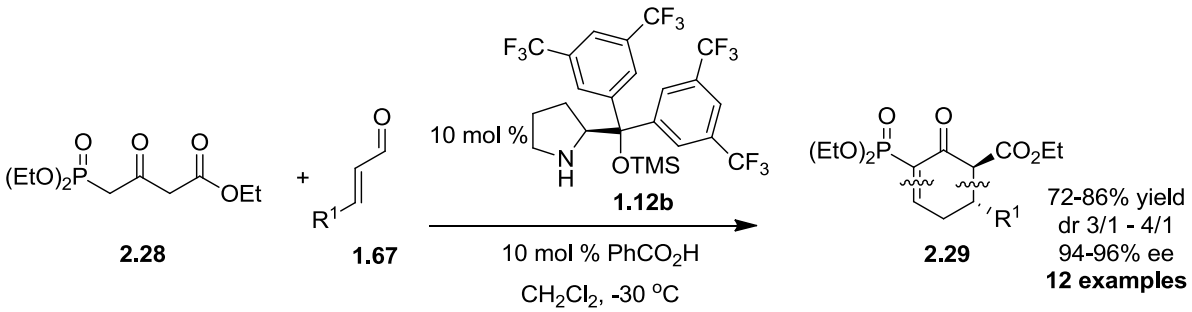
The first diarylprolinol silyl ether catalyzed Michael–Knoevenagel condensation was performed by the Hayashi group.[16] The optimal catalyst for this cascade reaction was found to be **1.12d**. The reaction involved tricarbonyl Michael donor **2.25** and generated products of type **2.26** with just one chiral center (**Scheme 2.10**). However, the products could be subjected to a simple in situ $NaBH_4$ reduction to give products, **2.27**, which contains four chiral centers. Another Michael–Knoevenagel cascade reaction involving **2.25** was used by Jørgensen et al. in a quadruple cascade process.[17]

Scheme 2.10 Michael–Knoevenagel Condensation with Tricarbonyls



The Michael–Knoevenagel cascade reaction shown in **Scheme 2.11** was developed by Jørgensen and co-workers as well.[18] The reaction utilized phosphorous containing dicarbonyl Michael donors **2.28** to generate products of type **2.29** containing two chiral centers. These products were quite valuable as they could be further manipulated (i.e. reduction, conjugate addition, Horner–Wadsworth–Emmons reaction) to give interesting synthetic intermediates.

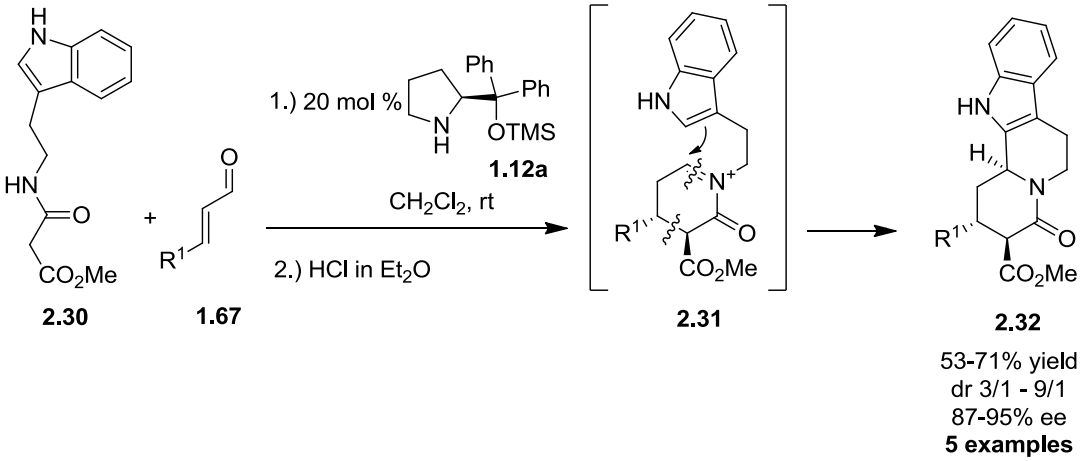
Scheme 2.11 Michael–Knoevenagel Condensation With Phosphorous Containing Dicarbonyls



2.1.1.5 Michael–Pictet–Spengler Reactions

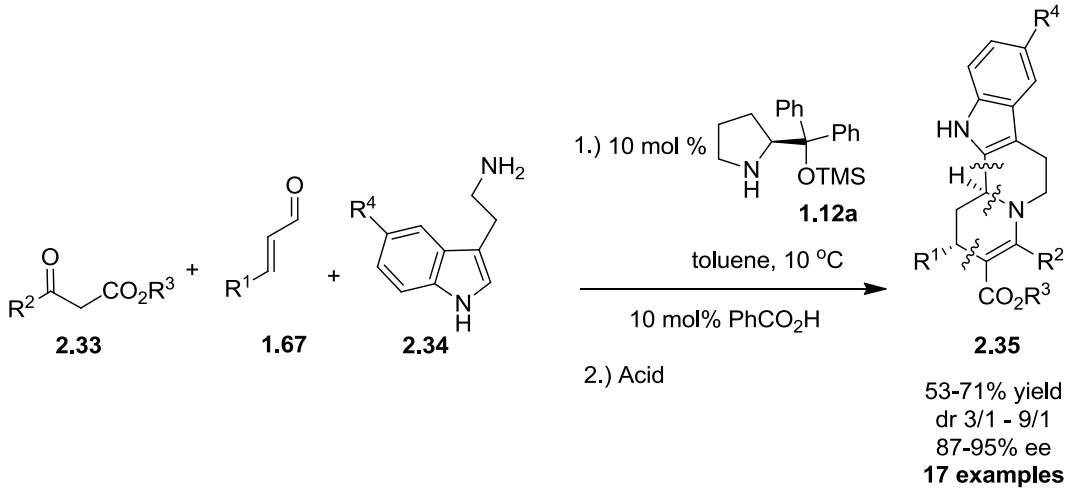
In studying the addition of indole substituted amide **2.30** to α,β-unsaturated aldehydes, Franzén et al. developed a Michael–Pictet–Spengler cascade reaction for the synthesis of chiral indolo[2,3-a]quinolizidines and chiral benzo[2,3-a]quinolizidines (**Scheme 2.12**).[19] The initial conjugate addition by the dicarbonyl was followed by acid–catalyzed intramolecular iminium ion formation involving the aldehyde and the amide nitrogen to form intermediates of type **2.31**. This was followed by an intramolecular Friedel–Crafts addition of the indole ring to the iminium ion to generate tetracyclic products, **2.32**. A similar process was used with β-keto amide Michael donors as well.[20] In both cases the products were generated in good yield with good diastereoselectivity and excellent enantioselectivity.

Scheme 2.12 Two Component Michael–Pictet–Spengler Cascade Reaction



A one–pot, three–component reaction involving β-keto ester Michael donors of type **2.33** and tryptamines (**2.34)** was used to generate similar tetracyclic skeletons of type **2.35** (**Scheme 2.13**).[21] The initial conjugate addition is followed sequentially by intermolecular iminium ion formation and the same Friedel–Crafts type addition of the indole ring in tryptamine.

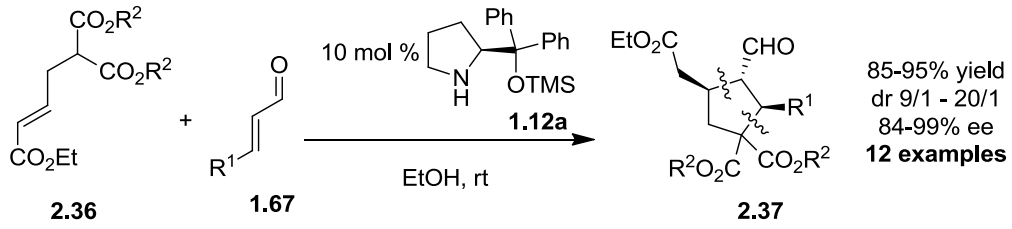
Scheme 2.13 Three Component Michael–Pictet–Spengler Cascade Reaction



2.1.1.6 Michael–Michael Reactions

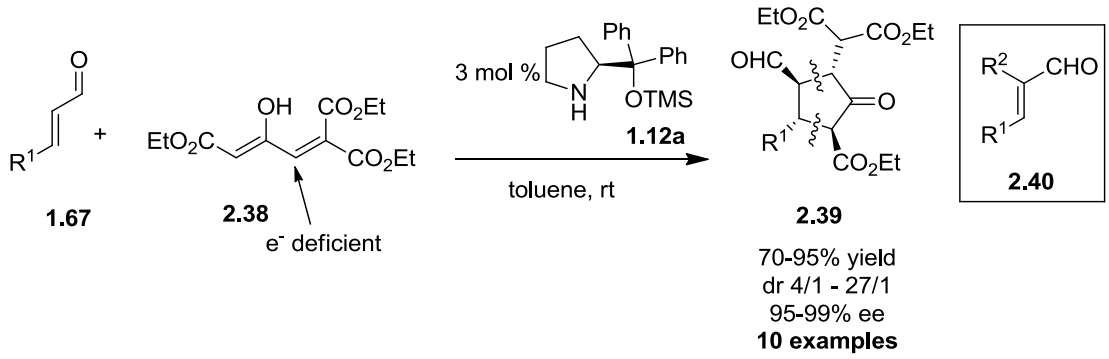
The first iminium–initiated Michael–Michael cascade reaction catalyzed by diarylprolinol silyl ethers utilizing a dicarbonyl Michael donor was developed by the Wang group in 2007.[22] This reaction utilized monosubstituted malonate Michael donors (**2.36)** to generate densely functionalized cyclopentanes of type **2.37** (**Scheme 2.14**).

Scheme 2.14 Michael–Michael Cascade Reaction Gives Substituted Cyclopentanes



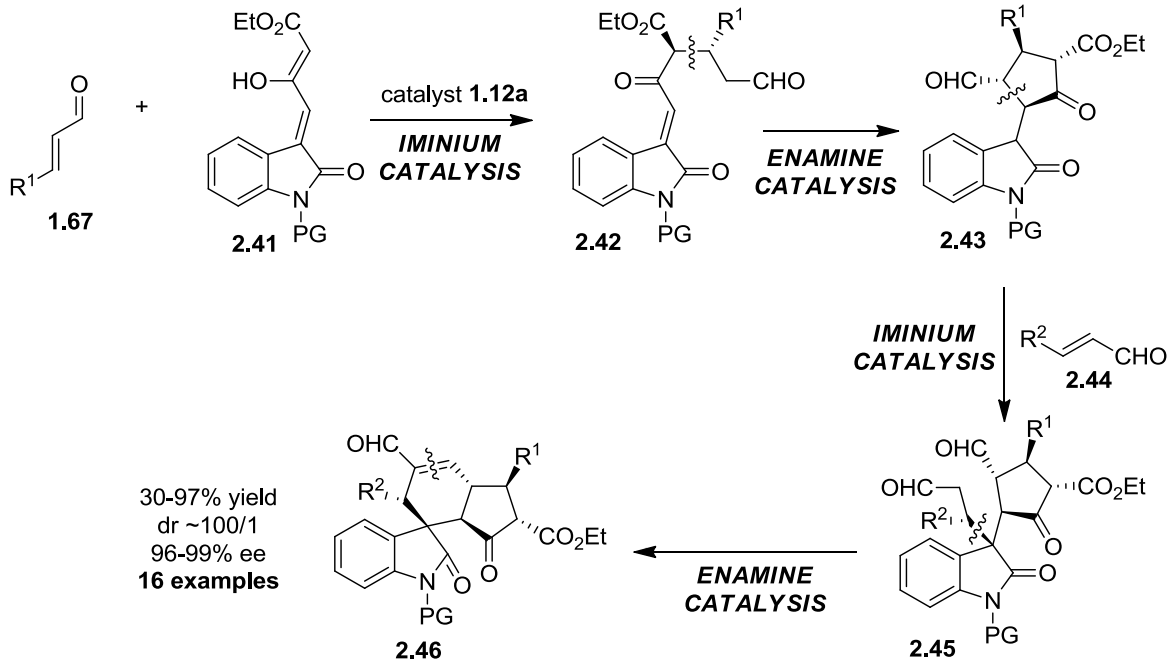
Recently, two other Michael–Michael cascade reactions utilizing dicarbonyl Michael donors, which were catalyzed by diarylprolinol silyl ethers, were developed. The first was an iminium–enamine cascade sequence with β-keto ester **2.38** which gave substituted cyclopentanones, **2.39** (**Scheme 2.15**).[23] The initial Michael addition was followed by an enamine–catalyzed conjugate addition to the electron deficient olefin moiety in substrate **2.38**. Interestingly, this reaction could be extended to α-branched α,β-unsaturated aldehydes of type **2.40**.

Scheme 2.15 Michael–Michael Cascade Reaction Gives Substituted Cyclopentanones



The second recently developed Michael–Michael initiated cascade reaction was extended into a quadruple cascade for the synthesis of spirooxindoles from oxindoles of type **2.41**.[24] The resulting Michael–Michael–Michael–aldol cascade reaction is illustrated in **Scheme 2.16**. Intermediates **2.42**, which were the products of the initial Michael addition, underwent an enamine–catalyzed second Michael addition to give intermediates of type **2.43**. These intermediates reacted with α,β-unsaturated aldehydes (**2.44**) via a second iminium–catalyzed Michael addition to give intermediates **2.45**. The cascade reaction was concluded with an enamine–catalyzed intramolecular aldol reaction which gave products of type **2.46**, containing six new stereocenters.

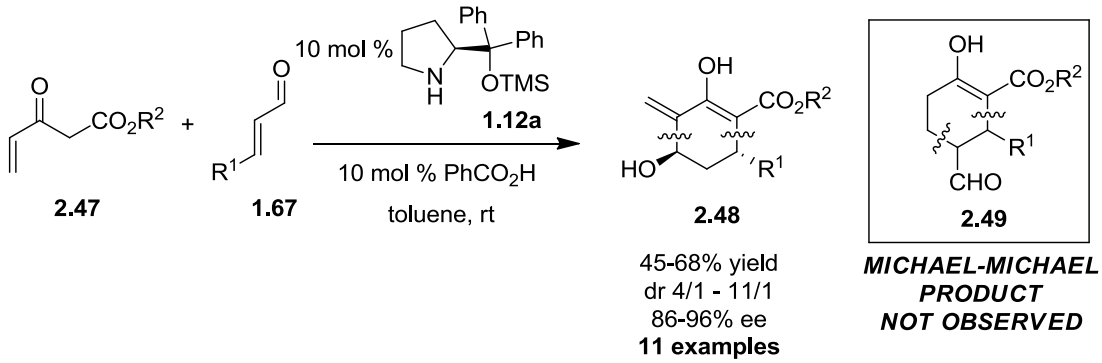
Scheme 2.16 Michael–Michael–Michael–Aldol Quadruple Cascade Reaction



2.1.1.7 Michael–Morita–Baylis–Hillman Reactions

Only one Michael–Morita–Baylis–Hillman cascade reaction has been catalyzed by diarylprolinol silyl ethers. This reaction was developed by Jørgensen et al. (**Scheme 2.17**)[25] The reaction was performed with the expectation that the conjugated β-keto esters of type **2.47** would generate Michael–Michael cascade products of type **2.49**. However, products of type **2.49** were not observed. Instead, a Michael–Morita–Baylis–Hillman reaction gave conjugated cyclohexenes of type **2.48**, which were collected in good yield with excellent selectivity.

Scheme 2.17 Michael–Morita–Baylis–Hillman Cascade Reaction

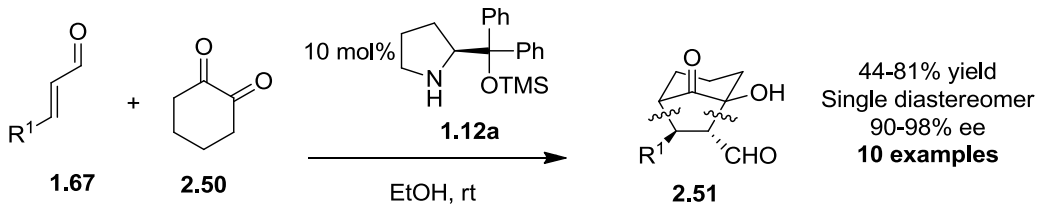


2.1.2 Monocarbonyl Michael Donors

2.1.2.1 Michael–Aldol Reactions

Several activated monocarbonyl Michael donors have been utilized in Michael–aldol cascade reactions catalyzed by diarylprolinol silyl ethers. The first was developed by Reuping and co-workers in 2008 for the synthesis of bicyclic compounds **2.51** from Michael donor 1,2-cyclohexanedione **2.50** (**Scheme 2.18**).[26] This iminium–enamine cascade reaction gave compounds with four chiral centers with one being set during the initial conjugate addition and the other three being set during the subsequent intramolecular aldol reaction.

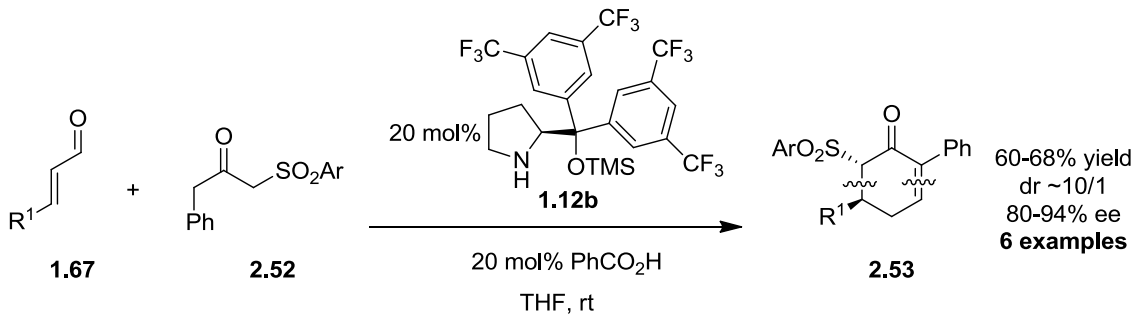
Scheme 2.18 Michael–Aldol Cascade Reaction with 1,2-Cyclohexanedione



Another Michael–aldol cascade reaction utilized β-keto sulfone **2.52** as the Michael donor in the synthesis of substituted cyclohexenes of type **2.53** (**Scheme 2.19**).[27] The products

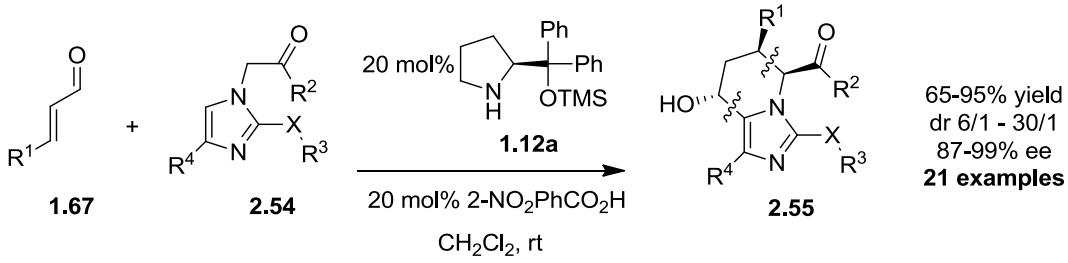
of this reaction, similar to those observed in **Scheme 2.10** and **Scheme 2.11**, could be further manipulated via several different one–pot processes to give a variety of valuable synthetic intermediates.

Scheme 2.19 Michael–Aldol Cascade Reaction with β-Keto Sulfones



Activated imidazole derivatives of type **2.54** have also been used as Michael donors in a Michael–aldol cascade reaction (**Scheme 2.20**).[28] The iminium–enamine activation sequence gave bicyclic products, **2.55**. An extensive substrate study was conducted and several different products were synthesized in excellent yield with excellent selectivity.

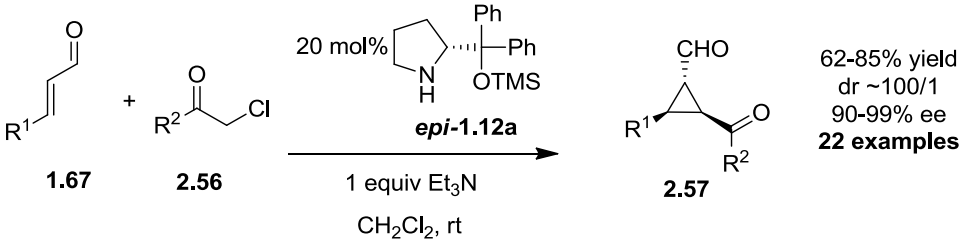
Scheme 2.20 Michael–Aldol Cascade Reaction with Imidazole Derivatives



2.1.2.2 Michael–Alkylation Reactions

A diarylprolinol silyl ether catalyzed Michael–alkylation cascade reaction utilizing α-chloro ketones (**2.56**) as Michael donors was developed (**Scheme 2.21**).[29] This cyclopropanation reaction generated products of type **2.57** with three contiguous chiral centers. As with the reactions illustrated in **Schemes 2.7**–**2.9**, at least a full equivalent of base was required to neutralize the hydrochloric acid produced by the substitution reaction.

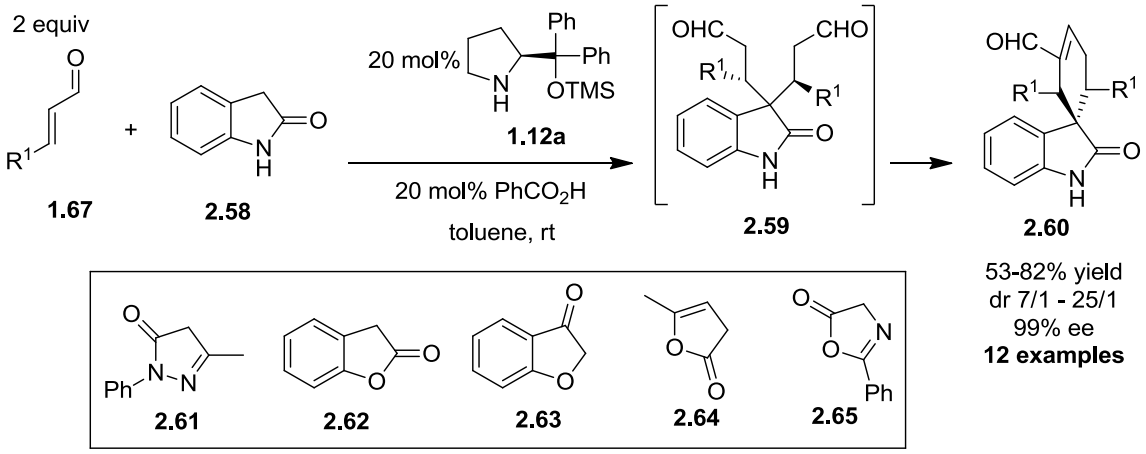
Scheme 2.21 Michael–Alkylation Cascade Reaction Generates Substituted Cyclopropanes



2.1.2.3 Michael–Michael–Aldol Reactions

A diarylprolinol silyl ether catalyzed Michael–Michael–aldol cascade reaction which utilized heterocyclic monocarbonyl Michael donor **2.58** was developed by the Rios group (**Scheme 2.22**).[30,31] The reaction involved two sequential Michael additions with the same heterocyclic Michael donor to two molecules of α,β-unsaturated aldehyde, which gave intermediates of type **2.59**. The cascade reaction was concluded with an enamine–catalyzed intramolecular aldol reaction to generate spiro products of type **2.60**. Interestingly, this reaction could be extended to include a number of other heterocyclic Michael donors, such as **2.61**–**2.65**.

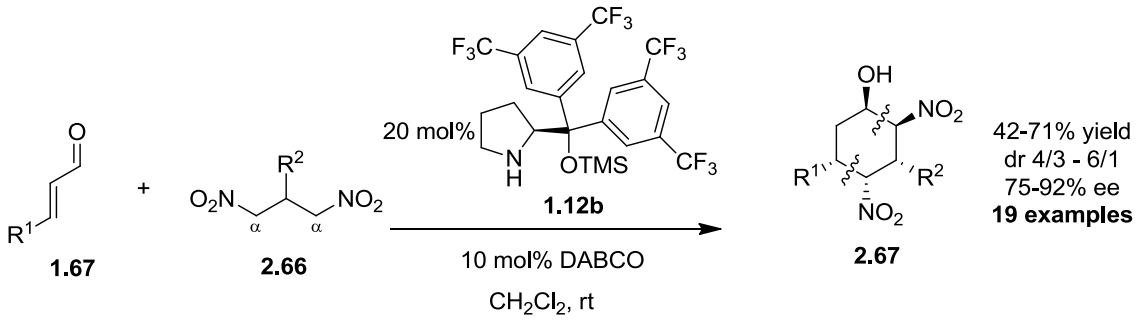
Scheme 2.22 Michael–Michael–Aldol Cascade Reaction With Activated Monocarbonyls



2.1.3 Nitro Michael Donors

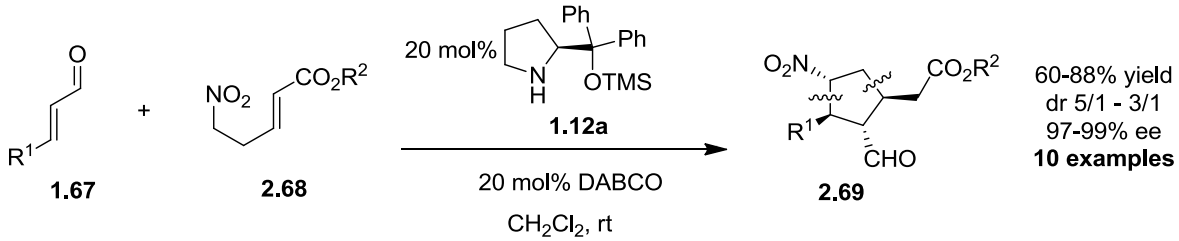
The acidity of the α-position protons in aliphatic nitro–containing compounds makes them easily deprotonated. Their resultant anions are extremely efficient Michael donors for iminium–catalyzed conjugate additions using diarylprolinol silyl ethers.[32] Indeed, these types of Michael donors have been used to initiate a variety of cascade reactions catalyzed by diarylprolinol silyl ethers. The first of these cascade reactions was developed in 2007 by Jørgensen et al.[33] This reaction involved dinitro substrates of type **2.66** participating in a Michael–Henry cascade reaction giving products, **2.67**, with five contiguous stereocenters (**Scheme 2.23**). This reaction gave products in moderate yield, with moderate diastereoselectivity, but with excellent enantioselectivity.

Scheme 2.23 Michael–Henry Cascade Reaction With Nitro Michael Donor



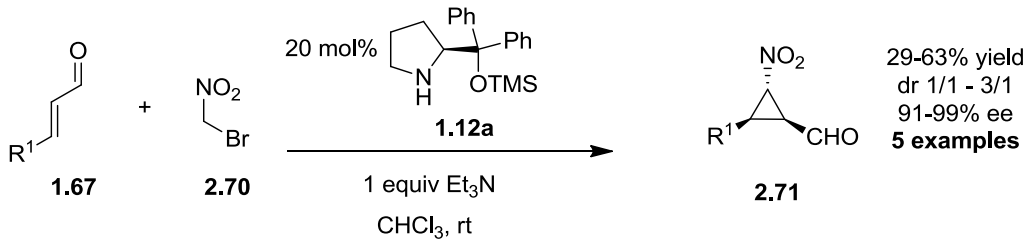
A Michael–Michael cascade reaction using unsaturated ester–substituted nitro Michael donors of type **2.68** was developed by Córdova and co-workers (**Scheme 2.24**).[34] This iminium–enamine catalyzed reaction gave substituted cyclopentanes (**2.69**) which contained four contiguous stereocenters. The synthetic versatility of the product was demonstrated by its conversion to various valuable synthetic intermediates.

Scheme 2.24 Michael–Michael Cascade Reaction With Nitro Michael Donor



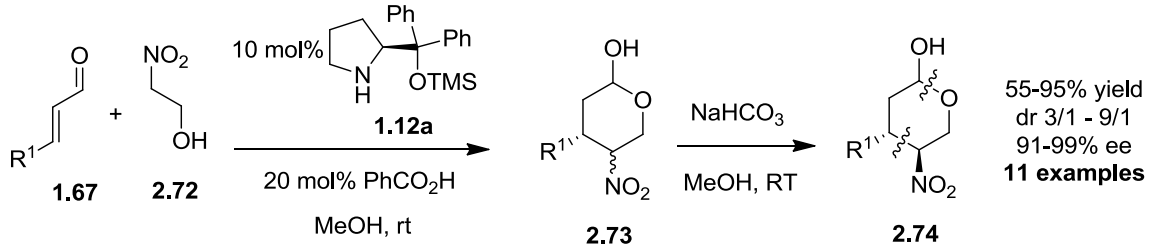
A similar Michael–alkylation cascade reaction was developed by the same group, using the bromo–substituted Michael donor **2.70** (**Scheme 2.25**).[35] The yield and diasteroselectivity of the cyclopropane products, **2.71**, were only moderate compared to those achieved in other cyclopropanation reactions utilizing diarylprolinol silyl ether organocatalysts.

Scheme 2.25 Michael–Alkylation Cascade Reaction With Nitro Michael Donor



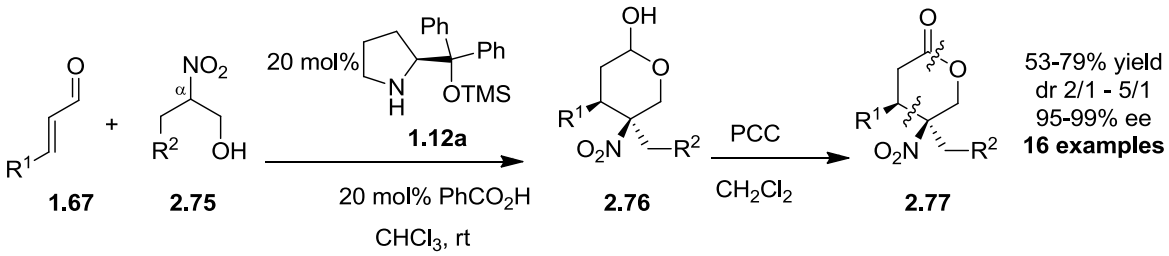
A Michael–acetalization cascade reaction, which utilized alcohol substituted nitro compound **2.72** as the Michael donor, was developed (**Scheme 2.26**).[36] The diastereomeric products of type **2.73** were collected in good yield with high enantioselectivity. Good diastereoselectivity was achieved by adding $NaHCO_3$ and MeOH in situ, which induced epimerization to the thermodynamically more stable products, **2.74**.

Scheme 2.26 Michael–Acetalization Cascade Reaction With Nitro Michael Donor



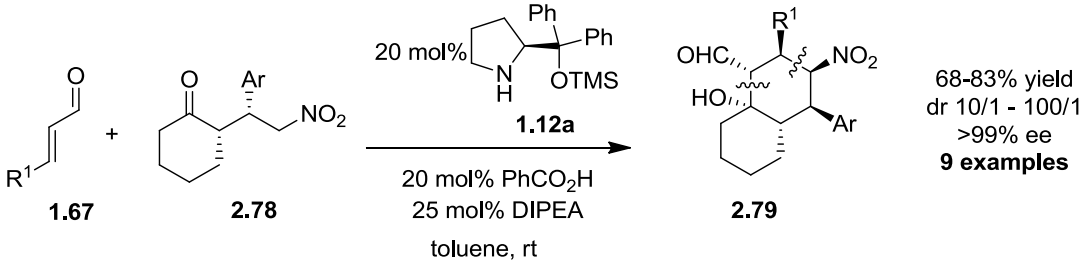
This same reaction was extended to include nitro substrates of type **2.75**, which contain branching at the α-position (**Scheme 2.27**).[37] After in situ oxidation of products of type **2.76** using PCC, the corresponding δ-lactol products, **2.77**, were collected with moderate diastereoselectivity and excellent enantioselectivity.

Scheme 2.27 Michael–Acetalization Cascade Reaction With Nitro Michael Donor, α-Branching



A Michael–aldol reaction which utilized chiral substrates of type **2.78** was developed.[38] The iminium–enamine catalyzed reaction gave bicyclic products (**2.79**) with four new stereocenters being set during the cascade process (**Scheme 2.28**). It is worth noting that starting materials of type **2.78** were also accessed organocatalytically, via *L*-proline catalyzed Michael additions.

Scheme 2.28 Michael–Aldol Cascade Reaction With A Chiral Nitro Michael Donor

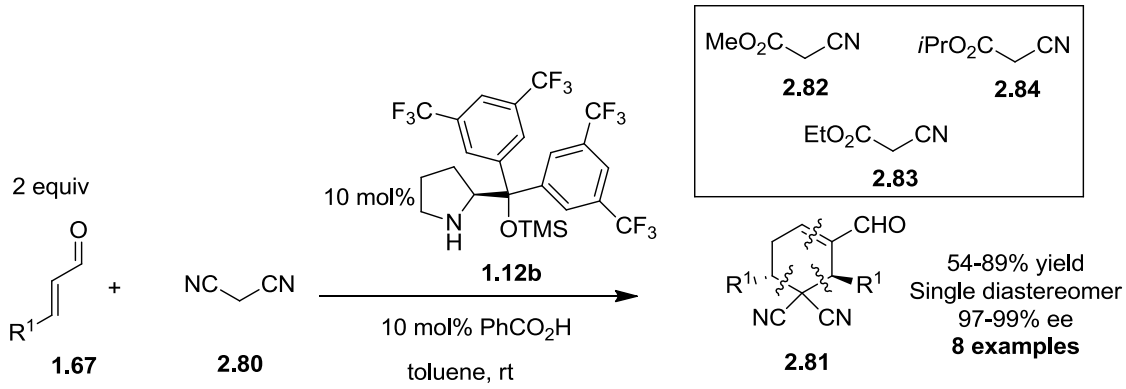


2.1.4 Malonitrile Michael Donors

There have been two iminium–initiated cascade reactions catalyzed by diarylprolinol silyl ethers which utilized malonitrile Michael donors. The first reaction, developed by the Jørgensen group,[39] is very similar to that shown in **Scheme 2.22**. The reaction was initiated with two sequential Michael additions of the malonitrile Michael donor **2.80** to two equivalents of α,β-

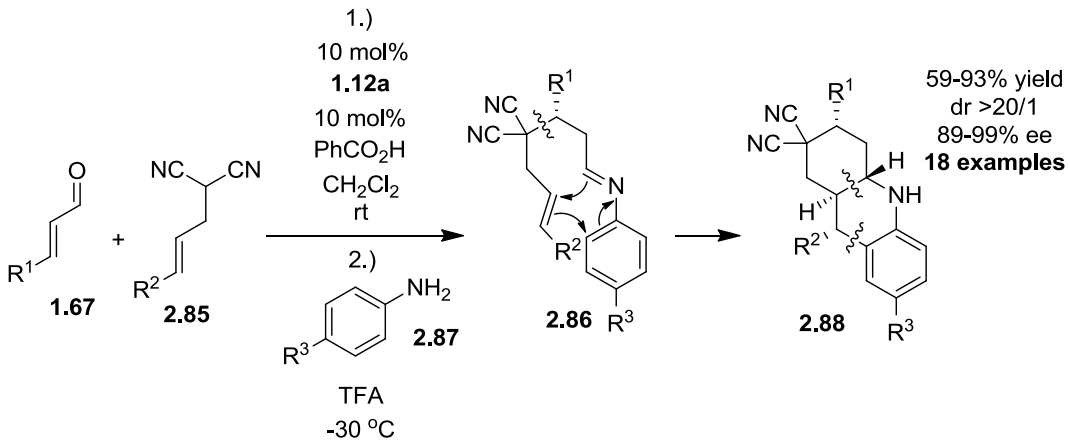
unsaturated aldehydes of type **1.67** (**Scheme 2.29**). This was followed by an enamine–catalyzed intramolecular aldol reaction to give cyclic products of type **2.81** with excellent enantio– and diastereoselectivity. Interestingly, this reaction could be extended to nonsymmetric nitrile containing Michael donors, such as **2.82**–**2.84**, while still achieving high stereocontrol of the product.

Scheme 2.29 Michael–Michael–Aldol Cascade Reaction With Malonitrile Michael Donor



In the second reaction of this type, the initial Michael addition was followed by in situ imine formation using a stoichiometric amount of an external primary amine of type **2.87** (**Scheme 2.30**).[40] The initial Michael addition of malonitriles (**2.85**) to aldehydes of type **1.67**, followed by imine formation, produced reactive intermediates, **2.86**. These imines underwent an *intra*molecular [4+2] cycloaddition with the alkene moiety in the compound. This asymmetric process gave ocathydroacridines of type **2.88** in good yield with excellent selectivity.

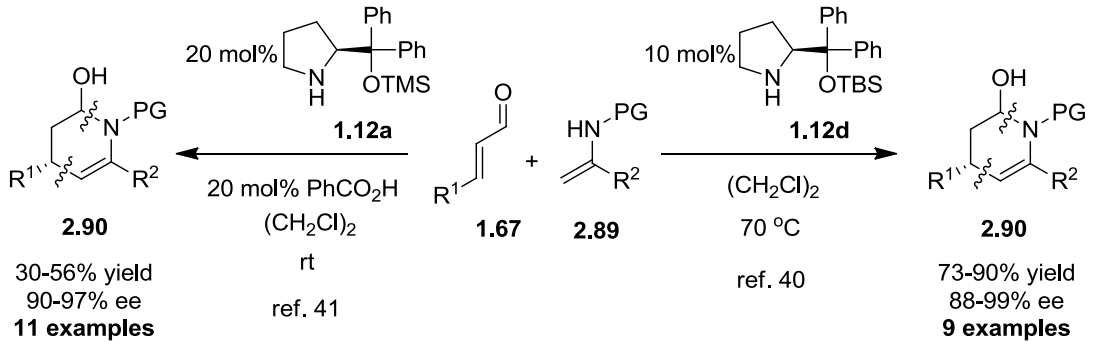
Scheme 2.30 Michael–Cycloaddition Cascade Reaction With Malonitrile Michael Donor



2.1.5 Enamine Michael Donors

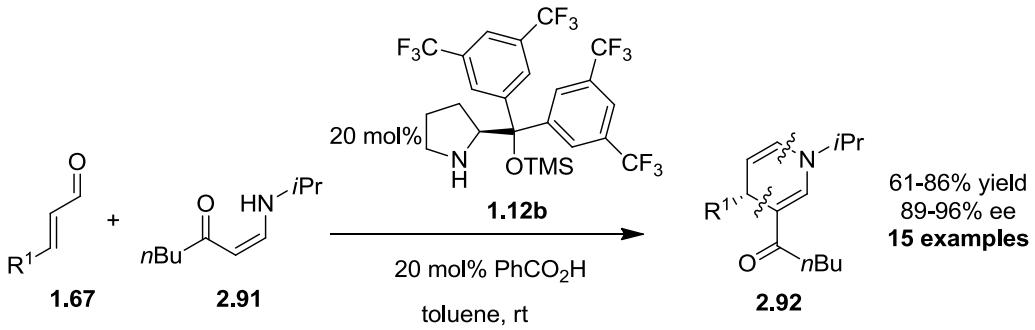
Two iminium–initiated cascade reactions, catalyzed by diarylprolinol silyl ethers, which utilized enamine Michael donors were developed independently by Hayashi et al.[41] and Wang et al.[42] in 2008. In both cases, the initial Michael addition of protected enamines of type **2.89** to aldehydes (**1.67**) generated one chiral center (**Scheme 2.31**). This initial step was followed by catalyst release and *intra*molecular nucleophilic attack of the amine nitrogen on the aldehyde carbon to give piperidine products of, **2.90**. Further elaboration of the products gave access to various valuable synthetic intermediates.

Scheme 2.31 Cascade Reaction With Enamine Michael Donor



Recently, another reaction of this type was developed for the synthesis of 1,4-dihydropyridines.[43] The β-enamino ketone substrate **2.91** gave chiral products of type **2.92** with good selectivity (**Scheme 2.32).** The same reaction was used with β-enamino ester substrates as well. This reaction was the first cascade reaction of this type, using β-enamino ketone Michael donors, catalyzed by a secondary amine organocatalyst.

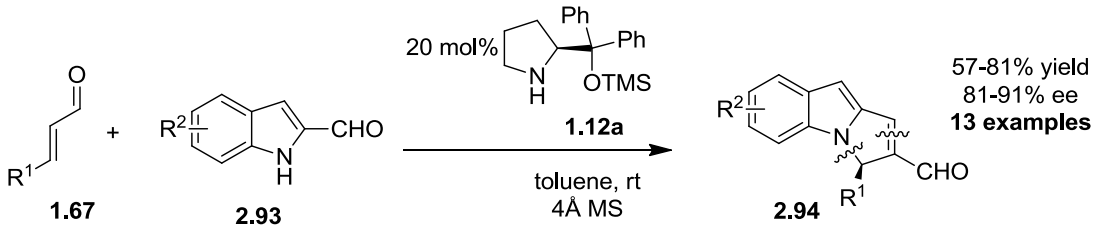
Scheme 2.32 Cascade Reaction With β-Enamino Ketone Michael Donor



2.1.6 Aromatic Michael Donors

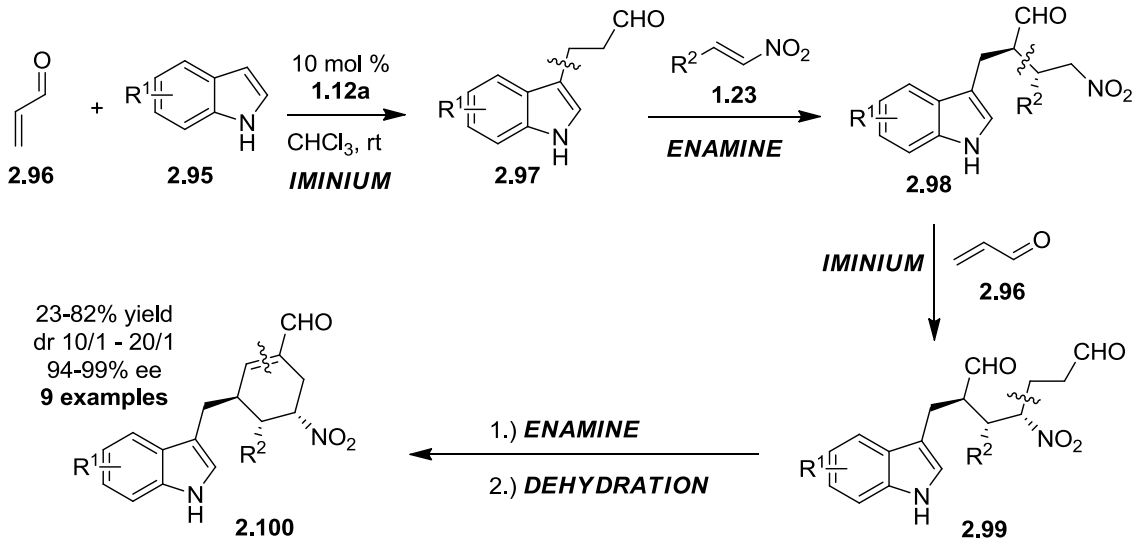
Most of the iminium–initiated cascade reactions that have been developed using these catalysts, which have utilized aromatic Michael donors, have involved indole Michael donors. The first of these, which involved aldehyde substituted indole substrates of type **2.93**, was developed in 2010 (**Scheme 2.33**).[44] This Michael–aldol cascade reaction utilized an iminium–enamine activation sequence to give pyrrolo[1,2-*a*]indole-2-carbaldehydes, **2.94**. The authors indicated that products of this type have been difficult to access via asymmetric catalysis. The products were collected in good yield with great selectivity.

Scheme 2.33 Michael–Aldol Cascade Reaction With an Indole Michael Donor



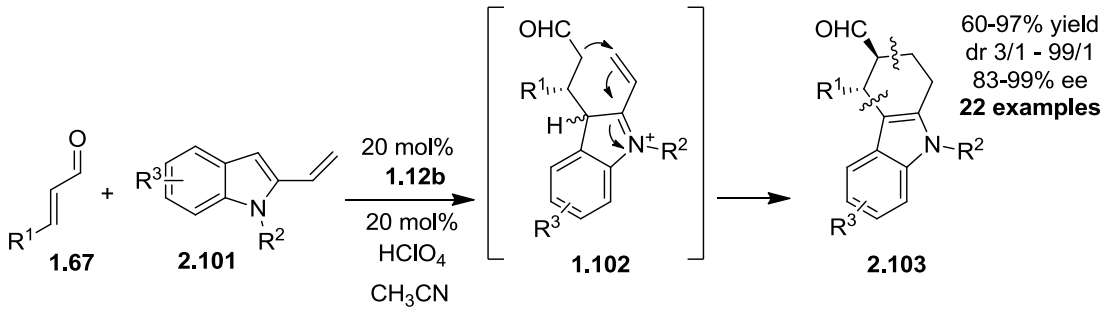
Another iminium–initiated cascade reaction, involving an indole Michael donor, was extended into a quadruple cascade reaction similar to that shown in **Scheme 1.12**. The four component reaction involved indoles of type **2.95**, nitroolefins of type **1.23**, and two equivalents of acrolein **2.96** (**Scheme 2.34**).[45] The initial Michael addition of indoles, **2.95**, to acrolein gave intermediates of type **2.97.** These intermediates underwent an enamine–catalyzed Michael addition to nitroolefins (**1.23**) to give intermediates of type **2.98**. The intermediates reacted with a second equivalent of acrolein via a third Michael addition to give intermediates of type **2.99**. Finally, these intermediates cyclized via an enamine–catalyzed *intra*molecular aldol reaction and gave products **2.100**.

Scheme 2.34 Quadruple Cascade Reaction With an Indole Michael Donor



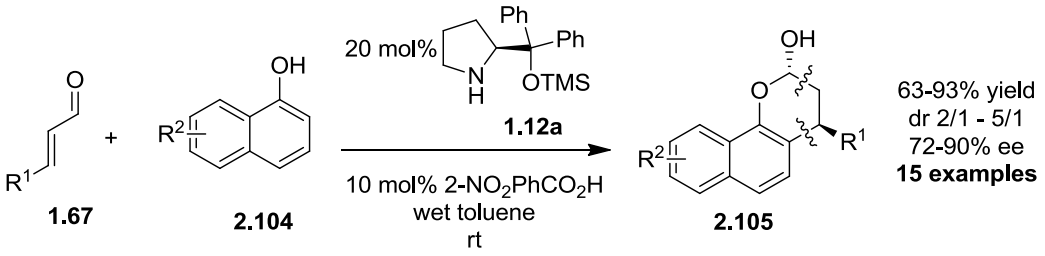
Another cascade reaction was developed using alkene substituted indole rings, **2.101 (Scheme 2.35)**.[46] In this reaction the initial iminium–catalyzed Michael addition, producing **2.102**, was followed by a second Michael addition to the resulting conjugated iminium ion contained in the indole ring. This gave tetrahydrocarbazoles of type **2.103** after a Michael–rearomatization sequence. Studies utilizing *E*- and *Z*- α,β-unsaturated aldehydes were conducted to test whether the reaction may occur via a Diels–Alder mechanism. However, both *E*- and *Z*- α,β-unsaturated aldehydes (**1.67**) gave products with the same configuration, indicating that the reaction did not occur through a concerted Diels–Alder mechanism, which would give products with different configurations.

Scheme 2.35 Michael–Michael Cascade Reaction With an Indole Michael Donor



Another reaction, which involved an aromatic Michael donor, utilized napthol **2.104** to perform the initial conjugate addition (**Scheme 2.36**).[47] This initial step was followed by acetalization, which gave tricyclic products of type **2.105**. This reaction gave the products in high yield but with only moderate selectivity. The chromane products are substructures of many natural products and could also be converted to other synthetically useful derivatives.

Scheme 2.36 Michael–Acetalization Cascade Reaction With A Napthol Michael Donor



2.2 Heteroatom Michael Donors

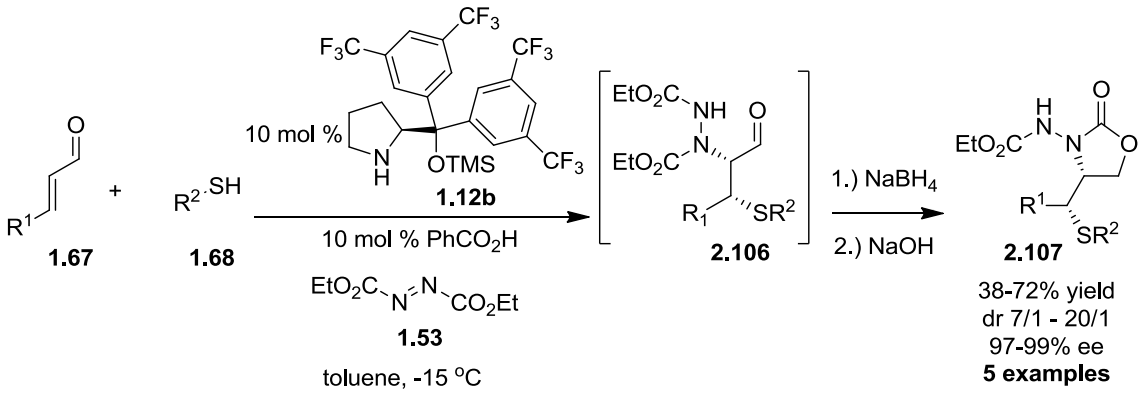
In addition to the conjugate additions involving carbon-centered nucleophiles, there is also a great diversity of organocatalyzed conjugate additions involving heteroatom nucleophiles.[48] A number of these reactions have been iminium–initiated cascade reactions involving

diarylprolinol silyl ether organocatalysts. Sulfur, nitrogen, and oxygen Michael donors have been employed in these iminium–initiated cascade reactions.

2.2.1 Sulfur Michael Donors

The first multi–component cascade reaction utilizing a diarylprolinol silyl ether organocatalyst involved a sulfa-Michael addition as the initial step. This reaction, which used optimal catalyst **1.12b**, was developed by the Jørgensen group in 2005 (**Scheme 2.37**).[49] The initial Michael addition of thiols of type **1.68** to aldehydes (**1.67**) was followed by an enamine catalyzed α-amination using DEAD (**1.53**). The α,β-functionalized intermediates, **2.106**, were then subjected to reduction and base–catalyzed cyclization conditions to give final products of type **2.107**. It was demonstrated that the same reaction, catalyzed by *L*-proline, gave the product with poor enantioselectivity and diastereoselectivity. Amino–thiols in general are known to exhibit interesting biological properties.[50,51]

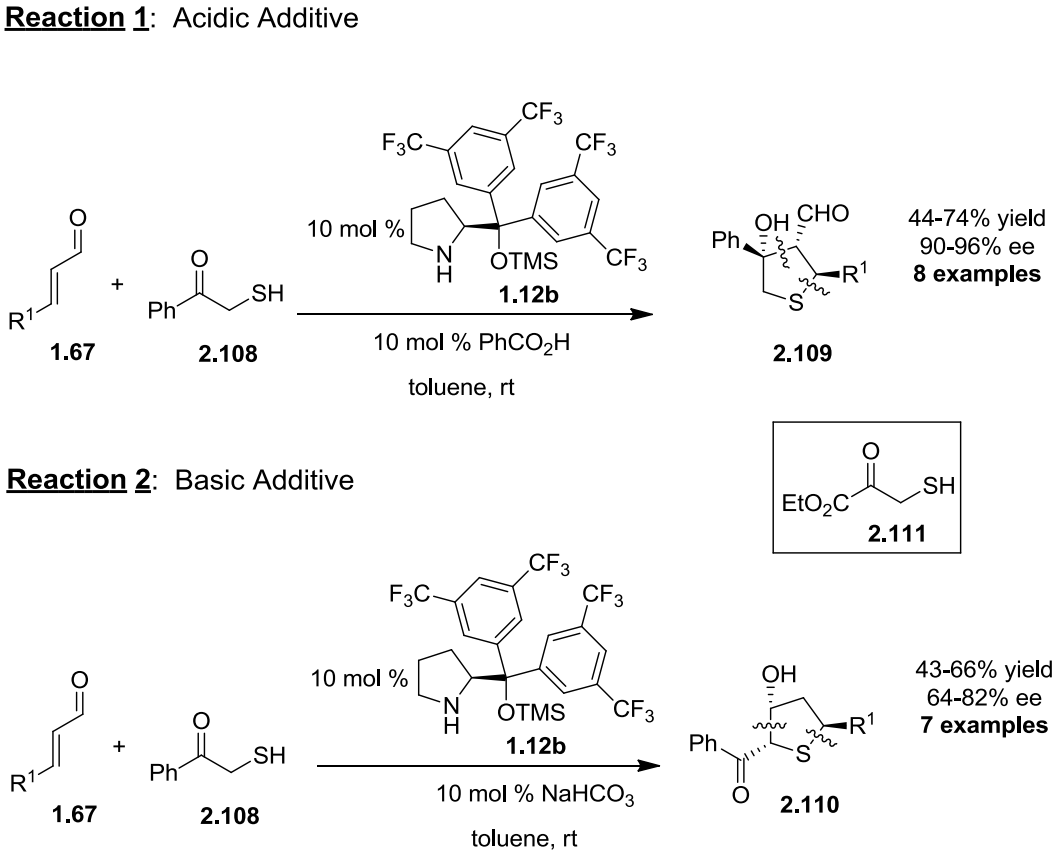
Scheme 2.37 Sulfa-Michael–α-Amination Cascade Reaction



The same group also developed a sulfa-Michael–aldol cascade reaction which also occurred through an iminium–enamine process (**Reaction 1**, **Scheme 2.38**).[52] The thiol–

substituted ketone **2.108** was used as the Michael donor to give tetrahydrothiophene products of type **2.109**. Interestingly, when a basic additive was used instead of an acidic additive, the reaction gave the alternate Michael–aldol products, **2.110**, with slightly lower selectivity (**Reaction 2**, **Scheme 2.38**). Another research group developed a reaction similar to **Reaction 1** using Michael donor **2.111**, which gave products with the same stereochemistry.[53]

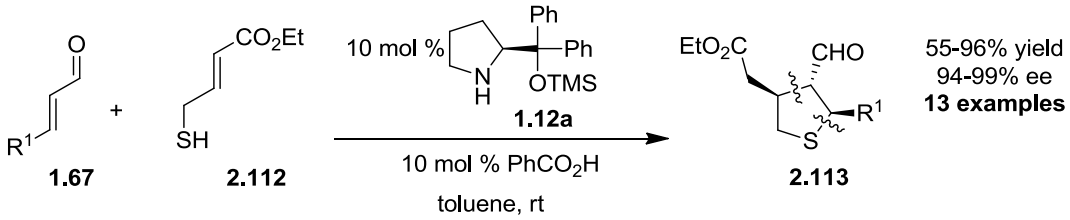
Scheme 2.38 Sulfa-Michael–Aldol Cascade Reactions Give Tetrahydrothiophenes



A similar iminium–enamine catalyzed sulfa-Michael–Michael cascade reaction, using Michael donor **2.112** and catalyst **1.12a**, was also developed (**Scheme 2.39**).[54] This reaction gave tetrahydrothiophene products of type **2.113**, which have a slightly different substitution

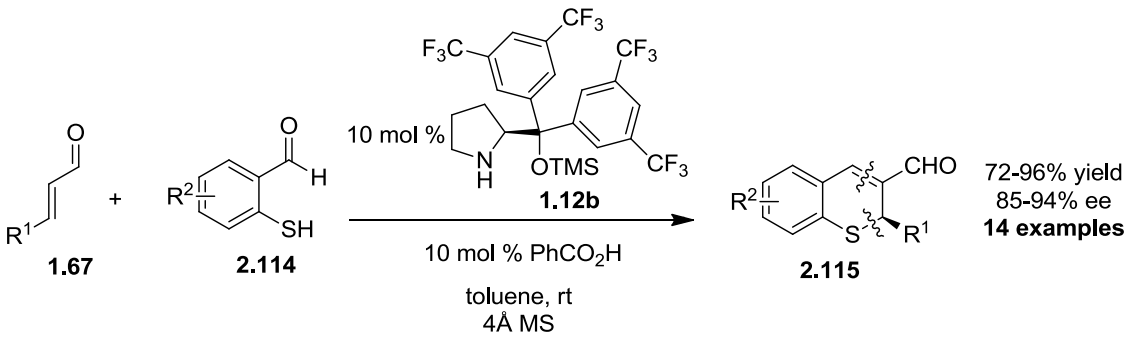
pattern than those observed in the sulfa-Michael–aldol cascade reactions illustrated in **Scheme 2.38**. Interestingly, catalyst **1.12b**, which was used in the reactions in **Scheme 2.38**, did not yield any product after several days.

Scheme 2.39 Sulfa-Michael–Michael Cascade Reaction



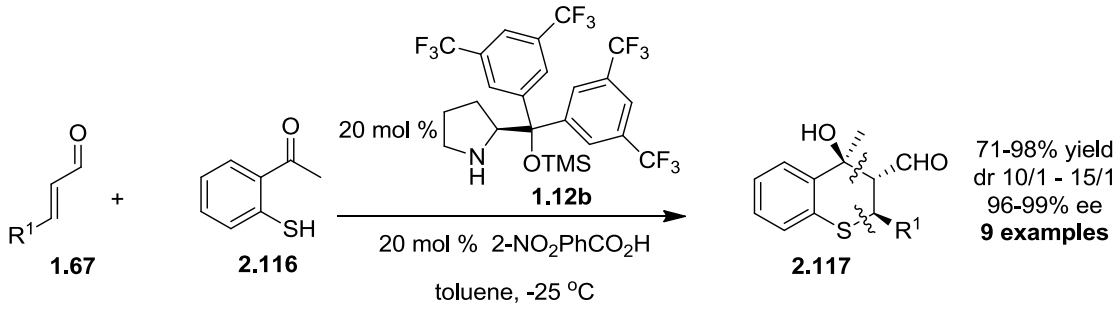
Another sulfa-Michael–aldol cascade reaction, which utilized thiophenol Michael donors, was developed independently by Wang et al.[55] and Córdova et al.[56] These reactions used aldehyde–substituted thiophenols of type **2.114** as Michael donors to produce thiochromene products (**2.115**) via an iminium–enamine process (**Scheme 2.40**). The conditions used by Wang et al. are displayed in **Scheme 2.40**.

Scheme 2.40 Sulfa-Michael–Aldol Cascade Reaction Gives Thiochromenes



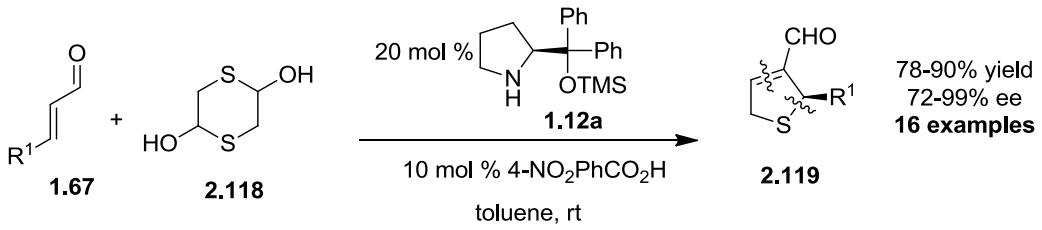
The Córdova group extended their methodology to a similar reaction utilizing keto–substituted thiol **2.116** (**Scheme 2.41**).[57] This reaction gave thiochromene products of type **2.117**, containing three stereocenters, with excellent enantio– and diastereoselectivity.

Scheme 2.41 Cascade Reaction Gives Thiochromenes With Three Stereocenters



Another sulfa-Michael–aldol cascade reaction was developed to give access to dihydrothiophenes (**Scheme 2.42**).[58] This reaction used **2.118** (masked α-thiol–acetaledehyde) as the Michael donor to give products of type **2.119**. The iminium–enamine cascade gave products with one stereocenter in excellent yield and with excellent enantioselectivity.

Scheme 2.42 Sulfa-Michael–Aldol Cascade Reaction Gives Dihydrothiophenes

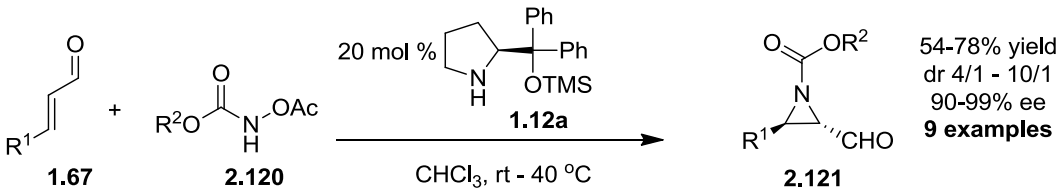


2.2.2 Nitrogen Michael Donors

2.2.2.1 Aziridination Cascade Reactions

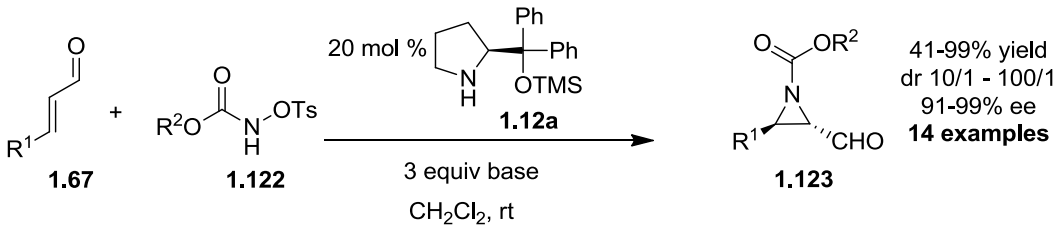
Most of the iminium–initiated cascade reactions catalyzed by diarylprolinol silyl ethers, which utilize nitrogen Michael donors, are aziridination reactions. The first of these aziridination reactions was developed in 2007 by Córdova and co-workers.[59] This reaction utilized acylated hydroxycarbamates of type **2.120** as the Michael donor for the initial iminium–catalyzed conjugate addition (**Scheme 2.43**). The initial Michael addition was followed by an enamine–catalyzed substitution reaction at the nitrogen atom with the acetate ion acting as the leaving group. This reaction gave products, **2.121**, with good diastereoselectivity and excellent enantioselectivity. However, this reaction was only applicable to aldehydes of type **1.67** with alkyl R^1 groups.

Scheme 2.43 Aziridination Cascade Reaction With Acylated Hydroxycarbamates



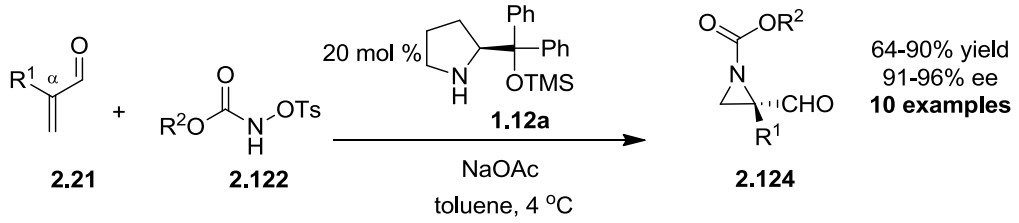
Another aziridination cascade reaction, which was developed later, utilized *N*-arenesulfonylocycarbamate **2.122** as the Michael donor (**Scheme 2.44**).[60] In this reaction an external base was necessary to give the products of type **2.123** in good yield with high selectivity. This reaction was applicable to aldehydes of type **1.67** containing both aryl and alkyl R^1 groups.

Scheme 2.44 Aziridination Cascade Reaction With *N*-arenesulfonylocycarbamates



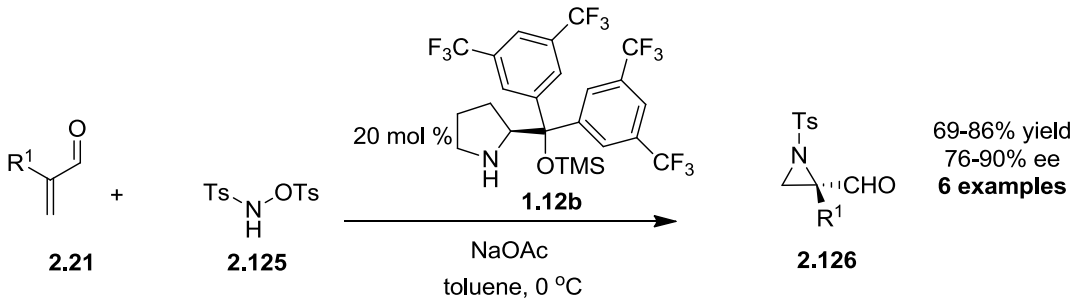
A reaction using similar conditions was used for the aziridination of α-branched aldehydes of type **2.21** (**Scheme 2.45**).[61] This reaction gave aziridine products, **2.124**, containing a chiral quaternary center.

Scheme 2.45 Aziridination Cascade Reaction With α-Branched Aldehydes



A similar protocol for the aziridination of α-branched aldehydes was used to generate tosyl protected aziridines of type **2.126** from sulfonamide **2.125** (**Scheme 2.46**).[62] Studies on the ring opening of the obtained aziridines were conducted with success.

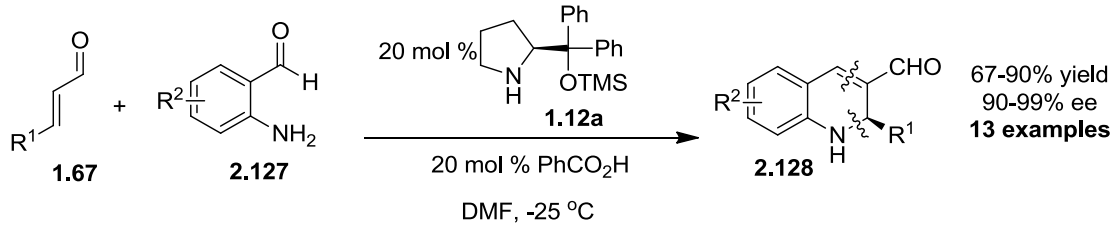
Scheme 2.46 Synthesis of Ts-Protected Aziridines From α-Branched Aldehydes



2.2.2.2 Aza-Michael–Aldol Cascade Reactions

There have also been several iminium–initiated aza-Michael–aldol cascade reactions catalyzed by diarylprolinol silyl ethers, most of which involve substituted aniline Michael donors. The first of these was developed by Córdova et al. in 2007.[63] This reaction involved aldehyde–substituted anilines of type **2.127** adding to α,β-unsaturated aldehydes of type **1.67** to form 1,2-dihydroquinolines, **2.128** (**Scheme 2.47**). Interestingly, this iminium–enamine catalyzed process gave the best results using DMF, a solvent which is rarely used with these catalysts.

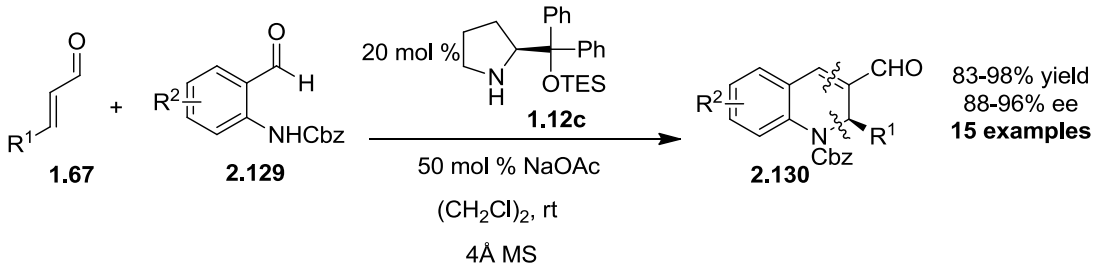
Scheme 2.47 Aza-Michael–Aldol Cascade With Unprotected Anilines



A similar reaction, using catalyst **1.12c**, was performed around the same time by Wang et al.[64] This reaction utilized Cbz-protected aniline Michael donors of type **2.129** to generate protected 1,2-dihydroquinolines of type **2.130** (**Scheme 2.48**). This reaction was highly

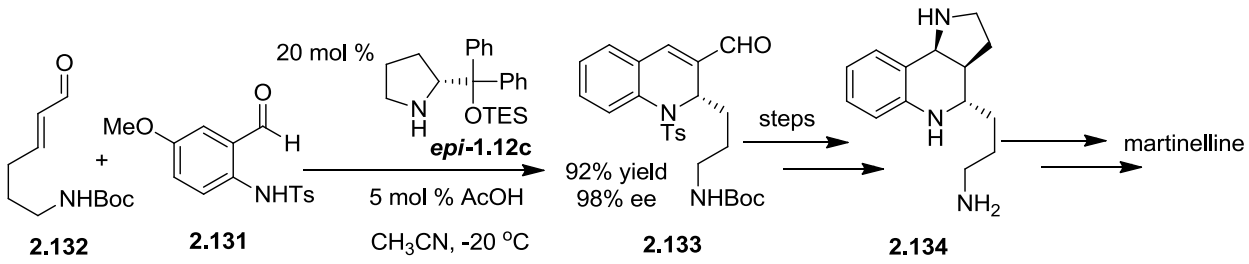
enantioselective and gave the products in higher yields than those achieved using the unprotected Michael donors of type **2.127**.

Scheme 2.48 Aza-Michael–Aldol Cascade With Cbz-Protected Anilines



This same type of reaction was used in the total synthesis of the chiral core of martinelline, a naturally occurring pyrroloquinoline alkaloid which exhibits biological activity.[65] This reaction involved the addition of the Ts-protected Michael donor **2.131** to aldehyde **2.132** to give product **2.133** (**Scheme 2.49**). Compound **2.133** was further manipulated to give the target compound **2.134**.

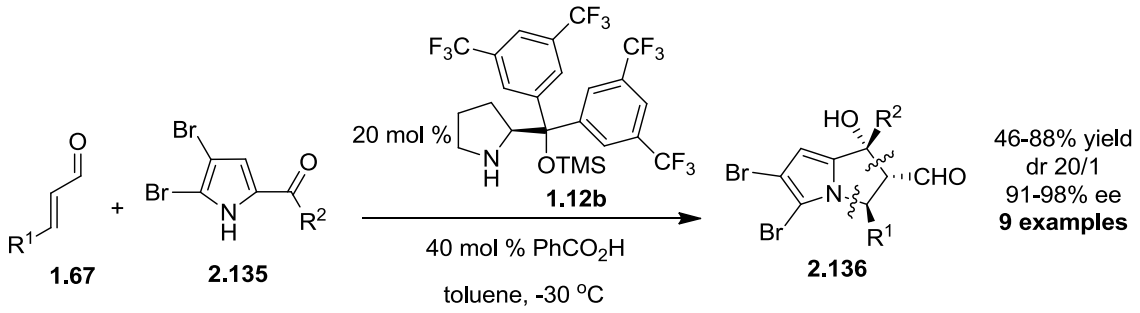
Scheme 2.49 Application to the Total Synthesis of the Chiral Core of Martinelline



An aza-Michael–aldol cascade reaction using a different aza-Michael donor was developed using dibromo–substituted pyrrole Michael donors of type **2.135**.[66] This reaction

produced chiral pyrrolizines, **2.136**, with three contiguous stereocenters being set during the process (**Scheme 2.50**). Dibromopyrroles were used because they occur in a large class of marine natural products. Fortunately, the reaction conditions could also be extended to pyrroles with other substitution patterns.

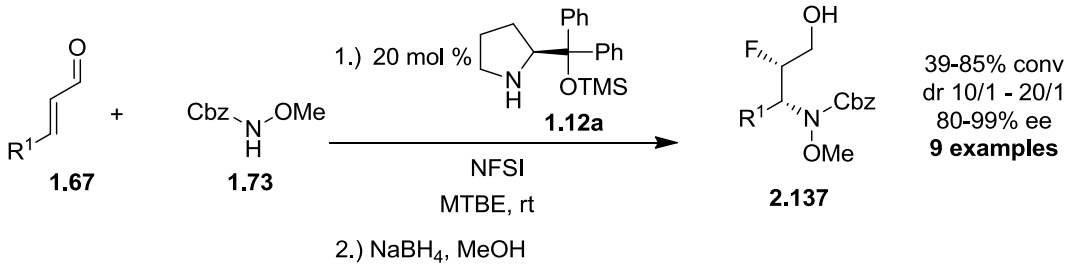
Scheme 2.50 Aza-Michael–Aldol Cascade Reaction With Pyrrole Michael Donors



2.2.2.3 β-Amination–α-Fluorination Cascade Reaction

The β-fluoroamine moiety has been increasingly incorporated into medicinal compounds, but there is lack of efficient methods for its preparation. In 2010, a unique aminofluorination cascade reaction was developed in the Brenner lab.[67] This three–component reaction involved the addition of Cbz-protected methoxyamine **1.73** to the β-position of α,β-unsaturated aldehydes (**1.67**), followed by enamine–mediated α-fluorination using NFSI as the fluorinating agent (**Scheme 2.51**). The aldehyde product was reduced in situ using $NaBH_4$ to give functionalized alcohols of type **2.137**.

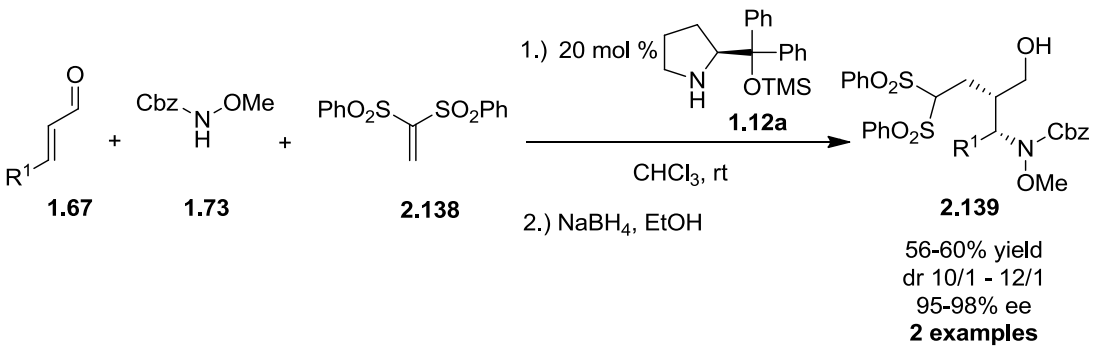
Scheme 2.51 β-Amination–α-Fluorination Cascade Reaction



2.2.2.4 Aza-Michael–Michael Cascade Reaction

An aza-Michael–Michael cascade reaction and a sulfa-Michael–Michael cascade reaction, both using catalyst **1.12a**, have recently been developed (**Scheme 2.52**).[68] The iminium–enamine process was initiated by addition of **1.73** to aldehydes (**1.67**), followed by an enamine catalyzed Michael addition to vinyl sulfone **2.138** to give products of type **2.139** (after in situ reduction). Although this reaction was performed with only two substrates, it is a fine example of how two known reactions can be combined into an efficient one–pot procedure. One reaction of this type was also performed using BnSH as the Michael donor.

Scheme 2.52 Aza-Michael–Michael Cascade Reaction With Vinyl Sulfones

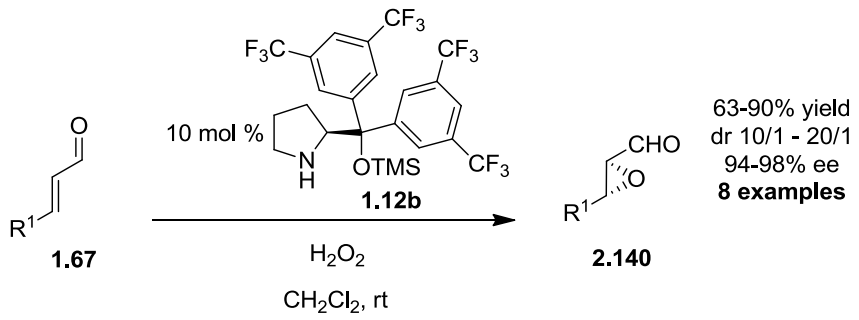


2.2.3 Oxygen Michael Donors

2.2.3.1 Epoxidation Cascade Reactions

The first iminium–initiated cascade reactions catalyzed by diarylprolinol silyl ethers that utilized oxygen Michael donors were epoxidation reactions. This type of reaction was first devloped by the Jørgensen group to generate chiral epoxides of type **2.140** (**Scheme 2.53**).[69] This reaction proceeded with high selectivity for both aryl and alkyl substituted α,β-unsaturated aldehydes (**1.67**). This same reaction, giving similar results, was conducted by Córdova et al.[70] around the same time. Córdova's group also coupled this type of epoxidation reaction with in situ Wittig or Mannich reactions to give a variety of synthetically useful intermediates.[71]

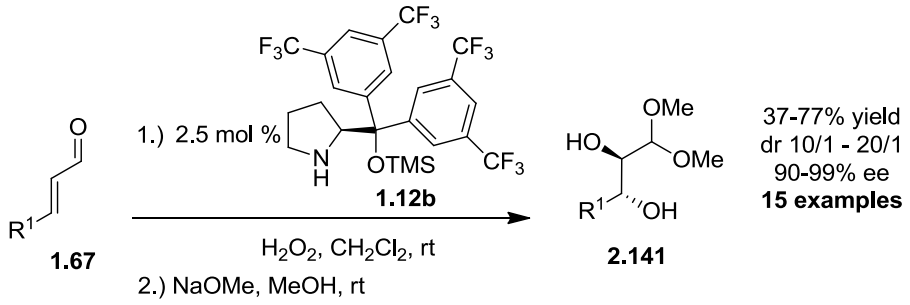
Scheme 2.53 Epoxidation Cascade Reaction



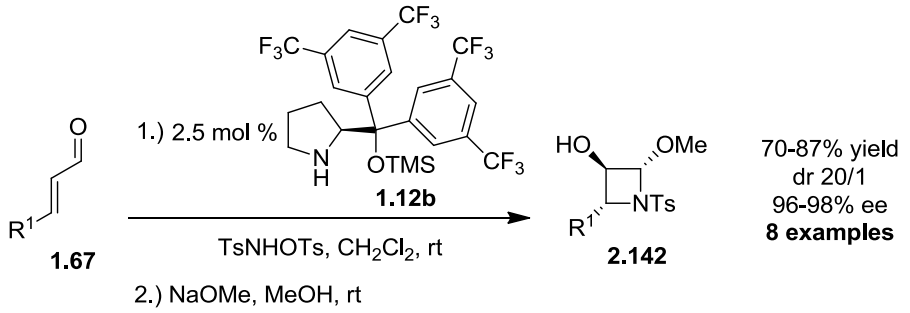
Asymmetric epoxidation reactions with diarylprolinol silyl ethers have been expanded into some other interesting reactions. One of these reactions was used to generate dihydroxylated, protected aldehydes of type **2.141** (**Reaction 1, Scheme 2.54**).[72] This type of manipulation was extended to aziridination reactions in order to form cyclic *N,O*-acetals, **2.142** (**Reaction 2, Scheme 2.54**).

Scheme 2.54 Epoxidation Cascade Reactions Generate Dimethyl Acetates and *N*,*O*-Acetals

REACTION 1

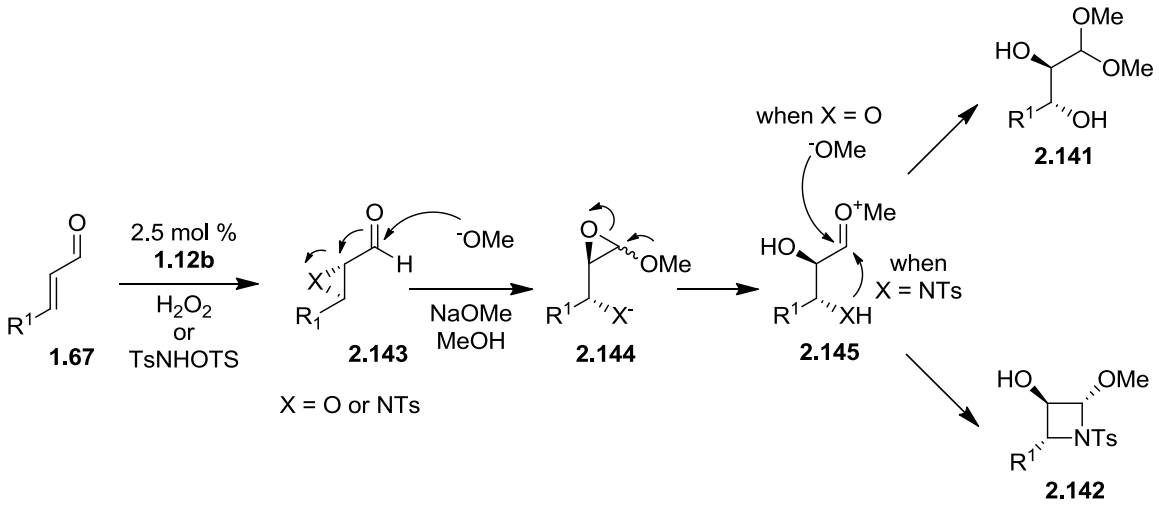


REACTION 2



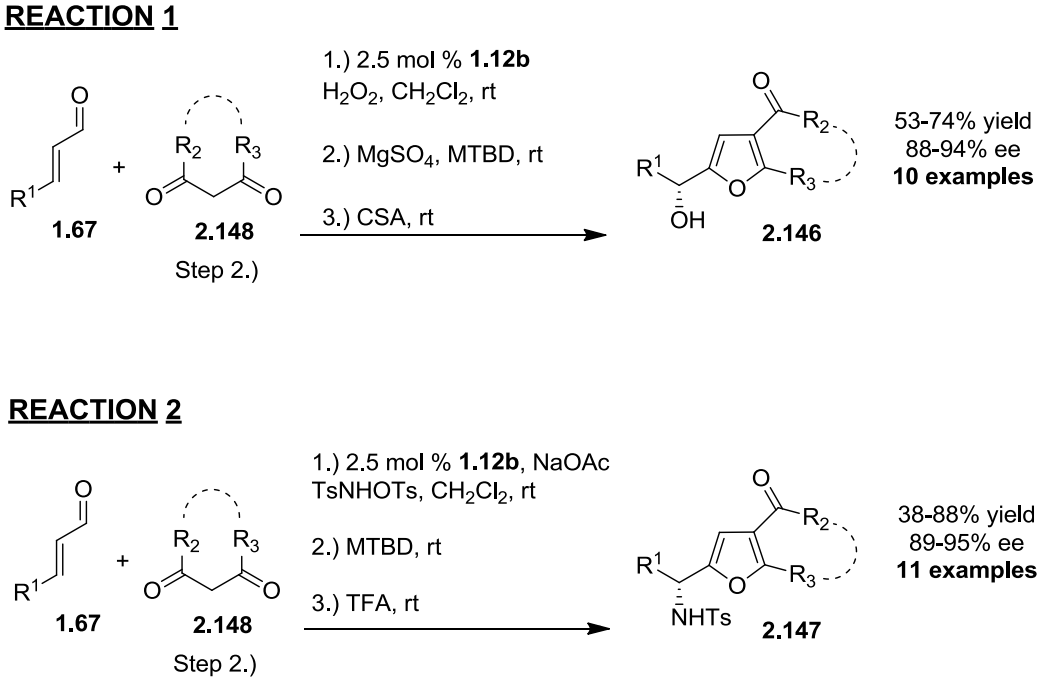
The mechanism for these transformations is illustrated in **Scheme 2.55**. The initially formed three–membered rings, **2.143**, were subjected to nucleophilic attack with a methoxide ion, which allowed them to form epoxide rings, **2.144**. These intermediates underwent ring opening to form intermediates of type **2.145**. When X = O, intermediate **2.145** formed dimethyl acetal products of type **2.141** in the presence of the methoxide ion. When X = NTs, intermediate **2.145** experienced intramolecular nucleophilic attack of the nitrogen atom, which gave cyclic *N*,*O*-acetals of type **2.142**. **Reaction 2** is a rare example of an organocatalytic process which generates four–membered rings.

Scheme 2.55 Mechanism For Generation of Dimethyl Acetates and *N*,*O*-Acetals



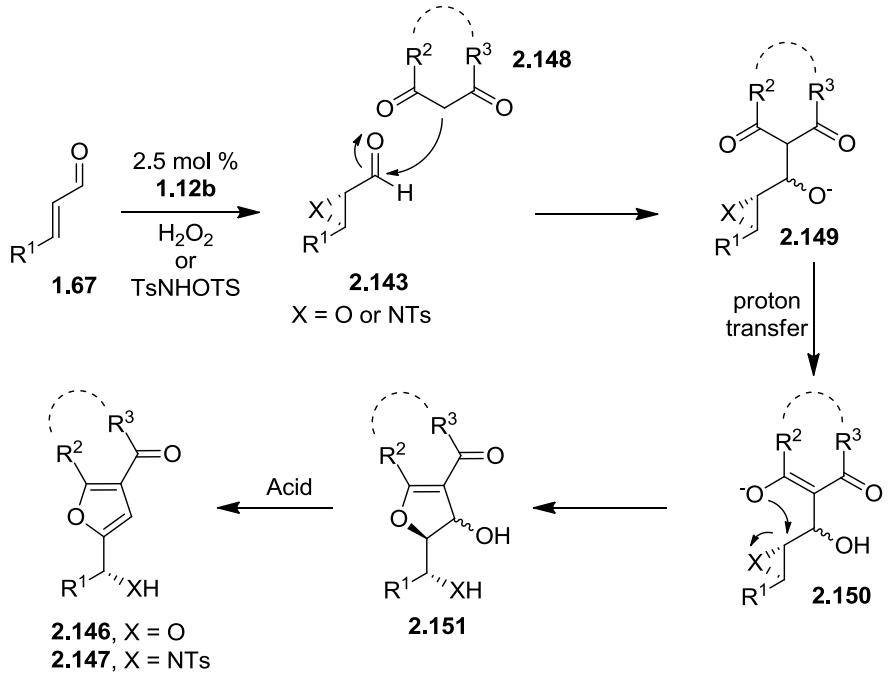
A similar approach was used to synthesize 2-hydroxyalkyl furanes, **2.146** (**Reaction 1, Scheme 2.56**), and 2-aminoalkyl furanes, **2.147** (**Reaction 2, Scheme 2.56**), using cyclic dicarbonyl nucleophiles of type **2.148**.[73]

Scheme 2.56 Epoxidation Cascade Reactions Generate Substituted Furanes



The mechanism for these transformations is illustrated in **Scheme 2.57**. Once again, three–membered rings, **2.143**, were formed initially. These were subjected to nucleophilic attack with dicarbonyl compounds of type **2.148** which gave intermediates, **2.149**. Proton transfer gave intermediates of type **2.150** which underwent an intramolecular epoxide opening/ring forming reaction to give five–membered rings of type **2.151**. In the presence of acid, elimination occurs to give the final products (**2.146** when X = O, **2.147** when X = NTs).

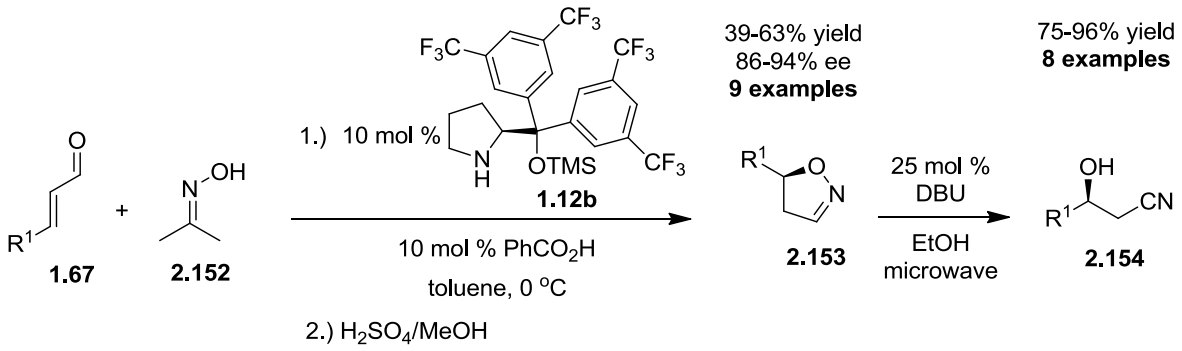
Scheme 2.57 Mechanism For Generation of Substituted Furanes



2.2.3.2 Oxime Michael Donors

There has also been an iminium–initiated cascade reaction catalyzed by a diarylprolinol silyl ether which utilized an oxime Michael donor. The cascade process developed was a Michael–oxime transfer cascade reaction used to synthesize 2-isooxazolines of type **2.153** (**Scheme 2.58**).[74] The acetone–derived oxime **2.152** was used as the Michael donor for this reaction. Several secondary amine catalysts were screened, but **1.12b** was the only catalyst that exhibited any selectivity in product formation. Product yields were only moderate, but the reaction was highly enantioselective. Products of type **2.153** could be converted to β-hydroxynitriles, **2.154**, which are generally difficult to access in enantiopure form.[75]

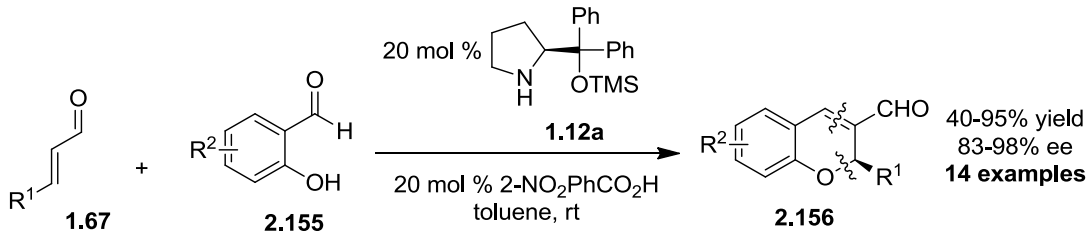
Scheme 2.58 Oxa-Michael–Oxime Transfer Cascade Reaction



2.2.3.3 Phenol Michael Donors

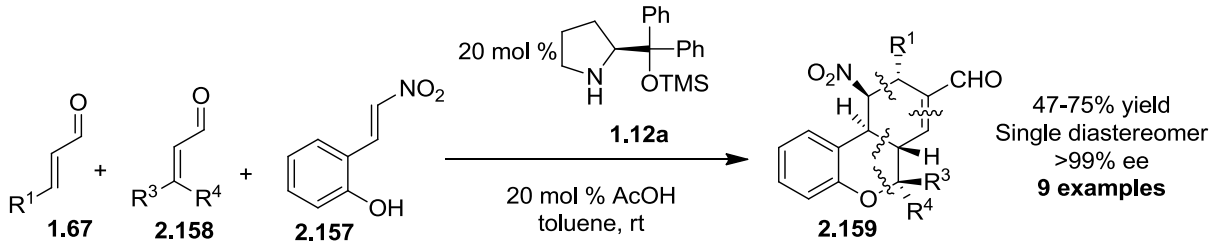
Many of the diphenylprolinol silyl ether catalyzed oxa-Michael–initiated cascade reactions that have been developed utilize phenol nucleophiles. An oxa-Michael–aldol cascade reaction, using aldehyde substituted phenol Michael donors of type **2.155**, was developed independently by Arvidsson et al.,[76] Wang et al.[77] and Córdova et al.[78] (**Scheme 2.59**). The conditions used by each group were slightly different, but in all cases, the benzopyran products of type **2.156** were collected in moderate to good yield with excellent enantioselectivity. The Córdova group's conditions and results are displayed in **Scheme 2.59**.

Scheme 2.59 Oxa-Michael–Aldol Cascade Reaction With Phenol Michael Donors



Wang et al. used nitroolefin–substituted phenol Michael donor **2.157** in a three–component quadruple cascade reaction (**Scheme 2.60**).[79] This Michael–Michael–Michael–aldol cascade reaction, involving Michael acceptors of type **1.67** and type **2.158**, generated tetrahydro-6*H*-benzo[*c*]chromenes, **2.159**, as single diastereomers with outstanding enantioselectivity.

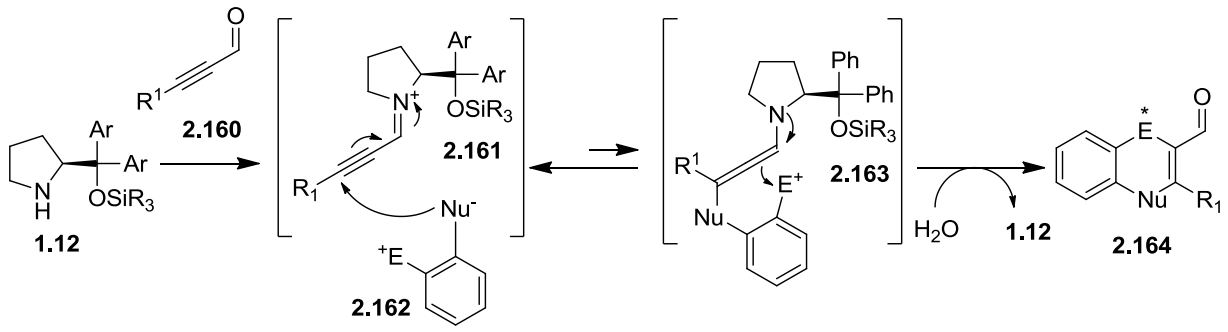
Scheme 2.60 Oxa-Michael–Michael–Michael–Aldol Cascade Reaction



2.2.3.4 Phenol Michael Donors With Alkyne Michael Acceptors

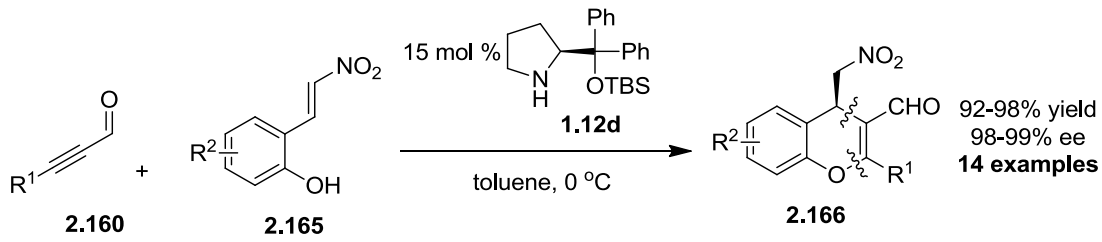
There have also been reactions developed, similar to that displayed in **Scheme 2.59**, which require alkynal oxa-Michael acceptors. These types of cascade reactions proceed via the iminium–allenamine mechanism shown in **Scheme 2.61**. The general alkynal substrate **2.160** is activated as intermediate **2.161**, which is susceptible to nucleophilic attack at the β-position with **2.162**. The resulting allenamine intermediate **2.163** performs an intramolecular nucleophilic attack on the electrophilic portion of the original Michael donor. This cyclization process, followed by catalyst turnover, gives products of type **2.164**. Asymmetric induction occurs during the enamine–catalyzed step.

Scheme 2.61 Iminium–Allenamine Catalysis Using Diarylprolinol Silyl Ethers



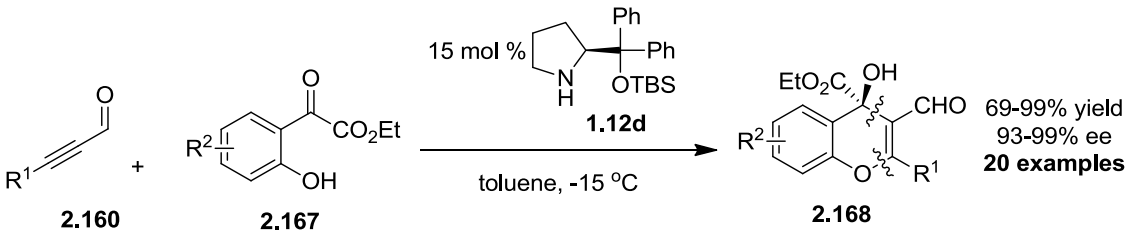
The first reaction of this type, catalyzed by bulky catalyst **1.12d**, was developed by Wang and co-workers in 2010 (**Scheme 2.62**).[80] The Michael–Michael cascade reaction utilized Michael donors of type **2.165** to give access to chiral 4*H*-chromenes (**2.166**). This reaction generated the products in excellent yield with excellent enantioselectivity.

Scheme 2.62 Oxa-Michael–Michael Cascade Reaction With Alkynal Michael Acceptors



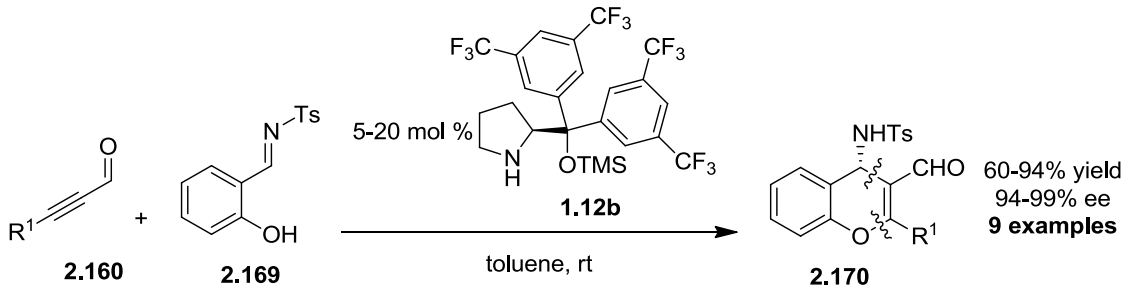
A similar oxa-Michael–aldol cascade reaction was developed using keto–substituted phenol Michael donors of type **2.167** (**Scheme 2.63**).[81] The 4*H*-cromene products, **2.168**, which contain a versatile α-hydroxy carboxylate moiety, are valuable intermediates for the synthesis of biologically active molecules. Once again, the products were collected in excellent yield with excellent enantioselectivity.

Scheme 2.63 Oxa-Michael–Aldol Cascade Reaction With Alkynal Michael Acceptors



This same protocol was extended to an oxa-Michael–Mannich cascade reaction using imine–substituted phenol **2.169** (**Scheme 2.64**).[82] The reaction was used to generate 4-amino-4*H*-chromenes of type **2.170**. The type of structural motif that exists in the products (**2.170**) is also observed in many biologically active natural products.

Scheme 2.64 Oxa-Michael–Mannich Cascade Reaction With Alkynal Michael Acceptors

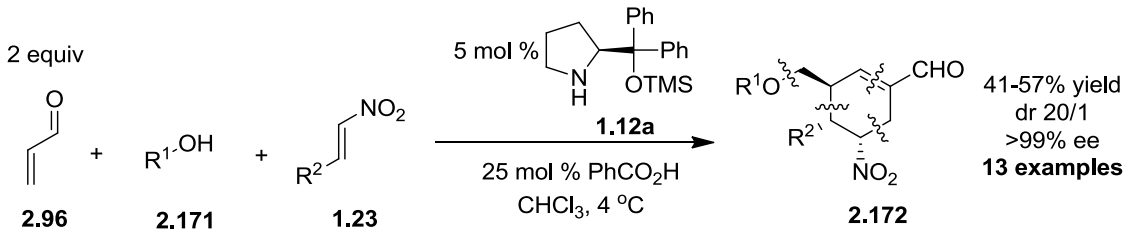


2.2.3.5 Aliphatic Alcohol Michael Donors

There have been only two diphenylprolinol silyl ether catalyzed oxa-Michael–initiated cascade reactions using aliphatic alcohol Michael donors. One of these is illustrated in **Scheme 2.65**.[83] This reaction is nearly identical to that displayed in **Scheme 2.34** except that the initial Michael donor in this reaction is an alcohol of type **2.171**, as opposed to an indole (as in **Scheme 2.34**). This reaction progressed, with nitroolefins of type **1.23** and two equivalents of acrolein **2.96**, via

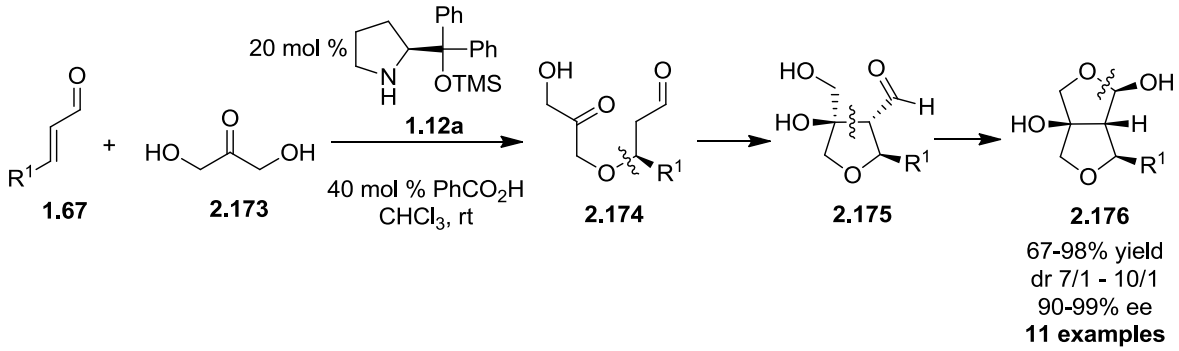
the same Michael–Michael–Michael–aldol mechanism and generated products with the same stereochemistry. The cyclohexene products, **2.172**, were collected in only moderate yield, but with excellent selectivity. It is worth pointing out that the initial oxa-Michael addition, with the aliphatic alcohol Michael donor, does not generate a stereocenter.

Scheme 2.65 Oxa-Michael–Initiated Quadruple Cascade Reaction



An oxa-Michael initiated cascade reaction where a chiral center *is* generated during the initial step with an aliphatic alcohol Michael donor is displayed in **Scheme 2.66**.[84] This reaction was conducted using dihydroxyketone **2.173** as the oxa-Michael donor for the initial step of the reaction. The resulting oxa-Michael adducts, **2.174**, participated in an enamine–catalyzed intramolecular aldol reaction to give intermediates, **2.175**. The last step involved an intramolecular acetalization to give products of type **2.176**. The substituted furofurane products, which were collected in good yield with excellent selectivity, contained four new stereocenters and could be further manipulated to give useful chiral building blocks.

Scheme 2.66 Oxa-Michael Cascade Reaction With An Aliphatic Alcohol Michael Donor



It is clear that diaryl prolinol silyl ethers are extremely versatile organocatalysts which can participate in a wide array of different iminium–initiated cascade reactions. The fact that these catalysts can participate in enamine catalysis as well, allows them to be used with a vast collection of substrates to give many synthetically useful products. Using these types of catalyzed reactions, a great deal of chemical diversity can be generated from simple starting materials in a one-pot process.

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Chapter 3.

Novel Bifunctional Bissulfonamides

Catalyze a Conjugate Addition

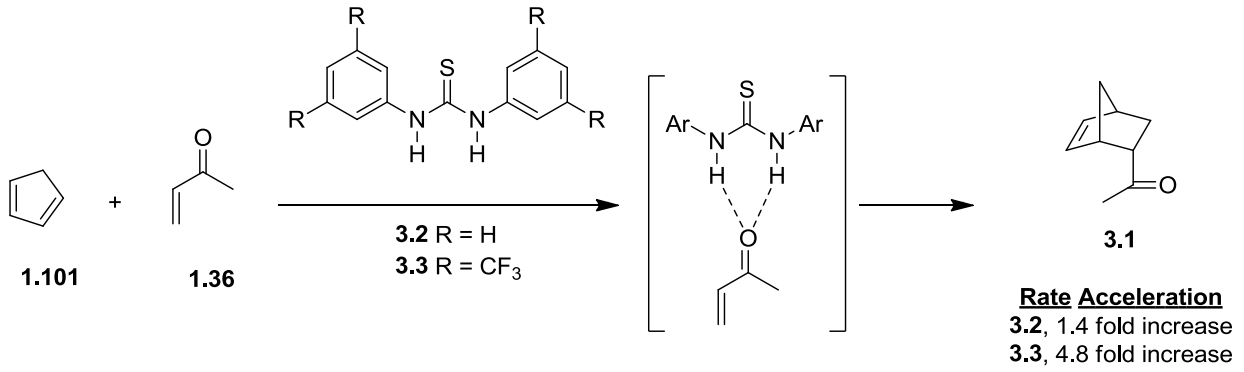
3.1 Introduction

3.1.1 Thiourea Organocatalysts

As mentioned in Chapter 1, hydrogen bonding organocatalysts are quite effective at catalyzing a variety of conjugate additions involving dicarbonyl Michael donors.[1,2] In general, all hydrogen–bonding catalysts operate through the donation of hydrogen bonds to electron–rich regions in the substrate. This leads to a change in electron density in the substrate, which enhances the substrate's reactivity. When asymmetric hydrogen bond donors are utilized, they can affect the directionality of new bond formation, resulting in chiral products. Hydrogen–bonding thiourea and urea catalysts have been extensively studied in the last ten years. Jacobsen and others have used chiral thiourea and urea derivatives to catalyze a number of asymmetric reactions (i.e. Strecker,[3] Mannich,[4] Morita–Baylis–Hillman,[5] hydrophosphonylation,[6] Michael addition[7]).

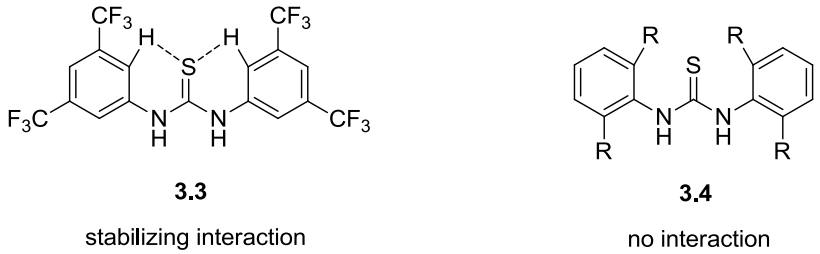
An extensive study by Schreiner et al. analyzed how achiral thioureas catalyzed the Diels–Alder reaction between cyclopentadiene **1.101** and α,β-unsaturated ketone **1.36** to give the bicyclic product **3.1**.[8] Large rate increases were observed with catalysts **3.2** and **3.3** (**Scheme 3.1**).

Scheme 3.1 Thiourea Catalyzed Diels–Alder Reaction



The increased acidity of the thiourea hydrogen atoms gained by replacing the phenyl hydrogens with trifluoromethyl groups dramatically increased the rate of the reaction even with only 1 mol % catalyst loading. It was also shown that all *ortho*–substituted phenyl thioureas of type **3.4** were much less active (**Figure 3.1**). From this result, it was proposed that the hydrogen–bonding interaction between the sulfur atom and the indicated phenylic protons increased the rigidity of the catalyst, minimizing the entropic penalty for binding of the catalyst to the substrate in the transition state. The reaction could be carried out in a variety of solvents including water. It was postulated by Schreiner that carrying out the reaction in water forced the substrates and catalyst together into hydrophobic pockets, allowing for an increase in reaction rate.

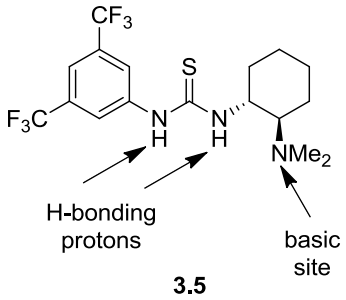
Figure 3.1 Intramolecular Interactions in Thiourea Catalysts



3.1.2 Bifunctional Thiourea Organocatalysts

Another development in thiourea catalysis has been the use of chiral, bifunctional thiourea catalysts like **3.5** shown in **Figure 3.2**. In addition to the thiourea functionality, these catalysts incorporate a tertiary amine moiety into the catalyst scaffold. These asymmetric catalysts can simultaneously interact with substrates through the hydrogen bond donors and the basic amine group. This has allowed these chiral "bifunctional" thioureas to participate in new classes of enantioselective reactions that monofunctional hydrogen–bonding thioureas cannot. While there are many other types of bifunctional hydrogen–bonding organocatalysts, including cinchona alkaloids[9] and bis–phenols[10], the thiourea catalysts have proven to be privileged catalysts, because they have found general use as efficient catalysts in a wide array of organic reactions.[11]

Figure 3.2 Bifunctional Thiourea

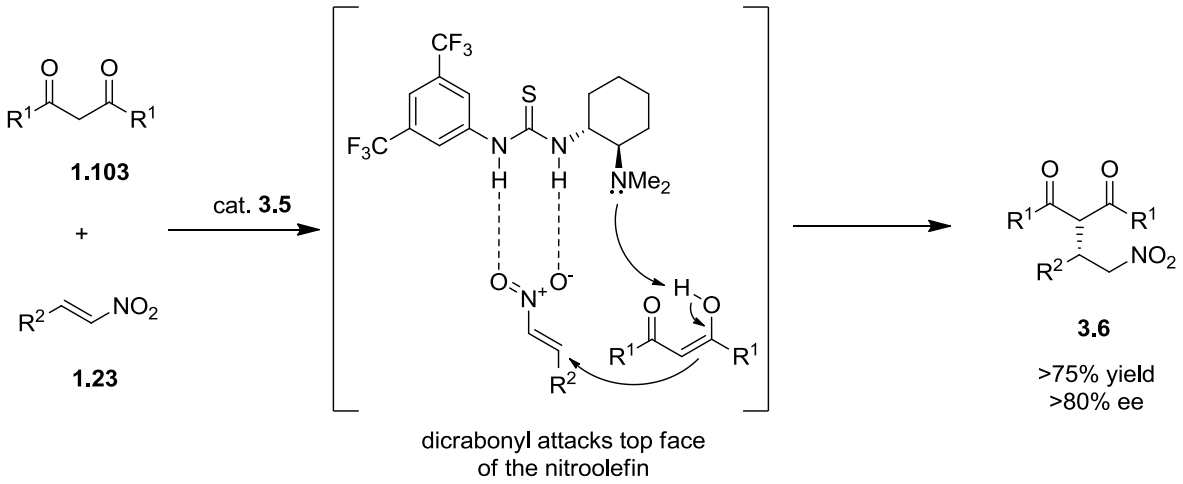


3.5

The Michael addition of 1,3-dicarbonyl compounds of type **1.103** to nitroolefins of type **1.23** to give enantioenriched products of type **3.6** is a common reaction in which bifunctional thiourea catalysts have been used (**Scheme 3.2**).[12-16] The hydrogen–bonding interaction with the electron–rich nitro group and the interaction between the tertiary amine and the acidic proton of the dicarbonyl compound are the critical interactions involved in the catalysis. When used with a

variety of substrates and a catalyst loading of 10 mol %, these catalysts gave products in >75% yield in >80% ee.[13]

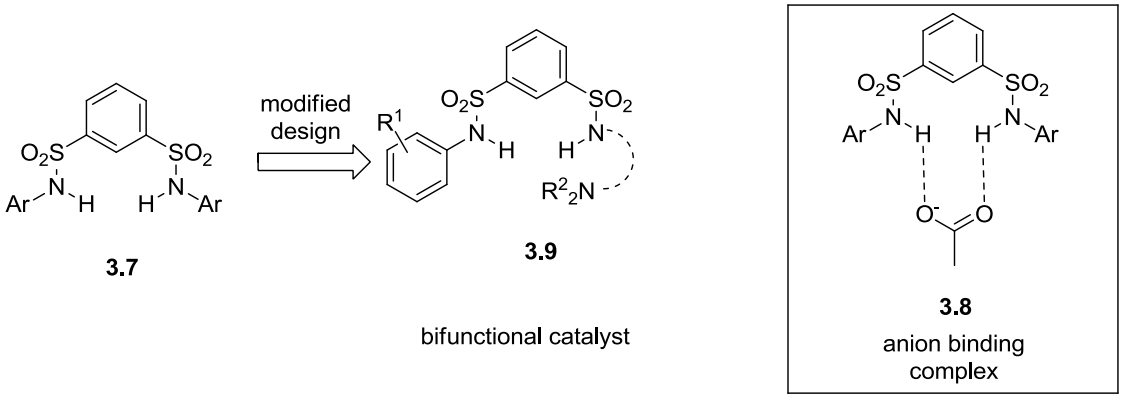
Scheme 3.2 Bifunctional Thiourea Catalyzed Michael Addition



3.1.3 Bissulfonamide Organocatalysts

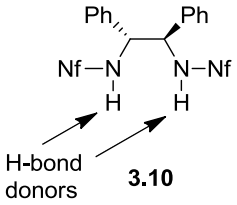
In the search for new (and hopefully improved) structural motifs for bifunctional hydrogen bonding organocatalysts, bissulfonamide **3.7** in **Figure 3.3** was considered. This bissulfonamide had been used by Crabtree as an acetate and halide anion receptor and a catalyst for the simple imination of *p*-methyl benzaldehyde with benzylamine.[17,18] While the barriers for rotation of the sulfur–carbon bonds in **3.7** are small, when in the presence of an anion in solution, **3.7** adopts a rigid structure (forming complex **3.8**), which is similar to that of the thiourea catalysts. Bissulfonamide **3.7** was shown, through X-ray crystallography, to bind anions through double hydrogen bond donation. It was postulated to do the same in the catalyzed imination, based on association constants.[19]

Figure 3.3 Anion Binder And Bifunctional Organocatalyst



In addition, chiral monofunctional bissulfonamides have been used to catalyze enantioselective reactions. As an example, catalyst **3.10** (**Figure 3.4**) was used to catalyze the hetero Diels–Alder reaction between **3.11** and **3.12** to form the asymmetric product **3.13** in 86% ee (**Scheme 3.3**).[20] It was also shown to catalyze the Friedel–Crafts reaction between **3.14** and **3.15** to give **3.16** in 63% ee (**Scheme 3.3**).[21]

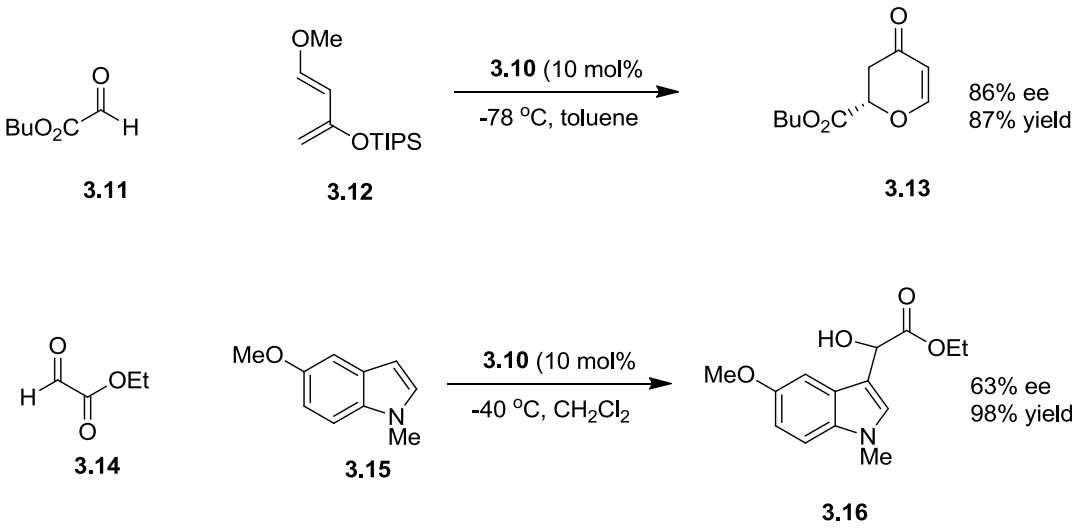
Figure 3.4 Monofunctional Bissulfonamide



Unfortunately, there is no facile way to render a bissulfonamide, of type **3.10**, bifunctional. Indeed, a chiral, bifunctional bissulfonamide had never been used as an organocatalyst. It was hypothesized that by incorporating a chiral tertiary amine element into

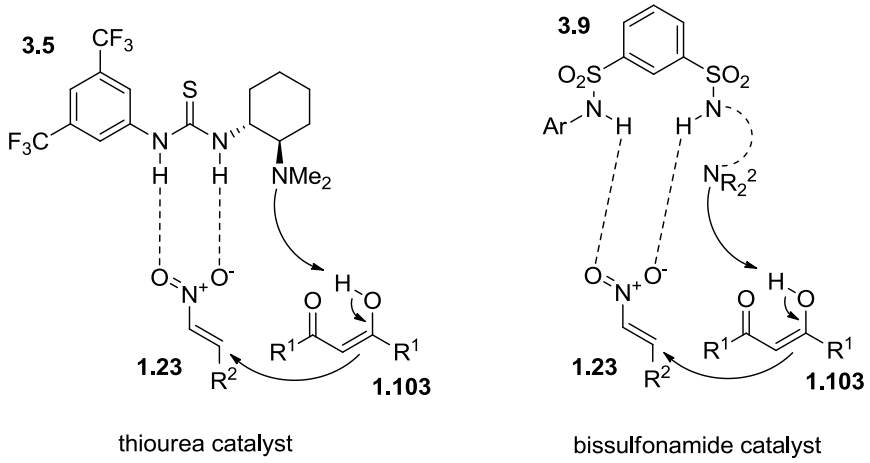
the scaffold shown in **Figure 3.3**, a new family of bifunctional organocatalysts of type **3.9** could potentially be developed.

Scheme 3.3 Monofunctional Sulfonamide Catalyzed Reactions



More importantly, incorporation of sulfonamide protons (pKa ~ 16.1),[22] being more acidic than thiourea protons (pKa ~ 21.0),[23] could potentially result in more efficient hydrogen bonding catalysts with regard to percent yield and enantiomeric excess. As discussed earlier, this correlation between catalyst acidity and catalyst efficiency has been documented with other hydrogen bonding organocatalysts.[10,24] Based on their increased acidity, it was postulated that these bifunctional bissulfonamide catalysts could simultaneously activate both substrates in a conjugate addition similar to that catalyzed by bifunctional thiourea catalysts, but with potentially better yields and ee's (**Figure 3.5**). This would be achieved through activation of the nitroolefin through hydrogen bond donation and activation of the dicarbonyl compound through the basic amine group.

Figure 3.5 Thiourea and Bissulfonamide Activation

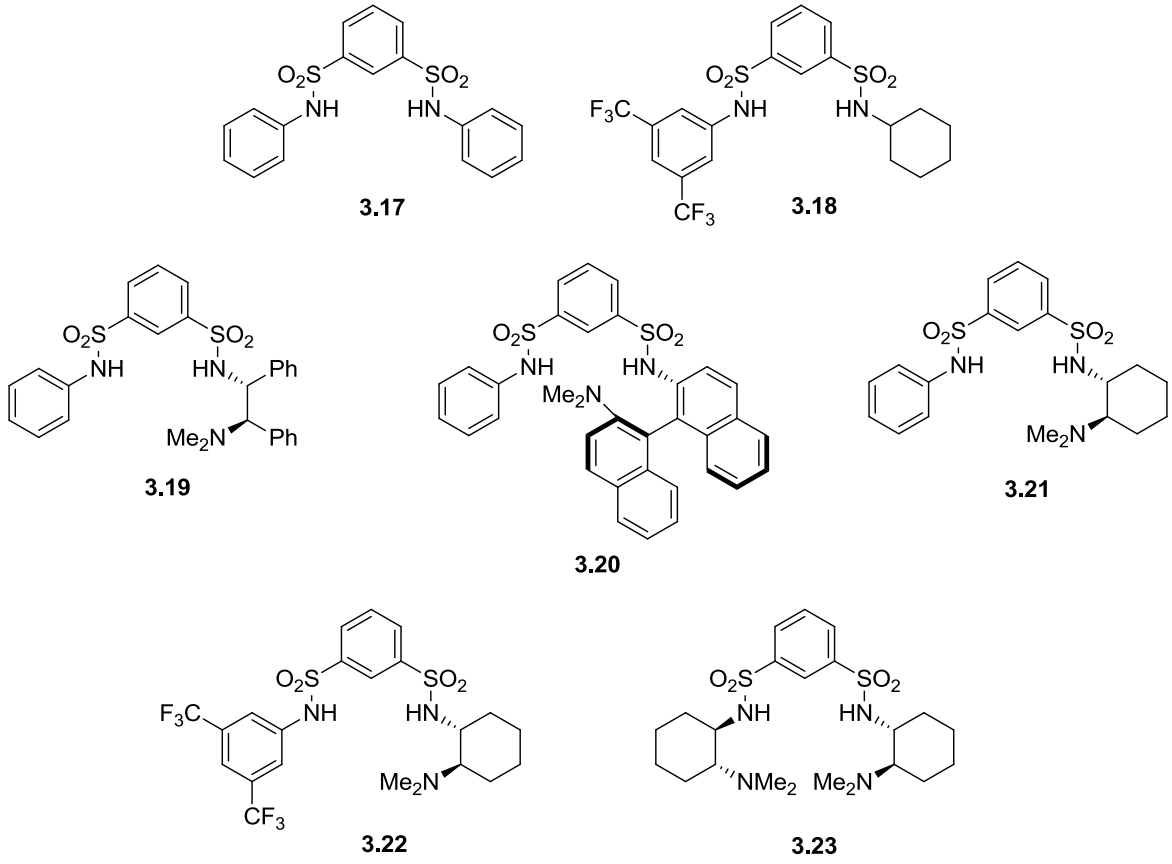


3.2 Results And Discussion

3.2.1 Preparation Of Bifunctional Bissulfonamide Organocatalysts

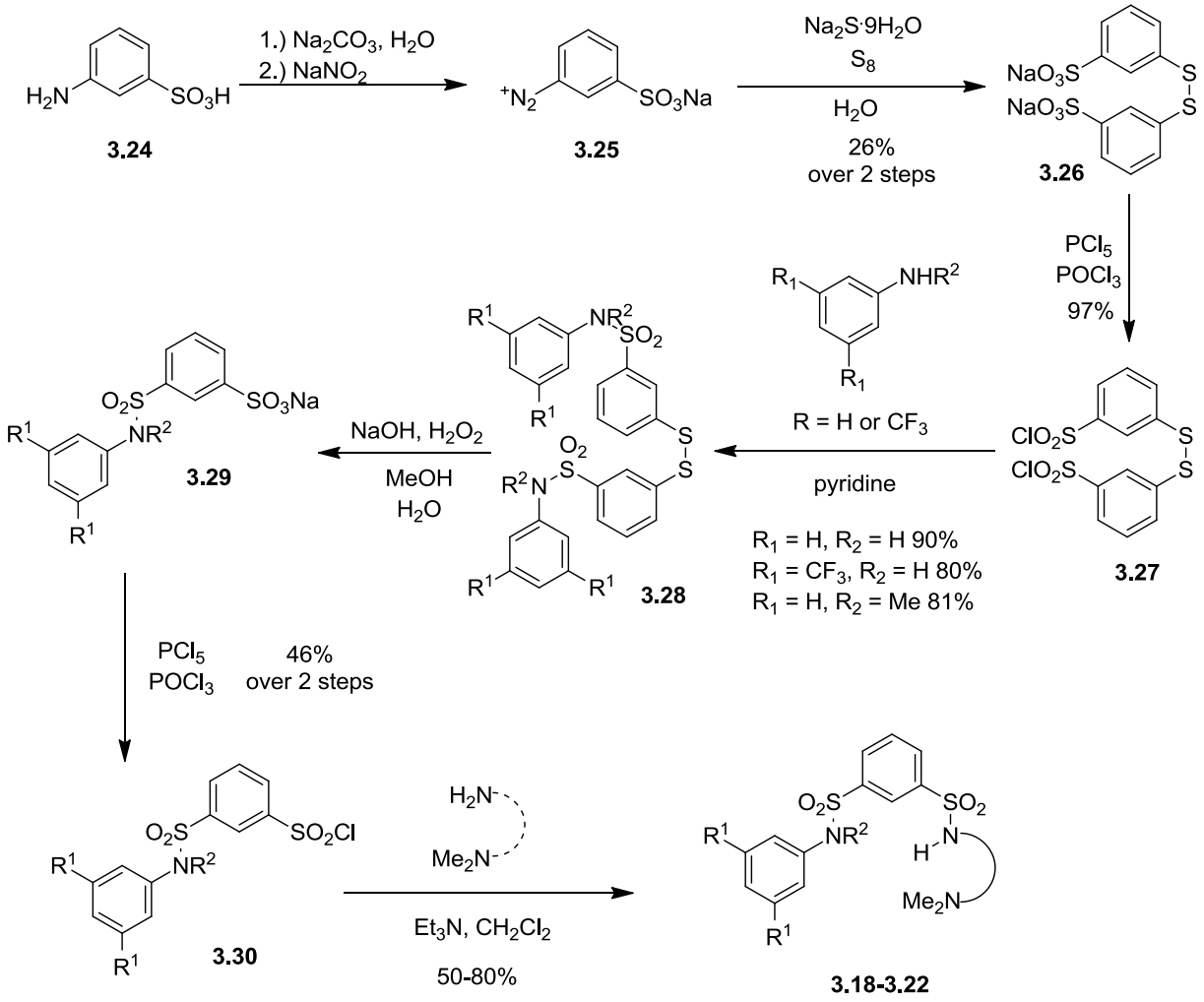
The catalysts shown in **Figure 3.6** were synthesized to be used in the enantioselective Michael addition of diethyl malonate to β-nitrostyrene.

Figure 3.6 Bifunctional Bissulfonamide Catalysts



The C2–symmetric catalysts **3.17** and **3.23**, were synthesized by coupling the appropriate amine with commercially available 1,3-benzenedisulfonyl chloride.[17,25] Catalysts **3.18**–**3.22** were synthesized using a modified literature procedure according to the synthesis illustrated in **Scheme 3.4**.[26]

Scheme 3.4 Synthesis of Catalysts

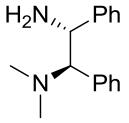


Generation of the diazonium salt **3.25** from 3-aminobenzenesulfonic acid **3.24** was achieved with sodium carbonate and sodium nitrite. The diazonium salt was immediately used in a reaction with powdered sulfur and sodium sulfide to form the disulfide bridged compound **3.26**. This disodium salt was chlorinated using phosphorous oxychloride and phosphorous pentachloride to give the disulfonyl chloride **3.27**. The disulfonyl chloride was coupled with an aryl amine to give the corresponding bissulfonamides of type **3.28**. Oxidative cleavage of the disulfide linkage using hydrogen peroxide yielded monosulfonic acid salts of type **3.29**. The

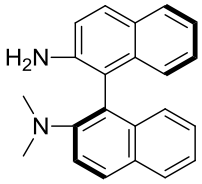
crude sodium salts were carried into the chlorination step to give monosulfonyl chlorides of type **3.30**. Finally, the monosulfonyl chlorides were coupled with an amine to give asymmetric bissulfonamide catalysts **3.18**–**3.22** (**Figure 3.9**).

Three different chiral amines **3.31**–**3.33** were synthesized in 4–6 steps, according to established literature procedures,[27] for incorporation into the above catalysts (**Figure 3.7**). These amines were chosen because they are standard chiral components used in organocatalysis.[12-16] and they are also readily available from the chiral pool. Unfortunately, attempts to synthesize a cinchona alkaloid derived catalyst resulted in a mixture of inseparable products.

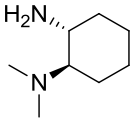
Figure 3.7 Diamine Ligands



3.31



3.32

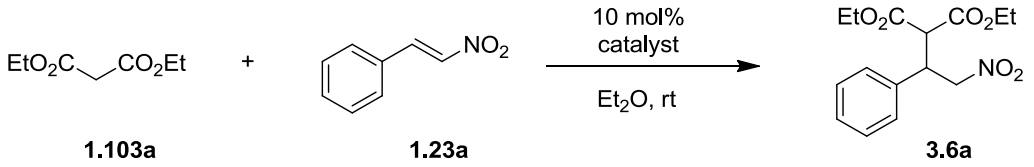


3.33

3.2.2 Catalyst Screening

Monofunctional catalysts **3.17** and **3.18** were used in conjunction with Et_3N in order to assess their affect on rate acceleration. It was found that both catalyst **3.17** and **3.18** accelerated the reaction of **1.23a** with **1.103a** to form **3.6a**. A 2.2–fold and 2.4–fold rate acceleration were observed using catalysts **3.17** and **3.18**, respectively (Entries 2 and 3, **Table 3.1**). This suggested that incorporation of a chiral amine moiety into a 1,3-bissulfonamide could produce an effective bifunctional catalyst for the asymmetric version of the reaction.

Table 3.1 Monofunctional Catalysts



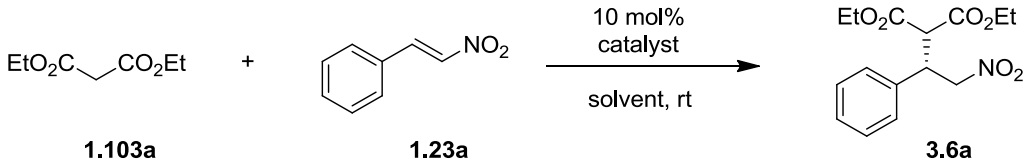
1.103a **1.23a** **3.6a**

Entry	Catalyst	Equiv **1.103a**	% Yield[a]	% ee[b,c]
1	Et_3N	2	26	--
2	**3.17** + Et_3N	2	56	--
3	**3.18** + Et_3N	2	62	--

Reaction Conditions: **1.103a** (1 mmol), **1.23a** (0.5 mmol), catalyst (0.05 mmol), solvent (1 mL), rt, 144 hours. [a] Isolated yield. [b] Enantiomeric excess was determined by chiral phase HPLC analysis. [c] Absolute configuration was determined by comparison of the specific rotation of **3.6a** with the literature value.[28]

The chiral bifunctional catalysts **3.19**–**3.23** were synthesized to study several factors that may affect catalyst activity. The acidity of the aryl sulfonamide proton was one area of interest (catalyst **3.21** vs. **3.22**). The proton in catalyst **3.22** is more acidic than that in catalyst **3.21** by virtue of the presence of trifluoromethyl groups on the aryl group. Also under investigation was the effect of different chiral amine moieties (catalysts **3.19**–**3.21**). Catalyst **3.23** was synthesized in order to analyze the effect of having multiple basic groups incorporated into the catalyst structure. The results of this initial catalyst screening are shown in **Table 3.2**.

Table 3.2 Bifunctional Catalysts



1.103a **1.23a** **3.6a**

Entry	Catalyst	Solvent	Equiv **1.103a**	% Yield[a]	% ee[b,c]
1	**3.19**	Et_2O	2	15	20
2	**3.20**	CH_2Cl_2	2	trace	--
3	**3.21**	CH_2Cl_2	2	5	50[d]
4	**3.22**	CH_2Cl_2	2	7	72
5	**3.23**	CH_2Cl_2	2	8	53

Reaction Conditions: **1.103a** (1 mmol), **1.23a** (0.5 mmol), catalyst (0.05 mmol), solvent (1 mL), rt, 72 hours. [a] Isolated yield. [b] Enantiomeric excess was determined by chiral phase HPLC analysis. [c] Absolute configuration was determined by comparison of the specific rotation of **3.6a** with the literature value.[28] [d] Similar ee's obtained in Et_2O.

The 1,2-diphenyl–derived catalyst, **3.19**, gave the best yields but with very low enantiomeric excesses (Entry 1). The solvent was changed from Et_2O to CH_2Cl_2 during the course of the experiments due to solubility restrictions. The sterically demanding binapthyl–derived catalyst, **3.20**, afforded only trace product (Entry 2). This may be a result of sterics or of the decreased basicity of the aryl amine relative to the aliphatic amine moiety in the other bifunctional catalysts. The 1,2-diaminocyclohexane–derived catalysts, **3.21**-**3.23**, all gave products in reduced yields but with improved ee's. As suspected, the increased acidity of **3.22** resulted in a dramatic increase in enantioselectivity relative to the reactions catalyzed by the less acidic catalysts, **3.21** and **3.23** (Entries 3-5)**.** Adding another basic group, as in catalyst **3.23**, did not increase the enantioselectivity or yield of the reaction significantly (Entry 5).

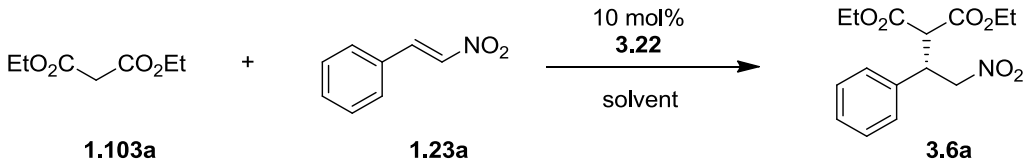
Interestingly, none of the bifunctional catalysts gave an enhanced rate of reaction similar to that of catalysts **3.17** and **3.18** in the presence of triethylamine. To test whether the reaction was reversible, and simply reaching equilibrium, catalyst **3.22** and the product **3.6a** were stirred at room temperature for ten days. After ten days no reactants had formed, demonstrating that the

reaction simply proceeded slower with the bifunctional catalysts than with catalysts **3.17** and **3.18**. While the yields achieved in CH_2Cl_2 were still quite low, catalyst **3.22** was chosen for further studies as it produced the highest ee of any of the catalysts (Entry 4).

3.2.3 Solvent Study and Optimization

A solvent study of the catalyzed reaction was undertaken (**Table 3.3**). The most polar solvent, acetonitrile, gave the product in the lowest yield (Entry 1). Other polar solvents, such as THF and CH_2Cl_2, gave slightly higher yields (Entries 2 and 3). The highest yields were achieved using non–polar solvents such as toluene or Et_2O (Entries 4 and 5). Moderate to good ee's were achieved in all solvents except THF (Entry 3). This may be due to the large background reaction observed in that solvent. The best ee's were achieved with non–coordinating solvents such as toluene and CH_2Cl_2 (Entries 2 and 5). The solventless reaction gave higher yields but with reduced enantioselectivity (Entry 6). Attempting to reduce the temperature of the solventless reaction gave only a slight increase in enantioselectivity, but with a significant drop in yield (Entry 7). Toluene was chosen as the optimal solvent, because it is both non–polar and non–coordinating, giving the best combination of yield and enantioselectivity.

Table 3.3 Solvent Study



1.103a **1.23a** **3.6a**

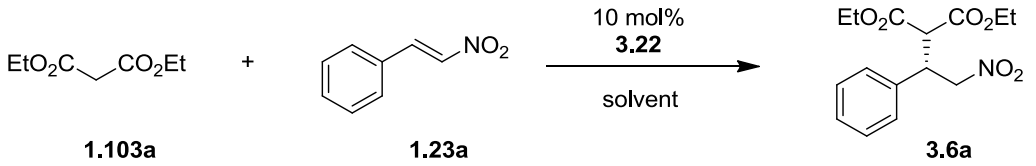
Entry	Solvent	Temp. (^{o}C)	Equiv **1.103a**	% Yield[a]	% ee[b,c]
1	MeCN	rt	2	4	47
2	CH_2Cl_2	rt	2	7	72
3	THF	rt	2	7	27
4	Et_2O	rt	2	15	65
5	toluene	rt	2	13	70
6	--	rt	2	68	49
7	--	0	2	42	53

Reaction Conditions: **1.103a** (1 mmol), **1.23a** (0.5 mmol), catalyst **3.22** (0.05 mmol), solvent (1 mL), 72 hours. [a] Isolated yield. [b] Enantiomeric excess was determined by chiral phase HPLC analysis. [c] Absolute configuration was determined by comparison of the specific rotation of **3.6a** with the literature value.[28]

Other variables such as catalyst loading, reaction time, temperature, and reactant equivalents were also examined in order to achieve optimal product percent yields and enantioselectivities (**Table 3.4**). Tripling the catalyst loading to 30 mol % resulted in a nearly doubled percent yield, but led to a decrease in enantioselectivity (Entry 2, **Table 3.4** vs. Entry 2, **Table 3.3**). Doubling the reaction concentration or doubling the equivalents of **1.103a** both accelerated the reaction but led to drops in enantioselectivity (Entries 3 and 4 vs. Entry 1). However, doubling the equivalents of **1.103a** in conjunction with longer reaction times restored the enantioselectivity of the reaction (Entry 5 vs. Entry 1). Increasing the equivalents of **1.103a** further to 6 and 10 equivalents did not give a further increase in yield (Entries 6 and 7). Allowing the reaction to progress for even longer periods of time resulted in still greater yields (Entry 8 vs. Entry 5). Raising the reaction temperature to 50 ^{o}C led to an increased yield with

only a small drop in enantioselectivity (Entry 9). The last two sets of conditions in **Table 3.4** (Entries 8 and 9) were chosen as the optimal conditions for this reaction.

Table 3.4 Equivalents of Diethyl Malonate



1.103a **1.23a** **3.6a**

Entry	Solvent	Time (h)	Temp. (^{o}C)	Equiv **1.103a**	% Yield[a]	% ee[b,c]
1	toluene	72	rt	2	13	70
2	CH_2Cl_2	72	rt	2	16	60[d]
3	toluene	72	rt	2	22	62[e]
4	toluene	72	rt	4	20	66
5	toluene	168	rt	4	45	68
6	toluene	168	rt	6	45	65
7	toluene	168	rt	10	45	66
8	toluene	240	rt	4	57	69
9	toluene	168	50	2	66	64

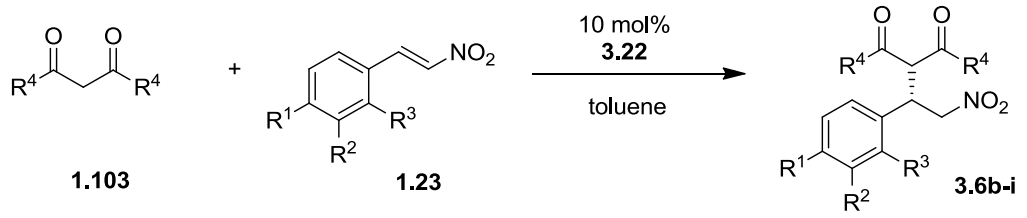
Reaction Conditions: **1.103**, **1.23a** (0.5 mmol), catalyst **3.22** (0.05 mmol), solvent (1 mL). [a] Isolated yield. [b] Enantiomeric excess was determined by chiral phase HPLC analysis. [c] Absolute configuration was determined by comparison of the specific rotation of **3.6a** with the literature value.[28] [d] 30 mol % **3.22** was used. [e] Reaction concentration doubled.

3.2.4 Substrate Scope

With two sets of optimal conditions in hand, a substrate study was undertaken to examine the scope of the reaction. The results of the substrate study are summarized in **Table 3.5**. All products were collected in moderate to good yields with moderate to good enantioselectivity. When the electron–poor β-nitrostyrene **3.6b** was subjected to higher temperatures the formation of side products resulted in a reduced yield of the desired product (Entry 1 vs. Entry 2). As a result of this, two different types of reaction conditions were used based on the reactivity of the substrates. Reactions involving slower–reacting, electron–rich β-nitrostyrenes were carried out

at elevated temperatures (Method B**,** Entry 9**, Table 3.4**). Reactions involving faster–reacting, electron–poor β-nitrostyrenes were carried out at room temperature (Method A**,** Entry 8, **Table 3.4**), but with longer reaction times and with increased equivalents of **1.103**. *Para*– and *meta*–substituted, electron–poor β-nitrostyrenes **3.6b**–**d** gave the best yields and enantioselectivities (Entries 1–4). This is probably due to their higher electrophilicity. *Para*–substituted, electron–rich β-nitrostyrenes **3.6e**–**f** gave lower yields but comparable ee's to those of the *para*–substituted, electron–poor β-nitrostyrenes (Entries 5 and 6). Substitution at the *ortho*–position, as in **1.23g**, was not well tolerated and resulted in lower ee's (Entry 7). This may be the result of a perturbation in the transition state due to the close proximity of the bromine to the site of bond formation. The conjugate addition of dimethyl malonate **1.103b** to β-nitrostyrene afforded the desired product in good yield with good enantioselectivity (Entry 8). Use of the more reactive electrophile, 1,3-pentandione **1.103c**, resulted in a much higher yield but with only moderate enantioselectivity (Entry 9).

Table 3.5 Substrate Scope

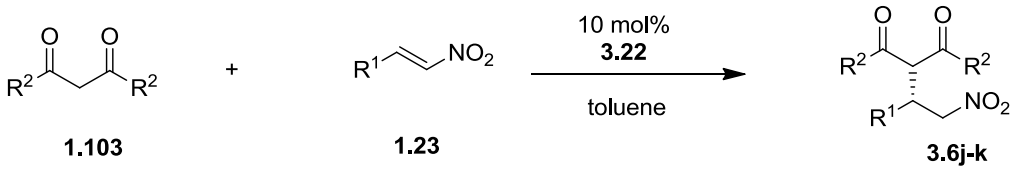


Entry	**9**	R^1	R^2	R^3	**8**	R^4	Method	% Yield[a]	% ee[b]
1	**1.23b**	Br	H	H	**1.103a**	OEt	B	60	62[c]
2	**1.23b**	Br	H	H	**1.103a**	OEt	A	69	69[c]
3	**1.23c**	F	H	H	**1.103a**	OEt	A	64	79[c]
4	**1.23d**	Cl	Cl	H	**1.103a**	OEt	A	75	77[d]
5	**1.23e**	Me	H	H	**1.103a**	OEt	B	51	66[c]
6	**1.23f**	MeO	H	H	**1.103a**	OEt	B	56	64[c]
7	**1.23g**	H	H	Br	**1.103a**	OEt	A	70	57[c]
8	**1.23a**	H	H	H	**1.103b**	OMe	B	69	63[c]
9	**1.23a**	H	H	H	**1.103c**	Me	A	91	49[c]

Reaction Conditions: Method A: **1.103** (2 mmol), **1.23** (0.5 mmol), **3.22** (0.05 mmol), solvent (1 mL), rt. Method B: **1.103** (1 mmol), **1.23** (0.5 mmol), **3.22** (0.05 mmol), solvent (1 mL), 50 ^{o}C. [a] Isolated yield. [b] Enantiomeric excess was determined by chiral phase HPLC analysis. [c] Absolute configuration was determined by comparison of the specific rotation of **3.6** with the literature value.[28-30] [d] Absolute configuration was not determined.

Unfortunately, attempts to catalyze the reaction of dicarbonyls with *alkyl* substituted nitroolefins of type **1.23** to give *alkyl* substituted products of type **3.6** resulted in poor yields and poor to moderate ee's (**Table 3.6**). By TLC analysis it appeared that a significant amount of starting material remained in the reaction mixtures using both Method A and Method B. In addition several byproducts were formed under both types of reaction conditions. Interestingly, the cyclohexane–derived nitroolefin, **1.23i**, afforded much better ee's than the *n*-pentyl–derived nitroolefin, **1.23h** (Entries 1 and 2 vs. Entries 3 and 4). This may be a result of the increased steric bulk on the carbon adjacent to the bond forming event.

Table 3.6 Alkyl Substituted Nitroolefins



Entry	**1.23**	R^1	**8**	R^2	Method	% Yield[a]	% ee[b]
1	**1.23h**	*n*-pentyl	**1.103a**	OEt	A	12	24[c]
2	**1.23h**	*n*-pentyl	**1.103a**	OEt	B	7	22[c]
3	**1.23i**	cyclohexyl	**1.103b**	OMe	A	7	58[c]
4	**1.23i**	cyclohexyl	**1.103b**	OMe	B	5	54[c]

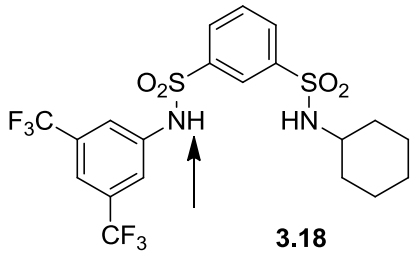
Reaction Conditions: Method A: **1.103** (2 mmol), **1.23** (0.5 mmol), **3.22** (0.05 mmol), solvent (1 mL), rt. Method B: **1.103** (1 mmol), **1.23** (0.5 mmol), **3.22** (0.05 mmol), solvent (1 mL), 50 °C. [a] Isolated yield. [b] Enantiomeric excess was determined by chiral phase HPLC analysis. [c] Absolute configuration was determined by comparison of the specific rotation of **3.6** with the literature value.[28-30]

3.2.5 Mechanistic Studies

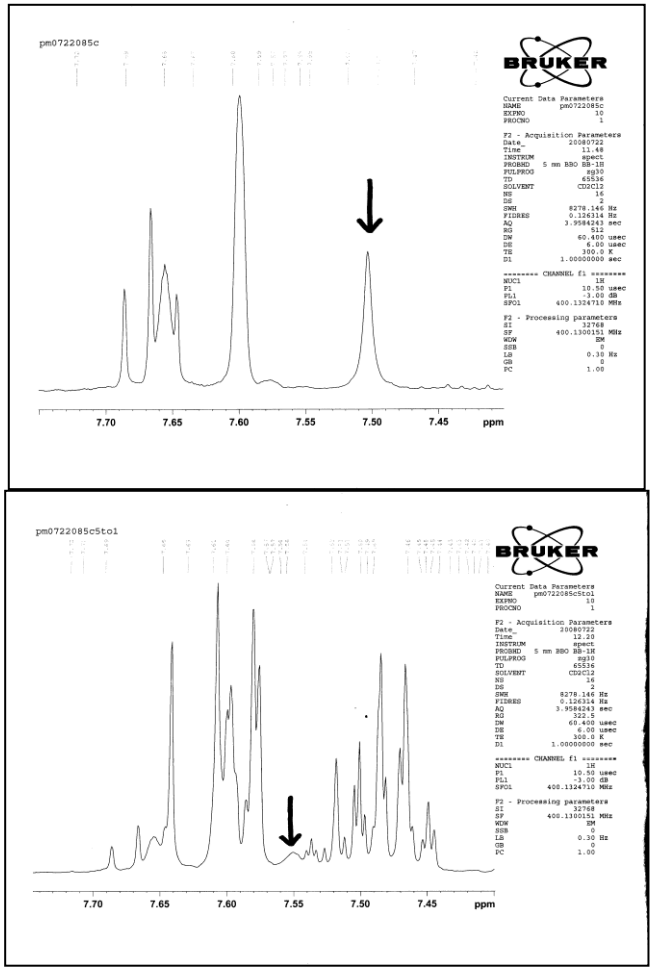
These catalysts were designed to be bifunctional, double hydrogen bond donors. Synthetic and analytical data were collected in order to investigate if this was in fact the mechanism by which these bissulfonamide catalysts were functioning. A series of ^{1}H NMR titration studies using catalyst **3.18** in CD_2Cl_2 were undertaken. Catalyst **3.18** was chosen because it contained an N_{ALKYL} sulfonamide proton and an N_{ARYL} sulfonamide proton, thus resembling optimal catalyst **3.22**. It was also chosen because its two sulfonamide protons were distinguishable in the ^{1}NMR spectra. In catalyst **3.22** these two protons are not distinguishable. The N_{ALKYL}–H sulfonamide in **3.18** appeared as a sharp doublet at 4.82 ppm (spectra not shown). As seen in **Figure 3.8**, the N_{ARYL}–H sulfonamide peak appeared as a singlet at 7.50 ppm. As β-nitrostyrene was titrated in in increasing amounts, the N_{ARYL} sulfonamide proton was observed to broaden and shift downfield, whereas no change was observed in the N_{ALKYL} sulfonamide proton. When four equivalents of β-nitrostyrene had been added the N_{ARYL}–H had shifted from 7.50 ppm to 7.55 ppm (**Figure 3.8**). This subtle shift downfield of the N_{ARYL} sulfonamide proton, combined with

peak broadening is consistent with hydrogen bond donation and is comparable to that observed with thiourea catalysts by Takemoto et. al.[13] From this result it would appear that the N_{ARYL} sulfonamide proton plays an important role in hydrogen–bonding while the N_{ALKYL} sulfonamide proton may not.

Figure 3.8 Shift of N_{ARYL} Sulfonamide Proton in ^1H NMR of **3.18**



3.18



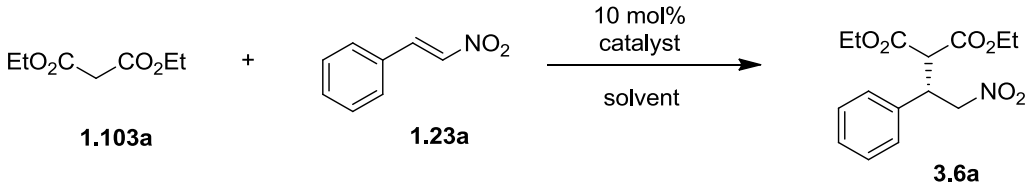
TOP: N_{ARYL} sulfonamide proton in **3.18** at 13.4 mM in CD_2Cl_2

BOTTOM: N_{ARYL} sulfonamide proton in **3.18** at 13.4 mM in CD_2Cl_2 with 4 equiv β-nitrostyrene

Synthetic evidence also supports the role of hydrogen–bonding in these bissulfonamide catalysts (**Table 3.7**). First, as mentioned previously, increasing the acidity of the N_{ARYL}

sulfonamide proton in the 1,2-diaminocyclohexane derived catalysts resulted in higher enantioselectivities (**Table 3.2**, Entries 3 and 4). An increase in hydrogen bond donor acidity resulting in enhanced enantioselectivity has been observed with other hydrogen–bonding organocatalysts.[8,17] Also, running the reaction with catalyst **3.22** in a protic solvent such as methanol gave a significantly higher yield of product **3.6a** but in extremely poor ee (**Table 3.7**, Entry 1). Most likely, methanol accelerated the reaction through hydrogen bond donation, which interfered with the interaction between the substrate and the catalyst resulting in a lack of enantioselectivity.

Table 3.7 Mechanistic Studies



1.103a **1.23a** **3.6a**

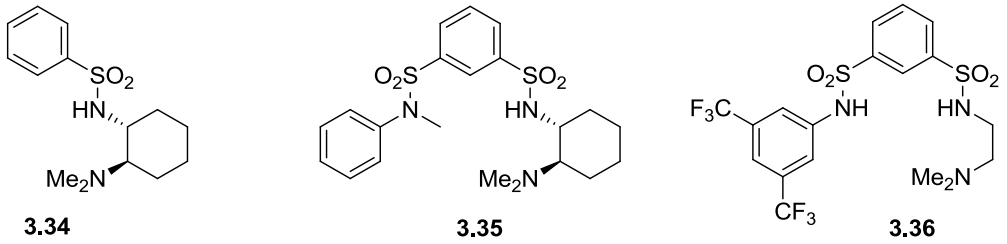
Entry	Catalyst	Solvent	Time (h)	Equiv **1.103a**	% Yield[a]	% ee[b,c]
1	**3.22**	MeOH	72	2	35	5
2	**3.34**	CH_2Cl_2	72	2	<2	41
3	**3.35**	CH_2Cl_2	72	2	<2	nd
4	**3.18**	THF	144	2	0	--
5	Et_3N	THF	144	2	48	--
6	**3.18**+Et_3N	THF	144	2	69	--
7	**3.36**	THF	144	2	21	--

Reaction Conditions: **1.103a** (1 mmol), **1.23a** (0.5 mmol), catalyst (0.05 mmol), solvent (1 mL), rt. [a] Isolated yield. [b] Enantiomeric excess was determined by chiral phase HPLC analysis. [c] Absolute configuration was determined by comparison of the specific rotation of **3.6a** with the literature value.[28]

Catalysts **3.34** and **3.35** were synthesized to determine the effect of removing the N_{ARYL} sulfonamide proton from the catalyst structure **(Figure 3.9)**. Both catalysts gave only small amounts of product and a significant drop in enantioselectivity was observed with catalyst **3.34** (**Table 3.7**, Entries 2 and 3). This suggests that the N_{ARYL} sulfonamide proton is necessary in

order for these bifunctional catalysts to exhibit optimal activity. Additionally, in the absence of a tertiary amine, monofunctional catalyst **3.18** gave no product (**Table 3.7**, Entry 4). These results indicated that both the N_{ARYL} sulfonamide proton and the tertiary amine are necessary for optimal catalytic activity.

Figure 3.9 Catalysts for Mechanistic Studies

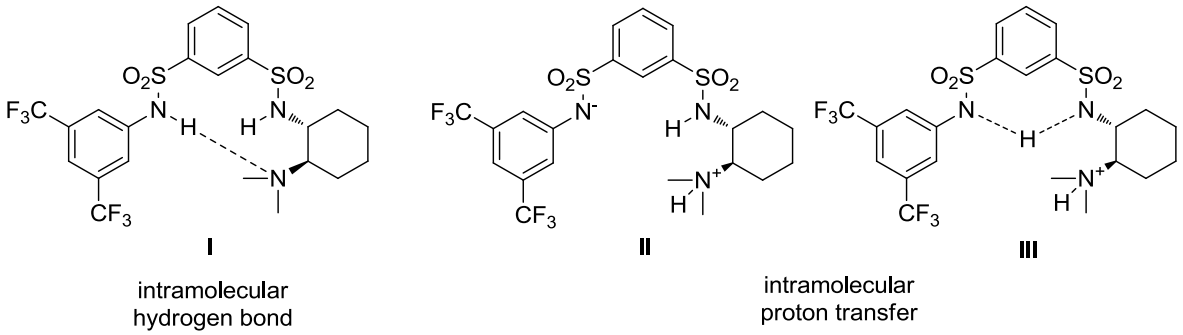


3.34 **3.35** **3.36**

We were intrigued as to why catalyst **3.22,** containing both hydrogen bond donors and a tertiary amine moiety**,** did not exhibit the same rate enhancement effect demonstrated by catalyst **3.18** when used in conjunction with triethylamine (**Table 3.1**, Entry 3 vs. **Table 3.3**, Entry 6). One possibility is that this is due to the sterically congested 1,2-diamine incorporated into catalyst **3.22**. It is also possible that a two–carbon tether, inherent in the 1,2-diamine, is not optimal for this family of catalysts. The third possibility is that there is an intramolecular interaction that is hampering the activity of the bifunctional catalysts. Catalyst **3.36** was synthesized and screened in order to test the effect of using a sterically uncongested 1,2-diamine ligand on the rate of reaction when compared to using an untethered amine. The reaction catalyzed by **3.36** proceeded slower than both the reaction catalyzed by **3.18** with triethylamine and the reaction catalyzed by triethylamine by itself (**Table 3.7**, Entry 7 vs. Entries 5 and 6). This rules out the possibility that the reduced rate is due to the sterically congested 1,2-diamine incorporated into catalyst **3.22.** However, the reduced rate may be a function of the two carbon

tether or of an intramolecular interaction that hampers catalytic activity when the tertiary amine is tethered to the hydrogen bond donor as in catalyst **3.22**. Three possibilities for the latter scenario are illustrated in **Figure 3.10**.

Figure 3.10 Possible Intramolecular Interactions in Catalyst **3.22**

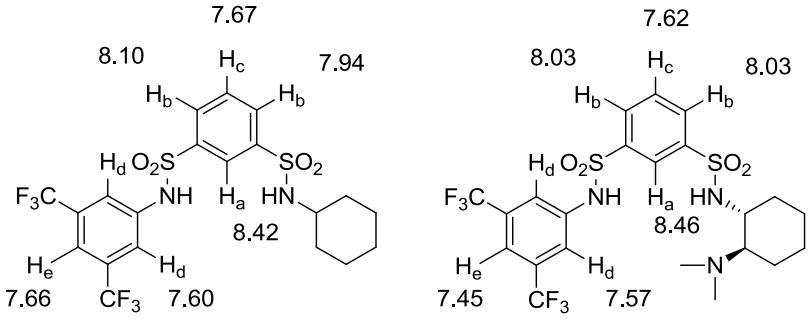


In CD_2Cl_2, catalyst **3.18** showed two distinct peaks for each sulfonamide proton while catalyst **3.22** showed only one broad singlet, integrating as two sulfonamide protons, at 6.50 ppm. In addition, the N_{ALKYL} sulfonamide proton in catalyst **3.18** which had appeared as a doublet at 4.82 ppm is shifted far downfield and broadened in catalyst **3.22** (6.50 ppm). These results are not consistent with structure **I** in **Figure 3.10** where the less acidic N_{ALKYL} sulfonamide proton is not involved in an *intra*molecular interaction. The results indicate that both sulfonamide protons are equivalent, and may thus be represented as in **III**, or they may be involved in proton shuffling in the bifunctional catalyst as in **II**.

The different chemical shifts for the aromatic protons in catalysts **3.18** and **3.22** are illustrated in **Figure 3.11**. In CD_2Cl_2 at 13.4 mM protons H_a, H_c, and H_d show similar shifts in both catalysts. However, proton H_e is shifted far upfield in catalyst **3.22** (7.45 ppm) relative to that in catalyst **3.18** (7.66 ppm). If there was a build up of negative charge on the N_{ARYL} nitrogen

as a result of proton transfer in catalyst **3.22**, one would see an upfield shift of H_e as is seen here. This is consistent with structures **II** and **III** in **Figure 3.10**. In catalyst **3.18**, two distinct shifts for the H_b protons are observed (7.94 and 8.10 ppm), but in catalyst **3.22**, both H_b protons shift towards a common frequency (8.03 ppm). This appears to be more consistent with structure **III** in **Figure 3.10** where there is not such a drastic difference in the formal charges on the sulfonamide nitrogens. Based on the differences in the ^{1}H NMR spectra of catalyst **3.18** and catalyst **3.22**, it appears as though an intramolecular interaction may exist and that this may be hampering the activity of the bifunctional catalysts, resulting in lower yields than those achieved with the monofunctional catalysts used in conjunction with an untethered base.

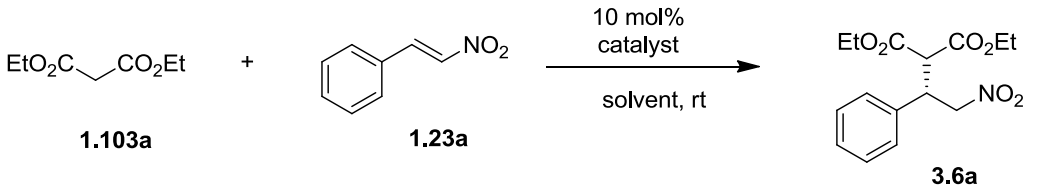
Figure 3.11 ^{1}H NMR shifts of Catalysts **3.18** and **3.22**

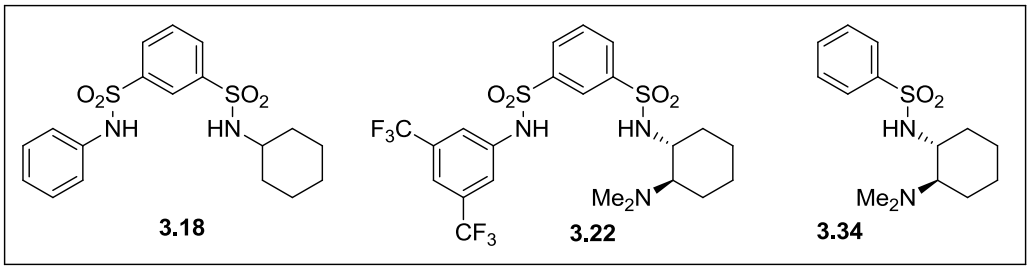


It was also considered that perhaps one molecule of optimal catalyst **3.22** was not efficient at activating both β-nitrostyrene **1.23** through hydrogen bond donation and diethyl malonate **1.103** through the tertiary amine (possibly due to the intramolecular interaction in the catalyst). Instead, perhaps one molecule of **3.22** was responsible for hydrogen bond donation to the β-nitrostyrene and another molecule of **3.22** was responsible for activating diethyl malonate through its basic tertiary amine moiety. If this were the case, it might be possible to use a chiral external base (similar in catalyst structure) *in conjunction* with catalyst **3.22**, to see if one could

potentially enhance the catalytic activity, or at least observe whether the catalysts were working cooperatively. Catalyst **3.34** was chosen as the external base for the reaction (**Table 3.8**). Catalyst **3.34** does not have an acidic proton as strong as the N_{ARYL} sulfonamide proton in **3.22**. As a consequence, an intramolecular interaction should not exist within **3.34**, and catalyst **3.34** is only weakly catalytically active (Entry 1). As a result, it might be possible for **3.22** to activate the β-nitrostyrene through hydrogen bond donation and for catalyst **3.34** to act as the base, activating the diethyl malonate. However, the results seem to indicate that catalyst **3.22** and catalyst **3.34** are acting independently rather than cooperatively (Entry 3 vs. Entry 2). The percent yield and enantiomeric excess of product **3.6a**, achieved by catalyst **3.22** and **3.34** together, are similar to those achieved by **3.22** alone. The slight increase in yield and decrease in enantiomeric excess are probably due to catalyst **3.34** catalyzing the reaction by itself, but less effectively. Unfortunately, there was no benefit to using catalysts **3.22** and **3.34** cooperatively.

Table 3.8 Studies with a Combination of Catalysts





Entry	Catalyst	Time (h)	Solvent	% Yield[a]	% ee[b,c]
1	**3.34**	72	CH_2Cl_2	2	41
2	**3.22**	240	toluene	57	69
3	**3.22**+**3.34**	240	toluene	65	66
4[d]	**3.18**+Et_3N	144	THF	69	--
5	**3.18**+**3.34**	240	toluene	26	46

Reaction Conditions: **1.103a** (2.0 mmol), **1.23a** (0.5 mmol), cat. (0.05 mmol), solvent (1 mL), rt. [a] Isolated yield. [b] Enantiomeric excess was determined by chiral phase HPLC analysis. [c] Absolute configuration was determined by comparison of the specific rotation of **3.6a** with the literature value.[28] [d] Performed with 1.0 mmol **1.103a**.

Another reaction was attempted using **3.18** as a hydrogen bond donor and **3.34** as a chiral base catalyst. It was hypothesized, as an alternate possible mechanism, that **3.18** would act as the hydrogen bond donor, activating the β-nitrostyrene, and that **3.34** would activate the diethyl malonate and impart stereoselectivity. Catalyst **3.18** had proven to be an efficient hydrogen bond donor in its catalysis of the reaction with triethylamine (Entry 4). However, when **3.18** was used in conjunction with **3.34**, the reaction afforded a higher yield of product than the reaction catalyzed by **3.34** alone, but less than that of the reaction catalyzed by **3.22** and less than that of the reaction catalyzed by **3.18** in conjunction with Et_3N. The results of this reaction seem to suggest that catalyst **3.18** is activating **1.23a** through hydrogen bond donation but that **3.34** is not as efficient at activating **1.103a** as triethylamine (Entry 4 vs. Entry 5). This could potentially be

due to the size of **3.34** relative to triethylamine. The enantiomeric excess achieved in the reaction is very similar to that achieved by **3.34** alone (Entry 1 vs. Entry 5). Although the yield of the reaction catalyzed by **3.34** benefited from the addition of hydrogen bond donor **3.18** (Entry 1 vs. Entry 5), the reaction did not show the same acceleration as when both functional groups are contained within the same molecular scaffold, as in **3.22** (Entry 2 vs. Entry 5). In summary, these results seem to suggest that only one molecule of **3.22** is responsible for activation of both the nitroolefin and the dicarbonyl in the optimized reaction.

3.3 Conclusions

In conclusion, the novel bissulfonamide catalyst **3.22** was developed for the addition of dicarbonyl compounds to nitroolefins.[31] This catalyst is bifunctional, requiring a hydrogen bond donating N_{ARYL} sulfonamide proton and a tertiary amine moiety to exhibit optimal activity. It is thought to operate through the donation of at least one hydrogen bond to nitroolefins and coordination of its basic site to dicarbonyl compounds. This catalyst exhibited moderate to good enantioselectivity, but it did not accelerate the reaction as well as monofunctional bissulfonamide **3.18** used in conjunction with an untethered amine. Proton NMR studies suggested that an intramolecular interaction may have been hampering the activity of the bifunctional catalyst. It is also possible that a bifunctional catalyst with a longer amine tether would provide a more efficient catalyst.

3.4 References

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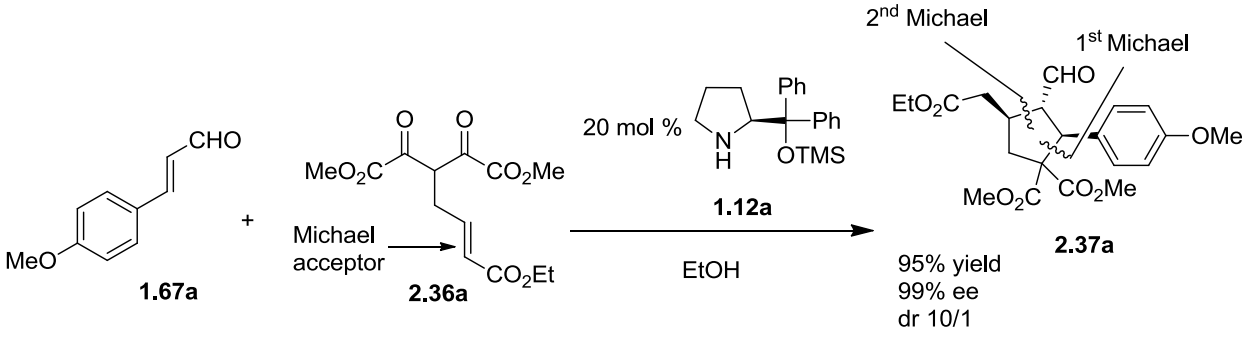
Chapter 4.

A Novel Michael–Michael Cascade Reaction Generates Fused Carbocycles

4.1 Introduction

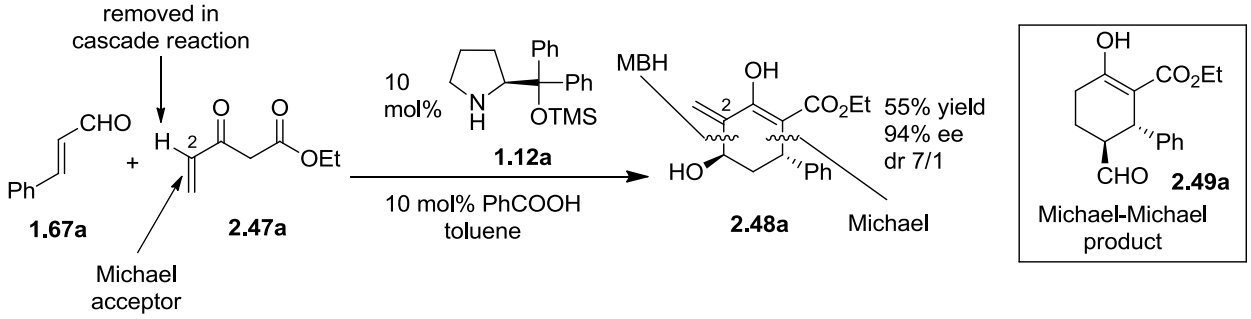
As illustrated in **Chapter 2**, there have been many diarylprolinol silyl ether catalyzed iminium–enamine cascade reactions initiated by a C–C bond–forming conjugate addition. Of the Michael–Michael cascade reactions of this type that had been developed using diarylprolinol silyl ethers, only one utilized a 1,3-dicarbonyl species as the Michael donor in the initial iminium–catalyzed step (**Scheme 4.1**).[1] This reaction was catalyzed by **1.12a** and involved the formation of highly functionalized cycopentane **2.37a** from enal **1.67a** and malonate **2.36a**.

Scheme 4.1 Michael–Michael Reaction Gives Cyclopentanes



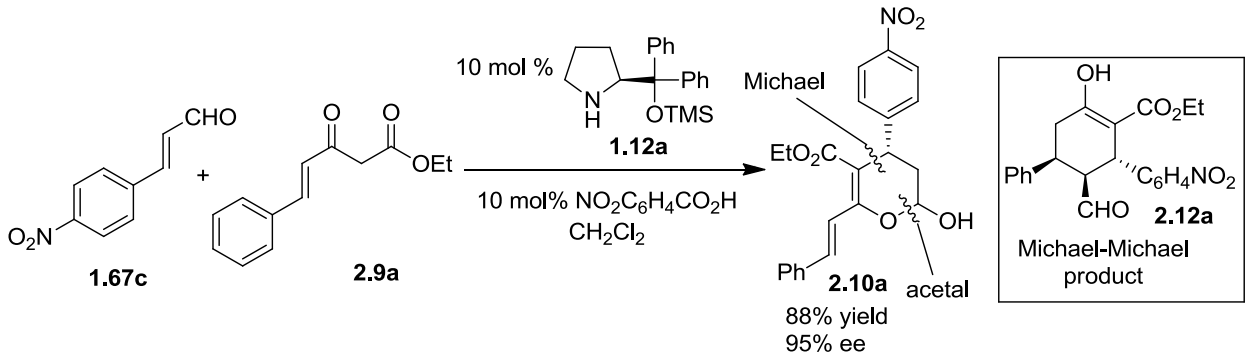
When the conjugated β-ketoester **2.47a** was used to generate highly functionalized cyclohexane ring **2.49a**, the initial Michael addition between **2.47a** and enal **1.67b** was not followed by a subsequent Michael addition as expected (**Scheme 4.2**). Instead, an unexpected Morita–Baylis–Hillman reaction followed to afford substituted cyclohexanone **2.48a**.[2]

Scheme 4.2 Michael–Morita–Baylis–Hillman Cascade Reaction



In addition, a reaction involving a similar β-ketoester with aromatic group substitution (**2.9a**), resulted in an initial Michael addition to enal **1.67c**, which was again not followed by the expected Michael addition. Instead, acetal formation subsequently occurred to produce cyclic ether **2.10a** (**Scheme 4.3**).[3] It is possible that the second Michael addition did not occur for kinetic reasons, but the acetalization reaction was presumably favored because the second Michael addition would disrupt the highly conjugated system in **2.9a**. In both reactions (**Scheme 4.2** and **4.3**) the Michael–Michael products (**2.49a** and **2.12a)** were not observed.

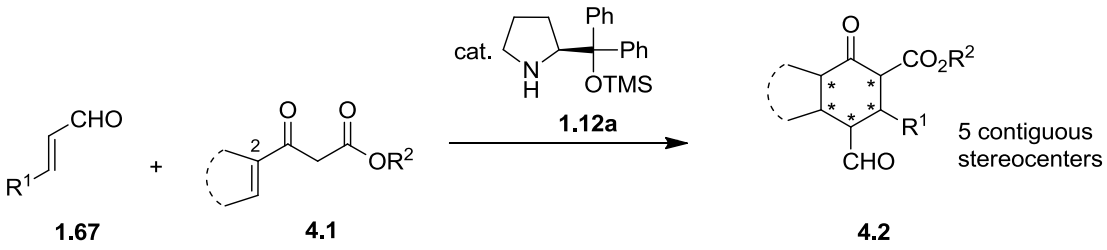
Scheme 4.3 Michael–Acetalization Cascade Reaction



It was speculated that by using β-ketoesters of type **4.1**, with the unsaturation incorporated into a ring, one could prevent the Morita–Baylis–Hillman and the acetalization

pathways, in favor of the Michael–Michael cascade reaction pathway (**Scheme 4.4**). First, the lack of a proton at the 2-position in **4.1** would prevent the Morita–Baylis–Hillman reaction from occurring. Second, the fact that the unsaturation in **4.1** is not part of a highly conjugated system could make a second Michael addition thermodynamically more favorable relative to acetalization.

Scheme 4.4 Michael–Michael Cascade Reaction



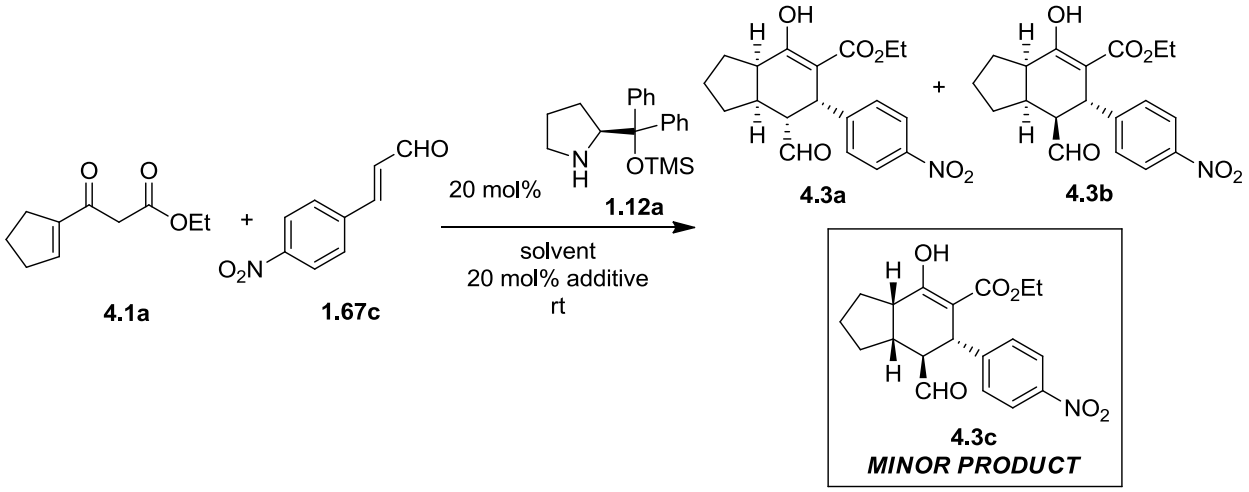
In addition, there may be a thermodynamic preference for a *cis*, or *trans*, ring junction in the product, **4.2**. This Michael–Michael cascade between **4.1** and **1.67** would give densely functionalized fused carbocycles with up to five contiguous stereocenters. Because of the synthetic utility of such a reaction, this course was pursued.

4.2 Results And Discussion

4.2.1 Initial Results

Catalyst **1.12a** was chosen for the reaction of β-ketoester **4.1a** with α,β-unsaturated aldehyde **1.67c** in dichloroethane. These initial results are summarized in **Table 4.1**.

Table 4.1 Initial Results

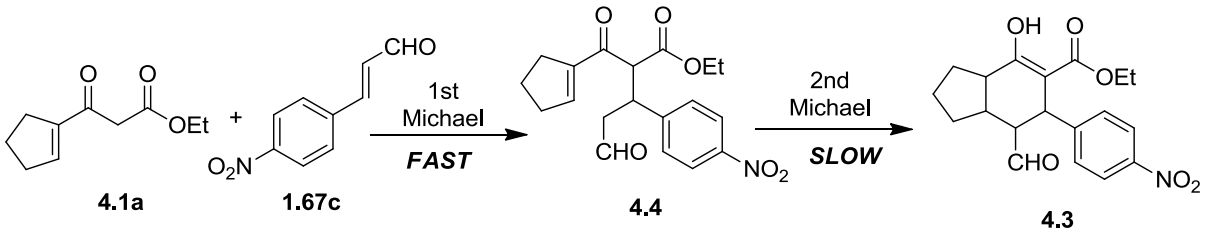


Entry	Solvent	Additive	Time (h)	% conv[a]	dr (**4.3a**+**4.3b**)/**4.3c**[a]	% ee (**4.3a**)[b]	% ee (**4.3b**)[b]
1	DCE	--	240	13	78/22	--	--
2	DCE	NaOAc	72	0	--	--	--
3	DCE	Et_3N	72	0	--	--	--
4	DCE	$PhCO_2H$	168	25	84/16	99	99
5	EtOH	$PhCO_2H$	168	61	78/22	99	99

Reaction Conditions: **4.1a** (1 equiv), **1.67c** (1 equiv), **1.12a** (20 mol %), additive (20 mol %), solvent (0.3 M), rt. [a] Determined by ^{1}H NMR of crude reaction mixture with internal standard. [b] Determined by chiral phase HPLC.

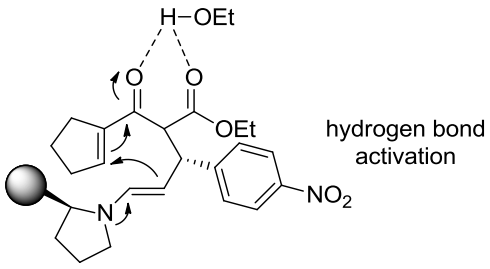
Desired product **4.3** was observed after 240 hours, but in very low conversion (Entry 1). Complete conversion to the intermediate **4.4** was observed after only 12 hours but the second Michael addition, giving product **4.3**, appeared to be very sluggish (**Scheme 4.5**).

Scheme 4.5 1st and 2nd Michael Addition



In order to boost the reaction rate, a series of additives were screened. Basic additives, such as Et_3N and NaOAc were screened, because they are known to assist in generating the reactive enamine intermediate needed for the second Michael addition. Benzoic acid, which is known to assist in catalyst turnover, was screened as well. The basic additives showed no rate enhancement (Entries 2–3). However, the benzoic acid showed some reaction acceleration, improving the conversion to 25% after 168 hours (Entry 4). To our delight, both major diastereomers **4.3a** and **4.3b** were collected in 99% ee. A protic solvent, ethanol, was tested to see if hydrogen bonding interactions would speed up the reaction. It was speculated that hydrogen bonding would activate the β-ketoester moiety, making it more susceptible to the second Michael addition (**Figure 4.1**). As suspected, ethanol gave greatly enhanced reaction rates, leading to 61% conversion to **4.3** after 168 hours, while maintaining the high selectivity (Entry 5).

Figure 4.1 Hydrogen Bonding Activation with EtOH

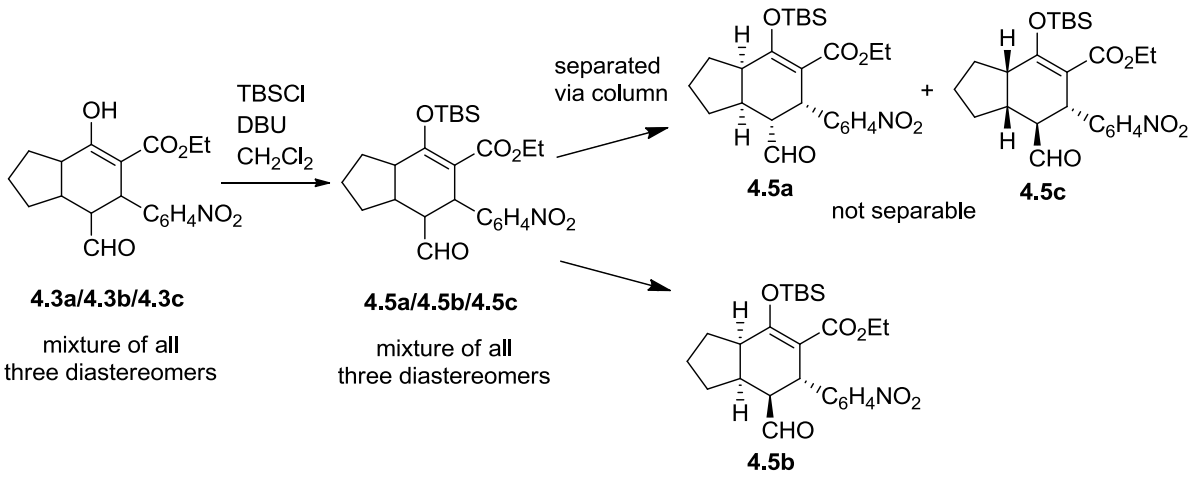


In all of these preliminary reactions, as well as subsequent reactions, three diastereomers of **4.3** were formed (**4.3a**–**c**). The two major diastereomers, **4.3a** and **4.3b,** were generally found to exist in a ~1/1 ratio in all of these preliminary reactions.

4.2.2 Separation Of Diastereomers

Separation of the three diastereomers **4.3a**, **4.3b**, and **4.3c** was non–trivial and required an additional synthetic step. Diastereomer **4.3a** could be separated from **4.3b** and **4.3c** via conventional column chromatography. However, diastereomers **4.3b** and **4.3c** were inseparable. Silylation of all three diastereomers of **4.3** with TBSCl and DBU gave a mixture of the three silylated products **4.5a**–**c** (**Scheme 4.6**). Diastereomer **4.5b** could be separated from diastereomers **4.5a** and **4.5c**. However, **4.5a** and **4.5c** could not be separated.

