STUDIES TOWARDS THE SYNTHESIS OF PANCRATISTATIN ANALOGUES EMPLOYING PET-INITIATED CARBOCYCLIZATION OF SILYLENOLETHERS

A THESIS
SUBMITTED TO THE
UNIVERSITY OF PUNE
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN
CHEMISTRY

BY
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To

My beloved Parents

DECLARATION

I hereby declare that the work presented in the thesis entitled "**Studies Towards the Synthesis of Pancratistatin Analogues Employing PET-initiated Carbocyclization of Silylenolethers**" submitted for Ph. D. degree to the University of Poona has been carried out by me at 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.

Date: 25-07-2002 (A. Murugan)

Division of Organic Chemistry (Synthesis)

National Chemical Laboratory

Pune-411008.

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled" **Studies Towards the Synthesis of Pancratistatin Analogues Employing PET-initiated Carbocyclization of Silylenolethers**" submitted by Mr. A. Murugan was carried out by him under my supervision at National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in the thesis.

Date:25-07-2002

(Dr. Ganesh Pandey)

Research Guide

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A. Murugan

CONTENTS

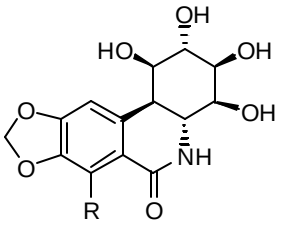
List of Abbreviations

aq	aqueous
Bn	benzyl
bp	boiling point
Bu	butyl
DCM	dichloromethane
DMF	N,N-dimethylformamide
Et	ethyl
g	gram
h	hour
IR	infrared
M	molar
mL	milliliter
mmol	millimole
mp	melting point
rt	room temperature
TEA	triethyl amine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMS	trimethylsilyl
TBS	*tert*-butyldimethylsilyl

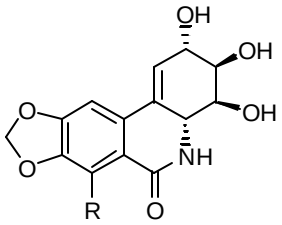
Abstract of the Thesis: Studies Towards the Synthesis of Pancratistatin Analogues Employing PET-Initiated Carbocyclization of Silylenolethers.

Chapter-I: Introduction

This chapter describes an account of the isolation, biological importance and synthetic approaches developed towards Pancratistatin and its co-engeners.



1: R = OH, Pancratistatin
2: R = H, 7-deoxypancratistatin



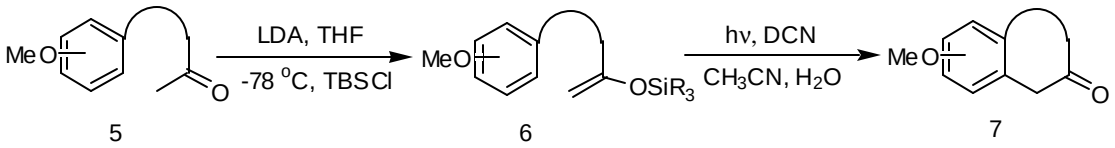
3: R = OH, Narciclasine
4: R = H, Lycoricidine

(+)- Pancratistatin (**1**), was first isolated by Pettit and co-workers in 1984 from the plant *Pancratum littorale*. It showed most promising anti-cancer and antiviral activities. It was found to be active against murine P-5076 ovarian sarcoma as well as against P-388 lymphotic leukemia. Five years later, Ghosal and co-workers isolated 7-deoxypancratistatin (**2**) from the bulbs of *Haemanthus kalbreyeri* which also showed similar biological activities with better therapeutic index due to decreased toxicity. Although Narciclasine (**3**) and Lycoricidine (**4**) were isolated from *Lycoris radiate* by Okamoto and co-workers in 1968, their activity in inhibiting the binding of tRNA to the peptide transferase centre of ribosomal subunit and thereby disrupting the protein biosynthesis in eukaryotic cells, was unveiled much later.

Chapter-II: Synthetic studies towards Pancratistatin

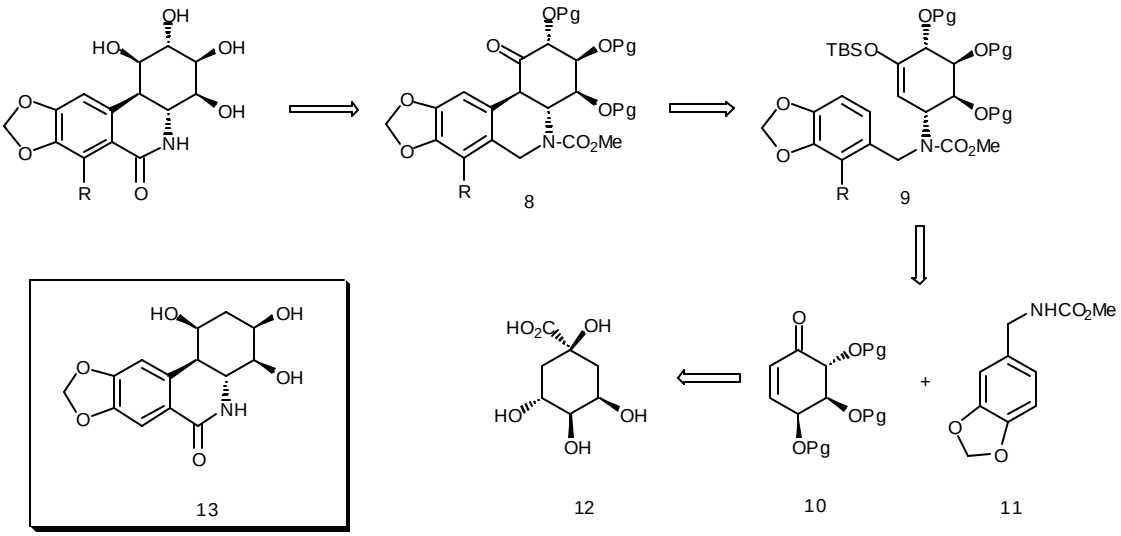
The main challenge involved in designing any synthetic route for **1** lies into the control of the *trans*-fused BC-ring junction (4a, 10b) and the stereo controlled

installation of contiguous hydroxy functionalities located around the perimeter of the C-ring moiety. Our group have successfully demonstrated an efficient strategy for the intramolecular α-arylation of ketones by the reaction of silylenolethers to photoinduced electron transfer (PET) generated arene radical cations as shown in Scheme-I.



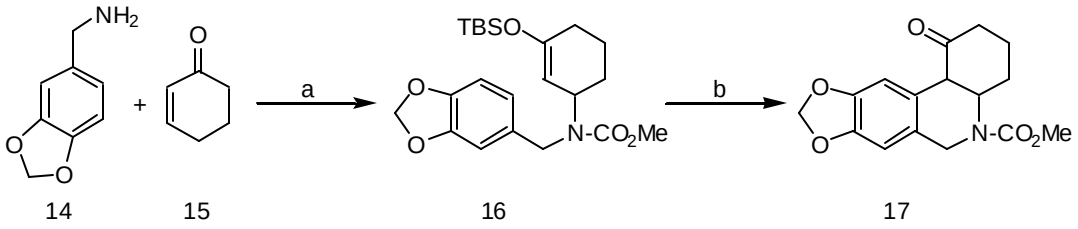
Scheme-I

In the context of above strategy, we viewed a new synthetic approach for **1** based on this new concept and also making use of naturally abundant D-(-)-quinic acid (**12**) as chiral source to build the highly oxygenated C-ring system as depicted retrosynthetically in Scheme- II.



Scheme-II

In order to evaluate the success of above strategy towards pancratistatin synthesis, we first synthesized the Phenanthridone skeleton (**17**) as depicted in Scheme-III.

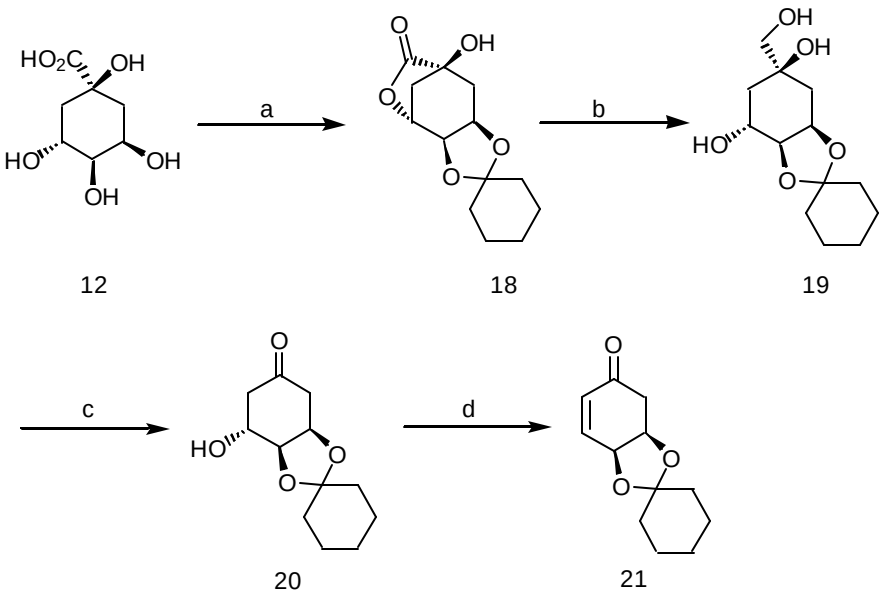


Scheme-III

Reagents and Conditions: *a) TBSOTf, -50 ^{o}C, ether, 3h, then 0 ^{o}C, TEA, $ClCO_2Me$, 70 %; b) hn, DCN, H_2O, 6h, 72 %.*

Conjugate addition of piperonyl amine (**14**) to 2- cyclohexen-1-one (**15**) in the presence of TBSOTf in ether solution at –50 ^{o}C followed by the *insitu* protection of amino group gave silylenolether (**16**) in 70 % yield. PET-cyclization **16** in CH_3CN : H_2O (24:1) system, afforded the Phenanthridone skeleton (**17**) in good yield. The stereochemistry of BC ring fusion (4a, 10b) was found to be *trans* based on PMR spectrum.

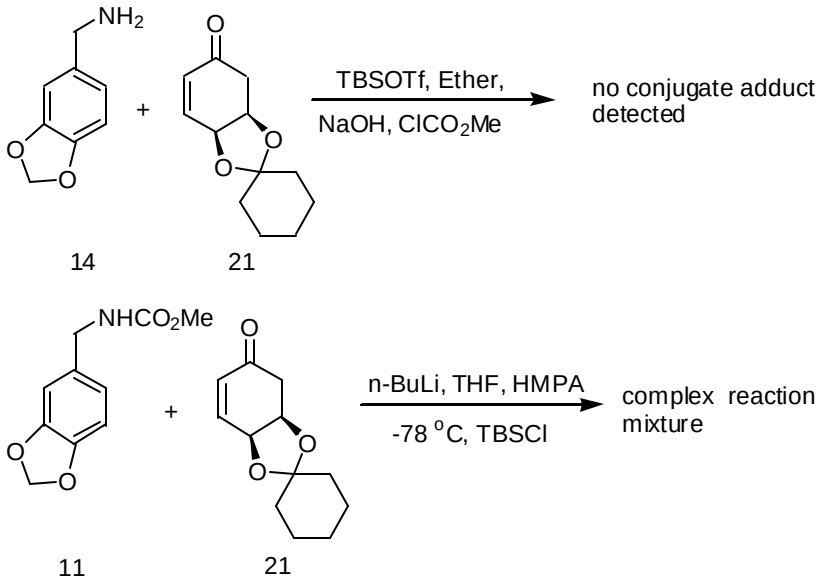
After the successful prepararion of **17**, we moved on to design the synthesis of (+)-2,7-dideoxypancratistatin (**13**) as an advanced model of **2**. Initially we synthesized the cyclohexylidine protected enone (**21**) in four steps starting from **12** (Scheme-IV).



12 18 19 20 21

Scheme-IV

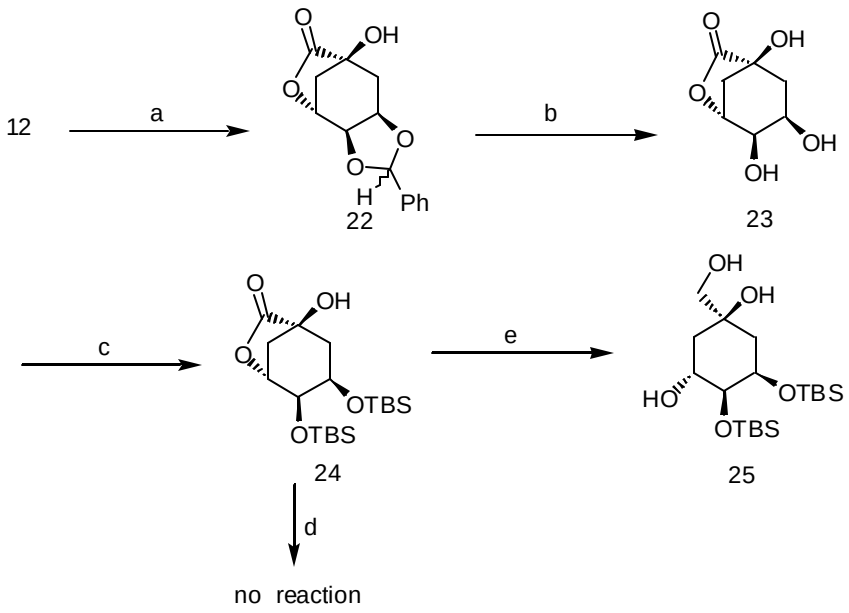
Reagents and Conditions: *a) Cyclohexanone, p-TSA, PhH, DMF, reflux, 95 %; b) $NaBH_4$, EtOH, rt, 2 days, 90 %; c) $NaIO_4$, H_2O, 0 ^oC, 0.5 h, 95 %; d) MsCl, TEA, DCM, 0 ^oC, 1.5 h, 90 %.*



14 21 11 21

Scheme-V

Various attempts were made towards the conjugate addition of piperonyl amine (**14**) to **21**, however, all were unsuccessful. At this stage it was decided to change the protecting group. We felt that instead of cyclohexylidine protecting group, TBS protection would be ideal. The synthetic effort towards the making of diTBS proteted enone is shown in the Scheme- VI**.**



Scheme-VI

Reagents and Conditions: *a) PhCHO, PhH, DMF, p-TSA, reflux, 2 h, 80 %; b) H_2/Pd-C, EtOH, 1 atm, 92 %; c) TBSCl, ImH, DMAP, DMF, rt, 72 %; d) $NaBH_4$, EtOH, rt; e) LAH, THF, reflux, 30 %.*

The poor yield during the reduction of lactone **24** with LAH forced us to change the strategy. We could successfully over come this problem by protecting the triol **19** as tri-O-benzylether followed by cyclohexylidine deprotection with HOAc : H_2O (80:20) system and subsequent protection as TBS ether afforded **28**. Debenzylation followed by periodate oxidation gave the β-hydroxy ketone **29** which

on β-elimination with MsCl/TEA gave the diTBS ether protected enone **30** as depicted in Scheme-VII.

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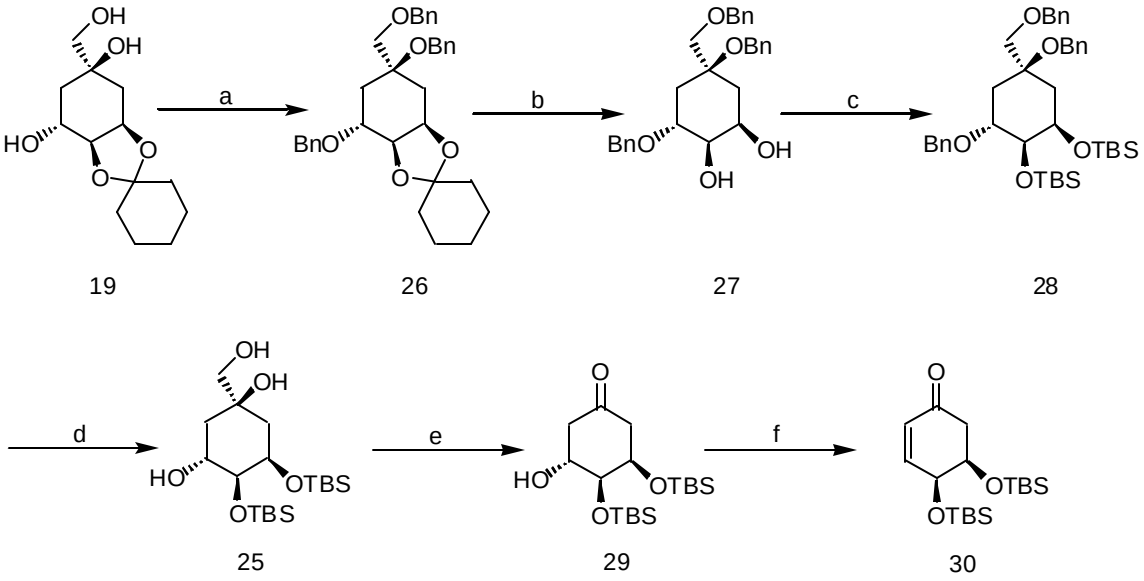
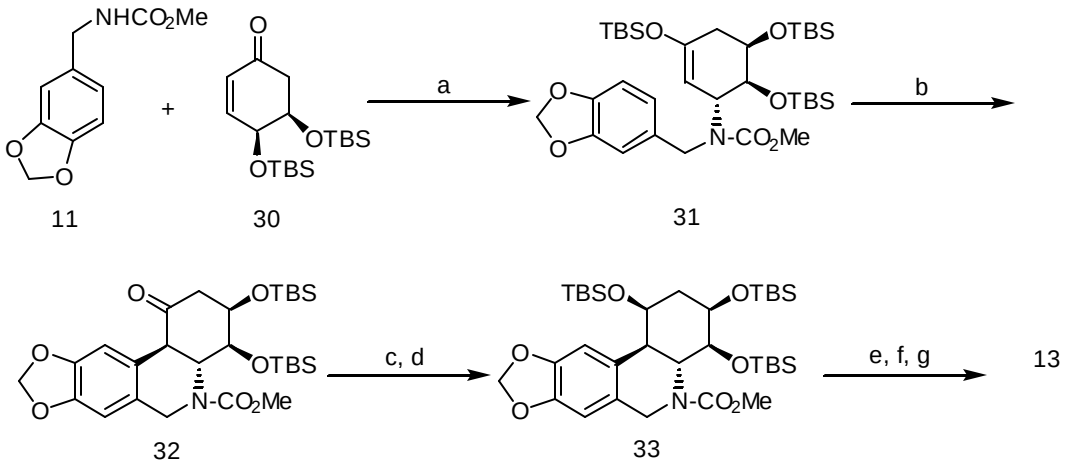


Scheme-VII

Reagents and Conditions: *a) NaH, DMF, 50 ^{o}C, BnCl, rt, 85 %; b) HOAc, H_2O, 50 ^{o}C, 10 h, 95 %; c) TBSCl, ImH, DMAP, DCM, DMF, rt, 80 %; d) H_2/Pd-C, EtOH, 1 atm, 100 %; e) $NaIO_4$, EtOH, rt, 100 %; f) MsCl, TEA, DCM, 0 ^{o}C, 95 %.*

Conjugate addition of *N*-lithiated piperonyl amine carbamate, prepared by the treatment of **11** with n-BuLi in HMPA at –78 ^{o}C, followed by trapping of the resultant enolate ion as TBS enolether afforded silylenolether **31** in 95 % yield.



Scheme-VIII

Reagents and Condiotns: *a) n-BuLi, THF, -78 °C, TBSCl, 95 %; b) hn, DCN, CH_3CN, H_2O, 6 h, 68 %; c) $NaBH_4$, iPrOH, rt, 12 h; d) TBSCl, ImH, DMAP, DCM, rt, 24 h, 85 % over two steps; e) RuO_2, $NaIO_4$, EtOAc, H_2O; f) NaOMe, MeOH, reflux; g) TBAF, THF, 82 % over three steps.*

PET-cyclization by irradiating (Pyrex filter, >280nm, 450W Hanovia medium pressure lamp, 6h) a mixture of **31** and 1,4-dicyanonaphthalene (DCN) in CH_3CN:H_2O (24:1) system and usual work up and chromatographic purification of the crude photolysate gave cyclized product **32** in 68 % yield as a single diastereomer

Sodium borohydride reduction of **32** followed by the protection of the resultant alcohol moiety as TBS ether gave **33** in 85 % yield as a single diastereomer. Benzylic oxidation of **33** by utilizing a catalytic amount of RuO_2 and $NaIO_4$ followed by carbamate and silyl deprotection gave **13**, $[\alpha]_D^{25}$ = +90.91° (*c* 0.055, MeOH), in overall 23 % yield.

Chapter-lll: **Experimental**

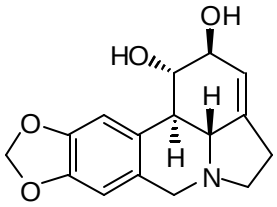
This chapter gives detailed experimental procedures and spectral characterization of all the new molecules.

CHAPTER-I

INTRODUCTION

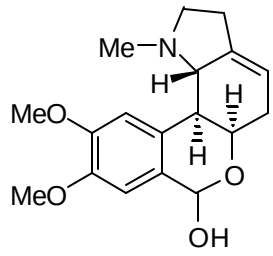
1. Introduction

The use of *Amaryllidaceae* plant extracts for medicinal purpose dates back to at least the fourth century[1]. In recent times, a large number of alkaloids, possessing a wide spectrum of biological activities have been isolated from these species [2]. These alkaloids constitute an important group of naturally occurring bases possessing a diversity of functionality and structure. Indeed, over hundred alkaloids have been isolated from the members of the *Amaryllidaceae* plants and most of them may be classified into ten principal skeletally homogeneous subgroups, although, there are several other alkaloids having structures derived from these main molecular frame works. Representative alkaloids from each of these classes include lycorine (**1**), lycorenine (**2**), pancratistatin (**3**), galanthamine (**4**), crinine (**5**), latisoline (**6**), mesembrine (**7**), augustamine (**8**), montanine (**9**) and latifine(**10**). These alkaloids are listed below with their structural frame works and pharmacological activities [fig 1].



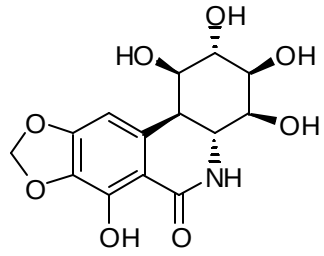
1

Lycorine Class of Alkaloids: Constitutes a group of 33 alkaloids.
Activity: Anriviral, antineoplastic, hypotensive, insect antifeedant.



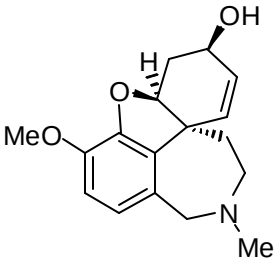
2

Lycorenine Class of Alkaloids: Constitutes a group of 15 alkaloids.
Activity: Insect antifeedant.



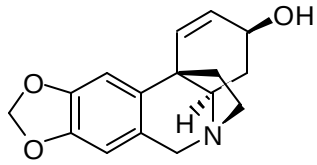
3

Pancratistatin Class of Alkaloids: Conctitutes a group of 10 alkaloids.
Activities: Antitumor, antiviral and antifeedant.



