A novel organocatalytic asymmetric approach towards prismatomerin type Iridoid class of terpenes

THESIS

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In

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By

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To my two mothers,

who molded me

Akka (Smt. Anusaya Vankhade)

and

my mother (Smt. Mangala Adate)

सीएसआयआर-राष्ट्रीय रासायनिक प्रयोगशाला
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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**A novel organocatalytic asymmetric approach towards prismatomerin type Iridoid class of terpenes**" which is being submitted to the **University of Pune** for the award of **Doctor of Philosophy in Chemistry** by **Ms. Priyanka A. Adate** was carried out by her under my supervision at the **National Chemical Laboratory, Pune**. A material that has been obtained from other sources has been duly acknowledged in the thesis.

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DECLARATION

I hereby declare that the work presented in the thesis entitled **"A novel organocatalytic asymmetric approach towards prismatomerin type Iridoid class of terpenes"** submitted for Ph. D. Degree to the **University of Pune**, has been carried out by me at the **National Chemical Laboratory**, **Pune**, under the supervision of **Dr. Ganesh Pandey**. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University/Institute.

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....Priyanka

Contents

Abbreviations

aq.	aqueous	NMR	Nuclear magnetic resonance
mL	Milliliter	*p*-TSA	*p*-Toluenesulfonic acid
mmol	Millimole	TBS	*tert*-Butyldimethylsilyl
m.p.	melting point	COSY	Correlation Spectroscopy
DBU	1,8- Diazabicyclo [5.4.0]undec-7-ene	NOE	Nuclear overhauser effect/enhancement
DEPT	Distortionless enhancement by polarization transfer	HSQC	Heteronuclear Single Quantum Coherence)
DMAP	*N*,*N*-Dimethylaminopyridine	THF	Tetrahydrofuran
DMF	*N*,*N*-dimethylformamide	TLC	Thin layer chromatography
DMSO	Dimethylsulfoxide	PMB	*p*-methoxy benzyl
g	gram	SM	Starting material
GC	Gas chromatography	Ac	Acetyl
h	hour	HMDS	Hexamethyldisilazane
Hz	Hertz	LDA	Lithium diisopropylamide
M	Molarity (molar)	TMEDA	Tetramethylethylenediamine
N	Normality	mCPBA	m-chloroperoxybenzoic acid
min.	Minute(s)	IBX	2-Iodoxybenzoic acid
TMS	Trimethylsilyl	MPO	4-Methoxy pyridine N-oxide
MS	Mass spectrum	HMBC	*Heteronuclear Multiple Bond Correlation*

General Remarks

- All the solvents were purified according to literature procedure.[1]
- Petroleum ether used in the experiments was of 60−80 ˚C boiling range.
- Column chromatographic separations were carried out by gradient elution with suitable combination of two solvents and silica gel (60−120 mesh/100−200 mesh/230−400 mesh).
- Reaction progress was monitored by TLC or GC. TLC was performed E-Merck pre-coated 60 F254 plates and the spots were rendered visible by exposing to UV light, Iodine, phosphomolibdic acid, *o*-Anisol, KMnO4. GC analysis was performed on Perkin Elmer 8700 and Varian CP 3800 GCs using SGE BP1, BP20 and Varian Chromopack CP-Sil-5CB columns.
- IR spectra were recorded on FTIR instrument, for solid either as nujol mull, neat in case of liquid compounds or their solution in chloroform.
- NMR spectra were recorded on Bruker AV 200 (200 MHz ^{1}H NMR and 50 MHz ^{13}C NMR), Bruker AV 400 (400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR) and Bruker DRX 500 (500 MHz ^{1}H NMR and 126 MHz ^{13}C NMR).
- ^{13}C peak multiplicity assignments were made based on DEPT data.
- Mass spectra were recorded on PE SCIEX API QSTAR pulser (LC-MS) and Shimadzu QP 5000 GC/MS coupled to Shimadzu 17A GC using a DBI column.
- High resolution mass (HR-ESI-MS) spectra was recorded on a Thermo scientific make Q-exactive model spectrometer using electrospray ionization
- Optical rotations were measured on a JASCO P-1020 polarimeter.
- HPLC were performed on Shimadzu Class-VP V6.12 SP5 with UV detector.
- All the melting points recorded are uncorrected and were recorded using electrothermal melting point apparatus.
- Starting materials were obtained from commercial sources.
- **Numbering of compounds, schemes, tables, referencing and figures for each chapter as well as abstract are independent.**

Perrin, D. D., Armarego, W. L. F., Purification of Laboratory Chemicals, 4th ed., Butterworth Heinemann, **1999**

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Chapter 1 An overview on iridoid class of terpenes

This chapter portrays an introduction to iridoids class of terpenes, their classification and biosynthetic pathway for synthesis of Plumeria type higher iridoids. For simplicity throughout the thesis, we will be indicating Plumeria type higher iridoids as higher iridoids.

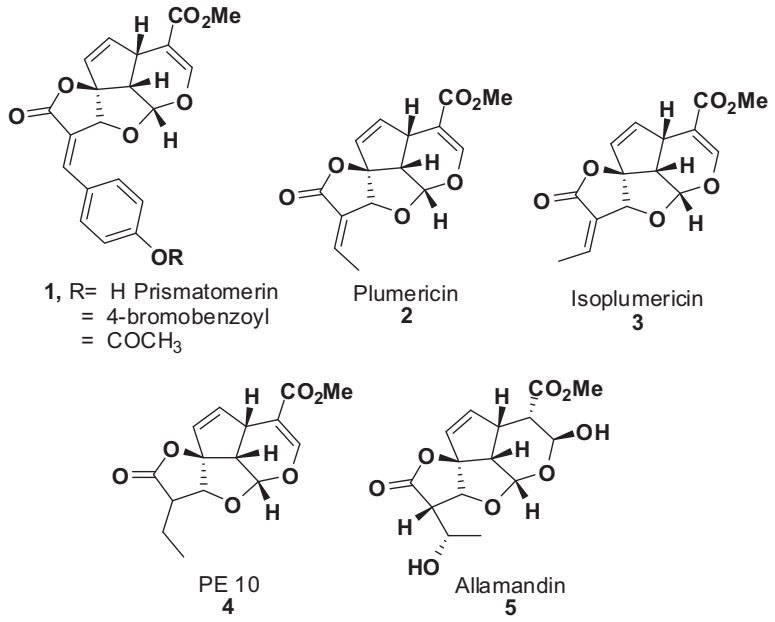
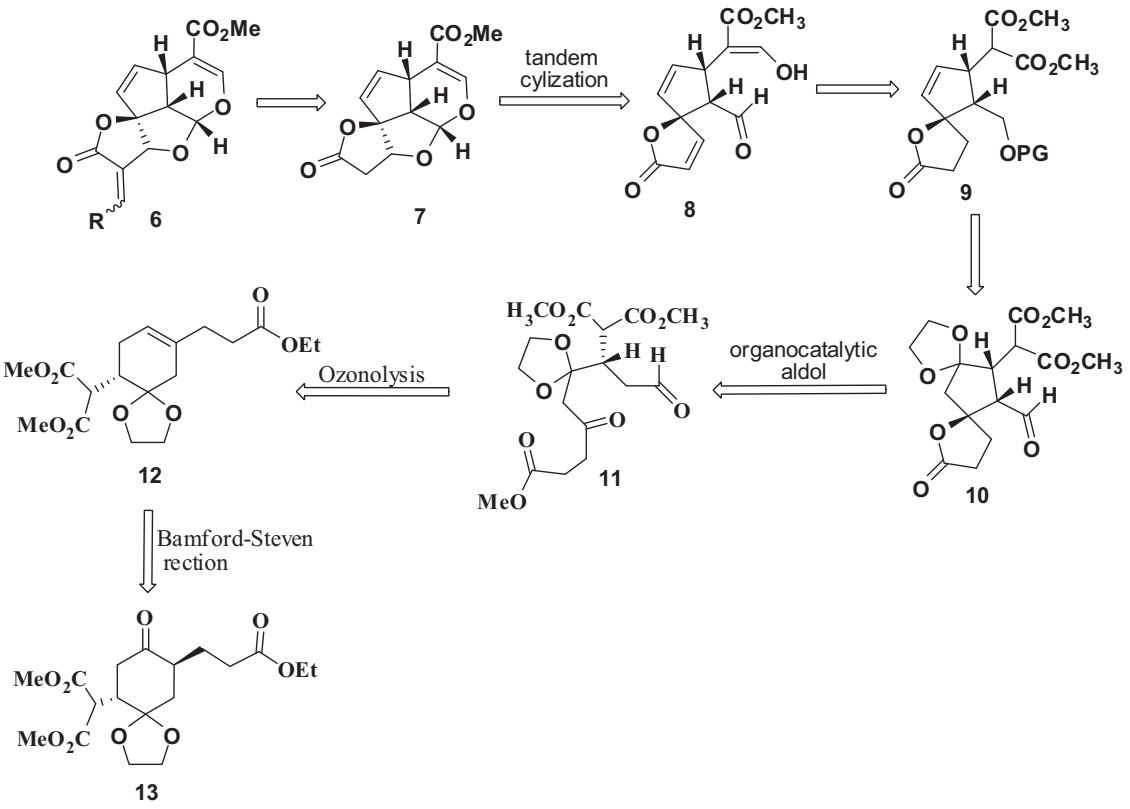


Figure 1: Plumeria type higher iridoids

Iridoids are a class of secondary metabolites found in a wide variety of plants and animals. They are structurally diverse natural cyclopentanopyran monoterpenes and often involved as intermediates in the biosynthesis of alkaloids. Iridoids are typically found in

plants as glycosides, most often bound to glucose. Isolated and purified Iridoids exhibit a wide range of bioactivities including cardiovascular, antihepatotoxic, choleretic, hypoglycemic, analgesic, anti-inflammatory, antimutagenic, antispasmodic, antitumor, antiviral, immune-modulator, and purgative activities. Members of higher iridoids exhibit potent anti-tumor activity.

We were especially attracted towards the synthesis of higher Iridoids mainly for the structural complexity comprising (Figure 1) of cyclic hemi-acetal ring portion and a spiro-fused α-ethylidene-β-oxy-γ-butyrolactone ring system. Till date only two racemic syntheses are known for these higher Iridoids and asymmetric total synthesis is still eluding.



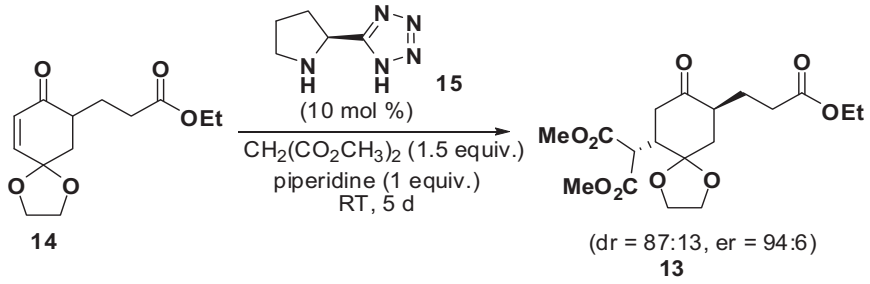
Scheme 1: Retrosynthetic analysis

Close look at the structures of most of the members of higher iridoid (Figure 1) revealed that, they differ only in their alkyl side chain on spiro butanolide which was visualized to be installed by simple aldol condensation with an aldehydic moiety. Having this idea in mind, we planned our retrosynthetic analysis as outline in Scheme 1. We

proposed proline catalyzed tandem sequence for the synthesis of spirobutyrolactone **10**. **10** was visualized to be synthesized from **11** through organocatalytic intramolecular aldol reaction followed by *in-situ* lactonization to obtain γ-butyrolactone. Dicarbonyl **11** was visualized to be realized easily from **12** by ozonolysis, which in turn could be synthesized from chiral chiral 2,5-dialkyl cyclohexanone **13**.

Chapter 2 Organocatalytic dynamic kinetic resolution via conjugate addition: Synthesis of chiral *trans*-2, 5- dialkylcyclohexanones

In this chapter we have discussed literature reports for synthesis of higher iridoids followed by methodology for accessing chiral-2,5-dialkyl cyclohexanones, required as starting material for our designed synthesis. *trans*-2,5-dialkylcyclohexanone is also an important structural motifs in several naturally occurring terpenes. We have discussed the development of a conceptually new strategy for synthesis of chiral *trans*-2,5-dialkylcyclohexanones (*dr* up to 99:1and *er* up to 94:6.) by organocatalytic dynamic kinetic resolution (DKR) via conjugate addition of dimethylmalonate on racemic 6-alkyl cyclohexenones using proline tetrazole derivative as catalyst along with piperidine as a base.



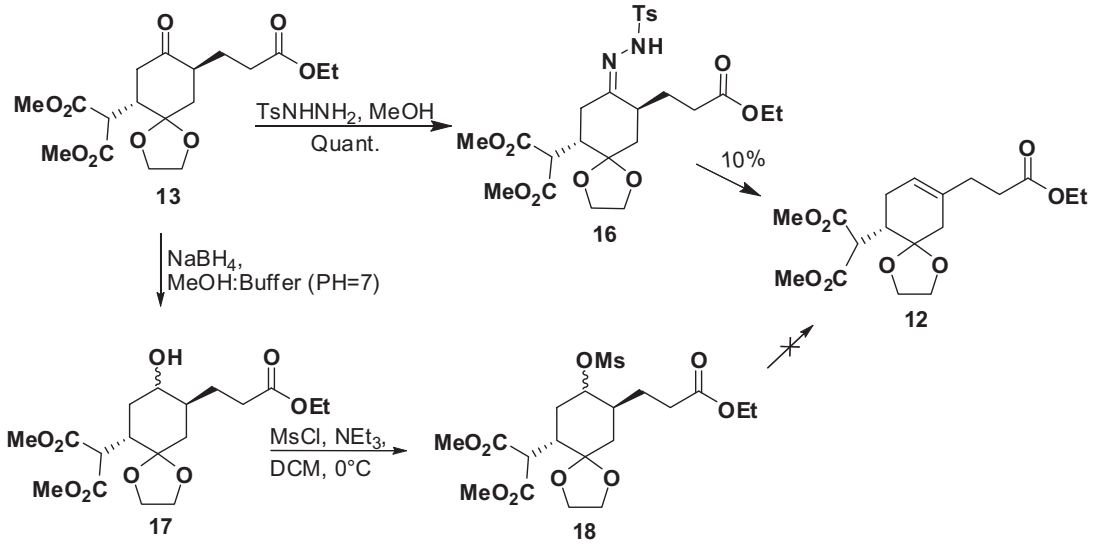
Scheme 2: synthesis of trans-2,5-dialkylcyclohexanones

Study on effect of ring size of enone on DKR, shows best stereoselectivity for 6-substituted cyclohexenone as compared to pentenone, heptenone and octenone. Scope of the DKR using various substituted 6-alkyl cyclohexenone was explored using dimethyl or diethyl malonate as Michael donor. Generally better enantioselectivity was observed using diethyl malonate as a nucleophile in comparison to dimethyl malonate. DKR of aliphatic enone gave very low diastereoselectivity and enantioselectivity.

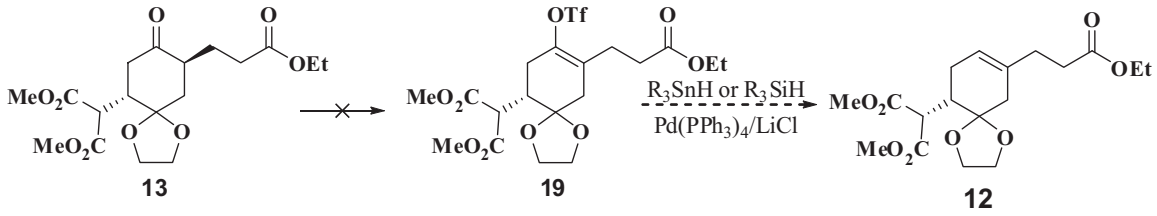
Relative stereochemistry of chiral 2,5-dialkyl cyclohexanones obtained by DKR of 6-alkyl cyclohexenone were confirmed to be *trans* by extensive NMR studies and X-ray crystallographic analysis of compound **13**. DKR of **14** was scaled up to 20.0 g scale producing **13** with almost same stereoselectivity (*dr* = 70:30, *er* = 94:6).

Chapter 3 Synthesis of tertacyclic core of higher iridoid from chiral-2,5-dialkyl cyclohexanone

In Chapter 3, synthetic efforts towards the synthesis **7** starting with **13** are described. Tosyl hydrazone derivative of **16** on subjecting to Bamford-Steven reaction gave desired olefin **12** but in low yield of 10 %. Surprisingly, dehydration of **17** *via* elimination of mesylate in **18** also failed to give the desired **12** (Scheme 3).

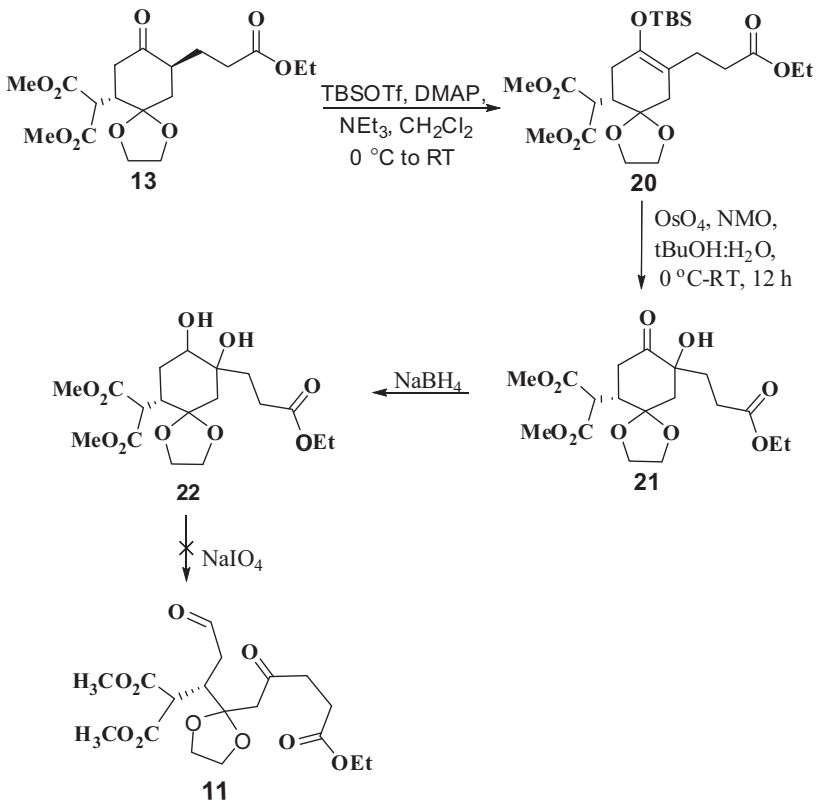


Scheme 3



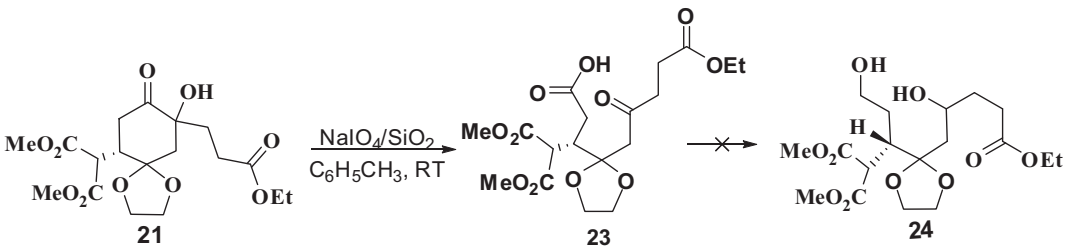
Scheme 4

Even the conversion of **13** to corresponding vinyl triflate **19** failed; reductive elimination of **19** with tetrakistriphenylphosphine palladium could have given desired **12** (Scheme 4).



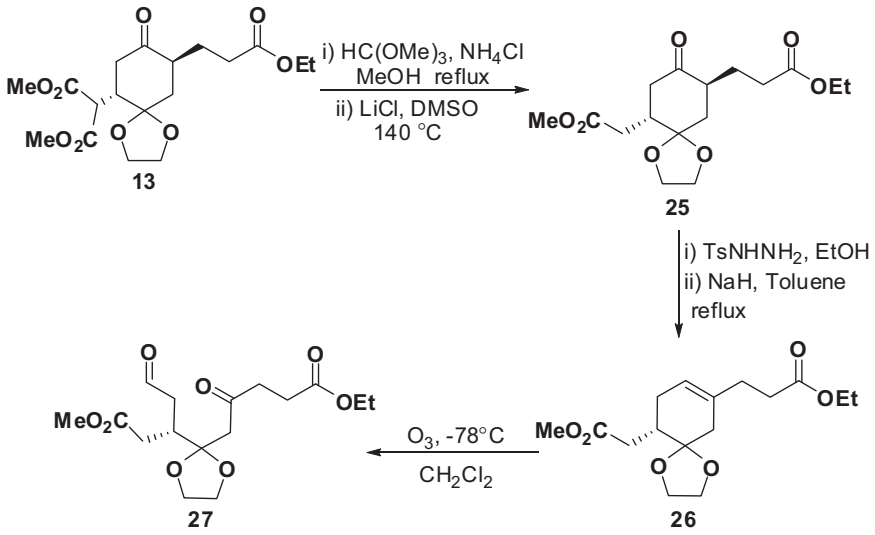
Scheme 5

Therefore, α-hydroxy functionalization of **13** followed by oxidative cleavage was visualized as a viable alternative. Towards this end **13** was converted to **20** using TBSOTf in the presence of Et_3N. Oxidation of TBS enol ether **20** with osmium tetraoxide gave required **21** in 70 % yield. However, further experiments with **21** utilizing sequential reduction followed by oxidative cleavage failed to give required **11** (Scheme 5). Reason for this failure may be formation of 5 and 6-membered lactone with the two hydroxy. Thus oxidative cleavage of **21** was carried out to afford **23**. However, further selective reduction of **23** (Scheme 6) using various condition furnished complex reaction mixture.



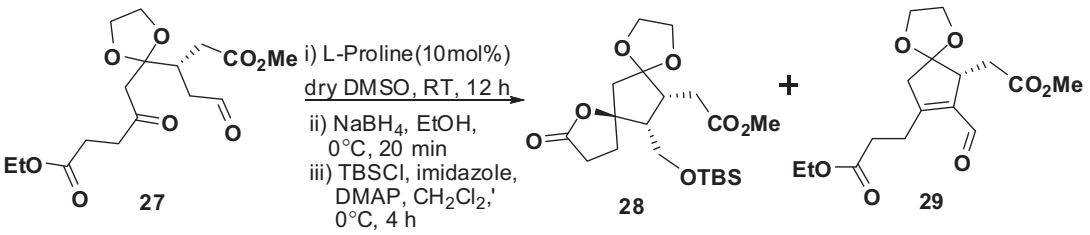
Scheme 6

These failures led us to conclude that synthesis of **11** was difficult and proceeding with **12** was not practical owing to low yield. We thought presence of malonate functionality could be reason for the low yield with Bamford-Steven reaction.



Scheme 7

As a last trial, **13** was mono-decarboxylated following Krapcho protocol to afford **25** which was converted to desired olefin **26** *via* tosyl hydrazone derivative. Olefin **26** on ozonolysis delivered desired **27** in 70 % yield. Among the catalyst and Solvents screened for aldol cyclization only L-Proline in dry DMSO was found to provide **28** as a single diastereomer along with enal **29** (Scheme 8). The final confirmation for stereochemistry of stereocentres on **29** was tentatively assigned from NOESY studies

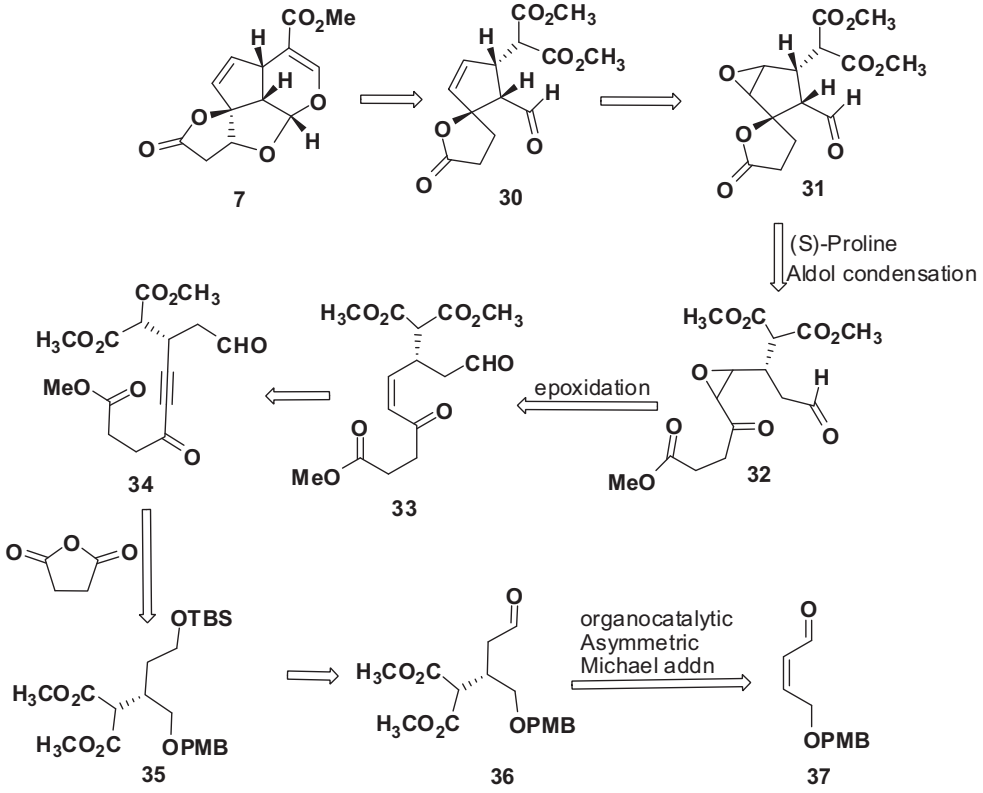


Scheme 8

Thus we could synthesize an advanced chiral intermediate **28**, adorned with all requisite functionalities for further elaboration to tetracyclic core of higher Iridoid, has been synthesized employing organocatalytic intra-molecular aldol cyclization of **27**. Further transformation of **28** to target tetracyclic core **7** is in progress.

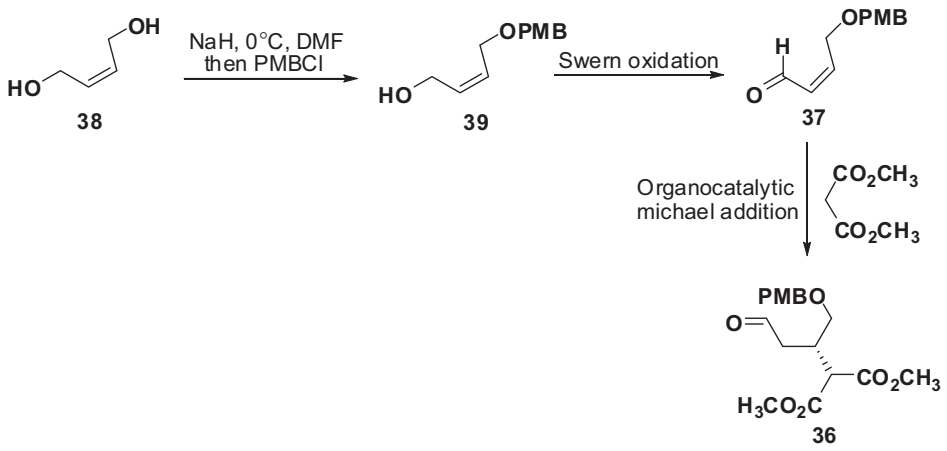
Chapter 4 Alternative strategy towards the synthesis of the tetracyclic core structure of higher iridoid

In this chapter, a synthetic study towards synthesis of 33 is described.



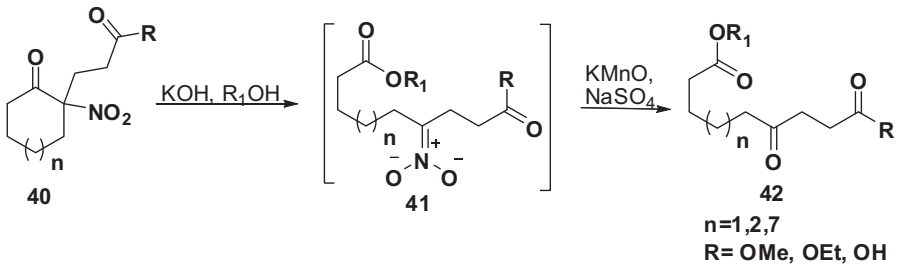
Scheme 9 Retrosynthetic analysis

Conjugate addition of dimethyl malonate on *cis*-**38** using different organocatalyst gave conjugate adduct **37** either in very low yield or with poor enantioselectivity.



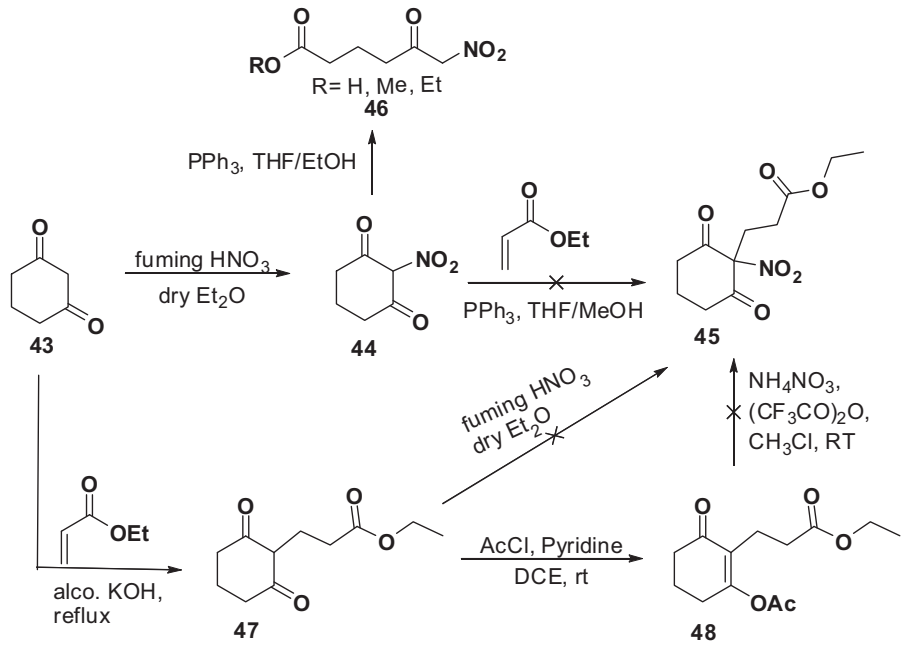
Scheme 10

Since it was known that **40** can be converted to corresponding open chain **42** *via* nitronate anion **41** followed by Nef reaction (Scheme 11), we attempted the synthesis of **45**, which could be eventually converted to **53**, as shown in Scheme-12.



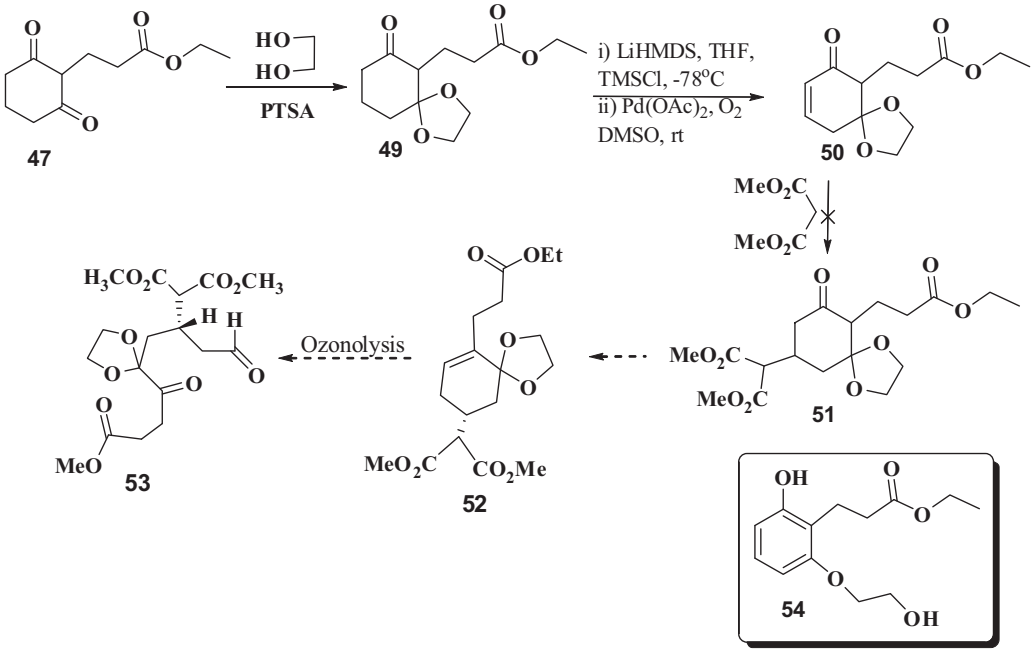
Scheme 11

Nitration of **43** with fuming nitric acid provided **44**. **44** when subjected to conjugate addition with ethyl acrylate in alcoholic solvent gave open chain nitroketo-ester or acid **46** instead of desired **45**. We thought increased increased nucleophilicity of carbonyl carbon could be reason for this ring opened product, so we planned to reverse the reaction sequence. Reversing the sequence of reaction, such as initial conjugate addition on acrylate followed by nitration of **47** even failed to give **45**.



Scheme 12

With these frustrating and unanticipated hurdles in obtaining **45**, we evaluated the synthesis of **53** from **47** as shown in Scheme-13. Towards this end, **47** was mono-ketal protected followed by oxidation to obtain **50**. However, further



Scheme 13

attempt to transform **50** to **51** via conjugate addition of dimethylmalonatedesired failed, instead produced aromatized **54** (Scheme 13).

In summary, we have developed a conceptually new DKR strategy for synthesis of chiral trans-2,5-dialkylcyclohexanones by organocatalyzed asymmetric conjugate addition of malonate on to 6-substituted cyclohexenones. We have successfully synthesized spiro-butenolide 28, and further trial for its transformation to tetracyclic core 7 is in progress.

Note: Compound numbers in the abstract are different from those in the thesis

Chapter 1

An overview on iridoid class of terpenes

1.1 Introduction

Iridoids are a large class of naturally occurring compounds with over 1200 members in the family which are almost exclusively of plant origin. However, the name 'iridoid' is a generic term derived from the fact that the first iridoid was isolated from the defensive secretion of ants belonging to genus *Iridomyrmex*[1]. Various plants containing iridoids have been used in a variety of folk medicines for centuries as a bitter tonic, an expectorant, a purgative and as a treatment for certain skin diseases. Chemical interest in the iridoids is stimulated because of their role in the defense mechanism of ants and the key role played by one compound, secologanin[2], in the biosynthesis of indolo-monoterpene alkaloids and certain isoquinoline alkaloids found in the *Apocynaceae, Loganiaceae and Rubiaceae*.

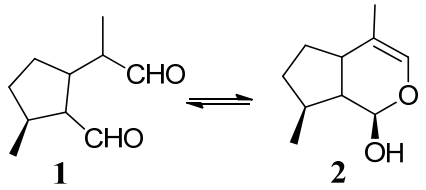


Figure 1.1: Isomeric form of Iridodial

Iridoids are structurally characterized by the presence of a partially hydrogenated *cis* fused *cy*clopenta[c]pyran (**2**) system which can be derived by the intramolecular acetalization of a 1,5-cyclopentandialdehyde[3] (**1**) (Figure 1.1). The unique *cis*-fused cyclopenta[c]pyran ring (Figure 1.2) system has presented a variety of challenge for chemical synthesis and in analyses of biological activities.

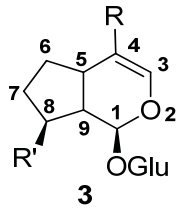


Figure 1.2: Basic **structure of iridoid**

General characteristic features[4] of iridoids are as follows (Figure 1.2):

1. An enol-ether system involving C1, C3 and C4, where C3 is never substituted.
2. *S* - Configuration at C1, commonly substituted by acetalic oxygen which may be linked to a glucosidic moiety.
3. *cis*-linkage involving C5, sometimes, substituted by an oxygen and C9 always substituted with the hydrogen with β-configuration.
4. Possible presence of an additional double bond between C6 and C7 or more rarely C7–C8.

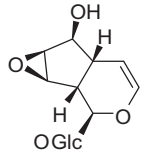
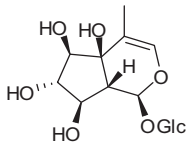
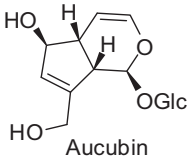
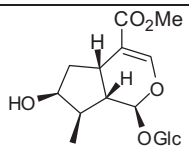
1.2 Classification of iridoid

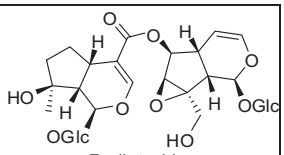
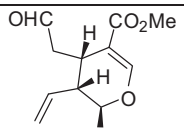
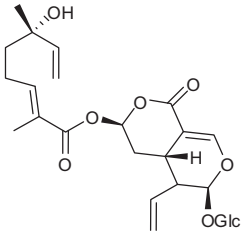
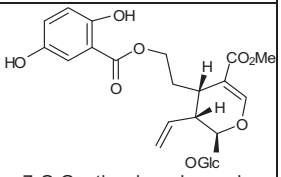
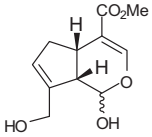
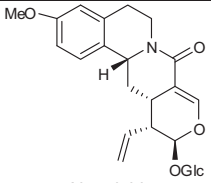
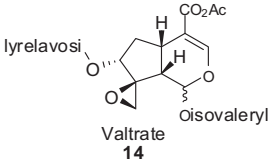
Naturally occurring iridoids are classified into different subclasses by several authors based on their structure, biosynthesis and chemical properties.[1,5] Of all the classifications presented, the one given by Franzyk[6] seems to be the most recent and fundamental, considering all the members of iridoid family. Iridoids can be fundamentally classified into 4-groups based on their structural frameworks such as iridoid glycosides, non-glycosidic iridoids, iridoid alkaloids (nitrogen containing Iridoids) and special iridoids as shown in Table 1.1.

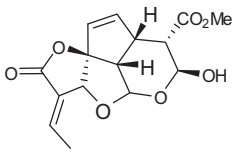
Each group can be further divided into subgroups as shown in Table 1.1. The non-glycosidic part of an iridoid is called the aglycone or the genin. The glycosidic iridoid can be further subdivided into carbocyclic iridoids and seco-iridoids, having dihydropyran ring system as common moiety. Even though most carbocylic iridoids have *cis* fused cyclopentane ring with substituent at C5 and C9 in β-position, some *trans* fused compounds are also characterized. Carbocyclic glycosidic iridoids can also be sub-divided into four sub groups based on the number of carbon atoms present. Seco-iridoids are carbocyclic iridoids in which C-C bond between C7 and C8 is cleaved. Another class is iridoid alkaloids or pseudoalkaloids regarded as a genuine type of iridoids, since they have proved to be natural constituents and not mere artifacts formed during isolation (*i.e.* when ammonia is applied during extraction),[7,8] as previously assumed. Lastly there are two groups of special iridoids, Valeriana and Plumeria type which can be classified as glycosidic or aglycosidic, but for their unusual substitution patterns they are treated as

independent structural assembly. For simplicity throughout the thesis, we will be indicating Plumeria type higher iridoids as higher iridoids.

Table 1.1: Classification of iridoids

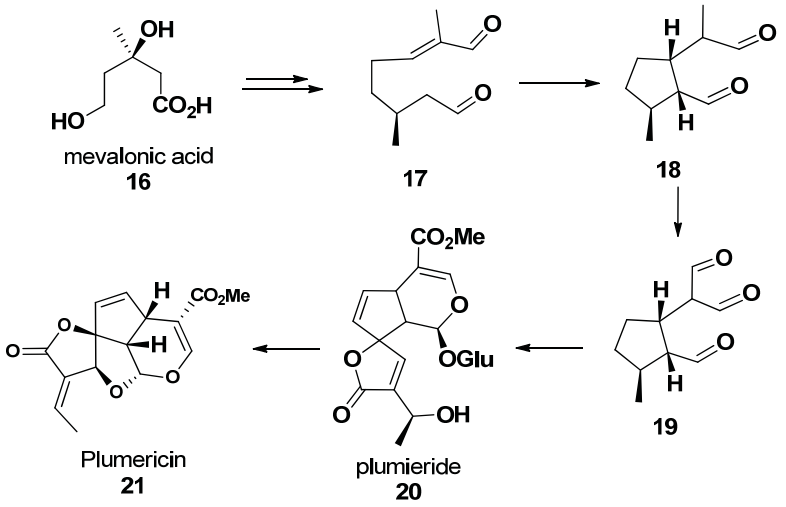
Group	Sub-group	class	Structural charcteristic	Representative molecule
Glycosidic iridoids	Carbocyclic	C_8 iridoids	Glycon has 8 no. of carbon atoms	 Unedoside **4**
		C_9 iridoids	Glycon has 9 no. of carbon atoms	C_9 Iridoid with 9th carbon on C_4  Scabrosidol **5**
				C_9 Iridoid with 9th carbon on C_8  Aucubin **6**
		C_{10} iridoids	Glycon has 10 no. of carbon atoms	 Loganin **7**

		bis-iridoid	Two iridoid units bonded together	 Radiatoside **8**
	Secoiridoid	Simple	carbon-carbon bond between C-7 and C-8 has been cleaved	 Secologanin **9**
		Terpene conjugated	conjugated with a terpene type moiety	 Menthiafolin **10**
		Phenolic conjugated	carry a phenolic moiety as a substituent	 7-O-Gentisoylsecologanol **11**
Non-glycosidic iridoids			Absence of any glycosidic group	 Genipin **12**
iridoid alkaloids (pseudo-alkaloids)			alkaloids with an iridoid part	 Alangiside **13**
	Valeriana type			 Valtrate **14**

special iridoids	Plumeria type (higher iridoids)			 Allamandin **15**

1.3 Biosynthetic approach

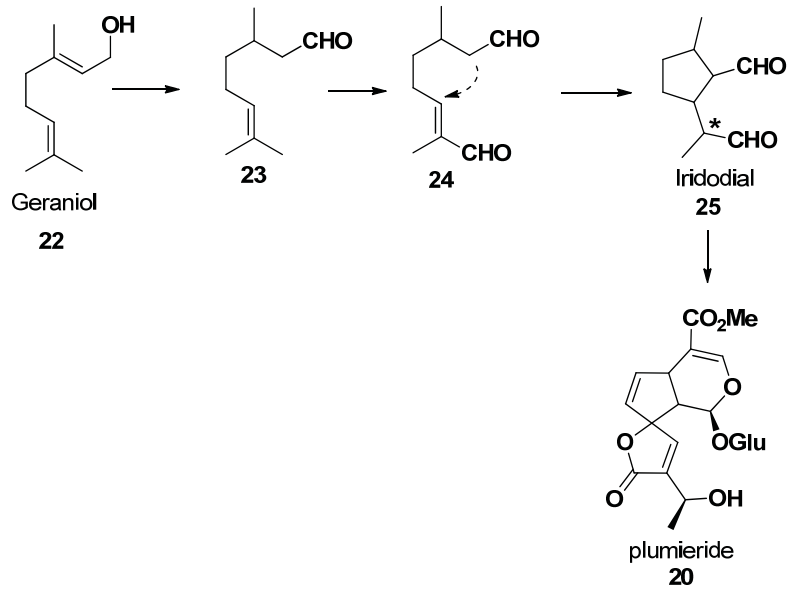
Biosynthesis of iridoids has attracted attention of many research groups mainly owing to observed biogenetic relationship between carbon framework of iridoids and indole-isoquinoline alkaloid skeleton[1]. It was proposed that Plumieride (**20**) may be a biosynthetic precursor of Plumericin (**21**)[9]. This possibility led to consider conjugate addition-elimination approach for the formation of tetrahydrofuran unit in higher iridoids. Biosynthesis of plumeride was investigated by Schmid *et al*. through the administration



Scheme 1.1: Biosynthetic pathway starting with Mevalonic acid

^{14}C labeled mevalonic acid and reported incorporation of two units each of mevalonic acid and acetic acid into aglycon moiety of plumieride[10]. Based on this observation, it was speculated the biosynthesis of Plumieride (**20**) as shown in Scheme 1.1. Plumieride (**20**) is biosynthesized through a Michael-type cyclization of 10-oxocitronellal (**17**) to iridodial **18** followed by further oxidation to iridiotrial **19** and conversion to Plumieride (**20**).

Second possible biosynthetic route for Plumieride was given by Leete *et al.* from geraniol[11] as shown in Scheme 1.2 based on the labeling studies.



Scheme 1.2: Hypothetical Biosynthetic Route from Geraniol **22** to Plumieride **20**

1.4 Special interest in higher iridoids

In 1951, Little and Johnstone isolated a sesquiterpene named Plumericin (**20**) from the roots of *Plumeria multiflora* which exhibited *in vitro* activity against fungi, bacteria including *Mycobacterium tuberculosis-607* and subsequently antitumor activity.[12] Later in 1961, Schonberg and Schmid proposed present structure for Plumericin.[13] Closely related to Plumericin is a hydrated analogue Allamandin (**31**), known to posses high antitumor activity.[14] Recently in 2007 Krohn and Nahar *et al.* isolated a new complex iridoid, Prismatomerin (**26**) from the leaves of *Prismatomeria tetranda* which exhibited remarkable growth inhibition as well as cell killing effect in solid tumor cell lines (LC > 100 to 0.6 μM) and was also found to interfere with mitotic spindle formation.[15]

Broad diversity of biological activity showed by different members of iridoid family has specially attracted many organic chemists for its synthesis.[1] We are especially attracted by synthetic challenge posed by Plumeria and related higher iridoids due to following reasons:

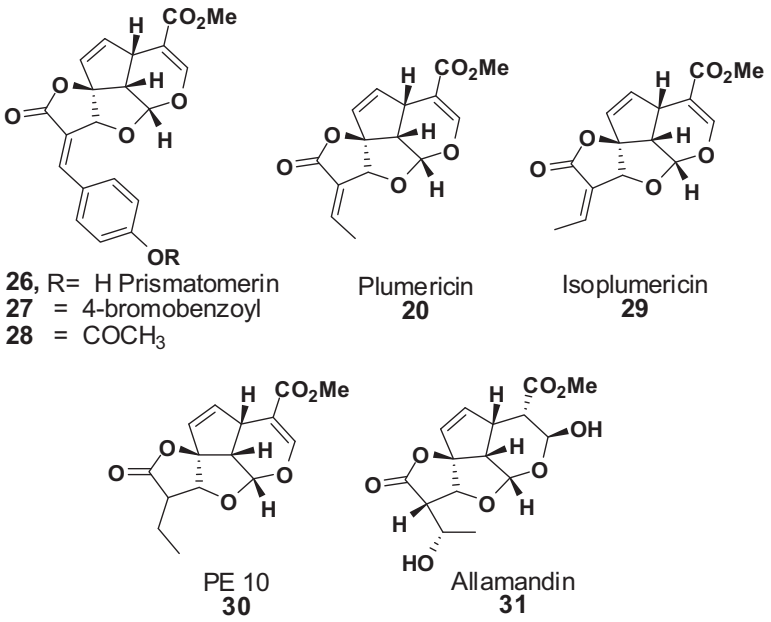


Figure 1.3: Plumeria type higher iridoids

1. Their densely functionalized skeleton possesing five contigious stereocentres
2. Interesting cyclic hemi-acetal ring portion, which also makes up part of a cyclic acetal, one 'ether' residue of which constitutes the β-oxygen of a spiro-fused α-ethylidene-β-oxy-γ-butyrolactone ring system.
3. No asymmetric total synthesis of prismatomerin type iridoid is known till date.
4. Members of this class of iridoids exhibit various biological activities[9] such as cytotoxic, antileukemic,[14] antimicrobial and antifungal activity.

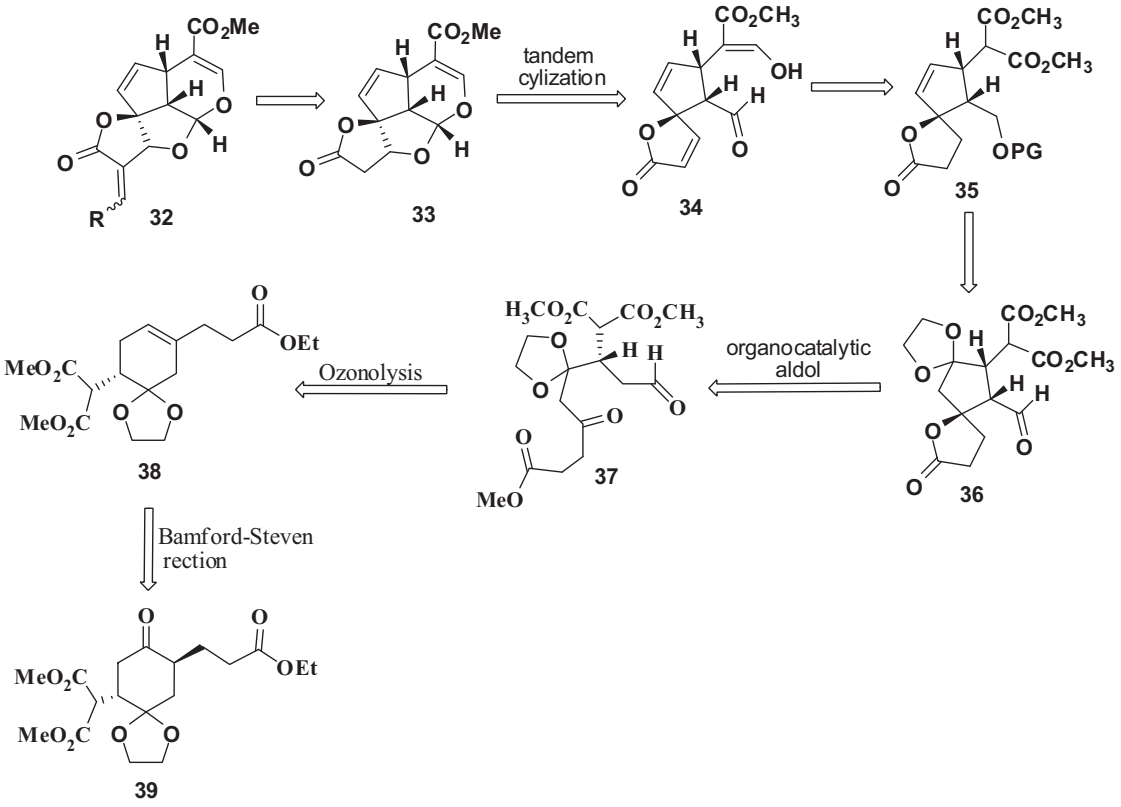
Only two racemic synthesis of these higher iridoids are known in literature[16,17] starting with the bicyclo[3.3.0]octenone as starting material.

1.5 Objective of present desertation:

Since most of the members of Plumeria type higher iridoids differ only in alkyl side chain on *spiro*-butenolide, we would like present in this dissertation design of novel strategy for the synthesis of basic tetracyclic core structure of iridoids which would allow access to the synthesis of all members of higher iridoids.

1.6 Retrosynthetic analysis:

On careful scrutiny of the structures of higher iridoids, we planned our retro-synthesis as shown in Scheme 1.5.



Scheme 1.5: Retrosynthetic analysis

We proposed proline catalyzed tandem sequence for the synthesis of spirobutyrolactone **36**. Spirobutyrolactone **36** was visualized to be synthesized from **37** through organocatalytic intramolecular aldol reaction followed by *in-situ* lactonization to obtain γ-butyrolactone. Dicarbonyl **37** was visualized to be realized easily from **38** by ozonolysis, which in turn could be synthesized from chiral **39**.

Proceeding chapter would describe a general strategy for the stereoselective synthesis of chiral 2,5-dialkyl cyclohexanones.

1.7 References:

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Chapter 2

Organocatalytic dynamic kinetic resolution *via* conjugate addition: Synthesis of chiral *trans*-2, 5-dialkylcyclohexanones

2.1 Introduction

The densely functionalized core structure of higher iridoids - comprising a highly substituted cyclopentene ring with three contiguous stereocentres, one of which is oxa-quaternary represents a substantial synthetic challenge (Figure 2.1) to the organic chemist. In the previous chapter, we discussed our retrosynthetic route for the synthesis of the tetracyclic core, common for all higher iridoids. However, before presenting our designed strategy for the synthesis of higher iridoids it may be imperative to examine the literature reports in this area.

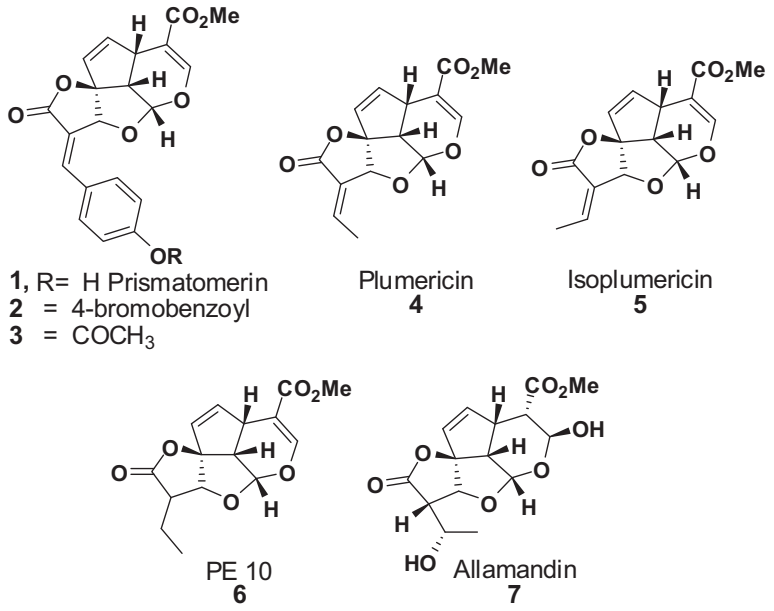
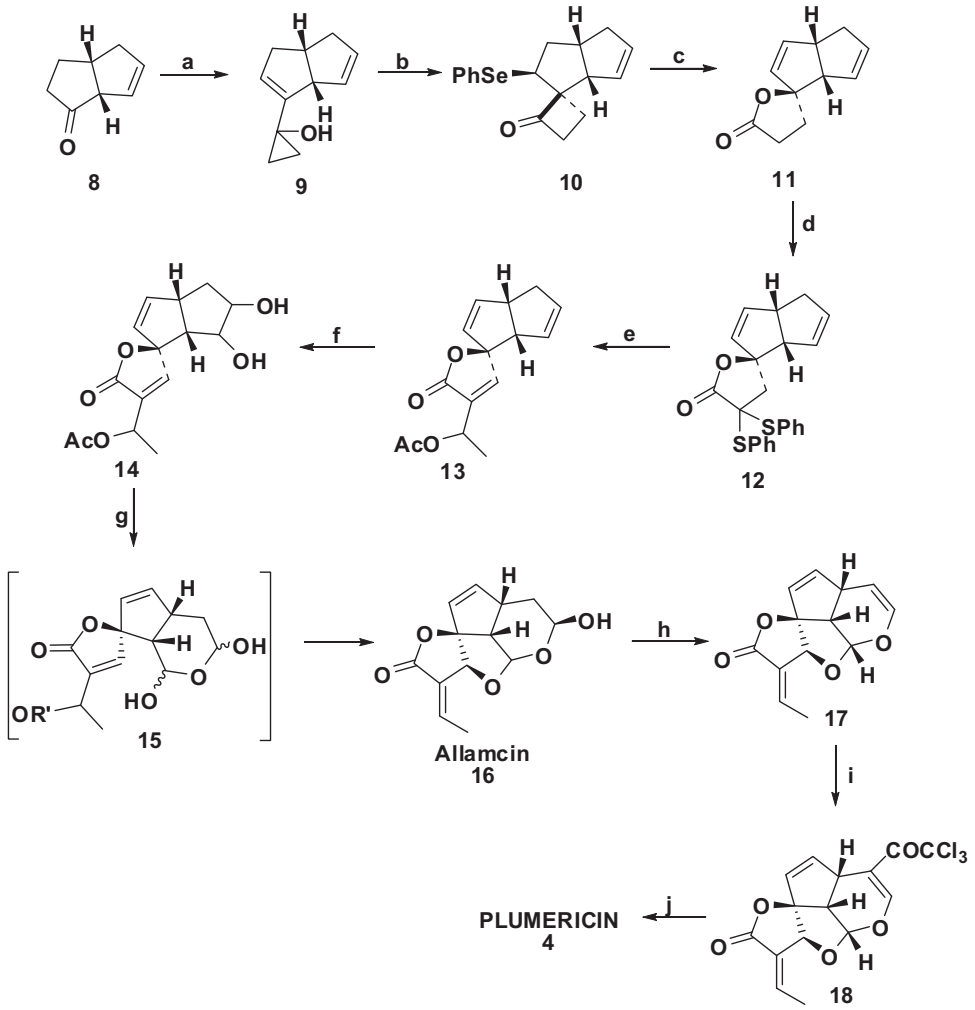


Figure 2.1: Higher iridoids

2.2 Synthetic methodologies for the synthesis of higher iridoids

Trost's approach:[1] First total synthesis of (±)-Plumericin was reported by Trost *et al.* in 1983 (Scheme 2.1). The approach involved the formation of spiro-butenone **13** from bicyclo[3.3.0]octenone (**8**) using the concept of substitutive spiroannulation followed by γ-butyrolactone elaboration via sulfenylated intermediates **12**. Later, **s**elective oxidative cleavage of olefinic moiety of **13** afforded (±)-Allamcin (**16)** which on subsequent hydroxyl elimination and selective carbomethoxylation led to formation of **4** in total 16 steps from **8**.

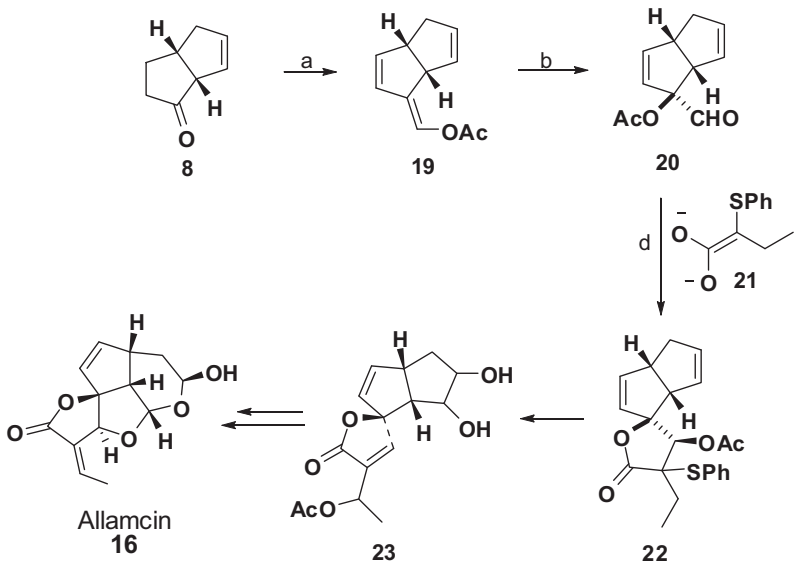


Reagents: (a) i) cyclopropyl $S^{+}Ph_2BF_4^{-}$, KOH, Me_2SO_4, RT ii) $LiN(C_2H_5)_2$, pentane, RT; (b) PhSeBr **(1.5** equiv), $N(C_2H_5)_3$ (2.0 equiv), CH_2Cl_2, -40 **ºC;** (c) *m*-CPBA, CH_2Cl_2, -78 ºC to RT then add $CH_2{=}CHOC_2H_5$, RT; (d) LDA, THF, then $PhSSO_2Ph$, THF, -78 ºC to RT; (e) i)C_2H_5MgBr, ether, THF, 0 ºC, then CH_3CHO; ii)*m*-CPBA, CH_2Cl_2, -78 ºC to RT, then CCl_4, $CaCO_3$, reflux; iii) Ac_2O, C_5H_5N, DMAP, 0 ºC; (f) cat OsO_4, THF, H_2O, 0 ºC; (g) $NaIO_4$ (3 equiv), ether, H_2O, room temperature, then add NaOAc; (h) Ac_2O, DMAP, (i-$C_3H_7)_2NC_2H_5$, CH_2Cl_2, RT, and distill crude through quartz tube at 500 **ºC**; (i) $CC1_3COCl$ (50 equiv), 2,6-(*t*-$C_4H_9)_2C_5H_3N$ (5 equiv), CH_2Cl_2, RT; (j) $Mg(OCH_3)_2$, CH_3OH, THF, -45 ºC**.**

Scheme 2.1: Trost synthesis of Plumericin

Pattenden's approach:[2] Pattenden's group also utilized bicyclo[3.3.0]octenone (**8**) as a starting material for the synthesis of (±)-Allamcin following the sequence as shown in Scheme-2.2. The strategy exploited β-oxy-γ-butyrolactone ring system spiroannulation on

to the bicyclo[3.3.0]octenone (**8**) via acetoxy-aldehyde intermediate (**20**). The synthesis of (±)-allamcin **17** involved 7 steps starting from **8**.



Reagents: (a) i) 2,4,6-triisopropylbenzenesulphonylhydrazine, MeOH, RT, ii) *n*-BuLi, TMEDA, -78 ºC to 0 ºC; then DMF (b) isopropenyl acetate, *p*-TSA, RT; (c) peracetic acid, Na_2CO_3, CH_2Cl_2, -80 ºC**;** (d) LDA, THF, 0 ºC.

Scheme 2.2: Pattenden synthesis of Allamcin **16**

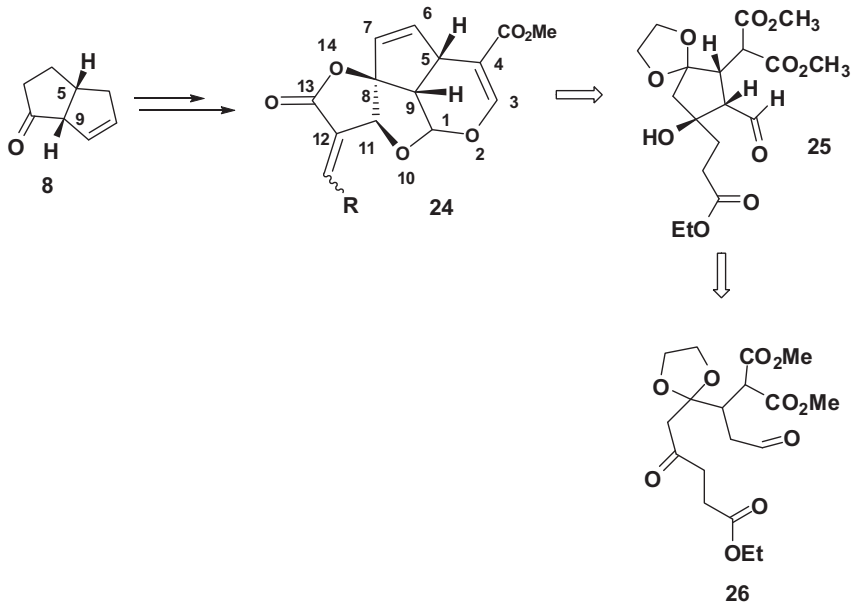
From the above literature reports it is evident that:

i) These syntheses utilize *cis*-ring junction stereochemistry in bicyclo[3.3.0]octenone (**8**) as a handle for installing the remaining stereocentres on the tetracyclic core of higher iridoids.

ii) No chiral synthesis is yet known for these molecules to establish optical purity and absolute stereochemistry.

iii) No attempt has been made to build a suitably substituted central pentane ring containing three contiguous stereocentres, one of which is oxa-quaternary.

Therefore, we surmised that if a strategy could be developed which would deliver suitably substituted cyclopentane structural framework **25**, the rest of the tetracyclic core of iridoids can be built up by simple functional group manipulations (Scheme 2.3).



Scheme 2.3: Simplification of basic tetracyclic core of higher iridoids

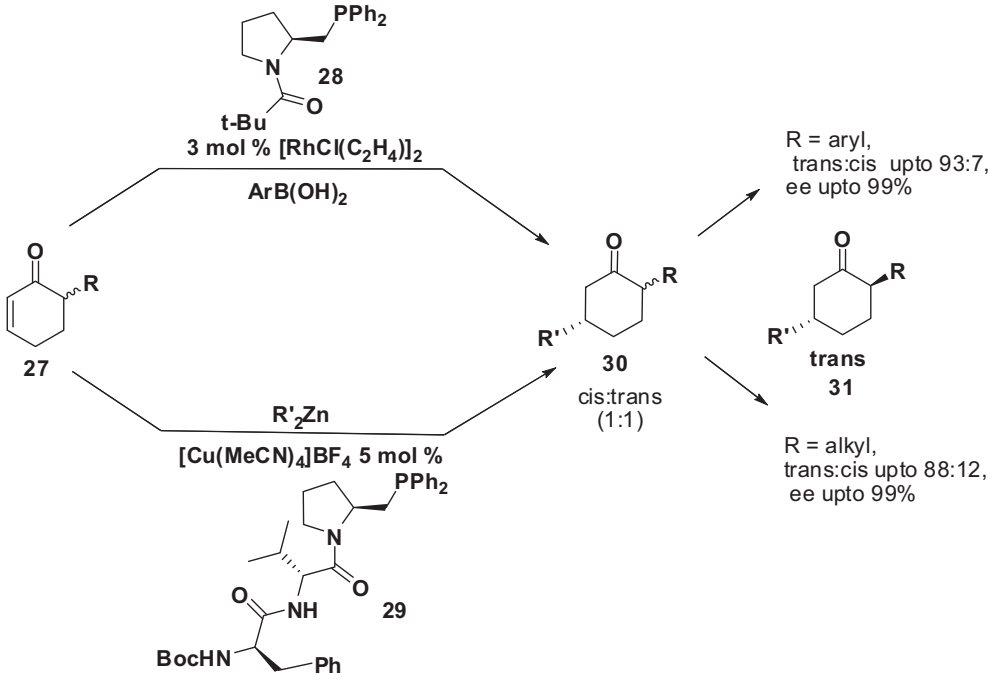
We visualized the synthesis of cyclopentane framework **25,** holding three contigious stereocentres with required stereochemistry, utilizing the organocatalyzed intramolecular aldol cyclization of precursor **26** as a key step. An advantage of using this strategy is that either enantiomeric product may be obtained simply by using (*S*)- or (*R*)-proline, whereas the biocatalysis route may be limited to products of a single absolute configuration.

As our retrosynthetic design (discussed in Chapter 1) for the synthesis of **26** requires *chiral* 2,5-dialkylcyclohexanone as starting material, we initially focused our attention on developing a new methodology for its scalable synthesis. We planned the synthesis of *chiral* 2,5-dialkylcyclohexanone *via* catalytic asymmetric conjugate addition reaction, one of the most powerful C-C bond-forming reactions.[3]

2.3 Synthetic approaches towards the synthesis of 2,5-dialkyl cyclohexanones

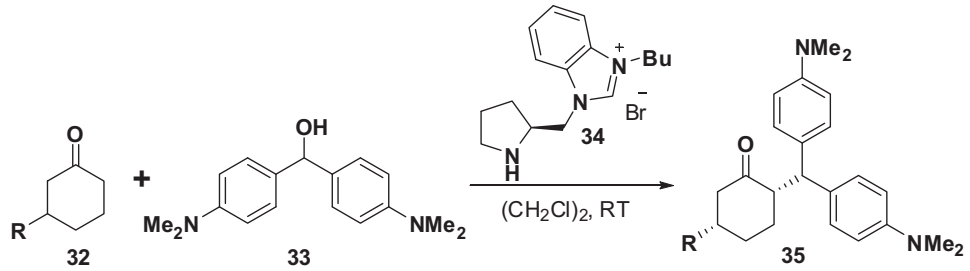
Careful literature survey revealed that only three methods are known for the synthesis of chiral 2,5-dialkyl cyclohexanones. Tomioka *et al.* have reported the synthesis of 2,5-dialkyl cyclohexanones (Scheme 2.4) by catalytic asymmetric conjugate addition of arylboronic acids on racemic 6-substituted cyclohexenones (**27**) catalyzed by chiral amidophosphane-$[RhCl(C_2H_4)]_2$.[4] They have also demonstrated the kinetic resolution of 6-substituted cyclohexenone **27** utilizing asymmetric conjugate addition of dialkylzinc

reagents to 6-substituted cyclohexenones using chiral amidophosphane–copper (I) complexes[5] (**29**). In both these cases conjugate addition gave nearly equimolar mixture of the corresponding *trans*- and *cis*- disubstituted cyclohexanones **30** with good enantioselectivity. Epimerization of the *cis/trans* mixture with DBU or NaOMe led to the formation of thermodynamically more stable *trans* **31** with good enantioselectivity (up to 98% *ee*) but moderate *trans:cis* ratio (max. 5:1).



Scheme 2.4: Tomioka *et al.* approach for 2,5-dialkyl cyclohexanones

Luo *et al*. observed kinetic resolution while synthesizing *cis*-2,5-disubstituted cyclohexanones by α-alkylation of 3-substituted cyclohexanone (**32**), catalyzed by functionalized Chiral Ionic Liquid. Although, diasteterselectivity for this reaction was good, reaction suffered from moderate to low enantioselectivity[6] (59-80%) (Scheme 2.5).



Scheme 2.5: Luo's approach for 2,5-dialkyl cyclohexanones

From the above reports it appeared to us that known methods for the preparation of 2,5-dialkyl cyclohexanones have following drawbacks:

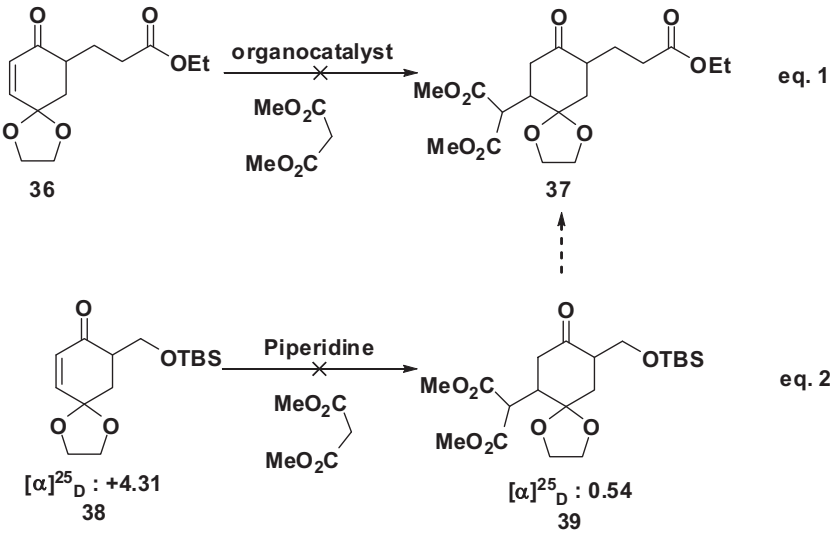
Tamioka's approach suffers from the use of a strong base in addition to an organometallic reagent which limits the choice of functional groups on the cyclohexanone. On the other hand, the approach of Luo *et al.* is based on kinetic resolution resulting the required molecule in only moderate yield (50-80%) and enantioselectivity (59-80%). We, therefore, felt that there is a scope for substantial improvement in selectivity and functional group tolerance in the synthesis of these classes of molecules. We planned the synthesis of 2,5-dialkyl cyclohexanones utilizing an organocatalytic conjugate addition reaction owing to its following advantages over organometallics catalysts[7]:

i) Organic molecules are generally insensitive to oxygen and moisture in the atmosphere.

ii) Simple organocatalysts are usually cheap to prepare and readily accessible and, thus, suitable for small-scale reactions to industrial-scale reactions.

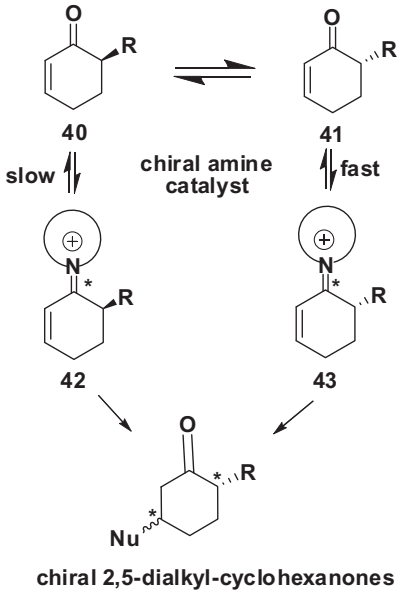
iii) Organocatalyst are non-toxic and environmentally friendly, making it attractive for synthesis of pharmaceutical products.

2.4 Developing new concept for the synthesis of 2,5-dialkyl cyclohexanones:



Scheme 2.6: Initial attempts for synthesis of chiral-2,5-dialkylcyclohexanone

In our preliminary studies, we investigated conjugate addition of dimethyl malonate on *rac* 6-substituted cyclohexenone **36** using organocatalyst **45a** (Figure 2.2) for the synthesis of **37**(Scheme 2.6, eq. 1). However, the attempt failed to produce any result. Further, we attempted conjugate addition of malonate on enantioenriched enone **38** in the presence of organocatalyst **45a** and piperidine (or pyrrolidine) as a base, the desired product **39** was not detected instead racemization of starting material occurred (Scheme 2.6, eq. 2).



Scheme 2.7: DKR Hypothesis

This unexpected racemization was tentatively rationalized by implicating iminium/enamine tautomerization as shown in Scheme 2.7. In presence of a base, the enatiomers of 6-substituted enones (**40** and **41**) were considered to be in equilibrium with each other and rate for formation of iminium ion with each of these enantiomers (**40** and **41)** may vary[8]. This difference in rate for the formation of iminium ion will lead to the enantioenriched iminium ion diastereomer and conjugate addition on which (mixture of **42** and **43**) would produce enantiomerically enriched 2,5-dialkylcyclohexanones stereoselectively. Further, fast equilibration of slower-forming diastereomer **42** in presence of a base will result in dynamic kinetic resolution (Scheme 2.7). To our knowledge

dynamic kinetic resolution of 6-substituted cyclohexanone via an organocatalytic conjugate addition is still unexplored.[9]

2.5 Preliminary studies for dynamic kinetic resolution of 6-alkyl cyclohexenones

We selected enone **36** for optimization of reaction conditions as masked ketone functionality at C4 was visualized as an additional handle in synthesising highly substituted cyclohexanone moiety. Enone **36** was synthesized from the ketone by IBX.MPO oxidation of the corresponding silylenol ether.[10] The initial studies for conjugate addition of the malonate to enone **36** began with scanning a series of optically pure secondary amines as a catalysts. The results obtained are summarized in Table 2.1. Tetrazole derivative of proline **48**[11] (Table 2.1, entry 6), turned out to be a good catalyst, giving 50% conversion and 86% enantioselectivity. Methylated tetrazole derivative of proline **49** could mediate the addition but with disappointing yield and enantioselectivity (Table 2.1, entry 7). Isolated conjugate adduct **37** was analysed by chiral stationary phase HPLC, and was indicated to be an enantiomerically enriched diastereomeric mixture (*dr* = 85:15, *er* = 93:7) **(**Table 1, entry 6). Compound **37** was characterised by ^{1}H and ^{13}C NMR studies. The ^{1}H spectrum showed the disappearance of enone proton at δ 5.99 (d, *J*=10.0 Hz, 1 H), 6.56 (dd, *J*=10.2, 1.9Hz, 1 H) and appearance of a doublet at δ 3.68 (d, *J* = 7.3 Hz, 1 H) and two sharp singlets at δ 3.72 and 3.73, each integrating for three protons indicating the presence of malonate group in conjugate adduct **37**. Similarly ^{13}C NMR spectrum showed disappearance of enone olefinic peaks at δ 130.2 and 145.2, and appearance of peaks at δ 52.6, 52.4, 168.3 and 168.4 indicating presence of dimethyl malonate group in conjugate adduct.

The stereochemical assignments for major and minor diastereomer of **37** was done as *trans* and *cis* respectively (isolated by preparative HPLC column: Kromasil RP-8, acetinitrile: H_2O = 35:65, wavelength: 220 nm) based on extensive (HSQC, COSY, HMBC and NOESY) NMR spectral studies (Figure 2.3). The relative stereochemistry of 2,5-dialkyl substituents of major diastereomer of **37** was further confirmed to be *trans* using X-Ray crystallographic analysis[12] (Figure 2.4). Origin of *trans* stereoselectivity in this reaction can be attributed to combined effects of electronic and steric factors[13] directed by the tetrazole moiety from only one face of the enone moiety. We were delighted to find the

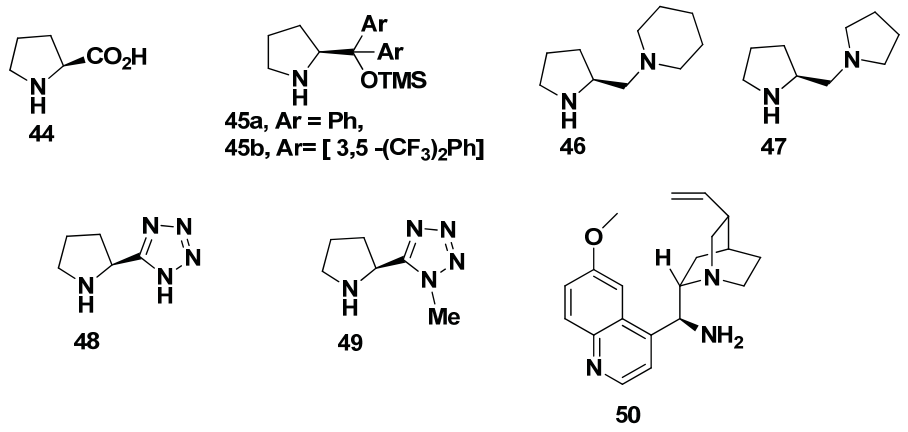
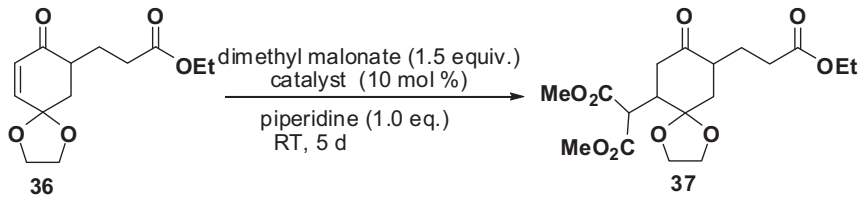


Figure 2.2: Catalyst scanned

Table 2.1 Screening of catalyst for DKR studies[a]



Sr.no.	Catalyst	Solvent	Convertion[b] %	*dr* [c]	*er* [d]
1	**44**	CH_2Cl_2	NR	-	-
2	**45a**	CH_2Cl_2	NR	-	-
3	**45b**	CH_2Cl_2	NR	-	-
4	**46**	CH_2Cl_2	NR	-	-
5	**47**	CH_2Cl_2	NR	-	-
6	**48**	CH_2Cl_2	50	85:15	93:7
7	**49**	CH_2Cl_2	5	65:35	47:53
8	**50**	CH_2Cl_2	5	49:51	92:8

[a]Enone (1 mmol), catalyst (10 mol%), dimethyl malonate (1.5 mmol), piperidine (1 mmol), solvent 3 mL, 5 days, RT (25°C). [b]Conversion monitored by GC. [c]Diastereomeric ratio determined either by HPLC or NMR. [d] Enantiomeric excess determined by chiral stationary phase HPLC. NR = no reaction.

recovered starting material **36** as a racemic mixture on analysis by chiral stationary phase HPLC. Furthermore, the recovered **36** when reused for the reaction gave identical results, indicating its reusability.