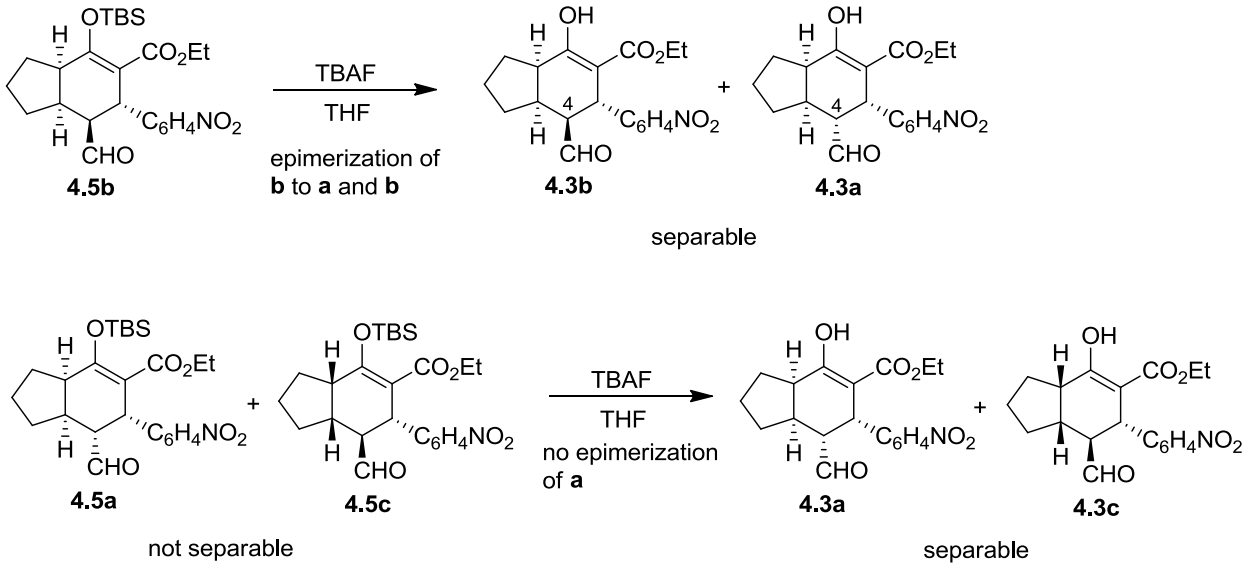
Scheme 4.6 Conversion of Products to Silyl Enol Ethers



Interestingly, subjecting pure **4.5b** to desilylation conditions (TBAF in THF) gave both **4.3b** *and* **4.3a**, as displayed in **Scheme 4.7** (this, in addition to the fact that **4.3a** and **4.3b** were present in crude reaction mixtures in a ~1/1 ratio, caused us to believe that **4.3a** and **4.3b** were C4 epimers of each other). Diastereomer **4.3b** could be isolated from **4.3a** via column chromatography. A rapid (5 min.) desilylation of the mixture of **4.5a** and **4.5c** yielded only **4.3a** and **4.3c** as products (**Scheme 4.7**). These could also be easily separated via column

chromatography, so minor diastereomer **4.3c** was thus isolated. The synthetic sequence outlined in **Schemes 4.6** and **4.7** allowed all three diastereomers, **4.3a-c**, to be isolated and characterized.

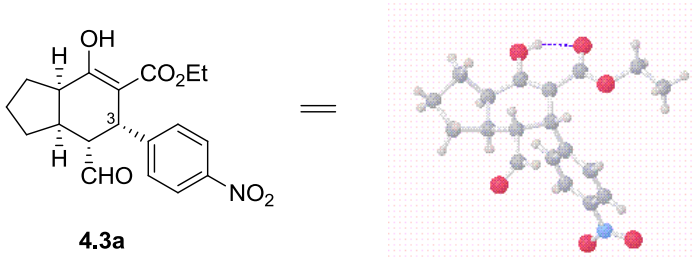
Scheme 4.7 Separation of Diastereomers After Desilylation



4.2.3 Determination Of Configurations

It was assumed that the stereochemistry at C3 was established as (*R*) during the initial Michael addition step (**Figure 4.2**), in accord with other Michael additions catalyzed by **1.12a** (**Schemes 4.1**–**4.3**). Diastereomer **4.3a** was recrystallized and the relative configuration was determined via X-ray crystallography. Thus the absolute configuration of **4.3a** was established as indicated in **Figure 4.2**.

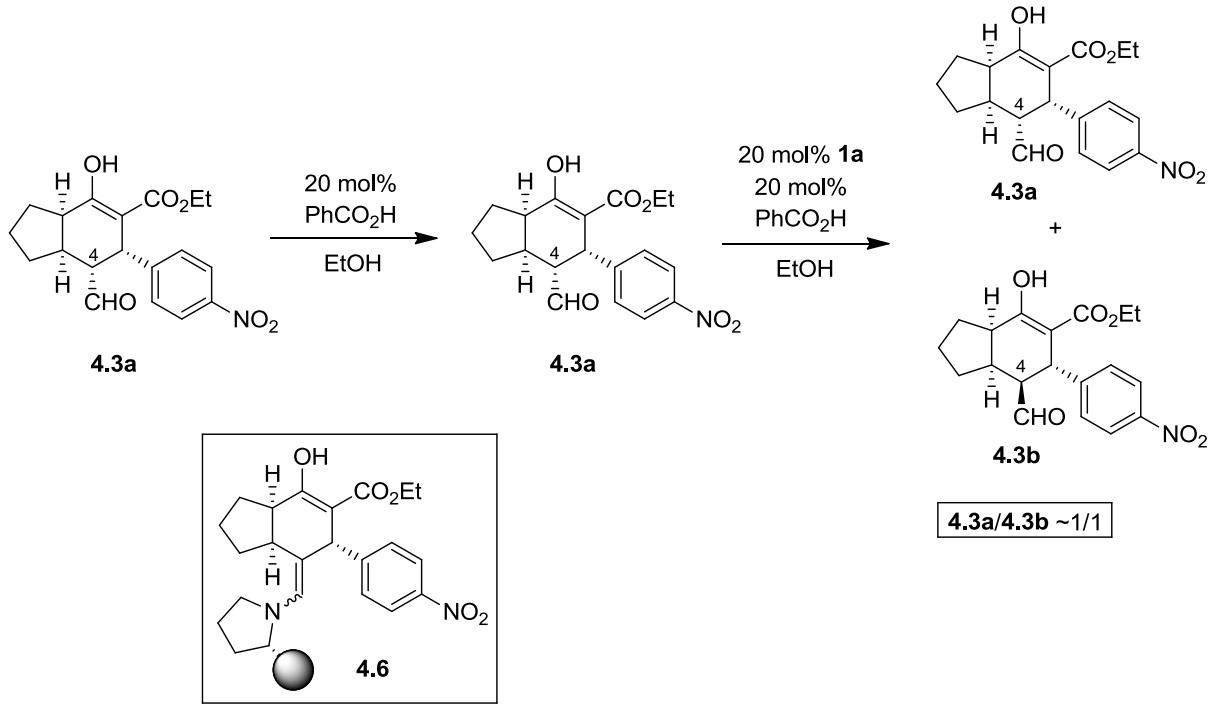
Figure 4.2 X-ray Structure of **4.3a**



4.3a

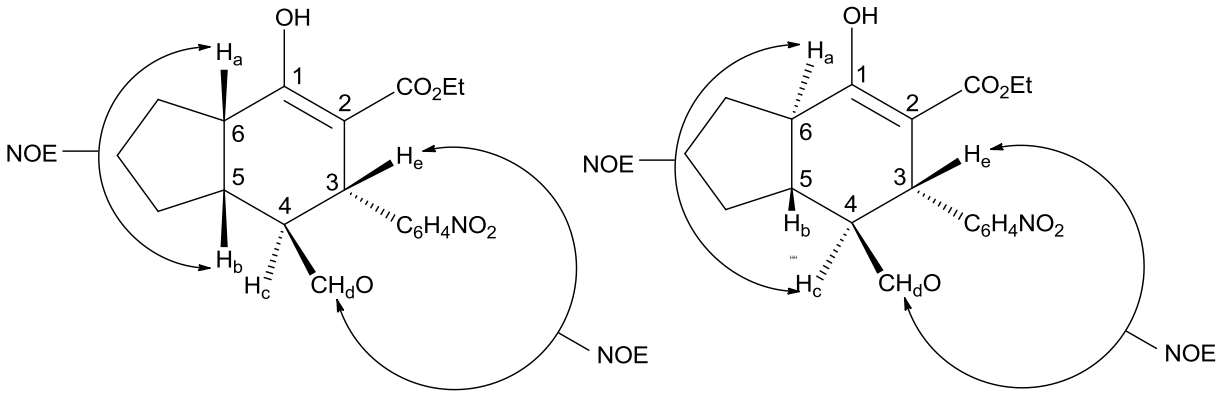
As explained previously, it was suspected that **4.3a** and **4.3b** were C4 epimers. To test this hypothesis, pure diastereomer **4.3a** was stirred in the presence of benzoic acid (20 mol %) in EtOH (**Scheme 4.8**). A crude ^{1}H NMR of the reaction revealed that no epimerization had occurred and **4.3a** was recovered. When pure diastereomer **4.3a** was stirred in EtOH in the presence of benzoic acid (20 mol %) *and* catalyst **1.12a** (20 mol %), a crude ^{1}H NMR of the reaction revealed that a ~1/1 mixture of **4.3a**/**4.3b** had formed, suggesting that epimerization had taken place and that **4.3a** and **4.3b** are related by epimerization at C4. Thus, the absolute configuration of **4.3b** was established. Because epimerization of **4.3a** to **4.3b** took place in the presence of catalyst **1.12a** and not with benzoic acid alone, epimerization was believed to proceed via enamine intermediate **4.6** and not through an enol intermediate.

Scheme 4.8 Epimerization of **4.3a**



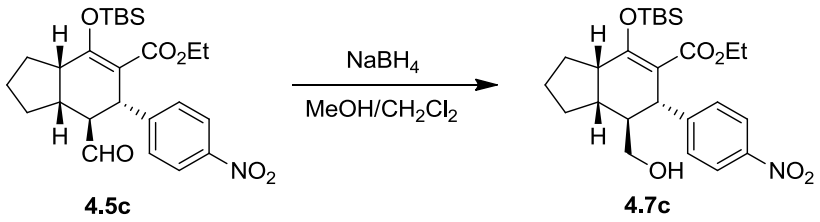
The absolute configuration of the minor diastereomer **4.3c** was established via NOESY (**Figure 4.3**). An NOE interaction between H_e and H_d was observed, indicating that the aldehyde functionality at the C4 position was *cis* to H_e. The signals for H_b and H_c overlapped completely, complicating further analysis of NOE interactions. However, another NOE interaction was observed between H_a and the overlapping ^1H signals for H_b and H_c.

Figure 4.3 Possible Structure of **4.3c** from NOESY Interactions



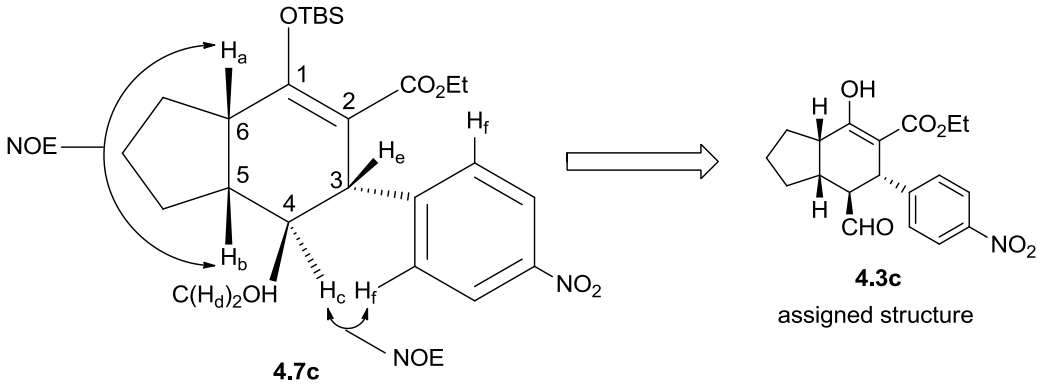
This indicated that the H_a proton was *cis* to either H_b or H_c. From this result, we were able to narrow the possibilities down to the two structures shown in **Figure 4.3**. Reduction of **4.5c** with $NaBH_4$ afforded the corresponding alcohol **4.7c** (**Scheme 4.9**).

Scheme 4.9 Reduction of **4.5c**



In this compound the ^1H NMR peak for H_c was shifted farther upfield and no longer overlapped with the peak for H_b. An NOE was observed between H_a and H_b, showing that **4.7c**, and thus **4.3c**, both contained a *cis* ring junction (**Figure 4.4**). Another NOE interaction was observed between H_c and H_f. This further confirmed a *cis* relationship between H_c and the aryl group in **4.7c** and in **4.3c**. Due to these observed interactions in **4.7c**, diastereomer **4.3c** was assigned the structure shown in **Figure 4.4**.

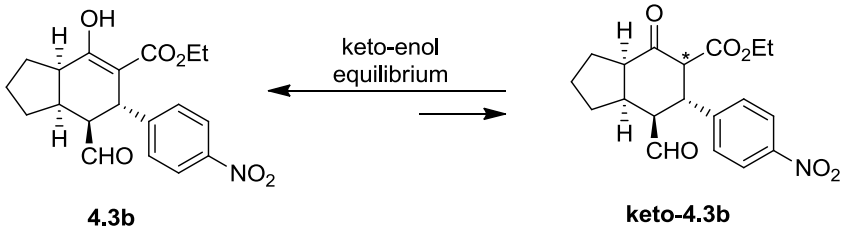
Figure 4.4 Assignment of Configuration of **4.3c**



4.2.4 Keto–Enol Tautomerism

It was observed that diastereomers **4.3a** and **4.3c** existed purely in the enol tautomer form. However, diastereomer **4.3b** existed in equilibrium with the keto form of **4.3b** (**keto–4.3b**) (**Scheme 4.10**).

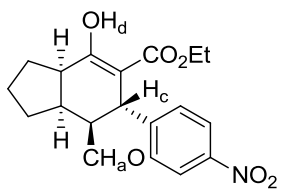
Scheme 4.10 Tautomerism of **4.3b**



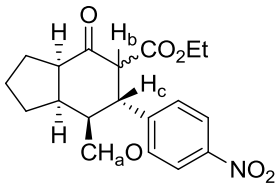
A ^{1}H NMR spectrum of the crude reaction mixture of the **1.12a** catalyzed reaction between **4.1a** and **1.67c** in ethanol showed a clearly resolved aldehyde doublet (H_a) at 9.52 ppm in addition to the aldehyde (H_a) peaks for **4.3a**–**c**. This aldehyde peak at 9.52 ppm (H_a) did not correspond to any ^{1}H peak in the enol region. Unfortunately, **keto**–**4.3b** could not be fully characterized, because it always existed in the presence of its enol form, **4.3b**. However, several

characteristic peaks in the NMR spectrum of the keto–enol mixture of **4.3b** could be resolved. Characteristic peaks in the ^{1}H NMR spectrum for the different tautomers of **4.3b** are summarized in **Table 4.2**.

Table 4.2 4.3b and **keto–4.3b** ^{1}H NMR Peaks



4.3b



keto-4.3b

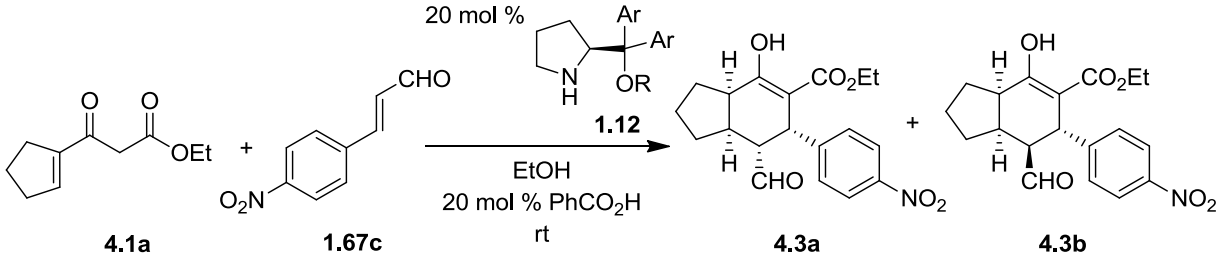
Structure	H_a (ppm)	H_b (ppm)	H_c (ppm)	H_d (ppm)
4.3b	d, 9.65	--	d, 4.34	s, 12.65
keto–4.3b	d, 9.52	d, 3.73	dd, 3.60	--

In **keto–4.3b**, H_b appears as a doublet at 3.73 ppm, due to splitting by H_c. In the enol form of **4.3b**, H_c appears as a doublet at 4.34 ppm. In **keto–4.3b**, H_c exists as a doublet of doublets at 3.60 ppm, due to the additional splitting of H_c by H_b. Fortunately, the keto–enol tautomerism could be biased toward the enol form of **4.3b** by column chromatography of the reaction mixture in non–polar solvents (Et_2O/petroleum ether). This allowed **keto–4.3b** to persist in only trace amounts relative to the enol form, **4.3b**.

4.2.5 Catalyst And Solvent Screening

Catalysts **1.12a–e** were screened in ethanol with benzoic acid as an additive for the Michael–Michael cascade reaction between **4.1a** and **1.67c** (**Table 4.3**).

Table 4.3 Catalyst Screening



1.12a Ar = Ph, R = TMS
1.12b Ar = 3,5-CF_3-C_6H_3-, R = TMS
1.12c Ar = Ph, R = TES
1.12d Ar = Ph, R = TBS
1.12e Ar = 4-OMe-C_6H_4-, R = TMS

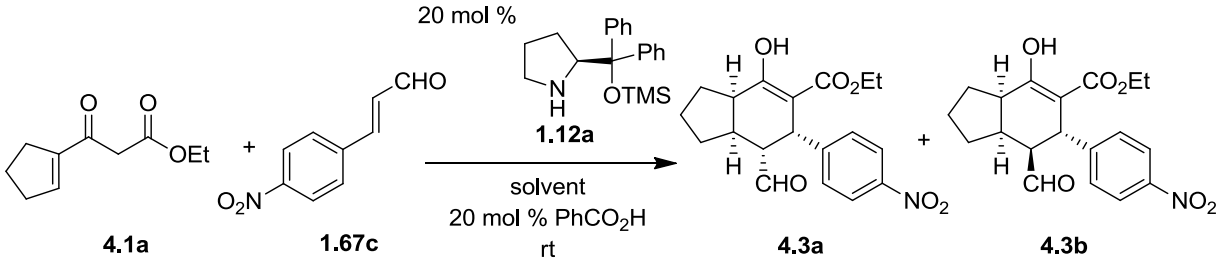
Entry	Catalyst	Time (h)	% conv[a]	dr (**4.3a**+**4.3b**)/**4.3c**[a]	% ee (**4.3a**)[b]	% ee (**4.3b**)[b]
1	**1.12a**	168	61	78/22	99	99
2	**1.12b**	168	0	--	--	--
3	**1.12c**	168	66	79/21	99	98
4	**1.12d**	216	65	80/20	87	96
5	**1.12e**	168	20	85/15	87	99

Reaction Conditions: **4.1a** (1 equiv), **1.67c** (1 equiv), **1.12** (20 mol %), $PhCO_2H$ (20 mol %), EtOH (0.3 M), rt. [a] Determined by ^1H NMR of crude reaction mixture with internal standard. [b] Determined by chiral phase HPLC.

Electron–deficient catalyst **1.12b** completely suppressed the first Michael addition giving no product at all (Entry 2). The more electron–rich catalyst **1.12e** gave some product but slowed the second Michael addition (Entry 5). Catalysts **1.12c** and **1.12d**, containing bulkier silyl groups, showed comparable conversions to that achieved by **1.12a**, but produced enantiomeric excesses less than 99% (Entries 3–4). The diastereoselectivities achieved with catalysts **1.12a**, **1.12c**, **1.12d** and **1.12e** did not vary dramatically. In all cases the ratio of **4.3a**/**4.3b** was ~1/1, ranging from 1/1.4 to 1.7/1. It's worth noting that the enantioselectivity of the minor diastereomer **4.3c** varied significantly from catalyst to catalyst but was always less than that of the two major diastereomers **4.3a** and **4.3b**.

Polar and non–polar aprotic solvents were screened in the reaction catalyzed by **1.12a** (**Table 4.4**). Polar solvents such as MeCN and DCE gave reasonable yields of product, while maintaining the high selectivity (Entries 2–3). Non–polar solvents such as toluene, Et_2O and THF lead to dramatically reduced yields (Entries 4–6). Unfortunately, none of these solvents afforded higher conversions than those achieved in EtOH (**Entry 1**).

Table 4.4 Solvent Screening



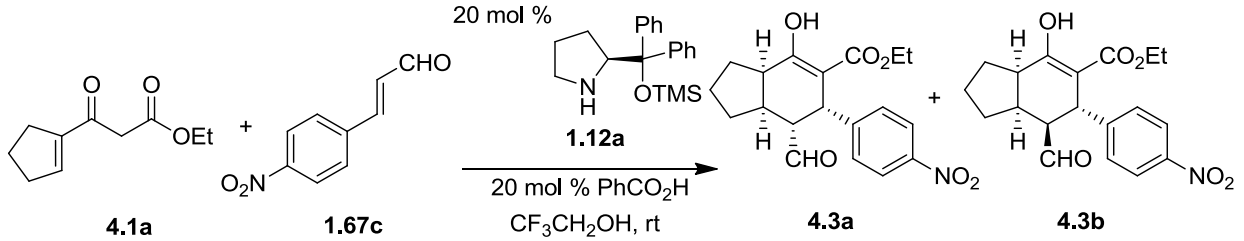
Entry	Solvent	Time (h)	% conv[a]	dr (**4.3a**+**4.3b**)/**4.3c**[a]	% ee (**4.3a**)[b]	% ee (**4.3b**)[b]
1	EtOH	168	61	78/22	99	99
2	MeCN	168	32	93/7	99	99
3	DCE	168	25	84/16	99	99
4	toluene	168	5	80/20	nd	nd
5	Et_2O	168	<1	nd	nd	nd
6	THF	168	0	--	--	--

Reaction Conditions: **4.1a** (1 equiv), **1.67c** (1 equiv), **1.12a** (20 mol %), $PhCO_2H$ (20 mol %), solvent (0.3 M), rt. [a] Determined by ^1H NMR of crude reaction mixture with internal standard. [b] Determined by chiral phase HPLC.

4.2.6 Trifluoroethanol As Solvent

Because the hydrogen bond donating solvent, EtOH, gave the most promising results, it was decided to test the effect of using the much more powerful hydrogen bond donating solvent, 2,2,2-trifluoroethanol. The results are presented in **Table 4.5**.

Table 4.5 Trifluoroethanol As Solvent



Entry	Time (h)	% conv[a]	dr (**4.3a**+**4.3b**)/**4.3c**[a]	**4.3a**/**4.3b**	% ee (**4.3a**)[b]	% ee (**4.3b**)[b]
1	2	12	89/11	1/29	nd	nd
2	41	17	91/9	1/5	99	99

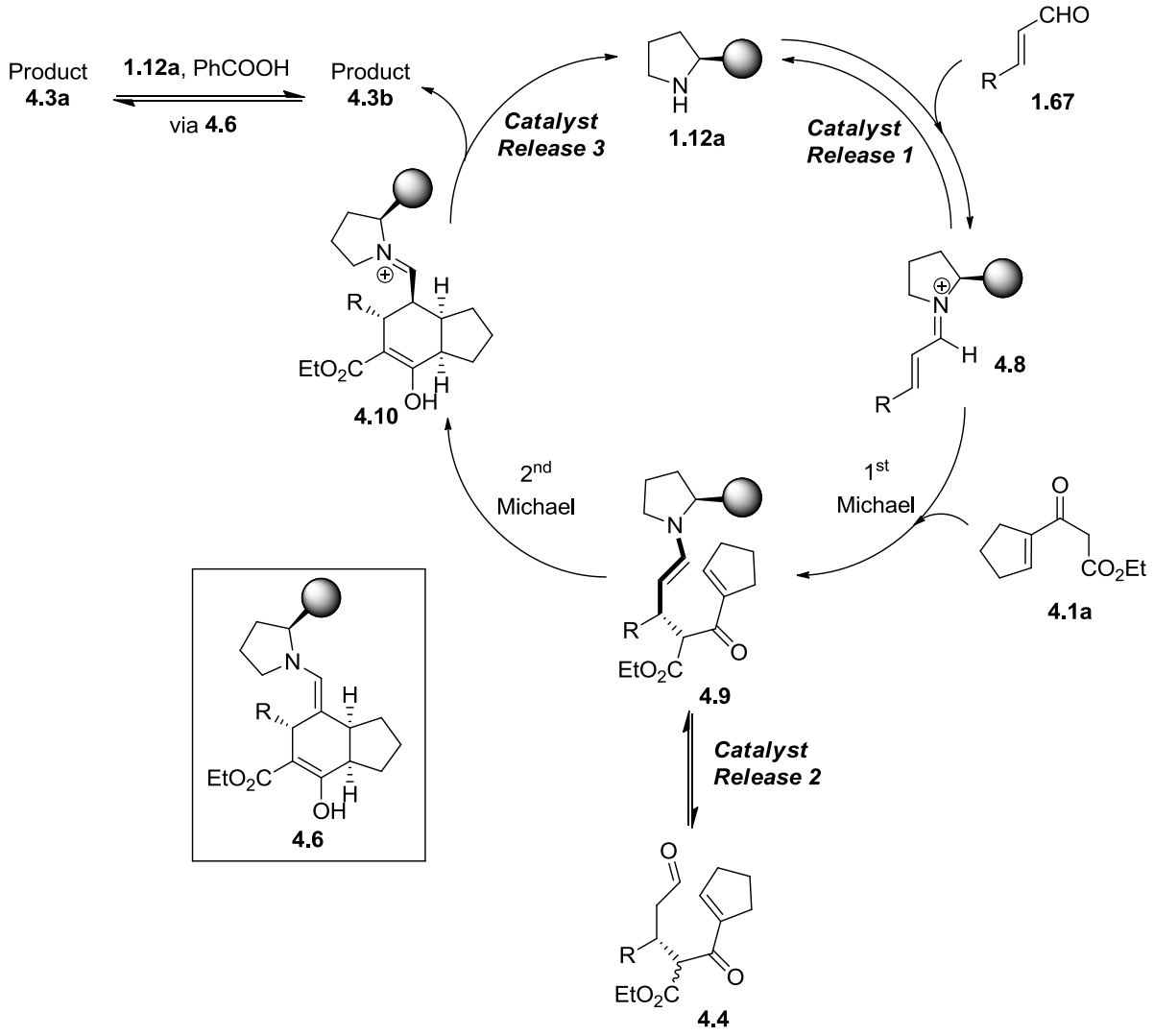
Reaction Conditions: **4.1a** (1 equiv), **1.67c** (1 equiv), **1.12a** (20 mol %), $PhCO_2H$ (20 mol %), CF_3CH_2OH (0.3 M), rt. [a] Determined by ^1H NMR of crude reaction mixture with internal standard. [b] Determined by chiral phase HPLC.

Formation of product **4.3** was observed after only 2 hours, and the ratio of **4.3a**/**4.3b** was 1/29 (Entry 1). Allowing the reaction to progress for 41 hours only slightly improved the conversion, while the ratio of **4.3a**/**4.3b** was reduced to 1/5 (Entry 2). In both reactions a significant amount of starting materials **4.1a** and **1.67c,** along with single Michael adduct **4.4**, were still present at the time the reaction was quenched. The enantiomeric excesses and diastereoselectivities achieved in this solvent were remarkably high, so further experiments with 2,2,2-trifluoroethanol as solvent were undertaken.

4.2.7 Mechanistic Studies

The proposed mechanism of catalytic activation for the **1.12a**–catalyzed Michael–Michael cascade between **4.1a** and **1.67c** is illustrated in **Scheme 4.11**.

Scheme 4.11 Catalytic Cycle



In all solvents except 2,2,2-trifluoroethanol, the first Michael addition went to completion within approximately 17 hours. At this time, intermediate **4.4** was present, but starting materials **4.1a** and **1.67** were completely consumed (**Scheme 4.5**). In 2,2,2-trifluroethanol, the fact that a significant amount of **4.1a** and **1.67** still existed in the reaction mixture, even after 41 hours, indicated that either the first Michael addition was reversible or that intermediate **4.8** preferred the "Catalyst Release 1" pathway over the productive Michael addition to form **4.9**.

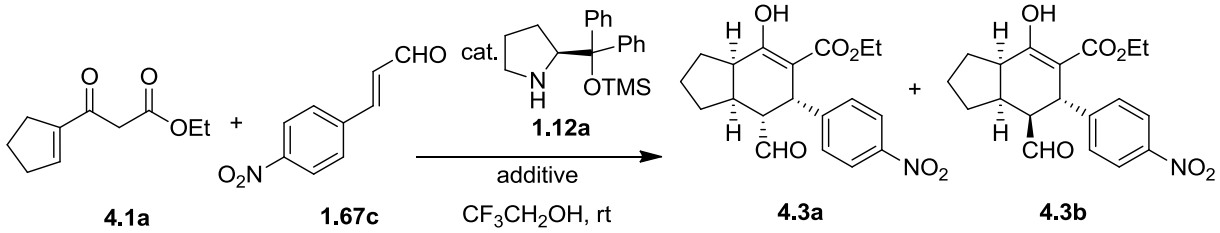
Resubjecting intermediate **4.4** to catalyst **1.12a** (20 mol %) and benzoic acid (20 mol %) in trifluoroethanol rapidly yielded only product **4.3**. This indicated that the first Michael addition was *not* reversible. Instead, "Catalyst Release 1" appeared to be favored over the productive Michael addition only in 2,2,2-trifluoroethanol.

In trifluoroethanol, once enamine intermediate **4.9** was formed via the first Michael addition, the second Michael addition was very fast, as evidenced by the presence of **4.3** after only 2 hours. However, "Catalyst Release 2" appeared to be heavily favored in trifluoroethanol, as in other solvents. Although intermediate **4.4** was rapidly converted to **4.3** by catalyst **1.12a** in the absence of **1.67** (as discussed in the previous paragraph), under the reaction conditions, **1.67** was still present in substantial quantities and was evidently competing for catalyst **1.12a**. All together, this explained why intermediate **4.4** was still present in the reaction mixture after 41 hours, and why the reaction rate to product **4.3** plateaued over time.

It was explained earlier that diastereomers **4.3a** and **4.3b** were epimers and that they could be interconverted by catalyst **1.12a** via enamine intermediate **4.6**. In trifluoroethanol, it was observed that the ratio of **4.3a**/**4.3b** was different than in other solvents. It was also observed that the conversion to **4.3a** and **4.3b** did not change very much from 2 hours to 41 hours, but that their relative ratios did (**Table 4.5**). This indicated that product **4.3b** was formed initially from the second Michael addition and that it slowly epimerized in the presence of catalyst **1.12a** to form a mixture of **4.3a** and **4.3b**. The fact that this epimerization was so much slower in trifluoroethanol than in other solvents indicated that "Catalyst Release 3" was preferred over formation of the enamine intermediate **4.6** from **4.10** (or from **4.3b** after ejection from the catalytic cycle) which leads to the epimeric mixture.

In other solvents it was a sluggish second Michael addition that hindered conversion. However, in trifluoroethanol with benzoic acid, it seemed that favored catalyst turnover was the problem. If intermediate **4.9** persisted without releasing intermediate **4.4** so that the second Michael addition occurred, rapid conversion to product **4.3** should be observed. With this hypothesis in mind, the reaction was run in trifluoroethanol *without* benzoic acid which, as previously stated, is known to facilitate catalyst turnover. As expected, running the reaction in trifluoroethanol without benzoic acid gave 85% conversion to **4.3** in just 17 hours (Entry 1, **Table 4.6**). The high selectivity of the reaction was also retained and the 1/1 ratio of **4.3a**/**4.3b** was restored.

Table 4.6 Further Optimization



Entry	Loading	Additive	Time (h)	% conv[a]	dr (**4.3a**+**4.3b**)/**4.3c**[a]	% ee (**4.3a**)[b]	% ee (**4.3b**)[b]
1	20 mol %	--	17	85	90/10	99	99
2	20 mol %	20 mol% NaOAc	17	85	91/9	99	99
3	10 mol %	--	17	87	91/9	99	99
4	5 mol %	--	17	80	91/9	99	99
5	1 mol %	--	88	25	88/12	99	99
6[e]	5 mol %	--	46	76	92/8	99	99

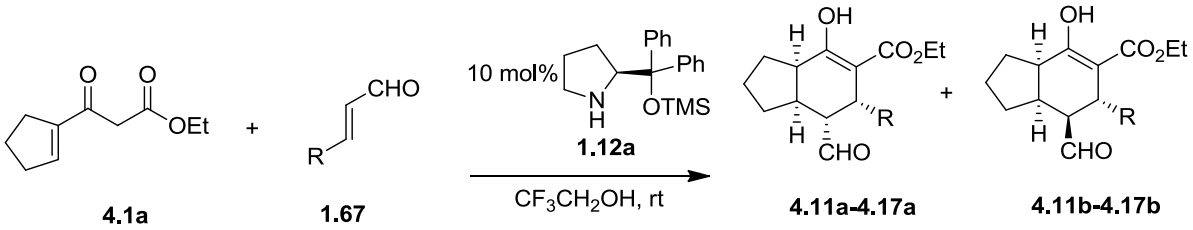
Reaction Conditions: **4.1a** (1 equiv), **1.67c** (1 equiv), **1.12a** (1-20 mol %), additive (1-20 mol %), CF_3CH_2OH (0.3 M), rt. [a] Determined by ^1H NMR of crude reaction mixture with internal standard. [b] Determined by chiral phase HPLC. [e] Reaction was run at 0 °C.

Because running the reaction without acid significantly improved the conversion of the reaction, a basic additive was screened. However, running the reaction with a catalytic amount of NaOAc did not aid in conversion to the product (Entry 2). Lowering the catalyst loading to 10 mol % resulted in greater conversion to product and a higher diastereomeric ratio of (**4.3a+4.3b**)/**4.3c** (Entry 3). Further lowering the catalyst loading to 5 mol % gave slightly decreased conversion but did not affect the selectivity of the reaction (Entry 4). A catalyst loading of 1 mol % reduced conversion dramatically (Entry 5). Lowering the temperature of the reaction to 0 ^{o}C reduced the conversion while extending reaction times, while only slightly improving the diastereoselectivity of the reaction (Entry 6).

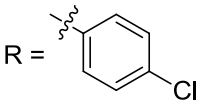
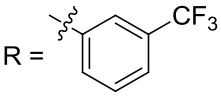
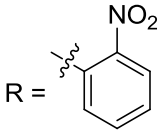
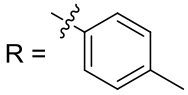
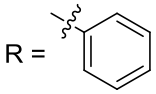
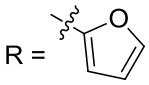
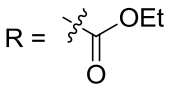
4.2.8 Substrate Scope

An investigation of the scope of this reaction was undertaken with the optimized reaction conditions (**Table 4.7**). Nearly all products **4.11**–**4.17** were collected in high yields and with outstanding selectivity. Substitution of electron–withdrawing groups at the *para*– and *meta*–positions on the aromatic ring of the enal (**1.67d**–**e**) were both well tolerated (Entries 1–2). Unfortunately, *ortho*–substitution on the enal (**1.67f**) was not well tolerated giving 0% conversion to **4.13** after 14 days (Entry 3). Electronically neutral aromatic enals and electron–rich aromatic enals (**1.67g** and **1.67b**) were also compatible with the reaction conditions, but required longer reaction times to afford products **4.14** and **4.15** respectively (Entries 4–5). The reaction was performed with heterocyclic enal **1.67h** and also with non–aromatic enal **1.67i**. Both provided products in good yields and excellent selectivities for **4.16** and **4.17** respectively (Entries 6–7).

Table 4.7 Aldehyde Scope



4.1a **1.67** **4.11a-4.17a** **4.11b-4.17b**

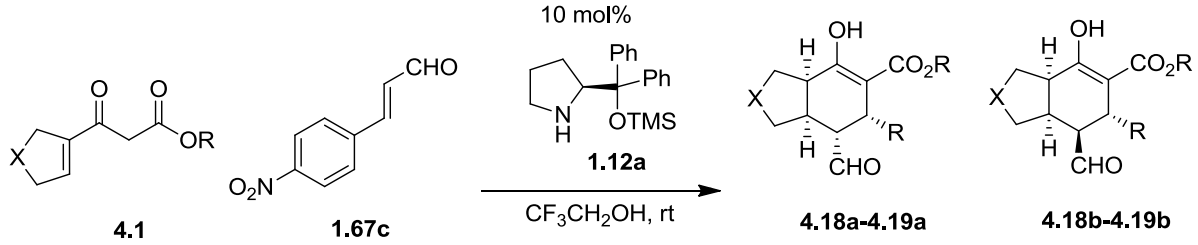
Entry	Product	Product	Time (h)	% Yield[a]	dr (**a**+**b**)/**c**[b]	% ee (**a**)[c]	% ee (**b**)[c]
1	R =  **1.67d**	**4.11**	20	82	92/8	99	98
2	R =  **1.67e**	**4.12**	17	79	93/7	99	99
3	R =  **1.67f**	**4.13**	336	0	NA	NA	NA
4	R =  **1.67g**	**4.14**	168	79	93/7	99	99
5	R =  **1.67b**	**4.15**	40	87	92/8	99	98
6	R =  **1.67h**	**4.16**	142	61	97/3	98	98
7	R =  **1.67i**	**4.17**	22	67	97/3	98	98

Reaction Conditions: **4.1a** (1 equiv), **1.67** (1 equiv), **1.12a** (10 mol %), CF_3CH_2OH (0.3 M), rt. [a] Isolated yield. [b] Determined by ^1H NMR of isolated product. [c] Determined by chiral phase HPLC.

The reaction was also run with different β-ketoesters (**Table 4.8**). The reaction with methyl ester **4.1b** lead to good product yields of **4.18** with only a negligible reduction in

selectivity (Entry 1). The dihydrothiophene substituted β-ketoester **4.1c** also produced good yields of the hetero–bicyclic product **4.19** with excellent selectivity (Entry 2). The reaction was attempted with the cyclohexene derived β-ketoester, where X = $(CH_2)_2$. Unfortunately, a complex mixture of multiple inseparable diastereomers was formed.

Table 4.8 β-Ketoester Scope

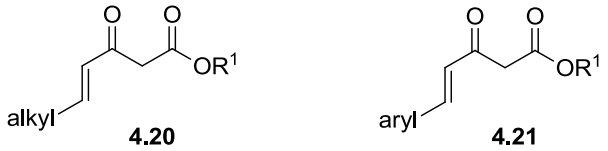


Entry	β-ketoester	Product	Time (h)	% Yield[a]	dr (**a**+**b**)/**c**[b]	% ee (**a**)[c]	% ee (**b**)[c]
1	**4.1b** (R = Me, X = CH_2)	**4.18**	21	76	91/9	97	98
2	**4.1c** (R = Et, X = S)	**4.19**	28	80	93/7	98	96

Reaction Conditions: **4.1** (1 equiv), **1.67c** (1 equiv), **1.12a** (10 mol %), CF_3CH_2OH (0.3 M), rt. [a] Isolated yield. [b] Determined by ^1H NMR of isolated product. [c] Determined by chiral HPLC.

These same Michael–Michael cascade reaction conditions were later extended to non–cyclic β-ketoester substrates of type **4.20** and **4.21** (**Figure 4.5**).[4]

Figure 4.5 β-Ketoester Substrates Used In Michael–Michael Cascade Reaction



4.3 Conclusions

A new organocatalytic Michael–Michael cascade reaction was developed.[5] The cascade reaction

gave access to highly functionalized fused carbocycles containing four contiguous stereocenters. Substrate **4.1** was developed using rational design, and was found to be capable of participating in a cascade reaction in which other similar substrates were not. In addition, thoughtful consideration of the catalytic cycle allowed for the development of this Michael–Michael cascade reaction as an efficient process. The stereochemistry at the ring junction of the product was set during the second Michael addition, affording *cis* fused bicyclic products with yields up to 87% in >96% ee. This reaction extended the use of diarylprolinol silyl ethers as efficient organocatalysts for Michael–Michael cascade reactions involving 1,3-dicarbonyl nucleophiles. A thorough study of the catalytic cycle, including solvent and additive effects, was accomplished.

4.4 References

(1) Zu, L.; Li, H.; Xie, H.; Wang, J.; Jiang, W.; Tang, Y.; Wang, W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3732–3734.
(2) Cabrera, S.; Alemán, J.; Bolze, P.; Bertelsen, S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 121–125.
(3) Zhu, M.-K.; Wei, Q.; Gong, L.-Z. *Adv. Synth. Catal.* **2008**, *350*, 1281–1285.
(4) McGarraugh, P. G.; Jones, J. H.; Brenner-Moyer, S. E. *J. Org. Chem.* **2011**, *76*, 6309–6319.
(5) McGarraugh, P. G.; Brenner, S. E. *Org. Lett.* **2009**, *11*, 5654–5657.

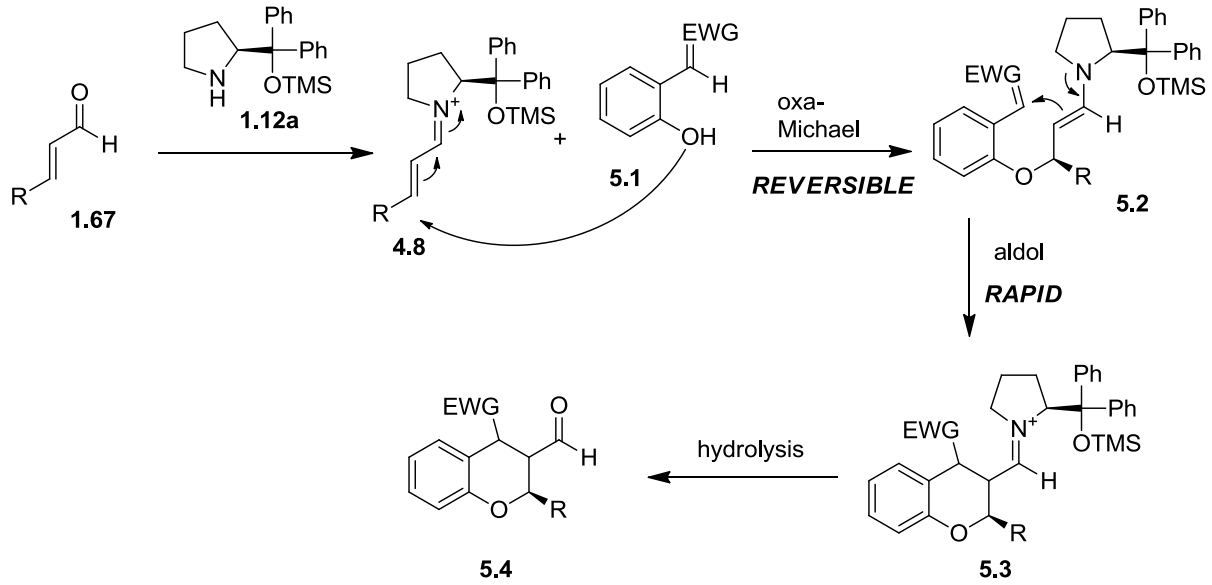
Chapter 5.

An Organocascade Kinetic Resolution Generates Chiral Pyrans And Furans

5.1 Introduction

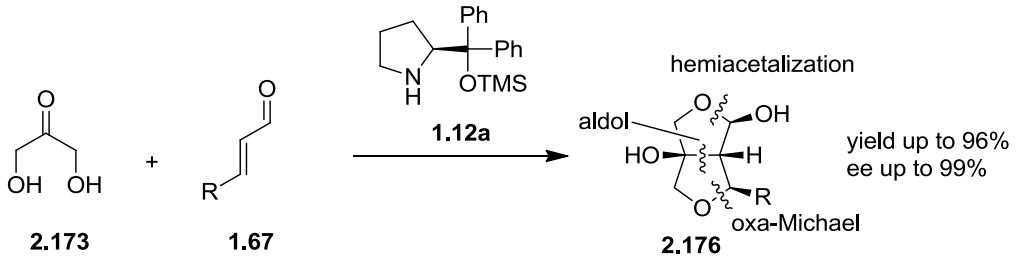
As illustrated in **Chapter 2**, there have been many heteroatom–Michael initiated iminium–enamine cascade reactions catalyzed by diarylprolinol silyl ether organocatalysts. Oxa-Michael reactions are complicated by their reversibility, which can lead to low yields and selectivities.[1] Oxa-Michael–initiated iminium–enamine cascade reactions involving aldehydes of type **1.67**, catalyzed by **1.12a** and similar catalysts, have primarily been limited to epoxidation reactions[2-6] and reactions initiated by phenol Michael donors of type **5.1** (**Scheme 5.1**).[7-13] While the initial oxa-Michael addition to iminium ions of type **4.8** may be reversible, the enamine intermediates of type **5.2**, that are formed, will react rapidly in an intramolecular reaction with an electron withdrawing group attached to the aromatic ring of the phenol to form bicyclic compounds of type **5.3**. Catalyst release via hydrolysis gives final products of type **5.4**. By coupling the initial oxa-Michael addition to an enamine–catalyzed intramolecular reaction, the proclivity of oxa-Michael additions to be reversible is overcome.

Scheme 5.1 General Oxa-Michael–Michael Cascade with a Phenol Michael Donor



There is only one example of a stereoselective oxa-Michael–initiated cascade reaction using this class of catalysts in conjunction with an aliphatic alcohol Michael donor (**Scheme 5.2**). This reaction, between dihydroxyacetone (**2.173**) and α,β-unsaturated aldehydes (**1.67)**, was used to generate polysubstituted furofuranes of type **2.176** containing four stereocenters.[14]

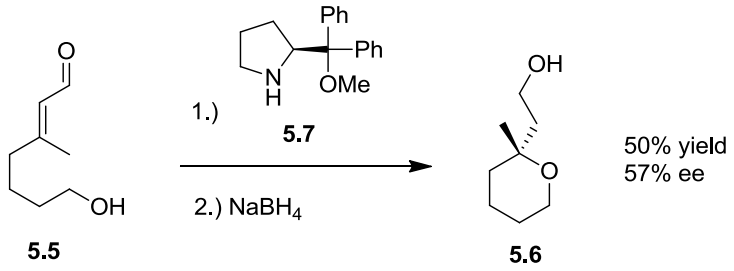
Scheme 5.2 Oxa-Michael Cascade Reaction Initiated by an Aliphatic Alcohol



There have also been very few *intra*molecular oxa-Michael additions using iminium catalysts similar to **1.12a**. An intramolecular oxa-Michael addition using the hydroxy substituted enal **5.5** to generate tetrahydropyran **5.6** has been reported (**Scheme 5.3**).[15] After an extensive

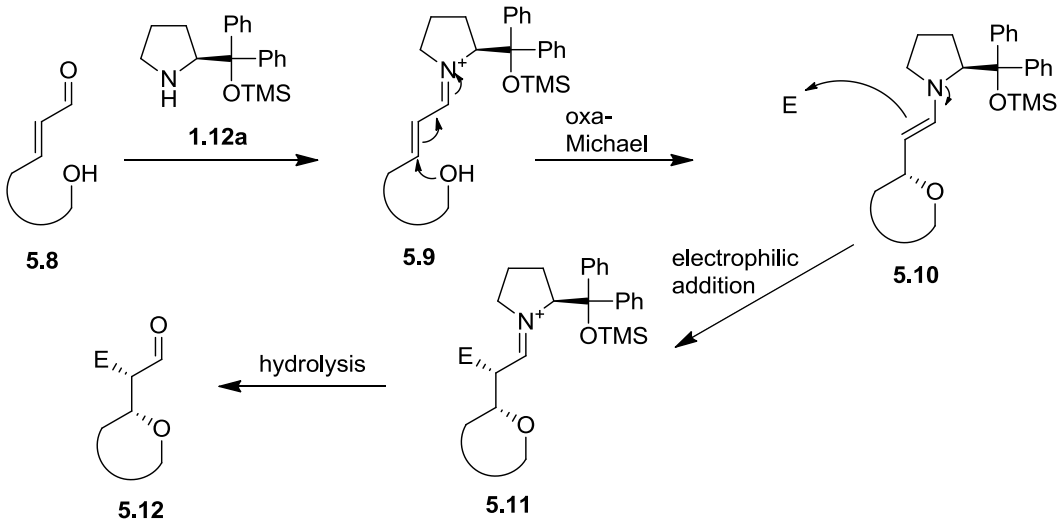
screening, the optimal catalyst for this reaction was found to be diarylprolinol ether **5.7**. While novel, the enantioselectivity (57% ee) and yield (50%) were only moderate and the scope of the reaction was limited to the substrate shown.

Scheme 5.3 Intramolecular Oxa-Michael Reaction Generates a Tetrahydropyran



It was hypothesized that one could develop a similar intramolecular oxa-Michael reaction with hydroxy–substituted aldehydes of type **5.8** and incorporate it into an iminium–enamine cascade reaction with an external electrophile (**Scheme 5.4**). This reaction, going through intermediates of type **5.9**, **5.10**, and **5.11,** could be used to gain access to chiral furans and pyrans (**5.12**), with two stereocenters being established during the cascade process.

Scheme 5.4 Proposed Oxa-Michael Initiated Cascade Reaction

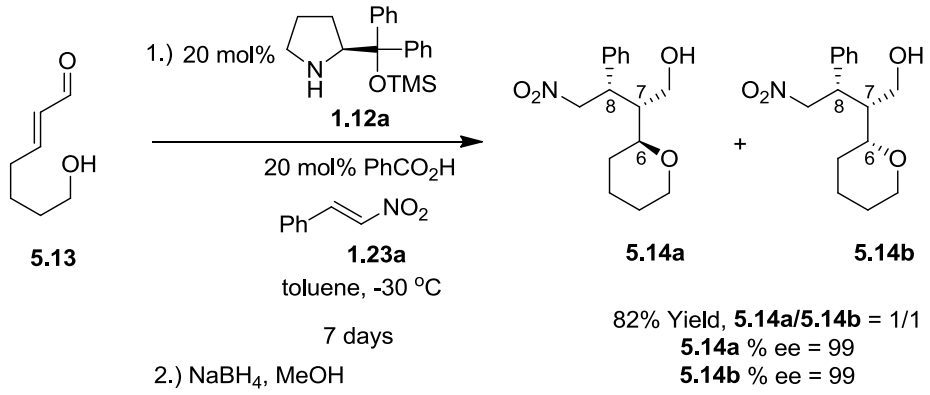


5.2 Results And Discussion

5.2.1 Initial Cascade Reaction

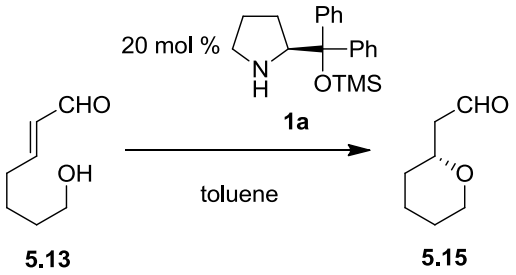
The study of this reaction was initiated using hydroxy–substituted enal **5.13** and β-nitrostyrene (**1.23a**) as the external electrophile (**Scheme 5.5**). An in situ reduction of aldehyde products using sodium borohydride was performed to prevent epimerization at the 7-position. The products were generated in good yield with excellent enantioselectivity. However, the diastereoselectivity was poor, giving two major diastereomers, **5.14a** and **5.14b**, in a 1/1 ratio. It was initially unclear at which position(s) (C6, C7, or C8) the two diastereomers differed in stereochemistry. If they differed at position C6, this would mean the oxa-Michael addition was non–selective.

Scheme 5.5 Initial Results For Oxa-Michael Cascade Reaction



The same reaction was therefore performed in the absence of β-nitrostyrene (giving oxa-Michael product **5.15**) in order to examine the selectivity of the initial oxa-Michael reaction (**Table 5.1**). It was discovered that the enantioselectivity of the reaction was eroding over time (Entries 1–3). This result suggested that the two major diastereomers generated in the reaction in **Scheme 5.5** were epimeric at the chiral center generated by the oxa-Michael addition (C6).

Table 5.1 Oxa-Michael Addition with Eroding Selectivity



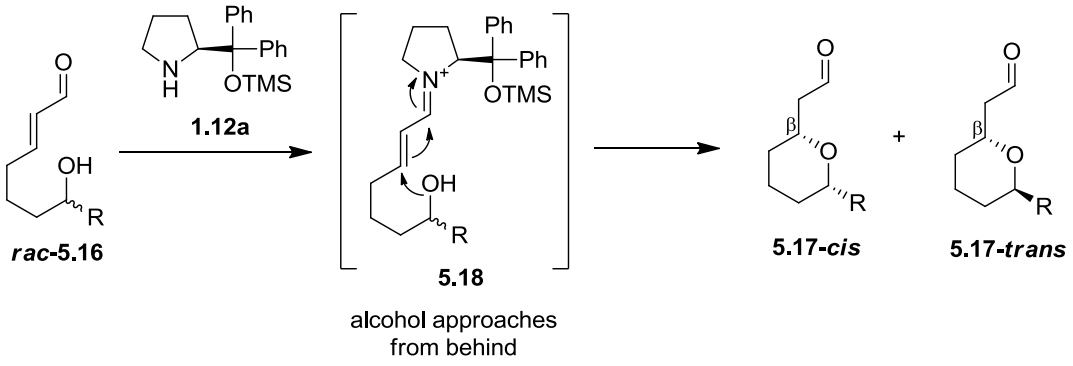
Entry	Temp (°C)	Time (h)	% conv[a]	% ee[b]
1	0	1	~100	43
2	0	2	~100	29
3	0	3	~100	25

Reaction Conditions: **5.13** (0.4 mmol), **1.12a** (0.08 mmol), toluene (1 mL), 0 °C. [a] Conversion data based on TLC analysis. [b] Determined by chiral phase HPLC of PNB protected corresponding alcohol generated by in situ reduction of **5.15**.

At this point, the proposed oxa-Michael–initiated cascade reaction being developed had two disadvantages. The first was that the selectivity of the oxa-Michael reaction was decreasing with time (most likely due to the reversibility of the reaction), and the second was that the reaction was not amenable to substrate variation.

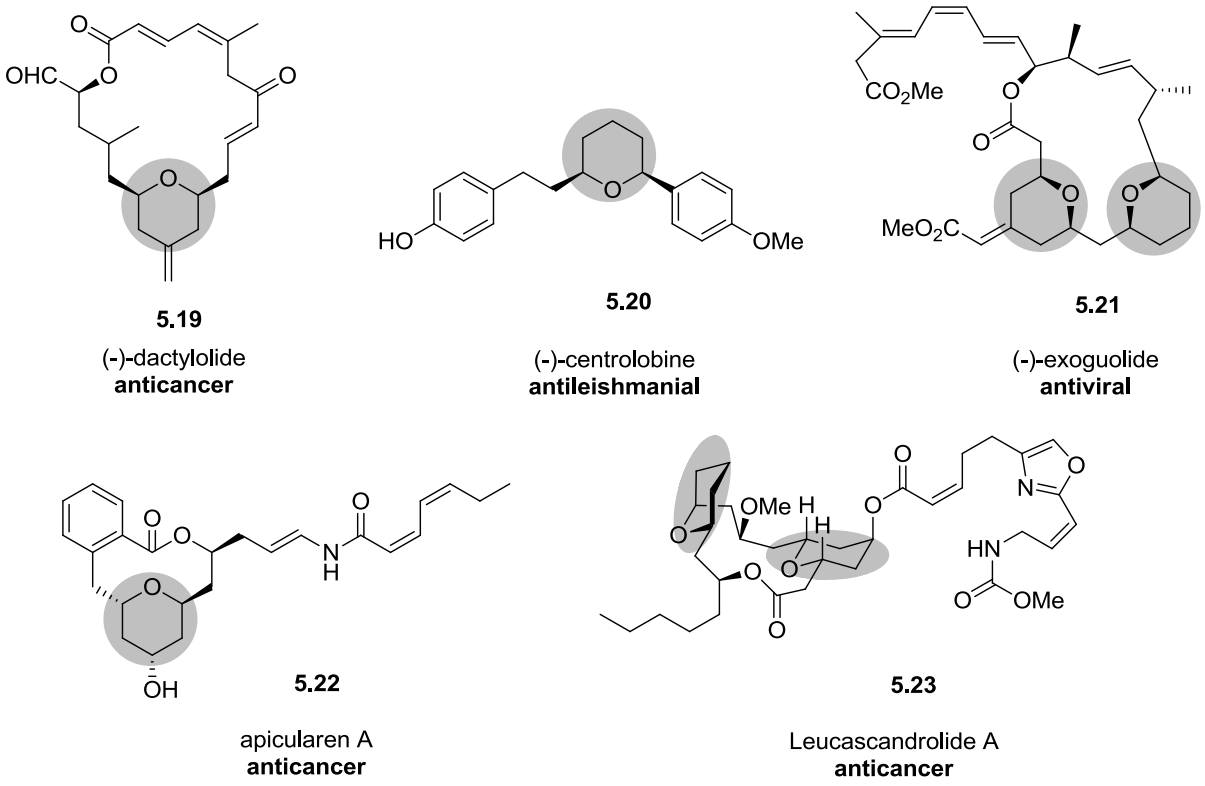
To address the issue of substrate variability, a similar reaction was pursued (**Scheme 5.6**). It was predicted that racemic secondary alcohol substrates of type ***rac*–5.16** would react to give equal amounts of the *cis* and *trans* diastereomers of pyran products of type **5.17** (**5.17**–***cis*** and **5.17**–***trans*** respectively) via enamine intermediate **5.18**.

Scheme 5.6 Oxa-Michael Reaction Generates *Cis* and *Trans* Pyrans



If this reaction proceeded as predicted, it could be performed with a variety of secondary alcohols with different R groups. Chiral *cis* and *trans* 2,6–substituted tetrahydropyrans, which would be produced by such a reaction, are extremely prevalent in many biologically active compounds such as **5.19**–**5.23** (**Figure 5.1**). In addition, if this reaction was incorporated into a cascade process, it could potentially, depending on the electrophile, be used to generate up to three chiral centers in a one pot process.

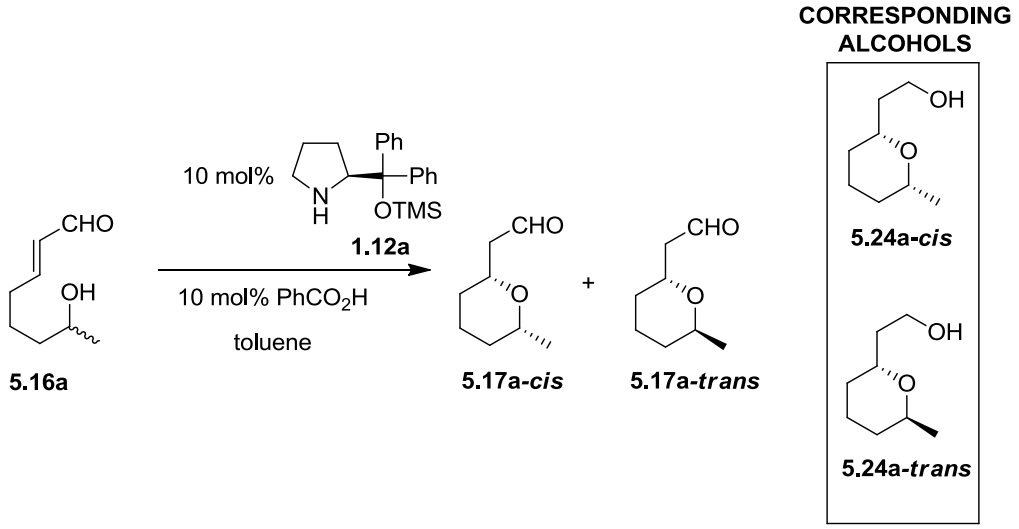
Figure 5.1 Biologically Active 2,6-disubstituted Pyran Containing Compounds



5.2.2 Oxa-Michael Reaction

The initial results were collected using the methyl substituted substrate **5.16a** (**Table 5.2**). The aldehyde products, **5.17a**–***cis*** and **5.17a**–***trans***, were subjected to an in situ reduction and were isolated as their corresponding alcohols **5.24a**–***cis*** and **5.24a**–***trans***. The reaction was observed over time (Entries 1–3). The reaction was initially fast (Entry 1), but slowed over time (Entries 2–3). Two major trends in the selectivity of the reaction were observed. Initially the reaction produced an approximately 1/1 mixture of **5.17a**–***trans***/**5.17a**–***cis***, as desired (Entry 1). However, this ratio eroded over time to eventually provide **5.17a**–***cis*** exclusively (Entries 2–3). The enantiomeric excess of **5.17a**–***trans*** was excellent regardless of when the reaction was stopped (Entries 1–2), but the enantiomeric excess of **5.17a**–***cis*** eroded over time (Entries 1–3).

Table 5.2 Oxa-Michael Kinetic Resolution: Selectivity Erodes Over Time



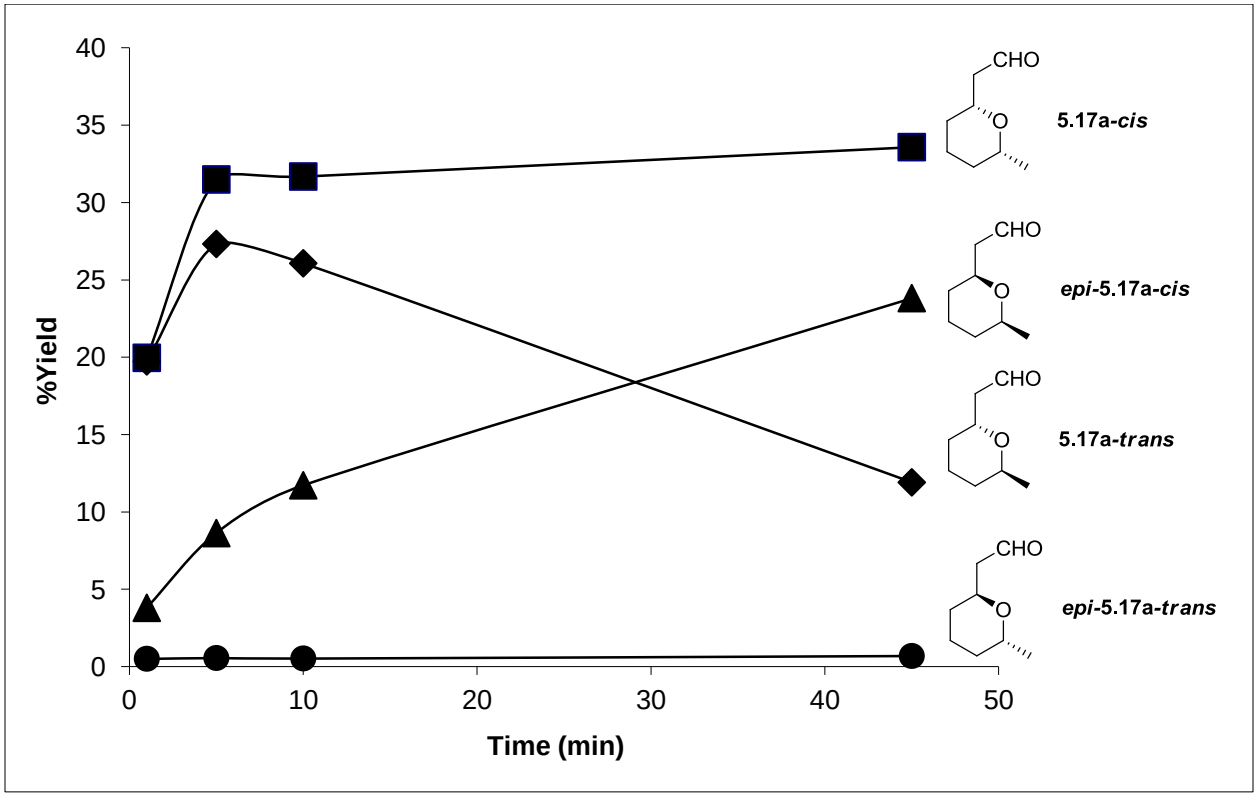
Entry	Additive	Time	% Yield[a]	dr (*cis*/*trans*)[b]	% ee (*cis*/*trans*)[c]
1	none	0.5 h	<20	60/40	63/94
2	none	2 h	<20	67/33	45/96
3	none	96 h	~100[d]	99/1	12/--
4	$PhCO_2H$	1 min	44	54/46	68/95
5	$PhCO_2H$	5 min	68	59/41	57/96
6	$PhCO_2H$	10	70	62/38	46/96
7	$PhCO_2H$	45	70	82/18	17/89
8	$PhCO_2H$	45	0	--	--
9	$PhCO_2H/Et_3N$	45	0	--	--

Reaction Conditions: **5.16a** (0.4 mmol), **1.12a** (0.04 mmol), $PhCO_2H$ (0.04 mmol), toluene (1 mL), 0 °C. [a] Isolated yield of corresponding alcohol generated by in situ reduction. [b] Determined by ^1H NMR of the isolated alcohol products. [c] Determined by chiral phase HPLC of PNB derivative of the corresponding alcohols of **5.17a-*cis*** and **5.17a-*trans*.** [d] Conversion data based on TLC analysis.

The oxa-Michael reaction was much faster when benzoic acid was added in a catalytic amount (Entries 4–7). As stated earlier, benzoic acid is known to increase catalyst turnover. The same two trends in the selectivity of the reaction were observed with the acidic additive. The ratio of **5.17a**–***trans***/**5.17a**–***cis*** eroded over time to eventually afford only **5.17a**–***cis***, and the

enantiomeric excess of **5.17a**–***cis*** decreased over time (Entries 4–7). It was confirmed that the reaction was promoted through iminium catalysis, because the reaction did not proceed in the presence of exclusively acid or in the presence of a mixture of acid and base (Entries 8–9). Using the yield, diastereomeric ratio, and enantiomeric excess data from Entries 4–7, a graph of the amounts of each stereoisomer of product **5.17a** vs. time was constructed (**Figure 5.2**).

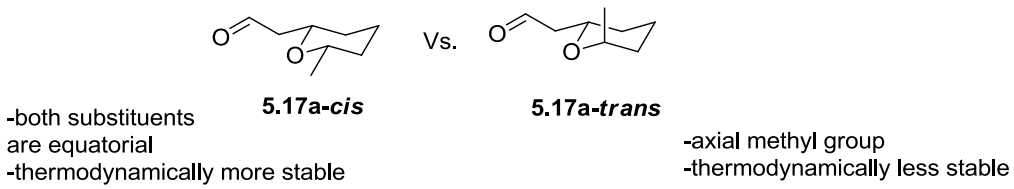
Figure 5.2 Graph of % Yield of Diastereomers of **5.17a** Versus Time



This graph revealed that **5.17a**–***trans*** was converting to ***epi***–**5.17a**–***cis*** over time. This accounted for the erosion of the **5.17a**–***trans*****/5.17a**–***cis*** ratio and the erosion of the enantiomeric excess of **5.17a**–***cis*** as the reaction progressed. It was predicted that the observed conversion of

5.17a–***trans*** to ***epi***–**5.17a**–***cis*** was the result of the increased thermodynamic stability of the *cis* configuration relative to the *trans* configuration (**Figure 5.3**).

Figure 5.3 Thermodynamic Stability of **5.17a**–***cis*** Versus **5.17a**–***trans***

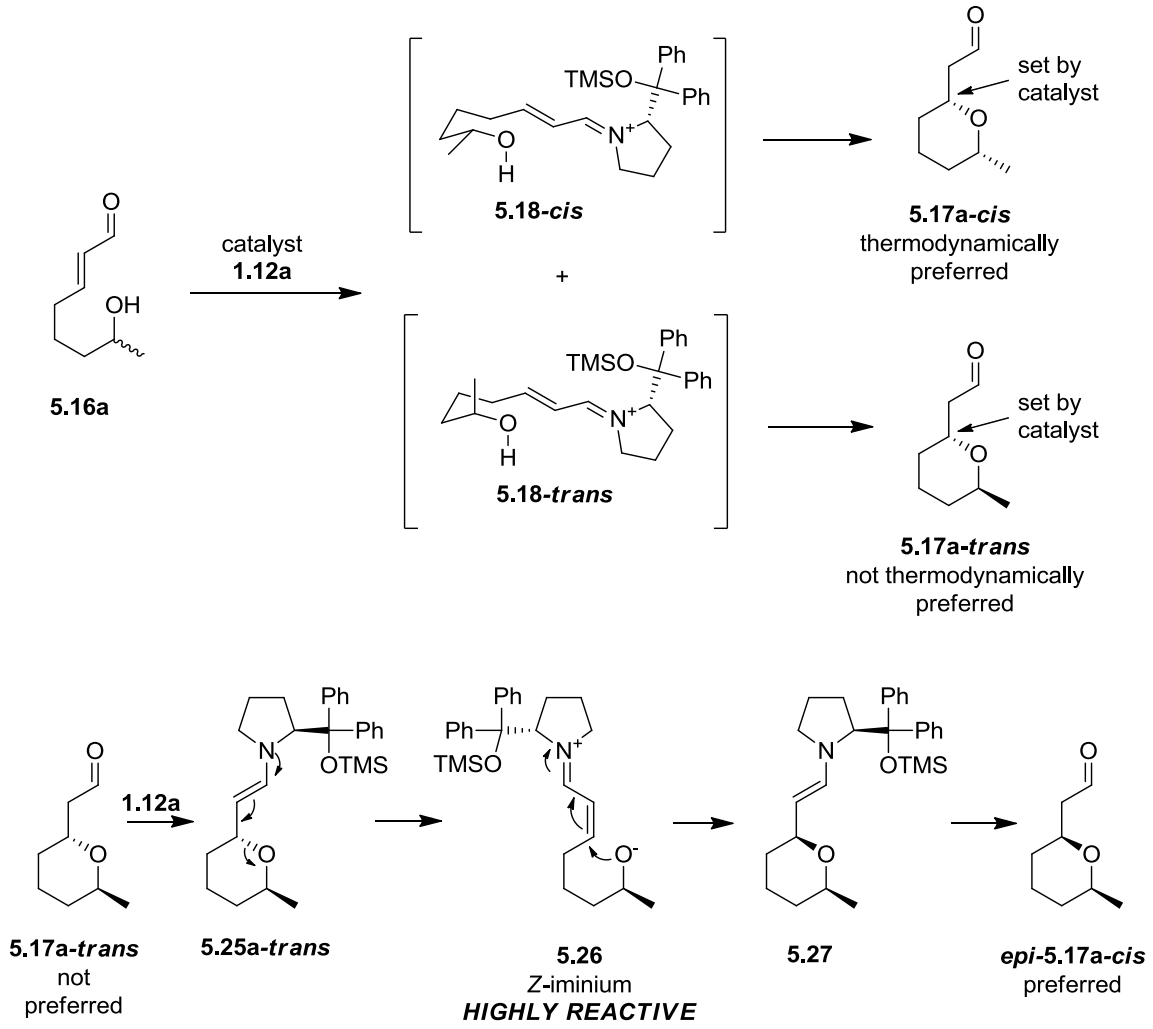


A plausible mechanism for this oxa-Michael addition is illustrated in **Scheme 5.7**. Products **5.17a**–***cis*** and **5.17a**–***trans*** were formed in the initial reaction (**Table 5.2**, Entry 1 and 4). It was speculated that these two products may form via chair-like transition states, **5.18**–***cis*** and **5.18**–***trans***, where the approach of the alcohol to the C=C double bond comes from opposite the bulky group of the catalyst. In transition state **5.18**–***cis*** the methyl group is allowed to occupy an equatorial position in the chair-like transition state which is energetically favorable. In transition state **5.18**–***trans*** the methyl group must occupy an axial position in the chair-like transition state. Due to the fact that both **5.18**–***cis*** and **5.18**–***trans*** are high–energy iminium intermediates, the energy required for the methyl group in **5.18**–***trans*** to occupy an axial position may be negligible. It is also possible that **5.17a**–***trans*** is formed via a non-chair transition state.

The conversion of **5.17a**–***trans*** to ***epi***–**5.17a**–***cis*** may occur through the mechanism also illustrated in **Scheme 5.7**. Product **5.17a**–***trans*** can form enamine **5.25a**–***trans*** in the presence of catalyst **1.12a**. The retro–oxa-Michael reaction may occur to form the energetically unstable *Z*-iminium **5.26**. This *Z*-iminium now directs approach of the alkoxide from the top face, producing enamine **5.27**, which affords ***epi***–**5.17a**–***cis***, the thermodynamically preferred

diastereomer. In this proposed mechanism, the thermodynamic stability of ***epi*–5.17a–*cis*** outweighs the instability of the *Z*-iminium intermediate **5.26** through which its formation may occur. The existence of *Z*-iminium species has been invoked by others.[2]

Scheme 5.7 Mechanism of Conversion of **5.17a**–***trans*** to ***epi*–5.17a–*cis***



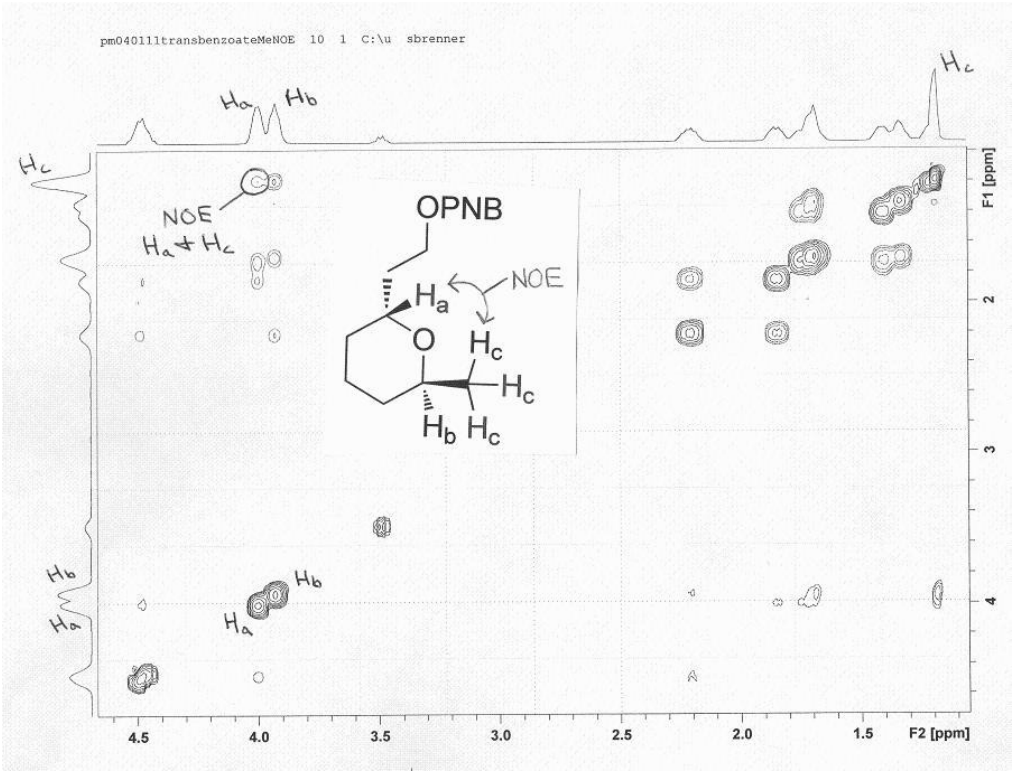
This mechanism also accounts for the rate of the reaction decreasing over time (**Table 5.2,** Entries 1-3 and 4–7). The catalyst is not only converting starting material to product, but it is also converting **5.17a**–***trans*** to ***epi*–5.17a–*cis***. Because there is more product (**5.17a**) than

starting material (**5.16a**) present as the reaction progresses, product inhibition increases and the conversion of starting material to product slows as the reaction continues. As a result of this phenomenon, the best results for selectivity and yield were obtained when the reaction was halted prior to 100% conversion.

5.2.3 Determination of Configurations

The absolute configuration of **5.17a**–***cis*** was determined by comparison to the literature data for the corresponding alcohol **5.24a**–***cis***.[16] The other diastereomer of the oxa-Michael addition, **5.17a**–***trans***, was confirmed to be *trans* via NOE of the *p*-nitrobenzoate derivative (**5.28a**–***trans***) of its corresponding alcohol, **5.24a**–***trans*** (**Figure 5.4**).

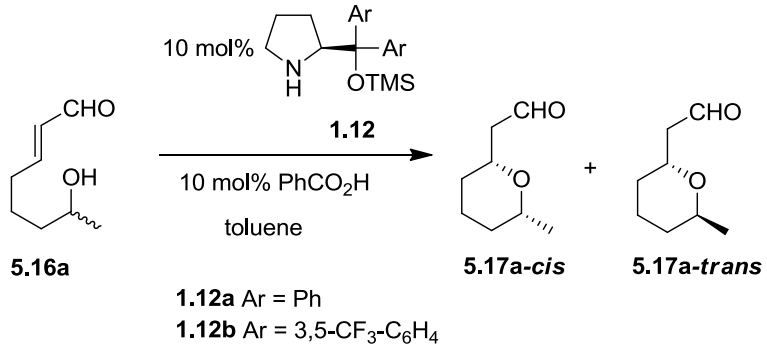
Figure 5.4 NOE NMR of **5.28a**–***trans***



5.2.4 Optimization of Oxa-Michael Reaction

Efforts to subvert the conversion of **5.17a**–***trans*** to ***epi***–**5.17a**–***cis*** (and retain the kinetic product: **5.17a**–***trans***) began by adjusting the temperature of the reaction (**Table 5.3,** Entries 1–2). However, at –30 °C the same ratio of *trans* to *cis* was observed (Entry 1), and at –78 °C the reaction was too slow to be practical (Entry 2). Unfortunately, using another catalyst (**1.12b**) did not subvert the conversion of *trans* to *cis* either (Entry 3).

Table 5.3 Catalyst and Temperature Optimization

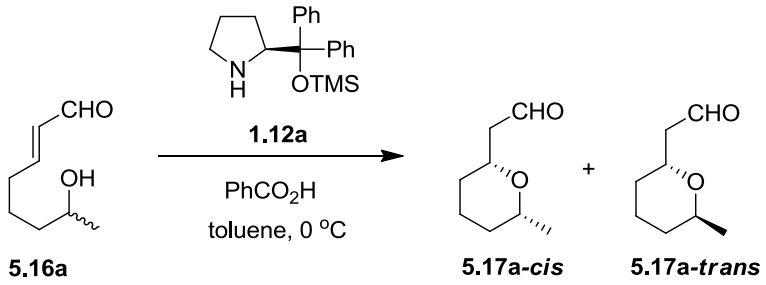


Entry	Catalyst	Temp (°C)	Time (h)	% Yield[a]	dr (*cis*/*trans*)[b]	% ee (*cis*/*trans*)[c]
1	**1.12a**	–30	3	73	63/37	53/99
2	**1.12a**	–78	22	<20	58/42	60/93
3	**1.12b**	0	1	76	63/37	52/95

Reaction Conditions: **5.16a** (0.4 mmol), **1.12** (0.04 mmol), $PhCO_2H$ (0.04 mmol), toluene (1 mL). [a] Isolated yield of corresponding alcohol generated by in situ reduction. [b] Determined by ^1H NMR of the isolated alcohol products. [c] Determined by chiral phase HPLC of PNB derivative of the corresponding alcohols of **5.17a-*cis*** and **5.17a-*trans*.**

Lowering the catalyst loading did improve the overall product yield (**Table 5.4,** Entry 1 vs. 2 and 4). However, it still did not prevent the conversion of *trans* to *cis* (Entries 3–5).

Table 5.4 Lower Catalyst Loading



Entry	Loading	Time (min)	% Yield[a]	dr (*cis*/*trans*)[b]	% ee (*cis*/*trans*)[c]
1	10 mol %	10	70	62/38	46/96
2	5 mol %	20	80	62/38	52/99
3	1 mol %	150	55	55/45	72/99
4	1 mol %	300	84	61/39	61/97
5	1 mol %	450	90	76/24	28/95

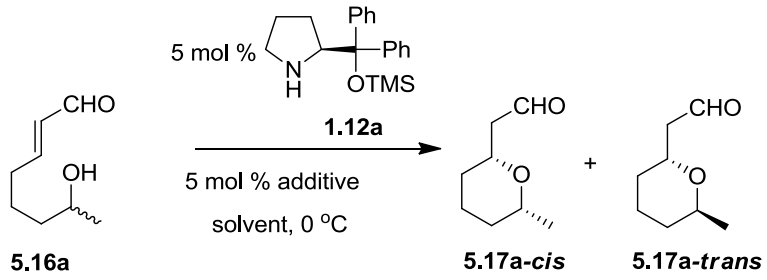
Reaction Conditions: **5.16a** (0.4 mmol), **1.12a** (1-5 mol %), $PhCO_2H$ (0.04 mmol), toluene (1 mL), 0 °C. [a] Isolated yield of corresponding alcohol generated by in situ reduction. [b] Determined by ^1H NMR of the isolated alcohol products. [c] Determined by chiral phase HPLC of PNB derivative of the corresponding alcohols of **5.17a-*cis*** and **5.17a-*trans*.**

Changing the solvent from toluene to chloroform enhanced the conversion of **5.17a**–***trans*** to ***epi***–**5.17a**–***cis*** (**Table 5.5,** Entry 1 vs. 2). Using a strongly protic solvent such as trifluoroethanol greatly reduced the reaction rate and gave almost exclusively the *cis* diastereomer in low enantiomeric excess (**Table 5.5**, Entry 3).

Using triethylamine as an additive instead of benzoic acid slowed the rate of reaction as well as the conversion of **5.17a**–***trans*** to ***epi***–**5.17a**–***cis*** (**Table 5.5,** Entry 4). However, the overall yield and enantiomeric excess for **5.17a**–***trans*** were not better than the best results using benzoic acid as an additive (**Table 5.5,** Entry 1 vs. 4). Using sodium acetate as a basic additive also resulted in a slower reaction rate with a poor **5.17a**–***cis*****/5.17a**–***trans*** ratio (Entry 5). Using

the less acidic additive, *p*-nitrophenol, gave nearly exclusively **5.17a**–***cis*** but in poor enantiomeric excess (Entry 6).

Table 5.5 Solvent and Additive Optimization



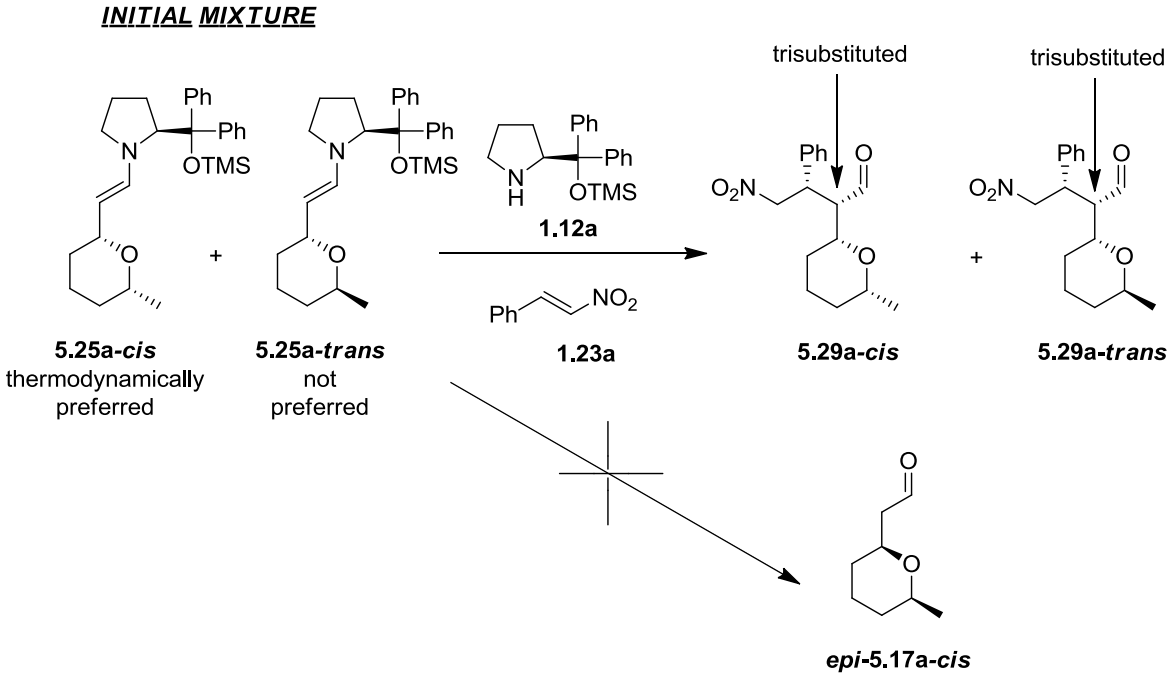
Entry	Solvent	Additive	Time	% Yield[a]	dr (*cis*/*trans*)[b]	%ee (*cis*/*trans*)[c]
1	toluene	$PhCO_2H$	20 min	80	62/38	52/99
2	$CHCl_3$	$PhCO_2H$	27 min	69	71/29	36/95
3	CF_3CH_2OH	$PhCO_2H$	20 h	66	94/6	22/10
4	toluene	Et_3N	40 h	72	59/41	63/96
5	toluene	NaOAc	17 h	76	70/30	38/96
6	toluene	*p*-NO_2-phenol	80 min	71	92/8	6/99

Reaction Conditions: **5.16a** (0.4 mmol), **1.12a** (0.02 mmol), additive (0.02 mmol), solvent (1 mL), 0 °C. [a] Isolated yield of corresponding alcohol generated by in situ reduction. [b] Determined by ^{1}H NMR of the isolated alcohol products. [c] Determined by chiral HPLC of PNB derivative of the corresponding alcohols of **5.17a-*cis*** and **5.17a-*trans*.**

It was postulated that one could trap **5.17a**–***trans*** (and **5.17a**–***cis***) as enamine **5.26a**–***trans*** prior to its conversion to ***epi***–**5.17a**–***cis*** by incorporating the initial oxa-Michael addition into an iminium–enamine cascade reaction. As described previously, enamine–catalyzed *intra*molecular reactions have been used to trap oxa-Michael adducts (**Scheme 5.1**). However, an enamine–catalyzed *inter*molecular reaction has never been used for this purpose. We decided to use β-nitrostyrene **1.23a** as the external electrophile in an enamine–catalyzed *inter*molecular reaction

(**Scheme 5.8**). The enamine adducts of **5.17a**–***cis*** and **5.17a**–***trans*** (**5.25a**–***cis*** and **5.25a**–***trans***) could be formed initially, and could then react with β-nitrostyrene **1.23a** via enamine catalysis giving **5.29a**–***cis*** and **5.29a**–***trans***. Product **5.29a**–***trans*** contains a trisubstituted carbon α to the aldehyde, so it is no longer a good substrate for the catalyst. This would hamper epimerization via catalyst mediated ring opening/reclosing (as in **Scheme 5.7**). Ideally, this reaction would give both cascade products **5.29a**–***cis*** and **5.29a**–***trans*** in an approximately 1/1 ratio, both in high enantiomeric excesses.

Scheme 5.8 Oxa-Michael Cascade Reaction with β-nitrostyrene to Prevent Epimerization



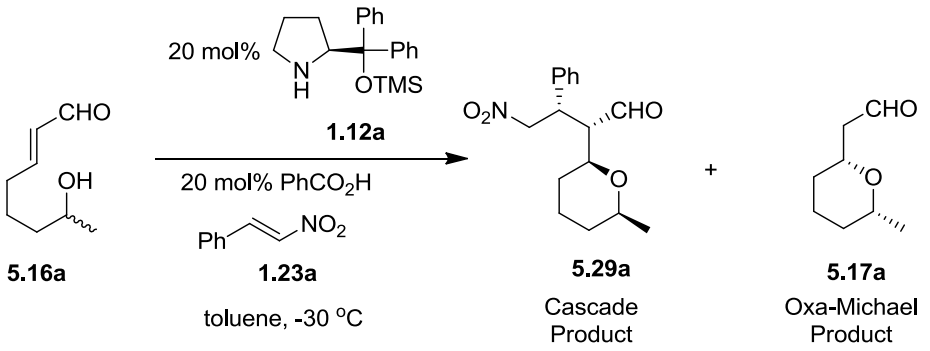
5.2.5 Organocascade Kinetic Resolution

The reaction was conducted in toluene with 20 mol % catalyst and 20 mol % $PhCO_2H$ at –30 ^oC. It was monitored over several days via ^1H NMR (**Table 5.6,** Entries 1–5). After 64 hours (Entry 1), the oxa-Michael product **5.17a** existed exclusively as the *cis* diastereomer, meaning the conversion of **5.17a**–***trans*** to ***epi***–**5.17a**–***cis*** was faster than the intermolecular enamine–

catalyzed Michael addition to β-nitrostyrene. However, only one major diastereomer of the cascade product **5.29a** was being formed. Thus, only ***epi***–**5.17a**–***cis*** was reacting with β-nitrostyrene via enamine catalysis to form the cascade product **5.29a**, while **5.17a**–***cis*** was not reacting (or at least reacting at a much slower rate). What was observed was a kinetic resolution, where one enantiomer is "matched" for chiral catalysis, while the other is "mismatched" and does not react.

After 112 hours (Entry 3), both the oxa-Michael product **5.17a** and the cascade product **5.29a** were observed with high conversions and were collected with high enantiomeric excesses. After 170 hours (Entry 5), the enantiomeric excess of the oxa-Michael product **5.17a** was slightly increased, but its conversion was reduced. It was decided that 112 hours was an ideal time to stop the reaction with this substrate, as it gave both the oxa-Michael product **5.17a** and the cascade product **5.29a** in roughly equal amounts in high enantiomeric excesses.

Table 5.6 Iminium–Enamine Organocascade Kinetic Resolution



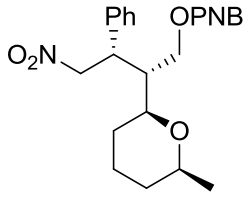
Entry	Time (h)	% conv **5.29a**/**5.17**a[a]	dr (**5.29a**)[a]	% ee (**5.29a**/**5.17a**)[b]
1	64	30/59	89/11	99/55
2	90	36/53	91/9	--
3	112	42/45	91/9	99/90
4	136	45/38	91/9	--
5	170	47/32	88/12	99/93

Reaction Conditions: **5.16a** (0.44 mmol), **1.23a** (0.88 mmol), **1.12a** (0.088 mmol), $PhCO_2H$ (0.088 mmol), toluene (1.1 mL), -30 °C. [a] Determined by ^1H NMR of the crude reaction mixture prior to in situ reduction. [b] Determined by chiral phase HPLC of PNB derivative of the corresponding alcohols of **5.17a** and **5.29a**.

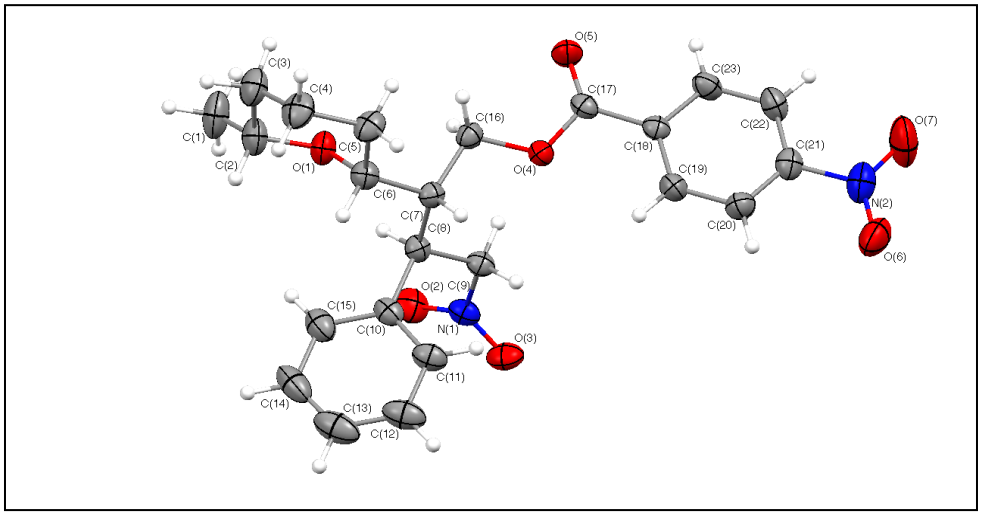
5.2.6 Determination of Configurations

The relative configuration of **5.29a** was determined by X-ray crystallography of the racemic *p*-nitrobenzoate derivative (**5.30a**) of the corresponding alcohol of **5.29a** (**Figure 5.5**).

Figure 5.5 X-ray Structure of **5.30a**

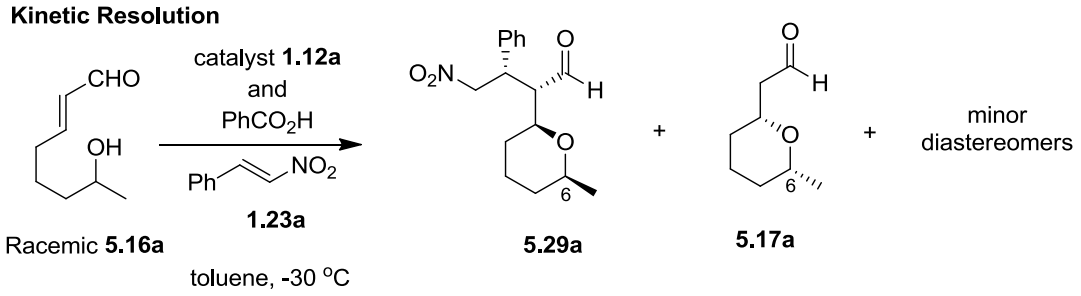


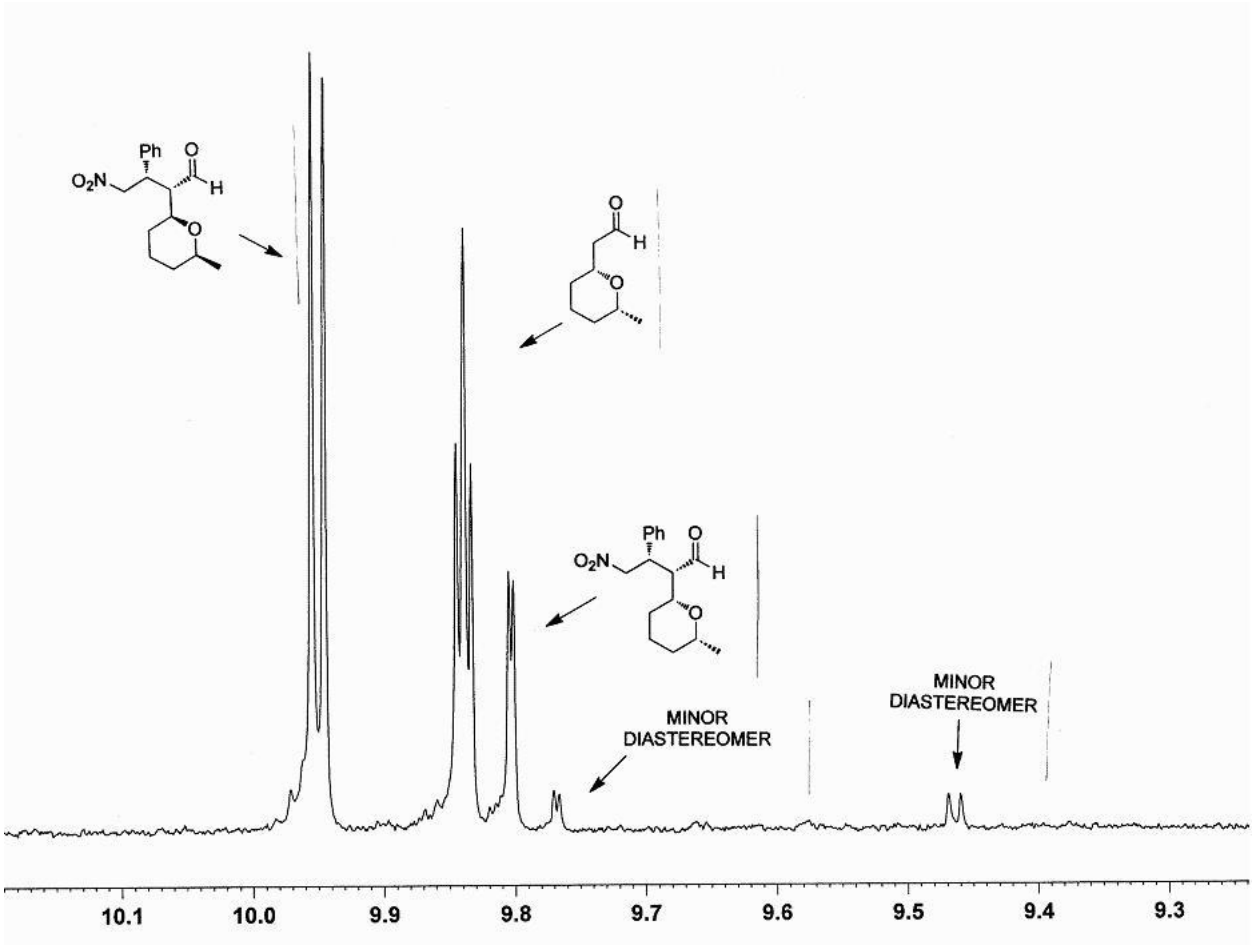
5.30a



The absolute configurations of **5.17a** and **5.29a** at the 6-position were determined by subjecting the pure chiral substrates **(*S*)**–**5.16a** and **(*R*)**–**5.16a** to the same kinetic resolution conditions as described above for racemic **5.16a** (**Scheme 5.9**). The spectra illustrated is representative of the kinetic resolution (**Table 5.6**, Entry 3), where **5.29a** and **5.17a** are formed as the major products in roughly equal amounts. This figure depicts the aldehyde portion of the ^{1}H NMR spectrum.

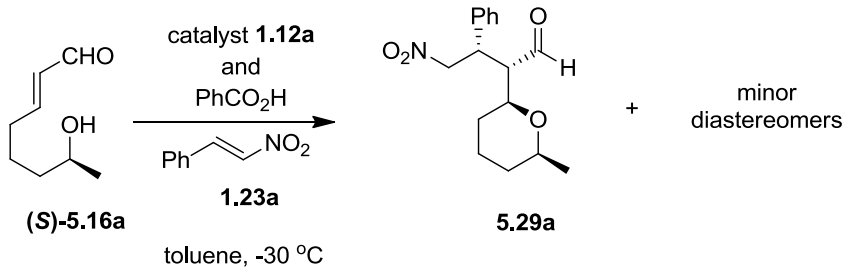
Scheme 5.9 ^{1}H NMR Spectra of the Organocascade Kinetic Resolution

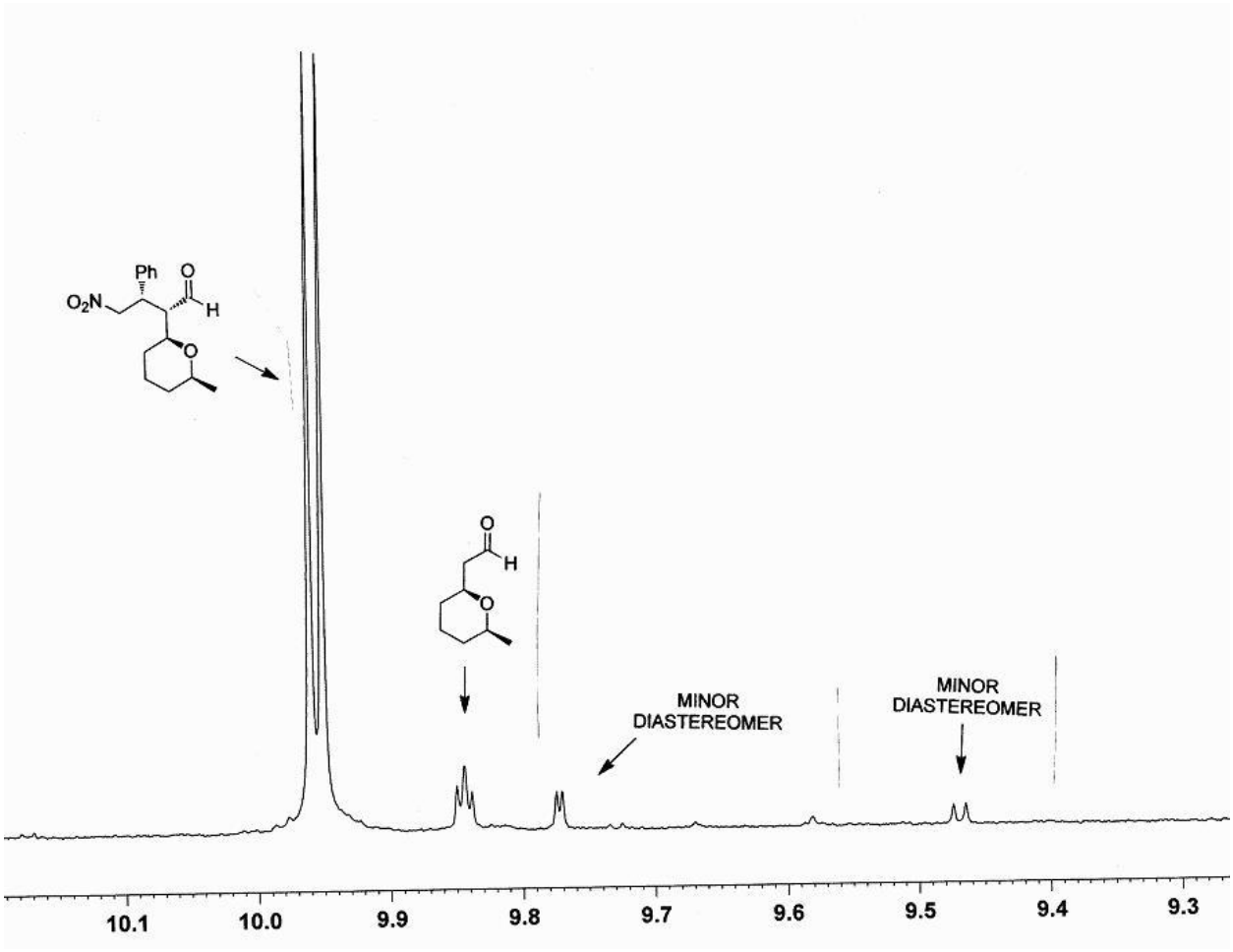




NMR analysis of the reaction in **Scheme 5.10** with **(*S*)**–**5.16a** showed a distinct major peak for the aldehyde proton of **5.29a** as a doublet (J = 3.9 Hz) at 9.95 ppm, confirming that the configuration at C6 of the major cascade product, **5.29a**, was *S*. Very minor peaks for the minor diastereomers of **5.29** arising from **(*S*)**–**5.16a** were also observed.

Scheme 5.10 Reaction with **(*S*)-5.16a**

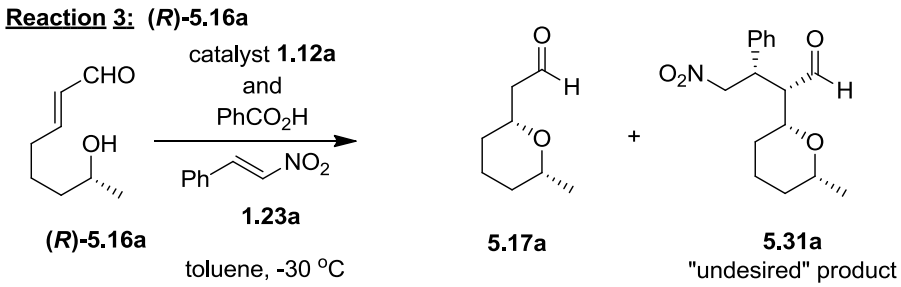


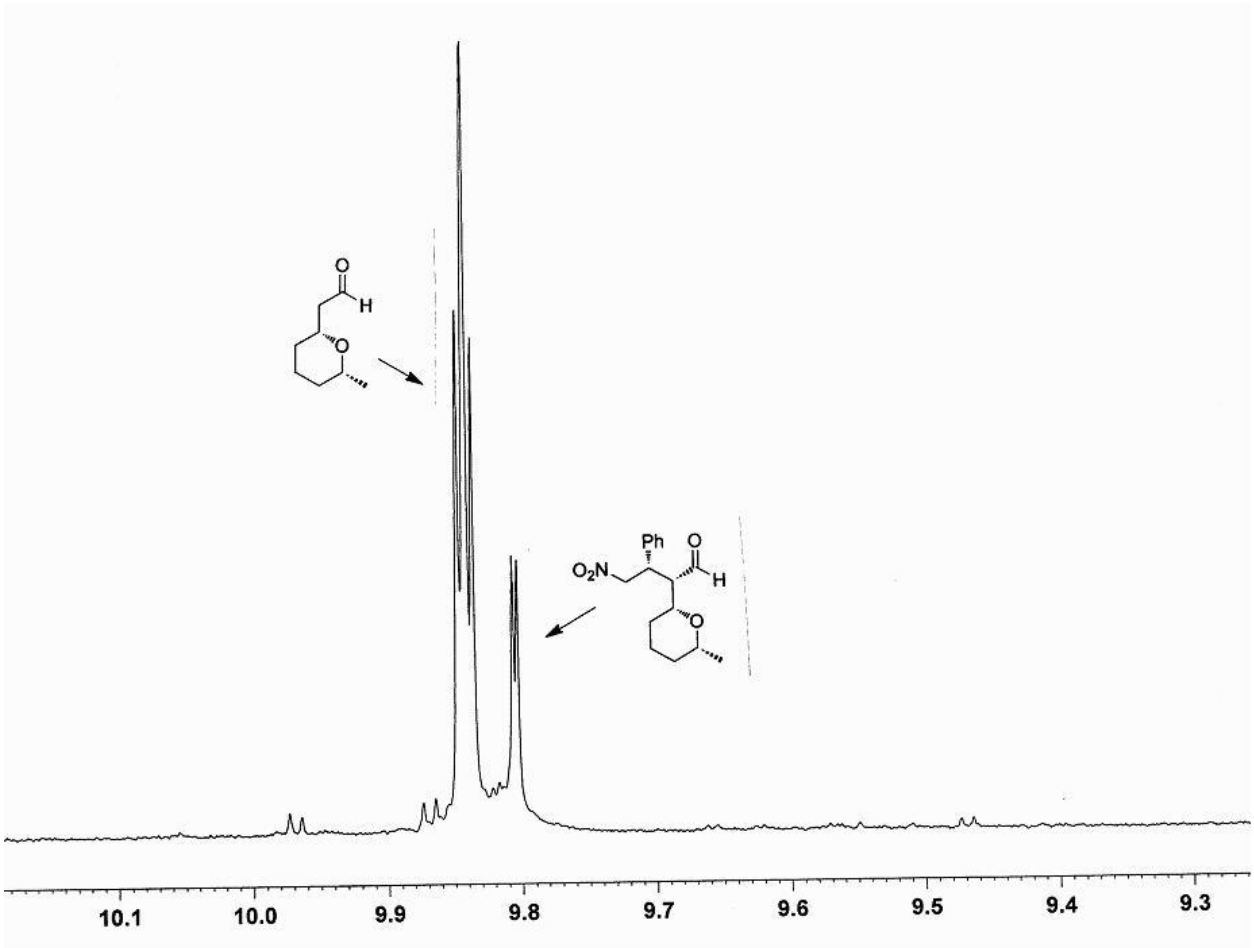


NMR analysis of the reaction with **(*R*)-5.16a**, depicted in **Scheme 5.11**, showed a distinct major peak for aldehyde **5.17a** as a multiplet at 9.84 ppm. The absolute configuration of **5.17a** was determined by comparison to the optical rotation data in the literature.[16] A small amount of "undesired" aldehyde **5.31a** (a result of the "undesired" reaction of **(*R*)**–**5.16a** with **1.23a**) is

observed as well. The "undesired" product **5.31a** was determined to have a *cis* configuration via NOE NMR.

Scheme 5.11 Reaction with **(*R*)-5.16a**

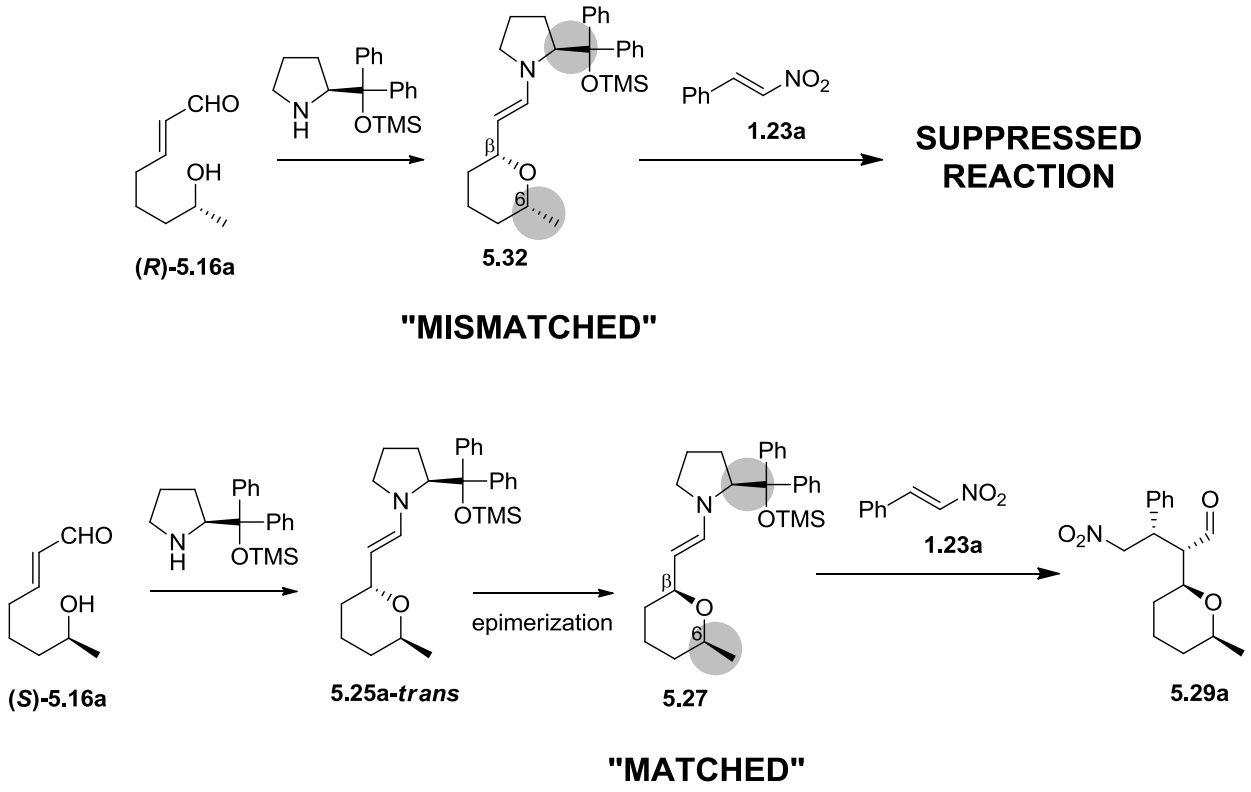




The initial stereochemical model that was conceived for this organocascade kinetic resolution process is illustrated in **Figure 5.6**. Enamine **5.32** is formed after the initial oxa-Michael addition and enamine **5.27** is formed after the initial oxa-Michael addition, and

epimerization of **5.25a-*trans***. Enamine **5.27** has the bulky group of the catalyst and the methyl group at the 6-position of the substrate shielding the same face of the complex. This synergistic relationship allows the β-nitrostyrene to approach from the opposite face to form cascade product **5.29a**. In the "mismatched" enamine, **5.32**, the bulky group of the catalyst and the methyl group at the 6-position of the substrate shield opposite faces. This was thought to suppress the reaction with β-nitrosyrene almost completely, because **1.23a** cannot readily approach from either face.

Figure 5.6 Initial Stereochemical Model for the Kinetic Resolution

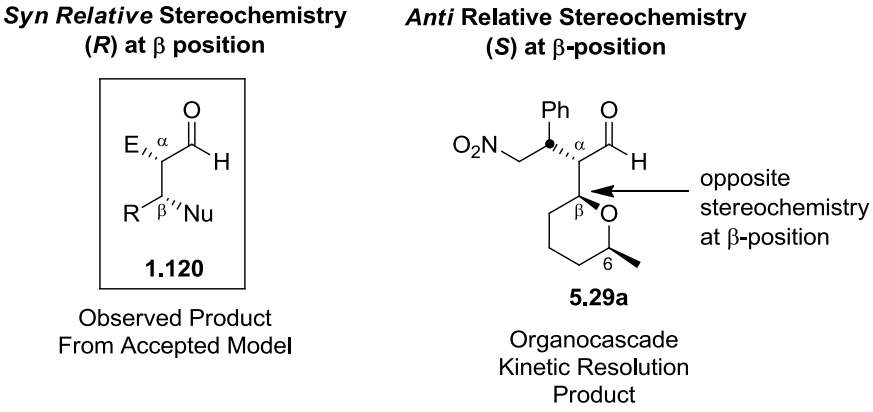


It could be suggested that the difference in stereochemistry at the β-position could also be responsible for the observed kinetic resolution. However, as previously demonstrated in **Scheme 5.5**, the same reaction involving a substrate without a substituent at the 6-position gave both

cascade product **5.14a** and cascade product **5.14b** in approximately a 1/1 ratio. From this result, it seemed that the stereocenter at the 6-position of the oxa-Michael enamine intermediate is responsible for this kinetic resolution, while the stereochemical configuration at the β-position is largely irrelevant for these substrates.

As discussed earlier, the accepted model for iminium–enamine cascade reactions catalyzed by **1.12a**, involves α and β functionalization of the α,β-unsaturated aldehyde starting material from the opposite face of the bulky group of the catalyst to give cascade products of type **1.120** with a *syn* stereochemical relationship between the α and β substituents and an absolute stereochemistry of (*R*) at the β position (**Figure 5.7**). Interestingly, the organocascade kinetic resolution process which was developed provided the *anti* iminium–enamine cascade product **5.29a**, with (*S*) absolute stereochemistry at the β position of the aldehyde. The accepted model proposes that the catalyst has exclusive control over the stereochemistry of the product, but in this kinetic resolution, the configuration at the 6-position of the substrate also seems to control the stereochemical outcome of the reaction, suggesting that the stereochemical outcome of reactions catalyzed by **1.12a** may be more complex than has been previously reported.

Figure 5.7 *Anti* stereochemistry of Cascade Product **5.29a**

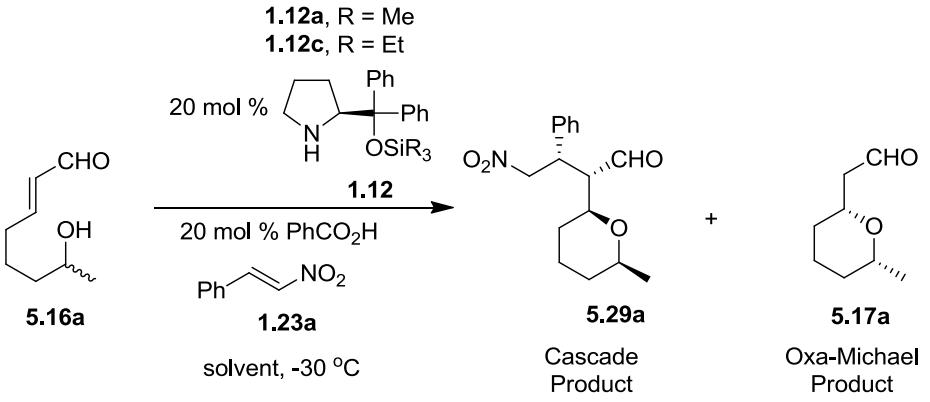


Additionally, the reaction developed was the first organocascade kinetic resolution. There are only a few examples of kinetic resolutions which are mediated by enamine catalysis.[17-21] Moreover, of those kinetic resolutions, only one of them utilized diarylprolinol silyl ether organocatalysts.[21]

5.2.7 Optimization of Organocascade Kinetic Resolution

A few optimization steps were undertaken for the newly developed organocascade kinetic resolution process (**Table 5.7**). The bulkier catalyst **1.12c** furnished similar results to those of **1.12a**, but with a slightly lower enantiomeric excess for the oxa-Michael product **5.17a (**Entry 1 vs. 2**)**. Interestingly, this kinetic resolution was found to be highly solvent dependent. There was no kinetic resolution observed in $CHCl_3$ (Entry 3). The reaction provided both cascade products in approximately a 1/1 ratio. In THF, the enamine–catalyzed Michael addition to β-nitrostyrene was completely suppressed (Entry 4) giving only the oxa-Michael product **5.17a** as a racemic mixture. In *i*PrOH the selectivity of the kinetic resolution was markedly reduced relative to that when the reaction was conducted in toluene (Entry 5 vs. Entry 1).

Table 5.7 Optimization Of the Organocascade Kinetic Resolution

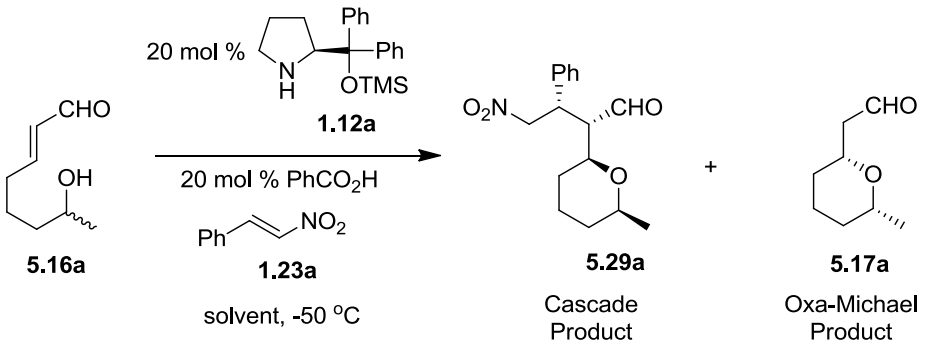


Entry	Catalyst	Solvent	Time (h)	% conv **5.29a**/**5.17a**[a]	dr (**5.29a**)[a]	ee **5.29a**/**5.17a**[b]
1	**1.12a**	toluene	112	42/45	91/9	99/90
2	**1.12c**	toluene	144	42/43	89/11	99/89
3	**1.12a**	$CHCl_3$	66	39/0	63/37	99/NA
4	**1.12a**	THF	66	0/69	NA	NA
5	**1.12a**	*i*PrOH	72	27/45	67/33	NA

Reaction Conditions: **5.16a** (0.44 mmol), **1.23a** (0.88 mmol), **1.12** (0.088 mmol), $PhCO_2H$ (0.088 mmol), solvent (1.1 mL), -30 °C. [a] Determined by ^1H NMR of the crude reaction mixture prior to in situ reduction. [b] Determined by chiral phase HPLC of PNB derivative of the corresponding alcohols of **5.17a** and **5.29a**.

Using lower temperatures in an effort to improve the selectivity of the kinetic resolution required the use of solvents other than toluene, as there were issues with the solubility of the catalyst and $PhCO_2H$ in toluene at lower temperatures. The reaction was set up with $CHCl_3$ at –50 °C due to the increased solubility of the catalyst in $CHCl_3$ at low temperatures. Once again no kinetic resolution was observed in $CHCl_3$ (Entry 1, **Table 5.8**). Running the reaction at –50 °C in toluene/$CHCl_3$ (3/1) gave poor results as well, relative to the reaction in toluene at –30 °C (Entry 2, **Table 5.8** vs. Entry 1, **Table 5.7**).

Table 5.8 Lower temperatures in the Optimization Of the Organocascade Kinetic Resolution



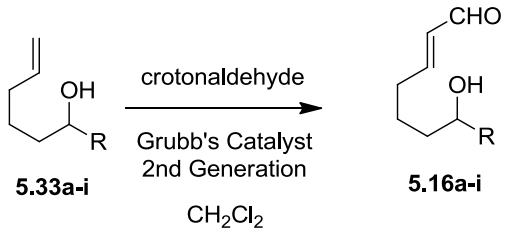
Entry	Solvent	Time (h)	% conv **5.29a**/**5.17a**[a]	dr (**5.29a**)[a]	% ee **5.29a**/**5.17a**[b]
1	$CHCl_3$	72	25/19	66/34	NA
2	toluene/$CHCl_3$	120	29/45	85/15	NA

Reaction Conditions: **5.16a** (0.44 mmol), **1.23a** (0.88 mmol), **1.12a** (0.088 mmol), $PhCO_2H$ (0.088 mmol), solvent (1.1 mL), -50 °C. [a] Determined by ^1H NMR of the crude reaction mixture prior to in situ reduction. [b] Determined by chiral phase HPLC of PNB derivative of the corresponding alcohols of **5.17a** and **5.29a**.

5.2.8 Organocascade Kinetic Resolution Substrate Scope

With the optimal conditions in hand (**Table 5.7,** Entry 1) an investigation of the substrate scope of the reaction was undertaken. Alcohols **5.33a–i** were subjected to a cross metathesis reaction with crotonaldehyde to give substrates **5.16a–i** (**Scheme 5.12**).

Scheme 5.12 Synthesis of Substrates Via Cross Metathesis

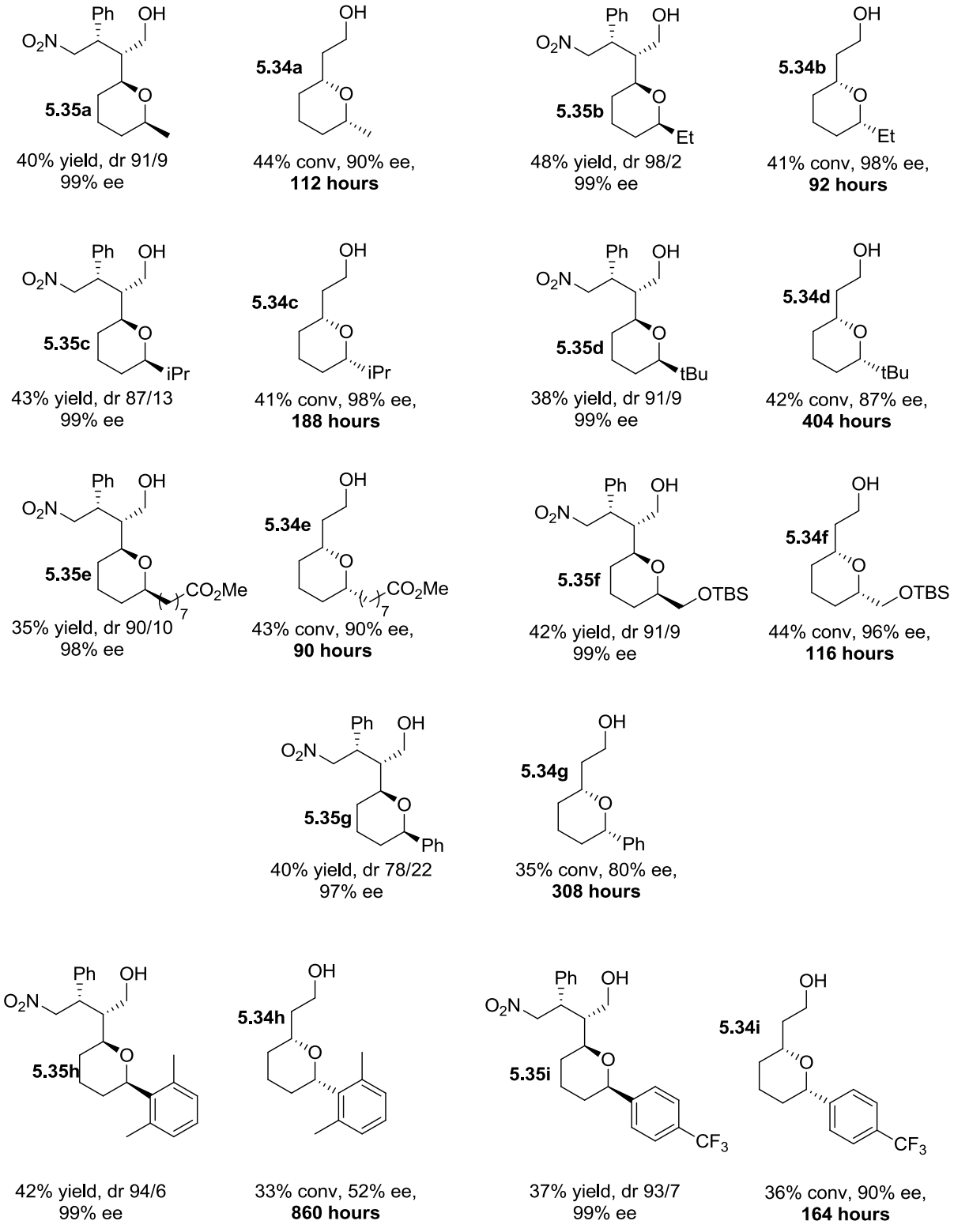


5.16a, R = Me, 80%
5.16b, R = Et, 75%
5.16c, R = *i*Pr, 73%
5.16d, R = *t*Bu, 70%
5.16e, R = $(CH_2)_7CO_2Me$, 79%
5.16f, R = CH_2OTBS, 62%
5.16g, R = Ph, 80%
5.16h, R = 2,6-Me-C_6H_3, 86%
5.16i, R = 4-CF_3-C_6H_4, 73%

The results of the initial study with substrates **5.16a**–**i** are illustrated in **Figure 5.8**. All products were isolated and characterized as the corresponding alcohols after in situ reduction of the reaction mixture, giving oxa-Michael products **5.34a**–**i** and cascade products **5.35a**–**i**.

The kinetic resolution was very efficient for substrates with sp^3–hybridized R groups (**5.16a**–**f**), with both products **5.34a**–**f** and **5.35a**–**f** being collected in high conversion and high yield, and with great diastereo– and enantioselectivity. The ethyl and isopropyl substituted substrates (**5.16b** and **5.16c**) afforded excellent enantiomeric excesses for the cascade products (**5.35b** and **5.35c**) as well as for the oxa-Michael products (**5.34b** and **5.34c**). The reaction with the *tert*-butyl substituted substrate **5.16d** required a slightly longer reaction time, but it produced both products **5.34d** and **5.35d** in good conversion and yield respectively, but with a slightly reduced enantiomeric excess for the oxa-Michael product **5.34d**. The ester substrate **5.16e** and the silyl protected alcohol substrate **5.16f** also furnished high yields of **5.35e**–**f** and high conversion to **5.34e**–**f** with excellent diastereo– and enantioselectivities.

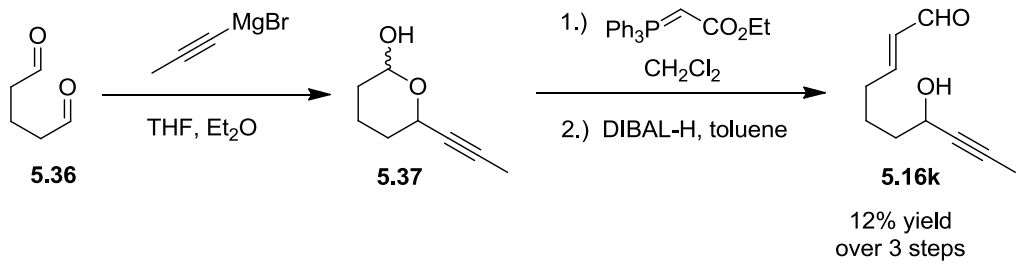
Figure 5.8 Organocascade Kinetic Resolution: Initial Substrate Study



Interestingly, substrates containing sp^2–hybridized R groups were not as well tolerated (**5.16g**–**i**). A much larger amount of the "undesired" cascade product (the product of **5.17**–***cis*** reacting with β-nitrostyrene) was observed. This less efficient resolution resulted in reduced conversions to, and enantiomeric excesses of, the oxa-Michael product **5.34**. The phenyl substituted substrate **5.16g** required longer reaction times and exhibited only moderate diastereoselectivity for cascade product **5.35g**. The cascade product **5.35g** was isolated with excellent enantioselectivity, but the oxa-Michael product **5.34g** was isolated in 80% ee (slightly less than that observed for substrates with sp^3–hybridized substituents). The sterically hindered dimethylated substrate **5.16h** required extended reaction times, but yielded less of the "undesired" cascade product than the phenyl substituted substrate. The product distribution of the oxa-Michael and cascade products was similar to that observed with other substrates which afforded high ee's of both products, but the oxa-Michael product **5.34h** was collected in only 50% ee (much less than that observed with other substrates). As stated before, this reaction required extended reaction times and it is hypothesized that epimerization may have occurred at the β position via a retro-oxa-Michael process and at the benzylic carbon through a carbocation intermediate, significantly reducing the ee of oxa-Michael product **5.34h**. The electron–poor trifluoromethyl–substituted substrate **5.16i** required a slightly shorter reaction time than **5.16g**. It also underwent a slightly better resolution than **5.16g**, giving both products **5.34i** and **5.35i** in good conversion and yield respectively, and giving cascade product **5.35i** with much better diastereoselectivity than that observed for **5.35g**. The oxa-Michael product **5.34i** was also collected with much better enantioselectivity relative to **5.34g** as well.

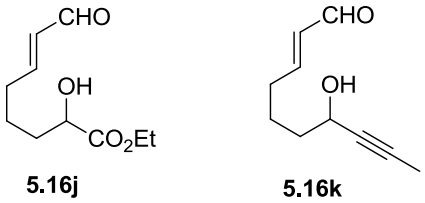
Substrate **5.16j** (**Figure 5.9**) was synthesized in 75% yield using the same cross metathesis procedure used for the synthesis of **5.16a**–**i**. Substrate **5.16k** was synthesized using the three–step process shown in **Scheme 5.13**.

Scheme 5.13 Synthesis of Substrate **5.16k**



Glutaraldehyde **5.36** was reacted with an alkynyl Grignard reagent to give hemiacetal **5.37**. Hemiacetal **5.37** was subjected to Wittig olefination to give an ester which was then reduced to the corresponding aldehyde **5.16k** using DIBAL-H. Attempts to conduct the same organocascade kinetic resolution with substrates **5.16j** and **5.16k** (**Figure 5.9**), containing sterically smaller R groups, were unsuccessful.

Figure 5.9 Substrates with Smaller R groups

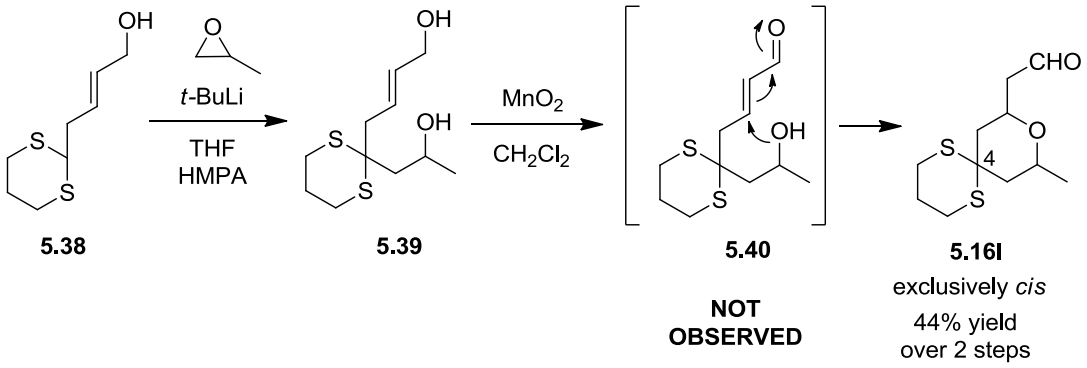


For both substrates **5.16j** an **5.16k**, ^{1}H NMR revealed that the *trans* oxa-Michael intermediate (i.e. analogous to **5.17a**–***trans***) persisted in the reaction mixture. It was suspected that this was due to the fact that there is a smaller energy difference between the preferred

conformations of the *cis* and *trans* configurations of the oxa-Michael intermediate **5.17** when a less bulky tetrahydropyrnayl substituent is involved. As a result of this, the *trans* intermediates, in addition to the *cis* intermediates, might have been reacting with β-nitrostyrene via enamine catalysis. This afforded a much more complex mixture of cascade reaction products, as opposed to one major cascade product, as was observed with substrates **5.16a**–**i**.

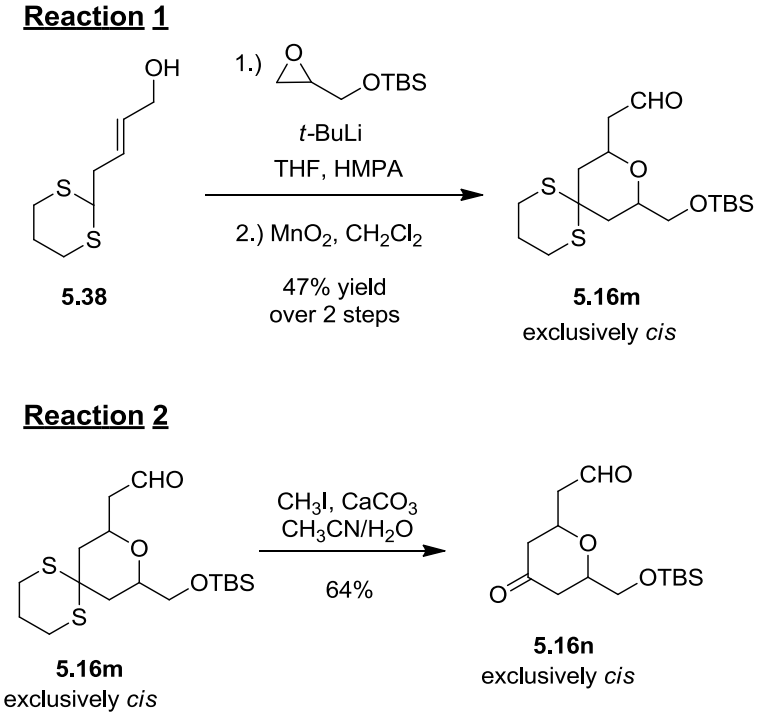
Attempts to expand the scope of the kinetic resolution to aldehydes substituted at the 4-position of the pyran ring were undertaken as well (**Scheme 5.14**). Dithiane **5.38**[22] was used in an epoxide ring opening reaction to give diol **5.39**. Subjecting diol **5.39** to allylic oxidation conditions resulted in an oxidation and in situ oxa-Michael addition which produced **5.16l**, exclusively as the *cis* diastereomer. None of the uncyclized aldehyde **5.40** was observed. This induced cyclization of **5.40** was likely due to the Thorpe–Ingold effect created by the dithiane ring.

Scheme 5.14 Synthesis of Substrate **5.16l**



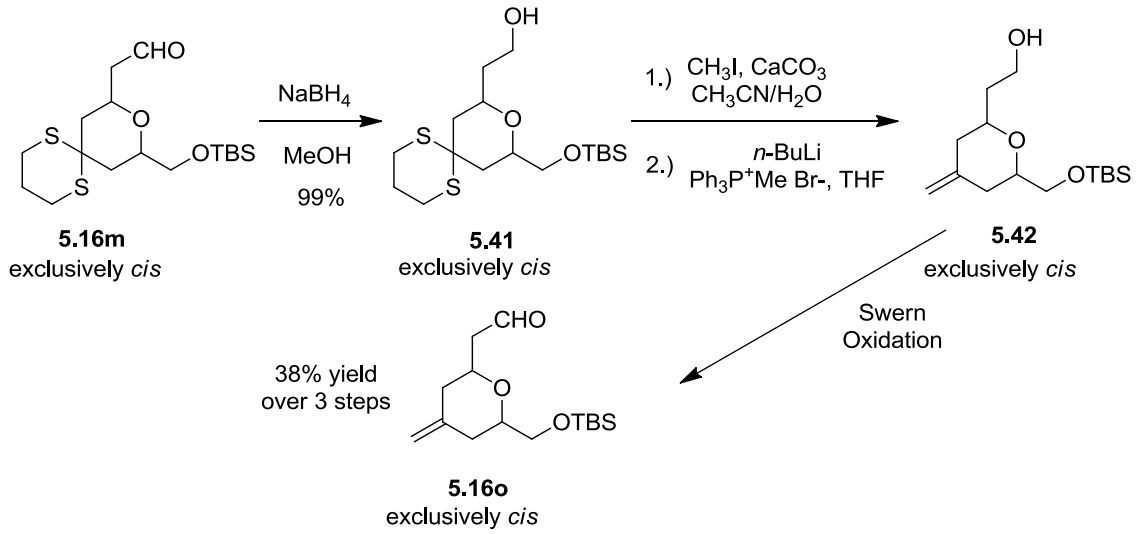
Substrate **5.16m** was synthesized as well using the same two–step process (**Scheme 5.15**, Reaction 1). A portion of dithiane substrate **5.16m** was deprotected to give substrate **5.16n** (**Scheme 5.15**, Reaction 2).

Scheme 5.15 Synthesis of Substrates **5.16m** and **5.16n**



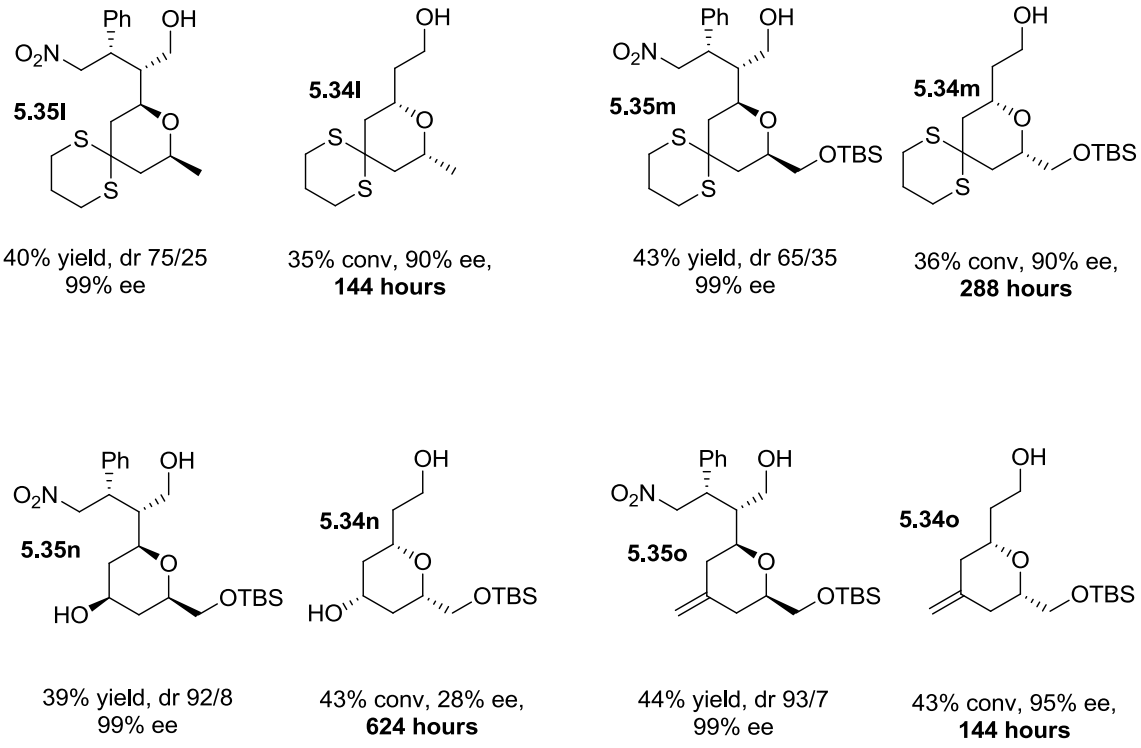
Substrate **5.16m** was also reduced with $NaBH_4$ affording alcohol **5.41**. After removal of the dithiane ring and olefination of the resulting ketone, **5.42** was produced and subsequently reoxidixed to give olefin substrate, **5.16o** (**Scheme 5.16**).

Scheme 5.16 Synthesis of Substrate **5.16o**



The results for the organocatalytic resolution with substrates **5.16l**–**o** are shown in **Figure 5.10**. Substrates **5.16l**–**o** were subjected to the organocascade kinetic resolution reaction conditions as racemic *cis* tetrahydropyrans. Dithianes **5.16l** and **5.16m** furnished the cascade products (**5.35l** and **5.35m** respectively) and oxa-Michael products (**5.34l** and **5.34m** respectively) in good yields and conversions with excellent enantioselectivity. However, the diastereomeric ratio of the cascade products **5.35l** and **5.35m** was moderate, being 75/25 and 65/35 respectively.

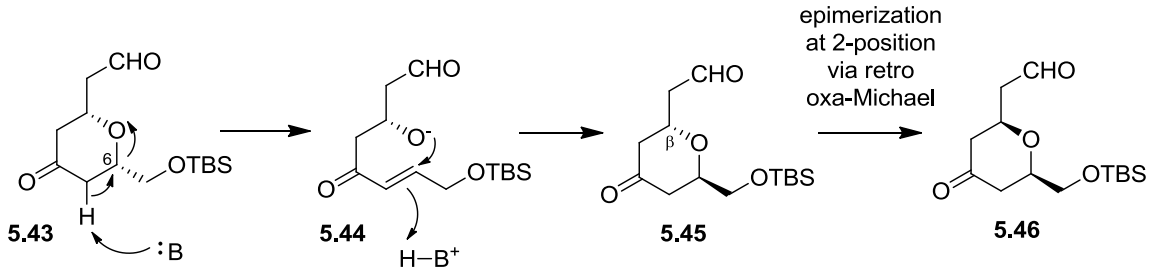
Figure 5.10 Organocascade Kinetic Resolution: 4-position Substrate Study



The reaction with ketone substrate **5.16n**, in which both the aldehyde and the ketone were reduced during the in situ reduction at the conclusion of the reaction, gave a good yield of cascade product **5.35n** with great enantioselectivity, despite extended reaction times. Although the oxa-Michael product **5.34n** was collected in good yield, and the reaction was stopped when the cascade product and the oxa-Michael product were in an approximately 1/1 ratio (with no other side products observed), the enantiomeric excess of oxa-Michael product **5.34n** was only 28%, which is markedly reduced from that normally observed with other substrates. It was speculated that the oxa-Michael intermediate **5.43** may have undergone base–catalyzed epimerization at the 6-position via β-alkoxide elimination, with catalyst **1.12a** possibly acting as the base (**Scheme 5.17**). This process could have afforded the *trans* intermediate, **5.45** (via intermediate **5.44**), which could undergo thermodynamically driven epimerization at the β-

position, via a retro–oxa-Michael reaction, to give **5.46**, the enantiomer of **5.43**. This ring opening/closing process could have led to the reduced % ee of **5.32n**, and is a dynamic kinetic resolution process.

Scheme 5.17 Epimerization in Reaction with Substrate **5.16n**



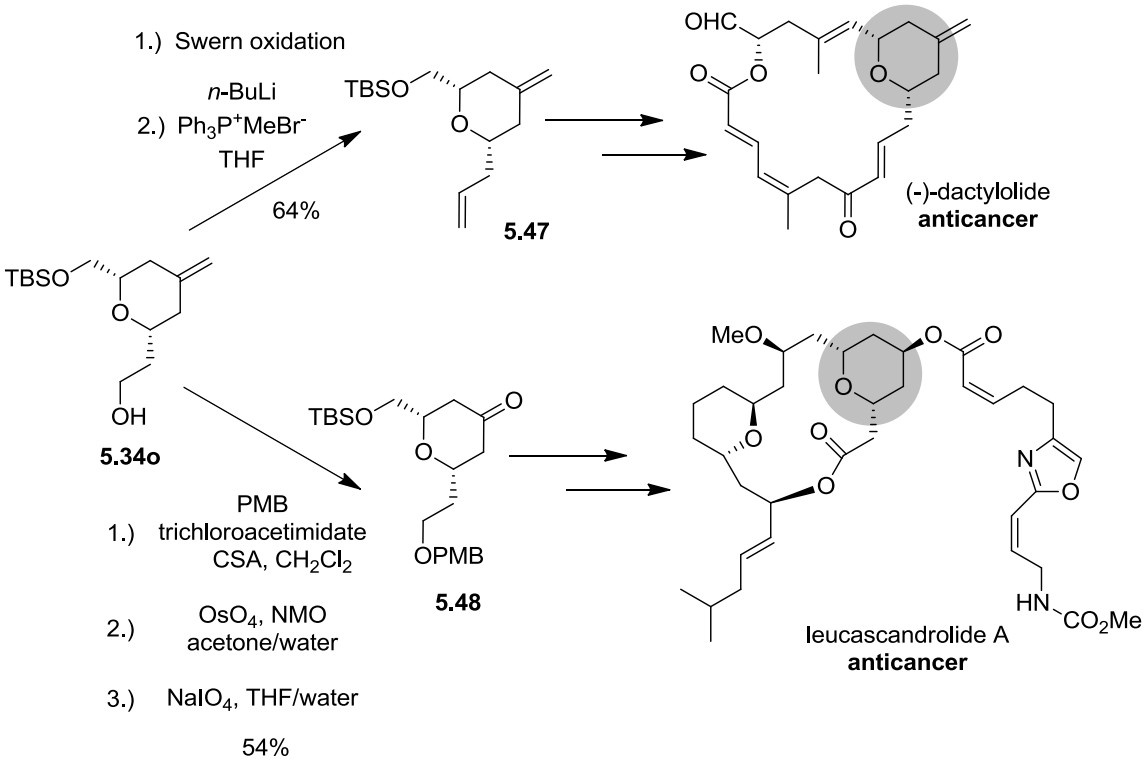
The reaction with substrate **5.16o** gave excellent yields and conversions to **5.35o** and **5.34o**. Both were collected with excellent enantioselectivity and cascade product **5.35o** exhibited a very good diastereomeric ratio. This same reaction was conducted on a large scale (1 gram) as well, without any serious reduction in yield or selectivity. On this larger scale, oxa-Michael product **5.34o** was collected in 45% conversion in 95% ee and cascade product **5.35o** was collected in 42% yield with a dr of 16/1 and and in 99% ee.

5.2.9 Synthesis of Natural Product Precursors

Oxa-Michael product **5.34o** is synthetically useful in that it can be converted to precursors for two different biologically active natural products (**Scheme 5.18**). Product **5.34o** was oxidized and then subjected to olefination conditions to give **5.47**, a precursor to (-)-dactylolide.[23] This natural product has displayed cytotoxicity toward L1210 (lymphatic leukemia) and SK-OV-3 (ovarian cancer) cell lines. The alcohol in **5.34o** was protected as its PMB ether.

Dihydroxylation of the olefin, followed by oxidative cleavage gave the corresponding ketone, **5.48**. Product **5.48** is a precursor to leucascandrolide A, which shows strong cytotoxic activity towards KB and P388 cancer cell lines as well as antifungal activity.[24]

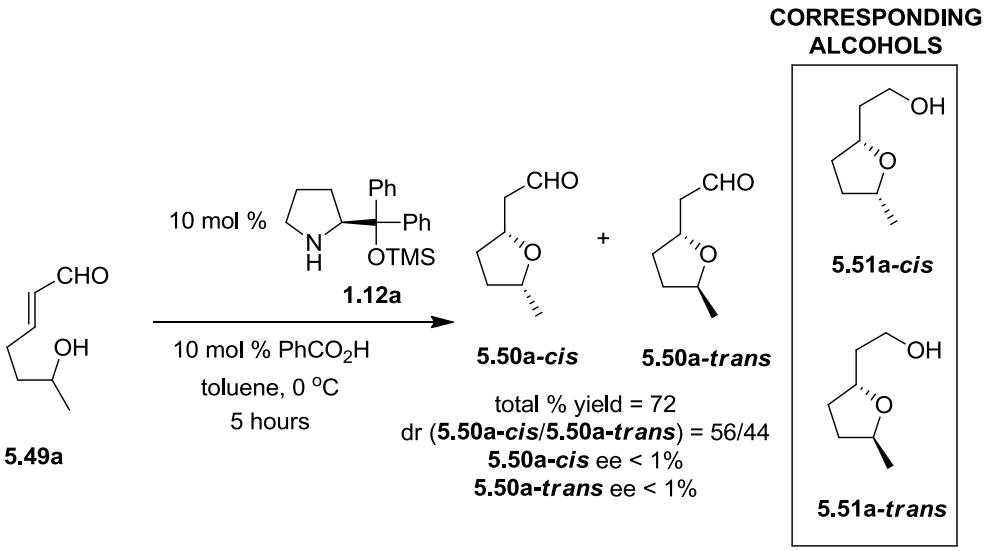
Scheme 5.18 Synthesis of Precursors to Biologically Active Natural Products



5.2.10 Synthesis of Chiral Furans: Oxa-Michael Reaction

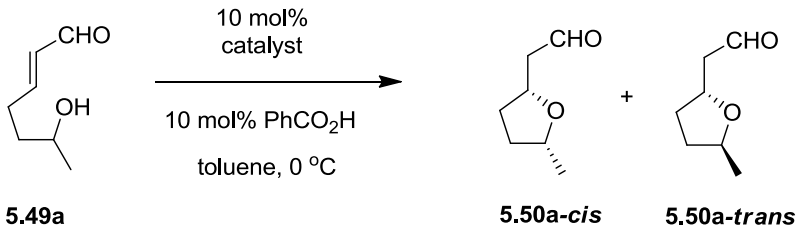
Attempts to extend this organocascade kinetic resolution reaction to generate 2,5-disubstituted tetrahydrofurans were undertaken. This study began with the examination of the intramolecular oxa-Michael reaction of racemic **5.49a** to **5.50a**–***cis*** and **5.50a**–***trans***, catalyzed by **1.12a**. The initial results of this study are summarized in **Scheme 5.19**.

Scheme 5.19 Oxa-Michael Addition to Give Furans: Initial Results



The product aldehydes **5.50a**–***cis*** and **5.50a**–***trans*** were reduced in situ to their corresponding alcohols **5.51a**–***cis*** and **5.51a**–***trans***. The reaction gave both diastereomers in a combined yield of 72% with an approximately 1/1 ratio of **5.50a**–***cis***/**5.50a**–***trans***. Interestingly the reaction was not enantioselective, giving both **5.50a**–***cis*** and **5.50a**–***trans*** in <1% ee. Acid or base catalysis (rather than iminium catalysis) of this reaction would result in a non–selective reaction. The base–catalyzed reaction and the acid–catalyzed reaction were both set up to test this possibility. Those results, along with the initial results, are shown in **Table 5.9**. The relative configurations of **5.51a**-*cis* and **5.51a**-*trans* were determined by NOE.

Table 5.9 Oxa-Michael Addition to Give Furans: Base and Acid Catalysts



5.49a **5.50a-*cis*** **5.50a-*trans***

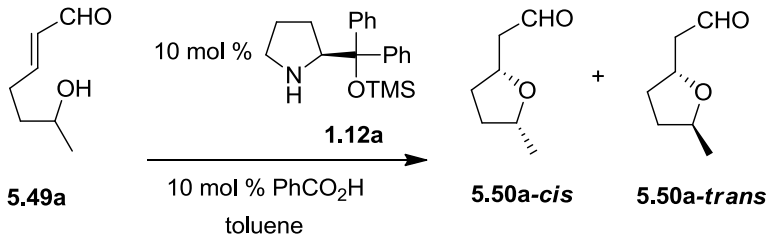
Entry	Catalyst	Time (h)	% Yield[a]	dr *cis*/*trans*[b]	% ee *cis*/*trans*[c]
1	**1.12a**[e]	5	72	56/44	<1/<1
2	Et_3N	20	10[d]	--	--
3	--	20	6[d]	--	--

Reaction Conditions: **5.49a** (0.4 mmol), cat. (0.04 mmol), $PhCO_2H$ (0.04 mmol), toluene (1 mL). [a] Isolated yield of corresponding alcohol generated by in situ reduction. [b] Determined by ^1H NMR of the isolated alcohol products. [c] Determined by chiral phase HPLC of PNB derivative of the corresponding alcohols of **5.50a-*cis*** and **5.50a-*trans*.** [d] % conversion determined by ^1H NMR of reaction mixture. [e] 10 mol % $PhCO_2H$ additive used.

The **1.12a** catalyzed reaction afforded the products in 72% yield after only 5 hours (Entry 1). The base–catalyzed reaction with Et_3N gave only 10% conversion to product after 20 hours (Entry 2) and the acid–catalyzed reaction with $PhCO_2H$ gave only 6% conversion to product after 20 hours (Entry 3). From these results it was deduced that the process was most likely iminium–catalyzed (as with the pyran forming oxa-Michael addition).

The reaction was analyzed at various time points (prior to 100% conversion) to see if the enantioselectivity of the reaction was eroding over the 5 hour reaction time, ultimately leading to a racemic reaction mixture. The same reaction, catalyzed by **1.12a**, when stopped after 3 minutes, showed the exact same lack of enantioselectivity (**Table 5.10**, Entry 1 vs. Entry 2). Conducting the reaction at a lower temperature (Entry 3) and with a lower catalyst loading (Entry 4) both resulted in a reaction with no apparent enantioselectivity.

Table 5.10 Oxa-Michael Addition to Give Furans: Temperature and Catalyst Loading



Entry	Temp (^{o}C)	Time	% Yield[a]	dr *cis*/*trans*[b]	% ee *cis*/*trans*[c]
1	0	5 h	72	56/44	<1/<1
2	0	3 min	49	54/46	<1/<1
3	–30	2.5 h	60	57/43	<1/<1
4[d]	0	20 h	75	57/43	<1/<1

Reaction Conditions: **5.49a** (0.4 mmol), **1.12a** (0.04 mmol), $PhCO_2H$ (0.04 mmol), toluene (1 mL). [a] Isolated yield of corresponding alcohol generated by in situ reduction. [b] Determined by ^{1}H NMR of the isolated alcohol products. [c] Determined by chiral phase HPLC of PNB derivative of the corresponding alcohols of **5.50a-*cis*** and **5.50a-*trans*.** [d] 1 mol % **1.12a** and 1 mol % $PhCO_2H$ used.

Interestingly, the ratio of **5.48a**–***cis***/**5.48a**–***trans*** did not change over time (**Table 5.10**, Entry 1 vs. Entry 2). This was in contrast to the corresponding pyran forming reaction described earlier, where the *trans* product rapidly converted to the *cis* product, thereby changing the *cis*/*trans* ratio (**Table 5.2**). Evidently, this same thermodynamic preference for the *cis* product did not exist for the furan forming reaction, as **5.50a**–***cis*** and **5.50a**–***trans*** were collected in approximately a 1/1 ratio for all reactions catalyzed by **1.12a**.

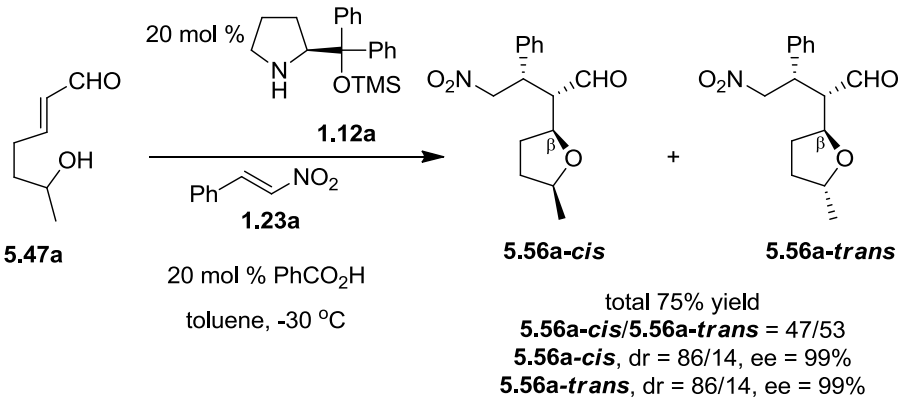
In total, these results suggested two potential reasons for the reaction's apparent lack of enantioselectivity. The first was simply that this iminium–catalyzed oxa-Michael addition was not selective. The second was that rapid interconversion of the oxa-Michael products (**5.50a**–***cis*** interconverting with ***epi***–**5.50a**–***trans*** and **5.50a**–***trans*** interconverting with ***epi***–**5.50a**–***cis***) was

occurring via an equilibrium process to give an approximately 1/1/1/1 mixture of all four stereoisomers.

5.2.11 Syntheis of Chiral Furans: Organocascade DKR

The same conditions used for the organocascade kinetic resolution for the synthesis of 2,6–disubstituted pyrans were applied to the 2,5–disubstituted furan forming reaction (**Scheme 5.20**).

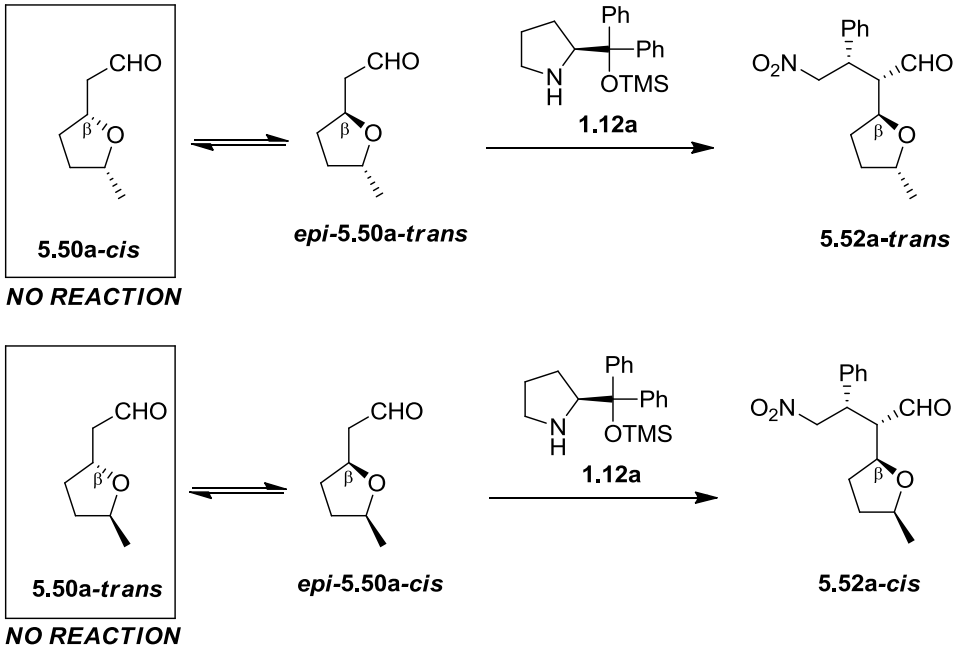
Scheme 5.20 Organocascade Dynamic Kinetic Resolution Forming Substituted Furans



In the presence of β-nitrostyrene (**1.23a**), only two major diastereomers, **5.52a**–***cis*** and **5.52a**–***trans***, were formed in approximately a 1/1 ratio, both with excellent enantio– and diastereoselectivity. While four oxa-Michael intermediates **5.50a**–***cis***, **5.50a**–***trans***, ***epi***–**5.50a**–***trans***, and ***epi***–**5.50a**–***cis*** existed in equilibrium in the reaction mixture after the initial oxa-Michael addition, only ***epi***–**5.50a**–***cis***, and ***epi***–**5.50a**–***trans*** went on to react with β-nitrostyrene to form the major cascade products, **5.52a**–***cis*** and **5.52a**–***trans***, via a dynamic kinetic resolution of the β-stereocenter (DKR) (**Scheme 5.21**). As ***epi***–**5.50a**–***trans*** and ***epi***–**5.50a**–***cis*** reacted with β-nitrostyrene, the equilibrium shifted from **5.50a**–***cis*** to ***epi***–**5.50a**–***trans*** and from **5.50a**–***trans***

to ***epi*–5.50a–*cis***. In this way, the equilibrium between the oxa-Michael intermediates and the propensity of the catalyst to react with only ***epi*–5.50a–*trans*** and ***epi*–5.50a–*cis*** resulted in the formation of only two major cascade products, **5.52a–*cis*** and **5.52a–*trans***. Unlike the organocascade kinetic resolution to generate pyrans described previously, this organocascade DKR to generate chiral furans gave access to both *cis* and *trans* cascade products.

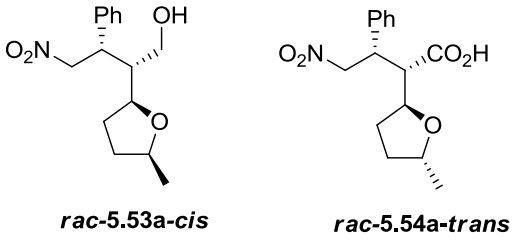
Scheme 5.21 Only Two Oxa-Michael Products React with β-nitrostyrene



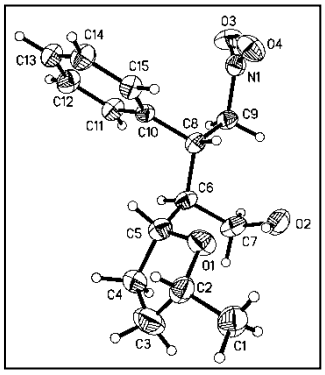
5.2.12 Determination of Configurations

The relative configuration of **5.52a–*cis*** was determined by X-ray crystallography of ***rac*–5.53a–*cis***, the corresponding alcohol of ***rac*-5.52a-*cis***. The relative configuration of **5.52a–*trans*** was determined by X-ray crystallography of ***rac*–5.54a–*cis***, the corresponding carboxylic acid of ***rac*-5.52a-*trans*** (**Figure 5.11**).

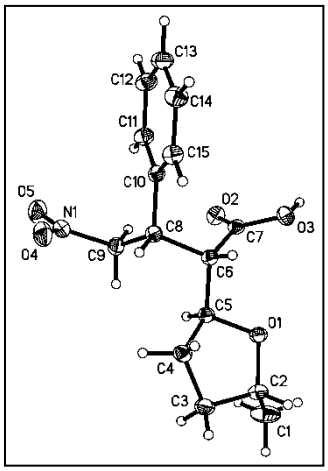
Figure 5.11 X-ray Structures of ***rac*–5.53a–*cis*** and ***rac*–5.54a–*cis***



rac*-5.53a-*cis ***rac*-5.54a-*trans***



rac*–5.53a–*cis

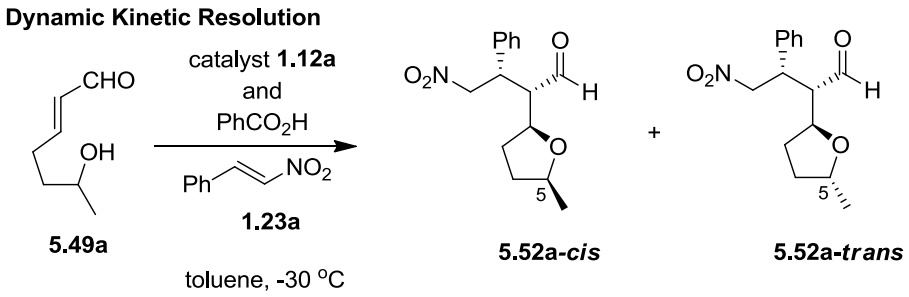


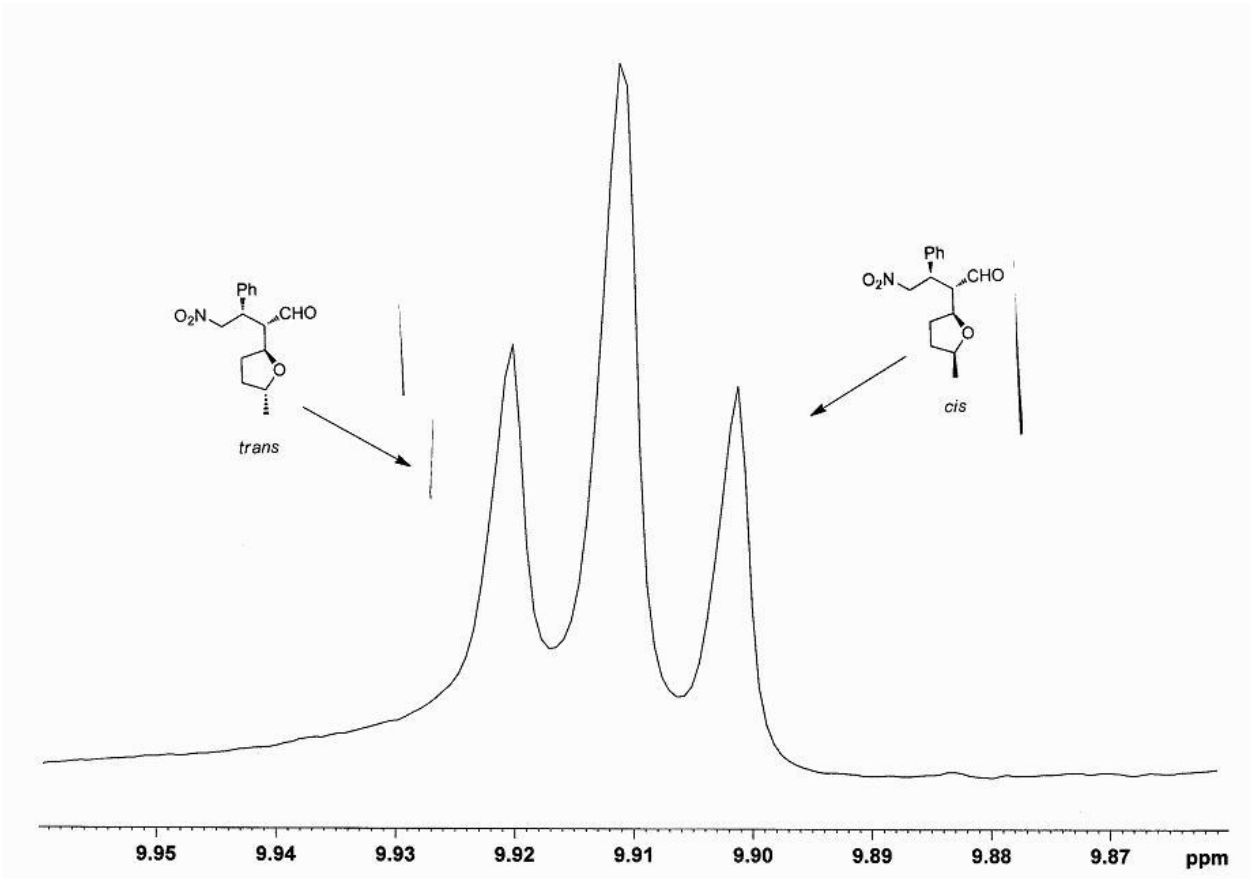
rac*–5.54a–*trans

The absolute configurations of **5.52a**–***cis*** and **5.52a**–***trans*** at the 5-position were determined by subjecting the pure chiral substrates **(*S*)**–**5.49a** and **(*R*)**–**5.49a** to the same kinetic resolution conditions as described above for **5.49a** (**Scheme 5.22**). The ^{1}H NMR spectra illustrated is for the organocascade DKR performed with **5.49a**. Products **5.52a**–***cis*** and **5.52a**–

trans are formed as the major products. The aldehyde protons for **5.52a**–***cis*** and **5.52a**–***trans*** appear in the proton NMR spectrum as two overlapping doublets at 9.916 ppm and 9.906 ppm, both with J = 3.6 Hz.

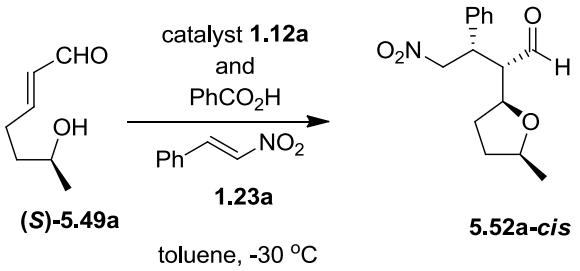
Scheme 5.22 ^{1}H NMR Spectra of the Organocascade DKR

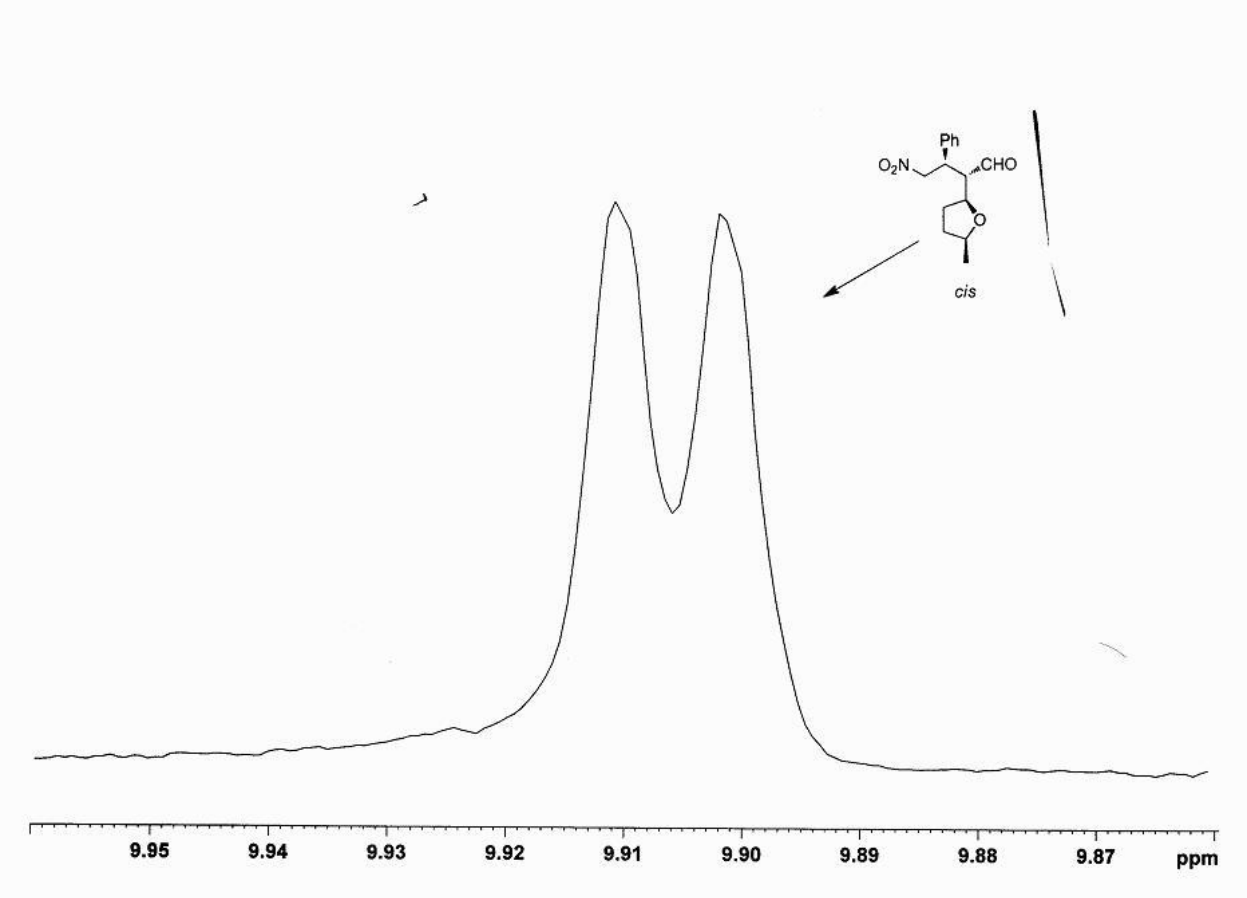




NMR analysis of the reaction with **(*S*)–5.49a** is depicted in **Scheme 5.23**. The ^{1}H NMR spectrum showed a distinct major peak for the aldehyde proton of **5.52a–*cis*** as a doublet (J = 3.6 Hz) at 9.906 ppm, confirming that 5.52a-cis has an *S*-configuration at the 5-position.

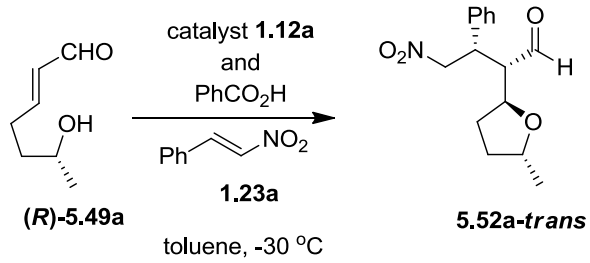
Scheme 5.23 Reaction with **(*S*)-5.49a**

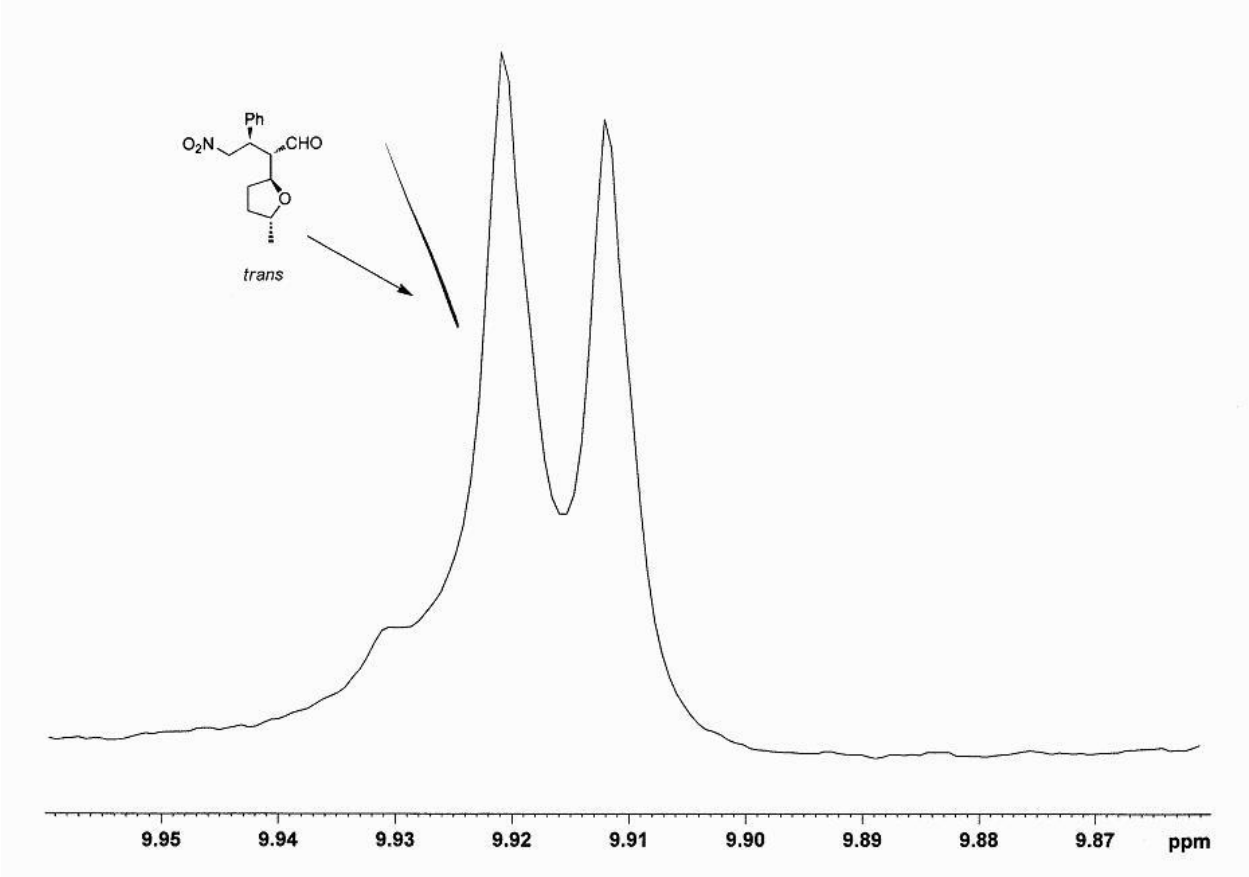




NMR analysis of the reaction with **(*R*)–5.49a** is depicted in **Scheme 5.24**. The ^{1}H NMR spectrum showed a distinct major peak for the aldehyde proton of **5.52a**–***trans*** as a doublet (J = 3.6 Hz) at 9.916 ppm, confirming that **5.52a**–***trans*** has an *R*-configuration at the 5-position.

Scheme 5.24 Reaction with **(*R*)-5.49a**

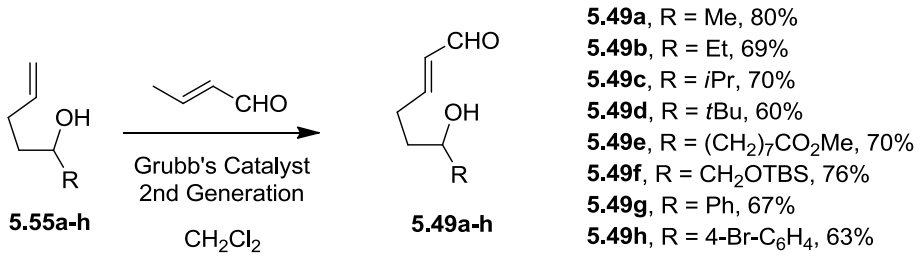




5.2.13 Substrate Scope of Organocascade DKR

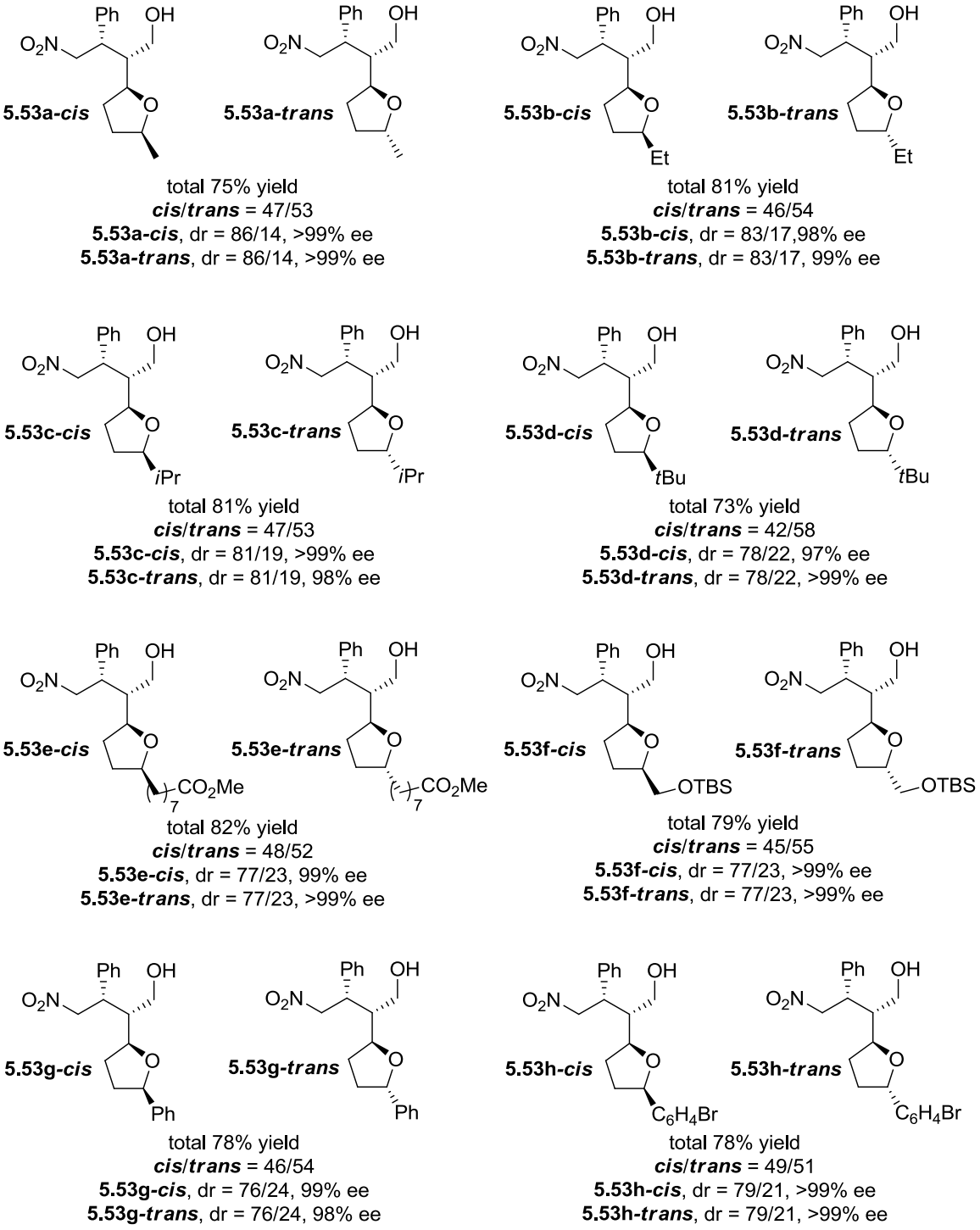
A study of the substrate scope of this organocascade DKR was undertaken. Substrates **5.49a**–**h** were synthesized from the corresponding secondary alcohols **5.55a**–**h**[25] via the cross metathesis reaction shown below in **Scheme 5.25**.