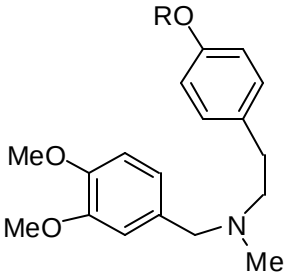
4

Glanthamine Class of Alkaloids: Constitutes a group of 13 alkaloids.
Activities: Analgesic, Insectiside and hypotensive



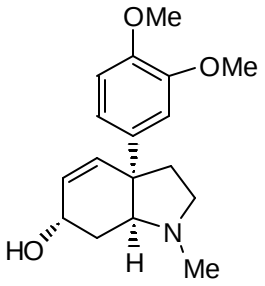
5

Crinine type of Alkaloids: Constitutes a group of 48 alkaloids.
Activities: Immunostimulant, antitumor and antiviral



6

Latisoline Class of Alkaloids: Constitutes a group of 3 alkaloids.



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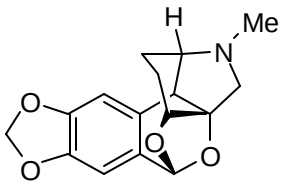
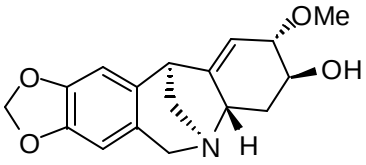
Mesembrine Type Alkaloids: Constitutes only 2 alkaloids



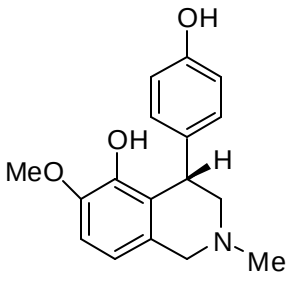
8

Augustamine is the only alkaloid possessing unique structure.



9

Montanine Class of Alkaloids: Constitutes a group of 6 alkaloids.
Activities: Convulsive and weak hypotensive activities.

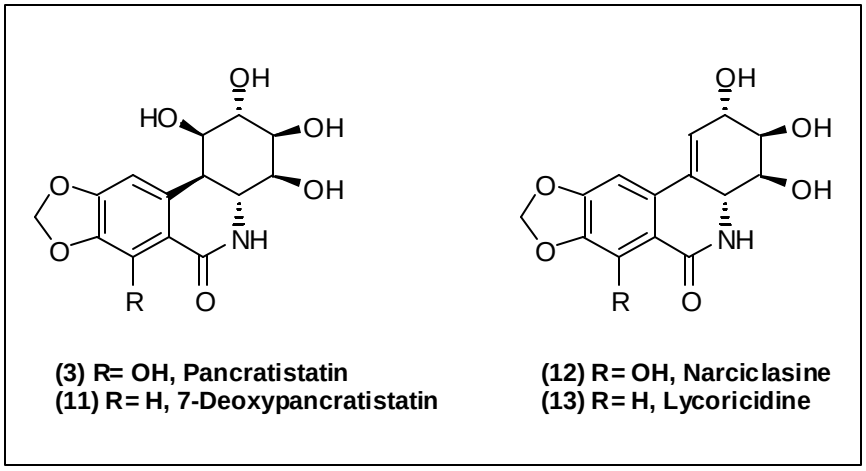


10

Latifine Type of Alkaloids: Constitutes 2 alkaloids.

Fig. 1

Since the detailed discussion on all of these alkaloids are beyond the scope of this dissertation, we will be concentrating mainly on the Pancratistatin analogues viz 7-deoxypancratistatin (**11**), narciclasine(**12**) and lycoricidine(**13**) (Fig. 2).



(3) R= OH, Pancratistatin
(11) R= H, 7-Deoxypancratistatin

(12) R= OH, Narciclasine
(13) R= H, Lycoricidine

Fig. 2

Narciclasine (**12**) and lycoricidine (**13**) were discovered in 1968 from the bulbs of the plant *Lycoris radiate*[3]. Sixteen years later, another highly oxygenated phenanthridone alkaloid was extracted from the bulbs of *Pancratum littorale* by Pettit and co-workers[4] that showed more potent antineoplastic and antiviral activities[5]. The studies have indicated that the mechanism of action of narciclasine (**12**) involves the inhibition of the growth of the eukaryotic cells by the disruption in protein biosynthesis. Narciclasine is known to inhibit the binding of tRNA to the peptidal transferase center of the 60s ribosomal subunit[6]. Although both **12** and **13** show activities against Ehlich carcinoma[3], the most promising activity resides with the pancratistatin (**3**), which is active against murine P-5076 ovarian sarcoma as well as murine P-388 lymphotic leukemia[5]. In 1989, Ghosal and co-workers[7] isolated the latest member of phenanthridone class of alkaloids, 7-deoxypancratistatin, which showed similar activities as **3** but *invitro* antiviral assays showed that **11** has better therapeutic index than **3** due to its decreased toxicity[8].

Driven by the promising biological activities, interesting structural features and low natural abundance (0.0028% yield in isolation),[4a,5] these alkaloids have garnered considerable attention from the synthetic community. The main challenge

concerning the synthesis of these alkaloids include the elaboration of the *trans* fused BC ring junction and the stereo controlled installation of the contiguous hydroxy functions located around the perimeter of the C-ring moiety[9]. The foregoing discussion would mainly focus on to the discussion on the reported syntheses of **3** and **11** to put the dissertation in proper perspectives.

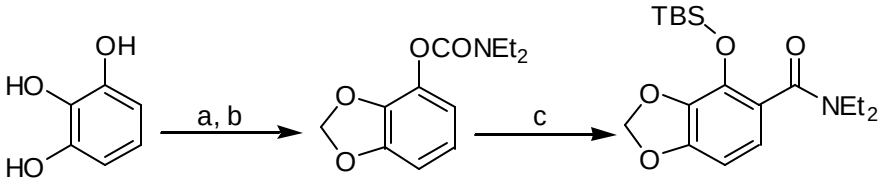
2. Synthetic studies concerning with the Pancratistatin and 7-Deoxypancratistatin

2.1. Synthetic Approaches to Pancratistatin

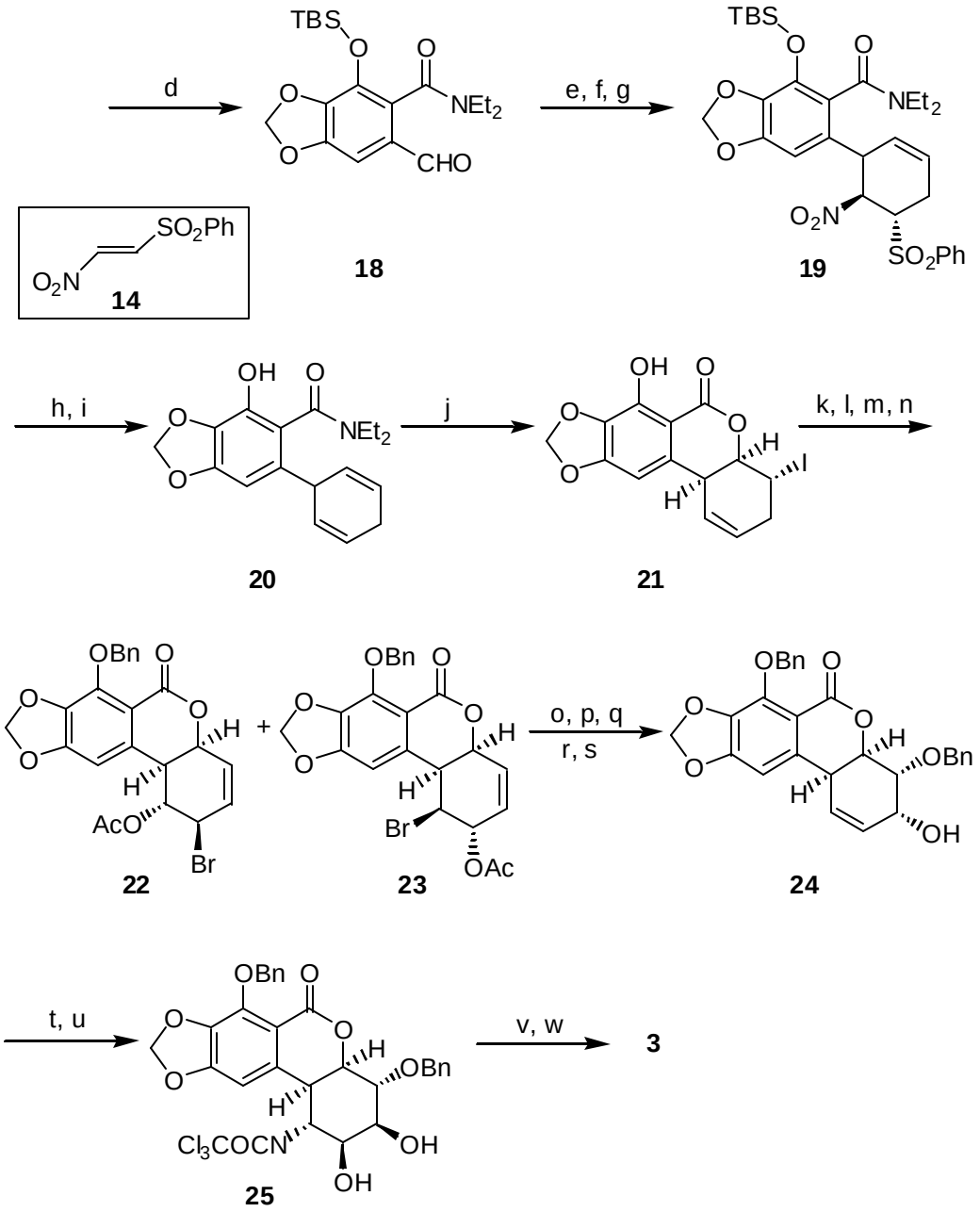
The first total synthesis of pancratistatin was reported by Danishefsky in 1989 in its racemic form[10]. The first enantioselective synthesis was reported by Hudlicky in 1995[11]. In the same year, Trost et al. presented an enantioselective synthesis with high overall yield[12]. Since then, Haseltine[13], Magnus[14], Rigby[15] have also presented new synthetic routes to (+)- pancratistatin (**3**). Recently Pettit achieved the synthesis of **3** from the more abundant alkaloid narciclasine (**12**)[16]. All the above mentioned syntheses are described schematically as follows.

2.1a Danishefsky's Approach. (*J. Am. Chem. Soc.* **1989**, *111*, 4829)[10]

Total of 25 steps and <1 % overall yield.



15 **16** **17**



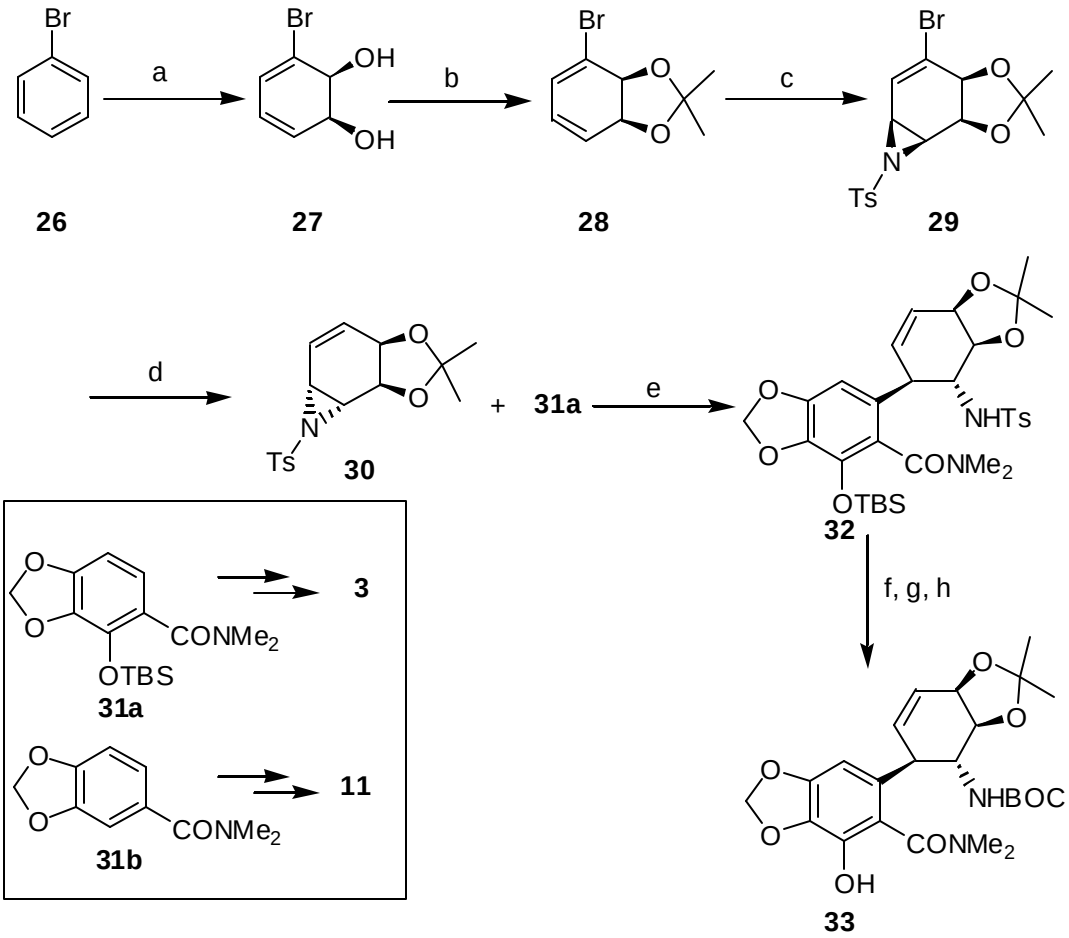
Scheme-I

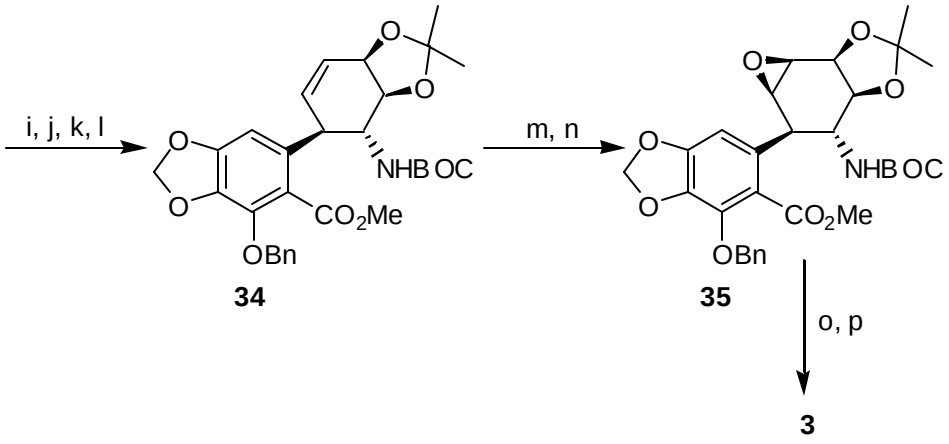
Reagents and Conditions*: a) $CH(OEt)_3$, Ambetlist-15, PhH, reflux, 12 h; b) (i) NaH, Et_2NCOCl, DMAP, THF, rt , p-TSA, MeOH, rt, 4h; (ii) CH_2Br_2, K_2CO_3, CuO, DMF, reflux, 4h; c) (i) s-BuLi, TMEDA, THF, -78 ^oC; (ii) TBSCl, ImH, DCM, rt, 0.5 h; d) s-BuLi, TMEDA, DMF, THF, -78 ^oC; e) AllylMgBr, Et_2O, -78 ^oC; f) MsCl, TEA, DBU, DCM; g)* ***14****, $CHCl_3$, reflux; h) $(Bu_3Sn)_2O$, AIBN, $PhCH_3$, reflux; i) TBAF, THF, 0 ^oC; j) $(Bu_3Sn)_2O$, $PhCH_3$, 2h, I_2; k)Ag_2O, DMF, BnBr, rt; l) OsO_4, NMO, DCM; m) DBU,*

PhH, reflux; n) 2-acetoxyisobutyryl bromide, CH_3CN, rt; o) OsO_4, NMO, DCM, THF, rt; p) Bu_2SnO, PMBBr, $PhCH_3$; q) Ag_2O, BnCl, DMF; r) DDQ, DCM, H_2O; s) Zn, HOAc; t) NaH, CCl_3CN, THF, 100 ^oC; u) OsO_4, NMO, THF, rt; v) K_2CO_3, MeOH, DCM, reflux; w) H_2/ $Pd(OH)_2$, 1 atm.

2.1b Hudlicky's Approach. (*J. Am. Chem. Soc.* **1995**, *117*, 3643)[11]

Total 14 steps and 2 % overall yield.



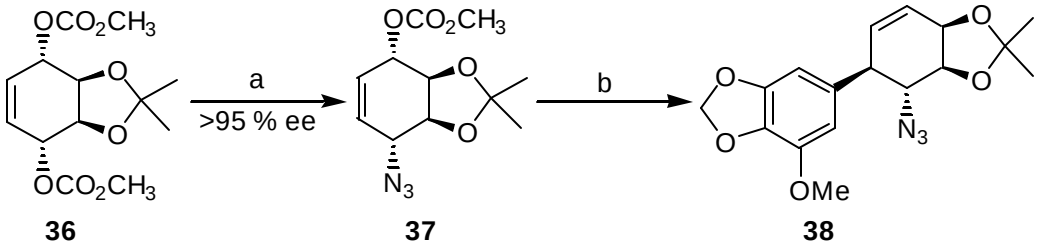


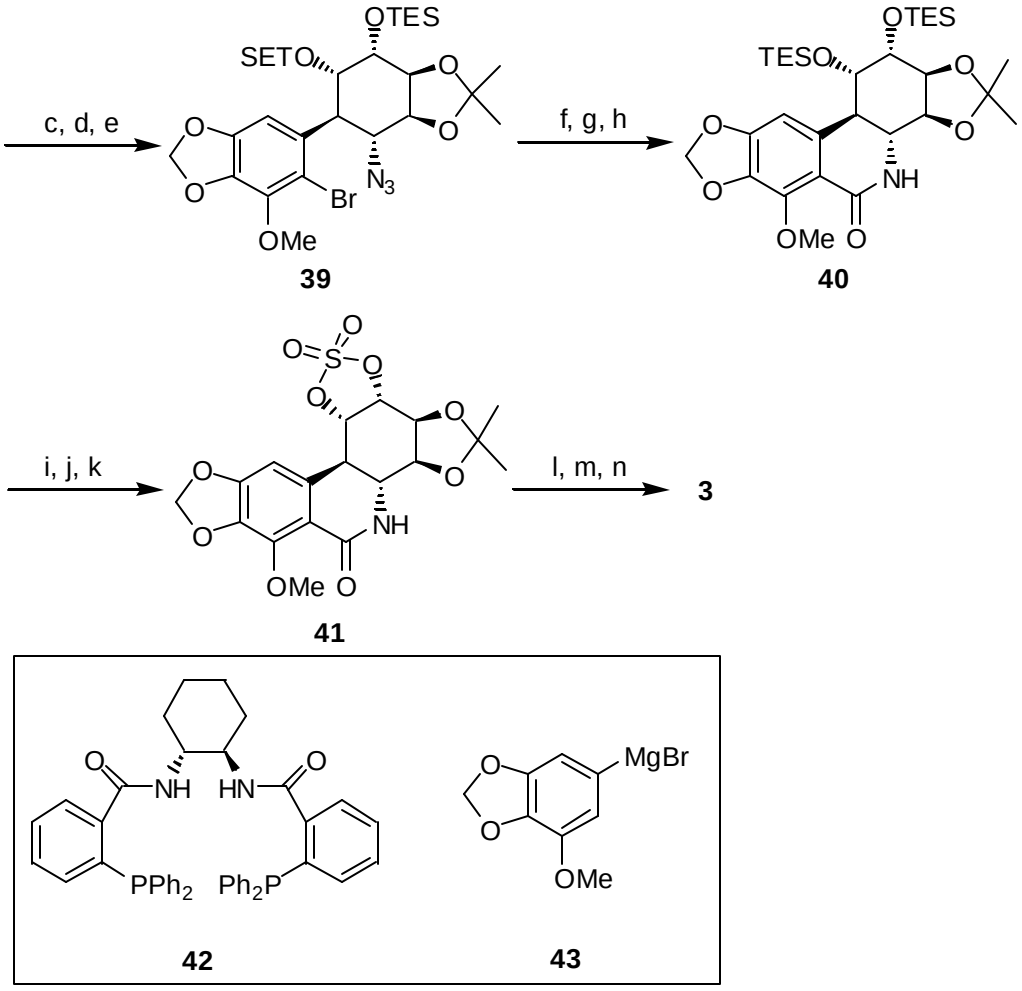
Scheme-II

Reagents and Conditions*: a) Pp-39D, $PhCH_3$; b) $Me_2C(OMe)_2$, TsOH, DCM, rt; c) PhI=NTs, $Cu(acac)_2$, CH_3CN; d) Bu_3SnH, AIBN, THF, reflux; e) s-BuLi, TMEDA, THF, -90 ^oC, CuCN; f) s-BuLi, THF, $(BOC)_2O$; g) Na/anthracene, DME, -78 ^oC; h) TBAF, THF; i) SMEAH, morpholine, -45 ^oC, THF; j) BnBr, K_2CO_3, DMF; k) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, tBuOH, H_2O; l) CH_2N_2; m) HOAc, THF, H_2O, 60 ^oC; n) tBuOOH, $VO(acac)_2$, PhH, 60 ^oC; o) BzONa(cat), H_2O, 100 ^oC; p) H_2, $Pd(OH)_2/C$, EtOAc.*

2.1c Trost's Approach. (*J. Am. Chem. Soc.* **1995**, *117*, 10143)[12]

Total 13 steps and 11 % overall yield.