In order to further improve enantioselectivity and diastereoselectivity, we even evaluated primary amine based catalyst **50**,[14] derived from cinchona alkaloid, but the results were not very encouraging as **37** was formed only with 5% conversion and without any diastereoselectivity, however, the enantioselectivity (*er* = 92:8) obtained was excellent.

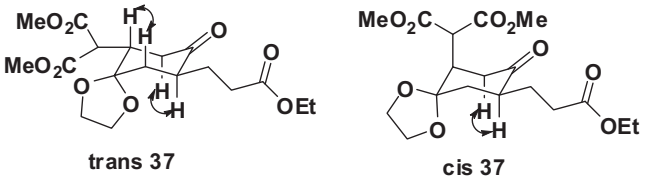


Figure 2.3: Relative stereochemistry of diastereomers of **37**

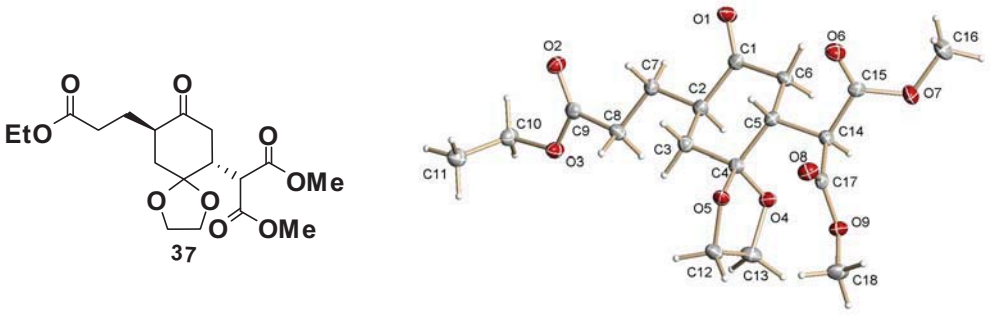


Fig.2.4 ORTEP diagrams of **37**. Ellipsoids are drawn at 50% probability. Hydrogen atoms omitted for clarity.

In addition to our requirement of chiral *trans*-2,5-dialkylcyclohexanones in the proposed total synthesis of iridoids, they are also structural component of several biologically active natural terpenes such as Eudesmalonide[15a] (**51**), Meristotropic acid[15b] (**52**), Wiedemannic acid[15c] (**53**) (Figure 2.5). These structural frameworks have even been used as versatile building blocks for the synthesis of many complex structures with pharmacological importance.[16] Most of the syntheses of such compounds have either relied on the chiral pool approach[16] starting with menthone (**54**), dihydrocarvone (**55**) and isopulgenone (**56**) (Figure 2.5) or kinetic resolution of racemic substituted cyclohexanones.

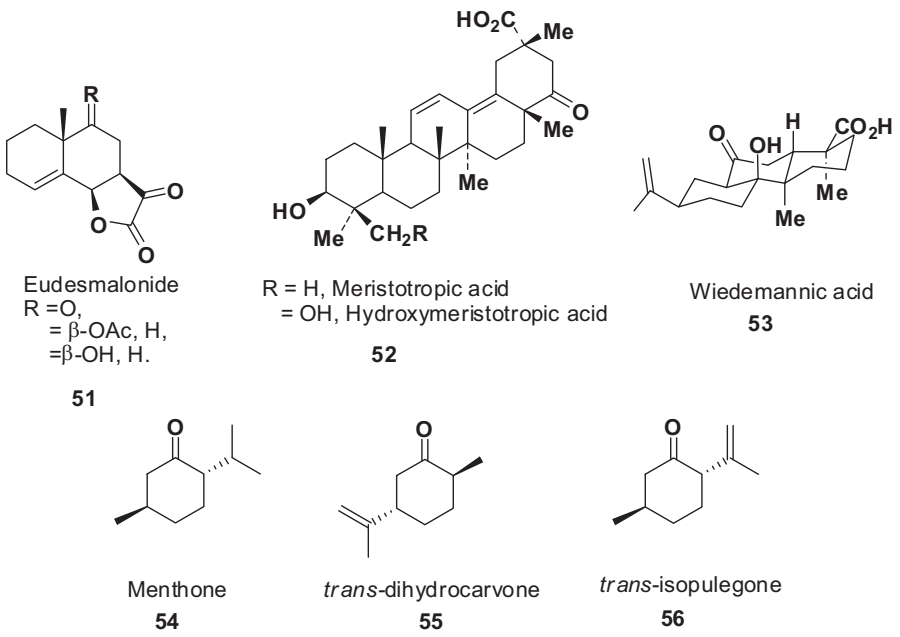


Figure 2.5: Natural products with *trans*-2,5-dialkyl cyclohexanone framework

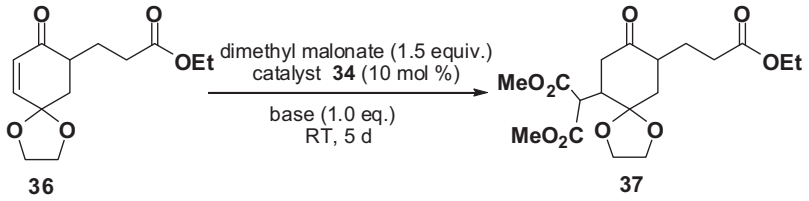
In order to further optimise the yield and enantioselectivity of **37** from our DKR strategy, different solvent-base combinations were tried and the results are discussed in the proceeding sections.

2.6 Optimization studies with different Solvent-base combinations

The effects of various solvents on conjugate addition of malonate on enone **36** were examined to improve enantioselectivity and diastereoselectivity, and the results are summarized in Table 2.2. Most organic solvents were ineffective except for chlorinated solvents such as dichloromethane and chloroform. In chloroform the reaction could proceed with 70% conversion with 85:15 *dr* and 94:6 *er* (Table 2.2, entry 7). This observation can be correlated with Guttman's acceptor number[17] (AN) (AN of acetonitrile 18.9, DMSO 19.3, CH_2Cl_2 20.4, $CHCl_3$ 23.1), as solvent with a higher AN is known to enhance the reactivity of intermediate iminium cation thus improving the conversion. Among the solvents screened, chloroform was the best and provided conjugate adduct in 70% yield and was therefore chosen for further synthetic studies. It was clear from the recorded results during the optimization of DKR that changing the base, affects diastereoselectivity as well as enantioselectivity. It may be possible that malonate and the base form a contact ion pair

which participates in conjugate addition, thus, affecting diastereoselectivity and enantioselectivity. Among the different solvents and bases screened for DKR, a

Table 2.2: Base and solvent studies[a]



36 37

Sr.no.	Solvent	Base	Conversion %[b]	*dr*[c]	*er*[d] (major diastereomer)
1	MeCN	piperidine	4	2:1	ND
2	THF	piperidine	NR	-	-
3	$PhCH_3$	piperidine	NR	-	-
4	EtOH	piperidine	NR	-	-
5	DMF	piperidine	3	-	ND
6	DMSO	piperidine	10	1:5	12:88
7	$CHCl_3$	piperidine	70	85:15	94:6
8[e]	$CHCl_3$	piperidine	NR	-	-
9	$CHCl_3$	-	NR	-	-
10	$CHCl_3$	NEt_3	NR	-	-
11	$CHCl_3$	DBU	20	3:1	60:40
12	$CHCl_3$	pyrrolidine	60	87:13	72:28
13	$CHCl_3$	K_2CO_3	NR	-	-
14	$CHCl_3$	pyridine	SM decompose	-	-

[a]Enone (1.0 mmol), catalyst **48** (10 mol%), dimethylmalonate (1.5 mmol), base (1.0 mmol), solvent (3 mL), 5 days, RT (25 °C). [b]Determined by GC analysis. [c]Diastereomeric ratio determined either by HPLC or NMR. [d]Enantiomeric excess determined by chiral stationary phase HPLC and mentioned only for major diastereomer. [e]No catalyst used. NR = no reaction, ND = not determined. THF = tetrahydrofuran, DMF = dimethylformamide, DMSO = dimethylsulfoxide.

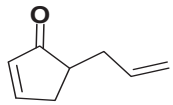
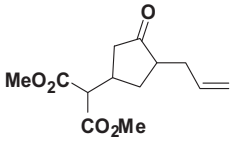
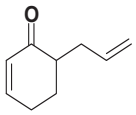
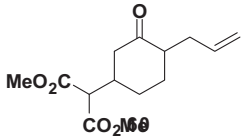
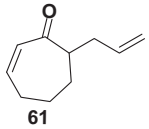
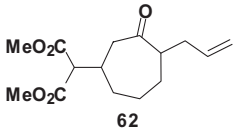
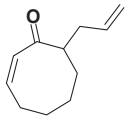
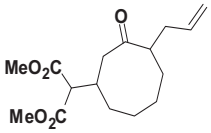
combination of chloroform and piperidine was found to be the best, giving better

conversion and stereoselectivity. The bulk scale (up to 20.0 g of **36**) DKR gave **37** with almost same enantioselectivity and diastereoselectivity (*dr* = 70:30, *er* = 94:6) providing a scalable methodology for the synthesis of chiral *trans*-2,5-dialkylcyclohexanone. Without any catalyst or base additive, the formation of conjugate adduct was not observed (Table 2.2, entries 8 and 9). Other variations in reaction conditions such as the effect of malonate concentration and temperature were also evaluated systematically in an attempt to improve the yield and selectivity. For example, increasing the malonate concentration (3 equiv.) did not improve reaction conversion rather made purification of **37** difficult, as the difference in R_f between dimethyl malonate, the starting enone and the conjugate adduct (product) was very small. Surprisingly, conducting reaction at a lower temperature (10 $^{\circ}$C) did not improve enantioselectivity (*dr* = 87:13, er = 94:6), instead, merely decreased the rate of reaction.

2.7 Effect of ring size on DKR

Having established the optimal reaction condition, effect of ring sizes of enones on DKR was examined and results are summarized in Table 2.3. For example, 5-allylcyclopentenone (**57**) underwent conjugate addition with good conversion (80%) but with low stereoselectivity (*dr* = 82:18, *er* = 66:34) as compared to its 6-membered congener (**59**). 6-Allylcyclohexenone (**59**) gave the required conjugate adduct (**60**) with excellent diastereoselectivity (Table 2.3, entry 2). Surprisingly, **61** did not undergo DKR under our standard reaction conditions.[18] In contrast, **63** underwent conjugate addition (60% conversion) with poor diastereoselectivity (60:40) but without any enantioselectivity (52.15:47.85) (Table 2.3, entry 4).

Table 2.3 Studies on effect of ring size of enones on DKR[a]

Sr.no.	Starting enone	Donor	Product	Yields % [b]	dr [c]	er [d] Major (Minor)
1	 57	A	 58	80	82:18	66:34 (41:59)
2	 59	A		92	99:1	87:13
3	 61	A	 62	NR	-	-
4	 63	A	 64	70	60:40	50.4:49.6 (52.2:47.8)

A = dimethylmalonate

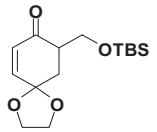
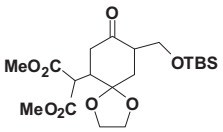
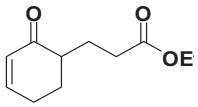
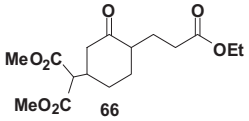
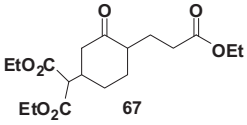
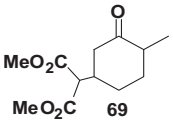
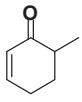
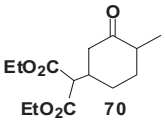
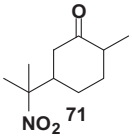
[a]Enone (1 mmol), catalyst **48** (10 mol %), malonate (1.5 mmol), piperidine (1 mmol), $CHCl_3$ (3 mL), 5 days, RT (25°C). [b]Isolated yields on purification [c]Diastereomeric ratio determined either by HPLC or NMR [d]Enantiomeric excess determined by chiral stationary phase HPLC.

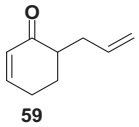
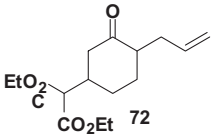
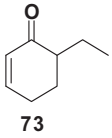
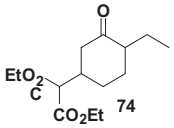
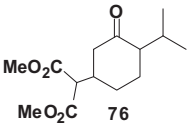
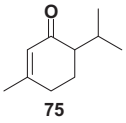
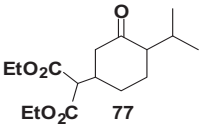
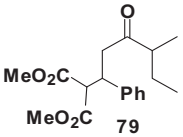
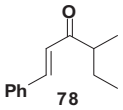
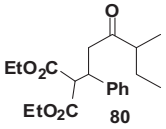
2.8 Evaluation of the Scope of DKR

In order to widen the scope of the methodology and to study the tolerance of common functional groups, we decided to study different 6-alkyl substituted cyclohexenones under standard reaction conditions. We restricted our study with the use of dimethyl and diethyl malonate only, owing to the utility of the conjugate addition product.[19]

It was observed that **38**, having the sterically bulky TBS group on an alkyl chain at C6 decreased diastereoselectivity (*dr* = 60:40) and enantioselectivity *(er* = 90:10) as compared to **36**. Enones without any substitution at C4 (e.g. **65**, **68**, **59**, **73**) gave **e**xcellent yields (92-95%) (Table 2.4).

Table 2.4 Generalization of substrate scope for DKR[a]

Sr.no.	Starting enone	Michael donor	Conjugate adduct	yield[b] %	*dr* [c]	*er* [d] Major (Minor)
1	 **38**	A	 **39**	80	60:40	90:10 (81:19)
2	 **65**	A	 **66**	95	85:15	84:16 (86:14)
3		B	 **67**	95	96:4	90:10
4		A	 **69**	95	99:1	79:21
5	 **68**	B	 **70**	95	42:58	88:12 (87:13)
6		C	 **71**	75	94:6	88:12

7	 59	B	 72	90	91:9	91:9 (89:11)
8	 73	B	 74	95	75:25	88:12 (87:13)
9		A	 76	NR	-	-
	 75					
10		B	 77	NR	-	-
11		A	 79	40	50.2:49.8	52:48 (51:49)
	 78					
12		B	 80	35	78:22	50.5:49.5 (92.1:7.9)

A = dimethylmalonate, B = diethylmalonate, C = 2-nitropropane;

[a]Enone (1 mmol), catalyst **48** (10 mol %), malonate (1.5 mmol), piperidine (1 mmol), $CHCl_3$ (3 mL), 5 days, RT (25°C).[b]Isolated yields on purification [c]Diastereomeric ratio determined either by HPLC or NMR. [d]Enantiomeric excess determined by chiral stationary phase HPLC. NR = no reaction.

Generally, better enantiomeric ratios were observed using diethyl malonate as nucleophile in comparison to dimethyl malonate (Table 2.4, entries 2 and 3; 4 and 5; table 2.3, entry 2 and Table 2.4, entry 7). 6-Methyl cyclohexenone (**68**), gave considerable lower

diastereoselectivity on conjugate addition with diethyl malonate in comparison to dimethyl malonate (Table 2.4, entries 4, 5). Since compound **60** and **69** were diastereomerically pure, we carried out extensive NMR studies to generalise the *trans*-relative stereochemical outcome of DKR (Figure 2.6).

Next we planned quaternary centre generation by conjugate addition on piperitone (**76**), however, no conjugate addition product was isolated. Aliphatic enone **78**, when used as a substrate for DKR, gave very low diastereoselectivity and enantioselectivity (Table 2.4, entry 11, 12).

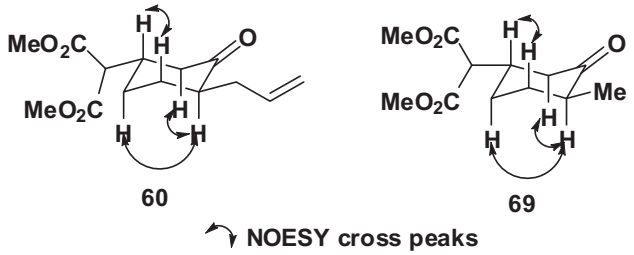


Figure 2.6 Relative stereochemistry confirmation using NMR

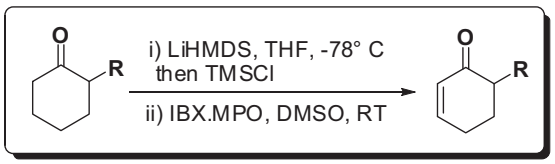
To further broaden the scope of the reaction, we carried out the conjugate addition of 2-nitropropane on **68** which gave corresponding conjugate adduct **71** in excellent diastereoselectivity (*dr* = 94:6) and enantioselectivity (*er* = 88:12) (Table 2.4, entry 6).

2.9 Conclusion

In summary, we have reported for the first time a conceptually new strategy for the synthesis of chiral *trans*-2,5-dialkylcyclohexanones by organocatalyzed DKR via asymmetric conjugate addition of dialkylmalonate on 6-substituted cyclohexenones. Reaction conditions show high functional group tolerance. As required, we could scale up this reaction up to 20.0 g starting from enone without significant change in stereochemical outcome. In the proceeding chapter, we shall comprehensively describe our efforts towards the synthesis of tetracyclic core of higher iridoids starting with compound **37**.

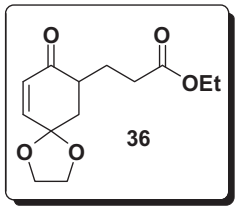
2.10 Experimental Section

General procedure for synthesis of enone:[9]



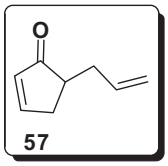
To a cold (-78 °C) solution of ketone (2.0 mmol, 1.0 equiv.) in THF (20 mL) was added LiHMDS (5.0 mmol, 2.5equiv. 1.0 M in hexanes) dropwise over period of 10 min. After stirring for 30 min. at same temperature, TMSCl (5.0 mmol, 2.5 equiv.) was added drop wise over period of 5 min and reaction mixture was stirred for another 30 min, and then warmed to room temperature. Upon disappearance of the starting material (monitored by TLC), the reaction mixture was poured in water (10 mL) and the biphasic reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (1 × 20 mL) and concentrated. The crude TMS enol ether was dried under reduced pressure to minimize the amount of $(TMS)_2O$ present, as this was known to be detrimental for the desired reaction. The IBX.MPO solution (prepared by dissolving IBX and MPO (4.0 equiv.) in DMSO (0.4 M) in an equimolar ratio at room temperature) was added in one portion at ambient temperature to the crude TMS enol ether dissolved in a minimum of DMSO. Reaction mixture was stirred vigorously and progress was monitored by means of thin-layer chromatography. Upon completion, the reaction mixture was diluted with aqueous $NaHCO_3$ (5%) and extracted with EtOAc (3 times). The combined organic phase was filtered through a pad of celite, washed with saturated aqueous $NaHCO_3$, water, and brine. After drying over anhy. $NaSO_4$, the solvent was removed under reduced pressure to yield the crude product, which was purified further by means of column chromatography.

Ethyl 3-(8-oxo-1,4-dioxaspiro[4.5]dec-9-en-7-yl)propanoate (36):



Yield:	**:**	95 %
M.P.	**:**	55 ºC
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	2981, 3892, 1731, 1683, 1421, 1447, 1380, 1252, 1195, 1096, 1031, 949
^{1}H NMR ($CDCl_3$, 400 MHz) δ	**:**	1.26 (t, *J* = 7.1 Hz, 3 H), 1.75 (d, *J* = 6.3 Hz, 1 H), 2.00 - 2.08 (m, 1 H), 2.11 - 2.23 (m, 2 H), 2.38 - 2.46 (m, 2 H), 2.68 - 2.78 (m, 1 H), 3.94 - 4.18 (m, 6 H), 5.99 (d, *J* = 10.0 Hz, 1 H), 6.56 (dd, *J* = 10.2, 1.9 Hz, 1 H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	14.2, 24.7, 31.6, 38.6, 43.6, 60.4, 64.9, 65.2, 104.2, 130.2, 145.2, 173.3, 200.2
Mass: m/z (%)	**:**	409.14 (M + Na, 100), 387.2 (M+H, 25), 341(45), 249 (16), 241(22)

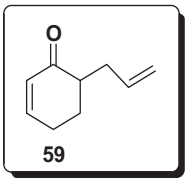
5-allylcyclopent-2-enone (57):



57

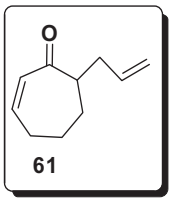
Yield:	**:**	75 %
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	3019, 2983, 1701, 1588, 1429, 1215, 1046, 755, 669
^{1}H NMR ($CDCl_3$, 500 MHz) δ	**:**	2.10 - 2.18 (m, 1 H), 2.37 - 2.45 (m, 2 H), 2.50 - 2.58 (m, 1 H), 2.79 - 2.87 (m, 1 H), 4.98 - 5.14 (m, 2 H), 5.74 (ddt, *J* = 17.0, 10.1, 6.9 Hz, 1 H), 6.10 - 6.24 (m, 1 H), 7.63 - 7.76 (m, 1 H)
^{13}C NMR ($CDCl_3$, 126 MHz) δ	**:**	34.8, 35.2, 43.9, 116.9, 133.7, 135.1, 163.8, 211.6
Mass: m/z (%)	**:**	145.46 (M + Na, 100), 123.16 (M+H, 25)

6-allylcyclohex-2-enone (59):



Yield:	**:**	90 %
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	2930, 2862, 1677, 1639, 1388, 1222, 912
^{1}H NMR ($CDCl_3$, 500 MHz) δ	**:**	1.68 – 1.82 (m, 1H), 2.07 - 2.17 (m, 2 H), 2.31 - 2.41 (m, 3 H), 2.59 - 2.66 (m, 1 H), 5.02 - 5.09 (m, 2 H), 5.73 - 5.83 (m, 1 H), 6.00 (dt, *J* = 9.99, 1.72 Hz, 1 H), 6.91 - 6.98 (m, 1 H)
^{13}C NMR ($CDCl_3$, 126 MHz) δ	**:**	25.2, 27.3, 33.6, 46.1, 116.7, 129.5, 136.1, 149.8, 200.9
Mass: m/z (%)	**:**	159.15 (M + Na, 100), 137.45 (M+H, 25)

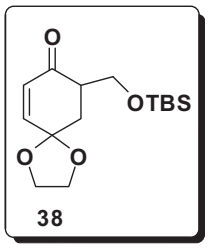
7-allylcyclohept-2-enone (61):



Yield:	**:**	87 %
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	3017, 2931, 1705, 1454, 1216, 1048, 915, 755, 667
^{1}H NMR ($CDCl_3$, 400 MHz) δ	**:**	1.43 - 1.53 (m, 1 H), 1.65 - 1.75 (m, 1 H), 1.84 - 1.98 (m, 2 H), 2.05 - 2.19 (m, 1 H), 2.39 - 2.50 (m, 2 H), 2.52 - 2.61 (m, 1 H), 2.63 - 2.74 (m, 1 H), 4.97 - 5.09 (m, 2 H), 5.77 (ddt, *J* = 17.0, 10.1, 6.9, 6.9 Hz, 1 H), 5.99 - 6.07 (m, 1 H), 6.61 (ddd, *J* = 11.7, 6.6, 4.5 Hz, 1 H)

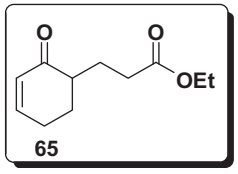
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	25.2, 28.7, 29.8, 35.7, 51.6, 116.6, 132.7, 136.4, 146.0, 205.2
Mass: m/z (%)	**:**	183.16 (M + Na, 100), 151.49 (M + H, 51)

9-(((tert-butyldimethylsilyl)oxy)methyl)-1,4-dioxaspiro[4.5]dec-6-en-8-one (38):



Yield:	**:**	95 %
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	3583, 3444, 2957, 2930, 1683, 1216, 1141, 758
^{1}H NMR ($CDCl_3$, 400 MHz) δ	**:**	: 0.05 (d, *J* = 2.0 Hz, 6 H), 0.87 (s, 9 H), 2.21 - 2.31 (m, 2 H), 2.73 - 2.82 (m, 1 H), 3.81 - 3.88 (m, 1 H), 3.91 - 4.00 (m, 2 H), 4.01 - 4.15 (m, 3 H), 5.99 (d, *J* = 10.0 Hz, 1 H), 6.60 (dd, *J* = 10.0, 1.7 Hz, 1 H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	5.5, 18.2, 25.8, 35.5, 46.6, 61.4, 64.8, 65.1, 104.5, 130.5, 145.9, 198.8
Mass: m/z (%)	**:**	321.1 (M + Na, 100), 310.3 (4), 283.1 (1)

Ethyl 3-(2-oxocyclohex-3-en-1-yl)propanoate (65):



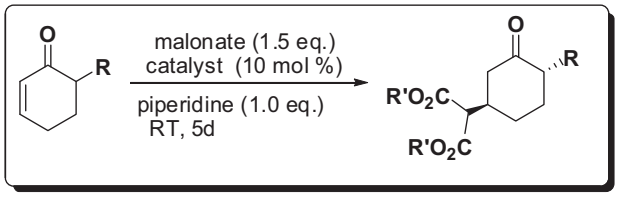
Yield:	**:**	90 %
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	2934, 1732, 1676, 1425, 1388, 1177, 1032
^{1}H NMR ($CDCl_3$, 500 MHz) δ	**:**	1.25 (*J* = 7.2, 3 H), 1.67 - 1.81 (m, 2 H), 2.07 - 2.18 (m, 2 H), 2.31 - 2.44 (m, 5 H), 4.12 (q, *J* = 7.1 Hz, 2

H), 5.98 (dt, *J* = 10.1, 1.9 Hz, 1 H), 6.89 - 6.96 (m, 1 H)

^{13}C NMR ($CDCl_3$, 126 MHz) δ : 14.1, 24.7, 25.2, 28.1, 31.8, 45.7, 60.3, 129.4, 149.5, 173.5, 201.1

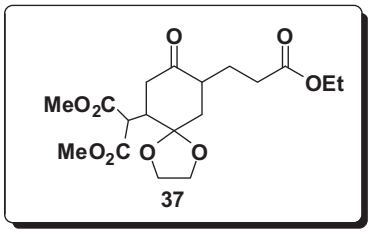
Mass: m/z (%) : 219.15 (M + Na, 100), 197.56 (M + H)

General procedure for DKR reaction:



To a stirred suspension of 6-substituted enones (0.2 mmol) and catalyst (10 mol %) in $CHCl_3$ (2 mL) was added dialkylmalonate (0.3 mmol) and piperidine (0.2 mmol) at room temperature. The progress of the reaction was monitored by thin layer chromatography and gas chromatography. After 5 days of stirring when no further conversion was noticed, reaction was quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to obtain conjugate addition product.

Dimethyl-2-(9-(3-ethoxy-3-oxopropyl)-8-oxo-1,4-dioxaspiro[4.5]decan-6-yl)malonate (37):



Yield: : 68 %

M.P.	**:**	81.9 ºC
$[\alpha]^{25}_{D}$		+19.12 (*c* 1.9, $CHCl_3$, 70 % *de*, 88 % *ee*)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	2982, 2955, 2903, 1732, 1435, 1155
^{1}H NMR ($CDCl_3$, 500 MHz) δ	**:**	1.23 (t, *J* = 5.0 Hz, 3 H), 1.47 - 1.60 (m, 2 H), 2.03 (dd, *J* = 14.8, 7.2 Hz, 1 H), 2.11 (dd, *J* = 13.4, 5.8 Hz, 1 H), 2.25 - 2.43 (m, 2 H), 2.50 (dd, *J* = 13.9, 4.7 Hz, 1 H), 2.63 (dd, *J* = 12.8, 7.0 Hz, 1 H), 2.69 - 2.78 (m, 1 H), 2.99 (ddd, *J* = 13.9, 7.0, 4.7 Hz, 1 H), 3.68 (d, *J* = 7.3 Hz, 1 H), 3.70 (s, 3 H), 3.72 (s, 3 H), 3.9 - 4.1 (m, 4 H), 4.1 - 4.1 (m, 2 H)
^{13}C NMR ($CDCl_3$, 126 MHz) δ (only for major diastereomer)	**:**	14.2, 23.9, 31.7, 39.0, 41.4 , 44.4, 45.4, 50.6, 52.4, 52.6, 60.3, 64.7, 65.0, 107.8, 168.3, 168.4, 173.3, 208.5
Mass: m/z (%)	**:**	425.28 (M + K, 41), 409.29 (M + Na, 100), 237 (50), 221 (47)
HRMS ESI (*m/z*):	**:**	$[M + H]^+$ calcd for $C_{18}H_{27}O_9$, 387.1650; found, 387.1654
HPLC(Kromasil OJ-H, *i-propanol: petroleum ether* 20:80, 0.5 mL/min, 220 nm)	**:**	major diastereomer: τ_R = 70.01 min. (major enantiomer), τ_R = 64.2 min. (minor enantiomer); minor diastereomer: τ_R = 53.15 min. (major enantiomer), τ_R = 44.03 min. (minor enantiomer)

Data for *trans* 37:

^{1}H NMR ($CDCl_3$, 500 MHz) δ	**:**	1.24 (t, *J* = 7.02 Hz, 3 H), 1.49 - 1.60 (m, 2 H), 2.04 (dq, *J* = 14.27, 7.25 Hz, 1 H), 2.12 (dd, *J* = 13.43, 5.80 Hz, 1 H), 2.31 (dt, *J* = 15.87, 7.63 Hz, 1 H), 2.35 - 2.44 (m, 1 H), 2.51 (dd, *J* = 14.04, 4.58 Hz, 1 H), 2.64 (dd, *J* = 13.12, 6.71 Hz, 1 H), 2.75 (t, *J* = 13.89 Hz, 1 H), 2.96 - 3.03 (m, 1 H), 3.69 (d, *J* = 7.02 Hz, 1 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 3.98 - 4.07 (m, 4 H),

4.11 (q, *J* = 7.22 Hz, 2 H)

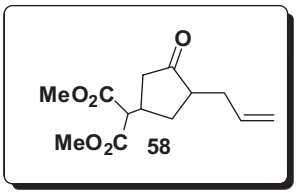
^{13}C NMR ($CDCl_3$, 126 MHz) δ : 14.2, 23.9, 31.9, 39.0, 41.4, 44.4, 45.1, 50.8, 52.4, 52.8, 60.3, 64.6, 65.0, 107.9, 166.3, 166.4, 173.3, 206.5

Data for *cis* 37:

^{1}H NMR ($CDCl_3$, 500 MHz) δ : 1.24 - 1.27 (t, 3 H), 1.61 (d, *J* = 6.71 Hz, 1 H), 1.90 - 1.98 (m, 1 H), 2.01 - 2.16 (m, 2 H), 2.30 - 2.37 (m, 2 H), 2.42 (dd, *J* = 15.26, 5.80 Hz, 1 H), 2.67 (dd, *J* = 10.83, 6.26 Hz, 1 H), 2.75 - 2.84 (m, 1 H), 2.98 - 3.10 (m, 1 H), 3.43 (d, *J* = 9.46 Hz, 1 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.92 - 4.09 (m, 4 H), 4.10 - 4.17 (m, 2 H)

^{13}C NMR ($CDCl_3$, 126 MHz) δ : 14.2, 24.7, 31.7, 37.7, 40.7, 43.2, 45.9, 51.9, 52.7, 60.4, 64.7, 64.8, 107.9, 168.1, 168.5, 173.2, 209.6

Dimethyl-2-(4-allyl-3-oxocyclopentyl)malonate (58):



58

Yield : 80 %

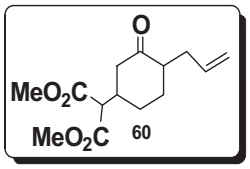
$[\alpha]^{25}_D$: +29.01 (*c* 1.2, $CHCl_3$, 64 % *de*, 32 % *ee*)

IR ν_{max} cm^{-1} ($CHCl_3$) : 2956, 1735, 1437, 1223, 1156

^{1}H NMR ($CDCl_3$, 400 MHz) δ : 1.27 - 1.38 (m, 1 H), 1.96 (dd, *J* = 18.70, 11.67 Hz, 1 H), 2.03 - 2.19 (m, 1 H), 2.25 - 2.44 (m, 2 H), 2.44 - 2.63 (m, 2 H), 2.71 - 2.84 (m, 0.77 H), 2.9-2.96 (m, 0.19 H), 3.30 - 3.39 (d, *J* = 10.04, 1 H), 3.74 (s, 3 H), 3.77 (s, 3 H), 4.93 - 5.12 (m, 2 H), 5.63 - 5.78 (m, 1

		H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	33.4, 33.6, 34.1, 42.8, 49.3, 52.6, 56.2, 116.81, 135.3, 168.4, 168.5, 216.8
Mass: m/z (%)	**:**	277 (M + Na, 100), 240 (12), 195 (8)
HRMS ESI (*m/z*):	**:**	$[M + Na]^+$ calcd for $C_{13}H_{18}O_5Na$, 277.1046; found, 277.1054
HPLC(Chiralpak AS-H, *i-propanol* : *petroleum ether* 2.0:98.0, 0.5 mL/min, 230 nm)	**:**	major diastereomer: τ_R = 57.392 min. (major enantiomer), τ_R = 69.808 min. (minor enantiomer); minor diastereomer: τ_R = 87.192 min. (major enantiomer), τ_R = 65.525 min. (minor enantiomer)

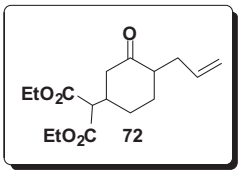
Dimethyl 2-(4-allyl-3-oxocyclohexyl)malonate (60):



Yield	**:**	92 %
$[\alpha]^{25}_D$	:	+6.12 (*c* 1.03, $CHCl_3$, 98 % *de*, 74 % *ee*)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	2953, 1752, 1735, 1710, 1435, 1252, 1157
^{1}H NMR ($CDCl_3$, 400 MHz) δ	**:**	1.27 - 1.40 (m, 1 H), 1.49 - 1.62 (m, 1 H), 1.93 - 2.02 (m, 2 H), 2.12 - 2.20 (m, 1 H), 2.24 - 2.34 (m, 2 H), 2.40 - 2.60 (m, 3 H), 3.34 (d, *J* = 7.53 Hz, 1 H), 3.75 (s, 3 H), 3.75(s, 3 H), 4.97 - 5.06 (m, 2 H), 5.70 - 5.83 (m, 1 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	29.29, 31.1, 33.2, 39.1, 45.4, 49.46, 52. 6, 56.8, 116.5, 136.1, 168.1, 168.2, 209.5
Mass: m/z (%)	**:**	307.31 (M + K, 20), 291.14 (M + Na, 100)
HRMS ESI (*m/z*):	**:**	$[M + Na]^+$ calcd for $C_{14}H_{20}O_5Na$, 291.1203; found, 291.1210
HPLC (Chiralcel OJ-H, *i-propanol* : *petroleum*	**:**	major diastereomer: τ_R = 19.308 min. (major enantiomer), τ_R = 70.667 min. (minor enantiomer);

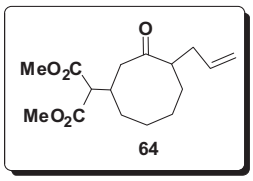
ether 05:95, 0.5 mL/min, 230 nm)	minor diastereomer: τ_R = 62.317 min. (major enantiomer), τ_R = 58.517 min. (minor enantiomer)

Diethyl 2-(4-allyl-3-oxocyclohexyl)malonate (72):



Yield:	**:**	90 %
$[\alpha]^{25}_D$	:	7.38 (*c* 1.45, $CHCl_3$, 82 % *de*, 82 % *ee*)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	2981, 2937, 1750, 1732, 1713, 1155
^1H NMR ($CDCl_3$, 400 MHz) δ	**:**	1.27 (td, *J* = 7.15, 1.00 Hz, 6 H), 1.30 - 1.40 (m, 1 H), 1.57 (qd, *J* = 12.72, 3.26 Hz, 1 H), 1.91 - 2.03 (m, 2 H), 2.09 - 2.21 (m, 1 H), 2.24 - 2.35 (m, 2 H), 2.42 - 2.59 (m, 3 H), 3.29 (d, *J* = 7.53 Hz, 1 H), 4.16 - 4.25 (m, 4 H), 4.96 - 5.08 (m, 2 H), 5.70 - 5.83 (m, 1 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	14.0, 29.3, 31.2, 33.2, 39.02, 45.4, 49.5, 57.0, 61.5, 116.4, 136.2, 167.7, 167.8, 209.7
Mass: m/z (%)	**:**	319.93 (M + Na, 25), 318.99 (100), 296.99(M + H, 32), 161.83 (33), 160.5 (100), 136.56 (100), 132.82(31)
HRMS ESI (*m/z*):	**:**	$[M + Na]^+$ calcd for $C_{16}H_{24}O_5Na$, 319.1516; found, 319.1523
HPLC (Chiralcel OJ-H, *i-propanol* : *petroleum ether* 0.5:99.5, 0.5 mL/min, 230 nm)	**:**	major diastereomer: τ_R = 38.183 min. (major enantiomer), τ_R = 42.85 min. (minor enantiomer); minor diastereomer: τ_R = 51.342 min. (major enantiomer), τ_R = 47.617 min. (minor enantiomer)

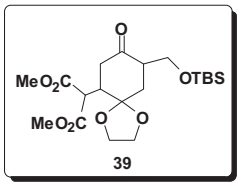
Dimethyl 2-(4-allyl-3-oxocyclooctyl) malonate (64):



64

Yield:	:	70 %
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2932, 1751, 1735, 1701, 1437, 1195, 1157
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	1.34 - 1.46 (m, 2 H), 1.50 - 1.63 (m, 3 H), 1.64 - 1.83 (m, 4 H), 2.05 - 2.14 (m, 1 H), 2.24 - 2.48 (m, 3 H), 2.75 - 2.85 (m, 1 H), 2.90 - 3.02 (m, 1 H), 3.35 (d, *J* = 7.53 Hz, 0.62 H), 3.46 (d, *J* = 7.53 Hz, 0.27 H), 3.72 - 3.78 (m, 6 H), 4.91 - 5.09 (m, 2 H), 5.59 - 5.82 (m, 1 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ (only for major diastereomer)	:	23.6, 25.4, 31.9, 33.2, 35.1, 37.2, 45.9, 50.0, 52.5, 52.5, 57.1, 116.7, 135.5, 168.7, 168.8, 216.8
Mass: m/z (%)	:	319.66 (M+23, 100), 297.72 (M+1,100), 265.92 (55), 264.58 (100), 246 (12), 232.91 (100)
HRMS ESI (*m/z*):	:	$[M + Na]^+$ calcd for $C_{16}H_{24}O_5Na$, 319.1516; found, 319.1524
HPLC (Kromasil 5-Amycoat, *EtOH:n-Hexane* 2.0:98.0, 0.5 mL/min, 230 nm)	:	major diastereomer: τ_R = 22.517 min. (major enantiomer), τ_R = 28.058 min. (minor enantiomer); minor diastereomer: τ_R = 46.867 min. (major enantiomer), τ_R = 83.650 min. (minor enantiomer)

Dimethyl 2- (9-((tert-butyldimethylsilyloxy)methyl)-8-oxo-1,4-dioxaspiro[4.5] decan-6-yl)malonate (39):

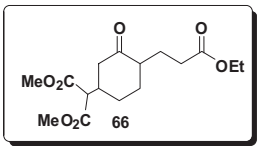


39

Yield:	:	80 %

$[\alpha]^{25}_D$	:	+ 6.0 (*c* 0.57, $CHCl_3$, 20 % *de*, 80 % *ee*)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2955, 2630, 1736, 1435, 1257, 1153, 837, 757
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	0.04 (s, 6 H), 0.87 (s, 9 H), 1.64 - 1.70 (m, 0.7 H), 1.79 (s, 0.3H), 2.30 (dd, *J* = 13.69, 5.87 Hz, 1 H), 2.51 (dd, *J* = 14.43, 4.65 Hz, 1 H), 2.66 - 2.81 (m, 2 H), 2.97 - 3.09 (m, 1 H), 3.64 - 3.72 (m, 2 H), 3.73 (s, 2 H), 3.72 (s, 4 H), 3.78 (d, *J* = 5.68 Hz, 0.3H), 3.87 (dd, *J* = 10.51, 4.16 Hz, 1 H), 3.97 - 4.08 (m, 4 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	:	-5.5, 18.2, 25.8, 35.7, 41.6, 43.9, 48.7, 50.8, 52.5, 52.6, 61.13, 64.6, 64.7, 64.9, 108.1, 168.4, 168.5, 207.9
Mass: m/z (%)	:	469.15 (M + K, 70), 453.21 (M + Na, 100), 150.25 (10)
HRMS ESI (*m/z*):	:	$[M + Na]^+$ calcd for $C_{20}H_{34}O_8NaSi$, 453.1915; found, 453.1930
HPLC (Kromasil 5-Amycoat, *i-propanol : petroleum ether* 1.5:98.5, 0.5 mL/min, 220 nm)	:	major diastereomer: τ_R = 20.14 min. (major enantiomer), τ_R = 21.78 min. (minor enantiomer); minor diastereomer: τ_R = 18.91 min. (major enantiomer), τ_R = 18.11 min. (minor enantiomer)

Dimethyl-2-(4-(3-ethoxy-3-oxopropyl)-3-oxocyclohexyl) malonate (66):

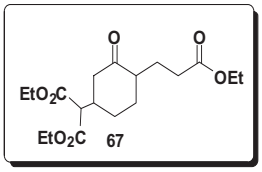


66

Yield:	:	95 %
$[\alpha]^{25}_D$	:	+6.42 (*c* 2.93, $CHCl_3$, 70 % *de*, 68 % *ee*)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2955, 1755, 1738, 1732, 1714, 1435, 1250, 1179, 1155

^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	1.24 (t, *J* = 7.09 Hz, 3 H), 1.31 - 1.44 (m, 1 H), 1.48 - 1.69 (m, 2 H), 1.91 - 2.17 (m, 3 H), 2.24 - 2.54 (m, 6 H), 3.29 - 3.36 (m, 1 H), 3.74 (s, 3 H), 3.75(s, 3H), 4.11 (q, *J* = 7.09 Hz, 2 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	:	14.2 , 24.3, 29.3, 31.7, 31.8, 39.2, 45.4, 48.9, 52.6, 56.7, 60.3, 168.09, 168.2, 173.5, 209.7
Mass: m/z (%)	:	351.54 (M + Na, 100), 319.78 (10), 297 (25), 151.15 (5)
HRMS ESI (*m/z*):	:	$[M + Na]^+$ calcd for $C_{16}H_{24}O_7Na$, 351.1414; found, 351.1422
HPLC (Chiralcel OD-H, *Et*OH: *n*-hexane 1.5:98.5, 0.5 mL/min, 230 nm)	:	major diastereomer: τ_R = 90.38 min. (major enantiomer), τ_R = 98.43 min. (minor enantiomer); minor diastereomer: τ_R = 70.03 min. (major enantiomer), τ_R = 66.67 min. (minor enantiomer)

Diethyl-2-(4-(3-ethoxy-3-oxopropyl)-3-oxocyclohexyl) malonate (67):

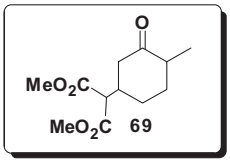


67

Yield:	:	95 %
$[\alpha]^{25}_D$	:	+7.91 (*c* 1.92, $CHCl_3$, 92 % *de*, 80 % *ee*)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2982, 2937, 1751, 1735, 1725, 1719, 1710, 1369, 1247, 1222, 1178, 1154
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	1.21 - 1.30 (m, 9 H), 1.31 - 1.44 (m, 1 H), 1.48 - 1.63 (m, 2 H), 1.94 - 2.17 (m, 3 H), 2.25 - 2.55 (m, 6 H), 3.27 - 3.31 (d, *J* = 7.53Hz, 1 H), 4.11 (q, *J* = 7.28 Hz, 2 H), 4.20 (qd, *J* = 7.19, 3.26 Hz, 4 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	:	14.0, 14.2, 24.3, 29.3, 31.7, 31.9, 39.1, 45.5, 48.9, 57.0, 60.3, 61.5, 167.7, 167.8, 173.5, 209.8
Mass: m/z (%)	:	379.14 (M + Na, 100), 368.5 (2), 151.44 (1)

HRMS ESI (*m/z*):	**:**	$[M + Na]^+$ calcd for $C_{18}H_{28}O_7Na$, 379.1727; found, 379.1738
HPLC (Chiralcel OD-H, *Et*OH: *n*-hexane 1.5:98.5, 0.5 mL/min, 230 nm)	**:**	major diastereomer: τ_R = 48.5 min. (major enantiomer), τ_R = 57.14 min. (minor enantiomer); minor diastereomer: τ_R = 40.5 min. (major enantiomer), τ_R = 37.5 min. (minor enantiomer)

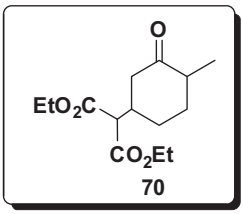
dimethyl 2-(4-methyl-3-oxocyclohexyl)malonate (69):



69

Yield:	**:**	95 %
$[\alpha]^{25}_D$	:	+3.98 (*c* 1.08, $CHCl_3$, 98 % *de*, 58 % *ee*)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	2935, 2956, 1735, 1713, 1436, 1251, 1157
^1H NMR ($CDCl_3$, 400 MHz) δ	**:**	1.02 (d, *J* = 6.53 Hz, 3 H), 1.38 (qd, *J* = 13.09, 3.39 Hz, 1 H), 1.58 (qd, *J* = 12.72, 3.51 Hz, 1 H), 1.88 - 1.98 (m, 1 H), 2.09 (ddd, *J* = 13.24, 6.09, 3.26 Hz, 1 H), 2.25 - 2.54 (m, 4 H), 3.34 (d, *J* = 7.78 Hz, 1 H), 3.74 (s, 3 H), 3.75 (s, 3 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	14.2, 29.4, 33.9, 39.1, 44.7, 45.1, 52.5, 56.8, 168.1, 168.2, 210.6
Mass: m/z (%)	**:**	281.15 (M + K, 100), 265.49 (M + Na , 42), 257.14(10)
HRMS ESI (*m/z*):	**:**	$[M + Na]^+$ calcd for $C_{12}H_{18}O_5Na$, 265.1046; found, 265.1054
HPLC (Chiralcel OD-H, *EtOH* :*n-hexane* 0.4:99.6, 0.5 mL/min, 230 nm)	**:**	major diastereomer: τ_R = 74.26 min. (major enantiomer), τ_R = 67.33 min. (minor enantiomer); minor diastereomer: τ_R = 58.33 min. (major enantiomer), τ_R = 54.95 min. (minor enantiomer)

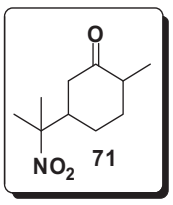
Diethyl 2-(4-methyl-3-oxocyclohexyl)malonate (70):



70

Yield:	**:**	95 %
$[\alpha]^{25}_D$	:	+ 5.26 (*c* 5.25, $CHCl_3$, 16 % *de*, 76 % *ee*)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	2964, 2937, 1715, 1733, 1713, 1243, 1156, 1032
^{1}H NMR ($CDCl_3$, 400 MHz) δ	**:**	1.03 (d, *J* = 6.53 Hz, 2.26 H), 1.10 (d, *J* = 7.03 Hz, 0.75 H), 1.27 (td, *J* = 7.09, 1.63 Hz, 6 H), 1.38 (qd, *J* = 13.13, 3.26 Hz, 0.8 H), 1.53 - 1.71 (m, 1.3 H), 1.89 - 2.00 (m, 1.27 H), 2.05 - 2.14 (m, 0.75 H), 2.27 - 2.54 (m, 4 H), 3.24 - 3.32 (m, 1 H), 4.20 (qd, *J* = 7.11, 3.51 Hz, 4 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	11.6, 11.7, 14.1, 21.8, 23.5, 25.0, 28.6, 29.4, 31.3, 37.8, 39.1, 42.8, 45.5, 51.2, 51.5, 56.0, 57.1, 61.5, 61.6, 61.7, 77.3, 167.8, 167.9, 167.9, 210.5, 212.5
Mass: m/z (%)	**:**	309.18 (M + K, 100), 293.43 (M + Na, 45), 154.46 (5)
HRMS ESI (*m/z*):	**:**	$[M + Na]^+$ calcd for $C_{14}H_{22}O_5Na$, 293.1359; found 293.1369
HPLC (Chiralcel OJ-H, *Et*OH:*n*-hexane 0.6:99.4, 0.7 mL/min, 230 nm)	**:**	major diastereomer: τ_R = 30.267 min. (major enantiomer), τ_R = 26.45 min. (minor enantiomer); minor diastereomer: τ_R = 25.008 min. (major enantiomer), τ_R = 28.5 min. (minor enantiomer)

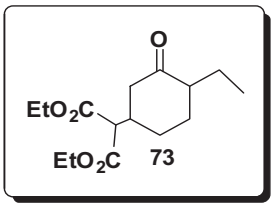
2-methyl-5-(2-nitropropan-2-yl)cyclohexanone (71):



71

Yield:	**:**	75 %
M.P.	**:**	Compound decomposes above 189 ºC
$[\alpha]^{25}_D$	:	9.67 (*c* 0.34, $CHCl_3$, 88 % *de*, 76 % *ee*)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	3019, 2400, 1540, 1475, 1215, 758, 66
^{1}H NMR ($CDCl_3$, 500 MHz) δ	**:**	0.97 (td, *J* = 7.32, 2.44 Hz, 0.6 H), 1.04 (d, *J* = 6.41 Hz, 3 H), 1.12-1.17 (m, 0.4 H), 1.30 - 1.39 (m, 1 H), 1.49 - 1.55 (m, 1 H), 1.58 (s, 3 H), 1.57 (s, 2 H), 1.76 - 1.82 (m, 1 H), 2.11 - 2.19 (m, 2 H), 2.30 - 2.44 (m, 3 H)
^{13}C NMR ($CDCl_3$, 126 MHz) δ	**:**	14.1, 22.5, 23.8, 26. 6, 33.7, 42.8, 44.7, 47.6, 90.6, 210.1
Mass: m/z (%)	**:**	254.06 (20), 222.05 (M+Na, 100), 102.31 (5)
HPLC (Chiralcel OD-H, *i-propanol: petroleum ether* 05:95, 0.5 mL/min, 230 nm)	**:**	major diastereomer: τ_R = 19.008 min. (major enantiomer), τ_R = 22.358 min. (minor enantiomer); minor diastereomer: τ_R = 20.417 min. (major enantiomer), τ_R = 21.283 min. (minor enantiomer)

Diethyl 2-(4-ethyl-3-oxocyclohexyl)malonate (73) :

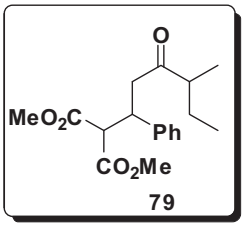


73

Yield:	**:**	95 %
$[\alpha]^{25}_D$	:	+5.04 (*c* 1.2, $CHCl_3$, 50 % *de*, 76 %)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	2937, 2872, 1750, 1732, 1716, 1224, 1174
^{1}H NMR ($CDCl_3$, 400 MHz) δ (diastereomeric mixture 3:1)	**:**	0.89 (td, *J* = 7.34, 1.63 Hz, 3 H), 1.27 (t, *J* = 7.03 Hz, 6 H), 1.34 - 1.48 (m, 1 H), 1.56-1.6(m, 0.4 H), 1.65 - 1.94 (m, 4 H), 2.08 - 2.20 (m, 1 H), 2.22 - 2.33 (m, 1 H), 2.36 - 2.56 (m, 2 H), 2.61 - 2.72 (m, 0.51 H), 3.26 - 3.32 (m, 0.88 H), 3.45-3.49 (m, 0.11 H), 4.17 -

		4.26 (m, 4 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	:	14.0, 14.2, 29.4, 33.9, 39.0, 44.7, 45.2, 57.1, 61.5, 167.8, 167.9, 210.8
Mass: m/z (%)	:	323.3 (M + K, 15), 307.15 (M + Na, 100), 284.27 (M+1, 10)
HPLC (Kromasil 5-Amycoat, *Et*OH: *n-hexane* 02:98.0, 0.7 mL/min, 230 nm)	:	major diastereomer: τ_R = 35.717 min. (major enantiomer), τ_R = 41.6 min. (minor enantiomer); minor diastereomer: τ_R = 26.892 min. (major enantiomer), τ_R = 33.792 min. (minor enantiomer)

Dimethyl 2-(4-methyl-3-oxo-1-phenylhexyl) malonate (79):



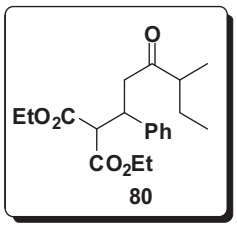
79

Yield:	:	40 %
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2963, 1752, 1735, 1710, 1434, 1253, 1157
^{1}H NMR ($CDCl_3$, 400 MHz) δ (diastereomeric mixture 1:1)	:	0.61 - 0.70 (m, 1 H), 0.74 (t, *J* = 7.40 Hz, 2 H), 0.87 (d, *J* = 7.03 Hz, 1 H), 0.94 (d, *J* = 6.78 Hz, 2 H), 1.17 - 1.33 (m, 1 H), 1.53 (ddt, *J* = 18.51, 14.05, 6.93, 6.93 Hz, 1 H), 2.31 (dq, *J* = 15.65, 6.83 Hz, 1 H), 2.86 - 3.07 (m, 2 H), 3.51 (s, 2 H), 3.56 (s, 1 H), 3.71 - 3.84 (m, 4 H), 4.01 (ddt, *J* = 11.67, 9.10, 2.42, 2.42 Hz, 1 H), 7.14 - 7.35 (m, 5 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ (diastereomeric mixture 1:1)	:	11.2, 11.5, 15.2, 15.4, 25.5, 25.5 , 40.3, 44.6, 44.7, 47.9, 48.1, 52.3, 52.6, 57.0, 127.1, 128.1 , 128.4, 140.6, 168.1, 168.6, 211.7
Mass: m/z (%)	:	359 (M + K, 10), 343(M + Na, 100), 321 (M + H, 30), 274 (37), 239 (34)
HRMS ESI (*m/z*):	:	$[M + Na]^+$ calcd for $C_{18}H_{24}O_5Na$, 343.1516; found,

343.1522

HPLC (Kromasil 5-Amycoat, *EtOH:n-Hexane* 7.0:93.0, 0.5 mL/min, 230 nm)	:	major diastereomer: τ_R = 20.500 min. (major enantiomer), τ_R = 24.033 min. (minor enantiomer); minor diastereomer: τ_R = 32.325 min. (major enantiomer) τ_R = 42.231 min. (minor enantiomer)

Diethyl 2-(4-methyl-3-oxo-1-phenylhexyl) malonate (80):



80

Yield:	:	35 %
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2966, 1788, 1734, 1722, 1369, 1299, 1250
^{1}H NMR ($CDCl_3$, 500 MHz) δ (diastereomeric mixture 4:1)	:	0.64 (t, *J* = 7.48 Hz, 1.5 H), 0.73 (t, *J* = 7.48 Hz, 1.5 H), 0.86 (d, *J* = 7.02 Hz, 1.5 H), 0.93 (d, *J* = 7.02 Hz, 1.5 H), 1.01 (t, *J* = 7.17 Hz, 3 H), 1.16 - 1.31 (m, 4 H), 1.45 - 1.58 (m, 1 H), 2.30 (dq, *J* = 18.92, 6.82 Hz, 1 H), 2.85 - 3.04 (m, 2 H), 3.73 (dd, *J* = 9.92, 1.68 Hz, 1 H), 3.95 (q, J = 7, 2H), 3.98 - 4.03 (m, 1 H), 4.20 (qdd, *J* = 7.12, 7.12, 7.12, 2.29, 1.07 Hz, 2 H), 7.15 - 7.20 (m, 1 H), 7.23 - 7.26 (m, 4 H)
^{13}C NMR ($CDCl_3$, 126 MHz) δ (diastereomeric mixture 4:1)	:	11.2, 11.5, 13.7, 14.0, 15.2, 15.4 , 40.3, 44.9, 44.9, 47.9, 48.1, 57.3, 61.3, 61.5, 127.0, 128.3, 167.7, 168.3 211.7, 211.8
Mass: m/z (%)	:	256.92 (100), 387.01 (M + K, 8), 371.94 (M + Na, 31), 370.94 (98), 349.07 (M+1, 95), 302.92 (81)
HRMS ESI (*m/z*):	:	$[M + Na]^+$ calcd for $C_{20}H_{28}O_5Na$, 371.1829; found, 371.1841
HPLC (Kromasil 5-	:	major diastereomer: τ_R = 35.342 min. (major

Amycoat, *i-PrOH:n-Hexane* 2.5:97.5, 0.5 mL/min, 230 nm)	enantiomer), τ_R = 39.825 min. (minor enantiomer); minor diastereomer: τ_R = 68.767 min. (major enantiomer), τ_R = 78.158 min. (minor enantiomer)

2.11 References

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12. CCDC-861580 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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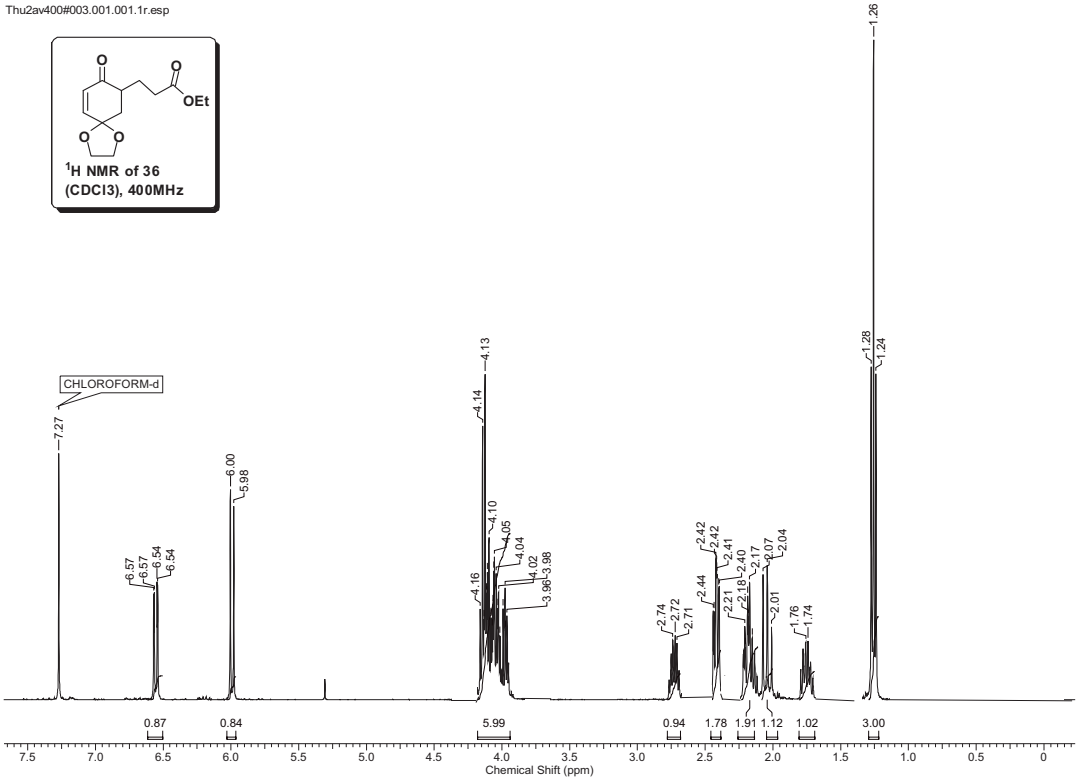
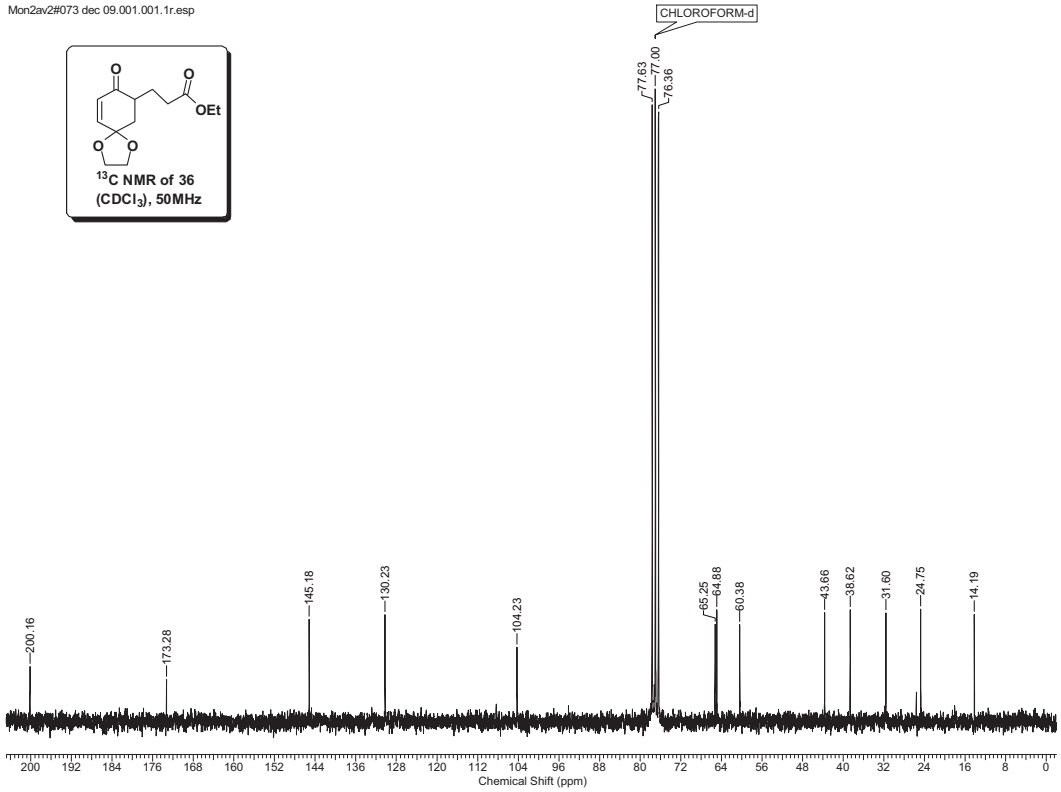
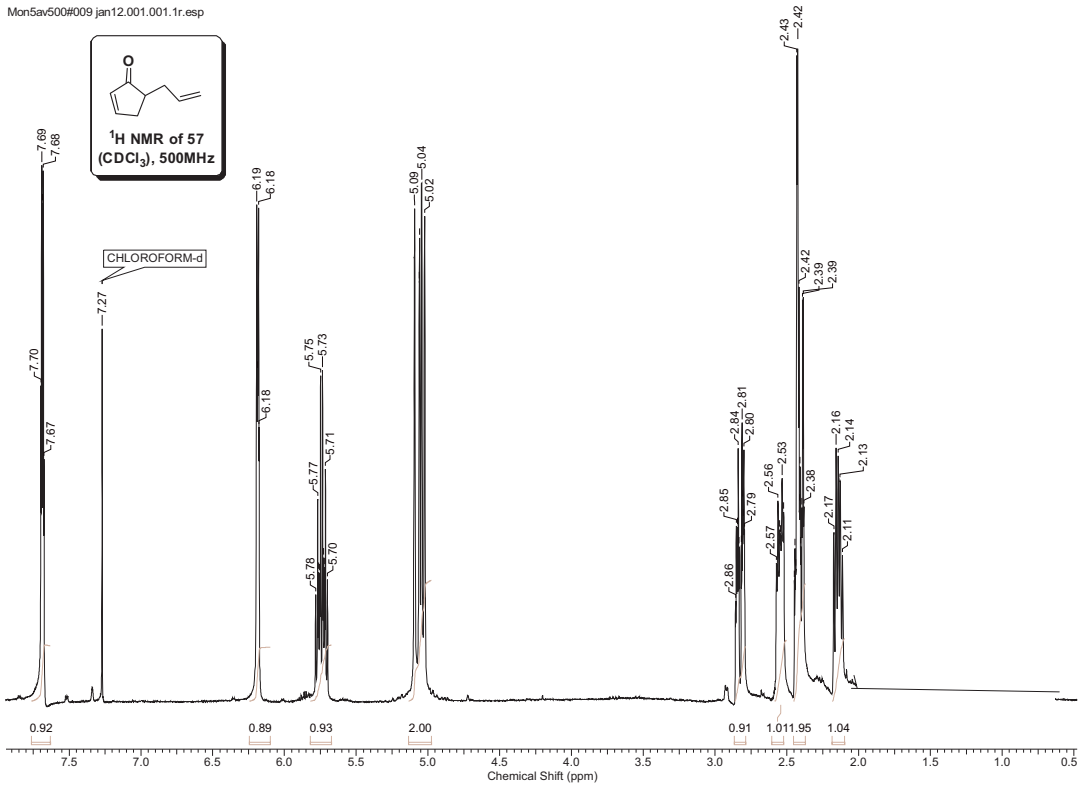
18. It might be due to the conformation of 7-substituted cycloheptenone but at present we are unable to reason this observation.
19. a) Krapcho A. P., Synthesis, **1982**, 805; b) Krapcho A. P., Synthesis, **1982**, 893.