Scheme 5.25 Synthesis of Substrates **5.49a**–**h**



The results for this initial substrate study are displayed in **Figure 5.12**. All products were isolated and characterized as the corresponding alcohols after in situ reduction of the reaction mixture, giving both *cis* and *trans* products of **5.53a**–**h**.

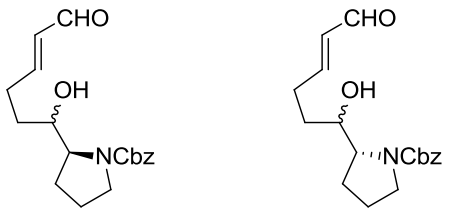
Figure 5.12 Organocascade DKR with Furans: Scope of the Reaction



All *cis* and *trans* products of **5.53a**–**h** were collected in good yields with excellent enantioselectivities, ranging from 97–99% ee. Substrates **5.49a**–**c**, containing small to medium sized sp^3–hybridized R groups, all furnished the *cis* and *trans* products of **5.53a**–**c**, in approximately a 1/1 ratio, with a slight excess of the *trans* product. The dr's for both the *cis* and *trans* products given by **5.49a**–**c** were greater than or equal to 4/1. Interestingly, substrate **5.49d**, containing a bulkier sp^3–hybridized R group, exhibited a smaller *cis*/*trans* ratio (**5.53d**–***cis***/**5.53d**–***trans*** = 42/58) than substrates **5.49a**–**c** and **5.49f**, containing smaller R groups. These results seemed to indicate that the larger the R group is, the more the *trans* isomer is thermodynamically favored over the *cis* isomer. Bulkier substrates **5.49d**–**f** also exhibited dr's less than 4/1 for both the *cis* and *trans* isomers, slightly lower than those observed with the less bulky substrates **5.49a**–**c**. Substrates **5.49g** and **5.49h**, containing sp^2–hybridized R groups, produced dr's for the *cis* and *trans* products slightly lower than 4/1 as well, however the *cis*/*trans* ratio for both **5.53g** and **5.53h** was nearly 1/1.

The two substrates depicted in **Figure 5.13**, **5.49i** and **5.49j**, were synthesized as 1/1 mixtures of diastereomers using the same cross metathesis reaction used for the synthesis of **5.49a**–**h**.

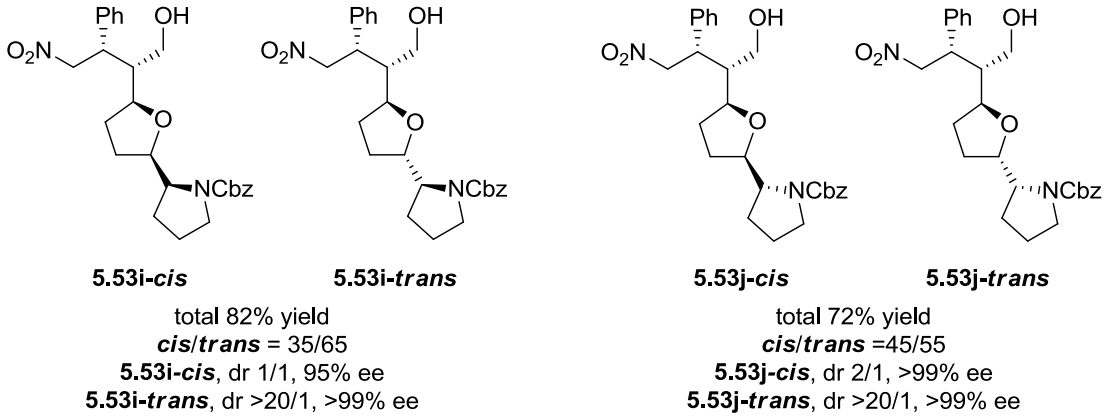
Figure 5.13 Proline Derived Substrates **5.49i** and **5.49j**



5.49i **5.49j**

The reason the organocascade DKR was conducted with these substrates was to assess the effect of an additional chiral center on the selectivity of the reaction. The results of the organocascade DKR conducted with these substrates are displayed in **Figure 5.14**.

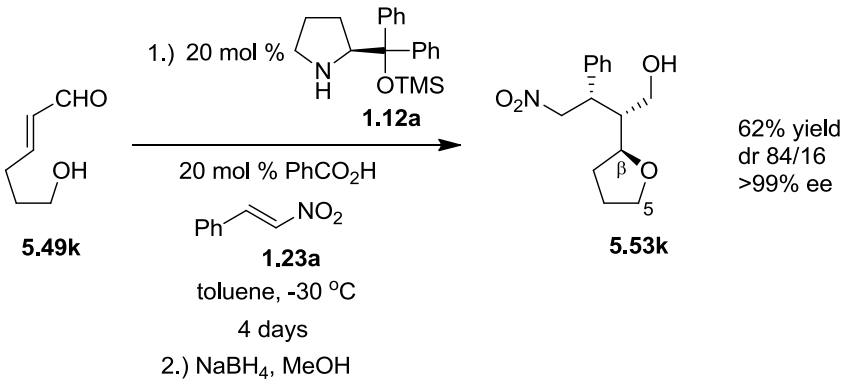
Figure 5.14 Proline Derived Products of Organocascade Kinetic Resolution



Both substrates **5.49i** and **5.49j** afforded the products, **5.53i** and **5.53j**, in good yield, and both the *cis* and *trans* diastereomers were collected with excellent enantioselectivity. The additional chiral center did have a dramatic effect on the diastereoselectivity of the organocascade DKR. The *cis* products for both reactions, **5.53i**–***cis*** and **5.53j**–***cis***, were collected with little to no diastereoselectivity. However, the *trans* products, **5.53i**–***trans*** and **5.53j**–***trans***, were collected with excellent diastereoselectivity.

The reaction with substrate **5.49k** (**Scheme 5.26**) was conducted to see if a selective resolution would occur when there was no stereocenter at the 5-position of the furan ring. Interestingly, this reaction demonstrated good selectivity, and provided only one major cascade product **5.53k**. This result contrasted with the result obtained from the corresponding *pyran* forming reaction (**Scheme 5.5**), which exhibited no kinetic resolution.

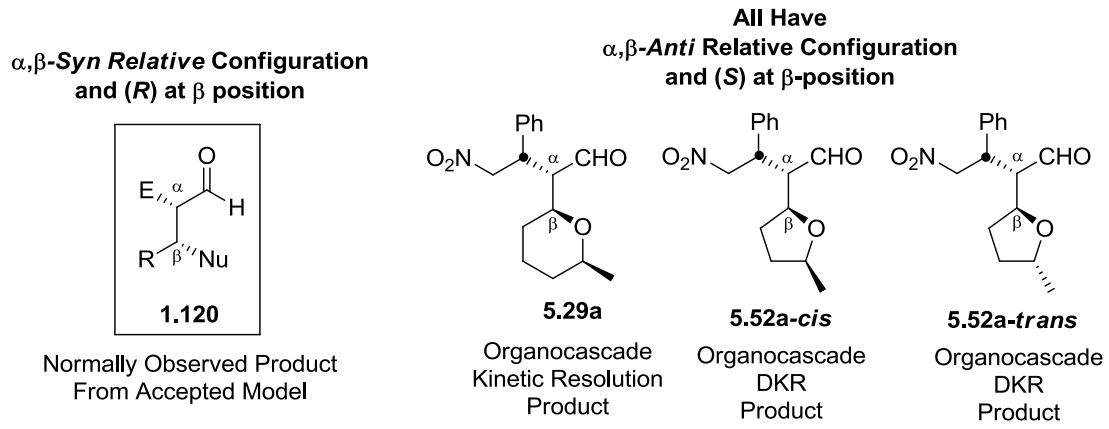
Scheme 5.26 Furan Cascade Reaction with No R Substituent



5.2.14 Stereochemical Modeling Study

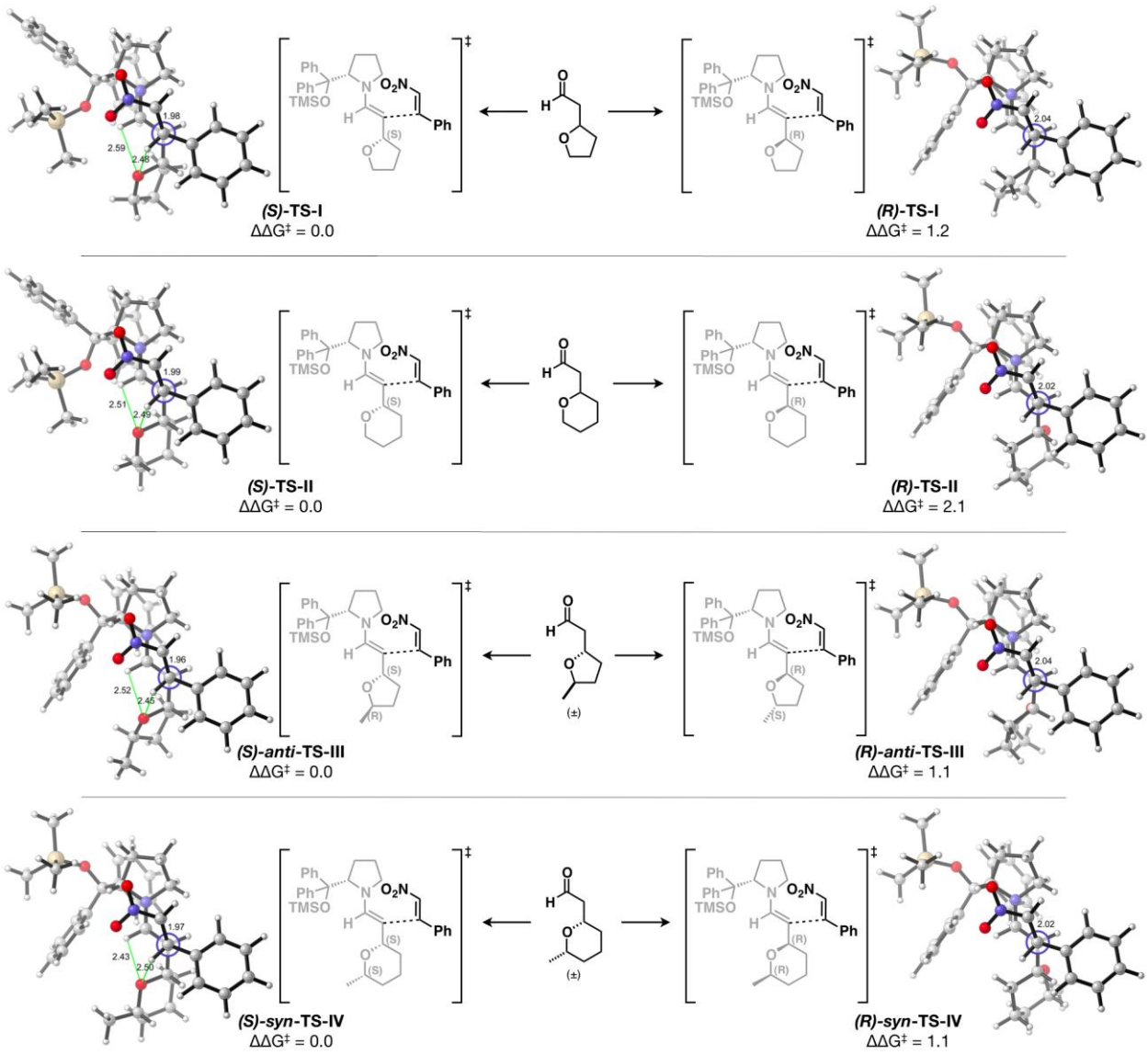
As with the *pyran* cascade products, all of the *furan* cascade products contained the same (*S*) absolute configuration at the β position and the same *anti* relative configuration between the α and β substituents (**Figure 5.15**). As described earlier, the relative configuration at the α and β positions and the absolute configuration at the β position are different than the configurations normally observed with catalyst **1.12a**. Once again, the fact that the stereochemical configuration of the substrate plays a large role in the stereochemical outcome of the reaction, suggests that the stereochemical outcome of reactions catalyzed by **1.12a** may not be exclusively dictated by the catalyst, as was previously imagined.

Figure 5.15 *Anti* and (*S*) Stereochemistry of Cascade Products



In seeking an explanation for this unprecedented stereochemical outcome, a computational study was undertaken in collaboration with Professor Paul Ha-Yeon Cheong at Oregon State University. Prior to studies with furan–forming substrates, as discussed earlier, it was proposed that synergistic blocking effects of the bulky catalyst and the substituent on the pyran were responsible for the reactivity of the enamine intermediates (**Figure 5.6**). Professor Cheong's modeling of various enamine intermediates revealed no difference in the accessibility of the reactive faces of the enamines, but modeling of the transition state of the C–C bond forming event between enamine intermediates and β-nitrostyrene revealed that transition states which give products with an (*S*)–configuration at the β-position are favored by >1.0 kcal/mol (**Figure 5.16**). As depicted in **Figure 5.16**, this is due to the presence of a stabilizing nonclassical hydrogen bond between the benzylic hydrogen in β-nitrostyrene and the oxygen of the heterocycle in the enamines. This type of stabilizing interaction has been demonstrated to affect the stereochemical outcome of other organocatalytic reactions as well.[26-31]

Figure 5.16 Transition State Modeling For Various Enamines

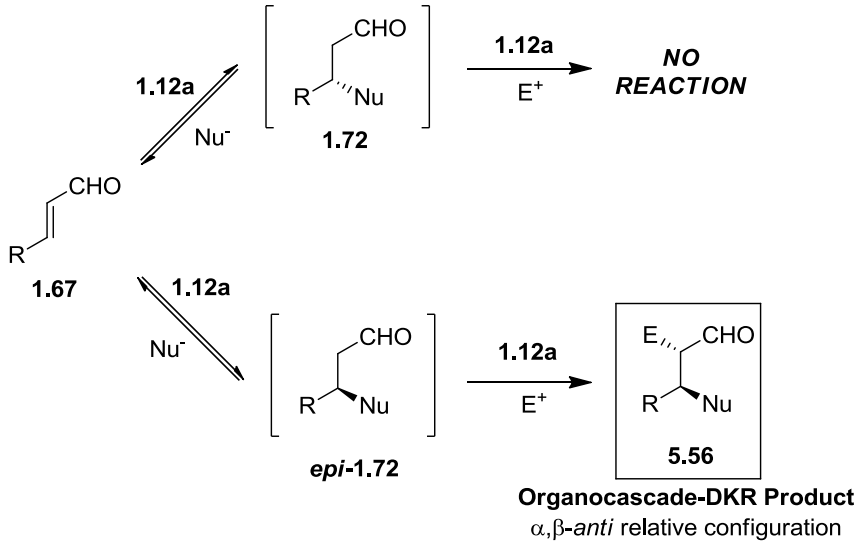


The modeling studies which were conducted for **TS-I**, **TS-III**, and **TS-IV** may explain the selectivity of this organocascade process for all substrates which demonstrated a resolution. However, the computational data does not account for the lack of selectivity arising from the reaction using substrate **5.13** (**Scheme 5.5**). An experiment was conducted to see if the corresponding aldehyde of **5.14a**, which has a (*S*)-configuration at the β-position, may have epimerized in the reaction mixture furnishing the unfavored (*R*)-aldehyde. However, when the

corresponding aldehyde of **5.14a** was resubjected to the original reaction conditions, no epimerization occurred.

The fact that the organocascade kinetic resolution and organocascade DKR that were developed exhibited significant substrate control of the stereochemical outcome, both experimentally and computationally, sheds new light on diphenylprolinol silyl ether catalyzed reactions, which were previously believed to be purely reagent controlled. It is possible that this type of process could be applied to a general organocascade DKR (**Scheme 5.27**). In this process, α,β-unsaturated aldehydes (**1.67**) could be modified via a reversible intermolecular Michael addition furnishing intermediates of type **1.72** and ***epi*–1.72**. This initial step could be followed by a dynamic kinetic resolution in which solely ***epi*-1.72** reacts with a general electrophile (E^+) due to a combination of substrate and catalyst control of the reaction. This type of process would represent a new mechanism in cascade catalysis and would afford uncommon cascade products (**5.56**) containing an *anti* relative configuration between the α and β positions.

Scheme 5.27 A General Organocascade DKR



5.3 Conclusions

In conclusion, the first organocascade kinetic resolution and a novel organocascade DKR were developed. These reactions gave access to chiral 2,6-disubstituted tetrahydropyrans and chiral 2,5-disubstituted tetrahydrofurans respectively, which are both prevalent substructures of various natural products.[32] These cascade processes both involved an iminium–catalyzed intramolecular oxa-Michael addition with an aliphatic alcohol Michael donor followed by an enamine–catalyzed intermolecular Michael addition. These iminium–enamine cascade reactions gave products with an *anti* relative stereochemistry between the α and β substituents and an (*S*) absolute stereochemistry at the β-position of the product aldehyde, making the stereochemical outcome different than that usually observed in iminium–enamine cascade reactions catalyzed by **1.12a**. The fact that the resolutions demonstrated significant substrate control of the stereochemical outcome shows that there is a more complex relationship between the role of the substrate and that of the catalyst in reactions catalyzed by **1.12a** than has been previously observed. The organocascade kinetic resolution which was developed is one of the rare examples of an enamine–catalyzed kinetic resolution, and the work described could potentially lead to the broader application of catalysts of type **1.12** in organocascade kinetic resolutions and organocascade DKR's.

5.4 References

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Chapter 6.

Experimental And Characterization

6.1 General Information

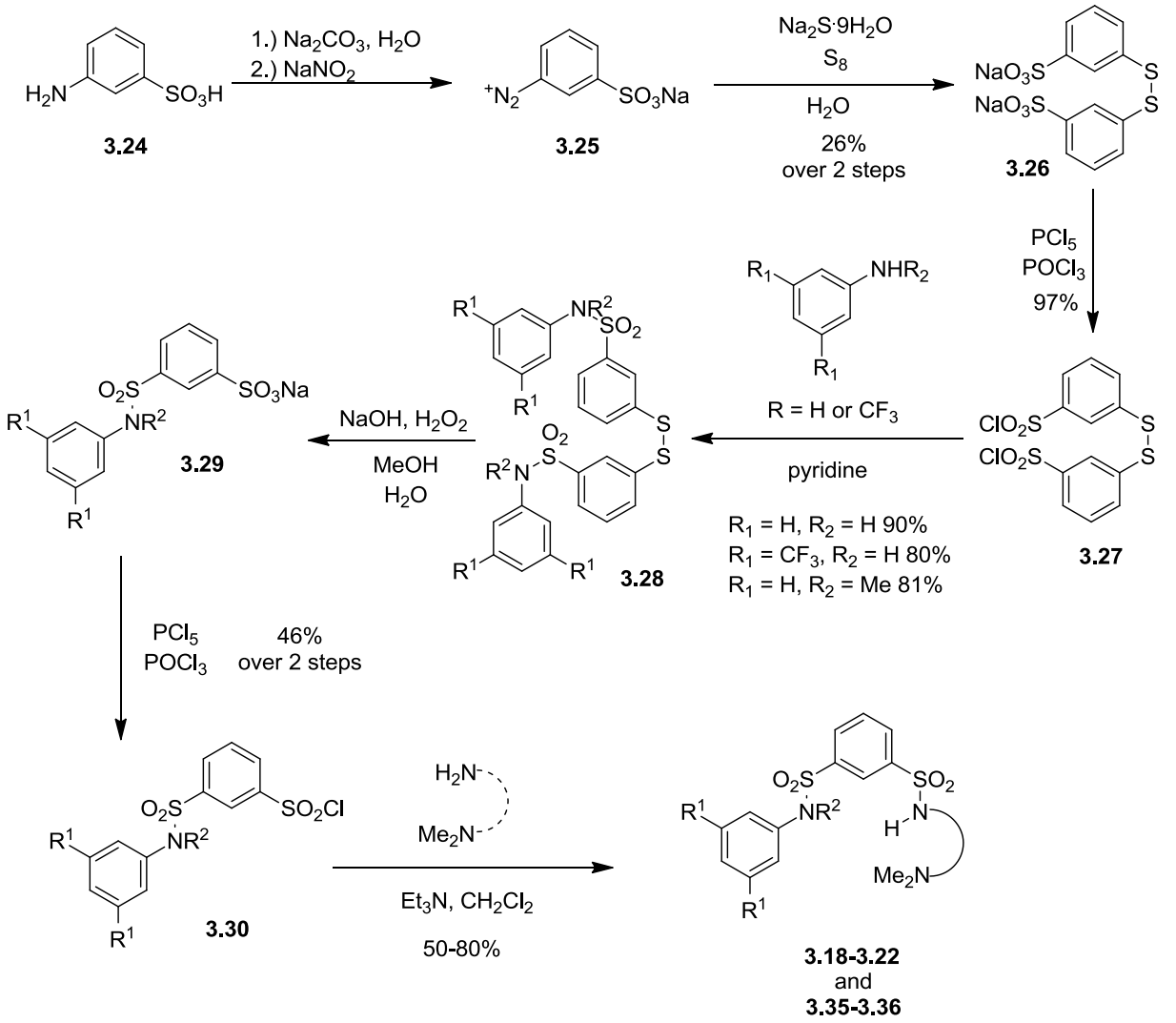
All chemicals and solvents were purchased from Sigma–Aldrich, Fisher Scientific or VWR International. ^{1}H and ^{13}C NMR spectra were collected using a Bruker 400 MHz Biospin. The NMR data herein uses the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, td = triplet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets. Enantiomeric excesses were determined using a Perkin Elmer Series 200 HPLC with Daicel Chemical Industries, LTD. Chiralpak AD-H (0.46 x 25 cm), Chiralpak OD-H (0.46 x 25 cm), and Chiralpak AS-H (0.46 x 25 cm) columns. Optical rotations were determined using a Jasco P-1020 polarimeter. IR spectra were collected using a Nicolet 6700 FT-IR. High resolution mass spectra were collected using an Agilent 6520 Q-TOF. Flash chromatography was carried out with Merck, grade 9385, 230-400 mesh, 600 Å silica gel and with Merck, silica 60F-254 on glass, 250 µm layer TLC plates with fluorescent indicator. Solvents were dried and kept air free in a solvent purification unit. Solvents were evaporated using a standard rotovapor and a high vacuum. All reactions were carried out in oven dried glassware and conducted under an argon atmosphere.

6.2 Experimental and Characterization for Chapter 3

Determination of Enantiomeric Excesses
Enantiomeric excesses were determined by comparison to a racemic sample (prepared using the same general procedure, but with one equivalent of Et_3N instead of the catalyst).

Preparation of Catalyst (3.17)
Catalyst **3.17** was prepared using a known procedure and characterization agreed with the literature.[1]

Preparation of catalysts (3.18–3.22 and 3.35–3.36)
Catalysts **3.18**–**3.22** and **3.35**–**3.36** were prepared according to a modified procedure.[2]



Compound **3.24** (11.9 g, 69 mmol) was added to a flask followed by Na_2CO_3 (7.3 g, 69 mmol) and water (12.5 mL). The solids were dissolved and the solution was cooled to 15 ^oC. A solution of $NaNO_2$ (5.1 g, 74 mmol) in water (12.5 mL) was added to the reaction mixture. The reaction mixture was then poured slowly into a flask containing stirring concentrated HCl (13.1 mL) and ice (75 g). The reaction was stirred for 15 minutes generating a solution of **3.25**. $Na_2S{\cdot}9H_2O$ (17.8 g, 74 mmol), powdered sulfur (2.37 g, 74 mmol), and water (18.8 mL) were combined in a flask and stirred at 100 ^oC until all solids dissolved. Once dissolved, a solution of NaOH (2.76 g, 69 mmol) in water (25 mL) was added and the reaction was cooled to 5 ^oC. The solution of **3.25** was added over 45 minutes with stirring while adding ice to keep the reaction temperature below 10 ^oC. Reaction was allowed to warm to room temperature overnight. The solution was acidified to pH = 2 with concentrated HCl, filtered, and concentrated to 125 mL at atmospheric pressure. The solution was allowed to cool and was then neutralized with 10% aqueous NaOH. The solution was left overnight and filtered to give **3.26** as a yellow powder (3.80 g, 26% over two steps).

$POCl_3$ (9.6 mL) was added to a flask containing PCl_5 (1.9 g) and **3.26** (3.8 g, 9.0 mmol). The reaction was refluxed overnight. The reaction mixture was diluted with $CHCl_3$ (60 mL) and poured into ice (30 g) and stirred for 45 minutes. The layers were separated and the $CHCl_3$ layer was stirred with saturated aqueous $NaHCO_3$ (12.5 mL) for 45 minutes. The layers were separated and the $CHCl_3$ layer was dried over Na_2SO_4, filtered and concentrated to yield **3.27** as an oil (3.63 g, 97%).

Compound **3.27** (1.93 g, 4.65mmol), CH_2Cl_2 (34 mL), pyridine (1.96 mL, 24.2 mmol) and aryl amine (10.21 mmol) were stirred at room temperature overnight. The reaction mixture was concentrated and purified via column chromatography (EtOAc/petroleum ether, 20/80) to yield pure **3.28** (80–90%).

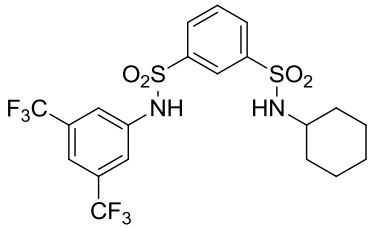
Compound **3.28** (2.22g, 4.2 mmol) was dissolved in methanol (33 mL). Aqueous 2M NaOH (6.73 mL, 16.8 mmol) was added followed by 30% aqueous H_2O_2 (3.0 mL). The reaction was stirred at room temperature for 2 hours and more 30% aqueous H_2O_2 (1.25 mL) was added. The reaction mixture was stirred overnight at room temperature. Saturated aqueous $NaHSO_3$ (6.6 mL) was added and the reaction was stirred for 2 hours. The reaction mixture was concentrated and vacuum dried overnight to yield a white solid (**3.29**, crude with inorganic salts). $POCl_3$ (4.0 mL) was added to PCl_5 (0.63 g) and crude **3.29** (1.26 g, 3.77 mmol). The reaction was refluxed for two hours. The reaction mixture was diluted with $CHCl_3$ (25 mL) and poured into ice (12.5 g) and stirred for 45 minutes. The layers were separated and the $CHCl_3$ layer was stirred with saturated aqueous $NaHCO_3$ (12.5 mL) for 45 minutes. The layers were separated and the $CHCl_3$ layer was dried over Na_2SO_4, filtered and concentrated to yield **3.30** (46% over two steps).

Compound **3.30** (2.0 g, 4.27 mmol) was dissolved in CH_2Cl_2 (6.5 mL). This solution was added over 10 minutes to a stirring solution of amine/diamine (5.66 mmol), Et_3N (1.58 mL, 11.32 mmol) and CH_2Cl_2 (11 mL) at 0 ^oC. The reaction was allowed to warm to room temperature overnight. The reaction mixture was concentrated and purified via column chromatography (CH_2Cl_2/MeOH, 20/1) to yield the product (50–80%).

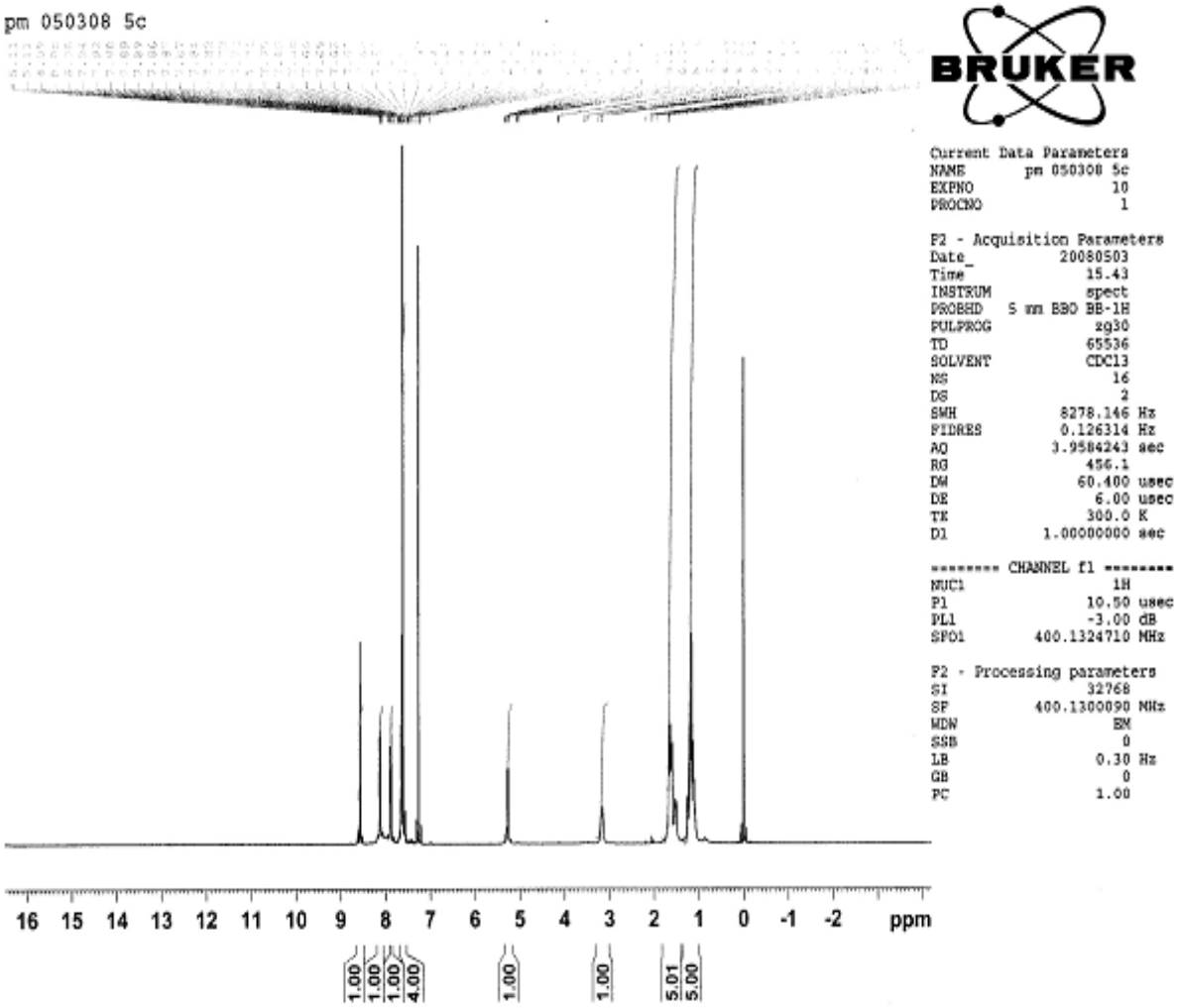
Preparation of Catalyst (3.23 and 3.34)

Sulfonyl chloride (0.91 mmol) was dissolved in CH_2Cl_2 (1.4 mL). This solution was added over 10 minutes to a stirring solution of amine/diamine (2.42 mol for **3.23**, 1.21 mmol for **3.34**), Et_3N (670 µL, 4.84 mmol for **3.23**, 335 µL, 2.42 mmol for **3.34**) and CH_2Cl_2 (2.25 mL) at 0 ^oC. The reaction was allowed to warm to room temperature overnight. The reaction mixture was concentrated and purified via column chromatography (CH_2Cl_2/MeOH, 20/1) to yield the product (50–60%).

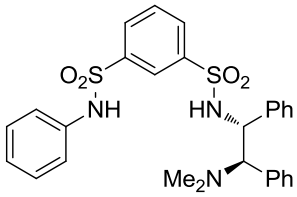
3.18: *N^1-(3,5-bis(trifluoromethyl)phenyl)-N^3-cyclohexylbenzene-1,3-disulfonamide*



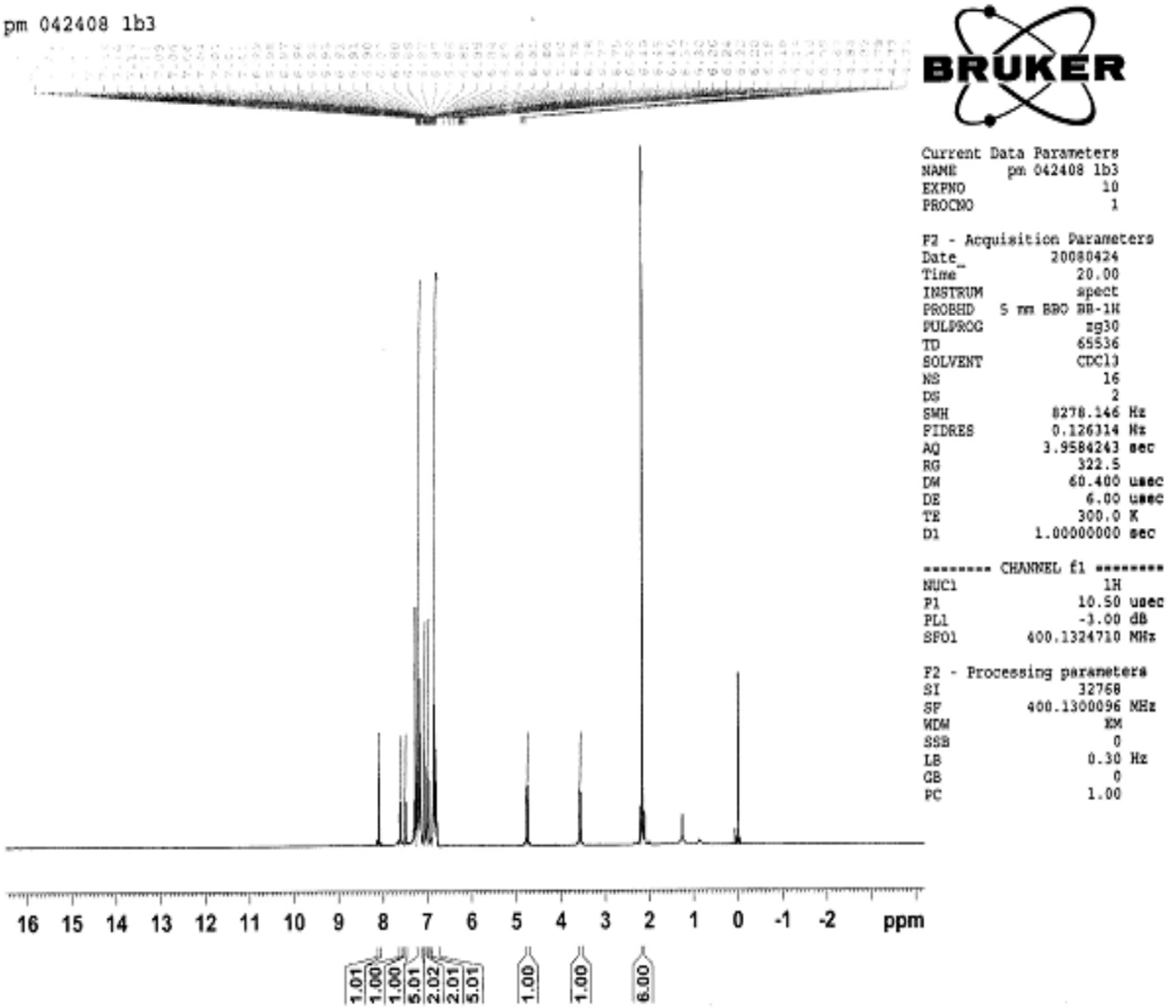
colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (t, *J* = 1.5 Hz, 1H), 8.12 (dt, *J* = 1.5, 7.8 Hz, 1H), 7.89 (dt, *J* = 1.5, 7.8 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.61 (s, 3H), 5.27 (d, *J* = 7.6 Hz, 1H), 3.17 (m, 1H), 1.74-1.45 (m, 5H), 1.31-1.04 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 140.1, 138.1, 133.7, 133.3, 133.0, 132.7, 131.7, 131.0, 130.3, 125.9, 120.9, 119.1, 53.4, 33.9, 25.1, 24.6 ppm; IR (film) ν 3277, 2933, 2856, 1377, 1279, 1136 cm^{-1}; HRMS calcd for $C_{20}H_{20}F_6N_2O_4S_2$ (M^+) 530.0769, obsd 530.0765.



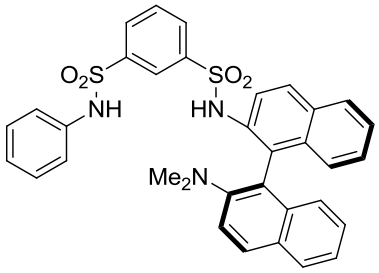
3.19: *N^1-((1R,2R)-2-(dimethylamino)-1,2-diphenylethyl)-N^3-phenylbenzene-1,3-disulfonamide*



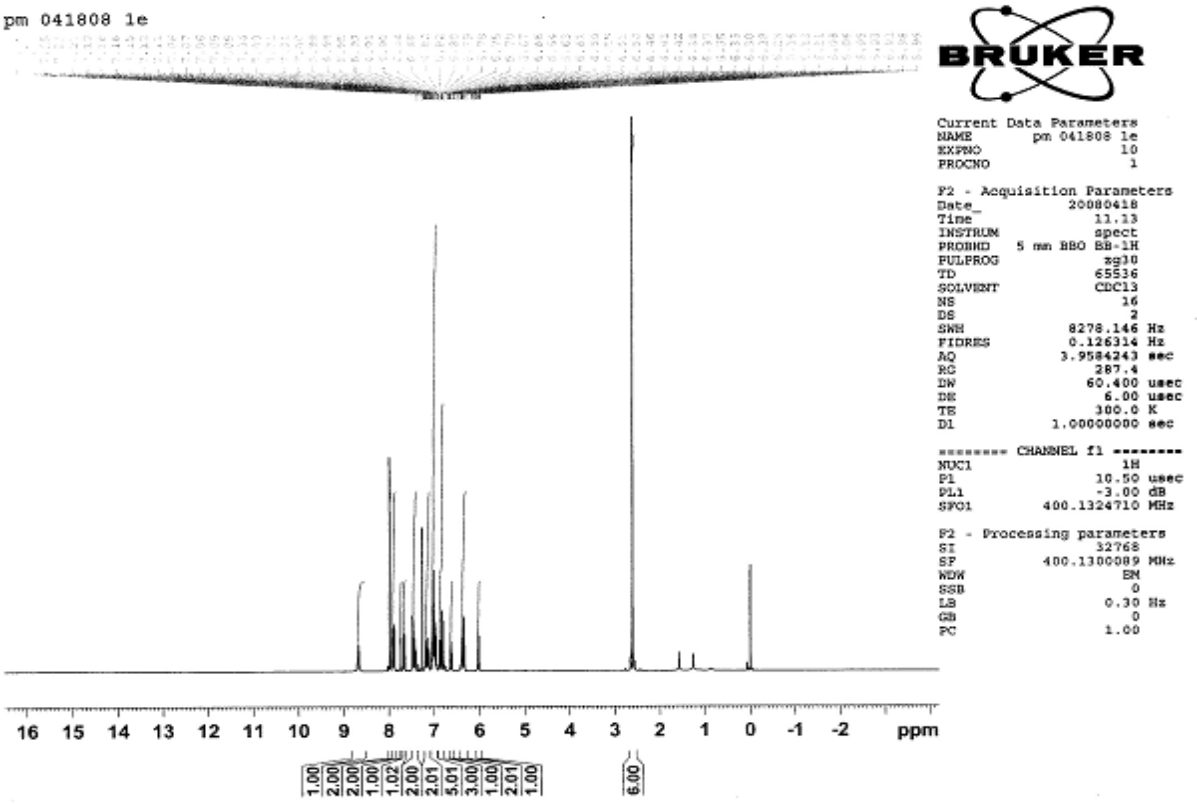
colorless amorphous solid; $[\alpha]_D^{28}$ = +128.5 (*c* 1.03, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (t, *J* = 1.8 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.31-7.23 (m, 2H), 7.23-7.12 (m, 5H), 7.08-7.03 (m, 2H), 7.00-6.94 (m, 2H), 6.89-6.76 (m, 5H), 4.76 (d, *J* = 11.1 Hz, 1H), 3.57 (d, *J* = 11.1 Hz, 1H), 2.16 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 139.9, 137.0, 136.1, 131.3, 130.9, 130.3, 129.9, 129.6, 129.1, 128.7, 128.0, 128.0, 127.6, 126.3, 126.1, 122.2, 73.1, 57.6, 40.3 ppm; IR (film) ν 3256, 2933, 2790, 1593, 1348, 1176, 1148 cm^{-1}; HRMS calcd for $C_{28}H_{29}N_3O_4S_2$ (M^+) 535.1600, obsd 535.1608.



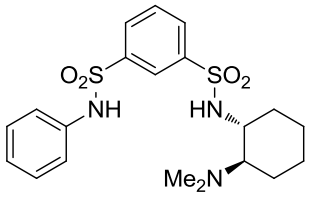
3.20: *N^1-(2'-(dimethylamino)-[1,1'-binaphthalen]-2-yl)-N^3-phenylbenzene-1,3-disulfonamide*



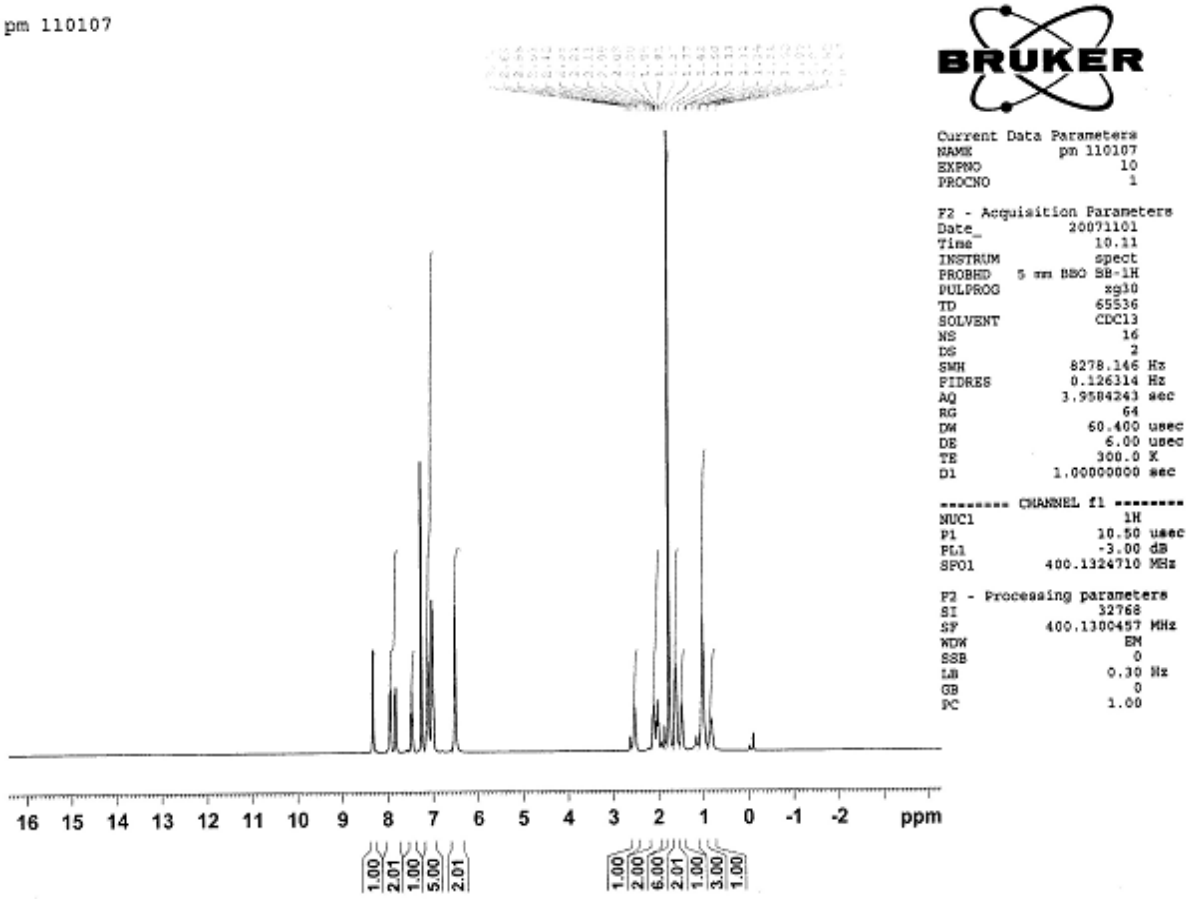
white crystals; m.p. 194-197 ˚C; $[\alpha]_D^{27}$ = -207.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.99 (s, 2H), 7.91 (m, 2H), 7.74 (m, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 9.1 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.07-6.94 (m, 5H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.82 (m, 2H), 6.63 (t, *J* = 7.8 Hz, 1H), 6.38 (s, 1H), 6.35 (t, *J* = 7.8 Hz, 1H), 6.02 (d, *J* = 8.8 Hz, 1H), 2.61 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 140.9, 138.9, 135.8, 133.8, 133.7, 132.3, 131.3, 130.8, 130.2, 129.5, 129.5, 129.4, 129.2, 128.8, 128.5, 128.4, 127.9, 127.2, 126.9, 126.7, 125.9, 125.6, 125.1, 124.9, 124.0, 123.6, 122.5, 122.2, 118.0, 43.7 ppm; IR (film) ν 3264, 3060, 2843, 2795, 1589, 1348, 1180, 1156 cm^{-1}; HRMS calcd for $C_{34}H_{29}N_3O_4S_2$ (M^+) 607.1600, obsd 607.1599.



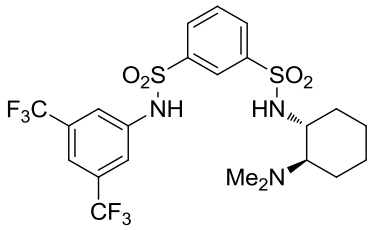
3.21: *N^1-((1R,2R)-2-(dimethylamino)cyclohexyl)-N^3-phenylbenzene-1,3-disulfonamide*



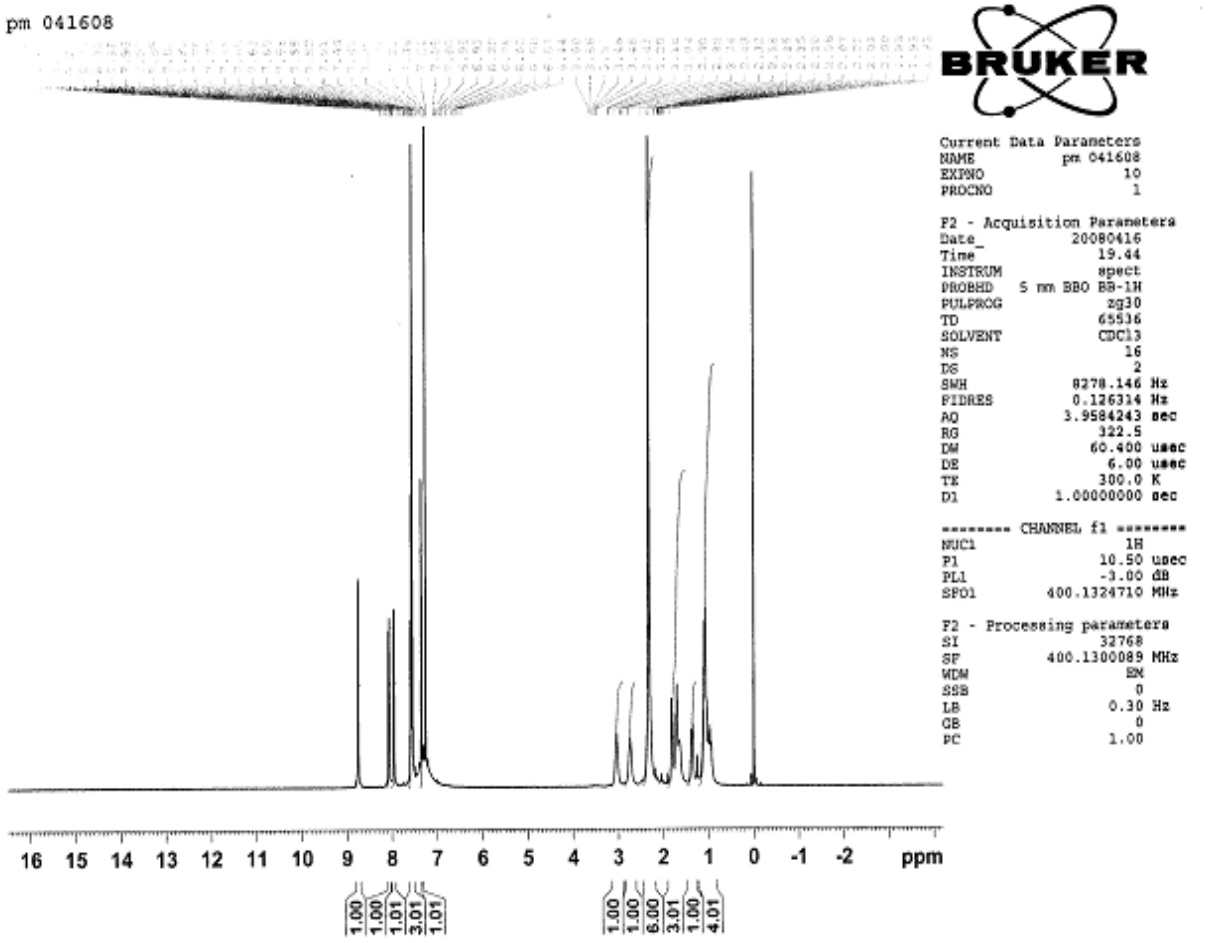
colorless amorphous solid; $[\alpha]_D^{28}$ = -61.6 (*c* 1.03, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.95 (d, *J* = 7.1 Hz, 1H), 7.83 (s, *J* = 7.1 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.19-6.95 (m, 5H), 6.52 (s, 2H), 2.53 (m, 1H), 2.11 (m, 1H), 2.03 (t, *J* = 11.1 Hz, 1H), 1.77 (s, 6H), 1.63 (m, 2H), 1.50 (m, 1H), 1.02 (m, 3H), 0.84 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 140.6, 136.1, 131.4, 131.0, 129.9, 129.6, 126.3, 126.0, 122.1, 66.4, 54.4, 39.7, 32.7, 25.0, 24.3, 21.2 ppm; IR (film) ν 2925, 2852, 1597, 1454, 1344, 1180, 1152, 1111, 1082 cm^{-1}; HRMS calcd for $C_{20}H_{27}N_3O_4S_2$ (M^+) 437.1443, obsd 437.1450.



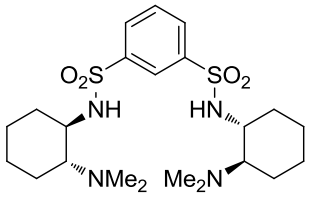
3.22: *N^1-(3,5-bis(trifluoromethyl)phenyl)-N^3-((1R,2R)-2-(dimethylamino)cyclohexyl)benzene-1,3-disulfonamide*



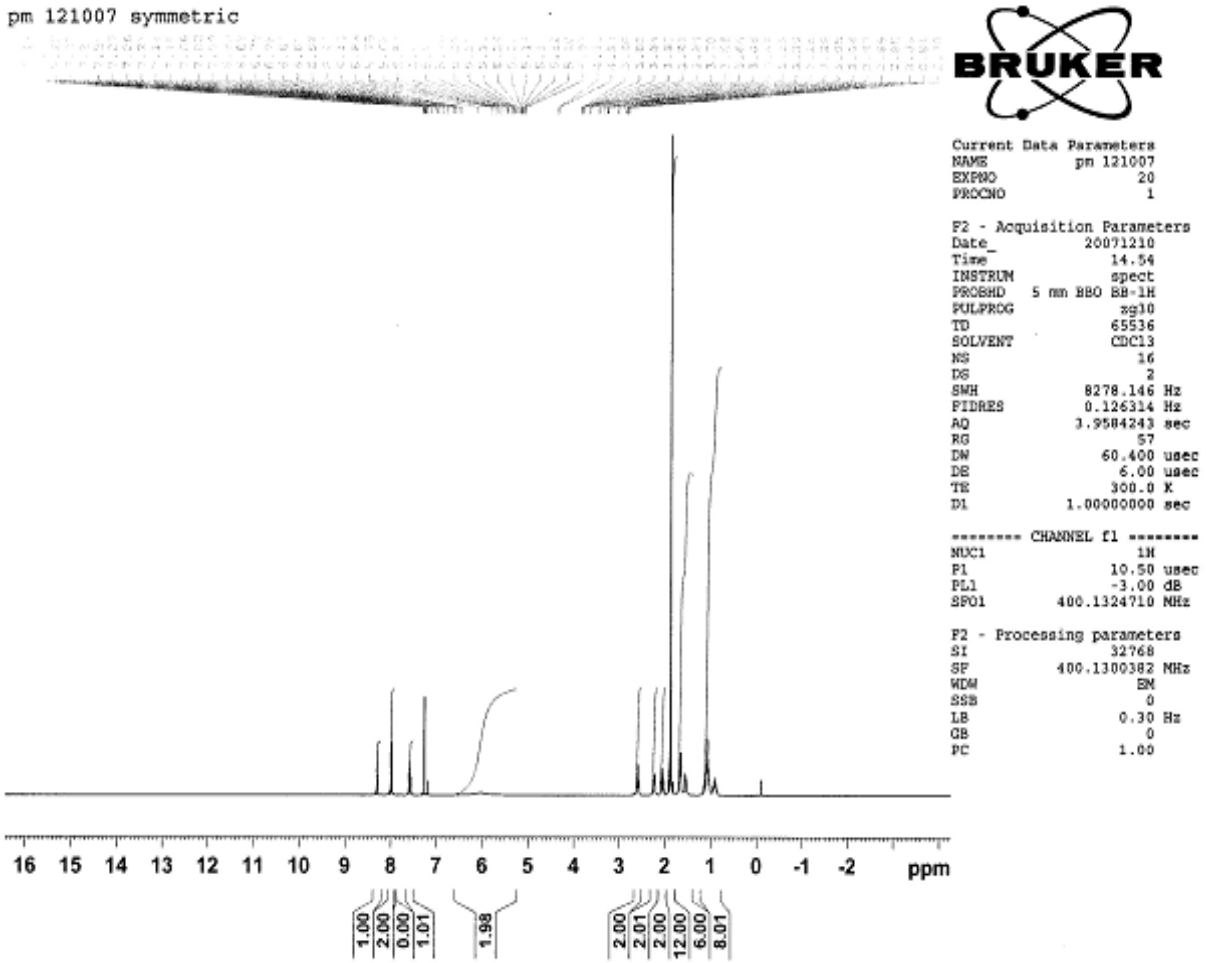
colorless amorphous solid; $[\alpha]_D^{27}$ = -32.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.55 (s, 2H), 7.35 (s, 1H), 7.32 (broad s, 2H), 3.04 (m, 1H), 2.74 (m, 1H), 2.32 (s, 6H), 1.81 (m, 1H), 1.69 (m, 2H), 1.37 (m, 1H), 1.18-0.85 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 145.4, 135.4, 135.1, 134.7, 134.4, 133.7, 132.2, 132.1, 128.8, 126.8, 124.0, 122.5, 117.1, 66.6, 52.8, 38.1, 30.4, 21.9, 21.7, 19.4 ppm; IR (film) ν 2921, 2852, 1609, 1466, 1381, 1176, 1131, 1012 cm^{-1}; HRMS calcd for $C_{22}H_{25}F_6N_3O_4S_2$ (M^+) 573.1191, obsd 573.1202.



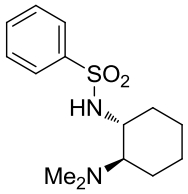
3.23: *N^1,N^3-bis((1R,2R)-2-(dimethylamino)cyclohexyl)benzene-1,3-disulfonamide*



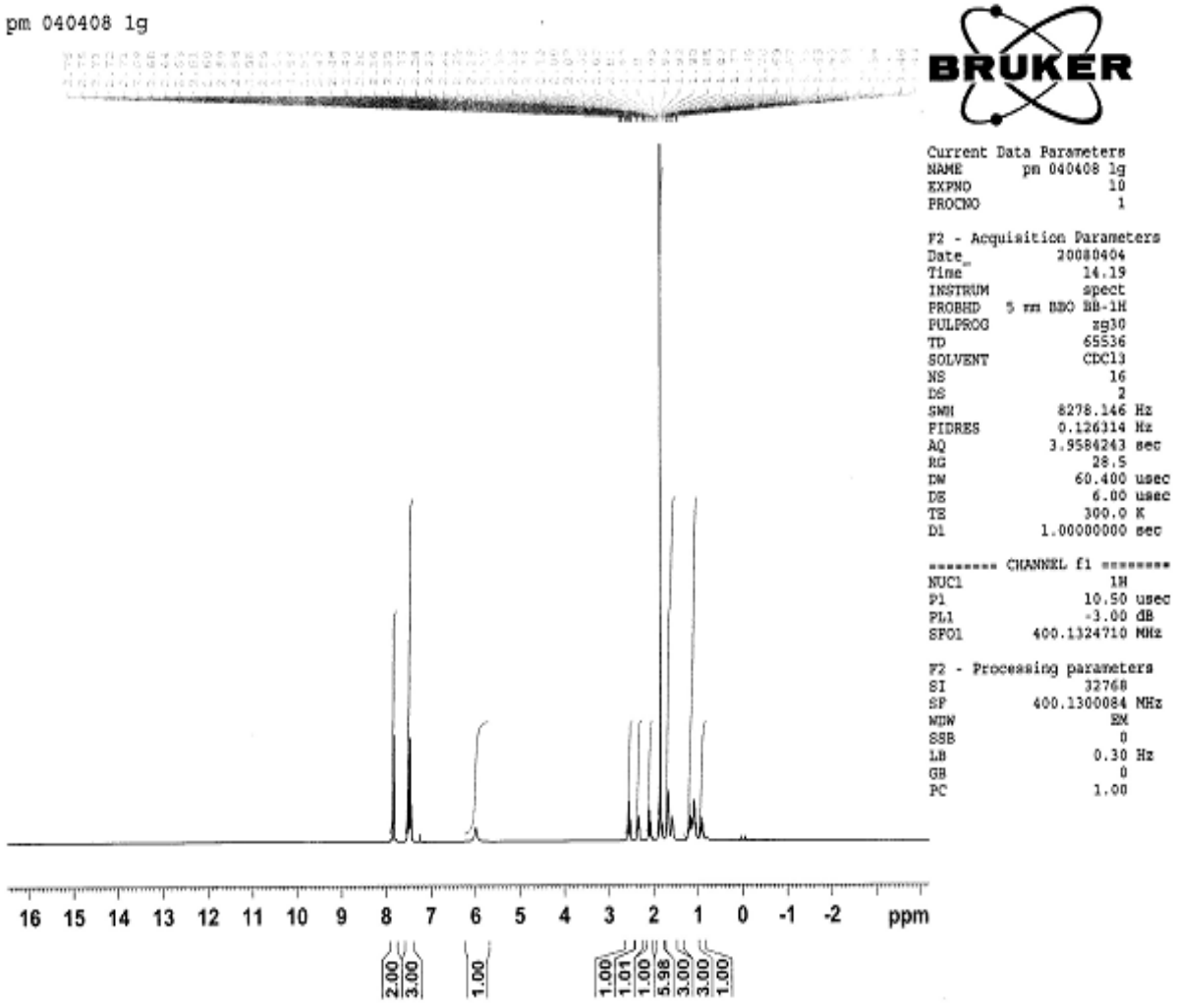
white crystals; m.p. 167-170 ˚C; $[\alpha]_D^{27}$ = -144.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (t, *J* = 1.8 Hz, 1H), 7.99 (dd, *J* = 1.8, 7.8 Hz, 2H), 7.58 (t, *J* = 7.8 Hz, 1H), 6.03 (broad s, 2H), 2.59 (m, 2H), 2.23 (m, 2H), 2.05 (td, *J* = 3.0, 11.9 Hz, 2H), 1.97 (s, 12H), 1.66 (m, 4H), 1.54 (m, 2H), 1.18-0.98 (m, 6H), 0.97-0.83 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 130.9, 129.7, 126.1, 66.3, 54.3, 39.7, 32.6, 25.0., 24.2, 21.1 ppm; IR (film) ν 3191, 2993, 2860, 2782, 1454, 1344, 1180, 1157, 1086, 1042 cm^{-1}; HRMS calcd for $C_{22}H_{38}N_4O_4S_2$ (M^+) 486.2335, obsd 486.2342.



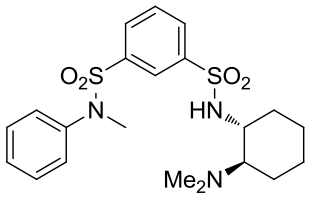
3.34: *N-((1R,2R)-2-(dimethylamino)cyclohexyl)benzenesulfonamide*



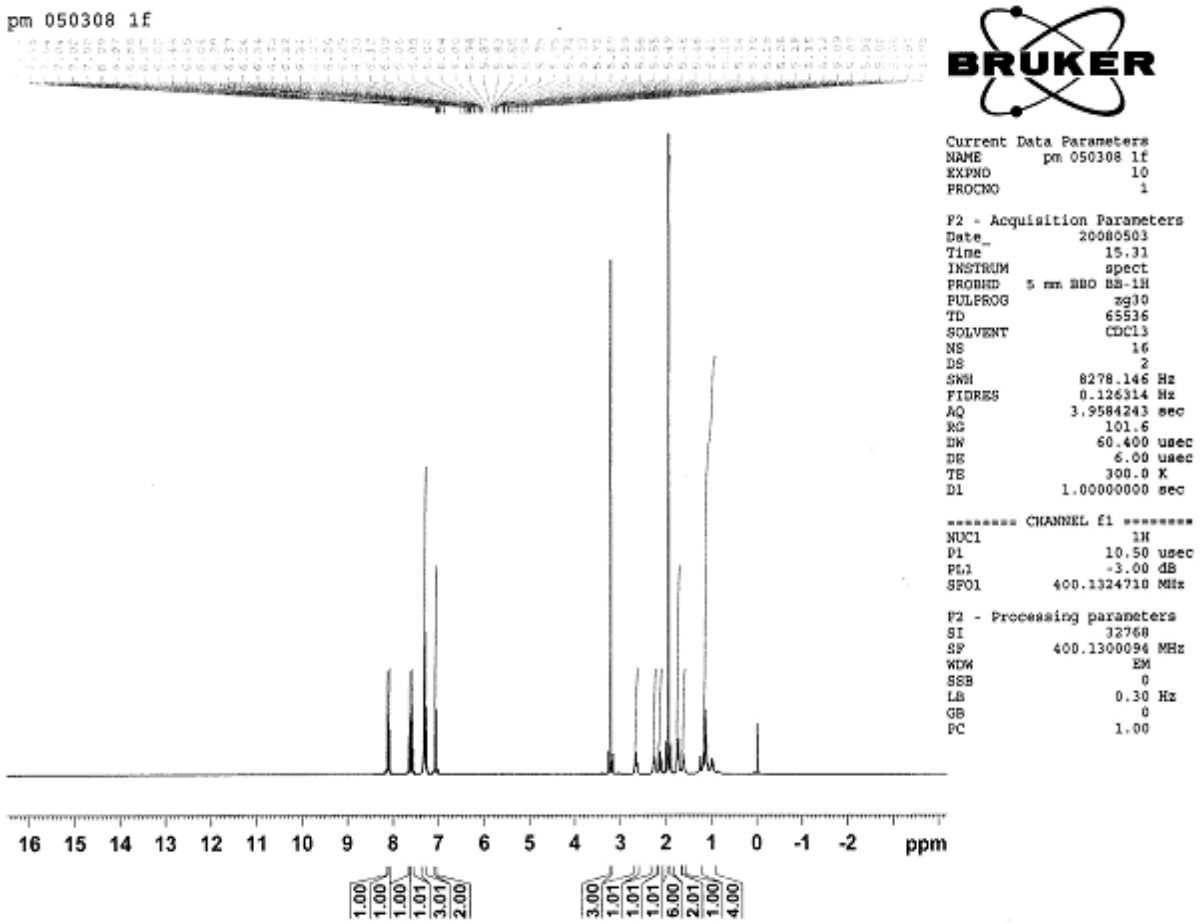
white crystals; m.p. 77-82 ˚C; $[\alpha]_D^{27}$ = -118.4 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.56-7.42 (m, 3H), 5.99 (broad s, 1H), 2.56 (td, *J* = 4.0, 10.6 Hz, 1H), 2.35 (m, 1H), 2.09 (td, *J* = 3.8, 10.4 Hz, 1H), 1.85 (s, 6H), 1.68 (m, 2H), 1.58 (m, 1H), 1.30-1.01 (m, 3H), 0.93 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 132.5, 129.0, 127.4, 66.4, 54.2, 39.7, 32.8, 25.2, 24.3, 21.1 ppm; IR (film) ν 3199, 2933, 2860, 2786, 1720, 1446, 1340, 1164, 1091 cm^{-1}; HRMS calcd for $C_{14}H_{22}N_2O_2S$ (M^+) 282.1402, obsd 282.1407.



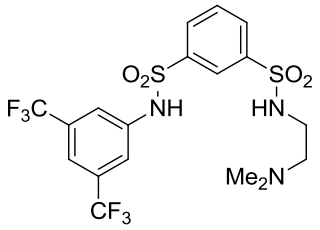
3.35: *N^1-((1R,2R)-2-(dimethylamino)cyclohexyl)-N^3-methyl-N^3-phenylbenzene-1,3-disulfonamide*



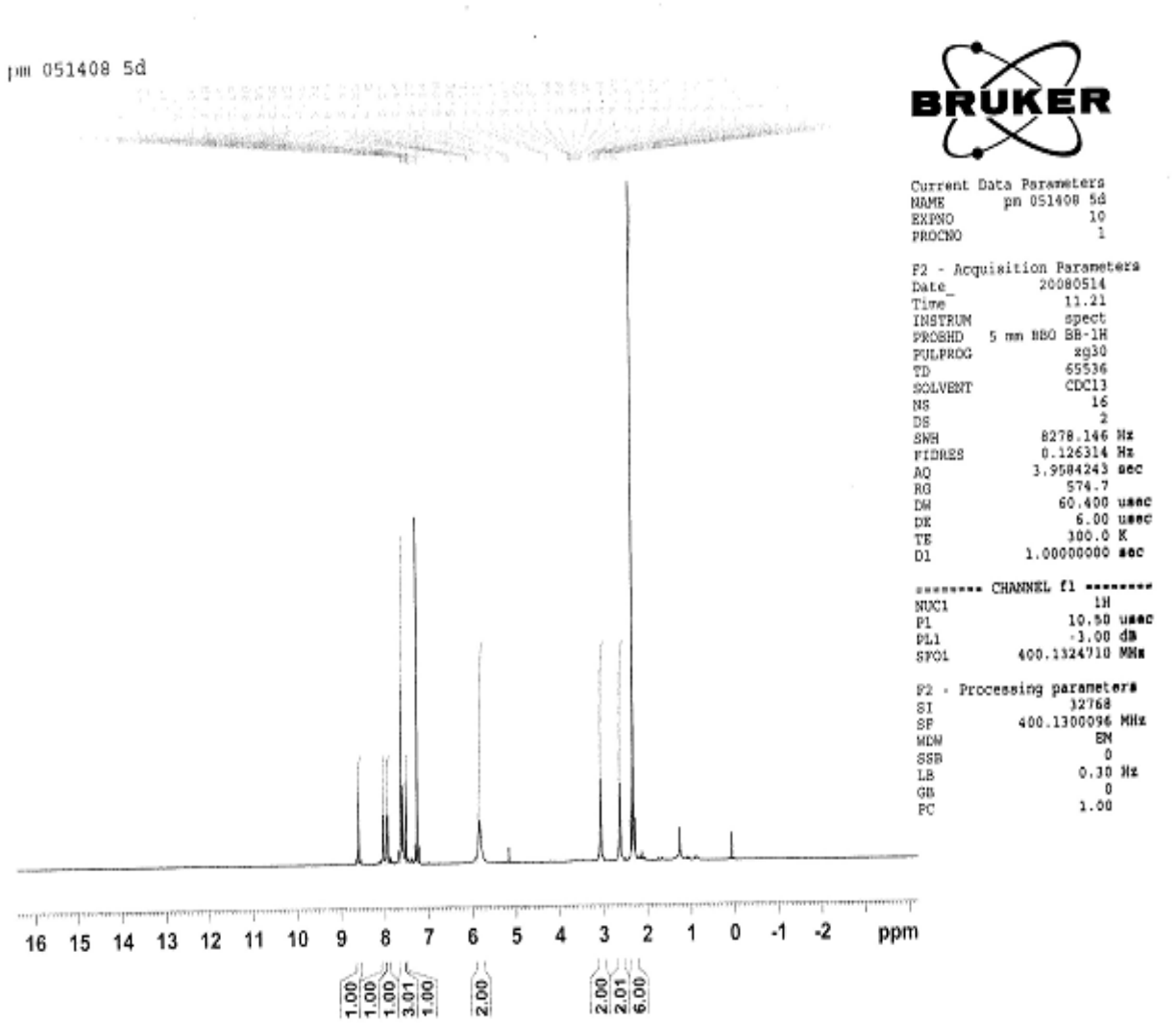
colorless amorphous solid; $[\alpha]_D^{27}$ = -79.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (t, *J* = 1.5 Hz, 1H), 8.09 (dt, *J* = 1.5, 7.6 Hz, 1H), 7.64 (dt, *J* = 1.5, 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.38-7.27 (m, 3H), 7.07 (m, 2H), 3.21 (s, 3H), 2.66 (td, *J* = 4.0, 10.4 Hz, 1H), 2.26 (m, 1H), 2.13 (td, *J* = 4.0, 10.4 Hz, 1H), 1.95 (s, 6H), 1.74 (m, 2H), 1.62 (m, 1H), 1.39-0.75 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.0, 138.3, 131.4, 131.2, 129.6, 129.3, 127.9, 126.8, 126.6, 66.4, 54.4, 39.7, 38.6, 32.6, 25.1, 24.3, 21.1 ppm; IR (film) ν 2933, 2860, 2782, 1491, 1450, 1356, 1185, 1152, 1074 cm^{-1}; HRMS calcd for $C_{21}H_{29}N_3O_4S_2$ (M^+) 451.1600, obsd 451.1609.



3.36: *N^1-(3,5-bis(trifluoromethyl)phenyl)-N^3-(2-(dimethylamino)ethyl)benzene-1,3-disulfonamide*



white crystals; m.p. 158-162 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (m, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.63 (s, 2H), 7.60 (t, J = 7.8 Hz, 1H), 7.52 (s, 1H), 5.83 (broad s, 2H), 3.06 (t, J = 5.8 Hz, 2H), 2.62 (t, J = 5.8 Hz, 2H), 2.32 (s, 6H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 144.4, 143.4, 142.3, 133.3, 133.0, 132.7, 132.3, 131.8, 131.6, 131.4, 126.4, 122.2, 116.8, 58.2, 44.8, 40.6 ppm; IR (film) ν 1610, 1642, 1373, 1274, 1168, 1127, 1021 cm^{-1}; HRMS calcd for $C_{18}H_{19}F_6N_3O_4S_2$ (M^+) 519.0721, obsd 519.0723.



General procedure for enantioselective catalysis of Michael addition of 1,3-dicarbonyl compounds to nitroolefins (10a–i)

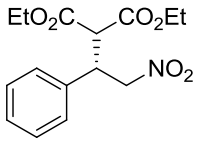
Method A: To an oven dried flask under an argon atmosphere was added dicarbonyl **1.103** (2.0 mmol), toluene (1.0 mL), and β-nitrostyrene **1.23** (0.5 mmol) at room temperature. The bissulfonamide catalyst (0.05 mmol, 28.7 mg) was added and reaction was allowed to stir at room temperature for 240 hours. The reaction mixture was purified via column chromatography (petroleum ether/EtOAc, 90/10) to give the desired product **3.6**.

Method B: To an oven dried flask under an argon atmosphere was added dicarbonyl **1.103** (1.0 mmol), toluene (1.0 mL), and β-nitrostyrene **1.23** (0.5 mmol) at room temperature. The bissulfonamide catalyst (0.05 mmol, 28.7 mg) was added and reaction was allowed to stir in an oil bath at 50 ˚C for 168 hours. The reaction mixture was cooled to room temperature and purified via column chromatography (petroleum ether/EtOAc, 90/10) to give the desired product **3.6**.

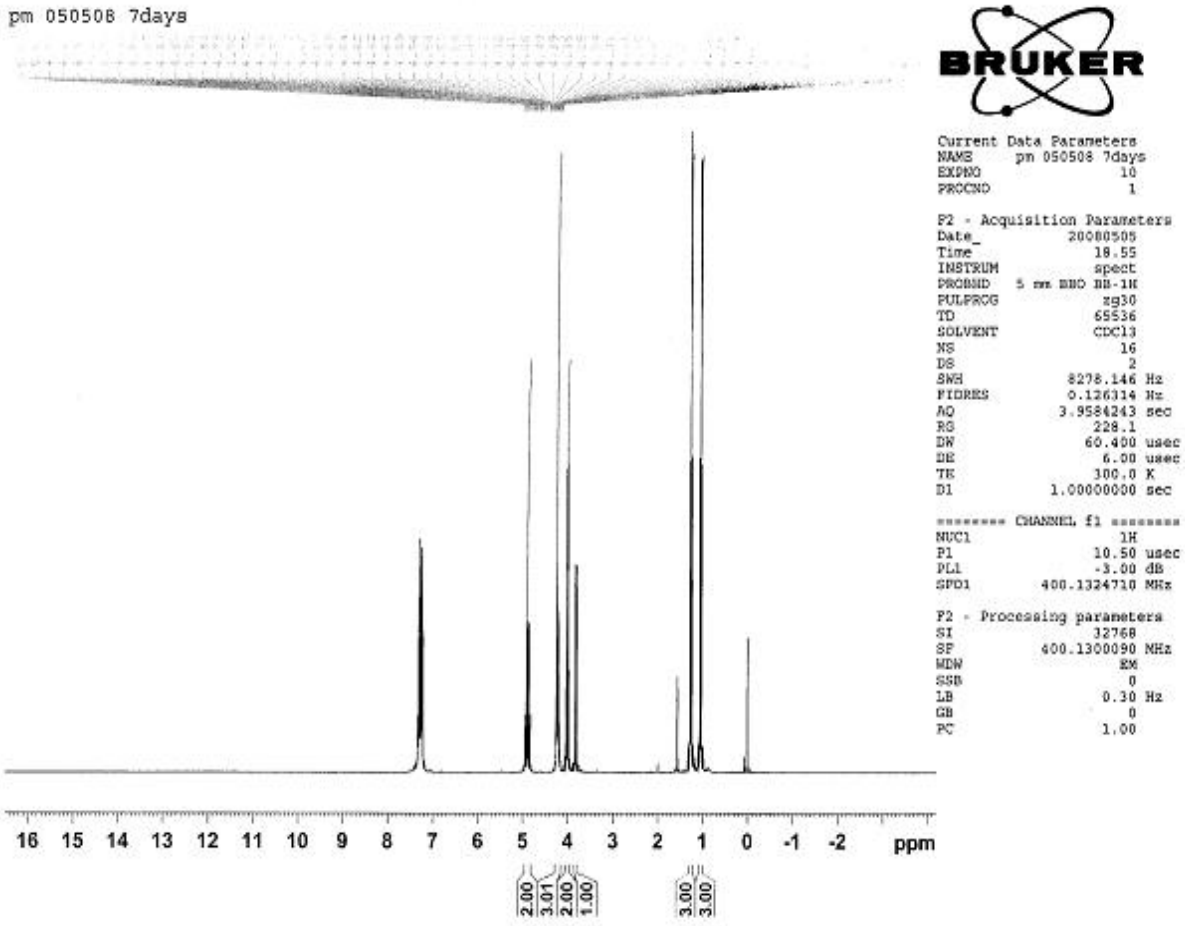
NMR Experiments with Catalyst 3.18

Measurements were carried out using a Bruker 400 MHz NMR Spectrometer. CD_2Cl_2 99.9% D was dried over molecular sieves, 4Å, 1.6 mm pellets in a glove box for 4 days. Samples were prepared in a glove box with both vacuum dried catalyst **3.18** and β-nitrostyrene **1.23a** using oven dried glassware and needles. 0.5 mL NMR samples were prepared from a 13.4 mM catalyst **3.18** stock solution to which were added a proportionate amount of β-nitrostyrene **1.23a**.

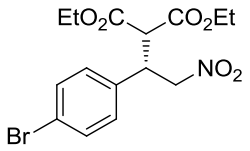
3.6a: *(S)-diethyl 2-(2-nitro-1-phenylethyl)malonate*[3]



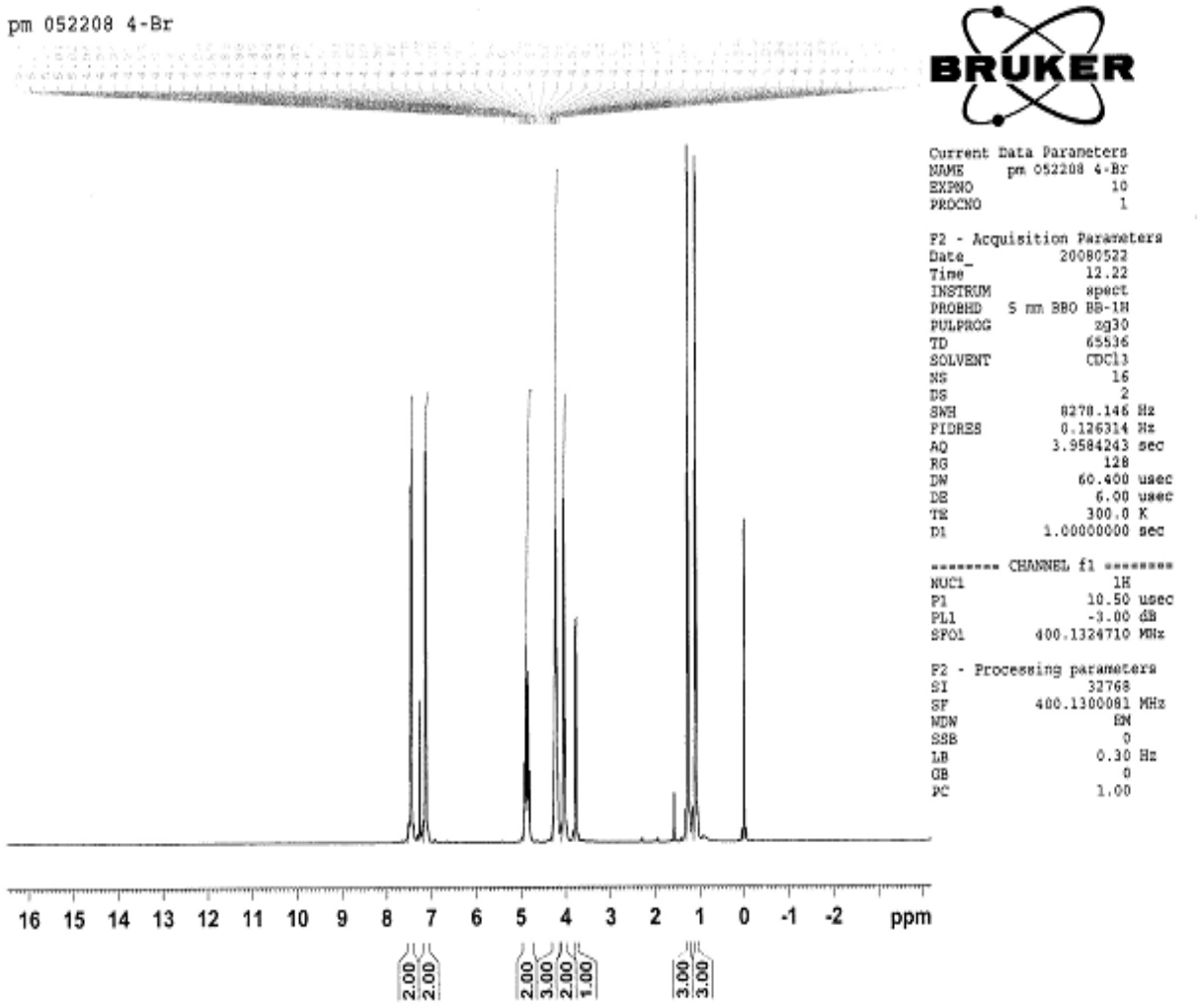
colorless oil; $[\alpha]_D^{27}$ = -4.6 (*c* 1.00, $CHCl_3$, 69% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.21 (m, 5H), 4.90 (m, 2H), 4.23 (m, 3H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.83 (d, *J* = 9.4 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 166.9, 136.5, 129.1, 128.5, 128.2, 77.8, 62.2, 62.0, 55.2, 43.1, 14.1, 13.8 ppm; HPLC [Chiralcel AD-H, hexane/ethanol = 95/5, 1.0 mL/min, λ = 254 nm, retention times: (R) (major) 14.4 min, (S) (minor) 18.8 min].



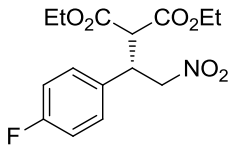
3.6b: *(S)-diethyl 2-(1-(4-bromophenyl)-2-nitroethyl)malonate*[3]



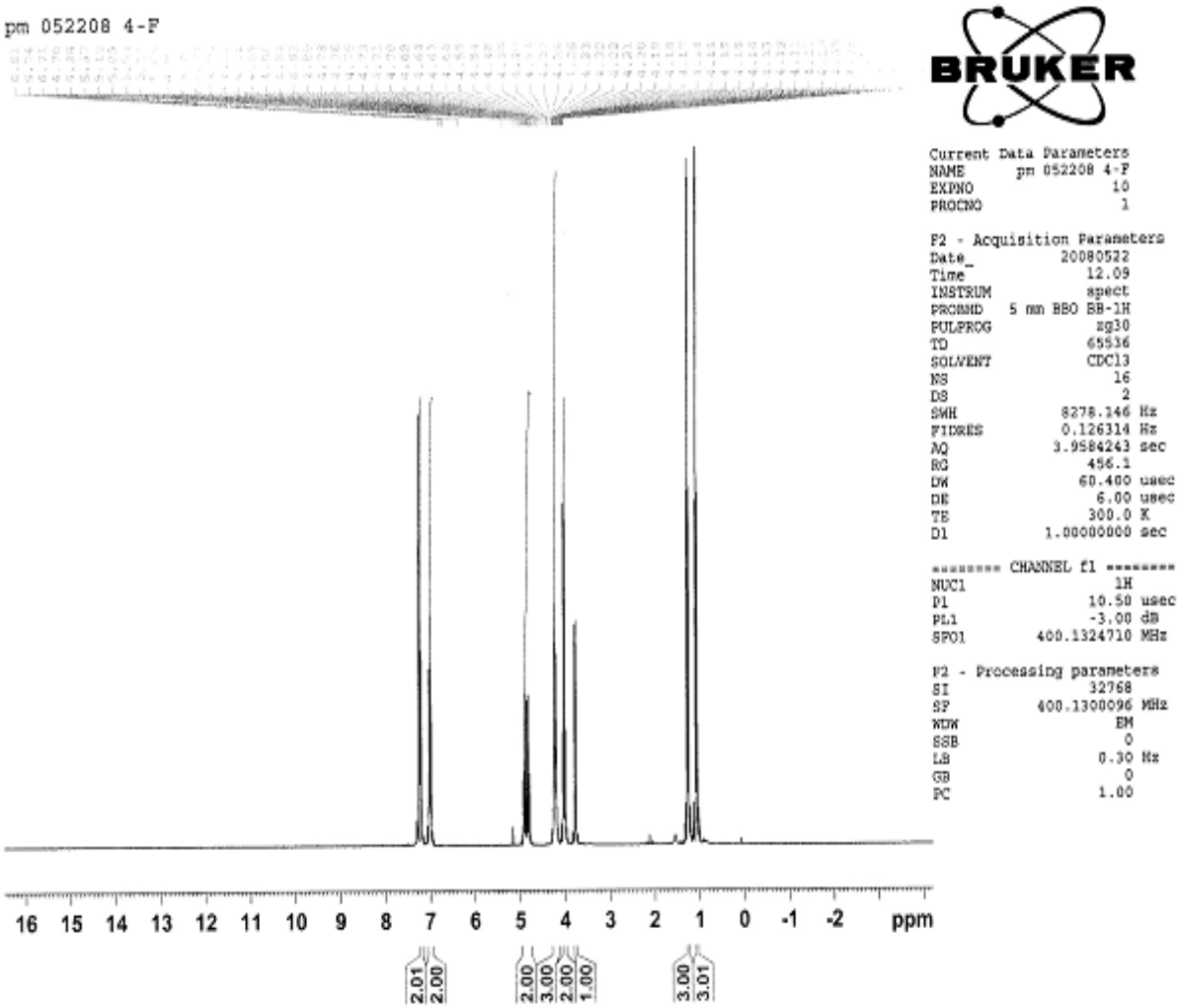
white solid; m.p. 56-57 ˚C; $[\alpha]_D^{28}$ = -6.8 (*c* 1.00, $CHCl_3$, 69% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H) 4.86 (m, 2H), 4.22 (m, 3H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.77 (d, *J* = 9.4 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 166.7, 135.5, 132.2, 129.9, 122.5, 77.4, 62.3, 62.1, 54.8, 42.5, 14.0, 13.8 ppm; HPLC [Chiralcel AD-H, hexane/2-propanol = 90/10, 1.0 mL/min, = 254 nm, retention times: (R) (major) 21.7 min, (S) (minor) 57.3 min].



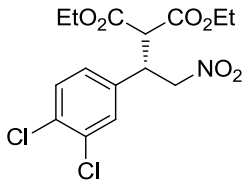
3.6c: *(S)-diethyl 2-(1-(4-fluorophenyl)-2-nitroethyl)malonate*[3]



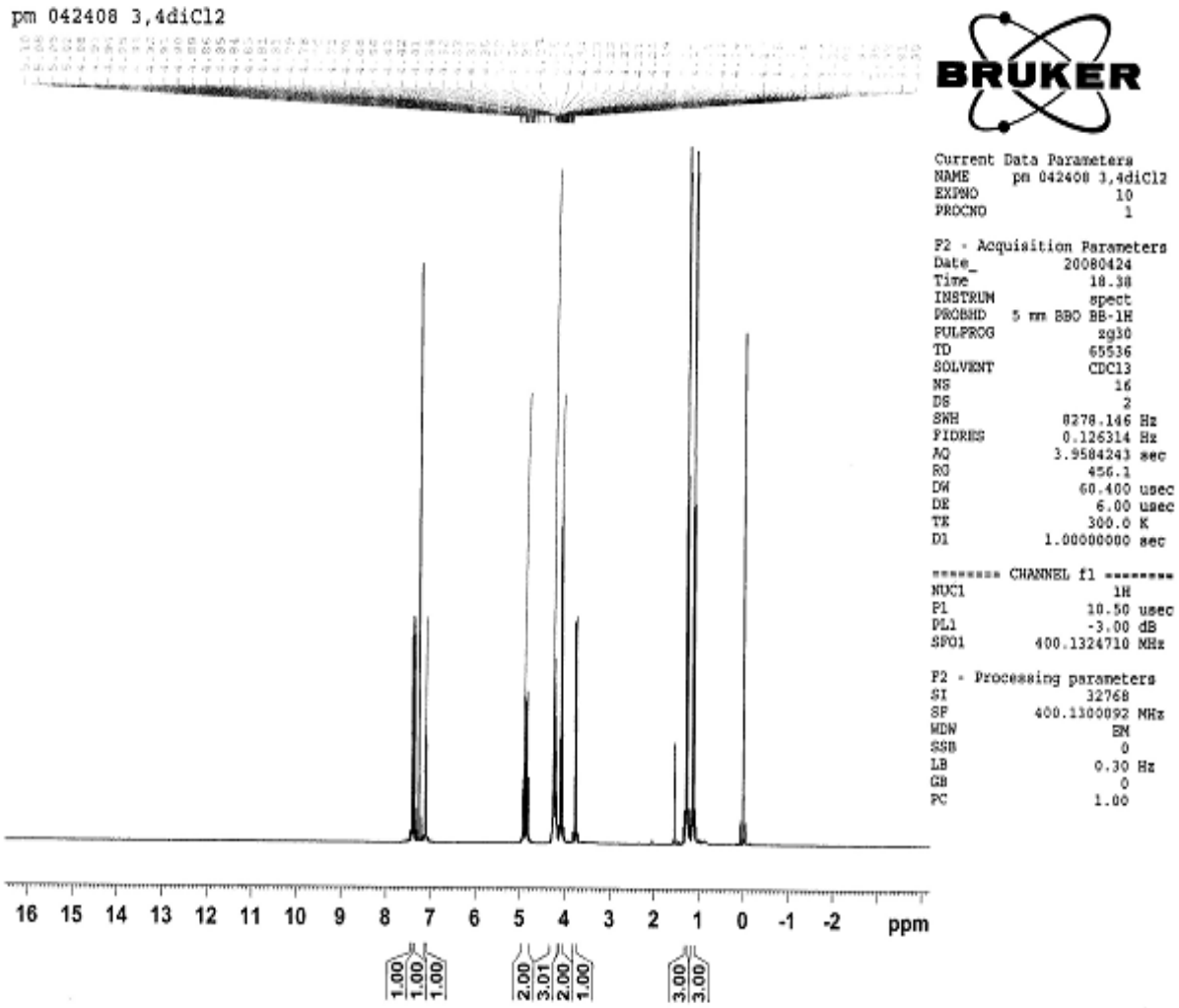
colorless oil; $[\alpha]_D^{28}$ = -4.9 (*c* 1.00, $CHCl_3$, 79% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 2H), 7.01 (t, *J* = 8.6 Hz, 2H), 4.87 (m, 2H), 4.23 (m, 3H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.78 (d, *J* = 9.3 Hz, 1H), 1.27 (t, *J* = 7.3 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 166.8, 130.0, 129.9, 116.1, 115.9, 77.8, 62.3, 62.1, 55.1, 42.5, 14.1, 13.9 ppm; HPLC [Chiralcel AD-H, hexane/ethanol = 95/5, 1.0 mL/min, λ = 254 nm, retention times: (S) (major) 21.0 min, (R) (minor) 31.8 min].



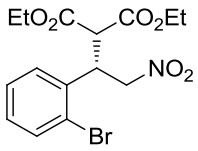
3.6d: *(S)-diethyl 2-(1-(3,4-dichlorophenyl)-2-nitroethyl)malonate*



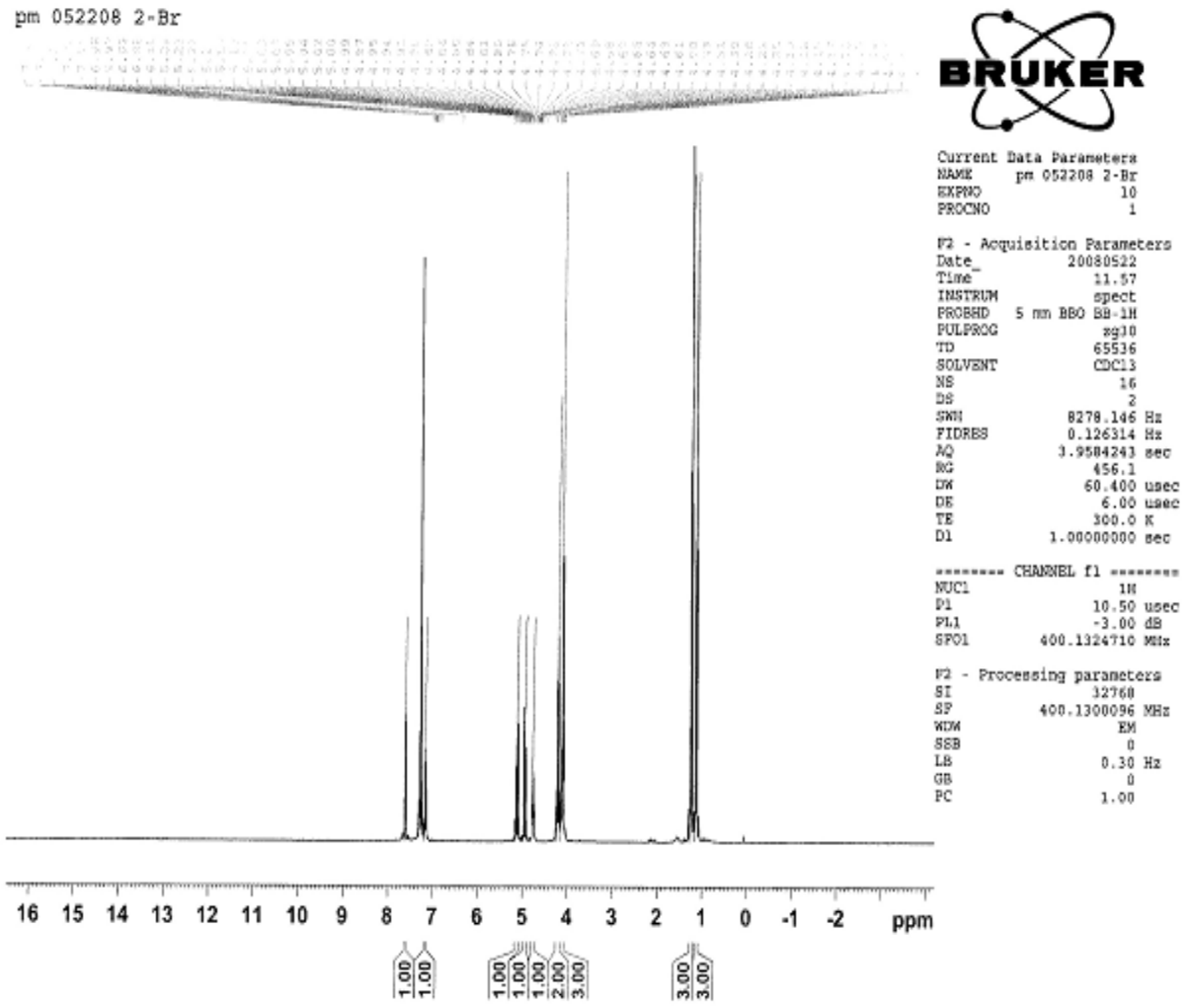
white solid; m.p. 59-60 ˚C; $[\alpha]_D^{28}$ = 1.1 (*c* 1.00, $CHCl_3$, 77% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.3 Hz, 1H), 7.36 (d, *J* = 2.0 Hz, 1H), 7.11 (dd, *J* = 2.0, 8.3 Hz, 1H), 4.87 (m, 2H), 4.22 (m, 3H), 4.08 (q, *J* = 7.3 Hz, 2H), 3.76 (d, *J* = 8.8 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 166.6, 136.8, 133.3, 132.9, 131.0, 130.4, 127.6, 77.2, 62.5, 62.3, 54.8, 42.2, 14.1, 13.9 ppm; IR (film) ν 3412, 2983, 2929, 1728, 1552, 1471, 1176, 1152, 1033 cm^{-1}; HRMS calcd for $C_{15}H_{17}Cl_2NO_6$ (M^+) 377.0433, obsd 377.0441; HPLC [Chiralcel AD-H, hexane/2-propanol = 90/10, 1.0 mL/min, λ = 254 nm, retention times: (major) 20.8 min, (minor) 27.9 min].



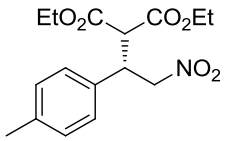
3.6e: *(S)-diethyl 2-(1-(2-bromophenyl)-2-nitroethyl)malonate*[4]



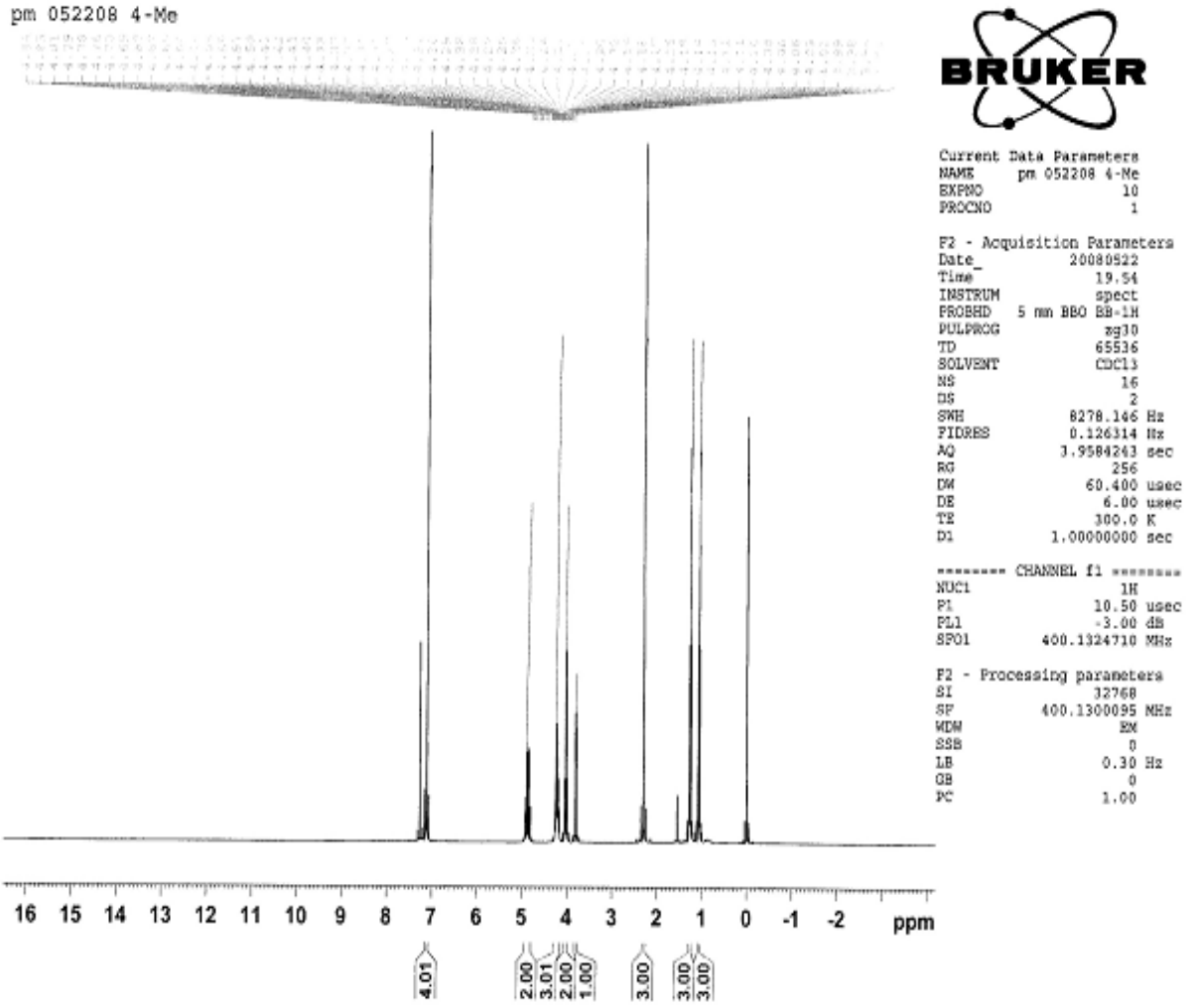
orange oil; $[\alpha]_D^{28}$ = -5.5 (*c* 1.00, $CHCl_3$, 57% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 1H), 7.28-7.12 (m, 3H), 5.12 (m, 1H), 4.94 (dd, *J* = 4.3, 13.6 Hz, 1H), 4.75 (m, 1H), 4.32-4.01 (m, 5H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 166.9, 135.7, 134.0, 129.8, 128.7, 128.0, 125.0, 75.9, 62.2, 62.2, 53.5, 41.7, 14.1, 13.9 ppm; HPLC [Chiralcel OD-H, hexane/2-propanol = 95/5, 1.0 mL/min, λ = 254 nm, retention times: (minor) 15.4 min, (major) 21.8min].



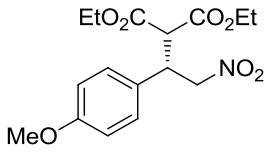
3.6f: *(S)-diethyl 2-(2-nitro-1-(p-tolyl)ethyl)malonate*[3]



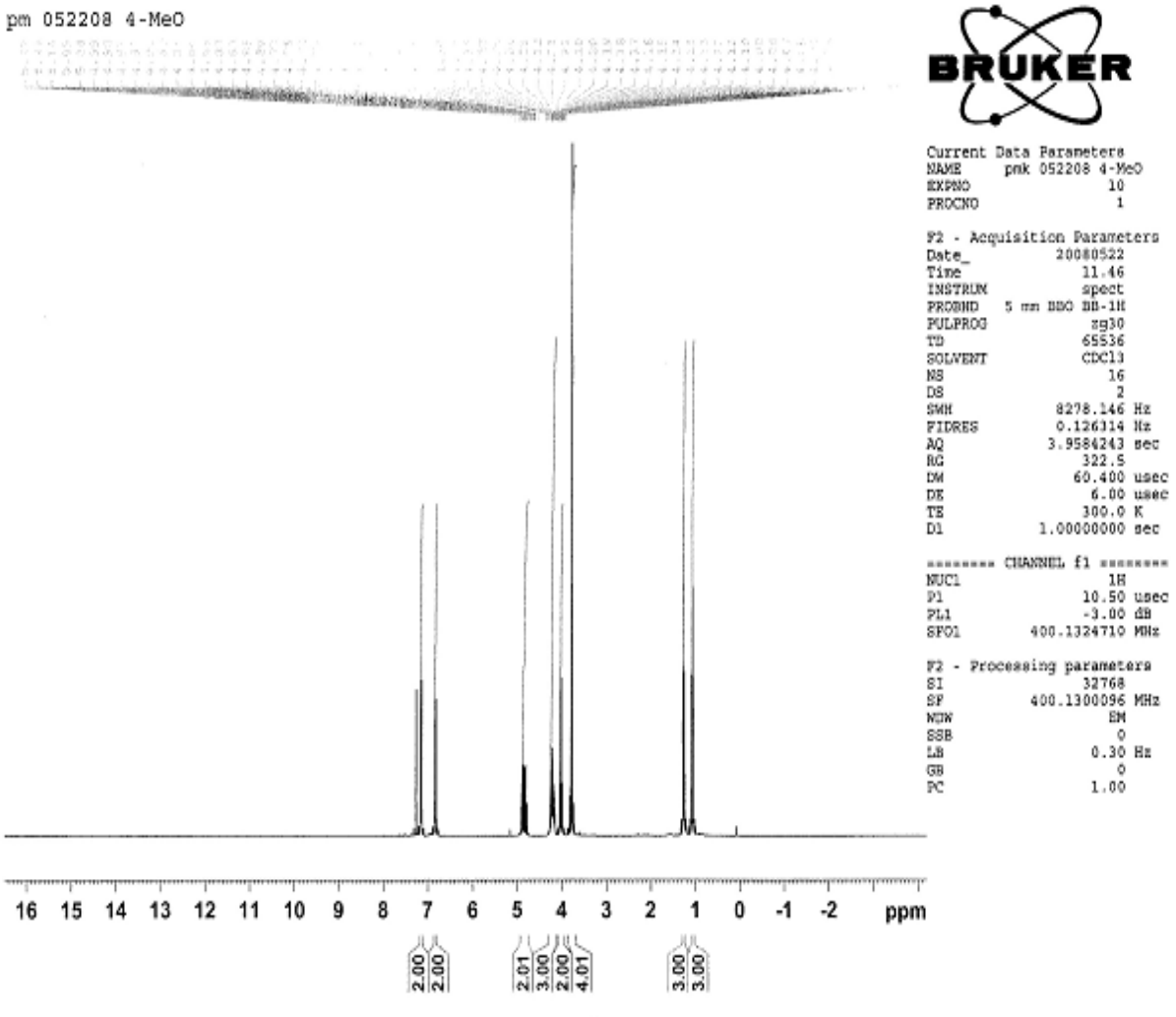
colorless oil; $[\alpha]_D^{28}$ = -3.3 (*c* 1.00, $CHCl_3$, 66% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 4H), 4.86 (m, 2H), 4.21 (m, 3H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.80 (d, *J* = 9.4 Hz, 1H), 2.30 (s, 3H), 1.26 (t, *J* = 7.6 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 167.0, 138.1, 133.4, 129.7, 128.0, 77.9, 62.1, 61.9, 55.2, 42.8, 21.12, 14.1, 13.8 ppm; HPLC [Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, λ = 254 nm, retention times: (R) (major) 20.8 min, (S) (minor) 53.1 min].



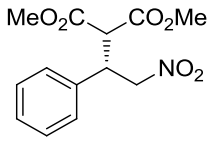
3.6g: *(S)-diethyl 2-(1-(4-methoxyphenyl)-2-nitroethyl)malonate*[3]



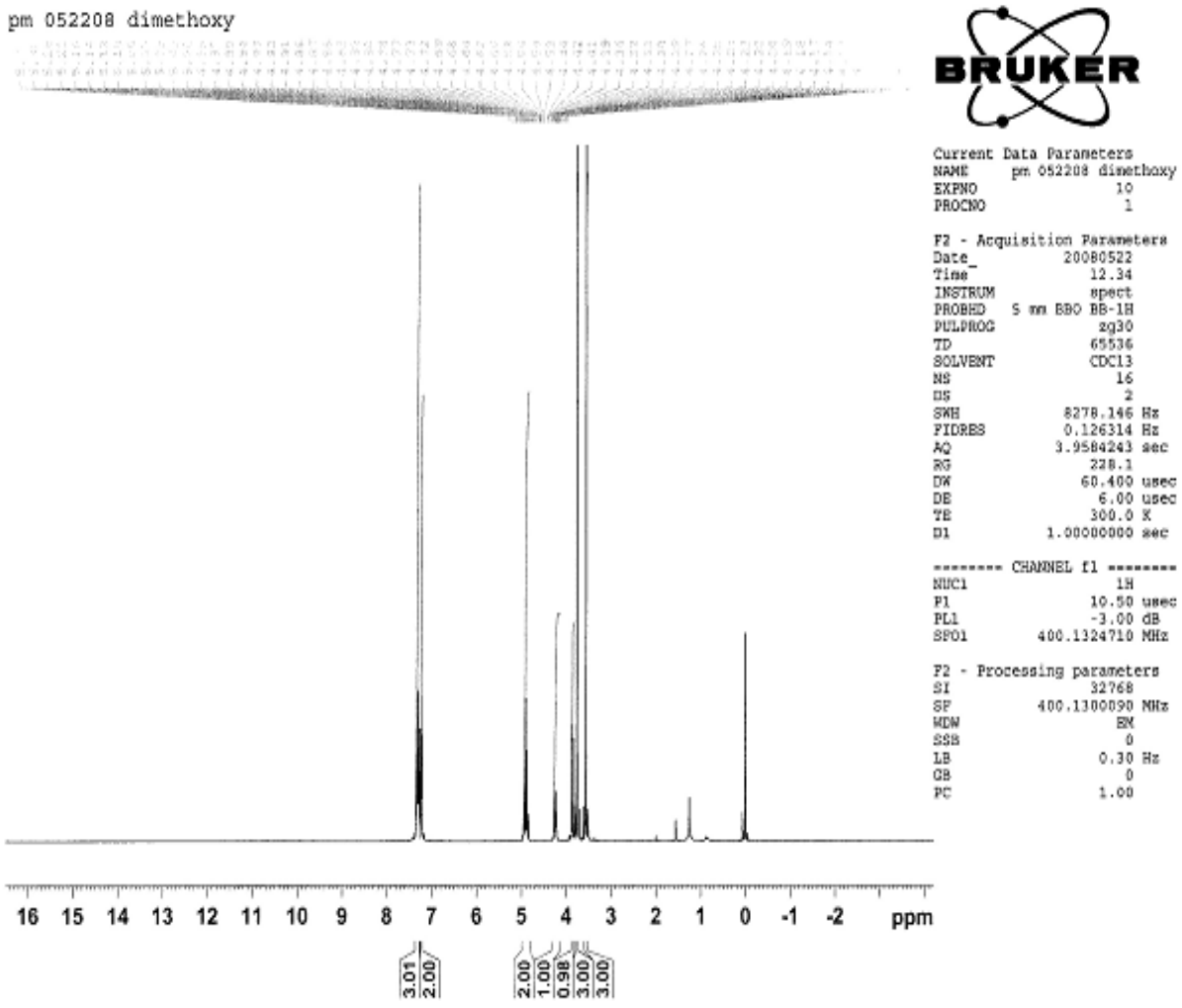
yellow oil; $[\alpha]_D^{28}$ = -4.9 (*c* 1.00, $CHCl_3$, 64% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 4.85 (m, 2H), 4.20 (m, 3H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.77 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 167.0, 159.6, 129.3, 128.2, 114.4, 78.0, 62.2, 61.9, 55.3, 55.3, 42.5, 14.1, 13.9 ppm; HPLC [Chiralcel AD-H, hexane/ethanol = 90/10, 1.0 mL/min, λ = 254 nm, retention times: (R) (major) 21.8 min, (S) (minor) 34.0 min].



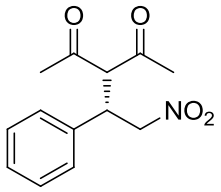
3.6h: *(S)-dimethyl 2-(2-nitro-1-phenylethyl)malonate*[3]



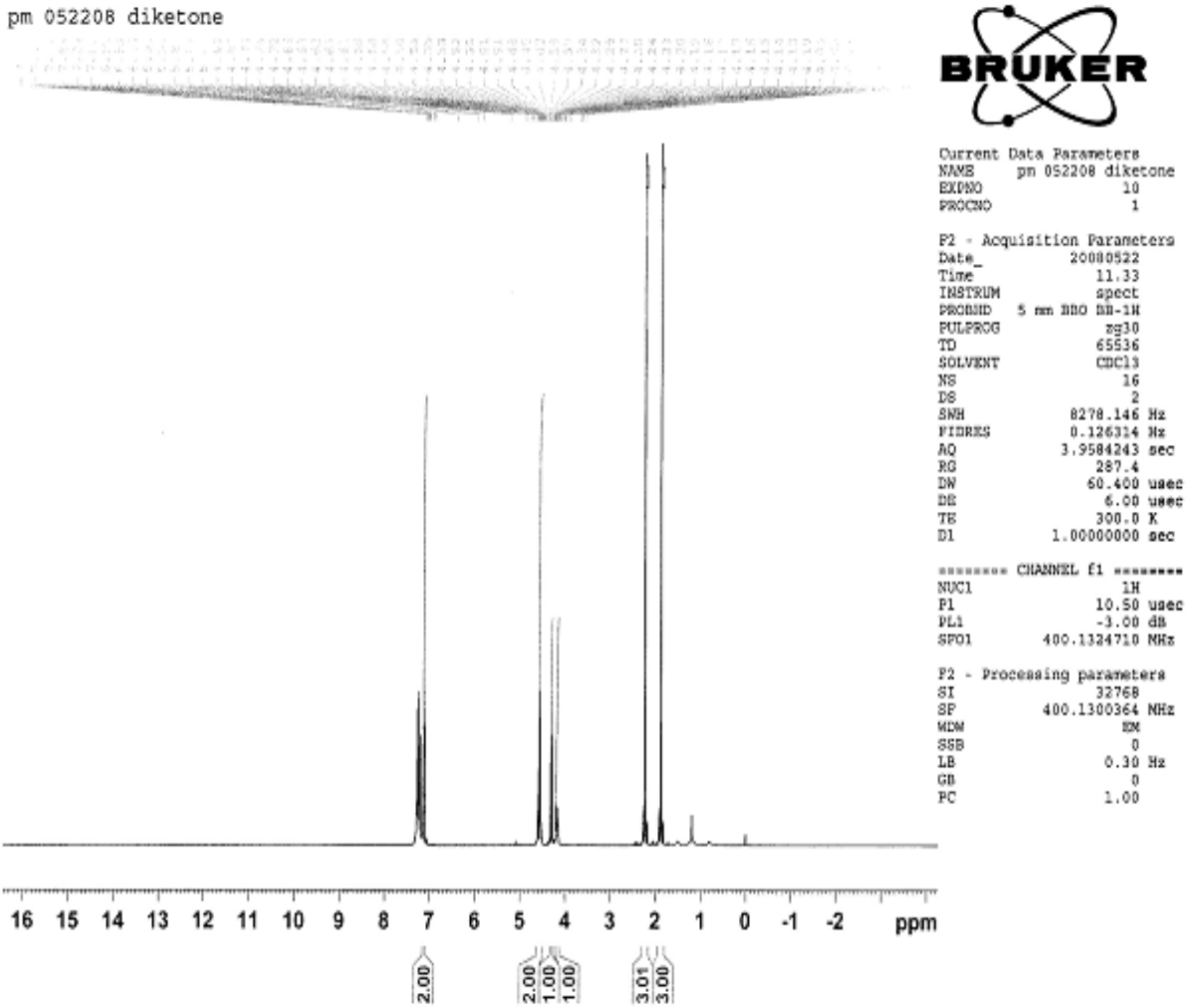
white solid; m.p. 53-54 ˚C; $[\alpha]_D^{28}$ = -4.6 (*c* 1.00, $CHCl_3$, 63% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.2 (m, 5H), 4.91 (m, 2H), 4.25 (td, *J* = 5.3, 8.8 Hz, 1H), 3.87 (d, *J* = 9.1 Hz, 1H), 3.76 (s, 3H), 3.56 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 167.3, 136.3, 129.1, 128.5, 128.0 77.5, 54.9, 53.0, 52.8, 43.0 ppm; HPLC [Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, λ = 254 nm, retention times: (R) (major) 26.2 min, (S) (minor) 40.8 min].



3.6i: *(S)-3-(2-nitro-1-phenylethyl)pentane-2,4-dione*[5]



white solid; m.p. 110-111 ˚C; $[\alpha]_D^{28}$ = -95.4 (*c* 1.00, $CHCl_3$, 49% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 3H), 7.19 (m, 2H), 4.63 (m, 2H), 4.37 (d, *J* = 10.9 Hz, 1H), 4.24 (m, 1H), 2.30 (s, 3H), 1.94 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 201.1, 136.3, 129.5, 128.7, 128.1, 78.3, 70.9, 43.0, 30.5, 29.7 ppm; HPLC [Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, λ = 254 nm, retention times: (S) (minor) 18.2 min, (R) (major) 25.6 min].

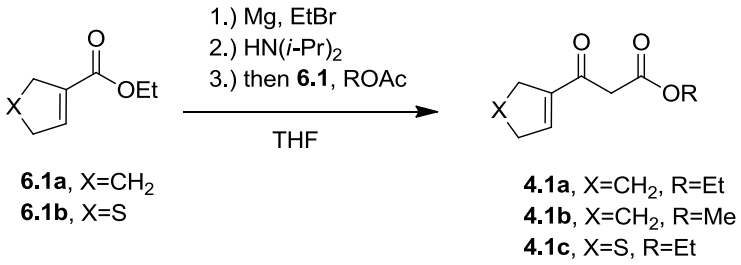


6.3 Experimental and Characterization for Chapter 4

Determination of Enantiomeric Excesses
Enantiomeric excesses were determined by comparison to a racemic sample (prepared with the corresponding racemic catalyst ***rac*–1.12a**).

Preparation of catalysts and starting enals (1.12a-e, 1.67d, 1.67e, 1.67g)
Catalysts **1.12a**–**e**[6-7] were prepared from the corresponding diarylprolinols[8] using known procedures. Noncommercially available enals **1.67d**, **1.67e**, and **1.67g,** were prepared according to a known procedure.[9]

Preparation of β-ketoesters (4.1a–c)



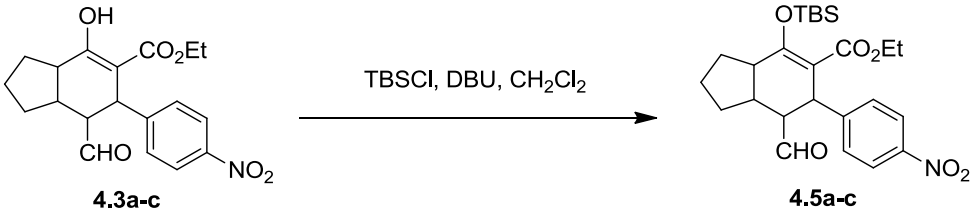
The β-ketoester **4.1a** was prepared using an adapted procedure.[10] To a two–neck, round–bottom flask equipped with an internal thermometer was added magnesium metal (2.5 g, 103 mmol) and THF (21 mL). Bromoethane (7.5 mL, 100 mmol) was slowly added to this solution while maintaining the internal temperature below 25 ºC. The mixture was allowed to stir at room temperature until all the metal had reacted (~1h). The flask was equipped with an outlet and a solution of diisopropylamine (14.2 ml, 100 mmol) in THF (21 mL) was slowly added while maintaining the internal temperature below 25 ºC. The mixture was allowed to stir at room temperature for 3 hours. The temperature of the mixture was lowered to 10 ºC and a solution of **6.1a**[11] (7.0 g, 50 mmol), ethyl acetate (4.90 mL, 50 mmol), and THF (35 mL) was added while maintaining the internal temperature between 10–15 ºC. The reaction was allowed to stir at room temperature for 3 hours and the reaction was poured into aqueous H_2SO_4 (4M) with ice. The mixture was extracted three times with Et_2O. The ether extracts were combined, dried over $MgSO_4$, filtered and concentrated. The mixture was purified via flash chromatography (petroleum ether/Et_2O, 97/3) and β-ketoester **4.1a** was isolated in 70% yield. Characterization of **4.1a** was in agreement with experimental data.[10]

β-ketoesters **4.1b** and **4.1c** were prepared from **6.1a**[11] and **6.1b**[12], respectively, using the same procedure and were obtained in similar yields.

General Procedure for synthesis of carbocycles (4.3a–c and **4.11–4.12** and **4.14–4.19)**
To an oven dried flask was added catalyst **1.12a** (32.6 mg, 0.1 mmol), toluene (3.33 mL), β-ketoester **4.1** (182.2 mg, 1.0 mmol), and enal **1.67** (177.2 mg, 1.0 mmol). The reaction was allowed to stir for the indicated time at room temperature. The reaction mixture was filtered through a plug of silica and concentrated. The percent conversion of the crude reaction mixture could be determined by ^{1}H NMR using an internal standard. The diastereomeric mixture of **4.3a**,

4.3b and **4.3c** was then purified via column chromatography (petroleum ether/Et_2O, 85/15) and an isolated yield was determined. The diastereomeric ratio of the isolated product was determined through comparison of the relative integrations of the aldehyde and/or enol peaks in the ^1H NMR spectrum. Samples of the pure diastereomers **4.3a**, **4.3b** and **4.3c** were obtained through further flash chromatography. Carbocycles **4.11**–**4.12** and **4.14**–**4.19** were prepared and purified using the same procedure.

Silylation Of Carbocycles for (4.5a–c)



4.3a-c **4.5a-c**

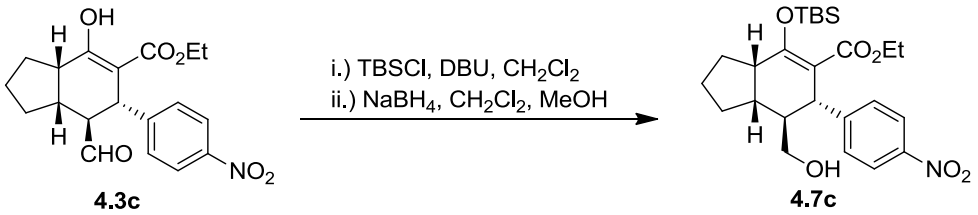
To an oven dried flask was added **4.3** (270 mg, 0.75 mmol), CH_2Cl_2 (29 mL), and TBSCl (234 mg, 1.55 mmol). DBU (232 µL, 1.55 mmol) was added dropwise to the stirring solution of **4.3**. The reaction was monitored by TLC and was quenched when **4.3** was completely consumed (~1.5 h). The reaction was diluted with CH_2Cl_2 and washed with saturated aqueous NH_4Cl. The aqueous layer was washed with two portions of CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4 and concentrated. Product **4.5b** and **4.5a/4.5c** were purified via column chromatography (petroleum ether/Et_2O, 90/10).

Desilylation of Silyl Enol Ethers (4.3a–c)

4.5a-c **4.3a-c**

To an oven dried flask was added **4.5** (93.9 mg, 0.20 mmol) and THF (7 mL). A 1.0 M THF solution of TBAF (285 µL) was added dropwise to the stirring solution of **4.5** in an ice bath. The reaction was stirred for only five minutes to prevent epimerization. The reaction was diluted with Et_2O and washed with saturated aqueous NH_4Cl. The aqueous layer was washed with Et_2O and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The diastereomers of **4.3** were separated via column chromatography (petroleum ether/Et_2O, 85/15).

Preparation and Characterization of Alcohol 4.7c

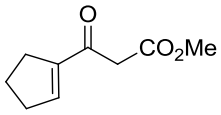


4.3c **4.7c**

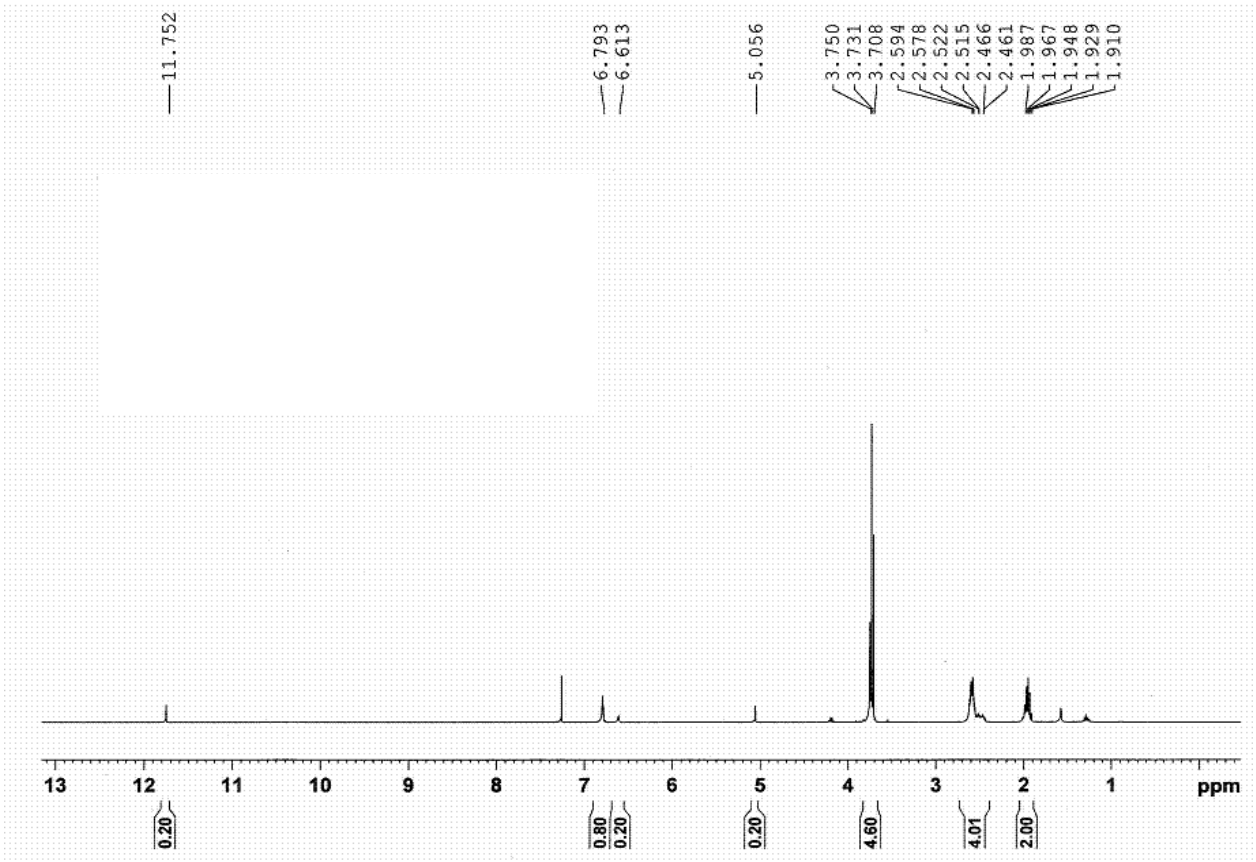
To an oven dried flask was added **4.3c** (13.0 mg, 36 µmol), CH_2Cl_2 (1.4 mL), and TBSCl (11.3 mg, 75 µmol). DBU (11.2 µL, 75 µmol) was added dropwise to the stirring solution of **4.3c**. The reaction was monitored by TLC and was quenched when **4.3c** was completely consumed (~1.5 h). The reaction was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous NH_4Cl (15 mL). The aqueous layer was washed with CH_2Cl_2 (2 x 15 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The silylated intermediate was purified via column chromatography (petroleum ether/Et_2O, 90/10) and used in step ii.).

To an oven dried flask was added, the silylated intermediate from step i.) (17.1 mg, 36 µmol) and a 1/1 mixture of MeOH/CH_2Cl_2 (1 mL). The stirring solution was cooled in an ice bath and $NaBH_4$ (9.5 mg, 252 µmol) was added. The reaction was stirred at 0º C and was monitored by TLC. The reaction was quenched after the silylated intermediate was completely consumed (~30 min). The reaction was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous NH_4Cl (15 mL). The aqueous layer was washed with CH_2Cl_2 (2 x 15 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. Alcohol **4.7c** was purified via column chromatography (petroleum ether/EtOAc, 80/20).

4.1b: *methyl 3-cyclopentenyl-3-oxopropanoate*



pale yellow oil. IR (thin film, KBr): 2954, 2843, 1747, 1656, 1588, 1445, 1363, 1263, 1209, 1063, 1004, 954, 800, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), keto form: δ 6.79 (m, 1H), 3.73 (s, 3H), 3.71 (s, 2H), 2.59 (m, 4H), 1.95 (quintet, J = 7.6 Hz, 2H) ppm, enol form: δ 11.75 (s, 1H), 6.61 (m, 1H), 5.06 (s, 1H), 3.75 (s, 3H), 2.52-2.46 (m, 4H), 1.97 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$), keto and enol form: δ 190.3, 173.5, 168.5, 168.1, 146.1, 145.5, 138.2, 137.6, 88.5, 52.4, 51.3, 46.1, 31.2, 33.6, 31.0, 30.7, 23.2, 22.9 ppm. HRMS (ESI) : [M^+] calcd for [$C_9H_{12}O_3$]: 168.0786, found: 168.0790.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5.056
3.750
3.731
3.708
2.594
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2.522
2.515
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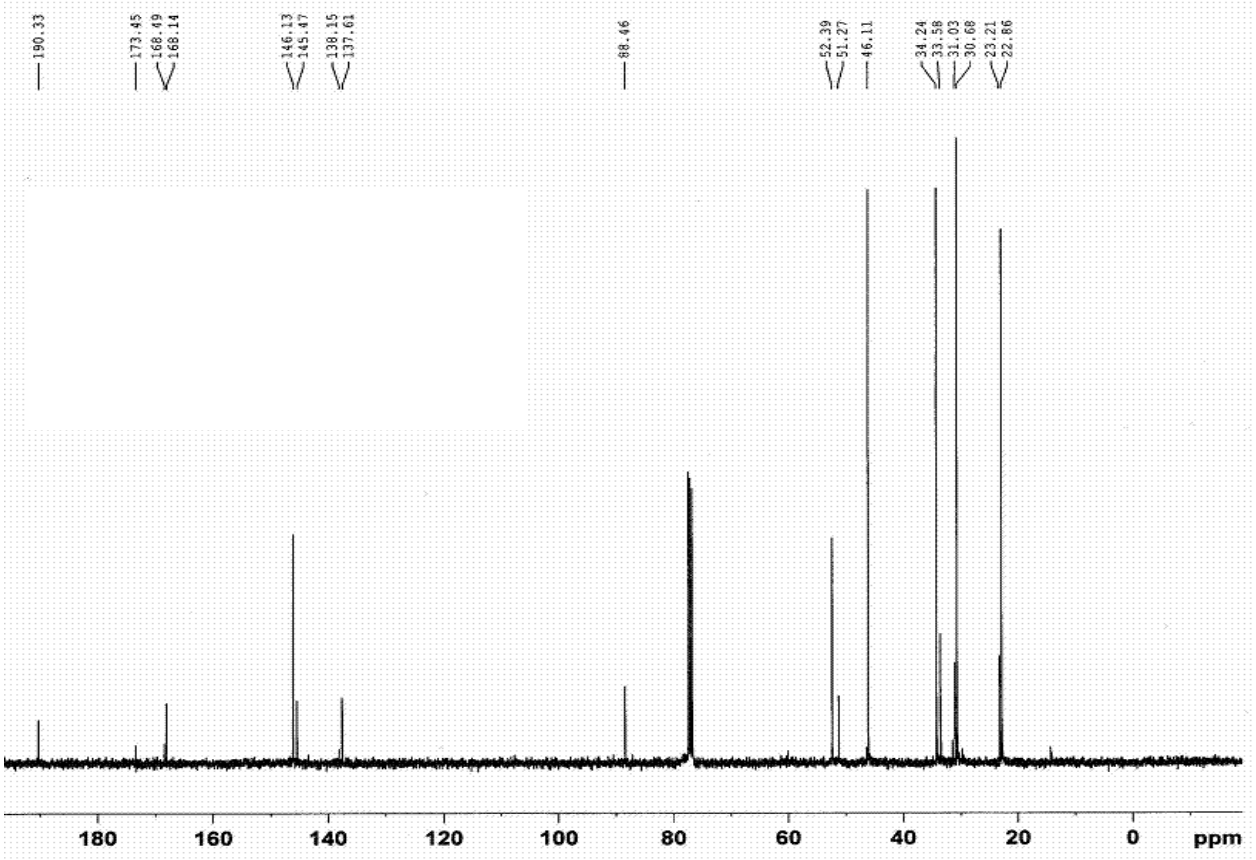
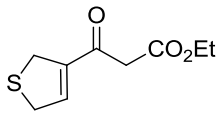
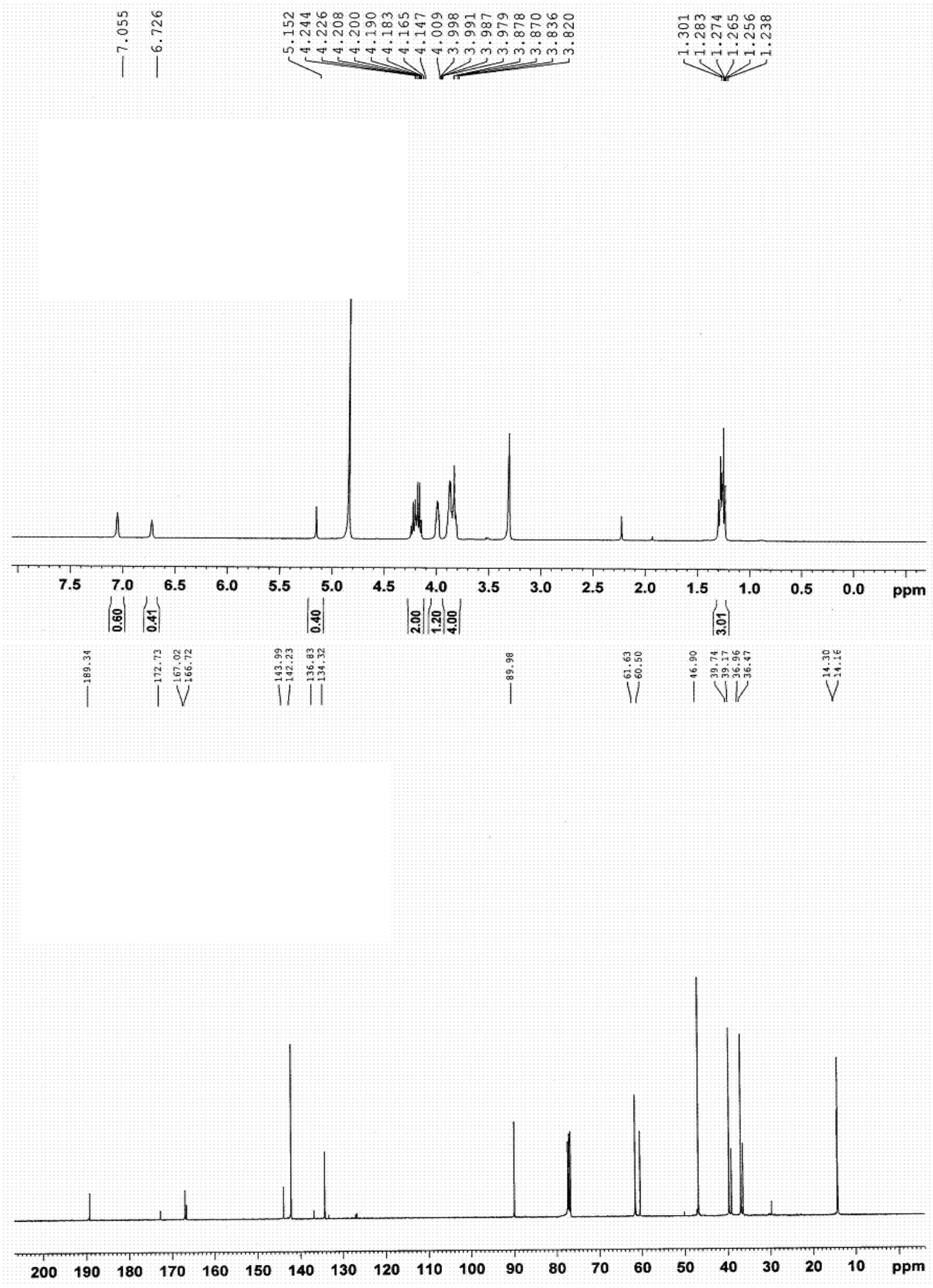
1.987
1.967
1.948
1.929
1.910
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.20
0.80
0.20
0.20
4.60
4.01
2.00


190.33
173.45
168.49
168.14
146.13
145.47
138.15
137.61
88.46
52.39
51.27
46.11
34.24
33.58
31.03
30.68
23.21
22.86
180
160
140
120
100
80
60
40
20
0
ppm

4.1c: *ethyl 3-(2,5-dihydrothiophen-3-yl)-3-oxopropanoate*



pale yellow oil. IR (thin film, KBr): 2982, 1740, 1675, 1599, 1422, 1252, 1222, 1182, 1034, 797 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD), keto form: δ 7.06 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.00 (m, 2H), 3.87 (m, 2H), 3.84 (s, 2H), 1.26 (t, *J* = 7.2 Hz, 3H) ppm, enol form: δ 6.73 (m, 1H), 5.15 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.88-3.82 (m, 4H), 1.28 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$), keto and enol form: δ 189.3, 172.7, 167.0, 166.7, 144.0, 142.2, 136.8, 134.3, 90.0, 61.6, 60.5, 46.9, 39.7, 39.2, 37.0, 36.5, 14.3, 14.2 ppm. HRMS (ESI) : $[M^+]$ calcd for $[C_9H_{12}O_3S]$: 200.0507, found: 200.0512.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4.226
4.208
4.200
4.190
4.183
4.165
4.147
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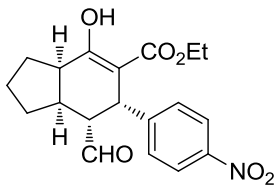
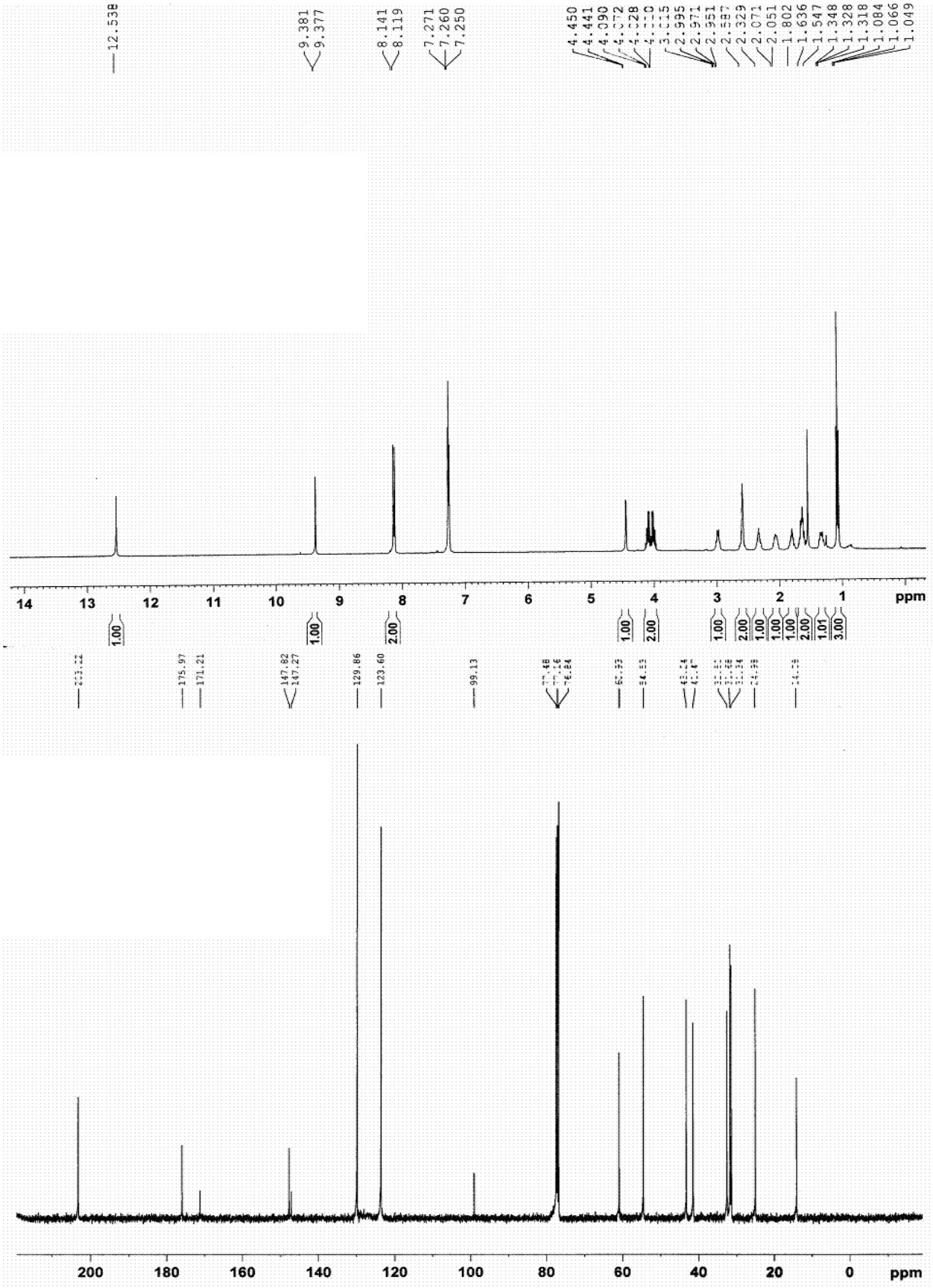
3.991
3.987
3.979
3.878
3.870
3.836
3.820
1.301
1.283
1.274
1.265
1.256
1.238
ppm
0.60
0.41
0.40
2.00
1.20
4.00
3.01
189.34
172.73
167.02
166.72
143.99
142.23
136.83
134.32
89.98
61.63
60.50
46.90
39.74
39.17
36.96
36.47
14.30
14.16
ppm

4.3a: *(3aR,6S,7R,7aS)-ethyl 7-formyl-4-hydroxy-6-(4-nitrophenyl)-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate*



colorless crystals. m.p.: 84-86 °C. $[\alpha]_D^{23}$ = +177.8 (*c* 1.00, CH_2Cl_2, 99% ee); IR (thin film, KBr): 2962, 2870, 1721, 1650, 1615, 1519, 1348, 1280, 1243, 1213, 855, 826, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.54 (s, 1H), 9.38 (d, *J* = 1.7 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 4.45 (d, *J* = 3.9 Hz, 1H), 4.05 (m, 2H), 2.98 (q, *J* = 8.2 Hz, 1H), 2.59 (m, 2H), 2.32 (m, 1H), 2.06 (m, 1H), 1.80 (m, 1H), 1.59 (m, 2H), 1.33 (m, 1H), 1.07 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 176.0, 171.2, 147.8, 147.3, 129.9, 123.6, 99.1, 60.9, 54.5, 43.2, 41.5, 32.5, 31.7, 31.3, 25.0, 14.1 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 99:1), 1.0 mL/min; major enantiomer t_R = 20.7 min, minor enantiomer t_R = 24.8 min. HRMS (ESI) : $[M^-]$ calcd for $[C_{19}H_{21}NO_6]$: 359.1369, found: 359.1377.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9.377
8.141
8.119
7.271
7.260
7.250
4.450
4.441
4.090
1.802
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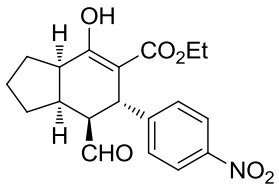
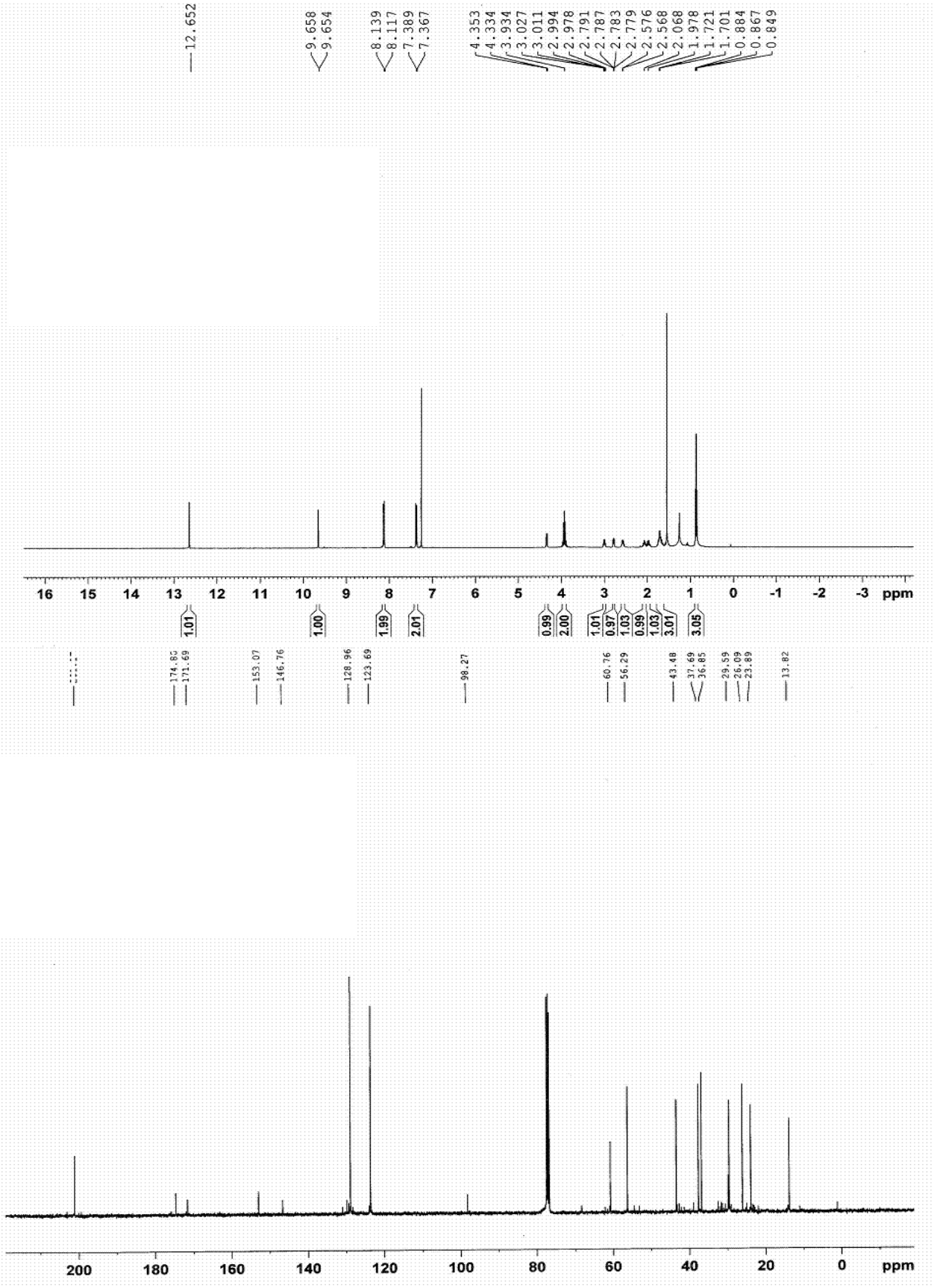
1.547
1.348
1.328
1.318
1.084
1.066
1.049
ppm
223.22
175.97
171.21
147.82
147.27
129.86
123.60
99.13
77.48
77.16
76.84
67.33
54.83
43.24
41.47
32.61
31.68
31.34
24.98
14.78
200
180
160
140
120
100
80
60
40
20
0
ppm

4.3b: *(3aR,6S,7S,7aS)-ethyl 7-formyl-4-hydroxy-6-(4-nitrophenyl)-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate*



colorless amorphous solid. $[\alpha]_D^{23}$ = +65.9 (*c* 0.500, CH_2Cl_2, 99% ee); IR (thin film, KBr): 2958, 1721, 1647, 1608, 1519, 1347, 1235, 1109, 853 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.65 (s, 1H), 9.66 (d, *J* = 1.5 Hz, 1H), 8.13 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 4.34 (d, *J* = 7.8 Hz, 1H), 3.93 (m, 2H), 3.00 (q, *J* = 6.3 Hz, 1H), 2.79 (m, 1H), 2.57 (m, 1H), 2.07 (m, 1H), 1.98 (m, 1H), 1.71 (m, 3H), 1.55 (m, 1H), 0.87 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 174.8, 171.7, 153.1, 146.8, 129.0, 123.7, 98.3, 60.8, 56.3, 43.5, 37.7, 36.9, 29.6. 26.1. 23.9. 13.8 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 99:1), 1.0 mL/min; minor enantiomer t_R = 27.4 min, major enantiomer t_R = 32.3 min. HRMS (ESI) : $[M^-]$ calcd for $[C_{19}H_{21}NO_6]$: 359.1369, found: 359.1370.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7.367
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4.334
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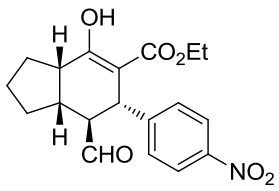
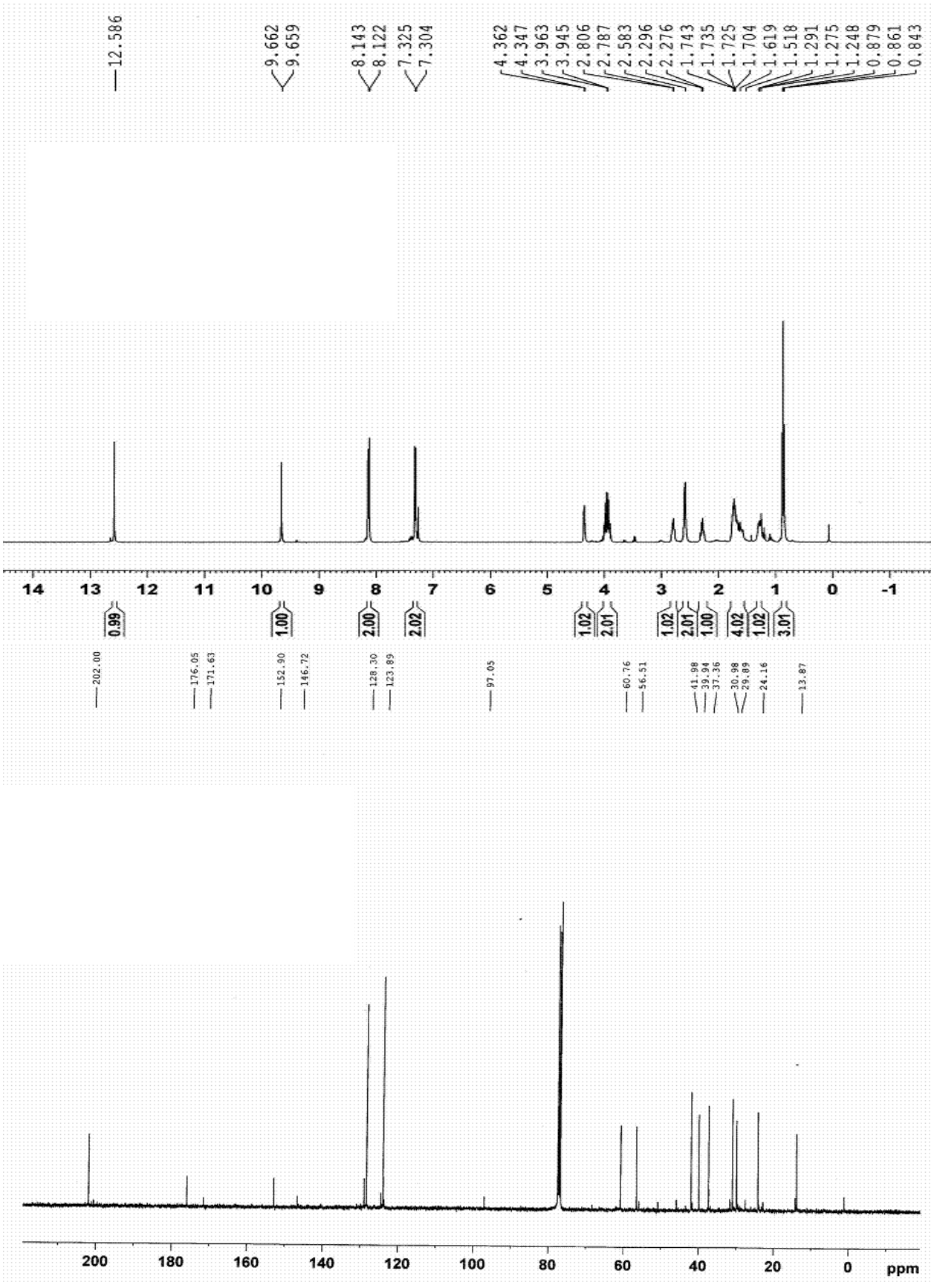
2.978
2.791
2.787
2.783
2.779
2.576
2.568
2.068
1.978
1.721
1.701
0.884
0.867
0.849
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm
1.01 1.00 1.99 2.01 0.99 2.00 1.01 0.97 1.03 0.99 1.03 3.01 3.05
174.80
171.69
153.07
146.76
128.96
123.69
98.27
60.76
56.29
43.48
37.69
36.85
29.59
26.09
23.89
13.82
200 180 160 140 120 100 80 60 40 20 0 ppm

4.3c: *(6S,7S,7aR)-ethyl 7-formyl-4-hydroxy-6-(4-nitrophenyl)-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate*



colorless crystals. m.p.: 95-97 °C. $[\alpha]_D^{25}$ = +20.1 (*c* 0.500, CH_2Cl_2, 37% ee); IR (thin film, KBr): 2963, 2874, 1725, 1650, 1613, 1519, 1348, 1286, 1228, 855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.59 (s, 1H), 9.66 (d, *J* = 1.2 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 4.35 (d, *J* = 5.9 Hz, 1H), 3.95 (m, 2H), 2.80 (q, *J* = 7.6 Hz, 1H), 2.58 (m, 2H), 2.29 (m, 1H), 1.52-1.78 (m, 4H), 1.28 (m, 1H), 0.86 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 176.1, 171.6, 152.9, 146.7, 128.3, 123.9, 97.1, 60.8, 56.5, 42.0, 39.9, 37.4, 31.0, 29.9, 24.2, 13.9 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 22.5 min, minor enantiomer t_R = 66.5 min. HRMS (ESI) : $[M^-]$ calcd for $[C_{19}H_{21}NO_6]$: 359.1369, found: 359.1370.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7.325
7.304
4.362
4.347
3.963
3.945
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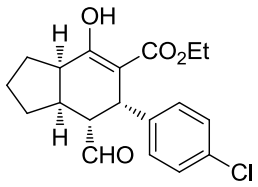
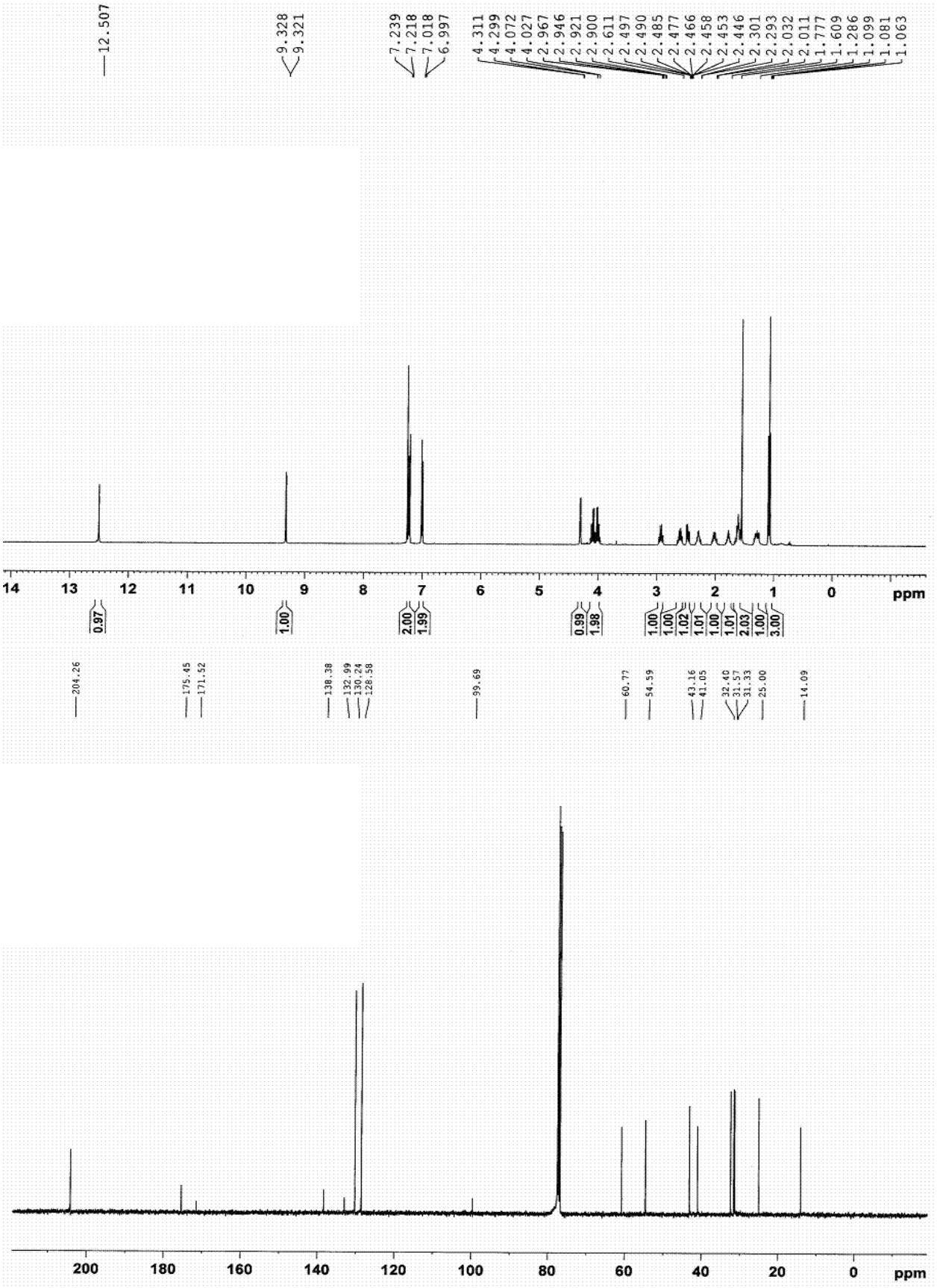
2.583
2.296
2.276
1.743
1.735
1.725
1.704
1.619
1.518
1.291
1.275
1.248
0.879
0.861
0.843
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
0.99
1.00
2.00
2.02
1.02
2.01
1.02
2.01
1.00
4.02
1.02
3.01
202.00
176.05
171.63
152.90
146.72
128.30
123.89
97.05
60.76
56.51
41.98
39.94
37.36
30.98
29.89
24.16
13.87
200 180 160 140 120 100 80 60 40 20 0 ppm

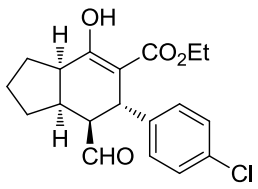
4.11a: *(3aR,6S,7R,7aS)-ethyl 6-(4-chlorophenyl)-7-formyl-4-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate*



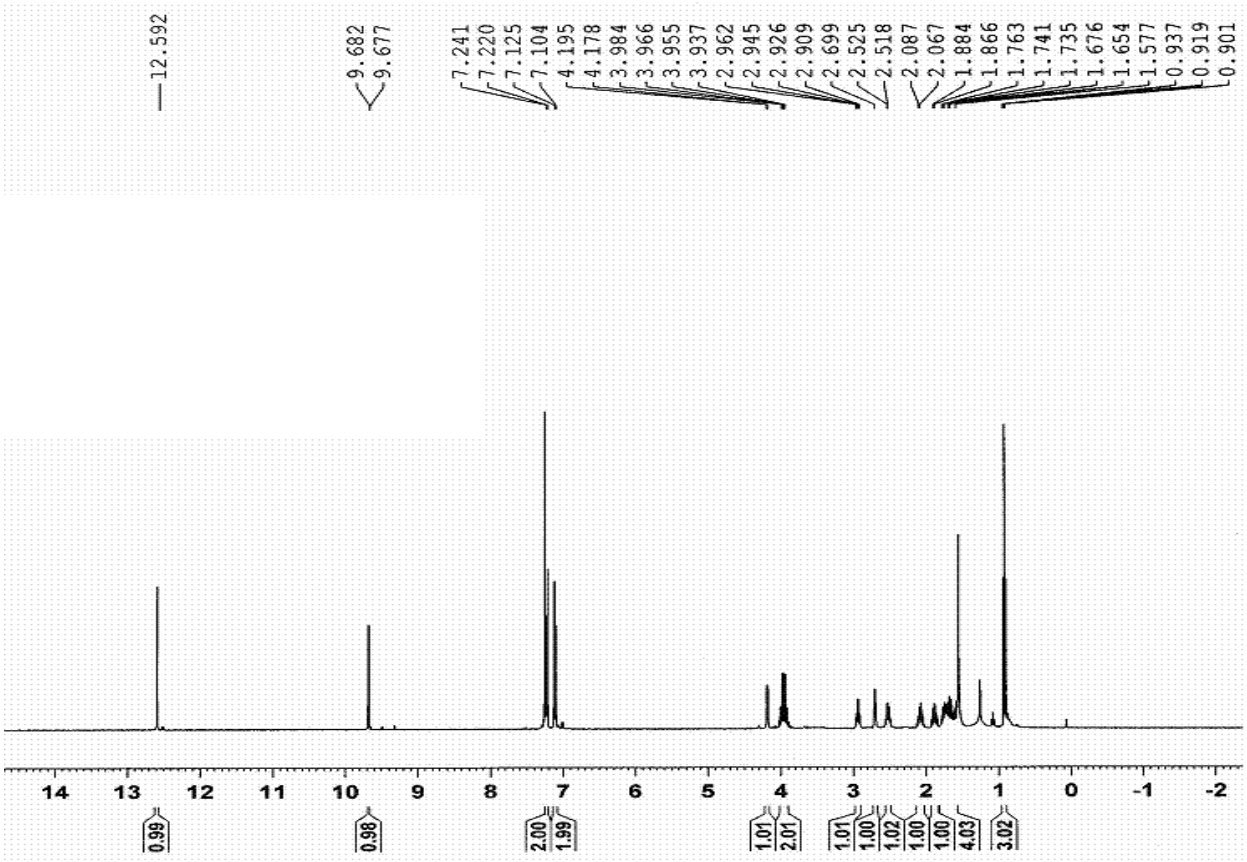
colorless amorphous solid. $[\alpha]_D^{24}$ = +120.7 (*c* 1.00, CH_2Cl_2, 99% ee); IR (thin film, KBr): 2961, 2871, 1723, 1650, 1616, 1279, 1242, 1213, 1093, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.51 (s, 1H), 9.32 (d, *J* = 2.8 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 4.31 (d, *J* = 4.9 Hz, 1H), 4.05 (m, 2H), 2.88 (q, *J* = 8.6 Hz, 1H), 2.60 (m, 1H), 2.48 (m, 1H), 2.29 (m, 1H), 2.02 (m, 1H), 1.78 (m, 1H), 1.61 (m, 2H), 1.29 (m, 1H), 1.08 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 175.4, 171.5, 138.4, 133.0, 130.2, 128.6, 99.7, 60.8, 54.6, 43.2, 41.0, 32.4, 31.6, 31.3, 25.0, 14.1 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 99:1), 0.5 mL/min; major enantiomer t_R = 14.3 min, minor enantiomer t_R = 18.7 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{19}H_{21}ClO_4]$: 348.1128, found: 348.1129.

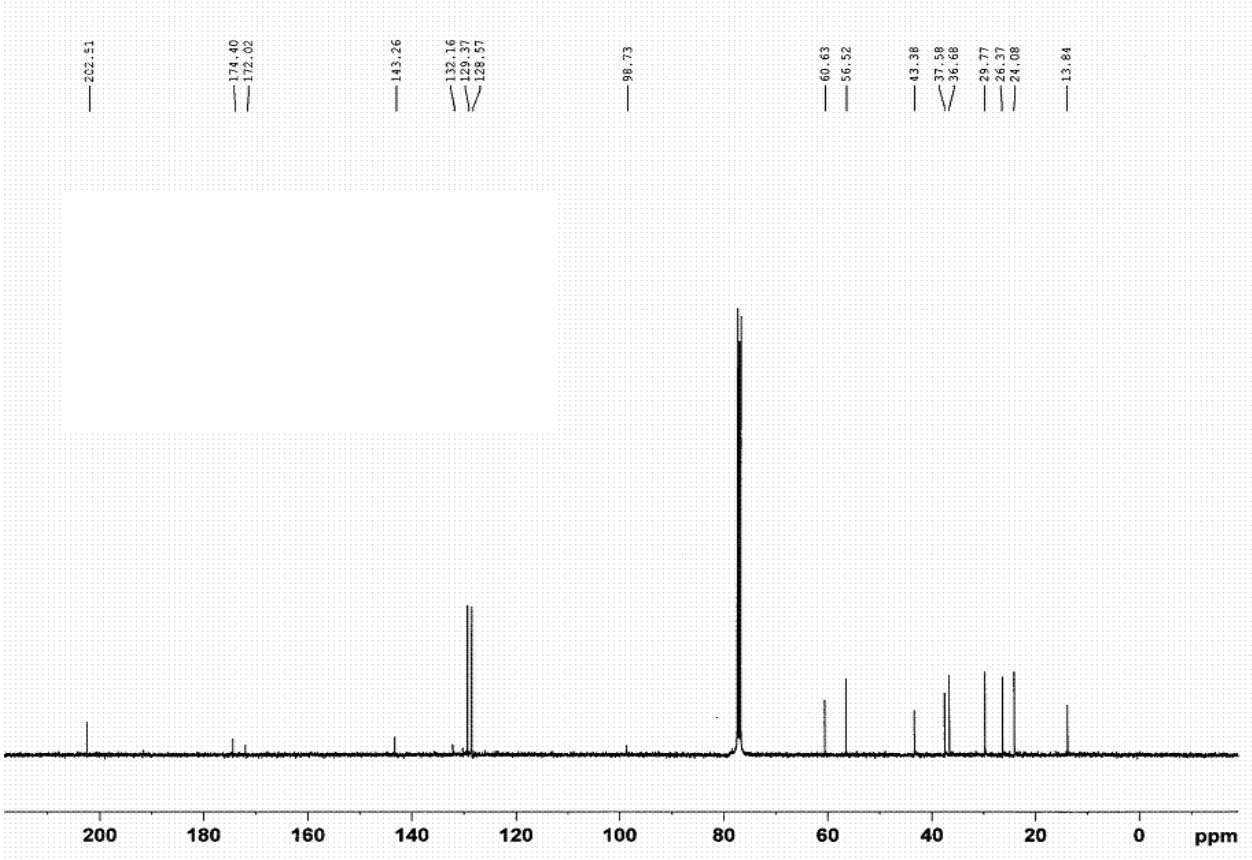

12.507
9.328
9.321
7.239
7.218
7.018
6.997
4.311
4.299
4.072
4.027
2.967
2.946
2.921
2.900
2.611
2.497
2.490
2.485
2.477
2.466
2.458
2.453
2.446
2.301
2.293
2.032
2.011
1.777
1.609
1.286
1.099
1.081
1.063
ppm
0.97
1.00
2.00
1.99
0.99
1.98
1.00
1.00
1.02
1.01
1.00
1.01
2.03
1.00
3.00
204.26
175.45
171.52
138.38
132.99
130.24
128.58
99.69
60.77
54.59
43.16
41.05
32.40
31.57
31.33
25.00
14.09
ppm

4.11b: *(3aR,6S,7S,7aS)-ethyl 6-(4-chlorophenyl)-7-formyl-4-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate*

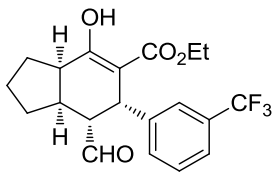


colorless oil. $[\alpha]_D^{24}$ = +31.3 (*c* 0.500, CH_2Cl_2, 98% ee); IR (thin film, KBr): 2958, 2874, 1723, 1647, 1613, 1490, 1308, 1235, 1091, 1014, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.59 (s, 1H), 9.68 (d, *J* = 1.7 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 4.19 (d, *J* = 7.0 Hz, 1H), 3.96 (m, 2H), 2.94 (q, *J* = 7.3 Hz, 1H), 2.70 (m, 1H), 2.52 (m, 1H), 2.08 (m, 1H), 1.88 (m, 1H), 1.78-1.87 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 174.4, 172.0, 143.3, 132.2, 129.4, 128.6, 98.7, 60.6, 56.5, 43.4, 37.6, 36.7, 29.8, 26.4, 24.1, 13.8 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 99:1), 0.3 mL/min; major enantiomer t_R = 24.3 min, minor enantiomer t_R = 31.6 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{19}H_{21}ClO_4]$: 348.1128, found: 348.1131.

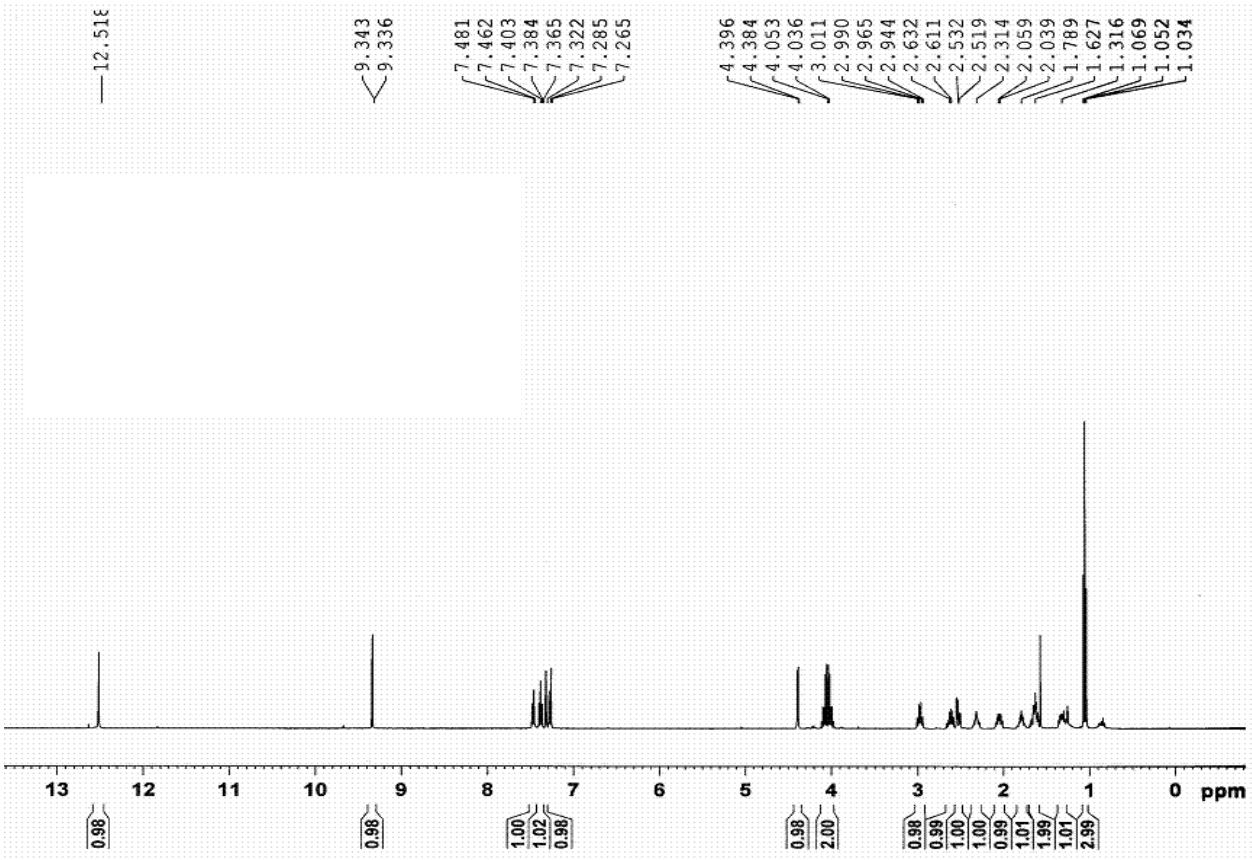

12.592
9.682
9.677
7.241
7.220
7.125
7.104
4.195
4.178
3.984
3.966
3.955
3.937
2.962
2.945
2.926
2.909
2.699
2.525
2.518
2.087
2.067
1.884
1.866
1.763
1.741
1.735
1.676
1.654
1.577
0.937
0.919
0.901
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
0.99
0.98
2.00
1.99
1.01
2.01
1.01
1.00
1.02
1.00
1.00
4.03
3.02

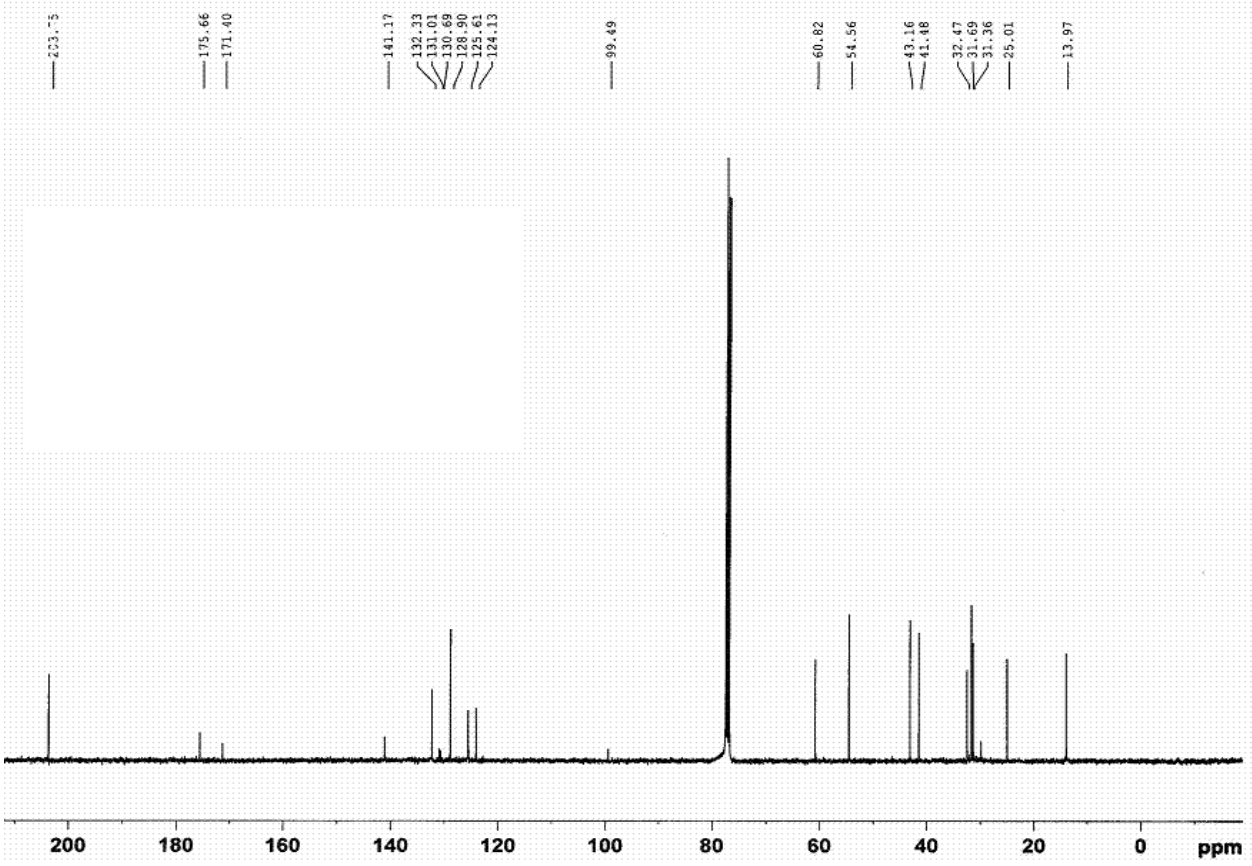

202.51
174.40
172.02
143.26
132.16
129.37
128.57
98.73
60.63
56.52
43.38
37.58
36.68
29.77
26.37
24.08
13.84
200 180 160 140 120 100 80 60 40 20 0 ppm

4.12a: *(3aR,6S,7R,7aS)-ethyl 7-formyl-4-hydroxy-6-(3-(trifluoromethyl)phenyl)-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate*

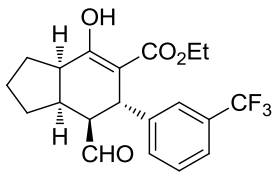


colorless oil. $[\alpha]_D^{24}$ = +126.1 (*c* 1.00, CH_2Cl_2, 99% ee); IR (thin film, KBr): 2964, 2872, 1724, 1651, 1618, 1328, 1244, 1165, 1126, 1033, 831, 806, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.52 (s, 1H), 9.34 (d, *J* = 2.6 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.32 (s, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 4.39 (d, *J* = 4.9 Hz, 1H), 4.04 (m, 2H), 2.98 (q, *J* = 8.5 Hz, 1H), 2.62 (m, 1H), 2.53 (m, 1H), 2.31 (m, 1H), 2.05 (m, 1H), 1.79 (m, 1H), 1.63 (m, 2H), 1.07 (m, 1H), 1.05 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 175.7, 171.4, 141.2, 132.3, 131.0, 130.7, 128.9, 125.6, 124.1, 99.5, 60.8, 54.6, 43.2, 41.5, 32.5, 31.7, 31.4, 25.0, 14.0 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 99:1), 0.2 mL/min; major enantiomer t_R = 38.4 min, minor enantiomer t_R = 43.8 min. HRMS (ESI) : $[M^-]$ calcd for $[C_{20}H_{21}F_3O_4]$: 382.1392, found: 382.1395.