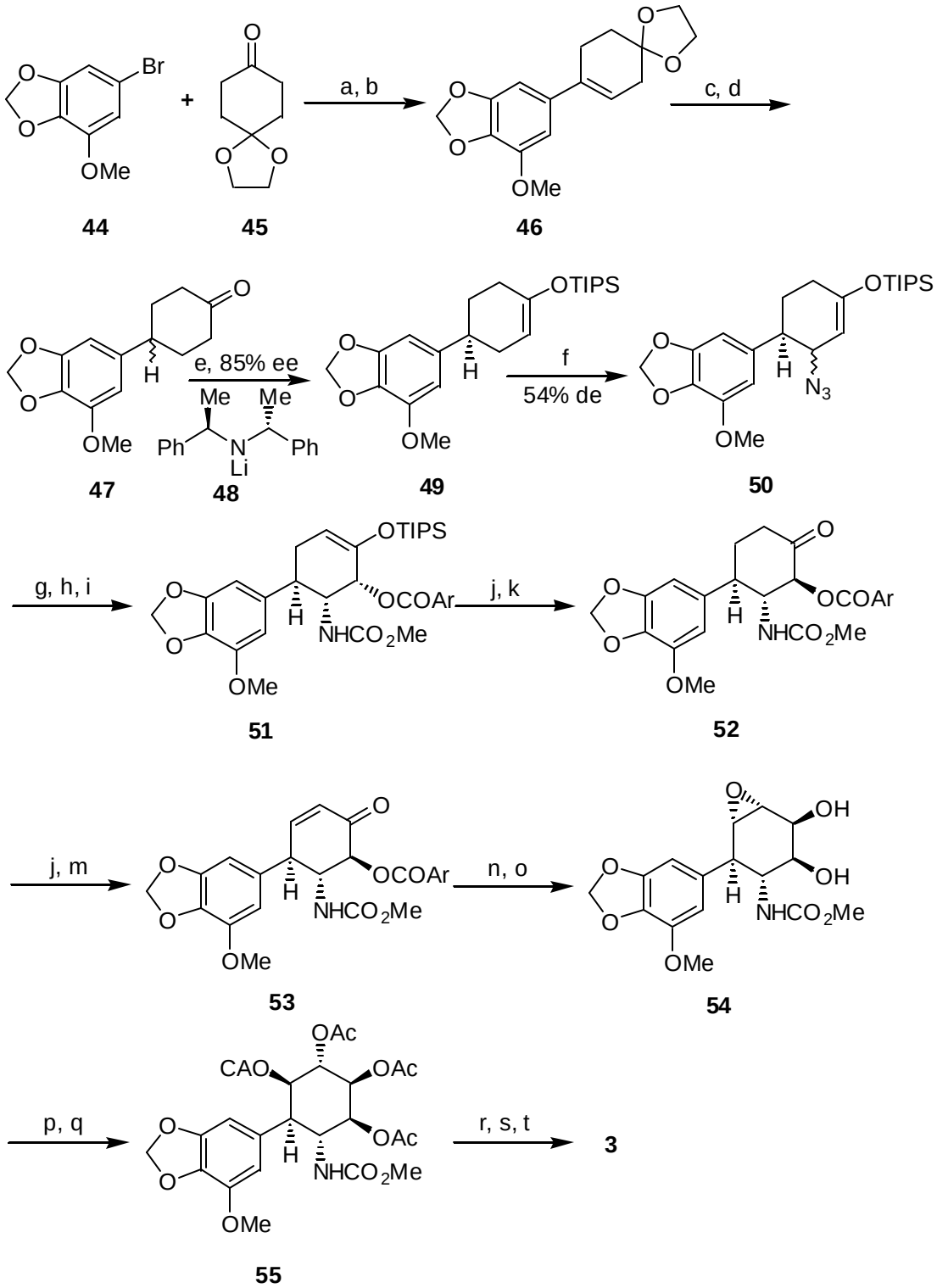


Scheme - III

Reagents and Conditions*: a) (?-$C_3H_3PdCl)_2$, 0.78mol % of* ***42****, $TMSN_3$, DCM, RT; b)* ***43****, CuCN, THE, Ether, 0 ^oC; c) OsO_4, NMO.H_2O, DCM; d) TESOTf, 2,6-lutidine, DCM; e) NBS, DMF; f) $(CH_3)_3P$, THF, H_2O; g) $COCl_2$, THF, TEA; h) t-BuLi, Ether, -78 ^oC; I) TBAF, THF; j) $SOCl_2$, TEA; k) $RuCl_3.H_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O, RT; l) $PhCO_2Cs$, DMF, work up H_2O, cat. H_2SO_4; m) K_2CO_3, MeOH, rt; n) LiI, DMF, 80 ^oC.*

2.1d Magnus's Approach. (*J. Am. Chem. Soc.* **1998**, *120*, 5341)[14]

Total of 21 steps and in 3 % overall yield.

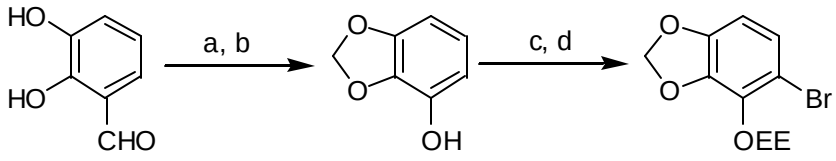


Scheme - IV

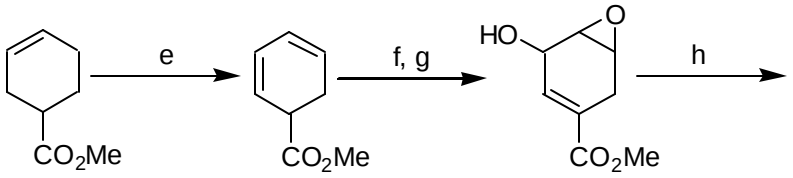
Reagents and conditions: *a) n-BuLi, THF, -78 °C; b) $POCl_3$, DBU, Py; c) H_2/Pd-C, EtOH; d) TsOH, MeOH; e)* ***48****, LiCl, TIPSOTf, THF, -78 °C; f) $(PhIO)_n$, $TMSN_3$, DCM, -15 °C; g) LAH, Et_2O; h) MeOCOCl, Py; i) MCPBA; j) $H_3O^{Å}$; k) KO^{t}Bu, HMPA; l) TMSOTf, TEA; m) $PhSeOCOCF_3$ then H_2O_2; n) $NaHCO_3$, H_2O_2, MeOH; o) L-selectride, THF; p) $PhCO_2Na$, H_2O; q) Ac_2O, Py; r) Tf_2O, DMAP; s) BBr_3; t) NaOMe, MeOH.*

2.1e Rigby's Approach. (*J. Am. Chem. Soc.* **2000**, *122*, 6624)[15]

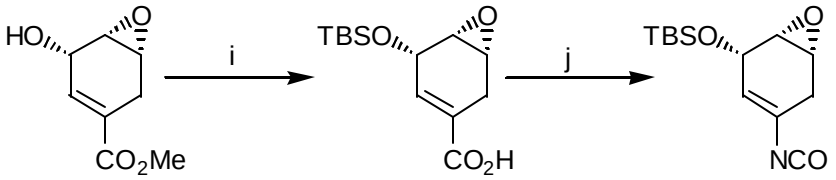
Total of 27 steps and in <1 % overall yield.



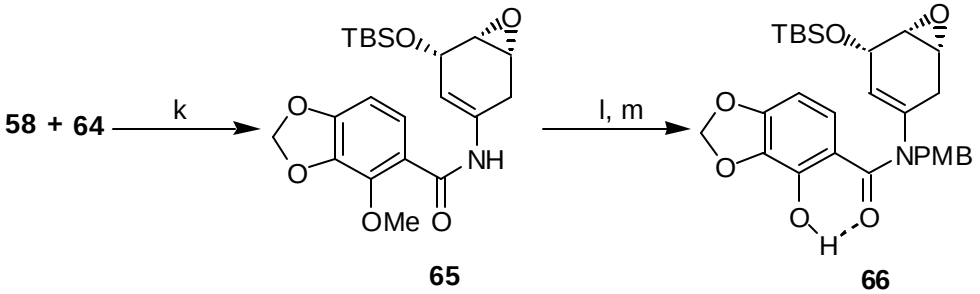
56 **57** **58**



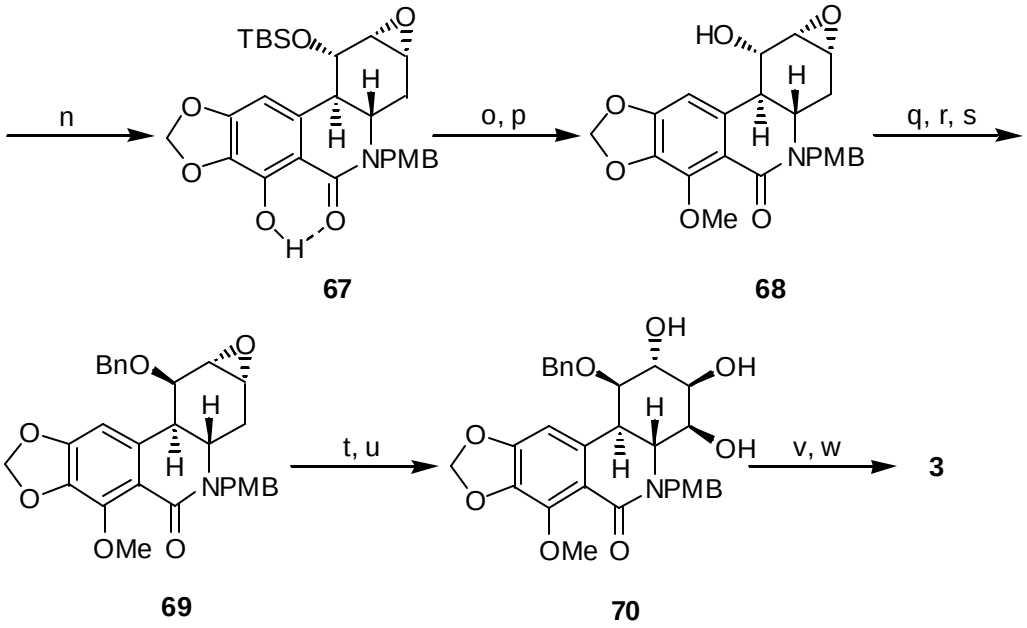
59 **60** **61**



62 **63** **64**



65 **66**



Scheme-V

Reagents and conditions: *a) CH_2Br_2, K_2CO_3, DMF; b) (i) mCPBA; (ii) KOH, MeOH; c) CF_3CO_2Ag, Br_2; d) EVE, PPTs, DCM; e) (i) NBS, AIBN, $PhCH_3$; (ii) Bu_3SnH, $PhCH_3$; f) (i) O_2, Rose Bengal, hn; (ii) $RuCl_2(PPh_3)_2$; g) NaOMe, MeOH; i) (i) TBSCl, ImH, DCM; (ii) LiOH, MeOH; j) DPPA, $PhCH_3$, 110 ^oC; k) nBuLi, THF, -70 ^oC; l) NaH, PMBBr; m) PPTS, MeOH; n) hn, PhH; o) NaH, MeI, THF; p) TBAF, THF; q) Dess-Martin; r) $NaBH_4$, -20 ^oC; s) NaH, BnBr; t) $(PhSe)_2$, $NaBH_4$, H_2O_2, reflux; u) OsO_4, NMO, t-BuOH; v) $Pd(OH)_2/H_2$; w) LiCl, DMF.*

Apart from the successes cataloged above, Haseltine[13] has presented a formal synthesis based on aromatic electrophilic substitution in which he has synthesized optically pure **24**, which is advanced intermediate in Danishefsky's synthesis[10]. Recently, Pettit achieved the synthesis of **3** from more abundant **12**[17].

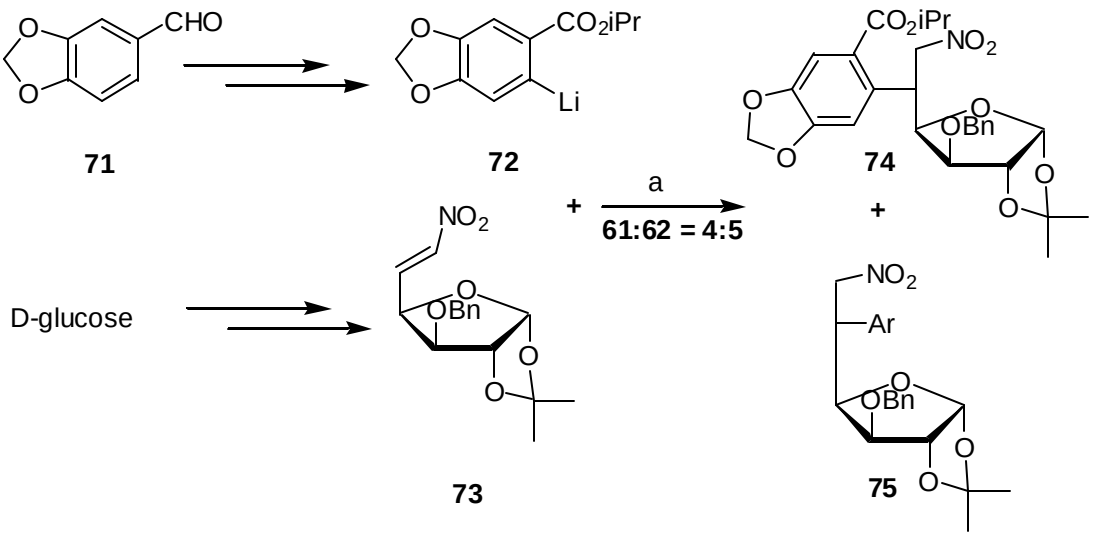
Kim and coworkers[17] have synthesized racemic **3** utilizing Claisen rearrangement as a key step.

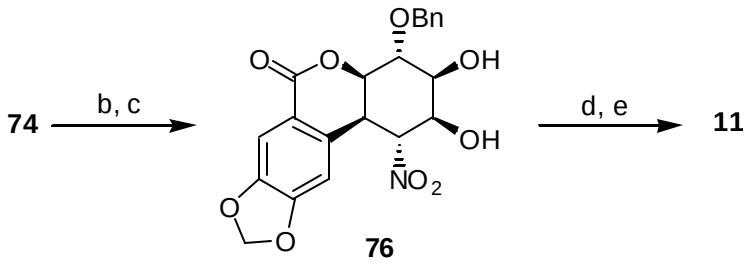
2.2 Synthetic approaches to 7-Deoxypancratistatin.

The first total synthesis of 7-deoxypancratistatin (**11**) was achieved by Paulsen and coworkers[18], en-route to lycoricidine (**13**), prior to its isolation from natural source. In 1995, Hudlicky has reported[11,19] the total synthesis of **11** by utilizing aziridine ring opening with higher order cupprates as a key step, along with the synthesis of **3** which has already been discussed earlier. Keck and coworkers published two different approaches to **11**, one based on 6-exo radical cyclizations of oxime ethers[20], and the other one based on a second generation radical cyclizations of oxime ethers[21]. Recently, Plumet[22] and coworkers synthesized **11**, using the ring opening of vinylsulphone-furan adduct with metallated aromatic system.

2.2a Paulsen's Approach. (*Liebigs. Ann. Chem.* **1983**, 535)[18]

Total of 10 steps and in 1.1 % overall yield starting from 71 and 73.





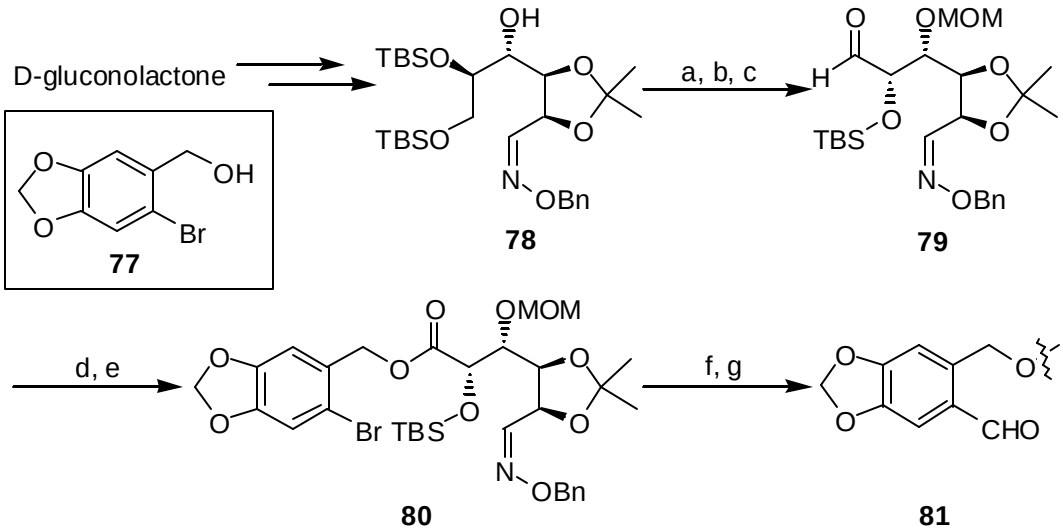
Scheme - VI

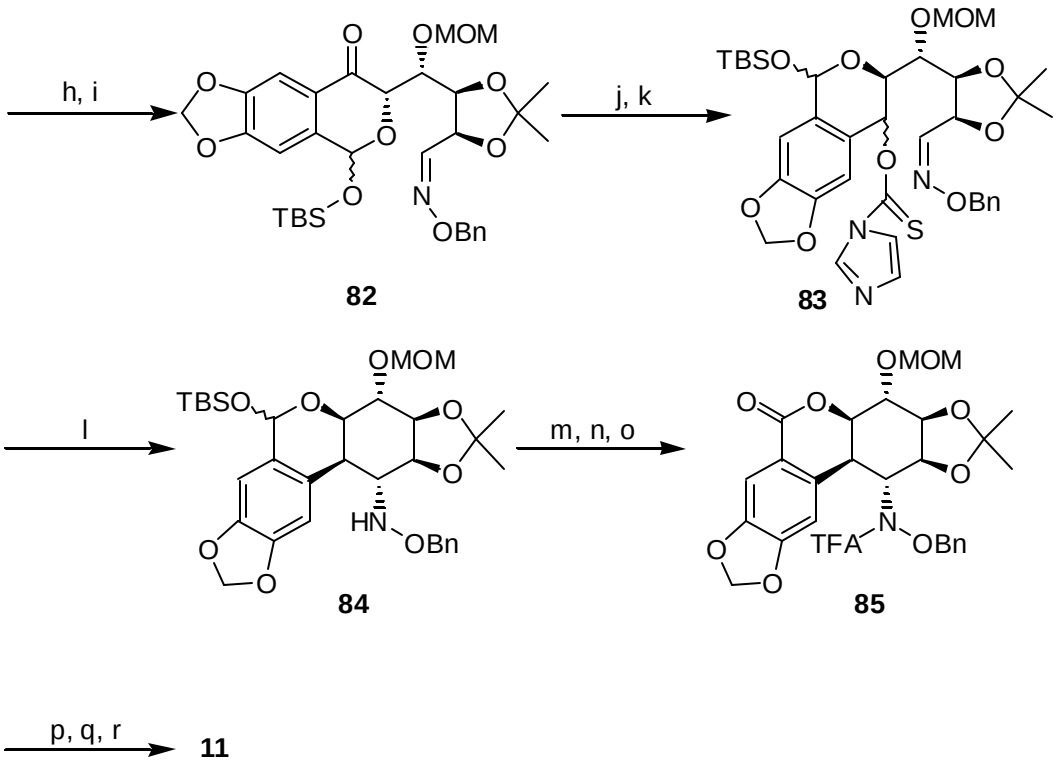
Reagents and conditions: *a) THF, -78 ^{o}C; b) HOAc; c) K_2CO_3, MeOH; d) Pd/H_2, EtOH; e) K_2CO_3, MeOH.*

2.2b Keck's Approaches:

Approach-I (*J. Am. Chem. Soc.* **1995**, *117*, 7289. and *J. Org. Chem.* **1999**, *64*, 4465)[20]

Total of 21 steps and in 7 % overall yield.



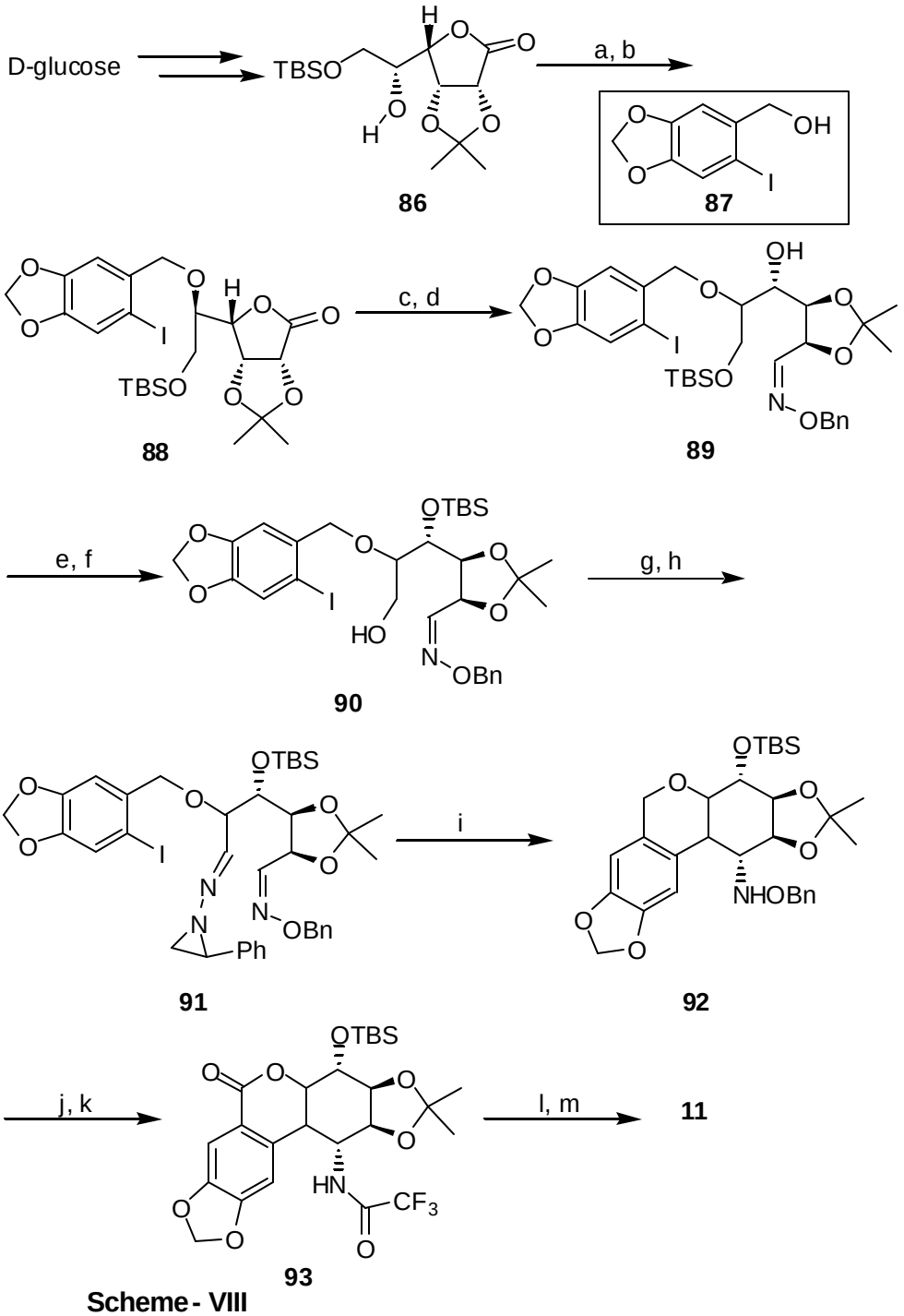


Scheme - VII.

Reagents and Conditions: *a) MOMCl, DIEA; b) HF-Py; c) TPAP, NMO; d) $NaClO_2$, KH_2PO_4; e) PPh_3, DEAD,* ***77****; f) n-BuLi,-98 ^oC to –78 ^oC; g) TPAP, NMO; h) HF-Py; I) TBSCl, ImH; j) $NaBH_4$, MeOH; k) TCDI, DMAP, 1,2-dichloroethane; l) Bu_3SnH, AIBN, $PhCH_3$; m) TFAA, DMAP; n) TBAF, THF; o) TPAP, NMO; p) SmI_2, THF; q) DOWEX-H^+; r) K_2CO_3, MeOH.*

Approach –II: (*J. Org. Chem.* **1998**, *63*, 9164)[21]

Total of 13 steps and in 21 % overall yield.