2.12 Spectra of all new compounds



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($CDCl_3$), 500MHz
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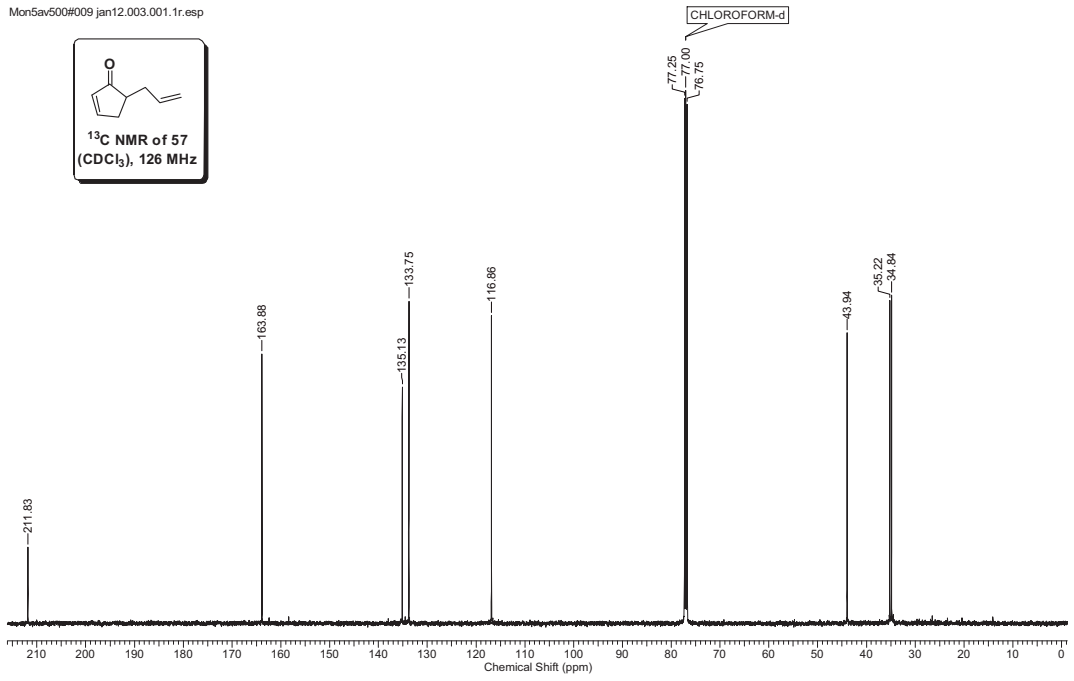
7.69
7.68
7.70
7.67
7.27
6.19
6.18
6.18
5.75
5.73
5.77
5.71
5.78
5.70
5.09
5.04
5.02
2.43
2.42
2.42
2.39
2.39
2.84
2.81
2.80
2.85
2.79
2.86
2.56
2.53
2.57
2.38
2.16
2.14
2.13
2.17
2.11
0.92
0.89
0.93
2.00
0.91
1.01
1.95
1.04
Chemical Shift (ppm)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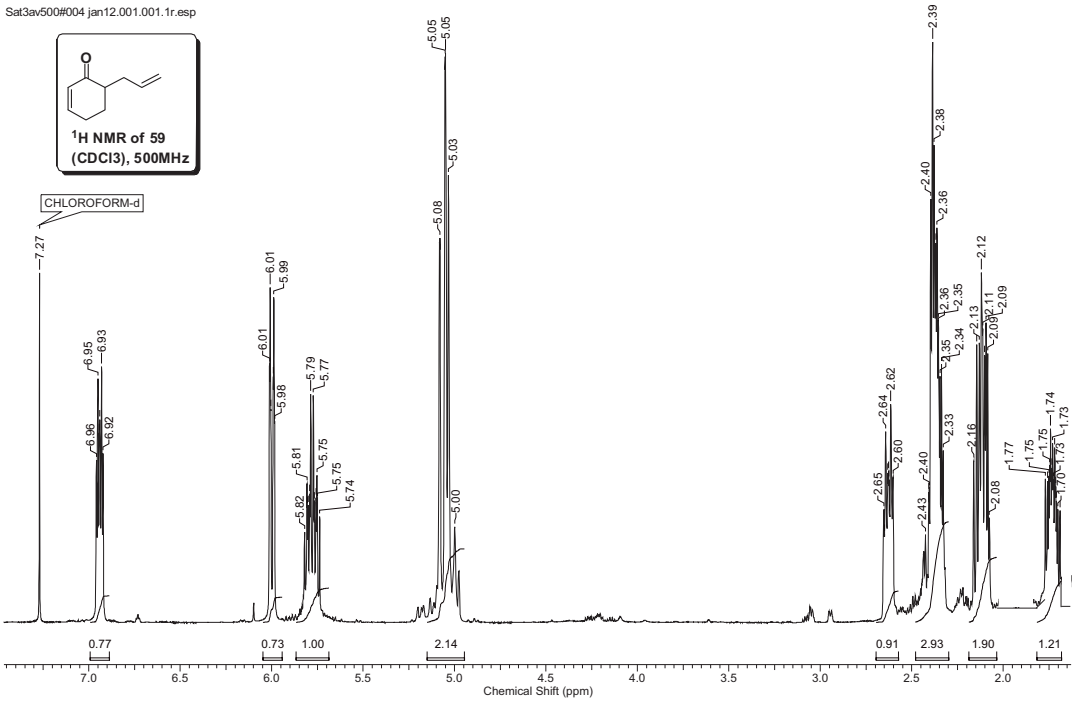
^{13}C NMR of 57
($CDCl_3$), 126 MHz
CHLOROFORM-d
77.25
77.00
76.75
211.83
163.88
135.13
133.75
116.86
43.94
35.22
34.84
Chemical Shift (ppm)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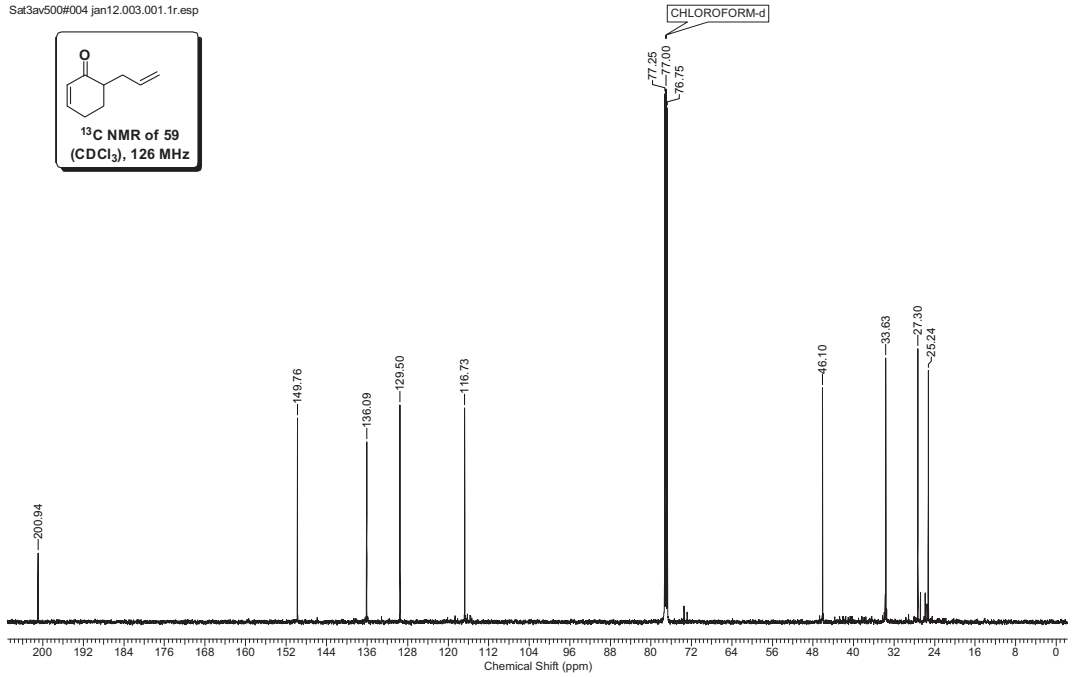
CHLOROFORM-d
Chemical Shift (ppm)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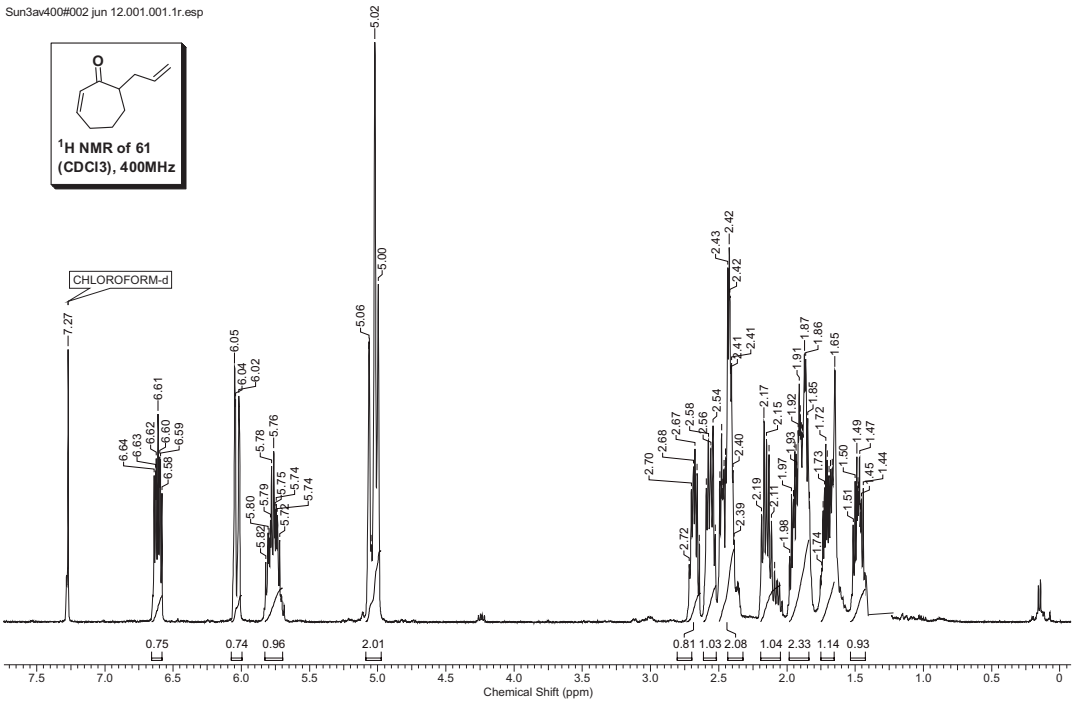
($CDCl_3$), 126 MHz
CHLOROFORM-d
Chemical Shift (ppm)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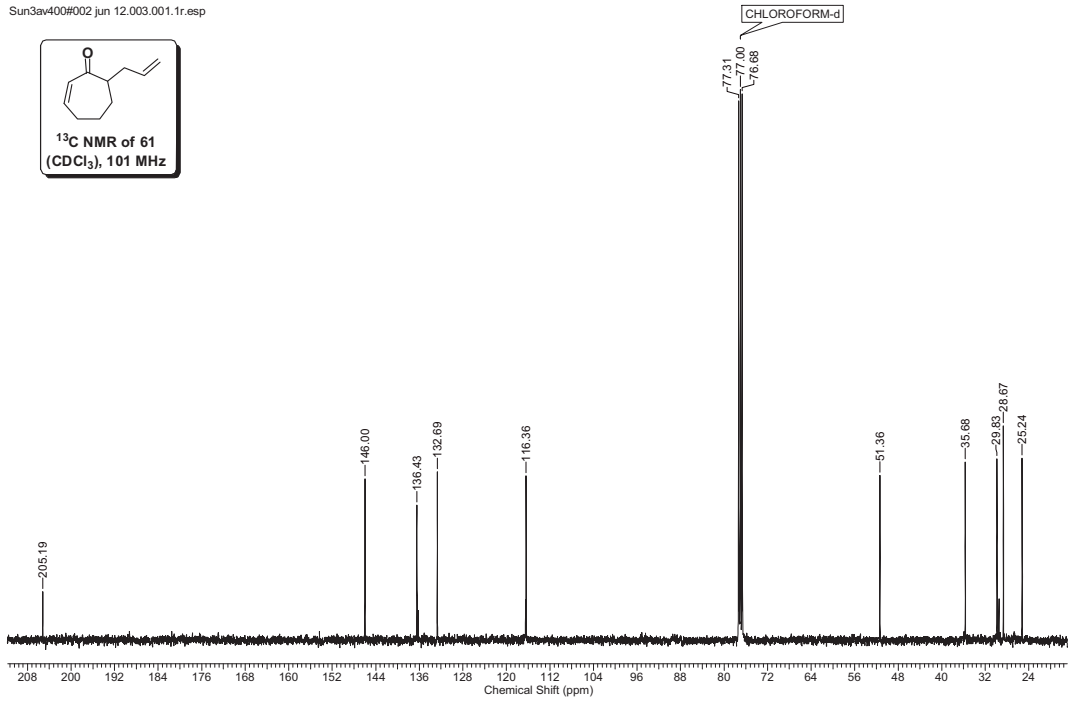
(CDCl3), 400MHz
CHLOROFORM-d
Chemical Shift (ppm)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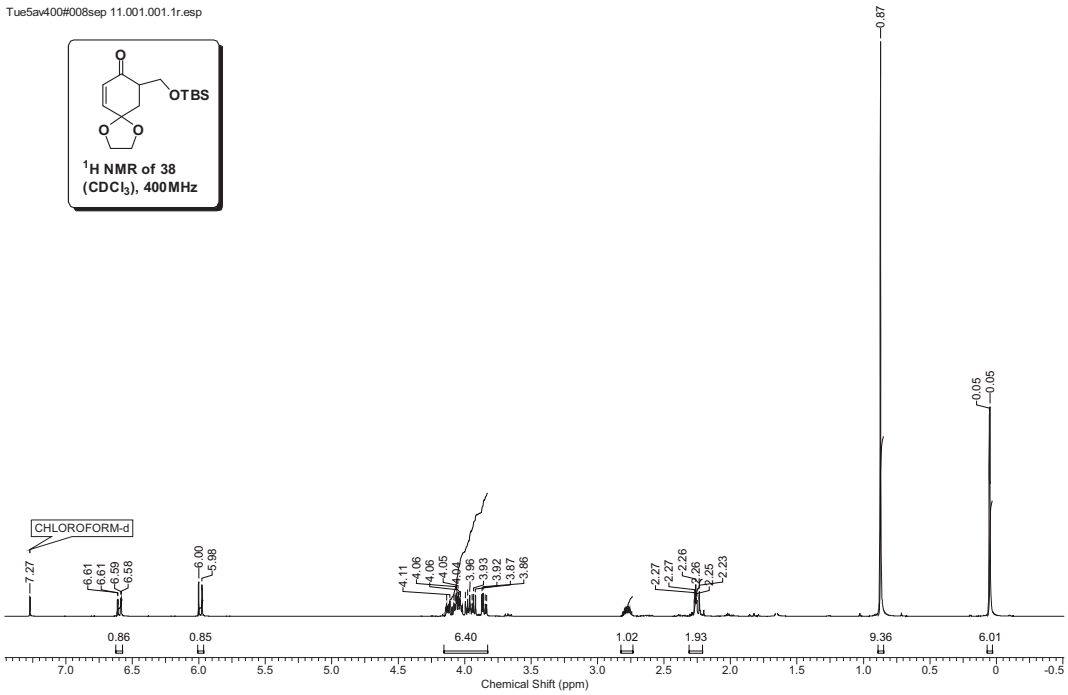
($CDCl_3$), 101 MHz
CHLOROFORM-d
Chemical Shift (ppm)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OTBS
^{1}H NMR of 38
($CDCl_3$), 400MHz
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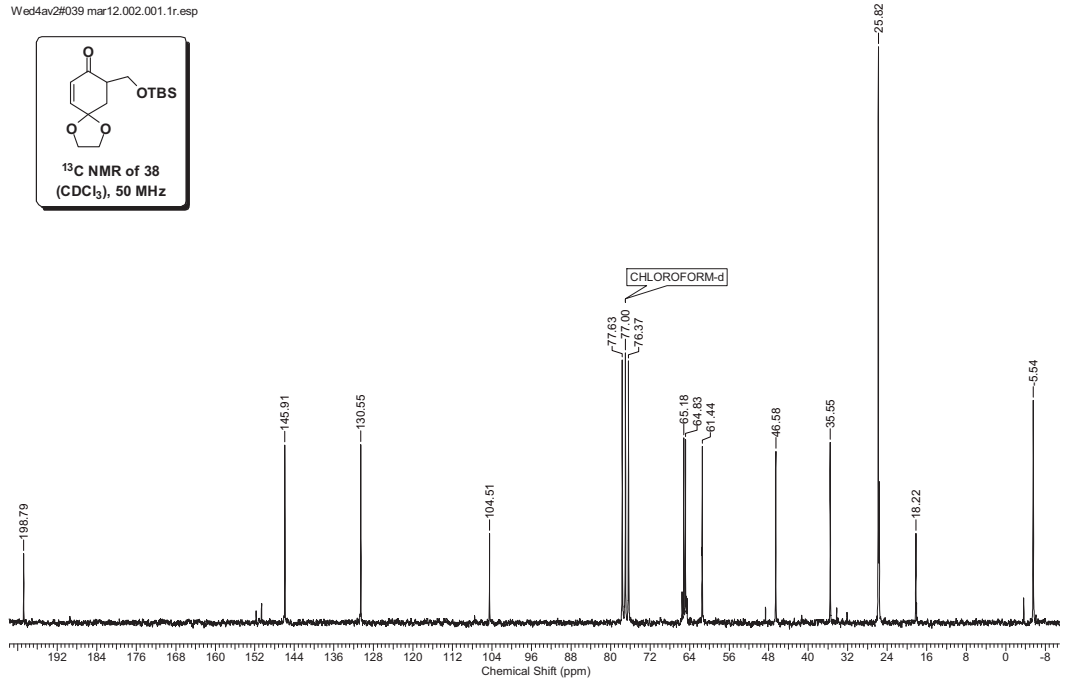
7.27
6.61
6.61
6.59
6.58
6.00
5.98
4.11
4.06
4.06
4.05
4.04
3.96
3.93
3.92
3.87
3.86
2.27
2.27
2.26
2.26
2.25
2.23
0.87
0.05
0.05
0.86
0.85
6.40
1.02
1.93
9.36
6.01
Chemical Shift (ppm)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OTBS
^{13}C NMR of 38
($CDCl_3$), 50 MHz
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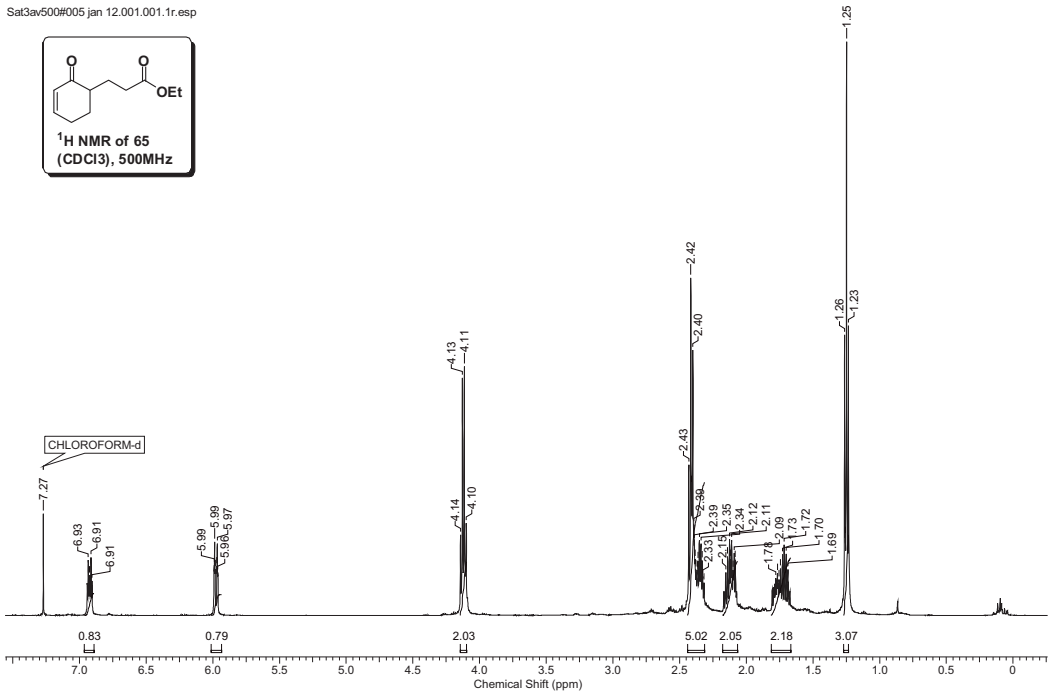
76.37
145.91
130.55
104.51
65.18
64.83
61.44
46.58
35.55
25.82
18.22
5.54
198.79
Chemical Shift (ppm)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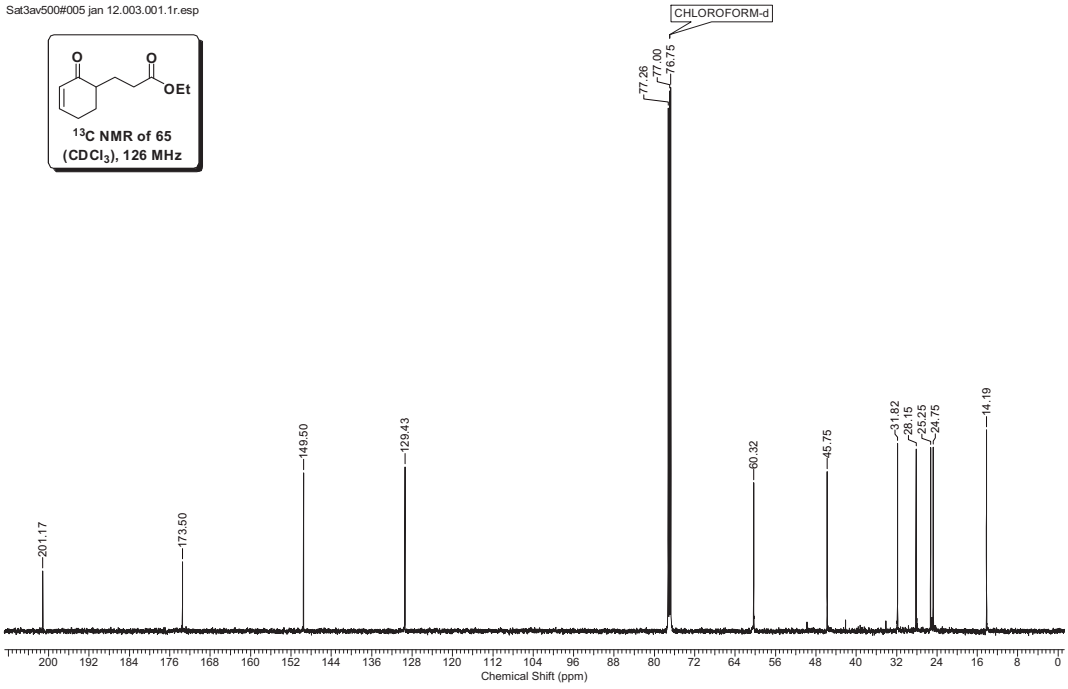
OEt
^{1}H NMR of 65
(CDCl3), 500MHz
CHLOROFORM-d
7.27
6.93
6.91
6.91
5.99
5.99
5.98
5.97
4.13
4.11
4.14
4.10
2.42
2.40
2.43
2.39
2.38
2.35
2.34
2.33
2.15
2.12
2.11
2.09
1.78
1.73
1.72
1.70
1.69
1.26
1.23
1.25
0.83
0.79
2.03
5.02
2.05
2.18
3.07
Chemical Shift (ppm)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OEt
^{13}C NMR of 65
($CDCl_3$), 126 MHz
CHLOROFORM-d
77.26
77.00
76.75
201.17
173.50
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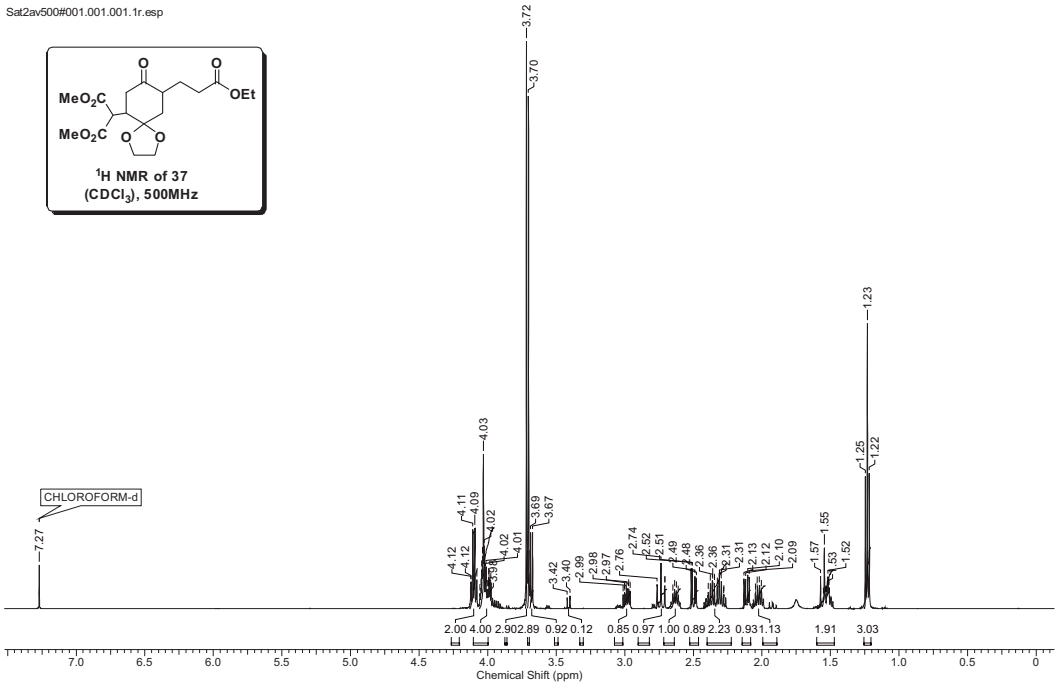
129.43
60.32
45.75
31.82
28.15
25.25
24.75
14.19
Chemical Shift (ppm)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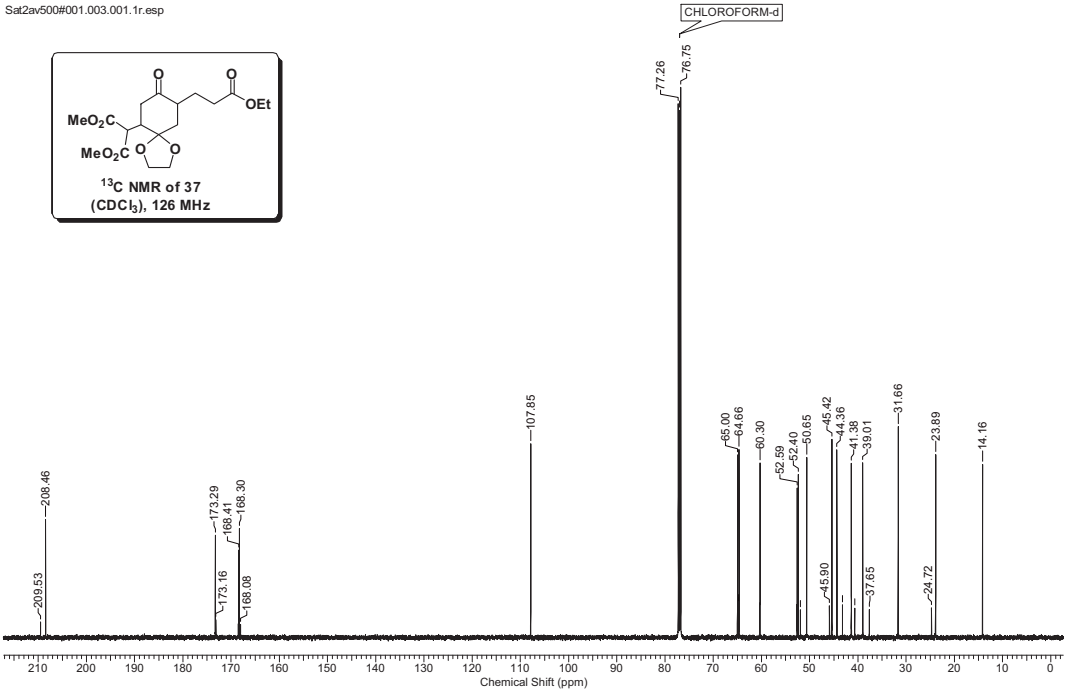
MeO2C
OEt
1H NMR of 37
(CDCl3), 500MHz
CHLOROFORM-d
7.27
3.72
3.70
4.03
4.11
4.09
4.02
3.69
3.67
1.23
1.25
1.22
2.00 4.00 2.90 2.89 0.92 0.12 0.85 0.97 1.00 0.89 2.23 0.93 1.13 1.91 3.03
Chemical Shift (ppm)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MeO2C
OEt
13C NMR of 37
(CDCl3), 126 MHz
CHLOROFORM-d
77.26
76.75
208.46
209.53
173.29
173.16
168.41
168.30
168.08
107.85
65.00
64.66
60.30
52.59
52.40
50.65
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44.36
41.38
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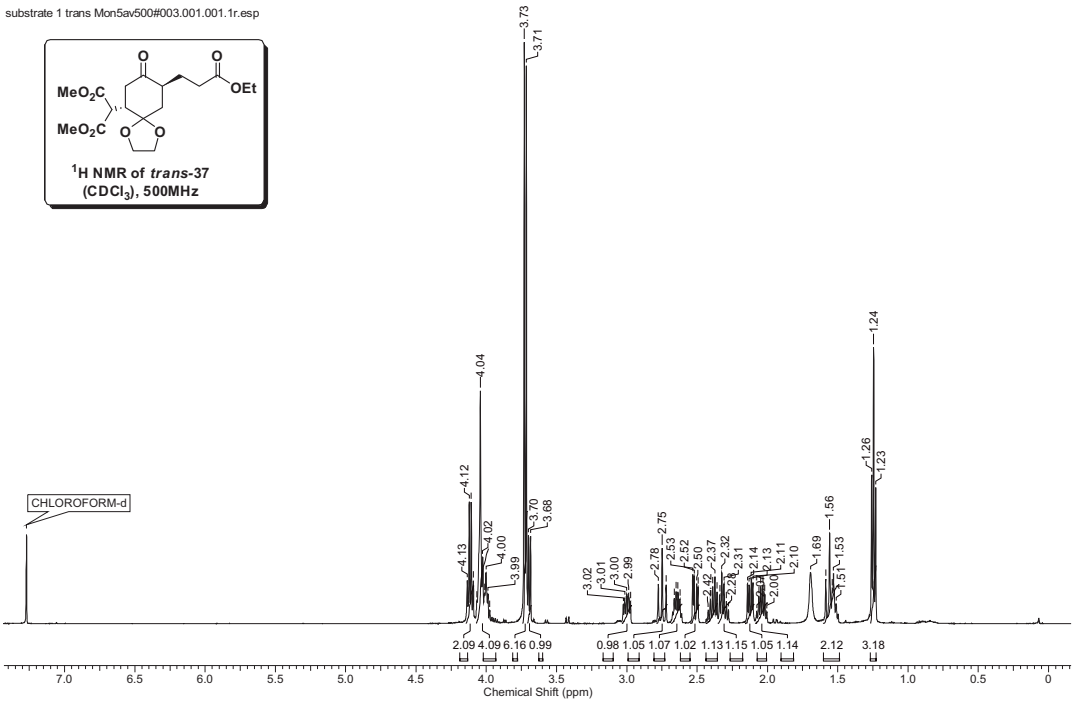
37.65
31.66
24.72
23.89
14.16
Chemical Shift (ppm)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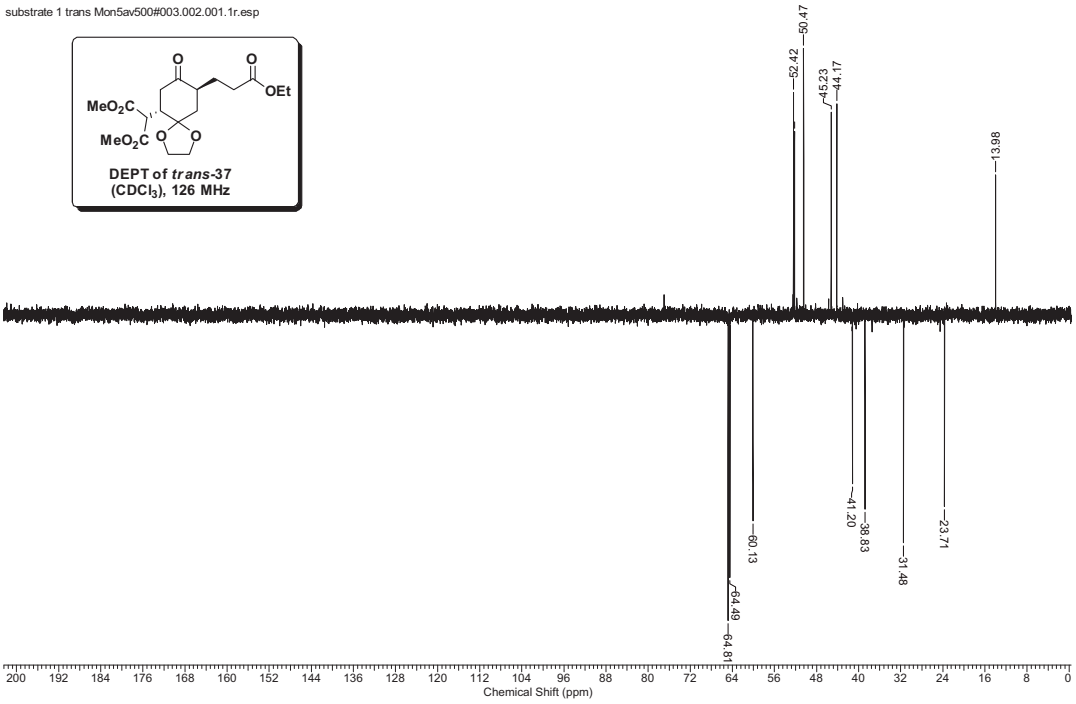
MeO2C
OEt
1H NMR of trans-37
(CDCl3), 500MHz
CHLOROFORM-d
Chemical Shift (ppm)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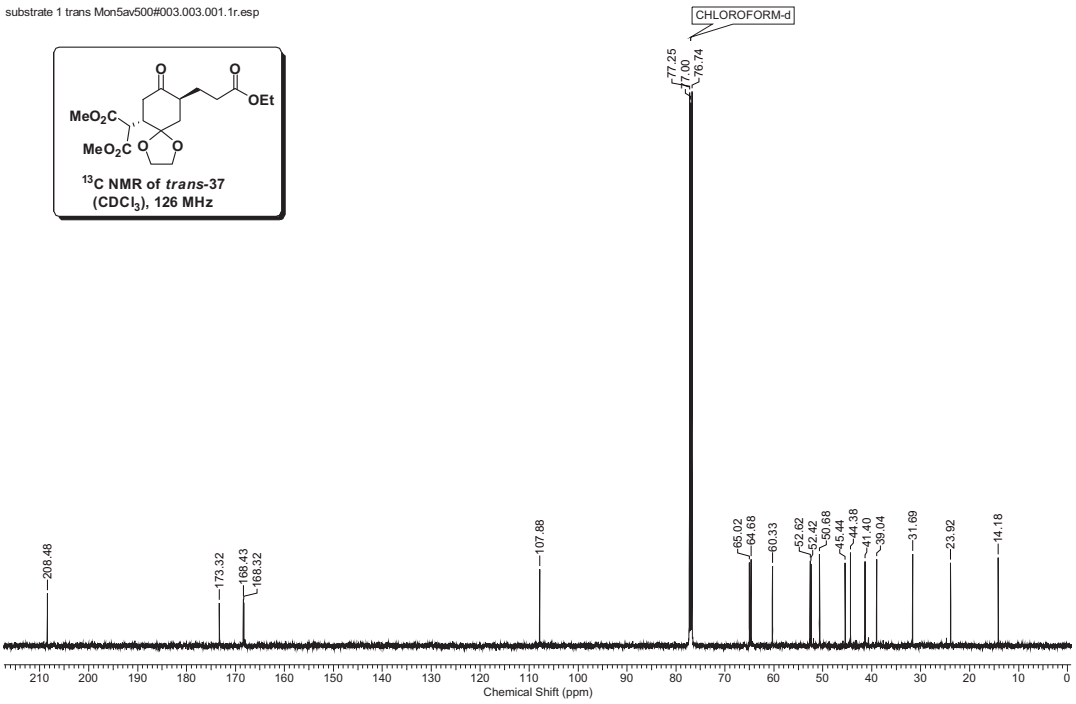
MeO2C
OEt
DEPT of trans-37
(CDCl3), 126 MHz
Chemical Shift (ppm)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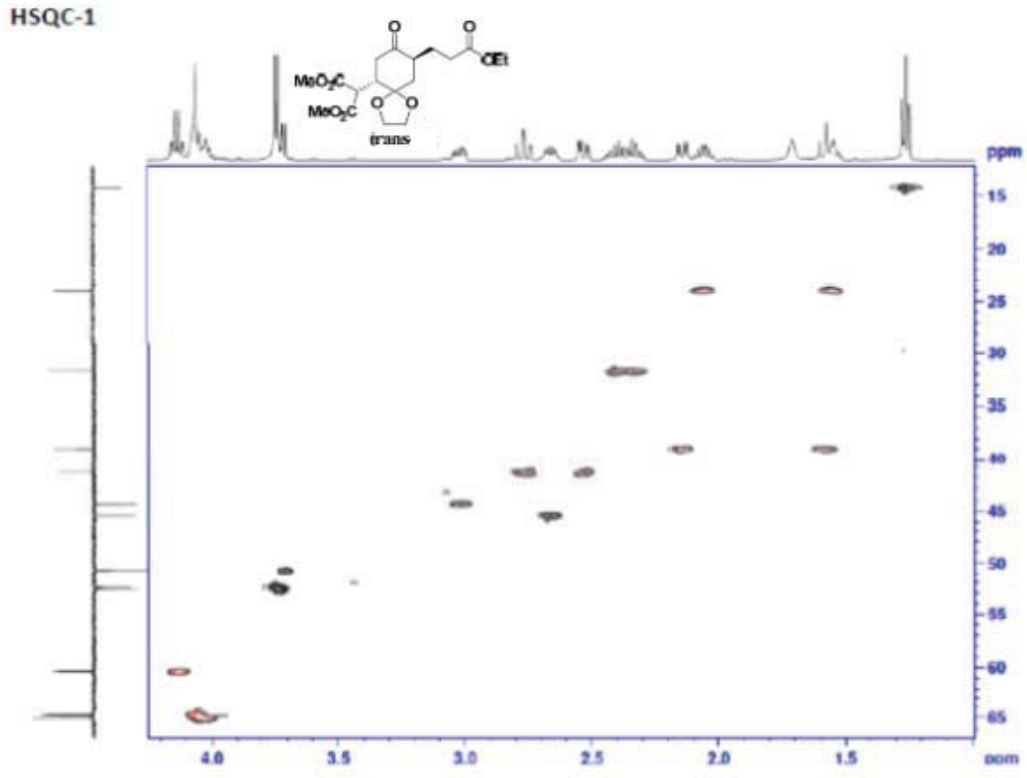
76.74
208.48
173.32
168.43
168.32
107.88
65.02
64.68
60.33
52.62
52.42
50.68
45.44
44.38
41.40
39.04
31.69
23.92
14.18
Chemical Shift (ppm)
13C NMR of trans-37
(CDCl3), 126 MHz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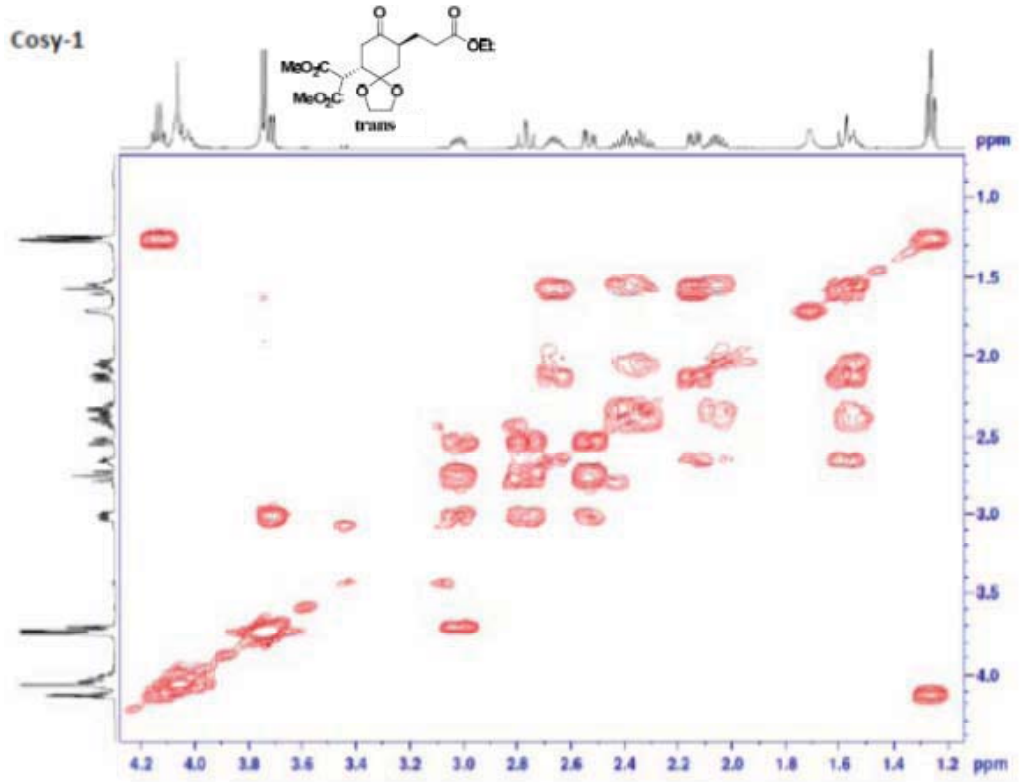
ppm
ppm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MeO2C
MeO2C
OEt
trans
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1.5
2.0
2.5
3.0
3.5
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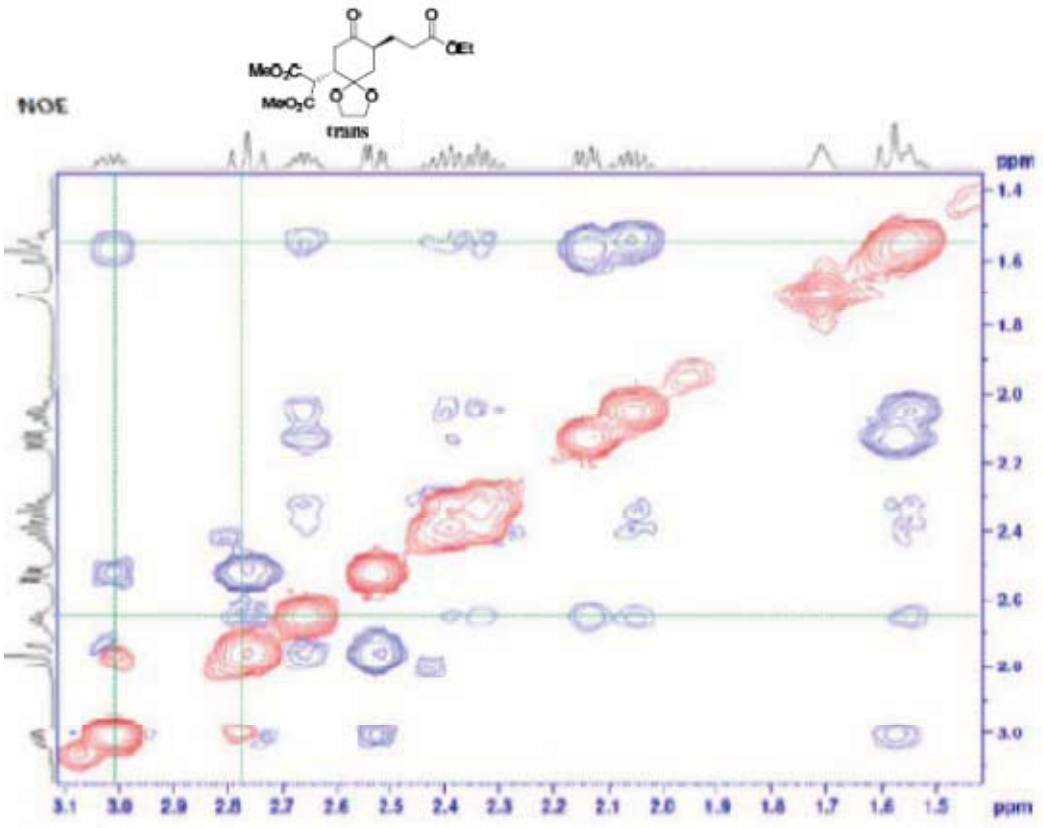
NOE
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MeO2C
OEt
trans
ppm
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1.8
2.0
2.2
2.4
2.6
2.8
3.0
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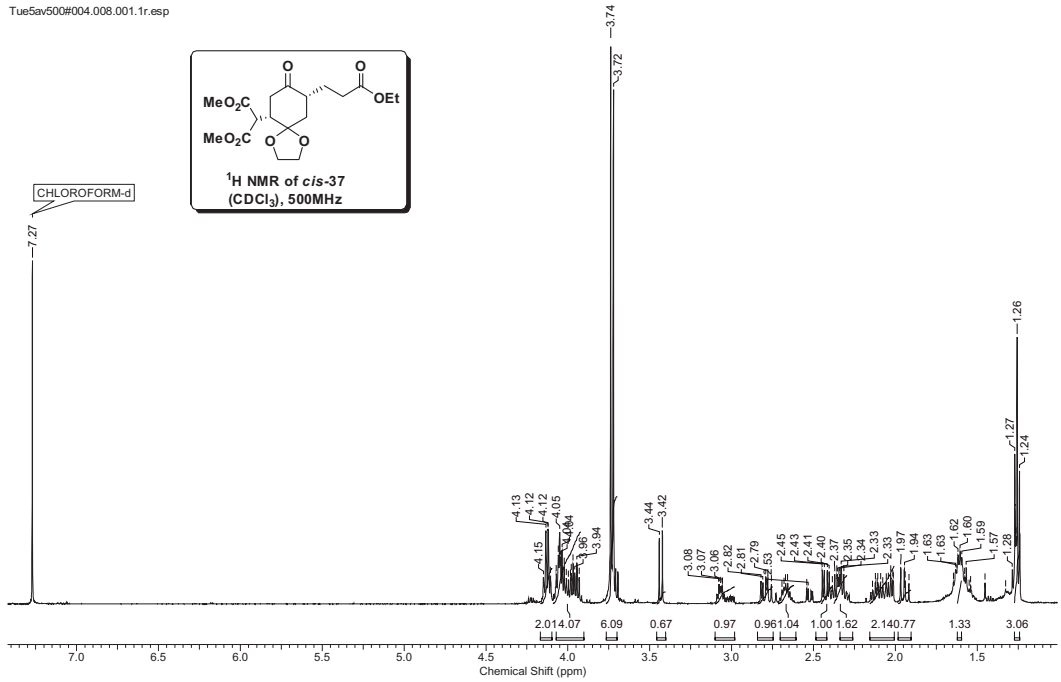
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MeO2C
MeO2C
OEt
O
O
O
O
O
1H NMR of cis-37
(CDCl3), 500MHz
CHLOROFORM-d
7.27
3.74
3.72
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4.12
4.12
4.05
4.04
4.04
4.15
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2.33
1.97
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1.62
1.60
1.59
1.57
1.28
1.26
1.27
1.24
2.01 4.07
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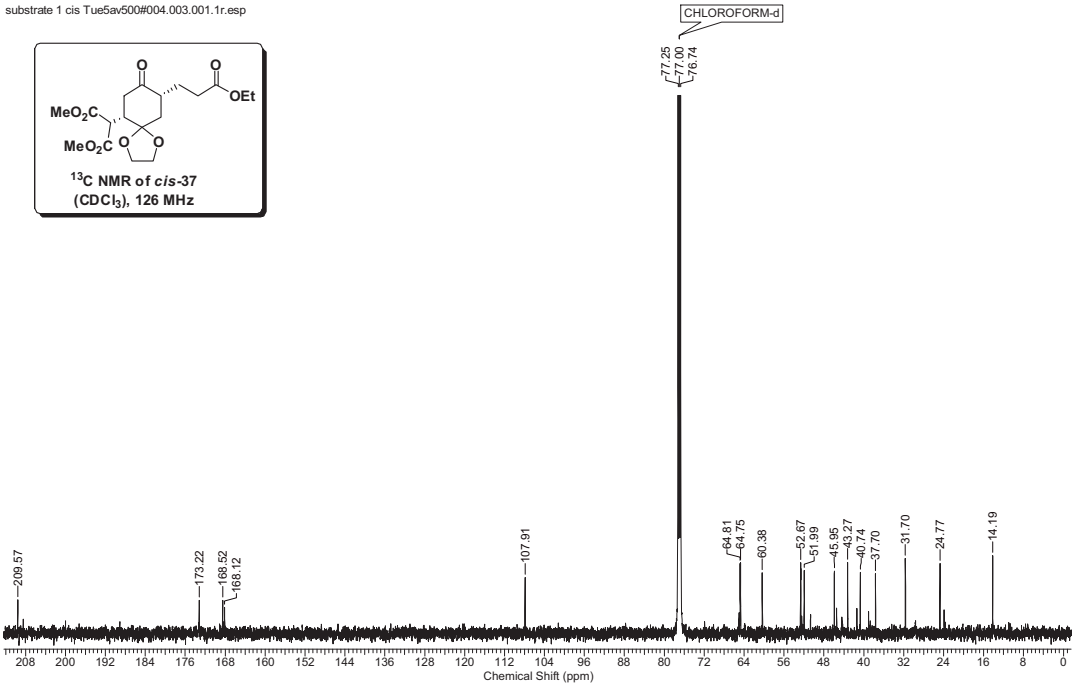
0.97
0.96 1.04
1.00 1.62
2.14 0.77
1.33
3.06
Chemical Shift (ppm)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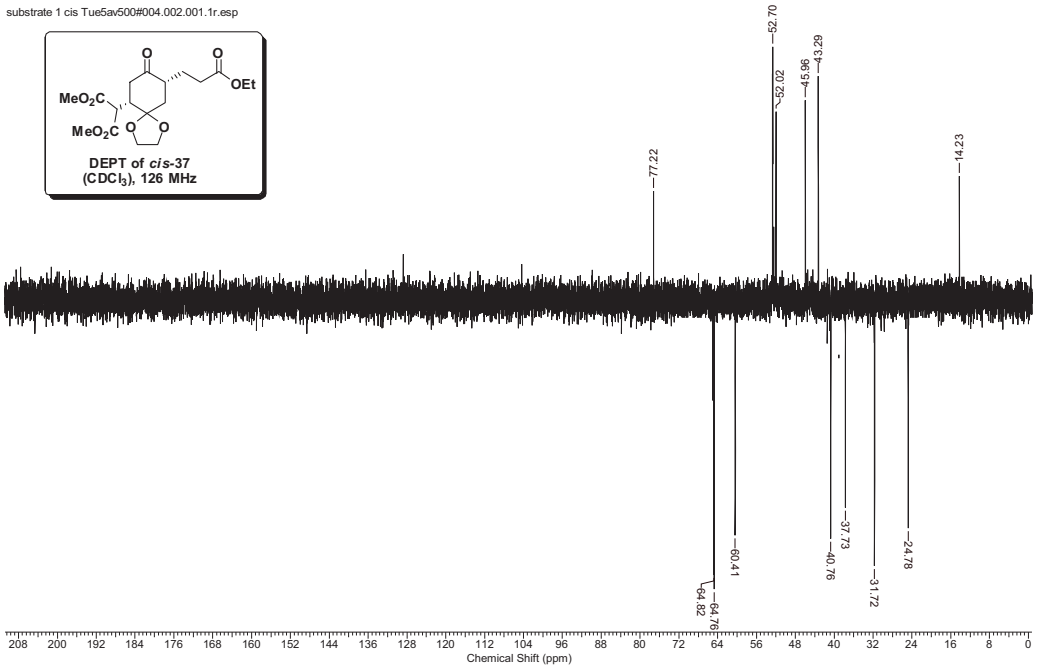
MeO2C
OEt
O
O
O
O
O
13C NMR of cis-37
(CDCl3), 126 MHz
CHLOROFORM-d
77.25
77.00
76.74
209.57
173.22
168.52
168.12
107.91
84.81
64.75
60.38
52.67
51.99
45.95
43.27
40.74
37.70
31.70
24.77
14.19
Chemical Shift (ppm)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DEPT of cis-37
(CDCl3), 126 MHz
52.70
52.02
45.96
43.29
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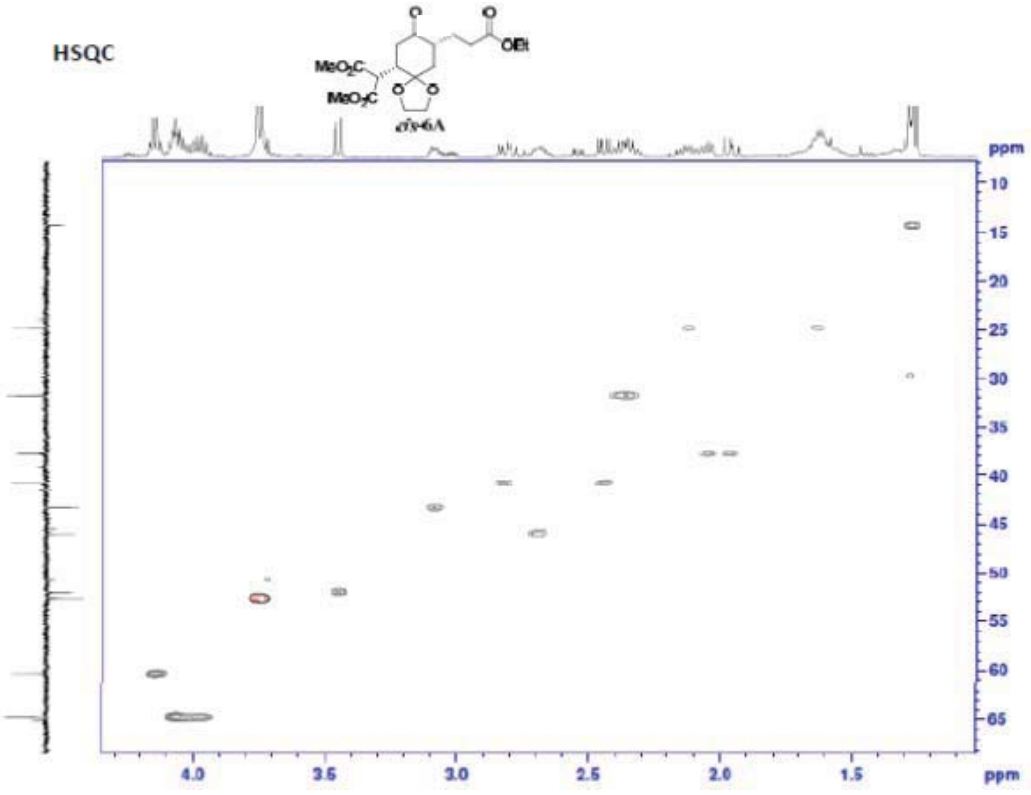
40.76
37.73
31.72
24.78
Chemical Shift (ppm)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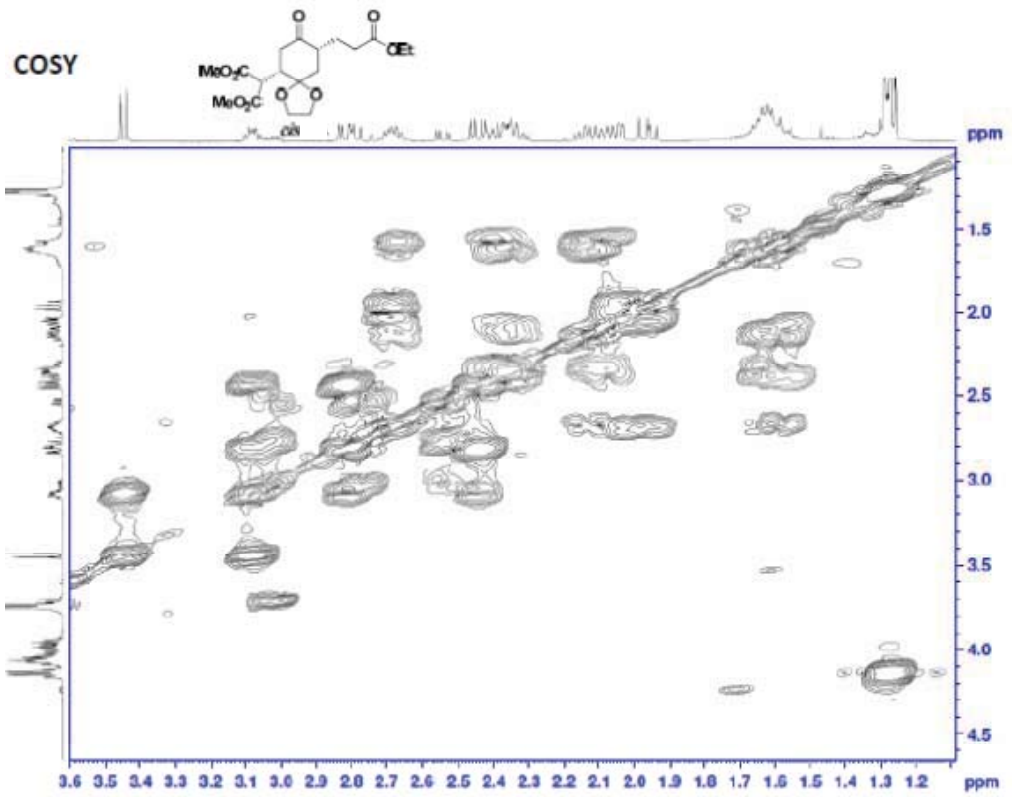
COSY
MeO2C
MeO2C
OEt
cis
ppm
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2.0
2.5
3.0
3.5
4.0
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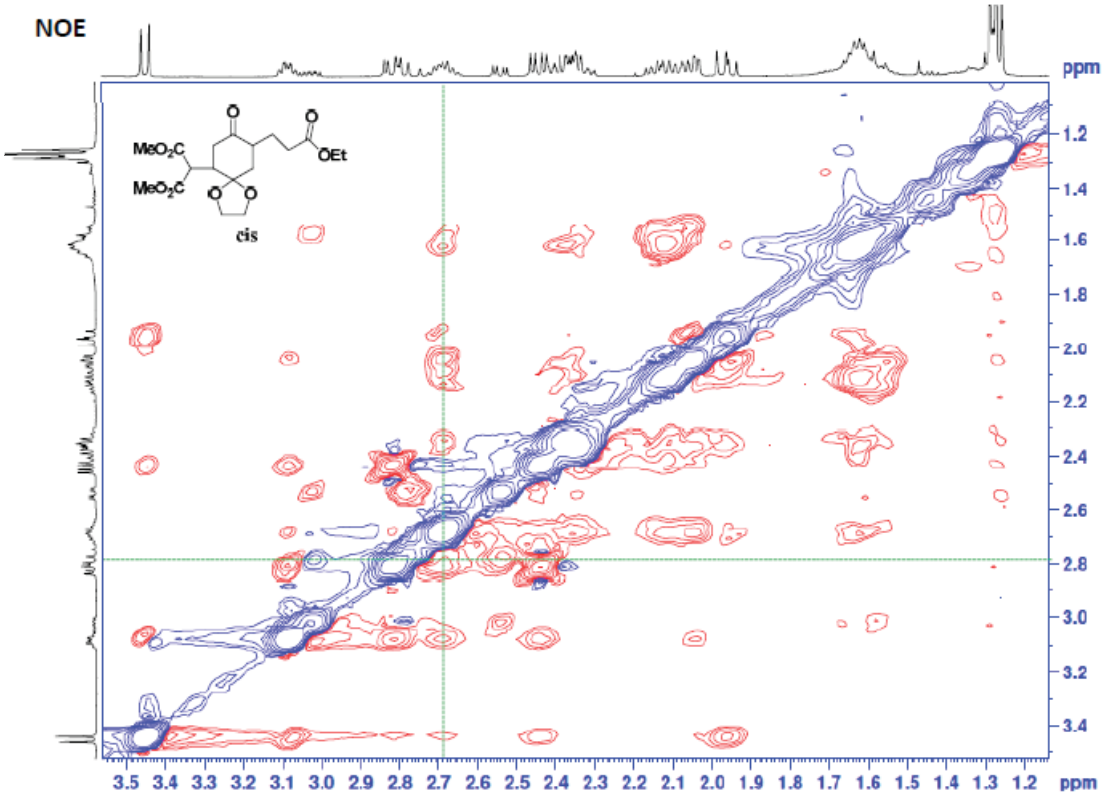
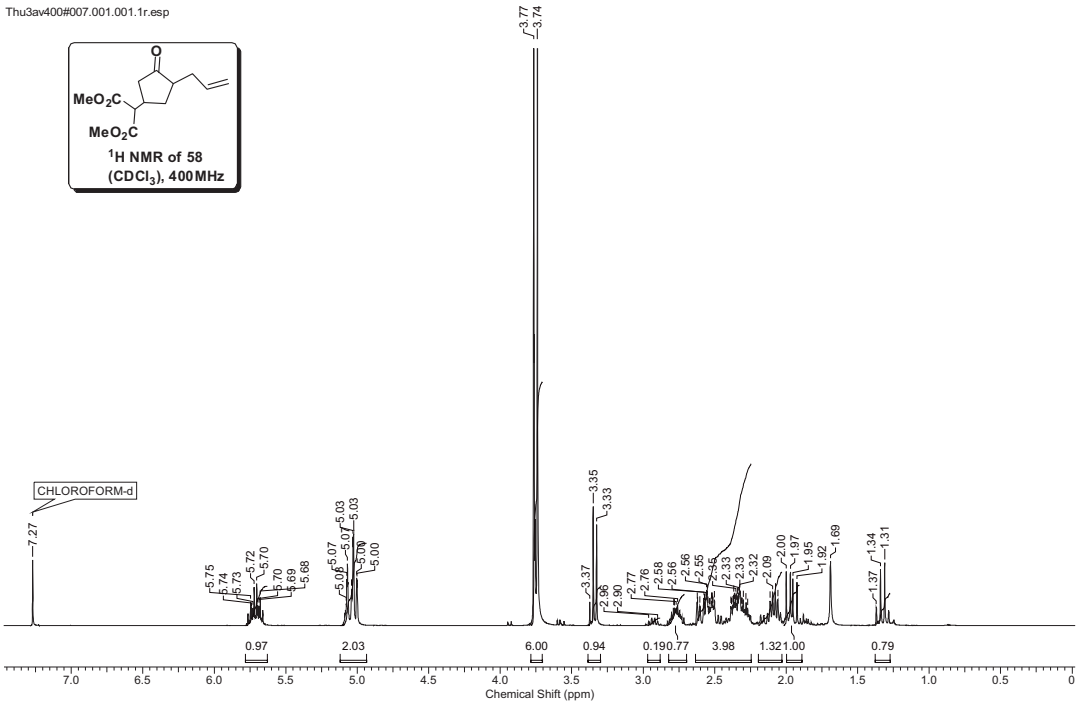
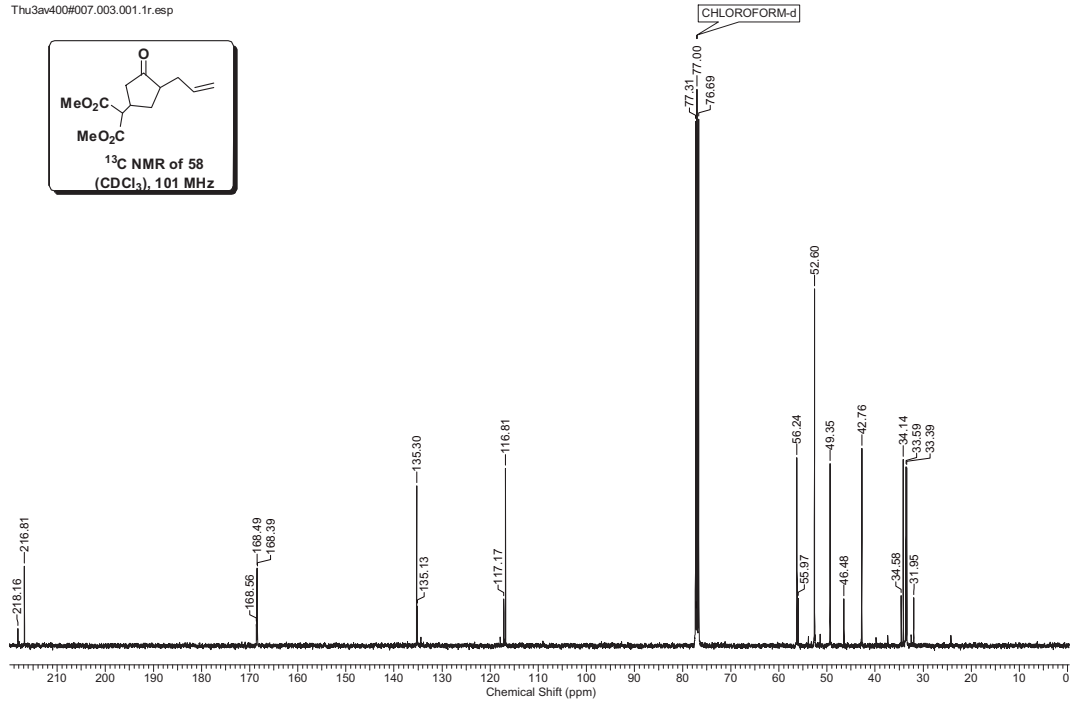
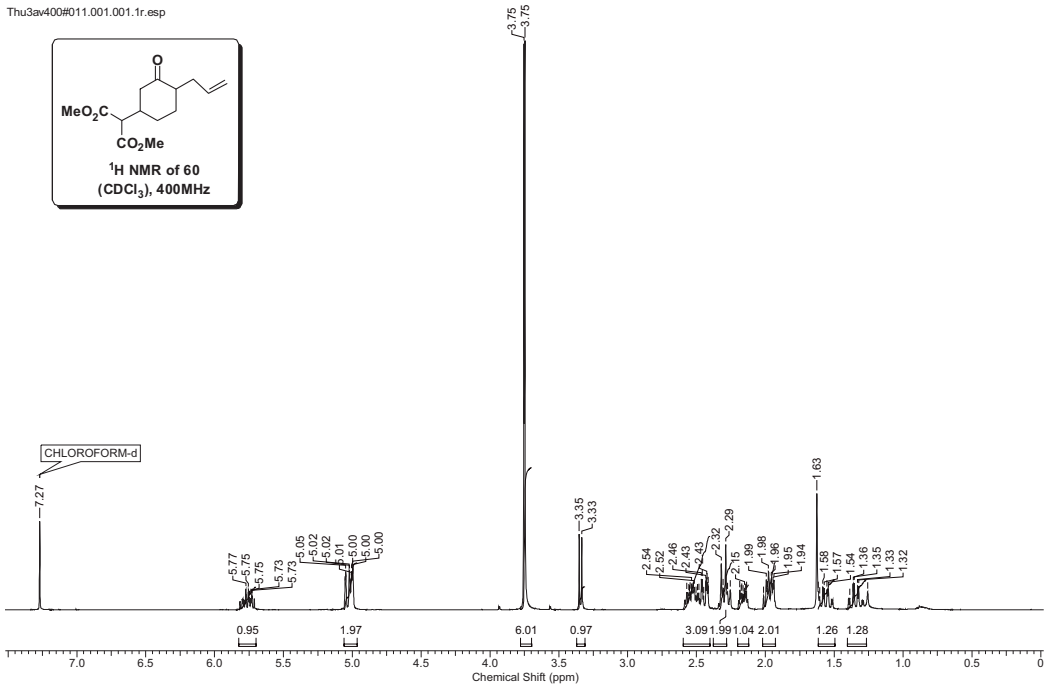
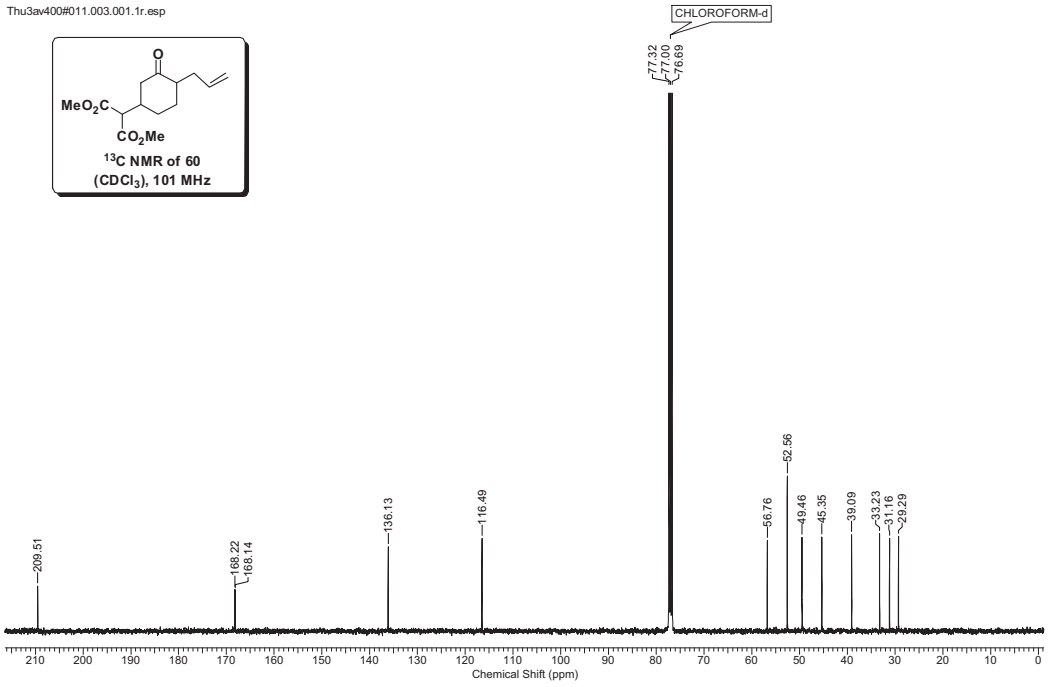
3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2
ppm

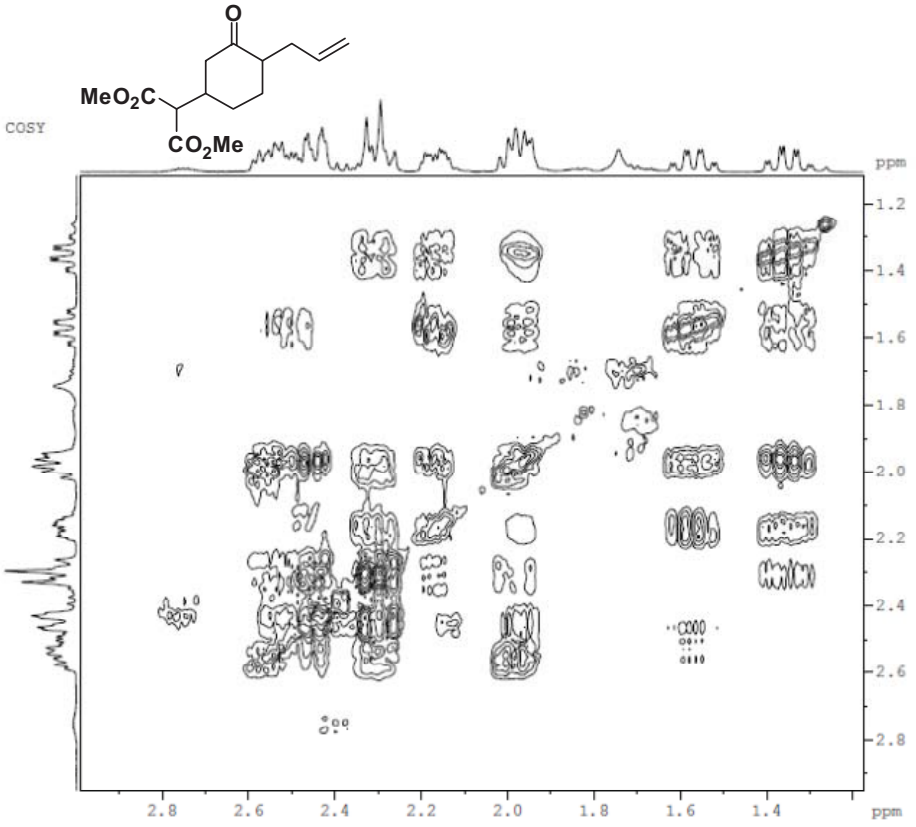

NOE
MeO2C
MeO2C
OEt
cis
ppm
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2
ppm


Thu3av400#007.001.001.1r.esp
MeO2C
MeO2C
1H NMR of 58
(CDCl3), 400MHz
CHLOROFORM-d
Chemical Shift (ppm)

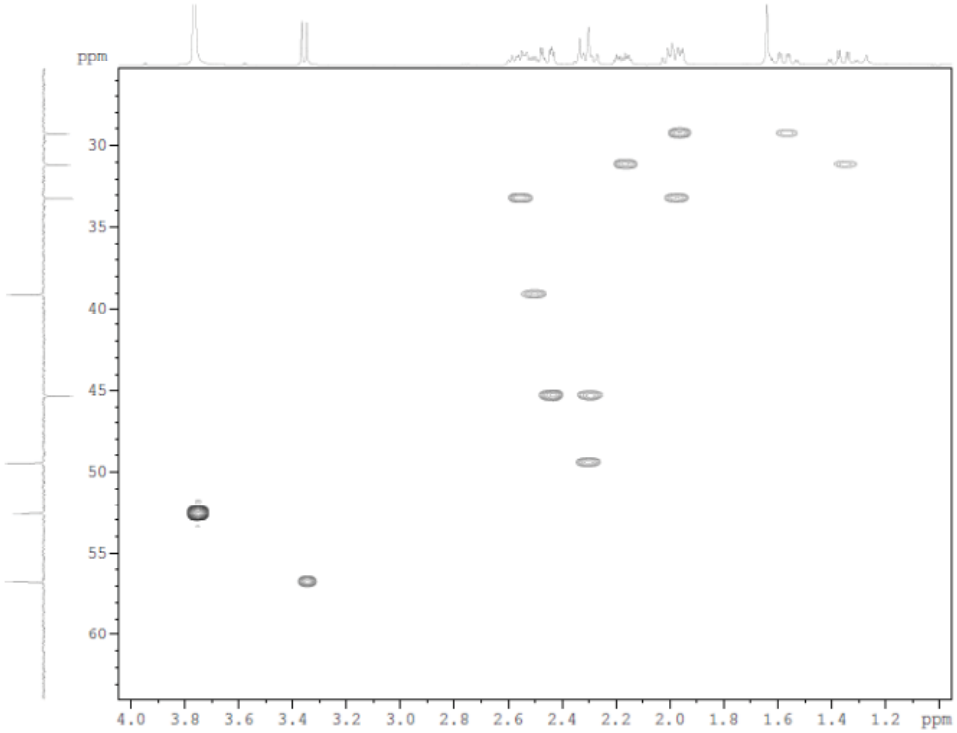

Thu3av400#007.003.001.1r.esp
MeO2C
MeO2C
13C NMR of 58
(CDCl3), 101 MHz
CHLOROFORM-d
Chemical Shift (ppm)


Thu3av400#011.001.001.1r.esp
MeO2C
CO2Me
1H NMR of 60
(CDCl3), 400MHz
CHLOROFORM-d
Chemical Shift (ppm)

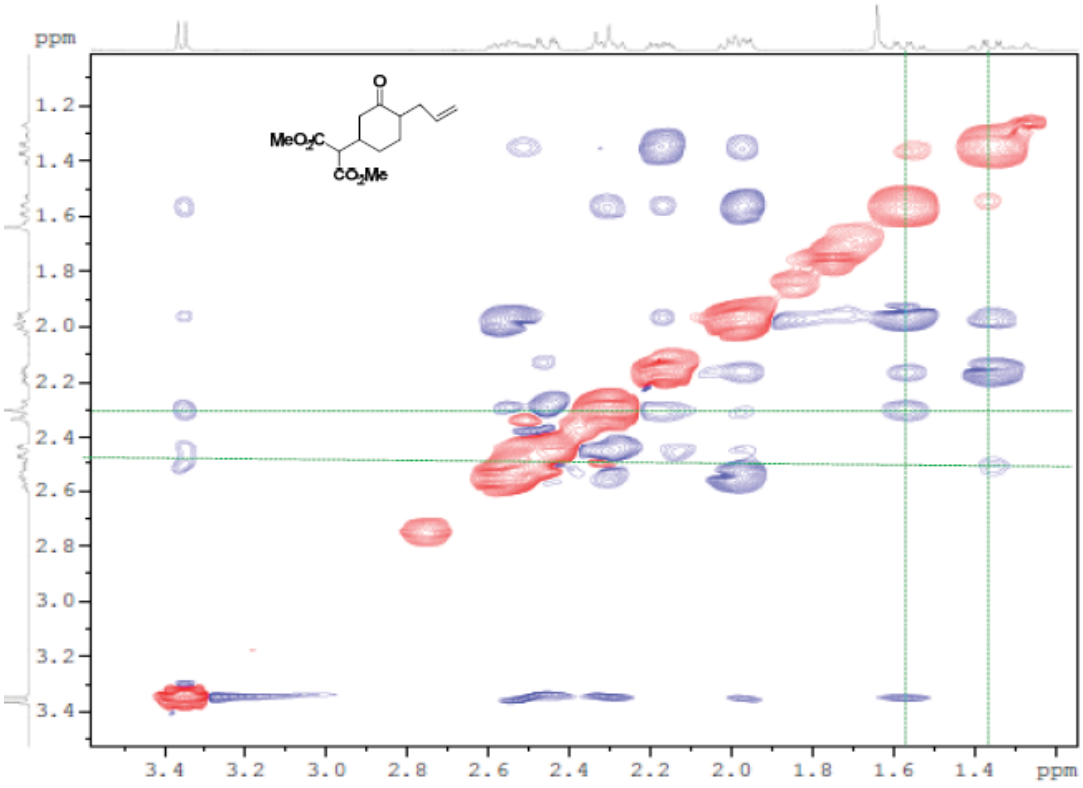

Thu3av400#011.003.001.1r.esp
MeO2C
CO2Me
13C NMR of 60
(CDCl3), 101 MHz
CHLOROFORM-d
Chemical Shift (ppm)

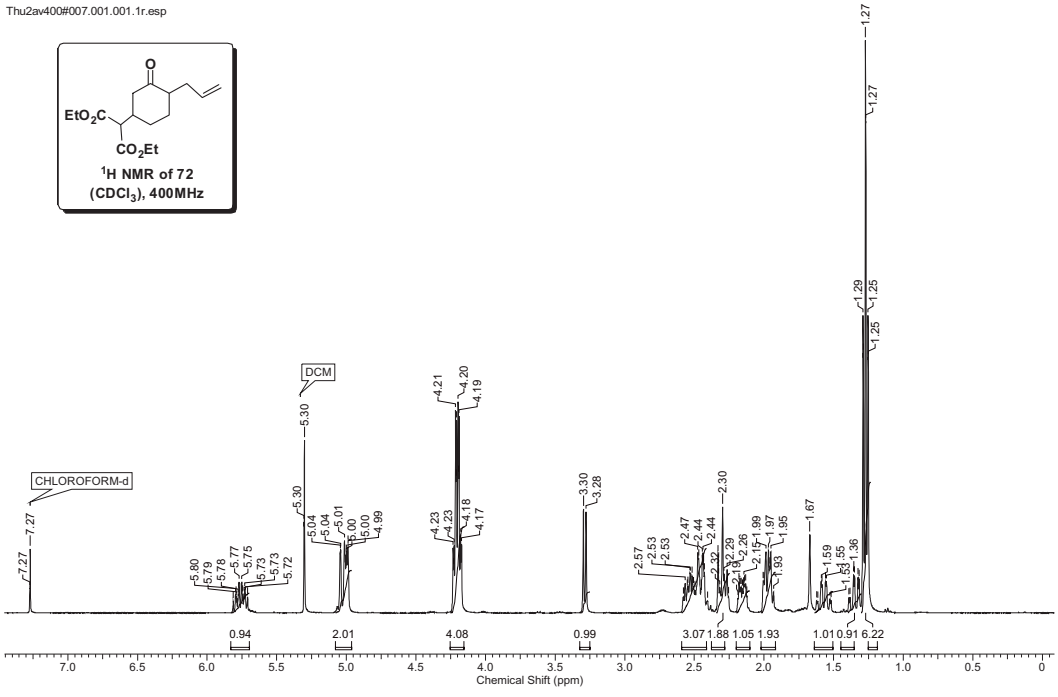

O
MeO2C
CO2Me
COSY
ppm
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
ppm

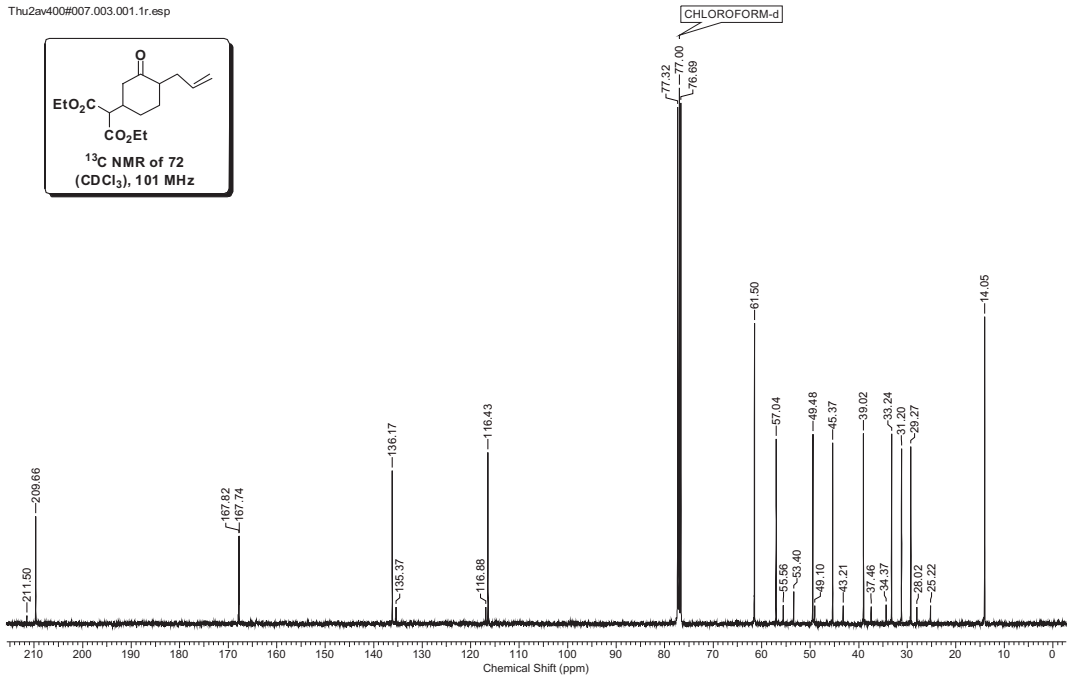
HSQC

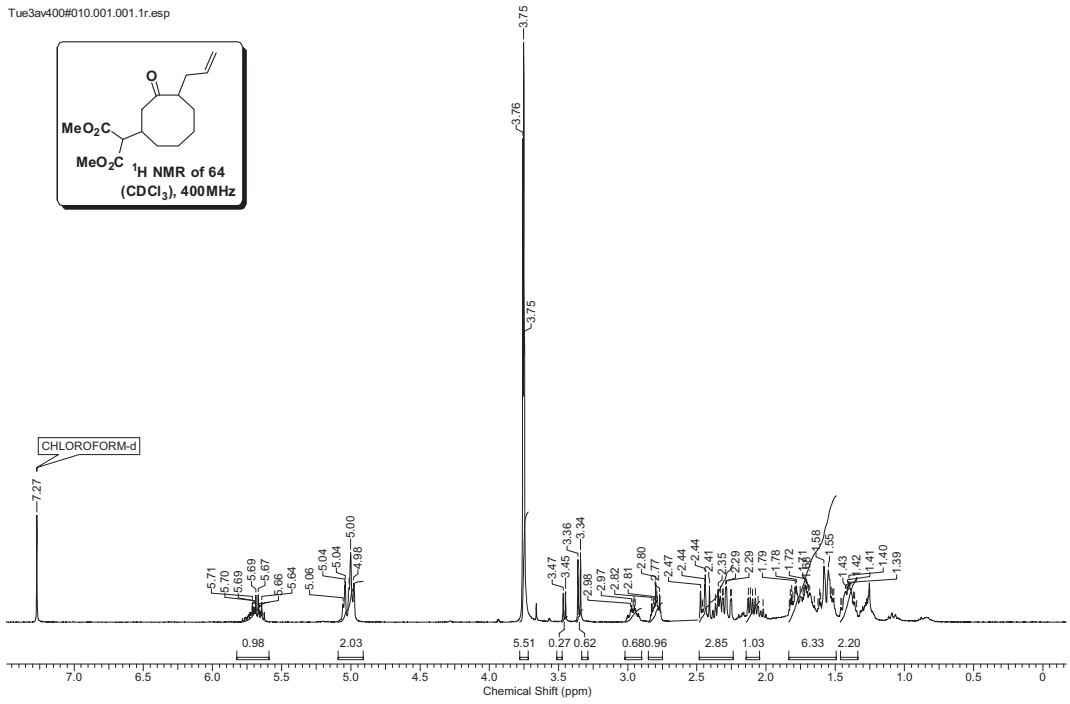

ppm
30
35
40
45
50
55
60
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
ppm

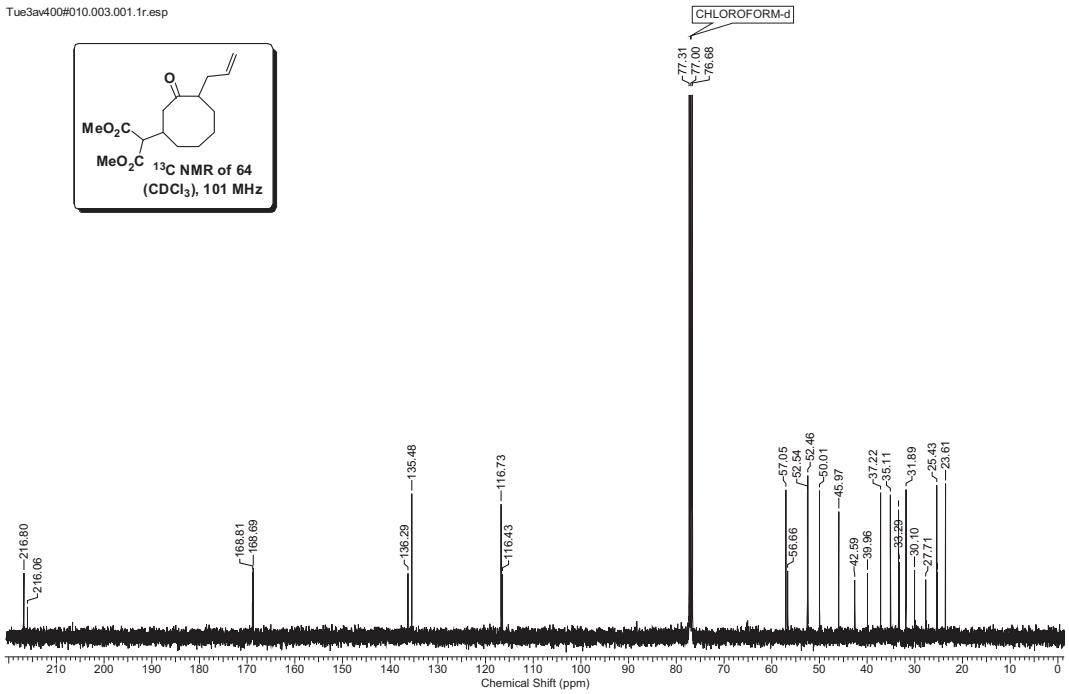
NOE

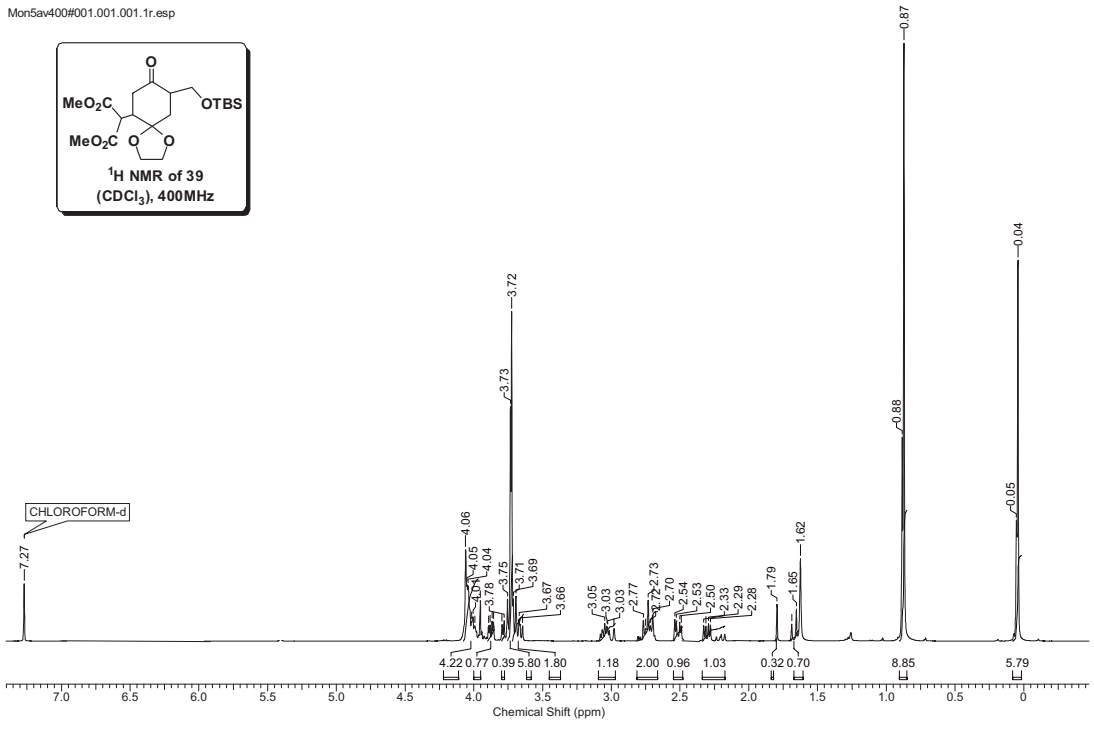

ppm
MeO2C
CO2Me
O
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 ppm

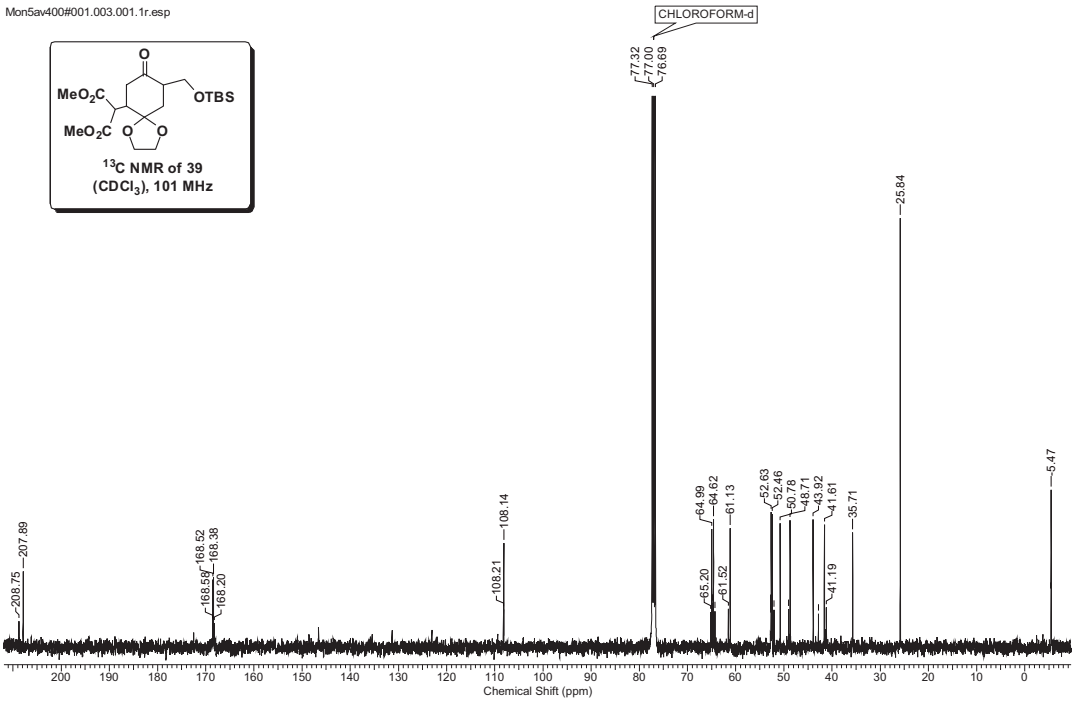

Thu2av400#007.001.001.1r.esp
EtO2C
CO2Et
O
1H NMR of 72
(CDCl3), 400MHz
CHLOROFORM-d
DCM
7.27
5.80 5.79 5.78 5.77 5.75 5.73 5.73 5.72
5.30 5.30 5.04 5.04 5.01 5.00 5.00 4.99
4.21 4.20 4.19
4.23 4.23 4.18 4.17
3.30 3.28
2.57 2.53 2.53 2.47 2.44 2.44 2.32 2.30 2.29 2.26 2.15 1.99 1.97 1.95 1.93
1.67
1.59 1.55 1.53 1.36
1.29 1.27 1.25 1.25
0.94 2.01 4.08 0.99 3.07 1.88 1.05 1.93 1.01 0.91 6.22
Chemical Shift (ppm)