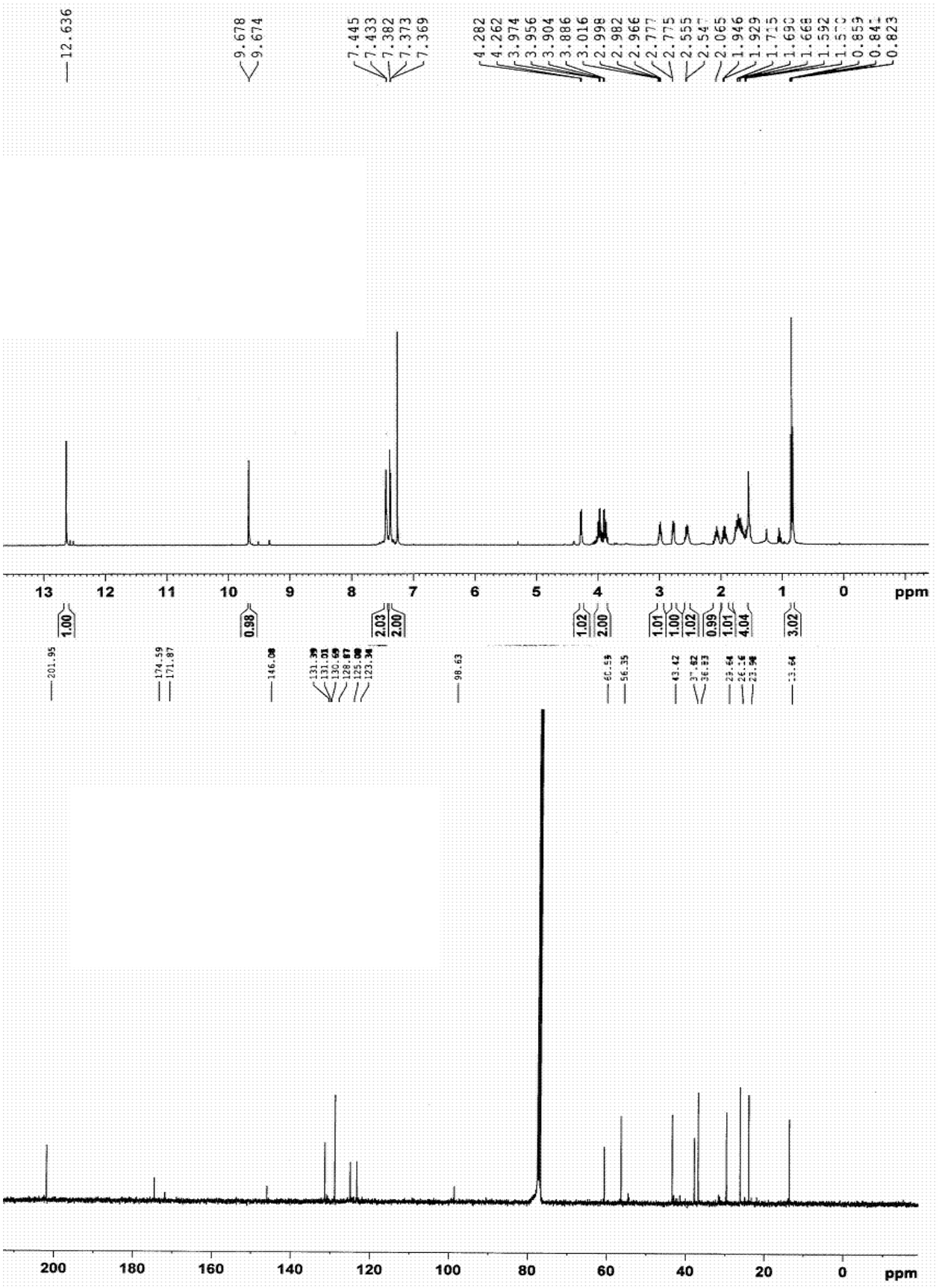

12.518
9.343
9.336
7.481
7.462
7.403
7.384
7.365
7.322
7.285
7.265
4.396
4.384
4.053
4.036
3.011
2.990
2.965
2.944
2.632
2.611
2.532
2.519
2.314
2.059
2.039
1.789
1.627
1.316
1.069
1.052
1.034
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.98 0.98 1.00 1.02 0.98 0.98 2.00 0.98 0.99 1.00 1.00 0.99 1.01 1.99 1.01 2.99


203.75
175.66
171.40
141.17
132.33
131.01
130.69
128.90
125.61
124.13
99.49
60.82
54.56
43.16
41.48
32.47
31.69
31.36
25.01
13.97
200 180 160 140 120 100 80 60 40 20 0 ppm

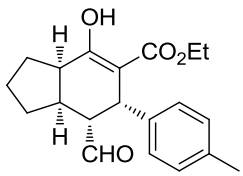
4.12b: *(3aR,6S,7S,7aS)-ethyl 7-formyl-4-hydroxy-6-(3-(trifluoromethyl)phenyl)-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate*



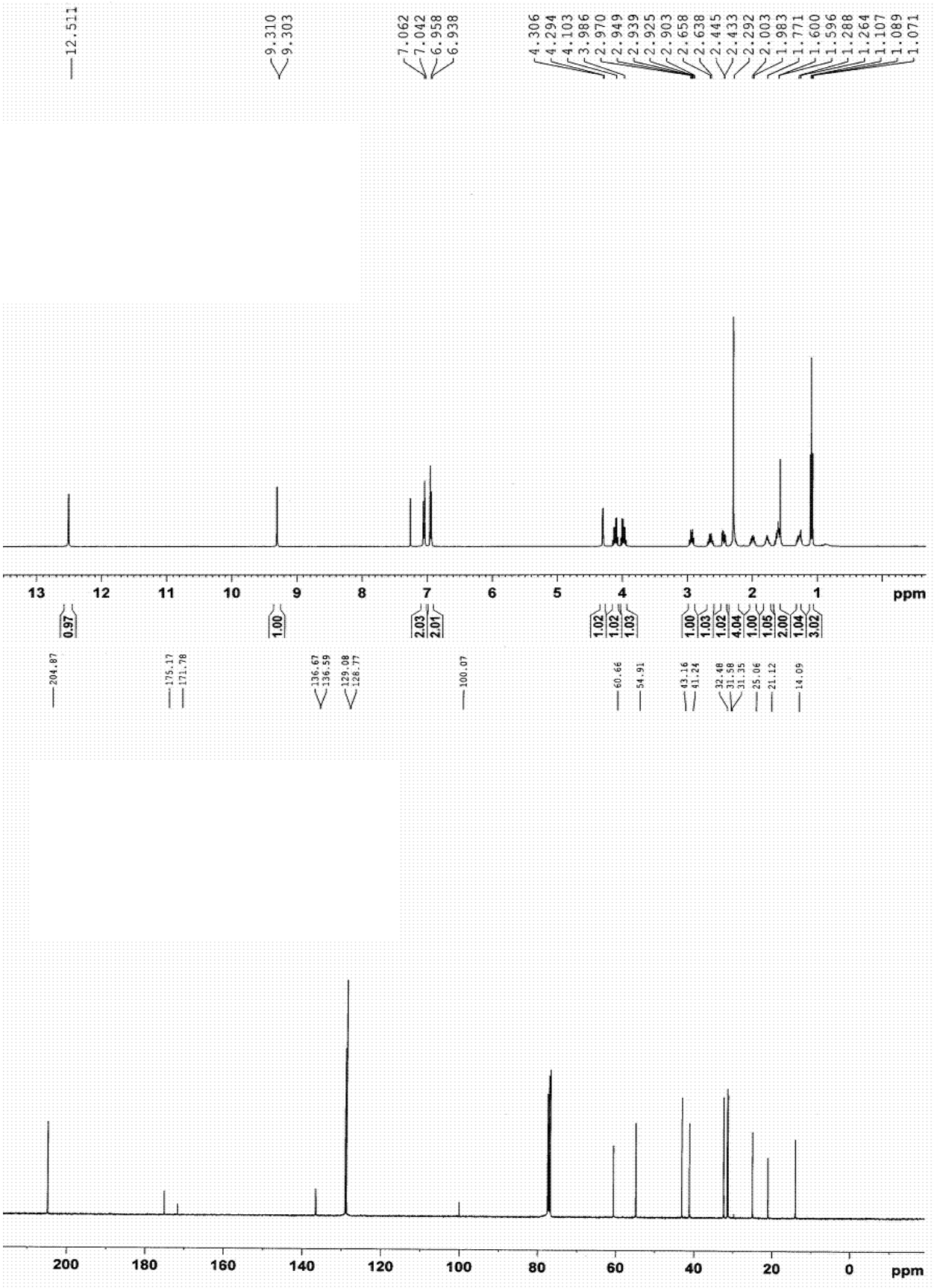
colorless oil. $[\alpha]_D^{23}$ = +18.7 (*c* 1.00, CH_2Cl_2, 99% ee); IR (thin film, KBr): 2962, 2877, 1724, 1648, 1613, 1329, 1236, 1163, 1125, 836, 802, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.63 (s, 1H), 9.68 (d, *J* = 1.8 Hz, 1H), 7.45 (m, 2H), 7.38 (m, 2H), 4.28 (dd, *J* = 7.6, 1.2 Hz, 1H), 3.93 (m, 2H), 2.99 (q, *J* = 6.5 Hz, 1H), 2.78 (m, 1H), 2.55 (m, 1H), 2.07 (m, 1H), 1.95 (m, 1H), 1.57-1.79 (m, 4H), 0.84 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 174.6, 171.9, 146.1, 131.4, 131.0, 130.7, 128.9, 125.0, 123.3, 98.6, 60.6, 56.4, 43.4, 37.8, 36.8, 29.6, 26.2, 24.0, 13.6 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 99:1), 0.3 mL/min; minor enantiomer t_R = 25.3 min, major enantiomer t_R = 30.3 min. HRMS (ESI) : $[M^-]$ calcd for $[C_{20}H_{21}F_3O_4]$: 382.1392, found: 382.1395.


12.636
9.678
9.674
7.445
7.433
7.382
7.373
7.369
4.282
4.262
3.974
3.956
3.904
3.886
3.016
2.998
2.982
2.966
2.777
2.775
2.555
2.547
2.065
1.946
1.929
1.668
1.592
0.853
0.841
0.823
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00 0.98 2.03 2.00 1.02 2.00 1.01 1.00 1.02 0.99 1.01 4.04 3.02
201.95
174.59
171.87
146.08
131.39
131.01
130.69
128.87
125.08
123.34
98.63
66.58
56.35
43.42
37.82
36.83
23.64
26.16
23.98
13.64
200 180 160 140 120 100 80 60 40 20 0 ppm

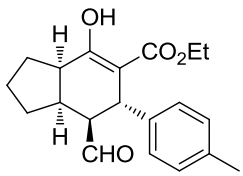
4.14a: *(3aR,6S,7R,7aS)-ethyl 7-formyl-4-hydroxy-6-p-tolyl-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate*



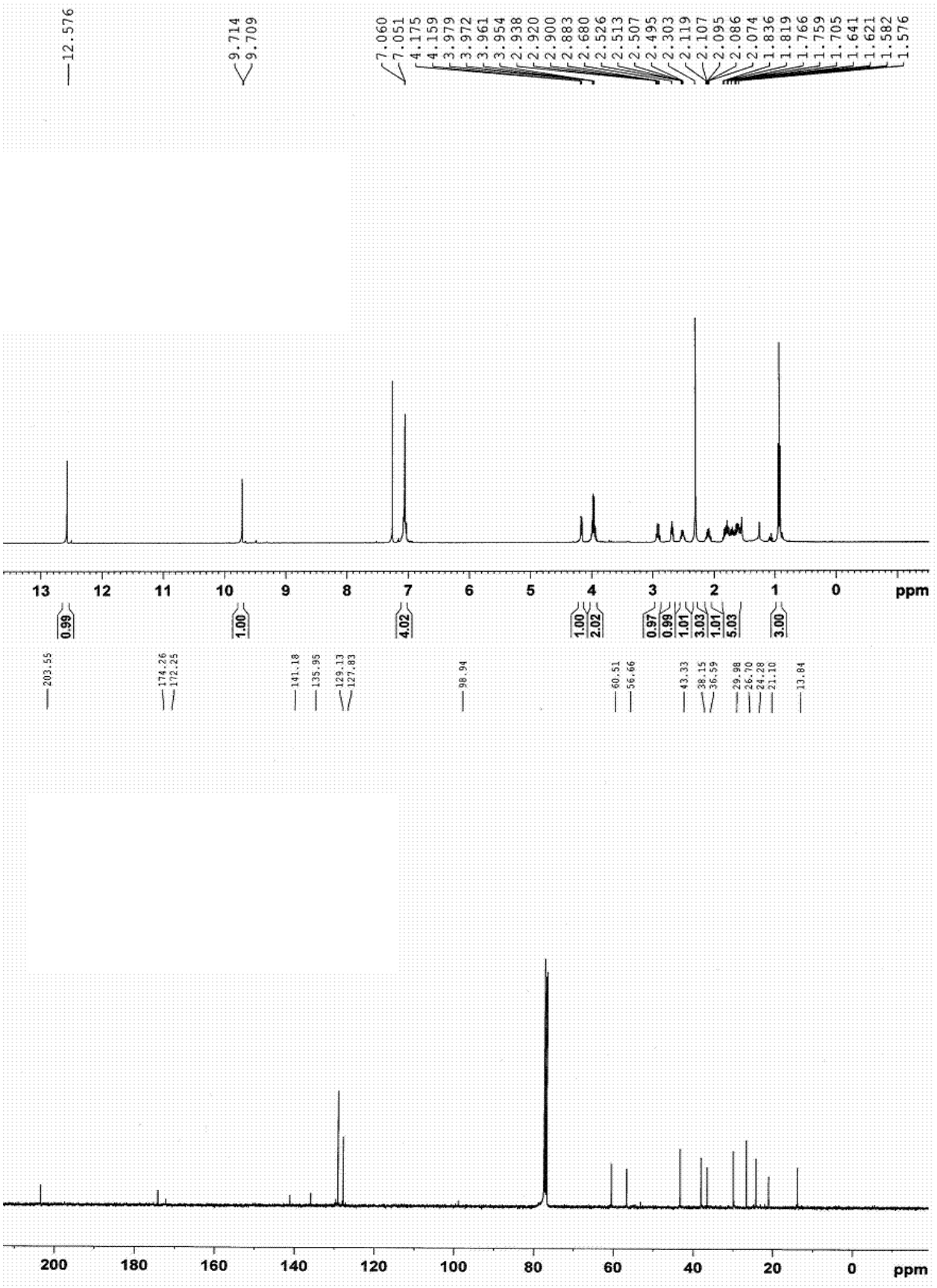
colorless oil. $[\alpha]_D^{26}$ = +109.4 (*c* 1.00, CH_2Cl_2, 99% ee); IR (thin film, KBr): 2962, 2870, 1722, 1648, 1401, 1379, 1242, 1212, 1083, 1034, 821 cm^{-1}; NMR (400 MHz, $CDCl_3$) δ 12.51 (s, 1H), 9.31 (d, *J* = 3.0 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.95 (d, *J* = 7.8 Hz, 2H), 4.30 (d, *J* = 4.8 Hz, 1H), 4.10 (m, 1H), 3.99 (m, 1H), 2.94 (q, *J* = 8.6 Hz, 1H), 2.65 (m, 1H), 2.44 (m, 1H), 2.29 (s, 3H), 2.29 (m, 1H), 1.99 (m, 1H), 1.77 (m, 1H), 1.60 (m, 2H), 1.27 (m, 1H), 1.09 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 175.2, 171.8, 136.7, 136.6, 129.1, 128.8, 100.1, 60.7, 54.9, 43.2, 41.2, 32.5, 31.6, 31.4, 25.1, 21.1, 14.1 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 99:1), 0.5 mL/min; major enantiomer t_R = 13.0 min, minor enantiomer t_R = 15.1 min. HRMS (ESI) : $[M^-]$ calcd for $[C_{20}H_{24}O_4]$: 328.1675, found: 328.1676.


12.511
9.310
9.303
7.062
7.042
6.958
6.938
4.306
4.294
4.103
3.986
2.970
2.949
2.939
2.925
2.903
2.658
2.638
2.445
2.433
2.292
2.003
1.983
1.771
1.600
1.596
1.288
1.264
1.107
1.089
1.071
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.97
1.00
2.03
2.01
1.02
1.02
1.03
1.00
1.03
1.02
4.04
1.00
1.05
2.00
1.04
3.02
204.87
175.17
171.78
136.67
136.59
129.08
128.77
100.07
60.66
54.91
43.16
41.24
32.48
31.58
31.35
25.06
21.12
14.09
200
180
160
140
120
100
80
60
40
20
0
ppm

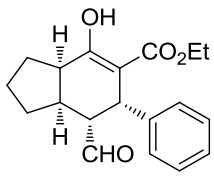
4.14b: *(3aR,6S,7S,7aS)-ethyl 7-formyl-4-hydroxy-6-p-tolyl-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate*



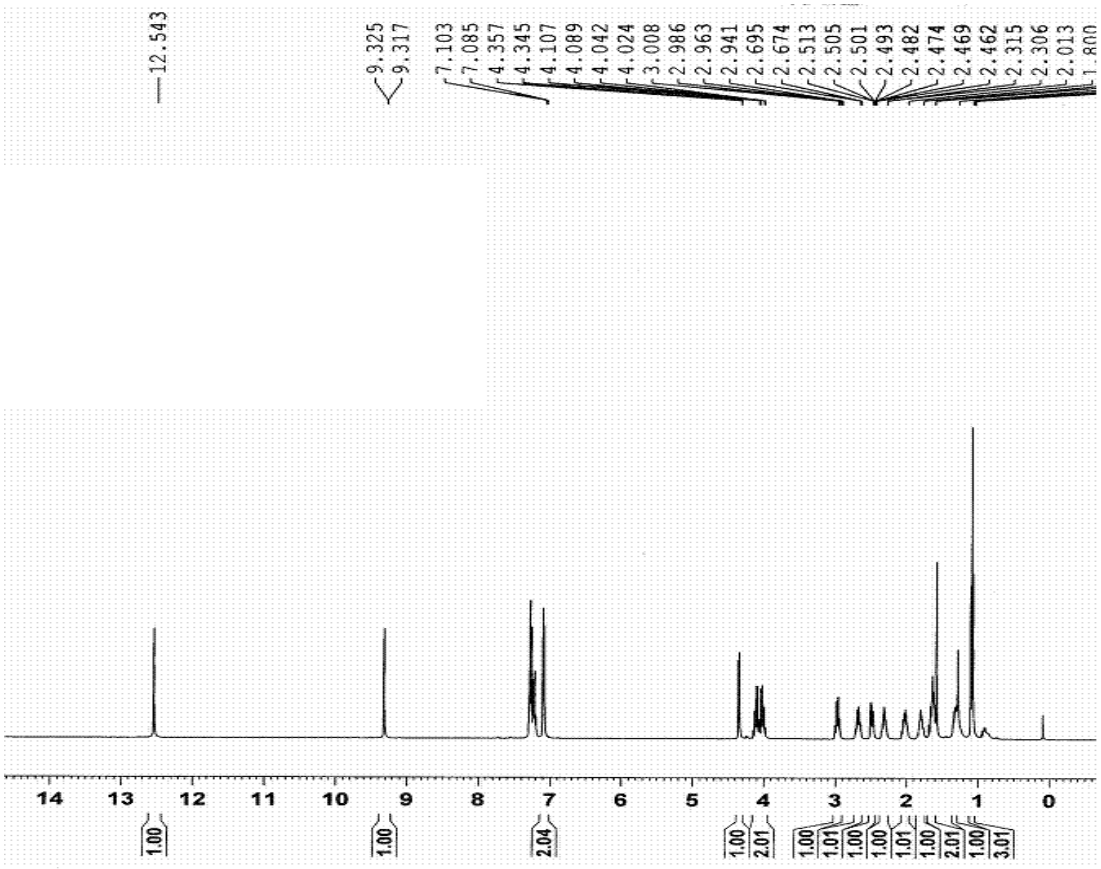
colorless oil. $[\alpha]_D^{24}$ = +26.3 (*c* 0.800, CH_2Cl_2, 99% ee); IR (thin film, KBr): 2958, 2875, 1721, 1646, 1613, 1307, 1272, 1233, 812 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.58 (s, 1H), 9.71 (d, *J* = 2.2 Hz, 1H), 7.06 (m, 4H), 4.17 (d, *J* = 6.2 Hz, 1H), 3.97 (m, 2H), 2.91 (q, *J* = 7.3 Hz, 1H), 2.68 (m, 1H), 2.51 (m, 1H), 2.30 (s, 3H), 2.10 (m, 1H), 1.58-1.85 (m, 5H), 0.93 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 175.2, 171.8, 136.7, 136.6, 129.1, 128.8, 100.1, 60.7, 54.9, 43.2, 41.2, 32.5, 31.6, 31.4, 25.1, 21.1, 14.1 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 99:1), 0.5 mL/min; major enantiomer t_R = 15.7 min, minor enantiomer t_R = 16.9 min. HRMS (ESI) : $[M^-]$ calcd for $[C_{20}H_{24}O_4]$: 328.1675, found: 328.1681.

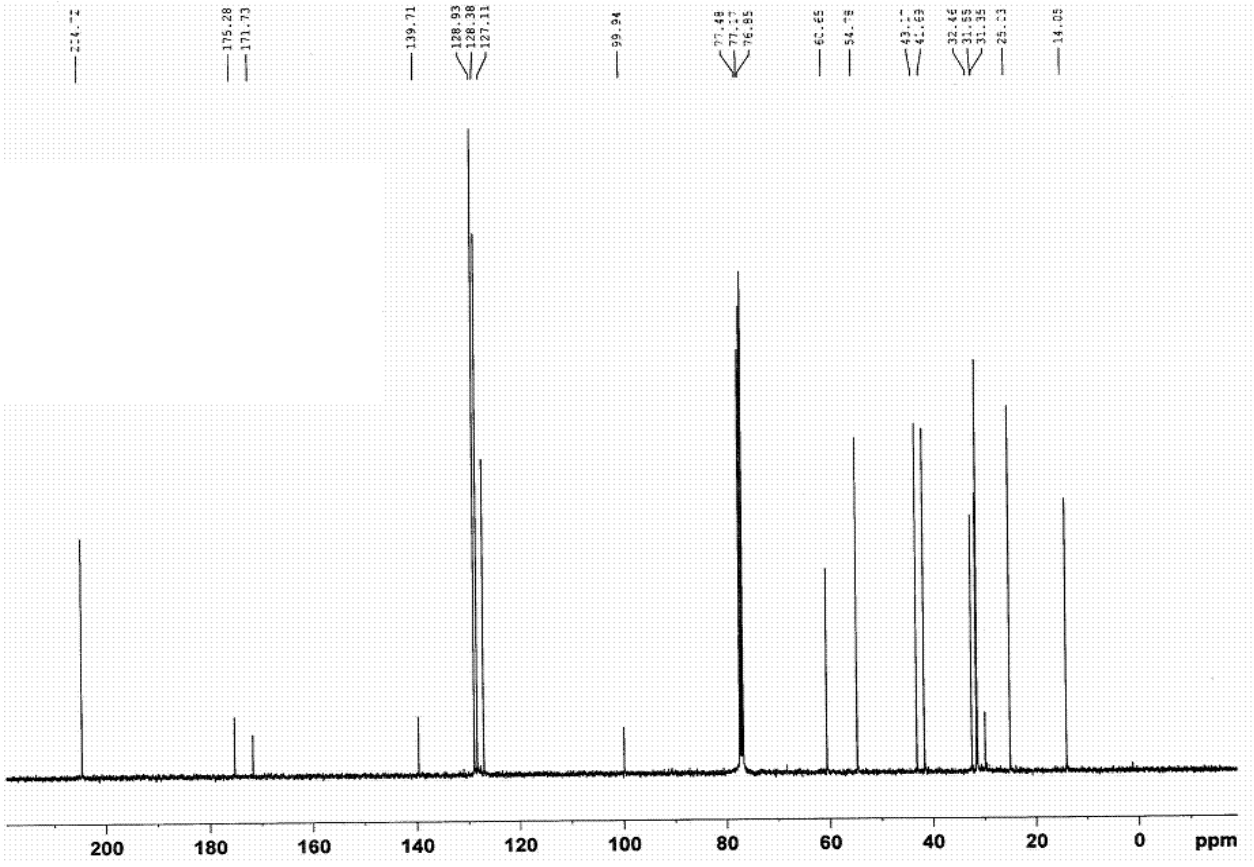

12.576
9.714
9.709
7.060
7.051
4.175
4.159
3.979
3.972
3.961
3.954
2.938
2.920
2.900
2.883
2.680
2.526
2.513
2.507
2.495
2.303
2.119
2.107
2.095
2.086
2.074
1.836
1.819
1.766
1.759
1.705
1.641
1.621
1.582
1.576
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.99 1.00 4.02 1.00 2.02 0.97 0.99 1.01 3.03 1.01 5.03 3.00
203.55
174.26
172.25
141.18
135.95
129.13
127.83
98.94
60.51
56.66
43.33
38.15
36.59
29.98
26.70
24.28
21.10
13.84
200 180 160 140 120 100 80 60 40 20 0 ppm

4.15a: *(3aR,6S,7R,7aS)-ethyl 7-formyl-4-hydroxy-6-phenyl-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate*

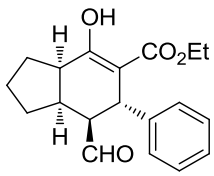


colorless oil. $[\alpha]_D^{23}$ = +117.4 (*c* 1.00, CH_2Cl_2, 99% ee); IR (thin film, KBr): 2962, 1722, 1648, 1617, 1280, 1243, 1212, 1084, 832, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.54 (s, 1H), 9.32 (d, *J* = 3.0 Hz, 1H), 7.26 (m, 3H), 7.09 (d, *J* = 7.2 Hz, 2H), 4.35 (d, *J* = 4.9 Hz, 1H), 4.07 (m, 2H), 2.97 (q, *J* = 9.4 Hz, 1H), 2.59 (m, 1H), 2.49 (m, 1H), 2.31 (m, 1H), 2.01 (m, 1H), 1.80 (m, 1H), 1.63 (m, 2H), 1.30 (m, 1H), 1.09 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 175.3, 171.7, 139.7, 128.9, 128.4, 127.1, 99.9, 60.7, 54.8, 43.2, 41.7, 32.5, 31.6, 31.4, 25.0, 14.1 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 99:1), 1.0 mL/min; minor enantiomer t_R = 7.0 min, major enantiomer t_R = 8.9 min. HRMS (ESI) : [M^+] calcd for [$C_{19}H_{22}O_4$]: 314.1518, found: 314.1520.

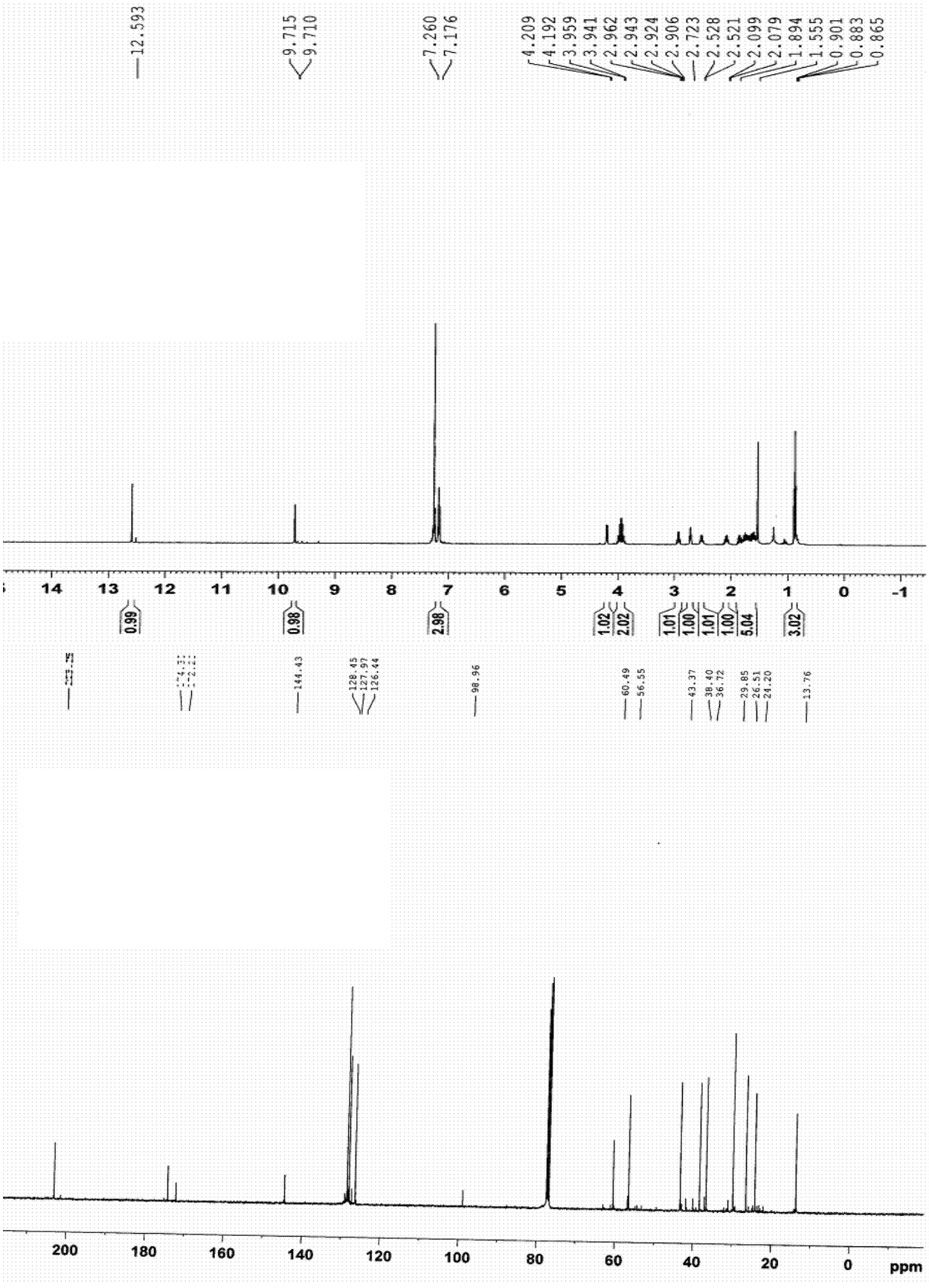

12.543
9.325
9.317
7.103
7.085
4.357
4.345
4.107
4.089
4.042
4.024
3.008
2.986
2.963
2.941
2.695
2.674
2.513
2.505
2.501
2.493
2.482
2.474
2.469
2.462
2.315
2.306
2.013
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
1.00 1.00 2.04 1.00 2.01 1.00 1.01 1.00 1.00 1.01 1.00 2.01 1.00 3.01


175.28
171.73
139.71
128.93
128.38
127.11
99.94
14.05
200 180 160 140 120 100 80 60 40 20 0 ppm

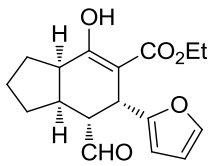
4.15b: *(3aR,6S,7S,7aS)-ethyl 7-formyl-4-hydroxy-6-phenyl-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate*



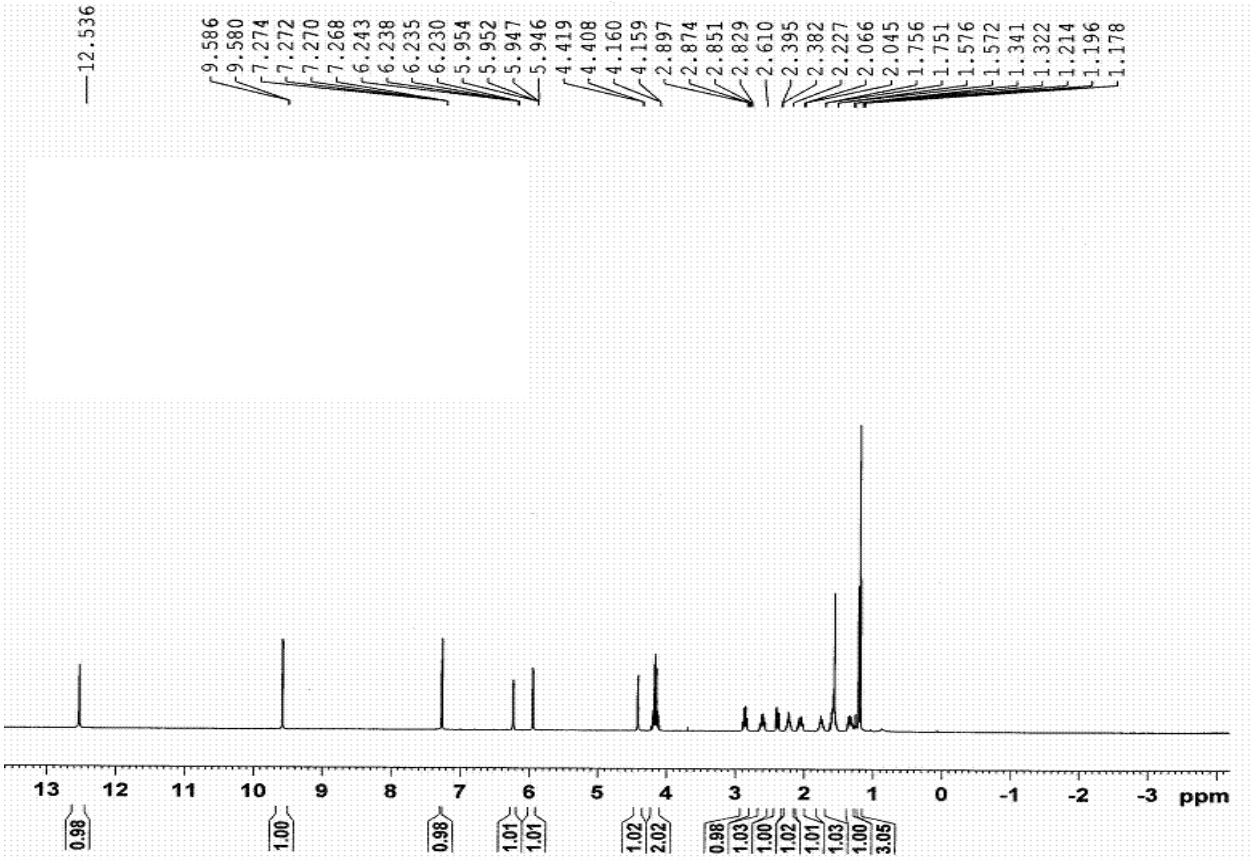
colorless oil. $[\alpha]_D^{21}$ = +23.6 (*c* 0.500, CH_2Cl_2, 98% ee); IR (thin film, KBr): 2958, 2874, 1720, 1646, 1614, 1234, 1096, 1029, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.59 (s, 1H), 9.71 (d, *J* = 2.0 Hz, 1H), 7.26 (m, 2H), 7.18 (m, 3H), 4.20 (d, *J* = 6.8 Hz, 1H), 3.95 (m, 2H), 2.93 (q, *J* = 7.7 Hz, 1H), 2.72 (m, 1H), 2.52 (m, 1H), 2.09 (m, 1H), 1.58-1.89 (m, 5H), 0.88 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 174.3, 172.2, 144.4, 128.5, 128.0, 126.4, 99.0, 60.5, 56.6, 43.4, 38.4, 36.7, 29.9, 26.5, 24.2, 13.8 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 99:1), 0.3 mL/min; minor enantiomer t_R = 24.0 min, major enantiomer t_R = 41.4 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{19}H_{22}O_4]$: 314.1518, found: 314.1521.

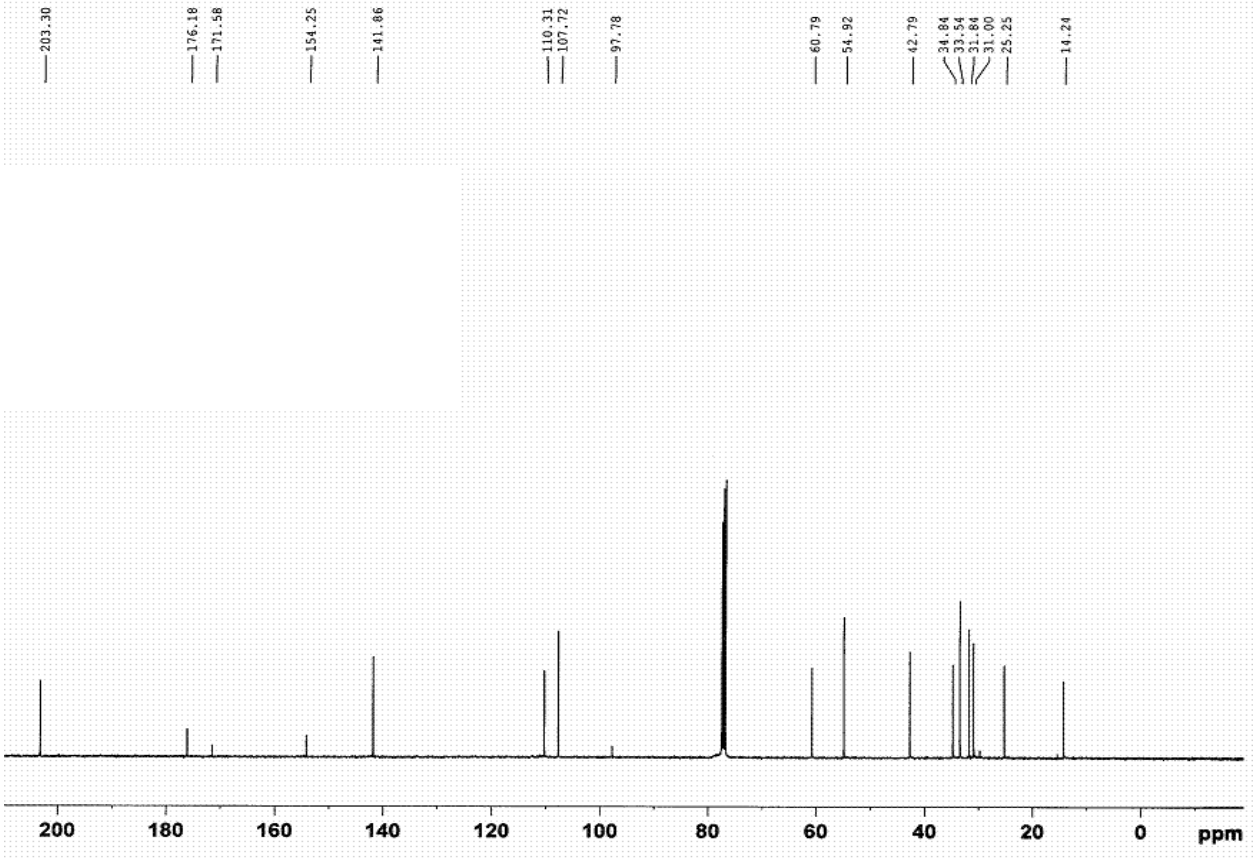

12.593
9.715
9.710
7.260
7.176
4.209
4.192
3.959
3.941
2.962
2.943
2.924
2.906
2.723
2.528
2.521
2.099
2.079
1.894
1.555
0.901
0.883
0.865
0.99
0.98
2.98
1.02
2.02
1.01
1.00
1.01
1.00
5.04
3.02
144.43
128.45
127.97
126.44
98.96
60.49
56.55
43.37
38.40
36.72
29.85
26.51
24.20
13.76
ppm

4.16a: *(3aR,6R,7R,7aS)-ethyl 7-formyl-6-(furan-2-yl)-4-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate*

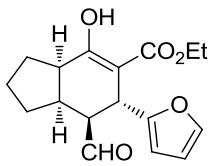


colorless oil. $[\alpha]_D^{23}$ = +58.9 (*c* 1.00, CH_2Cl_2, 98% ee); IR (thin film, KBr): 2963, 2870, 1724, 1648, 1288, 1242, 1081, 834, 741, 599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.54 (s, 1H), 9.58 (d, *J* = 2.4 Hz, 1H), 7.27 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.24 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.95 (dd, *J* = 2.5, 0.7 Hz, 1H), 4.41 (d, *J* = 4.3 Hz, 1H), 4.16 (m, 2H), 2.86 (q, *J* = 8.9 Hz, 1H), 2.61 (m, 1H), 2.39 (m, 1H), 2.23 (m, 1H), 2.06 (m, 1H), 1.75 (m, 1H), 1.57 (m, 2H), 1.33 (m, 1H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 176.2, 171.6, 154.3, 141.9, 110.3, 107.7, 97.8, 60.8, 54.9, 42.8, 34.8, 33.5, 31.8, 31.0, 25.3, 14.2 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 99:1), 0.5 mL/min; major enantiomer t_R = 23.6 min, minor enantiomer t_R = 27.2 min. HRMS (ESI) : $[M^-]$ calcd for $[C_{17}H_{20}O_5]$: 304.1311, found: 304.1316.

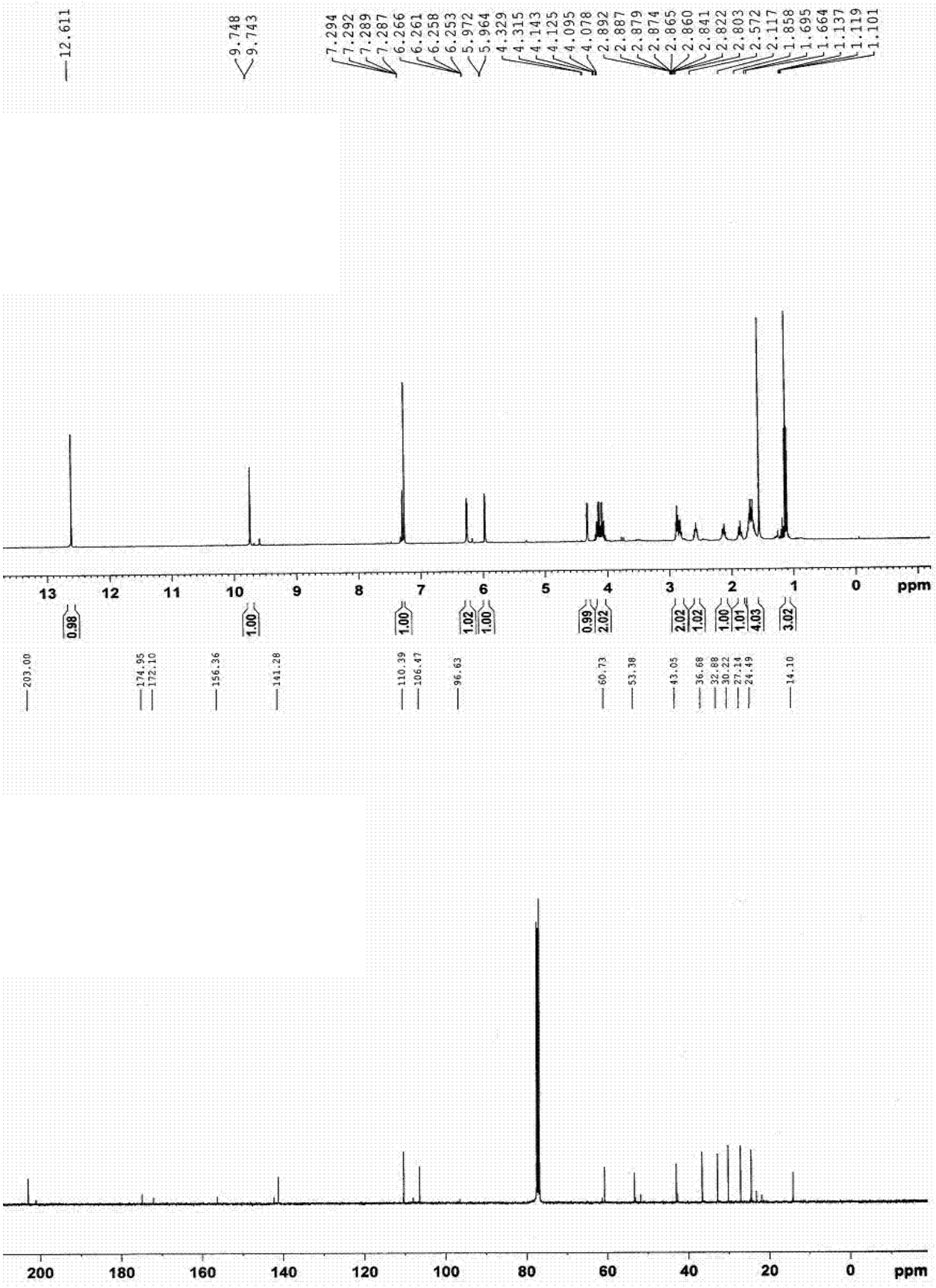

12.536
9.586
9.580
7.274
7.272
7.270
7.268
6.243
6.238
6.235
6.230
5.954
5.952
5.947
5.946
4.419
4.408
4.160
4.159
2.897
2.874
2.851
2.829
2.610
2.395
2.382
2.227
2.066
2.045
1.756
1.751
1.576
1.572
1.341
1.322
1.214
1.196
1.178
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm
0.98 1.00 0.98 1.01 1.01 1.02 2.02 0.98 1.03 1.00 1.02 1.01 1.03 1.00 3.05


203.30
176.18
171.58
154.25
141.86
110.31
107.72
97.78
60.79
54.92
42.79
34.84
33.54
31.84
31.00
25.25
14.24
200 180 160 140 120 100 80 60 40 20 0 ppm

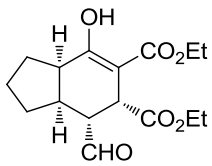
4.16b: *(3aR,6R,7S,7aS)-ethyl 7-formyl-6-(furan-2-yl)-4-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate*



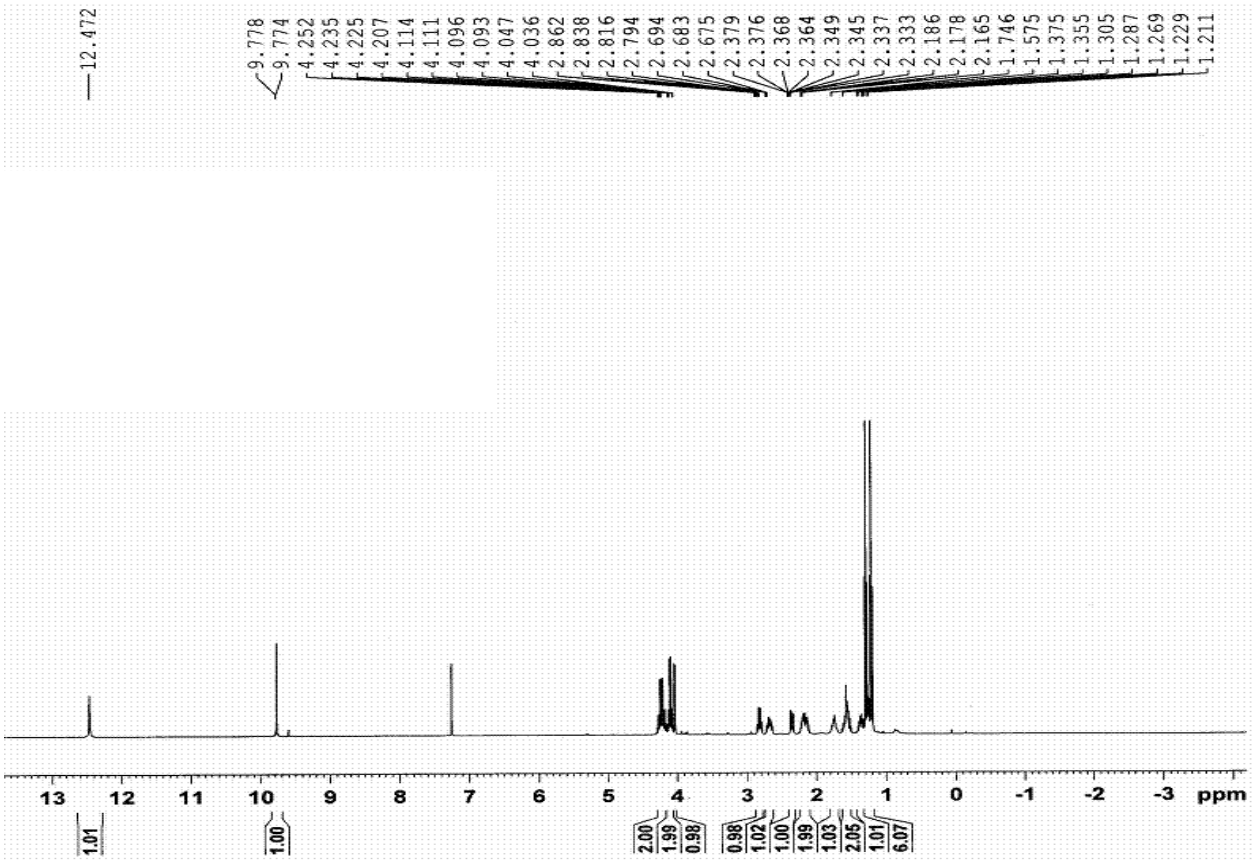
colorless oil. $[\alpha]_D^{22}$ = -12.3 (*c* 1.00, CH_2Cl_2, 98% ee); IR (thin film, KBr): 2961, 2876, 1720, 1647, 1276, 1222, 1086, 1011, 837, 736, 599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.61 (s, 1H), 9.75 (d, *J* = 1.8 Hz, 1H), 7.29 (d, *J* = 1.0 Hz, 1H), 6.26 (dd, *J* = 3.1, 1.8 Hz, 1H), 5.97 (d, *J* = 3.2 Hz, 1H), 4.32 (d, *J* = 5.4 Hz, 1H), 4.11 (m, 2H), 2.88 (td, *J* = 5.4, 2.1 Hz, 1H), 2.83 (q, *J* = 8.0 Hz, 1H), 2.57 (m, 1H), 2.12 (m, 1H), 1.86 (m, 1H), 1.59-1.77 (m, 4H), 1.12 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 175.0, 172.1, 156.4, 141.3, 110.4, 106.5, 96.6, 60.7, 53.4, 43.1, 36.7, 32.9, 30.2, 27.1, 24.5, 14.1 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 99:1), 0.5 mL/min; major enantiomer t_R = 21.5 min, minor enantiomer t_R = 27.6 min. HRMS (ESI) : $[M^-]$ calcd for $[C_{17}H_{20}O_5]$: 304.1311, found: 304.1316.

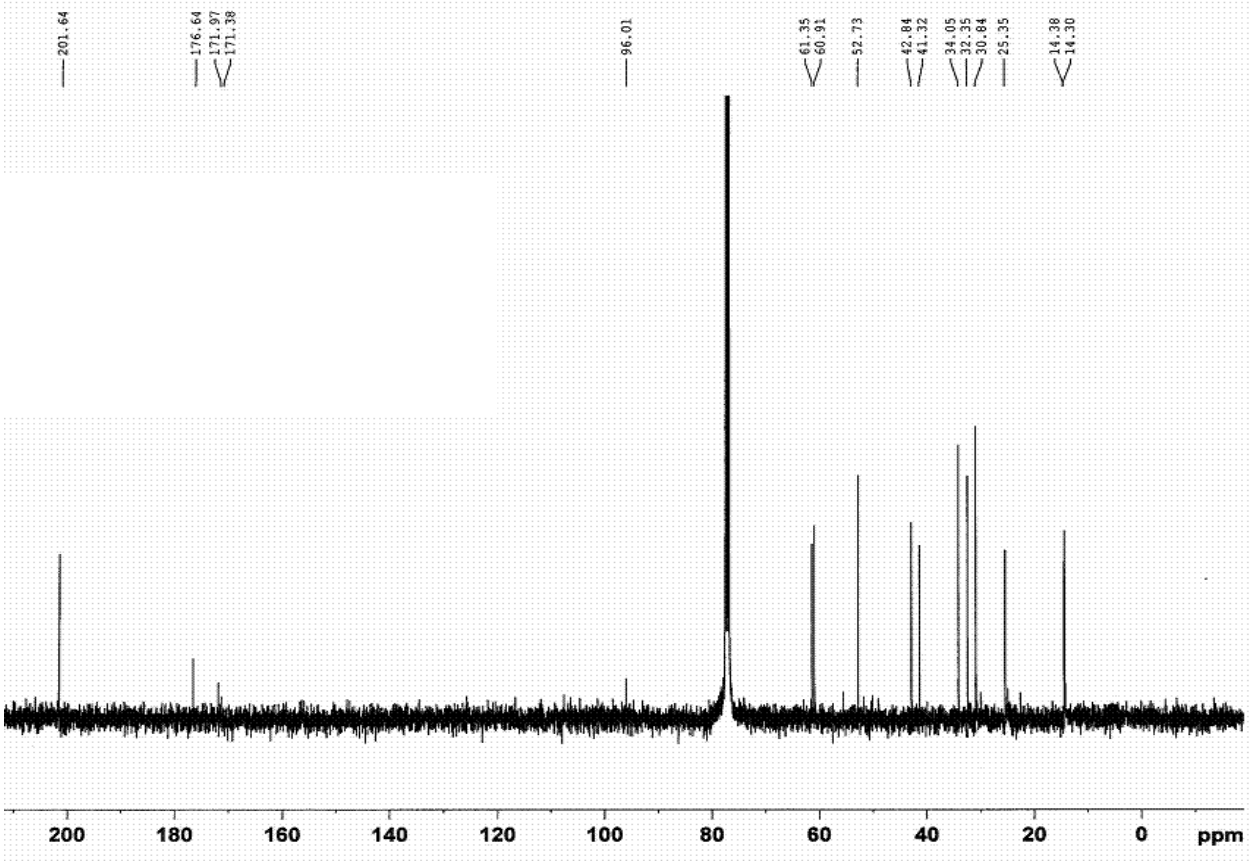

12.611
9.748
9.743
7.294
7.292
7.289
7.287
6.266
6.261
6.258
6.253
5.972
5.964
4.329
4.315
4.143
4.125
4.095
4.078
2.892
2.887
2.879
2.874
2.865
2.860
2.841
2.822
2.803
2.572
2.117
1.858
1.695
1.664
1.137
1.119
1.101
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.98 1.00 1.00 1.02 1.00 0.99 2.02 2.02 1.02 1.00 1.01 4.03 3.02
203.00
174.95
172.10
156.36
141.28
110.39
106.47
96.63
60.73
53.38
43.05
36.68
32.88
30.22
27.14
24.49
14.10
200 180 160 140 120 100 80 60 40 20 0 ppm

4.17a: *(3aS,4R,5R,7aR)-diethyl 4-formyl-7-hydroxy-2,3,3a,4,5,7a-hexahydro-1H-indene-5,6-dicarboxylate*

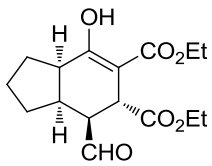


colorless oil. $[\alpha]_D^{24}$ = +30.2 (*c* 1.00, CH_2Cl_2, 98% ee); IR (thin film, KBr): 2979, 2872, 1728, 1652, 1618, 1243, 1189, 1095, 1035, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.47 (s, 1H), 9.78 (d, *J* = 1.5 Hz, 1H), 4.23 (m, 2H), 4.10 (m, 2H), 4.04 (d, *J* = 4.6 Hz, 1H), 2.83 (q, *J* = 9.4 Hz, 1H), 2.68 (m, 1H), 2.36 (m, 1H), 2.18 (m, 2H), 1.75 (m, 1H), 1.58 (m, 2H), 1.37 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 176.6, 172.0, 171.4, 96.0, 61.3, 60.9, 52.7, 42.8, 41.3, 34.1, 32.4, 30.8, 25.3, 14.4, 14.3 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 99:1), 1.0 mL/min; major enantiomer t_R = 15.1 min, minor enantiomer t_R = 26.4 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{16}H_{22}O_6]$: 310.1416, found: 310.1416.

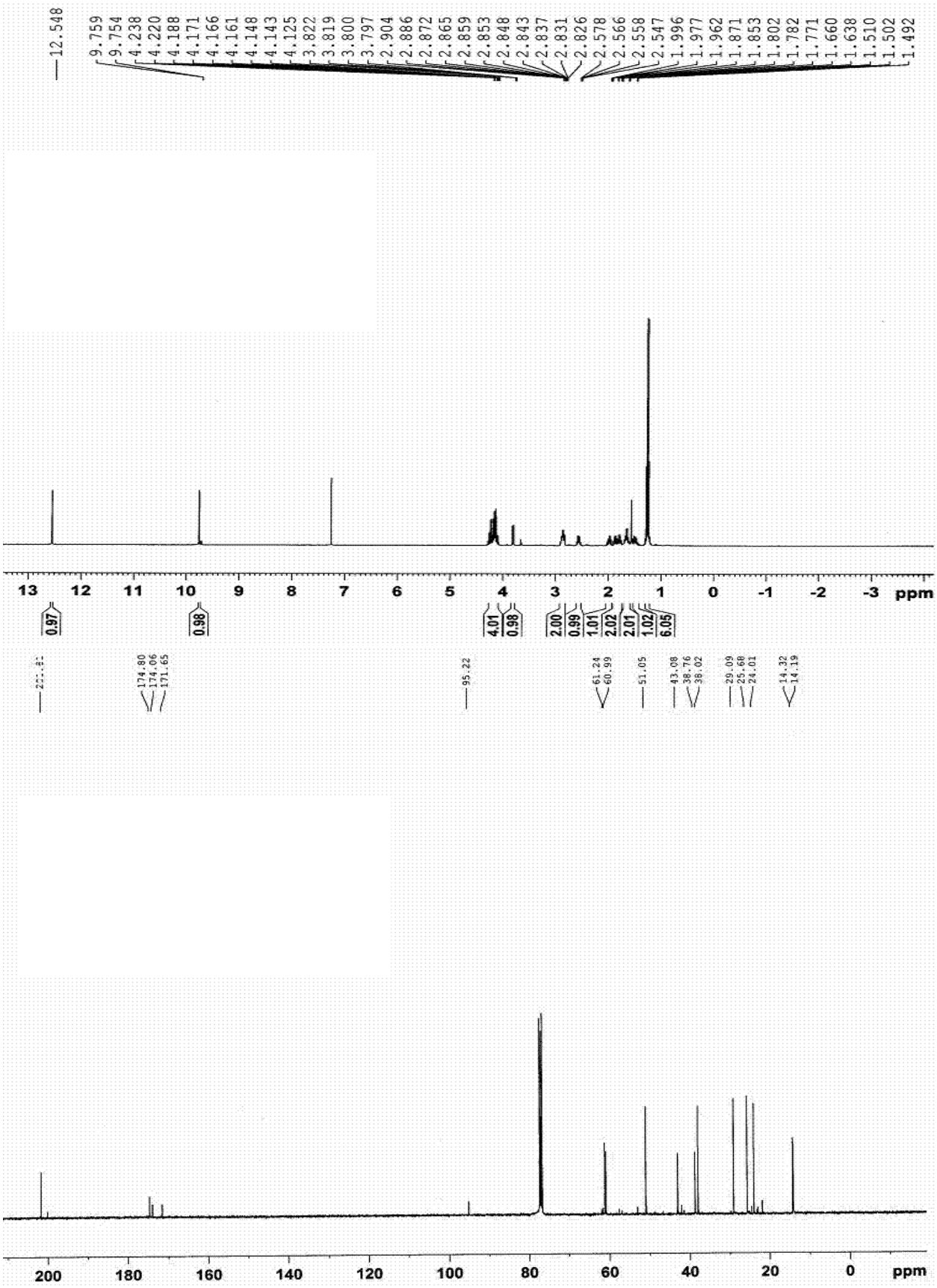

12.472
9.778
9.774
4.252
4.235
4.225
4.207
4.114
4.111
4.096
4.093
4.047
4.036
2.862
2.838
2.816
2.794
2.694
2.683
2.675
2.379
2.376
2.368
2.364
2.349
2.345
2.337
2.333
2.186
2.178
2.165
1.746
1.575
1.375
1.355
1.305
1.287
1.269
1.229
1.211
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm
1.01
1.00
2.00
1.99
0.98
0.98
1.02
1.00
1.99
1.03
2.05
1.01
6.07


201.64
176.64
171.97
171.38
96.01
61.35
60.91
52.73
42.84
41.32
34.05
32.35
30.84
25.35
14.38
14.30
200 180 160 140 120 100 80 60 40 20 0 ppm

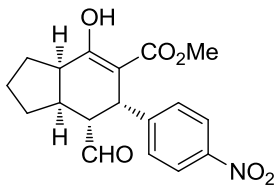
4.17b: *(3aS,4S,5R,7aR)-diethyl 4-formyl-7-hydroxy-2,3,3a,4,5,7a-hexahydro-1H-indene-5,6-dicarboxylate*



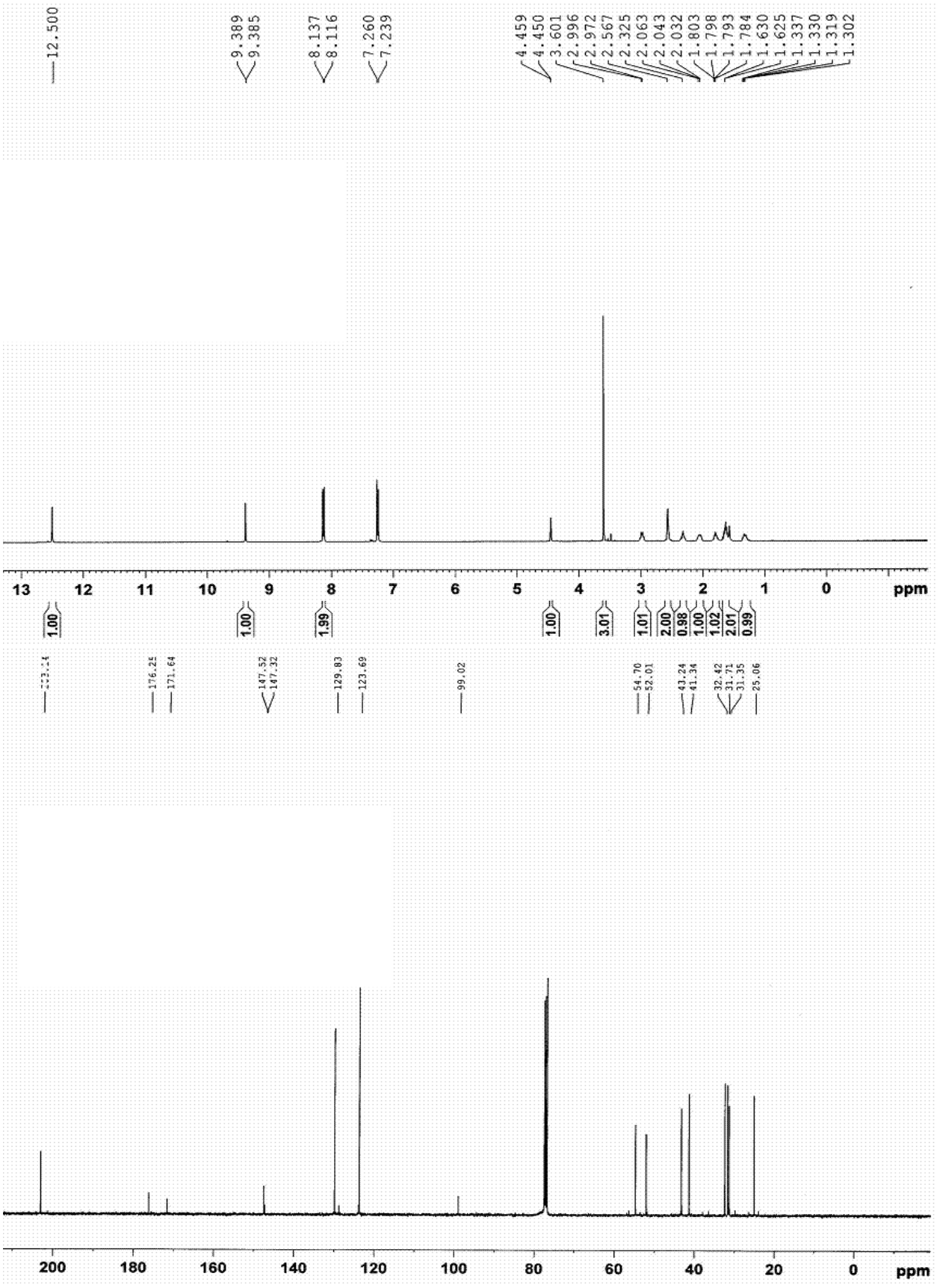
colorless oil. $[\alpha]_D^{24}$ = -18.8 (*c* 1.00, CH_2Cl_2, 98% ee); IR (thin film, KBr): 2979, 1728, 1654, 1616, 1234, 1183, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.55 (s, 1H), 9.76 (d, *J* = 2.2 Hz, 1H), 4.10-4.27 (m, 4H), 3.82 (dd, *J* = 8.9, 1.5 Hz, 1H), 2.87 (m, 2H), 2.56 (m, 1H), 1.98 (m, 1H), 1.86 (m, 1H), 1.79 (m, 1H), 1.65 (m, 2H), 1.49 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 174.8, 174.1, 171.7, 95.2, 61.2, 61.0, 51.1, 43.1, 38.8, 38.0, 29.1, 25.7, 24.0, 14.3, 14.2 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 99:1), 1.0 mL/min; minor enantiomer t_R = 29.2 min, major enantiomer t_R = 39.5 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{16}H_{22}O_6]$: 310.1416, found: 310.1422.


12.548
9.759
9.754
4.238
4.220
4.188
4.171
4.166
4.161
4.148
4.143
4.125
3.822
3.819
3.800
3.797
2.904
2.886
2.872
2.865
2.859
2.853
2.848
2.843
2.837
2.831
2.826
2.578
2.566
2.558
2.547
1.996
1.977
1.962
1.871
1.853
1.802
1.782
1.771
1.660
1.638
1.510
1.502
1.492
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm
0.97
0.98
4.01
0.98
2.00
0.99
1.01
2.02
2.01
1.02
6.05
174.80
174.06
171.65
95.22
61.24
60.99
51.05
43.08
38.76
38.02
29.09
25.68
24.01
14.32
14.19
200 180 160 140 120 100 80 60 40 20 0 ppm

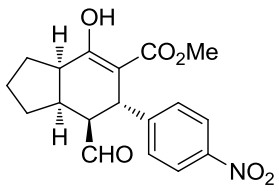
4.18a: *(3aR,6S,7R,7aS)-methyl 7-formyl-4-hydroxy-6-(4-nitrophenyl)-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate*



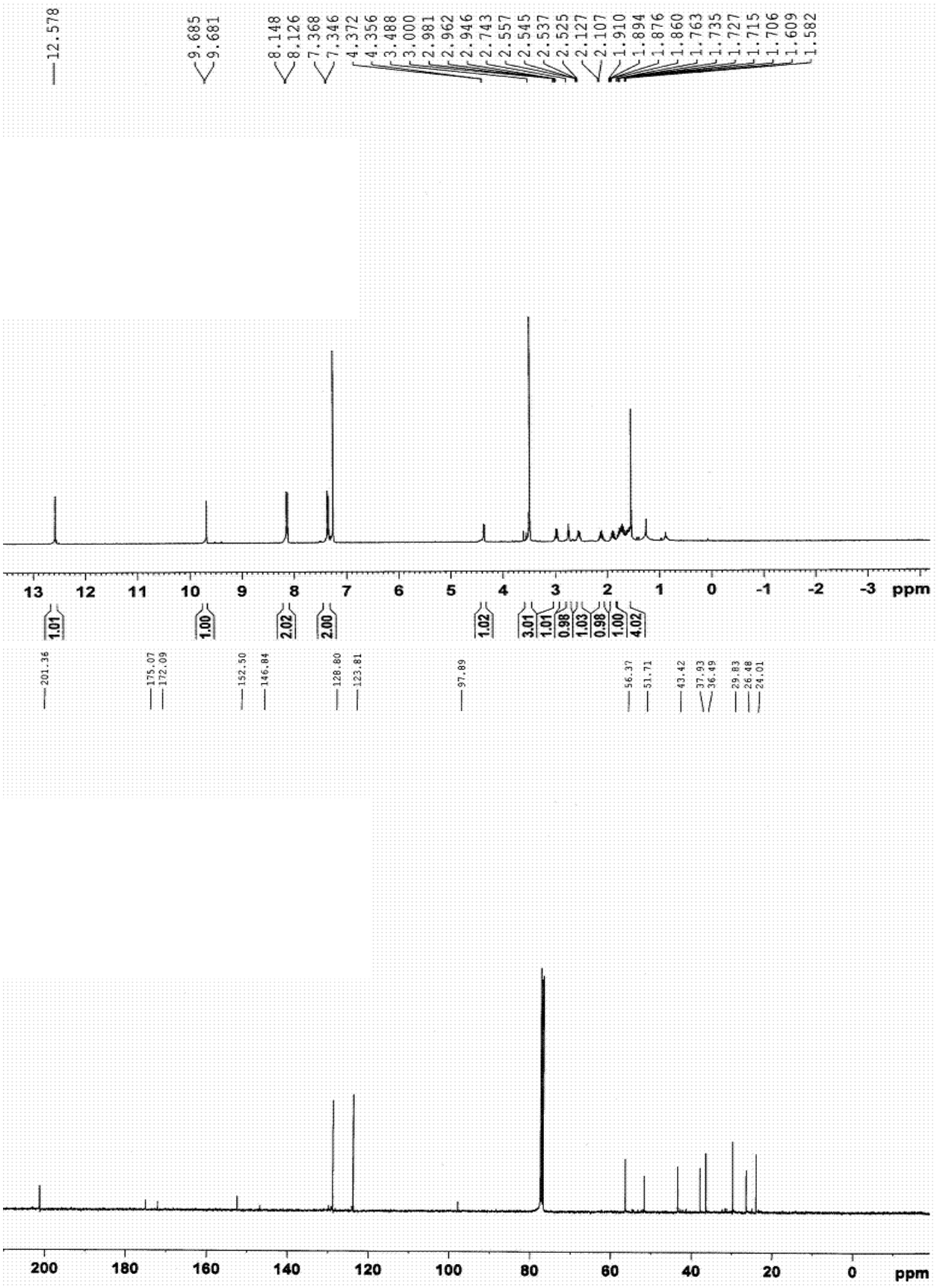
white powder. m.p.: 104-107 °C. $[\alpha]_D^{23}$ = +194.4 (*c* 1.00, CH_2Cl_2, 97% ee); IR (thin film, KBr): 2955, 2870, 1722, 1653, 1614, 1520, 1442, 1349, 1246, 856, 824, 736, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.50 (s, 1H), 9.39 (d, *J* = 1.3 Hz, 1H), 8.13 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 4.45 (d, *J* = 3.8 Hz, 1H), 3.60 (s, 3H), 2.98 (m, 1H), 2.57 (m, 2H), 2.33 (m, 1H), 2.05 (m, 1H), 1.80 (m, 1H), 1.63 (m, 2H), 1.32 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 176.3, 171.7, 147.5, 147.3, 129.8, 123.7, 99.0, 54.7, 52.0, 43.2, 41.3, 32.4, 31.7, 31.3, 25.1 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 18.4 min, minor enantiomer t_R = 27.4 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{18}H_{19}NO_6]$: 345.1212, found: 345.1218.


12.500
9.389
9.385
8.137
8.116
7.260
7.239
4.459
4.450
3.601
2.996
2.972
2.567
2.325
2.063
2.043
2.032
1.803
1.798
1.793
1.784
1.630
1.625
1.337
1.330
1.319
1.302
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00 1.00 1.99 1.00 3.01 1.01 2.00 0.98 1.00 1.02 2.01 0.99
176.25
171.64
147.52
147.32
129.83
123.69
99.02
54.70
52.01
43.24
41.34
32.42
31.71
31.35
25.06
200 180 160 140 120 100 80 60 40 20 0 ppm

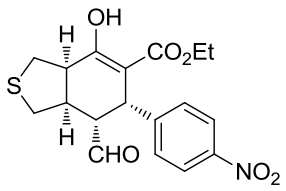
4.18b: *(3aR,6S,7S,7aS)-methyl 7-formyl-4-hydroxy-6-(4-nitrophenyl)-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate*



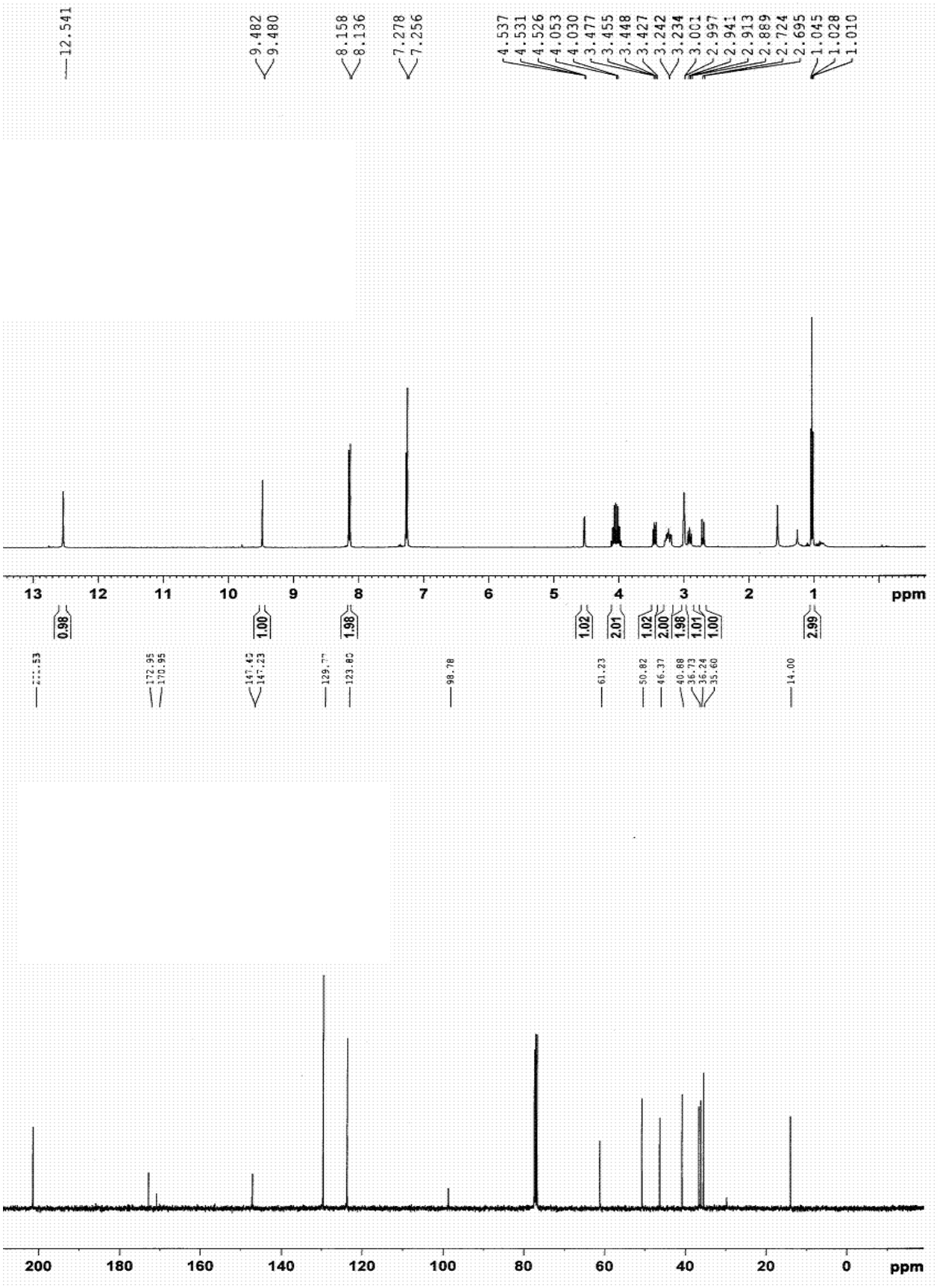
colorless amorphous solid. $[\alpha]_D^{24}$ = +73.8 (*c* 0.500, CH_2Cl_2, 98% ee); IR (thin film, KBr): 2955, 1721, 1652, 1519, 1441, 1348, 1237, 1109, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.58 (s, 1H), 9.68 (d, *J* = 1.6 Hz, 1H), 8.14 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 4.36 (d, *J* = 6.6 Hz, 1H), 3.49 (s, 3H), 2.97 (q, *J* = 7.4 Hz, 1H), 2.74 (m, 1H), 2.54 (m, 1H), 2.12 (m, 1H), 1.87 (m, 1H), 1.58-1.76 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 175.1, 172.1, 152.5, 146.8, 128.8, 123.8, 97.9, 56.4, 51.7, 43.4, 37.9, 36.5, 29.8, 26.5, 24.0 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 99:1), 1.0 mL/min; major enantiomer t_R = 46.6 min, minor enantiomer t_R = 52.3 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{18}H_{19}NO_6]$: 345.1212, found: 345.1216.


12.578
9.685
9.681
8.148
8.126
7.368
7.346
4.372
4.356
3.488
3.000
2.981
2.962
2.946
2.743
2.557
2.545
2.537
2.525
2.127
2.107
1.910
1.894
1.876
1.860
1.763
1.735
1.727
1.715
1.706
1.609
1.582
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm
1.01 1.00 2.02 2.00 1.02 3.01 1.01 0.98 1.03 0.98 1.00 4.02
201.36
175.07
172.09
152.50
146.84
128.80
123.81
97.89
56.37
51.71
43.42
37.93
36.49
29.83
26.48
24.01
200 180 160 140 120 100 80 60 40 20 0 ppm

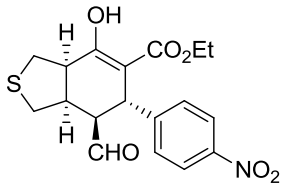
4.19a: *(3aR,6S,7S,7aR)-ethyl 7-formyl-4-hydroxy-6-(4-nitrophenyl)-1,3,3a,6,7,7a-hexahydrobenzo[c]thiophene-5-carboxylate*



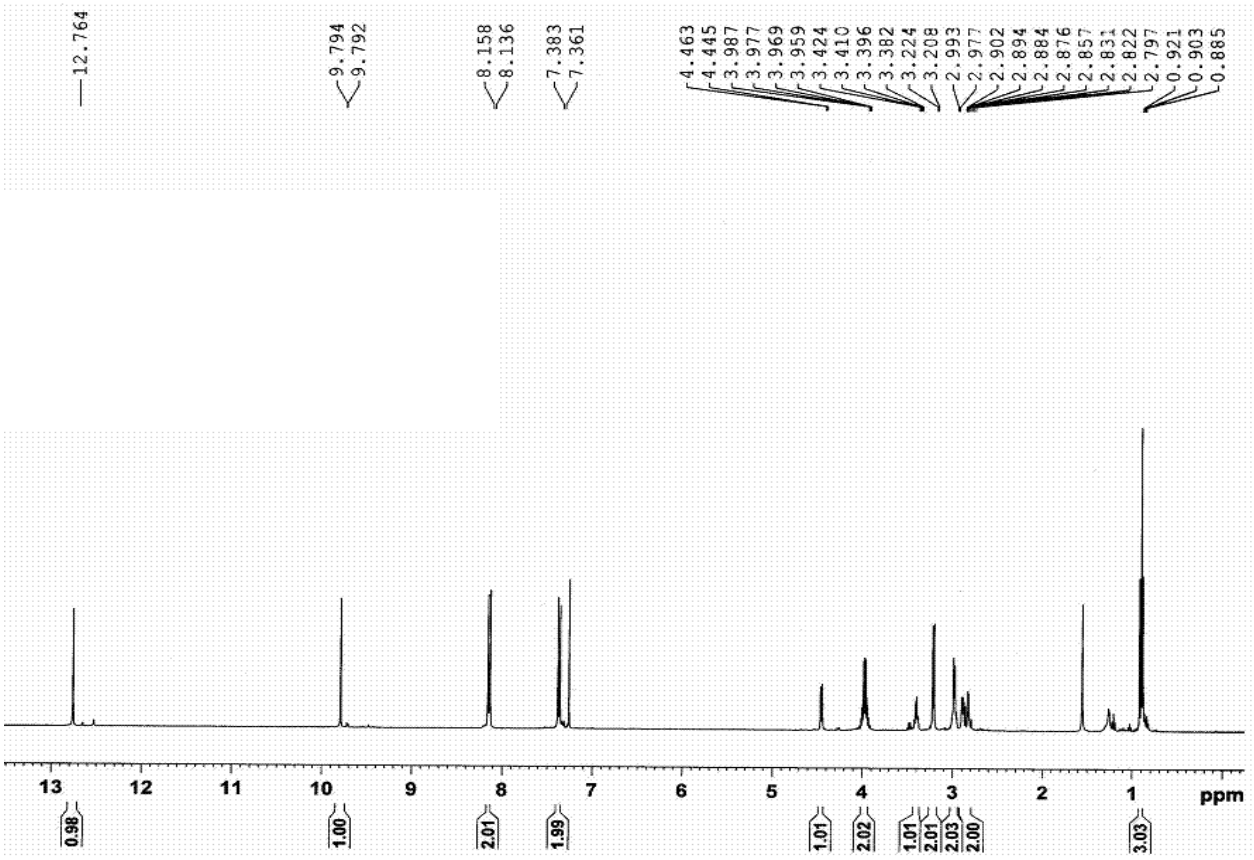
yellow crystals. m.p.: 180-183 °C. $[\alpha]_D^{22}$ = +86.7 (*c* 1.00, CH_2Cl_2, 98% ee); IR (thin film, KBr): 2927, 1654, 1519, 1350, 1248, 1225, 857, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.54 (s, 1H), 9.48 (d, *J* = 0.8 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 4.53 (m, 1H), 4.04 (m, 2H), 3.45 (dd, *J* = 11.3, 8.6 Hz, 1H), 3.24 (m, 2H), 3.00 (d, *J* = 1.5 Hz, 2H), 2.91 (dd, *J* = 11.3, 9.7 Hz, 1H), 2.71 (d, *J* = 12.1 Hz, 1H), 1.03 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 173.0, 171.0, 147.4, 147.2, 129.8, 123.8, 98.8, 61.2, 50.8, 46.4, 40.9, 36.7, 36.2, 35.6, 14.0 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 22.7 min, minor enantiomer t_R = 35.7 min. HRMS (ESI) : $[M^-]$ calcd for $[C_{18}H_{19}NO_6S]$: 377.0933, found: 377.0938.

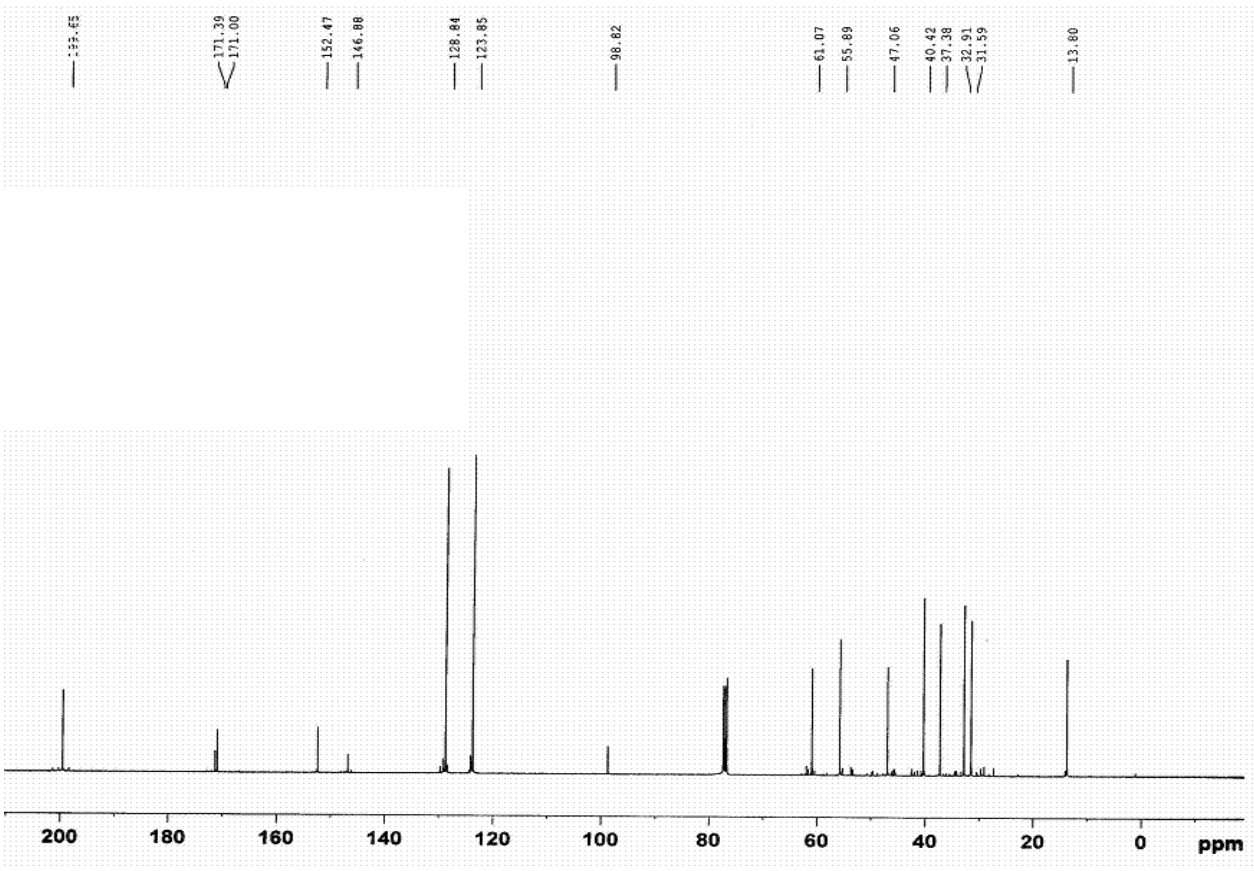

12.541
9.482
9.480
8.158
8.136
7.278
7.256
4.537
4.531
4.526
4.053
4.030
3.477
3.455
3.448
3.427
3.242
3.234
3.001
2.997
2.941
2.913
2.889
2.724
2.695
1.045
1.028
1.010
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.98
1.00
1.98
1.02
2.01
1.02
2.00
1.98
1.01
1.00
2.99
172.95
170.95
147.42
147.23
129.77
123.80
98.78
61.23
50.82
46.37
40.88
36.73
36.24
35.60
14.00
200
180
160
140
120
100
80
60
40
20
0
ppm

4.19b: *(3aR,6S,7R,7aR)-ethyl 7-formyl-4-hydroxy-6-(4-nitrophenyl)-1,3,3a,6,7,7a-hexahydrobenzo[c]thiophene-5-carboxylate*

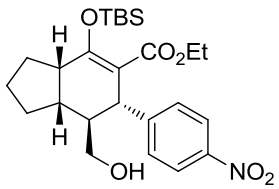


colorless crystals. m.p.: 101-104 °C. $[\alpha]_D^{23}$ = +46.8 (*c* 1.00, CH_2Cl_2, 96% ee); IR (thin film, KBr): 2937, 1721, 1651, 1518, 1348, 1237, 848, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.76 (s, 1H), 9.79 (d, *J* = 0.9 Hz, 1H), 8.14 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.7 Hz, 2H), 4.45 (d, *J* = 7.0 Hz, 1H), 3.97 (m, 2H), 3.40 (q, *J* = 4.5 Hz, 1H), 3.21 (d, *J* = 5.9 Hz, 2H), 2.99 (m, 2H), 2.82-2.90 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 171.4, 171.0, 152.5, 146.9, 128.8, 123.9, 98.8, 61.1, 55.9, 47.1, 40.4, 37.4, 32.9, 31.6, 13.8 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 20.2 min, minor enantiomer t_R = 25.2 min. HRMS (ESI) : [M^-] calcd for [$C_{18}H_{19}NO_6S$]: 377.0933, found: 377.0940.

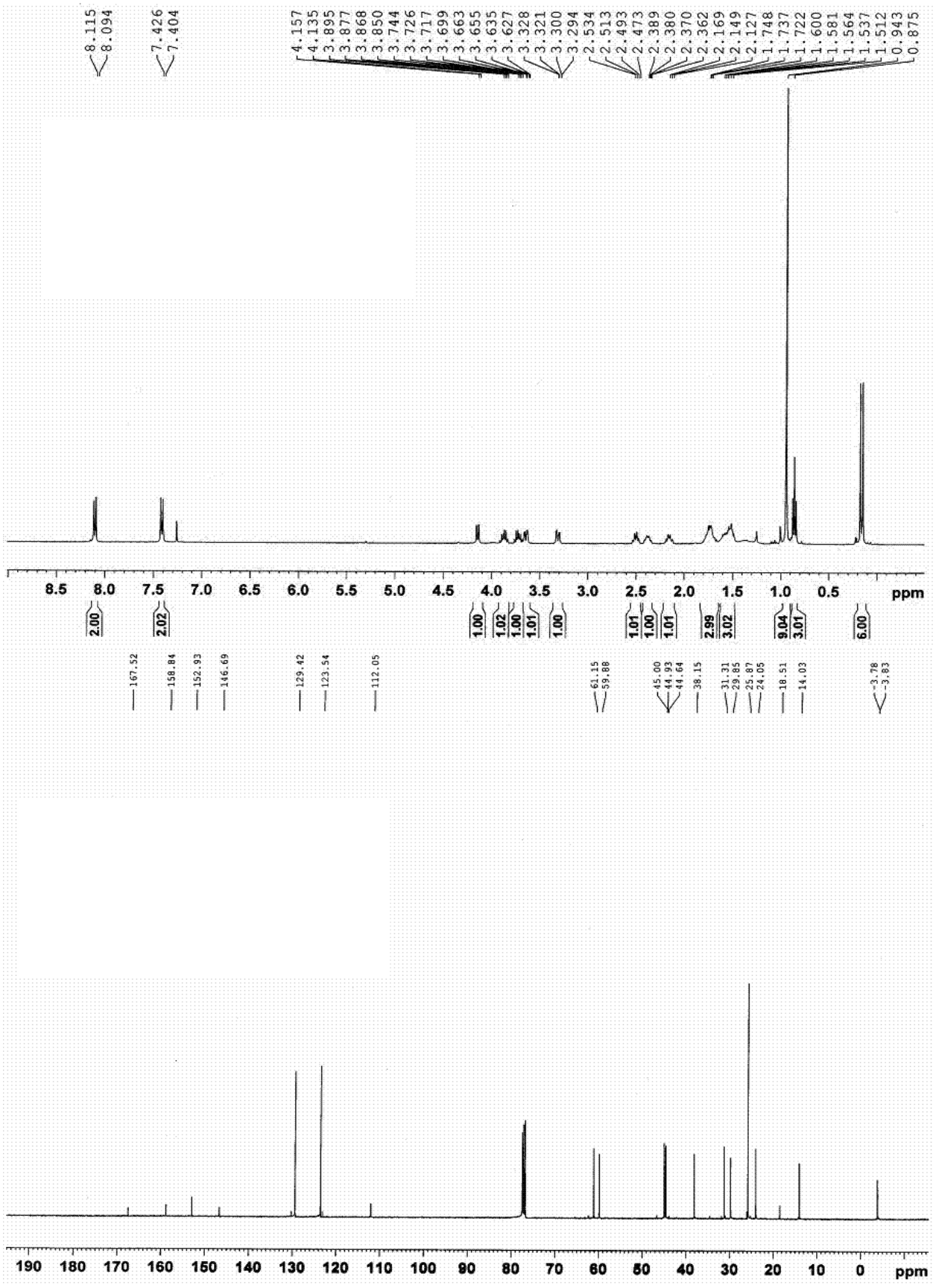

12.764
9.794
9.792
8.158
8.136
7.383
7.361
4.463
4.445
3.987
3.977
3.969
3.959
3.424
3.410
3.396
3.382
3.224
3.208
2.993
2.977
2.902
2.894
2.884
2.876
2.857
2.831
2.822
2.797
0.921
0.903
0.885
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.98
1.00
2.01
1.99
1.01
2.02
1.01
2.01
2.03
2.00
3.03


171.39
171.00
152.47
146.88
128.84
123.85
98.82
61.07
55.89
47.06
40.42
37.38
32.91
31.59
13.80
200
180
160
140
120
100
80
60
40
20
0
ppm

4.7c: *(3aS,6S,7S,7aS)-ethyl 4-(tert-butyldimethylsilyloxy)-7-(hydroxymethyl)-6-(4-nitrophenyl)-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate*



colorless crystals. m.p.: 135-137 °C. IR (thin film, KBr): 3444, 2956, 2931, 2859, 1704, 1519, 1347, 1255, 1201, 1062, 781, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 4.15 (d, *J* = 9.0 Hz, 1H), 3.87 (m, 1H), 3.72 (m, 1H), 3.65 (dd, *J* = 3.4, 11.1 Hz, 1H), 3.31 (dd, *J* = 2.6, 11.1 Hz, 1H), 2.50 (q, *J* = 8.1 Hz, 1H), 2.38 (m, 1H), 2.14 (m, 1H), 1.74 (m, 3H), 1.51-1.60 (m, 3H), 0.94 (s, 9H), 0.86 (t, *J* = 7.1 Hz, 3H), 0.17 (s, 3H), 0.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 158.8, 152.9, 146.7, 129.4, 123.5, 112.1, 61.2, 59.9, 45.0, 44.9, 44.6, 38.2, 31.3, 29.9, 25.9, 24.1, 18.5, 14.0, -3.8, -3.8 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_{25}H_{37}NO_6Si]$: 475.2390, found: 475.2390.


8.115
8.094
7.426
7.404
4.157
4.135
3.895
3.877
3.868
3.850
3.744
3.726
3.717
3.699
3.663
3.655
3.635
3.627
3.328
3.321
3.300
3.294
2.534
2.513
2.493
2.473
2.389
2.380
2.370
2.362
2.169
2.149
2.127
1.748
1.737
1.722
1.600
1.581
1.564
1.537
1.512
0.943
0.875
ppm
2.00
2.02
1.00
1.02
1.00
1.01
1.00
1.01
1.00
1.01
2.99
3.02
9.04
3.01
6.00
167.52
158.84
152.93
146.69
129.42
123.54
112.05
61.15
59.88
45.00
44.93
44.64
38.15
31.31
29.85
25.87
24.05
18.51
14.03
-3.78
-3.83
ppm

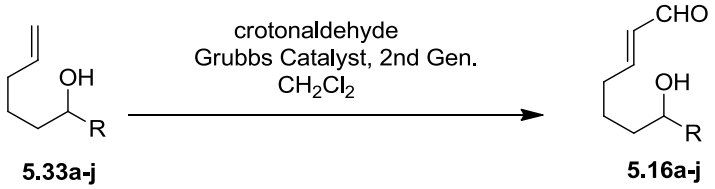
6.4 Experimental and Characterization for Chapter 5

Determination of Enantiomeric Excesses
Enantiomeric excesses were determined by comparison to a racemic sample (prepared with the corresponding racemic catalyst ***rac*–1.12a**).

Preparation of Substrate (5.13)
Substrate **5.13** was prepared according to an exact literature procedure.[13]

Oxa-Michael Cascade Reaction Forming Monosubstituted Pyrans (5.14a–b)
Catalyst **1.12a** (28.6 mg, 0.088 mmol) and $PhCO_2H$ (10.7 mg, 0.088 mmol) were dissolved in dry toluene (1.1 mL) and cooled to –30 ^oC. Substrate **5.13** (0.44 mmol) was added in one portion. Compound **1.23a** (131.2 mg, 0.88 mmol) was added after 5 minutes and the reaction was stirred at –30 ^oC. The reaction was complete after 7 days by ^1H NMR, and the dr was determined by integration of the aldehyde peaks corresponding to **5.14a** and **5.14b**. The reaction mixture was diluted with MeOH (2.2 mL), and $NaBH_4$ (75.7 mg, 2.0 mmol) was added. The reaction was stirred at –30 ^oC for 15 minutes and was quenched by slowly adding saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 15mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Both products **5.14a** and **5.14b** were purified from the residue via column chromatography (EtOAc/petroleum ether, 30/70).

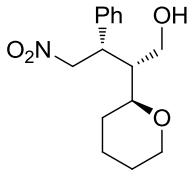
Preparation of Substrates (5.16a–5.16j)
The substrates **5.16a–j** were prepared by cross metathesis of alcohols **5.31a–j**[14] using the procedure described below.



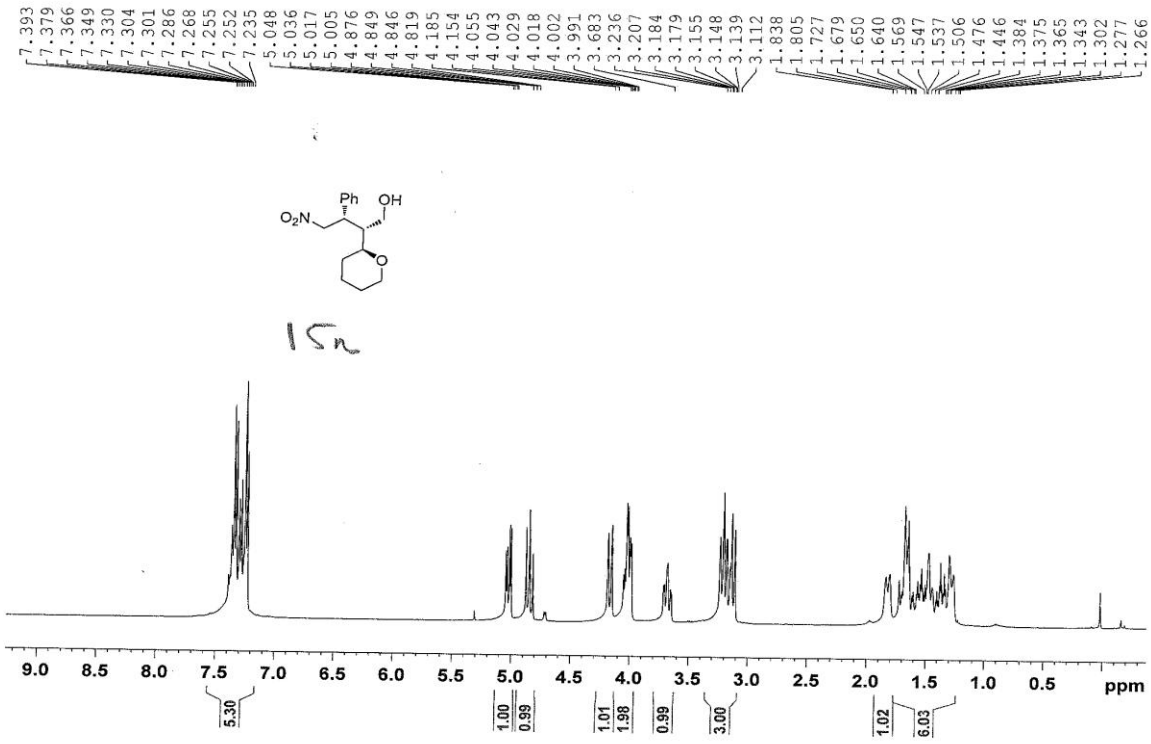
5.33a-j **5.16a-j**

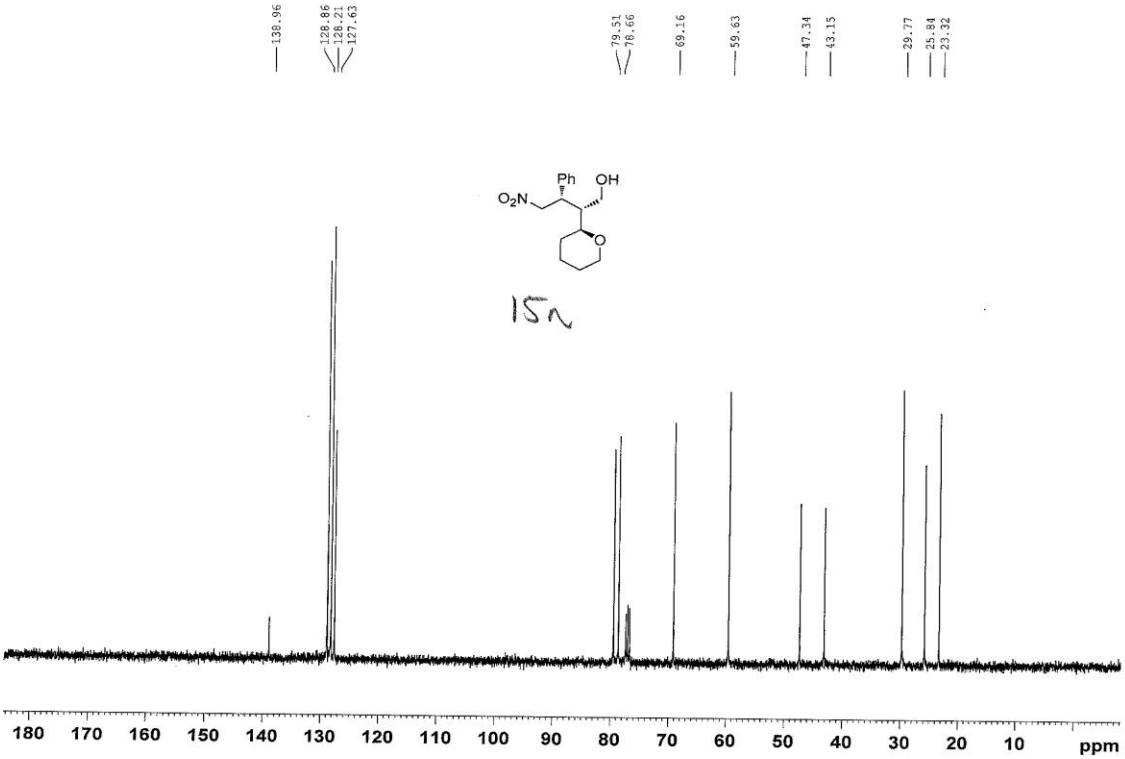
The secondary alcohol **38** (5.0 mmol) was dissolved in dry CH_2Cl_2 (25.0 mL). Crotonaldehyde (2.07 mL, 25.0 mmol) was added followed by Grubbs Catalyst, 2nd Generation (42.4 mg, 0.050 mmol). The reaction was refluxed for 1.5 h and then concentrated at reduced pressure. The residue was purified via column chromatography (EtOAc/petroleum ether, 35/65).

5.14a: *(2R,3S)-4-nitro-3-phenyl-2-((S)-tetrahydro-2H-pyran-2-yl)butan-1-ol*

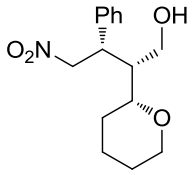


colorless oil. $[\alpha]_D^{23}$ = -11.1 (*c* 1.00, $CHCl_3$, 99% ee); IR (thin film, KBr): 35.4, 2939, 2858, 1552, 1381, 1209, 1084, 1041, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.21 (m, 5H), 5.03 (dd, *J* = 12.4, 4.6 Hz, 1H), 4.84 (dd, *J* = 12.4, 10.9 Hz, 1H), 4.18 (d, *J* = 12.5 Hz, 1H), 4.02 (m, 2H), 3.68 (m, 1H), 3.28-3.08 (m, 3H), 1.81 (m, 1H), 1.75-1.25 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 128.9, 128.2, 127.6, 79.5, 78.7, 69.2, 59.6, 47.3, 43.2, 29.8, 25.8, 23.3 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 95:5), 0.5 mL/min; major enantiomer t_R = 40.7 min, minor enantiomer t_R = 46.4 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{15}H_{21}NO_4]$: 279.1471, found: 279.1473.

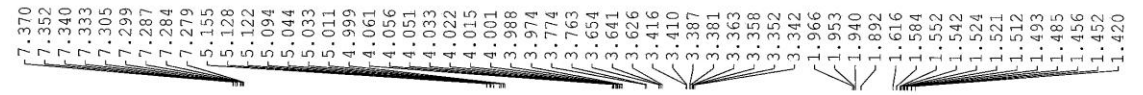

7.393
7.379
7.366
7.349
7.330
7.304
7.301
7.286
7.268
7.255
7.252
7.235
5.048
5.036
5.017
5.005
4.876
4.849
4.846
4.819
4.185
4.154
4.055
4.043
4.029
4.018
4.002
3.991
3.683
3.236
3.207
3.184
3.179
3.155
3.148
3.139
3.112
1.838
1.805
1.727
1.679
1.650
1.640
1.569
1.547
1.537
1.506
1.476
1.446
1.384
1.375
1.365
1.343
1.302
1.277
1.266
Ph
OH
O2N
O
15n
9.0 8.5 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 ppm
5.30
1.00
0.99
1.01
1.98
0.99
3.00
1.02
6.03

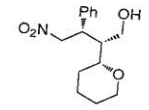

138.96
128.86
128.21
127.63
79.51
78.66
69.16
59.63
47.34
43.15
29.77
25.84
23.32
Ph
OH
O2N
O
15n
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

5.14b: *(2R,3S)-4-nitro-3-phenyl-2-((R)-tetrahydro-2H-pyran-2-yl)butan-1-ol*

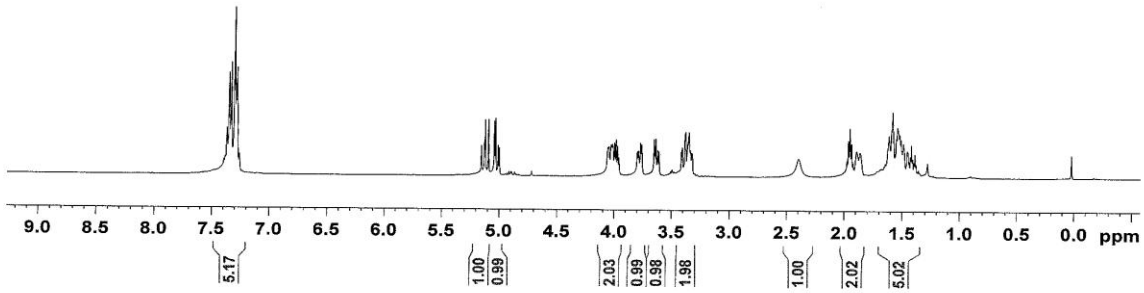


colorless oil. $[\alpha]_D^{22}$ = -33.4(*c* 1.00, $CHCl_3$, >99% ee); IR (thin film, KBr): 3411, 2939, 2853, 1550, 1380, 1087, 1047, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.24 (m, 5H), 5.12 (dd, *J* = 13.4, 10.9 Hz, 1H), 5.03 (dd, *J* = 13.4, 4.5 Hz, 1H), 4.10-3.95 (m, 2H), 3.79 (dd, *J* = 11.3, 4.4 Hz, 1H), 3.63 (dd, *J* = 11.3, 5.0 Hz, 1H), 3.44-3.30 (m, 2H), 2.40 (bs, 1H), 2.00-1.84 (m, 2H), 1.69-1.33 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 128.8, 128.2, 127.5, 79.0, 78.6, 68.9, 61.8, 48.9, 42.9, 28.6, 25.9, 23.3 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 95:5), 0.5 mL/min; major enantiomer t_R = 54.2 min, minor enantiomer t_R = 79.3 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{15}H_{21}NO_4]$: 279.1471, found: 279.1472.

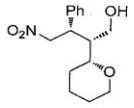

7.370
7.352
7.340
7.333
7.305
7.299
7.287
7.284
7.279
5.155
5.128
5.122
5.094
5.044
5.033
5.011
4.999
4.061
4.056
4.051
4.033
4.022
4.015
4.001
3.988
3.974
3.774
3.763
3.654
3.641
3.626
3.416
3.410
3.387
3.381
3.363
3.358
3.352
3.342
1.966
1.953
1.940
1.892
1.616
1.584
1.552
1.542
1.524
1.521
1.512
1.493
1.485
1.456
1.452
1.420


Ph
OH
O2N
O

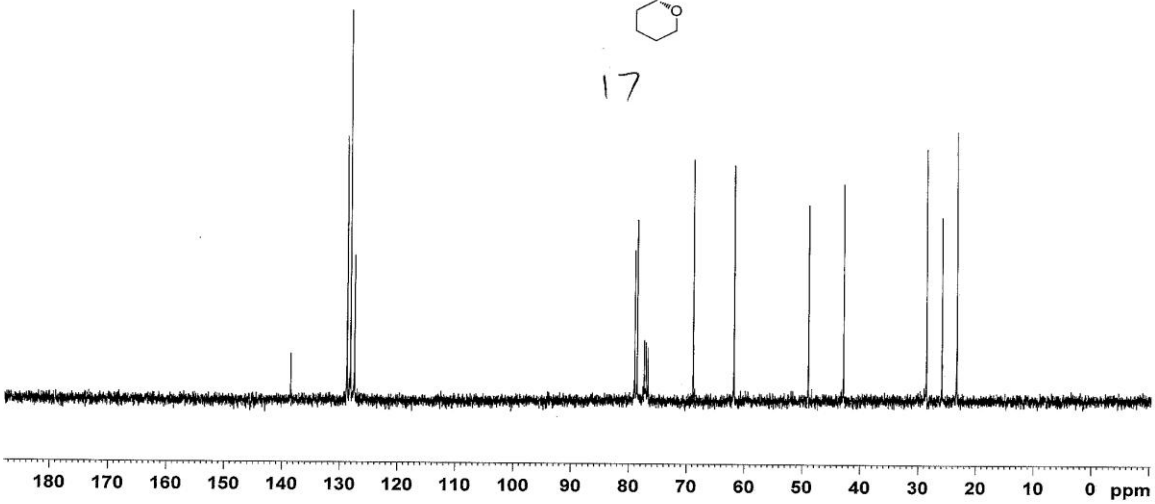
17


9.0 8.5 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 ppm
5.17
1.00
0.99
2.03
0.99
0.98
1.98
1.00
2.02
5.02

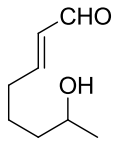

138.51
128.80
128.21
127.49
79.02
78.60
68.86
61.82
48.93
42.85
28.56
25.89
23.29


Ph
OH
O2N
O

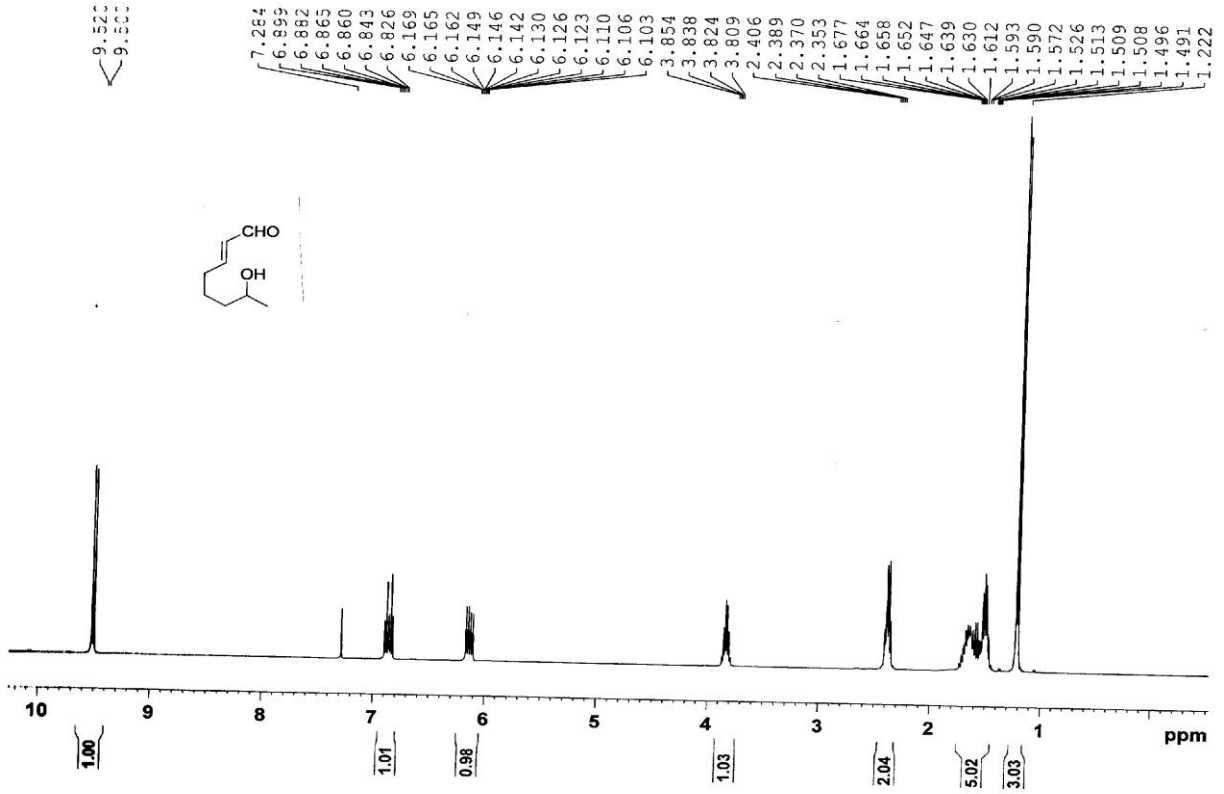
17

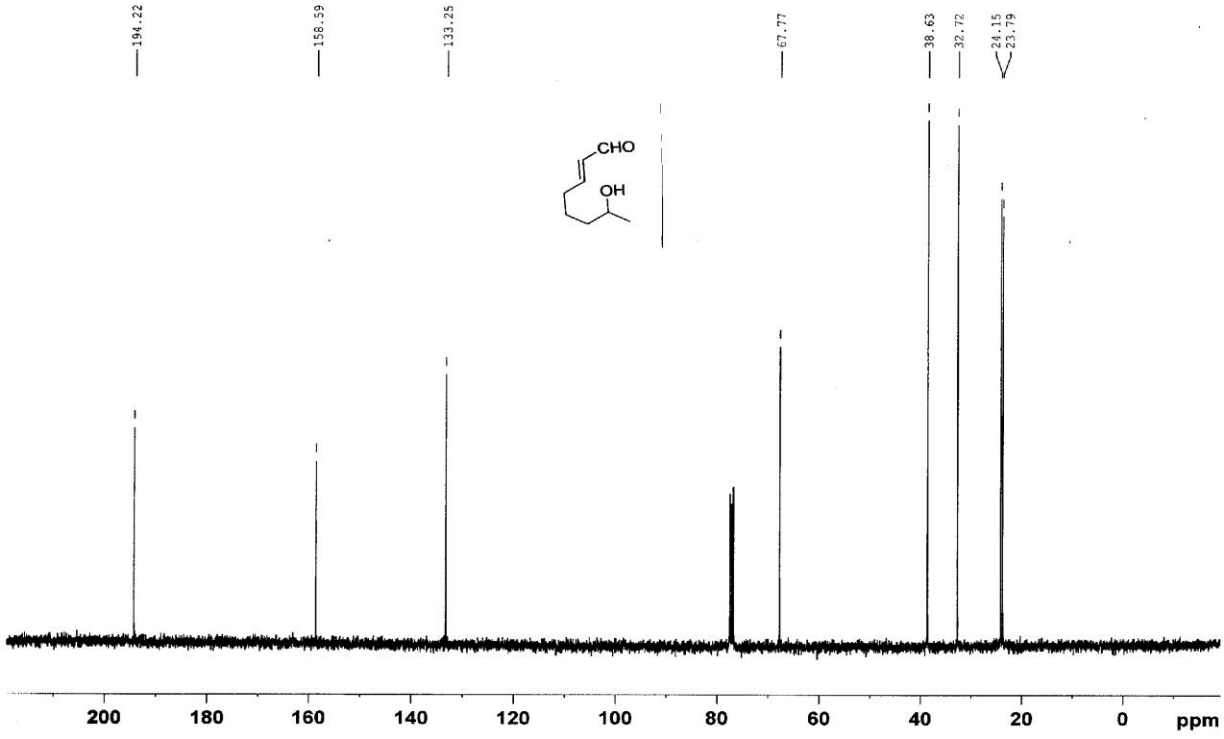

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

5.16a: *(E)-7-hydroxyoct-2-enal*

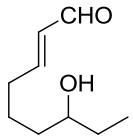


brown oil. Collected in 80% yield. IR (thin film, KBr): 3419, 2966, 2931, 2864, 2737, 1690, 1143, 977 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, *J* = 7.9 Hz, 1H), 6.86 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.14 (m, 1H), 3.83 (m, 1H), 2.38 (m, 2H), 1.67-1.49 (m, 5H), 1.21 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 158.6, 133.3, 67.8, 38.6, 32.7, 24.2, 23.8 ppm; HRMS (ESI) : [M^+] calcd for [$C_8H_{14}O_2$]: 142.0994, found: 142.0993.

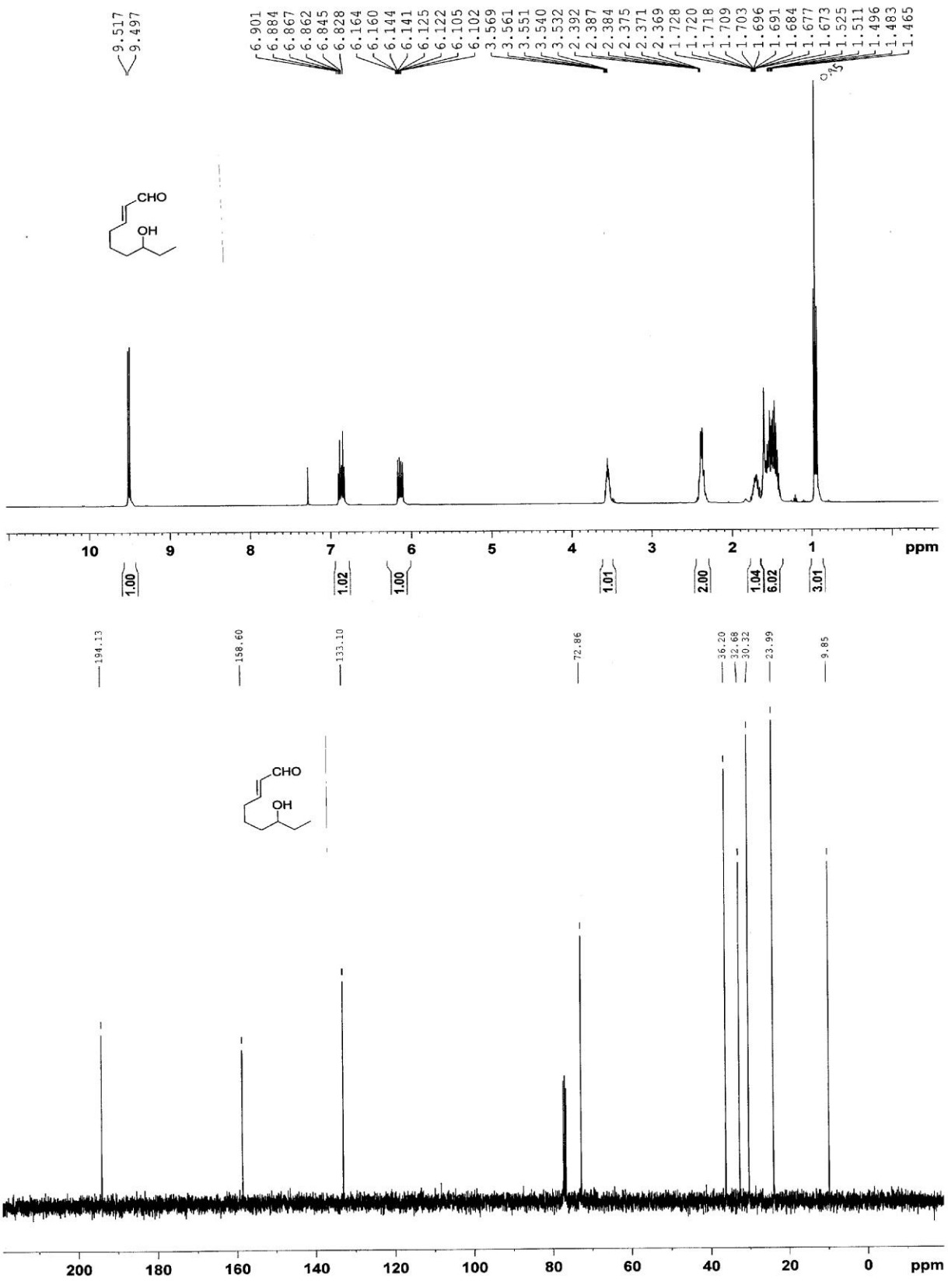

9.520
9.503
7.264
6.899
6.882
6.865
6.860
6.843
6.826
6.169
6.165
6.162
6.149
6.146
6.142
6.130
6.126
6.123
6.110
6.106
6.103
3.854
3.838
3.824
3.809
2.406
2.389
2.370
2.353
1.677
1.664
1.658
1.652
1.647
1.639
1.630
1.612
1.593
1.590
1.572
1.526
1.513
1.509
1.508
1.496
1.491
1.222
CHO
OH
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.01
0.98
1.03
2.04
5.02
3.03


194.22
158.59
133.25
67.77
38.63
32.72
24.15
23.79
CHO
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

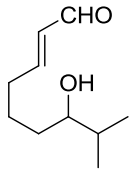
5.16b: *(E)-7-hydroxynon-2-enal*



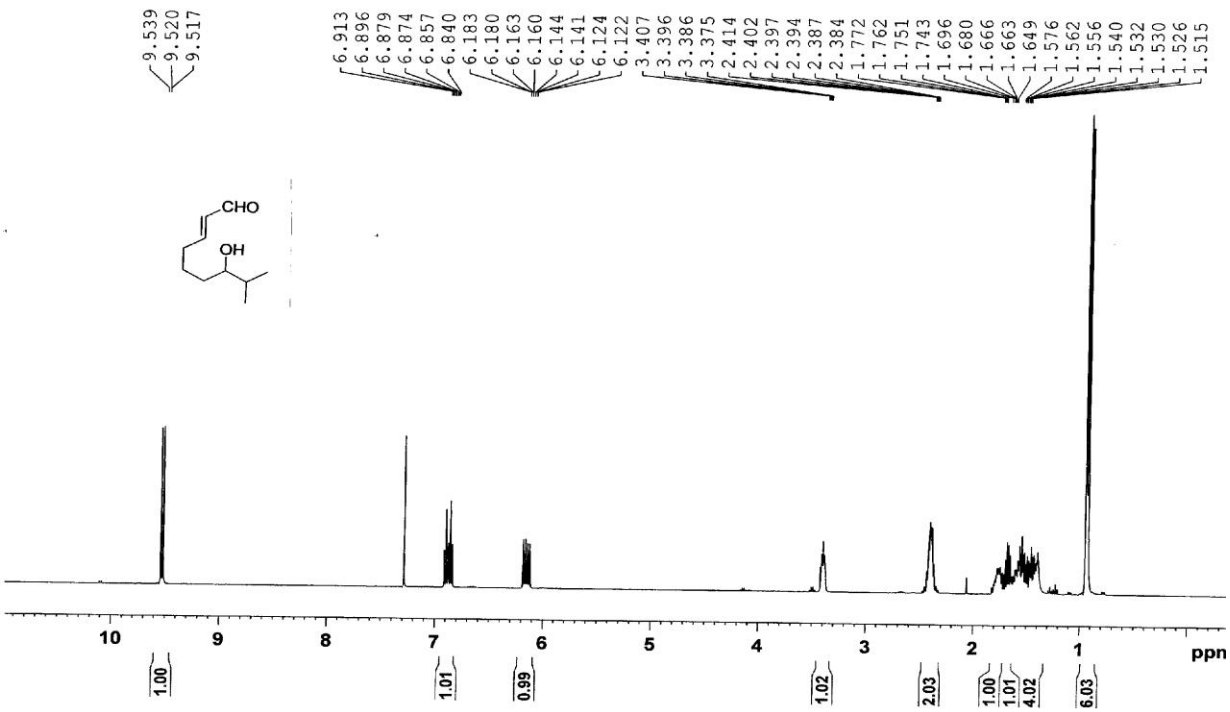
brown oil. Collected in 75% yield. IR (thin film, KBr): 3424, 3935, 3876, 2738, 1690, 1459, 1141, 975 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, *J* = 7.9 Hz, 1H), 6.86 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.13 (m, 1H), 3.55 (m, 1H), 2.38 (m, 2H), 1.78-1.65 (m, 1H), 1.64-1.37(m, 6H), 0.95 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 158.6, 133.1, 72.9, 36.2, 32.7, 30.3, 24.0, 9.9 ppm; HRMS (ESI) : [M^+] calcd for [$C_9H_{16}O_2$]: 156.1150, found: 156.1151.

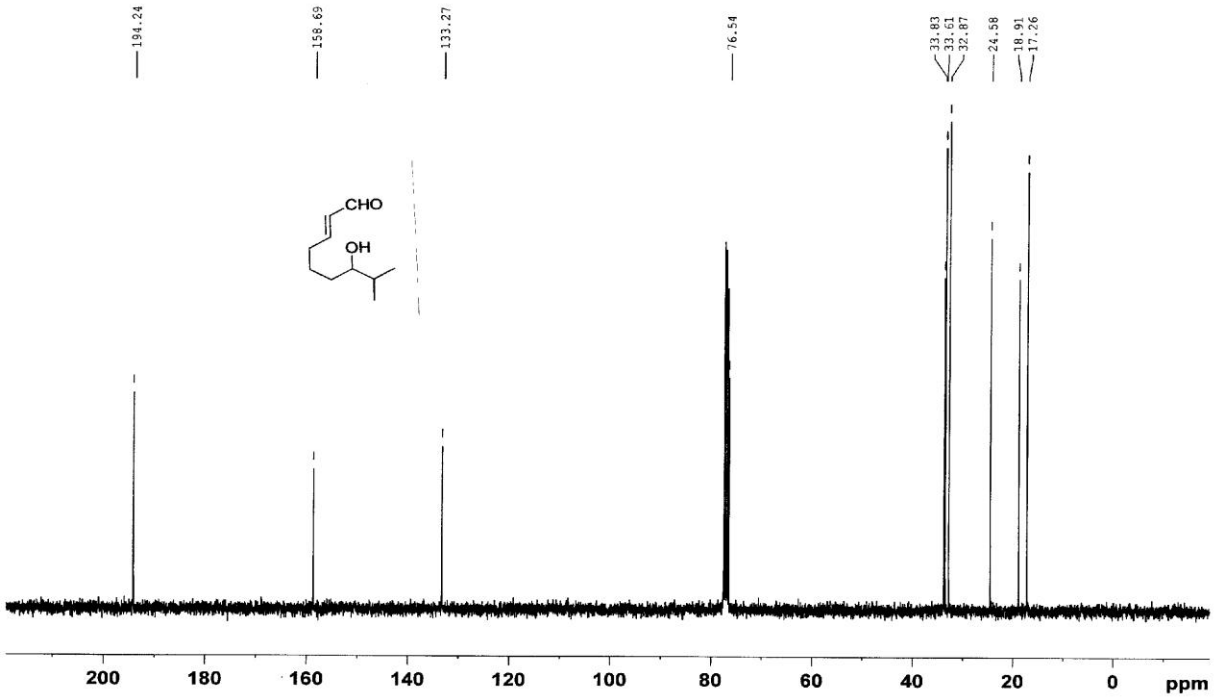

9.517
9.497
6.901
6.884
6.867
6.862
6.845
6.828
6.164
6.160
6.144
6.141
6.125
6.122
6.105
6.102
3.569
3.561
3.551
3.540
3.532
2.392
2.387
2.384
2.375
2.371
2.369
1.728
1.720
1.718
1.709
1.703
1.696
1.691
1.684
1.677
1.673
1.525
1.511
1.496
1.483
1.465
0.915
CHO
OH
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.02
1.00
1.01
2.00
1.04
6.02
3.01
194.13
158.60
133.10
72.86
36.20
32.68
30.32
23.99
9.85
CHO
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

5.16c: *(E)-7-hydroxy-8-methylnon-2-enal*

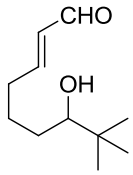


brown oil. Collected in 73% yield. IR (thin film, KBr): 3439, 3957, 2872, 1692, 1461, 1141, 979 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, *J* = 7.9 Hz, 1H), 6.88 (dt, *J* = 15.6, 6.8Hz, 1H), 6.15 (m, 1H), 3.39 (m, 1H), 2.39 (m, 2H), 1.83-1.35 (m, 6H), 0.93 (dd, *J* = 6.9, 2.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 158.7, 133.3, 76.5, 33.8, 33.6, 32.9, 24.6, 18.9, 17.3 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_{10}H_{18}O_2]$: 170.1307, found: 170.1303.

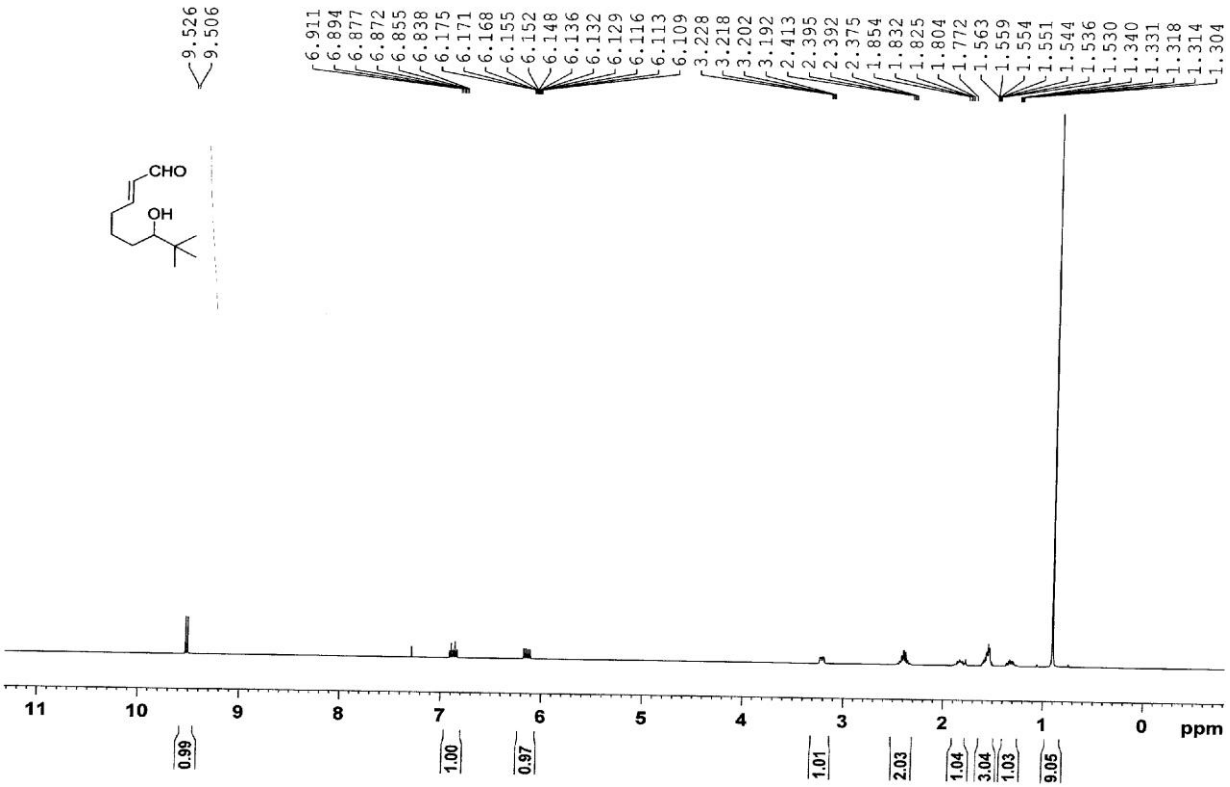

9.539
9.520
9.517
6.913
6.896
6.879
6.874
6.857
6.840
6.183
6.180
6.163
6.160
6.144
6.141
6.124
6.122
3.407
3.396
3.386
3.375
2.414
2.402
2.397
2.394
2.387
2.384
1.772
1.762
1.751
1.743
1.696
1.680
1.666
1.663
1.649
1.576
1.562
1.556
1.540
1.532
1.530
1.526
1.515
CHO
OH
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.01
0.99
1.02
2.03
1.00
1.01
4.02
6.03

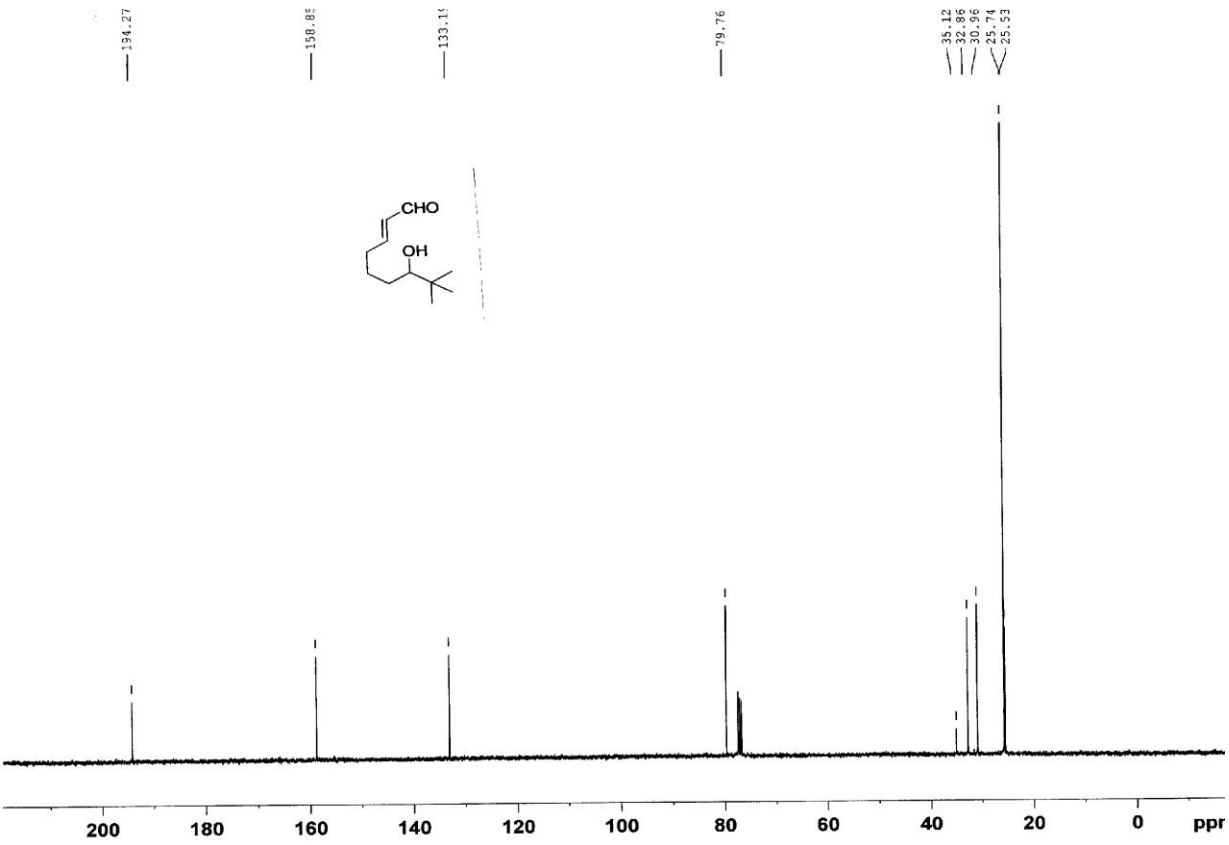

194.24
158.69
133.27
76.54
33.83
33.61
32.87
24.58
18.91
17.26
CHO
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

5.16d: *(E)-7-hydroxy-8,8-dimethylnon-2-enal*

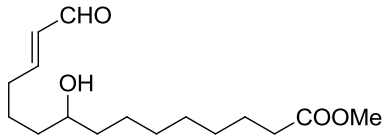


brown oil. Collected in 70% yield. IR (thin film, KBr): 3461, 3953, 2868, 1690, 1130, 978 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, *J* = 7.9 Hz, 1H), 6.86 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.14 (m, 1H), 3.21 (m, 1H), 2.39 (m, 2H), 1.83 (m, 1H), 1.63-1.49 (m, 3H), 1.32 (m, 1H), 0.90 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 158.9, 133.2, 79.8, 35.1, 32.9, 31.0, 25.7, 25.5 ppm; HRMS (ESI) : [M^+] calcd for [$C_{11}H_{20}O_2$]: 184.1463, found: 184.1464.

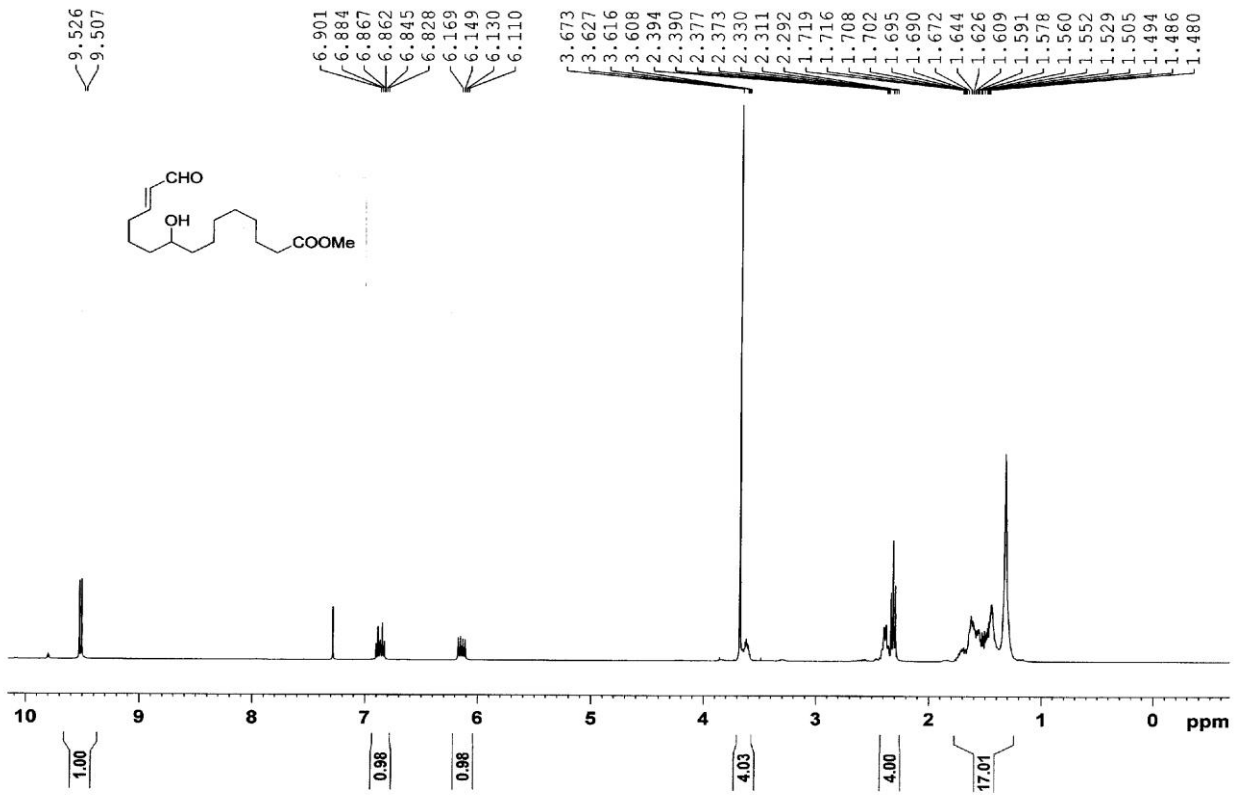

9.526
9.506
6.911
6.894
6.877
6.872
6.855
6.838
6.175
6.171
6.168
6.155
6.152
6.148
6.136
6.132
6.129
6.116
6.113
6.109
3.228
3.218
3.202
3.192
2.413
2.395
2.392
2.375
1.854
1.832
1.825
1.804
1.772
1.563
1.559
1.554
1.551
1.544
1.536
1.530
1.340
1.331
1.318
1.314
1.304
CHO
OH
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.99
1.00
0.97
1.01
2.03
1.04
3.04
1.03
9.05

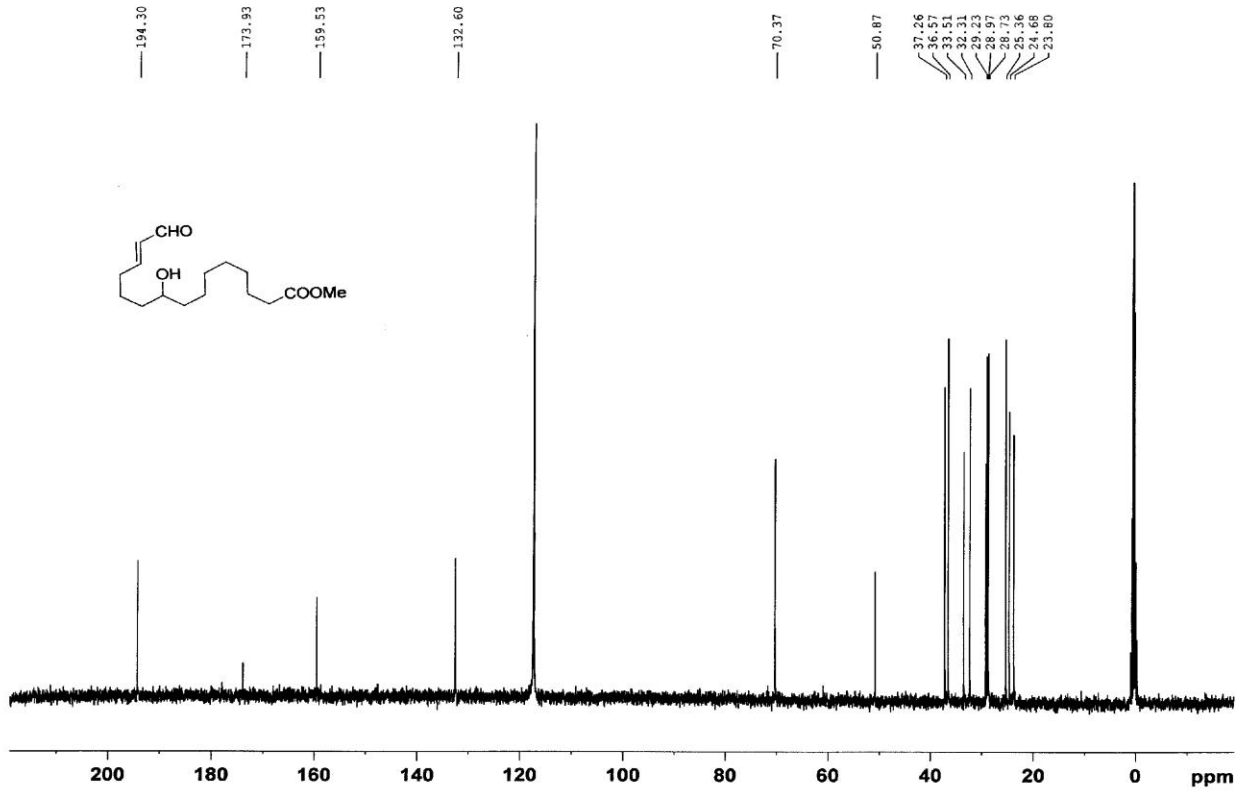

194.27
158.88
133.19
79.76
35.12
32.86
30.96
25.74
25.53
CHO
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

5.16e: *(E)-methyl 9-hydroxy-15-oxopentadec-13-enoate*

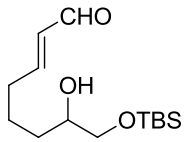


tan powder. Collected in 79% yield. IR (thin film, KBr): 3496, 2932, 2856, 2732, 1738, 1691, 1437, 1199, 1171, 977 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, *J* = 7.9 Hz, 1H), 6.86 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.14 (m, 1H), 3.67 (s, 3H), 3.62 (m, 1H), 2.39 (m, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.80-1.24 (m, 17H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 194.3, 173.9, 159.5, 132.6, 70.4, 50.9, 37.3, 36.6, 33.5, 32.3, 29.2, 29.0, 28.7, 25.4, 24.7, 23.8 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_{16}H_{28}O_4]$: 284.1988, found: 284.1981.

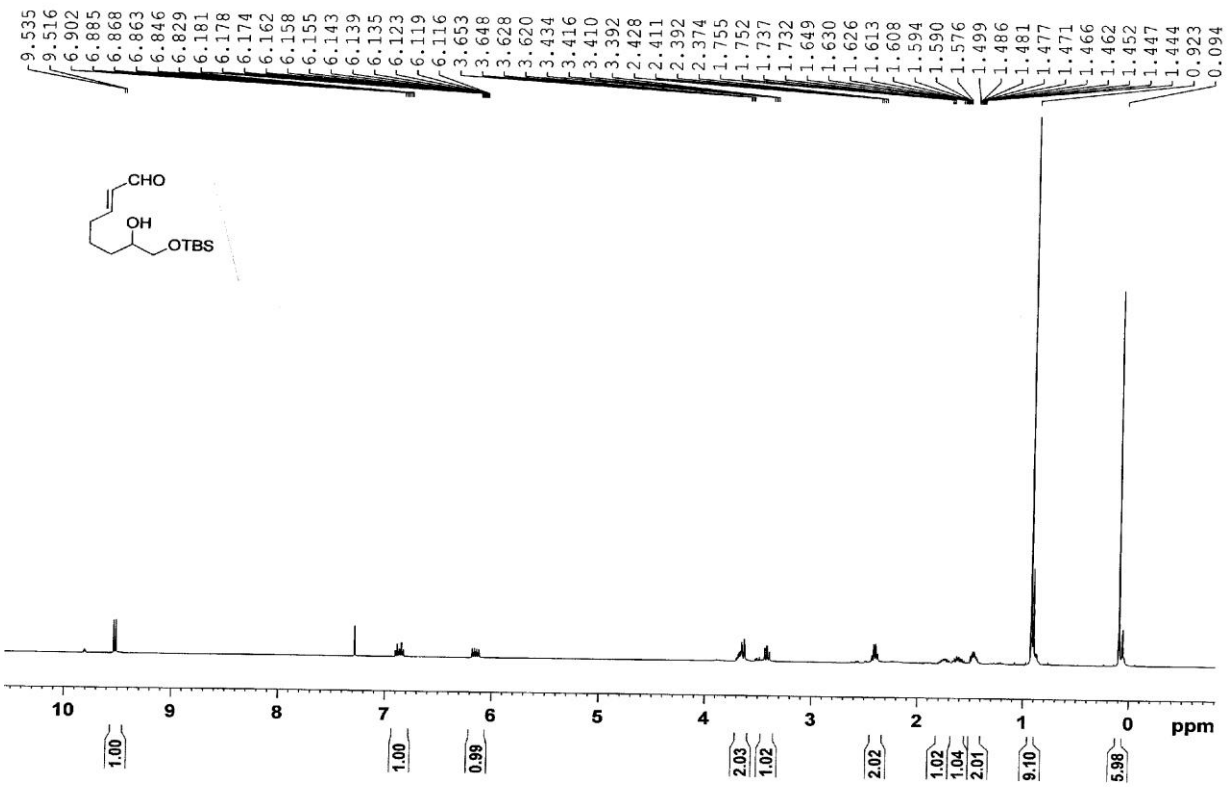

9.526
9.507
6.901
6.884
6.867
6.862
6.845
6.828
6.169
6.149
6.130
6.110
3.673
3.627
3.616
3.608
2.394
2.390
2.377
2.373
2.330
2.311
2.292
1.719
1.716
1.708
1.702
1.695
1.690
1.672
1.644
1.626
1.609
1.591
1.578
1.560
1.552
1.529
1.505
1.494
1.486
1.480
CHO
OH
COOMe
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.98
0.98
4.03
4.00
17.01

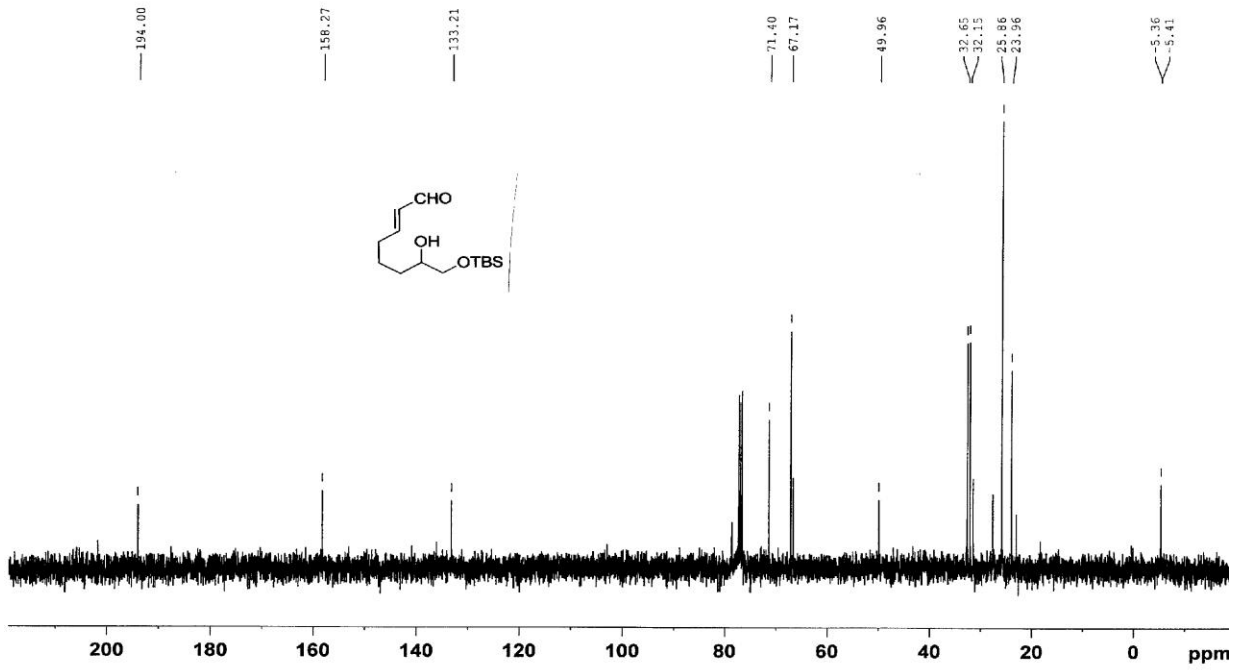

194.30
173.93
159.53
132.60
70.37
50.87
37.26
36.57
33.51
32.31
29.23
28.97
28.73
25.36
24.68
23.80
CHO
OH
COOMe
200
180
160
140
120
100
80
60
40
20
0
ppm

5.16f: *(E)-8-((tert-butyldimethylsilyl)oxy)-7-hydroxyoct-2-enal*

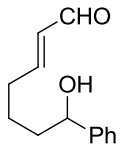


brown oil. Collected in 62% yield. IR (thin film, KBr): 3460, 2929, 2857, 2738, 1694, 1255, 1119, 838, 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, *J* = 7.9 Hz, 1H), 6.87 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.15 (m, 1H), 3.64 (m, 2H), 3.41 (m, 1H), 2.40 (m, 2H), 1.73 (m, 1H), 1.62 (m, 1H), 1.48 (m, 2H), 0.92 (s, 9H), 0.09 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 158.3, 133.2, 71.4, 67.2, 50.0, 32.7, 32.2, 25.9, 24.0, -5.4, -5.4 ppm; HRMS (ESI) : [M^+] calcd for [$C_{14}H_{28}O_3Si$]: 272.1808, found: 272.1804.

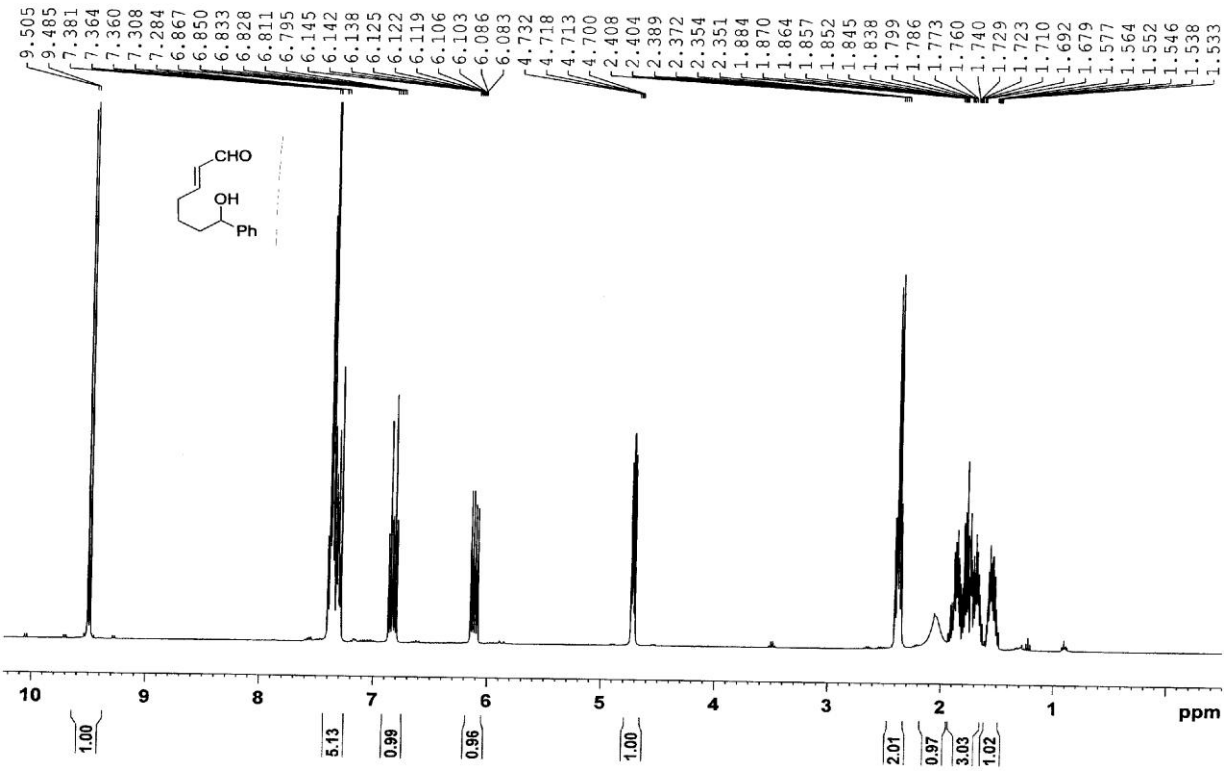

9.535
9.516
6.902
6.885
6.868
6.863
6.846
6.829
6.181
6.178
6.174
6.162
6.158
6.155
6.143
6.139
6.135
6.123
6.119
6.116
3.653
3.648
3.628
3.620
3.434
3.416
3.410
3.392
2.428
2.411
2.392
2.374
1.755
1.752
1.737
1.732
1.649
1.630
1.626
1.613
1.608
1.594
1.590
1.576
1.499
1.486
1.481
1.477
1.471
1.466
1.462
1.452
1.447
1.444
0.923
0.094
CHO
OH
OTBS
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.00
0.99
2.03
1.02
2.02
1.02
1.04
2.01
9.10
5.98

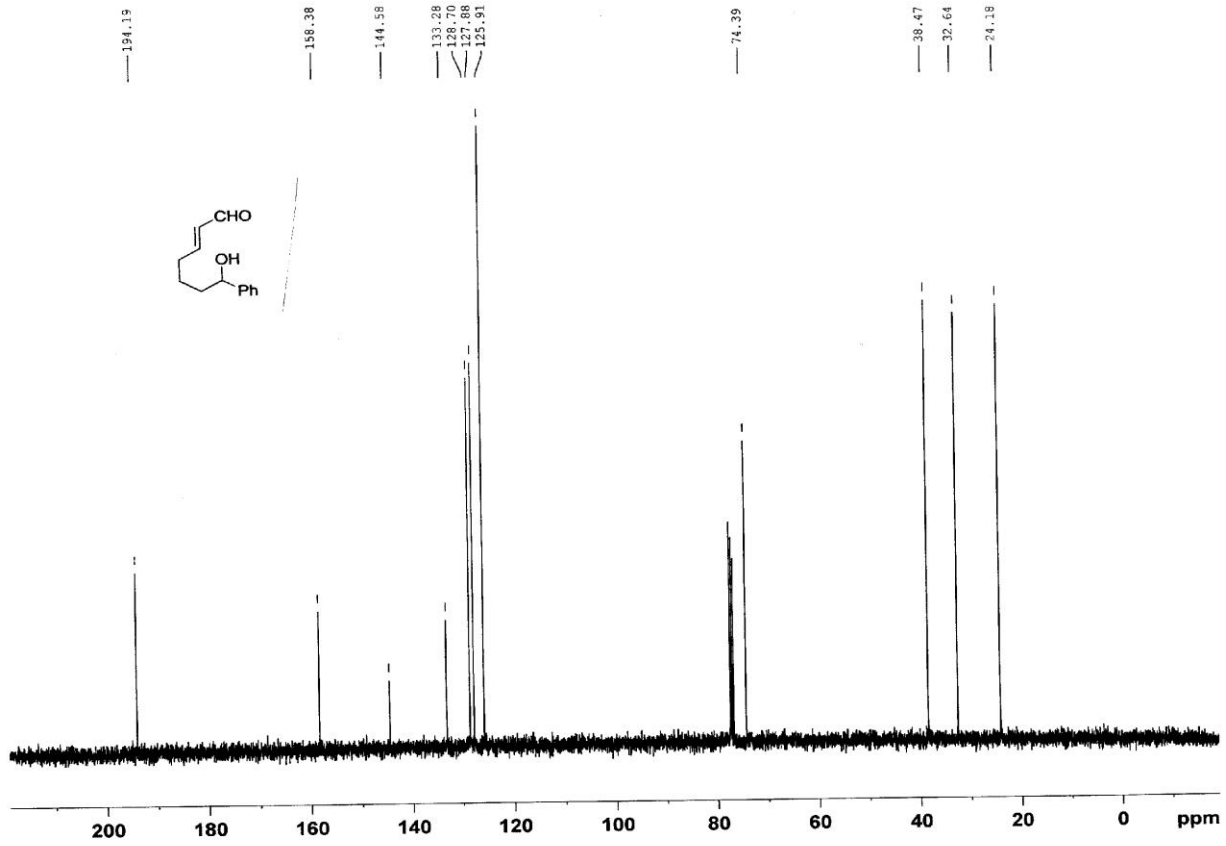

194.00
158.27
133.21
71.40
67.17
49.96
32.65
32.15
25.86
23.96
-5.36
-5.41
CHO
OH
OTBS
200
180
160
140
120
100
80
60
40
20
0
ppm

5.16g: *(E)-7-hydroxy-7-phenylhept-2-enal*

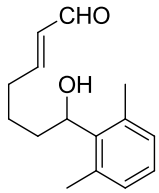


tan powder. Collected in 80% yield. IR (thin film, KBr): 3428, 2938, 2863, 1687, 1454, 1130, 976, 763, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, *J* = 7.9 Hz, 1H), 7.43-7.26 (m, 5H), 6.83 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.12 (m, 1H), 4.72 (m, 1H), 2.04 (bs, 1H) 2.38 (m, 2H), 1.95-1.48 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 158.4, 144.6, 133.3, 128.7, 127.9, 125.9, 74.4, 38.5, 32.6, 34.2 ppm; LRMS (ESI) : $[M^+]$ calcd for $[C_{13}H_{16}O_2]$: 204.1150, found: 204.1149.

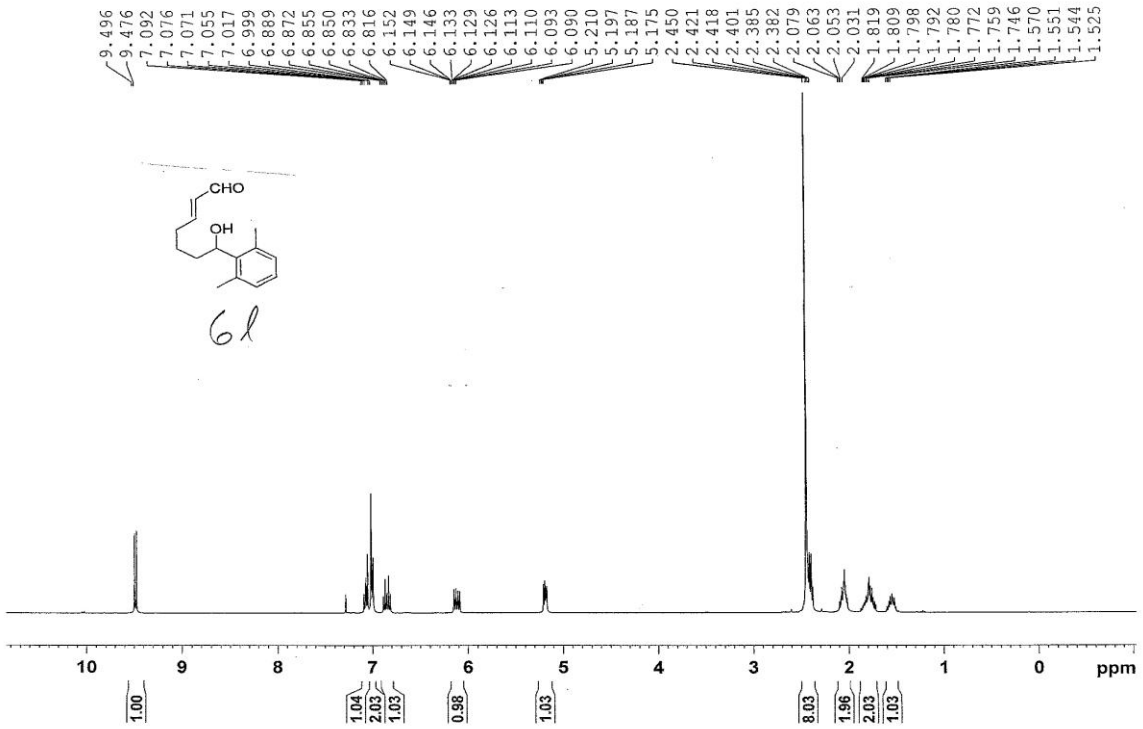

9.505
9.485
7.381
7.364
7.360
7.308
7.284
6.867
6.850
6.833
6.828
6.811
6.795
6.145
6.142
6.138
6.125
6.122
6.119
6.106
6.103
6.086
6.083
4.732
4.718
4.713
4.700
2.408
2.404
2.389
2.372
2.354
2.351
1.884
1.870
1.864
1.857
1.852
1.845
1.838
1.799
1.786
1.773
1.760
1.740
1.729
1.723
1.710
1.692
1.679
1.577
1.564
1.552
1.546
1.538
1.533
CHO
OH
Ph
10
9
8
7
6
5
4
3
2
1
ppm
1.00
5.13
0.99
0.96
1.00
2.01
0.97
3.03
1.02

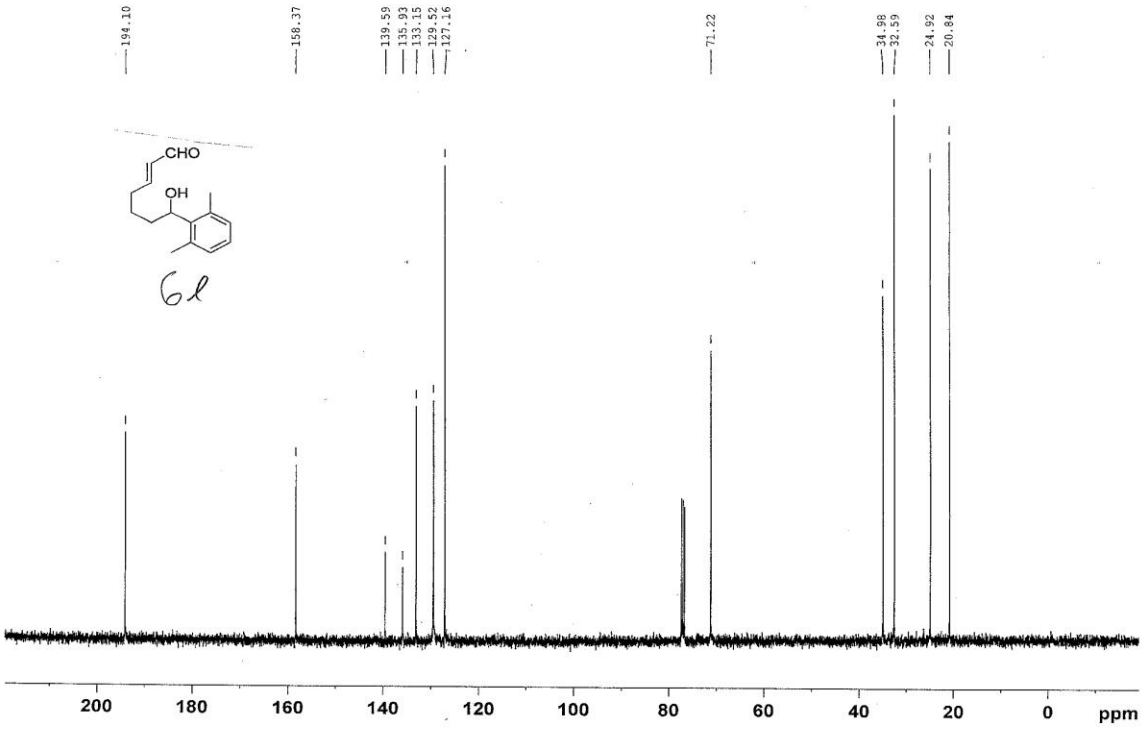

194.19
158.38
144.58
133.28
128.70
127.88
125.91
74.39
38.47
32.64
24.18
CHO
OH
Ph
200
180
160
140
120
100
80
60
40
20
0
ppm

5.16h: *(E)-7-(2,6-dimethylphenyl)-7-hydroxyhept-2-enal*

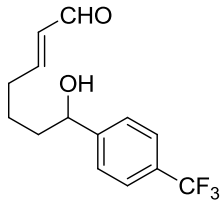


brown oil. Collected in 86% yield. IR (thin film, KBr): 3447, 2946, 2862, 2736, 1690, 1468, 1130, 976, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (d, *J* = 7.9 Hz, 1H), 7.13-6.97 (m, 3H), 6.85 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.13 (m, 1H), 5.19 (m, 1H), 2.45 (s, 6H), 2.39 (m, 2H), 2.06 (m, 2H), 1.79 (m, 2H), 1.55 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 158.4, 139.6, 135.9, 133.2, 129.5, 127.2, 71.2, 35.0, 32.6, 24.9, 20.9 ppm; LRMS (ESI) : [M^+] calcd for [$C_{15}H_{20}O_2$]: 232.1463, found: 232.1465.

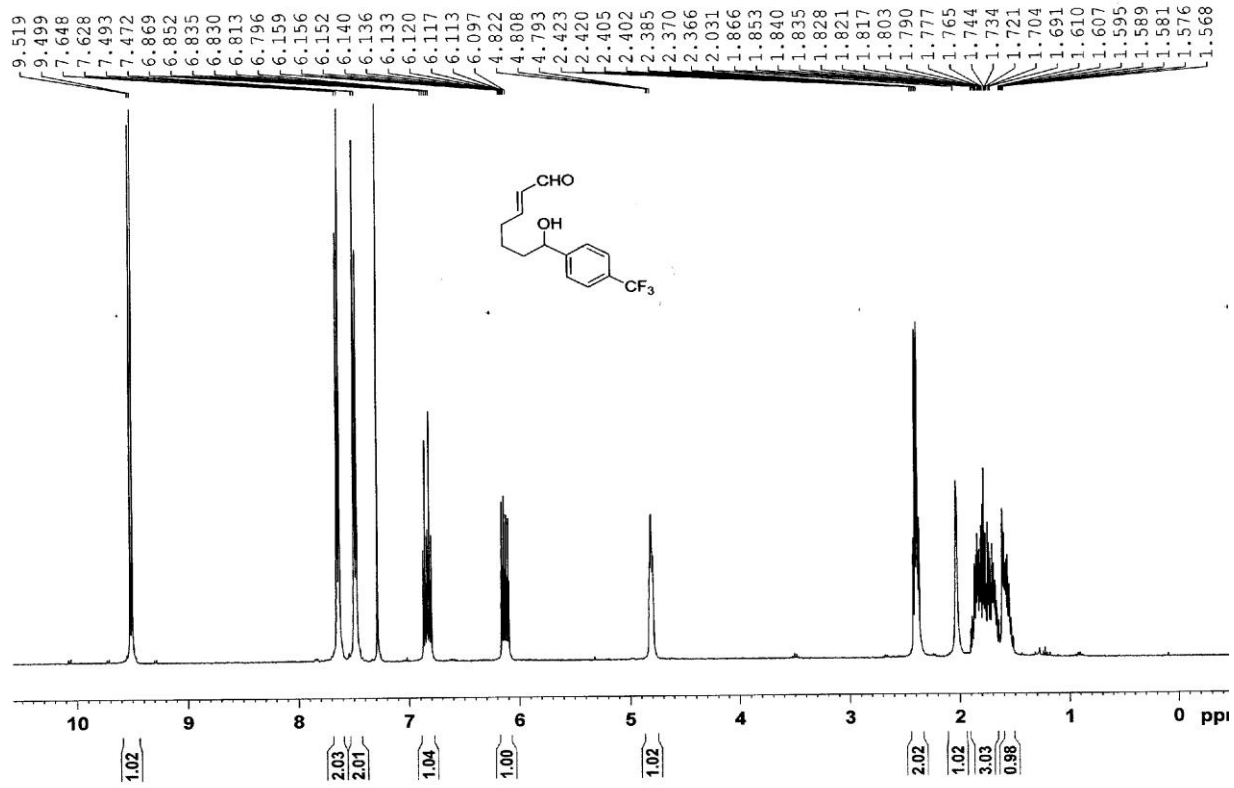

9.496
9.476
7.092
7.076
7.071
7.055
7.017
6.999
6.889
6.872
6.855
6.850
6.833
6.816
6.152
6.149
6.146
6.133
6.129
6.126
6.113
6.110
6.093
6.090
5.210
5.197
5.187
5.175
2.450
2.421
2.418
2.401
2.385
2.382
2.079
2.063
2.053
2.031
1.819
1.809
1.798
1.792
1.780
1.772
1.759
1.746
1.570
1.551
1.544
1.525
CHO
OH
6l
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.04
2.03
1.03
0.98
1.03
8.03
1.96
2.03
1.03

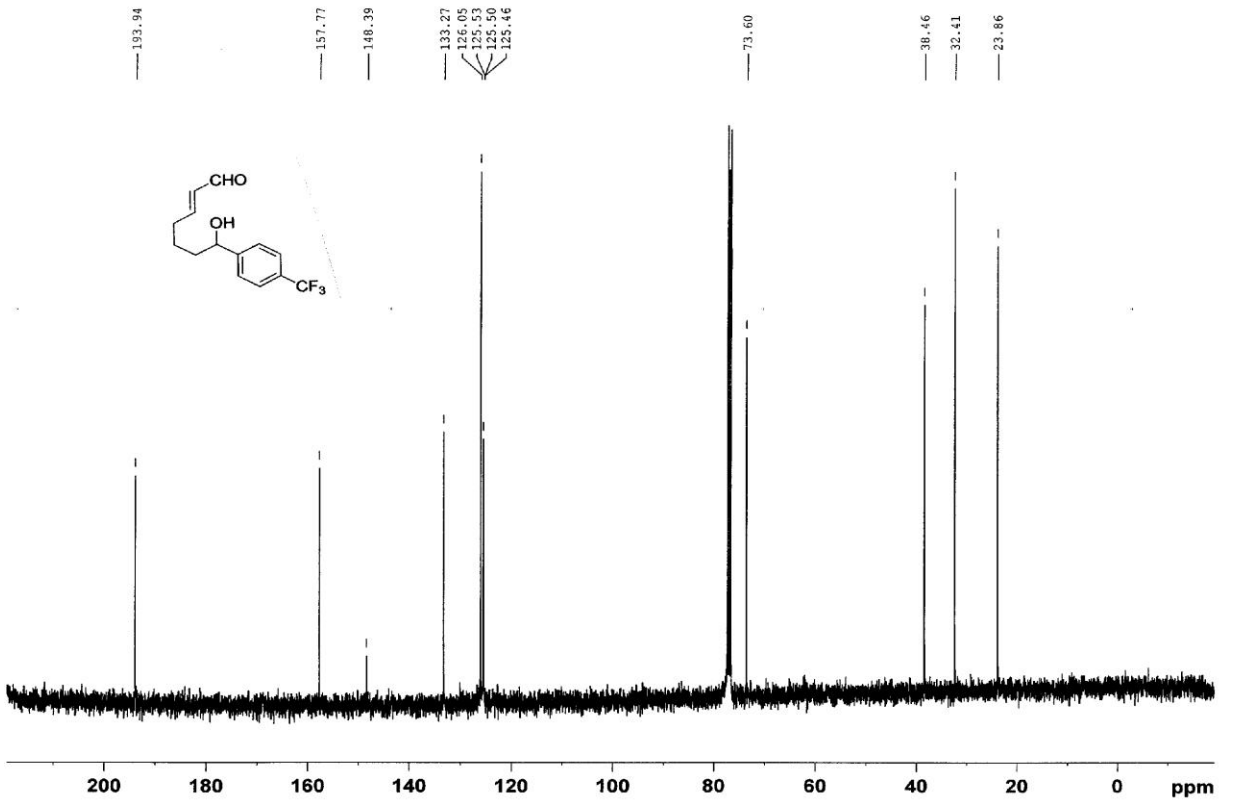

194.10
158.37
139.59
135.93
133.15
129.52
127.16
71.22
34.98
32.59
24.92
20.84
CHO
OH
6l
200
180
160
140
120
100
80
60
40
20
0
ppm

5.16i: *(E)-7-hydroxy-7-(4-(trifluoromethyl)phenyl)hept-2-enal*

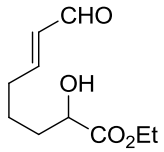


brown oil. Collected in 73% yield. IR (thin film, KBr): 3428, 2941, 2866, 1690, 1328, 1165, 1124, 1068, 1017, 845, 608 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 6.83 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.13 (m, 1H), 4.80 (m, 1H), 2.40 (m, 2H), 2.03 (bs, 1H), 1.93-1.50 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 157.8, 148.4, 133.3, 126.1, 125.5, 125.5, 125.5, 73.6, 38.5, 32.4, 23.9 ppm; LRMS (ESI) : [M^+] calcd for [$C_{14}H_{15}F_3O_2$]: 272.1, found: 272.2.

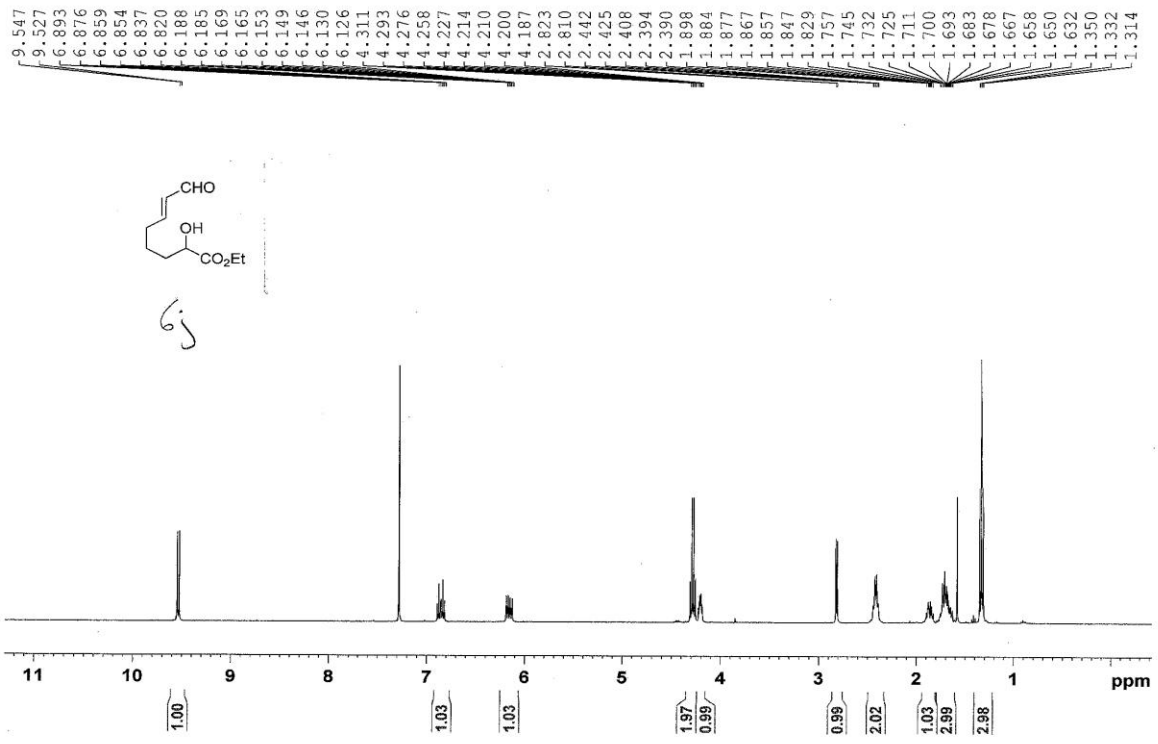

9.519
9.499
7.648
7.628
7.493
7.472
6.869
6.852
6.835
6.830
6.813
6.796
6.159
6.156
6.152
6.140
6.136
6.133
6.120
6.117
6.113
6.097
4.822
4.808
4.793
2.423
2.420
2.405
2.402
2.385
2.370
2.366
2.031
1.866
1.853
1.840
1.835
1.828
1.821
1.817
1.803
1.790
1.777
1.765
1.744
1.734
1.721
1.704
1.691
1.610
1.607
1.595
1.589
1.581
1.576
1.568
CHO
OH
CF3
10
9
8
7
6
5
4
3
2
1
0
1.02
2.03
2.01
1.04
1.00
1.02
2.02
1.02
3.03
0.98

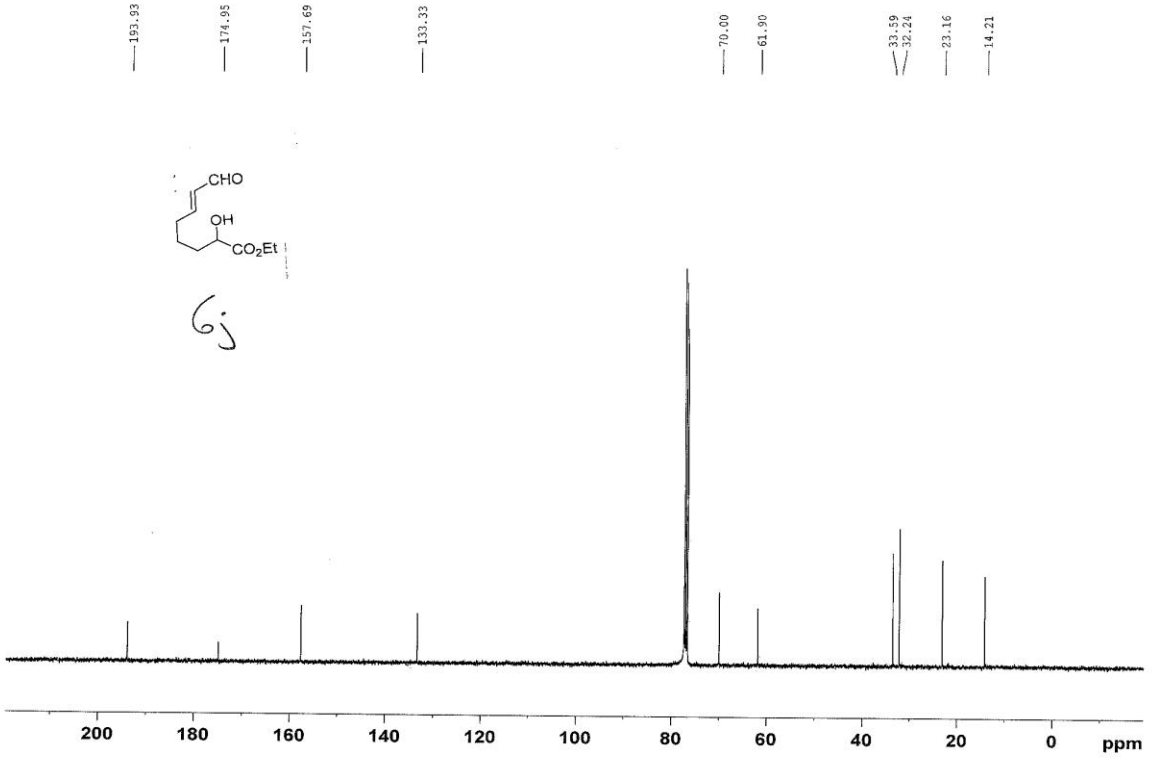

193.94
157.77
148.39
133.27
126.05
125.53
125.50
125.46
73.60
38.46
32.41
23.86
CHO
OH
CF3
200
180
160
140
120
100
80
60
40
20
0
ppm

5.16j: *(E)-ethyl 2-hydroxy-8-oxooct-6-enoate*

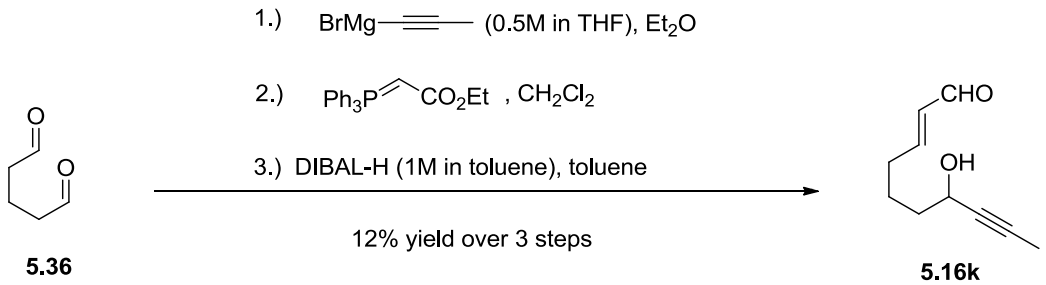


Brown oil. Collected in 75% yield. IR (thin film, KBr): 3456, 2983, 2938, 2869, 1737, 1690, 1208, 1137, 1104, 1023, 978 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, *J* = 7.9 Hz, 1H), 6.86 (dt, *J* = 15.6, 6.7 Hz, 1H), 6.15 (ddt, *J* = 15.6, 7.8, 1.3 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.21 (m, 1H), 2.82 (d, *J* = 5.2 Hz, 1H), 2.41 (m, 2H), 1.88 (m, 1H), 1.80-1.60 (m, 3H), 1.33 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 175.0, 157.7, 133.3, 70.0, 61.9, 33.6, 32.2, 23.2, 14.2 ppm; HRMS (ESI) : [M^+] calcd for [$C_{10}H_{16}O_4$]: 200.1049, found: 200.1052.


