Studies Towards the Synthesis of Phenanthridone Alkaloids Employing PET Initiated α-Arylation of Ketones

THESIS

Submitted To The

UNIVERSITY OF PUNE

For The Degree Of

DOCTOR OF PHILOSOPHY

In

CHEMISTRY

By

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Studies Towards the Synthesis of Phenanthridone Alkaloids Employing PET Initiated α-Arylation of Ketones**" which is being submitted to the **University of Pune** for the award of **Doctor of Philosophy in Chemistry** by **Mr. P. Siva Swaroop** was carried out by him under my supervision at the **National Chemical Laboratory**, **Pune**. A material that has been obtained from other sources has been duly acknowledged in the thesis.

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DECLARATION

I hereby declare that the work presented in the thesis entitled **"Studies Towards the Synthesis of Phenanthridone Alkaloids Employing PET Initiated α-Arylation of Ketones"** submitted for Ph. D. Degree to the **University of Pune**, has been carried out by me at the **National Chemical Laboratory**, **Pune**, under the supervision of **Dr. Ganesh Pandey**. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University/Institute.

Date: (**P. Siva Swaroop**)

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Acknowledgement

This work has been completed with the generous help and encouragement of a number of people. I would like to thank every one of them for their support they have rendered for the accomplishment of the work presented in this dissertation.

I would like to express my deep sense of gratitude to my research guide, ***Dr. Ganesh Pandey****, for introducing me to this fascinating field of Organic Chemistry, also for his support and guidance throughout my association with him. My special thanks to Dr. (Mrs.) S. R. Gadre and for her support during my research. I am grateful to my senior colleagues Dr. Murugan and Dr. Balakrishnan for their sincere advice and guidance during the course of study. I really appreciate and thankful to my colleagues Dr. Shrinivas, Dr. Sanjay, Dr. Prabal, Dr. Kishore, Dr. Keshri, Shrikant, Rajender, Dr. Debasish G, Ravi, Gaikwad, Prasanna, Dr. Nishant, Sujit, Debasis D, Dharmender, Deepak, Priyanka, Rajesh, Binoy, Tukaram, Nitesh, Deepali and newly joined colleagues Dr. Asha, Dr. Gumaste, Durga, Shiva, Animesh, Laha, Janaki Ram, Bhushan, Jagadish and Vinit. I will always cherish memories of these days. I also thank Pawarji for his help during research work.*

Help from the NMR division and CMC group is gratefully acknowledged. Special thanks to Mrs. Kunte, Mr. Sonawane, Mrs. Shantha Kumari and Mrs. Tambe who went out of their way in helping me out in collecting HPLC and LCMS data.

I would like to extend my special thanks to Raman, Seenanna, Sreedhar, Sureshanna, Umashankar, Prakash, Sunilanna and Satya. My special thanks also go to my tablemates, to all my friends from G.J Hostel and NCL -DOC,

Biochemistry, Chemical Engeneering-Polymer Science (a huge list!!) for their constant help and encouragement.

There are no words to acknowledge my parents for their blessings, Love, Care and Continuous encouragement and relatives for their love and support.

Finally, I thank CSIR, New Delhi, for the award of Research Fellowship and Director, N. C. L., for the infra-structural facilities.

Swaroop…

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Section-B

Synthetic studies towards (+)-7-Deoxypancratistatin.

Erratum

Abbreviations

aq.	aqueous	mp	Melting point
bp	boiling point	NMR	Nuclear magnetic resonance
Bn	Benzyl	ORTEP	Orthogonal thermal ellipsoid plots
CSA	Camphorsulfonic acid	PDC	Pyridinium dichromate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene	*p*-TSA	*p*-Toluenesulfonic acid
		py	Pyridine
DCM	Dichloromethane	rt	Room temperature
DEPT	Distortionless enhancement by polarization transfer	TBS	*tert*-Butyldimethylsilyl
		TEA	Triethylamine
DIPEA	*N*,*N*-Diisopropylethylamine	THF	Tetrahydrofuran
DMAP	*N*,*N*-Dimethylaminopyridine	TLC	Thin layer chromatography
DMF	*N*,*N*-dimethylformamide	TMS	Trimethylsilyl
DMSO	Dimethylsulfoxide		
g	gram		
GC	Gas chromatography		
h	hour		
HMPA	Hexamethylphosphoramide		
Hz	Hertz		
ImH	Imidazole		
LAH	Lithium aluminum hydride		
LDA	Lithium diisopropylamide		
mg	Milligram		
min	Minute(s)		
MS	Mass spectrum		
mL	Milliliter		
mmol	Millimole		
MOM	Methoxymethyl		

General Remarks

- All the solvents were purified according to literature procedure.[1]
- Petroleum ether used in the experiments was of 60–80 ^{o}C boiling range.
- Column chromatographic separations were carried out by gradient elution with suitable combination of two solvents and silica gel (60–120 mesh/100–200 mesh/230–400 mesh).
- Reaction progress was monitored by TLC or HPLC. TLC was performed on manually prepared silica gel plates and E-Merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, Iodine, phosphomolibdic acid, *p*-Anisol, $KMnO_4$.
- IR spectra were recorded on Scimatzu, FTIR instrument, for solid either as nujol mull, neat in case of liquid compounds or their solution in chloroform.
- NMR spectra were recorded on Bruker AV 200 (200 MHz ^{1}H NMR and 50 MHz ^{13}C NMR), Bruker AV 400 (400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR) and Bruker DRX 500 (500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR). ^{13}C peak multiplicity assignments were made based on DEPT data.
- Mass spectra were recorded on PE SCIEX API QSTAR pulsar (LC-MS)
- All the melting points recorded are uncorrected and were recorded using Buchi electrothermal melting point apparatus.
- Starting materials were obtained from commercial sources.
- Numbering of compounds, schemes, tables, referencing and figures for each chapter as well as abstract are independent.

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

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Research Guide	Dr. Ganesh Pandey
Title of Thesis	Studies Towards the Synthesis of Phenanthridone Alkaloids Employing PET Initiated α– Arylation of Ketones.
Registration no.	E1/70/Ph.D/2005
Date of Registration	27.4.2004
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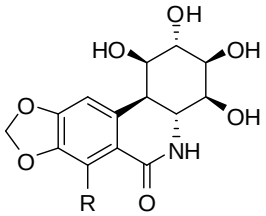
Thesis Abstract

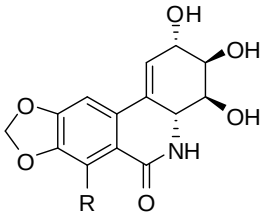
The present dissertation is divided into three chapters.

Chapter 1: Introduction and Importance of Isocarbostyril alkaloids of Amaryllidaceae family.

This chapter gives a brief account on isolation, biological significance and mode of action of isocarbostyril constituents (**1-4**) of *Amaryllidaceae* family. Additionally, this chapter also provides a current understanding regarding the essential and variable pharmacophores of pancratistatin (**1**) and narciclasine (**3**) responsible for biological activities, through structure activity relationship (SAR) studies.



1 R = OH; (+)-Pancratistatin
2 R = H; (+)-7-deoxypancratistatin



3 R = OH; (+)-Narciclasine
4 R = H; (+)-Lycoricidine

Figure: 1: Structure's of Isocarbostyril alkaloids.

Chapter 2: Synthetic Approaches Towards Isocarbostyril type of *Amaryllidaceae* alkaloids: Literature Reports

Amaryllidaceae constituents represent ideal targets on which synthetic design can be practiced in esthetic manner because of their interesting structural features. This chapter summarizes few of the important synthetic approaches reported in the literature by different groups towards the total synthesis of isocarbostyril alkaloids e.g. lycoricidine (**4**), 7-(+)-deoxypancratistatin (**3**) and pancratistatin (**1**).

Chapter 3: Synthetic studies towards (+)-lycoricidine (4) and (+)-7-deoxypacratistatin (2)

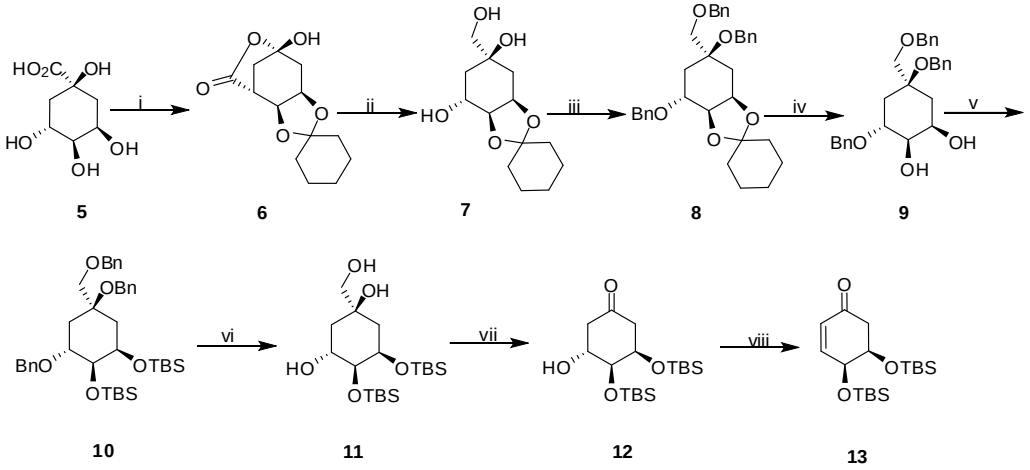
This chapter is divided into two sections. While Section-A describes synthetic attempts towards (+)-lycoricidine (**4**), section-B presents efforts towards the synthesis of (+)-7-deoxypancratistatin (**2**). This chapter, also, discusses briefly about a protocol developed earlier in our laboratory for the synthesis of benzannulated compounds by generating arene radical cations, through photoinduced electron transfer processes and their intramolecular cyclization with tethered enol silyl ethers acting as nucleophiles.

Section-A: Synthetic studies towards (+)-lycoricidine (4)

Our continuing interest in exploring the application of our methodology, in the total synthesis of architecturally complex alkaloids (**1**-**4**), encouraged us to synthesize **4** by following the sequences as discussed below:

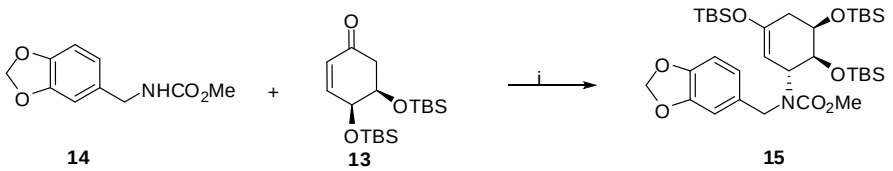
Synthesis of chiral enone 13

The similarities in the stereochemistries of C_3 and C_4 between enone **13** and lycoricidine **4**, led us to visualize an approach outlined in Scheme-1.



Scheme-1 ***Reagents and conditions:*** *i) Cyclohexanone, DMF, p-TSA (cat), PhH, reflux, 8 h, 95 %; ii) $NaBH_4$, EtOH, rt, 2 h, 90 %; iii) NaH, DMF, 60 ^oC, BnCl, rt, 24 h, 88 %; iv) HOAc-H_2O (8:2), 80 ^oC, 8 h, 96 %; v) TBSCl, ImH, DCM, DMF, rt, 24 h, 97 %; vi) H_2/Pd-C, EtOH, 60psi, 6 h, quant; vii) $NaIO_4$, EtOH-H_2O (9:1), rt, 0.5 h, 95 %; viii) MsCl, TEA, DCM, 0 ^oC, 90 %.*

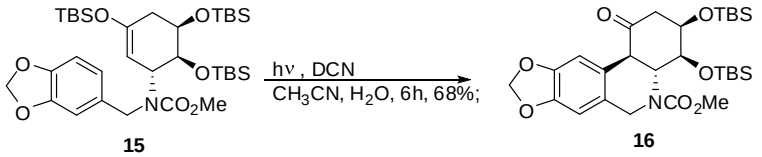
Carrying out an aza-Michael addition with N-lithiated piperonyl carbamate, followed by trapping of the lithium enolate as its TBS enol silyl ether, afforded a conjugate adduct **15**. The C_4 carbon stereochemistry of the enone directed the anti approach to it producing **15** as a single isomer (Scheme-2).



Scheme-2 *Reagents and conditions**:** i) n-BuLi, THF, HMPA, -78 ^oC, TBSCl, 95 %.*

Synthesis of phenanthridone 16

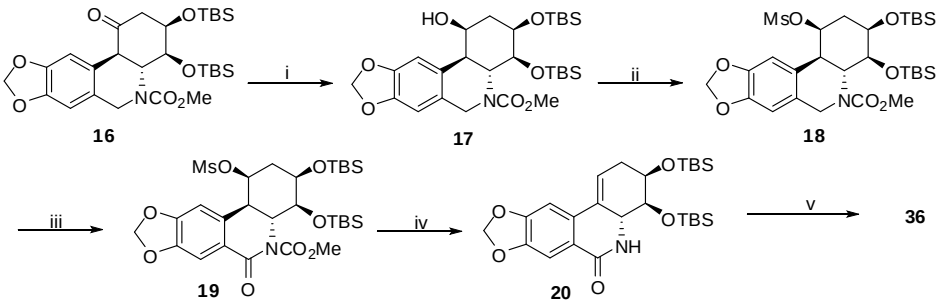
PET cyclization of **15** (0.6 g, 0.88 mmol) was carried out by irradiating (Pyrex filter, >280 nm, 450 W Hanovia medium pressure lamp) it with 1, 4-Dicyanonaphthalene (0.05 g, 0.28 mmol) in acetonitrile: water (24:1) 250 ml for 6 h gave cyclized phenanthridone **16** (Scheme-3).



15 **16**

Scheme-3

In order to synthesize the compound **20**, simple functional group transformations were carried out on **16**, which are out lined in the scheme-4. Removal of TBS by TBAF/THF in the molecule **20**, led to the synthesis of deoxy analogue of **4** *i.e*, (+)-7-deoxylycoricidine **36** (Scheme-4).

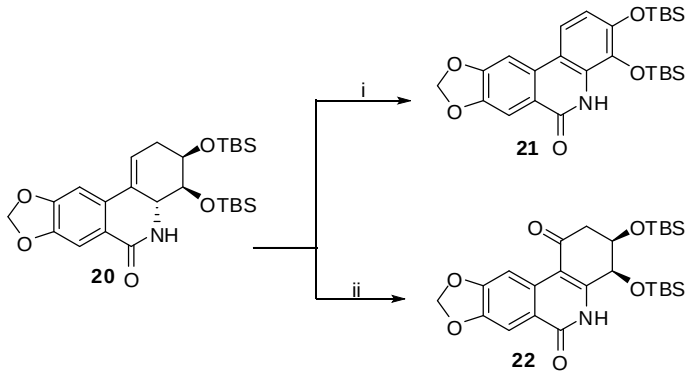


16 **17** **18** **19** **20**

Scheme-4 *Reagents and conditions: i) $NaBH_4$, EtOH, 0 ^oC-rt, quant; ii) MsCl, Et_3N, DCM, 0 ^oC-rt, 87 %; iii) $RuCl_3$ (cat), $NaIO_4$, CCl_4-CH_3CN-H_2O (2:2:3), rt, 1 h, 60 %. iv) DBU, toluene, 80 ^oC, 12 h, 78 %. v) TBAF, THF, 0 ^oC, 8 h, 81 %.*

Synthetic attempts towards (+)-lycoricidine (4)

With the rapid construction of lycoricidine frame work, installation of C_2 hydroxy group on the C-ring with the correct relative stereochemistry was investigated. NBS mediated Allylic bromination reaction and Selenium dioxide mediated oxidations on compound **20** resulted in producing the totally aromatized product **21.** Allylic oxidation with $NaClO_2$/TBHP gave a rearranged product **22** (Scheme-5). Palladium catalyzed allylic oxidations and PDC/TBHP oxidation on **20** both produced minor amounts of **21** and **22** mixtures along with the starting material.



Scheme-5

Reagents and conditions: *i) NBS, CCl_4, reflux, 12 h; ii) $NaClO_2$, TBHP, CH_3CN-H_2O (3:1), 50 ^oC, 30 h.*

In conclusion, we have demonstrated the application of our PET mediated C-C bond forming strategy to carry out studies toward the synthesis of lycoricidine (**4**), which posed several difficulties during the final radical mediated allylic C_2 oxidation to complete the synthesis.

Section-B: Synthetic studies towards (+)-7-deoxypancratistatin (2)

Owing to significant stereochemical complexity, we took the challenge of synthesizing **2** using PET mediated α-arylation of ketones as the key strategy. In this context, we designed two different parallel routes to synthesize this alkaloid. The corresponding synthetic routes are discussed below.

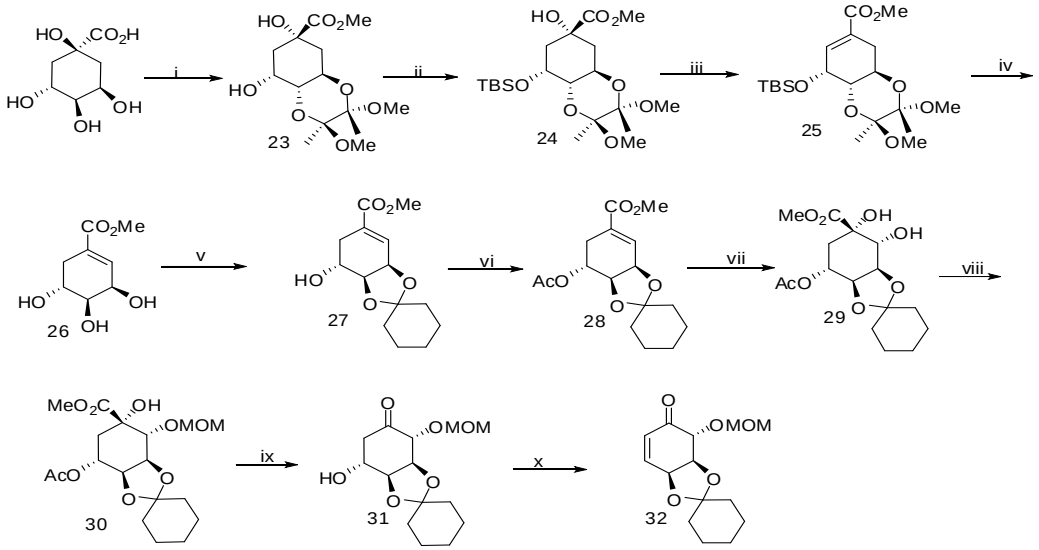
Investigation of Strategy-I

Synthesis of **2**, started with the preparation of enone **32**, and silylenol ether **33** followed by the crucial intramolecular carbocyclization reaction.

Synthesis of enone 32

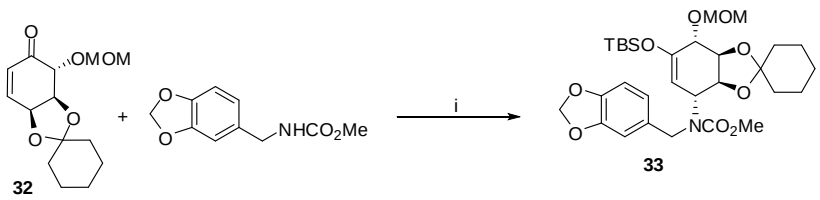
In our planned approach towards the synthesis of 7-deoxypancratistatin (**2**), the required suitably substituted chiral enone was synthesized from D-(-)-quinic acid (**5**), considering the resemblance of 3, 4-*syn* hydroxyl functionalities of both starting material and final natural pancratistatins. The C_2 position was equipped with the hydroxyl functionality through the osmium tetroxide mediated

dihydroxylation of Shikimic acid derivative (**28**). While the quaternary center was easily converted to ketone, elimination of C_5 hydroxyl group yielded the trisubstitued enone (**32**) (Scheme-6).



Scheme:6 *Reagents and conditions: i) 2,3-butanedione, $CH(OMe)_3$, CSA (cat), MeOH, reflux, 16 h, 98 %; ii) TBSCl, ImH, DMF, 24 h, 95 %; iii) $POCl_3$, Py, 3days, 40 ^oC, 83 %; iv) 80 % AcOH-H_2O, 24 h, 86 %; v) cyclohexanone, DMF, PhH, 8 h, 90 %; vi) AcCl, py, dry DCM, rt, 6 h, quant; vii) OsO_4, TMO, Py, H_2O, Bu^tOH, 8 h, reflux, 86 %; viii) MOMCl, DIPEA, dry DCM; ix) a) LAH, THF, 3 days, 50 ^oC; b) $NaIO_4$, p^H 7 buffer, 0.5 h, 60 %; x) $POCl_3$, Py, 3 h, rt, 62 %.*

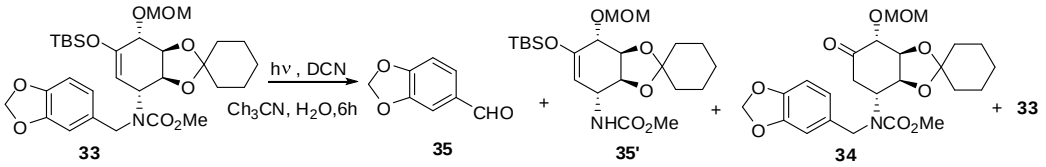
Carrying out an aza-Michael addition with N-lithiated piperonyl carbamate, followed by trapping of the lithium enolate as its TBS enol ether afforded **33 (**Scheme-7).



Scheme-7: *Reagents and conditions. i) n-BuLi, THF, HMPA, -78 ^oC, TBSCl, 88 %.*

Investigation of the carbocyclization reaction on 33

The planned intramolecular carbocyclization by irradiating **33** with a mixture of DCN in CH_3CN:H_2O (24:1) failed to yield the expected cyclized product. Only un-reacted **33** along with a minor amount of benzyl cleaved products **35** and **35'** could be isolated at the end of the reaction (Scheme-8). The possible explanation to this failure could be advanced by considering the high conformational rigidity developed by the C_3-C_4 cyclohexylidine ketal and functionalization on C_2 (-OMOM) which restricted the flexibility of C ring preventing the nucleophilic attack of silyl enol ether to arene radical cation.



Scheme-8:

Investigation of Strategy-II

Attempts carried out for the regioselective electrophilic oxidation of kinetic enolate of **16**, with different bases and oxidizing agents failed. It was realized from the results that, possibly the steric bulk created by the TBS group at C_3 position, may be preventing the approach of the oxidizing agent to the enolate moiety.

In conclution, the present routes indicate few shortcomings in structural confirmations in current substrates **16** and **33** that if resolved, may provide efficient synthesis of (+)-7-deoxypancratistatin (**2**).

Summary

The overall synthetic construct was a valuable matrix of experiments, which culminated in the attempts towards the total synthesis of **2** and **4**

Experimental section at the end of each section in this chapter provides detailed experimental procedures, tabulated spectral data and copies of ^{1}H & ^{13}C NMR spectra of all new compounds.

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

Chapter -1

Introduction and Importance of Isocarbostyril alkaloids of Amaryllidaceae family.

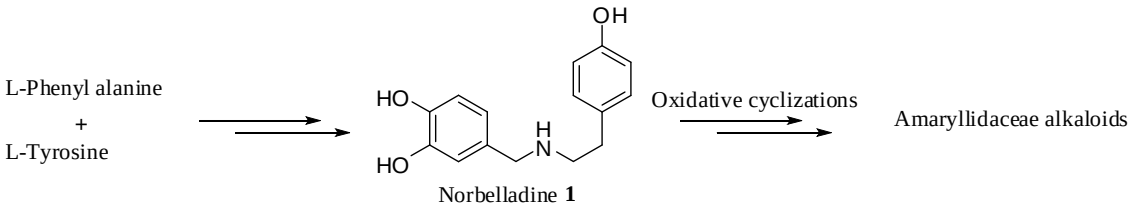
1.1. Introduction

The natural products are chemical compounds produced by living organisms found in nature. They can be extracted from tissues of terrestrial plants, marine organisms and microorganism's fermentation broths. Not only they offer an invaluable source of lead compounds with a wide variety of chemical structures and biological activities, they also play highly significant role in the discovery and development of new drugs for the treatment of human diseases.

During early years of 19^{th} century, it was found that the plant extracts which contained nitrogen bases formed salts with acids. Therefore, they got classified as the vegetable alkalis or alkaloids. Alkaloids may be grouped according to their plant sources e.g. *Aconitum, Amaryllidaceae, Cinchona, Curare, Ergot, Opium, Senecio and Vinca*. Another classification is based on the structure of the ring system containing the nitrogen atom e.g. piperidine, isoquinoline and indole. Mostly, alkaloids reflect their biosynthetic origin from amino acids such as ornithine, lysine, phenylalanine, tyrosine and tryptophan.

1.2. Amaryllidaceae class of alkaloids.

The *Amaryllidaceae* class of alkaloids; representing a group of isoquinoline alkaloids, are known to be formed biogenetically by intramolecular oxidative coupling of norbelladines derived from L-phenylalanine and L-tyrosine (Figure-1). The alkaloids under this family mainly consist of 7 structural types, *viz.* lycorine (**6**) (1H-pyrrolo [3,2,1-d,e] phenanthridine type), crinine (**9**) (5,10b-ethanophenanthridine type), pancratistatin (**2**) (isocarbostyril type), galanthamine (**8**) (6H-benzofuro [3a,3,2-e,f]-2-benzazepine type), tazettine (**10**) (2-benzopyrano [3,4-c] indole type), lycorenine (**11**) (2-benzopyrano [3,4-g] indole type) and montanine (**7**) (5,11-methanomorphanthridine type) (Figure-2).



Figure–1

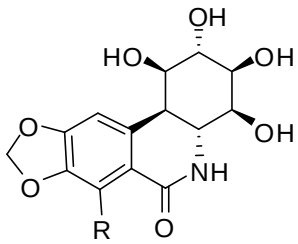
Category

Alkaloid structure

Isocarbostyril type

R= OH, Pancratistatin (**2**)

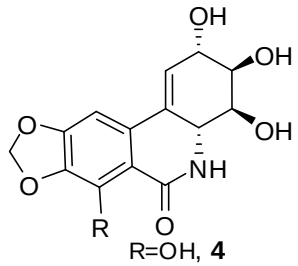
R= H, Deoxypancratistatin (**3**)



R=OH, **2**
R=H, **3**

R= OH, Narciclasine (**4**)

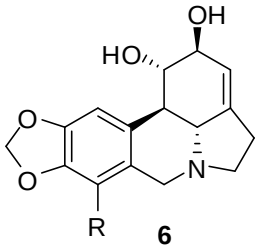
R= H, Lycoricidine (**5**)



R=OH, **4**
R=H, **5**

1H-pyrrolo [3,2,1-d,e] phenanthridine type

Lycorine (**6**)



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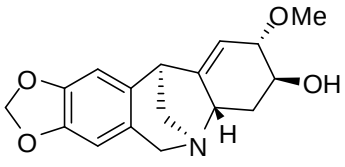
5,11- methanomorphanthridine type

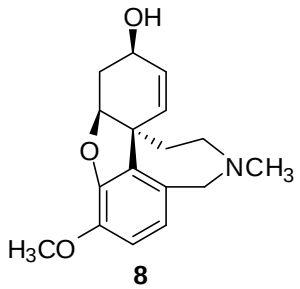
Montanine (**7**)



7

6H-benzofuro [3a,3,2-e,f]-2-benzazepine type

Galanthamine (**8**)



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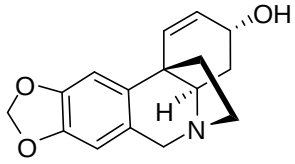
5,10b-ethanophenanthridine type

Crinine (**9**)



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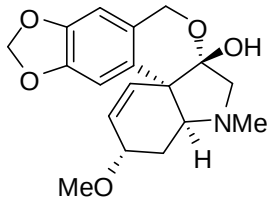
2-benzopyrano [3,4-c] indole type

Tazettine (**10**)



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2-benzopyrano [3,4- g] indole type

Lycorenine (**11**)

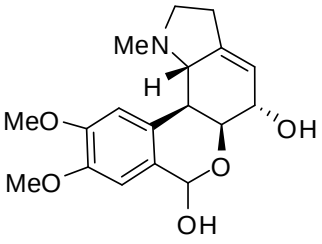

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Figure-2: *Types of Amaryllidaceae plant alkaloids.*

1.3. Importance of Amaryllidaceae alkaloids.

These classes of alkaloids have been known for their medicinal and also toxic values since ancient Greek[1]. It dates back to at least the 4th century BC, when Hippocrates used oil from the Daffodil bulbs Narcissus poeticus L. for the treatment of cancer[1]. Lycorine (**6**), the first member of this class was studied for its antitumor activity.[3,4] The antitumor potential of other amaryllidaceae isocarbostyril derivatives e.g. narciclasine (**4**), lycoricidine (**5**), and pancratistatin (**2**), have long been studied and recently reviewed.[5] Other than anti-tumor activities, these alkaloids were also known to exhibit anti viral and anti feedant activities. Presently, galanthamine (**8**) which belongs to this class of alkaloid is commercially successful as acetylcholinesterase inhibitor (used for the treatment of Alzheimer's disease) and is marketed under the trade name Razadyne. ®

1.4. Natural sources of the Isocarbostyril alkaloids of Amaryllidaceae family.

One of the most widely reported source of narciclasine (**4**)[2] is the bulbs of *Narcissus incomparabilis* (yield 0.2 g/kg during flowering stage of the plant) and can also be isolated from Zephyranthes *flava*, a tropical and subtropical plant cultivated in India[2]. The deoxy analog of **4**, generally known as lycoricidine (**5**) was first discovered in L. *radiata* in 1968[18] and is isolated in good amount from wild Hawaiian bulbs of H. *littoralis* (yield ~ 0.12 g/kg).[18b] The structurally similar analog of **4**, pancratistatin (**2**) was found in low quantities in plant bulbs such as P. *maritinum,* Z. *flava*, H. *kalbreyeri and* P. *littorale*,[7] however, the rare tropical bulbs of H. *littoralis* seem to be the good source of **2.**

1.5. Biological Evaluation of Isocarbostyril type of Amaryllidaceae alkaloids:

1.5.1. Antitumor activity of natural analogs.

a) Derivatives of Narciclasine (4).

The biosynthetic derivative of narciclasine (**4**), 2-O-β-D-glucopyranoside derivative kalbreclasine (**12**)[2] provoked significant activation of spleenic lymphocytes *in vitro*, a feature characteristic of immunostimulants.[2b] Another natural β-D- glucose derivative **13** showed cytotoxic activities against Artemia *salina* and anti tumor properties against potato discs infected with Agrobacterium *tumifaciens* (53 % inhibition of crown gall) which are comparable to **4**. Recently, the *trans*-dihydronarciclasine (**14**)[2c] was found to be active against murine P-388 lymphocytic leukemia cells (Fig-3).

b) Derivatives of lycoricidine (5).

The *trans*-dihydrolycoricidine (**15**), a derivative of **5** in which the B/C rings are *trans* linked, is shown to possess antitumor activity[2d] against melanoma subpanel cell lines, NSC lung, colon, brain and renal cell lines.

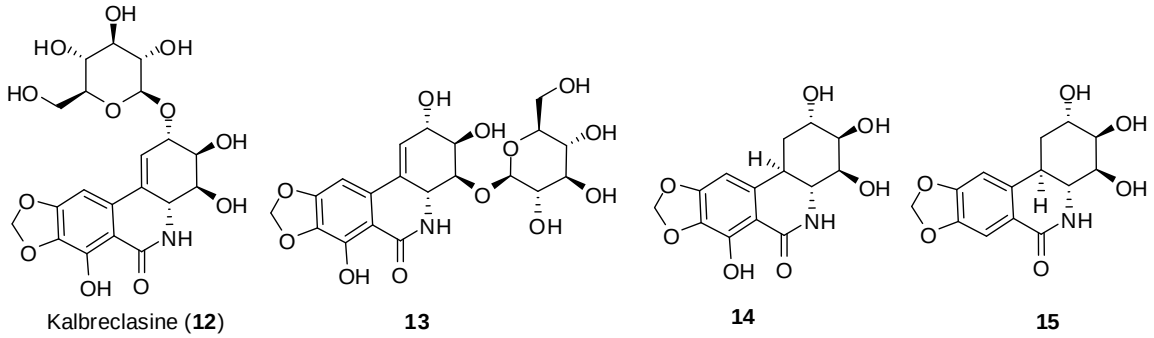


Figure: 3 Chemical structures of natural derivatives of Narciclasine and Lycoricidine

c) Derivatives of pancratistatin (2).

The 2-O- β-D-glucopyranoside derivative[2e] **16** of pancratistatin (**2**) was found to promote germination of seeds and the growth of roots. Other natural derivatives such as **17**, **18**, **19** and **20** exhibited appreciable cytotoxicities (Fig-4).

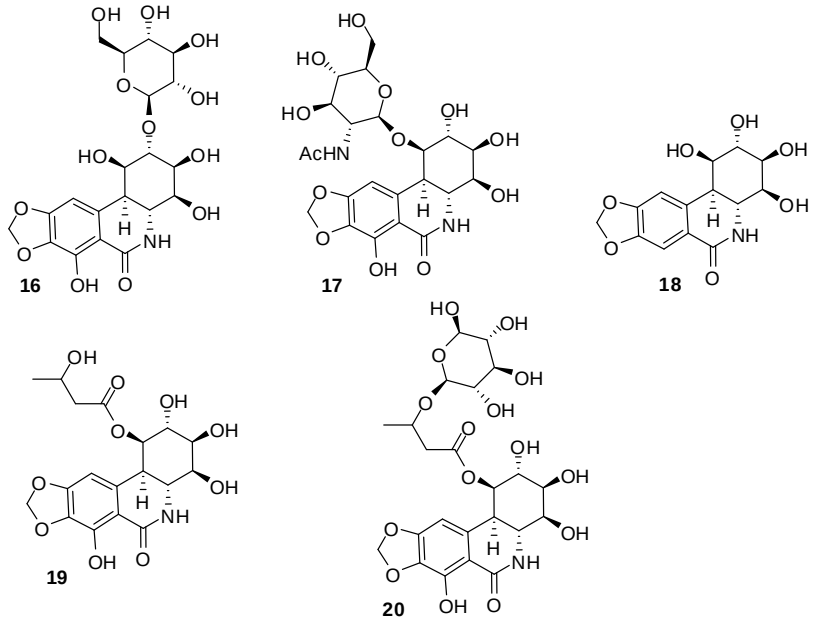


Figure: 4 Chemical structures of natural derivatives of pancratistatin **2**

1.5.2. Antitumor activity of unnatural analogues.

Unnatural analogues – SAR studies.

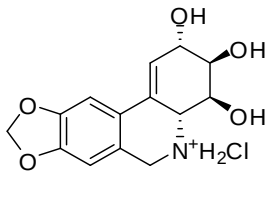
The search for the minimum pharmacophore and to understand the mode of the action, resulted in the syntheses and biological screening of many unnatural derivatives which provided essential information about some of the functional groups required for the activity. As a result, series of derivatives and analogues were synthesized (fully or semisynthetic) to obtain more active and/or soluble products (Fig-5). Some of these analogues were selected for the preclinical development as anticancer agents and also their structure–activity relationship was explored. Several key positions in the molecule were modified. For example, one such modification involved the reduction of the lactam carbonyl group to obtain amine hydrochloride salt of lycoricidine (**21**) but this modification was found to have low impact on cytotoxicity. Fully synthetic compounds **22** and **23** in which the lactam carbonyl was replaced by lactone functionality, showed no significant cytotoxic activity against L1210 murine leukemia cells[13]. All these modifications indicate that the lactam carbonyl is essential for cytotoxic activity.

Three deoxy analogs of these alkaloids **24**, **25**, **26**, showing weak antitumor activity, revealed that the C_2, C_3, and C_4 hydroxyl groups were essential for showing the

cytotoxicity and can be considered as a minimum required pharmacophore. Another modification concerning the B/C ring junction stereochemistry (e.g. **27**, **28** and **29**) were also carried out and all these compounds showed weaker cytotoxicity than the parent natural products. The cytotoxicity of **29** against P388 murine leukemia and several human cancer cell lines was found to be about 1000 times less potent than pancratistatin (**2**).

Modification of the benzodioxole moiety of **2** was investigated through the synthesis of the analogs *i.e.*, the methoxy analog **30** and β–carboline analog **31** and evaluation of their activity revealed that these are 100 times less potent against P388 lymphocytic leukemia and other human cancer cell lines (BXPC-3, MCF-7 and KM20L2).[12b] These results show that an intact methylenedioxyphenyl or benzodioxole functionality is essential for significant cancer cell cytotoxicity in these classes of natural compounds. The only unnatural analogue that has been found to be 10 times more active than **2** is phenpanstatin (**32**) [12a] (Fig-5).

Since, pancratistatin (**2**) exhibited very low water solubility (53 μl/ml),[12] to increase aqueous solubility phosphate prodrugs were also synthesized, but they all displayed markedly lower cytotoxicity *in vitro*.[11]



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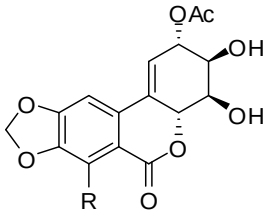
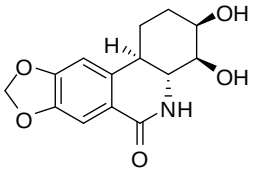


R=H,**22**
R=OH,**23**



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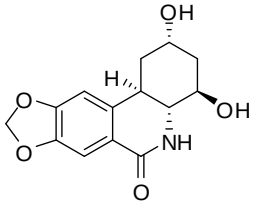

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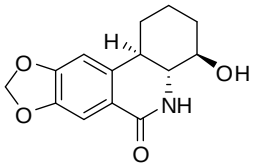

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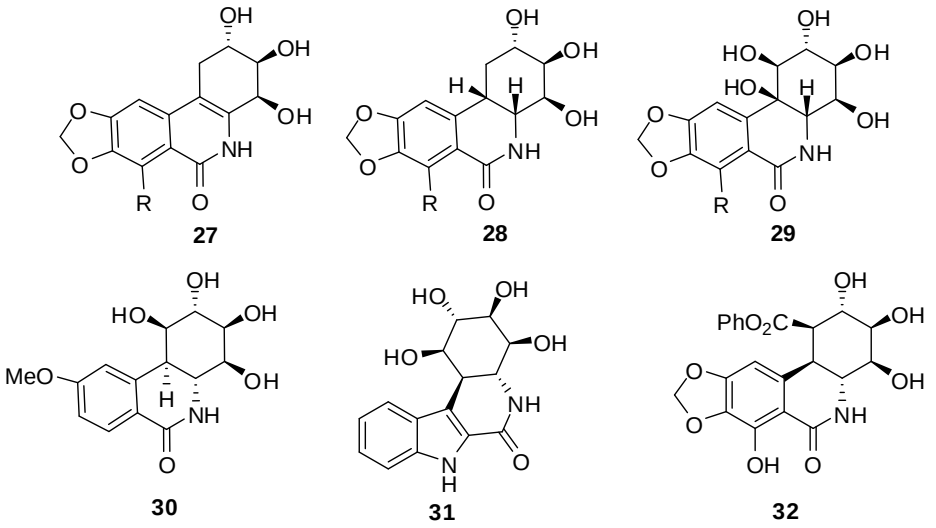

Figure: 5 *Chemical structures of fully and hemi synthesized isocarbostyril derivatives.*

1.5.3. Mechanism of action.

Narciclasine (**4**) and lycoricidine (**5**) were first identified as plant growth inhibitors involved in inhibiting the synthesis of proteins and the development of chloroplasts. Narciclasine (**4**), although, not effective in *in vitro* protease activity, is known to inhibit protein synthesis at the ribosomal level and is also described as an anti mitotic substance displaying colchicines-like activities.[7] It was also found to be an inhibitor for peptide bond formation in eukaryotic ribosomes considering its ability to bind to the 60-S ribosomal subunit or more precisely to the peptidyltransferase center.[8] It is also known to prevent the transfer of the N-acetylleucyl residue from CACCA-leu-Ac onto puromycin. Therefore, it is postulated that these alkaloids are inhibitors of the transpeptidation reaction. Narciclasine (**4**) induces apoptosis by triggering the activation of the initiator caspases (caspase-8 and -10) in human MCF-7 breast and PC-3 prostate carcinoma cells.[11] Unlike **4**, pancratistatin (**2**) is known to induce rapid apoptosis in neuroblastoma cells in murine P388, lymphocytic leukemia and M-5076 ovary sarcoma models *in vivo*[13] by disruption of the mitochondrial membrane potential and DNA fragmentation.[9]

1.5.4. Conclusions from SAR studies of pancratistatin.

There has been serious research activity over the years concerning SAR with pancratistatin analogues in order to identify active pharmacophore and to discover more bioavailable derivative or potential prodrugs. From these studies, it has emerged that regions crucial for maintaining the activity of **2** are as follows:

1) The presence of phenolic and / or phenanthridone functionalities as a potential donor- acceptor pair is essential.[17]
2) The piperonyl type ring A is must for enhanced activity. Changes in the substitution pattern or functionalities elsewhere in the aromatic core structure leads to decreased activity.[14]
3) The correct spacial orientation of the peripheral hydroxyl functions in the aminocyclitol-type ring C and the aminoinositol moiety must remain essentially intact, except for variations of substituents, functionalities and configuration at C_1.
4) The *trans* stereochemistry of the B/C ring junction is essential for activity.[15] Therefore, the potential of variation in structure appears to be the greatest in the region between C_1 and $C_8/C_9/C_{10}$ portion of the aromatic core.

1.5.5. Conclusions from SAR studies in narciclasine.

A comprehensive view of the cytochrome P450 3A4 inhibitory pharmacophore has been developed through SAR studies on **4** which reveal the following points.

1) A small substituent such as hydroxyl and acetoxyl contributes to cytochrome interaction at H-bond acceptor region at C_1.
2) The cytochrome interaction is enhanced when a bulky lipophilic substituent such as silyl group is placed at C_2 or C_4 indicating a strong interaction with a large hydrophobic binding pocket in the cytochrome active site.
3) A double bond between the C_1-C_{10b} elicits strong interaction with the cytochrome alone.

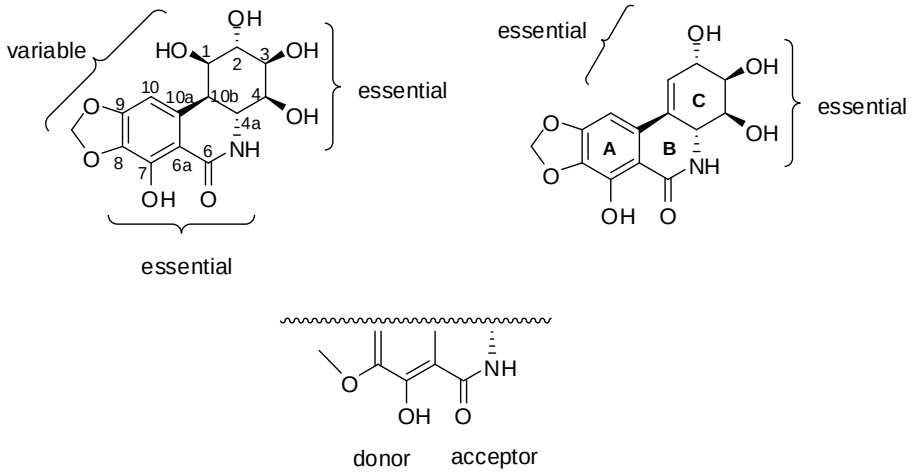

Figure: 6

1.6. Summary

1. Since the discovery of narciclasine (**4**), the first member of isocarbostyril class of alkaloids in 1967, the search for new natural compounds from the *Amaryllidaceae* plant family has resulted in the isolation of other isocarbostyrils such as **2**, **3** and **5**.
2. The search for new anticancer drug analogues that resemble the structural motifs of natural products represents an endeavor with the potential for discovery as well as the eventual deciphering of the mode of action of these compounds.
3. It is clear from the results of the biological screening that none of the unnatural derivatives rival the potency of either **2** or **4**.
4. *Amaryllidaceae* constituents represent ideal targets on which synthetic design may be practiced in esthetic manner. There is no doubt that the activity in this field will continue at the interface of biology (activity screening) and chemistry (synthetic design). The potential for discovery in both disciplines is enormous and valuable results will surely be forthcoming.

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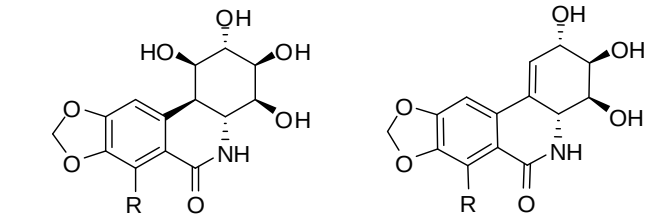
Chapter -2

Synthetic Approaches Towards Isocarbostyril type of Amaryllidaceae alkaloids: Literature Reports.

2.1 Introduction.

Over the years, plants of the *Amaryllidaceae* family have long been known for their medicinal and toxic properties[1]. These alkaloids have attracted considerable attention from the synthetic community because of their interesting structures and potent biological activities[1]. Extremely low natural abundance as well as practical complications in the separation of the desired compounds from plant constituents diminishes the probability of reasonable supply by means of isolation. Therefore, significant efforts have been made in developing viable synthetic routes.



R=OH (+) Pancratistatin **1**
R=H (+) Deoxypancratistatin **2**

R=OH (+) Narciclasine **3**
R=H (+) Lycoricidine **4**

Figure: 1: Structure's of Isocarbostyril alkaloids.

The task has been addressed by various research groups in two different dimensions over two decades, one of the two has been dealing with the quest for short, high yielding synthesis of the naturally occurring isocarbostyril's which promoted the screening and development of great number of existing and new methodologies[3-38] for their capabilities. The other dimension is looking for the potential and more bioavailable derivatives to substitute them in all respects. This particular search resulted in the syntheses of various truncated and unnatural derivatives[39–47] through which the scientific community has been enlightened with the substantial amount of this information regarding essential and variable pharmacophores of these molecules.