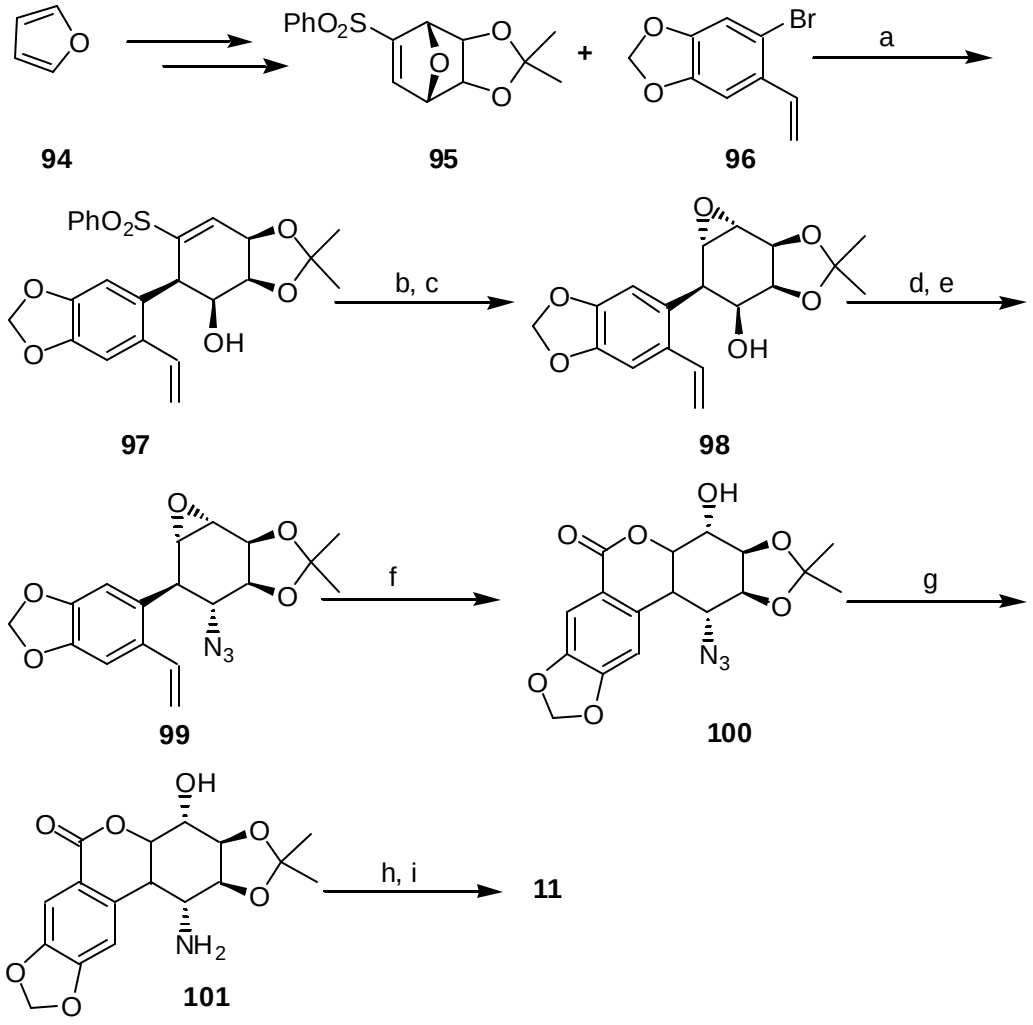


Scheme - VIII

Reagents and Conditions: *a) NaH, Cl_3CCN, THF; b)* ***74****, pTSA, THF, 0 ^oC; c) L-Selectride, DCM, -78 ^oC; d) HCl.H_2NOBn, Py; e) TBSOTf, 2,6-lutidine, DCM; f) HF.Py, THF; g) TPAP, NMO, THF; h) 1-amino-2-phennylaziridine, EtOH, 0 ^oC; I) Ph_3SnH, AIBN, PhH; j) SmI_2, THF then TFAA; k) PCC, DCM; l) $BF_3.OEt_2$, DCM; m) K_2CO_3, MeOH.*

2.2c Plumet's Approach: (*Org. Lett.* **2000**, *2*, 3683)[22]

Total of 19 steps and in 8 % overall yield.



Scheme - IX

Reagents and conditions: *a) n-BuLi, THF, $PhCH_3$, -78 ^oC; b) t-BuOOH, n-BuLi, THF, -78 ^oC; c) Na-Hg, MeOH, THF; d) Tf_2O, Py, DCM, 0 ^oC; e) Bu_4NN_3, PhH; f) $NaIO_4$, $RuCl_3$, CH_3CN, CCl_4, H_2O; g) H_2/Pd-C, 40 psi, MeOH; h) CF_3CO_2H, 0 ^oC; I) K_2CO_3, MeOH, reflux.*

Despite the successes cataloged above, it is clear that in spite of the considerable efforts expended by numerous research groups over many years on the synthesis of these alkaloids, total synthesis of these alkaloids remain particularly formidable targets for synthetic chemists. We have taken up the challenge to develop a short and conceptually new synthesis for **3** and **11**. The foregoing chapters will discuss our progress towards this endeavor.

3. References

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CHAPTER-II

SYNTHETIC STUDIES

TOWARDS PANCRATISTATIN

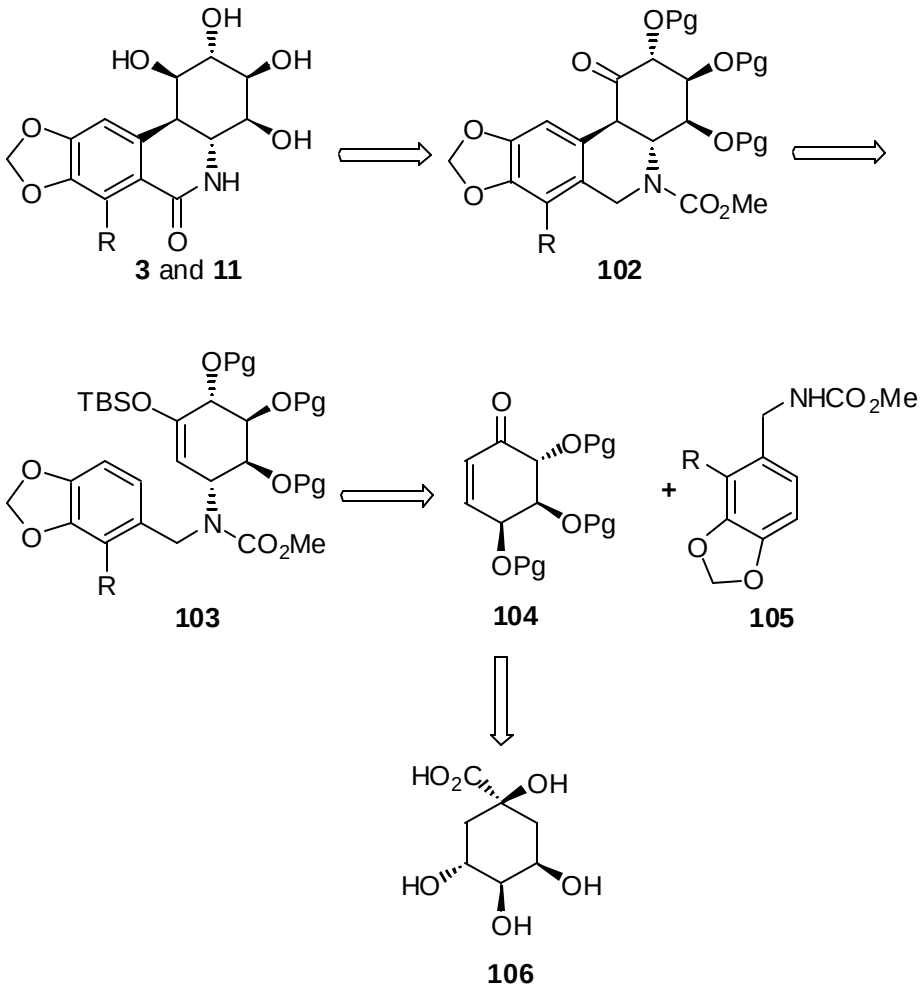
Synthetic Studies towards Pancratistatin

1. Introduction

Due to intriguing pharmacological activities, interesting structural features and scarcity in nature (0.0028% yield in isolation[1]), pancratistatin and 7-deoxypancratistatin have generated considerable attention from the numerous research groups over many years, however, these alkaloids still remain formidable targets for organic synthesis as evident from the discussion appended in the previous chapter. In fact, these alkaloids possess deceptively simple looking molecular structure that present a number of challenges to the capabilities of the contemporary organic synthesis. The principal hurdles in the synthesis include elaboration of *trans* fused BC-ring system and the stereocontrolled installation of the hydroxy functionalities located around the perimeter of the C-ring moiety. We envisaged a new synthetic approach for **3** and **11** utilizing PET-initiated α-arylation of ketones, a new C-C- bond formation strategy developed earlier from our group,[2,3] as a key step and also making use of commercially available D-(-)-quinic acid as the chiral source to build the highly oxygenated C-ring system.

2. Retrosynthetic Analysis and Design.

We viewed our new synthetic approach for **3** and **11** through the retrosynthetic route as outlined in the Scheme-X. The key step envisaged in our approach was the photoinduced electron transfer (PET) initiated intramolecular carbocyclization of silylenolethers to a tethered electron rich aromatic ring (**103** to **102**). We anticipated the cyclization would undergo in a *trans* fashion, owing to the stability of [6,6] *trans*-ring fusion over [6,6] *cis*-ring fusion.



Scheme-X

The requisite silylenolether precursor **103** for this crucial transformation could be prepared by the conjugate addition of *N*-metallated piperonyl amine carbamate **105** to the enone **104**. We expected that the conjugate additions would undergo in *trans* fashion as observed in the conjugate addition on various substituted cyclohexenones.[4] The carbonyl functionality at C_6 position could be introduced at relatively later stages of the synthesis to avoid any unforeseen complications in the

cyclization step. The enone precursor **104** can be obtained from D-(-)-quinic acid through simple synthetic transformations.

Since our synthetic endeavor towards pancratistatins involves α-arylation of ketones as key the step, it would be appropriate to highlight the salient features of the protocol developed in our laboratory for the generation of arene radical cation and its intramolecular cyclization with silylenol ethers.

3. a -Arylation of ketones- Our Concept and Protocol.

α-Arylation of ketones, although infrequently used, is an important C-C bond formation strategy, which could be used for the rapid access of otherwise inaccessible molecules. Particularly, intramolecular α-arylation of ketones could provide an easy access to benzannulated carbocyclic compounds. Pandey et al[5] have developed a new protocol for α-arylation of ketones following their previous work on the generation of arene radical cations through photoinduced electron transfer reactions and subsequent intramolecular cyclization with various heteroatom nucleophiles as shown in Figure-3. The generation of arene radical cation involved single electron transfer from the excited state of an electron rich arene to the ground state of electron deficient aromatic system like 1,4-dicyanonaphthalene (DCN).

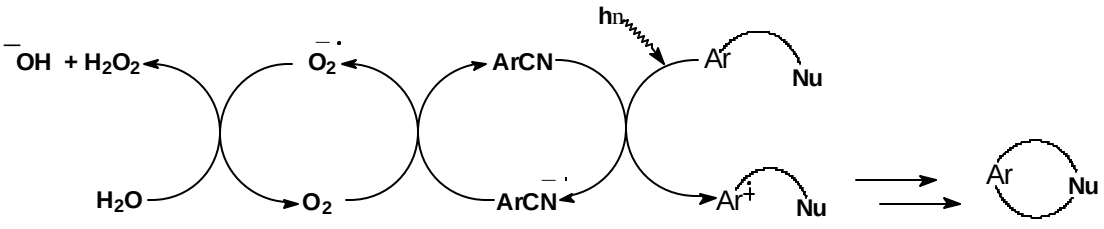
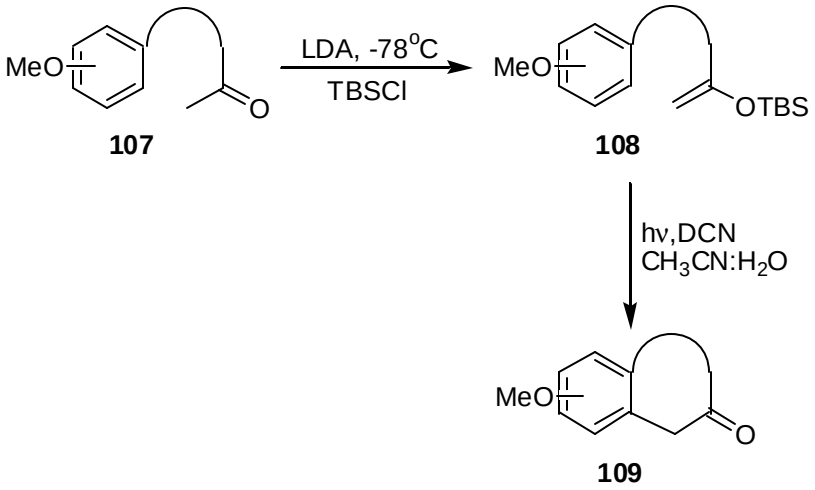


Figure- 3

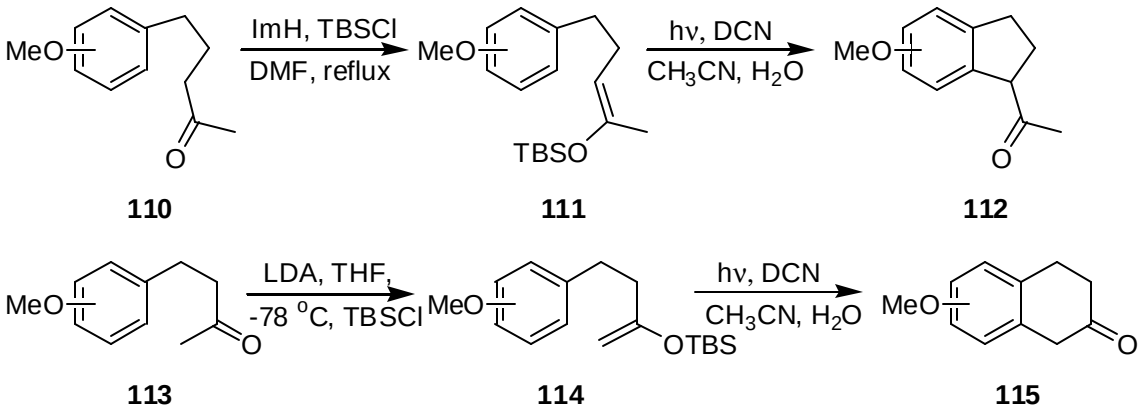
The arene radical cation thus generated was utilized for the direct aromatic nucleophilic substitution reaction of aromatic ring with highly polarized enol silyl ether as shown in Scheme-XI.



107 **108** **109**

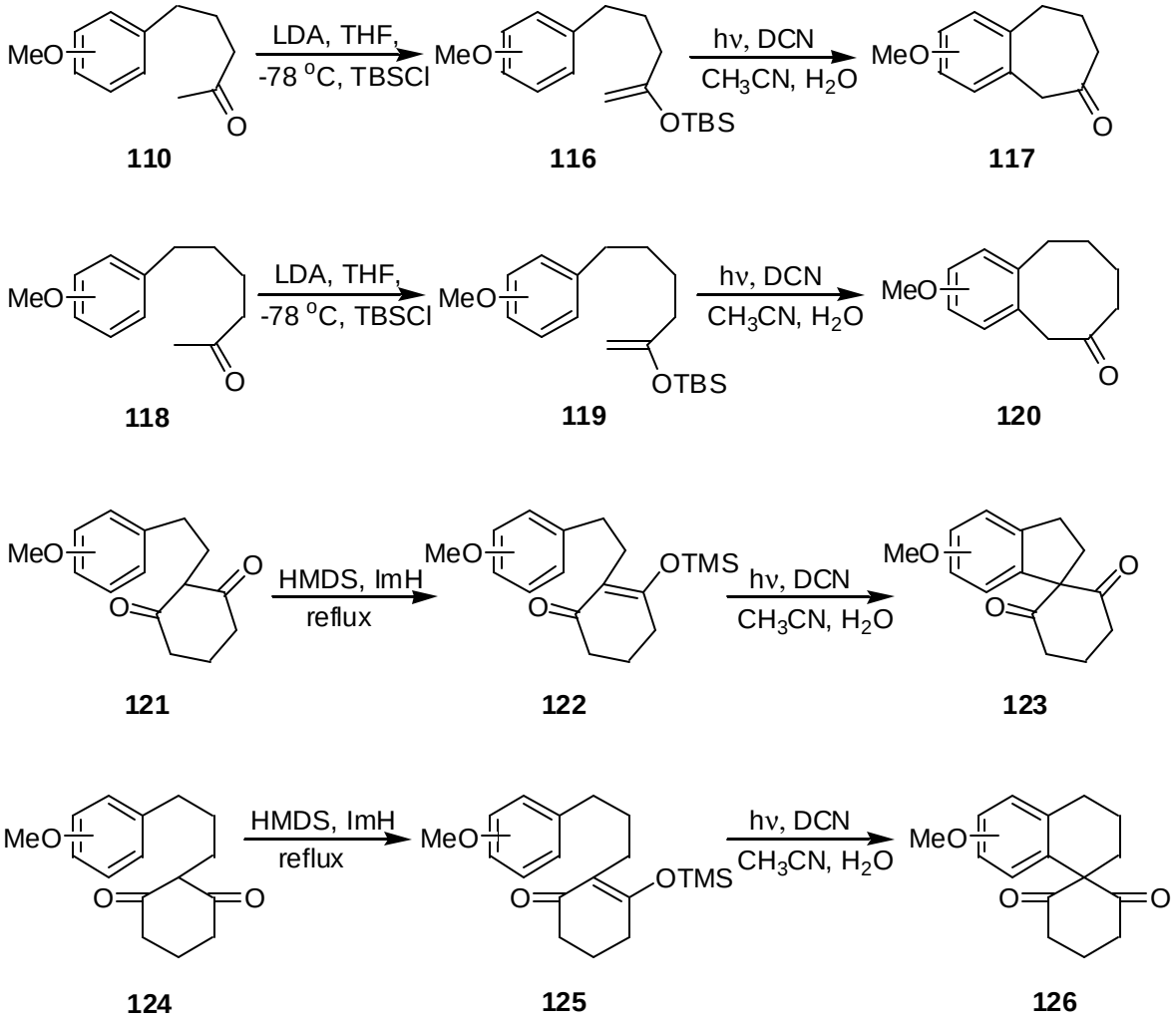
Scheme-XI

The efficiency of this methodology has been demonstrated by constructing five, six, seven and eight membered benzannulated and benzospiroannulated compounds[3]. (Scheme-XII)



110 **111** **112**

113 **114** **115**



Scheme-XII

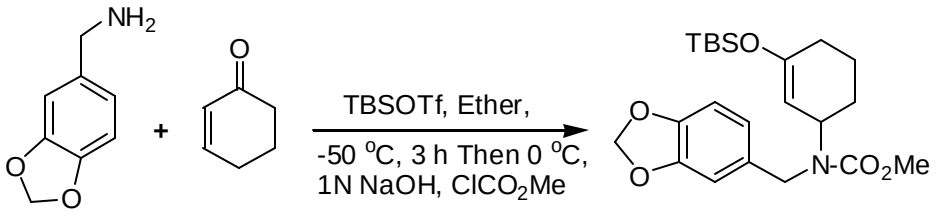
The success of the methodology prompted us to examine its potentiality in the total synthesis of natural products. For this purpose we chose pancratistatins as our synthetic targets.

Results and discussion

To begin our study, we intended to check the efficiency of this methodology by synthesizing the phenanthridone skeleton, the carbon framework of pancratistatins.

4. Synthesis of Phenanthridone Skeleton.

The synthesis of phenanthridone skeleton involves the preparation of silylenolether **129** followed by cyclization by PET reaction. It is known in the literature[6] that conjugate addition with any nucleophile to cyclohexenone in the presence of TBSOTf results in the formation of silylenolether having the nucleophiles at the β-position. Keeping this fact in mind, we reacted piperonyl amine (**127**) with 2-cyclohexen-1-one (**128**) in the presence of TBSOTf in the ether solvent at –50 ^{o}C to form the corresponding silylenolether ammonium complex. The complex was basified to release the corresponding silylenolether having secondary amine at the β-position. The secondary amine was protected as its methyl carbamate by reacting with methyl chlorofomate affording required silylenolether precursor **129**.



127 **128** **129**

Scheme-XIII

The IR spectrum of the compound **129** showed strong bands at 1693 cm^{-1} and 1251 cm^{-1} indicating the presence of both carbamate and silylenolether functionalities, respectively.

^{1}H NMR spectrum displayed a multiplet at δ6.8 integrating for three protons, which were assigned for the aromatic protons. The methylenedioxy protons appeared as a sharp singlet at δ5.90. A multiplet between δ5.05- 4.65, integrating for one proton, was assigned to –N-C<u>H</u>- proton of the cyclohexyl ring. A broad singlet at δ4.60 was attributed to the olefinic proton of the silylenolether moiety. The benzylic protons appeared as two doublets at δ4.35 and δ4.28 (J = 17 Hz), respectively. The three methyl protons of the carbomethoxyl group appeared as a singlet at δ3.65. A multiplet between δ2.05- 1.20, integrating for six protons, could be assigned to the remaining six methylenic protons of the cyclohexyl ring. A singlet at δ0.85, integrating for nine protons, was assigned to *t*-butyl of the TBS group. The two singlets at δ0.05 and δ0.00, integrating for three protons each, were assigned to the dimethyl protons of the TBS group.

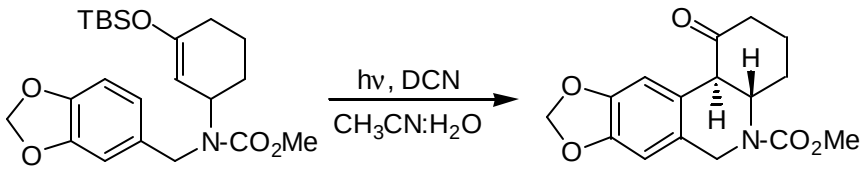
^{13}C NMR spectrum of **129** revealed a total of nineteen signals at δ157.0, 154.0, 147.4, 145.9, 133.7, 119.2, 107.7, 106.9, 104.8, 100.5, 53.2, 52.3, 45.7, 29.2, 27.7, 25.3, 20.6, 17.7, and -4.9. In the DEPT spectrum, the three aromatic methine carbons appeared at δ119.2, 107.7 and 106.9, respectively. The olefinic methine carbon of silylenolether appeared at δ104.8. The methylene carbon of the methylenedioxy group appeared at δ100.5. The methine carbon of –<u>C</u>H-N- appeared at δ53.2 and the methyl carbon of the carbamate moiety appeared at δ52.3. The methylenic carbon at δ45.7 was assigned to the benzylic carbon and the other three methylenic carbons (δ29.2, 27.7, 20.6) were assigned to the three methylene groups

of cyclohexyl ring. The signal at δ25.3 was assigned to the three methyl carbons of t-butyl of TBS group. The other two methyl carbons attached to Si atom of TBS group appeared at δ-4.9. The quaternary carbon (which is absent in DEPT spectrum) at δ157.0 was assigned as carbonyl carbon of the carbamate moiety. The three quaternary carbons at δ154.0, 147.4, and 145.9 were attributed to the three quaternary aromatic carbons. The olefinic quaternary carbon of silylenolether appeared at δ133.7. The quaternary carbon at δ17.7 was assigned to *t*-butyl quaternary carbon of the TBS group.

Mass spectrum of **129** displayed molecular ion peak at 419 along with the peaks at 362 (M^+-57), 305, 252 and 211. The base peak was noticed at 284.

4. 1. PET Cyclization of 129 to Phenanthridone skeleton 130.

The PET cyclization was carried out by irradiating a mixture of **129** (0.5 g, 1.19 mmol) and DCN (0.05 g, 0.28 mmol) in acetonitrile:water (24:1, 250 mL) solvent system using Hanovia medium pressure lamp (450 W, Pyrex filter, >280 nm) as UV radiation source for 6 h. The progress of the reaction was monitored periodically by TLC. Concentration of the resulting photolysate followed by column chromatographic purification gave cyclized product **130** in 72 % yield.



