STUDIES DIRECTED TOWARDS THE SYNTHESIS OF NATURALLY OCCURRING SPIROACETALS, LACTONES AND BIOLOGICALLY ACTIVE [1,2,4]TRIAZINO DERIVATIVES

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

TO

UNIVERSITY OF PUNE

BY

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ORGANIC CHEMISTRY DIVISION

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PUNE-411008

January 2013

CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "**Studies Directed Towards the Synthesis of Naturally Occurring Spiroacetals, Lactones and Biologically active [1,2,4]triazino derivatives "** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune has not been submitted by me to any other University or Institution. This work was carried out at the National Chemical Laboratory, Pune, India.

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CERTIFICATE

The research work presented in thesis entitled "**Studies Directed Towards the Synthesis of Naturally Occurring Spiroacetals, Lactones and Biologically active [1,2,4]triazino derivatives**" has been carried out under my supervision and is a bonafide work of **Mr. Anand Harbindu**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

(Dr. Pradeep Kumar)

January 2013 **Research Guide**

DEDICATED

TO MY BELOVED

FAMILY

Acknowledgements

It gives me great pleasure to express my deep sense of gratitude to my teacher and research guide Dr. Pradeep Kumar, who has helped me a lot to learn and think more about chemistry. I thank him for his excellent and inspiring guidance, constant encouragement, sincere advice and unstinted support during all the times of my Ph.D. work. Working with him was a great pleasure and learning experience.

I take this opportunity to specially thank Dr. Santosh Mhaske, Dr. H. B. Borate, Mr. I. Shivakumar, Dr. S. P. Chavan, Dr. N. N. Joshi, Dr. R. A. Joshi, Dr. R. R. Joshi, Dr D. S. Reddy, Dr. R. P. Singh, Dr. Muthukrishnan, Dr. Ashish Bhattacharya, Dr. Jayant Gajbhiye, Dr. Kiran Sonawane, Dr. Borikar, Mr. Kalal, Mrs. Kunte, Late. Dr. D. D. Sawaikar and Dr. Ashish K. Tiwari (BHU) for their helpful suggestions and encouragement.

Help from the spectroscopy, and mass group are gratefully acknowledged. I sincerely thank Dr. Rajmohanan, for his helpful discussions and cooperation.

My sincere thanks to Mrs. C. Raphel, Mrs. P. Kulkarni, Mr. Iyer, Mr. K. Thangaraj, Mr. Babus, Mr. Ranade and all other office staffs for their cooperation.

My sincere thanks to Dr. G. Panday, Head, DOC for his cooperation and support.

The warm and friendly attitude of my seniors Dr. Chinmoy, Dr. Rahman, Dr. Sahoo, Dr. Rosy, Dr. Seetaram, Dr. Sabita, Dr. Rita, Dr. Ramesh, Dr. Pradip, Dr. Ganesh, Dr. Sunil, Dr. Kesari, Dr. Satyendra, Dr. Priti, Dr. Puspesh, Dr. Nagendra, Dr. Namarta, Mr. Shijo, Dr. Divya, Dr. Ruchi, Dr. Eeshwar is gratefully acknowledged. I take this opportunity to thank my colleagues Vishwajeet, Partha, Menaka, Mujaheed, Krishanu, Kiran, Shruti, Nookaraju, Brijesh for their help and cheerful atmosphere in the laboratory. I extend my deep sense of gratitude towards my senior as well as friend Dr. Abhishek and Mr. Ankush for helping me in all aspect of research and personal life. Also I heartedly thank friends at NCL and GJ hostel especially Umesh, Nawab, Negi, Sunil, Maurya, Ravi, Ajay, Krunal, Gupta, Mishra, Ajeet, Prince, Pitamber, Baba, Malvi,

Prakesh, Kiran, Seema, Gowri, Atul, Asif, Abhijeet, Tamboli, Dumare, Chand, Mangesh, Pankaj, Jyoti, Ranjeet, Sangmesh, Paresh, Sutar, Deepak, Satish.

I extend my thanks to my childhood friends Javed, Amit, Arvind and my roommate ShyamSundar and friends at spn Amit, Pawan, Namita, Brijesh, Rakesh, Vipin M. Sc. friends Narendra, Shweta, Samareen who made the life memorable.

Special thanks to my M.Sc. teachers Dr. Abdul Hasnaat, Prof. S. W. I. Naqvi and my Delhi teachers Dr. H. P. Gupta, and Dr. Raj Tripathi for their constant encouragement and inspiration.

It is impossible to express my sense of gratitude for my parent, in mere words. Whatever I am and whatever I will be in future is because of their commitments to my ambitions and their selfless sacrifices. Words fall short to thank my brother Mr. Rajeev, Dr. Ashish, Sister-in-law Ruchi, Neeti, Sister Dr. Arti, Jyoti, Brother-in-law Dr. Vishnu, Rajat, Nephew Avi, Saksham, Niece Shubhi and Shanvi for their never ending encouragement, love and support, I am indeed thankful to my fiancé Kavita for her encouragement and support at the final stage of my thesis, which enable me to pursue my goal whole heartedly.

Finally I thank Director, National Chemical Laboratory, Pune for providing infrastructural facilities to complete my work successfully. I am also thankful to UGC/CSIR, New Delhi for the financial assistance in the form of fellowship.

Anand

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ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
BuLi	-	Butyl Lithium
DCM	-	Dichloromethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	-	Diastereomeric excess
ds	-	Diastereoselectivity
DIBAL-H	-	Diisobutylaluminiumhydride
DMP	-	Dess–Martin periodinane
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N′*-Dimethylformamide
DMAP	-	*N,N′*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
ee	-	Enantiomeric excess
eq. or equiv	-	Equivalents
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
h	-	Hours
Hz	-	Hertz
HMPA	-	Hexamethylphosphoramide
IBX	-	Iodoxybenzoic Acid

Im	-	Imidazole
i-Pr	-	Isopropyl
IR	-	Infrared
m-CPBA	-	*m*-Chloroperbenzoic acid
MeOH	-	Methanol
Me	-	Methyl
MeI	-	Methyl iodide
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
Ph	-	Phenyl
Py	-	Pyridine
PDC	-	Pyridiniumdichromate
p-TSA	-	*para*-Toluenesulfonic acid
RCM	-	Ring closing metathesis
TEA	-	Triethylamine
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMSCl	-	*tert*-Butyldimethyl chlorosilane
TBDMS	-	*tert*-Butyldimethyl silyl
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
*P*TSA	-	*p*-Toluenesulphonic acid
TsCl	-	*p*-Toluenesulphonyl chloride

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, and DRX-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometer.
- EI Mass spectra were recorded on Finnigan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.
- Silica gel (60–120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.

ABSTRACT

The thesis entitled "**Studies Directed Towards the Synthesis of Naturally Occurring Spiroacetals, Lactones and Biologically active [1,2,4]triazino derivatives"** has been divided into four chapters.

Chapter 1: Introduction to Proline-Catalyzed Reactions, Jacobsen's Hydrolytic Kinetic Resolution and Ring Closing Metathesis (RCM)

Chapter 2:

Section A: Synthesis of Aculeatins A and B via Iterative Hydrolytic Kinetic Resolution and PIFA Promoted Tandem Phenolic Oxidation/Dithiane Deprotection Sequence

Section B: Synthesis of Aculeatin F and *epi*-F

Section C: Studies towards the Synthesis of Modiolide B

Chapter 3:

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<u>Chapter 1:</u> Introduction to Proline-Catalyzed Reactions, Jacobsen's Hydrolytic Kinetic Resolution and Ring Closing Metathesis (RCM)

This chapter gives a brief introduction to proline-catalyzed organic transformations, Jacobsen's hydrolytic kinetic resolution (HKR) and ring closing metathesis (RCM).

In recent years, area of organocatalysis has emerged as a promising strategy and as an alternative to expensive protein catalysis and toxic metal catalysis, thus becoming a fundamental tool in the

catalysis toolbox available for asymmetric synthesis.[1] Proline has been defined as a "universal catalyst" because of its high utility in variety of asymmetric organic transformations. Proline is the only natural amino acid with a secondary amine functionality, which raises the pKa value and better nucleophilicity as compared to other amino acids. It can act as a nucleophile to carbonyl groups (iminium intermediate) or Michael acceptors (enamines). It can be regarded as a bifunctional catalyst as the secondary amine acts as Lewis base and the acid group acts as Brönsted acid.

The hydrolytic kinetic resolution (HKR)[2] of terminal epoxide catalyzed by chiral (salen) Co(III)OAc complex affords both recovered epoxide and 1,2-diol product in highly enantio-enriched form. In many cases there exist no practical alternatives for accessing these valuable chiral building blocks from inexpensive racemic materials.

Ring closing metathesis (RCM)[3] is a unique carbon skeleton redistribution in which unsaturated carbon-carbon bonds are rearranged to give cycloalkene. It utilizes no additional reagents beyond a catalytic amount of metal carbene. Various well-defined metathesis catalysts which are tolerant to many functional groups as well as reactive towards a diverse range of substrates have been developed.

These methods have contributed to more advances in research not only in chemistry but also in material science, biology and medicine. This work gave access to new molecules needed to investigate hitherto undiscovered and unexplained phenomena in the molecular world.

Chapter 2:

Section A: Synthesis of Aculeatins A and B via Iterative Hydrolytic Kinetic Resolution and PIFA Promoted Tandem Phenolic Oxidation/Dithiane Deprotection Sequence

Aculeatins A **1** and B **2** (Figure 1) were isolated by Heilmann and coworkers in 2000 from *Amomum Aculeatum rhizomes.*[4] They were found to inhibit the growth of human cancer KB cell lines, MFC-7 human breast cancer cells.[5] They also display antiprotozoal activity against *Trypanosoma* and both the NF54 and chloroquine-resistant K1 strains of the malarial parasite *Plasmodium falciparum*. Interestingly these compounds are endowed with a unique and unprecedented 1, 7-dioxa-dispiro[5.1.5.2]pentadecane tricyclic ring system which makes them an attractive synthetic target.

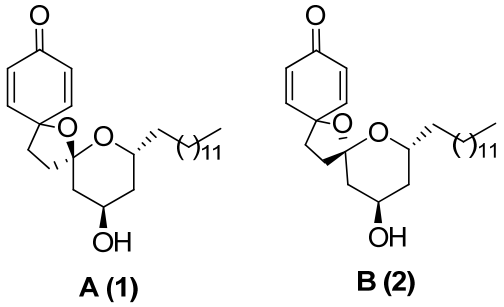
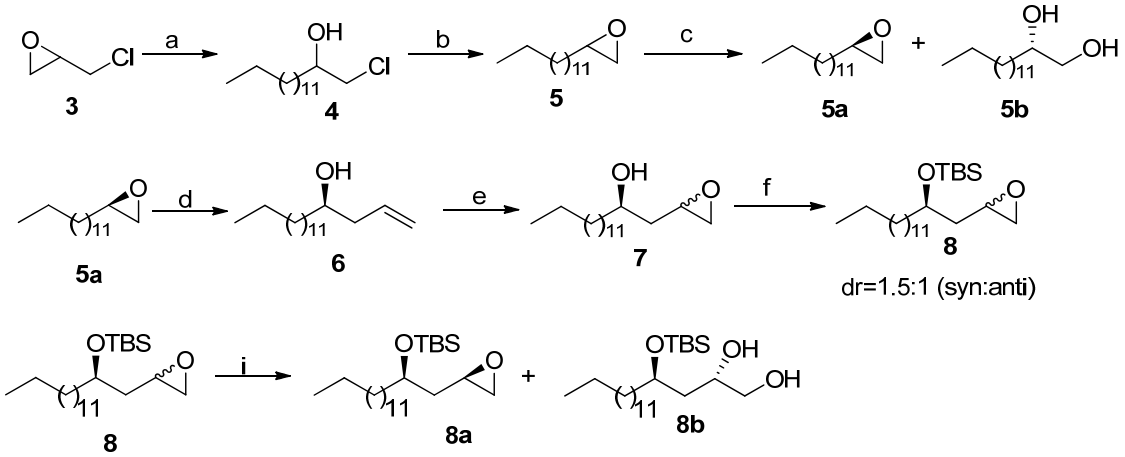


Figure 1. Aculeatins A **1** and B **2**

Aculeatins A **1** and B **2** could be synthesised by the Linchpin coupling of epoxide **8a** and dithiane **13**. The epoxide **8a** in turn could be prepared from (±) epichlorohydrin while the dithiane fragment **13** would be synthesised from *p*-anisaldehyde.

The synthesis of the epoxide fragment as illustrated in scheme 1 started from the commercially available (±) epichlorohydrin which on ring opening with dodecylmagnesium bromide followed by base treatment gave the epoxide **5** in 92% yield. The *rac*-epoxide **5** was subjected to Jacobsen's HKR using (*R,R*)-salen-Co(OAc) catalyst to give enantiopure epoxide (*R*)**-5a**[6] in 46% yield along with diol **5b** in 45% yield, which were separated by silica gel column chromatography.

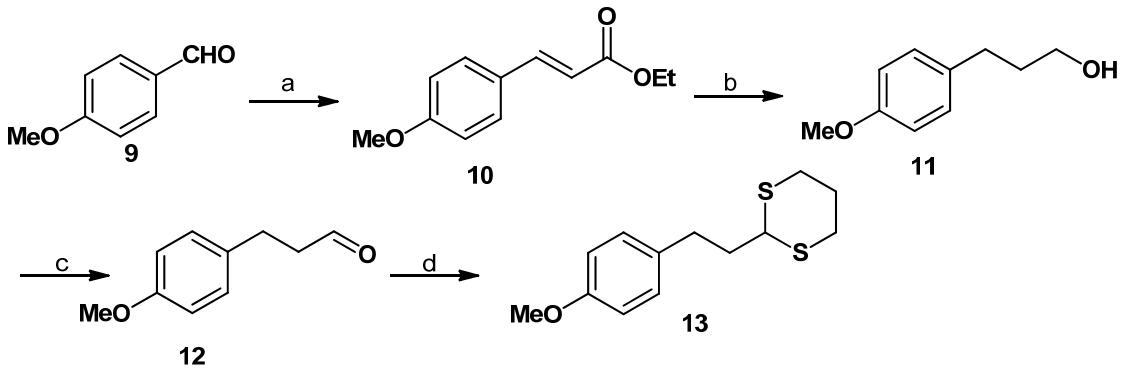
Thus epoxide **5a** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol **6** in 89% yield. The epoxidation of homoallylic alcohol **6** with *m*CPBA,



Scheme 1. Reagents and conditions: (a) Dodecylmagnesium bromide, THF, CuI, -40 ^{o}C, 12 h, 84%; (b) KOH, CH_2Cl_2, rt, 1 h, 92%; (c) *R,R*-salen-Co-(OAc) (0.5 mol %), dist. H_2O (0.55 equiv), 0 ^{o}C, 14 h, (46% for **8a**, 45% for **8b**); (d) Vinylmagnesium bromide, THF, CuI, -20 ^{o}C, 12 h, 89%; (e) *m*-CPBA, CH_2Cl_2, 0 ^{o}C to rt, 10 h, 96%; (f) TBDMSCl, imidazole, CH_2Cl_2, 0 ^{o}C to rt, 4 h, 95%; (g) *R,R*-salen-Co-(OAc) (0.5 mol %), dist. H_2O (0.55 equiv), 0 ^{o}C, 24 h, (49% for **4,** 37% for **4a**).

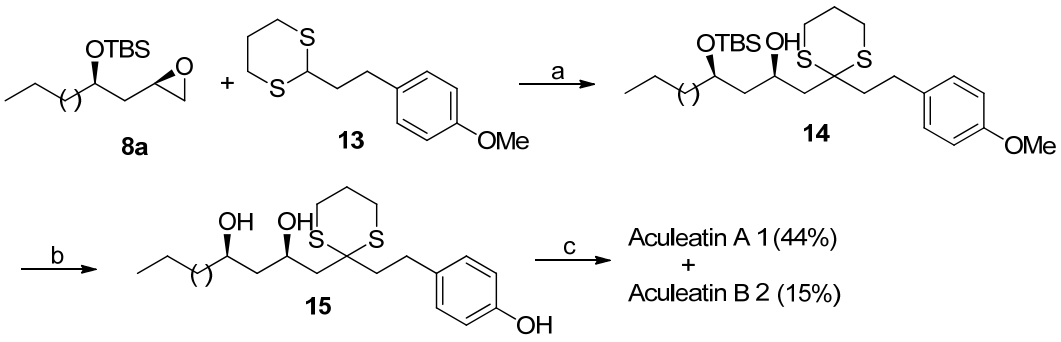
followed by hydroxy-group protection as the TBS ether produced the epoxide **8** in favor of the desired *syn*-isomer (*syn/anti* 1.5:1). The two diastereomers could not be differentiated by TLC. In order to improve the diastereoselectivity, the epoxide **8** was further subjected to HKR with (*R,R*)-salen-Co(OAc) complex (0.5 mol %) and water (0.55 equiv) to afford the diastereomerically pure epoxide **8a** as a single diastereomer in good yield.

Synthesis of dithiane fragment **13** (Scheme 2) started from the commercially available *p*-anisaldehyde which on two-carbon homologation via Wittig reaction provided the olefin **10** as a *cis-trans* mixture. The double bond reduction was carried out under hydrogenation conditions using 10% Pd/C at 60 *psi* followed by ester reduction with LAH to afford the alcohol **11** in 81% overall yield. The alcohol **11** was oxidized by IBX to give the aldehyde **12** which on subsequent treatment with 1, 3-propane dithiol in the presence of a catalytic amount of $BF_3.OEt_2$[7] at room temperature furnished the dithiane fragment **13** in excellent yield.



Scheme 2. Reagents and conditions: (a) $Ph_3P{=}CHCO_2Et$, toluene, reflux, 6 h, 86%; (b) (i) 10% Pd/C, H_2 (60 *psi*), EtOAc, rt, 1 h; (ii) $LiAlH_4$, THF, rt to reflux, 12 h, (81% for two steps). (c) IBX, DMSO: THF (1:1), 0 °C-rt, 6 h 84%; (d) 1,3-Propanedithiol, cat. $BF_3.Et_2O$, CH_2Cl_2, 0 ^oC, 12 h, 88%.

With substantial amount of both the fragments in hand, the coupling of epoxide **8a** and dithiane **13** was accomplished using Linchpin coupling (Scheme 3). Towards this end, the generation of lithiated anion of dithiane **13** was carried out using *n*-BuLi in THF at -78 ^oC, followed by quenching with epoxide **8a** which eventually resulted in the coupled product **14**. One-pot deprotection of methyl and TBS group using BBr_3 followed by reaction with $PhI(O_2CCF_3)_2$ in Me_2CO/H_2O (9:1 v/v)[8] at room temperature furnished a mixture of aculeatins A **1** and B **2** in 2.93 :1 ratio which was easily separated by silica gel column chromatography.

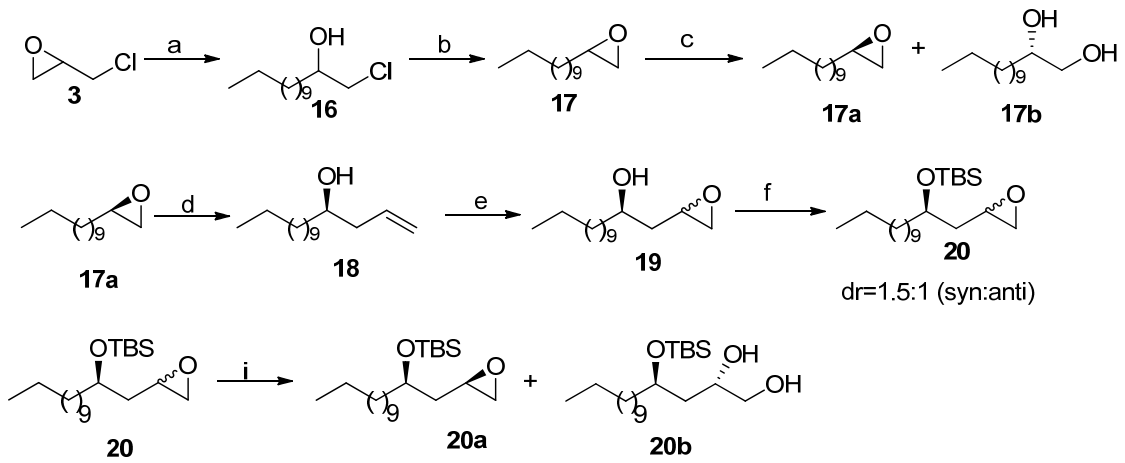


Scheme 3. Reagents and conditions: (a) *n*-BuLi, HMPA, THF, -78 ^{o}C, 1 h, 87%; (b) BBr_3, CH_2Cl_2, rt to -78 ^{o}C, 2 h; (c) $PhI(OOCCF_3)_2$, Me_2CO/H_2O (9:1), rt, 4 h, 64% overall (2 steps), 2.93:1 mixture of aculeatins A **1** and B **2**.

Section B: Synthesis of Aculeatin F and *epi*-F

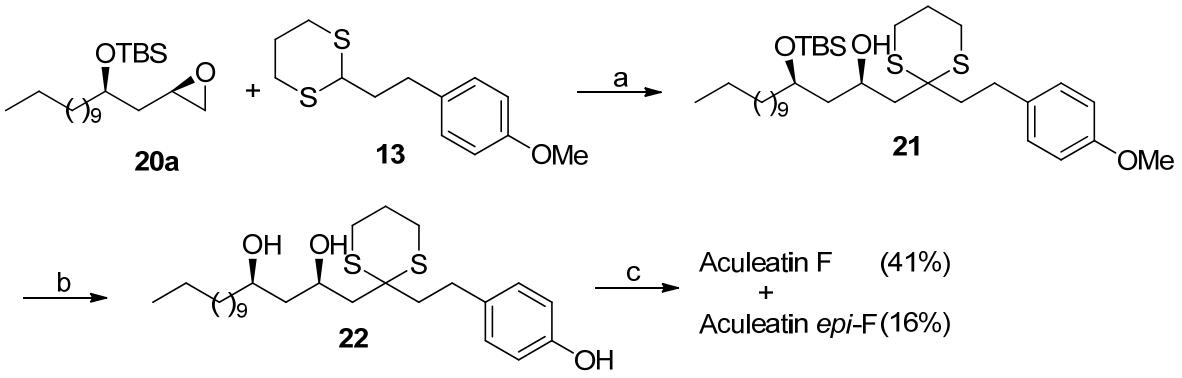
In 2007, Kinghorn *et al*[9]. reported the isolation of aculeatins A and B related metabolites aculeatols A–D; the C (9) hydroxylated aculeatins A or B having either the same or two carbon truncated side chains. Subsequently, the isolation of truncated aculeatins A and D, named, respectively as aculeatins F and E, were reported by the same group. As mentioned in the preceding section we have extended the protocol developed for the synthesis of aculeatins A **1** and B **2.**

Aculeatins F and *epi*-F could be synthesised by the Linchpin coupling of epoxide **20a** and dithiane **13**.



Scheme 4. Reagents and conditions: (a) Decylmagnesium bromide, THF, CuI, -40 ^{o}C, 12 h, 83%; (b) KOH, CH_2Cl_2, rt, 1 h, 91%; (c) *R,R*-salen-Co-(OAc) (0.5 mol %), dist. H_2O (0.55 equiv), 0 ^{o}C, 14 h, (45% for **4a**, 44% for **4b**); (d) Vinylmagnesium bromide, THF, CuI, -20 ^{o}C, 12 h, 88%; (e) *m*-CPBA, CH_2Cl_2, 0 ^{o}C to rt, 10 h, 95%; (f) TBDMSCl, imidazole, CH_2Cl_2, 0 ^{o}C to rt, 3 h, 91%.

As depicted in scheme 4, enantiopure epoxide **20a** was prepared using the similar synthetic sequence as shown for the epoxide **8a** in scheme 1. With sufficient amount of both the fragments in hand the coupling of epoxide **20a** and previously reported dithiane **13** was accomplished using Linchpin coupling (Scheme 5). Towards this end, the generation of lithiated anion of dithiane was carried out using *n*-BuLi in THF at -78 ^{o}C, followed by quenching with epoxide **20a** which eventually resulted in the coupled product **21**. One-pot deprotection of methyl and TBS group using BBr_3 followed by reaction with $PhI(O_2CCF_3)_2$ in Me_2CO/H_2O (9:1 v/v)[9] at room temperature furnished a mixture of aculeatins F and epi-F in 2.56 :1 ratio which was easily separated by silica gel column chromatography



Scheme 5. Reagents and conditions: (a) *n*-BuLi, HMPA, THF, -78 ^{o}C, 1 h, 86%; (b) BBr_3, CH_2Cl_2, rt to -78 ^{o}C, 2 h; (c) $PhI(OOCCF_3)_2$, Me_2CO/H_2O (9:1), rt, 4 h, 57% overall (2 steps), 2.56:1 mixture of aculeatins F and epi-F.

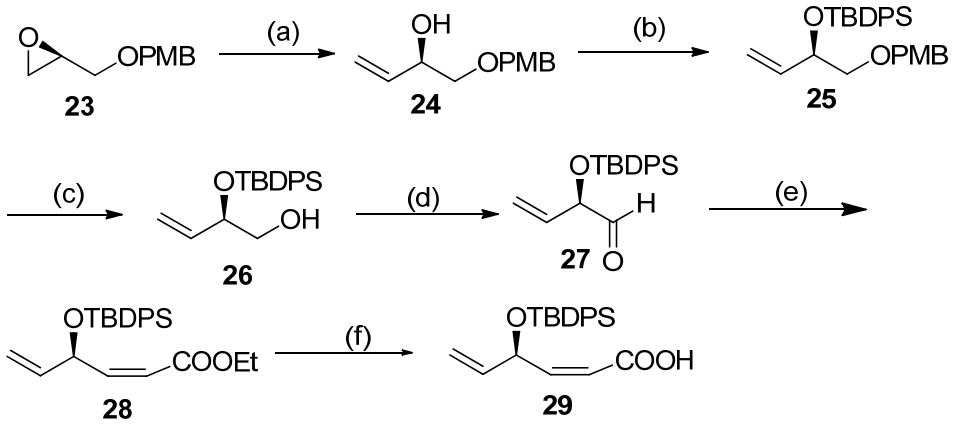
Section C: Studies towards the Synthesis of Modiolide B

Modiolides A and B were isolated[10] from the cultured broth of the fungus *Paraphaeosphaeria* sp., which was separated from a marine horse mussel. Modiolides A and B showed antibacterial activity against *Micrococcus luteus* (MIC value 16.7 *i*g/mL) and antifungal activity against *Neurospora crassa* (MIC value 33.3 *i*g/mL).

Total synthesis of Modiolide B **33** has been attempted using ring-closing metathesis and Yamaguchi coupling as key steps. The stereogenic centres were generated by means of iterative hydrolytic kinetic resolution (HKR) of racemic epoxides.

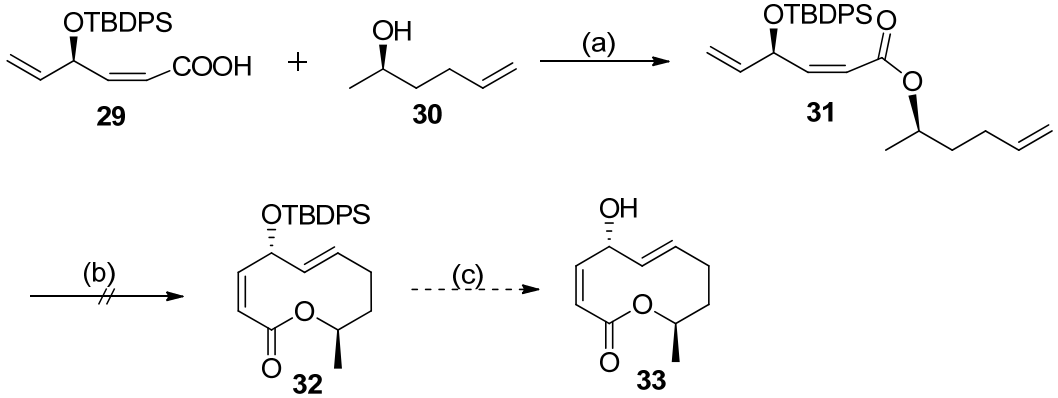
As depicted in scheme 6, synthesis of acid fragment **29** commenced from commercially available *R*-glycidol which on hydroxy group protection with PMBCl followed by ring-opening of epoxide

with dimethylsulfonium methylide gave the allylic alcohol **24** in excellent yield. Subsequent hydroxyl group protection as its TBDPS ether followed by PMB removal furnished the alcohol **26**, which on oxidation using IBX followed by Ando wittig reaction furnished α, β-unsatured ester **28** (97:3, Z:E). Subsequent hydrolysis using LiOH afforded the acid fragment **29** in 64% yield.



Scheme 6. Reagents and conditions: (a) $(CH_3)_3SI$, n-BuLi, THF, 4h, 73%; (b) TBDPSCl, Imidazole, CH_2Cl_2, 14h, 74%; (c) DDQ, CH_2Cl_2:H_2O (9:1), rt, 86%; (d) IBX, DMSO:THF (1:1), 84%; (e) $(CH_3\text{-}C_6H_4O)_2P(O)CH_2CO_2Et$, NaH, -78 ^oC, THF, 5 h, 72%; (f) LiOH, MeOH, H_2O, rt, 10h, 64%.

With substantial amount of acid fragment in hand, the coupling of acid **29** and commercially available alcohol **30** was achieved by using the intermolecular Yamaguchi coupling to afford the diene ester **31.**



Scheme 7. Reagents and conditions: (a) 2,4,6–Trichlorobenzoyl chloride, Et_3N, THF, rt then DMAP, tolune, reflux, 73%; (b) Grubb's catalyst II, CH_2Cl_2, reflux, 12h.

To obtain macrolactone **32**, the bis olefin moiety was subjected to ring-closing metathesis (RCM) using Grubb´s II generation catalyst in dichloromethane, however it provided the unidentified products. We tried several reaction conditions by changing the solvents like toluene,

dichloroethane with increase in the reaction timings and loading the catalyst at different concentrations, but we failed to get the desired product. Based on the literature survey on RCM for constructing 10-membered macrolides, presumably the bulkiness of TBDPS group and its spatial arrangement around the olefinic bonds did not allow the cyclization. Due to the failure to obtain lactone through RCM protocol, alternate synthetic strategy is underway in our laboratory to obtain lactone under Yamaguchi lactonization conditions.

Chapter 3:

Section A: Organocatalytic Enantioselective Approach to the Synthesis of Verbalactone

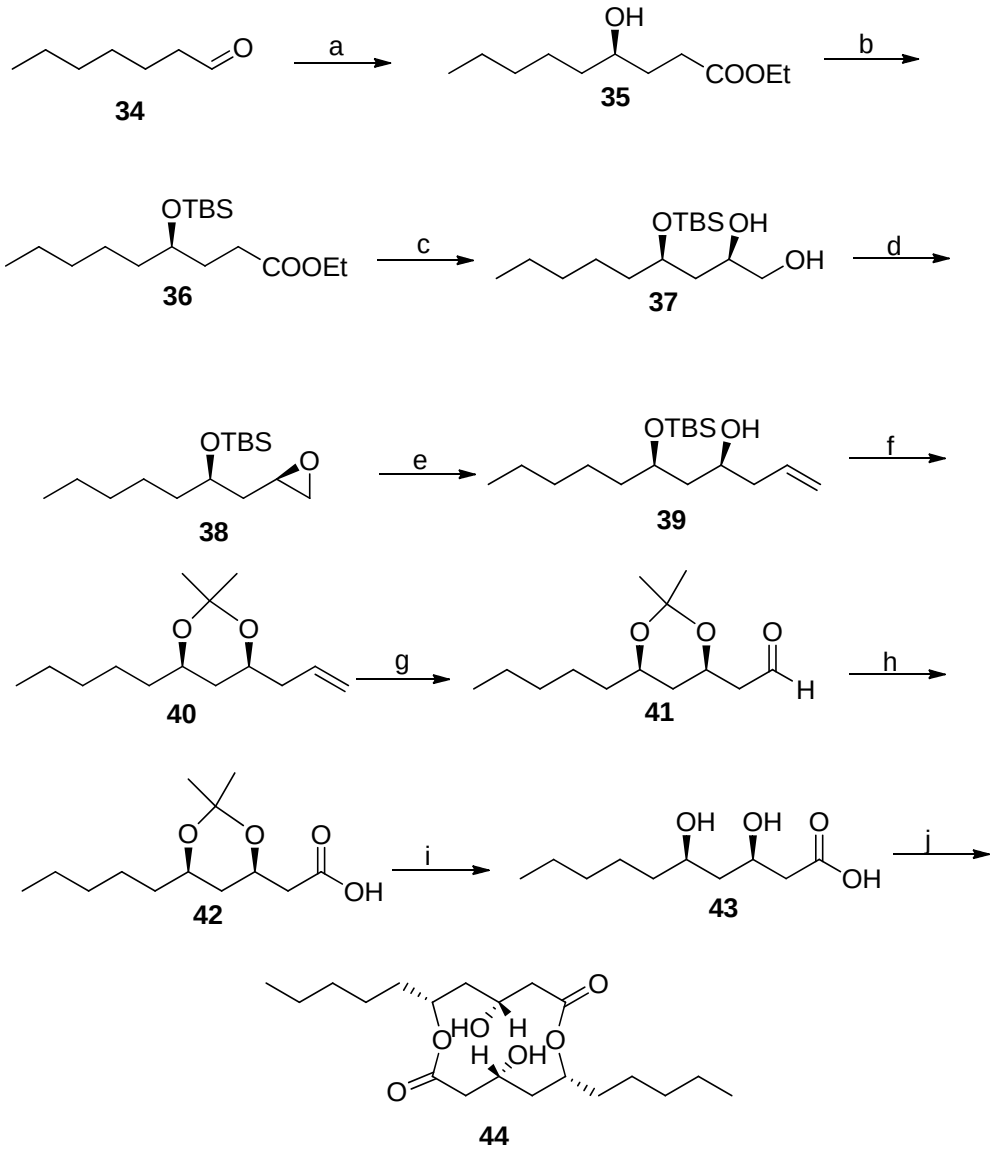
Verbalactone was isolated by Mitaku and co-workers in 2001 from the roots of *Verbascum undulactum*.[11] Verbalactone displays the interesting antibacterial activity against various *Gram*-positive and *Gram*-negative bacteria. Verbalactone is a novel macrocyclic symmetrical dimeric lactone.

As depicted in scheme 8, synthesis of verbalactone starts with heptanal **34** which was subjected to sequential α-aminoxylation using nitrosobenzene as the oxygen source and L-proline as a catalyst and subsequent HWE olefination using triethyl phosphonoacetate followed by reductive hydrogenation using a catalytic amount of Pd/C to furnish the *γ*-hydroxy ester **35** in 68% yield and 97% ee.[12]

The free hydroxyl group of *γ*-hydroxy ester **35** was protected as TBS ether using TBSCl to furnish compound **36** in 94% yield. With protected *γ*-hydroxy ester **36** in hand, the stage was set for introduction of another hydroxyl group at 3-position. Thus DIBAL- H reduction of ester **36** furnished the corresponding aldehyde which was then subjected to α-aminoxylation using L-proline as a catalyst followed by $NaBH_4$ reduction and subsequent Pd/C reduction to give the *syn*-diol **37** in 78% yield. The ^{1}H NMR analysis revealed the diastereomeric purity (de) of **37** to be >95%. The primary hydroxyl group of **37** was converted into tosyl derivative using TsCl, Et_3N and catalytic amount of *n*-Bu_2SnO which on subsequent base treatment furnished the epoxide **38**. Epoxide **38** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol **39**. Deprotection of TBS group and subsequent treatment of resulting 1,3-syn diol with 2,2-dimethoxy propane in the presence of catalytic amount of PPTS gave the isopropylidene derivative **40**. Dihydroxylation of **40** followed by oxidative cleavage using silica

supported $NaIO_4$ gave aldehyde **41** which on subsequent oxidation resulted in the formation of acid **42** in good yield. Deprotection of the isopropylidene group was achieved with cat. CSA (5 mol %) in methanol to provide the (3*R*,5*R*)-3,5-dihydroxydecanoic acid **43**.

The pH during the deprotection of **42** was crucial and had to be carefully controlled as the



Scheme 8. Reagents and conditions (a) (i) nitrosobenzene, L-proline, DMSO, HWE salt, DBU, LiCl,CH_3CN; (ii) H_2/Pd-C,EtOAc, 68% (over two steps); (b) TBSCl, imidazole, DCM, 14 h, 94%; (c) (i) DIBAL-H, DCM,-78^oC; (ii) L-proline, nitrosobenzene, DMSO; (ii) $NaBH_4$, MeOH; (iii) H_2/Pd-C, EtOAc 78%; (d) (i) TsCl, Bu_2SnO, Et_3N; (ii) K_2CO_3, MeOH,room temp, 82%; (e) Vinylmagnesium bromide, THF, CuI, -20 ^oC, 12 h, 89%; (f) (i) TBAF, THF; (ii) 2,2–dimethoxyproapane, PPTS, DCM, 0^oC, 92%; (g) (i) 0.1M OsO_4 (0.4 mol%), K_2CO_3, $K_3Fe(CN)_6$, t-BuOH/H_2O

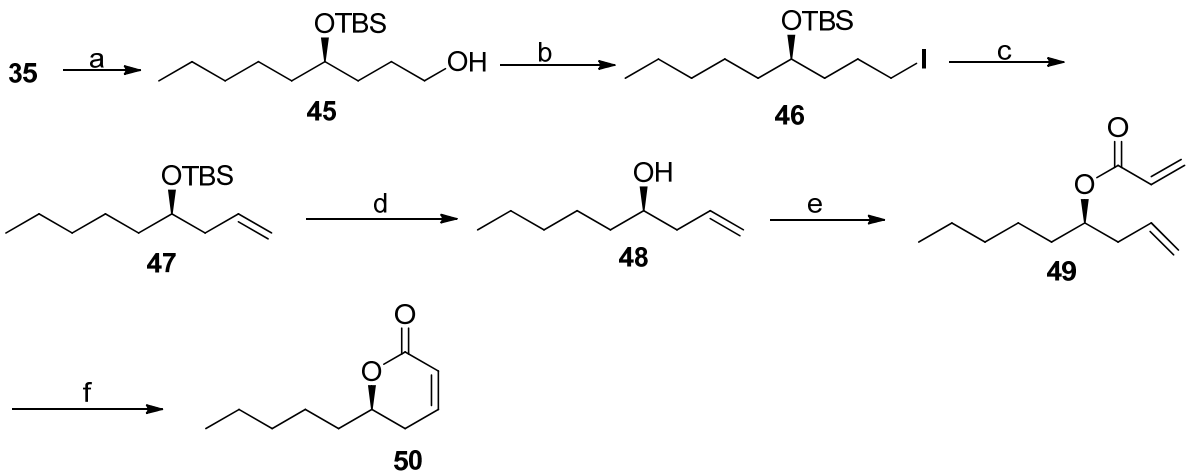
1:1, 0°C, 24 h; (ii) Silica supported $NaIO_4$, DCM, 1 h, rt, 82% (over two steps); (h) $NaClO_2$, $NaH_2PO_4.2H_2O$, *t*-BuOH:H_2O (3:1), 0°C-rt, 3 h, 96%; (i) camphorsulfonic acid , MeOH, rt, 1 h, 80%; (j) 2,4,6–trichlorobenzoyl chloride, Et_3N, THF, rt then DMAP, tolune, reflux, 53%.

formation of the monomeric lactone was observed in previous reports at higher acidic pH. Thus, a citric acid-sodium hydroxide buffer solution (pH = 6) was used during the work-up.[12] The compound **43** was found to be unstable as on standing for longer time, lactonization to form compound monomeric lactone was the major pathway. Consequently acid **43** without any further purification was subjected to Yamaguchi macrolactonization to afford verbalactone **44** in 53% yield.

Section B: Organocatalytic route to the Synthesis of (*R*)- Massoialactone

Massoialactone[13, 14] was isolated for the first time in 1937 by Abe[15] from the bark of *Cryptocarya massoia*. It is skin irritant and produces systolic standstill in frog heart muscle. This lactone has also been isolated from cane molasses[16] and jasmine blossoms[17] as a flavor substance. In 1968 it was isolated from the secretion of two species of formicine ants of the genus *Componotus* collected in western Australia.

Towards the synthesis of massoialactone **50**, TBS protected *γ*-hydroxy ester **35** was subjected to

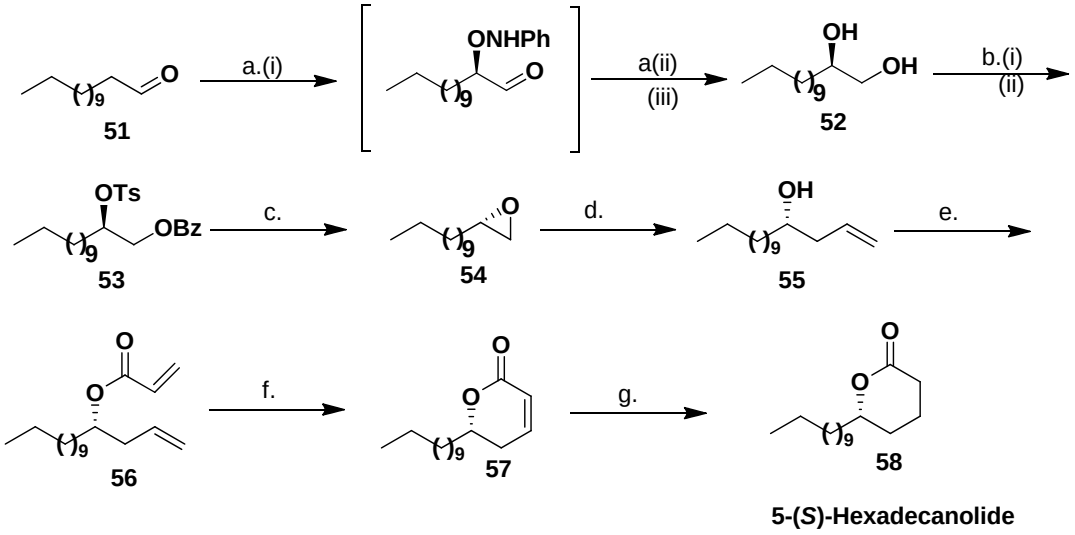


Scheme 8. Reagents and conditions: (a) DIBAL-H, DCM, -78°C, 2h, 83%; (b) TPP, imidazole, iodine, rt, 2 h, 72%; (c) 1 N KtBD, benzene, 30 min., rt, 69%; (d) TBAF, THF, 2h, rt, 88%; (e) Acryloyl chloride, Et_3N, CH_2Cl_2, 0°C, 6 h, 82%; (f) $(PCy_3)_2$ $Ru(Cl)_2$=CH–Ph (20 mol %), CH_2Cl_2, $Ti(O\text{-}i\text{-}Pr)_4$, reflux, overnight, 86%.

DIBAL- H reduction to furnish the corresponding alcohol **45** in 83% yield **(**Scheme 8). Alcohol **45** was converted to the iodo derivative **46** which on reaction with KtBD[18] in benzene afforded TBS protected homoallylic alcohol **47** in 69% yield. TBS deprotection followed by esterification of resultant alcohol with acryloyl chloride in presence of triethylamine gave **49** in 82% yield. Subsequent ring-closing metathesis of **49** under reflux in high dilution condition using first generation Grubbs's catalyst and catalytic amount of Ti(O-*i*-Pr)$_4$ provided (*R*)-massoialactone in good yield.

Section C: Synthesis of insect pheromone, 5-(*S*)-Hexadecanolide and its enantiomer

(S)-5-Hexadecanolide (**58**), a natural pheromone was isolated from the mandibular glands of the oriental hornet *Vespa* orientals.[19] It has six membered lactone in the structure and its unsaturated analog (6-substituted 5,6-dihydro-2*H*-pyran-2-one) **57** is the key synthon for several biologically important molecules. Various methods for the synthesis of *(S)*-5-hexadecanolide (**58**) and its



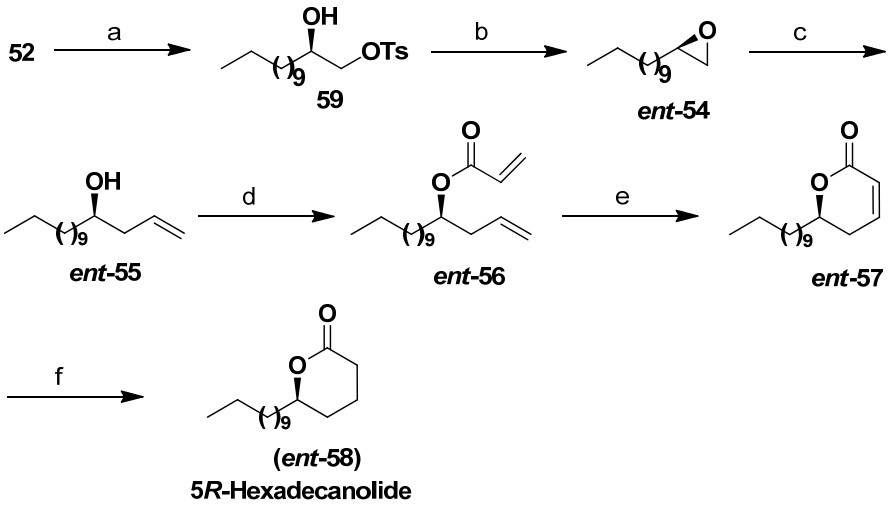
***Scheme 9. Reagents and conditions*:** (a) (i) L-proline, DMSO, Nitrosobenzene; (ii) $NaBH_4$, MeOH, 2h ;(iii) H_2/Pd-C, EtOAc , 60 psi, 6 h, 72% (over three steps); (b)(i) Benzoyl Chloride, Et_3N, CH_2Cl_2, 0^{o}C, 2 h; (ii) TsCl, Et_3N, CH_2Cl_2, rt, 8 h, 84% (over two steps); (c) K_2CO_3, MeOH, rt, 3 h, 81%; (d) Vinylmagnesium bromide, THF, CuI, -20 ^{o}C, 5 h, 82%; (e) Acryloyl Chloride, Et_3N, DCM, 2 h, cat. DMAP, 86%; (f) Grubb's I gen. Cat.,CH_2Cl_2, 12 h, reflux, 80%; (g) Pd/C, H_2, balloon press., 4 h, 84%.

enantiomer have been reported in literature. As shown in Scheme 9, the synthesis of target molecule started from aldehyde **51** which was subjected to α-aminoxylation using L- proline and

subsequent in situ $NaBH_4$ reduction followed by Pd/C reduction to furnish the enantiomerically pure diol **52** in 72% yield. Subsequent primary hydroxy group of diol **52** as its benzoyl ether followed by secondary hydroxyl group protection as tosyl afforded **53** in 84% yield over two steps. Base treatment resulted into epoxide **54** by intramolecular nucleophilic displacement of tosyl group. Epoxide **54** was opened with vinylmagnesium bromide to give the homoallylic alcohol **55** in excellent yield.

The alcohol **55** was esterified using acryloyl chloride in the presence of triethyl amine in dry CH_2Cl_2 to afford ester **56**. Ring closing metathesis of **56** using Grubbs' I'st generation catalyst afforded lactone **57** which was hydrogenated using Pd/C to furnish the hexadecanolide **58**.

Towards the synthesis of 5*R*-hexadecanolide (***ent*-58**), the primary hydroxyl of diol **52** was converted into its tosyl derivative **59**. Subsequent base treatment furnished the desired epoxide ***ent*-54.**



***Scheme 10. Reagents and conditions*:** (a) TsCl, Et_3N, Bu_2SnO,CH_2Cl_2, rt, 4 h, 85%; (b) K_2CO_3, MeOH, rt, 3h, 86%; (c) Vinylmagnesium bromide, THF, CuI, -20 ^oC, 10 h, 86%; (d) Acryloyl Chloride, Et_3N, DCM, 2 h, cat. DMAP, 88%; (e) Grubb's I gen. Cat.,CH_2Cl_2, 12 h, reflux, 78%; (f) Pd/C, H_2, balloon press., 4 h, 89%.

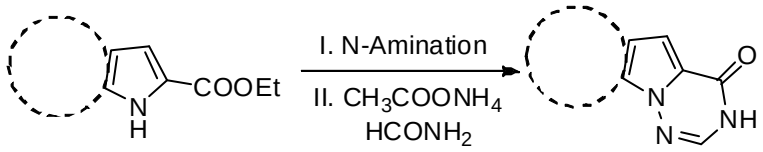
A similar sequence of reaction as described in scheme 9 was followed which eventually led to the formation of the target molecule (***ent-58***) (Scheme-10).

Chapter 4:

Section A: Novel application of Leuckart Reaction for the synthesis of [1,2,4]Triazino[1,6-a]indol-4(3*H*)-one and pyrrolo[2,1-*f*][1,2,4]Triazine-4(3*H*)-one

The pyrrolo [2,1-*f*][1,2,4]triazine nucleus was identified as a novel kinase inhibitor[20] template which effectively mimics the well-known quinazoline kinase inhibitor scaffold. In the development of synthetic program directed towards the preparation of various fused nitrogen ring system derivatives, a number of pyrrole and indole triazines were synthesized. A very short and efficient route for the synthesis of pyrrole triazinones and indole triazinones has been accomplished here using Leuckart reaction conditions.

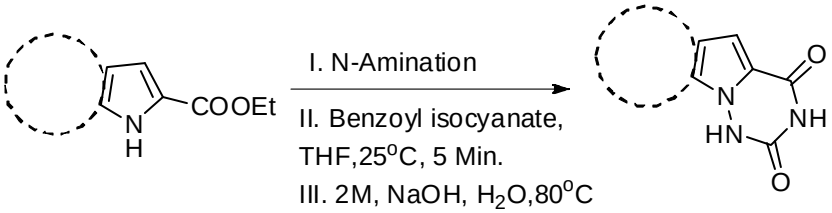
N-Amination of various commercially available pyrrole-2-carboxylates and indole-2-carboxylates is carried out using mono chloramine. N-Amino pyrrole-2-carboxylate and N-amino-indole-2-carboxylates were heated at 140^{o}C under nitrogen atmosphere in di methylformamide and ammonium formate to give various pyrrole and indole triazines.



Section B: Studies towards synthesis of [1,2,4]Triazino[1,6-a]indole-2,4(1*H*,3*H*)-dione and Pyrrolo[1,2-*f*][1,2,4]Triazine-2,4(1*H*,3*H*)-dione.

A general method for the synthesis of [1,2,4]triazino[1,6-a]indole-2,4(1*H*,3*H*)-dione and pyrrolo[2,1-*f*][1,2,4]triazine-2,4(1*H*,3*H*)-diones was developed, Alcohols and phenols readily attack isocyanates to give carbamates. Similarly, amines give ureas which under basic condition cyclise to give triazino-diones.[21]

N-Amino-pyrrole-2-carboxylate and N-Amino-indole-2-carboxylates were treated with benzoyl isocyante at room temperature to give carbamates which on reation with 2M solution of NaOH furnished [1,2,4]triazino[1,6-a]indole-2,4(1*H*,3*H*)-dione and pyrrolo[2,1-*f*][1,2,4]triazine-2,4(1*H*,3*H*)- diones.



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Chapter I

Chapter I

Introduction to Jacobsen's Hydrolytic Kinetic Resolution, Proline-Catalyzed Reactions and Ring Closing Metathesis (RCM)

HYDROLYTIC KINETIC RESOLUTION (HKR)

Introduction

Enormous advances have been made over the past several years in asymmetric synthesis, with particular emphasis having been placed on the development of enantioselective catalytic reactions.[1] Different factors influence the practicality of an asymmetric reaction.[2] A list of the features that would describe the ideal enantioselective transformation is necessarily subjective, but it could include:

· Products are obtained in quantitative yield.

· Reaction provides product in 100% enantiomeric excess (ee).

· Starting materials are inexpensive.

· Reaction times are short.

· Large amounts of product can be obtained with available glassware/equipment (high volumetric throughput).

· The chiral catalyst, reagent, or auxiliary is inexpensive and available, and does not contribute to the overall cost.

· Products are easily isolated, with little-or-no purification necessary.

· There is minimal generation of byproducts and waste.

· The reaction can be applied reliably and reproducibly on any scale.

· The reaction displays broad substrate scope, including high functional group compatibility.

· There is no better way to make the product in question.

Arguably no reactions discovered to date meet all of these criteria. To the extent that no enantioselective process is perfect, it is interesting to compare asymmetric reactions to the best methods for synthesizing the corresponding products in racemic

form. In a few cases, e. g., for the laboratory synthesis of 1,2-diols, epoxy alcohols, and certain hydrogenation products, asymmetric catalytic methodologies do in fact exist that make it as easy to prepare highly enantio-enriched materials as it is to prepare racemic mixtures. However, in a far greater number of cases, it is still much easier and less expensive to access racemates. As a result, despite what they might lack in "elegance", resolution strategies must always be evaluated carefully against any asymmetric process.[3]

Resolutions fall broadly into three classes. Classical resolutions involve the use of a stoichiometric amount of a chiral resolving agent.[4] The resolving agent is associated to the substrate, either covalently or non-covalently, to generate a pair of diastereomers. The diastereomers are separated and, through a separate chemical transformation, the substrate is released from the resolving agent. This approach has proven to be especially useful if salt formation is straightforward, as in the case of amines and carboxylic acids.[5] Chiral chromatography generally relies on the use of a chiral stationary phase to resolve enantiomers contained in a mobile phase, and in principle it can be carried out on analytical or preparative scale. In reality, the large solvent volumes, long separation times, and relatively high costs of chiral chromatography supports often limit the scale at which chromatographic separations can be carried out. Kinetic resolution involves using a chiral catalyst or reagent to promote selective reaction of one enantiomer over the other giving a mixture of enantio-enriched starting material and product, and the desired component is then isolated.[6]

As noted above, the theoretical yields for such resolutions are usually 50%. If the "undesired" resolution byproduct can be racemized or otherwise converted back to the desired enantiomer, then this can improve the yield, and therefore the practicality, of the resolution process, provided the additional cost in time and materials does not eclipse the cost of the initial resolution. In some special circumstances, it is possible to induce substrate racemization under the conditions of resolution. It then becomes possible in principle to convert essentially 100% of the racemate to the desired product. Such processes constitute a very special subclass of kinetic resolution reactions known as dynamic kinetic resolutions.

For the most part, however, racemization is not readily effected and the issue of a maximum yield of 50% holds. This applies equally to parallel kinetic resolutions, an additional subclass of kinetic resolution reactions. However, given that racemates can often be much less than half as expensive than their enantiopure counterparts, it is clearly simplistic to consider resolutions as being inherently inelegant or impractical. Indeed, the fact that resolution remains so widely used is probably the best evidence that it can in fact be the most attractive option for accessing enantioenriched compounds. Catalytic kinetic resolutions are particularly attractive, at least in principle, because of the need for only small amounts of chiral "resolving agent". However, kinetic resolution has been used very little in a commercial context compared to classical or even chromatographic resolution. The following conditions must be met in order for kinetic resolution to be practical:

· The racemate is cheap and no good enantioselective, chiral pool, or classical resolution route to the product exists.

· The catalyst is highly selective for one enantiomer and is effective at low loadings.

· The catalyst is inexpensive or it can be recycled efficiently.

· The reaction is economical and safe (i. e., inexpensive stoichiometric reagents, no undue dangers associated with the reagents, high volumetric throughput, and a minimum of waste generated).

· The resolved starting material and converted product are easily separated.

· In the ideal case, both the product and the resolved substrate are valuable and recoverable in highly enantio-enriched form.

The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products[39] but more so because the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation of new carbon-carbon bonds. Indeed, reactions of epoxides with nucleophiles, Lewis acids, radicals, reducing agents, oxidizing agents, acids, and bases have all been well documented and utilized in synthesis.[7] Further, the stereospecific manner in which epoxides generally react renders these compounds attractive chiral building blocks for asymmetric synthesis.

Since those epoxides that are produced naturally are typically complex compounds available only in limited amounts, Nature's chiral pool has not proven to be a useful direct source of optically active epoxides for use in organic synthesis. Instead, enantio-enriched epoxides have been accessed indirectly from the chiral pool via multistep procedures.[8] These, however, tend to be inherently inefficient, and the range of epoxides available by this approach is also quite limited. As a consequence, the preparation of enantio-enriched epoxides has long stood as a most significant target for asymmetric synthesis. In particular, the identification of catalytic asymmetric olefin oxidation methods has been an area of active research for several decades, and the advances made in this field have increased greatly the number of enantiomerically enriched epoxides available for use in organic synthesis.

Among available methods for the preparation of enantio-enriched epoxides, the Sharpless epoxidation reaction has arguably had the most profound impact of any asymmetric catalytic reaction discovered thus far, providing general access to highly enantio-enriched epoxyalcohols.[9] More recently, the epoxidation of unfunctionalized conjugated olefins by chiral (salen)Mn^{III} complexes has enabled the practical synthesis of certain classes of enantiomerically enriched epoxides.[10] A highly complementary strategy for epoxidation of simple olefins involving chiral dioxirane intermediates has expanded the range of chiral epoxides now accessible in enantio-enriched form to a significant extent.[11] Indirect routes to enantiopure epoxides involving asymmetric catalytic dihydroxylation or reduction reactions have also proven highly valuable in specific contexts.[12] Despite these considerable advances in asymmetric catalytic synthesis of epoxides, no general methods have been identified for the direct preparation of highly enantio-enriched 1-oxiranes, arguably the most valuable class of epoxides for organic synthesis.[13] The utility of terminal epoxides as chiral building blocks is perhaps best illustrated by the fact that the few examples for which effective catalytic approaches exist have found extensive use in asymmetric synthesis. In particular, glycidol and a number of its derivatives are available in enantiomerically enriched form using the Sharpless epoxidation technology[14] or by enzymatic kinetic resolution methods,[15] and these compounds have become widely used starting materials for target-oriented synthesis.[16] Epichlorohydrin has been rendered commercially available in bulk by microbial resolution of ((±)-2,3-dichloro-1-propanol, and it, too, has found widespread application.

Recently Jacobsen had discovered the (salen)Co complex **1** (Figure 1) catalyzed efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (Scheme 1).[17-19] This new method appeared to hold considerable promise with regard to meeting all of the criteria outlined above for kinetic resolution to be practical. Racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive olefins or aldehydes. In fact, certain racemic epoxides, such as propylene oxide, epichlorohydrin, styrene oxide, and butadiene monoepoxide, are commodity chemicals and are no more expensive than common organic solvents. Second, the ligands for catalyst **1** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts.[20] The cobalt analogues (*R*,*R*)-**1** and (*S*,*S*)-**1** proved equally accessible, and these are also now available in bulk.[21] Third, water is perhaps the ideal reagent for effecting the resolution reaction: it is inexpensive and safe, and the rate of the ring-opening reaction can be controlled simply by modulating the rate of addition of water to the epoxide-catalyst mixture.[22] Fourth, for those examples that were described in the preliminary report, highly enantio-enriched epoxides were recovered from the HKR. Finally, the HKR provided useful enantio-enriched 1,2-diols, including many that are otherwise not readily accessible using existing asymmetric dihydroxylation methods.[23]

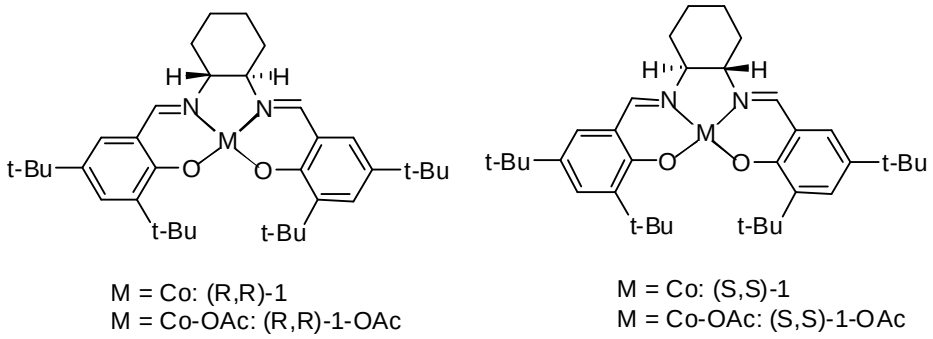
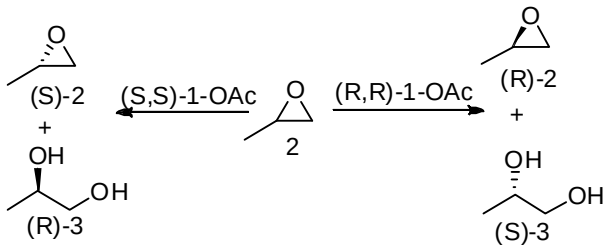


Figure 1. Jacobsen catalyst

The HKR has seen rapid adoption as the method of choice for the preparation of a variety of terminal epoxides in enantio-enriched form, and a number of applications in target oriented synthesis have been reported already.[24] In addition, the commercial

manufacture of enantio-enriched propylene oxide, epichlorohydrin, and styrene oxide using HKR methodology has been implemented, thereby reducing the cost of these



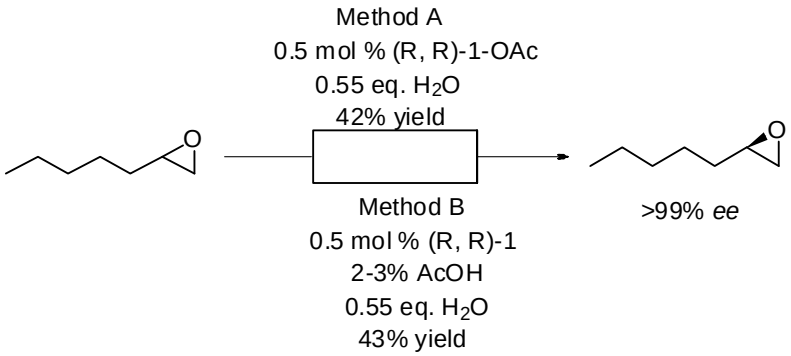
Scheme 1. Hydrolytic kinetic resolution reaction

useful chiral building blocks.[21] Jacobsen has discovered that the HKR is an extraordinarily general reaction, allowing efficient kinetic resolution of virtually any type of terminal epoxide.

Preparation of Catalyst and General Experimental Considerations

Both enantiomers of the (salen)CoII complex **1** are available commercially on research or commercial scale,[21] or they can be prepared from the commercially available ligands using $Co(OAc)_2$. The Co(II) complex **1** is catalytically inactive, however, and it must be subjected to one-electron oxidation to produce a (salen)CoIIIX complex (X) anionic ligand) prior to the HKR. This may be done conveniently by aerobic oxidation in the presence of a mild Brönsted acid. Water alone was found not to mediate the oxidation reaction, but a screen of additives revealed that acetic acid was effective and that the corresponding Co(III) precatalyst **1**.OAc is convenient for use in HKR reactions both in terms of its preparation and reactivity (eq 1). Two useful methods for the generation of complex **1**.OAc have been developed. Method A involves isolation of **1**.OAc as a crude solid prior to the HKR. The Co(II) complex **1** is dissolved in toluene to generate a ca. 1 M solution, and acetic acid (2 equiv) is added. The resulting solution is stirred open to air at room temperature for 30 min, during which time the color of the mixture changes from orange to dark brown. All volatile materials are removed in vacuo, affording **1**.OAc as a brown solid residue that can be used without further purification. Method B involves in situ generation of **1**.OAc under HKR conditions by suspension of the Co(II) complex **1** in epoxide or epoxide/solvent and addition of HOAc under an aerobic

atmosphere. Catalyst obtained by both methods was examined for each of the epoxides described in this study. For certain substrates such as 1-hexene oxide, catalyst prepared by either method leads to essentially identical results. In these situations, in situ catalyst generation (method B) is preferable since the procedure avoids an extra solvent removal step. On the other hand, catalyst prepared by method A was found to be more effective with less reactive substrates (vide infra) and was applicable to all substrates examined. Therefore, if HKR did not afford epoxide in >99% ee with catalyst prepared by method B after optimization of solvent and catalyst loading, then catalyst prepared by method A was employed.



Scheme 2.

Aside from the method of generation of **1**.OAc, the only reaction parameters in the HKR that required optimization for individual substrates were catalyst loading and choice of solvent. With few exceptions, epoxide of >99% ee could be obtained using 0.55 equiv of water relative to racemate. Relatively small epoxides with some degree of water solubility could be resolved effectively without added solvent. However, the HKR of more lipophilic substrates did benefit from inclusion of a water miscible organic solvent such as tetrahydrofuran (THF), 2-propanol, or 1,2-hexanediol. In general, one volume of solvent relative to racemic epoxides was sufficient to allow efficient HKR. Catalyst loadings of 0.5 mol % or lower relative to racemic epoxide were effective for many substrates, but epoxides bearing sterically hindered or unsaturated substituents often required more catalyst (up to 2 mol %) to attain complete resolution. Reactions were initiated at 0 °C and then allowed to warm to room temperature with continued stirring for 12- 18 h.

[(*R*,*R*)-*N*,*N*'-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) ((*R*,*R*)-1).

A solution of cobalt(II) acetate tetrahydrate (5.98 g, 24.0 mmol) in MeOH (80 mL was added to a solution of ligand [(*R*,*R*)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine] (10.9 g, 20.0 mmol) in CH_2Cl_2 (80 mL) via cannula under an atmosphere of N_2 with careful exclusion of air. A brick-red solid began to precipitate before addition was complete. The sides of the reaction flask were rinsed with MeOH (20 mL), and the mixture was allowed to stir for 15 min at room temperature and then 30 min at 0 °C. Precipitated solids were isolated by vacuum filtration and rinsed with cold (0 °C) MeOH (2 x 75 mL). The red solid was collected and dried in vacuo to yield [(*R*,*R*)-*N*,*N*'-bis(3,5-di-*tert*butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) ((*R*,*R*)-**1**) (11.6 g, 19.2 mmol, 96%).

Representative Procedures for the HKR of Terminal Epoxides

(a) Method A. (*S*)-Propylene Oxide. A 100 mL flask equipped with a stir bar was charged with (*S*,*S*)-**1** (242 mg, 400 μmol, 0.002 equiv). The catalyst was dissolved in 5 mL of PhMe and treated with AcOH (240 μL, 4.2 mmol). The solution was allowed to stir at room temperature open to air for 30 min over which time the color changed from orange-red to a dark brown. The solution was concentrated in vacuo to leave a crude brown solid. The resulting catalyst residue was dissolved in propylene oxide (14.0 mL, 11.6 g, 200 mmol) at room temperature, the reaction flask was cooled to 0 °C, and H_2O (1.98 mL, 110 mmol, 0.55 equiv) was added dropwise over 5 min. The reaction was allowed to warm to room temperature and stir for 14 h at which time (*S*)-propylene oxide (5.35 g, 92.1 mmol, 46%) was isolated by distillation from the reaction mixture at atmospheric pressure and 36 °C. Propylene diol was removed by vacuum distillation (65 °C, 0.25 Torr). The catalyst was recovered by suspension in MeOH and collection by vacuum filtration. The ee of the propylene oxide was determined to be 99.7% by chiral GC analysis of the 1-azido-2-trimethylsiloxypropane derivative obtained by opening the epoxide with $TMSN_3$ (Cyclodex-B, 55 °C, isothermal, *t*R(minor)) 12.29 min, *t*R(major)) 12.57 min).

(b) Method B. (*R*)-1,2-Epoxy-5-hexene. A 100 mL flask equipped with a stir bar was charged with (*R*,*R*)-**1** (302 mg, 500 μmol, 0.005 equiv). The catalyst was treated with

((±)-1,2-epoxy-5-hexene (11.3 mL, 9.81 g, 100 mmol), AcOH (120 μL, 2.1 mmol, 0.02 equiv), and 1 mL of THF. The reaction flask was cooled to 0 °C, and H_2O (1.0 mL, 55 mmol, 0.55 equiv) was added in one portion. The reaction was allowed to warm to room temperature and stir 16 h at which time the volatile materials were isolated by vacuum transfer at 0.25 Torr into a cooled (-78 °C) receiving flask. The recovered epoxide was filtered through a silica plug to remove residual water, and the THF was removed by rotary evaporation to yield (*R*)-1,2-epoxy-5-hexene (4.23 g, 43.1 mmol). The diol was distilled under reduced pressure (56 °C, 0.25 Torr). The catalyst was recovered by suspension in MeOH and vacuum filtration. The ee of the recovered epoxide was determined to be 99.5% by chiral GC analysis of the 1-azido-2-trimethylsiloxy-5-hexene derivative obtained by opening the epoxide with $TMSN_3$ (Cyclodex-B, 70 °C, isothermal, *t*R(minor), 38.00 min, *t*R(major), 39.06 min).

Catalyst Recycling

The possibility of recycling a catalyst has obvious practical appeal, particularly in cases where the catalyst is precious due to cost or limited availability. Catalyst **1** is prepared in bulk from low-cost components, and as a result it is quite inexpensive relative to most chiral catalysts. On the other hand, the HKR employs reactants (racemic epoxide, water, minimal if any solvent) that impact the cost of the overall process to an almost negligible extent in many cases, and as a result the catalyst is a significant contributor to the material costs. Accordingly, efforts were directed toward identifying practical methods for effecting catalyst recovery and recycling. The HKR reaction of propylene oxide presents an especially straightforward scenario with respect to catalyst recovery because both the epoxide and the diol are relatively volatile and can be removed by distillation. The solid residue remaining in the reaction vessel after product separation was found to have the characteristic red-brick color of the reduced (salen)CoII complex **1**. Reoxidation to **1**.OAc with air and AcOH led to catalyst with undiminished levels of reactivity and selectivity.

Thus the HKR provides a straightforward method for the preparation of a wide assortment of terminal epoxides in highly enantio-enriched form. Given that in many cases there exist no practical alternatives for accessing the valuable chiral building blocks, it is hoped that the HKR will have a beneficial and enabling effect on the field of organic synthesis.

PROLINE CATALYZED ASYMMETRIC ORGANIC TRANSFORMATIONS

Introduction to organocatalysis

The broad utility of synthetic chiral molecules as single-enantiomer pharmaceuticals, in electronic and optical devices, as components in polymers with novel properties, and as probes of biological function, has made asymmetric catalysis a prominent area of investigation. Organocatalysis, or the use of small organic molecules to catalyse organic transformations, is a relatively new and popular field within the domain of chiral molecule (or enantioselective) synthesis. Although chemical transformations that use organic catalysts, or organocatalysts, have been documented sporadically over the past century, it was not until the late 1990s that the field of organocatalysis was 'born'.[25] It is now widely accepted that organocatalysis is one of the main branches of enantioselective synthesis (the other, previously accepted, branches being enzymatic catalysis and organometallic catalysis), and those who are involved in the synthesis of chiral molecules consider organocatalysis to be a fundamental tool in their catalysis toolbox.

This rediscovery has initiated an explosive growth of research activities in organocatalysis both in industry and in academia. The 1970s brought a milestone in the area of asymmetric organocatalysis, when two industrial groups led by Hajos and Wiechert published the first and highly enantioselective catalytic aldol reactions using simple amino acid proline as the catalyst. Organocatalysis is the catalysis of chemical transformations using a purely organic molecule, which is composed of mainly carbon, hydrogen, nitrogen, sulfur, and phosphorus, and does not contain any metals. The advent of organocatalysis brought the prospect of a complementary mode of catalysis, with the potential for savings in cost, time and energy, an easier experimental procedure, and reductions in chemical waste, which confers a huge direct benefit in the production of pharmaceutical intermediates when compared with transition metal catalysts. Organic molecules not only have ease of manipulation and a "green" advantage but also can be very efficient catalysts. Several aspects of organocatalysis will undoubtedly attract researchers' attention. Tremendous efforts

will continue to be directed towards the discovery and design of catalysts with better efficiency, new reactivities and greater turnover numbers. And in near future asymmetric organocatalysis may begin to catch up with the spectacular advancements of enantioselective transition metal catalysis.

Recently, List[26] introduced a system of classification based on the mechanism of catalysis (Figure 2). The four categories are Lewis base, Lewis acid, Bronsted base and Bronsted acid catalysis. Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle via nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Brønsted base and acid catalytic cycles are initiated via a (partial) deprotonation or protonation, respectively.

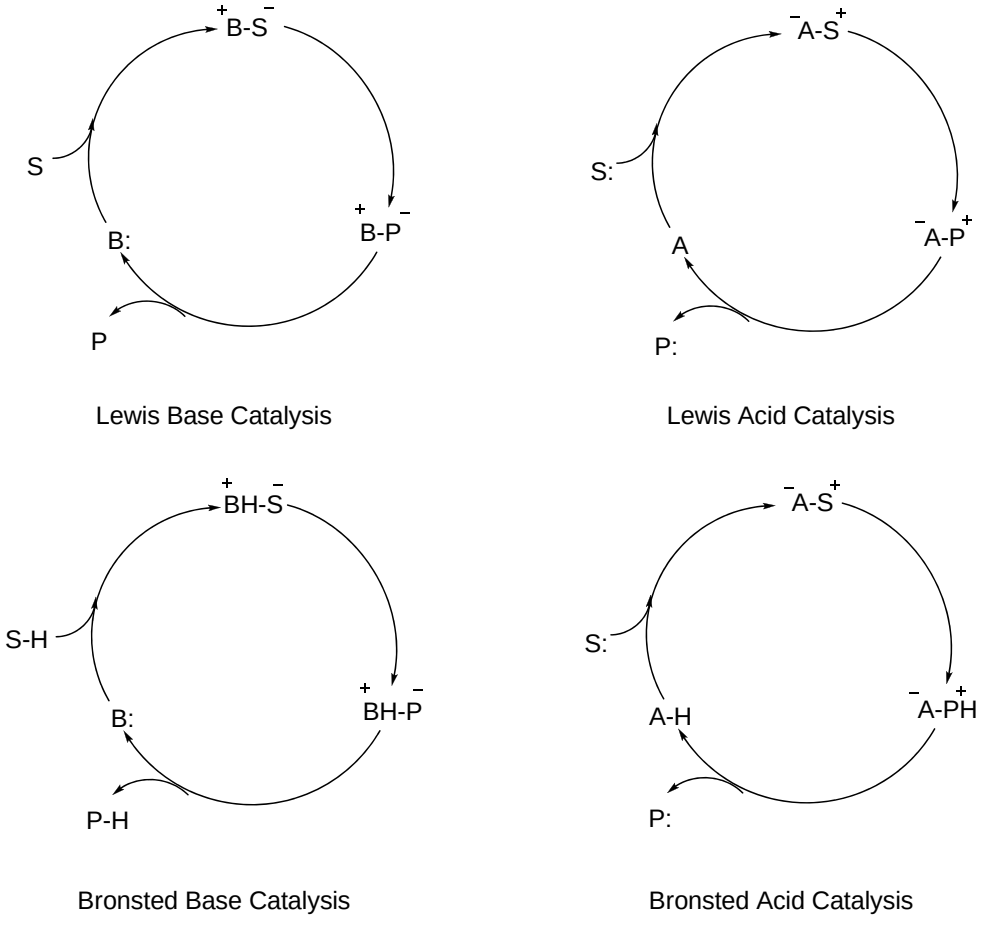


Figure 2. Organocatalytic cycles

Proline a "Universal catalyst"

Proline has been defined as a "universal catalyst" because of its high utility in variety of asymmetric organic transformations. Proline is the only natural amino acid with a secondary amine functionality, which raises the pKa value and better nucleophilicity as compared to other amino acids. It can act as a nucleophile to carbonyl groups (iminium intermediate) or Michael acceptors (enamines). It can be regarded as a bifunctional catalyst as the secondary amine acts as Lewis base and the acid group acts as Bronsted acid (Figure 3). The high stereoselectivity in the proline-catalyzed reactions is possibly due to its formation of organized transition states with many hydrogen bonding frameworks. Proline is not the only molecule to promote catalysis, but it still seems to be one of the best in the diversity of transformations.

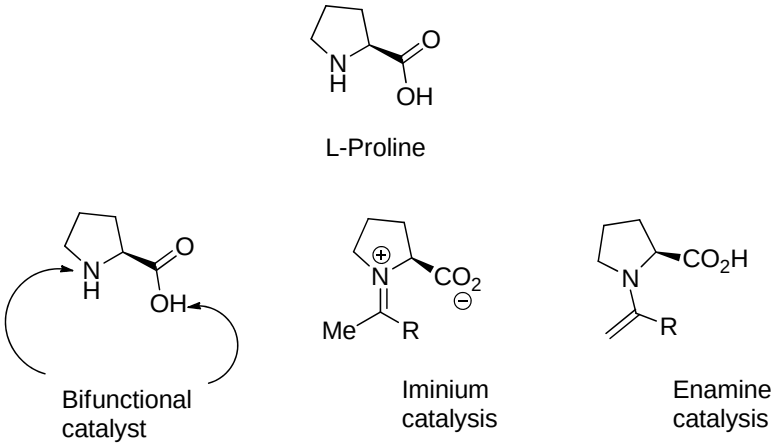


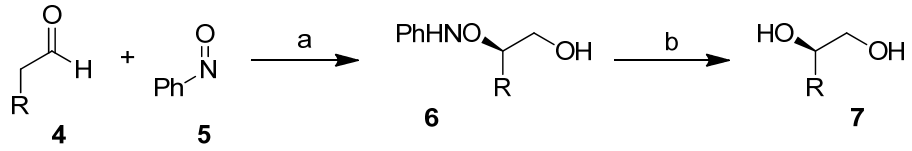
Figure 3. Modes of proline catalysis

It is known to catalyze aldol,[27] Diels-Alder,[28] Michael addition[29] and α-functionalization[30] among many other organic transformations.[31] Particularly proline-catalyzed α-aminoxylation[32] and α-amination[33] of carbonyl compounds have emerged as powerful methods because chiral building materials can be synthesized in effective manner starting from easily available materials.

Proline-catalyzed α-aminoxylation

Optically active α-hydroxyaldehydes and ketones are important intermediates in organic synthesis as they are direct precursors to 1,2-diols. Because of this utility

many methods have been developed for their preparation. The more prominent, well-established methods of enantioselective α-oxygenations include the use of Davis oxaziridine,[34a] Sharpless dihydroxylation of enol ethers,[34b] manganese–salen epoxidation of enol ethers,[34c] and Shi epoxidation of enol ethers.[34d] It is only rather recently that direct catalytic, asymmetric variants have been reported.[35] Most of these methods, however, require multiple manipulations and there is no direct method, nor catalytic asymmetric method for their synthesis from the corresponding aldehyde. Recently, proline has been found to be an excellent asymmetric catalyst for α-aminoxylation[32] of carbonyl compounds. When an aldehyde **4** without substitution at α-position was reacted with nitrosobenzene **5** in presence of L-proline in DMSO at ambient temperature, aminoxylation of the aldehyde takes place at the α-position. Aldehyde can be reduced *in situ* with sodium borohydride and the aminoxyl moiety undergoes hydrogenolysis with Pd/C, H_2 or $CuSO_4$ to give the corresponding diols **7** in very high enantioselectivities (Scheme 3).



Scheme 3. *Reaction and reagents*: (a) (i) S-proline (20 mol%), DMSO, 25 °C; (ii) $NaBH_4$, MeOH; (b) Pd/C, H_2 or 30 mol% $CuSO_4$. R = Ph, *i*-Pr, *n*-Bu, CH_2Ph etc. > 99% ee

The mechanism of the α-aminoxylation reaction is shown in figure 4. The observed enantioselectivitiy of the catalytic α-aminoxylation of aldehydes can be rationalized by invoking an enamine mechanism operating through a chair transition state where the *Si* face of an α-enamine formed from the aldehyde and L-proline approaches the less hindered oxygen atom of nitrosobenzene to provide a chiral α-aminoxyaldehyde with *R* configuration. Since proline is commercially available in both enantiopure forms, a one pot sequential catalytic α-aminoxylation of aldehydes followed by *in situ* reduction with $NaBH_4$ affords *R*- or *S*- configured 1,2-diol units (the secondary alcohol "protected" by an *O*-amino group) with excellent enantioselectivities and in good yields.

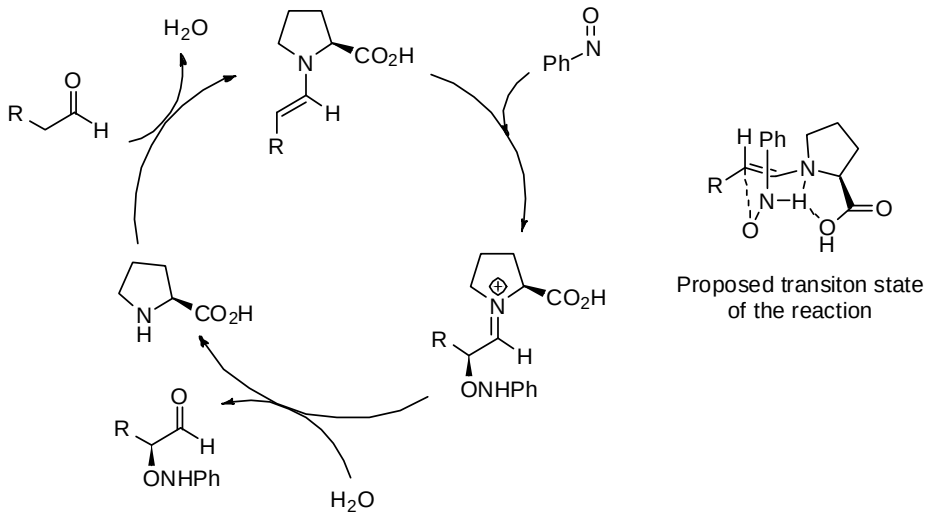
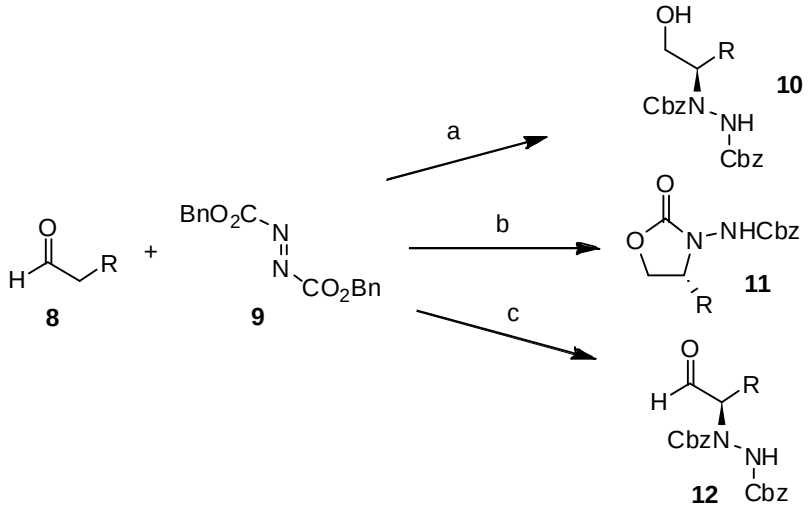


Figure 4. Proposed mechanism of the α-aminoxylation reaction

Proline-catalyzed α-amination

The importance of optically active α-amino acids, α-amino aldehydes, and α-amino alcohols, formed by asymmetric catalysis, has stimulated an enormous development in synthetic strategies, and two different catalytic, enantioselective approaches are attractive: the *C-C* and the *C-N* bond-forming reactions.



Scheme 4.*Reactions and conditions*: (a) L-proline (10 mol%), CH_3CN, 0 °C, 3 h; $NaBH_4$, EtOH; (b) L-proline (10 mol%), CH_2Cl_2, 25 °C; $NaBH_4$, MeOH; 0.5 N NaOH; (c) L-proline (10 mol%), CH_2Cl_2, 25 °C; H_2O.

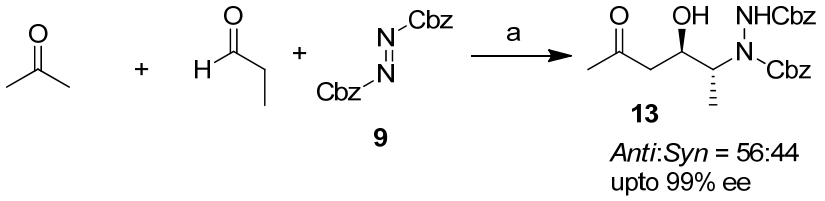
Asymmetric α-amination[33] of aldehydes using proline-catalyzed reactions represent a direct approach synthesizing chiral building blocks such as α-amino acids, α-amino aldehydes, and α-amino alcohols. The use of organocatalysis, in particular proline represents a drastic change in approach to asymmetric α-amination. Recently, both List[33a] and Jørgensen[33b] disclosed the asymmetric α-amination of aldehydes (Scheme 4) using catalytic quantities of proline. While both transition structures lead to identical products directed by the hydrogen bond from the carboxylic acid of proline, they presumably possess unique energies, so one transition state should be favored. However, the operative transition state has yet to be established.

Proline-catalyzed sequential transformations

Proline-catalyzed sequential transformations,[36] is a emerging research field in organic synthesis as synthesis of complex organic molecules could be accessible in one-pot procedure. Recently a variety of such transformations has been developed by different research groups, some of them are described below.

Sequential amination-aldol[36a]

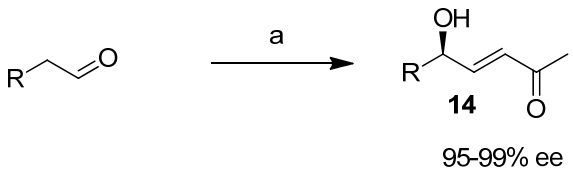
Barbas III *et al*. have developed a one-pot protocol for the synthesis of functionalized β-amino alcohols **30** from aldehydes, ketones and azodicarboxylates (Scheme 5).



Scheme 5. *Reactions and conditions*: (a) L-proline (20 mol%), CH_3CN, rt, 72 h, 80%.

Sequential aminoxylation-olefination[36b]

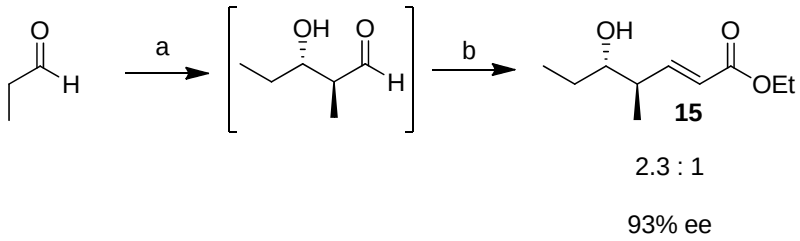
Zhong *et al*. have reported sequential asymmetric α-aminoxylation/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active *O*-amino-substituted allylic alcohols **14** in good enantioselectivities using cesium carbonate as base (Scheme 6).



Scheme 6. *Reactions and conditions*: (a) L-proline (20 mol%), nitrosobenzene (1.0 equiv.), DMSO, rt, 10-20 min then diethyl(2-oxopropyl)phosphonate, cesium carbonate (1.5 equiv.).

Sequential aldol-olefination[36c]

Cordova *et al*. have reported one-pot organocatalytic asymmetric tandem cross-aldol/Horner-Wittig-Emmons olefination for the synthesis of polyketide and carbohydrate derivatives (Scheme 7).

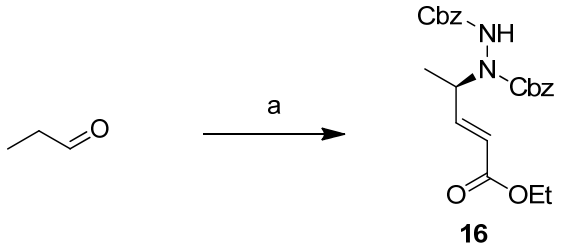


Scheme 7. *Reactions and conditions*: (a) L-proline (10 mol%), DMF; (b) Diethyl(2-oxopropyl)phosphonate, cesium carbonate (1.5 equiv.).

Apart from this transformation, Cordova *et al*. have also reported tandem Mannich olefination reaction.[36d]

Sequential α-amination-olefination[36e]

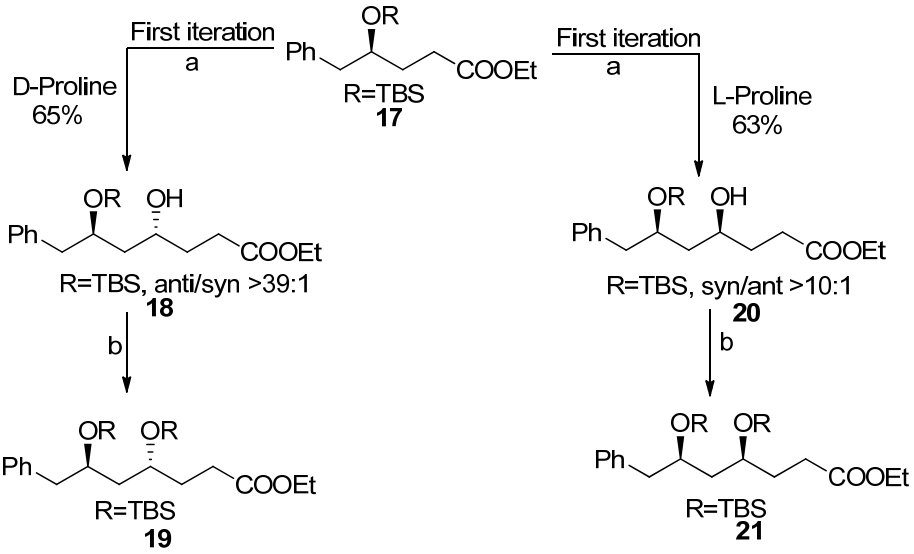
Sudalai *et al*. have reported sequential asymmetric α-amination/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active allylic amine in good enantioselectivities and yields (Scheme 8).



Scheme 8. *Reactions and conditions*: (a) L-proline (20 mol%), DBAD (1.0 equiv.), CH_3CN, rt, 10-20 min then diethyl(2-oxopropyl)phosphonate, cesium carbonate (1.5 equiv.).

An organocatalytic approach to *syn*- and *anti*-1,3-polyols[36f]

Recently, Zhong *et al*. have reported an α-aminoxylation directed tandem reaction catalyzed by proline which involves a sequential α-aminoxylation, HWE-olefination reaction at ambient temperature furnishing *O*-amino-substituted allylic alcohol from readily available achiral aldehydes. We envisioned that this reaction could give us stereocontrolled synthetic access to 1,3-polyol motifs. We have developed proline catalyzed new enantioselective approach to synthesize both syn/anti-1,3-polyols by tandem α-aminoxylation and HWE olefination of aldehyde.[36f] Our iterative strategy for the synthesis of polyols is outlined in Scheme 9.