This chapter constitutes an update of the major developments in *Amaryllidaceae* isocarbostryls (a summary of the total syntheses is depicted in the form of a table-1). Since the detailed discussion of all the literature reported syntheses have already been reviewed by many others[2] and also it would be beyond the scope of this dissertation, the foregoing discussion would mainly focus on few of the important methodologies involved in the literature reported syntheses of (**1-4**).

Table-1: Reported Total Syntheses of the *Amaryllidaceae* Isocarbstyrils.

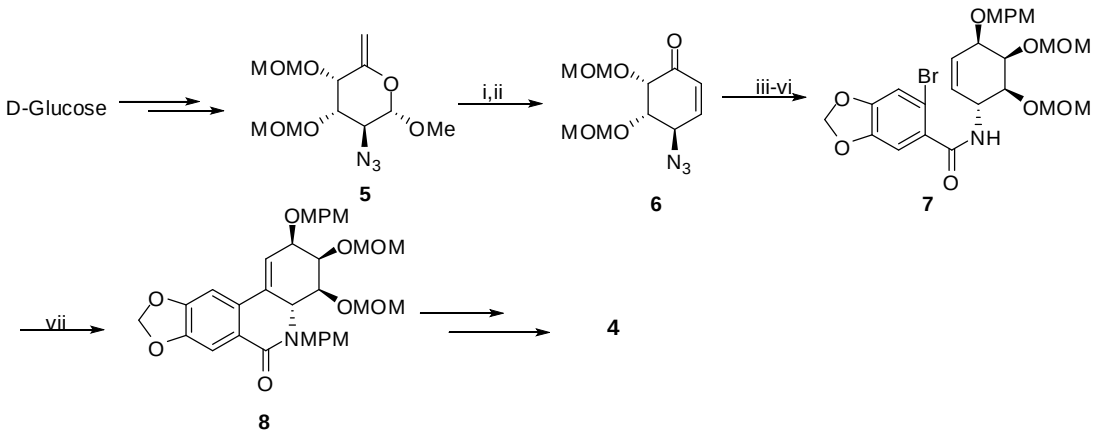
Isocarbostyril	Research group	Publication year	No.of steps	Overall yield(%)	refs
(±)-Lycoricidine	Ohta, Kimoto	1975	20	1.5	3
(+)-Lycoricidine	Paulsen	1982	12	4	4
(±)-Lycoricidine	Schubert	1987	18	7.2	5
(+)-Lycoricidine	Ogawa	1991	23	0.04	6
(+)-Lycoricidine	Hudlicky	1992	8	12	7
(±)-Lycoricidine	Martin	1993	11	4	8
ent-Lycoricidine	Keck	1996	14	11	9,10
(+)-Lycoricidine	Keck	1999	11	27	10
(+)-Lycoricidine	Yan	2002	15	11	11
(±)-Lycoricidine	Padwa	2006	15	10	12,13
(+)- Narciclasine	Rigby	1997	23	0.2	14,15
(+)- Narciclasine	Hudlicky	1999	9	0.6	16,17
(+)- Narciclasine	Keck	1999	14	16	10
(+)- Narciclasine	Yan	2002	13	17	18
(±)-Pancratistatin	Danishefky	1989	27	0.16	19
(+)-Pancratistatin	Hudlicky	1995	14	2	20,21
(+)-Pancratistatin	Trost	1995	19	8	22
(+)-Pancratistatin	Haseltine	1997	24	0.97	23
(+)-Pancratistatin	Magnus	1998	22	1.2	24
(+)-Pancratistatin	Rigby	2000	23	0.35	15
(+)-Pancratistatin	Pettit	2001	10	3.6	25
(±)-Pancratistatin	Kim	2002	21	4	26
(+)-Pancratistatin	Li	2006	13	9	27
(+)-7-Deoxypancratistatin	Paulsen	1982	9	6.5	4
(+)-7-Deoxypancratistatin	Keck	1995	21	7	28
(+)-7-Deoxypancratistatin	Hudlicky	1995	12	2.6	29
(+)-7-Deoxypancratistatin	Hudlicky	1995	10	3	21,29
(+)-7-Deoxypancratistatin	Chida	1996	29	0.03	30
(+)-7-Deoxypancratistatin	Keck	1998	13	21	31
ent-(-)-7-Deoxypancratistatin	Hudlicky	1999	14	1	32
(+)-7-Deoxypancratistatin	Plumet	2000	21	3	33
(+)-7-Deoxypancratistatin	Madsen	2006	13	1.4	34
(+)-7-Deoxypancratistatin	Madsen	2006	23	4.3	34
(±)-7-Deoxypancratistatin	Padwa	2006	23	3	13,35
(±)-*trans*-dihydronarciclasine	Cho	2007	15	11	36
(±)-*trans*-dihydrolycoricidine	Tsuda	1978	16	1.1	37
(+)-*trans*-dihydrolycoricidine	Chida	1996	24	0.18	30
(+)-*trans*-dihydrolycoricidine	Iwabuchi	2005	24	1.4	38

2.2.1. Synthetic approaches towards (+)-lycoricidine (4).

The first total synthesis of **4** was reported in 1975 in its racemic form by S.Ohta[3] and the chiral synthesis was reported by Paulsen in 1982[4]. Few of the more important ones are described as follows:

a) Ogawa's approach (Chida, N.; Ohtsuka, M.; Ogawa, S. *Tetrahedron Lett.* **1991**, *32*, 4525)

Stereoselective synthesis of **4** was accomplished starting from D-glucose employing catalytic version of the Ferrier rearrangement[6c,d] to prepare substituted cyclohexenone derivative **6** (C-ring of **4**) which was elaborated into **7.** Pd-Catalyzed intramolecular Heck-type reaction of **7** resulted phenanthridone skeleton **8**, further with few functional group transformations completed the total synthesis of **4** with 0.04 % overall yield in 23 steps (Scheme-1).



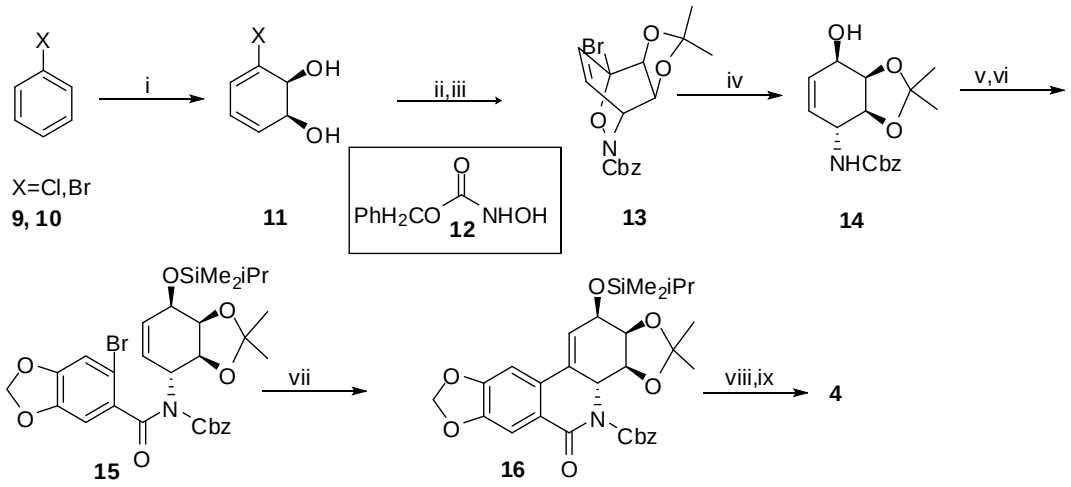
Scheme-1

Reagents and conditions: *i) $(CF_3CO_2)_2Hg$, (1mol %), acetone-water (2:1), rt; ii) MsCl, Et_3N, CH_2Cl_2, (69 %, two steps); iii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 86 %; iv) NaH, MPMCl, DMF, 69 %; v) $LiAlH_4$, ether.; vi) 6- bromopiperonylic acid, $(EtO)_2P(O)CN$, Et_3N, DMF, (89 %, two steps); vii) a)iv.; b) $Pd(OAc)_2$ (20mol %), DIPHOS (40 mol %), TlOAc (2mol equiv), DMF, 140 ^oC, 68 %.*

b) Hudlicky's approach (Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694.**)**

Cyclohexadiene *cis*- diol **11**, obtained by the dioxygenation of either **9** or **10** using *Pseudomonas putida*, was utilized for the cycloaddition reaction with acyl nitroso

compound to obtain **13** stereoselectively. Its reduction gave amino alcohol **14** which on acylation using bromo piperonyl chloride followed by intramolecular Heck reaction provided **4** in total 8 steps with 12 % overall yield (Scheme-2).

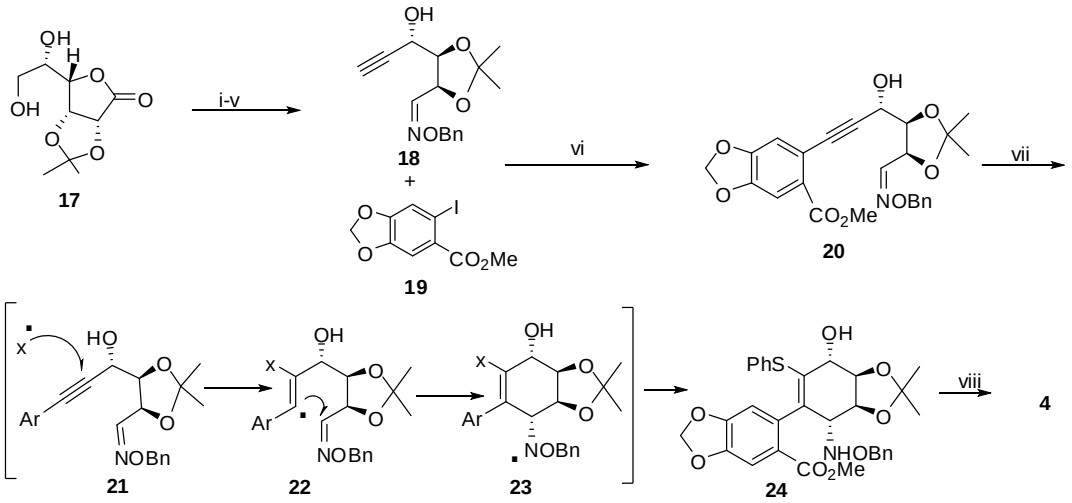


Scheme-2

Reagents and Conditions: *i) Pseudomonas putida.; ii) DMP, acetone, p-TsOH; iii)* ***12****, Bu_4NIO_4, CH_2Cl_2, 74 %; iv) Al (Hg), THF; v) $ClSiMe_2Pr^i$, Im, 98 %; vi) BuLi, THF, -78 ^oC, then Br-piperonyloyl chloride, 77 %; vii) $Pd(OAc)_2$, Tl (OAc), DIPHOS, anisole, 27 %; vii) Pd (C), cyclohexene, EtOH, 99 %; viii) CF_3CO_2H, 0 ^oC, 85 %.*

c) Keck's approach (Keck, G. E.; Wager, T. T.; Duarte Rodriquez, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 5176).

Stereoselective 6-*exo* radical cyclization of a vinyl radical **22**, obtained by the regioselective addition of phenylthiyl radical on O-benzyloxime **21**, formed the key strategy for assembling the functionalized cyclohexene **24**. Finally, the SmI_2 mediated reduction of **24** effected the completion of the synthesis of **4** in total 11 linear steps and 27 % overall yield (Scheme-3).

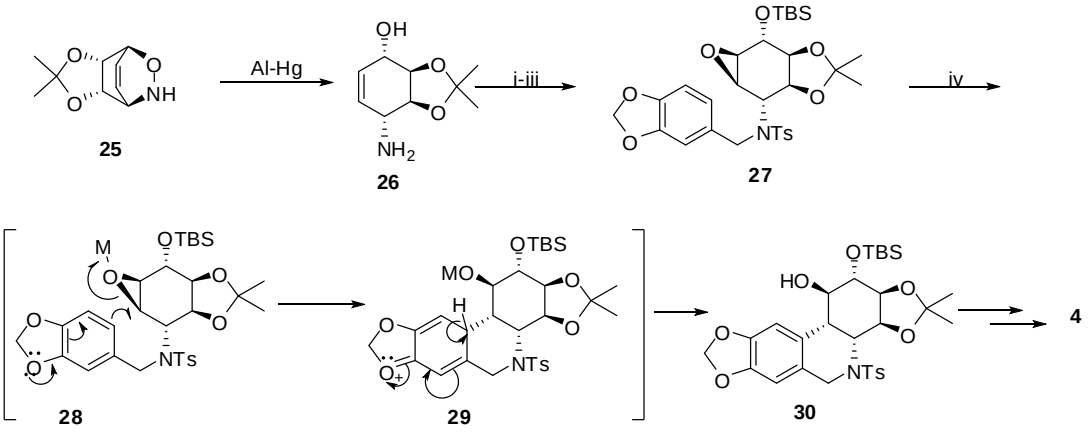


Scheme-3

Reagents and conditions*: i) $NaIO_4$, CH_2Cl_2; ii) CBr_4, PPh_3, NEt_3, 80 % (two steps); iii) L-Selectride, Et_2O, -78 °C; iv) $HCl.H_2NOBn$, pyridine, 90 % (two steps); v) ^nBuLi, Et_2O, - 90 °C, 93 %; vi) $Pd(OAc)_2$, Et_3N, PPh_3, CuI, THF, 95 %; vii) PhSH, hν, tol, 27 °C, 90 %; viii) a) SmI_2, THF, 86 %; b) TFA, 90 %.*

d) Yan's approach (Elango, S.; Yan, T. H. *Tetrahedron*. **2002**, 58, 7335)

Enantiopure amino cyclohexenol **26**, prepared by the reduction of cycloadduct **25**, was utilized as the key precursor in the synthesis of **27** which on treatment with $SnCl_4$ (cat.) effected intramolecular arylation providing main structural framework of **4.** Finally, the target molecule **4** was obtained in total 15 steps and 11 % overall yield as shown in Scheme-4.

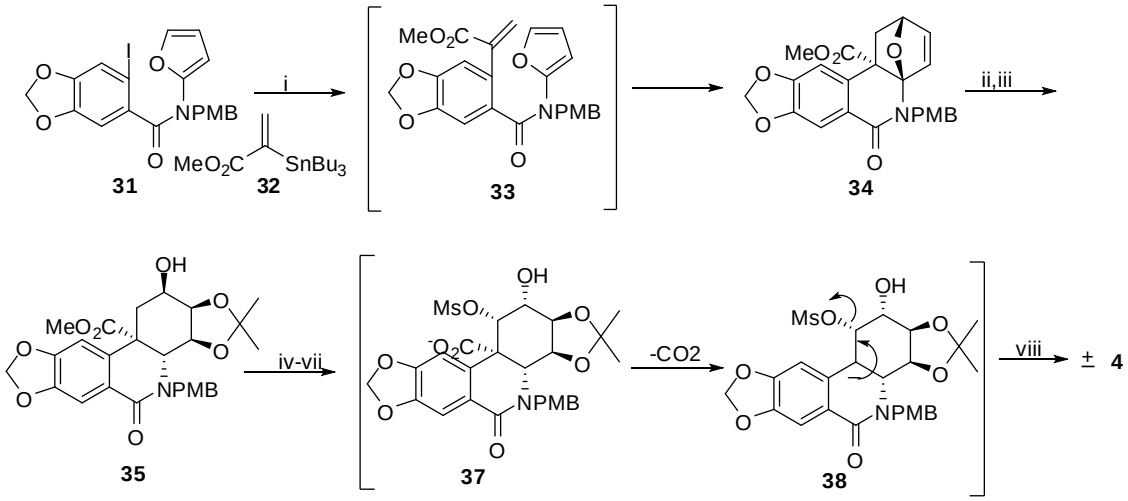


Scheme-4

Reagents and conditions: *i) TsCl, CH_3CN, NEt_3; then TBSCl, DBU r.t, 78 %; ii) NBS, H_2O, acetone, r.t, 98 %; iii) piperonyl bromide, aq. NaOH, Bu_4NHSO_4, CH_2Cl_2, r.t, 91 %; iv) 20 mol % $SnCl_4$, CH_2Cl_2, r.t, then Ac_2O, K_2CO_3 DMAP, Pyridine, 93 %.*

e) Padwa's approach (Padwa, A.; Zang, H. *Org. Lett.* **2006**, *8*, 247)

A racemic synthesis of **4** was achieved involving **34**, obtained by the tandem Stille \ intramolecular Diels-Alder cycloaddition of **31**, as the precursor. The carbomethoxy substituent on the olefin not only facilitated the [4+2] cycloaddition but also provided handle for setting up the right stereochemistry at the C_{4a} ring junction. The racemic synthesis of **4** was completed in total 15 steps and 10 % overall yield (Scheme-5).



Scheme-5

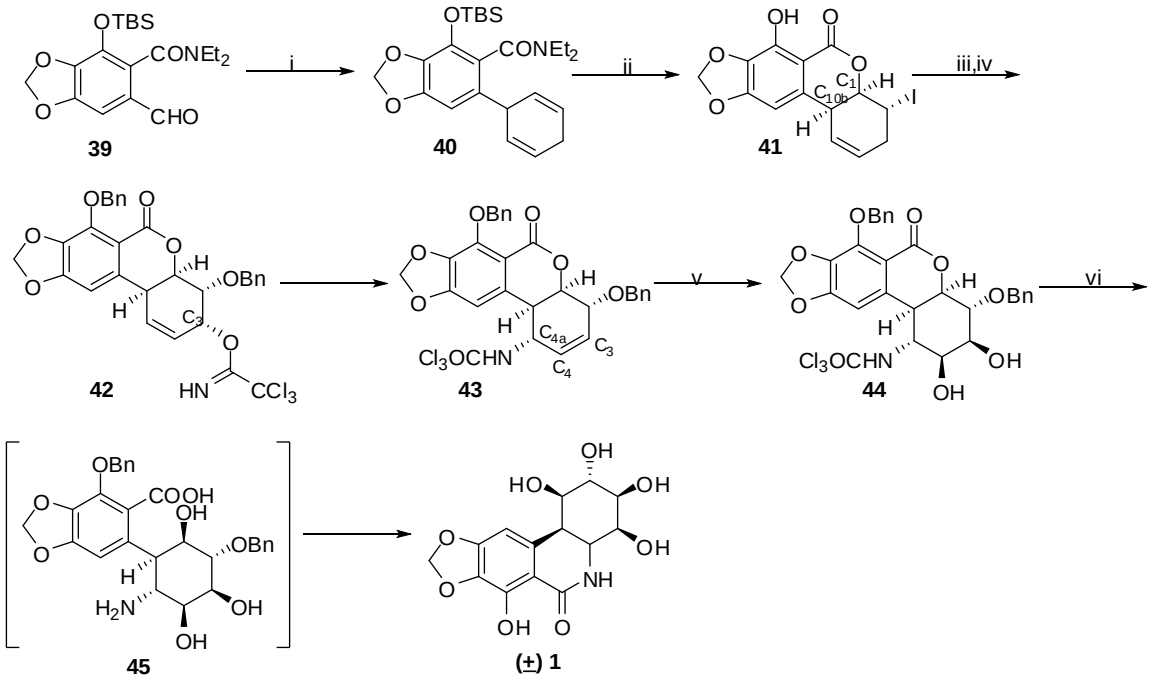
Reagents and conditions: *i) Pd(0), **32**, 82 %; ii) a) OsO_4, NMO, 98 %; b) 2,2- Dimethoxy propane, PPTS, 80 %; iii) TMSOTf, $Zn(BH_4)_2$,74 %; iv) NaH, CS_2, MeI, heat, 94 %; v) a) OsO_4, NMO, b) MsCl, Et_3N, 76 % (two steps); vi) $PdCl_2$, CH_3COOH; vii) LiOH; viii) TFA 90 %.*

2.2.2. Synthetic approaches towards pancratistatin (1).

a) Danishefky's approach (Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829).

The first total synthesis of the racemic **1** was accomplished in 27 steps and in less than 1 % overall yield by employing iodolactonization on aryl cyclohexadiene **40** to obtain C_1-C_{10b} *cis*-relationship in **41**. The Overman rearrangement of **42** gave the required C_{4a}

amino group stereochemistry**.** Finally, vicinal *cis* oxygenation of C_3-C_4 double bond of **43** followed by lactamisation gave racemic **1** (Scheme-6).

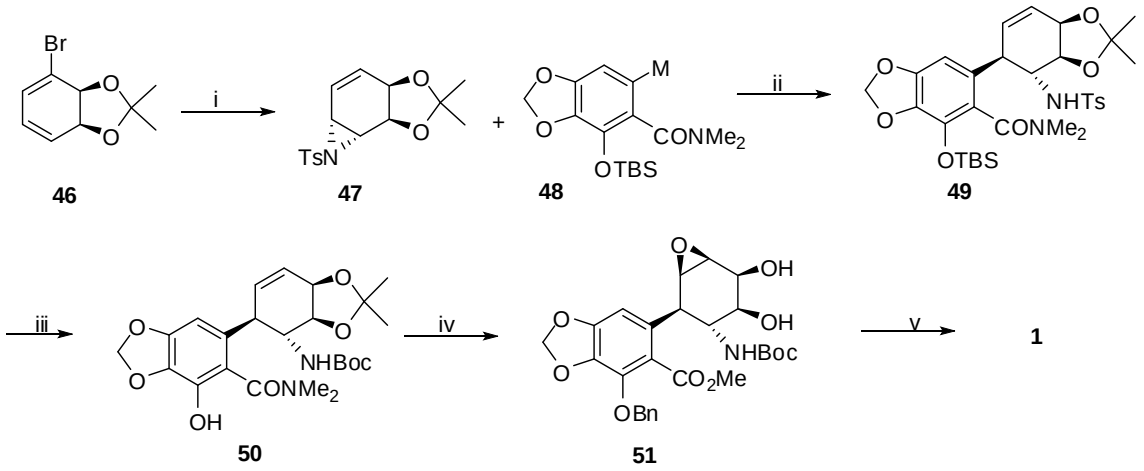


Scheme-6

Reagents and Conditions: *i) a) AllylMgBr, Et_2O, -78 ^oC; b) MsCl, TEA, DBU, DCM; c) (E)-(2-nitrovinylsulfonyl) benzene, $CHCl_3$, reflux; d) Bu_3SnH, AIBN, $PhCH_3$, reflux; ii) a) TBAF, THF, 0 ^oC; b) $(Bu_2Sn)_2O$, $PhCH_3$, 2h, I_2; iii) a) Ag_2O, DMF, BnBr, rt; b) OsO_4, NMO, DCM, THF, rt; c) DBU, toluene, reflux, 1.5 h; d) 2-acetoxyisobutyryl bromide, CH_3CN, 0 ^oC, 5min; e) OsO_4, NMO, THF, rt; f) $(Bu_2Sn)_2O$, PMBBr, $PhCH_3$; Ag_2O, BnCl, DMF g) DDQ, DCM, H_2O; h) Zn, HOAc; iv) NaH, CCl_3CN, THF, 100 ^oC; v) OsO_4, NMO, THF, rt; vi) a) K_2CO_3, MeOH, DCM, reflux; b) H_2/Pd $(OH)_2$, 1 atm.*

b) Hudlicky's approach (Tian, X.; Hudlicky, T.; Konigsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643.)

A concise total synthesis of **1** was accomplished in 14 steps and in 2 % overall yield. This route involved the regioselective aziridine (derived form cyclohexadiene *cis*-diol **46**) ring opening of **47** using higher order cyano cuprate **48** to afford **49.** Finally, setreospecific opening of epoxide in **51** followed by lactamisation afforded **1** (Scheme-7).

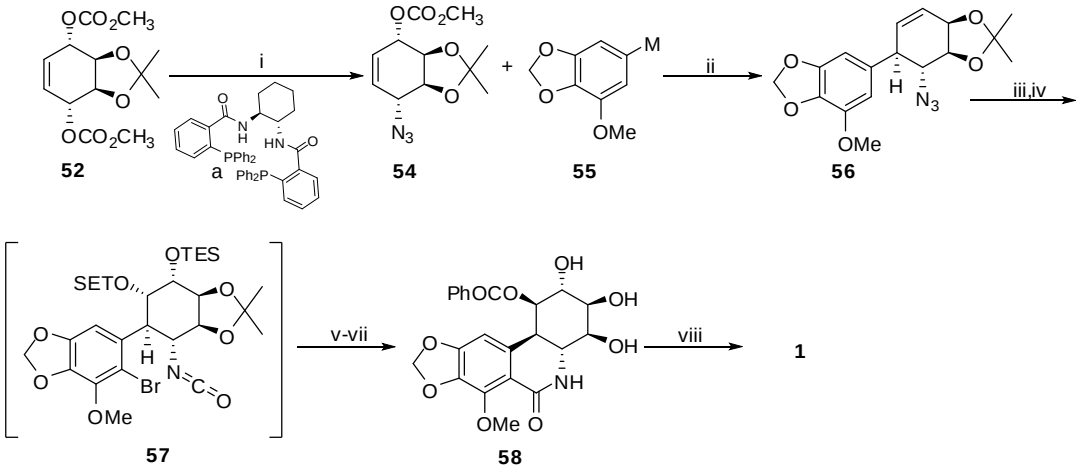


Scheme-7

Reagents and Conditions: *a) PhI=NTs, Cu (acac)$_2$, CH$_3$CN; b) BuSnH, AIBN, THF, ii) a) s-BuLi, TMEDA, THF, -90 ^{o}C; b) CuCN, -90 to -20 ^{o}C; c) Tosyl azide, -78 ^{o}C to rt; iii) a) s- BuLi, THF; b) (Boc)$_2$O; c) Na/anthracene DME, 78 ^{o}C; d) TBAF, THF; iv) a) SMEAH/Morpholine, -45 ^{o}C, THF; b) BnBr, K$_2$CO$_3$, DMF; c) NaClO$_2$, KH$_2$PO$_4$, 2-methyl-2-butene, t-BuOH, H$_2$O; d) CH$_2$N$_2$; e) HOAc, THF, H$_2$O, 60 ^{o}C; f) t-BuOOH, VO(acac)$_2$, PhH, 60 ^{o}C; v) a) H$_2$O, BzONa (cat), 100 ^{o}C; b) H$_2$, Pd(OH)$_2$/C, EtOAc.*

c) Trost's approach (Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143.)

An effective total synthesis of **1** was developed in 19 steps and in 8 % overall yield by combining the palladium-catalyzed desymmetrization protocol[22b] with a novel cyclization strategy (Scheme-8).

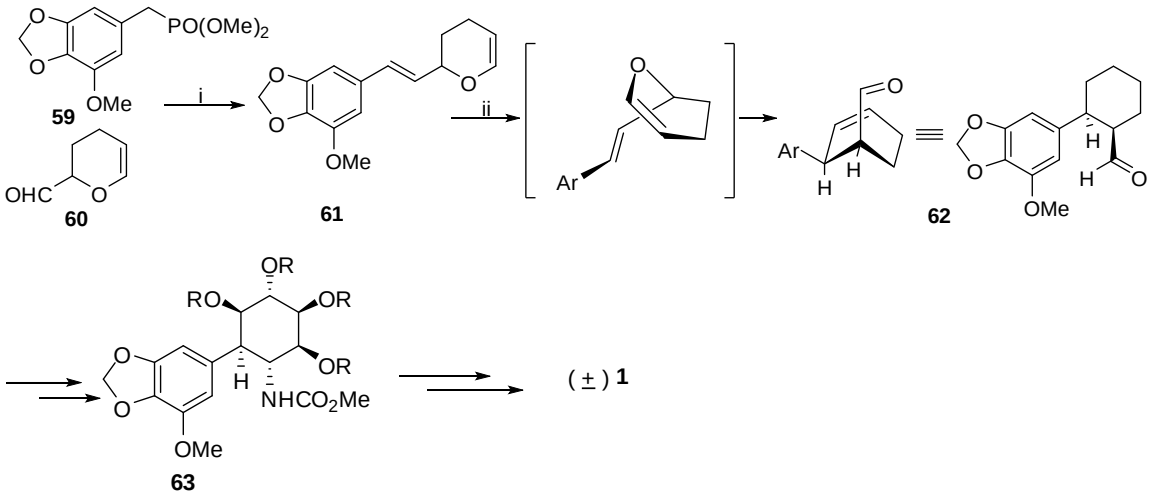


Scheme-8

Reagents and Conditions: *i) 0.5 mol % (π-$C_3H_7PdCl)_2$, **a**, 0.75 mol % , $TMSN_3$, CH_2Cl_2, rt, (> 95% ee), 83 %; ii) **55**, CuCN, THF, ether, 0 ^oC; iii) a) Cat, OsO_4, NMO.H_2O, DCM, rt, 62 % (two steps); b) TESOTf, 2,6-Lutidine, CH_2Cl_2, quant; c) NBS, DMF, 75 %; iv) a) $(CH_3)_3P$, THF, H_2O; b) $COCl_2$, THF, Et_3N; c) t-C_4H_9Li, ether, -78 ^oC, 62 % (three steps); v) a) TBAF, THF, -78 ^oC; b) $SOCl_2$, Et_3N; c) cat. $RuCl_3.H_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O, rt, 72 %; vi) $PhCO_2Cs$, DMF, THF, H_2O, cat. H_2SO_4, 75 %; viii) a) CH_3OH, K_2CO_3, rt; b) LiI, DMF, 80 ^oC, 85 %.*

d) Kim's approach (Kim, S.; Ko, H.; Kim, E.; Kim, D. *Org. Lett.* **2002**, *44*, 1343)

A new total synthesis of pancratistatin (**1**) was accomplished in 21 steps and 4 % overall yield by employing Claisen rearrangement of dihydropyranethylene **61** as a key step for the construction of A and C-rings in **62**, followed by stereo and regio controlled functional group interchange affording the final molecule (Scheme-9).

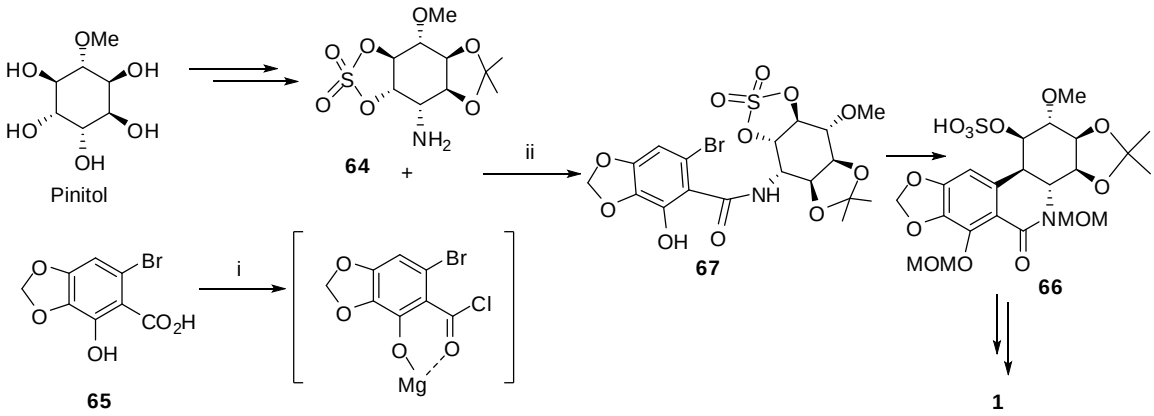


Scheme-9

Reagents and Conditions: *i) LHMDS, THF, 0 °C to rt, 22 h, 60 %; ii) Toluene, sealed tube, 250 °C, 20 h, 78 %.*

d) Li's Approach (Li, M.; Wu, A.; Zhou, P. *Tetrahedron Lett.* **2006**, *47*, 3707)

A concise approach towards (+)-Pancratistatin (**1**) was developed in 13 steps and 9 % overall yield starting from pinitol by employing an ultrasound assisted arylcerium induced ring opening of cyclic sulfate **67** as a key step (Scheme-10).



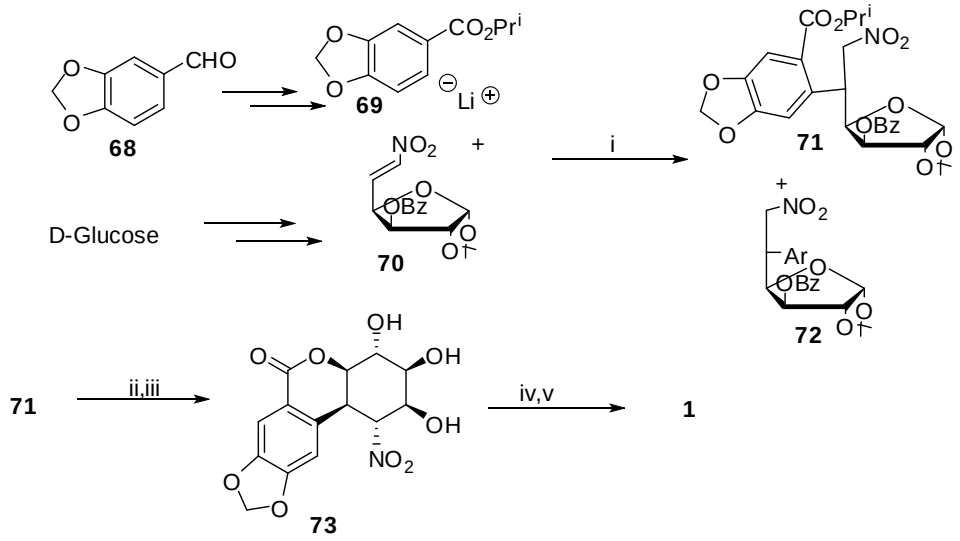
Scheme-10

Reagents and Conditions**:** *i) $MgBr_2$ OEt_2, $COCl_2$, ether, 0 ^oC, **64**, 64 %; ii) t-BuLi, $CeCl_3$, ultrasound, THF, -78 ^oC to rt, 72 %.*

2.2.3. Approaches towards (+)-7-deoxypancratistatin (2).

a) Paulsen's approach (Paulsen, H.; Stubbe, M. *Liebigs Ann. Chem.* **1983**, 535)

The first chiral synthesis of (+)-7-deoxypancratistatin (**2**) was accomplished by conjugate addition of **69** to nitroolefin **70** (derived from D-glucose) followed by lactamization to afford the final molecule in total 9 steps and 6.5 % overall yield (Scheme-11).

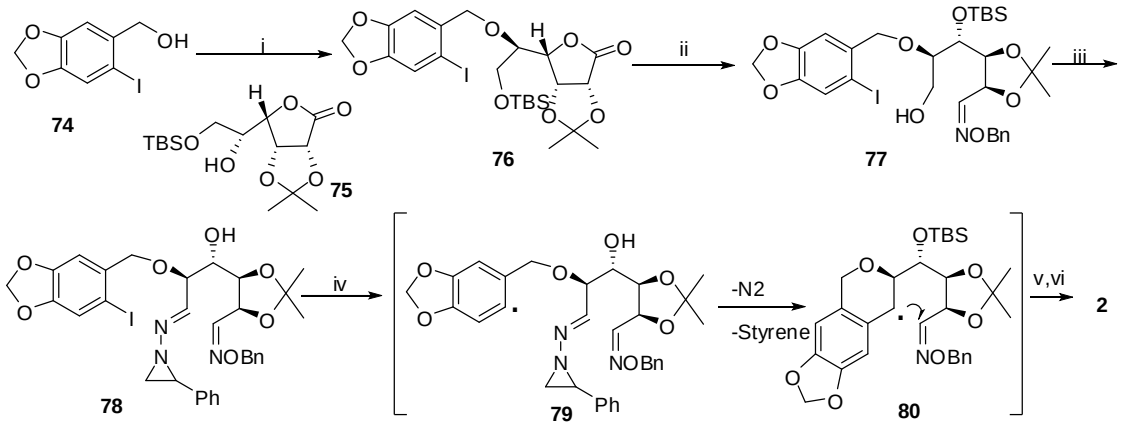


Scheme-11

Reagents and Conditions: *i) THF, -78 ^oC; ii) HOAc; iii) K_2CO_3, MeOH; iv) Pd/H_2, EtOH; v) K_2CO_3, MeOH.*

b) Keck's approach (Keck, G. E.; Wager, T. T.; McHardy, S. F. *J. Org. Chem.* **1998**, *63*, 9164)

An efficient total synthesis of **2** was accomplished in 13 steps and 21 % overall yield by employing a radical cascade strategy involving 6-*exo* radical cyclization of phenyl radical **79** as the key step (Scheme-12).

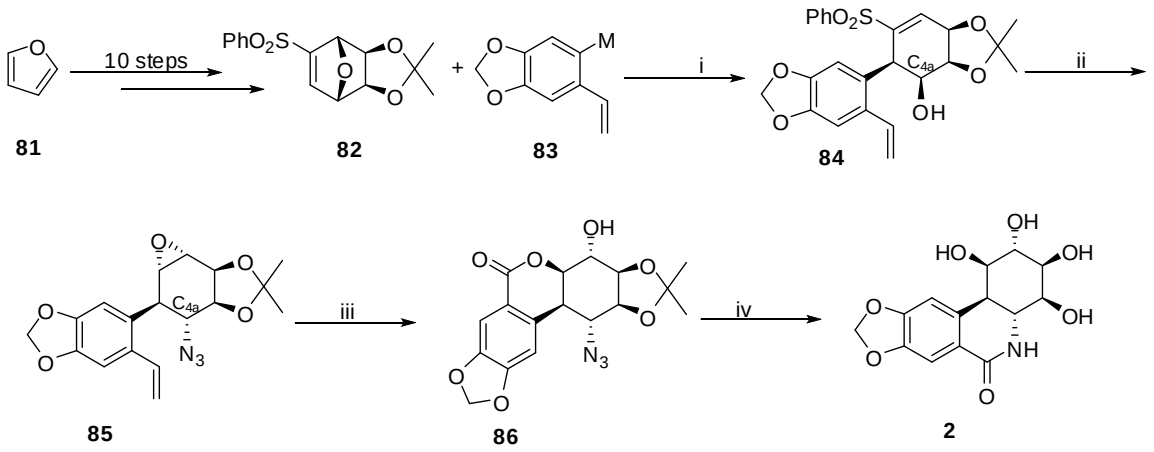


Scheme-12

Reagents and Conditions: *i) a) NaH, Cl_3CCN, 0 ^oC; b) TfOH, THF, 0 ^oC, 75 % (two steps); ii) a) L- Selectride, DCM, -78 ^oC; b) HCl.H_2NOBn, Pyridine 96 %, (two steps); c) TBSOTf, 2,6-lutidine, DCM, 0 ^oC; d) HF.Pyridine, THF; iii) a) TPAP, NMO, 4 A^o MS; b) 1-amino-2-phenylaziridine, EtOH, 0 ^oC. 83 % (two steps); iv) a) Ph_3SnH, AIBN, PhH, 78 %; v) SmI_2, TFAA, 88 %; vi) a) PCC, 83 %; b) $BF_3.OEt_2$; b) K_2CO_3, MeOH, 88 % (two steps).*

c) Plumet's approach (Acena, J. L.; Arjona, O.; Leo´n, M. L.; Plumet, J. *Org. Lett.* **2000**, *2*, 3683)

A new total synthesis of **2** was accomplished in 21 steps with 3 % overall yield starting from readily available furan and *trans*-1,2-bis (phenylsulfonyl) ethylene **82** by following the sequence as shown in Scheme 13.



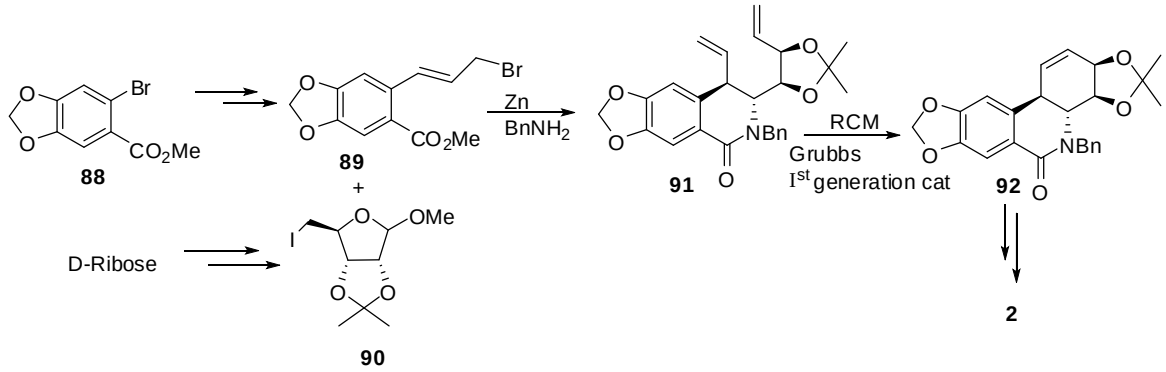
Scheme-13

Reagents and Conditions: *i) a) BuLi, THF/Tol, -78 ^{o}C; ii) a) Bu^{t}OOH, BuLi, THF, -78 ^{o}C, 84 %; b) Na-Hg, MeOH/THF, -23 ^{o}C, 81 %; c) Tf_2O, pyr, CH_2Cl_2, 0 ^{o}C; d) Bu_4NN_3, benzene, 82 %; iii) a) $NaIO_4/RuCl_3$, $CH_3CN/CCl_4/H_2O$; iv) a) H_2, 40 psi, Pd(C) 10 %, MeOH, 88 %; b) CF_3COOH, 0 ^{o}C; c) K_2CO_3, MeOH, reflux, 82 %.*

d) Madsen's Approaches (Hakansson, A. E.; Palmelund, A.; Holm, H.; Madsen, R. *Chem. Eur. J.* **2006**, *12*, 3243)

Approach-1

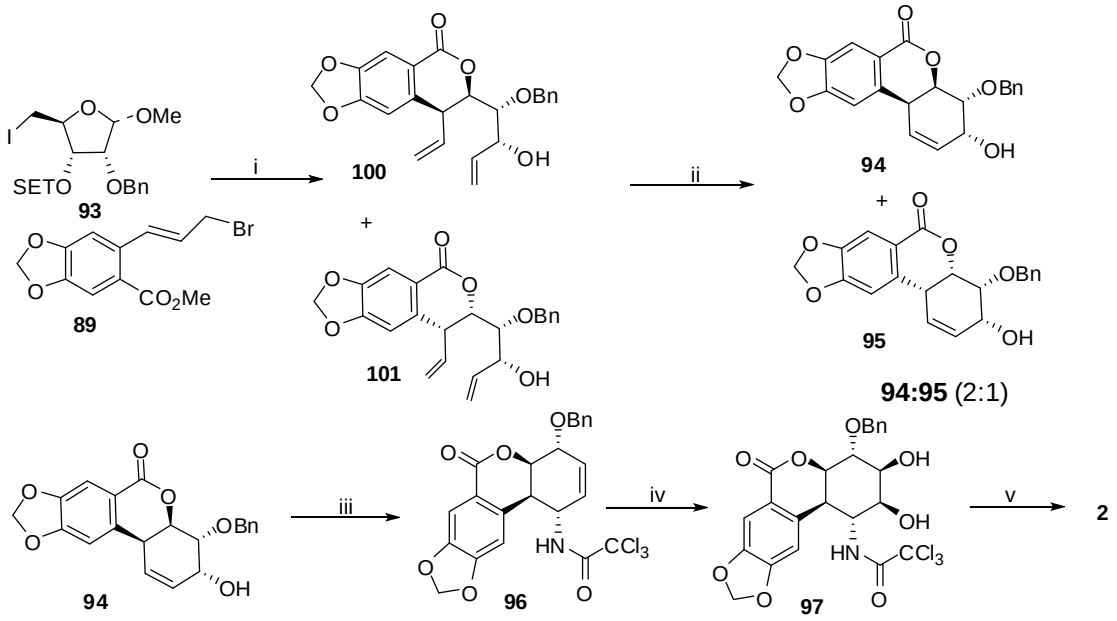
The utility of olefin metathesis was explored in the elaboration of C-ring of 7-deoxypancratistatin (**2**) by Madsen *et al.* in total 13 steps and 1.4 % overall yield. (Scheme14). In their synthesis, the diene **91** was subjected to metathesis with Grubbs' first-generation catalyst to afford cyclohexene **92** which was oxygenated to complete the synthesis of the natural product. The derivation of chiral diene **91** from D-ribose included zinc mediated tandem reactions.



Scheme-14

Approach-2

In this second strategy, reaction between ribofuranoside **93** (derived from D-Xylose) and compound **89** in the presence of zinc followed by ring-closing metathesis yielded **94:95** in 2:1 ratio. Subsequent Overman rearrangement of **94**, dihydroxylation and deprotection afforded the **2** in 23 steps with 4.3 % overall yield (Scheme-15).

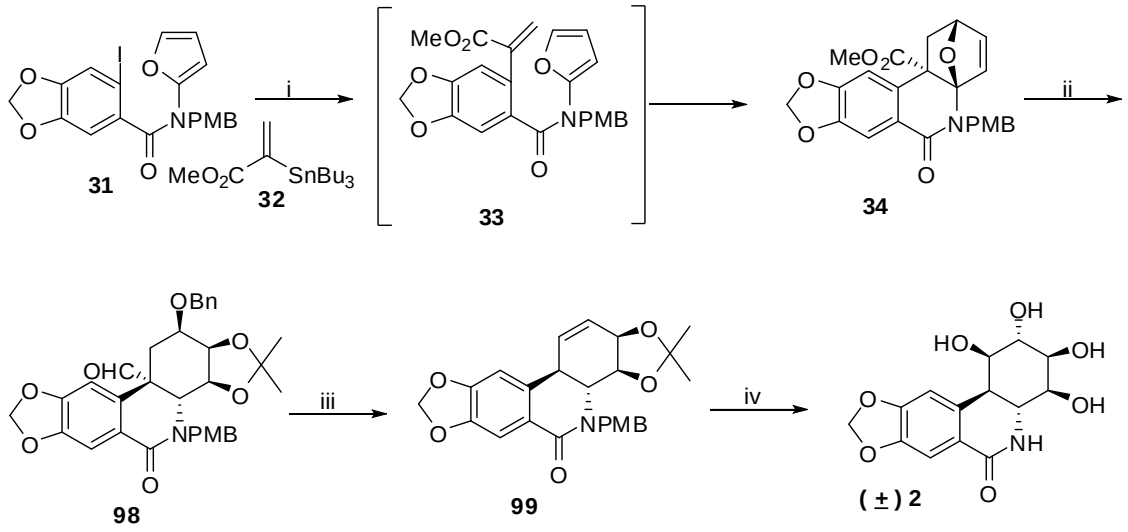


Scheme-15

Reagents and Conditions: *i) a) Zn, THF, H_2O, 40 ^oC, ultrasound, then H^+-resin, MeOH, 50 ^oC, b) Grubbs I^{st} generation catalyst, CH_2Cl_2, 40 ^oC; ii) CCl_3CN, DBU, CH_2Cl_2, -45 ^oC to -20 ^oC, then 1 mmHg, neat, 120 ^oC; iii) OsO_4, NMO, THF; iv) K_2CO_3, MeOH, 65 ^oC, v) H_2, Pd $(OH)_2$/C, EtOAc.*

e) Padwa's approach. (Padwa, A.; Zhang, H. *J. Org. Chem.* **2007**, *72*, 2570.)