9.547
9.527
6.893
6.876
6.859
6.854
6.837
6.820
6.188
6.185
6.169
6.165
6.153
6.149
6.146
6.130
6.126
4.311
4.293
4.276
4.258
4.227
4.214
4.210
4.200
4.187
2.823
2.810
2.442
2.425
2.408
2.394
2.390
1.898
1.884
1.877
1.867
1.857
1.847
1.829
1.757
1.745
1.732
1.725
1.711
1.700
1.693
1.683
1.678
1.667
1.658
1.650
1.632
1.350
1.332
1.314
CHO
OH
CO2Et
6j
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.03
1.03
1.97
0.99
0.99
2.02
1.03
2.99
2.98


193.93
174.95
157.69
133.33
70.00
61.90
33.59
32.24
23.16
14.21
CHO
OH
CO2Et
6j
200
180
160
140
120
100
80
60
40
20
0
ppm

Preparation of Substrate (5.16k)



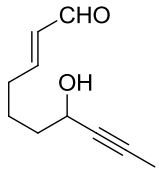
5.36 **5.16k**

An aqueous solution of 25% glutaraldehyde **5.36** (14 mL, 35 mmol) was saturated with NaCl and extracted with Et_2O (5 x 35 mL). The Et_2O layers were combined dried over $MgSO_4$, filtered and concentrated to a volume of ~70 mL and cooled to 0 ^oC. Then 1-propynylmagnesium bromide (0.5 M in THF, 70mL, 35 mmol) was added to the solution over 90 minutes while maintaining the temperature at 0 ^oC with stirring. The reaction was stirred for 1 h at 0 ^oC and then quenched by slowly adding saturated aqueous NH_4Cl (100 mL). The layers were separated and the aqueous layer was washed with 100 mL Et_2O. The Et_2O layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified via column chromatography (30/70, EtOAc/petroleum ether) to give the hemiacetal intermediate (2.00 g, 14.29 mmol).

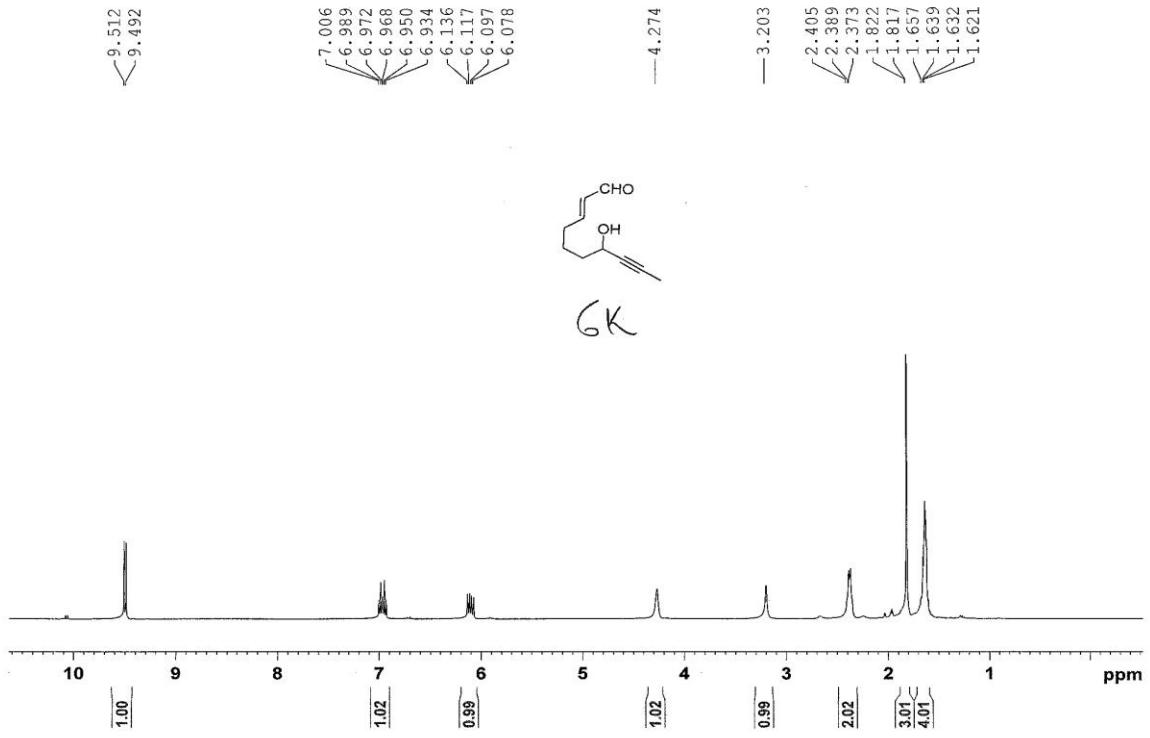
The hemiacetal (2.00 g, 14.29 mmol) was dissolved in CH_2Cl_2 (11.3 mL). This solution was added, with stirring, to a solution of Wittig reagent (6.79 g, 19.39 mmol) in CH_2Cl_2 at 0 ^oC. The reaction was warmed to room temperature and stirred for 48 h. The reaction was concentrated and purified via column chromatography (25/75, EtOAc/petroleum ether) to give the *E*-olefin intermediate (2.46 g, 11.68 mmol).

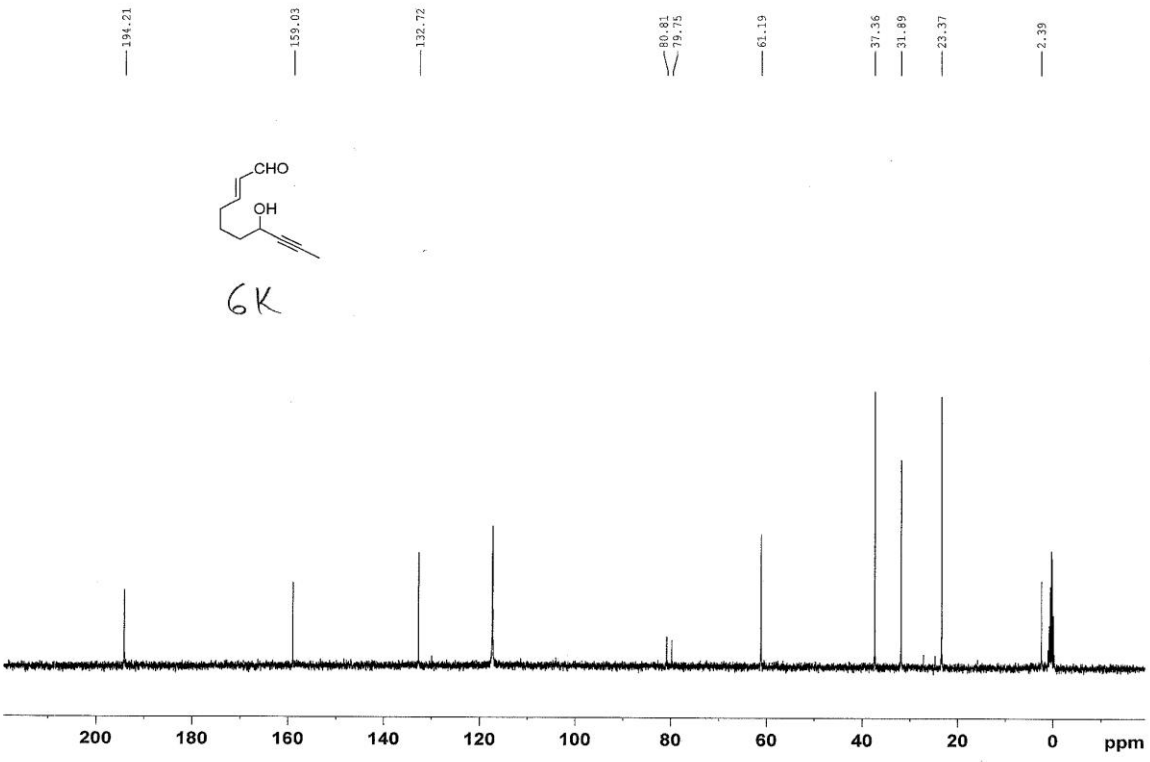
The ester (1.50 g, 7.07 mmol) was dissolved in toluene (56 mL) and cooled to –90 ^oC. Then DIBAL-H (1.0 M in toluene, 14.8 mL, 14.8 mmol) was added over 45 minutes while maintaining the temperature at –90 ^oC. The reaction was stirred for another 30 minutes, and then 4.90 mL MeOH was added dropwise to the reaction and the reaction was stirred for 5 minutes at –90 ^oC. The reaction was quenched by slowly adding 1.0 M aqueous HCl (35 mL). The reaction was allowed to warm to room temperature and was diluted with Et_2O (50 mL). The layers were separated and the aqueous layer was washed with Et_2O (50 mL). The Et_2O layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified via column chromatography (40/60, Et_2O/petroleum ether) to give substrate **5.16k** (387.3 mg, 2.33 mmol).

5.16k: *(E)-7-hydroxydec-2-en-8-ynal*

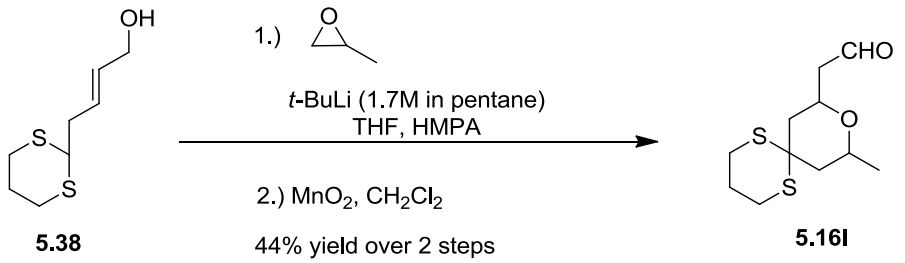


Colorless oil. Collected in 12% yield over 3 steps. IR (thin film, KBr): 3400, 2921, 2860, 1678, 1124, 1015, 975 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.50 (d, *J* = 7.9 Hz, 1H), 6.97 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.11 (m, 1H), 4.27 (bs, 1H), 3.20 (bs, 1H), 2.39 (m, 2H), 1.82 (d, *J* = 2.1 Hz, 3H), 1.63 (m, 4H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 194.2, 159.0, 132.7, 80.8, 79.8, 61.2, 37.4, 31.9, 23.4, 2.4 ppm; HRMS (ESI) : [M^+] calcd for [$C_{10}H_{14}O_2$]: 166.0994, found: 166.0992.


9.512
9.492
7.006
6.989
6.972
6.968
6.950
6.934
6.136
6.117
6.097
6.078
4.274
3.203
2.405
2.389
2.373
1.822
1.817
1.657
1.639
1.632
1.621
CHO
OH
6K
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.02
0.99
1.02
0.99
2.02
3.01
4.01


194.21
159.03
132.72
80.81
79.75
61.19
37.36
31.89
23.37
2.39
CHO
OH
6K
200
180
160
140
120
100
80
60
40
20
0
ppm

Preparation of Substrate (5.16l)

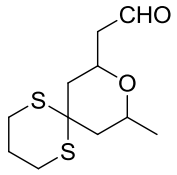


5.38 **5.16l**

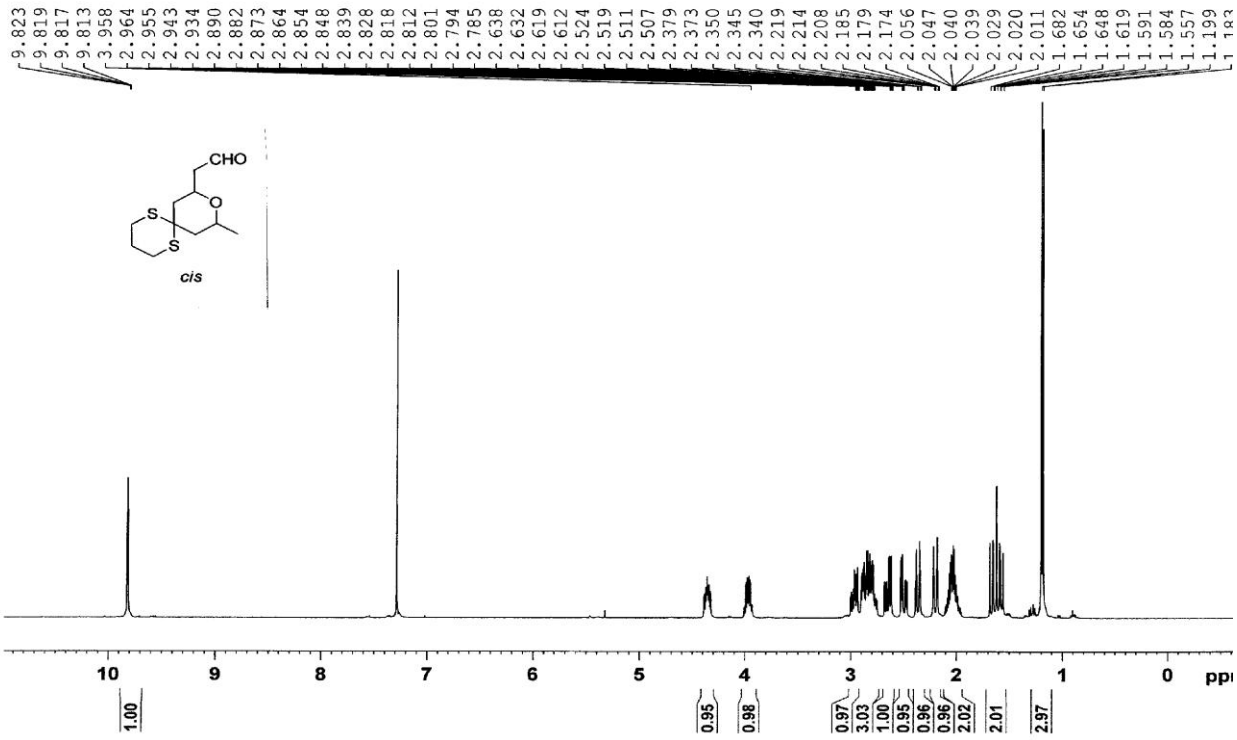
Allylic alcohol **5.38**[167] (472 mg, 2.48 mmol) was dissolved in dry THF (50.0 mL) and HMPA (5.0 mL). The temperature was cooled to –78 ^{o}C and *t*-BuLi, 1.7 M in pentane (3.65 mL, 6.20 mmol) was added dropwise over 10 minutes with stirring. The reaction was stirred for 5 minutes at –78 ^{o}C and then the epoxide (350 µL, 4.96 mmol) was added dropwise over 10 minutes at –78 ^{o}C. The reaction was stirred for 45 minutes at –78 ^{o}C and saturated aqueous NH_4Cl was slowly added and the reaction was allowed to warm to room temperature. The mixture was diluted with EtOAc. The organic layer was separated and the aqueous layer was washed with EtOAc (2 x 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated. The diol product was purified via column chromatography (EtOAc/petroleum ether, 50/50).

The diol product (496.8 mg, 2.0 mmol) was dissolved in dry CH_2Cl_2 (25.0 mL) and activated MnO_2 (870 mg, 10.0 mmol) was added. The reaction was stirred at room temperature. MnO_2 (870 mg, 10.0 mmol) was added after 20 minutes. The same amount of MnO_2 was added after 40 minutes and 60 minutes. The reaction was stirred overnight at room temperature. The reaction was filtered through Celite. The Celite was washed with Et_2O (3 x 50 mL). The solvent was evaporated to give the crude cyclized aldehyde which was purified via column chromatography (EtOAc/petroleum ether, 20/80) to give 268.9 mg of the pure *cis* aldehyde **5.16l** (44% yield over 2 steps).

5.16l: *cis-2-(10-methyl-9-oxa-1,5-dithiaspiro[5.5]undecan-8-yl)acetaldehyde*



yellow oil. Collected in 44% yield over 2 steps. IR (thin film, KBr): 2906, 2730, 1724, 1424, 1372, 1150, 1130, 1107, 1044, 910, 534 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (m, 1H), 4.36 (m, 1H), 3.96 (m, 1H), 2.96 (m, 1H), 2.91-2.73 (m, 3H), 2.64 (ddd, *J* = 16.5, 7.9, 2.5 Hz, 1H), 2.49 (ddd, *J* = 16.5, 5.0, 1.8 Hz, 1H), 2.37 (dt, *J* = 13.6, 2.1 Hz, 1H), 2.20 (dt, *J* = 13.8, 2.1 Hz, 1H), 2.13-1.95 (m, 2H), 1.62 (m, 2H), 1.19 (d, *J* =6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 68.8, 68.3, 49.1, 47.8, 44.7, 42.4, 25.9, 25.8, 25.7, 21.3 ppm; LRMS (ESI) : [M^+] calcd for [$C_{11}H_{18}O_2S_2$]: 246.1, found: 246.0.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9.817
9.813
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2.964
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2.943
2.934
2.890
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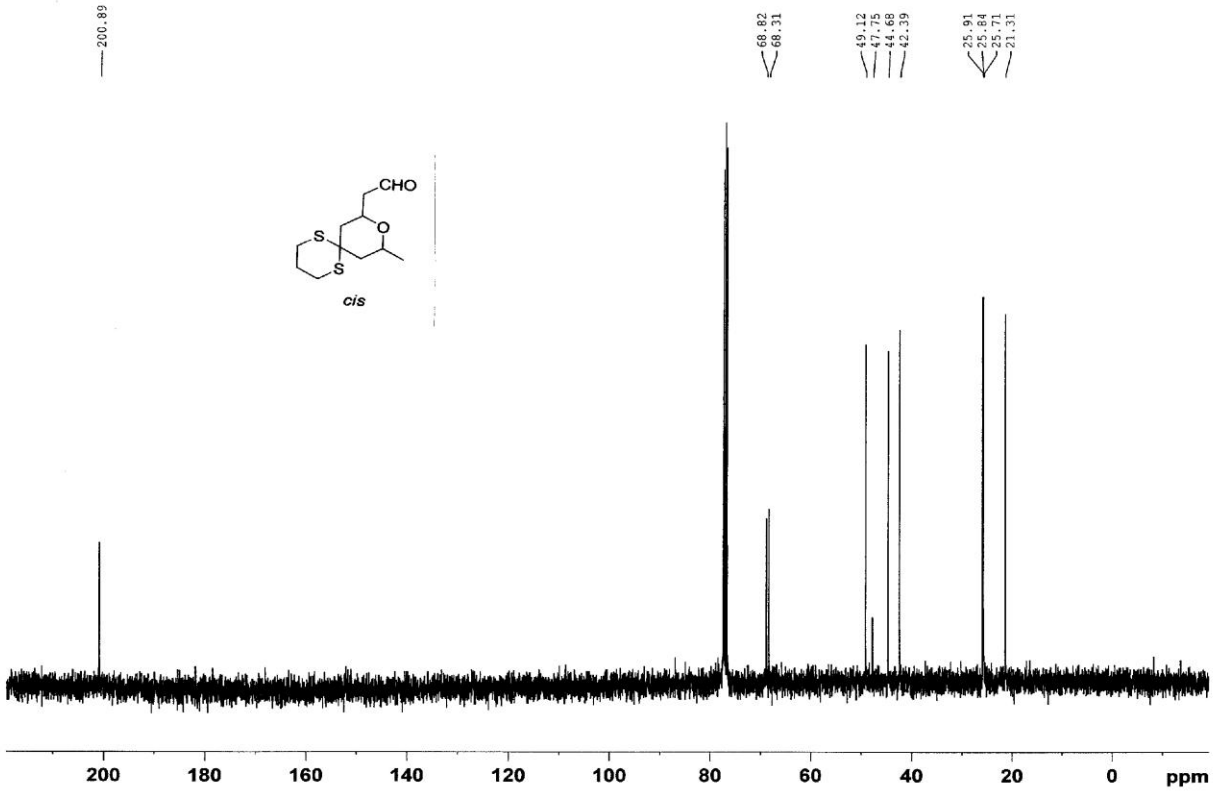
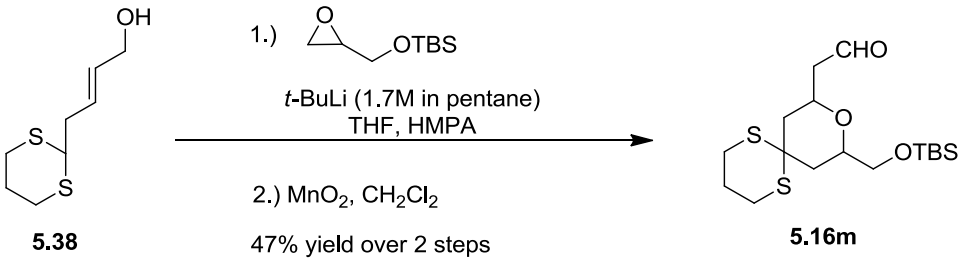
2.864
2.854
2.848
2.839
2.828
2.818
2.812
2.801
2.794
2.785
2.638
2.632
2.619
2.612
2.524
2.519
2.511
2.507
2.379
2.373
2.350
2.345
2.340
2.219
2.214
2.208
2.185
2.179
2.174
2.056
2.047
2.040
2.039
2.029
2.020
2.011
1.682
1.654
1.648
1.619
1.591
1.584
1.557
1.199
CHO
S
S
O
cis
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.95
0.98
0.97
3.03
1.00
0.95
0.96
0.96
2.02
2.01
2.97

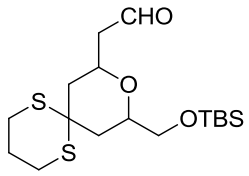

200.89
68.82
68.31
49.12
47.75
44.68
42.39
25.91
25.84
25.71
21.31
CHO
S
S
O
cis
200
180
160
140
120
100
80
60
40
20
0
ppm

Preparation of Substrate (5.16m)

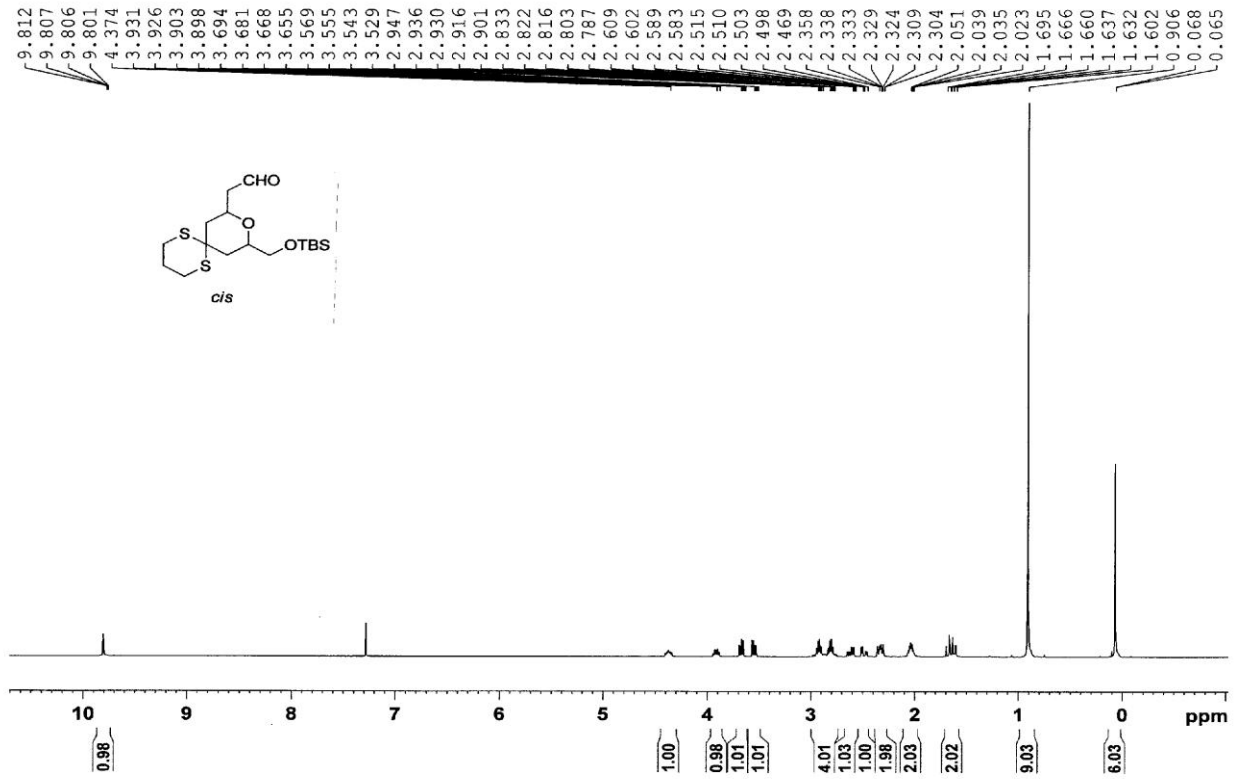
Substrate **5.16m** was prepared in the same manner as substrate **5.16l,** in 47% yield over 2 steps.



5.16m: *cis-2-(10-(((tert-butyldimethylsilyl)oxy)methyl)-9-oxa-1,5-dithiaspiro[5.5]undecan-8-yl)acetaldehyde*



yellow oil. Collected in 47% yield over 2 steps. IR (thin film, KBr): 2929, 2856, 2731, 1728, 1472, 1425, 1251, 1113, 1043, 838, 778, 668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (m, 1H), 4.37 (m, 1H), 3.91 (m, 1H), 3.67 (dd, *J* = 10.6, 5.1 Hz, 1H), 3.55 (dd, *J* = 10.6, 5.4 Hz, 1H), 2.97-2.75 (m, 4H), 2.60 (ddd, *J* = 16.4, 7.9, 2.6 Hz, 1H), 2.50 (ddd, *J* = 16.4, 4.8, 1.8 Hz, 1H), 2.33 (m, 2H), 2.03 (m, 2H), 1.65 (dt, *J* = 13.8, 11.5 Hz, 2H), 0.91 (s, 9H), 0.07 (d, *J* = 1.3 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 73.5, 68.3, 65.9, 49.0, 47.6, 42.7, 39.5, 26.0, 25.9, 25.8, 25.7, 18.3, -5.2, -5.3 ppm; LRMS (ESI) : [M^+] calcd for [$C_{17}H_{32}O_3S_2Si$]: 376.2, found: 376.1.


9.812
9.807
9.806
9.801
4.374
3.931
3.926
3.903
3.898
3.694
3.681
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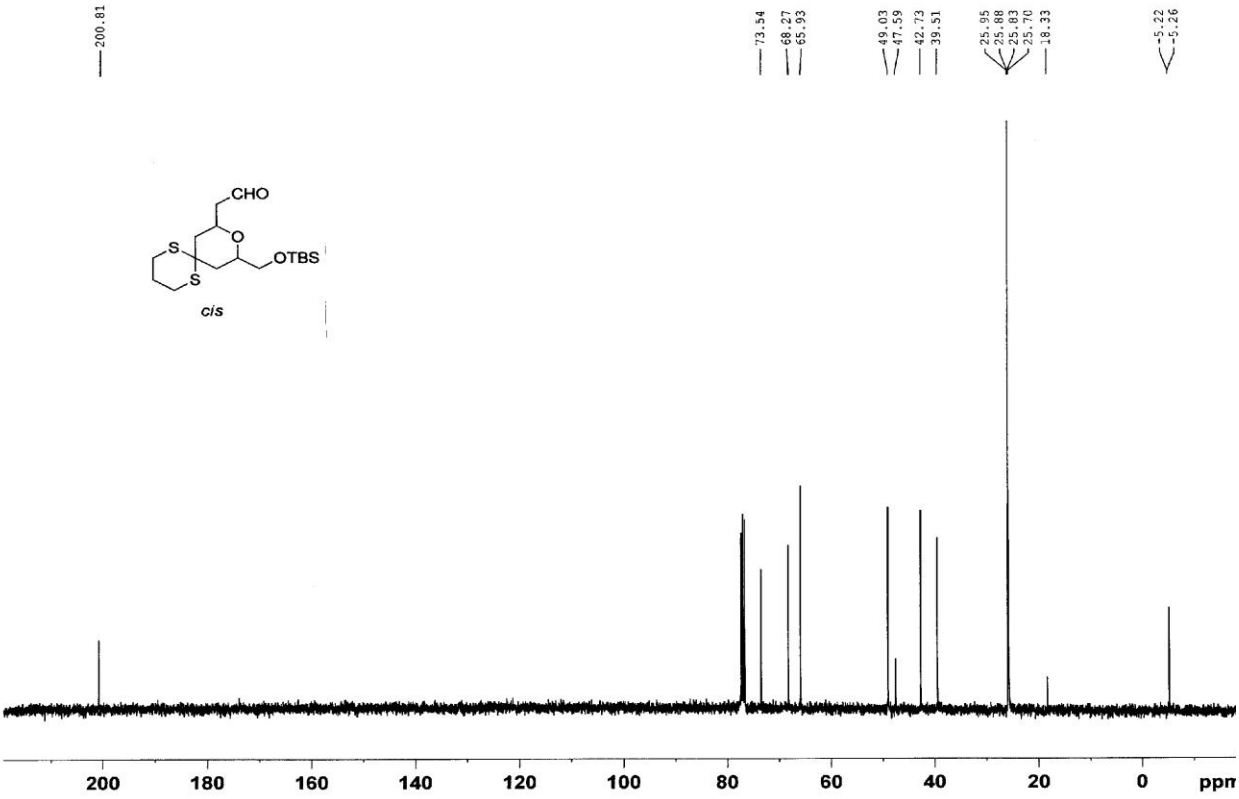
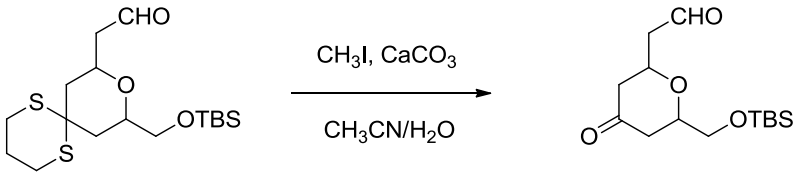
3.569
3.555
3.543
3.529
2.947
2.936
2.930
2.916
2.901
2.833
2.822
2.816
2.803
2.787
2.609
2.602
2.589
2.583
2.515
2.510
2.503
2.498
2.469
2.358
2.338
2.333
2.329
2.324
2.309
2.304
2.051
2.039
2.035
2.023
1.695
1.666
1.660
1.637
1.632
1.602
0.906
0.068
0.065
CHO
O
S
S
OTBS
cis
10
9
8
7
6
5
4
3
2
1
0
ppm
0.98
1.00
0.98
1.01
1.01
4.01
1.03
1.00
1.98
2.03
2.02
9.03
6.03


200.81
73.54
68.27
65.93
49.03
47.59
42.73
39.51
25.95
25.88
25.83
25.70
18.33
-5.22
-5.26
CHO
O
S
S
OTBS
cis
200
180
160
140
120
100
80
60
40
20
0
ppm

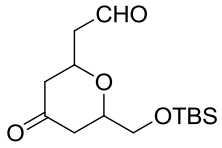
Preparation of Substrate (5.16n)



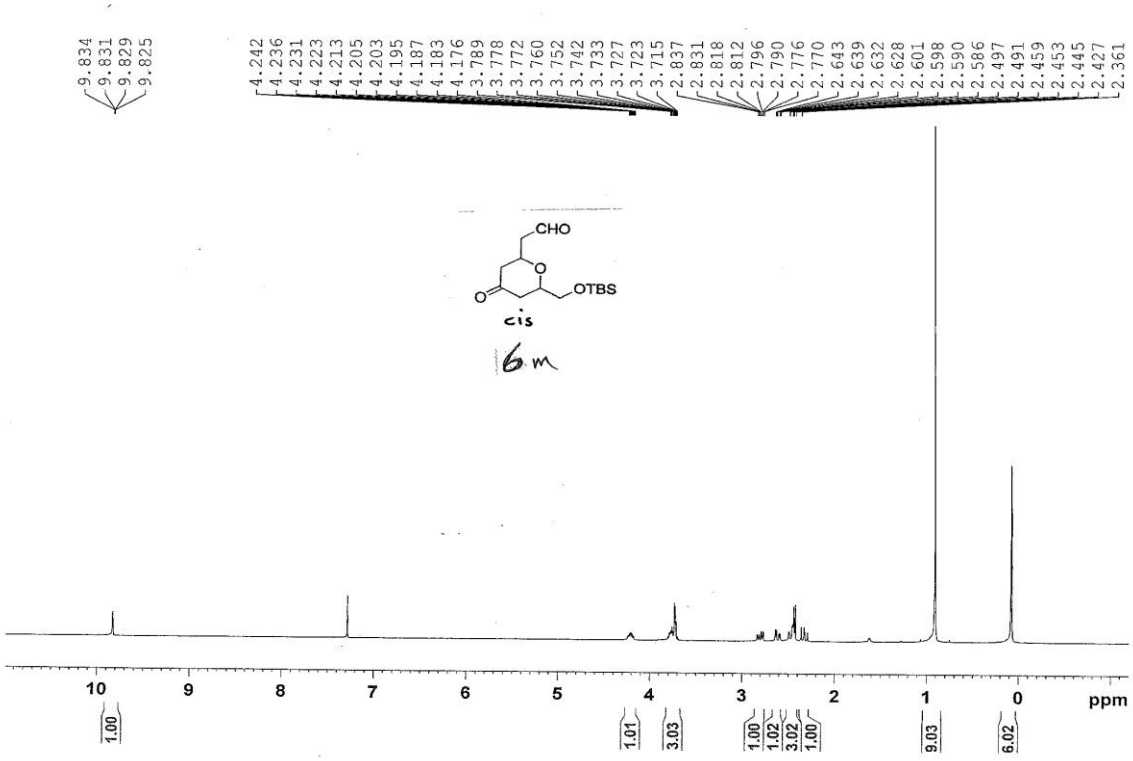
5.16m 64% yield **5.16n**

Substrate **5.16m** (325.6 mg, 0.86 mmol) was dissolved in CH_3CN (7.25 mL) and H_2O (2.41 mL). Calcium carbonate (258.3 mg, 2.58 mmol) was added followed by MeI (2.15 mL, 34.4 mmol). The reaction was stirred at room temperature for 48 hours. The reaction was diluted with Et_2O and water and the layers were separated. The water layer was washed with Et_2O and the Et_2O layers were combined, dried over $MgSO_4$, filtered, and concentrated. Substrate **5.16n** was purified via column chromatography (25/75, EtOAc/petroleum ether) and collected in 64% yield (156.7 mg).

5.16n: *cis-2-(6-(((tert-butyldimethylsilyl)oxy)methyl)-4-oxotetrahydro-2H-pyran-2-yl)acetaldehyde*



colorless oil. Collected in 64% yield. IR (thin film, KBr): 3448, 2956, 2858, 1716, 1640, 1254, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (m, 1H), 4.21 (m, 1H), 3.83-3.68 (m, 3H), 2.81 (ddd, *J* = 16.8, 7.9, 2.3 Hz, 1H), 2.61 (ddd, *J* = 16.7, 4.4, 2.3 Hz, 1H), 2.53-2.40 (m, 3H), 2.33 (dd, *J* = 14.5, 11.6 Hz, 1H), 0.92 (s, 9H), 0.09 (d, *J* = 2.5 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 199.4, 77.6, 72.0, 65.6, 49.4, 47.1, 43.8, 25.8, 18.3, -5.3 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_{14}H_{26}O_4Si]$: 286.1600, found: 286.1600.


9.834
9.831
9.829
9.825
4.242
4.236
4.231
4.223
4.213
4.205
4.203
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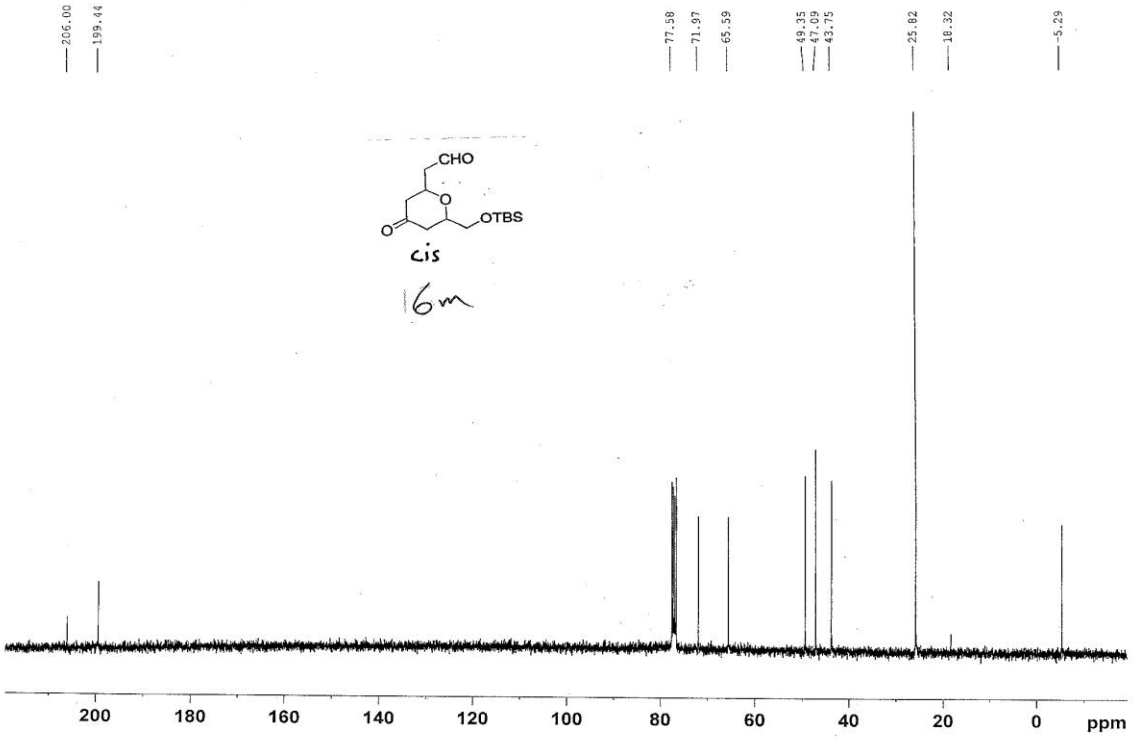
4.187
4.183
4.176
3.789
3.778
3.772
3.760
3.752
3.742
3.733
3.727
3.723
3.715
2.837
2.831
2.818
2.812
2.796
2.790
2.776
2.770
2.643
2.639
2.632
2.628
2.601
2.598
2.590
2.586
2.497
2.491
2.459
2.453
2.445
2.427
2.361
CHO
O
OTBS
cis
6m
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.01
3.03
1.00
1.02
3.02
1.00
9.03
6.02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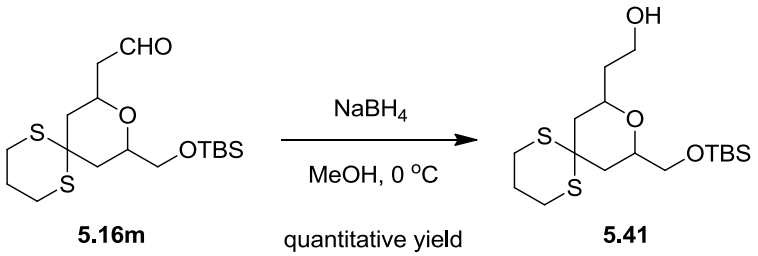
199.44
77.58
71.97
65.59
49.35
47.09
43.75
25.82
18.32
-5.29
CHO
O
OTBS
cis
6m
200
180
160
140
120
100
80
60
40
20
0
ppm

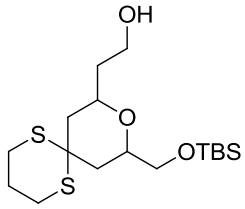
Preparation of Substrate (5.16o)



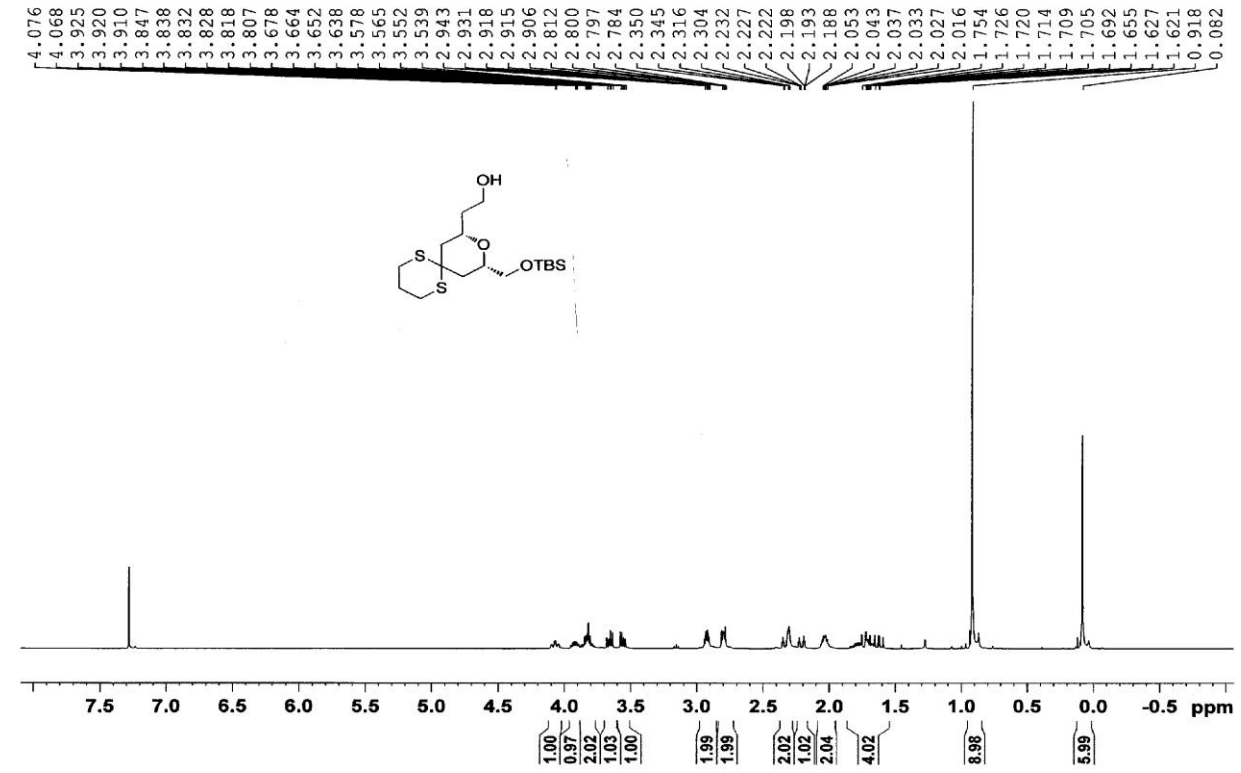
5.16m quantitative yield **5.41**

Aldehyde **5.16m** (1.288 g, 3.42 mmol) was dissolved in MeOH (25 mL) and the temperature was lowered to 0 ^{o}C. Sodium borohydride (194 mg, 5.13 mmol) was added in portions over 15 minutes. The reaction was stirred at 0 ^{o}C until complete by TLC. The reaction was quenched by the dropwise addition of saturated aqueous NH_4Cl (50 mL). The MeOH was removed from the mixture via rotary evaporation. The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The CH_2Cl_2 layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified via column chromatography (EtOAc/petroleum ether, 30/70) to give alcohol **5.41** in quantitative yield.

5.41: *cis-2-(10-(((tert-butyldimethylsilyl)oxy)methyl)-9-oxa-1,5-dithiaspiro[5.5]undecan-8-yl)ethanol*



colorless oil. IR (thin film, KBr): 3436, 2929, 2857, 1425, 1252, 1092, 834, 777, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (m, 1H), 3.92 (m, 1H), 3.82 (m, 2H), 3.65 (dd, *J* = 10.4, 5.9 Hz, 1H), 3.56 (dd, *J* = 10.4, 5.1 Hz, 1H), 2.93 (m, 1H), 2.80 (m, 1H), 2.32 (m, 2H), 2.21 (dt, *J* = 13.7, 2.1 Hz, 1H), 2.04 (m, 2H), 1.85-1.58 (m, 4H), 0.91 (s, 9H), 0.09 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.6, 73.5, 65.9, 61.6, 47.6, 43.3, 39.4, 37.2, 25.9, 25.9, 25.8, 18.3, -5.2, -5.4 ppm; HRMS (ESI) : [M^+] calcd for [$C_{17}H_{34}O_3S_2Si$]: 378.1719, found: 378.1719.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4.068
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3.920
3.910
3.847
3.838
3.832
3.828
3.818
3.807
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3.664
3.652
3.638
3.578
3.565
3.552
3.539
2.943
2.931
2.918
2.915
2.906
2.812
2.800
2.797
2.784
2.350
2.345
2.316
2.304
2.232
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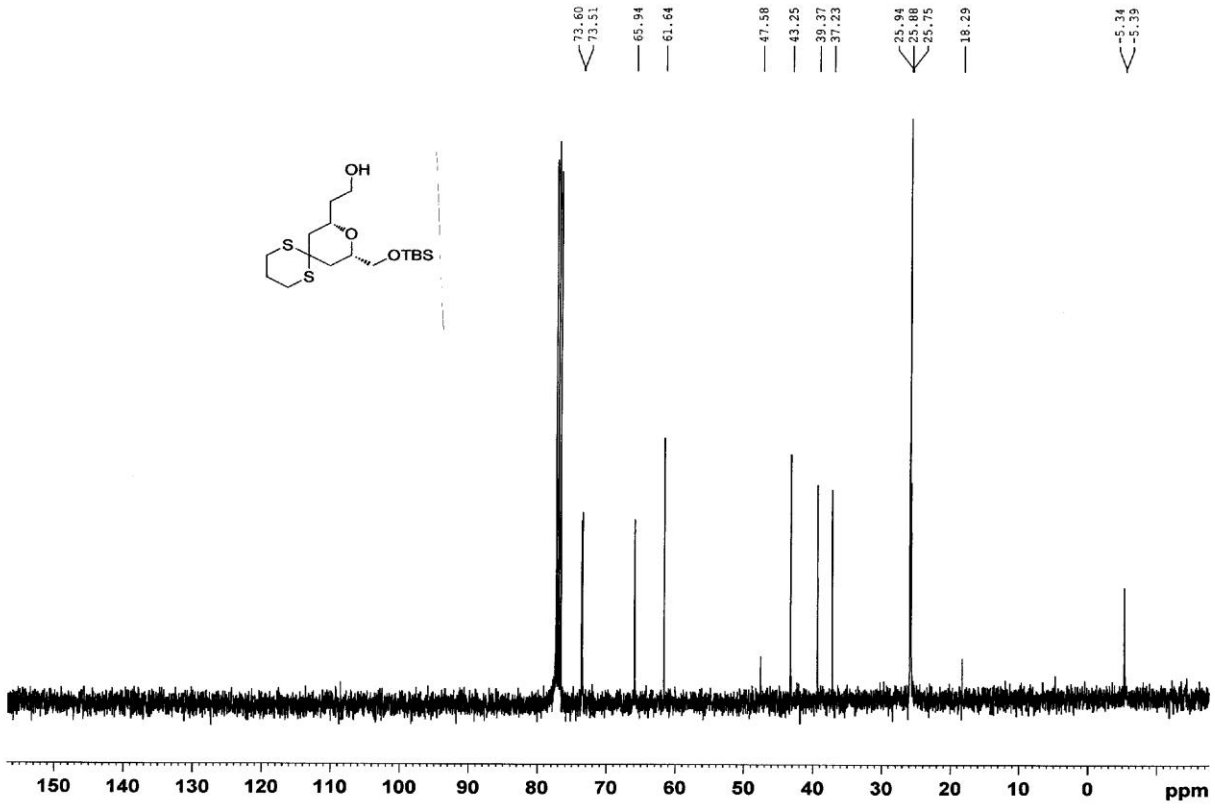
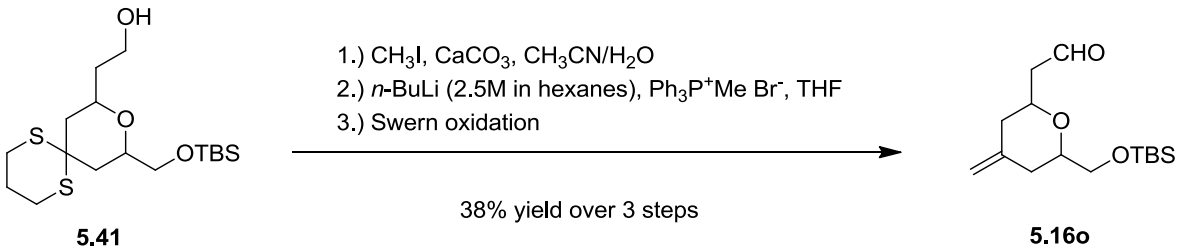
2.027
2.016
1.754
1.726
1.720
1.714
1.709
1.705
1.692
1.655
1.627
1.621
0.918
0.082
OH
O
S
S
OTBS
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
1.00
0.97
2.02
1.03
1.00
1.99
1.99
2.02
1.02
2.04
4.02
8.98
5.99


73.60
73.51
65.94
61.64
47.58
43.25
39.37
37.23
25.94
25.88
25.75
18.29
-5.34
-5.39
OH
O
S
S
OTBS
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



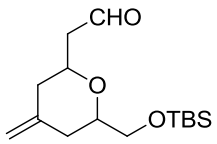
5.41 **5.16o**

Dithiane **5.41** (4.56 g, 12.04 mmol) was dissolved in CH_3CN (101 mL) and H_2O (33.6 mL). Calcium carbonate (3.62 g, 36.15 mmol) was added followed by MeI (30.1 mL, 482 mmol). The reaction was stirred at room temperature for 48 hours. The reaction was diluted with Et_2O and water and the layers were separated. The water layer was washed with Et_2O and the Et_2O layers were combined, dried over $MgSO_4$, filtered, and concentrated. The ketone product was purified via column chromatography (EtOAc/petroleum ether, 50/50) and collected in 76% yield (2.64 g).

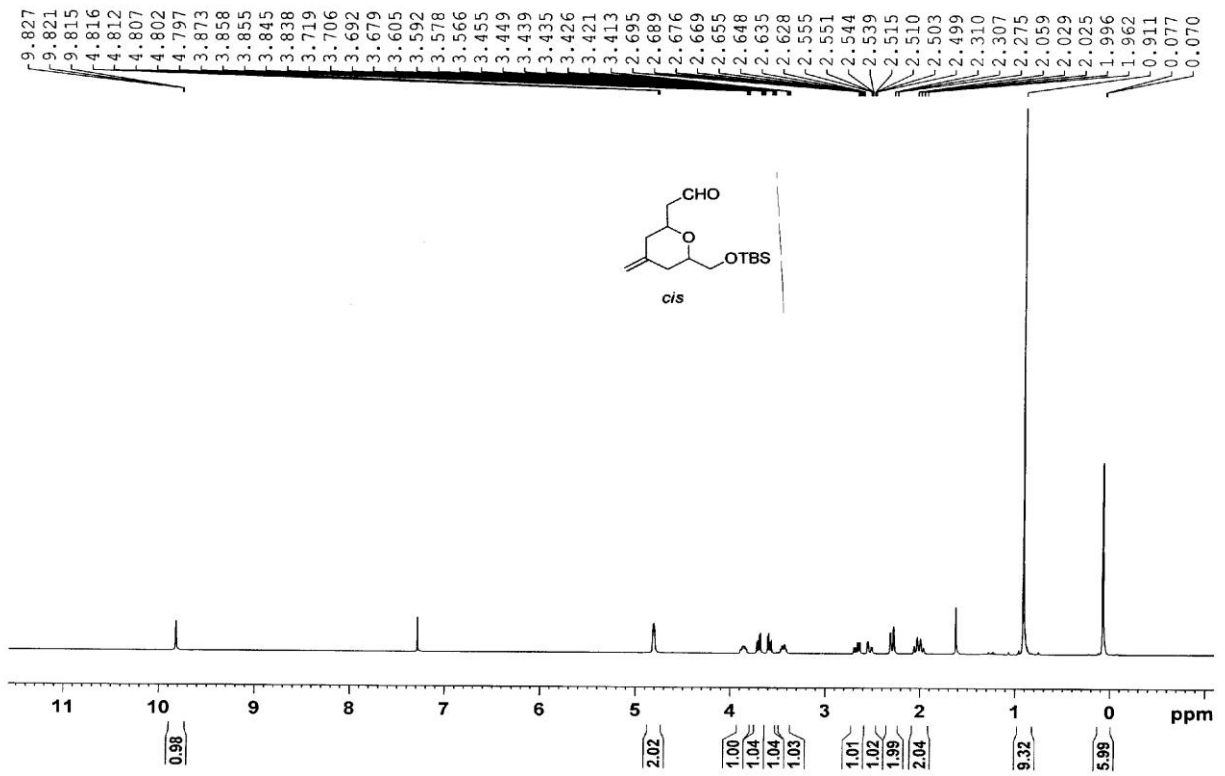
Triphenylphosphonium bromide (8.73 g, 24.4 mmol) was suspended in THF (116 mL) and cooled to 0 ^oC. *n*-BuLi (8.5 mL, 2.5 M in hexanes, 21.2 mmol) was added dropwise and the reaction was stirred for 2 h at 0 ^oC. The ketone product from step 1 (2.64 g, 9.15 mmol) was dissolved in THF (63 mL) and added to the triphenylphosphonium bromide solution dropwise at 0 ^oC. After stirring for 1h at 0 ^oC the reaction was poured into water (100 mL) and the water layer was extracted with Et_2O (3 x 100 mL). The Et_2O layers were combined, dried over $MgSO_4$, filtered and concentrated. The olefin product was purified via column chromatography (EtOAc/petroleum ether, 15/85).

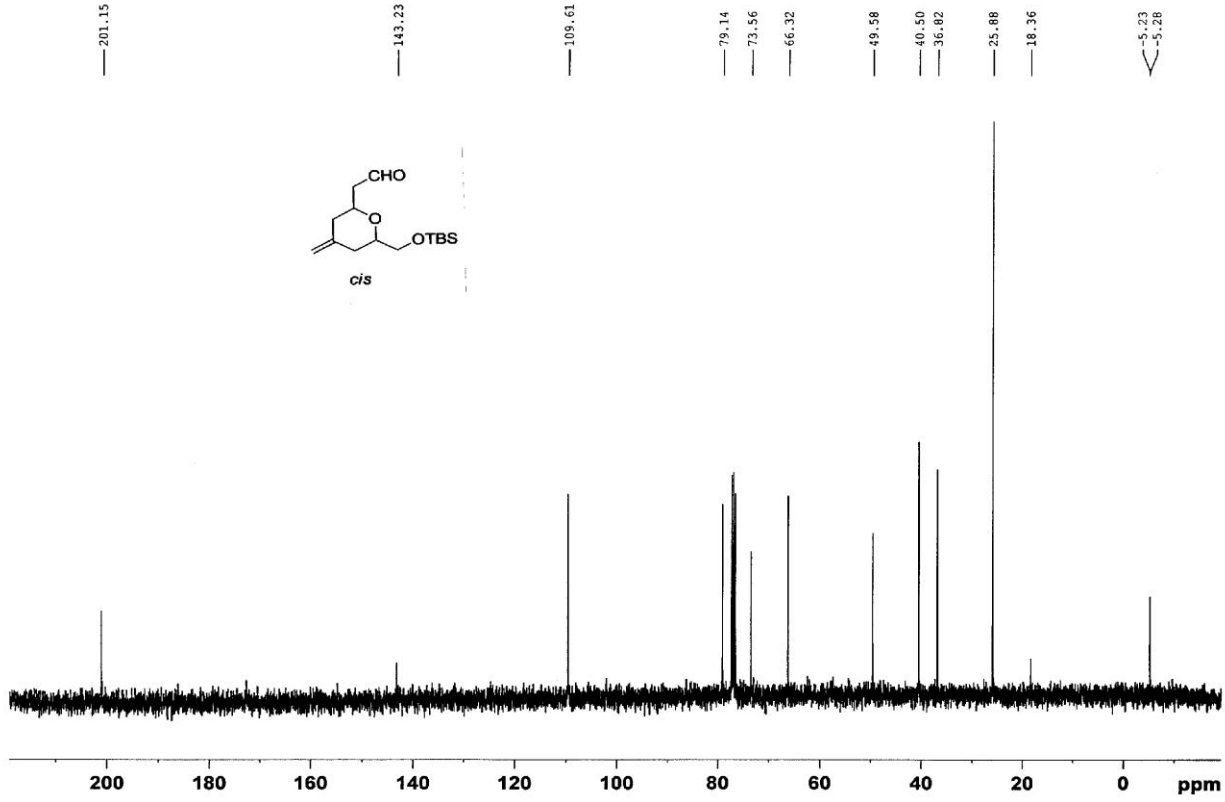
The olefin product from step 2 was then oxidized to the aldehyde using a Swern oxidation. Oxalyl chloride (678 µL, 7.8 mmol) was dissolved in CH_2Cl_2 (12 mL) and cooled to –78 ^oC. The flask was equipped with an outlet and a solution of DMSO (1.13 mL, 15.82 mmol) in CH_2Cl_2 (12 mL) was added dropwise. The reaction was stirred at –78 ^oC for 10 minutes. A solution of the olefin product from the previous step (1.874 g, 6.60 mmol) in CH_2Cl_2 (12 mL) was added dropwise to the solution. The reaction was stirred at –78 ^oC for 15 minutes. Triethylamine (4.6 mL, 33 mmol) was added in one portion and the reaction was stirred at –78 ^oC for 15 minutes then allowed to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated aqueous NH_4Cl (100 mL). The aqueous layer was washed with CH_2Cl_2 (50 mL). The CH_2Cl_2 layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified via column chromatography (Et_2O/petroleum ether, 10/90) to give substrate **5.16o** (1.2895 g) in 50% yield over 2 steps.

5.16o: *cis-2-(6-(((tert-butyldimethylsilyl)oxy)methyl)-4-methylenetetrahydro-2H-pyran-2-yl)acetaldehyde*

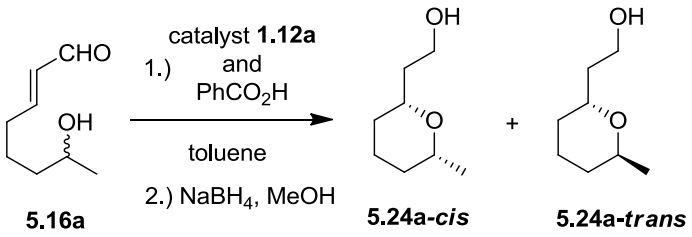


colorless oil. Collected in 38% yield over 3 steps. IR (thin film, KBr): 2956, 2857, 1727, 1361, 1252, 1108, 835, 777, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (t, *J* = 2.4 Hz, 1H), 4.81 (m, 2H), 3.87 (m, 1H), 3.68 (dd, *J* = 10.6, 5.4 Hz, 1H), 3.58 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.44 (m, 1H), 2.66 (ddd, *J* = 16.3, 7.9, 2.7 Hz, 1H), 2.53 (ddd, *J* = 16.3, 4.6, 1.9 Hz, 1H), 2.30 (m, 2H), 2.01 (m, 2H), 0.91 (s, 9H), 0.07 (d, *J* = 2.8 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 143.2, 109.6, 79.1, 73.6, 66.3, 49.6, 40.5, 36.8, 25.9, 18.4, -5.2, -5.3 ppm; LRMS (ESI) : [M^+] calcd for [$C_{15}H_{28}O_3Si$]: 284.2, found: 284.1.


9.827
9.821
9.815
4.816
4.812
4.807
4.802
4.797
3.873
3.858
3.855
3.845
3.838
3.719
3.706
3.692
3.679
3.605
3.592
3.578
3.566
3.455
3.449
3.439
3.435
3.426
3.421
3.413
2.695
2.689
2.676
2.669
2.655
2.648
2.635
2.628
2.555
2.551
2.544
2.539
2.515
2.510
2.503
2.499
2.310
2.307
2.275
2.059
2.029
2.025
1.996
1.962
0.911
0.077
0.070
CHO
O
OTBS
cis
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.98
2.02
1.00
1.04
1.04
1.03
1.01
1.02
1.99
2.04
9.32
5.99

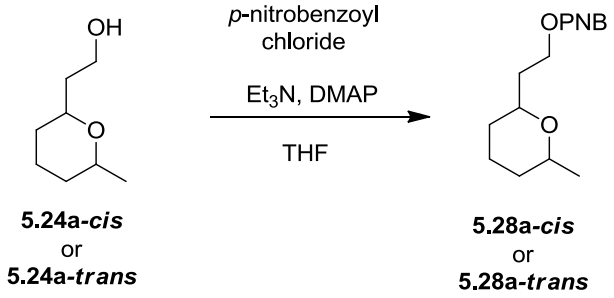

201.15
143.23
109.61
79.14
73.56
66.32
49.58
40.50
36.82
25.88
18.36
-5.23
-5.28
CHO
O
OTBS
cis
200
180
160
140
120
100
80
60
40
20
0
ppm

Organocatalyzed Oxa-Michael Addition with in situ Reduction (5.24a–*cis*/5.24a–*trans*)



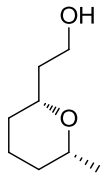
Catalyst **1.12a** (13.0 mg, 0.04 mmol) and $PhCO_2H$ (4.9 mg, 0.04 mmol) were dissolved in toluene (1.0 mL) and cooled to 0 ^oC or –30 ^oC. Substrate **5.16a** (59.9 µL, 0.40 mmol) was added in one portion and the reaction was stirred at the same temperature and monitored by TLC. After the indicated time, MeOH (1 mL) and $NaBH_4$ (30.3 mg, 0.80 mmol) were added to the reaction mixture. After 30 minutes the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The corresponding alcohols **5.24a**–**cis** and **5.24a**–***trans*** were purified from the residue via column chromatography (EtOAc/petroleum ether, 40/60).

Both **5.24a**–***cis*** and **5.24a**–***trans*** alcohol products were PNB protected for chiral HPLC analysis.

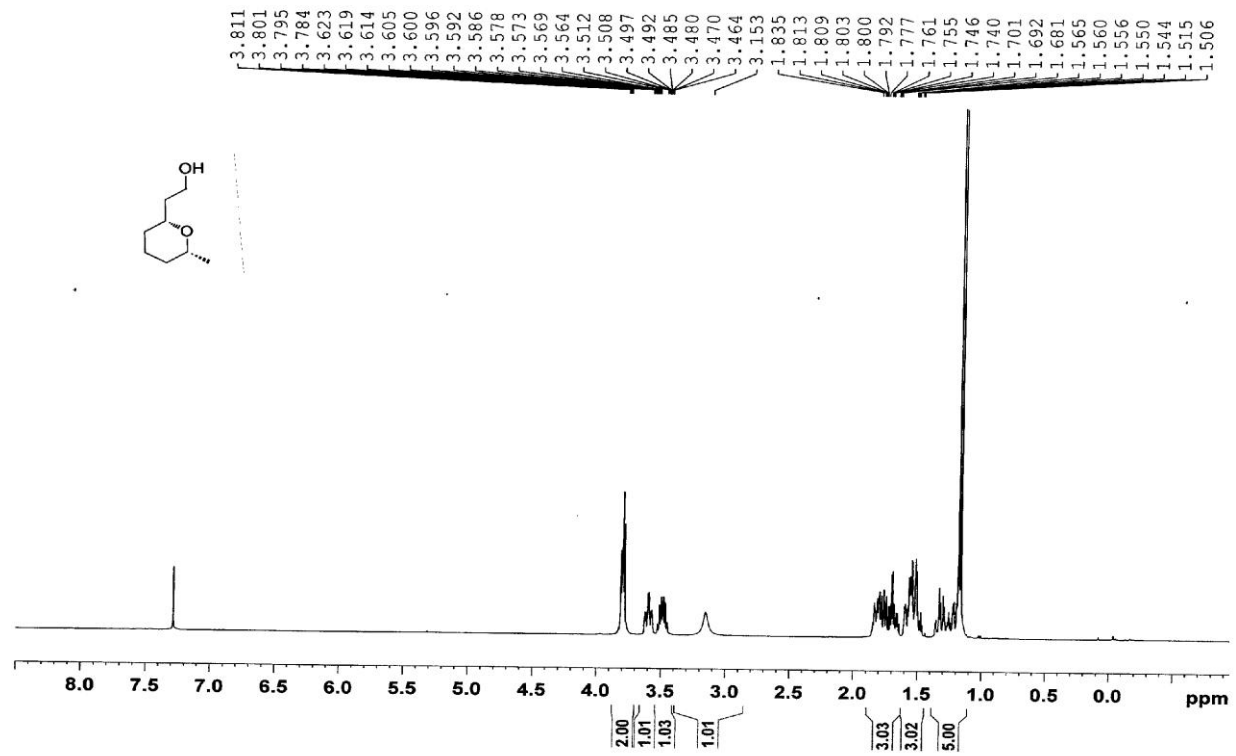


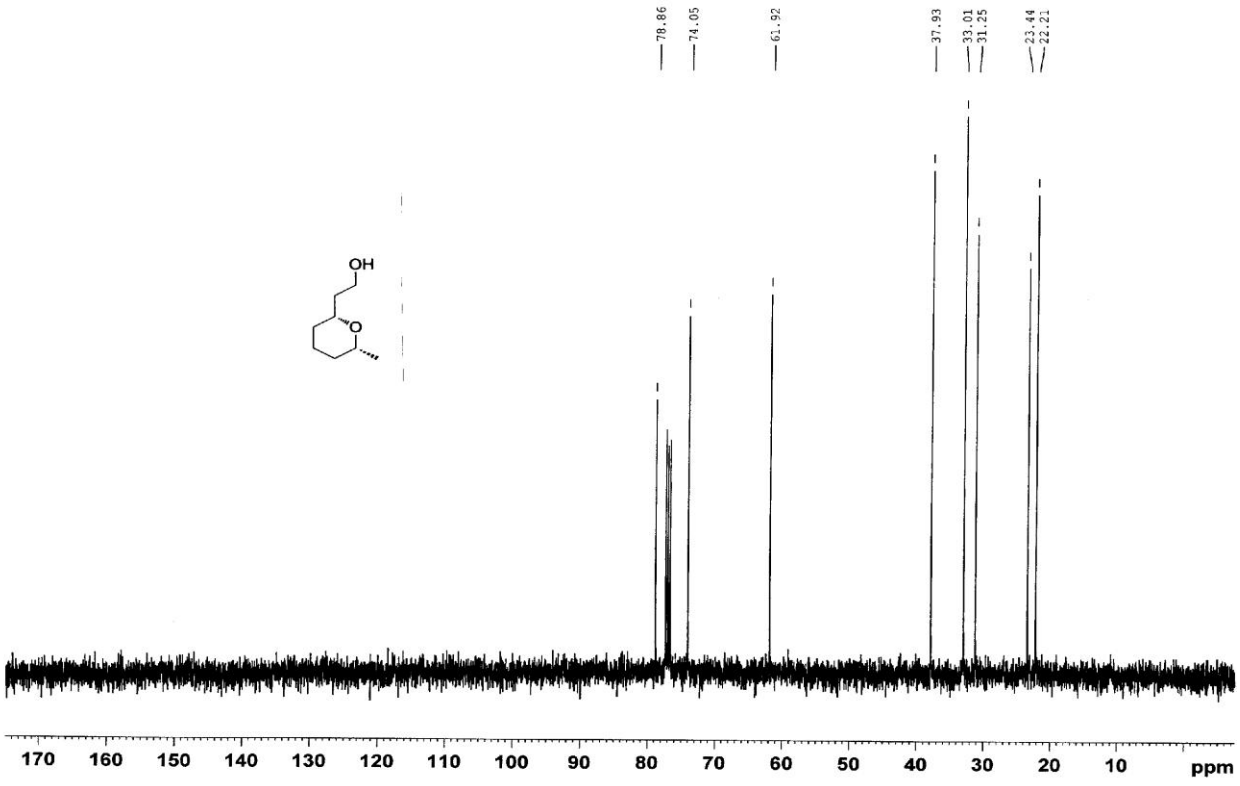
The alcohol, **5.24a**–***cis*** or **5.24a**–***trans***, (21.6 mg, 0.15 mmol) was dissolved in dry THF (4 mL) and DMAP (4.2 mg, 0.035 mmol), Et_3N (63 µL, 0.45 mmol), and *p*-nitrobenzoyl chloride (55.7 mg, 0.30 mmol) were added. The reaction was stirred for 1 hour at room temperature. The reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (2 x 15mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The *p*-nitrobenzoate protected alcohol, **5.28a**–***cis*** or **5.28a**–***trans***, was purified via column chromatography (EtOAc/petroleum ether, 10/90). The products were collected in near quantitative yields.

5.24a–***cis***: *2-((2R,6R)-6-methyltetrahydro-2H-pyran-2-yl)ethanol*[15]

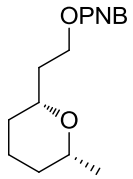


colorless oil. $[\alpha]_D^{23}$ = -18.6 (*c* 2.00, $CHCl_3$, 90% ee); IR (thin film, KBr): 3390, 2970, 2934, 2860, 1372, 1202, 1081, 1044, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (m, 2H), 3.59 (m, 1H), 3.49 (m, 1H), 3.15 (bs, 1H), 1.87-1.63 (m, 3H), 1.62-1.45 (m, 3H), 1.47-1.20 (m, 2H), 1.18 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.9, 74.1, 61.9, 37.9, 33.0, 31.3, 23.4, 22.2 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_8H_{16}O_2]$: 144.1150, found: 144.1148.

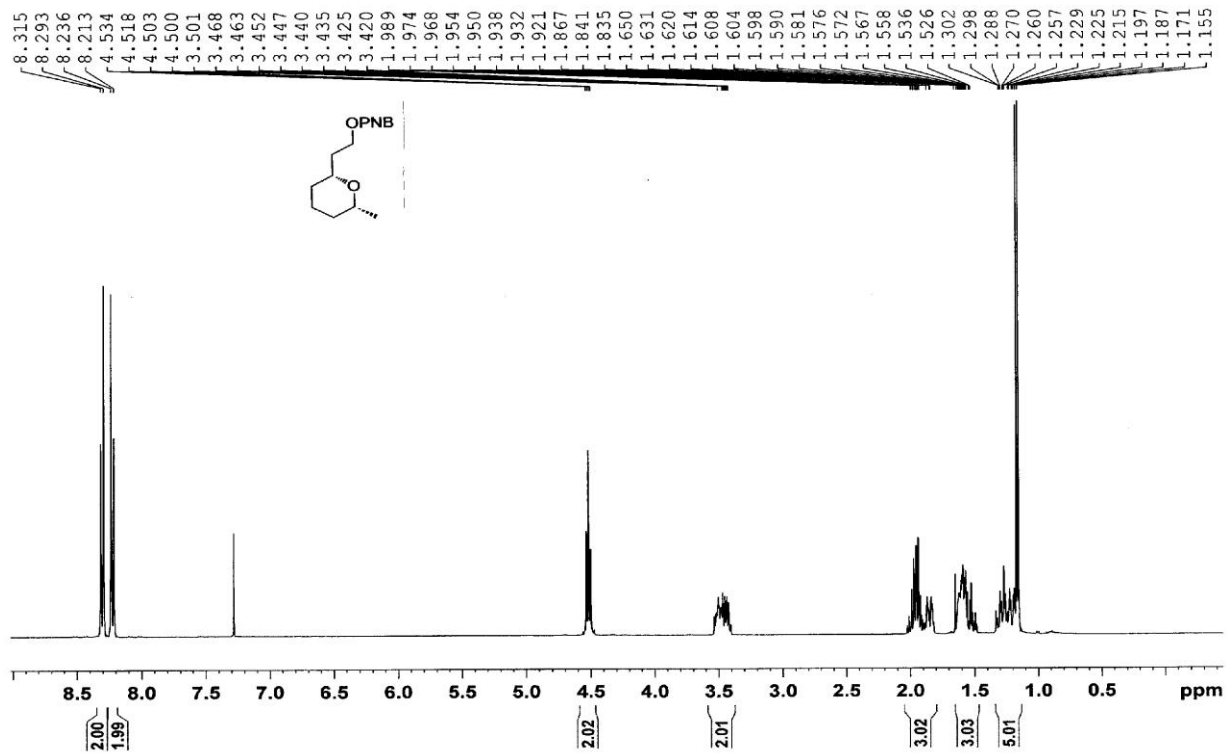

3.811
3.801
3.795
3.784
3.623
3.619
3.614
3.605
3.600
3.596
3.592
3.586
3.578
3.573
3.569
3.564
3.512
3.508
3.497
3.492
3.485
3.480
3.470
3.464
3.153
1.835
1.813
1.809
1.803
1.800
1.792
1.777
1.761
1.755
1.746
1.740
1.701
1.692
1.681
1.565
1.560
1.556
1.550
1.544
1.515
1.506
OH
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.00
1.01
1.03
1.01
3.03
3.02
5.00

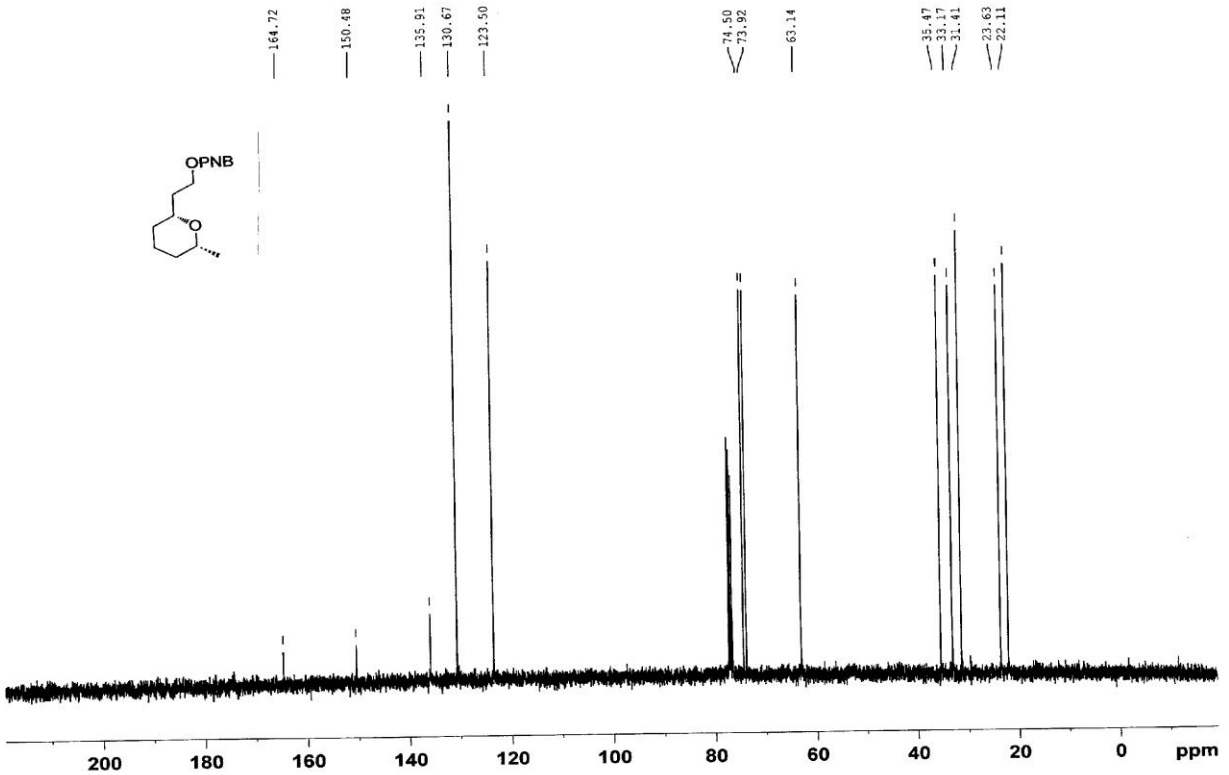

78.86
74.05
61.92
37.93
33.01
31.25
23.44
22.21
OH
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

5.28a–***cis***: *2-((2R,6R)-6-methyltetrahydro-2H-pyran-2-yl)ethyl 4-nitrobenzoate*

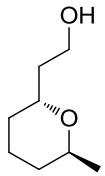


colorless amorphous solid. $[\alpha]_D^{25}$ = -32.6 (*c* 2.00, $CHCl_3$, 90% ee); IR (thin film, KBr): 2969, 2932, 2846, 1725, 1529, 1281, 1082, 874, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.9 Hz, 2H), 8.22 (d, *J* = 8.9 Hz, 2H), 4.51 (m, 2H), 3.55-3.38 (m, 2H), 2.05-1.80 (m, 3H), 1.68-1.47 (m, 3H), 1.44-1.15 (m, 2H), 1.17 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 150.5, 135.9, 130.7, 123.5, 74.5, 73.9, 63.1, 35.5, 33.2, 31.4, 23.6, 22.1 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 97:3), 0.5 mL/min; minor enantiomer t_R = 14.3 min, major enantiomer t_R = 18.8 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{15}H_{19}NO_5]$: 293.1263, found: 293.1267.

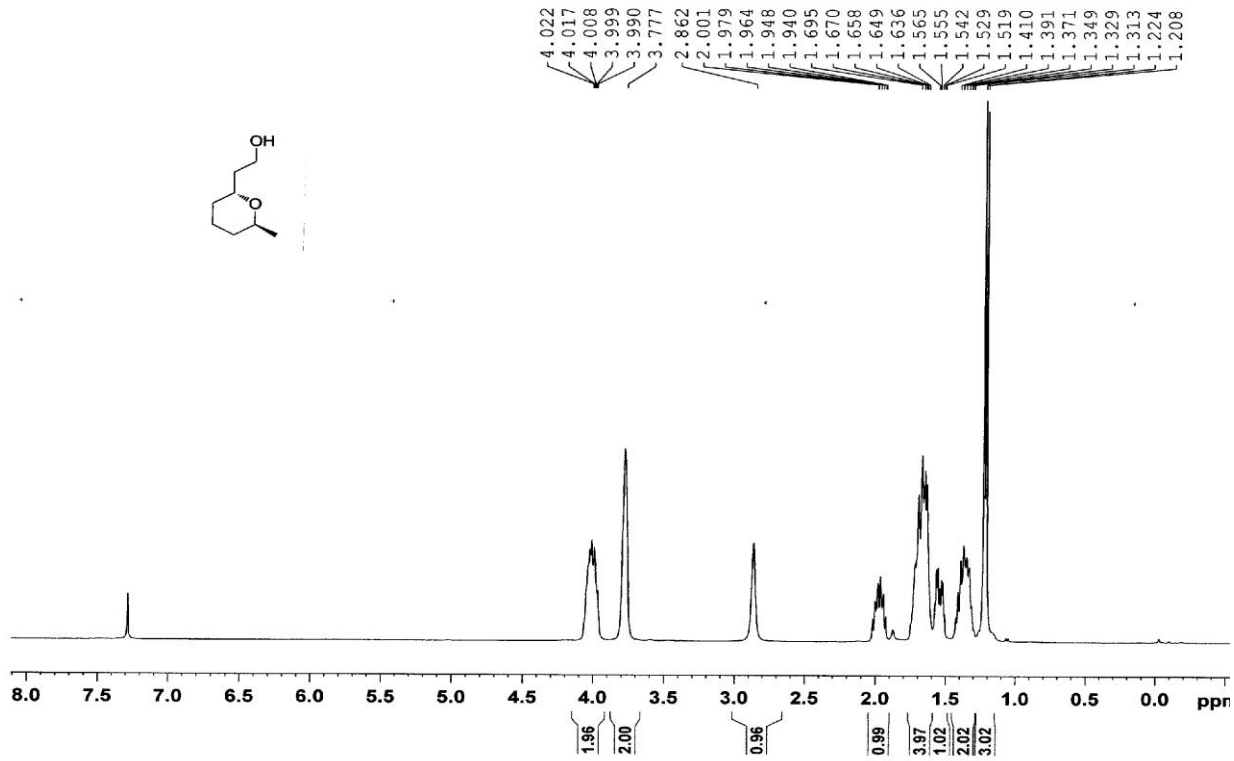

8.315
8.293
8.236
8.213
4.534
4.518
4.503
4.500
3.501
3.468
3.463
3.452
3.447
3.440
3.435
3.425
3.420
1.989
1.974
1.968
1.954
1.950
1.938
1.932
1.921
1.867
1.841
1.835
1.650
1.631
1.620
1.614
1.608
1.604
1.598
1.590
1.581
1.576
1.572
1.567
1.558
1.536
1.526
1.302
1.298
1.288
1.270
1.260
1.257
1.229
1.225
1.215
1.197
1.187
1.171
1.155
OPNB
O
8.5
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
ppm
2.00
1.99
2.02
2.01
3.02
3.03
5.01

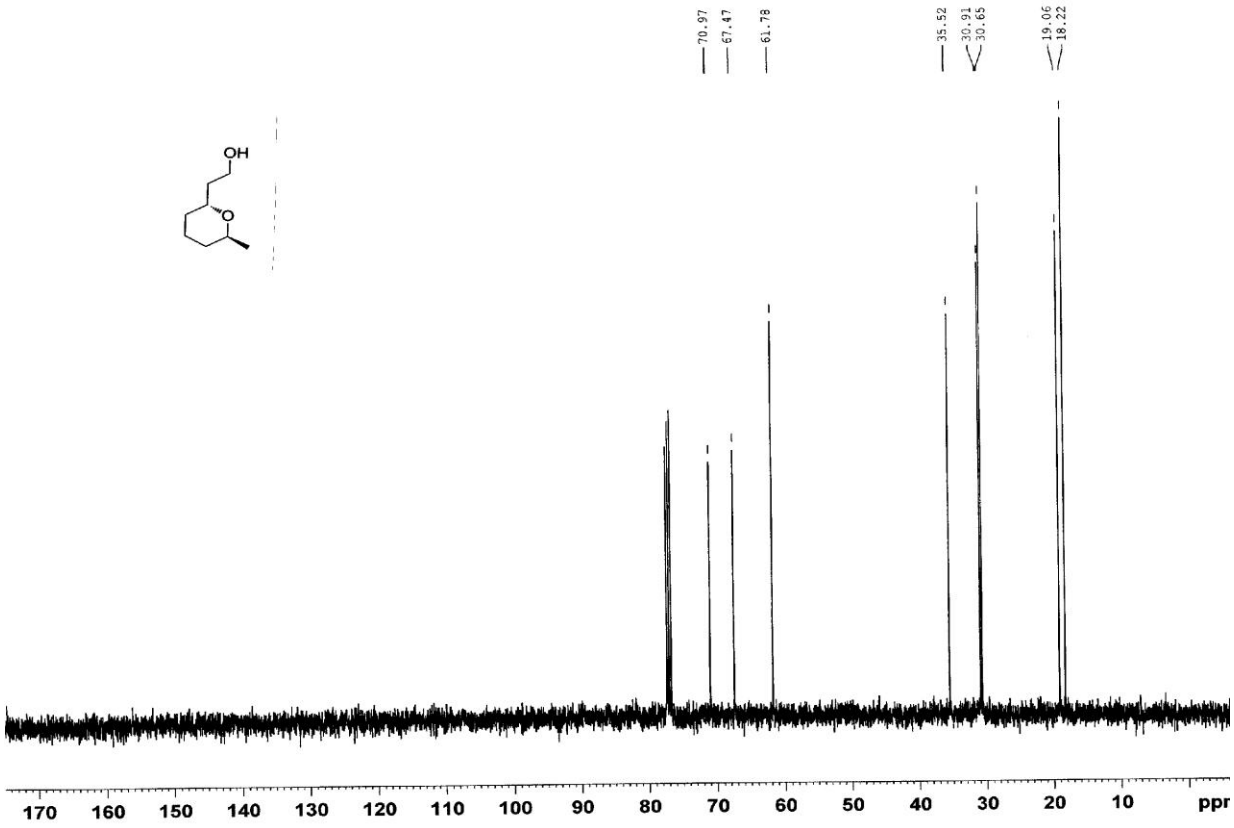

164.72
150.48
135.91
130.67
123.50
74.50
73.92
63.14
35.47
33.17
31.41
23.63
22.11
OPNB
O
200
180
160
140
120
100
80
60
40
20
0
ppm

5.24a–***trans***: *2-((2R,6S)-6-methyltetrahydro-2H-pyran-2-yl)ethanol*

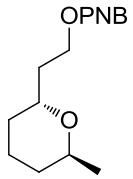


colorless oil. $[\alpha]_D^{23}$ = -43.1 (*c* 2. 00, $CHCl_3$, 99% ee); IR (thin film, KBr): 3389, 2936, 2868, 1444, 1381, 1054, 1028, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (m, 2H), 3.78 (m, 2H), 2.86 (bs, 1H), 1.95 (m, 1H), 1.77-1.57 (m, 4H), 1.56-1.48 (m, 1H), 1.46-1.28 (m, 2H), 1.21 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.0, 67.5, 61.8, 35.5, 30.9, 30.7, 19.1, 18.2 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_8H_{16}O_2]$: 144.1150, found: 144.1147.

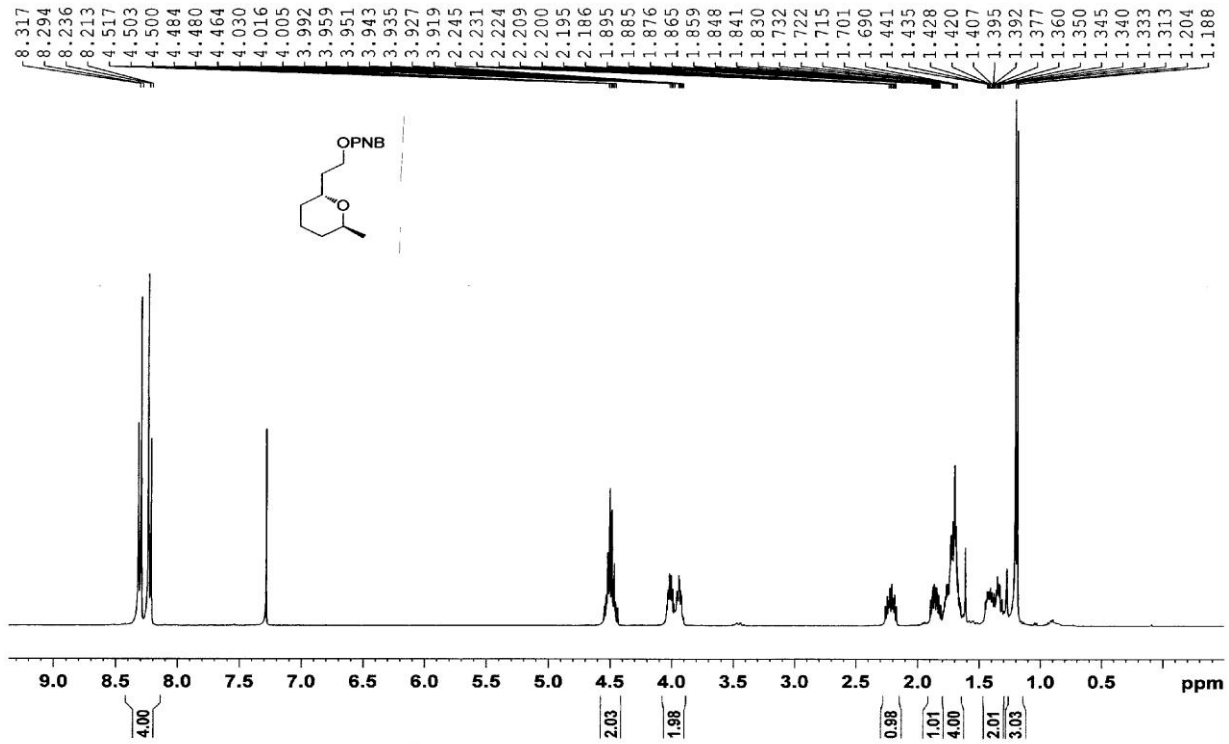

4.022
4.017
4.008
3.999
3.990
3.777
2.862
2.001
1.979
1.964
1.948
1.940
1.695
1.670
1.658
1.649
1.636
1.565
1.555
1.542
1.529
1.519
1.410
1.391
1.371
1.349
1.329
1.313
1.224
1.208
OH
O
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.96
2.00
0.96
0.99
3.97
1.02
2.02
3.02


70.97
67.47
61.78
35.52
30.91
30.65
19.06
18.22
OH
O
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

5.28a–***trans***: *2-((2R,6S)-6-methyltetrahydro-2H-pyran-2-yl)ethyl 4-nitrobenzoate*



colorless amorphous solid. $[\alpha]_D^{23}$ = -43.5 (*c* 2.00, $CHCl_3$, 99% ee); IR (thin film, KBr): 3440, 2933, 1725, 1529, 1281, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 9.0 Hz, 2H), 8.22 (d, *J* = 9.0 Hz, 2H), 4.49 (m, 2H), 4.07-3.89 (m, 2H), 2.21 (m, 1H), 1.86 (m, 1H), 1.81-1.65 (m, 4H), 1.48-1.25 (m, 2H), 1.20 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 150.5, 135.8, 130.7, 123.5, 67.8, 66.9, 63.3, 32.0, 31.6, 30.0, 19.8, 18.4 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 7.7 min, minor enantiomer t_R = 14.7 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{15}H_{19}NO_5]$: 293.1263, found: 293.1267.


8.317
8.294
8.236
8.213
4.517
4.503
4.500
4.484
4.480
4.464
4.030
4.016
4.005
3.992
3.959
3.951
3.943
3.935
3.927
3.919
2.245
2.231
2.224
2.209
2.200
2.195
2.186
1.895
1.885
1.876
1.865
1.859
1.848
1.841
1.830
1.732
1.722
1.715
1.701
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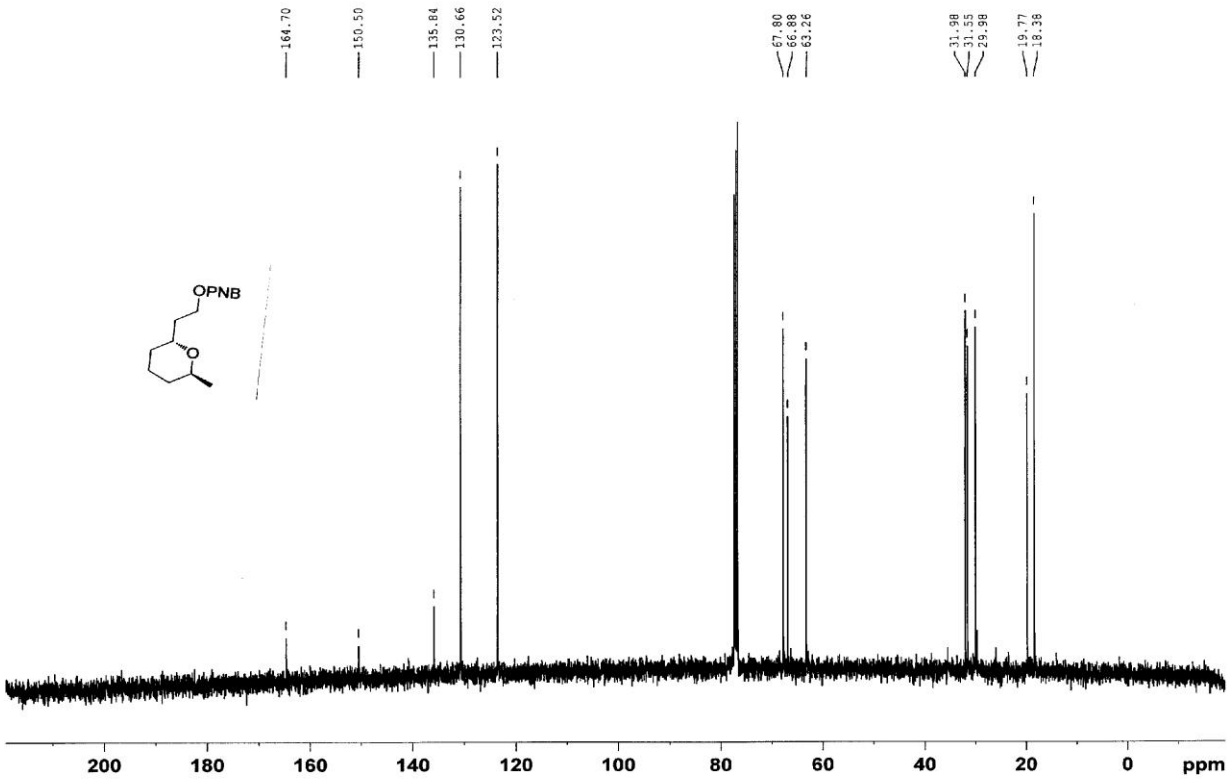
1.395
1.392
1.377
1.360
1.350
1.345
1.340
1.333
1.313
1.204
1.188
OPNB
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.00
2.03
1.98
0.98
1.01
4.00
2.01
3.03


164.70
150.50
135.84
130.66
123.52
67.80
66.88
63.26
31.98
31.55
29.98
19.77
18.38
OPNB
200
180
160
140
120
100
80
60
40
20
0
ppm

Organocascade Kinetic Resolution of Pyrans (5.34a–i and 5.34l–o/5.35a–i and 5.35l–o)
Catalyst **1.12a** (28.6 mg, 0.088 mmol) and $PhCO_2H$ (10.7 mg, 0.088 mmol) were dissolved in dry toluene (1.1 mL) and cooled to –30 ^oC. Substrate **5.16** (0.44 mmol) was added in one portion (note that substrates **5.16l**–**o** were cyclized prior to reaction). Compound **1.23a** (131.2 mg, 0.88 mmol) was added after 5 minutes and the reaction was stirred at –30 ^oC. The reaction was monitored by ^1H NMR. Once the resolution was judged to be complete (the corresponding aldehyde of **5.34** and the corresponding aldehyde of **5.35** are present in the reaction mixture in roughly equal amounts, as determined by ^1H NMR of the reaction mixture), the conversion to **5.34** and the dr of **5.35** were determined by ^1H NMR of the crude reaction mixture. The dr of **5.35** was calculated via integration of the aldehyde peaks of all diastereomers of the corresponding aldehyde of **5.35** resulting from the (*S*) configuration of **5.16**. An in situ reduction was performed using conditions A or B below.

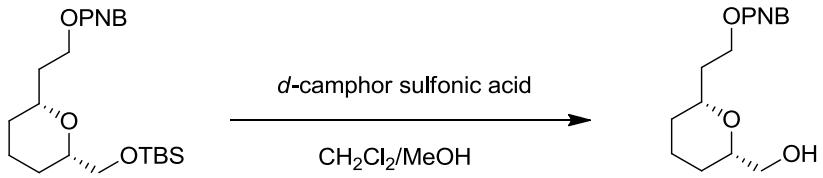
Reduction Conditions A
For substrates **5.16a**–**i** and **5.16l**–**m**, BH_3•THF (1.0 M in THF, 0.50 mL) was added dropwise to the reaction mixture and the reaction was allowed to warm to 0 ^oC over 30 minutes. The reaction was quenched by adding 1.0 M aqueous HCl (4 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 15mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated.

Reduction Conditions B
For substrates **5.16n**–**o**, the reaction mixture was diluted with MeOH (4.4 mL), and $NaBH_4$ (75.7 mg, 2.0 mmol) was added. The reaction was stirred at –30 ^oC for 15 minutes and was quenched by slowly adding saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 15mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated.

Both oxa-Michael product **5.34** and cascade product **5.35** were purified from the residue via column chromatography (EtOAc/petroleum ether, 30/70).

Modification Of Products for Chiral HPLC Analysis
Certain products (**5.35a**, **5.34b**, **5.34c**, **5.34d**, **5.34e**, **5.34n** and **5.34o**) were further modified by PNB protection in order to obtain ee information through chiral HPLC analysis. The PNB protection conditions were the same conditions used for the synthesis of **5.28**–***cis*** and **5.28**–***trans***. Products were collected in near quantitative yields. The compound characterization data for all PNB protected alcohols (**5.30a**, **5.28b**, **5.28c**, **5.28d**, **5.28e**, **5.28n** and **5.28o**) is shown below.

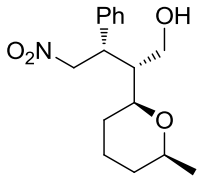
Product **5.34f** was PNB protected to give **5.28f**, using the same conditions used for the synthesis of **5.28a**–***cis*** and **5.28a**–***trans***, and was then desilylated to give **6.2f** in order to obtain ee information through chiral HPLC analysis.



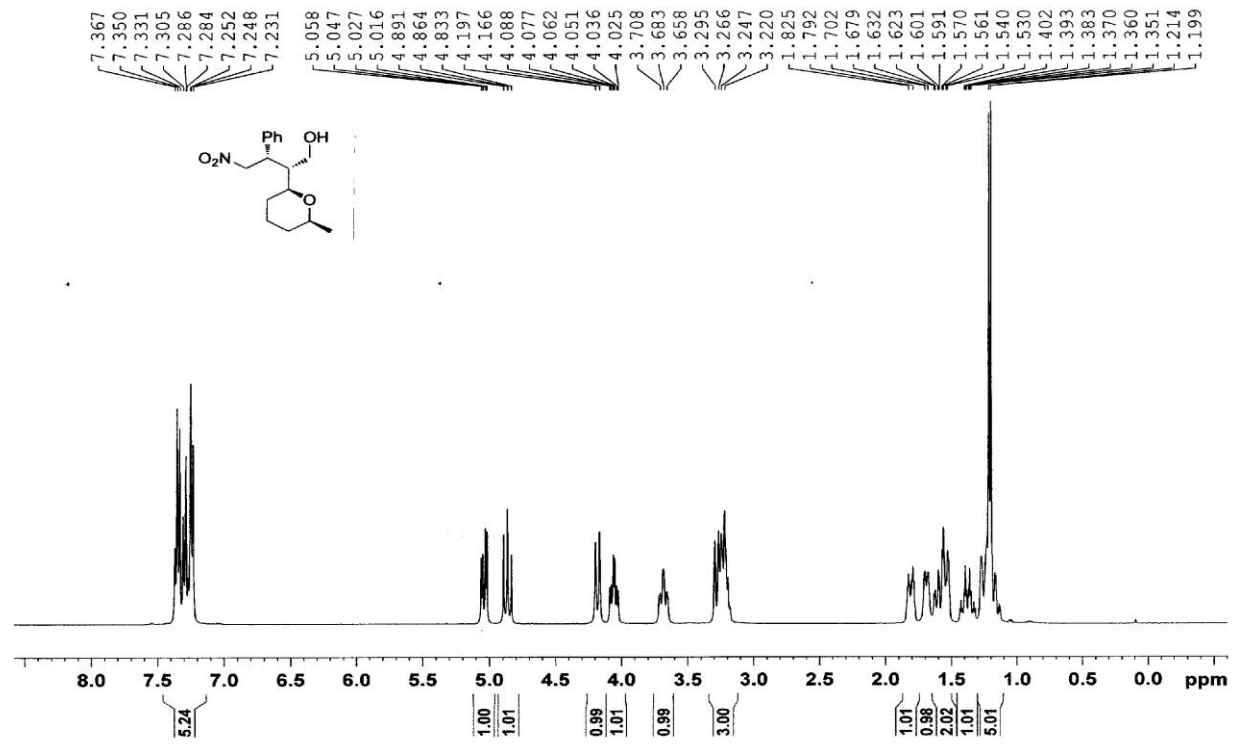
6.2f **6.4f**

The *p*-nitrobenzoate **5.28f** (31.6 mg, 0.075 mmol) was dissolved in dry MeOH (1.25 mL) and dry CH_2Cl_2 (1.25 mL). Then *d*-camphor sulfonic acid (17.5 mg, 0.075 mmol) was added and the reaction was stirred at room temperature for approximately 30 minutes. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The deprotected alcohol was purified via column chromatography (EtOAc/petroleum ether, 50/50). The desilylated product **6.2f** was collected in near quantitative yield. The compound characterization data for **6.2f** is shown.

5.35a: *(2R,3S)-2-((2S,6S)-6-methyltetrahydro-2H-pyran-2-yl)-4-nitro-3-phenylbutan-1-ol*



colorless oil. $[\alpha]_D^{23}$ = +27.4 (*c* 2.00, $CHCl_3$, 99% ee); IR (thin film, KBr): 3503, 2934, 2863, 1552, 1380, 1085, 1043, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 5.04 (dd, *J* = 12.3, 4.6 Hz, 1H), 4.85 (dd, *J* = 12.3, 10.8 Hz, 1H), 4.18 (d, *J* = 12.4 Hz, 1H), 4.08 (td, *J* = 10.4, 4.6 Hz, 1H), 3.68 (m, 1H), 3.32-3.16 (m, 3H), 1.81 (m, 1H), 1.69 (d, *J* = 9.4 Hz, 1H), 1.65-1.50 (m, 2H), 1.38 (m, 1H), 1.31-1.10 (m, 2H), 1.21 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 128.9, 128.2, 127.6, 79.3, 78.6, 75.0, 59.6, 47.1, 43.1, 33.0, 29.1, 23.4, 22.3 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_{16}H_{23}NO_4]$: 293.1627, found: 293.1632.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7.284
7.252
7.248
7.231
5.058
5.047
5.027
5.016
4.891
4.864
4.833
4.197
4.166
4.088
4.077
4.062
4.051
4.036
4.025
3.708
3.683
3.658
3.295
3.266
3.247
3.220
1.825
1.792
1.702
1.679
1.632
1.623
1.601
1.591
1.570
1.561
1.540
1.530
1.402
1.393
1.383
1.370
1.360
1.351
1.214
1.199
Ph
OH
O2N
O
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
ppm
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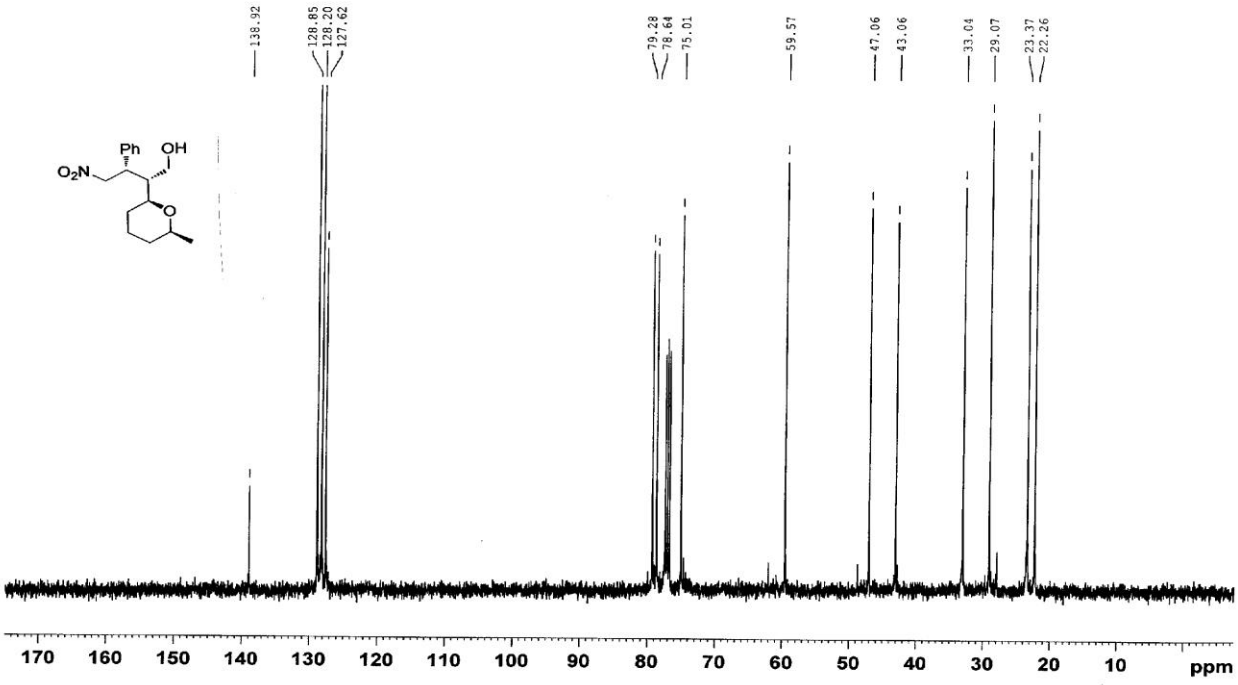
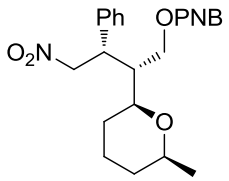
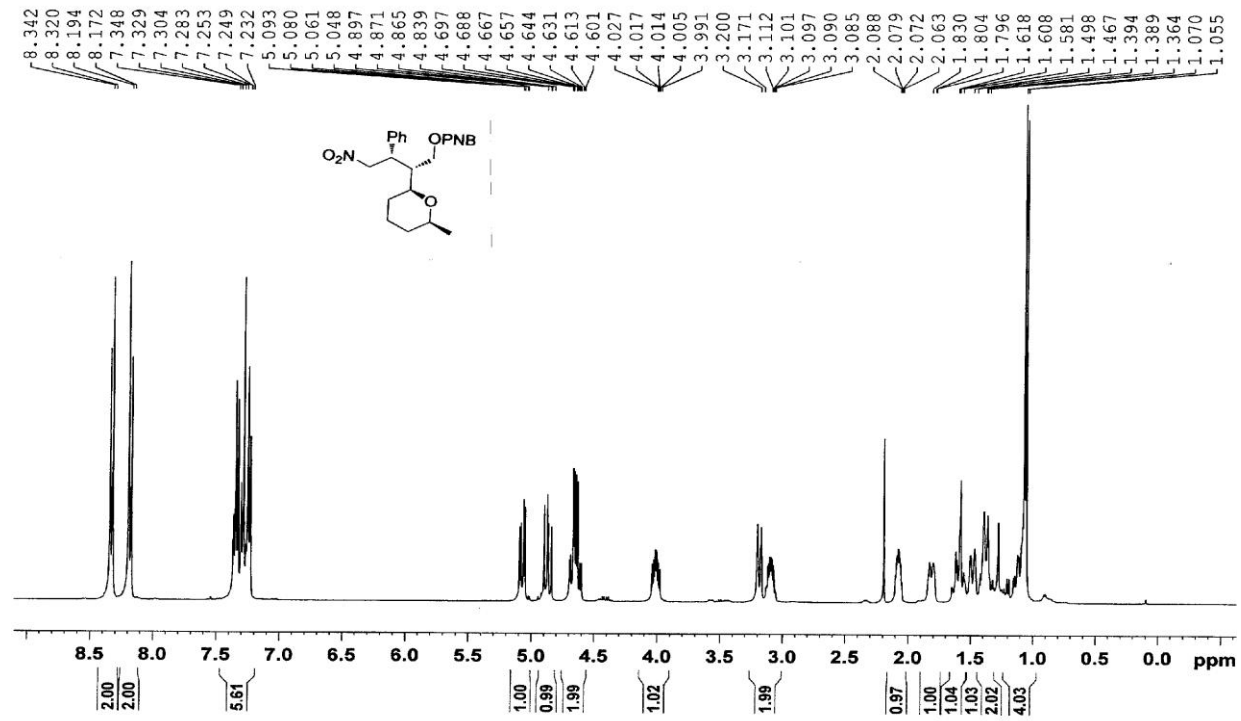
1.01
0.99
1.01
0.99
3.00
1.01
0.98
2.02
1.01
5.01


138.92
128.85
128.20
127.62
79.28
78.64
75.01
59.57
47.06
43.06
33.04
29.07
23.37
22.26
Ph
OH
O2N
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

5.30a: *(2R,3S)-2-((2S,6S)-6-methyltetrahydro-2H-pyran-2-yl)-4-nitro-3-phenylbutyl 4-nitrobenzoate*



colorless amorphous solid. $[\alpha]_D^{23}$ = -12.2 (*c* 2.00, $CHCl_3$, 99% ee); IR (thin film, KBr): 3449, 1724, 1636, 1554, 1528, 1277, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.9 Hz, 2H), 8.18 (d, *J* = 8.9 Hz, 2H), 7.40-7.20 (m, 5H), 5.07 (dd, *J* = 12.8, 5.0 Hz, 1H), 4.87 (dd, *J* = 12.8, 10.5 Hz, 1H), 4.64 (m, 2H), 4.01 (m, 1H), 3.19 (m, 1H), 3.09 (m, 1H), 2.08 (m, 1H), 1.82 (m, 1H), 1.70-1.30 (m, 4H), 1.23-1.10 (m, 1H), 1.06 (d, *J* = 6.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 150.7, 138.5, 135.4, 130.7, 128.9, 127.9, 127.7, 123.7, 78.4, 76.6, 74.2, 63.5, 46.8, 44.8, 32.9, 28.9, 23.7, 22.0 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 14.2 min, minor enantiomer t_R = 18.5 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{23}H_{26}N_2O_7]$: 442.1740, found: 442.1745.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8.320
8.194
8.172
7.348
7.329
7.304
7.283
7.253
7.249
7.232
5.093
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5.061
5.048
4.897
4.871
4.865
4.839
4.697
4.688
4.667
4.657
4.644
4.631
4.613
4.601
4.027
4.017
4.014
4.005
3.991
3.200
3.171
3.112
3.101
3.097
3.090
3.085
2.088
2.079
2.072
2.063
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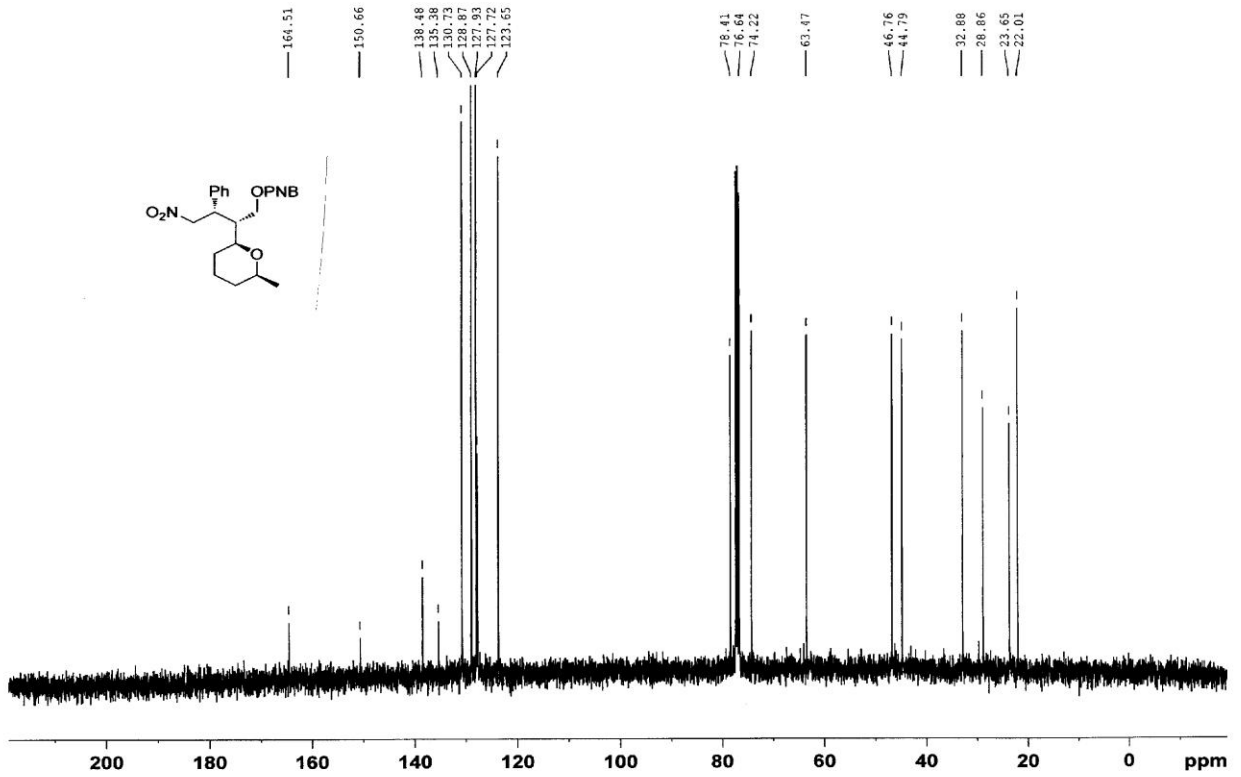
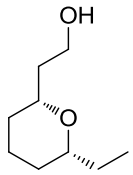
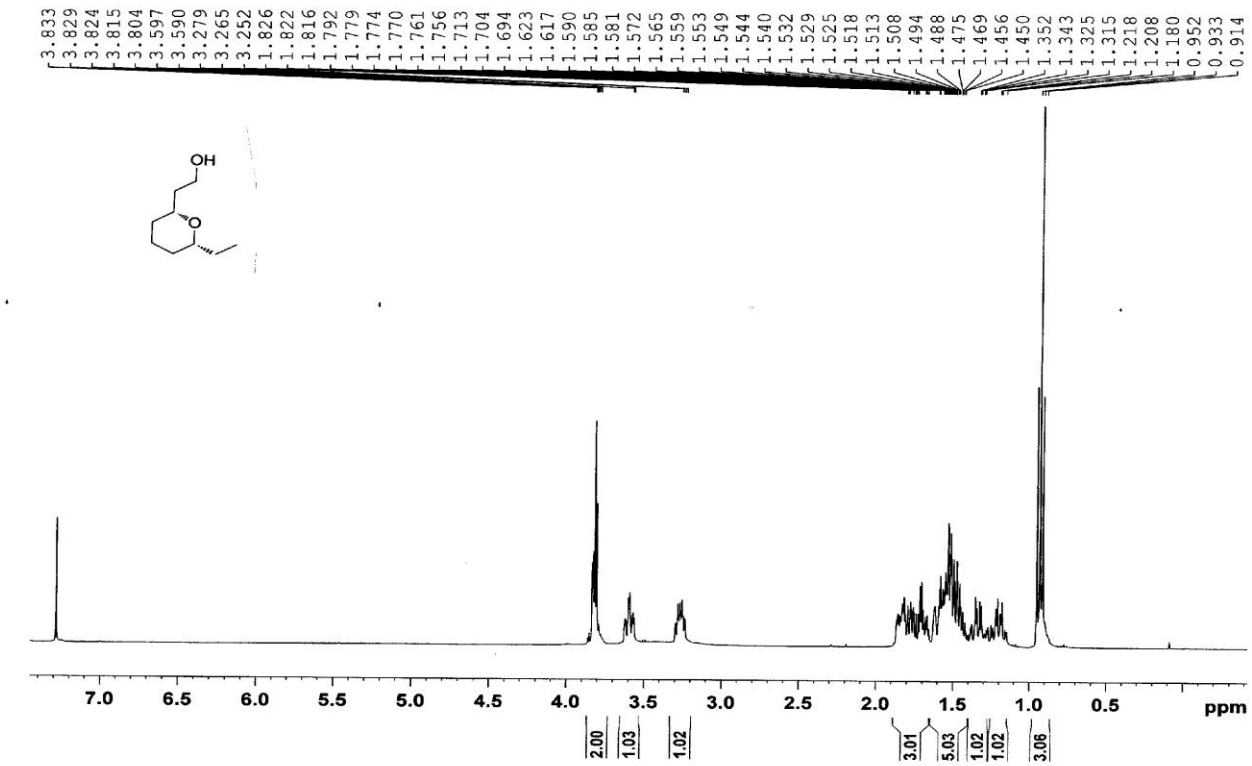
1.618
1.608
1.581
1.498
1.467
1.394
1.389
1.364
1.070
1.055
Ph
OPNB
O2N
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.00
2.00
5.61
1.00
0.99
1.99
1.02
1.99
0.97
1.00
1.04
1.03
2.02
4.03


164.51
150.66
138.48
135.38
130.73
128.87
127.93
127.72
123.65
78.41
76.64
74.22
63.47
46.76
44.79
32.88
28.86
23.65
22.01
Ph
OPNB
O2N
O
200
180
160
140
120
100
80
60
40
20
0
ppm

5.34b: *2-((2R,6R)-6-ethyltetrahydro-2H-pyran-2-yl)ethanol*



colorless oil. $[\alpha]_D^{23}$ = -2.5 (*c* 0.713, $CHCl_3$, 98% ee); IR (thin film, KBr): 3412, 2935, 2859, 1720, 1200, 1084, 1038, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (m, 2H), 3.59 (m, 1H), 3.27 (m, 1H), 1.87-1.63 (m, 3H), 1.62-1.39 (m, 5H), 1.38-1.13 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.5, 79.1, 62.1, 37.8, 31.6, 30.9, 29.3, 23.4, 10.1 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_9H_{18}O_2]$: 158.1307, found: 158.1304.


3.833
3.829
3.824
3.815
3.804
3.597
3.590
3.279
3.265
3.252
1.826
1.822
1.816
1.792
1.779
1.774
1.770
1.761
1.756
1.713
1.704
1.694
1.623
1.617
1.590
1.585
1.581
1.572
1.565
1.559
1.553
1.549
1.544
1.540
1.532
1.529
1.525
1.518
1.513
1.508
1.494
1.488
1.475
1.469
1.456
1.450
1.352
1.343
1.325
1.315
1.218
1.208
1.180
0.952
0.933
0.914
OH
O
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
ppm
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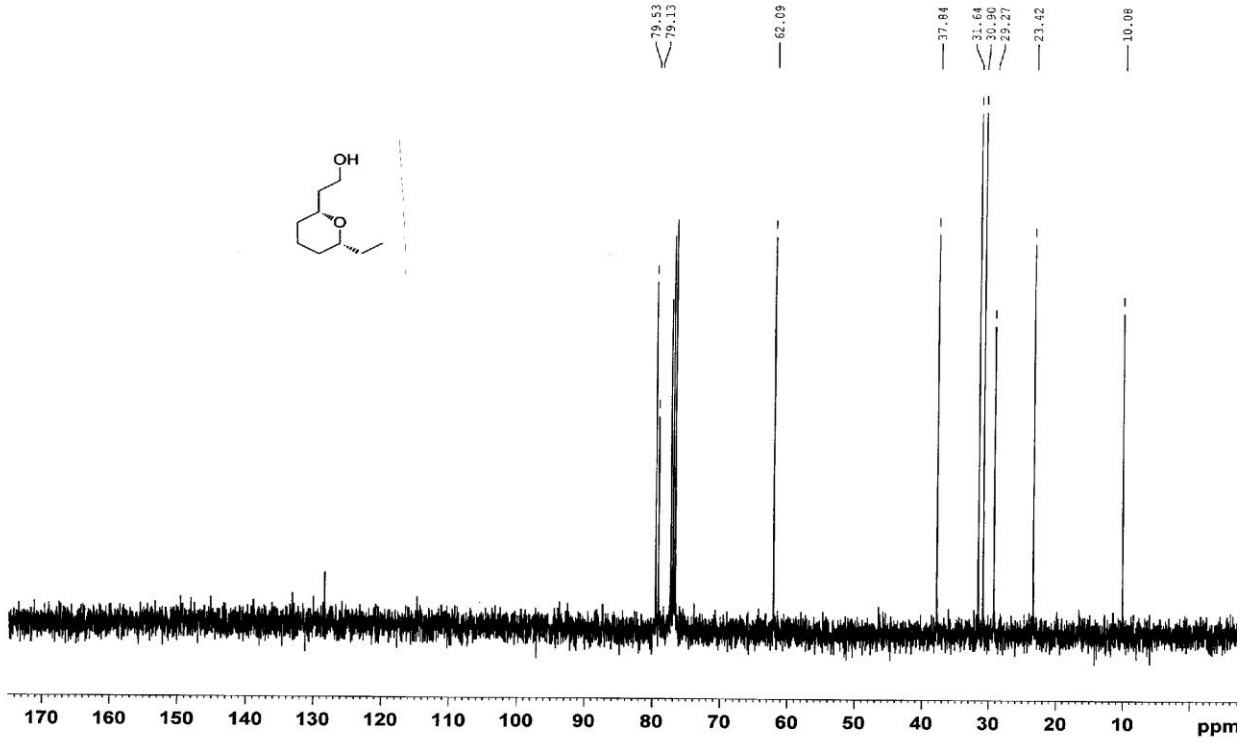
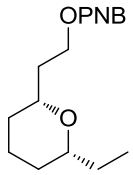
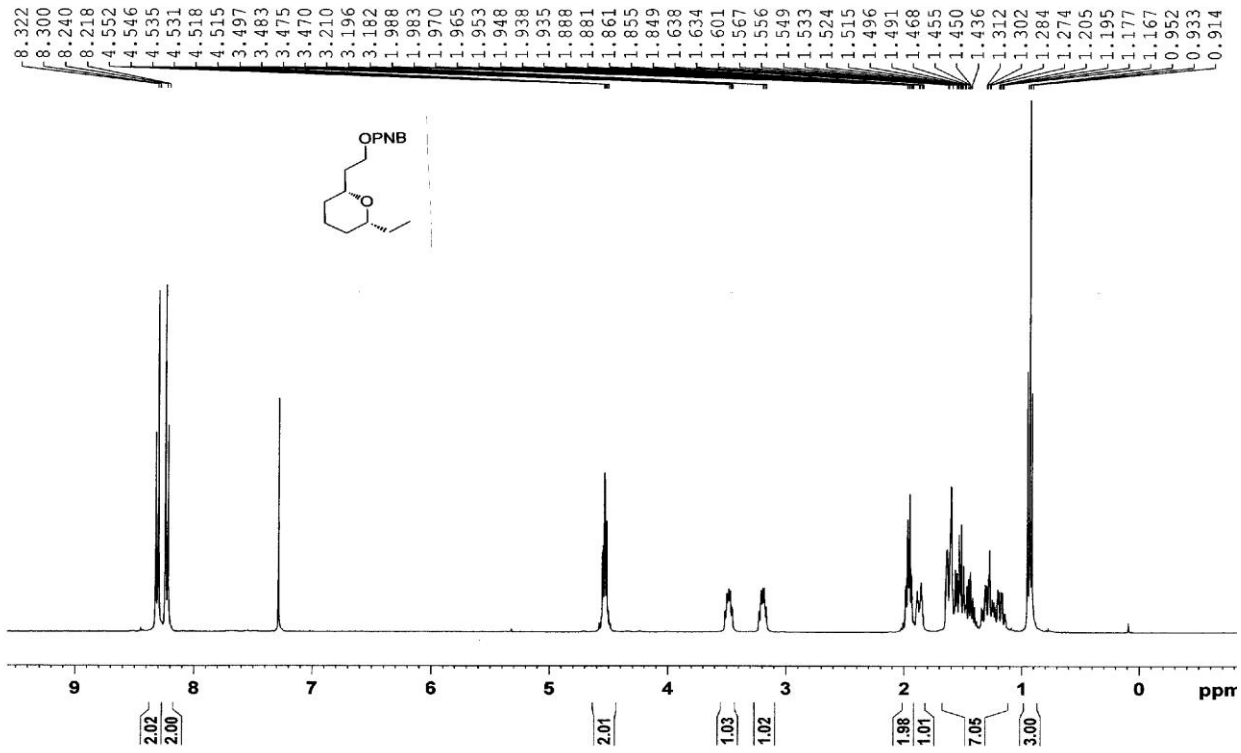
1.03
1.02
3.01
5.03
1.02
1.02
3.06


79.53
79.13
62.09
37.84
31.64
30.90
29.27
23.42
10.08
OH
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

5.28b: *2-((2R,6R)-6-ethyltetrahydro-2H-pyran-2-yl)ethyl 4-nitrobenzoate*



colorless amorphous solid. $[\alpha]_D^{23}$ = -29.5 (*c* 1.00, $CHCl_3$, 98% ee); IR (thin film, KBr): 2935, 2847, 1727, 1529, 1280, 1103, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.9 Hz, 2H), 8.23 (d, *J* = 8.9 Hz, 2H), 4.52 (m, 2H), 3.49 (m, 1H), 3.20 (m, 1H), 2.02-1.82 (m, 3H), 1.67-1.10 (m, 7H), 0.93 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 150.5, 135.9, 130.7, 123.5, 79.4, 74.4, 63.1, 35.5, 31.8, 31.1, 29.4, 23.6, 10.0 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 97:3), 0.5 mL/min; minor enantiomer t_R = 13.2 min, major enantiomer t_R = 17.8 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{16}H_{21}NO_5]$: 307.1420, found: 307.1419.


8.322
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8.218
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4.546
4.535
4.531
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4.515
3.497
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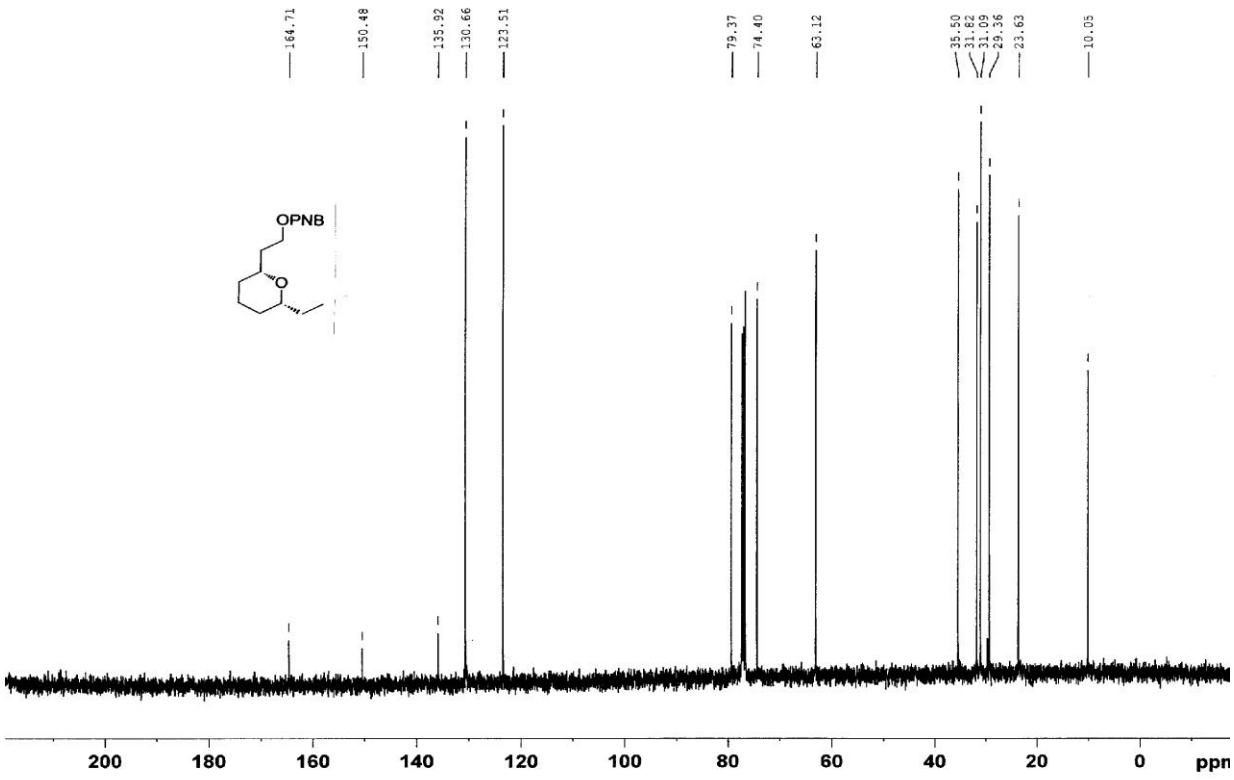
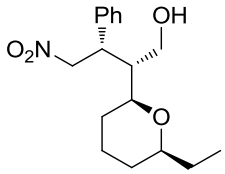
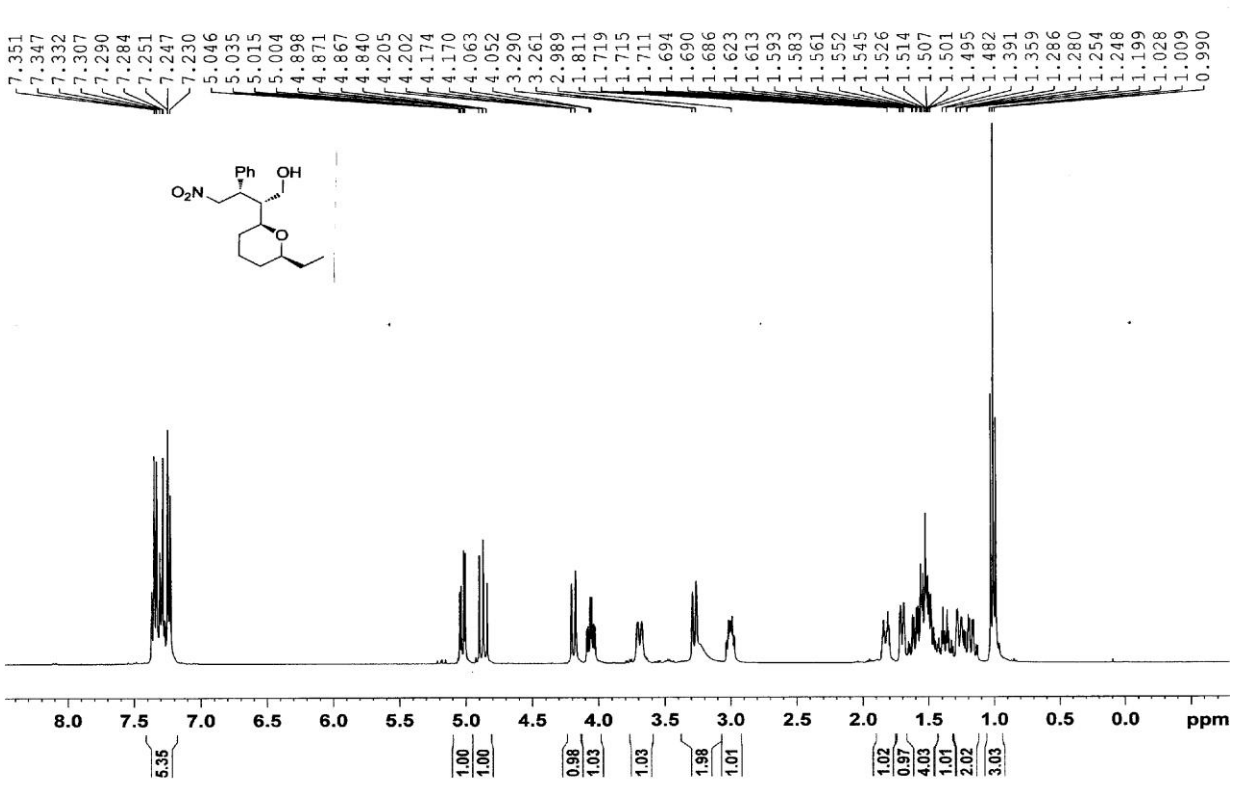
3.470
3.210
3.196
3.182
1.988
1.983
1.970
1.965
1.953
1.948
1.938
1.935
1.888
1.881
1.861
1.855
1.849
1.638
1.634
1.601
1.567
1.556
1.549
1.533
1.524
1.515
1.496
1.491
1.468
1.455
1.450
1.436
1.312
1.302
1.284
1.274
1.205
1.195
1.177
1.167
0.952
0.933
0.914
OPNB
O
9
8
7
6
5
4
3
2
1
0
ppm
2.02
2.00
2.01
1.03
1.02
1.98
1.01
7.05
3.00


164.71
150.48
135.92
130.66
123.51
79.37
74.40
63.12
35.50
31.82
31.09
29.36
23.63
10.05
OPNB
O
200
180
160
140
120
100
80
60
40
20
0
ppm

5.35b: *(2R,3S)-2-((2S,6S)-6-ethyltetrahydro-2H-pyran-2-yl)-4-nitro-3-phenylbutan-1-ol*



colorless oil. $[\alpha]_D^{25}$ = -6.4(*c* 1.00, $CHCl_3$, 99% ee); IR (thin film, KBr): 3506, 2936, 1552, 1380, 1042, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.18 (m, 5H), 5.03 (dd, *J* = 12.3, 4.6 Hz, 1H), 4.87 (dd, *J* = 12.3, 10.8 Hz, 1H), 4.19 (d, *J* = 12.4, 1.3 Hz, 1H), 4.06 (td, *J* = 10.4, 4.6 Hz, 1H), 3.69 (m, 1H), 3.32-3.10 (m, 2H), 2.99 (m, 1H), 1.81 (m, 1H), 1.70 (m, 1H), 1.65-1.42 (m, 4H), 1.38 (m, 1H), 1.31-1.10 (m, 2H), 1.01 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 128.9, 128.2, 127.6, 80.4, 79.3, 78.7, 59.6, 47.1, 43.1, 31.0, 29.4, 29.4, 23.4, 10.2 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 95:5), 0.5 mL/min; minor enantiomer t_R = 23.5 min, major enantiomer t_R = 25.9 min. HRMS (ESI) : [M^+] calcd for [$C_{17}H_{25}NO_4$]: 307.1784, found: 307.1789.


7.351
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7.284
7.251
7.247
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5.046
5.035
5.015
5.004
4.898
4.871
4.867
4.840
4.205
4.202
4.174
4.170
4.063
4.052
3.290
3.261
2.989
1.811
1.719
1.715
1.711
1.694
1.690
1.686
1.623
1.613
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1.501
1.495
1.482
1.391
1.359
1.286
1.280
1.254
1.248
1.199
1.028
1.009
0.990
Ph
OH
O2N
O
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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
ppm
5.35
1.00
1.00
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1.02
0.97
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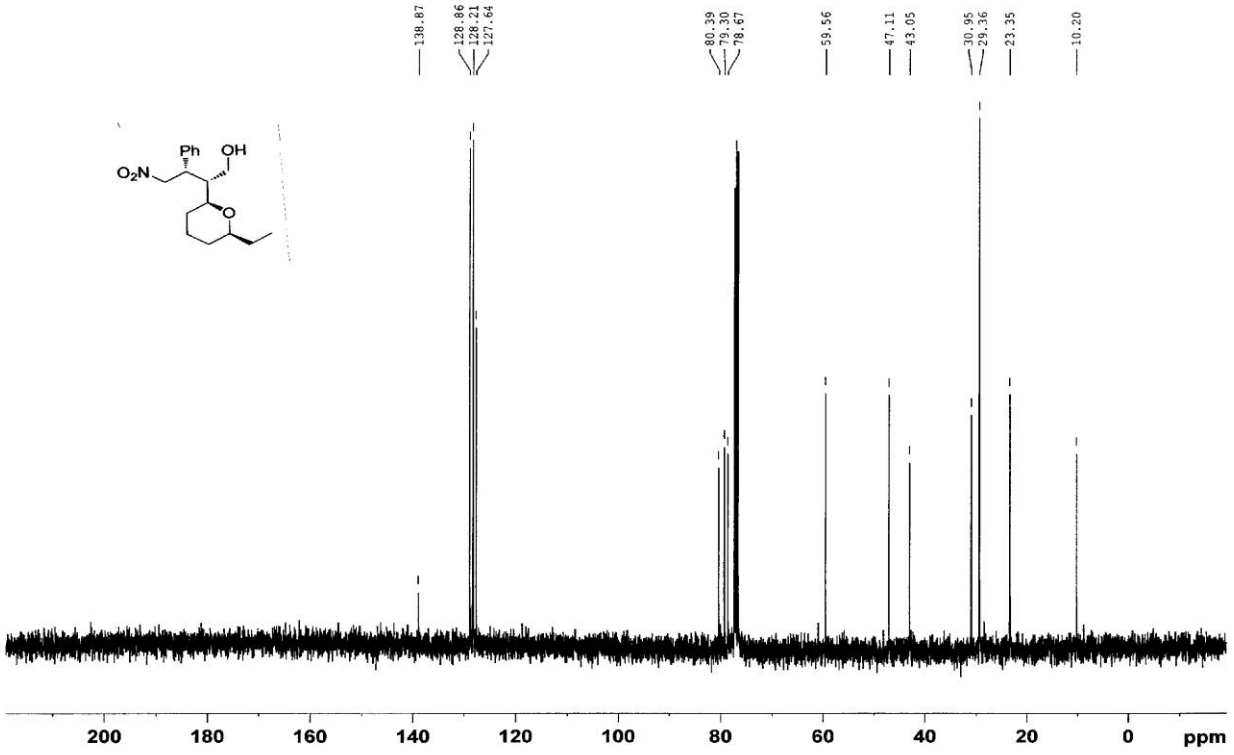
1.01
2.02
3.03


138.87
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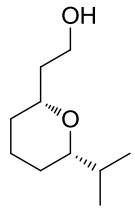
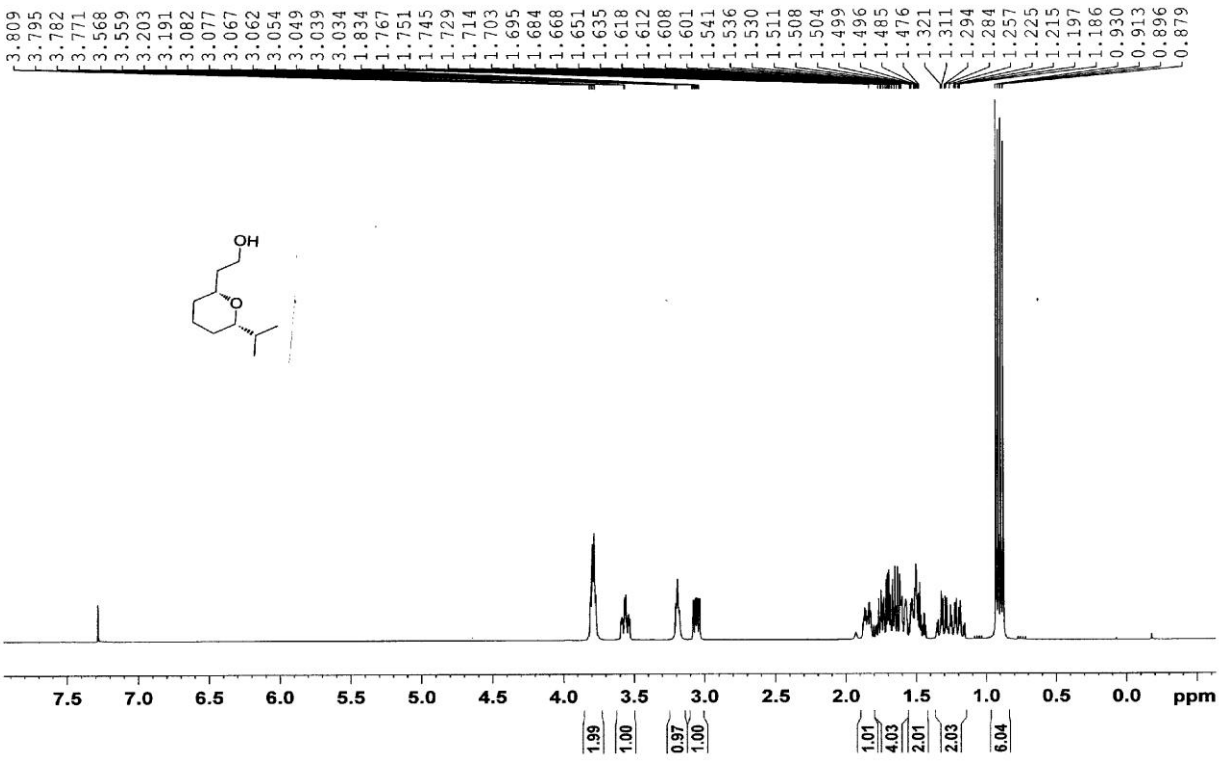
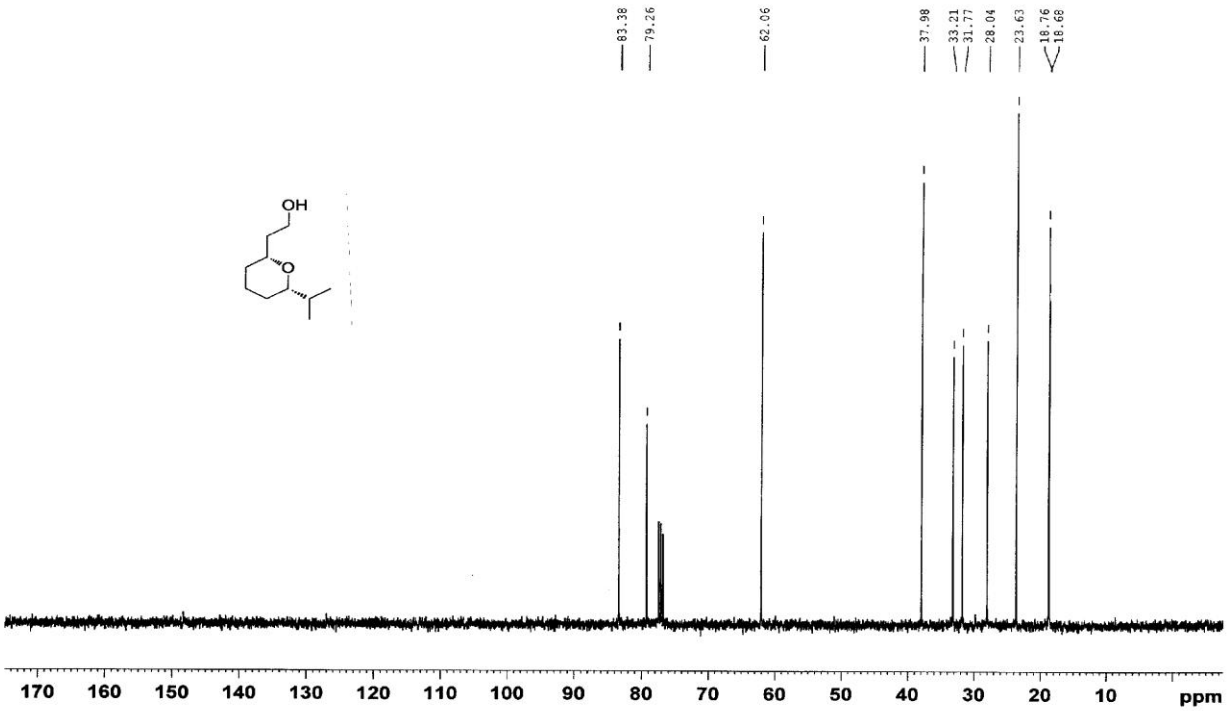
127.64
80.39
79.30
78.67
59.56
47.11
43.05
30.95
29.36
23.35
10.20
Ph
OH
O2N
O
200
180
160
140
120
100
80
60
40
20
0
ppm

5.34c: *2-((2R,6S)-6-isopropyltetrahydro-2H-pyran-2-yl)ethanol*

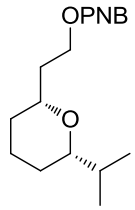


colorless oil. $[\alpha]_D^{24}$ = -7.0 (*c* 1.00, $CHCl_3$, 98% ee); IR (thin film, KBr): 3373, 2938, 2872, 1382, 1203, 1083, 1046, 906 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.79 (m, 2H), 3.56 (m, 1H), 3.20 (m, 1H), 3.05 (m, 1H), 1.95-1.82 (m, 1H), 1.81-1.43 (m, 6H), 1.37-1.15 (m, 2H), 0.91 (dd, *J* = 13.8, 6.8 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.4, 79.3, 62.1, 38.0, 33.2, 31.8, 28.0, 23.6, 18.8, 18.7 ppm; HRMS (ESI) : [M^+] calcd for [$C_{10}H_{20}O_2$]: 172.1463, found: 172.1458.

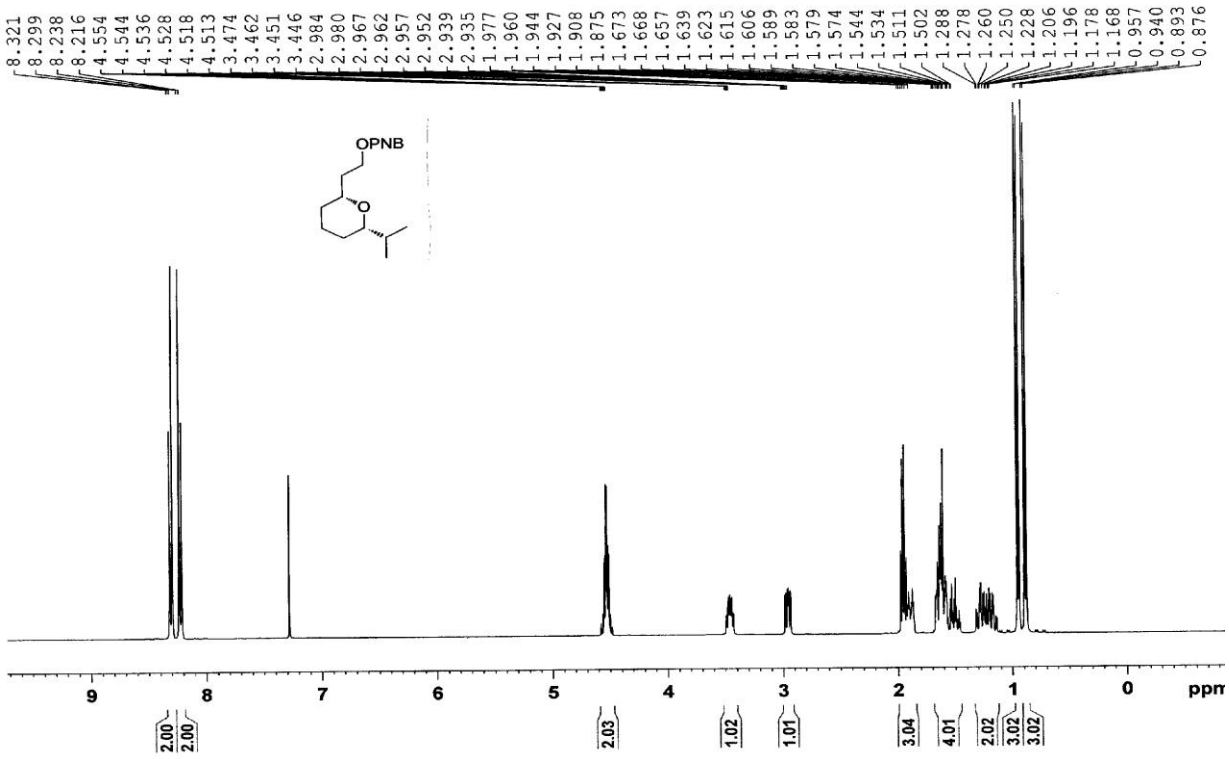

3.809
3.795
3.782
3.771
3.568
3.559
3.203
3.191
3.082
3.077
3.067
3.062
3.054
3.049
3.039
3.034
1.834
1.767
1.751
1.745
1.729
1.714
1.703
1.695
1.684
1.668
1.651
1.635
1.618
1.612
1.608
1.601
1.541
1.536
1.530
1.511
1.508
1.504
1.499
1.496
1.485
1.476
1.321
1.311
1.294
1.284
1.257
1.225
1.215
1.197
1.186
0.930
0.913
0.896
0.879
OH
O
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 ppm
1.99
1.00
0.97
1.00
1.01
4.03
2.01
2.03
6.04

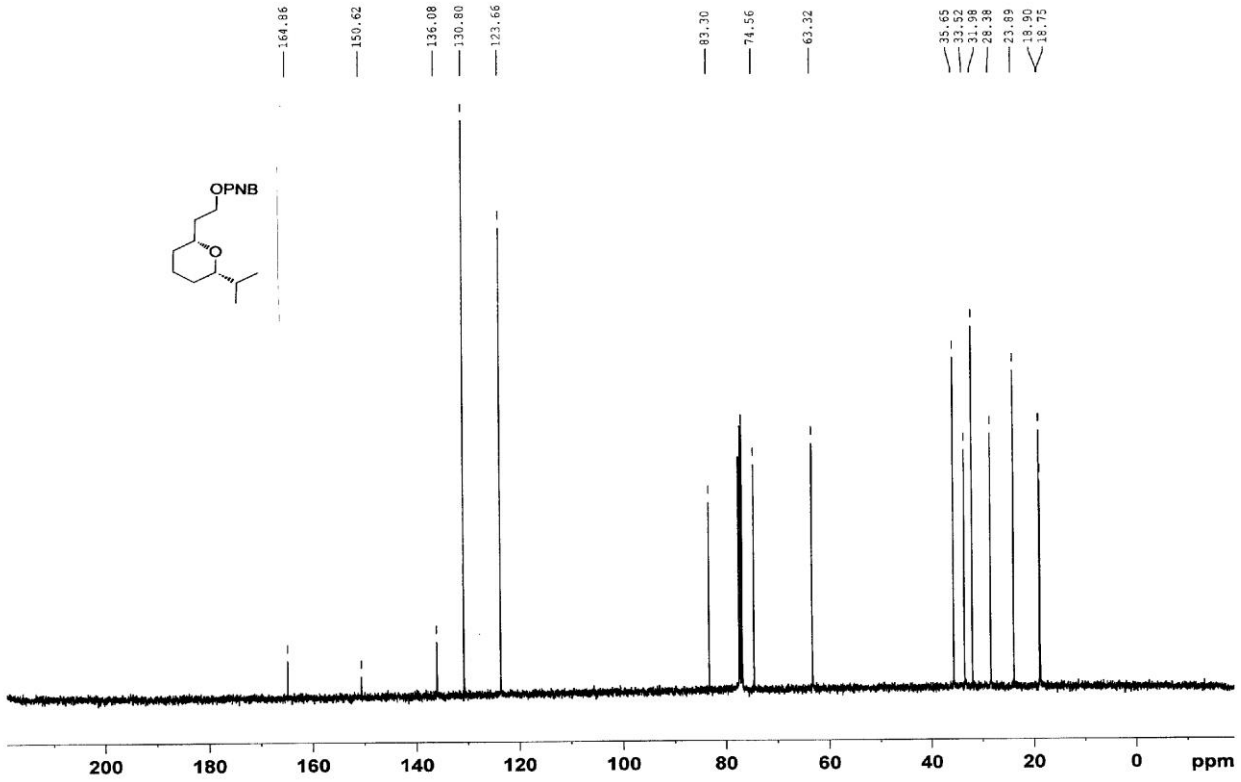

83.38
79.26
62.06
37.98
33.21
31.77
28.04
23.63
18.76
18.68
OH
O
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

5.28c: *2-((2R,6S)-6-isopropyltetrahydro-2H-pyran-2-yl)ethyl 4-nitrobenzoate*

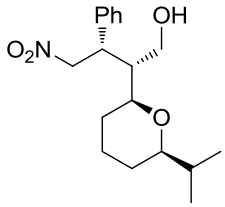


colorless amorphous solid. $[\alpha]_D^{23}$ = -32.7 (*c* 1.00, $CHCl_3$, 98% ee); IR (thin film, KBr): 2938, 1726, 1529, 1278, 1102, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.9 Hz, 2H), 8.23 (d, *J* = 8.9 Hz, 2H), 4.52 (m, 2H), 3.47 (m, 1H), 2.96 (m, 1H), 2.01-1.85 (m, 3H), 1.68-1.45 (m, 4H), 1.33-1.12 (m, 2H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 150.6, 136.1, 130.8, 123.7, 83.3, 74.6, 63.3, 35.7, 33.5, 32.0, 28.4, 23.9, 18.9, 18.8 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 97:3), 0.5 mL/min; minor enantiomer t_R = 9.9 min, major enantiomer t_R = 11.0 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{17}H_{23}NO_5]$: 321.1576, found: 321.1584.

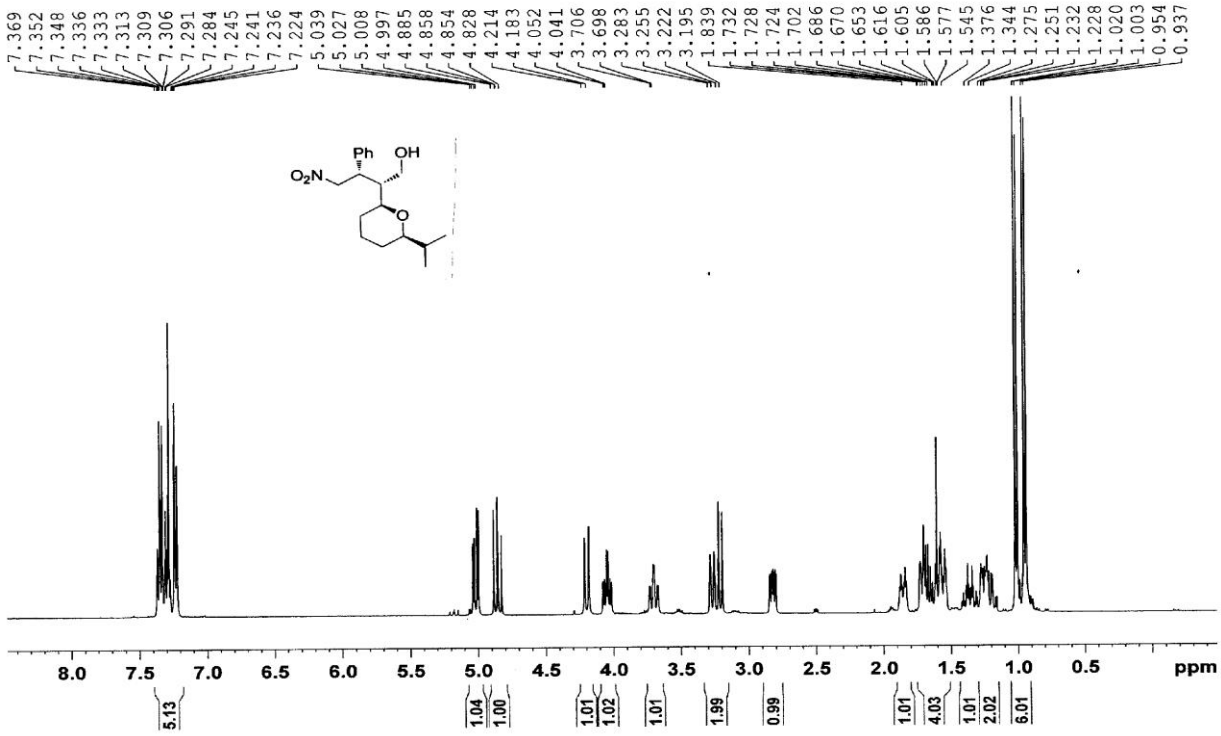

8.321
8.299
8.238
8.216
4.554
4.544
4.536
4.528
4.518
4.513
3.474
3.462
3.451
3.446
2.984
2.980
2.967
2.962
2.957
2.952
2.939
2.935
1.977
1.960
1.944
1.927
1.908
1.875
1.673
1.668
1.657
1.639
1.623
1.615
1.606
1.589
1.583
1.579
1.574
1.544
1.534
1.511
1.502
1.288
1.278
1.260
1.250
1.228
1.206
1.196
1.178
1.168
0.957
0.940
0.893
0.876
OPNB
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.00
2.03
1.02
1.01
3.04
4.01
2.02
3.02
3.02

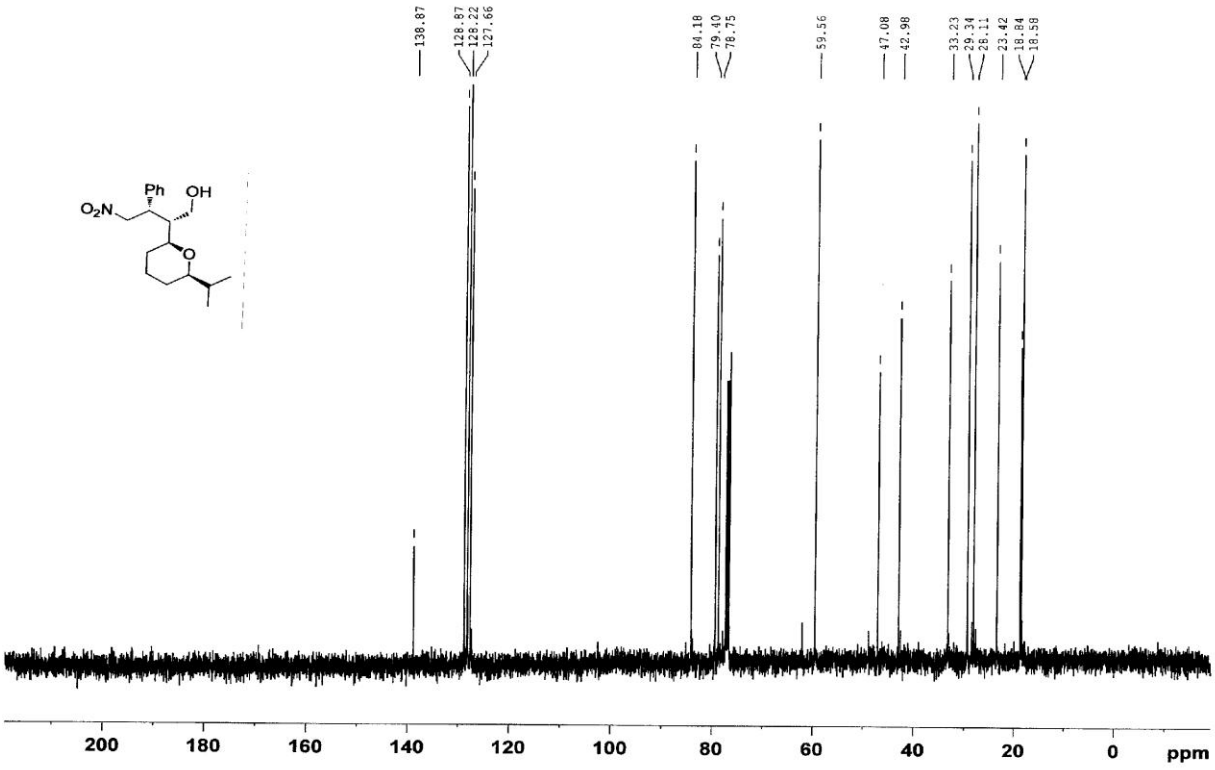

164.86
150.62
136.08
130.80
123.66
83.30
74.56
63.32
35.65
33.52
31.98
28.38
23.89
18.90
18.75
OPNB
200
180
160
140
120
100
80
60
40
20
0
ppm

5.35c: *(2R,3S)-2-((2S,6R)-6-isopropyltetrahydro-2H-pyran-2-yl)-4-nitro-3-phenylbutan-1-ol*

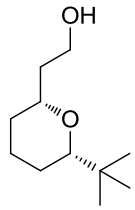


colorless oil. $[\alpha]_D^{22}$ = +4.5 (*c* 1.00, $CHCl_3$, 99% ee); IR (thin film, KBr): 3493, 2940, 1552, 1379, 1043, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.19 (m, 5H), 5.02 (dd, *J* = 12.3, 4.6 Hz, 1H), 4.86 (dd, *J* = 12.3, 10.8 Hz, 1H), 4.20 (d, *J* = 12.4 Hz, 1H), 4.05 (td, *J* = 10.4, 4.6 Hz, 1H), 3.70 (m, 1H), 3.27 (d, *J* = 11.6 Hz, 1H), 3.21 (d, *J* = 10.9 Hz, 1H), 2.82 (m, 1H), 1.86 (m, 1H), 1.75-1.52 (m, 4H), 1.36 (m, 1H), 1.30-1.14 (m, 2H), 1.01 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 128.9, 128.2, 127.7, 84.2, 79.4, 78.8, 59.6, 47.1, 43.0, 33.2, 29.3, 28.1, 23.4, 18.8, 18.6 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 95:5), 0.5 mL/min; minor enantiomer t_R = 20.7 min, major enantiomer t_R = 24.0 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{18}H_{27}NO_4]$: 321.1940, found: 321.1943.

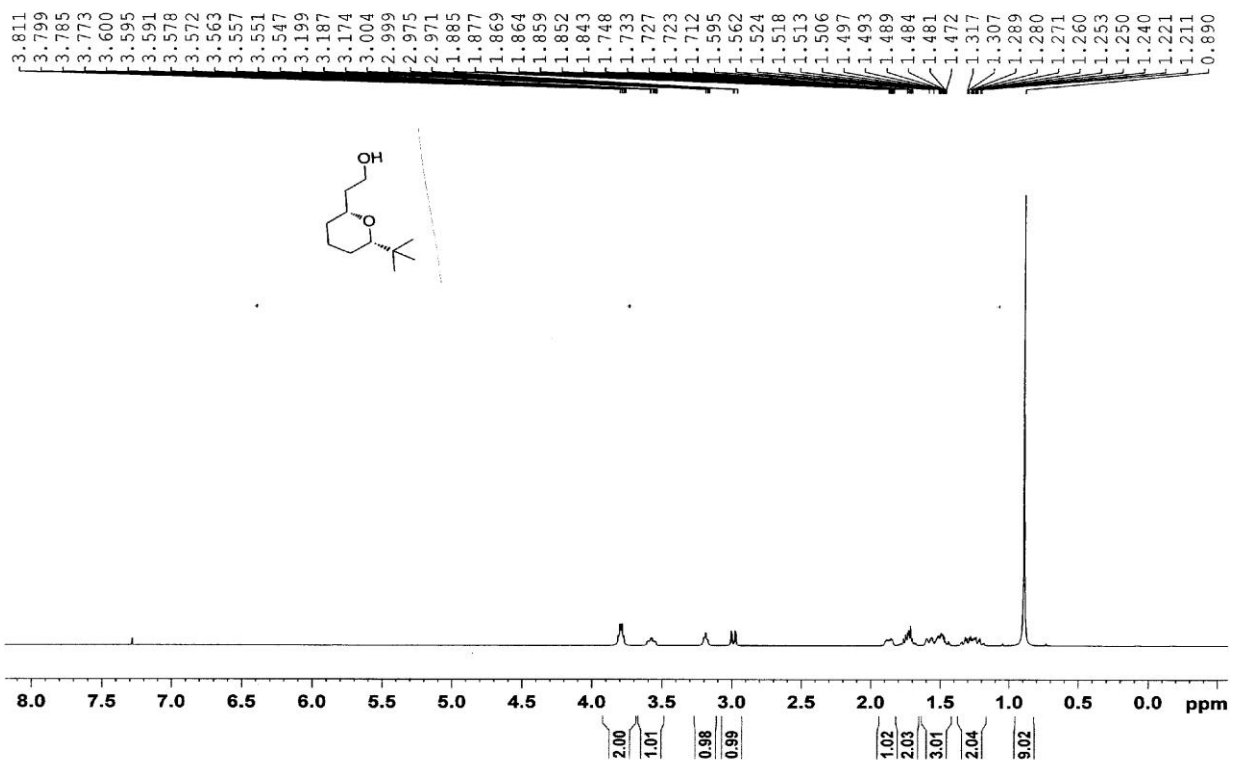

7.369
7.352
7.348
7.336
7.333
7.313
7.309
7.306
7.291
7.284
7.245
7.241
7.236
7.224
5.039
5.027
5.008
4.997
4.885
4.858
4.854
4.828
4.214
4.183
4.052
4.041
3.706
3.698
3.283
3.255
3.222
3.195
1.839
1.732
1.728
1.724
1.702
1.686
1.670
1.653
1.616
1.605
1.586
1.577
1.545
1.376
1.344
1.275
1.251
1.232
1.228
1.020
1.003
0.954
0.937
Ph
OH
O2N
O
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
ppm
5.13
1.04
1.00
1.01
1.02
1.01
1.99
0.99
1.01
4.03
1.01
2.02
6.01

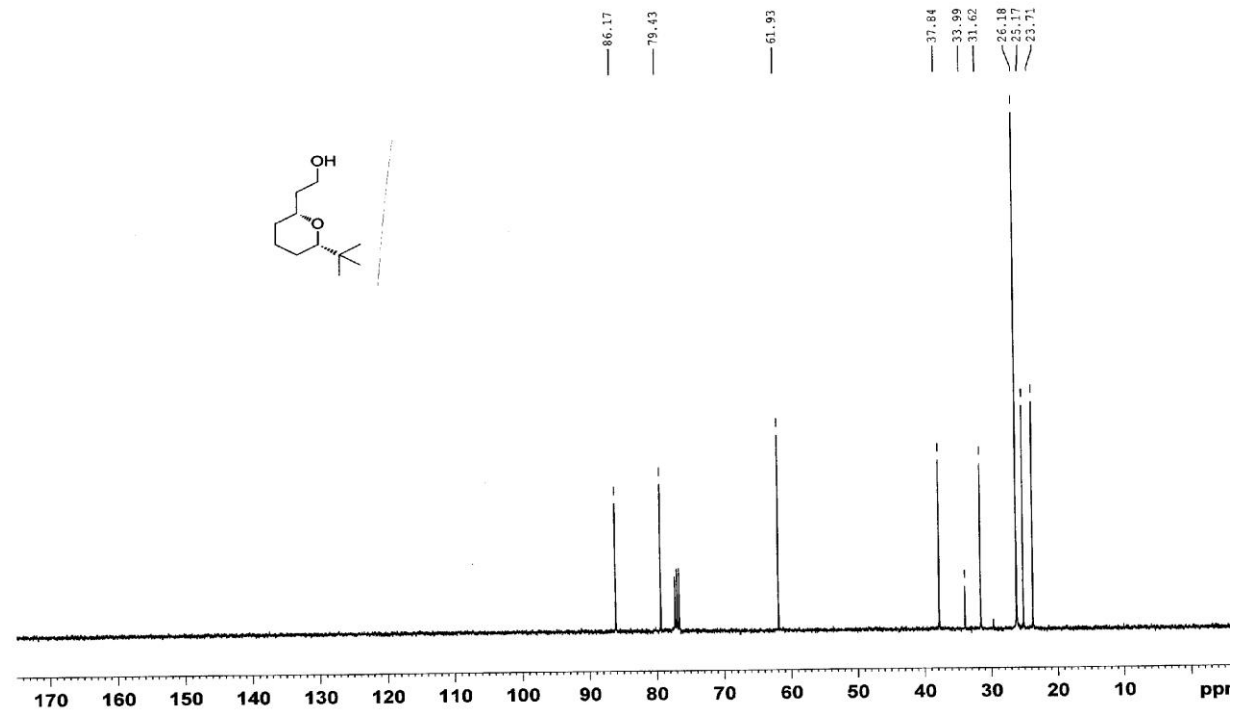

138.87
128.87
128.22
127.66
84.18
79.40
78.75
59.56
47.08
42.98
33.23
29.34
26.11
23.42
18.84
18.58
Ph
OH
O2N
O
200
180
160
140
120
100
80
60
40
20
0
ppm

5.34d: *2-((2R,6S)-6-(tert-butyl)tetrahydro-2H-pyran-2-yl)ethanol*

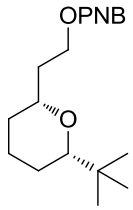


colorless oil. $[\alpha]_D^{23}$ = -6.5 (*c* 1.33, $CHCl_3$, 87% ee); IR (thin film, KBr): 3417, 2944, 2863, 1638, 1362, 1194, 1088, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (m, 2H), 3.59 (m, 1H), 3.19 (m, 1H), 2.99 (dd, *J* = 11.2, 1.8 Hz, 1H), 1.86 (m, 1H), 1.72 (m, 2H), 1.62-1.43 (m, 3H), 1.38-1.18 (m, 2H), 0.89 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.2, 79.4, 61.9, 37.8, 34.0, 31.6, 26.2, 25.2, 23.7 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_{11}H_{22}O_2]$: 186.1620, found: 286.1622.

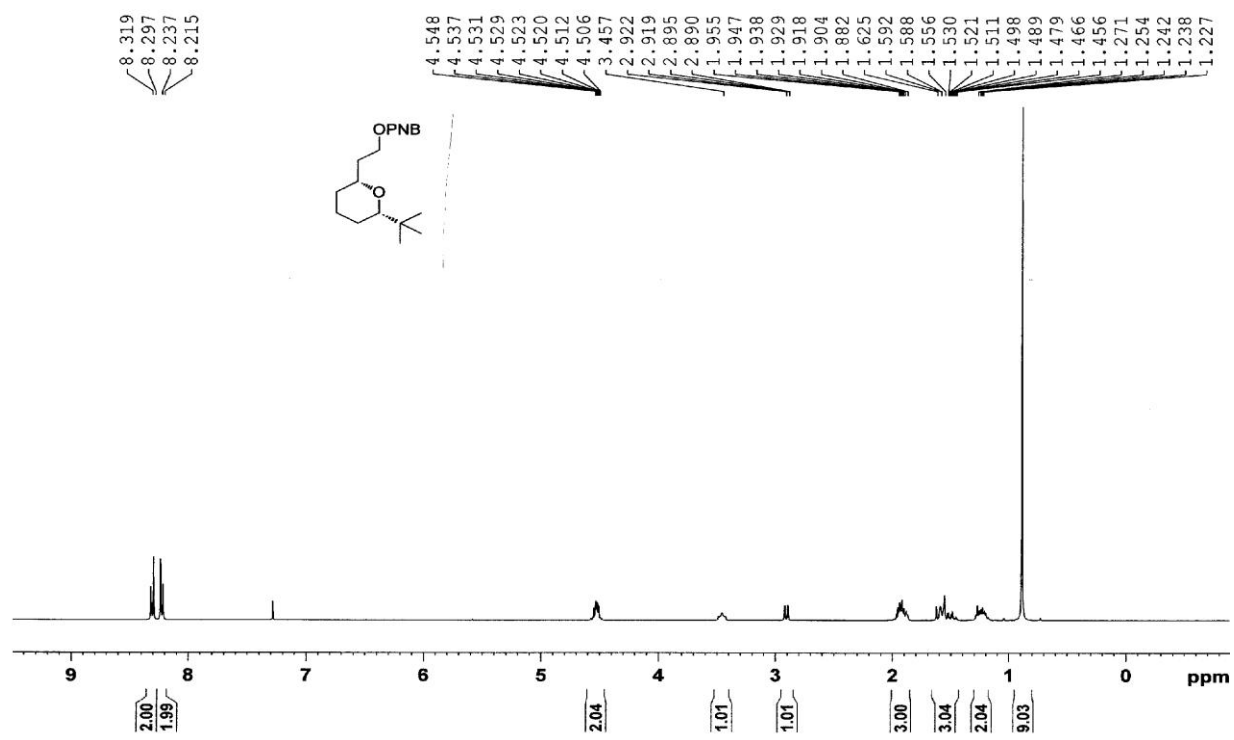

3.811
3.799
3.785
3.773
3.600
3.595
3.591
3.578
3.572
3.563
3.557
3.551
3.547
3.199
3.187
3.174
3.004
2.999
2.975
2.971
1.885
1.877
1.869
1.864
1.859
1.852
1.843
1.748
1.733
1.727
1.723
1.712
1.595
1.562
1.524
1.518
1.513
1.506
1.497
1.493
1.489
1.484
1.481
1.472
1.317
1.307
1.289
1.280
1.271
1.260
1.253
1.250
1.240
1.221
1.211
0.890
OH
O
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
ppm
2.00
1.01
0.98
0.99
1.02
2.03
3.01
2.04
9.02

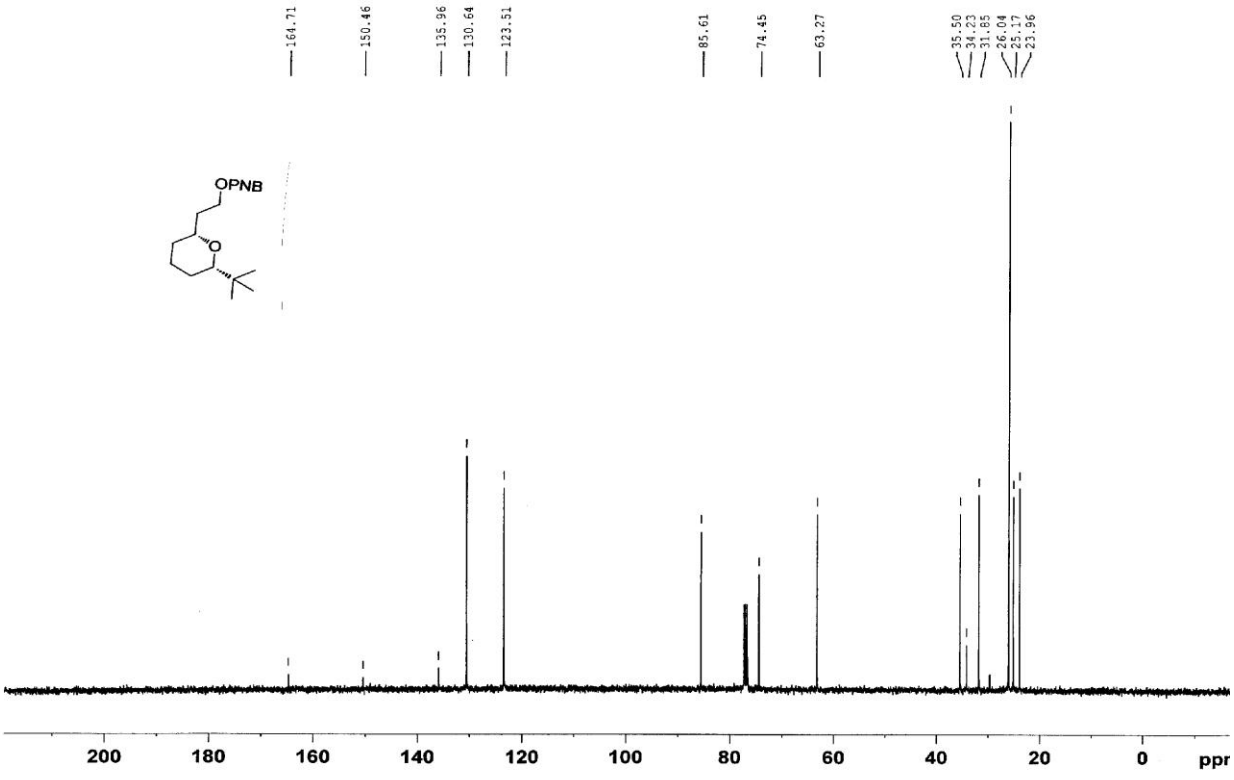

86.17
79.43
61.93
37.84
33.99
31.62
26.18
25.17
23.71
OH
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppr

5.28d: *2-((2R,6S)-6-(tert-butyl)tetrahydro-2H-pyran-2-yl)ethyl 4-nitrobenzoate*

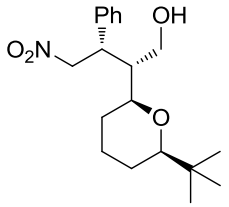


colorless amorphous solid. $[\alpha]_D^{22}$ = -50.5 (*c* 1.15, $CHCl_3$, 87% ee); IR (thin film, KBr): 2952, 2864, 1727, 1530, 1281, 1103, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.8 Hz, 2H), 8.23 (d, *J* = 8.8 Hz, 2H), 4.53 (m, 2H), 3.47 (m, 1H), 2.91 (dd, *J* = 9.8, 1.6 Hz, 1H), 1.98-1.85 (m, 3H), 1.65-1.44 (m, 3H), 1.31-1.15 (m, 2H), 0.89 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 150.5, 136.0, 130.6, 123.5, 85.6, 74.5, 63.3, 35.5, 34.2, 31.9, 26.0, 25.2, 24.0 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 99:1), 0.5 mL/min; minor enantiomer t_R = 11.1 min, major enantiomer t_R = 12.9 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{18}H_{25}NO_5]$: 335.1733, found: 335.1739.