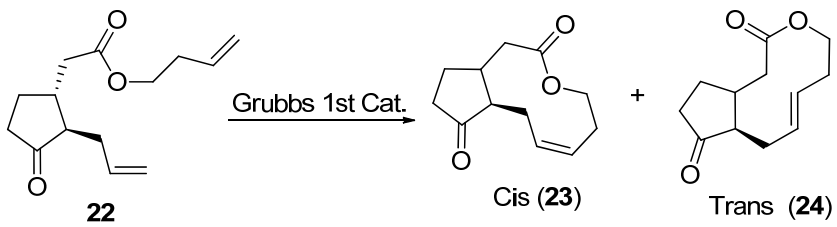


Scheme 9. *Reagents and Condition*s: (a) (i) DIBAL-H, -78 °C; (ii) Nitroso benzene, D/L Proline, DMSO, HWE salt, DBU, LiCl, CH_3CN; (iii) H_2/Pd-C, EtOAc; (b) TBSOTf, 2,6-lutidine, DCM.

Introduction

The ring closing metathesis has emerged as a powerful tool for organic synthesis and extensively employed in the construction of medium and large ring structures with multiple functionality. The efficiency of this method is demonstrated by the syntheses of a large number of natural products including ten-membered lactones.

A typical example that illustrates the efficiency as well as the limitation of RCM in this arena is a synthesis of jasmine ketolactone,[37] RCM reaction on diene with high dilution by using Grubbs first-generation catalyst to afford the targeted ten-membered lactones as a mixture of *cis* and *trans* isomers (2.5:1) in remarkable yield.



Over the past ten years, the area of olefin metathesis that has expanded most dramatically is the catalytic ring-closing metathesis (RCM).[38] RCM has developed into a versatile synthetic tool for carbon-carbon double bond construction. In particular, medium (5-8) to large (10-13 and higher) carbon or heterocyclic rings can be very effectively constructed, and thus RCM became a reliable tool for synthesis of the natural products and spurred the synthesis of even more varied structural variants.

The word metathesis is derived from Greek word meta (change) and thesis (position). Metathesis is the exchange of parts of two substances or interchange of covalent bonds between two molecules. In the generic reaction, AB + CD → AC + BD, B has changed position with C. An example is olefin metathesis. It refers to the redistribution of alkylidene moieties between two alkenes in the presence of a catalytic amount of a metal carbene. A compound with a C=C double bond, in which the strongest bond in an alkene is broken and remade. The 2005 Nobel Prize in Chemistry was awarded to Yves Chauvin, Robert H. Grubbs and Richard R. Schrock

for development of the metathesis method in organic chemistry. History of transition metal-catalyzed olefin metathesis was discovered in the 1950's by industrial chemists at DuPont, Standard oil, and Phillips petroleum (H. S. Eleuterio, E. F. Peters, B. L. Evering, R. L. Banks, and G. C. Bailey) who reported that propene reacted to form ethylene and 2-butenes when passed over molybdenum on alumina catalyst at high temperature. Olefin metathesis catalyzed by carbene complex has been known in polymer chemistry for 40 years. However, the reaction has been limited to simple, unfunctionalized olefin. After development of new catalyst by Schrock and Grubbs, chemists realized the potential utility of this methodology in organic synthesis.

Olefin metathesis has been utilized in three closely related types of reactions.

a) Ring opening metathesis polymerization (ROMP):

In which a cyclic olefin is the substrate and a polymer is the product. ROMP is the thermodynamically favored for strained ring system, such as 3, 4-, 8- and large-membered compound (Figure-5).

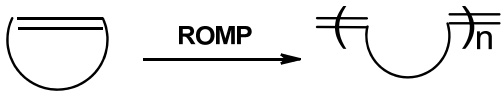


Figure-5

b) Ring-closing metathesis (RCM):

Acyclic diene is converted into cyclic olefin, in which a loss of ethylene takes place (Figure-6).

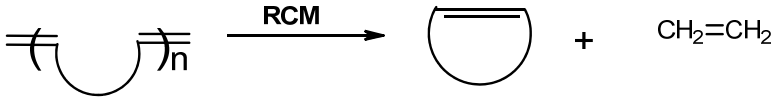


Figure-6

c) Cross metathesis

Two different olefins react to form a new product olefin and a by-product as a volatile olefin (usually ethylene).

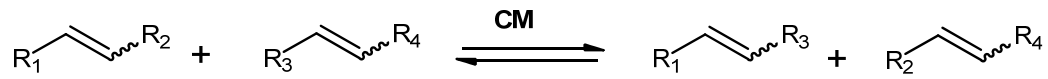


Figure-7

Another variant of the reaction is the metathesis of an alkene and an alkyne, popularly known as enyne metathesis (EM).

Although a number of catalyst have been developed for metathesis and related reactions, the Schrock's catalyst, Hoveyda-Grubbs catalyst, Grubbs 1st and 2nd generation catalyst, the distinct catalysts shown in figure 8 and 9 have been used widely for olefin metathesis reaction.

Titanium and tungsten-based catalyst have been also developed but are less used. Schrock's alkoxy imidomolybdenum (fig 25, 26 and 27) complex is highly reactive toward a broad range of substrate; however, this Mo-based has moderate to poor functional group tolerance, high sensitivity to air, moisture or even to trace impurities present in solvents and exhibits thermal instability.

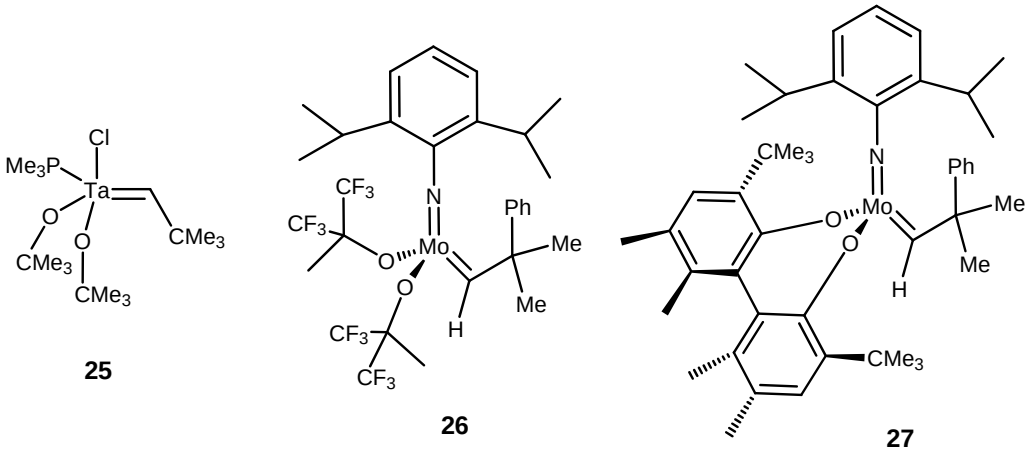


Figure-8. Tantalum and molybdenum metathesis catalyst

In particular, the ruthenium-based catalyst (Grubbs 1st and 2nd generation) have been used extensively in organic and polymeric chemistry due to its high reactivity with olefin substrate in presence of most common functional groups. Homogeneous Ruthenium catalysts are (generally) stable, more selective and highly active at mild condition. It has superior activity over other cyclization methods like macrocyclization, Diels-alder etc., and adaptable for both solution and solid phase reactions.

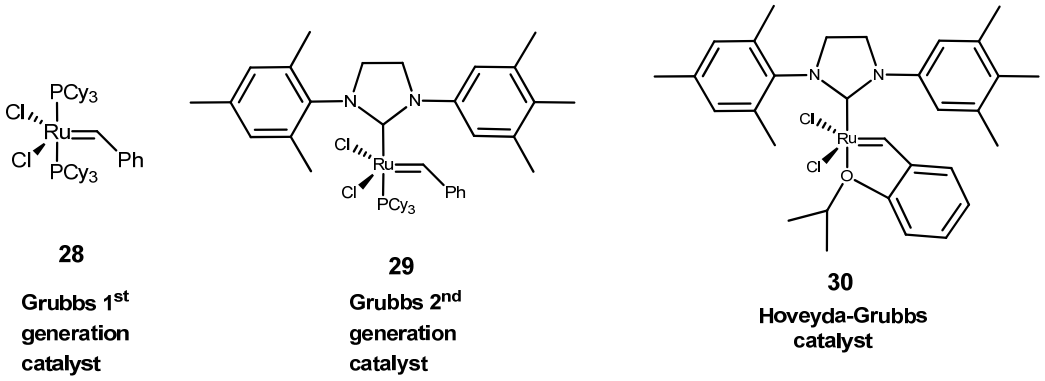


Figure-9. Ruthenium based metathesis catalyst

The construction of a 10-membered ring is by using RCM was first reported by Frustner and Muller in 1997 for the synthesis of Jasmine ketolactone (**23** & **24**). Frustner also synthesized herbarium I and herbarium II by RCM strategy.

RCM Mechanism:

The mechanism of the RCM reaction has been extensively studied both experimentally and theoretically. It is now well accepted that, during the reaction the

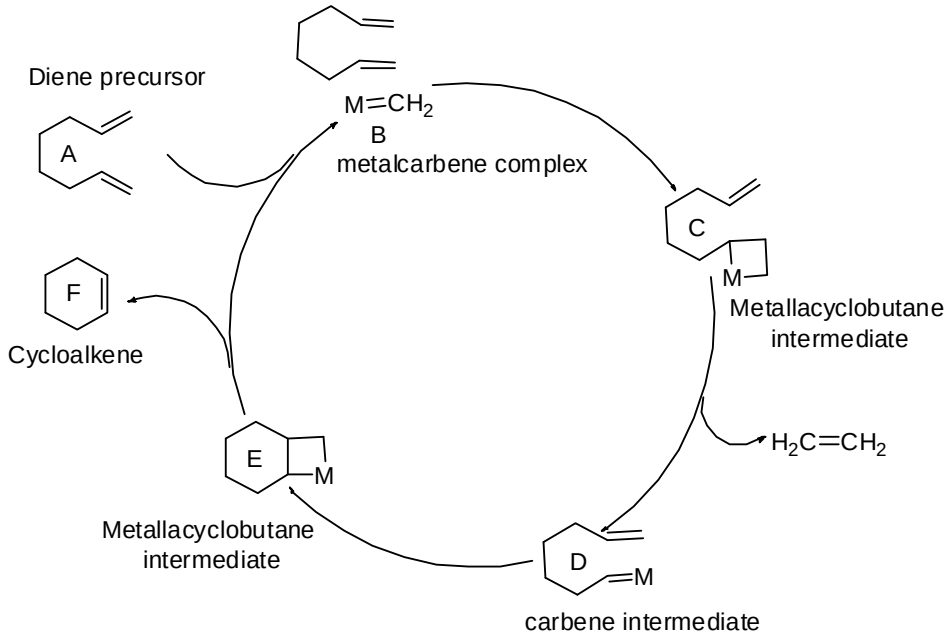


Figure-10. RCM mechanism

catalytically active metalacarbene complex such as [M] = CH_2 (**B**) is formed from the diene precursor (**A**) (figure-10) and the overall reaction mechanism involves,

effectively, a series of alternating [2+2] cycloadditions. Metallacyclobutane intermediate such as (**C**) is formed, which opens in retro [2+2] fashion to form the carbene (**D**) as intermediate. The latter then undergoes re-cyclization to form the new metallacyclobutane (**E**), which analogously open to the product cycloalkene (**F**) and catalyst is regenerated. The mechanism is depicted schematically in figure-10. The equilibrium is continuously shifted towards the cycloalkene, due to the release of a volatile olefin (usually ethylene).

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Chapter II

Introduction:

Acetals in which the two ether groups are connected by a bridge are called spiroacetals.[1] Spiroaetals occur in nature predominant as a sub-units of naturally occurring substances from many resources, including insects, microbes, plants, fungi, and marine organisms. It is a cyclic ketal in which two rings are joined by a single atom, the spiro atom, and the two ketal oxygens flanking the spiro atom, each belonging to one of the rings. There are an enormous range of structural complexity ranging from the relatively simple fly pheromones to the intricate frameworks of the polyether antibiotics and the spiroketal macrolides. Several of these have potent pharmacological activity. The vast majority of chemistry in this area is focused on the

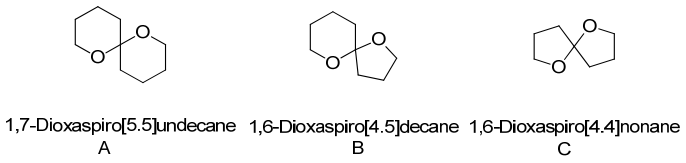


Figure 1: *Most commonly known spiroketals*

spiroketal general ring systems A, B and C presumably because most of the natural products fall into one of these structure categories (Figure 1).[2]

Conformational aspects of spiroketals

1,7-Dioxaspiro [5.5] undecanes have been studied intently and are the most easily analysed for preferred conformations. Three factors have been observed to influence conformation preferences in the system: (1) steric influences (2) anomeric and related effects (3) intramolecular hydrogen boinding and other chelation effects. As expected, the typical preference for the substituents to reside in equatorial position is important and in carbocyclic systems normally an overriding factor. However, as will become evident, this must be balanced against the stabilizing consequences of anomeric and related effects in tetrahydopyrans. There are cases in which the anomeric effect outweighs the equatorial preferences of alkyl substitutents .

Spiroketals can be doubly anomeric (in which both rings benefit from anomeric stabilization associated with placing the oxygen of the other ring into an axial orientation), singly anomeric, or fully non-anomeric (Figure 2).[3]

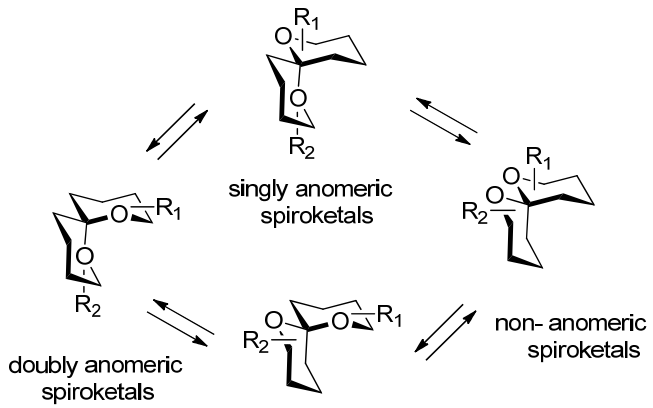


Figure 2: Anomeric, singly anomeric and non-anomeric configurations available for a 6,6-spiroketal

Studies by Deslongchamps[4] have determined that 1,7-dioxaspiro[5.5]undecane **A** exists exclusively in conformation $\mathbf{A_1}$ (Figure 3). This experimental observation has been explained by the fact that conformation $\mathbf{A_1}$ is stereoelectronically and sterically more stable than conformations $\mathbf{A_2}$ and $\mathbf{A_3}$ which were estimated to be less stable by a value of 2.4 and 4.8 Kcal/mol, respectively.

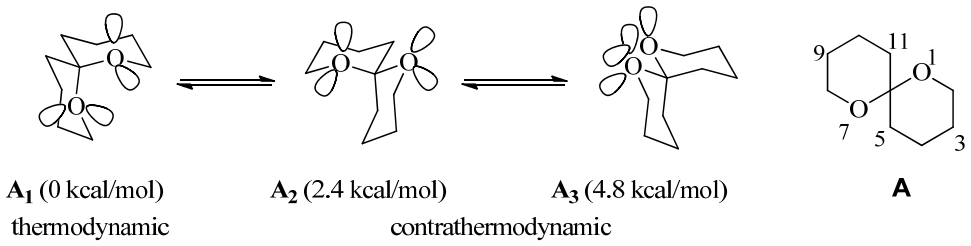


Figure 3: *Relative energies of the three possible chair-chair conformations of* ***A***

Spiroketals are readily formed by the acid-catalyzed convergence of two tethered alcohols onto a central ketone. During this process, only a single spiroacetal conformation is formed *i.e* conformer $\mathbf{A_1}$. Conformer $\mathbf{A_1}$ can be considered a *thermodynamic* spiroketal due to the existence of two anomeric stabilizing interactions wherein both acetal oxygen atoms have a set of lone pairs able to mutually donate into the C-O σ* of the other oxygen. Conformers $\mathbf{A_2}$ and $\mathbf{A_3}$, which are not formed under these conditions, can be considered *contrathermodynamic* spiroketals because they lack atleast one anomeric stabilizing effect. Representative examples (Figure 4) are the ABCD subunit of azaspiracid **1**, dianomycine,

leuseramycin, aplysiatoxin, spirofungin A, BCD subunit of salinomycin, ABC subunit of (+)-pinnatoxin (Figure 4).[5]

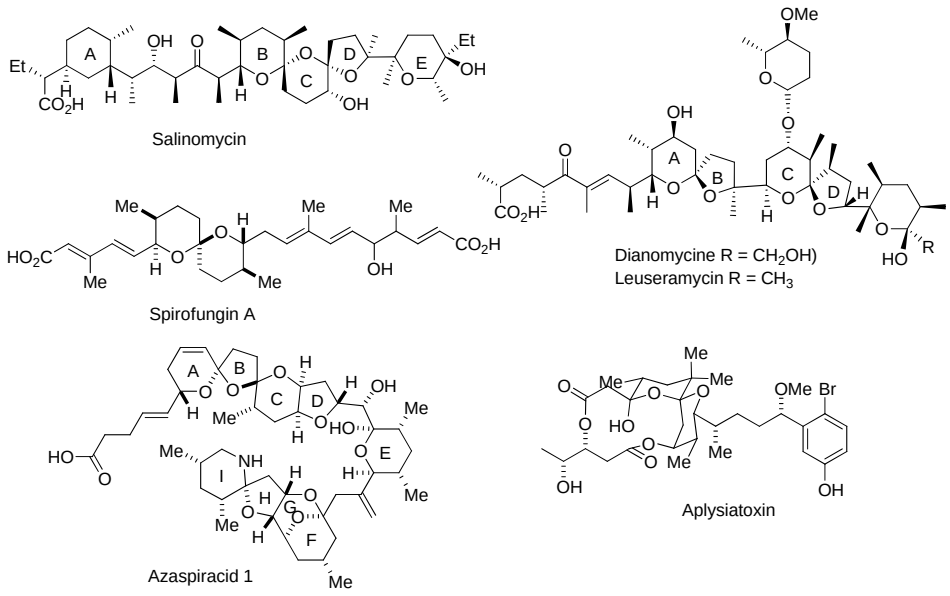


Figure 4: *Contrathermodynamic spiroketal motifs in natural products*

The earliest example of spiroketal structure in nature are steroidal saponins and sapogenins (Figure 5),[6, 7] the compound in this class are glycosides in which aglycone consists of a steroidal nucleus containing a spiroketal assembly fused to the D-ring. Glycosylation is usually found on the A-ring. At that time, the steroid nucleus was more interest to synthetic chemist and spiroketal chemistry was relatively neglected.

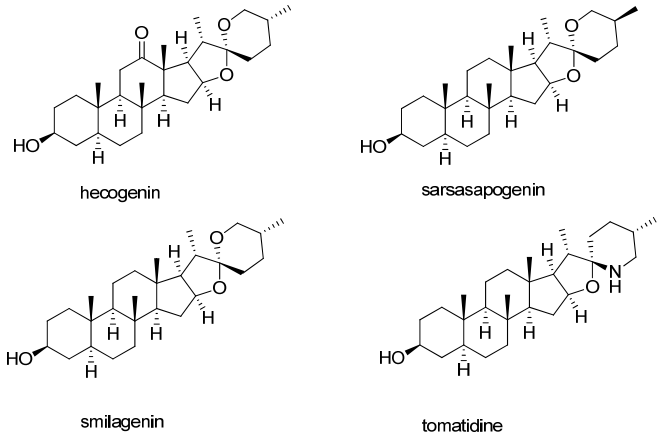


Figure 5: Earliest examples of spiroketal compounds

The spiroketal structure itself is directly associated with the biological activity. Some representative biologically active natural products containing the spiroketal motifs were given in Figure 6.[8]

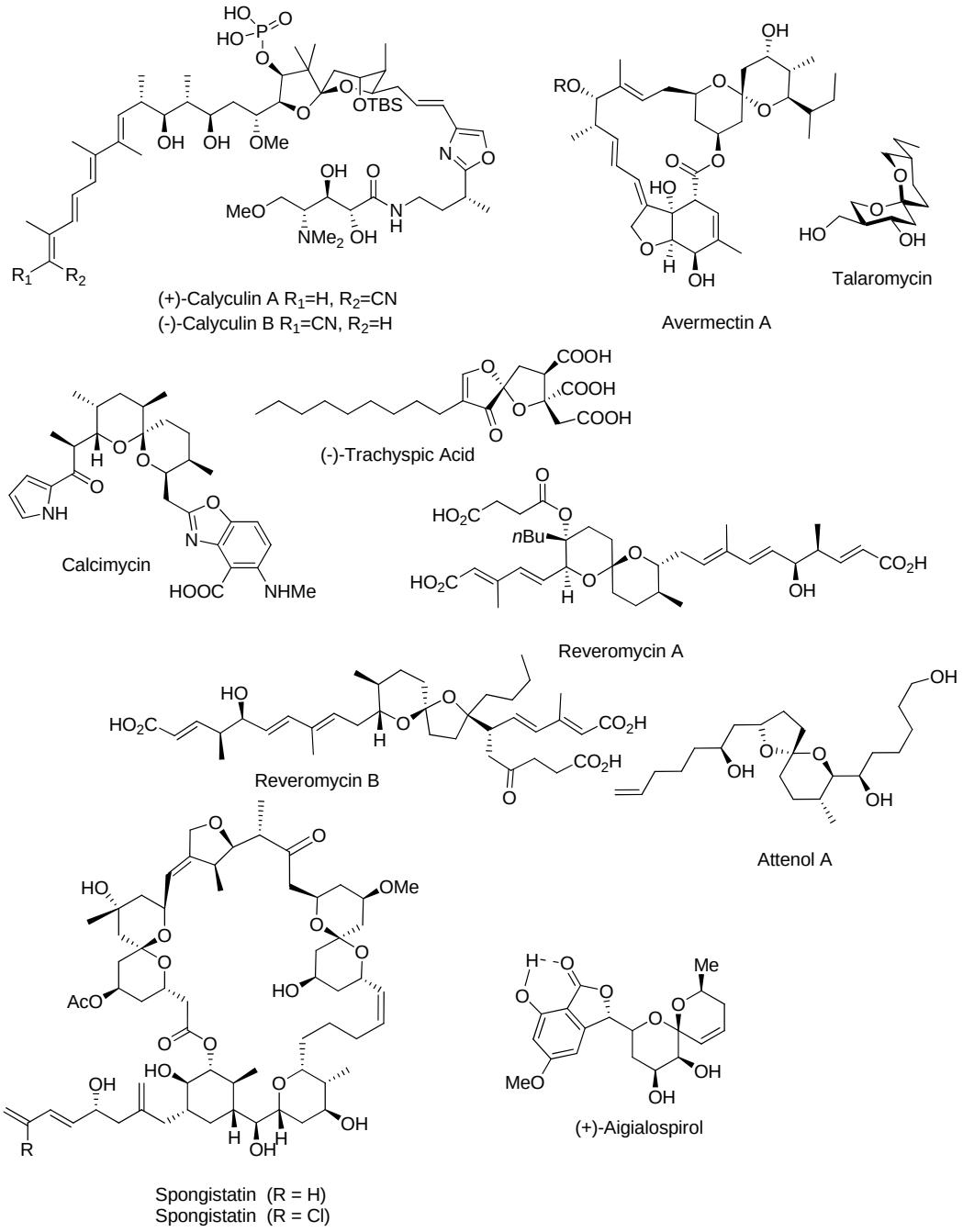


Figure 6: Some examples of naturally occurring spiroketals

Talaromycin is a small spiroketal natural product that is a potent mycotoxin. Trachyspic acid was isolated from the culture broth of Talaromyces trachyspermu

SANK 12191 and was identified as a potent inhibitor of herparanase with an IC_{50} of 36μM. The exocyclic spiroketal in the avermectin class of anti-parasitic compounds exhibits a pronounced, narrow structure-activity relationship profile, indicating that it is likely the spiroketal unit directly involved in target binding.

Reveromycins A and B are the members of a novel family of bioactive spiroketal containing natural product isolated from a soil actinomycete belonging to the *Streptomyces* genus. Reveromycin A is an inhibitor of the mitogenic activity of epidermal growth factor (EFG) and may represent a new class of antitumor agents. In addition, reveromycin A also exhibits antifungal activity (MIC) 2.0 μg mL^{-1}, pH 3) and it has been identified as a specific inhibitor of *Saccharomyces cerevisiae* isoleucyl-*t*RNA synthetase (IleRS). Calcimycin has been shown to be an ionophore antibiotic. It selectively transports divalent cations, and has been used for specific perturbation of transmembrane Ca^{2+} gradients in complex systems such as cells. Calyculin A and B are naturally occurring spiroketal isolated from the marine Discodermia calyx and potent serine-threonine protein phosphatase (PP1 and PP2A) inhibitors with remarkable cell membrane permeability.

The spiroketal unit in several natural products has been also identified as rigid scaffolds that can display complex side chains along various well-defined three-dimensional vectors. The spongistatins are the classical examples. They have been found to be inhibiting tubulin protein-protein interactions. However, some recent reports indicate that simple spiroketal analogs of spongistatin exhibit a similar activity of their own. The increasing pharmacological importance of compounds containing spiroketal assemblies has ascertained importance of spiroketals as valuable pharmacophore and has attracted considerable attention in both target- and diversity-oriented synthesis. In the latter context, spiroketals present an excellent opportunity to exploit stereochemical diversity, wherein these rigid scaffolds can be used to display substituents along various well-defined three-dimensional vectors.

Aculeatins:

Aculeatins A–D (**1**–**4**, respectively) were isolated from the petroleum ether extracts of the rhizomes of *Amomum aculeatum*. With the help of extensive 2D-NMR experiments, the structures of aculeatins A–D were characterized by the presence of a fascinating 1,7-dioxadispiro[5.1.5.2]-pentadecane spirocyclic architecture.[9] Aculeatin

D (**4**) showed the remarkably high cytotoxicity, anti-bacterial and anti-protozoal activities. Kinghorn *et.al* reported the isolation[10] of related metabolites in 2007, truncated aculeatins A and D, named respectively as aculeatins F (**6**) and E (**5**), were reported by the same group, having the novel dioxadispirocyclic architecture present in aculeatins and showing the broad spectrum of biological activity,

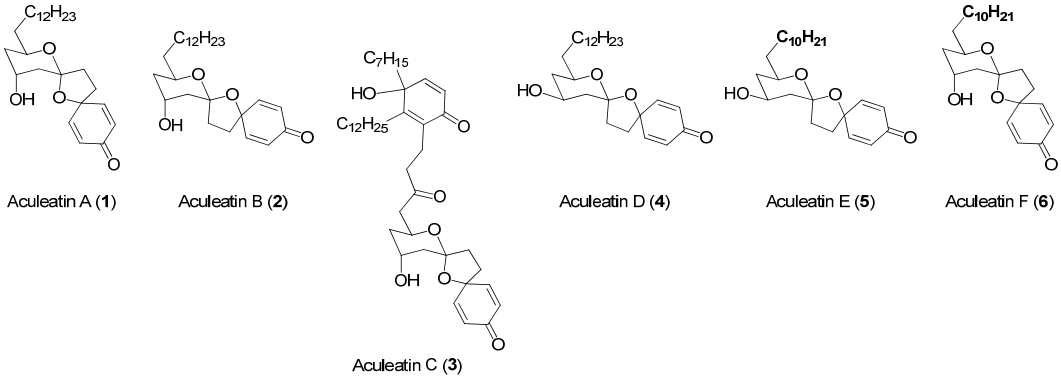
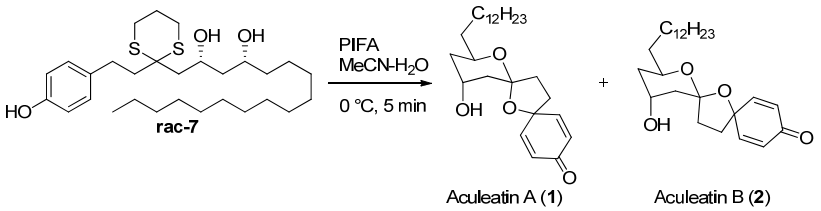


Figure 7: Naturally Ocurring Aculeatins A-F (1-6)

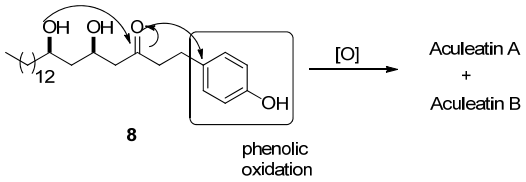
Total Synthesis of Aculeatins: Many synthetic efforts have been reported in literature involving a final key oxidative spirocyclisation of phenolic precursors. At this point it would be relevant to summarize some of the synthetic endeavors reported before or concurrent to our work.

1. Wong *et al.* [11]

The first total synthesis of aculeatins A (**1**) and B (**2**) was achieved by employing the spiroketalisation as the key transformation and PIFA as the reagent of choice (Scheme 1). The initial success of this reaction has been accepted as the key disconnection approach in the syntheses of aculeatins reported later by other groups. The key retron used for this particular transformation was a 1,3-diol-5-ketone (Scheme 2) and synthesis of which has been designated as the essence of various aculeatins total syntheses documented.



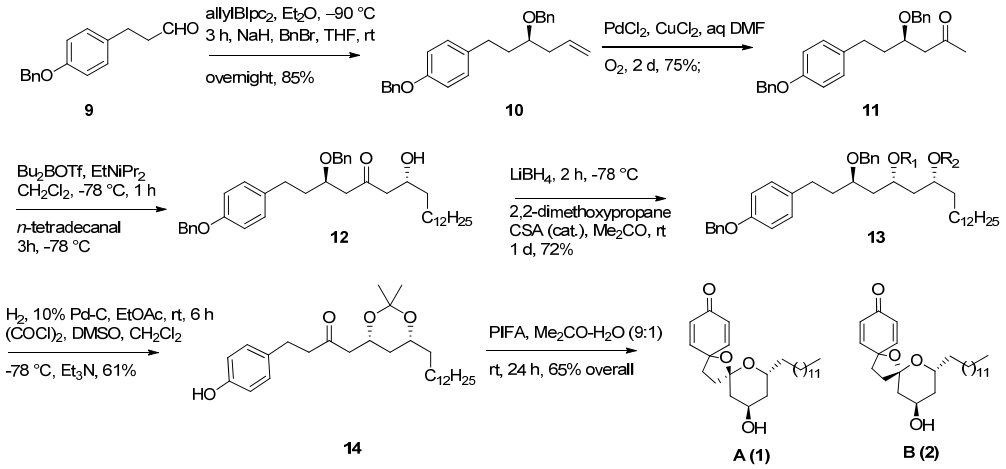
Scheme 1. *Spiroketalization to the aculeatin A and B*



Scheme 2. *Mechanism of oxidative spirocyclization*

2. Marco *et al.* [12]

Marco and coworkers described the enantioselective synthesis of aculeatins A, B, D and *epi*-D by using asymmetric allylations. A further key step was a stereoselective aldol reaction with remote stereochemical induction. The absolute configurations of the natural products have been established and an erroneous structural assignment has been corrected. The synthesis starts with asymmetric allylation of 3-(*p*-benzyloxyphenyl)propanal **9** using the chiral allylborane prepared from allylmagnesium bromide and (–)-DIP-Cl [(–)-diisopinocamphenylchloroborane] leading to homoallyl alcohol with 96% ee which was benzylated to get **10**. Wacker



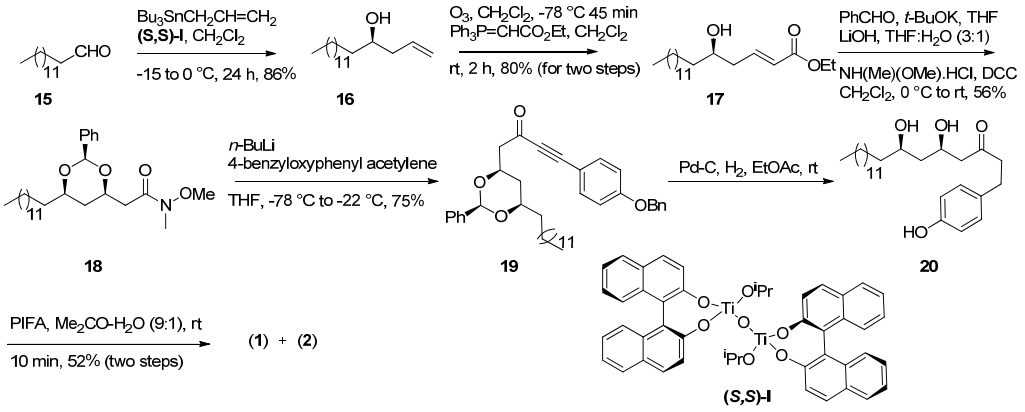
Scheme 3. *Synthesis of aculeatins A and B.*

oxidation of **10** followed by boron aldol reaction provides the desired aldol **12** as a single disastereomer. The aldol is then reduced *in situ* to the monobenzylated *anti*, *syn*-1,3,5-triol with $LiBH_4$ followed by acetonide protection of the two free hydroxyl groups by using dimethoxy propane to give **13**. The hydrogenolytic debenzylation

followed by under Swern oxidation furnished ketone **14**. The ketone **14** is then subjected to hydrolytic cleavage of the acetonide moiety but the yield of expected β,δ-dihydroxy ketone was low (<35%). The treatment of acetonide **14** with phenyliodonium bis(trifluoroacetate) not only causes the desired phenolic oxidation, but also acetonide hydrolysis and subsequent spiroacetalization (Scheme 3). This cleanly gives a 5.5:1 mixture of two optically active products with spectral properties identical to those reported for aculeatins A (**1**) and B (**2**).

3. Chandrasekhar *et al.*[13]

Chandrasekhar *et al*. reported the synthesis of aculeatins A and B starting from the tetradecanal **15** *via* a tethered oxa-Michael approach. The homoallylic alcohol **16** is synthesized from aldehyde **15** using a Maruoka allylation. This compound is then converted to unsaturated ester **17** by ozonolysis and subsequent two-carbon homologation and is used for the tethered intramolecular oxa-Michael reaction to

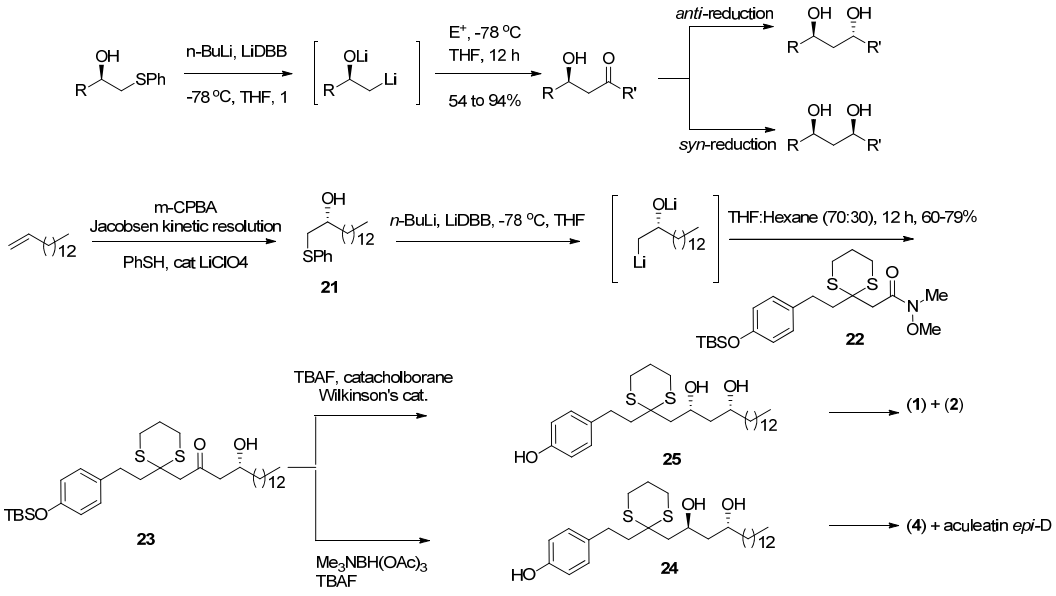


Scheme 4. *Synthesis of aculeatins A and B*

install the second stereocenter. Thus, reaction of **17** with benzaldehyde and potassium *tert*-butoxide affords benzylidene acetal with 95% diastereoselectivity favouring the more stable *syn*-isomer. Acetal is converted to Weinreb amide **18**, which upon treatment with lithiated 4-benzyloxyphenylacetylene affords fragment alkynone **19**. Catalytic hydrogenation of **19** gives intermediate **20**, which on treatment with phenyliodonium (III) bis(trifluoroacetate) (PIFA) affords aculeatins A (**1**) and B (**2**) as a 5:2 mixture (Scheme 4).

4. Rychnovsky *et al.* [14]

Rychnovsky *et al*. developed a new method to synthesize the *β*-hydroxy ketone by using a non-aldol route. The *β*-phenylthio alcohols were prepared from optically pure oxiranes. Deprotonation and reductive lithiation generated the key intermediate, a *β*-oxyanionic alkyllithium reagent, addition of which to a Weinreb amide produced the *β*-hydroxy ketone. Stereoselective reduction of the ketone led to either the *syn*- or *anti*-1,3-diol. By employing this simple, convergent strategy, they synthesized the aculeatins A, B, and D from a common intermediate.



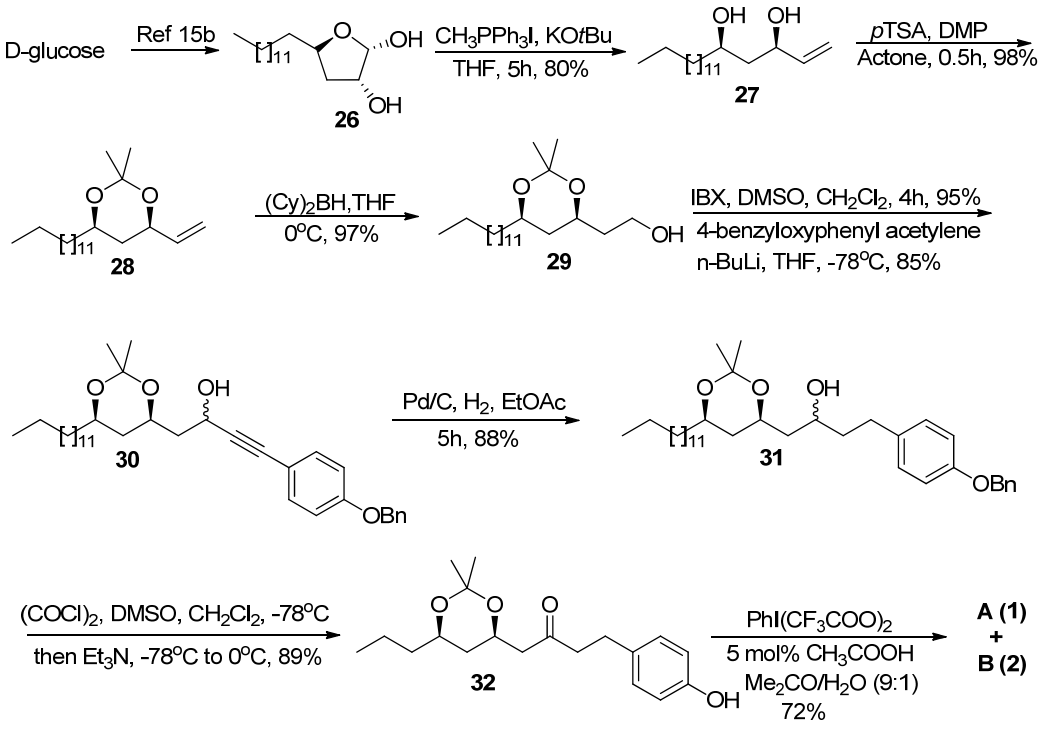
Scheme 5: *Total synthesis of Aculetins A, B, D and epi-D*

The journey of synthesis started with the epoxidation of 1-pentadodecene followed by the Jacobsen kinetic resolution to get the chiral epoxide which was treated with thiophenol to obtain **21**. The lithiation of **21** followed by the addition of Weinreb amide **22** delivered the aldol adduct **23**. The ketone **23** was the common intermediate for all three aculeatins. Anti reduction using Evan's method and deprotection led to *anti*-1,3-diol **24** as a 10:1 dr in very good yield. The final oxidative cyclization of **24** was conducted under citrate-buffered conditions to generate aculeatin D in 30% yield, accompanied by the separable C6 epimer in 35% yield. Without the added buffer, only the C-6 epimer was produced. Selective *syn*-reduction of **23** afforded **25,**

Compound **25** on similar sequence of reactions gave aculeatin A (38%) and aculeatin B (20%).

5. Venkateshwarlu *et al.*[15a]

Venkateshwarlu *et al.* reported the synthesis of aculeatin A and B using D-glucose as starting material. Synthesis started with 3-deoxy-1,2: 5,6-di-*O*-isoproylidine-α-D-glucose, which was prepared from D-glucose following the reported procedures. Deprotection of 5,6-di-*O*-isoproylidine moiety and simple manipulations yielded (2S,3R,5S)-5-tridecyltetrahydrofuran-2,3-diol (**26**).



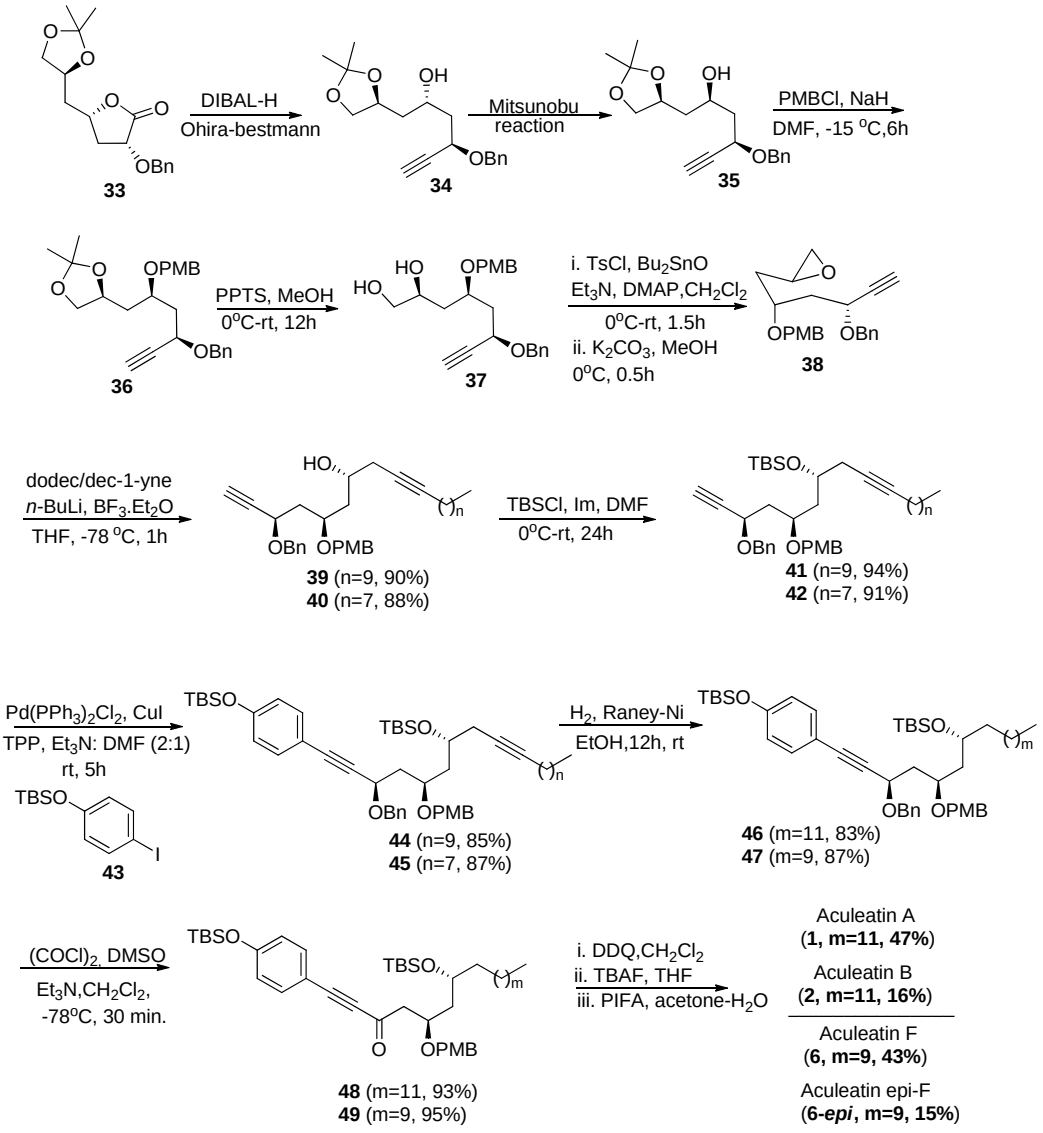
Scheme 6: *Total synthesis of Aculetin A and B*

This was subjected to Wittig olefination with in situ generated methylene triphenyl phosphorane to afford 3,5-syn diol olefinic intermediate **27**. Protection of 1,3-syn diol intermediate **27** using 2,2-dimethoxy propane in acetone using *p*-TSA afforded **28** in 98% yield, followed by selective hydroboration furnishing alcohol **29** in 97% yield,. This alcohol **29** was oxidized using IBX to furnish aldehyde which was subjected to reaction with lithiated 4-benzyloxyphenyl acetylene to yield the

corresponding alkynols **30** in 85% yield. Benzyl deprotection of alkynols **30** using 10% Pd-C/H_2 in EtOAc gave a mixture of **31** in 88% yield. Alcohol **31** was oxidized under Swern condition to afford **32**. Phenolic oxidation and spiroacetalization of **32** using PIFA in acetone-H_2O (9:1) gave aculatin A and B in 5.5:1 ratio.

6. Ramana *et al.*[16]

The synthesis starts from the preparation of the γ-lactone **33** following the reported procedures. The controlled DIBAL-H reduction of the γ-lactone **33** in DCM at -78°C



Scheme 7: Total synthesis of Aculetins A, B, F and *epi*-F

gave the intermediate, which upon alkynylation using Ohira-Bestmann reagent resulted in the formation of alkynol **34.** To access the oxirane **38** with central syn, syn-1,3-polyol configuration at C (4) center had to be inverted. The Mitsunobu inversion of alkynol **34** by using DEAD, TPP could be conducted in good yield by employing the p-nitrobenzoic acid as the nucleophile followed by saponification with NaOMe in MeOH to give *syn,syn*-alkynol **35,** which was protected as its PMB ether by employing NaH and PMB-Cl in DMF at -15^{o}C. Subsequently, the acetonide group of resulted compound **36** was deprotected by employing PPTS im MeOH to afford diol **37**. The primary hydroxyl was selectively tosylated and resulting tosylate was employed without any purification for oxirane **38** using base.

The *syn,syn*-oxirane **38** served as the common starting point for the synthesis of aculeatin A, B and F. The regioselective opening of epoxide **38** with either dodec-1-yne or dec-1-yne using n-BuLi at -78^{o}C and $BF_3.Et_2O$ followed by the introduction of epoxide **38** after short interval. Under these conditions, the diynes **39** and **40** were obtained in 90% and 88% yields, respectively and which were converted to the corresponding TBS-ethers **41** and **42** by treatment with TBS-Cl/imdiazole in DMF. Our next concern was the extension of the alkyne end in **41** and **42** through the Sonogashira coupling with a p-iodophenol **43** derivative, The sonogashira coupling of **41** and **42** with **43** was best effected by a through degassing of the reaction mixture prior to the addition of CuI to give the coupled products **44** (85%) and **45** (87%). After this extension at both the ends, the hydrogenolysis of both alkyne group and seclective debenzylation of compound **44** and **45** was carried out and resulting products **46** and **47** were oxidized under Swern condition to afford keto compound **48** and **49**, their one-pot sequential TBS and PMB ethers deprotection followed by key phenol oxidative spiroketalization completed the synthesis of aculeatins A and F and their spiro-epimers aculeatin B and 6-api-aculeatin F.

Thus the inspection of the available synthesis of aculeatins reveals that in majority of the cases they are linear in nature and the options for the synthesis of analogues are limited. Considering the promising biological activities reported for the aculeatins, we were interested to develop a simple and straightforward synthesis of aculeatins .The details of our efforts in this direction will be discussed in the next part of this Chapter.

Chapter II, Section A

Synthesis of Aculeatins A and B via Iterative Hydrolytic Kinetic Resolution and PIFA Promoted Tandem Phenolic Oxidation/Dithiane Deprotection Sequence

Present work

Objective

Aculeatins A **1** and B **2** (Figure 1) were isolated by Heilmann and coworkers in 2000 from *Amomum Aculeatum rhizomes.*[9b] They were found to inhibit the growth of human cancer KB cell lines, MFC-7 human breast cancer cells.[9] They also display antiprotozoal activity against *Trypanosoma* and both the NF54 and chloroquine-resistant K1 strains of the malarial parasite *Plasmodium falciparum*. Interestingly these compounds are endowed with a unique and unprecedented 1, 7-dioxa-dispiro[5.1.5.2]pentadecane tricyclic ring system which makes them an attractive synthetic target. In view of the important biological activities and unusual and challenging structural feature, aculeatins have attracted considerable attention among the synthetic organic chemists worldwide.

Wong and coworkers reported in 2002 the first synthesis of racemic aculeatin A **1** and B **2** in which the spiroketal tricyclic framework was generated by intramolecular cyclisation[11] initiated by phenolic oxidation. Marco and coworkers synthesized **1** & **2** in enantiomerically pure form for the first time using an asymmetric allylation. Meanwhile several other asymmetric synthesis reported for aculeatins were mainly based on using either the chiral pool starting material or stereoselective methods to generate the stereogenic centres and subseqent oxidative cyclisation[17] was performed using phenyl iodonium (III) bis(trifluoroacetate) (PIFA).

As a part of our research program aimed at developing enantioselective synthesis of biologically active products based on hydrolytic kinetic resolution (HKR), we became interested in devising a simple and concise route to aculeatins A and B. Herein, we describe our successful endeavors towards the total synthesis of **1** and **2** employing HKR[18] and and Linchpin coupling [19] as the key steps.

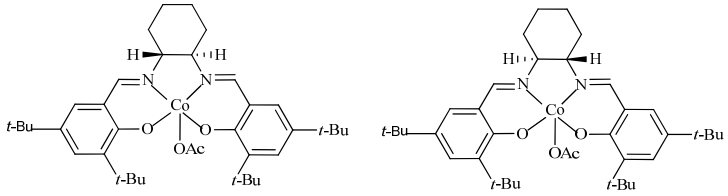
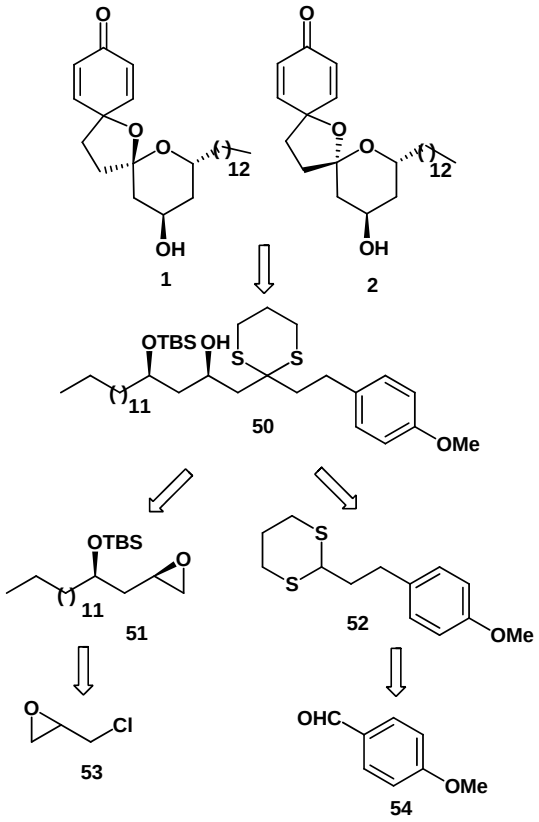


Figure 8. (*R*,*R*)-(salen)Co(III)(OAc) & (*S*,*S*)-(salen)Co(III)(OAc)

The HKR method involves the readily accessible cobalt-based chiral salen complex as catalyst (Figure 8) and water to resolve a racemic epoxide into enantiomerically enriched epoxide and diol, which serve as useful precursor in the synthesis of various compounds of biological importance.

Retrosynthetic analysis of aculeatin A 1 and B 2:

Our retrosynthetic analysis for the target compound is based on convergent approach as delineated in Scheme 8. We envisioned that the precursor **50** required for aculeatins A **1** and B **2** could be synthesised by the Linchpin coupling of epoxide **51** and dithiane **52**. The epoxide **51** in turn could be prepared from (±) epichlorohydrin **53** while the dithiane fragment **52** would be synthesised from *p*-anisaldehyde **54**.

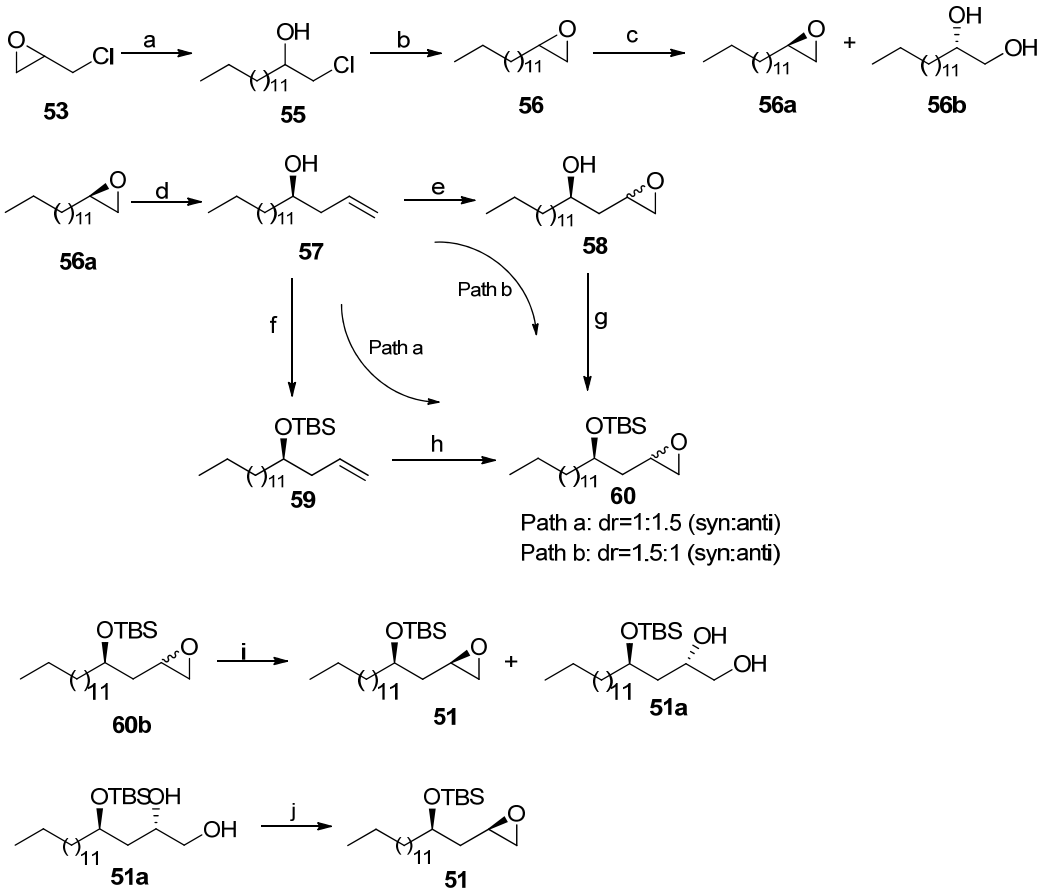


Scheme-8. Retrosynthetic route to aculeatin A **1** and B **2.**

Results and Discussion

As shown in Scheme 9, the synthesis of the epoxide fragment started from the commercially available (±) epichlorohydrin which on ring opening with

dodecylmagnesium bromide followed by base treatment gave the epoxide **56** in 92% yield. The *rac*-epoxide **56** was subjected to Jacobsen's HKR using (*R,R*)-salen-Co(OAc) catalyst to give enantiopure epoxide (*R*)-**56a** in 46% yield along with diol **56b** in 45% yield, which were separated by silica gel column chromatography.



Scheme 9. Synthesis of epoxide **51**.

Reagents and conditions: (a) Dodecylmagnesium bromide, THF, CuI, -40 ^{o}C, 12 h, 84%; (b) KOH, CH_2Cl_2, rt, 1 h, 92%; (c) *R,R*-salen-Co-(OAc) (0.5 mol %), dist. H_2O (0.55 equiv), 0 ^{o}C, 14 h, (46% for **56a**, 45% for **56b**); (d) Vinylmagnesium bromide, THF, CuI, -20 ^{o}C, 12 h, 89%; (e) *m*-CPBA, CH_2Cl_2, 0 ^{o}C to rt, 10 h, 96%; (f) TBDMSCl, imidazole, CH_2Cl_2, 0 ^{o}C to rt, 3 h, 92%; (g) TBDMSCl, imidazole, CH_2Cl_2, 0 ^{o}C to rt, 4 h, 95%; (h) *m*-CPBA, CH_2Cl_2, 0 ^{o}C to rt, 8 h, 95%; (i) *R,R*-salen-Co-(OAc) (0.5 mol %), dist. H_2O (0.55 equiv), 0 ^{o}C, 24 h, (49% for **51,** 37% for **51a**); (j) (i) PivCl, Et_3N, cat. DMAP, rt, 2 h; (ii) MsCl, Et_3N, DMAP, 0 ^{o}C to rt, 1 h; (iii) K_2CO_3, MeOH, rt, overnight (61% for three steps).

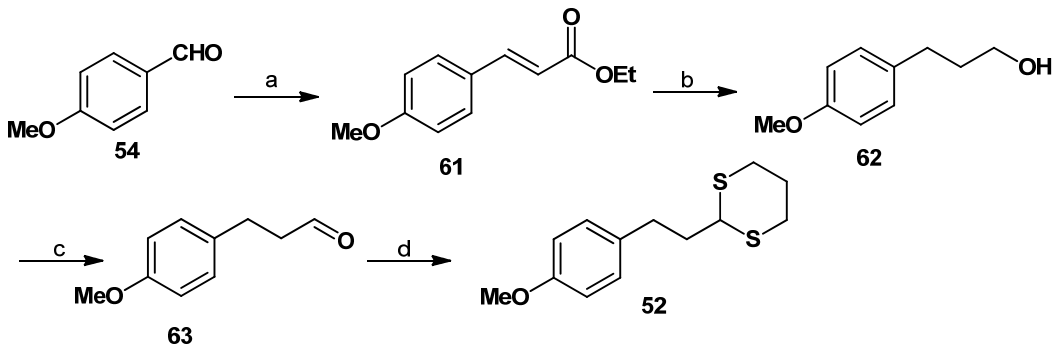
With enantiomerically pure epoxide (*R*)-**56a** in hand, our next task was to establish the second stereogenic center with required stereochemistry. Thus epoxide **56a** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol **57** in 89% yield; $[\alpha]_D^{25}$ +4.92 (*c* 1.0, $CHCl_3$) [Ref. 13 $[\alpha]_D^{25}$ +5.0 (*c* 1.0, $CHCl_3$)]. We then proceeded to explore the stereoselective outcome of the epoxidation reaction with and without hydroxyl-group protection. To this end, the hydroxyl group of homoallylic alcohol **57** was first protected as the TBS ether, followed by epoxidation with *m*CPBA (path a). The epoxide **60a** thus produced was found to be a mixture of two diastereomers (*syn anti/* :1:1.5) with the desired *syn*-isomer obtained as the minor component.

In contrast, the epoxidation of homoallylic alcohol **57**, followed by hydroxy-group protection as the TBS ether produced the epoxide **60b** in favor of the desired *syn*-isomer (*syn/anti* 1.5:1) (path b). The two diastereomers could not be differentiated by TLC. ^{1}H NMR spectrum of ***60a***-syn/anti showed epoxide protons at δ 2.45 (doublet of doublet, 0.4 H, with coupling constant *J* = 2.72, 5.07 Hz) and 2.48 (doublet of doublet, 0.6 H, with coupling constant *J* = 2.68, 5.06 Hz) and δ 2.75 (triplet, 0.4 H, with coupling constant *J* = 4.53 Hz) and 2.79 (triplet, 0.6 H, with coupling constant *J* = 4.97 Hz) and ^{1}H NMR spectrum of ***60b***-syn/anti showed epoxide protons at δ 2.46 (doublet of doublet, 0.57 H, with coupling constant *J* = 2.72, 5.07 Hz) and 2.48 (doublet of doublet, 0.43 H, with coupling constant *J* = 2.68, 5.06 Hz) and δ 2.76 (triplet, 0.57 H, with coupling constant *J* = 4.53 Hz) and 2.80 (triplet, 0.43 H, with coupling constant *J* = 4.90 Hz) In order to improve the diastereoselectivity, epoxide **60b** was further subjected to HKR with (*R,R*)-salen-Co(OAc) complex (0.5 mol %) and water (0.55 equiv) to afford the diastereomerically pure epoxide **51** as a single diastereomer in good yield. ^{1}H NMR spectrum of (*60*)-syn showed epoxide protons at δ 2.46 (doublet of doublet, 1 H, with coupling constant *J* = 2.72, 5.07 Hz) and δ 2.76 (triplet, 1 H, with coupling constant *J* = 4.52 Hz).

As the HKR method provided the desired epoxide along with unwanted diol **51a** in almost equal amounts, we thought that it would be appropriate to convert diol **51a** into the required epoxide **51** via internal nucleophilic substitution of a secondary mesylate.[20] Accordingly chemoselective pivalation of diol **51a** with pivaloyl chloride followed by mesylation of the secondary hydroxyl

and treatment of the crude mesylate with K_2CO_3 in methanol led to deprotection of the pivaloyl ester. Concomitant ring closure via intramolecular S_N2 displacement of the mesylate furnished the epoxide **51** in 61% overall yield.

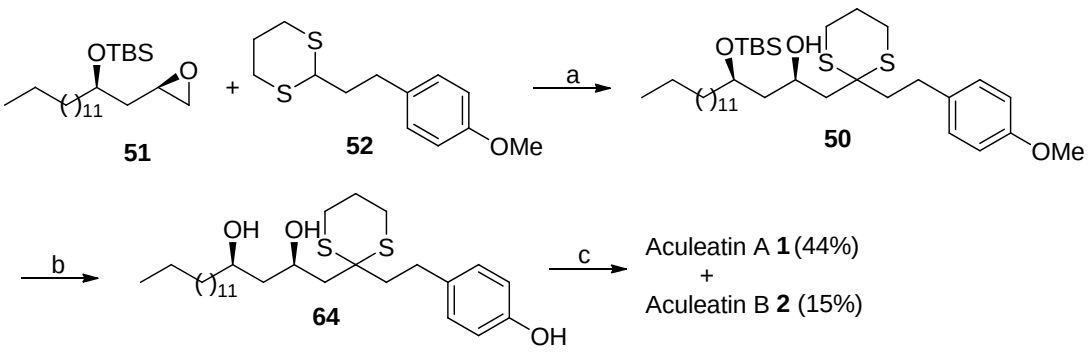
Synthesis of dithiane fragment **52** (Scheme 10) started from the commercially available *p*-anisaldehyde which on two carbon homologation via Wittig reaction provided the olefin **61** as a *cis-trans* mixture. The double bond reduction was carried out under hydrogenation conditions using 10% Pd/C at 60 *psi* followed by ester reduction with LAH to afford the alcohol **62** in 81% overall yield. The alcohol **62** was oxidized by IBX to give the aldehyde **63** which on subsequent treatment with 1, 3-propane dithiol in the presence of a catalytic amount of $BF_3.OEt_2$ at room temperature furnished the dithiane fragment **52** in excellent yield.



Scheme 10. Synthesis of dithiane **52**.

Reagents and conditions: (a) $Ph_3P{=}CHCO_2Et$, toluene, reflux, 6 h, 86%; (b) (i) 10% Pd/C, H_2 (60 *psi*), EtOAc, rt, 1 h; (ii) $LiAlH_4$, THF, rt to reflux, 12 h, (81% for two steps). (c) IBX, DMSO: THF (1:1), 0 °C-rt, 6 h 84%; (d) 1,3-Propanedithiol, cat. $BF_3.Et_2O$, CH_2Cl_2, 0 ^oC, 12 h, 88%.

With substantial amount of both the fragments in hand the coupling of epoxide **51** and dithiane **52** was accomplished using Linchpin coupling (Scheme 11). Towards this end, the generation of lithiated anion of dithiane **52** was carried out using *n*-BuLi in THF at -78 ^oC, followed by quenching with epoxide **51** which eventually resulted in the coupled product **50**. One-pot deprotection of methyl and TBS group using BBr_3[21]



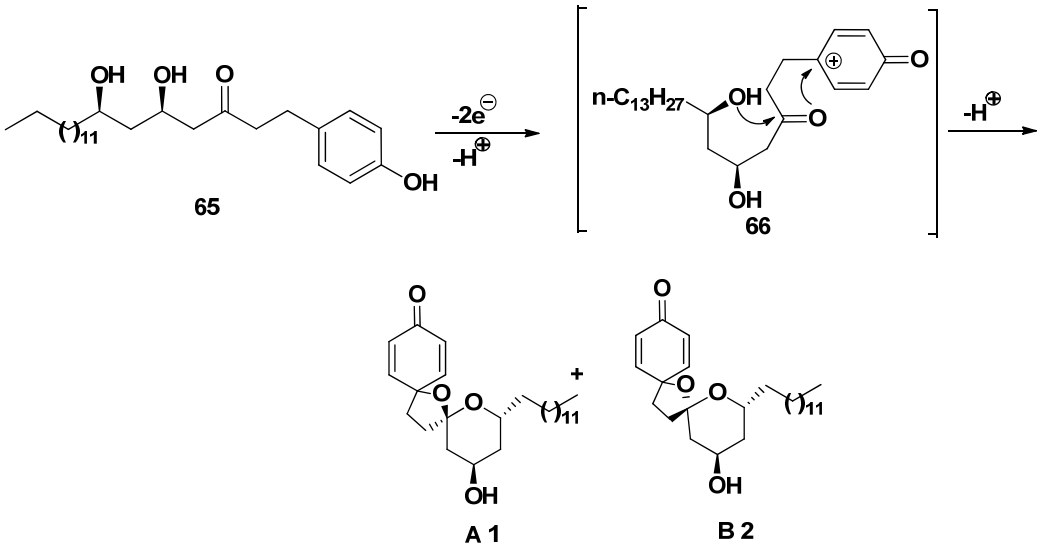
Scheme 11. Reagents and conditions: (a) *n*-BuLi, HMPA, THF, -78 ^{o}C, 1 h, 87%; (b) BBr_3, CH_2Cl_2, rt to -78 ^{o}C, 2 h; (c) $PhI(OOCCF_3)_2$, Me_2CO/H_2O (9:1), rt, 4 h, 64% overall (2 steps), 2.93:1 mixture of aculeatins A **1** and B **2**.

followed by reaction with $PhI(O_2CCF_3)_2$ in Me_2CO/H_2O (9:1 v/v)[16] at room temperature furnished a mixture of aculeatins A **1** and B **2** in 2.93 :1 ratio which was easily separated by silica gel column chromatography. In the ^{1}H NMR spectrum of **1**, conjugated olefinic protons resonated at δ 6.85 (dd, *J* = 9.99, 2.92 Hz, 1H) and 6.76 (dd, *J* = 9.99, 3.05 Hz, 1H), 6.15 (dd, *J* = 10.5, 1.9 Hz, 1H), 6.11 (dd, *J* = 10.5, 1.9 Hz, 1H). In the ^{13}C NMR spectrum, conjugated carbonyl carbon was observed at δ 185.3 as a singlet. In the IR spectrum, O–H stretching was observed at 3491 cm^{-1} and C=O stretching was observed at 1673 cm^{-1}. In the ^{1}H NMR spectrum of **2**, conjugated olefinic protons resonated at δ 6.99 (dd, *J* = 10.5, 2.93 Hz, 1H) and 6.77 (dd, *J* = 10.5, 3.00 Hz, 1H), 6.15 (dd, *J* = 10.5, 1.9 Hz, 1H), 6.11 (dd, *J* = 10.5, 1.9 Hz, 1H). In the ^{13}C NMR spectrum, conjugated carbonyl carbon was observed at δ 185.3 as a singlet. In the IR spectrum, O–H stretching was observed at 3486 cm^{-1} and C=O stretching was observed at 1671 $cm.^{-1}$

Compounds **1** and **2** were fully characterized by ^{1}H NMR, ^{13}C NMR, Mass, IR spectroscopy data which were in accord with those described in the literature.[12]

Mechanistic and Stereochemical pathway for the oxidative cyclization process

The oxidative double cyclization of the *syn*-1,3-diol **65** using PIFA would be expected to generate aculeatin A **1** and B **2**, which would arise as the result of cyclization of C-2 hydroxyl group onto the *Re* and *Si* diastereotopic faces of C-6 ketone group in the intermediate **66** respectively.



Scheme 12. Pathway for the double oxidative cyclization process

Conclusion

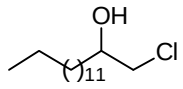
A concise and efficient total synthesis of aculeatin A **1** and B **2** with high enantioselectivities has been accomplished in which the stereocentres were generated by means of iterative Jacobsen's hydrolytic kinetic resolution, and cyclisation was achieved by PIFA.

Experimental Section

General information

All reactions were carried out under inert atmosphere, unless otherwise mentioned, following standard syringe septa techniques. Solvents were dried and purified by conventional methods prior to use. The progress of all the reactions was monitored by TLC using glass plates precoated with silica gel 60 F254 to a thickness of 0.25 mm (Merck). Column chromatography was performed on silica gel (60 and 230 mesh) using EtOAc, and petroleum ether as the eluents. Optical rotations were measured with JASCO DIP-360 digital polarimeter at 25 °C. IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz or DRX-500 MHz and ^{13}C NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometer, TMS as an internal standard in $CDCl_3$. EI Mass spectra were recorded on Finnigan MAT- 1020 spectrometer at 70 *eV* using a direct inlet system.

1-chloropentadecan-2-ol (55)



To a stirred solution of (±)-epichlorohydrin **53** (14.00 g, 152.3 mmol) and CuI (2.90 g, 15.2 mmol) in dry THF (150 mL), was added a solution dodecylmagnesium bromide prepared form dodecyl bromide (113.12 g, 453.9 mmol) and Mg turning (7.40 g, 304.6 mmol) in dry THF, dropwise at –40 °C. The mixture was warmed to -20 °C over 12 h and poured into a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined solvent extracts were dried over Na_2SO_4. The extracts were concentrated to near dryness and purified on silica gel column chromatography (EtOAc/petroleum ether, 1:9) to give **55** (9.06 g, 84%) as colorless oil.

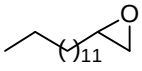
IR (neat): ν_{max} 3409, 2955, 1467, 1216 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, 3H), 1.26 (s, 20H), 1.43-1.64 (m, 4H), 2.02 (s, 1H), 3.40-3.55 (m, 1H), 3.57-3.72 (m, 1H), 3.75-3.89 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ14.0, 22.6, 25.4, 29.3-29.6 (br, several overlapped signals), 31.8, 34.1, 50.4, 71.4.

ESI-MS: *m/z* = 285 $[M + Na]^+$

2-Tridecyloxirane (56)



To a solution of crude compound **55** (8g, 30.43 mmol) in Et_2O (50 mL) was added finely powdered KOH (5.12 g, 91.3 mmol). The mixture was stirred vigorously for 6 h and poured into 50 mL water. After separation of the layers, the aqueous layer was extracted with Et_2O (3 x 150 mL) and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent and silica gel column chromatographic

purification (petroleum ether) of the crude product gave **56** (6.35 g, 92%) as a colorless liquid.

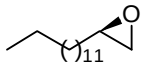
IR ($CHCl_3$): ν_{max} 3018, 2952, 2929, 2862, 1472, 1466, 1379, 1260, 1022, 916, 828 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J*= 6.57, 3H), 1.26 (s, 20H), 1.42-1.59 (m, 4H), 2.46 (dd, *J* = 2.78, 5.06 Hz, 1H), 2.75 (dd, *J* = 4.03, 5.03 Hz, 1H), 2.87-2.95 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.6, 25.9, 29.6-29.3(br, several overlapped signals), 31.9, 32.5, 47.0, 52.3.

ESI-MS: *m/z* = 249 $[M + Na]^+$

(*R*)-2-Tridecyloxirane (56a)



A solution of epoxide **56** (7.5 g, 33.13 mmol) and (*R,R*)-Salen-Co(III)-OAc (0.109 g, 0.17 mmol) in THF (0.5 mL) was stirred at 0^{o}C for 5 min, and then distilled water (327 μL, 18.22 mmol) was added. After stirring for 24 h, it was concentrated and purified by silica gel column chromatography using pet ether to afford **56a (**3.45 g, 46%) as a yellow color liquid. Continued chromatography with pet ether/EtOAc (4:1) provided the diol **56b** as a brown color liquid as a single diastereomer.

Yield: 3.45 g, 46%. $[\alpha]_D^{25}$ +6.54 (*c* 1.0, $CHCl_3$).

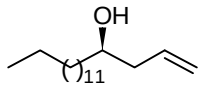
IR (neat): ν_{max} 3018, 2869, 1736, 1467, 1216, 915, 828 cm^{-1}.

^{1}H NMR (200 MHz, CDCl3): δ 0.88 (t, *J*= 6.57, 3H), 1.26 (s, 20H), 1.42-1.59 (m, 4H), 2.45 (dd, *J* = 2.80, 5.05 Hz, 1H), 2.77 (dd, *J* = 4.04, 5.06 Hz, 1H), 2.84-2.93 (m, 1H).

^{13}C NMR (50 MHz, CDCl3): δ 14.0, 22.6, 25.9, 29.6-29.3(br, several overlapped signals), 31.9, 32.4, 46.9, 52.1.

ESI-MS: *m/z* = 249 $[M + Na]^+$

(*R*)-Heptadec-1-en-4-ol (57)



To a stirred solution of **56a** (3.25 g, 14.36 mmol) and CuI (274 mg, 1.44 mmol) in dry THF (30 mL), was added , 1 M solution of vinylmagnesium bromide in THF (3.07 g, 28.72 mmol, 28.72 ml, 1M solution in THF) dropwise over a period of 30 min. at -20 °C and stirred for 12 h. The mixture was allowed to warm up to 0 °C, before it was quenched with a saturated NH_4Cl solution (20 mL). The layers were separated, the aqueous layer extracted with Et_2O (3 x 50 mL), the combined ethereal extracts were washed with brine (20 mL) and dried (Na_2SO_4) Evaporation of the solvent and silica gel column chromatographic purification (EtOAc/ petroleum ether 1:19) of the crude product gave **57** as a colorless oil.

Yield: 3.24 g, 89%; $[\alpha]_D^{25}$ +4.92 (*c* 1.0, $CHCl_3$).

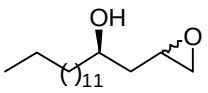
IR ($CHCl_3$): υ_{max} 3372, 2955, 1640, 1467, 1216 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3H), 1.26 (s, 22H), 1.46–1.44 (m, 2H), 1.65 (s, 1H), 2.21–2.05 (m, 1H), 2.38– 2.24 (m, 1H), 3.70–3.57 (m, 1H), 5.19–5.08 (m, 2H), 5.94– 5.73 (m, 1H).

^{13}C NMR (50 MHz, CDCl3): δ 14.1, 22.7, 25.7, 29.3-29.6 (br, several overlapped signals), 31.9, 36.8, 41.9, 70.7, 118.0, 134.9.

ESI-MS: *m/z* = 277 $[M + Na]^+$

(2*R*)-1-(Oxiran-2-yl)pentadecan-2-ol (58)



To a stirred solution of olefin **57** (2.5 g, 87.08 mmol) in CH_2Cl_2 (30 mL) at 0 ^oC was added *m*-CPBA (50%) (5.10 g, 14.75 mmol). The reaction mixture was stirred at room temperature for 10 h and quenched by saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography using pet ether/EtOAc (9:1) as eluent to yield the epoxide **58** as a white solid in diastereomeric mixture (1.5:1).

Yield: 2.55 g, 96%.

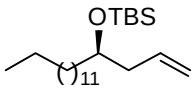
IR ($CHCl_3$): υ_{max} 3436, 3192, 2968, 2932, 2852, 1471, 1379, 1265, 1206, 1101, 944, 878 $cm.^{-1}$

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 3H), 1.26 (s, 22H), 1.40-1.68 (m, 4H), 1.79-1.94 (m, 1H), 2.52 (dd, *J*= 2.78, 4.93, 0.4 H), 2.64 (dd, *J*=2.90, 4.93, 0.6H), 2.79-2.87 (m, 1H), 3.07-3.23 (m, 1H), 3.78-3.97 (m, 1H), 4.52 (brs, 1H) (mixture of diastereomers).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.1, 22.6, 25.4, 25.5, 29.3, 29.6 (br, several overlapped signals), 31.9, 37.4, 37.5, 38.8, 39.6, 46.6, 46.9, 50.3, 50.7, 69.3, 70.6 (mixture of diastereomers).

ESI-MS: *m/z* = 293 $[M + Na]^+$

(*R*)-*Tert*-butyl(heptadec-1-en-4-yloxy)dimethylsilane (59)



To a stirred solution of alcohol **57** (1 g, 3.93 mmol) in CH_2Cl_2 (15 mL) was added imidazole (0.53 g, 7.86 mmol). To this solution *t*-butyl dimethylchlorosilane (0.77 g, 5.10 mmol) was added at 0 ^oC and reaction was stirred at room temperature for 3 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 x 20 mL). The extract was washed with brine, dried

(Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether as eluent provided **59** as a colorless liquid (1.33 g, 92%). $[\alpha]_D^{25}$ +5.37 (*c* 1.0, $CHCl_3$).

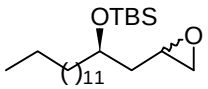
IR ($CHCl_3$): ν_{max} 3088, 2929, 2896, 1642, 1255, 1129 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.90 (s, 9H), 0.90 (merged t, 3H), 1.27 (s, 22H), 1.36-1.43 (m, 2H), 2.18-2.25 (m, 2H), 3.69 (quintet, *J*=5.69, 1H), 4.99-5.03 (m, 1H), 5.05-5.09 (m, 1H), 5.73-5.93 (m, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = -4.5, -4.3, 14.1, 18.1, 22.7, 25.3, 25.7, 25.9, 29.4, 29.7 (br, several overlapped signals), 31.9, 36.8, 41.9, 72.0, 116.4, 135.5

ESI-MS: *m/z* = 391 $[M + Na]^+$

***tert*-Butyldimethyl(((2*R*)-1-(oxiran-2-yl)pentadecan-2-yl)oxy)silane (60b)**



To a stirred solution of alcohol **58** (2 g, 7.40 mmol) in CH_2Cl_2 (25 mL) was added imidazole (1.00 g, 14.81 mmol). To this solution *t*-butyl dimethylchlorosilane (1.45 g, 9.63 mmol) was added at 0 ^oC and reaction was stirred at room temperature for 4 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 x 20 mL). The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (19:1) as eluent provided **60b** as a colorless liquid (2.72 g, 95%).

Compound 60a:

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.05, 0.06 (2s, 2.4H), 0.08 (s, 3.6H), 0.88 (t, *J*=7.03, 3H), 0.89 (s, 3.6H), 0.90 (s, 5.4H), 1.26 (s, 22H), 1.48-1.53 (m, 2H), 1.58-1.64 (m,1H), 1.65-1.75 (m, 1H), 2.45 (dd, *J* = 2.72, 5.07, 0.4H), 2.48 (dd, *J* = 2.68, 5.06, 0.6H), 2.75 (t, *J* = 4.53, 0.4H), 2.79 (t, *J* = 4.97, 0.6H), 3.00-3.06 (m, 1H), 3.82-3.91 (m, 1H) (mixture of diastereomers).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = -4.7, -4.6, -4.5, -4.4, 14.9, 18.0, 22.6, 25.0, 25.4, 25.8, 29.3, 29.6 (br, several overlapped signals), 31.9, 37.1, 37.9, 40.1, 40.2, 46.8, 47.7, 49.5, 49.9, 70.1, 70.4 (mixture of diastereomers).

Compound 60b:

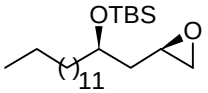
^{1}H NMR (500 MHz, $CDCl_3$): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.06, 0.07 (2s, 3.6H), 0.09 (2s, 2.4H), 0.89 (t, *J*=7.05, 3H), 0.90 (2s, 9H), 1.26 (s, 22H), 1.48-1.55 (m, 2H), 1.60-1.64 (m,1H), 1.70-1.76 (m, 1H), 2.46 (dd, *J* = 2.72, 5.07, 0.57H), 2.48 (dd, *J* = 2.68, 5.06, 0.43H), 2.76 (t, *J*= 4.53, 0.57H), 2.80 (t, *J* = 4.90, 0.43H), 3.01-3.07 (m, 1H), 3.84-3.91 (m, 1H) (mixture of diastereomers).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = -4.7, -4.6, -4.5, -4.4, 14.9, 18.0, 22.7, 25.0, 25.4, 25.8, 29.3, 29.6 (br, several overlapped signals), 31.9, 37.1, 37.9, 40.1, 40.2, 46.8, 47.7, 49.5, 50.0, 70.1, 70.4 (mixture of diastereomers).

IR ($CHCl_3$): υ_{max} 3041, 2926, 2854, 1465, 1255, 1070, 835, 773 cm^{-1}

ESI-MS: *m/z* =407 $[M + Na]^+$

***tert*-Butyldimethyl(((*R*)-1-((*R*)-oxiran-2-yl)pentadecan-2-yl)oxy)silane (51)**



A solution of epoxide **60b** (2.5 g, 6.49 mmol) and (*R,R*)-Salen-Co(III)-OAc (0.021 g, 0.32 mmol) in THF (0.3 mL) was stirred at 0 ^{o}C for 5 min, and then distilled water (64 μL, 3.57 mmol) was added. After stirring for 24 h, it was concentrated and purified by silica gel column chromatography using pet ether/EtOAc (19:1) to afford **51 (**1.23 g, 49%) as a yellow color liquid. Continued chromatography with pet ether/EtOAc (3:2) provided the diol **51a** as a brown color liquid as a single diastereomer. The diastereoselectivity was determined from ^{1}H NMR and ^{13}C NMR spectral data. $[\alpha]_D^{25}$ -8.42 (*c* 1.0, $CHCl_3$).

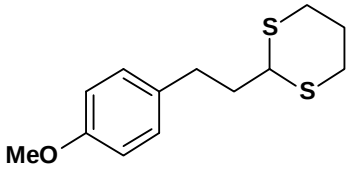
IR ($CHCl_3$): υ_{max} 3041, 2926, 2854, 1465, 1255, 1070, 835, 773 $cm.^{-1}$

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (t, *J*=7.03 Hz, 3H), 0.90 (s, 9H), 1.26 (s, 22H), 1.51-1.54 (m, 2H), 1.61 (dt, *J* =5.77 Hz, 13.81, 1H), 1.73 (dt, *J* = 5.83, 13.80 Hz, 1H), 2.46 (dd, *J* = 2.76, 5.02 Hz, 1H), 2.76 (t, *J* = 4.52 Hz, 1H), 3.02-3.07 (m,1H),3.85 (quintet, J =5.77, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = -4.5, -4.6, 14.11, 18.0, 22.7, 25.8, 29.4, 29.6, 29.7, 31.92, 37.2, 40.1, 46.8, 49.6, 70.4.

ESI-MS: *m/z* =407 $[M + Na]^+$

2-(4-Methoxyphenethyl)-1, 3-dithiane (52)



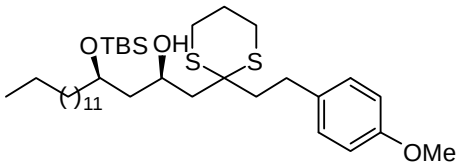
To a solution of aldehyde **63** (4.0 g, 24.09 mmol) in 40 mL of anhydrous DCM cooled to 0 ^oC was added 1,3-propanedithiol (2.93 mL, 28.90 mmol) and a catalytic amount of $BF_3.Et_2O$. The reaction mixture was allowed to stir at room temperature for 12 h. After completion of the reaction (TLC monitored), the reaction mixture was quenched with saturated solution of $NaHCO_3$, diluted with water and extracted with ethyl acetate (3 × 30 mL). The pooled organic layers were washed with saturated brine solution, dried over anhydrous Na_2SO_4, concentrated *in vacuo*. and residue was purified by silica gel column chromatography using pet ether/EtOAc (1:4) to afford dithiane **52** (5.46 g, 88 %) as white color liquid. .

IR ($CHCl_3$): υ_{max} 2995, 2904, 2831, 1654, 1610, 1512, 1438, 1246,1176, 1035, 908, 827 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.82-1.93 (m, 1H), 2.04 (q, *J* =7.27 Hz, 2H), 2.09-2.15 (m, 1H), 2.78 (t, *J* =7.72 Hz, 2H), 2.83-2.86 (m, 4H), 3.80 (s, 3H), 3.98 (t, *J*=7.03 Hz, 1H), 6.84 (d, *J* =8.78 Hz, 2H), 7.14 (d, *J*=8.78 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.9, 30.2, 31.5, 37.0, 46.4, 55.1, 113.7, 129.4, 132.8, 157.8.

(2*R*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-(2-(4-methoxyphenethyl)-1,3-dithian-2-yl)heptadecan-2-ol (50)



A flame dried two neck round bottom flask was charged with dithiane **52** (0.71 g, 2.81 mmol) under nitrogen and was added 10 mL of anhydrous THF and 1 mL of HMPA. The solution was cooled to -78 ^oC and to this was added *n*-BuLi (0.24g, 3.74 mmol, 2.34 mL of 1.6M in hexane) drop wise. The dark brown reaction mixture was stirred for 30 min and to this was added epoxide **51** (.70 g, 1.87 mmol) dissolved in 5 mL of anhydrous THF and 0.5 mL of HMPA drop wise. The reaction mixture was stirred for additional 30 min, then quenched with saturated solution of NH_4Cl, diluted with water (5 mL) and extracted with ethyl acetate (3 × 20 mL). Pooled organic layers were washed with saturated brine solution, dried over anhydrous Na_2SO_4, concentrated *in vacuo.* and residue was purified using silica gel column chromatography using a gradient of (10→20 %) ethyl acetate and light petroleum to afford coupled product **50** (1.25g, 87 %) as thick syrup. $[\alpha]_D^{25}$ -3.10 (*c* 1.0, $CHCl_3$).

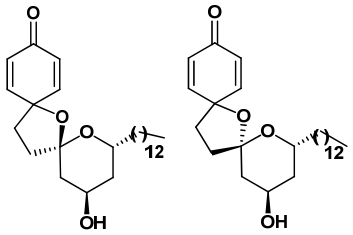
IR ($CHCl_3$): υ_{max} 3485, 2987, 2924, 2852, 2360, 1612, 1512, 1448, 1246,1055, 813,767 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.09 (s, 3H), 0.11 (s, 3H), 0.09 (t, *J*=3.46 Hz, 3H), 0.91 (s, 9H), 1.25 (s, 22H), 1.42-1.73 (m, 4H), 1.89-2.06 (m, 3H), 2.13-2.38 (m, 3H), 2.62-3.00 (m, 6H), 3.78 (s, 3H), 3.86-4.00(m, 1H), 4.06-4.35 (m, 1H), 6.83 (d, *J*=8.71 Hz, 2H), 7.14 (d, *J*=8.71 Hz, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = -4.5, -4.2, 14.1, 18.0, 22.7, 24.9, 25.1, 25.3, 25.9, 26.1, 26.2, 29.3, 29.6, 29.7, 29.8, 31.9, 37.2, 41.8, 44.7, 45.8, 52.1, 55.2, 66.9, 71.4, 113.8, 129.3, 133.9, 157.8 .

ESI-MS: ***m/z*** = 661 $[M + Na]^+$

(2*R*, 4*R*, 6*R*)-4-Hydroxy-2-tridecyl-1,7-dioxadispiro[5.1.5.2]pentadeca-9,12-dien-11-one (Aculeatin A, 1) and (2*R*,4*R*,6*S*)-4-Hydroxy- 2-tridecyl-1,7-dioxadispiro[5.1.5.2]pentadeca-9,12-dien- 11-one (Aculeatin B, 2)



A solution of compound **50** (0.50 g, 0.78 mmol) in 5 mL of dry CH_2Cl_2 was added at -78 ^oC a solution of 0.30 mL of BBr_3, (0.79g, 3.14 mmol, 3.14 mL of 1.0M in dichloromethane). After 2 h the mixture was warmed to -25 ^oC. The reaction was monitored by TLC; after completion, the mixture was quenched with saturated sodium hydrogen carbonate. After usual workup organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*. and residue after dryness and without purification was used for the next reaction.

To a solution of crude product **64** (0.10 g, 0.196 mmol) in an acetone + water mixture (9:1, 5 mL) was added $PhI(OCOCF_3)_2$ (0.21 g, 0.489 mmol) in a single portion. The reaction mixture was stirred for 4 h at room temperature. After completion of the reaction, saturated solution of $NaHCO_3$ was added and organic layers extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to give crude mixture of aculeatin A 1 and aculeatin B 2 which was purified on flash silica column chromatography using a gradient of (25→40 %) ethyl acetate and light petroleum to afford aculeatin A 1 (.039 g, 44%) and aculeatin B 2 (0.013 g, 15%).

Aculeatin A 1: $[\alpha]_D^{25}$ -5.3 (*c* 0.9, $CHCl_3$); lit[16].$[\alpha]_D^{25}$ -4.7 (*c* 2.0, $CHCl_3$).