A racemic synthesis was reported by Padwa *et al.* in 23 steps and 3 % overall yield. Key features of the synthetic strategy included 1) one-pot Stille/intramolecular Diels-Alder cycloaddition cascade to construct the core skeleton 2) conversion of the initially formed Diels-Alder adduct into an aldehyde intermediate **98** which undergoes a stereospecific decarbonylation reaction mediated by Wilkinson's catalyst to set the *trans*-B-C ring junction of **2**.



Scheme-16

Reagents and Conditions: *i) Pd (0), **32**, 82 %; ii) a) NaH, $PhCH_2Br$, b) LiOH, THF; c) $(COCl)_2$, $ZnBH_4$; c) TPAP, NMO,70 %; iii) a) $RhCl(PPh_3)_3$, heat, 63 %, b) H_2, Pd $(OH)_2$, c) NaH, CS_2, MeI, heat, 85 %; iv) a) OsO_4/NMO, 68 %, b) $SOCl_2$, c) $NaIO_4/RuCl_3$, 82 %, d) $PhCO_2Cs$, e) H^+, 75 %, f) LiOH, g) H_2, Pd $(OH)_2$, 80 %.*

2.3. Summary

The literature survey of the synthetic reports reveal that the more practical approach emphasized cyclization of B-ring with the preconstructed A and C-rings in convergent fashion. Different modes of cyclizations reported for the formation of B-ring included,

1) C_6–N bond formation by lactamization and transamidation reactions. [4,9,10,33]

2) C_6–C_{6a} bond formation. [22,26.]

3) C_{10a}–C_{10b} bond formation. [6,7,11,19,27]

4) C_{4a}–C_{10b} bond formation.[13,35.]

2.4. Objective of present study

A number of creative new approaches to the syntheses of *Amaryllidaceae* constituents (**1-4**) continue to appear despite the fact that twenty years elapsed since the first synthesis of pancratistatin (**1**). Several groups continue a multi-generational effort for the syntheses of these compounds to this date. *Amaryllidaceae* constituents represent ideal targets on which synthetic design may be practiced in an aesthetic manner. Towards

this end, we have taken up the challenge to develop a practical and conceptually new strategy for the syntheses of highly oxygenated phenanthridones **2** and **4**. The foregoing chapter will discuss our explorations and progress in this endeavor.

2.5. References.

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Chapter -3

Synthetic studies towards (+)-lycoricidine (4) and (+)-7-deoxypacratistatin (2)

This chapter is divided into two sections. While Section- A describes synthetic attempts towards (+)-lycoricidine (**4**), section-B presents efforts towards the synthesis of (+)-7-deoxypancratistatin (**2**).

3.1. Introduction

The highly oxygenated phenanthridone alkaloids (**1**−**4**, Fig-1) of pancratistatin class, isolated from the plants of *Amaryllidaceae* species, have been the subject of several elegant total syntheses and efforts were directed towards overcoming the major difficulty of a controlled installation of five to six contiguous stereogenic centers in the C-ring and *trans*-fused BC-ring junction.

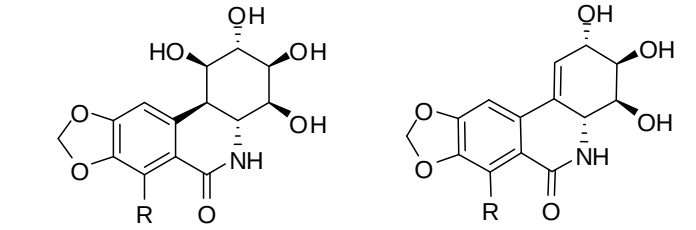


Figure: 1: Structure's of Isocarbostyril alkaloids of *Amaryllidaceae* family.

Two main approaches have generally been practiced for synthesizing **1**-**4**. One of these has dealt with a convergent route, constructing two fragments representing the A and C- rings and finally coupling them together to form the B-ring. This approach included the construction of *trans*-fused C_{10a}−C_{10b} bond for BC-ring junction as the crucial point. The other approach employed construction of C-ring from a suitable precursor in which the elements required for the *trans* BC-ring fusion were already installed. The crucial points in both these methodologies were the stereocontrolled installations of the oxygen functionalities around the C-ring. Evaluation of the known synthetic strategies in this context revealed that the more practical approach emphasized the first method. In this regard, we have developed a new strategy based on benzannulation, which is described as follows:

3.2. Intramolecular arylation of silyl enol ethers via PET generated arene radical cations: New benzannulation strategy

Sometime back our group had developed a protocol[2] for generating arene radical cation through photoinduced electron transfer processes and its intramolecular cyclization with tethered enol silyl ether as nucleophiles for benzannulation reaction. The reaction is initiated through single electron transfer processes from excited state of electron rich arenes to the ground state of electron deficient 1, 4-dicyanonaphthalene (DCN) as represented in the fig-2.

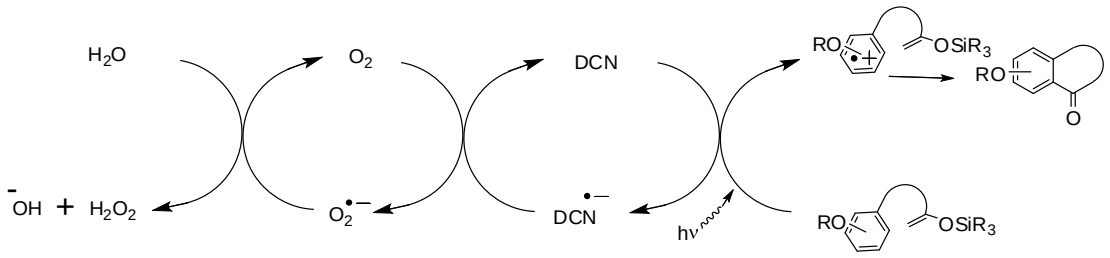
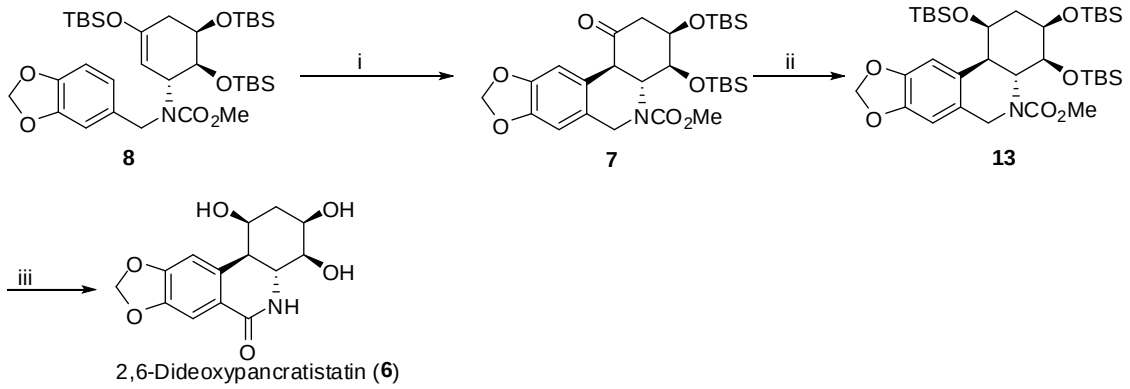


Figure-2 Proposed mechanism for PET initiated intramolecular carbocyclization reaction.

The viability of our methodology was tested earlier by the successful synthesis of (+)-2, 7-dideoxypancratistatin[1] (**6**), as outlined in the Scheme-1.



Scheme-1

Reagents and conditions: *i) hν, DCN, CH_3CN, H_2O, 6 h, 68 %;ii) a) $NaBH_4$, EtOH, 0 ^oC-rt, quant; b) TBSCl, ImH, DMAP, DCM, 85 % over two steps; iii) a) $RuCl_3$, $NaIO_4$, EtOAc, H_2O, 90 %; b) NaOMe, MeOH, reflux; c) TBAF, THF, 90 % over two steps.*

With this background information, we set out our synthetic journey to synthesize molecules **2** and **4** utilizing intramolecular α-arylation of ketones, mediated by

photoinduced electron transfer processes as shown in Fig. 2, as the key step. The foregoing sections A and B will discuss our explorations and progress in this endeavor.

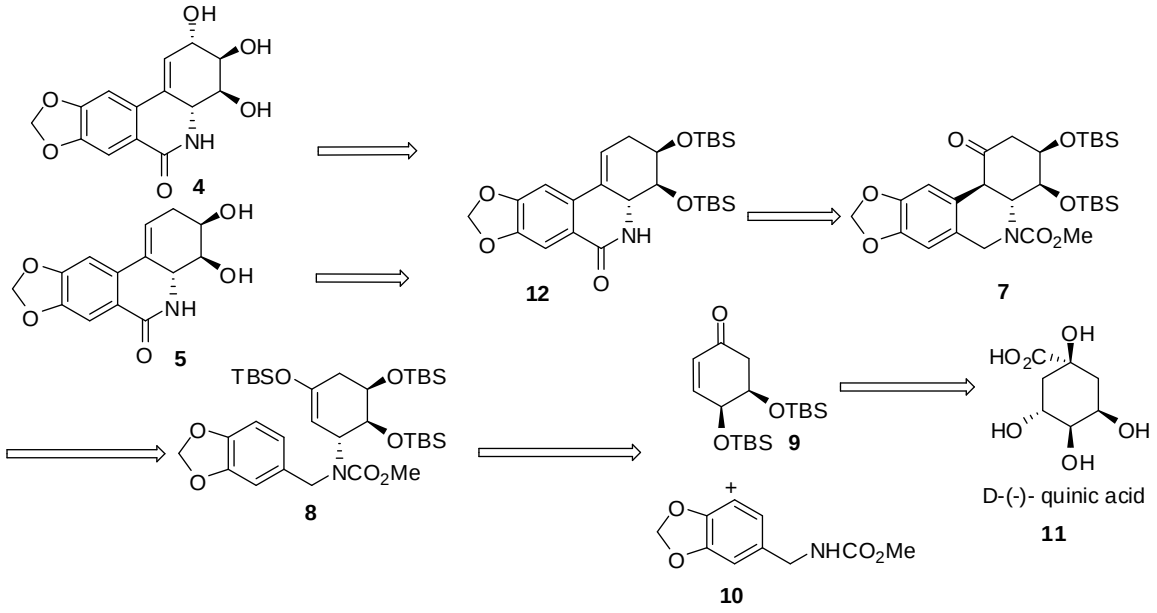
Section.A

Synthetic studies towards (+)-lycoricidine (4)

Our continuing interest in exploring the application of the methodology, as shown in Fig. 2, in the total synthesis of architecturally complex alkaloids (**1-4**) encouraged us to synthesize **4** by following the sequences as discussed below:

3A.1. Retrosynthetic analysis and design

It seemed plausible that a sequence similar to that described for **6** could be used to construct highly functionalized lycoricidine (**4**) structure. The retrosynthetic analysis of **4** led us to visualize intermediate **12** as a potential precursor which could be obtained from **7**. The intermediate **7** is proposed to be easily generated by PET mediated intra-molecular carbocyclization of corresponding **8** which in turn can be obtained by the aza-Michael reaction between piperonyl carbamate **10** and **9**, derived from commercially available D-(-)-quinic acid (**11**) (Scheme-2).



Scheme-2

3A.2. Results and discussion

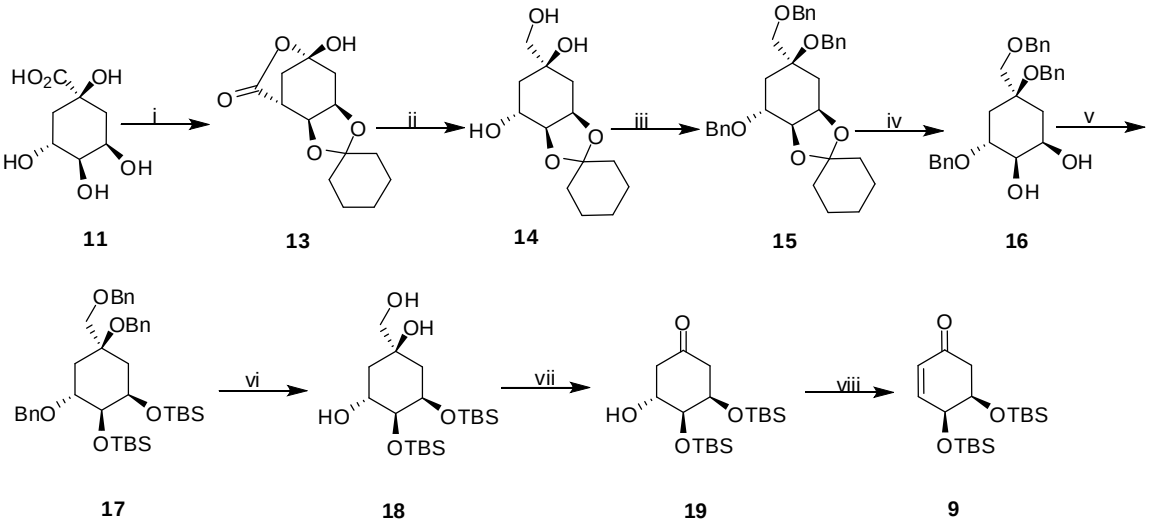
Synthesis of **4**, as perceived through the retrosynthetic strategy, started with the silylenol ether **8** followed by the crucial carboannulation reaction.

3A.2.1 Synthesis of enone 9

The selection of **11** as suitable precursor for **9** was visualized owing to following considerations.

1. The natural abundance.
2. Similarities in the stereochemistries at C_3 and C_4.
3. The directional ability of these stereocenters to chirality generation at C_{4a}.

The synthesis of **9** was accomplished as outlined in Scheme-3 in 60 % overall yield.



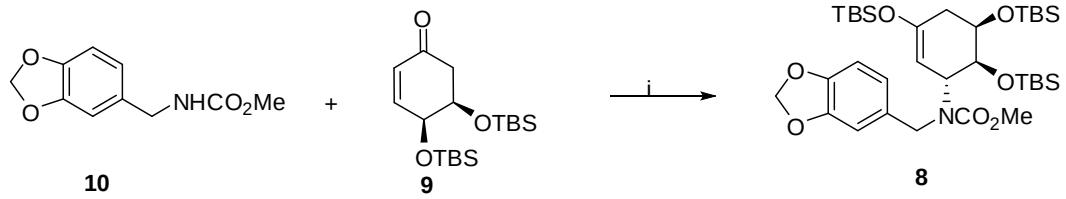
Scheme-3

Reagents and conditions: *i) Cyclohexanone, DMF, p-TSA (cat), PhH, reflux, 8 h, 95 %; ii) $NaBH_4$, EtOH, rt, 2 h, 90 %; iii) NaH, DMF, 60 ^oC, BnCl, rt, 24 h, 88 %; iv) HOAc-H_2O (8:2), 80 ^oC, 8 h, 96 %; v) TBSCl, ImH, DCM, DMF, rt, 24 h, 97 %; vi) H_2/Pd-C, EtOH, 60psi, 6 h, quant; vii) $NaIO_4$, EtOH-H_2O (9:1), rt, 0.5 h, 95 %; viii) MsCl, TEA, DCM, 0 ^oC, 90 %.*

3A.2.2. Synthesis of 8

With stereodefined enone **9** in hand, we focused our attention to the introduction of the arene unit at its C_3 position by carrying out an aza-Michael addition with N-lithiated

piperonyl carbamate followed by trapping of the corresponding lithium enolate as its TBS enol silyl ether which afforded conjugate adduct **8** in 95 % yield. The C_4 carbon stereochemistry of the enone directed an *anti* approach of the nucleophile producing **8** as a single isomer (Scheme-4).



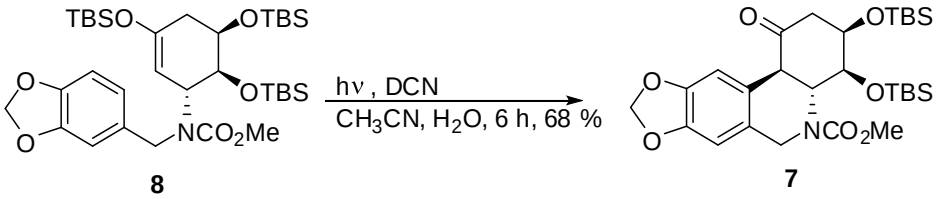
10 **9** **8**

Scheme-4

Reagents and conditions: *i) n-BuLi, THF, HMPA, -78 °C, TBSCl, 95 %.*

3A.2.3. Synthesis of phenanthridone skeleton 7

PET mediated intramolecular carbocyclization of **8** (0.6 g, 0.88 mmol) was carried out by irradiating (Pyrex filter, >280 nm, 450 W, Hanovia medium pressure lamp) with 1, 4-dicyanonaphthalene (0.05 g, 0.28 mmol) in 250 mL CH_3CN: H_2O (24:1) solution. Progress of the reaction was monitored by TLC at different intervals of time and irradiation was discontinued (6 h) when significant amount of **8** was consumed. Usual work up and chromatographic purification of the crude mixture gave cyclized phenanthridone **7** in 68 % yield (Scheme-5).



8 **7**

Scheme-5

The resulting phenanthridone **7** showed two aromatic proton signals in the ^{1}H NMR spectrum as sharp singlets at δ 6.63 and δ 6.51 which was supported by the presence of two aromatic methine carbon signals at δ 106.8 and δ 106.6 in ^{13}C NMR. In addition, the methine signals resonating at δ 70.7, 70.5, 52.7 and 51.4 corresponded to C_3, C_4, C_{4a} and C_{10b} respectively. After confirming the structure of **7**, we first reduced the carbonyl group

of **7** with $NaBH_4$ and obtained **20** (Scheme-6). The β-OH stereochemistry was anticipated considering the axial steric bulk exerted by C_3-OTBS group (Fig-3).

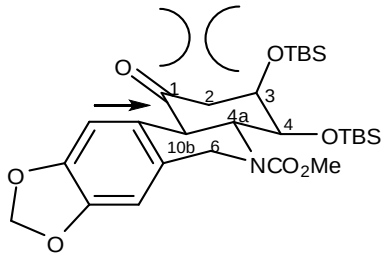
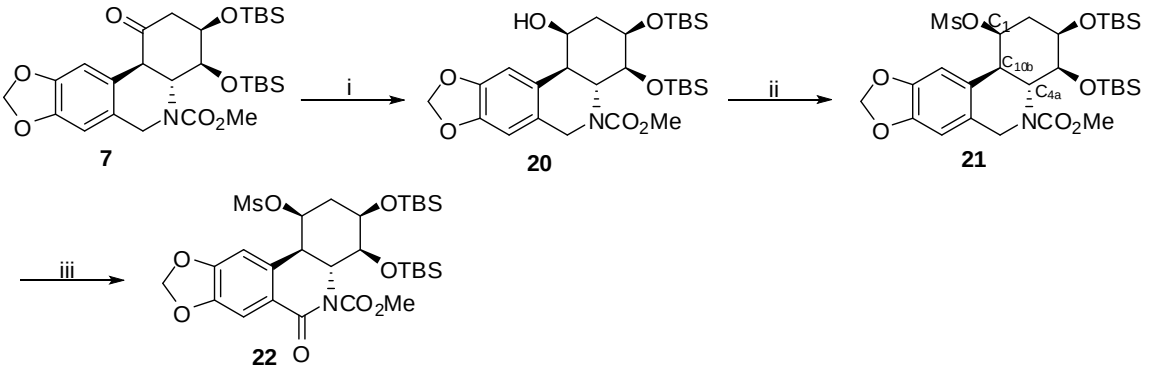


Figure-3

Compound **20** was mesylated using MsCl/Et_3N in DCM to obtain **21** in 87 % yield which was characterized by ^1H NMR and ^{13}C NMR spectra**.** The relative *trans* and *cis* stereochemistries of H_{4a}- H_{10b} and H_1- H_{10b}, respectively, were deduced by examining the coupling pattern of H_{10b} which appeared as doublet of a doublet at δ 3.24 (*J* = 10.2, 6.0 Hz). Compound **21** was subjected to benzylic oxidation using $RuCl_3$–$NaIO_4$ which gave **22** smoothly in 60 % yield (scheme-6).



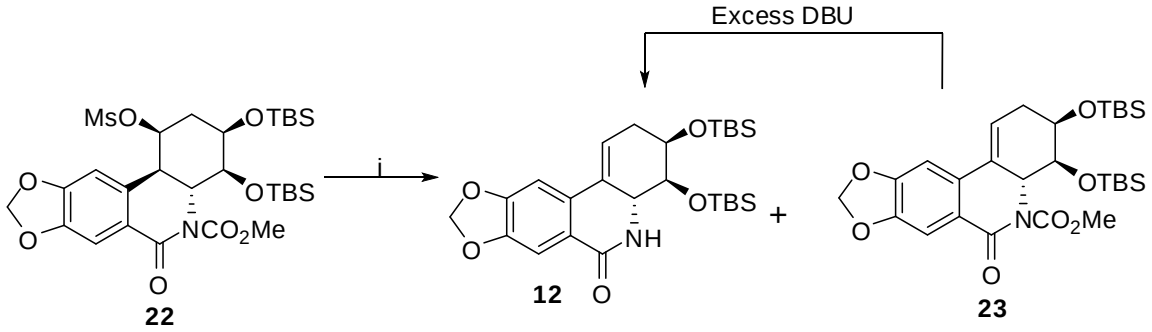
Scheme-6

Reagents and conditions: *i) $NaBH_4$, EtOH, 0 ^oC-rt, quant; ii) MsCl, Et_3N, DCM, 0 ^oC-rt, 87 %; iii) $RuCl_3$ (cat), $NaIO_4$, CCl_4-CH_3CN-H_2O (2:2:3), rt, 1 h, 60 %.*

3A.2.4. Synthesis of 12

In order to generate a double bond at C_{10b}-C_1 position in **22**, elimination of the mesylate moiety was carried out by refluxing in toluene using DBU as a base. During this process, it was also observed that there was partial deprotection of the carbamate moiety

producing a mixture of compounds **12** (20 %) and **23** (80 %). Upon standardization of the reaction by the addition of increased amounts of the base, fortunately, the reaction underwent smoothly to yield **12** as single product in 78 % yield (Scheme-7).



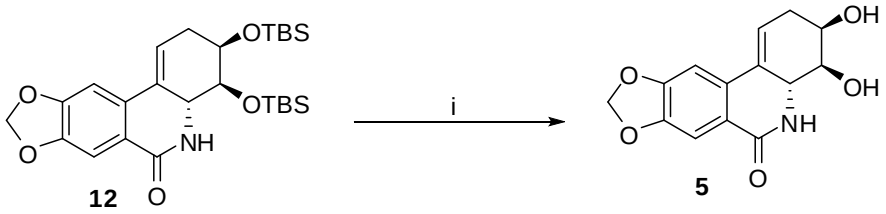
Scheme-7

Reagents and conditions: *i) DBU, toluene, 80 ^{o}C, 12 h, 78 %.*

The disappearance of H_{10b} proton and the appearance of vinylic peak in the ^{1}H NMR spectrum of **12** at δ 5.91 (m, 1H) along with the presence of other proton signals at δ 4.52 (m, 1H), δ 4.06 (m, 1H) and δ 3.74 (dd, J = 8.9, 1.4 Hz, 1H) corresponding to H_{4a}, H_3 and H_4, respectively, clearly indicated the elimination of the –OMs group. The formation of **12** which was further supported by observing H_{4a} signals shifting more downfield in comparison to H_3 and H_4 in ^{1}H NMR.

3A.3. Synthesis of (+)-deoxylycoricidine (5)

The synthesis of (+)-deoxylycoricidine (**5**) was accomplished (81 % yield) by removing TBS group from **12** by treating with TBAF in THF for 8 h at 0 ^{o}C (Scheme-8). The disappearance of the –OTBS groups were obvious by the ^{1}H NMR spectrum recorded in deuterated methanol. Further, unambiguous stereochemical support as assignment for **5** was confirmed by X-ray crystallographic analysis (corresponding structure refinement data of **5** is provided at the end of this section) (*Fig* 4).



Scheme 8

Reagents and conditions: *i) TBAF, THF, 0 ^{o}C, 8 h, 81 %.*

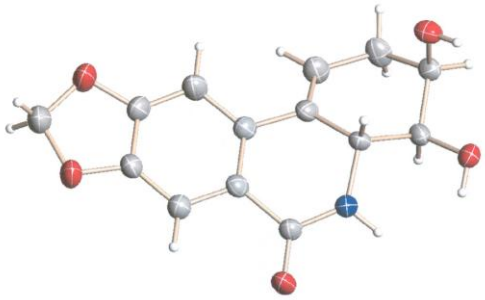


Figure-4 *ORTEP diagram of (+)-2- Deoxylycoricidine (**5**).*

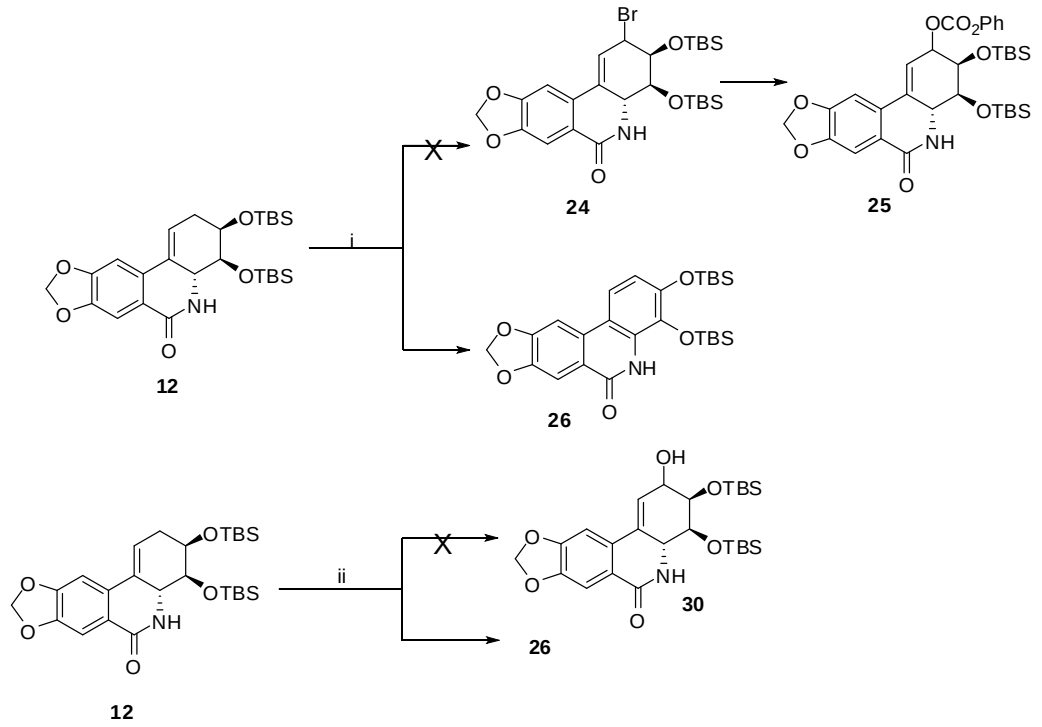
To achieve target **4**, the installation of hydroxyl group at C_2 with correct relative stereochemistry was required. Different attempts were carried out to accomplish this task, employing several protocols which are discussed in the foregoing sections.

3A.4. Synthetic attempts towards (+)-lycoricidine (4)

3A.4.1. Allylic bromination of compound 12

Initially, we investigated the possibility of C_2 functionalization through allylic bromination[3] followed by nucleophilic displacement with alkali benzoate which was expected to produce required **25**. However, when the reaction was performed using NBS in CCL_4 under reflux condition, formation of an undesired aromatized **26** was obtained. Alternatively, direct allylic oxidation using selenium dioxide[4] in dioxane-water (9:1) was also tried; however, unfortunately it also gave only **26** within few minutes (Scheme-9) of the reaction.

The ^{13}C spectrum of **26**, displayed twelve aromatic signals at δ152.6, 147.7, 146.4, 132.3, 132.2, 129.4, 115.96, 115.92, 115.5, 113.4, 106.4 and δ101.9 corresponding to the carbons of A and C-rings confirming formation of completely aromatized product. Presence of all aromatic protons was further supported by observing only three proton signals in the downfield region at δ 7.82 (s, 1H), δ 7.49 (m, 2H) and δ 6.83 (d, J = 8.9 Hz, 1H) including methylenedioxy protons (s, 2H) other than –OTBS group signals.

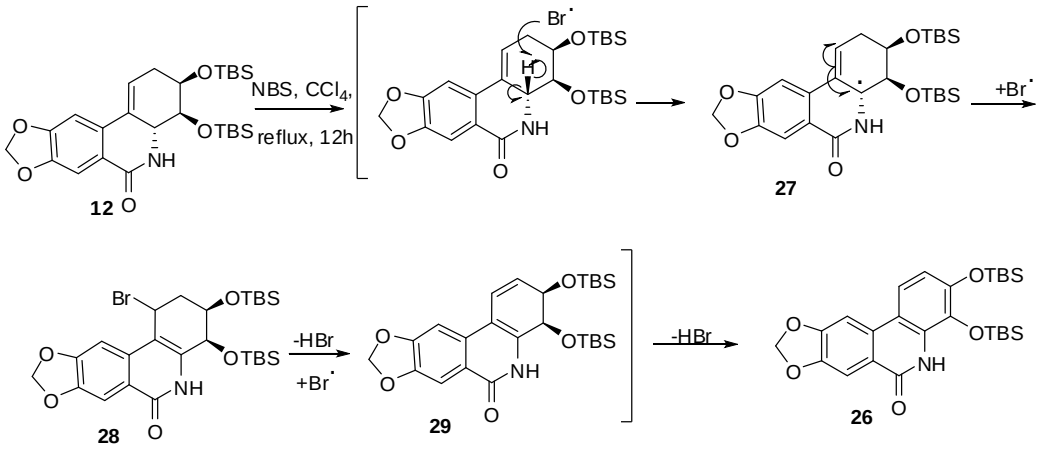


Scheme-9

Reagents and conditions: *i) NBS, CCl_4, reflux, 12 h; ii) SeO_2, Dioxane-H_2O (9:1), reflux, 0.5 h.*

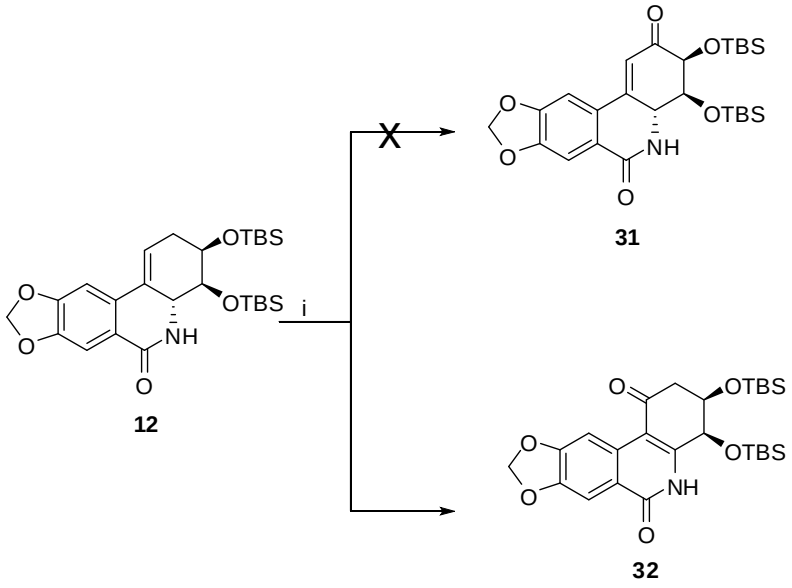
Mechanism for the formation of 26:

The plausible mechanism proposed for the aromatization of **12** under allylic bromination or SeO_2 mediated oxidation to **26** is depicted in the Scheme-10. Bromine radical generated from NBS possibly abstracts more acidic H_{4a} leading to the formation of C_{4a} radical. The migration of the allylic C_{4a} radical to C_1 followed by bromination gives rise to **28** which gets eliminated easily producing completely aromatized **26**.



Scheme 10 - Plausible mechanism of formation of **26**.

Since our above efforts failed to bring about desired results, we got interested in evaluating this transformation using transition metal based oxidizing reagents. Recently, TBHP (100 %, *tert*-butyl hydroperoxide in hexane) and T-HYDRO (70 %, *tert*-butyl hydroperoxide in water) in the presence of transition metals such as chromium (VI),[5] palladium[6] or even by sodium chlorite[7] have become the oxidants of choice for allylic oxidations. Initially allylic oxidation was evaluated using PDC/TBHP in DCM but it produced a complex reaction mixture (Table-1). Subsequently, transition metal free oxidizing agent $NaClO_2/H_2O$ in combination with TBHP was also tried. However, unfortunately, a rather unusual rearrangement took place producing an unexpected enone **32** (Scheme-11).



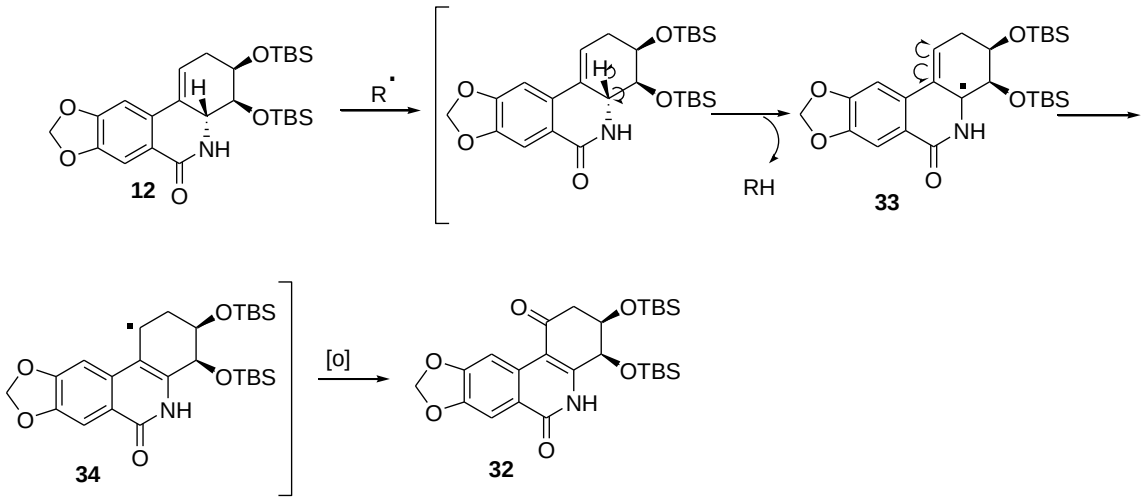
Scheme-11

Reagents and conditions: *i) $NaClO_2$, TBHP, CH_3CN-H_2O (3:1), 50 ^oC, 30 h.*

Formation of **32** was supported by observing the disappearance of H_1 and H_{4a} protons from **12** which was further confirmed by the appearance of C_{4a} and C_{10b} quaternary alkenic carbon signals in ^{13}C NMR spectrum at δ 147.5 and δ 132.3, respectively. Additionally, the appearance of methylene protons α-to carbonyl as two doublet of doublets at δ 2.86 (J = 17.0, 3.5 Hz) and δ 2.73 (J = 17.0, 2.2 Hz) confirmed the proposed structure. The LC-MS also showed the presence of ($M + Na^+ + MeOH$) at 572.

Plausible mechanism of formation of 32:

This rearrangement can be rationalized by considering the H-abstraction from C_{4a} by *tert*-butyl peroxy radicals, generated by homolytic cleavage of TBHP by ClO_2 radicals[8] followed by isomerization of olefinic double bond to **34** giving rise to C_1 radical which undergoes oxidation to form enone **32** (Scheme-12).



Scheme-12: Plausible mechanism of $NaClO_2$ oxidation.

In our final attempt, we also evaluated palladium / TBHP allylic oxidation, a protocol described by Corey *et al.*[6] and the corresponding results are represented in Table-1.

Table-1: Method of comparison for oxidation of **12** by *tert*-butyl hydroperoxide.

Catalyst/ Additive (mol%/equiv)	Oxidant (TBHP/T-HYDRO)	TBHP/T-HYDRO (equiv)	Solvent	Time (h)	Temp (^oC)	Product obtained	Compound recovered (%)
PDC (2-3)	T-HYDRO	2	DCM	24h	45	CM	-
PDC (2-3)	TBHP	2	DCM	12h	45	32,26	70
$NaClO_2$(1.2)	T-HYDRO	5	$CH_3CN:H_2O$ (3:1)	30h	50	32	-
Pd/C (2.5 mol%)	T-HYDRO	5	DCM	3days	-10	-	95
Pd/C (2.5 mol%)	TBHP	5	DCM	3days	0	32(major) 26(minor)	-

Pd/C (2.5 mol%)	TBHP	5	DCM	30h	0-25	CM	-
$Pd(OAc)_2$	T-HYDRO	5	DCM	7days	-15	-	80
$Pd(OAc)_2$	TBHP	5	DCM	5days	-10	-	70
$Pd(OAc)_2$	TBHP	5	DCM	3days	0	CM	40
$Pd(OAc)_2$	TBHP	5	DCM	2days	0-25	CM	-

CM= Complex reaction mixture

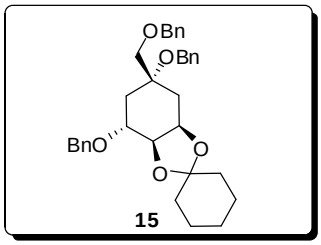
This observed failure and unusual results could be attributed to radical rearrangement due to extensive conjugation of aromatic ring-A on ring-B. The outcome of our above described studies reduced confidence level for exploring further the radical mediated allylic oxidation of **12** to **30** or **31** and therefore, we suspended synthetic activity at this stage.

3A.5. Summary

In conclusion, we have demonstrated the application of our PET mediated C-C bond forming strategy to carry out studies toward the synthesis of lycoricidine (**4**) which posed several difficulties during the final radical mediated allylic C_2 oxidation to complete the synthesis.

3A.6. Experimental Section

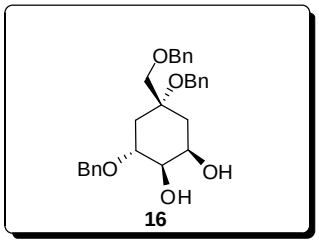
1. Preparation of (3a*S*, 4*R*, 6*S*, 7*aR*)-4, 6-bis (benzyloxy) -6-(benzyloxymethyl) hexahydrospiro [benzo [d] [1, 3] dioxole-2, 1[1]-cyclohexane] (15):



To a suspension of NaH (0.77 g, 19.37 mmol, pre washed with dry pet ether to remove mineral oil) in dry DMF (5 mL) was added drop wise at 0 ^{o}C **14** (1 g, 3.87 mmol) in dry DMF (5 mL). The reaction mixture was stirred to room temperature and heated to 60 ^{o}C until a light brown colored thick viscous mass was formed, cooled to 0 ^{o}C and to it was added drop wise benzyl chloride (2.2 mL, 19.37 mmol) with vigorous stirring. After 24 h, the reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (2x150 mL), brine (1x50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was column chromatographed over silica gel using pet ether: ethyl acetate (9:1) as eluant to yield **53** as colorless oil (1.8 g, 88 %).

$[\alpha]^{23}_{D}$	:	- 21.4^{o} (*c* 2.0, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2935, 1454, 1091
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	7.40-7.22 (m, 15H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 12 Hz, 1H), 4.57 (d, *J* = 10.9 Hz, 1H), 4.53 (s, 2H), 4.42 (d, *J* = 10.9 Hz, 1H), 4.37 (m, 1H), 4.08-3.88 (m, 2H), 3.47 (dd, *J* = 10.7, 9.5 Hz, 2H), 2.40 (dt, *J* = 15.6, 2.9 Hz, 1H), 2.16 (ddd, *J* = 13.7, 3.6, 2.2 Hz, 1H), 1.86 (dd, *J* = 15.6, 5.05 Hz, 1H), 1.68-1.26 (m, 11H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	139.1, 138.6, 137.9, 128.1-126.7 (multiple peaks), 108.9, 79.7, 76.0, 75.1, 74.8, 73.1, 71.4, 64.3, 37.8, 34.9, 30.5, 24.9, 23.8, 23.6.
Mass: m/z (%)	:	551 ($M+Na^+$, 100), 567 ($M+K^+$, 14), 529 (MH^+, 7), 462 (14), 422 (14), 382 (14).

2. Preparation of (1*R*, 2*R*, 3*R*, 5*R*)-3, 5-bis (benzyloxy) -5-(benzyloxymethyl) cyclohexane-1, 2-diol (16):

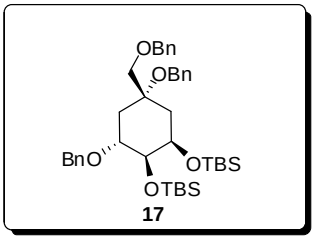


16

A solution of **15** (1 g, 1.89 mmol) in acetic acid: water (8:2, 10 mL) was stirred at 80 ^{o}C for 8 h. After completion of the reaction, was monitored by TLC, acetic acid was distilled off under reduced pressure from the reaction mixture and diluted with ethyl acetate (75 mL), washed with saturated $NaHCO_3$ (1x25 mL), water (1x25 mL) and brine (1x10 mL). The organic extract was dried over Na_2SO_4, concentrated under reduced pressure and the residue was column chromatographed over silica gel using pet ether: ethyl acetate (1:1) gave **16** as colorless gummy mass (0.81 g, 96 %).

$[\alpha]^{25}_{D}$	:	-5.0^{o} (*c* 1, $CHCl_3$).
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3476, 2242
^{1}H NMR (D_2O, 200 MHz) δ	:	7.41-7.11 (m, 15H), 4.78 (d, *J* = 12.0, 1H), 4.70 (d, *J* = 12.1, 1H), 4.51 (s, 2H), 4.46 (d, *J* = 10.49 Hz, 1H), 4.24 (d, *J* = 10.49 Hz, 1H), 4.03 (m, 1H), 3.72 (m, 1H), 3.47 (m, 3H), 2.50 (dt, *J* = 14.1, 3.8 Hz, 1H), 2.29 (dt, *J* = 15.0, 3.1 Hz, 2H), 1.64 (dd, *J* = 15.0, 3.2 Hz, 1H), 1.41 (dd, *J* = 14.0, 11.5 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	138.5, 137.67, 137.64, 128.4-127.5 (multiple peaks), 79.6, 76.1, 74.4, 73.9, 73.2, 72.2, 70.3, 64.8, 36.3, 33.4.
Mass: m/z (%)	:	471 ($M+Na^+$, 100), 449 (MH^+, 7), 301 (10).

3. Preparation of ((1*R*, 2*S*, 3*R*, 5*S*)-3, 5-bis (benzyloxy) -5-(benzyloxymethyl) cyclohexane-1, 2-diyl) bis (Oxy) bis (*tert*-butyldimethylsilane) (17):



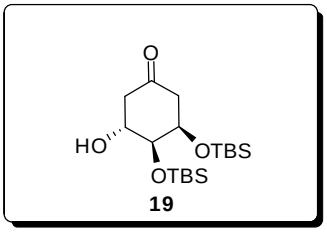
17

To a mixture of **16** (1 g, 2.23 mmol) and imidazole (0.45 g, 6.69 mmol) in dry DMF (2 mL) was added TBSCl (0.737 g, 4.91 mmol) and stirred for 24 h. The reaction mixture

was diluted with water (25 mL), extracted with ethyl acetate: pet ether (1:1, 3x25 mL) and the combined organic extracts were washed with water (2x25 mL), brine (1x10 mL) and dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified over silica gel using pet ether: ethyl acetate (95:5) which gave **17** (1.45 g, 97 %) as colorless oil.

$[\alpha]^{25}_D$	:	-8.0^o (*c* 0.75, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3018, 2929, 1215
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	7.32-7.15 (m, 15H), 4.59-4.34 (m, 6H), 3.90 (ddd, *J* = 11.3, 4.5, 2.2, 1H), 3.76 (m, 2H), 3.56 (m, 2H), 2.08-1.79 (m, 4H), 0.85 (s, 9H), 0.83 (s, 9H), 0.03 (s, 3H), 0.02 (s, 6H), -0.05 (s, 3H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	140.1, 138.7, 138.5, 128.3-126.8 (multiple peaks), 78.2, 77.6, 74.0, 73.3, 72.0, 71.1, 67.9, 63.9, 33.9, 29.3, 26.1, 25.8, 18.3, 18.1, -4.3, -4.5, -4.6, -5.0.
Mass: m/z (%)	:	699 ($M+Na^+$, 100), 694 ($M+NH_4^+$, 32), 677 (MH^+, 7), 569 (10), 437 (10).