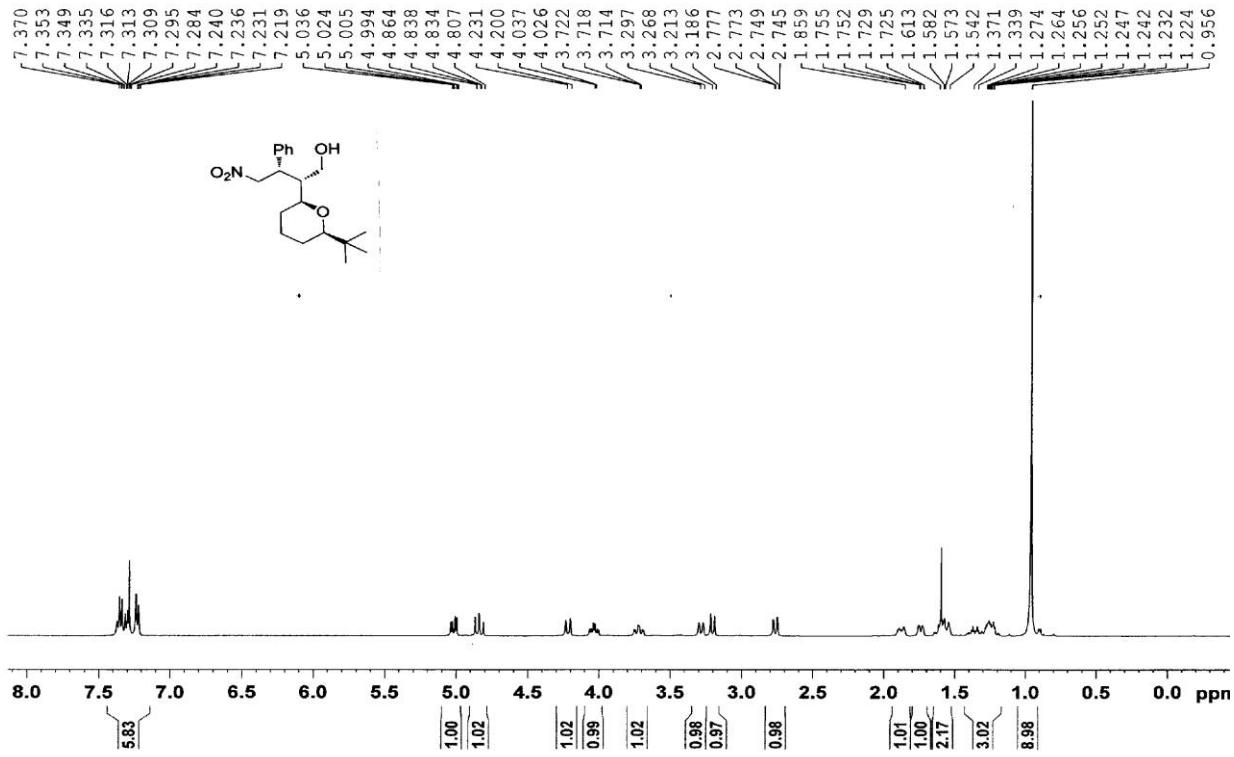

8.319
8.297
8.237
8.215
4.548
4.537
4.531
4.529
4.523
4.520
4.512
4.506
3.457
2.922
2.919
2.895
2.890
1.955
1.947
1.938
1.929
1.918
1.904
1.882
1.625
1.592
1.588
1.556
1.530
1.521
1.511
1.498
1.489
1.479
1.466
1.456
1.271
1.254
1.242
1.238
1.227
OPNB
9
8
7
6
5
4
3
2
1
0
ppm
2.00
1.99
2.04
1.01
1.01
3.00
3.04
2.04
9.03

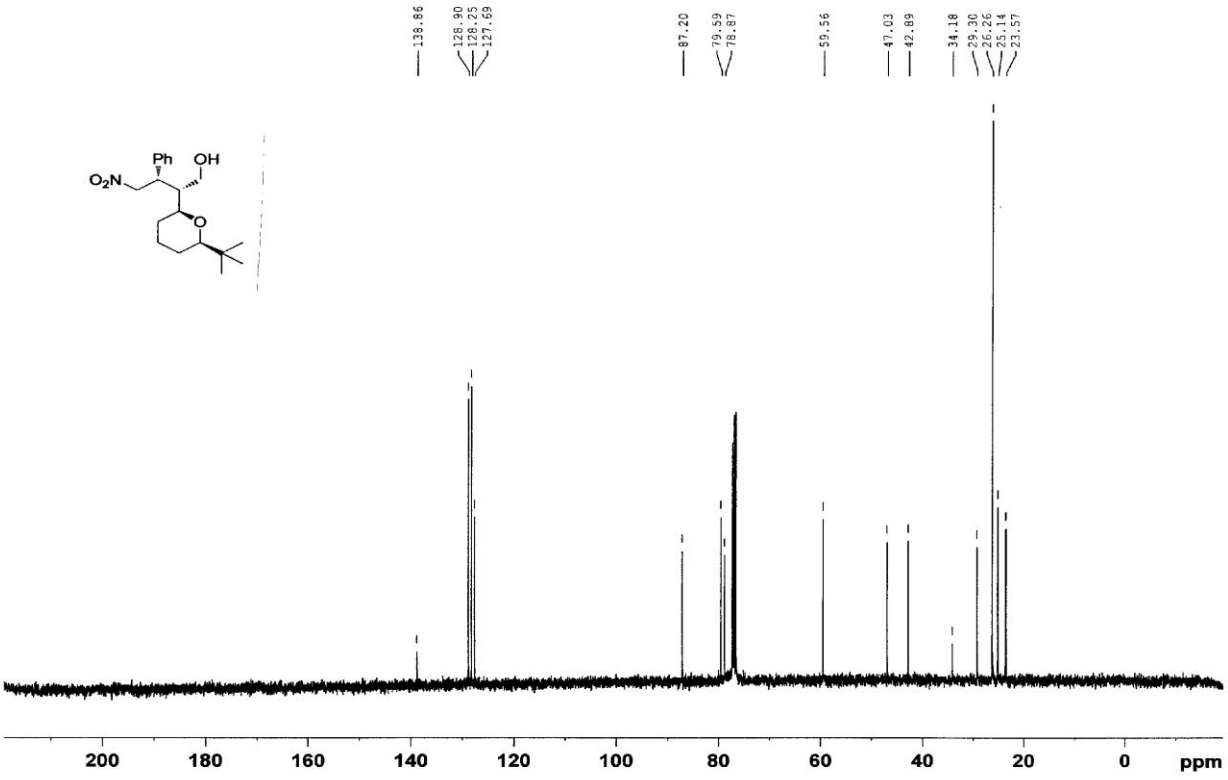

164.71
150.46
135.96
130.64
123.51
85.61
74.45
63.27
35.50
34.23
31.85
26.04
25.17
23.96
OPNB
200
180
160
140
120
100
80
60
40
20
0
ppm

5.35d: *(2R,3S)-2-((2S,6R)-6-(tert-butyl)tetrahydro-2H-pyran-2-yl)-4-nitro-3-phenylbutan-1-ol*

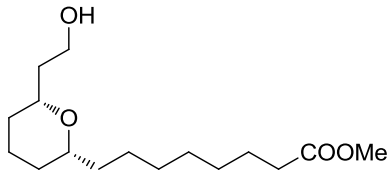


colorless oil. $[\alpha]_D^{23}$ = +3.1 (*c* 1.56, $CHCl_3$, 99% ee); IR (thin film, KBr): 3502, 2952, 2867, 1638, 1553, 1046, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 5.02 (dd, *J* = 12.3, 4.6 Hz, 1H), 4.84 (dd, *J* = 12.3, 10.8 Hz, 1H), 4.22 (d, *J* = 12.4 Hz, 1H), 4.03 (td, *J* = 10.4, 4.6 Hz, 1H), 3.72 (m, 1H), 3.29 (d, *J* = 11.6 Hz, 1H), 3.20 (d, *J* = 10.9 Hz, 1H), 2.76 (dd, *J* = 11.2, 1.9 Hz, 1H), 1.88 (m, 1H), 1.74 (m, 1H), 1.65-1.52 (m, 2H), 1.47-1.17 (m, 3H), 0.96 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 128.9, 128.3, 127.7, 87.2, 79.6, 78.9, 59.6, 47.0,42.9, 34.2, 29.3, 26.3, 24.1, 23.6 ppm; the enantiomeric excess was determined by HPLC with an OD-H column (*n*-hexane: *i*-PrOH = 99:1), 1.0 mL/min; minor enantiomer t_R = 32.6 min, major enantiomer t_R = 39.6 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{19}H_{29}NO_4]$: 335.2097, found: 335.2100.

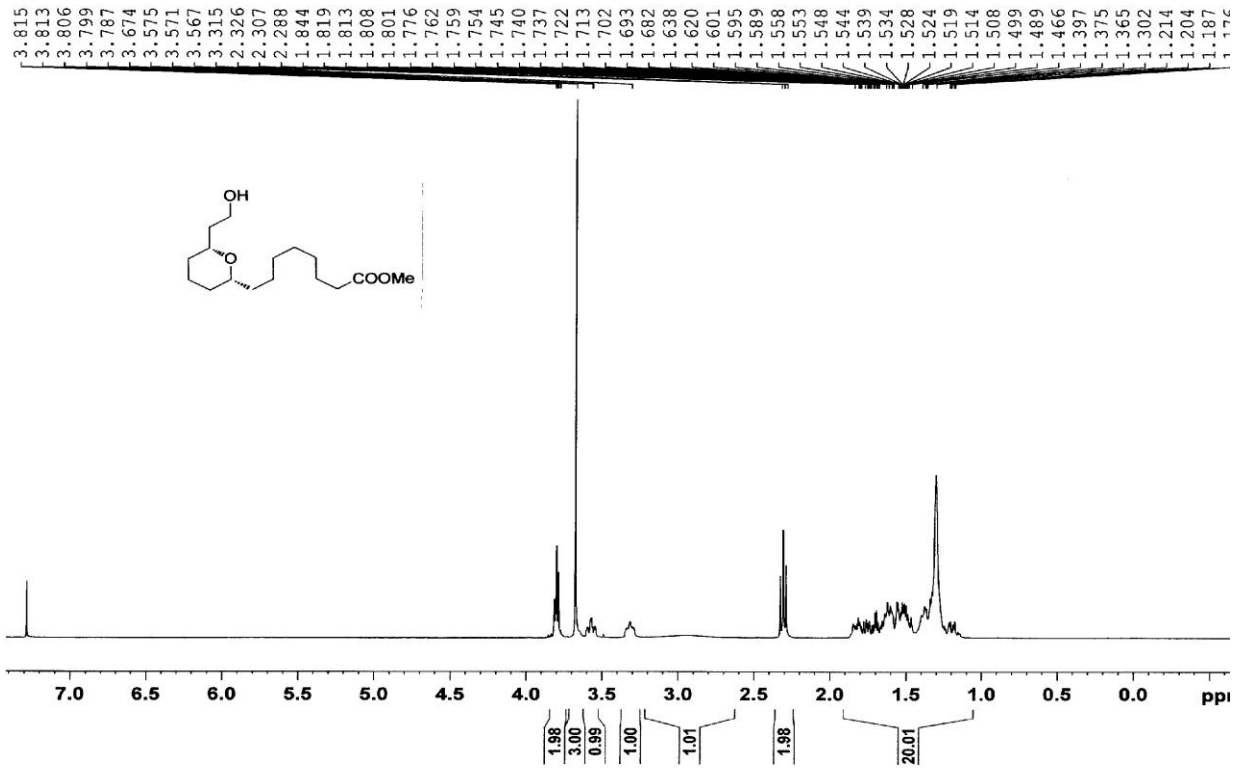

7.370
7.353
7.349
7.335
7.316
7.313
7.309
7.295
7.284
7.240
7.236
7.231
7.219
5.036
5.024
5.005
4.994
4.864
4.838
4.834
4.807
4.231
4.200
4.037
4.026
3.722
3.718
3.714
3.297
3.268
3.213
3.186
2.777
2.773
2.749
2.745
1.859
1.755
1.752
1.729
1.725
1.613
1.582
1.573
1.542
1.371
1.339
1.274
1.264
1.256
1.252
1.247
1.242
1.232
1.224
0.956
Ph
OH
O2N
O
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
ppm
5.83
1.00
1.02
1.02
0.99
1.02
0.98
0.97
0.98
1.01
1.00
2.17
3.02
8.98

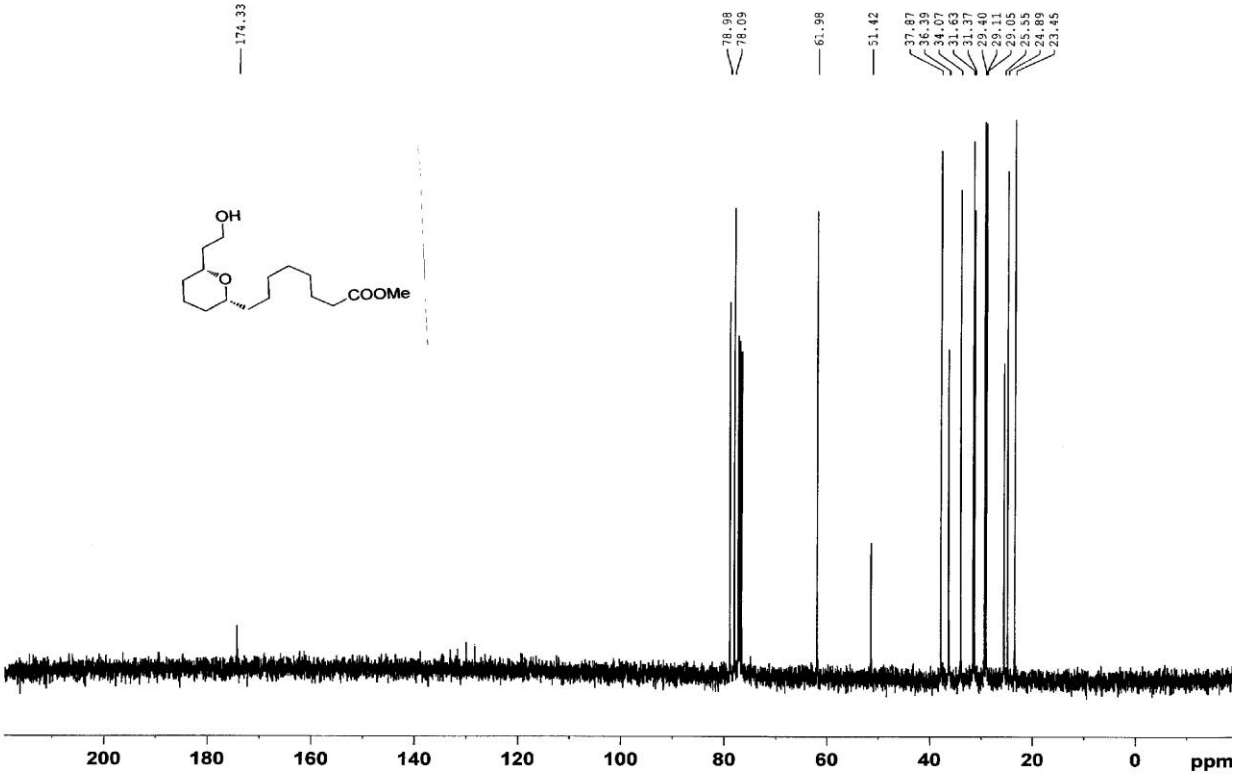

138.86
128.90
128.25
127.69
87.20
79.59
78.87
59.56
47.03
42.89
34.18
29.30
26.26
25.14
23.57
Ph
OH
O2N
O
200
180
160
140
120
100
80
60
40
20
0
ppm

5.34e: *methyl 8-((2R,6R)-6-(2-hydroxyethyl)tetrahydro-2H-pyran-2-yl)octanoate*

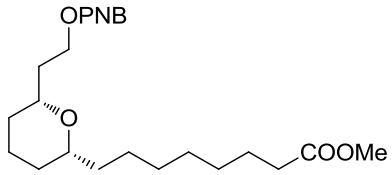


colorless oil. $[\alpha]_D^{23}$ = -5.6 (*c* 1.375, $CHCl_3$, 90% ee); IR (thin film, KBr): 3451, 2932, 2857, 1740, 1437, 1198, 1171, 1085, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (m, 2H), 3.67 (s, 3H), 3.57 (m, 1H), 3.32 (m, 1H), 2.93 (bs, 1H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.88-1.13 (m, 20H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 79.0, 78.1, 62.0, 51.4, 37.9, 36.4, 34.1, 31.6, 31.4, 29.4, 29.1, 29.1, 25.6, 24.9, 23.5 ppm; LRMS (ESI) : $[M^+]$ calcd for $[C_{16}H_{30}O_4]$: 286.2, found: 286.2.

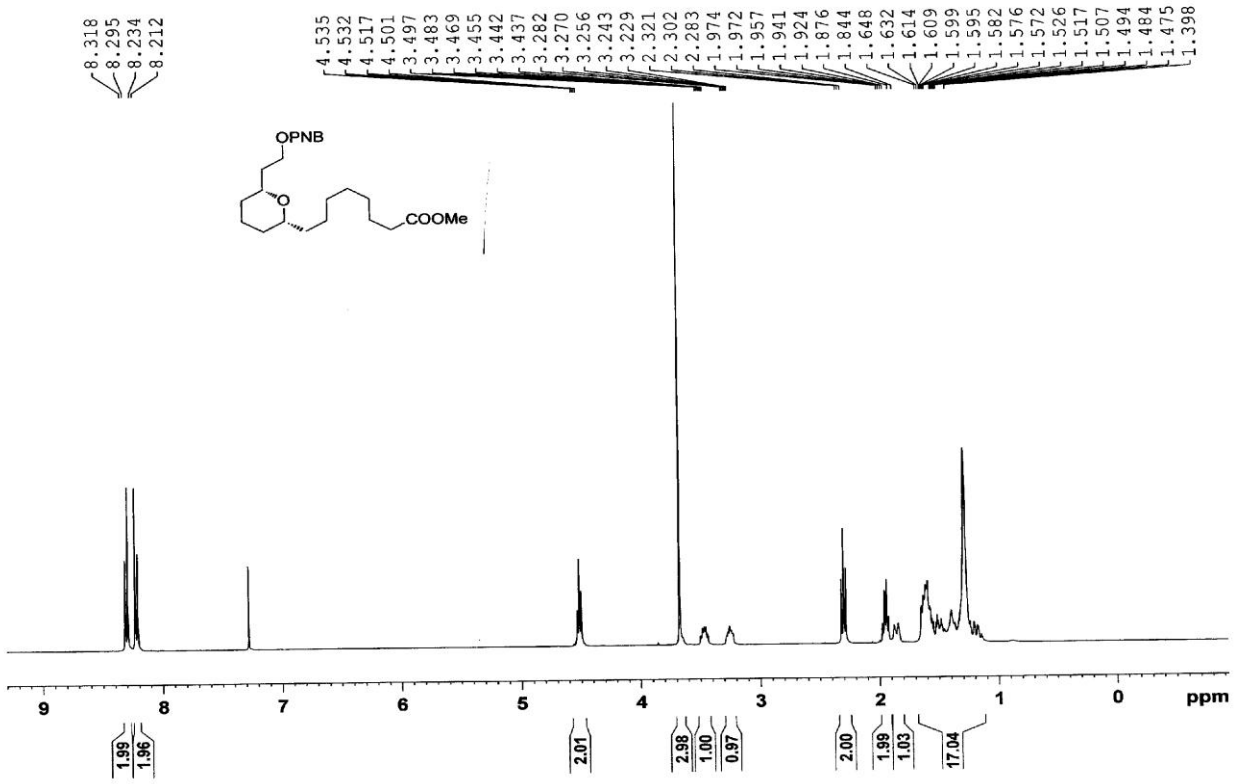

3.815
3.813
3.806
3.799
3.787
3.674
3.575
3.571
3.567
3.315
2.326
2.307
2.288
1.844
1.819
1.813
1.808
1.801
1.776
1.762
1.759
1.754
1.745
1.740
1.737
1.722
1.713
1.702
1.693
1.682
1.638
1.620
1.601
1.595
1.589
1.558
1.553
1.548
1.544
1.539
1.534
1.528
1.524
1.519
1.514
1.508
1.499
1.489
1.466
1.397
1.375
1.365
1.302
1.214
1.204
1.187
OH
O
COOMe
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
1.98
3.00
0.99
1.00
1.01
1.98
20.01

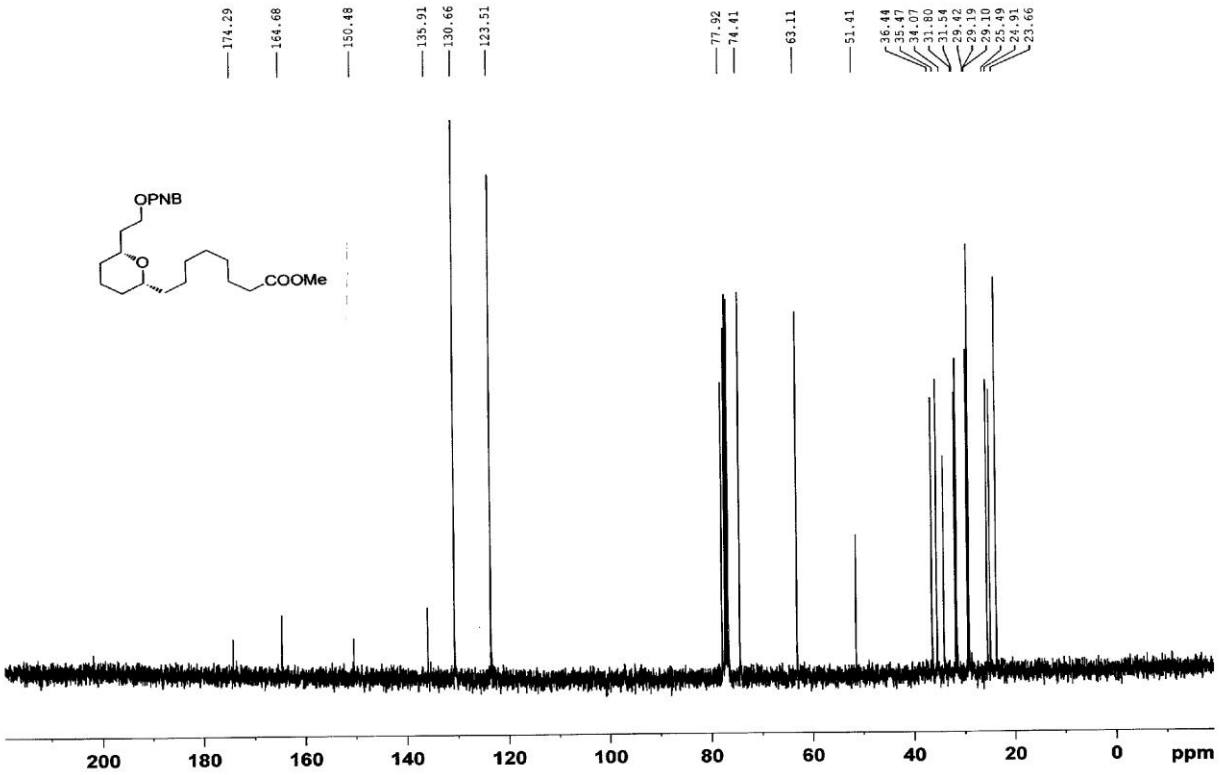

174.33
78.98
78.09
61.98
51.42
37.87
36.39
34.07
31.63
31.37
29.40
29.11
29.05
25.55
24.89
23.45
OH
O
COOMe
200
180
160
140
120
100
80
60
40
20
0
ppm

5.28e: *2-((2R,6R)-6-(8-methoxy-8-oxooctyl)tetrahydro-2H-pyran-2-yl)ethyl 4-nitrobenzoate*

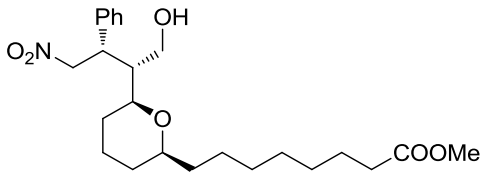


colorless oil. $[\alpha]_D^{23}$ = -20.7 (*c* 1.675, $CHCl_3$, 90% ee); IR (thin film, KBr): 2932, 2856, 1728, 16.9, 1530, 1437, 1350, 1280, 1103, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.9 Hz, 2H), 8.22 (d, *J* = 8.9 Hz, 2H), 4.53 (m, 2H), 3.67 (s, 3H), 3.46 (m, 1H), 3.26 (m, 1H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.94 (m, 2H), 1.87 (m, 1H), 1.70-1.13 (m, 17H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 164.7, 150.5, 135.9, 130.7, 123.5, 77.9, 74.4, 63.1, 51.4, 36.4, 35.5, 34.1, 31.8, 31.5, 29.4, 29.2, 29.1, 25.5, 24.9, 23.7 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 16.3 min, major enantiomer t_R = 19.2 min. LRMS (ESI) : $[M^+]$ calcd for $[C_{23}H_{33}NO_7]$: 435.2, found: 435.2.

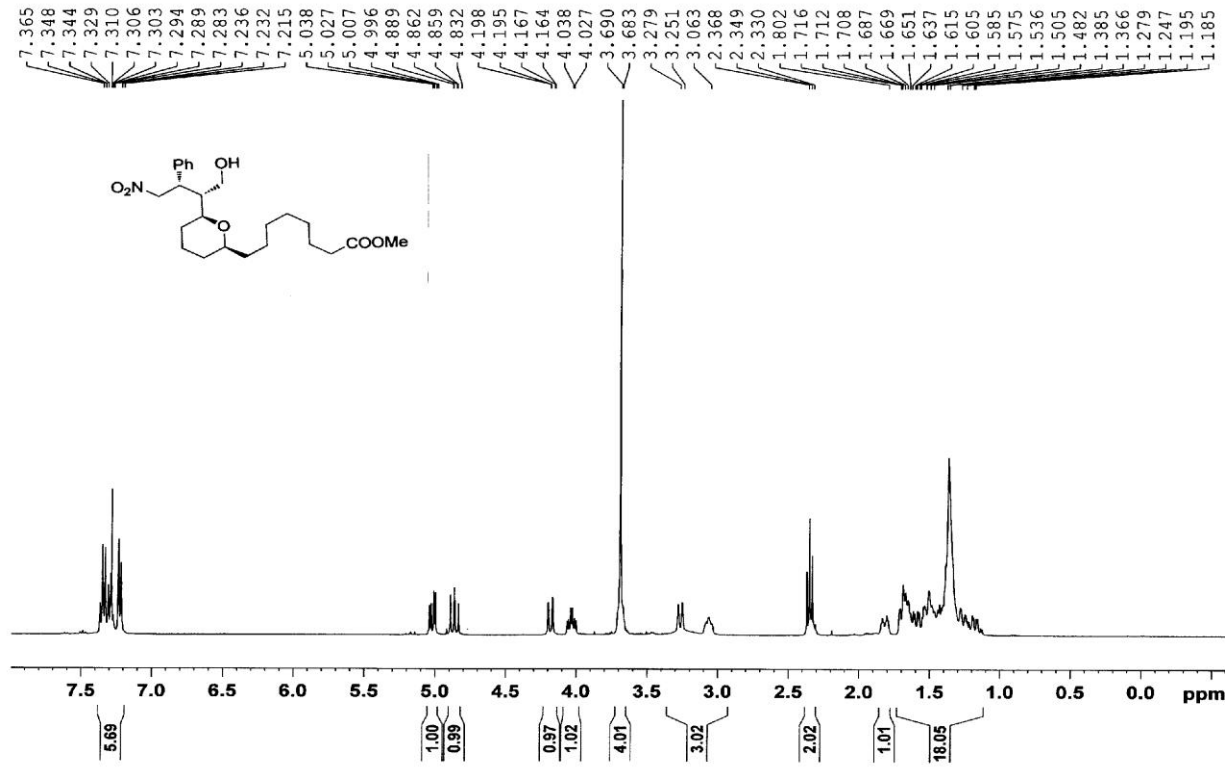

8.318
8.295
8.234
8.212
4.535
4.532
4.517
4.501
3.497
3.483
3.469
3.455
3.442
3.437
3.282
3.270
3.256
3.243
3.229
2.321
2.302
2.283
1.974
1.972
1.957
1.941
1.924
1.876
1.844
1.648
1.632
1.614
1.609
1.599
1.595
1.582
1.576
1.572
1.526
1.517
1.507
1.494
1.484
1.475
1.398
OPNB
O
COOMe
9
8
7
6
5
4
3
2
1
0
ppm
1.99
1.96
2.01
2.98
1.00
0.97
2.00
1.98
1.03
17.04

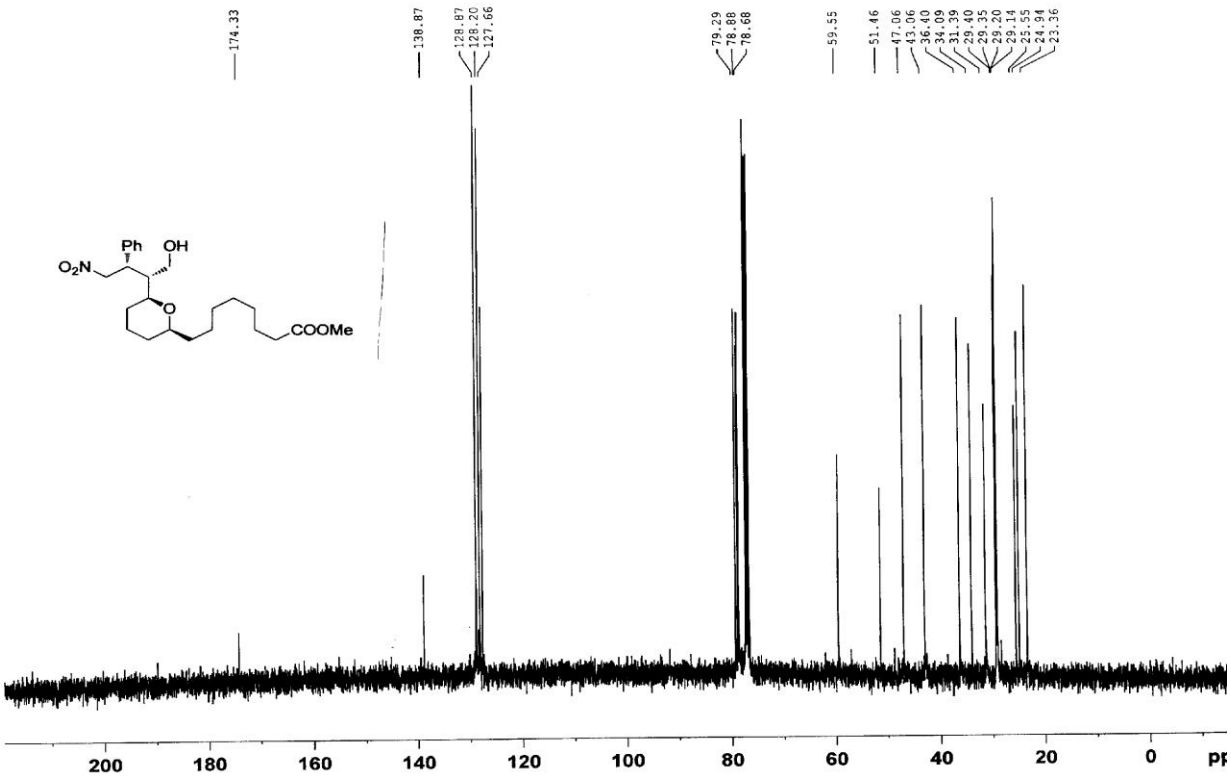

174.29
164.68
150.48
135.91
130.66
123.51
77.92
74.41
63.11
51.41
36.44
35.47
34.07
31.80
31.54
29.42
29.19
29.10
25.49
24.91
23.66
OPNB
O
COOMe
200
180
160
140
120
100
80
60
40
20
0
ppm

5.35e: *methyl-8-((2S,6S)-6-((2R,3S)-1-hydroxy-4-nitro-3-phenylbutan-2-yl)tetrahydro-2H-pyran 2-yl)octanoate*

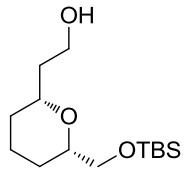


colorless oil. $[\alpha]_D^{24}$ = +19.0 (*c* 2.00, $CHCl_3$, 98% ee); IR (thin film, KBr): 3508, 2933, 2857, 1736, 1552, 1437, 1379, 1201, 1039, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.17 (m, 5H), 5.02 (dd, *J* = 12.3, 4.5 Hz, 1H), 4.86 (dd, *J* = 12.3, 10.7 Hz, 1H), 4.18 (dd, *J* = 12.4, 1.3 Hz, 1H), 4.03 (td, *J* = 10.4, 4.5 Hz, 1H), 3.69 (s, 3H), 3.68 (m, 1H), 3.35-2.94 (m, 3H), 2.35 (t, *J* = 7.6 Hz, 2H), 1.82 (m, 1H), 1.75-1.10 (m, 18H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 138.9, 1283.9, 128.2, 127.7, 79.3, 78.9, 78.7, 59.6, 51.5, 47.1, 43.1, 36.4, 34.1, 31.4, 29.4, 29.4, 29.2, 29.1, 25.6, 24.9, 23.4 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 24.3 min, major enantiomer t_R = 34.5 min. LRMS (ESI) : $[M^+]$ calcd for $[C_{24}H_{37}NO_6]$: 435.3, found: 435.3.

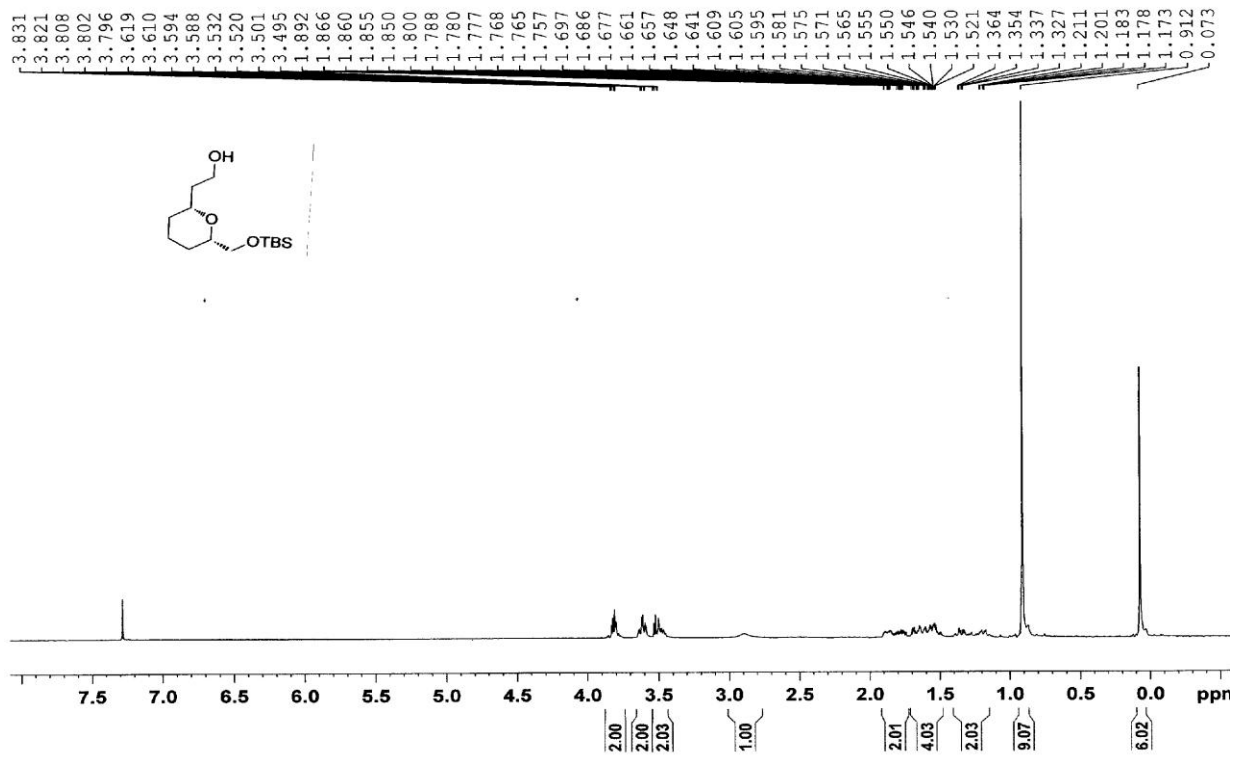

7.365
7.348
7.344
7.329
7.310
7.306
7.303
7.294
7.289
7.283
7.236
7.232
7.215
5.038
5.027
5.007
4.996
4.889
4.862
4.859
4.832
4.198
4.195
4.167
4.164
4.038
4.027
3.690
3.683
3.279
3.251
3.063
2.368
2.349
2.330
1.802
1.716
1.712
1.708
1.687
1.669
1.651
1.637
1.615
1.605
1.585
1.575
1.536
1.505
1.482
1.385
1.366
1.279
1.247
1.195
1.185
Ph
OH
O2N
O
COOMe
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
ppm
5.69
1.00
0.99
0.97
1.02
4.01
3.02
2.02
1.01
18.05

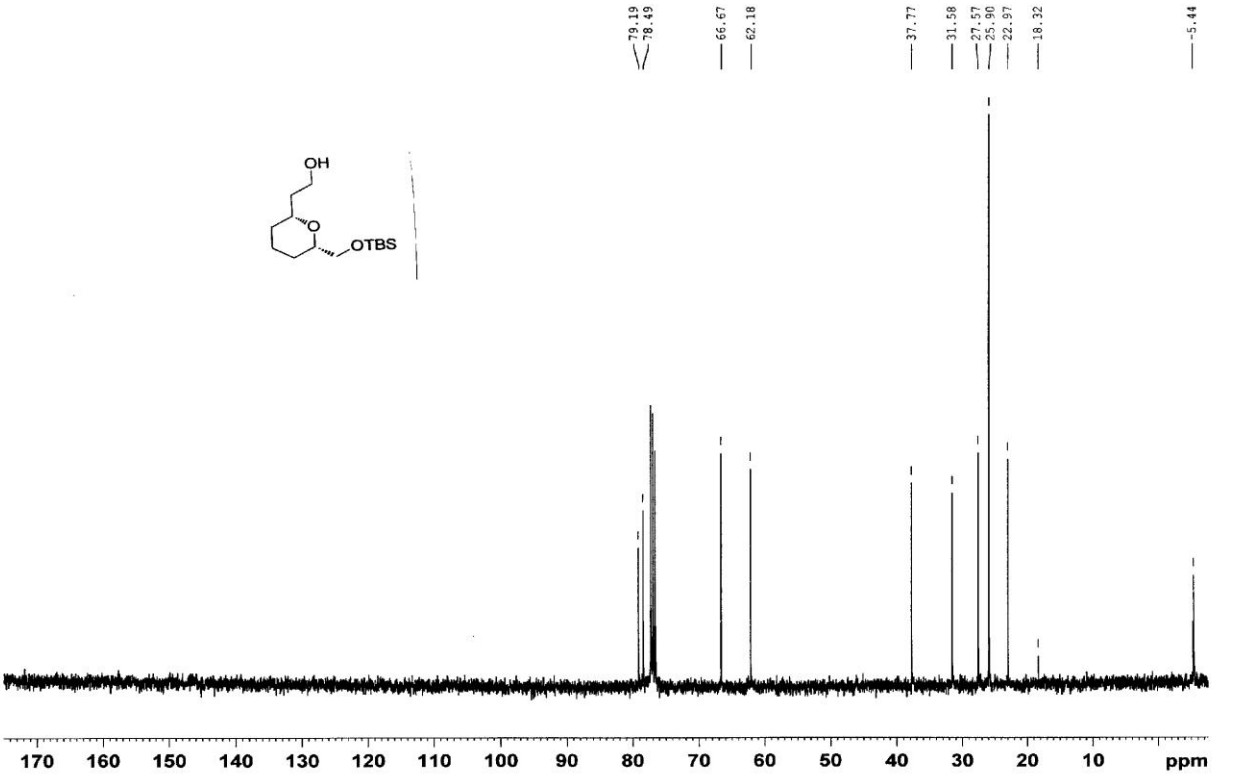

174.33
138.87
128.87
128.20
127.66
79.29
78.88
78.68
59.55
51.46
47.06
43.06
36.40
34.09
31.39
29.40
29.35
29.20
29.14
25.55
24.94
23.36
Ph
OH
O2N
O
COOMe
200
180
160
140
120
100
80
60
40
20
0

5.34f: *2-((2R,6S)-6-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)ethanol*

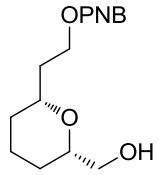


colorless oil. $[\alpha]_D^{23}$ = -7.8 (*c* 2.00, $CHCl_3$, 96% ee); IR (thin film, KBr): 3438, 2931, 2857, 1252, 1114, 1081, 837, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (m, 2H), 3.60 (m, 2H), 3.51 (m, 2H), 2.89 (bs, 1H), 1.92-1.72 (m, 2H), 1.71-1.48 (m, 4H), 1.41-1.13 (m, 2H), 0.91 (s, 9H), 0.07 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.2, 78.5, 66.7, 62.2, 37.8, 31.6, 27.6, 25.9, 23.0, 18.3, -5.4 ppm; LRMS (ESI) : [M^+] calcd for [$C_{14}H_{30}O_3Si$]: 274.2, found: 274.2.

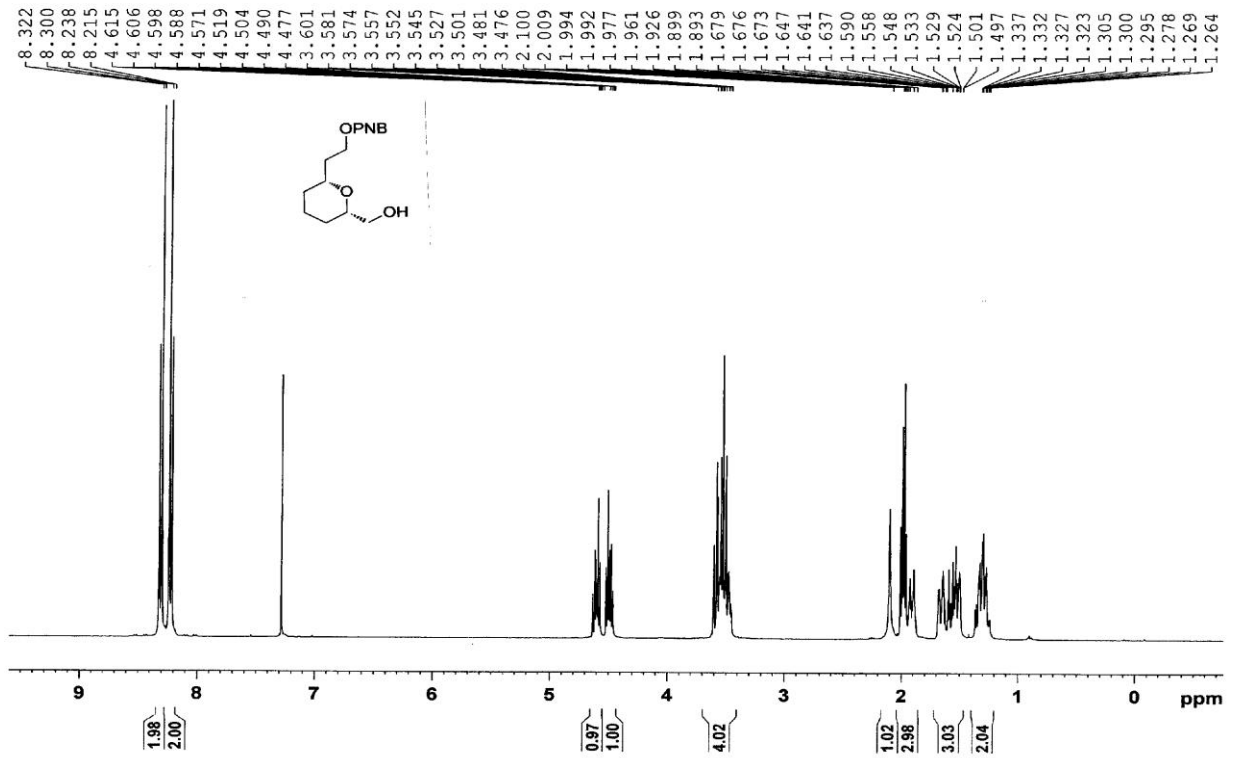

3.831
3.821
3.808
3.802
3.796
3.619
3.610
3.594
3.588
3.532
3.520
3.501
3.495
1.892
1.866
1.860
1.855
1.850
1.800
1.788
1.780
1.777
1.768
1.765
1.757
1.697
1.686
1.677
1.661
1.657
1.648
1.641
1.609
1.605
1.595
1.581
1.575
1.571
1.565
1.555
1.550
1.546
1.540
1.530
1.521
1.364
1.354
1.337
1.327
1.211
1.201
1.183
1.178
1.173
0.912
0.073
OH
O
OTBS
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
ppm
2.00
2.00
2.03
1.00
2.01
4.03
2.03
9.07
6.02

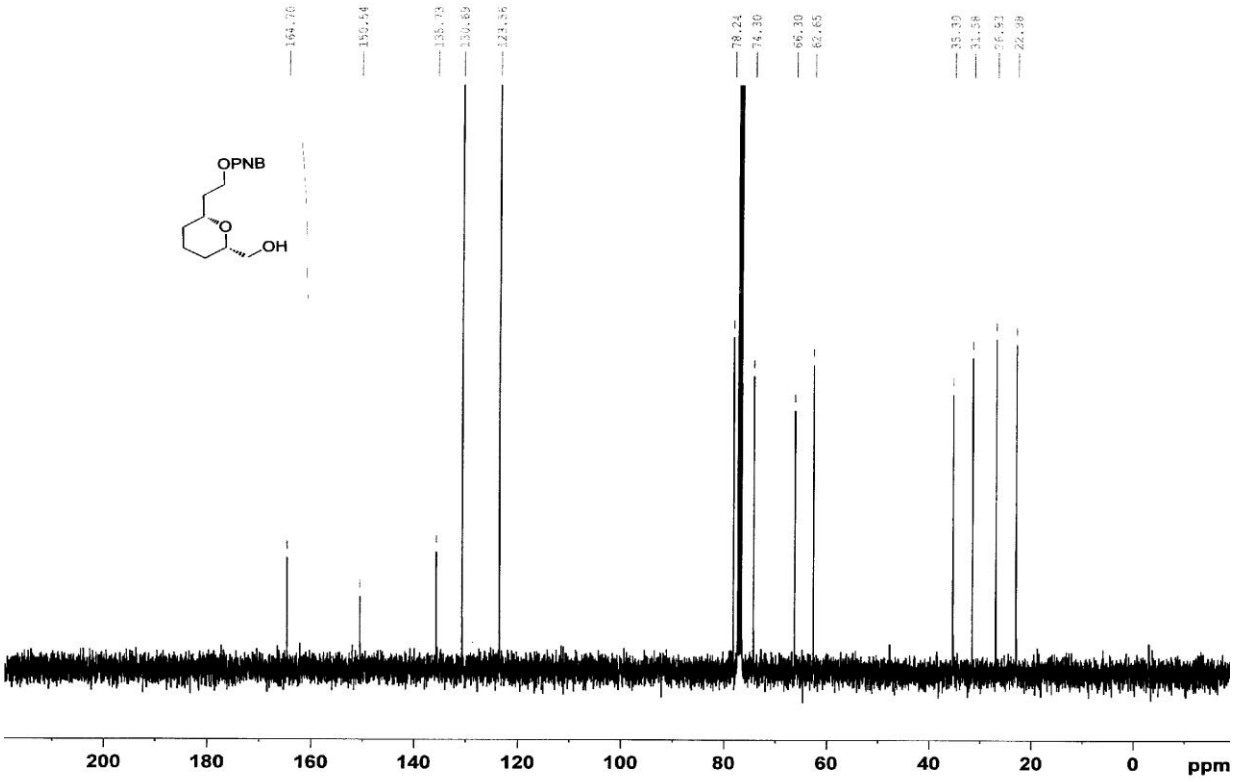

79.19
78.49
66.67
62.18
37.77
31.58
27.57
25.90
22.97
18.32
-5.44
OH
O
OTBS
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

6.2f: *2-((2R,6S)-6-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)ethyl 4-nitrobenzoate*

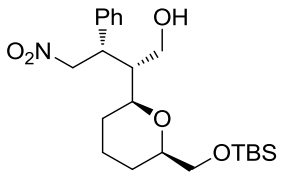


colorless amorphous solid. $[\alpha]_D^{23}$ = -31.5 (*c* 0.820, $CHCl_3$, 96% ee); IR (thin film, KBr): 3436, 2936, 2859, 1724, 1528, 1280, 1104, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.9 Hz, 2H), 8.23 (d, *J* = 8.9 Hz, 2H), 4.60 (m, 1H), 4.50 (m, 1H), 3.65-3.43 (m, 4H), 2.10 (bs, 1H), 2.05-1.85 (m, 3H), 1.70-1.46 (m, 3H), 1.40-1.21 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 150.5, 135.7, 130.7, 123.6, 78.2, 74.3, 66.3, 62.7, 35.4, 31.6, 26.9, 23.0 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 45.5 min, major enantiomer t_R = 51.4 min. LRMS (ESI) : $[M^+]$ calcd for $[C_{15}H_{19}NO_6]$: 309.1, found: 309.1.

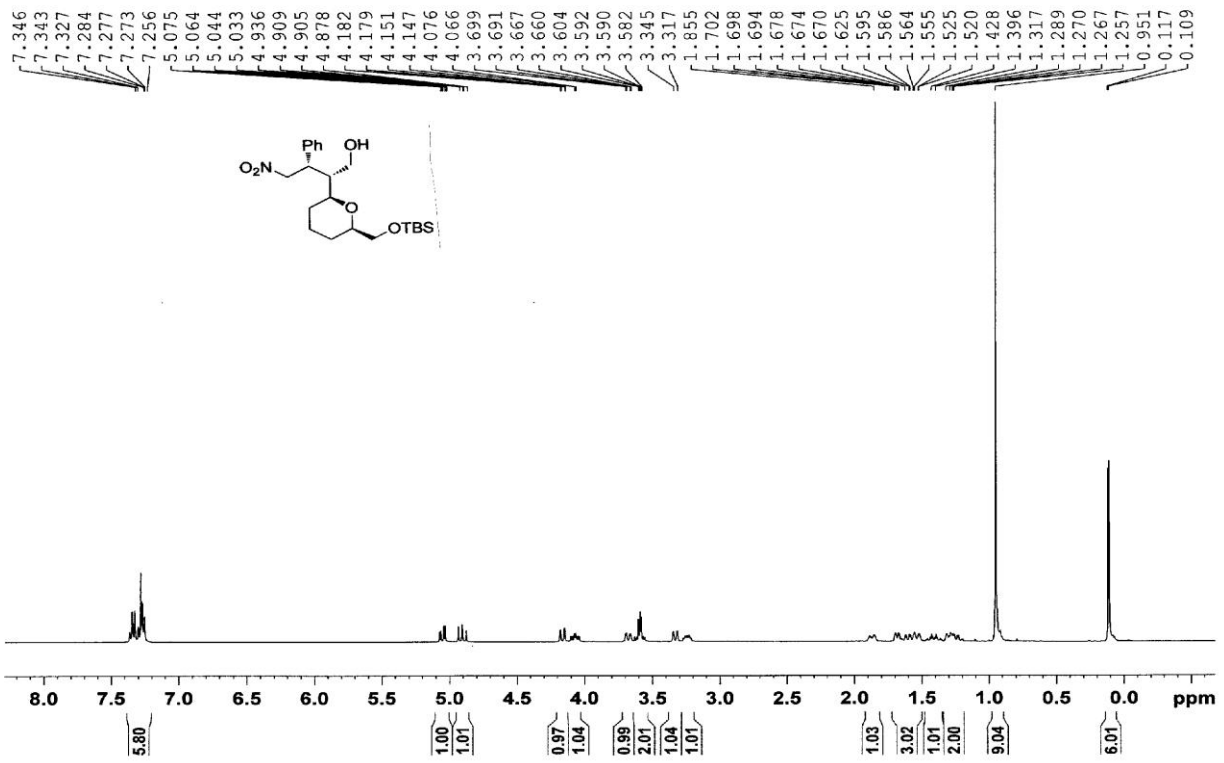

8.322
8.300
8.238
8.215
4.615
4.606
4.598
4.588
4.571
4.519
4.504
4.490
4.477
3.601
3.581
3.574
3.557
3.552
3.545
3.527
3.501
3.481
3.476
2.100
2.009
1.994
1.992
1.977
1.961
1.926
1.899
1.893
1.679
1.676
1.673
1.647
1.641
1.637
1.590
1.558
1.548
1.533
1.529
1.524
1.501
1.497
1.337
1.332
1.327
1.323
1.305
1.300
1.295
1.278
1.269
1.264
OPNB
O
OH
9
8
7
6
5
4
3
2
1
0
ppm
1.98
2.00
0.97
1.00
4.02
1.02
2.98
3.03
2.04

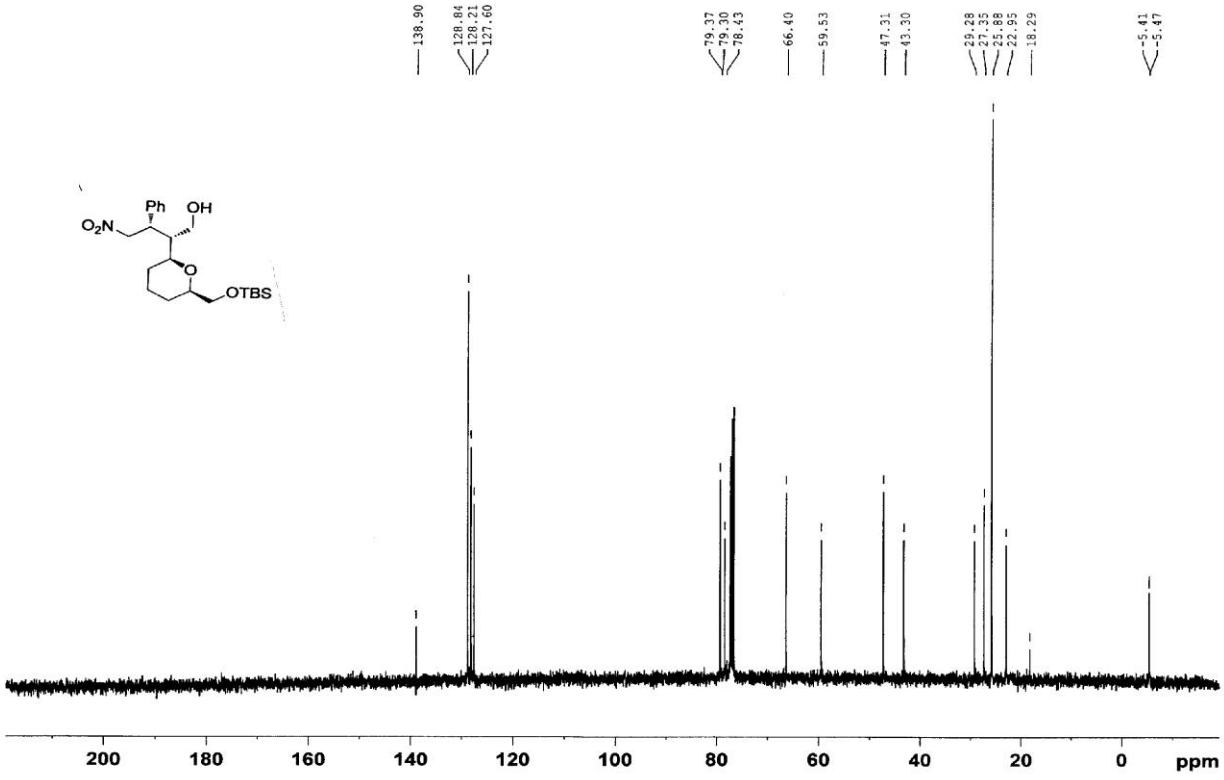

164.70
150.54
135.73
130.89
123.56
78.24
74.30
66.30
62.65
35.30
31.58
26.92
22.30
OPNB
O
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

5.35f: *(2R,3S)-2-((2S,6R)-6-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)-4-nitro-3-phenylbutan-1-ol*

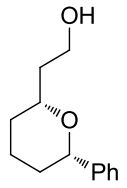


colorless oil. $[\alpha]_D^{24}$ = +21.7 (*c* 2.00, $CHCl_3$, 98% ee); IR (thin film, KBr): 3514, 2930, 2858, 1553, 1380, 1256, 1078, 838, 778, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H), 5.05 (dd, *J* = 12.3, 4.6 Hz, 1H), 4.91 (dd, *J* = 12.3, 10.8 Hz, 1H), 4.17 (dd, *J* = 12.4, 1.4 Hz, 1H), 4.07 (td, *J* = 10.4, 4.6 Hz, 1H), 3.68 (m, 1H), 3.59 (m, 2H), 3.33 (m, 1H), 3.25 (m, 1H), 1.87 (m, 1H), 1.72-1.50 (m, 3H), 1.41 (m, 1H), 1.30 (m, 2H), 0.95 (s, 9H), 0.10 (d, *J* = 3.4 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 128.8, 128.2, 127.6, 79.4, 79.3, 78.4, 66.4, 59.5, 47.3, 43.3, 29.3, 27.4, 25.9, 23.0, 18.3, -5.4, -5.5 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 95:5), 0.5 mL/min; major enantiomer t_R = 11.1 min, minor enantiomer t_R = 13.1 min. LRMS (ESI) : $[M^+]$ calcd for $[C_{22}H_{37}NO_5Si]$: 423.2, found: 423.2.

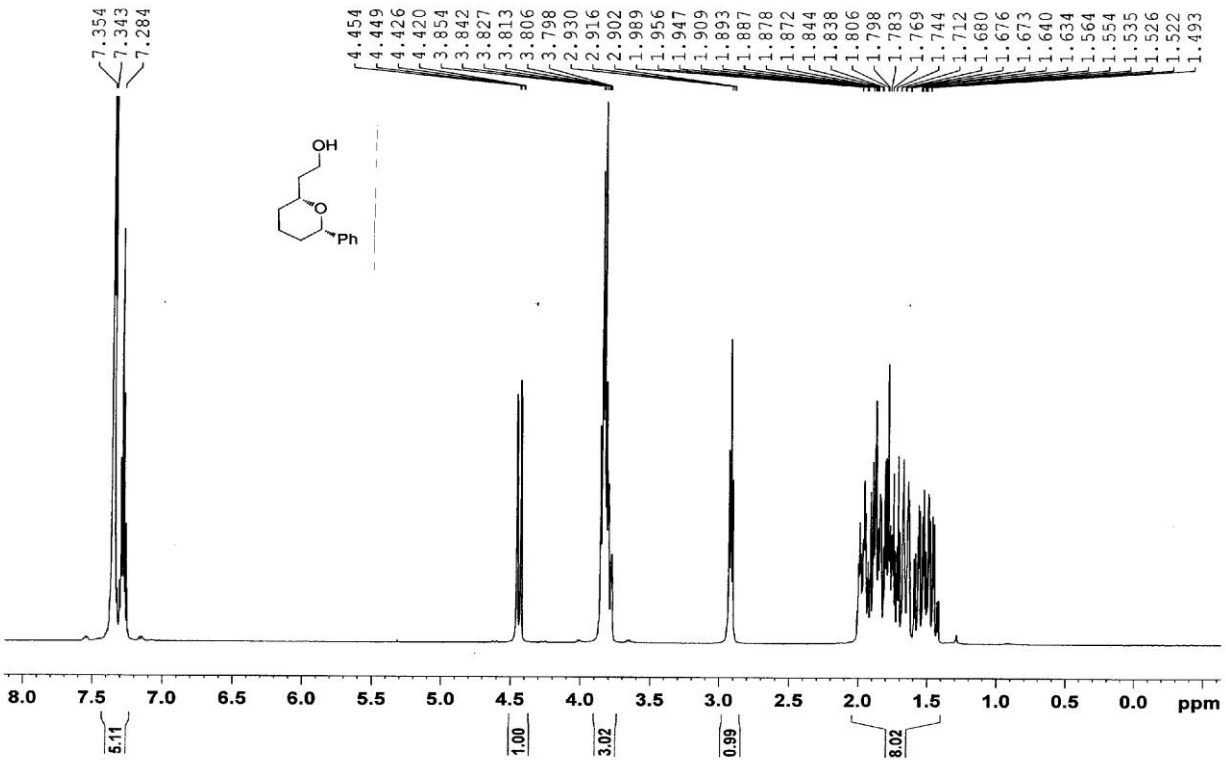

7.346
7.343
7.327
7.284
7.277
7.273
7.256
5.075
5.064
5.044
5.033
4.936
4.909
4.905
4.878
4.182
4.179
4.151
4.147
4.076
4.066
3.699
3.691
3.667
3.660
3.604
3.592
3.590
3.582
3.345
3.317
1.855
1.702
1.698
1.694
1.678
1.674
1.670
1.625
1.595
1.586
1.564
1.555
1.525
1.520
1.428
1.396
1.317
1.289
1.270
1.267
1.257
0.951
0.117
0.109
Ph
OH
O2N
O
OTBS
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
ppm
5.80
1.00
1.01
0.97
1.04
0.98
2.01
1.04
1.01
1.03
3.02
1.01
2.00
9.04
6.01

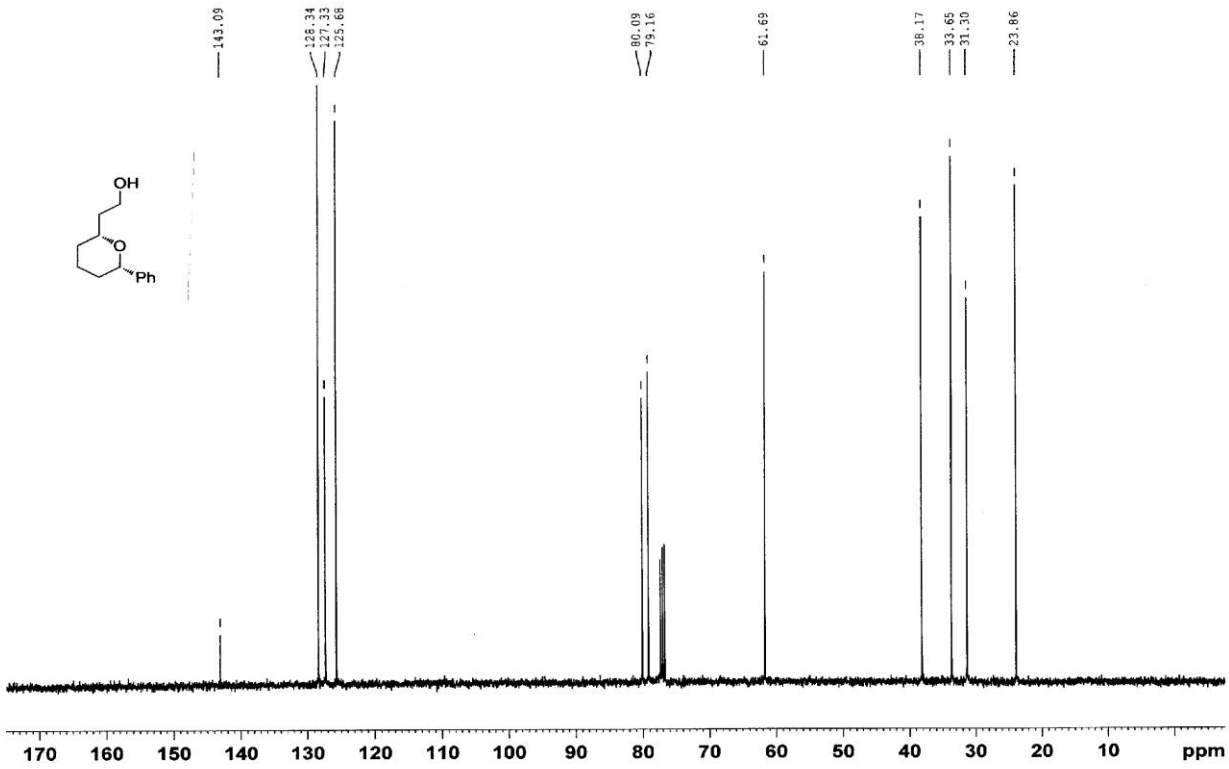

138.90
128.84
128.21
127.60
79.37
79.30
78.43
66.40
59.53
47.31
43.30
29.28
27.35
25.88
22.95
18.29
-5.41
-5.47
Ph
OH
O2N
O
OTBS
200
180
160
140
120
100
80
60
40
20
0
ppm

5.34g: *2-((2R,6S)-6-phenyltetrahydro-2H-pyran-2-yl)ethanol*[15]

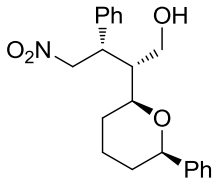


colorless oil. $[\alpha]_D^{23}$ = -89.1 (*c* 0.600, $CHCl_3$, 80% ee); IR (thin film, KBr): 3352, 2934, 2857, 1452, 1083, 1042, 753, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.23 (m, 5H), 4.44 (dd, *J* = 11.3, 2.2 Hz, 1H), 3.90-3.75 (m, 3H), 2.92 (t, *J* = 5.4 Hz, 1H), 2.05-1.40 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 128.3, 127.3, 125.7, 80.1, 79.2, 61.7, 38.2, 33.7, 31.3, 23.9 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; minor enantiomer t_R = 5.9 min, major enantiomer t_R = 6.7 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{13}H_{18}O_2]$: 206.1307, found: 206.1308.

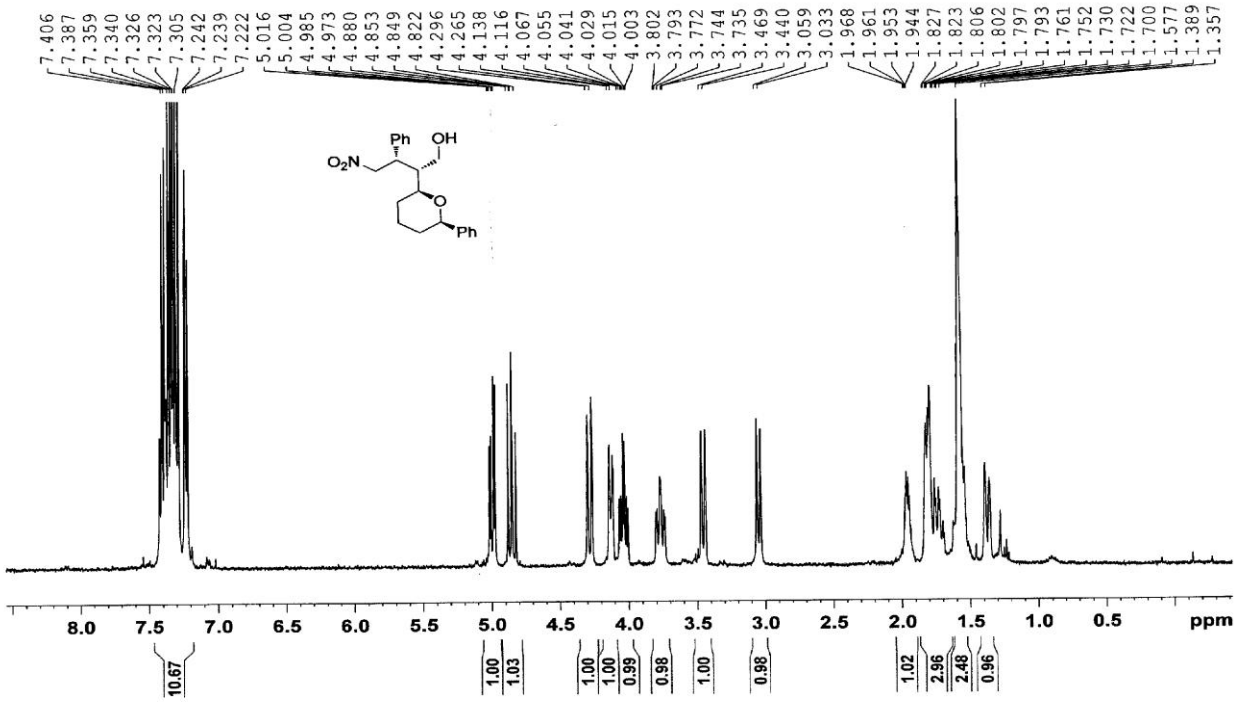

7.354
7.343
7.284
4.454
4.449
4.426
4.420
3.854
3.842
3.827
3.813
3.806
3.798
2.930
2.916
2.902
1.989
1.956
1.947
1.909
1.893
1.887
1.878
1.872
1.844
1.838
1.806
1.798
1.783
1.769
1.744
1.712
1.680
1.676
1.673
1.640
1.634
1.564
1.554
1.535
1.526
1.522
1.493
OH
O
Ph
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
5.11
1.00
3.02
0.99
8.02

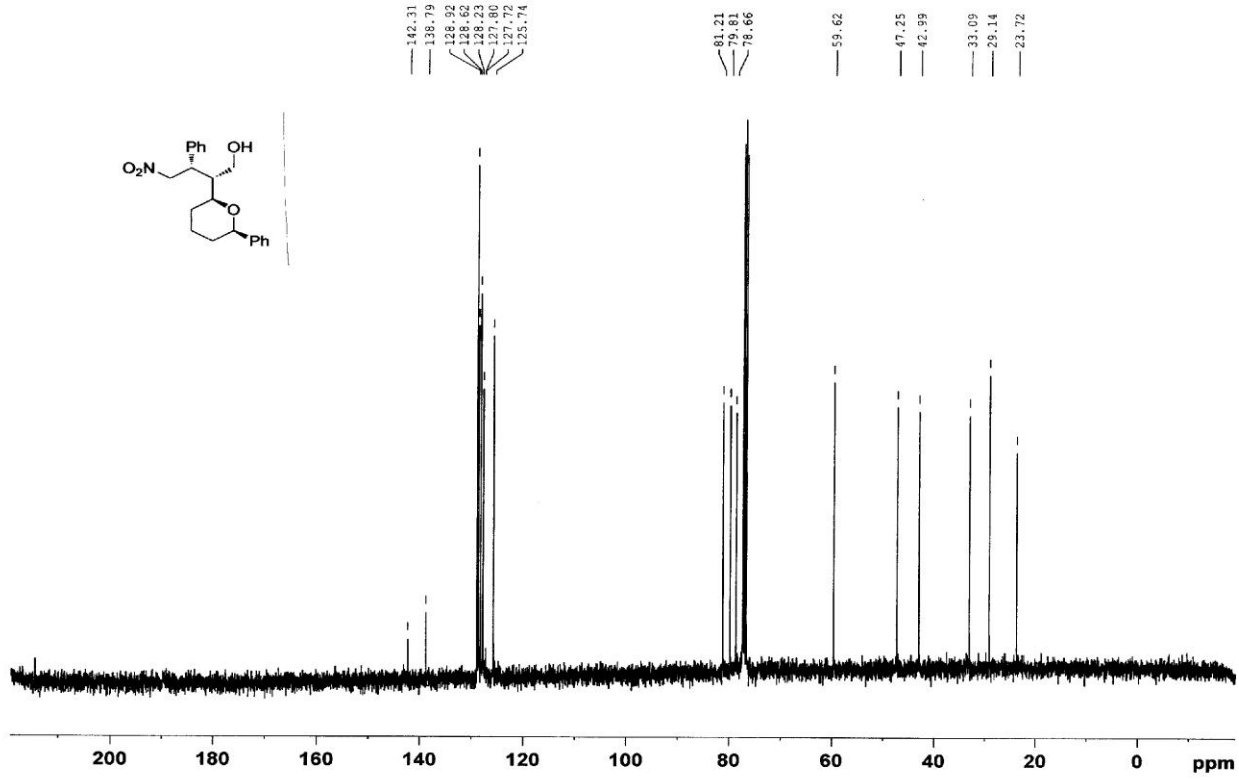

143.09
128.34
127.33
125.68
80.09
79.16
61.69
38.17
33.65
31.30
23.86
OH
O
Ph
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

5.35g: *(2R,3S)-4-nitro-3-phenyl-2-((2S,6R)-6-phenyltetrahydro-2H-pyran-2-yl)butan-1-ol*

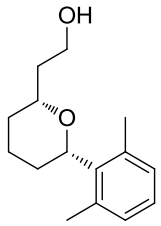


colorless amorphous solid. $[\alpha]_D^{22}$ = +116.6 (*c* 1.25, $CHCl_3$, 97% ee); IR (thin film, KBr): 3455, 1636, 1551, 1039, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.18 (m, 10H), 4.99 (dd, *J* = 12.3, 4.6 Hz, 1H), 4.85 (dd, *J* = 12.3, 10.8 Hz, 1H), 4.28 (d, 1H), 4.12 (m, 1H), 4.02 (td, *J* = 10.4, 4.6 Hz, 1H), 3.79 (m, 1H), 3.46 (d, *J* = 11.5 Hz, 1H), 3.05 (d, *J* = 10.7 Hz, 1H), 1.95 (m, 1H), 1.88-1.67 (m, 3H), 1.66-1.1.49 (m, 2H), 1.37 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 138.8, 128.9, 128.6, 128.2, 127.8, 127.7, 125.7, 81.2, 79.8, 78.7, 59.6, 47.3, 43.0, 33.1, 29.1, 23.7 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 23.3 min, major enantiomer t_R = 24.5 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{21}H_{25}NO_4]$: 355.1784, found: 355.1785.

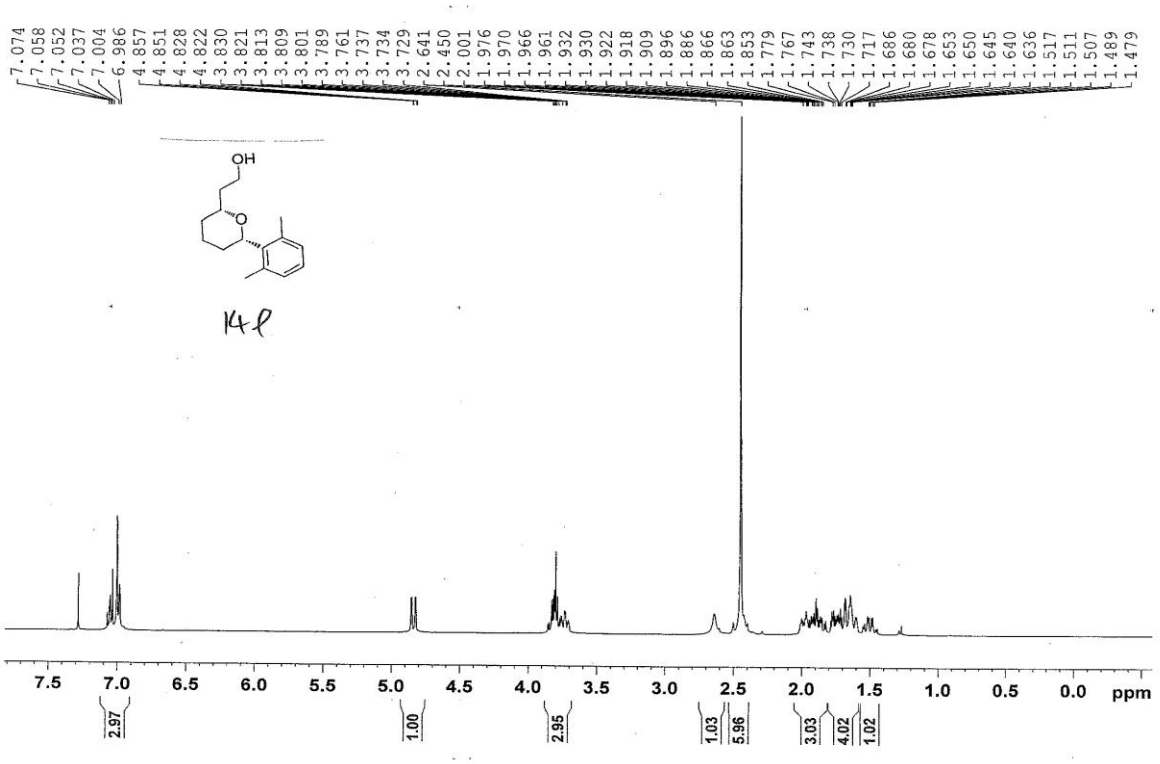

7.406
7.387
7.359
7.340
7.326
7.323
7.305
7.242
7.239
7.222
5.016
5.004
4.985
4.973
4.880
4.853
4.849
4.822
4.296
4.265
4.138
4.116
4.067
4.055
4.041
4.029
4.015
4.003
3.802
3.793
3.772
3.744
3.735
3.469
3.440
3.059
3.033
1.968
1.961
1.953
1.944
1.827
1.823
1.806
1.802
1.797
1.793
1.761
1.752
1.730
1.722
1.700
1.577
1.389
1.357
Ph
OH
O2N
O
Ph
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
ppm
10.67
1.00
1.03
1.00
1.00
0.99
0.98
1.00
0.98
1.02
2.96
2.48
0.96

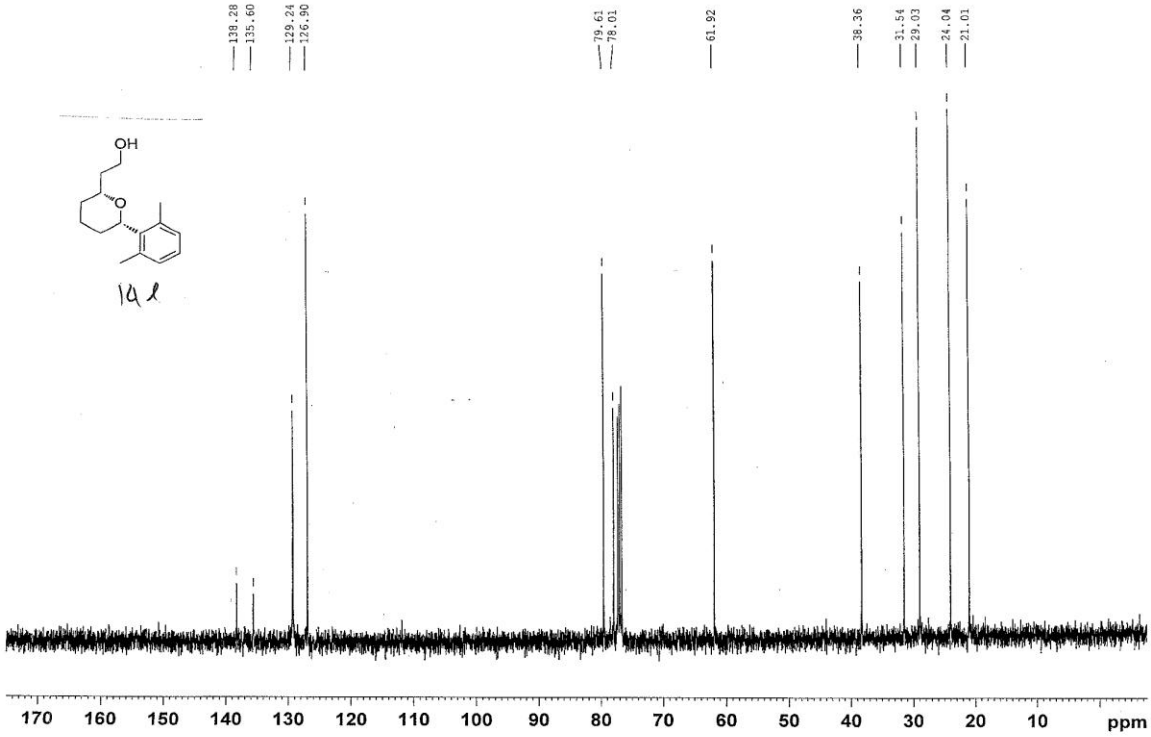

142.31
138.79
128.92
128.62
128.23
127.80
127.72
125.74
81.21
79.81
78.66
59.62
47.25
42.99
33.09
29.14
23.72
Ph
OH
O2N
O
Ph
200
180
160
140
120
100
80
60
40
20
0
ppm

5.34h: *2-((2R,6S)-6-(2,6-dimethylphenyl)tetrahydro-2H-pyran-2-yl)ethanol*

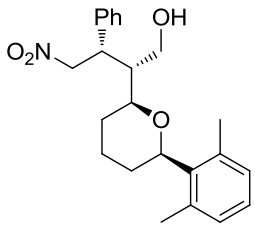


colorless oil. $[\alpha]_D^{23}$ = -59.1 (*c* 0.800, $CHCl_3$, 52% ee); IR (thin film, KBr): 3394, 2936, 2857, 1378, 1207, 1079, 1041, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10-6.95 (m, 3H), 4.84 (dd, *J* = 11.6, 2.5 Hz, 1H), 3.86-3.69 (m, 3H), 2.64 (bs, 1H), 2.45 (s, 6H), 2.04-1.80 (m, 3H), 1.79-1.56 (m, 4H), 1.50 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 135.6, 129.2, 126.9, 79.6, 78.0, 61.9, 38.4, 31.5, 29.0, 24.0, 21.0 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 99:1), 0.5 mL/min; major enantiomer t_R = 34.8 min, minor enantiomer t_R = 37.4 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{15}H_{22}O_2]$: 234.1620, found: 234.1623.

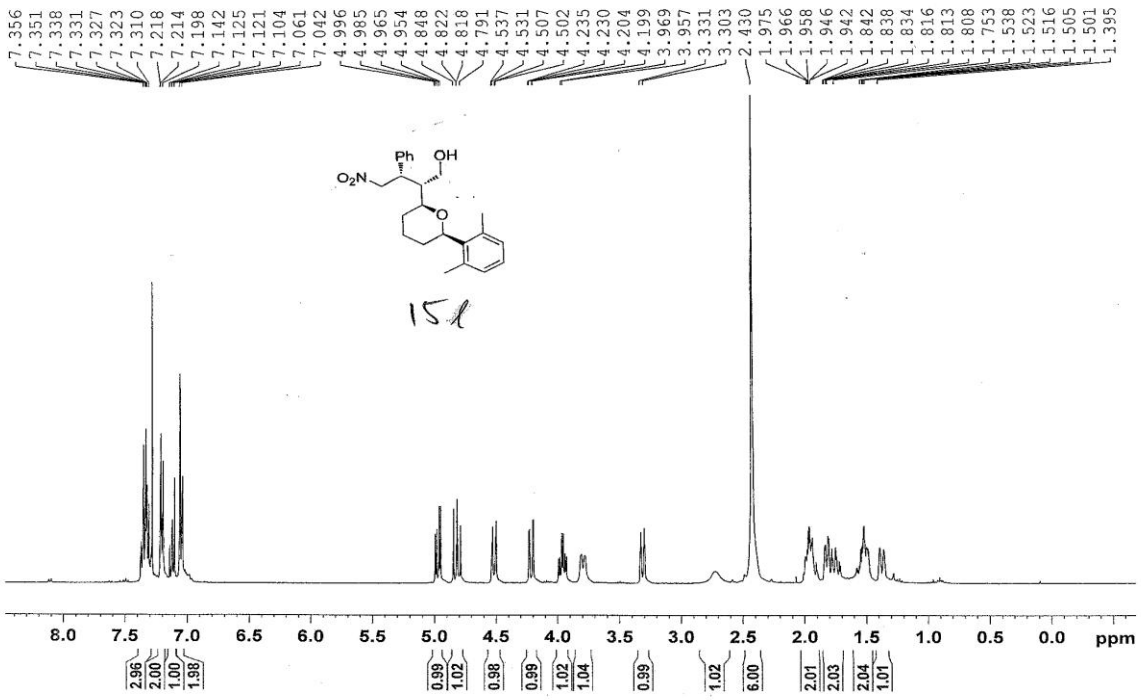

7.074
7.058
7.052
7.037
7.004
6.986
4.857
4.851
4.828
4.822
3.830
3.821
3.813
3.809
3.801
3.789
3.761
3.737
3.734
3.729
2.641
2.450
2.001
1.976
1.970
1.966
1.961
1.932
1.930
1.922
1.918
1.909
1.896
1.886
1.866
1.863
1.853
1.779
1.767
1.743
1.738
1.730
1.717
1.686
1.680
1.678
1.653
1.650
1.645
1.640
1.636
1.517
1.511
1.507
1.489
1.479
OH
O
14l
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
ppm
2.97
1.00
2.95
1.03
5.96
3.03
4.02
1.02

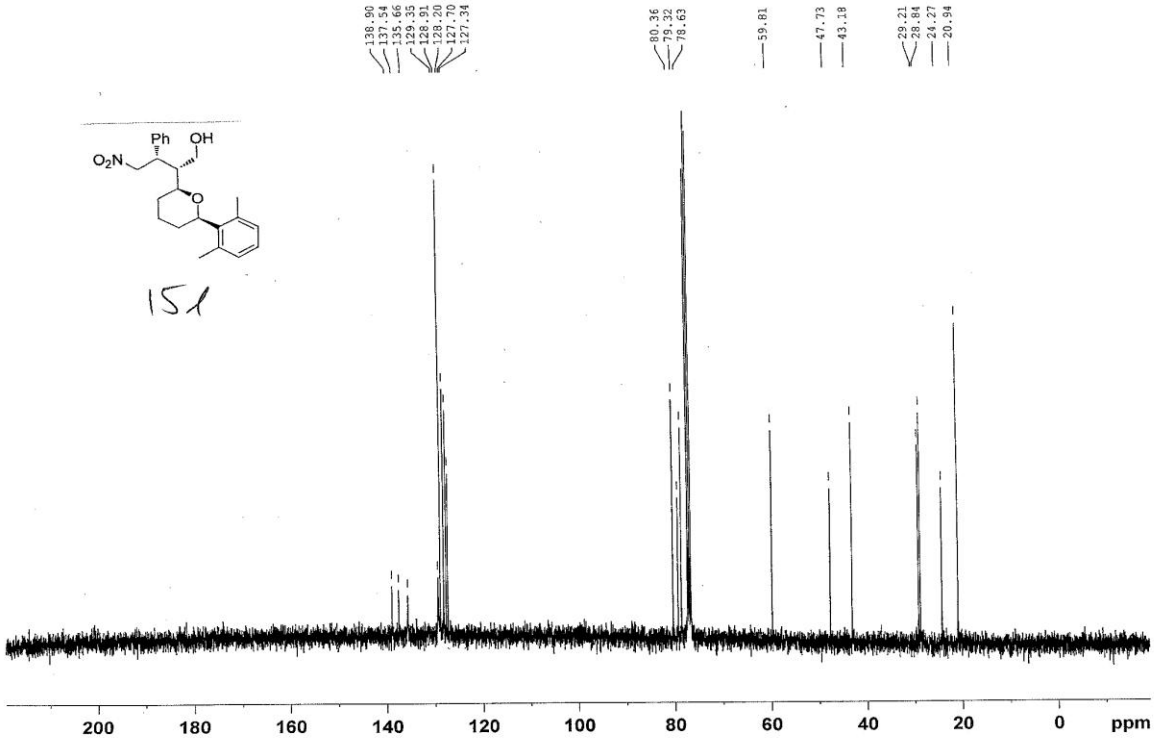

138.28
135.60
129.24
126.90
79.61
78.01
61.92
38.36
31.54
29.03
24.04
21.01
OH
O
14l
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

5.35h: *(2R,3S)-2-((2S,6R)-6-(2,6-dimethylphenyl)tetrahydro-2H-pyran-2-yl)-4-nitro-3-phenylbutan-1-ol*

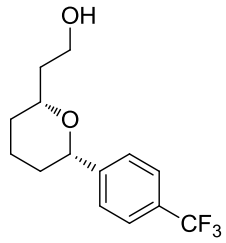


colorless amorphous solid. $[\alpha]_D^{23}$ = +83.4 (*c* 1.50, $CHCl_3$, 99% ee); IR (thin film, KBr): 3455, 2938, 1736, 1552, 1379, 1075, 1036, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-6.95 (m, 8H), 4.97 (dd, *J* = 12.3, 4.6 Hz, 1H), 4.82 (dd, *J* = 12.3, 10.8 Hz, 1H), 4.52 (dd, *J* = 11.9, 2.5 Hz, 1H), 4.22 (dd, *J* = 12.2, 2.1 Hz, 1H), 3.96 (td, *J* = 10.4, 4.6 Hz, 1H), 3.80 (m, 1H), 3.32 (m, 1H), 2.63 (bs, 1H), 2.43 (s, 6H), 2.04-1.86 (m, 2H), 1.85-1.71 (m, 2H), 1.64-1.43 (m, 2H), 1.38 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 137.5, 135.7, 129.4, 128.9, 128.2, 127.7, 127.3, 80.4, 79.3, 78.6, 59.8, 47.7, 43.2, 29.2, 28.8, 24.3, 20.9 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 95:5), 0.5 mL/min; minor enantiomer t_R = 29.7 min, major enantiomer t_R = 33.9 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{23}H_{29}NO_4]$: 383.2097, found: 283.2098.

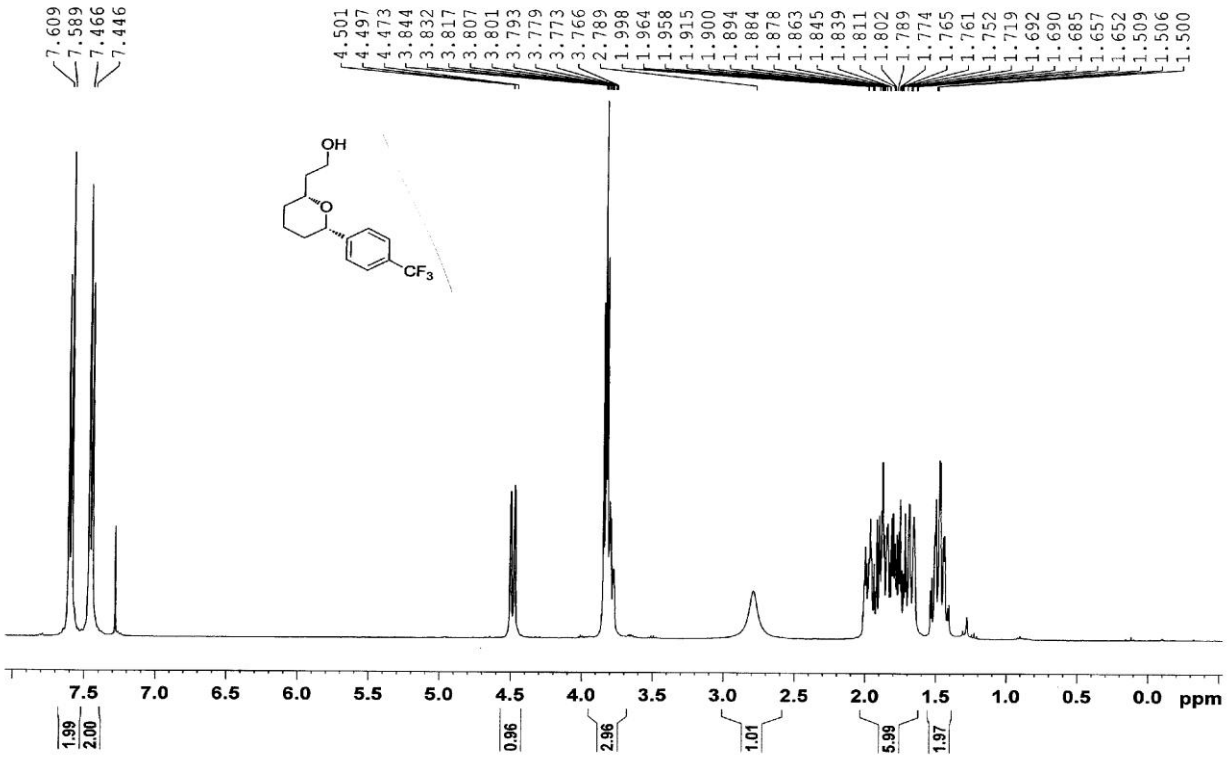

7.356
7.351
7.338
7.331
7.327
7.323
7.310
7.218
7.214
7.198
7.142
7.125
7.121
7.104
7.061
7.042
4.996
4.985
4.965
4.954
4.848
4.822
4.818
4.791
4.537
4.531
4.507
4.502
4.235
4.230
4.204
4.199
3.969
3.957
3.331
3.303
2.430
1.975
1.966
1.958
1.946
1.942
1.842
1.838
1.834
1.816
1.813
1.808
1.753
1.538
1.523
1.516
1.505
1.501
1.395
Ph
OH
O2N
O
151
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
ppm
2.96
2.00
1.00
1.98
0.99
1.02
0.98
0.99
1.02
1.04
0.99
1.02
6.00
2.01
2.03
2.04
1.01

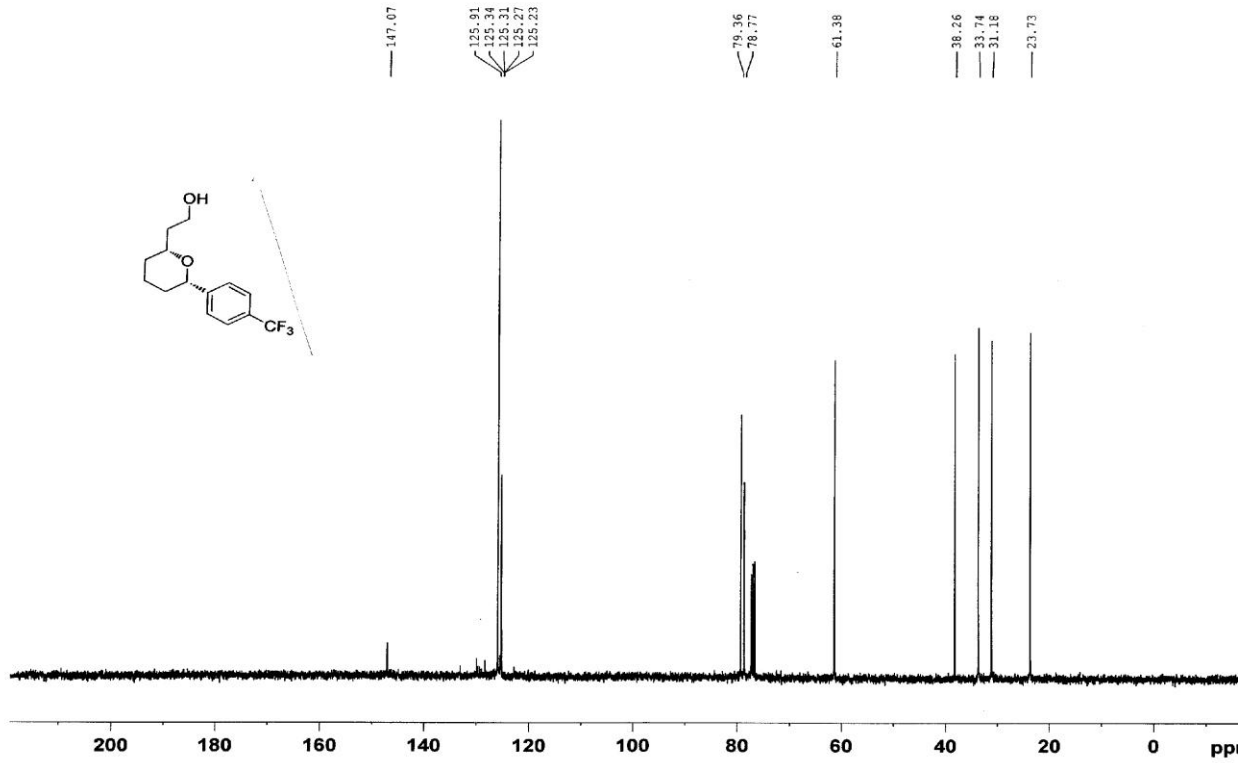

138.90
137.54
135.66
129.35
128.91
128.20
127.70
127.34
80.36
79.32
78.63
59.81
47.73
43.18
29.21
28.84
24.27
20.94
Ph
OH
O2N
O
151
200
180
160
140
120
100
80
60
40
20
0
ppm

5.34i: *2-((2R,6S)-6-(4-(trifluoromethyl)phenyl)tetrahydro-2H-pyran-2-yl)ethanol*

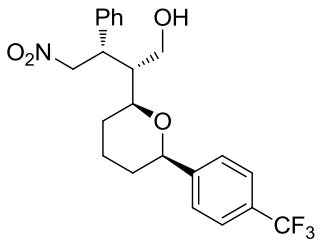


colorless oil. $[\alpha]_D^{21}$ = -96.1 (*c* 0.500, $CHCl_3$, 90% ee); IR (thin film, KBr): 3355, 2940, 2861, 1623, 1325, 1163, 1124, 1067, 1017, 839, 662, 603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 4.48 (m, 1H), 3.83 (t, *J* = 5.2 Hz, 2H), 3.84-3.75 (m, 1H), 2.79 (bs, 1H), 2.04-1.61 (m, 6H), 1.55-1.38 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 125.9, 125.3, 125.3, 125.3, 125.2, 79.4, 78.8, 61.4, 38.3, 33.7, 31.2, 23.7 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 9.4 min, major enantiomer t_R = 10.0 min. LRMS (ESI) : $[M^+]$ calcd for $[C_{14}H_{17}F_3O_2]$: 274.1, found: 274.1.

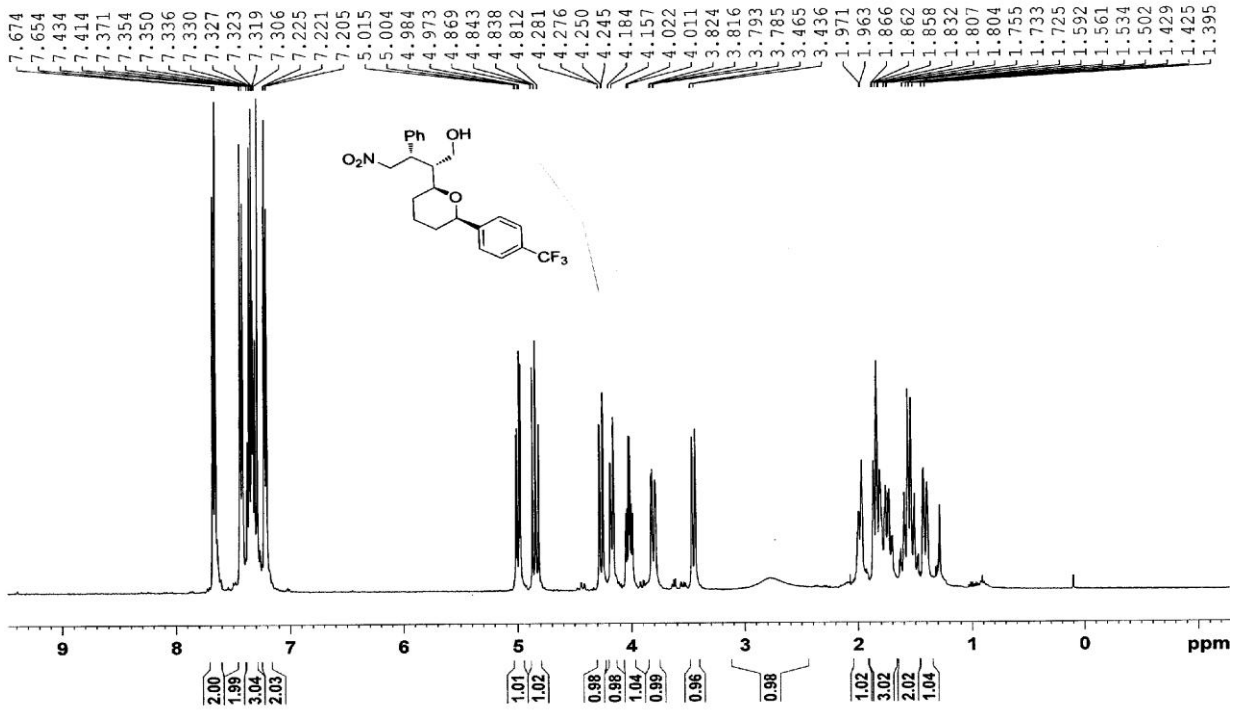

7.609
7.589
7.466
7.446
4.501
4.497
4.473
3.844
3.832
3.817
3.807
3.801
3.793
3.779
3.773
3.766
2.789
1.998
1.964
1.958
1.915
1.900
1.894
1.884
1.878
1.863
1.845
1.839
1.811
1.802
1.789
1.774
1.765
1.761
1.752
1.719
1.692
1.690
1.685
1.657
1.652
1.509
1.506
1.500
OH
O
CF3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.99
2.00
0.96
2.96
1.01
5.99
1.97

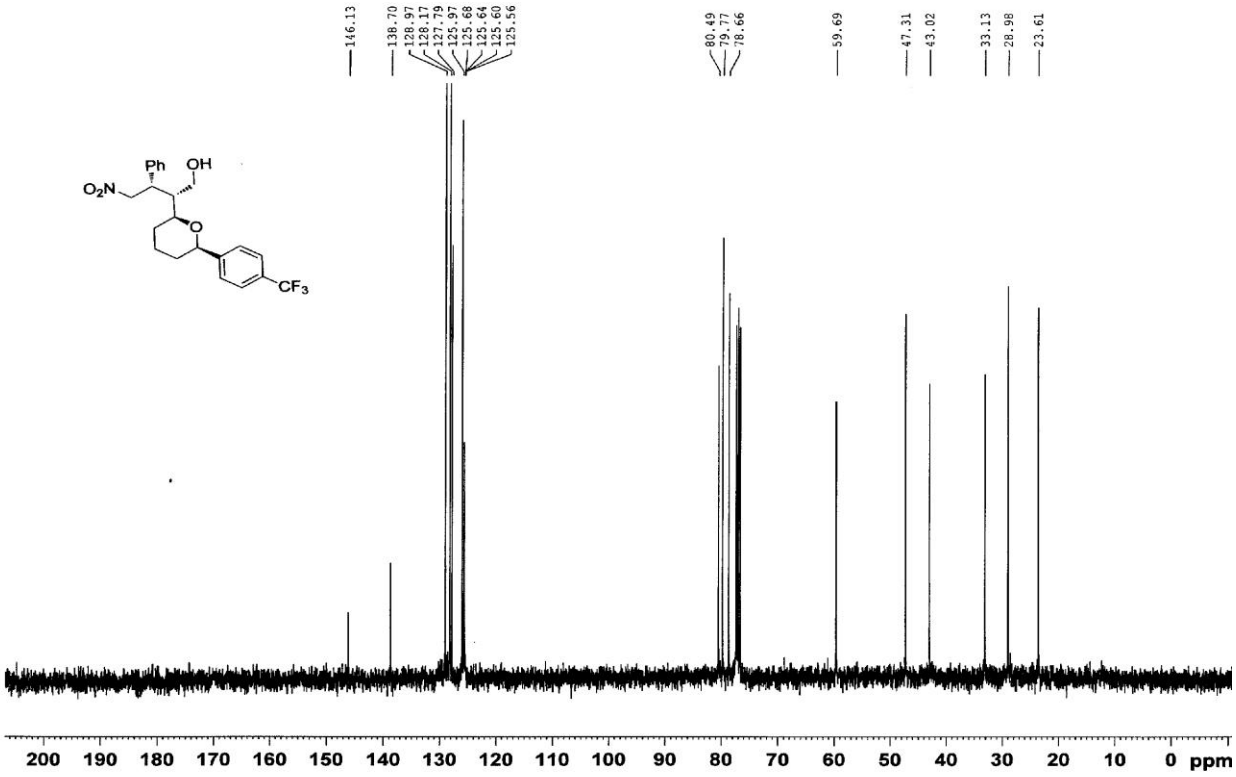

147.07
125.91
125.34
125.31
125.27
125.23
79.36
78.77
61.38
38.26
33.74
31.18
23.73
OH
O
CF3
200
180
160
140
120
100
80
60
40
20
0

5.35i: *(2R,3S)-4-nitro-3-phenyl-2-((2S,6R)-6-(4-(trifluoromethyl)phenyl)tetrahydro-2H-pyran-2-yl)butan-1-ol*

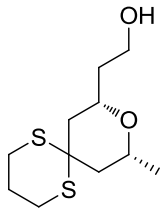


colorless amorphous solid. $[\alpha]_D^{23}$ = +137.6 (*c* 0.500, $CHCl_3$, 99% ee); IR (thin film, KBr): 3531, 2941, 1553, 1326, 1165, 1124, 1068, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.41-7.17 (m, 5H), 4.99 (dd, *J* = 12.4, 4.6 Hz, 1H), 4.84 (dd, *J* = 12.4, 10.5 Hz, 1H), 4.26 (dd, *J* = 12.5, 1.9 Hz, 1H), 4.17 (m, 1H), 4.01 (td, *J* = 10.4, 4.6 Hz, 1H), 3.80 (dd, *J* = 12.4, 3.3 Hz, 1H), 3.45 (d, *J* = 11.5 Hz, 1H), 2.78 (bs, 1H), 1.97 (m, 1H), 1.90-1.65 (m, 3H), 1.64-1.35 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 138.7, 129.0, 128.2, 127.8, 126.0, 125.7, 125.6, 125.6, 125.6, 80.5, 79.8, 78.7, 59.7, 47.3, 43.0, 33.1, 29.0, 23.6 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 95:5), 0.5 mL/min; minor enantiomer t_R = 52.9 min, major enantiomer t_R = 59.4 min. LRMS (ESI) : $[M^+]$ calcd for $[C_{22}H_{24}F_3NO_4]$: 423.2, found: 423.1.

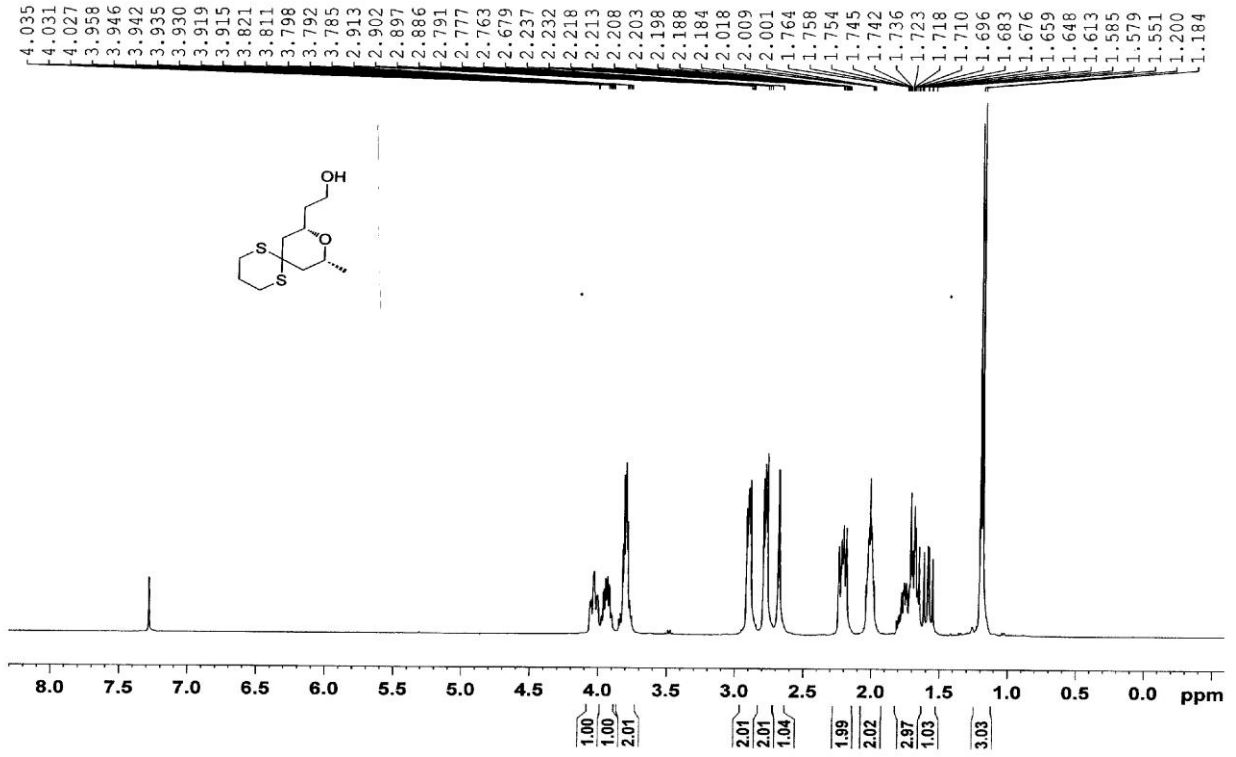

7.674
7.654
7.434
7.414
7.371
7.354
7.350
7.336
7.330
7.327
7.323
7.319
7.306
7.225
7.221
7.205
5.015
5.004
4.984
4.973
4.869
4.843
4.838
4.812
4.281
4.276
4.250
4.245
4.184
4.157
4.022
4.011
3.824
3.816
3.793
3.785
3.465
3.436
1.971
1.963
1.866
1.862
1.858
1.832
1.807
1.804
1.755
1.733
1.725
1.592
1.561
1.534
1.502
1.429
1.425
1.395
Ph
OH
O2N
O
CF3
9
8
7
6
5
4
3
2
1
0
ppm
2.00
1.99
3.04
2.03
1.01
1.02
0.98
0.98
1.04
0.99
0.96
0.98
1.02
3.02
2.02
1.04

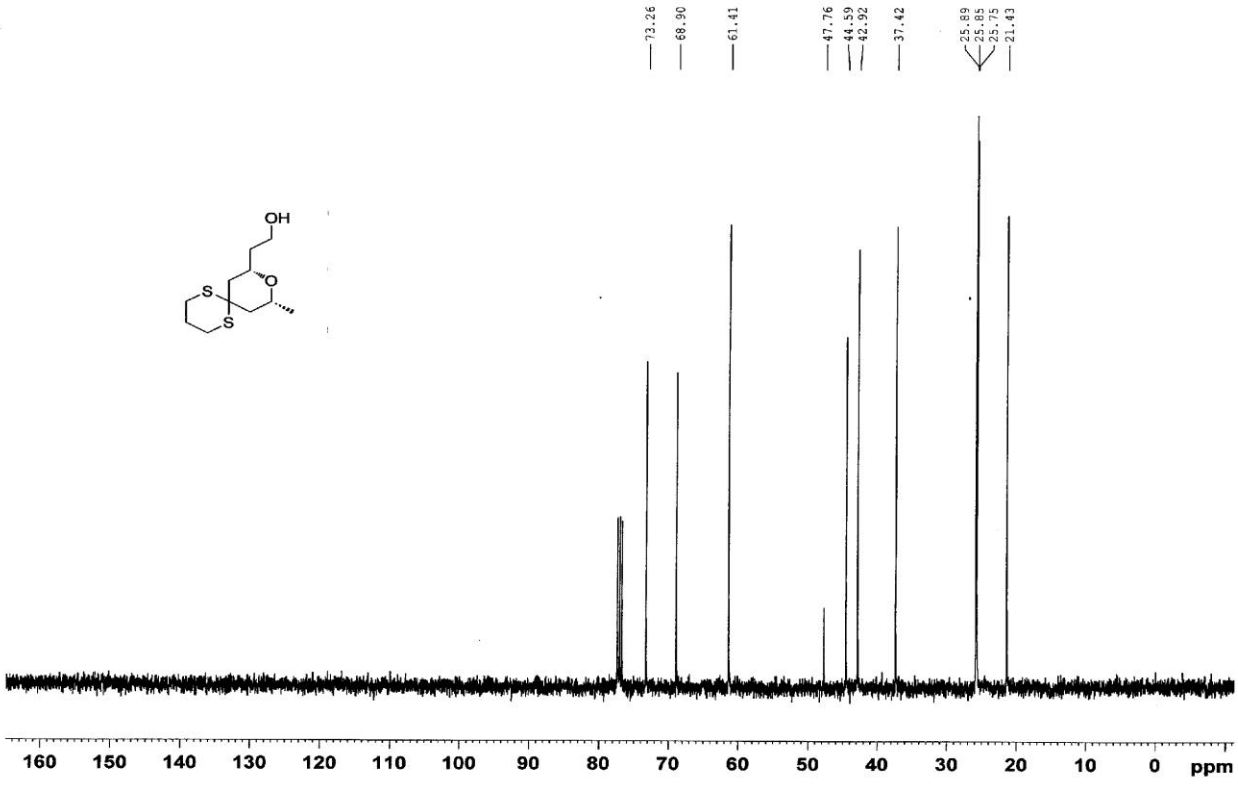

146.13
138.70
128.97
128.17
127.79
125.97
125.68
125.64
125.60
125.56
80.49
79.77
78.66
59.69
47.31
43.02
33.13
28.98
23.61
Ph
OH
O2N
O
CF3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

5.34l: *2-((8S,10R)-10-methyl-9-oxa-1,5-dithiaspiro[5.5]undecan-8-yl)ethanol*

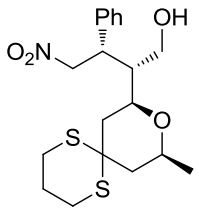


colorless oil. $[\alpha]_D^{23}$ = -3.5 (*c* 1.00, $CHCl_3$, 91% ee); IR (thin film, KBr): 3432, 2935, 2907, 2238, 1424, 1098, 1057, 911, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.04 (m, 1H), 3.94 (m, 1H), 3.80 (m, 2H), 2.89 (m, 2H), 2.77 (m, 2H), 2.68 (bs, 1H), 2.20 (m, 2H), 2.01 (m, 2H), 1.83-1.52 (m, 4H), 1.19 (d, *J* =6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.3, 68.9, 51.4, 47.8, 44.6, 42.9, 37.4, 25.9, 25.9, 25.8, 21.4 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 0.5 mL/min; major enantiomer t_R = 21.0 min, minor enantiomer t_R = 24.3 min. LRMS (ESI) : $[M^+]$ calcd for $[C_{11}H_{20}O_2S_2]$: 248.1, found: 248.0.

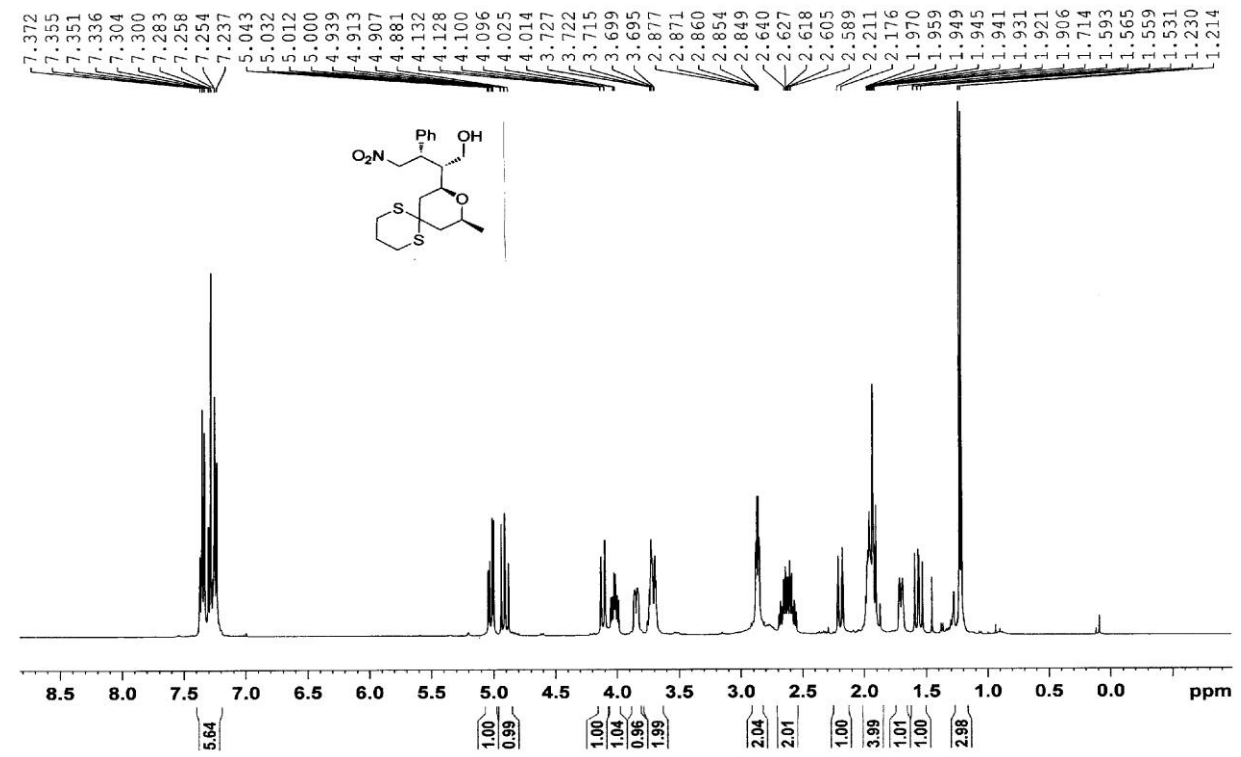

4.035
4.031
4.027
3.958
3.946
3.942
3.935
3.930
3.919
3.915
3.821
3.811
3.798
3.792
3.785
2.913
2.902
2.897
2.886
2.791
2.777
2.763
2.679
2.237
2.232
2.218
2.213
2.208
2.203
2.198
2.188
2.184
2.018
2.009
2.001
1.764
1.758
1.754
1.745
1.742
1.736
1.723
1.718
1.710
1.696
1.683
1.676
1.659
1.648
1.613
1.585
1.579
1.551
1.200
1.184
OH
S
O
S
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 ppm
1.00 1.00 2.01 2.01 2.01 1.04 1.99 2.02 2.97 1.03 3.03

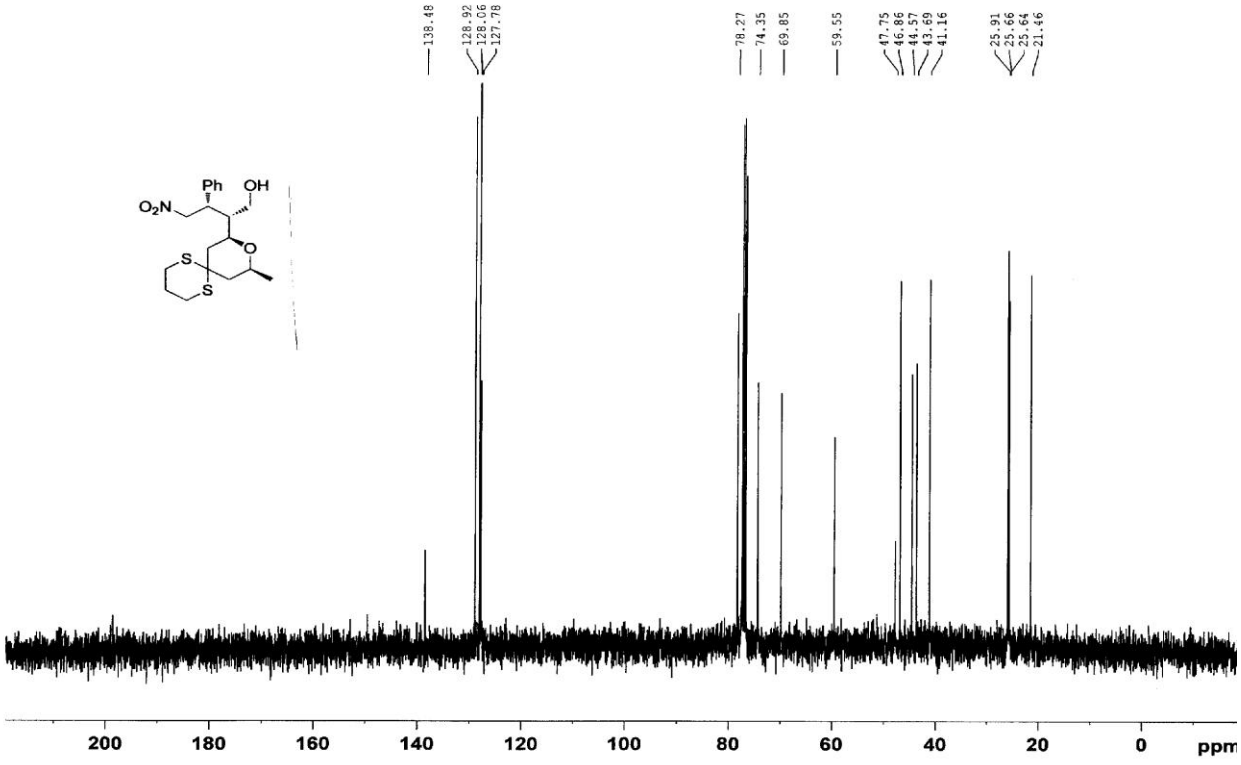

73.26
68.90
61.41
47.76
44.59
42.92
37.42
25.89
25.85
25.75
21.43
OH
S
O
S
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

5.35l: *(2R,3S)-2-((8S,10S)-10-methyl-9-oxa-1,5-dithiaspiro[5.5]undecan-8-yl)-4-nitro-3-phenylbutan-1-ol*

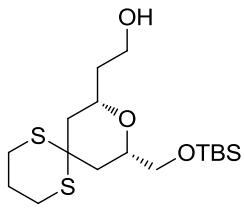


colorless amorphous solid. $[\alpha]_D^{22}$ = -17.3 (*c* 1.00, $CHCl_3$, 99% ee); IR (thin film, KBr): 3516, 29.7, 1552, 1380, 1146, 1068, 702, 545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.18 (m, 5H), 5.02 (dd, *J* = 12.5, 4.7 Hz, 1H), 4.91 (dd, *J* = 12.5, 10.5 Hz, 1H), 4.11 (dd, *J* = 12.7, 1.6 Hz, 1H), 4.02 (td, *J* = 10.0, 4.7 Hz, 1H), 3.84 (m, 1H), 3.71 (m, 2H), 2.86 (m, 2H), 2.62 (m, 2H), 2.20 (m, 1H), 2.03-1.86 (m, 4H), 1.70 (m, 1H), 1.56 (dd, *J* = 13.9, 11.2 Hz, 1H), 1.22 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 128.9, 128.1, 127.8, 78.3, 74.4, 69.9, 59.6, 47.8, 46.9, 44.6, 43.7, 41.2, 25.9, 25.7, 25.6, 21.5 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 0.5 mL/min; major enantiomer t_R = 43.2 min, minor enantiomer t_R = 70.9. LRMS (ESI) : $[M^+]$ calcd for $[C_{19}H_{27}NO_4S_2]$: 397.1, found: 397.1.

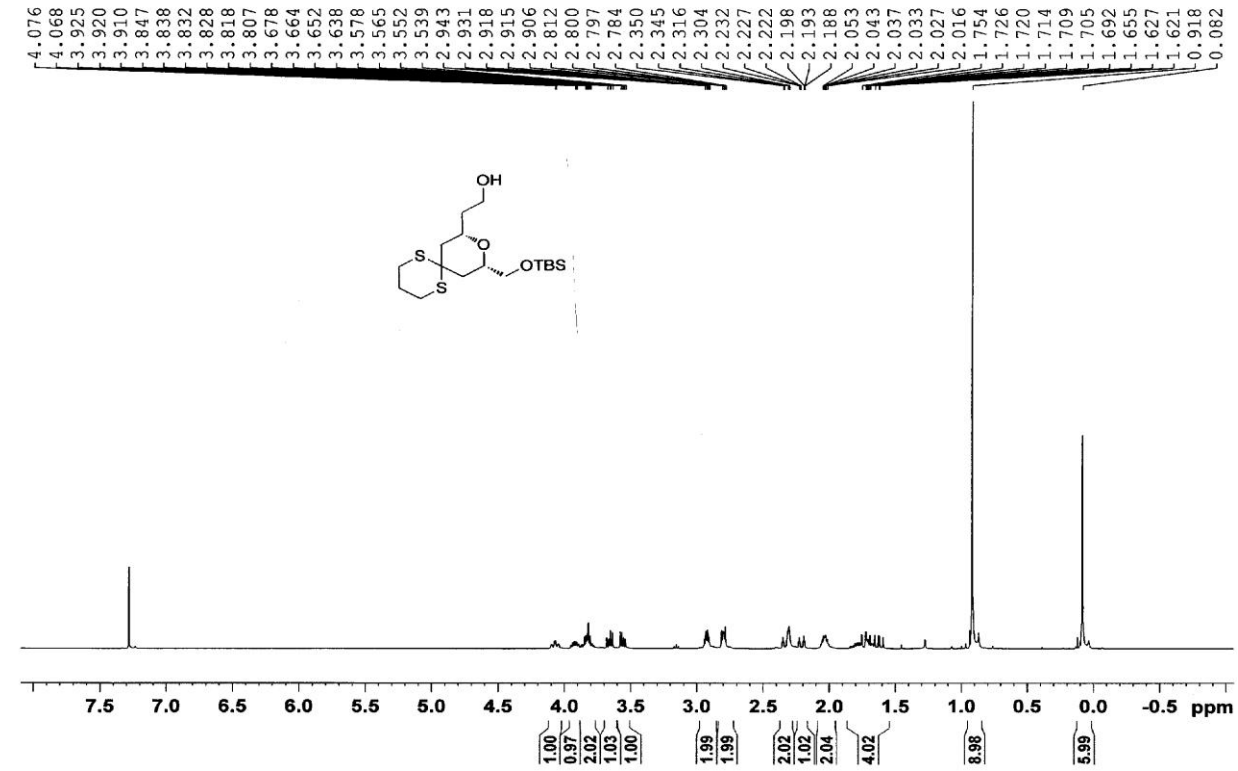

7.372
7.355
7.351
7.336
7.304
7.300
7.283
7.258
7.254
7.237
5.043
5.032
5.012
5.000
4.939
4.913
4.907
4.881
4.132
4.128
4.100
4.096
4.025
4.014
3.727
3.722
3.715
3.699
3.695
2.877
2.871
2.860
2.854
2.849
2.640
2.627
2.618
2.605
2.589
2.211
2.176
1.970
1.959
1.949
1.945
1.941
1.931
1.921
1.906
1.714
1.593
1.565
1.559
1.531
1.230
1.214
Ph
OH
O2N
S
S
O
8.5 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 ppm
5.64
1.00
0.99
1.00
1.04
0.96
1.99
2.04
2.01
1.00
3.99
1.01
1.00
2.98

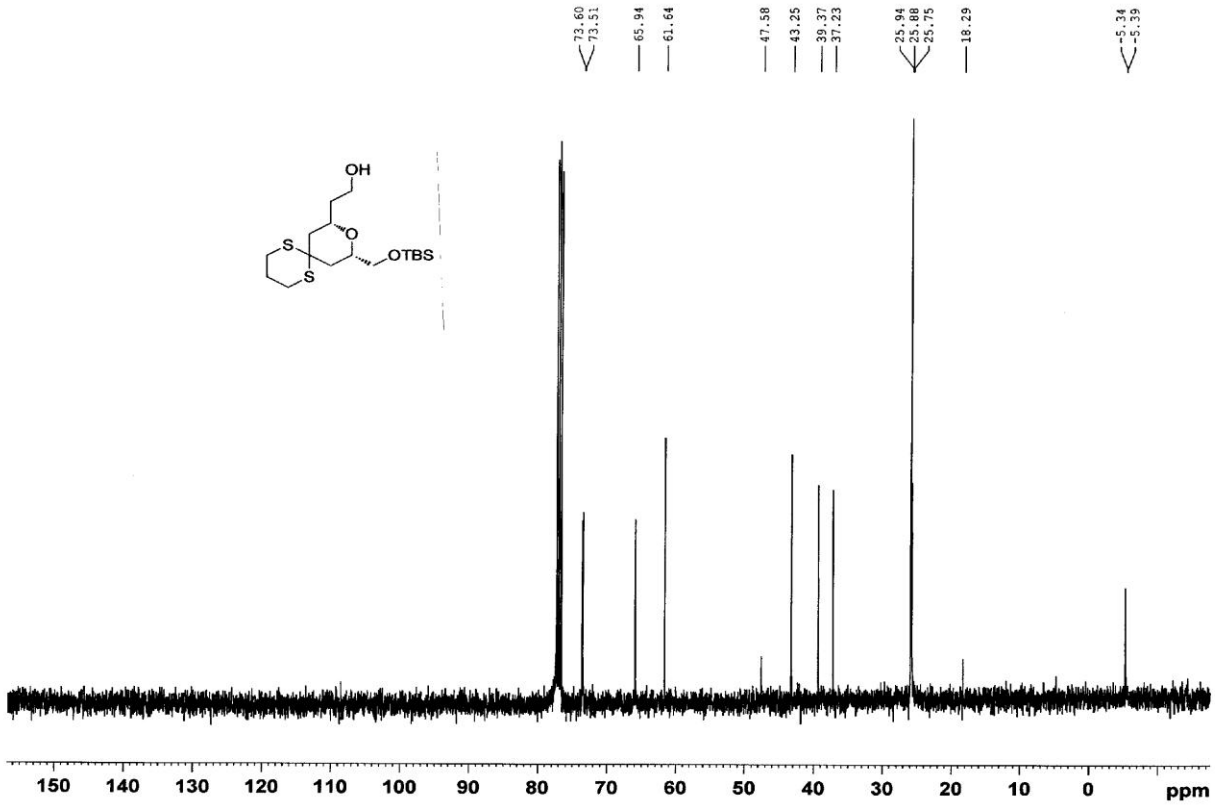

138.48
128.92
128.66
127.78
78.27
74.35
69.85
59.55
47.75
46.86
44.57
43.69
41.16
25.91
25.66
25.64
21.46
Ph
OH
O2N
S
S
O
200 180 160 140 120 100 80 60 40 20 0 ppm

5.34m: *2-((8S,10S)-10-(((tert-butyldimethylsilyl)oxy)methyl)-9-oxa-1,5-dithiaspiro[5.5]undecan-8-yl)ethanol*

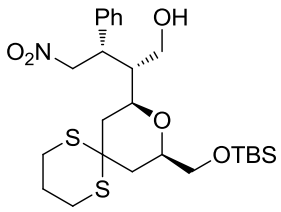


colorless oil. $[\alpha]_D^{24}$ = -7.9 (*c* 1.00, $CHCl_3$, 90% ee); IR (thin film, KBr): 3436, 2929, 2857, 1425, 1252, 1092, 834, 777, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.08 (m, 1H), 3.92 (m, 1H), 3.82 (m, 2H), 3.65 (dd, *J* = 10.4, 5.9 Hz, 1H), 3.56 (dd, *J* = 10.4, 5.1 Hz, 1H), 2.93 (m, 1H), 2.80 (m, 1H), 2.32 (m, 2H), 2.21 (dt, *J* = 13.7, 2.1 Hz, 1H), 2.04 (m, 2H), 1.85-1.58 (m, 4H), 0.91 (s, 9H), 0.09 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.6, 73.5, 65.9, 61.6, 47.6, 43.3, 39.4, 37.2, 25.9, 25.9, 25.8, 18.3, -5.2, -5.4 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 95:5), 0.5 mL/min; major enantiomer t_R = 18.6 min, minor enantiomer t_R = 21.3 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{17}H_{34}O_3S_2Si]$: 378.1719, found: 378.1718.

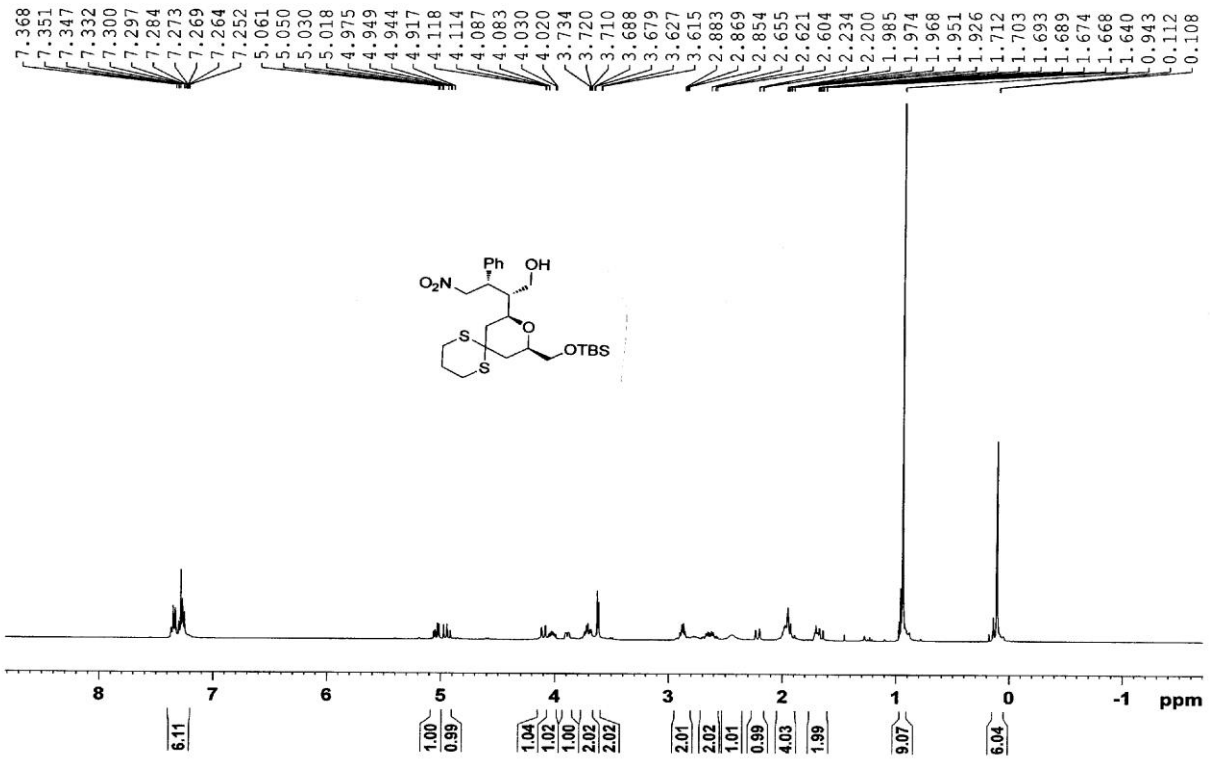

4.076
4.068
3.925
3.920
3.910
3.847
3.838
3.832
3.828
3.818
3.807
3.678
3.664
3.652
3.638
3.578
3.565
3.552
3.539
2.943
2.931
2.918
2.915
2.906
2.812
2.800
2.797
2.784
2.350
2.345
2.316
2.304
2.232
2.227
2.222
2.198
2.193
2.188
2.053
2.043
2.037
2.033
2.027
2.016
1.754
1.726
1.720
1.714
1.709
1.705
1.692
1.655
1.627
1.621
0.918
0.082
OH
O
S
S
OTBS
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
-0.5
ppm
1.00
0.97
2.02
1.03
1.00
1.99
1.99
2.02
1.02
2.04
4.02
8.98
5.99


73.60
73.51
65.94
61.64
47.58
43.25
39.37
37.23
25.94
25.88
25.75
18.29
-5.34
-5.39
OH
O
S
S
OTBS
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

5.35m: *(2R,3S)-2-((8S,10R)-10-(((tert-butyldimethylsilyl)oxy)methyl)-9-oxa-1,5-dithiaspiro[5.5]undecan-8-yl)-4-nitro-3-phenylbutan-1-ol*



colorless amorphous solid. $[\alpha]_D^{23}$ = +5.0 (*c* 1.00, $CHCl_3$, 99% ee); IR (thin film, KBr): 3491, 2953, 2929, 2857, 1631, 1552, 1380, 1252, 1073, 837, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.20 (m, 5H), 5.04 (dd, *J* = 12.7, 4.7 Hz, 1H), 4.94 (dd, *J* = 12.7, 10.5 Hz, 1H), 4.11 (dd, *J* = 12.7, 1.7 Hz, 1H), 4.03 (td, *J* = 10.7, 4.2 Hz, 1H), 3.89 (m, 1H), 3.71 (m, 2H), 3.61 (d, *J* = 4.9 Hz, 2H), 2.89 (m, 2H), 2.62 (m, 2H), 2.44 (bs, 1H), 2.21 (m, 1H), 2.03-1.89 (m, 4H), 1.70 (m, 2H), 0.94 (s, 9H), 0.11 (d, *J* = 1.7 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 128.9, 128.1, 127.8, 78.1, 74.4, 74.2, 64.6, 59.5, 47.6, 47.0, 43.9, 41.3, 39.1, 26.0, 25.9, 25.7, 25.6, 18.3, -5.4, -5.5 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 0.5 mL/min; major enantiomer t_R = 15.8 min, minor enantiomer t_R = 20.9 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{25}H_{41}NO_5S_2Si]$: 527.2195, found: 527.2197.


7.368
7.351
7.347
7.332
7.300
7.297
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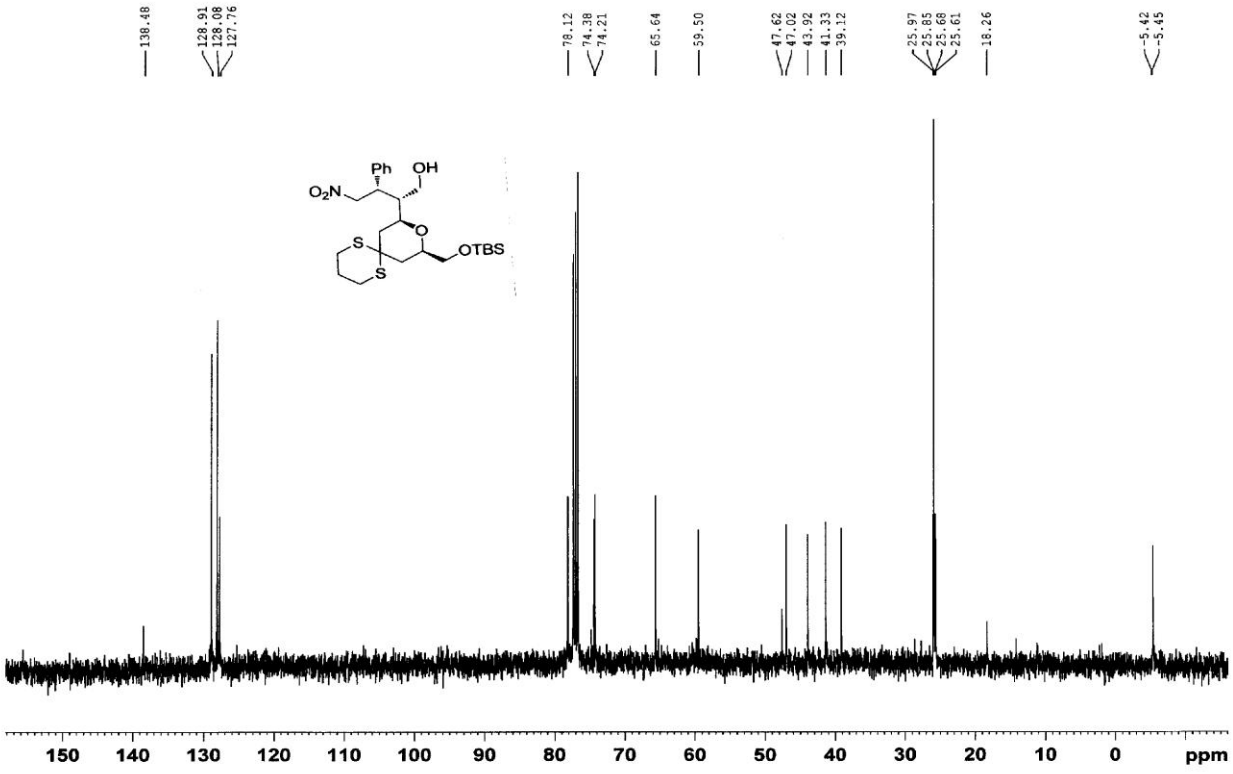
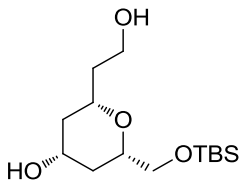
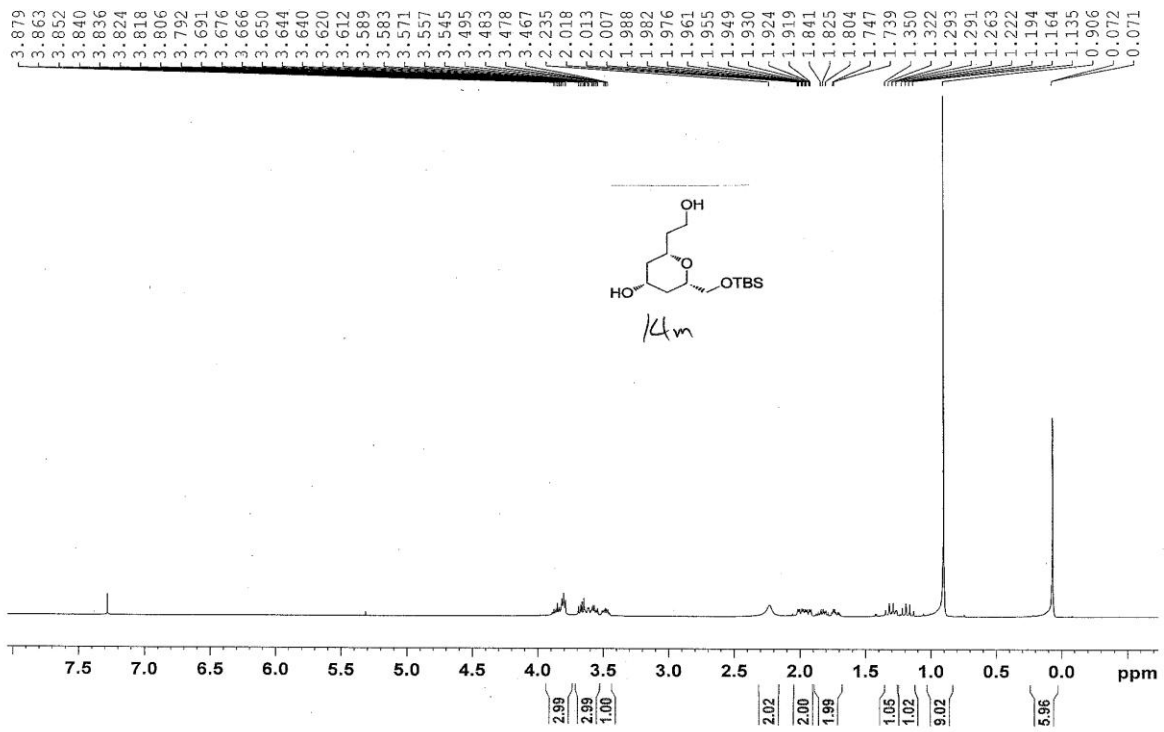
7.273
7.269
7.264
7.252
5.061
5.050
5.030
5.018
4.975
4.949
4.944
4.917
4.118
4.114
4.087
4.083
4.030
4.020
3.734
3.720
3.710
3.688
3.679
3.627
3.615
2.883
2.869
2.854
2.655
2.621
2.604
2.234
2.200
1.985
1.974
1.968
1.951
1.926
1.712
1.703
1.693
1.689
1.674
1.668
1.640
0.943
0.112
0.108
Ph
OH
O2N
O
S
S
OTBS
8
7
6
5
4
3
2
1
0
-1
ppm
6.11
1.00
0.99
1.04
1.02
1.00
2.02
2.02
2.01
2.02
1.01
0.99
4.03
1.99
9.07
6.04

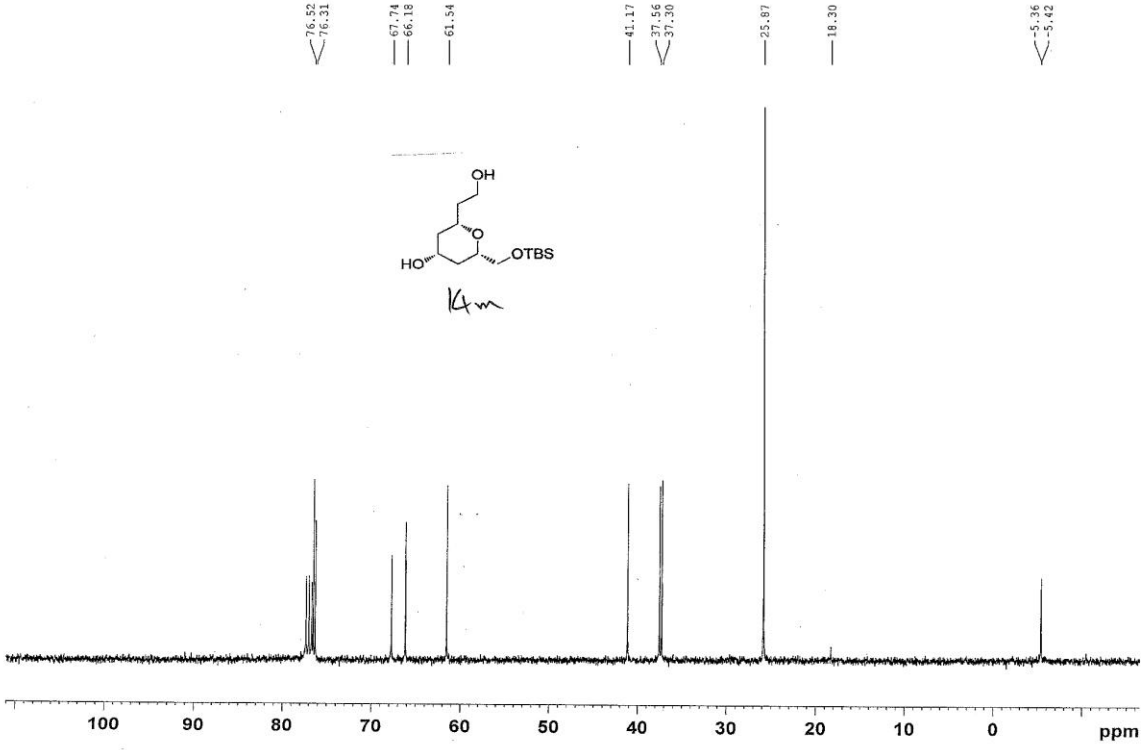

138.48
128.91
128.08
127.76
78.12
74.38
74.21
65.64
59.50
47.62
47.02
43.92
41.33
39.12
25.97
25.85
25.68
25.61
18.26
-5.42
-5.45
Ph
OH
O2N
O
S
S
OTBS
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

5.34n: *(2S,4R,6S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-6-(2-hydroxyethyl)tetrahydro-2H-pyran-4-ol*

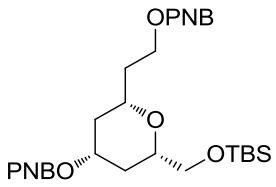


colorless oil. $[\alpha]_D^{22}$ = -2.8 (*c* 1.25, $CHCl_3$, 28% ee); IR (thin film, KBr): 3428, 2953, 1641, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.91-3.78 (m, 3H), 3.70-3.54 (m, 3H), 3.48 (m, 1H), 2.24 (bs, 2H), 1.96 (m, 2H), 1.90-1.67 (m, 2H), 1.30 (q, *J* = 11.3 Hz, 1H), 1.18 (q, *J* = 11.3 Hz, 1H), 0.91 (s, 9H), 0.07 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.5, 76.3, 67.7, 66.2, 61.5, 41.2, 37.6, 37.3, 25.9, 18.3, -5.4, -5.4 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_{14}H_{30}O_4Si]$: 290.1913, found: 290.1917.

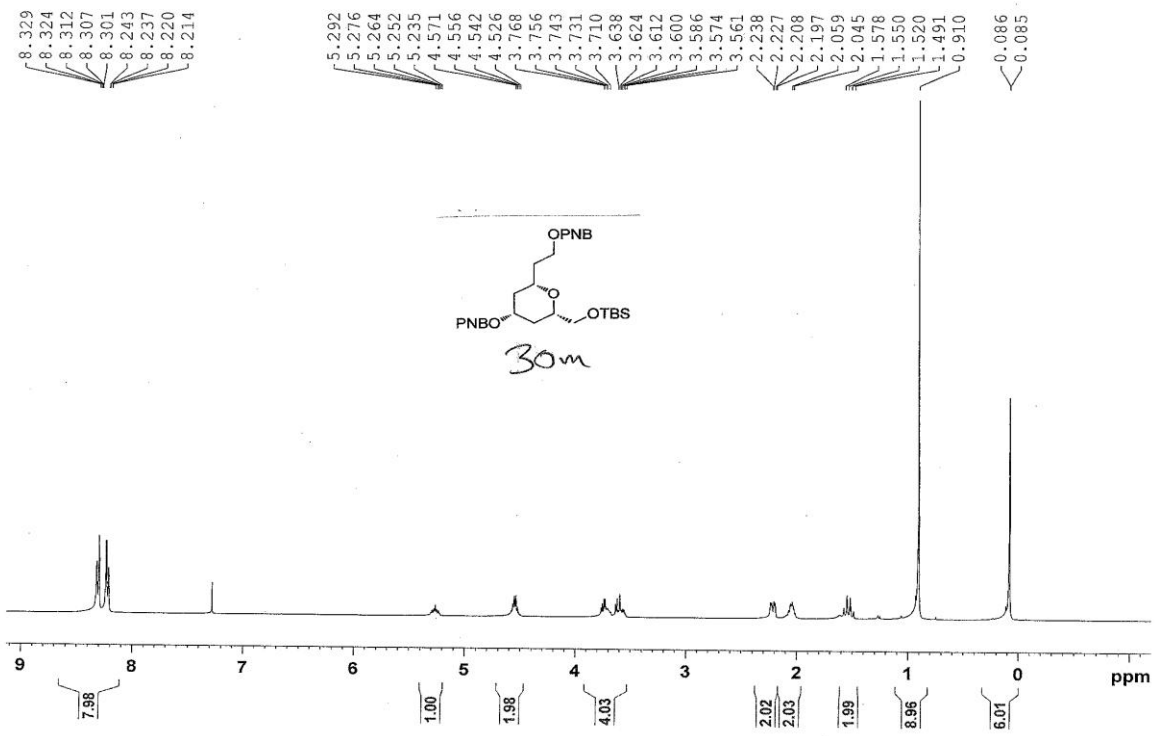

3.879
3.863
3.852
3.840
3.836
3.824
3.818
3.806
3.792
3.691
3.676
3.666
3.650
3.644
3.640
3.620
3.612
3.589
3.583
3.571
3.557
3.545
3.495
3.483
3.478
3.467
2.235
2.018
2.013
2.007
1.988
1.982
1.976
1.961
1.955
1.949
1.930
1.924
1.919
1.841
1.825
1.804
1.747
1.739
1.350
1.322
1.293
1.291
1.263
1.222
1.194
1.164
1.135
0.906
0.072
0.071
OH
O
HO
OTBS
14m
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
ppm
2.99
2.99
1.00
2.02
2.00
1.99
1.05
1.02
9.02
5.96

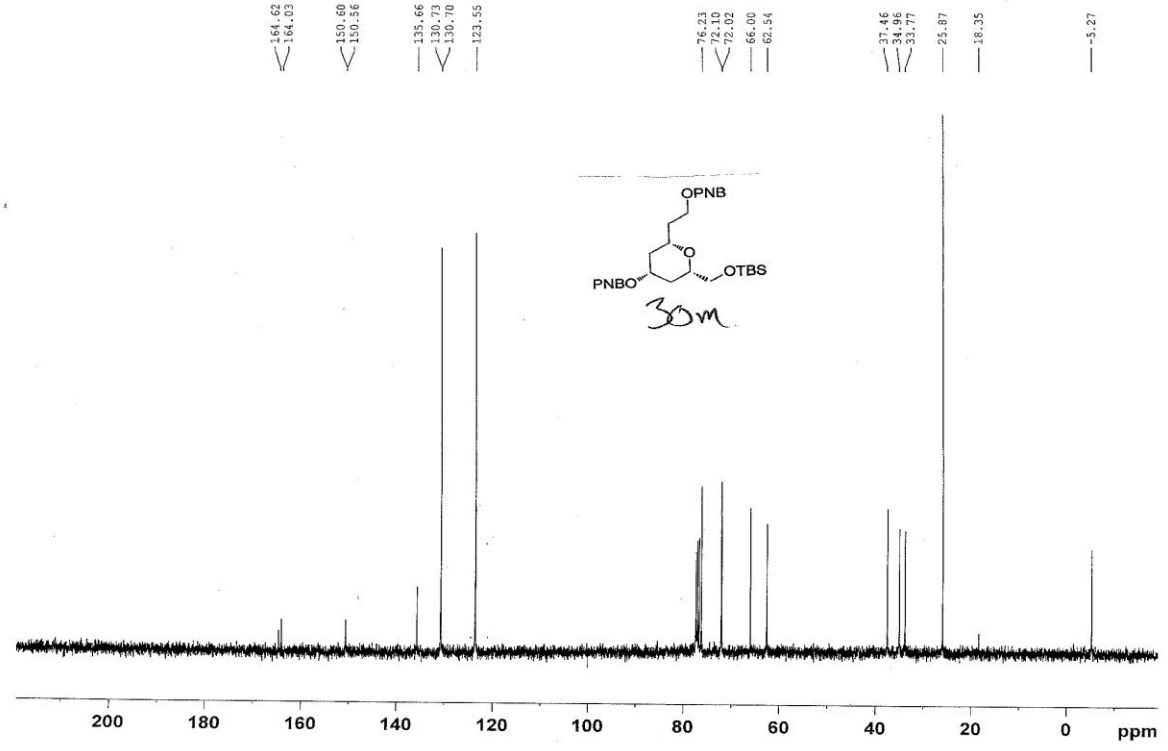

76.52
76.31
67.74
66.18
61.54
41.17
37.56
37.30
25.87
18.30
-5.36
-5.42
OH
O
HO
OTBS
14m
100
90
80
70
60
50
40
30
20
10
0
ppm

5.28n: *2-((2S,4R,6S)-6-(((tert-butyldimethylsilyl)oxy)methyl)-4-((4-nitrobenzoyl)oxy)tetrahydro-2H-pyran-2-yl)ethyl 4-nitrobenzoate*

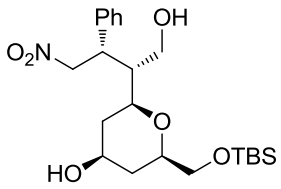


colorless oil. $[\alpha]_D^{23}$ = -1.2 (*c* 1.83, $CHCl_3$, 28% ee); IR (thin film, KBr): 3436, 2955, 2929, 2856, 1724, 1608, 1529, 1350, 1275, 1102, 836, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (m, 4H), 8.23 (m, 4H), 5.26 (m, 1H), 4.55 (m, 2H), 3.80-3.52 (m, 4H), 2.22 (m, 2H), 2.05 (m, 2H), 1.54 (m, 2H), 0.91 (s, 9H), 0.9 (d, *J* = 0.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 164.0, 150.6, 150.6, 135.7, 130.7, 130.7, 123.6, 76.2, 72.1, 72.0, 66.0, 62.5, 37.5, 35.0, 33.8, 25.9, 18.4, -5.3 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; minor enantiomer t_R = 17.6 min, major enantiomer t_R = 23.6 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{28}H_{36}N_2O_{10}Si]$: 588.2139, found: 588.2144.

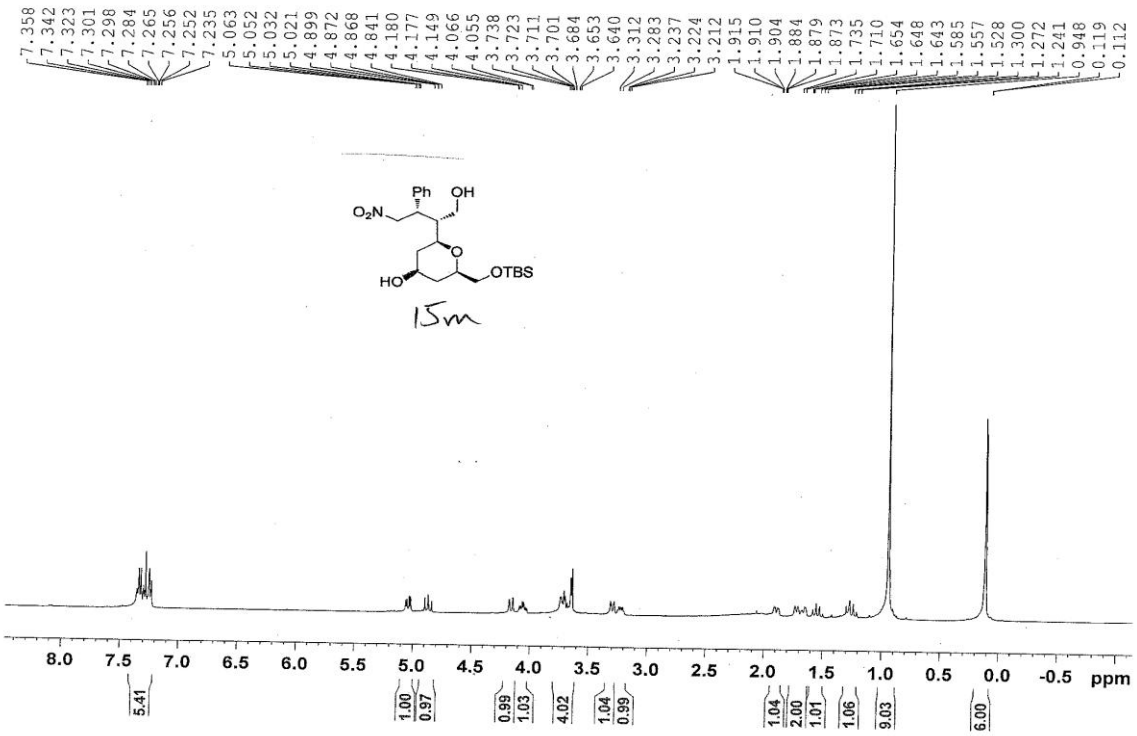

8.329
8.324
8.312
8.307
8.301
8.243
8.237
8.220
8.214
5.292
5.276
5.264
5.252
5.235
4.571
4.556
4.542
4.526
3.768
3.756
3.743
3.731
3.710
3.638
3.624
3.612
3.600
3.586
3.574
3.561
2.238
2.227
2.208
2.197
2.059
2.045
1.578
1.550
1.520
1.491
0.910
0.086
0.085
OPNB
PNBO
OTBS
30m
9
8
7
6
5
4
3
2
1
0
ppm
7.98
1.00
1.98
4.03
2.02
2.03
1.99
8.96
6.01

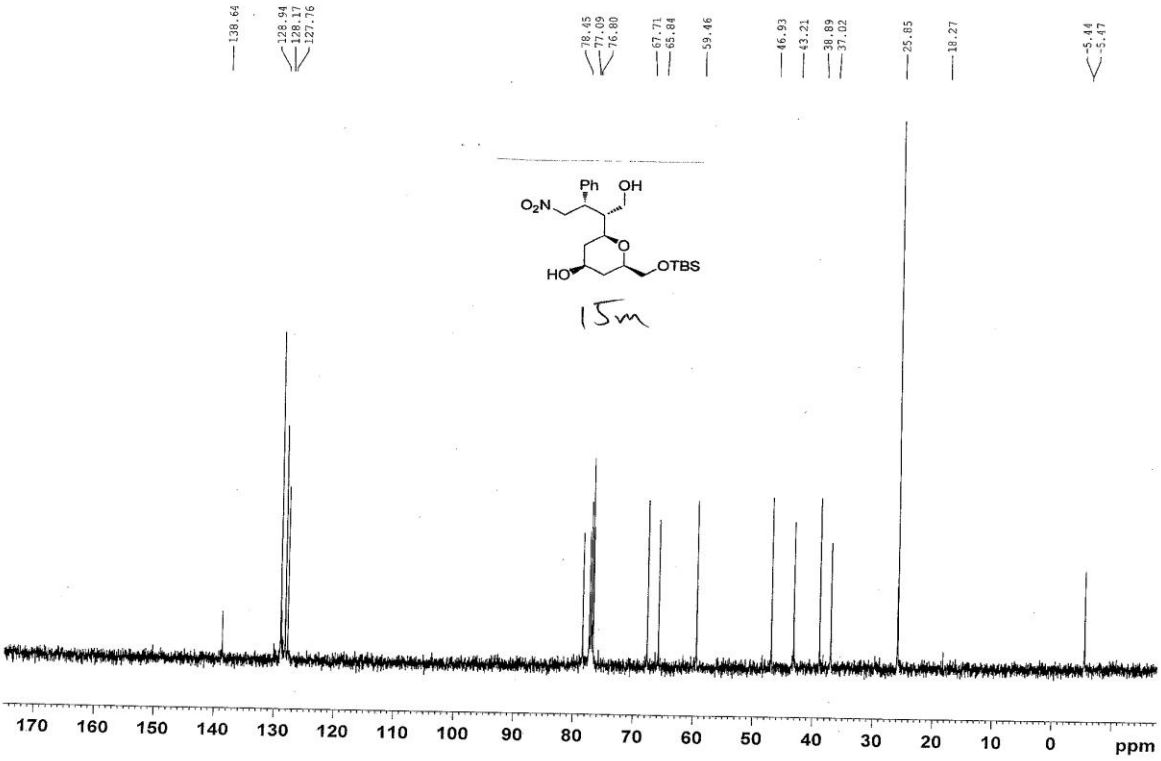

164.62
164.03
150.60
150.56
135.66
130.73
130.70
123.55
76.23
72.10
72.02
66.00
62.54
37.46
34.96
33.77
25.87
18.35
-5.27
OPNB
PNBO
OTBS
30m
200
180
160
140
120
100
80
60
40
20
0
ppm

5.35n: *(2R,4S,6S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-6-((2R,3S)-1-hydroxy-4-nitro-3-phenylbutan-2-yl)tetrahydro-2H-pyran-4-ol*

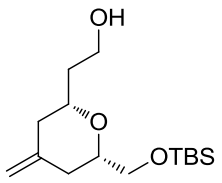


colorless amorphous solid. $[\alpha]_D^{23}$ = +9.6 (*c* 1.00, $CHCl_3$, 99% ee); IR (thin film, KBr): 3389, 2929, 2857, 1640, 1552, 1381, 1255, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.21 (m, 5H), 5.04 (dd, *J* = 12.5, 4.5 Hz, 1H), 4.87 (dd, *J* = 12.5, 10.8 Hz, 1H), 4.16 (dd, *J* = 12.7, 1.5 Hz, 1H), 4.06 (td, *J* = 10.4, 4.5 Hz, 1H), 3.76-3.62 (m, 4H), 3.30 (m, 1H), 3.24 (m, 1H), 1.40 (m, 1H), 1.75-1.62 (m, 2H), 1.54 (q, *J* = 11.3 Hz, 1H), 1.26 (q, *J* = 11.3 Hz, 1H), 0.95 (s, 9H), 0.12 (d, *J* = 2.7 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 128.9, 128.2, 127.8, 78.5, 77.1, 76.8, 67.7, 65.8, 59.5, 46.9, 43.2, 38.9, 37.0, 25.9, 18.3, -5.4, -5.5 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 80:20), 1.0 mL/min; minor enantiomer t_R = 10.4 min, major enantiomer t_R = 12.0 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{22}H_{37}NO_6Si]$: 439.2390, found: 439.2391.

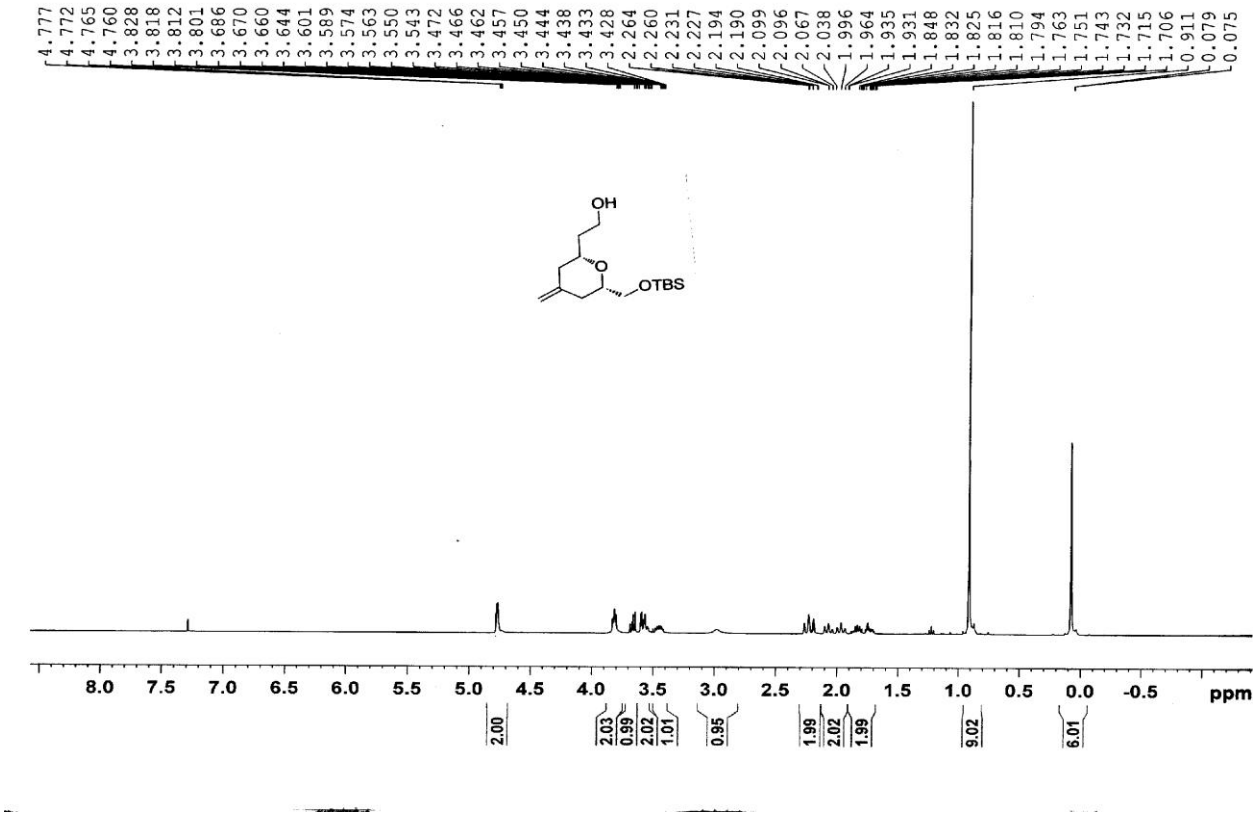

7.358
7.342
7.323
7.301
7.298
7.284
7.265
7.256
7.252
7.235
5.063
5.052
5.032
5.021
4.899
4.872
4.868
4.841
4.180
4.177
4.149
4.066
4.055
3.738
3.723
3.711
3.701
3.684
3.653
3.640
3.312
3.283
3.237
3.224
3.212
1.915
1.910
1.904
1.884
1.879
1.873
1.735
1.710
1.654
1.648
1.643
1.585
1.557
1.528
1.300
1.272
1.241
0.948
0.119
0.112
Ph
OH
O2N
O
HO
OTBS
15m
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
-0.5
ppm
5.41
1.00
0.97
0.99
1.03
4.02
1.04
0.99
1.04
2.00
1.01
1.06
9.03
6.00


138.64
128.94
128.17
127.76
78.45
77.09
76.80
67.71
65.84
59.46
46.93
43.21
38.89
37.02
25.85
18.27
-5.44
-5.47
Ph
OH
O2N
O
HO
OTBS
15m
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

5.34o: *2-((2R,6S)-6-(((tert-butyldimethylsilyl)oxy)methyl)-4-methylenetetrahydro-2H-pyran-2-yl)ethanol*



colorless oil. $[\alpha]_D^{22}$ = +0.8 (*c* 0.900, $CHCl_3$, 95% ee); IR (thin film, KBr): 3420, 3074, 2930, 2858, 1653, 1253, 1117, 889, 835, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.77 (m, 2H), 3.70 (m, 2H), 3.66 (dd, *J* = 10.5, 6.2 Hz, 1H), 3.59 (m, 2H), 3.45 (m, 1H), 2.97 (bs, 1H), 2.22 (m, 2H), 2.11-1.91 (m, 2H), 1.90-1.68 (m, 2H), 0.91 (s, 9H), 0.08 (d, *J* = 1.5 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 109.2, 79.3, 79.0, 66.3, 61.7, 40.8, 37.7, 36.8, 25.9, 18.3, -5.4, -5.4 ppm; LRMS (ESI) : $[M^+]$ calcd for $[C_{15}H_{30}O_3Si]$: 286.2, found: 286.2.


4.777
4.772
4.765
4.760
3.828
3.818
3.812
3.801
3.686
3.670
3.660
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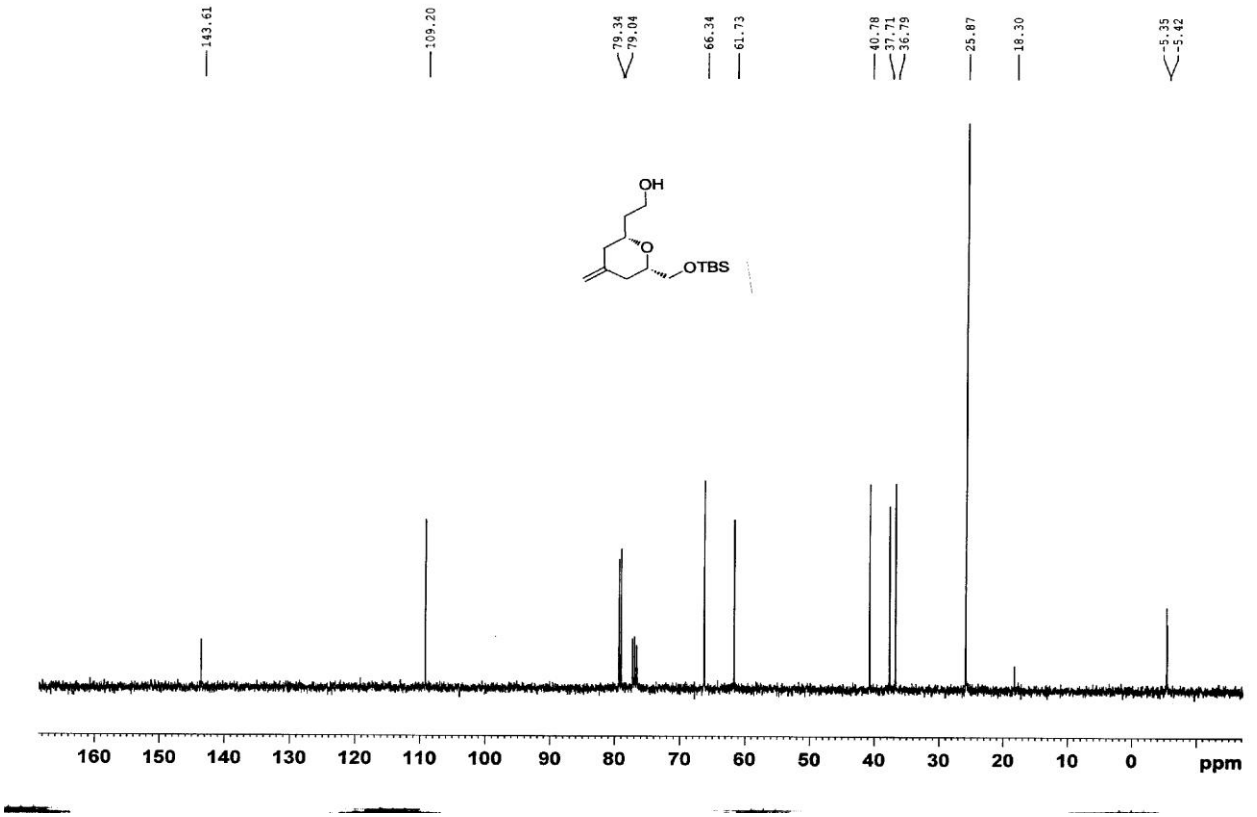
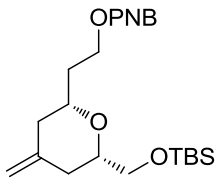
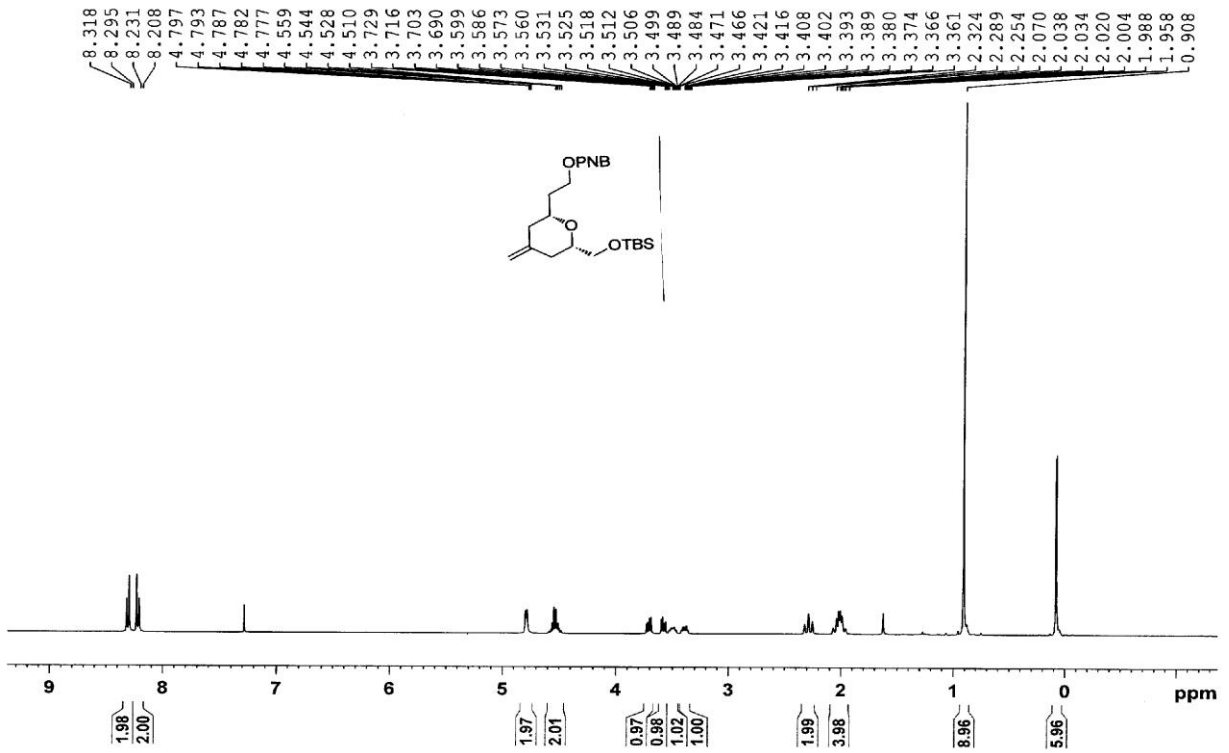
3.601
3.589
3.574
3.563
3.550
3.543
3.472
3.466
3.462
3.457
3.450
3.444
3.438
3.433
3.428
2.264
2.260
2.231
2.227
2.194
2.190
2.099
2.096
2.067
2.038
1.996
1.964
1.935
1.931
1.848
1.832
1.825
1.816
1.810
1.794
1.763
1.751
1.743
1.732
1.715
1.706
0.911
0.079
0.075
OH
O
OTBS
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
2.00
2.03
0.99
2.02
1.01
0.95
1.99
2.02
1.99
9.02
6.01

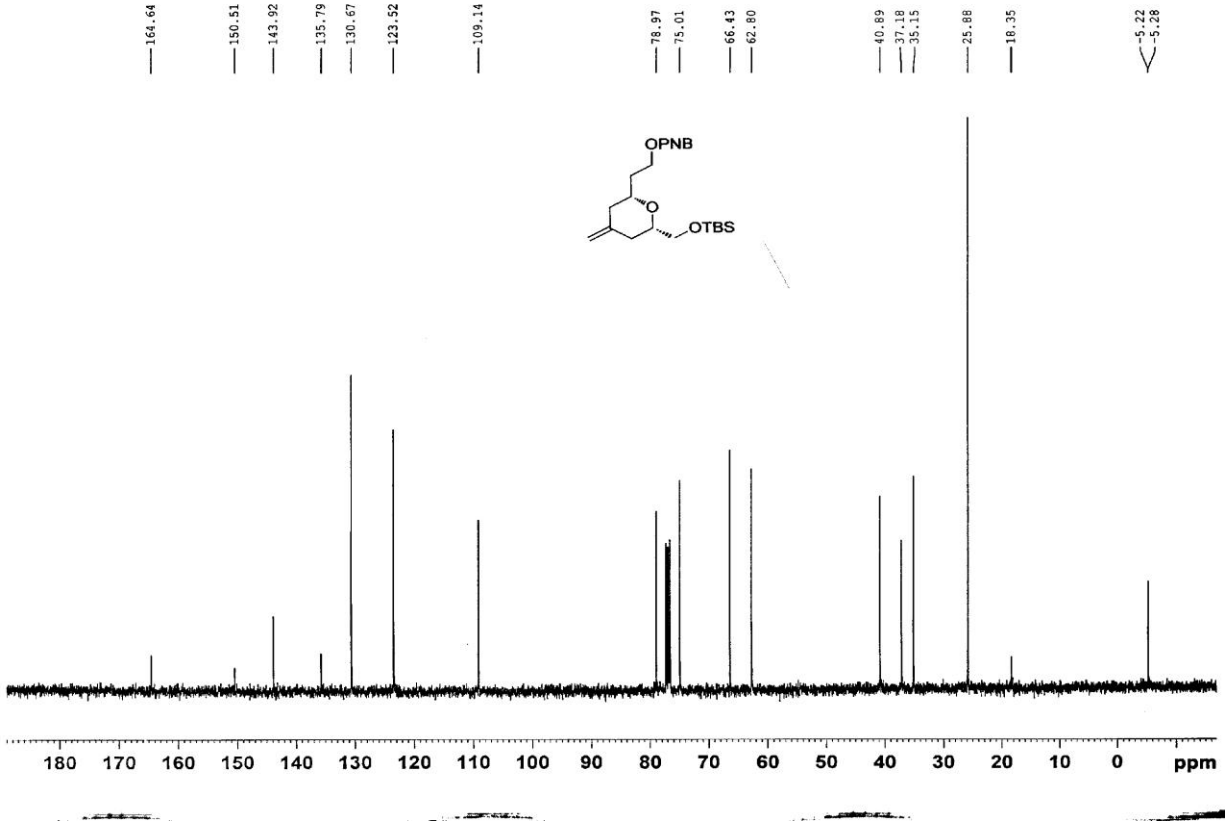

143.61
109.20
79.34
79.04
66.34
61.73
40.78
37.71
36.79
25.87
18.30
5.35
5.42
OH
O
OTBS
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

5.28o: *2-((2R,6S)-6-(((tert-butyldimethylsilyl)oxy)methyl)-4-methylenetetrahydro-2H-pyran-2-yl)ethyl 4-nitrobenzoate*

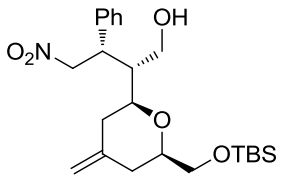


colorless oil. $[\alpha]_D^{23}$ = -21.9 (*c* 1.675, $CHCl_3$, 95% ee); IR (thin film, KBr): 2954, 2929, 2857, 1728, 1654, 1609, 1530, 1350, 1276, 1102, 836, 779, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.8 Hz, 2H), 8.22 (d, *J* = 8.8 Hz, 2H), 4.79 (m, 2H), 4.52 (m, 2H), 3.70 (dd, J = 10.5, 5.3 Hz, 1H), 3.57 (dd, *J* = 10.5, 5.3 Hz, 1H), 3.50 (m, 1H), 3.40 (m, 1H), 2.29 (m, 2H), 2.01 (m, 4H), 0.91 (s, 9H), 0.08 (d, *J* = 2.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 150.5, 143.9, 135.8, 130.7, 123.5, 109.1, 79.0, 75.0, 66.4, 62.8, 40.9, 37.2, 35.2, 25.9, 18.4, -5.2, -5.3 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 99:1), 0.3 mL/min; minor enantiomer t_R = 15.6 min, major enantiomer t_R = 16.9 min. LRMS (ESI) : $[M^+]$ calcd for $[C_{22}H_{33}NO_6Si]$: 435.2, found: 435.2.