129 **(±)-130**

Scheme-XIV

The IR spectrum of **130** showed strong absorption bands at 1715 cm^{-1} and 1695 cm^{-1} indicating the presence of both keto carbonyl group and carbamate functionality.

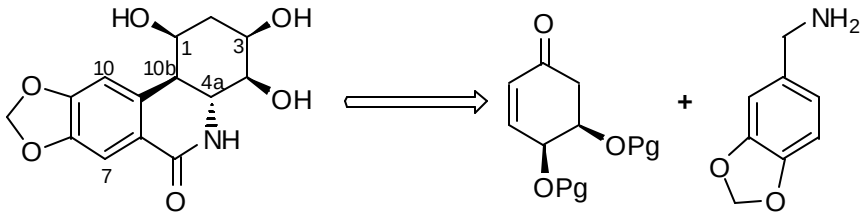
^{1}H NMR spectrum displayed two singlets at δ6.65 and 6.45, integrating to one proton each, which were assigned to H_7 and H_{10} aromatic protons. The methylenedioxy protons (-O-C$\underline{H}_2$-O-) were observed as a sharp singlet at δ5.95. A multiplet between δ5.0-4.50, integrating for two protons, was assigned to the two H_6 benzylic protons. A doublet at δ4.20 (J = 12.5 Hz) was assigned as H_{10b} proton, confirming the BC *trans* ring fusion. A multiplet between δ3.85- 3.7, integrating for four protons, was assigned as three of the methylcarbamate protons and one H_{4a} proton. The two H_2 protons appeared as a multiplet at δ2.3. A multiplet between δ2.0- 1.5, integrating for four protons, was assigned to two protons each of H_3 and H_4 protons.

^{13}C NMR spectrum showed a total of sixteen carbon signals at δ209.0, 155.4, 147.2, 147.1, 125.0, 122.7, 106.7, 106.4, 101.0, 54.0, 52.6, 52.0, 42.6, 37.9, 24.9 and 22.0. DEPT experiment revealed the presence of six quaternary carbon signals at δ209.0, 155.4, 147.2, 147.1, 125.0 and 122.7. These quaternary carbons were assigned to C_1 carbonyl (δ209.0), carbonyl of carbamate (δ155.4) and four aromatic quaternary carbons (δ147.2, 147.1, 125.0 and 122.7). Two signals at δ106.7 and 106.4 were assignable to two aromatic methine carbons (C_7 and C_{10}). The methylenedioxy carbon appeared at δ101.0 and the benzylic methylenic carbon (C_6) appeared at δ42.6. The three methylenic carbons of the C-ring appeared at δ37.9, 24.9 and 22.0, respectively.

Mass spectrum **130** showed molecular ion peak at 303 (50) and base peak at 42. The other fragments were observed at 288 (M^+-15, 24), 244 (M+-59, 26), 232 (27), 188 (32), 174 (33) and 59 (94)

5. Synthesis of (+)-2,7-Dideoxypancratistatin (131).

The success of the above reaction prompted us to prepare (+)-2,7-dideoxypancratistatin (**131**) as an advanced model of (+)-7-deoxypancratistatin (**11**). Our synthetic plan to **131** is depicted in the following Scheme-XV.

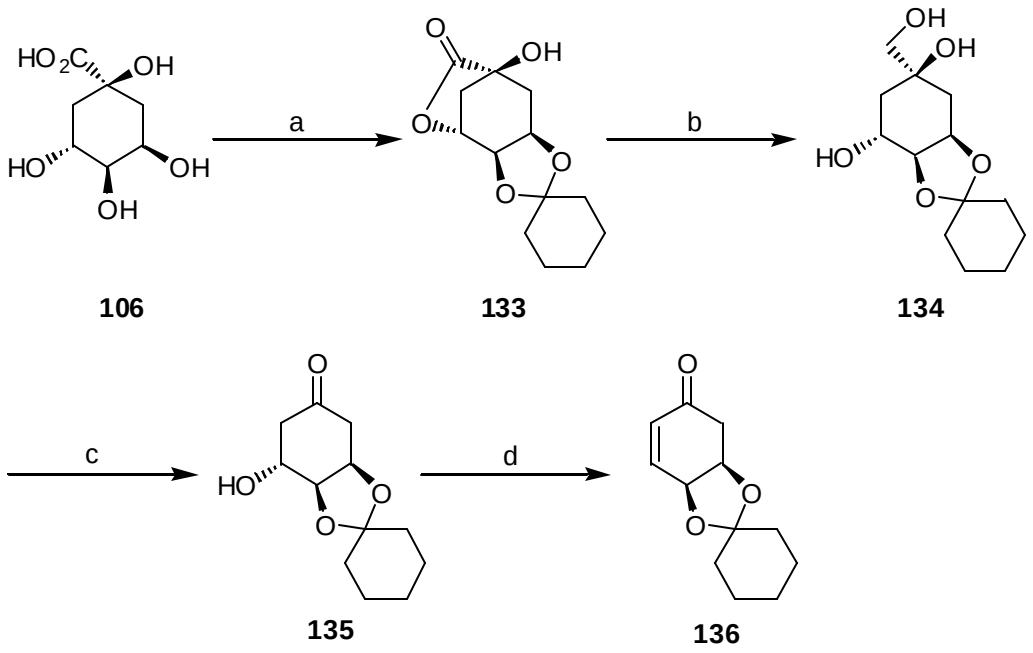


131 **132** **127**

Scheme-XV

Our first task was to prepare a suitably protected 4,5-dihydroxy protected enone **132** from D-(-)-quinic acid. The synthesis of cyclohexylidine protected enone **136** was achieved in four steps as shown in the Scheme-XVI.

First, we lactonized **106** by refluxing with a mixture of cyclohexanone, p-TSA (catalytic), DMF in benzene under Dean-Stark conditions for four hours. The usual work up and the crystallization of the crude product from pet ether: acetone gave **133** in 95 % yield.



106 **133** **134**

135 **136**

Scheme-XVI

Reagents and conditions: *a) Cyclohexanone, p-TSA, PhH, DMF, reflux, 4 h, 95 %; b) $NaBH_4$, EtOH, rt, 24 h, 90 %; c) $NaIO_4$, H_2O, 0 ^oC, 0.5 h; d) MsCl, TEA, DCM, 0 ^oC, 1.5 h, 90 %.*

The IR spectrum of **133** showed strong absorption band at 3429 cm^{-1} and 1767 cm^{-1}, characteristics of hydroxy and lactone functionalities, respectively.

^1H NMR spectrum of **133** displayed a doublet of doublet at δ4.72 (*J* = 6.0, 2.5 Hz), assignable to H_5 proton. The H_3 and H_4 protons appeared as ddd at δ4.46 (*J* = 7.0, 7.0, 3.0 Hz) and δ4.28 (*J* = 6.0, 2.0, 1.2 Hz), respectively. The C_1 hydroxy proton appeared as a singlet at δ3.15. A doublet at δ2.63 (*J* = 11.8 Hz), a multiplet between δ2.45- 2.23 and a doublet of doublet at δ2.16 (*J* = 14.6, 3.0 Hz) were assigned to four methylene protons present at C_2 and C_5 positions. The complex multiplet

between δ1.72- 1.20, integrating for ten protons, was assigned to the cyclohexyl protons of the cyclohexylidene ring.

^{13}C NMR spectrum of **133** displayed a total of 13 signals at δ178.6, 110.2, 75.6, 71.3, 71.2, 70.7, 37.9, 36.5, 34.0, 33.3, 24.6, 23.5 and 23.1. DEPT experiment suggested the presence of three quaternary carbon signals at δ178.6, 110.2 and 71.3 which were assigned to the lactone carbonyl, one quaternary carbon at cyclohexylidine group and C_1 carbon, respectively. Three methine carbons at δ75.6, 71.2 and 70.7 were assigned as C_5, C_3 and C_4, respectively. The seven methylene carbons at δ37.9, 36.5, 34.0, 33.3, 24.6, 23.5 and 23.1, were assigned to C_2, C_6 and five methylenic carbons present in the cyclohexylidine moiety.

The mass spectrum of **133** showed molecular ion peak at 254 (7) and base peak at 55. The other fragments were observed at 225 (10), 211 (53), 139 (10), 111 (20), and 95 (23).

The reduction of **133** was carried out by reacting with sodium borohydride in ethanol at room temperature for 24 h followed by quenching with brine and usual workup afforded **134** in 90 % yield.

^{1}H NMR spectrum of **134** displayed a ddd at δ4.48 (J = 5.9, 3.9, 2.9 Hz), which was assigned as H_4 proton. Another ddd at δ4.10 (J = 10.2, 6.3, 4.3 Hz) was assigned to H_5 proton. The H_3 proton appeared as a triplet like doublet of doublet at δ3.97 (J = 6.3 Hz). The methylene protons (attached to C_1) appeared as a doublet of doublet at δ3.45 (J = 20, 10.8 Hz). The three hydroxyl protons appeared as a broad singlet at δ2.6. The signals at δ2.32 (ddd, J = 15.6, 2.5, 2.5 Hz), 2.00 (ddd, J = 13.7, 4.9, 2.4 Hz), 1.88 (d, J = 3.4 Hz) and 1.80 (d, J = 3.4 Hz) were assigned to methylene protons attached to C_2 and C_6. The ten-cyclohexylidene protons appeared as a complex multiplet between δ1.79- 1.25.

^{13}C NMR spectrum of **134** showed a total of thirteen signals at δ109.5, 79.5, 73.6, 72.3, 69.8, 68.9, 38.0, 37.8, 34.4, 32.9, 24.7, 23.7, 23.3. DEPT experiment indicated the presence of two quaternary carbons, one at δ109.5, assignable to quaternary carbon of cyclohexylidene moiety and the other one at δ72.3, assignable to C_1. The three methine carbon signals at δ79.5, 73.6, 68.9 were assigned to C_3, C_4 and C_5 carbons. The methylene carbon attached to C_1 appeared at δ69.8. The seven methylene signals at δ38.0, 37.8, 34.4, 32.9, 24.7, 23.7 and 23.3 were assigned to C_2, C_6 and five methylenic carbons of cyclohexylidene moiety.

Mass spectrum of **134** showed molecular ion peak at 258 (4) and base peak at 55. The other fragments were observed at 229 (4), 215 (17), 197 (4), 143 (8), 125 (10), 107 (13), 99 (28), 79 (33) and 69 (40).

The compound **134** was subjected to periodate cleavage with $NaIO_4$ in water at room temperature. After the reaction was over, extraction with ethyl acetate and column chromatographic purification of the residue gave corresponding β-hydroxyl ketone **135** in 90 % yield.

The IR spectrum of **135** displayed strong absorption bands at 3460 cm^{-1} and 1711 cm^{-1}, characteristic of the hydroxyl and keto carbonyl functionalities, respectively.

^1H NMR displayed two multiplets, one at δ4.70, integrating for one proton, which was assigned to H_5 and the other one at δ4.25, integrating for two protons, was assigned to H_3 and H_4 protons. Another multiplet appearing between δ2.80-2.30, integrating for four protons, was assigned to H_2 and H_6 protons. The β-hydroxyl

proton appeared as a broad singlet at δ1.90. The ten cyclohexylidene protons appeared as a complex multiplet between δ1.75- 1.25.

^{13}C NMR displayed a total of twelve peaks at δ208.8, 109.1, 74.3, 71.5, 67.7, 41.4, 40.0, 35.9, 32.9, 24.8, 23.6 and 23.2. DEPT experiment revealed the presence of two quaternary carbons one at δ208.8, assignable to C_1 carbonyl and another one at δ109.1, assignable to the quaternary carbon of cyclohexylidine moiety. The three methine carbons at δ74.3, 71.5 and 67.7 assignable to C_3, C_4 and C_5 carbons. The spectrum also had seven methylene carbons assignable to C_2, C_6 and five methylenic carbons of cyclohexylidene moiety.

The mass spectrum of **135** showed molecular ion peak at 226 (2) along with base peak at 55. The other fragments were observed at 197 (1), 183 (4), 111 (2), 81 (2), and 69 (14).

The β-elimination of **135** by treating it with MsCl and triethylamine in dry DCM at 0 ^{o}C for 1 h followed by usual workup and column chromatographic purification gave enone **136** in 90 % yield.

The IR spectrum of **136** showed strong absorption band at 1686 cm^{-1}, indicating the presence of enone carbonyl in the molecule.

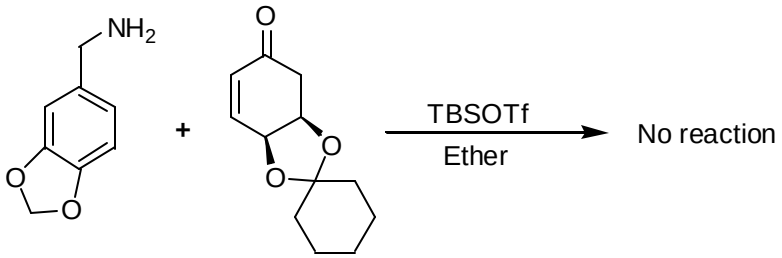
In the ^{1}H NMR spectrum; a doublet of doublet at δ6.65 (J = 10.3, 2.0 Hz), integrating for one proton, is attributed to H_3 olefinic proton. The H_2 olefinic proton appeared as a doublet at δ6.0 (J = 10.3 Hz). A multiplet at 4.7, integrating for two protons, was attributed to H_4 and H_5 protons. A doublet of doublet between δ3.05-2.85 (J = 17.6, 2.5 Hz) was assigned to one of the H_6 protons. Another doublet of

doublet between δ2.75- 2.10 (J = 17.6, 3.4 Hz) was assigned to the other H_6 proton. The cyclohexylidene protons appeared as a complex multiplet between δ1.75- 0.75.

The ^{13}C NMR of **136** consisted a total of eleven signals at δ195.4, 146.0, 128.2, 110.1, 72.7, 70.3, 38.5, 37.1, 35.6, 24.5, and 23.4. The DEPT experiment revealed the presence of two quaternary carbons at δ195.4 and 110.1, which were assigned to C_1 carbonyl carbon and the cyclohexylidene quaternary carbon. The C_3 olefinic methine carbon appeared at δ146.0 and the C_2 olefinic methine carbon appeared at δ128.2. The C_4 and C_5 methine carbons appeared at δ72.7 and 70.3, respectively. The five methylene carbon signals at δ38.5, 37.1, 35.6, 24.5 and 23.4 were attributed to C_6 and cyclohexylidene methylene carbons.

The mass spectrum of **136** possessed molecular ion peak at 208 (43) and base peak at 165. The other fragments were observed at 179 (27), 111 (10), 94 (16), 66 (47) and 55 (61).

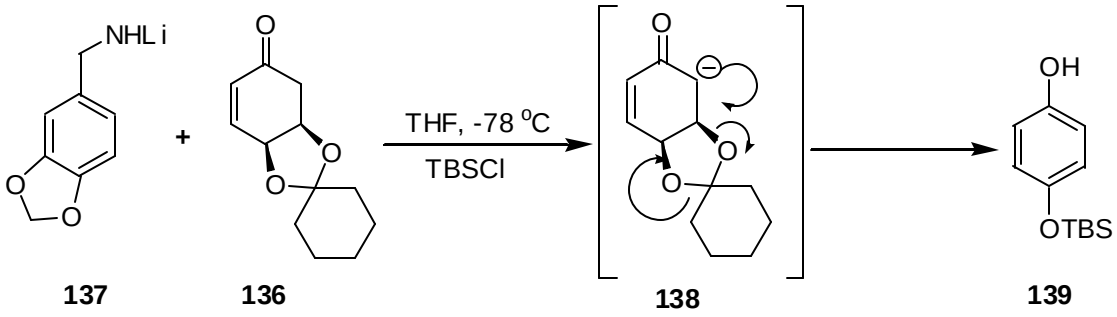
Now, the stage was set to carry out the conjugate addition of piperonyl amine on to **112**. The enone **136** was reacted with piperonyl amine and TBSOTf in ether. The reaction failed to give any product even at elevated temperature. The change of solvent to THF also did not help. So, it was presumed that the nucleophilicity of piperonyl amine might not be sufficient to overcome the stereoelectronic repulsion exerted on to enone by the C_3 and C_4 oxygen functionalities.



127 **136**

Scheme-XVII

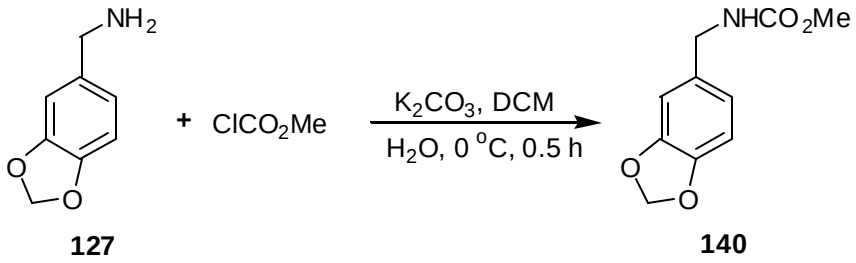
To counter this problem, we used lithium piperonyl amide (prepared by the treatment of piperonyl amine with n-BuLi) as nucleophile in dry THF at –78 °C. Unfortunately, this reaction resulted in the aromatization of the enone. The piperonyl amide anion acted as a base, which deprotonated one of the C_6 protons followed by β-elimination and aromatization.



137 **136** **138** **139**

Scheme-XIII

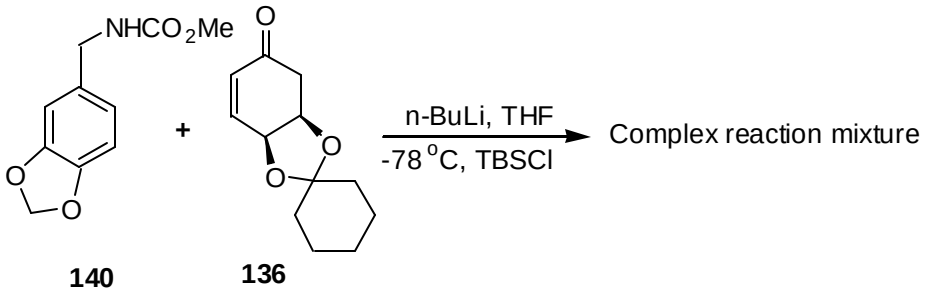
To reduce the basicity of the piperonyl amide anion and to have optimum nucleophilicity, we decided to stabilize the anion with an electron-withdrawing group on the nitrogen atom. Therefore, we protected the piperonyl amine (**127**) with methyl carbamate group by reacting with methyl chloroformate and K_2CO_3 in DCM solvent at 0 °C. The usual work up and crystallization from ethanol afforded the carbamate **140** in 93 % yield.



127 **140**

Scheme-XIX

The methyl carbamate, thus, prepared was treated with n-BuLi to form the corresponding amide anion. To this, the enone solution in THF was added at –78 °C followed by quenching with TBSCl. The reaction resulted in the formation of a complex mixture in which mono TBS protected hydroquinone **139** was one of the products. Variation of the temperature, change of the solvent and addition of HMPA also did not favor the reaction.



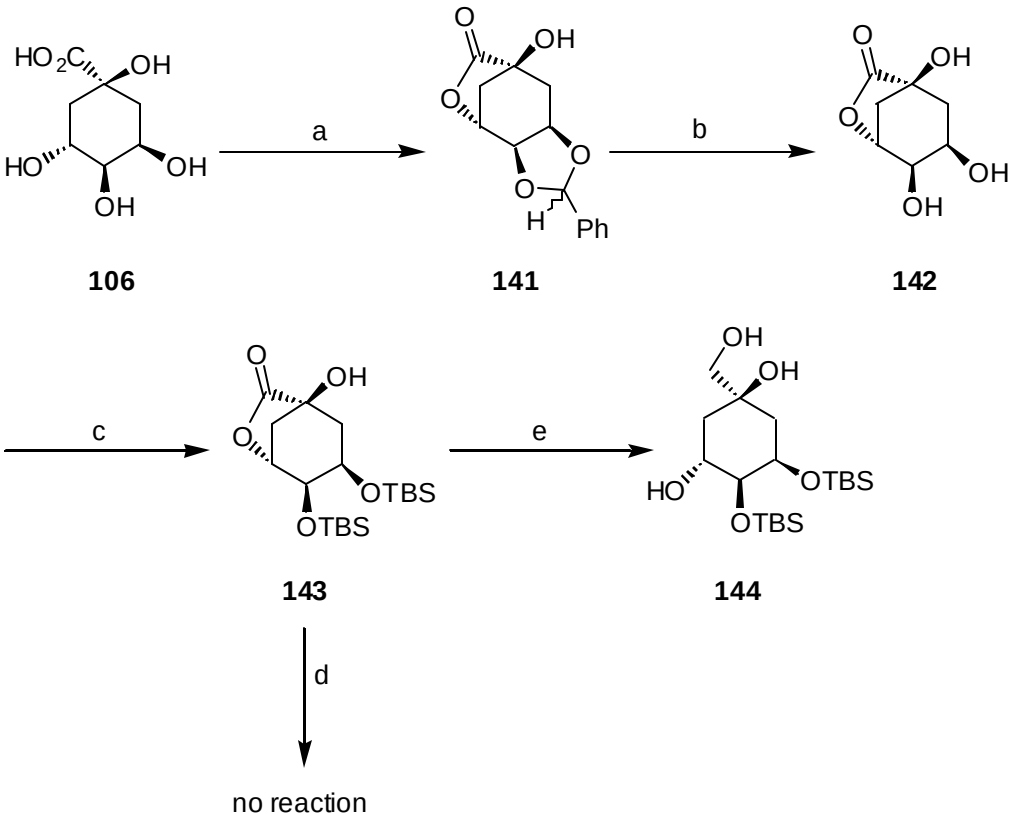
140 **136**

Scheme-XX

We felt that the electronic assistance exerted by the cyclohexylidene protecting group (as shown in the Scheme-XVIII) might be responsible for the increased acidity of the C_6 protons of the enone. In this context, we anticipated that the change of protecting group might be of some help. We chose TBS as our choice of protecting group as it would be stable towards the variety of basic reaction

conditions as well as under various redox reaction conditions and also could be removed under very mild condition using TBAF (tetra n-butyl ammonium fluoride) at room temperature.

Towards this endeavor, the following reaction sequence was adopted. The lactonization was carried out with benzaldehyde to form the benzylidine lactone **141**. Hydrogenation of **141** would produce the corresponding lactone **142**, which on TBS protection followed by lactone reduction produced **144**. The compound **144** could easily be converted into corresponding enone in two steps as described previously. (page no. 32)



Scheme-XXI

Reagents and Conditions: *a) PhCHO, PhH, DMF, pTSA, reflux, 2 h, 80 %; b) H_2/Pd-C, EtOH, 1 atm, 92 %; c) TBACl, ImH, DMAP, DMF, rt, 72 %; d) $NaBH_4$, EtOH, rt; e) LAH, THF, 0 ^oC to reflux, 20 h, 30 %.*

The lactone **141** was prepared by refluxing a mixture of quinic acid, benzaldehyde and DMF in benzene under Dean-Stark condition with a catalytic amount of p-TSA. Usual work up and column chromatographic purification gave diastereomeric mixture (3:1) of the benzylidine latone **141** in 80 % yield.

The IR spectrum of **141** showed strong absorption bands at 3439 cm^{-1} and 1787 cm^{-1}, characteristics of the hydroxyl and lactone functionalities, respectively.