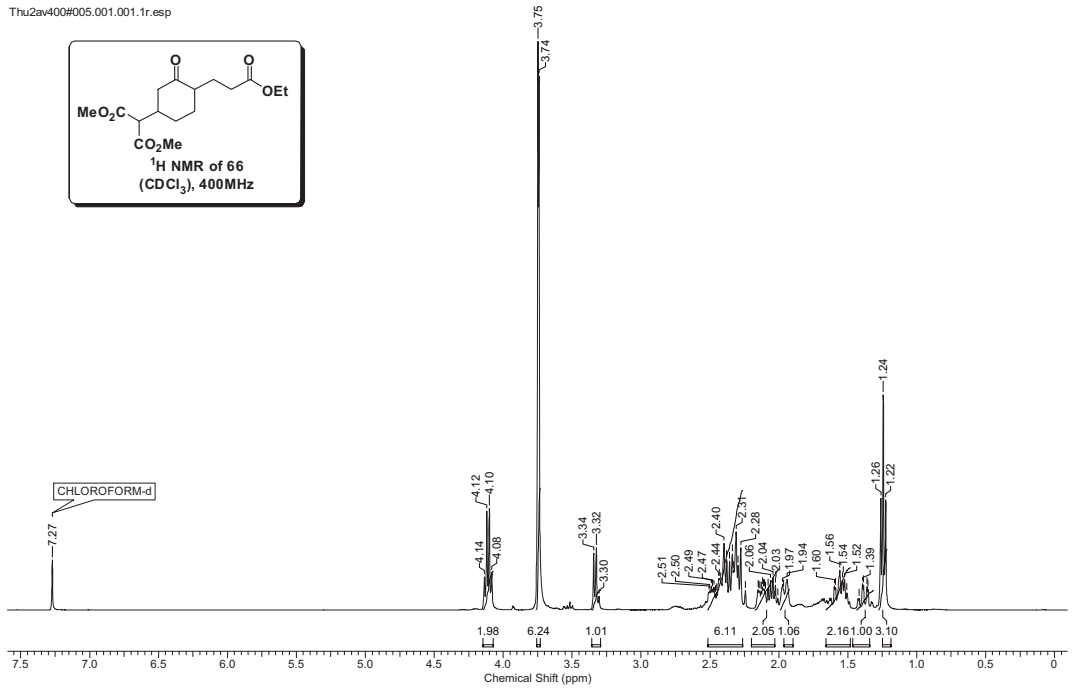

Thu2av400#007.003.001.1r.esp
CHLOROFORM-d
EtO2C
CO2Et
13C NMR of 72
(CDCl3), 101 MHz
77.32
77.00
76.69
61.50
14.05
57.04
49.48
45.37
39.02
33.24
31.20
29.27
136.17
116.43
209.66
167.82
167.74
135.37
116.88
211.50
55.56
53.40
49.10
43.21
37.46
34.37
28.02
25.22
Chemical Shift (ppm)

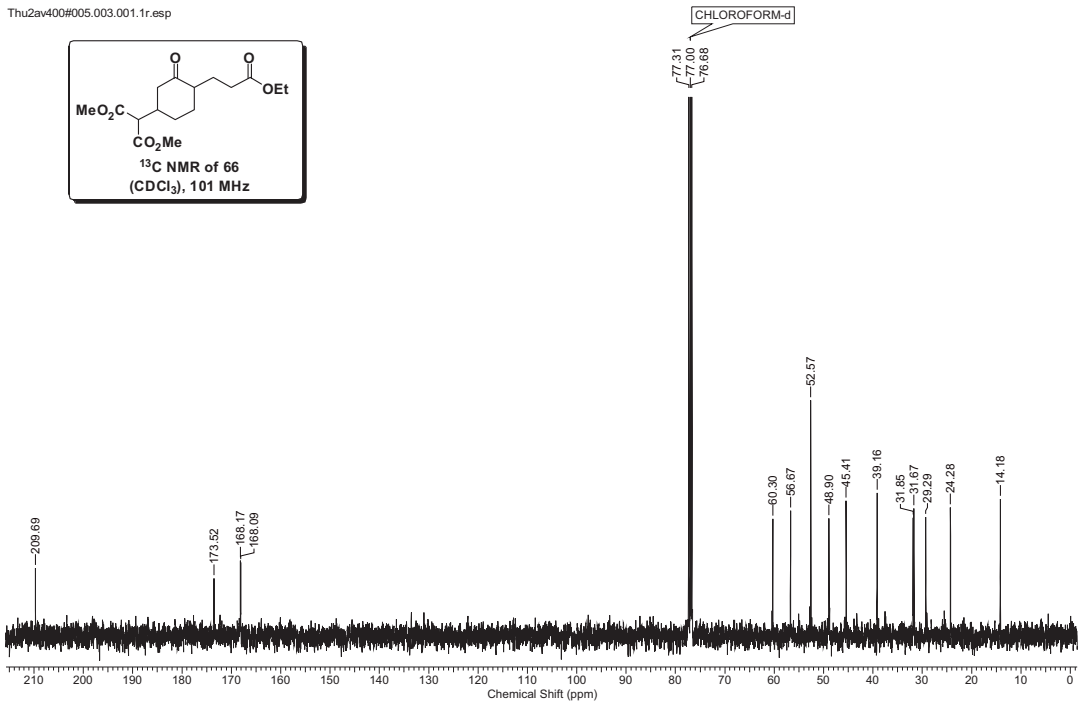

Tue3av400#010.001.001.1r.esp
MeO2C
MeO2C
1H NMR of 64
(CDCl3), 400MHz
3.75
3.76
3.75
CHLOROFORM-d
7.27
5.71
5.70
5.69
5.69
5.67
5.66
5.64
5.06
5.04
5.04
5.00
4.98
3.47
3.45
3.36
3.34
2.98
2.97
2.82
2.81
2.80
2.77
2.47
2.44
2.41
2.35
2.29
1.79
1.78
1.72
1.58
1.55
1.43
1.42
1.41
1.40
1.39
0.98
2.03
5.51
0.27
0.62
0.68
0.96
2.85
1.03
6.33
2.20
Chemical Shift (ppm)

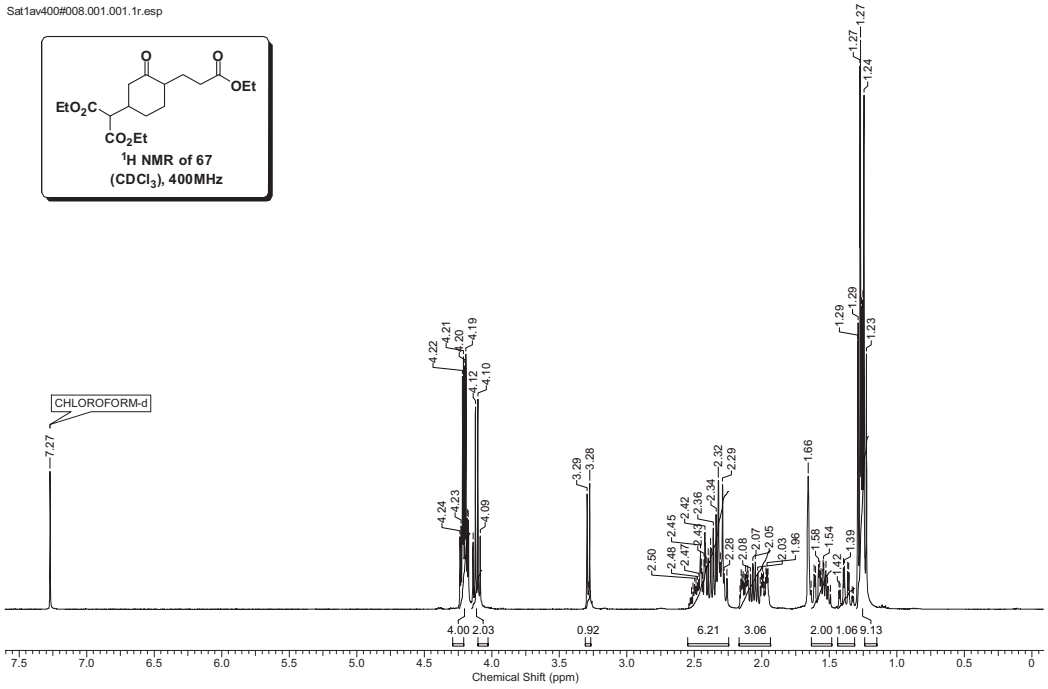

Tue3av400#010.003.001.1r.esp
CHLOROFORM-d
MeO2C
MeO2C
13C NMR of 64
(CDCl3), 101 MHz
77.31
77.00
76.68
216.80
216.06
168.81
168.69
136.29
135.48
116.73
116.43
57.05
56.66
52.54
52.46
50.01
45.97
42.59
39.96
37.22
35.11
33.29
31.89
30.10
27.71
25.43
23.61
Chemical Shift (ppm)

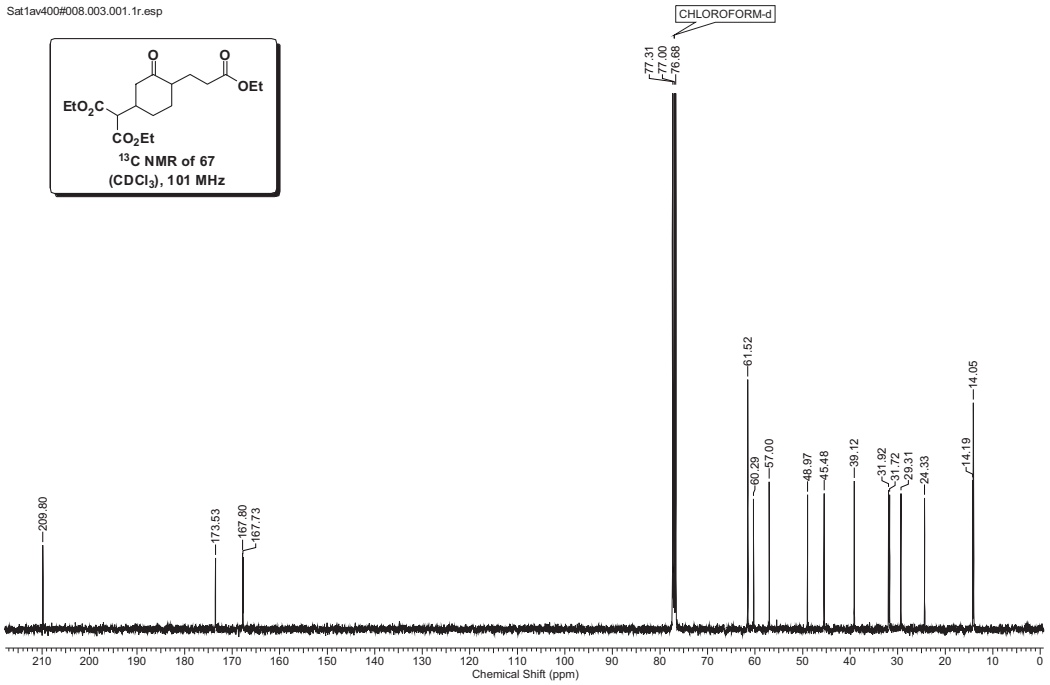

Mon5av400#001.001.001.1r.esp
MeO2C
MeO2C
OTBS
1H NMR of 39
(CDCl3), 400MHz
CHLOROFORM-d
7.27
4.06
4.05
4.04
4.01
3.78
3.75
3.72
3.73
3.71
3.69
3.67
3.66
3.05
3.03
3.03
2.77
2.73
2.72
2.70
2.54
2.53
2.50
2.33
2.29
2.28
1.79
1.65
1.62
0.87
0.88
0.05
0.04
4.22 0.77 0.39 5.80 1.80
1.18
2.00 0.96 1.03
0.32 0.70
8.85
5.79
Chemical Shift (ppm)

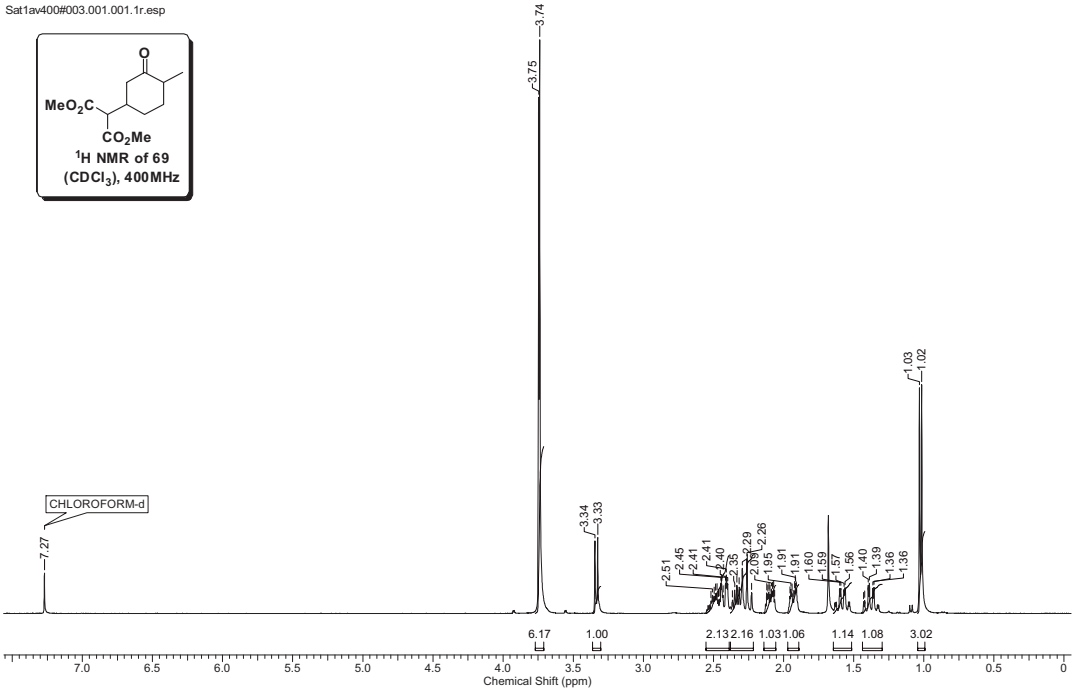

Mon5av400#001.003.001.1r.esp
CHLOROFORM-d
^{13}C NMR of 39
($CDCl_3$), 101 MHz
Chemical Shift (ppm)

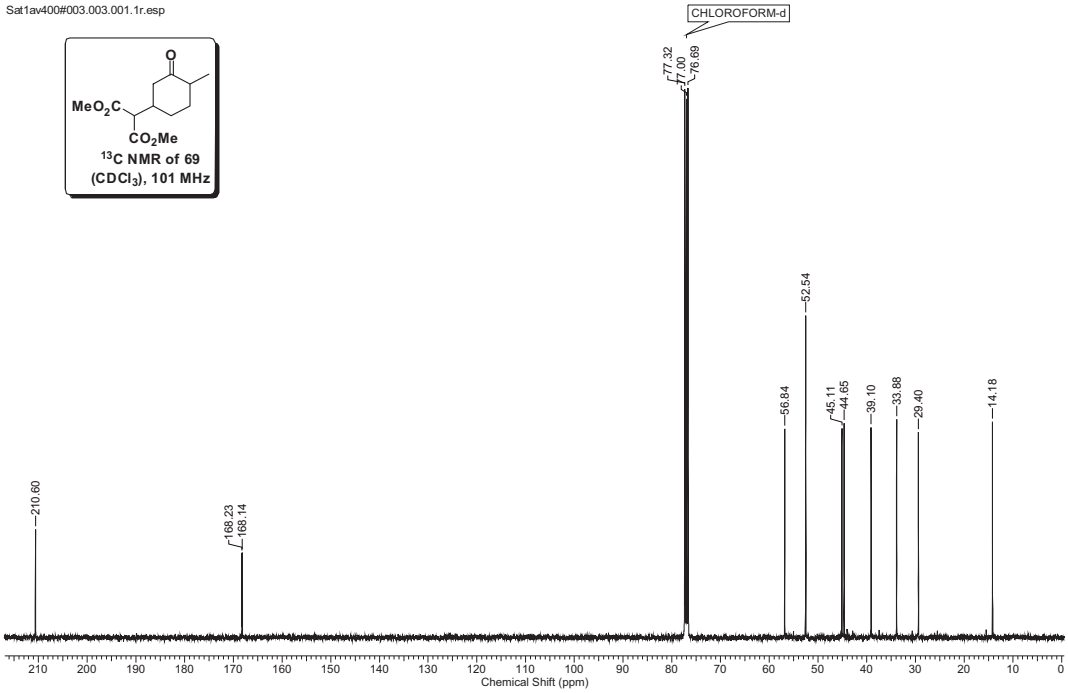

Thu2av400#005.001.001.1r.esp
CHLOROFORM-d
^{1}H NMR of 66
($CDCl_3$), 400MHz
Chemical Shift (ppm)

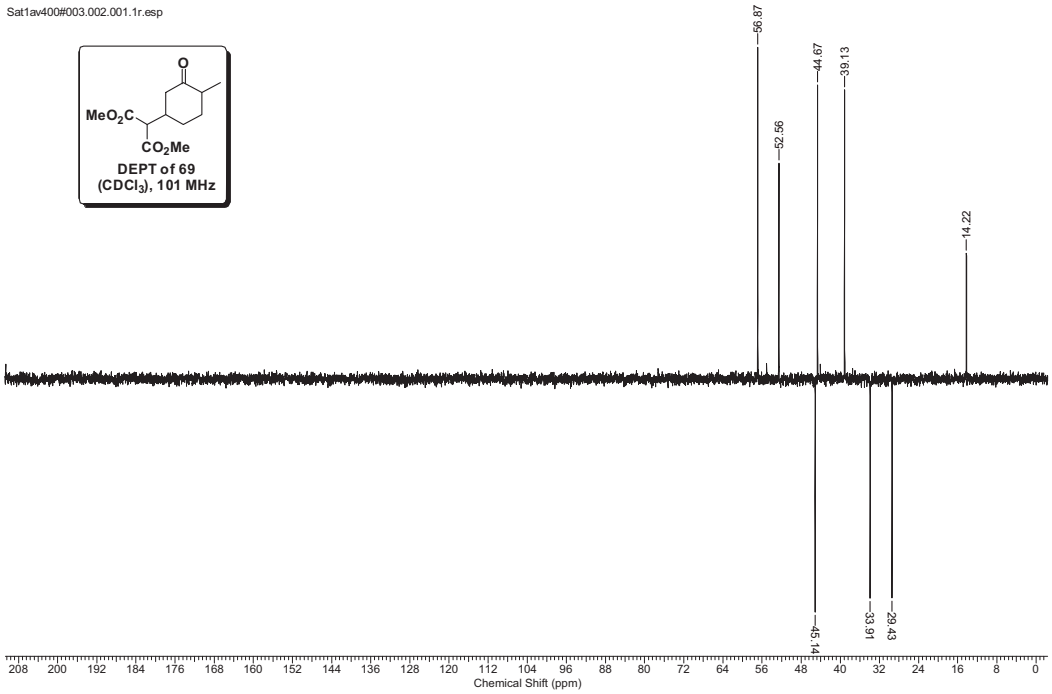

Thu2av400#005.003.001.1r.esp
CHLOROFORM-d
77.31
77.00
76.68
MeO2C
CO2Me
OEt
13C NMR of 66
(CDCl3), 101 MHz
209.69
173.52
168.17
168.09
60.30
56.67
52.57
48.90
45.41
39.16
31.85
31.67
29.29
24.28
14.18
Chemical Shift (ppm)

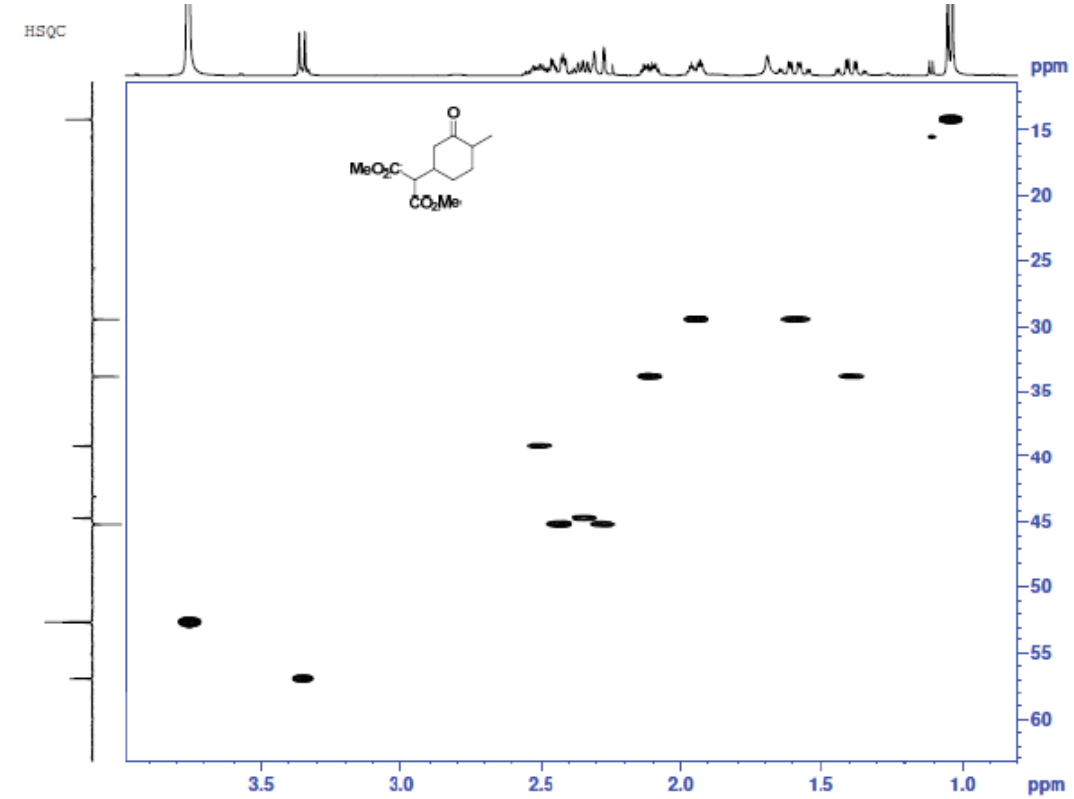

Sat1av400#008.001.001.1r.esp
EtO2C
CO2Et
OEt
1H NMR of 67
(CDCl3), 400MHz
CHLOROFORM-d
7.27
4.22
4.21
4.20
4.19
4.12
4.10
4.24
4.23
4.09
3.29
3.28
2.32
2.29
2.45
2.42
2.36
2.34
2.43
2.41
2.28
2.08
2.07
2.05
2.03
1.96
1.66
1.58
1.54
1.39
1.27
1.27
1.24
1.29
1.29
1.23
4.00
2.03
0.92
6.21
3.06
2.00
1.06
9.13
Chemical Shift (ppm)

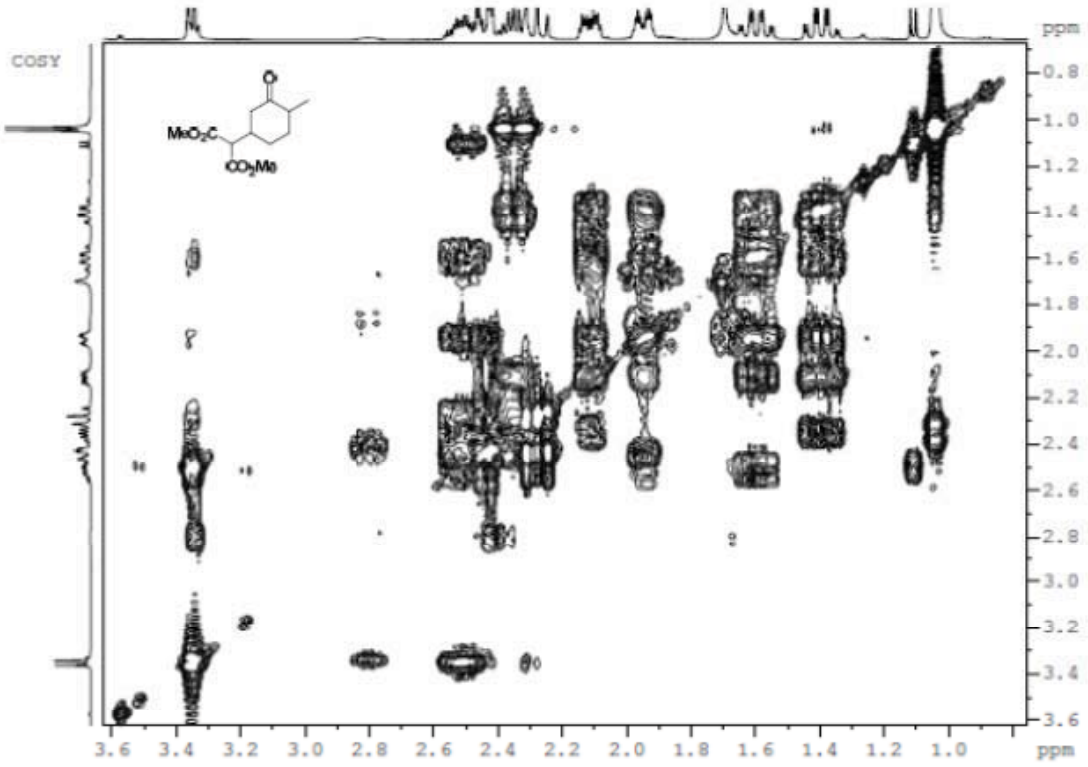

Sat1av400#008.003.001.1r.esp
CHLOROFORM-d
77.31
77.00
76.68
61.52
14.05
60.29
57.00
48.97
45.48
39.12
31.92
31.72
29.31
24.33
14.19
209.80
173.53
167.80
167.73
Chemical Shift (ppm)
EtO2C
CO2Et
OEt
13C NMR of 67
(CDCl3), 101 MHz

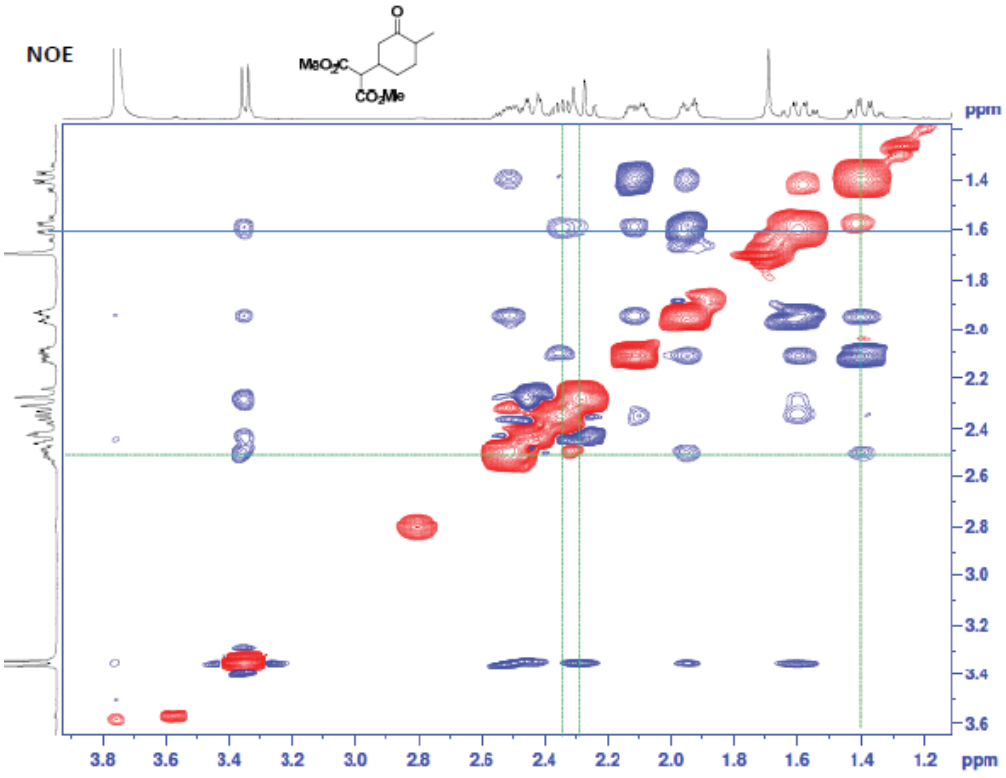

Sat1av400#003.001.001.1r.esp
CHLOROFORM-d
7.27
3.74
3.75
3.34
3.33
1.03
1.02
6.17
1.00
2.13
2.16
1.03
1.06
1.14
1.08
3.02
Chemical Shift (ppm)
MeO2C
CO2Me
1H NMR of 69
(CDCl3), 400MHz

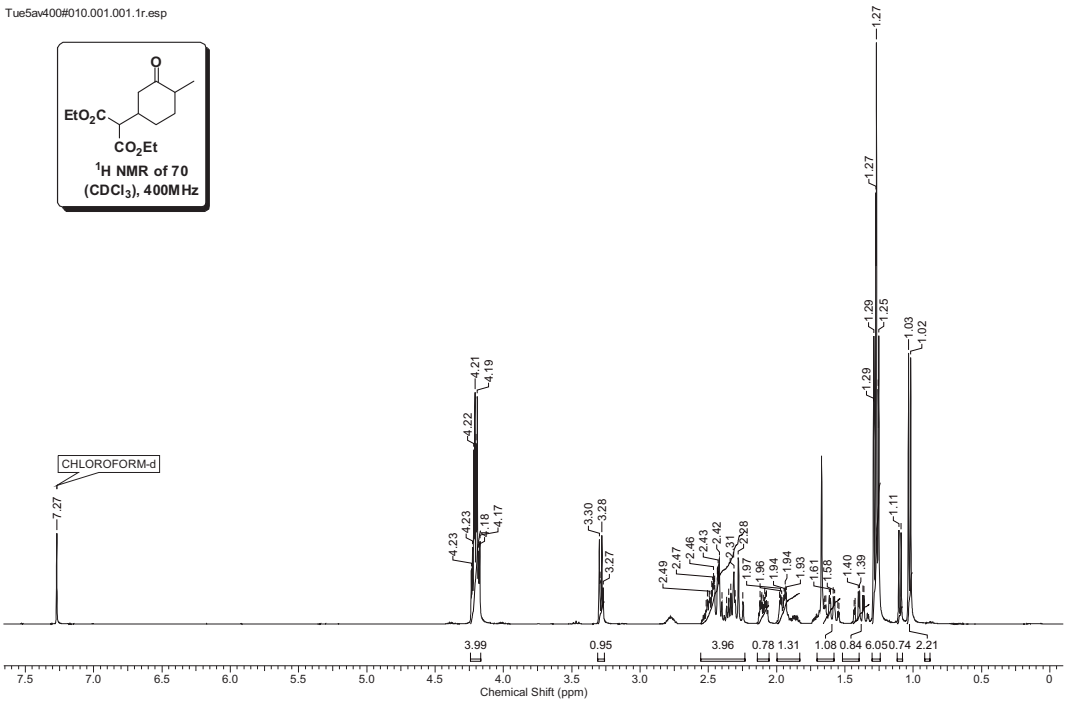

Sat1av400#003.003.001.1r.esp
CHLOROFORM-d
77.32
77.00
76.69
52.54
56.84
45.11
44.65
39.10
33.88
29.40
14.18
210.60
168.23
168.14
MeO2C
CO2Me
13C NMR of 69
(CDCl3), 101 MHz
Chemical Shift (ppm)

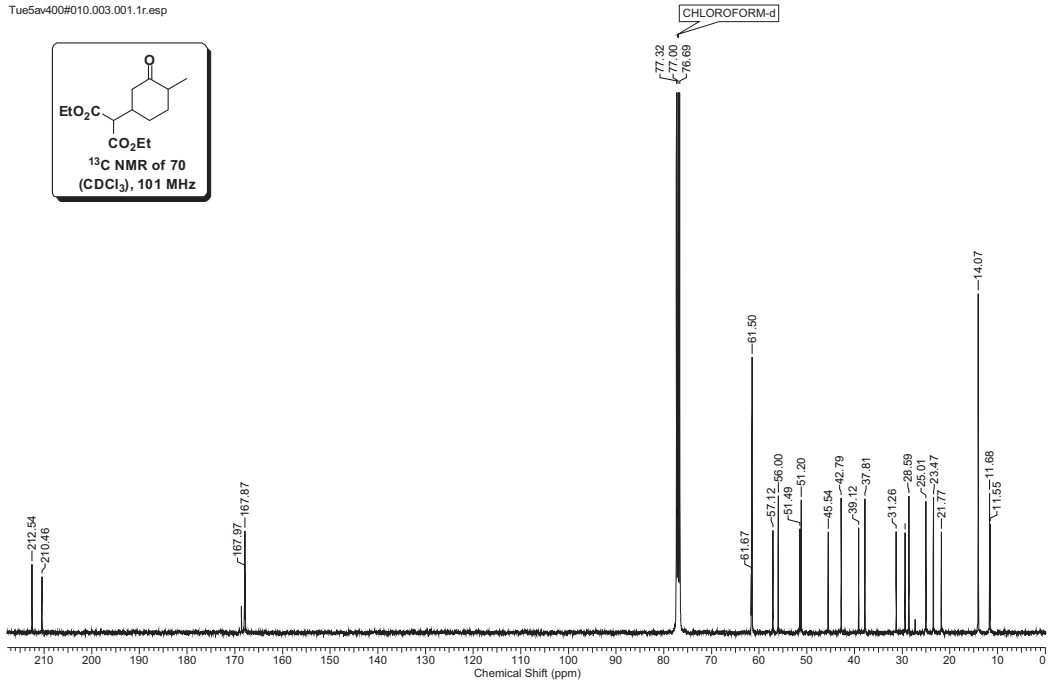

Sat1av400#003.002.001.1r.esp
56.87
44.67
39.13
52.56
14.22
45.14
33.91
29.43
MeO2C
CO2Me
DEPT of 69
(CDCl3), 101 MHz
Chemical Shift (ppm)

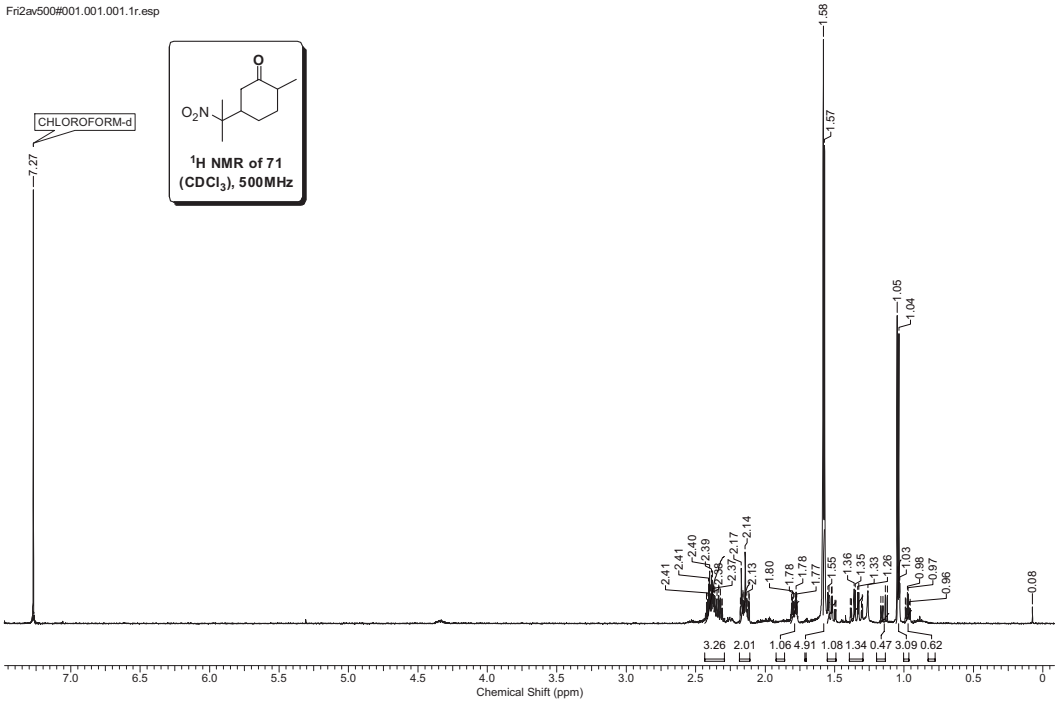

HSQC
ppm
15
20
25
30
35
40
45
50
55
60
3.5
3.0
2.5
2.0
1.5
1.0
ppm

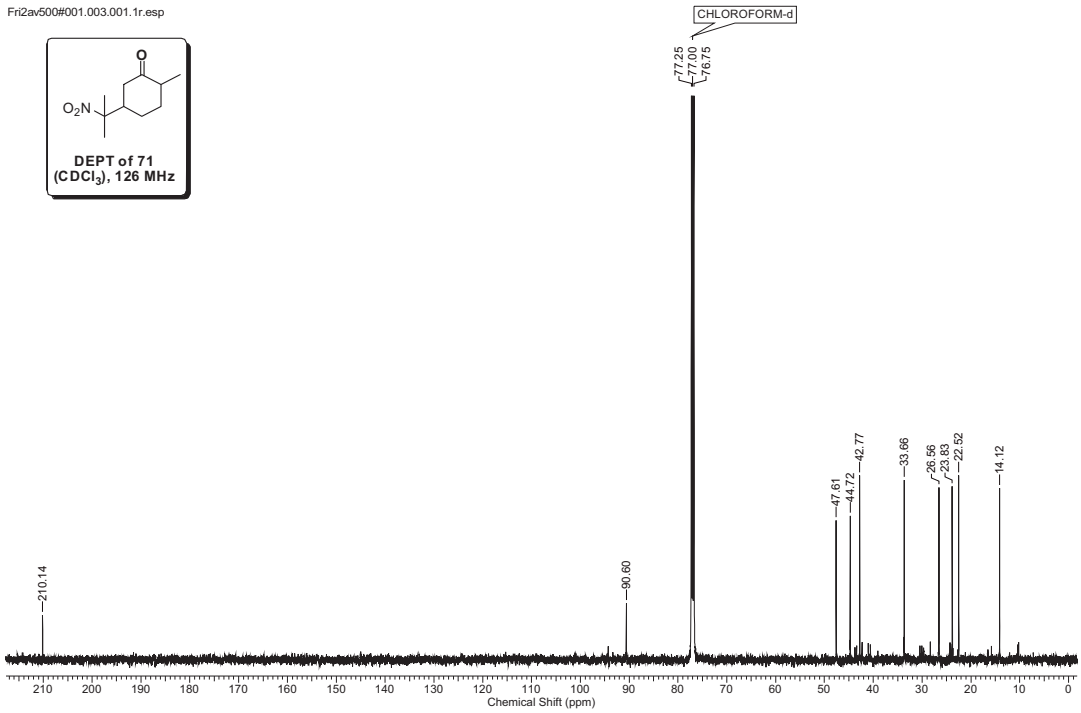

COSY
ppm
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
ppm

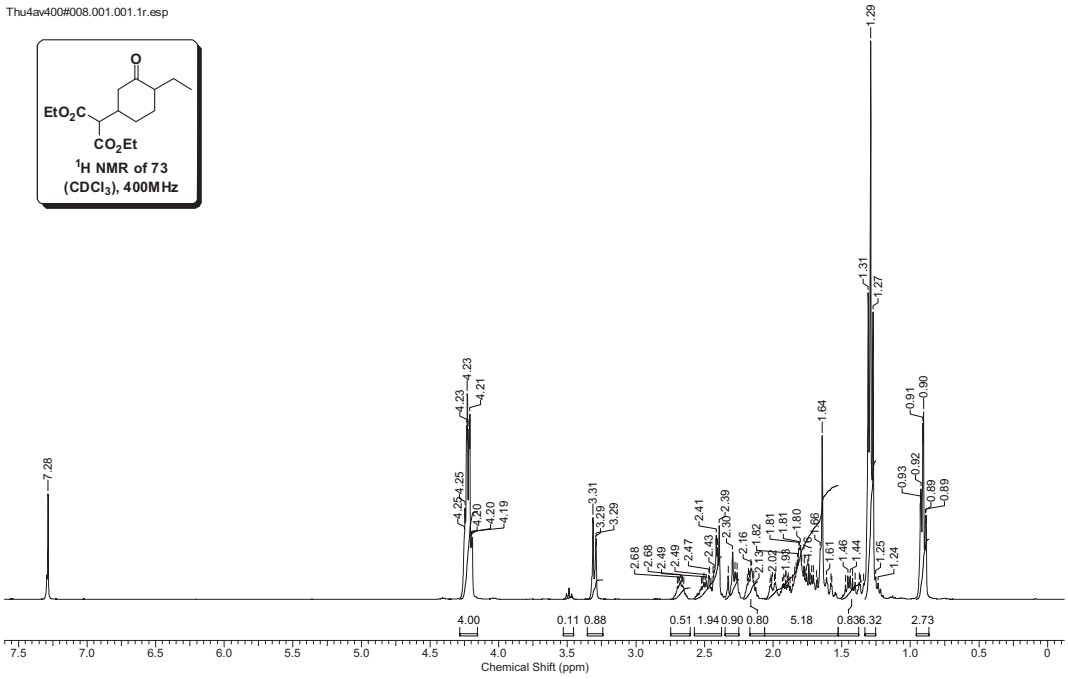

NOE
MeO2C
CO2Me
O
ppm
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
ppm

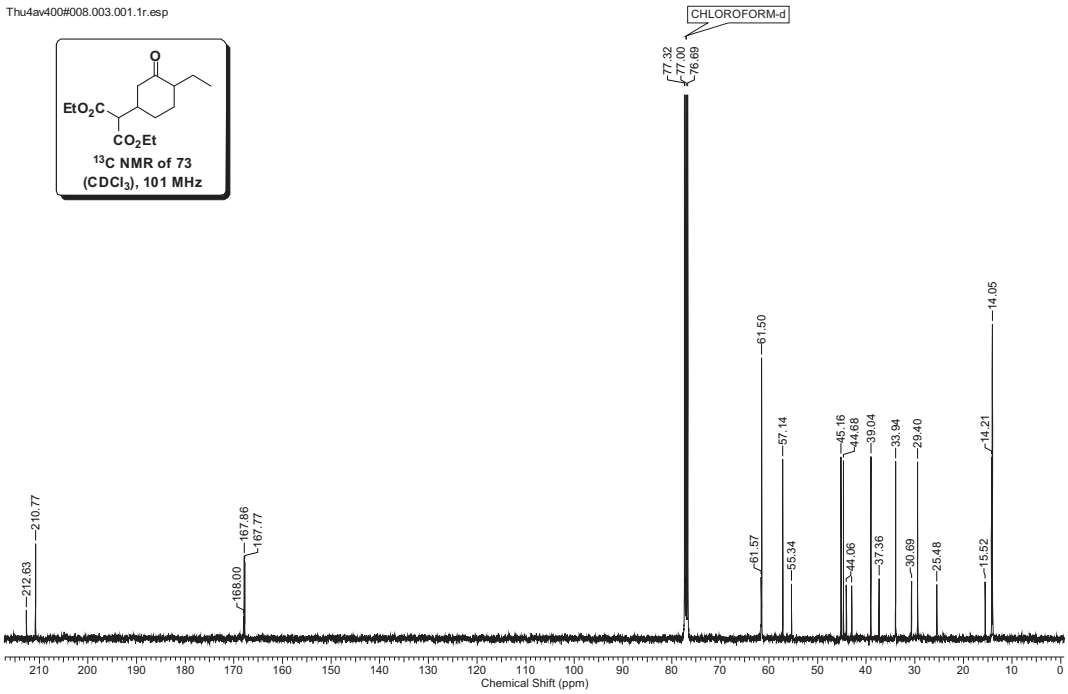

Tue5av400#010.001.001.1r.esp
EtO2C
CO2Et
O
1H NMR of 70
(CDCl3), 400MHz
CHLOROFORM-d
7.27
4.23
4.21
4.19
4.18
4.17
4.22
3.30
3.28
3.27
2.49
2.47
2.46
2.43
2.42
2.31
2.28
1.97
1.96
1.94
1.94
1.93
1.61
1.58
1.40
1.39
1.27
1.27
1.29
1.25
1.29
1.03
1.02
1.11
3.99
0.95
3.96
0.78
1.31
1.08
0.84
6.05
0.74
2.21
Chemical Shift (ppm)

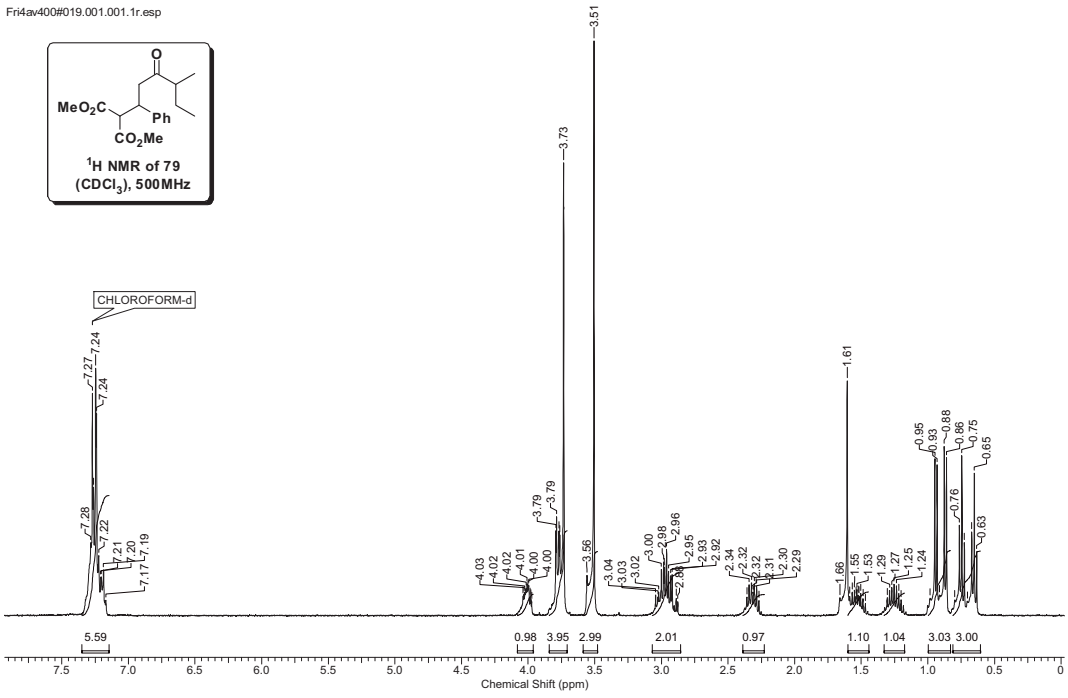

Tue5av400#010.003.001.1r.esp
CHLOROFORM-d
EtO2C
CO2Et
13C NMR of 70
(CDCl3), 101 MHz
77.32
77.00
76.69
212.54
210.46
167.97
167.87
61.67
61.50
57.12
56.00
51.49
51.20
45.54
42.79
39.12
37.81
31.26
28.59
25.01
23.47
21.77
14.07
11.68
11.55
Chemical Shift (ppm)

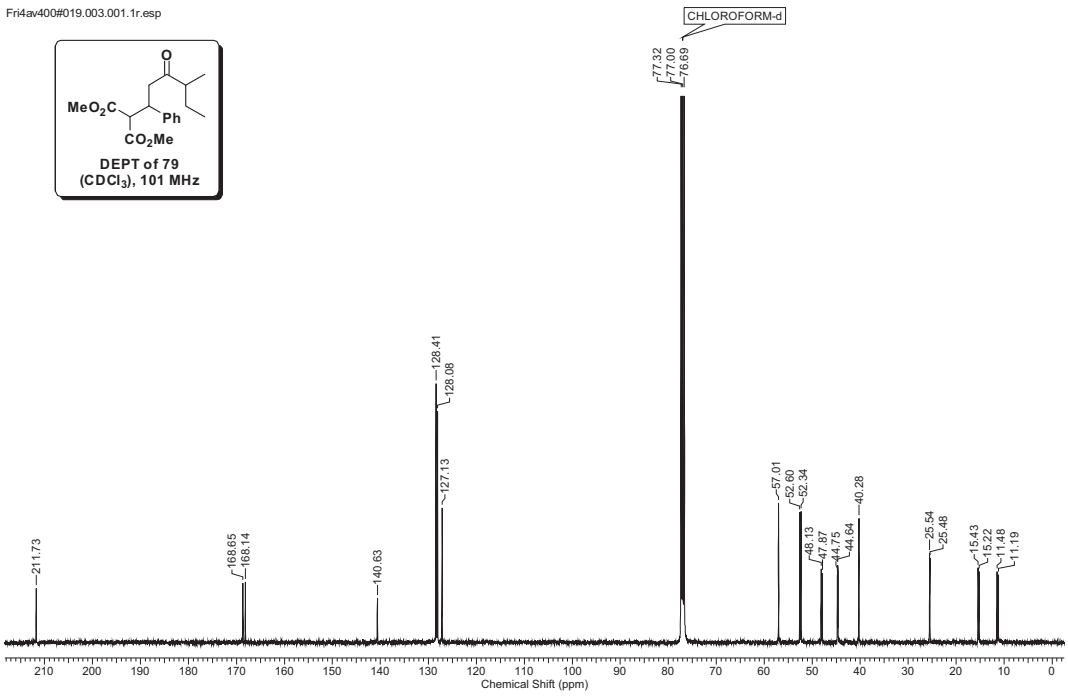

Fri2av500#001.001.001.1r.esp
CHLOROFORM-d
O2N
1H NMR of 71
(CDCl3), 500MHz
7.27
1.58
1.57
1.05
1.04
2.41
2.40
2.39
2.38
2.37
2.17
2.14
2.13
1.80
1.78
1.77
1.55
1.36
1.35
1.33
1.26
1.03
0.98
0.97
0.96
0.08
3.26 2.01 1.06 4.91 1.08 1.34 0.47 3.09 0.62
Chemical Shift (ppm)

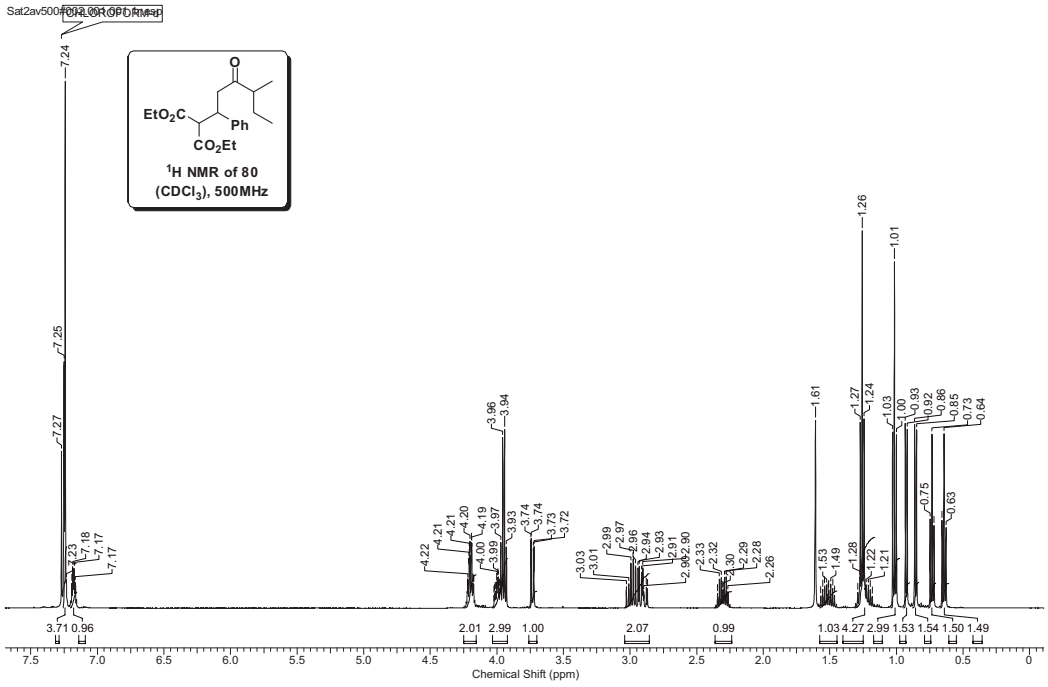

Fri2av500#001.003.001.1r.esp
CHLOROFORM-d
77.25
77.00
76.75
O
O2N
DEPT of 71
(CDCl3), 126 MHz
210.14
90.60
47.61
44.72
42.77
33.66
26.56
23.83
22.52
14.12
Chemical Shift (ppm)

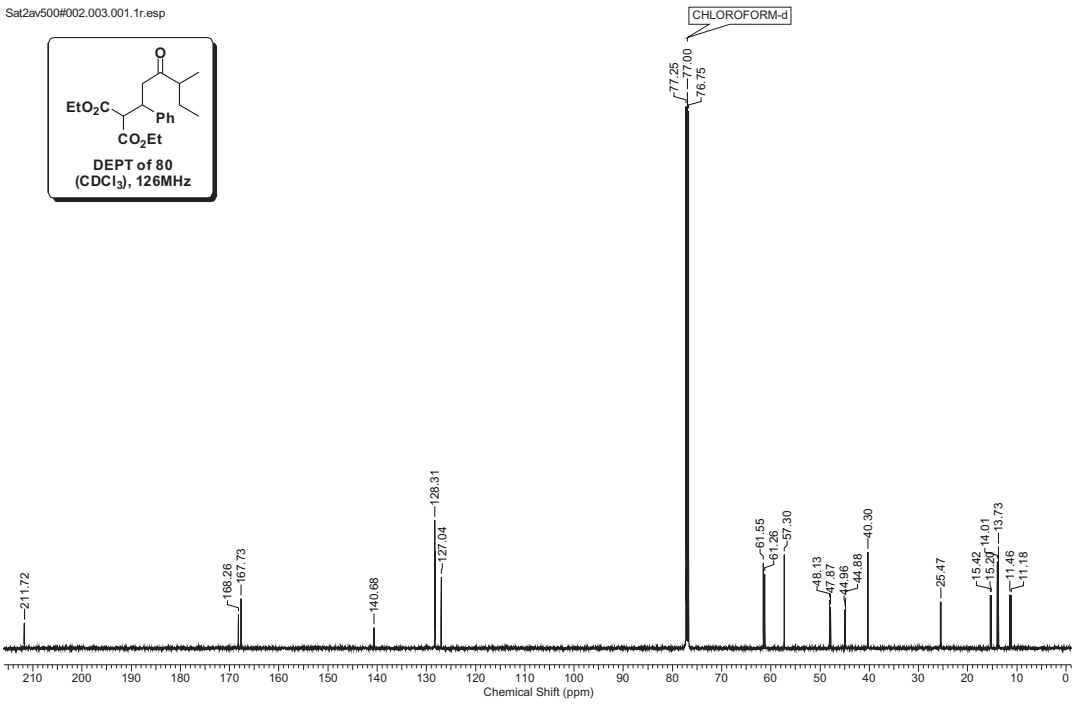

Thu4av400#008.001.001.1r.esp
O
EtO2C
CO2Et
1H NMR of 73
(CDCl3), 400MHz
7.28
4.25
4.23
4.21
4.20
4.19
3.31
3.29
2.68
2.49
2.47
2.43
2.41
2.39
2.30
2.16
1.82
1.81
1.80
1.66
1.64
1.61
1.46
1.44
1.31
1.29
1.27
1.25
1.24
0.93
0.92
0.91
0.90
0.89
0.88
4.00
0.11
0.88
0.51
1.94
0.90
0.80
5.18
0.83
6.32
2.73
Chemical Shift (ppm)


Thu4av400#008.003.001.1r.esp
EtO2C
CO2Et
O
13C NMR of 73
(CDCl3), 101 MHz
CHLOROFORM-d
77.32
77.00
76.69
210.77
212.63
167.86
167.77
168.00
61.50
61.57
57.14
55.34
45.16
44.68
44.06
39.04
37.36
33.94
30.69
29.40
25.48
14.05
14.21
15.52
Chemical Shift (ppm)

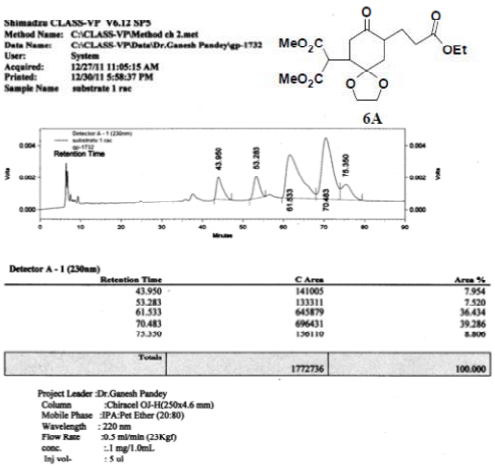

Fri4av400#019.001.001.1r.esp
MeO2C
Ph
CO2Me
O
1H NMR of 79
(CDCl3), 500MHz
CHLOROFORM-d
3.51
3.73
3.79
3.79
3.56
1.61
0.95
0.93
0.88
0.86
0.75
0.65
0.76
0.63
7.28
7.27
7.24
7.24
7.22
7.21
7.20
7.19
7.17
5.59
0.98
3.95
2.99
2.01
0.97
1.10
1.04
3.03
3.00
Chemical Shift (ppm)


Fri4av400#019.003.001.1r.esp
CHLOROFORM-d
MeO2C
Ph
CO2Me
DEPT of 79
(CDCl3), 101 MHz
77.32
77.00
76.69
128.41
128.08
127.13
211.73
168.65
168.14
140.63
57.01
52.60
52.34
48.13
47.87
44.75
44.64
40.28
25.54
25.48
15.43
15.22
11.48
11.19
Chemical Shift (ppm)


EtO2C
Ph
CO2Et
1H NMR of 80
(CDCl3), 500MHz
7.24
7.25
7.27
7.23
7.18
7.17
7.17
3.96
3.94
4.22
4.21
4.21
4.20
4.19
4.00
3.99
3.97
3.93
3.74
3.73
3.72
3.03
3.01
2.99
2.97
2.96
2.94
2.93
2.91
2.90
2.90
2.33
2.32
2.30
2.29
2.28
2.26
1.61
1.53
1.49
1.28
1.27
1.26
1.24
1.22
1.21
1.03
1.01
1.00
0.93
0.92
0.86
0.85
0.75
0.73
0.64
0.63
3.71
0.96
2.01
2.99
1.00
2.07
0.99
1.03
4.27
2.99
1.53
1.54
1.50
1.49
Chemical Shift (ppm)


Sat2av500#002.003.001.1r.esp
O
EtO2C
Ph
CO2Et
DEPT of 80
(CDCl3), 126MHz
CHLOROFORM-d
77.25
77.00
76.75
211.72
168.26
167.73
140.68
128.31
127.04
61.55
61.26
57.30
48.13
47.87
44.96
44.88
40.30
25.47
15.42
15.27
14.01
13.73
11.46
11.18
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)

2.11 HPLC spectras:



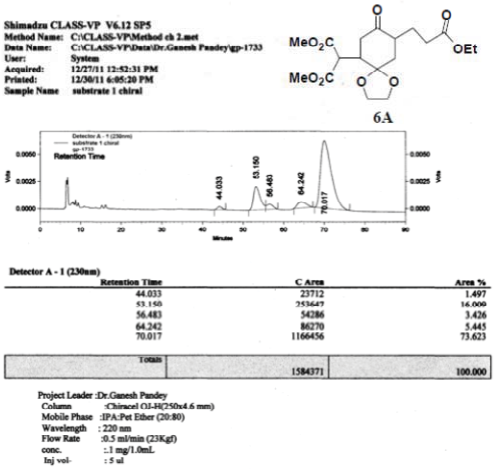
Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1732
User: System
Acquired: 12/27/11 11:05:15 AM
Printed: 12/30/11 5:58:37 PM
Sample Name substrate 1 rac

6A

Detector A - 1 (230nm)

Retention Time	C Area	Area %
43.950	141005	7.954
53.283	133311	7.520
61.533	645879	36.434
70.483	696431	39.286
75.350	156110	8.806
Totals	1772736	100.000

Project Leader :Dr.Ganesh Pandey
Column :Chiracel OJ-H(250x4.6 mm)
Mobile Phase :IPA:Pet Ether (20:80)
Wavelength : 220 nm
Flow Rate :0.5 ml/min (23Kgf)
conc. : 1 mg/1.0mL
Inj vol- : 5 ul



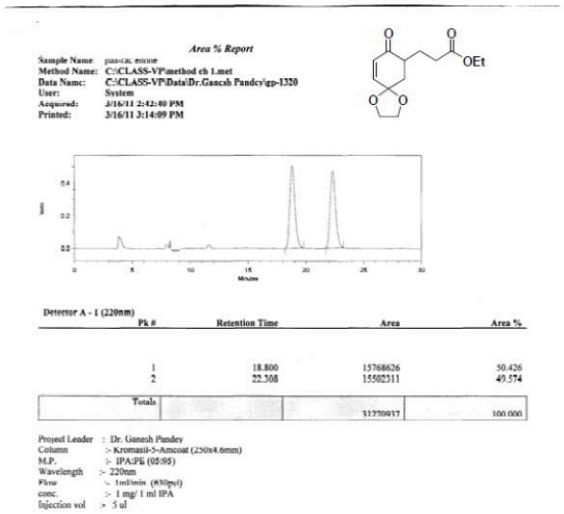
Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1733
User: System
Acquired: 12/27/11 12:52:31 PM
Printed: 12/30/11 6:05:20 PM
Sample Name substrate 1 chiral

6A

Detector A - 1 (230nm)

Retention Time	C Area	Area %
44.033	23712	1.497
53.150	253647	16.000
56.483	54286	3.426
64.242	86270	5.445
70.017	1166456	73.623
Totals	1584371	100.000

Project Leader :Dr.Ganesh Pandey
Column :Chiracel OJ-H(250x4.6 mm)
Mobile Phase :IPA:Pet Ether (20:80)
Wavelength : 220 nm
Flow Rate :0.5 ml/min (23Kgf)
conc. : 1 mg/1.0mL
Inj vol- : 5 ul



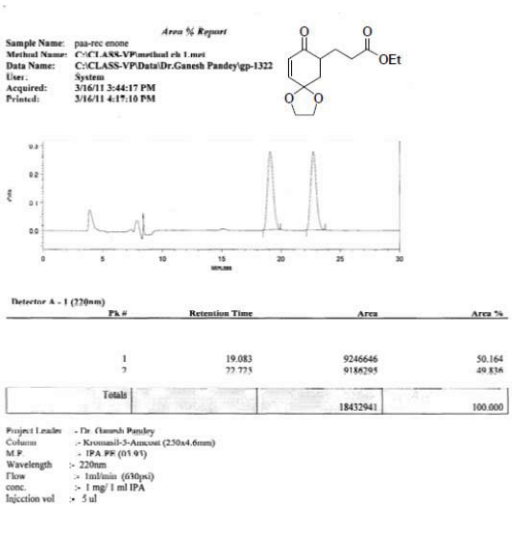
Area % Report

Sample Name pascal enone
Method Name: C:\CLASS-VP\method ch 1.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1320
User: System
Acquired: 3/16/11 2:42:40 PM
Printed: 3/16/11 3:14:09 PM

Detector A - 1 (220nm)

Pk #	Retention Time	Area	Area %
1	18.800	15768626	50.426
2	22.508	15502311	49.574
Totals		31270937	100.000

Project Leader : Dr. Ganesh Pandey
Column :- Kromasil-5-Amcoat (250x4.6mm)
M.P. :- IPA:PE (05:95)
Wavelength :- 220nm
Flow :- 1ml/min (630psi)
conc. :- 1 mg/ 1 ml IPA
Injection vol :- 5 ul



Area % Report

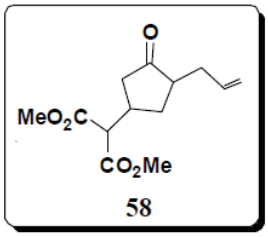
Sample Name: paa-rec enone
Method Name: C:\CLASS-VP\method ch 1.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1322
User: System
Acquired: 3/16/11 3:44:17 PM
Printed: 3/16/11 4:17:10 PM

Detector A - 1 (220nm)

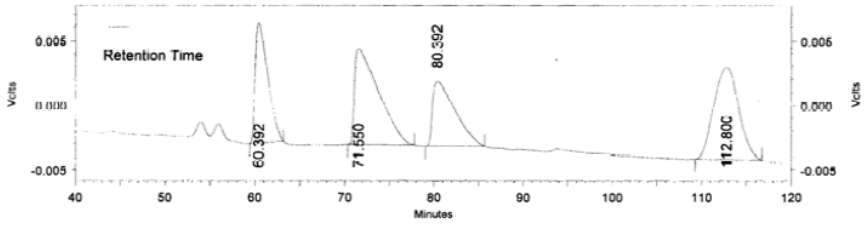
Pk #	Retention Time	Area	Area %
1	19.083	9246646	50.164
2	22.775	9186295	49.836
Totals		18432941	100.000

Project Leader :- Dr. Ganesh Pandey
Column :- Kromasil-5-Amcoat (250x4.6mm)
M.P. :- IPA:PE (05:95)
Wavelength :- 220nm
Flow :- 1ml/min (630psi)
conc. :- 1 mg/ 1 ml IPA
Injection vol :- 5 ul

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1469
User: System
Acquired: 6/27/11 2:17:13 PM
Printed: 6/29/11 5:47:44 PM
Sample Name PAA- pentane rac



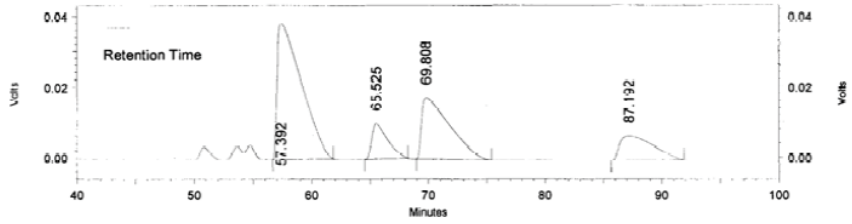
58



Detector A - 1 (230nm)

Retention Time	C Area	Area %
60.392	916559	19.924
71.550	1413445	30.725
80.392	894302	19.440
112.800	1375943	29.910
Totals	4600249	100.000

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1473
User: System
Acquired: 6/28/11 8:17:10 AM
Printed: 6/29/11 5:37:39 PM
Sample Name PAA- pentane chiral



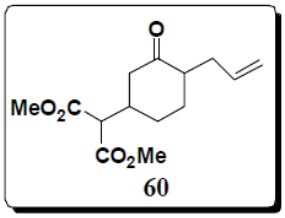
Detector A - 1 (230nm)

Retention Time	C Area	Area %
57.392	5475348	51.559
65.525	917351	8.638
69.808	2865756	26.985
87.192	1361180	12.818
Totals	10619635	100.000

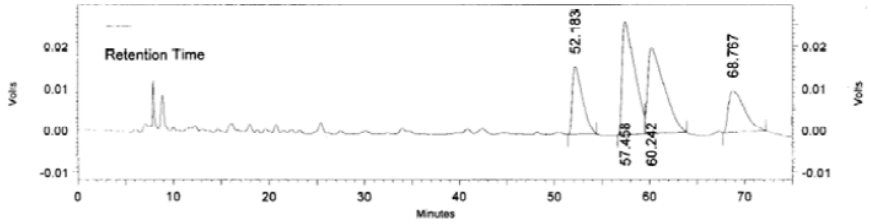
Project Leader :Dr. Ganesh Pandey
Column :Chiralpalpak AS-H (4.6x250 mm)
Mobile Phase :IPA : PE (2.0:98.0)
Flow Rate : 0.5ml/min (Pressure 235kgf)
Wavelength : 230nm
Con. : 2mg/0.5ml

Inject vol. :20uL

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1424
User: System
Acquired: 6/10/11 12:52:31 PM
Printed: 6/10/11 3:35:33 PM
Sample Name PAA- ALLYLCYCLOHEXANONE RAC



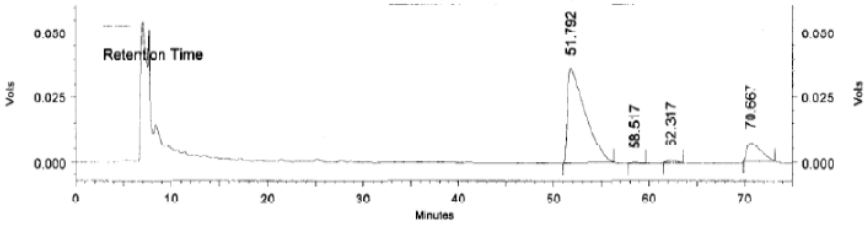
60



Detector A - 1 (230nm)

Retention Time	C Area	Area %
52.183	1223415	16.603
57.458	2479045	33.643
60.242	2481126	33.671
68.767	1185132	16.083
Totals	7368718	100.000

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1426
User: System
Acquired: 6/10/11 2:09:18 PM
Printed: 6/10/11 3:31:32 PM
Sample Name PAA- ALLYLCYCLOHEXANONE CHIRAL

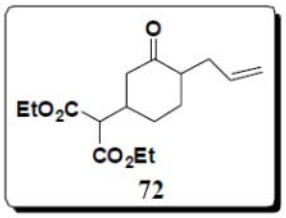


Detector A - 1 (230nm)

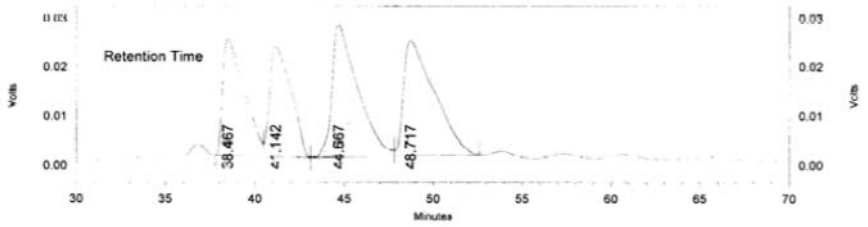
Retention Time	C Area	Area %
51.792	4738840	85.350
58.517	10641	0.192
62.317	76365	1.375
70.667	726393	13.083
Totals	5552239	100.000

Project Leader :Dr.Ganesh Pandey
Column :Chiralcel OJ-H (0.46cm X 25cm)
Mobile Phase :IPA:PE (2:98)
Flow Rate : 0.5 ml/min 246psi
Wavelength : 230nm
Con. : 3mg /0.5ml
Inject vol. :20uL

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1566
User: System
Acquired: 8/8/11 12:07:22 PM
Printed: 8/10/11 10:53:11 AM
Sample Name PAA- ETHYL-ALLYL HEX RAC



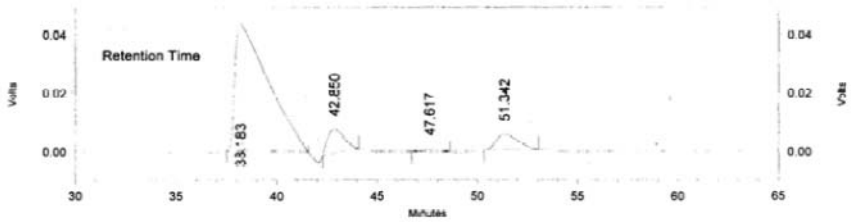
72



Detector A - 1 (230nm)

Retention Time	C Area	Area %
38.467	1973417	21.016
41.142	1870465	19.920
44.667	2732438	29.100
48.717	2813570	29.964
Totals	9389890	100.000

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1568
User: System
Acquired: 8/8/11 2:32:43 PM
Printed: 8/10/11 11:00:58 AM
Sample Name PAA- ETHYL-ALLYL HEX chiral

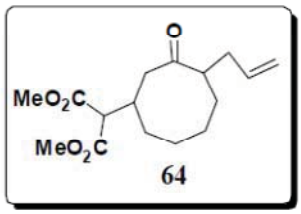


Detector A - 1 (230nm)

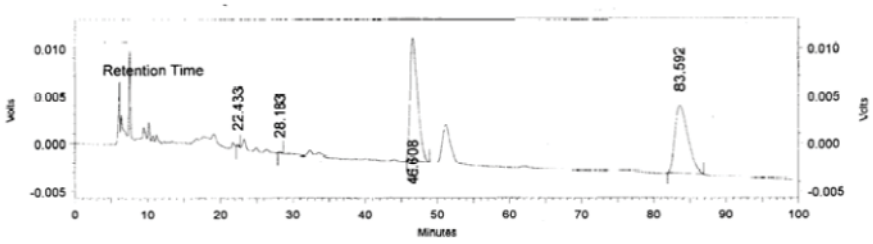
Retention Time	C Area	Area %
38.183	5013488	84.724
42.850	462574	7.817
47.617	51877	0.877
51.342	389518	6.583
Totals	5917457	100.000

Project Leader :Dr. Ganesh Pandey
Column :Chiralcel-OJ-H (4.6x250 mm)
Mobile Phase :IPA:PE (0.5:99.5)
Flow Rate : 0.5ml/min (Pressure25Kgf)
Wavelength : 230nm
Con. : 1mg/0.2ml
Inject vol. : 20 uL

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1525
User: System
Acquired: 7/14/11 3:13:26 PM
Printed: 7/14/11 5:27:44 PM
Sample Name PAA- OCTANE Rac



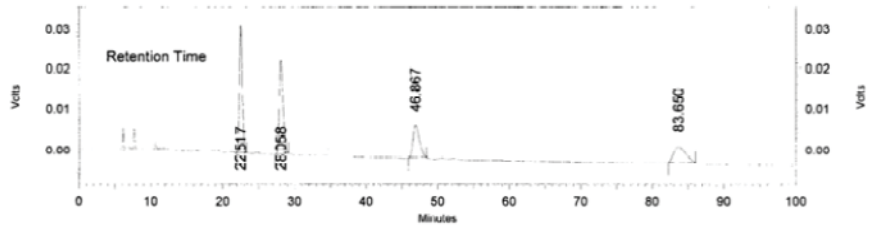
64



Detector A - 1 (230nm)

Retention Time	C Area	Area %
22.433	3700	0.207
28.183	3500	0.196
46.608	895689	50.118
83.592	884283	49.479
Totals	1787172	100.000

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1524
User: System
Acquired: 7/14/11 1:27:55 PM
Printed: 7/14/11 3:11:25 PM
Sample Name PAA- OCTANE CHIRAL

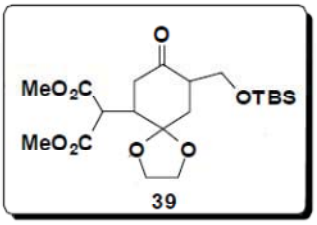


Detector A - 1 (230nm)

Retention Time	C Area	Area %
22.517	887523	31.971
28.058	873897	31.480
46.867	529112	19.060
83.650	485489	17.489
Totals	2776021	100.000

Project Leader :Dr. Ganesh Pandey
Column :Kromasil 5-AmyCoat (4.6x250 mm)
Mobile Phase :EtOH : n-Hexane (02:98)
Flow Rate : 0.5ml/min (Pressure 26kgf)
Wavelength : 230nm
Con. : 1mg/0.2ml
Inject vol. :20uL

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1718
User: System
Acquired: 11/22/11 3:06:23 PM
Printed: 11/22/11 5:50:18 PM
Sample Name PAA-TBS rac



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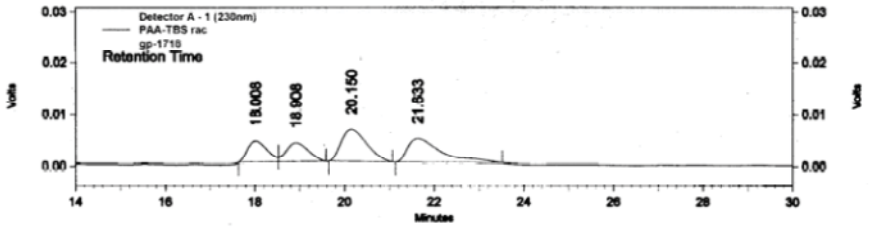
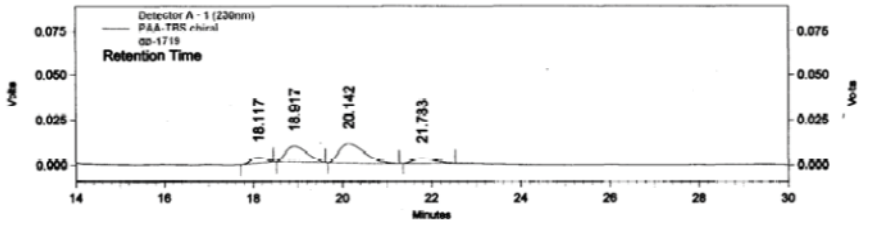


Detector A - 1 (230nm)

Retention Time	C Area	Area %
18.008	125498	16.848
18.908	125456	16.843
20.150	248433	33.353
21.633	245477	32.956
Totals	744864	100.000

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1719
User: System
Acquired: 11/22/11 3:42:30 PM
Printed: 11/22/11 5:56:36 PM
Sample Name PAA-TBS chiral

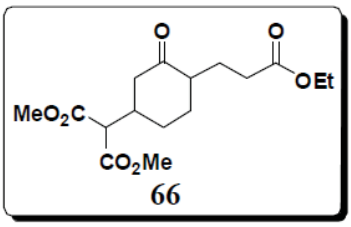


Detector A - 1 (230nm)

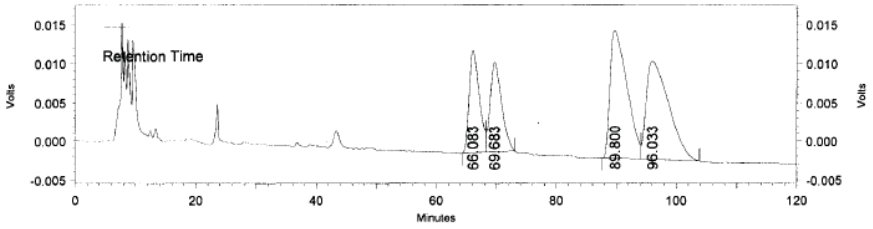
Retention Time	C Area	Area %
18.117	64915	7.923
18.917	265932	32.457
20.142	400777	48.916
21.783	87700	10.704
Totals	819324	100.000