IR (neat): υ_{max} 3491, 2934, 1673, 1622, 1516, 1463, 1099, 1053, 949, 846 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, *J*= 6.57, 3H), 1.27 (s, 21H), 1.40- 1.52 (m, 4H), 1.80 (d, *J* = 13.9 Hz, 1H), 1.93 (d, *J* = 13.9 Hz, 1H), 1.98-2.04 (m, 3H), 2.24 (dd, *J* = 7.26, 10.34 Hz, 1H), 2.33-2.43 (m, 1H), 3.37 (d, *J* = 9.76 Hz, 1H), 4.08-4.13 (m, 2H), 6.11(dd, *J* = 1.9,10.5 Hz, 1H), 6.15 (dd, *J* = 1.9, 10.5 Hz, 1H), 6.76 (dd, *J* = 3.05, 9.99 Hz, 1H), 6.85 (dd, *J* = 2.92, 9.99 Hz, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1, 22.6, 25.6, 29.3, 29.6 (br, several overlapped signals), 31.9, 34.1, 35.8, 37.9, 39.0, 64.8, 65.3, 79.7, 109.0, 127.0, 127.3, 148.7, 150.8, 185.3.

ESI-MS: *m/z* = 441 $[M + Na]^+$

Aculeatin B 2: $[\alpha]_D^{25}$ +47.2 (*c* 0.2, $CHCl_3$); lit.[16] $[\alpha]_D^{25}$ +46.8 (*c* 1.0, $CHCl_3$).

IR (neat): υ_{max} 3486, 2952, 1671, 1635, 1461, 1078, 980, 868 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, *J*= 6.52, 3H), 1.26 (s, 21H), 1.41- 1.52 (m, 4H), 1.56-1.64 (m, 2H), 1.87-1.97 (m, 2H), 2.01-2.11 (m, 2H), 2.33 (td, *J* = 7.36, 12.4 Hz, 1H), 2.69 (dd, *J* = 7.09, 13.07, 1H), 3.85-3.89 (m, 1H), 4.37-4.39 (m, 1H), 6.11 (dd, *J* = 1.9,10.5 Hz, 1H), 6.15 (dd, *J* = 1.9, 10.5 Hz, 1H), 6.77 (dd, *J* = 3.0, 10.5 Hz, 1H), 6.99 (dd, *J* = 2.93, 10.5 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1, 22.6, 25.9, 29.3, 29.4, 29.6 (br, several overlapped signals), 31.9, 35.2, 35.3, 35.7, 37.9, 40.5, 65.1, 69.4, 77.5, 108.4, 127.1, 149.1, 152.2, 185.6.

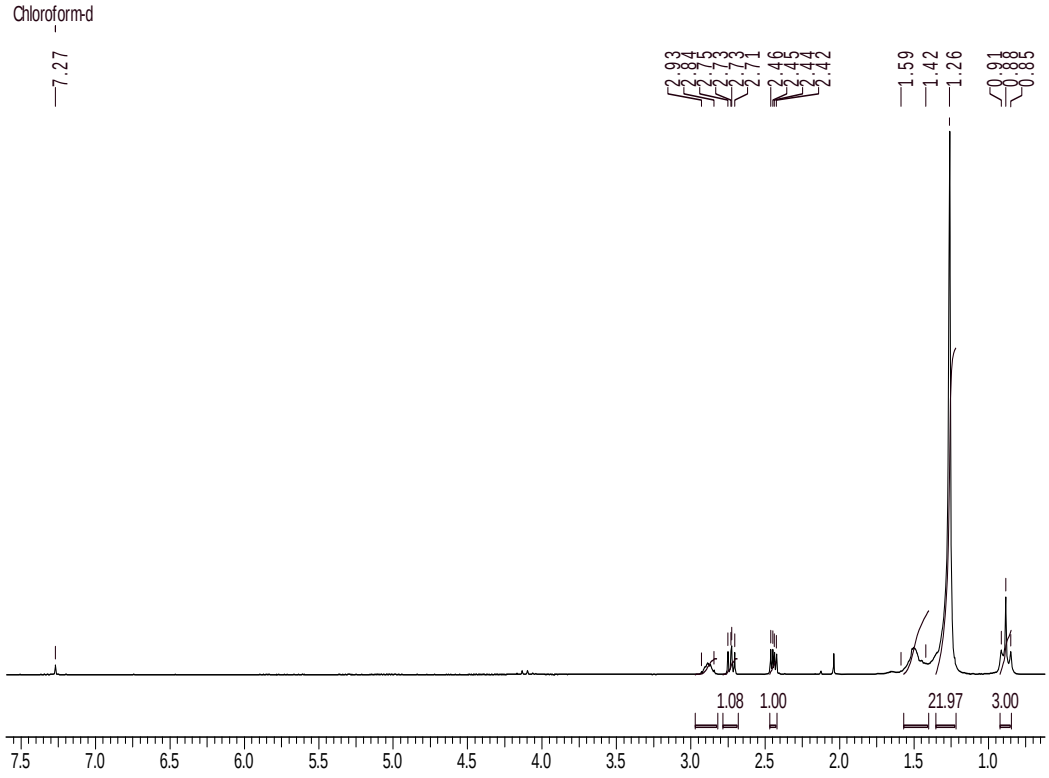
ESI-MS: *m/z* = 441 $[M + Na]^+$

Spectra

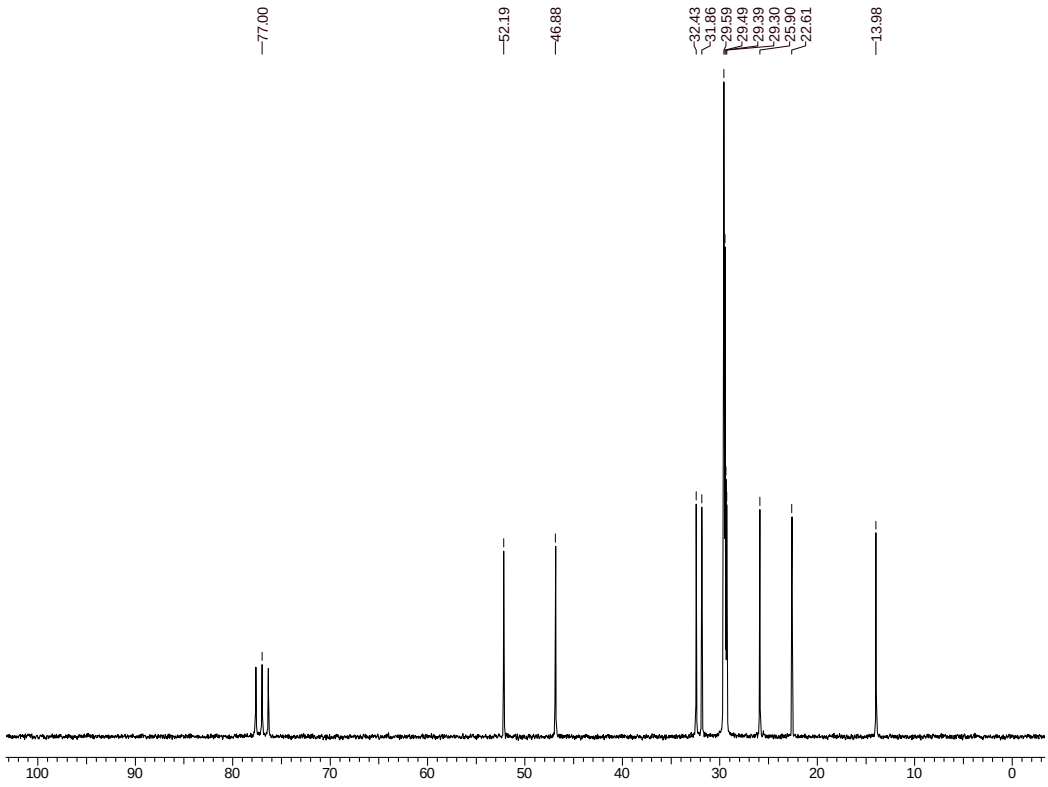
1. ^{1}H and ^{13}C NMR spectra of **56a**
2. ^{1}H and ^{13}C NMR spectra of **57**
3. ^{1}H and ^{13}C NMR spectra of **58**
4. ^{1}H and ^{13}C NMR spectra of **59**

5. ^{1}H and ^{13}C NMR spectra of **60a**
6. ^{1}H and ^{13}C NMR spectra of **60b**
7. ^{1}H and ^{13}C NMR spectra of **51**
8. ^{1}H and ^{13}C NMR spectra of **52**
9. ^{1}H and ^{13}C NMR spectra of **50**
10. ^{1}H and ^{13}C NMR spectra of **1**
11. ^{1}H and ^{13}C NMR spectra of **2**

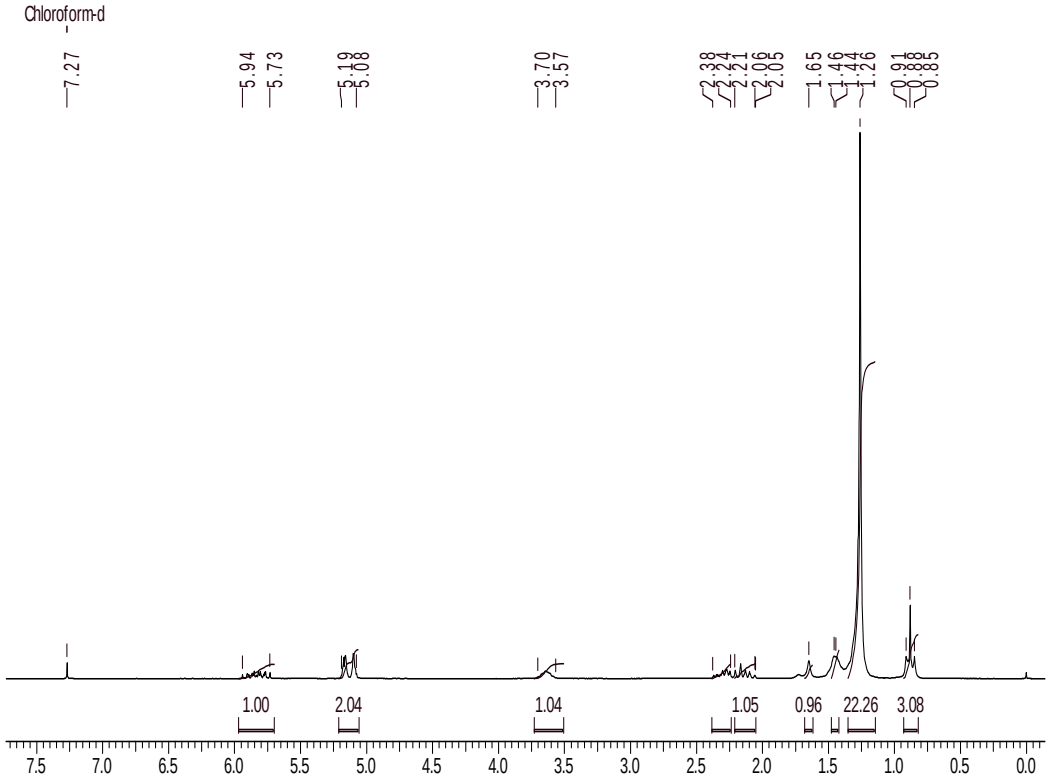
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*R*)-2-Tridecyloxirane (56a)



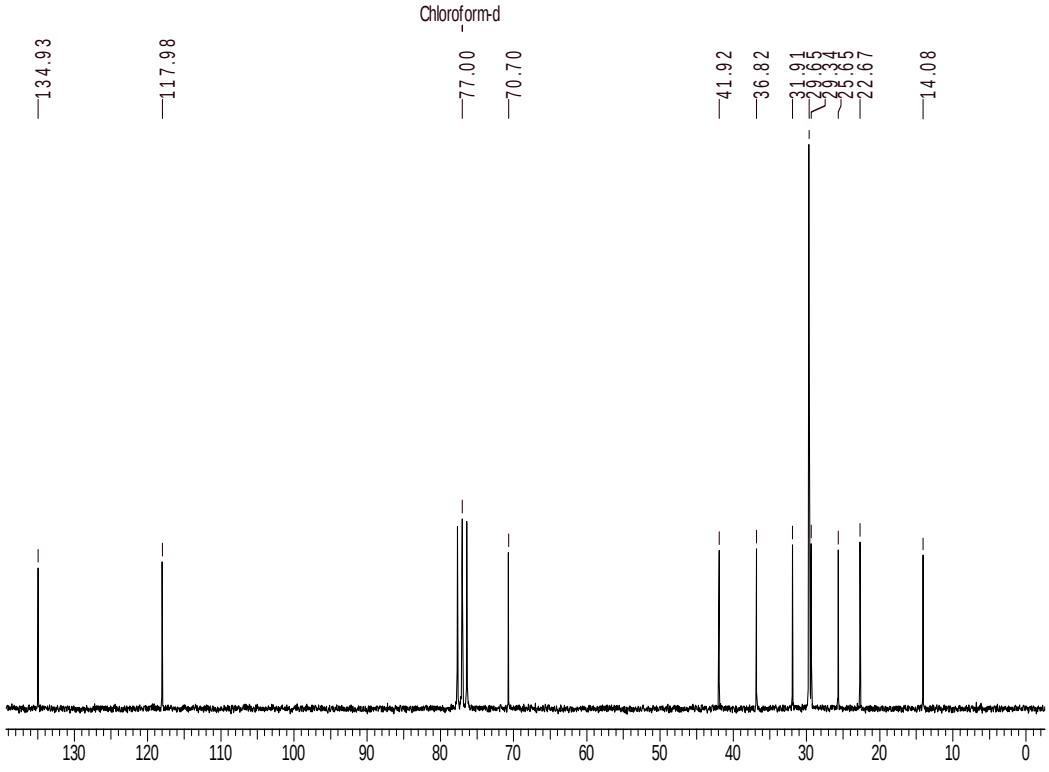
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*R*)-2-Tridecyloxirane (56a)



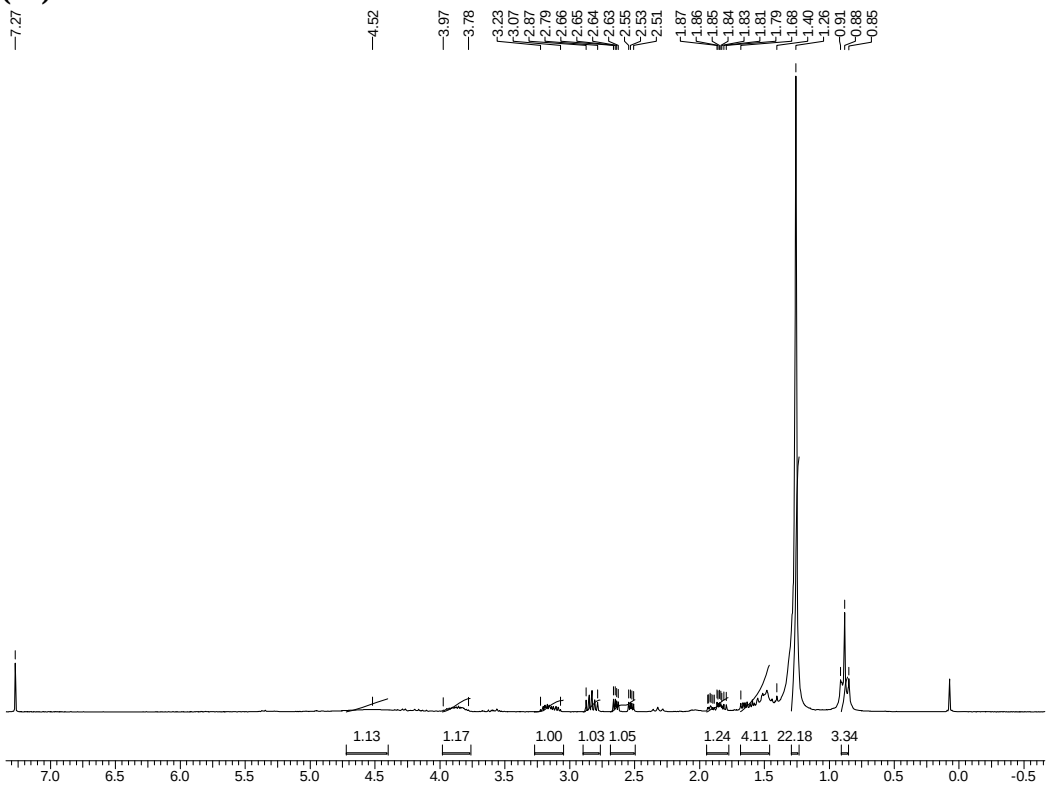
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*R*)-Heptadec-1-en-4-ol (57)



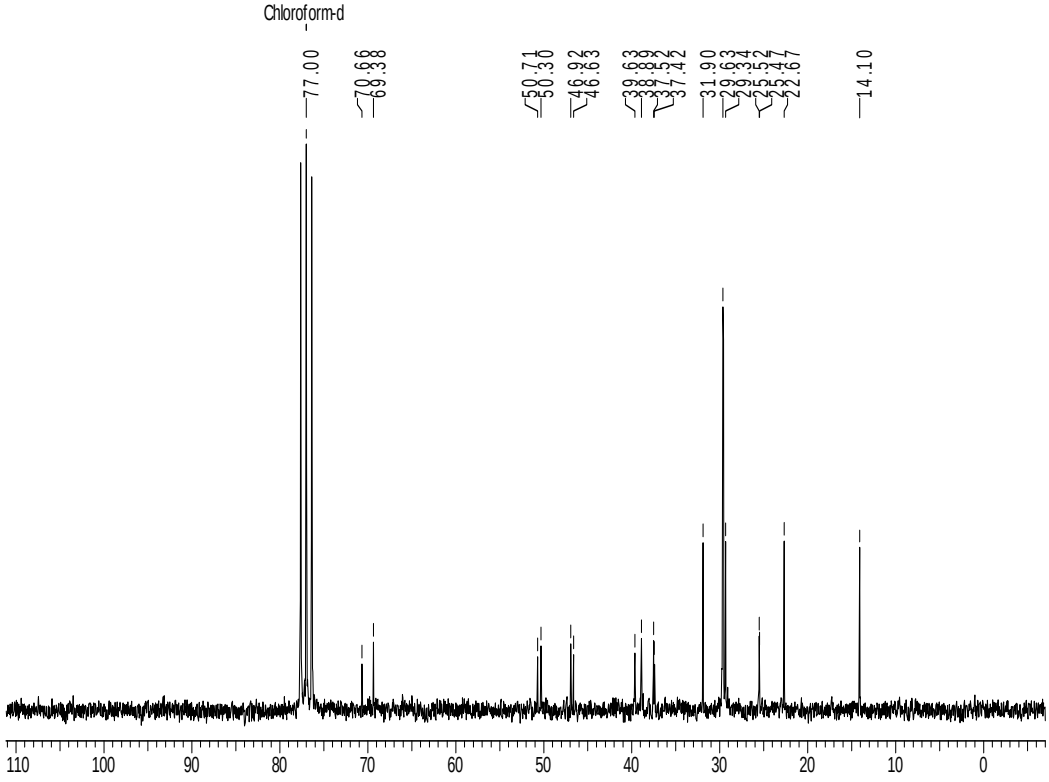
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*R*)-Heptadec-1-en-4-ol (57)



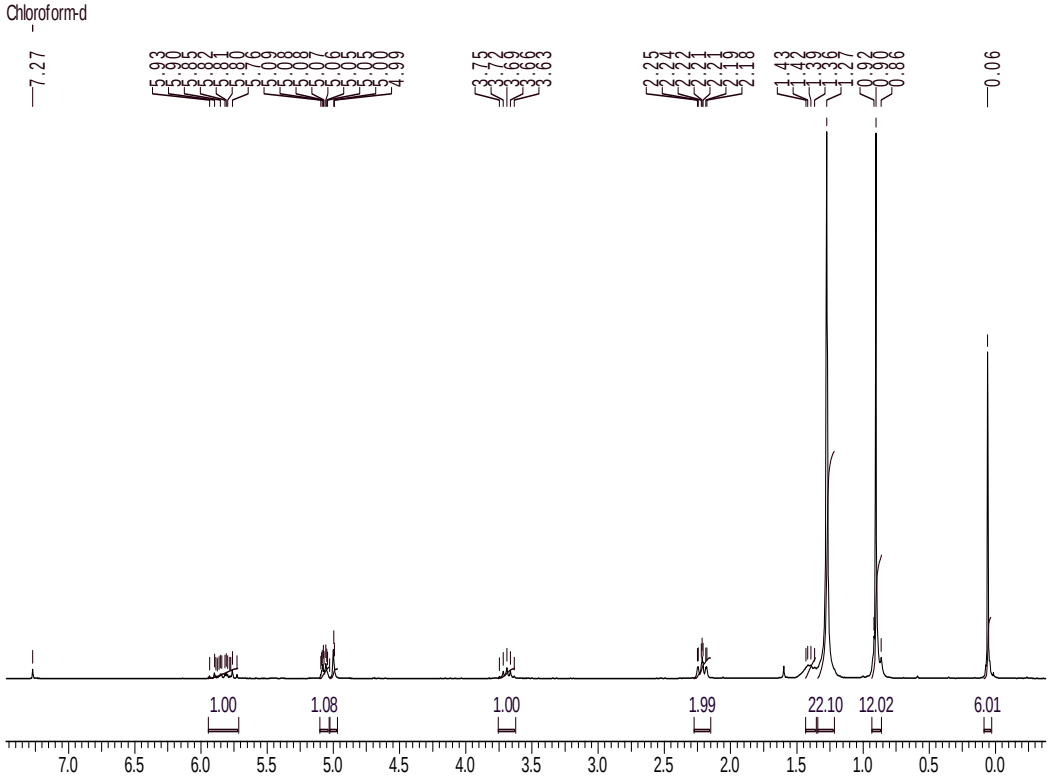
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (2*R*)-1-(Oxiran-2-yl)pentadecan-2-ol (58)



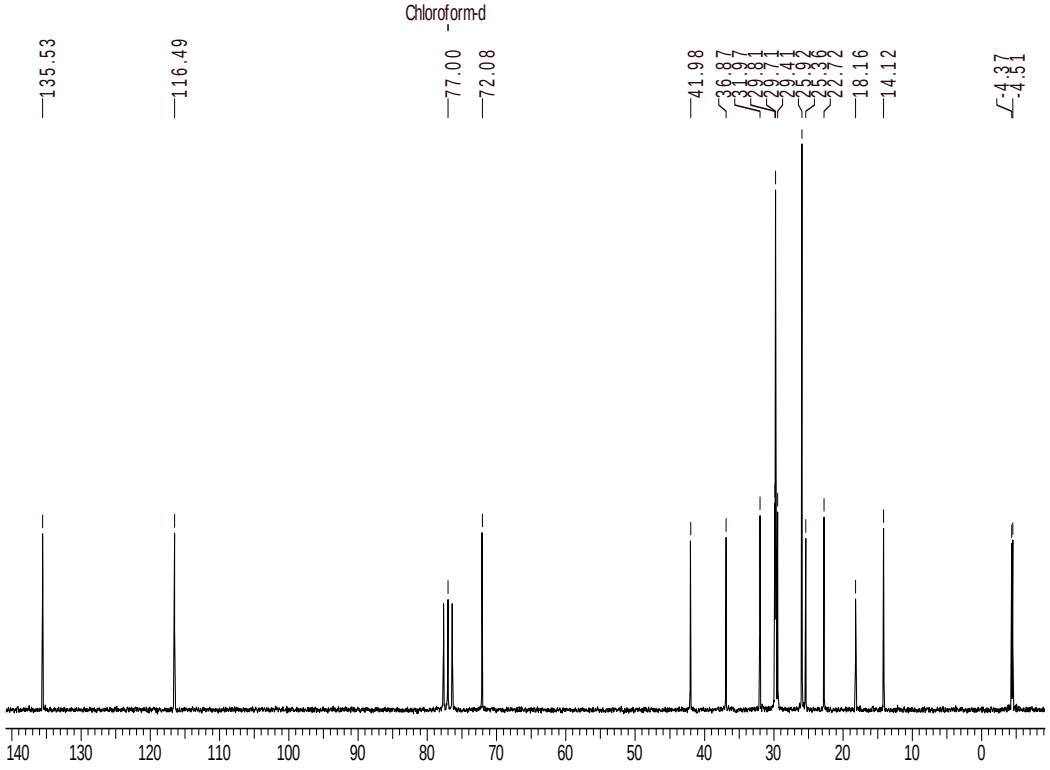
^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of of (2*R*)-1-(Oxiran-2-yl)pentadecan-2-ol (58)



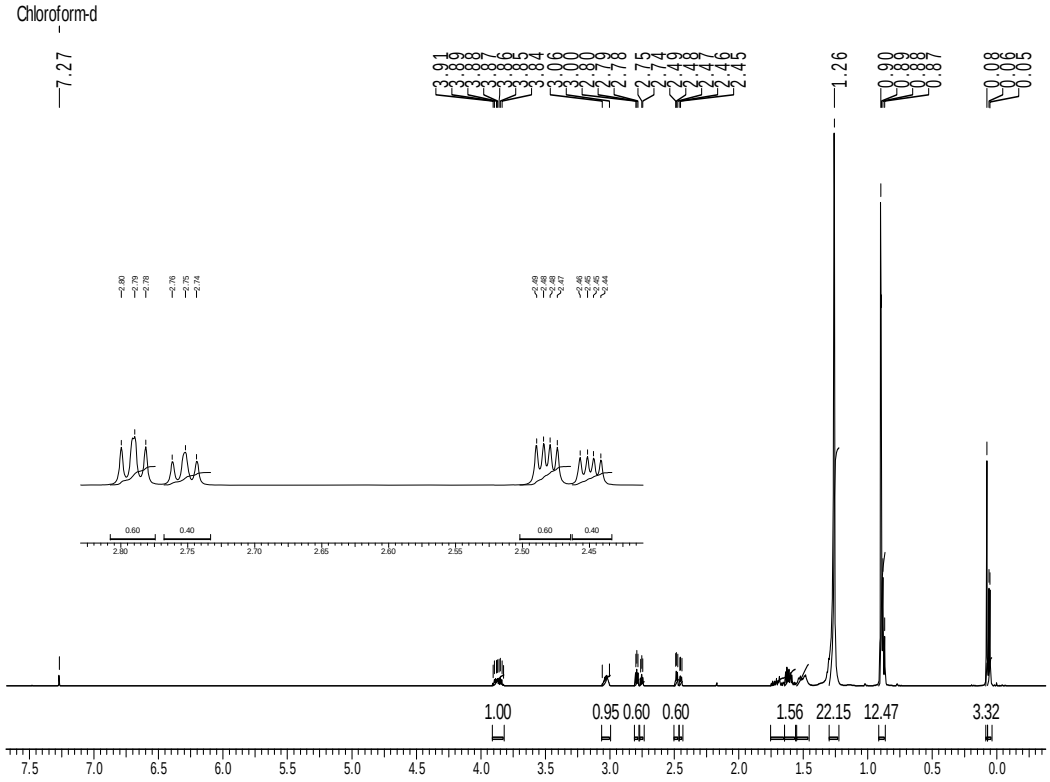
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*R*)-*Tert*-butyl(heptadec-1-en-4-yloxy)dimethylsilane (59)



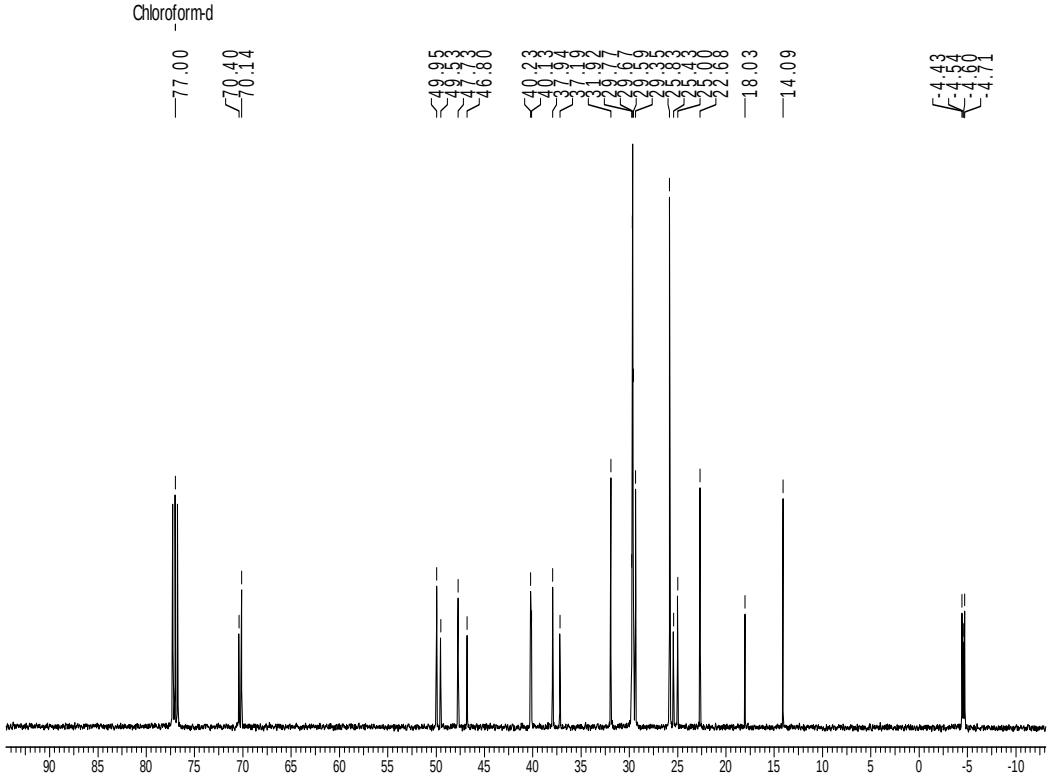
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*R*)-*Tert*-butyl(heptadec-1-en-4-yloxy)dimethylsilane (59)



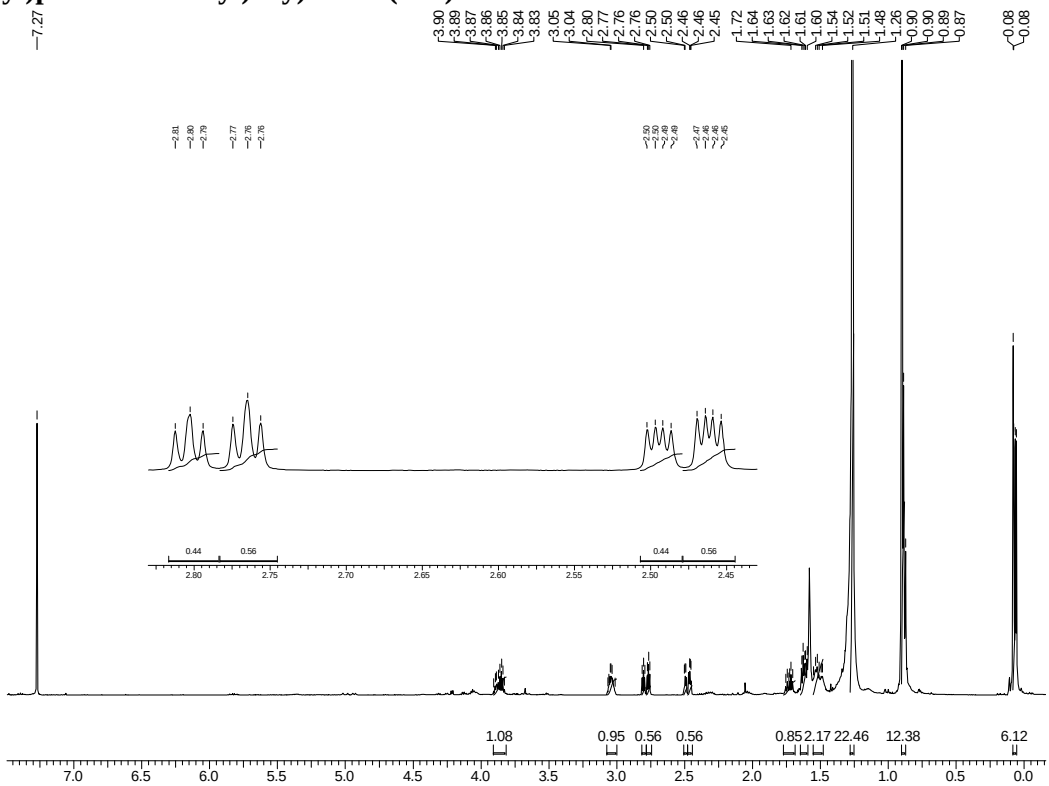
^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of *tert*-Butyldimethyl(((2*R*)-1-(oxiran-2-yl)pentadecan-2-yl)oxy)silane (60a)



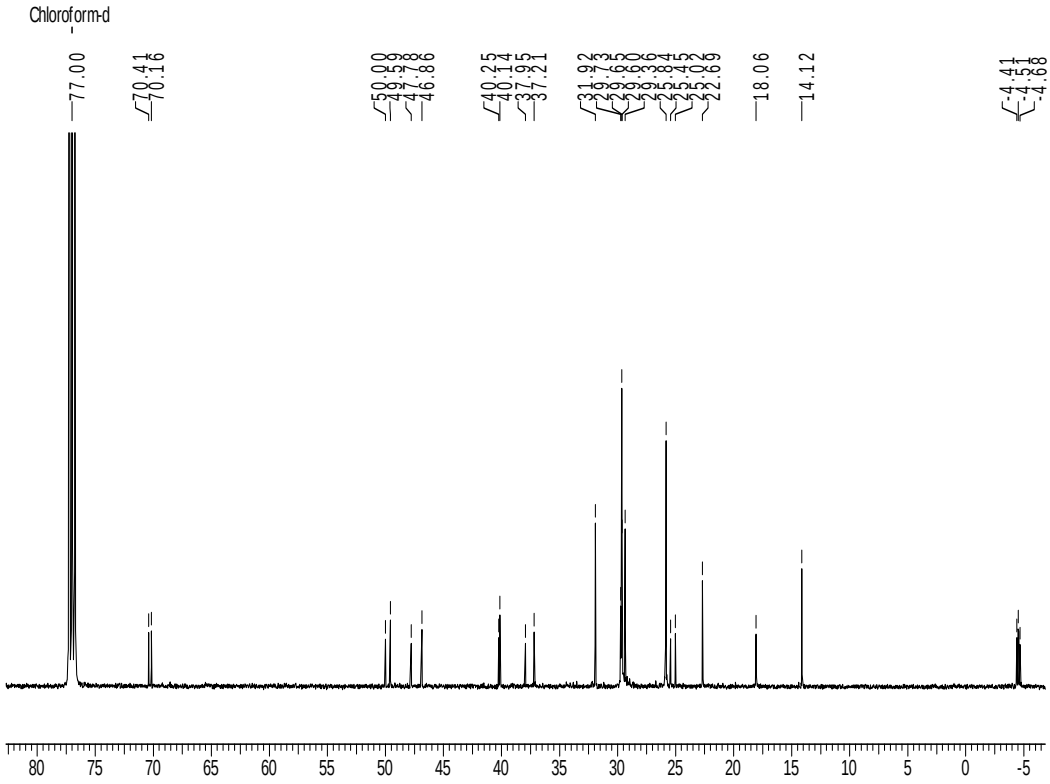
^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of *tert*-Butyldimethyl(((2*R*)-1-(oxiran-2-yl)pentadecan-2-yl)oxy)silane (60a)



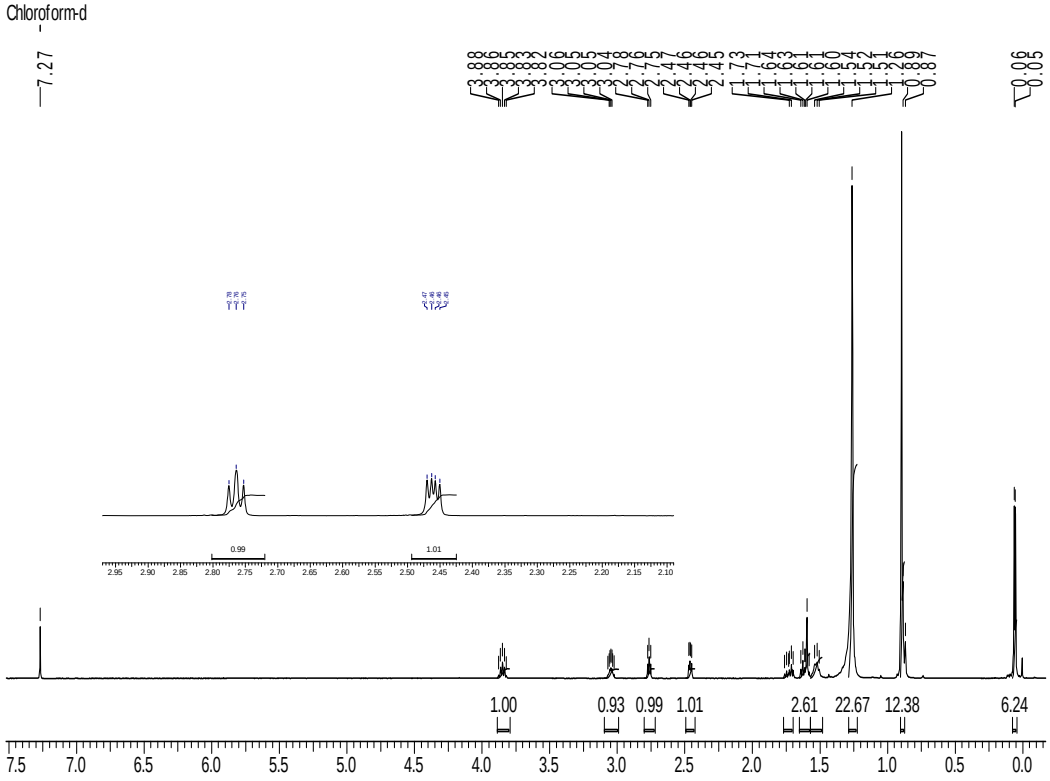
^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of *tert*-Butyldimethyl(((2*R*)-1-(oxiran-2-yl)pentadecan-2-yl)oxy)silane (60b)



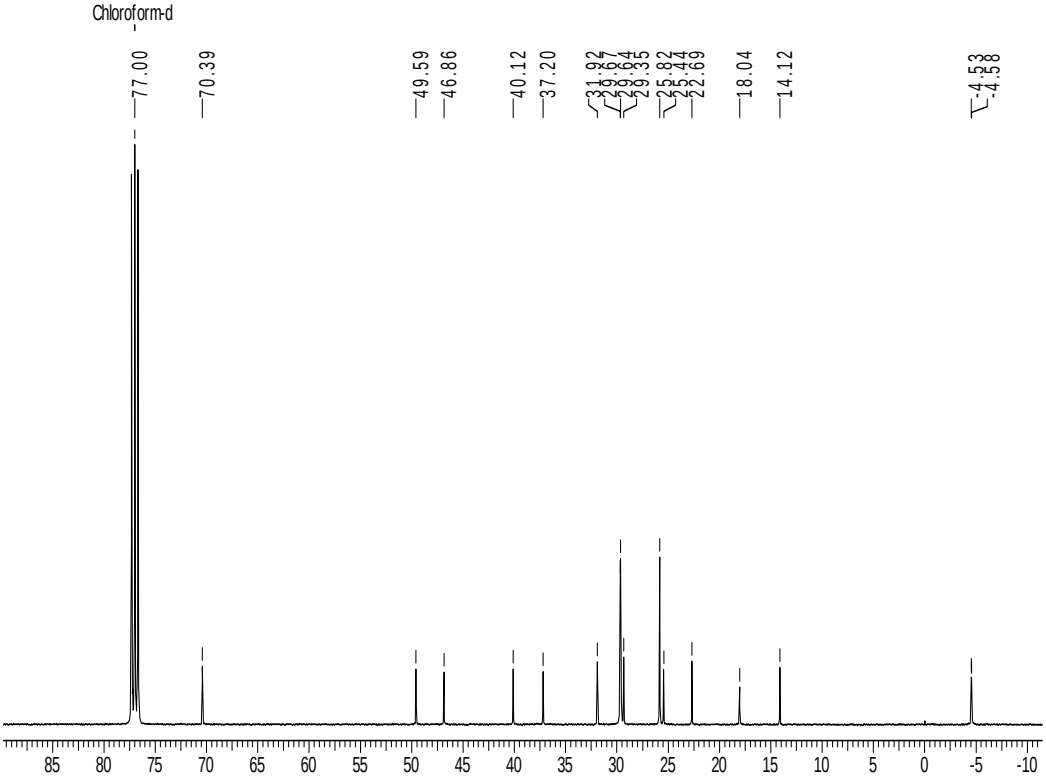
^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of *tert*-Butyldimethyl(((2*R*)-1-(oxiran-2-yl)pentadecan-2-yl)oxy)silane (60b)



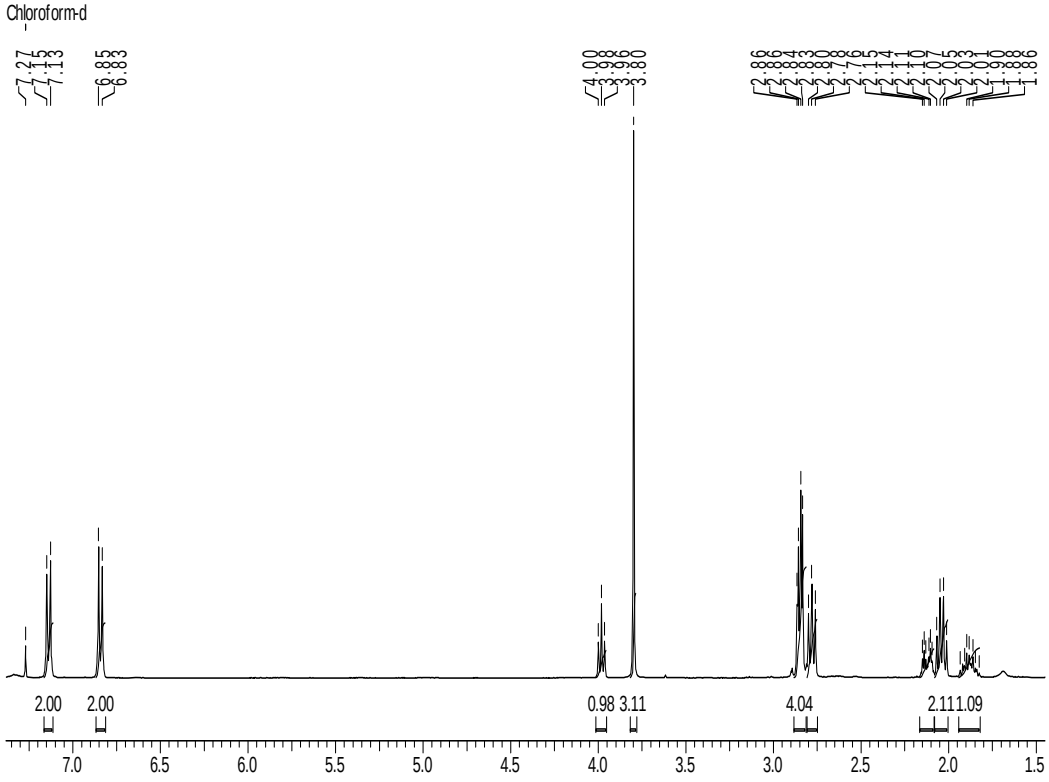
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *tert*-Butyldimethyl(((*R*)-1-((*R*)-oxiran-2-yl)pentadecan-2-yl)oxy)silane (51)



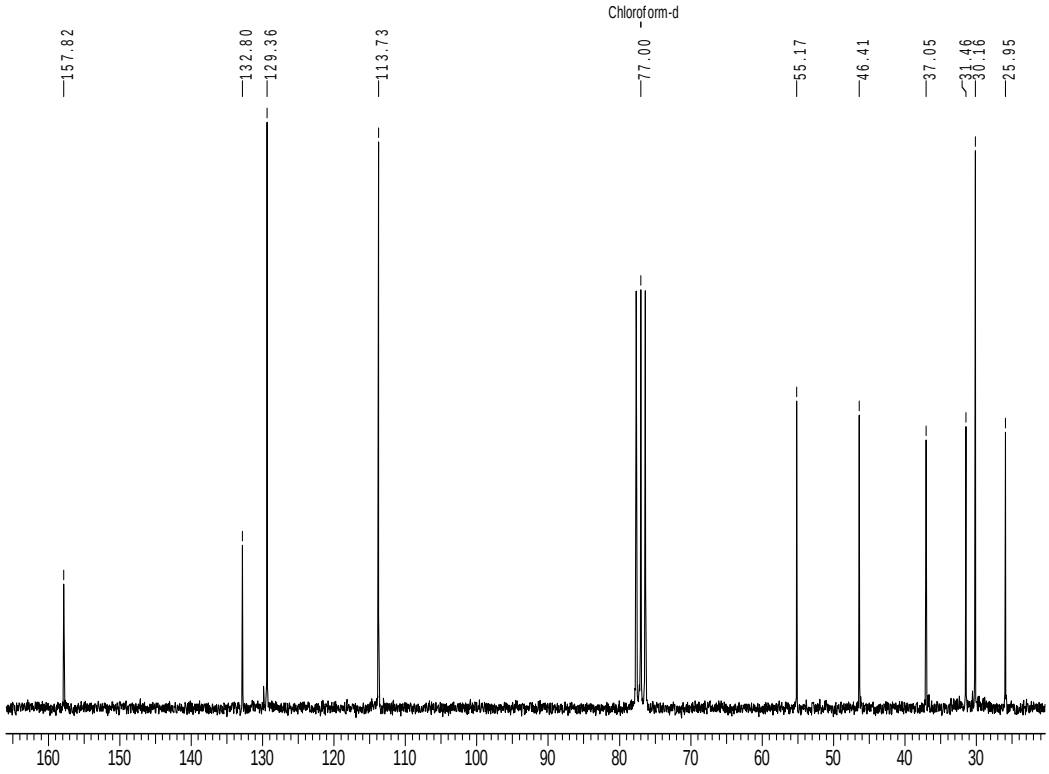
^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of *tert*-Butyldimethyl(((*R*)-1-((*R*)-oxiran-2-yl)pentadecan-2-yl)oxy)silane (51)



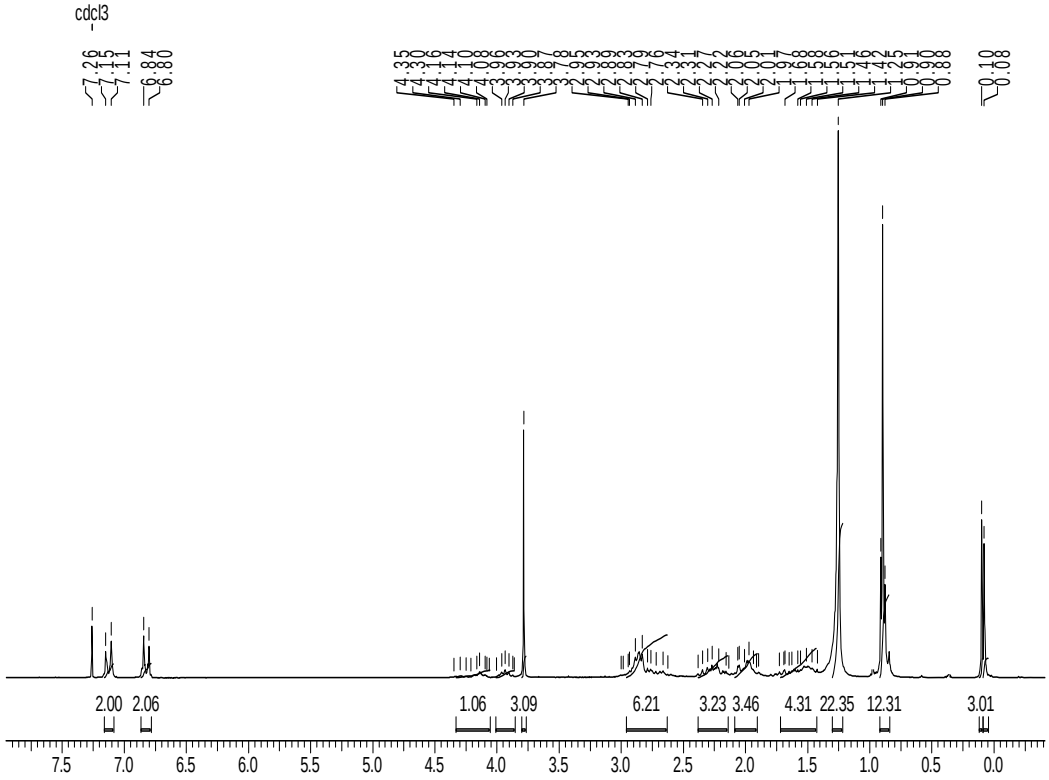
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of 2-(4-Methoxyphenethyl)-1, 3-dithiane (52)



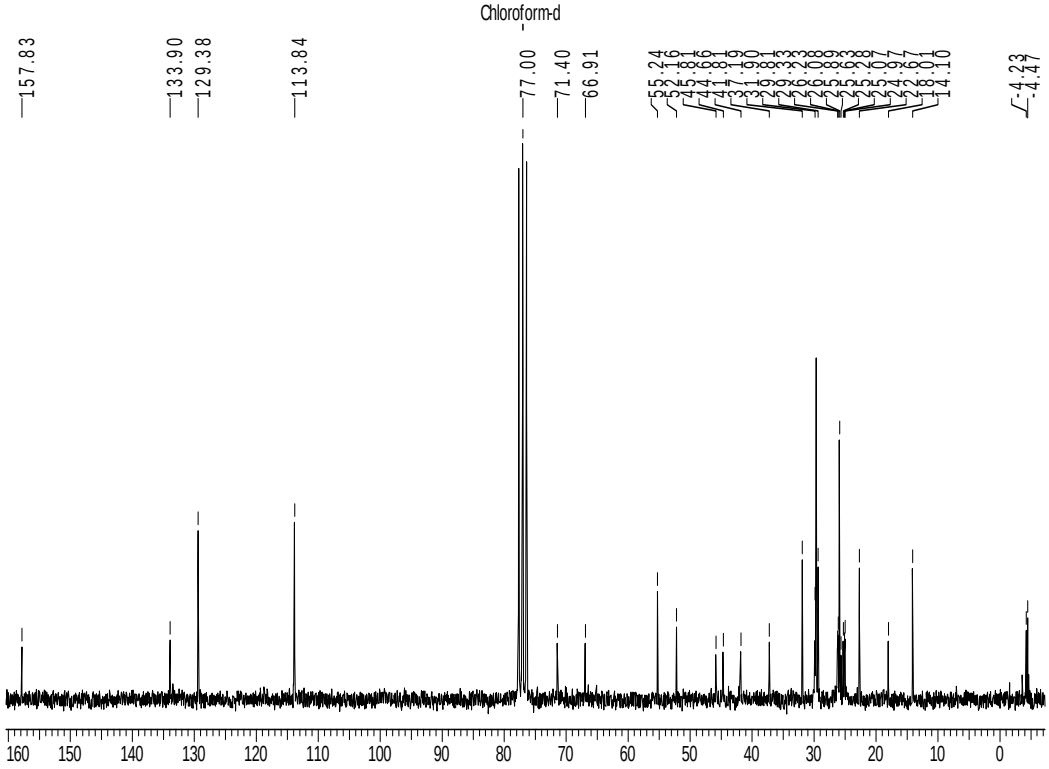
^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of 2-(4-Methoxyphenethyl)-1, 3-dithiane (52)



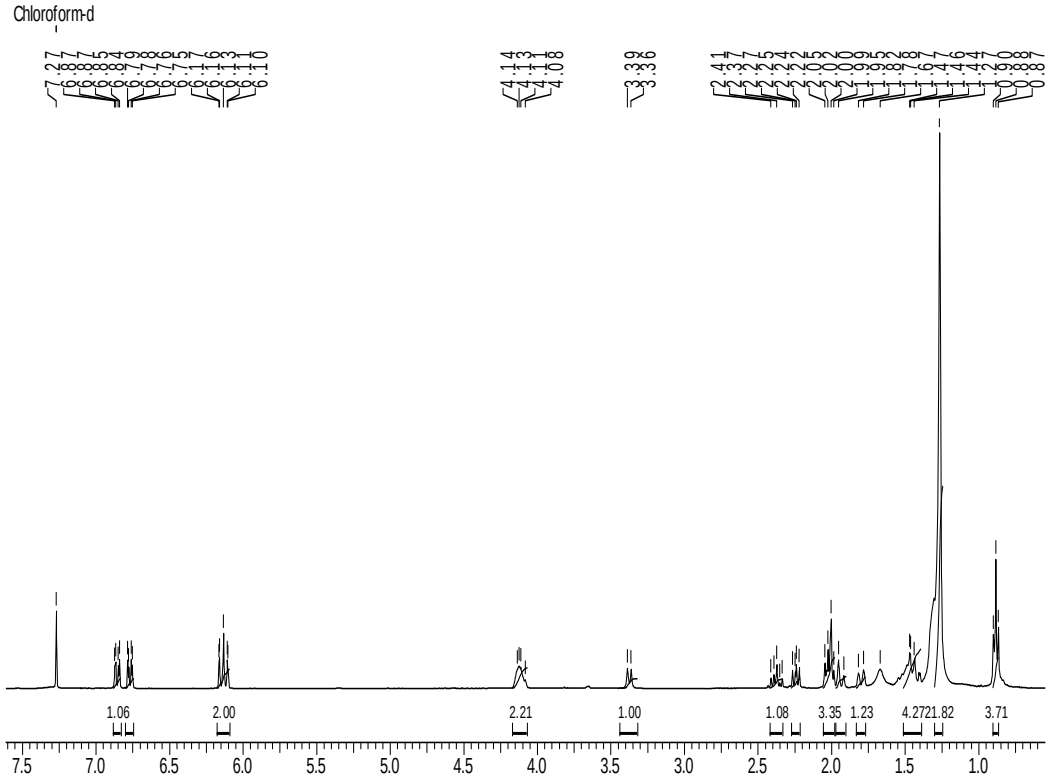
^{1}H NMR ($CDCl_3$, 200 MHz) (2*R*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-(2-(4-methoxyphenethyl)-1,3-dithian-2-yl)heptadecan-2-ol (50)



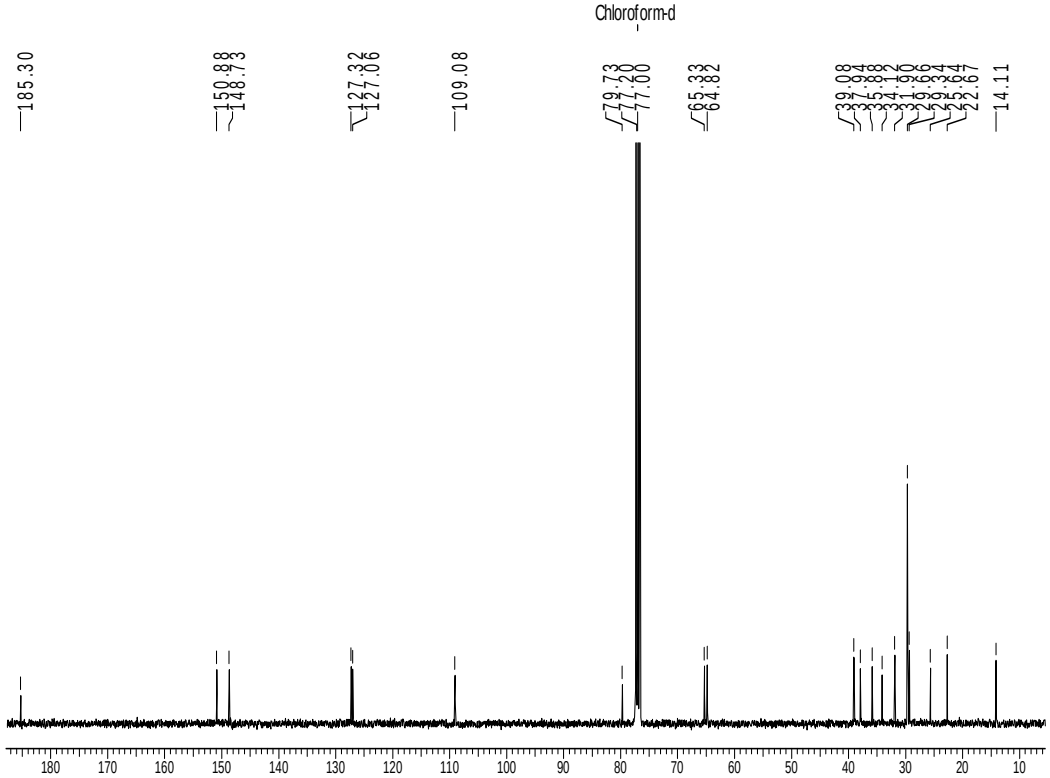
^{13}C NMR ($CDCl_3$, 50 MHz) (2*R*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-(2-(4-methoxyphenethyl)-1,3-dithian-2-yl)heptadecan-2-ol (50)



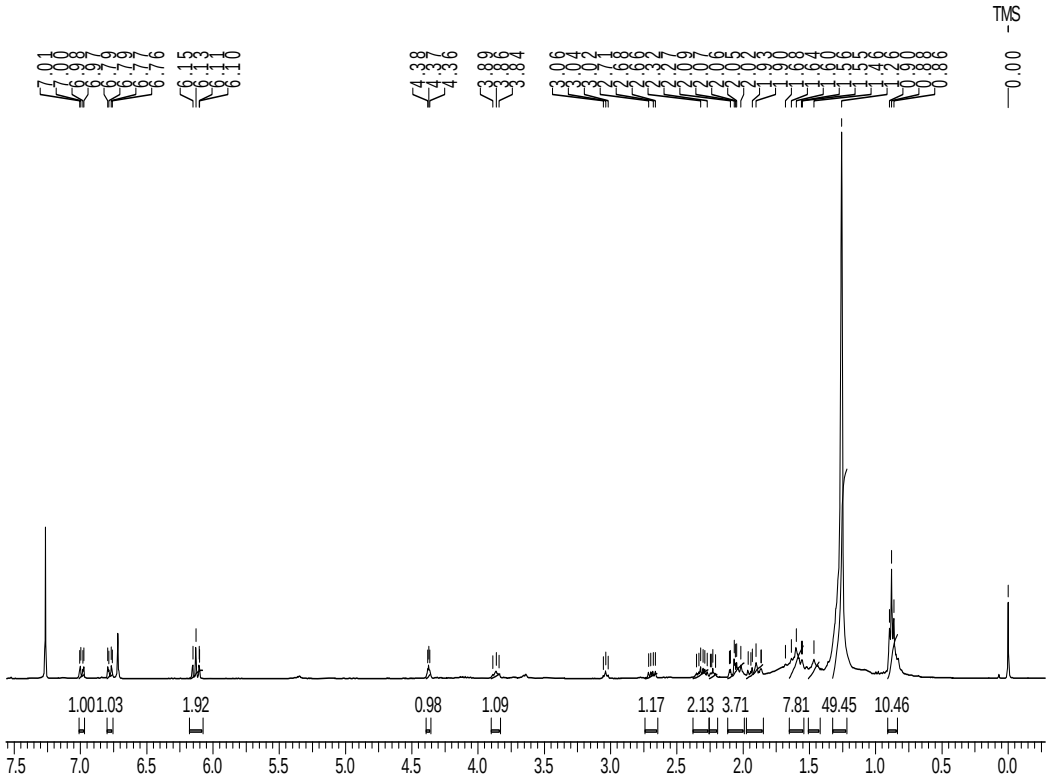
^{1}H NMR ($CDCl_3$, 400 MHz) (Aculeatin A, 1)



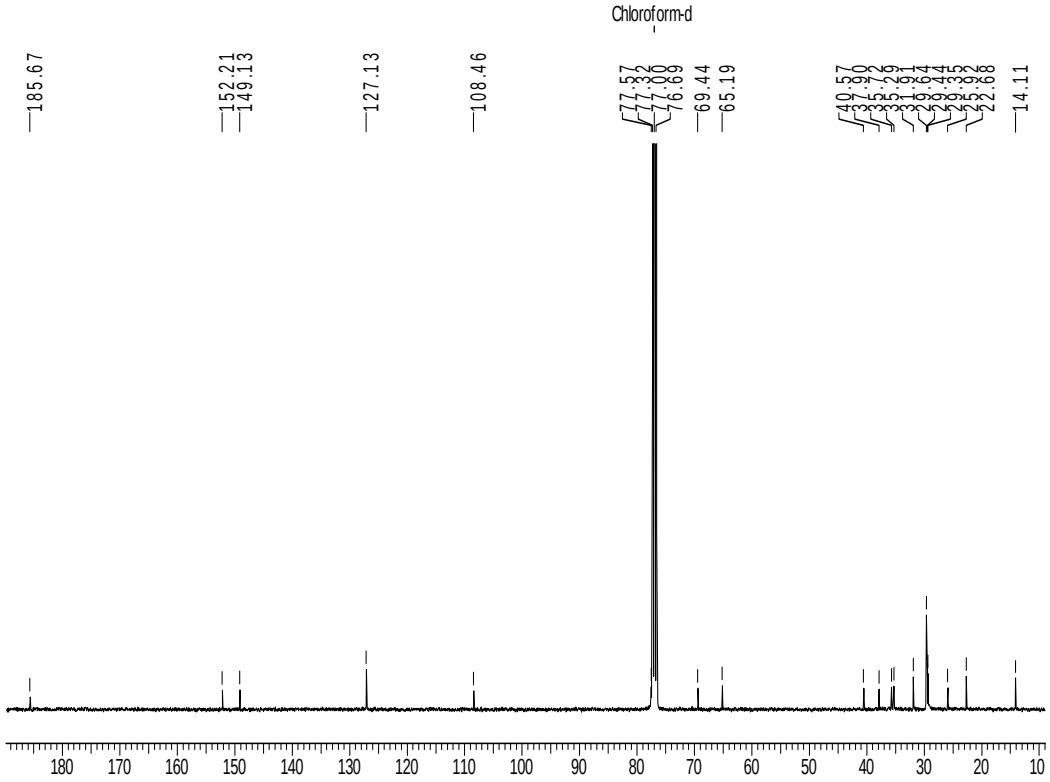
^{13}C NMR ($CDCl_3$, 100 MHz) (Aculeatin A, 1)



^{1}H NMR ($CDCl_3$, 400 MHz) (Aculeatin B, 2)



^{13}C NMR ($CDCl_3$, 100 MHz) (Aculeatin B, 2)



Chapter II, Section B

Synthesis of Aculeatins F and *epi*-F

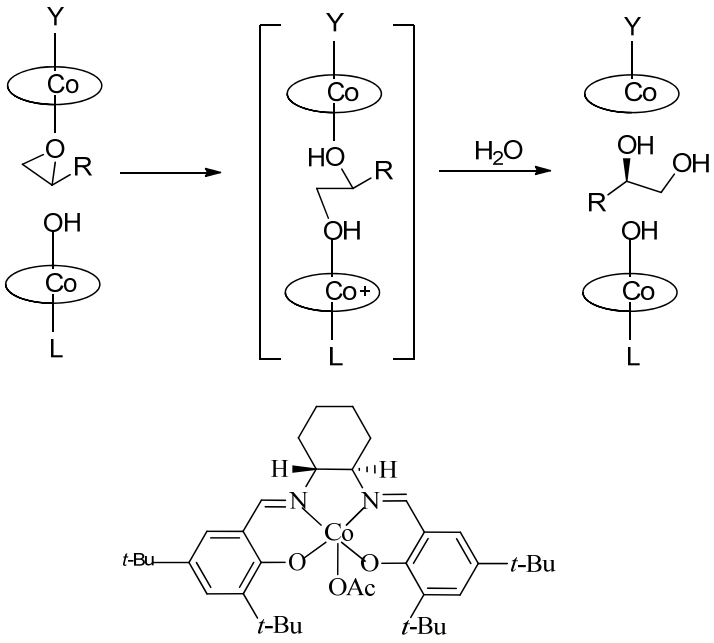
Present work

Objective

In the discovery of new anticancer agents of plant origin, Kinghorn *et al*. reported the isolation of related metabolites aculeatols A–D in 2007. Subsequently, the isolation of eleven carbon side chain containing aculeatins A and D, named, respectively as aculeatins F and E were reported from *Amomum aculeatum* Roxb. (Zingiberaceae)[10] a herbaceous plant, distributed in Indonesia, Malaysia, and Papua New Guinea, and has been used as a folk medicine for the treatment of fever and malaria. Due to its promising biological activity as potential cancer chemotherapeutic agents based on the unusual 1,7-dioxodispiro[5.1.5.2]pentadecane architecture, it has attracted a great deal of interest among synthetic organic chemists worldwide as an attractive synthetic targets.

Ramana and co-workers[16] reported the first total synthesis of aculeatin F and *epi*-F using a convergent approach. In this apporach the central 1,3,5-triol unit with the requisite stereochemistry was prepared from the commercially available α-D-glucoheptonic-γ-lactone and addition of both the terminal units (phenol and side chain) was performed at an advanced stage. Selective *O*- debenzylation during the hydrogenolysis of the diyne intermediate and the one-pot phenolic oxidation with concomitant spiroketalization were the key features of this synthesis.

As part of our research programme aimed at developing enantioselective syntheses of naturally occurring spiroacetals and lactones, we recently developed the asymmetric synthesis of aculeatins A and B using Jacobsen's hydrolytic kinetic resolution (HKR) as the key step.[18] In elaboration of our previous studies on aculetins using iterative hydrolytic kinetic resolution, linchpin coupling and oxidative double spirocyclization/ dithiane deprotection sequence using PIFA, a synthesis of natural aculeatin F and its epimer has been achieved, with the key stereogenic centers generated via hydrolytic kinetic resolution. The hydrolytic kinetic resolution (HKR) catalyzed by (salen)-Co(III) complex has emerged as a general and effective method for the preparation of highly enantioenriched terminal epoxides, with widespread use in both academic and industrial sectors. Jacobsen and Blackmond *et al.*[22] described a complete kinetic profile of HKR to elucidate the mechanistic basis for the counterion effect. These studies have revealed a fascinating mechanism of catalyst.

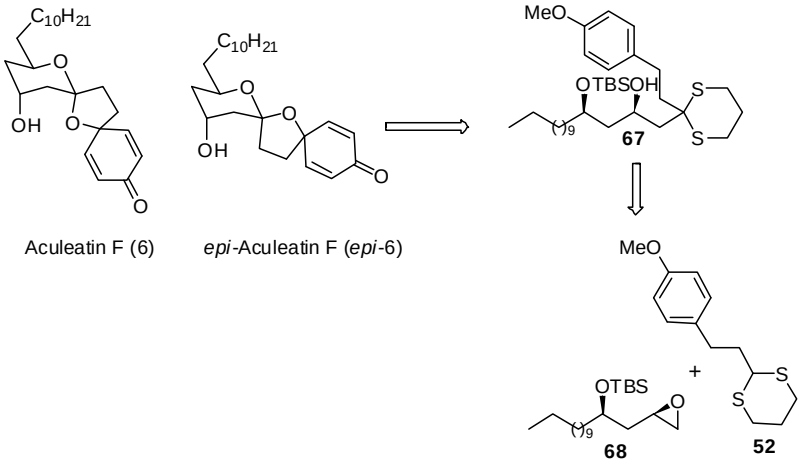


(*R,R*)-Salen-Co^{III}OAc Complex

Figure 9: Mechanistic Investigation of Hydrolytic Kinetic Resolution of Terminal Epoxides

Retrosynthetic analysis of aculeatin F and *epi*-F:

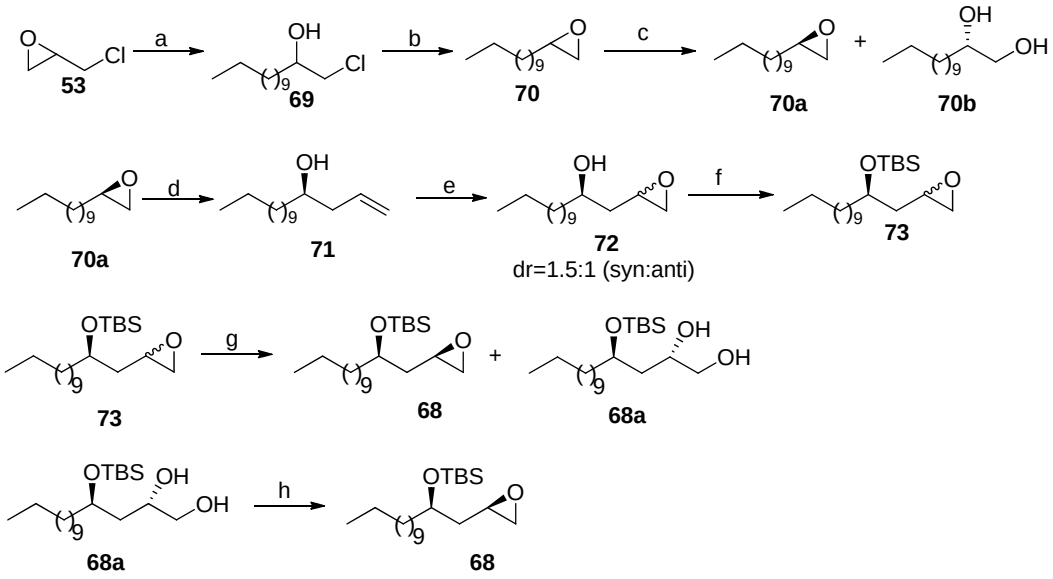
Aculeatins F and *epi*-F could be synthesized by the Linchpin coupling of epoxide **68** and previously synthesized dithiane **52**. The epoxide **68** in turn could be prepared from (±) epichlorohydrin (Scheme 13).



Scheme-13. Retrosynthetic route to aculeatin F **6** and *epi*-F (***epi*-6**).

Results and Discussion

As shown in Scheme 14, the synthesis of the epoxide fragment started from the commercially available (±) epichlorohydrin which on ring opening with decylmagnesium bromide followed by base treatment gave the epoxide **70** in 92% yield. The *rac*-epoxide **70** was subjected to Jacobsen's HKR using (*R,R*)-salen-Co(OAc) catalyst to give enantiopure epoxide (*R*)**-70a** in 45% yield along with diol **70b** in 44% yield, which were separated by silica gel column chromatography.



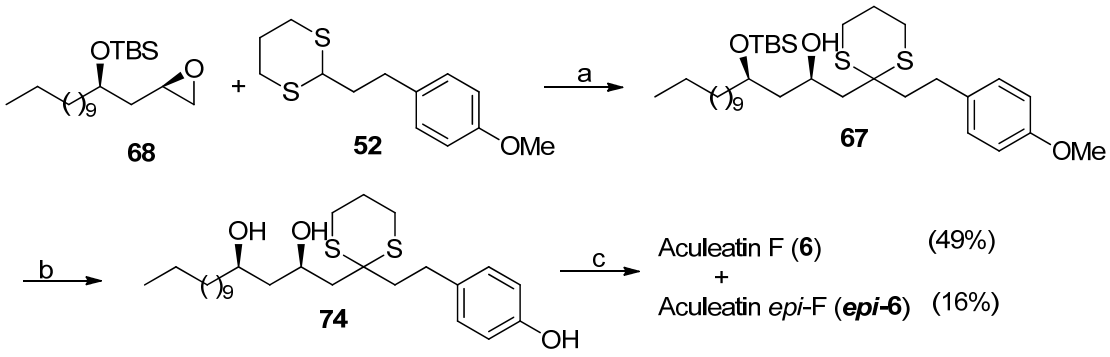
Scheme-14. Synthesis of epoxide 68.

Reagents and conditions: (a) Decylmagnesium bromide, THF, CuI, -40 ^{o}C, 12 h, 83%; (b) KOH, CH_2Cl_2, rt, 1 h, 92%; (c) *R,R*-salen-Co-(OAc) (0.5 mol %), dist. H_2O (0.55 equiv), 0 ^{o}C, 14 h, (45% for **70a**, 44% for **70b**); (d) Vinylmagnesium bromide, THF, CuI, -20 ^{o}C, 12 h, 89%; (e) *m*-CPBA, CH_2Cl_2, 0 ^{o}C to rt, 10 h, 96%; (f) TBDMSCl, imidazole, CH_2Cl_2, 0 ^{o}C to rt, 3 h, 90%;(g) *R,R*-salen-Co-(OAc) (0.5 mol %), dist. H_2O (0.55 equiv), 0 ^{o}C, 22 h, (46% for **68,** 39% for **68a**); (h) (i) PivCl, Et_3N, cat. DMAP, rt, 2 h; (ii) MsCl, Et_3N, DMAP, 0 ^{o}C to rt, 1 h; (iii) K_2CO_3, MeOH, rt, overnight (65% for three steps).

With enantiomerically pure epoxide (*R*)-**70a** in hand, our next task was to establish the second stereogenic center with required stereochemistry. Thus epoxide **70a** was treated with vinylmagnesium bromide in the presence of CuI to give the pentadec-1-en-4-ol **71** in 89% yield; $[\alpha]_D^{25}$ +5.5 (*c* 1.0, $CHCl_3$) [Ref. 23 $[\alpha]_D^{25}$ +5.52 (*c* 1.05,

$CHCl_3$)]. The epoxidation of homoallylic alcohol **71**, followed by hydroxy-group protection as the TBS ether produced the epoxide **73** in favor of the desired *syn*-isomer (*syn/anti* 1.5:1). The two diastereomers of epoxy alcohol could not be differentiated by thin-layer chromatography. ^{1}H NMR spectrum of **72**-syn/anti (1.5:1) showed epoxide protons at δ 2.52 (doublet of doublet, 0.60 H, with coupling constant J = 2.8, 4.9 Hz) and 2.62 (doublet of doublet, 0.40 H, with coupling constant J = 2.8, 4.8 Hz). In order to get better diastereoselectivity, epoxide **73** was again subjected to HKR with (*R,R*)-salen-Co(OAc) complex (0.5 mol %) and water (0.55 equiv) to afford the diastereomerically pure epoxide **68** as a single diastereomer in good yield.

As we know HKR method provided the desired epoxide along with corresponding diol **68a** in almost equal amounts, we thought that it would be appropriate to convert diol **68a** into the required epoxide **68.** Towards this, the chemoselective pivalation of diol **68a** with pivaloyl chloride followed by mesylation of the secondary hydroxyl and treatment of the crude mesylate with K_2CO_3 in methanol led to deprotection of the pivaloyl ester. Concomitant ring closure via intramolecular S_N2 displacement of the mesylate furnished the epoxide **68** in 65% overall yield.



Scheme 15. Reagents and conditions: (a) *n*-BuLi, HMPA, THF, -78 ^oC, 1 h, 85%; (b) (i) EtSH, NaH, DMF, 120^oC, 12 h, 80%; (c) $PhI(OOCCF_3)_2$, CH_3CN/H_2O (9:1) aculeatin F (**6)** (49%) and *epi*-F **(epi-6) (**16%**)**.

The dithiane fragment **52** was prepared using the same protocol as reported in scheme 10. Having both the fragments in hand next task was to couple the epoxide **68** and dithiane **52** using Linchpin coupling[19] (Scheme 15). Towards this end, the generation of lithiated anion of dithiane was carried out using *n*-BuLi in THF at -78 ^oC, followed by addition of epoxide **68** which resulted in the coupled product **67**. Deprotection of

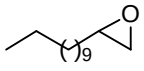
methyl and TBS group using EtSNa[24] followed by reaction with $PhI(O_2CCF_3)_2$ in CH_3CN/H_2O (9:1 v/v) at room temperature furnished a mixture of aculeatin F (41%) and epi-F (16%) yields which was easily separated by silica gel column chromatography. Spectroscopy data obtained were in accord with those described in the literature.[10, 16]

Conclusion

In summary, the present work discloses the total synthesis of aculeatin F and epi-F using hydrolytic kinetic resolution as a tool to generate sterero-centers and PIFA mediated oxidative cyclization/dithiane deprotection to construct the spiro-acetal moiety.

Experimental Section

2-Undecyloxirane (70)



To a solution of crude compound **69** (10g, 42.59 mmol) in Et_2O (60 mL) was added finely powdered KOH (7.17 g, 127.8 mmol). The mixture was stirred vigorously for 6 h and poured into 50 mL water. After separation of the layers, the aqueous layer was extracted with Et_2O (3 x 150 mL) and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent and silica gel column chromatographic purification (petroleum ether) of the crude product gave **70** (7.77 g, 92%) as a colorless liquid.

Mol. Formula: $C_{13}H_{26}O$

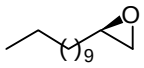
IR ($CHCl_3$, cm^{-1}): ν_{max} 3018, 2952, 2929, 2862, 1472, 1466, 1379, 1260, 1022, 916, 828.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.3 Hz, 3H), 1.27 (brs, 18 H), 1.48-1.54 (m, 2H), 2.47 (dd, *J* = 8.7 Hz, 1H), 2.76 (dd, *J* = 7.4 Hz, 1H), 2.89-2.93 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.6, 25.9, 26.8, 29.3, 29.4, 29.5, 29.6, 31.6, 32.4, 46.9, 52.3.

ESI-MS: *m/z* = 221 $[M+Na]^+$

(*R*)-2-Undecyloxirane (70a)



A solution of epoxide **70** (7.0 g, 35.29 mmol) and (*R,R*)-Salen-Co(III)-OAc (0.106 g, 0.18 mmol) in THF (0.5 mL) was stirred at 0^{o}C for 5 min, and then distilled water (350 μL, 19.41 mmol) was added. After stirring for 24 h, it was concentrated and purified by silica gel column chromatography using pet ether to afford **70a (**3.15 g, 45%) as a yellow color liquid. Continued chromatography with pet ether/EtOAc (4:1) provided the diol **70b** as a brown color liquid as a single diastereomer.
Yield: 3.15 g, 45%.

Mol. Formula: $C_{13}H_{26}O$

$[\alpha]_D^{25}$ +11.5 (*c* 1.1, THF)

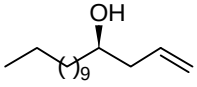
IR ($CHCl_3$, cm^{-1}): ν_{max} 3018, 2952, 2929, 2862, 1472, 1466, 1379, 1260, 1022, 916, 828.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.3 Hz, 3H), 1.26 (brs, 18 H), 1.44-1.58 (m, 2H), 2.46 (dd, *J* =8.6 Hz, 1H), 2.75 (dd, *J* = 7.4 Hz, 1H), 2.94-2.88 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.6, 25.9, 29.6-29.3 (br, several overlapped signals), 31.8, 32.4, 47.0, 52.3.

ESI-MS: *m/z* = 221 $[M+Na]^+$

(*R*)-Pentadec-1-en-4-ol (71)



A round bottomed flask was charged with copper (I) iodide (0.288 g, 0.10 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry

THF (60 mL) was added. This suspension was cooled to –20 ^{o}C and vigorously stirred, and vinylmagnesium bromide (1M in THF, 30.3 mL, 30.3 mmol) was injected to it. A solution of epoxide (*R*)- **70a** (3.0 g, 15.13 mmol) in THF (20 mL) was added slowly to the above reagent, and the mixture was stirred at –20 ^{o}C for 5 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was washed with brine (2 x 30 mL), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **71** (3.05 g, 89%) as a colorless syrupy liquid.

Mol. Formula: $C_{15}H_{30}O$

$[\alpha]^{D}_{25}$: +5.5 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3412, 2932, 2868, 1652, 1584, 1451, 1243, 1187, 1126, 837.

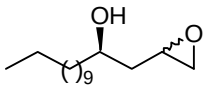
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.26 (brs, 18 H), 1.43-1.50 (m, 2H), 2.06-2.21 (m, 1H), 2.25-2.38 (m, 1H), 3.34-3.59 (m, 1H), 3.65 (brs, 1H), 5.09-5.18 (m, 2H), 5.74-5.90 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.6, 25.6, 29.3-29.6 (br, several overlapped signals), 31.8, 36.7, 41.9, 70.6, 118.0, 134.9.

Analysis Calcd.: C, 79.58; H, 13.36%; **Found:** C, 79.73; H, 13.39%.

ESI-MS: *m/z* = 249 $[M+Na]^{+}$

(2*R*)-1-(Oxiran-2-yl)tridecan-2-ol (72)



dr=1.5:1 (syn:anti)

To a stirred solution of olefin **71** (3.0 g, 13.26 mmol) in CH_2Cl_2 (60 mL) at 0 ^{o}C was added *m*-CPBA (50%) (6.84 g, 19.89 mmol). The reaction mixture was stirred

at room temperature for 10 h and quenched by saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography using pet ether/EtOAc (9:1) as eluent to yield the epoxide **72** as a white solid in diastereomeric mixture (1.5:1).
Yield: 3.08 g, 96%, $[\alpha]^{D}_{25}$: -0.53 (*c* 1.1, $CHCl_3$)

Mol. Formula: $C_{13}H_{30}O_2$

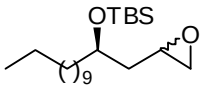
IR ($CHCl_3$): υ_{max} 3436, 3193, 2967, 2932, 2853, 1474, 1380, 1263, 1105, 944 $cm.^{-1}$

^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J*=6.8 3H), 1.26 (s, 18H), 1.57-1.68 (m, 2H), 1.82-2.04 (m, 2H), 2.52 (dd, *J*= 2.8, 4.9, 0.60 H), 2.62 (dd, *J*=2.8, 4.8, 0.40H), 2.76-2.87 (m, 1H), 3.05-3.20 (m, 1H), 3.74-3.86 (m, 1H), 4.46 (brs, 1H) (mixture of diastereomers).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.0, 22.6, 25.4, 25.5, 29.3, 29.6 (br, several overlapped signals), 31.9, 37.4, 37.5, 39.0, 39.6, 46.5, 46.8, 50.2, 50.6, 69.2, 70.5 (mixture of diastereomers).

ESI-MS: *m/z* = 265 $[M + Na]^+$

Tert-butyldimethyl(((2*R*)-1-(oxiran-2-yl)tridecan-2-yl)oxy)silane (73)



To a stirred solution of alcohol **72** (2.8 g, 11.56 mmol) in CH_2Cl_2 (40 mL) was added imidazole (1.57 g, 23.06 mmol). To this solution *t*-butyl dimethylchlorosilane (2.26 g, 15.02 mmol) was added at 0 ^oC and reaction was stirred at room temperature for 3 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 x 30 mL). The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (19:1) as eluent provided **73** as a colorless liquid (3.71 g, 90%). $[\alpha]^{D}_{25}$: -6.3 (*c* 2.0, $CHCl_3$)

Mol. Formula: $C_{21}H_{44}O_2Si$

IR ($CHCl_3$): υ_{max} 3043, 2924, 2855, 1465, 1255, 1072, 837, 775 cm^{-1}

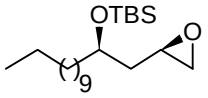
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.06, 0.08 (2s, 6H), 0.88 (t, *J*=7.0, 3H), 0.91 (s, 9H), 1.26 (s, 18H), 1.48-1.71 (m, 4H), 2.44-2.51 (m, 1H), 2.74-2.82 (m, 1H), 2.75 (m, 1H), 3.02-3.09 (m, 1H), 3.79-3.94 (m, 1H) (mixture of diastereomers).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = -4.7, -4.6, -4.5, -4.4, 14.1, 18.0, 22.7, 24.9, 25.4, 25.8, 29.3, 29.6 (br, several overlapped signals), 31.9, 37.9, 40.1, 40.2, 46.8, 47.7, 49.5, 49.9, 70.1, 70.3 (mixture of diastereomers).

Analysis Calcd.: C, 70.72; H, 12.43%; **Found:** C, 70.69; H, 12.47%.

ESI-MS: *m/z* =379 $[M + Na]^+$

Tert-butyldimethyl(((*R*)-1-((*R*)-oxiran-2-yl)tridecan-2-yl)oxy)silane (68)



A solution of epoxide **73** (3.5 g, 6.49 mmol) and (*R,R*)-Salen-Co(III)-OAc (0.030 g, 0.05 mmol) in THF (1 mL) was stirred at 0 ^oC for 5 min, and then distilled water (97 μL, 5.40 mmol) was added. After stirring for 24 h, it was concentrated and purified by silica gel column chromatography using pet ether/EtOAc (19:1) to afford **68 (**1.61 g, 46%) as a yellow color liquid. Continued chromatography with pet ether/EtOAc (3:2) provided the diol **68a** as a brown color liquid as a single diastereomer. The diastereoselectivity was determined from ^{1}H NMR and ^{13}C NMR spectral data. $[\alpha]_D^{25}$ - (*c* 1.0, $CHCl_3$).

Mol. Formula: $C_{21}H_{44}O_2Si$

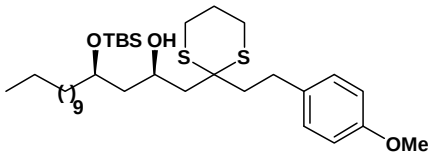
IR ($CHCl_3$): υ_{max} 3041, 2927, 2854, 1465, 1255, 1071, 835, 773 $cm.^{-1}$

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (t, *J*=7.2 Hz, 3H), 0.90 (s, 9H), 1.26 (s, 18H), 1.52-1.76 (m, 4H), 2.46 (dd, *J* = 2.8, 5.1 Hz, 1H), 2.76 (t, *J* = 4.5 Hz, 1H), 3.02-3.07 (m,1H),3.85 (quintet, J =5.8, 11.6, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = -4.5, -4.6, 14.1, 18.0, 22.7, 25.4, 25.6, 29.3, 29.6, 29.7, 31.9, 37.1, 40.1, 46.8, 49.5, 70.3.

ESI-MS: *m/z* =379 $[M + Na]^+$

(2*R*,4*R*)-4-((Tert-butyldimethylsilyl)oxy)-1-(2-(4-methoxyphenethyl)-1,3-dithian-2-yl)pentadecan-2-ol (67)



A flame dried two neck round bottom flask was charged with dithiane **52** (1.43 g, 5.61 mmol) under nitrogen and was added 30 mL of anhydrous THF and 5 mL of HMPA. The solution was cooled to -78 ^oC and to this was added *n*-BuLi (5.61 mmol, 3.51 mL of 1.6M in hexane) drop wise. The dark brown reaction mixture was stirred for 30 min and to this was added epoxide **68** (1.00 g, 2.80 mmol) dissolved in 10 mL of anhydrous THF and 1 mL of HMPA drop wise. The reaction mixture was stirred for additional 30 min, then quenched with saturated solution of NH_4Cl, diluted with water (10 mL) and extracted with ethyl acetate (3 × 30 mL). Pooled organic layers were washed with saturated brine solution, dried over anhydrous Na_2SO_4, concentrated *in vacuo*. and residue was purified using silica gel column chromatography using a gradient of (10→20 %) ethyl acetate and light petroleum to afford coupled product **67** (1.45g, 85 %) as thick syrup. $[\alpha]_D^{25}$ -3.6 (*c* 2.4, $CHCl_3$).

Mol. Formula: $C_{34}H_{62}O_3S_2Si$

IR ($CHCl_3$): υ_{max} 3487, 2987, 2926, 2853, 2360,1614, 1511, 1449, 1246,1056, 815,767 cm^{-1}

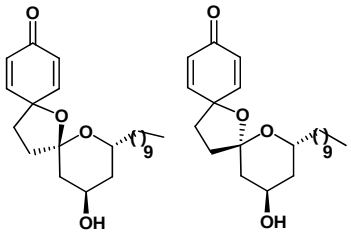
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.09 (s, 3H), 0.11 (s, 3H), 0.89 (t, *J*=3.6 Hz, 3H), 0.91 (s, 9H), 1.27 (s, 18H), 1.42-1.57 (m, 2H), 1.66-1.81 (m, 2H), 1.87-2.13 (m, 3H), 2.17-2.39 (m, 3H), 2.61-2.99 (m, 6H), 3.80 (s, 3H), 3.88-4.00(m, 1H), 4.07-4.23 (m, 1H), 6.83 (d, *J*=8.6 Hz, 2H), 7.14 (d, *J*=8.6 Hz, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = -4.6, -4.4, 14.1, 18.0, 22.6, 25.1, 25.3, 25.9, 26.1, 26.3, 29.3, 29.6, 29.8, 31.9, 37.2, 41.9, 43.7, 45.8, 55.2, 65.0, 70.1, 113.8, 129.3, 133.8, 157.8.

Analysis Calcd.: C, 66.83; H, 10.23; S, 10.49; **Found:** C, 66.75; H, 10.21; S, 10.36.

ESI-MS: *m/z* = 634 $[M + Na]^+$

(2*R*, 4*R*, 6*R*)-4-Hydroxy-2-undecyl-1,7-dioxadispiro[5.1.5.2]pentadeca-9,12-dien-11-one (Aculeatin F, 6) and (2*R*,4*R*,6*S*)-4-Hydroxy- 2-undecyl-1,7-dioxadispiro[5.1.5.2]pentadeca-9,12-dien- 11-one (Aculeatin *epi*-F, *epi*-6)



6 *epi*-6

A suspension of NaH (0.33 g, 8.15 mmol) in DMF (10 mL) was cooled to 0 °C and added EtSH (0.9 mL, 9.82 mmol). After stirring at 0 °C for 30 min, **67** (1.00 g, 1.63 mmol) in DMF (10 mL) was added. The solution was heated to 120 °C for 12 h and then cooled to room temperature. The reaction mixture was quenched with water. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with saturated aqueous $Na_2S_2O_7$, brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes = 2:3) to afford **74** (0.63g, 80%) as a colorless liquid.

To a solution of product **74** (0.10 g, 0.21 mmol) in an acetonitrile + water mixture (9:1, 5 mL) was added $PhI(OCOCF_3)_2$ (0.22 g, 0.52 mmol) in a single portion. The reaction mixture was stirred for 30 min. at room temperature. After completion of the

reaction, saturated solution of $NaHCO_3$ was added and organic layers extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to give crude mixture of aculeatin A 1 and aculeatin B 2 which was purified on flash silica column chromatography using a gradient of (24→30 %) ethyl acetate and light petroleum to afford aculeatin F (**6)** (0.026 g, 49%) and aculeatin epi-F ***(epi*-6)** (0.008 g, 16%).

Aculeatin F 6: $[\alpha]_D^{25}$ -3.9 (*c* 0.6, $CHCl_3$).

Mol. Formula: $C_{24}H_{38}O_4$

IR (neat): υ_{max} 3492, 2927, 2853, 1673, 1622, 1516, 1463, 1099, 1053, 949, 851 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, *J*= 6.8, 3H), 1.27 (s, 17H), 1.40- 1.55 (m, 4H), 1.82 (brd, *J* = 13.4 Hz, 1H), 1.90-2.05 (m, 4H), 2.22-2.27 (m, 1H), 2.34-2.42 (m, 1H), 3.38 (d, *J* = 10.2 Hz, 1H), 4.08-4.13 (m, 2H), 6.11(dd, *J* = 2.0,10.2 Hz, 1H), 6.16 (dd, *J* = 2.0, 10.1 Hz, 1H), 6.77 (dd, *J* = 2.8, 10.0 Hz, 1H), 6.86 (dd, *J* = 2.9, 10.0 Hz, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1, 22.7, 25.6, 29.3, 29.6, 29.7, 31.9, 34.1, 35.9, 37.9, 39.1, 64.8, 65.3, 79.7, 109.1, 127.0, 127.3, 148.8, 150.9, 185.3.