The ^1H NMR exhibited a multiplet between δ7.6- 7.3, integrating for five protons, was assigned to the aromatic protons of the bezylidene functionality. The diastereotopic benzylic proton appeared as two singlets, one at δ6.25, integrating for 0.3 proton and another one at δ5.80, integrating for 0.7 proton. The H_5 proton appeared as a ddd at δ4.95- 4.80 (J = 16.6, 5.9, 2.4 Hz) followed by H_3 proton at δ4.60 (ddd, J = 8.8, 6.8, 2.9 Hz). The H_4 proton appeared as a multiplet at δ4.40. The H_2 and H_6 methylenic protons appeared between δ2.8- 2.30.

The ^{13}C NMR revealed a total of nineteen signals including the diastereomeric carbon signals at δ178.8, 178.1, 137.5, 135.3, 129.6, 129.0, 128.3, 126.4, 125.8, 103.5, 75.3, 72.7, 72.5, 72.2, 72.0, 71.3, 37.3, 35.4 and 34.2.

The mass spectrum displayed a peak at 261 (M^+-1) as a base peak along with the fragmentation peaks at 105 (93), 91 (24) and at 77 (80).

The hydrogenation of benzylidine lactone **141** in ethanol at 1 atmospheric pressure for 24 h gave **142** in 92 % yield. The work up involved filtration of the catalyst and concentration under reduced pressure. The crude product was subjected to TBS protection by treatment with TBSCl, ImH and catalytic amount of DMAP in dry DMF at room temperature. The usual workup and column chromatographic purification afforded compound **143** in 72 % yield.

The IR spectrum of **143** showed strong characteristic absorption bands at 3466 cm^{-1} and 1730 cm^{-1}, indicating the presence of hydroxyl and lactone carbonyl functionalities.

The ^{1}H NMR spectrum of **143** displayed a ddd at δ4.30 (*J* = 11.2, 4.4, 2.9 Hz) assignable to H_5 proton. A doublet of doublet at δ4.10 (*J* = 5.9, 3.0 Hz) was assigned to H_3 proton. The H_4 proton appeared as a doublet of doublet at δ3.60 (*J* = 3.4, 3.0 Hz). A multiplet between δ2.65- 2.2, integrating for two protons, a doublet of doublet at δ1.95 (*J* = 12.7, 2.9 Hz) and triplet like doublet of doublet at δ1.75 (*J* = 11.7 Hz) were assigned to H_2 and H_6 protons. The two singlets at δ0.95 and 0.85, integrating for nine protons each, were assigned to *t*-butyl protons of TBS groups. A singlet at δ0.1, integrating for nine protons, was assigned to three methyl groups attached to Si of TBS groups. The other methyl appeared as a singlet at δ0.05.

The ^{13}C NMR revealed a total of thirteen signals at δ177.4, 75.3, 71.8, 69.3, 67.2, 38.2, 37.5, 25.5, 17.8, 2.8, -3.1, -5.0, and -5.25. DEPT experiment indicated the presence of three quaternary signals at δ177.4, 75.3 and 17.8, which were assigned to the lactone carbonyl carbon, C_1 carbon and *t*-butyl quaternary carbon, respectively. The C_3, C_4 and C_5 methine carbons appeared at δ71.8, 69.3 and 67.2, respectively. The C_2 and C_6 methylene carbon appeared at δ38.2 and 37.5. The six *t*-

butyl methyl carbons appeared at δ25.5. The other methyl carbon signals of TBS appeared at δ2.8, -3.1, -5.0, and -5.25.

The mass spectrum of **143** showed peak at 345, corresponding to M^+-57. The base peak was observed at 73 along with other fragmentation peaks at 327(29), 213 (36) and 149 (22), respectively.

The reduction of the lactone **143** with sodium borohydride as reducing agent did not proceed. Change of solvent and variation of temperature did not facilitate the reaction. So, we decided to go for stronger reducing agent lithium aluminium hydride.

The reduction of **143** was carried out by refluxing with a suspension of LAH in dry THF for 20 h. The usual work up and column chromatographic purification yielded **144** as a white solid in 30 % yield.

The ^{1}H NMR spectrum of **144** displayed a singlet at δ4.60, integrating for one proton, is assigned to one of the hydroxyl protons. A multiplet at δ4.15, integrating for two protons, was assigned to H_3 and H_4 protons. Another multiplet between δ3.50-3.20, integrating for three protons, was assigned as H_5 and methylenic protons attached to C_1. The H_2 and H_6 methylene protons appeared as two multiplets one between δ2.25- 1.95 and the other one between δ1.75- 1.25. Two singlets at δ0.95 and 0.90, integrating for nine protons each, were assigned to the t-butyl protons of TBS group. The three singlets at δ0.20, 0.10, 0.05, integrating for three, six and three respectively, were assigned to the methyl groups of TBS group.

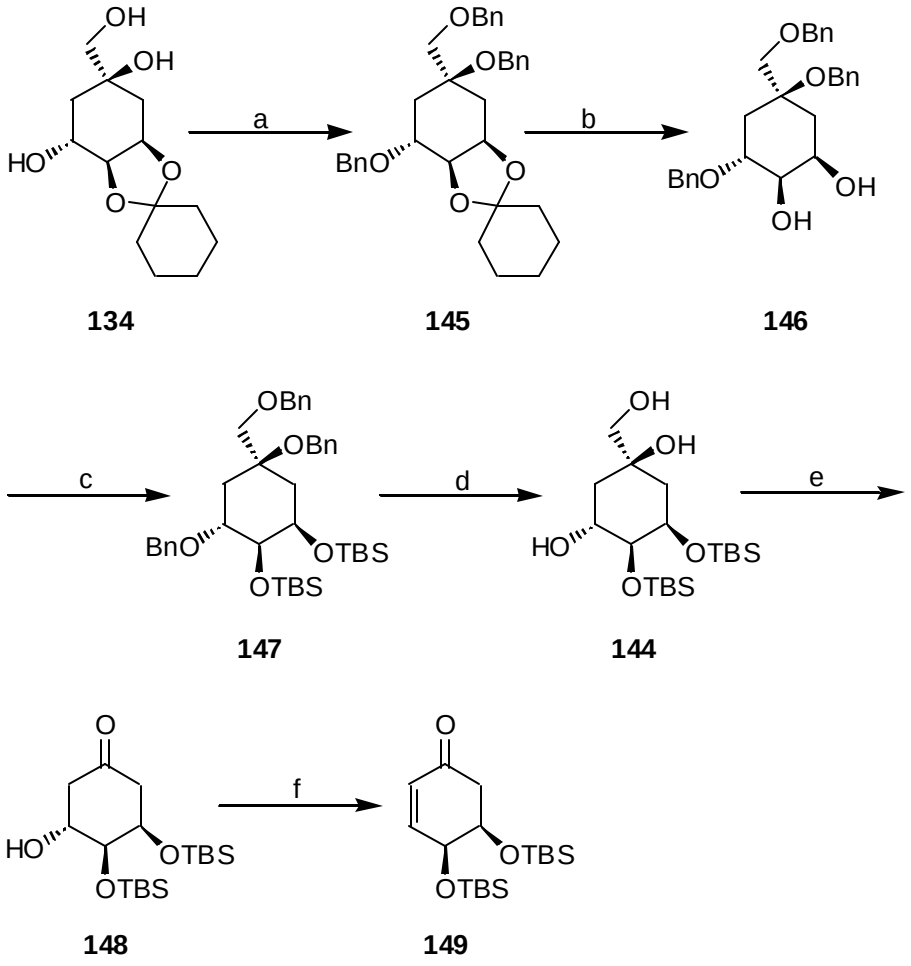
The ^{13}C NMR spectrum of **144** revealed a total of fourteen signals at δ78.7, 73.7, 73.5, 70.1, 66.7, 40.7, 37.4, 25.8, 25.5, 18.1, 17.7, -3.9, -4.8 and -5.0. DEPT experiment suggested the presence of three quaternary carbons at δ73.7, 25.8 and 25.5 which were assigned to C_1 carbon and *t*-butyl quaternary carbons of TBS

groups, respectively. The C_8, C_4 and C_5 methine carbons appeared at δ78.7, 73.5 and 66.7. The methylene attached to C_1 appeared at δ70.1. The C_2 and C_6 methylene carbons appeared at δ40.7 and 37.4. The two signals at δ25.8 and 25.5 were assigned to t-butyl methyl peaks of TBS group. The other four methyl carbons attached to Si of TBS appeared at δ-3.9, -4.8 and –5.0.

The mass spectrum of **144** showed peak at 349 (M+-57, 7) and base peak at 75. The other major fragments were observed at 257 (41), 199 (81), 147 (72) and 133 (46).

The efforts to improve the yield of LAH reduction were unsuccessful. This might be attributed to the TBS cleavage under the reaction conditions, which forced us to abandon the scheme and adopt a different strategy.

To overcome this problem, we envisaged a new synthetic route starting from **134**. Benzylation of the **134**, cyclohexylidine deprotection, diTBS protection of resulting diol followed by debenzylation would deliver the TBS protected compound **144** as shown in Scheme-XXIII.



Scheme-XXII

Reagents and conditions: *a) NaH, DMF, 50 ^{o}C, BnCl, rt, 24 h, 95 %; b) HOAc, H_2O, 50 ^{o}C, 10 h, 95 %; c) TBSCl, ImH, DMAP, DCM, DMF, 0 ^{o}C to rt, 24 h, 80 %; d) H_2/Pd-C, EtOH, 1atm, 24 h, quant.; e) $NaIO_4$, EtOH, rt, 6 h, quant.; f) MsCl, TEA, DCM, 0 ^{o}C, 95 %.*

The tribenzylation of **134** proved to be tricky. A solution of **134** in dry DMF was added to a suspension of NaH at 0 ^{o}C. The reaction mixture was allowed to warm to room temperature and finally was heated to 50 ^{o}C for 1 h. The reaction mixture was recooled to 0 ^{o}C and benzyl chloride was added dropwise while stirring at room temperature. Usual work up and column chromatographic purification afforded **145** in 95 % yield.

The ^{1}H NMR spectrum 0f **145** displayed a multiplet between δ7.45- 7.20, integrating for fifteen protons, for the aromatic protons of the three benzyl groups. A doublet at δ4.80 (*J* = 12.2 Hz, 1H), doublet at δ4.65 (*J* = 12.2 Hz, 1H), doublet at δ4.60 (*J* = 10.8 Hz, 1H), singlet at δ4.55 (2H) and a doublet at δ4.45 (*J* = 10.8 Hz, 1H) were assigned to six benzylic protons. The multiplets at δ4.35 (1H) and at δ4.20-3.90 (2H) were assigned to H_3, H_4 and H_5 protons, respectively. The methylenic protons attached to C_1 appeared as a doublet of doublet at δ3.5 (*J* = 10.8, 9.8 Hz, 2H). A doublet of triplet at δ2.45 (*J* = 15.6, 2.9 Hz, 1H), ddd at δ2.20 (*J* = 13.7, 3.9, 2.0 Hz, 1H) and a doublet of doublet at δ1.90 (*J* = 15.6, 4.8 Hz, 1H) were assignable to H_2 and H_6 protons. A complex multiplet between δ1.75- 1.3, integrating for eleven protons, was assigned to either one of the H_2 or H_6 protons and ten of the cyclohexylidene protons.

The ^{13}C NMR of **145** indicated seventeen signals at δ139.3, 138.8, 138.0, 109.0, 79.8, 76.1, 75.3, 75.1, 73.2, 71.5, 64.4, 37.9, 35.1, 30.8, 25.0, 24.0 and 23.7 along with a bunch of peaks between δ128.5- 126.5. DEPT spectrum revealed the presence of five quaternary signals at δ139.3, 138.0, 138.0, 109.0 and 76.1 and these were attributed to the three aromatic quaternary centers, one cyclohexylidine quaternary carbon and C_1 carbon, respectively. The bunch of peaks between δ128.5-

126.5 were assigned to the aromatic methine carbons. The methine signals at δ79.8, 75.3 and 73.2 were assigned as C_3, C_4 and C_5 carbons. The methylene signals at δ75.1, 73.2 and 71.5 were assigned to the three benzylic carbons. Another methylene signal at δ64.4 was assigned at the methylene attached to C_1. The other methylene carbon signals at δ37.9, 35.1, 30.8, 25.0, 24.0 and 23.7 were assigned to C_2, C_6 and cyclohexylidene methylene carbons.

The mass spectrum of **145** showed peak at 316 (M^+-212, 1) and base peak at 91. The major fragments were observed at 181 (2) and 105 (12).

The cyclohexylidene moiety of **145** was cleaved by stirring with acetic acid: water (80: 20) at 50 ^oC for 10 h. Removal of the acetic acid by distillation followed by column chromatographic purification of the residue afforded **146** in 95 % yield.

The IR spectrum of **146** showed strong absorption band at 3472 cm^{-1}, characteristic of hydroxy functionality.

The ^1H NMR spectrum of **146** displayed a multiplet for fifteen aromatic protons between δ7.60- 7.15. Two broad singlets at δ4.75, 4.55, integrating for two protons each, and two doublets at δ4.50 (J = 10.7 Hz) and 4.30 (J = 10.7 Hz), integrating for one proton each, were assigned to six benzylic protons. Two multiplets at δ4.05 and 3.75, integrating for one proton each, were assigned to H_3 and H_4 protons. A multiplet at δ3.50, integrating for three protons, was assigned to H_5 proton and methylenic protons attached to C_1. A broad singlet at δ2.95 was assigned to two hydroxy protons. A doublet of triplet at δ2.55 (J = 14.7, 3.9 Hz, 1H), a multiplet at δ2.30 (1H), a doublet of doublet at δ1.65 (J = 15.1, 3.4 Hz, 1H) and a doublet of doublet at δ1.45 (J = 14.1, 11.7 Hz, 1H) were assigned to H_2 and H_6 protons.

The ^{13}C NMR spectrum **142** displayed twelve carbon signals at δ138.5, 137.6, 79.6, 76.0, 74.5, 73.9, 73.2, 72.1, 70.2, 64.7, 36.2 and 33.5 along with a bunch of signals between δ129- 127. DEPT experiment revealed the presence three quaternary carbon signals at δ138.5, 137.6 and 79.6, assigned to the aromatic quaternary centers and C_1 carbon, respectively. The bunch of peaks between δ129-127 were assigned to the aromatic methine carbons and one aromatic quaternary carbon. The C_3, C_4 and C_5 methine carbon signals were observed at δ76.0, 74.5 and 70.2. The benzylic methylenic carbons were observed at δ73.9, 73.2 and 72.1. The methylene attached to C_1 was observed at δ64.7. The C_2 and C_6 methylenic carbon signals were observed at δ36.2 and 33.5.

The mass spectrum of **146** showed peak at 357 (M^+-91, 6) along with base peak at 91. The other major fragments were observed at 327 (4), 233 (4), 181 (30) and 107 (19).

The two hydroxy groups of **146** were protected as TBS ether by treatment with TBSCl, imidazole and DMAP in dry DMF and dry DCM solvent mixture at room temperature. The usual work up and column chromatographic purification gave **147** in 80 % yield as a colorless liquid.

In the ^1H NMR spectrum of **147**, fifteen aromatic protons appeared as a multiplet between δ7.45- 7.15. A multiplet between δ4.70- 4.40, integrating for six protons, was assigned to benzylic protons. A ddd at δ3.98 (*J* = 11.8, 4.9, 2.5 Hz, 1H) was assigned to H_5 proton. The H_3 and H_4 protons appeared as a multiplet at δ3.82. The methylenic protons attached to C_1 appeared as a multiplet at δ3.62. The H_2 and

H_6 methylenic protons appeared as a multiplet between δ2.20- 1.85. The two singlets at δ0.95 and 0.93, integrating for nine protons each, were assigned to *t*-butyl groups of TBS. The other methyl signals of TBS appeared at δ0.10 (3H), 0.07 (6H) and 0.00 (3H).

The ^{13}C NMR spectrum of **147** displayed a total of nineteen signals at δ140.0, 138.5, 78.0, 74.0, 73.1, 71.8, 70.9, 67.8, 63.7, 33.7, 29.1, 25.8, 25.6, 18.1, 17.9, -4.6, -4.8, -4.9 and –5.3 along with a bunch of peaks between δ128- 126. DEPT experiment revealed two aromatic quaternary carbons at δ140.0 and 138.5. A bunch of methine signals between δ128- 126 was assigned to aromatic methine carbons. Three methine signals at δ78.0, 71.8 and 67.8 were assigned to C_3, C_4 and C_5 carbons. The three benzylic methylene carbon signals appeared at δ74.0, 73.1 and 70.9. The methylene attached to C_1 appeared at δ63.7. The C_2 and C_6 methylene signals appeared at δ33.7 and 29.1. The methyl signals at δ25.8 and 25.6 were assigned to *t*-butyl methyl groups. The two quaternary centers of *t*-butyl appeared at δ18.1 and 17.9. The methyl signals of TBS appeared at δ-4.6, -4.8, -4.9 and –5.3.

The debenzylation of **147** was carried out by hydrogenation in ethanol at 1 atmospheric pressure of hydrogen gas using palladized charcoal (10 %) as catalyst. Filtration of the catalyst and concentration under reduced pressure afforded **144** as a white solid in quantitative yield. The spectral data of this compound was in excellent agreement with the earlier data. The crude product was subjected to periodate cleavage in ethanol: water (9:1) at room temperature. The usual work up and column chromatographic purification gave **148** as a white solid in quantitative yield.

The IR spectrum of **148** showed strong absorption bands at 3443 cm^{-1} and 1710 cm^{-1} characteristics of hydroxy and keto functionalities, respectively.

^{1}H NMR spectrum of **148** displayed a multiplet at δ4.2, integrating for two protons H_3 and H_4 protons. The C_5 proton appeared as a doublet of doublet at δ3.88 (*J* = 6.4, 2.0 Hz). The four-ddd signals, corresponding to one proton each, at δ2.83 (*J* = 15.1, 4.4, 1.0 Hz, 1H), 2.69 (*J* = 14.1, 8.3, 1.5 Hz, 1H), 2.45 (*J* = 14.1, 4.0, 1.0 Hz, 1H) and 2.31 (*J* = 15.1, 6.3, 1.0 Hz, 1H) were assigned to H_2 and H_6 methylene protons. The two singlets at δ0.95 and 0.85, integrating for nine protons each, were assigned to *t*-butyl groups of TBS. The other methyl protons of TBS groups appeared as singlets at δ0.15 (6H) and 0.05 (6H).

^{13}C NMR spectrum of **148** displayed a total of twelve signals at δ207.7, 74.7, 69.9, 69.8, 46.8, 44.8, 25.7, 18.0, -4.6, -4.7 and -4.9. DEPT experiment revealed the presence of two quaternary signals at δ207.7 and 18.0 which were assigned to carbonyl carbon and to *t*-butyl quaternary carbons, respectively. The C_3, C_4 and C_5 methine carbon signals appeared at δ74.7, 69.9 and 69.8, respectively. The methylene signals at δ46.8 and 44.8 were assigned to C_2 and C_6 methylenic carbons. The methyl signal at 25.7 was assigned to *t*-butyl methyl carbons. The other methyl carbons of TBS appeared at δ-4.6, -4.7 and –4.9.

The mass spectrum displayed a peak at 317 corresponding to M^{+}-57 along with base peak at 73. The other fragments were observed at 299 (15), 185 (45), 157 (21) and 147 (76).

The β-elimination of **148** was carried out by treatment with MsCl and triethyl amine in dry DCM at 0 ^{o}C. Usual work up and column chromatographic purification afforded **149** as a white solid in 95 % yield.

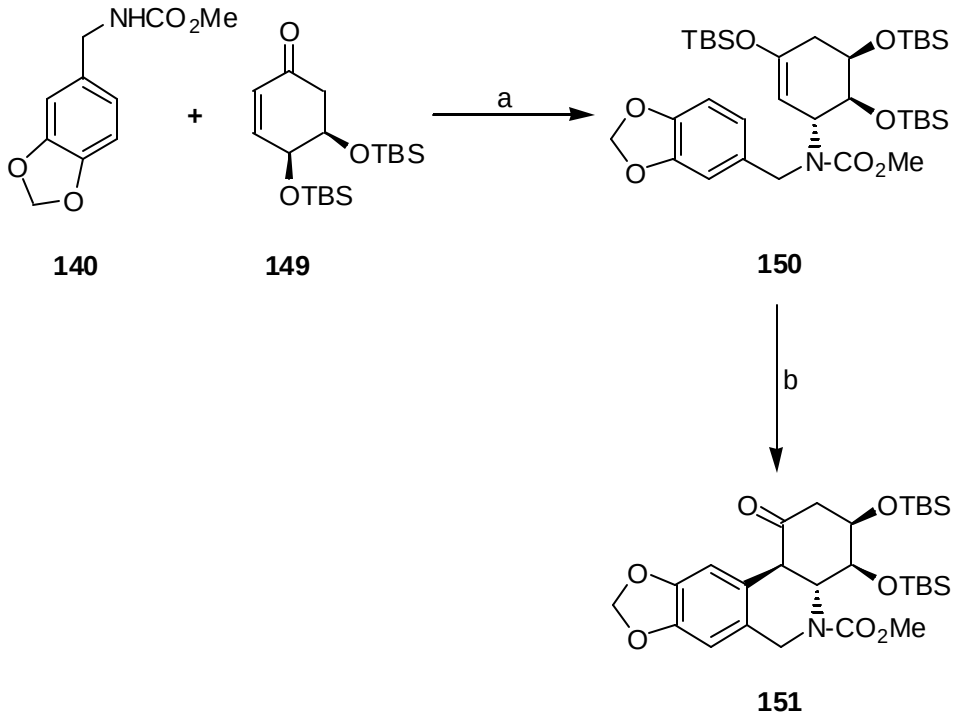
The IR spectrum of **149** showed a strong absorption band at 1685 cm^{-1} indicating the presence of an enone carbonyl.

The ^{1}H NMR spectrum of **149** displayed a doublet of doublet at δ6.70 (*J* = 10.3, 3.5 Hz, 1H) assignable to H_3 proton. A doublet at δ5.95 (*J* = 10.3 Hz) was assigned to H_2 proton. A broad singlet at δ4.45 was assigned to H_4 proton. The H_5 proton appeared as a doublet of doublet at δ4.15 (*J* = 6.8, 2.9 Hz). The two doublet of doublets at δ2.75 (*J* = 16.2, 6.8 Hz, 1H) and δ2.45 (*J* = 16.2, 2.9 Hz, 1H) were assigned to H_6 protons. The two singlets at δ0.95 and 0.85, integrating for nine protons each, were assigned for *t*-butyl of TBS group. The other two singlets at δ0.15 and 0.05, integrating for six protons each, were assigned to methyl protons of TBS.

^{13}C NMR of **149** displayed a total of nine signals at δ197.4, 148.7, 129.2, 71.5, 69.3, 44.0, 25.6, 18.1 and –4.7. DEPT experiment revealed the presence of two quaternary signals at δ197.4 and 18.1, assigned to C_1 carbonyl and *t*-butyl quaternary carbon of the TBS groups. The methine signal at 148.7 was assigned to C_3 and another signal at δ129.2 was assigned to C_2. The C_4 and C_5 methine signals appeared at δ71.5 and 69.3. The C_6 methylene appeared at δ44.0. The methyl signal at δ25.6 was assigned to *t*-butyl methyl carbons. The other methyl carbons of TBS groups appeared at δ-4.7.

The mass spectrum of **149** displayed molecular ion peak at 356 (1) along with base peak at 147. The other fragments were observed at 341 (2), 299 (50), 198 (24) and 73 (57).

The above spectral analysis confirmed the structure of the compound **149**. Now, the stage is set for carrying out the conjugate addition of piperonyl amine carbamate (**140**) on to **149**.