Project Leader :Dr. Ganesh Pandey
Column :Chiralcel OJ-H(250x4.6 mm)
Mobile Phase :IPA:Pet Ether (1.5:98.5)
Wavelength : 230 nm
Flow Rate : 0.5 ml/min (19 kgf)
conc. :1 mg/mL
Inj vol- : 5 ul

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1395
User: System
Acquired: 6/4/11 8:00:43 PM
Printed: 6/6/11 5:11:16 PM
Sample Name paa-274 I RAC



66

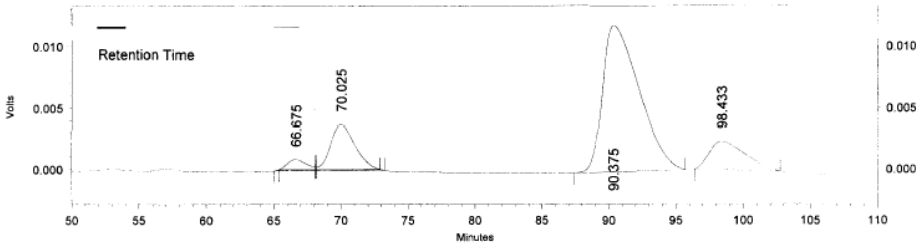


Detector A - 1 (230nm)

Retention Time	C Area	Area %
66.083	1556456	16.097
69.683	1542824	15.956
89.800	3235931	33.466
96.033	3334098	34.481
Totals	9669309	100.000

Shimadzu CLASS-VP V6.12 SP5 *Area % Report*
Page 1 of 1 paa-274 I B

Method Name: C:\CLASS-VP\Methods\Date6june.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1396
User: System
Acquired: 6/4/11 10:16:02 PM
Printed: 6/6/11 11:56:15 AM

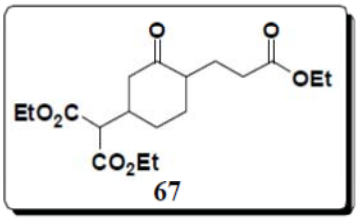


Detector A - 1 (230nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	66.675	81950	2.533	823	4.384
2	70.025	457712	14.149	3699	19.703
3	90.375	2264268	69.993	11919	63.487
4	98.433	431050	13.325	2333	12.427
Totals		3234980	100.000	18774	100.000

Project Leader :Dr. Ganesh Pandey
Column :Chiralcel OD-H0 0.46cm X 25cm
Mobile Phase :Ethanol: n-Hexane (1.5:98.5)
Flow Rate : 0.5 ml/min
Wavelength : 230nm
Con. :4mg 0.5ml
Inject vol. :15uL

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1478
User: System
Acquired: 6/28/11 4:30:42 PM
Printed: 6/29/11 5:20:55 PM
Sample Name PAA-286-10 RAC



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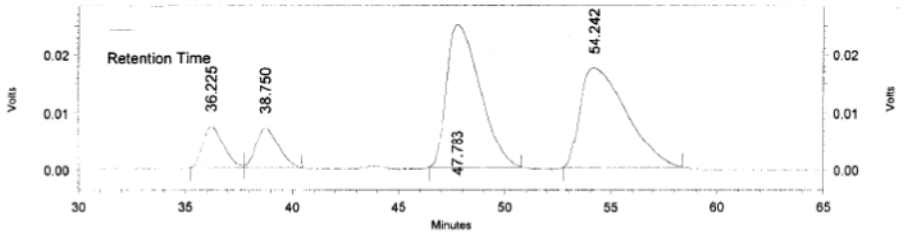
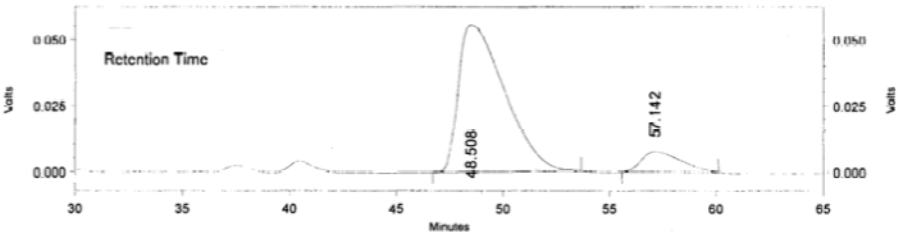


Detector A - 1 (230nm)

Retention Time	C Area	Area %
36.225	484977	7.674
38.750	502208	7.946
47.783	2710434	42.887
54.242	2622304	41.493

Totals	6319923	100.000

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1479
User: System
Acquired: 6/28/11 5:39:16 PM
Printed: 6/29/11 5:28:02 PM
Sample Name PAA-286-10 CHIRAL



Detector A - 1 (230nm)

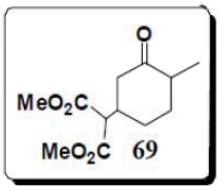
Retention Time	C Area	Area %
48.508	8296120	90.082
57.142	913427	9.918

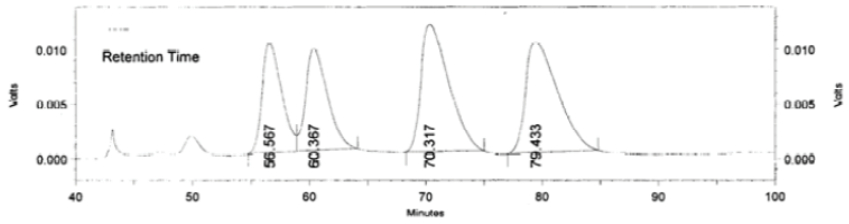
Totals	9209547	100.000

Project Leader :Dr. Ganesh Pandey
Column :Chiralcel OD-H (4.6x250 mm)
Mobile Phase :EtOH : n-Hexane (1.5:98.5)
Flow Rate : 0.5ml/min (Pressure 235kgf)
Wavelength : 230nm
Con. : 2mg/0.5ml

Inject vol. :20uL

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1486
User: System
Acquired: 6/30/11 12:34:35 PM
Printed: 6/30/11 2:54:17 PM
Sample Name PAA-287 iii Rac

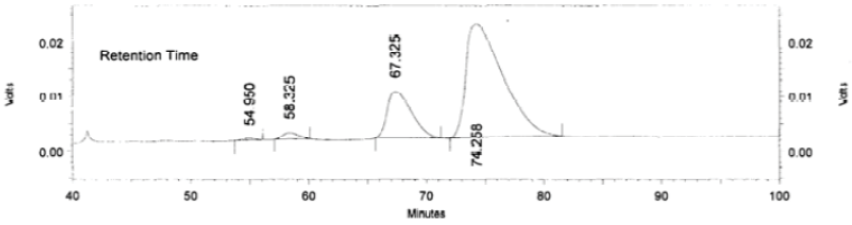




Detector A - 1 (230nm)

Retention Time	C Area	Area %
56.567	1185498	18.630
60.367	1233708	19.388
70.317	1974666	31.032
79.433	1969409	30.950
Totals	6363281	100.000

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1485
User: System
Acquired: 6/30/11 10:51:34 AM
Printed: 6/30/11 2:49:57 PM
Sample Name PAA-287 iii Chiral

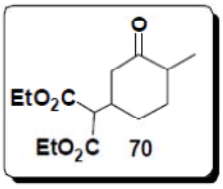


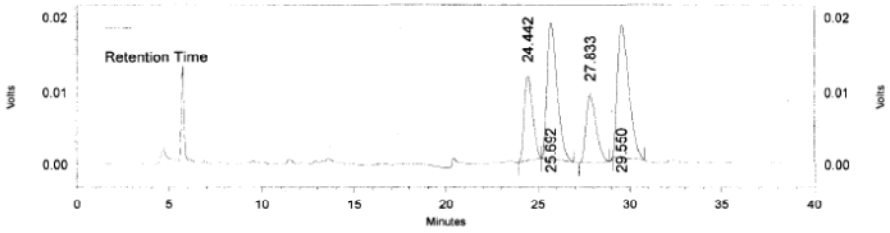
Detector A - 1 (230nm)

Retention Time	C Area	Area %
54.950	27708	0.465
58.325	115886	1.946
67.325	1227209	20.613
74.258	4582908	76.976
Totals	5953711	100.000

Project Leader :Dr. Ganesh Pandey
Column :Chiralpalpak OD-H (4.6x250 mm)
Mobile Phase :EtOH : n-Hexane (0.4:99.6)
Flow Rate : 0.5ml/min (Pressure 235kgf)
Wavelength : 230nm
Con. : 2mg/0.5ml

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1630
User: System
Acquired: 8/29/11 3:11:22 PM
Printed: 8/29/11 4:29:07 PM
Sample Name PAA-ETHYL-METHYL racemic

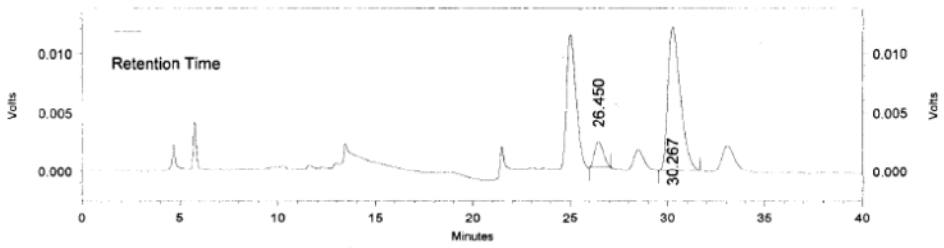




Detector A - 1 (230nm)

Retention Time	C Area	Area %
24.442	375714	16.750
25.692	715707	31.908
27.833	356823	15.908
29.550	794763	35.433
Totals	2243007	100.000

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1631
User: System
Acquired: 8/29/11 3:52:15 PM
Printed: 8/29/11 5:36:47 PM
Sample Name PAA-ETHYL-METHYL Chiral

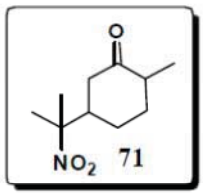


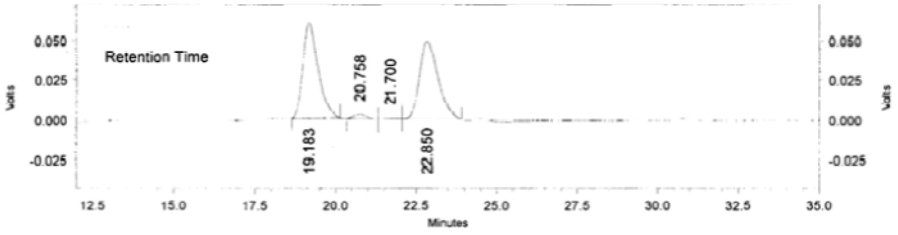
Detector A - 1 (230nm)

Retention Time	C Area	Area %
26.450	69472	11.409
30.267	539459	88.591
Totals	608931	100.000

Project Leader :Dr. Ganesh Pandey
Column :Chiralcel OJ-H (4.6x250 mm)
Mobile Phase :Ethanol:n-Hexane: (0.6:99.4)
Flow Rate : 0.7ml/min (Pressure 351 psi)
Wavelength : 230 nm
Con. : 0.5mg/1ml
Inject vol. :5uL

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1578
User: System
Acquired: 8/10/11 12:17:58 PM
Printed: 8/10/11 1:03:36 PM
Sample Name PAA- NITRO-METHYL-RACEMIC

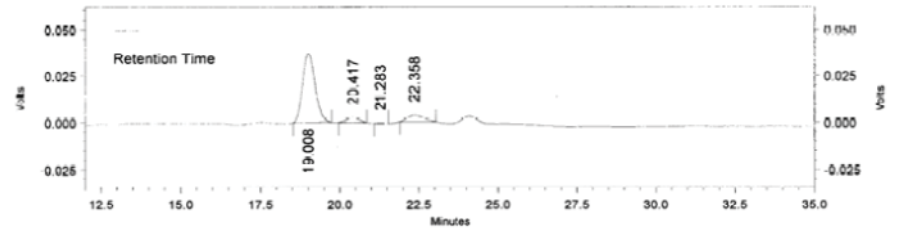




Detector A - 1 (230nm)

Retention Time	C Area	Area %
19.183	1994552	48.729
20.758	81851	2.000
21.700	20552	0.502
22.850	1996232	48.770
Totals	4093187	100.000

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1576
User: System
Acquired: 8/10/11 11:08:07 AM
Printed: 8/10/11 1:08:35 PM
Sample Name PAA- NITRO-METHYL-CHIRAL

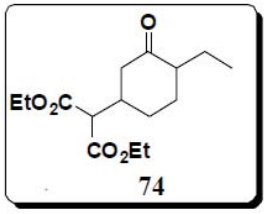


Detector A - 1 (230nm)

Retention Time	C Area	Area %
19.008	1035975	82.852
20.417	76093	6.086
21.283	2147	0.172
22.358	136170	10.890
Totals	1250385	100.000

Project Leader :Dr. Ganesh Pandey
Column :Chiralcel-OD-H (4.6x250 mm)
Mobile Phase :IPA:PE (5:95)
Flow Rate : 0.5ml/min (Pressure24Kgf)
Wavelength : 230nm
Con. : 1mg/0.2ml
Inject vol. : 10 uL

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1605
User: System
Acquired: 8/24/11 2:19:58 PM
Printed: 8/24/11 4:29:12 PM
Sample Name PAA-ETHYL-ETHYL RAC



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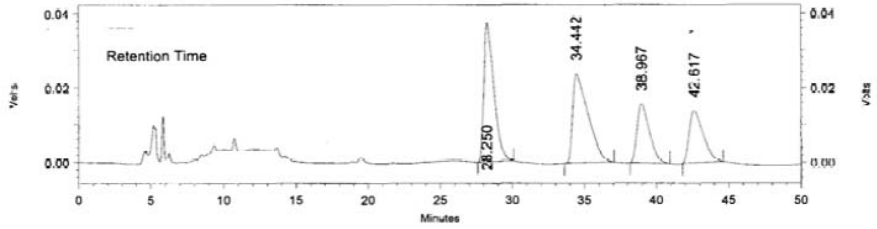
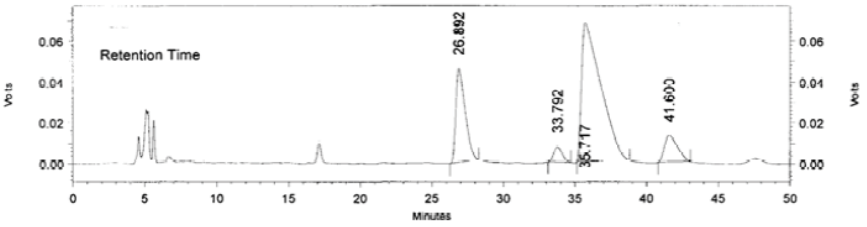


Detector A - 1 (230nm)

Retention Time	C Area	Area %
28.250	1785509	33.076
34.442	1757288	32.553
38.967	927855	17.188
42.617	927540	17.182
Totals	5398192	100.000

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1606
User: System
Acquired: 8/24/11 3:12:11 PM
Printed: 8/24/11 4:31:51 PM
Sample Name PAA-ETHYL-ETHYL Chiral

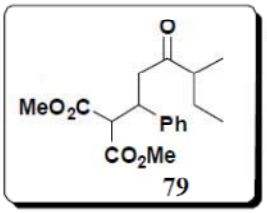


Detector A - 1 (230nm)

Retention Time	C Area	Area %
26.892	2072160	21.747
33.792	314032	3.296
35.717	6312377	66.246
41.600	830067	8.711
Totals	9528636	100.000

Project Leader :Dr. Ganesh Pandey
Column :Kromasil 5-AmyCoat (4.6x250 mm)
Mobile Phase :EtOH:n-Hexane (02:98.0)
Flow Rate : 0.7ml/min (Pressure 445psi)
Wavelength : 230 nm
Con. : 1mg/0.2ml
Inject vol. :20uL

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1596
User: System
Acquired: 8/19/11 12:39:24 PM
Printed: 8/19/11 6:09:15 PM
Sample Name PAA- methyl acyclic-Chiral



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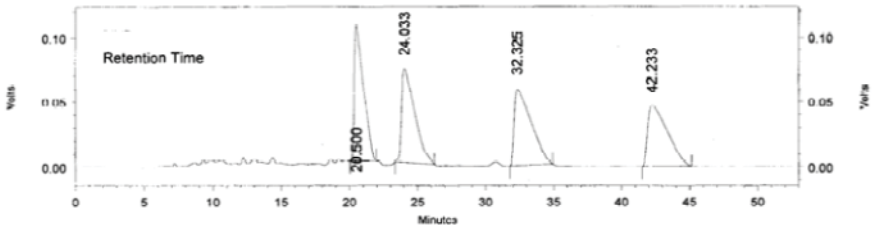
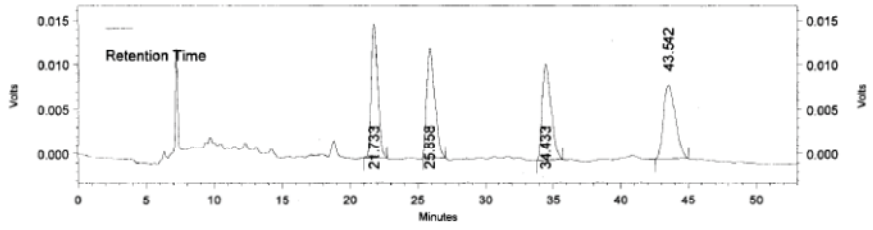


Detector A - 1 (230nm)

Retention Time	C Area	Area %
20.500	4952682	25.245
24.033	4816357	24.550
32.325	5103221	26.013
42.233	4745929	24.191
Totals	19618189	100.000

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1595
User: System
Acquired: 8/19/11 11:40:15 AM
Printed: 8/19/11 6:05:23 PM
Sample Name PAA- methyl acyclic

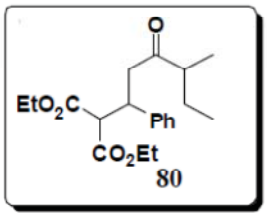


Detector A - 1 (230nm)

Retention Time	C Area	Area %
21.733	505982	25.065
25.858	505493	25.041
34.433	497050	24.623
43.542	510137	25.271
Totals	2018662	100.000

Project Leader :Dr. Ganesh Pandey
Column :Kromasil 5-Amycoat (4.6x250 mm)
Mobile Phase :EtOH:n-Hexane (07:93)
Flow Rate : 0.5ml/min (Pressure 30 kgf)
Wavelength : 230 nm
Con. : 2mg/0.5ml
Inject vol. :20uL

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1597
User: System
Aequired: 8/19/11 2:27:24 PM
Printed: 9/12/11 11:14:00 AM
Sample Name PAA- ethyl acyclic-rac



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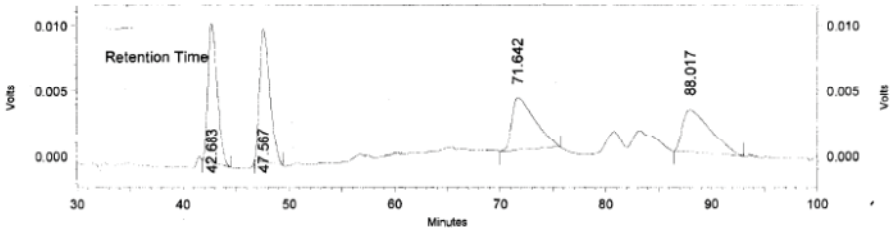
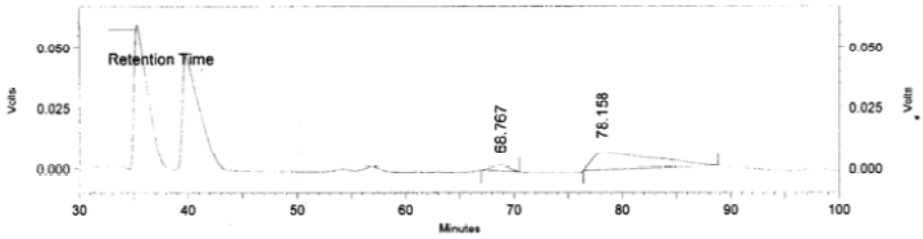


Detector A - 1 (230nm)

Retention Time	C Area	Area %
42.683	644851	25.093
47.567	685344	26.668
71.642	624421	24.298
88.017	615276	23.942
Totals	2569892	100.000

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1598
User: System
Acquired: 8/19/11 4:11:18 PM
Printed: 9/12/11 11:20:03 AM
Sample Name PAA- ethyl acyclic- chiral



Detector A - 1 (230nm)

Retention Time	C Area	Area %
68.767	234071	7.871
78.158	2739599	92.129
Totals	2973670	100.000

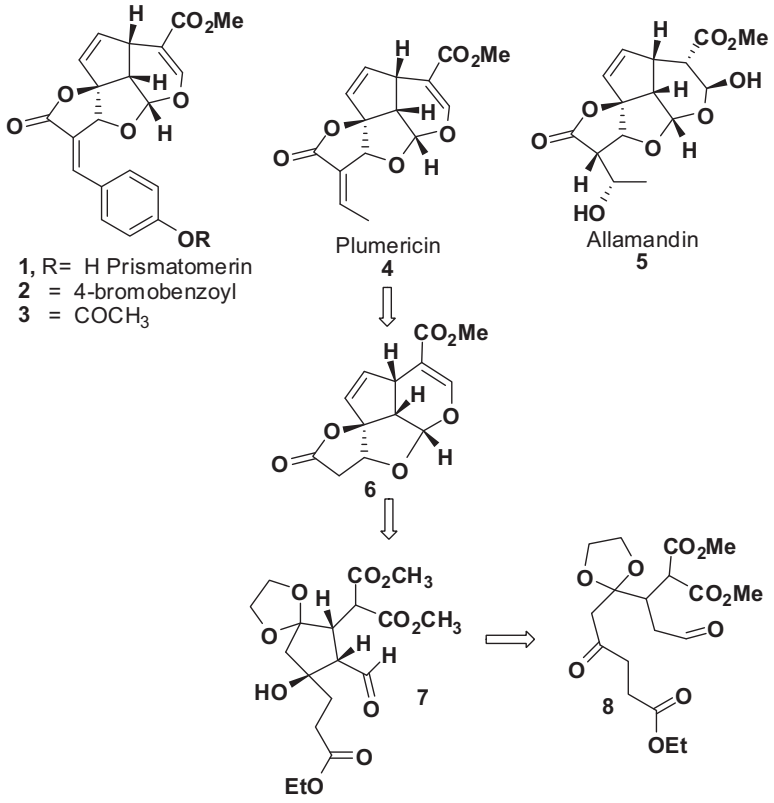
Project Leader : Dr. Ganesh Pandey
Column :Kromasil 5-Amycoat (250x4.6mm)
Mobile Phase :IPA:n-Hexane (2.5:97.5)
Wavelength : 230nm
Flow Rate : 0.5 ml/min 22kgf
conc. : 0.5mg/1.0ml
Inj vol- : 20ul

Chapter 3

Synthesis of tertacyclic core of higher iridoid from chiral-2,5-dialkyl cyclohexanone

3.1 Introduction

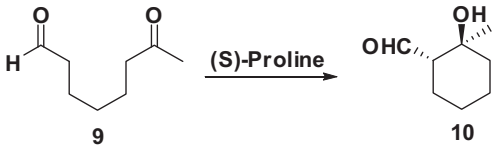
The higher iridoids featuring an interesting cyclic acetal and α-ethylidene-β-oxy-γ-butyrolactone ring system with six chiral centres have made synthesis of these molecules an intriguing and challenging target for organic chemists. Although, β-oxy-γ-butyrolactone ring system is found rarely in a natural product, Prismatomerin (**1**) recently isolated higher iridoid from the leaves of *Prismatomeris tetrandra* possessess this structural feature and have shown remarkable antitumor activity by interfering with the spindle formation without affecting microtubules directly.[1]



Scheme 3.1: Organocatalyzed asymmetric intra-molecular aldol reactions

Closely related to Prismatomerin (**1**) is Allamandin (**5**) and Plumericin (**4**) which are also known to exhibit high antileukemic[2] and antitumor[3] activity respectively. Allamandin (**5**) and Plumericin (**4**) has been subject of two elegant syntheses exploiting *cis*-ring junction stereochemistry of bicyclo[3.3.0]octenone as a handle for the installation of remaining stereocentres.[4] We visualized the synthesis of the tetracyclic core of higher iridoids differently, utilizing cyclopentane ring **6** with requisite three contiguous stereocentres. We

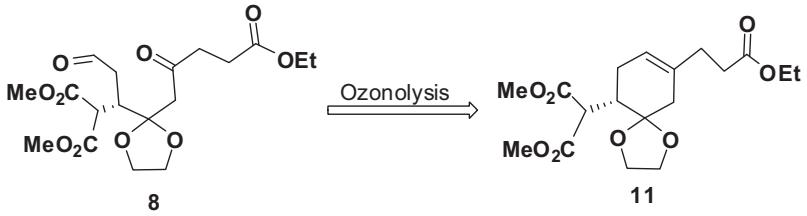
proposed synthesis of the cyclopentane **7** by organocatalytic intramolecular aldol cyclization of **8** considering the advantage of synthesizing both enantiomeric products simply by using (*S*)- or (*R*)-proline. Although, List *et al.* have reported proline-catalyzed asymmetric intramolecular aldol reaction[5] (Scheme 3.2) from **9** for the synthesis of β-hydroxy-cyclohexyl formaldehyde **10** with *anti*-diastereoselectivity, construction of corresponding cyclopentane ring system employing this strategy is still unexplored. With this background information, we set out our exploration of synthesizing **7** utilizing organocatalyzed intramolecular aldol cyclization as a key step starting with **8**. The proceeding Chapter will discuss our progress in this endeavor.



Scheme 3.2: List's protocoel for proline-catalyzed asymmetric intramolecular aldol reactions

3.2 Results and discussion

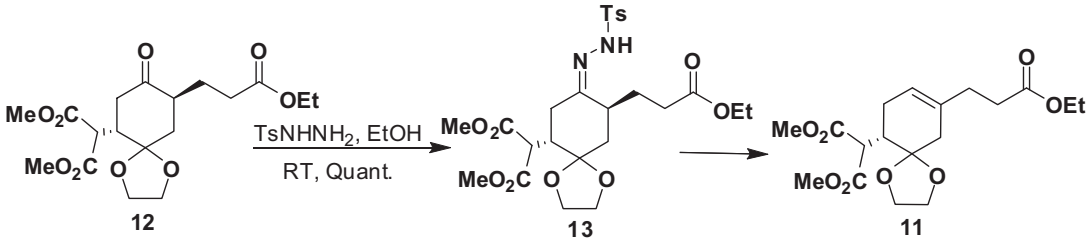
In Chapter 2, we have extensively discussed development of a synthetic methodology for the synthesis of chiral 2,5-dialkyl cyclohexanones **12**, required as a starting material for designed synthesis of tetracyclic core **6** common for all higher iridoids. Having achieved scalable synthesis of **12**, we focused our attention towards synthesizing **7** by organocatalytic intramolecular aldol cyclization of **8**, accessible from **11** by ozonolysis as shown in Scheme 3.3.



Scheme 3.3

3.2.1 1st Generation approach for the synthesis of 11

Initially, we planned the synthesis of **11** from **12** utilizing Bamford-Steven reaction on hydrazone **13**. As already known, in a Bamford- Steven reaction,[6] a tosylhydrazone on treatment with a strong base such as NaH, NaOMe in an aprotic solvent gives a more substituted alkene.



Scheme 3.4: Synthesis of olefin **11** utilizing Bamford-Steven reaction

Table 3.1: Various synthetic attempts for synthesis of **11** via Bamford-Steven reaction

Sr. no.	Reaction condition for Bamford-Steven reaction on 13	Yield of 11 (%)
1[7]	NaOMe, diglyme, 160 ºC	10
2	NaH, diglyme, 160 ºC	10
3[8]	LiH, toluene, reflux	5
4[9]	KH, 18-crown-6, diglyme 100 °C	No reaction
5[10]	$NaO(CH_2)_2ONa$, $HO(CH_2)_2OH$, 160 °C	5
6[11]	t-BuOK, N-methyl pyrrolidone, 150 °C	7

We treated **13**, synthesized in quantitative yield by treating **12** with tosylhydrazine in dry ethanol, with NaOMe (2.5 equiv.) in diglyme at 160 ºC which produced desired **11**, only in 10 % yield. The structural assignment of **11** was based on observing a broad singlet, integrating for one proton, at δ 5.38 for vinylic proton (C=C-H) in ^{1}H NMR spectra. ^{13}C NMR of **11** also showed one tertiary olefinic carbon at δ 119.4 along with a quaternary carbon at δ 133.7. Since **11** was obtained in only 10 % yield, we screened various other reaction conditions as mentioned in Table 3.1, however, all possible

attempts to further improve yield failed. Therefore, we designed another strategy of obtaining **11** from **12** as described in section 3.2.2.

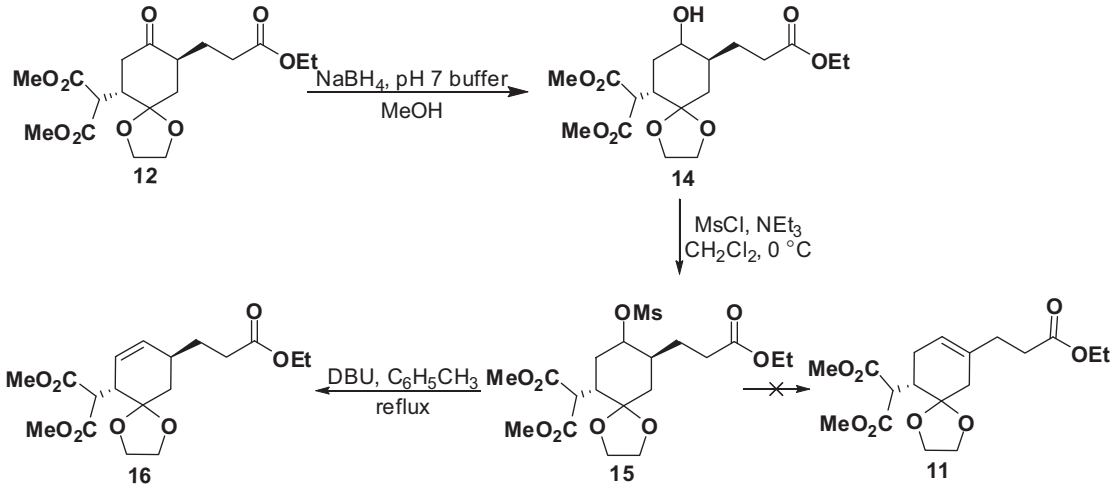
3.2.2 2nd Generation approach for synthesis of 11

Next we planned the synthesis of **11** by dehydration of **14** via corresponding mesylate derivative **15**. Compound **15** was obtained (60 % yield) by selective reduction of **12** with sodium borohydride in pH 7 buffer-MeOH conditions (1:1),[12] followed by mesylation with mesityl chloride at 0 ˚C. Subjecting **15** under various reaction conditions as shown in Table 3.2 did not give desired **11**.

Table 3.2: Attempts for mesylate elimination

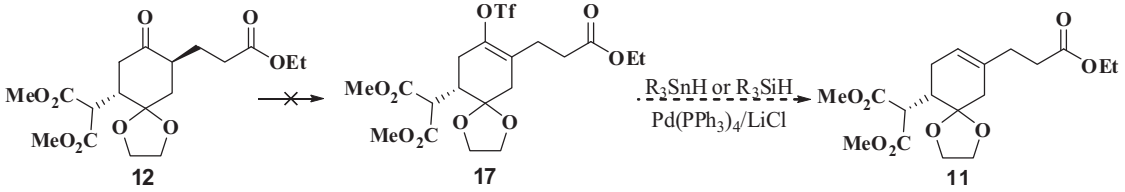
Sr.no.	Conditions tried for mesylate elimination	Result
1	NEt_3, DMAP, CH_2Cl_2, 12 h, reflux	SM recovered
2	Pyridine, CH_2Cl_2. Reflux	SM recovered
3	NaOMe, THF, RT	SM recovered
4	NaOMe, THF, reflux	Complex mixture
5[13]	DBU, toluene, reflux, 4 h	**16**:**11** (5:1)
6[14]	DMAP, DMSO, 170 ˚C	Monodecarboxylation of malonate group
7[15]	NaOAc, AcOH, 110 ˚C	Complex mixture
8[16]	KH, THF, 0 ˚C to RT	SM recovered

Surprisingly, refluxing **15** with DBU in dry toluene gave an inseparable mixture of **16** along with required **11** in a ratio of 5:1. Tentative structural assignment of **16** was based on observing two protons in olefinic region between δ 5.48 - 5.60 (m, 1 H), 5.71 (d, J = 10.29 Hz, 1 H) in the ^{1}H NMR spectra. ^{13}C NMR also confirmed the presence of two olefinic carbons at δ 124.9, 133.1 (H-C=C-H). Mass spectrum gave molecular ion peaks at *m/z* 393.2 (M + Na, 100), 371.1 (M+1, 10).



Scheme 3.5: Synthesis of olefin **11** via mesylate elimination

Having failed to obtain desired **11** again using the reaction conditions as mentioned in Table 3.2, we proposed to proceed via palladium catalyzed reductive elimination[17] of corresponding vinyl triflate **17** (Scheme 3.6). Towards this end, we attempted the transformation of **12** to **17** by screening various reaction conditions as shown in Table 3.3. However, unfortunately all our attempts to obtain **17** from ketone **12** failed.



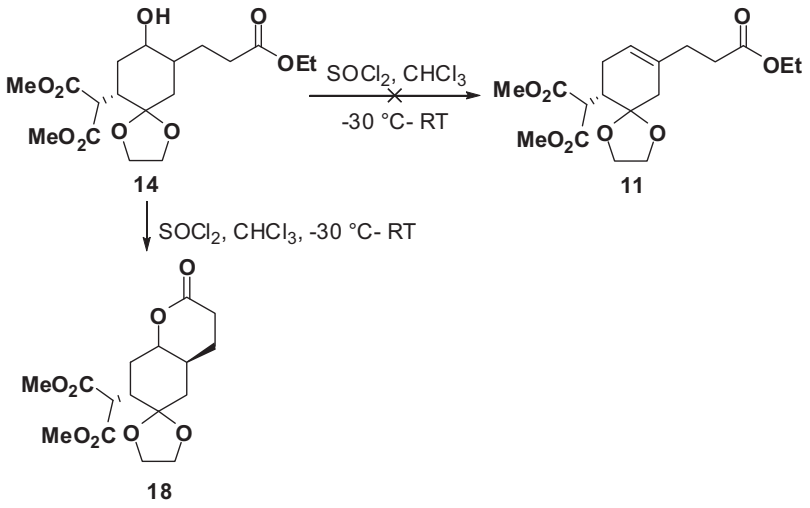
Scheme 3.6

Table 3.3: Attempts for synthesis of vinyl triflate 17

Sr. no.	Condition	Reaction outcome
1[18]	2,6-ditert-butyl-4-methylpyridine, $(Tf)_2O$, RT	SM decomposes
2[18]	$(Tf)_2O$, NEt_3, DMF, 110 °C	SM recovered
3	$(Tf)_2O$, Pyridine, CH_2Cl_2, Reflux	SM recovered
4[19]	NEt_3, $ClPhN(Tf)_2$, CH_3CN, reflux	SM recovered

5[20]	NaHMDS, THF, 0 ˚C TO RT then $PhN(Tf)_2$	SM recovered
6[21]	TMSOTf, NEt_3, CH_2Cl_2, 0 ˚C TO RT then MeLi (1.5 h) then $ClPhN(Tf)_2$	Complex mixture
7[22]	$(i\text{-}Pr)_2NMgBr$, HMPA, 6 h, RT then $PhN(Tf)_2$, reflux	SM recovered

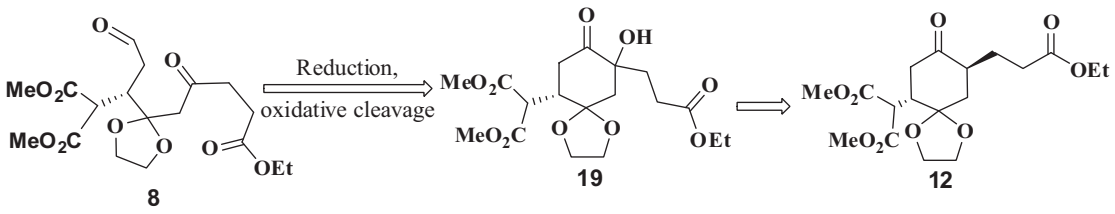
This frustrating observation led us to evaluate the dehydration of **14** itself using Overman's protocol.[23] Accordingly, **14** was stirred with $SOCl_2$ in $CHCl_3$ at room temperature for 12 h, however, we obtained **18** instead of **11**. Structure of **18** was assigned based on disappearance of signal corresponding to carboethoxy protons at δ 3.85 - 4.10 and 1.25 in ^{1}H NMR.



Scheme 3.7

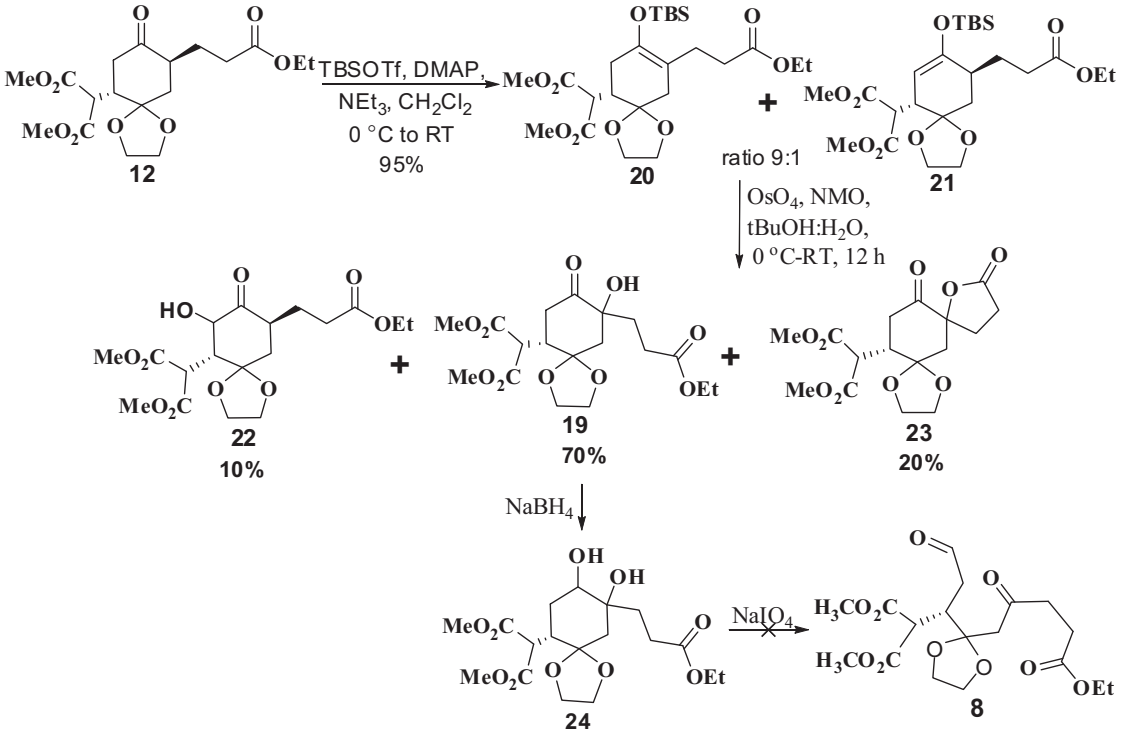
3.2.3 3rd Generation approach for the synthesis of 8

Faced with unforeseen problems of synthesizing **11** through the protocols as described above, we envisaged preparing **8** altogether in a different manner *via* oxidative cleavage of C1-C2 bond of **19 (**Scheme 3.8).



Scheme 3.8: 3rd Generation retrosynthetic analysis *via* hydroxyl ketone

In order to prepare **19**, compound **12** was treated with TBSOTf /Et_3N in the presence of catalytic amount of DMAP in dichloromethane at 0 ˚C which produced inseparable mixture **20** and **21** in 9:1 mixture. Treating the mixtures of **20** and **21** as such with OsO_4[24] followed by acidic workup gave required **19** in 70 % yield (*dr* = 4:1) along with **22** (10 %, *dr* = 4:1) and **23** (20 %).



Scheme 3.9

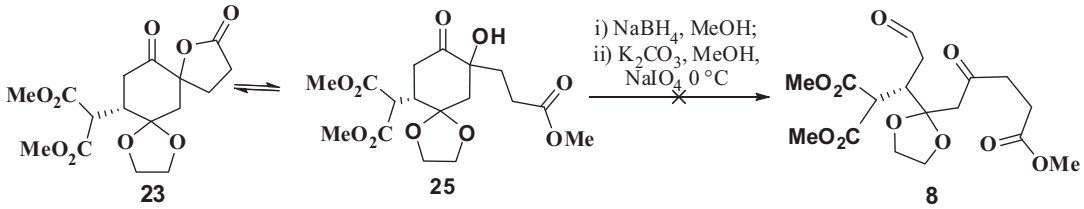
The IR spectra of **19** showed characteristic absorption band of a hydroxyl moiety at 3480 cm^{-1}. ^1H NMR of **19** showed disappearance of peaks at δ 0.11 (d, 6 H), 0.92 (s, 9 H)

corresponding to TBS ether. The assigned structure of **19** was further supported by carbon signal at δ 73.56 corresponding to oxa-quaternary carbon in ^{13}C NMR. Mass spectrum showed M + Na peak at 425.3.

^{1}H NMR spectra of **22** displayed a doublet at δ 4.80 (d, J = 12.30 Hz, 1 H), assigned to methine proton (-C<u>H</u>-OH), and a carbon signal at δ 73.6 in ^{13}C NMR respectively, indicating the presence of a tertiary hydroxyl functionality in the product. Peaks at 425 (M + Na, 100), 403 (M + 1, 10) in mass spectrum confirmed the structure of **22**.

The ^{1}H NMR and ^{13}C NMR spectra of **23** did not show characteristic signals corresponding to carboethoxy moiety, instead displayed C2 (oxa-quaternary) at δ 85.9. The assigned structure for **23** was confirmed undoubtedly by mass spectrum by observing M + Na at 388.5.

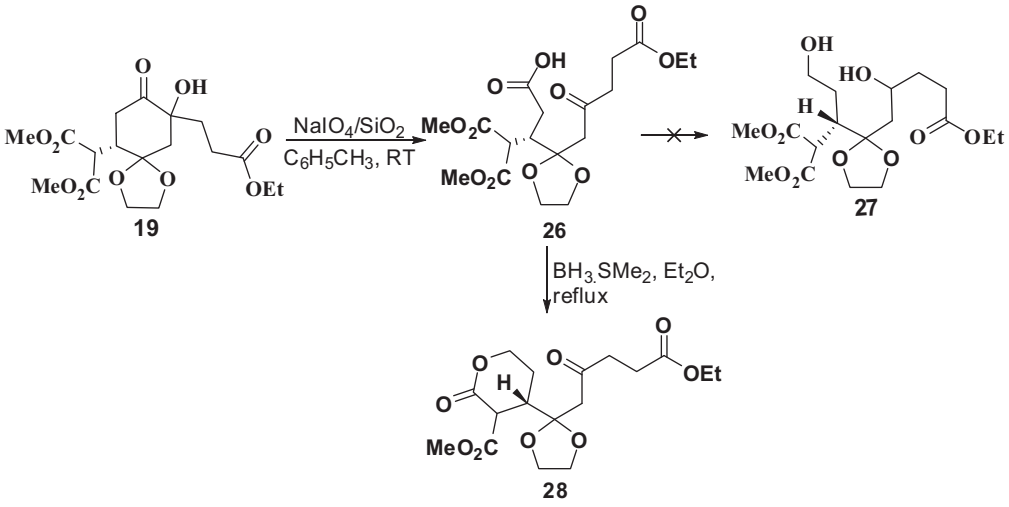
Reduction of **19** with $NaBH_4$ produced **24** (confirmed by mass) which on oxidative cleavage using sodium metaperiodate in acetone/water (9:1) gave complex reaction mixture. Since **23** is likely to be in equilibrium with **25** in a protic solvent (Scheme 3.10), we even tried one pot reduction followed by oxidative cleavage in MeOH: H_2O but still we could not obtain **8** (Scheme 3.10).



Scheme 3.10

This failure led us to revise our strategy once again for the synthesis of **8**, thus we proceeded towards synthesis of **8** as shown in Scheme-3.11. We surmised selective reduction of **26** to obtain **27** which could be eventually converted to **8**. As per our planned strategy, we subjected **19** directly to oxidative cleaved by stirring with silica gel-supported $NaIO_4$[25] in toluene which produced **26** quantitatively (Scheme 3.11). Disappearance of oxa-quaternary carbon signal at δ 76.65 present in starting **19** and other carbon signals at δ 168.6, 168.7, 172.8, 176.8, 205.1 confirmed the presence of three ester functionality along

with carboxylic acid group in the product. Further confirmation for the formation of **26** was obtained from mass spectrum (441.45, M+ Na, 100).



Scheme 3.11

With acid **26** in hand, stage was set for selective reduction of acid functionality. Towards this end, we tried various reaction conditions (Table 3.3), however all our attempts led to the formation of complex reaction mixture. Reduction using BH_3.DMS in dry Et_2O produced **28** instead of **27**.

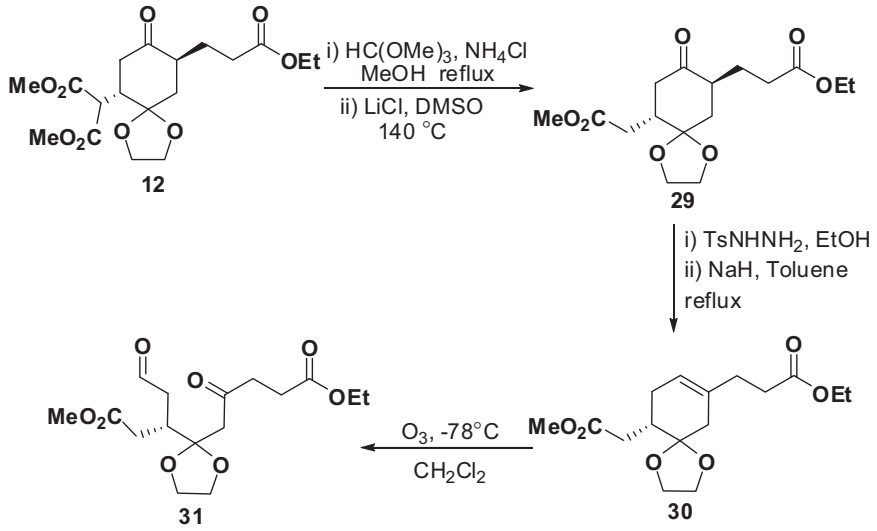
Table 3.3: Attempts for selective reduction of acid 26

Sr.no.	Condition A	Result
1[26]	BH_3.THF, THF, -15˚C, 1hr quenched with $NaHCO_3$	Complex reaction mixture
2	BH_3.THF, THF, -50˚C to RT, 8hr	Complex reaction mixture
3[27]	$NaBH_4$, I_2, THF, quenched with 5N HCl	Complex reaction mixture
4[28]	$BH_3.SMe_2$, Et_2O, RT, 0.5 hr reflux quenched with MeOH	Compound **28** (60 %)

These failures led us to conclude that synthesis of **8** was difficult and proceeding with **11** was not practical owing to low yield. We thought presence of malonate

functionality could be reason for the low yield. Therefore, we revised our strategy again utilizing **29** as starting material for synthesis of dicarbonyl **31**.

3.2.4 Synthesis of 31



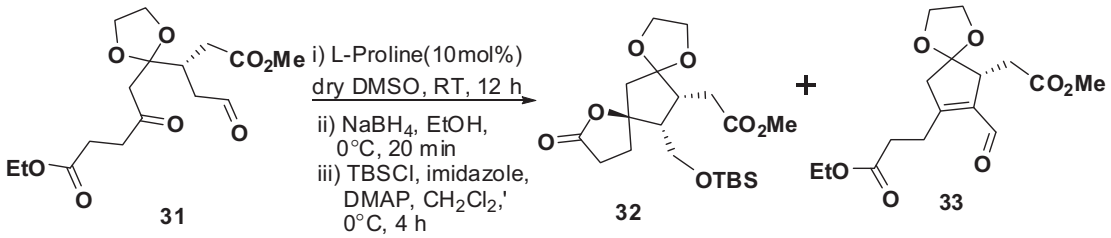
Scheme 3.12: Synthesis of **31**

To synthesize **31**, we again started with **12** which on carbonyl protection as a dimethylketal followed by decarboxylation with LiCl in DMSO[29] at 140˚C furnished **29** in excellent yield of 80 %. ^{1}H and ^{13}C NMR of **29** indicated it to be a mixture of diastereomers (*dr* = 4:1). Converting **29** to its Tosyl hydrazone derivative followed by subjecting it to Bamford-Steven reaction (NaH, Toluene, reflux) gave desired **30** in 60% yield and 95% optical purity (Chiralcel OD-H, *i-PrOH*:*petroleum ether* 20:80, 0.7 mL/min, 230 nm). Ozonolysis of **30** in CH_2Cl_2 at -78 ˚C gave **31** in 70 % yield. Compound **31** was characterized based on the observation of an aldehyde proton δ 9.63 (dd, *J* = 3.01, 1.25 Hz) in ^{1}H NMR and presence of signal at δ 200.3 and 205.3 in ^{13}C corresponding to aldehyde and ketone carbonyl.

3.2.5 Organocatalyzed Intramolecular aldol cyclization of 31

Having desired **31** in hand, stage was set to attempt organocatalytic intramolecular aldol cyclization. Different catalyst and solvent conditions as given in Table 3.4 were

examined for organocatalytic intramolecular aldol reaction. Complete consumption of starting **31** in aldol reaction was monitored by GC and after completion; reaction mixture was subjected to $NaBH_4$ reduction followed by TBS protection. Among the catalyst (Figure 3.1) and Solvents (Table 3.4) screened only L-Proline in dry DMSO was found to provide **32** as a single diastereomer along with enal **33** (Scheme 3.13). The ^{1}H NMR spectrum of **32** displayed signal at δ 0.05 and 0.88 characteristic for TBS ether and at 3.88 as multiplet



Scheme 3.13: Organocatalyzed Intramolecular aldol cyclization of **37**

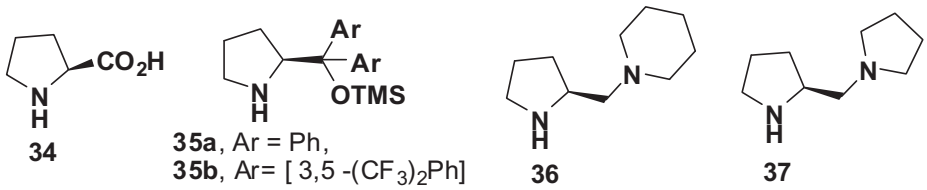
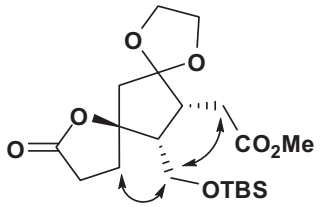


Figure 3.1: Catalyst screened

Table 3.4: Condition for organocatalytic intramolecular aldol reaction of 37

Sr.no.	Condition for aldol cyclization of 37	Result
1[5]	**34,** dry CH_2Cl_2, RT	Complex reaction mixture
2	**34,** dist CH_2Cl_2, RT	Enal **33**
2	**34,** dry $CHCl_3$, RT	No reaction
3	**35a,** dry CH_2Cl_2, RT	No reaction
4	**35b**, dry CH_2Cl_2, RT	No reaction
5[30]	**36**, DMF, RT	Complex reaction mixture
6[30]	**37**, DMF, RT	Complex reaction mixture
7	**34**, dry DMSO, RT, 12 h	**32** + **33**

integrating for six protons was assigned to ($C\underline{H_2}$-OTBS) and (($CH_2O)_2$). The assigned structure was ascertained by signal at δ 89.5 corresponding to oxaquaternary carbon in ^{13}C NMR. Further mass peak at 437.07 (M + Na) confirmed the proposed structure of **32**. The final confirmation for stereochemistry of stereocentres on **32** was tentatively assigned from NOESY studies (Figure 3.2).



32

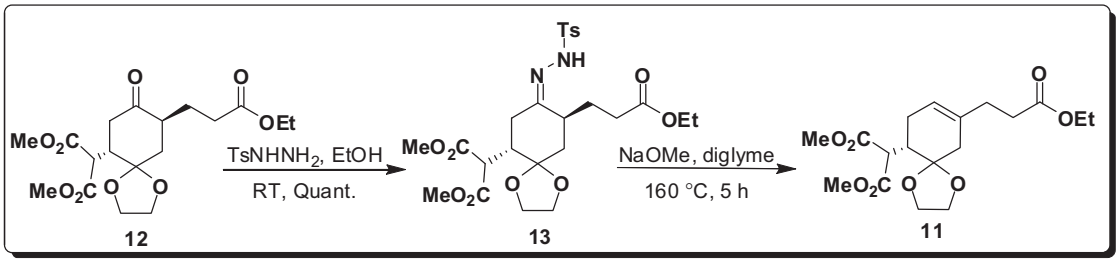
Figure 3.2 relative stereochemistry confirmations for **32** using NMR

3.3 Summary

An advanced chiral intermediate **32**, adorned with all requisite functionalities for further elaboration to tetracyclic core of higher Iridoid, has been synthesized employing organocatalytic intra-molecular aldol cyclization of **31**. Further transformation of **32** to target tetracyclic core **6** is in progress. Completion of chiral synthesis of iridoids will help to establish its optical purity and absolute stereochemistry.

3.4 Experimental section

Dimethyl-2-(9-(3-ethoxy-3-oxopropyl)-1,4-dioxaspiro[4.5]dec-8-en-6-yl)malonate (11):



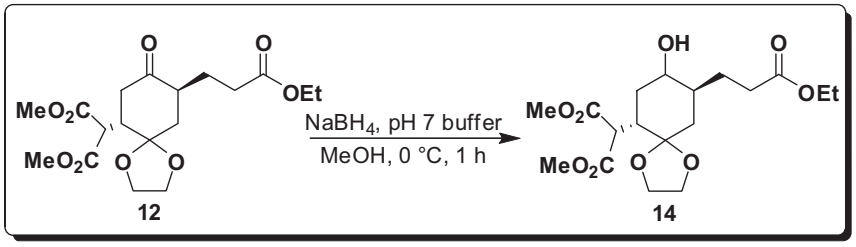
12 (0.1 g, 0.26 mmol) dissolved in 2 mL EtOH was added to a solution of tosyl hydrazine (0.058 g, 0.31 mmol) in 2 mL dry EtOH under argon. Reaction mixture was stirred at room temperature. After complete disappearance of starting material, monitored by TLC, reaction mixture was concentrated and dried under reduced pressure to obtain **13** which was used as such without further purification. To crude **13**, NaOMe (0.042 g, 0.78 mmol) and 4 mL of dry diglyme was added. The reaction mixture was stirred for 4 h at 160 °C and then cooled to RT. On complete consumption of **13,** monitored by TLC, reaction mixture was quenched with water, and extracted with EtOAc (3x10 mL). Combine organic layer was washed 5 times with H_2O (10 mL) to remove diglyme, dried over Na_2SO_4, and concentrated under reduced pressure. The residue obtained was purified by column chromatography to obtain **11** in 10 % yield as pale yellow liquid, eluting with EtOAc/petroleum ether (25:75).

Yield:	**:**	10 %
$\alpha_D^{32.1}$	:	+29.73 (*c* 1.12, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	3019, 1976, 2894, 2400, 1732, 1435, 1372, 1215, 1045, 760
^{1}H NMR ($CDCl_3$, 500 MHz) δ	**:**	1.25 (t, *J* = 7.2, 3 H), 2.5-2.16 (m, 1H), 2.17 - 2.37 (m, 5 H), 2.37 - 2.43 (m, 2 H), 2.80 (d, *J* = 5.80 Hz, 1 H), 3.50 (d, *J* = 9.77 Hz, 1 H), 3.68 - 3.74 (m, 6 H), 3.89 - 4.00 (m, 4 H), 4.12 (q, *J* = 7.22 Hz, 2 H), 5.38 (br s., 1 H)
^{13}C NMR ($CDCl_3$, 126 MHz) δ	**:**	14.2, 27.7, 31.9, 32.5, 37.8, 40.5, 51.6, 52.4, 52.4, 60.3, 64.2, 64.8, 108.6, 119.4, 133.7, 168.9, 169.2,

173.10

Mass: m/z (%) : 393.2 (M + Na, 100), 371.1 (M + H, 15)

Dimethyl-2-(9-(3-ethoxy-3-oxopropyl)-8-hydroxy-1,4-dioxaspiro[4.5]decan-6-yl) malonate (14):



To a solution of **12** (0.5 g, 1.95 mmol) in 6.0 mL MeOH and 6.0 mL pH 7 buffer at 0 ˚C was added solid sodium borohydride (0.037 g, 0.975 mmol) in one portions. After complete disappearance of the starting material, monitored by TLC, the reaction mixture was quenched by careful addition of saturated aqueous solution of ammonium chloride (10 mL) with vigorous stirring. Ethanol was removed under reduced pressure and the resulting aqueous solution was extracted with EtOAc (3x25 mL). Combined organic layers were washed with brine (1x30 mL), dried over anhy. Na_2SO_4 and concentrated under reduced pressure to afford **14** which was directly used for next step without any purification.

Note: 14 *was not very stable, forms a very polar spot at room temperature, which could not be analyzed, so was immediately forwarded for next step.*

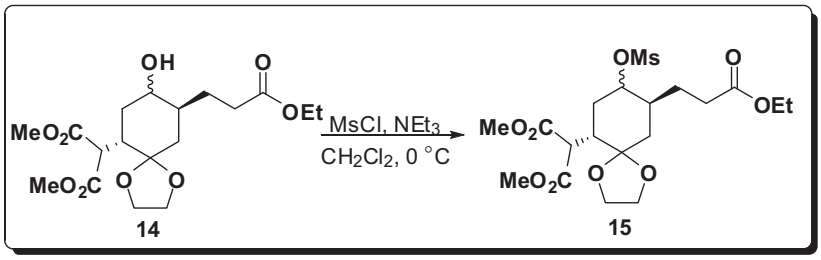
$\alpha_D^{31.5}$: +43.44 (*c* 3.23, $CHCl_3$)

IR ν_{max} cm^{-1} ($CHCl_3$) : 3451, 2954, 2396, 1731, 1436, 1315, 1217, 1153, 755

^{1}H NMR ($CDCl_3$, 200 MHz) δ : 1.25 (t, *J* = 7.01 Hz, 3 H), 1.46 - 1.64 (m, 2 H), 1.78 - 2.00 (m, 4 H), 2.03 - 2.25 (m, 2 H), 2.35 (s, 1 H), 2.46 - 2.60 (m, 1 H), 2.62 - 2.78 (m, 1 H), 3.62 - 3.78 (m, 8 H), 3.85 - 4.10 (m, 6 H).

Mass: m/z (%) : 411.03 (M + Na, 100), 365 (5).

Dimethyl-2-((6S,9S)-9-(3-ethoxy-3-oxopropyl)-8-((methylsulfonyl)oxy)-1,4-dioxaspiro [4.5] decan-6-yl)malonate (15):

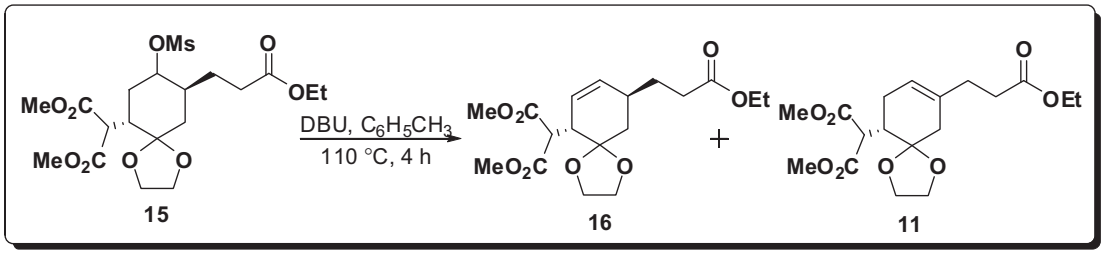


To a magnetically stirred solution of the **14** (0.379 g, 1.47 mmol) in 5 mL CH_2Cl_2 at 0 ºC was added NEt_3 (0.3 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.14 mL, 1.76 mmol) and the reaction mixture was stirred for 4 h. Reaction mixture was then diluted with 5 ml of water and extracted with CH_2Cl_2 (3 x 10 ml). The organic layer was washed with saturated aq. $NaHCO_3$, brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc:petroleum ether (35:65) as eluent furnished the mesylate **15** in 60 % yield (0.274 g).

Yield:	**:**	60 %
α_D^{25}	:	-6.8 (*c* 2.3, $CHCl_3$, *dr* = 2:1)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	2945, 2396, 2255, 1731, 1445, 1315, 1213, 1155, 1025, 715
^{1}H NMR ($CDCl_3$, 400 MHz) δ (diastereomeric ratio 2:1)	**:**	1.25 (t, *J* = 7.03 Hz, 3 H), 1.46 - 1.57 (m, 1 H) 1.79 - 1.98 (m, 2 H), 1.99 - 2.11 (m, 2 H), 2.22 - 2.43 (m, 3 H), 2.64 - 2.79 (m, 1 H), 3.08 (s, 1 H), 3.14 (s, 2 H), 3.13 - 3.21 (m, 1 H), 3.63 (d, *J* = 7.03 Hz, 1 H), 3.70 - 3.76 (m, 6 H), 3.82 - 4.00 (m, 4 H), 4.12 (q, *J* = 7.03 Hz, 2 H), 4.44 (td, *J* = 10.79, 4.52 Hz, 1 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ (diastereomeric ratio 2:1)	**:**	14.2, 26.6, 31.1, 37.0, 38.8, 38.8, 42.6, 50.3, 52.9, 52.6, 60.5, 64.5, 64.8, 77.2, 82.5, 107.7, 168.5, 168.72, 173.0
Mass: m/z (%)	**:**	489.2 (M + Na, 15), 393.1 (M–Ms + Na, 100), 371.1

(15), 365 (10), 349.1 (2)

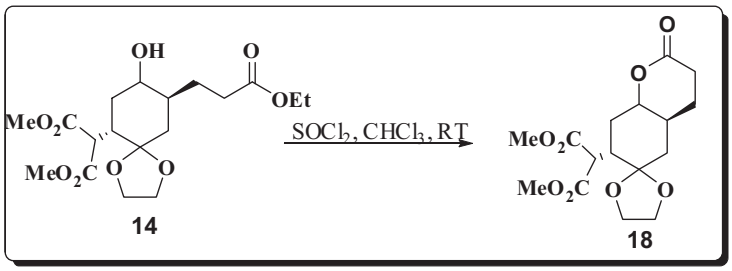
Dimethyl-2-(9-(3-ethoxy-3-oxopropyl)-1,4-dioxaspiro[4.5]dec-7-en-6-yl)malonate (16):



15 (0.04 g, 0.058 mmol) was heated at reflux with freshly distilled DBU (0.032 mL, 0.22) in dry toluene (4 mL) at 110 °C for 4 h. After completion of the reaction, monitored by TLC, the volatile material was evaporated and the residue was purified by flash chromatography using EtOAc:petroleum ether (25:75) as eluent to furnish the inseperable mixture of **16** and **11** in 5:1 ratio.

Yield:	**:**	90 % (16:11; 5:1)
α_D^{25}	:	+30.48 (*c* 0.87, $CHCl_3$, regio-isomer ratio 5:1)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	3019, 2976, 2400, 1731, 1520, 1435, 1216, 1046, 928, 877, 757, 669
^{1}H NMR ($CDCl_3$, 400 MHz) δ	**:**	1.26 (t, *J* = 7.03, 3 H), 1.49 - 1.63 (m, 2 H), 1.63 - 1.86 (m, 3 H), 2.26 - 2.50 (m, 3 H), 3.10 - 3.19 (m, 1 H), 3.39 (d, *J* = 10.04 Hz, 1 H), 3.65 - 3.78 (m, 6 H), 3.80 - 3.89 (m, 1 H), 3.89 - 4.04 (m, 3 H), 4.13 (q, *J* = 7.03 Hz, 2 H), 5.48 - 5.60 (m, 1 H), 5.71 (d, *J* = 10.29 Hz, 1 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	14.2, 30.2, 31.5, 34.6, 35.1, 43.1, 52.5, 52.6, 55.1, 60.4, 64.5, 64.9, 108.8, 124.9, 133.1, 168.2, 168.80, 173.4
Mass: m/z (%)	**:**	393.2 (M + Na, 100), 371.1 (M +1, 10), 304.5 (25)

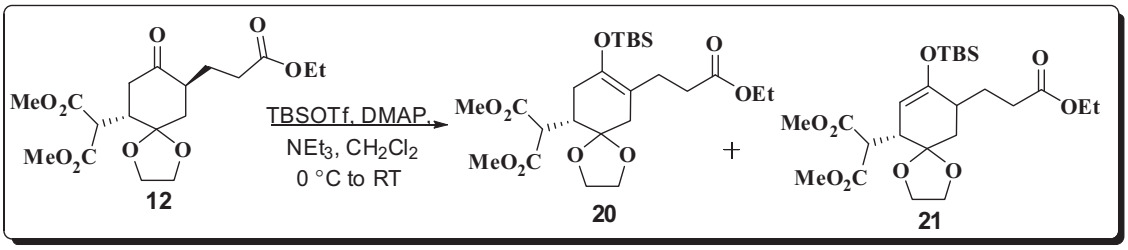
Dimethyl 2-(2-oxooctahydrospiro [chromene-6,2'-[1,3]dioxolan]-7-yl)malonate (18):



Compound **14** (0.108 g, 0.28 mmol) dissolved in $CHCl_3$ (10 mL) was added dropwise to cold freshly distilled $SOCl_2$ (0.1 mL, 1.4 mmol) at -30 ˚C. The resulting solution was allowed to warm to RT and allowed to stir for 20 h before volatile materials were removed under reduced pressure. The residue was partitioned between saturated $NaHCO_3$ (1x10 mL) and $CHCl_3$. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3x10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to viscous liquid, which was further purified by flash chromatography using EtOAc:petroleum ether (40:60) as eluent to obtain **18** in 70 % yield (0.067 g).

Yield:	**:**	70 %
α_D^{25}	:	+33.21 (*c* 2.09, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	3020, 2953, 2878, 1735, 1458, 1436, 1216, 1196, 1149, 937, 755
^{1}H NMR ($CDCl_3$, 400 MHz) δ	**:**	1.22 - 1.30 (m, 1 H), 1.47 - 1.60 (m, 1 H), 1.76 - 1.94 (m, 4 H), 2.15 (dt, *J* = 12.42, 3.95 Hz, 1 H), 2.47 - 2.57 (m, 1 H), 2.62 - 2.73 (m, 2 H), 3.61 (d, *J* = 7.78 Hz, 1 H), 3.69 (s, 3 H), 3.7 (s, 3 H), 3.88 - 4.04 (m, 5 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	25.6, 29.2, 32.2, 35.1, 37.9, 42.5, 50.6, 52.4, 52.5, 64.5, 64.8, 81.00, 108.1, 168.5, 168.8, 170.7
Mass: m/z (%)	**:**	397.13 (M + Na + MeOH, 100), 365 (M + Na, 7), 357 (2)

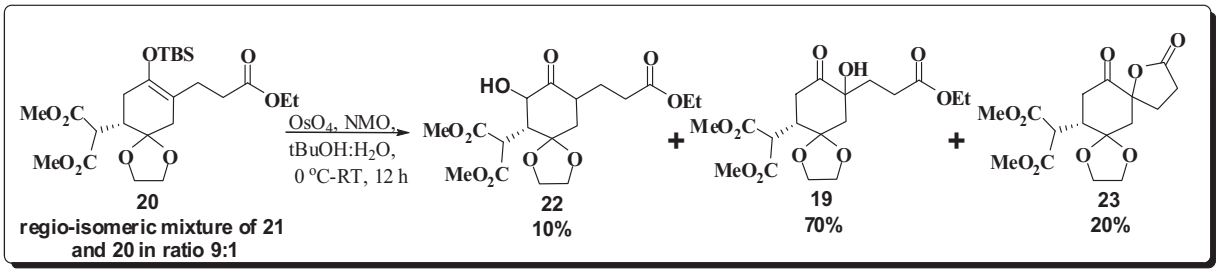
(S)-Dimethyl-2-(8-((tert-butyldimethylsilyl)oxy)-9-(3-ethoxy-3-oxopropyl)-1,4-dioxaspiro[4.5]dec-8-en-6-yl)malonate (20):



To **12** (1.54 g, 3.6 mmol), Et_3N (2.8 mL, 19.89 mmol) and catalytic DMAP (0.243 g, 1.99 mmol) in dry CH_2Cl_2 (15 mL) was added TBSOTf (4.6 mL, 19.89 mmol) at 0 °C. After stirring at same temperature for 1 h, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ and the mixture was extracted with CH_2Cl_2 (3x15 mL). The combined organic layer was washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4. The solution was then concentrated under reduced pressure and the crude silyl enol ether was further purified by column chromatography using EtOAc: petroleum ether (15:85) as eluent to furnish **20** as colourless liquid (95 %, 1.83 g).

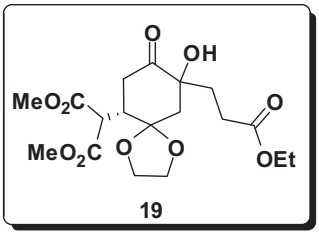
Yield:	**:**	95 %
α_D^{25}	:	+27.4 (*c* 1.85, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	3019, 2976, 2896, 2400, 1713, 1435, 1254, 1215, 1046, 840, 759, 669
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	0.11 (s, 3 H), 0.11 (s, 3 H), 0.92 (s, 9 H), 1.24 (t, *J* = 7.14 Hz, 3 H), 1.67 (s, 1 H), 2.14 - 2.46 (m, 7 H), 3.52 (d, *J* = 9.60 Hz, 1 H), 3.67 - 3.74 (m, 6 H), 3.87 - 4.05 (m, 4 H), 4.11 (q, *J* = 7.07 Hz, 2 H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	-3.9, -3.8, 14.17, 18.1, 25.6, 25.7, 32.2, 32.6, 36.5, 41.1, 51.4, 52.4, 60.2, 64.17, 64.86, 108.2, 110.2, 142.1, 168.8, 169.0, 173.5
Mass: m/z (%)	**:**	523.2 (M + Na, 100).

Procedure for oxidation of vinyl TBS ether to hydroxyl ketone:



A solution containing the **20** (1.2 g, 2.39 mmol) in 7 mL of *t*-butyl alcohol was added at 0 ˚C to a mixture containing 0.24 mmol of OsO_4 (added as a solution in 0.7 mL of t-butyl alcohol), NMO.H_20 (2.3 mL, 9.6 mmol), and 7.0 mL of H_2O. The resulting mixture was stirred at 0 °C for 3 h, then allowed to warm to room temperature and stirred for additional 10 h. Sodium hydrogen sulfite (0.3 g) were added, the suspension was stirred and filtered through a pad of celite to remove osmium-containing material. The filtrate was made acidic with 1 N HCl (checked by litmus), and saturation with NaCl, the mixture was extracted with ethyl acetate (4x15 mL). Combined organic layer was dried over $NaSO_4$ and concentrated to afford viscous liquid which was further purified by column chromatography using EtOAc:petroleum ether (40:60) as eluent to obtain pure **19**, **22**, **23**.

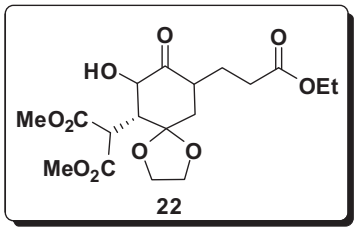
Dimethyl 2-((6S)-9-(3-ethoxy-3-oxopropyl)-9-hydroxy-8-oxo-1,4-dioxaspiro[4.5]decan-6-yl)malonate 19:



Yield:	**:**	70 %
$\alpha_D^{31.3}$	:	+35.60 (*c* 3.27, $CHCl_3$, 50 % *de*)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	3480.1, 3020.2, 2899.9, 2400, 1732.7, 1436.5, 1215.9, 1150.5, 759.9, 669.05
^{1}H NMR ($CDCl_3$, 500	**:**	1.19 - 1.30 (m, 3 H), 1.83 (d, *J* = 14.34 Hz, 1 H), 1.96

MHz) δ (diastereomeric ratio 3:1)		- 2.05 (m, 1 H), 2.14 - 2.23 (m, 1 H), 2.26 - 2.45 (m, 3 H), 2.69 (dd, *J* = 13.43, 3.66 Hz, 1 H), 2.94 - 3.01 (m, 1 H), 3.03 - 3.13 (m, 1 H), 3.72 (s, 3 H), 3.73-3.74 (m, 1H), 3.75 (s, 3 H), 3.95 - 4.13 (m, 6 H)
^{13}C NMR ($CDCl_3$, 125 MHz) δ (only more major diastereomer)	:	14.12, 28.0, 33.0, 36.9, 45.1, 45.5, 50.0, 52.5, 52.7, 60.5, 64.8, 64.9, 77.2, 107.6, 168.2, 173.2, 210.8
Mass: m/z (%)	:	827.7 (2M + Na, 50), 425.3 (M + Na, 100).

Dimethyl-2-((6R)-9-(3-ethoxy-3-oxopropyl)-7-hydroxy-8-oxo-1,4-dioxaspiro[4.5] decan-6-yl)malonate 22:

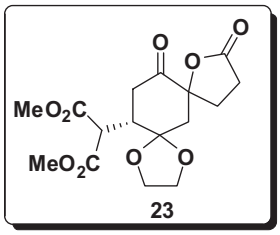


22

Yield:	:	10 %
$\alpha_D^{31.8}$	:	-22.9 (*c* 0.99, $CHCl_3$, 60 % *de*)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3485, 3021, 2899, 2410, 1732, 1436, 1215, 1150, 759, 669
^{1}H NMR ($CDCl_3$, 400 MHz) δ (diastereomeric ratio 1:4)	:	1.24 (t, *J* = 7.03 Hz, 3 H), 1.53 - 1.66 (m, 2 H), 2.06 - 2.20 (m, 2 H), 2.28 - 2.46 (m, 3 H), 2.71 - 2.81 (m, 1 H), 2.91 (dd, *J* = 12.17, 4.39 Hz, 1 H), 3.76 (s, 3 H), 3.72 (s, 3 H), 3.80 - 3.83 (m, 1 H), 3.98 - 4.07 (m, 4 H), 4.11 (q, *J* = 7.28 Hz, 2 H), 4.80 (d, *J* = 12.30 Hz, 1 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ (only for major diastereomers)	:	14.1, 23.4, 31.5, 39.8, 42.6, 48.1, 52.3, 52.6, 53.4, 60.4, 64.9, 73.5, 107.1, 168.7, 169.3, 173.0, 209.60

Mass: m/z (%) : 425 (M + Na, 100), 420 (45), 403 (M + 1, 10)

Compound 23:



23

Yield: : 20 %

α_D^{25} : -4.49 (*c* 1.77, $CHCl_3$, 50 % *de*)

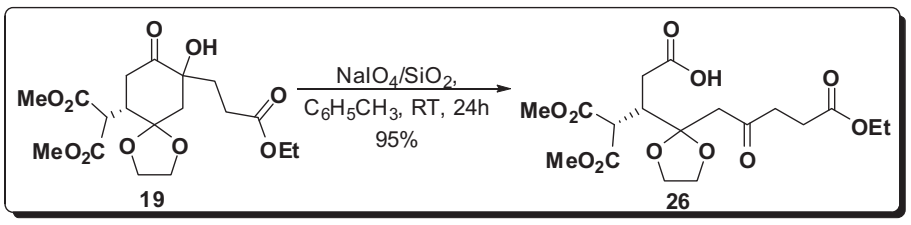
IR ν_{max} cm^{-1} ($CHCl_3$) : 3019, 2898, 2400, 1785, 1751, 1437, 1216, 1148, 1047, 756

^{1}H NMR ($CDCl_3$, 200 MHz) δ : 2.03 - 2.27 (m, 2 H), 2.34 (d, *J* = 4.80 Hz, 1 H), 2.40 - 2.58 (m, 3 H), 2.67 - 2.99 (m, 2 H), 3.03 - 3.18 (m, 1 H), 3.68 - 3.80 (m, 7 H), 4.01 - 4.13 (m, 4 H)

^{13}C NMR ($CDCl_3$, 50 MHz) δ : 27.3, 33.2, 37.3, 43.1, 43.3, 49.9, 52.6, 52.8, 64.9, 65.3, 85.9, 107.5, 168.1, 175.2, 203.2

Mass: m/z (%) : 411.03 (M + MeOH + Na, 100), 388.5 (M + Na), 349.28(56)

3-(2-(5-ethoxy-2,5-dioxopentyl)-1,3-dioxolan-2-yl)-5-methoxy-4-(methoxycarbonyl)-5-oxopentanoic acid (26):



19 26

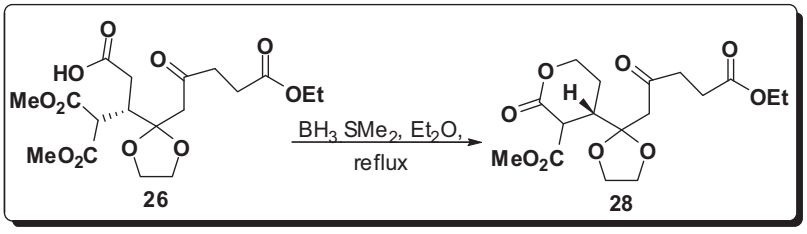
Preparation of silica gel-supported sodium metaperiodate: $NaIO_4$ (2.57 g, 12.0 mmol) was dissolved in 5 mL of hot water (70 °C) in a 25 mL round-bottomed flask. To the hot

solution silica gel (230-400 mesh, 10 g) was added with vigorous swirling and shaking. The resultant silica gel coated with $NaIO_4$ was in a powder form and was free-flowing, with a concentration of approximately 15% in $NaIO_4$.

Procedure for oxidative cleavage: **19** (0.753 g, 1.87 mmol) was dissolved in 10 mL toluene and silica-supported sodium metaperiodate (8.0 g, 3.0 equivalents in $NaIO_4$) was added to it. Reaction mixture was stirred at RT for 24 h. After complete consumption of starting material, checked by TLC, reaction mixture was filtered and silica was washed with EtOAc. Combine filtrate was concentrated under reduced pressure and crude reaction mixture is purified by column chromatography using EtOAc:petroleum ether (90:10) as eluent to obtain pure **26** in 95% yield.