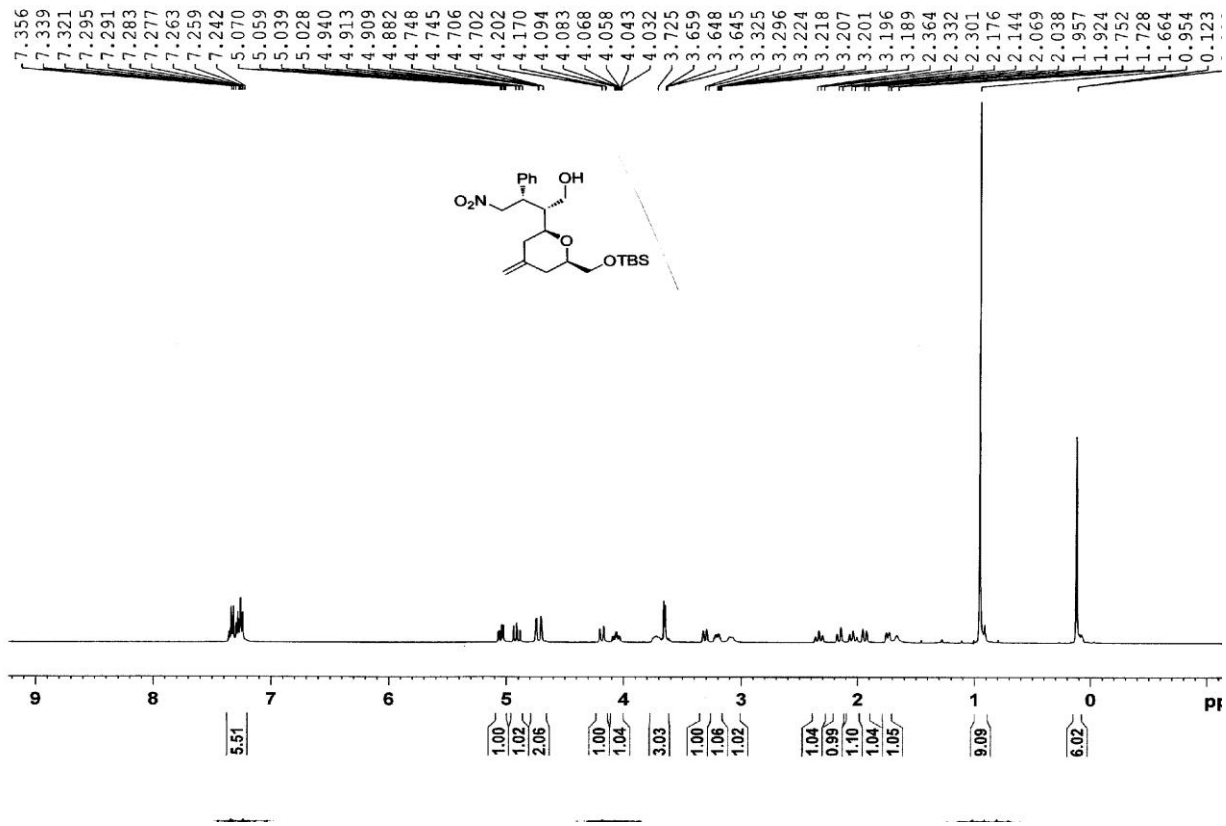

8.318
8.295
8.231
8.208
4.797
4.793
4.787
4.782
4.777
4.559
4.544
4.528
4.510
3.729
3.716
3.703
3.690
3.599
3.586
3.573
3.560
3.531
3.525
3.518
3.512
3.506
3.499
3.489
3.484
3.471
3.466
3.421
3.416
3.408
3.402
3.393
3.389
3.380
3.374
3.366
3.361
2.324
2.289
2.254
2.070
2.038
2.034
2.020
2.004
1.988
1.958
0.908
OPNB
O
OTBS
9
8
7
6
5
4
3
2
1
0
ppm
1.98
2.00
1.97
2.01
0.97
0.98
1.02
1.00
1.99
3.98
8.96
5.96

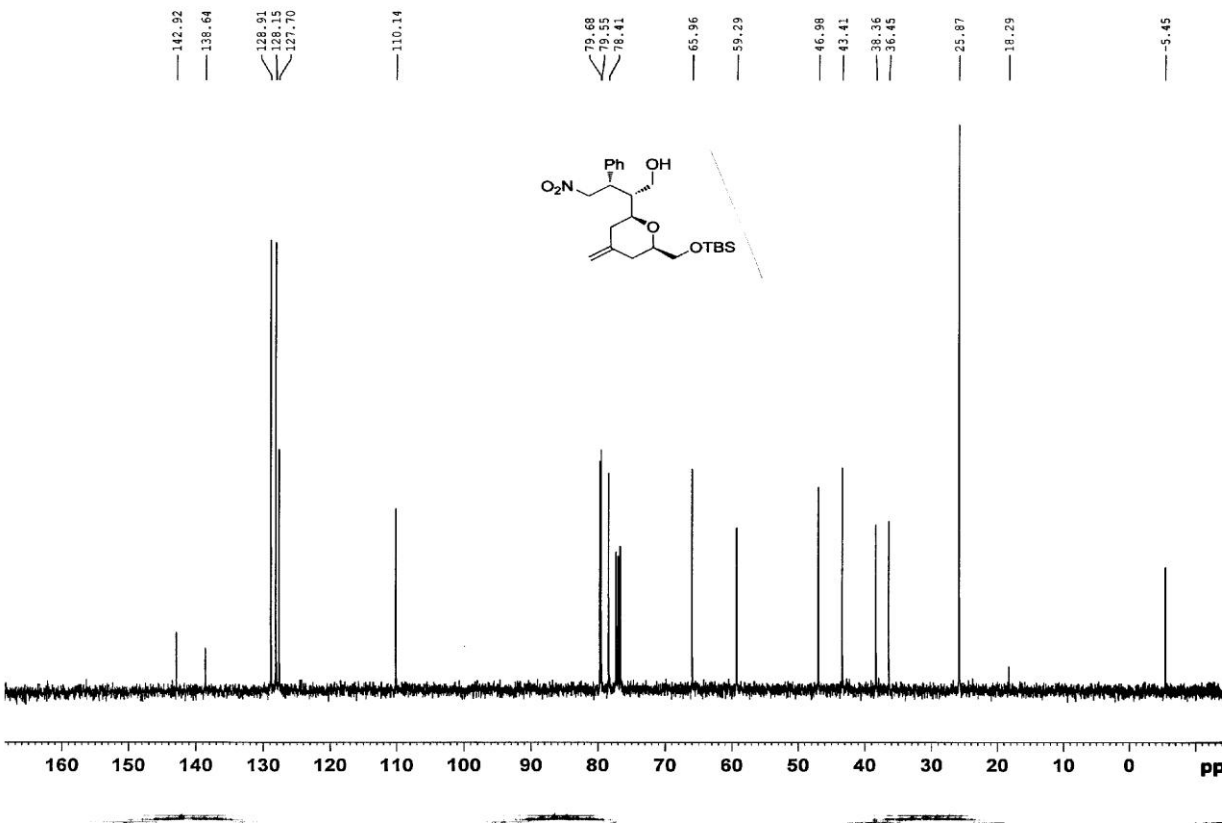

164.64
150.51
143.92
135.79
130.67
123.52
109.14
78.97
75.01
66.43
62.80
40.89
37.18
35.15
25.88
18.35
-5.22
-5.28
OPNB
O
OTBS
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

5.35o: *(2R,3S)-2-((2S,6R)-6-(((tert-butyldimethylsilyl)oxy)methyl)-4-methylenetetrahydro-2H-pyran-2-yl)-4-nitro-3-phenylbutan-1-ol*

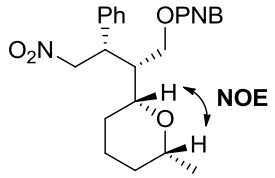


colorless amorphous solid. $[\alpha]_D^{23}$ = +2.9 (*c* 2.00, $CHCl_3$, 99% ee); IR (thin film, KBr): 3519, 2929, 2857, 1553, 1379, 1256, 1090, 837, 778, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.20 (m, 5H), 5.04 (dd, *J* = 12.6, 4.5 Hz, 1H), 4.91 (dd, *J* = 12.6, 10.9 Hz, 1H), 4.73 (dd, *J* = 17.2, 1.5 Hz, 2H), 4.19 (dd, *J* = 12.6, 1.3 Hz, 1H), 4.06 (td, *J* = 10.3, 4.6 Hz, 1H), 3.72 (m, 1H), 3.65 (m, 2H), 3.31 (m, 1H), 3.20 (m, 1H), 3.09 (m, 1H), 2.33 (m, 1H), 2.16 (m, 1H), 2.04 (m, 1H), 1.94 (m, 1H), 1.74 (m, 1H), 0.95 (s, 9H), 0.12 (d, *J* = 1.7 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 138.6, 128.9, 128.2, 127.7, 110.1, 79.7, 79.6, 78.4, 66.0, 59.3, 47.0, 43.4, 38.4, 36.5, 25.9, 18.3, -5.5 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 95:5), 0.5 mL/min; major enantiomer t_R = 13.0 min, minor enantiomer t_R = 15.6 min. LRMS (ESI) : $[M^+]$ calcd for $[C_{23}H_{37}NO_5Si]$: 435.2, found: 435.2.


7.356
7.339
7.321
7.295
7.291
7.283
7.277
7.263
7.259
7.242
5.070
5.059
5.039
5.028
4.940
4.913
4.909
4.882
4.748
4.745
4.706
4.702
4.202
4.170
4.094
4.083
4.068
4.058
4.043
4.032
3.725
3.659
3.648
3.645
3.325
3.296
3.224
3.218
3.207
3.201
3.196
3.189
2.364
2.332
2.301
2.176
2.144
2.069
2.038
1.957
1.924
1.752
1.728
1.664
0.954
0.123
Ph
OH
O2N
O
OTBS
9
8
7
6
5
4
3
2
1
0
5.51
1.00
1.02
2.06
1.00
1.04
3.03
1.00
1.06
1.02
1.04
0.99
1.10
1.04
1.05
9.09
6.02

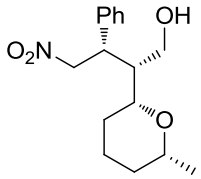

142.92
138.64
128.91
128.15
127.70
110.14
79.68
79.55
78.41
65.96
59.29
46.98
43.41
38.36
36.45
25.87
18.29
-5.45
Ph
OH
O2N
O
OTBS
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

The "undesired" product **5.31a** was determined to have a *cis* configuration via NOE NMR of the *p*-nitrobenzoate derivative (**6.4a**) of its corresponding alcohol (**6.3a**).

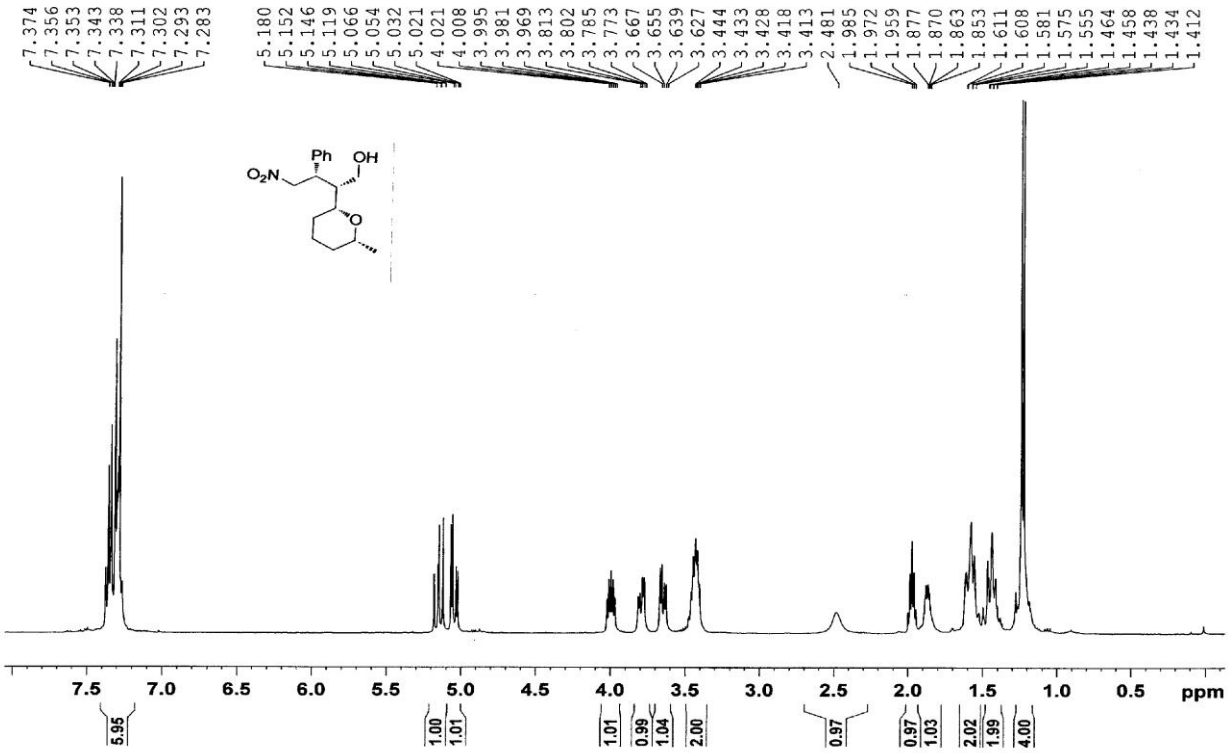


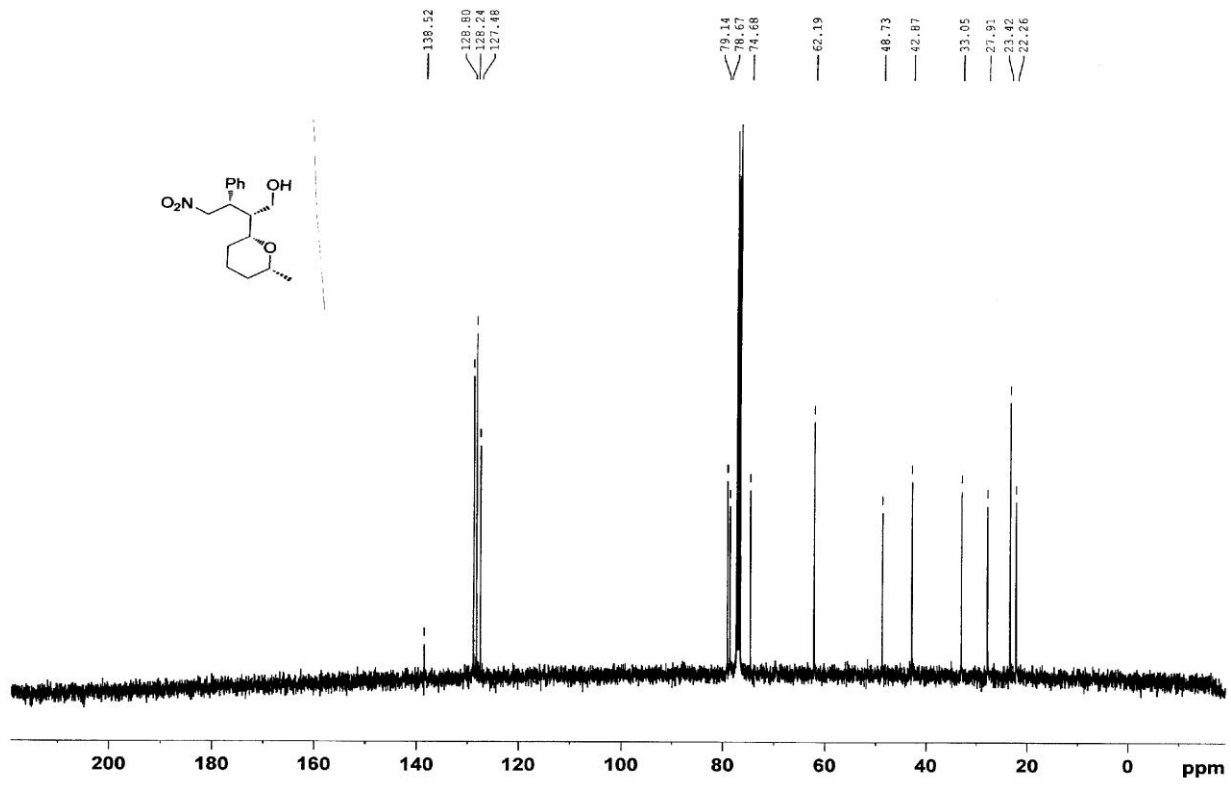
6.4a

6.3a: *(2R,3S)-2-((2R,6R)-6-methyltetrahydro-2H-pyran-2-yl)-4-nitro-3-phenylbutan-1-ol*

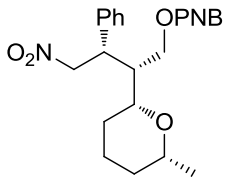


colorless oil. $[\alpha]_D^{23}$ = --55.7 (*c* 0.730, $CHCl_3$, 99% ee); IR (thin film, KBr): 3424, 2932, 2859, 1551, 1380, 1084, 1049, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.22 (m, 5H), 5.15 (dd, *J* = 13.4, 10.9 Hz, 1H), 5.04 (dd, *J* = 13.4, 4.4 Hz, 1H), 3.99 (m, 1H), 3.79 (dd, *J* = 11.3, 4.6 Hz, 1H), 3.65 (dd, *J* = 11.3, 4.8 Hz, 1H), 3.50-3.38 (m, 2H), 2.48 (bs, 1H), 1.97 (m, 1H), 1.86 (m, 1H), 1.58 (m, 2H), 1.43 (m, 2H), 1.31-1.15 (m, 1H), 1.22 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 128.8, 128.2, 127.5, 79.1, 78.7, 74.7, 62.2, 48.7, 42.9, 33.1, 27.9, 23.4, 22.3 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_{16}H_{23}NO_4]$: 293.1627, found: 293.1633.

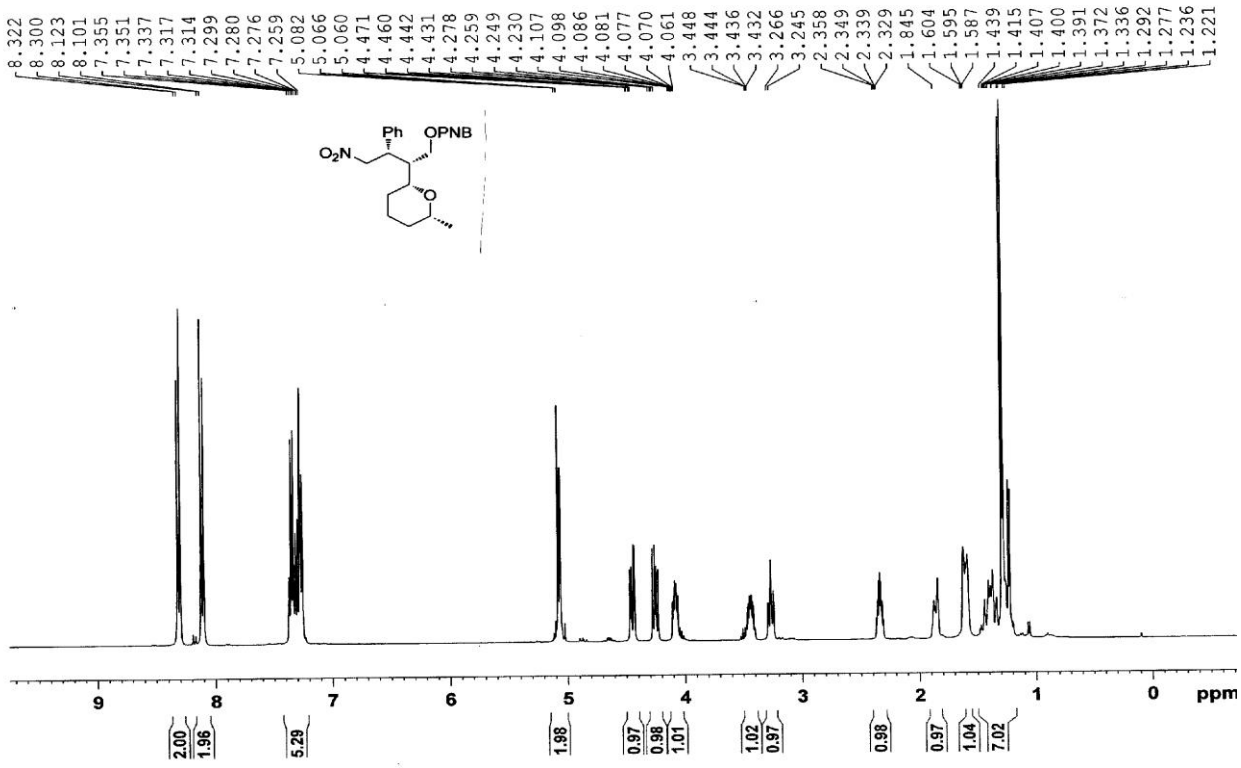

7.374
7.356
7.353
7.343
7.338
7.311
7.302
7.293
7.283
5.180
5.152
5.146
5.119
5.066
5.054
5.032
5.021
4.021
4.008
3.995
3.981
3.969
3.813
3.802
3.785
3.773
3.667
3.655
3.639
3.627
3.444
3.433
3.428
3.418
3.413
2.481
1.985
1.972
1.959
1.877
1.870
1.863
1.853
1.611
1.608
1.581
1.575
1.555
1.464
1.458
1.438
1.434
1.412
Ph
OH
O2N
O
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
ppm
5.95
1.00
1.01
1.01
0.99
1.04
2.00
0.97
0.97
1.03
2.02
1.99
4.00

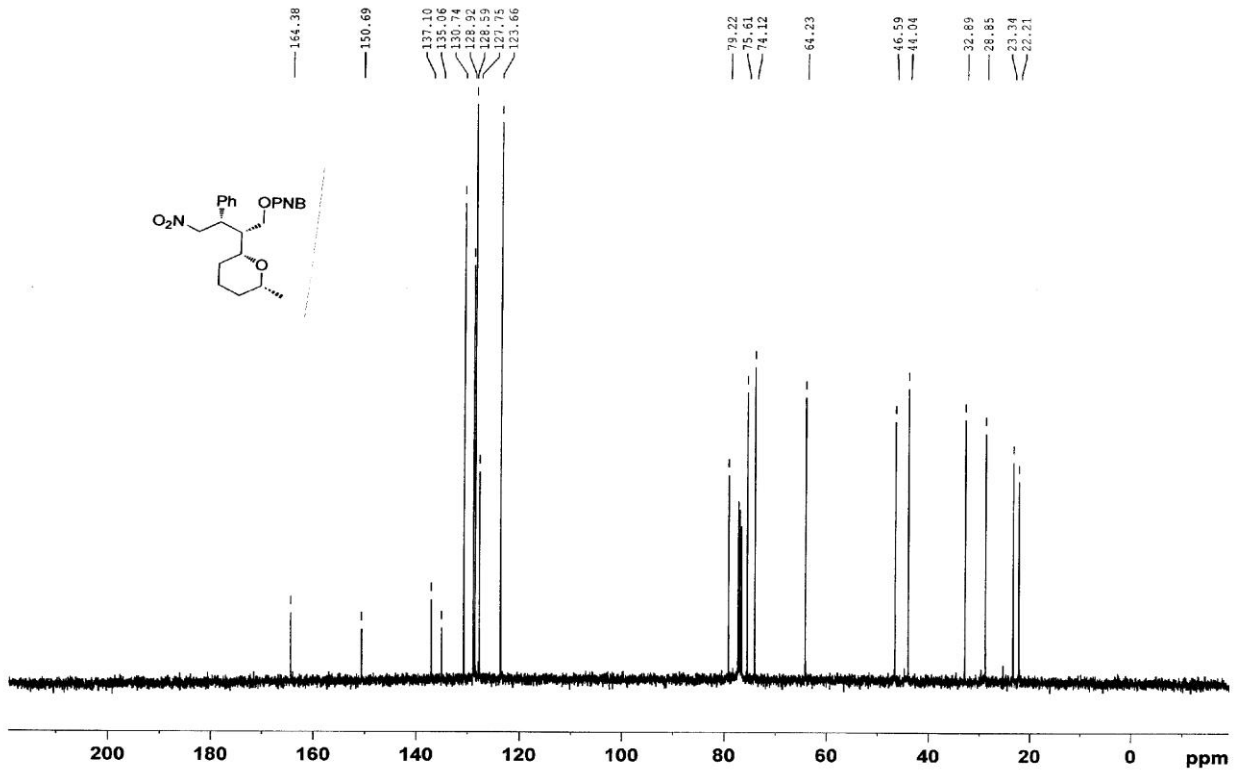

138.52
128.80
128.24
127.48
79.14
78.67
74.68
62.19
48.73
42.87
33.05
27.91
23.42
22.26
Ph
OH
O2N
O
200
180
160
140
120
100
80
60
40
20
0
ppm

6.4a: *(2R,3S)-2-((2R,6R)-6-methyltetrahydro-2H-pyran-2-yl)-4-nitro-3-phenylbutyl 4-nitrobenzoate*



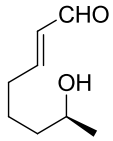
colorless amorphous solid. $[\alpha]_D^{24}$ = -12.6 (*c* 2.00, $CHCl_3$, 99% ee); IR (thin film, KBr): 3444, 2932, 2859, 1727, 1552, 1529, 1275, 1104, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.8 Hz, 2H), 7.40-7.21 (m, 5H), 5.07 (m, 2H), 4.45 (dd, *J* = 11.6, 4.2 Hz, 1H), 4.25 (dd, *J* = 11.6, 7.4 Hz, 1H), 4.07 (m, 1H), 3.44 (m, 1H), 3.27 (m, 1H), 2.34 (m, 1H), 1.87 (m, 1H), 1.60 (m, 1H), 1.50-1.20 (m, 4H), 1.28 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 150.7, 137.1, 135.1, 130.7, 128.9, 128.6, 127.8, 123.7, 79.2, 75.6, 74.1, 64.2, 46.6, 44.0, 32.9, 28.9, 23.3, 22.2 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 95:5), 0.5 mL/min; minor enantiomer t_R = 44.2 min, major enantiomer t_R = 54.2 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{23}H_{26}N_2O_7]$: 442.1740, found: 442.1748.


8.322
8.300
8.123
8.101
7.355
7.351
7.337
7.317
7.314
7.299
7.280
7.276
7.259
5.082
5.066
5.060
4.471
4.460
4.442
4.431
4.278
4.259
4.249
4.230
4.107
4.098
4.086
4.081
4.077
4.070
4.061
3.448
3.444
3.436
3.432
3.266
3.245
2.358
2.349
2.339
2.329
1.845
1.604
1.595
1.587
1.439
1.415
1.407
1.400
1.391
1.372
1.336
1.292
1.277
1.236
1.221
Ph
OPNB
O2N
O
9
8
7
6
5
4
3
2
1
0
ppm
2.00
1.96
5.29
1.98
0.97
0.98
1.01
1.02
0.97
0.98
0.97
1.04
7.02


164.38
150.69
137.10
135.06
130.74
128.92
128.59
127.75
123.66
79.22
75.61
74.12
64.23
46.59
44.04
32.89
28.85
23.34
22.21
Ph
OPNB
O2N
O
200
180
160
140
120
100
80
60
40
20
0
ppm

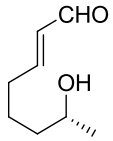
Chiral substrates **(*S*)**–**5.16a** and **(*R*)**–**5.16a** were prepared from the chiral secondary alcohols[16] using the cross metathesis method described above in the synthesis of **5.16a**.

(*S*)–**5.16a**: *(S,E)-7-hydroxyoct-2-enal*



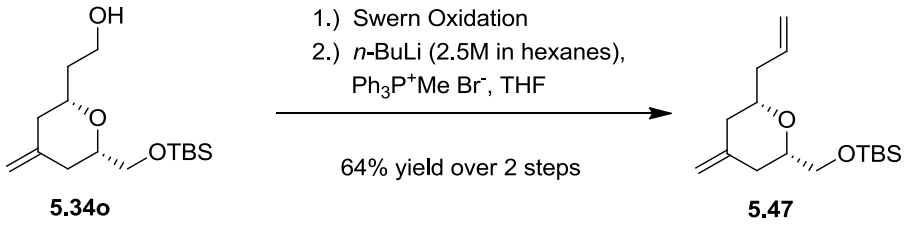
brown oil. Collected in 82% yield. $[\alpha]_D^{22}$ = +13.5 (*c* 2.00, $CHCl_3$); IR (thin film, KBr): 3419, 2966, 2931, 2864, 2737, 1690, 1143, 977 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, *J* = 7.9 Hz, 1H), 6.86 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.14 (m, 1H), 3.83 (m, 1H), 2.38 (m, 2H), 1.67-1.49 (m, 5H), 1.21 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 158.6, 133.3, 67.8, 38.6, 32.7, 24.2, 23.8 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_8H_{14}O_2]$: 142.0994, found: 142.0994.

(*R*)–**5.16a**: *(R,E)-7-hydroxyoct-2-enal*



brown oil. Collected in 76% yield. $[\alpha]_D^{24}$ = -13.2 (*c* 2.00, $CHCl_3$); IR (thin film, KBr): 3419, 2966, 2931, 2864, 2737, 1690, 1143, 977 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, *J* = 7.9 Hz, 1H), 6.86 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.14 (m, 1H), 3.83 (m, 1H), 2.38 (m, 2H), 1.67-1.49 (m, 5H), 1.21 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 158.6, 133.3, 67.8, 38.6, 32.7, 24.2, 23.8 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_8H_{14}O_2]$: 142.0994, found: 142.0994.

Synthesis of Diolefin (5.47)



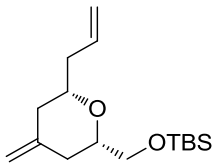
5.34o **5.47**

Product **5.34o** (54.4 mg, 0.19 mmol) was oxidized to the aldehyde via Swern Oxidation using the same conditions described above in the synthesis of **5.16o**. The reaction yielded 44.0 mg of the corresponding aldehyde (82% yield).

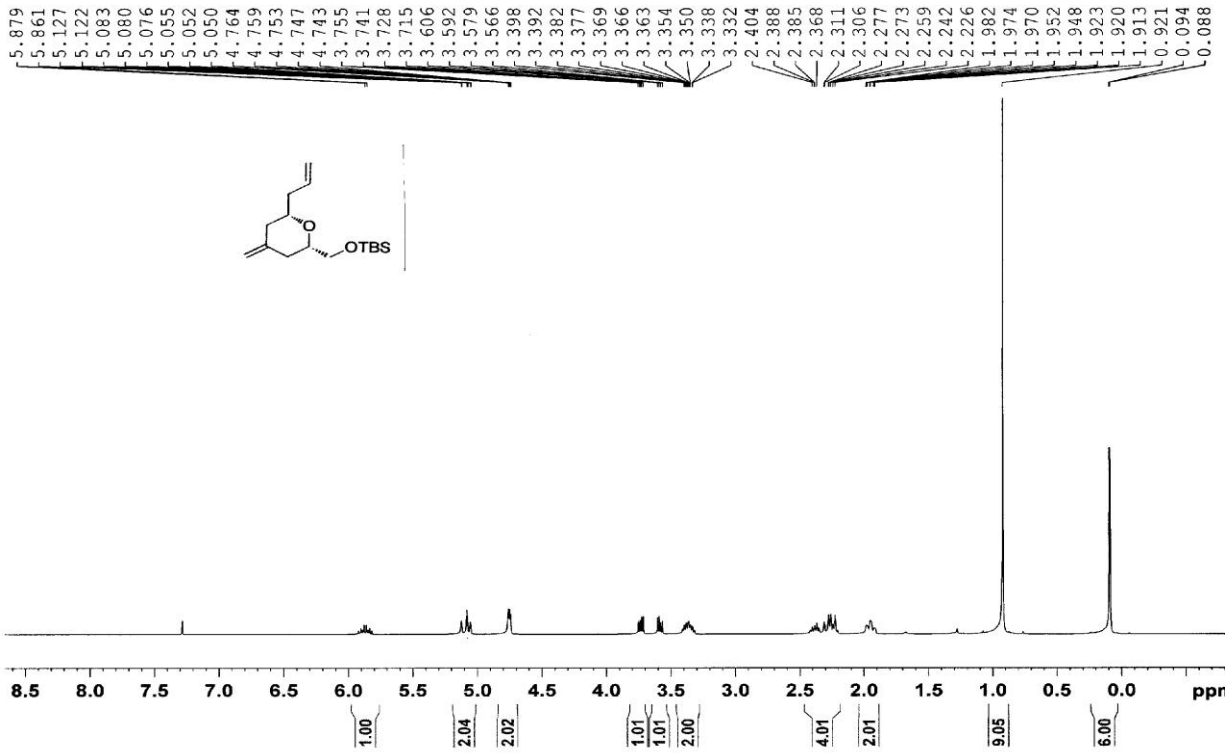
Triphenylphosphonium bromide (111 mg, 0.31 mmol) was suspended in THF (1.76 mL) and brought to 0 °C. *n*-BuLi (2.5M in hexanes, 0.12 mL, 0.279 mmol) was added dropwise and the reaction was stirred for 30 minutes at 0 °C. The reaction was then cooled to –78 °C. The aldehyde from step 1 (44.0 mg, 0.155 mmol) was dissolved in THF (1.17 mL) and added to the

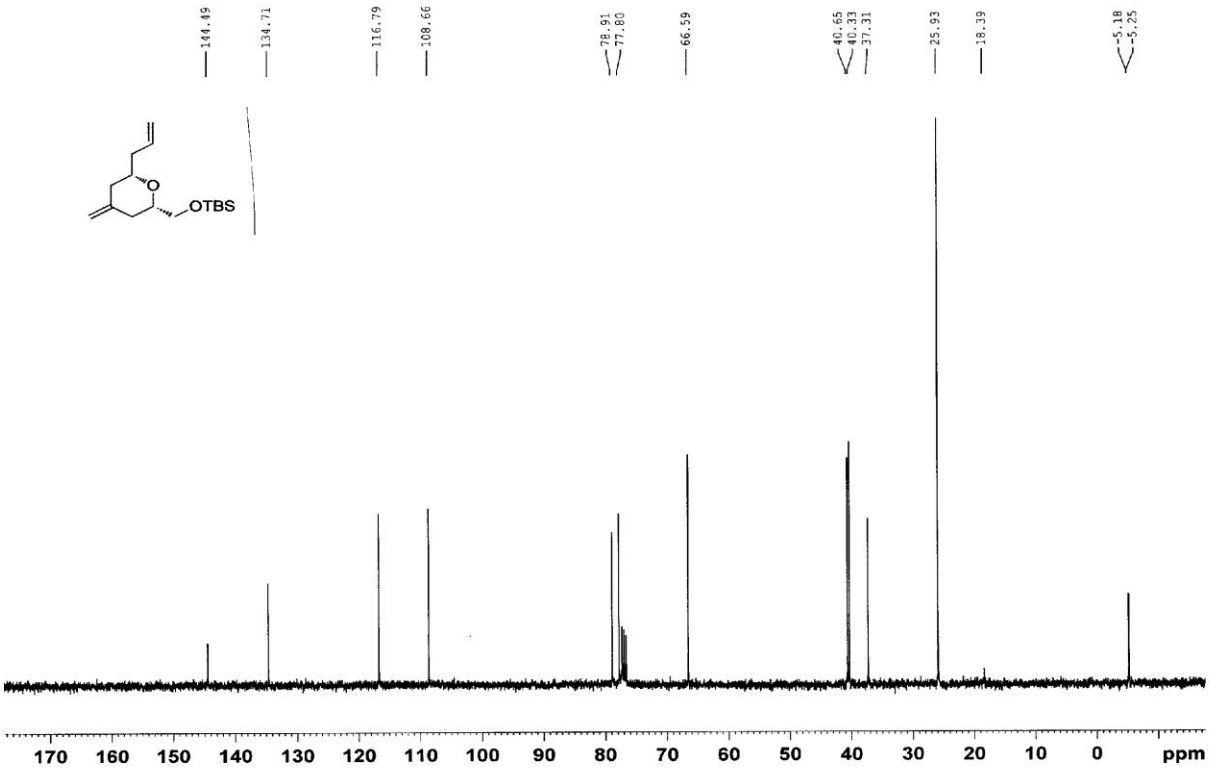
triphenylphosphonium bromide solution dropwise at –78 ^{o}C. The reaction was warmed to room temperature and after stirring for 1h the reaction was quenched with water (10 mL) and was extracted with Et_2O (2 x 15 mL). The Et_2O layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was purified via column chromatography (Et_2O/petroleum ether, 2/98) to give 34 mg of olefin **5.47** (78% yield).

5.47: *(((2S,6S)-6-allyl-4-methylenetetrahydro-2H-pyran-2-yl)methoxy)(tert-butyl)dimethylsilane*[17]

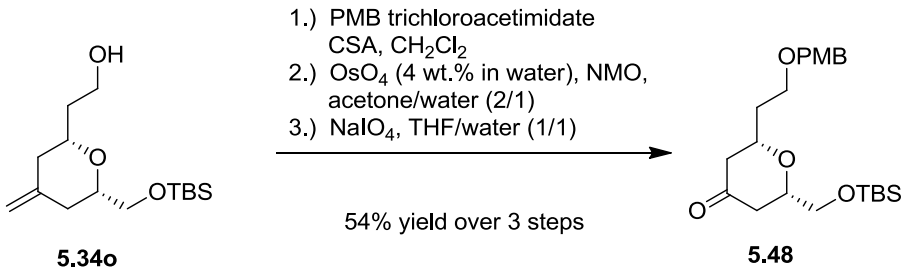


colorless oil. $[\alpha]_D^{22}$ = -19.0 (*c* 2.00, $CHCl_3$, 94% ee); IR (thin film, KBr): 3076, 2955, 2857, 1654, 1253, 1099, 835, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.10 (m, 2H), 4.75 (m, 2H), 3.73 (dd, *J* = 10.5, 5.3 Hz, 1H), 3.59 (dd, *J* = 10.4, 5.5 Hz, 1H), 3.37 (m, 2H), 2.43-2.20 (m, 4H), 1.95 (m, 2H), 0.92 (s, 9H), 0.09 (d, *J* = 2.6 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 134.7, 116.8, 108.7, 78.9, 77.8, 66.6, 40.7, 40.3, 37.3, 25.9, 18.4, -5.2, -5.3 ppm; LRMS (ESI) : [M^+] calcd for [$C_{16}H_{30}O_2Si$]: 282.2, found: 282.2.


5.879
5.861
5.127
5.122
5.083
5.080
5.076
5.055
5.052
5.050
4.764
4.759
4.753
4.747
4.743
3.755
3.741
3.728
3.715
3.606
3.592
3.579
3.566
3.398
3.392
3.382
3.377
3.369
3.366
3.363
3.354
3.350
3.338
3.332
2.404
2.388
2.385
2.368
2.311
2.306
2.277
2.273
2.259
2.242
2.226
1.982
1.974
1.970
1.952
1.948
1.923
1.920
1.913
0.921
0.094
0.088
OTBS
8.5 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 ppm
1.00
2.04
2.02
1.01
1.01
2.00
4.01
2.01
9.05
6.00


144.49
134.71
116.79
108.66
78.91
77.80
66.59
40.65
40.33
37.31
25.93
18.39
-5.18
-5.25
OTBS
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

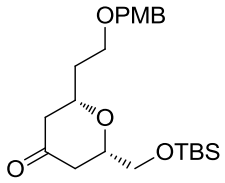
Synthesis of Ketone (5.48)



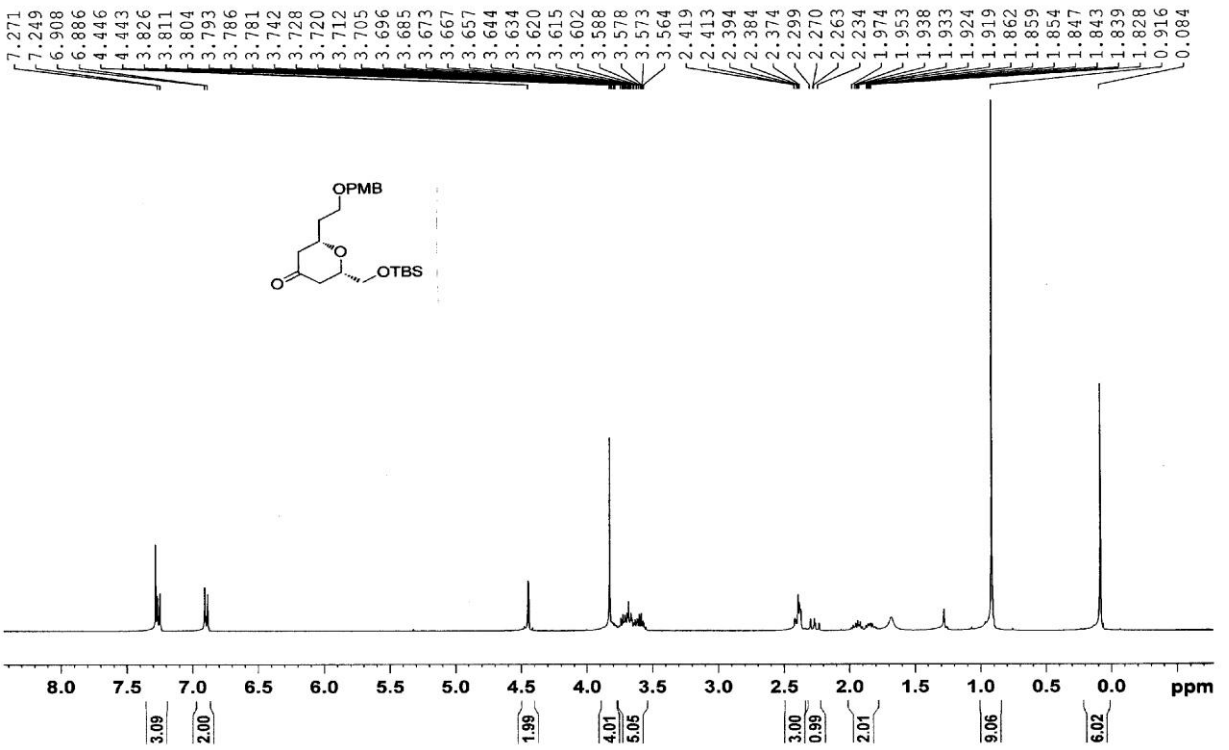
5.34o **5.48**

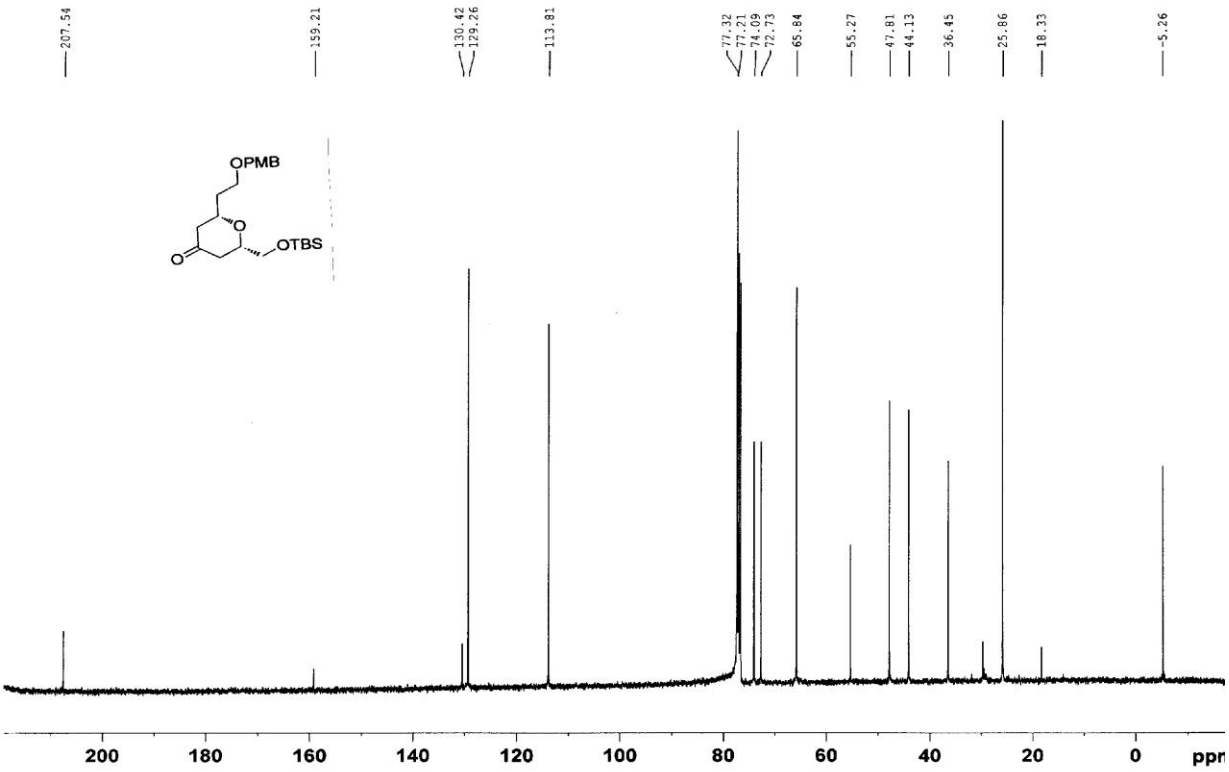
Product **5.34o** (33.0 mg, 0.115 mmol) was dissolved in CH_2Cl_2 at room temperature. PMB trichloroacetimidate (32 µL, 0.1725 mmol) was added followed by CSA (2.7 mg, 0.0115 mmol). The reaction was stirred at room temperature for 24 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (2 x 15 mL). The CH_2Cl_2 layers were combined, dried over $MgSO_4$, filtered, and concentrated. The PMB protected alcohol was purified via column chromatography (EtOAc/petroleum ether, 4/96). The PMB protected alcohol was dissolved in acetone/water (2/1, 2.5 mL). Then 4-methylmorpholine *N*-oxide (32 mg, 0.273 mol) was added at room temperature followed by OsO_4 (4 wt.% in water) (117 µL). The reaction was stirred at room temperature for 2 h. The reaction was quenched by the addition of 6 mL saturated aqueous Na_2SO_3. The aqueous layer was extracted with EtOAc (2 x 15 mL). The EtOAc layers were combined, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in THF/water (1/1, 2.5 mL). Solid sodium periodate (195 mg, 0.91 mmol) was added and the reaction was stirred for 1 h at room temperature. The reaction was then diluted with 6 mL water and the aqueous layer was extracted with EtOAc (2 x 15 mL). The EtOAc layers were combined, dried over $MgSO_4$, filtered, and concentrated. The residue was purified via column chromatography (Et_2O/petroleum ether, 30/70) to give 25.2 mg of ketone **5.46** (54% yield over 3 steps).

5.48: *(2S,6S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-6-(2-((4-methoxybenzyl)oxy)ethyl)dihydro-2H-pyran-4(3H)-one*[18]



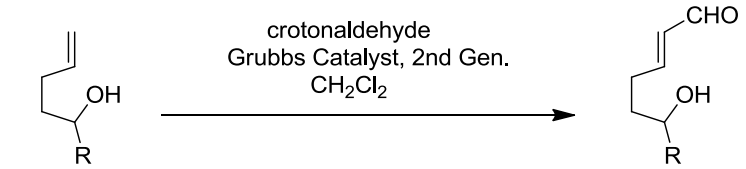
colorless oil. $[\alpha]_D^{21}$ = -16.7 (*c* 1.575, $CHCl_3$, 94% ee); IR (thin film, KBr): 2856, 1720, 1513, 1249, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 4.44 (m, 2H), 3.83 (s, 3H), 3.80-3.54 (m, 6H), 2.39 (m, 3H), 2.28 (dd, J = 14.6, 11.7 Hz, 1H), 2.00-1.75 (m, 2H), 0.92 (s, 9H), 0.08 (S, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 159.2, 130.4, 129.3, 113.8, 77.3, 77.2, 74.1, 72.7, 65.8, 55.3, 47.8, 44.1, 36.5, 25.9, 18.3, -5.3 ppm; LRMS (ESI) : $[M^+]$ calcd for $[C_{22}H_{36}O_5Si]$: 408.2, found: 408.2.


7.271
7.249
6.908
6.886
4.446
4.443
3.826
3.811
3.804
3.793
3.786
3.781
3.742
3.728
3.720
3.712
3.705
3.696
3.685
3.673
3.667
3.657
3.644
3.634
3.620
3.615
3.602
3.588
3.578
3.573
3.564
2.419
2.413
2.394
2.384
2.374
2.299
2.270
2.263
2.234
1.974
1.953
1.938
1.933
1.924
1.919
1.862
1.859
1.854
1.847
1.843
1.839
1.828
0.916
0.084
OPMB
OTBS
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
ppm
3.09
2.00
1.99
4.01
5.05
3.00
0.99
2.01
9.06
6.02


207.54
159.21
130.42
129.26
113.81
77.32
77.21
74.09
72.73
65.84
55.27
47.81
44.13
36.45
25.86
18.33
-5.26
OPMB
OTBS
200
180
160
140
120
100
80
60
40
20
0
ppm

Preparation of Substrates (5.49a–h and 5.49k)

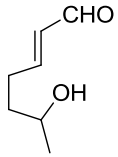
The substrates **5.49a–h** and **5.49k** were prepared by cross metathesis of the secondary alcohols **5.55a–h** and **5.55k**[14] using the procedure described below.



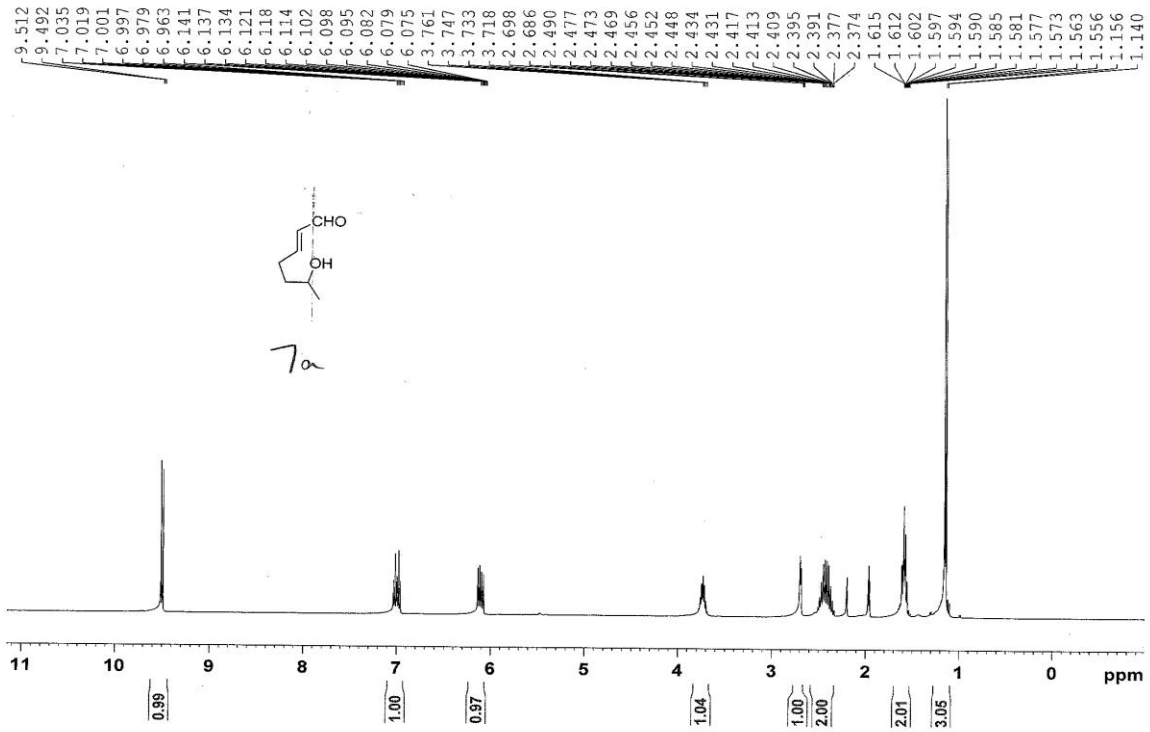
5.55a-i and **5.55k** **5.49a-i** and **5.49k**

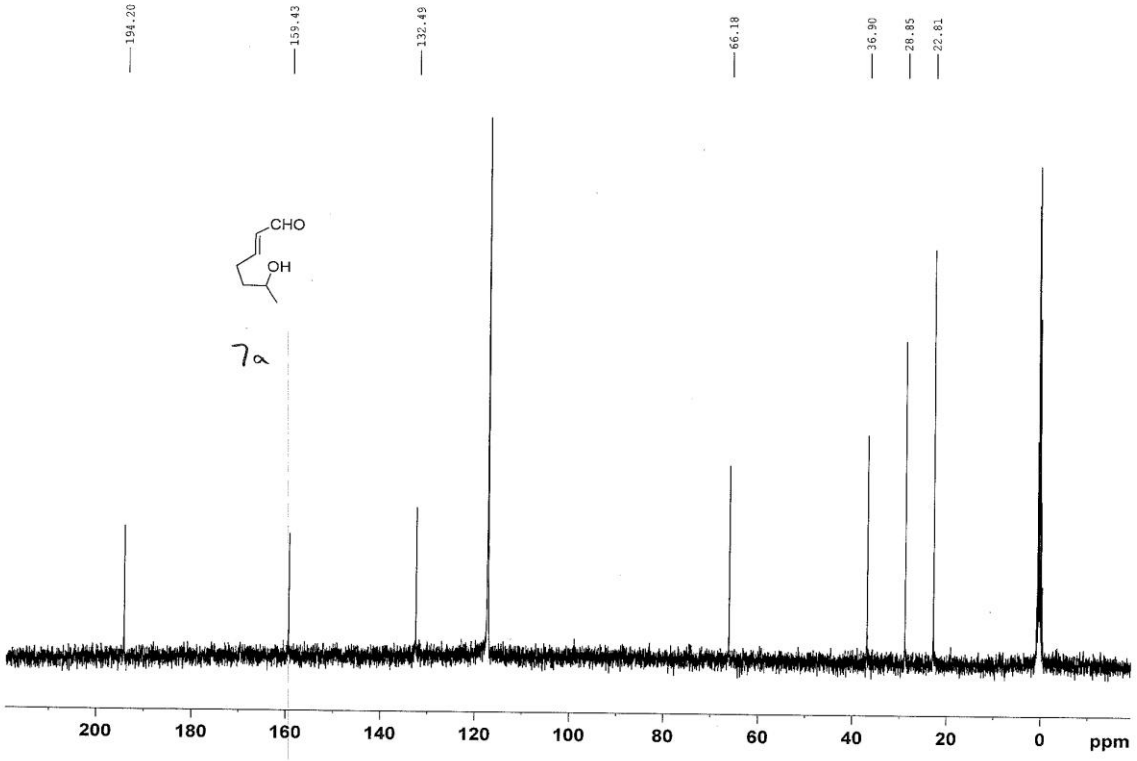
The secondary alcohol **5.55** (5.0 mmol) was dissolved in dry CH_2Cl_2 (25.0 mL). Crotonaldehyde (2.07 mL, 25.0 mmol) was added followed by Grubbs Catalyst, 2nd Generation (42.4 mg, 0.050 mmol). The reaction was refluxed for 1.5 h and then concentrated at reduced pressure. Substrate **5.49** was purified via column chromatography (EtOAc/petroleum ether, 35/65) and used immediately in the kinetic resolution reaction.

5.49a: *(E)-6-hydroxyhept-2-enal*

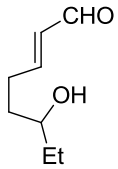


brown oil. Collected in 80% yield. IR (thin film, KBr): 3423, 2968, 2930, 2740, 1690, 1375 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.50 (d, *J* = 7.9 Hz, 1H), 7.00 (dt, *J* = 15.5, 6.8 Hz, 1H), 6.11 (ddt, *J* = 15.6, 7.9, 1.5 Hz, 1H), 3.73 (m, 1H), 2.70 (m, 1H), 2.55-2.33 (m, 2H), 1.65-1.53 (m, 2H), 1.15 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 194.2, 159.4, 132.5, 66.2, 36.9, 28.9, 22.8 ppm; HRMS (ESI) : [M^+] calcd for [$C_7H_{12}O_2$]: 128.0837, found: 128.0838.

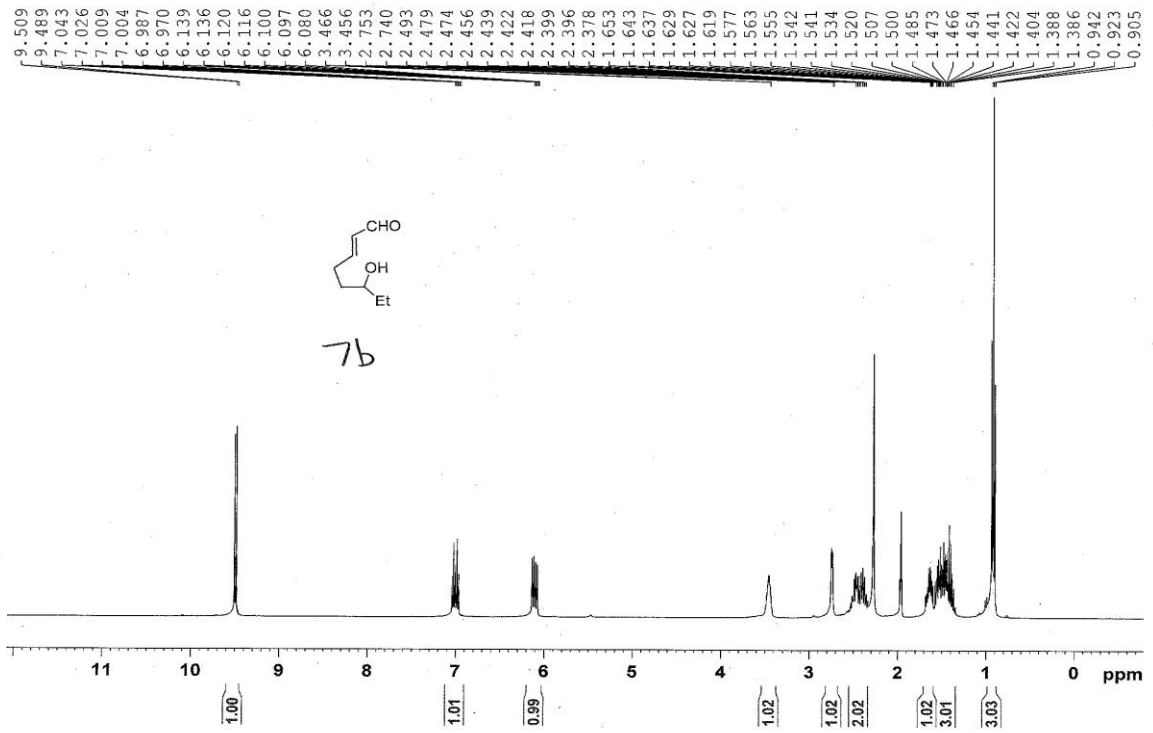

9.512
9.492
7.035
7.019
7.001
6.997
6.979
6.963
6.141
6.137
6.134
6.121
6.118
6.114
6.102
6.098
6.095
6.082
6.079
6.075
3.761
3.747
3.733
3.718
2.698
2.686
2.490
2.477
2.473
2.469
2.456
2.452
2.448
2.434
2.431
2.417
2.413
2.409
2.395
2.391
2.377
2.374
1.615
1.612
1.602
1.597
1.594
1.590
1.585
1.581
1.577
1.573
1.563
1.556
1.156
1.140
CHO
OH
7a
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.99
1.00
0.97
1.04
1.00
2.00
2.01
3.05

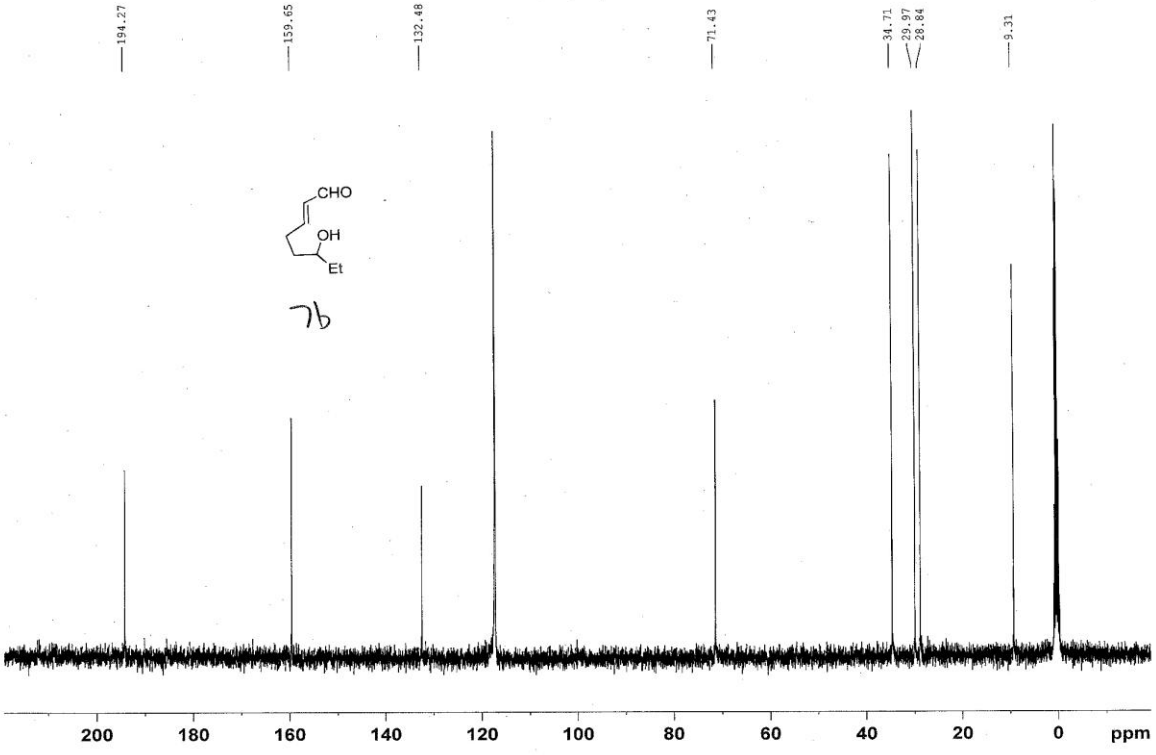

194.20
159.43
132.49
66.18
36.90
28.85
22.81
CHO
OH
7a
200
180
160
140
120
100
80
60
40
20
0
ppm

5.49b: *(E)-6-hydroxyoct-2-enal*

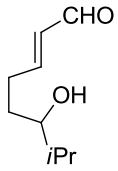


brown oil. Collected in 69% yield. IR (thin film, KBr): 3424, 2963, 2934, 2877, 1682, 1140, 973, 931 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.50 (d, *J* = 7.9 Hz, 1H), 7.00 (dt, *J* = 15.5, 6.8 Hz, 1H), 6.11 (ddt, *J* = 15.5, 7.9, 1.5 Hz, 1H), 3.46 (m, 1H), 2.75 (d, *J* = 5.1 Hz, 1H), 2.57-2.30 (m, 2H), 1.69-1.33 (m, 4H), 0.92 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 194.3, 159.7, 132.5, 71.4, 34.7, 30.0, 28.8, 9.3 ppm; HRMS (ESI) : [M^+] calcd for [$C_8H_{14}O_2$]: 142.0994, found: 142.0993.

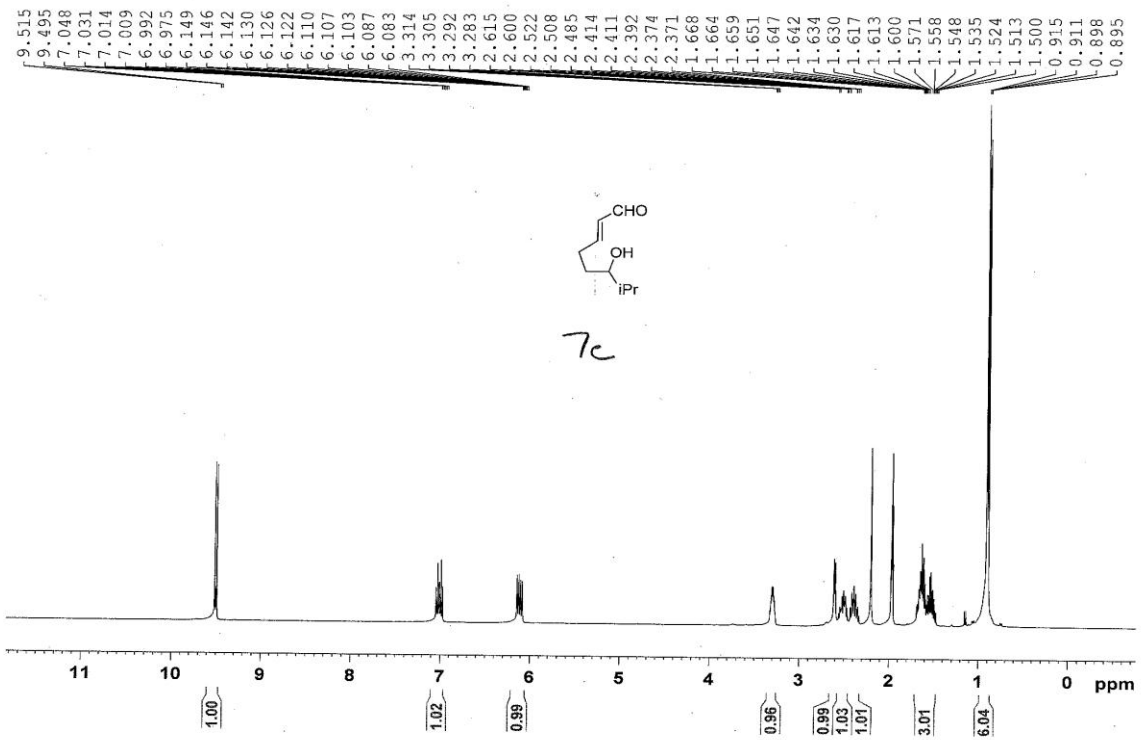

9.509
9.489
7.043
7.026
7.009
7.004
6.987
6.970
6.139
6.136
6.120
6.116
6.100
6.097
6.080
3.466
3.456
2.753
2.740
2.493
2.479
2.474
2.456
2.439
2.422
2.418
2.399
2.396
2.378
1.653
1.643
1.637
1.629
1.627
1.619
1.577
1.563
1.555
1.542
1.541
1.534
1.520
1.507
1.500
1.485
1.473
1.466
1.454
1.441
1.422
1.404
1.388
1.386
0.942
0.923
0.905
CHO
OH
Et
7b
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.01
0.99
1.02
1.02
2.02
1.02
3.01
3.03

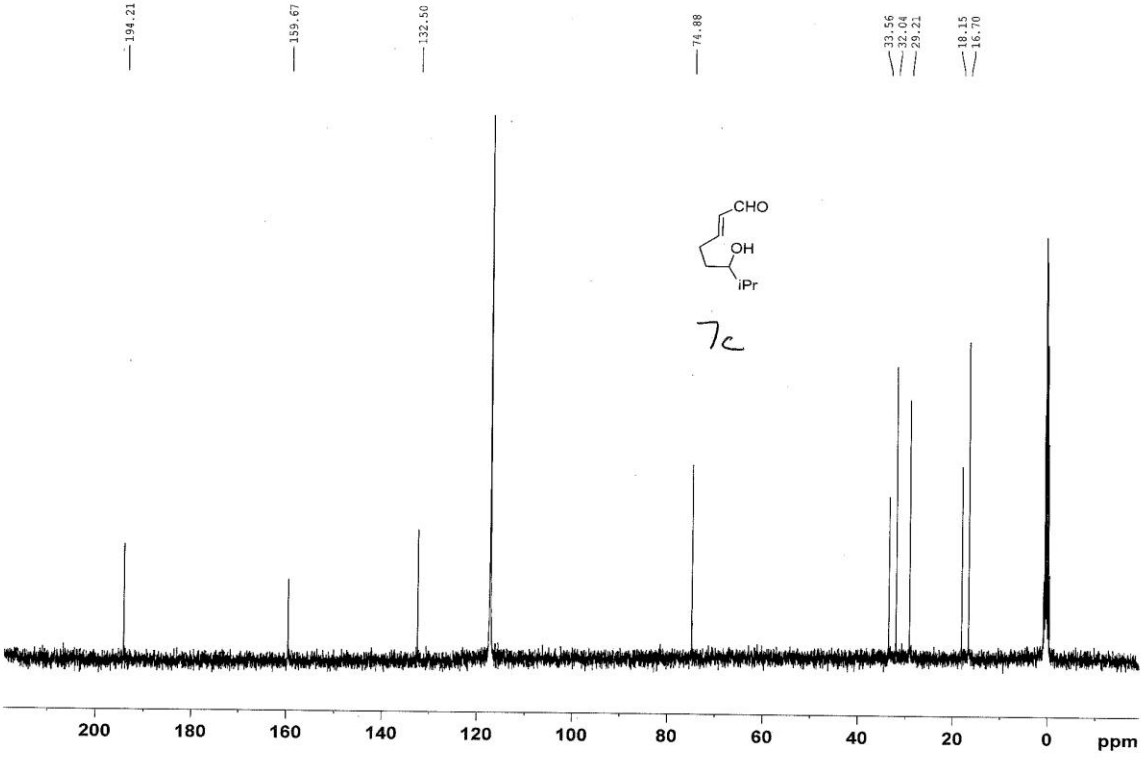

194.27
159.65
132.48
71.43
34.71
29.97
28.84
9.31
CHO
OH
Et
7b
200
180
160
140
120
100
80
60
40
20
0
ppm

5.49c: *(E)-6-hydroxy-7-methyloct-2-enal*

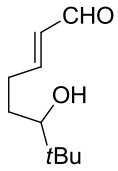


brown oil. Collected in 70% yield. IR (thin film, KBr): 3428, 2960, 2874, 2736, 1686, 1469, 1140 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.51 (d, *J* = 7.9 Hz, 1H), 7.01 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.12 (ddt, *J* = 15.6, 7.9, 1.5 Hz, 1H), 3.30 (m, 1H), 2.61 (m, 1H), 2.58-2.33 (m, 2H), 1.71-1.47 (m, 3H), 0.90 (dd, *J* = 6.8, 1.6 Hz, 6H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 194.2, 159.7, 132.5, 74.9, 33.6, 32.0, 29.2, 18.2, 16.7 ppm; HRMS (ESI) : [M^+] calcd for [$C_9H_{16}O_2$]: 156.1150, found: 156.1149.

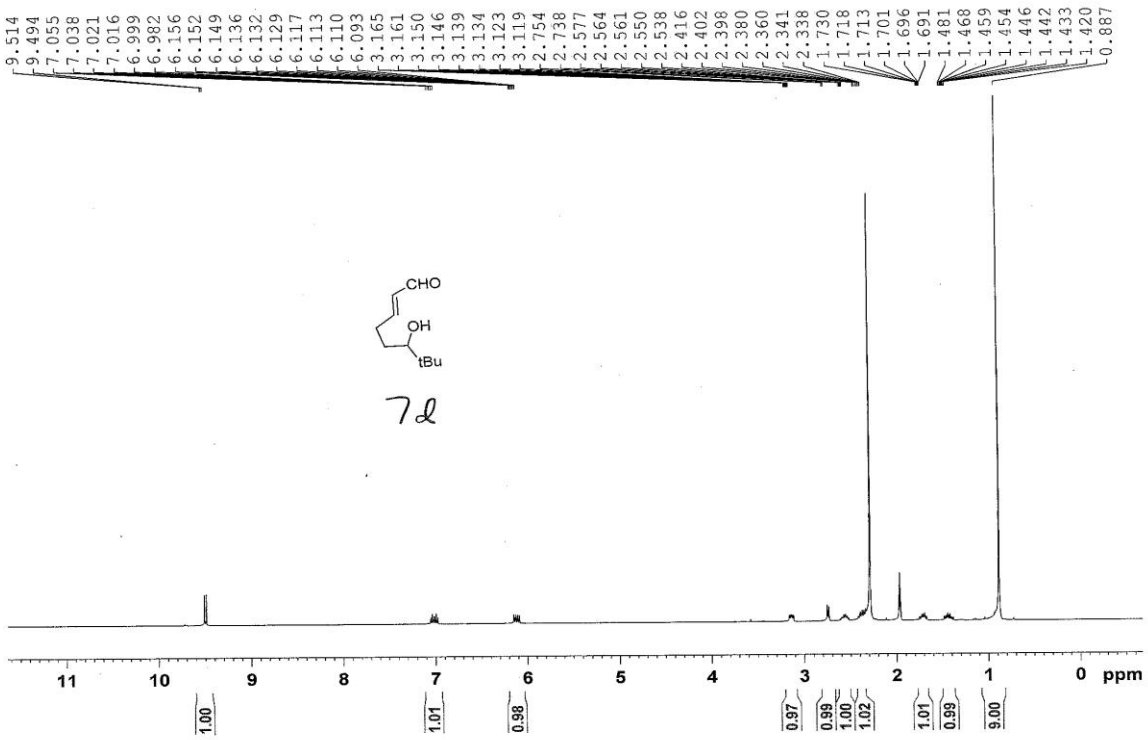

9.515
9.495
7.048
7.031
7.014
7.009
6.992
6.975
6.149
6.146
6.142
6.130
6.126
6.122
6.110
6.107
6.103
6.087
6.083
3.314
3.305
3.292
3.283
2.615
2.600
2.522
2.508
2.485
2.414
2.411
2.392
2.374
2.371
1.668
1.664
1.659
1.651
1.647
1.642
1.634
1.630
1.617
1.613
1.600
1.571
1.558
1.548
1.535
1.524
1.513
1.500
0.915
0.911
0.898
0.895
CHO
OH
iPr
7c
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.02
0.99
0.96
0.99
1.03
1.01
3.01
6.04

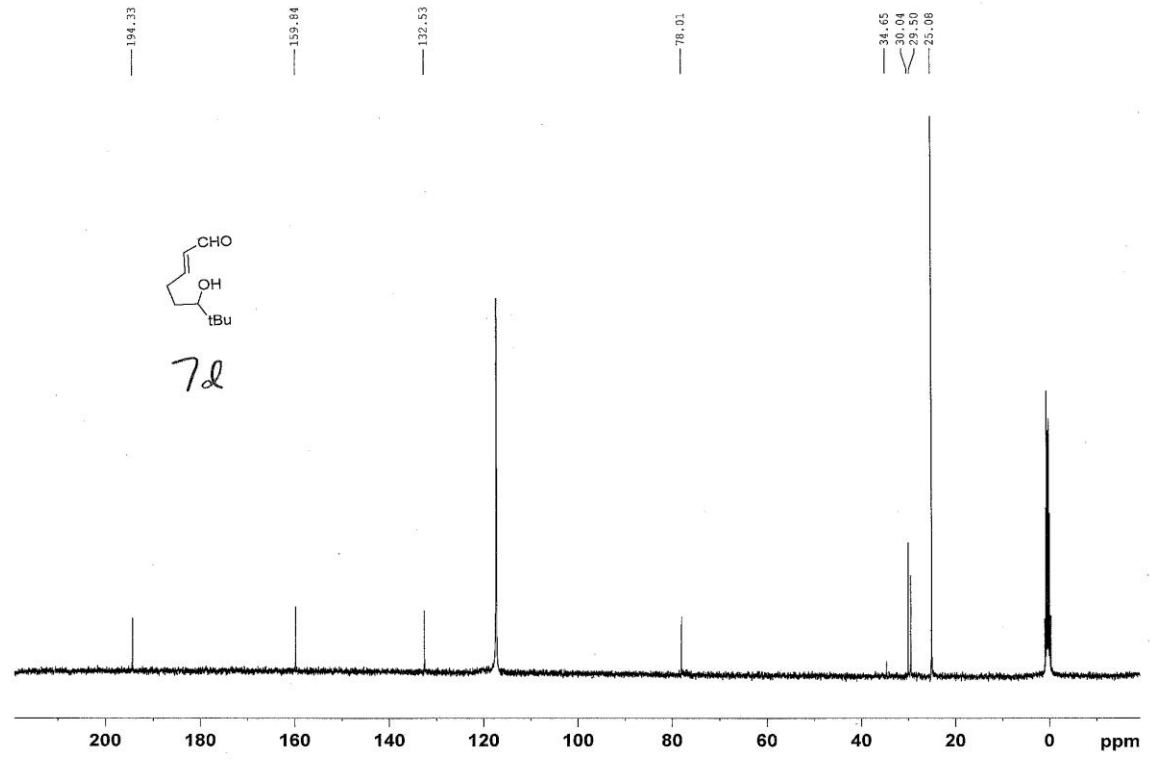

194.21
159.67
132.50
74.88
33.56
32.04
29.21
18.15
16.70
CHO
OH
iPr
7c
200
180
160
140
120
100
80
60
40
20
0
ppm

5.49d: *(E)-6-hydroxy-7,7-dimethyloct-2-enal*

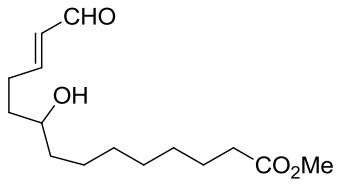


brown oil. Collected in 60% yield. IR (thin film, KBr): 3457, 2953, 2869, 1679, 1130, 1075 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.50 (d, *J* = 7.9 Hz, 1H), 7.02 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.14 (ddt, *J* = 15.6, 7.9, 1.5 Hz, 1H), 3.14 (m, 1H), 2.75 (d, *J* = 6.3 Hz, 1H), 2.56 (m, 1H), 2.37 (m, 1H), 1.71 (m, 1H), 1.45 (m, 1H), 0.89 (s, 9H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 194.3, 159.8, 132.5, 78.0, 34.7, 30.0, 29.5, 25.1 ppm; HRMS (ESI) : [M^+] calcd for [$C_{10}H_{18}O_2$]: 170.1307, found: 170.1306.

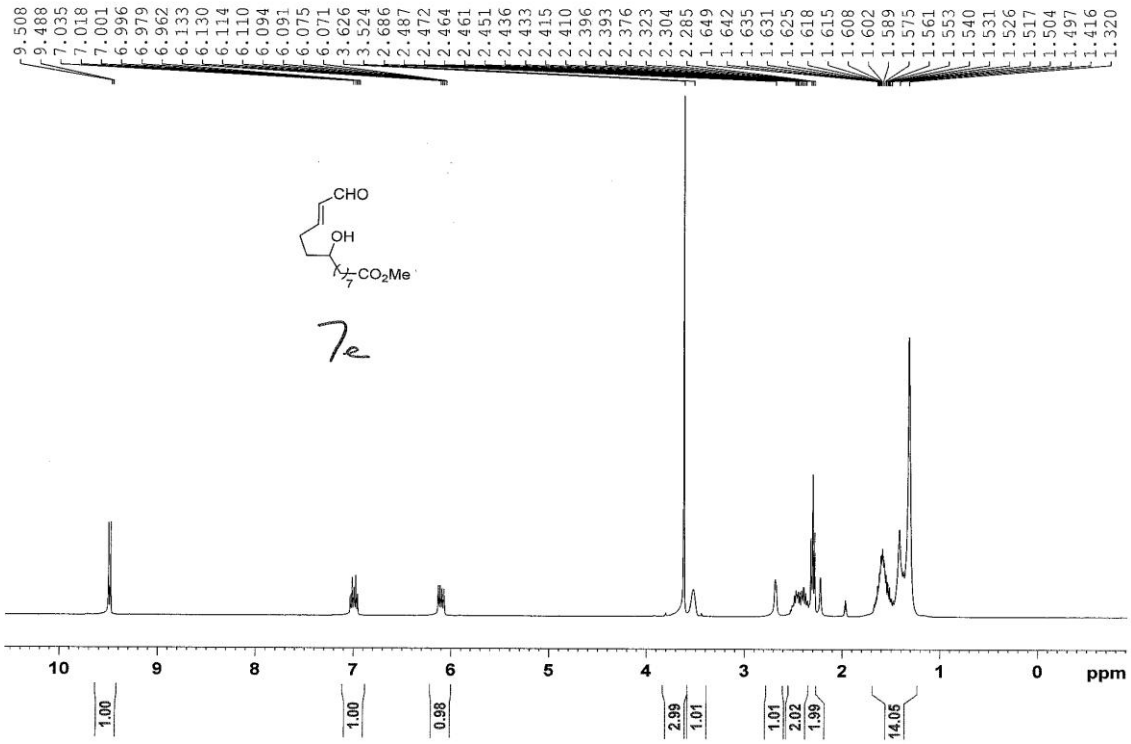

9.514
9.494
7.055
7.038
7.021
7.016
6.999
6.982
6.156
6.152
6.149
6.136
6.132
6.129
6.117
6.113
6.110
6.093
3.165
3.161
3.150
3.146
3.139
3.134
3.123
3.119
2.754
2.738
2.577
2.564
2.561
2.550
2.538
2.416
2.402
2.398
2.380
2.360
2.341
2.338
1.730
1.718
1.713
1.701
1.696
1.691
1.481
1.468
1.459
1.454
1.446
1.442
1.433
1.420
0.887
CHO
OH
tBu
7d
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.01
0.98
0.97
0.99
1.00
1.02
1.01
0.99
9.00


194.33
159.84
132.53
78.01
34.65
30.04
29.50
25.08
CHO
OH
tBu
7d
200
180
160
140
120
100
80
60
40
20
0
ppm

5.49e: *(E)-methyl 9-hydroxy-14-oxotetradec-12-enoate*



tan amorphous solid. Collected in 70% yield. IR (thin film, KBr): 3359, 2924, 2850, 1731, 1685 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.50 (d, *J* = 7.9 Hz, 1H), 7.00 (dt, *J* = 15.5, 6.8 Hz, 1H), 6.10 (ddt, *J* = 15.6, 7.9, 1.5 Hz, 1H), 3.63 (s, 3H), 3.52 (m, 1H), 2.69 (bs, 1H), 2.55-2.32 (m, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.69-1.23 (m, 14H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 194.2, 173.8, 159.6, 132.5, 70.0, 50.9, 37.2, 35.2, 33.5, 29.2, 29.0, 28.8, 28.7, 25.3, 24.7 ppm; HRMS (ESI) : [M^+] calcd for [$C_{15}H_{26}O_4$]: 270.1831, found: 270.1832.


9.508
9.488
7.035
7.018
7.001
6.996
6.979
6.962
6.133
6.130
6.114
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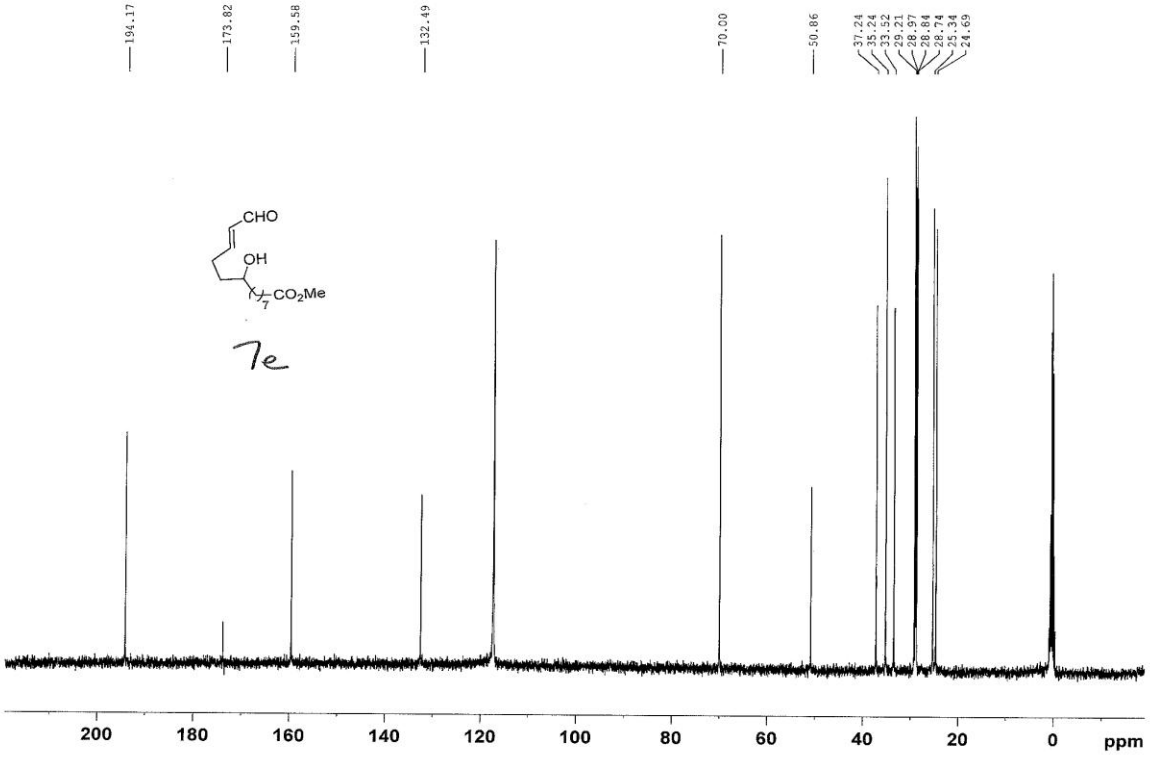
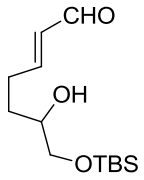
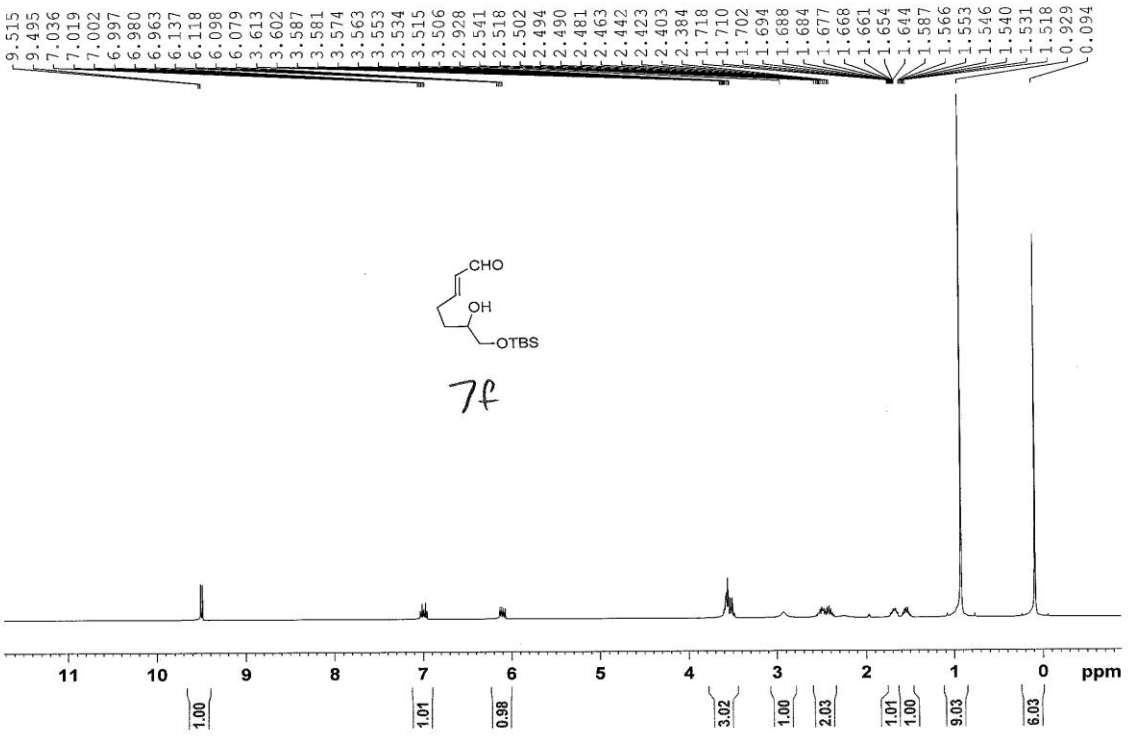
6.091
6.075
6.071
3.626
3.524
2.686
2.487
2.472
2.464
2.461
2.451
2.436
2.433
2.415
2.410
2.396
2.393
2.376
2.323
2.304
2.285
1.649
1.642
1.635
1.631
1.625
1.618
1.615
1.608
1.602
1.589
1.575
1.561
1.553
1.540
1.531
1.526
1.517
1.504
1.497
1.416
1.320
CHO
OH
CO2Me
7e
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.00
0.98
2.99
1.01
1.01
2.02
1.99
14.05

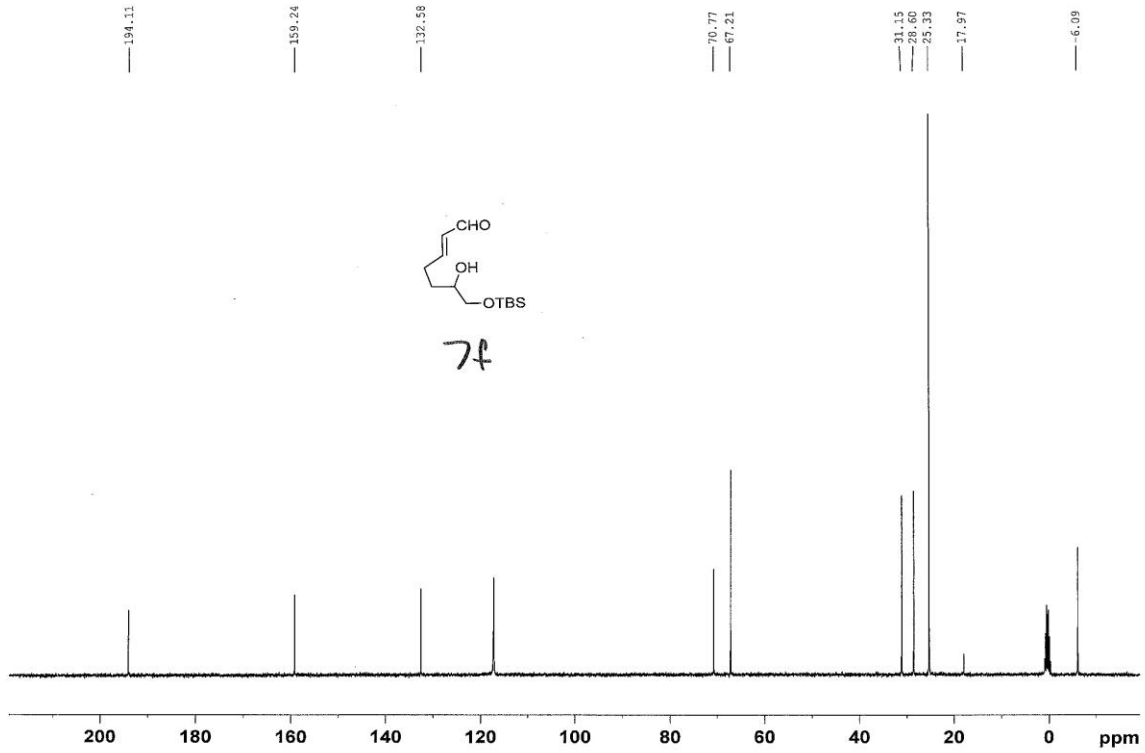

194.17
173.82
159.58
132.49
70.00
50.86
37.24
35.24
33.52
29.21
28.97
28.84
28.74
25.34
24.69
CHO
OH
CO2Me
7e
200
180
160
140
120
100
80
60
40
20
0
ppm

5.49f: *(E)-7-((tert-butyldimethylsilyl)oxy)-6-hydroxyhept-2-enal*

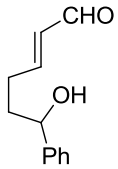


brown oil. Collected in 76% yield. IR (thin film, KBr): 3441, 2953, 2928, 2857, 1690, 1253, 1085, 834, 775 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.51 (d, *J* = 7.9 Hz, 1H), 7.00 (dt, *J* = 15.5, 6.9 Hz, 1H), 6.11 (m, 1H), 3.63-3.47 (m, 3H), 2.93 (bs, 1H), 2.58-2.35 (m, 2H), 1.69 (m, 1H), 1.56 (m, 1H), 0.93 (s, 9H), 0.09 (s, 6H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 194.1, 159.2, 132.6, 70.8, 67.2, 31.2, 28.6, 25.3, 18.0, -6.1 ppm; HRMS (ESI) : [M^+] calcd for [$C_{13}H_{26}O_3Si$]: 258.1651, found: 258.1654.

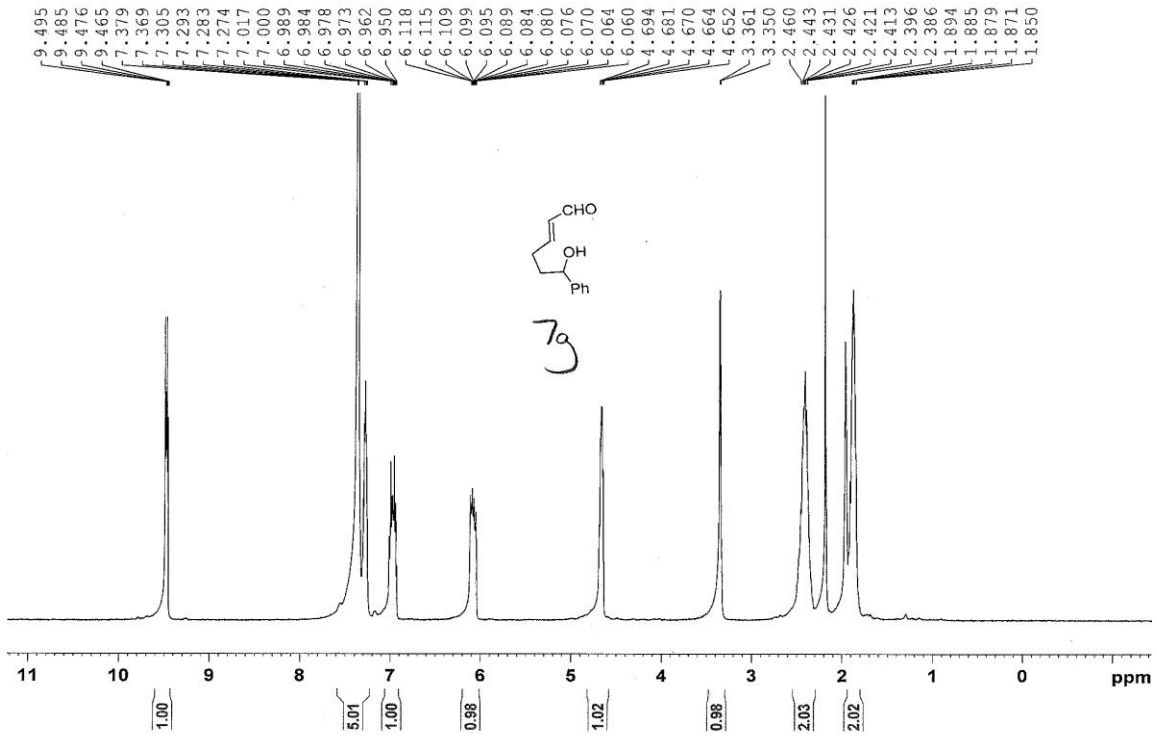

9.515
9.495
7.036
7.019
7.002
6.997
6.980
6.963
6.137
6.118
6.098
6.079
3.613
3.602
3.587
3.581
3.574
3.563
3.553
3.534
3.515
3.506
2.928
2.541
2.518
2.502
2.494
2.490
2.481
2.463
2.442
2.423
2.403
2.384
1.718
1.710
1.702
1.694
1.688
1.684
1.677
1.668
1.661
1.654
1.644
1.587
1.566
1.553
1.546
1.540
1.531
1.518
0.929
0.094
CHO
OH
OTBS
7f
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.01
0.98
3.02
1.00
2.03
1.01
1.00
9.03
6.03

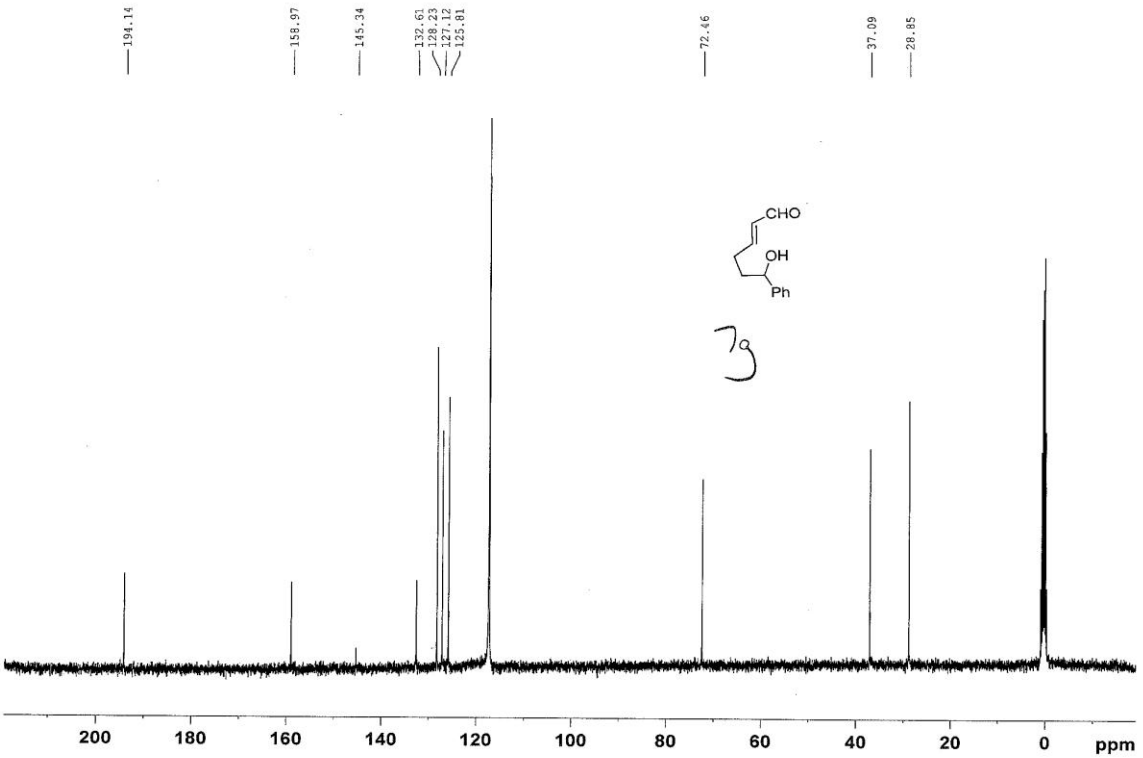

194.11
159.24
132.58
70.77
67.21
31.15
28.60
25.33
17.97
-6.09
CHO
OH
OTBS
7f
200
180
160
140
120
100
80
60
40
20
0
ppm

5.49g: *(E)-6-hydroxy-6-phenylhex-2-enal*

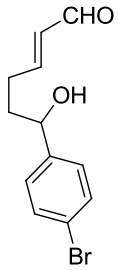


brown oil. Collected in 67% yield. IR (thin film, KBr): 3420, 3029, 2920, 2856, 1686, 1452, 1059, 763, 703 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.49 (dd, *J* = 7.9, 4.3 Hz, 1H), 7.55-7.25 (m, 5H), 7.00 (m, 1H), 6.10 (m, 1H), 4.67 (m, 1H), 3.36 (m, 1H), 2.42 (m, 2H), 2.10-1.80 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 194.1, 159.0, 145.3, 132.6, 128.2, 127.1, 125.8, 72.5, 37.1, 28.9 ppm; HRMS (ESI) : [M^+] calcd for [$C_{12}H_{14}O_2$]: 190.0994, found: 190.0995.

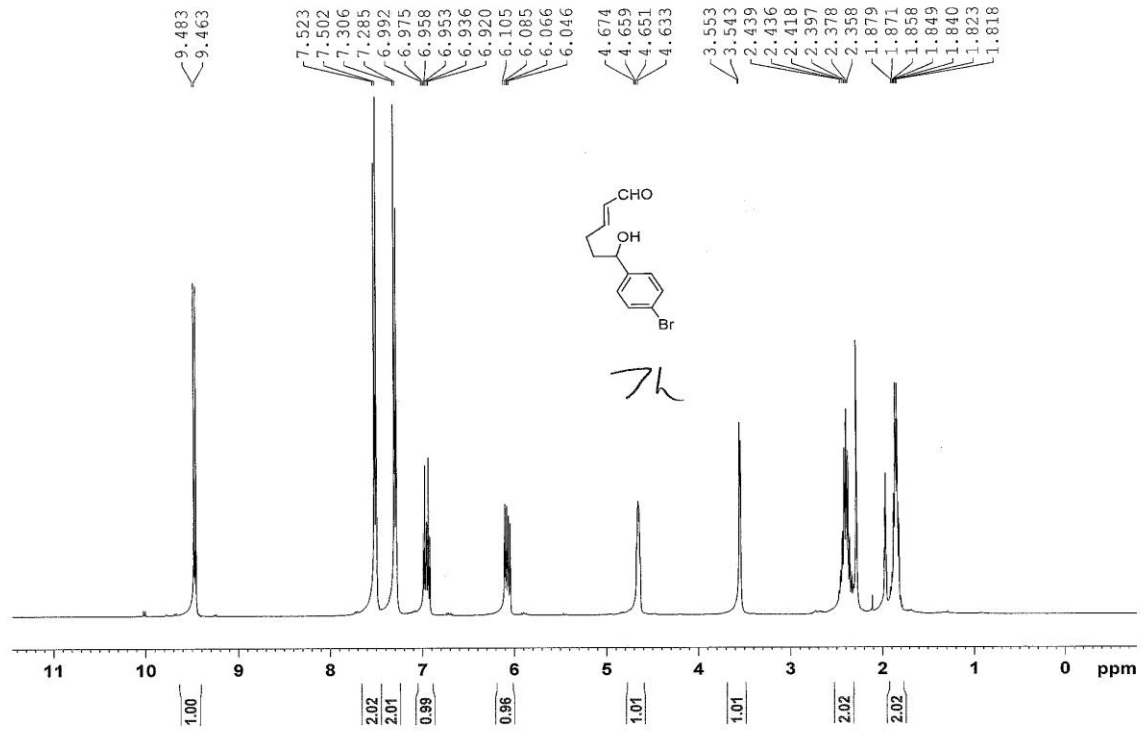

9.495
9.485
9.476
9.465
7.379
7.369
7.305
7.293
7.283
7.274
7.017
7.000
6.989
6.984
6.978
6.973
6.962
6.950
6.118
6.115
6.109
6.099
6.095
6.089
6.084
6.080
6.076
6.070
6.064
6.060
4.694
4.681
4.670
4.664
4.652
3.361
3.350
2.460
2.443
2.431
2.426
2.421
2.413
2.396
2.386
1.894
1.885
1.879
1.871
1.850
CHO
OH
Ph
7g
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
5.01
1.00
0.98
1.02
0.98
2.03
2.02

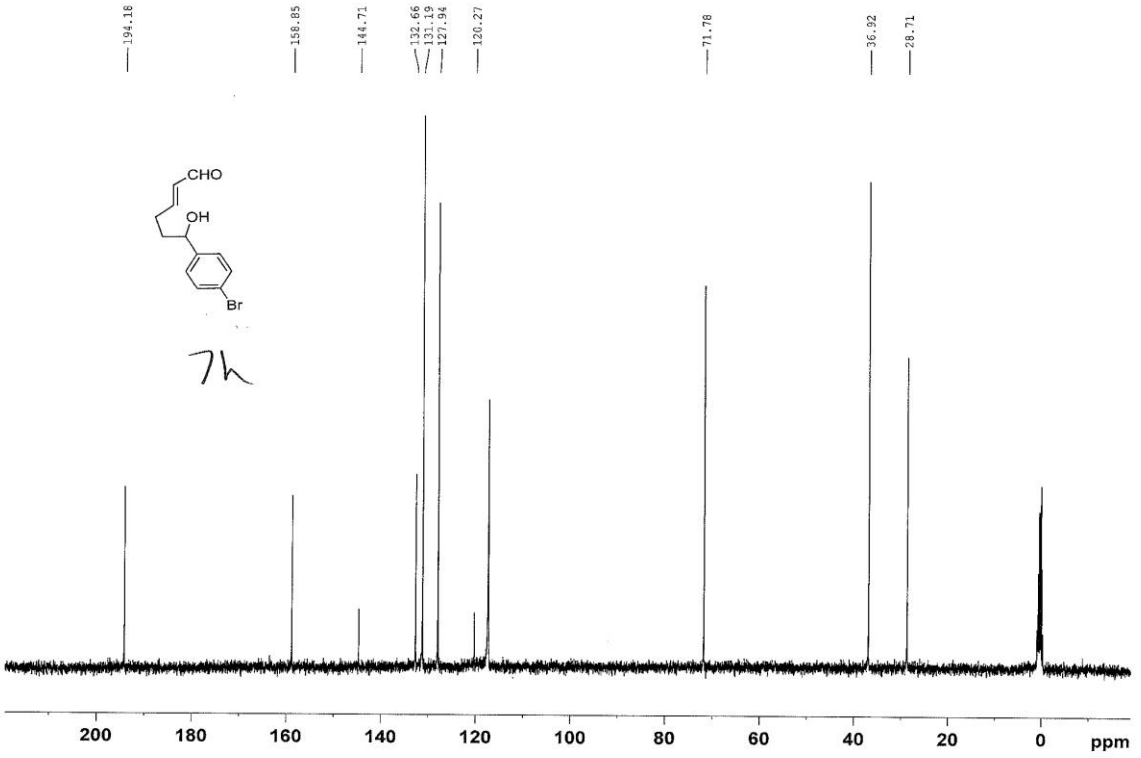

194.14
158.97
145.34
132.61
128.23
127.12
125.81
72.46
37.09
28.85
CHO
OH
Ph
7g
200
180
160
140
120
100
80
60
40
20
0
ppm

5.49h: *(E)-6-(4-bromophenyl)-6-hydroxyhex-2-enal*

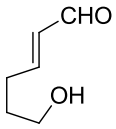


brown oil. Collected in 63% yield. IR (thin film, KBr): 3419, 3029, 2919, 1678, 1130, 1058, 972, 761, 700 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.47 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* =8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 6.96 (dt, *J* = 15.5, 6.8 Hz, 1H), 6.07 (m, 1H), 4.66 (m, 1H), 3.55 (d, *J* = 4.1 Hz, 1H), 2.52-2.32 (m, 2H), 1.95-1.79 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 194.2, 158.9, 144.7, 132.7, 131.2, 127.9, 120.3, 71.8, 36.9, 28.7 ppm; HRMS (ESI) : [M^+] calcd for [$C_{12}H_{13}BrO_2$]: 268.0099, found: 268.0100.

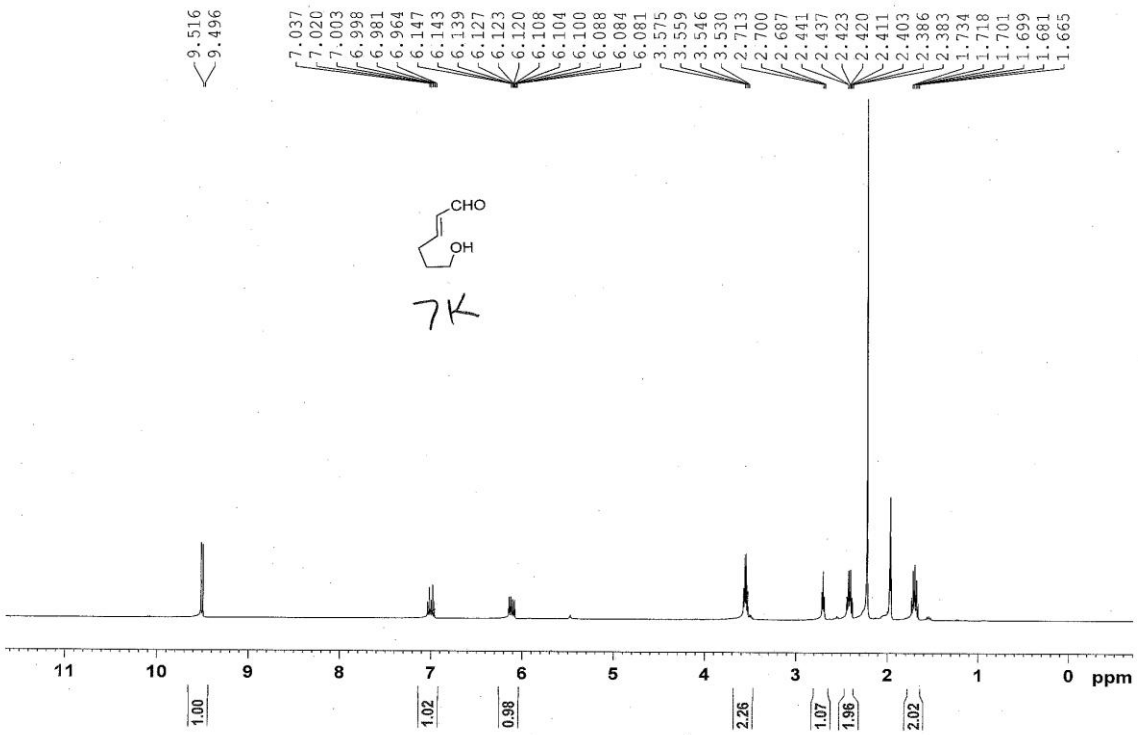

9.483
9.463
7.523
7.502
7.306
7.285
6.992
6.975
6.958
6.953
6.936
6.920
6.105
6.085
6.066
6.046
4.674
4.659
4.651
4.633
3.553
3.543
2.439
2.436
2.418
2.397
2.378
2.358
1.879
1.871
1.858
1.849
1.840
1.823
1.818
CHO
OH
Br
7h
11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
2.02
2.01
0.99
0.96
1.01
1.01
2.02
2.02

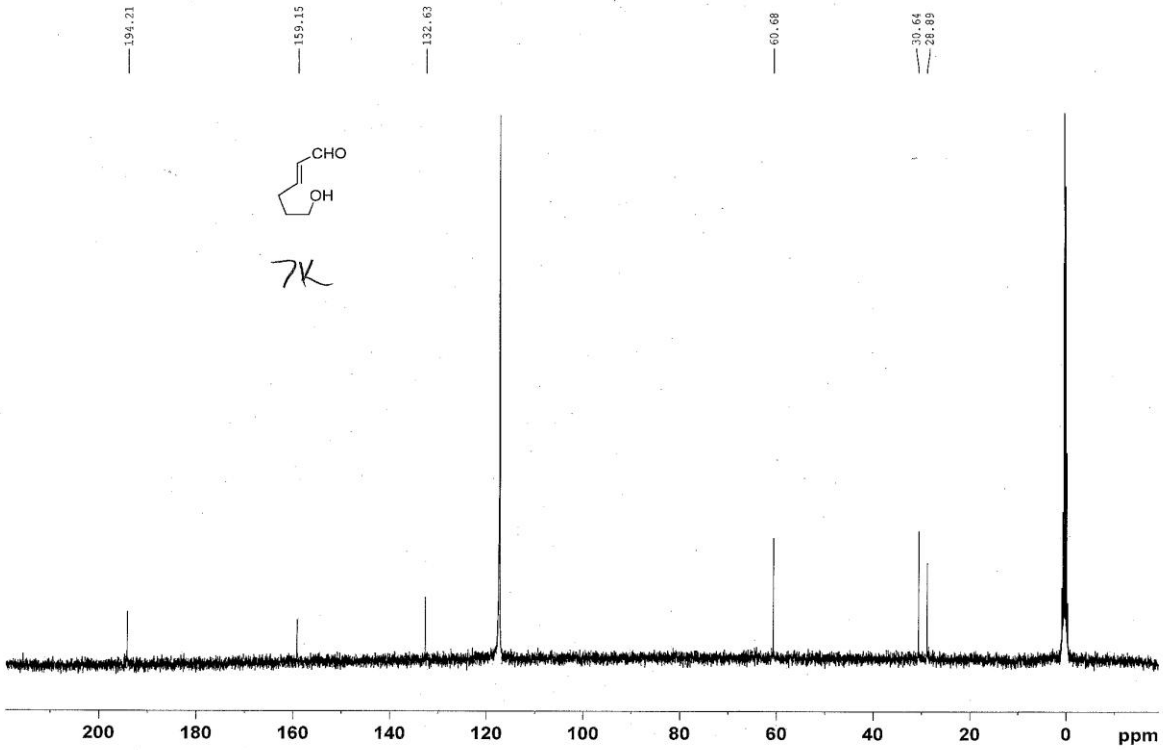

194.18
158.85
144.71
132.66
131.19
127.94
120.27
71.78
36.92
28.71
CHO
OH
Br
7h
200 180 160 140 120 100 80 60 40 20 0 ppm

5.49k: *(E)-6-hydroxyhex-2-enal*



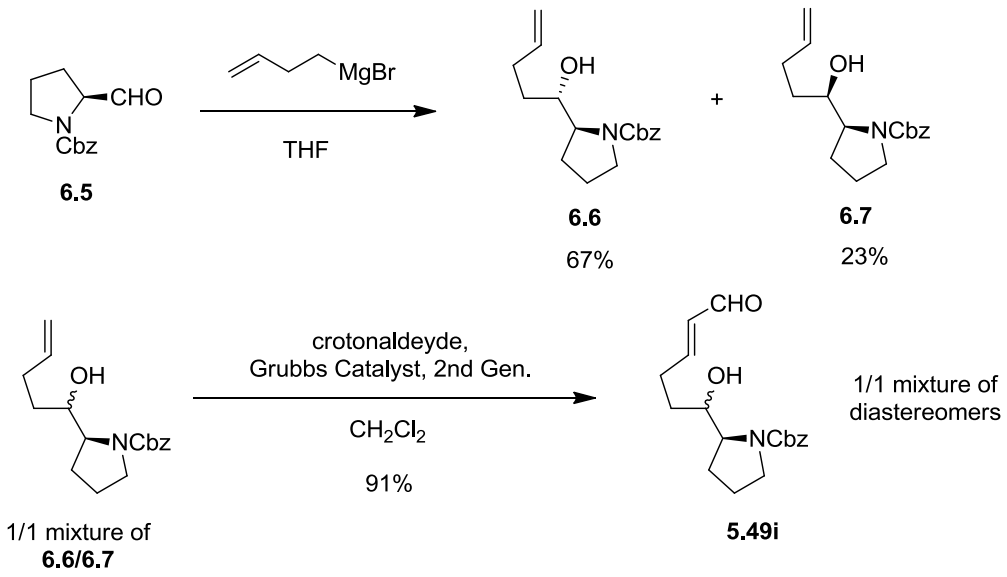
brown oil. Collected in 68% yield. IR (thin film, KBr): 3401, 2938, 2872, 1678, 1134, 1055, 974 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.51 (d, *J* = 7.9 Hz, 1H), 7.00 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.11 (ddt, *J* = 15.6, 7.9, 1.5 Hz, 1H), 3.55 (m, 2H), 2.70 (t, *J* = 5.3 Hz, 1H), 2.41 (m, 2H), 1.70 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 194.2, 159.2, 132.6, 60.7, 30.6, 28.9 ppm; HRMS (ESI) : [M^+] calcd for [$C_6H_{10}O_2$]: 114.0681, found: 114.0682.


9.516
9.496
7.037
7.020
7.003
6.998
6.981
6.964
6.147
6.143
6.139
6.127
6.123
6.120
6.108
6.104
6.100
6.088
6.084
6.081
3.575
3.559
3.546
3.530
2.713
2.700
2.687
2.441
2.437
2.423
2.420
2.411
2.403
2.386
2.383
1.734
1.718
1.701
1.699
1.681
1.665
CHO
OH
7K
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.02
0.98
2.26
1.07
1.96
2.02


194.21
159.15
132.63
60.68
30.64
28.89
CHO
OH
7K
200
180
160
140
120
100
80
60
40
20
0
ppm

Preparation of Substrates (5.49i–j)

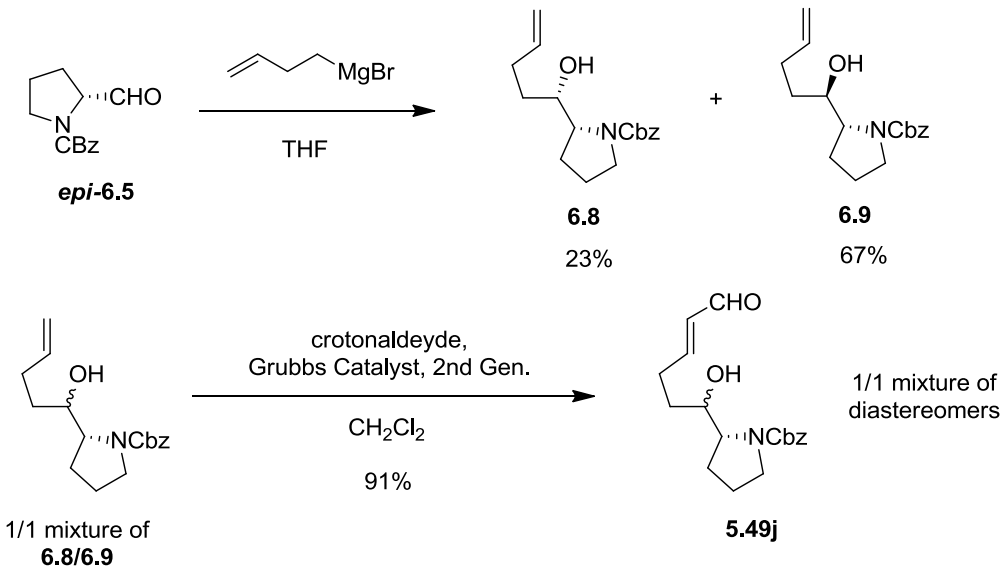
Substrate **5.49i** was prepared using the following two step synthesis.



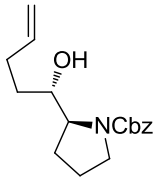
Tetrahydrofuran (19.0 mL) was added to magnesium metal (608 mg, 25.0 mmol) in a round bottom flask in an argon atmosphere. Then 4-bromo-1-butene (2.22 mL, 21.86 mmol) was added dropwise and the reaction was refluxed with stirring for 2 h and then cooled to room temperature. Compound **6.5** (2.53 g, 10.84 mmol) was dissolved in tetrahydrofuran (27.5 mL) and cooled to 0 ^{o}C. The Grignard reagent was added to the solution of **6.5** over 20 minutes with stirring. The reaction was warmed to room temperature and stirred for 1 h, at which time it was quenched by slowly adding saturated aqueous NH_4Cl (50 mL). The reaction was diluted with Et_2O (75 mL) and the layers were separated. The aqueous layer was washed with Et_2O (50 mL), the Et_2O layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified via column chromatography (EtOAc/CH_2Cl_2, 10/90). Diastereomer **6.6** (2.10 g, 67% yield) and **6.7** (0.72 g, 23% yield) were separated on the column.

A 1/1 mixture of **6.6** and **6.7** (1.41 g, 4.87 mmol) was prepared and subjected to the same cross metathesis conditions used in the preparation of substrates **5.49a**–**h** and **5.49k**. The reaction yielded 1.39 g of substrate **5.49i** (91% yield) as a 1/1 mixture of diastereomers.

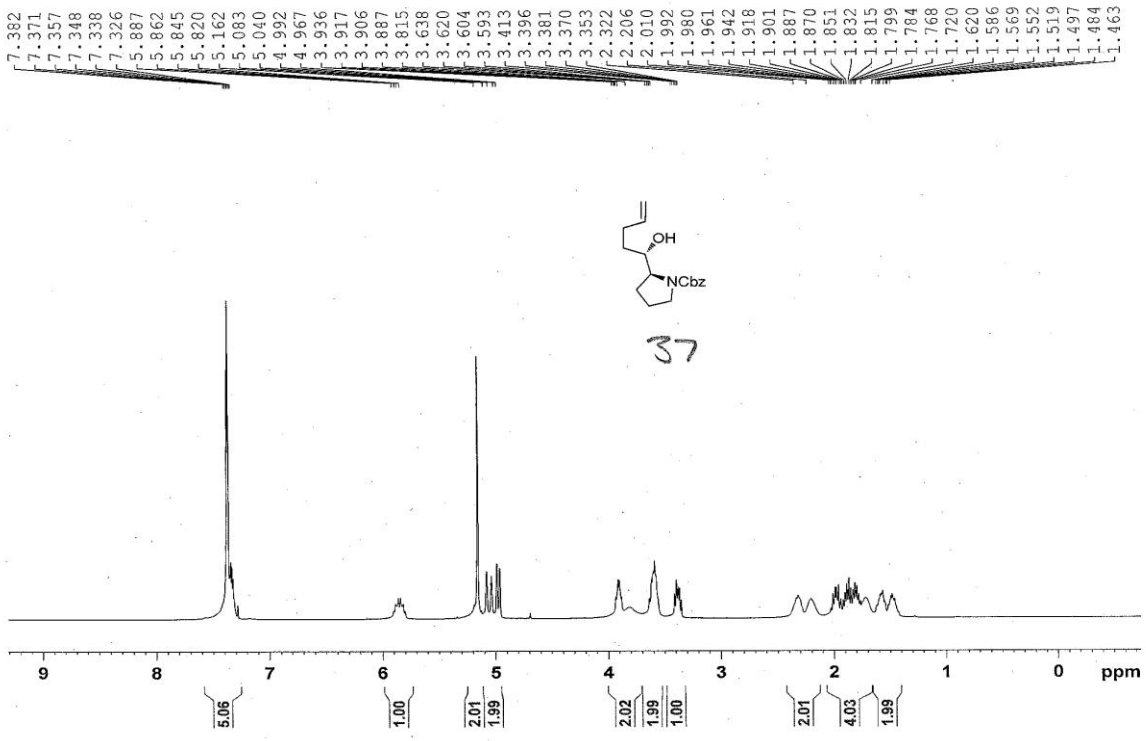
Compound ***epi*–6.5** was subjected to the same conditions in the preparation of substrate **5.49j**. Similar yields and diastereomeric ratios were achieved.

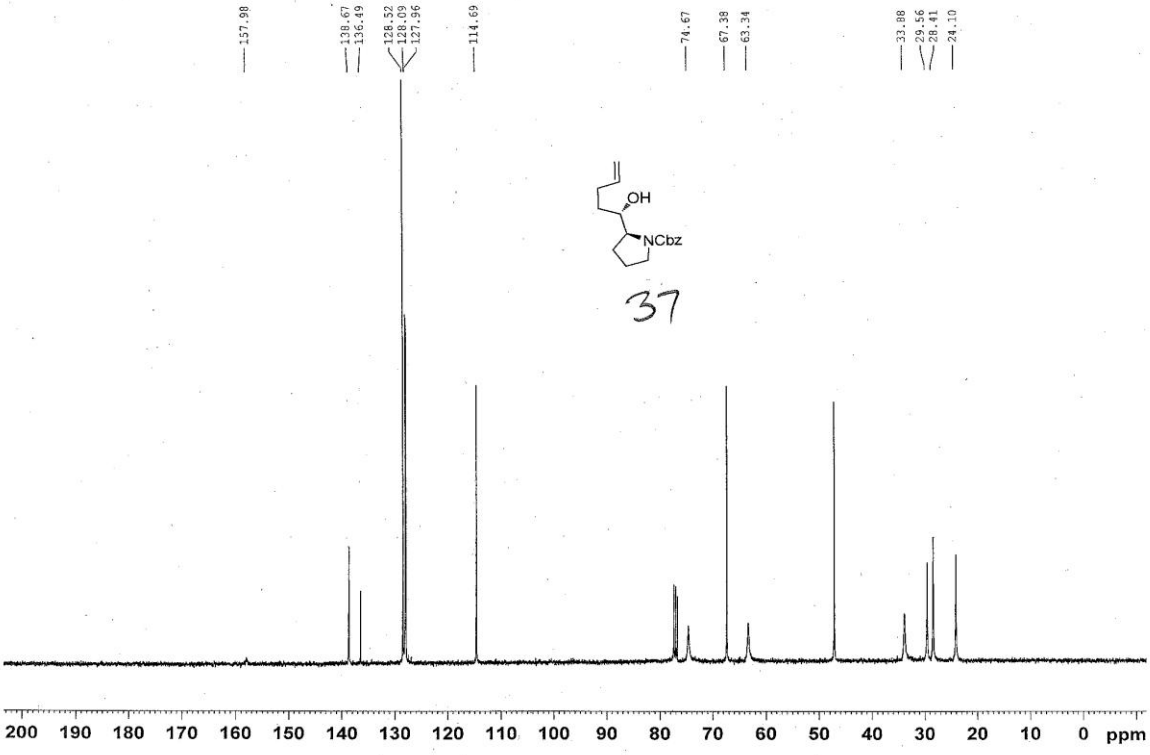


6.6: *(S)-benzyl 2-((S)-1-hydroxypent-4-en-1-yl)pyrrolidine-1-carboxylate*

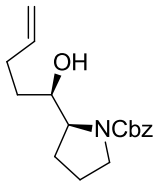


colorless oil. $[\alpha]_D^{23}$ = -81.3 (*c* 1.50, $CHCl_3$); IR (thin film, KBr): 3417, 2944, 1672, 1412, 1355, 1337, 1101, 910, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.28 (m, 5H), 5.85 (m, 1H), 5.16 (s, 2H), 5.06 (d, *J* = 17.1 Hz, 1H), 4.98 (d, *J* = 10.2 Hz, 1H), 3.97-3.70 (m, 2H), 3.60 (m, 2H), 3.39 (m, 1H), 2.42-2.10 (m, 2H), 2.06-1.65 (m, 4H), 1.65-1.42 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 138.7, 136.5, 128.5, 128.1, 128.0, 114.7, 74.7, 67.4, 63.3, 33.9, 29.6, 28.4, 24.1 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_{17}H_{23}NO_3]$: 289.1678, found: 289.1677.

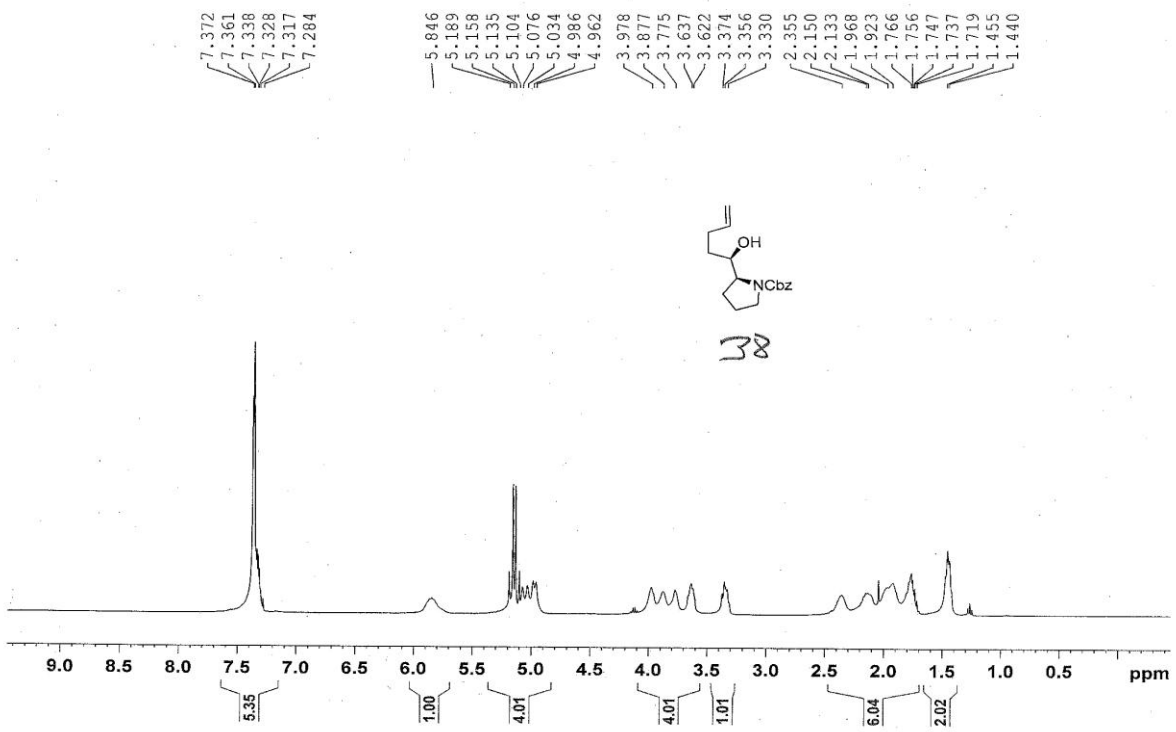

7.382
7.371
7.357
7.348
7.338
7.326
5.887
5.862
5.845
5.820
5.162
5.083
5.040
4.992
4.967
3.936
3.917
3.906
3.887
3.815
3.638
3.620
3.604
3.593
3.413
3.396
3.381
3.370
3.353
2.322
2.206
2.010
1.992
1.980
1.961
1.942
1.918
1.901
1.887
1.870
1.851
1.832
1.815
1.799
1.784
1.768
1.720
1.620
1.586
1.569
1.552
1.519
1.497
1.484
1.463
OH
NCbz
37
9
8
7
6
5
4
3
2
1
0
ppm
5.06
1.00
2.01
1.99
2.02
1.99
1.00
2.01
4.03
1.99

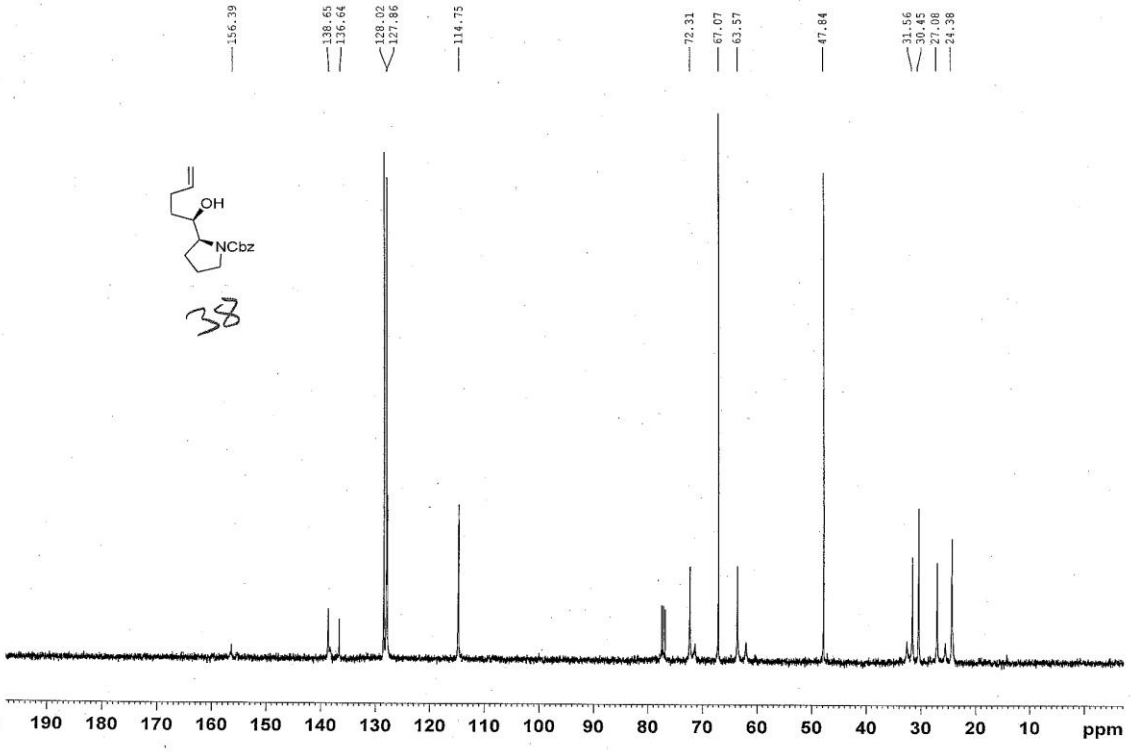

157.98
138.67
136.49
128.52
128.09
127.96
114.69
74.67
67.38
63.34
33.88
29.56
28.41
24.10
OH
NCbz
37
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

6.7: *(S)-benzyl 2-((R)-1-hydroxypent-4-en-1-yl)pyrrolidine-1-carboxylate*

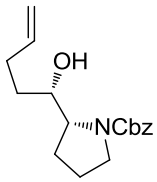


colorless oil. $[\alpha]_D^{22}$ = -54.3 (*c* 1.00, $CHCl_3$); IR (thin film, KBr): 3435, 2975, 2939, 1682, 1421, 1357, 1113, 912, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.27 (m, 5H), 5.85 (m, 1H), 5.20-4.91 (m, 4H), 4.03-3.59 (m, 4H), 3.85 (m, 1H), 2.45-1.72 (m, 6H), 1.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 138.7, 136.6, 128.5, 128.0, 127.9, 114.8, 72.3, 67.1, 63.6, 47.8, 31.6, 30.5, 27.1, 24.4 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_{17}H_{23}NO_3]$: 289.1678, found: 289.1678.

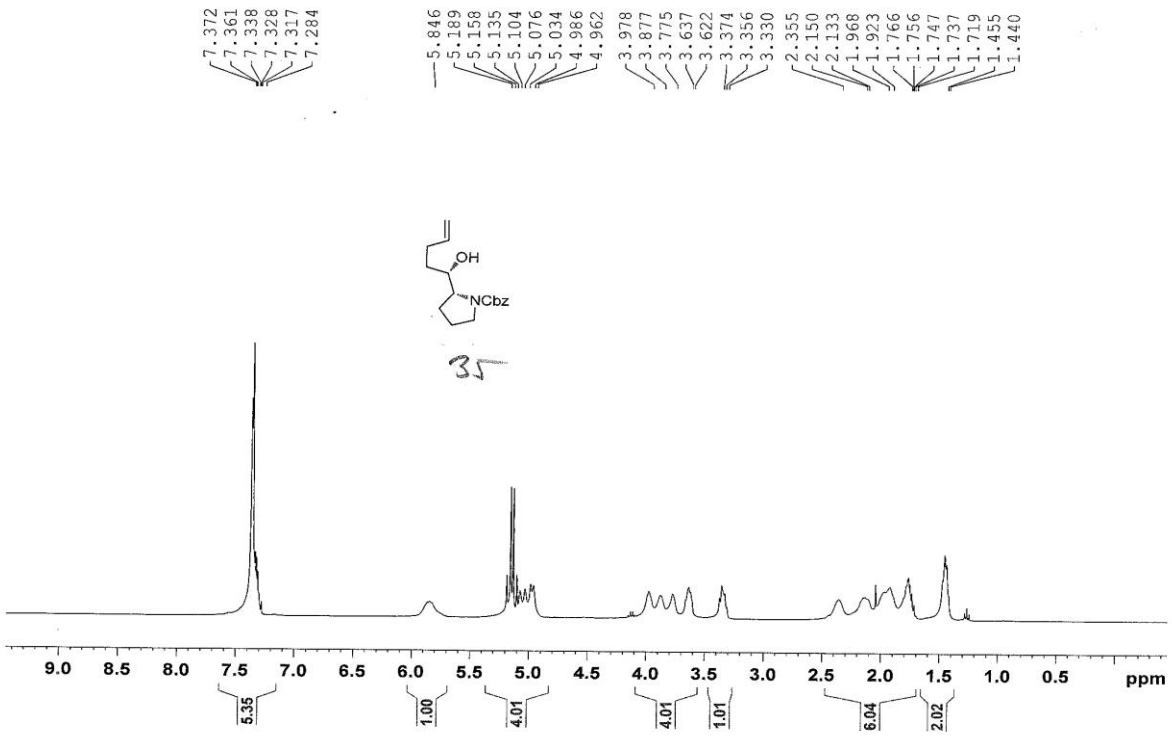

7.372
7.361
7.338
7.328
7.317
7.284
5.846
5.189
5.158
5.135
5.104
5.076
5.034
4.986
4.962
3.978
3.877
3.775
3.637
3.622
3.374
3.356
3.330
2.355
2.150
2.133
1.968
1.923
1.766
1.756
1.747
1.737
1.719
1.455
1.440
OH
NCbz
38
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5.35
1.00
4.01
4.01
1.01
6.04
2.02

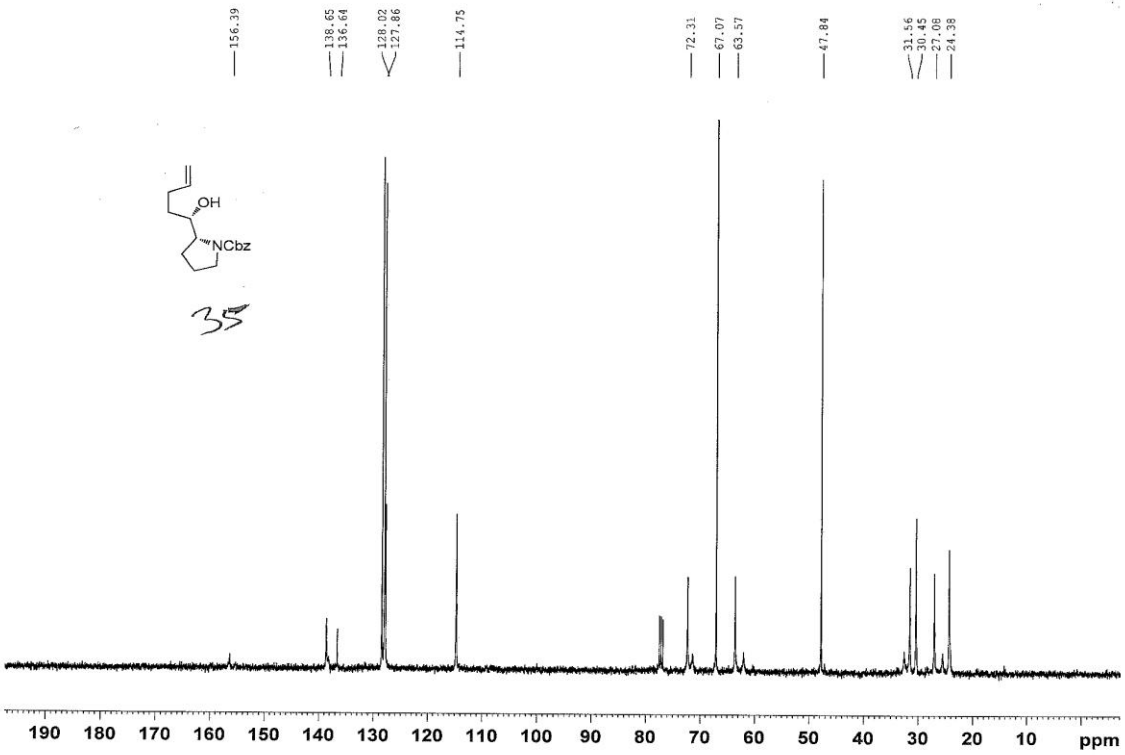

156.39
138.65
136.64
128.02
127.86
114.75
72.31
67.07
63.57
47.84
31.56
30.45
27.08
24.38
OH
NCbz
38
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

6.8: *(R)-benzyl 2-((S)-1-hydroxypent-4-en-1-yl)pyrrolidine-1-carboxylate*

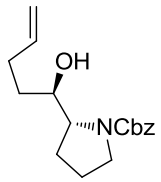


colorless oil. $[\alpha]_D^{21}$ = +50.7 (*c* 1.50, $CHCl_3$); IR (thin film, KBr): 3435, 2975, 2939, 1682, 1421, 1357, 1113, 912, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.27 (m, 5H), 5.85 (m, 1H), 5.20-4.91 (m, 4H), 4.03-3.59 (m, 4H), 3.85 (m, 1H), 2.45-1.72 (m, 6H), 1.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 138.7, 136.6, 128.5, 128.0, 127.9, 114.8, 72.3, 67.1, 63.6, 47.8, 31.6, 30.5, 27.1, 24.4 ppm; HRMS (ESI) : [M^+] calcd for [$C_{17}H_{23}NO_3$]: 289.1678, found: 289.1680.

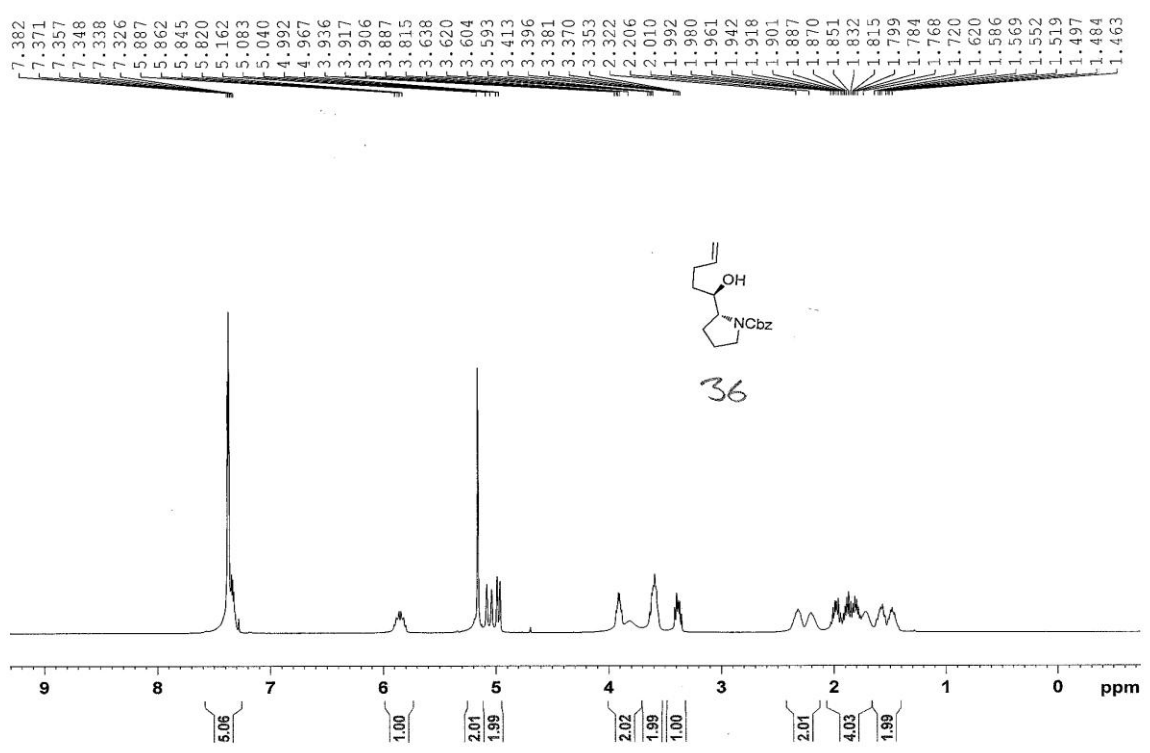

7.372
7.361
7.338
7.328
7.317
7.284
5.846
5.189
5.158
5.135
5.104
5.076
5.034
4.986
4.962
3.978
3.877
3.775
3.637
3.622
3.374
3.356
3.330
2.355
2.150
2.133
1.968
1.923
1.766
1.756
1.747
1.737
1.719
1.455
1.440
OH
NCbz
35
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5.35
1.00
4.01
4.01
1.01
6.04
2.02

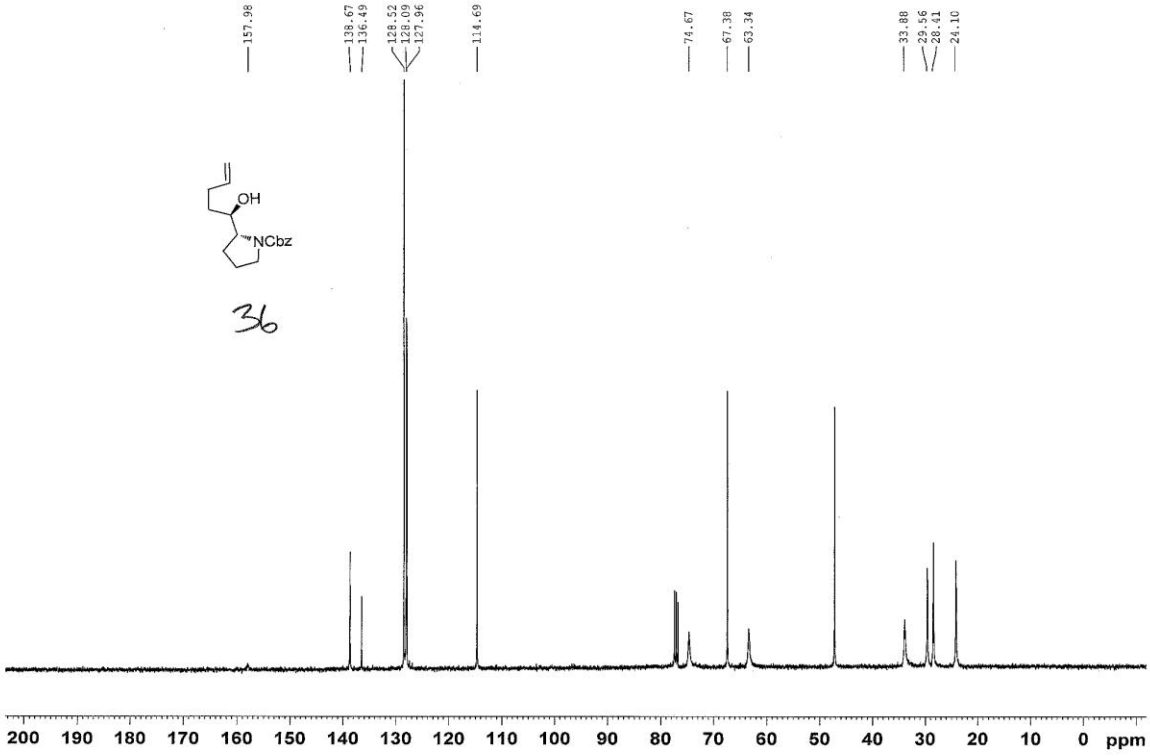

156.39
138.65
136.64
128.02
127.86
114.75
72.31
67.07
63.57
47.84
31.56
30.45
27.08
24.38
OH
NCbz
35
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

6.9: *(R)-benzyl 2-((R)-1-hydroxypent-4-en-1-yl)pyrrolidine-1-carboxylate*[19]

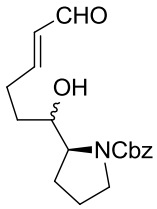


colorless oil. $[\alpha]_D^{21}$ = +78.3 (*c* 1.50, $CHCl_3$); IR (thin film, KBr): 3417, 2944, 1672, 1412, 1355, 1337, 1101, 910, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.28 (m, 5H), 5.85 (m, 1H), 5.16 (s, 2H), 5.06 (d, *J* = 17.1 Hz, 1H), 4.98 (d, *J* = 10.2 Hz, 1H), 3.97-3.70 (m, 2H), 3.60 (m, 2H), 3.39 (m, 1H), 2.42-2.10 (m, 2H), 2.06-1.65 (m, 4H), 1.65-1.42 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 138.7, 136.5, 128.5, 128.1, 128.0, 114.7, 74.7, 67.4, 63.3, 33.9, 29.6, 28.4, 24.1 ppm; HRMS (ESI) : [M^+] calcd for [$C_{17}H_{23}NO_3$]: 289.1678, found: 289.1680.

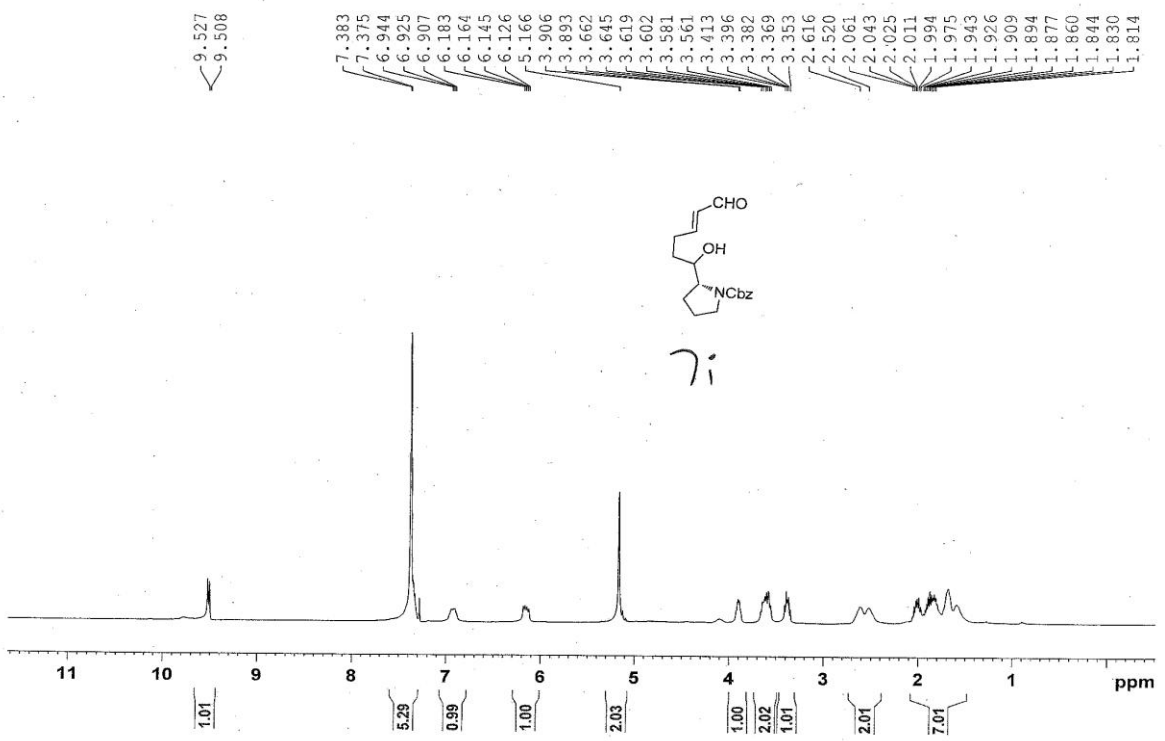

7.382
7.371
7.357
7.348
7.338
7.326
5.887
5.862
5.845
5.820
5.162
5.083
5.040
4.992
4.967
3.936
3.917
3.906
3.887
3.815
3.638
3.620
3.604
3.593
3.413
3.396
3.381
3.370
3.353
2.322
2.206
2.010
1.992
1.980
1.961
1.942
1.918
1.901
1.887
1.870
1.851
1.832
1.815
1.799
1.784
1.768
1.720
1.620
1.586
1.569
1.552
1.519
1.497
1.484
1.463
OH
NCbz
36
9
8
7
6
5
4
3
2
1
0
ppm
5.06
1.00
2.01
1.99
2.02
1.99
1.00
2.01
4.03
1.99

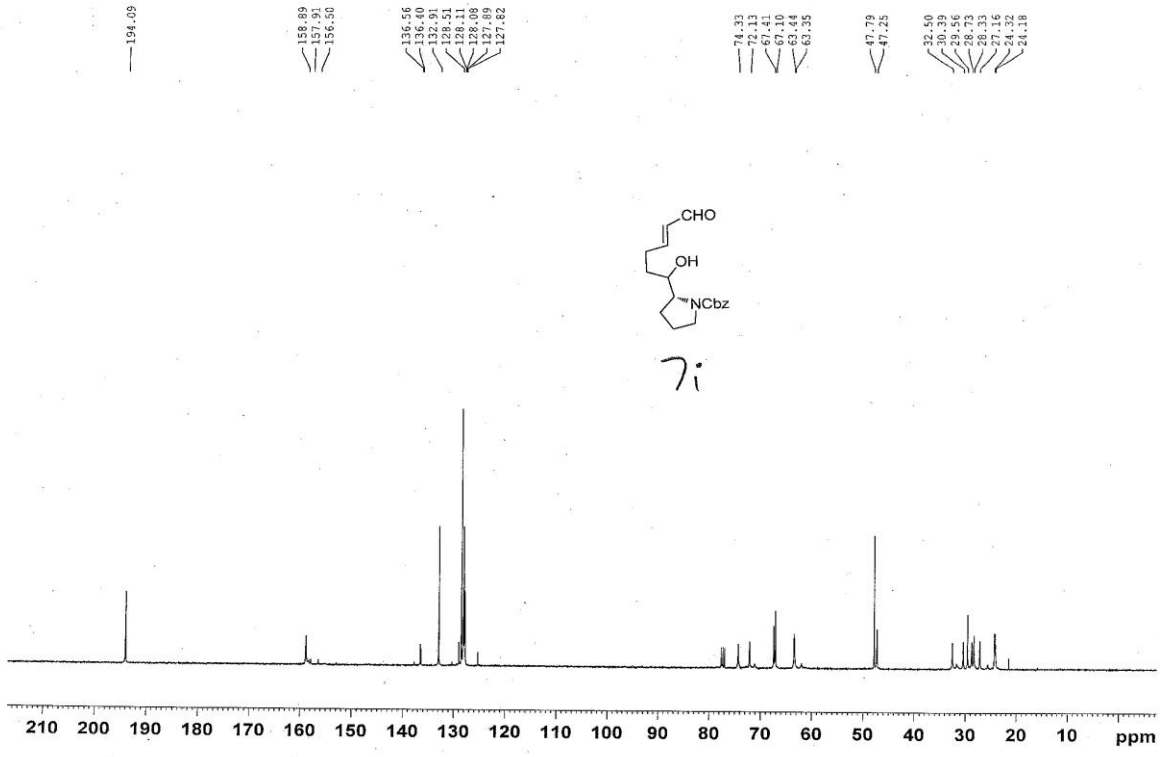

157.98
138.67
136.49
128.52
128.09
127.96
114.69
74.67
67.38
63.34
33.88
29.56
28.41
24.10
OH
NCbz
36
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

5.49i: *(2S)-benzyl 2-((E)-1-hydroxy-6-oxohex-4-en-1-yl)pyrrolidine-1-carboxylate*

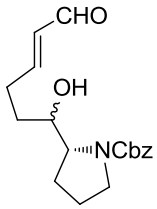


Characterized as a 1/1 mixture of diastereomers. brown oil. $[\alpha]_D^{24}$ = -68.0 (*c* 1.50, $CHCl_3$); IR (thin film, KBr): 3439, 2949, 1684, 1413, 1356, 1103, 732, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, *J* = 7.8 Hz, 1H), 7.45-7.29 (m, 5H), 6.92 (m, 1H), 6.16 (m, 1H), 5.17 (s, 2H), 3.89 (m, 1H), 3.60 (m, 2H), 3.40 (m, 1H), 2.70-2.45 (m, 2H), 2.10-1.45 (m, 7H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 158.9, 157.9, 156.5, 136.6, 136.4, 132.9, 128.5, 128.1, 128.1, 127.9, 127.8, 74.3, 72.1, 67.4, 67.1, 63.4, 63.4, 47.8, 47.3, 32.5, 30.4, 29.6, 28.7, 28.3, 27.2, 24.3, 24.2 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_{18}H_{23}NO_4]$: 317.1627, found: 317.1630.

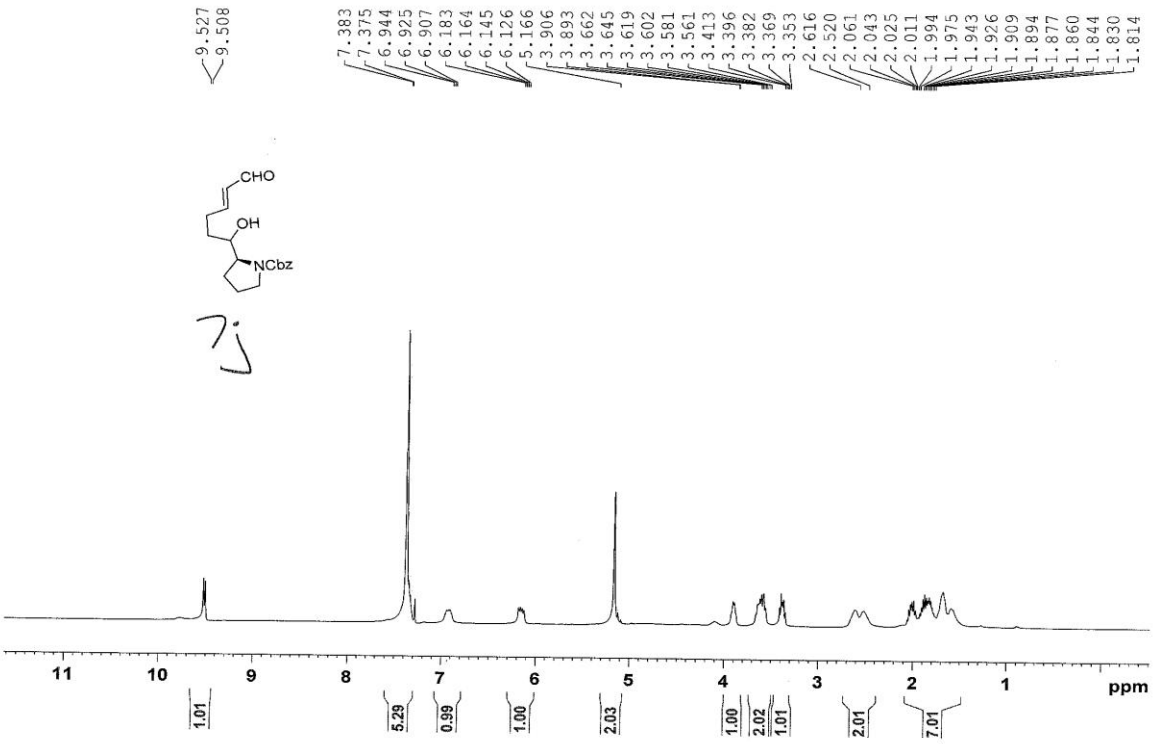

9.527
9.508
7.383
7.375
6.944
6.925
6.907
6.183
6.164
6.145
6.126
5.166
3.906
3.893
3.662
3.645
3.619
3.602
3.581
3.561
3.413
3.396
3.382
3.369
3.353
2.616
2.520
2.061
2.043
2.025
2.011
1.994
1.975
1.943
1.926
1.909
1.894
1.877
1.860
1.844
1.830
1.814
CHO
OH
NCbz
7i
11
10
9
8
7
6
5
4
3
2
1
ppm
1.01
5.29
0.99
1.00
2.03
1.00
2.02
1.01
2.01
7.01

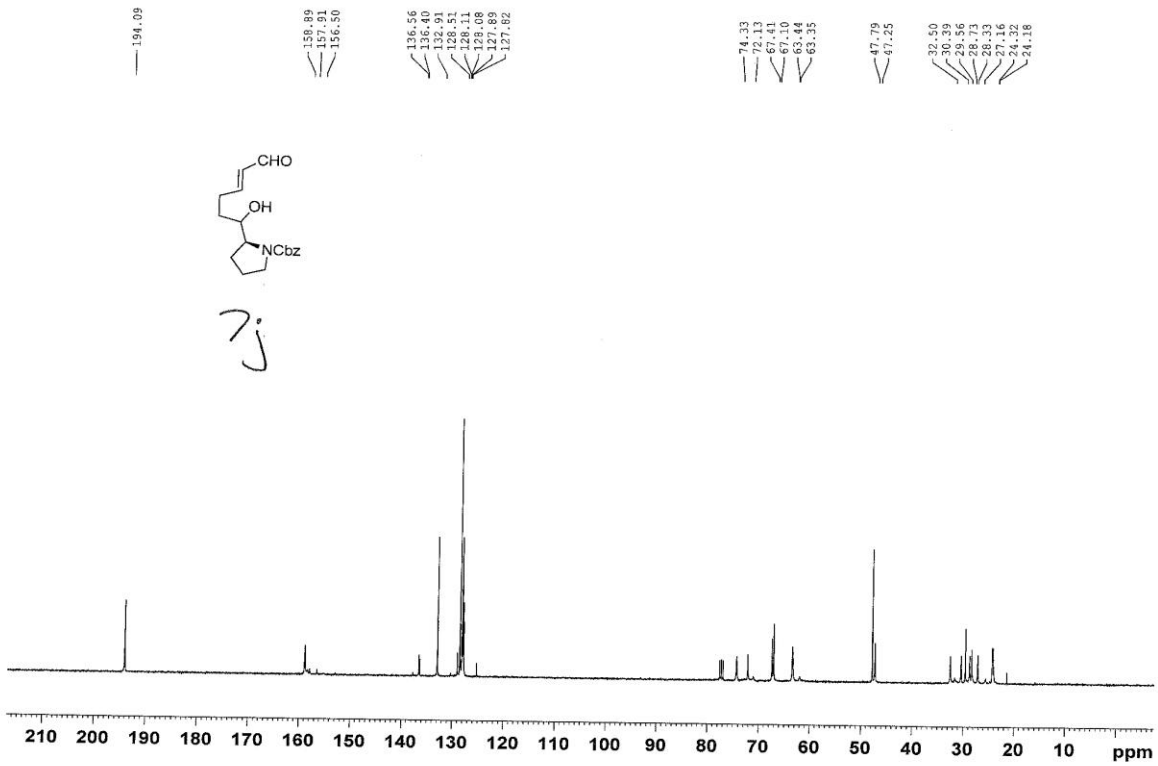

194.09
158.89
157.91
156.50
136.56
136.40
132.91
128.51
128.11
128.08
127.89
127.82
74.33
72.13
67.41
67.10
63.44
63.35
47.79
47.25
32.50
30.39
29.56
28.73
28.33
27.16
24.72
24.18
CHO
OH
NCbz
7i
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

5.49j: *(2R)-benzyl 2-((E)-1-hydroxy-6-oxohex-4-en-1-yl)pyrrolidine-1-carboxylate*

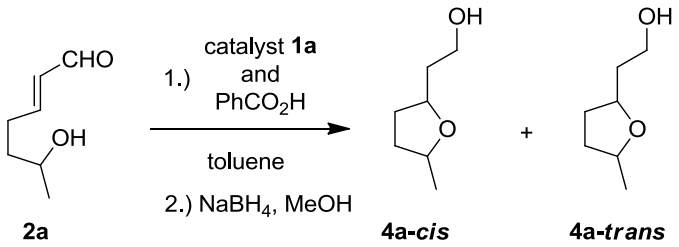


Characterized as a 1/1 mixture of diastereomers. brown oil. $[\alpha]_D^{23}$ = +68.8 (*c* 1.50, $CHCl_3$); IR (thin film, KBr): 3439, 2949, 1684, 1413, 1356, 1103, 732, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, *J* = 7.8 Hz, 1H), 7.45-7.29 (m, 5H), 6.92 (m, 1H), 6.16 (m, 1H), 5.17 (s, 2H), 3.89 (m, 1H), 3.60 (m, 2H), 3.40 (m, 1H), 2.70-2.45 (m, 2H), 2.10-1.45 (m, 7H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 158.9, 157.9, 156.5, 136.6, 136.4, 132.9, 128.5, 128.1, 128.1, 127.9, 127.8, 74.3, 72.1, 67.4, 67.1, 63.4, 63.4, 47.8, 47.3, 32.5, 30.4, 29.6, 28.7, 28.3, 27.2, 24.3, 24.2 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_{18}H_{23}NO_4]$: 317.1627, found: 317.1626.


9.527
9.508
7.383
7.375
6.944
6.925
6.907
6.183
6.164
6.145
6.126
5.166
3.906
3.893
3.662
3.645
3.619
3.602
3.581
3.561
3.413
3.396
3.382
3.369
3.353
2.616
2.520
2.061
2.043
2.025
2.011
1.994
1.975
1.943
1.926
1.909
1.894
1.877
1.860
1.844
1.830
1.814
CHO
OH
NCbz
11
10
9
8
7
6
5
4
3
2
1
ppm
1.01
5.29
0.99
1.00
2.03
1.00
2.02
1.01
2.01
7.01

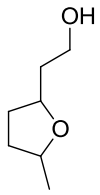

194.09
158.89
157.91
156.50
136.56
136.40
132.91
128.51
128.11
128.08
127.98
127.82
74.33
72.13
67.41
67.10
63.44
63.35
47.79
47.25
32.50
30.39
29.56
28.73
28.33
27.16
24.32
24.18
CHO
OH
NCbz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

Organocatalyzed Oxa-Michael Addition with in situ Reduction (5.51a–cis and 5.51a–trans)

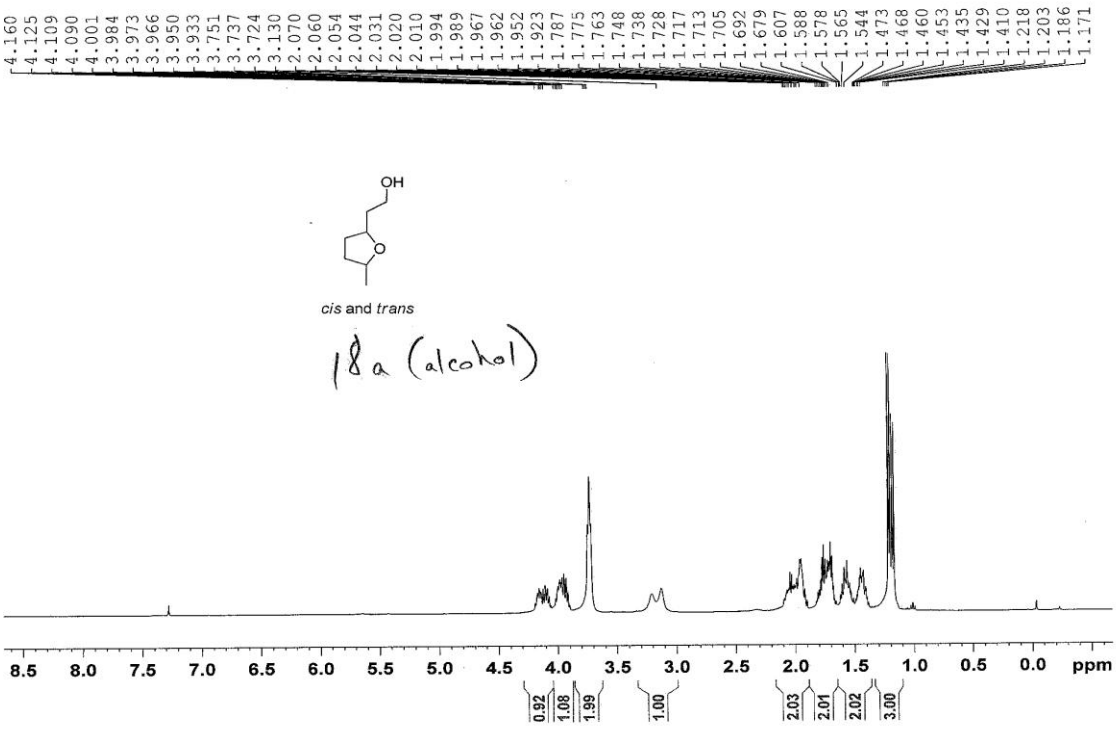


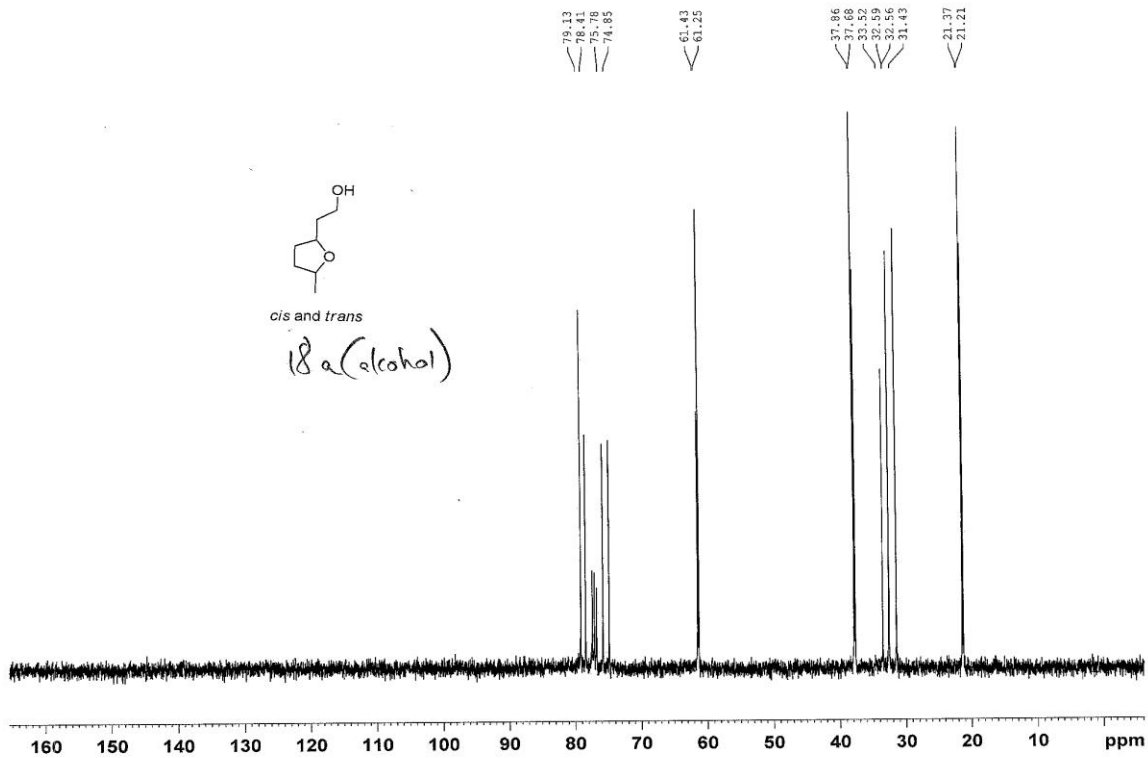
Catalyst **1.12a** (13.0 mg, 0.04 mmol) and $PhCO_2H$ (4.9 mg, 0.04 mmol) were dissolved in toluene (1.0 mL) and cooled to 0 ^oC or –30 ^oC. Substrate **5.49a** (59.9 µL, 0.40 mmol) was added in one portion and the reaction was stirred at the same temperature and monitored by TLC. After the indicated time, MeOH (1 mL) and $NaBH_4$ (30.3 mg, 0.80 mmol) were added to the reaction mixture. After 30 minutes the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Both **5.51a**–***cis*** and **5.51a**–***trans*** were isolated together and characterized as a mixture (**4a**) from the residue via column chromatography (EtOAc/petroleum ether, 40/60).

5.51a: *2-(5-methyltetrahydrofuran-2-yl)ethanol*

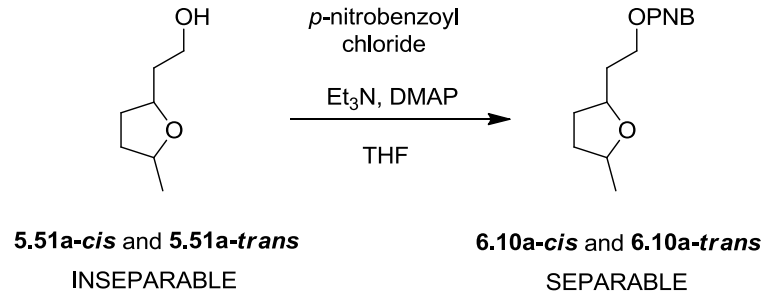


Characterized as a mixture of both *cis* and *trans* diastereomers. colorless oil. IR (thin film, KBr): 3385, 2967, 2933, 2871, 1445, 1375, 1080, 1052, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.21-4.05 (m, 2H-*cis*), 4.05-3.88 (m, 2H-*trans*), 3.27-3.05 (bd, 2H-*cis* and *trans*), 2.15-1.37 (m, 12H-*cis* and *trans*), 1.21 (d, J = 6.2 Hz, 3H-*cis*), 1.18 (d, J = 6.2 Hz, 3H-*trans*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.1, 78.4, 75.8, 74.9, 61.4, 61.3, 37.9, 37.7, 33.5, 32.6, 32.6, 31.4, 21.4, 21.2 ppm; HRMS (ESI) : [M^+] calcd for [$C_7H_{14}O_2$]: 130.0994, found: 130.0994.


4.160
4.125
4.109
4.090
4.001
3.984
3.973
3.966
3.950
3.933
3.751
3.737
3.724
3.130
2.070
2.060
2.054
2.044
2.031
2.020
2.010
1.994
1.989
1.967
1.962
1.952
1.923
1.787
1.775
1.763
1.748
1.738
1.728
1.717
1.713
1.705
1.692
1.679
1.607
1.588
1.578
1.565
1.544
1.473
1.468
1.460
1.453
1.435
1.429
1.410
1.218
1.203
1.186
1.171
OH
O
cis and trans
18a (alcohol)
8.5 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 ppm
0.92
1.08
1.99
1.00
2.03
2.01
2.02
3.00

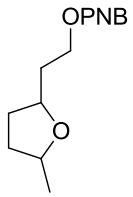

79.13
78.41
75.78
74.85
61.43
61.25
37.86
37.68
33.52
32.59
32.56
31.43
21.37
21.21
OH
O
cis and trans
18a (alcohol)
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

The mixture of **5.51a**–***cis*** and **5.51a**–***trans*** alcohol products were PNB protected for chiral HPLC analysis.

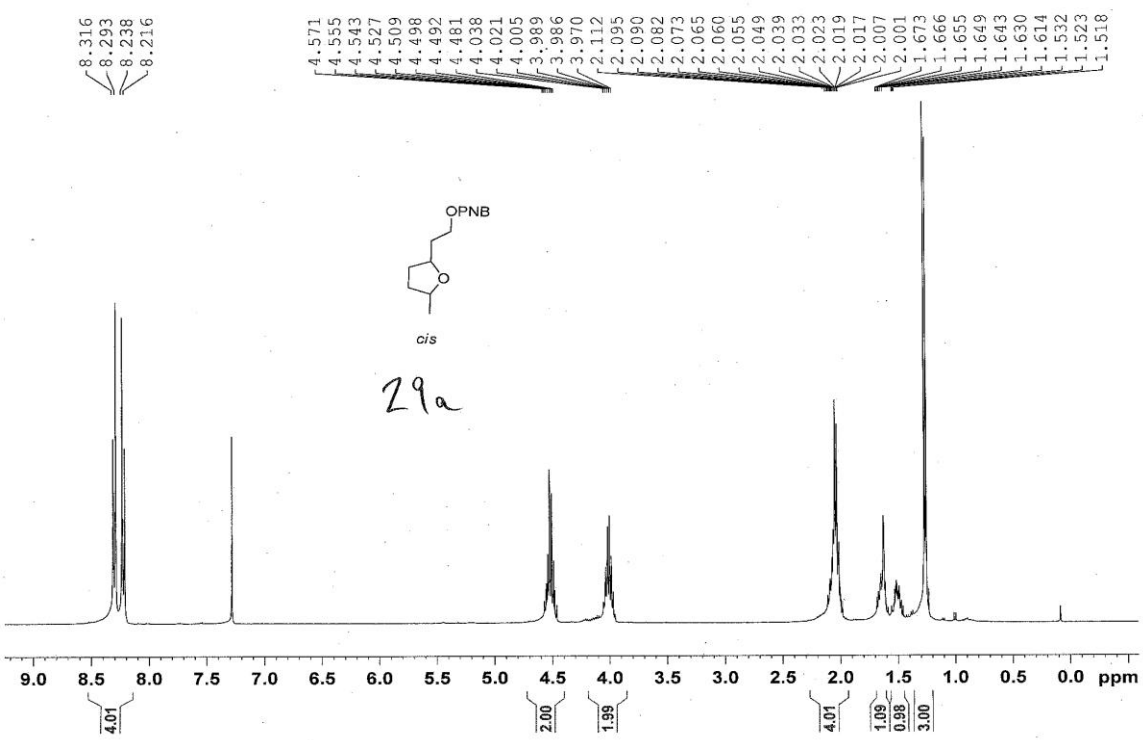


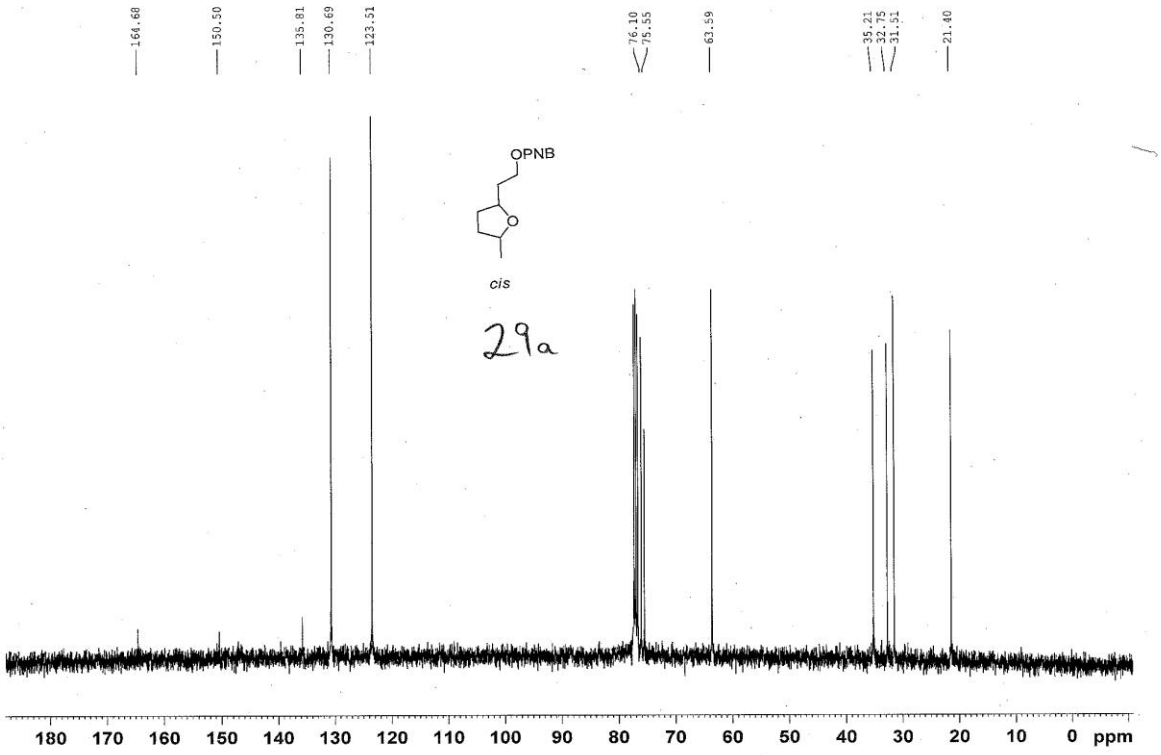
The mixture of **5.51a**–***cis*** and **5.51a**–***trans***, (21.6 mg, 0.15 mmol) was dissolved in dry THF (4 mL) and DMAP (4.2 mg, 0.035 mmol), Et_3N (63 µL, 0.45 mmol), and *p*-nitrobenzoyl chloride (55.7 mg, 0.30 mmol) were added. The reaction was stirred for 1 hour at room temperature. The reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (2 x 15mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The *p*-nitrobenzoate protected alcohols, **6.10a**–***cis*** and **6.10a**–***trans***, were separated and purified via column chromatography (EtOAc/petroleum ether, 10/90). Both products were collected in near quantitative yields.

6.10a–***cis***: *cis-2-(5-methyltetrahydrofuran-2-yl)ethyl 4-nitrobenzoate*

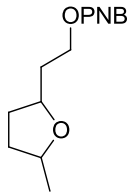


colorless amorphous solid. IR (thin film, KBr): 3437, 2967, 1722, 1526, 1274, 1100, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.9 Hz, 2H), 8.23 (d, *J* = 8.9 Hz, 2H), 4.52 (m, 2H), 4.02 (m, 2H), 2.14-1.97 (m, 4H), 1.65 (m, 1H), 1.51 (m, 1H), 1.28 (d, *J* = 6.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 150.5, 135.8, 130.7, 123.5, 76.1, 75.6, 63.6, 35.2, 32.8, 61.5, 21.4 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 99:1), 1.0 mL/min; minor enantiomer t_R = 23.4 min, major enantiomer t_R = 26.9 min. HRMS (ESI) : [M^+] calcd for [$C_{14}H_{17}NO_5$]: 279.1107, found: 279.1111.