ESI-MS: *m/z* = 413 $[M + Na]^+$

Aculeatin *epi*-F (*epi*-6): $[\alpha]_D^{25}$ +44.2 (*c* 0.6, $CHCl_3$).

Mol. Formula: $C_{24}H_{38}O_4$

IR (neat): υ_{max} 3524, 2916, 2852, 1671, 1635, 1461, 1078, 980, 869 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, *J*= 6.8, 3H), 1.27 (s, 17H), 1.41- 1.51 (m, 3H), 1.53-1.64 (m, 3H), 1.84-1.94 (m, 2H), 2.00-2.12 (m, 2H),2.28- 2.36 (m, 1H), 2.69 (dd, *J* = 7.4, 12.1, 1H), 3.84-3.90 (m, 1H), 4.37-4.40 (m, 1H), 6.11 (dd, *J* =

2.0,9.5 Hz, 1H), 6.16 (dd, *J* = 2.0, 9.5 Hz, 1H), 6.78 (dd, *J* = 2.8, 9.7 Hz, 1H), 6.99 (dd, *J* = 2.9, 10.0 Hz, 1H).

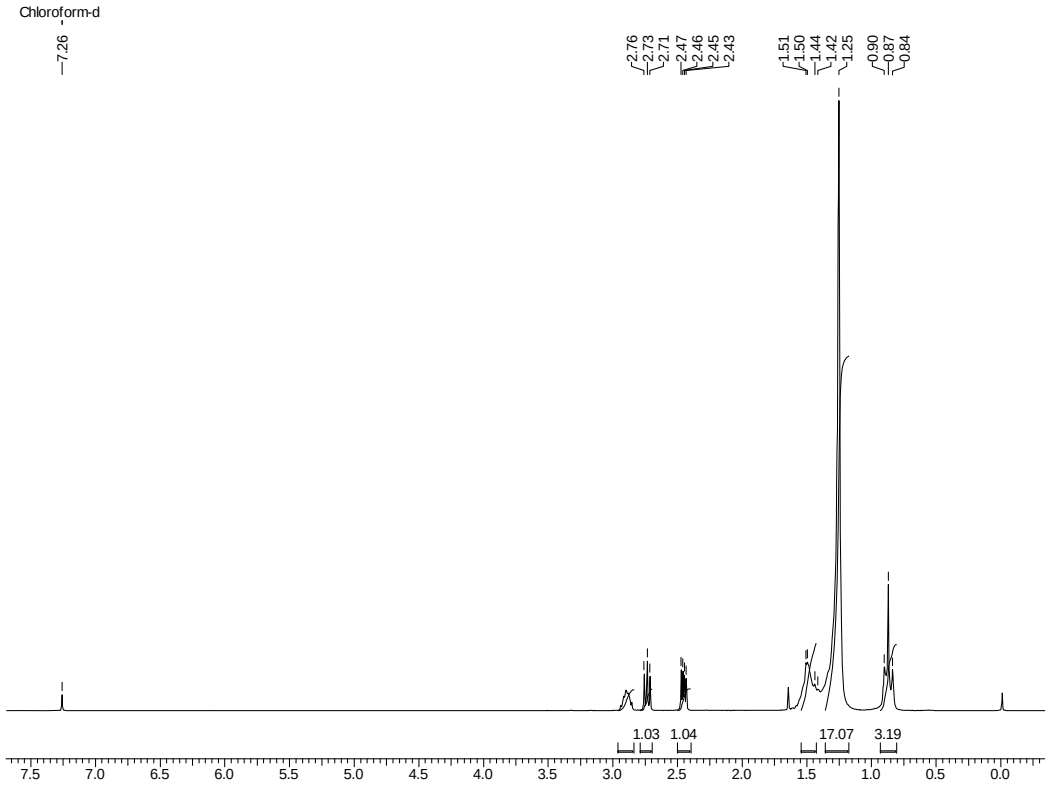
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1, 22.7, 25.9, 29.3, 29.4, 29.6 (br, several overlapped signals), 31.9, 35.2, 35.3, 35.7, 37.9, 40.5, 65.2, 69.4, 77.5, 108.4, 127.1, 149.1, 152.2, 185.7.

ESI-MS: *m/z* = 413 $[M + Na]^+$

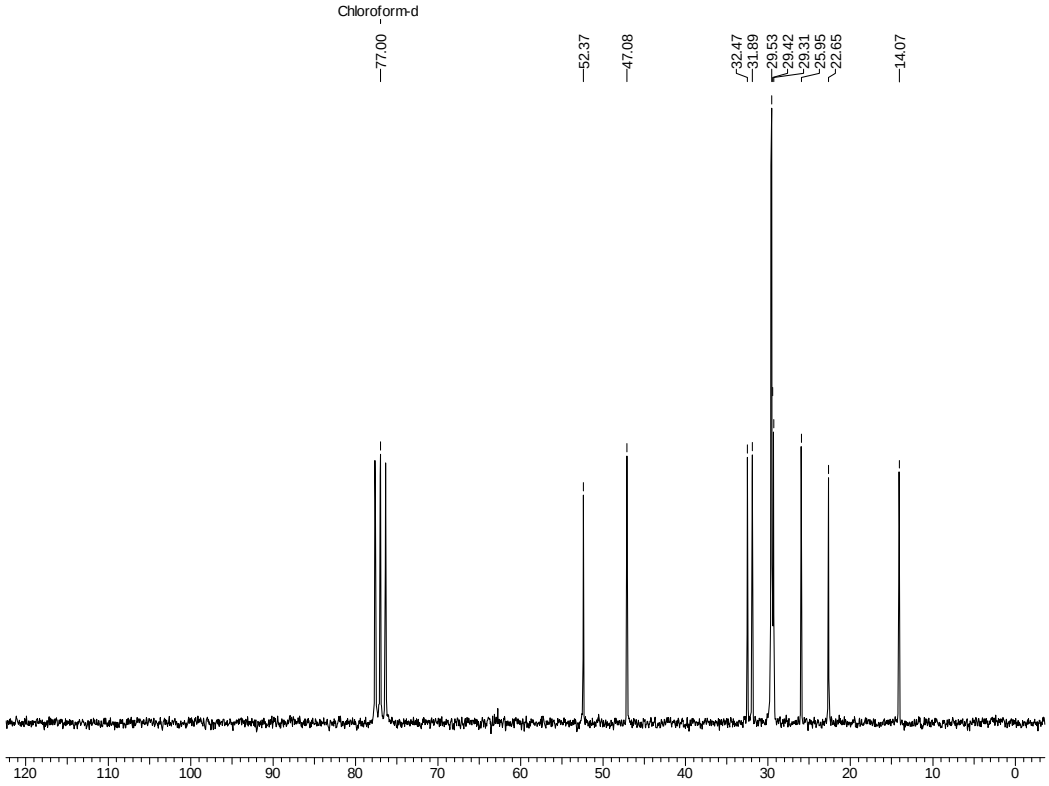
Spectra

1. ^{1}H and ^{13}C NMR spectra of **70a**
2. ^{1}H and ^{13}C NMR spectra of **71**
3. ^{1}H and ^{13}C NMR spectra of **72** -syn/anti (1:1.5)
4. ^{1}H and ^{13}C NMR spectra of **72-**syn/anti (1.5:1)
5. ^{1}H and ^{13}C NMR spectra of **73**
6. ^{1}H and ^{13}C NMR spectra of **68**
7. ^{1}H and ^{13}C NMR spectra of **67**
8. ^{1}H and ^{13}C NMR spectra of **6**
9. ^{1}H and ^{13}C NMR spectra of ***epi*-6**

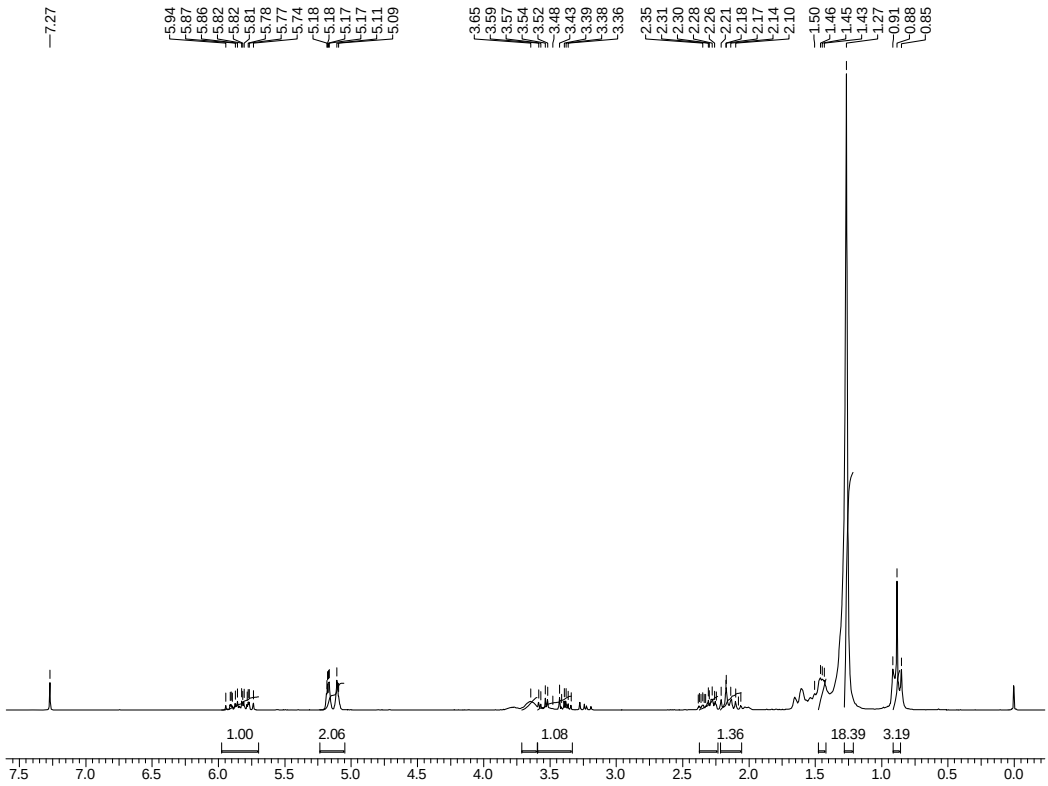
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (R)-2-Undecyloxirane (70a)



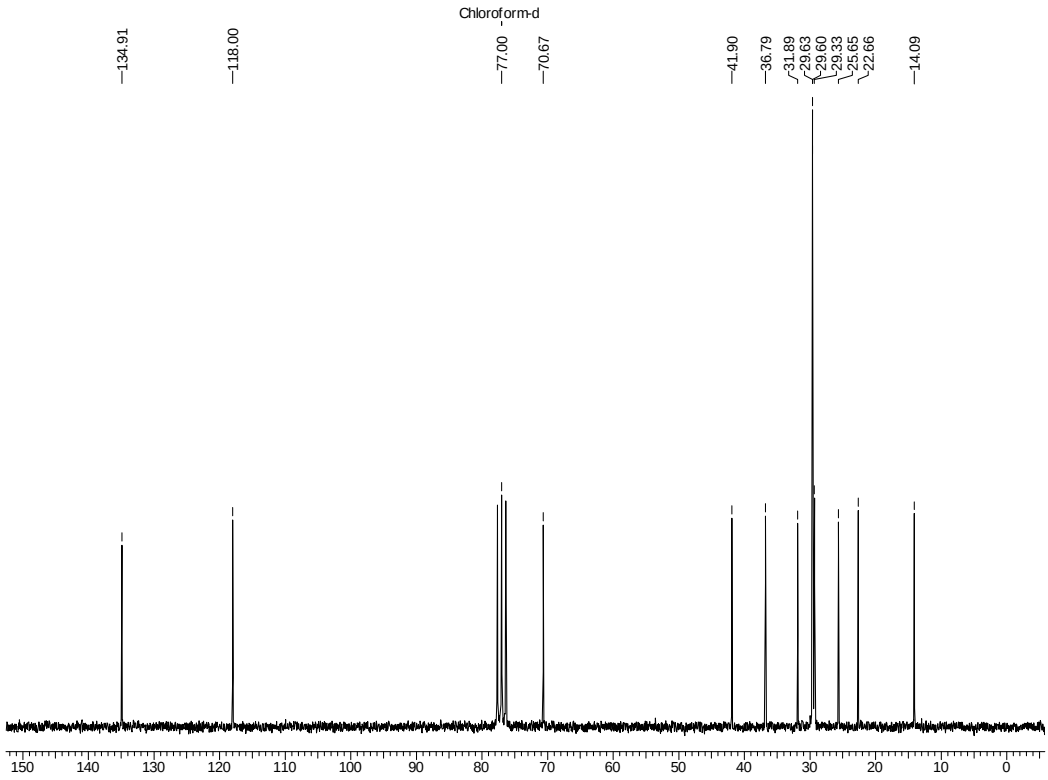
^{13}C NMR ($CDCl_3$, 200 MHz) spectrum of (R)-2-Undecyloxirane (70a)



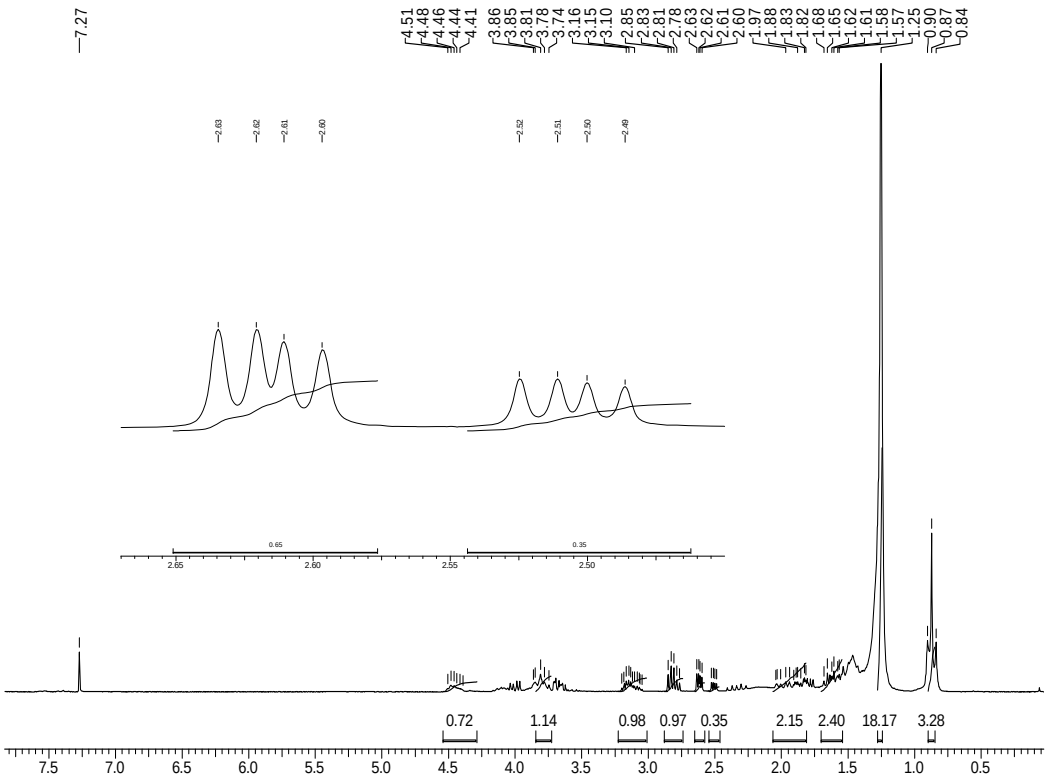
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (R)-Pentadec-1-en-4-ol (71)



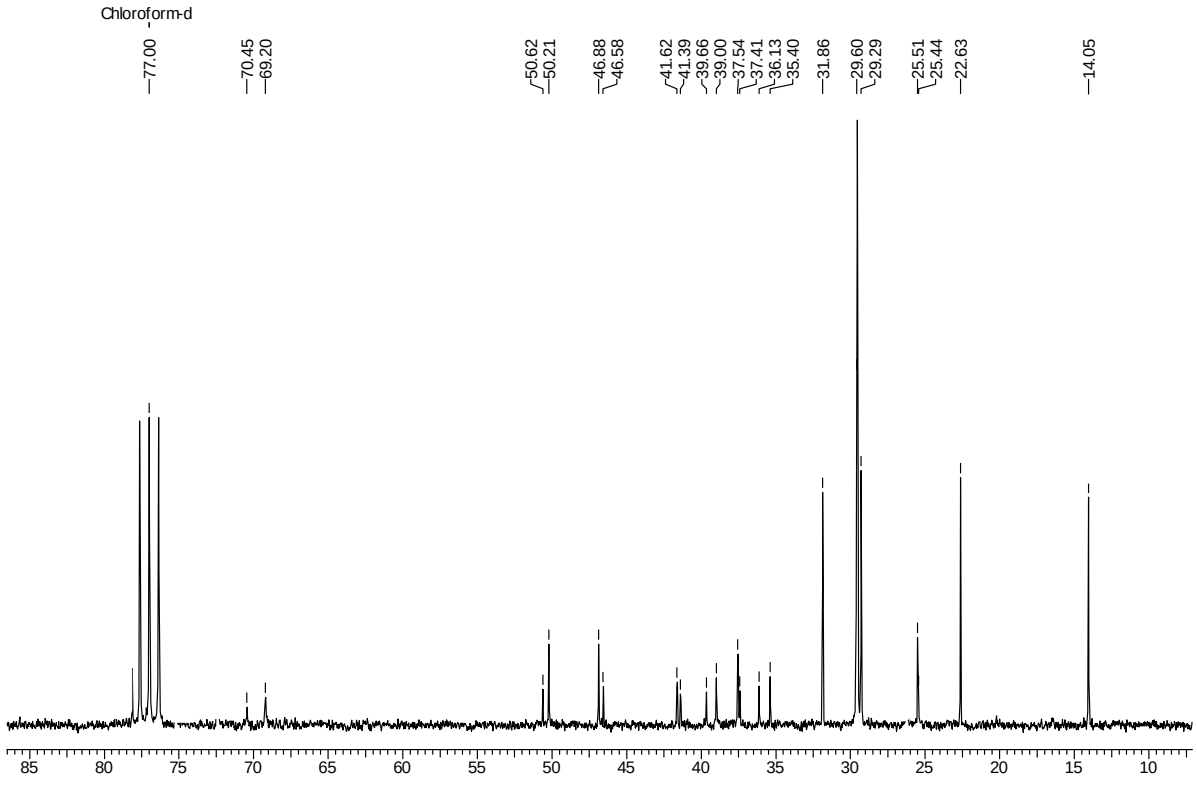
^{13}C NMR ($CDCl_3$, 200 MHz) spectrum of (R)-Pentadec-1-en-4-ol (71)



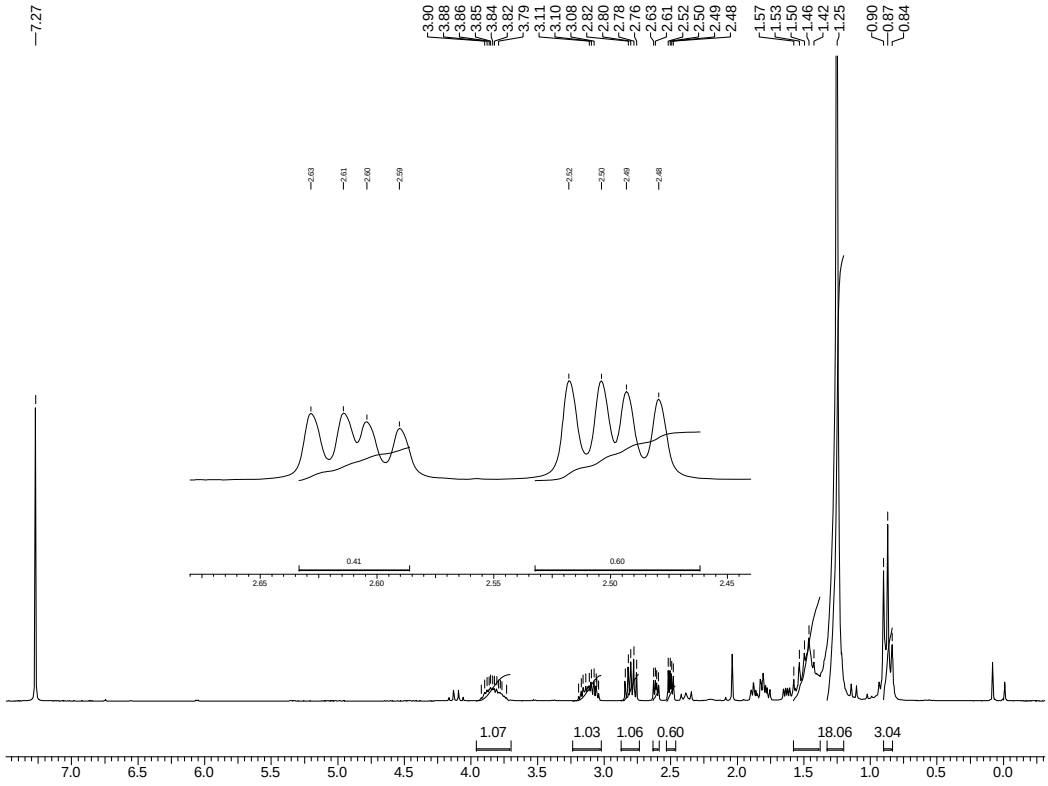
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (2*R*)-1-(Oxiran-2-yl)tridecan-2-ol (72)



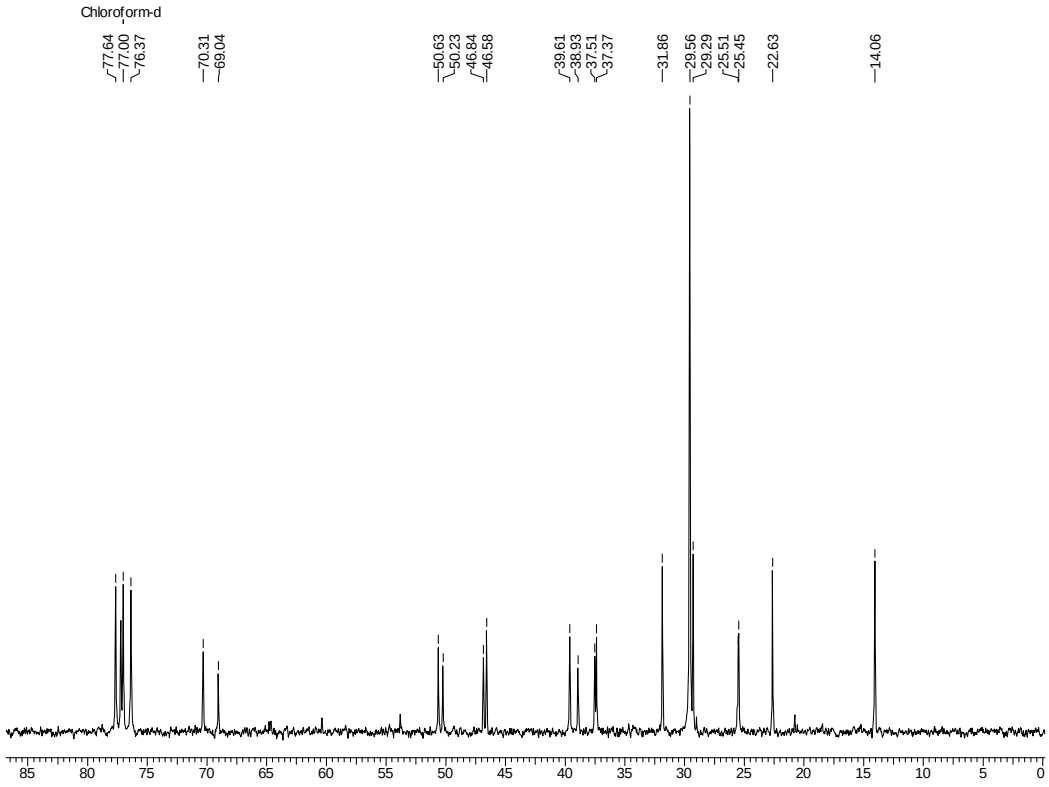
^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of (2*R*)-1-(Oxiran-2-yl)tridecan-2-ol (72)



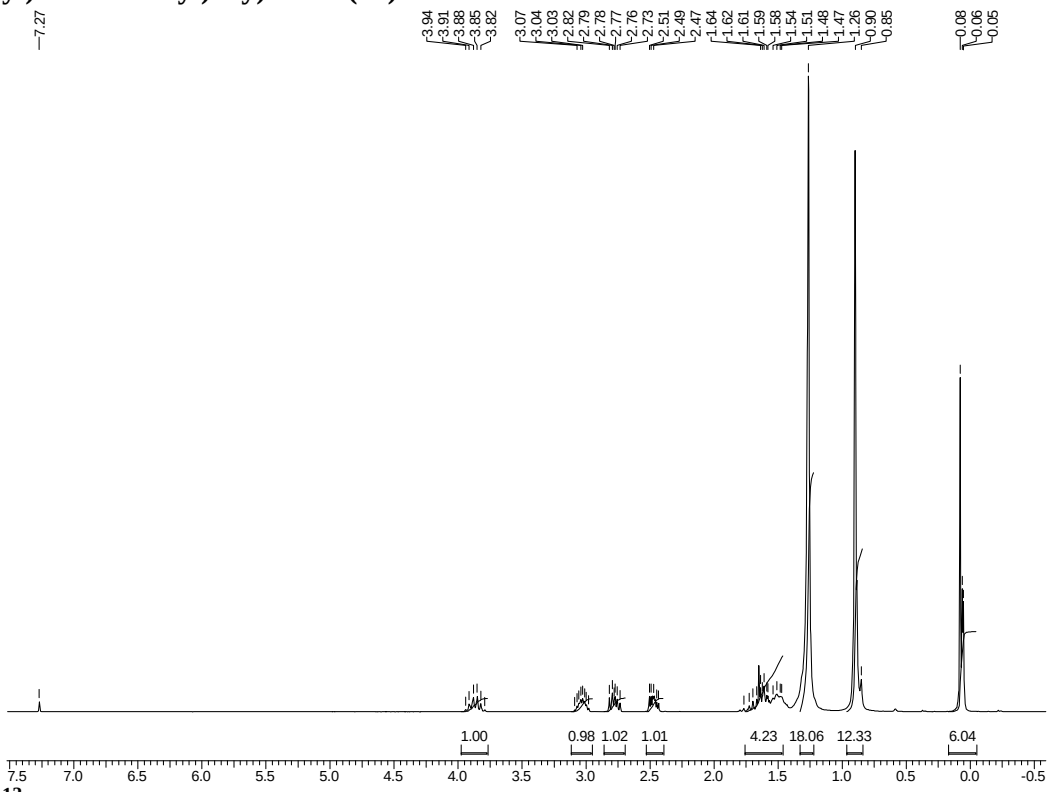
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (2*R*)-1-(Oxiran-2-yl)tridecan-2-ol (72)



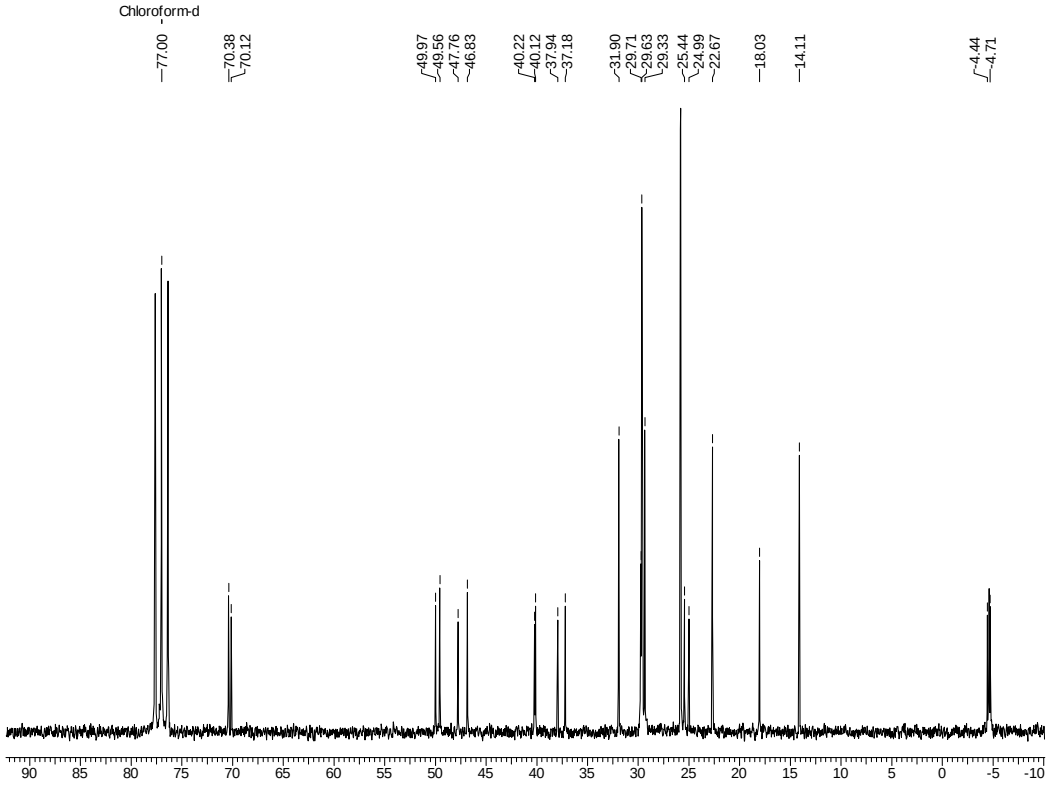
^{13}C NMR ($CDCl_3$, 200 MHz) spectrum of (2*R*)-1-(Oxiran-2-yl)tridecan-2-ol (72)



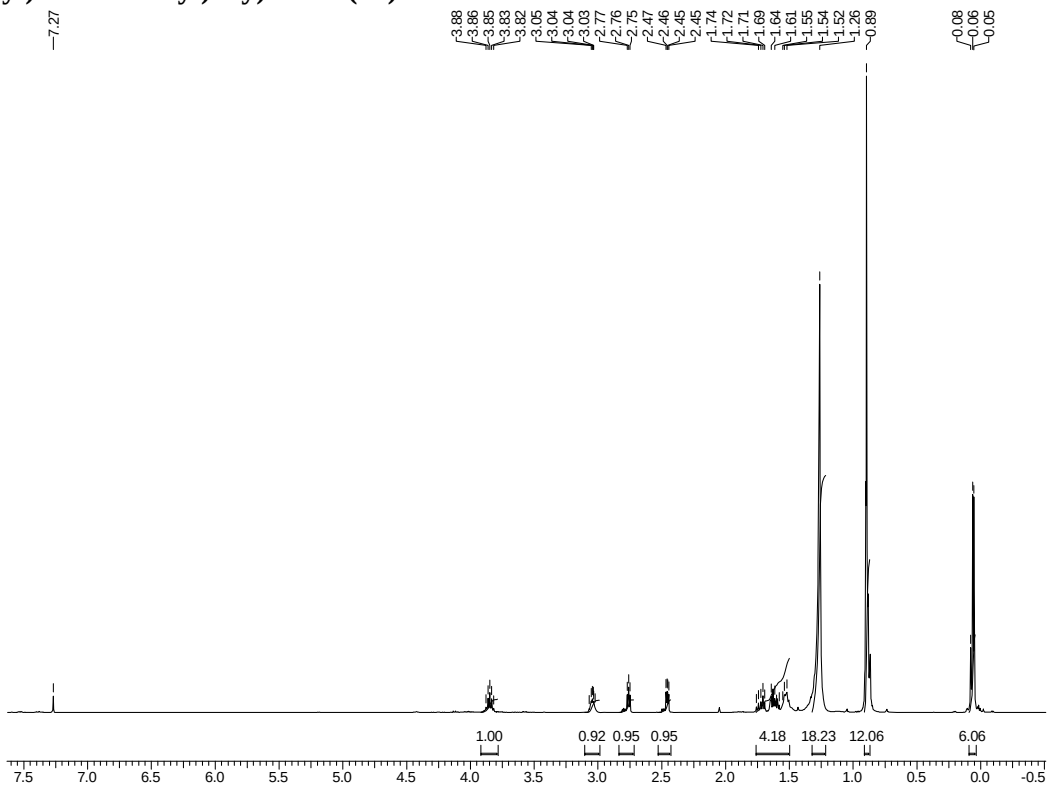
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of Tert-butyldimethyl(((2*R*)-1-(oxiran-2-yl)tridecan-2-yl)oxy)silane (73)



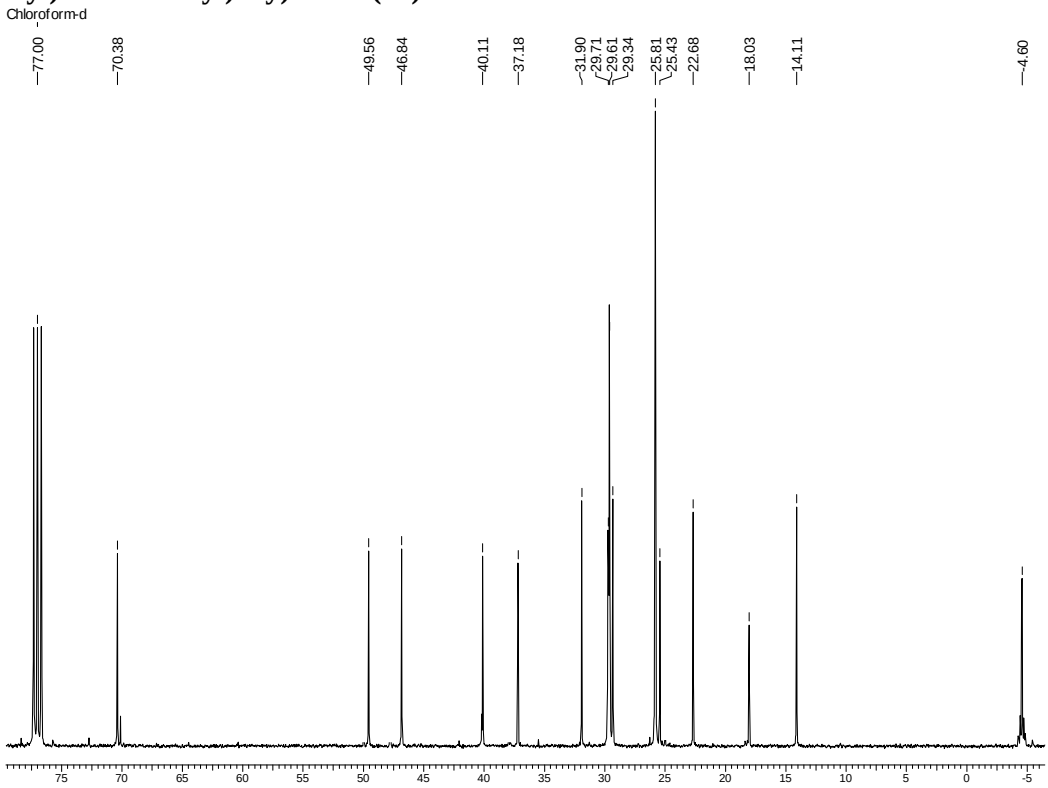
^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of Tert-butyldimethyl(((2*R*)-1-(oxiran-2-yl)tridecan-2-yl)oxy)silane (73)



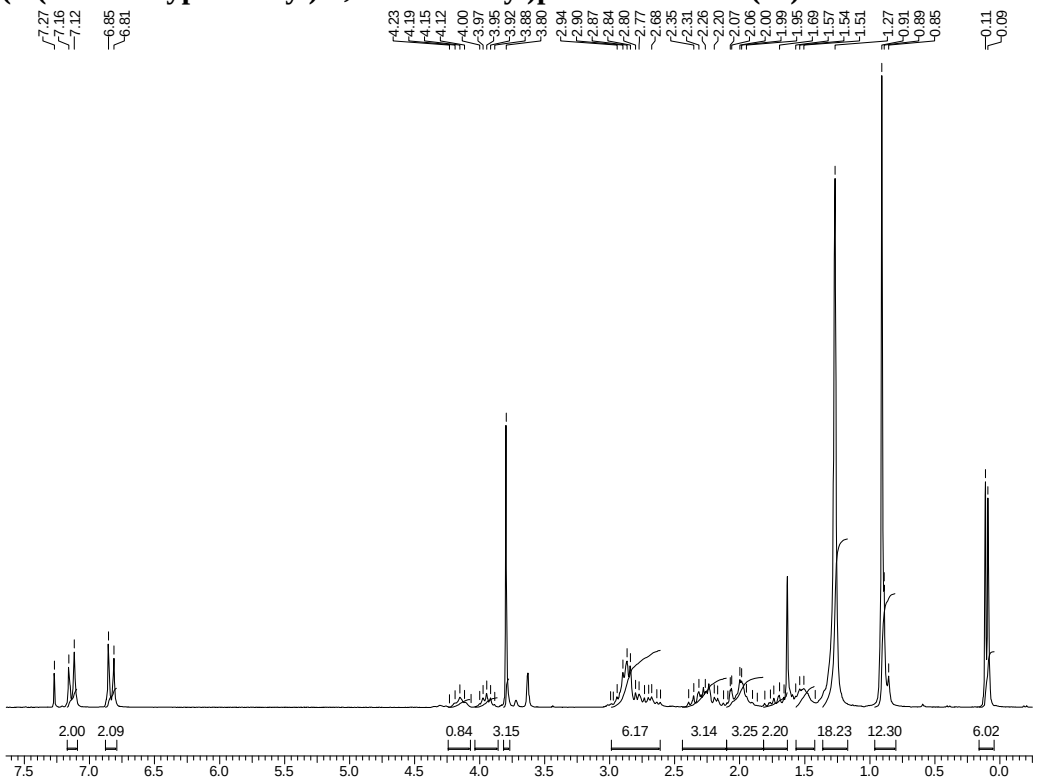
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of Tert-butyldimethyl(((*R*)-1-((*R*)-oxiran-2-yl)tridecan-2-yl)oxy)silane (68)



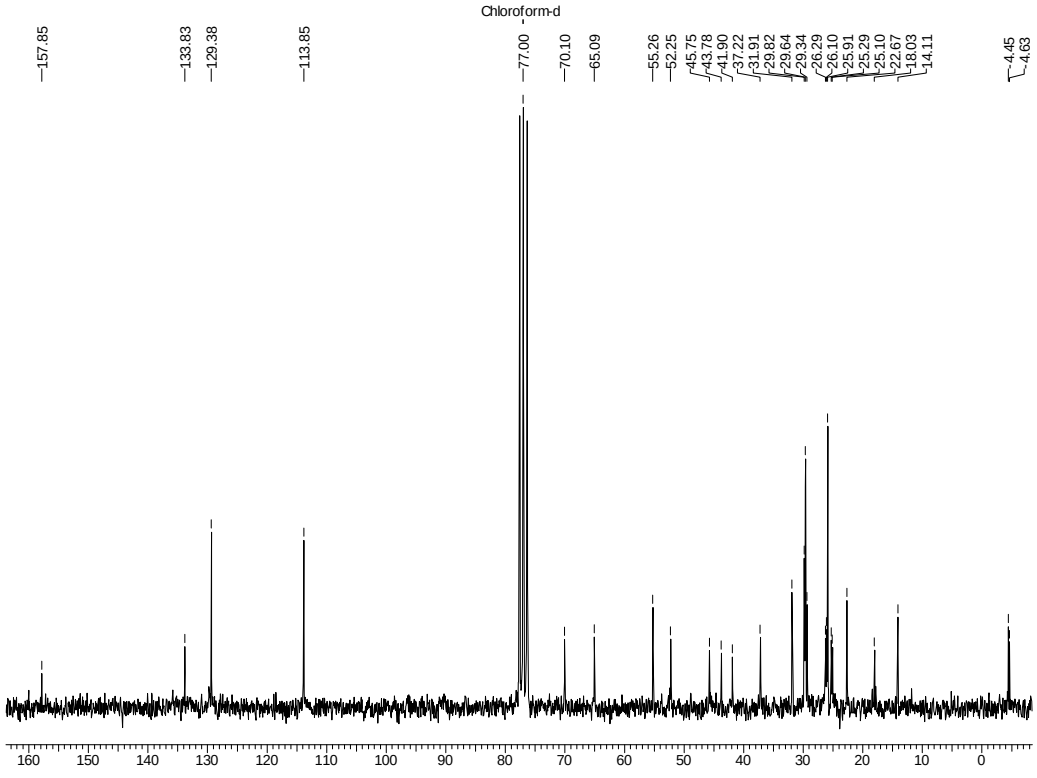
^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of Tert-butyldimethyl(((*R*)-1-((*R*)-oxiran-2-yl)tridecan-2-yl)oxy)silane (68)



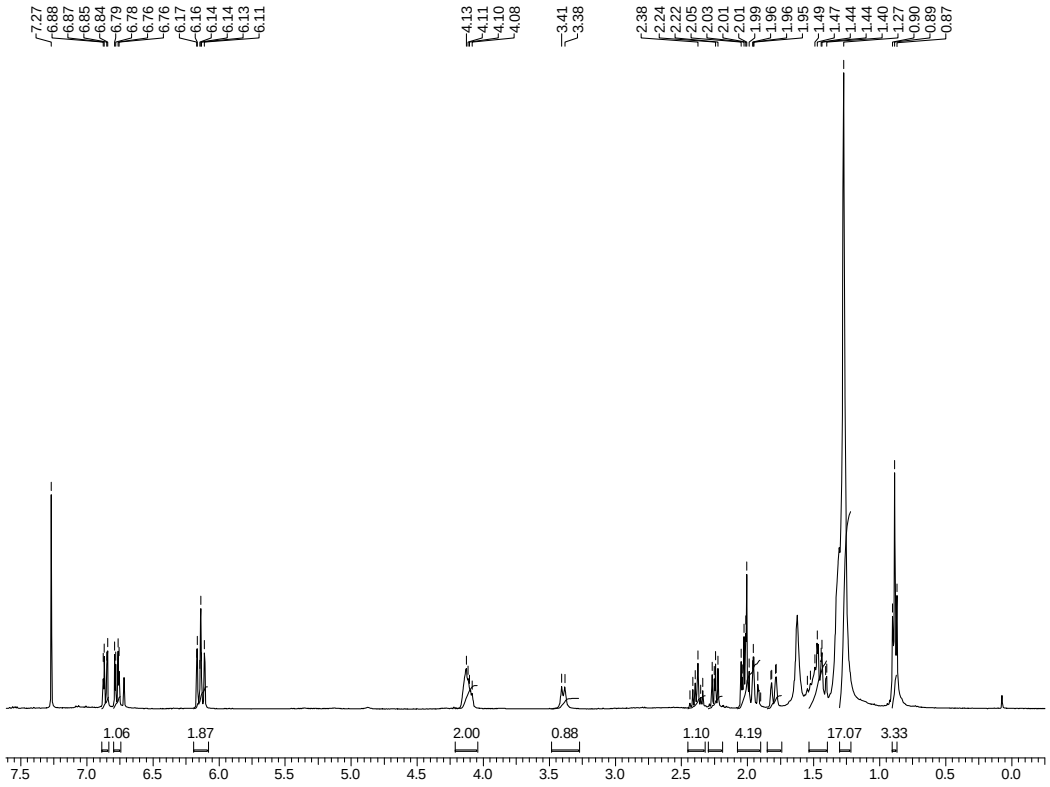
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (2*R*,4*R*)-4-((Tert-butyldimethylsilyl)oxy)-1-(2-(4-methoxyphenethyl)-1,3-dithian-2-yl)pentadecan-2-ol (67)



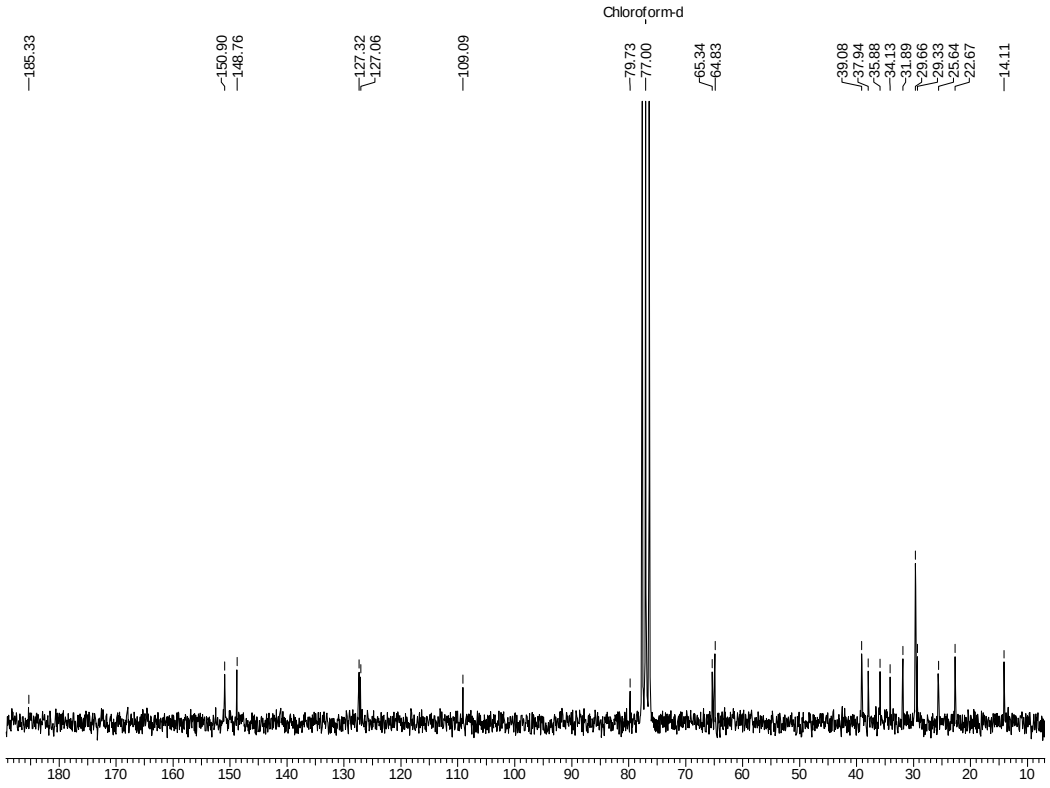
^{13}C NMR ($CDCl_3$, 200 MHz) spectrum of (2*R*,4*R*)-4-((Tert-butyldimethylsilyl)oxy)-1-(2-(4-methoxyphenethyl)-1,3-dithian-2-yl)pentadecan-2-ol (67)



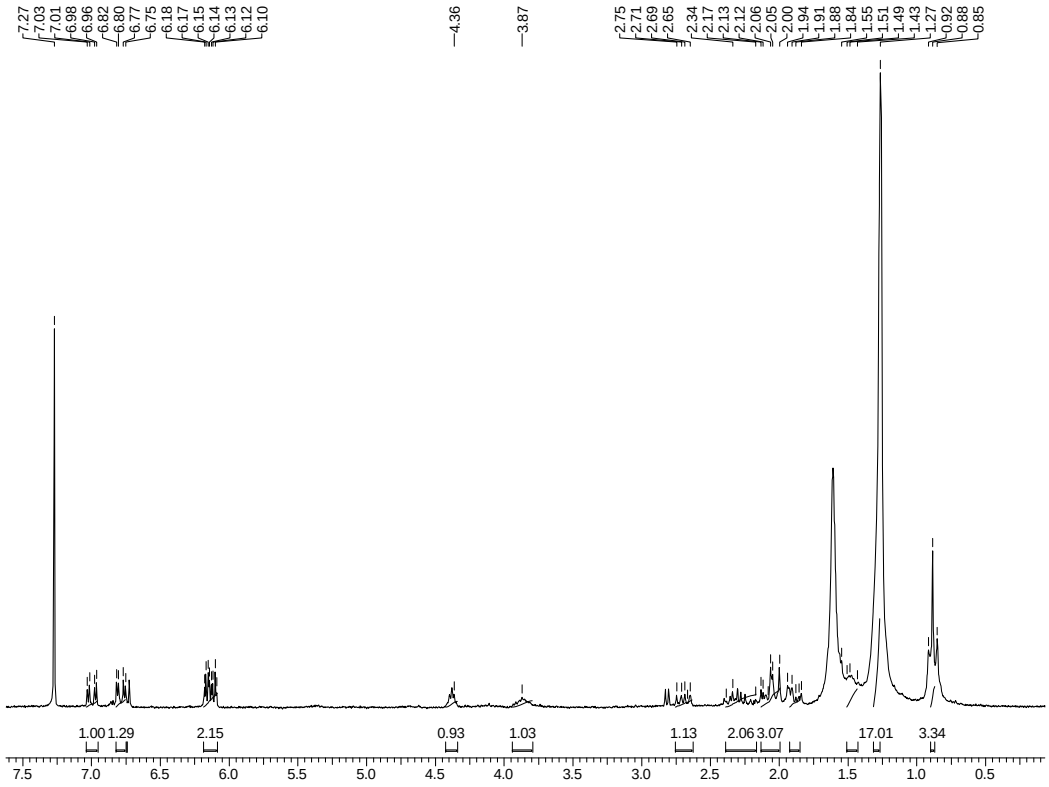
^{1}H NMR ($CDCl_3$, 500 MHz) (Aculeatin F, 6)



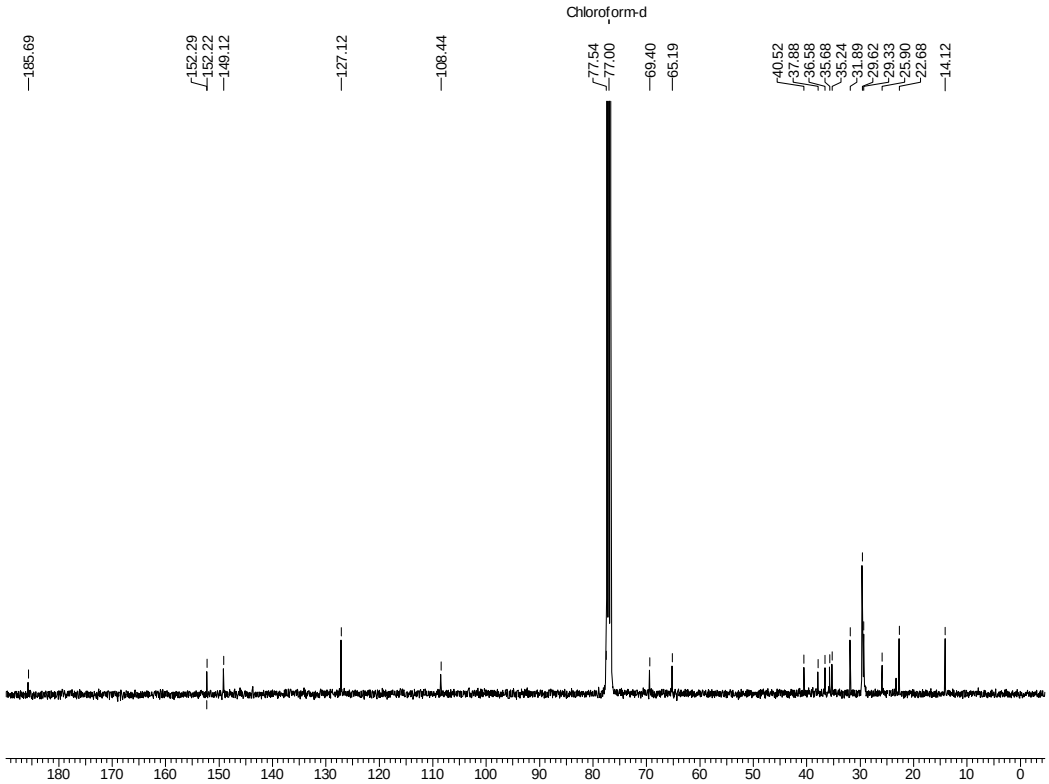
^{13}C NMR ($CDCl_3$, 100 MHz) (Aculeatin F, 6)



^{1}H NMR ($CDCl_3$, 500 MHz) (Aculeatin *epi*-F, *epi*-6)



^{13}C NMR ($CDCl_3$, 500 MHz) (Aculeatin *epi*-F, *epi*-6)



Chapter II, Section C

Studies towards the synthesis of Modiolide B

Present work

Objective

Marine-derived fungi have proven to be a rich source of structurally interesting and biologically active secondary metabolites. In search for new metabolites from marine-derived fungi, two new 10-membered macrolides, modiolides B (**75**) and A (**76**), and a new related linear pentaketide, modiolin (**77**), were isolated by Kobayashi *et al*.[25] from the cultured broth of the fungus *Paraphaeosphaeria* sp., which was separated from a marine horse mussel. The structures of **75-77** were elucidated by spectroscopic data. The fungus *Paraphaeosphaeria* sp. (strain N-119) was separated from the horse mussel *Modiolus auriculatus* collected at Hedo Cape, Okinawa Island, and grown in PMG liquid medium containing seawater for 14 days at 25 °C. The supernatant of the culture broth (1 L) was extracted with EtOAc, and the EtOAc-soluble portions were subjected to silica gel column chromatography and then C18 HPLC to afford modiolides A (**75**) and B (**76**) and modiolin (**77**). Modiolides A and B showed antibacterial activity against *Micrococcus luteus* (MIC value 16.7 *í*g/mL) and antifungal activity against *Neurospora crassa* (MIC value 33.3 *í*g/mL).

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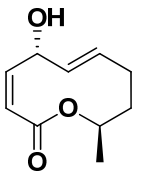
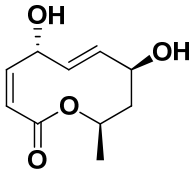
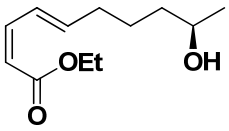


Modiolide B (75)



Modiolide A (76)

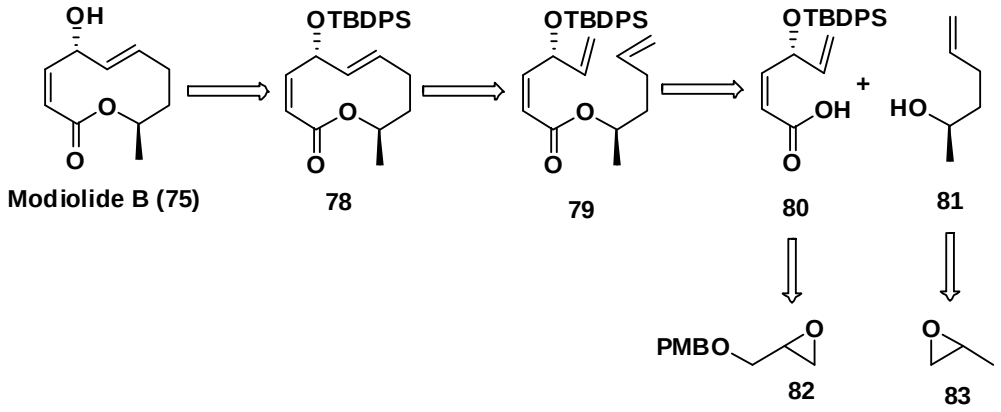


Modiolin (77)

As a part of our research programme aimed at developing enantioselective synthesis of biologically active natural products based on hydrolytic kinetic resolution (HKR), we became interested in designing a simple and concise route to modiolide B. Herein we describe our studies towards synthesis of modiolide B employing HKR, Yamaguchi coupling and ring- closing metathesis (RCM)[26] as the key steps.

In continuation of our ongoing interest in exploiting HKR method to install the stereocentres and ring-closing metathesis for making cyclic compounds *viz.* 10-memberd lactone rings based upon protecting group directed ring-closing metathesis protocol and generalizing its substrate based selectivity, we attempted to synthesize modiolide B.

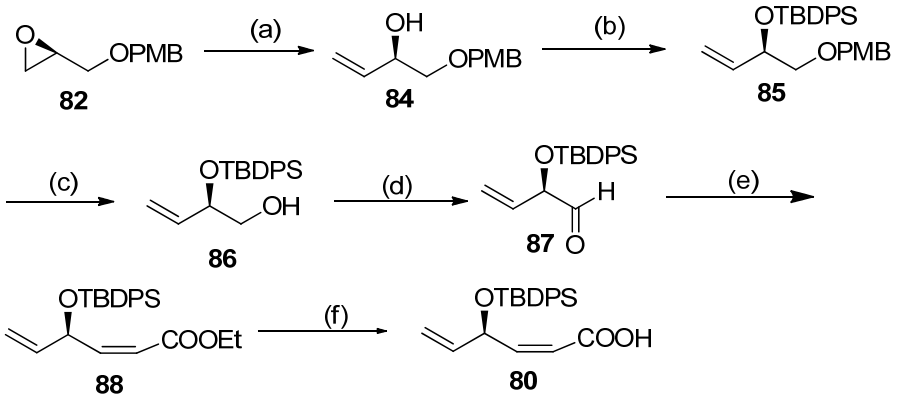
Our retrosynthetic analysis for modiolide B is based on the convergent approach as outlined in scheme 16. We envisioned that the natural product **75** could be obtained by ring-closing metathesis of diene precursor **79,** which in turn could be prepared by intermolecular Yamaguchi coupling of acid **80** and alcohol **81.** Acid **80** could be obtained from PMB protected (*R*)-glycidol (**82)** while the alcohol fragment could be prepared from *rac*-propylene oxide (**83)** via iterative HKR.



Scheme-16. Retrosynthetic route to modiolide B (**75**)**.**

Results and Discussion

As depicted in scheme 17, synthesis of acid fragment **80** commenced from commercially available *S*-glycidol which on hydroxy group protection with PMBCl followed by ring-opening of epoxide with dimethylsulfonium methylide gave the allylic alcohol **84** in excellent yield.

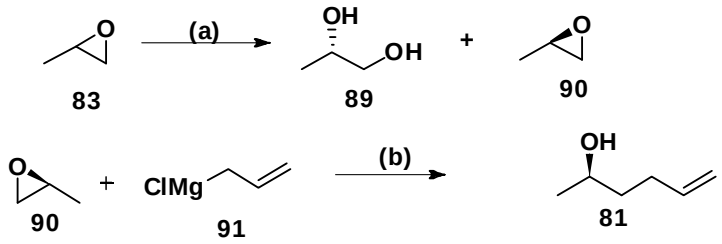


Scheme 17. Reagents and conditions: (a) $(CH_3)_3SI$, n-BuLi, THF, 4h, 73%; (b) TBDPSCl, Imidazole, CH_2Cl_2, 14h, 74%; (c) DDQ, CH_2Cl_2:H_2O (9:1), rt, 86%; (d)

IBX, DMSO:THF (1:1), 84%; (e) $(CH_3\text{-}C_6H_4O)_2P(O)CH_2CO_2Et$, NaH, -78 ^oC, THF, 5 h, 72%; (f) LiOH, MeOH, H_2O, rt, 12h, 64%.

Subsequent hydroxyl group protection as its TBDPS ether followed by PMB removal furnished the alcohol **86**, which on oxidation using IBX followed by Ando Wittig reaction furnished α, β-unsatured ester **88** (97:3, Z:E). The *Z*-selectivity of the (diarylphosphono) acetate reagent is a result of kinetic control and can be interpreted by the predominant formation of *erythro* adduct which irreversibly collapses to the *Z*-olefin. This could probably be attributed to the enhanced kinetic selectivity for the *erythro* adduct due to the steric hindrance of the aryl group and also silyloxy group at α-position rather than the electronic effect. ^1H NMR spectrum for compound **88** showed olefinic protons at δ 6.10 (dd, J = 7.8, 11.6 Hz, 1H), ester proton at δ 3.99 (q, J = 7.1, 14.3 Hz, 2H) and 11.6 (t, J = 7.1 Hz, 3H). Subsequent hydrolysis using LiOH afforded the acid fragment **80** in 64% yield. ^1H NMR spectrum confirmed the formation of compound **80** with *cis* selectivity δ 6.18 (dd, J = 7.8, 11.6 Hz, 1H) and δ 5.51 (dd, J = 1.4, 11.6 Hz, 1H).

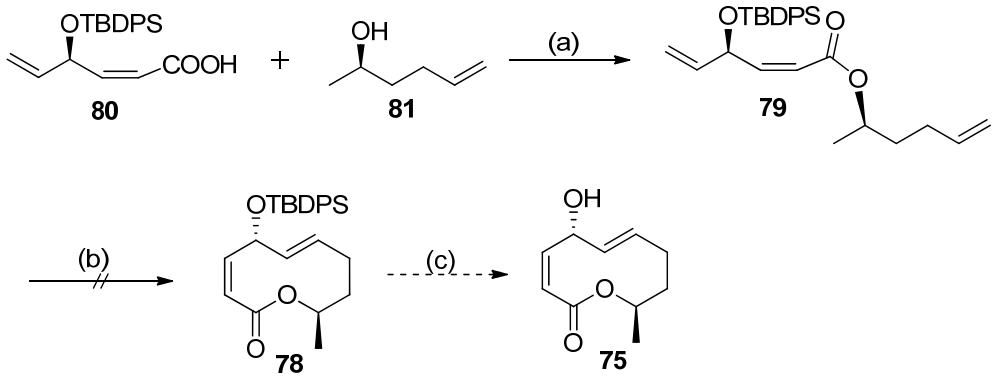
As illustrated in scheme 18, synthesis of alcohol fragment **81** started from commercially available (±) propylene oxide **83.** The racemic epoxide **83** was resolved using *(R,R)*-Salen Co^{III}-OAc to give enantiopure propylene oxide in 46% yield. The (*R*)-propylene oxide was opened with allylmagnesium chloride in the presence of CuCN to give the homoallylic alcohol **81** in 89% yield.



Scheme 18. Reagents and conditions: (a) *R,R*-salen-Co-(OAc) (0.5 mol %), dist. H_2O (0.55 equiv), 0^oC, 14h, (45% **89** for **,** 46% for **90**); (b) Allylmagnesium chloride, Ether, CuCN, -20^oC, 2h, 89%.

With substantial amount of both the fragments in hand the coupling of acid **80** and alcohol **81** was achieved by using the intermolecular Yamaguchi coupling to afford the diene ester **79** in 85% yield.

To obtain macrolactone **75**, the bis olefin moiety was subjected to ring-closing metathesis (RCM) using Grubb´s II generation catalyst in dichloromethane, however it provided the unidentified products. We tried several reaction conditions by changing the solvents like toluene, dichloroethane with increase in the reaction timings and loading the catalyst at different concentrations, but we failed to get the desired product. Based on the literature[27] survey on RCM for constructing 10-membered macrolides, presumably the bulkiness of TBDPS group and its spatial



Scheme 19. Reagents and conditions: (a) 2,4,6–Trichlorobenzoyl chloride, DIPEA, THF, rt then DMAP, toluene, reflux, 85%; (b) Grubb's catalyst II, CH_2Cl_2, reflux, 12h.

Table 1: *Conditions applied and results obtained in Ring-closing metathesis*

Entry	Reaction conditions	Result Obtained
1.	Grubb's catalyst II, CH_2Cl_2, reflux, 12h	Starting material recovered
2.	Grubb's catalyst II, CH_2Cl_2, reflux, 48h	Starting material decomposed
3.	Grubb's catalyst II, Toluene, reflux, 24h	Complex mixture
4.	Grubb's catalyst II, $(CH_2)_2Cl_2$, reflux, 24h	Complex mixture
5.	Hoveyda-Grubb's catalyst I, $(CH_2)_2Cl_2$, reflux, 24h	Complex mixture

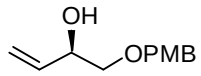
arrangement around the olefinic bonds did not allow the cyclisation. Due to the failure to obtain lactone through RCM protocol, alternate synthetic strategy is underway in our laboratory to obtain lactone under Yamaguchi lactonisation conditions.

Conclusion:

In conclusion, we attempted the synthesis of Modiolide B from *rac*-propylene oxide and (*S*)-glycidol using Yamaguchi coupling and ring closing metathesis as the key step.

Experimental Section

(*R*)-1-((4-Methoxybenzyl)oxy)but-3-en-2-ol (84)



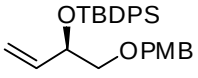
To a stirred solution of dry THF was added trimethylsulfonium iodide (26.3 g, 128.7 mmol) at -20^{o}C. The reaction was stirred for 20 min followed by addition of n-BuLi (80.44 mL, 1.6 M, 128.7 mmol). After 40 min, epoxide **82** (5 g, 25.74 mmol) in THF was added drop-wise. The reaction mixture was stirred at -20^{o}C for 3h and quenched by saturated solution of ammonium chloride. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (3 x 50 mL), brine, dried over Na_2SO_4 and concentrated. The residual oil was purified by silica gel column chromatography. (**Yield:** 3.90 g, 73%)

Mol. Formula: $C_{12}H_{16}O_3$

ESI-MS: *m/z* = 208 $[M + Na]^+$

Analysis Calcd.: C, 69.21; H, 7.74; **Found:** C, 79.32; H, 7.61.

(*R*)-*tert*-Butyl((1-((4-methoxybenzyl)oxy)but-3-en-2-yl)oxy)diphenylsilane (85)



To a stirred solution of **84** (2.0 g, 9.63mmol) in CH_2Cl_2 (10 mL) was added imidazole (1.29 g, 19.23 mmol). To this solution *t*-butyl diphenylchlorosilane (3.17 g, 11.55

mmol) and cat. DMAP was added at 0°C and reaction was stirred at room temperature for 12h. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 x 20 mL).The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using (petroleum ether : EtOAc, 99: 1) as eluent provided **85** (3.18 g, 74%) as a colorless liquid.

Mol. Formula: $C_{28}H_{34}O_3Si$

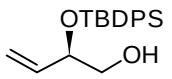
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.11 (s, 9H), 3.36 (dd, *J* = 5.7, 9.8 Hz, 1H), 3.44 (dd, *J* = 5.7, 9.8 Hz, 1H), 3.82 (s, 3H), 4.34 (s, 2H), 5.05 (dt, *J* = 1.5,10.5 Hz, 1H), 5.19 (dt, *J* = 1.4, 17.2 Hz, 1H), 5.92 (ddd, *J* = 5.9, 10.5, 17.2 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 2H), 7.27-7.45 (m, 6H), 7.66-7.75 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.3, 26.9, 55.2, 72.7, 73.2, 74.2, 113.5, 115.5, 127.4, 129.1, 129.5, 130.3, 133.7, 134.1, 135.8, 135.9, 138.3, 158.9.

ESI-MS: *m/z* = 447 $[M + Na]^+$

Analysis Calcd.: C, 75.29; H, 7.67; **Found:** C, 75.34; H, 7.63.

(*R*)-2-((*tert*-Butyldiphenylsilyl)oxy)but-3-en-1-ol (86)



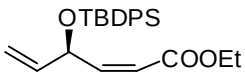
To a solution of **85** (0.50 g, 1.12 mmol) and DDQ (0.279 g, 1.23 mmol) in CH_2Cl_2:H_2O mixture (20:1) was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated solution of $NaHCO_3$, separated the organic layer, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60-120 mesh, eluted in 5% EtOAc-light petroleum ether) to afford **86** as a colorless liquid. (**Yield:** 0.31 g, 86%)

Mol. Formula: $C_{20}H_{26}O_2Si$

ESI-MS: *m/z* = 326 $[M + Na]^+$

Analysis Calcd.: C, 73.57; H, 8.03; **Found:** C, 73.86; H, 8.14.

(*R,Z*)-Ethyl 4-((*tert*-butyldiphenylsilyl)oxy)hexa-2,5-dienoate (88)



2-Iodobenzoic acid IBX (0.858 g, 3.07 mmol) was added to a solution of alcohol **86** (0.50 g, 1.53 mmol) in EtOAc (10 mL). After stirring at refluxing conditon for 4 h, the reaction mixture was filtered through celite pad and concentrated under vacuum. The crude aldehyde was pure enough to be used in a next step without further purification. (**Crude yield:** 0.42 g, 84%)

A solution of methyl (di-*o*-tolylphosphono) acetate (0.64 g, 1.85 mmol) in THF (10 mL) was treated with NaH (60%) (0.148 g, 3.70 mmol) at -78 ^{o}C for 15 min. To the above reaction mixture was added a freshly prepared aldehyde (0.50 g, 1.54 mmol) in THF (10 mL) and the resulting mixture was stirred at -78 ^{o}C for 5 h. After TLC showed completion of the starting material, the reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc (3 x 20 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (99:1) to give **88** as a colorless oil. (**Yield:** 0.438 g, 72%)

Mol. Formula: $C_{24}H_{30}O_3Si$

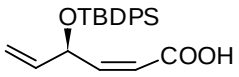
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.13 (s, 9H), 1.16 (t, *J* = 7.1 Hz, 3H), 3.99 (q, *J* = 7.1, 14.3 Hz, 2H), 5.13-5.19 (m, 1H), 5.41-5.57 (m, 2H), 5.83-5.99 (m, 2H), 6.10 (dd, *J* = 7.8, 11.6 Hz, 1H), 7.31-7.44 (m, 6H), 7.64-7.71 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.2, 19.4, 27.1, 60.1, 70.5, 114.7, 117.8, 127.5, 127.6, 129.7, 129.7, 133.7, 133.9, 135.8, 135.9, 137.7, 150.2, 165.6.

ESI-MS: *m/z* = 395 $[M + Na]^+$

Analysis Calcd.: C, 73.05; H, 7.66; **Found:** C, 73.34; H, 7.73.

(*R*,*Z*)-4-((*tert*-Butyldiphenylsilyl)oxy)hexa-2,5-dienoic acid (80)



A solution of ethyl ester **88** (0.40 g, 1.01 mmol) in methonal: water (1:1) was treated with LiOH (0.072 g, 3.04 mmol) at rt for 12h. After TLC showed completion of the starting material, methanol was removed under reduced pressure and remaining aq. solution was washed with EtOAc (3 x 20 mL) and neutralized using 0.1N HCl till the pH became 7 and then extracted with EtOAc, the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (7:3) to give **88** as a colorless oil. (**Yield:** 0.238, 64%)

Mol. Formula: $C_{22}H_{26}O_3Si$

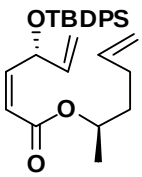
^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.11 (s, 9H), 5.15 (dt, *J* = 1.9, 10.5 Hz, 1H), 5.44 (dt, *J* = 1.6, 17.1 Hz, 1H), 5.51 (dd, *J* = 1.4, 11.6 Hz, 1H), 5.77-5.80 (m, 1H), 5.85 (ddd, *J* = 4.5, 10.5,17.1 Hz, 1H), 6.18 (dd, *J* = 7.8, 11.6 Hz, 1H), 7.27-7.44 (m, 6H), 7.64-7.71 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 19.3, 26.9, 70.2, 114.9, 116.9, 127.4, 127.5, 129.7, 129.8, 133.4, 133.6, 135.7, 135.8, 137.2, 152.7, 170.5.

ESI-MS: *m/z* = 367 $[M + Na]^+$

Analysis Calcd.: C, 72.09; H, 7.15; **Found:** C, 72.43; H, 7.11.

(*R*,*Z*)-(*R*)-Hex-5-en-2-yl 4-((*tert*-butyldiphenylsilyl)oxy)hexa-2,5-dienoate (79)



To a stirred solution of the acid fragment **80** (0.100 g, 0.273 mmol) in dry CH_2Cl_2 (10 mL), were added DIPEA (0.28 mL, 1.64 mmol) and a solution of 2,4,6-trichlorobenzyol chloride (0.079 g, 0.327 mmol) in dry CH_2Cl_2 (5 mL) and the mixture was stirred at 0 °C for 20 min. Then a solution of the alcohol fragment **81**

(0.027 g, 0.273 mmol) in dry CH_2Cl_2 (5 mL) and DMAP (catalytic) were added, stirred for 6 h at room temperature (Checked by TLC). The solvent was evaporated, the crude was purified by column chromatography using EtOAc:petroleum ether (1:9) as eluent to afford **79** (0.104 g, 85%) as a colorless liquid.

Mol. Formula: $C_{28}H_{36}O_3Si$

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.11 (s, 9H), 1.24 (d, *J* = 1.6 Hz, 3H), 1.58-1.64 (m, 2H), 1.68-1.77 (m, 1H), 2.03-2.14 (m, 2H), 4.75 (t, *J* = 5.1 Hz, 1H), 4.94-5.11 (m, 5H), 5.74-5.85 (m, 2H), 5.88 (dd, *J* = 1.6, 15.6 Hz, 1H), 6.78 (dd, *J* = 5.1, 15.6 Hz, 1H), 7.27-7.45 (m, 6H), 7.66 (t, *J* = 6.0 Hz, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 19.3, 19.9, 26.9, 35.1, 70.4, 73.9, 114.9, 115.9, 120.4, 127.5, 127.6, 129.7, 129.8, 133.3, 133.4, 135.8, 135.9, 137.8, 148.2, 166.1.

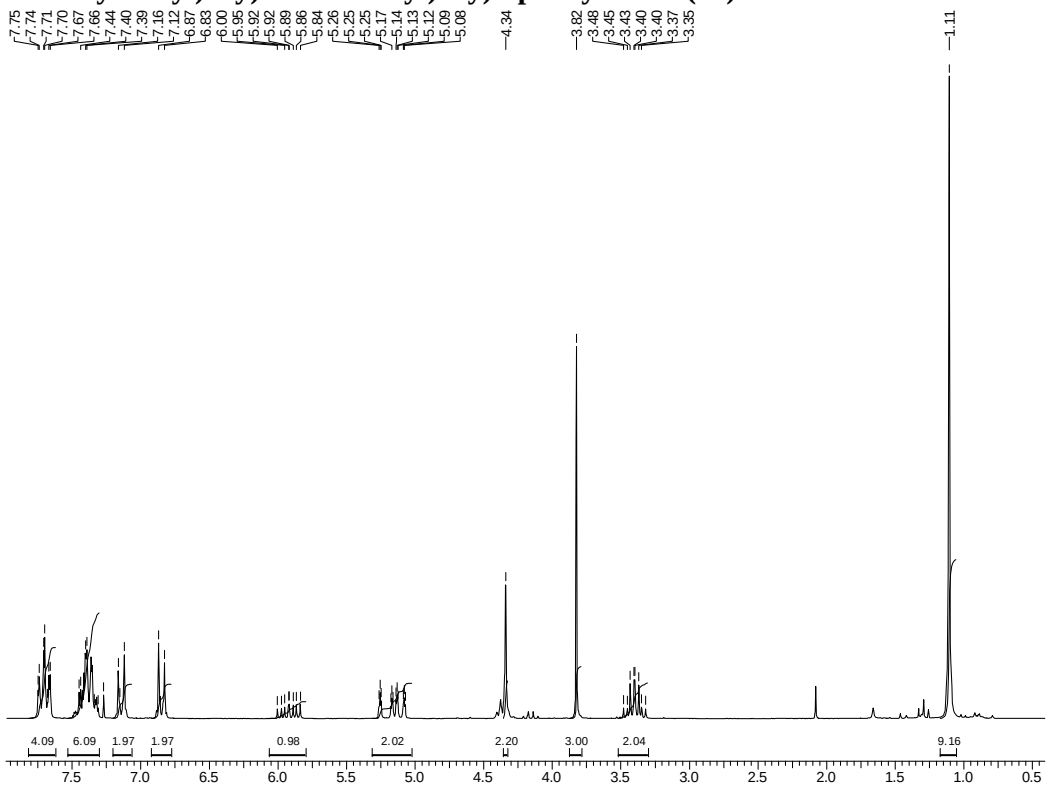
ESI-MS: *m/z* = 449 $[M + Na]^+$

Analysis Calcd.: C, 74.95; H, 8.09; **Found:** C, 74.72; H, 8.12.

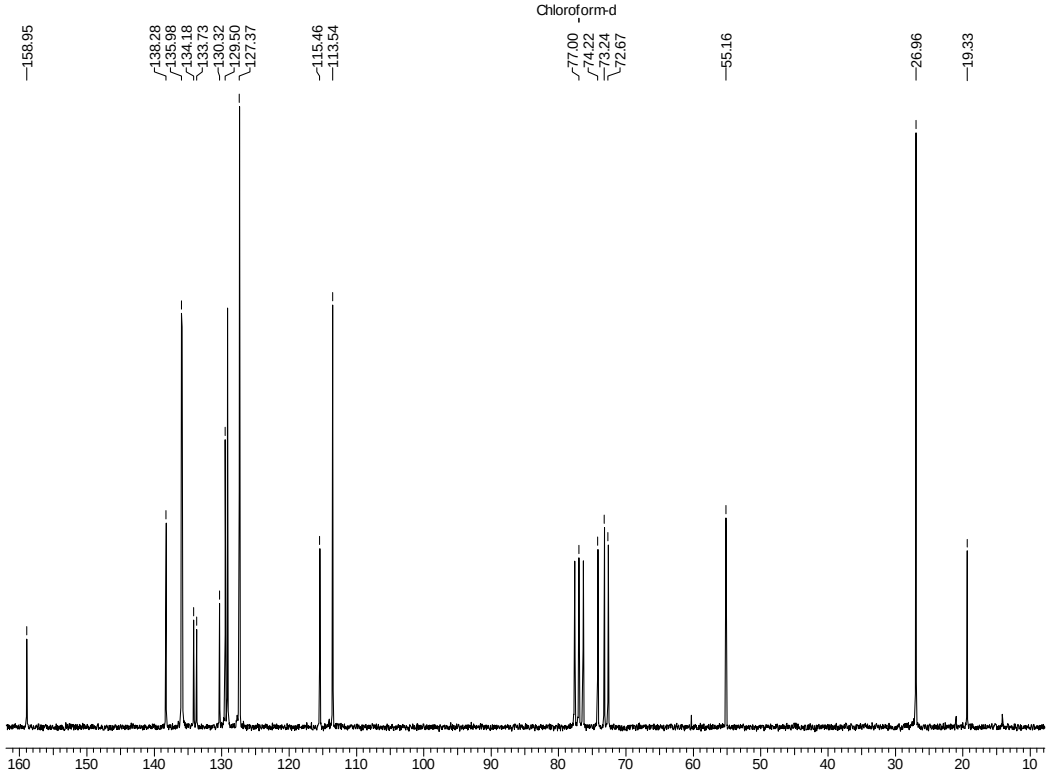
Spectra

1. ^{1}H and ^{13}C NMR spectra of **85**
2. ^{1}H and ^{13}C NMR spectra of **88**
3. ^{1}H and ^{13}C NMR spectra of **80**
4. ^{1}H and ^{13}C NMR spectra of **79**

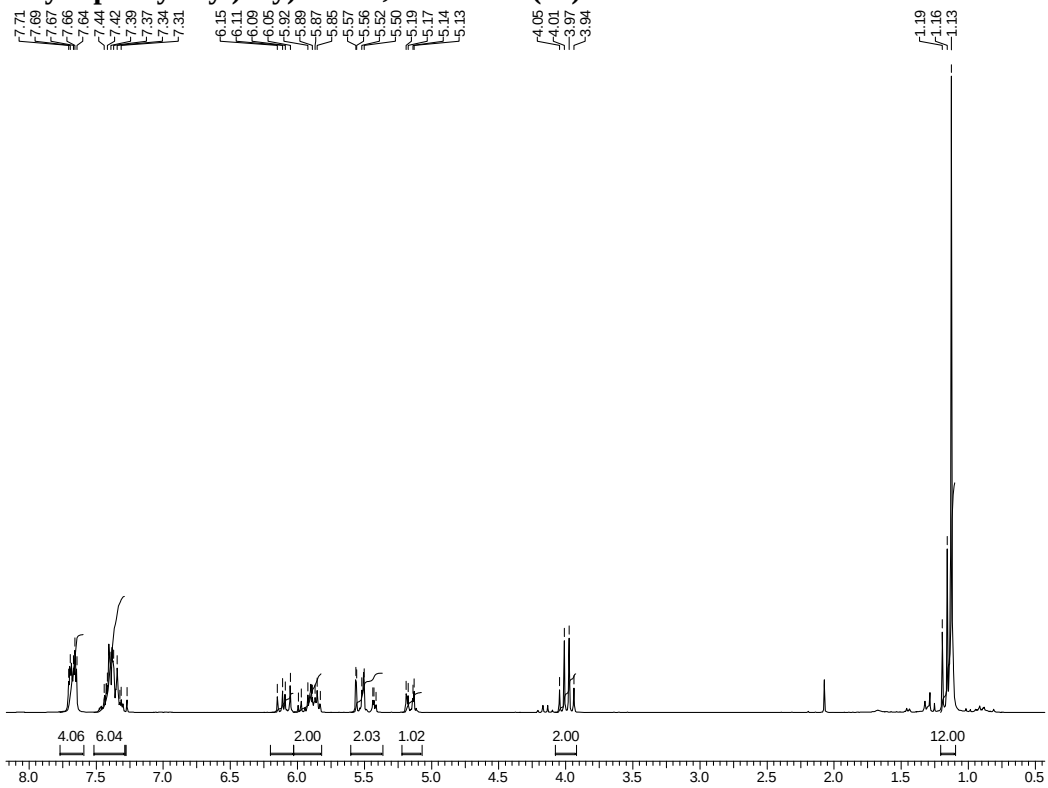
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*R*)-tert-butyl((1-((4-methoxybenzyl)oxy)but-3-en-2-yl)oxy)diphenylsilane (85)



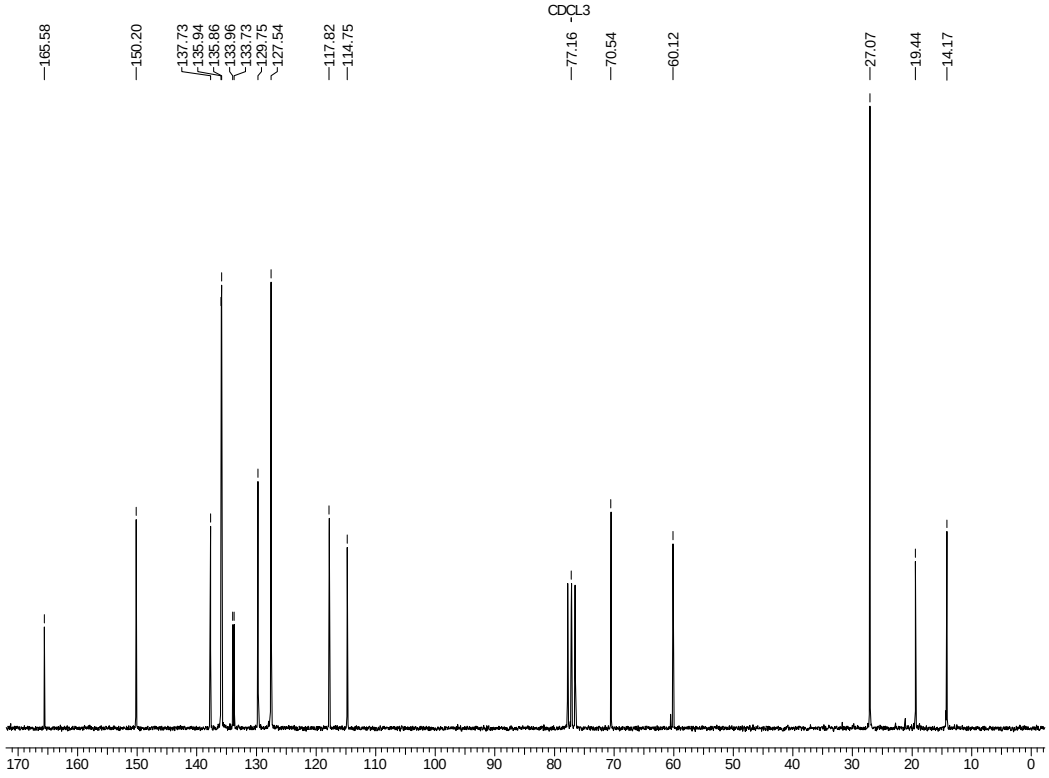
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*R*)-tert-butyl((1-((4-methoxybenzyl)oxy)but-3-en-2-yl)oxy)diphenylsilane (85)



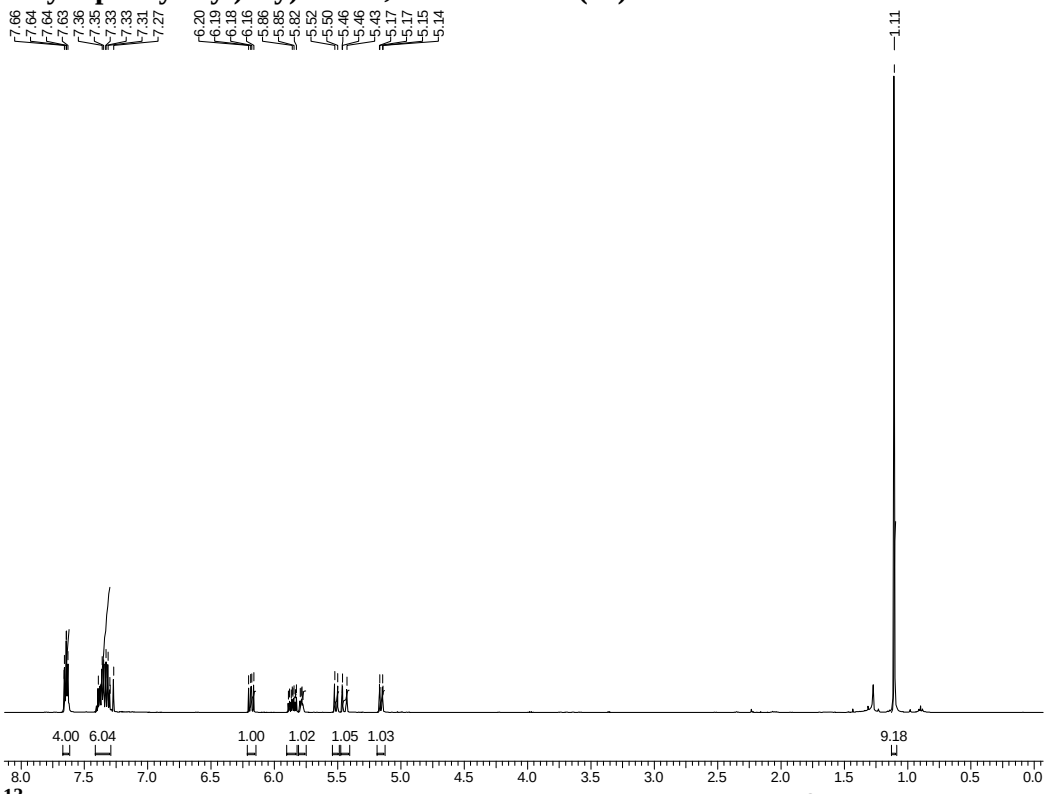
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of (*R*,*Z*)-ethyl 4-((tert-butyldiphenylsilyl)oxy)hexa-2,5-dienoate (88)



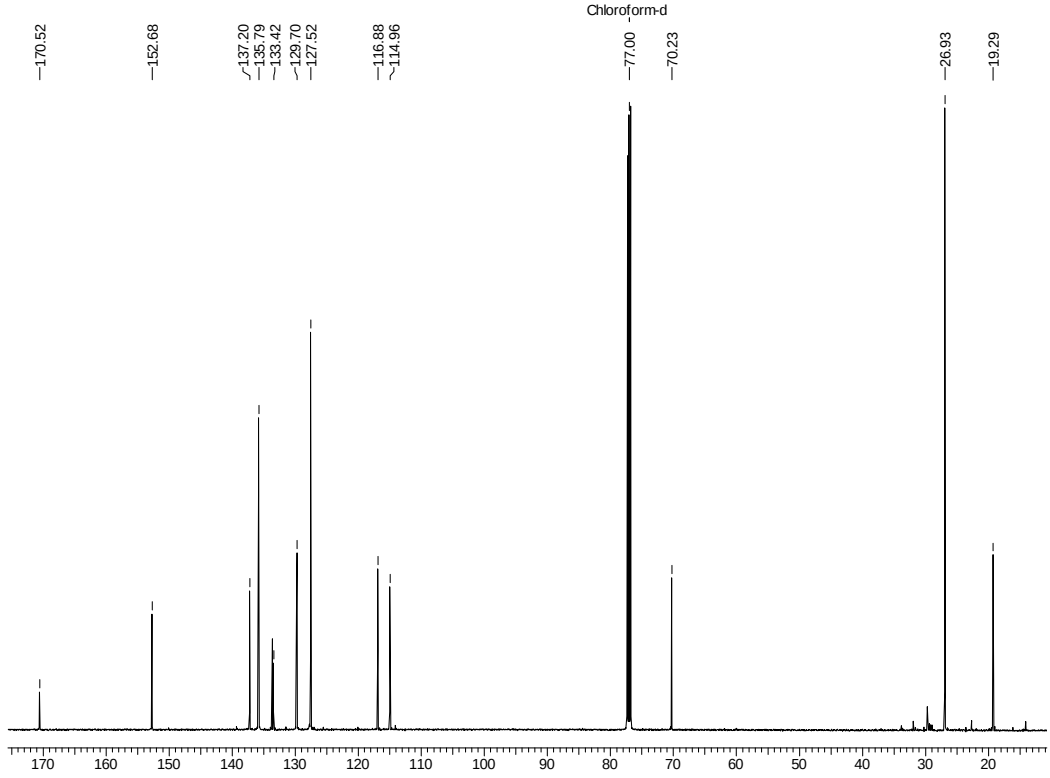
^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of (*R*,*Z*)-ethyl 4-((tert-butyldiphenylsilyl)oxy)hexa-2,5-dienoate (88)



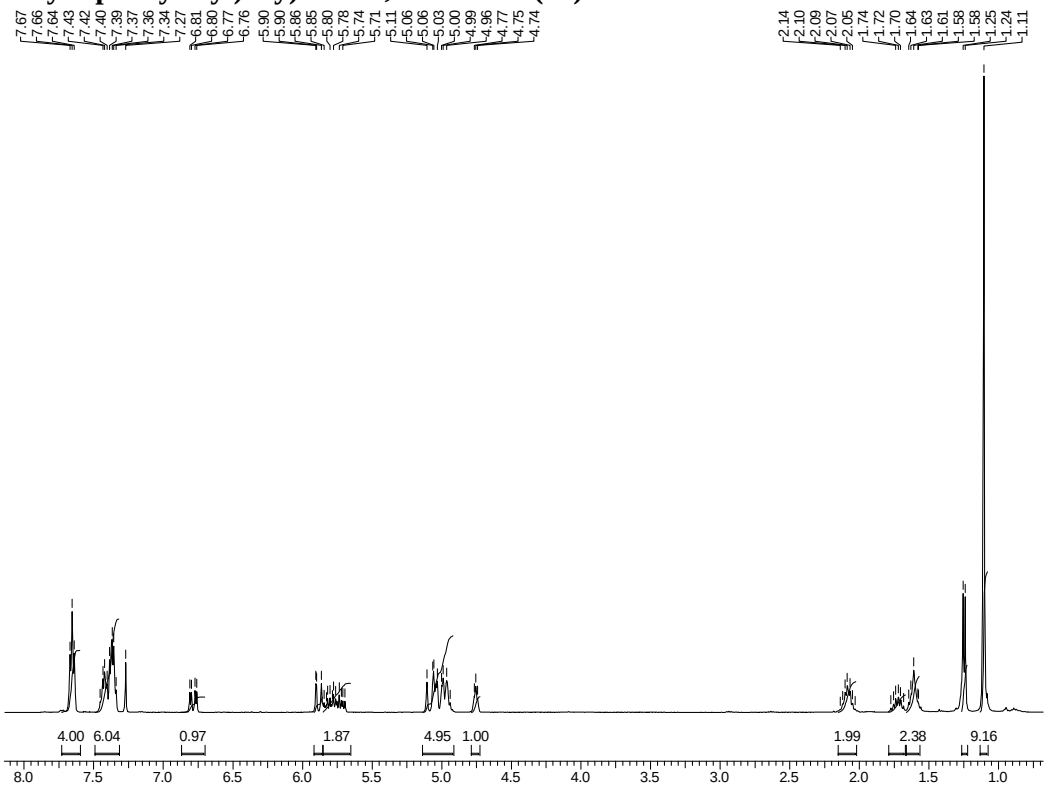
^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of (*R*,*Z*)-4-((tert-butyldiphenylsilyl)oxy)hexa-2,5-dienoic acid (80)



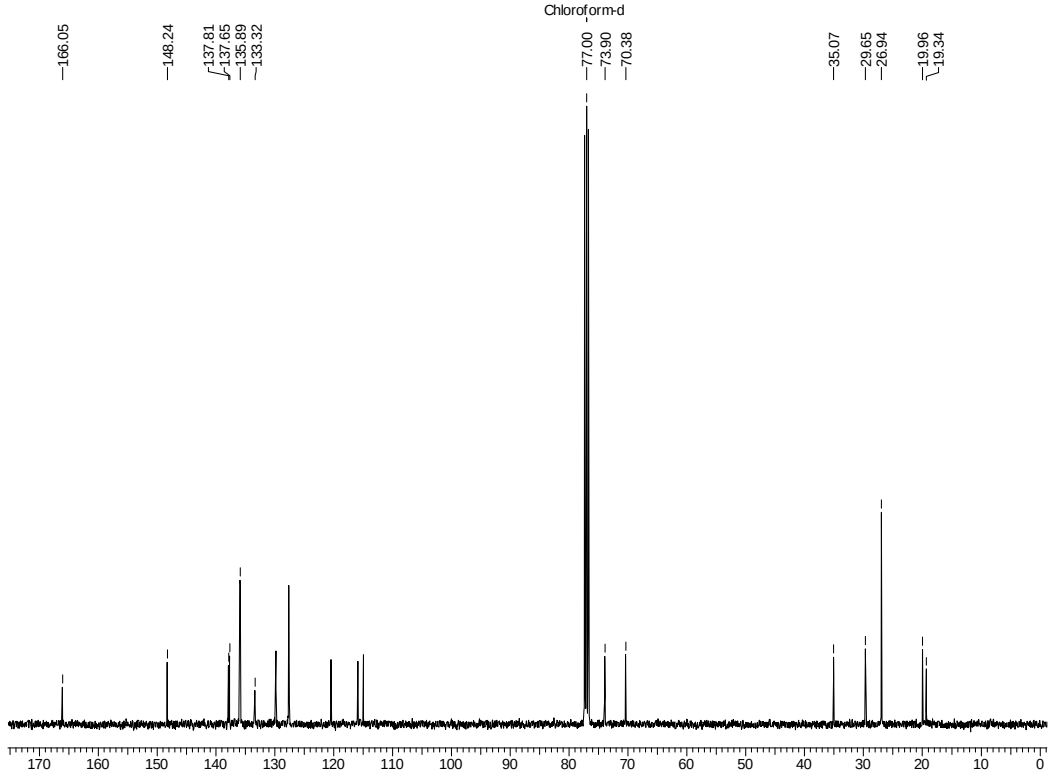
^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of (*R*,*Z*)-4-((tert-butyldiphenylsilyl)oxy)hexa-2,5-dienoic acid (80)



^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of (*R*,*Z*)-(*R*)-hex-5-en-2-yl 4-((tert-butyldiphenylsilyl)oxy)hexa-2,5-dienoate (79)



^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of (*R*,*Z*)-(*R*)-hex-5-en-2-yl 4-((tert-butyldiphenylsilyl)oxy)hexa-2,5-dienoate (79)



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Chapter III

Introduction:

Nature has been producing a range of diverse and highly complex macro - cyclic lactones. Macrocyclic lactones are an abundant naturally occurring group of heterocycles exibiting interesting biological activities and being used as potential drug members for decades. These macrolactones are found in a wide range of stuctural variations and often originate in very simple to most complex structures, which exhibit one or more variety of pharmacological activity. Also, the search for biologically active natural products in the nature for the development of new drugs has been a long tradition.[1] Most such compounds are isolated from plants, animals, fungi, and microorganisms like bacteria, which exist in great variety on earth. Total synthesis is playing a major role in the drug discovery process of such compounds since it allows exploration of chemical biology through molecular design and mechanistic study.[2]

With the advent of modern isolation techniques, numerous large-ring lactones that possess interesting biological activity have been isolated. The need for dependable methods of forming such lactones in the presence of sensitive functionality has led to the development of numerous methods. The most recognized of these is the Yamaguchi cyclization,[3] where the ester is activated as a mixed anhydride and esterification is facilitated by a high concentration of the acylation promoter 4-(dimethylamino)pyridine (DMAP).