Yield:	**:**	95 %
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	3500, 2988, 2937, 1724, 1435, 1383, 1219
^{1}H NMR ($CDCl_3$, 400 MHz) δ	**:**	1.25 (t, *J* = 7.2, 3 H), 2.52 - 2.60 (m, 2 H), 2.62 - 2.65 (m, 2 H), 2.66 (s, 1 H), 2.82 (t, *J* = 6.53 Hz, 2 H), 2.86 (d, *J* = 2.26 Hz, 1 H), 3.25 - 3.31 (m, 1 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 3.80 - 3.87 (m, 1 H), 3.94 - 4.04 (m, 4 H), 4.12 (q, *J* = 7.19 Hz, 2 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	14.1, 27.9, 32.5, 38.9, 42.3, 46.9, 51.0, 52.5, 52.8, 60.6, 65.0, 65.5, 109.9, 168.6, 168.7, 172.8, 176.8, 205.1
Mass: m/z (%)	**:**	441.45 (M + Na, 100), 419.03 (M + 1, 20)

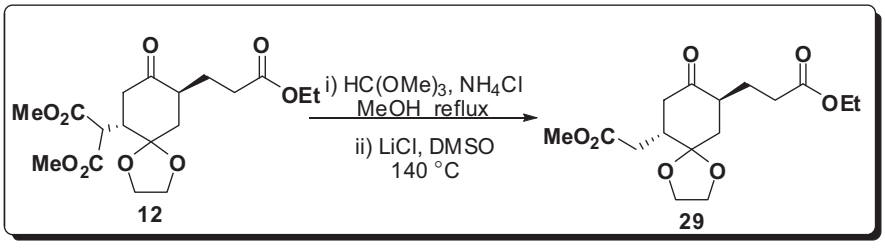
Methyl-5-(2-(5-ethoxy-2,5-dioxopentyl)-1,3-dioxolan-2-yl)-2-oxotetrahydro-2H-pyran-3-carboxylate (28):



20 (0.058 g, 418.3 mmol) was dissolved in 16 mL of dry diethyl ether and the reaction flask was briefly flushed with nitrogen. $BH_3.SMe_2$ (0.15 mL, 1.54 mmol) was added dropwise to the reaction mixture at RT, the hydrogen evolution can be observed while addition. The resulting mixture is heated to a gentle reflux in an oil bath. After refluxing for 1hr, methanol was added to reaction mixture. Solvent was removed under reduced pressure to obtain **28** as viscous liquid.

Yield:	**:**	60 %
$\alpha_D^{24.6}$	:	+6.22 (*c* 1.21, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	3021.2, 2955.4, 1772.3, 1437.3, 1217.2, 1035.3, 757.3
^{1}H NMR ($CDCl_3$, 400 MHz) δ	**:**	1.25 (t, *J* = 7.15 Hz, 3 H), 1.89 (dd, *J* = 9.29, 4.77 Hz, 1 H), 2.11 (s, 1 H), 2.49 - 2.65 (m, 2 H), 2.73 (d, *J* = 13.80 Hz, 1 H), 2.77 - 2.84 (m, 2 H), 2.89 (d, *J* = 14.05 Hz, 1 H), 3.09 (q, *J* = 7.03 Hz, 1 H), 3.52 (d, *J* = 8.03 Hz, 1 H), 3.77 (s, 3H), 4.04 (s, 4 H), 4.13 (q, *J* = 7.28 Hz, 2 H), 4.23 - 4.32 (m, 1 H), 4.34 - 4.42 (m, 1 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	14.0, 23.7, 27.8, 38.8, 40.8, 47.3, 47.7, 52.71, 60.57, 65.2, 65.3, 67.5, 109.6, 167.9, 169.15, 172.55, 205.2

Ethyl-3-(10-(2-methoxy-2-oxoethyl)-8-oxo-1,4-dioxaspiro[4.5]decan-7-yl)propanoate (29):

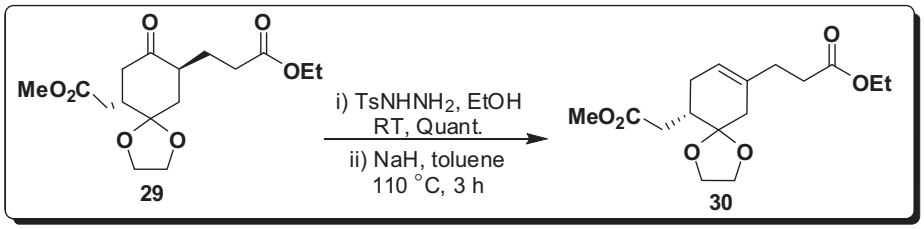


To a solution of **12** (2.0 g, 5.18 mmol) and trimethyl orthoformate (1.7 mL, 15.53 mmol) in 50 mL MeOH, NH_4Cl (0.05 g) was added Reaction mixture was then refluxed for 4h, and was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with EtOAc (3x20

mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to afford crude ketal, which was used for the next step without further purification. The residue was dissolved in DMSO (30 mL) then LiCl (0.263 g, 6.20 mol) was added. The reaction mixture was stirred for 5 h at 140 °C, cooled to RT, quenched by H_2O, and extracted with EtOAc (3x20 mL). The combined organic layers were stirred vigorously with 2N HCl aqueous solution (50 mL) and washed with saturated $NaHCO_3$ aqueous solution (1x20 mL) and brine (1x20 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (EtOAc:petroleum ether 1:3) to afford **29** as a yellow oil (1.831 g).

Yield:	**:**	80 %
$\alpha_D^{24.8}$	:	+44.22 (*c* 1.01, $CHCl_3$, 60 % *de*)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	2954, 2897, 1735, 1718, 1438, 1175
^{1}H NMR ($CDCl_3$, 500 MHz) δ (diastereomeric ratio 4:1)	**:**	1.24 (t, *J* = 7.17 Hz, 3 H), 1.48 - 1.60 (m, 2 H), 2.01 - 2.16 (m, 3 H), 2.29 - 2.41 (m, 2 H), 2.43 - 2.53 (m, 2 H), 2.55 - 2.71 (m, 3 H), 3.68 (s, 3 H), 3.96 - 4.07 (m, 4 H), 4.09 - 4.14 (q, *J* = 7.13 Hz, 2 H)
^{13}C NMR ($CDCl_3$, 126 MHz) δ (only for major diastereomer)	**:**	14.2, 24.0, 31.7, 34.1, 39.7, 41.9, 44.2, 45.6, 51.7, 60.3, 64.8, 64.9, 65.2, 108.1, 172.5, 173.3, 209.1

Ethyl 3-(10-(2-methoxy-2-oxoethyl)-1,4-dioxaspiro[4.5]dec-7-en-7-yl)propanoate (30):

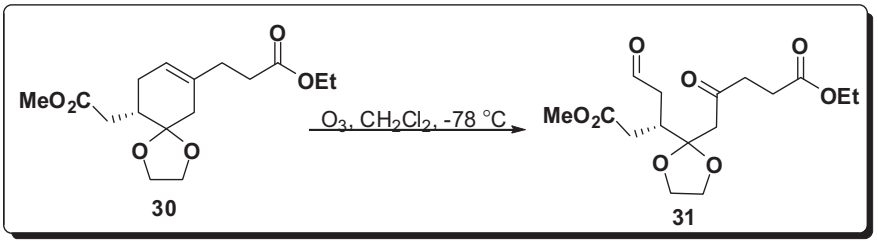


Procedure is same as for preparation of compound **11** except that base used was NaH along with toluene as solvent.

Yield:	**:**	60 %
$\alpha_D^{24.5}$	:	+27.8 (*c* 0.540, $CHCl_3$, 95 % *ee*)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	3020, 2983, 2907, 1731, 1438, 1216, 1038.8, 755

^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	1.25 (t, *J* = 7.09 Hz, 3 H), 2.04-2.11 (m, 1 H), 2.12 (dd, *J* = 15.28, 7.70 Hz, 1 H), 2.16 (bs, 2 H), 2.26 - 2.31 (m, 2 H), 2.34 (s, 1 H), 2.37 - 2.45 (m, 4 H), 2.51 - 2.58 (m, 1 H), 3.67 (s, 3 H) 3.94 - 4.00 (m, 4 H), 4.12 (q, *J* = 7.09 Hz, 2 H), 5.39 (s, 1 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	:	14.2, 30.0, 32.1, 32.5, 34.0, 37.2, 37.7, 51.5, 60.3, 64.5, 65.0, 109.1, 119.6, 133.8, 173.2, 173.6
Mass: m/z (%)	:	335.52 (M+Na, 100)
HPLC (Chiralcel OD-H, *i-PrOH*:*petroleum ether* 20:80, 0.7 mL/min, 230 nm)	:	τ_R = 8.65 min. (major enantiomer), τ_R = 5.858 min. .(minor enantiomer)

Ethyl 5-(2-(1-methoxy-1,5-dioxopentan-3-yl)-1,3-dioxolan-2-yl)-4-oxopentanoate 31:

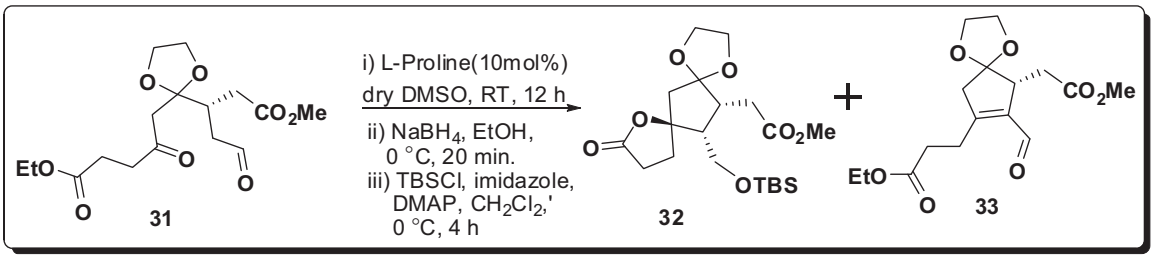


Ozone gas was bubbled through solution of **30** (0.5 g, 1.6 mmol) in dichloromethane (30 mL) at -78 ˚C till solution turns purple. Marking appearance of purple color as end point, argon was bubbled through the reaction mixture till it becomes colourless. Dimethyl sulphite (2.0 mL) was added to reaction mixture and solution was allowed to warm to room temperature over period of 2 h. Reaction mixture was concentrated under reduced pressure and residue was purified by flash column chromatography (EtOAc:petroleum ether 3:7) to afford **31** as a colorless liquid (0.386 g).

Yield:	:	70 %
$\alpha_D^{28.4}$	:	-28.7 (*c* 2.31, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3020, 2400, 1730, 1438, 1215, 1024, 756
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	1.24 (t, *J* = 7.15 Hz, 3 H), 2.28 (dd, *J* = 15.94, 8.91 Hz, 1 H), 2.33 - 2.41 (m, 1 H), 2.45 - 2.51 (m, 1 H),

		2.54 (t, *J* = 6.40 Hz, 2 H), 2.60 (dd, *J* = 15.94, 4.89 Hz, 1 H), 2.77 (s, 2 H), 2.81 (td, *J* = 6.46, 2.64 Hz, 2 H), 2.99 - 3.08 (m, 1 H), 3.67 (s, 3 H), 3.87 - 4.01 (m, 4 H), 4.08 - 4.15 (q, *J* = 7.15 Hz, 2 H), 9.63 (dd, *J* = 3.01, 1.25 Hz, 1 H).
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	14.1, 27.8, 34.6, 37.9, 39.0, 43.9, 47.0, 51.8, 60.6, 64.8, 65.4, 110.2, 172.4, 172.6, 200.3, 205.3
Mass: m/z (%)	**:**	367 (M + Na, 100)

Procedure for intranolecular aldol cyclization of (31):



To solution of **31** (0.15 g, 0.436 mmol) in dry DMSO (10 mL) L-proline (0.005 g, 0.044 mmol) was added. Reaction mixture was stirred at room temperature till complete disappearance of starting material (12 h), monitored by GC. After complete disappearance of starting material reaction was quenched with water and extracted with EtOAc (3x15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to afford aldol product, which was used for the next step without further purification. The residue obtained was dissolved in 10.0 mL EtOH at 0 ˚C and solid sodium borohydride (0.009 g, 0.2325 mmol) was added in one portions. After 20 min. the reaction mixture was quenched by careful addition of saturated aqueous solution of ammonium chloride (10 mL) with vigorous stirring. Ethanol was removed under reduced pressure and the resulting aqueous solution was extracted with EtOAc (3x10 mL). Combined organic layer was washed with brine, dried over Na_2SO_4 (0.009 g, 0.232 mmol) and concentrated under reduced pressure to afford alcohol which was directly subjected for alcohol protection. To a solution of crude alcohol, DMAP (.011 g, 0.093 mmol) and imidazole (0.035 g, 0.512 mmol) in dry CH_2Cl_2 (7 mL) at 0 °C was added solid TBSCl

(15. 27 g, 101.31 mmol) in one portion. The resulting yellow solution was stirred at 0 °C for 2 h and then gradually warmed to room temperature over period of 2 h. Reaction mixture was quenched with water (7 mL) and was extracted with CH_2Cl_2 (3×10 mL), dried over Na_2SO_4, filtered and concentrated in rotary evaporator to afford a yellow liquid. Purification by flash column chromatography (EtOAc:petroleum ether 1:4) to afford **32** as a yellow oil along with **33** (0.15 g).

Compound **32**

Yield:	**:**	5 % (over 3 steps)
$\alpha_D^{28.4}$	:	-45 (*c* 0.6, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 400 MHz) δ	**:**	0.02 - 0.10 (m, 6 H), 0.87 (s, 9 H), 2.06 - 2.20 (m, 3 H), 2.26 - 2.39 (m, 2 H), 2.47 - 2.54 (m, 3 H), 2.54 – 2.64 (m, 1 H), 3.64 - 3.70 (m, 1 H), 3.67 (s, 1H) 3.77 - 3.97 (m, 5 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	-5.7, -5.6, 18.1, 25.8, 28.6, 32.9, 34.0, 45.3, 49.9, 51.6, 53.8, 61.5, 64.7, 65.1, 89.5, 114.2, 172.9, 176.7
Mass: m/z (%)	**:**	437.07 (M + Na, 100), 382.98 (15), 323.02 (90), 282 (50)

Compound **33**

$\alpha_D^{28.4}$	:	-1.81 (c = 1.46, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3019, 2400, 1734, 1474, 1421, 1215, 1020, 757
^{1}H NMR ($CDCl_3$, 400 MHz) δ	**:**	1.24 (t, *J* = 7.02 Hz, 3 H), 2.33 (dd, *J* = 16.31, 10.29 Hz, 1 H), 2.49 - 2.60 (m, 3 H), 2.64 (d, *J* = 19.07 Hz, 1 H), 2.79 - 2.91 (m, 1 H), 2.95 - 3.02 (m, 1 H), 3.37 - 3.45 (m, 1 H), 3.67 (s, 3 H), 3.73 - 3.88 (m, 2 H), 3.93 - 4.04 (m, 2 H), 4.13 (q, *J* = 7.03 Hz, 2 H), 9.98 (s, 1 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	14.1, 23.5, 32.2, 33.3, 46.4, 47.6, 51.5, 60.8, 64.2, 65.5, 114.6, 139.0, 159.3, 171.7, 172.6, 186.79

3.5 References:

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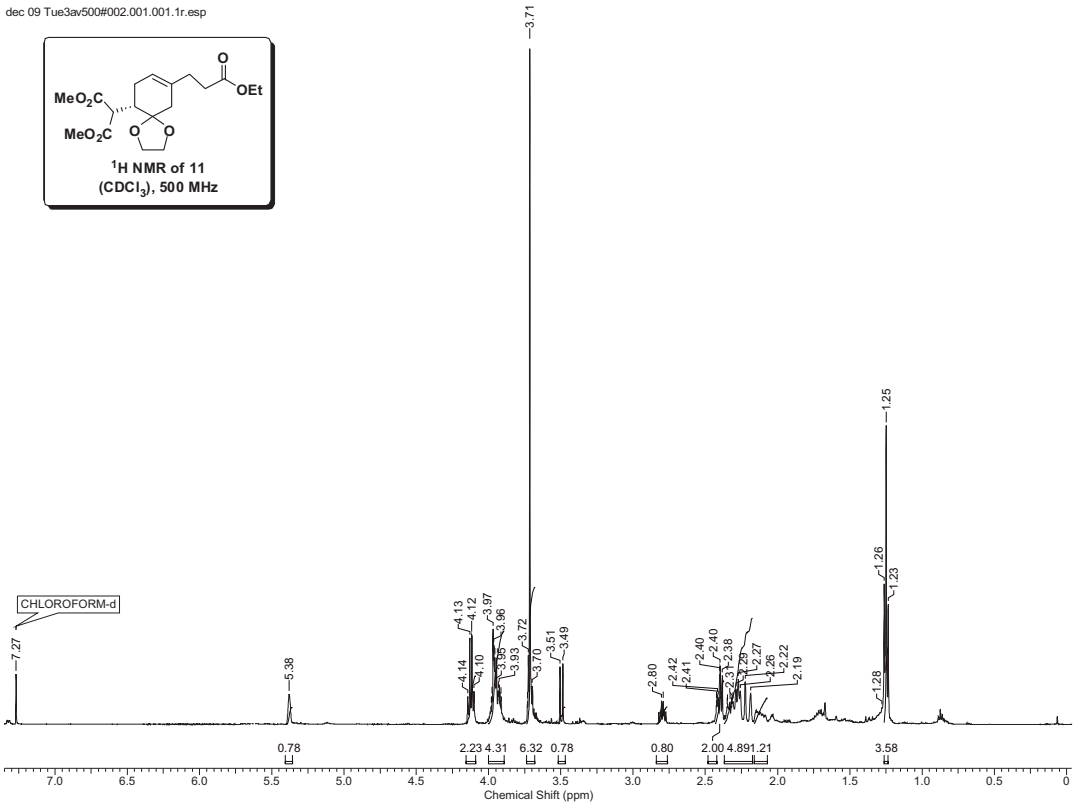
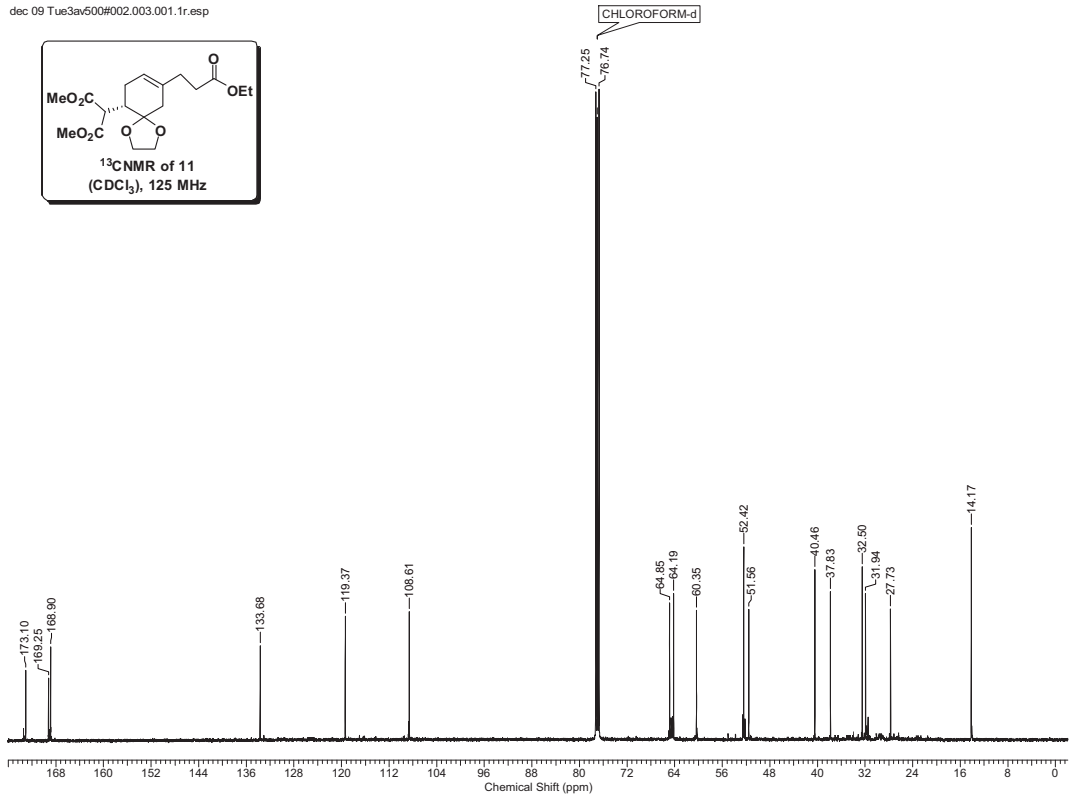
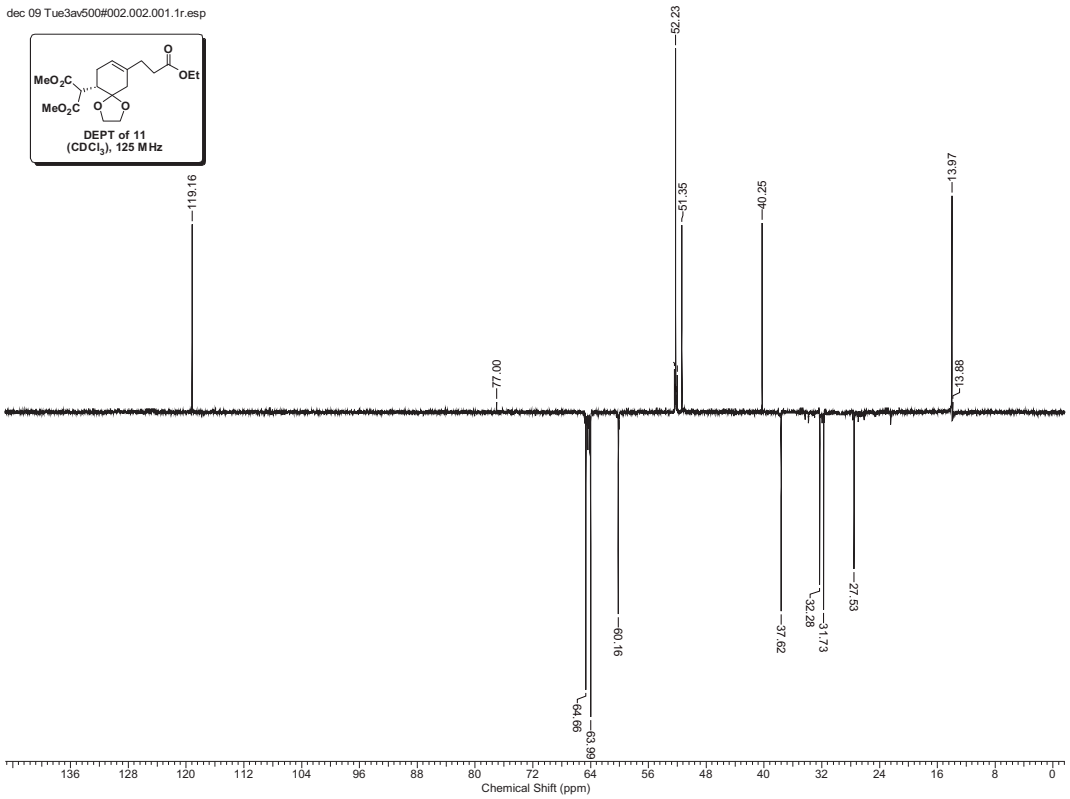
3.6 Spectra of all new compounds



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37.62
32.28
31.73
27.53
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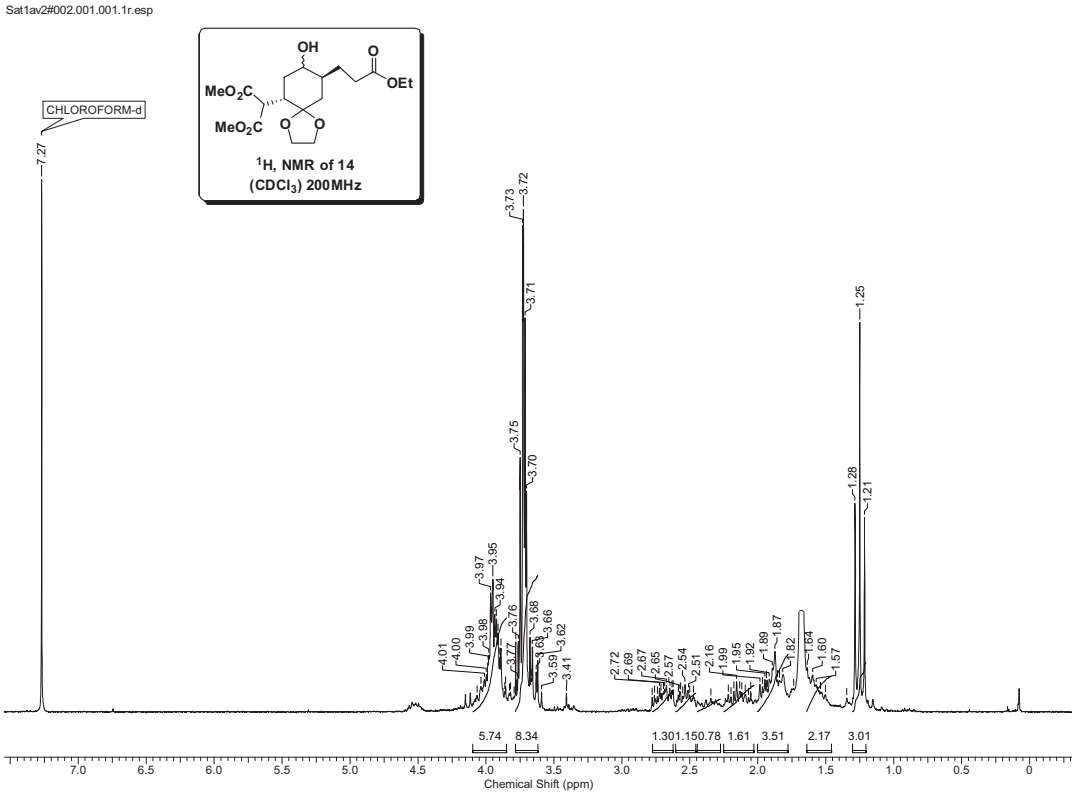
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3.75
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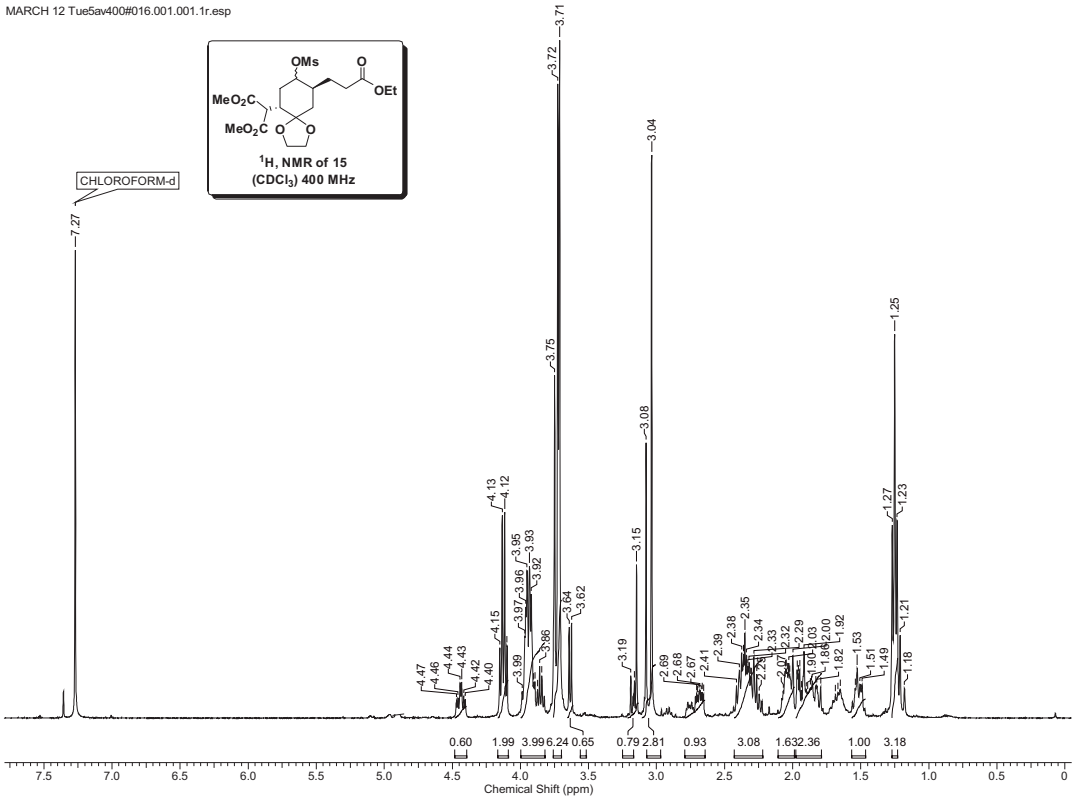
1.21
Chemical Shift (ppm)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MeO2C
O
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7.27
3.71
3.72
3.04
3.75
3.08
1.25
4.13
4.12
3.15
1.27
1.23
3.95
3.93
3.92
3.96
3.97
3.84
3.62
1.21
4.15
2.38
2.35
4.44
4.43
4.42
4.40
4.47
4.46
3.99
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3.19
2.69
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2.67
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2.39
2.34
2.33
2.32
2.29
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1.49
1.18
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2.36
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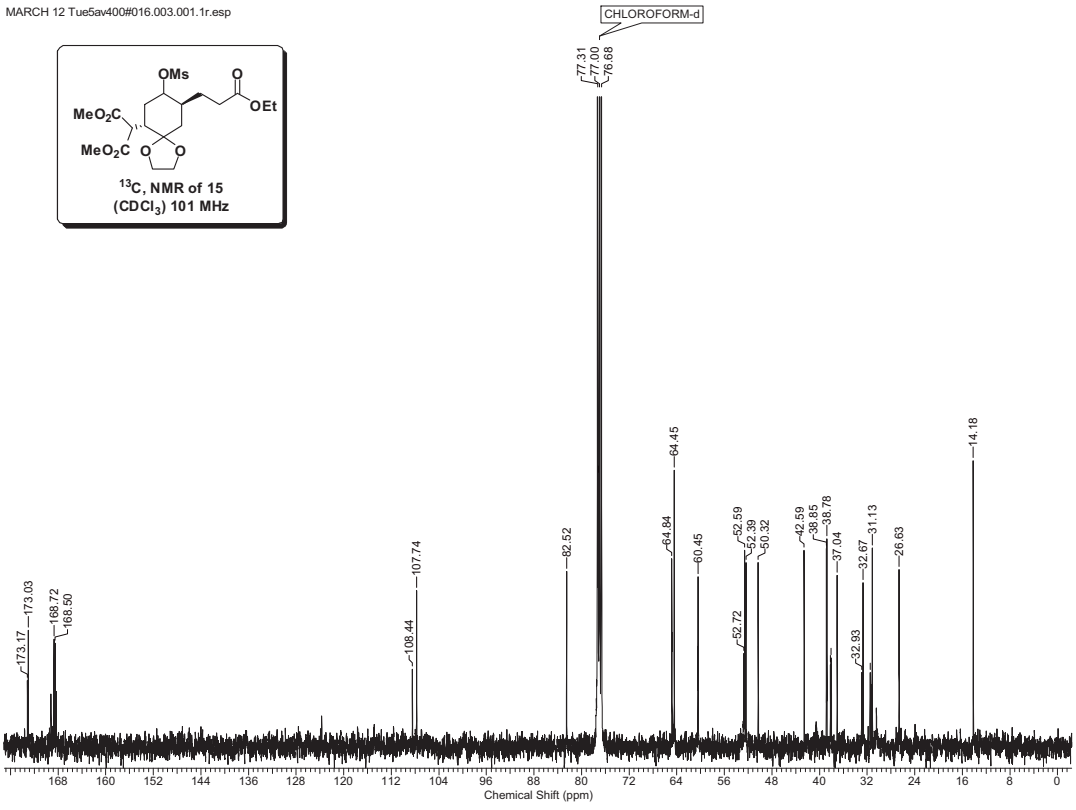
3.18
Chemical Shift (ppm)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OEt
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O
O
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37.04
31.13
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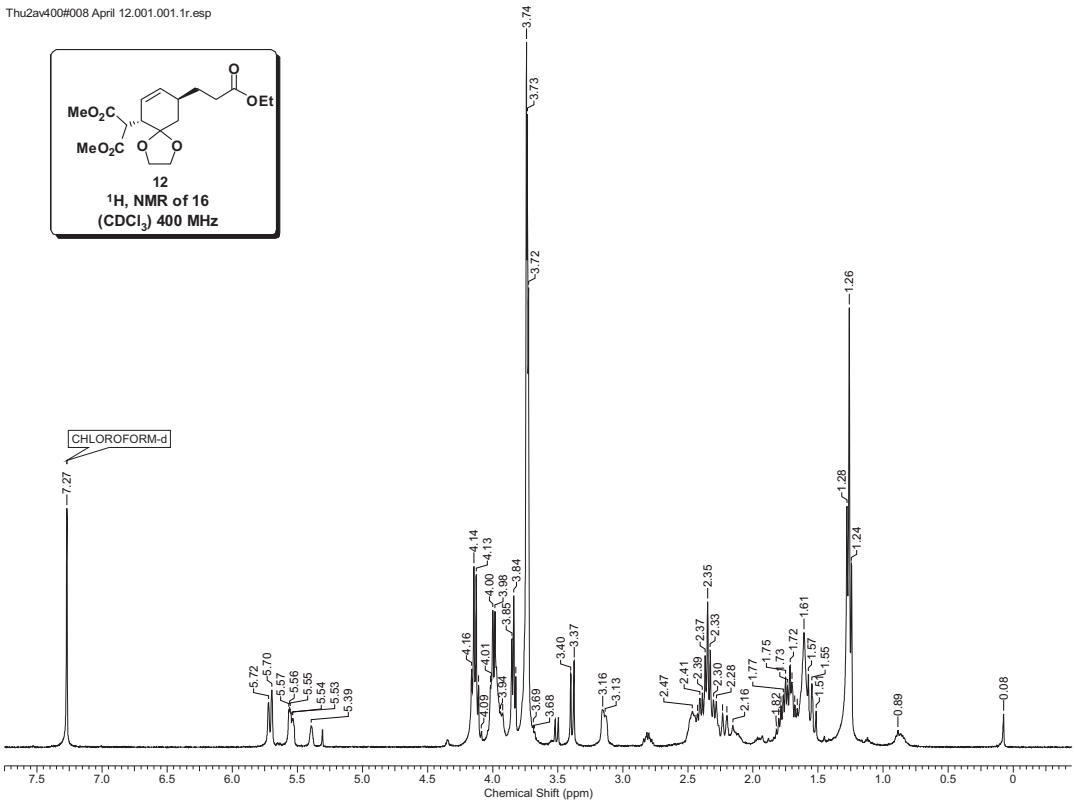
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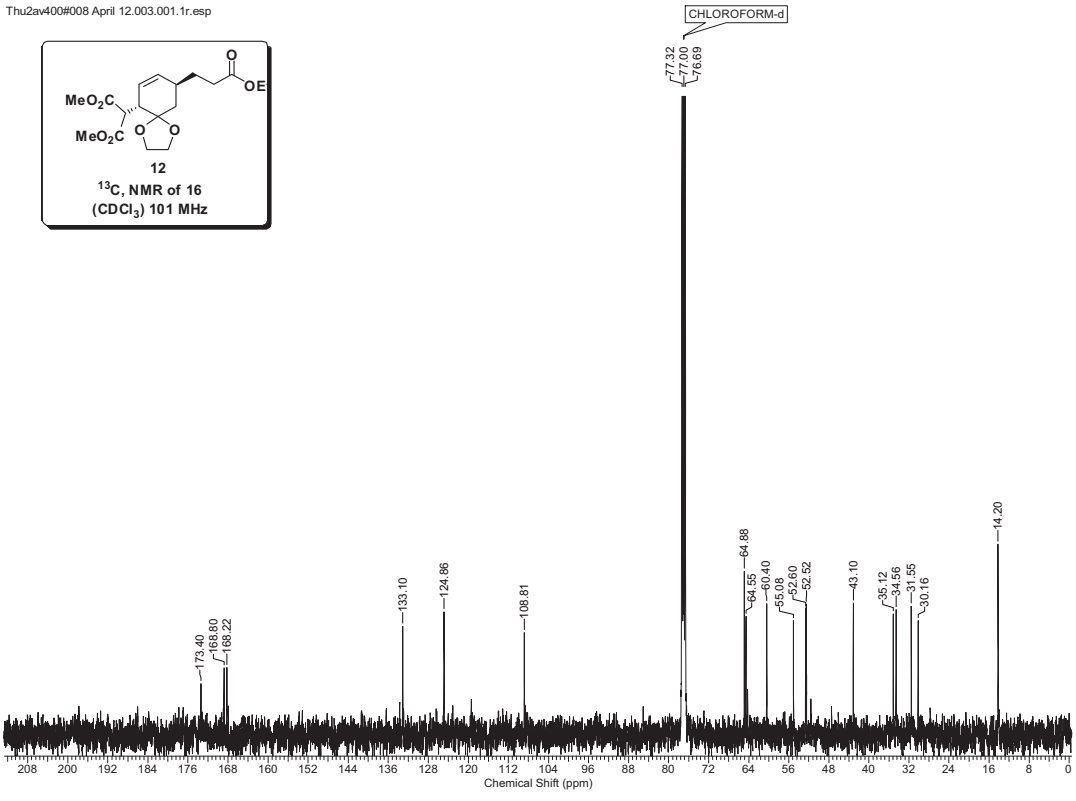
Chemical Shift (ppm)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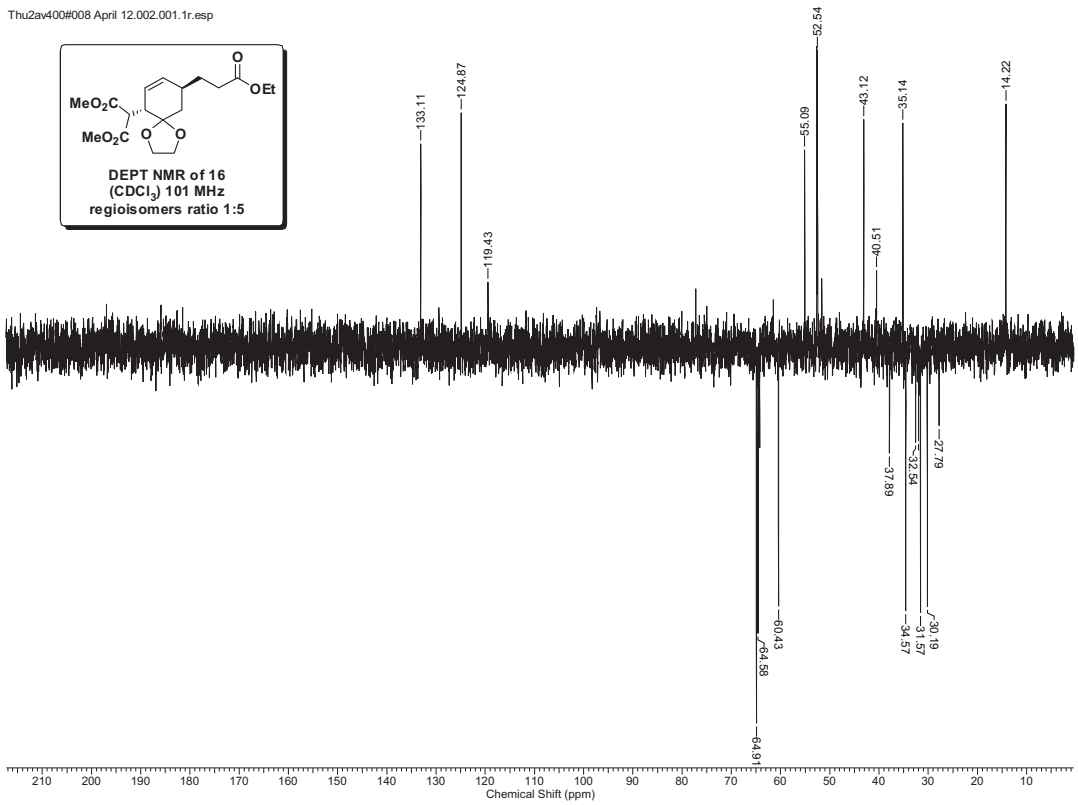
Chemical Shift (ppm)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64.16
55.09
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34.57
32.54
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30.19
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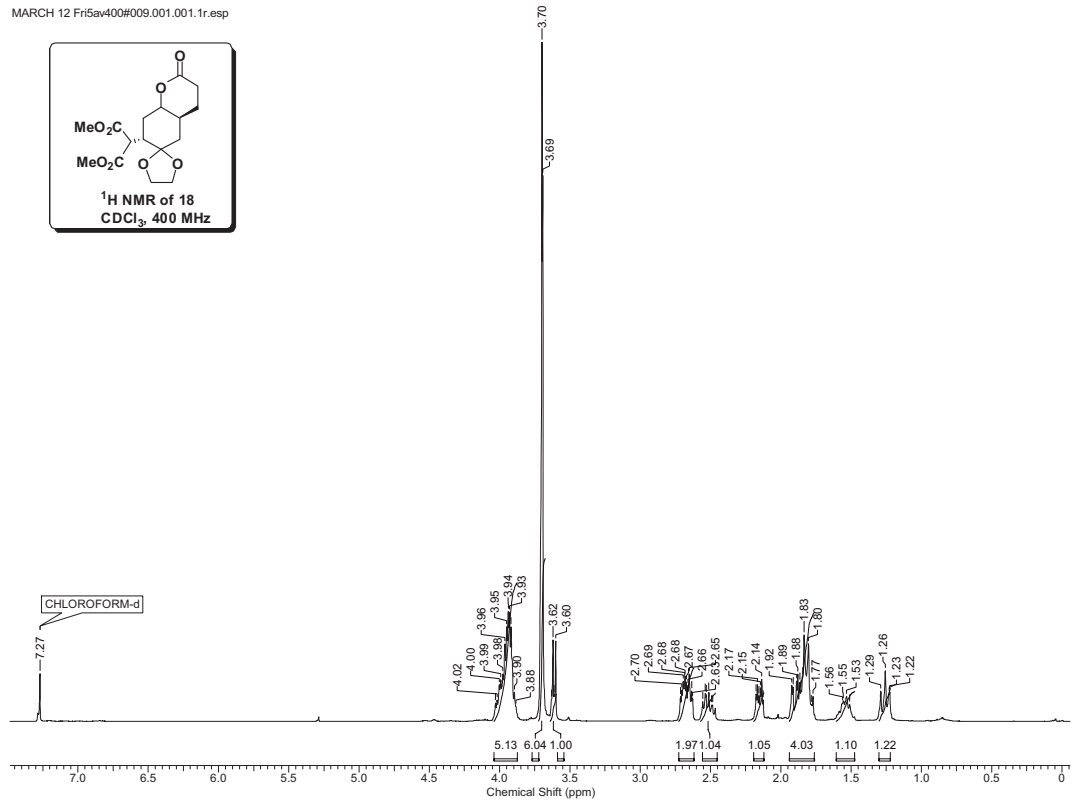
14.22
Chemical Shift (ppm)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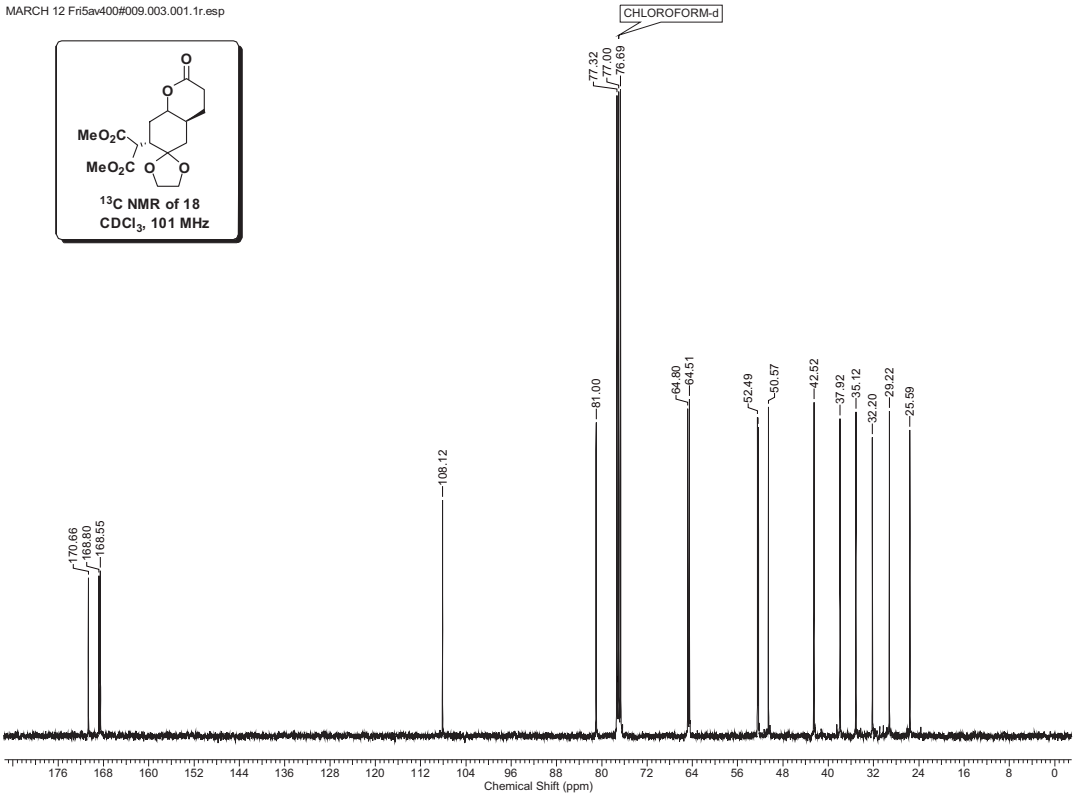
Chemical Shift (ppm)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32.20
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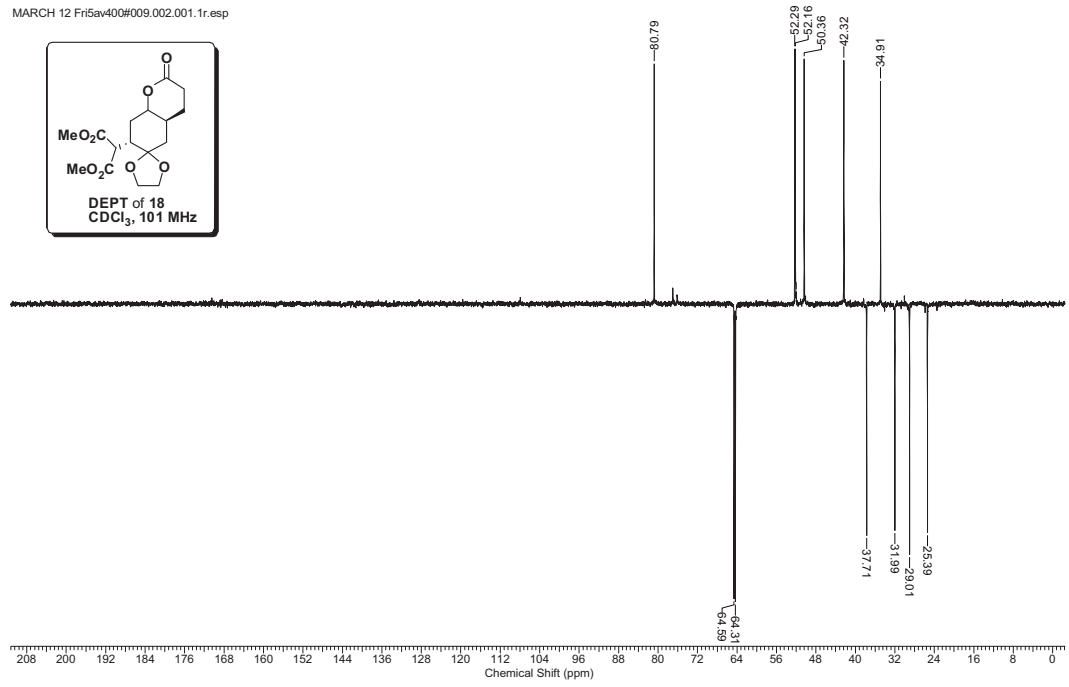
13C NMR of 18
CDCl3, 101 MHz
Chemical Shift (ppm)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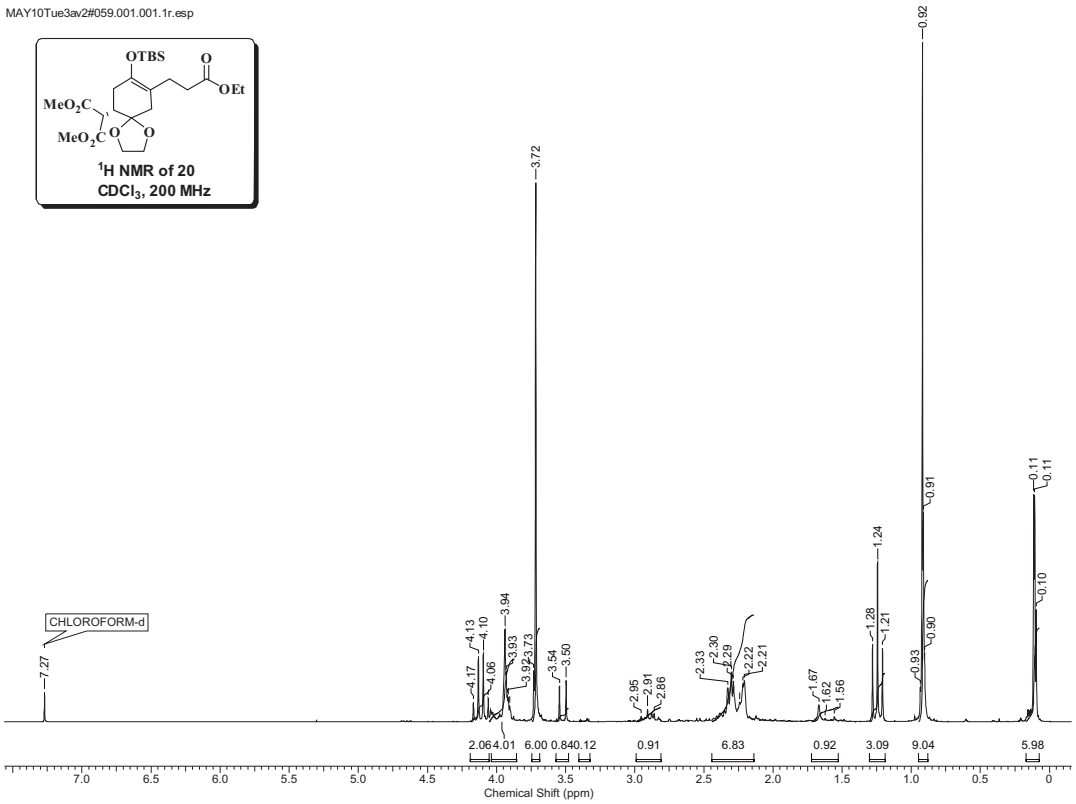
MeO2C
DEPT of 18
CDCl3, 101 MHz
Chemical Shift (ppm)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OEt
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MeO2C
O
O
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4.13
4.10
4.06
3.94
3.93
3.92
3.73
3.72
3.54
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2.22
2.21
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1.28
1.24
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0.92
0.91
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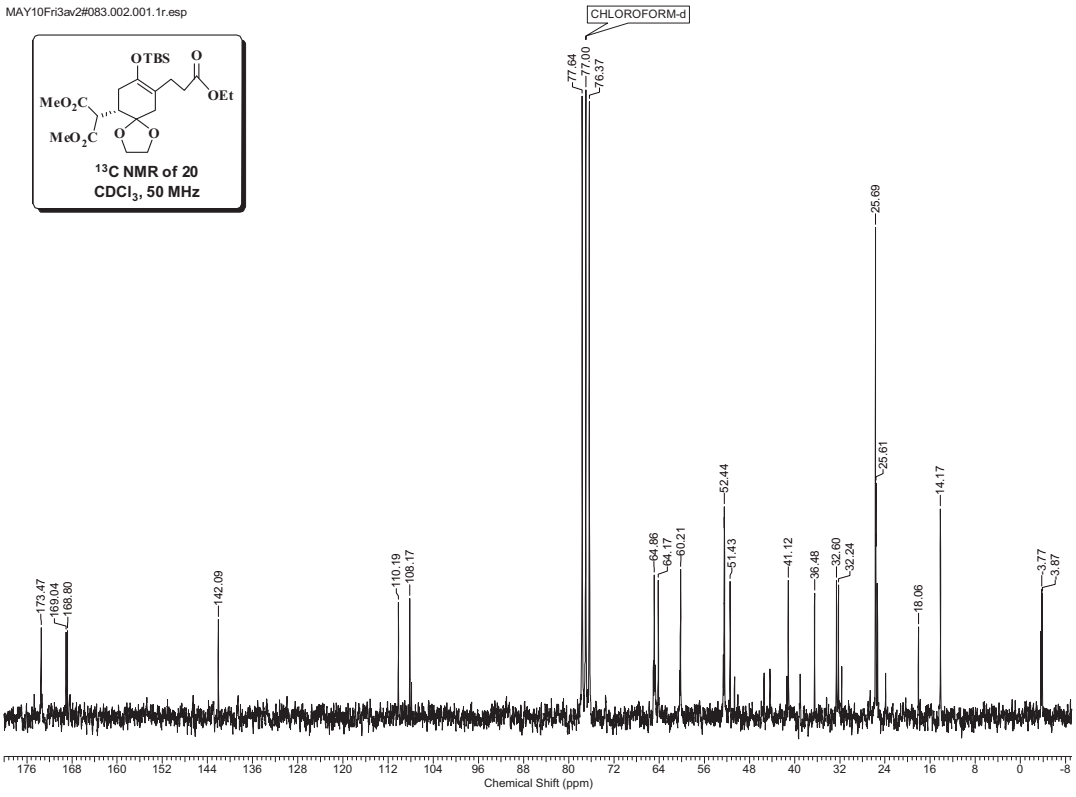
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O
O
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CDCl3, 50 MHz
CHLOROFORM-d
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168.80
142.09
110.19
108.17
77.64
77.00
76.37
64.86
64.17
60.21
52.44
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25.61
18.06
14.17
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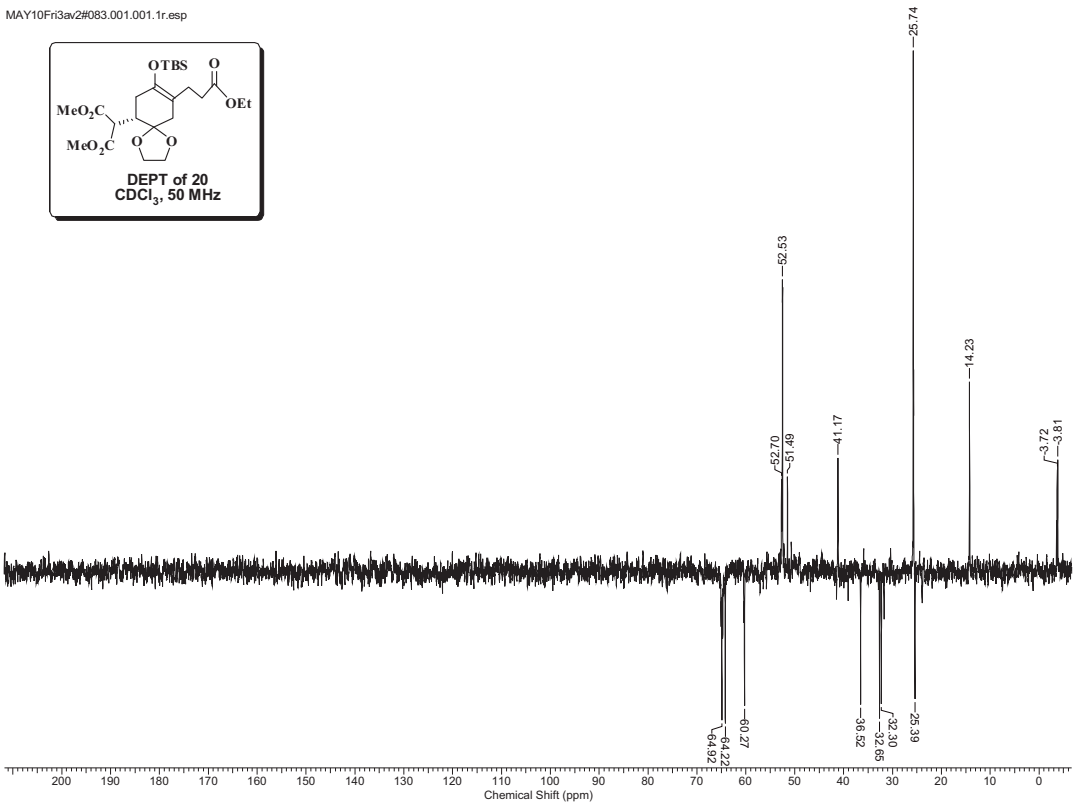
3.87
Chemical Shift (ppm)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MeO2C
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14.23
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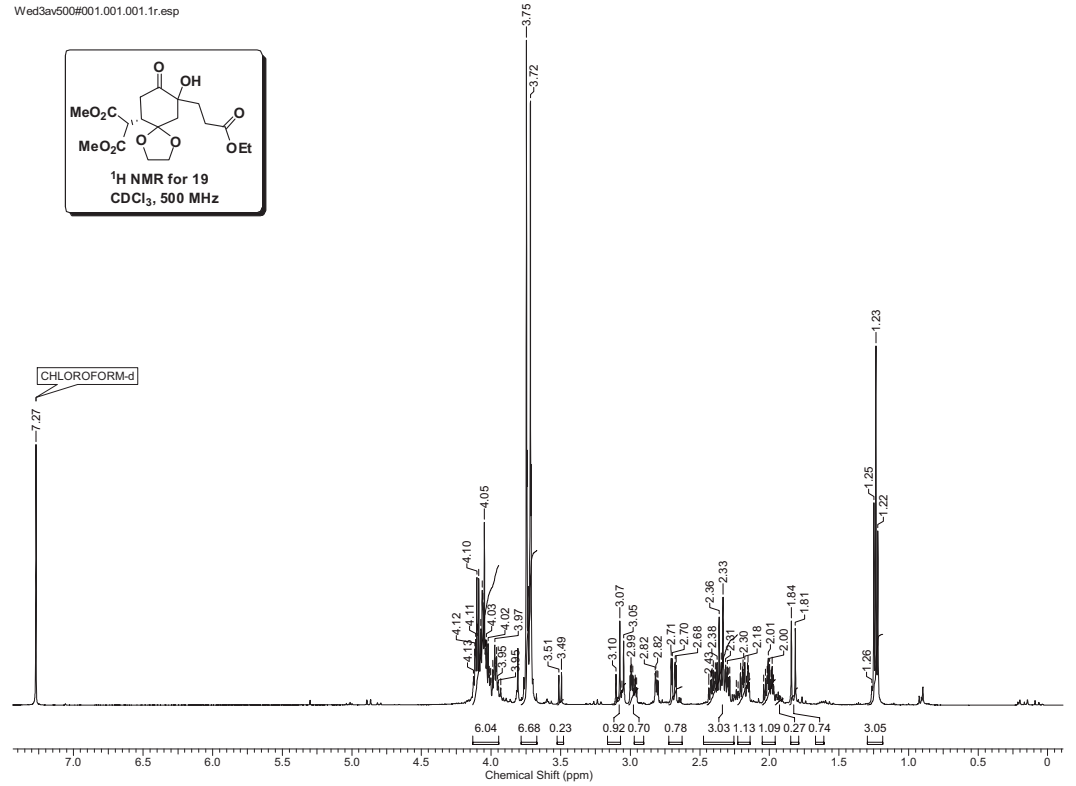
36.52
32.65
32.30
25.39
Chemical Shift (ppm)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MeO2C
O
O
O
OEt
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7.27
3.75
3.72
4.05
4.10
1.23
1.25
1.22
2.33
2.36
1.84
1.81
6.04
6.68
0.23
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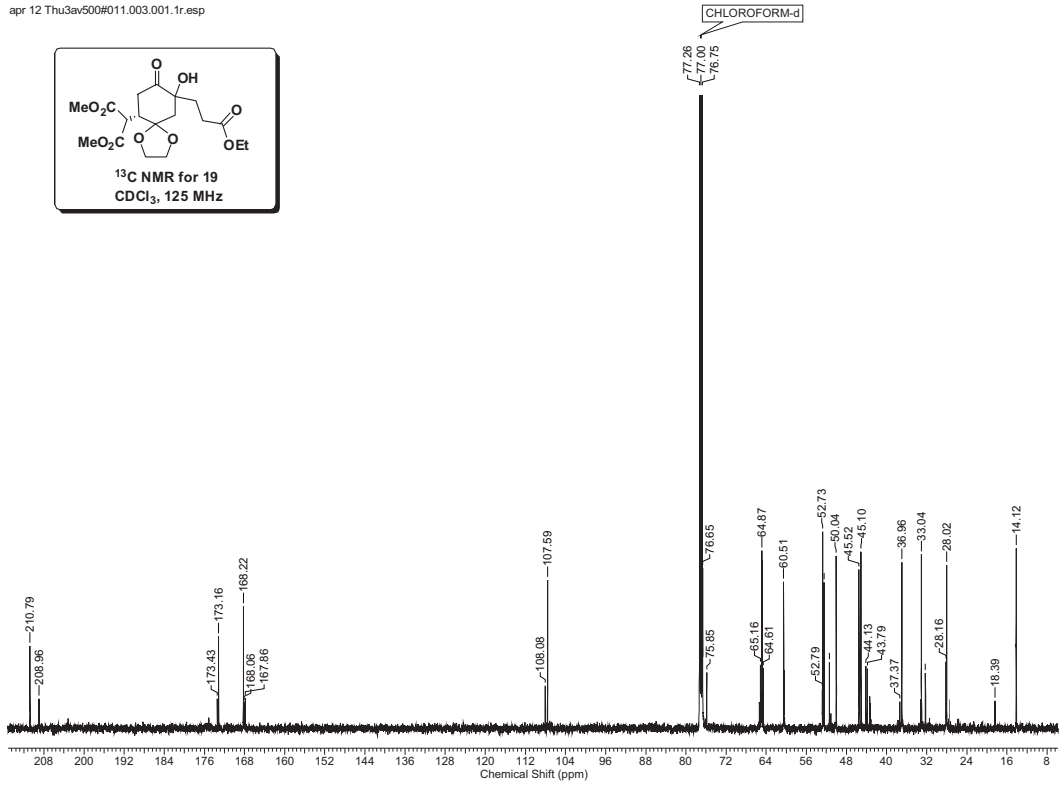
1.13
1.09
0.27
0.74
3.05
Chemical Shift (ppm)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76.75
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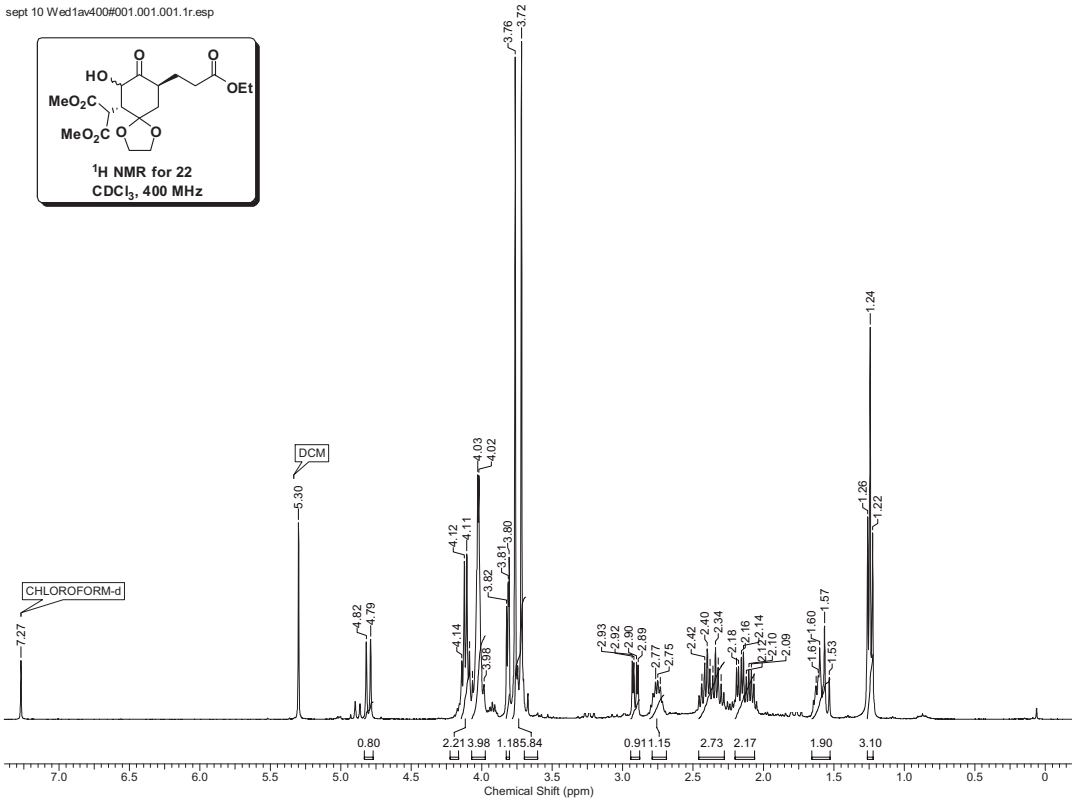
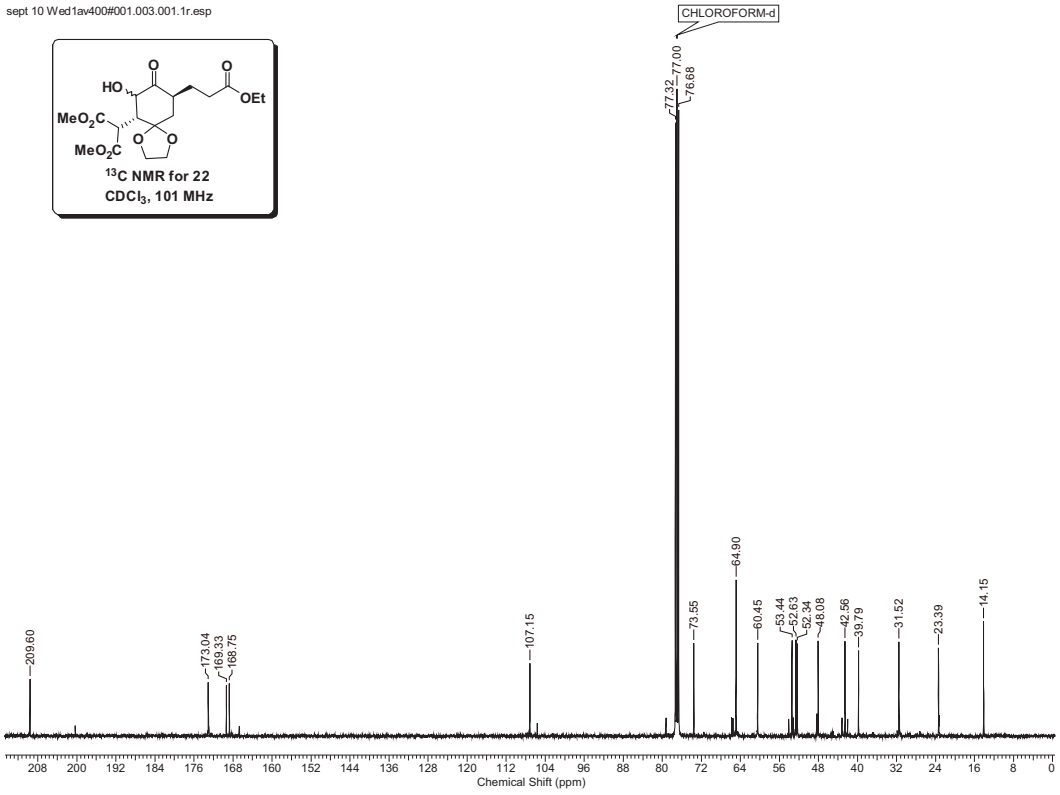
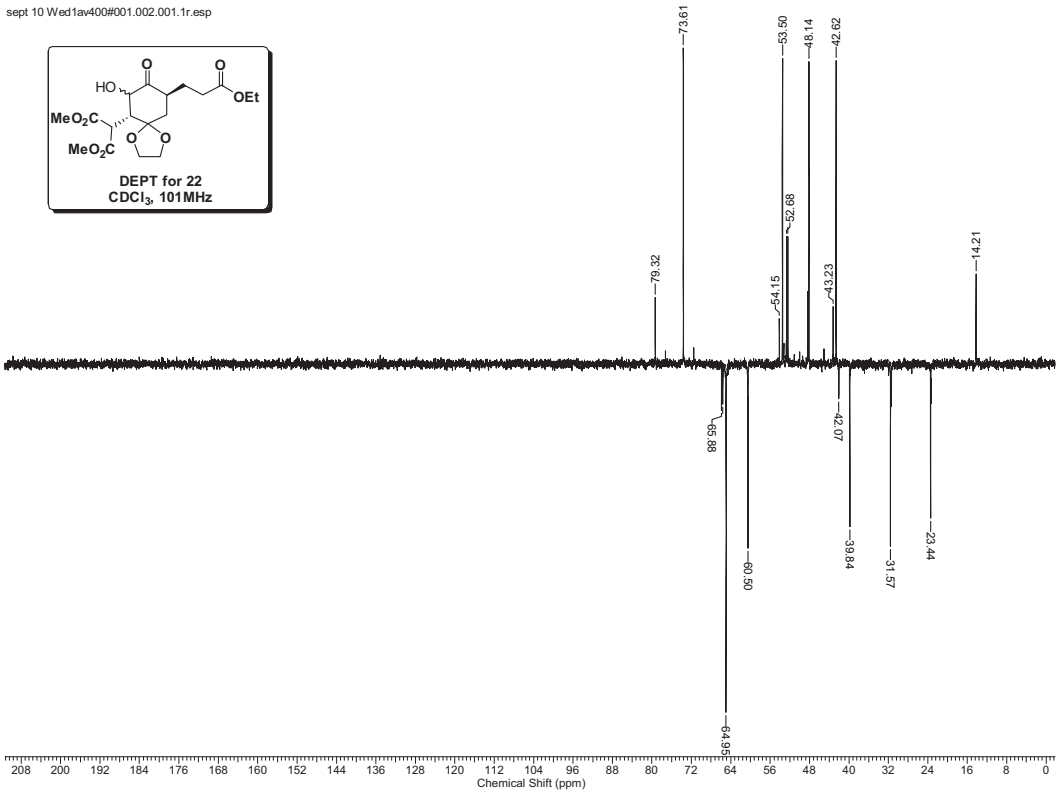
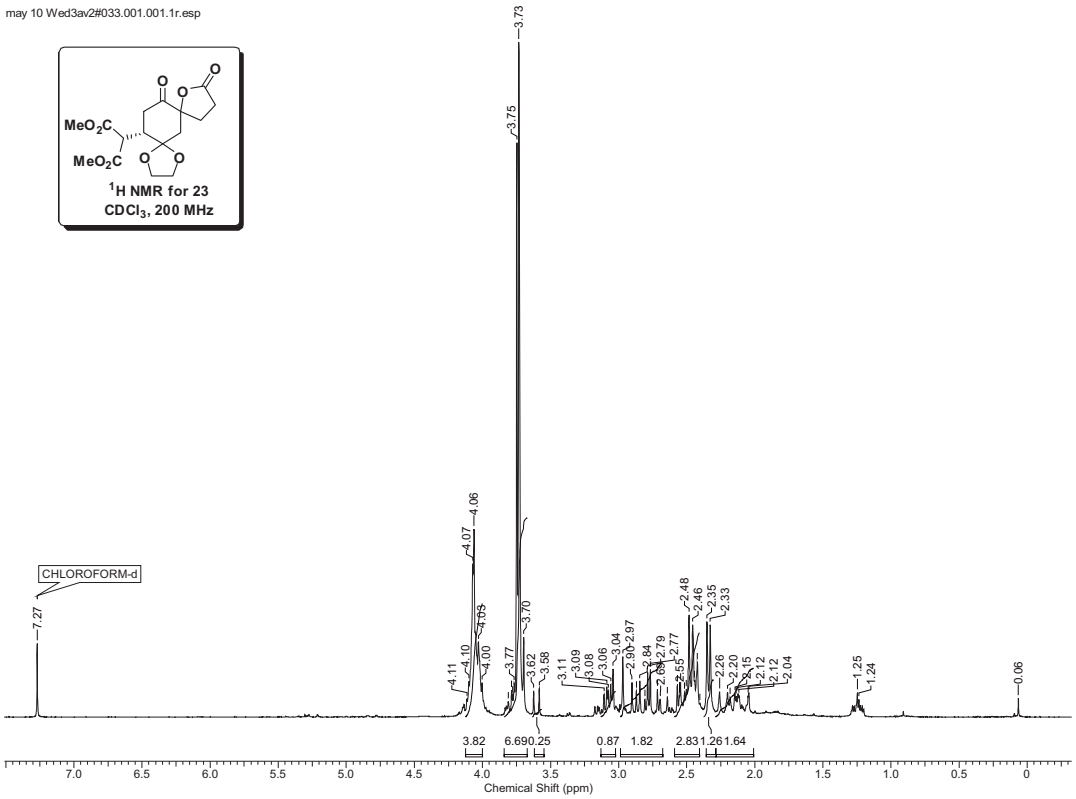
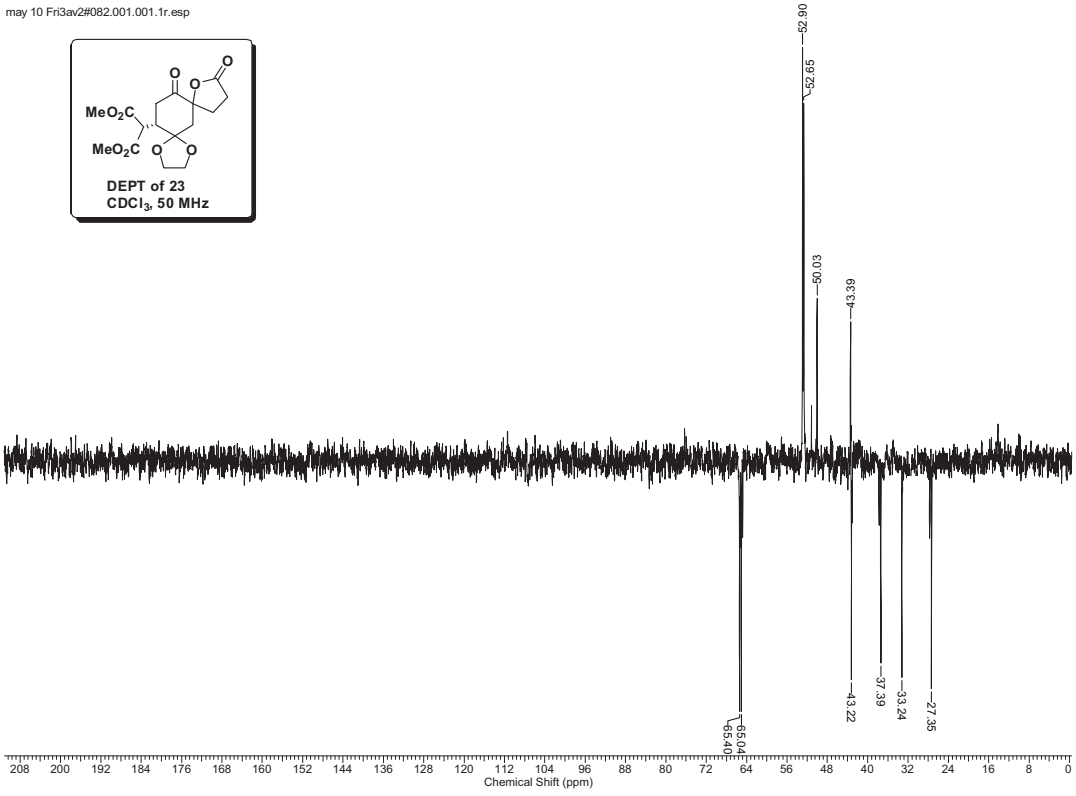
208.96
173.43
173.16
168.22
168.06
167.86
108.08
107.59
76.65
75.85
65.16
64.61
64.87
60.51
52.79
52.73
50.04
45.52
45.10
44.13
43.79
37.37
36.96
33.04
28.16
28.02
18.39
14.12
Chemical Shift (ppm)

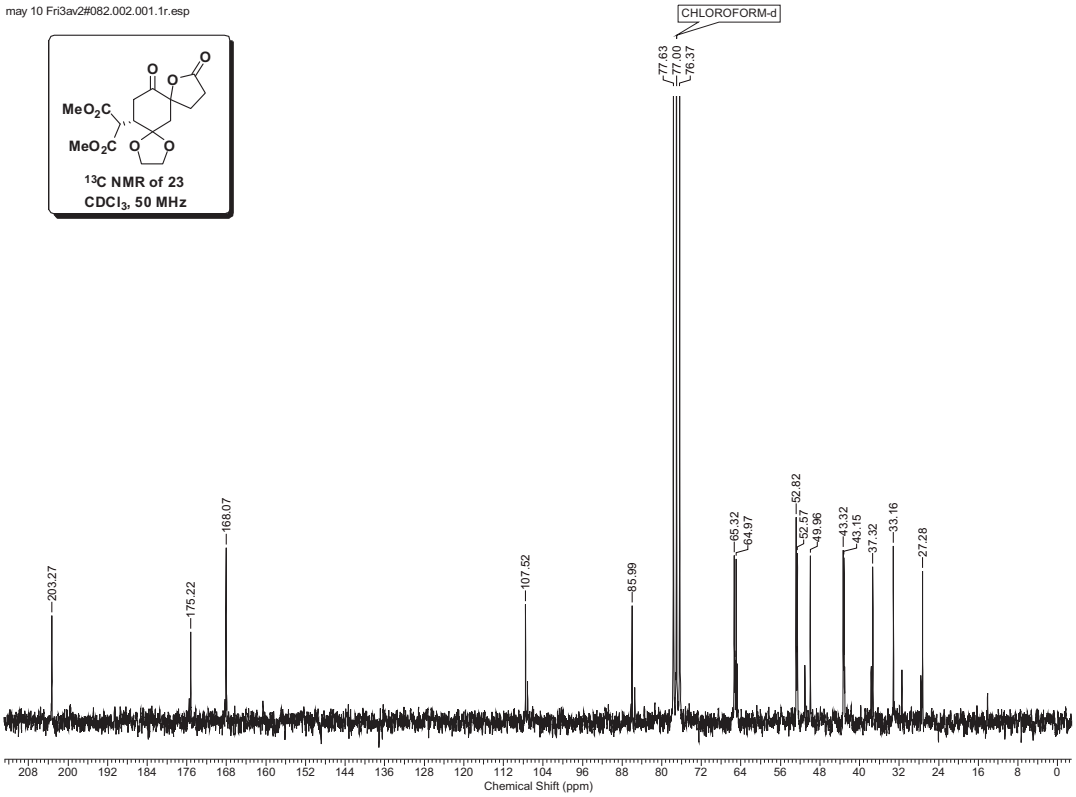

sept 10 Wed1av400#001.001.001.1r.esp
^{1}H NMR for 22
CDCl$_3$, 400 MHz
CHLOROFORM-d
DCM
7.27
5.30
4.82
4.79
4.14
4.12
4.11
4.03
4.02
3.98
3.82
3.81
3.80
3.76
3.72
2.93
2.92
2.90
2.89
2.77
2.75
2.42
2.40
2.34
2.18
2.16
2.14
2.10
2.09
1.60
1.57
1.53
1.26
1.24
1.22
0.80
2.21
3.98
1.18
5.84
0.91
1.15
2.73
2.17
1.90
3.10
Chemical Shift (ppm)