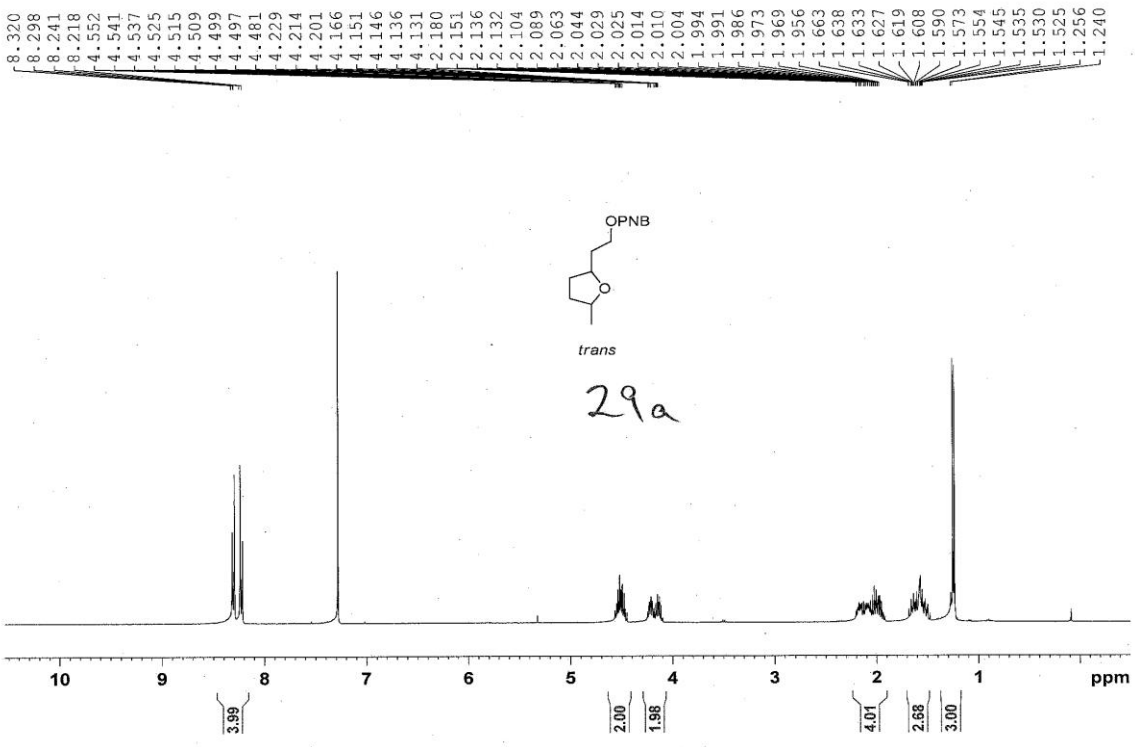

8.316
8.293
8.238
8.216
4.571
4.555
4.543
4.527
4.509
4.498
4.492
4.481
4.038
4.021
4.005
3.989
3.986
3.970
2.112
2.095
2.090
2.082
2.073
2.065
2.060
2.055
2.049
2.039
2.033
2.023
2.019
2.017
2.007
2.001
1.673
1.666
1.655
1.649
1.643
1.630
1.614
1.532
1.523
1.518
OPNB
cis
29a
9.0 8.5 8.0 7.5 7.0 6.5 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 ppm
4.01
2.00
1.99
4.01
1.09
0.98
3.00

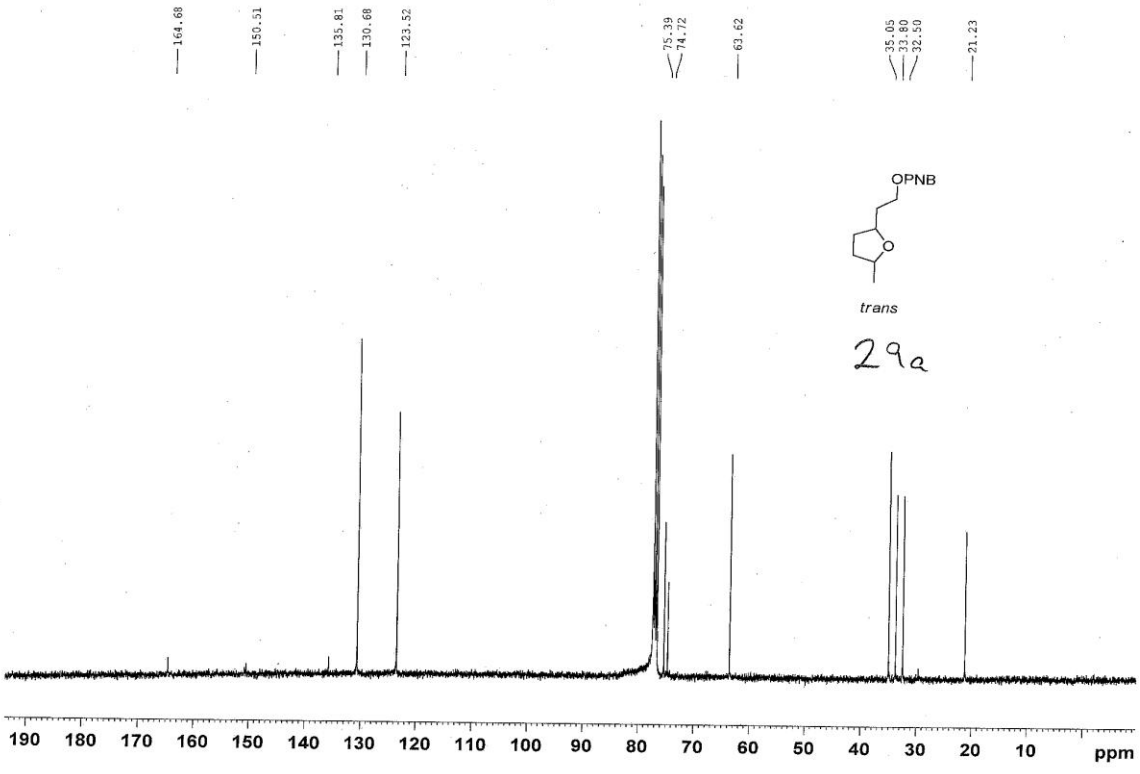

164.68
150.50
135.81
130.69
123.51
76.10
75.55
63.59
35.21
32.75
31.51
21.40
OPNB
cis
29a
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

6.10a–***trans***: *trans-2-(5-methyltetrahydrofuran-2-yl)ethyl 4-nitrobenzoate*



colorless oil. IR (thin film, KBr): 3447, 1723, 1637, 1276, 1102, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.9 Hz, 2H), 8.23 (d, *J* = 8.9 Hz, 2H), 4.52 (m, 2H), 4.26-4.10 (m, 2H), 2.22-1.92 (m, 4H), 1.70-1.47 (m, 2H), 1.25 (d, *J* = 6.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 150.5, 135.8, 130.7, 123.5, 75.4, 74.7, 63.6, 35.1, 33.8, 32.5, 21.2 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 9.4 min, minor enantiomer t_R = 12.3 min. HRMS (ESI) : [M^+] calcd for [$C_{14}H_{17}NO_5$]: 279.1107, found: 279.1111.


8.320
8.298
8.241
8.218
4.552
4.541
4.537
4.525
4.515
4.509
4.499
4.497
4.481
4.229
4.214
4.201
4.166
4.151
4.146
4.136
4.131
2.180
2.151
2.136
2.132
2.104
2.089
2.063
2.044
2.029
2.025
2.014
2.010
2.004
1.994
1.991
1.986
1.973
1.969
1.956
1.663
1.638
1.633
1.627
1.619
1.608
1.590
1.573
1.554
1.545
1.535
1.530
1.525
1.256
1.240
OPNB
trans
29a
10
9
8
7
6
5
4
3
2
1
ppm
3.99
2.00
1.98
4.01
2.68
3.00


164.68
150.51
135.81
130.68
123.52
75.39
74.72
63.62
35.05
33.80
32.50
21.23
OPNB
trans
29a
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

Organocascade DKR of Furans (5.53a–i *cis* and *trans*)
Two identical reactions were setup using the following conditions: Catalyst **1.12a** (28.6 mg, 0.088 mmol) and $PhCO_2H$ (10.7 mg, 0.088 mmol) were dissolved in dry toluene (1.1 mL) and cooled to –30 °C. Substrate **5.49** (0.44 mmol) was added in one portion. Compound **1.23a** (131.2 mg, 0.88 mmol) was added after 5 minutes and the reactions were stirred at –30 °C for the indicated time. One of the reactions was directly purified via column chromatography (EtOAc/petroleum ether, 15/85), isolating all diastereomeric aldehyde products **5.52** together as a mixture. This diastereomeric mixture was used for the determination of the diastereomeric ratio (see **Determination of Diastereomeric Ratios**).

The other reaction was diluted with MeOH (2.0 mL), and $NaBH_4$ (56.8 mg, 1.50 mmol) was added. The reaction was stirred for 20 minutes while warming to 0 °C and was then quenched by slowly adding saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 15mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Products **5.53**–***cis*** and **5.53**–***trans*** were purified from the residue via column chromatography (EtOAc/CH_2Cl_2, 2/98) and an isolated yield was determined. The major **5.53**–***cis*** diastereomer was isolated in this way. The major **5.53**–***trans*** diastereomer was further purified via prep TLC (EtOAc/petroleum ether, 25/75).

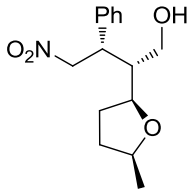
Determination of Diastereomeric Ratios
To 0.05 mmol of all diastereomeric aldehyde products **5.52**, was added 0.5 mL $CDCl_3$. Relative integration of the aldehyde proton peaks in the ^1H NMR spectrum was used to determine the dr of the two major products, **5.52**–***cis*** and **5.52**–***trans***, relative to any minor diastereomers.

Due to peak overlap, the **5.52**–***cis***/**5.52**–***trans*** ratio had to be determined in the presence of a chiral shift reagent, (–)-Eu(hfc)$_3$ or (+)-Eu(hfc)$_3$. A solution of 0.5 mL $CDCl_3$ and 15 mg Eu(hfc)$_3$ was prepared. The $CDCl_3$ solution of all diastereomeric aldehyde products **5.52** was titrated with the Eu(hfc)$_3$ solution, adding 50 µL at a time, until the aldehyde proton peaks for the corresponding aldehydes of **5.52**–***cis*** and **5.52**–***trans*** were separable and could be accurately integrated to determine the **5.52**–***cis***/**5.52**–***trans*** ratio. Titration with (+)-Eu(hfc)$_3$ was used for products **5.52b**, **5.52c, 5.52d, 5.52e,** and **5.52h.** Titration with (–)-Eu(hfc)$_3$ was used for products **5.52a** and **5.52g.** No chiral shift reagent was required for product **5.52f**.

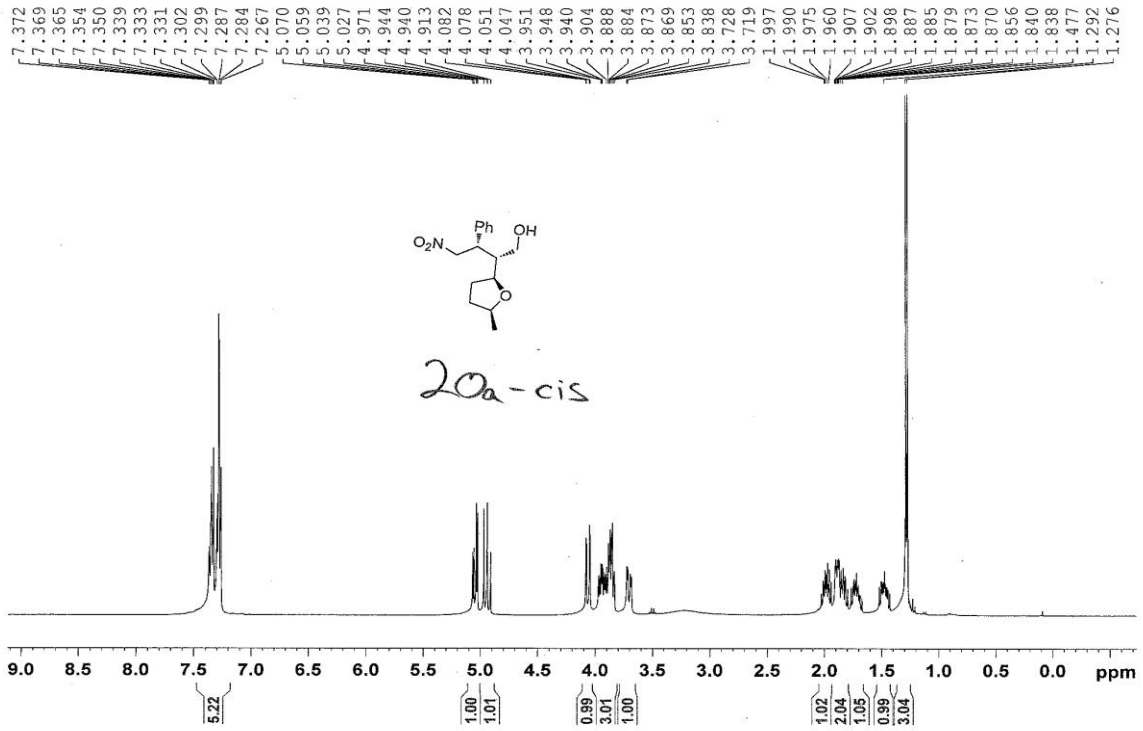
The dr and **5.53**–***cis***/**5.53**–***trans*** ratio for **5.53i** were determined by isolated yield of the different diastereomers of **5.53i** after chromatography.

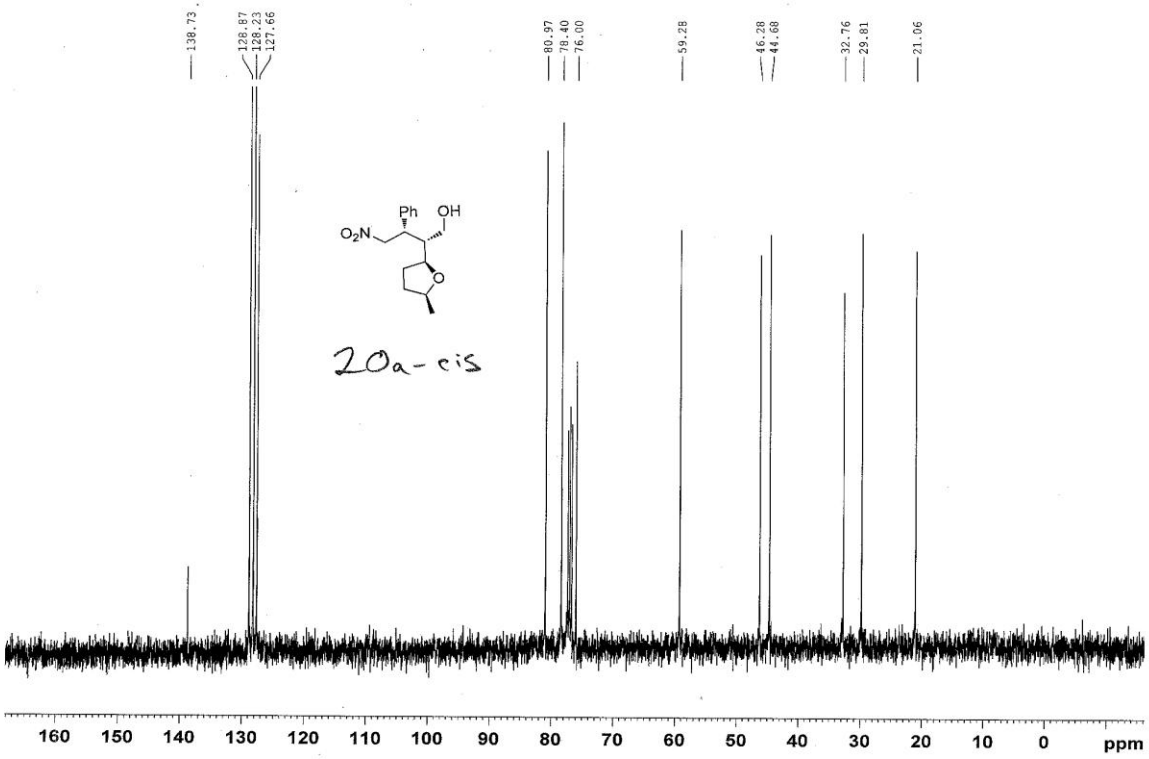
The dr and **5.53**–***cis***/**5.53**–***trans*** ratio for **5.53j** were determined by chiral HPLC of the mixture of all diastereomers of **5.53j** (AD-H column, *n*-hexane: *i*-PrOH = 90:10, 1.0 mL/min).

5.53a–***cis***: *(2R,3S)-2-((2S,5S)-5-methyltetrahydrofuran-2-yl)-4-nitro-3-phenylbutan-1-ol*

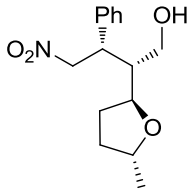


colorless amorphous solid. $[\alpha]_D^{21}$ = +21.2 (*c* 2.00, $CHCl_3$, >99% ee); IR (thin film, KBr): 3455, 2970, 1637, 1552, 1380, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H), 5.05 (dd, *J* = 12.6, 4.7 Hz, 1H), 4.94 (dd, *J* = 12.6, 10.7 Hz, 1H), 4.06 (dd, *J* = 12.4, 1.6 Hz, 1H), 3.97-3.82 (m, 3H), 3.70 (dd, *J* = 12.4, 3.7 Hz, 1H), 3.21 (bs, 1H), 1.98 (m, 1H), 1.93-1.79 (m, 2H), 1.72 (m, 1H), 1.48 (m, 1H), 1.29 (d, *J* = 6.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.9, 128.2, 127.7, 81.0, 78.4, 76.0, 59.3, 46.3, 44.7, 32.8, 29.8, 21.1 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 97:3), 0.3 mL/min; major enantiomer t_R = 73.7 min, minor enantiomer t_R = 83.5 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{15}H_{21}NO_4]$: 279.1471, found: 279.1472.

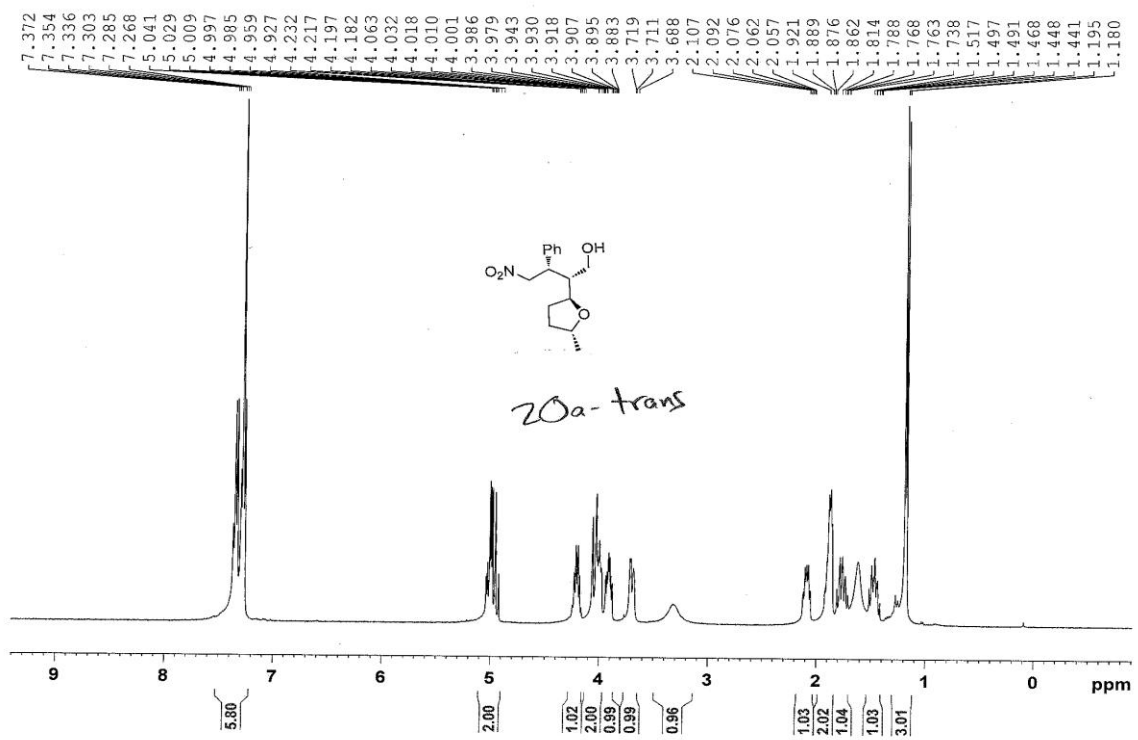

7.372
7.369
7.365
7.354
7.350
7.339
7.333
7.331
7.302
7.299
7.287
7.284
7.267
5.070
5.059
5.039
5.027
4.971
4.944
4.940
4.913
4.082
4.078
4.051
4.047
3.951
3.948
3.940
3.904
3.888
3.884
3.873
3.869
3.853
3.838
3.728
3.719
1.997
1.990
1.975
1.960
1.907
1.902
1.898
1.887
1.885
1.879
1.873
1.870
1.856
1.840
1.838
1.477
1.292
1.276
Ph
OH
O2N
O
20a-cis
9.0 8.5 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 ppm
5.22
1.00
1.01
0.99
3.01
1.00
1.02
2.04
1.05
0.99
3.04


138.73
128.87
128.23
127.66
80.97
78.40
76.00
59.28
46.28
44.68
32.76
29.81
21.06
Ph
OH
O2N
O
20a-cis
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

5.53a–***trans***: *(2R,3S)-2-((2S,5R)-5-methyltetrahydrofuran-2-yl)-4-nitro-3-phenylbutan-1-ol*



colorless amorphous solid. $[\alpha]_D^{23}$ = -10.7 (*c* 0.50, $CHCl_3$, >99% ee); IR (thin film, KBr): 3441, 2964, 1640, 1552, 1261, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.23 (m, 5H), 5.06-4.82 (m, 2H), 4.21 (m, 1H), 4.11-3.98 (m, 2H), 3.91 (m, 1H), 3.70 (m, 1H), 3.31 (bs, 1H), 2.10 (m, 1H), 1.89 (m, 2H), 1.77 (m, 1H), 1.48 (m, 1H), 1.20 (d, *J* = 6.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.9, 128.2, 127.7, 80.0, 78.1, 75.8, 59.5, 46.6, 44.8, 33.5, 31.3, 21.3 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 0.5 mL/min; major enantiomer t_R = 21.7 min, minor enantiomer t_R = 26.7 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{15}H_{21}NO_4]$: 279.1471, found: 279.1475.


7.372
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7.336
7.303
7.285
7.268
5.041
5.029
5.009
4.997
4.985
4.959
4.927
4.232
4.217
4.197
4.182
4.063
4.032
4.018
4.010
4.001
3.986
3.979
3.943
3.930
3.918
3.907
3.895
3.883
3.719
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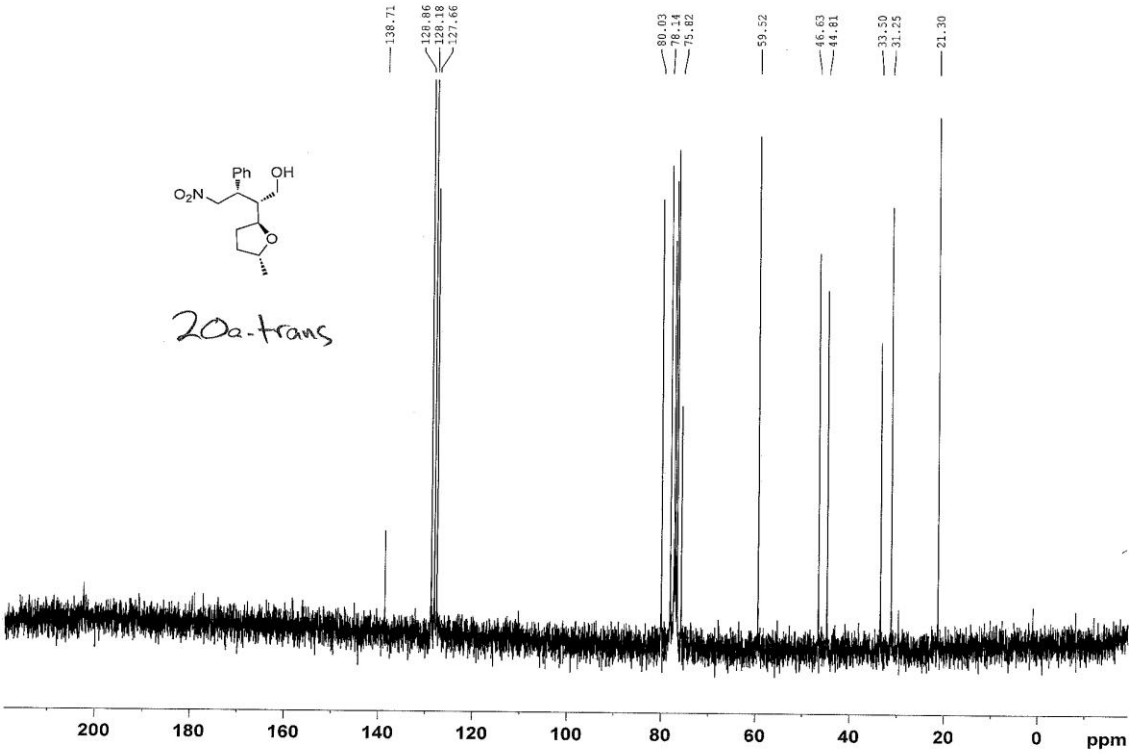
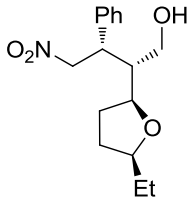
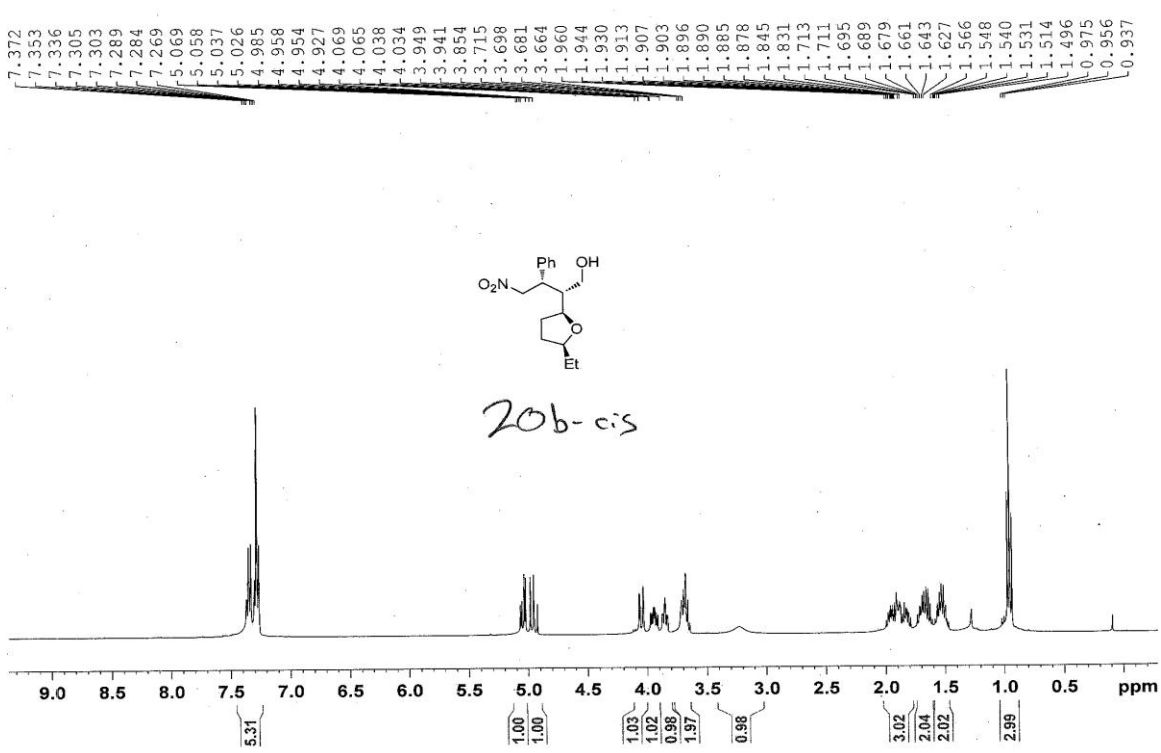
2.057
1.921
1.889
1.876
1.862
1.814
1.788
1.768
1.763
1.738
1.517
1.497
1.491
1.468
1.448
1.441
1.195
1.180
Ph
OH
O2N
20a-trans
9
8
7
6
5
4
3
2
1
0
ppm
5.80
2.00
1.02
2.00
0.99
0.99
0.96
1.03
2.02
1.04
1.03
3.01


138.71
128.86
128.18
127.66
80.03
78.14
75.82
59.52
46.63
44.81
33.50
31.25
21.30
Ph
OH
O2N
20a-trans
200
180
160
140
120
100
80
60
40
20
0
ppm

5.53b–***cis***: *(2R,3S)-2-((2S,5S)-5-ethyltetrahydrofuran-2-yl)-4-nitro-3-phenylbutan-1-ol*



colorless amorphous solid. $[\alpha]_D^{22}$ = +7.9 (*c* 1.00, $CHCl_3$, 98% ee); IR (thin film, KBr): 3463, 2964, 2926, 1552, 1380, 1042, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.24 (m, 5H), 5.04 (dd, *J* = 12.6, 4.6 Hz, 1H), 4.97 (dd, *J* = 12.6, 10.7 Hz, 1H), 4.05 (dd, *J* = 12.3, 1.5 Hz, 1H), 3.94 (td, *J* = 9.6, 4.9 Hz, 1H), 3.86 (m, 1H), 3.73-3.65 (m, 2H), 3.22 (bs, 1H), 2.00-1.78 (m, 3H), 1.75-1.60 (m, 2H), 1.59-1.47 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.9, 128.2, 127.7, 81.4, 80.8, 78.3, 59.3, 46.3, 44.7, 30.4, 29.6, 28.6, 10.4 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 97:3), 0.3 mL/min; major enantiomer t_R = 64.4 min, minor enantiomer t_R = 70.3 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{16}H_{23}NO_4]$: 293.1627, found: 293.1631.


7.372
7.353
7.336
7.305
7.303
7.289
7.284
7.269
5.069
5.058
5.037
5.026
4.985
4.958
4.954
4.927
4.069
4.065
4.038
4.034
3.949
3.941
3.854
3.715
3.698
3.681
3.664
1.960
1.944
1.930
1.913
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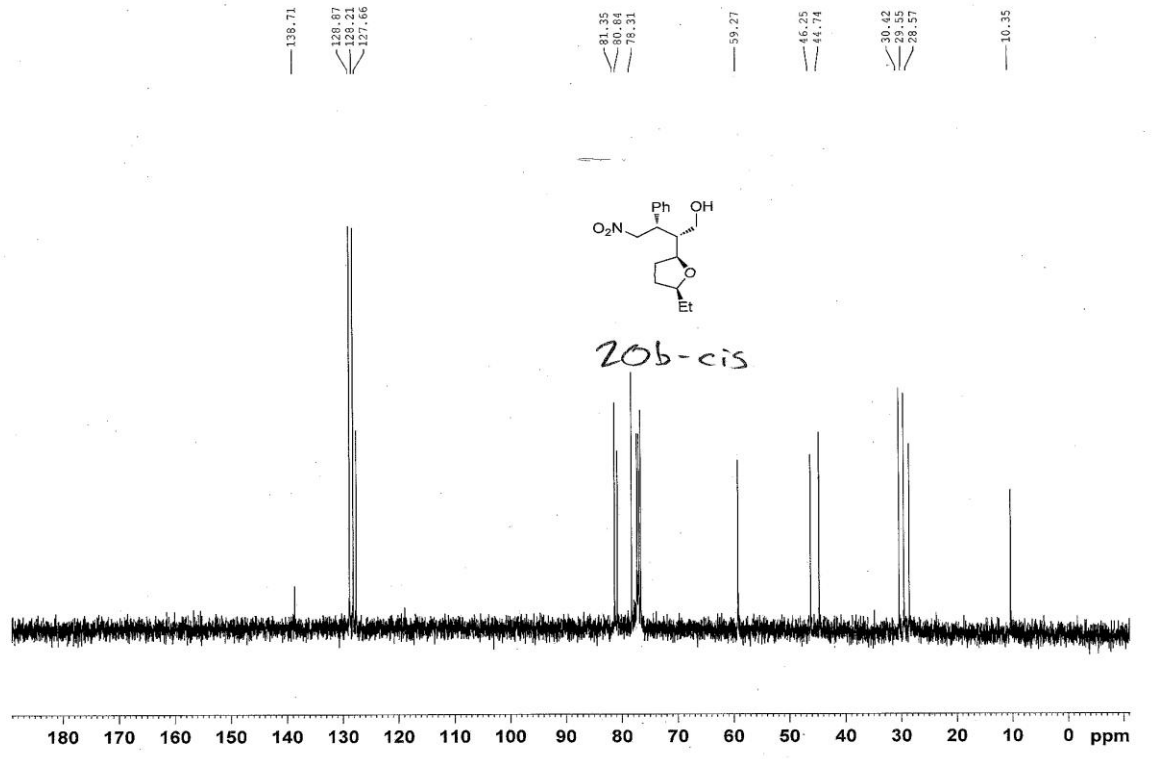
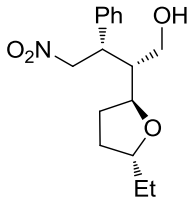
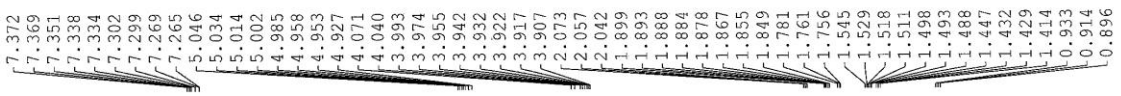
1.695
1.689
1.679
1.661
1.643
1.627
1.566
1.548
1.540
1.531
1.514
1.496
0.975
0.956
0.937
Ph
OH
O2N
O
Et
20b-cis
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
5.31
1.00
1.00
1.03
1.02
0.98
1.97
0.98
3.02
2.04
2.02
2.99

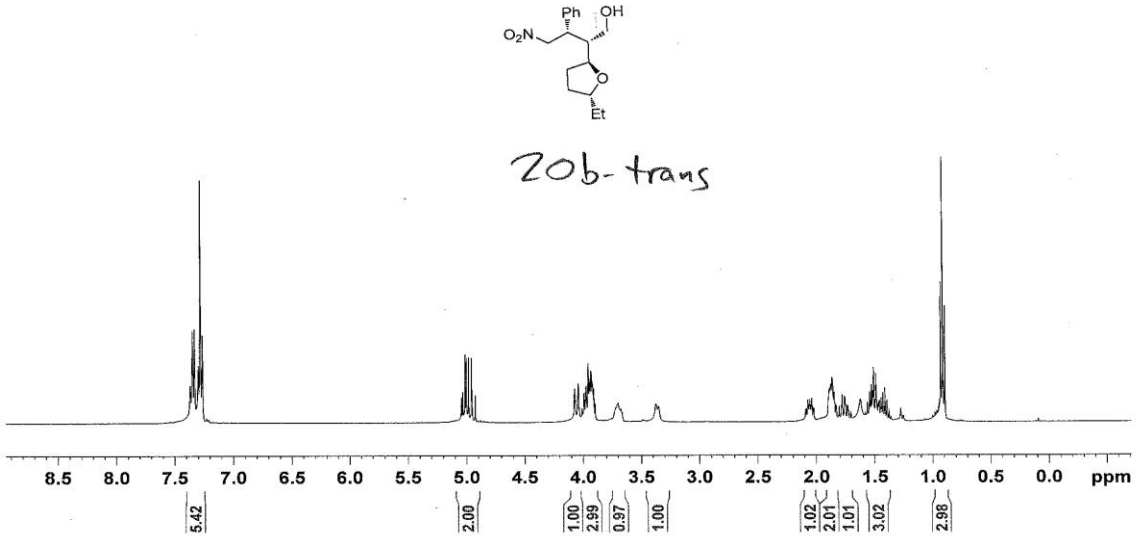

138.71
128.87
128.21
127.66
81.35
80.84
78.31
59.27
46.25
44.74
30.42
29.55
28.57
10.35
Ph
OH
O2N
O
Et
20b-cis
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

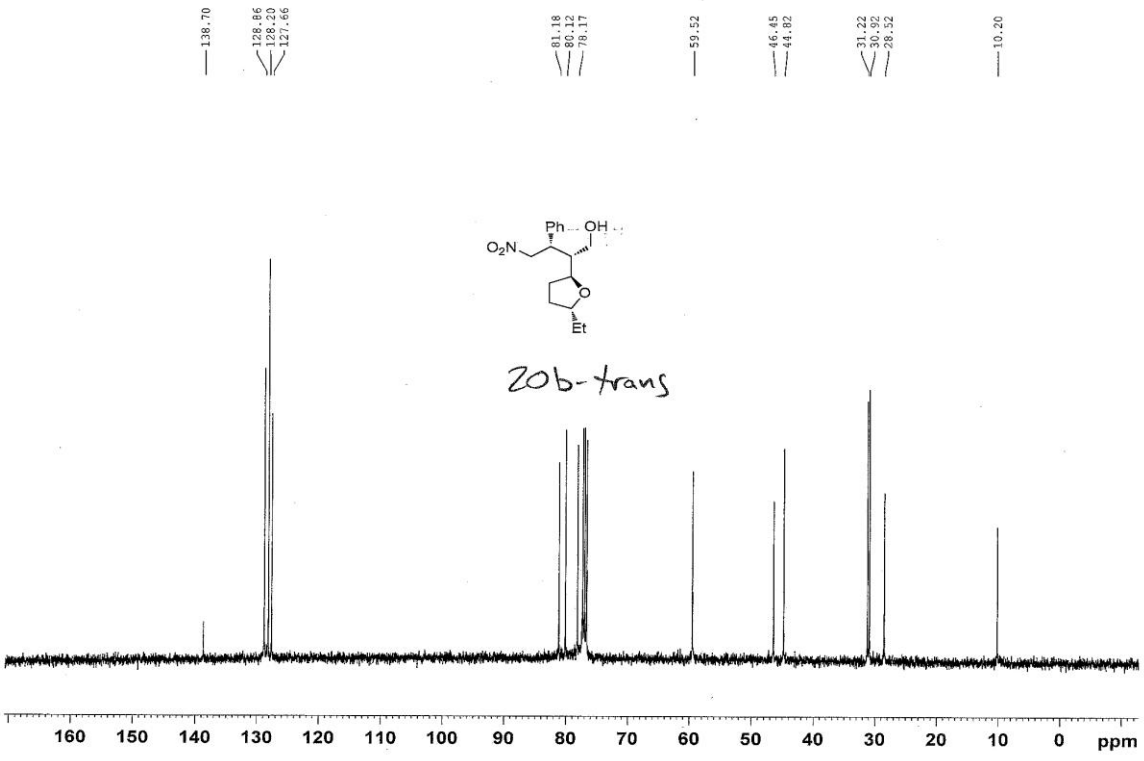
5.53b–***trans***: *(2R,3S)-2-((2S,5R)-5-ethyltetrahydrofuran-2-yl)-4-nitro-3-phenylbutan-1-ol*



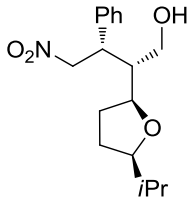
colorless oil. $[\alpha]_D^{22}$ = -0.5 (*c* 1.00, $CHCl_3$, 99% ee); IR (thin film, KBr): 3450, 2965, 2934, 1552, 1380, 1039, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H), 5.07-4.91 (m, 2H), 4.10-3.88 (m, 4H), 3.69 (m, 1H), 3.48 (bd, *J* = 8.9 Hz, 1H), 2.06 (m, 1H), 1.87 (m, 2H), 1.75 (m, 1H), 1.60-1.35 (m, 3H), 0.91 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.9, 128.2, 127.7, 81.2, 80.1, 78.2, 59.5, 46.5, 44.8, 31.2, 30.9, 28.5, 10.3 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 0.5 mL/min; major enantiomer t_R = 18.7 min, minor enantiomer t_R = 21.7 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{16}H_{23}NO_4]$: 293.1627, found: 293.1630.


7.372
7.369
7.351
7.338
7.334
7.302
7.299
7.269
7.265
5.046
5.034
5.014
5.002
4.985
4.958
4.953
4.927
4.071
4.040
3.993
3.974
3.955
3.942
3.932
3.922
3.917
3.907
2.073
2.057
2.042
1.899
1.893
1.888
1.884
1.878
1.867
1.855
1.849
1.781
1.761
1.756
1.545
1.529
1.518
1.511
1.498
1.493
1.488
1.447
1.432
1.429
1.414
0.933
0.914
0.896

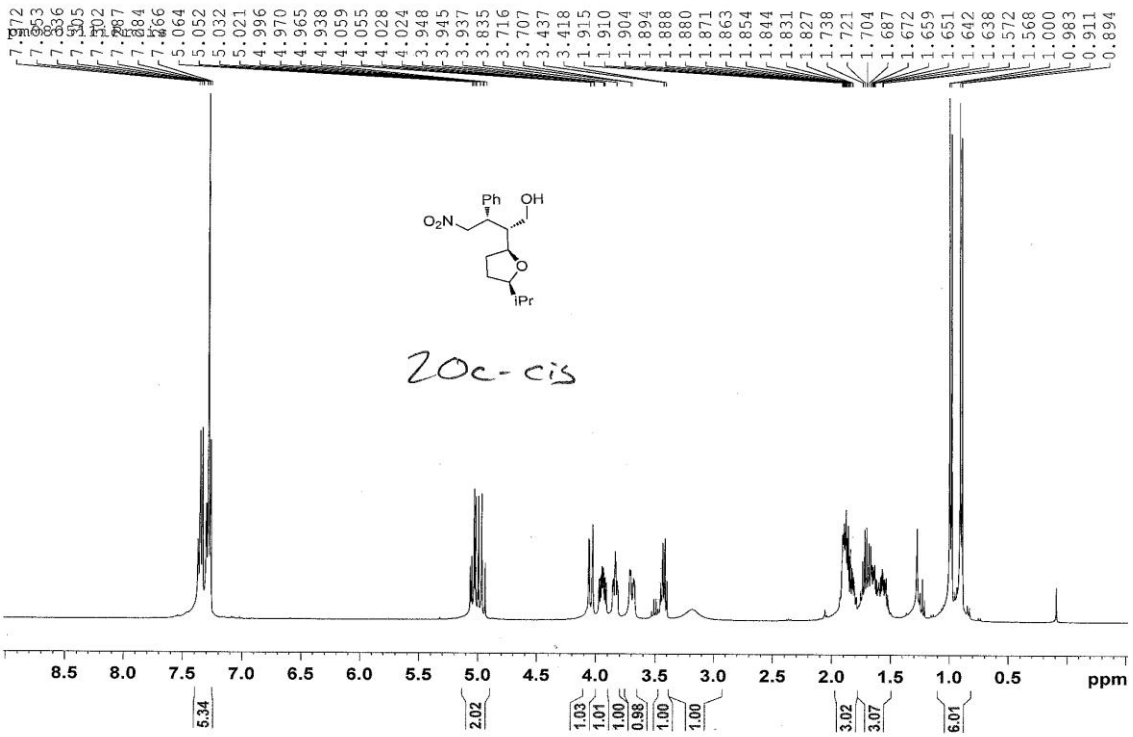

Ph
OH
O2N
O
Et
20b-trans
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
5.42
2.00
1.00
2.99
0.97
1.00
1.02
2.01
1.01
3.02
2.98

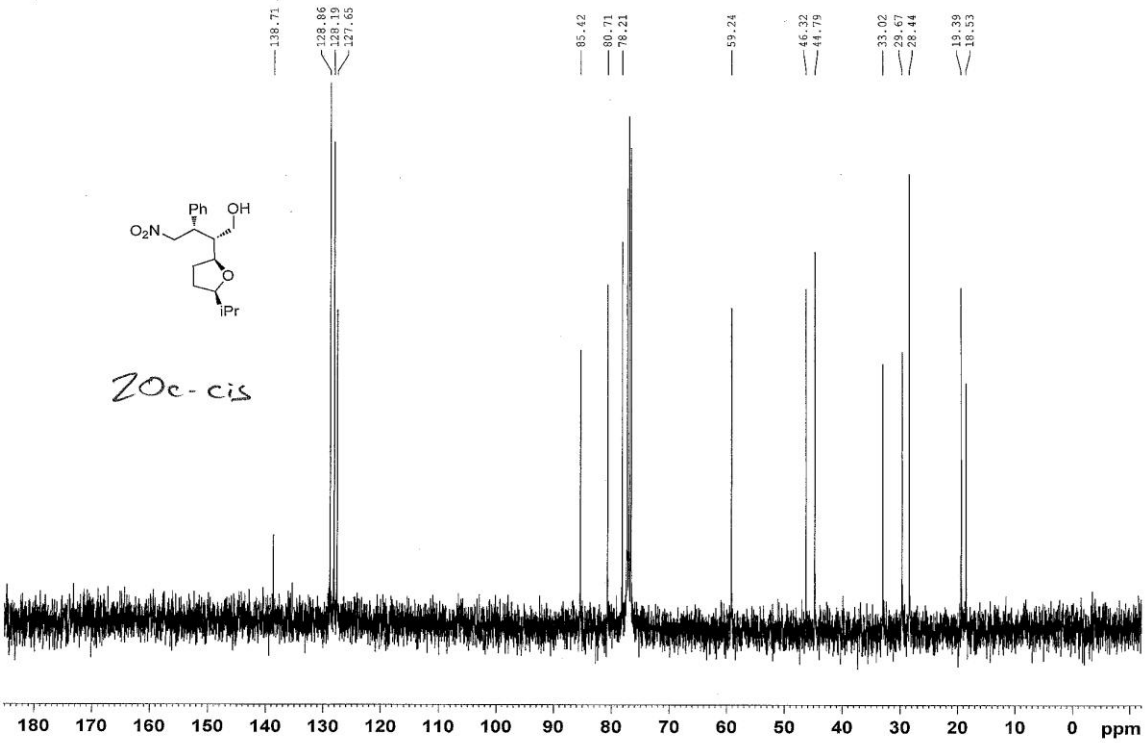

138.70
128.86
128.20
127.66
81.18
80.12
78.17
59.52
46.45
44.82
31.22
30.92
28.52
10.20
Ph
OH
O2N
O
Et
20b-trans
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

5.53c–***cis***: *(2R,3S)-2-((2S,5R)-5-isopropyltetrahydrofuran-2-yl)-4-nitro-3-phenylbutan-1-ol*

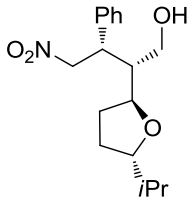


colorless amorphous solid. $[\alpha]_D^{21}$ = +10.5 (*c* 0.75, $CHCl_3$, >99% ee); IR (thin film, KBr): 3496, 2961, 2877, 1553, 1381, 1062, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.24 (m, 5H), 5.08-4.93 (m, 2H), 4.04 (dd, *J* = 12.4, 1.6 Hz, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.70 (dd, *J* = 12.4, 3.7 Hz, 1H), 3.43 (q, *J* = 7.4 Hz, 1H), 3.19 (bs, 1H), 1.96-1.50 (m, 6H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.9, 128.2, 127.7, 85.4, 80.7, 78.2, 59.2, 46.3, 44.8, 33.0, 29.7, 28.4, 19.4, 18.5 ppm; the enantiomeric excess was determined by HPLC with an OD-H column (*n*-hexane: *i*-PrOH = 97:3), 0.5 mL/min; minor enantiomer t_R = 36.3 min, major enantiomer t_R = 43.6 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{17}H_{25}NO_4]$: 307.1784, found: 307.1788.

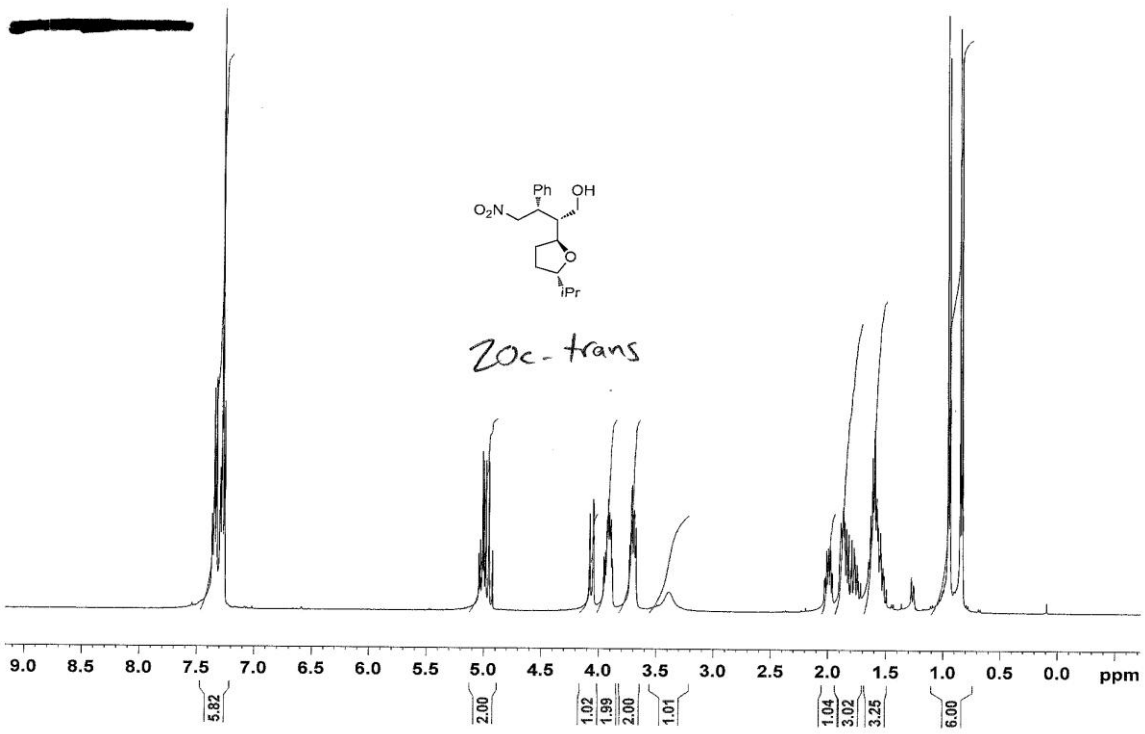

ppm
7.372
7.353
7.336
7.305
7.302
7.287
7.284
7.266
5.064
5.052
5.032
5.021
4.996
4.970
4.965
4.938
4.059
4.055
4.028
4.024
3.948
3.945
3.937
3.835
3.716
3.707
3.437
3.418
1.915
1.910
1.904
1.894
1.888
1.880
1.871
1.863
1.854
1.844
1.831
1.827
1.738
1.721
1.704
1.687
1.672
1.659
1.651
1.642
1.638
1.572
1.568
1.000
0.983
0.911
0.894
Ph
OH
O2N
O
iPr
20c-cis
8.5
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
ppm
5.34
2.02
1.03
1.01
1.00
0.98
1.00
1.00
3.02
3.07
6.01

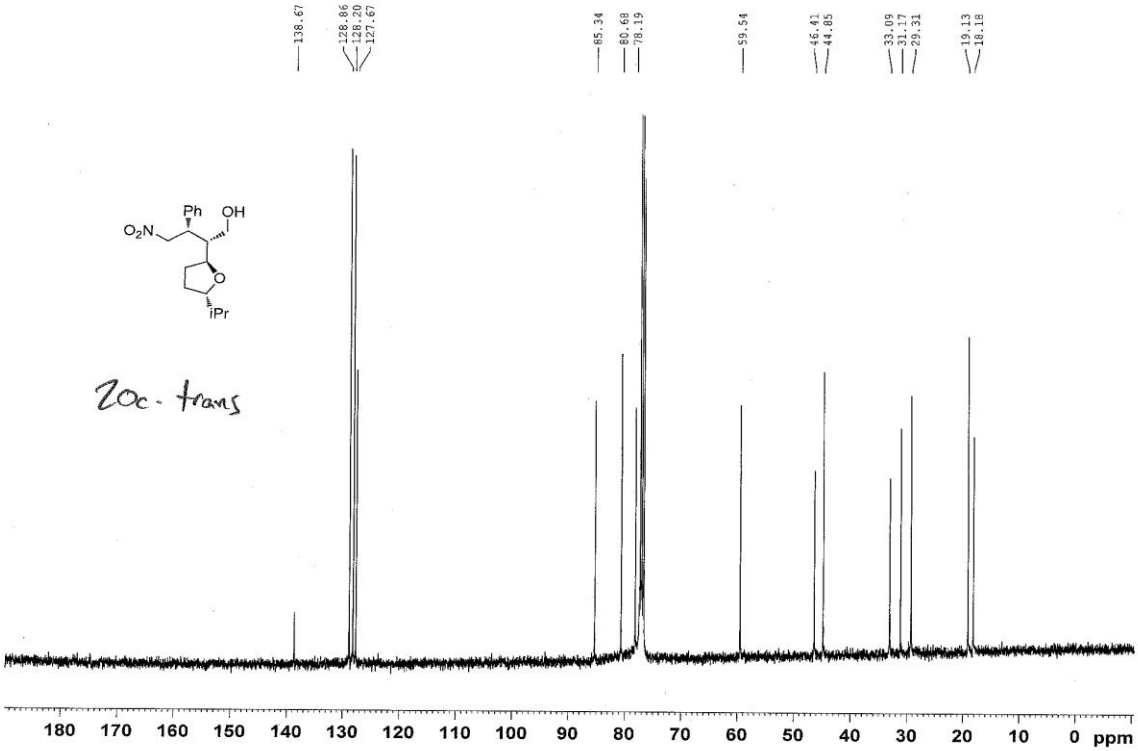

138.71
128.86
128.19
127.65
85.42
80.71
78.21
59.24
46.32
44.79
33.02
29.67
28.44
19.39
18.53
Ph
OH
O2N
O
iPr
20c-cis
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

5.53c–***trans***: *(2R,3S)-2-((2S,5S)-5-isopropyltetrahydrofuran-2-yl)-4-nitro-3-phenylbutan-1-ol*

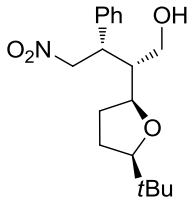


colorless amorphous solid. $[\alpha]_D^{22}$ = -2.0 (*c* 1.00, $CHCl_3$, 98% ee); IR (thin film, KBr): 3459, 2961, 2874, 1552, 1381, 1054, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.24 (m, 5H), 5.08-4.91 (m, 2H), 4.08 (dd, *J* = 12.3, 1.4 Hz, 1H), 3.93 (m, 2H), 3.71 (m, 2H), 3.39 (bs, 1H), 2.00 (m, 1H), 1.94-1.49 (m, 6H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.9, 128.2, 127.7, 85.3, 80.7, 78.2, 59.5, 46.4, 44.9, 33.1, 31.2, 29.3, 19.1, 18.2 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 97:3), 0.3 mL/min; minor enantiomer t_R = 58.8 min, major enantiomer t_R = 64.2 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{17}H_{25}NO_4]$: 307.1784, found: 307.1789.

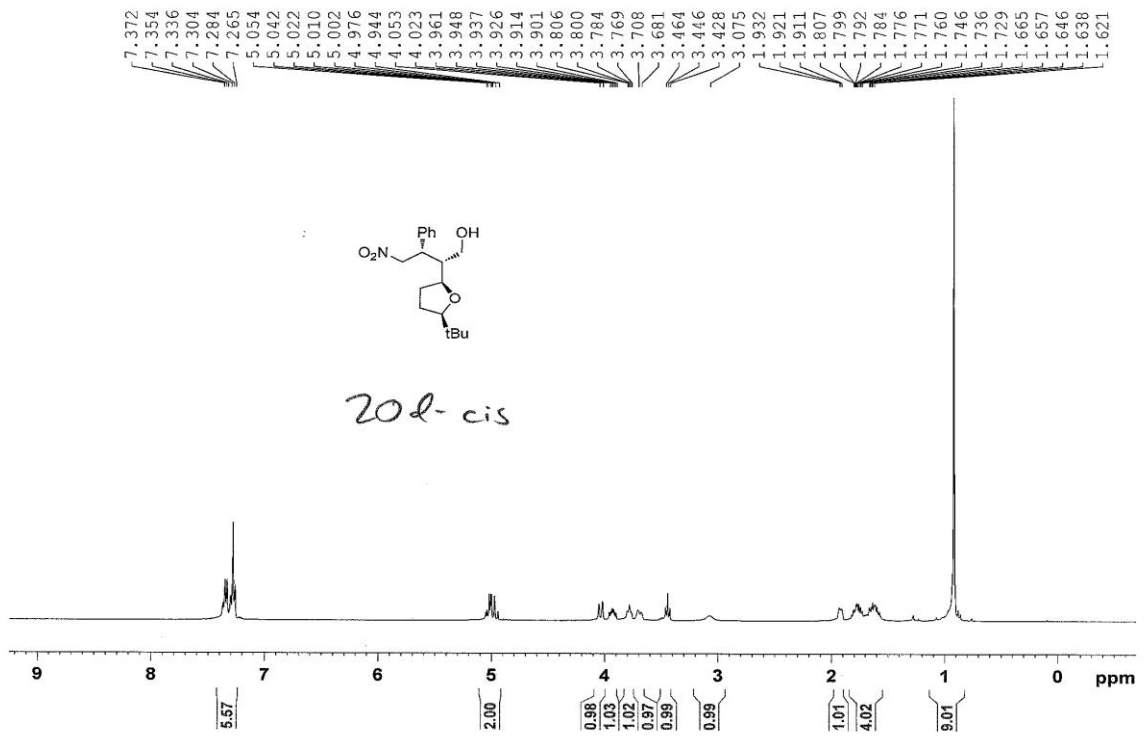

Ph
OH
O_2N
O
iPr
20c - trans
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
5.82
2.00
1.02
1.99
2.00
1.01
1.04
3.02
3.25
6.00

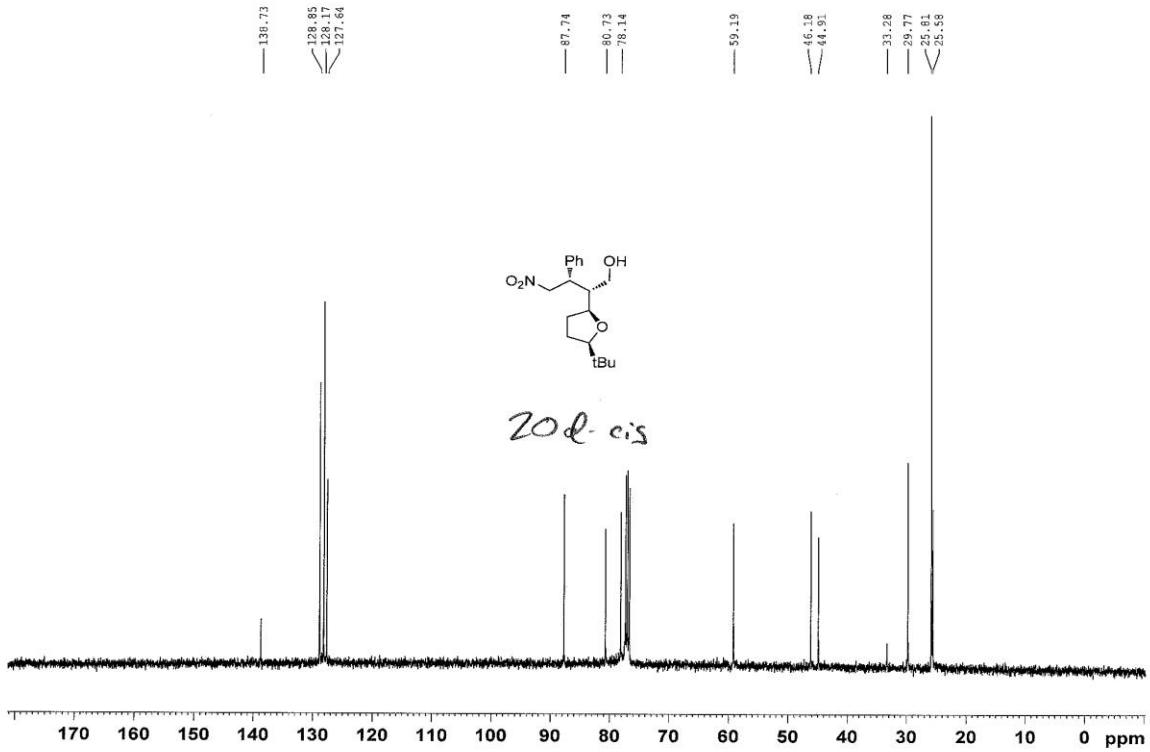

138.67
128.86
128.20
127.67
85.34
80.68
78.19
59.54
46.41
44.85
33.09
31.17
29.31
19.13
18.18
Ph
OH
O_2N
O
iPr
20c - trans
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

5.53d–***cis***: *(2R,3S)-2-((2S,5R)-5-(tert-butyl)tetrahydrofuran-2-yl)-4-nitro-3-phenylbutan-1-ol*

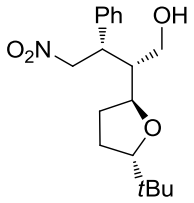


colorless amorphous solid. $[\alpha]_D^{24}$ = +4.8 (*c* 1.25, $CHCl_3$, 97% ee); IR (thin film, KBr): 3501, 2960, 1553, 1380, 1207, 1060, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.24 (m, 5H), 5.06-4.92 (m, 2H), 4.04 (d, *J* = 12.3 Hz, 1H), 3.93 (td, J = 9.5, 5.1 Hz, 1H), 3.79 (m, 1H), 3.70 (d, *J* = 11.4 Hz, 1H), 3.45 (t, *J* = 7.1 Hz, 1H), 3.08 (bs, 1H), 1.92 (m, 1H), 1.85-1.55 (m, 4H), 0.91 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.9, 128.2, 127.6, 87.7, 80.7, 78.1, 59.2, 46.2, 44.9, 33.3, 29.8, 25.8, 25.6 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 95:5), 0.5 mL/min; minor enantiomer t_R = 23.5 min, major enantiomer t_R = 24.9 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{18}H_{27}NO_4]$: 321.1940, found: 321.1944.

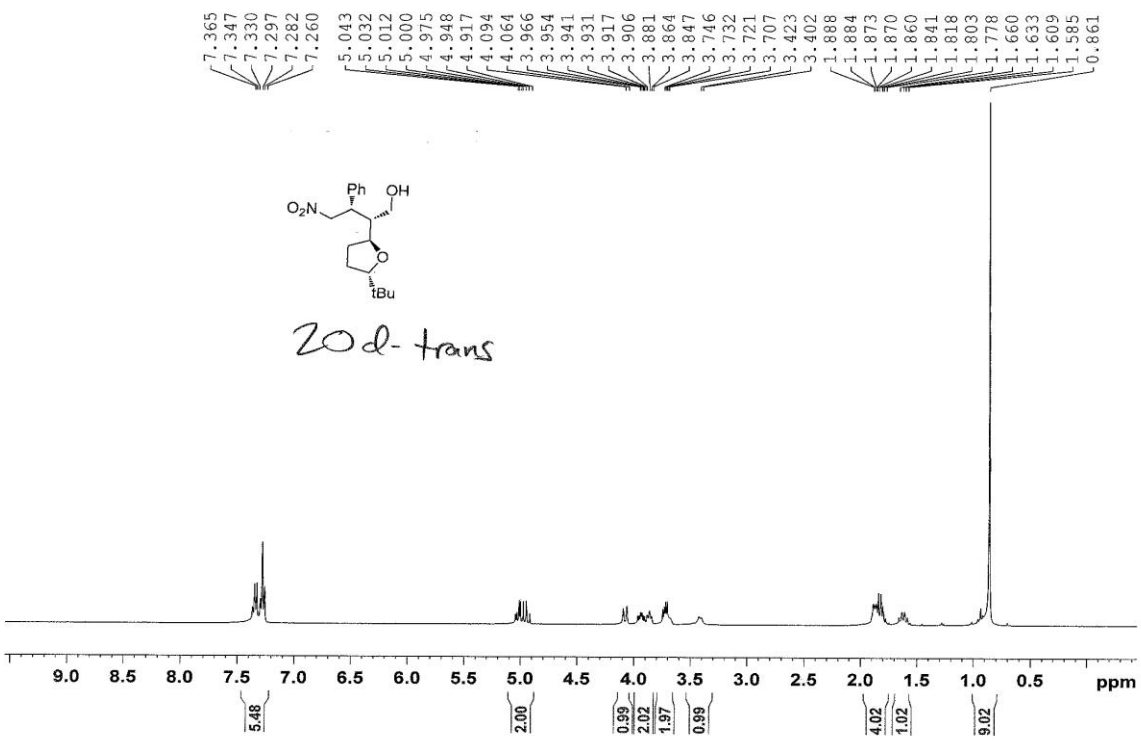

7.372
7.354
7.336
7.304
7.284
7.265
5.054
5.042
5.022
5.010
5.002
4.976
4.944
4.053
4.023
3.961
3.948
3.937
3.926
3.914
3.901
3.806
3.800
3.784
3.769
3.708
3.681
3.464
3.446
3.428
3.075
1.932
1.921
1.911
1.807
1.799
1.792
1.784
1.776
1.771
1.760
1.746
1.736
1.729
1.665
1.657
1.646
1.638
1.621
Ph
OH
O2N
tBu
20l- cis
9
8
7
6
5
4
3
2
1
0
ppm
5.57
2.00
0.98
1.03
1.02
0.97
0.99
0.99
1.01
4.02
9.01

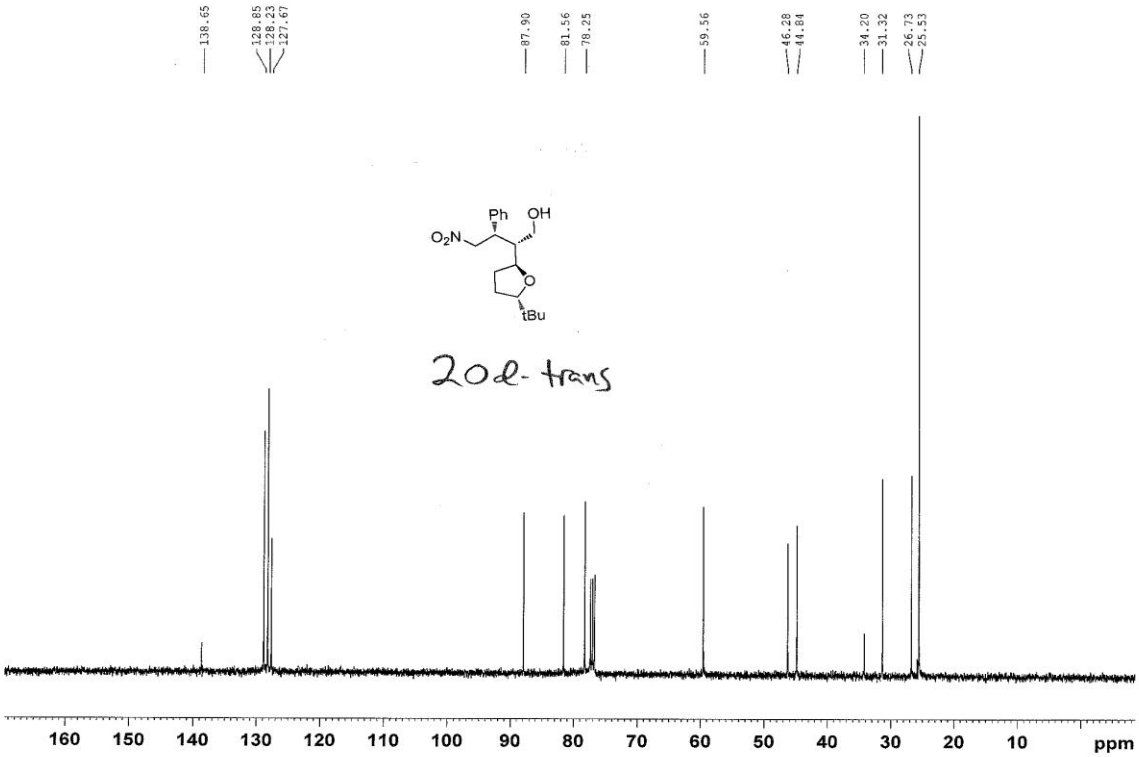

138.73
128.85
128.17
127.64
87.74
80.73
78.14
59.19
46.18
44.91
33.28
29.77
25.81
25.58
Ph
OH
O2N
tBu
20l- cis
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

5.53d–***trans***: *(2R,3S)-2-((2S,5S)-5-(tert-butyl)tetrahydrofuran-2-yl)-4-nitro-3-phenylbutan-1-ol*

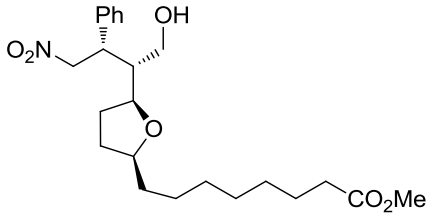


colorless amorphous solid. $[\alpha]_D^{22}$ = -3.4 (*c* 1.50, $CHCl_3$, >99% ee); IR (thin film, KBr): 3478, 2958, 2869, 1553, 1380, 1060, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H), 5.05-4.91 (m, 2H), 4.08 (d, *J* = 12.2 Hz, 1H), 3.97-3.84 (m, 2H), 3.76-3.65 (m, 2H), 3.41 (bd, *J* = 8.8 Hz, 1H), 1.91-1.76 (m, 4H), 1.62 (m, 1H), 0.86 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.9, 128.2, 127.7, 87.9, 81.6, 78.3, 59.6, 46.3, 44.8, 34.2, 31.3, 26.7, 25.5 ppm; the enantiomeric excess was determined by HPLC with an OD-H column (*n*-hexane: *i*-PrOH = 97:3), 0.3 mL/min; minor enantiomer t_R = 53.6 min, major enantiomer t_R = 72.5 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{18}H_{27}NO_4]$: 321.1940, found: 321.1940.

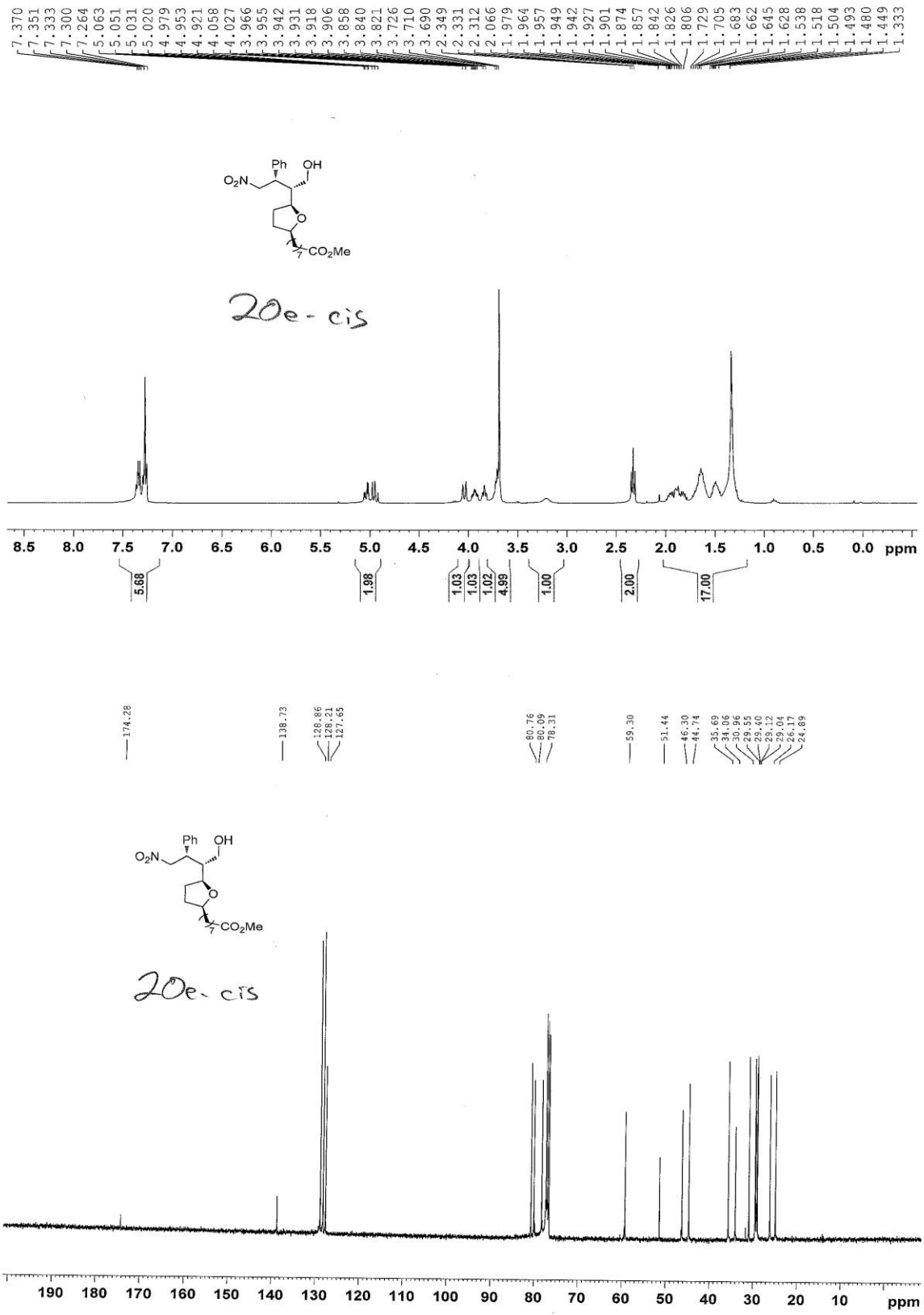

7.365
7.347
7.330
7.297
7.282
7.260
5.043
5.032
5.012
5.000
4.975
4.948
4.917
4.094
4.064
3.966
3.954
3.941
3.931
3.917
3.906
3.881
3.864
3.847
3.746
3.732
3.721
3.707
3.423
3.402
1.888
1.884
1.873
1.870
1.860
1.841
1.818
1.803
1.778
1.660
1.633
1.609
1.585
0.861
Ph
OH
O2N
O
tBu
20d- trans
9.0 8.5 8.0 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 ppm
5.48
2.00
0.99
2.02
1.97
0.99
4.02
1.02
9.02


138.65
128.85
128.23
127.67
87.90
81.56
78.25
59.56
46.28
44.84
34.20
31.32
26.73
25.53
Ph
OH
O2N
O
tBu
20d- trans
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

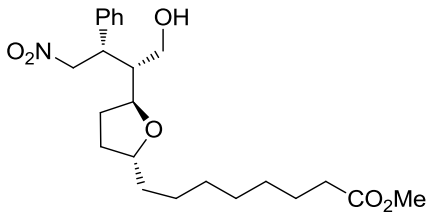
5.53e–***cis***: *methyl 8-((2S,5S)-5-((2R,3S)-1-hydroxy-4-nitro-3-phenylbutan-2-yl)tetrahydrofuran-2-yl)octanoate*



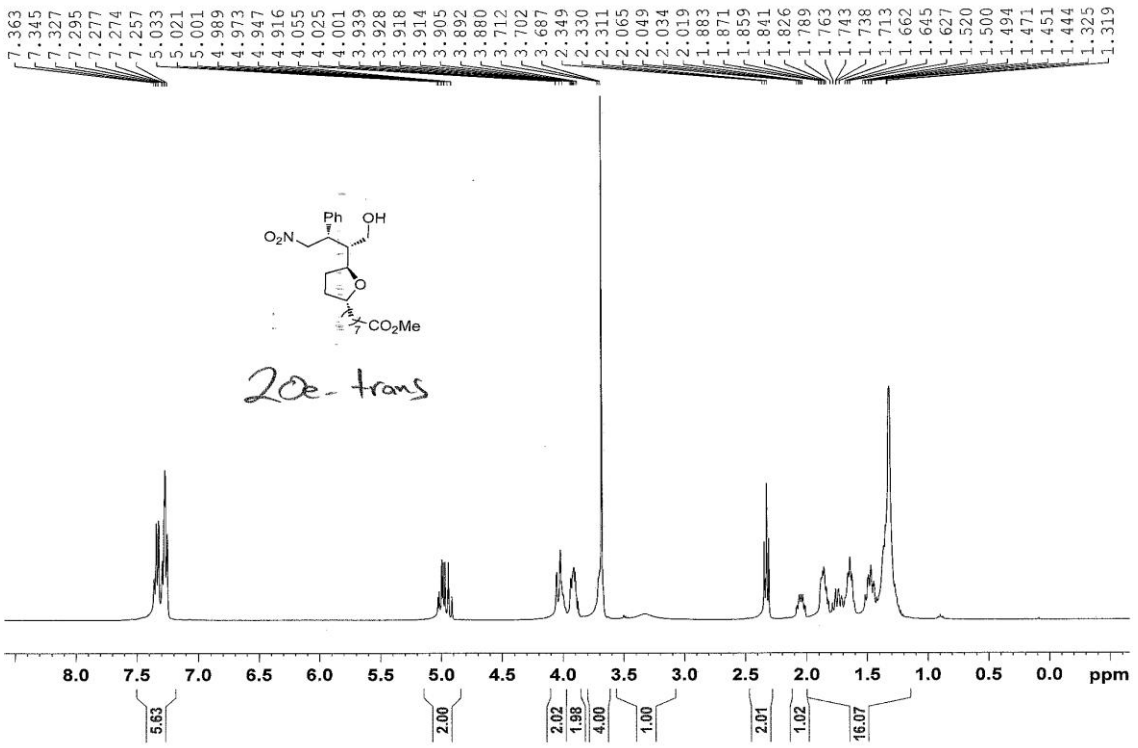
colorless oil. $[\alpha]_D^{22}$ = +14.5 (*c* 1.25, $CHCl_3$, 99% ee); IR (thin film, KBr): 3489, 2930, 2856, 1736, 1551, 1379, 1201, 1051, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H), 5.07-4.91 (m, 2H), 4.04 (d, *J* = 12.4 Hz, 1H), 3.94 (td, *J* = 9.9, 4.5 Hz, 1H), 3.84 (m, 1H), 3.76-3.66 (m, 5H), 3.21 (bs, 1H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.01-1.25 (m, 17H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 138.7, 128.9, 128.2, 127.7, 80.8, 80.1, 78.3, 59.3, 51.4, 46.3, 44.7, 35.7, 34.1, 31.0, 29.6, 29.4, 29.1, 29.0, 26.2, 24.9 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 15.3 min, minor enantiomer t_R = 18.0 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{23}H_{35}NO_6]$: 421.2464, found: 421.2468.

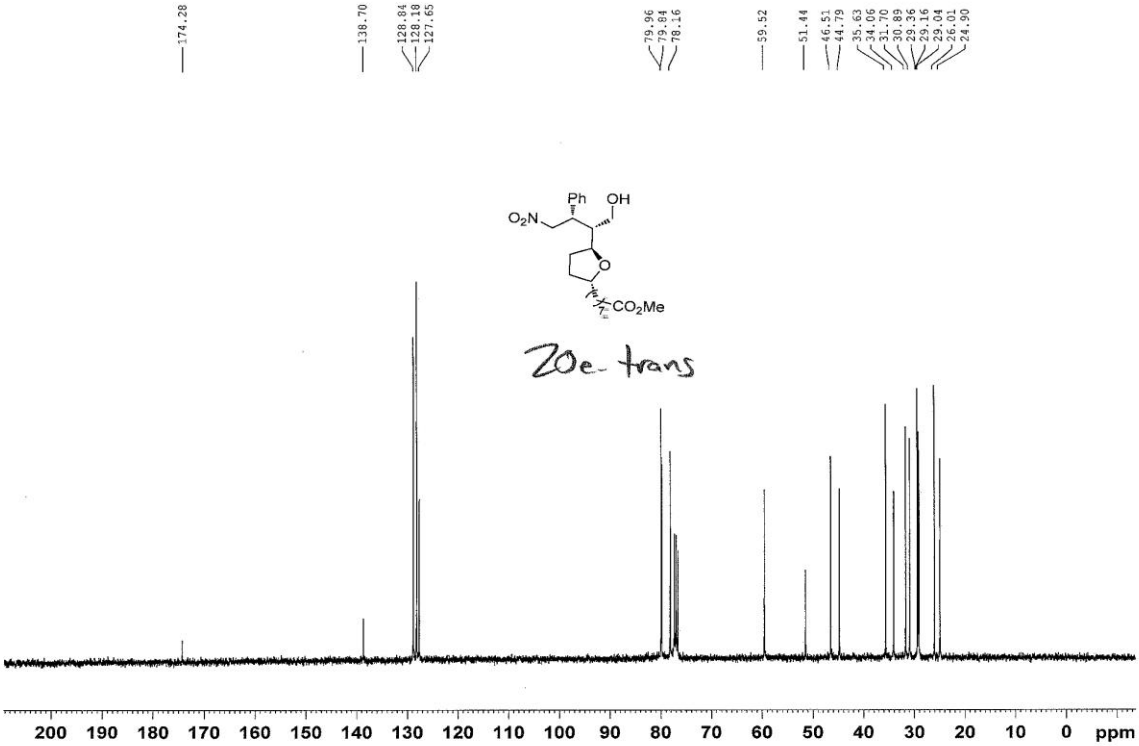

7.370
7.351
7.333
7.300
7.264
5.063
5.051
5.031
5.020
4.979
4.953
4.921
4.058
4.027
3.966
3.955
3.942
3.931
3.918
3.906
3.858
3.840
3.821
3.726
3.710
3.690
2.349
2.331
2.312
2.066
1.979
1.964
1.957
1.949
1.942
1.927
1.901
1.874
1.857
1.842
1.826
1.806
1.729
1.705
1.683
1.662
1.645
1.628
1.538
1.518
1.504
1.493
1.480
1.449
1.333
Ph
OH
O2N
CO2Me
20e - cis
8.5 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 ppm
5.68
1.98
1.03
1.03
1.02
4.99
1.00
2.00
17.00
174.28
138.73
128.86
128.21
127.65
80.76
80.09
78.31
59.30
51.44
46.30
44.74
35.69
34.06
30.96
29.55
29.40
29.12
29.04
26.17
24.89
Ph
OH
O2N
CO2Me
20e- cis
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

5.53e–***trans***: *methyl 8-((2R,5S)-5-((2R,3S)-1-hydroxy-4-nitro-3-phenylbutan-2-yl)tetrahydrofuran-2-yl)octanoate*

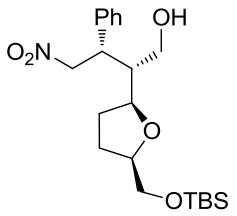


colorless oil. $[\alpha]_D^{25}$ = +12.4 (*c* 1.25, $CHCl_3$, >99% ee); IR (thin film, KBr): 3487, 2931, 2857, 1736, 1552, 1380, 1043, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.22 (m, 5H), 5.05-4.91 (m, 2H), 4.10-3.86 (m, 4H), 3.75-3.64 (m, 4H), 3.32 (bs, 1H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.05 (m, 1H), 1.92-1.23 (m, 16H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 138.7, 128.8, 128.2, 127.7, 80.0, 79.8, 78.2, 59.5, 51.4, 46.5, 44.8, 35.6, 34.1, 31.7, 30.9, 29.4, 29.2, 29.0, 26.0, 24.9 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; minor enantiomer t_R = 16.1 min, major enantiomer t_R = 18.1 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{23}H_{35}NO_6]$: 421.2464, found: 421.2470.

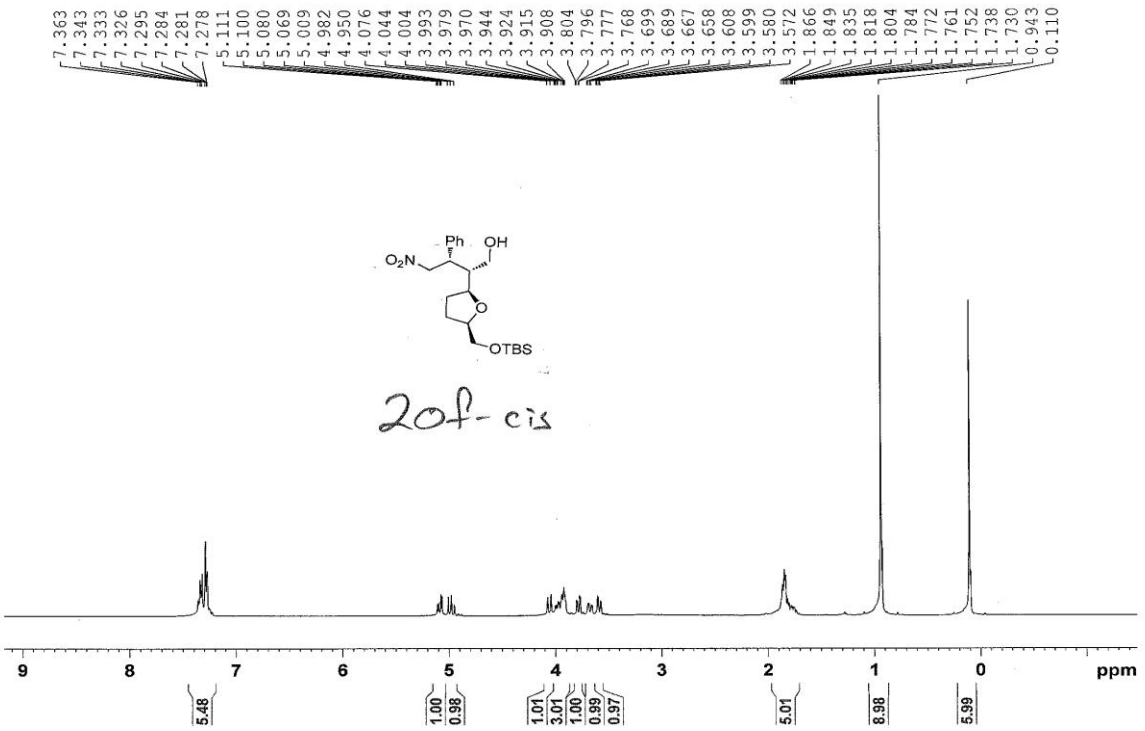

7.363
7.345
7.327
7.295
7.277
7.274
7.257
5.033
5.021
5.001
4.989
4.973
4.947
4.916
4.055
4.025
4.001
3.939
3.928
3.918
3.914
3.905
3.892
3.880
3.712
3.702
3.687
2.349
2.330
2.311
2.065
2.049
2.034
2.019
1.883
1.871
1.859
1.841
1.826
1.789
1.763
1.743
1.738
1.713
1.662
1.645
1.627
1.520
1.500
1.494
1.471
1.451
1.444
1.325
1.319
Ph
OH
O2N
O
CO2Me
20e- trans
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
ppm
5.63
2.00
2.02
1.98
4.00
1.00
2.01
1.02
16.07

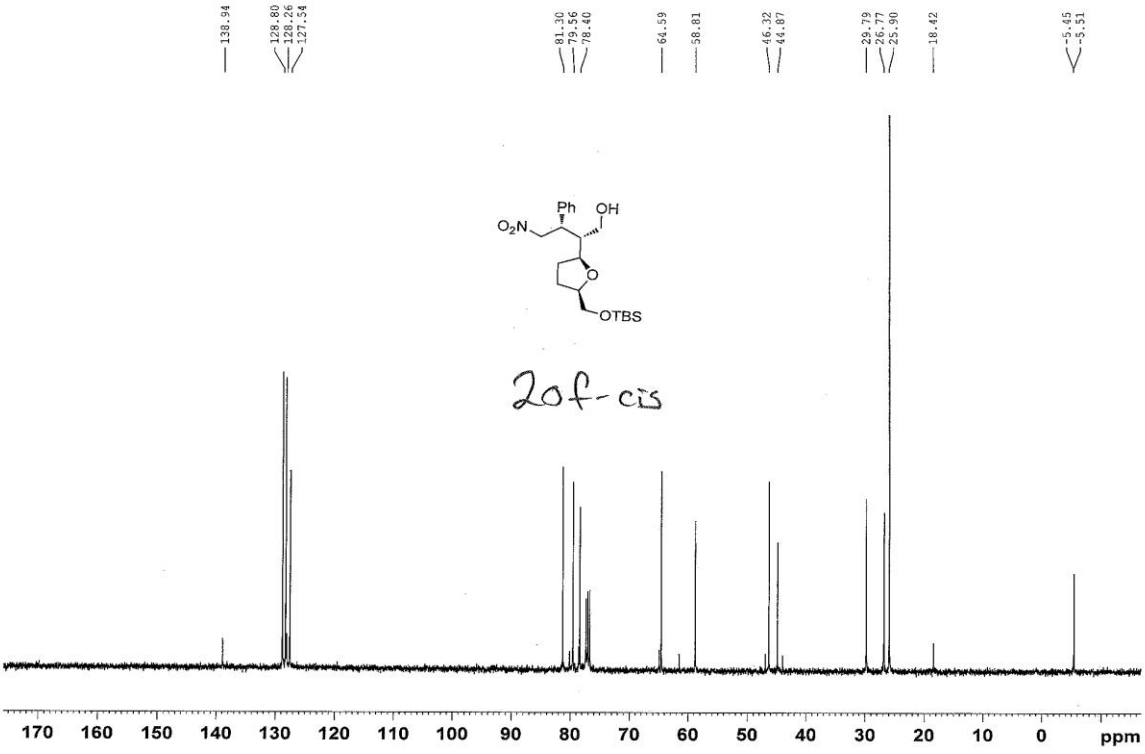

174.28
138.70
128.84
128.18
127.65
79.96
79.84
78.16
59.52
51.44
46.51
44.79
35.63
34.06
31.70
30.89
29.36
29.16
29.04
26.01
24.90
Ph
OH
O2N
O
CO2Me
20e- trans
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

5.53f–***cis***: *(2R,3S)-2-((2S,5R)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4-nitro-3-phenylbutan-1-ol*

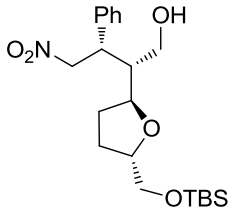


colorless oil. $[\alpha]_D^{23}$ = +16.4 (*c* 1.25, $CHCl_3$, >99% ee); IR (thin film, KBr): 3501, 2954, 2929, 2857, 1553, 1380, 1256, 1066, 837, 778, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.21 (m, 5H), 5.09 (dd, *J* = 12.7, 4.5 Hz, 1H), 4.98 (dd, *J* = 12.5, 10.7 Hz, 1H), 4.06 (d, *J* = 12.7 Hz, 1H), 4.03-3.88 (m, 3H), 3.79 (dd, *J* = 10.9, 3.3 Hz, 1H), 3.67 (dd, *J* = 12.7, 3.7 Hz, 1H), 3.59 (dd, *J* = 10.9, 3.6 Hz, 1H), 1.95-1.72 (m, 5H), 0.94 (s, 9H), 0.11 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 128.8, 128.3, 127.5, 81.3, 79.6, 78.4, 64.6, 58.8, 46.3, 44.9, 29.8, 26.8, 25.9, 18.4, -5.5, -5.5 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 95:5), 0.5 mL/min; major enantiomer t_R = 12.3 min, minor enantiomer t_R = 15.8 min. HRMS (ESI) : [M^+] calcd for [$C_{21}H_{35}NO_5Si$]: 409.2284, found: 409.2286.

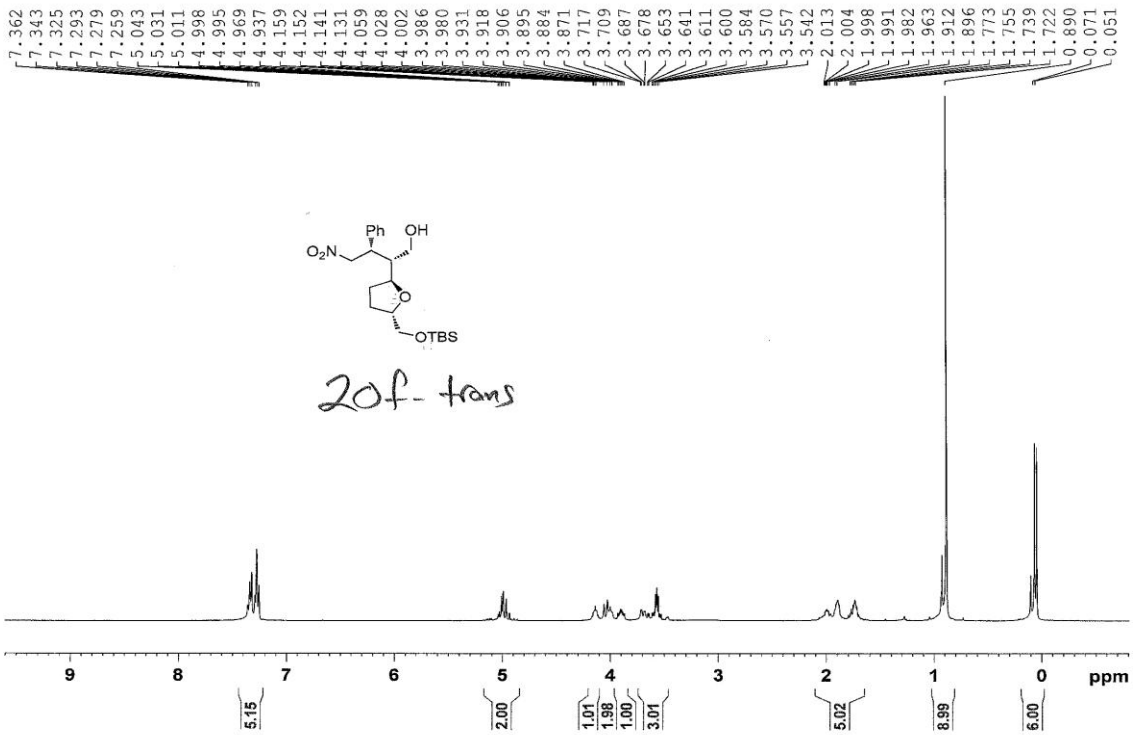

7.363
7.343
7.333
7.326
7.295
7.284
7.281
7.278
5.111
5.100
5.080
5.069
5.009
4.982
4.950
4.076
4.044
4.004
3.993
3.979
3.970
3.944
3.924
3.915
3.908
3.804
3.796
3.777
3.768
3.699
3.689
3.667
3.658
3.608
3.599
3.580
3.572
1.866
1.849
1.835
1.818
1.804
1.784
1.772
1.761
1.752
1.738
1.730
0.943
0.110
Ph
OH
O2N
O
OTBS
2of-cis
9
8
7
6
5
4
3
2
1
0
ppm
5.48
1.00
0.98
1.01
3.01
1.00
0.99
0.97
5.01
8.98
5.99

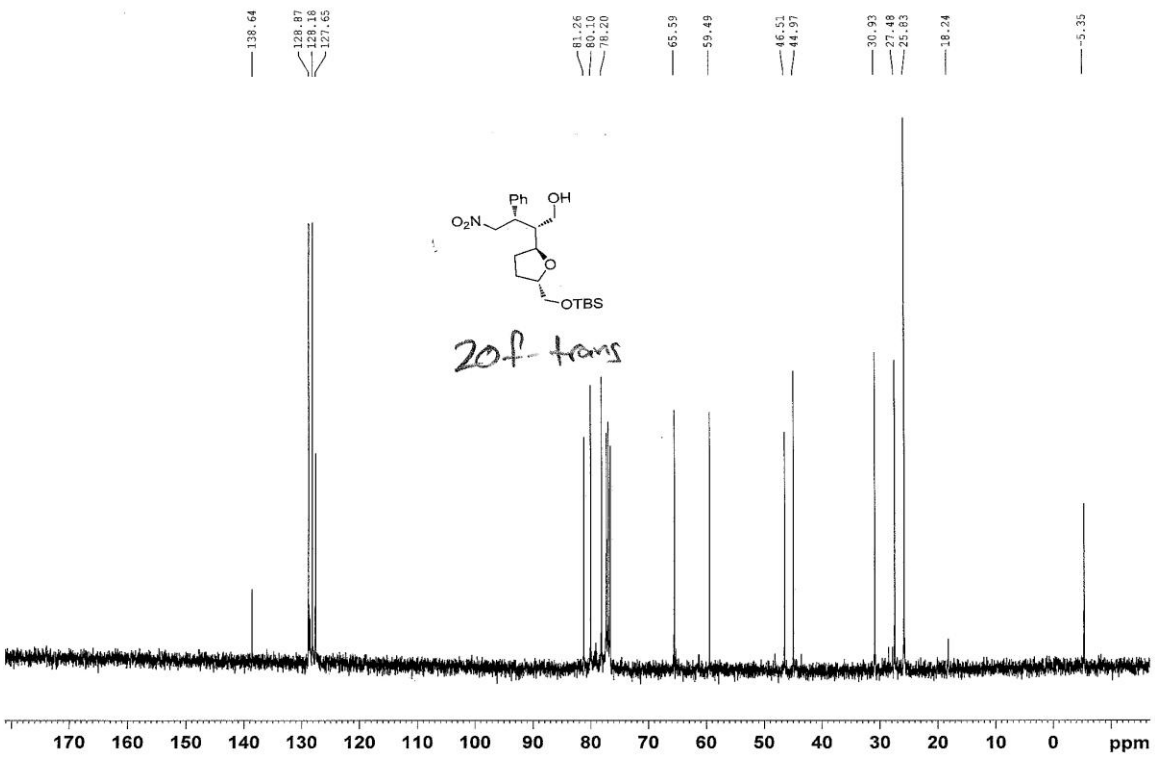

138.94
128.80
128.26
127.54
81.30
79.56
78.40
64.59
58.81
46.32
44.87
29.79
26.77
25.90
18.42
-5.45
-5.51
Ph
OH
O2N
O
OTBS
2of-cis
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

5.53f–***trans***: *(2R,3S)-2-((2S,5S)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4-nitro-3-phenylbutan-1-ol*



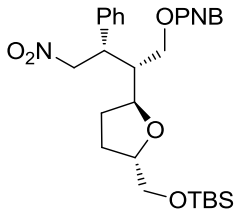
colorless oil. $[\alpha]_D^{22}$ = -4.4 (*c* 1.00, $CHCl_3$, >99% ee); IR (thin film, KBr): 3497, 2929, 2857, 1553, 1380, 1256, 837, 778, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.24 (m, 5H), 5.05-4.94 (m, 2H), 4.14 (m, 1H), 4.07-3.95 (m, 2H), 3.90 (td, *J* = 9.6, 4.9 Hz, 1H), 3.74-3.46 (m, 3H), 2.08-1.68 (m, 5H), 0.89 (s, 9H), 0.06 (d, J = 8.1 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 128.9, 128.2, 127.7, 81.3, 80.1, 78.2, 65.6, 59.5, 46.5, 45.0, 30.9, 27.5, 25.8, 18.2, -5.4 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_{21}H_{35}NO_5Si]$: 409.2284, found: 409.2289.


7.362
7.343
7.325
7.293
7.279
7.259
5.043
5.031
5.011
4.998
4.995
4.969
4.937
4.159
4.152
4.141
4.131
4.059
4.028
4.002
3.986
3.980
3.931
3.918
3.906
3.895
3.884
3.871
3.717
3.709
3.687
3.678
3.653
3.641
3.611
3.600
3.584
3.570
3.557
3.542
2.013
2.004
1.998
1.991
1.982
1.963
1.912
1.896
1.773
1.755
1.739
1.722
0.890
0.071
0.051
Ph
OH
O2N
O
OTBS
2of- trans
9
8
7
6
5
4
3
2
1
0
ppm
5.15
2.00
1.01
1.98
1.00
3.01
5.02
8.99
6.00

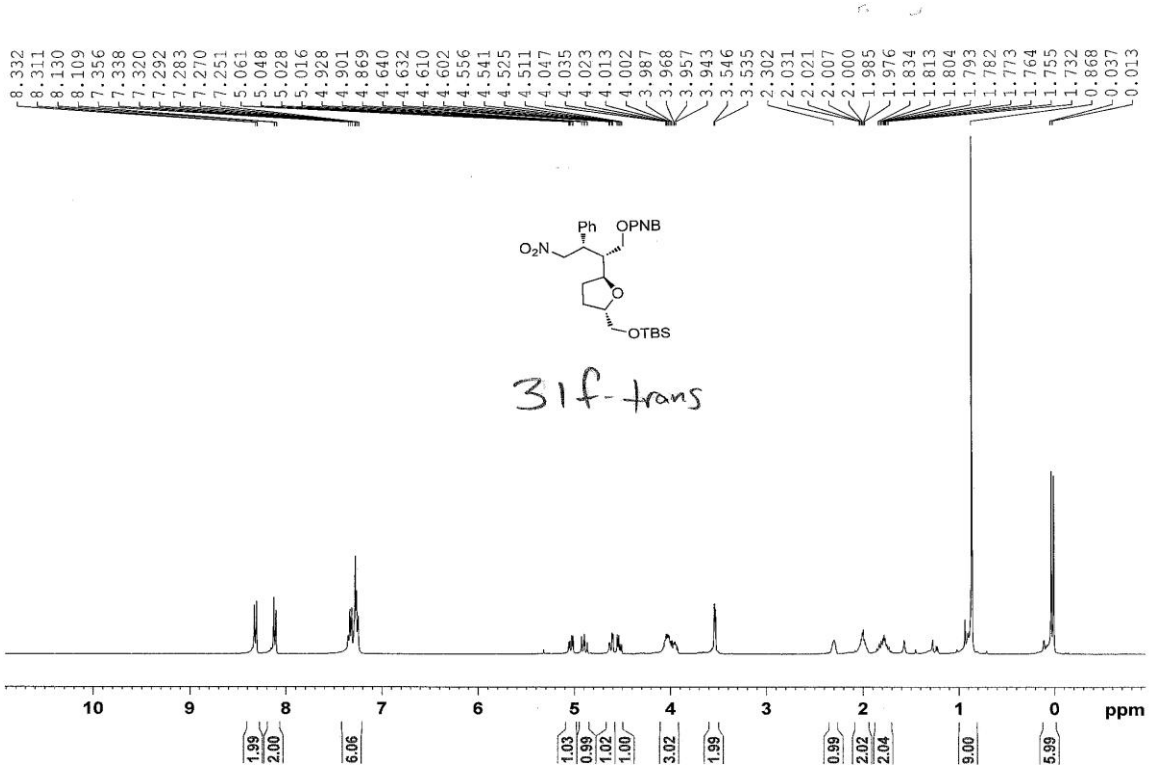

138.64
128.87
128.18
127.65
81.26
80.10
78.20
65.59
59.49
46.51
44.97
30.93
27.48
25.83
18.24
-5.35
Ph
OH
O2N
O
OTBS
2of- trans
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

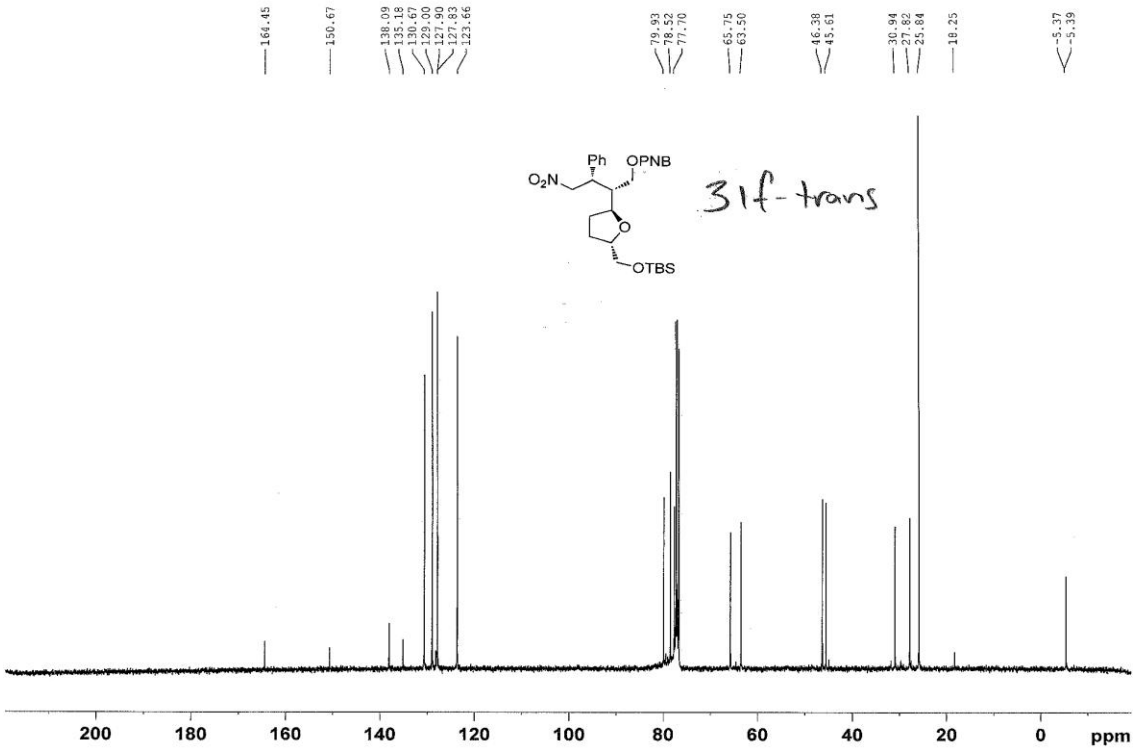
Alcohol **5.53f**–***trans*** was PNB protected to give **6.11f**–***trans*** for chiral HPLC analysis (synthesized in quantitative yield using the procedure described above for the synthesis of **6.10a**–***cis*** and **6.10a**–***trans***).

6.11f–***trans***: *(2R,3S)-2-((2S,5S)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4-nitro-3-phenylbutyl 4-nitrobenzoate*

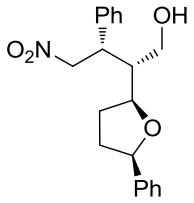


colorless amorphous solid. $[\alpha]_D^{23}$ = -8.5 (*c* 1.00, $CHCl_3$, >99% ee); IR (thin film, KBr): 3450, 2955, 2928, 1726, 1555, 1529, 1273, 1102, 837, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.6 Hz, 2H), 8.12 (d, *J* = 8.6 Hz, 2H), 7.40-7.22 (m, 5H), 5.03 (dd, *J* = 12.9, 4.9 Hz, 1H), 4.89 (dd, *J* = 12.7, 10.7 Hz, 1H), 4.61 (dd, *J* = 12.1, 3.2 Hz, 1H), 4.53 (dd, *J* = 12.1, 5.9 Hz, 1H), 4.09-3.91 (m, 3H), 3.54 (d, *J* = 4.3 Hz, 1H), 2.30 (m, 1H), 2.00 (m, 2H), 1.80 (m, 2H), 0.87 (s, 9H), 0.03 (d, *J* = 9.8 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 150.7, 138.1, 135.2, 130.7, 129.0, 127.9, 127.8, 123.7, 79.9, 78.5, 77.7, 65.8, 63.5, 46.4, 45.6, 30.9, 27.8, 25.8, 18.3, -5.4, -5.4 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 97:3), 1.0 mL/min; minor enantiomer t_R = 15.6 min, minor enantiomer t_R = 22.2 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{28}H_{38}N_2O_8Si]$: 558.2397, found: 558.2397.

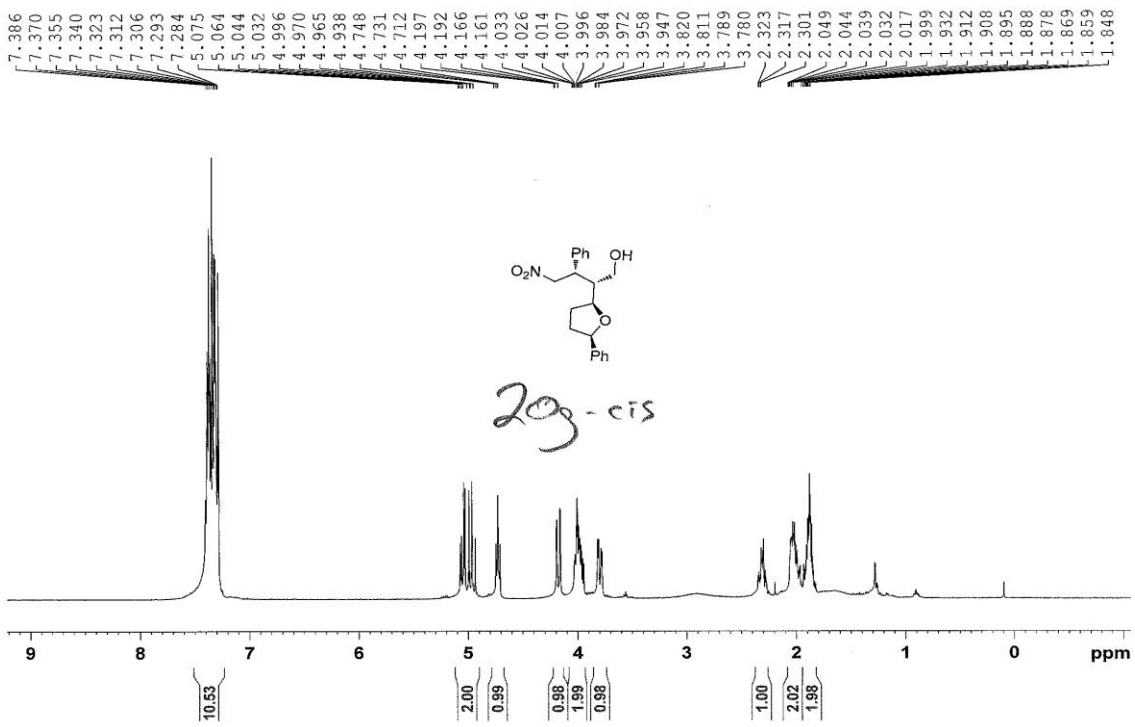

8.332
8.311
8.130
8.109
7.356
7.338
7.320
7.292
7.283
7.270
7.251
5.061
5.048
5.028
5.016
4.928
4.901
4.869
4.640
4.632
4.610
4.602
4.556
4.541
4.525
4.511
4.047
4.035
4.023
4.013
4.002
3.987
3.968
3.957
3.943
3.546
3.535
2.302
2.031
2.021
2.007
2.000
1.985
1.976
1.834
1.813
1.804
1.793
1.782
1.773
1.764
1.755
1.732
0.868
0.037
0.013
Ph
OPNB
O2N
O
OTBS
31f-trans
10
9
8
7
6
5
4
3
2
1
0
ppm
1.99
2.00
6.06
1.03
0.99
1.02
1.00
3.02
1.99
0.99
2.02
2.04
9.00
5.99

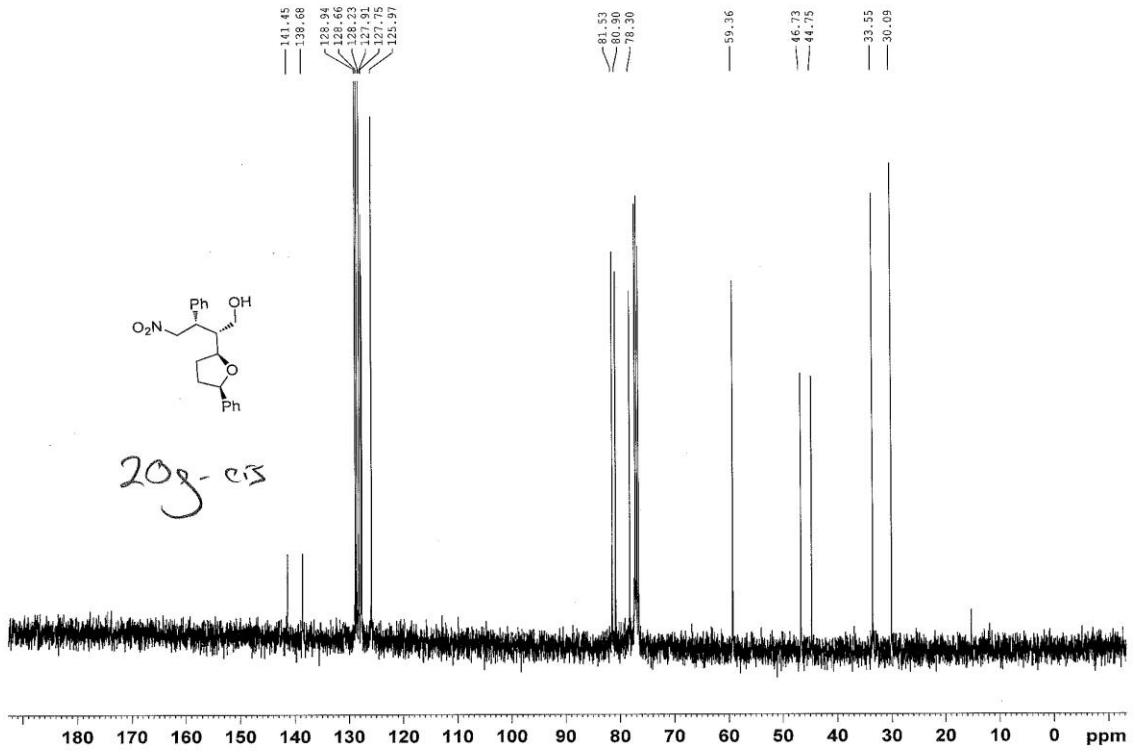

164.45
150.67
138.09
135.18
130.67
129.00
127.90
127.83
123.66
79.93
78.52
77.70
65.75
63.50
46.38
45.61
30.94
27.82
25.84
18.25
-5.37
-5.39
Ph
OPNB
O2N
O
OTBS
31f-trans
200
180
160
140
120
100
80
60
40
20
0
ppm

5.53g–***cis***: *(2R,3S)-4-nitro-3-phenyl-2-((2S,5R)-5-phenyltetrahydrofuran-2-yl)butan-1-ol*

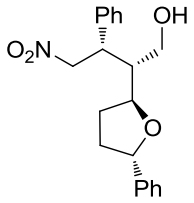


colorless amorphous solid. $[\alpha]_D^{22}$ = +82.9 (*c* 1.35, $CHCl_3$, 99% ee); IR (thin film, KBr): 3448, 2891, 1551, 1381, 1054, 760, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.25 (m, 10H), 5.05 (dd, *J* = 12.7, 4.6 Hz, 1H), 4.97 (dd, *J* = 12.6, 10.5 Hz, 1H), 4.73 (t, *J* = 7.2 Hz, 1H), 4.18 (dd, *J* = 12.4, 1.9 Hz, 1H), 4.08-3.93 (m, 2H), 3.80 (dd, *J* = 12.4, 3.8 Hz, 1H), 2.91 (bs, 1H), 2.31 (m, 1H), 2.09-1.81 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 138.7, 128.9, 128.7, 128.2, 127.9, 127.8, 126.0, 81.5, 80.9, 78.3, 59.4, 46.7, 44.8, 33.6, 30.1 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 0.5 mL/min; major enantiomer t_R = 34.2 min, minor enantiomer t_R = 42.8 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{20}H_{23}NO_4]$: 341.1627, found: 341.1631.

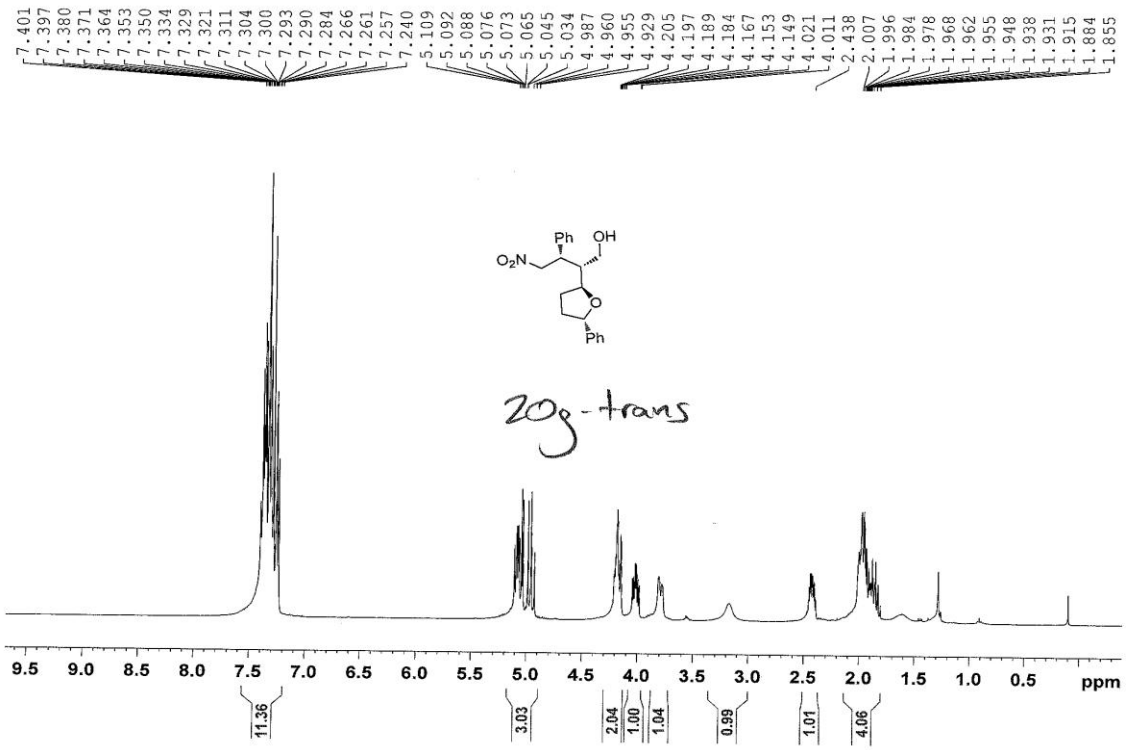

7.386
7.370
7.355
7.340
7.323
7.312
7.306
7.293
7.284
5.075
5.064
5.044
5.032
4.996
4.970
4.965
4.938
4.748
4.731
4.712
4.197
4.192
4.166
4.161
4.033
4.026
4.014
4.007
3.996
3.984
3.972
3.958
3.947
3.820
3.811
3.789
3.780
2.323
2.317
2.301
2.049
2.044
2.039
2.032
2.017
1.999
1.932
1.912
1.908
1.895
1.888
1.878
1.869
1.859
1.848
Ph
OH
O2N
O
Ph
20g - cis
9
8
7
6
5
4
3
2
1
0
ppm
10.53
2.00
0.99
0.98
1.99
0.98
1.00
2.02
1.98

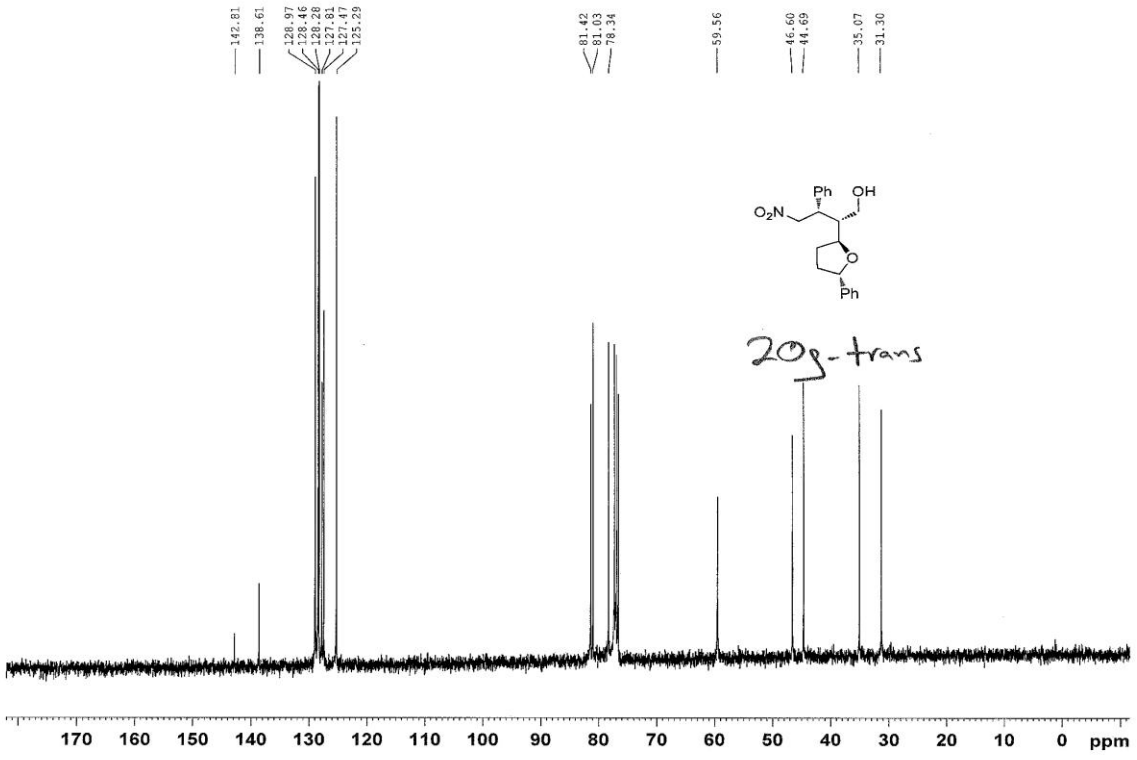

141.45
138.68
128.94
128.66
128.23
127.91
127.75
125.97
81.53
80.90
78.30
59.36
46.73
44.75
33.55
30.09
Ph
OH
O2N
O
Ph
20g - cis
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

5.53g–***trans***: *(2R,3S)-4-nitro-3-phenyl-2-((2S,5S)-5-phenyltetrahydrofuran-2-yl)butan-1-ol*

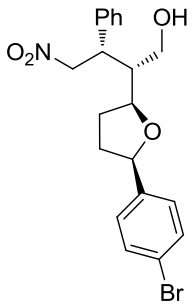


colorless oil. $[\alpha]_D^{24}$ = -1.1 (*c* 1.00, $CHCl_3$, 98% ee); IR (thin film, KBr): 3460, 2917, 1551, 1380, 1054, 759, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.21 (m, 10H), 5.15-4.90 (m, 3H), 4.19 (m, 2H), 4.02 (td, *J* = 9.9, 4.5 Hz, 1H), 3.79 (m, 1H), 3.19 (bs, 1H), 2.42 (m, 1H), 2.10-1.81 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 138.6, 129.0, 128.5, 128.3, 127.8, 127.5, 125.3, 81.4, 81.0, 78.3, 59.6, 46.6, 44.7, 35.1, 31.3 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 32.6 min, minor enantiomer t_R = 40.9 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{20}H_{23}NO_4]$: 341.1627, found: 341.1629.

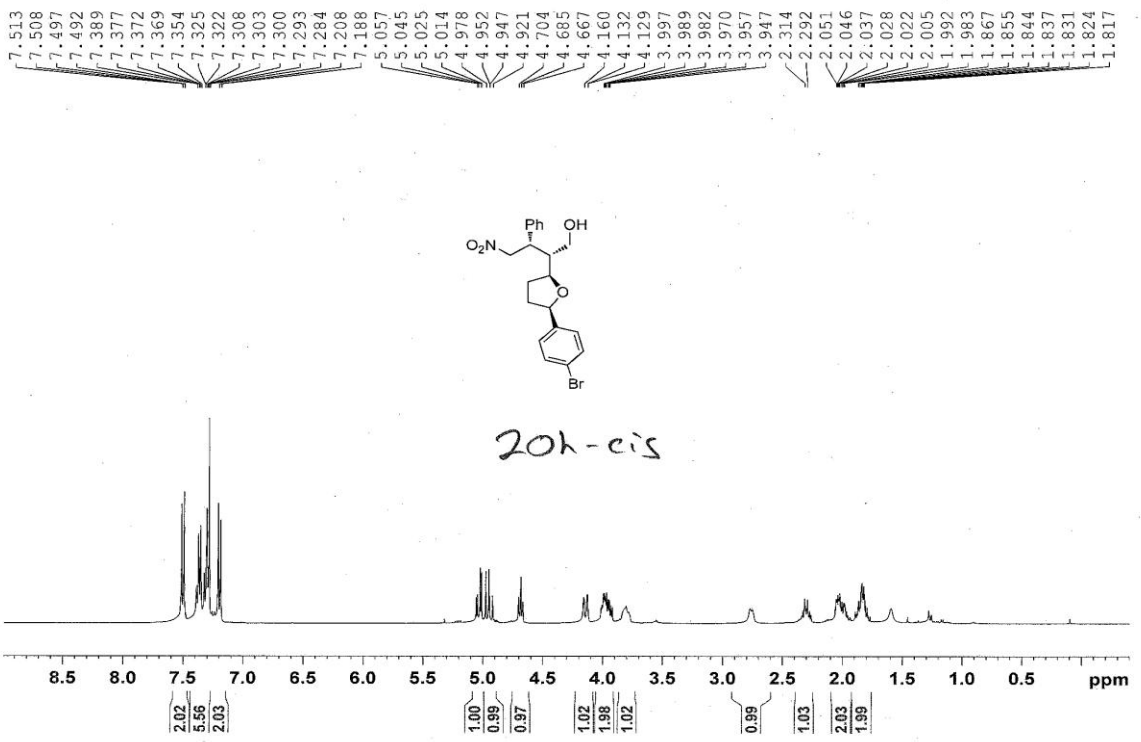

7.401
7.397
7.380
7.371
7.364
7.353
7.350
7.334
7.329
7.321
7.311
7.304
7.300
7.293
7.290
7.284
7.266
7.261
7.257
7.240
5.109
5.092
5.088
5.076
5.073
5.065
5.045
5.034
4.987
4.960
4.955
4.929
4.205
4.197
4.189
4.184
4.167
4.153
4.149
4.021
4.011
2.438
2.007
1.996
1.984
1.978
1.968
1.962
1.955
1.948
1.938
1.931
1.915
1.884
1.855
Ph
OH
O2N
O
Ph
20g-trans
9.5 9.0 8.5 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 ppm
11.36
3.03
2.04
1.00
1.04
0.99
1.01
4.06

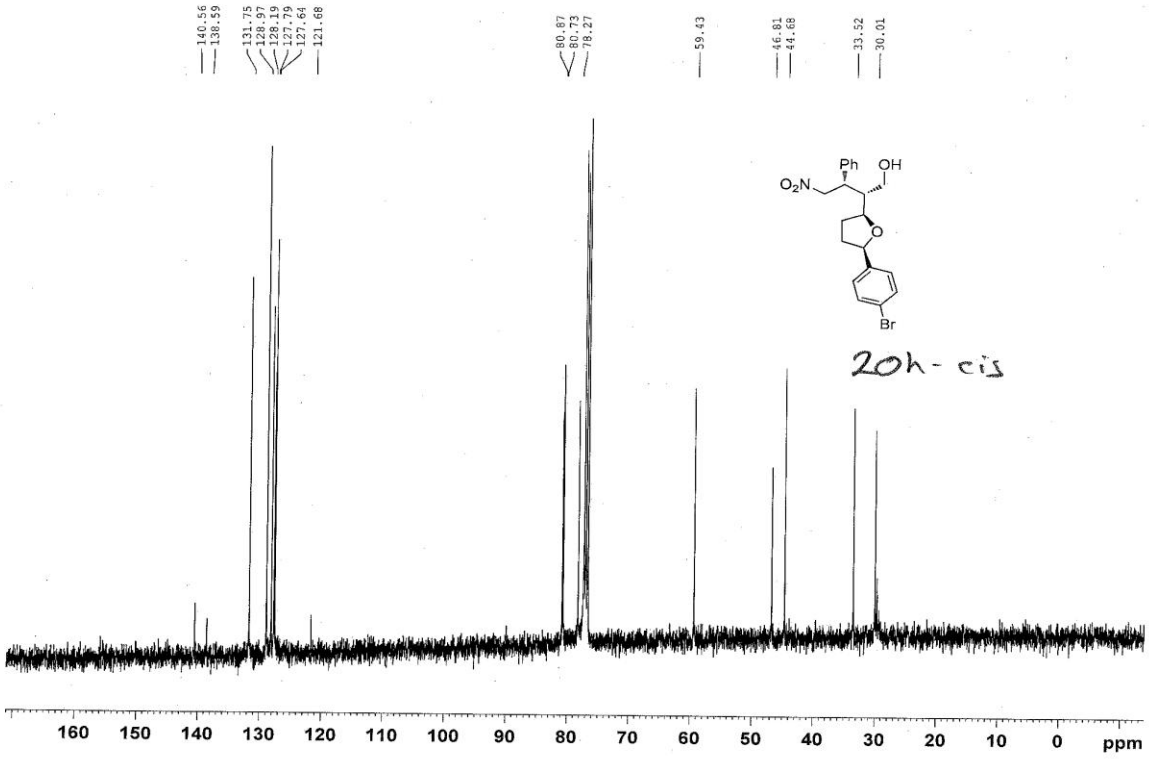

142.81
138.61
128.97
128.46
128.28
127.81
127.47
125.29
81.42
81.03
78.34
59.56
46.60
44.69
35.07
31.30
Ph
OH
O2N
O
Ph
20g-trans
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

5.53h–***cis***: *(2R,3S)-2-((2S,5R)-5-(4-bromophenyl)tetrahydrofuran-2-yl)-4-nitro-3-phenylbutan-1-ol*

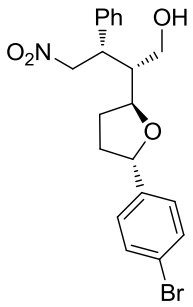


colorless amorphous solid. $[\alpha]_D^{21}$ = +82.1 (*c* 1.50, $CHCl_3$, >99% ee); IR (thin film, KBr): 3503, 2890, 1551, 1489, 1380, 1069, 1010, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.41-7.26 (m, 5H), 7.20 (d, *J* = 8.4 Hz, 2H), 5.04 (dd, *J* = 12.7, 4.7 Hz, 1H), 4.95 (dd, *J* = 12.7, 10.5 Hz, 1H), 4.69 (t, *J* = 7.6 Hz, 1H), 4.15 (dd, *J* = 12.4, 1.6 Hz, 1H), 4.03-3.91 (m, 2H), 3.70 (m, 1H), 2.77 (bd, *J* = 7.9 Hz, 1H), 2.31 (m, 1H), 2.07-1.92 (m, 2H), 1.90-1.77 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 138.6, 131.8, 129.0, 128.2, 127.8, 127.6, 121.7, 80.9, 80.7, 78.3, 59.4, 46.8, 44.7, 33.5, 30.0 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 42.3 min, minor enantiomer t_R = 52.6 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{20}H_{22}BrNO_4]$: 419.0732, found: 419.0733.

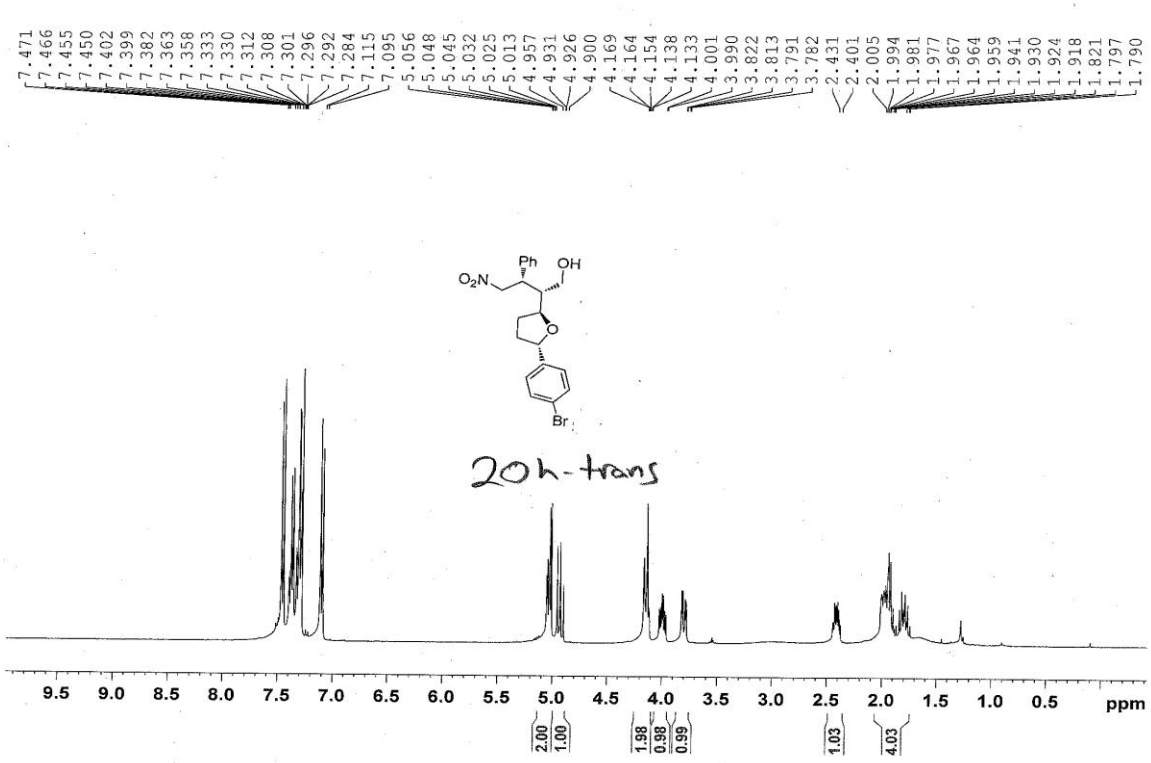

7.513
7.508
7.497
7.492
7.389
7.377
7.372
7.369
7.354
7.325
7.322
7.308
7.303
7.300
7.293
7.284
7.208
7.188
5.057
5.045
5.025
5.014
4.978
4.952
4.947
4.921
4.704
4.685
4.667
4.160
4.132
4.129
3.997
3.989
3.982
3.970
3.957
3.947
2.314
2.292
2.051
2.046
2.037
2.028
2.022
2.005
1.992
1.983
1.867
1.855
1.844
1.837
1.831
1.824
1.817
Ph
OH
O2N
O
Br
20h-cis
8.5 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 ppm
2.02 5.56 2.03 1.00 0.99 0.97 1.02 1.98 1.02 0.99 1.03 2.03 1.99

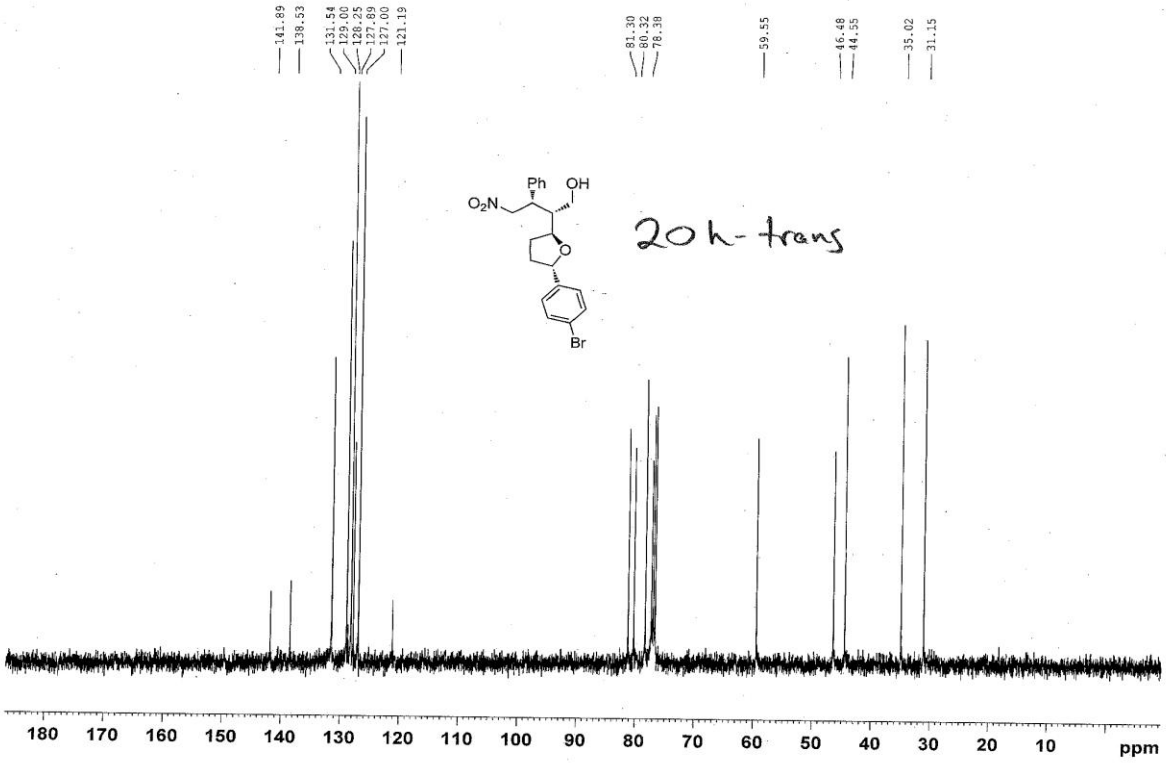

140.56
138.59
131.75
128.97
128.19
127.79
127.64
121.68
80.67
80.33
78.27
59.43
46.61
44.68
33.52
30.01
Ph
OH
O2N
O
Br
20h-cis
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

5.53h–***trans***: *(2R,3S)-2-((2S,5S)-5-(4-bromophenyl)tetrahydrofuran-2-yl)-4-nitro-3-phenylbutan-1-ol*

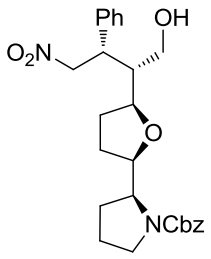


colorless amorphous solid. $[\alpha]_D^{22}$ = +24.9 (*c* 1.20, $CHCl_3$, >99% ee); IR (thin film, KBr): 3463, 2923, 1551, 1488, 1380, 1055, 1010, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.42-7.28 (m, 5H), 7.11 (d, *J* = 8.4 Hz, 2H), 5.04 (m, 2H), 4.93 (dd, *J* = 12.5, 10.5 Hz, 1H), 4.15 (m, 2H), 4.00 (td, *J* = 9.9, 4.7 Hz, 1H), 3.80 (dd, J = 12.3, 3.8 Hz, 1H), 2.42 (m, 1H), 2.05-1.73 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 138.5, 131.5, 129.0, 128.3, 127.9, 127.0, 121.2, 81.3, 80.3, 78.4, 59.6, 46.5, 44.6, 35.0, 31.2 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 21.3 min, minor enantiomer t_R = 75.6 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{20}H_{22}BrNO_4]$: 419.0732, found: 419.0732.

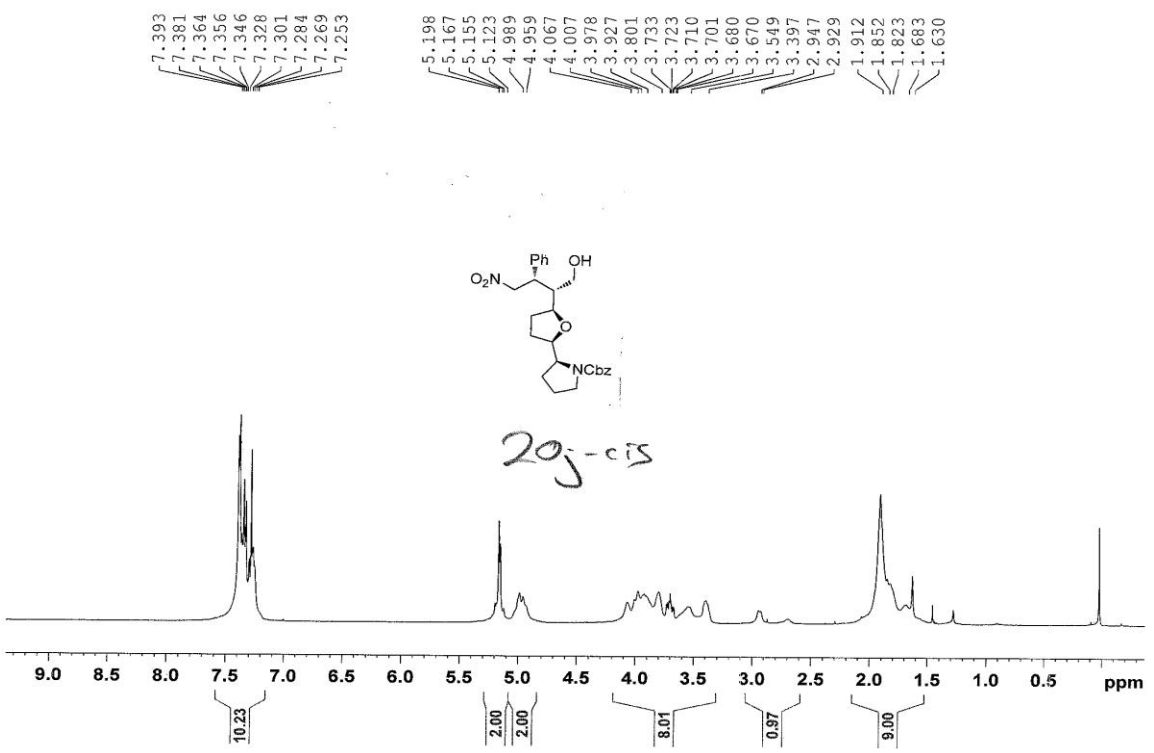

7.471
7.466
7.455
7.450
7.402
7.399
7.382
7.363
7.358
7.333
7.330
7.312
7.308
7.301
7.296
7.292
7.284
7.115
7.095
5.056
5.048
5.045
5.032
5.025
5.013
4.957
4.931
4.926
4.900
4.169
4.164
4.154
4.138
4.133
4.001
3.990
3.822
3.813
3.791
3.782
2.431
2.401
2.005
1.994
1.981
1.977
1.967
1.964
1.959
1.941
1.930
1.924
1.918
1.821
1.797
1.790
Ph
OH
O2N
Br
20h-trans
9.5 9.0 8.5 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 ppm
2.00
1.00
1.98
0.38
0.99
1.03
4.03

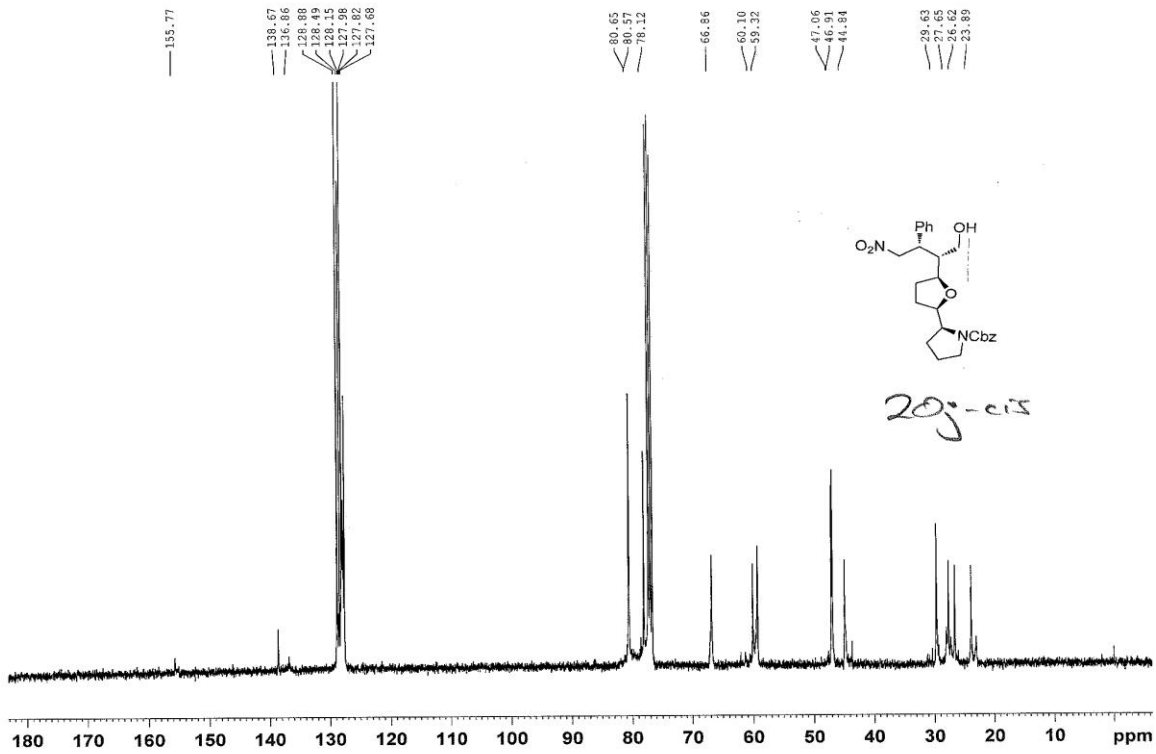

141.89
138.53
131.54
129.00
128.25
127.89
127.00
121.19
81.30
80.32
78.38
59.55
46.48
44.55
35.02
31.15
Ph
OH
O2N
Br
20h-trans
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

5.53i–***cis***: *(S)-benzyl 2-((2R,5S)-5-((2R,3S)-1-hydroxy-4-nitro-3-phenylbutan-2-yl) tetrahydrofuran-2-yl)pyrrolidine-1-carboxylate*

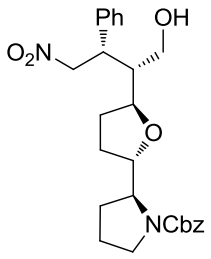


colorless amorphous solid. $[\alpha]_D^{22}$ = -46.9 (*c* 1.00, $CHCl_3$, 95% ee); IR (thin film, KBr): 3444, 2968, 2888, 1694, 1551, 1416, 1105, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.20 (m, 10H), 5.16 (m, 2H), 5.05-4.88 (m, 2H), 4.13-3.33 (m, 8H), 3.00-2.65 (m, 1H), 2.10-1.55 (m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 138.7, 136.9, 128.9, 128.5, 128.2, 128.0, 127.8, 127.7, 80.7, 80.6, 78.1, 66.9, 60.1, 59.3, 47.1, 46.9, 44.85, 29.6, 27.7, 26.6, 23.9 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 48.7 min, minor enantiomer t_R = 56.1 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{26}H_{32}N_2O_6]$: 468.2260, found: 468.2259.

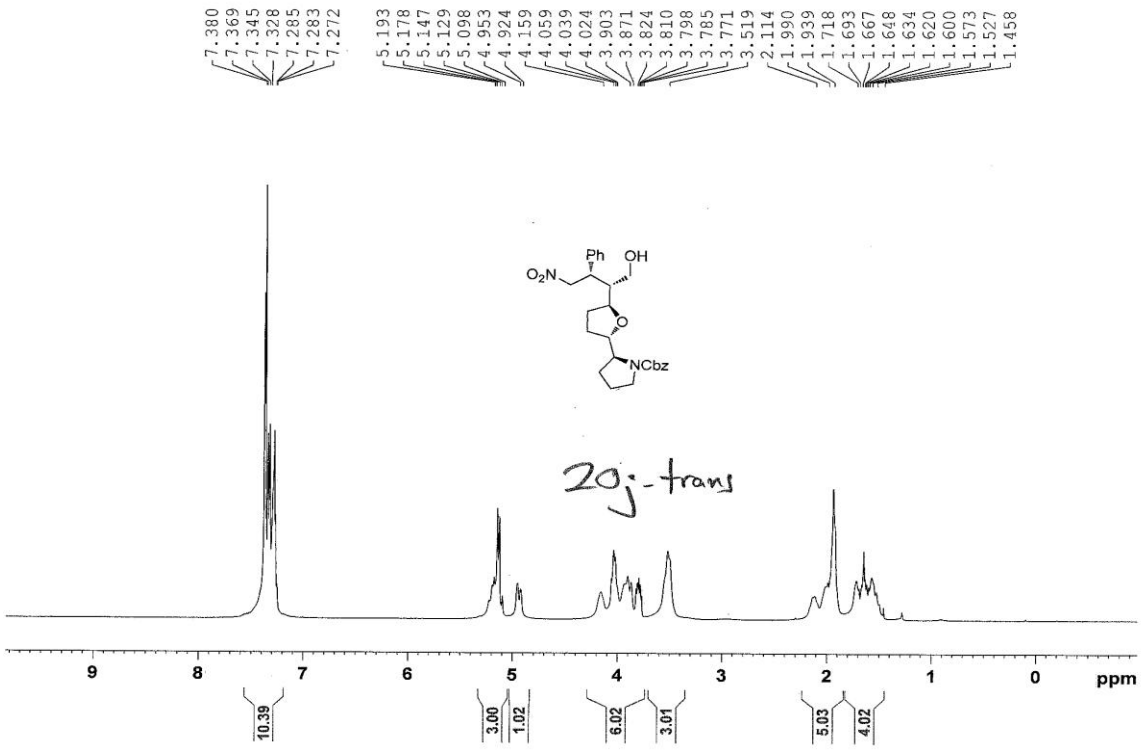

7.393
7.381
7.364
7.356
7.346
7.328
7.301
7.284
7.269
7.253
5.198
5.167
5.155
5.123
4.989
4.959
4.067
4.007
3.978
3.927
3.801
3.733
3.723
3.710
3.701
3.680
3.670
3.549
3.397
2.947
2.929
1.912
1.852
1.823
1.683
1.630
Ph
OH
O2N
NCbz
20j-cis
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
10.23
2.00
2.00
8.01
0.97
9.00

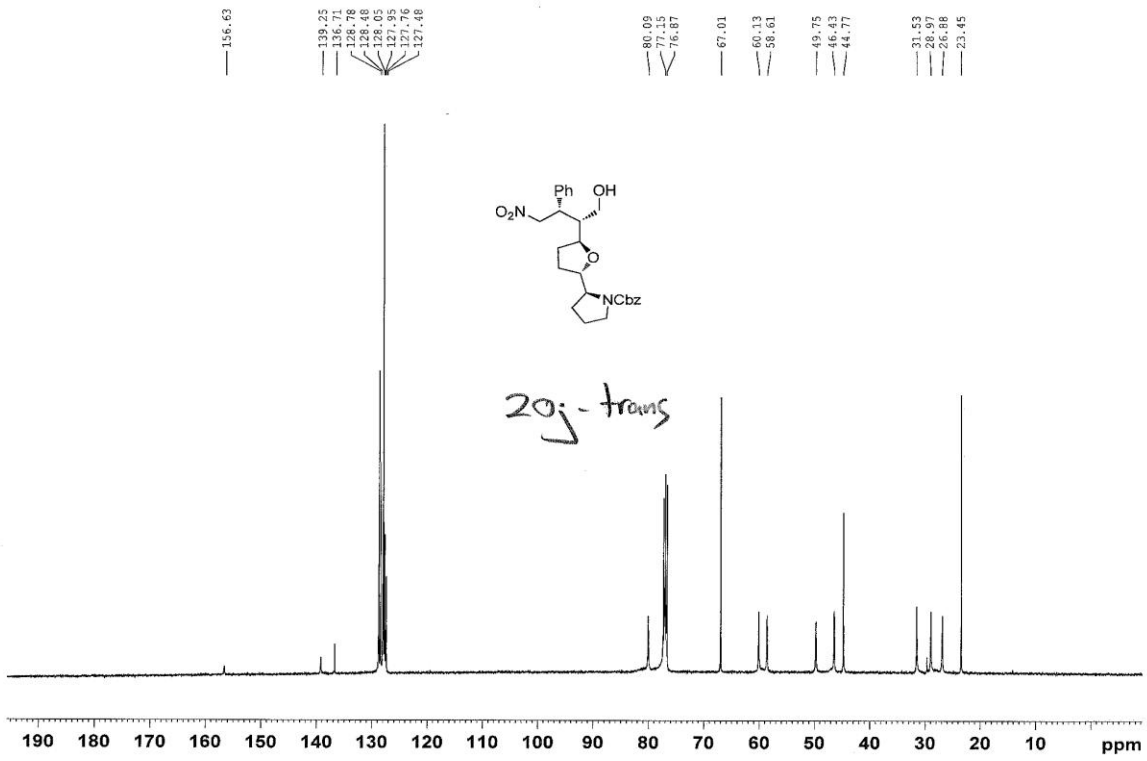

155.77
138.67
136.86
128.88
128.49
128.15
127.98
127.82
127.68
80.65
80.57
78.12
66.86
60.10
59.32
47.06
46.91
44.84
29.63
27.65
26.62
23.89
Ph
OH
O2N
NCbz
20j-cis
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

5.53i–***trans***: *(S)-benzyl2-((2S,5S)-5-((2R,3S)-1-hydroxy-4-nitro-3-phenylbutan-2-yl) tetrahydrofuran-2-yl)pyrrolidine-1-carboxylate*

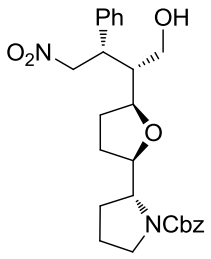


colorless amorphous solid. $[\alpha]_D^{22}$ = -19.4 (*c* 1.50, $CHCl_3$, >99% ee); IR (thin film, KBr): 3439, 2965, 1686, 1551, 1416, 1109, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.21 (m, 10H), 5.28-5.06 (m, 3H), 4.93 (m, 1H), 4.25-3.75 (m, 6H), 3.65-3.42 (m, 3H), 2.21-1.86 (m, 5H), 1.83 - 1.44 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 139.3, 136.7, 128.8, 128.5, 128.1, 128.0, 127.8, 127.5, 80.1, 77.2, 76.9, 67.0, 60.1, 58.6, 49.8, 46.4, 44.8, 31.5, 29.0, 26.9, 23.5 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 39.3 min, minor enantiomer t_R = 45.5 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{26}H_{32}N_2O_6]$: 468.2260, found: 468.2263.

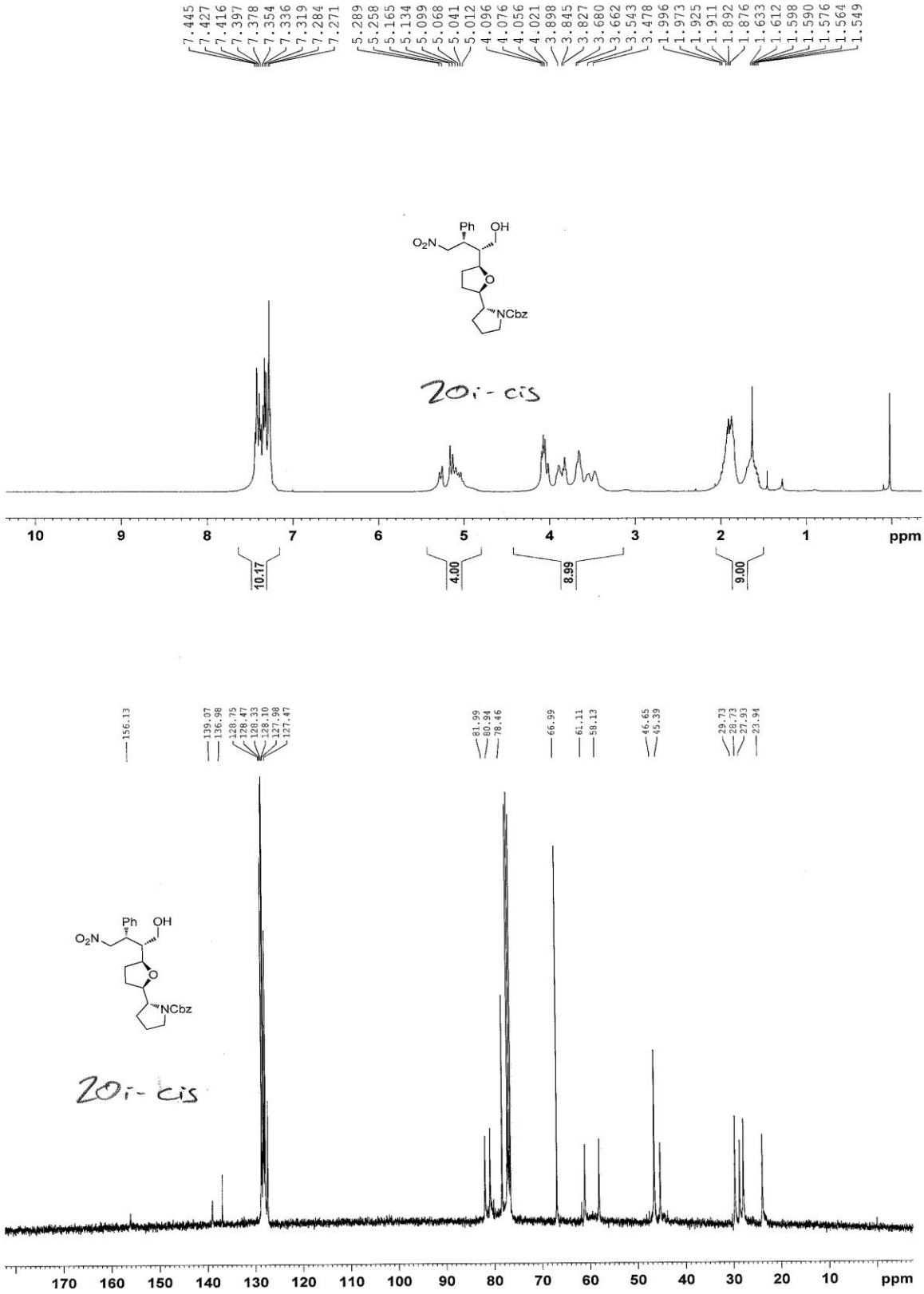

7.380
7.369
7.345
7.328
7.285
7.283
7.272
5.193
5.178
5.147
5.129
5.098
4.953
4.924
4.159
4.059
4.039
4.024
3.903
3.871
3.824
3.810
3.798
3.785
3.771
3.519
2.114
1.990
1.939
1.718
1.693
1.667
1.648
1.634
1.620
1.600
1.573
1.527
1.458
Ph
OH
O2N
O
NCbz
20j-trans
9
8
7
6
5
4
3
2
1
0
ppm
10.39
3.00
1.02
6.02
3.01
5.03
4.02


156.63
139.25
136.71
128.78
128.48
128.05
127.95
127.76
127.48
80.09
77.15
76.87
67.01
60.13
58.61
49.75
46.43
44.77
31.53
28.97
26.88
23.45
Ph
OH
O2N
O
NCbz
20j-trans
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

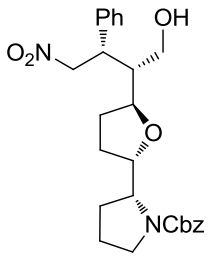
5.53j–***cis***: *(R)-benzyl 2-((2R,5S)-5-((2R,3S)-1-hydroxy-4-nitro-3-phenylbutan-2-yl) tetrahydrofuran-2-yl)pyrrolidine-1-carboxylate*



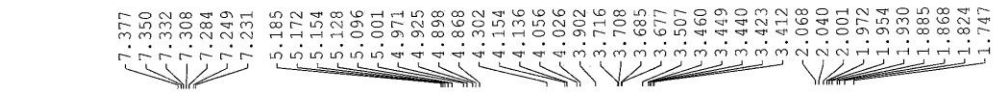
colorless amorphous solid. $[\alpha]_D^{22}$ = +39.0 (*c* 1.00, $CHCl_3$, >99% ee); IR (thin film, KBr): 3466, 2958, 2886, 1695, 1550, 1413, 1103, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.20 (m, 10H), 5.37-4.80 (m, 4H), 4.25-3.35 (m, 9H), 2.10-1.50 (m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 139.1, 137.0, 128.8, 128.5, 128.3, 128.1, 128.0, 127.5, 82.0, 80.9, 78.5, 67.0, 61.1, 58.1, 46.7, 45.4, 29.7, 28.7, 27.9, 23.9 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 46.1 min, minor enantiomer t_R = 58.1 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{26}H_{32}N_2O_6]$: 468.2260, found: 468.2260.

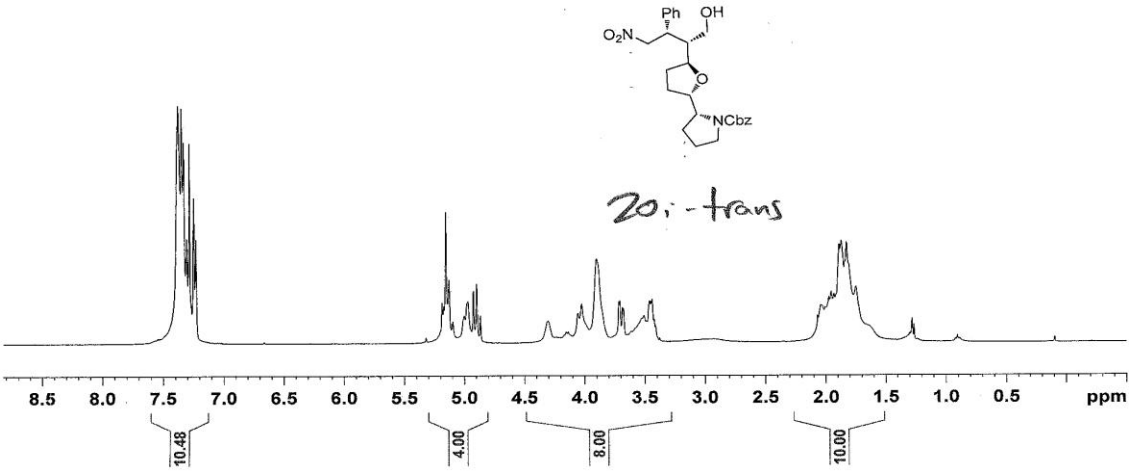

7.445
7.427
7.416
7.397
7.378
7.354
7.336
7.319
7.284
7.271
5.289
5.258
5.165
5.134
5.099
5.068
5.041
5.012
4.096
4.076
4.056
4.021
3.898
3.845
3.827
3.680
3.662
3.543
3.478
1.996
1.973
1.925
1.911
1.892
1.876
1.633
1.612
1.598
1.590
1.576
1.564
1.549
Ph
OH
O2N
O
NCbz
20i-cis
10
9
8
7
6
5
4
3
2
1
ppm
10.17
4.00
8.99
9.00
156.13
139.07
136.98
128.75
128.47
128.33
128.10
127.98
127.47
81.99
80.94
78.46
66.99
61.11
58.13
46.65
45.39
29.73
28.73
27.93
23.94
Ph
OH
O2N
O
NCbz
20i-cis
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

5.53j–***trans***: *(R)-benzyl2-((2S,5S)-5-((2R,3S)-1-hydroxy-4-nitro-3-phenylbutan-2-yl)tetrahydrofuran-2-yl)pyrrolidine-1-carboxylate*

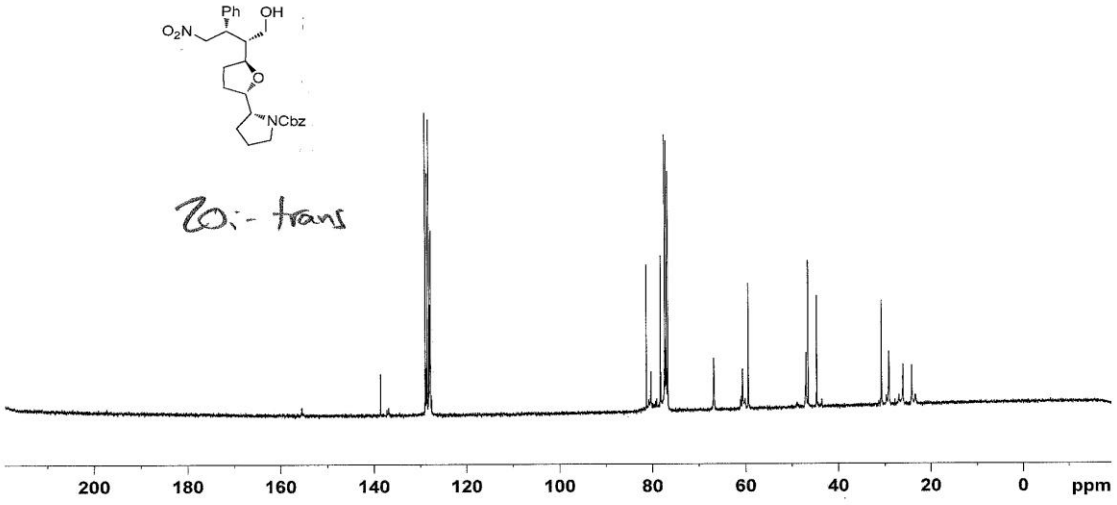


colorless amorphous solid. $[\alpha]_D^{23}$ = +45.5 (*c* 1.50, $CHCl_3$, >99% ee); IR (thin film, KBr): 3454, 2958, 2888, 1697, 1551, 1415, 1356, 1109, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.20 (m, 10H), 5.24-4.84 (m, 4H), 4.35-3.38 (m, 8H), 2.15-1.55 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 138.6, 136.9, 128.9, 128.7, 128.5, 128.2, 128.0, 127.8, 81.3, 80.3, 78.3, 66.8, 60.7, 59.5, 46.5, 44.6, 30.7, 29.1, 26.1, 24.2 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 40.5 min, minor enantiomer t_R = 47.6 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{26}H_{32}N_2O_6]$: 468.2260, found: 468.2259.


7.377
7.350
7.332
7.308
7.284
7.249
7.231
5.185
5.172
5.154
5.128
5.096
5.001
4.971
4.925
4.898
4.868
4.302
4.154
4.136
4.056
4.026
3.902
3.716
3.708
3.685
3.677
3.507
3.460
3.449
3.440
3.423
3.412
2.068
2.040
2.001
1.972
1.954
1.930
1.885
1.868
1.824
1.747


Ph
OH
O2N
O
NCbz
20;- trans
8.5
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
ppm
10.48
4.00
8.00
10.00

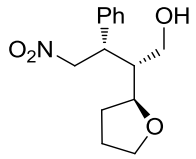

155.48
138.59
136.85
128.51
128.73
128.49
128.16
127.96
127.79
81.32
80.34
78.28
66.80
60.68
59.47
46.52
44.64
30.74
29.09
26.07
24.15


Ph
OH
O2N
O
NCbz
20;- trans
200
180
160
140
120
100
80
60
40
20
0
ppm

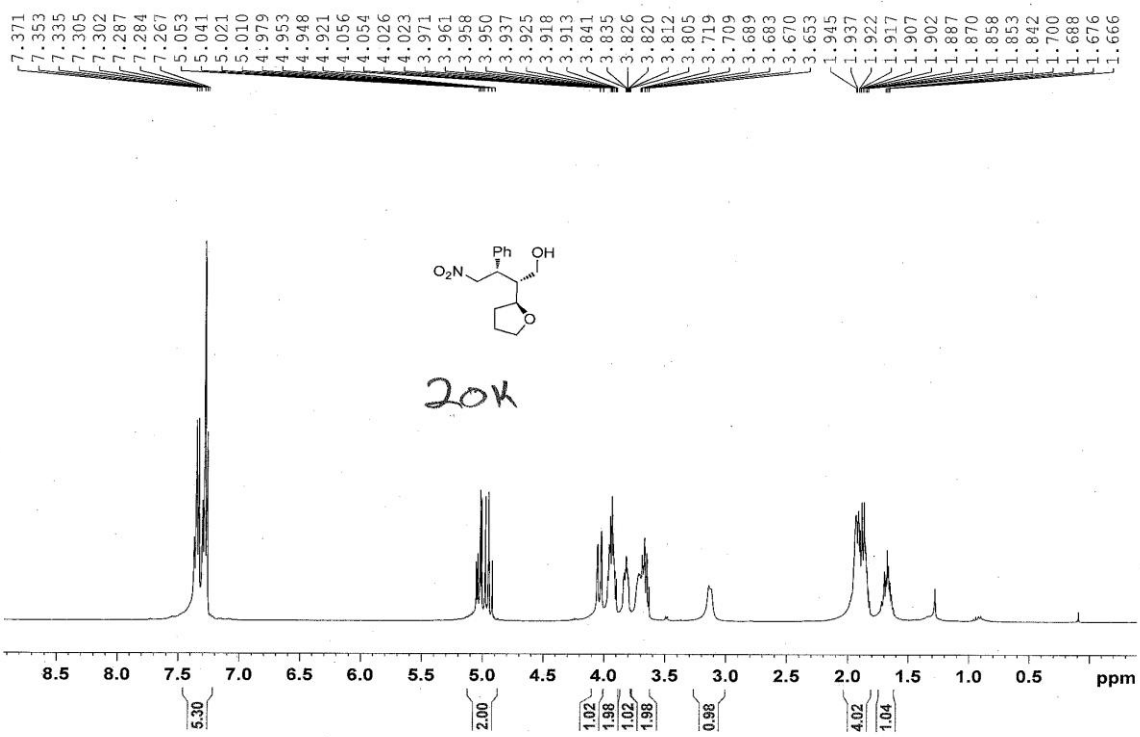
Oxa-Michael Cascade Reaction Forming Monosubstituted Furan (5.53k)

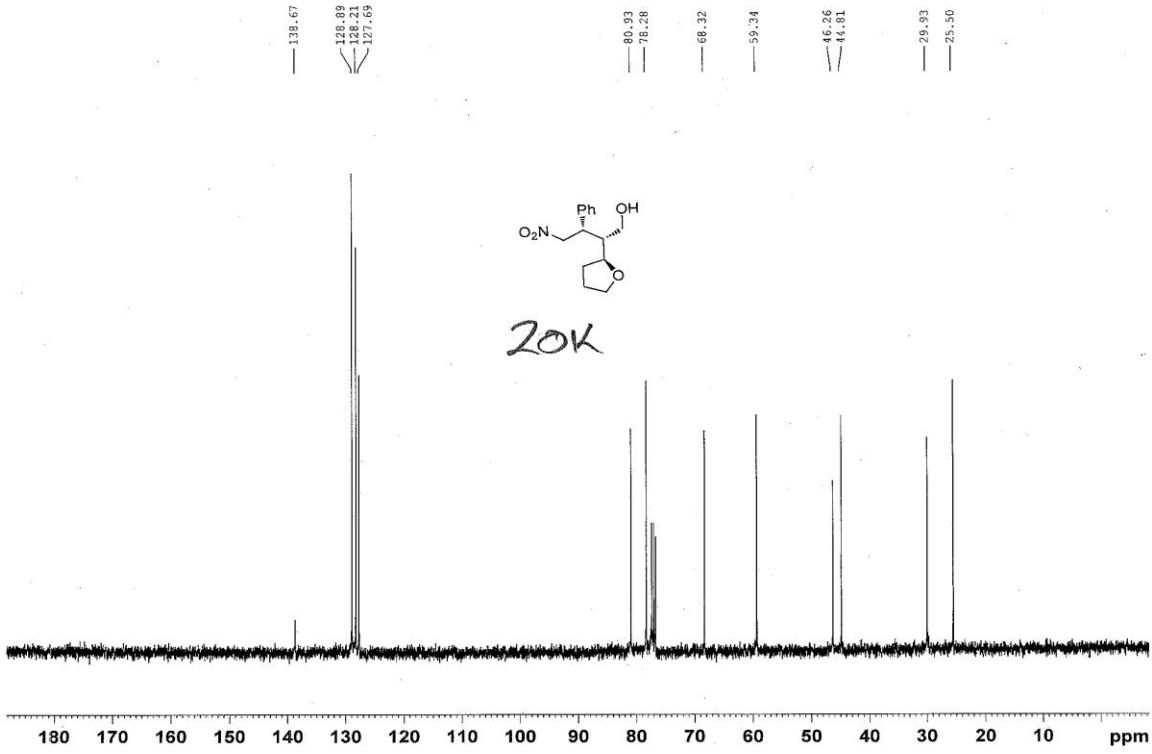
Catalyst **1.12a** (28.6 mg, 0.088 mmol) and $PhCO_2H$ (10.7 mg, 0.088 mmol) were dissolved in dry toluene (1.1 mL) and cooled to –30 ^oC. Substrate **5.49k** (0.44 mmol) was added in one portion. Compound **1.23a** (131.2 mg, 0.88 mmol) was added after 5 minutes and the reaction was stirred at –30 ^oC. The reaction was complete after 4 days by ^1H NMR and the dr was determined. The reaction mixture was diluted with MeOH (2.2 mL), and $NaBH_4$ (75.7 mg, 2.0 mmol) was added. The reaction was stirred at –30 ^oC for 15 minutes and was quenched by slowly adding saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 15mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Product **5.53k** was purified from the residue via column chromatography (EtOAc/petroleum ether, 30/70).

5.53k: *(2R,3S)-4-nitro-3-phenyl-2-((S)-tetrahydrofuran-2-yl)butan-1-ol*



colorless oil. $[\alpha]_D^{21}$ = -16.5 (*c* 1.48, $CHCl_3$, >99% ee); IR (thin film, KBr): 3442, 2882, 1551, 1381, 1059, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.25 (m, 5H), 5.03 (dd, *J* = 12.6, 4.7 Hz, 1H), 4.95 (dd, *J* = 12.6, 10.7 Hz, 1H), 4.04 (dd, *J* = 12.4, 1.6 Hz, 1H), 3.98-3.89 (m, 2H), 3.70 (m, 1H), 3.76-3.62 (m, 2H), 3.12 (bd, *J* = 7.3 Hz, 1H), 1.97-1.81 (m, 4H), 1.69 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.9, 128.2, 127.7, 80.9, 78.3, 68.3, 59.3, 46.3, 44.8, 29.9, 25.5 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 15.0 min, minor enantiomer t_R = 26.6 min. HRMS (ESI) : $[M^+]$ calcd for $[C_{14}H_{19}NO_4]$: 265.1314, found: 265.1319.

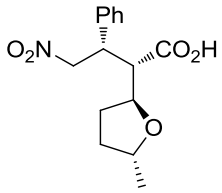

7.371
7.353
7.335
7.305
7.302
7.287
7.284
7.267
5.053
5.041
5.021
5.010
4.979
4.953
4.948
4.921
4.056
4.054
4.026
4.023
3.971
3.961
3.958
3.950
3.937
3.925
3.918
3.913
3.841
3.835
3.826
3.820
3.812
3.805
3.719
3.709
3.689
3.683
3.670
3.653
1.945
1.937
1.922
1.917
1.907
1.902
1.887
1.870
1.858
1.853
1.842
1.700
1.688
1.676
1.666
Ph
OH
O_2N
O
20K
8.5 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 ppm
5.30
2.00
1.02
1.98
1.02
1.98
0.98
4.02
1.04


138.67
128.89
128.21
127.69
80.93
78.28
68.32
59.34
46.26
44.81
29.93
25.50
Ph
OH
O_2N
O
20K
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

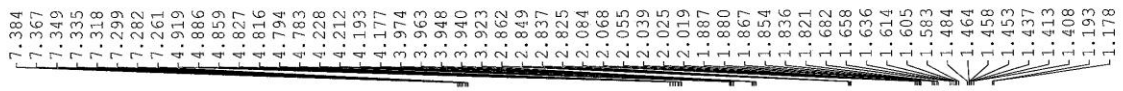
Oxidation of *rac*–5.53a–*trans* to give *rac*-5.54a–*trans*

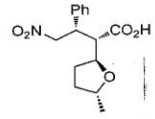
Jones reagent was prepared by adding concentrated H_2SO_4 (0.45 mL) to CrO_3 (500 mg) and cooling to 0 ^oC. Water (2.78 mL) was added dropwise with stirring until all solids had dissolved. Compound ***rac*–5.53a–*trans*** (100 mg, 0.36 mmol) was dissolved in acetone and cooled to 0 ^oC. To the solution of ***rac*–5.53a–*trans*** was added a portion of the Jones Reagent solution (0.54 mL). The reaction was stirred at 0 ^oC for 3 hours. The reaction mixture was concentrated at room temperature and filtered through a plug of silica, eluting with CH_2Cl_2 (50 mL) and then Et_2O (100 mL). The Et_2O solution was concentrated to give pure ***rac*–5.54a–*trans*** (97.7 mg, 93% yield).

rac*–5.54a–*trans: *(±)-(2S,3S)-2-((2S,5R)-5-methyltetrahydrofuran-2-yl)-4-nitro-3-phenylbutanoic acid*

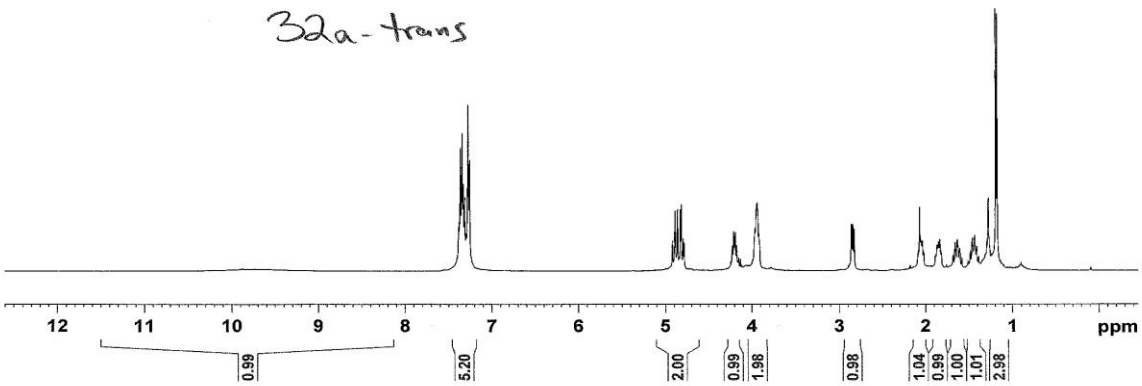


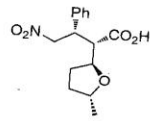
Colorless crystalline solid. m.p.: 107-110 ^oC; IR (thin film, KBr): 2970, 2876, 1722, 1541, 1380, 1062, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (bs, 1H), 7.45-7.20 (m, 5H), 4.95-4.78 (m, 2H), 4.20 (m, 1H), 3.95 (m, 2H), 2.84 (dd, J = 9.8, 5.0 Hz, 1H), 2.06 (m, 1H), 1.85 (m, 1H), 1.62 (m, 1H), 1.43 (m, 1H), 1.19 (d, J = 6.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 136.8, 129.1, 128.3, 128.0, 77.4, 77.0, 76.7, 53.9, 44.1, 33.4, 31.0, 21.1 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_{15}H_{19}NO_5]$: 293.1263, found: 279.1269.



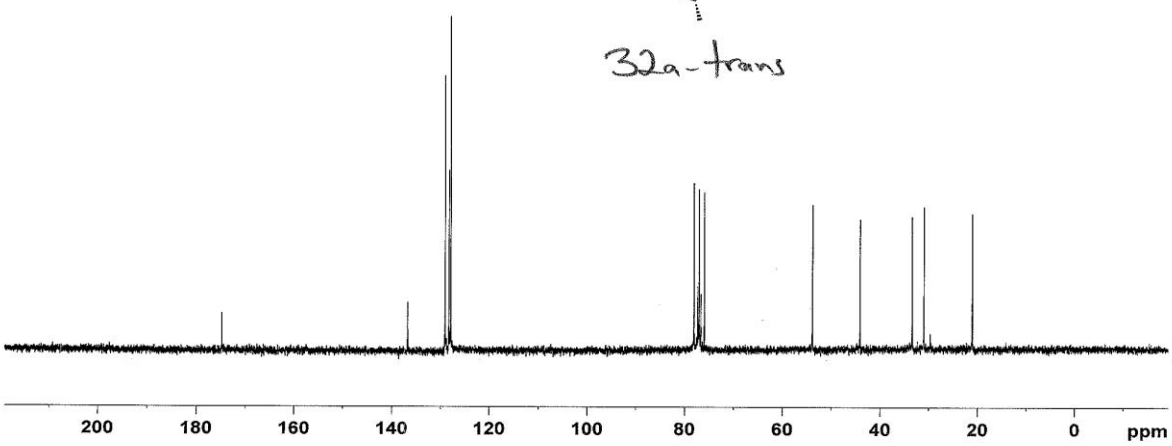


32a-trans





32a-trans

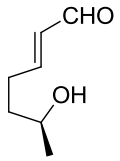


NOE Experiments

The relative configurations of **5.50a**–***cis*** and **5.50a**–***trans*** were determined by NOE NMR of the *p*-nitrobenzoate derivatives (**6.10a**–***cis*** and **6.10a**–***trans***) of their corresponding alcohols (**5.51a**–***cis*** and **5.51a**–***trans***).

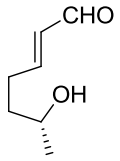
Chiral substrates **(*S*)**–**5.49a** and **(*R*)**–**5.49a** were prepared from the chiral secondary alcohols[20] using the cross metathesis method described above in the synthesis of **5.49a**.

(*S*)–**5.49a**: *(S,E)-6-hydroxyhept-2-enal*



brown oil. Collected in 78% yield. $[\alpha]_D^{21}$ = +16.3 (*c* 1.50, $CHCl_3$); IR (thin film, KBr): 3423, 2968, 2930, 2740, 1690, 1375 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 9.50 (d, *J* = 7.9 Hz, 1H), 7.00 (dt, *J* = 15.5, 6.8 Hz, 1H), 6.11 (ddt, *J* = 15.6, 7.9, 1.5 Hz, 1H), 3.73 (m, 1H), 2.70 (m, 1H), 2.55-2.33 (m, 2H), 1.65-1.53 (m, 2H), 1.15 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 194.2, 159.4, 132.5, 66.2, 36.9, 28.9, 22.8 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_7H_{12}O_2]$: 128.0837, found: 128.0838.

(*R*)–**5.49a**: *(R,E)-6-hydroxyhept-2-enal*



brown oil. Collected in 80% yield. $[\alpha]_D^{22}$ = -16.9 (*c* 1.50, $CHCl_3$); IR (thin film, KBr): 3423, 2968, 2930, 2740, 1690, 1375 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 9.50 (d, *J* = 7.9 Hz, 1H), 7.00 (dt, *J* = 15.5, 6.8 Hz, 1H), 6.11 (ddt, *J* = 15.6, 7.9, 1.5 Hz, 1H), 3.73 (m, 1H), 2.70 (m, 1H), 2.55-2.33 (m, 2H), 1.65-1.53 (m, 2H), 1.15 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 194.2, 159.4, 132.5, 66.2, 36.9, 28.9, 22.8 ppm; HRMS (ESI) : $[M^+]$ calcd for $[C_7H_{12}O_2]$: 128.0837, found: 128.0838.

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Chapter 2

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