Among the naturally occurring lactones of different ring sizes, the dimeric lactones show wide range of biologically active *viz*. antifungal and antibacterial. This class consists of C_2 symmetrical compounds such as verbalactone,[4] pyrenophorol, pyrenophorin, tetrahydropyrenophorol etc. (**Figure 1**).[5] Symmetrical dimeric lactones are an important class of natural products offering a wide array of structural complexity and bioactivity. These macrolides have become popular targets for synthetic chemists. The most direct way to construct these molecules is through the union of two monomeric species in a tandem dimerization and macrocyclization reaction. The most common version of this strategy utilizes two esterification.

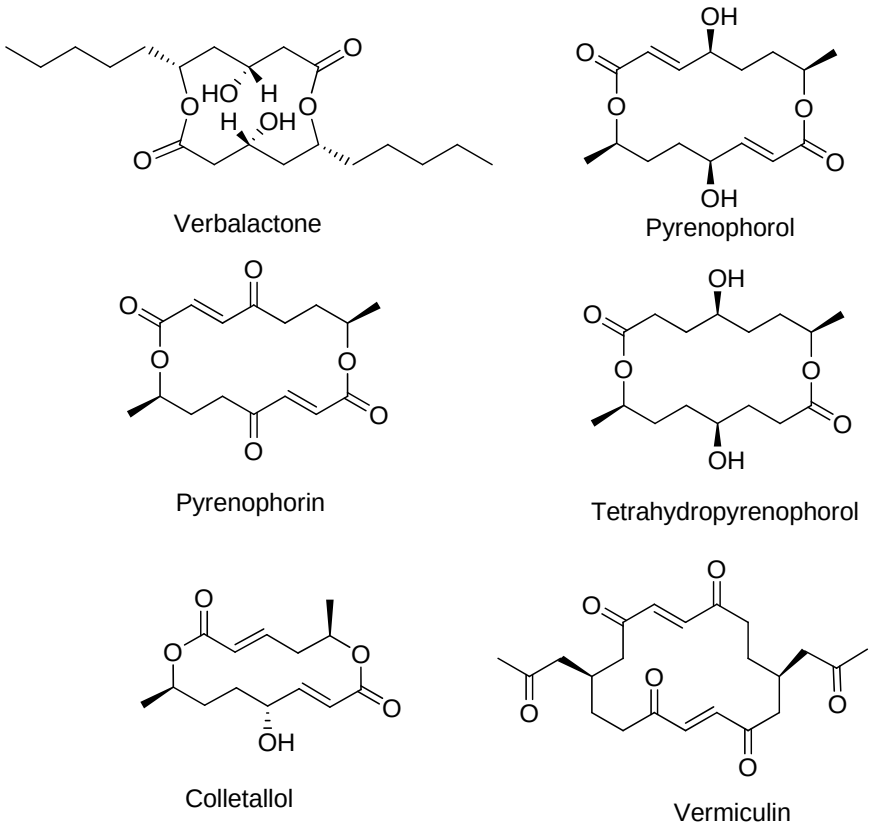


Figure 1. Few examples of dimeric C-2 symmetric lactones

Macrocyclic Lactones

Ever since the first isolation of exaltolide **1** (figure 2) in 1927 by Kerschbaum,[6] interest in macrocyclic lactones, defined as lactones with more than eight atoms in the ring, has been increasing. Indeed, natural macrocyclic lactones present a large spectrum of interesting properties from perfumery, to phytotoxicity, to pheromone or insecticide activity, to medicinal (antibiotic, cytotoxic, antiangiogenesis) properties and a wide range of structures from 8-membered ones such as octalactins **2**[7] to the 60-membered quinolidomicin **3**. From their first isolation in the 1950s, macrolide antibiotics, such as erythromycin **4**,[8] were widely used to treat bacterial infections, and because of their safety and efficacy, they are still the preferred therapeutic agents for treatment of respiratory infections. Another important class of macrolactones with a wide range of biological activities is the cyclodepsipeptides[9] such as, FK228 **5**, which is currently in phase II clinical trials as an anticancer drug and acts as a prodrug that undergoes disulfide reduction within the

cell to release a zinc-binding thiol. The biopesticide Spinosad, a mixture of spinosyn A **6**, is currently marketed for use against a wide variety of insects.

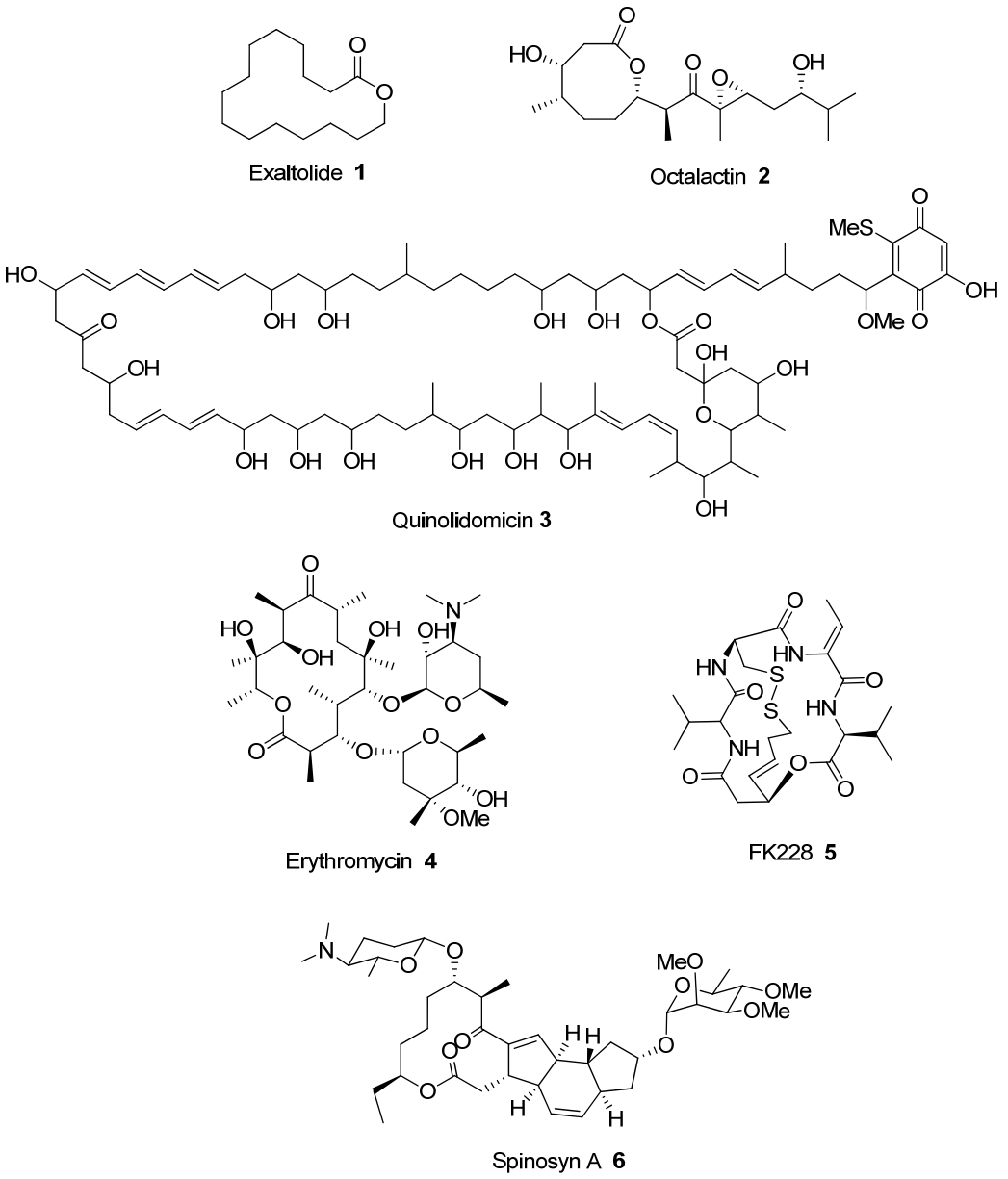


Figure 2: Few examples of natural macrolactones

Many efficient macrocyclization methods such as the RCM, intramolecular cross-coupling, Nozaki-Hiyama-Kishi, and HWE methods have been developed over the years, the lactonization of secoacids still appears to be one of the more frequently used approaches to obtain macrocyclic lactones. Due to entropic and enthalpic factors (v*ide infra*), direct cyclization is generally not possible without activation of either the alcohol or the carboxylic acid terminal group.

We have also been involved in total synthesis of some of the biologically active macrolactones employing Jacobson's hydrolytic kinetic resolution or recently, developed iterative approach to the enantiopure synthesis of syn/anti-1,3-polyols. A few representative examples of our recent synthetic targets are shown in figure 3.[10]

During the last decade it has been established that small organic molecules can be highly selective and efficient catalysts. As a result, the area of organocatalysis has emerged as a promising strategy and as an alternative to expensive protein catalysis and toxic metal catalysis, thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis.

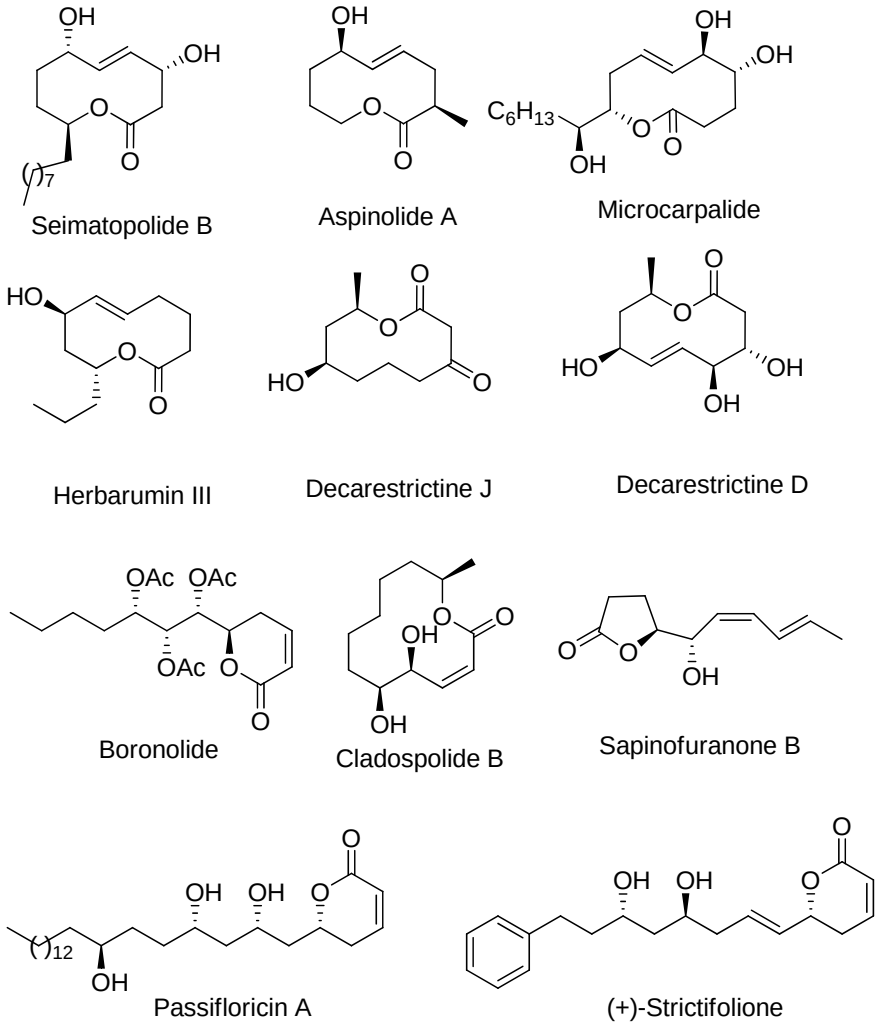


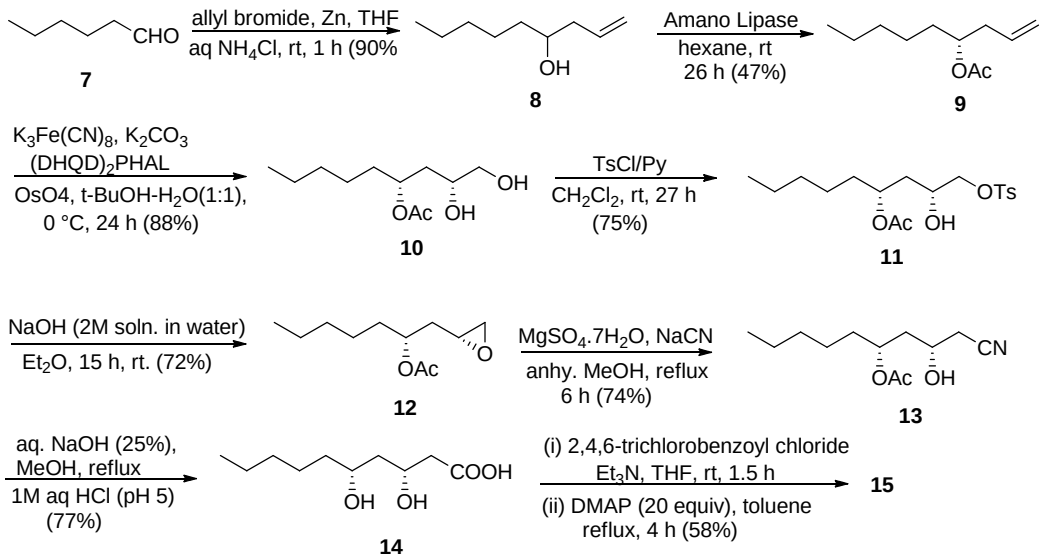
Figure 3: Representative examples of recently synthesized lactones in our group

Proline, in the recent past has been defined as a 'universal catalyst' because of its utility in different reactions providing rapid, catalytic, atom-economical access to enantiomerically pure products. Similarly, organocatalytic tandem processes provide efficient means to construct complex target molecules in an environmentally friendly and rapid way from simple and readily available precursors, while minimizing time and energy losses. Recently, we have developed an iterative approach[11] to the enantiopure synthesis of syn/anti-1,3-polyols, which is based on proline-catalyzed sequential α-aminoxylation and Horner–Wadsworth– Emmons (HWE) olefination of aldehydes. The interesting structural features of verbalactone and other six membered lactones combined with the biological activity drew our attention and, as a part of our research program aimed at developing enantioselective syntheses of biologically active natural products, we became interested in devising a simple and concise route to verbalactone, hexadecanolide and massoialactone via our recently developed organocatalytic methodology. Herein we describe our successful endeavours towards the total synthesis of these compounds employing proline catalyzed sequential α-aminoxylation and Horner–Wadsworth– Emmons (HWE) olefination of aldehyde as the key step.

Previous Approaches Towards the Synthesis of Verbalactone (15):

1. **Barua's Approach**[12]

The first total synthesis of **15** was reported out by Barua *et al.* in 2004



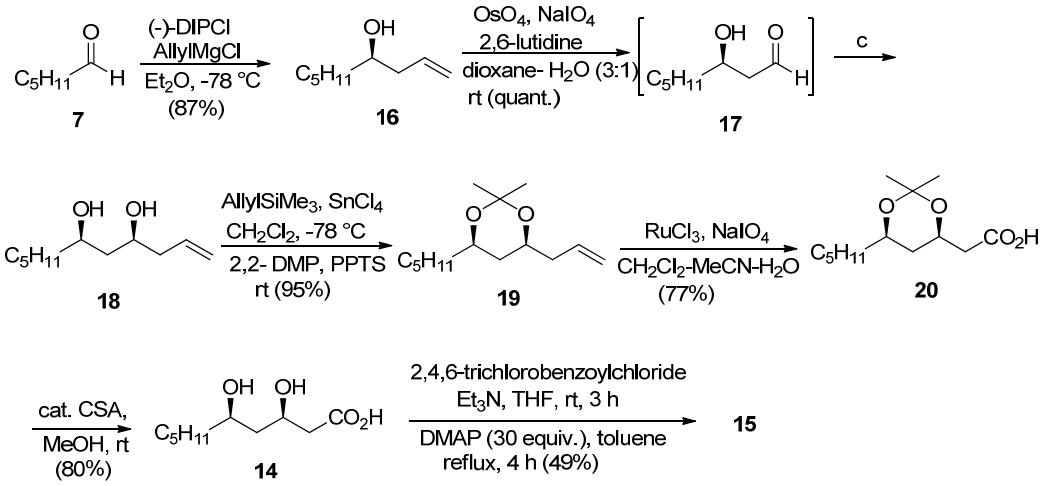
7 **8** **9** **10** **11** **12** **13** **14**

Scheme1: Synthesis of verbalactone **15**

who prepared the target molecule in eight steps beginning with hexanal (**scheme 1**). Their stereoselective synthesis involved Barbier-Grignard and Sharpless asymmetric dihydroxylation reactions as the key transformations.

2. Allais's Approach[13]

Another asymmetric synthesis of **15** was reported by Allais and coworkers in 2007. Their approach comprises a diastereo- and enantio-selective allylmetalation reactions to generate the stereochemistry of the molecule. The synthesis hinges on the same Yamaguchi macrolactonisation protocol used by earlier reporters at the later stages of the synthesis.



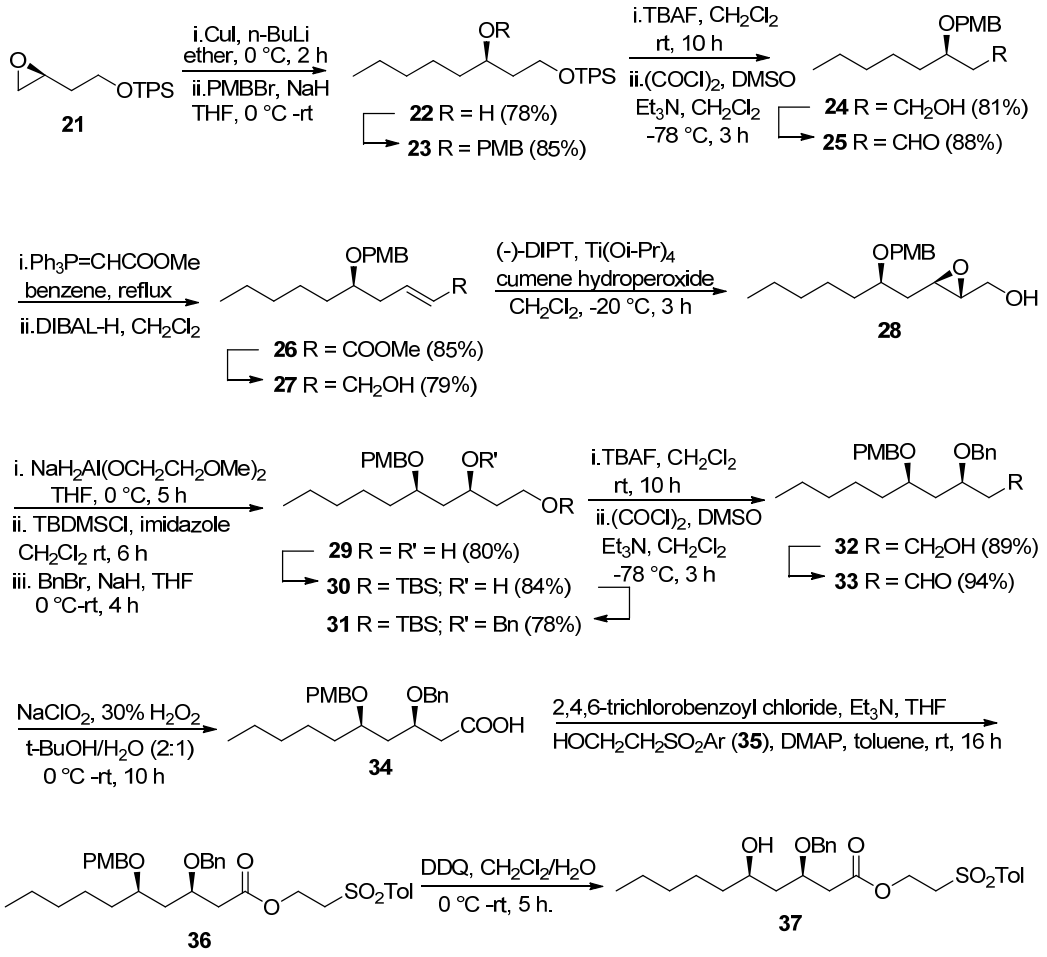
Scheme 2: Synthesis of verbalactone via asymmetric allylation

A seven steps synthesis begins with a stereoselective allylmetallation reaction on hexanal in presence of a chiral catalyst. The homoallylic alcohol **16** was converted to syn diol derivative **18** *via* a diastereoselective allylation by using allyltrimethylsilane. Once a suitable chiral carbon chain was availed, it was amended to the monomer seco acid **14** following a sequence of reactions (**Scheme 2**). Compound **14** was dimerised using 2,4,6-trichlorobenzoylchloride in the presence of triethyl amine and THF followed by high temperature heating in presence of excess of DMAP to furnish **15** in a good overall yield.

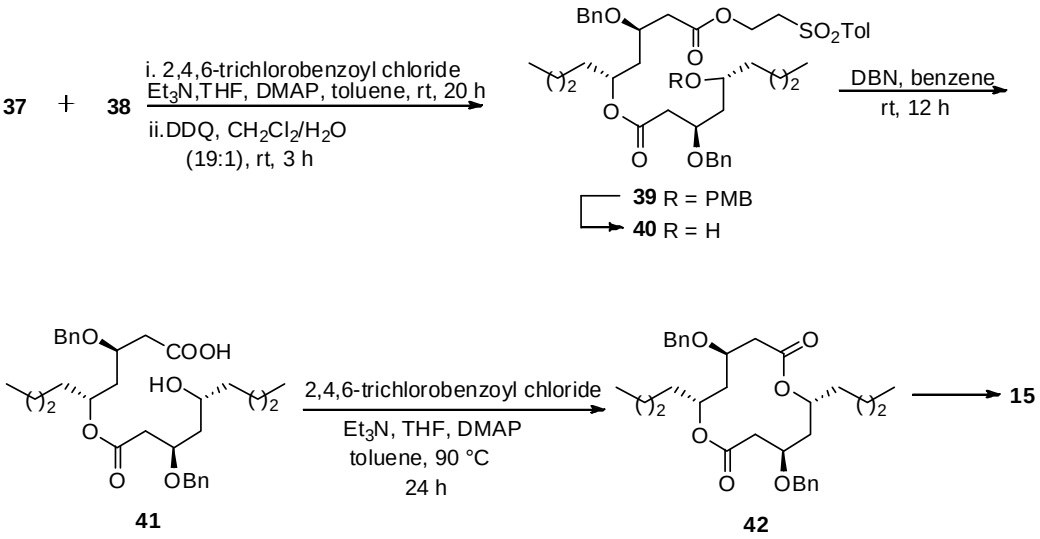
3. Sharma's Approach[14]

Sharma *et al.* reported another convergent strategy towards the total synthesis of verbalactone starting with L-malic acid (**Scheme 3**). The two appropriately protected

acid and alcohol segments were prepared from L-malic acid and lactonized under Yamaguchi conditions to avail the title compound.



L-Malic acid on several simple functional transformations gave epoxide **21**. CuI mediated opening of the epoxide **21** with *n*-BuLi elongated the carbon chain by four carbons to furnish alcohol **22** which was subjected to some sequential protection-deprotection and oxidation reactions as shown in **scheme 3** to provide aldehyde **25**. Two-carbon Wittig olefination of aldehyde **25**, DIBAL-H reduction of the resultant unsaturated ester and subsequent Sharpless asymmetric epoxidation afforded the epoxide **28**. Selective opening of the epoxide and supplementary functional group interpretations supplied the suitably protected seco acid **34** in good to excellent yields. In order to get a dimer of the seco acid **34**, it was coupled with alcohol **35** by using intermolecular Yamaguchi reaction to afford ester **36**. Removal of the PMB protection and the ester hydrolysis yielded compound **37** which on lactonization under Yamaguchi conditions



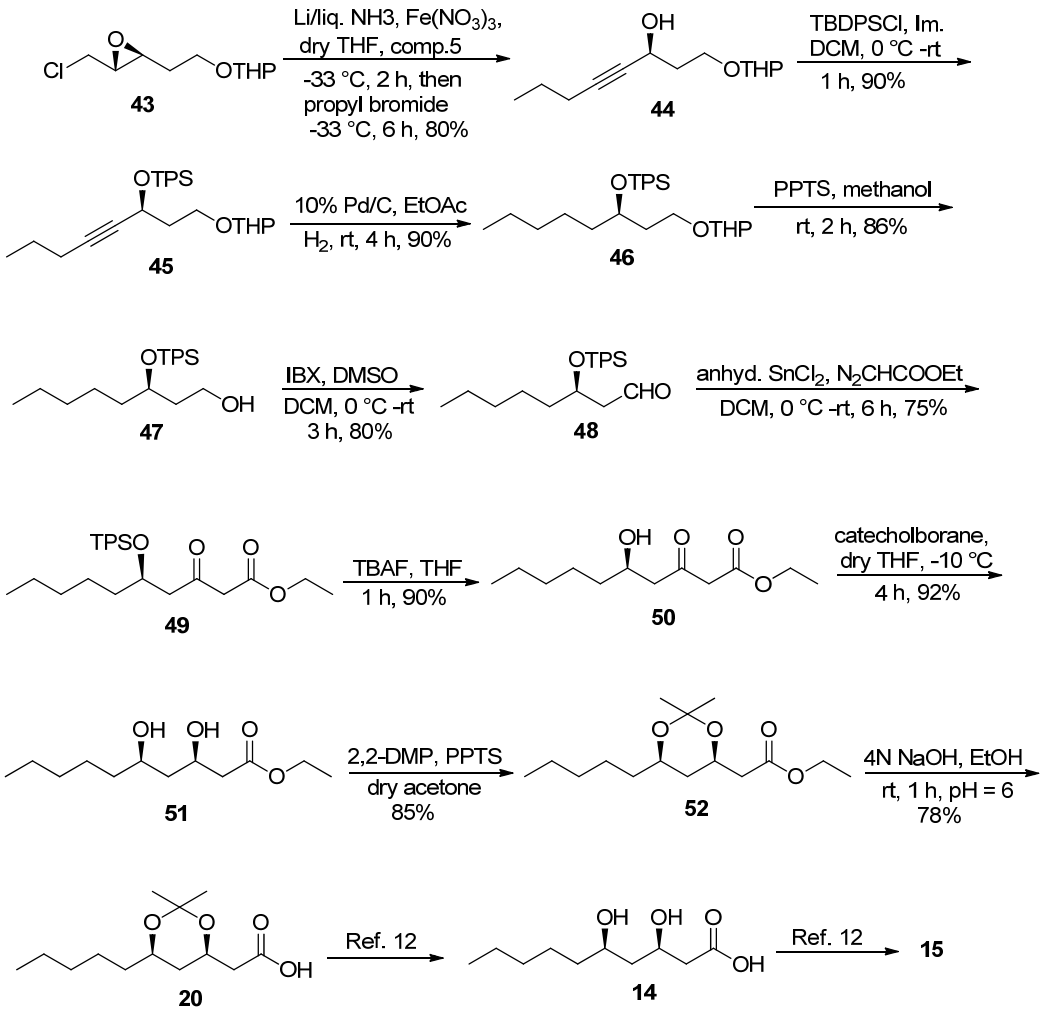
Scheme 3: Yamaguchi cyclisation of seco acid

furnished protected natural product. Global unmasking by the use of titanium tetrachloride finished the target molecule verbalactone.

Sabitha's Approach[15]

Sabitha and coworkers reported a formal synthesis of verbalactone (**Scheme 4**). Acetonide protected monomer acid **20** was procured in ten steps statrting with chiral chloro-epoxide **43**. Another stereocenter was availed through a diastereoselective reduction of the ketone precursor **50**.

Epoxide **43** was opened selectively to provide pentynyl alcohol **44**. Functional group interpretations smoothly led to the aldehyde **48**. Tin mediated addition of two carbons ester functionality launched ketone **49**. Deprotection of C5 hydroxy and consequent diastereoselective reduction with catecholborane provided syn diol **51** in an excellent yield, which on acetonide protection and ester hydrolysis produced the acid **20**. Acid **20** was transformed to verbalactone adopting Yamaguchi lactonization following literature procedure.[14]



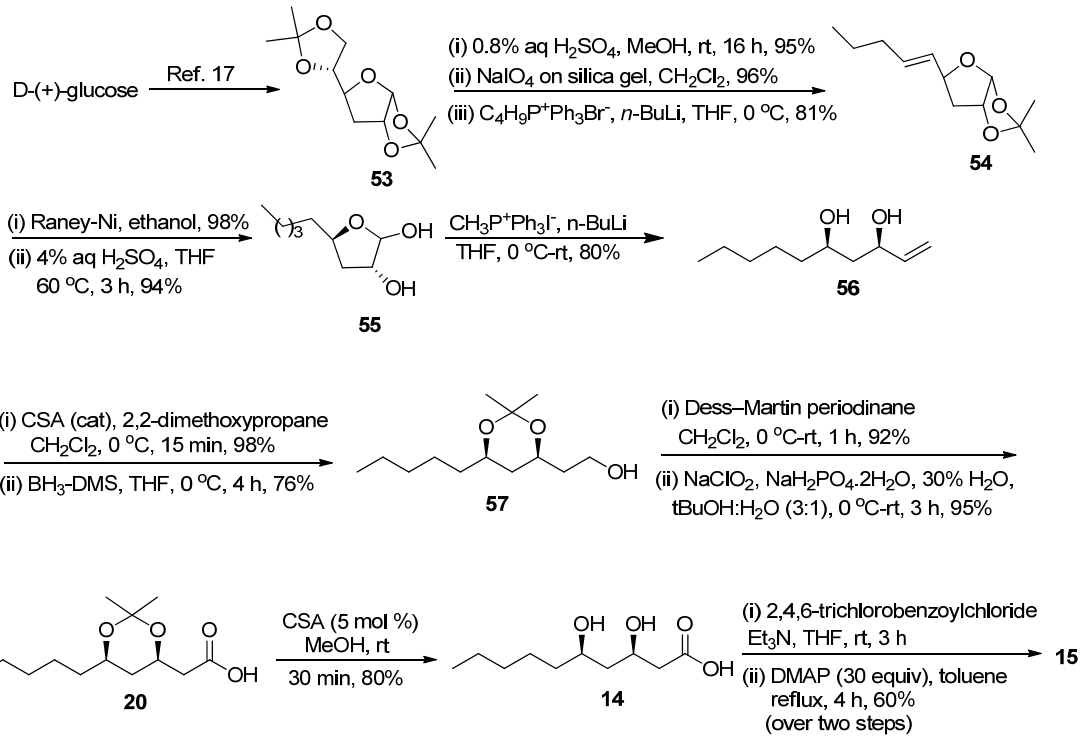
Scheme 4: Formal synthesis of verbalactone

4. Gurjar's Approach[16]

Verbalactone was synthesized by chiral pool approach as illustrated in **Scheme 5**. D - Glucose was first converted to 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose by treating with catalytic amount of conc. H_2SO_4 and anhydrous $CuSO_4$ in acetone. Diacetonide derivative on recrystallization from cyclohexane was transformed to 3-deoxy derivative **53** by means of Barton McCombie protocol.[17]

Selective deprotection of the 5,6-*O*-isopropylidene group of compound **53** with 0.8% H_2SO_4 in MeOH at ambient temperature afforded the C5-C6 diol in 94% yield. Diol was subjected to periodate mediated oxidative cleavage to give the furanaldehyde. Wittig olefination of aldehyde with butyltriphenylphosphorane (generated *in situ* from butyltriphenylphosphonium bromide by the action of *n*-BuLi in anhydrous THF)

furnished mixture of olefin derivatives **54** in the ratio 3:7 (*E*/*Z*). Hydrogenation of the alkene **54** using Raney-Ni in ethanol under hydrogen atmosphere and at balloon pressure gave the saturated derivative in quantitative yield. Cleavage of the 1,2-*O*-isopropylidene group with 4% aqueous sulfuric acid in THF at 60 ˚C afforded the diastereomeric lactol **55 .**



Scheme 5: Chiral-pool approach for the synthesis of verbalactone

One-carbon Wittig homologation of lactol **55** at 0˚C with *in situ*-generated methylenetriphenylphosphorane yielded *syn*-1,3-diol **56** and thus providing the desired ten-carbon chain of the verbalactone monomer. The *syn*-diol **56** was transformed quantitatively into its isopropylidene derivative by treating at 0 ˚C with 2,2-dimethoxypropane in presence of catalytic camphorsulfonic acid (CSA) and dichloromethane. Selective hydroboration of acetonide derivative with BH_3-DMS reagent at 0 ˚C afforded primary alcohol **57** in 76% yield. The alcohol **57** on treatment with Dess-Martin periodinane in dichloromethane at 0 ˚C gave the corresponding aldehyde. The aldehyde on further oxidation with sodium chlorite in presence of 30% H_2O_2, sodium dihydrogen phosphate dihydrate (buffer) and a 3:1 mixture of *t*-BuOH/H_2O gave acid **20.** Unmasking of the isopropylidene group was achieved by

treating **20** with cat. camphorsulfonic acid (CSA) in anhydrous methanol to provide the (3*R*,5*R*)-3,5-dihydroxydecanoic acid **14**. Yamaguchi macrolactonization of seco-acid **14** with (2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N) resulted in the ring-selective formation of macrocyclic verbalactone **15** in 60% yield a colorless oil.

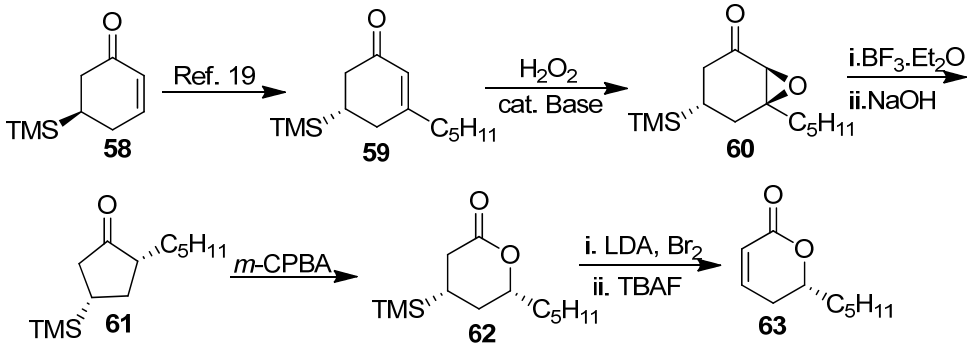
Synthesis of six membered lactones:

Chiral six membered lactones are functionalities commonly present in a number of natural products that function as pheromones or medicinal compounds. They often act as intermediates for the synthesis of other natural products. For example, (*S*)-(+)-5,6-dihydro-6-methyl-2*H*-pyran-2-one (parasorbic acid), a natural product isolated from mountain ash berries (*Sorbus aucuparia*), is an intermediate for the synthesis of several carbohydrate derived antibiotics. Similarly, (*R*)-(–)-5,6-dihydro-6-pentyl-2*H*-pyran-2-one (massoialactone), isolated from bark oil of *Cryptocarya massoia* and jasmine flowers is also found in the defense secretion of two species of formicin ants of the genus *Camponotus*. (*S*)-(–)-6-Undecyltetrahydropyran-2-one (hexadecanolide), isolated from the mandibular glands of the oriental hornet *Vespa orientalis*, also contains a δ-valerolactone moiety.

Previous Approaches Towards the Synthesis of Massoialactone:

Asaoka *et al.*[18]

Asaoka and co-workers synthesized massoialactone by employing ring contraction by $BF_3.Et_2O$ catalyzed epoxide rearrangement of 3-substituted 5-trimethylsilyl-2,3-epoxycyclohexanone as a key step. Thus, **58** was converted into enone **59** by the reported method which on epoxidation afforded epoxide **60**.

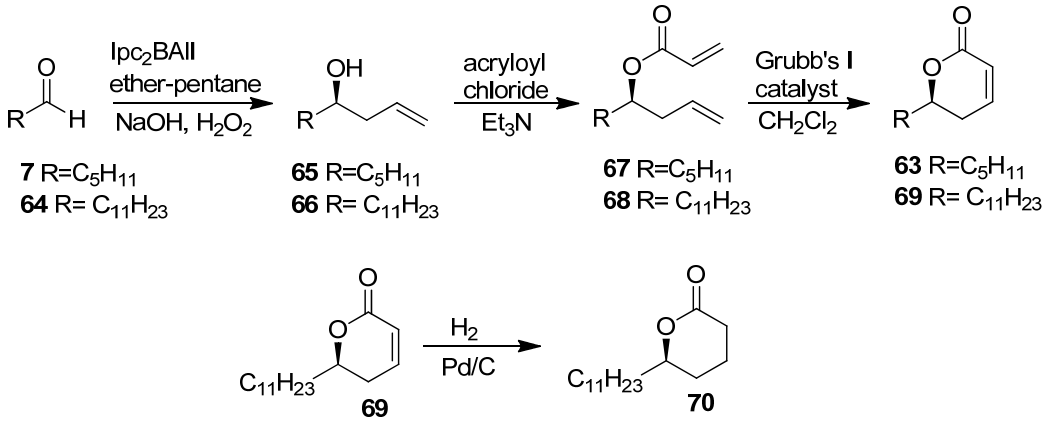


Scheme 6: Synthesis of massoialactone

The Lewis acid ($BF_3.Et_2O$) catalyzed epoxide rearrangement of **60** followed by base treatment afforded 2-substituted 4- (trimethylsilyl)cyclopentanone **61** with high diastereoselectivity. **61** was subjected to Baeyer-Villiger oxidation followed by bromination and debromosilylation to furnish target molecule (-)-massoialactone **63** (Scheme 6).

Ramachandran *et al.* [20]

Ramachandran and co-workers accomplished the asymmetric synthesis of massoialactone, hexadecanolide via asymmetric allylboration as the key step.

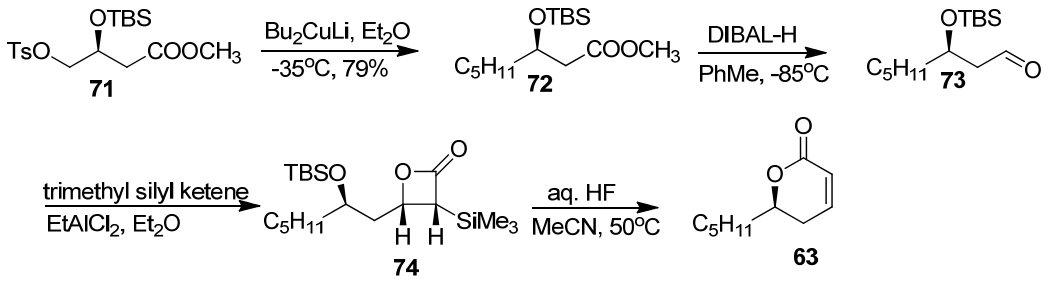


Scheme 7: Asymmetric allylation approach for the synthesis of massoialactone and hexadecanolide

Thus, allylboration of aldehydes **7**, **64** with *B*-allyldiisopinocampheylborane afforded homoallylic alcohols **65**, **66** respectively, which on esterification followed by ringclosing metathesis furnished lactones (**63** and **69**). Lactone **69** on hydrogenation afforded hexadecanolide **70** (Scheme 7).

Pons *et al.* [21]

Pons and co-workers accomplished the asymmetric synthesis of massoialactone, HF-induced translactonization of 2'-silyloxy-3-trimethylsilyl-2-oxetanones starting from 2-dimethyl malate. Thus, 2-dimethyl malate was transformed into ester **71** followed by treatment with the lithium dialkylcuprate generated from *n*-BuLi and CuI to give ester **72** which was reduced with Dibal-H to the corresponding aldehyde **73**.

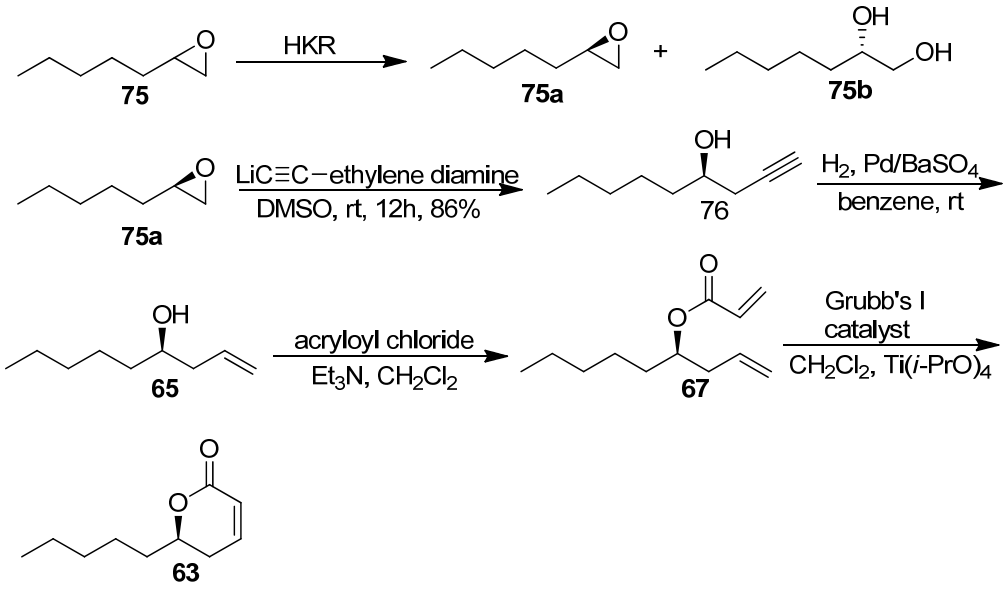


Scheme 8: Asymmetric synthesis of massoialactone

The [2+2]-cycloaddition of aldehyde **73** with trimethylsilylketene gave a diastereoisomeric mixture of four β-lactones **74** which were then treated with aq. HF in alcohols, to give (-)-massoialactone **63** (Scheme 8).

Kumar *et al.*[22]

(R)-Massoialactone **63** was synthesized starting from the epoxide **75** as illustrated in Scheme 9. rac-Epoxide **75** was subjected to hydrolytic kinetic resolution (HKR) to give enantiomerically pure epoxide **75a** and diol **75b.** Subsequent opening of **75a** with an excess of lithium acetylide followed by partial hydrogenation of the resultant acetylene **76** with Lindlar's catalyst furnished the homoallylic alcohol **65**. Compound **65** was esterified with acryloyl chloride in the presence of triethylamine to afford **67** in 89% yield.



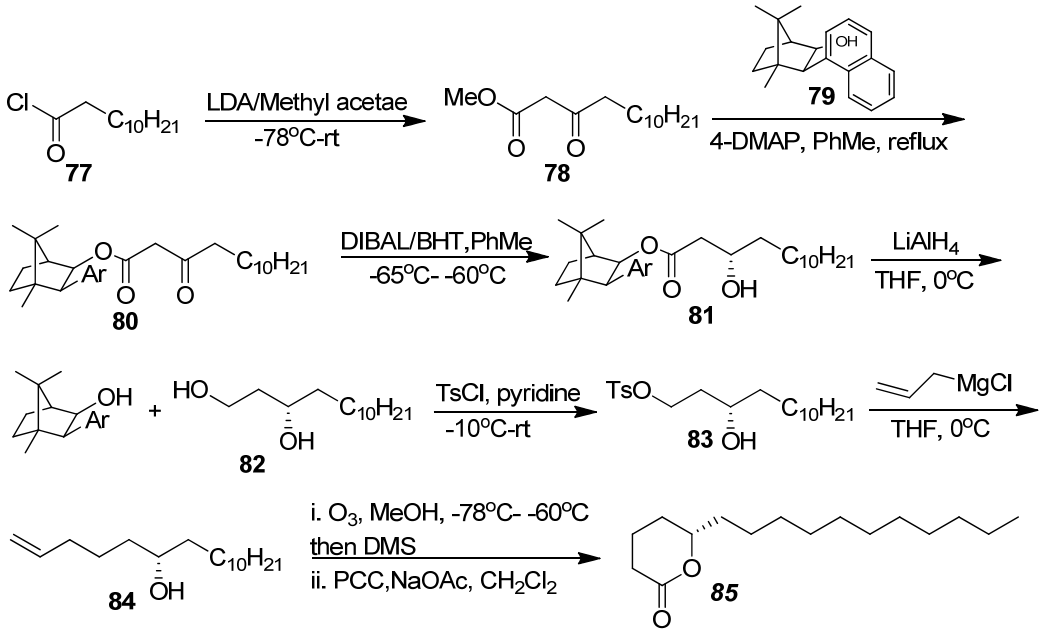
Scheme 9: Synthesis of massoialactone via HKR

The subsequent ring-closing metathesis in dichloromethane under reflux in high dilution conditions using the first generation Grubbs's catalyst, bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride and catalytic amount of $Ti(i\text{-}PrO)_4$ afforded (R)-massoialactone **63** in 84% yield.

Previous Approaches Towards the Synthesis of Hexadecanolide:

Taber *et al.*[23]

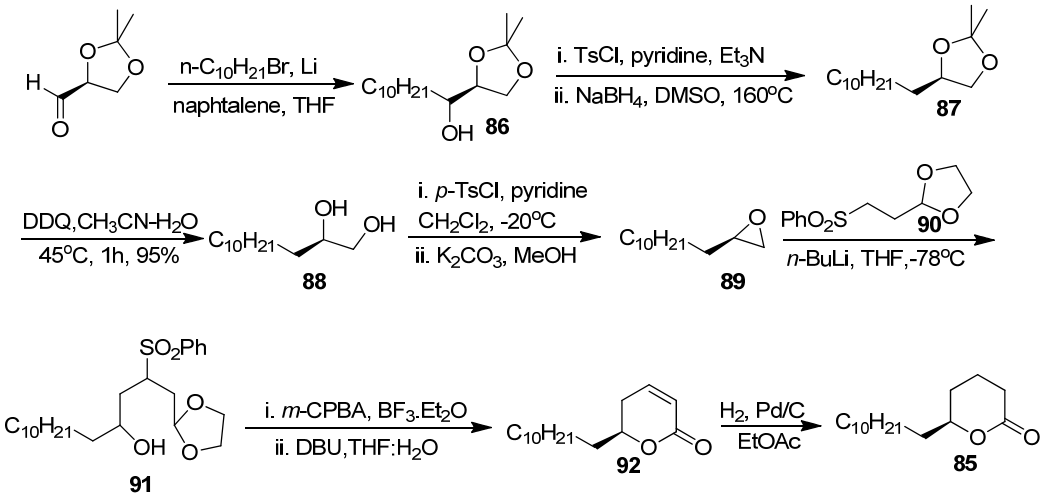
Alcohol **79** is designed to block one face of carbonyl **77** in the derived β-keto ester **78.** Hydride reduction via transition state in which the carbonyl are anti (DIBAL: BHT). Alkyl coupling using allyl magnesium chloride of the primary tosylate of the 1,3-diol obtained from $LiAlH_4$ reduction of **81** followed by ozonolysis of terminal olefin **84** , oxidation of aldehyde using PCC resulted into cyclised product hexadecanolide **85** (Scheme 10).



Scheme 10: Synthesis of hexadecanolide

Singh *et al.*[24]

Singh and co-workers accomplished the synthesis of 5-hexadecanolide **85** from a chiral epoxide. (*R*)-Isopropylidene glyceraldehyde, synthesized from the mannitol, was treated with 1-bromodecane to furnish the addition product **86**.

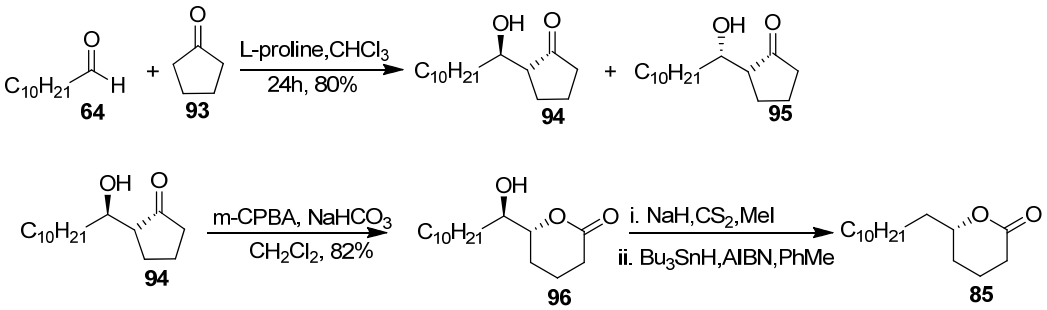


Scheme 11: Chiral -pool approach for hexadecanolide

Deoxygenation of the hydroxyl group followed by acetonide deprotection, tosylation and base treatment afforded epoxide (*S*)-**89**. The epoxide (*S*)-**89** was opened with sulphone reagent **90** to provide hydroxyl acetal **91** which, on treatment with $BF_3.OEt_2$ and *m*-CPBA gave a mixture of sulphone δ- lactone and unsaturated δ-lactone **92** in the ratio 9:1. The crude mixture without purification was treated with DBU in order to have complete conversion into unsaturated δ-lactone **92**. Finally hydrogenation of the double bond furnished target molecule **85** (Scheme 11).

Ying *et al.*[25]

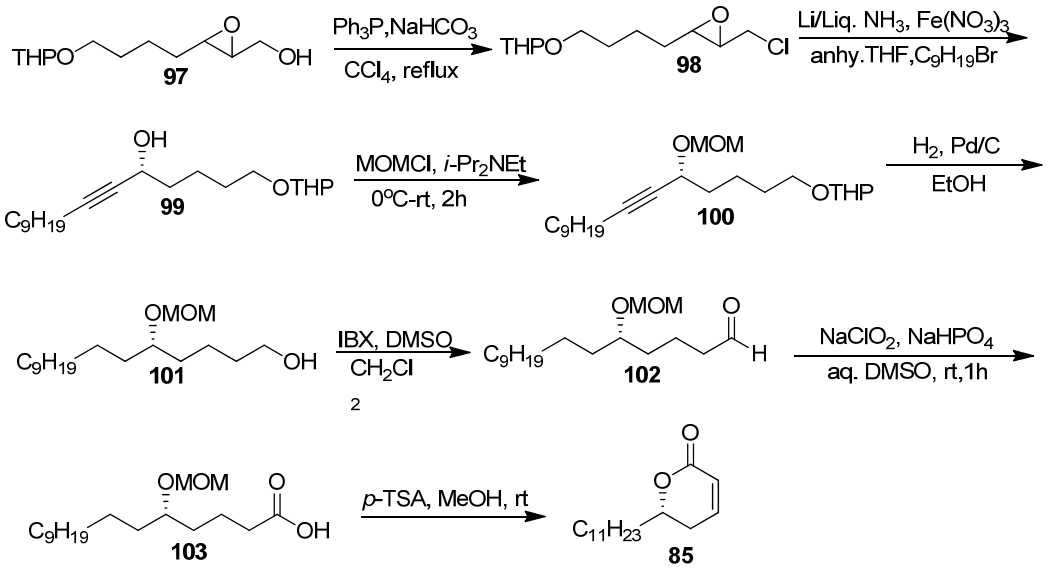
Ying and co-workers accomplished the synthesis of 5-hexadecanolide **85** using L-proline catalyzed asymmetric aldol reactions as the key step. Thus the synthesis commenced from the aldehyde **64** and cyclopentanone **93** catalyzed by L-proline to give the *syn*-aldol **94** along with its *anti*-isomer **95** in a ratio of 85:15. Baeyer-Villiger oxidation of the ketone **94** followed by deoxygenation using the Barton protocol gave target molecule **85** (Scheme 12).



Scheme 12: Oraganocatalytic approach for hexadecanolide

Sabitha *et al.*[26]

Sabitha and co-workers accomplished the synthesis of 5-hexadecanolide starting from 2,3- epoxy alcohol **97** (Scheme 13). The alcohol **97** was converted into the corresponding epoxy chloride **98** which was subjected to base-induced opening with lithium amide in liquid ammonia at –33 °C and further treated with nonyl bromide leading to the chiral acetylenic alcohol **99** directly in a one-pot procedure. The secondary hydroxyl group of compound **99** was protected as its methoxymethyl ether followed by reduction of the triple bond and subsequent deprotection of the tetrahydropyranyl group to give **101** in 80% yield. The alcohol **101** was oxidized to the aldehyde **102** which was further oxidized to afford the corresponding acid **103**. Finally in situ deprotection of the methoxymethyl group and subsequent cyclization afforded target molecule **85** in 80% yield.



Scheme 13: Synthesis of hexadecanolide

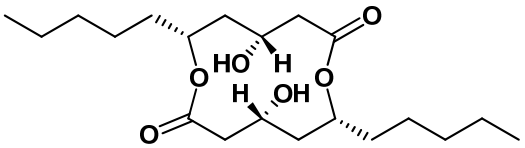
Chapter III, Section A

Organocatalytic Enantioselective Approach to the Synthesis of Verbalactone

Present work

Objective

Verbalactone (Figure 4) was isolated[4] by Mitaku and co-workers in 2001 from the roots of *Verbascum undulactum*. Verbalactone displays an interesting antibacterial activity against various *Gram*-positive and *Gram*-negative bacteria. Verbalactone is a novel macrocyclic symmetrical dimeric lactone. This is only the first natural product in which unique 1, 7-dioxacyclododecane cyclic ring system was found. The complex molecular architecture and interesting biological activity has stimulated many synthetic chemists worldwide towards the total synthesis of **15**. Barua *et al.* reported the first total synthesis of verbalactone in 2004 in which Barbier-Grignard and Sharpless asymmetric dihydroxylation reactions were employed as the key transformations. Subsequently Sharma and co-workers reported another convergent strategy for the synthesis of verbalactone starting from L-malic acid. Meanwhile several other syntheses reported for verbalactone were mainly based on using either the chiral pool starting material or stereoselective methods to generate the stereogenic centres and subsequent Yamaguchi esterification to bring out macrocyclisation.



15

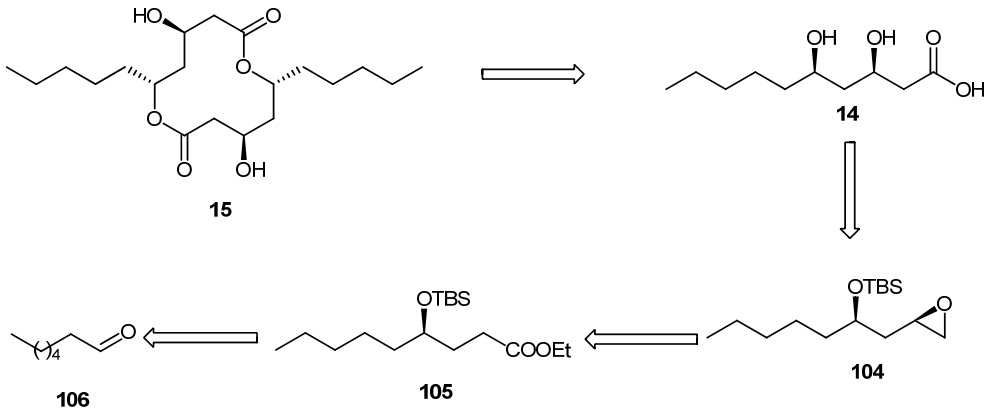
Figure 4. Structure of Verbalactone **15**

As a part of our ongoing research program[10] aimed at developing enantioselective synthesis of biologically active natural products, we have recently developed a novel and efficient protocol for 1,3-polyols based on iterative use of proline-catalyzed tandem α-aminoxylation[11] and HWE olefination of aldehydes. Now we have further extended the synthetic utility of this protocol to synthesize verbalactone in a most concise and efficient manner.

Our retrosynthetic route to verbalactone **15** is outlined in Scheme 14. Verbalactone **15** can simply be synthesized using Yamaguchi's macrolactonization of (3*R*,5*R*)-3,5-dihydroxy decanoic acid **14** which in turn could be obtained from epoxide **104**.

Results and Discussion

Epoxide **104** could easily be derived from TBS protected γ-hydroxy ester **105** which in turn could be synthesised from *n*-heptanal **106** *via* L-proline catalyzed α-aminoxylation and HWE olefination. As shown in Scheme **15,** commercially available heptanal **106** was subjected to sequential α-aminoxylation using nitroso benzene as the oxygen source and L-proline as a catalyst and subsequent HWE olefination using triethyl phosphonoacetate followed by reductive hydrogenation using a catalytic amount of Pd/C to furnish the *γ*-hydroxy ester **107** in 68% yield and 97% ee.[27]



Scheme-14. Retrosynthetic route to verbalactone **15**

The free hydroxyl group of *γ*-hydroxy ester **107** was protected as TBS ether using TBSCl to furnish compound **105** in 94% yield. With protected *γ*-hydroxy ester **105** in hand, the stage was set for introduction of another hydroxyl group at 3-position. Thus DIBAL- H reduction of ester **105** furnished the corresponding aldehyde which was then subjected to α-aminoxylation using L-proline as a catalyst followed by $NaBH_4$ reduction and subsequent Pd/C reduction to give the *syn*-diol **108** in 78% yield. The ^{1}H NMR analysis revealed the diastereomeric purity (de) of **108** to be >95%. The primary hydroxyl group of **108** was converted into tosyl derivative using TsCl, Et_3N and catalytic amount of *n*-Bu_2SnO which on subsequent base treatment furnished the epoxide **104**. ^{1}H NMR spectrum of **104** showed epoxide protons at δ 2.46 (doublet of doublet, 1H, with coupling constant *J* = 2.7, 5.1 Hz) and δ 2.74-2.79 (m, 1H). Epoxide **104** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol **109**. Deprotection of TBS group and subsequent treatment of

resulting 1,3-*syn* diol with 2,2-dimethoxy propane in the presence of catalytic amount of PPTS gave the isopropylidene derivative **110**.

In ^{1}H NMR spectrum of compound **110**, additional peaks attributable to acetonide methyl protons were located at δ 1.40 and δ 1.44 (both s, 3H). In ^{13}C NMR, three extra peaks attributed to the acetonide group carbon atoms were observed at δ 98.3, δ 30.2, δ 19.8 clearly indicating the 1,3-*syn* relationship of the carbinol stereocenters in **110** in accordance to Rychnovsky's[28] studies.

Rychnovsky[28] has shown that the acetonides of syn and anti-1,3-diols can be unambiguously distinguished by the ^{13}C chemical shifts of the acetonide methyl groups and the acetal carbon atom. The ^{13}C NMR spectra of syn-1,3-diol acetonides show an axial methyl group carbon at δc 19.6 and the corresponding equatorial one at δc 30.0. This is in contrast to the spectra of the anti-1,3-diol acetonides, which shows the methyl resonances at δc 24.7. The acetal carbon chemical shifts are also indicative of the stereochemistry δc 98.5 for the syn-1,3-diol acetonides and δc 100.4 for the anti-stereoisomer.

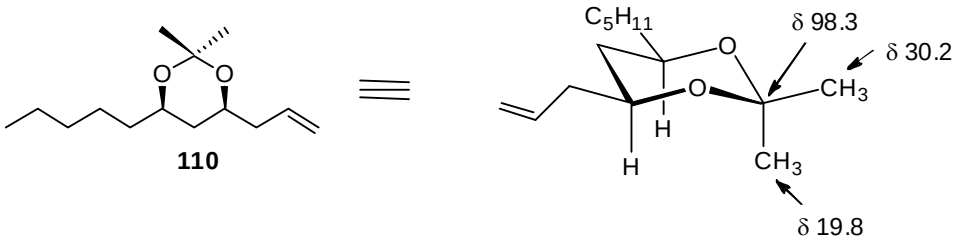
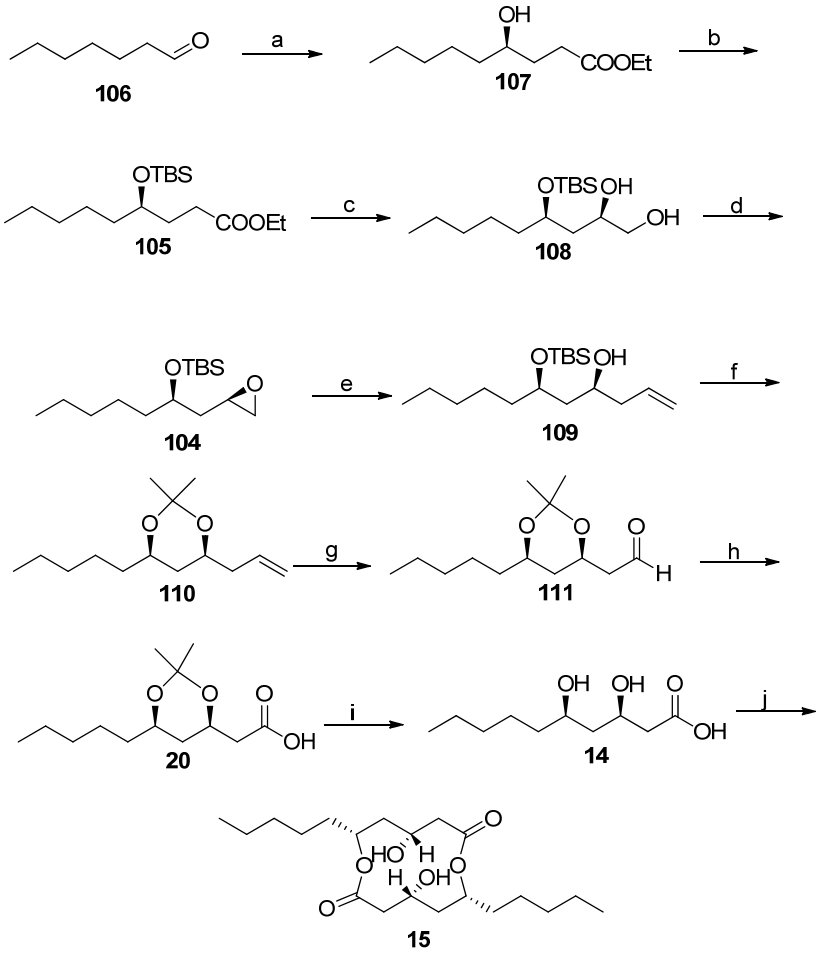


Figure 5: ^{13}C NMR studies confirming the stereochemistry at 1,3-diol carbinol centers

Dihydroxylation of **110** followed by oxidative cleavage using silica supported $NaIO_4$ gave aldehyde **111.** ^{1}H NMR of aldehyde **111** displayed the characteristic aldehyde proton resonating at δ 9.79 whereas the two methylenic protons at C1 were disappeared. In ^{13}C NMR the aldehyde carbon was seen at δ 201.1. IR specrum showed the carbonyl stretching frequency at 1728 cm^{-1} characteristic to aldehyde functional group. Mass spectral and elemental analyses were consistant to the proposed structure of **111**, which on subsequent oxidation resulted in the formation of acid **20** in good yield. In ^{1}H NMR of acid **20,** the aldehyde proton of parent aldehyde **111**, resonating at δ 9.78, disappeared. ^{13}C NMR exhibited the acid carbon at δ 176.0

(s). IR spectrum illustrated the carbonyl stretching frequency at 1713 $cm.^{-1}$ Deprotection of the isopropylidene group was achieved with cat. CSA (5 mol %) in methanol to provide the (3*R*,5*R*)-3,5-dihydroxydecanoic acid **14**.



Scheme-15. Reagents and conditions (a) (i) nitrosobenzene, L-proline, DMSO, HWE salt, DBU, LiCl,CH_3CN; (ii) H_2/Pd-C,EtOAc, 68% (over two steps); (b) TBSCl, imidazole, DCM, 14 h, 94%; (c) (i) DIBAL-H, DCM,-78^oC; (ii) L-proline, nitrosobenzene, DMSO; (ii) $NaBH_4$, MeOH; (iii) H_2/Pd-C, EtOAc 78%; (d) (i) TsCl, Bu_2SnO, Et_3N; (ii) K_2CO_3, MeOH,room temp, 82%; (e) Vinylmagnesium bromide, THF, CuI, -20 ^oC, 12 h, 89%; (f) (i) TBAF, THF; (ii) 2,2–dimethoxyproapane, PPTS, DCM, 0^oC, 92%; (g) (i) 0.1M OsO_4 (0.4 mol%), K_2CO_3, $K_3Fe(CN)_6$, t-BuOH/H_2O 1:1, 0^oC, 24 h; (ii) Silica supported $NaIO_4$, DCM, 1 h, rt, 82% (over two steps); (h) $NaClO_2$, $NaH_2PO_4.2H_2O$, *t*-BuOH:H_2O (3:1), 0^oC-rt, 3 h, 96%; (i) camphorsulfonic acid , MeOH, rt, 1 h, 80%; (j) 2,4,6–trichlorobenzoyl chloride, Et_3N, THF, rt then DMAP, tolune, reflux, 53%.

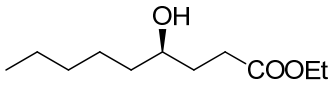
The pH during the deprotection of **20** was crucial and had to be carefully controlled as the formation of the monomeric lactone was observed in previous reports at higher acidic pH. Thus, a citric acid-sodium hydroxide buffer solution (pH = 6) was used during the work-up.[12,13] The compound **14** was found to be unstable as on standing for longer time, lactonization to form monomeric lactone was the major pathway. Consequently acid **14** without any further purification was subjected to Yamaguchi macrolactonization to afford verbalactone **15** in 53% yield. The ^{1}H and ^{13}C NMR spectra as well as other analytical data of synthetic **15** were identical with those of the natural product.[16]

Conclusion

In summary, a concise and efficient total synthesis of verbalactone with high enantioselectivities has been accomplished in which the stereocentres were generated by means of L-proline catalyzed α-aminoxylation and HWE olefination. The synthetic approach is amenable for other macrolactones of this class. Currently work is in progress in this direction.

Experimental Section

(*R*)-Ethyl 4-hydroxynonanoate (107)



To a solution of *n*-heptanal (3.0 g, 26.3 mmol) and nitroso benzene (2.81 g, 26.3 mmol) in anhydrous DMSO (40 mL) was added L-proline (1.2 g, 10.5 mmol) at 20 °C. The mixture was vigorously stirred for 30 min under argon (the color of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) solution of triethylphosphonoacetate (15.65 mL, 78.9 mmol), DBU (11.77 mL, 78.9 mmol) and LiCl (3.35 g, 78.9 mmol) in CH_3CN (40 mL) was added quickly at 0 °C. The resulting mixture was allowed to warm to room temperature over 1 h, and quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. This reaction mixture was then poured into water (100 mL) and extracted with Et_2O (5×100 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo to give crude product which was directly subjected to next step without purification. To the

crude allylic alcohol in ethyl acetate was added Pd-C (10%) under hydrogenation conditions and the reaction mixture was allowed to stir overnight. On completion of reaction (until ^{1}H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of celite and concentrated in vacuo to give the crude product which was purified by using flash column chromatography using pet ether: EtOAc (95:5) as eluent to give (*R*)-ethyl 4-hydroxynonanoate **107** as a yellow colored liquid.

Yield: 3.61 g, 68%

IR ($CHCl_3$, cm^{-1}): ν_{max} 3432, 2934, 1713, 1465, 1177.

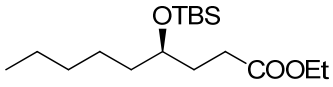
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.84-0.90 (m, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.38-1.32 (m, 3H), 1.36-1.44 (m, 4H), 1.52-1.94 (m, 4H), 2.44 (t, J = 7.2 Hz, 2H), 3.54-3.63 (m, 1H), 4.12 (q, J = 7.2 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7, 22.3, 24.7, 27.8, 28.7, 31.6, 35.3, 60.3, 71.0, 177.0 ppm.

Elemental Analysis: ($C_{11}H_{22}O_3$), Calcd: C, 65.31; H, 10.96% Found: C, 65.11; H, 10.81%

ESI-MS *m/z***:** 225 [M+Na]+

(*R*)-Ethyl 4-((*tert*-butyldimethylsilyl)oxy)nonanoate (105)



To a stirred solution of alcohol **107** (3 g, 14.83 mmol) in CH_2Cl_2 (40 mL) was added imidazole (1.99 g, 29.68 mmol). To this solution *t*-butyl dimethylchlorosilane (2.90 g, 19.29 mmol) was added at 0 ^{o}C and reaction was stirred at room temperature for 14 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 x 30 mL). The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column

chromatography of the crude product using pet ether as eluent provided **105** as a colorless liquid (4.42 g, 94%).

$[\alpha]_D^{25}$ -8.96 (*c* 1.4, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 2856, 1725, 1463, 1258.

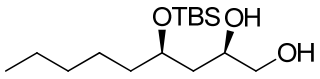
^{1}H NMR (400 MHz, $CDCl_3$): δ -0.04 (s, 6H), 0.89 (s, 12H), 1.22-1.32 (m, 9H), 1.37-1.43 (m, 2H), 1.59-1.90 (m, 2H), 2.32-2.40 (m, 2H), 3.66-3.72 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ -4.6, -4.5, 14.0, 14.2, 18.0, 22.6, 24.8, 25.8, 30.0, 31.7, 31.9, 36.9, 60.2, 71.1, 174.0 ppm.

Elemental Analysis: ($C_{17}H_{36}O_3Si$)**,** Calcd: C, 64.50; H, 11.46% Found: C, 64.74; H, 11.58%

ESI-MS ***m/z*****:** 339 [M+Na]+

(2*R*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)nonane-1,2-diol (108)



To a solution of ester **105** (4.0 g, 12.64 mmol) in CH_2Cl_2 (60 mL), was added DIBAL-H (7.44 mL 1.87 M solution in toluene, 13.90 mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 40 min. Then a solution of tartaric acid (15 mL) was added. The resulting mixture was stirred for 15 min and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL), the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give aldehyde as a colorless liquid, which was directly used in the next step without further purification. To the crude solution of aldehyde (3.98 g, 14.62 mmol) was added nitroso benzene (1.54 g, 14.62 mmol) in anhydrous DMSO (40 mL) followed by addition of L-proline (0.67 g, 5.85 mmol) in one portion at 25 °C . After 1 h, the temperature was lowered to 0 °C, followed by dilution with anhyd. MeOH (30 mL) and careful addition of excess $NaBH_4$ (2.22 g, 58.38 mmol). The

reaction was quenched after 10 min by pouring the reaction mixture into a vigorously stirred biphasic solution of Et_2O and aqueous HCl (2 M). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3x30 mL). The combined organic phase was dried with anhyd Na_2SO_4, concentrated, and passed through the silica gel plug using EtOAc/petroleum ether (20:80) as eluent to give aminoxy alcohol. The crude aminoxy alcohol (4.26 g) was dissolved in EtOAc (30 mL) and to the solution was added 10% Pd/C in catalytic amount and the reaction mixture was stirred in a hydrogen atmosphere (60 psi) for 2 h. After completion of the reaction (monitored by TLC) the reaction mixture was filtered through a Celite pad, concentrated, and the crude product was then purified by silica gel chromatography using petroleum ether/ethyl acetate (70:30) as eluent to give pure diol **108** (2.86 g, 78%) as a colorless liquid.

$[\alpha]_D^{25}$ -14.98 (*c* 0.9, $CHCl_3$).

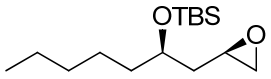
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.11 (s, 3H), 0.12 (s, 3H), 0.91(s, 12H), 1.22-1.32 (m, 6H), 1.46-1.56 (m, 2H), 1.59-1.66 (m, 2H), 2.28 (brs, 1H), 3.47 (dd, J = 6.2, 11.0 Hz, 1H), 3.62 (dd, J = 3.7, 11.0 Hz, 1H), 3.83-4.01 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.7, -4.0, 13.9, 17.9, 22.5, 24.3, 25.7, 31.9, 37.9, 38.9, 66.9, 71.3, 73.1 ppm.

Elemental Analysis: ($C_{15}H_{34}O_3Si$), Calcd: C, 62.01; H, 11.80% Found: C, 61.95; H, 11.47%

ESI-MS *m/z* **:** 313 [M+Na]+

***tert*-Butyldimethyl(((*R*)-1-((*R*)-oxiran-2-yl)heptan-2-yl)oxy)silane (104)**



To a mixture of diol **108** (1.00 g, 3.44 mmol), in dry DCM (15 mL) was added dibutyltin oxide (0.49 g, 1.72 mol) followed by the addition of *p*-toluenesulfonyl chloride (0.66 g, 3.44 mmol) and triethylamine (0.53 mL, 3.79 mmol) and reaction

was stirred at room temperature under nitrogen. The reaction was monitored by TLC, after completion of reaction the mixture was quenched by adding water. The solution was extracted with DCM (3x20 mL) and then combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. To this crude mixture in MeOH at 0 °C was added K_2CO_3 (1.03g, 3.78 mmol) and the resultant mixture was allowed to stir for 1 h at room temperature. After completion of reaction as indicated by TLC, the reaction was quenched by addition of ice pieces and methanol was evaporated. The concentrated reaction mixture was then extracted with ethyl acetate (3x30 mL), the combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The column chromatography of crude product using petroleum ether: ethyl acetate (96:4) gave the epoxide **104** (0.77 g, 82%) as a colorless liquid.

$[\alpha]_D^{25}$ +4.2 (*c* 2.0, $CHCl_3$).

IR ($CHCl_3$): υ_{max} 3041, 2926, 2854, 1465, 1255, 1070, 835, 773 $cm.^{-1}$

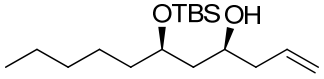
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (s, 12H), 1.27-1.37 (m, 6H), 1.48-1.57 (m, 2H), 1.60-1.80 (m, 2H), 2.46 (dd, *J*= 2.7,5.09 Hz, 1H), 2.74-2.79 (m, 1H), 3.0-3.09 (m,1H), 3.85 (qui, *J* = 5.9, 11.5 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ -4.6, -4.5, 14.0, 18.0, 22.6, 25.1, 25.8, 31.9, 37.1, 40.1, 46.8, 49.5, 70.3 ppm.

Elemental Analysis: ($C_{15}H_{32}O_2Si$), Calcd: C, 66.11; H, 11.84% Found: C, 65.87; H, 11.63%

ESI-MS *m/z* **:** 273 [M+H]+

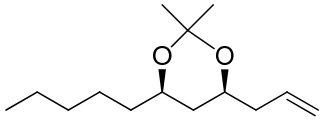
(4*S*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)undec-1-en-4-ol (109)



To a stirred solution of epoxide **104** (0.50 g, 1.83 mmol) and CuI (35 mg, 0.18 mmol) in dry THF (5 mL), was added vinylmagnesium bromide in THF (392 mg, 3.67 mmol,

3.67 ml, 1M solution in THF) dropwise over a period of 30 min. at -20 °C and stirred for 12 h. The mixture was allowed to warm up to 0 °C, before it was quenched with a saturated NH_4Cl solution (2 mL). The layers were separated, the aqueous layer was extracted with Et_2O (3 x 10 mL), the combined ethereal extracts were washed with brine (2 mL) and dried (Na_2SO_4). Evaporation of the solvent and silica gel column chromatographic purification (EtOAc/ petroleum ether, 5:95) of the crude product gave pure compound **109** (0.49 g, 89%) as a colorless oil.

(4*S*,6*R*)-4-Allyl-2,2-dimethyl-6-pentyl-1,3-dioxane (110)



To a stirred solution of compound **109** (400 mg, 1.33 mmol) in dry THF, was added, 1 M solution of TBAF (1.46 mL, 1.46 mmol) at room temperature and after completion of reaction (2h), some ice flakes added into it and then extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford crude diol which was directly used for the next step. To a solution of crude diol (248 mg) in dry DCM (10 mL) and 2,2-dimethoxypropane (0.33 mL, 2.66 mmol) was added catalytic amount of PPTS and activated 3 Å molecular sieves (0.2 g) at 0 ^oC, after which the reaction was stirred for 30 min at room temperature. After completion of the reaction, the molecular sieves were filtered and aqueous saturated $NaHCO_3$ solution (5 mL) was added and extracted into CH_2Cl_2 (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford crude compound **110** as colorless syrup. Purification of the crude product on silica gel column chromatography (pet ether/ethyl acetate = 9:1) gave **110** (277 mg, 92% yield) as a colorless liquid.

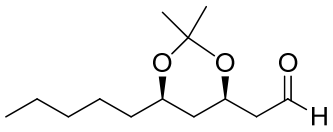
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, J = 6.7, 3H), 1.40 (s, 3H), 1.44 (s, 3H), 1.02-1.57 (m, 10H), 2.07-2.39 (m, 2H), 3.73-3.94 (m, 2H), 5.04-5.14 (m, 2H), 5.71-5.92 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 19.8, 22.5, 24.6, 30.2, 31.8, 36.4, 40.9, 68.6, 68.9, 98.3, 116.9, 134.2 ppm.

Elemental Analysis : ($C_{14}H_{26}O_2$), Calcd: C, 73.43; H, 10.27% Found: C, 73.57; H, 10.43%

ESI-MS *m/z***:** 249 [M+Na]+

2-((4*R*,6*R*)-2,2-Dimethyl-6-pentyl-1,3-dioxan-4-yl)acetaldehyde (111)



To a mixture of $K_3Fe(CN)_6$ (0.87 g, 2.65 mmol), K_2CO_3 (0.37 g, 2.65 mmol) in *t*-BuOH-H_2O (1:1, 8mL) cooled at 0 ^oC was added OsO_4 (0.035 mL, 0.1 M sol in toluene, 0.4 mol%) . After stirring for 5 min at 0 ^oC, the olefin **110** (0.20 g, 0.884 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC for 24 h and then quenched with solid sodium sulphite. The stirring was continued for 45 min and the solution was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed (10% KOH, then brine), dried (Na_2SO_4) and concentrated to give crude diol (0.23 g) as a colorless syrupy liquid which was pure enough for the next step.

To a vigorously stirred suspension of silica gel- supported $NaIO_4$ reagent (1.77 g,) in CH_2Cl_2 (400 ml) was added a solution of crude diol (0.23g, .883 mmol) in CH_2Cl_2 (20 ml).The reaction was monitored by TLC, after 1h on completion of reaction the reaction mixture was filtered through a sintered glass funnel, and the silica gel was thoroughly washed with $CHCl_3$. Removal of solvent and silica gel column chromatography of the crude product using petroleum ether/EtOAc (15:1) as eluent afforded aldehyde **111** (165mg, 82%) as colorless liquid.

[α**]** $^{\mathbf{D}}_{25}$ **:** -134.2 (*c* 1, $CHCl_3$)

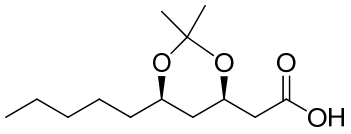
^{1}H NMR (400 MHz, $CDCl_3$) **:** δ 0.89 (t, *J* = 6.4, 3H), 1.38 (s, 3H), 1.47 (s, 3H), 1.1-1.7 (m, 10H), 2.50 (ddd, *J* = 1.7, 5.1, 16.4 Hz, 1H), 2.59 (ddd, *J* = 2.3, 7.3, 16.4 Hz, 1H), 3.89-3.80 (m, 1H), 4.45-4.35 (m, 1H), 9.79 (t, *J* = 1.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) **:** δ 14.0, 19.7, 22.6, 24.5, 30.1, 31.7, 36.3, 49.9, 64.7, 68.8, 98.7, 201.1.

Elemental Analysis: ($C_{13}H_{24}O_3$), Calcd: C, 68.38; H, 10.59% Found: C, 68.50; H, 10.87%

ESI-MS *m/z* **:** 229 [M+H]+

2-((4*R*,6*R*)-2,2-Dimethyl-6-pentyl-1,3-dioxan-4-yl)acetic acid (20)



To an ice-cold solution of aldehyde **111** (20 mg 87.6 mmol) in *t*-BuOH/H_2O (3:1, 6 mL) was added successively NaH_2PO_4 **.**$2H_2O$ (28 mg, 306.58 μmol), 30% aqueous H_2O_2 (0.10 mL) and sodium chlorite (15.84 mg, 175.18 μmol). The reaction mixture was gradually warmed to rt and stirred for 3 h. After completion of the reaction, it was diluted with ethyl acetate and the aqueous layer was extracted in ethyl acetate (4 x 20 mL). The combined extract was dried over sodium sulfate and concentrated to afford a crude product, which on purification over silica gel by eluting with ethyl acetate/light petroleum ether (1:1) afforded **20** as a colorless oil (18 mg, 96%).

[α**]$^{D}_{25}$:** +13.3 (*c* 0.5, $CHCl_3$)

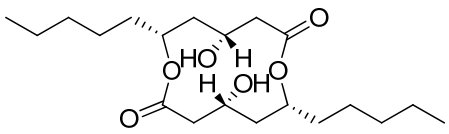
^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 0.89 (t, *J*=6.7 Hz, 3H), 1.40 (s, 3H),1.44 (s,3H), 1.24-1.54 (m,10H), 2.46 (dd, *J*= 15.4, 5.6, 1H), 2.58 (dd, *J* = 15.4, 6.8, 1H), 3.79-3.88 (m, 1H), 4.26- 4.35 (m, 1H),

^{13}C NMR (100 MHz, $CDCl_3$)**:** δ 14.0, 19.8, 22.5, 24.5, 30.2, 31.8, 36.3, 41.4, 65.8, 68.9, 99.3, 176.2 ppm

Elemental Analysis: ($C_{13}H_{24}O_4$), Calcd: C, 63.91; H, 9.90% Found: C, 63.83; H, 9.67%

ESI-MS *m/z* **:** 267 [M+Na]+

Verbalactone (15)



A solution of **20** (120 mg, 49.12 μmol) and camphor sulfonic acid (5.70 mg, 24.6 μmol) in anhydrous MeOH (10 mL) was stirred at ambient temperature for 1h. A citric acid-sodium hydroxide buffer solution (pH = 6) was added and extracted with ethyl acetate (5 x 20 mL). The combined extract was dried over sodium sulfate and concentrated to afford **14** (80 mg) as a colorless syrup which was found to be unstable (on standing undergoes lactonization to form monomeric lactone**)** and directly taken for next reaction without further purification. To a solution of seco acid **14** (24 mg, 117.5 μmol) in THF (4 mL) was added Et_3N (18.02 mmL, 129.24 μmol) at rt. The mixture was treated with 2,4,6-trichlorobenzoyl chloride (18.36 mmL, 117.5 μmol) and stirred for 2 h at rt. The mixture was diluted with anhydrous toluene (4 mL) and added dropwise over a period of 3 h to a refluxing solution of DMAP (187.7 mg, 1536.44 μmol) in dry toluene (40 mL). After completion of the addition, the mixture was refluxed for an additional hour and then concentrated in vacuo to provide crude product which on purification over silica gel by eluting with ethyl acetate/light petroleum (1:5) furnished verbalactone **15** (9 mg, 53%).

[α**]$^{D}_{25}$:** +8.7 (*c* 0.9, $CHCl_3$). **[**lit.[4]**[**α**]$^{D}_{20}$:** +7.3 (*c* 0.9, $CHCl_3$)]

^{1}H NMR (200 MHz, $CDCl_3$)**:** δ 4.97–4.90 (m, 2H), 4.08–4.03 (m, 2H), 3.73 (br s, 2H), 2.67 (d, *J* = 3.6 Hz, 4H), 2.10–2.02 (ddd, *J* = 14.5, 9.7, 3.1 Hz, 2H), 1.97 (td, *J* = 15.1, 4.5 Hz, 2H), 1.60–1.45 (m, 4 H), 1.31–1.16 (m, 12H), 0.86 (t, *J* = 6.9 Hz, 6H).