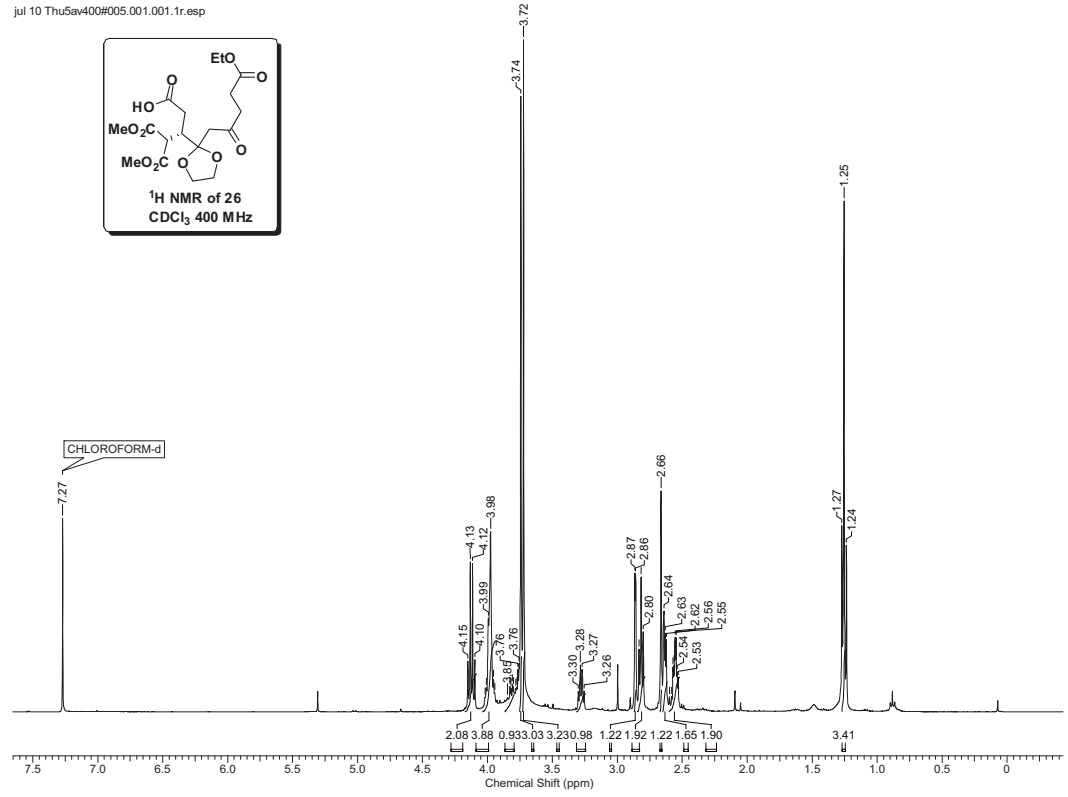

sept 10 Wed1av400#001.003.001.1r.esp
CHLOROFORM-d
77.32
77.00
76.68
64.90
209.60
173.04
169.33
168.75
107.15
73.55
60.45
53.44
52.63
52.34
48.08
42.56
39.79
31.52
23.39
14.15
208 200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)
HO
OEt
MeO2C
MeO2C
13C NMR for 22
CDCl3, 101 MHz

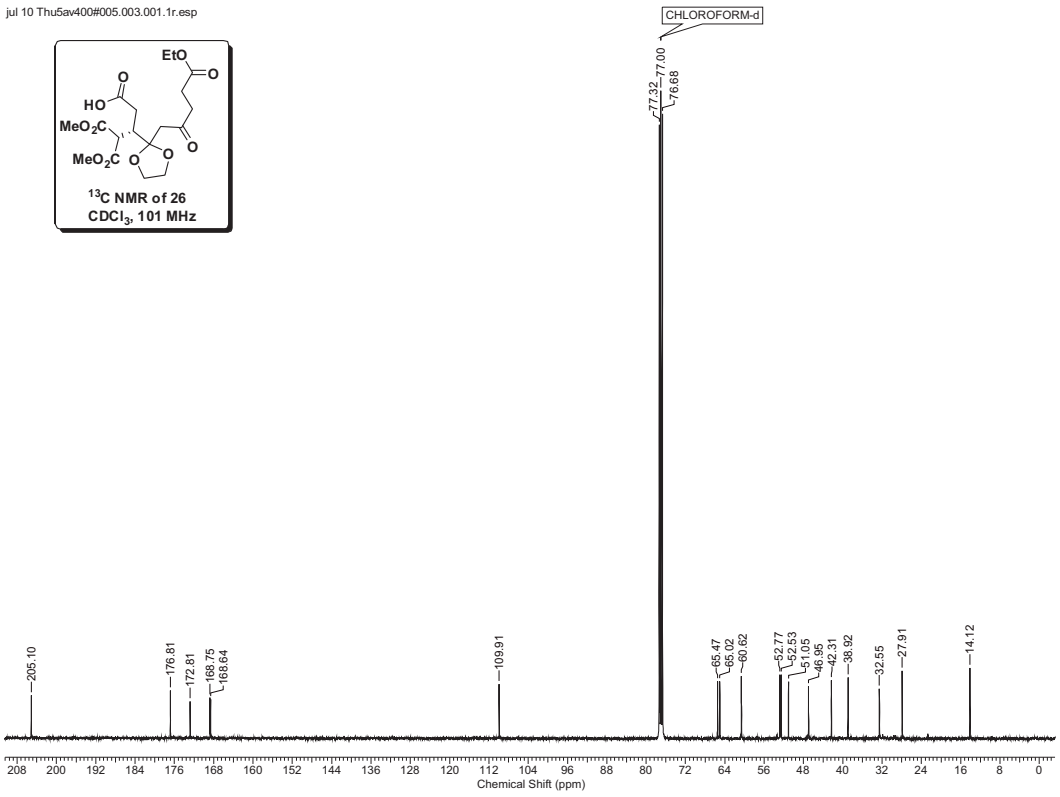

sept 10 Wed1av400#001.002.001.1r.esp
73.61
53.50
48.14
42.62
52.68
79.32
54.15
43.23
14.21
66.88
42.07
39.84
31.57
23.44
60.50
64.95
208 200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)
HO
OEt
MeO2C
MeO2C
DEPT for 22
CDCl3, 101MHz

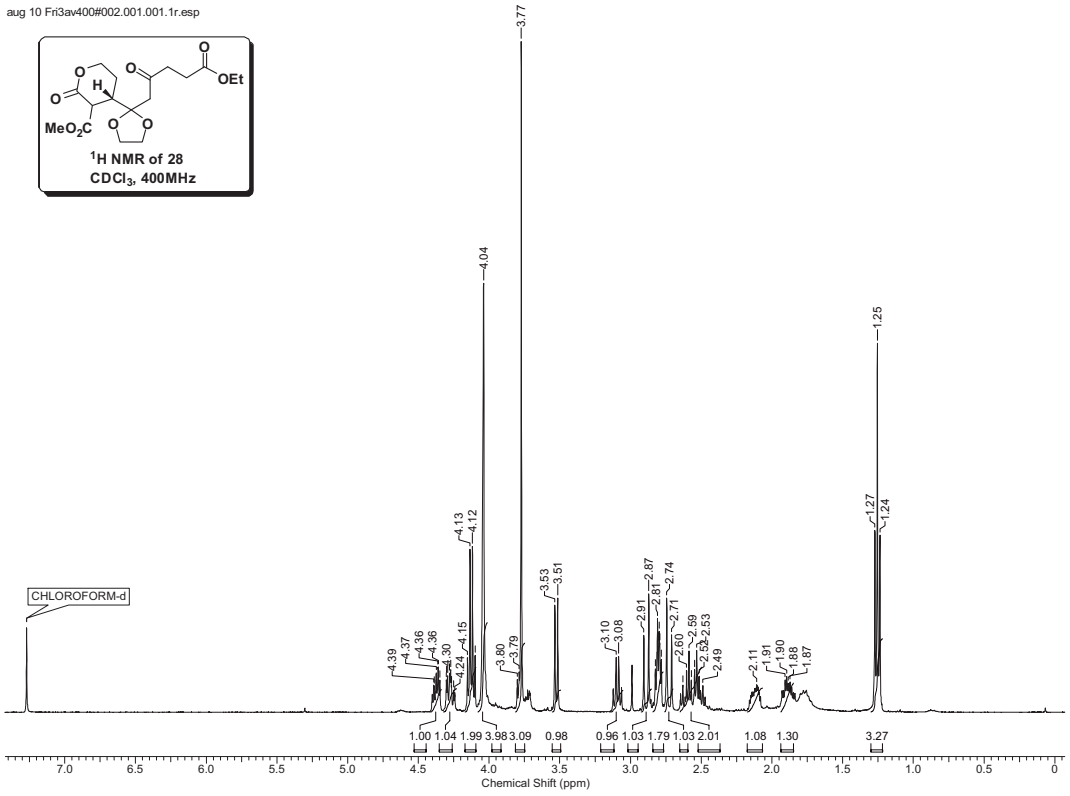

may 10 Wed3av2#033.001.001.1r.esp
MeO2C
MeO2C
1H NMR for 23
CDCl3, 200 MHz
CHLOROFORM-d
7.27
4.11
4.10
4.07
4.06
4.00
3.77
3.75
3.73
3.70
3.62
3.58
3.11
3.09
3.08
3.06
3.04
2.97
2.90
2.84
2.79
2.77
2.55
2.48
2.46
2.35
2.33
2.26
2.20
2.15
2.12
2.04
1.25
1.24
0.06
3.82
6.69
0.25
0.87
1.82
2.83
1.26
1.64
Chemical Shift (ppm)

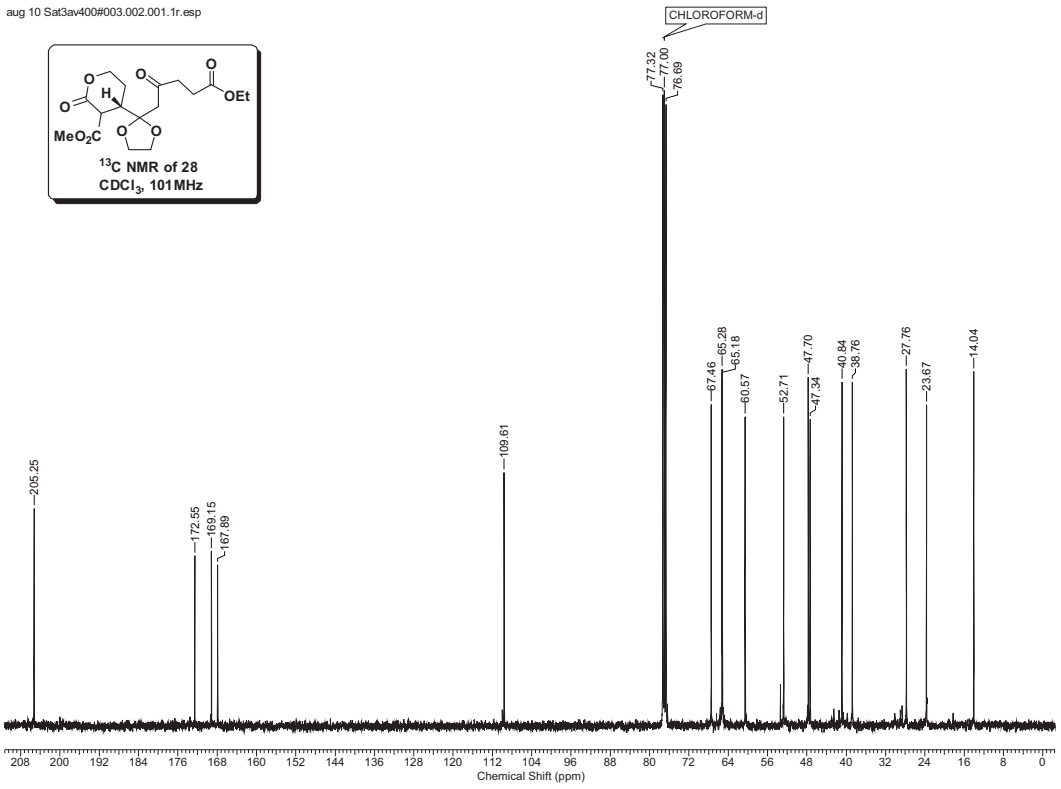

may 10 Fri3av2#082.001.001.1r.esp
MeO2C
MeO2C
DEPT of 23
CDCl3, 50 MHz
52.90
52.65
50.03
43.39
43.22
37.39
33.24
27.35
65.40
65.04
Chemical Shift (ppm)

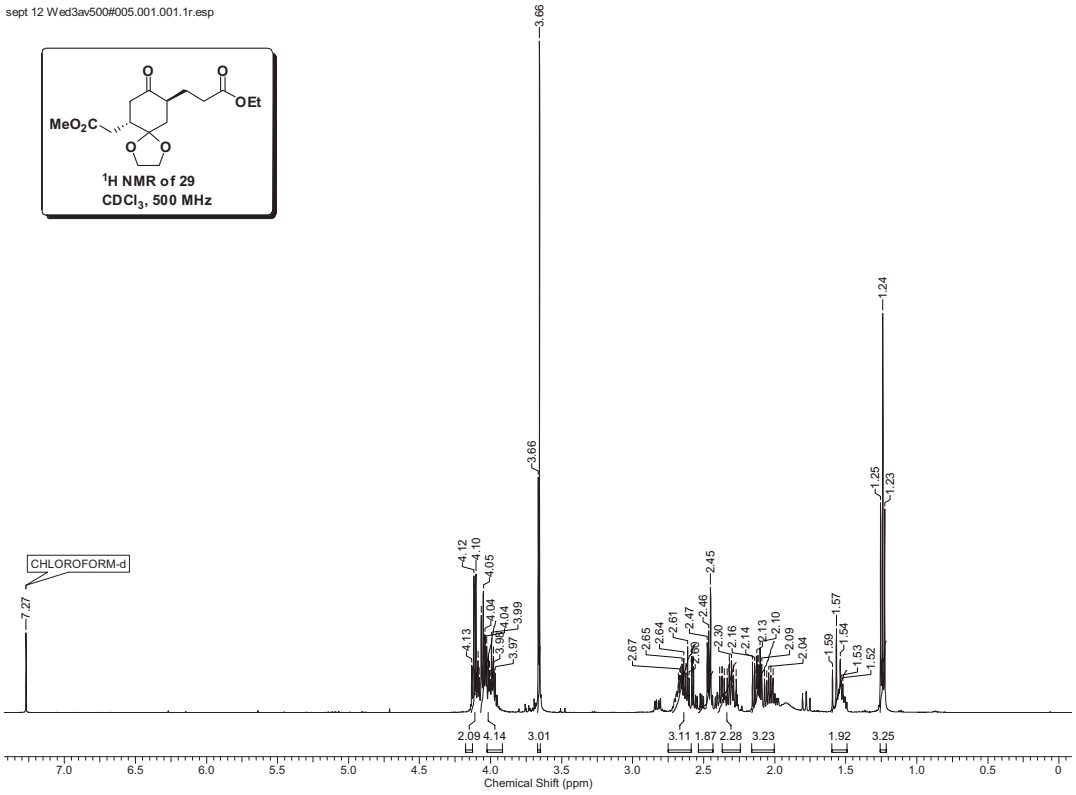

may 10 Fri3av2#082.002.001.1r.esp
CHLOROFORM-d
77.63
77.00
76.37
MeO2C
MeO2C
13C NMR of 23
CDCl3, 50 MHz
203.27
175.22
168.07
107.52
85.99
65.32
64.97
52.82
52.57
49.96
43.32
43.15
37.32
33.16
27.28
Chemical Shift (ppm)

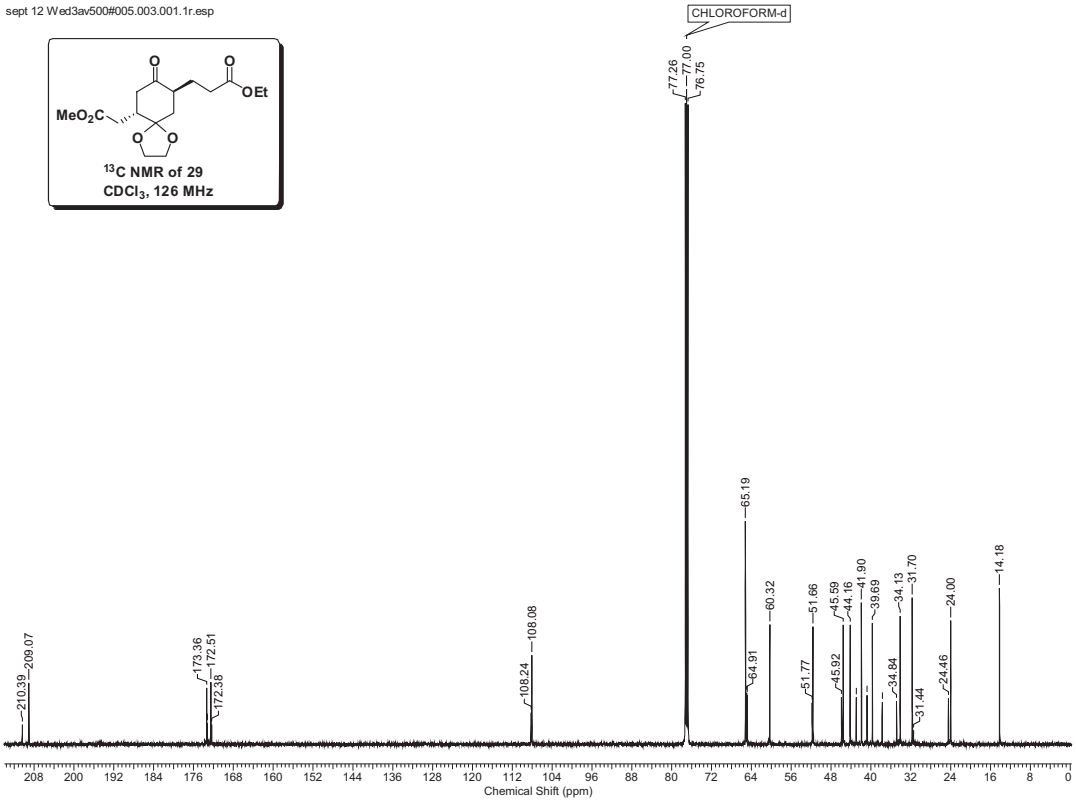

jul 10 Thu5av400#005.001.001.1r.esp
EtO
HO
MeO2C
MeO2C
1H NMR of 26
CDCl3 400 MHz
CHLOROFORM-d
7.27
3.72
3.74
4.13
4.12
3.98
3.99
4.15
4.10
3.76
3.76
3.85
3.30
3.28
3.27
3.26
2.87
2.86
2.66
2.80
2.64
2.63
2.62
2.56
2.55
2.54
2.53
1.25
1.27
1.24
2.08 3.88 0.93 3.03 3.23 0.98 1.22 1.92 1.22 1.65 1.90
3.41
Chemical Shift (ppm)

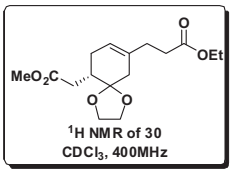

jul 10 Thu5av400#005.003.001.1r.esp
EtO
HO
MeO2C
MeO2C
13C NMR of 26
CDCl3, 101 MHz
CHLOROFORM-d
77.32
77.00
76.68
205.10
176.81
172.81
168.75
168.64
109.91
65.47
65.02
60.62
52.77
52.53
51.05
46.95
42.31
38.92
32.55
27.91
14.12
Chemical Shift (ppm)


aug 10 Fri3av400#002.001.001.1r.esp
OEt
MeO2C
1H NMR of 28
CDCl3, 400MHz
CHLOROFORM-d
3.77
4.04
1.25
4.13
4.12
1.27
1.24
3.53
3.51
2.87
2.74
4.39
4.37
4.36
4.36
4.30
4.15
4.24
3.80
3.79
3.10
3.08
2.91
2.81
2.71
2.60
2.59
2.53
2.49
2.11
1.91
1.90
1.88
1.87
1.00 1.04 1.99 3.98 3.09 0.98 0.96 1.03 1.79 1.03 2.01 1.08 1.30 3.27
Chemical Shift (ppm)


aug 10 Sat3av400#003.002.001.1r.esp
CHLOROFORM-d
77.32
77.00
76.69
67.46
65.28
65.18
60.57
52.71
47.70
47.34
40.84
38.76
27.76
23.67
14.04
205.25
172.55
169.15
167.89
109.61
OEt
MeO2C
13C NMR of 28
CDCl3, 101MHz
Chemical Shift (ppm)

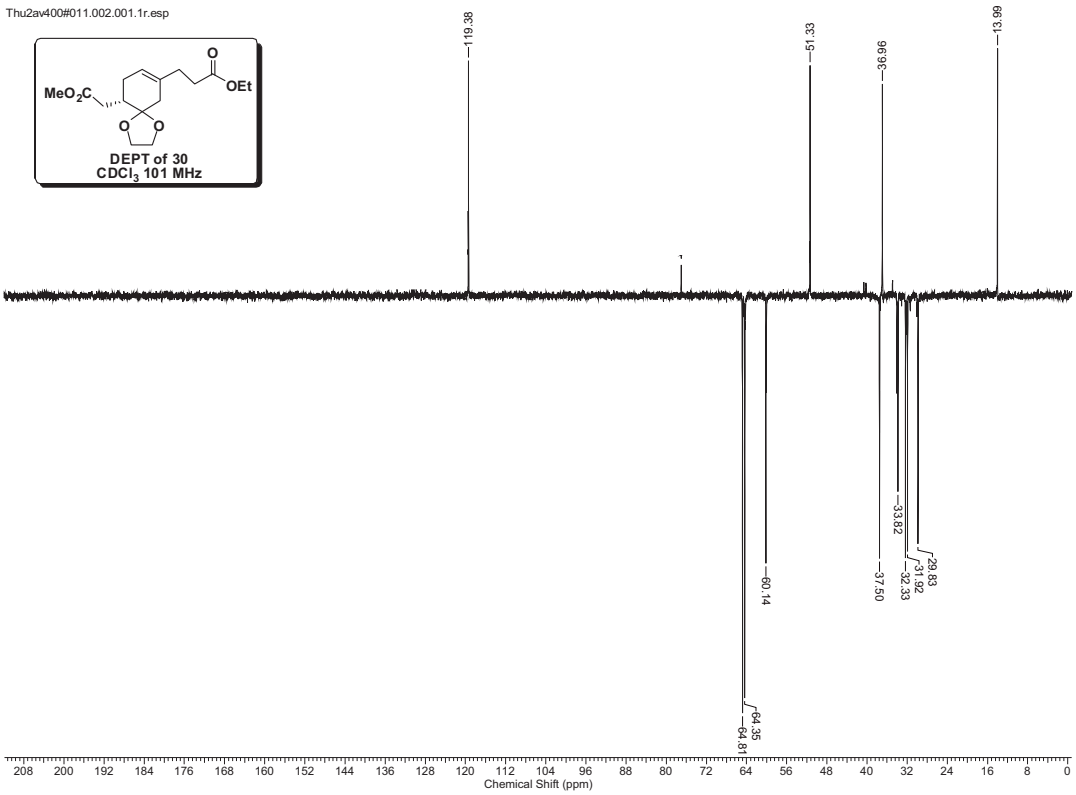

sept 12 Wed3av500#005.001.001.1r.esp
3.66
OEt
MeO2C
1H NMR of 29
CDCl3, 500 MHz
CHLOROFORM-d
7.27
4.12
4.10
4.05
4.04
4.04
3.99
4.13
3.98
3.97
3.66
2.45
2.67
2.65
2.64
2.61
2.47
2.46
2.30
2.16
2.14
2.13
2.10
2.09
2.04
1.57
1.59
1.54
1.53
1.52
1.24
1.25
1.23
2.09
4.14
3.01
3.11
1.87
2.28
3.23
1.92
3.25
Chemical Shift (ppm)

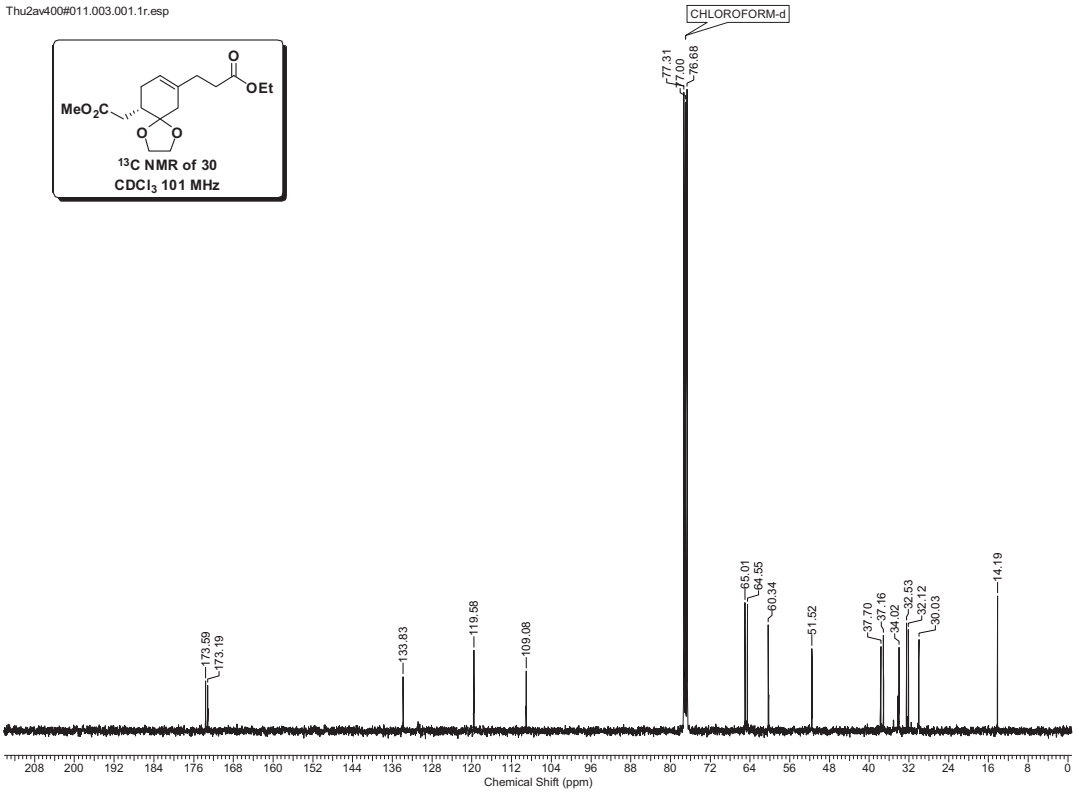

sept 12 Wed3av500#005.003.001.1r.esp
CHLOROFORM-d
77.26
77.00
76.75
65.19
60.32
51.66
45.59
44.16
41.90
39.69
34.13
31.70
24.00
14.18
64.91
51.77
45.92
34.84
31.44
24.46
108.08
108.24
173.36
172.51
172.38
210.39
209.07
Chemical Shift (ppm)


MeO2C
OEt
13C NMR of 29
CDCl3, 126 MHz

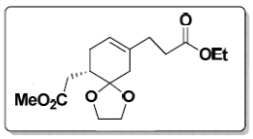
Thu2av400#011.001.001.1r.esp
CHLOROFORM-d
7.27
3.67
5.39
4.13
4.11
3.98
3.97
3.96
4.15
4.10
3.94
3.92
2.56
2.52
2.42
2.40
2.39
2.30
2.28
2.26
2.16
2.15
2.13
2.11
2.09
1.68
1.25
1.27
1.23
1.04
2.12
4.01
2.96
1.09
3.90
1.06
2.10
2.02
1.13
1.07
3.21
Chemical Shift (ppm)

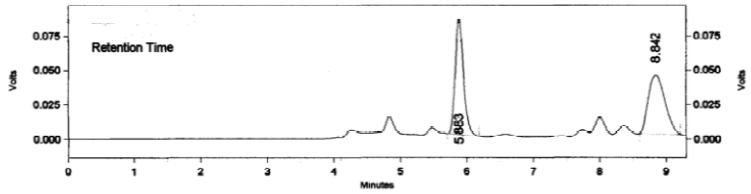
MeO2C
OEt
1H NMR of 30
CDCl3, 400MHz


Thu2av400#011.002.001.1r.esp
DEPT of 30
CDCl3 101 MHz
119.38
51.33
36.96
13.99
64.81
64.35
60.14
37.50
33.82
32.33
31.92
29.83
Chemical Shift (ppm)


Thu2av400#011.003.001.1r.esp
13C NMR of 30
CDCl3 101 MHz
CHLOROFORM-d
77.31
77.00
76.68
173.59
173.19
133.83
119.58
109.08
65.01
64.55
60.34
51.52
37.70
37.16
34.02
32.53
32.12
30.03
14.19
Chemical Shift (ppm)

Method Name: C:\CLASS-VP\Data\Dr. CHAVAN S. P\PAPAL FH10 % IPAPE
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1824
User: System
Acquired: 10/16/12 4:05:34 PM
Printed: 10/16/12 8:39:38 PM
Sample Name PAA- OLEFIN RAC



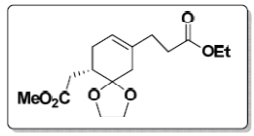


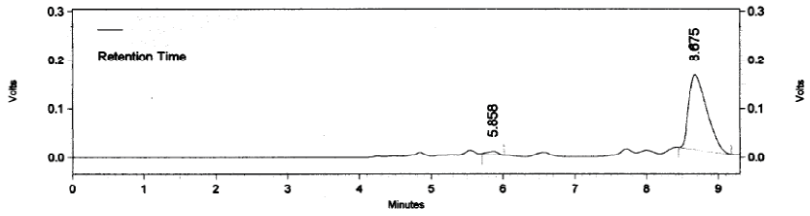
Retention Time	C Area	Area %
5.883	723251	49.862
8.842	727240	50.138

Totals	1450491	100.000

Project Leader : Dr. GANESH PANDEY
Column : Chiralcel OD-H (250x4.6 mm)
Mobile Phase :IPA: Pet ether (20:80)
Wavelength :230nm
Flow Rate :0.7ml/min (50kgf)
conc. : 4.0mg/1.0 mL
Inj vol- :20ul

Method Name: C:\CLASS-VP\Data\Dr. CHAVAN S. P\PAPAL FH10 % IPAPE
Data Name: C:\CLASS-VP\Data\Dr.Ganesh Pandey\gp-1825
User: System
Acquired: 10/16/12 4:32:03 PM
Printed: 10/16/12 8:48:28 PM
Sample Name PAA- OLEFIN C

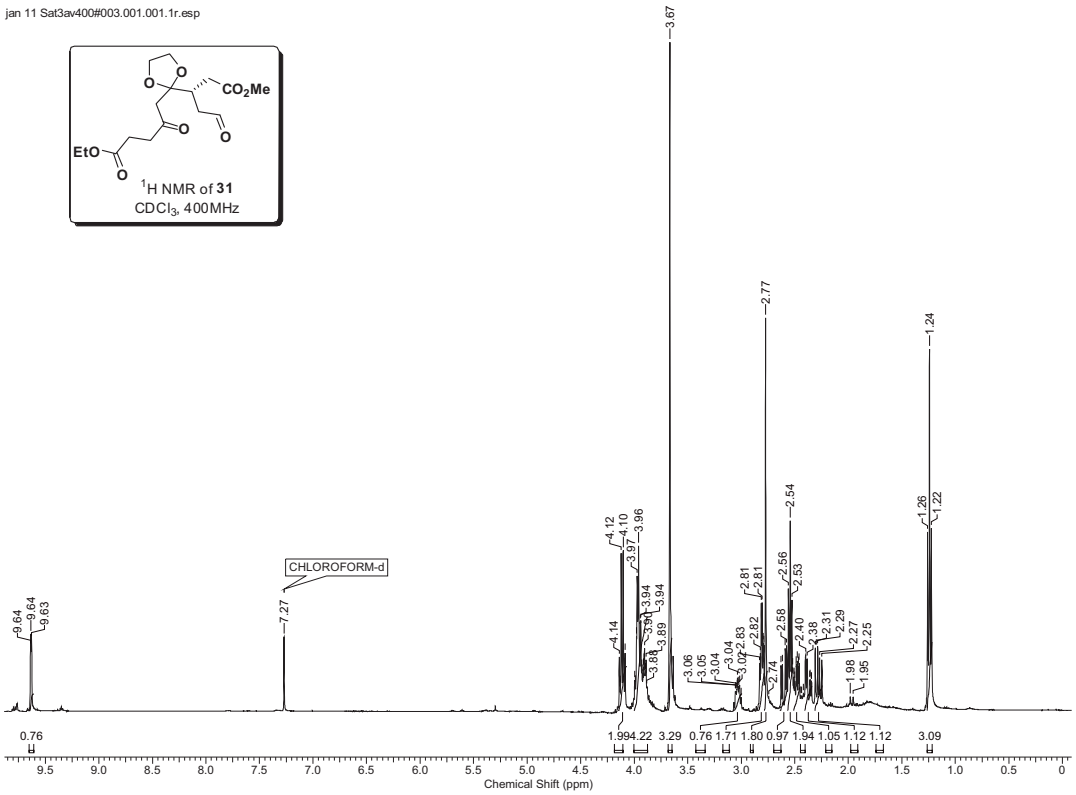


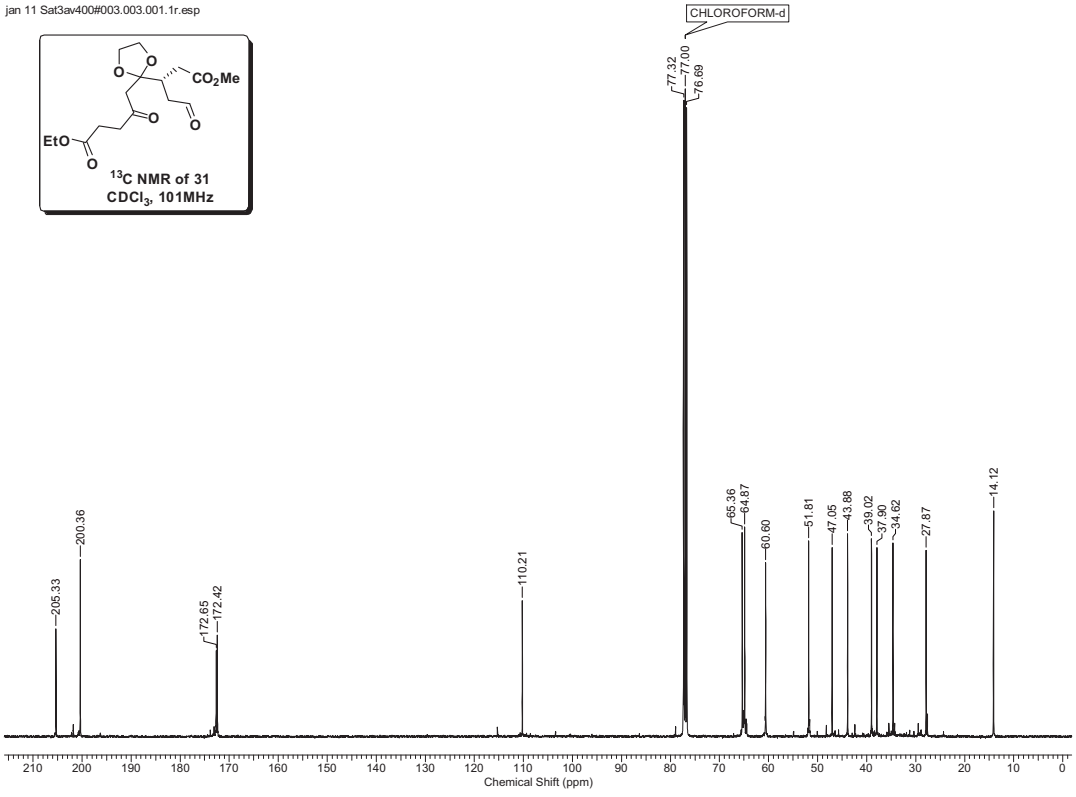


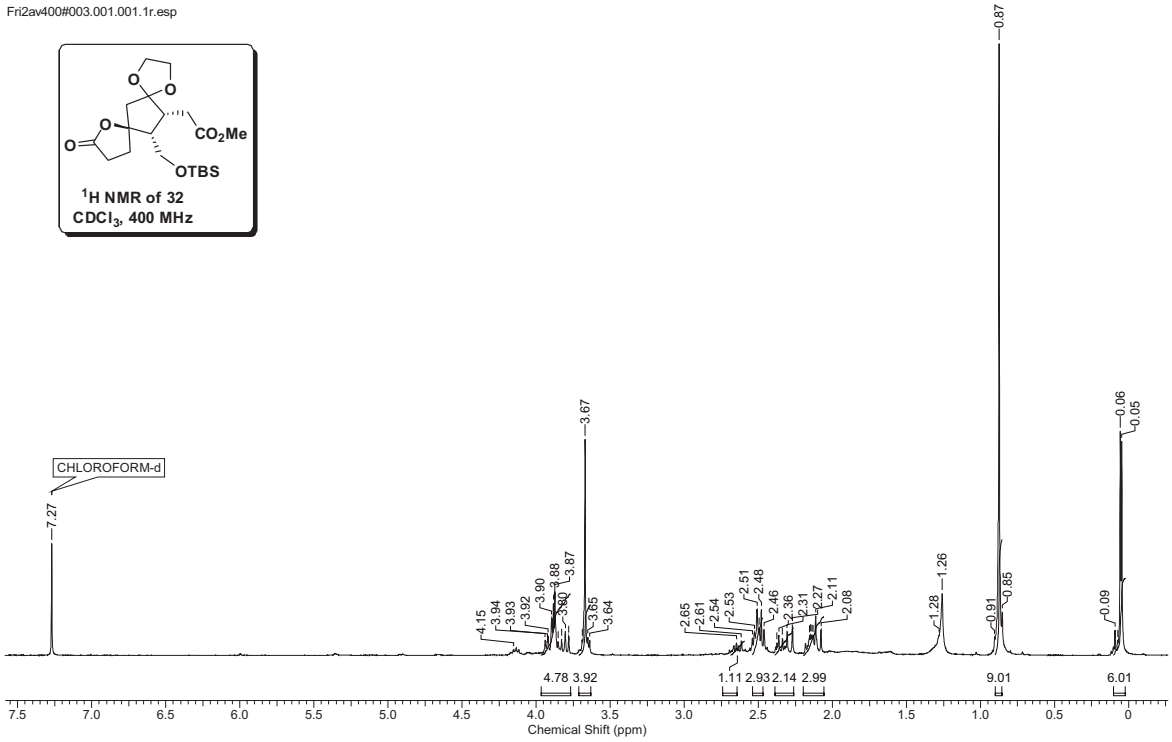
Retention Time	C Area	Area %
5.858	57648	2.124
8.675	2655860	97.876

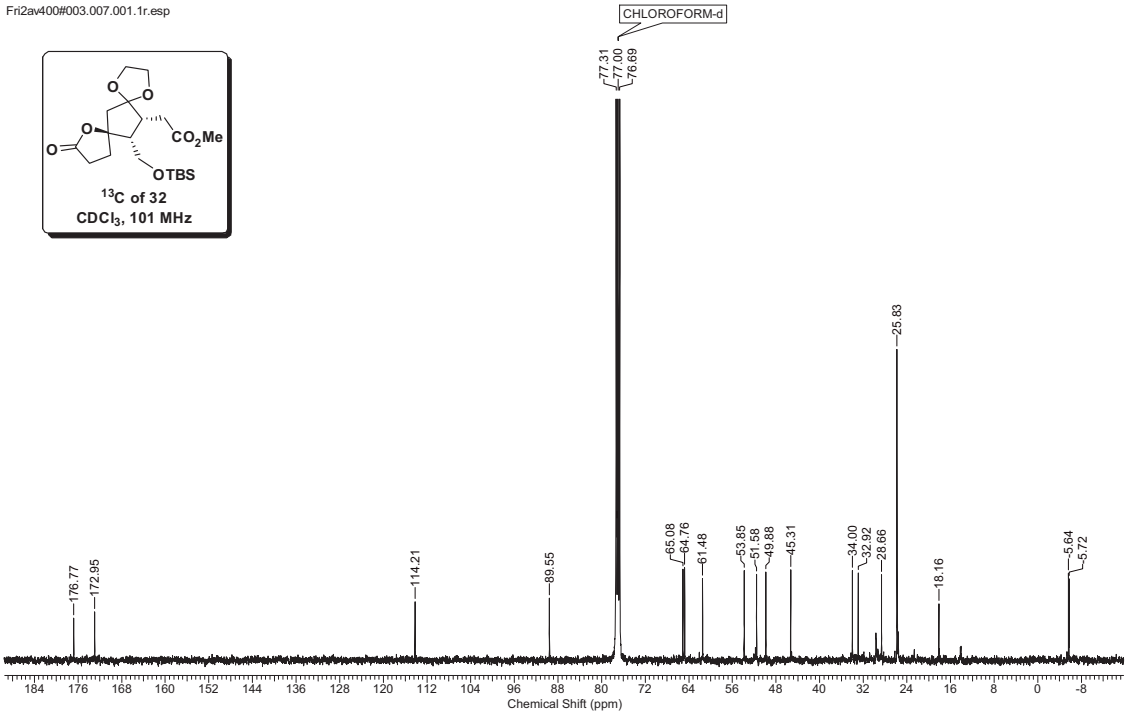
Totals	2713508	100.000

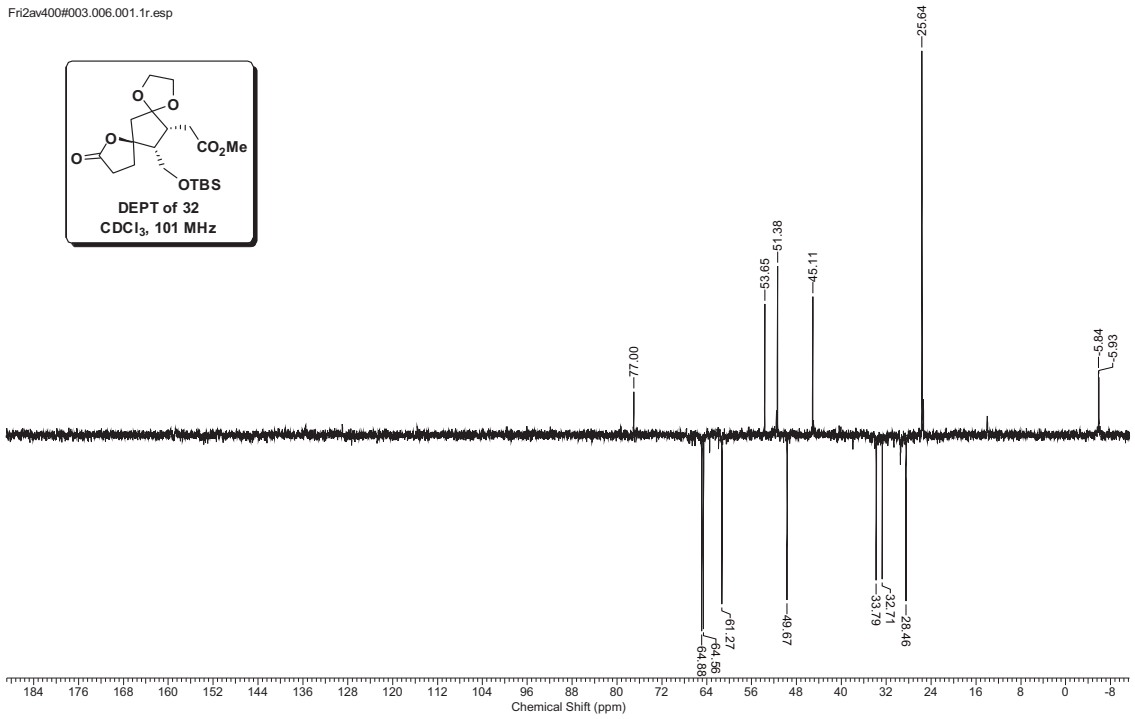
Project Leader : Dr. GANESH PANDEY
Column : Chiralcel OD-H (250x4.6 mm)
Mobile Phase :IPA: Pet ether (20:80)
Wavelength :230nm
Flow Rate :0.7ml/min (50kgf)
conc. : 4.0mg/1.0 mL
Inj vol- :20ul

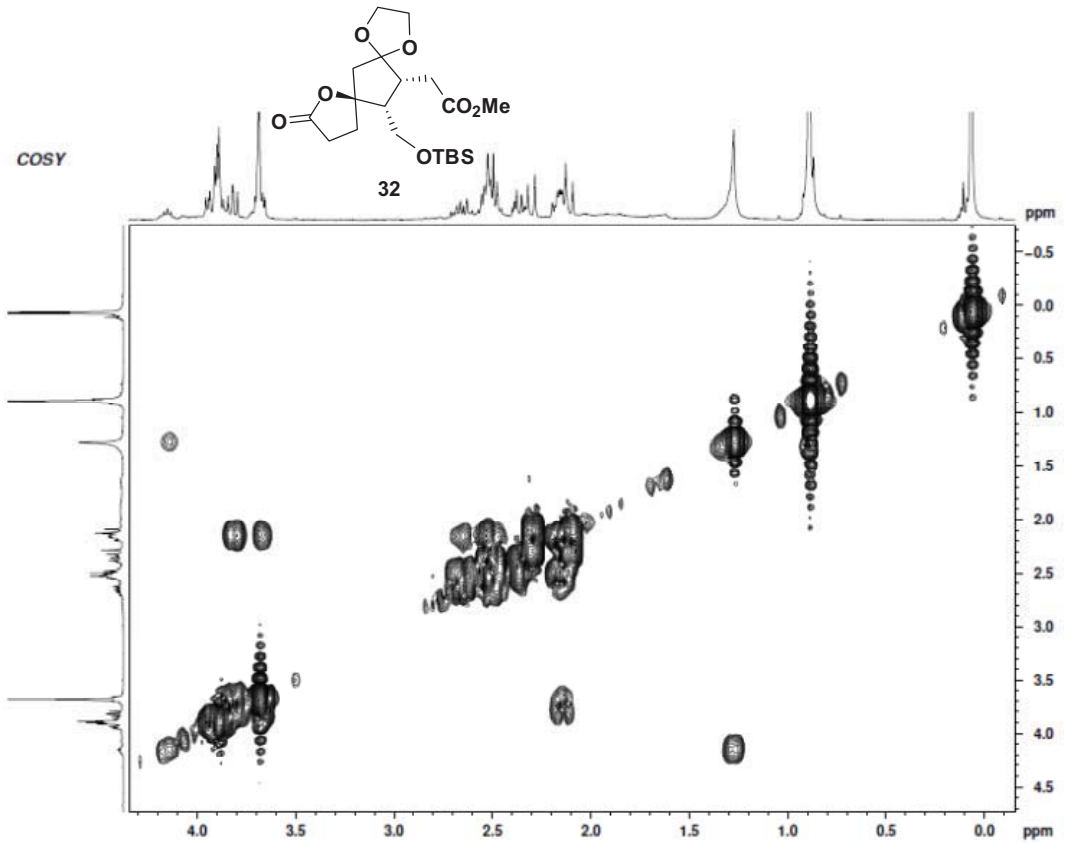

jan 11 Sat3av400#003.001.001.1r.esp
^{1}H NMR of 31
$CDCl_3$, 400MHz
CHLOROFORM-d
Chemical Shift (ppm)

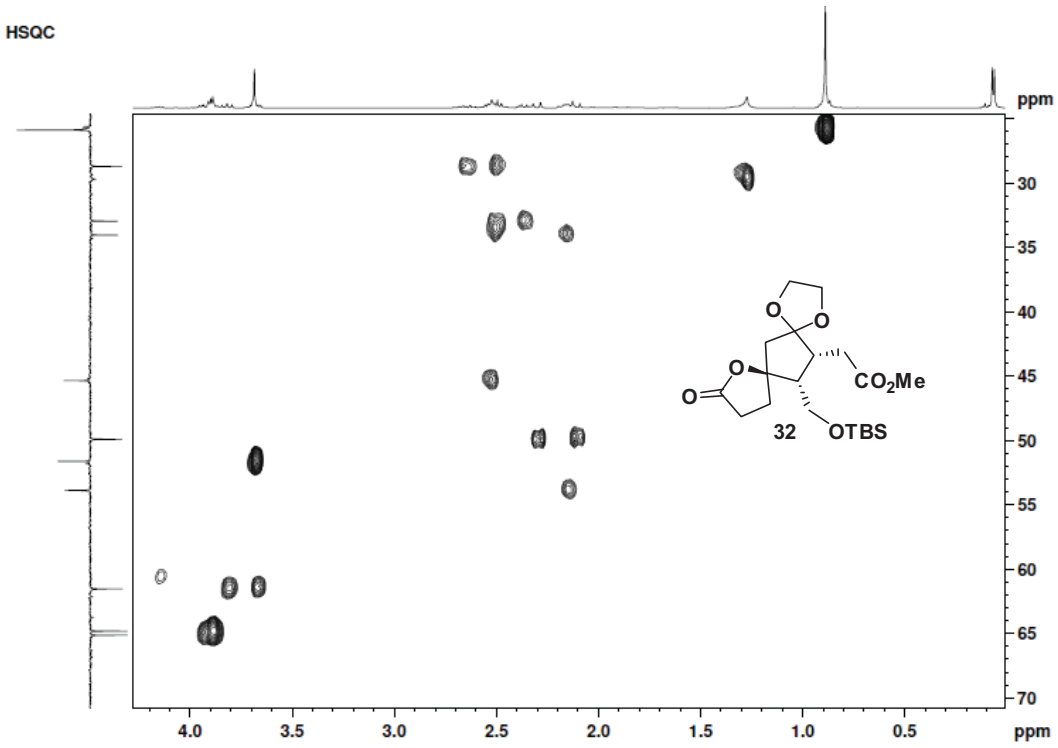

jan 11 Sat3av400#003.003.001.1r.esp
^{13}C NMR of 31
$CDCl_3$, 101MHz
CHLOROFORM-d
Chemical Shift (ppm)

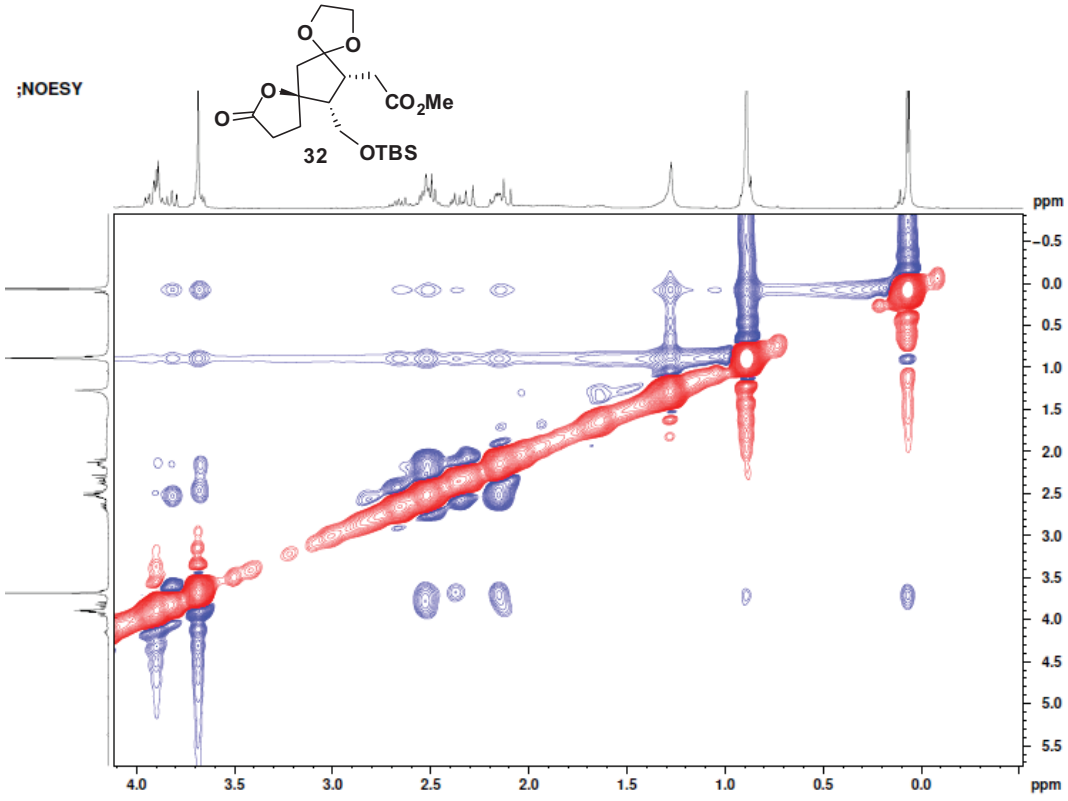

Fri2av400#003.001.001.1r.esp
CO2Me
OTBS
1H NMR of 32
CDCl3, 400 MHz
CHLOROFORM-d
7.27
3.67
0.87
0.06
0.05
4.15
3.94
3.93
3.92
3.90
3.88
3.87
3.86
3.85
3.64
2.65
2.61
2.54
2.53
2.51
2.48
2.46
2.36
2.31
2.27
2.11
2.08
1.28
1.26
0.91
0.85
0.09
4.78 3.92 1.11 2.93 2.14 2.99 9.01 6.01
Chemical Shift (ppm)


Fri2av400#003.007.001.1r.esp
CO2Me
OTBS
13C of 32
CDCl3, 101 MHz
CHLOROFORM-d
77.31
77.00
76.69
176.77
172.95
114.21
89.55
65.08
64.76
61.48
53.85
51.58
49.88
45.31
34.00
32.92
28.66
25.83
18.16
5.64
5.72
Chemical Shift (ppm)


Fri2av400#003.006.001.1r.esp
DEPT of 32
CDCl3, 101 MHz
CO2Me
OTBS
25.64
53.65
51.38
45.11
77.00
5.84
5.93
64.88
64.56
61.27
49.67
33.79
32.71
28.46
Chemical Shift (ppm)


COSY
CO2Me
OTBS
32
ppm
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


HSQC
ppm
30
35
40
45
50
55
60
65
70
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
O
O
O
O
CO2Me
32
OTBS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CO2Me
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OTBS
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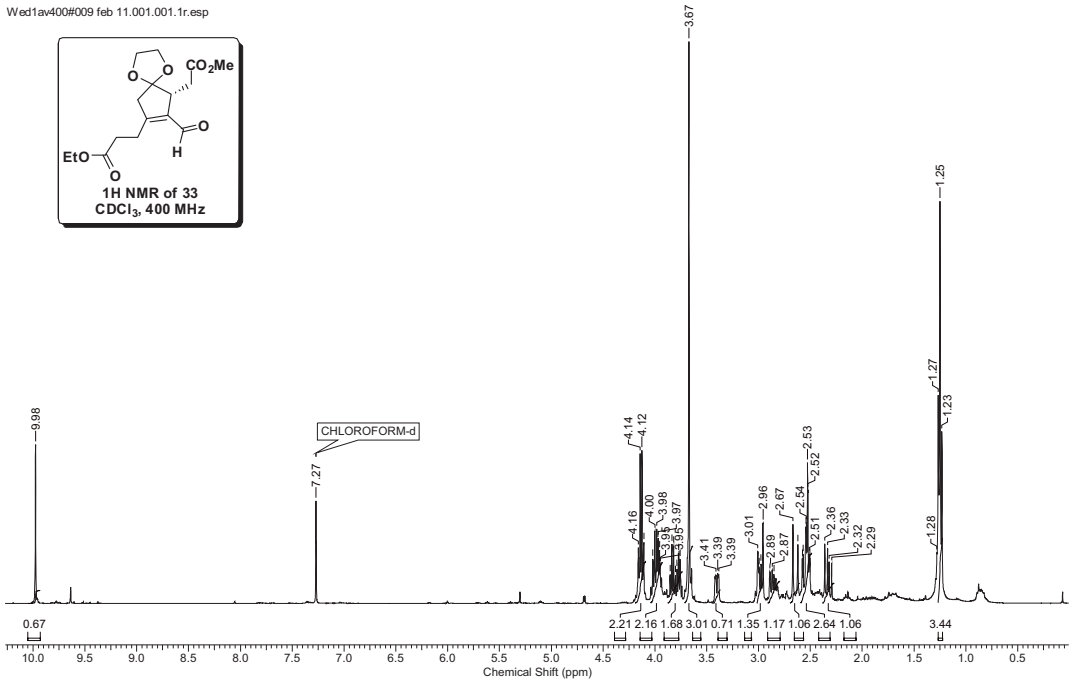
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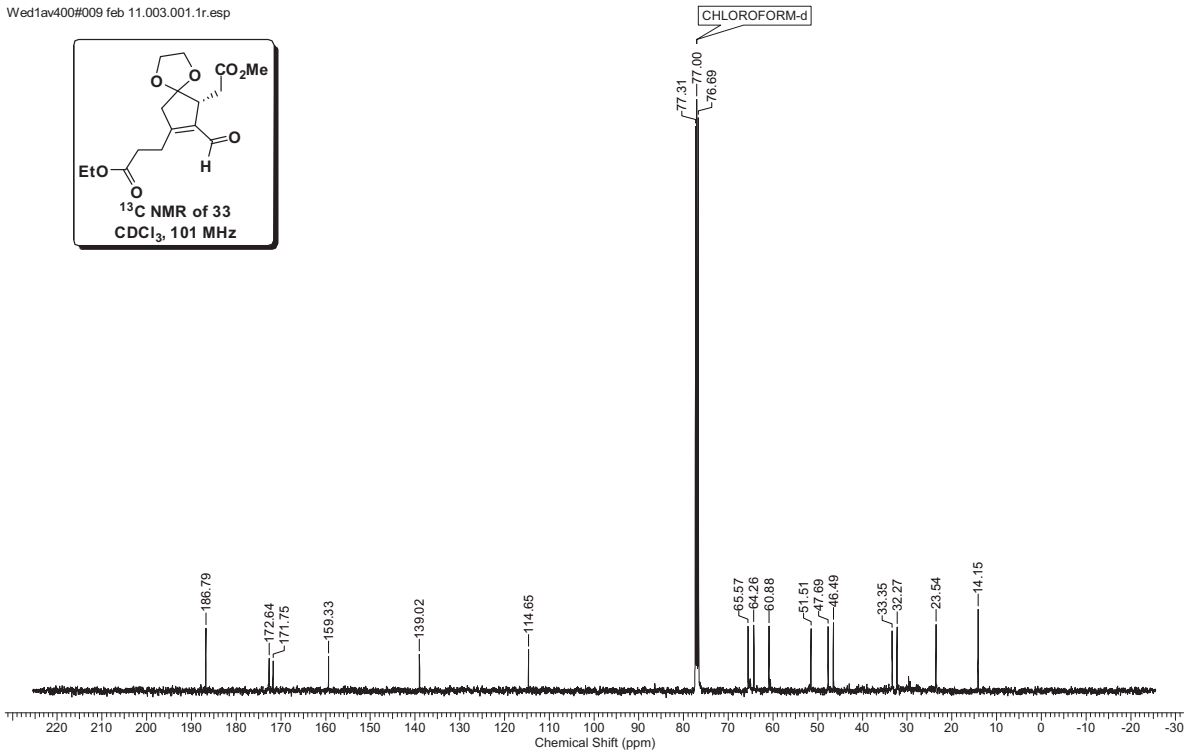
1H NMR of 33
CDCl3, 400 MHz
CHLOROFORM-d
Chemical Shift (ppm)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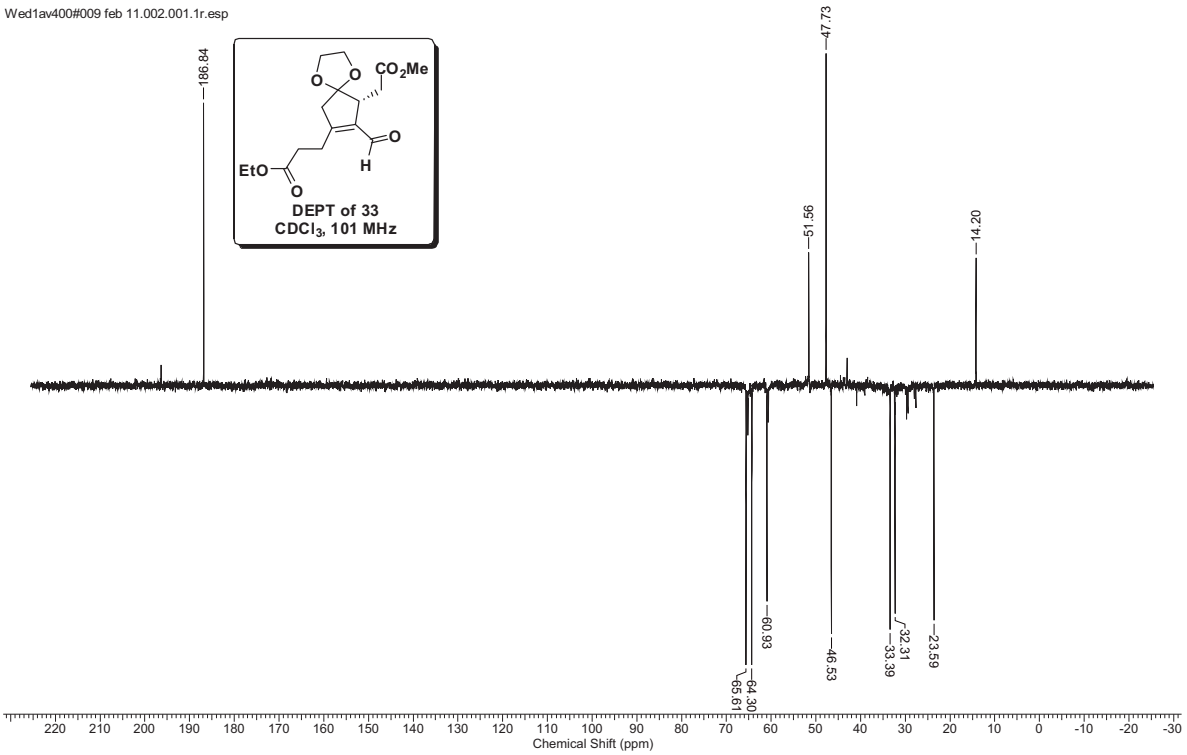
CHLOROFORM-d
Chemical Shift (ppm)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46.53
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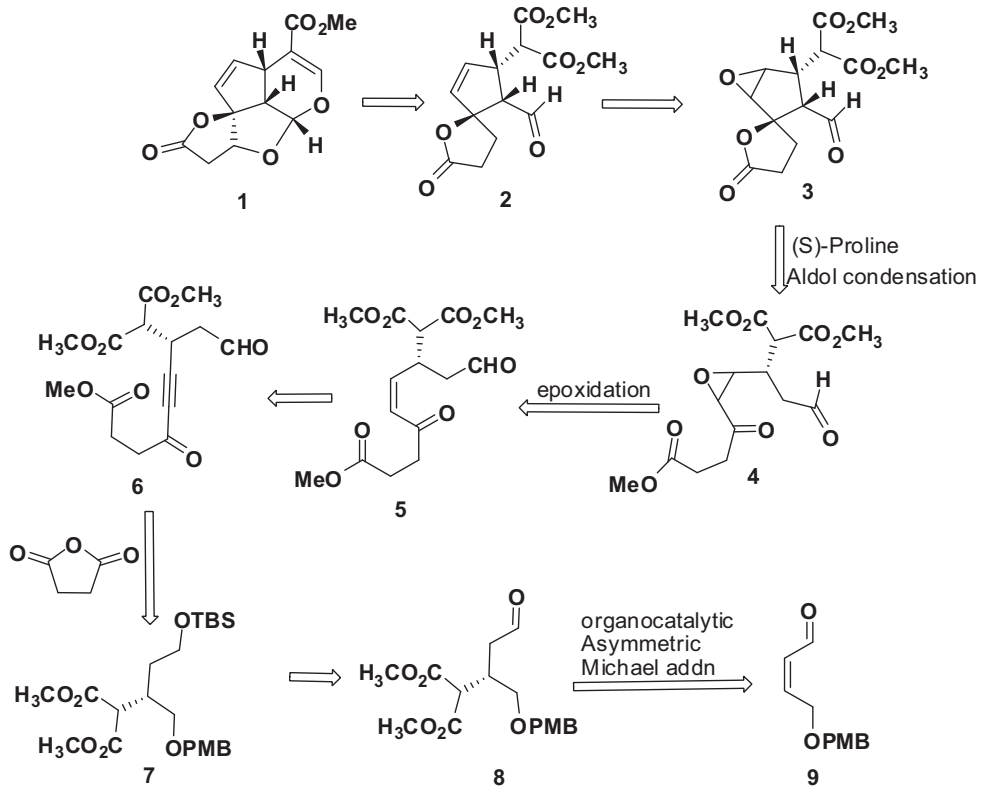
23.59
65.61
64.30
DEPT of 33
CDCl3, 101 MHz
Chemical Shift (ppm)

Chapter 4:

Alternative strategy towards the synthesis of the tetracyclic core structure of higher iridoid

Owing to significant stereochemical complexity, we took the challenge of synthesizing tetracyclic core of higher Iridoid using organocatalytic intramolecular aldol cyclization as the key strategy. In this context, in addition to synthetic efforts shown in Chapter 3, we designed different route to synthesize this tetracyclic core of higher iridoid as shown retrosynthetically in Scheme- 4.1.

4.1 Retrosynthetic analysis

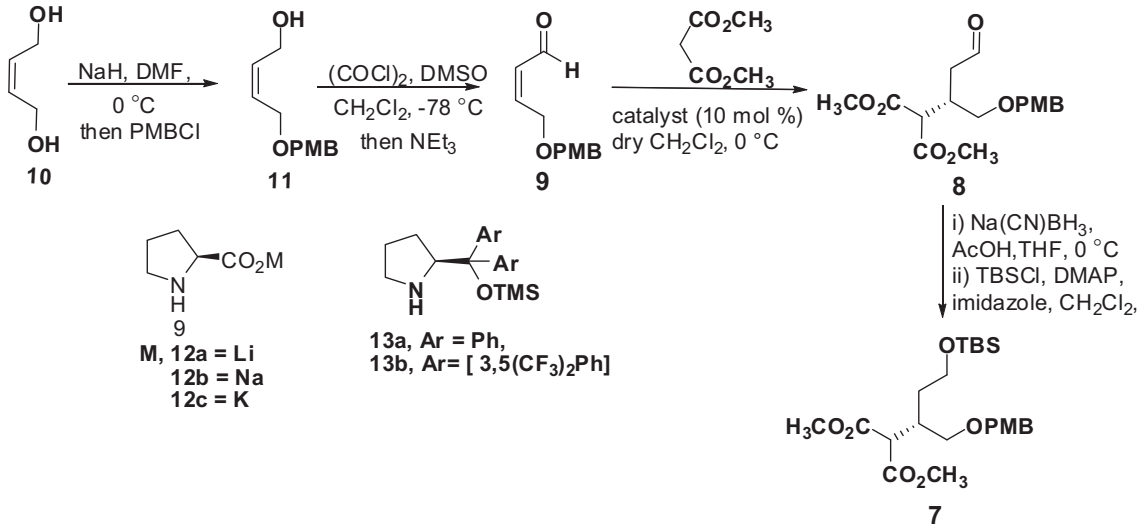


Scheme 4.1 First generation retrosynthetic analysis

We envisaged a new synthetic strategy for **1** through the retro-synthetic route as outlined in Scheme-4.1. The key step in this approach was again visualized through organocatalysed intramolecular aldol cyclization of **4** to **3**. The requisite **4** for this crucial transformation was proposed to be synthesized by alkynylation-partial reduction-epoxidation sequence starting from **7**. Aldehyde **8** can be derived from enal **9** by organocatalytic asymmetric conjugate addition.

4.2 Results and discussion

Synthesis of **4**, as perceived through the 1st generation retrosynthetic strategy (Scheme 4.1), started with the preparation of aldehyde **8** as shown in Scheme-4.2.



Scheme 4.2

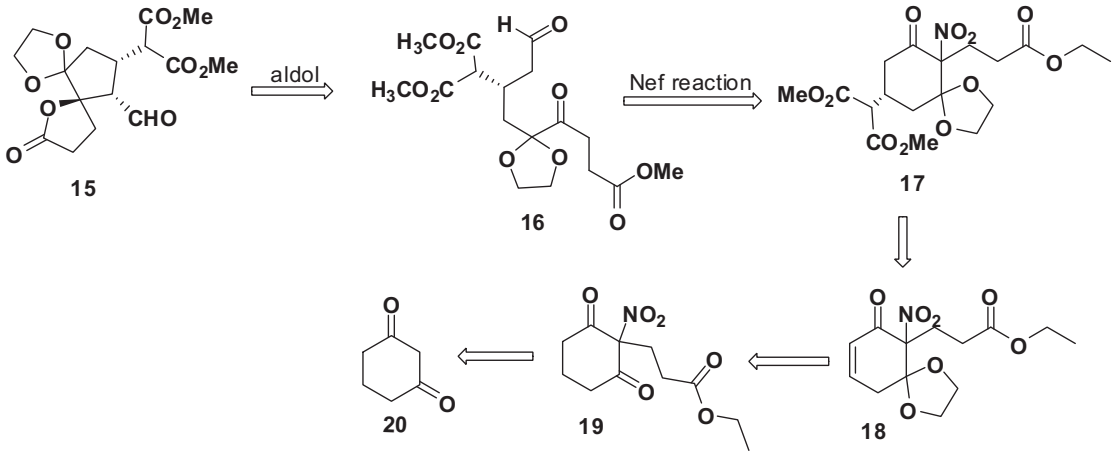
In order to prepare **9**, compound **10** was monoprotected as PMB ether **11** employing NaH and PMBCl in DMF at 0 ˚C. Swern oxidation [$(COCl)_2$, Me_2SO, Et_3N] of **11** at -78 ˚C gave **9** in quantitative yield. The IR spectrum of **9** showed aldehyde peak at 1691 cm^{-1}. Presence of α, β-unsaturated aldehyde functionality in **9** was also confirmed by observing a proton signal at δ 9.60 (d, J = 8.03 Hz, 1 H) and two other protons appearing at δ 6.41 and 6.8, integrating for one proton each, in ^1H NMR spectrum.

In order to obtain **8** by conjugate addition of dimethyl malonate on **9,** we evaluated several catalyst as shown in Table 4.1. For determining enantioselectivity of **8** by chiral stationary phase HPLC, it was converted to corresponding -OTBS derivative **7**. Using **12a** as a catalyst, **8** was obtained in 90 % yield and 46 % *ee*. Use of catalyst **13b** gave **8** in very low yield (5%), however, with excellent *ee* (91 %). Unfortunately various other attempts to improve yield as well as enantioselectivity remained a dream.

Table 4.1 Attempts for conjugate addition of malonate on **9**

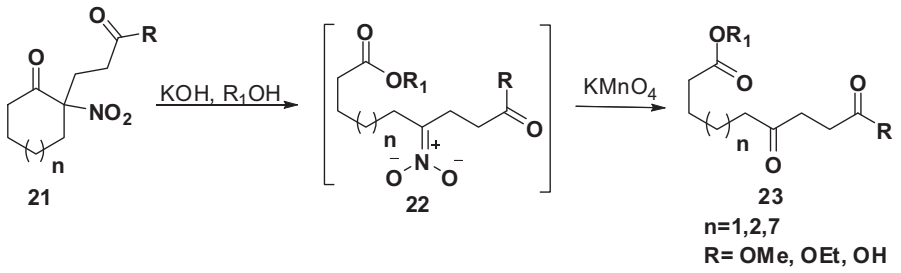
Sr.no.	Condition for conjugate addition on 9	Yield of 8 (%) (ee of corresponding 7)
1[1]	**12a,** dry MeOH, RT	90 (46%)
2[2]	**12b,** dist MeOH, RT	Decomposition of SM
3	**12c,** dry MeOH, RT	Decomposition of SM
4[3]	**13a,** dry CH_2Cl_2, RT	No reaction
5[4]	**13b**, dry CH_2Cl_2, RT	5 (91%)

Therefore, we revised our retrosynthetic plan for the synthesis of **16** as shown in Scheme-4.3. The crucial step for construction of **16** is based on C1-C2 cleavage of **17** followed by *in situ* Nef reaction. The requisite **17** for this crucial transformation was proposed to be synthesized from **20** as shown in Scheme-4.3. Idea of C1-C2 cleavage in **21** emerged from Balini's approach[5] for the synthesis of **23** as shown in Scheme-4.4.



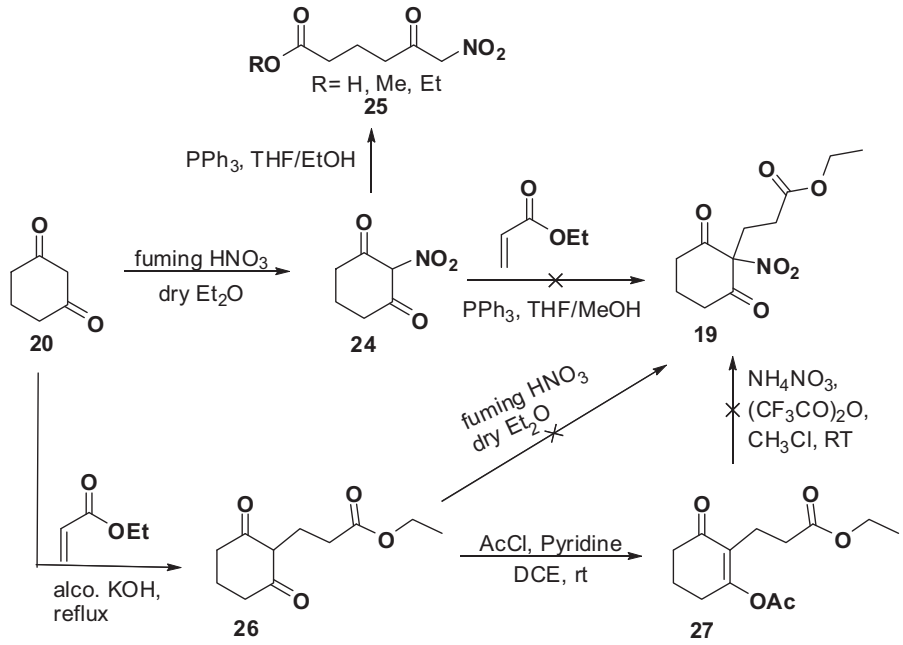
Scheme 4.3 Retrosynthetic analysis

In order to synthesize **19**, compound **20** was nitrated using fuming nitric acid[6] in dry diethyl ether at 0 ˚C which provided **24** in quantitative yield. When **24** was subjected to conjugate addition on ethyl acrylate in methanol, an open chain compound **25** was isolated instead of expected **19**. We explained this observation by considering the increased

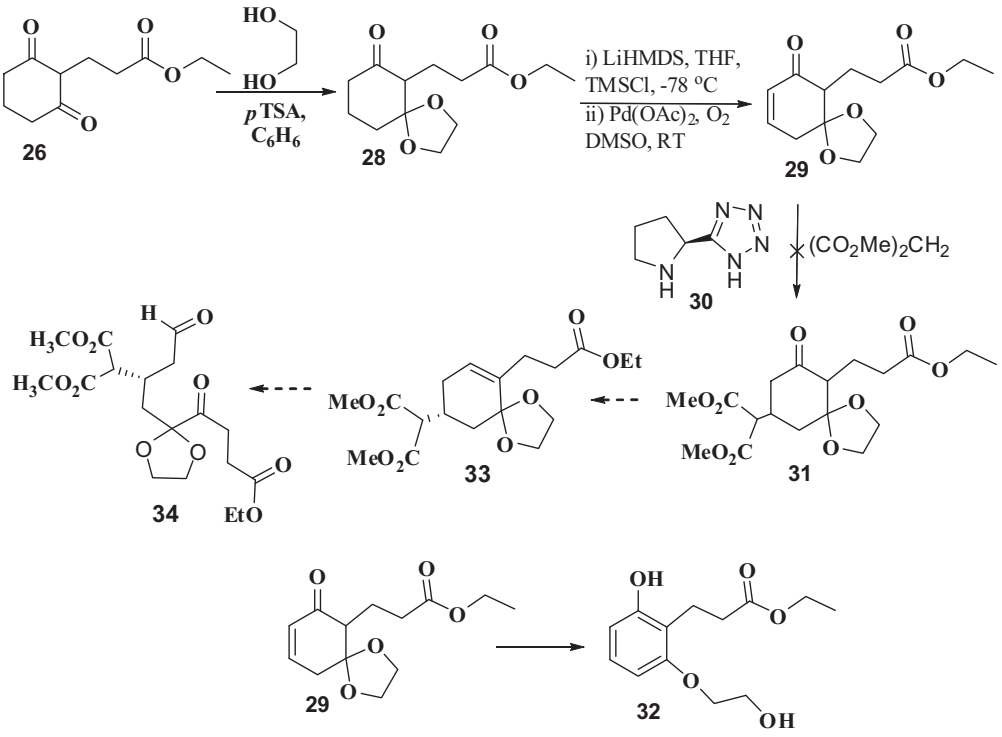


Scheme 4.4 Balini's approach for the synthesis of ω-oxoalkenoate

electrophilicity at carbonyl carbon in **24.** In order to avoid this problem, we first synthesized **26**[7] (60 %) by conjugate addition of **20** on to acrylate which on nitration using fuming nitric acid as well as *via* its enol acetate[8,9] derivative **27** gave complex reaction mixture. With these frustrating and unanticipated hurdles in obtaining **19**, we evaluated the synthesis of **16** from **26** as shown in Scheme-4.6.



Scheme 4.5



Scheme 4.6

Towards this endeavor, the carbonyl moiety of **26** was first monoprotected as a ketal **28**, which on enolization followed by oxidation [$Pd(OAc)_2$, O_2, RT],[10] gave **29** in 40% yield. Subjecting **29** to conjugate addition under various reaction conditions, as shown in Table 4.2, gave aromatized **32** instead of **31**. It was observed that simply stirring **29** with a

Table 4.2: Attempted conjugate addition of malonate on 30

Sr.no.	Reaction Conditions	Results
1[11]	**35**, piperidine, $CHCl_3$	**32**
2	**13a**, $CHCl_3$, NEt_3, RT	**32**
2	**12a**, $CHCl_3$, RT	**32**
3[1]	$LiClO_4$, NEt_3, dry CH_2Cl_2, RT	**32**
4	NaOMe, dry MeOH	**32**
5	KOtBu, THF, RT	**32**
6	NEt_3, dry CH_2Cl_2, RT	**32**

base leads to its aromatization (Table 4.2, entry 6). Structure of **32** was assigned based on the presence of aromatic peaks at δ 6.45 (d, *J* = 8.08 Hz, 1 H), 6.59 (d, *J* = 7.96 Hz, 1 H), 6.99 - 7.14 (m, 1 H) in ^{1}H NMR and signals at δ 103.6, 110.6, 116.05, 127.7, 155.5, 157.4 in ^{13}C NMR, respectively.