4. Preparation of (3*R*, 4*S*, 5*R*)-3, 4-bis (*tert*-butyl dimethylsilyloxy)-5-hydroxycyclohexanone (19):



19

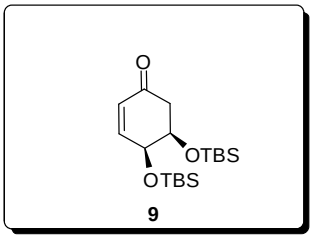
A mixture of **17** (1 g, 1.47 mmol) and Pd-C (20 mg, 10 % on activated carbon) in ethanol (10 mL) was hydrogenated at 60 psi in a parr hydrogenator for 6 h. The reaction mixture was filtered using a short pad of celite after the completion of the reaction. The filtrate was concentrated to give **18** quantitatively as a white solid which was forwarded as such to the next step.

To a solution of **18** (1 g, 2.46 mmol) in ethanol : water (9:1, 10 mL) was added portion wise sodium periodate (0.632 g, 2.95 mmol) and allowed to stir for 0.5 h. After the reaction was completed, the reaction mixture filtered through a short bed of silica gel and the filtrate was concentrated, diluted with ethyl acetate, given a water wash (1x10 mL), brine wash (1x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure.

The crude residue was column chromatographed over silica gel using ethyl acetate: pet ether (1:9) which yielded **19** (0.87 g, 95 %) as a white solid.

mp	:	96-97 ^{o}C
$[\alpha]^{25}_{D}$	:	-10.8^{o} (*c* 0.6, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3443, 1710, 1461
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	4.16 (m, 2H), 3.86 (dd, *J* = 6.1, 2.0 Hz, 1H), 2.81 (ddd, *J* = 15.0, 6.1, 1.5 Hz, 1H), 2.67 (ddd, *J* = 14.0, 8.0, 1.5 Hz, 1H), 2.42 (ddd, *J* = 14.0, 4.5, 1.1 Hz, 1H), 2.29 (ddd, *J* = 14.0, 6.3, 1.2 Hz, 1H), 1.91 (d, 1H), 0.91 (s, 9H), 0.88 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 0.06 (s,3H), 0.05 (s, 3H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	208.1, 74.7, 69.9, 69.7, 46.9, 44.9, 29.6, 25.8, 18.14, 18.1, -4.1, -4.5, -4.7, -4.8.
Mass: m/z (%)	:	397 (M+Na,100), 392 (M+NH_4^+,99), 375 (MH^+,35), 243 (25), 301 (18), 413 (M+K^+, 14), 227 (10).

5. Preparation of (4*S*, 5*R*)-4, 5-bis (*tert*-butyl dimethylsilyloxy) cyclohex-2-enone (9).



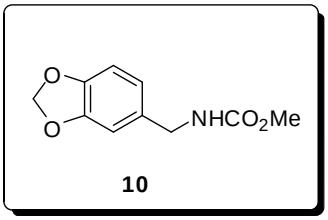
9

To a mixture of **19** (1 g, 2.67 mmol) and triethyl amine (0.81 ml, 5.87 mmol) in dry DCM (7 mL) at 0 ^{o}C was added drop wise mesyl chloride (0.24 mL, 3.20 mmol) in dry DCM (3 mL) for over an hour by using syringe pump. The reaction was monitored by TLC. After the reaction was completed, it was diluted with DCM (20 mL) and washed with water (2x20 mL), brine (1x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography using silica gel with ethyl acetate: pet ether (5:95) as eluant to yield **9** (0.85, 90 %) as white crystalline solid.

mp	:	57-59 ^{o}C
$[\alpha]^{27}_{D}$	:	+106.7^{o} (*c* 0.6, $CHCl_3$)

IR ν_{max} cm^{-1} ($CHCl_3$)	:	1685
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	6.68 (ddd, *J* = 10.2, 3.4, 1.3 Hz, 1H), 5.93 (ddd, *J* = 10.2, 1.5, 0.6 Hz, 1H), 4.43 (m, 1H), 4.17 (m, 1H), 2.75 (dd, *J* = 16.3, 6.8 Hz, 1H), 2.45 (dd, *J* = 16.2, 3.0 Hz, 1H), 0.90 (s, 9H), 0.84 (s, 9H), 0.11 (s, 6H), 0.05 (s, 6H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	197.8, 149.1, 129.2, 71.5, 69.3, 44.4, 25.8, 25.6, 18.2, 18.0, -4.5, -4.7, -4.8.
Mass: m/z (%)	:	379 (M+Na, 100), 374 (M+NH_4^+, 46), 357 (MH^+, 46), 225 (35), 301.

6. Preparation of Methyl benzo [d] [1, 3] dioxol-5 -ylmethylcarbamate (10):

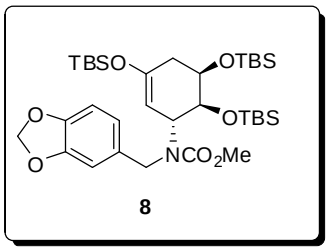


10

To a solution of potassium carbonate (7.93 mmol, 1 g) in DCM: H_2O (2:1) (30 mL) piperonyl amine (1 g, 6.61 mmol) was added and allowed to stir vigorously at 0 ^oC. After five minutes methyl chloroformate was added in the reaction mixture and stirred for further 15 minutes. After completion of the reaction, the water layer was extracted with DCM (1x20 mL). The combined organic extracts were given water (1x20 mL), brine wash (1x5 mL) and dried over Na_2SO_4, concentrated under reduced pressure to yield **10** as a white solid. The crude solid was recrystallized in pet ether: ethyl acetate, which yielded long colorless flakes in 94 % yield.

mp	:	99-100 ^oC.
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3019, 1719
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	6.73 (m, 3H), 5.93 (s, 2H), 4.97 (br s, 1H), 4.26 (d, *J* = 5.9 Hz, 2H), 3.68 (s, 3H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	156.9, 147.7, 146.7, 132.3, 120.6, 108.07, 108.0, 100.9, 52.0, 44.7.
Mass: m/z (%)	:	232 (M+Na^+, 100).

7. Preparation of methyl benzo [d] [1, 3] dioxolo-5-ylmethyl ((1*R*, 5*R*, 6*S*)-3, 5, 6-tris (*tert*-butyldimethylsilyloxy) cyclohex-2-enyl) carbamate (8):

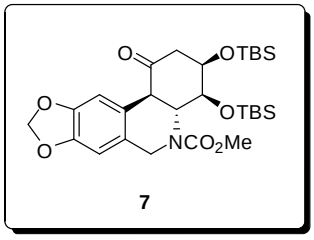


8

To a solution of compound **10** (0.88 g, 4.21 mmol) and HMPA (1.2 mL) in dry THF (8 mL) at -78 ^{o}C was added *n*-BuLi drop wise and allowed to stir for 15 minutes. Compound **9** (1 g, 2.6 mmol) in THF (2 mL) was added drop wise to the reaction mixture. After half an hour the lithium enolate was trapped by quenching with TBSCl (0.63 g, 4.21 mmol) and the reaction was brought slowly to the room temperature. The work up was carried out by adding water (4 mL) and was extracted with ethyl acetate: pet ether (1:1, 3x10 mL). The combined organic extracts were washed with water (1x10 mL), brine (1x5 mL), dried using Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography, eluting with pet ether: ethyl acetate (98:2) which yielded **8** (1.81 g) in 95 % yield.

$[\alpha]^{27}_{D}$	:	- 54.1^{o} (*c* 2, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	1704, 1462, 1251
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	6.69 (m, 3H), 5.90 (s, 2H), 4.60-4.23 (m, 3H), 4.20-3.51 (m, 6H), 2.14 (br s, 2H), 0.88 (s, 9H), 0.85 (s, 18H), 0.15--0.14 (m, 18H).
Mass: m/z (%)	:	702 ($M+Na^+$,100), 680 (MH^+, 53), 697 ($M+NH_4^+$, 18) ,379 (35), 471 (14), 357 (10).

8. Preparation of (3*R*, 4*S*, 4a*R*, 11b*R*)-methyl 3, 4-bis (*tert*-butyldimethylsilyloxy)-1-oxo-1, 2, 3, 4, 4a, 11b-Hexahydro [1, 3] dioxolo [4, 5-j] phenanthridine-5 (6H)-carboxylate (7):



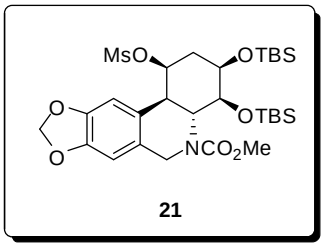
7

A solution of **8** (0.6 g, 0.88 mmol), 1, 4-dicyanonaphthalene (DCN, 0.05 g, 0.28 mmol) in CH_3CN: H_2O (24:1, 250 mL) was irradiated (Pyrex filter, > 280nm, 450 W

Hanovia medium pressure lamp) for 6 h. Solvent was evaporated under reduced pressure and the residue was column chromatographed over silica gel using pet ether: ethyl acetate (19:1) as eluant to give **7** as a single diastereomer (0.34 g, 68 %).

$[\alpha]^{27}_D$	:	$+17.5^o$ (*c* 2.1, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	1717, 1695, 1215
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	6.63 (s, 1H), 6.51 (s, 1H), 5.92 (s, 2H), 4.87 (br d, *J* = 17.4 Hz, 2H), 4.23-3.59 (m, 7H), 2.47 (m, 2H), 0.90 (s, 18H), 0.08 (s, 12H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	206.8, 156.3, 147.1, 147.0, 126.2, 122.2, 106.8, 106.6, 101.1, 77.2, 70.7, 70.5, 52.7, 51.4, 45.5, 42.6, 25.7, 18.1, 17.8, -3.4, -4.2, -4.7, -4.9.
Mass: m/z (%)	:	586 ($M+Na^+$, 100).

9. Preparation of (1*S*, 3*R*, 4*S*, 4a*R*, 11b*R*)-methyl 3, 4-bis (*tert*-butyldimethylsilyloxy)-1-(methylsulfonyloxy)-1, 2, 3, 4, 4a, 11b-hexahydro-[1, 3] dioxolo [4, 5-j] phenanthridine-5 (6H)-carboxylate (21):



21

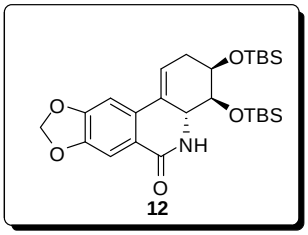
To a solution of **7** (0.50 g, 0.88 mmol) in ethanol (3 mL) was added sodium borohydride (0.04 g, 1.06 mmol) at 0 ^oC. The resulting mixture was stirred at room temperature for 6 h. Saturated sodium chloride solution (1 mL) was added and the stirring was continued for further 6 h. The reaction mixture was extracted with ethyl acetate (3x5 mL). The combined organic extracts were washed successively with water (2x5 mL), brine (1x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was subjected to mesyl protection without further purification.

To a mixture of compound **21** (0.1 g, 0.17 mmol) and triethyl amine (0.02 mL, 0.211 mmol) in dry DCM (1 mL) at 0 ^oC was added MsCl (0.01 mL, 0.19 mmol) and allowed to stir for half an hour. After the reaction was completed, it was diluted with additional DCM (2 mL) and washed with water (2x2 mL), brine (1x1 mL) dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by silica gel

column chromatography, eluting with pet ether: ethyl acetate (85:15) which gave 0.98 g of (**21**) in 87 % yield as colorless gummy mass.

$[\alpha]^{27}_D$	:	+24.2° (*c* 2.5, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3020, 1689
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	6.76 (s, 1H), 6.68 (s, 1H), 5.92 (2d, *J* = 1.0 Hz, 2H), 5.05 (d, *J* = 15.5 Hz, 1H), 4.44 (m, 1H), 4.32 (m, 1H), 4.00 (d, *J* = 15.8 Hz, 1H), 3.80 (m, 1H), 3.72 (s, 3H), 3.69 (m, 1H), 3.24 (dd, *J* = 10.2, 6.0 Hz, 1H), 2.38 (m, 4H), 2.09 (m, 1H), 0.91 (s, 9H), 0.88 (s, 9H), 0.12 (m, 6H), 0.06 (s, 6H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	171.1, 156.9, 147.0, 128.8, 128.4, 110.0, 107.4, 101.1, 81.4, 71.5, 67.7, 58.0, 53.0, 45.7, 40.4, 37.4, 33.9, 25.9, 25.8, 18.3, 18.0, -4.4, -4.7, -4.7, -4.8.
Mass: m/z (%)	:	666 ($M+Na^+$, 100).

10. Preparation of (3*R*, 4*S*, 4a*R*)-3, 4-bis (*tert*-butyldimethylsilyloxy)-3, 4, 4a, 5-tetrahydro-[1, 3] dioxolo [4, 5-j] phenanthridin-6 (2H)-one (12):



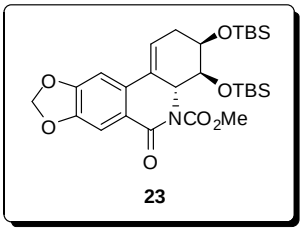
12

To the solution of **22** (100 mg, 0.15 mmol) in toluene (1 mL) was added DBU (0.22 mL, 1.52 mmol) and heated at 80 °C for 12 h. Reaction mixture was allowed to cool to room temperature and solvent was removed under reduced pressure, diluted with DCM (2 mL), washed with water (2x2 mL), brine (1x1 mL), dried (Na_2SO_4), filtered, concentrated under reduced pressure and purified by silica gel column chromatography using pet ether: ethyl acetate (9:1) as eluant to obtain **12** (60 mg, 78 %) as colorless white solid.

mp	:	162 °C
$[\alpha]^{25}_D$	:	+24.4° (*c* 1.25 , $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3142, 3019, 1658, 1417
^{1}H NMR	:	7.55 (s, 1H), 6.92 (s, 1H), 6.00 (2d, *J* = 1.1 Hz, 2H), 5.91 (m, 1H),

($CDCl_3$, 500 MHz) δ		5.76 (s, 1H), 4.52 (m, 1H), 4.06 (m, 1H), 3.74 (dd, *J* = 8.9, 1.4 Hz, 1H), 2.59 (m, 1H), 2.34 (m, 1H), 0.97 (s, 9H), 0.83 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H).
^{13}C NMR	:	164.5, 151.3, 147.7, 132.2, 129.0, 121.4, 119.5, 107.4, 102.6,
($CDCl_3$, 125 MHz) δ		101.6, 75.5, 69.4, 52.7, 35.0, 25.9, 25.6, 18.1, 18.0, -3.6, -4.40, -4.46, -4.7.
Mass: m/z (%)	:	526 ($M+Na^+$, 100).

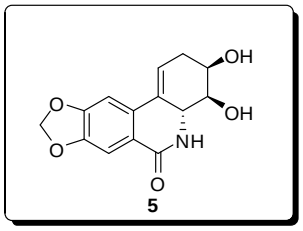
11. Data of (3*R*, 4*S*, 4a*R*)-methyl 3, 4-bis (*tert*-butyldimethylsilyloxy)-6-oxo- 2, 3, 4, 4a-tetrahydro-[1, 3] dioxolo [4, 5-j] phenanthridine-5(6H)-carboxylate (23):



23

$[\alpha]^{26}_D$	:	$+43.9^o$ (*c* 1.1, $CHCl_3$)
IR	:	2930, 1696, 1694 cm^{-1}
^{1}H NMR	:	7.48 (s, 1H), 6.86 (s, 1H), 6.02 (m, 3H), 4.31 (m, 1H), 4.12 (m, 1H),
($CDCl_3$, 500 MHz) δ		3.94 (s, 3H), 3.80 (dd, *J* = 10.0, 5.8 Hz, 1H), 2.56 (dd, *J* = 16.8, 9.7 Hz, 1H), 2.19 (m, 1H), 0.89 (s, 9H), 0.86 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.04 (s,3H), 0.05 (s, 3H).
^{13}C NMR	:	164.7, 155.8, 152.2, 147.8, 136.0, 128.2, 127.0, 120.6, 108.0,
($CDCl_3$, 125 MHz) δ		102.7, 101.8, 71.0, 68.7, 61.9, 54.4, 29.6, 25.9, 25.8, 18.2, 18.1, -4.6, -4.7, -4.9.
Mass: m/z (%)	:	586 (M+Na, 100).

12. Preparation of (3*R*, 4*S*, 4a*R*)-3, 4-dihydroxy-3, 4, 4a, 5-tetrahydro-[1, 3] dioxolo [4, 5-j] Phenanthridin-6 (2H)-one (5):



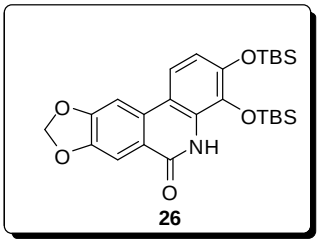
5

To the solution of **12** (18 mg, 0.03 mmol) in dry THF (1 mL) was added a solution of TBAF in THF (0.07 mL, 1M, 0.07 mol) at 0 ^oC. The resulting mixture was allowed to stir for 8 h before quenching with water (1 mL). The mixture was evaporated to dryness and

the residue was column chromatographed over flash silica gel using ethyl acetate: methanol (96:4) as eluant to give **5** (8 mg, 81 %) as a white solid.

mp	:	220–253 °C
$[\alpha]^{27}_D$	:	+ 52.14^o (*c* 0.4, MeOH)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3341, 3019, 1657
^{1}H NMR (CD_3OD, 500 MHz) δ	:	7.24 (s, 1H), 6.96 (s, 1H), 5.98 (m, 1H), 5.92 (2d, *J* = 1.1 Hz, 2H), 4.51 (s, 1H), 4.27 (m, 1H), 3.96 (m, 1H), 3.58 (dd, *J* = 9.3, 2.2 Hz, 1H), 2.57 (ddd, *J* = 19.8, 7.1, 4.1 Hz, 1 H), 2.31 (m, 1H).
^{13}C NMR (CD_3OD, 125 MHz) δ	:	166.9, 153.4, 149.4, 134.2, 129.1, 122.3, 121.9, 107.5, 104.1, 103.4, 74.3, 69.2, 53.7, 34.4.
Mass: m/z (%)	:	236 (100), 298 (M+Na$^+$, 25), 237 (14), 202 (14), 276 (MH$^+$, 7)

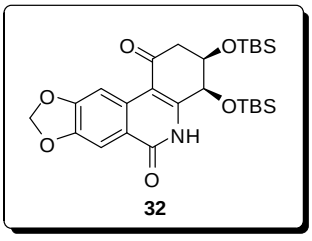
13. Data of 3, 4-bis (*tert*-butyldimethylsilyloxy)-[1, 3] Dioxolo [4, 5-j] Phenanthridin-6 (5H)-one (26):



26

IR		3019, 1651, 1215 cm^{-1}
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	8.88 (br s, 1H), 7.82 (s, 1H), 7.49 (m, 2H), 6.83 (d, *J* = 8.9 Hz, 1H), 6.11 (s, 2H), 1.10 (s, 9H), 0.97 (s, 9H), 0.27 (s, 6H), 0.21 (s, 6H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	160.6, 152.6, 147.7, 146.4, 132.3, 132.2, 129.4, 115.96, 115.92, 115.5, 113.4, 106.4, 101.9, 100.6, 26.1, 26.0, 18.8, 18.5, -3.4, -3.9.
Mass: m/z (%)	:	522 (M+Na$^+$, 100), 336 (20).

14. Preparation of (3*R*, 4*S*)-3, 4-bis (*tert*-butyl dimethylsilyloxy)-3, 4-dihydro-[1, 3] dioxolo [4, 5-j] Phenanthridine-1, 6 (2H, 5H)-dione (32):



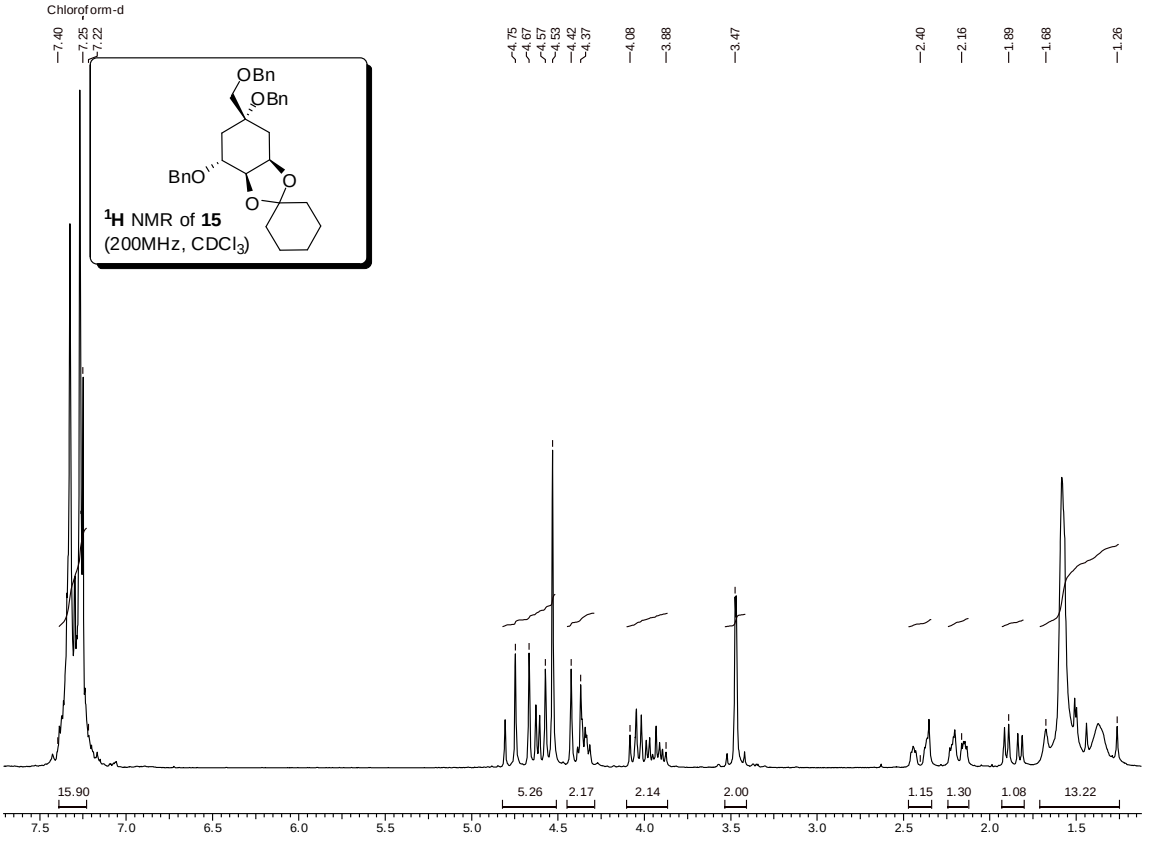
32

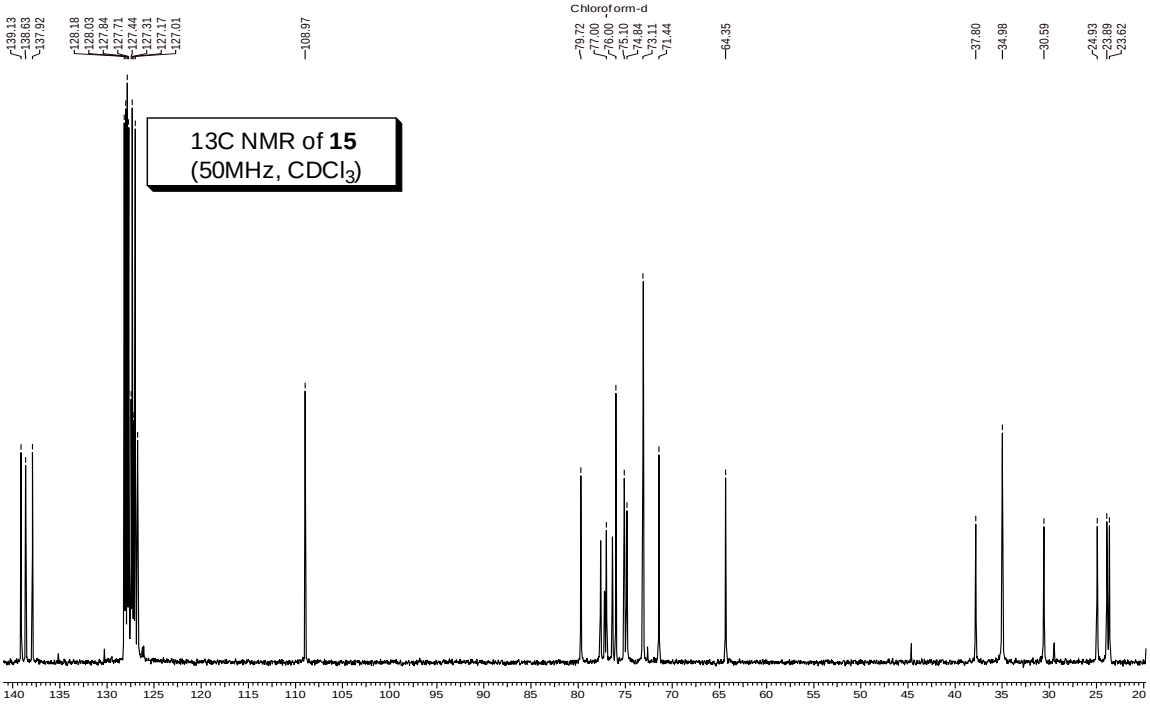
To a solution of **12** (0.01 g, 0.20 mmol) in CH_3CN/H_2O (3:1 v/v) (3 mL), T-HYDRO (70 % aqueous solution of TBHP) (0.1 ml, 1 mmol) was added $NaClO_2$ (0.021 g, 0.23

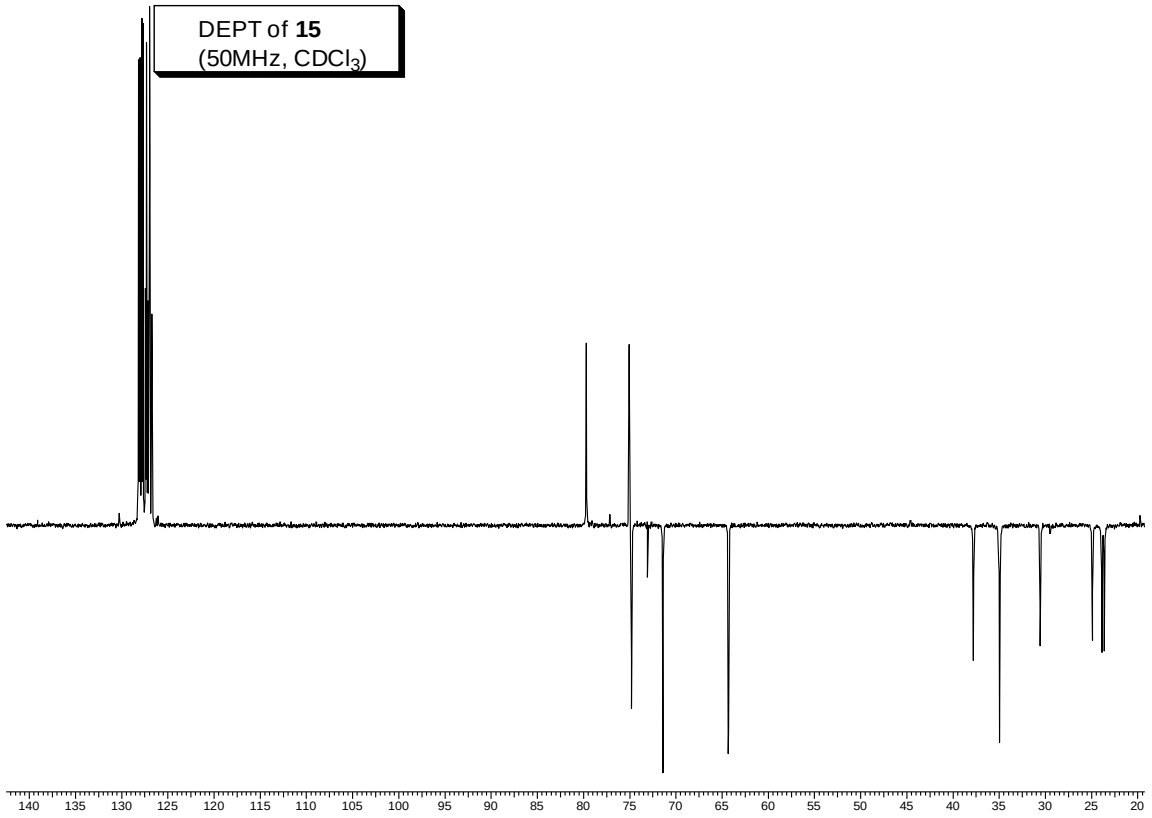
mmol). The resulting mixture was allowed to stir at 50 ^{o}C for 30 h. After the reaction was completed, sodium sulfite solution (10 % aqueous) was added and mixture extracted with ethyl acetate (3x5 mL). The combined organic extracts were washed successively with sat. $NaHCO_3$ (1x5 mL), water (1x5 mL), brine (1x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was column chromatographed over silica gel using pet ether: ethyl acetate (9:1) as eluant to yield **32** as colorless viscous mass.

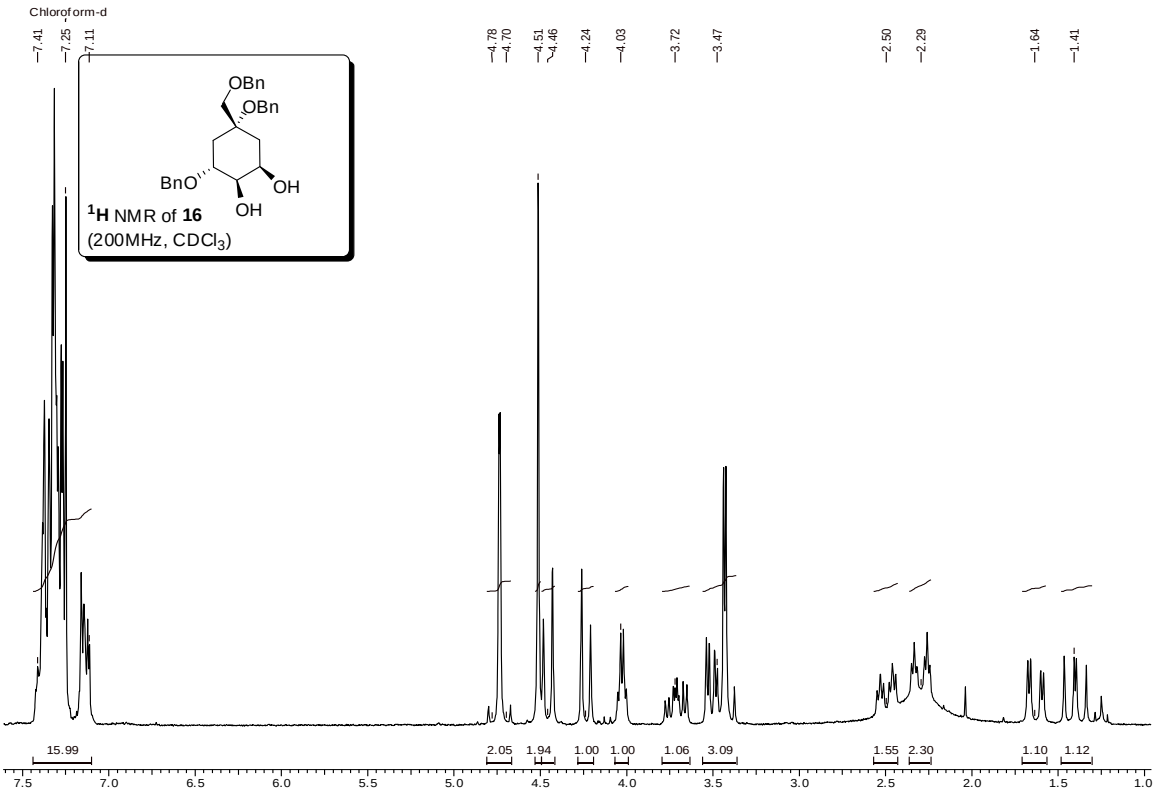
IR ν_{max} cm^{-1} ($CHCl_3$)		3019,1642,1215
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	8.78 (s,1H), 7.73 (s, 1H), 6.10 (m, 2H), 4.48 (m, 1H), 4.39 (m, 1H), 2.86 (dd, *J* = 17.0, 3.5 Hz, 1H), 2.73 (dd, *J* = 17.0, 2.2 Hz, 1H), 1.03 (s, 9H), 0.73 (s, 9H), 0.25 (s, 6H), 0.05 (s, 6H).
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	192.4, 161.1, 153.4, 149.4, 147.5, 132.3, 122.8, 120.3, 105.0, 104.8, 101.9, 77.2, 71.0, 29.6, 25.9, 25.5, 18.3, 17.9, -3.8, -4.4, -4.5, -5.0.
Mass: m/z (%)	:	572 (M+Na^++ MeOH).

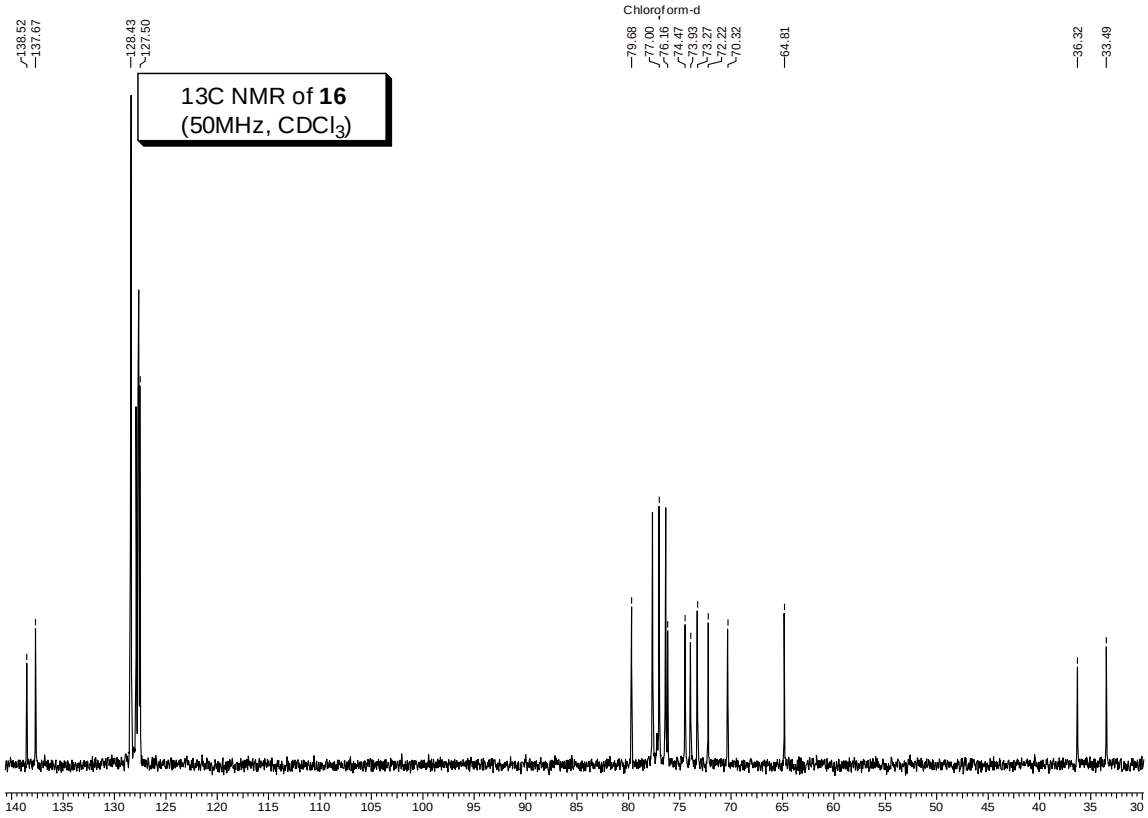
3A.7. Spectral Data and X-ray data

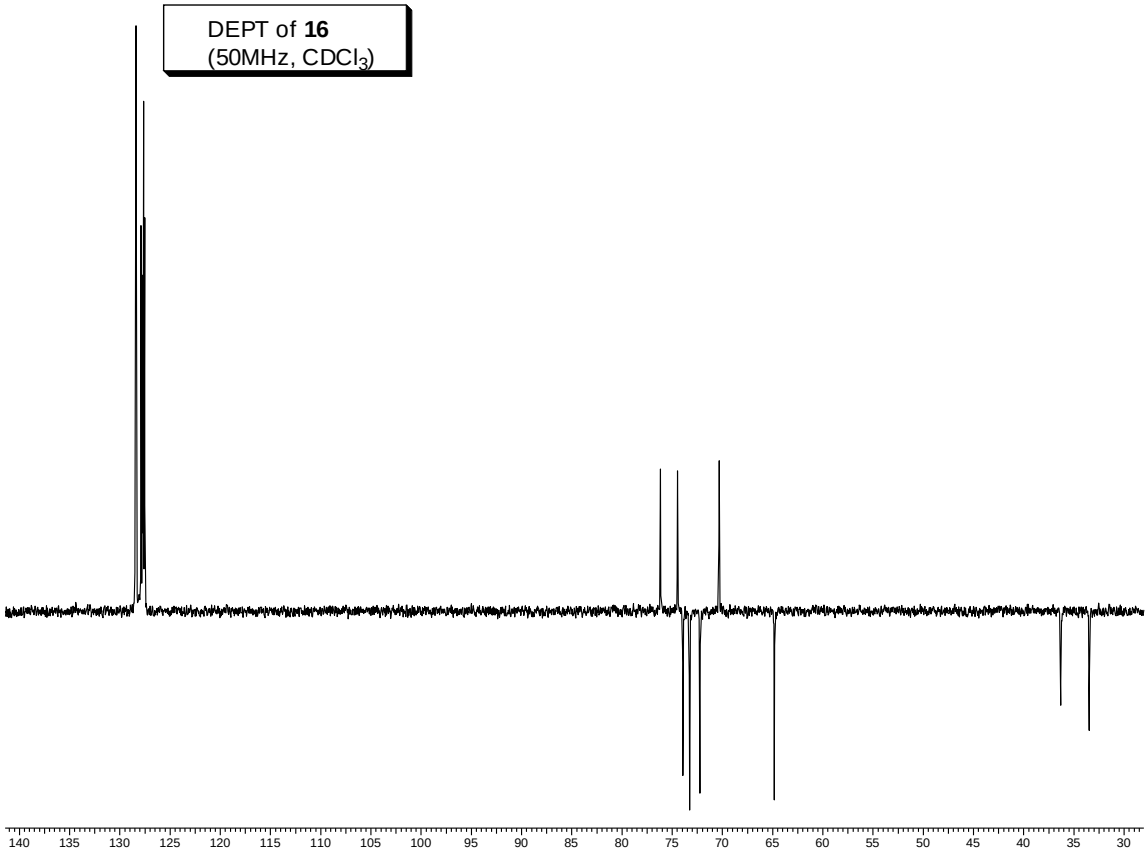


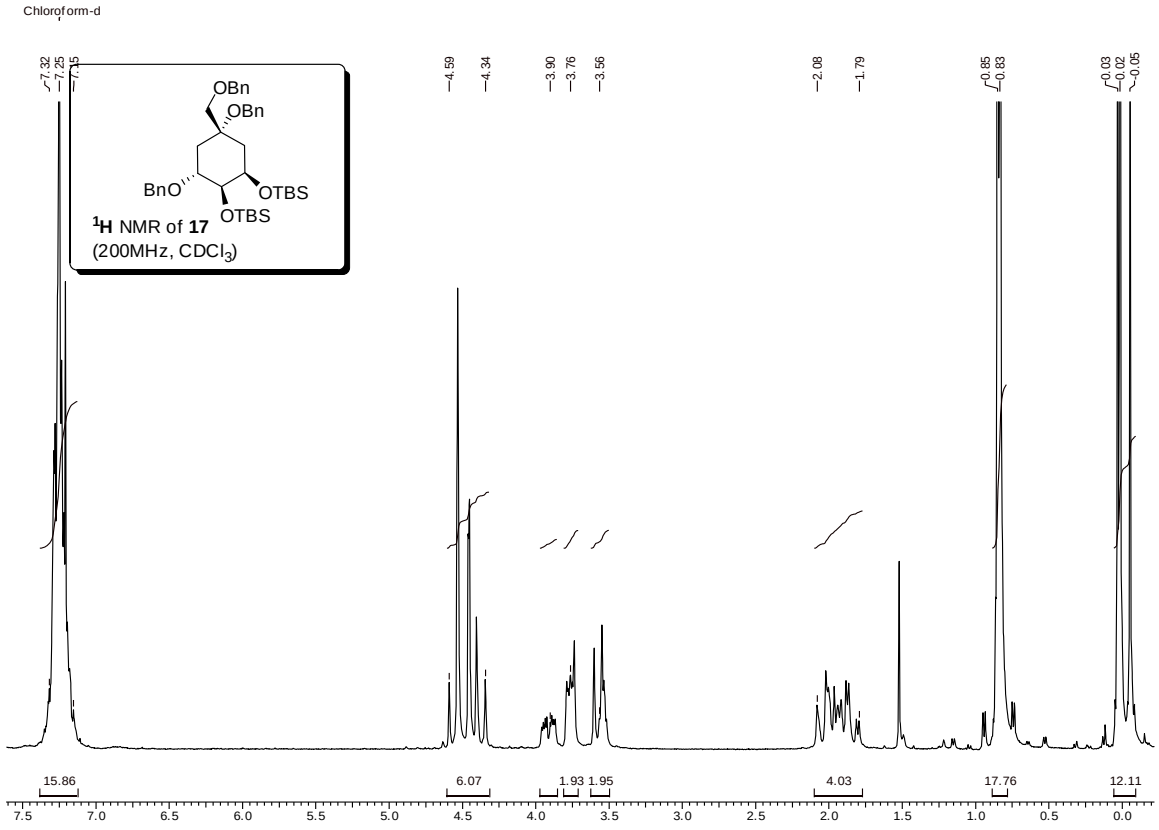


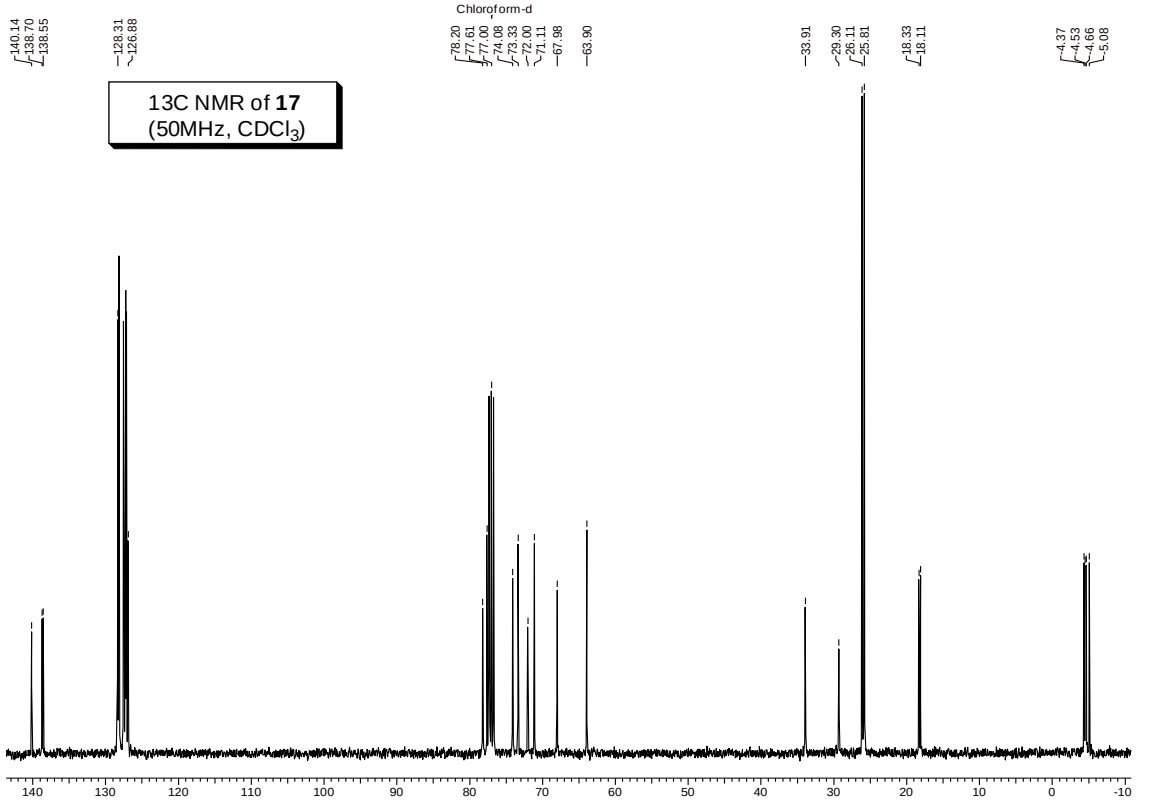

DEPT of **15**
(50MHz, $CDCl_3$)


Chloroform-d
7.41
7.25
7.11
4.78
4.70
4.51
4.46
4.24
4.03
3.72
3.47
2.50
2.29
1.64
1.41
OBn
OBn
BnO
OH
OH
^{1}H NMR of **16**
(200MHz, $CDCl_3$)
15.99
2.05
1.94
1.00
1.00
1.06
3.09
1.55
2.30
1.10
1.12