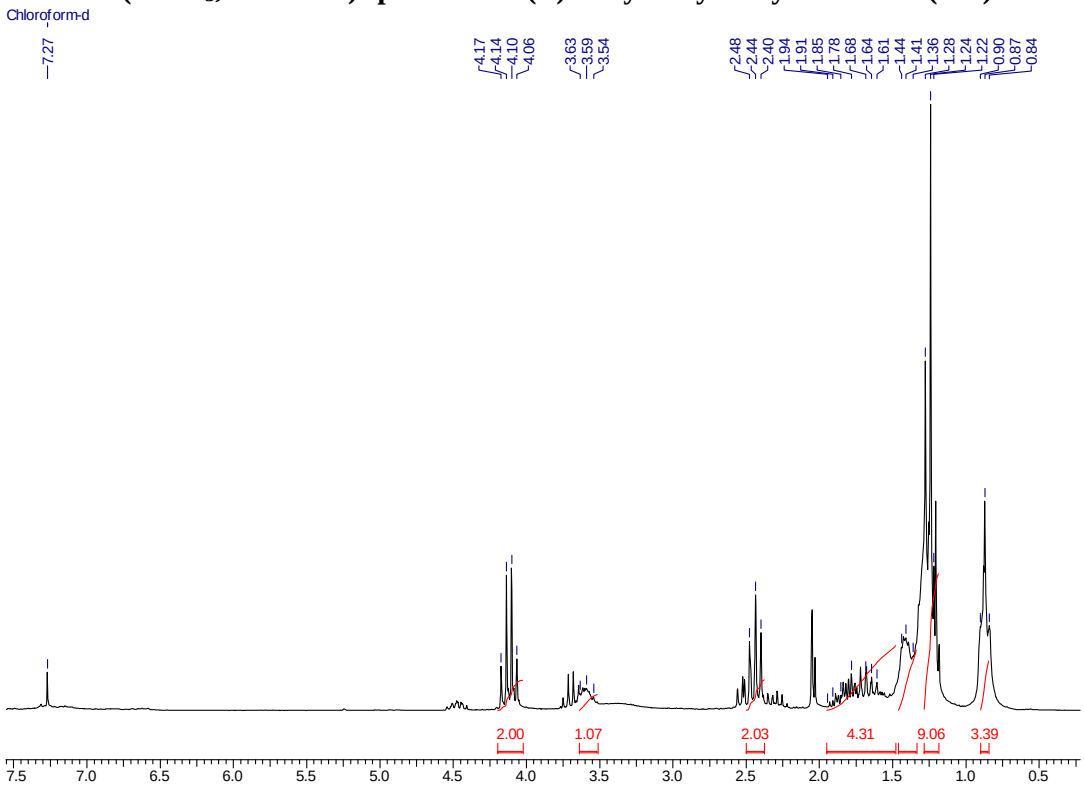
^{13}C NMR (50 MHz, $CDCl_3$)**:** δ 172.9, 72.5, 64.7, 39.4, 36.2, 31.6, 31.3, 25.4, 22.4, 14.0.

ESI-MS *m/z* **:** 373 [M+H]+

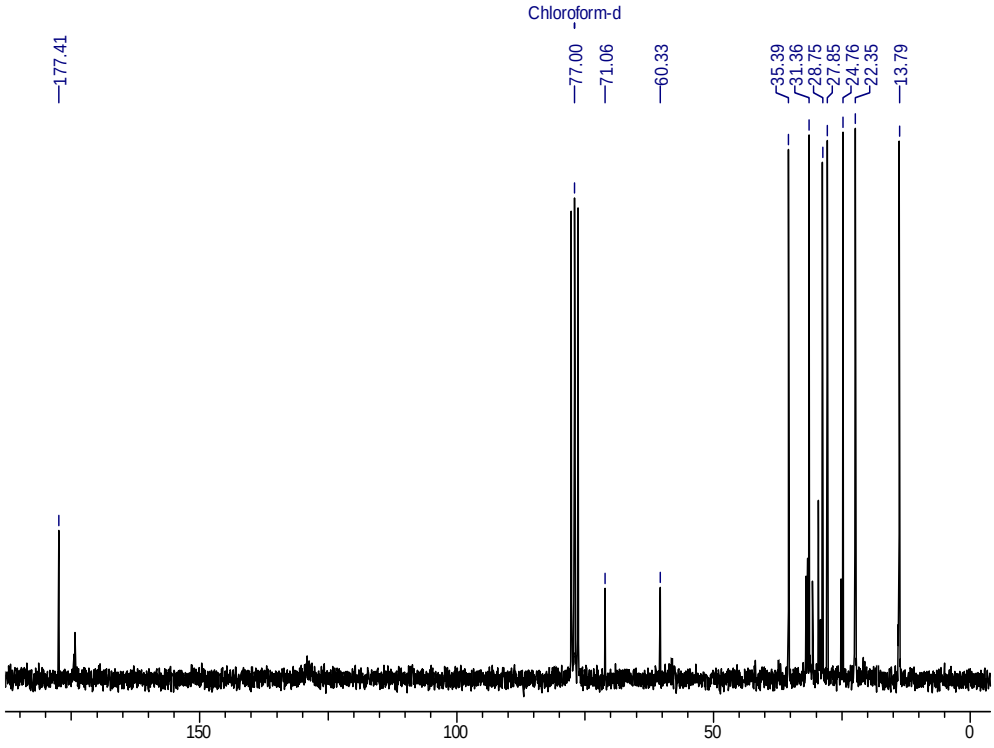
Spectra

1. ^{1}H and ^{13}C NMR spectra of **107**
2. ^{1}H and ^{13}C NMR spectra of **105**
3. ^{1}H and ^{13}C NMR spectra of **108**
4. ^{1}H and ^{13}C NMR spectra of **104**
5. ^{1}H and ^{13}C NMR spectra of **110**
6. ^{1}H and ^{13}C NMR spectra of **111**
7. ^{1}H and ^{13}C NMR spectra of **20**
8. ^{1}H and ^{13}C NMR spectra of **15**

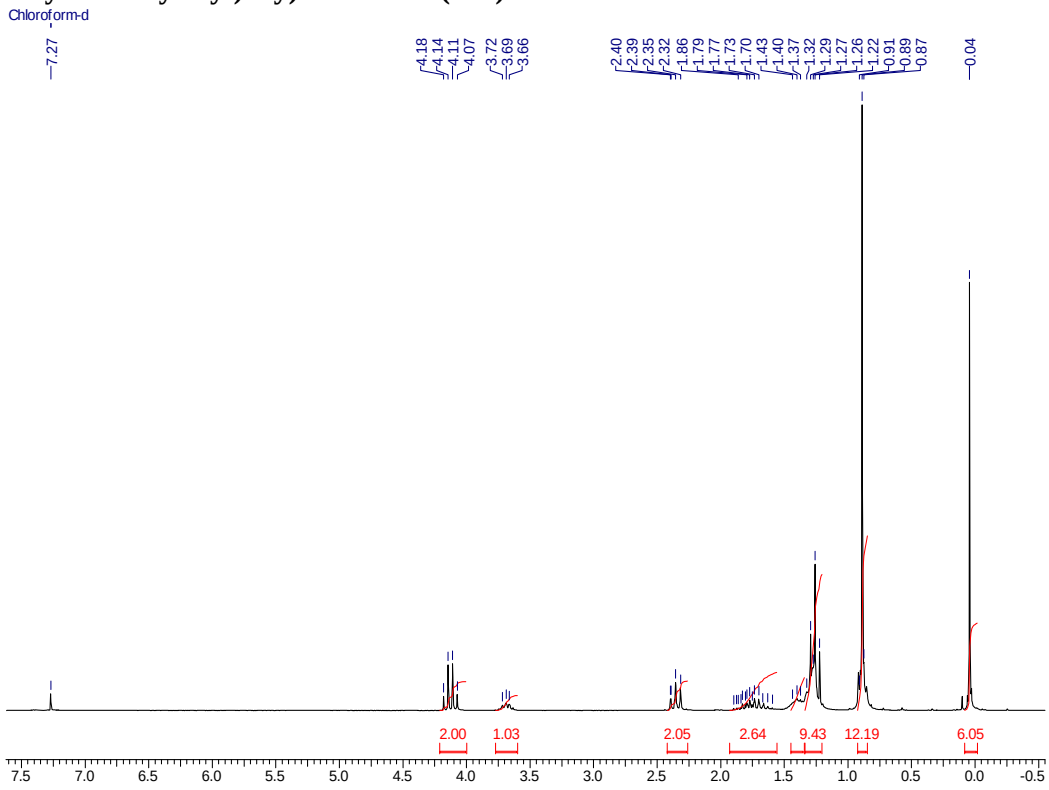
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*R*)-Ethyl 4-hydroxynonanoate (107)



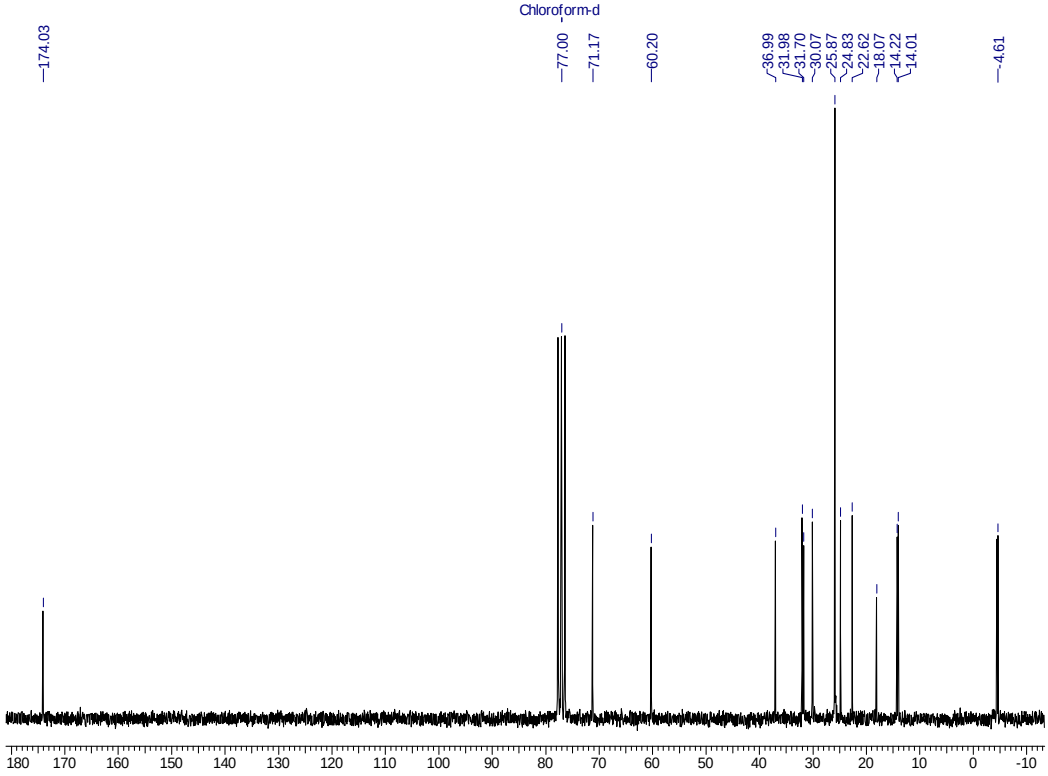
^{13}CNMR ($CDCl_3$, 50 MHz) spectrum of (*R*)-Ethyl 4-hydroxynonanoate (107)



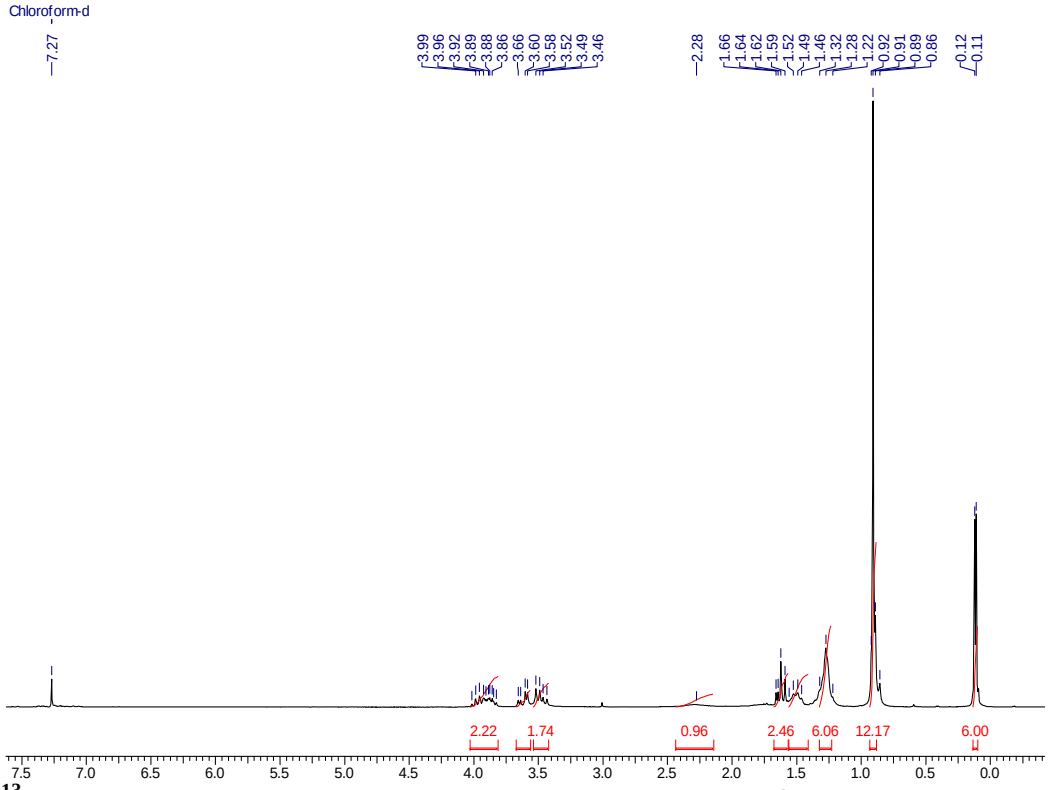
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*R*)-Ethyl 4-((*tert*-butyldimethylsilyl)oxy)nonanoate (105)



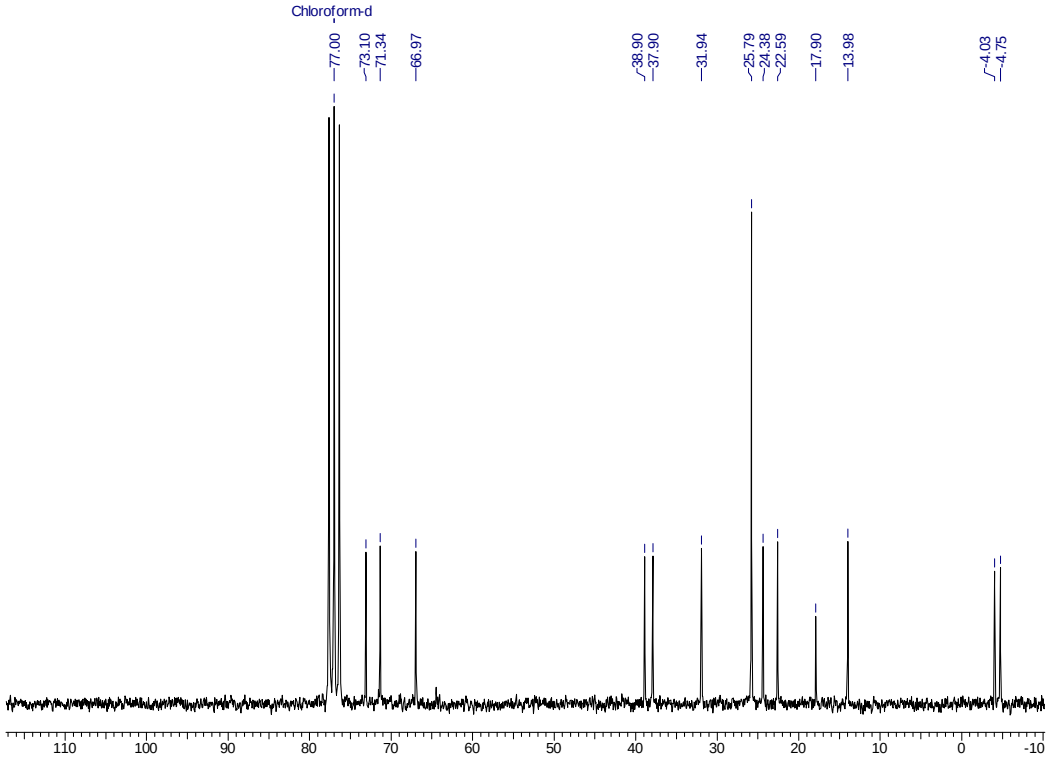
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*R*)-Ethyl 4-((*tert*-butyldimethylsilyl)oxy)nonanoate (105)



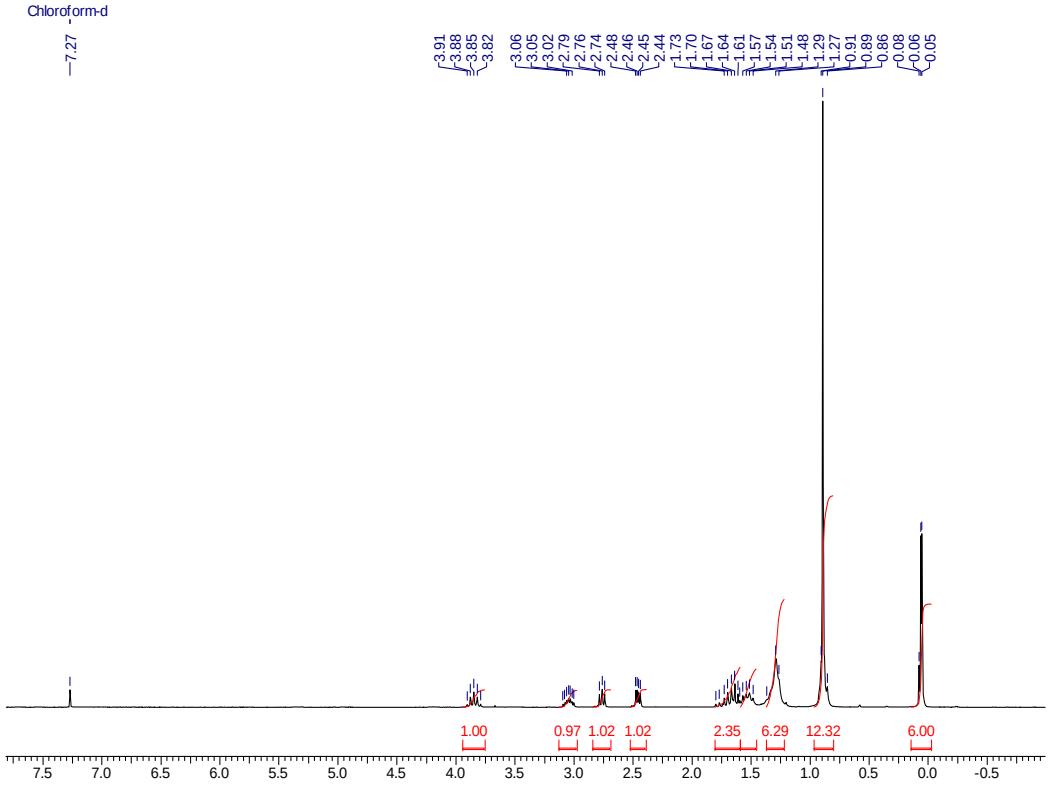
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (2*R*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)nonane-1,2-diol (108)



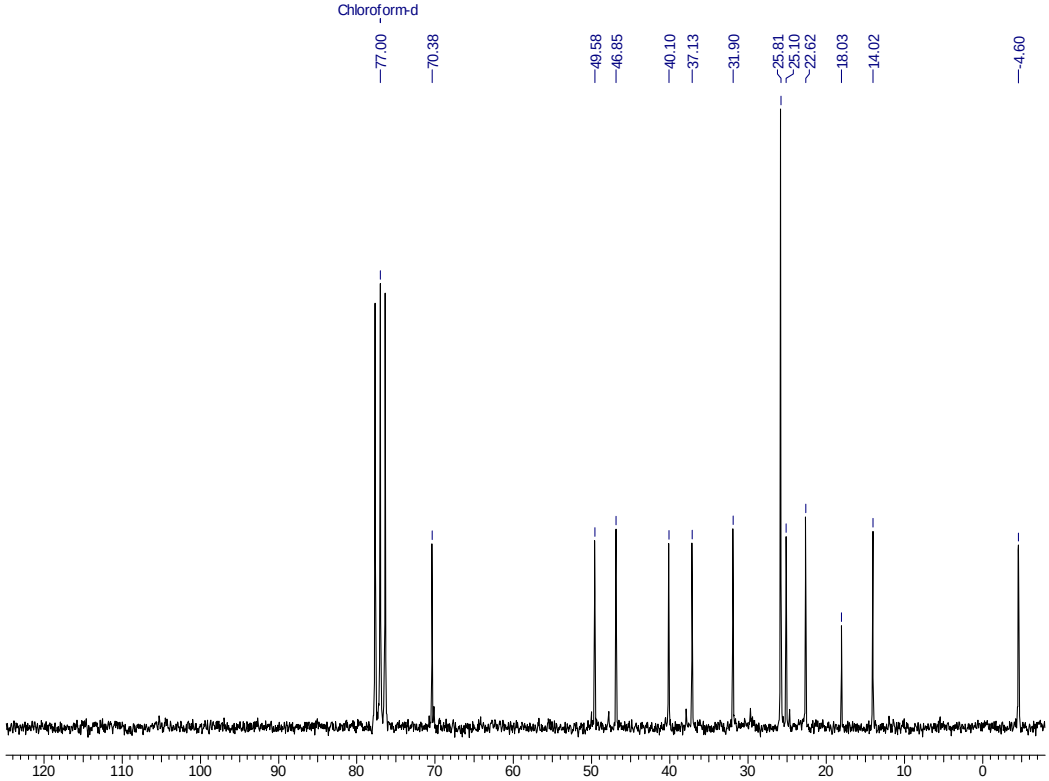
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (2*R*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)nonane-1,2-diol (108)



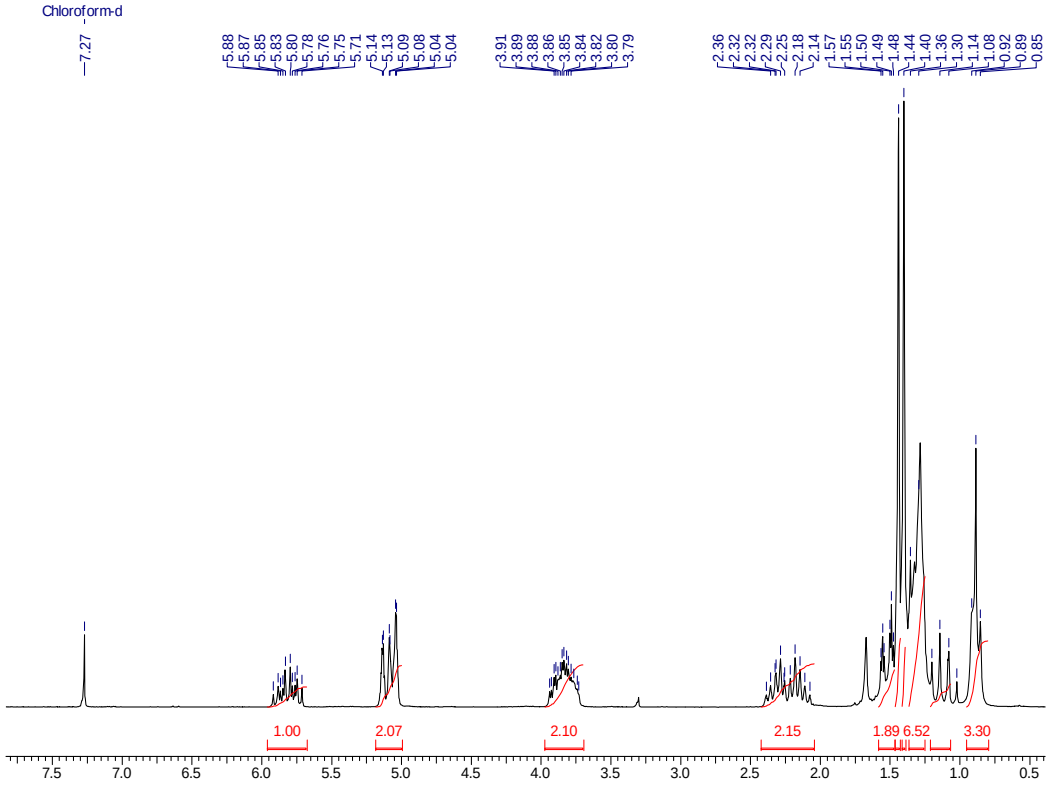
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of *tert*-Butyldimethyl(((*R*)-1-((*R*)-oxiran-2-yl)heptan-2-yl)oxy)silane (104)



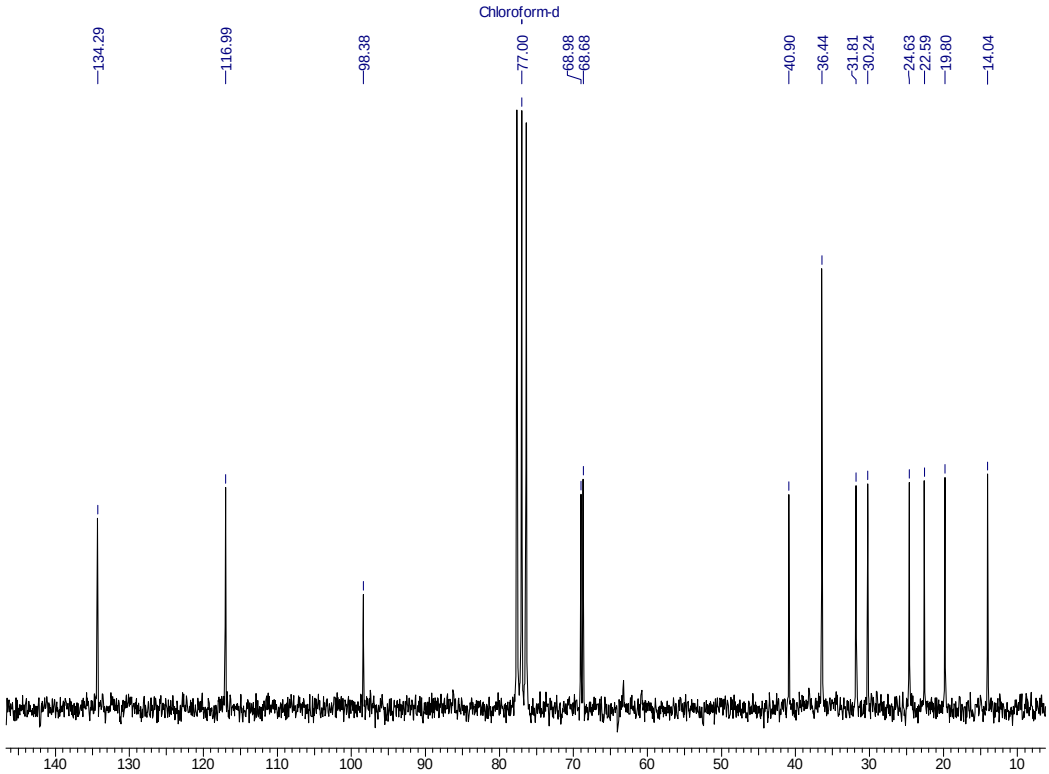
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of *tert*-Butyldimethyl(((*R*)-1-((*R*)-oxiran-2-yl)heptan-2-yl)oxy)silane (104)



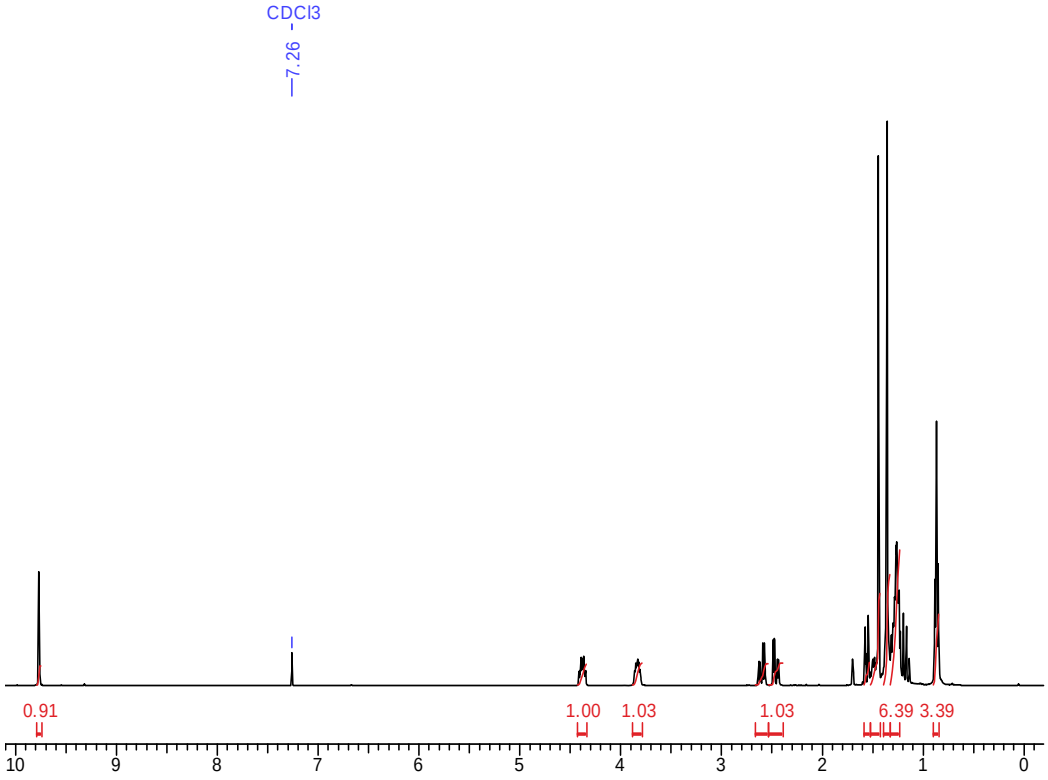
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (4*S*,6*R*)-4-Allyl-2,2-dimethyl-6-pentyl-1,3-dioxane (110)



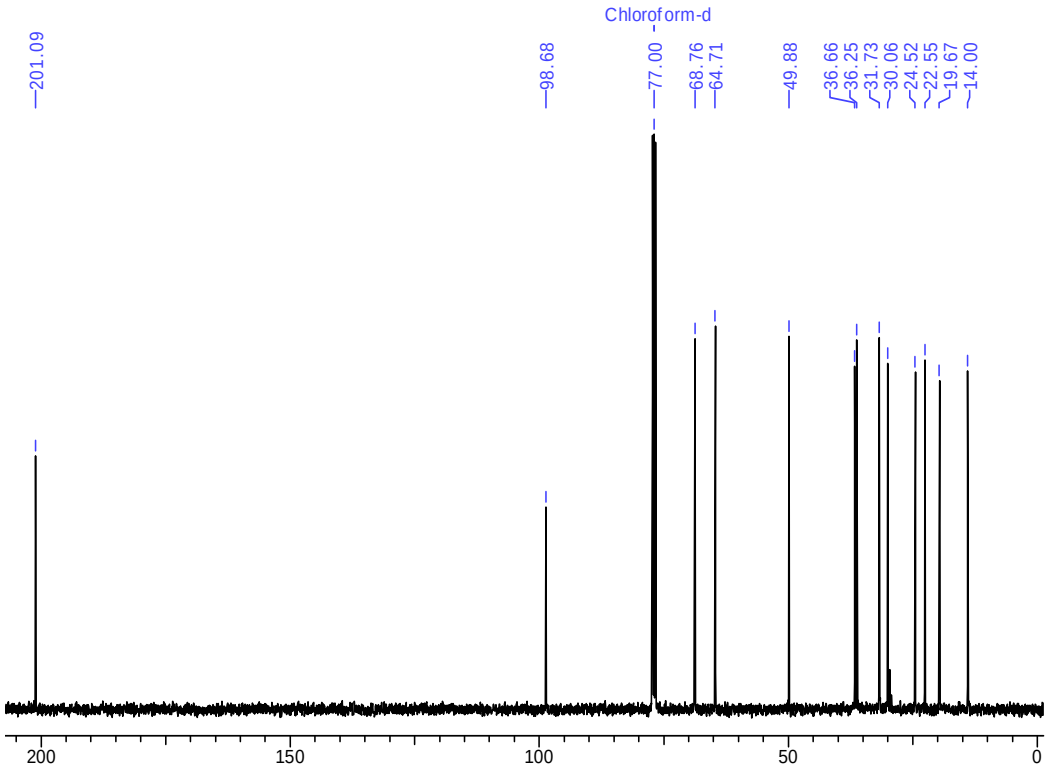
^{1}C NMR ($CDCl_3$, 50 MHz) spectrum of (4*S*,6*R*)-4-Allyl-2,2-dimethyl-6-pentyl-1,3-dioxane (110)



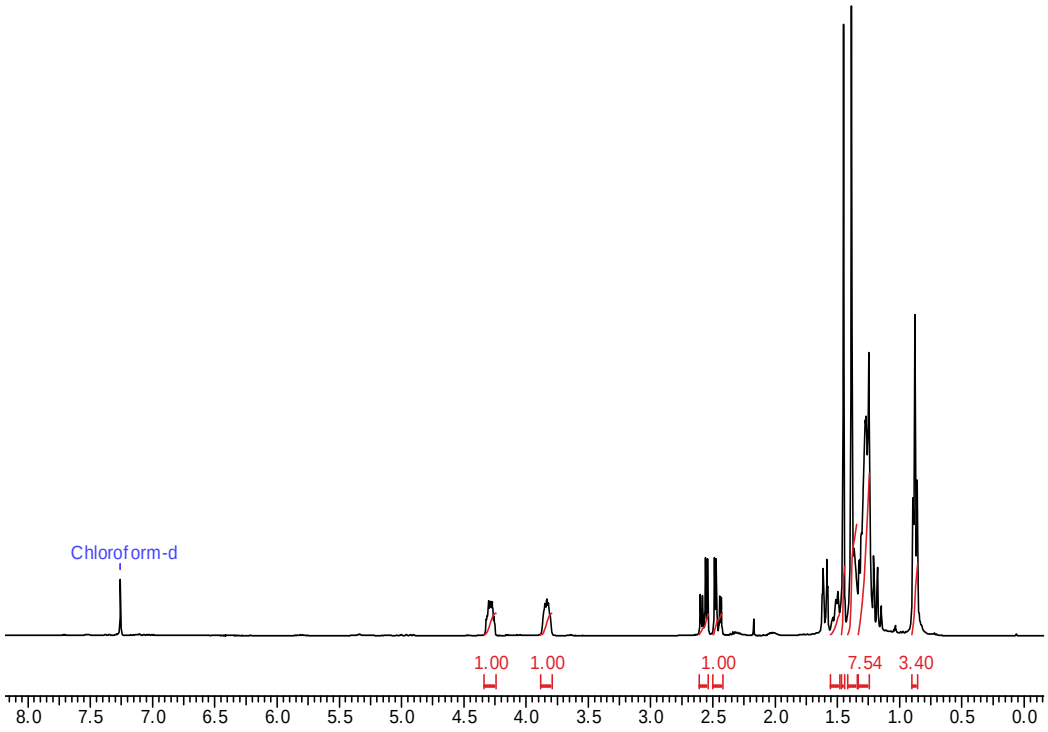
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of 2-((4*R*,6*R*)-2,2-Dimethyl-6-pentyl-1,3-dioxan-4-yl)acetaldehyde (111)



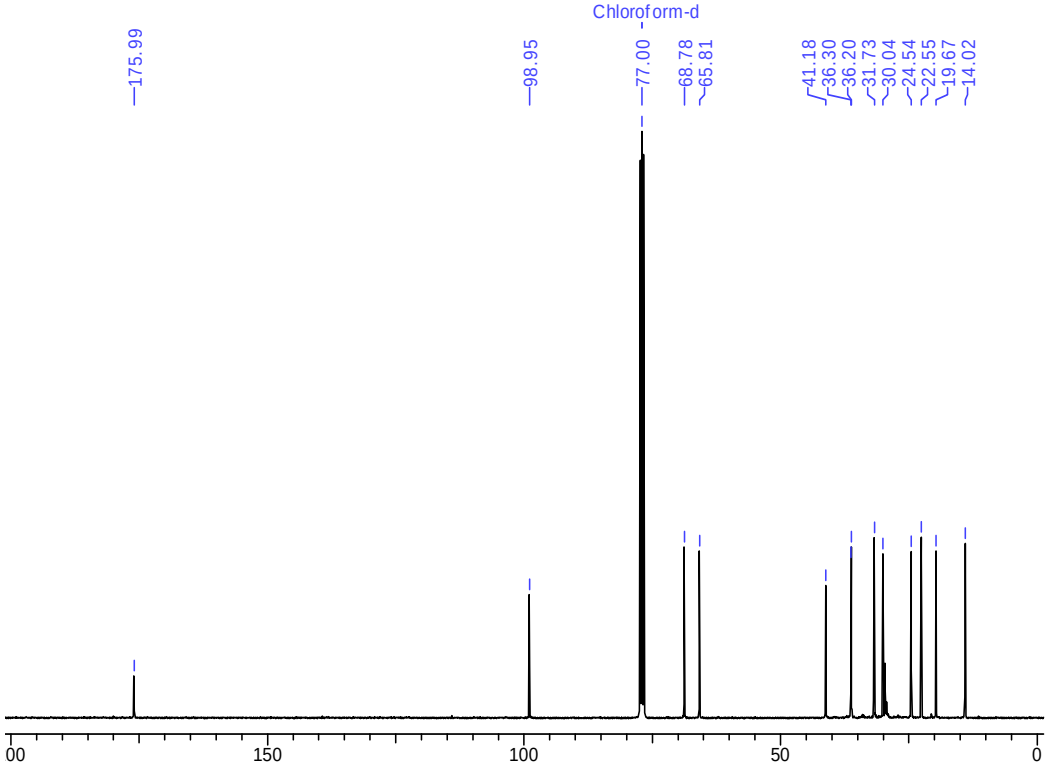
^{1}C NMR ($CDCl_3$, 50 MHz) spectrum of 2-((4*R*,6*R*)-2,2-Dimethyl-6-pentyl-1,3-dioxan-4-yl)acetaldehyde (111)



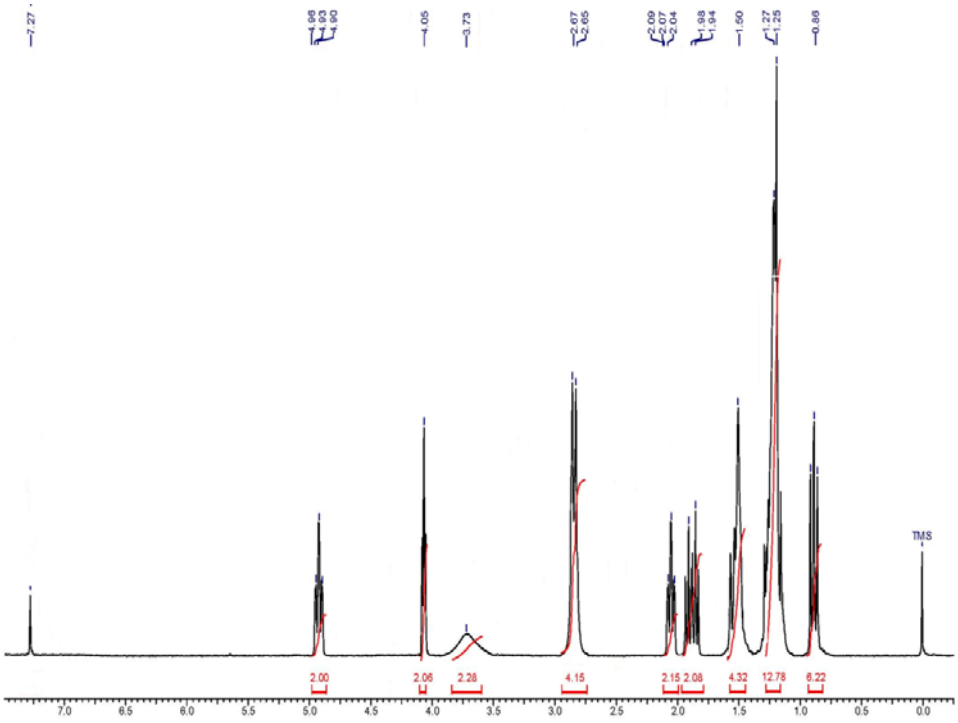
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of 2-((4*R*,6*R*)-2,2-Dimethyl-6-pentyl-1,3-dioxan-4-yl)acetic acid (20)



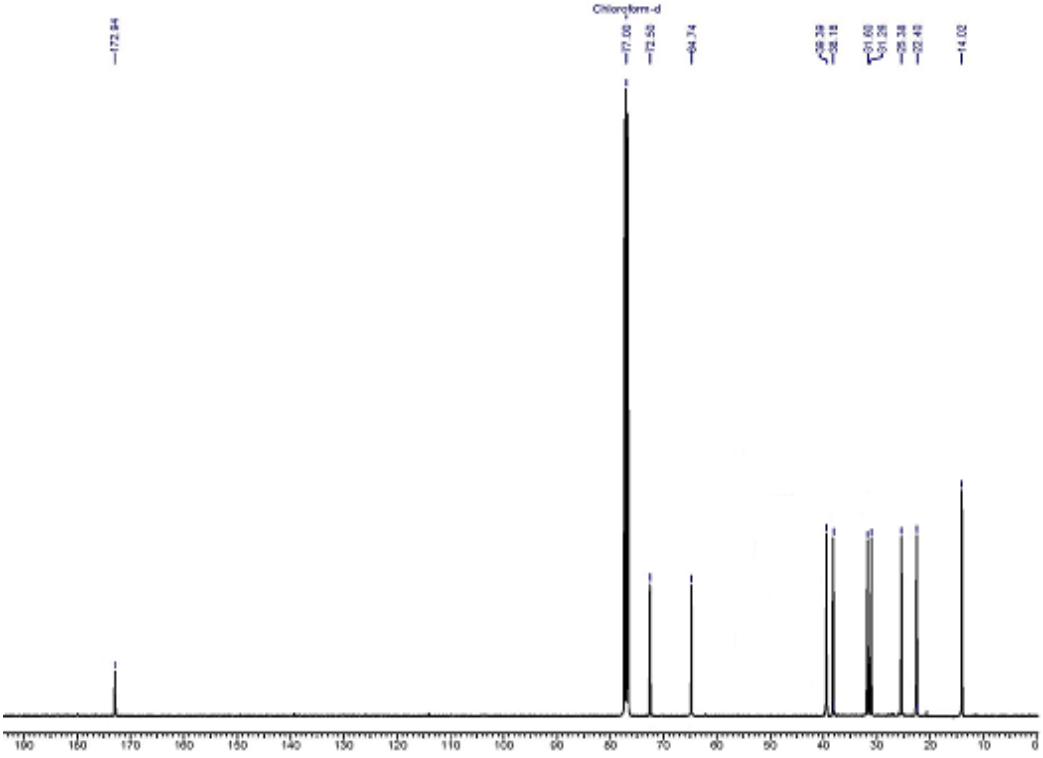
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of 2-((4*R*,6*R*)-2,2-Dimethyl-6-pentyl-1,3-dioxan-4-yl)acetic acid (20)



^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of Verbalactone (15)



^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of Verbalactone (15)



Chapter III, Section B

Organocatalytic route to the Synthesis of (*R*)-Massoialactone

Present work

Objective

Flavor or flavour is the sensory impression of a food or other substance, and is determined mainly by the chemical senses of taste and smell. The "trigeminal senses", which detect chemical irritants in the mouth and throat as well as temperature and texture, are also very important to the overall Gestalt of flavor perception. The flavor of the food, as such, can be altered with natural or artificial flavorants, which affect these senses.

Massoialactone[29,30] is isolated for the first time from the bark of *Cryptocarya massoia* by Abe[31] in 1937. It is skin irritant and produces systolic standstill in frog heart muscles. This lactone has also been isolated from cane molasses[32] and jasmine blossoms[33] as a flavour substance. Massoialactone is widely used as a natural coconut flavouring. Later it was isolated from secretion of two species of Formicin ants of the genus *Componotus* collected in Western Australia.[34] Various methods for the synthesis of massoialactone utilising either the chiral pool as a starting material, asymmetric synthesis or the chromatographic resolution of the diastereomeric derivatives of the lactone precursor have been reported.[18,20-22]

Massoialactone is useful for preventing or at least inhibiting growth of a fungus. Accordingly, a fungicidal composition has massoialactone as an active antifungal compound together with an agronomically acceptable carrier therefor. Additional antifungal ingredients can be added to the composition. The composition can be applied to surfaces, including surfaces of plants and plant parts, such as seeds.

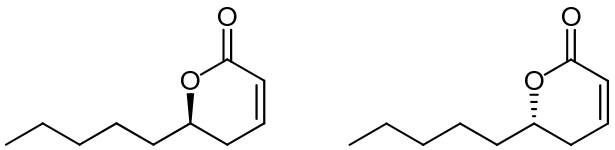
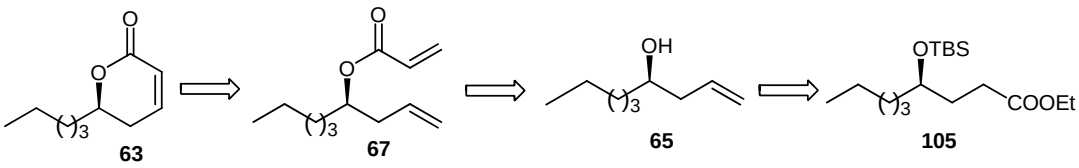


Figure 6. Structures of (*R*)- massoialactone **63** and (*S*)- massoialactone ***ent*-63**

Several methods for the synthesis of either enantiomer of massoialactone have been reported from a chiral pool starting material, hydrolytic kinetic resolution reaction or the resolution of racemic mixtures of the lactone precursor. Despite the numerous strategies available to synthesize massoialactone, interests in new methods

of its synthesis continues unabated. As discussed in previous section, we have developed a novel and efficient protocol for 1,3-polyols based on iterative use of proline-catalyzed tandem α-aminoxylation and HWE olefination of aldehydes. Now we have further extended the synthetic utility of this protocol to synthesize (R)-massoialactone.

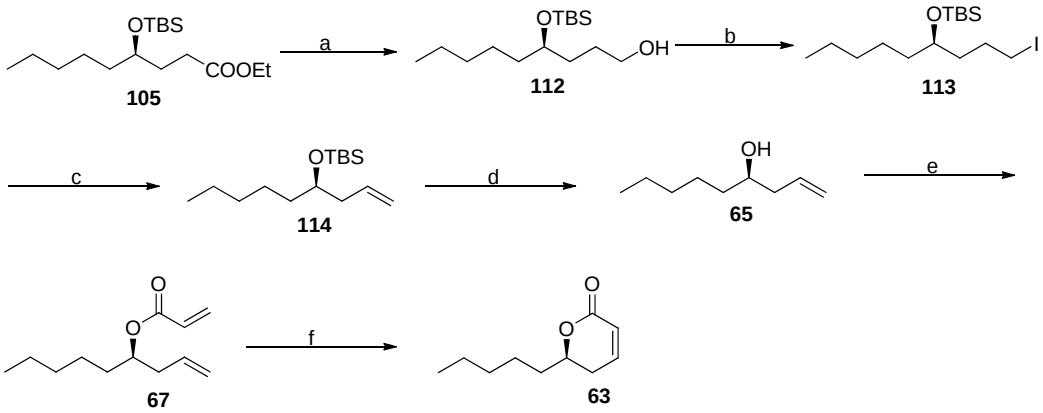
Retrosynthetic analysis for the target compound **63** is delineated in Scheme 16. (*R*)- Massioalactone **63** could be synthesized by ring-closing metathesis of diene precursor **67** which in turn could be obtained from esterification of homoallylic alcohol **65.** We envisioned that homoallylic alcohol **65** required to construct **67**, could easily be synthesized from TBS protected *γ*-hydroxy ester **105** by standard synthetic manipulations.



Scheme 16. Retrosynthetic route to (*R*)- massioalactone **63**

Results and Discussion

Towards the synthesis of massoialactone **63**, TBS protected *γ*-hydroxy ester **105** was subjected to DIBAL-H reduction to furnish the corresponding alcohol **112** in 83% yield **(**Scheme 17).



Scheme-17. Reagents and conditions: (a) DIBAL-H, DCM, -78^{o}C, 2h, 83%; (b) TPP, imidazole, iodine, rt, 2 h, 72%; (c) 1 N KtBD, benzene, 30 min., rt, 69%; (d) TBAF, THF, 2h, rt, 88%; (e) Acryloyl chloride, Et_3N, CH_2Cl_2, 0^{o}C, 6 h, 82%; (f) $(PCy_3)_2$ $Ru(Cl)_2$=CH–Ph (20 mol %), CH_2Cl_2, Ti(O-*i*-Pr)$_4$, reflux, overnight, 86%.

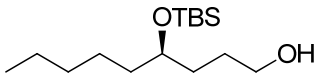
Alcohol **112** was converted to the iodo derivative **113** which on reaction with KtBD[35] in benzene afforded TBS protected homoallylic alcohol **114** in 69% yield.TBS deprotection followed by esterification of resultant alcohol with acryloyl chloride in presence of triethylamine gave **67** in 82% yield. Subsequent ring closing metathesis of **67** under reflux in high dilution condition using first generation Grubbs's catalyst and catalytic amount of Ti(O-*i*-Pr)$_4$ provided (*R*)-massoialactone **63** in good yield. The physical and spectroscopic data were in accord with those described in literature.[36]

Conclusion

In conclusion, a facile total synthesis of *R* (-)-massoialactone has been achieved *via* organo-catalytic approach. The synthetic strategy described here has significant potential to synthesize a variety of other biologically important analogues of δ-lactone natural products like hexadecanolide and parasorbic acid.

Experimental Section

(*R*)-4-((*tert*-Butyldimethylsilyl)oxy)nonan-1-ol (112)



To a solution of ester **105** (3.0 g, 9.48 mmol) in CH_2Cl_2 (40 mL), was added DIBAL-H (12.67 mL 1.87 M solution in toluene, 23.69 mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 2h. Then a solution of tartaric acid (10 mL) was added. The resulting mixture was stirred for 15 min and the organic layer separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL), the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure which on purification over silica gel by eluting with ethyl acetate/light petroleum ether (1:9) afforded **112** as a colorless oil (2.16 g, 83%) .

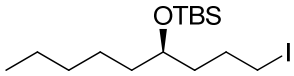
^{1}H NMR (200MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.91 (s, 12H), 1.20-1.27 (m, 6H), 1.45-1.67 (m, 6H), 3.55-3.77 (m, 3H), ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.5, 14.0, 18.0, 22.6, 25.1, 25.8, 31.9, 33.3, 36.4, 41.9, 63.1, 72.1 ppm.

Elemental Analysis : ($C_{15}H_{34}O_2Si$), Calcd: C, 65.63; H, 12.48% Found: C, 65.31; H, 12.57%

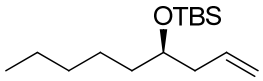
ESI-MS *m/z* **:** 297 [M+Na]+

(*R*)-*tert*-Butyl((1-iodononan-4-yl)oxy)dimethylsilane (113)



To a cooled (0 ^oC), stirred solution of PPh_3 (2.10 g, 8.01 mmol) in THF/MeCN (6:5, 30 ml) were added imidazole (0.60 g, 8.74 mmol) and I_2 (2.03 g, 8.01 mmol). The mixture was stirred for 2h and then a solution of **112** (2 g, 7.29 mmol) in THF was added at 0 ^oC. After being stirred for 2h, the mixture was diluted with 10% aqueous $Na_2S_2O_3$ (40 ml). This was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo and used without purification for next step.

(*R*)-*tert*-Butyldimethyl(non-1-en-4-yloxy)silane (114)



To the crude iodo compound (2.8 g., 5.20 mmoles) dissolved in 25 mL of benzene was added 10.4 mL of 1 ***N*** KtBD. The mixture was stirred for 30 min. at room temperature. The resulting mixture was poured into water and organic layer was separated. The aqueous layer was extracted with ether (3 x 20 mL) and combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Purification of crude product by silica gel column chromatography using pet ether as eluent afforded **114** as a colorless liquid. **Yield:** 1.29 g, 69%

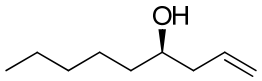
^{1}H NMR (200MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.90 (s, 12H), 1.27-1.45 (m, 8H), 2.18-2.25 (m, 2H), 3.63-3.74 (m, 1H), 5.00-5.09 (m, 2H), 5.72-5.93 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.5, -4.4, 14.0, 18.1, 22.6, 25.0, 25.8, 31.9, 36.7, 41.9, 72.0, 116.5, 135.5 ppm.

Elemental Analysis : ($C_{15}H_{34}OSi$), Calcd: C, 70.24; H, 12.57% Found: C, 69.88; H, 12.83%

ESI-MS *m/z* **:** 257 [M+H]+

(*R*)-Non-1-en-4-ol (65)



To a stirred solution of compound **114** (500 mg, 1.95 mmol) in dry THF was added 1 M solution of TBAF (2.15 mL, 2.15 mmol) at room temperature and after completion of reaction (2 h), some ice flakes added to it and then extracted with ethyl acetate (3 x 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford crude homoallylic alcohol, Purification of the crude product on silica gel column chromatography (pet ether/ethyl acetate = 9:1) gave **65** (244 mg, 88% yield) as a colorless liquid.

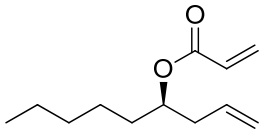
$[\alpha]^{D}_{25}$ = + 12.5 (*c*, 0.9, $CHCl_3$)

IR ($CHCl_3$, cm-1): ν_{max} 3351, 2926, 2854, 1641, 1589, 1457, 1378, 1259, 1156, 999, 836.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.4 Hz, 3H), 1.47-1.26 (m, 8H), 1.70 (brs, 1H), 2.19-2.09 (m, 1H), 2.35-2.27 (m, 1H), 3.69-3.65 (m, 1H), 5.16-5.12 (m, 2H), 5.91-5.77 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 22.5, 25.2, 31.8, 36.7, 41.8, 70.7, 117.6, 134.9 ppm.

(*R*)-Non-1-en-4-yl acrylate (67)



Acryloyl chloride (0.95 g, 0.86 mL, 10.55 mmol) was added drop wise under argon to a solution of **65** (1.5 g, 10.55 mmol) and triethylamine (4.27 g, 5.9 mL, 42.18 mmol) in dry CH_2Cl_2 (15 mL) at 0 ^oC. The mixture was stirred for 5-6 h at room temperature. The resulting mixture was filtered through a pad of celite and poured into water and organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Purification of crude product by silica gel column chromatography using pet ether/EtOAc (19:1) as eluent afforded **67** as a colorless liquid.

Yield: 1.08 g, 82%

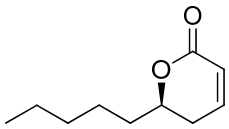
$[\alpha]^{D}_{25}$: +19.93 (*c*, 1.1, $CHCl_3$).

IR ($CHCl_3$, cm-1): ν_{max} 2956, 2930, 2859, 1742, 1725, 1640, 1620, 1549, 1406, 1296, 1271, 1195, 1048, 986, 917, 809.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3 H), 1.29-1.18 (m, 8H), 2.37-2.33 (m, 2H), 5.11-4.96 (m, 3H), 5.83- 5.72 (m, 2H), 6.10 (dd, *J* = 15 Hz, 1H), 6.42 (d, *J* = 18 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 22.5, 24.9, 31.6, 33.5, 38.6, 73.6, 117.5, 128.9, 130.0, 132.7, 165.4 ppm.

(*R*)-Massoialactone (63)



Grubb's catalyst (0.169 g, 0.20 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise to a refluxing solution of acrylate **67** (0.200 g, 1.02 mmol), Ti(*i*-PrO)$_4$ (86 mg, 0.03 mmol) in dry CH_2Cl_2 (50 mL). Refluxing was continued for overnight by which time all the starting material was consumed. The solvent was removed under

reduced pressure and the crude product was purified by silica gel column chromatography using pet ether/EtOAc (4:1) as eluent to afford **63** as colorless oil.
Yield: 0.147 g, 86%

$[\alpha]^{D}_{25}$: -114.5 (*c* 1, $CHCl_3$) [lit.[20] $[\alpha]^{D}_{25}$: -113.6 (*c* 1, $CHCl_3$)]

IR (neat, cm-1): ν_{max} 2931, 2860, 1725, 1630, 1466, 1388, 1251, 1155, 1118, 1059, 1039, 955, 815.

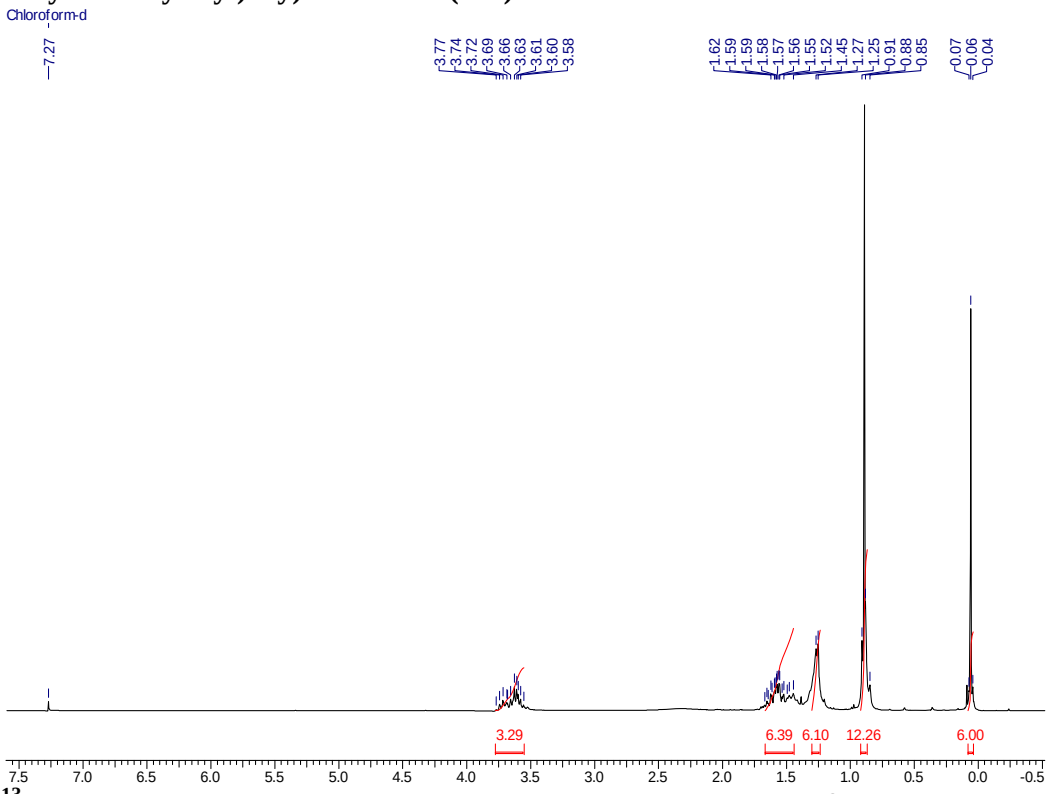
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.9 Hz, 3H), 1.34-1.26 (m, 5H), 1.82-1.64 (m, 3H), 2.38-2.32 (m, 2H), 4.45-4.41 (m, 1H), 6.04 (d, *J* = 10Hz, 1H), 6.90-6.87 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 22.4, 24.5, 29.4, 31.5, 34.8, 78.0, 121.5, 144.9, 164.4 ppm.

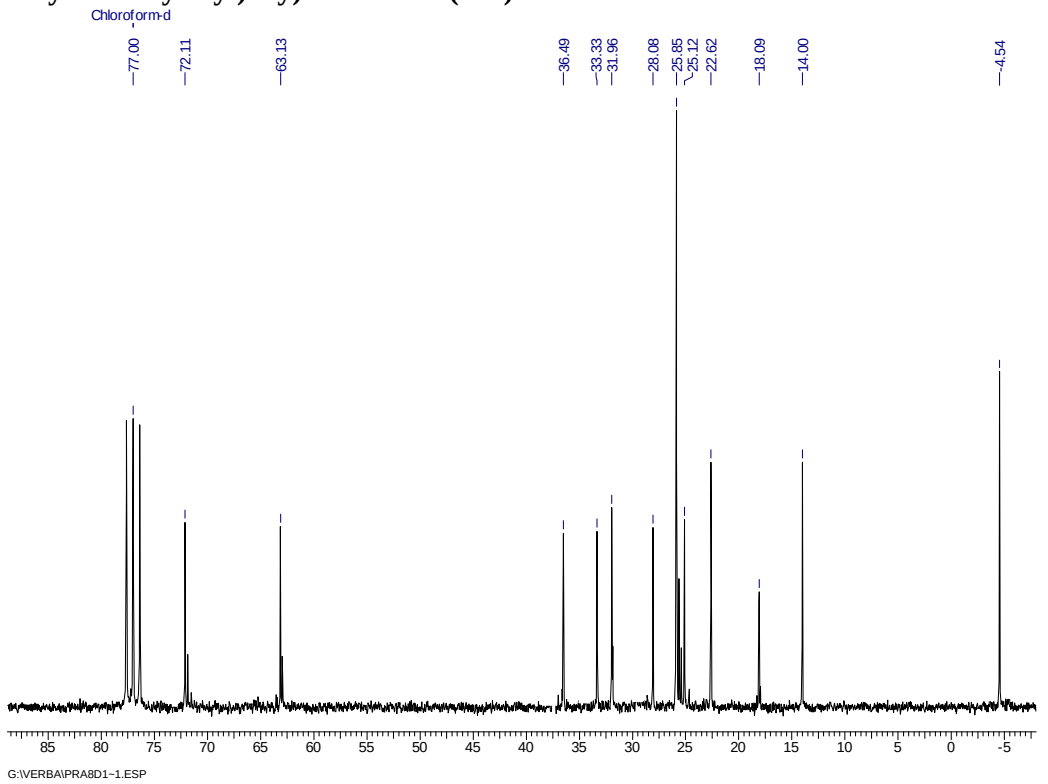
Spectra

1. ^{1}H and ^{13}C NMR spectra of **112**
2. ^{1}H and ^{13}C NMR spectra of **114**
3. ^{1}H and ^{13}C NMR spectra of **65**
4. ^{1}H and ^{13}C NMR spectra of **67**
5. ^{1}H and ^{13}C NMR spectra of **63**

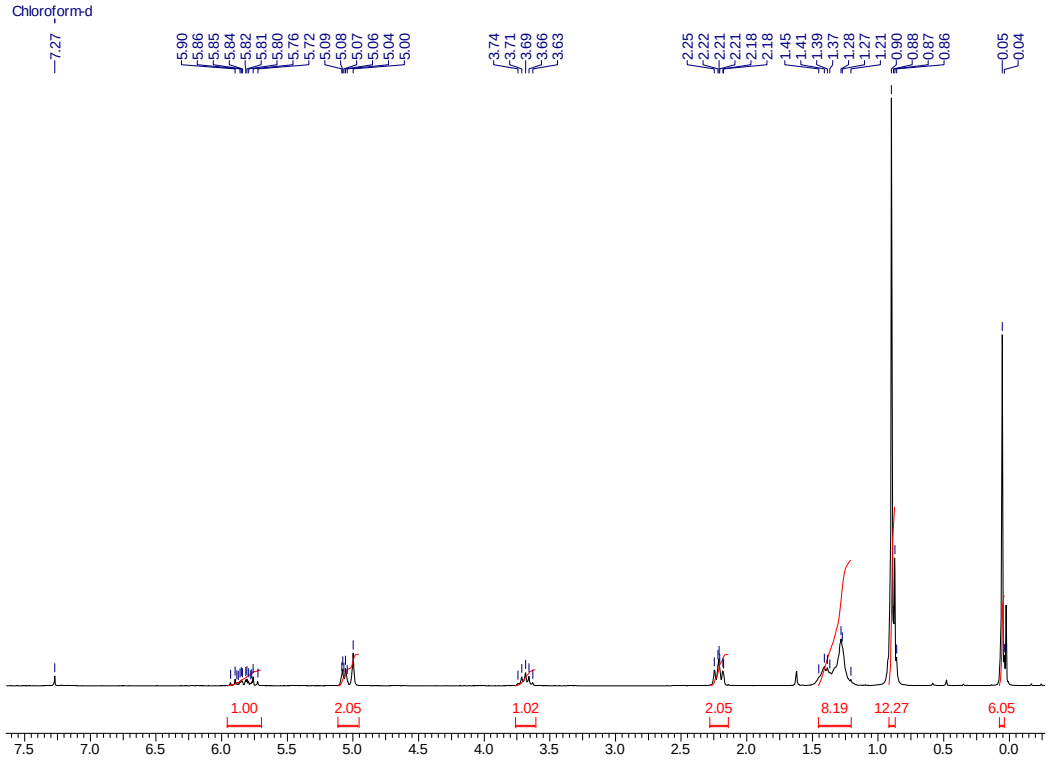
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*R*)-4-((*tert*-Butyldimethylsilyl)oxy)nonan-1-ol (112)



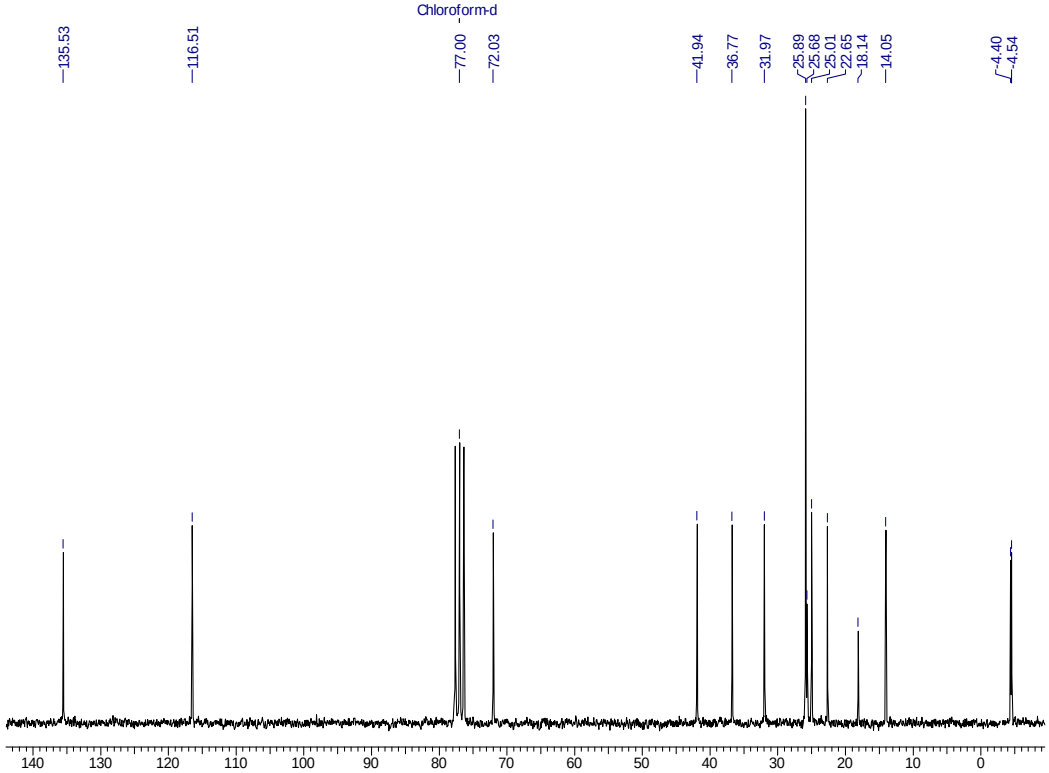
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*R*)-4-((*tert*-Butyldimethylsilyl)oxy)nonan-1-ol (112)



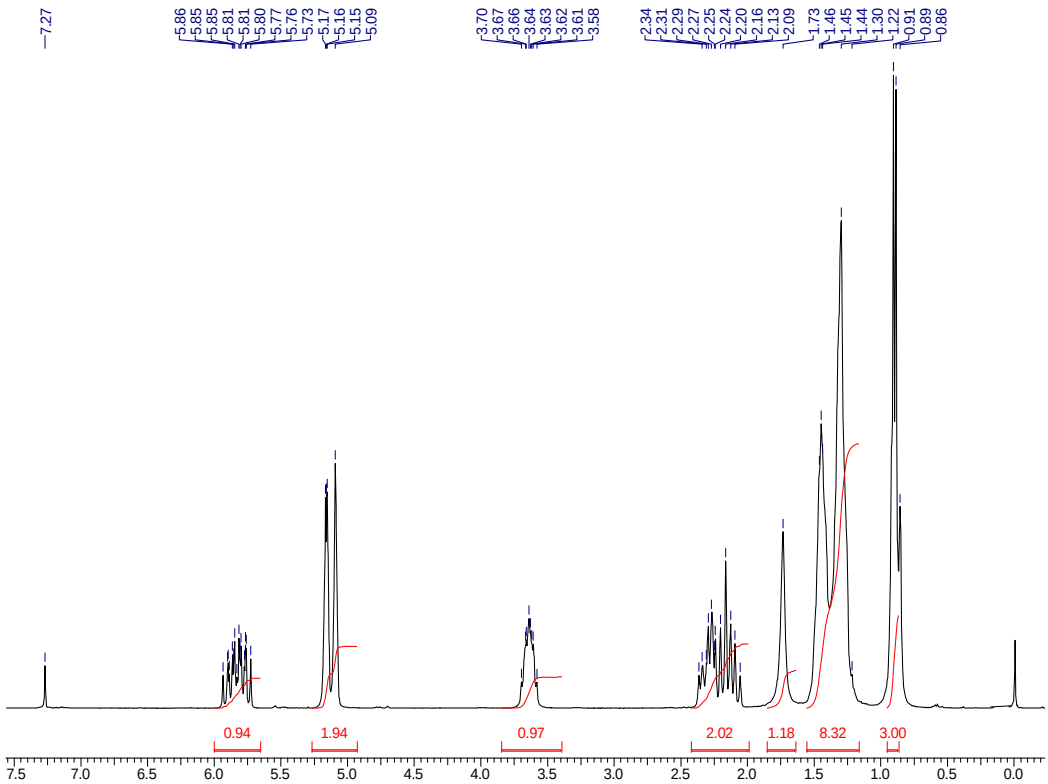
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*R*)-*tert*-Butyldimethyl(non-1-en-4-yloxy)silane (114)



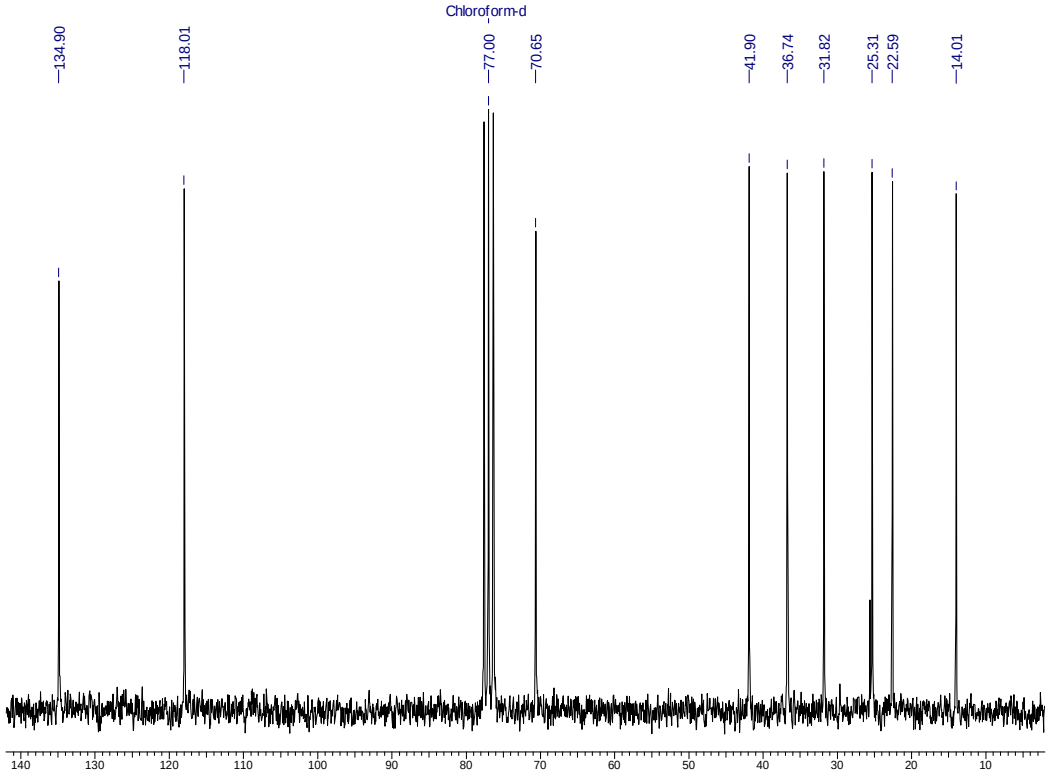
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*R*)-*tert*-Butyldimethyl(non-1-en-4-yloxy)silane (114)



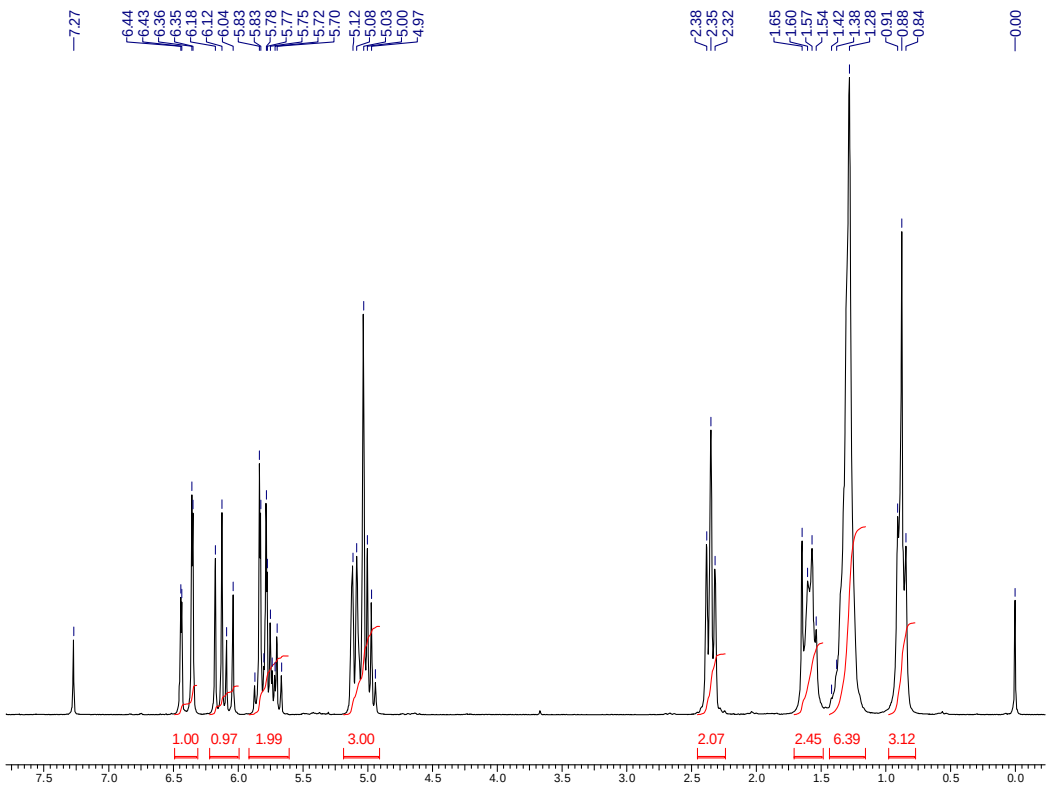
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*R*)-Non-1-en-4-ol (65)



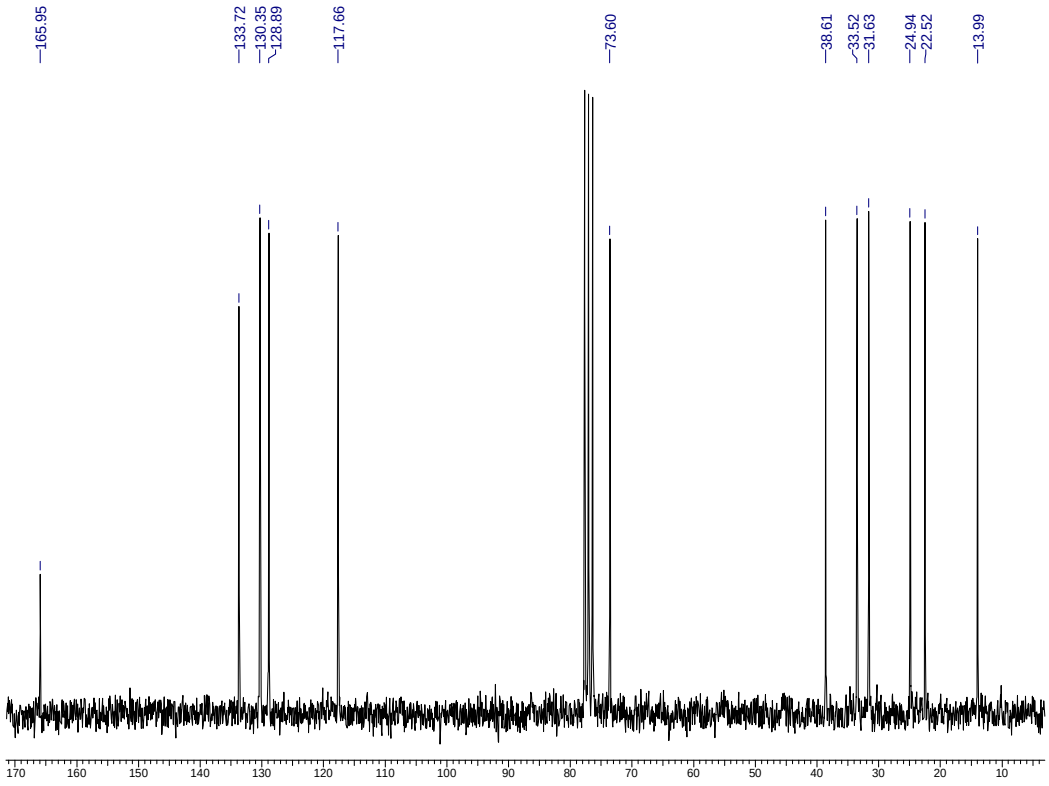
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*R*)-Non-1-en-4-ol (65)



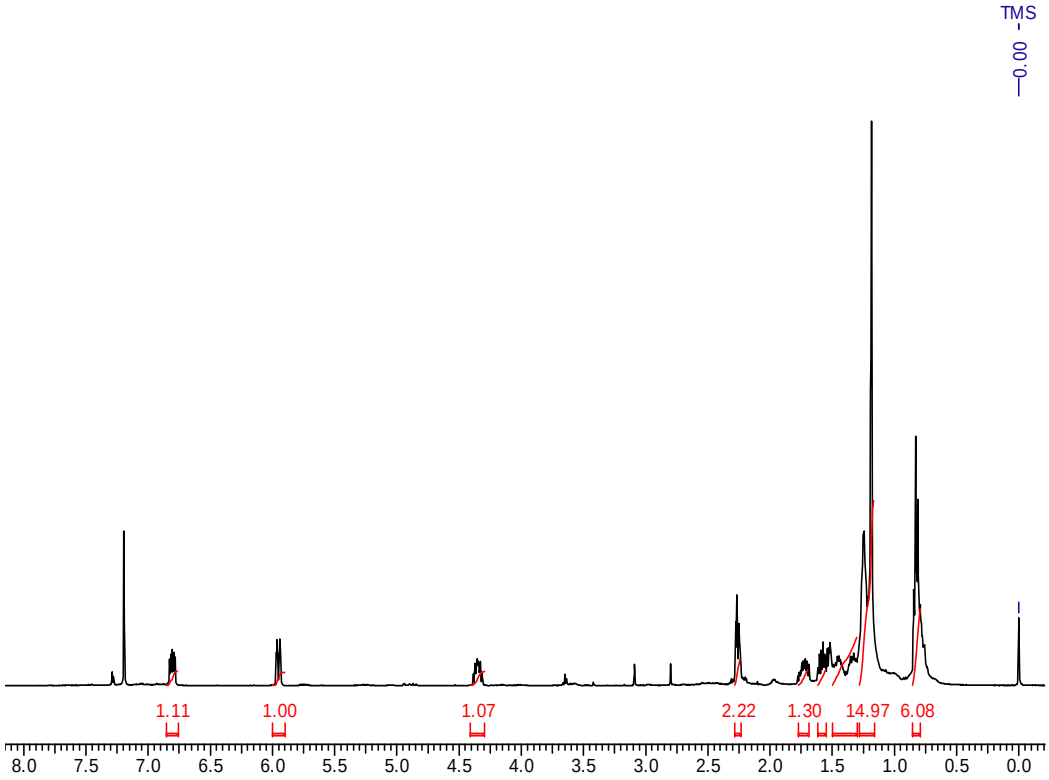
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*R*)-Non-1-en-4-yl acrylate (67)



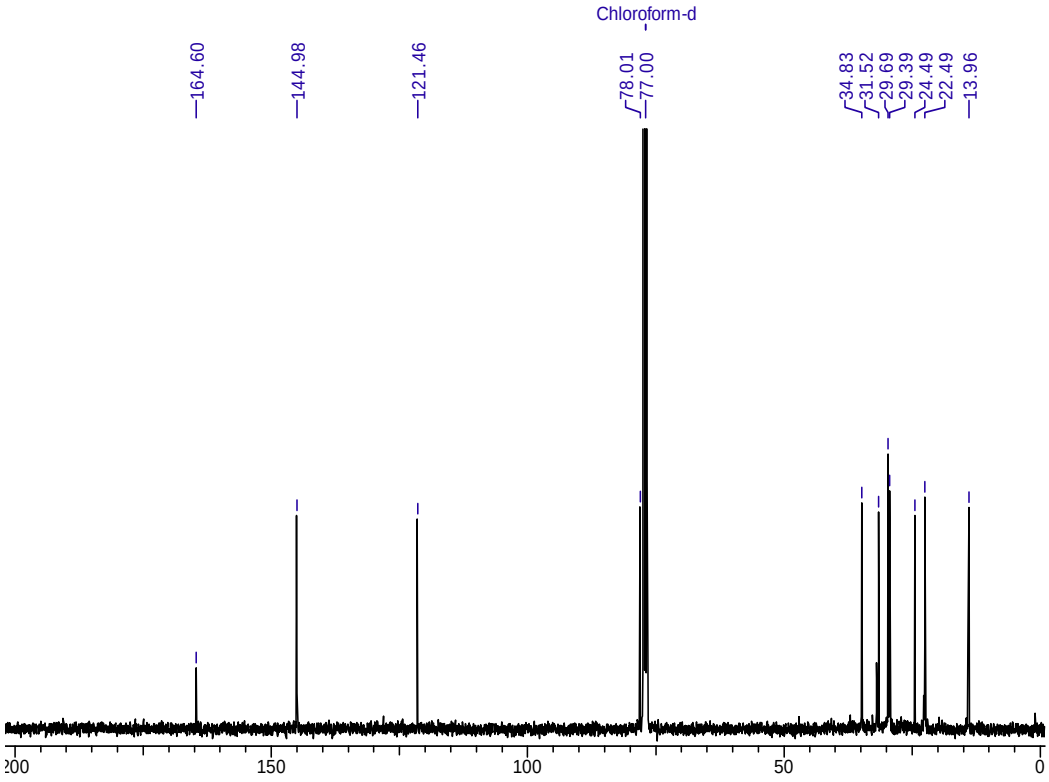
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*R*)-Non-1-en-4-yl acrylate (67)



^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*R*)-Massoialactone (63)



^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*R*)-Massoialactone (63)



Chapter III, Section C

Synthesis of insect pheromone, 5-(*S*)-Hexadecanolide and its enantiomer

Present work

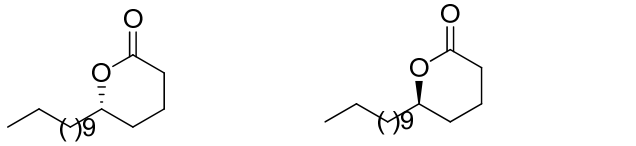
Objective

Pheromones, allomones and kairomones are chemical substances[37] that control the inter- and intraspecific behavior of a variety of bioorganisms e.g. flies, ants, cockroaches, rootworms, beetles, bees etc. There are alarm pheromones, food trail pheromones, sex pheromones, and many others that affect behavior or physiology. Their use among insects has been particularly well documented. In addition, some vertebrates and plants communicate by using pheromones. Karlson and Luscher coined the word 'pheromones' to this group of active substances. The name is derived from the Greek *Pherin* (to transfer) and *hormone* (to excite). Thus, pheromones are secreted by individual bioorganisms and are received by a second individual of the same species to produce a specific reaction. Compounds used for interspecific communication are called allomones (favoring the producer) and kairomones (favoring their receivers). The term semiochemicals is used as a generic name for the signal substances such as pheromones, allomones and kairomones.

Sex Pheromones

Pheromones are employed by a large number of insects in bringing the sexes together. These pheromones are known as sex pheromones. Many insect species release sex pheromones to attract a mate and many lepidopterans (moths and butterflies) can detect a potential mate from as far away as 10 kilometers. Traps containing pheromones are used by farmers to detect and monitor insect population in orchards like apple, pear, peach and walnut. At the microscopic level, a gamete pheromone may provide a trail leading the opposite sex's gametes towards it to accomplish fertilization. Pheromones are also used in the detection of oestrus in sows. Boar pheromones are sprayed into the sty, and those sows which exhibit sexual arousal are known to be currently available for breeding. Sea urchins release pheromones into the surrounding water, sending a chemical message that triggers other urchins in the colony to eject their sex cells simultaneously. Sex pheromones are widespread amongst *Lipidoptera* and also in some *Dictyoptera caleoptera*, hymenoptera and some other orders.[38] Generally the pheromone is produced by the female to attract the male, while less frequently a male pheromone attracts the male or both sexes may be attracted by the odour.

(S)-5-Hexadecanolide (**85**), a natural pheromone was isolated from the mandibular glands of the oriental hornet *Vespa* orientals.[39] It has six membered lactone in the structure and its unsaturated analog (6-substituted 5,6-dihydro-2*H*-pyran-2-one) is the key synthon for several biologically important molecules.Various methods for the synthesis of *(S)*-5-hexadecanolide (**85**) and its enantiomer (Figure 7). have been reported in literature.[20,23-26]



5S-Hexadecanolide (**85**) 5R-Hexadecanolide (***ent*-85**)

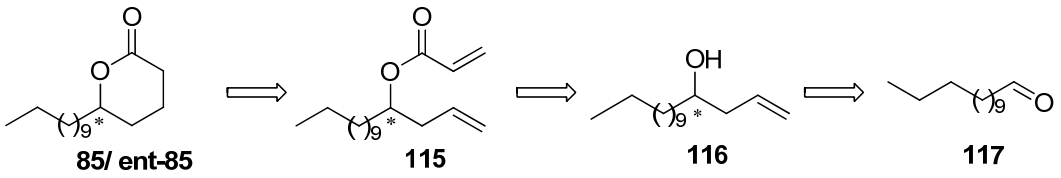
Figure 7. 5*S*-Hexadecanolide **85** and 5*R*-Hexadecanolide (***ent*-85**)

Servi reported[40] the first synthesis of enantiomerically pure 5*S*-hexadecanolide **85** in which the stereogenic centre was generated by enzyme catalysis. Singh *et* al. reported[24] its synthesis from chiral epoxides derived from chiral pool starting material such as mannitol and ascorbic acid. Zhang *et* al. described[25] the synthesis of target compound **85** in enantiomerically pure form using L-proline-catalyzed asymmetric aldol reaction. In another approach, the target molecule was constructed via the asymmetric allylboration of appropriate aldehyde and ring closing metathesis.

As part of our research program aimed at developing methodology and its application towards synthesis of naturally occurring lactons based on organocatalytic approaches,[11,41] we became interested in developing a simple and short route to 5*S*-hexadecanolide (**85**) and its enantiomer (***ent*-85**). Herein, we report our successful endeavors towards the synthesis of **85** and ***ent*-85** using aminoxylation and ring-closing metathesis as the key steps. Recently, Zhong *et* al. have reported α-aminoxylation directed tandem reaction catalyzed by proline. *O*-Amino-substituted diol obtained from proline catalyzed α-aminoxylation of achiral aldehydes followed by in situ reduction using $NaBH_4$ serves as useful precursor in the synthesis of various compounds of biological importance.

Our retrosynthetic analysis for the target compound **85** and ***ent*-85** is delineated in Scheme **18**. 5-Hexadecanolide could be synthesized by reduction of dihydro-2*H*-pyran derivative which in turn could be obtained from a diene precursor **115.** We

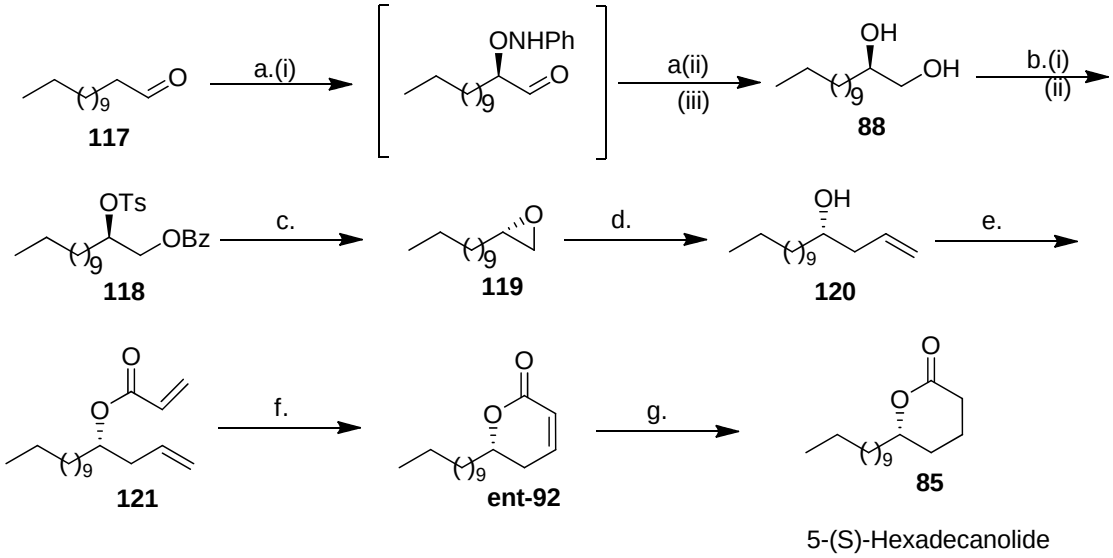
envisioned that homoallylic alcohol **116** required to construct **115**, could easily be synthesized from aldehyde **117** by standard synthetic manipulations.



Scheme 18. Retrosynthetic route to 5*S*-hexadecanolide (**85**) & its enantiomer (***ent*-85**)

Results and Discussion

As shown in Scheme 19, the synthesis of target molecule started from aldehyde **117** which was subjected to α-aminoxylation using L-proline and subsequent in situ $NaBH_4$ reduction followed by Pd/C reduction to furnish the enantiomerically pure diol **88**[42] in 72% yield. Subsequently primary hydroxy group of diol **88** was protected as its benzoyl ether followed by secondary hydroxyl group protection as tosyl to afford **118** in 84% yield over two steps. Base treatment resulted into epoxide **119** by intramolecular nucleophilic displacement of tosyl group. Epoxide **119** was opened with vinylmagnesium bromide to give the homoallylic alcohol **120** in excellent yield.