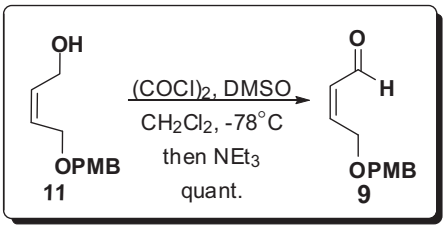
The outcome of our above discussed studies further reduced our confidence in exploring other routes for the synthesis of **16** and therefore, we suspended our synthetic trials at this stage.

4.3 Summary

In conclusion, we have demonstrated different bond disconnections for synthesis of desired precursor **4**/**16** for aldol cyclization which posed several unforeseen difficulties. However, this failure has helped us in understanding complexity involved in its synthesis.

4.4 Experimental section

4-((4-methoxybenzyl)oxy)but-2-enal (9):

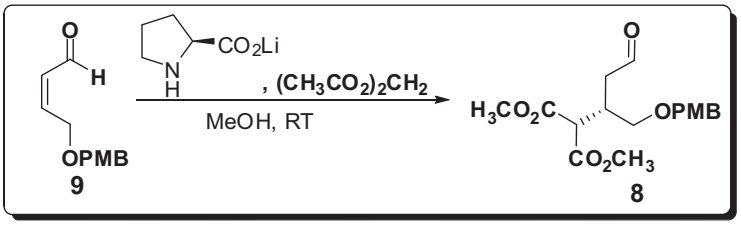


To a dichloromethane (19 mL) suspension of dimethyl sulfoxide (0.81 mL, 11.5 mmol), oxalyl chloride (0.45 mL, 5.26 mmol) was added dropwise at -78 ˚C, and the resulting mixture was stirred for 15 min. A solution of **11** (1.0 g, 4.8 mmol) in 5 mL dichloromethane was added dropwise to the reaction flask at -78 ˚C. Resulting mixture was stirred for an hour, NEt_3 (3.3 mL, 101.2 mmol) was added dropwise and reaction mixture was gradually warmed to room temperature over period of 1 h by removing the cooling bath. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3x20 mL). The combined organic layer was washed with brine (1x25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by silica gel column

chromatography using EtOAc: Petroleum ether (20:80) as eluant afforded **9** as yellow liquid (0.978 g)

Yield:	**:**	98 %
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	2935, 2837, 1691 ,1249, 1107, 1033, 820
^{1}H NMR ($CDCl_3$, 400 MHz) δ	**:**	3.80 - 3.86 (m, 3 H), 4.28 (dd, *J* = 4.02, 2.01 Hz, 2 H), 4.54 (s, 2 H), 6.41 (ddt, *J* = 15.87, 8.0, 1.91, 1 H), 6.92 (d, *J* = 8.53 Hz, 3 H), 7.30 (d, *J* = 8.53 Hz, 2 H), 9.60 (d, *J* = 8.03 Hz, 1 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	55.2, 68.2, 72.6, 113.8, 129.3, 131.7, 153.3, 159.3, 193.3
Mass: m/z (%)	**:**	207 (M + H, 14), 137 (100), 121 (100), 109 (35), 91 (33), 77 (100)

Dimethyl 2-(1-((4-methoxybenzyl)oxy)-4-oxobutan-2-yl)malonate (8):

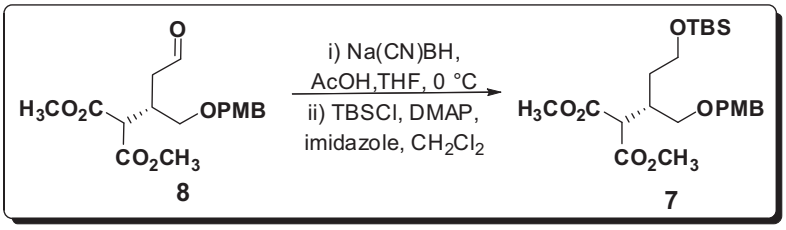


Under a nitrogen atmosphere, a mixture of dimethyl malonate (0.23 mL, 2.18 mmol), **9** (0.3 g, 1.45 mmol), and proline salt (0.21 mmol) in MeOH (7 ml) was stirred for 1 h. The reaction was quenched by adding 2 N HCI, and organic materials were extracted with ethyl acetate (3x10 mL). The Michael adduct was obtained as colourless liquid by a standard work-up, concentration and silica gel column chromatography using EtOAc: Petroleum ether (25:75) as an elutant.

Yield:	**:**	90 %
α_D^{25}	:	-1.0585 (*c* 0.65, $CHCl_3$, *ee* = 50 %)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	2837, 2125, 1435, 1598, 1249, 1168, 1036, 889
^{1}H NMR ($CDCl_3$, 500	**:**	2.54 - 2.74 (m, 2 H), 3.00 - 3.09 (m, 1 H), 3.47 (t, *J* =

MHz) δ		5.36 Hz, 2 H), 3.69 (s, 3H), 3.7 (s, 3 H), 3.7 - 3.71 (m, 1 H) 3.80 (s, 3 H) 4.38 (s, 2 H) 6.87 (m, *J* = 8.53 Hz, 2 H) 7.21 (m, *J* = 8.53 Hz, 2 H) 9.71 (s, 1 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	:	32.16, 35.18, 52.37, 52.41, 52.48, 52.50, 52.82, 53.22, 55.22, 57.54, 71.53, 72.94 , 78.66, 113.68, 129.21, 130.33, 159.11,168.91, 168.9, 204.12
Mass: m/z (%)	:	393.3 (M + MeOH, 100), 361.3 (M + H, 93), 254 (8), 203 (9)

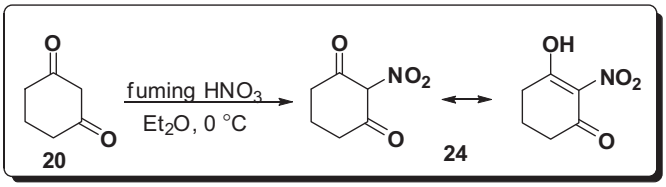
Dimethyl-2-(4-((tert-butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)butan-2-yl)malonate (7):



8 (0.1 mg, 0.3 mmol) was solved in 4 mL THF and the solution was cooled to 0 °C. 0.5 mL concentrated AcOH and $Na(CN)BH_3$ (0.031 mg, 0.44 mmol) (95%) were subsequently added to reaction mixture. The reaction mixture was warmed up to room temperature over period of 12 h. 5 mL brine was added and the pH was adjusted to 7.0 with saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3x10 mL) and the combined organic layers were dried over Na_2SO_4. After evapouration of the solvents under reduced pressure the crude product obtained was subjected for TBS protection without further purification. Crude alcohol obtained, DMAP (0.004 g, 0.03 mmol) and imidazole (0.04 g, 0.58 mmol) were dissolved in 4.0 mL dry CH_2Cl_2 followed by addition of TBSCl (0.053 g, 0.35 mmol) at 0 °C. The reaction mixture was stirred for 3 h, quenched with water and extracted with ethyl acetate (3x10 mL). The combined organic extracts were washed with brine (1x10 mL) and dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was purified over flash silica gel using ethyl acetate:pet ether (20:80) which gave **7** as colorless oil.

Yield:	**:**	95 %
α_D^{25}	:	-4.26 (*c* 2.93, $CHCl_3$, *ee* = 50 %)
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	3019, 2954, 1734, 1611, 1513, 1436, 1215, 1161, 1092, 756
^{1}H NMR ($CDCl_3$, 400 MHz) δ	**:**	0.03 (s, 6 H), 0.88 (s, 9 H), 1.59 - 1.70 (m, 2 H), 2.52 - 2.65 (m, 1 H), 3.46 - 3.57 (m, 2 H), 3.61 - 3.73 (m, 9 H), 3.81 (s, 3 H), 4.38 (s, 2 H) 6.83 - 6.90 (m, 2 H), 7.21-7.25 (m, 2 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	-5.4, 18.2, 25.9, 31.9, 36.4, 52.23, 53.03, 55.2, 61.2, 70.0, 72.7, 76.7, 77.3, 113.6, 129.3, 130.3, 159.1, 169.4
Mass: m/z (%)	**:**	517.2 (25), 491.1 (50), 477.2 (M + 23, 100), 385.1 (10)
HPLC (Chiracel OJ-H, *EtOH: petroleum ether* 2:98, 0.5 mL/min, 220 nm)	**:**	τ_R = 19.93 min. (major enantiomer), τ_R = 17.35 min. (minor enantiomer)

3-hydroxy-2-nitrocyclohex-2-enone (24):



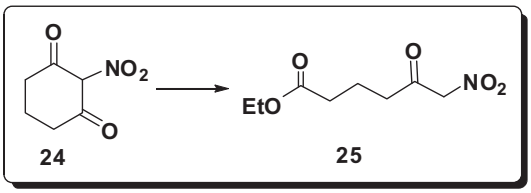
Fuming HNO_3 (2.2 mL, 53.5 mmol) was added dropwise to a stirred suspension of **20** (5.0 g, 44.6 mmol) in dry Et_2O under argon at 0 ˚C. After stirring for further 15 min. at same temperature the reaction mixture was filtered under argon and washed well with dry Et_2O to obtain **24** as orange solid.

Yield:	**:**	95 %
IR ν_{max} cm^{-1} ($CHCl_3$)	**:**	3020, 2964, 2400, 1707, 1686, 1560, 1534, 1420, 1347, 1216, 770

^{1}H NMR ($CDCl_3$, 400 MHz) δ : 2.05 (quin, *J* = 6.46 Hz, 2 H), 2.60 (s, 2 H) 2.89 (s, 2 H)

^{13}C NMR ($CDCl_3$, 101 MHz) δ : 18.2, 31.2, 38.3, 127.6, 184.5, 185.96

Ethyl 6-nitro-5-oxohexanoate (25):



To a solution of compound **24** (0.3 g, 1.9 mmol) in ethanol (4.0 ml) was added the ethyl acrylate (0.22 mL, 2.1 mmol) and a catalytic amount of Ph_3P (0.05 g, 0.2 mmol). After stirring at room temperature for 4 h, water was added to reaction mixture and extraction with Et_2O (1x10 mL). The combined organic phase was dried, evaporated and the crude **25** obtained was purified by silica gel column chromatography using EtOAc: Petroleum ether (30:70) as elutant.

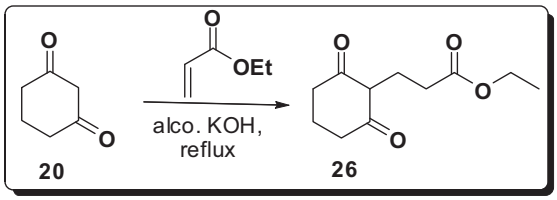
Yield: : 98 %

IR ν_{max} cm^{-1} ($CHCl_3$) : 3026, 2892, 2658, 1786, 1922, 1523, 1516, 1510, 1333

^{1}H NMR ($CDCl_3$, 200 MHz) δ : 1.22 - 1.30 (m, 3 H), 1.97 (t, *J* = 6.95 Hz, 2 H), 2.32 - 2.44 (m, 2 H), 2.66 (t, *J* = 7.07 Hz, 2 H), 4.12 (q, *J* = 7.07 Hz, 2 H), 5.30 (s, 2 H)

Mass: m/z (%) : 204.23 (M + H, 100)

Ethyl 3-(2,6-dioxocyclohexyl)propanoate (26):



An alcohol KOH solution (0.2 g of KOH and 10 mL of dry ethanol) was added to compound 20 (1.0 g, 8.9 mmol) and reaction mixture was heated to 110 °C with stirring. Then the ethyl acrylate (1.2 mL, 10.7 mmol) was added dropwise to the reaction mixture. The reaction mixture was further stirred for additional 4 h, and cooled. The cooled reaction mixture was neutralized with diluted AcOH and extracted with toluene (1x20 mL); the extract was washed with cold water (2x10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure the obtained pasty material was purified by column chromatography over silica gel using EtOAc: Petroleum ether (20:80) as eluent.

Yield: : 60 %

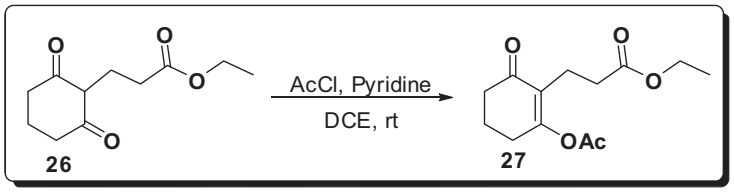
IR ν_{max} cm^{-1} ($CHCl_3$) : 2976, 3020, 2401, 1689, 1567, 1537, 1416, 1348, 1286, 1216, 1044, 767

^{1}H NMR ($CDCl_3$, 500 MHz) δ : 1.19 - 1.31 (td, *J* = 7.15, 1.26 Hz, 3 H), 1.90 (quin, *J* = 6.36 Hz, 2 H), 2.33 - 2.44 (m, 4 H), 2.45 - 2.59 (m, 4 H), 4.15 (qd, *J* = 7.13, 1.35 Hz, 2 H)

^{13}C NMR ($CDCl_3$, 126 MHz) δ : 14.0, 16.6, 20.4, 33.1, 61.6, 114.5, 178.0

Mass: m/z (%) : 250.96 (M + K, 100), 235.0 (M + Na, 90), 217.0 (70), 213 (M + H, 20), 139 (100)

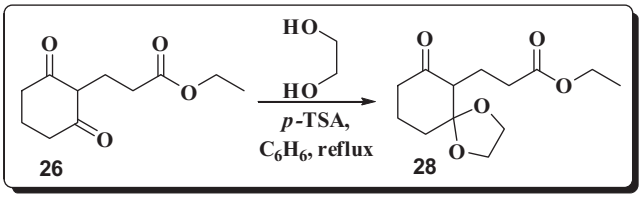
Ethyl 3-(2-acetoxy-6-oxocyclohex-1-en-1-yl)propanoate (27):



The acetyl chloride (0.11 mL, 1.55 mmol) was added to stirred solution of the **26** and pyridine (0.11 mL, 1.4 mmol) in dry 1,2-dichloroethane (7 mL). Reaction mixture was later stirred at room temperature for 1 h, and then washed with water (1x10 mL), 2N HCl (1x20 mL), saturated aqueous $NaHCO_3$ (2x20 mL) and brine (1x10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain **27**.

Yield:	:	98 %
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2943, 1767, 1734, 1674, 1655, 1431, 1361, 1196, 1150, 1066, 1042, 931
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	1.23 (t, *J* = 7.15 Hz, 3 H), 2.01 (quin, *J* = 6.46 Hz, 2 H), 2.24 (s, 3 H), 2.30 - 2.37 (m, 2 H), 2.41 - 2.46 (m, 2 H), 2.46 - 2.53 (m, 2 H), 2.56 (t, *J* = 6.15 Hz, 2 H), 4.09 (q, *J* = 7.03 Hz, 2 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	:	14.2, 18.8, 20.8, 20.9, 28.7, 32.7, 37.1, 60.3, 127.2, 165.4, 167.7, 173.0, 198.7
Mass: m/z (%)	:	255 (M + H, 100), 232 (90), 219 (80), 191(35), 139 (70)

Ethyl 3-(7-oxo-1,4-dioxaspiro[4.5]decan-6-yl)propanoate (28):



A mixture of **26** (2.5 g, 202.2 mmol) and ethylene glycol (0.73 mL, 12.9 mmol) and *p*-TSA (0.23 g, 0.178 mmol) was refluxed in 70 mL benzene for 10 h under Dean-Stark condition. The reaction mixture was cooled, solvent was evaporated under reduced pressure and whole residue was dissolved in ethyl acetate. The organic layer was washed with water (1x50 mL), brine (1x50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Column purification of the crude reaction mixture using EtOAc: Petroleum ether (15:85) as elutant afforded **28** as yellow liquid.

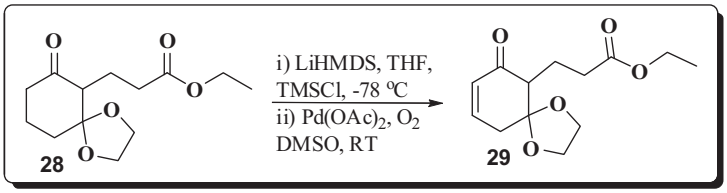
Yield:	:	40 %
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2890, 2980, 1732, 1682, 1420, 1377, 1266, 1215, 1059, 949
^{1}H NMR ($CDCl_3$, 500 MHz) δ	:	1.20 - 1.27 (m, 3 H) 1.67 - 1.90 (m, 5 H) 1.94 - 2.02 (m, 2 H) 2.22 - 2.32 (m, 2 H) 2.39 - 2.48 (m, 2 H) 2.64

(dd, *J* = 9.41, 3.30 Hz, 1 H) 3.89 - 4.00 (m, 4 H) 4.06 - 4.14 (m, 2 H)

^{13}C NMR ($CDCl_3$, 126 MHz) δ : 14.2, 18.7, 20.0, 32.5, 33.5, 39.9, 58.9, 60.2, 65.0, 65.2, 111.9, 173.5, 208.4

Mass: m/z (%) : 295.4 (M + K, 9), 279.2 (M + Na, 100), 257.5 (M + H, 10)

Ethyl 3-(7-oxo-1,4-dioxaspiro[4.5]dec-8-en-6-yl)propanoate (29):



To a solution of ketone **28** (0.83 g, 32.2 mmol) in dry THF (32 mL) at -78 ˚C was added LiHMDS (9.7 mL, 1.0 M in THF, 9.7 mmol) dropwise over 10 min., followed by TMSCl (1.3mL, 9.7 mmol) dropwise addition over the period of 5 min. The reaction mixture was stirred for 20 min. at -78 ˚C, and then warmed to 25 °C. Upon disappearance of the starting material (checked by TLC), the reaction mixture was quenched with H_2O (1x50 mL) and the biphasic reaction mixture was extracted with EtOAc (1x40 mL), and the combined organic layers were washed with brine and concentrated. The residual oil obtained was dissolved in DMSO (140 mL), $Pd(OAc)_2$ (0.15 g, 0.64 mmol) was added in one portion. Reaction mixture was further stirred under an oxygen atmosphere (balloon pressure) at 25 °C for 12 h and quenched with H_2O (150 mL). It was then extracted with EtOAc (3x50 mL), the combined organic layers were dried over Na_2SO_4 and concentrated. Silica gel column chromatography of crude oil mixture using EtOAc: Petroleum ether (20:80) as elutant gave 0.52 g of **29**.

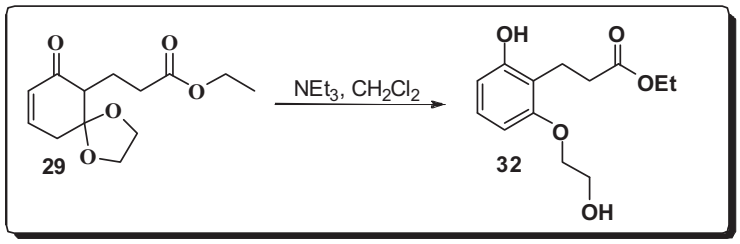
Yield: : 64 %

IR ν_{max} cm^{-1} ($CHCl_3$) : 3019, 2928, 2856, 1713, 1595, 1470, 1455, 1353, 1377, 1216, 1098, 1047, 768, 668

^{1}H NMR ($CDCl_3$, 500 : 1.24 (t, *J* = 7.2 Hz, 3 H), 1.77 - 1.90 (m, 2 H), 2.04

MHz) δ		(dddd, *J* =13.89, 9.31, 7.02, 4.27 Hz, 1 H), 2.39 - 2.56 (m, 3 H), 2.59 (dd, *J* = 9.61, 4.12 Hz, 1 H) 2.67 - 2.73 (m, 1 H), 3.89 - 4.03 (m, 4 H), 4.11 (q, *J* = 7.2 Hz, 2 H), 6.04 (dt, *J* =10.15, 2.10 Hz, 1 H) 6.85 (dt, *J* =10.30, 4.01 Hz, 1 H)
^{13}C NMR ($CDCl_3$, 126 MHz) δ	:	14.1, 20.9, 32.1, 35.3, 55.9, 60.3, 64.8, 64.9, 110.4, 128.4, 145., 173.2, 199.5
Mass: m/z (%)	:	293.1 (M + 39, 5), 277.1 (M + 23, 100), 255.1 (M + 1, 4), 209.2 (10), 181.1 (5)

Ethyl 3-(2-hydroxy-6-(2-hydroxyethoxy)phenyl)propanoate (32):



Compound **29** (0.1 g, 0.394 mmol) was dissolved in dichloromethane and NEt_3 (0.055 mL, 0.394 mmol) was added to it at room temperature. After 1 h reaction was concentrated and was purified by column chromatography using EtOAc: Petroleum ether (25:75) as elutant gave 0.095 g of **32**.

Yield:	:	95 %
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3351, 3020, 1711, 1469, 1216, 1100, 757
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	1.18 - 1.27 (m, 3 H), 2.63 - 2.82 (m, 2 H), 2.82 - 3.00 (m, 2 H), 3.76 (s, 1 H), 3.93 - 4.02 (m, 2 H), 4.03 - 4.20 (m, 5 H), 6.45 (d, *J* = 8.08 Hz, 1 H), 6.59 (d, *J* = 7.96 Hz, 1 H), 6.99 - 7.14 (m, 1 H), 7.64 (s, 1 H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	14.0, 18.2, 33.7, 61.3, 61.6, 69.4, 103.6, 110.6, 116.05, 127.7, 155.5, 157.4, 176.5
Mass: m/z (%)	:	279.1 (100), 277 (M + 23, 20), 263.1 (18), 225.1 (35)

4.5 References:

1. Yamaguchi M., Yokota N., Minami T., *J. Chem. Soc. Chem. Commun.*, **1991**, 1088.
2. Yamaguchi M., Shiraishi T., Hirama M., *J. Org. Chem.*, **1996**, *61***,** 3530.
3. Ma A., Zhu S., Ma D., *Tetrahedron Lett.*, **2008**, *49*, 3075.
4. Brandau S., Landa A., Franzén J., Marigo M., Jørgensen K. A., *Angew. Chem. Int. Ed.*, **2006,** *45*, 4305.
5. i) Ballini R., Bosica G., Gigli F., *Tetrahedron*, **1998**, *54*, 7573; ii) Ballini R., Petrini M., Polzonetti. V., *Synthesis*, **1992**, 355.
6. Buckle D. R., Morgan N. J., Smith H., *J. Med. Chem.*, **1975**, *18,* 203.
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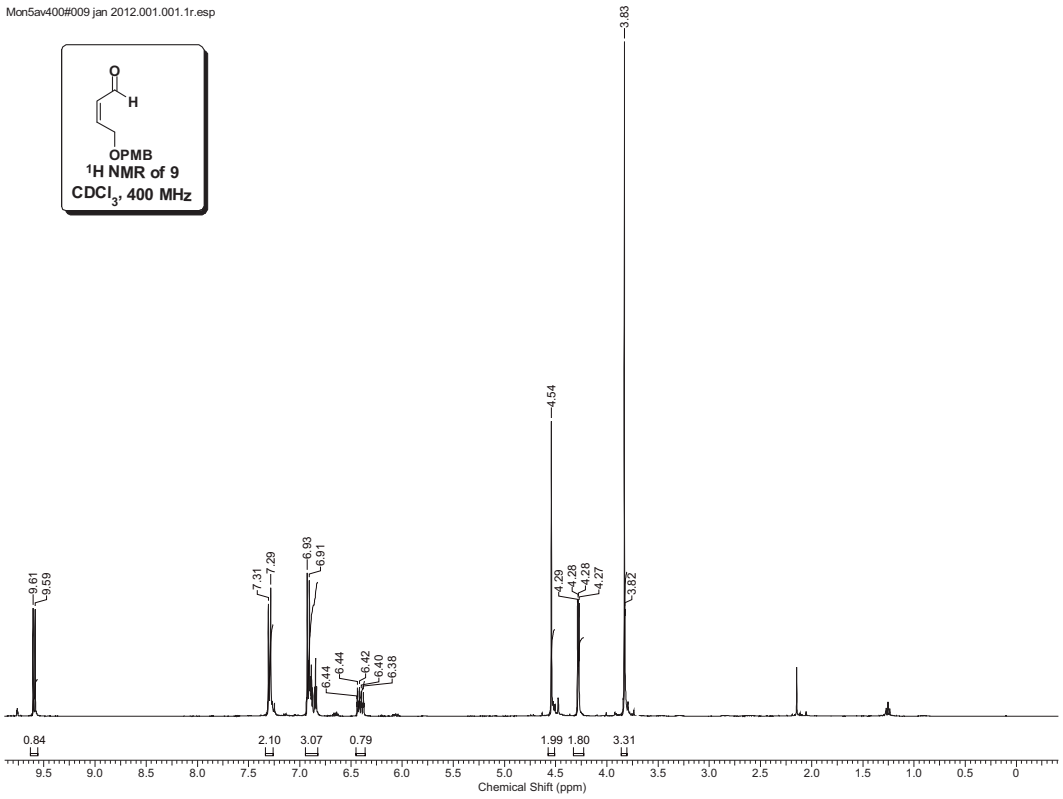
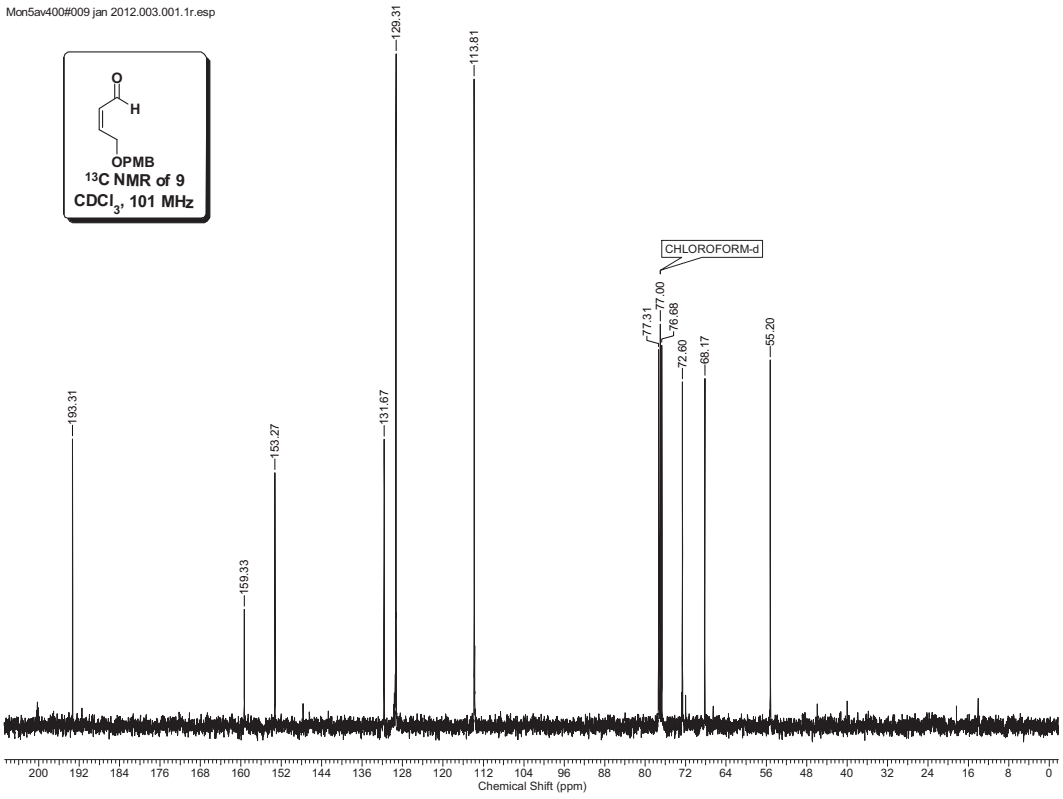
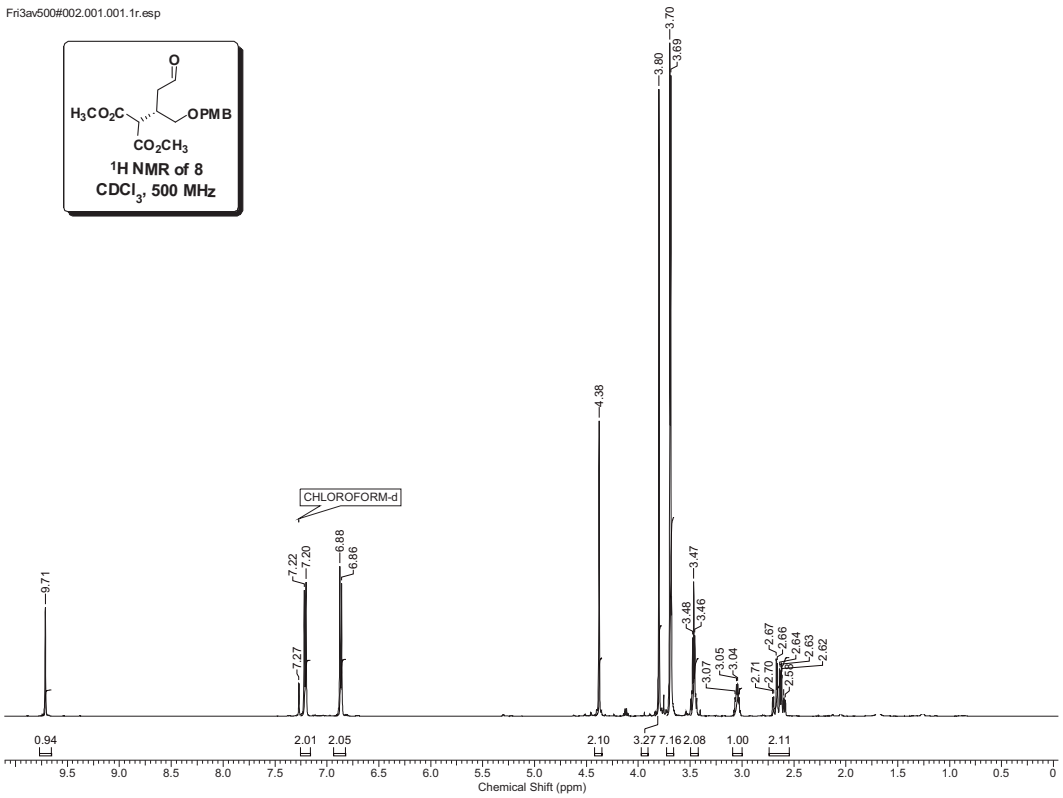
8. Theilacker W., Schmid W., *Justus Liebigs Ann. Chem*., **1950**, *16*, 670.
9. Dampawan P., Zajac W. W., *Synthetic commun*., **1983**, 545.
10. Nicolaou K. C., Li H., Nold A. L., Pappo D., Lenzen A., *J. Am. Chem. Soc.*, **2007**, *129*, 10356.
11. Wascholowski V., Knudsen K. R., Mitchell C. E. T., Ley S. V., *Chem. Eur. J.,* **2008**, 6155.

4.6 Spectras of all new compounds



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6.86
4.38
3.80
3.70
3.69
3.47
3.48
3.46
3.07
3.05
3.04
2.71
2.70
2.67
2.66
2.64
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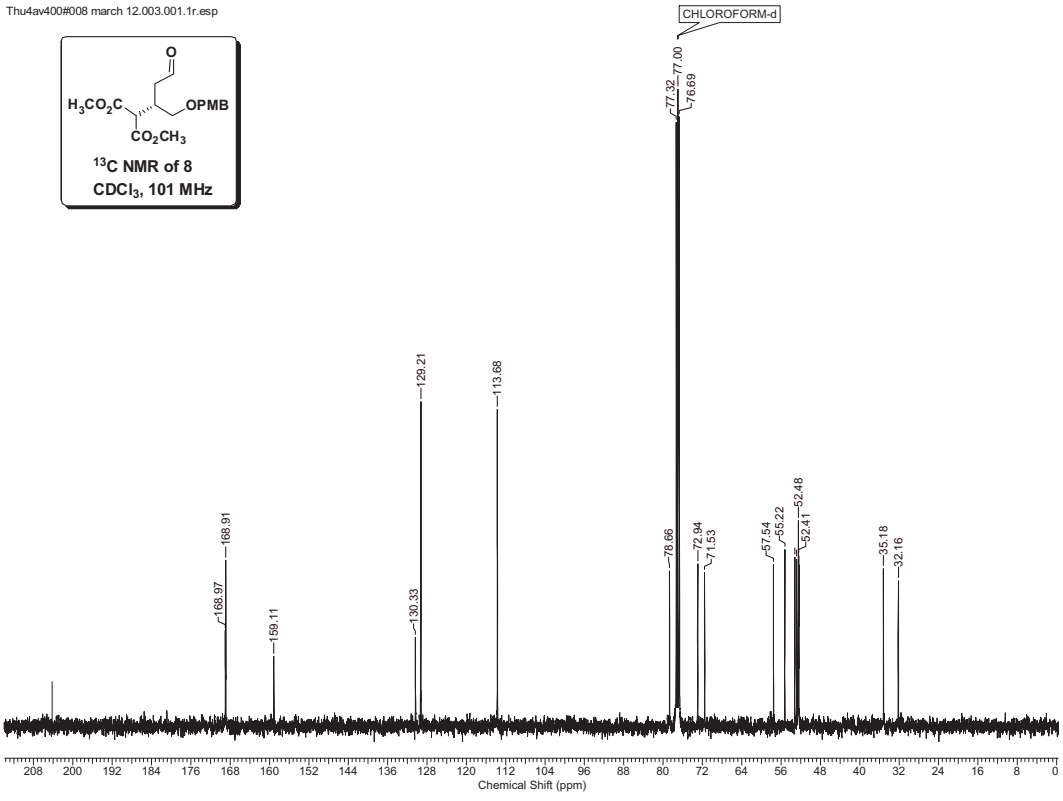
Chemical Shift (ppm)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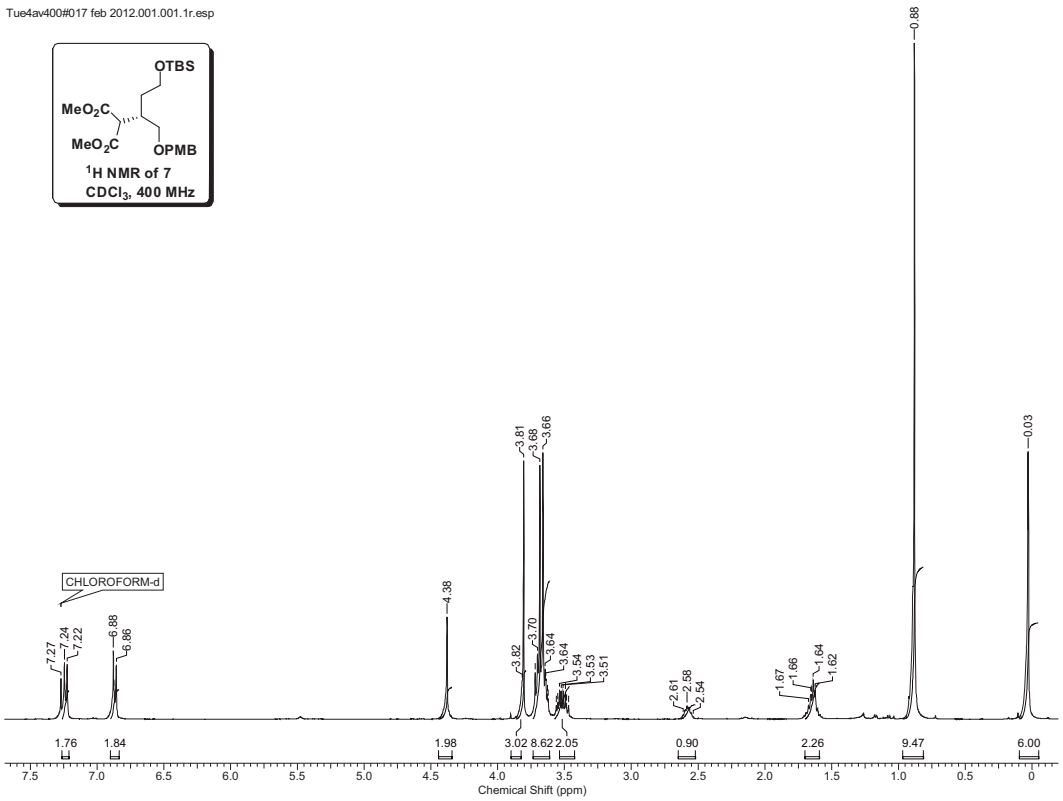
Chemical Shift (ppm)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OPMB
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7.22
6.88
6.86
4.38
3.82
3.81
3.70
3.68
3.66
3.64
3.54
3.53
3.51
2.61
2.58
2.54
1.67
1.66
1.64
1.62
0.88
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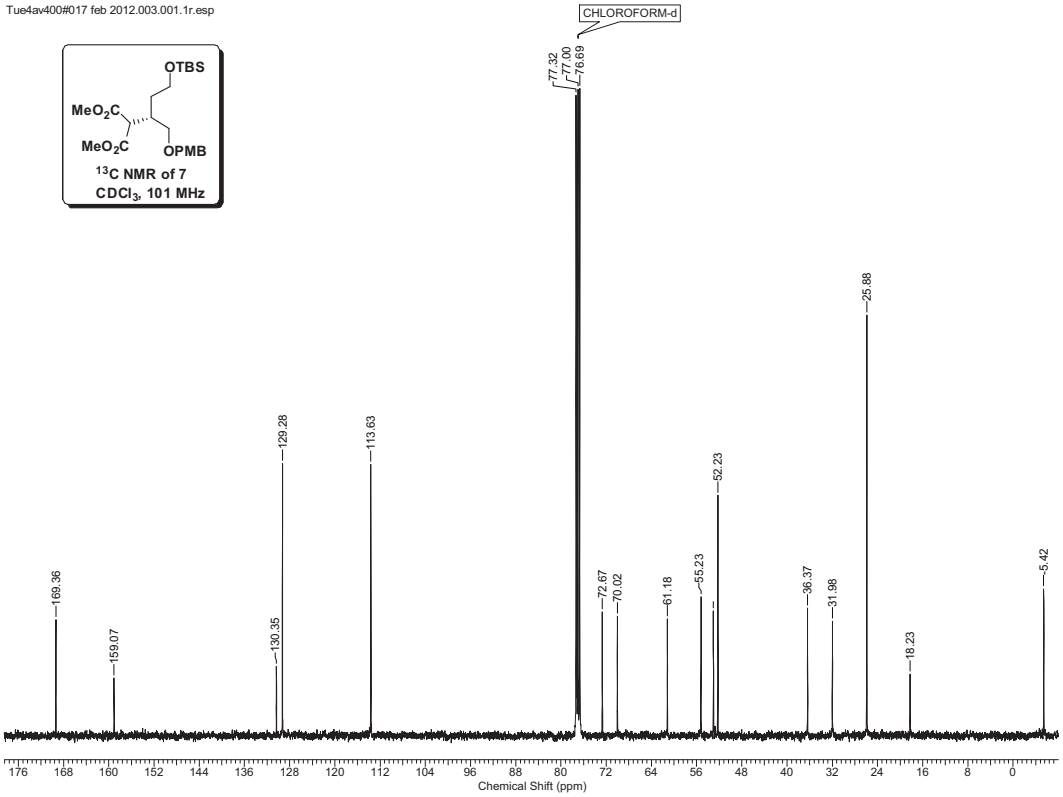
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Chemical Shift (ppm)

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Reported: 12/29/08 02:37 PM
Processed: 12/29/08 02:37 PM

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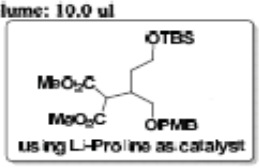
Processing Method: SANTOSHH

System(acquisition): Sys 1
Application: HPLC
Sample Name: Rac-PAA-70A
Injection from this vial: 1 of 1
Sample Description: Ethanol:PE(02:98)

Series:5609
Volume: 10.0 ul



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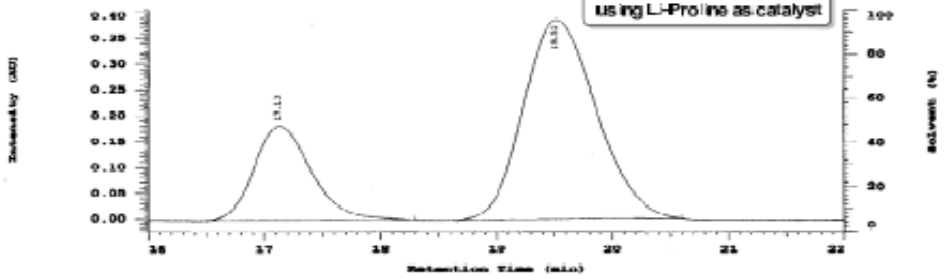

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D-7000 HPLC System Manager Report

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Processed: 12/29/08 02:28 PM

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System(acquisition): Sys 1
Application: HPLC
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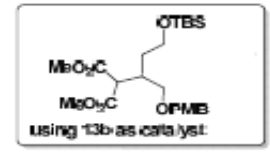
Injection from this vial: 1 of 1
Sample Description: Ethanol:PE(02:98)

Series:5610
Volume: 10.0 ul



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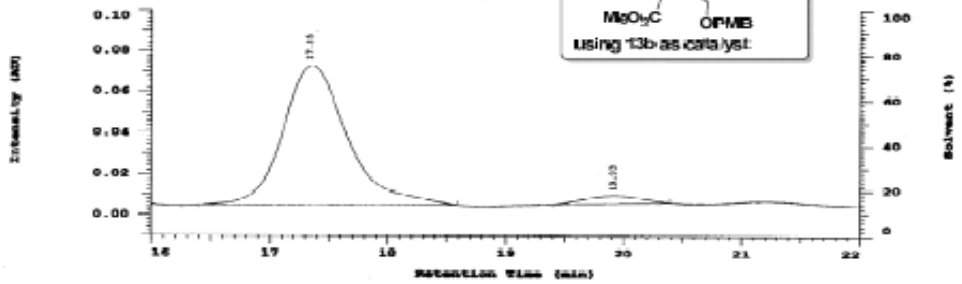

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Peak rejection level: 0

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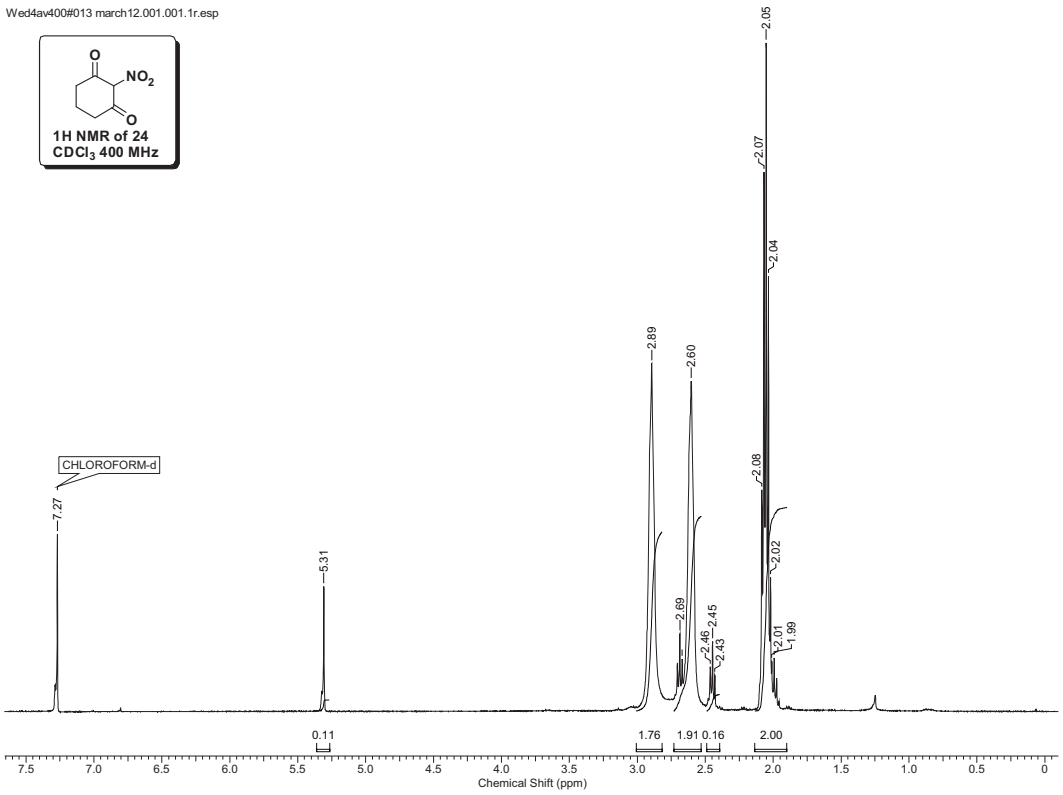
FLOW RATE :-0.5 ml/min (250psi)
SAMPLE CONC :-0.98mg /2.0 ml X (Inj vol- 2.5ul)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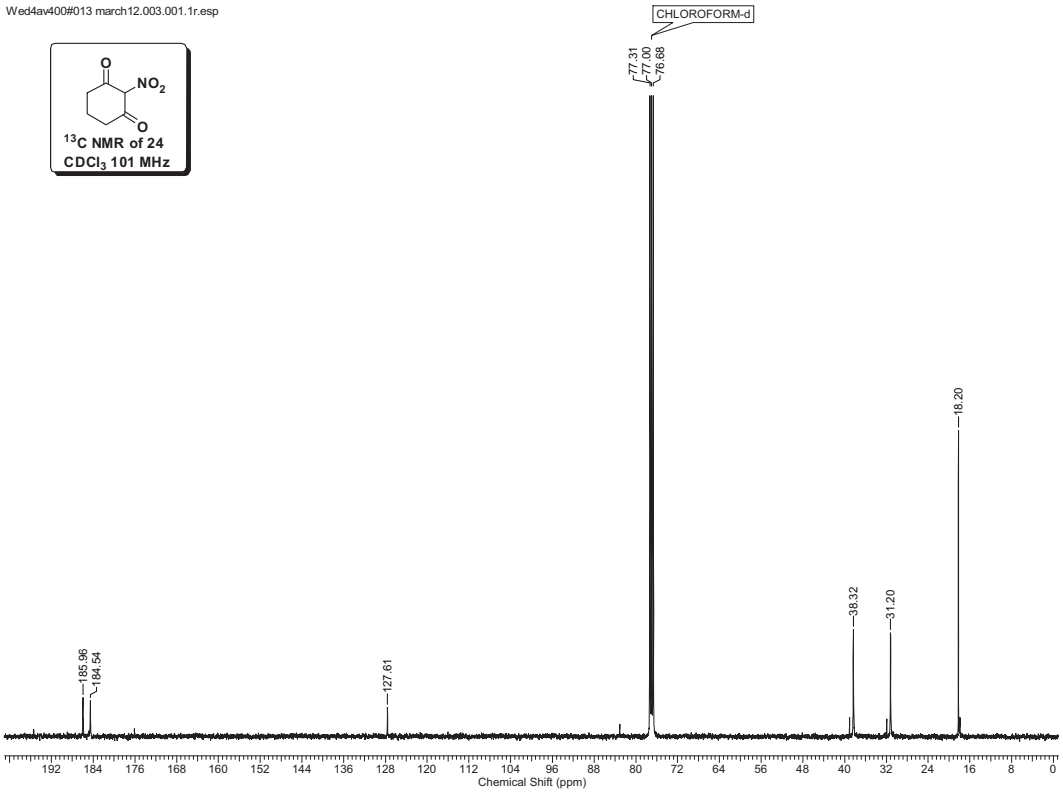
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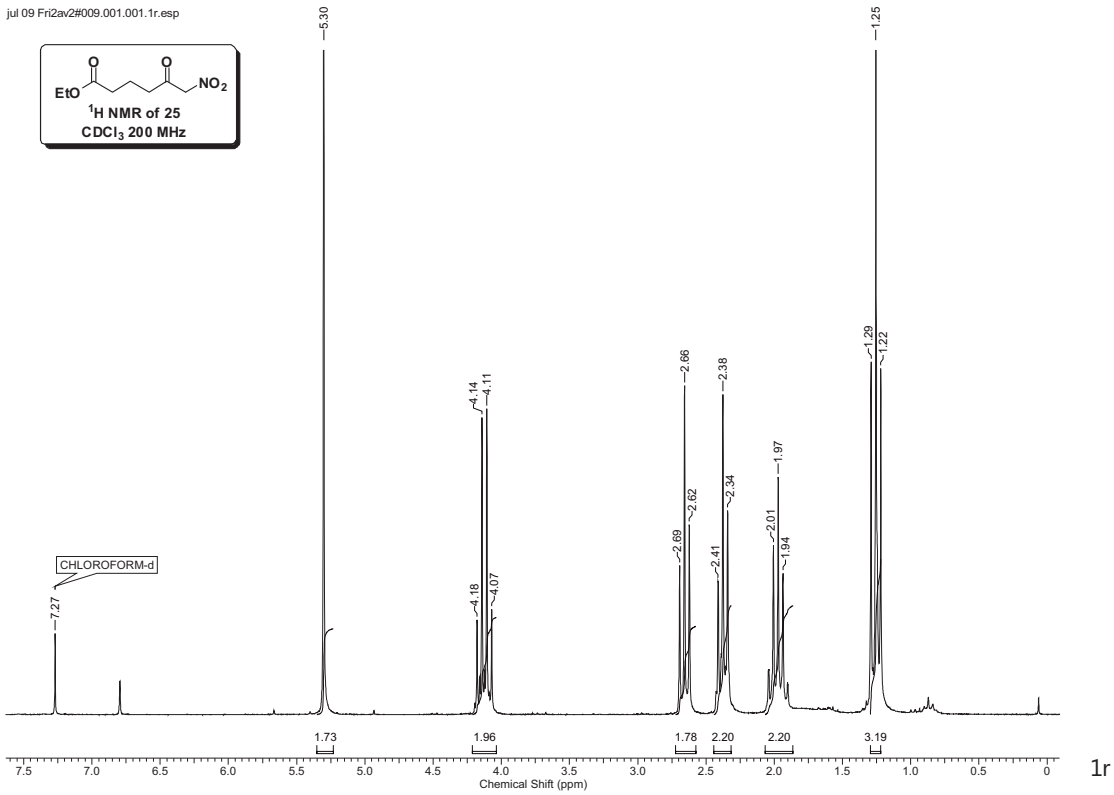
Chemical Shift (ppm)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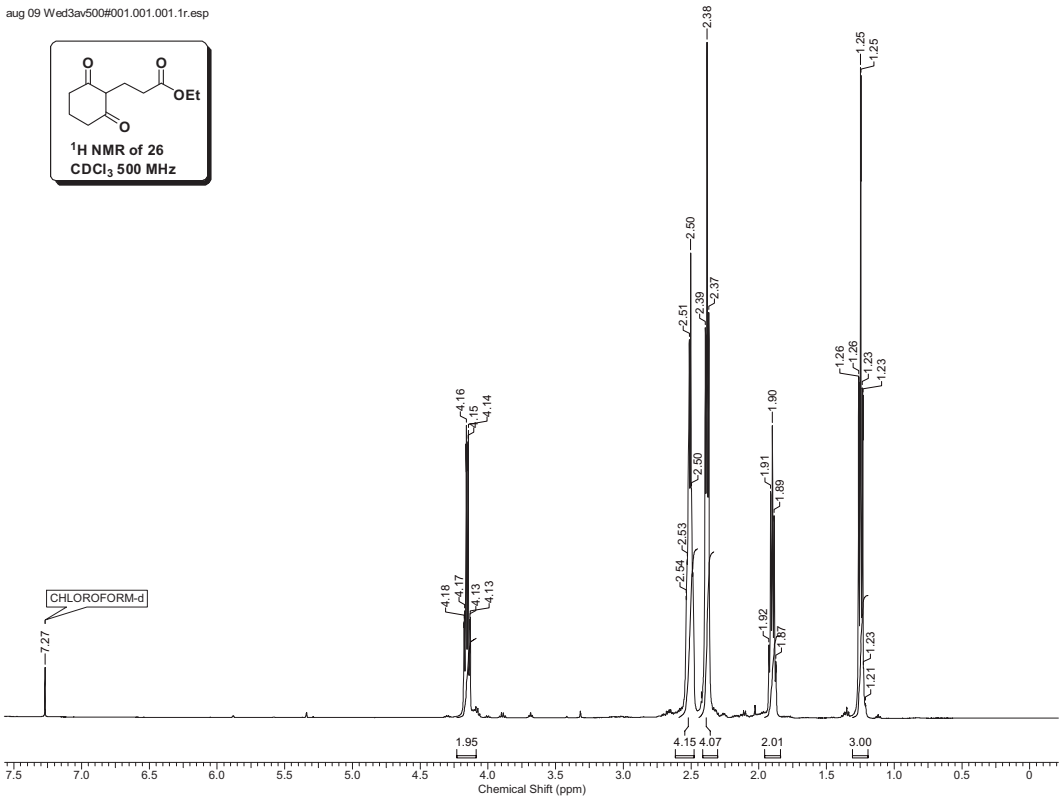
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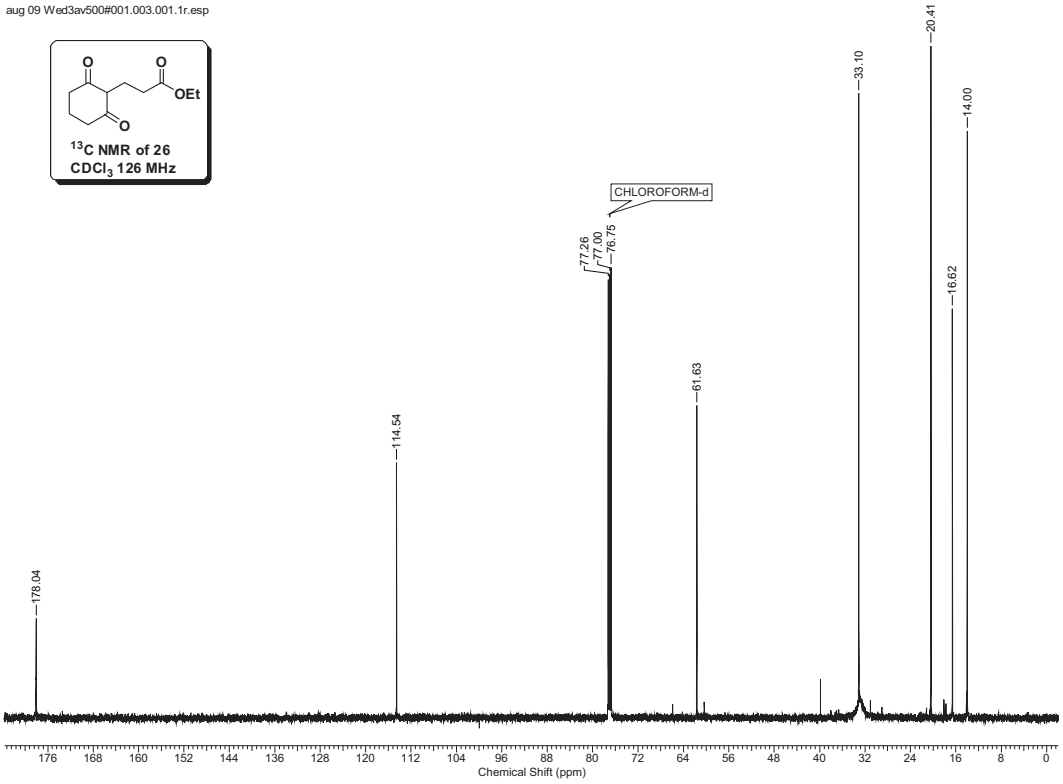
Chemical Shift (ppm)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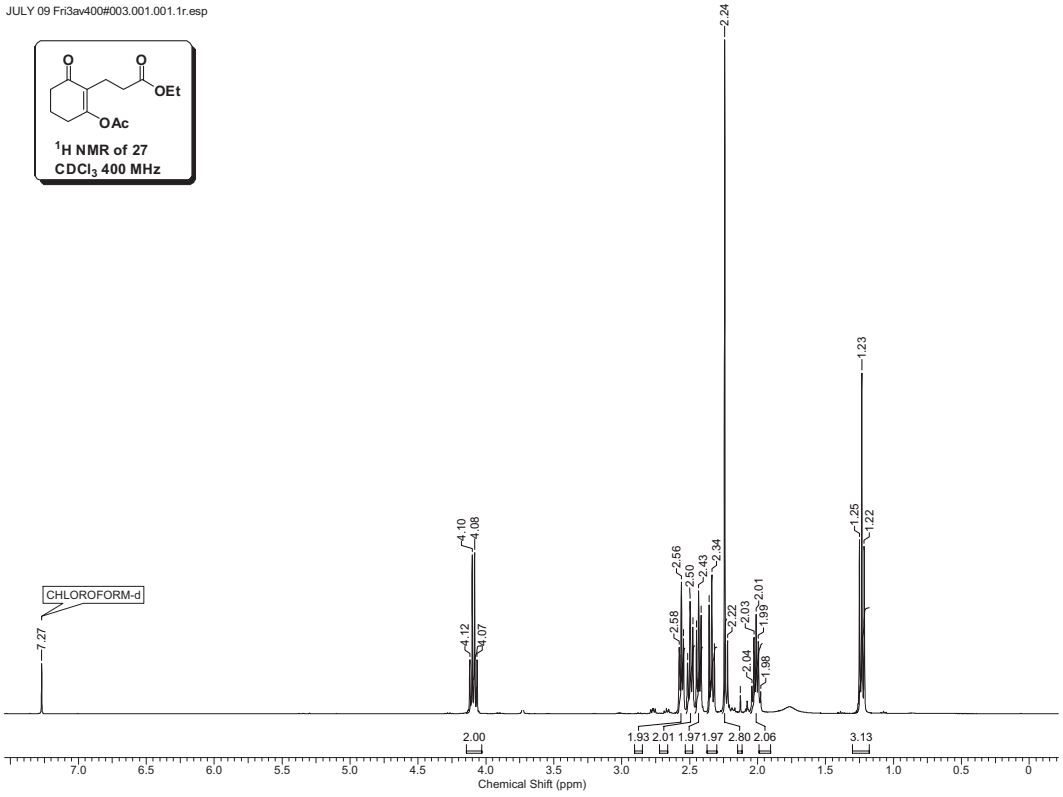
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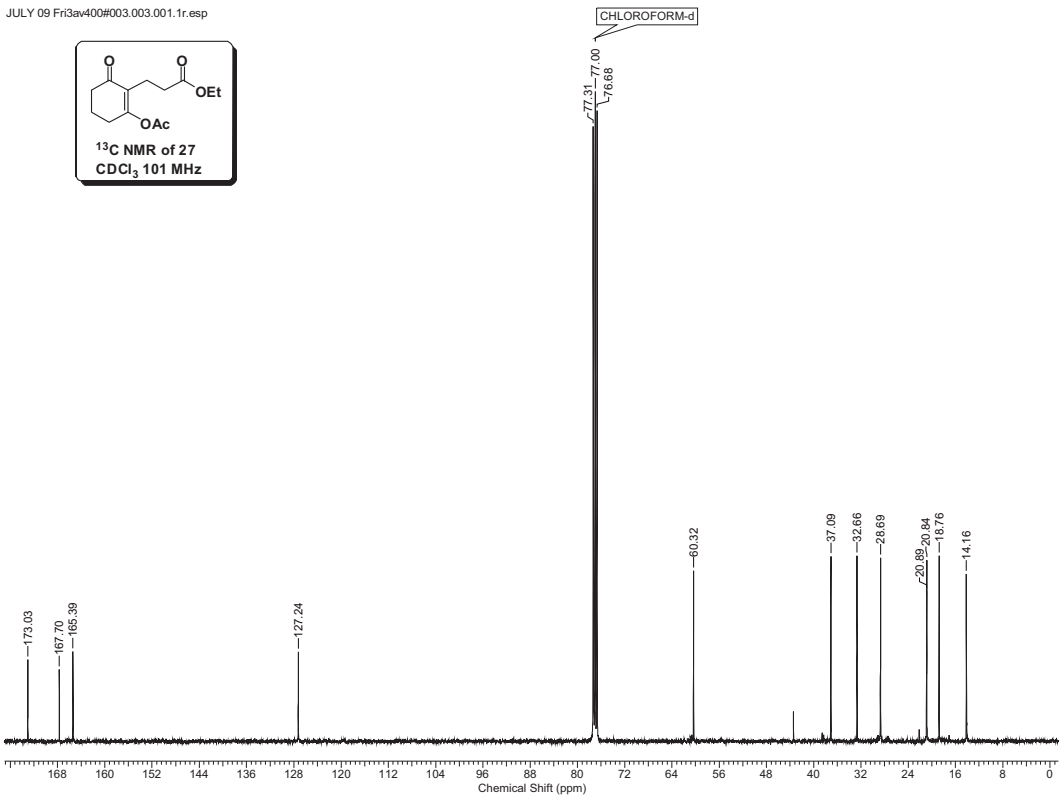
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OAc
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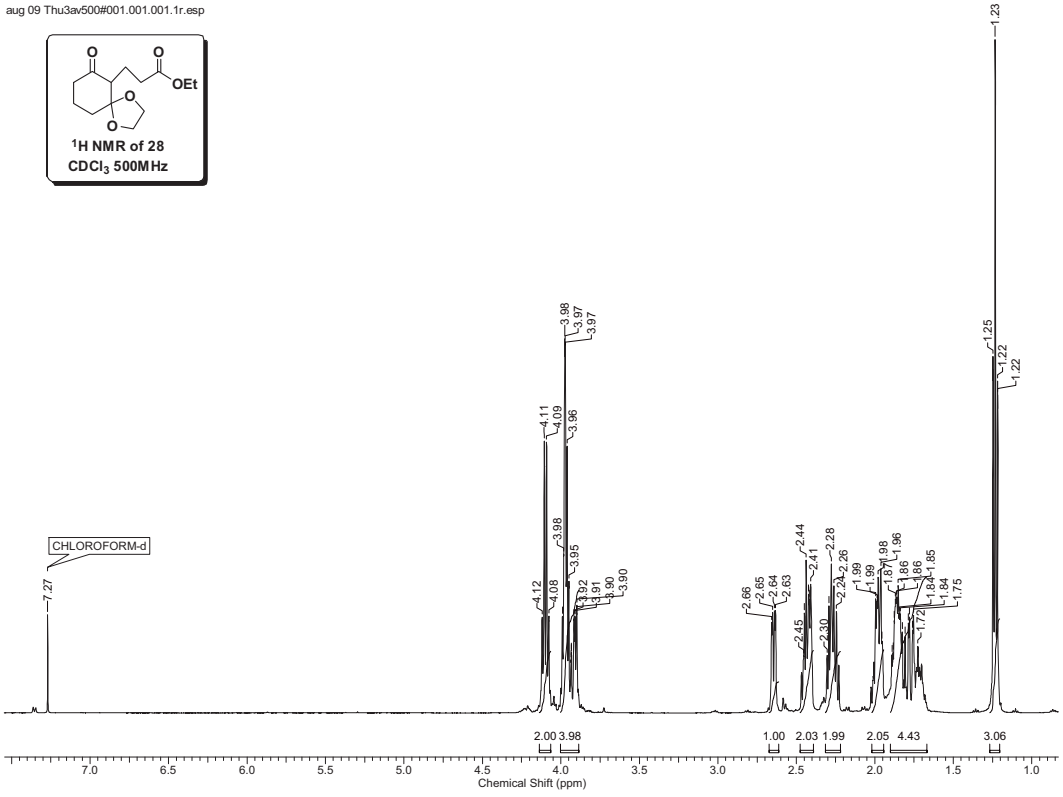
Chemical Shift (ppm)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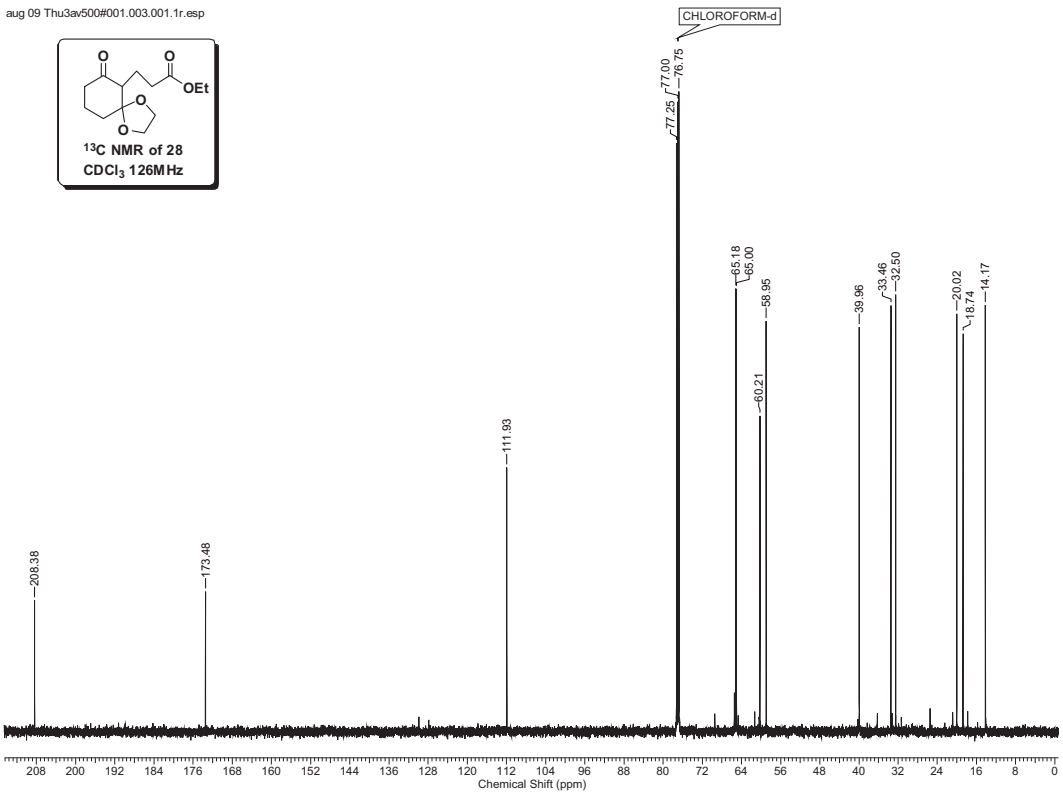
Chemical Shift (ppm)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OEt
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58.95
60.21
39.96
33.46
32.50
20.02
18.74
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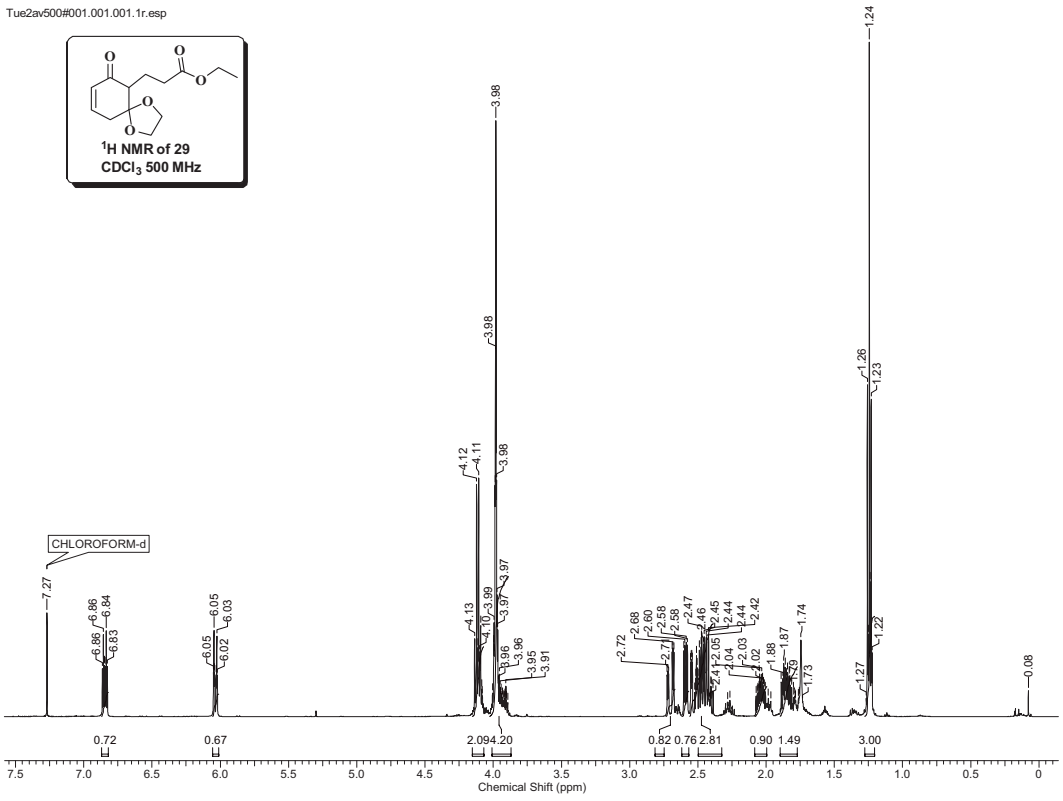
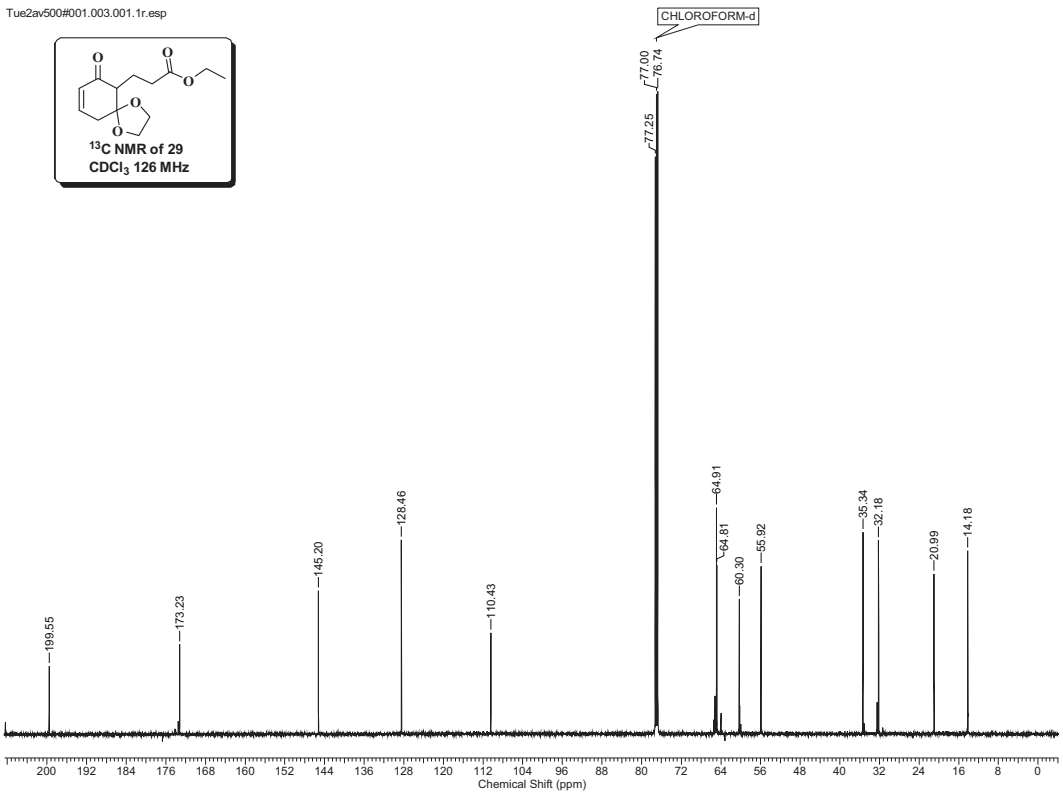
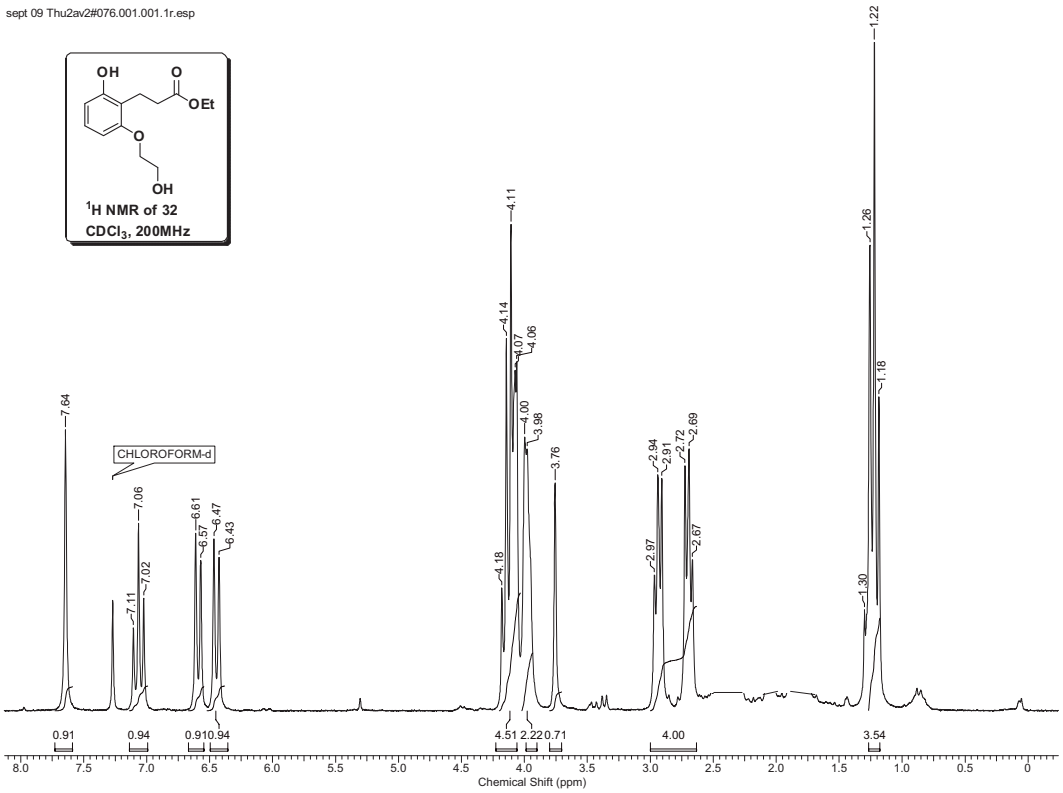
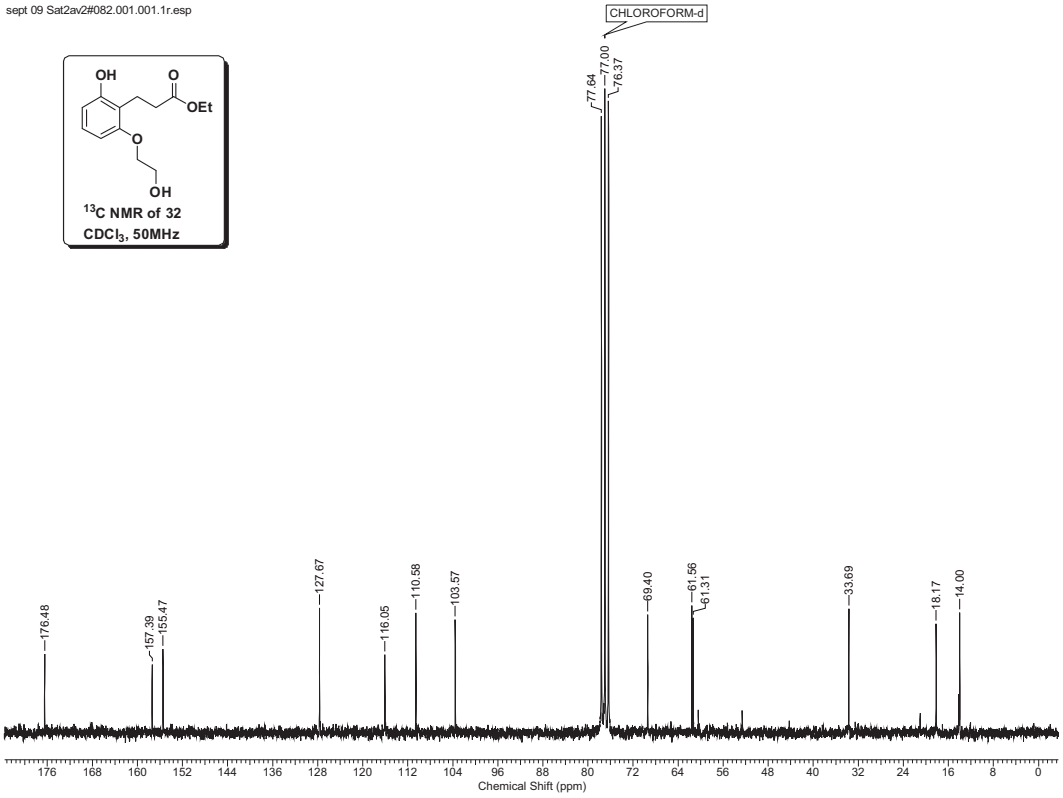
111.93
208.38
173.48
Chemical Shift (ppm)


Tue2av500#001.001.001.1r.esp
1H NMR of 29
CDCl3 500 MHz
CHLOROFORM-d
7.27
6.86
6.84
6.83
6.05
6.03
6.02
4.13
4.12
4.11
4.10
3.99
3.98
3.97
3.96
3.95
3.91
2.72
2.68
2.66
2.58
2.47
2.46
2.45
2.44
2.42
2.41
2.05
2.04
2.03
2.02
1.88
1.87
1.79
1.74
1.73
1.27
1.26
1.24
1.23
1.22
0.08
0.72
0.67
2.09
4.20
0.82
0.76
2.81
0.90
1.49
3.00
Chemical Shift (ppm)


Tue2av500#001.003.001.1r.esp
CHLOROFORM-d
^{13}C NMR of 29
$CDCl_3$ 126 MHz
77.00
76.74
77.25
64.91
64.81
60.30
55.92
35.34
32.18
20.99
14.18
199.55
173.23
145.20
128.46
110.43
Chemical Shift (ppm)


sept 09 Thu2av2#076.001.001.1r.esp
^{1}H NMR of 32
$CDCl_3$, 200MHz
CHLOROFORM-d
7.64
7.06
7.11
7.02
6.61
6.57
6.47
6.43
4.11
4.14
4.07
4.06
4.00
3.98
3.76
4.18
2.94
2.91
2.72
2.69
2.97
2.67
1.22
1.26
1.18
1.30
0.91
0.94
0.91
0.94
4.51
2.22
0.71
4.00
3.54
Chemical Shift (ppm)


sept 09 Sat2av2#082.001.001.1r.esp
CHLOROFORM-d
77.64
77.00
76.37
OH
O
OEt
O
OH
13C NMR of 32
CDCl3, 50MHz
176.48
157.39
155.47
127.67
116.05
110.58
103.57
69.40
61.56
61.31
33.69
18.17
14.00
176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

List of Publication

1. Organocatalytic dynamic kinetic resolution *via* conjugate addition: Synthesis of chiral *trans*-2,5-dialkylcyclohexanones

   Ganesh Pandey, Priyanka A. Adate, Vedavati G. Puranik

   Org. Biomol. Chem., **2012**, *10*, 8260-8267

   DOI: 10.1039/C2OB26597D

2. Formal synthesis of tetracyclic core of higher Iridoids

   Ganesh Pandey, Priyanka A. Adate (to be communicated)

Erratum