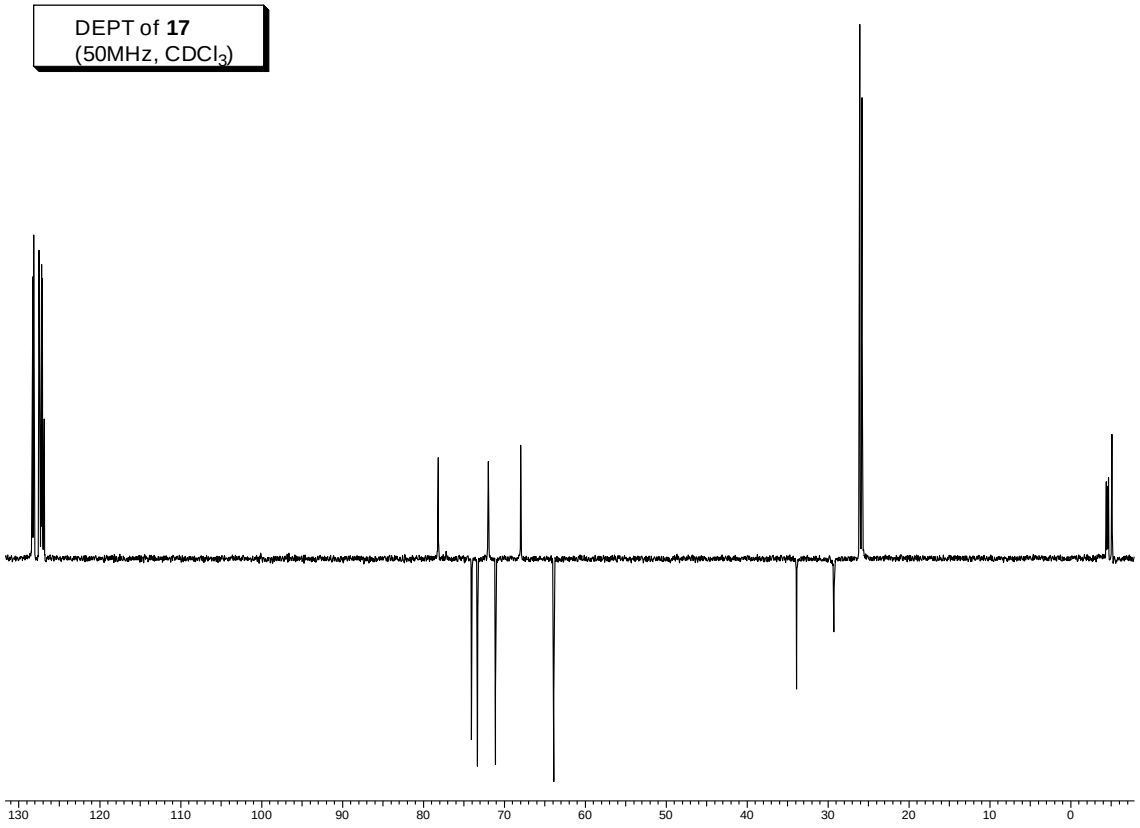

Chloroform-d
138.52
137.67
128.43
127.50
79.68
77.00
76.16
74.47
73.93
73.27
72.22
70.32
64.81
36.32
33.49
13C NMR of **16**
(50MHz, $CDCl_3$)
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30

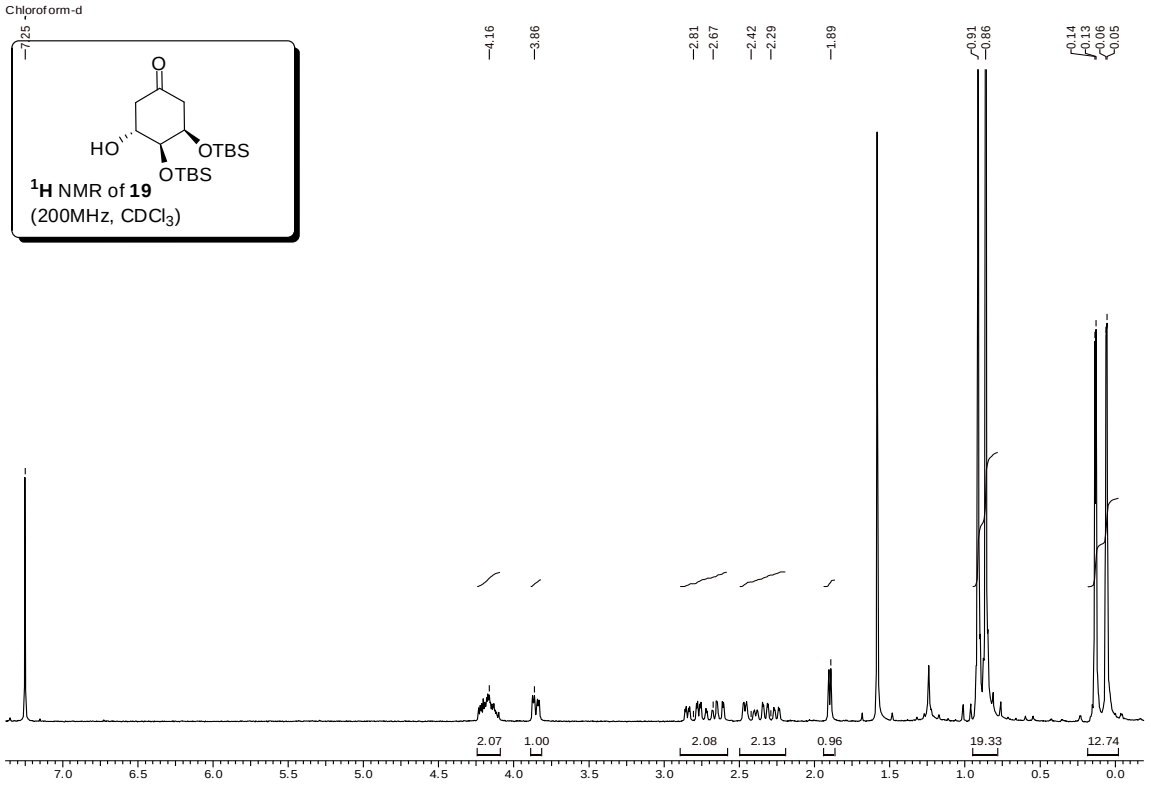

DEPT of **16**
(50MHz, $CDCl_3$)
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30


Chloroform-d
7.32
7.25
4.59
4.34
3.90
3.76
3.56
2.08
1.79
0.85
0.83
0.03
0.02
-0.05
OBn
OBn
BnO
OTBS
OTBS
1H NMR of 17
(200MHz, CDCl3)
15.86
6.07
1.93
1.95
4.03
17.76
12.11

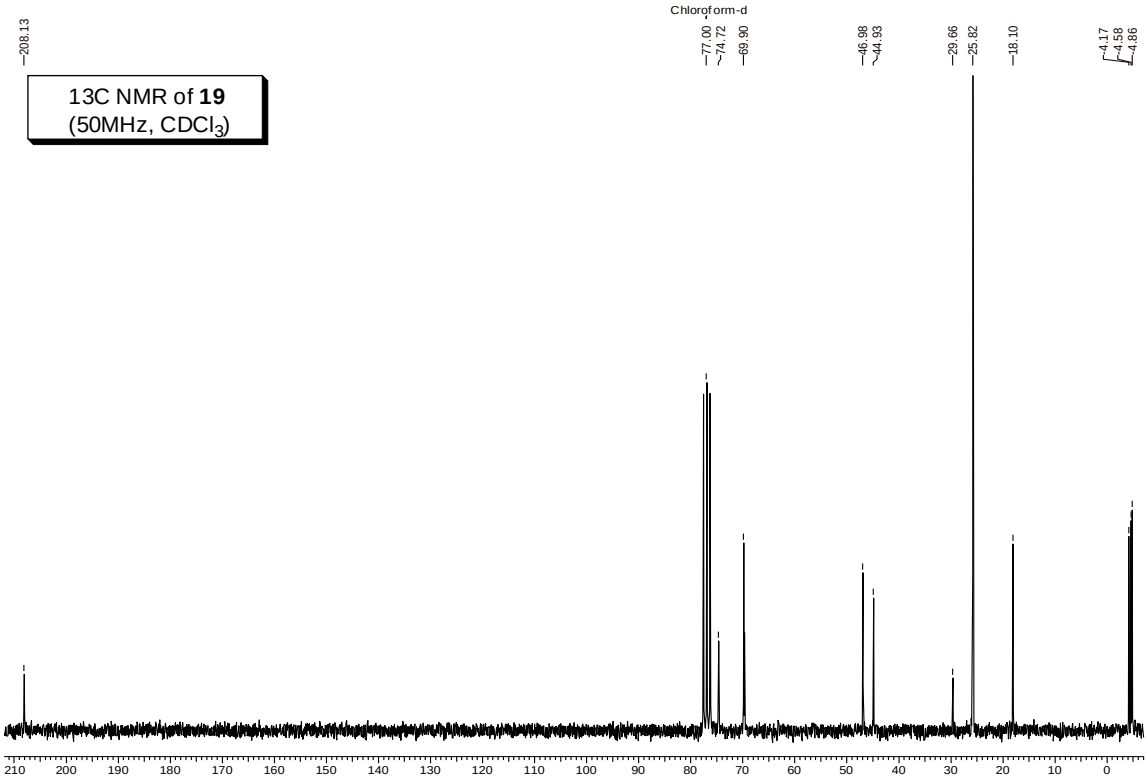

Chloroform-d
140.14
138.70
138.55
128.31
126.88
78.20
77.61
77.00
74.08
73.33
72.00
71.11
67.98
63.90
33.91
29.30
26.11
25.81
18.33
18.11
-4.37
-4.53
-4.66
-5.08
13C NMR of 17
(50MHz, CDCl3)

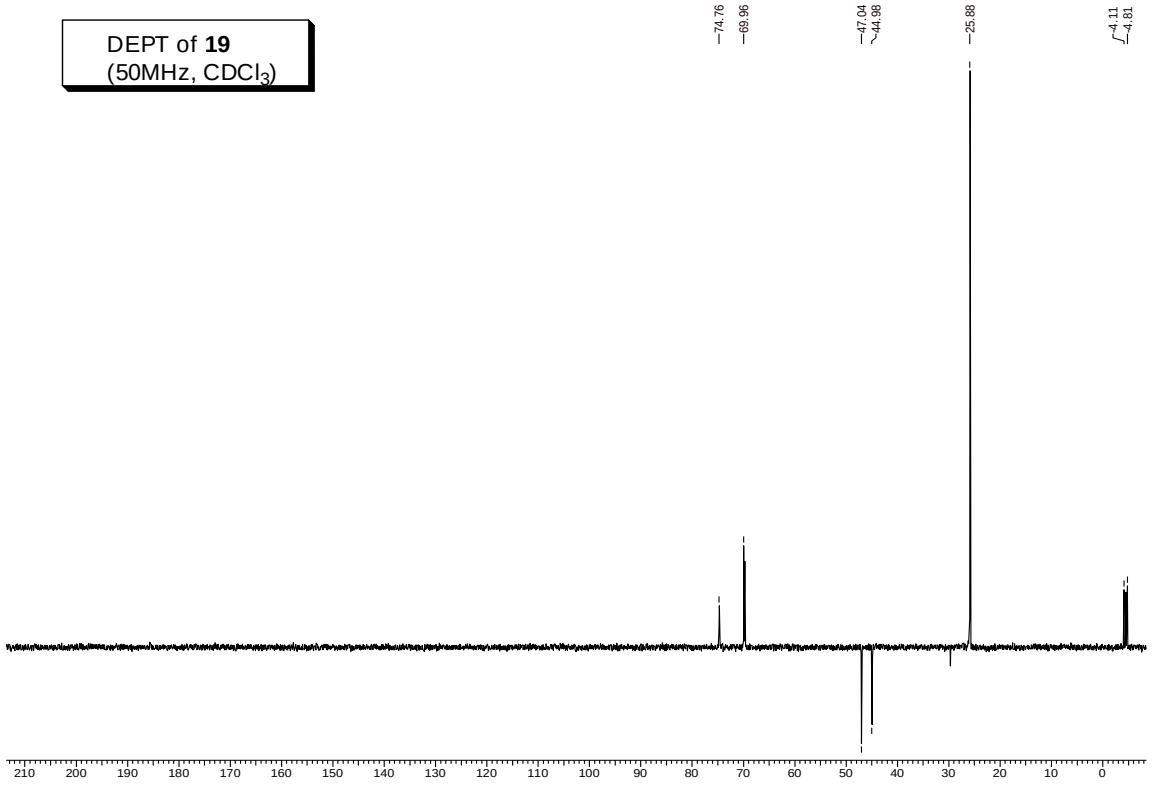
DEPT of **17**
(50MHz, $CDCl_3$)

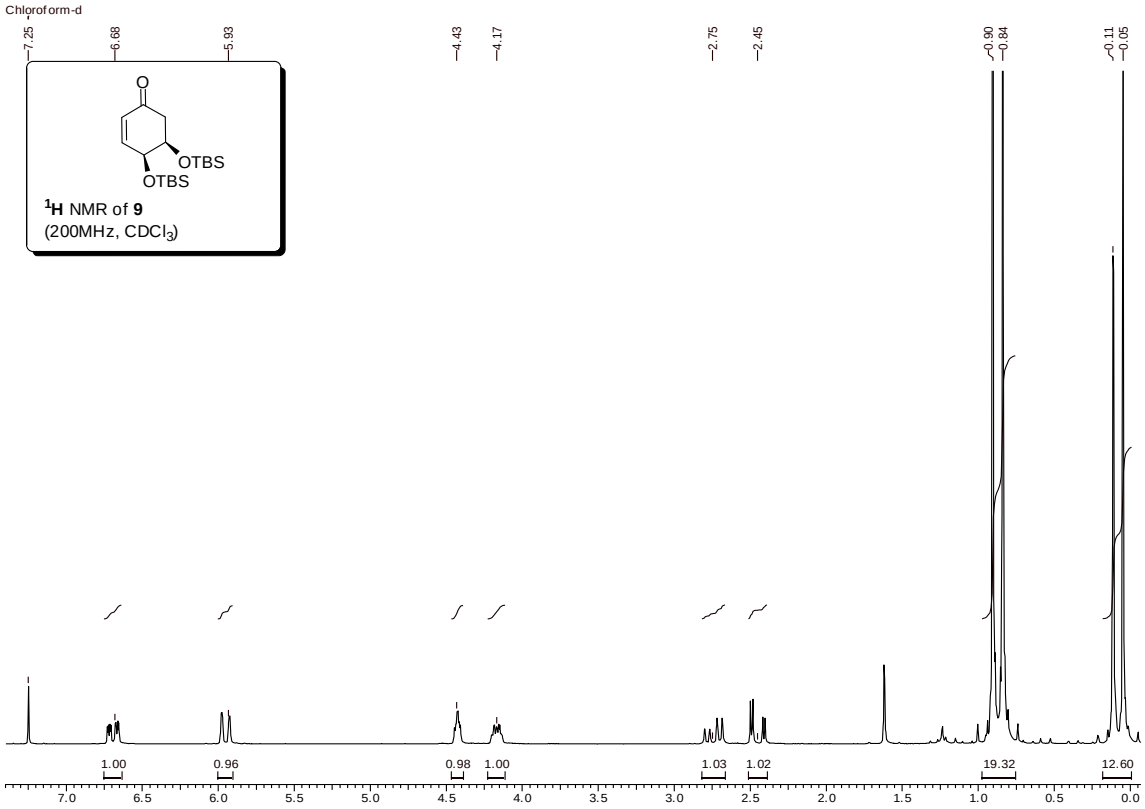


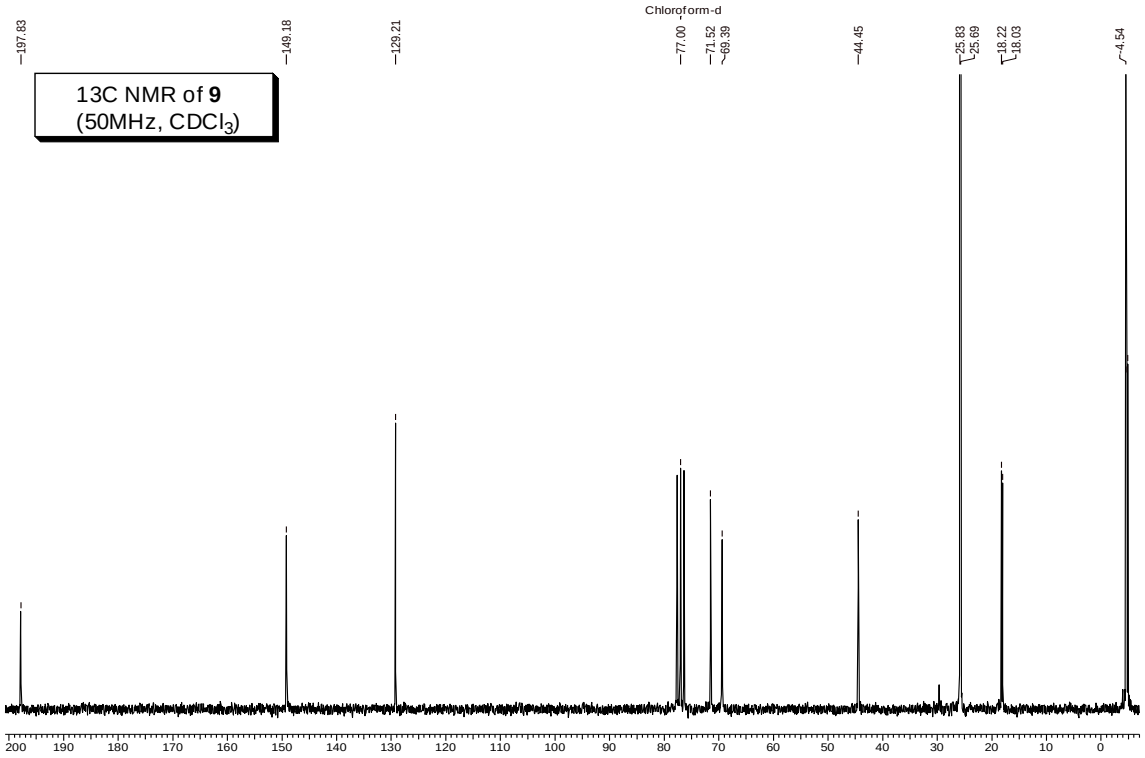


^{1}H NMR of **19**
(200MHz, $CDCl_3$)

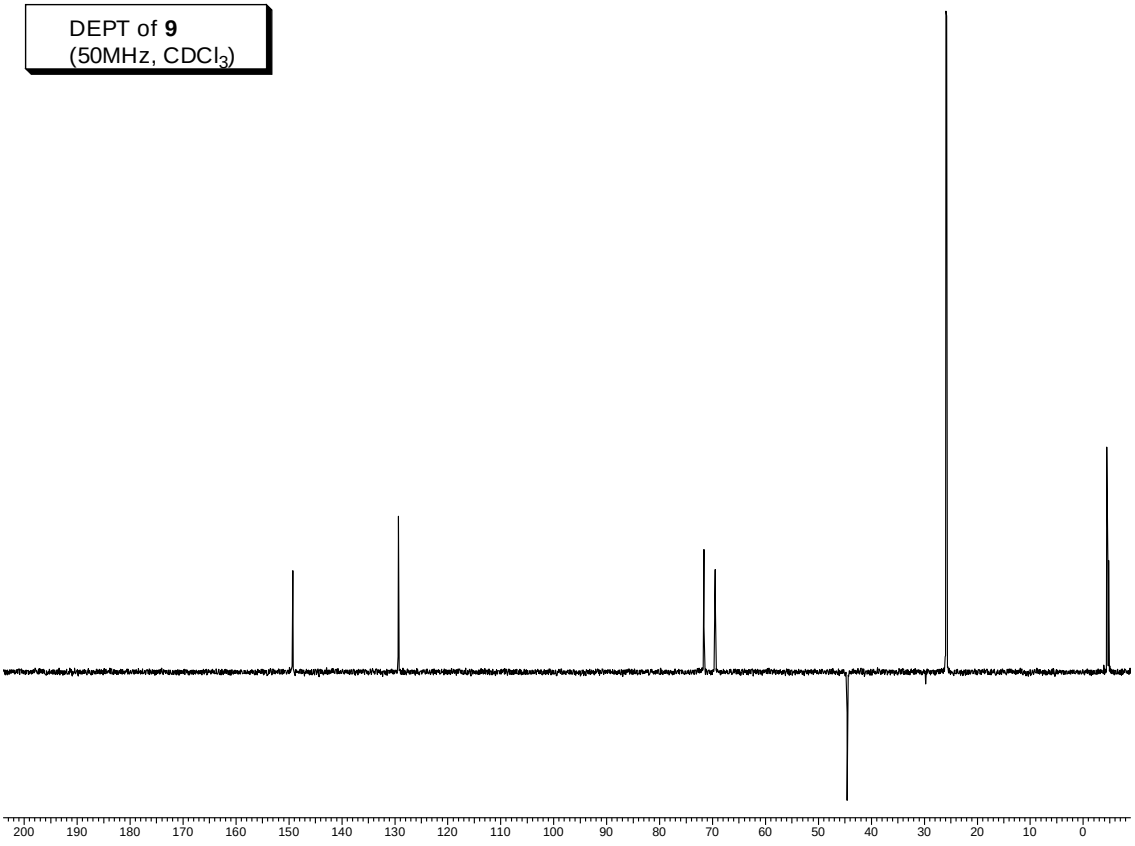

13C NMR of **19**
(50MHz, $CDCl_3$)
Chloroform-d
208.13
77.00
74.72
69.90
46.98
44.93
29.66
25.82
18.10
4.17
4.58
4.86
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

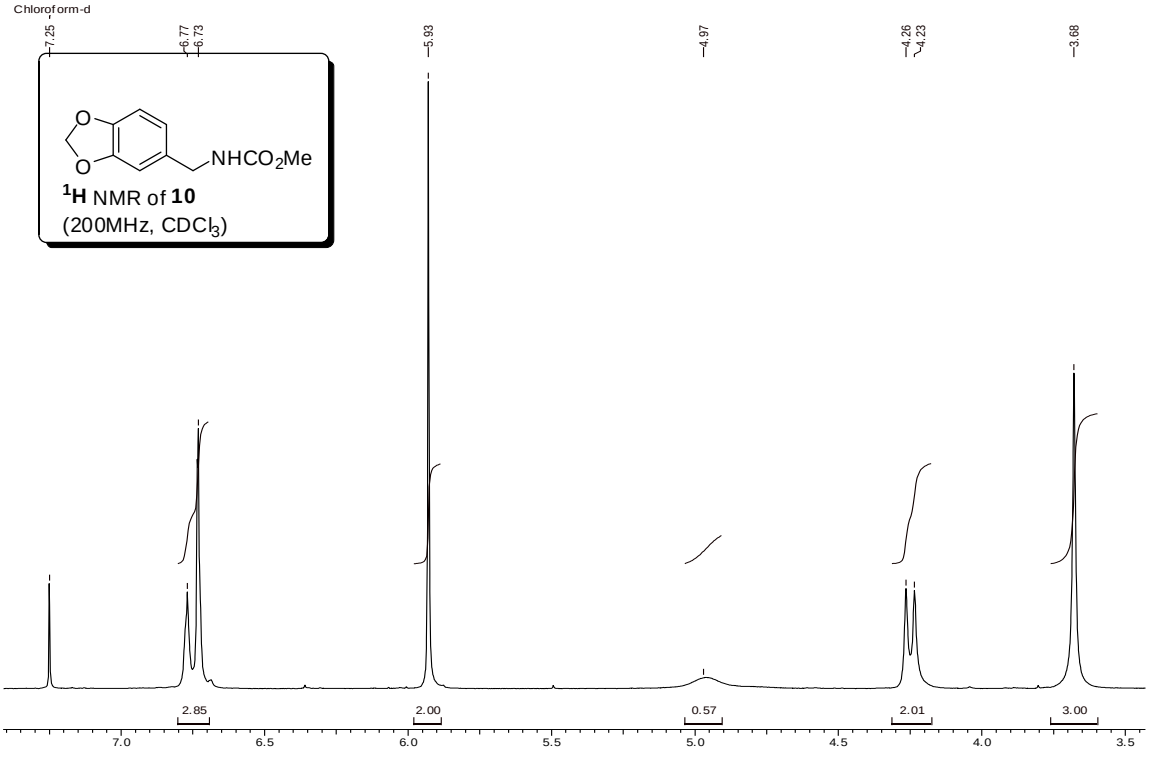

DEPT of **19**
(50MHz, $CDCl_3$)
74.76
69.96
47.04
44.98
25.88
4.11
4.81
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


Chloroform-d
7.25
6.68
5.93
4.43
4.17
2.75
2.45
0.90
0.84
0.11
0.05
O
OTBS
OTBS
1H NMR of 9
(200MHz, CDCl3)
1.00
0.96
0.98
1.00
1.03
1.02
19.32
12.60

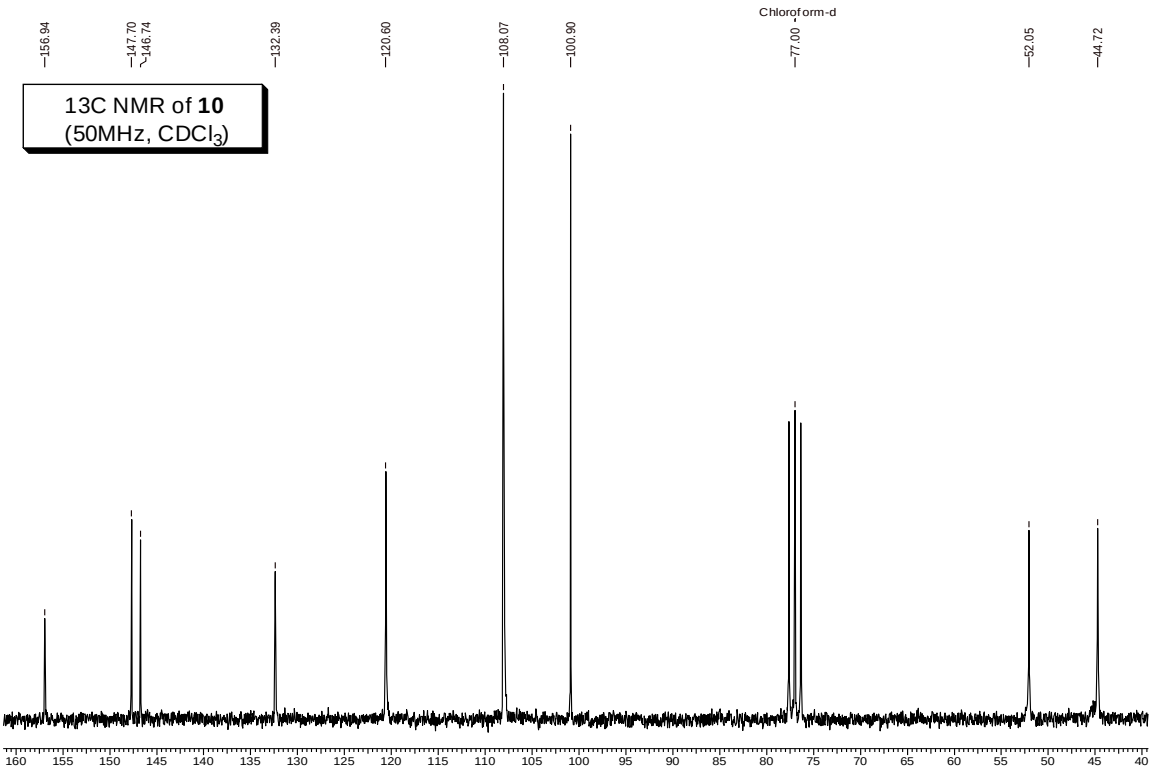

Chloroform-d
197.83
149.18
129.21
77.00
71.52
69.39
44.45
25.83
25.69
18.22
18.03
-4.54
13C NMR of 9
(50MHz, CDCl3)

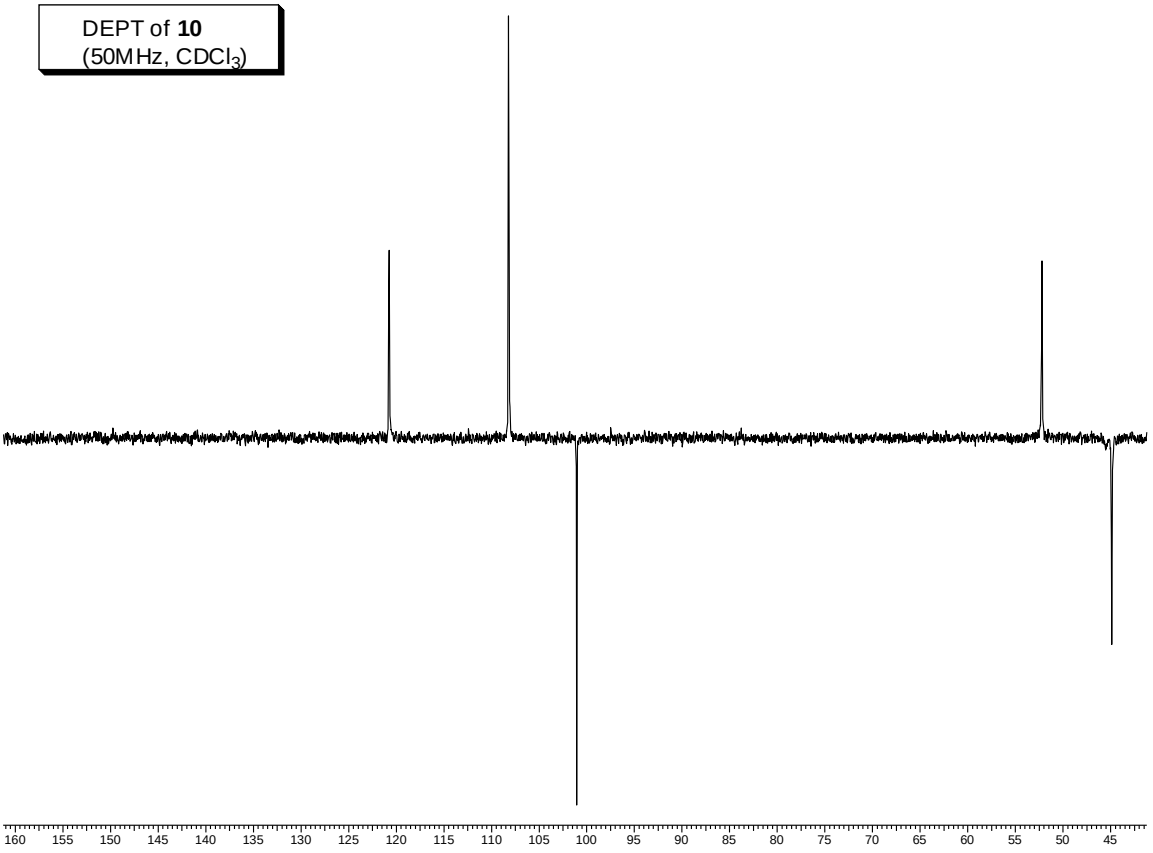
DEPT of **9**
(50MHz, $CDCl_3$)

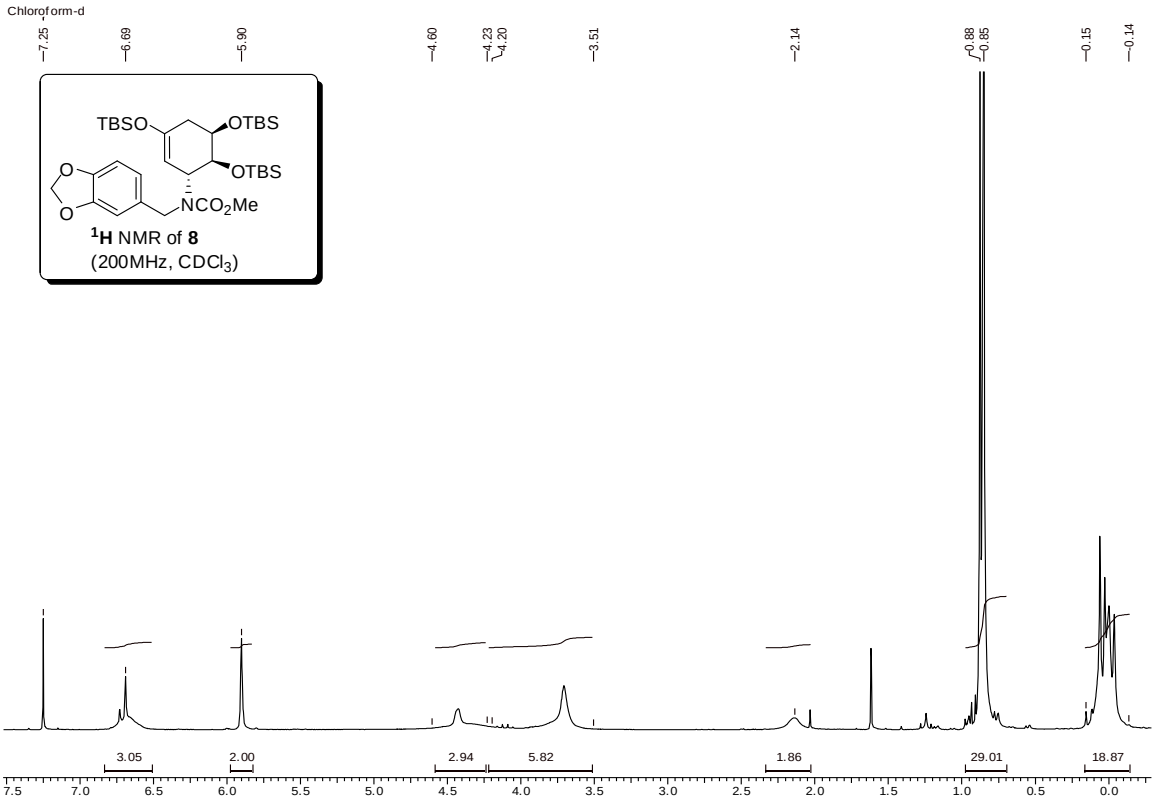


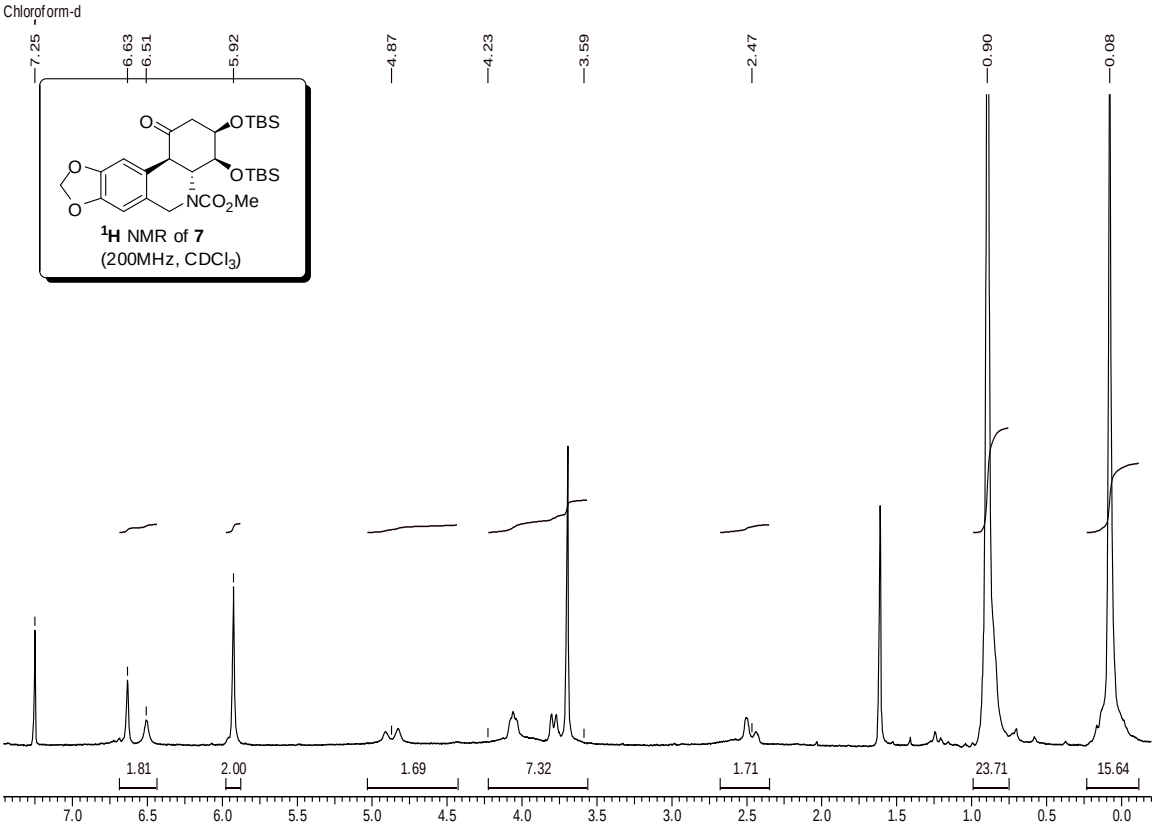


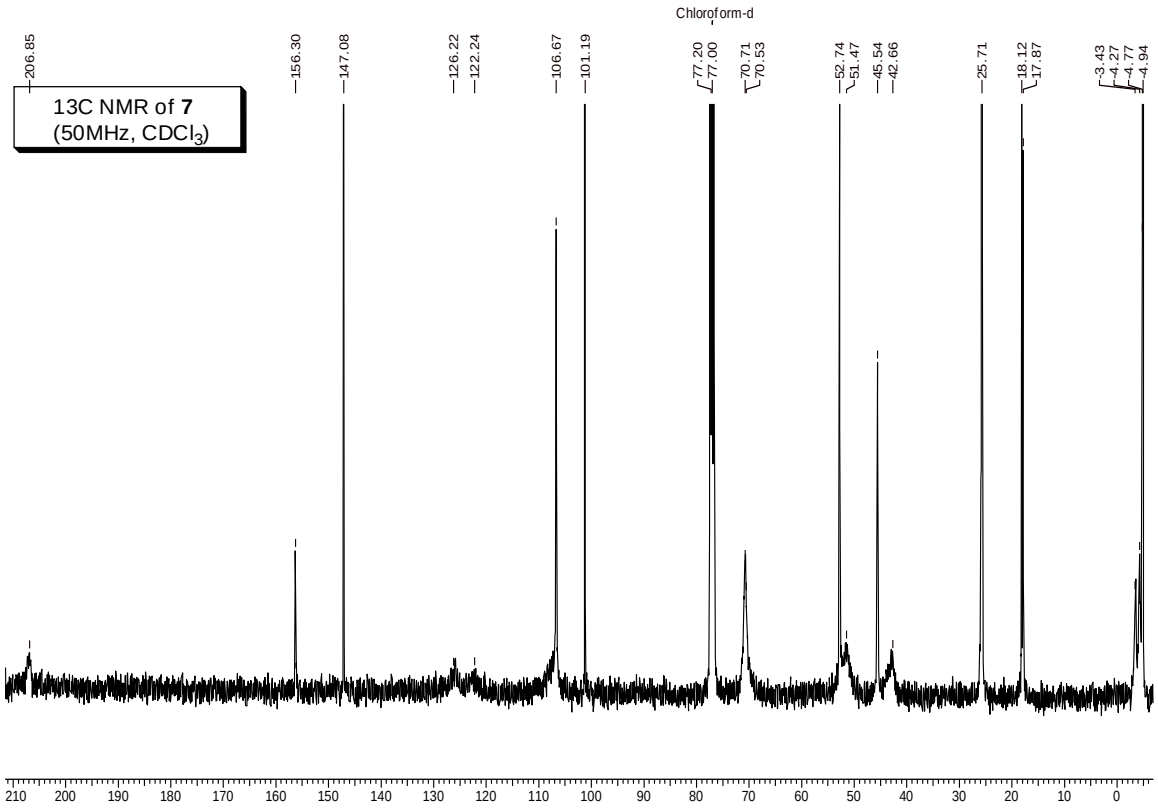
^{1}H NMR of **10**
(200MHz, $CDCl_3$)

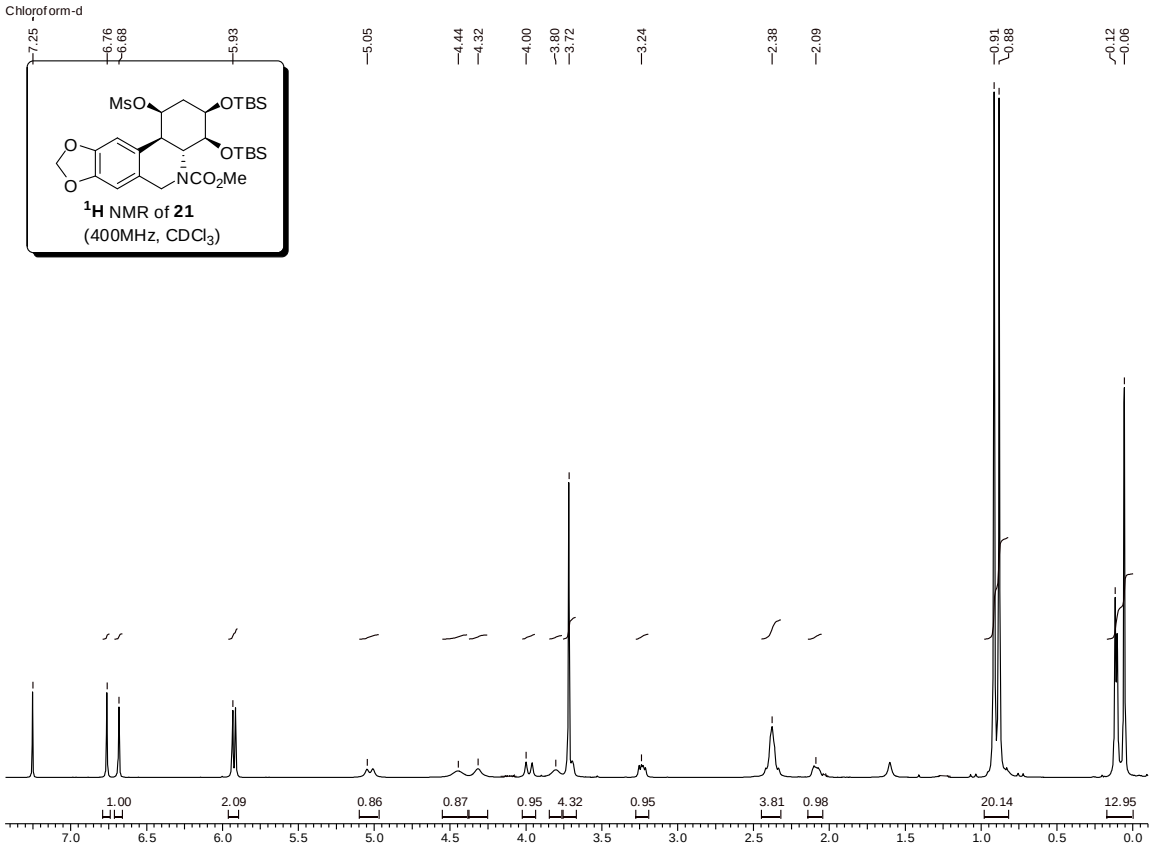

13C NMR of **10**
(50MHz, $CDCl_3$)
156.94
147.70
146.74
132.39
120.60
108.07
100.90
Chloroform-d
77.00
52.05
44.72

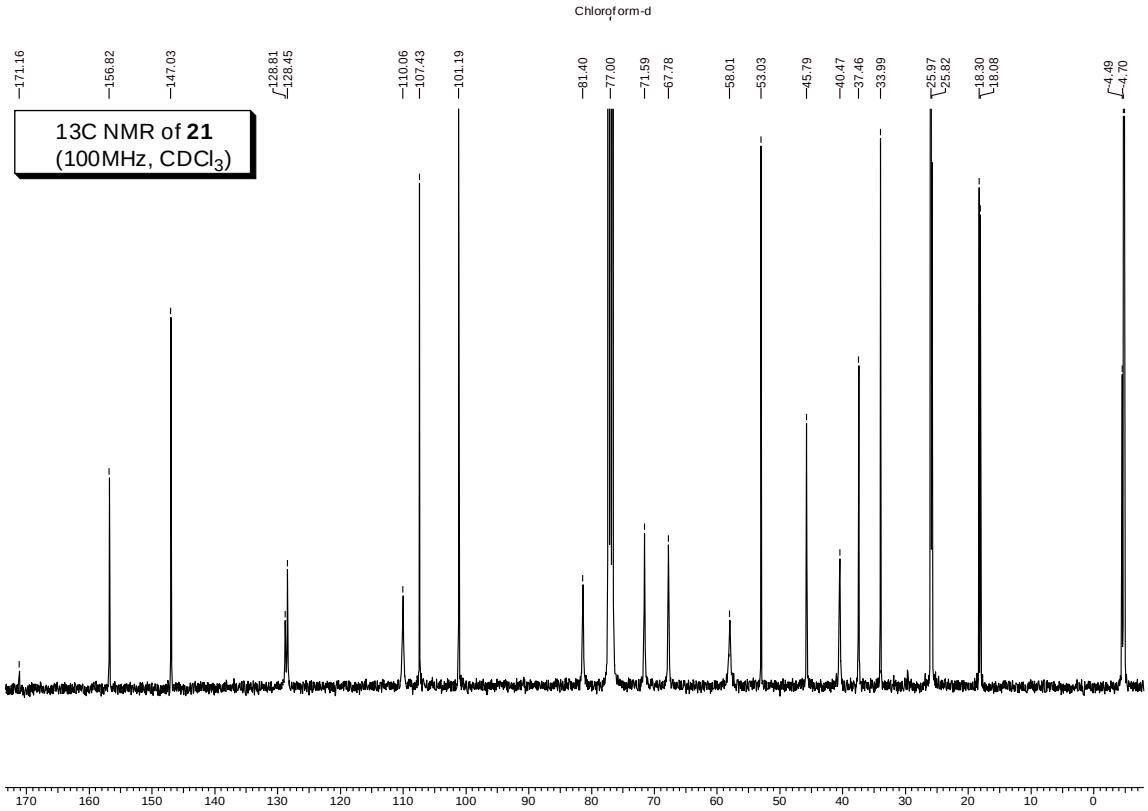

DEPT of **10**
(50MHz, $CDCl_3$)