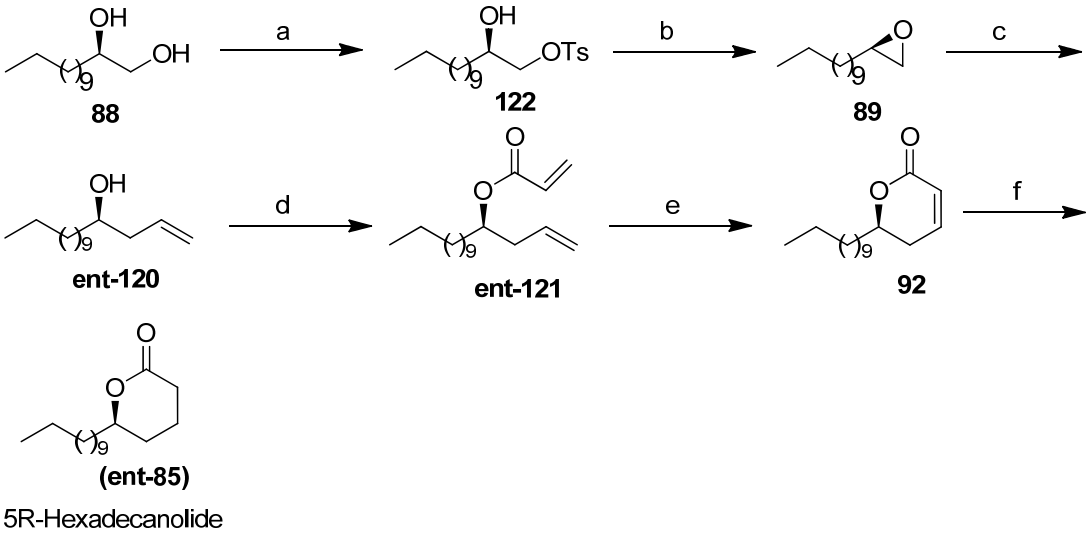


Scheme-19. Synthesis of 5*S*-Hexadecanolide **85**.

Reagents and conditions: (a) (i) L-proline, DMSO, Nitrosobenzene; (ii) $NaBH_4$, MeOH, 2 h ;(iii) H_2/Pd-C, EtOAc , 60 psi, 6 h, 72% (over three steps); (b)(i) Benzoyl chloride, Et_3N, CH_2Cl_2, 0°C, 2 h; (ii) TsCl, Et_3N, Bu_2SnO,CH_2Cl_2, rt, 8 h, 84% (over

two steps); (c) K_2CO_3, MeOH, rt, 3 h, 81%; (d) Vinylmagnesium bromide, THF, CuI, -20 ^oC, 5 h, 82%; (e) Acryloyl chloride, Et_3N, DCM, 2 h, cat. DMAP, 86%; (f) Grubb's I gen. Cat.,CH_2Cl_2, 12 h, reflux, 80%; (g) Pd/C, H_2, balloon press., 4 h, 84%.

In ^{1}HNMR spectrum the terminal olefinic group of **120** showed peaks at δ 5.91-5.73 (multiplet, 1H) and 5.18-5.09 (m, 2H). All other protons resonated at the expected chemical shift. The ^{13}C spectrum displayed peaks at δ 118.0 and δ 134.9 corresponding to olefinic carbons. The alcohol **120** was esterified using acryloyl chloride in the presence of triethyl amine in dry CH_2Cl_2 to afford ester **121**. Ring closing metathesis[43] of **121** using Grubbs' I'st generation catalyst afforded lactone ***ent*-92** which was hydrogenated using Pd/C to furnish the hexadecanolide **85** (Scheme 19). The physical and spectroscopic data of **85** were in full agreement with the literature.[24]



Scheme-20. Synthesis of 5*R*-Hexadecanolide (***ent*-85**).

Reagents and conditions: (a) TsCl, Et_3N, Bu_2SnO,CH_2Cl_2, rt, 4 h, 85%; (b) K_2CO_3, MeOH, rt, 3h, 86%; (c) Vinylmagnesium bromide, THF, CuI, -20 ^oC, 10 h, 86%; (d) Acryloyl Chloride, Et_3N, DCM, 2 h, cat. DMAP, 88%; (e) Grubb's I gen. Cat.,CH_2Cl_2, 12 h, reflux, 78%; (f) Pd/C, H_2, balloon press., 4 h, 89%.

As depicted in Scheme 20, towards the synthesis of 5*R*-hexadecanolide (***ent*-85**), the primary hydroxyl of diol **88** was converted into its tosyl derivative **122**. Subsequent base treatment furnished the desired epoxide **89.** A similar sequence of reaction as

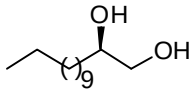
described in scheme 19 was followed which eventually led to the formation of the target molecule (***ent-85***) (Scheme-20). The physical and spectroscopic data of ***ent*-85** were in full agreement with the literature.[24]

Conclusion

In conclusion, the synthesis of *(S)*-5-hexadecanolide (**85**) and *(R)*-5-hexadecanolide (***ent*-85**) has been accomplished in high enantioselectivities in which the stereocentres were generated by means of α-aminoxylation reaction, and cyclization was achieved by ring closing metathesis.

Experimental Section

(*R*)-Tridecane-1,2-diol (88):



To a stirred solution of aldehye **117** (3.00 g, 15.12 mmol) and nitrosobenzene (1.61 g, 15.12 mmol) in DMSO (27 mL) was added L-proline (0.70 g, 6.04 mmol) in one portion at 25 °C. After 1 h, the temperature was lowered to 0 °C, followed by dilution with anhyd. MeOH (30 mL) and careful addition of excess $NaBH_4$ (2.29 g, 60.49 mmol). The reaction was quenched after 10 min by pouring the reaction mixture into a vigorously stirred biphasic solution of Et_2O and aqueous HCl (1 M). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic phases were dried over anhyd Na_2SO_4, concentrated to give crude aminoxy alcohol.

The aminoxy alcohol (4.65 g) was dissolved in methanol (30 mL) and to the solution was added 10% Pd/C (0.050 g) and the reaction mixture was stirred in a hydrogen atmosphere at 60 *psi* for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a celite pad, concentrated, and the crude product was then purified by silica gel chromatography using EtOAc/Pet. ether (40:60) as eluent to give pure diol **88** as white solid (1.52 g, 72%).

Mol. Formula: $C_{13}H_{28}O_2$

m. p. 68 ^{o}C

$[\alpha]_D^{25}$ +9.98 (*c*, 1.00, MeOH)

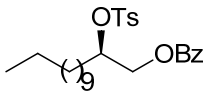
IR ($CHCl_3$, cm^{-1}): ν_{max} 3391, 2957, 2932, 2861, 1466, 1216, 1069, 869.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.80-3.59 (m, 2H), 3.53-3.35 (m, 1H), 2.39-2.13 (m, 2H), 1.52-1.41 (m, 2H), 1.25 (s, 18H), 0.87 (t, *J* = 6.73 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 72.2, 66.7, 33.2, 31.8, 29.6-29.3 (br, several overlapped signals), 25.5, 22.6, 14.1.

MS (ESI): m/z 239.1 $(M+Na)^+$

(*R*)-2-(Tosyloxy)tridecyl benzoate (118) :



To a mixture of diol **88** (1.50 g, 6.93 mmol) in dry CH_2Cl_2 (20 mL), benzoyl chloride (0.80 mL, 6.93 mmol) and triethylamine (0.97 mL, 6.93 mmol) was added and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC, after completion of reaction, the mixture was quenched by adding water. The solution was extracted with CH_2Cl_2 (3 × 20 mL) and then the combined organic phase was washed with water (2 x 20 mL), dried (Na_2SO_4) and concentrated. To this crude mixture (2.22 g) in dry CH_2Cl_2 (25 mL), *p*-toluenesulfonyl chloride (2.66 g, 8.31 mmol) and triethylamine (1.16 mL, 8.31 mmol) was added and reaction was stirred at room temperature under nitrogen. After completion of reaction, the mixture was quenched by adding water. The solution was extracted with CH_2Cl_2 (3 × 20 ml) and then the combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. The column chromatography of crude product using petroleum ether : ethyl acetate (95 : 5) gave the compound **118** (2.76 g, 84%) as a white color solid.

Mol. Formula: $C_{27}H_{38}O_5S$

m. p. 39-40 ^{o}C

$[\alpha]^{D}_{25}$: -9.76 (*c* 1, $CHCl_3$).

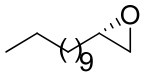
IR ($CHCl_3$): ν_{max} 3436, 2924, 2853, 1715, 1636, 1353, 1269, 1174, 1119, 928 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.99-7.89 (m, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.64-7.52 (m, 1H), 7.50-7.37-3 (m, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 4.92-4.81 (m, 1H), 4.45-4.26 (m, 2H) 2.35 (s, 3H), 1.84-1.65 (m, 1H), 1.25 (brs, 18 H), 0.89 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 21.5, 22.6, 24.6, 29.5-29.1 (br, several overlapped signals), 31.6, 31.8, 65.2, 80.4, 127.6, 128.3, 129.4, 129.7 (br, two overlapped signals), 133.1, 134.1, 144.5, 166.

MS (ESI): m/z 497.23 $(M+Na)^{+}$

(*S*)-2-Undecyloxirane (119):



To a solution of compound **118** (2.00 g, 4.21 mmol) in MeOH at 0°C, K_2CO_3 (1.75 g, 12.64 mmol) was added and the resultant mixture was allowed to stir for 1 h at same temperature. After completion of reaction (as indicated by TLC) the reaction was quenched by addition of ice pieces and methanol was evaporated. The concentrated reaction mixture was then extracted with ethyl acetate (3 × 30 mL), the combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The column chromatography of crude product using petroleum ether : ethyl acetate (98 : 2) gave the epoxide **119** (0.68 g, 81%) as a colorless liquid.

Mol. Formula: $C_{13}H_{26}O$

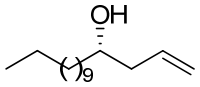
$[\alpha]_{D}^{25}$ -11.5 (*c* 1.1, THF)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3018, 2952, 2929, 2862, 1472, 1466, 1379, 1260, 1022, 916, 828.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.94-2.88 (m, 1H) 2.75 (dd, *J* = 7.4 Hz, 1H), 2.46 (dd, *J* =8.6 Hz, 1H), 1.58-1.44 (m, 2H), 1.26 (brs, 18 H), 0.89 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 52.3, 47.0, 32.4, 31.8, 29.6-29.3 (br, several overlapped signals), 25.9, 22.6, 14.0.

(*S*)-Pentadec-1-en-4-ol (120):



A round bottomed flask was charged with copper (I) iodide (0.12 g, 0.61 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry THF (20 mL) was added. This suspension was cooled to –20 ^oC and vigorously stirred, and vinylmagnesium bromide (1M in THF, 12.1 mL, 12.1 mmol) was injected to it. A solution of epoxide (*S*)- **119** (1.2 g, 6.05 mmol) in THF (10 mL) was added slowly to the above reagent, and the mixture was stirred at –20 ^oC for 5 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was washed with brine (2 x 10 mL), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **120** (1.12 g, 82%) as a colorless syrupy liquid.

Mol. Formula: $C_{15}H_{30}O$

$[\alpha]^D_{25}$: -15.8 (*c* 0.8, $CHCl_3$)

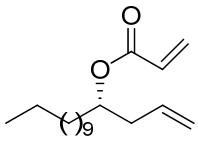
IR ($CHCl_3$, cm^{-1}): ν_{max} 3412, 2932, 2868, 1652, 1584, 1451, 1243, 1187, 1126, 837.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.91-5.73 (m, 1H), 5.18-5.09 (m, 2H), 3.70-3.58 (m, 1H), 2.37-2.28 (m, 1H), 2.25-2.10 (m, 1H), 1.52-1.44 (m, 2H), 1.26 (brs, 18 H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 134.9, 118.0, 70.6, 41.9, 36.7, 31.8, 29.6-29.3 (br, several overlapped signals, 25.6, 22.6, 14.0

Analysis Calcd.: C, 79.58; H, 13.36%; **Found:** C, 79.73; H, 13.39%.

(S)-Pentadec-1-en-4-yl acrylate (121):



Acryloyl chloride (0.20 mL, 2.43 mmol) was added drop wise under argon to a solution of **120** (0.5 g, 2.21 mmol) and triethylamine (0.62 mL, 4.42 mmol) in dry CH_2Cl_2 (5 mL) at 0 ^oC. The mixture was stirred for 5-6 h at room temperature. The resulting mixture was filtered through a pad of celite and poured into water and organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and combined organic layer was washed with brine (2 x 20 mL), dried (Na_2SO_4) and concentrated. Purification of crude product by silica gel column chromatography using pet ether/EtOAc (19:1) as eluent afforded **121** (0.53 g, 86%) as a colorless liquid.

Mol. Formula: $C_{18}H_{32}O_2$

$[\alpha]^D_{25}$: +14.2 (*c* 0.7, $CHCl_3$).

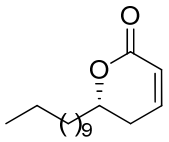
IR ($CHCl_3$, cm^{-1}): ν_{max} 2945, 2921, 2864, 1741, 1719, 1645, 1622, 1554, 1421, 1283, 1249, 1065.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.43-6.34 (dd, *J* = 1.7, 17.1 Hz, 1H), 6.17-6.03 (dd, *J* = 10.1, 17.1 Hz, 1H), 5.82-5.76 (dd, *J* = 1.7, 10.1 Hz, 2H), 5.74-5.66 (m, 1H) 5.11-4.96 (m, 2H), 2.34 (t, *J* = 6.6 Hz, 2H), 1.60-1.53 (m, 2H), 1.25 (brs, 18 H), 0.87 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 166.0, 133.8, 130.4, 129.0, 117.7, 73.7, 38.7, 33.7, 32.0, 29.7- 29.6 (br, several overlapped signals), 25.4, 22.8, 14.2.

Analysis Calcd.: C, 77.09; H, 11.50%, **Found:** C, 77.28; H, 11.54%.

(*S*)-5,6-Dihydro-6-undecylpyran-2-one (ent-92):



Grubb's catalyst (0.146 g, 0.18 mmol) dissolved in CH_2Cl_2 (20 mL) was added dropwise to a refluxing solution of acrylate **121** (0.500 g, 1.78 mmol), $Ti(i\text{-}PrO)_4$ (0.13 g, 0.45 mmol) in dry CH_2Cl_2 (50 mL). Refluxing was continued for 12 h by which time all the starting material was consumed. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using pet ether/EtOAc (4:1) as eluent to afford **ent-92** (0.36 g, 80%) as a solid compound.

Mol. Formula: $C_{16}H_{28}O_2$

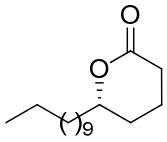
$[\alpha]^{D}_{25}$: -78.2 (*c*, 0.9, THF), lit[3c]. $[\alpha]^{D}_{25}$: –78.7 (*c* 1.0, THF).

IR ($CHCl_3$, cm-1): ν_{max} 3060, 1720, 1256, 1187, 1040, 875.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.90-6.81 (m, 1H), 6.01-5.94 (dt, *J* =2, 8 Hz, 1H), 4.45-4.31 (m, 1H), 2.33-2.26 (m, 2H), 1.69-1.53 (m, 2H), 1.23 (brs, 18 H), 0.85 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 164.6, 145.1, 121.4, 78.1, 34.9, 31.9, 29.6- 29.4 (br, several overlapped signals), 24.8, 22.7, 14.1.

(*S*)-Tetrahydro-6-undecylpyran-2-one (85):



To a solution of **ent-92** (0.2 g, 0.79 mmol) in ethyl acetate (5 mL) was added catalytic amount of 10% Pd/C. The reaction mixture was stirred for 12 h under a balloon of H_2 at room temperature and filtered through a celite pad. The filtrate was concentrated and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give **85** (0.17 g, 84%) as a white solid.

Mol. Formula: $C_{16}H_{30}O_2$

m. p. 37-38 ^oC, lit[37] m. p. 37 ^oC

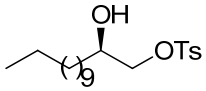
$[\alpha]^D_{25}$: -42.2 (*c*, 1.2, THF), lit[37] $[\alpha]^D_{25}$: –40.2 (*c* 1.5, THF).

IR ($CHCl_3$, cm^{-1}): ν_{max} 1740, 1240, 1050.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.30-4.19 (m, 1H), 2.61-2.32 (m, 2H), 1.93-1.79 (m, 2H), 1.71-1.38 (m, 2H), 1.23 (brs, 18H), 0.85 (t, J = 6.8 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 172.0, 80.5, 35.7, 31.7, 29.5- 29.4 (br, several overlapped signals), 27.6, 24.8, 22.5, 18.0, 14.1.

(*R*)-2-Hydroxytridecyl 4-methylbenzenesulfonate (122):



To a mixture of diol **88** (1.00 g, 4.62 mmol), in dry CH_2Cl_2 (20 mL) dibutyltin oxide (catalytic) was added followed by the addition of p-toluenesulfonyl chloride (0.88 g, 4.62 mmol) and triethylamine (0.64 mL, 4.62 mmol) and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC, after completion of reaction the mixture was quenched by adding water. The solution

was extracted with CH_2Cl_2 (3 × 20 ml) and then the combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. The column chromatography of crude product using petroleum ether : ethyl acetate (92 : 8) gave the compound **122** (1.46 g, 85%) as a solid.

Mol. Formula: $C_{20}H_{34}O_4S$

m. p. 70-71 ^oC

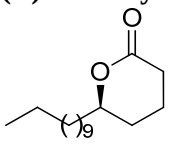
$[\alpha]^D_{25}$: -6.91 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3550, 2922, 2852, 1470, 1348, 1174, 955, 817.

^{1}H NMR (200 MHz, $CDCl_3$): δ), 7.70 (d, *J* = 8.3 Hz, 2H),), 7.36 (d, *J* = 8.3 Hz, 2H), 4.06-3.99 (m, 1H), 3.94-3.79 (m, 2H), 2.45 (s, 3H), 1.48-1.33 (m, 2H), 1.24 (brs, 18H), 0.87 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 145.0, 132.6, 129.9, 127.9, 73.9, 69.4, 32.6, 31.8, 29.5- 29.3 (br, several overlapped signals), 25.1, 22.6, 21.6, 14.0.
MS (ESI): m/z 393.15 $(M+Na)^+$

(*R*)-Tetrahydro-6-undecylpyran-2-one (*ent*-85):



Prepared in a similar way as described for **85.**

m. p. 37-38 ^oC, lit[44] m. p. 37 ^oC

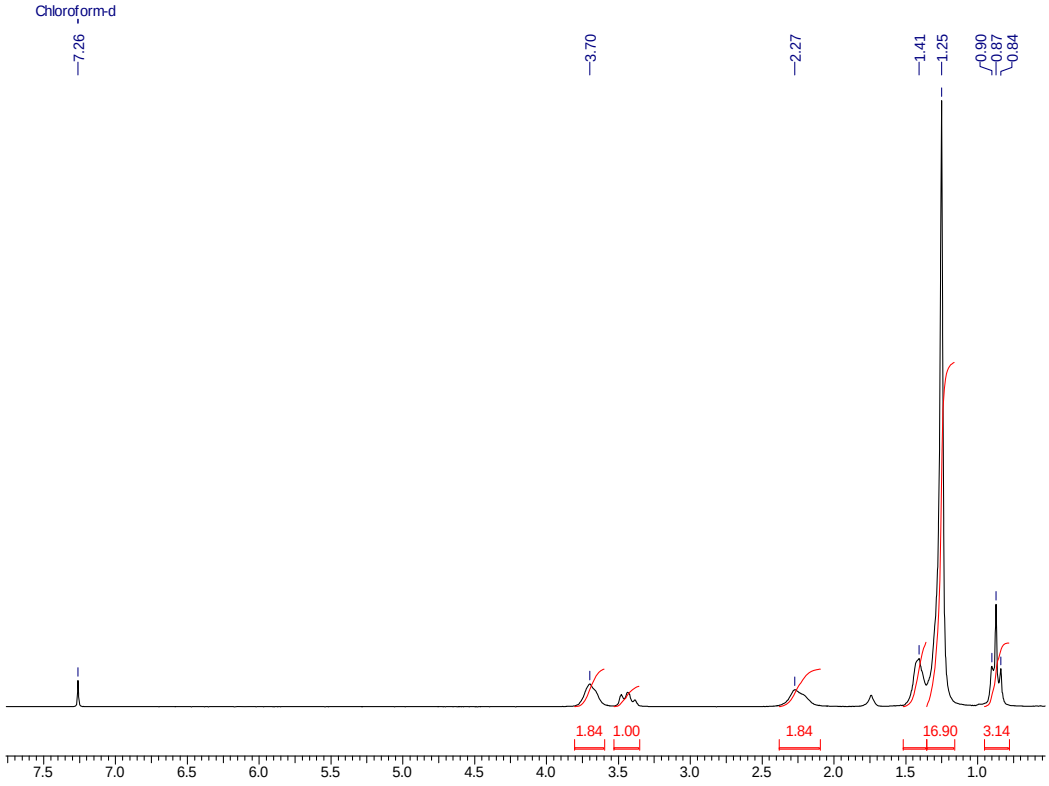
$[\alpha]^D_{25}$: +41.8 (*c*, 1.5, THF), lit[44] $[\alpha]^D_{25}$: +40.2 (*c* 1.7, THF).

Spectra

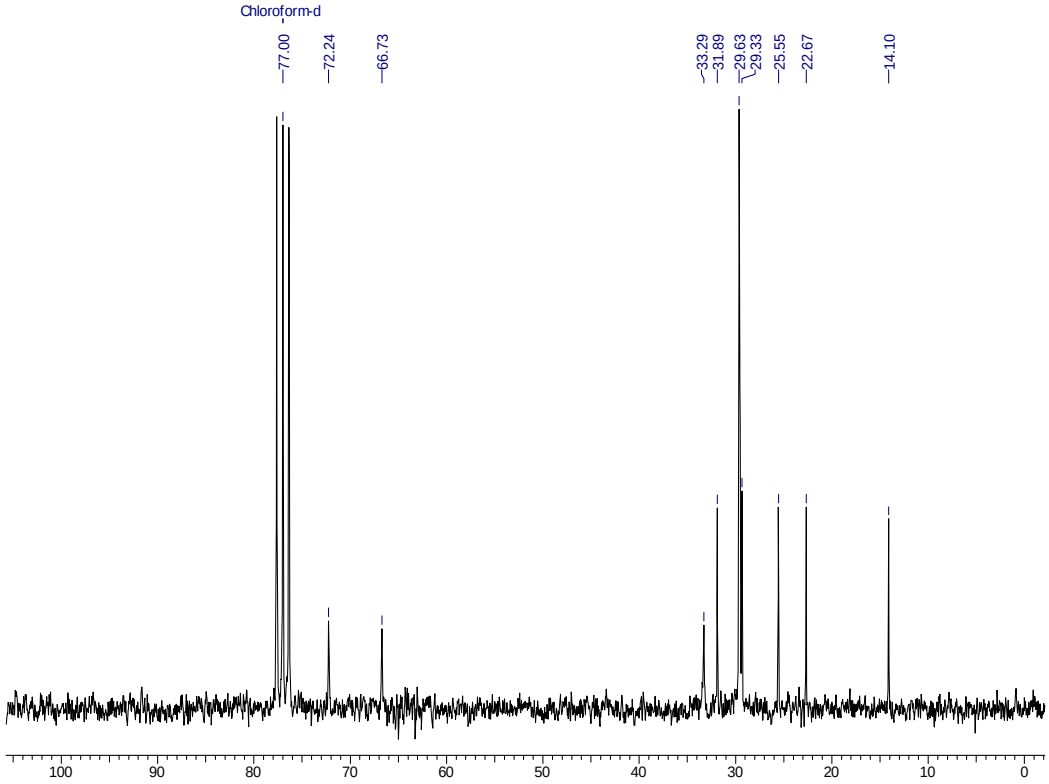
1. ^{1}H and ^{13}C NMR spectra of **88**
2. ^{1}H and ^{13}C NMR spectra of **118**

3. ^{1}H and ^{13}C NMR spectra of **119**
4. ^{1}H and ^{13}C NMR spectra of **120**
5. ^{1}H and ^{13}C NMR spectra of **121**
6. ^{1}H and ^{13}C NMR spectra of ***ent*-92**
7. ^{1}H and ^{13}C NMR spectra of **85**
8. ^{1}H and ^{13}C NMR spectra of **122**

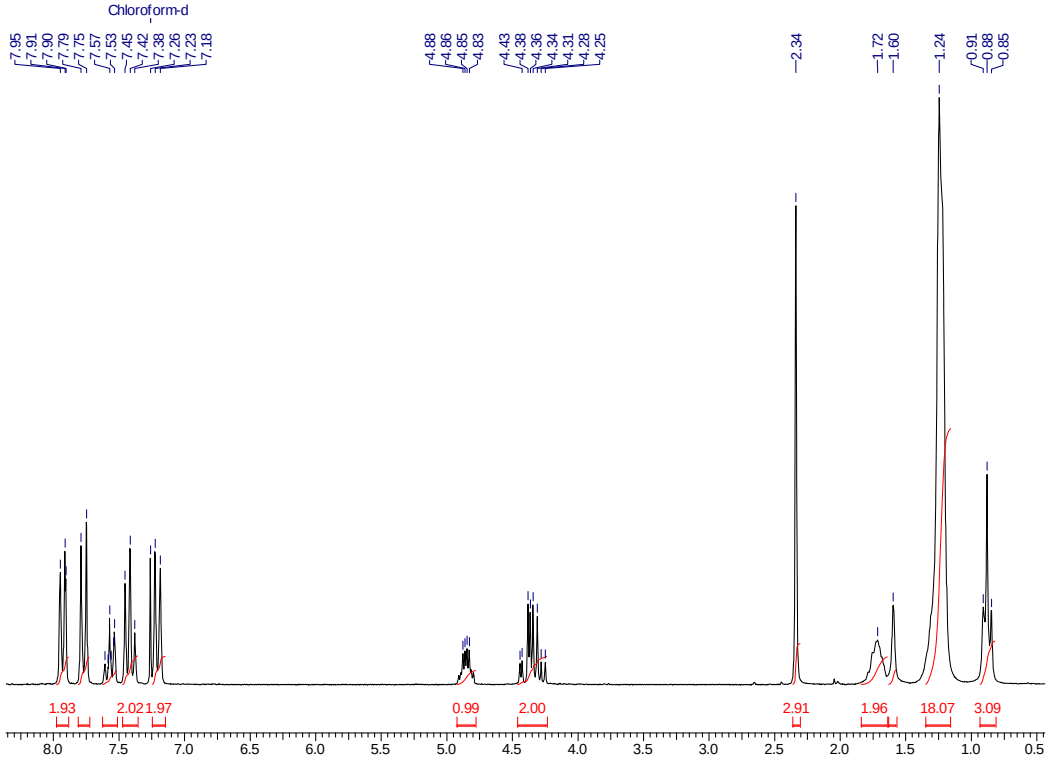
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*R*)-Tridecane-1,2-diol (88)



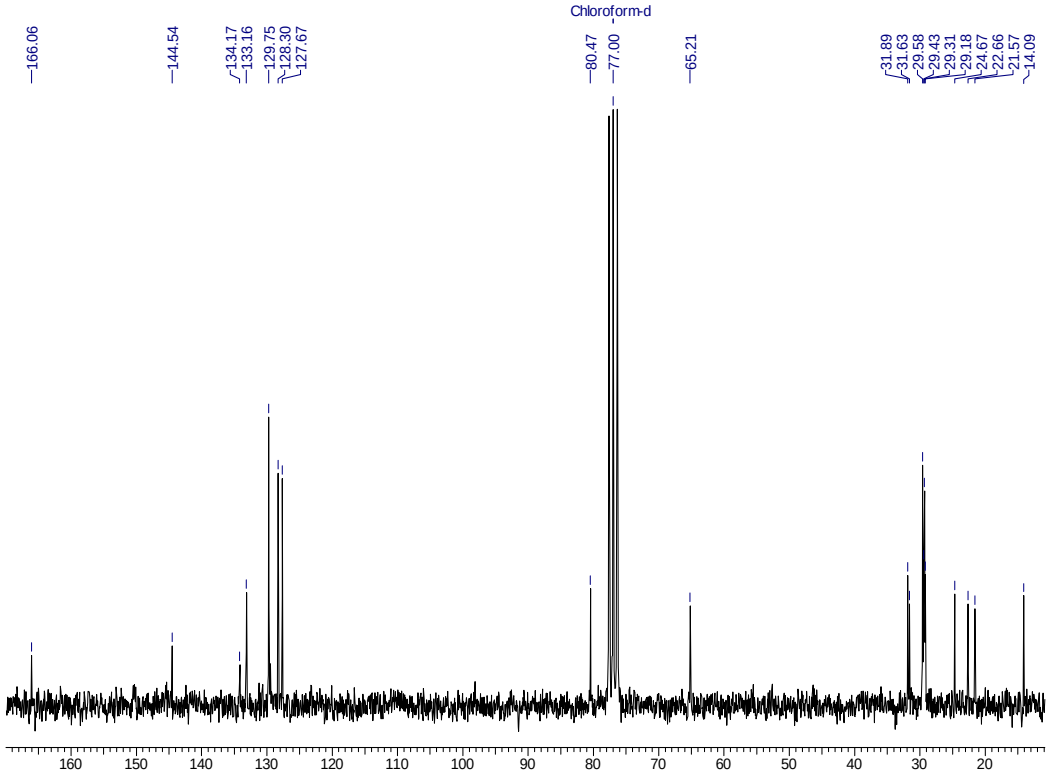
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*R*)-Tridecane-1,2-diol (88)



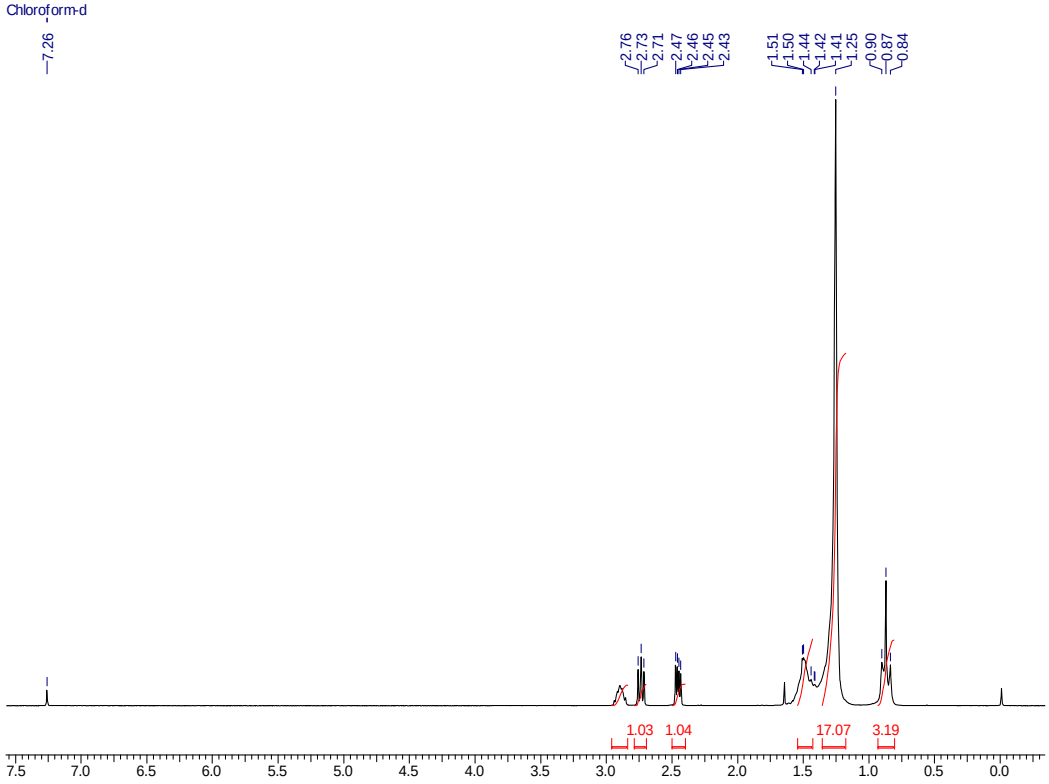
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*R*)-2-(Tosyloxy)tridecyl benzoate (118)



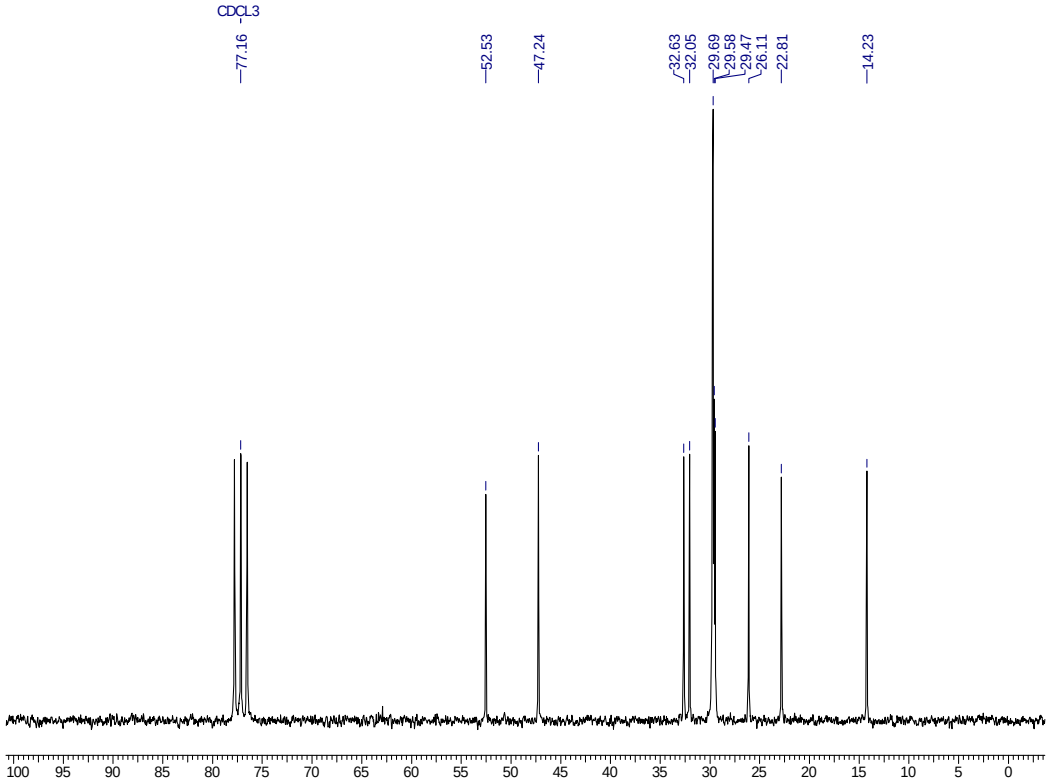
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*R*)-2-(Tosyloxy)tridecyl benzoate (118)



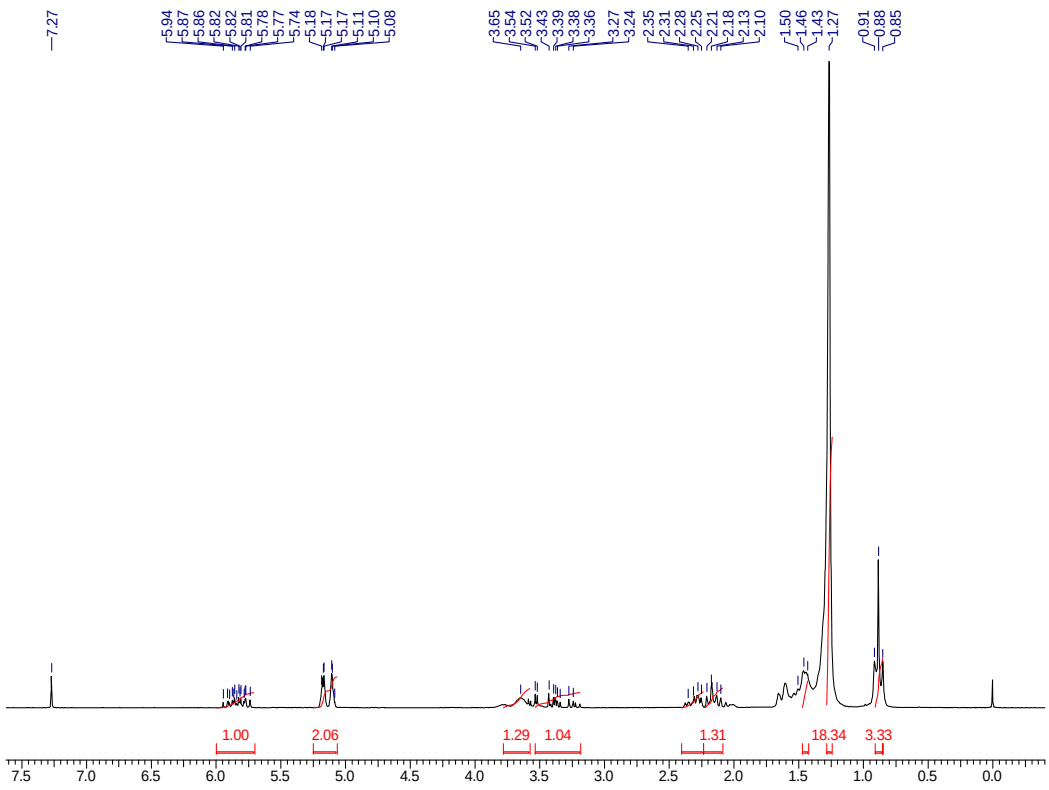
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*S*)-2-Undecyloxirane (119)



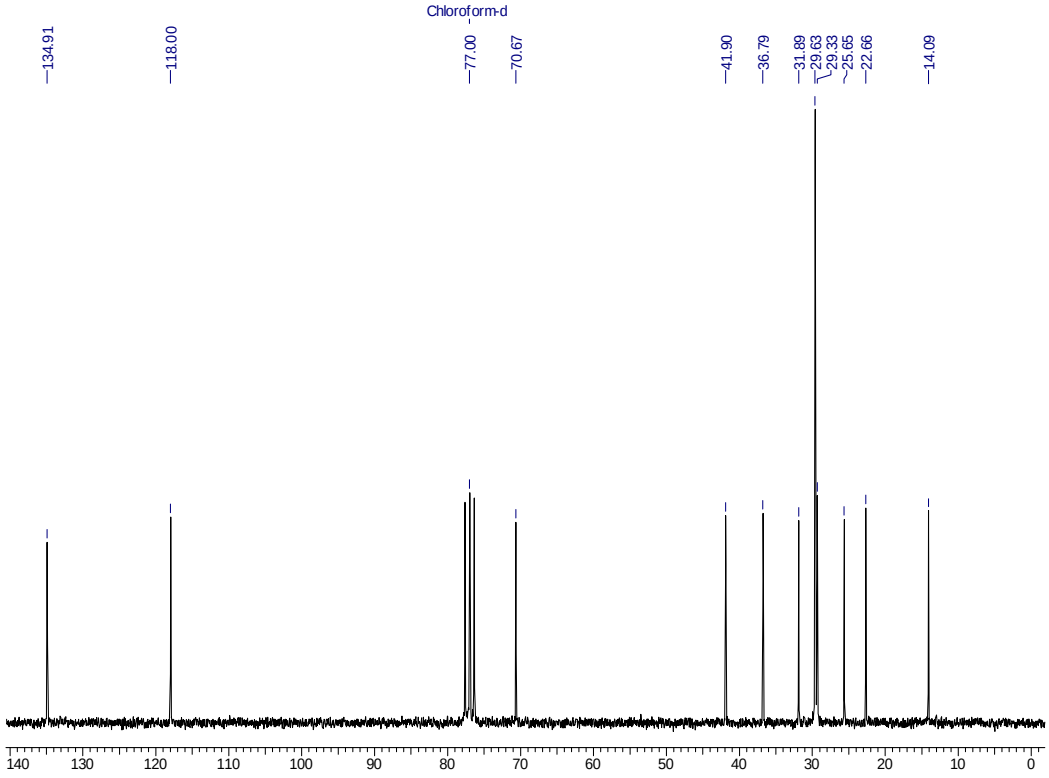
^{1}H NMR ($CDCl_3$, 50 MHz) spectrum of (*S*)-2-Undecyloxirane (119)



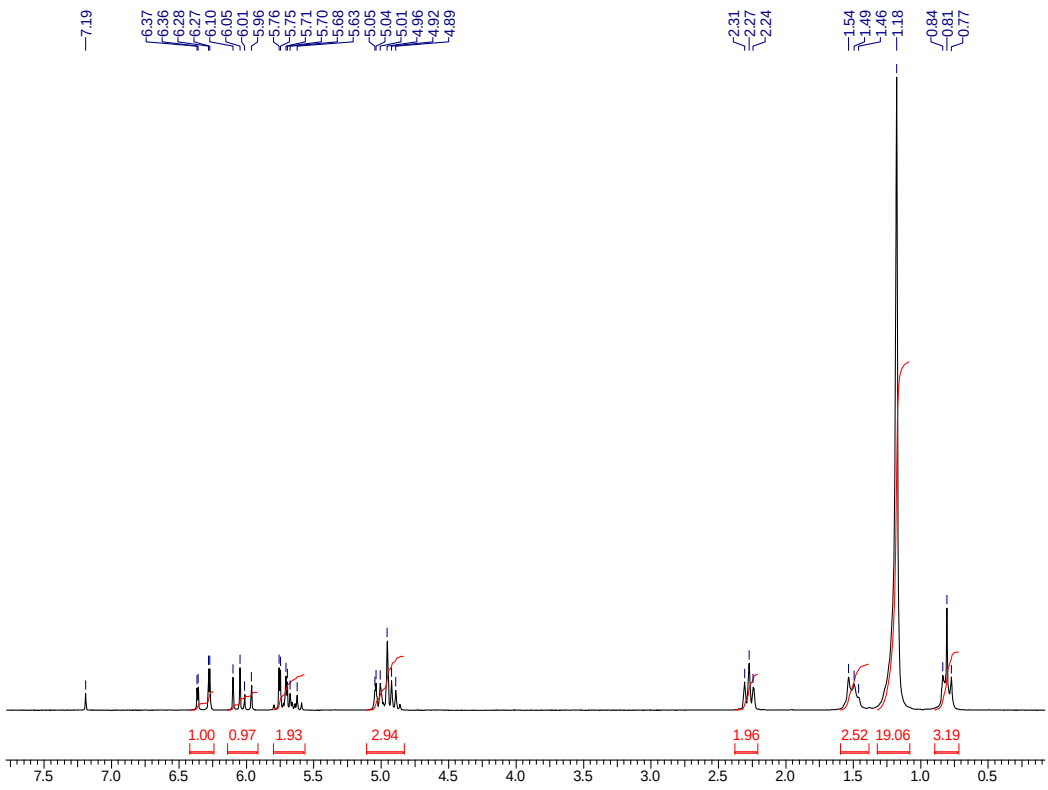
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*S*)-Pentadec-1-en-4-ol (120)



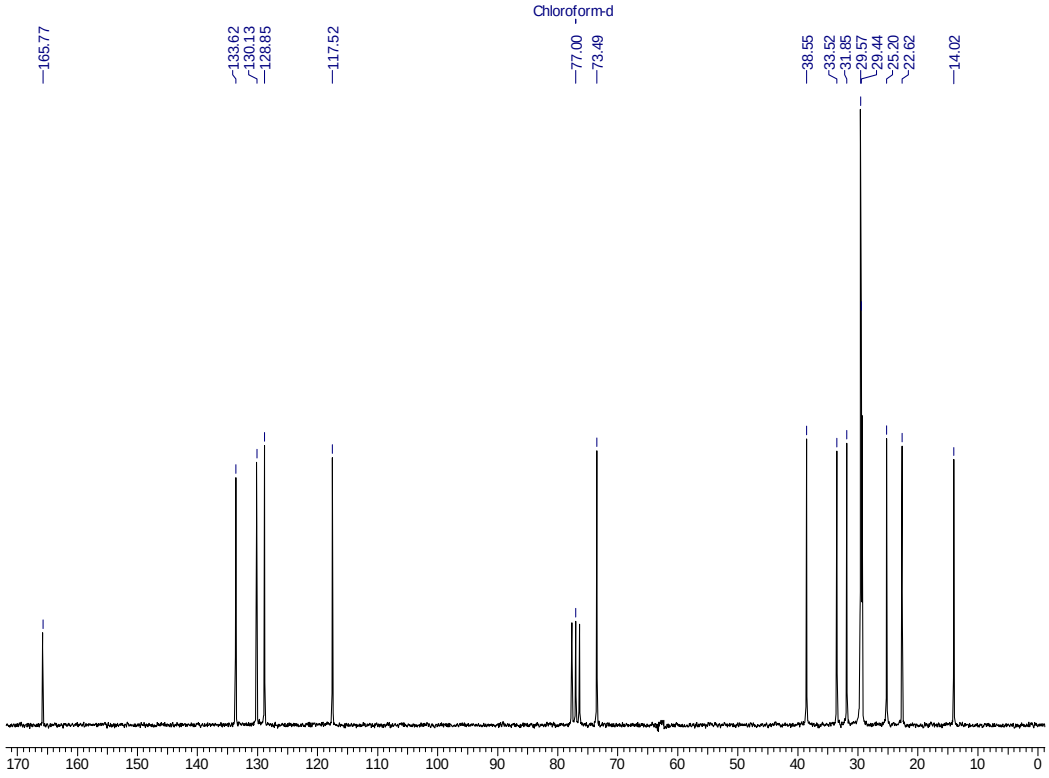
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*S*)-Pentadec-1-en-4-ol (120)



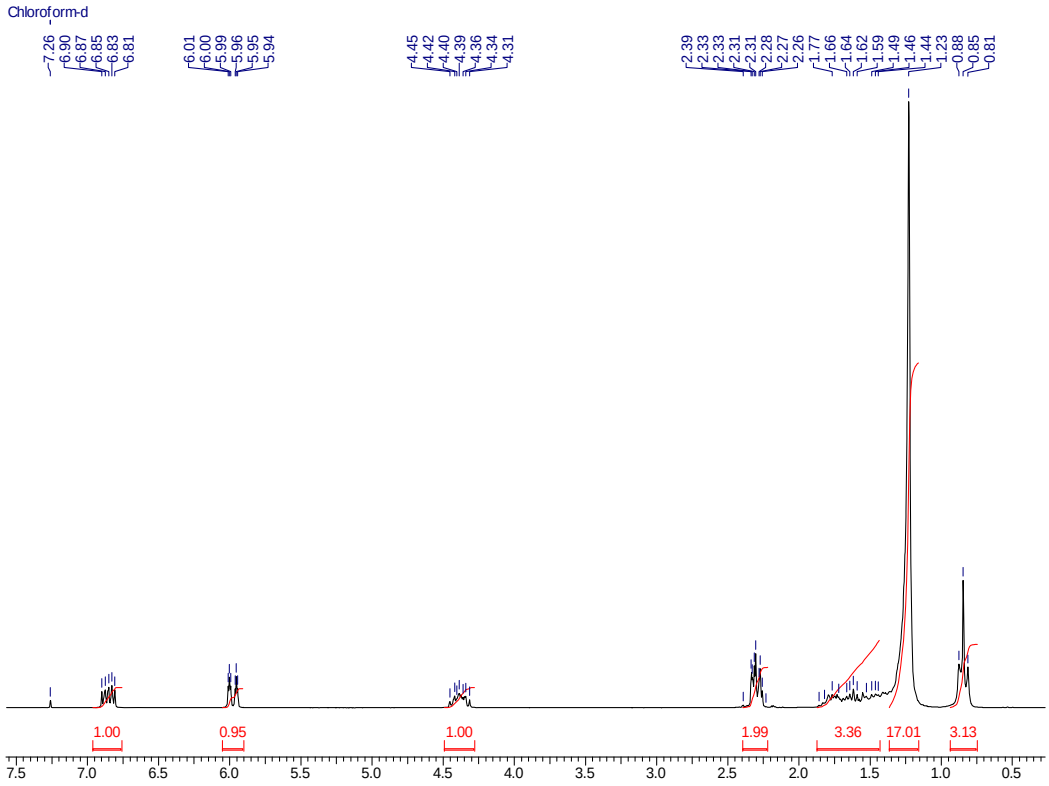
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (S)-Pentadec-1-en-4-yl acrylate (121)



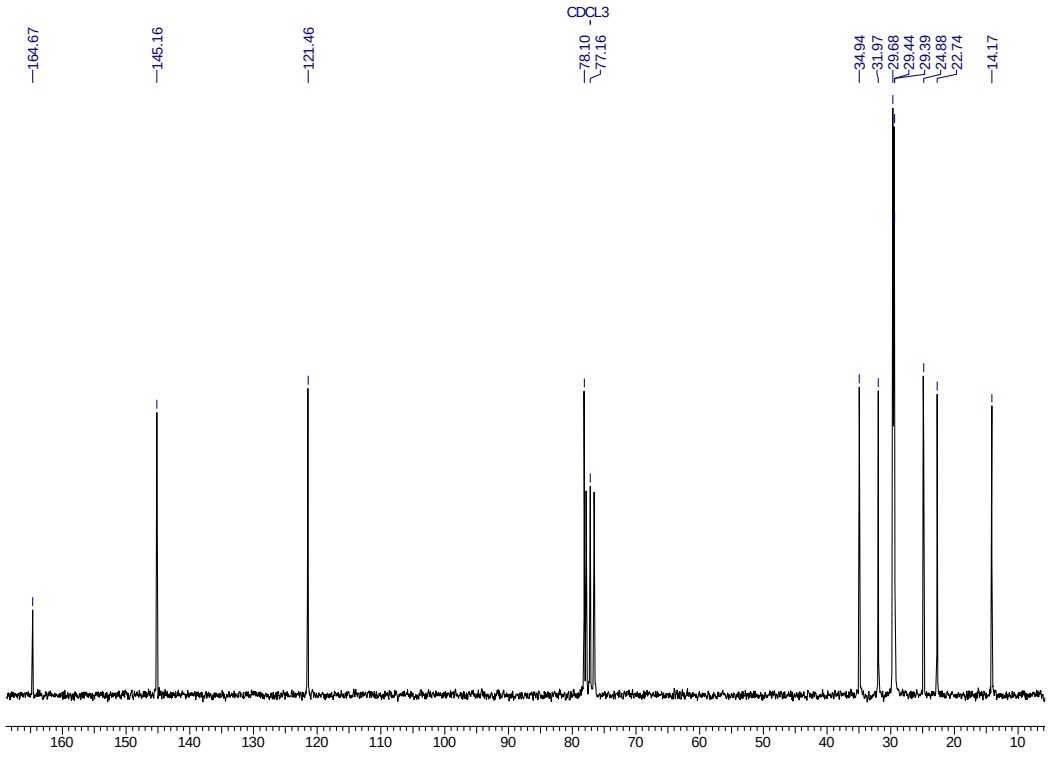
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (S)-Pentadec-1-en-4-yl acrylate (121)



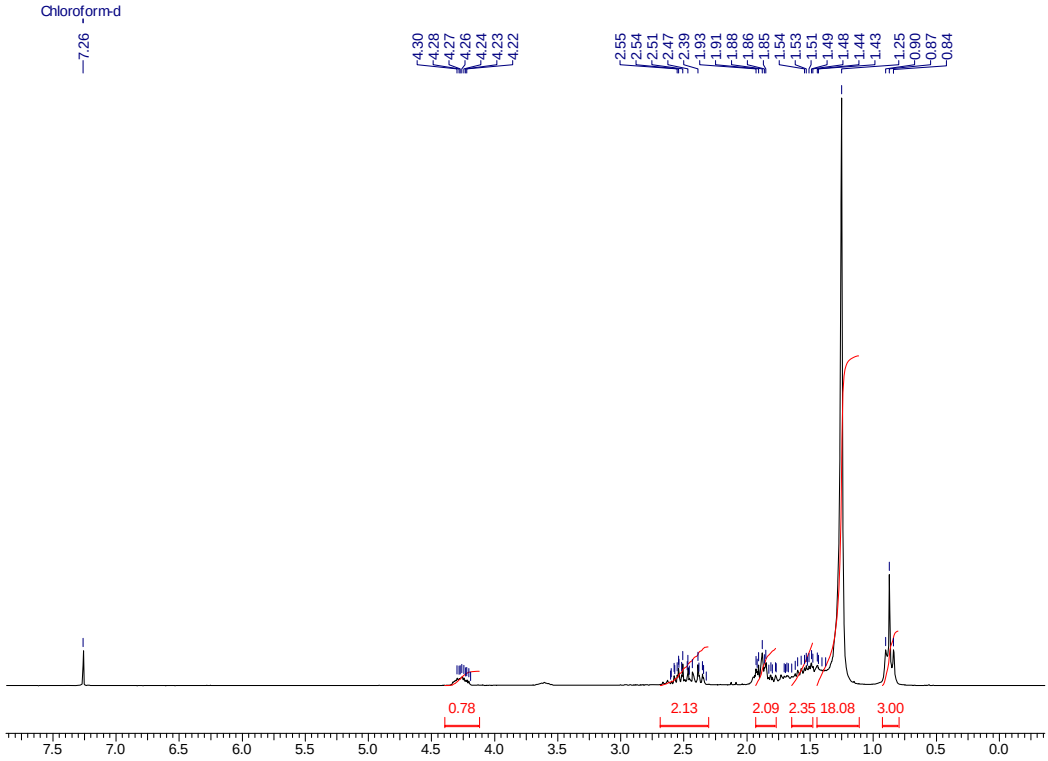
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*S*)-5,6-Dihydro-6-undecylpyran-2-one (*ent*-92)



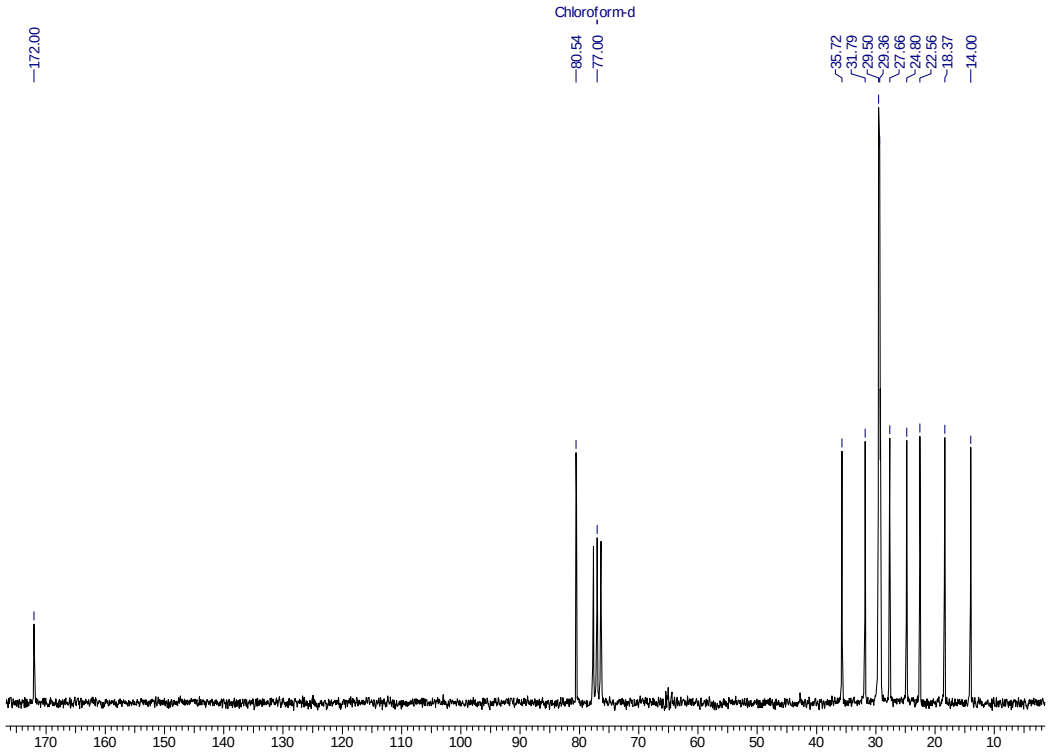
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*S*)-5,6-Dihydro-6-undecylpyran-2-one (*ent*-92)



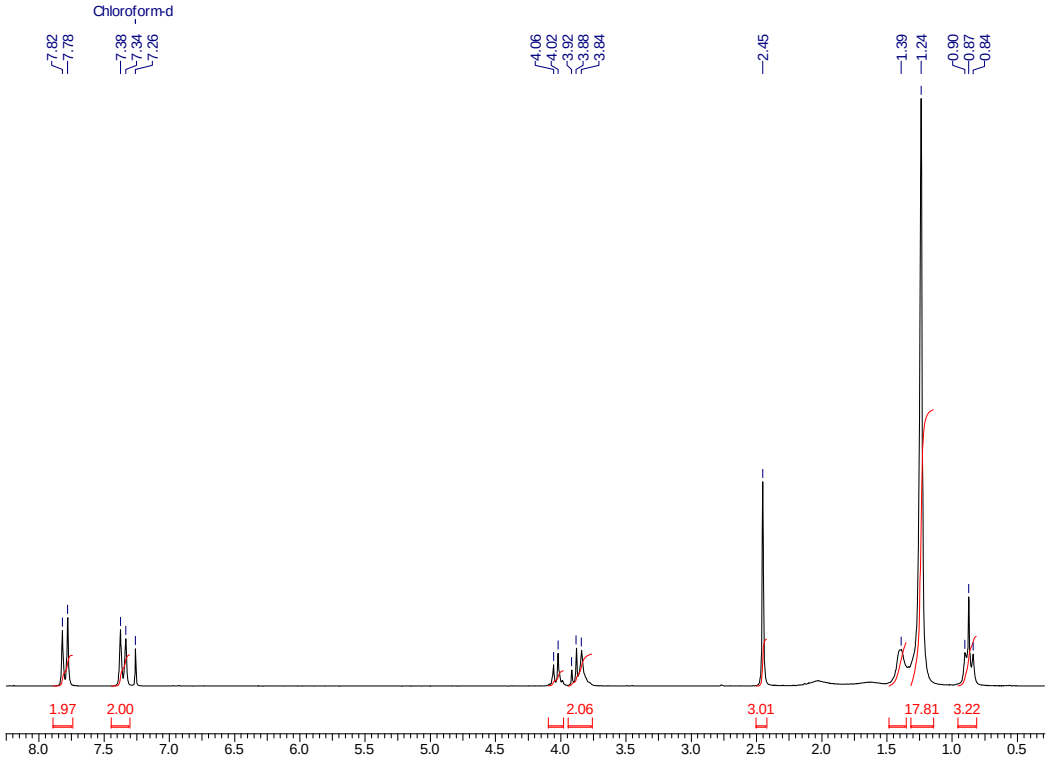
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*S*)-Tetrahydro-6-undecylpyran-2-one (85)



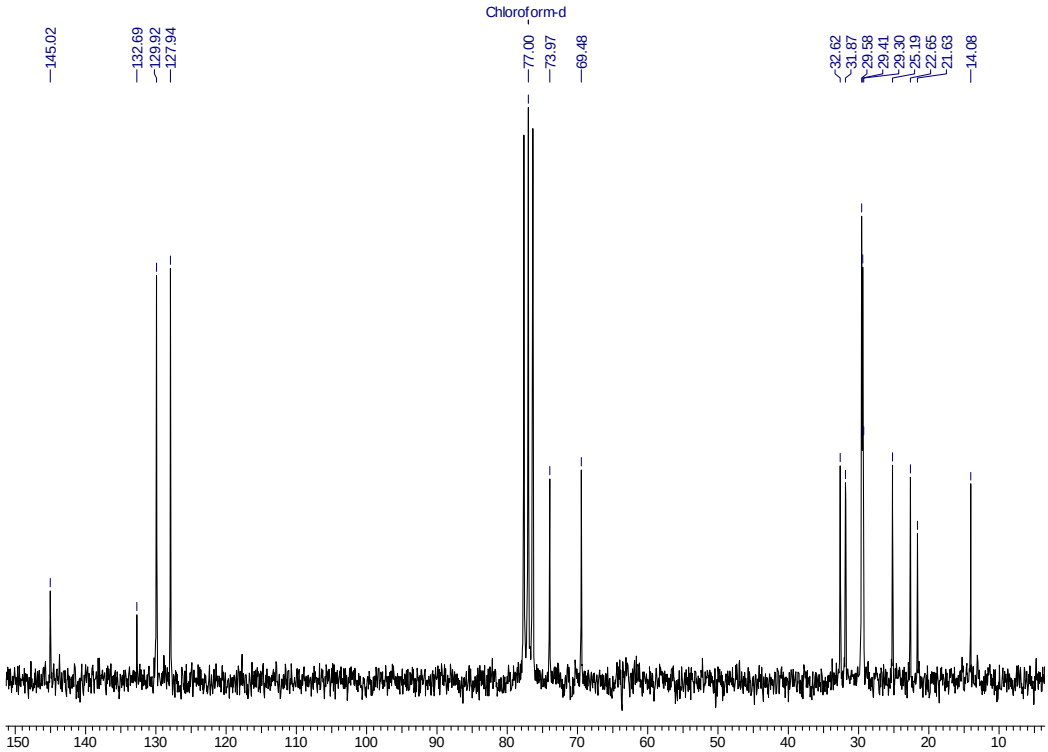
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*S*)-Tetrahydro-6-undecylpyran-2-one (85)



^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*R*)-2-Hydroxytridecyl 4-methylbenzenesulfonate (122)



^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*R*)-2-Hydroxytridecyl 4-methylbenzenesulfonate (122)



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Chapter IV

Introduction:

Heterocyclic compounds are cyclic compounds with at least one hetero (i.e., noncarbon) atom in the ring.[1] The most common hetero-atoms are oxygen, nitrogen and sulfur, although other elements do participate. Heterocyclic compounds are very important class of compound because more than half of all natural products are heterocyclic. The majority of pharmaceuticals are heterocyclic small molecules. Heterocyclic compounds can be usefully classified based on their electronic structure.

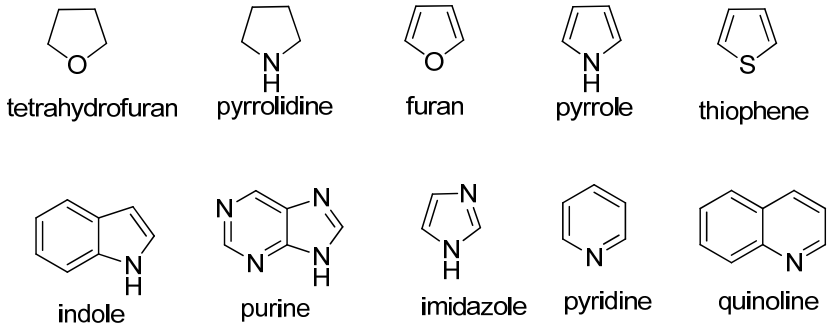


Figure1. Structures of few very common heterocyclic compounds

The saturated heterocycles behave like the acyclic derivatives. Thus, piperidine and tetrahydrofuran are conventional amines and ethers, with modified steric profiles. Therefore, the study of heterocyclic chemistry focuses especially on unsaturated derivatives, and the predominance of work and applications involve unstrained 5- and 6-membered rings. Included are pyridine, thiophene, pyrrole, and furan.

Another large class of heterocycles are fused to benzene rings, which for pyridine, thiophene, pyrrole, and furan are quinoline, benzothiophene, indole, and benzofuran, respectively. Fusion of two benzene rings gives rise to a third large family of compounds, respectively the acridine, dibenzothiophene, carbazole, and dibenzofuran. The unsaturated rings can be classified according to the participation of the heteroatom in the pi-system.

Heterocyclic structures are found in many natural products. Examples of some nitrogen compounds are known as alkaloids because of their basic properties. Some other examples are displayed in the figure 2. Camptothecin[2] is a quinoline alkaloid

which inhibits the DNA enzyme topoisomerase I. Reserpine is an indole alkaloid, which has been used for the control of high blood pressure and the treatment of psychotic behavior. Ajmaline[3] and strychnine[4] are also indole alkaloids, the former being an antiarrhythmic agent and latter an extremely toxic pesticide. Flinderoles[5] B and C were isolated through an initial antimalarial natural product extract screening program. All of the flinderoles have shown impressive selective antimalarial activity against the P. *falciparum parasite.* Acortatarin[6,7] A contains unique pyrrole-fused morpholine spiroketal structure. It was isolated from bee-collected Brassica campestris (rapeseed) pollen. Acortatarin A has shown antitumor and antioxidant properties. Hirsutine[8] an indole alkaloids isolated from the Uncaria species, have been demonstrated to exert central depressive and vasodilatory effects as well as protective effects (through inhibition of Ca^{+2} influx) against neuronal death in cultured rat cerebellar granule cells. In addition, hirsutine displays antihypertensive, negative chronotropic, and antiarrhythmic activity.

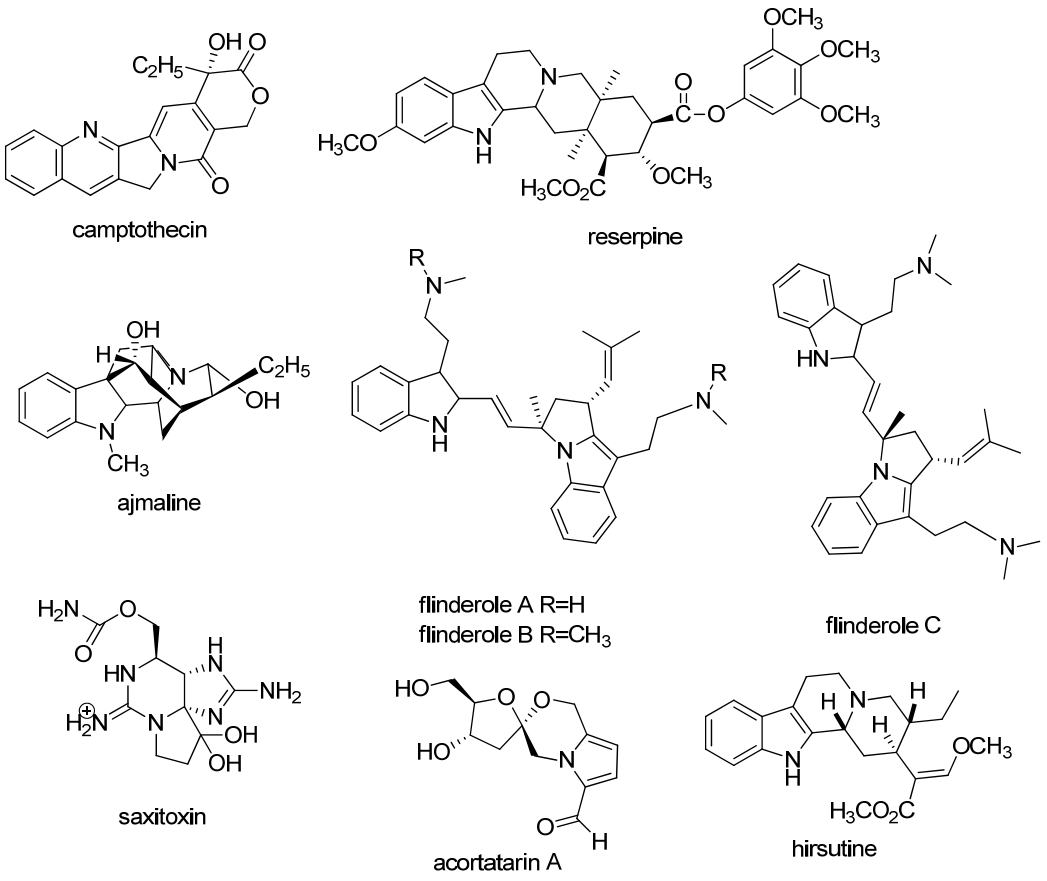


Figure2. Some examples of biologically important heterocyclic natural product

Cancers are the leading cause of death among humans[9]. Current chemotherapeutics and radiation therapies are targeted towards inducing DNA damage that indiscriminately kills cells, with the hope that cancerous cells will die more rapidly than healthy cells. Unfortunately, these treatments are often not effective and are associated with severe side effects resulting in prolonged suffering for the patient. Microtubules are an array of fibrous cytoskeletal proteins that are essential for the actual separation and division of cellular components and distribution of DNA during mitosis. Interruption of this process can halt cell division without any inherent cytotoxic effects. Several tubulin-binding drugs such as colchinines and taxols have shown promise as potential anti-cancer drugs. However, problems with inherent toxicity, low solubility of the drug, availability in quantity, and multi-drug resistance still exist. As most of the lead compounds originated from naturally occurring sources, an alternative approach may involve screening of small synthetic molecules for tubulin-binding compounds. Myoseverin, a recently discovered small-molecule tubulin-binder has demonstrated a promising ability to surmount the major problems associated with currently available tubulin-binding drugs. Nevertheless problems with low-level activity and activation of biochemical pathways involved with wound healing remain unresolved. These findings indicate that high-throughput screening of small-molecule libraries is an attractive approach to identifying novel anti-cancer therapeutics.

Triazines:

The chemistry of heterocyclic compound continues to be an explored field in the organic or pharmaceutical chemistry. The importance of triazine derivatives lies in the field that these have occupied a unique position in heterocyclic chemistry, due to its various biological activities.

Triazines, which are structurally similar to purines or pyrimidines, are attractive therapeutics because of their small molecular size and highly flexible scaffold. Furthermore, the starting materials and all the required building blocks are relatively inexpensive. For these reasons, triazine has elicited significant interest as an ideal scaffold. The present inventions describe the creation of a triazine library using a proprietary synthetic pathway that allows for a more diverse library of small molecules.

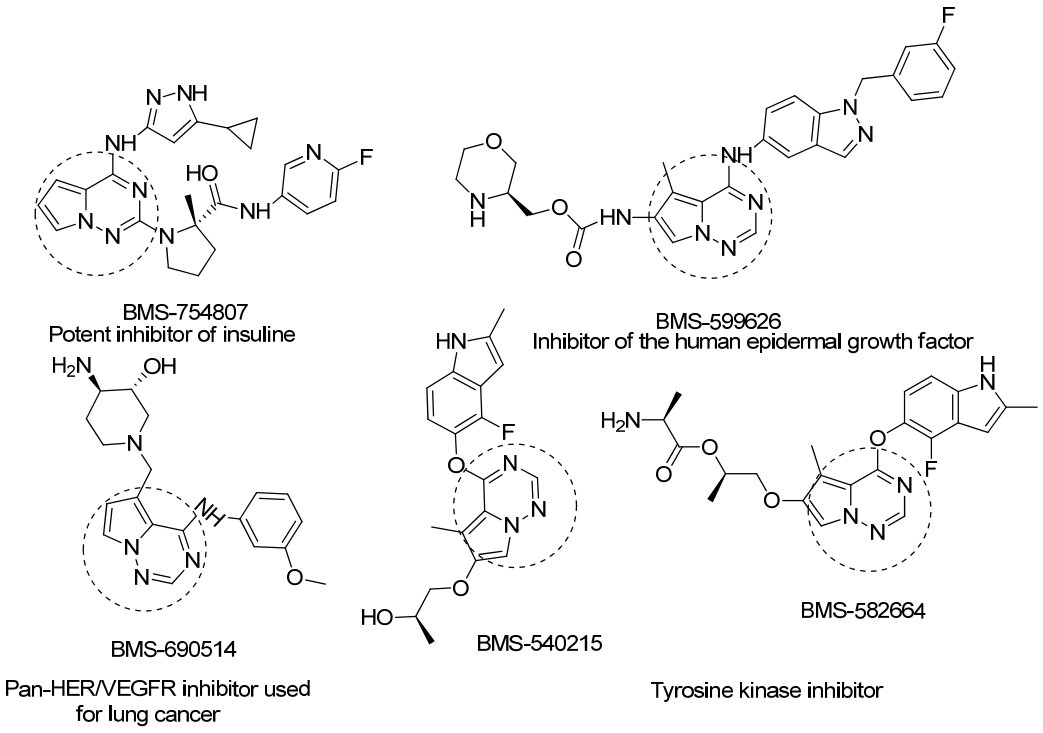
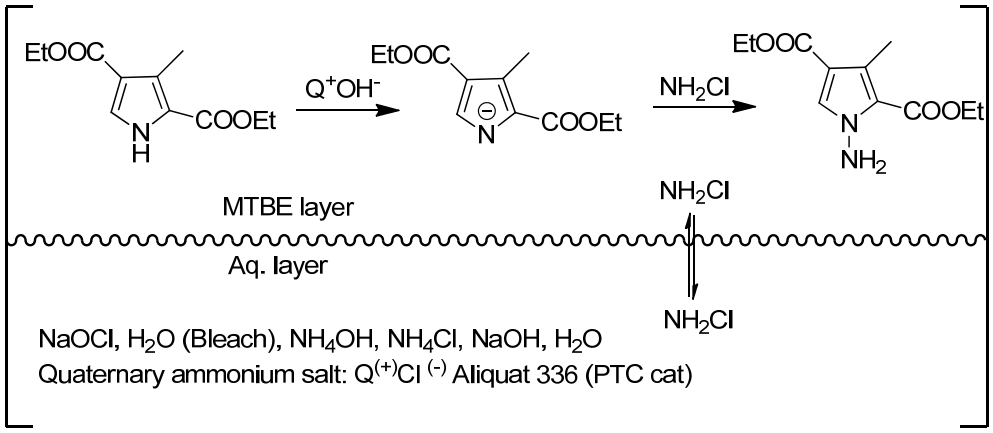


Figure 3. Some examples of biologically important triazine containing synthetic heterocyclic compounds

An efficient electrophilic *N*-amination[10]

N-Amination of pyrroles and indoles utilizing chloramine (NH_2Cl) was recently reported by researchers at Bristol-Myers Squibb. This *N*-amination protocol involves initial generation of NH_2Cl from aqueous NH_4OH, NH_4Cl and bleach, followed by extraction of NH_2Cl with methyl tert-butyl ether (MTBE) from the aqueous mixture. The chloramine solution is dried with anhydrous $CaCl_2$ and then reacted in a separate vessel with the pyrrole anion generated from NaH in DMF, to produce the corresponding N-aminated pyrroles. Bhattacharya *et al.* improved this method for greater safety, efficiency and operational simplicity.

In the optimal procedure, chloramine is generated in the aqueous layer through oxidation of ammonia by NaOCl. At the same time, the substrate is deprotonated in the organic phase with the aid of a small amount of Aliquat-336 (methyltrioctylammonium chloride) and promptly reacts with the small portion of chloramines present in the organic layer, affording the desired N– NH_2 derivative in high yield. An excess of base (aq NaOH) is necessary to efficiently achieve the



Scheme 1. One-pot, phase transfer N-amination of pyrrole with chloramine.

deprotonation. After reaction completion, the organic layer is separated and can be utilized directly in the next step without further purification.

Experimental Procedure:

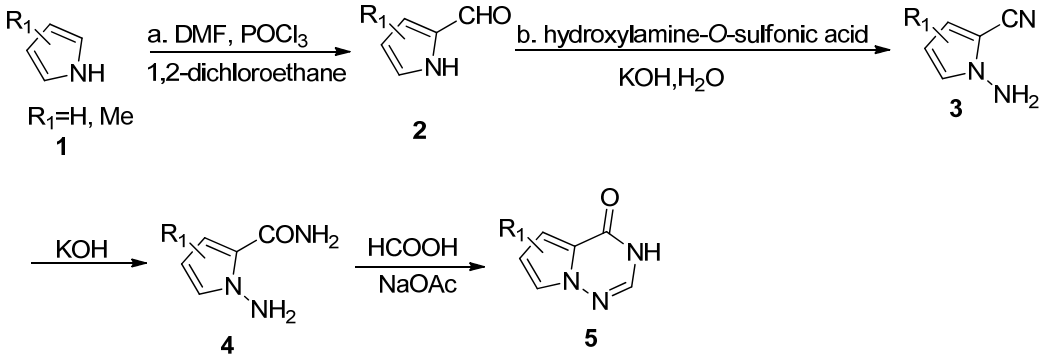
A typical experimental procedure is as follows: aqueous sodium hypochlorite (58.76 ml of ca. 9% solution) was added over a period of 20 min, at room temperature, to a vigorously stirred mixture of 3-methyl-1*H*-pyrrole-2,4-dicarboxylic acid diethyl ester (2 g, 8.9 mmol) in MTBE (24 ml, ammonium chloride (2.9 g, 53.2 mmol), Aliquat-336 (0.1 g), aqueous NaOH (25.6 ml of 28.4% solution) and aqueous NH_4OH (8.28 ml of 28% solution). The resulting reaction mixture was stirred at room temperature for an additional 2–4 h at the end of which time the complete disappearance of starting material and formation of product is observed by capillary GC and HPLC. The upper product-rich organic layer was separated from the spent aqueous layer and washed with aqueous $Na_2S_2O_3$ (40 ml). The organic layer was then dried over anhydrous Na_2SO4 and evaporated in vacuo to produce 2.01 g of 1-amino-3-methyl-1*H*-pyrrole-2,4-dicarboxylic acid diethyl ester (94% yield).

Some synthetic efforts have been reported in literature for the synthesis of [1,2,4]triazino derivatives. At this point it would be relevant to summarize some of the synthetic endeavors reported before or concurrent to our work.

Klein *et al.*[11]

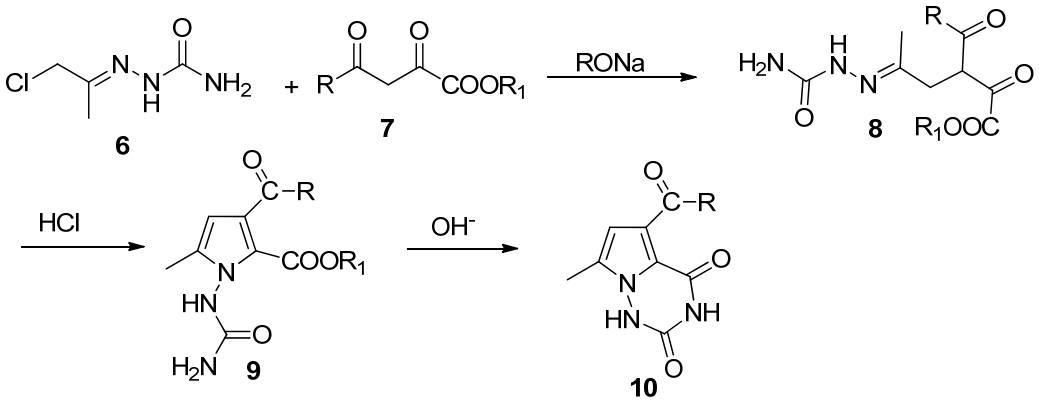
The methyl-substituted 2-formylpyrroles **2** were prepared from the pyrroles **1** by reaction with phosphorus oxychloride and DMF. An isomeric mixture of 2-formyl-3-

methylpyrrole and 2-formyl-4-methylpyrrole in a 4:1 ratio was produced from the formylation of 3-methylpyrrole. Amination of this mixture with hydroxylamine *O*-sulfonic acid produced both *N*-amination as well as transformation of the aldehyde to the nitrile **3**. Hydrolysis of the pure 1-amino-2-cyano-3-methylpyrrole was achieved with KOH in aqueous ethanol at reflux to form compound **4**, heating of compound **4** at 65°C in a mixture of formic acid and sodium acetate led directly to the cyclized product **5.**



Scheme 2. Synthesis of [1,2,4]triazino-pyrrole-4(3*H*)-one.

Sprio *et al.*[12]



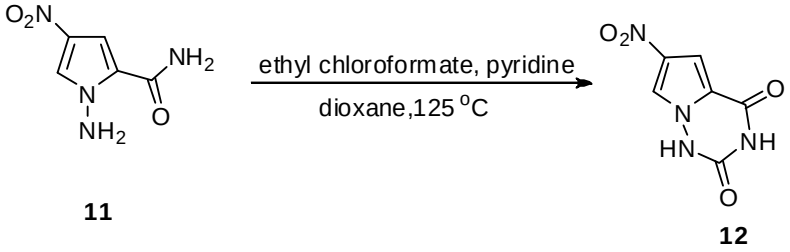
Scheme 3. Synthesis of [1,2,4]triazino-pyrrole-2,4(1*H*,3*H*)-dione

Sprio *et al.* synthesized [1,2,4]triazino derivatives in 1979 using semicarbazones, semicarbazone **8** which was synthesized by the action of chloroacetone semicarbazone **6** on the sodium salts of compound **7** in dry methanol or ethanol. The cyclodehydration of **8** was carried out using ethanol or methanol saturated with

hydrochloric acid as condensing agent. Further condensation of 1-ureidopyrrole **9** in base afforded the bicyclic compound **10.**

Liu *et al.*[13]

In search of novel lead molecule based on the N-(1*H*-pyrazol-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine scaffold, Liu *et al.* synthesized [1,2,4]triazino derivative starting from the nitro amino pyrrole.



11 **12**

Scheme 4. Synthesis of [1,2,4]triazino-pyrrole-2,4(1*H*,3*H*)-dione using ethyl formate

In the present work, we considered developing protocol for an eco-friendly, one-pot synthesis of novel class of kinase inhibitors, such as [1,2,4]triazino[1,6-a]indol-4(3H)-one, [1,2,4]triazino[1,6-a]pyrrole-4(3H)-one, [1,2,4]triazino[1,6-a]indole-2,4(1*H*,3H)-dione and [1,2,4]triazino[1,6-a]pyrrole-2,4(1*H*,3*H*)-dione and their analogs with a view to screen them against protein kinases. The details of our efforts in this direction are discussed in the following Chapter.

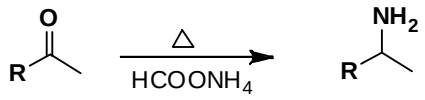
Chapter IV, Section A

Novel application of Leuckart reaction for the synthesis of [1,2,4]Triazino[1,6-a]indol-4(3*H*)-one and pyrrolo[2,1-*f*][1,2,4]Triazine-4(3*H*)-one

Present work

Objective

The Leuckart reaction[14] is the chemical reaction of ammonium salts of formic acid with aldehydes (or ketones) to form amines by reductive amination. The reaction is named after Rudolf Leuckart.



Scheme 5. Example of Leukart reaction

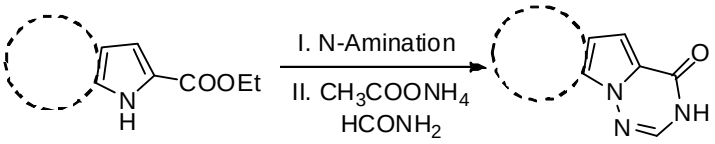
The Leuckart reaction is a method of reductive amination that uses a carbonyl compound and formamide. Formic acid acts as the reducing agent in the reaction. The amine (ammonia) acts as a base[15] and adds to the carbonyl group to form an α-amino alcohol. This complex dehydrates to form an iminium ion. Formic acid then reduces the iminium into an amine.

Some notable examples of its use include synthesis of tetrahydro-1,4 benzodiazepin-5-ones, a molecule that is part of the benzodiazepine family. Many compounds in this family of molecules are central nervous system suppressants and are associated with therapeutic uses and a variety of medications, such as antibiotics, antiulcer, and anti-HIV agents.

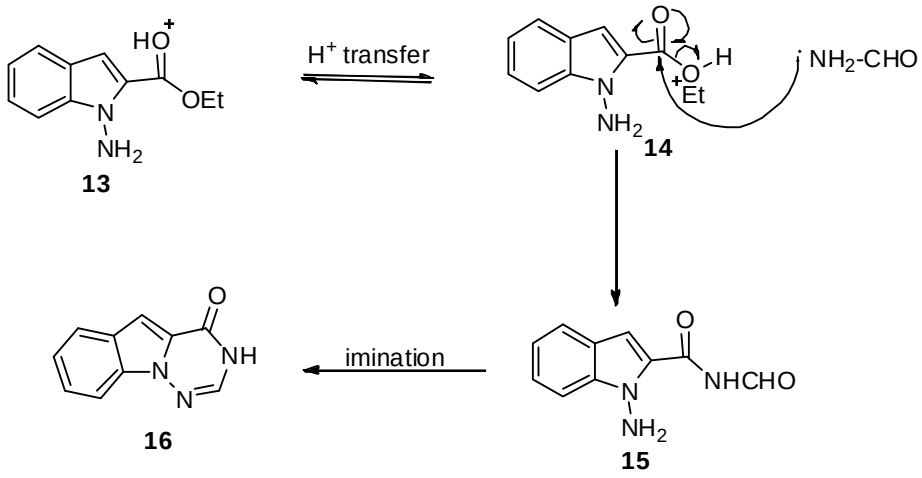
The Leuckart reaction has been used for the synthesis of methylamphetamine starting with phenylacetone using methylamine and formic acid or using *N*-methylformamide it has also been applied to synthesis of riboflavin.

The pyrrolo [2,1-*f*][1,2,4]triazine nucleus[16] was identified as a novel kinase inhibitor[17] template which effectively mimics the well-known quinazoline kinase inhibitor scaffold. In the development of synthetic program directed towards the preparation of various fused nitrogen ring system derivatives, a number of pyrrole and indole triazines were synthesized. A very short and efficient route for the synthesis of pyrrole triazinones and indole triazinones has been accomplished here using Leuckart reaction conditions.

N-Amination of various commercially available pyrrole-2-carboxylates and indole-2-carboxylates is carried out using mono chloramine. N-Amino pyrrole-2-carboxylate and N-amino-indole-2-carboxylates were overnight heated at 140^{o}C under nitrogen atmosphere in dimethylformamide and ammonium formate to give various pyrrole and indole triazines.



Proposed mechanism for cyclization using Leuckart condition: Scheme 5

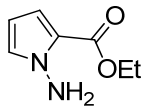
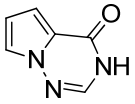
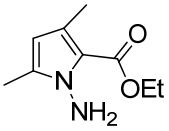
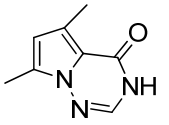
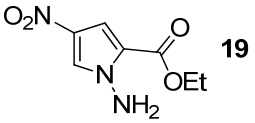
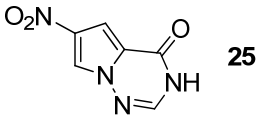
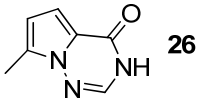
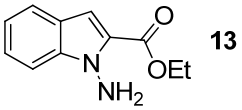
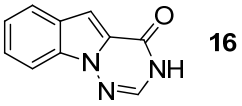
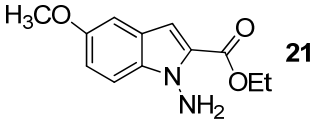
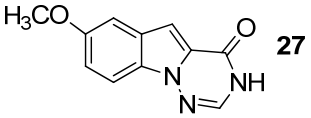
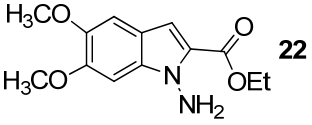
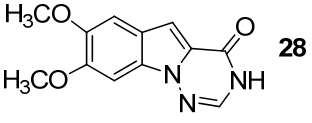


Results and Discussion:

N-Amination of indole-2-caroboxylate, pyrrole-2-carboxylate and their derivatives has been achieved using chloramine, chloramine is generated in the aqueous layer through oxidation of ammonia by NaOCl. At the same time, the substrate is deprotonated in the organic phase (MTBE) with the addition of a small amount of Aliquat-336 (methyltrioctylammonium chloride) and promptly reacts with the small portion of chloramines present in the organic layer, affording the desired N–NH_2 derivative in high yields. The ^{1}H NMR spectrum of **13** clearly indicated broad singlet for –NH_2 at δ 4.68. Derivatives of N-amino pyrrole-2-carboxylate and N-amino-

indole-2-carboxylates were overnight heated at 140°C under nitrogen atmosphere in formamide and ammonium acetate to give cyclized pyrrole and indole triazines.

Table 1: One-pot synthesis of [1,2,4]triazino[1,6-a]indol-4(3H)-one and [1,2,4]triazino[1,6-a]pyrrole-4(3H)-one compounds:

Entry No.	N-Amination precursors	Products	Yields
1.	 **17**	 **23**	83%
2.	 **18**	 **24**	84%
3.	 **19**	 **25**	78%
4.	 **20**	 **26**	81%
5.	 **13**	 **16**	85%
6.	 **21**	 **27**	73%
7.	 **22**	 **28**	67%

The ^{1}H NMR spectrum of compound **24** showed the presence of olefinic proton at δ 7.52 (s, 1H) and in ^{13}C NMR spectrum the presence of amide carbonyl was observed at 155.9 ppm. confirming the formation of [1,2,4]triazino[1,6-a]indol-4(3H)-one and [1,2,4]triazino[1,6-a]pyrrole-4(3*H*)-one. Further in order to confirm reaction product **24**, recrystallisation was done by slow evaporation of the solution mixture of ethyl acetate and hexane to give the clear crystalline solid, which was analysed for single X-ray crystallography. The ORTEP diagram (**Fig. 4**) clearly established the formation of triazines.

X-ray Crystal Structure Analysis For compound 24

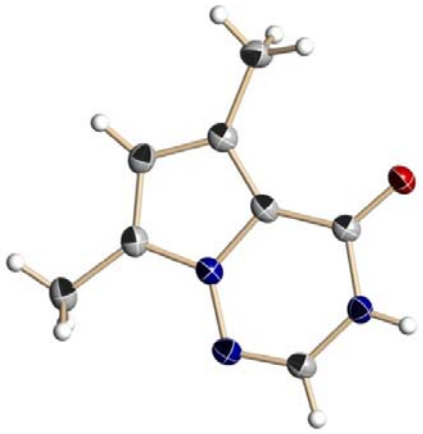
Crystal Data: Single crystals of the compound were grown by slow evaporation of the solution mixture of ethyl acetate and hexane. X-ray intensity data measurements of compound **24** was carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK_{α}= 0.71073Å) radiation at 100 (2) K. The X-ray generator was operated at 50 kV and 30 mA. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 15 sec keeping the sample-to-detector distance fixed at 50 mm. The X-ray data collection was monitored by APEX2 program (Bruker, 2006).[18] The data was corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs integrated in APEX2 program package (Bruker, 2006). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2.[19] All H-atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms except the methyl H-atoms bound to carbon C8 were located in the difference Fourier map and were refined isotropically.