140 **149** **150**

151

Scheme-XXIII

Reagents and Conditions: *a) n-BuLi, THF, HMPA, -78 °C, TBSCl, 95 %; (b) hn, DCN, CH_3CN, H_2O, 6 h, 68 %.*

5. 1. Conjugate addition of 149 with 140.

To a solution of **140** in dry THF and HMPA was added n-BuLi at –78 °C. After stirring for 0.5 h, a solution of **149** in dry THF was added drop wise and stirring was continued for additional 0.5 h followed by the addition of TBSCl. The reaction mixture

was allowed to warm to room temperature. The usual work up and column chromatographic purification gave silylenolether **150** as a pasty mass in 95 % yield.

The IR spectrum of **146** showed strong absorption bands at 1704 cm^{-1} and 1254 cm^{-1}, characteristics of carbonyl and silylenolether, respectively.

The ^{1}H NMR of **150** displayed a multiplet at δ6.7, integrating for three protons, for the aromatic protons. A sharp singlet at δ5.92, integrating for two protons, was assigned to the methylene dioxy protons. A multiplet between δ4.55-4.25, integrating for three protons, was assigned to the benzylic and one olefinic proton. A multiplet between δ3.9- 3.6, integrating for six protons, was assigned to the methyl carbamate protons, two –C<u>H</u>-O- protons and one –C<u>H</u>-N- proton of cyclohexyl ring. The methylene protons of cyclohexyl ring appeared as a multiplet at δ2.15. Two singlets at δ0.93 and 0.87, integrating for nine and eighteen protons, respectively, were assigned to *t*-butyl methyl protons of TBS groups. The other methyl protons of TBS groups appeared between δ0.2- -0.1.

The ^{13}C NMR of **150** displayed a total of twenty one signals at δ156.8, 151.0, 147.5, 146.2, 120.0, 107.7, 107.6, 101.1, 100.6, 73.0, 68.9, 58.2, 52.0, 48.6, 36.2, 25.6, 25.3, 17.8, -4.7, -5.0 and –5.1.

The mass spectrum of **150** displayed peak at 623 (M^{+}-56, 33) and base peak at 73. The fragments were observed at 548 (11), 289 (3), 200 (3) and 136 (29).

5. 2. PET- Cyclization of silylenolether 150 to 151.

A solution of **150** (600 mg) and DCN (50 mg) in acetonitrile:water system (24:1, 250 mL) was irradiated by using Hanovia medium pressure lamp (450W,

Pyrex filter, >280 nm) for 6 h. The reaction was monitored by TLC, periodically. Concentration of the photolysate followed by column chromatographic purification of the residue gave **151** as a pasty mass in 68 % yield.

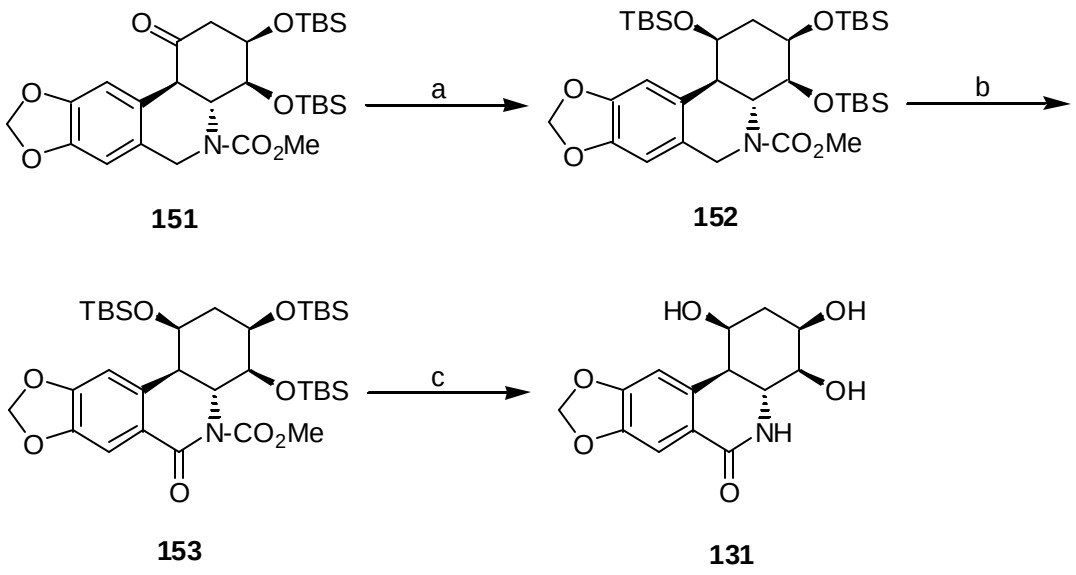
The IR spectrum of **151** showed strong absorption bands at 1717 cm^{-1} and 1695 cm^{-1}, indicating the presence of keto carbonyl and carbamate carbonyl in the molecule, respectively.

The ^{1}H NMR spectrum displayed two singlets at δ6.65 and 6.48, integrating for one proton each, were assigned to the aromatic protons. The methylenedioxy proton appeared as a singlet at δ5.94. A broad doublet at δ4.87 (*J* = 17.9 Hz, 2H) was assigned to the benzylic protons. A multiplet between δ4.25 to 3.60, integrating for seven protons, was assigned to H_3, H_4, H_{4a}, H_{10b} and methyl carbamate protons. The H_2 methylene appeared as a multiplet at δ2.50. The *t*-butyl protons of TBS appeared as a singlet at δ0.90. The methyl protons of TBS appeared at δ0.10.

The ^{13}C NMR of **151** displayed a total of twenty one signals at δ206.7, 156.0, 146.9, 126.2, 107.2, 106.4, 100.9, 70.6, 70.3, 52.4, 51.3, 45.3, 43.2, 29.4, 25.4, 17.8, 17.6, -3.8, -4.6, -5.0 and-5.2.

The mass spectrum of **151** showed molecular ion peak at 563 (2) along with base peak at 73. The other fragments were observed at 548 (2), 506 (93), 374 (4), 232 (19) and 147 (57).

The above spectral analysis confirmed the structure of the cyclized compound **151**. The reduction of C_1 carbonyl and oxidation of C_6 position followed by deprotection of the protecting groups was expected to lead to the target molecule **131**.



151 **152**

153 **131**

Scheme-XXIV

Reagents and Conditions: *a) (i) $NaBH_4$, $^{i}PrOH$, rt, 12 h; (ii), TBSCl, ImH, DMAP, DMF, DCM, 85 %; (b) RuO_2, $NaIO_4$, EtOAc, H_2O, 88 %; (c) (i) NaOMe, MeOH, reflux; (ii), TBAF, THF, 10 h, 90 %.*

We anticipated that the sodium borohydride reduction would give the β-hydroxy since the axial C_8 OTBS group would hinder the attack of hydride from β phase. The α-phase attack would result in the β-alcohol.

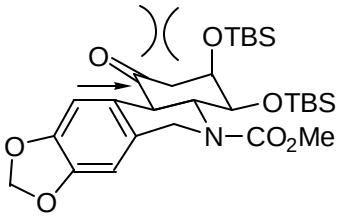


Fig. 4

The C_1 carbonyl of **151** was reduced by treatment with $NaBH_4$ in isopropyl alcohol at room temperature. The usual work up gave the crude product, which was subjected to TBS protection with TBSCl, ImH, and catalytic DMAP in dry DCM at room temperature for 24 h. The usual work up and column chromatographic purification gave **152** as a pasty mass in 85 % yield.

The ^{1}H NMR spectrum of **152** displayed two singlets at δ6.74 and 6.65, integrating for one proton each, assignable as the aromatic protons. The methylene dioxy protons appeared as a sharp singlet at δ5.90. The two doublets at δ4.97 (J = 16.0 Hz, 1H) and 3.93 (J = 16.0 Hz, 1H) were assigned to H_6 benzylic protons. A multiplet between δ3.80- 3.47, integrating for seven protons, was assigned to H_1, H_3, H_4, H_5 and methyl carbamate protons. The H_{10b} proton appeared as a doublet of doublet at δ2.95 (J = 10.3, 6.3 Hz, 1H). One of the H_2 protons appeared as a doublet of doublet at δ2.10 (J = 24.0, 12.3 Hz, 1H) and the other proton appeared as a multiplet at δ1.75. The singlets at δ0.95, 0.90 and 0.80, integrating for nine protons each, were assigned to t-butyl protons. The other methyl protons of TBS groups appeared at δ0.15 (6H), 0.05 (6H), -0.25 (3H) and –0.45 (3H).

The ^{13}C NMR spectrum of **152** displayed a total of twenty signals at δ156.9, 146.5, 146.0, 131.0, 127.8, 111.2, 106.6, 100.5, 72.0, 70.3, 68.6, 58.0, 52.7, 45.9, 44.0, 36.2, 26.0, 18.0, -4.5, -5.0, -5.3 and –6.0. DEPT experiment revealed the presence of five quaternary carbons at δ156.9, 146.5, 146.0, 131.0 and 127.8 which were assigned to carbonyl of carbamate group and four aromatic quaternary carbons, respectively. The two aromatic methine signals appeared at δ111.2 and 106.6. The methylenedioxy carbon appeared at δ100.5. The C_1, C_3 and C_4 methine

carbon signals appeared at δ72.0, 70.3 and 68.6. The C_{4a} methine carbon appeared at δ58.0. The methyl signals at δ52.7 was assigned to the methyl carbamate. The C_{10b} methine signal appeared at δ44.0. The methylene signal at δ45.9 was assigned to C_6 benzylic methylene carbon. The C_2 methylene appeared at δ36.2. The *t*-butyl methyl signals appeared as a bunch at δ26.0. The quaternary carbons of *t*-butyl appeared as a bunch at δ18.0. The other methyl carbons of TBS appeared at δ-4.5, -5.0, -5.3 and –6.0.

The mass spectrum showed one peak at 623 (M^+-57, 17) and the base peak at 73. The other fragments were observed at 390 (7), 232 (4) and 147 (23).

The benzylic oxidation was carried out using a protocol reported by Smith III and co-workers[7]. A catalytic amount of RuO_2 was added to a stirred solution of $NaIO_4$ in water at room temperature and the resulting mixture was stirred for 10 minutes. To this yellow solution, was added a solution of **152** in the ethyl acetate and the stirring was continued for 30 minutes. The reaction mixture was quenched by the addition of isopropyl alcohol and filtered through a pad of Celite. Concentration and column chromatographic purification afforded **153** as a pasty mass in 88 % yield.

The ^1H NMR spectrum **153** displayed two singlets at δ7.52 and 6.74, integrating for one proton each, assigned to H_7 and H_{10} protons. The methylene dioxy protons appeared as a singlet at δ6.0. A multiplet between δ4.2- 3.75, integrating for six protons, was assigned to H_1, H_3 and H_4 and methyl carbamate protons. The H_{4a} proton appeared as a multiplet at δ3.65. The H_{10b} proton appeared as a doublet of doublet at δ2.95 (J = 10.3, 3.7 Hz). The H_2 methylenic protons appeared as a multiplet at δ2.0. The *t*-butyl methyl protons appeared as three

singlets at δ0.93, 0.90 and 0.80, integrating for nine protons each. The other methyl protons of TBS appeared at δ0.10 (3H), 0.07 (3H), 0.04 (6H), -0.25 (3H) and –0.52 (3H).

The ^{13}C NMR of **153** displayed a total of twenty one signals at δ163.5, 155.0, 151.5, 147.2, 136.5, 120.4, 111.5, 108.6, 102.4, 70.0, 69.5, 67.4, 60.4, 54.5, 42.7, 38.2, 14.0, -4.6, -4.7, -4.9, -5.1 and –5.8 along with bunch of other peaks at δ26.0 and 18.0. The DEPT spectrum revealed the presence of six quaternary centers at δ163.5, 155.0, 151.5, 147.2, 136.5 and 120.4, assignable to two carbonyl carbons and four aromatic quaternary carbons, respectively. The two methine carbons of aromatic ring appeared at δ111.5 and 108.6. The methylenedioxy carbon appeared at δ102.4. The C_1, C_3 and C_4 methine carbon signals appeared at δ70.0, 69.5 and 67.4. The C_{4a} methine carbon appeared at δ60.4. Methyl carbamate appeared at δ54.5. The C_{10b} methine carbon appeared at δ42.7. The C_2 methylene carbon signal appeared at δ38.2. The bunch of peaks at δ26.0 were assigned to *t*-butyl methyl carbons. The other bunch at δ18.0 was assigned to *t*-butyl quaternary carbons. The other methyl carbon signals of TBS groups appeared at δ-4.6, -4.7, -4.9, -5.1 and –5.8.

The mass spectrum of **153** displayed peak at 636 (M^+-57, 59) and base peak at 147. The other major fragments were observed at 389 (16), 248 (20) and 189 (13).

5. 4. Preparation of (+)-2,7-Dideoxypancratistatin(131).

The carbamate deprotection was carried out by refluxing with sodium methoxide in methanol. The reaction was over in 30 minutes. The usual work up and concentration gave crude carbamate deprotected compound.

The above crude compound was subjected for TBS deprotection with 1M TBAF in dry THF. The reaction mixture was stirred for 10 h. The usual work up and column chromatographic purification gave the target molecule **131** as a white solid in 90 % yield.

5. 5. Characterization of (+)-2,7-Dideoxypancratistatin (131).

The ^{1}H NMR spectrum of **131** displayed two singlets at δ7.38 and 6.86, integrating for one proton each, assignable to H_7 and H_{10} aromatic protons. The methylenedioxy protons appeared as a broad singlet at δ6.05. A multiplet between δ4.03- 3.92, integrating for three protons, was assigned to H_1, H_3 and H_4 protons. The H_{4a} proton appeared as a multiplet at δ3.63. The H_{10b} proton appeared as a doublet of doublet at δ2.74 (J = 10.4, 3.4 Hz). The H_2 methylene protons appeared as a multiplet at δ1.92.

The ^{13}C NMR spectrum of **131** displayed a total of fourteen signals at δ166.3, 150.3, 147.1, 136.7, 121.3, 109.3, 106.3, 101.4, 69.0, 68.4, 66.4, 55.6, 42.3 and 35.7. The DEPT experiment revealed the presence of five quaternary centers at δ166.3, 150.5, 147.1, 136.7 and 121.3, which were assigned to C_6 carbonyl carbon and four aromatic quaternary carbons, respectively. The methine carbon signals at δ109.3 and 106.3 were assigned to C_7 and C_{10} aromatic carbons. The methylene dioxy carbon appeared at δ101.4. The three methine signals at δ69.0, 68.4 and 66.4 were assigned to C_1, C_3 and C_4. The C_{4a} methine carbon appeared at δ55.6. The C_{10b} methine carbon appeared at δ42.3. The methylene signal at δ35.7 was assigned to C_2 carbon.

The mass spectrum of **131** displayed molecular ion peak at 293 (7) along with base peak at 190. The fragments were observed at 172 (16), 132 (6), 85 (29), 69 (50) and 57 (92).

The above spectral analysis confirmed the structure of (+)-2,7-dideoxypancratistatin.

6. Summary

In summary, we have successfully demonstrated the synthesis (+)-2,7-dideoxypancratistatin using PET-initiated α-arylation of ketones as the key step. The synthesis also made use of naturally available D-(-)-quinic acid as the chiral source. The further studies towards the synthesis of (+)-pancratistatin and 7-deoxypanratistatin are in progress in the group.

7. References

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CHAPTER-III

EXPERIMENTAL

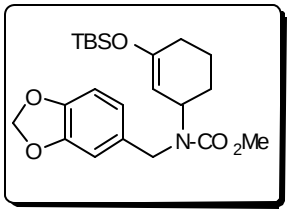
General

All commercial reagents were obtained from Aldrich Chemical Company and Lancaster Chemical Company and used as such. Progress of the reaction was monitored by TLC and was visualized by UV absorption by fluorescence quenching or I_2 staining or by both. Silica gel for column chromatography was 60-120 mesh size and was obtained from S. D. Fine Chemical Co. India or SRL India Ltd.

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven dried glassware (110 ^{o}C). All the organic layers obtained from extractions were dried over anhydrous Na_2SO_4. All the commercial grade solvents were distilled prior to use. Dichloromethane and *N,N*-dimethylformamide for dry reactions were distilled from CaH_2 under argon and were stored over molecular sieves. Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone ketyl prior to use.

All the melting points are uncorrected in degree Celsius and were recorded on a Thermonik Campbell melting point apparatus. Optical rotations were measured using JASCO 181 digital polarimeter using Na lamp. ^{1}H and ^{13}C NMR spectra were run on Bruker AC-200, MSL-300 and DRX-500 instruments. IR spectra were recorded on a Perkin Elmer FT-IR model 1620. Mass spectra (EI, 70 eV) were obtained on a Finnigan-Mat 1020 instrument.

1. Preparation of Methyl 1,3-benzodioxol-5-ylmethyl(3-methoxycyclohexe-2-ene-1-yl)carbamate 129:



To a solution of cyclohex-2-en-1-one (1 mL, 10.34 mmol), TBSOTf (2.85 mL, 12.41 mmol) in dry ether (40 mL) was added piperonyl amine (1.6 mL, 12.86 mmol) at –50 ^{o}C. The resulting white suspension was further allowed to stir for 3 h at the same temperature. The mixture was warmed to 0 ^{o}C followed by the addition of 1 *N* NaOH solution (1 mL). Methyl chloroformate (1.2 mL, 15.51 mmol) was added to the reaction mixture and stirring was continued for an additional 30 minutes. The solution was diluted with ether (50 mL) and washed successively with water (3x50 mL) and brine (1x30 mL). The organic layer was dried over Na_2SO_4 before concentrating under reduced pressure. The residue was column chromatographed over silica gel using pet ether: ethyl acetate (19:1) as an eluant to give **129** (3.03 g, 70 %) as a colorless pasty mass.

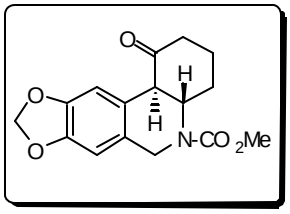
IR ($CHCl_3$) : 1693, 1251 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.8 (m, 3H), 5.90 (s, 2H), 5.05- 4.65 (m, 1H), 4.60 (bs, 1H), 4.35 (d, *J* = 17 Hz, 1H), 4.25 (d, *J* = 17 Hz, 1H), 3.65 (s, 3H), 2.05- 1.20 (m, 6H), 0.85 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 157.0, 154.0, 147.4, 145.9, 133.7, 119.2, 107.7, 106.9, 104.8, 100.5, 53.2, 52.3, 45.7, 29.2, 27.7, 25.3, 20.6, 17.7, -4.9

Mass m/z (%) : 419 (M^{+}, 2), 362 (38), 305 (11), 284 (100), 252 (8), 211 (61)

2. Preparation of 1-Oxo-2,3,4,4a,6,11b-hexahydro-1*H*-[1,3]dioxolo[4,5-*j*]phenanthridine-5-carboxylic acid methyl ester 130:



A solution of **129** (0.5 g, 1.19 mmol), 1,4-dicyanonaphthalene (DCN, 0.05 g, 0.28 mmol) in acetonitrile: water (24:1, 250 mL) was irradiated using Hanovia medium pressure lamp (Pyrex filter, >280 nm) for 6 h. The resulting solution was concentrated under reduced pressure. The residue was column chromatographed over silica gel using pet ether: ethyl acetate (85:15) as an eluant to afford **130** (0.26 g, 72 %) as a colorless pasty mass.

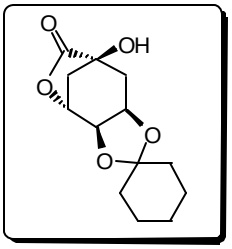
IR ($CHCl_3$) : 1715, 1695 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.65 (s, 1H), 6.45 (s, 1H), 5.95 (s, 2H), 5.00- 4.5 (m, 2H), 4.20 (d, *J* = 12.5 Hz, 1H) 3.85- 3.7 (m, 4H), 2.3 (m, 2H), 2.0-1.5 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 209.0, 155.4, 147.2, 147.1, 125.0, 122.7, 106.7, 106.4, 101.0, 54.0, 52.6, 52.0, 42.6, 37.9, 24.9, 22.0.

Mass *m/z* (%) : 303 (M^+, 50), 288 (24), 244 (26), 232 (27), 188 (32), 174 (33), 135 (41), 116 (35), 89 (30), 77 (29), 59 (94), 42 (100).

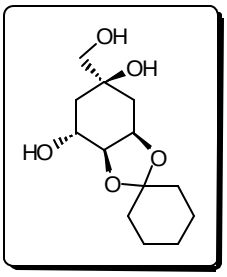
3. Preparation of (1*S*,3*R*,4*R*,5*R*)-3,4-*O*-Cyclohexylidene-1,3,4-trihydroxy-6-oxabicyclo[3.2.1]octan-7-one 133:



A solution of D-(-)-quinic acid (10 g, 52.08 mmol), p-toluenesulfonic acid (0.11 g, 0.60 mmol), cyclohexanone (10mL) and *N,N*-dimethylformamide (25 mL) in benzene (150 mL) were stirred under reflux for 4 h using Dean-Stark trap until no more water was separated. After the solution had cooled to room temperature, it was diluted with ethyl acetate (300 mL) and washed with saturated sodium bicarbonate solution (2x100 mL), water (2x200 mL), brine (1x100 mL). After drying over anhydrous Na_2SO_4, the organic extracts were concentrated under reduced pressure. The crude mixture was crystallized from pet ether: acetone mixture (9:1) to give colorless crystals (12.5 g, 95 % yield) of **133**.

Melting point	**:**	140- 142 ^{o}C
$[a]_D^{25}$	**:**	-33.5^{o} (*c* 2.0, MeOH)
IR (nujol)	**:**	3429, 1767 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 4.72(dd, *J* = 6.0, 2.5 Hz, 1H), 4.46 (ddd, *J* = 7.0, 7.0, 3.0 Hz, 1H), 4.28 (ddd, *J* = 6.0, 2.0, 1.2 Hz, 1H), 3.15 (s, 1H), 2.63 (d, *J* = 11.8 Hz, 1H), 2.45- 2.23 (m, 2H), 2.16, (dd, *J* = 14.6, 3.0 Hz, 1H), 1.72- 1.20 (complex multiplet, 10 H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	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* (%)	**:**	254 (M^+, 7), 225 (10), 211 (53), 139 (10), 111 (20), 95 (23), 55 (100).

4. Preparation of (1*R*,2*S*,3*R*,5*R*)-1,2-*O*-Cyclohexylidene-1,2,3,5-tetrahydroxy-5-(hydroxymethyl)cyclohexane 134:



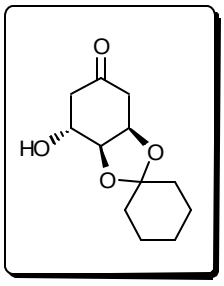
A solution of **133** (10 g, 39.37 mmol) in ethanol (120mL) was stirred at room temperature with sodium borohydride (10 g, 0.29 mol) for 24 h. Saturated, aqueous sodium chloride solution (150 mL) was added and the mixture was stirred for additional 12 h. The white precipitate from the reaction mixture was filtered through filter paper and the filter cake was washed with ethyl acetate. The combined filtrate was concentrated to half of its original volume and was extracted with ethyl acetate (3x100 mL). The combined organic extracts were washed with water (2x100 mL), brine (1x100 mL) and dried over anhydrous Na_2SO_4. The ethyl acetate extract was concentrated under reduced pressure and the residue was crystallized from chloroform:pet ether (2:10) to afford **134** as a colorless crystals (9.1 g, 90 %).