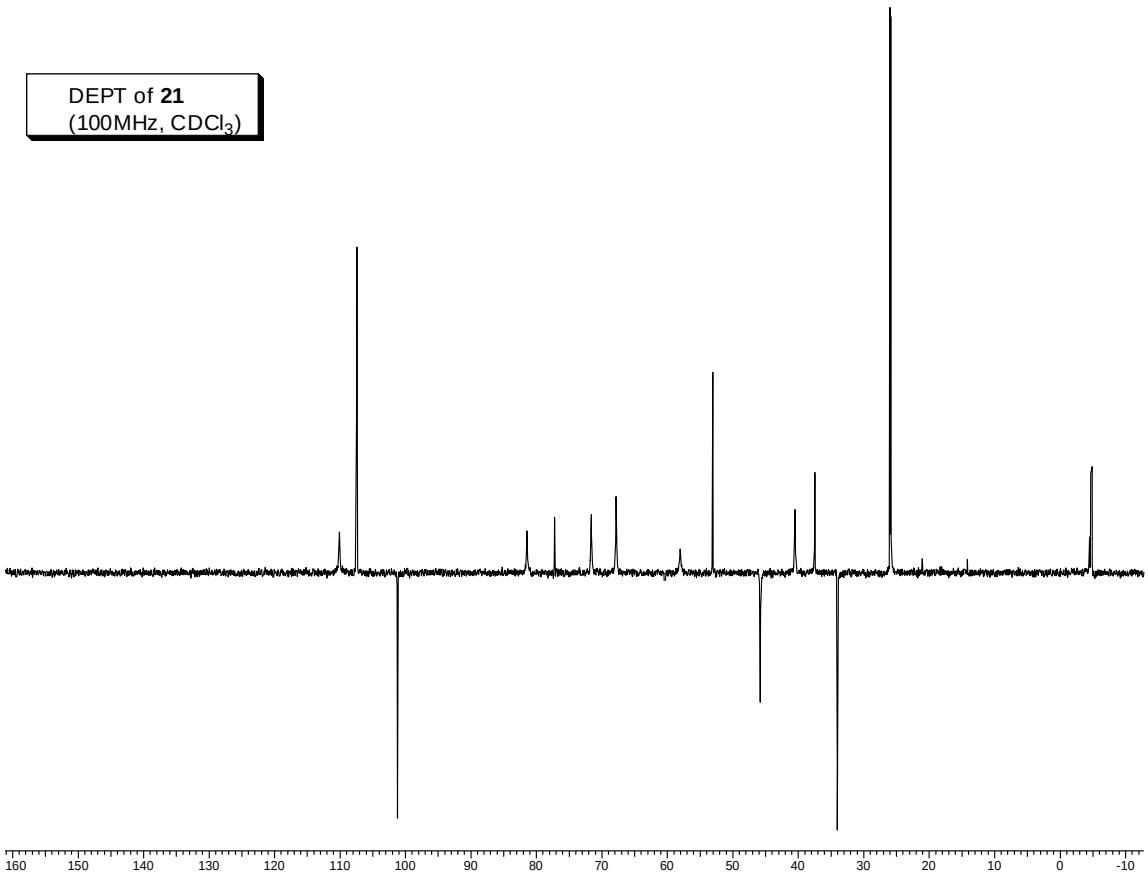

Chloroform-d
7.25
6.69
5.90
4.60
4.23
4.20
3.51
2.14
0.88
0.85
0.15
0.14
TBSO
OTBS
OTBS
O
O
NCO2Me
1H NMR of 8
(200MHz, CDCl3)
3.05
2.00
2.94
5.82
1.86
29.01
18.87

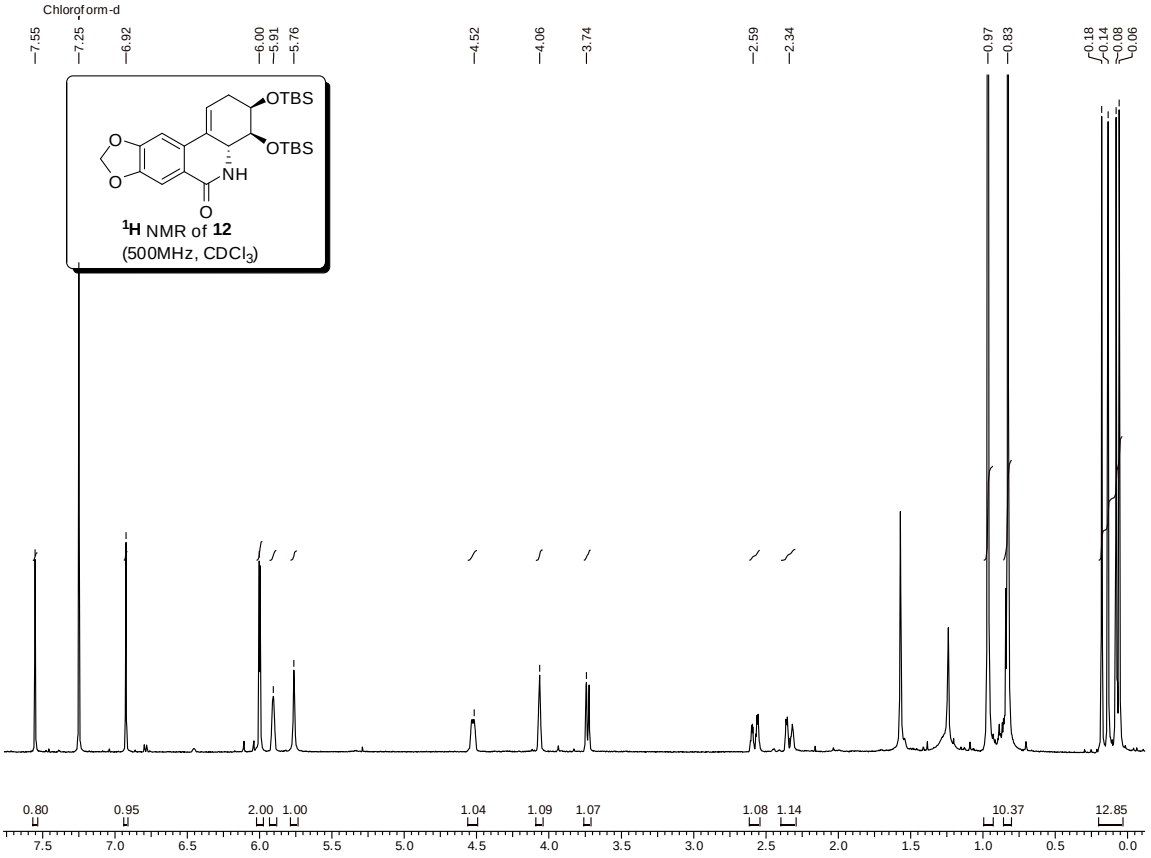

Chloroform-d
7.25
6.63
6.51
5.92
4.87
4.23
3.59
2.47
0.90
0.08
O
OTBS
OTBS
O
O
NCO2Me
1H NMR of 7
(200MHz, CDCl3)
1.81
2.00
1.69
7.32
1.71
23.71
15.64

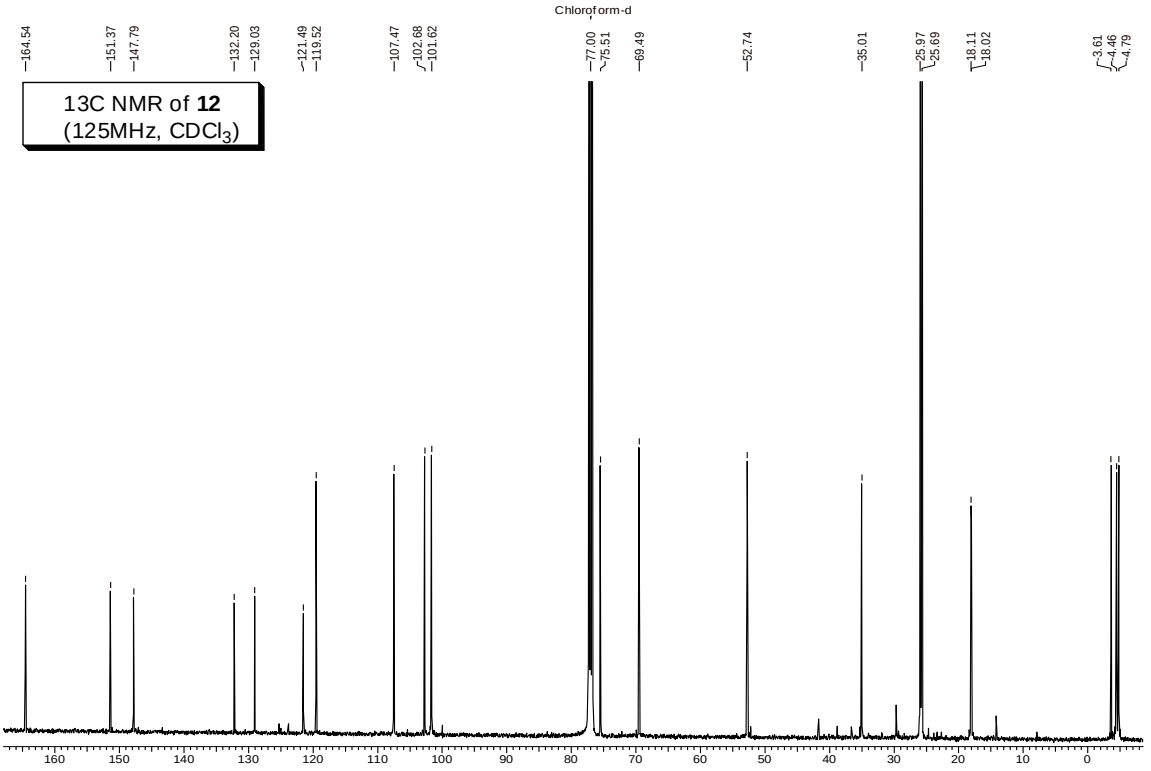

13C NMR of 7
(50MHz, CDCl3)
Chloroform-d
206.85
156.30
147.08
126.22
122.24
106.67
101.19
77.20
77.00
70.71
70.53
52.74
51.47
45.54
42.66
25.71
18.12
17.87
-3.43
-4.27
-4.77
-4.94


Chloroform-d
7.25
6.76
6.68
5.93
5.05
4.44
4.32
4.00
3.80
3.72
3.24
2.38
2.09
0.91
0.88
0.12
0.06
MsO
OTBS
OTBS
NCO2Me
1H NMR of 21
(400MHz, CDCl3)
1.00
2.09
0.86
0.87
0.95
4.32
0.95
3.81
0.98
20.14
12.95

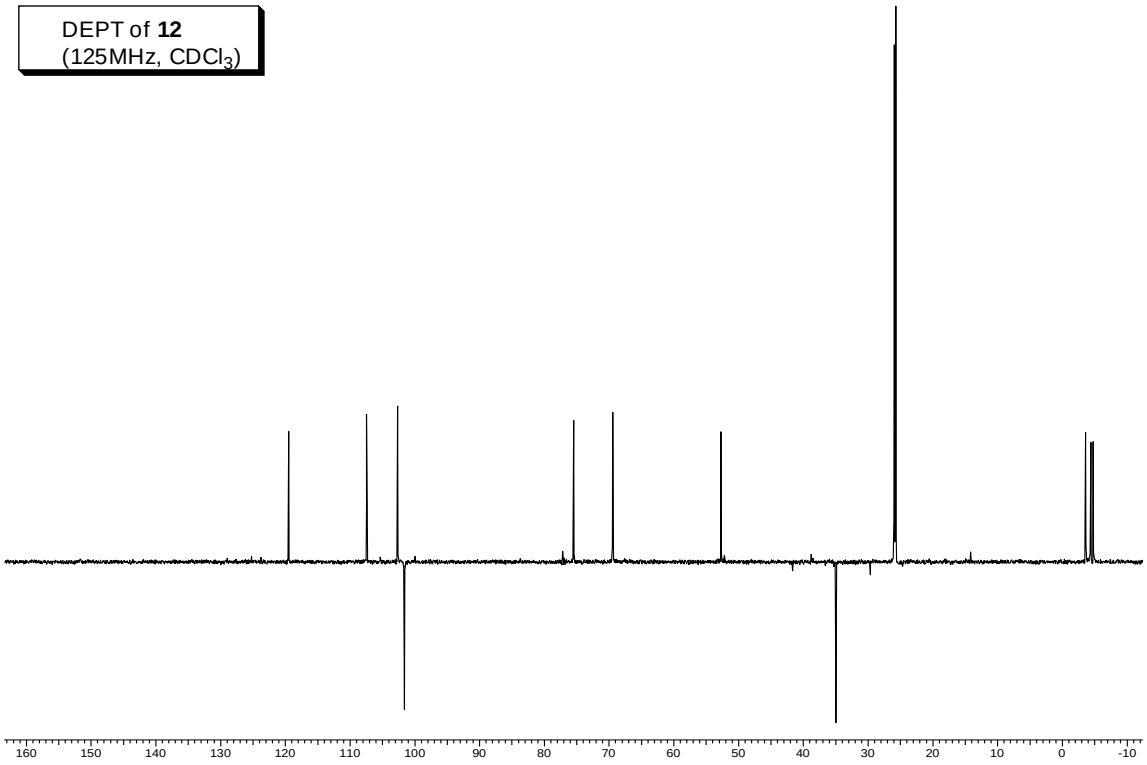

Chloroform-d
171.16
156.82
147.03
128.81
128.45
110.06
107.43
101.19
81.40
77.00
71.59
67.78
58.01
53.03
45.79
40.47
37.46
33.99
25.97
25.82
18.30
18.08
4.49
4.70
13C NMR of 21
(100MHz, CDCl3)
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

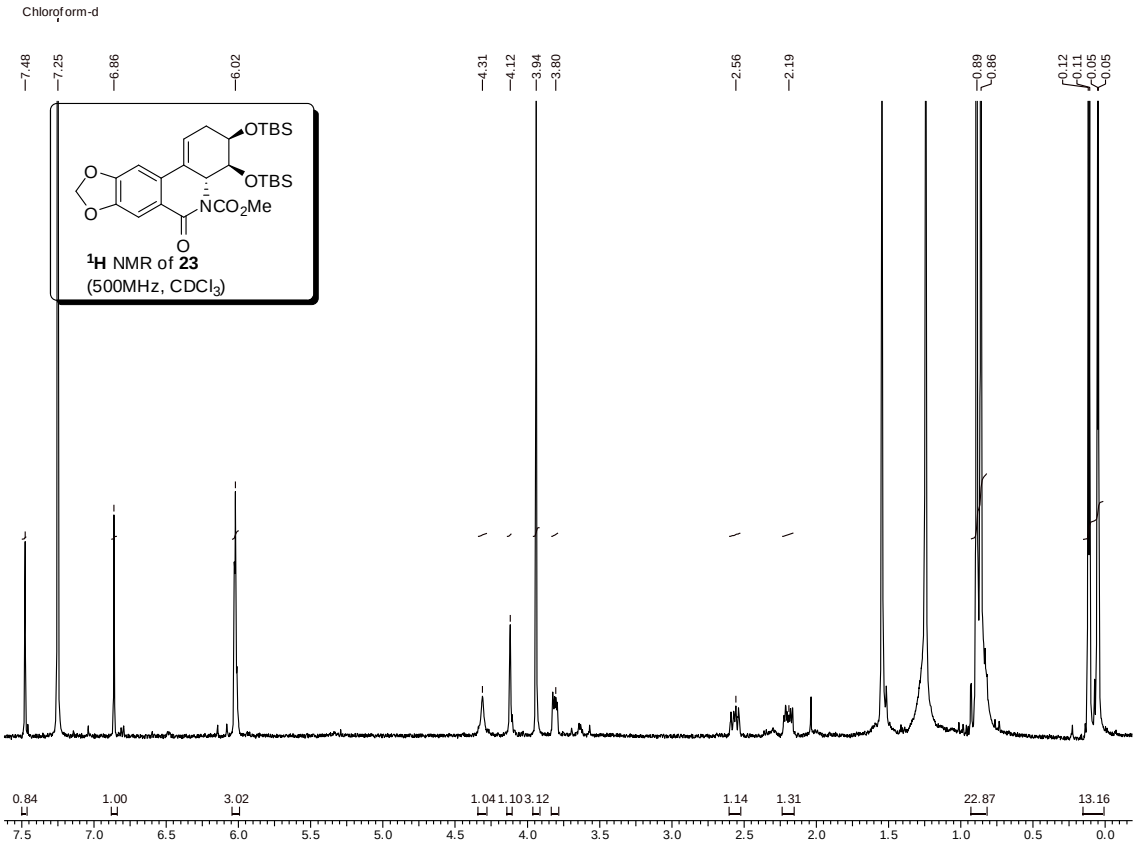

DEPT of 21
(100MHz, CDCl3)
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


Chloroform-d
7.55
7.25
6.92
6.00
5.91
5.76
4.52
4.06
3.74
2.59
2.34
0.97
0.83
0.18
0.14
0.08
0.06
OTBS
OTBS
O
O
NH
O
1H NMR of 12
(500MHz, CDCl3)
0.80
0.95
2.00
1.00
1.04
1.09
1.07
1.08
1.14
10.37
12.85
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

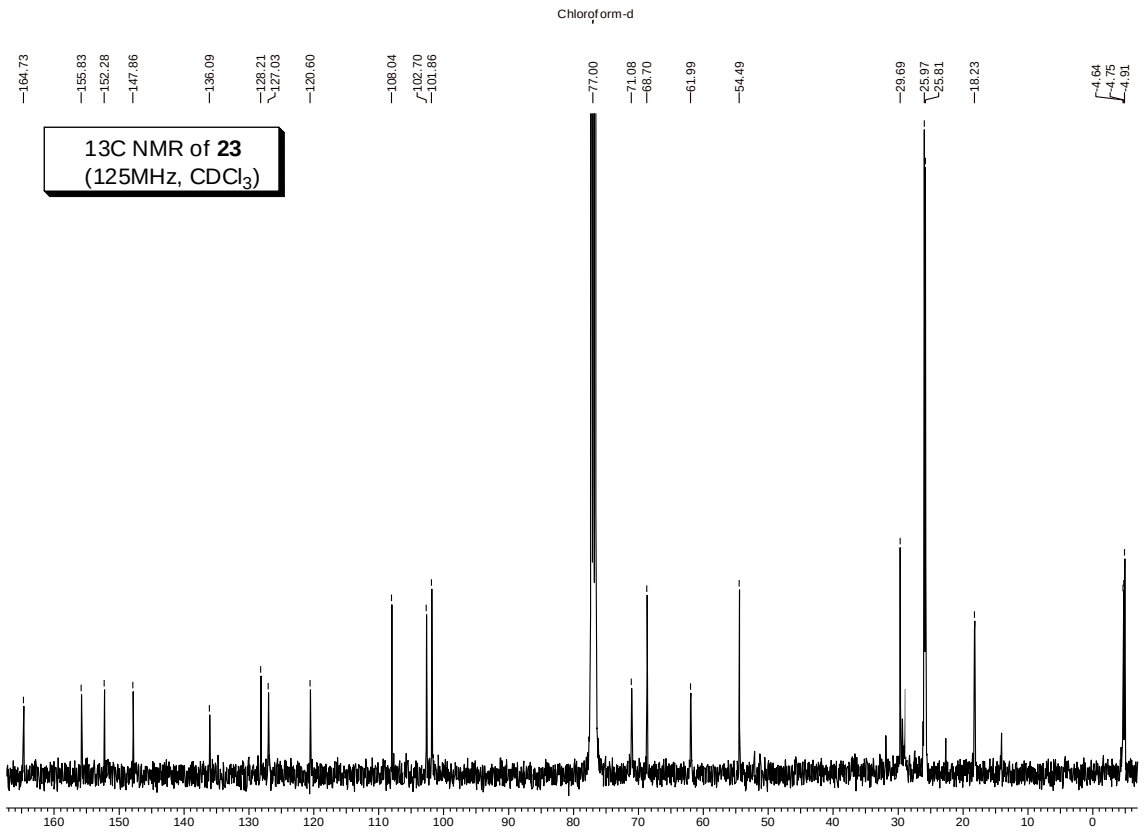

Chloroform-d
164.54
151.37
147.79
132.20
129.03
121.49
119.52
107.47
102.68
101.62
77.00
75.51
69.49
52.74
35.01
25.97
25.69
18.11
18.02
-3.61
-4.46
-4.79
13C NMR of 12
(125MHz, CDCl3)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

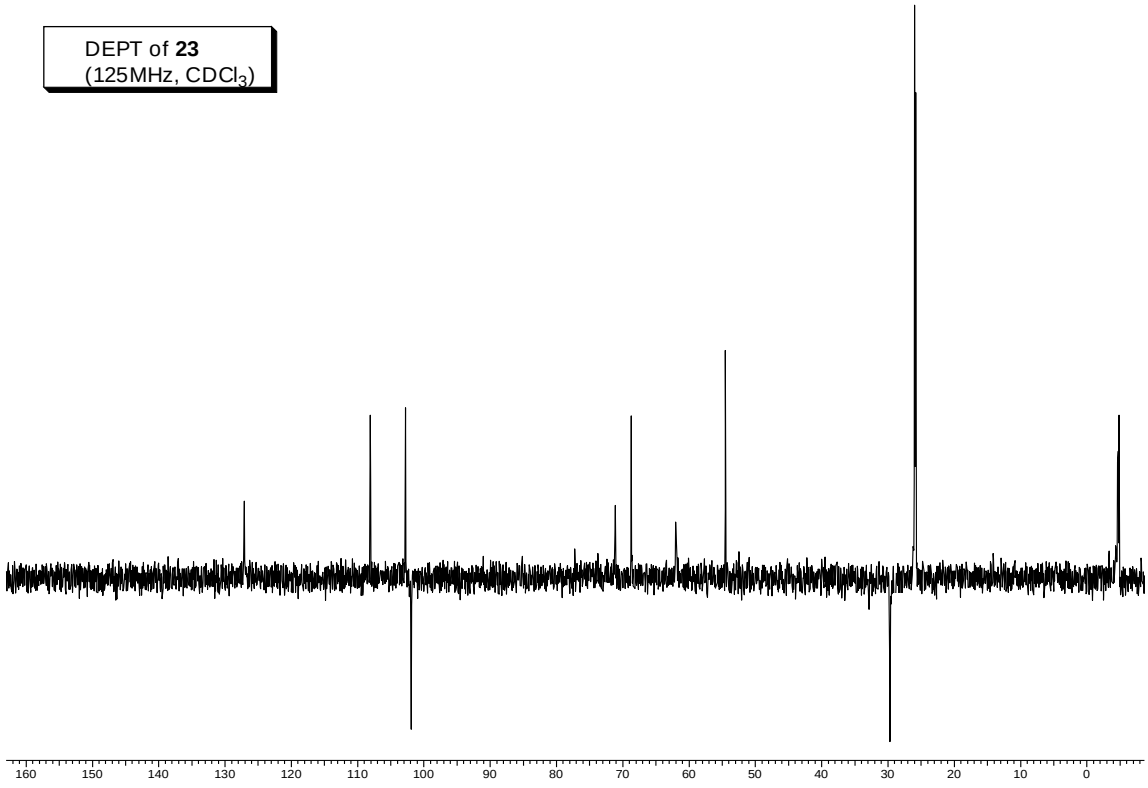
DEPT of **12**
(125MHz, $CDCl_3$)

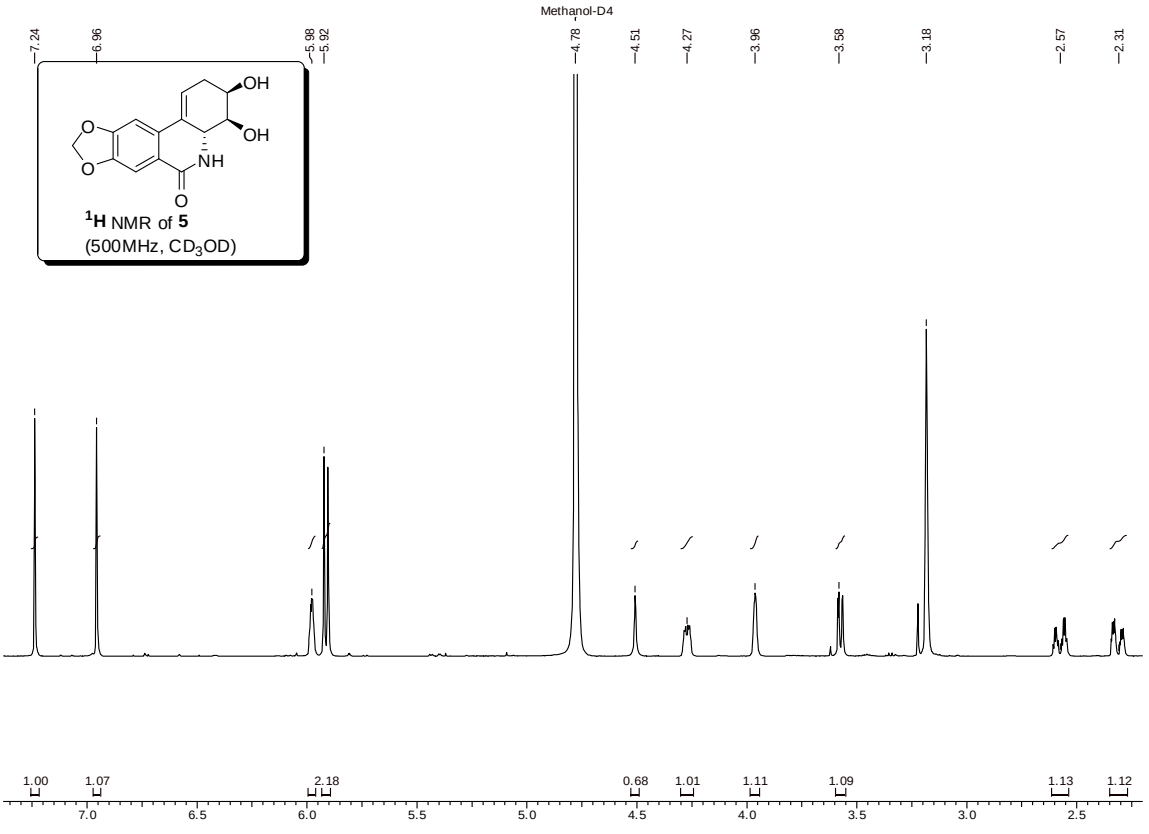


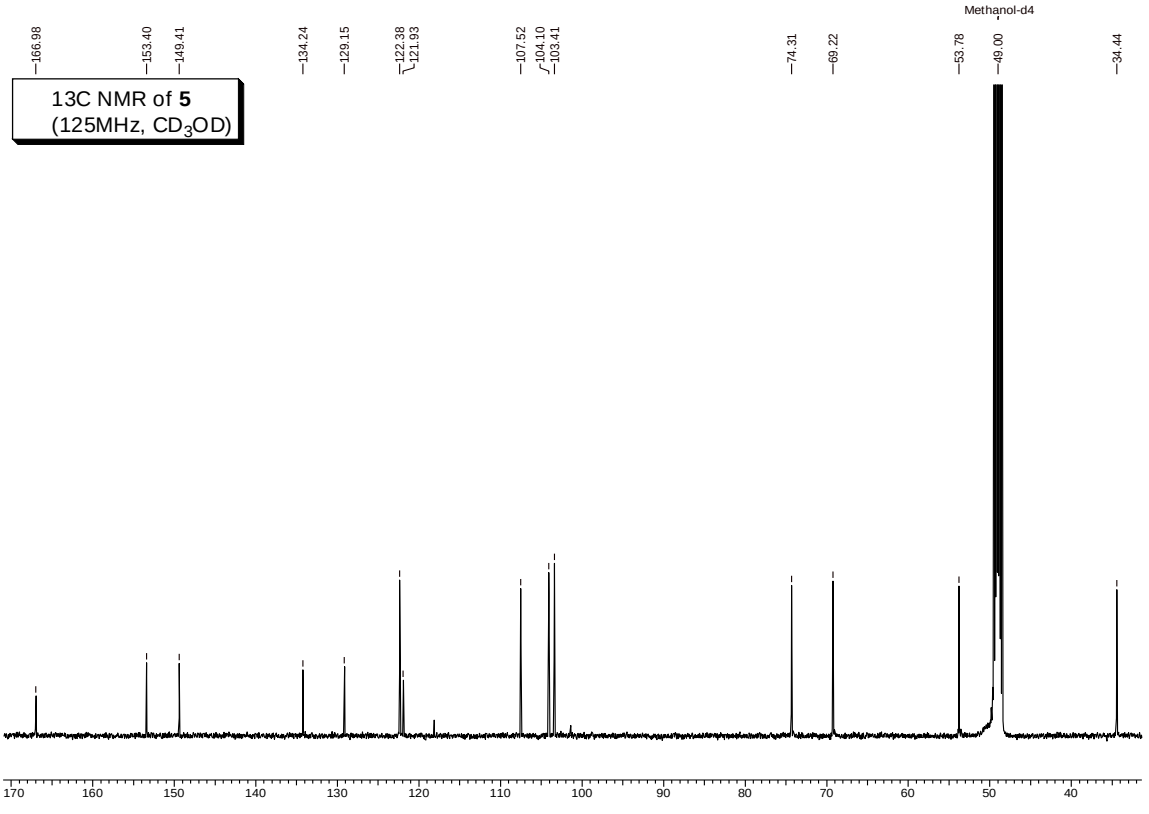


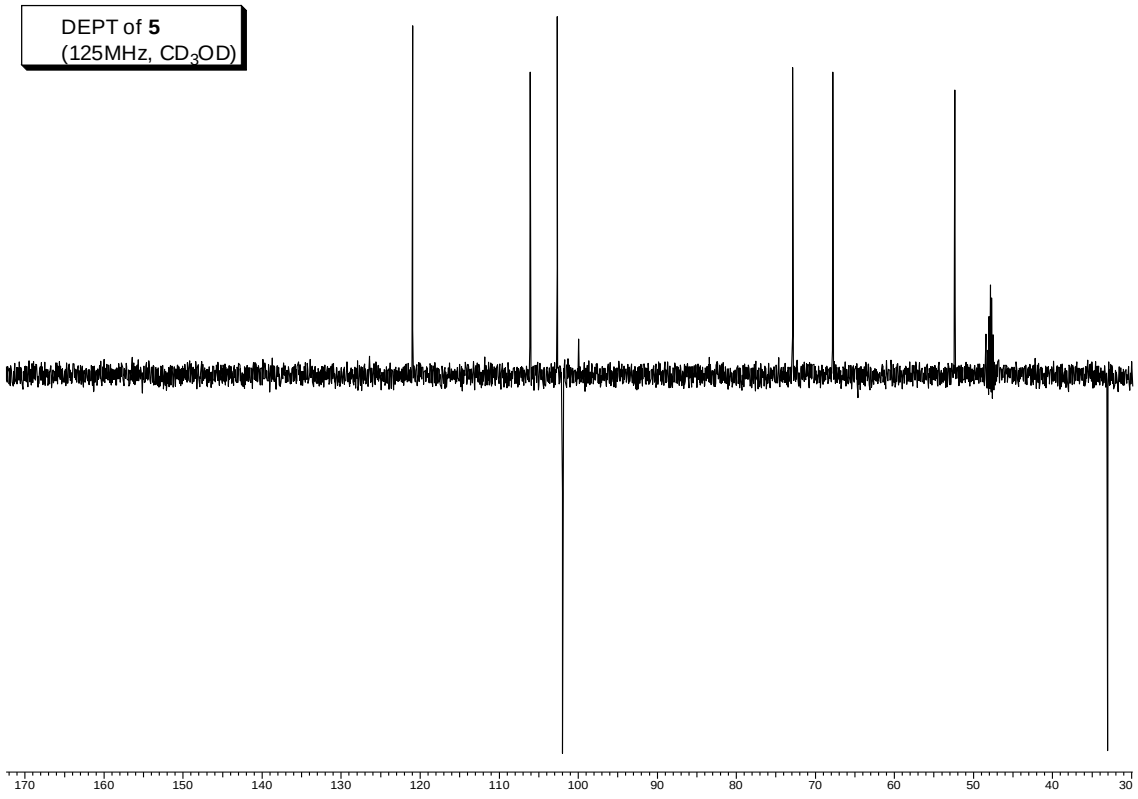
^{1}H NMR of **23**
(500MHz, $CDCl_3$)

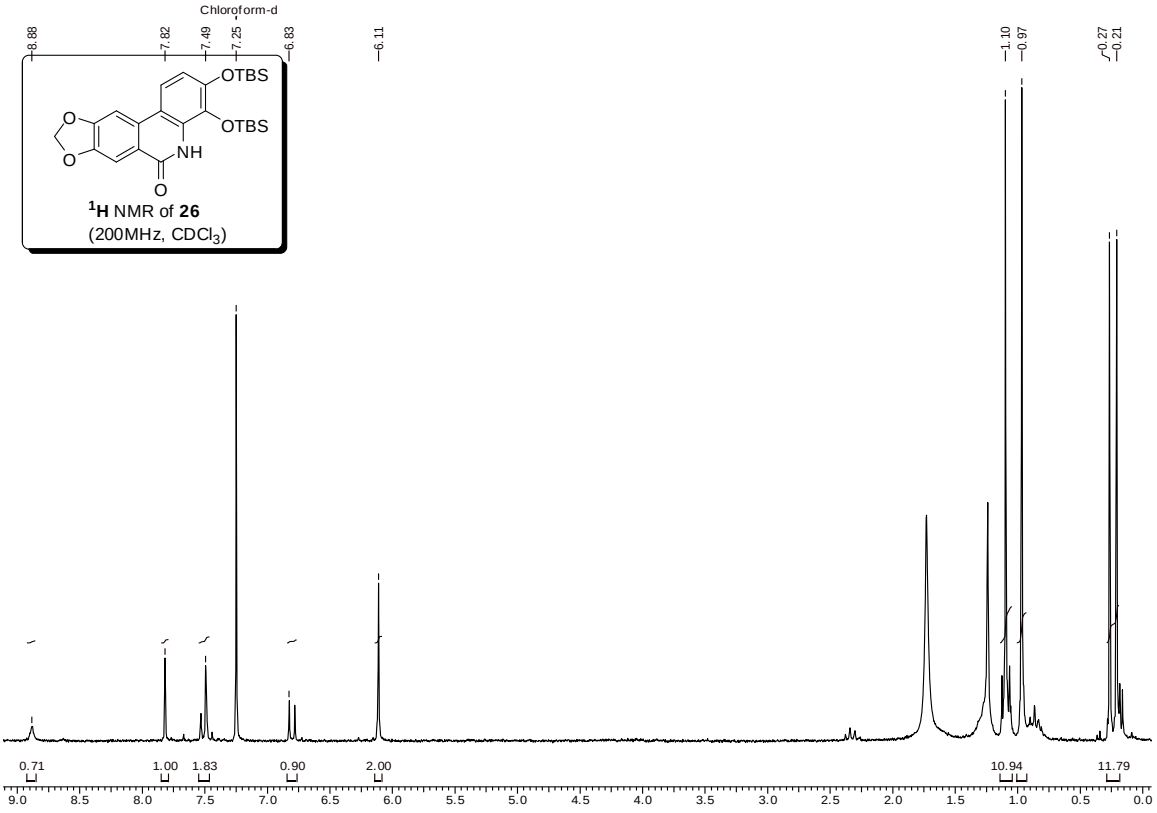

Chloroform-d
164.73
155.83
152.28
147.86
136.09
128.21
127.03
120.60
108.04
102.70
101.86
77.00
71.08
68.70
61.99
54.49
29.69
25.97
25.81
18.23
4.64
4.75
4.91
13C NMR of 23
(125MHz, CDCl3)
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

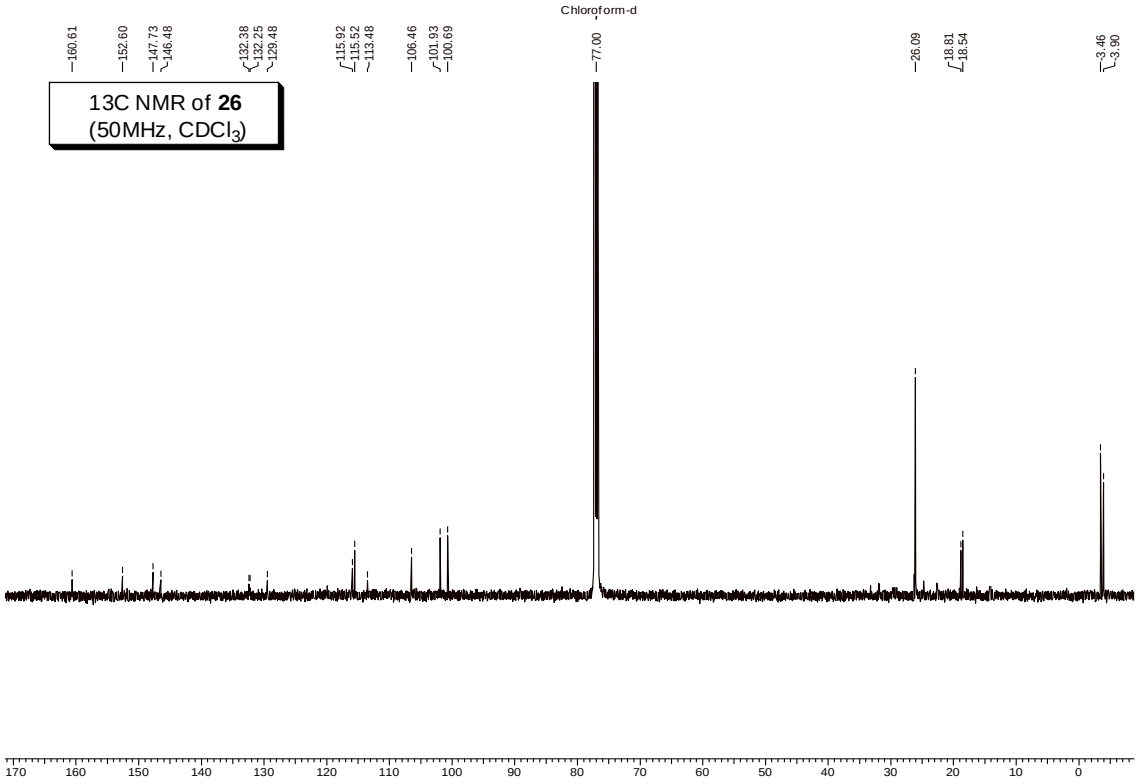

DEPT of 23
(125MHz, CDCl3)
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

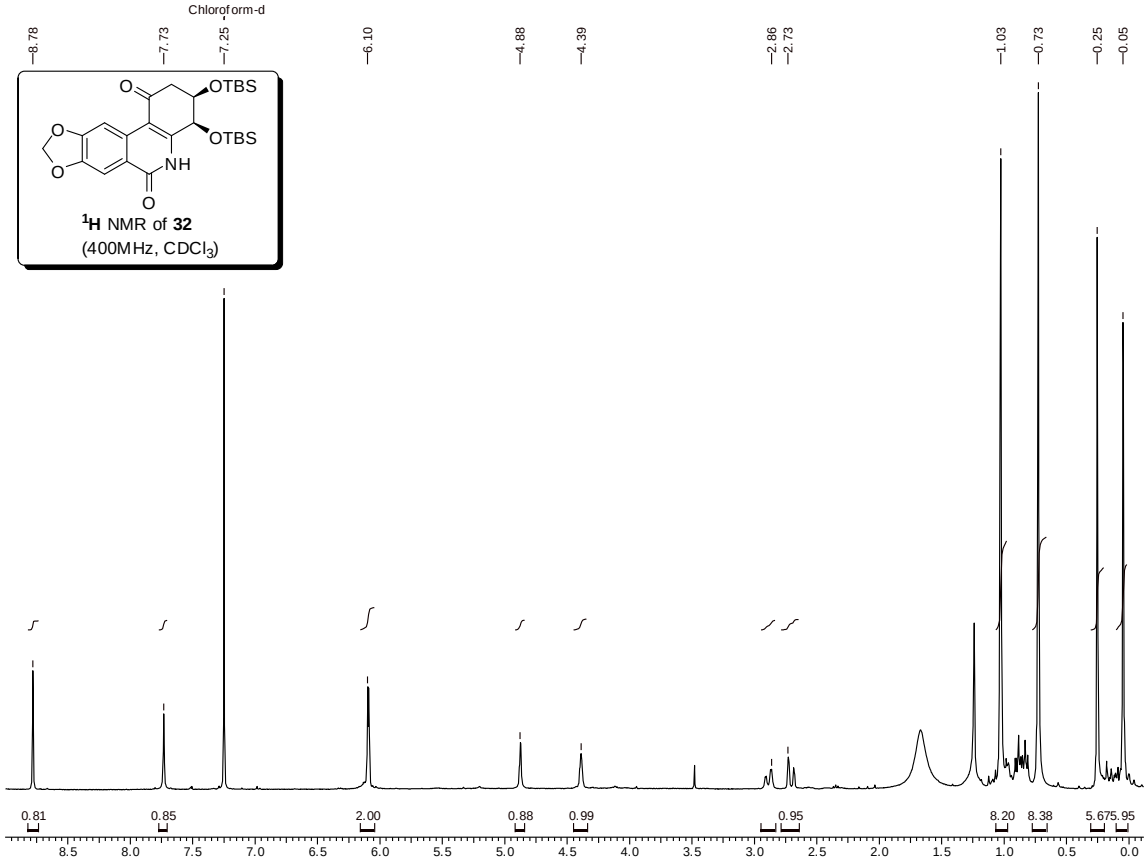

Methanol-D4
7.24
6.96
5.98
5.92
4.78
4.51
4.27
3.96
3.58
3.18
2.57
2.31
OH
OH
O
O
NH
O
1H NMR of 5
(500MHz, CD3OD)
1.00
1.07
2.18
0.68
1.01
1.11
1.09
1.13
1.12

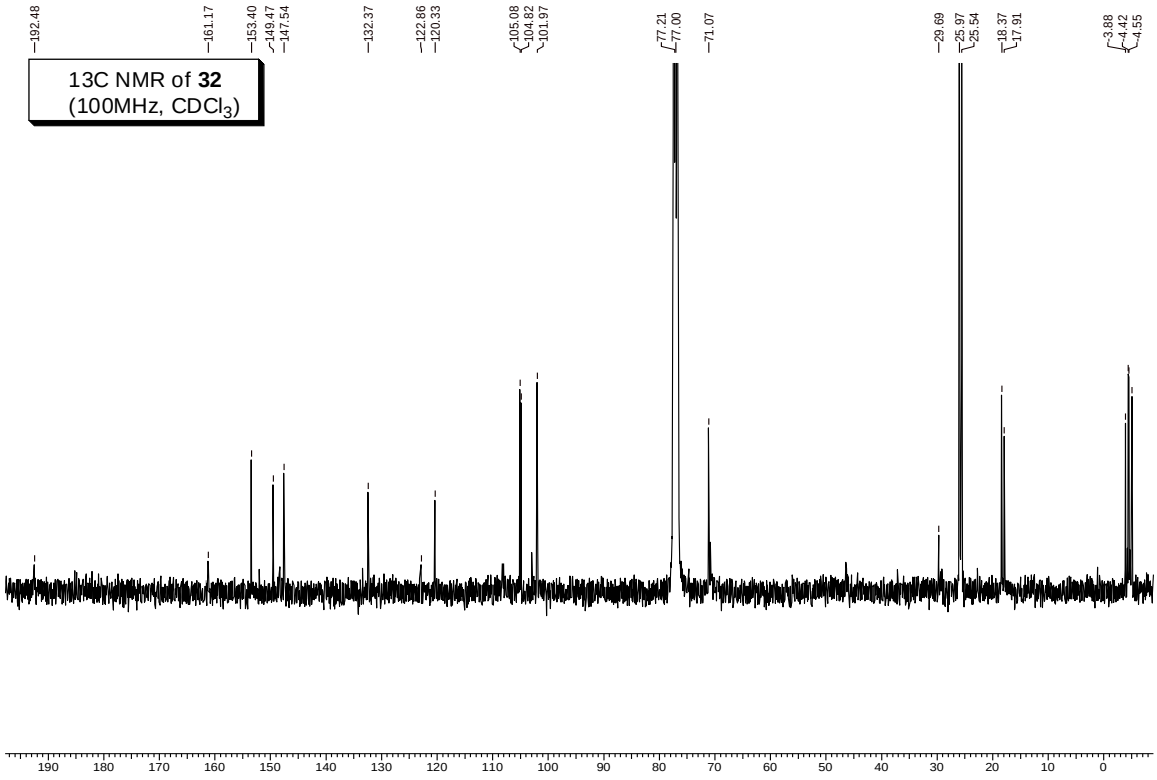

Methanol-d4
166.98
153.40
149.41
134.24
129.15
122.38
121.93
107.52
104.10
103.41
74.31
69.22
53.78
49.00
34.44
13C NMR of 5
(125MHz, CD3OD)

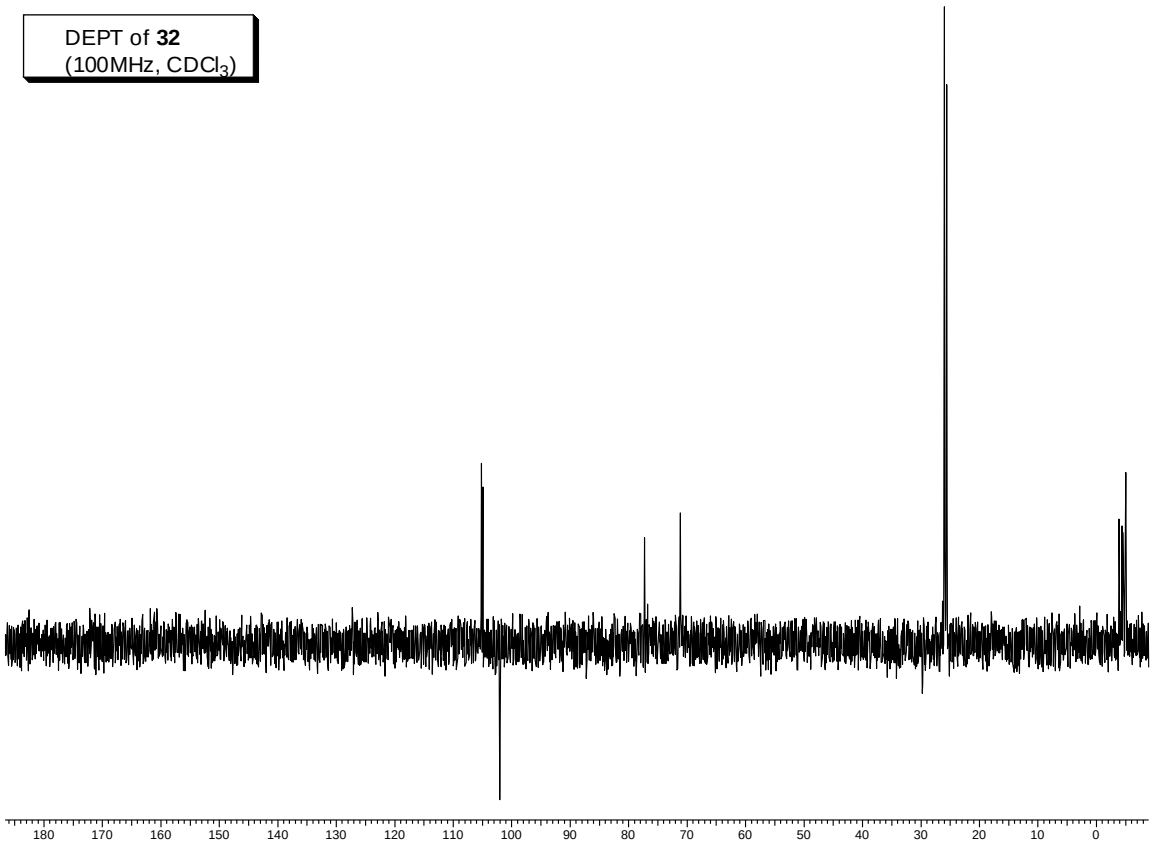

DEPT of **5**
(125MHz, CD_3OD)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30


Chloroform-d
8.88
7.82
7.49
7.25
6.83
6.11
1.10
0.97
0.27
0.21
OTBS
OTBS
O
O
NH
O
^{1}H NMR of **26**
(200MHz, $CDCl_3$)
0.71
1.00
1.83
0.90
2.00
10.94
11.79
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Chloroform-d
160.61
152.60
147.73
146.48
132.38
132.25
129.48
115.92
115.52
113.48
106.46
101.93
100.69
77.00
26.09
18.81
18.54
3.46
3.90
13C NMR of 26
(50MHz, CDCl3)


Chloroform-d
8.78
7.73
7.25
6.10
4.88
4.39
2.86
2.73
1.03
0.73
0.25
0.05
OTBS
OTBS
NH
O
1H NMR of 32
(400MHz, CDCl3)
0.81
0.85
2.00
0.88
0.99
0.95
8.20
8.38
5.67
5.95


192.48
161.17
153.40
149.47
147.54
132.37
122.86
120.33
105.08
104.82
101.97
77.21
77.00
71.07
29.69
25.97
25.54
18.37
17.91
3.88
-4.42
-4.55
13C NMR of 32
(100MHz, CDCl3)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


DEPT of 32
(100MHz, CDCl3)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

3A.8. X-ray crystal data for compound 5

Single crystals of the compound were grown by slow evaporation of the solution mixture in methanol. Colorless crystal of 0.349 x 0.144 x 0.014 mm, was used for data collection on bruker SMART APEX CCD diffractometer using Mo Kα radiation with fine focus tube with 50kV and 30mA.