X-ray crystal data of compound 24:

Crystal data of **24.** $C_8H_9N_3O$, M = 163.18, colorless plate, 0.66 x 0.18 x 0.16 mm^3, monoclinic, space group $P2_1/c$, a = 10.9374(8), b = 4.2779(4), c = 17.7778(13) Å, β = 106.880(5)°, V = 795.97(11) Å^3, Z = 4, T = 100(2) K, $2\theta_{max}$ = 52.00°, D_{calc} (g cm^{-3}) = 1.362, $F(000)$ =344, μ (mm^{-1}) = 0.095, 7429 reflections collected, 1570 unique reflections (R_{int}=0.0467), 1296 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.940, T_{max} = 0.985, 122 refined parameters, S = 1.108,

*R*1=0.0424, *wR*2=0.1102 (all data *R* = 0.0539, *wR*2 = 0.1199), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.22, $\Delta\rho_{min}$= -0.22 (eÅ^{-3}).

Fig 4: ORTEP diagram of the compound **24**.



Conclusion:

In conclusion, an efficient and novel protocol for a variety of [1,2,4]triazino[1,6-a]indol-4(3*H*)-one and pyrrolo[2,1-*f*][1,2,4]triazine-4(3H)-one has been developed. To the best of our knowledge, this is the first report of [1,2,4]triazines synthesis via Leuckart reaction condition.

Experimental Section

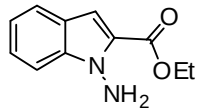
General information

All reactions were carried out under inert atmosphere, unless otherwise mentioned, following standard syringe septa techniques. Solvents were dried and purified by conventional methods prior to use. The progress of all the reactions was monitored by TLC using glass plates precoated with silica gel 60 F254 to a thickness of 0.25 mm (Merck). Column chromatography was performed on silica gel (60 and 230 mesh) using EtOAc, and petroleum ether as the eluents. Optical rotations were measured with JASCO DIP-360 digital polarimeter at 25 °C. IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz or DRX-500 MHz and ^{13}C NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometer, TMS as an internal standard in $CDCl_3$. EI Mass spectra were recorded on Finnigan MAT- 1020 spectrometer at 70 *eV* using a direct inlet system.

General Procedure

To a stirring solution of N-aminated ethyl 3,5-dimethyl-1*H*-pyrrole-2-carboxylate **18** (0.5 g, 2.74 mmol) in formamide was added NH_4OAc (0.31 g, 4.12 mmol). The resulting mixture was stirred for 12-14 h at reflux. The mixture was poured into cold water and further diluted with ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as colorless solid. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:1) as eluent gave **24** (0.37 g, 83% yield) as a colorless crystalline solid.

Ethyl 1-amino-1*H*-indole-2-carboxylate 13



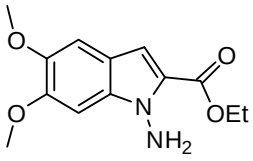
Mol. Formula: $C_{11}H_{12}N_2O_2$

^{1}H NMR (CD_3OD: $CDCl_3$, 500 MHz): δ 1.38 (t, *J*= 7.5 Hz, 3H), 3.83 (s, 3H), 4.36 (q, *J*= 7.5, 14.3 Hz, 2H), 4.77 (m, 2H), 7.02-7.10 (m, 2H), 7.29 (t, *J*= 8.1 Hz, 1H), 7.55-7.60 (m, 2H)

^{13}C NMR (CD_3OD, 125 MHz): δ = 14.7, 61.7, 108.4, 111.7, 121.6, 123.1, 124.6, 126.1, 127.8, 140.6, 163.6

LCMS: *m/z* = 227 $[M + Na]^+$

Ethyl 1-amino-5,6-dimethoxy-1*H*-indole-2-carboxylate 22



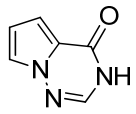
Mol. Formula: $C_{13}H_{16}N_2O_4$

^{1}H NMR (CD_3OD: $CDCl_3$, 500 MHz): δ 1.38 (t, *J*= 7.5 Hz, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 4.33 (q, *J*= 7.5, 14.6 Hz, 2H), 4.77 (m, 2H), 6.92 (s, 1H), 7.04 (d, *J*= 2.43 Hz, 1H), 7.06 (d, *J*= 0.66 Hz, 1H),

^{13}C NMR (CD_3OD: $CDCl_3$, 125 MHz): δ = 13.3, 54.9, 55.1, 59.9, 93.6, 102.0, 108.0, 119.8, 125.3, 132.4, 145.3, 149.3, 161.9

LCMS: *m/z* = 287 $[M + Na]^+$

Pyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one 23



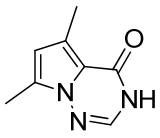
Mol. Formula: $C_6H_5N_3O$

^{1}H NMR (CD_3OD, 400 MHz): δ 6.53 (dd, *J*= 3.4, 2.3 Hz, 1H), 7.01 (dd, *J*= 3.4, 0.82 Hz, 1H), 7.42 (dd, *J*= 2.3, 0.82 Hz, 1H), 7.55 (s, 1H)

^{13}C NMR (CD_3OD: $CDCl_3$, 100 MHz): δ = 107.9, 110.0, 119.0, 121.0, 136.4, 155.0

LCMS: *m/z* = 158 $[M + Na]^+$

5,7-Dimethylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one 24



Mol. Formula: $C_8H_9N_3O$

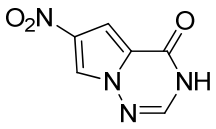
^{1}H NMR (CD_3OD, 500 MHz): δ 2.37 (s, 1H), 2.44 (s, 1H), 6.15 (s, 1H), 7.52 (s, 1H)

^{13}C NMR (CD_3OD: $CDCl_3$, 125 MHz): δ = 10.4, 12.0, 111.2, 115.1, 122.1, 129.5, 135.6, 155.9

LCMS: *m/z* = 186 $[M + Na]^+$

Analysis Calcd.: C, 58.88%; H, 5.56%; N, 25.75% **Found:** C, 58.72%; H, 5.61%; N, 25.73%.

6-Nitropyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one 25



Mol. Formula: $C_6H_4N_4O_3$

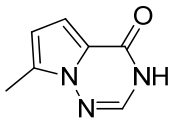
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.42 (d, *J*= 1.86 Hz, 1H), 7.95 (s, 1H), 8.49 (d, *J*= 1.86 Hz, 1H)

^{13}C NMR (DMSO-d_6, 100 MHz): δ 103.9, 120.8, 121.5, 136.7, 142,4, 155.0

LCMS: *m/z* = 203 $[M + Na]^+$

Analysis Calcd.: C, 40.01%; H, 2.24%; N, 31.11% **Found:** C, 40.12%; H, 2.27%; N, 31.07%.

7-Methylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one 26



Mol. Formula: $C_7H_7N_3O$

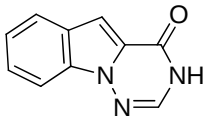
^{1}H NMR (CD_3OD, 200 MHz): δ 7 2.10 (s, 1H), 6.55 (d, *J*= 3.46 Hz, 1H), 6.95 (d, *J*= 3.46 Hz, 1H), 7.94 (s, 1H)

^{13}C NMR (CD_3OD: $CDCl_3$, 50 MHz): δ =10.2, 109.9, 118.2, 122.3, 134.5, 136.2, 155.5

LCMS: *m/z* = 172 $[M + Na]^+$

Analysis Calcd.: C, 40.01%; H, 2.24%; N, 31.11% **Found:** C, 40.12%; H, 2.27%; N, 31.07%.

[1,2,4]Triazino [1,6-a]indol-4(3*H*)-one 16



Mol. Formula: $C_{10}H_7N_3O$

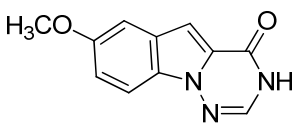
^{1}H NMR (CD_3OD, 200 MHz): δ 4.62 (s, 1H), 7.27-7.31 (m, 2H), 7.41-7.49 (m, 1H), 7.74 (s, 1H), 7.79-7.83 (m, 1H), 7.92 (dd, *J*= 1.01, 8.54 Hz, 1H)

^{13}C NMR (CD_3OD: $CDCl_3$, 50 MHz): δ =100.3, 111.1, 122.1, 122.6, 123.6, 124.9, 125.0, 133.4, 134.0, 156.7

LCMS: *m/z* = 208 $[M + Na]^+$

Analysis Calcd.: C, 64.86%; H, 3.81%; N, 22.69% **Found:** C, 64.71%; H, 3.92%; N, 22.83%.

7-Methoxy-[1,2,4]triazino[1,6-a]indol-4(3*H*)-one 27



Mol. Formula: $C_{11}H_9N_3O_2$

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.72 (s, 3H), 6.13-1.15 (m, 2H), 6.62-6.64 (m, 1H), 6.77-6.79 (m, 1H), 6.99 (m, 1H), 7.07-7.09 (m, 1H)

^{13}C NMR (CD_3OD: $CDCl_3$, 50 MHz): δ =55.1, 99.4, 101.2, 117.1, 123.7, 125.5, 128.9, 133.9, 155.8

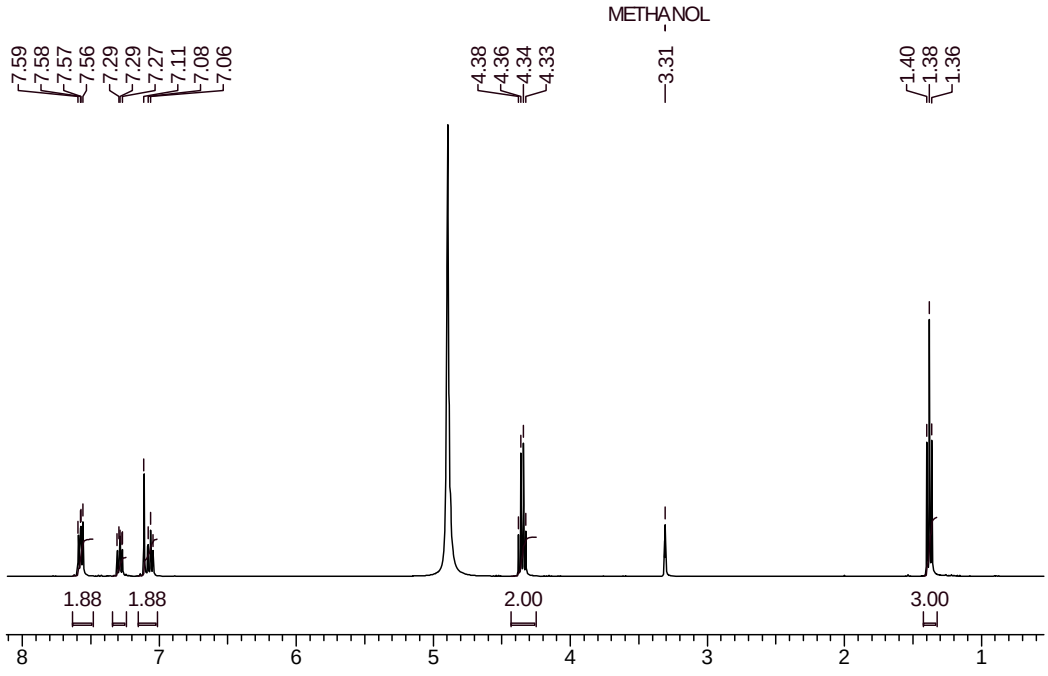
LCMS: *m/z* = 238 $[M + Na]^+$

Analysis Calcd.: C, 61.39%; H, 4.22%; N, 19.53% **Found:** C, 61.31%; H, 4.23%; N, 19.61%.

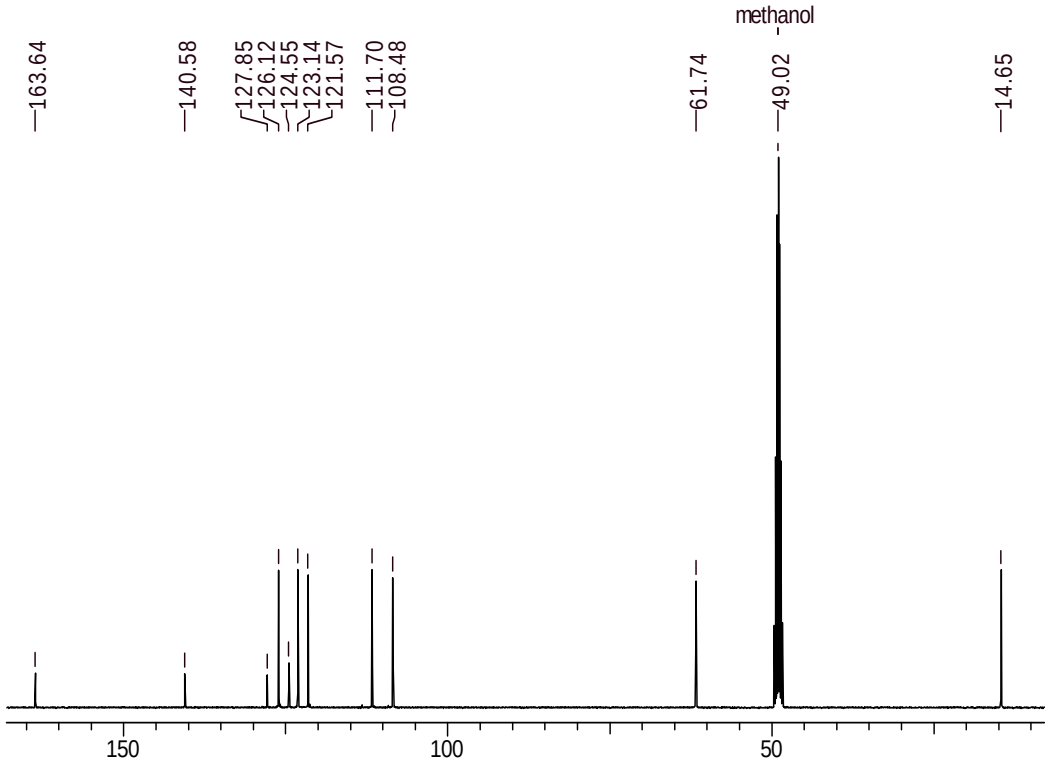
Spectra

1. ^{1}H and ^{13}C NMR spectra of **13**
2. ^{1}H and ^{13}C NMR spectra of **22**
3. ^{1}H and ^{13}C NMR spectra of **24**
4. ^{1}H and ^{13}C NMR spectra of **23**
5. ^{1}H and ^{13}C NMR spectra of **27**
6. ^{1}H and ^{13}C NMR spectra of **25**
7. ^{1}H and ^{13}C NMR spectra of **16**

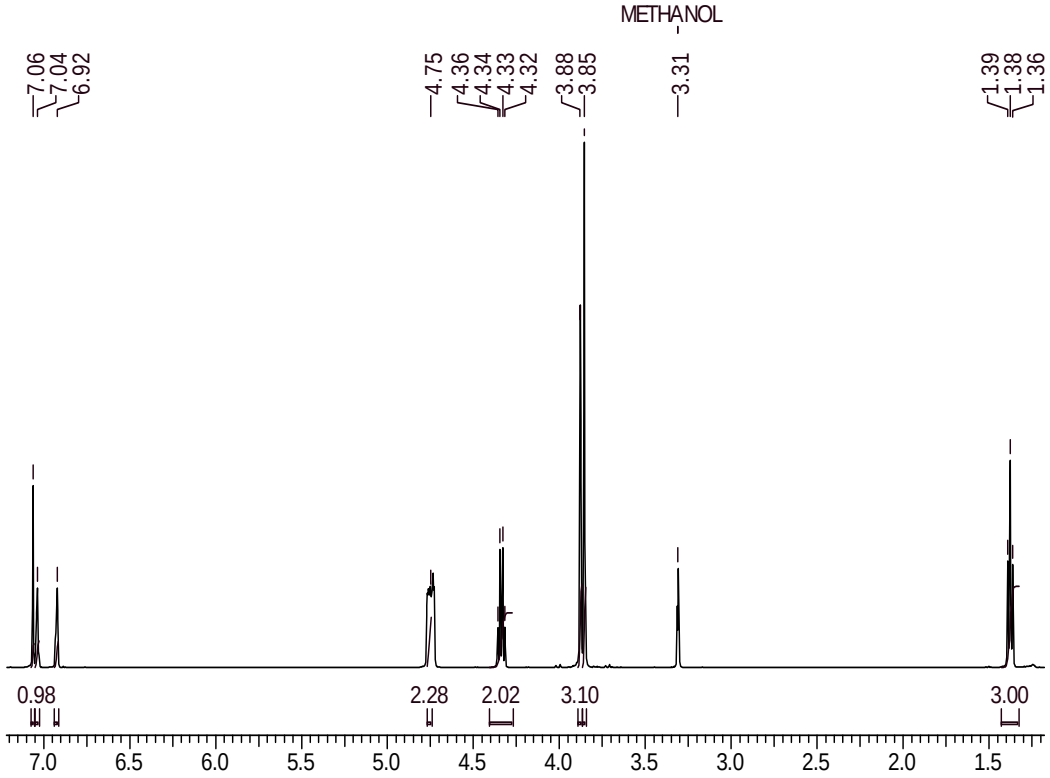
^{1}H NMR (CD_3OD: $CDCl_3$, 200 MHz) spectrum of ethyl 1-amino-1*H*-indole-2-carboxylate 13



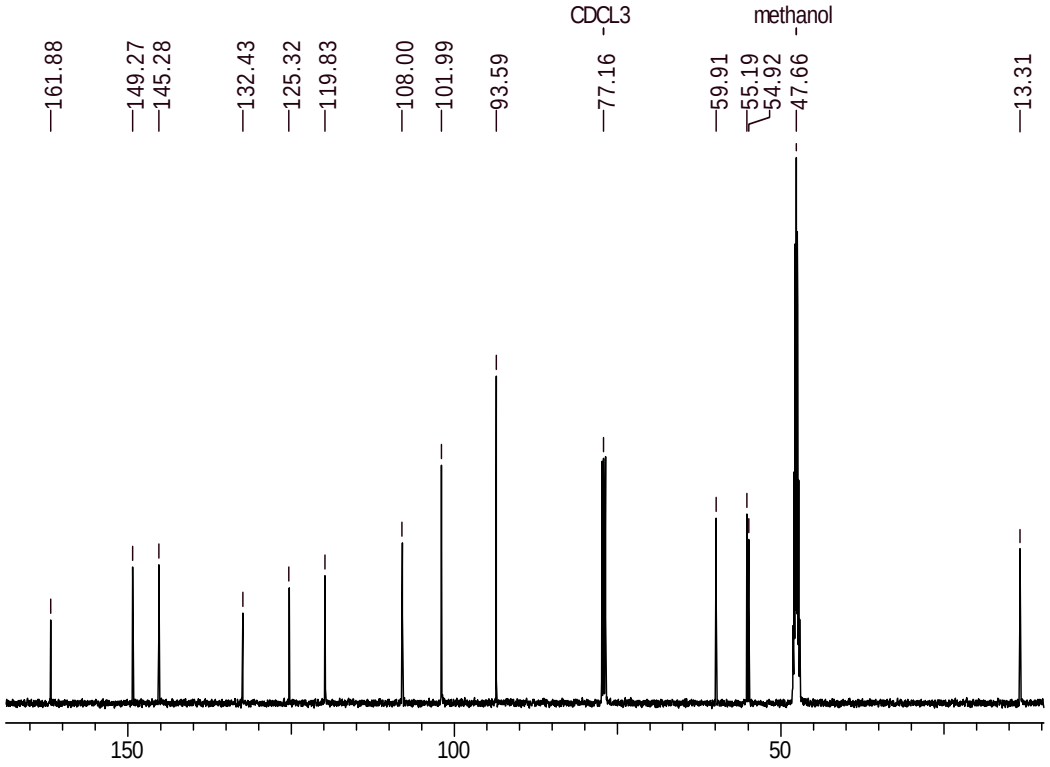
^{13}C NMR (CD_3OD, 50 MHz) spectrum of ethyl 1-amino-1*H*-indole-2-carboxylate 13



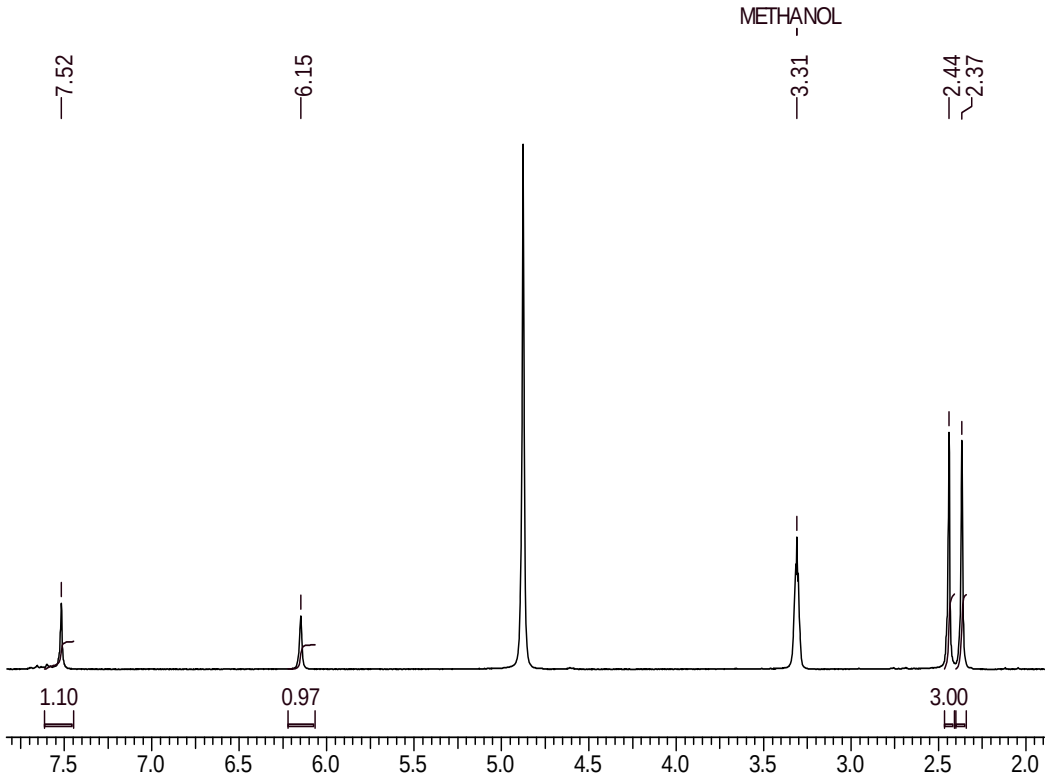
^{1}H NMR (CD_3OD: $CDCl_3$, 500 MHz) spectrum of ethyl 1-amino-5,6-dimethoxy-1*H*-indole-2-carboxylate 22



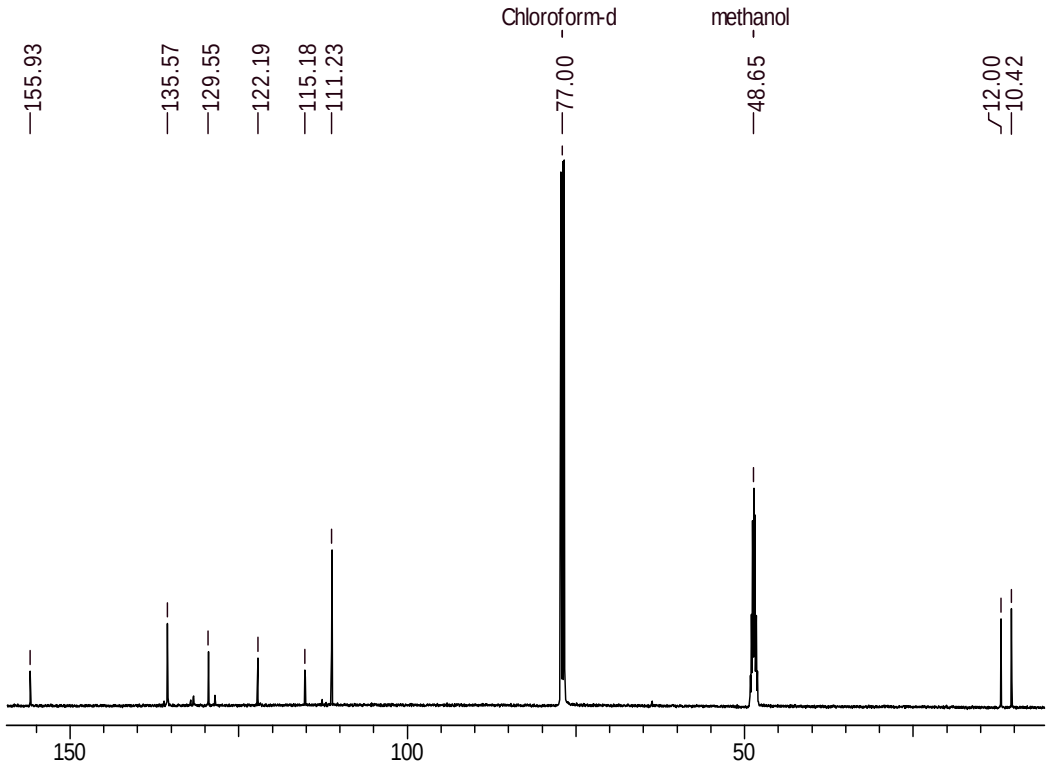
^{13}C NMR (CD_3OD: $CDCl_3$, 100 MHz) spectrum of ethyl 1-amino-5,6-dimethoxy-1*H*-indole-2-carboxylate 22



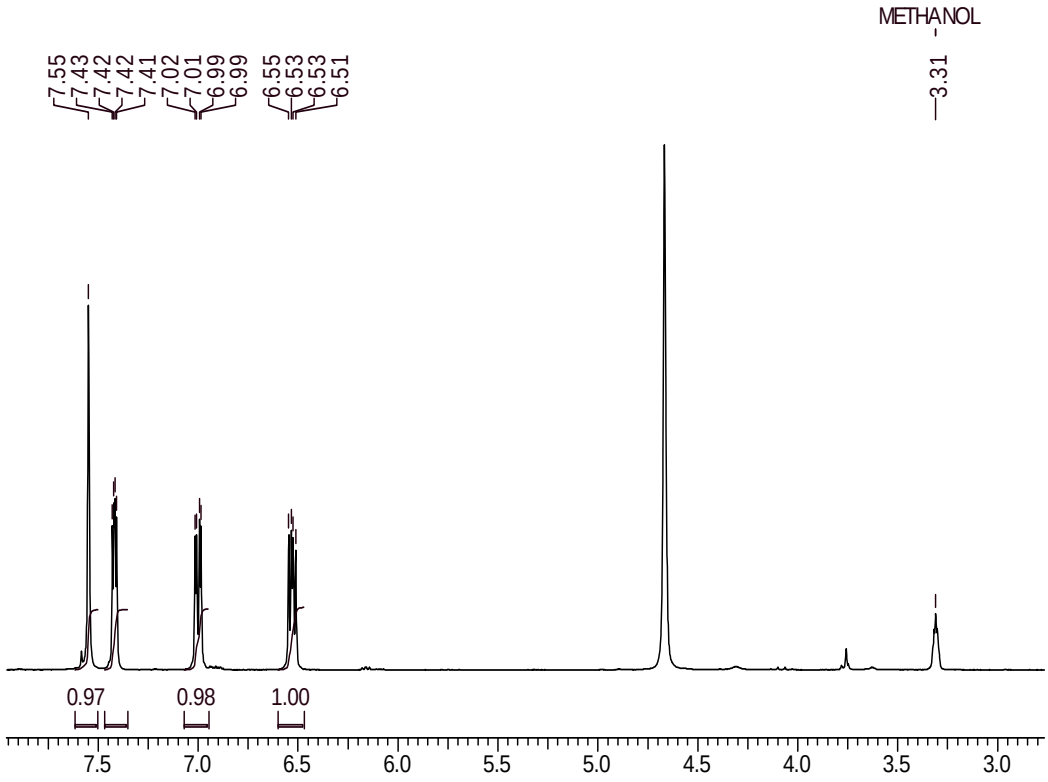
^{1}H NMR (CD_3OD, 200 MHz) spectrum of 5,7-dimethylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one 24



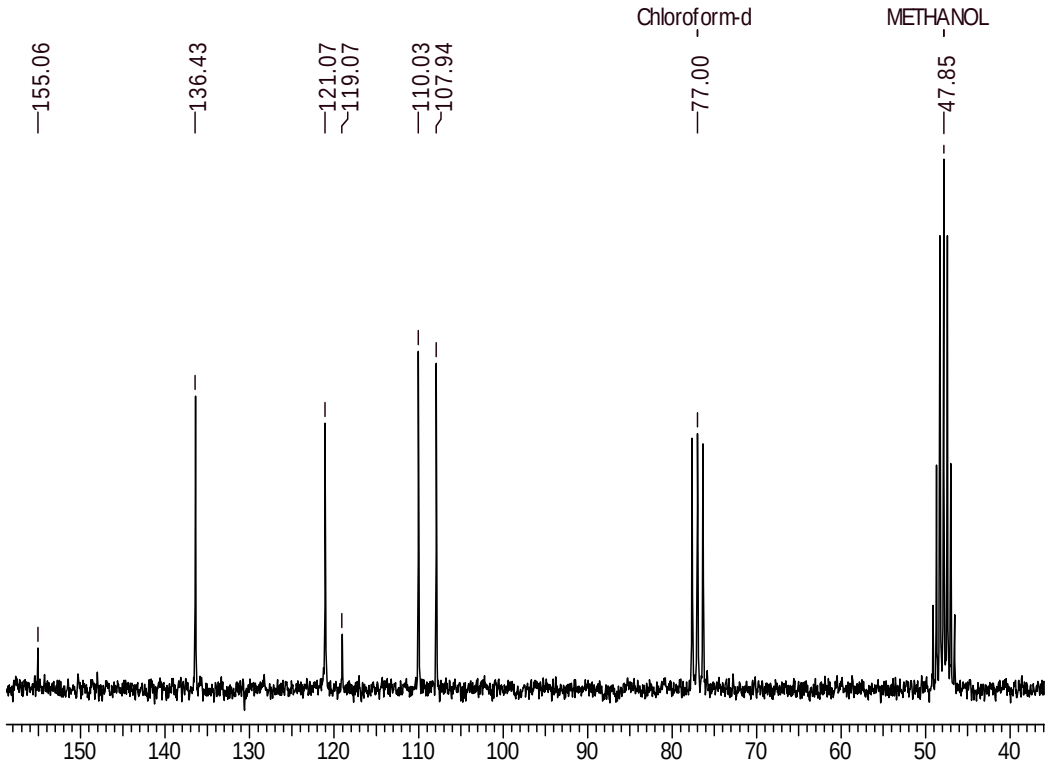
^{13}C NMR (CD_3OD: $CDCl_3$, 50 MHz) spectrum of 5,7-dimethylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one 24



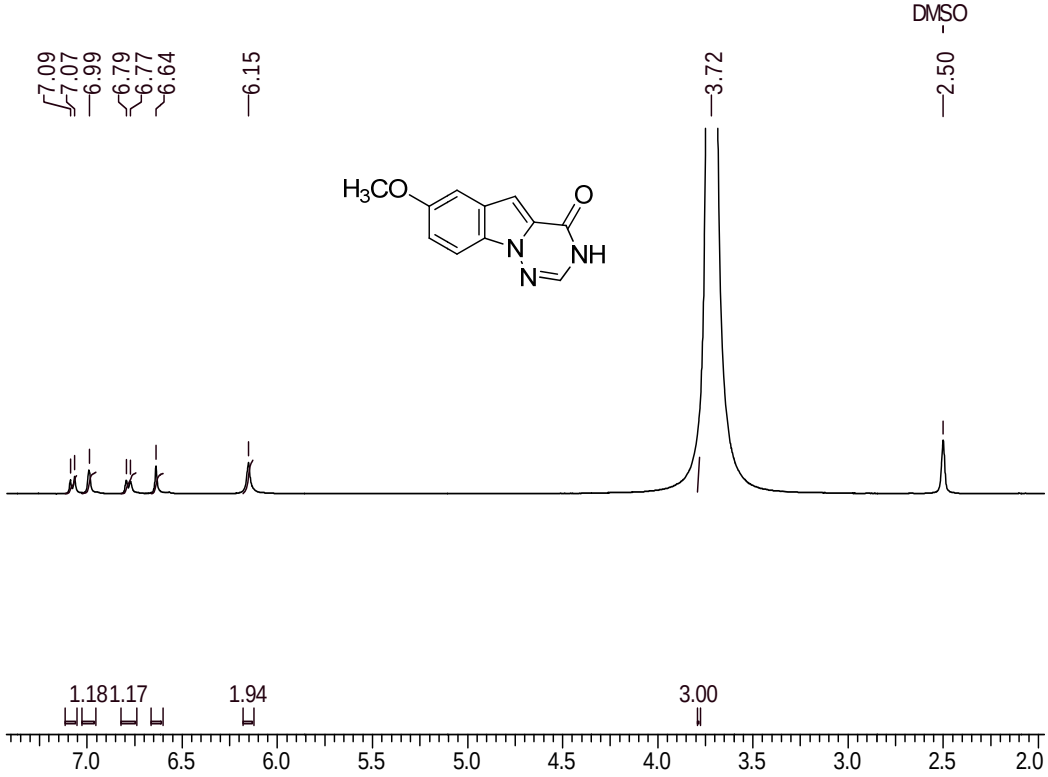
^{1}H NMR (CD_3OD, 200 MHz) spectrum of pyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one 23



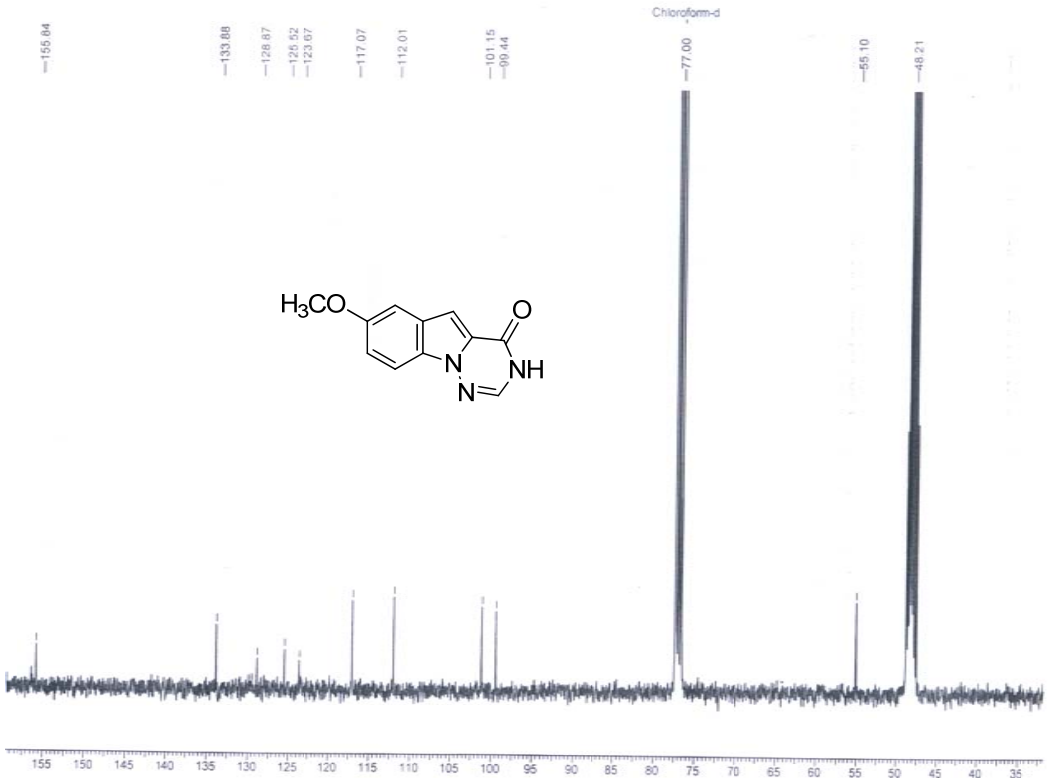
^{13}C NMR (CD_3OD: $CDCl_3$, 50 MHz) spectrum of pyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one 23



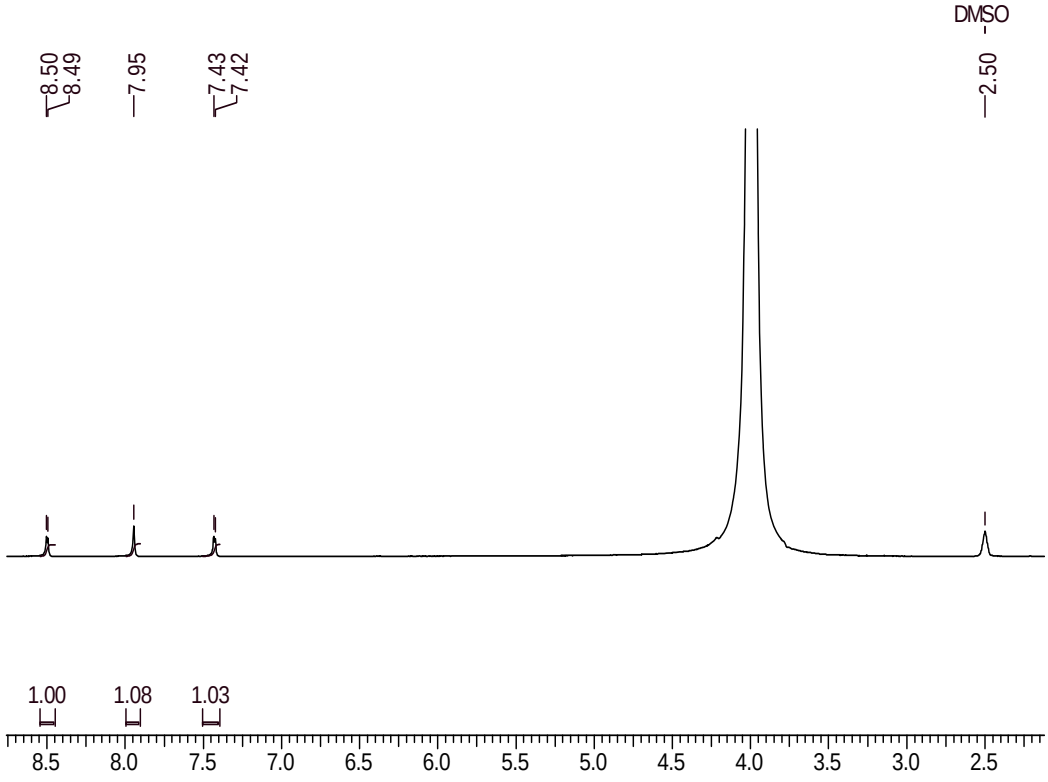
^{1}H NMR (DMSO-d_6, 200 MHz) spectrum of 7-methoxy-[1,2,4]triazino[1,6-a]indol-4(3*H*)-one 27



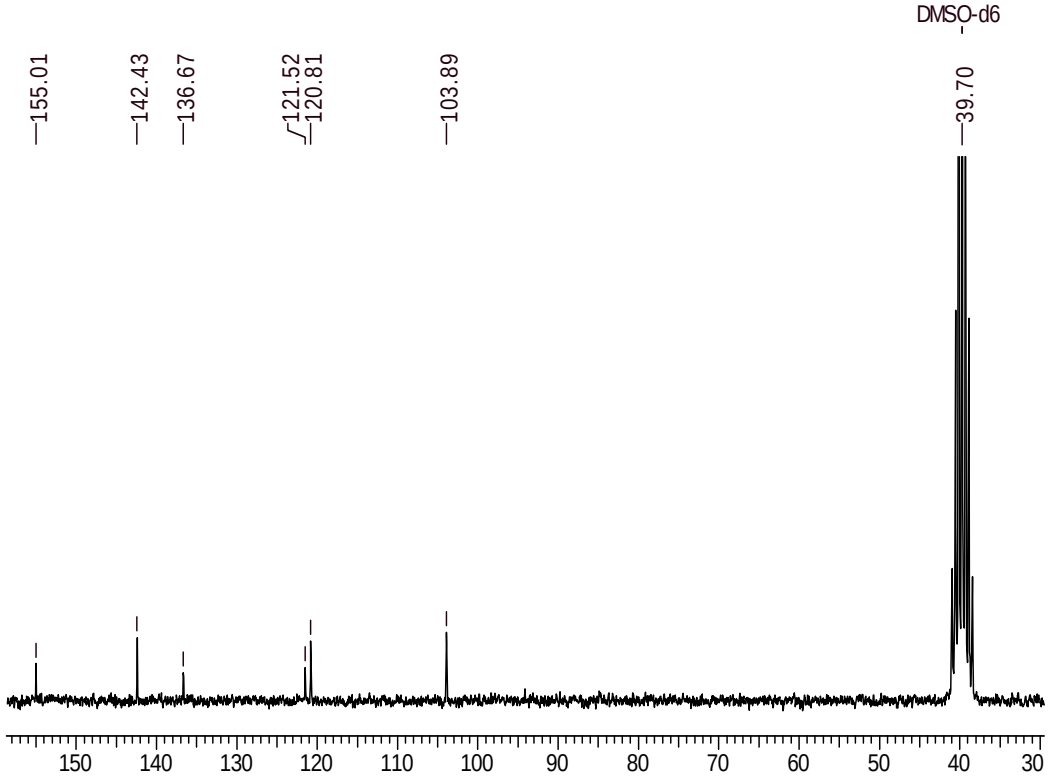
^{1}H NMR (CD_3OD: $CDCl_3$, 200 MHz) spectrum of 7-methoxy-[1,2,4]triazino[1,6-a]indol-4(3*H*)-one 27



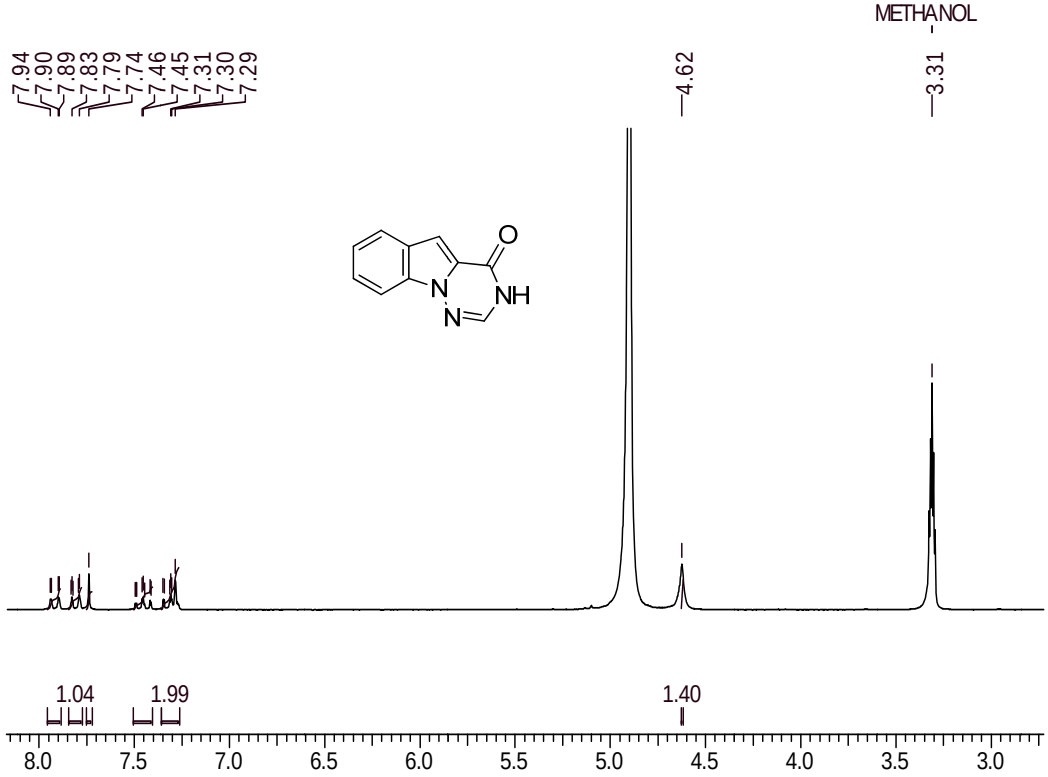
^{1}H NMR (DMSO-d$_6$, 400 MHz) spectrum of 6-nitropyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one 25



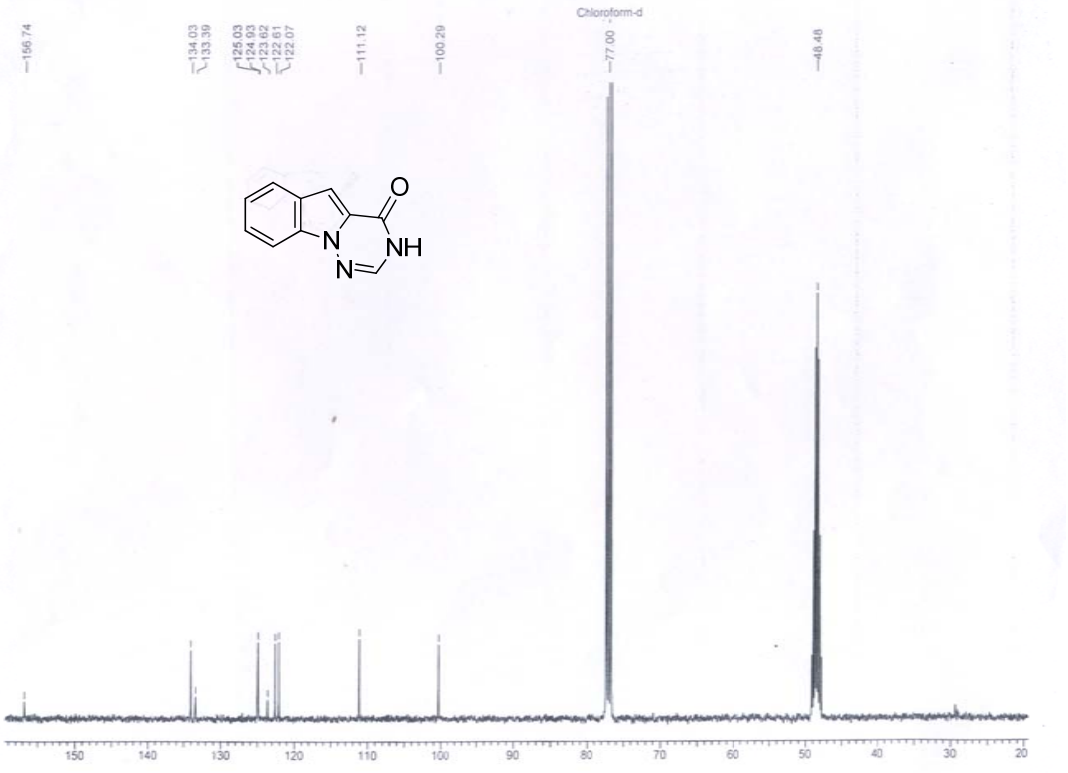
^{13}C NMR (DMSO-d$_6$, 100 MHz) spectrum of 6-nitropyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one 25



^{1}H NMR (CD_3OD, 400 MHz) spectrum of [1,2,4]triazino[1,6-a]indol-4(3*H*)-one 16



^{13}C NMR (CD_3OD: $CDCl_3$, 100 MHz) spectrum of [1,2,4]triazino[1,6-a]indol-4(3*H*)-one 16



Chapter IV, Section B

Studies towards synthesis of [1,2,4]Triazino[1,6-a]indole-2,4(1*H*,3*H*)-dione and Pyrrolo[2,1-*f*][1,2,4]Triazine-2,4(1*H*,3*H*)-dione

Present work

Objective

In the development of a synthetic program directed towards the preparation of various fused bridgehead nitrogen ring system derivatives, a number of pyrrolo [2,1-*f*] [1,2,3]-triazines were synthesized. Compounds of this type have very few reports in literature. A unique bridgehead nitrogen heterocycle pyrrolo[2,1-*f*]- [1,2,4]triazine (Figure 5) was first reported by Neunhoeffer via addition/fragmentation of 1,2,4-triazines with dimethyl acetylenedicarboxylate to give **29**.[20] It was two years later that Migliara reported the synthesis of **30** via acid-mediated cyclization of a semicarbazone onto a pendant α-ketoester, followed by base-promoted cyclization.[21] More than a decade later Hayashi introduced C7-linked pyrrolotriazines to the medicinal chemistry field as novel C-nucleoside mimics (**31**), implementing similar chemistry to Migliara.[22] A novel pyrrole N-amination approach for formation of the key N-N bond, reported by Klein and co-workers, described syntheses of both C-nucleoside congeners[23] and minimally substituted pyrrolotriazines (**32**).[24]

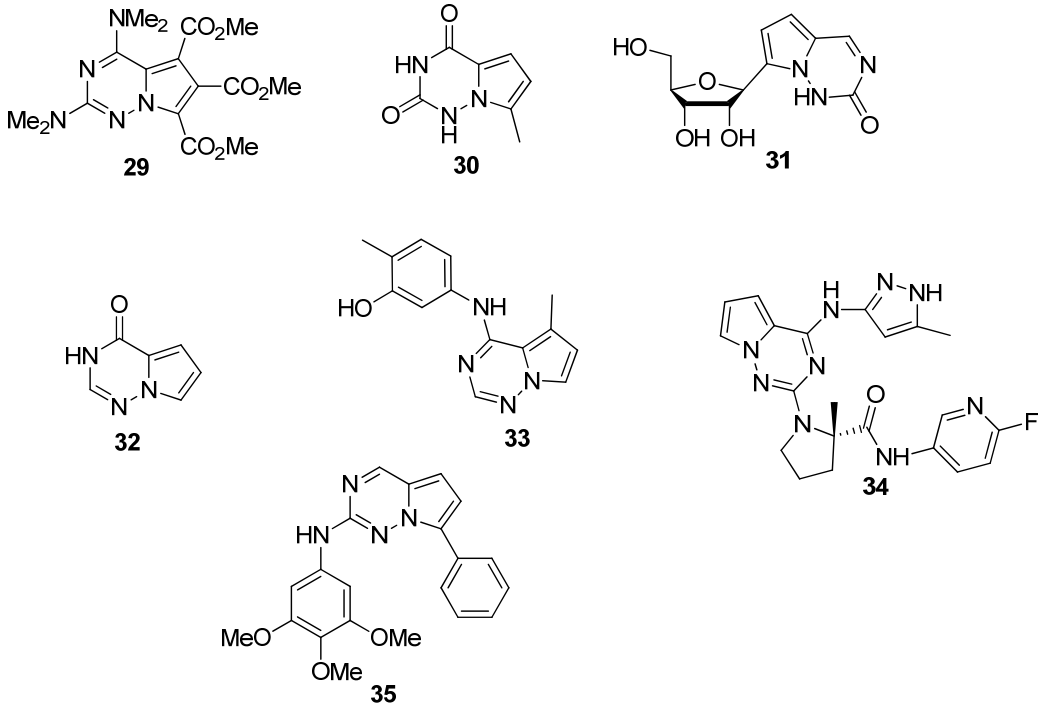
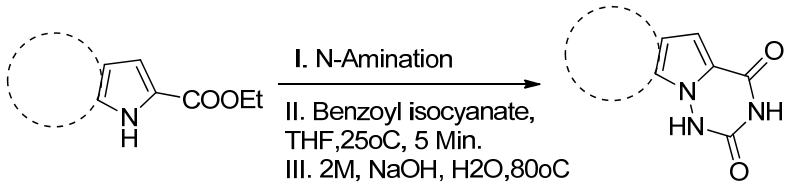


Figure 5: Pyrrolo [2,1-*f*] [1,2,3]-triazine derivatives

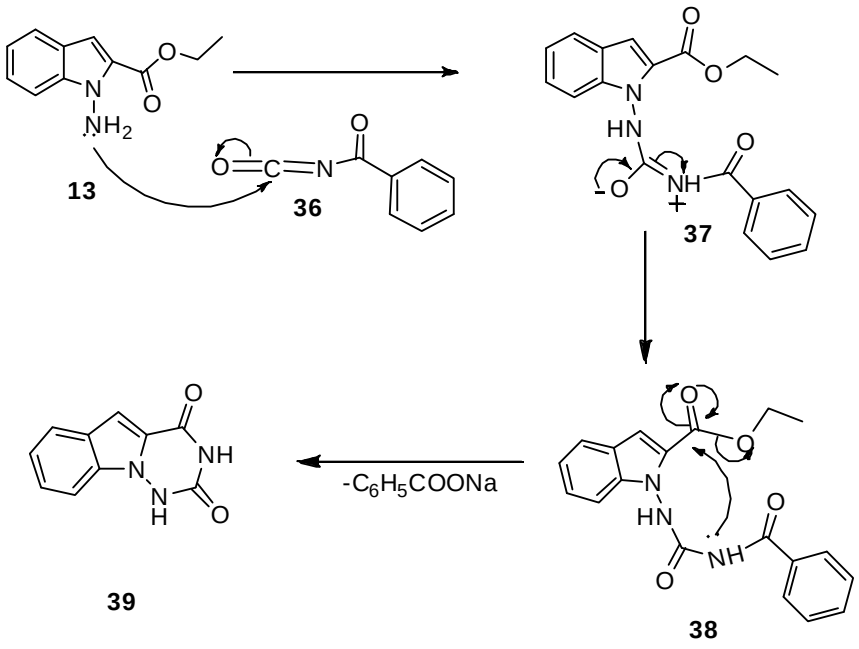
Limited new developments around this nucleus had been reported[25, 26] until Hunt and co-workers described the design, synthesis, and utility of C4-substituted

pyrrolotriazines (**33**) as quinazoline hinge-binding mimics in the discovery of ATP competitive kinase[16] inhibitors. This discovery has had a profound impact on the kinase inhibitor field and has led to numerous candidates in late stages of clinical development. Further expansion of the utility of this heterocycle has led to the discovery of the clinical level IGF-1R inhibitor **34**.[17] Recently, Thieu et *al*. reported[27] novel diaminopyrimidine ATP competitive inhibitors of anaplastic lymphoma kinase (ALK). In an effort to mimic the bioactive conformation they proposed constraining the diaminopyrimidine into a 2-anilino-7-aryl-pyrrolo[2,1-*f*][1,2,4]triazine **35**.

In continuation of our interest in triazine based compounds, we further extended the scope of reaction described in forgoing section (chapter iv, section A), and developed a method for the synthesis of [1,2,4]triazino[1,6-a]indole-2,4(1*H*,3*H*)-dione and pyrrolo[2,1-*f*][1,2,4]triazine-2,4(1*H*,3*H*)-diones was developed, Alcohols and phenols readily attack isocyanates[28] to give carbamates. Similarly, amines give ureas which under basic condition cyclize to give triazino-diones.



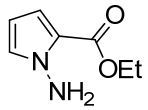
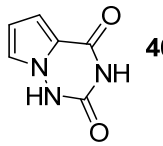
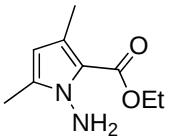
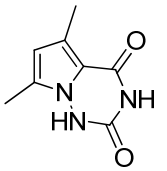
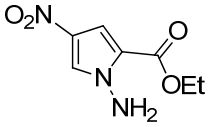
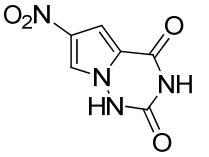
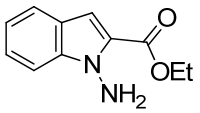
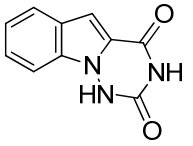
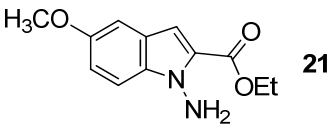
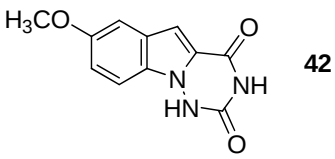
Proposed mechanism for cyclization: Scheme 6



Results and Discussion:

N-Amination of indole-2-caroboxylate, pyrrole-2-carboxylate and their derivatives has been achieved using chloramines as reported in previous section. N-Amino-pyrrole-2-carboxylate and N-Amino-indole-2-carboxylates were then treated with benzoyl isocyante at room temperature to give carbamates. The structure of these carbamates was confirmed by proton and carbon NMR spectroscopy, IR spectroscopy and elemental analysis. After confirmation of structure these carbamates were treated with 2M solution of NaOH to furnish [1,2,4]triazino[1,6-a]indole-2,4(1*H*,3*H*)-dione and pyrrolo[2,1-*f*][1,2,4]triazine-2,4(1*H*,3*H*)-diones. The mechanism of formation of products is shown in detail in scheme 6.

Table 2: One-pot synthesis of [1,2,4]triazino[1,6-a]indole-2,4(1*H*,3*H*)-dione and pyrrolo[2,1-*f*][1,2,4]triazine-2,4(1*H*,3*H*)-diones compounds:

Entry No.	N-Amination precursors	Products	Yields
1.	 **17**	 **40**	78%
2.	 **18**	 **41**	74%
3.	 **19**	 **12**	75%
4.	 **13**	 **39**	81%
5.	 **21**	 **42**	65%

Conclusion:

In conclusion, an efficient protocol for the synthesis of a variety of [1,2,4]triazino[1,6-a]indole-2,4(1*H*,3*H*)-dione and pyrrolo[2,1-*f*][1,2,4]triazine-2,4(1*H*,3*H*)-diones has been developed. To the best of our knowledge, this is the first report of [1,2,4]triazine-2,4(1*H*,3*H*)-diones synthesis using isocynate and carbamates.

Experimental Section

General information

All reactions were carried out under inert atmosphere, unless otherwise mentioned, following standard syringe septa techniques. Solvents were dried and purified by conventional methods prior to use. The progress of all the reactions was monitored by TLC using glass plates precoated with silica gel 60 F254 to a thickness of 0.25 mm (Merck). Column chromatography was performed on silica gel (60 and 230 mesh) using EtOAc, and petroleum ether as the eluents. Optical rotations were measured with JASCO DIP-360 digital polarimeter at 25 °C. IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz or DRX-500 MHz and ^{13}C NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometer, TMS as an internal standard in $CDCl_3$. EI Mass spectra were recorded on Finnigan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.

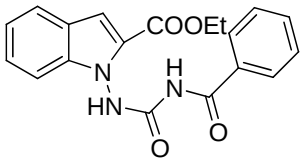
General Procedure

To a stirring solution of N-aminated ethyl 1*H*-indole-2-carboxylate **13** (0.5 g, 2.45 mmol) in tetrahydrofuran (10 mL) benzoyl isothiocyanate (0.43 g, 2.94 mol) in tetrahydrofuran (10 mL) was added drop-wise at 24 °C. The reaction mixture was stirred for 10 min. The solvent was evaporated under reduced pressure. The resulting crude product was triturated with diethyl ether (20 mL) for 30 minutes, then collected by filtration and washed with hexane/ diethyl ether (9:1 v/v) to give ethyl 1-(3-benzoylureido)-1*H*-indole-2-carboxylate (**37**, 0.55 g, 64%) as an off-white solid.

To a 50 mL round bottom flask, ethyl 1-(3-benzoylureido)-1*H*-indole-2-carboxylate (**37**, 0.30 g, 0.85 mmol) and 2.00 M of sodium hydroxide in water (1.7 mL, 3.40 mmol) were added. The reaction was heated at 85 °C for 75 minutes. The reaction

was allowed to cool to 24 °C. The precipitate was partitioned with ethanol (10 mL). Acetic acid (0.26 mL, 3.43 mmol) was then added at 0 °C to stir for 30 minutes. The resulting precipitate was collected by filtration and washed with cold ethanol (5 mL) to afford a white solid. The white solid was successively triturated in diethyl ether (15 mL) for 20 minutes, collected by filtration, and washed with diethyl ether (20 mL) to give white solid [1,2,4]triazino[1,6-a]indole-2,4(1*H*,3*H*)-dione (**43**, 0.14 g, 81%).

Ethyl 1-(3-benzoylureido)-1H-indole-2-carboxylate 37



Mol. Formula: $C_{19}H_{17}N_3O_4$

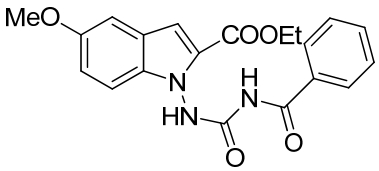
^{1}H NMR (CD_3OD, 500 MHz): δ1.30 (t, *J*= 7.13Hz, 3H), 4.28 (q, *J*= 7.1, 13.5 Hz, 2H), 7.13-7.15 (m, 2H), 7.24-7.29 (m, 1H), 7.38-7.442 (m, 2H), 7.47-7.50 (m, 2H), 7.75 (d, *J*= 8.1Hz, 1H), 7.86 (d, *J*= 8.1Hz, 2H) 10.3 (brs, 1H)

^{13}C NMR (CD_3OD:$CDCl_3$, 125 MHz): δ = 14.2, 60.8, 109.9, 110.3, 121.8, 122.3, 122.6, 123.7, 126.3, 126.9, 128.1, 128.6, 131.0, 133.3, 139.3, 155.8, 160.5, 167.9

LCMS: *m/z* = 374 $[M + Na]^+$

Analysis Calcd.: C, 64.95%; H, 4.88%; N, 11.96% **Found:** C, 64.72%; H, 4.91%; N, 11.73%.

Ethyl 1-(3-benzoylureido)-5-methoxy-1H-indole-2-carboxylate



Mol. Formula: $C_{20}H_{19}N_3O_5$

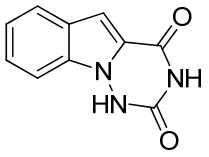
^{1}H NMR (CD_3OD, 500 MHz): δ δ1.33 (t, *J*= 7.13Hz, 3H), 3.64 (s, 3H), 4.31 (q, *J*= 7.1, 13.9 Hz, 2H), 4.57 (brs, 1H), 7.04 (dd, *J*= 2.5, 9.0 Hz, 1H, 7.14 (d, *J*= 2.5 Hz, 1H, 7.28 (d, *J*= 0.89 Hz, 1H), 7.36(d, *J*= 9.0 Hz, 1H), 7.55 (t, *J*= 7.6 Hz, 1H), 7.66 (t, *J*= 7.6 Hz, 1H), 8.00-8.02 (m, 2H)

^{13}C NMR (CD_3OD: $CDCl_3$, 125 MHz): δ = 14.5, 56.1, 61.8, 103.7, 110.8, 111.6, 118.6, 125.4, 128.4, 129.2, 129.8, 134.3, 158.9, 161.9

LCMS: *m/z* = 404 $[M + Na]^+$

Analysis Calcd.: C, 62.99%; H, 5.02%; N, 11.02% **Found:** C, 62.72%; H, 4.98%; N, 11.13%.

[1,2,4]Triazino[1,6-a]indole-2,4(1H,3H)-dione 39



Mol. Formula: $C_{10}H_7N_3O_2$

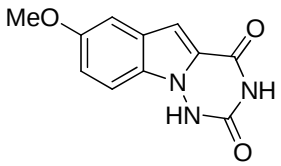
^{1}H NMR (CD_3OD, 500 MHz): δ 7.02 (s, 1H), 7.08 (t, *J*= 7.8 Hz, 1H), 7.25 (t, *J*= 7.8 Hz, 1H), 7.38 (d, *J*= 7.8 Hz, 1H), 7.55 (t, *J*= 7.8 Hz, 1H)

^{13}C NMR (CD_3OD: $CDCl_3$, 125 MHz): δ = 106.9, 110.3, 121.5, 122.4, 124.9, 125.1, 135.0, 139.0, 162.6, 168.0

LCMS: *m/z* = 224 $[M + Na]^+$

Analysis Calcd.: C, 59.70%; H, 3.51%; N, 20.89% **Found:** C, 59.61%; H, 3.48%; N, 21.02%.

7-Methoxy-[1,2,4]triazino[1,6-a]indole-2,4(1H,3H)-dione 42



Mol. Formula: $C_{11}H_9N_3O_3$

^{1}H NMR (CF_3COOD, 500 MHz): δ 4.01 (s, 3H), 7.24-7.26 (m, 2H), 7.41-7.44 (m, 2H)

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 56.0, 102.9, 103.8, 111.4, 113.9, 124.4, 133.5, 136.8, 154.4, 160.1, 165.1

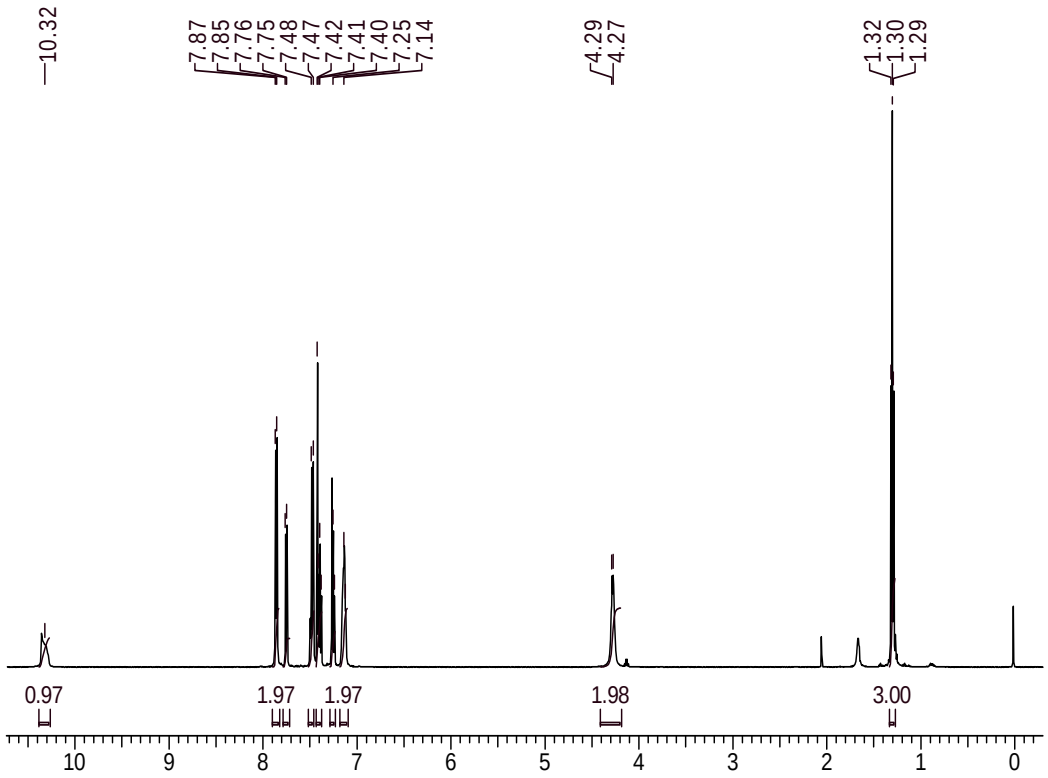
LCMS: *m/z* = 254 $[M + Na]^+$

Analysis Calcd.: C, 57.14%; H, 3.92%; N, 18.17% **Found:** C, 57.31%; H, 3.82%; N, 18.05%.

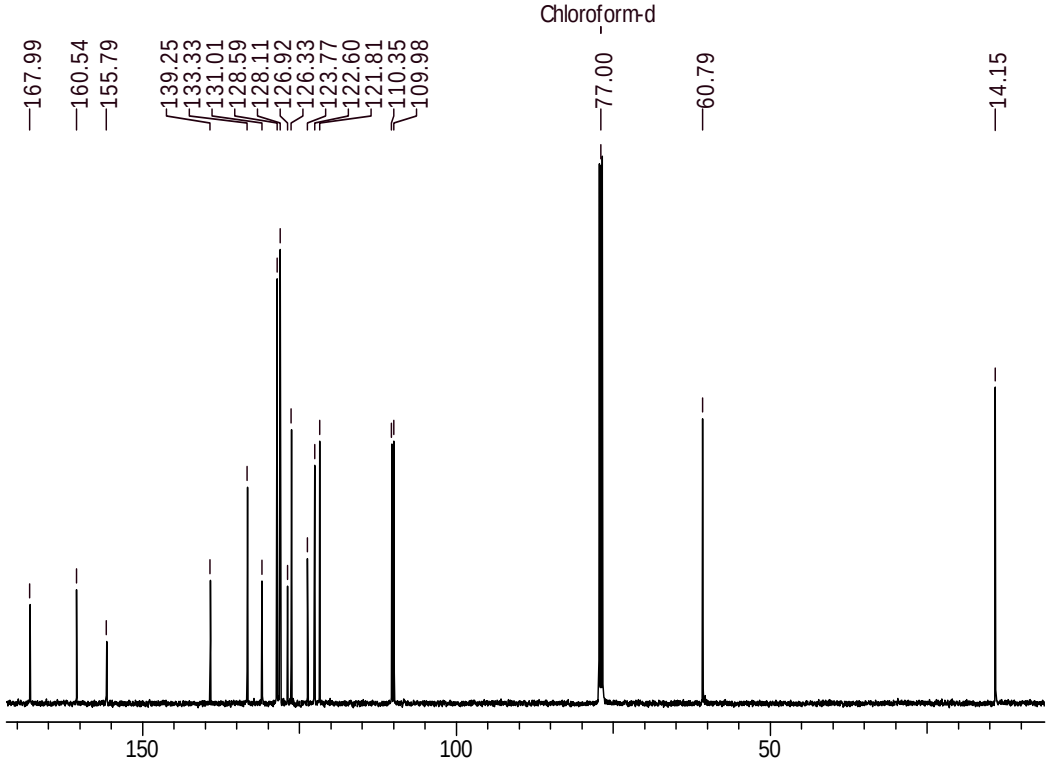
Spectra

1. ^{1}H and ^{13}C NMR spectra of **21**
2. ^{1}H and ^{13}C NMR spectra of **37**
3. ^{1}H and ^{13}C NMR spectra of **44**
4. ^{1}H and ^{13}C NMR spectra of **43**

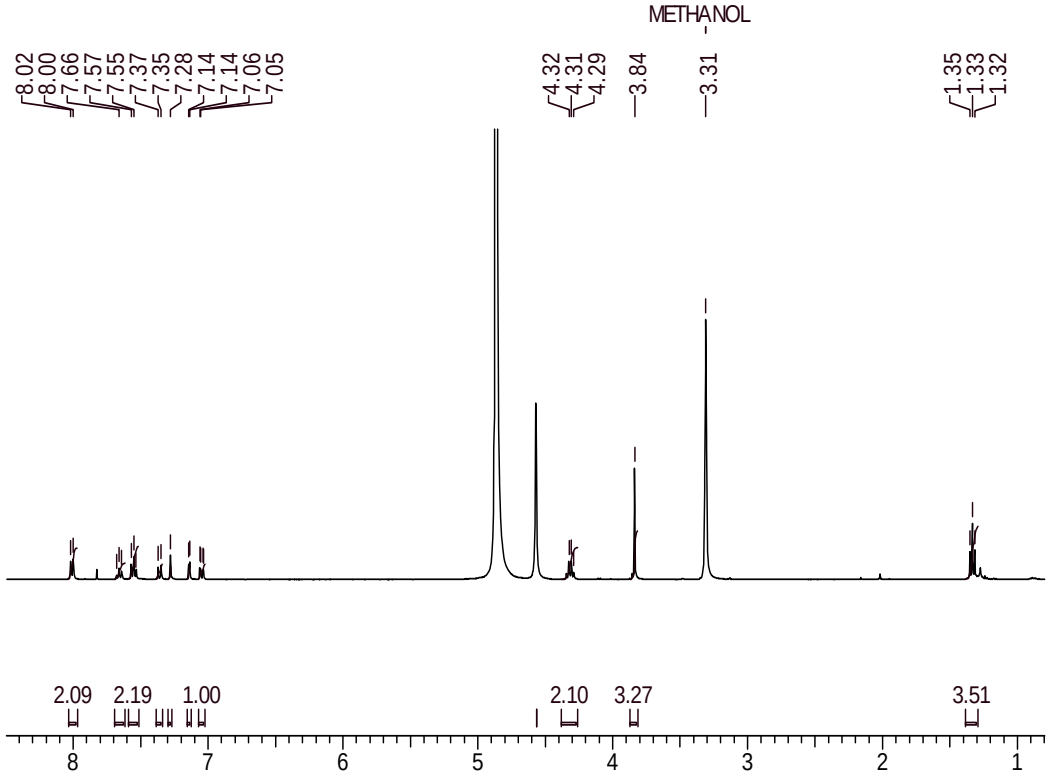
^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of ethyl 1-(3-benzoylureido)-1H-indole-2-carboxylate 37



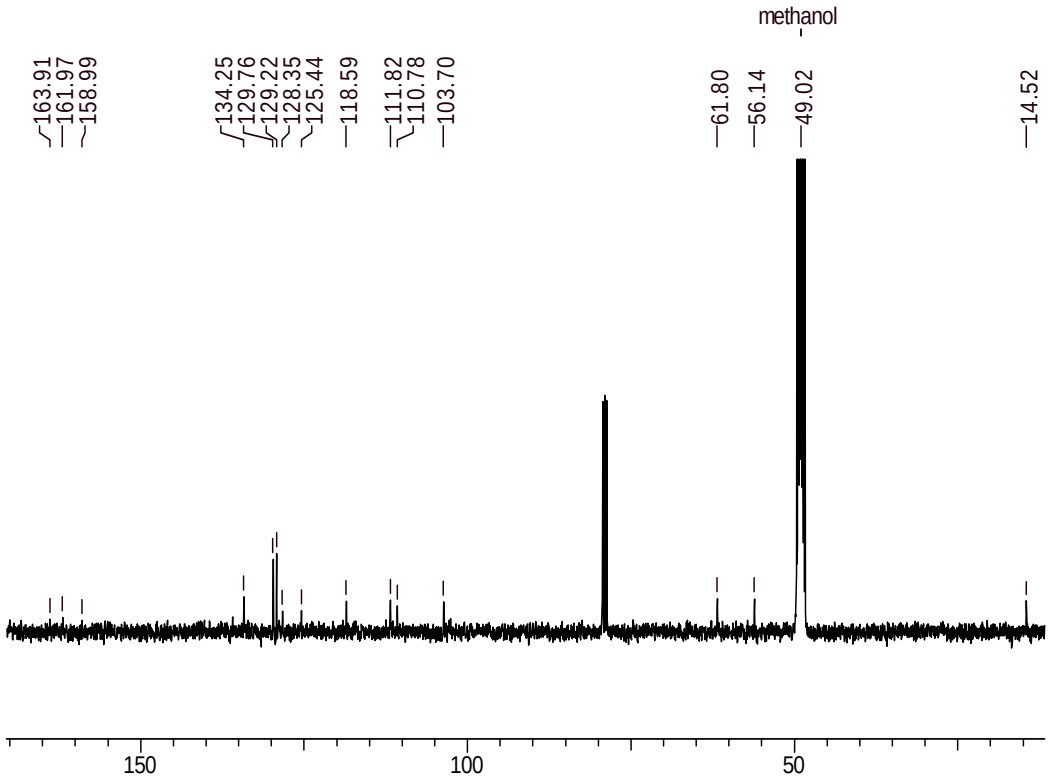
^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of ethyl 1-(3-benzoylureido)-1H-indole-2-carboxylate 37



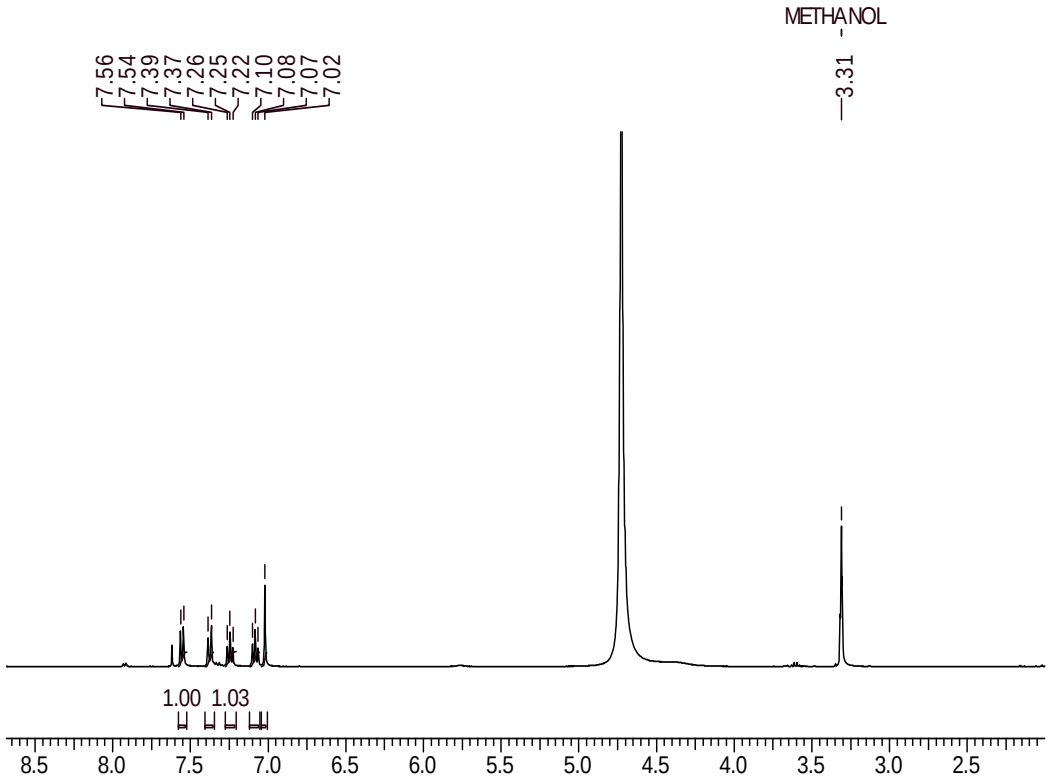
^{1}H NMR (CD_3OD, 200 MHz) spectrum of ethyl 1-(3-benzoylureido)-5-methoxy-1H-indole-2-carboxylate



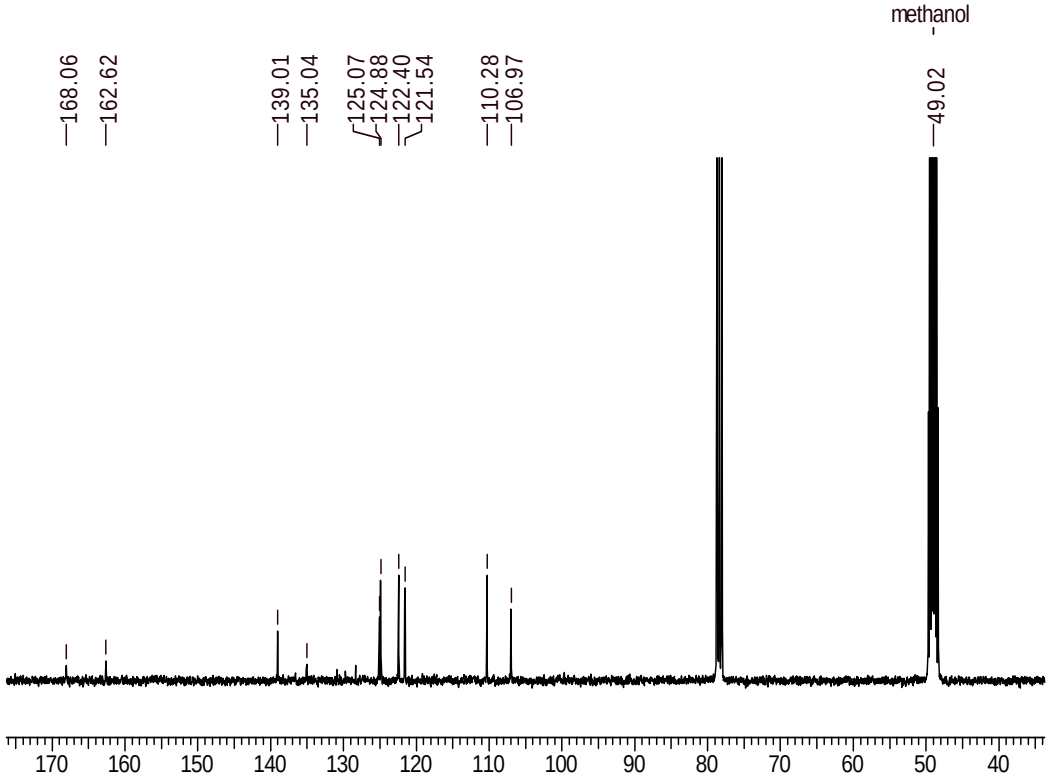
^{13}C NMR (CD_3OD:$CDCl_3$, 50 MHz) spectrum of ethyl 1-(3-benzoylureido)-5-methoxy-1H-indole-2-carboxylate



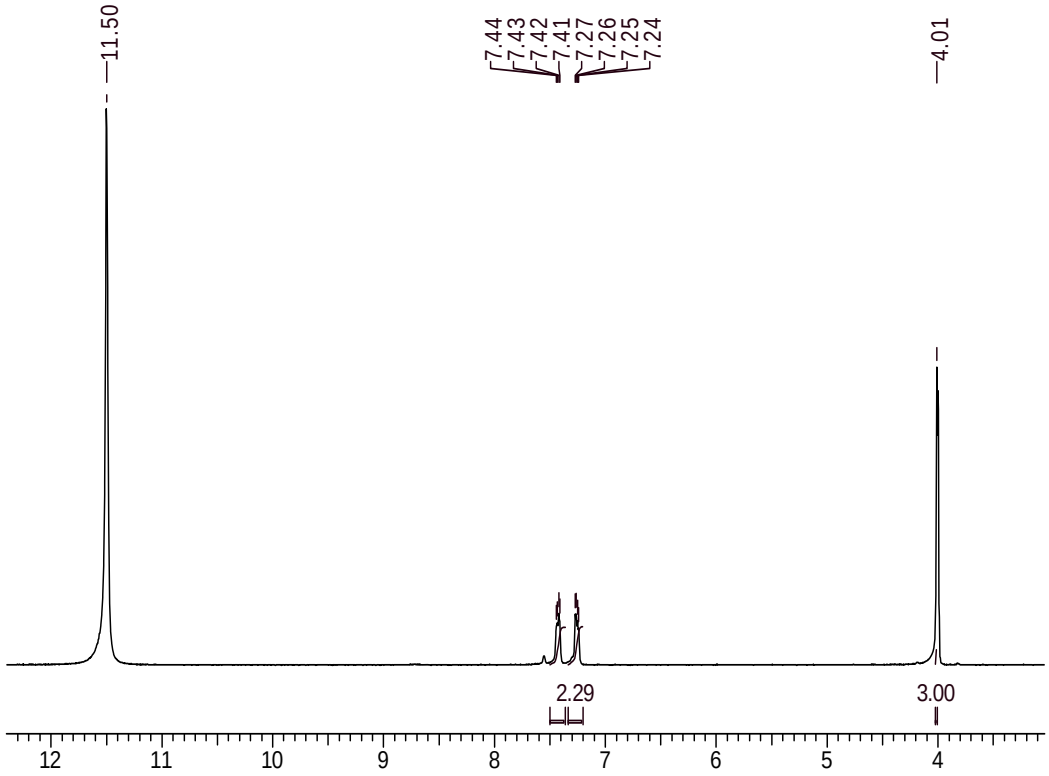
^{1}H NMR (CD_3OD, 200 MHz) spectrum of [1,2,4]triazino[1,6-a]indole-2,4(1H,3H)-dione 39



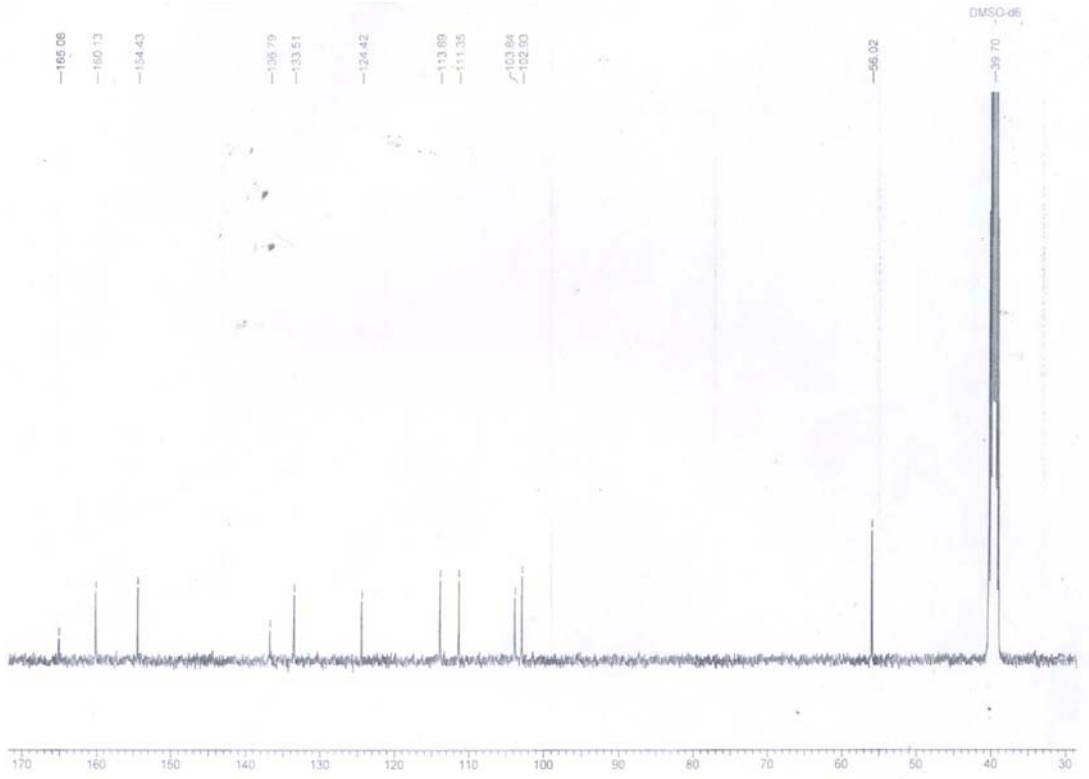
^{13}C NMR (CD_3OD:$CDCl_3$, 50 MHz) spectrum of [1,2,4]triazino[1,6-a]indole-2,4(1H,3H)-dione 39



^{1}H NMR (CF_3COOD, 500 MHz) spectrum of 7-methoxy-[1,2,4]triazino[1,6-a]indole-2,4(1H,3H)-dione 42



^{13}C NMR (DMSO-d_6, 125 MHz) spectrum of 7-methoxy-[1,2,4]triazino[1,6-a]indole-2,4(1H,3H)-dione 42



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Curriculum Vitae

Educational Qualifications

M.Sc. (Master of Science)	**Organic Chemistry (First Division)** M. J. P. Rohilkhand University Uttar Pradesh, India. **2005**.
B.Sc. (Bachelor of Science)	**Chemistry**, Physics, Maths **(First Division)** M. J. P. Rohilkhand University Uttar Pradesh, India. **2003**.

Examinations Qualified

- Qualified *National Eligibility Test* (NET), Eligibility test for the lecturership/JRF Conducted by Council of Scientific and Industrial Research (CSIR) and University Grant Commission , **June 2006**

Award and Fellowships

- **II**nd Prize in College level seminar held at G.F.College, Shahjahanpur (U.P.), India during Master of Science (Chemistry) **2003-2005**

- Junior Research Fellowship Awarded by Council of Scientific and Industrial Research (CSIR), India (www.csir.res.in) **2007-2009**

- Senior Research Fellowship Awarded by Council of Scientific and Industrial Research (CSIR), India (www.csir.res.in) **2009-2012**

Research Interests

- Development of new asymmetric synthetic methodologies and its applications to the synthesis of bioactive molecules with special emphasis on organocatalysis.

- Total synthesis of bioactive molecules and their application to the medicinal chemistry and material chemistry.

Publications

1. "Synthesis of Aculeatins A and B via Iterative Hydrolytic Kinetic Resolution" **Anand Harbindu**, Pradeep Kumar,* *Synthesis* **2010**, *9*, 1479-1484.
2. "Stereoselective synthesis of (-)-galantinic acid" Abhishek Dubey, **Anand Harbindu**, Pradeep Kumar,* *Synthesis* **2011**, *6*, 0901-0904.
3. "Organocatalytic Enantioselective Approach to the Synthesis of Verbalactone and (*R*)-Massoialactone" **Anand Harbindu**, Pradeep Kumar* *Synthesis* **2011**, *12*, 1954-1959.
4. "Enantio- and Diastereocontrolled Conversion of Chiral epoxides to *trans*-Cyclopropane carboxylates: Application to the synthesis of Cascarillic acid, Grenadamide and L-(-)-CCG-II" Abhishek Dubey**, Anand Harbindu,** Pradeep Kumar,* *Organic and Biomolecular Chemistry* **2012,** *10*, 6987-6994.
5. "First total synthesis of Seimatopolide B" U. Nookaraju, **Anand Harbindu**, Ankushkumar D. Bhise, Brijesh M. Sharma, Pradeep Kumar* *RSC Advances*, **2012**, *2*, 11231-11234.
6. "Asymmetric route to pentadec-1-en-4-ol: Application to the synthesis of aculeatins F and *epi*-F, insect pheromone *S*/*R*-5-hexadecanolide and solenopsin" **Anand Harbindu**, Brijesh M. Sharma, Pradeep Kumar* *Tetrahedron Asymmetry*, **2012** (Communicated)
7. "Synthesis of Biologically Important motifs of Pyrrole Triazinones and Indole Triazinones" **Anand Harbindu**, Brijesh M. Sharma, Pradeep Kumar* (Manuscript under preparation).
8. Novel application of Leuckart Reaction for the synthesis of [1,2,4]triazino[1,6-a]indol-4(3H)-one and [1,2,4]triazino[1,6-a]pyrrole-4(3H)-one- **Anand Harbindu**, Pradeep Kumar* (Manuscript under preparation).

9. "First Asymmetric total synthesis of Modiolide B" **Anand Harbindu**, Pradeep Kumar* (Manuscript under preparation).
10. "Tricycle structure of substituted sugar drived 1, 2, 3 Triazol derivatives: Small-Molecule Library of Potential Anti-Cancer Therapeutics" **Anand Harbindu**, Brijesh M. Sharma, Pradeep Kumar* (Manuscript under preparation).

Posters presented at symposia / conferences attended

- Attended 4th INSA-KOSEF symposium in Organic Chemistry: Contemporary Organic Chemistry and its Future directions, **Jan 12−13, 2009** conducted at National Chemical Laboratory, Pune, India.
- Attended 11th CRSI National Symposium in Chemistry 2010 held at National Chemical Laboratory (NCL), Pune in **February 2009**.
- Presented poster at 12th CRSI National Symposium in Chemistry 2010 held at Indian Institute of Chemical Technology (IICT), Hyderabad in **February 2010**.
- Presented poster at National Science Day 2010 held at National Chemical Laboratory, Pune, India.
- Attended 8th Indo-French International Symposium in Chemistry, **Jan 6–8, 2012** conducted at National Chemical Laboratory, Pune, India.
- Attended ACS on Campus event, **October 1–12, 2012** conducted at National Chemical Laboratory, Pune, India.

Anand Harbindu