Table-2 Crystal structure data and structure refinement values of **5**.

Empirical formula	$C1_4\ H_{15}\ N\ O_6$	
Formula weight	293.27	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12$	
Unit cell dimensions	a = 14.297(3) Å	α= 90°.
	b = 19.834(4) Å	β= 90°.
	c = 4.6223(9) Å	γ = 90°.
Volume	1310.7(4) $Å^3$	
Z	4	
Density (calculated)	1.486 g/cc	
Crystal size	0.349 x 0.144 x 0.014 mm^3	
Reflections collected	9635	
Independent reflections	2319 [R(int) = 0.0270]	
Completeness to theta = 24.99°	100.0 %	
Refinement method	Full-matrix least-squares on F^2	
Final R indices [I>2sigma(I)]	R1 = 0.0406, wR2 = 0.0996	

Section.B

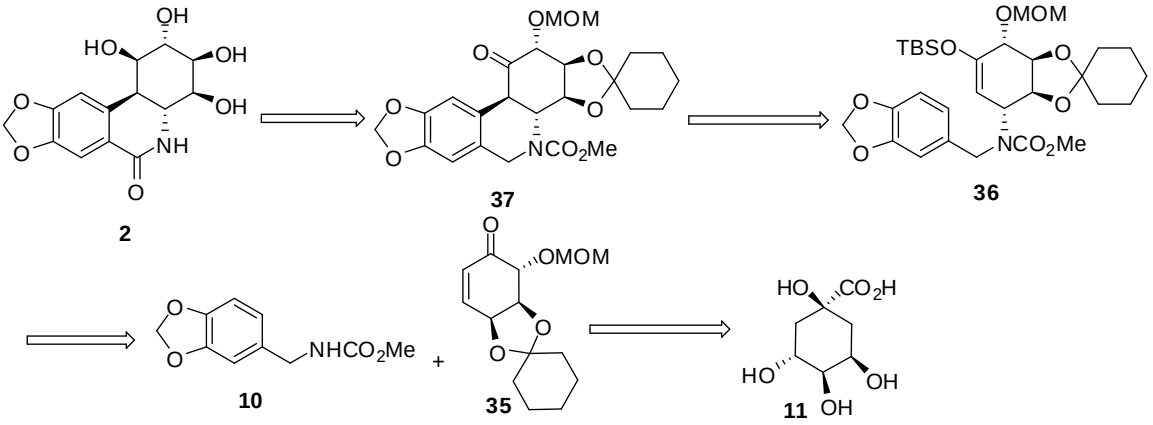
Synthetic studies towards (+)-7-deoxypancratistatin (2)

Owing to significant stereochemical complexity, we took the challenge of synthesizing **2** using PET mediated α-arylation of ketones as the key strategy. In this context, we designed two different parallel routes to synthesize this alkaloid as shown retrosynthetically in Schemes-13 and 14, respectively.

Retrosynthetic analysis and design

3B.1 Strategy-I

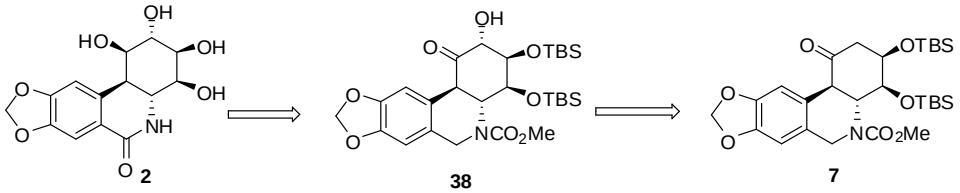
We envisaged a new synthetic strategy for **2** through the retro synthetic route as outlined in the Scheme-13. The key step in this approach was the PET initiated intramolecular carbocyclization of **36** to **37**. The requisite silylenolether precursor **36** for this crucial transformation was proposed to be synthesized by intermolecular aza-Michael addition of piperonyl amide **10** to enone **35** derived from D-(-)-quinic acid (**11**).



Scheme-13

3B.2. Strategy- II

This strategy is based on the successful synthesis of phenanthridone **7** (Scheme-1) as discussed previously and exploring the possibility of its transformation into **2** *via* **38** as shown in Scheme 14.



Scheme-14

3B.3. Results and Discussion

Synthesis of **2**, as perceived through the retrosynthetic strategy-I, started with the preparation of silylenol ether **36** followed by the crucial intramolecular carbocyclization reaction.

3B.3.1. Synthesis of enone 35

By comparing the stereochemistries of C_3 and C_4 of enone **35** and of quinic acid (**11**), we envisioned that few functional group manipulations on quinic acid (**11**) such as regioselective elimination of C_1, stereoselective C_2 oxygenation, conversion of C_1 into carbonyl functionality followed by elimination of C_5 hydroxyl group to enone should provide chiral enone **35** (Fig 6).

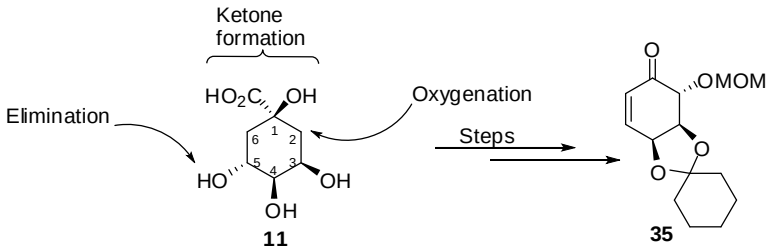
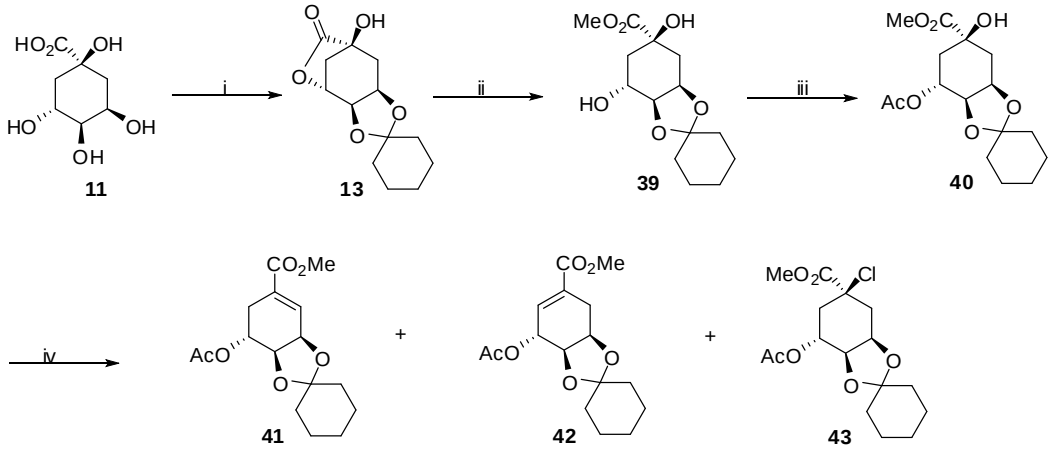


Figure: 6 Functionalization of Quinic acid (**11**).

In this context, initially we set out to eliminate C_1 hydroxyl group of **11** by following the procedure established by Grierson *et al.*[9] Towards this endeavor, the cyclohexylidine derivative **40** was synthesized in three-steps (77 % overall yield) as shown in Scheme 15. The elimination of **40** using $POCl_3$/Py to **41** practically proved to be low yielding while the report claimed the formation of a single product. The low yield is accounted due to the formation of unwanted regio isomer **42** and chlorinated derivative **43**. The usage of

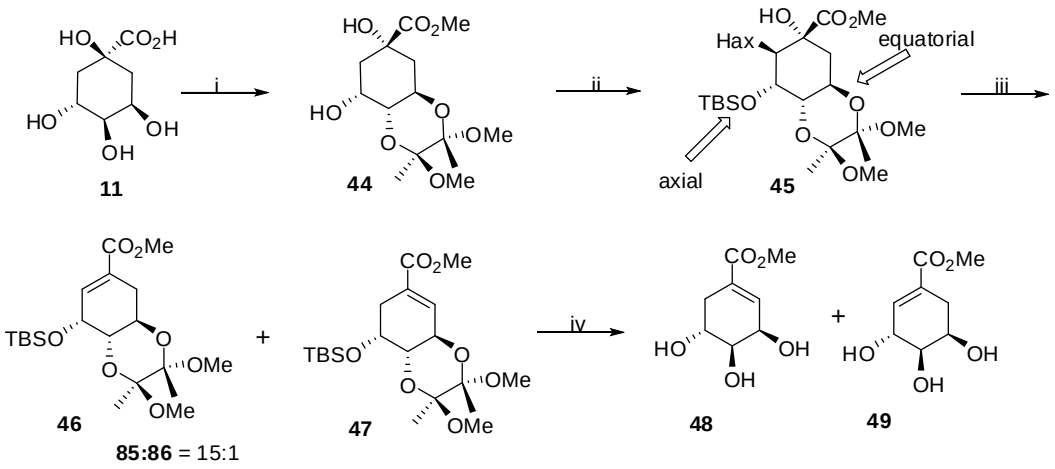
several other reagent combinations, including $SOCl_2$/Py, SO_2Cl_2/Py, NBS/SO_2/Py were not rewarding as the yields of the required regiomer **41** were never more than 40 %.



Scheme-15

Reagents and conditions: *i) cyclohexanone, p-TSA (cat), DMF, PhH, reflux, 4 h, 98 %; ii) NaOMe, dry MeOH, 6 h, 75 %; iii) AcCl, Py, 6 h, dry DCM, 95 %; iv)* $POCl_3$, Py, *DCM, 30 %.*

Therefore, our attention was drawn towards another sequence of reactions reported by Whitehead *et al.*[10] for the C_1 hydroxyl elimination from **11** which had claimed to be regioselective and high yielding (Scheme 16). Towards this end, the 4, 5-*trans*-diols of **11** were selectively protected as butane diacetal to afford **44** in 98 % yield. The *sec*-hydroxyl group of **44** was selectively protected as its *O*-silylether **45** which on treating with $POCl_3$/Py at 40 °C for 3 days afforded mixtures of **46** and **47** in the ratio of 15:1. The observed regioselectivity was attributed to the constrained *trans*-decalin like structure of **45** in which the butane diacetal protecting group enforced silyloxy group at C_3 to adopt axial orientation. This axially disposed silyloxy group enhanced the acidity of $C_2{-}H_{ax}$ and due to the antiperiplanar arrangements, preferential regioselective dehydration of the alcohol occurred. To avoid unforeseen complications during the advanced stage of the synthesis, the butane diacetal and silyl protections were removed by heating with 80 % aqueous acetic acid at 80 °C (Scheme-16).

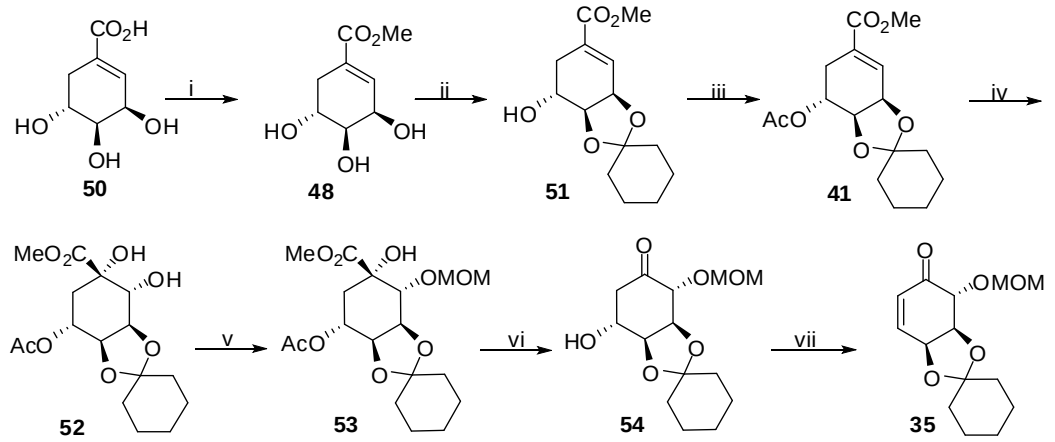


Scheme-16

Reagents and conditions: *i) 2,3-butanedione, $CH(OMe)_3$, CSA (cat), MeOH, reflux, 16 h, 98 %; ii) TBSCl, ImH ,DMF, 24 h, 95 %; iii) $POCl_3$, Py, 3 days, 40 ^oC, 83 %; iv) 80 % AcOH-H_2O, 24 h, 86 %.*

3B.3.2. Synthesis of 35 from Shikimic acid (50)

Since, in the above synthetic sequence, (Scheme-16) shikimate ester **48** was required as a precursor, we visualized its synthesis from shikimic acid (**50**) in the reduced number of steps (Scheme-17). The shikimic acid (**50**) was esterified to its corresponding methyl ester **48** by refluxing with methanol in the presence of catalytic amount of camphor sulphonic acid (CSA) followed by the protection of the *cis*-diol moiety of **48** as its cyclohexylidine ketal **51** in 90 % yield.



Scheme-17

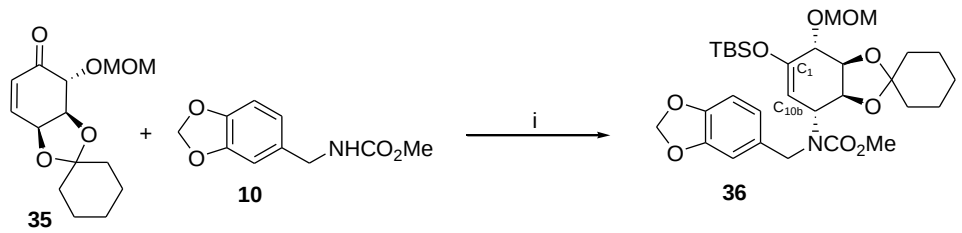
***Reagents and conditions**: i) MeOH, CSA, reflux, 18 h; ii) cyclohexanone, DMF, PhH, 8 h, 90 %; iii) AcCl, py, dry DCM, rt, 6 h, quant; iv) OsO_4, TMO, Py, H_2O, Bu^tOH, 8 h, reflux, 86 %; v) MOMCl, DIPEA, dry DCM, 6 h; vi) a) LAH, THF, 3 days, 50 ^oC, b) $NaIO_4$, p^H 7 buffer, 0.5 h, 60 %; vii) $POCl_3$, Py, 3 h, rt, 62 %.*

Acetylation of **51** followed by *cis*-dihydroxylation of **41** gave corresponding diol **52** in 86 % yield. The oxygen stereochemistry adjacent to olefin directed the osmiumtetraoxide to approach stereoselectively from the α-position, providing required stereochemistry at the C_2 carbon (pancratistatin numbering). The complete disappearance of vinylic proton and appearance of –C-H proton signals at δ 5.18 (m, 1H), δ 4.28 (m, 2H) and δ 3.94 (d, J = 7.4 Hz, 1H) in the ^{1}H NMR spectrum clearly indicated the formation of dihydroxylated product **52**. Selective mono protection of the secondary hydroxyl group using MOMCl / DIEPA in DCM at high dilution yielded **53** in 76 % yield. The appearance of a characteristic set of two doublets in the ^{1}H NMR at δ 4.93 (J = 6.9, 1H) and δ 4.59 (J = 6.9, 1H) indicated the presence of methylene dioxy protons of the MOM group in **53**.

Reduction of **53** with LAH \ THF produced corresponding diol which upon oxidative cleavage using $NaIO_4$ furnished **54** in 60 % yield. The IR spectrum of **54** showed strong absorptions at 3458 cm^{-1} and 1732 cm^{-1} indicating the presence of an alcohol and ketone functionality, respectively, in the product. The presence of ketone functionality in **54** was further confirmed by observing a peak at δ 204.3 in the ^{13}C NMR spectrum. Elimination of C_5 hydroxy group by reacting it with $POCl_3$ in the presence of pyridine gave **35** in 62 % yield. The appearance of a doublet of a doublet (J = 10.2, 3.7 Hz, 1H) at δ 6.78 and a doublet (J = 10.2 Hz, 1H) at δ 6.08 clearly indicated the presence of α, β unsaturated carbonyl functionality in the molecule. Further support for the presence of α, β-unsaturated ketone functionality was obtained by observing an absorption band at 1705 cm^{-1} in its IR spectrum.

With stereodefined enone **35** in hand, we focused our attention to the introduction of the arene unit at its C_3 position by carrying out an aza-Michael addition reaction using *N*-lithiated piperonyl carbamate followed by trapping of the corresponding lithium enolate as its -OTBS ether to obtain **36** in 95 % yield. The stereochemistry at C_4 of **35** directed

the *anti* approach of the incoming nucleophile resulting required stereochemistry (Scheme-18)



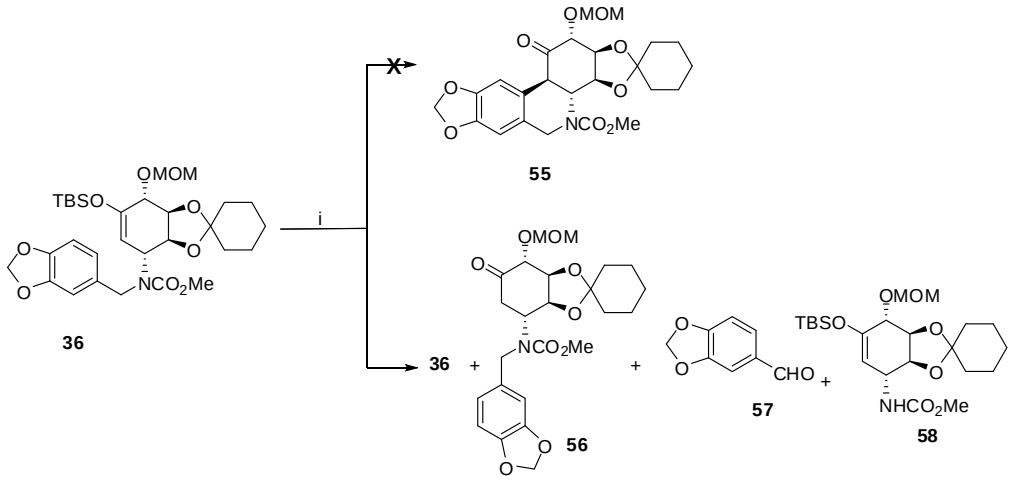
Scheme-18

Reagents and conditions*: i) n-BuLi, THF, HMPA, -78 °C, TBSCl, 88 %.*

The appearance of characteristic peaks related to enol silyl ether in ^{1}H and ^{13}C NMR indicated the presence of trapped conjugate adduct **36**. The ^{13}C NMR showed a quaternary and a methine peak at δ 132.6 and δ 103.8 corresponding to C_1 and C_{10b} of enol silyl ether, respectively, along with the peaks corresponding to -OTBS group in the upfield region**.**

3B.3.3. PET initiated carbocyclization of precursor 36

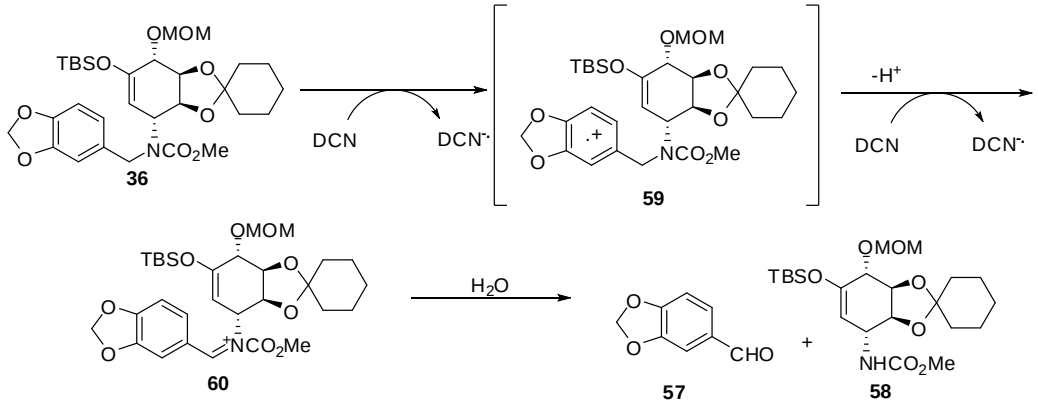
The planned intramolecular carbocyclization by irradiating (Pyrex filter, >280 nm, 450 W Hanovia medium pressure lamp) a mixture of **36**, (0.6 g, 1.01 mmol) and 1, 4-dicyanonaphthalene (0.054 g, 0.30 mmol) in 250 mL CH_3CN: H_2O (24:1) solution for 6 h failed to yield the expected **55**. Only un-reacted **36** along with a minor amount of benzyl cleaved products **57** and **58** could be isolated at the end of the reaction (Scheme-19).



Scheme-19

Reagents and conditions*: i) hν, DCN, CH_3CN, H_2O, 6 h.*

The possible explanation to this failure could be advanced by considering the high conformational rigidity developed by the C_3-C_4 cyclohexylidine ketal and functionalization on C_2 (-OMOM) which restricted the flexibility of C ring preventing the nucleophilic attack of silyl enol ether to arene radical cation. The plausible route for the formation of **57** and **58** involving iminium cation **60** formed by sequential proton-electron loss from **59** is shown in Scheme-20.

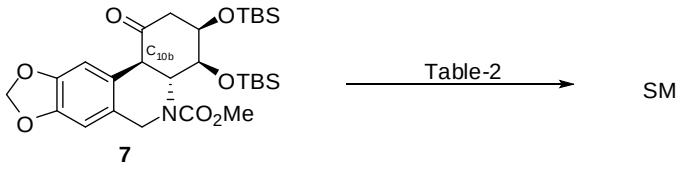


Scheme-20: Plausible Mechanism of formation of **57** and **58**.

Further attempt of cyclization is in progress by replacing the cyclohexylidine protecting group with –OTBS ether in order to remove conformational strain.

3B.4. Investigation of Strategy-II

As perceived through the retrosynthetic strategy II (Scheme-14), synthesis of **38** was attempted by the electrophilic oxidation of kinetic enolate, generated by treating **7** with LDA at -78 ^{o}C in dry THF as well as in diethyl ether followed by quenching with Davies oxaziridine[11] or DMDO[12], however, to our bad luck no reaction took place. Alternatively, an attempt was also made to oxidize the silyl enol ether with *m*-CPBA or OsO_4[13] but this also failed to give any product. Results of various attempts with different bases and oxidizing agents are summarized in the Table-2. With these observations, it was realized that possibly the steric bulk created by the TBS group at C_3 position may be preventing the approach of the oxidizing agent to the enolate moiety.



7

Scheme-21

Table-2: Method of comparison for oxidation of **7**

Base	Reagent	Base (mol%/equiv)	Solvent	Time (hrs)	Temp (^oC)	% SM recovered
LiHMDS	mCPBA	1.5	THF	24	-78	90
LiHMDS	Davies Oxaziridine.	1.5	THF	24	-78	95
LiHMDS	DMDO	1.5	THF	1	-78	95
LDA	TMSCl, mCPBA.	1.5	THF	6	-78	95
LDA	TMSCl, OsO_4.	1.5	THF	6	-78	95

SM= Starting material

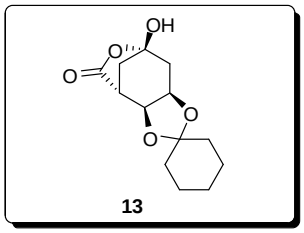
3B.5. Summary

1) The present routes indicate few shortcomings in structural confirmations in current substrates **7** and **36** that if resolved, may provide efficient synthesis of (+)-7-deoxypancratistatin (**2**).

2) The overall synthetic construct was a valuable matrix of experiments, which culminated in the attempts towards the total synthesis of **2**.

3B.6. Experimental section

1. Preparation of 3, 4-*O*-cyclohexylidene quinic acid 1, 5-lactone (13):

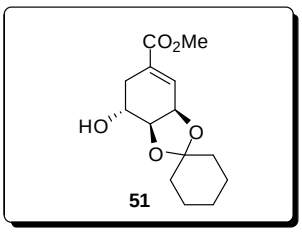


13

A suspension of D-(-)-quinic acid (**11**) (1 g, 5.2 mmol), *p*-toluenesulfonic acid (10 mg, 0.052 mmol), cylcohexanone (1 mL), and *N*,*N*-dimethylformamide (2 mL) in benzene (15 mL) were stirred under reflux for 4 h by using Dean-Stark trap until no more water was separated. After the solution had cooled down to room temperature, it was diluted with ethyl acetate (30 mL) and washed with saturated $NaHCO_3$ (1x5 mL), water (2x10 mL), brine (1x5 mL). After drying over anhydrous Na_2SO_4, the organic extracts were concentrated under reduced pressure. The solid obtained was recrystallized from pet ether: ethyl acetate (9:1) to give colorless crystals (1.25 g, 95 % yield) of **13**.

mp	:	140-142 ^{o}C
$[\alpha]^{27}_{D}$	:	-33.5^{o} (c 2.0, MeOH)
IR ν_{max} cm^{-1} (nujol)	:	3429, 1767
^{1}H NMR (CDCl$_3$, 200 MHz) δ	:	4.74 (dd, *J* = 6.0, 2.5 Hz, 1H), 4.46 (ddd, *J* = 13.7, 6.9, 3.1 Hz, 1H), 4.29 (ddd, *J* = 6.4, 2.4, 1.2 Hz, 1H), 2.65 (d, *J* = 11.7 Hz, 1H), 2.33 (m, 2H), 2.17 (dd, *J* = 14.6, 3.0 Hz, 1H), 1.68-1.38 (m, 10H).
^{13}C NMR (CDCl$_3$, 50 MHz) δ	:	178.6, 110.2, 75.6, 71.3, 71.2, 70.7, 37.9, 36.5, 34.0, 33.3, 24.6, 23.5, 23.1.
Mass: m/z (%)	:	277 (M+Na$^+$, 100), 272 (M+NH$_4^+$, 35), 255 (M+H$^+$, 10).

2. Preparation of (3a*S*, 4*R*, 7a*R*)-methyl 4-hydroxy -3a, 4, 5, 7a-tetrahydrospiro [benzo [*d*] [1, 3] dioxole-2, 1^1 -cyclohexane]-6-carboxylate (51):



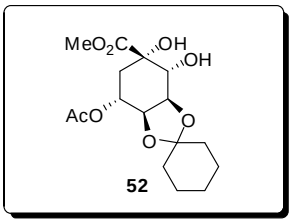
51

A mixture of shikimic acid (**50**) (1 g, 5.74 mmol) and camphor sulfonic acid (0.13 g , 0.57 mmol) was allowed to dissolve in dry methanol (20 mL) and refluxed for 18 h. After the completion of reaction, the reaction mixture was cooled to room temperature and the

methanol was distilled off under reduced pressure. The crude reaction mixture was mixed with cyclohexanone (1.1 mL), DMF (2 mL) in benzene (15 mL) and stirred under reflux for 8 h by using Dean-Stark trap until no water was separated. After the solution had cooled to room temperature, it was diluted with ethyl acetate (30 mL) and washed with saturated $NaHCO_3$ (1x5 mL), water (2x10 mL), brine (1x5 mL) dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture obtained was subjected to column chromatography by using pet ether: ethyl acetate (6:4) to give colorless gummy mass (1.27 g, 90 % yield) of **51**.

$[\alpha]^{27}_D$	:	- 68.3° (*c* 3 .0, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3470, 3019, 1716
^{1}H NMR ($CDCl_3$, 200 MHz) *δ*	:	δ 6.93 (m, 1H), 4.72 (m, 1H), 4.06 (m, 1H), 3.87 (m, 1H), 3.76 (s, 3H), 2.79 (dd, *J* = 17.4, 4.6 Hz, 1H), 2.21 (m, 2H), 1.70-1.24 (m, 10H).
^{13}C NMR ($CDCl_3$, 50 MHz) *δ*	:	δ 166.6, 134.1, 130.4, 110.3, 77.4, 71.7, 68.8, 52.1, 37.7, 35.0, 29.2, 24.9, 23.9, 23.6.
Mass: m/z (%)	:	291 ($M+Na^+$, 100), 269 ($M+H^+$, 5).

3. Preparation of (1*R*, 2*R*, 3*R*, 4*R*, 5*R*)-Methyl 1, 2 -dihydroxy-5-O-Acetyl-(3, 4-O-cyclohexylidene) cyclohexene carboxylate (52).



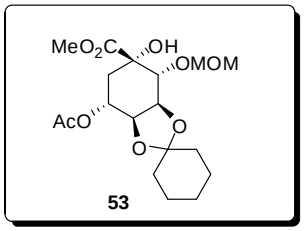
52

To a mixture of **41** (1 g, 3.22 mmol), trimethyl amine *N*-oxide dihydrate (0.5 g, 4.5 mmol), pyridine (0.51 mL) and water (0.28 mL) in *t*-BuOH (15 mL) was added a small crystal of OsO_4 at room temperature and allowed to stir for few minutes. The resulting mixture was heated to 80 °C for 8 h. The reaction mixture was cooled and quenched with solid Na_2SO_3 (0.2 g) and allowed to stir for 30 min. After solvent was removed by rotary-evaporation, the residue was dissolved in ethyl acetate (30 mL) and partitioned with minimum amount of water (30 mL). The aqueous layer was extracted with ethyl acetate (2x30 mL) and combined organic layers were washed with water (2x10 mL), brine (1x5

mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture obtained was purified by silica gel column chromatography with pet ether: ethyl acetate (1:1) as eluant gave **52** (1.1 g, 86 %) as a white colorless crystals.

mp	:	121 ^{o}C
$[\alpha]^{24}_{D}$	:	-6.9^{o} (*c* 2.1, MeOH)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3492, 1738
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	5.18 (m, 1H), 4.28 (m, 2H), 3.94 (d, *J* = 7.4 Hz, 1H), 3.82 (s, 3H), 2.47 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.08 (s, 3H), 1.84 (dd, *J* =15.0, 7.0 Hz, 1H), 1.72-1.28 (m, 10H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	174.9, 170.8, 110.7, 78.2, 77.6, 76.3, 74.1, 77.0, 69.9, 53.7, 37.9, 35.5, 35.1, 25.4, 24.3, 24.0, 21.6.
Mass: m/z (%)	:	367 (M+Na^{+}, 100), 301 (14), 247 (10), 345 (M+H^{+}, 1).

4. Preparation of (3a*S*, 4*R*, 5*S*, 7*R*, 7a*S*)-methyl 7 -acetoxy-5-hydroxy-4-(methoxymethoxy) Hexahydrospiro [benzo [d] [1, 3] dioxole-2, 1'-cyclohexane] -5-carboxylate (53):



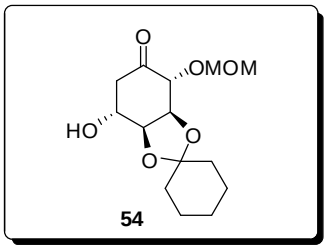
53

To a mixture of **52** (1 g, 2.90 mmol) and DIPEA (0.58 mL, 3.33 mmol) in dry DCM (12 mL) was added freshly distilled MOMCl (0.44 mL, 5.81 mmol) dropwise at room temperature. The reaction was stirred for further 6 h before the addition of water (10 mL). The aqueous layer was extracted with DCM (2x15 mL) and combined organic extracts were dried (Na_2SO_4). Removal of the solvent by rotary evaporation gave yellow oil which was purified by silica gel column chromatography using pet ether: ethyl acetate (2:8) to obtain **53** (0.86 g, 76 %) as pale yellow paste.

$[\alpha]^{25}_{D}$	:	-34.5^{o} (c 2, MeOH)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3544, 3020,1741
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	5.08 (m, 1H), 4.93 (d, *J* = 6.9 Hz, 1H), 4.59 (d, *J* = 6.9 Hz, 1H), 4.35 (m, 2H), 4.02, (m, 1H), 3.79 (s, 3H), 3.36 (s, 1H), 3.29 (s, 3H), 2.58 (dd, *J* = 14.9, 6.5 Hz, 1H), 2.06 (s, 3H), 1.75 (dd, *J* = 14.9, 7.3 Hz, 1H), 1.65 -1.27 (m, 10H).

^{13}C NMR	:	174.0, 170.2, 110.1, 95.9, 77.7, 76.9, 76.3, 75.9, 69.3, 55.9, 52.9,
($CDCl_3$, 50 MHz) δ		37.4, 35.5, 34.7, 24.9, 23.9, 23.6, 21.0.
Mass: m/z (%)	:	411 ($M+Na^+$, 100), 427 ($M+K^+$, 43), 406 ($M+H_2O$, 14).

5. Preparation of (2*R*, 3*R*, 4*S*, 5*R*)-methyl 4-hydroxy-2-9 methoxymethoxy)-(3,4-O-cyclohexylidene) cyclohexanone (54):



54

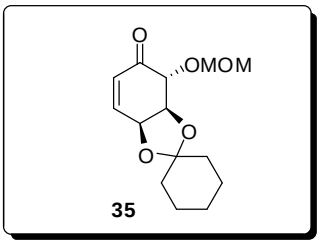
To a suspension of LAH (0.29 g, 7.73 mmol) in dry THF (5 mL) at 0 ^oC was added solution of **53** (1 g, 2.57 mmol) in dry THF (5 mL) drop wise. The reaction mixture was warmed to room temperature and stirred by maintaining the temperature at 50 ^oC in an oil bath for three days. The suspension was cooled to room temperature and poured cautiously by washing the flask with ethyl acetate into moistened Na_2SO_4 (approx 5 g). It was mixed thoroughly and kept aside for 0.5 h. The milky white suspension was filtered on a Buckner funnel and the inorganic material was washed with ethyl acetate (30 mL). The filtrate was dried (Na_2SO_4), concentrated under reduced pressure, gave crude triol (0.61 g) which was carried forward to the next step without any further purification.

The crude triol (0.61 g, 1.91 mmol) obtained above was dissolved in phosphate buffer (p^H 7, 8 mL) and cooled to 0 ^oC. Solid $NaIO_4$ (0.61 g, 2.87 mmol) was added in portions over a period of 10 min by maintaining the temperature 0-5 ^oC. The reaction mixture was stirred at the same temperature for additional 20 min and extracted with ethyl acetate (3x5 mL), dried (Na_2SO_4), filtered and concentrated under rotary evaporation. The residue was subjected to silica gel column chromatography using pet ether: ethyl acetate (6:4) as eluant which gave **54** (0.43 g, 60 % for two steps) as a colorless crystalline solid.

mp	:	94.8 ^oC
$[\alpha]^{29}_D$	:	+35.9^o (*c* 2, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3458, 2938, 1732
^{1}H NMR	:	4.76, (s, 2H), 4.44-4.24 (m, 4H), 3.41 (s, 3H), 2.83 (dd, *J* = 17.8,
($CDCl_3$, 200 MHz) δ		4.4 Hz, 2H), 2.45 (dd, *J* = 17.8, 7.5 Hz, 1H), 1.71-1.24 (m, 10H).

^{13}C NMR	:	204.3, 110.9, 95.7, 78.9, 77.4, 76.9, 67.9, 55.9, 42.0, 37.0, 34.1,
($CDCl_3$, 50 MHz) δ		24.9, 23.9, 23.5.
Mass: m/z (%)	:	309 ($M + Na^+$, 100), 325 ($M + K^+$, 5).

6. Preparation of (2*R*, 3*S*, 3*R*)-2 (methoxymethoxy)-(3, 4-O-cyclohexylidene) cyclohex-2-eneone (35):

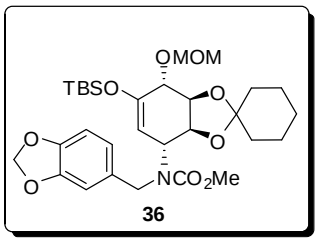


35

To a solution of **54** (1 g, 3.49 mmol) in dry pyridine (10 mL) was added freshly distilled phosphoryl chloride (0.42 mL, 4.54 mmol) by slow addition. The mixture was stirred at room temperature for 3 h. After the completion of the reaction, it was diluted with cold water (10 mL) and extracted with ethyl acetate (3x10 mL) and the combined organic extracts were washed with water (3x50 mL), brine (1x50 mL), dried (Na_2SO_4). Evaporation of the solvent under vacuum produced a pale yellow liquid which was purified by silica gel column chromatography using pet ether-ethyl acetate (8:2) as eluant to obtain **35** (0.58 g, 62 %) as a colorless gummy mass.

$[\alpha]^{27}_D$	:	$+145.6^o$ (*c* 3.5, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2940, 1705
^{1}H NMR	:	δ 6.78 (dd, *J* = 10.2, 3.7 Hz, 1H), 6.08 (d, *J* = 10.2 Hz, 1H), 4.81 (d,
($CDCl_3$, 200 MHz) δ		*J* = 6.7 Hz, 1H), 4.78 (m, 1H), 4.75 (d, *J* = 6.6 Hz, 1H), 4.49-4.35 (dd, *J* = 20.9, 6.9 Hz, 1H), 4.43 (d, *J* = 6.5 Hz, 1H), 3.41 (s, 3H), 1.66- 1.23 (m, 10 H).
^{13}C NMR	:	195.6, 142.0, 129.3, 112.0, 96.1, 77.0, 76.6, 70.9, 55.8, 37.6, 35.6,
($CDCl_3$, 50 MHz) δ		24.8, 23.9, 23.6.
Mass: m/z (%)	:	291 ($M + Na^+$, 100), 321 ($M + K^+$, 40).

7. Preparation of methylbenzo[d] [1, 3] dioxol-5-ylmethyl ((3a*S*, 4*R*, 7*R*, 7a*S*)-5-(*tert*-butyldimethyl silyloxy)-4-(methoxymethoxy)-3a, 4, 7, 7a-tetrahydrospiro [benzo [d] [1, 3] dioxole-2, 1'-cyclohexane]-7-yl) carbamate (36).

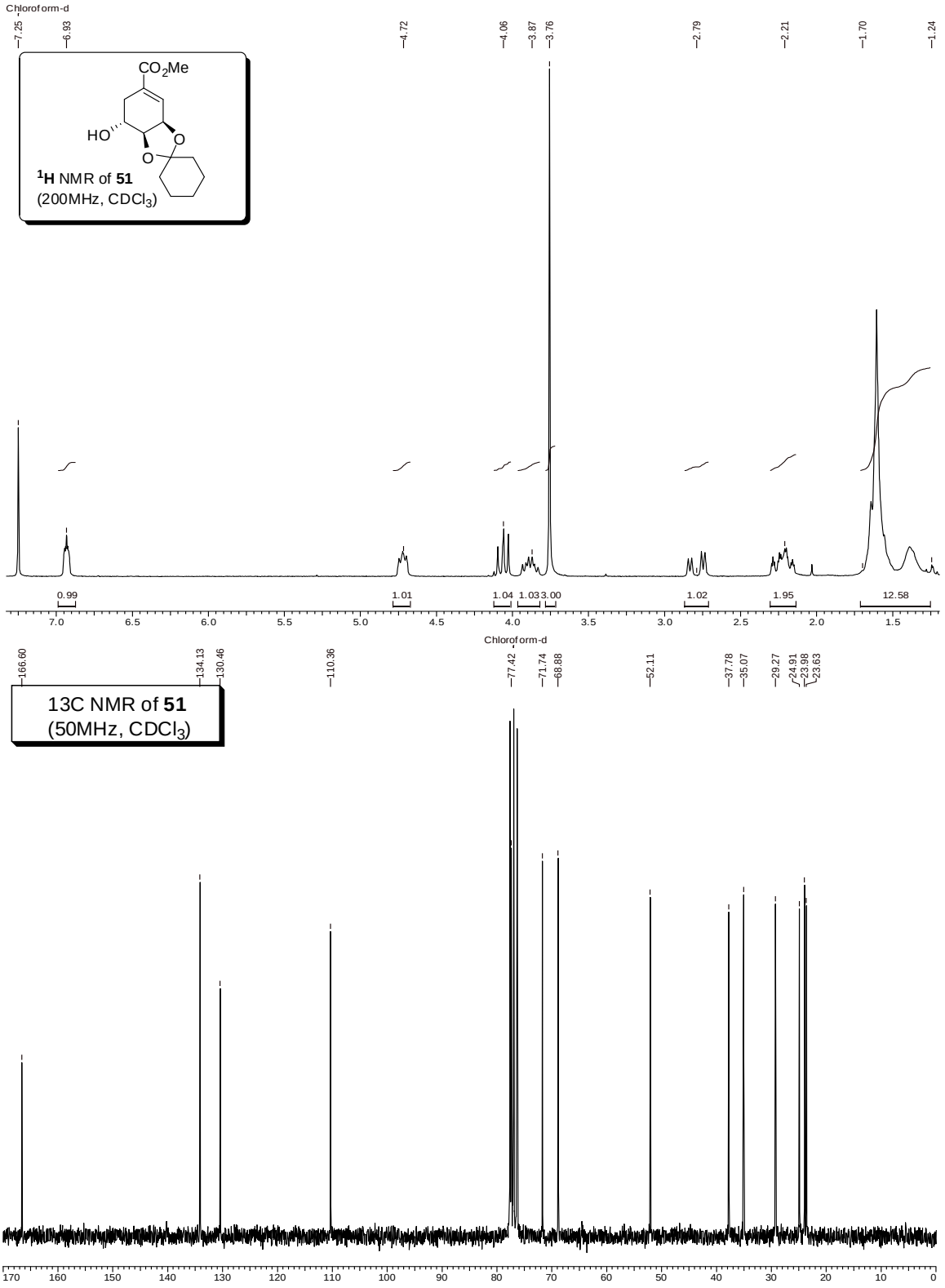


36

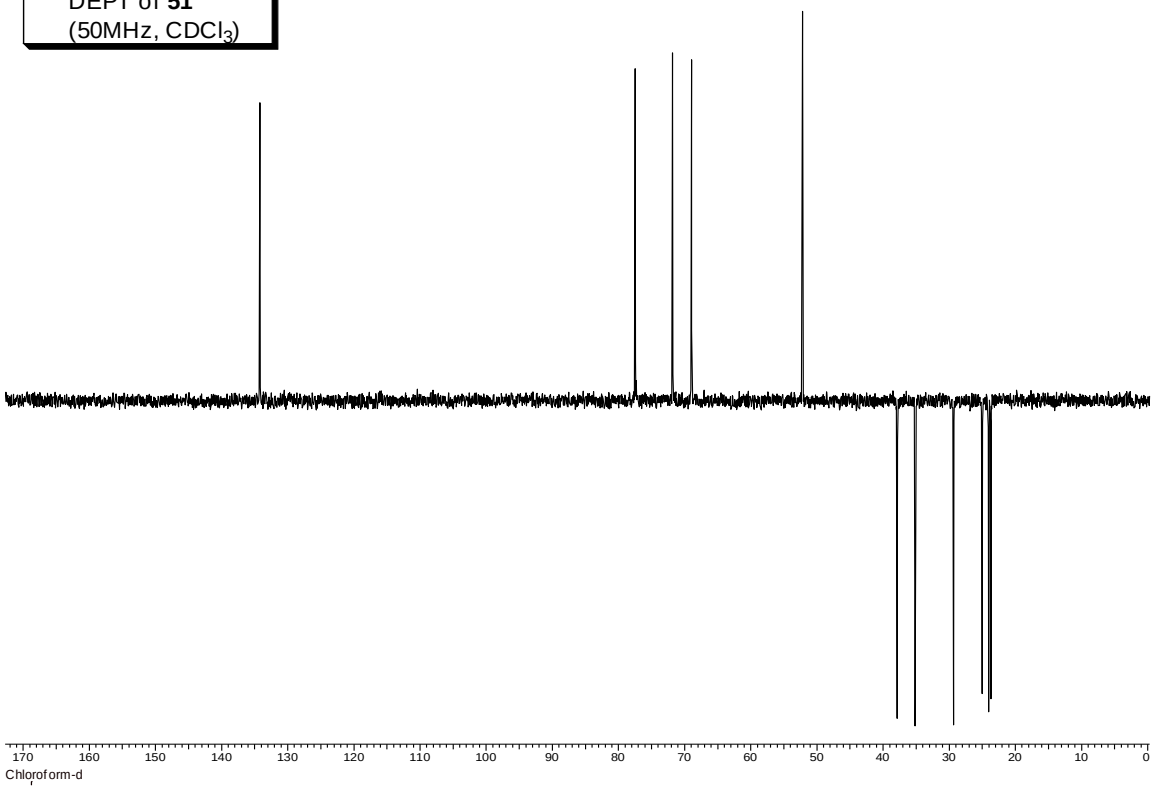
To a solution of **10** (0.93 g, 4.47 mmol) and HMPA (1.5 mL) in dry THF (10 mL) was added *n*-BuLi (2 M, 2.23 mL, 4.47 mmol) at -78 ^{o}C. The mixture was stirred at same temperature for 0.5 h. A solution of **35** (1.0 g, 3.73 mmol) in dry THF (3 mL) was added drop wise to the reaction mixture and allowed to stir for additional 1 h followed by the addition of TBSCl (0.67 g, 4.47 mmol) in dry THF (2 mL). The reaction mixture was allowed to warm to room temperature and quenched with water. The reaction mixture was extracted with pet ether: ethyl acetate (1:1, 2x10 mL). The combined organic extracts were treated successively with water (2x10 mL), brine (1x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was column chromatographed over silica gel using pet ether-ethyl acetate (9:1) as eluant to give **36** (1.94 g, 88 %) as a colorless gummy mass.

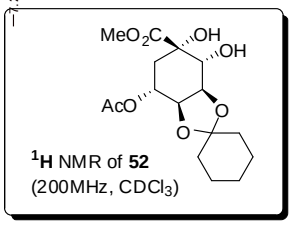
$[\alpha]^{24}_D$	:	+6.9^{o} (*c* 2.1, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3015, 2934, 2859, 1698
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	δ 6.71 (m, 3H), 5.91 (s, 2H), 4.81 (d, *J* = 6.6 Hz, 1H), 4.73 (d, *J* = 6.5 Hz, 1H), 4.54 (m, 3H), 4.35- 4.10 (m, 3H), 4.06 (m, 1H), 3.72 (s, 3H), 3.41 (s, 3H), 1.68-1.24 (m, 10H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	156.9, 150.2, 149.5, 147.6, 146.4, 132.6, 120.6, 119.9, 109.2, 103.8, 100.8, 96.2, 77.8, 74.9, 73.1, 57.0, 55.5, 52.6, 49.3, 37.2, 34.8, 25.5, 24.9, 23.8, 23.6, 17.9, -4.7
Mass: m/z (%)	:	614 (M+Na$^+$, 100), 592 (M+H$^+$, 32), 383(32), 402 (14), 324 (10).

3B.7. Spectral data

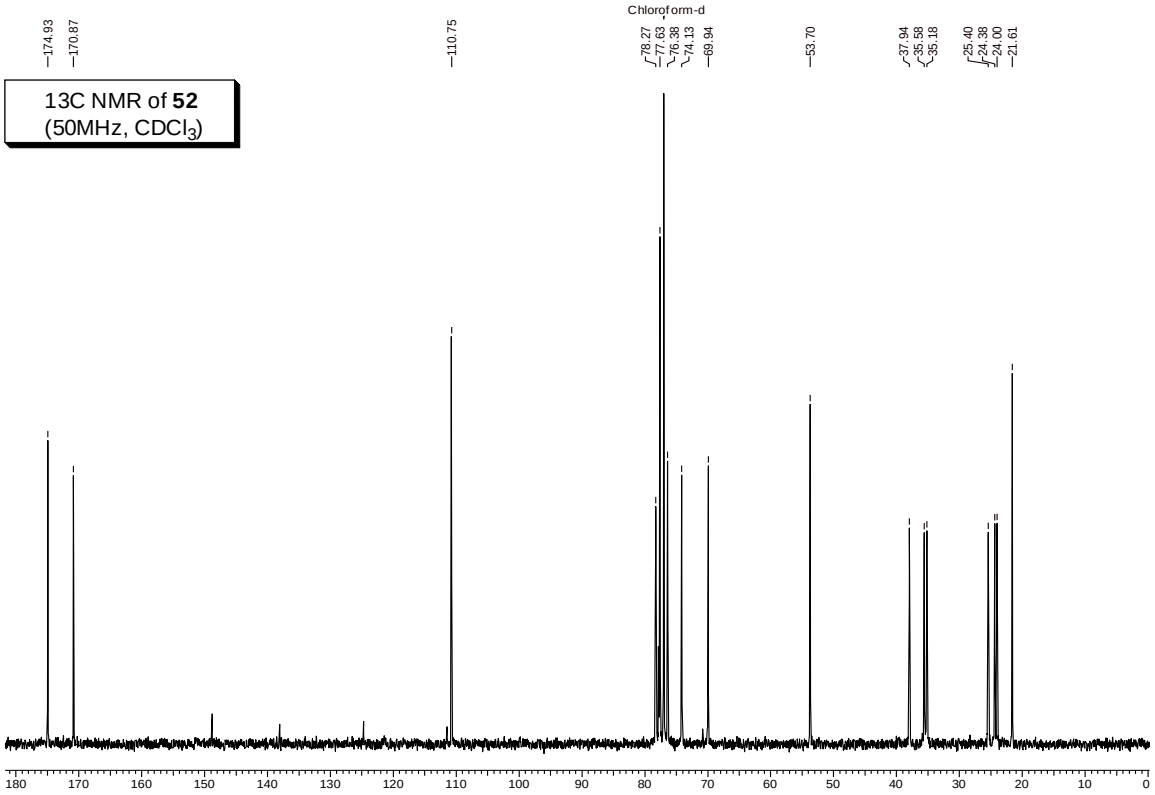


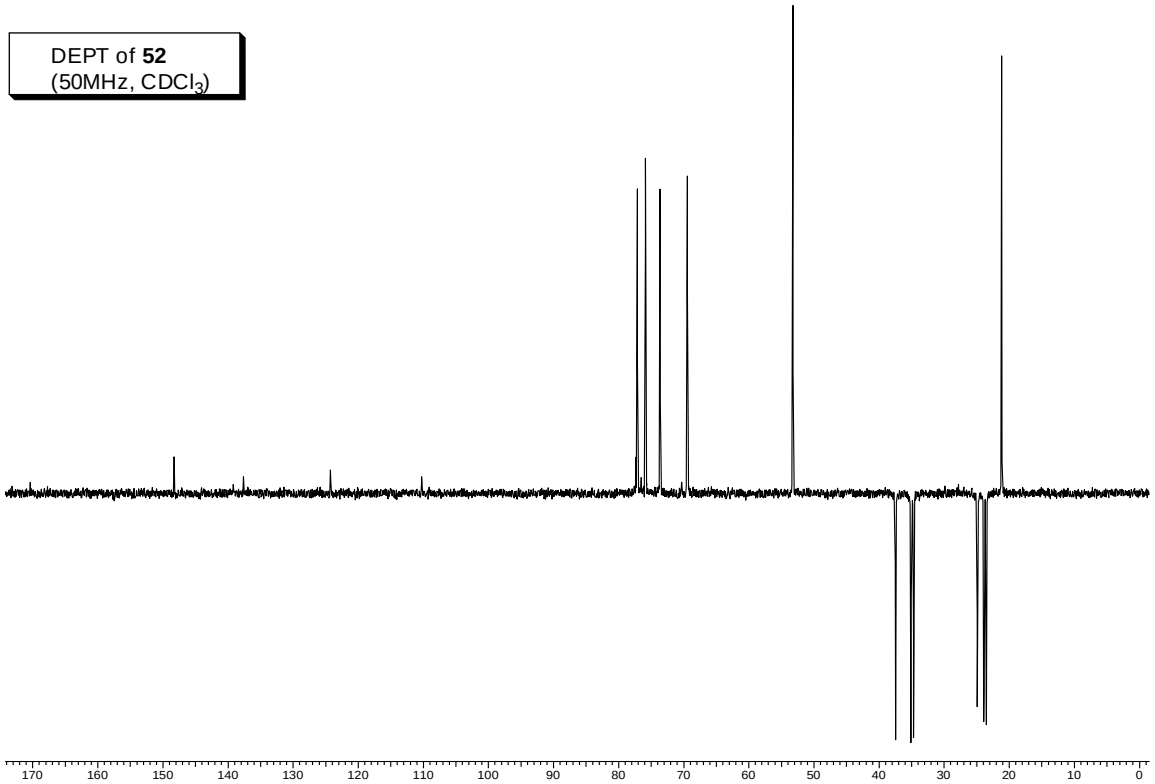
DEPT of **51**
(50MHz, $CDCl_3$)





^{1}H NMR of **52**
(200MHz, $CDCl_3$)


Chloroform-d
174.93
170.87
110.75
78.27
77.63
76.38
74.13
69.94
53.70
37.94
35.58
35.18
25.40
24.38
24.00
21.61
13C NMR of 52
(50MHz, CDCl3)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


DEPT of 52
(50MHz, CDCl3)
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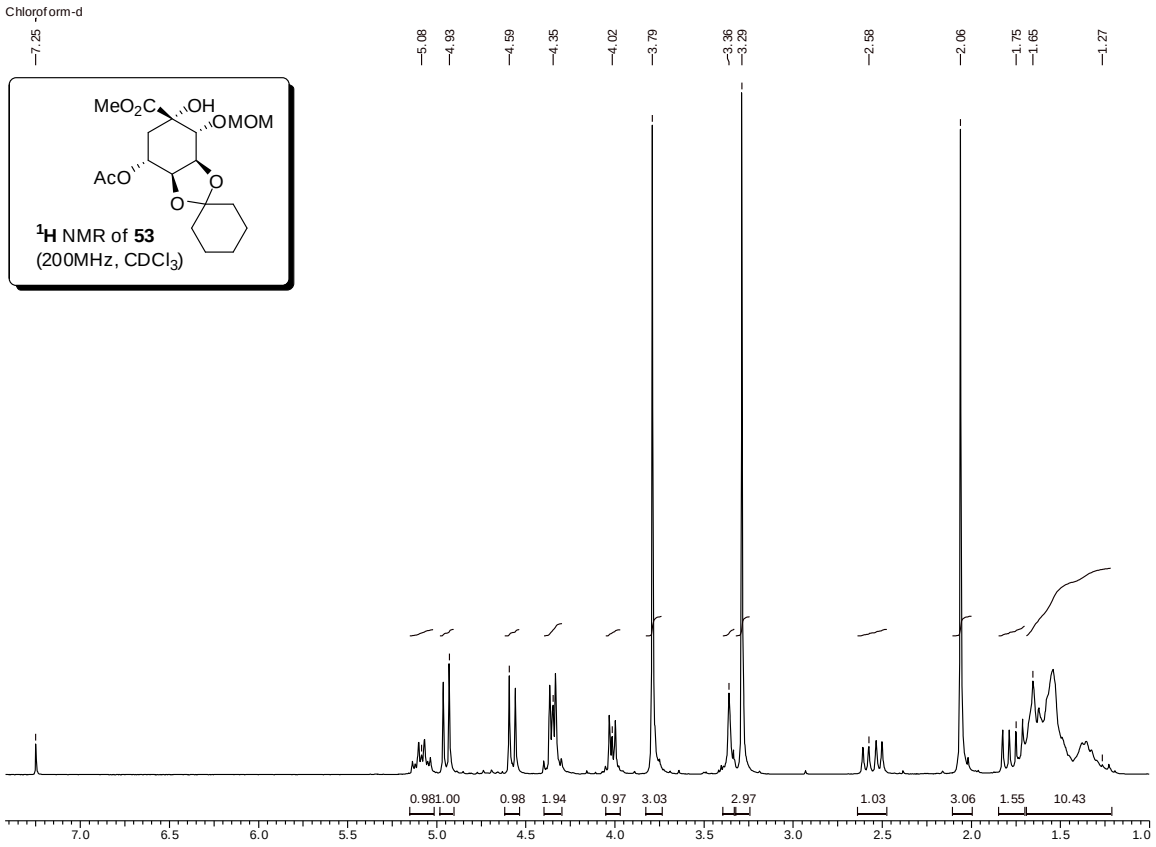
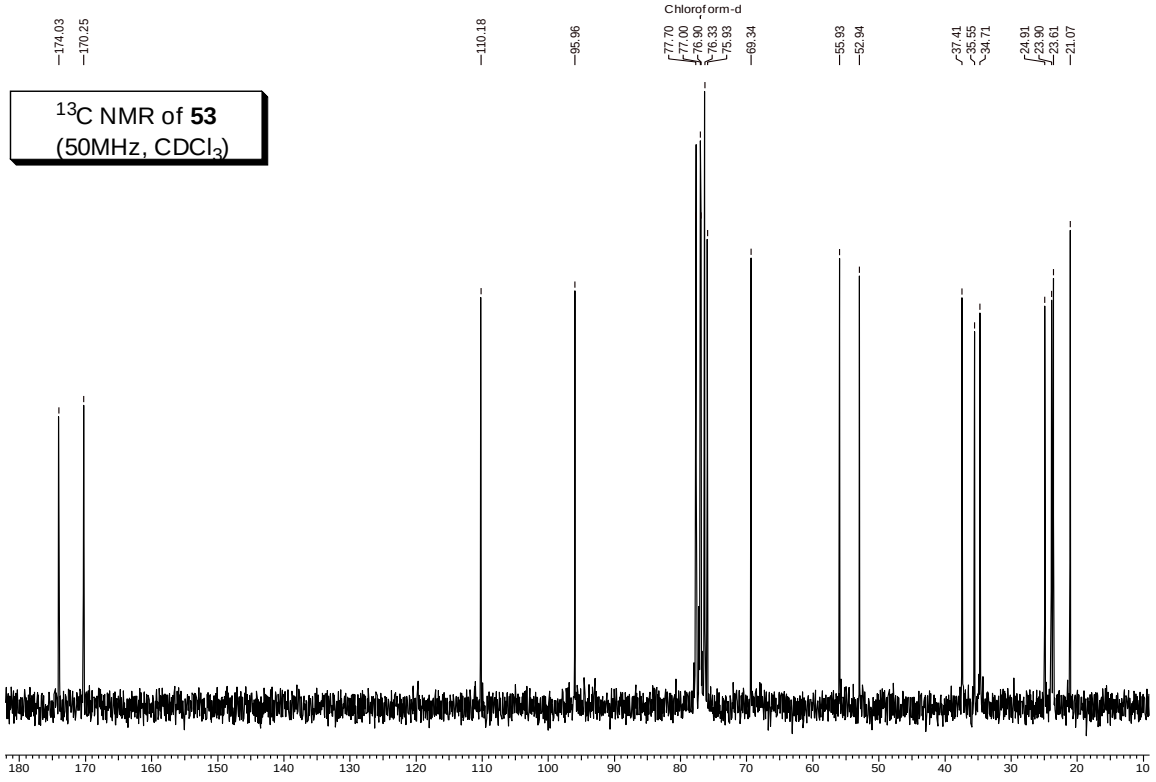
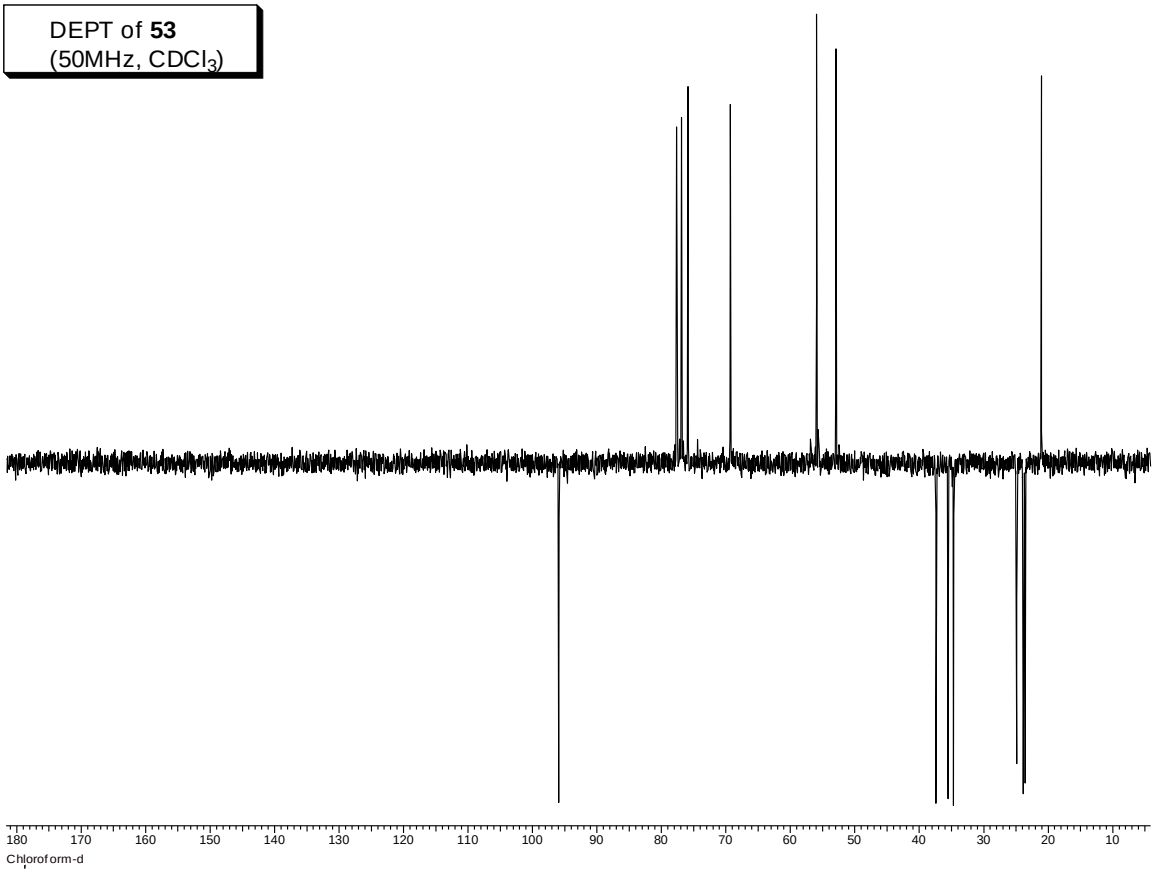
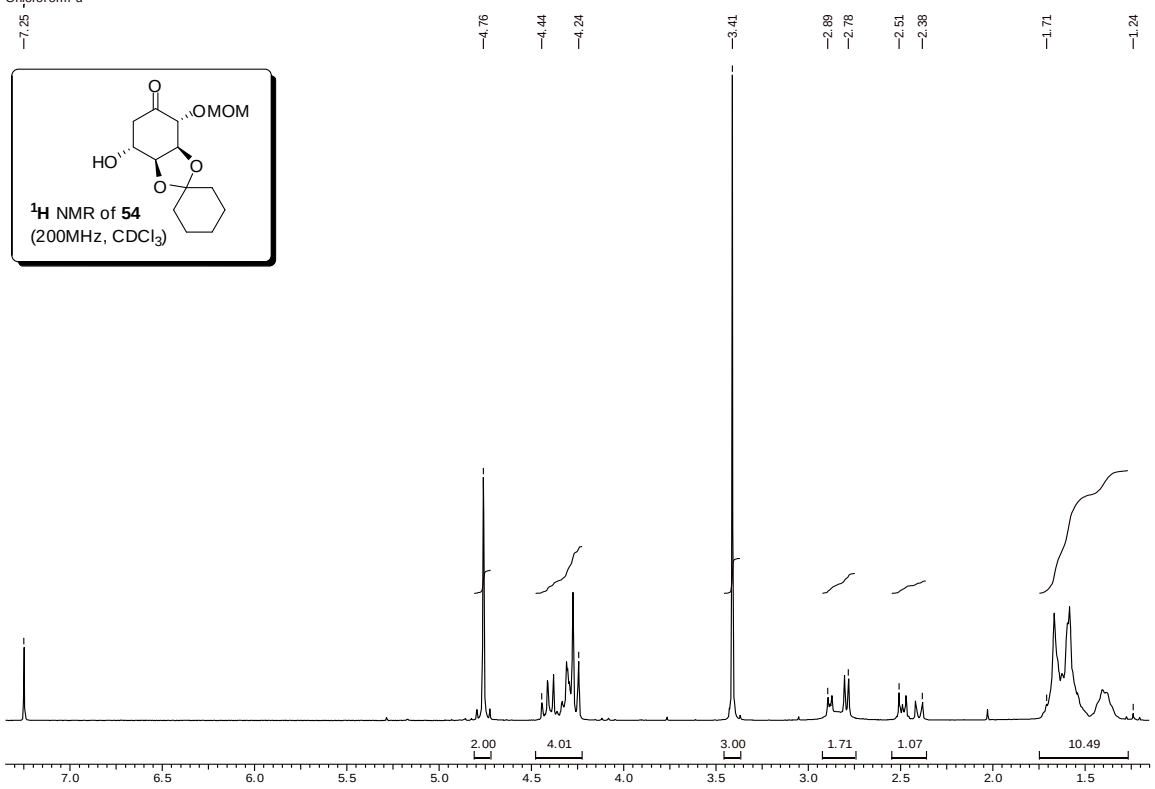

Chloroform-d
7.25
5.08
4.93
4.59
4.35
4.02
3.79
3.36
3.29
2.58
2.06
1.75
1.65
1.27
MeO2C
OH
OMOM
AcO
O
O
1H NMR of 53
(200MHz, CDCl3)
0.98 1.00 0.98 1.94 0.97 3.03 2.97 1.03 3.06 1.55 10.43
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0

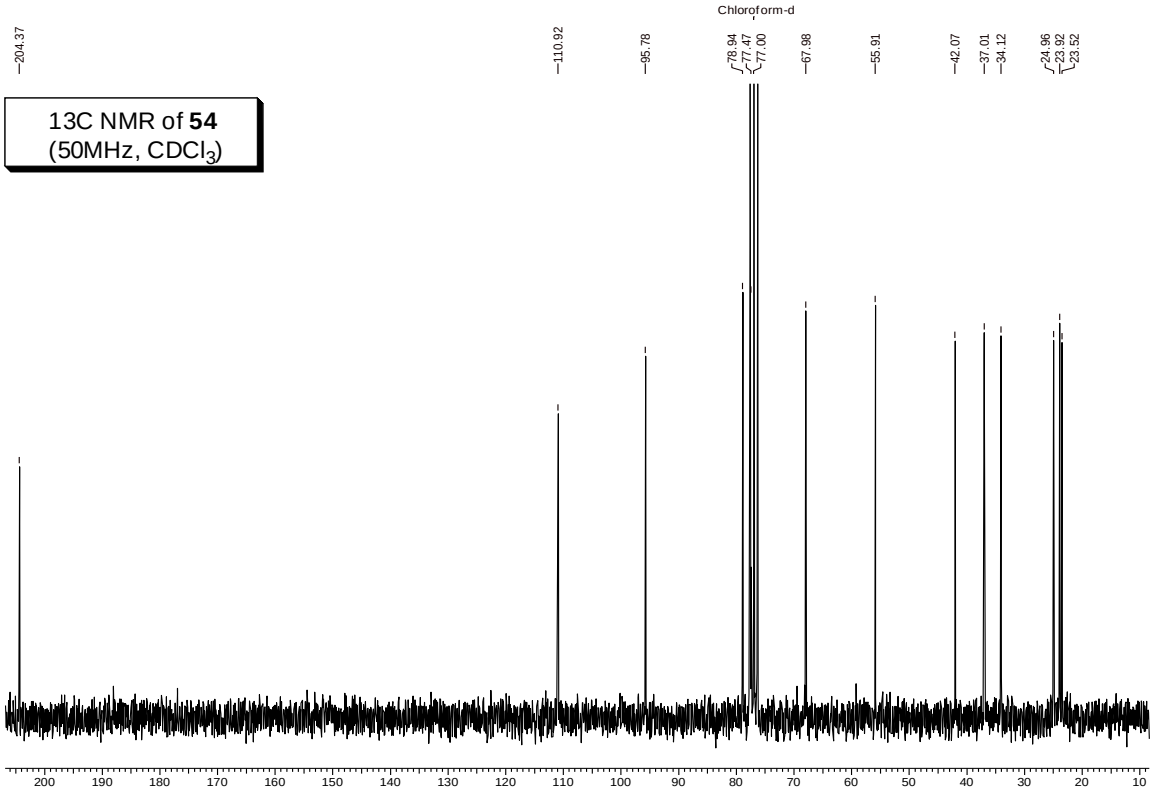

Chloroform-d
174.03
170.25
110.18
95.96
77.70
77.00
76.90
76.33
75.93
69.34
55.93
52.94
37.41
35.55
34.71
24.91
23.90
23.61
21.07
13C NMR of 53
(50MHz, CDCl3)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

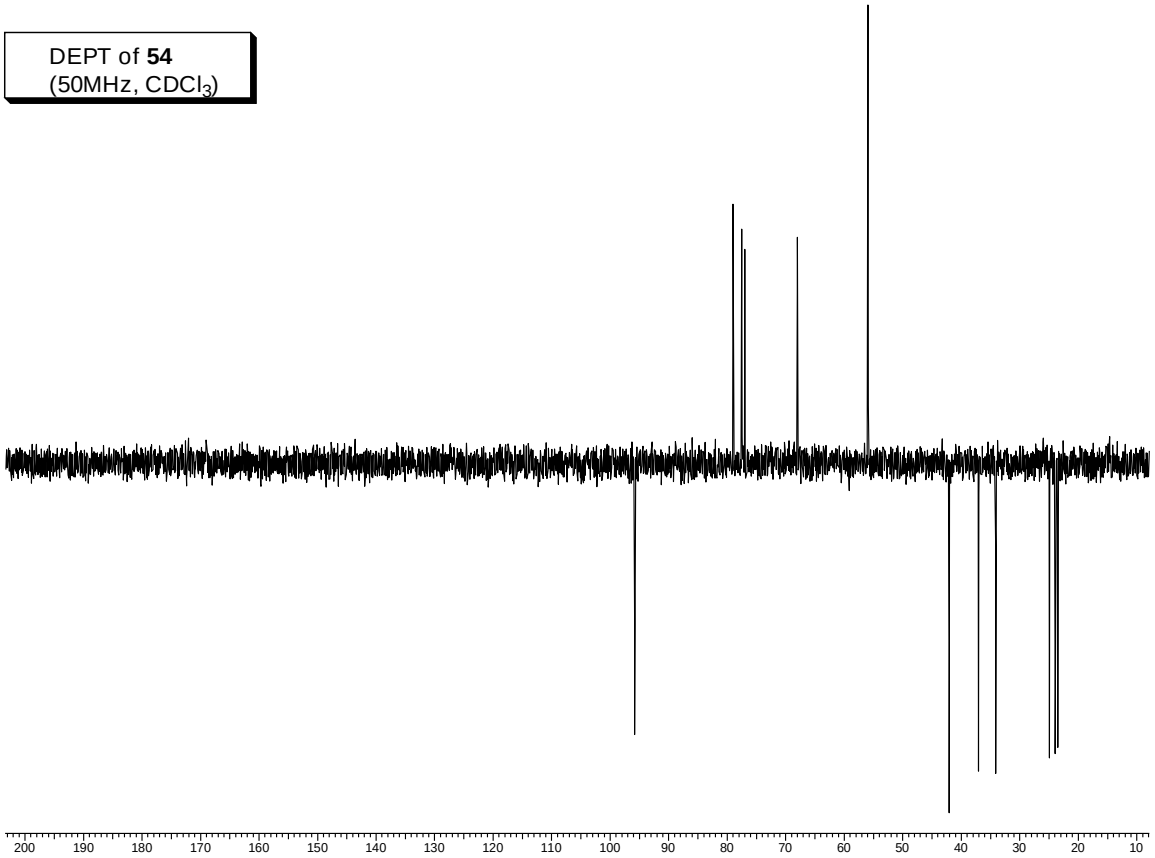
DEPT of **53**
(50MHz, $CDCl_3$)

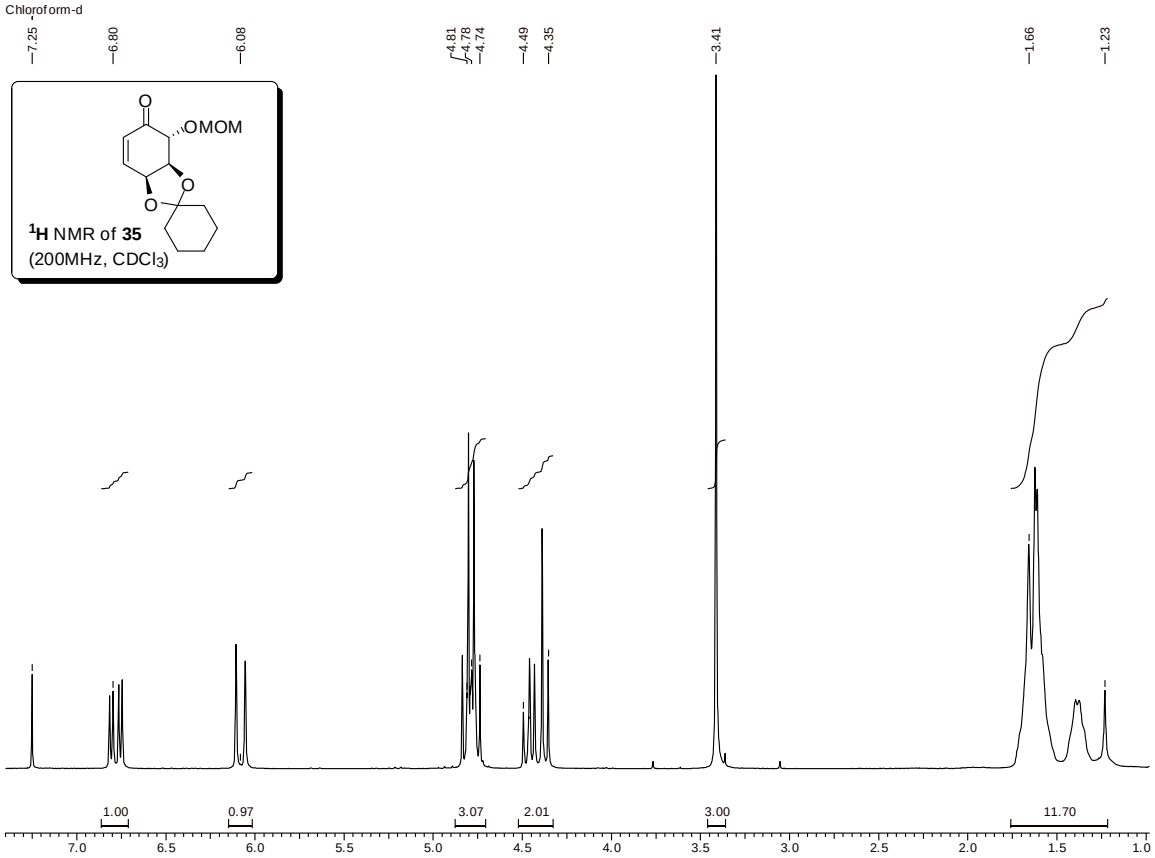


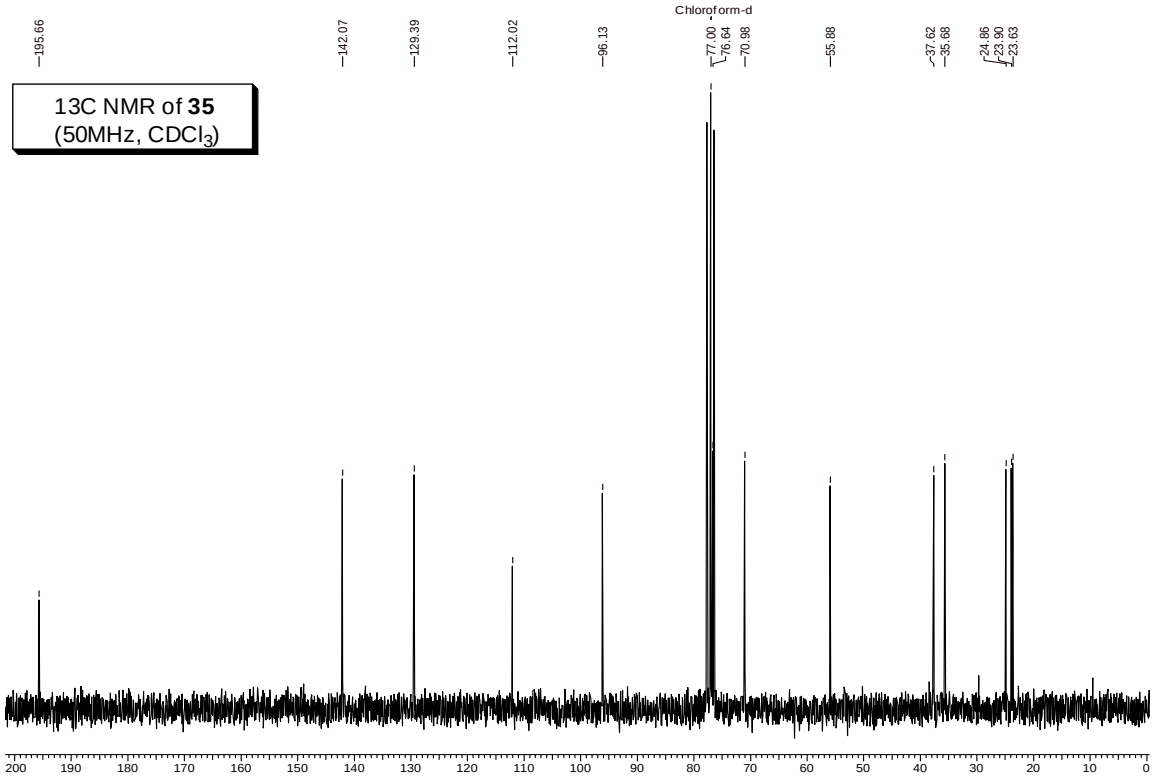


^{1}H NMR of **54**
(200MHz, $CDCl_3$)

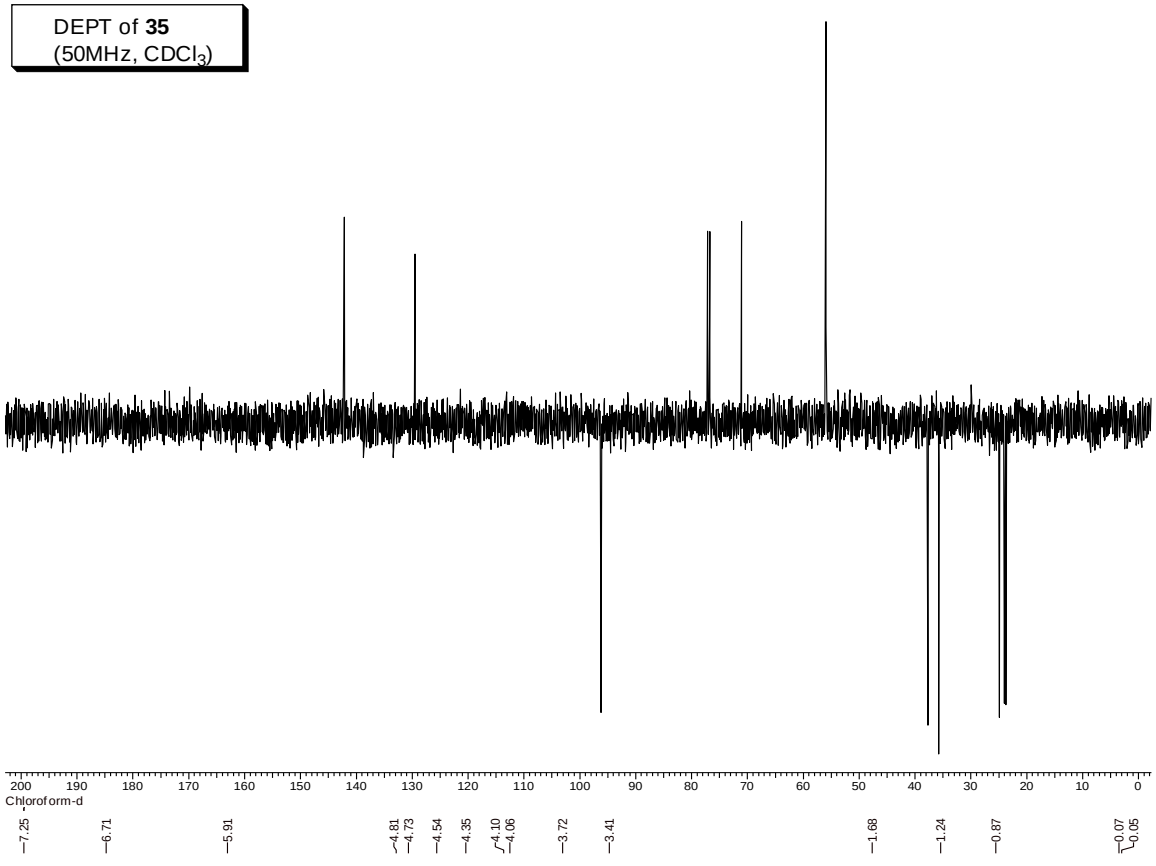

Chloroform-d
204.37
110.92
95.78
78.94
77.47
77.00
67.98
55.91
42.07
37.01
34.12
24.96
23.92
23.52
13C NMR of 54
(50MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

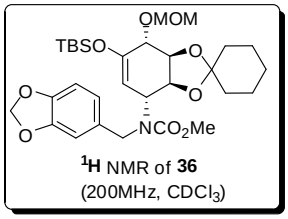

DEPT of 54
(50MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10


Chloroform-d
7.25
6.80
6.08
4.81
4.78
4.74
4.49
4.35
3.41
1.66
1.23
OMOM
O
O
O
1H NMR of 35
(200MHz, CDCl3)
1.00
0.97
3.07
2.01
3.00
11.70
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

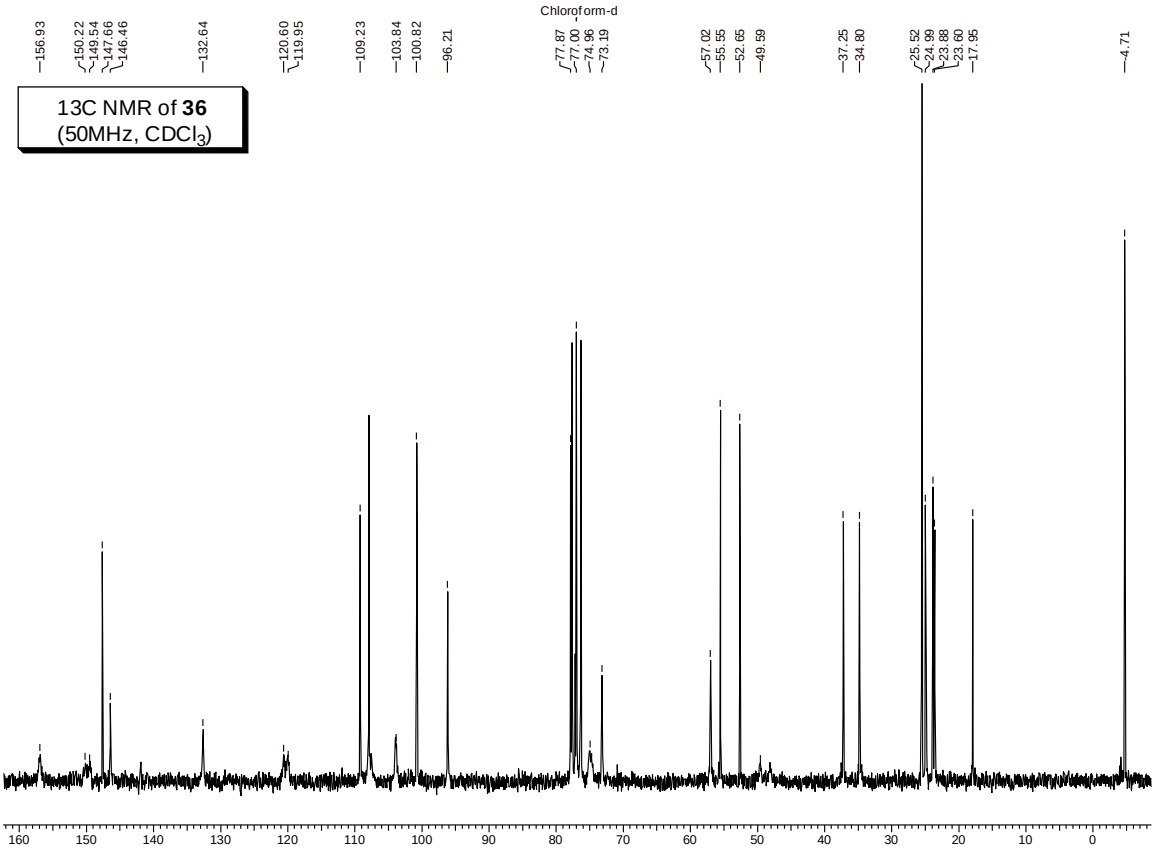

Chloroform-d
195.66
142.07
129.39
112.02
96.13
77.00
76.64
70.98
55.88
37.62
35.68
24.86
23.90
23.63
13C NMR of 35
(50MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

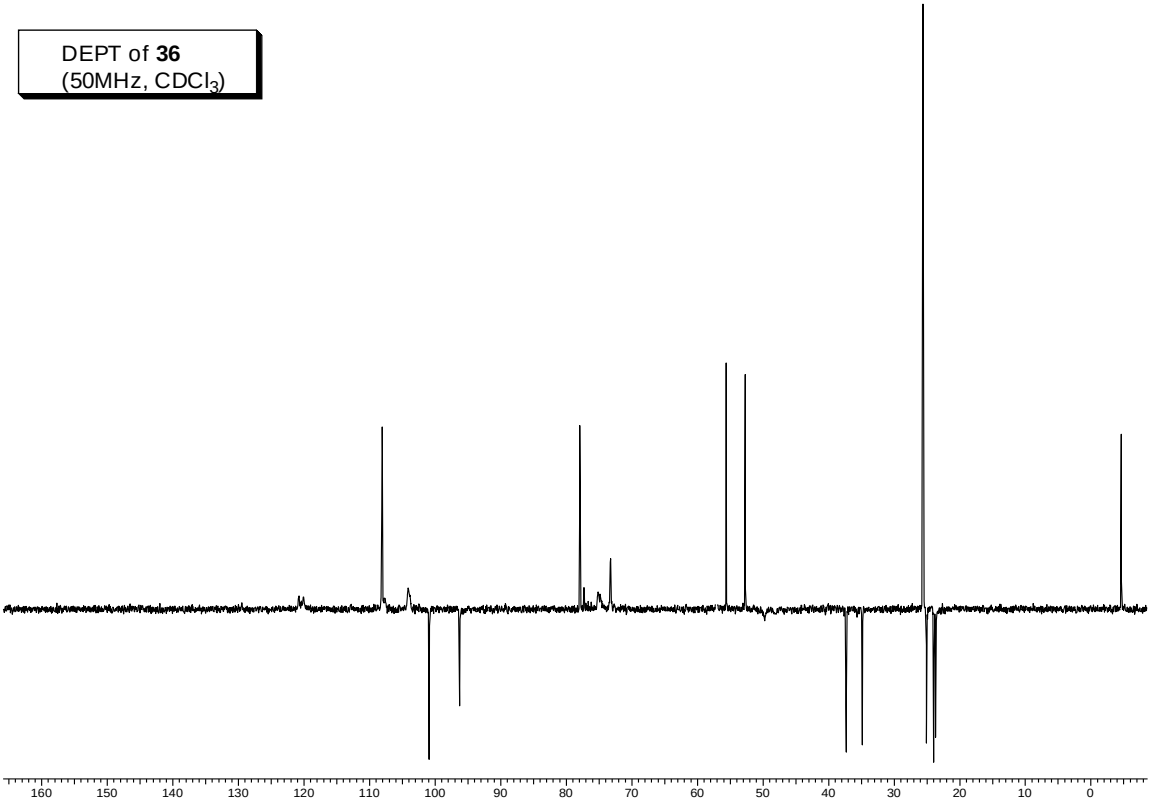
DEPT of **35**
(50MHz, $CDCl_3$)





^{1}H NMR of **36**
(200MHz, $CDCl_3$)


13C NMR of **36**
(50MHz, $CDCl_3$)
Chloroform-d
156.93
150.22
149.54
147.66
146.46
132.64
120.60
119.95
109.23
103.84
100.82
96.21
77.87
77.00
74.96
73.19
57.02
55.55
52.65
49.59
37.25
34.80
25.52
24.99
23.88
23.60
17.95
4.71
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


DEPT of **36**
(50MHz, $CDCl_3$)
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

3.3. References

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Erratum