$[a]_D^{25}$	**:**	-64^o (*c* 1, $CHCl_3$)
Melting point	**:**	90- 91 ^oC
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 4.48 (ddd, *J* = 5.9, 3.9, 2.9 Hz, 1H), 4.10 (ddd, *J* = 10.2, 6.3, 4.3 Hz, 1H), 3.97 (t like dd, *J* = 6.3 Hz, 1H), 3.45 (dd, *J* = 20, 10.8 Hz, 2H), 2.6 (bs, 1H), 2.32 (ddd, *J* = 15.6, 2.5, 2.5 Hz, 1H), 2.00 (ddd, *J* = 13.7, 4.9, 2.4 Hz, 1H), 1.88 (d, *J* = 3.4 Hz, 1H), 1.80 (d, *J* = 3.4 Hz, 1H), 1.79- 1.25 (complex multiplet, 10H).
^{13}C NMR	**:**	δ 109.5, 79.5, 73.6, 72.3, 69.8, 68.9, 38.0, 37.8, 34.4,

(50 MHz, $CDCl_3$) 32.9, 24.7, 23.7, 23.3.

Mass *m/z* (%) : 258 (M^+, 4), 229 (4), 215 (17), 197 (4), 143 (8), 125 (10), 107 (13), 99 (28), 79 (33), 69 (40), 55 (100).

5. Preparation of 3*R*,4*S*,5*R*-3,4-*O*-Cyclohexylidene-3,4,5-trihydroxycyclohexanone 135 :



To a solution of **134** (10 g, 38.76mmol) in water (100 mL) was added sodium meta periodate (12.4 g, 58.14 mmol) in parts at 0 °C. The pH of the solution was maintained between 6-7 by the addition of 1*N* sodium bicarbonate solution. The reaction mixture was stirred at the same temperature for additional 2 h and extracted with ethyl acetate. The combined organic extracts were washed with water (3x100 mL), brine (1x50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, with pet ether: ethyl acetate (7:3) as eluant to give 8.32 g (95 %) of **135** as a colorless solid.

Melting point : 97- 98 °C

$[a]_D^{25}$: -64° (*c* 1, $CHCl_3$)

IR ($CHCl_3$) : 3460, 1711 cm^{-1}

^{1}H NMR : δ 4.70 (m, 1H), 4.25 (m, 2H), 2.80- 2.30 (m, 4H), 1.9 (s, 1H),

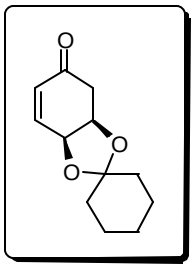
(200 MHz, $CDCl_3$) 1.75- 1.25 (m, 10 H).

^{13}C NMR : δ 208.8, 109.1, 74.3, 71.5, 67.7, 41.4, 40.0, 35.9, 32.9, 24.8,

(50 MHz, $CDCl_3$) 23.6, 23.2.

Mass *m/z* (%) **:** 226 (M^+, 2), 197 (1), 183 (4), 111 (2), 81 (2), 69 (14), 55 (100).

6. Preparation of (4*S*,5*R*)-4,5-*O*-Cyclohexylidene-4,5-dihydroxy-2-cyclohexenone 136:



To a solution of **135** (5 g, 22.12 mmol), triethylamine (6.7 mL, 48.67 mmol) in dry dichloromethane (60 mL) was added a solution of MsCl (2.17 mL, 26.54 mmol) in 10 mL of dichloromethane over 1 h at 0 ^oC. After the addition was over, the reaction mixture was further stirred at room temperature for an additional 1 h. The reaction mixture was washed with water (2x100 mL), brine (1x50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was column chromatographed on silica gel using pet ether: ethyl acetate (85:15) as eluant to give **136** as a white solid (4.2 g, 90 %).

Melting point **:** 56- 57 ^oC

$[a]_D^{25}$ **:** $+135^o$ (*c* 1, $CHCl_3$)

IR ($CHCl_3$) **:** 1686 cm^{-1}

^{1}H NMR **:** δ 6.65 (dd, *J* = 10.3, 2.0 Hz, 1H), 6.0 (d, *J* = 10.3 Hz, 1H), 4.7

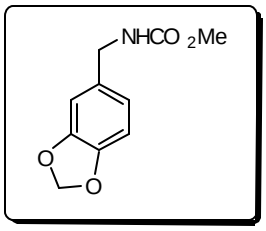
(200 MHz, $CDCl_3$) (m, 2H), 3.05-2.85 (dd, *J* = 17.6, 2.5 Hz, 1H), 2.75- 2.10 (dd, *J* = 17.6, 3.4 Hz, 1H), 1.75- 0.75 (m, 10H).

^{13}C NMR **:** δ 195.4, 146.0, 128.2, 110.1, 72.7, 70.3, 38.5, 37.1, 35.6,

(50 MHz, $CDCl_3$) 24.5, 23.4.

Mass *m/z* (%) : 208 (M^+, 43), 179 (27), 165 (100), 111 (10), 94 (16), 66 (47), 55 (61).

7. Preparation of Methyl-1,3-benzodioxol-5-ylmethylcarbamate 140:



To a mixture of piperonyl amine (5 g, 33.11mmol), K_2CO_3 (5.5 g, 39.74 mmol), dichloromethane (100 mL) and water (50 mL) was added methyl chloroformate (2.8 g, 36.42 mmol) at 0 ^oC. The mixture was further stirred for 0.5 h. The reaction mixture was extracted with dichloromethane (2x100 mL). The combined organic extracts were washed with water (2x100 mL), brine (1x50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was recrystallized from ethanol to give colorless plates (6.4 g, 93 %) of **140**.

Melting point : 99- 100 ^oC

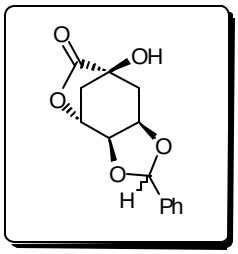
IR ($CHCl_3$) : 3301, 1693 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.80 (bs, 1H), 6.75 (bs, 2H), 5.95 (s, 2H), 4.95 (bs, 1H), 4.26 (d, *J* = 6.2 Hz, 2H), 3.70 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 156.8, 147.6, 146.5, 132.1, 120.5, 108.7, 100.5, 52.0, 44.5.

Mass *m/z* (%) **:** 209 (M^+, 18), 194 (22), 150 (29), 135 (36), 93 (45), 77 (76), 65 (100).

8. Preparation of (1*S*,3*R*,4*R*,5*R*)-3,4-*O*-Benzylidene-1,3,4-trihydroxy-6-oxabicyclo[3.2.1]octan-7-one 141:



A suspension of D-(-)-quinic acid (**106**) (10 g, 52.08 mmol) in benzene (150 mL), *N*,*N*-dimethylfomamide (25 mL) and benzaldehyde (10 mL) containing a catalytic amount of *p*-toluenesulfonic acid was refluxed for 4 h using Dean-Stark water separator. The resulting solution was cooled to room temperature, diluted with ethyl acetate (200 mL), washed successively with water (2x200 mL), 1 N sodium bisulphate (2x200 mL), water (2x200 mL), brine (1x100 mL) and dried over Na_2SO_4. The solvent was evaporated to leave (10.92 g, 80 %) **141** as a mixture of diastereomers. An analytical sample was prepared by chromatography on silica gel, with pet ether: ethyl acetate (1:1) as eluant.

IR ($CHCl_3$) **:** 3439, 1787 cm^{-1}

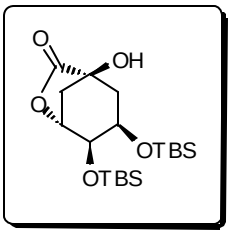
^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 7.6- 7.30 (m, 5H), 6.25 (s, 0.3H), 5.80 (s, 0.7H), 4.95-4.80 (ddd, *J* = 16.6, 5.9, 2.4 Hz, 1H), 4.60 (ddd, *J* = 8.8, 6.8, 2.9 Hz, 1H), 4.40 (m, 1H), 2.8 (d, *J* = 11.7 Hz, 1H), 2.60 (d, *J* = 11.7 Hz, 1H), 2.55- 2.30 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 178.8, 178.1, 137.5, 135.3, 129.6, 129.0,128.3, 126.4, 125.8, 103.5, 75.3, 72.7, 72.5, 72.2, 72.0, 71.3, 37.3,

35.4, 34.2.

Mass *m/z* (%) : 261 (M^+-1, 100), 122 (15), 105 (93), 91 (24), 77 (80).

9. Preparation of (1*S*,3*R*,4*R*,5*R*)-3,4-Bis[(tertbutyldimethylsilyl)oxy]-1-hydroxy-6-oxabicyclo[3.2.1]octan-7-one 143:



A suspension of **141** (10 g, 38.17 mmol), Pd-C (0.2 g, 10 % Pd on activated charcoal) in ethanol was hydrogenated at atmospheric pressure for 24 h. The progress of the reaction was monitored by TLC. After the reaction was over, the reaction was filtered and the filtrate was concentrated under reduced pressure to give **142** as a white solid (6.11 g, 92 %). The crude material was sufficiently pure enough for further reaction.

To a solution of **142** (6 g, 34.48 mmol), imidazole (7.04 g, 103.44 mmol) and catalytic amount of DMAP (0.1 g, 0.82 mmol) in dry DMF (150 mL) was added to a solution of TBSCl (13 g, 86.35 mmol) in dry DMF (20 mL) drop wise at room temperature. The resulting mixture was stirred for 24 h. The reaction mixture was diluted with water (100 mL) and extracted with pet ether: ethyl acetate (1:1) (3x100 mL). The organic extracts were washed with water (3x100 mL), brine (1x100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was column chromatographed over silica gel using pet ether: ethyl acetate (10:1) as eluant to give 9.98 g (72 %) of **143** as a white solid.

Melting point : 195- 196 ^oC

$[a]_D^{25}$: -5^o (*c* 1, $CHCl_3$)

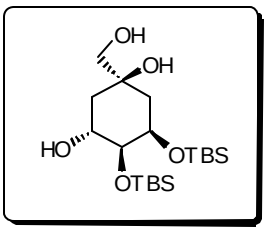
IR (CHCl3) : 3466, 1730, 1464, 1256 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.30 (ddd, *J* = 11.2, 4.4, 2.9 Hz, 1H), 4.10 (dd, *J* = 5.9, 3.0 Hz, 1H), 3.60 (dd, *J* =3.4, 3.0 Hz, 1H), 2.65- 2.2 (m, 2H), 1.95 (dd, *J* = 12.7, 2.9 Hz, 1H), 1.75 (t like dd, *J* = 11.7 Hz, 1H), 0.95 (s, 9H), 0.85 (s, 9H), 0.1 (s, 9H), 0.05 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 177.4, 75.3, 71.8, 69.3, 67.2, 38.2, 37.5, 25.5, 17.8, 2.8, 3.1, -5.0, -5.25.

Mass *m/z* (%) : 345 (M^+-57, 4), 327 (29), 231 (14), 213 (36), 185 (15), 149 (22), 73 (100).

10. Preparation of (1*R*,2*S*,3*R*,5*R*)-1,2-Di-*O*-tertbutyldimethylsilyl-1,2,3,5-tetrahydroxy-5-(hydroxymethyl)cyclohexane 144:



To a suspension of LAH (0.95 g, 24.88 mmol) in dry THF (50 mL) was added drop wise a solution of **143** (5 g, 12.44 mmol) in THF (10 mL) at 0 ^oC. After the addition was over, the reaction mixture was refluxed for 20 h. The reaction was quenched by sequential addition of ethyl acetate, NaOH solution (20 % 5 mL) and water. The white precipitate was filtered off. The filtrate was concentrated and the residue was column chromatographed over silica gel using pet ether: ethyl acetate (3:1) as eluant to give **144** (1.52 g, 30 %) as a white solid.

Melting point : 122- 123 ^oC

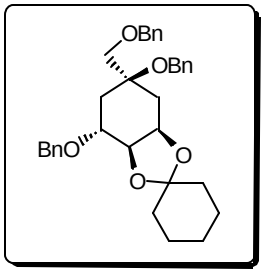
$[a]_D^{25}$: -63.3^o (*c* 0.15, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.60 (s, 1H), 4.15 (m, 2H), 3.50- 3.20 (m, 3H), 2.25- 1.95 (m, 3H), 1.75- 1.25 (m, 3H), 0.95 (s, 9H), 0.90 (s, 9H), 0.20 (s, 3H), 0.10 (s, 6H), 0.05 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 78.7, 73.7, 73.5, 70.1, 66.7, 40.7, 37.4, 25.8, 25.5, 18.1, 17.7, -3.9, -4.8, -5.0.

Mass *m/z* (%) : 349 (M^+-57, 7), 331 (13), 257 (41), 199 (81), 147 (72), 133 (46), 75 (100).

11. Preparation of (1*R*,2*S*,3*R*,5*R*)-1,2-*O*-Cyclohexylidene-3,5-di-*O*-benzyl-1,2,3,5-tetrahydroxy-5-(benzyloxymethyl)cyclohexane 145:



To a suspension of NaH (5.04 g, 60 % suspension in mineral oil, 126 mmol, previously washed with pet ether to remove the mineral oil) in dry DMF (150 mL) was added a solution of **134** (10 g, 39.37 mmol) in DMF (50 mL) drop wise at 0 ^oC. The mixture was allowed to warm to room temperature and was heated to 50 ^oC for 1h. The reaction mixture was recooled to 0 ^oC (forms a light brown suspension) followed by the addition of benzyl chloride (14.16 mL, 123.07 mmol). The resulting mixture was further stirred for 24 h. The reaction mixture was diluted with water (200 mL) and extracted with pet ether: ethyl acetate (1:1, 3x 200 mL). The combined organic extracts were washed with water (2x200 mL), brine (1x100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was column chromatographed over silica gel using pet ether: ethyl acetate (19:1) as eluant to yield **145** as colorless oil (17.7 g, 95 %).

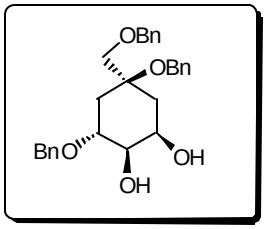
IR ($CHCl_3$) : 1452, 1093 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.45- 7.20 (m, 15H), 4.80 (d, *J* = 12.2 Hz, 1H), 4.65 (d, *J* = 12.2 Hz, 1H), 4.60 (d, *J* = 10.8 Hz, 1H), 4.55 (s, 2H), 4.45 (d, *J* = 10.8 Hz, 1H), 4.35 (m, 1H), 4.20- 3.90 (m, 2H), 3.5 (dd, *J* = 10.8, 9.8 Hz, 2H), 2.45 (dt, *J* = 15.6, 2.9 Hz, 1H), 2.20 (ddd, *J* = 13.7, 3.9, 2.0 Hz, 1H), 1.90 (dd, *J* = 15.6, 4.8 Hz, 1H), 1.75- 1.3 (m,11H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 139.3, 138.8, 138.0, 128.3, 128.1, 127.9, 127.7, 127.3, 127.2, 127.1, 126.8, 109.0, 79.8, 76.1, 75.3, 75.1, 73.2, 71.5, 64.4, 37.9, 35.1, 30.8, 25.0, 24.0, 23.7.

Mass *m/z* (%) : 316 (M^+- 212, 1), 181 (2), 105 (12), 91 (100)

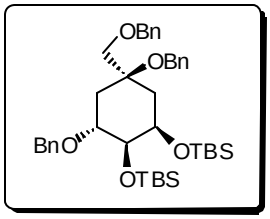
12. Preparation of (1*R*,2*R*,3*R*,5*R*)-3,5-Di-*O*-benzyl-1,2,3,5-tetrahydroxy-5-(benzyloxymethyl)cyclohexane 146:



A solution of **145** (10 g, 18.94 mmol) in acetic acid: water (8:2,100 mL) was warmed to 50 ^oC for 10 h. The progress of the reaction was monitored by TLC. After the reaction was over, acetic acid was distilled off under reduced pressure. The residue was dissolved in ethyl acetate (300 mL), washed with water (2x100 mL), brine (1x100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was column chromatographed over silica gel using pet ether: ethyl acetate (1:1) to give **146** (8.1 g, 95 %) as a colorless pasty mass.

$[a]_D^{25}$	**:**	-5.0^o (*c* 1, $CHCl_3$)
IR ($CHCl_3$)	**:**	3472, 2246 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 7.60- 7.15 (m, 15H), 4.75 (bs, 2H), 4.55 (bs, 2H), 4.50 (d, *J* = 10.7 Hz, 1H), 4.30 (d, *J* = 10.7 Hz, 1H), 4.05 (m, 1H), 3.75 (m, 1H), 3.5 (m, 3H), 2.95, (bs, 2H), 2.55 (dt, *J* = 14.7, 3.9 Hz, 1H), 2.30 (m, 1H), 1.65 (dd, *J* = 15.1, 3.4 Hz, 1H), 1.45 (dd, *J* = 14.1, 11.7 Hz, 1H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 138.5, 137.6, 129- 127 (multiple peaks), 79.6, 76.0, 74.5, 73.9, 73.2, 72.1, 70.2, 64.7, 36.2, 33.5.
Mass *m/z* (%)	**:**	357 (M+- 91, 6), 327 (4), 233 (4), 181 (30), 107 (19), 91 (100).

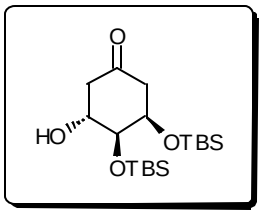
13. Preparation of (1*R*,2*S*,3*R*,5*R*)-1,2-Di-*O*-tertbutyldimethylsilyl-3,5-di-*O*-benzyl-1,2,3,5-tetrahydroxy-5-(benzyloxymethyl)cyclohaxane 147:



To a solution of **146** (8 g, 17.86 mmol), imidazole (3.65 g, 53.57 mmol), DMAP (0.1 g, 0.821 mmol) in dry DMF (50 mL) was added drop wise a solution of TBSCl (6.72 g, 44.65 mmol) in dry DCM (30 mL) at 0 ^oC. The resulting mixture was stirred at room temperature for 24 h. After the reaction was over, the mixture was diluted with water and extracted with pet ether: ethyl acetate (3:1, 3x200 mL). The combined organic extracts were washed with water (2x200 mL), brine (1x100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel using pet ether: ethyl acetate (98:2) as eluant to give **147** (9.7 g, 80 %) as a colorless oil.

$[a]_D^{25}$ ($CHCl_3$)	**:**	-8.0° (*c* 0.75, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 7.45- 7.15 (m, 15H), 4.70- 4.40 (m, 6H), 3.98 (ddd, *J* = 11.8, 4.9, 2.5 Hz, 1H), 3.82 (m, 2H), 3.62 (m, 2H), 2.20- 1.85 (m, 4H), 0.95 (s, 9H), 0.93 (s, 9H), 0.10 (s, 3H), 0.07 (s, 6H), 0.00 (s, 3H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 140.0, 138.5, 128- 126 (multiple peaks), 78.0, 74.0, 73.1, 71.8, 70.9, 67.8, 63.7, 33.7, 29.1, 25.8, 25.6, 18.1, 17.9, -4.6, -4.8, -4.9, -5.3.

14. Preparation of (3*R*,4*S*,5*R*)-3,4-Di-*O*-tertbutyldimethylsilyl-3,4,5-trihydroxycyclohexanone 148:



A mixture of **147** (10 g, 14.79 mmol), Pd-C (0.2 g, 10 % on activated charcoal) and ethanol (50 mL) was hydrogenated for 24 h at 1 atmosphere. After reaction was over, the mixture was filtered through a short pad of Celite. The filtrate was concentrated to afford **144** (6.0 g, 100 %) as a pure white solid which was used as such for the next step.

To a solution of **144** (5 g, 12.32 mmol) in ethanol: water (9:1, 60 mL) was added sodium metaperiodate (5.3 g, 24.63 mmol) portion wise at room temperature. The stirring was continued for additional 6 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was column chromatographed over silica gel using pet ether: ethyl acetate (10:1) as an eluant to yield **148** (4.6 g, 100 %) as a white solid.

Melting point : 96- 97 ^{o}C

$[a]_D^{25}$: -10.8^{o} (*c* 0.6, $CHCl_3$)

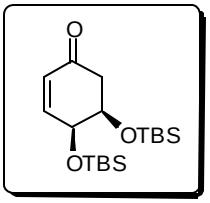
IR ($CHCl_3$) : 3443, 1710, 1461 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.2 (m, 2H), 3.88 (dd, *J* = 6.4, 2.0 Hz, 1H), 2.83 (ddd, *J* = 15.1, 4.4, 1.0 Hz, 1H), 2.69 (ddd, *J* = 14.1, 8.3, 1.5 Hz, 1H), 2.45 (ddd, *J* = 14.1, 4.0, 1.0 Hz, 1H), 2.31 (ddd, *J* = 15.1, 6.3, 1.0 Hz, 1H), 0.95 (s, 9H), 0.85 (s, 9H), 0.15 (s, 6H), 0.05 (s, 6H).

^{13}C NMR (200 MHz, $CDCl_3$) : δ 207.7, 74.7, 69.9, 69.8, 46.8, 44.8, 25.7, 18.0, -4.6, -4.7, -4.9.

Mass *m/z* (%) : 317 (M^{+}-57, 22), 299 (15), 185 (45), 157 (21), 147 (76), 73 (100)

15. Preparation of (4*S*,5*R*)-4,5-Di-*O*-tertbutyldimethylsilyl-4,5-dihydroxy-2-cyclohexenone 149:

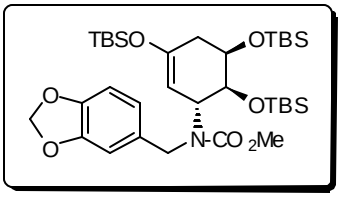


To a solution of **148** (5 g, 13.37 mmol), triethylamine (4.1 mL, 29.41 mmol) in dry DCM (50 mL) was added a solution of MsCl (1.3 mL, 16.04 mmol) in dry DCM (10 mL) over 1 h at 0 ^{o}C. After the addition was over, the mixture was allowed to stir at room temperature for 1.5 h. The reaction mixture was diluted with DCM, washed with water (2x100 mL), brine (1x50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography

using pet ether: ethyl acetate (97:3) as eluant to give **149** (4.5 g, 95 %) as a white solid.

Melting point	**:**	57-59 ^{o}C
$[a]_D^{25}$	**:**	+106.7^{o} (*c* 0.6, $CHCl_3$)
IR ($CHCl_3$)	**:**	1685 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 6.70 (dd, *J* = 10.3, 3.5 Hz, 1H), 5.95 (d, *J* = 10.3 Hz, 1H), 4.45 (bs, 1H), 4.15 (dd, *J* = 6.8, 2.9 Hz, 1H), 2.75 (dd, *J* = 16.2, 6.8 Hz, 1H), 2.45 (dd, *J* = 16.2, 2.9 Hz, 1H), 0.95 (s, 9H), 0.85 (s, 9H), 0.15 (s, 6H), 0.05 (s, 6H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 197.4, 148.7, 129.2, 71.5, 69.3, 44.0, 25.6, 18.1, -4.7.
Mass *m/z* (%)	**:**	356 (M^+, 1), 341 (2), 299 (50), 198 (24), 147 (100), 73 (57)

16. Preparation of Methyl-1,3-benzodioxol-5-ylmethyl[(1*R*,5*R*,6*S*)-5,6-di-*O*-tertbutyldimethylsilyl-5,6-dihydroxy-3-methoxycyclohex-2-en-1-yl]carbamate 150:

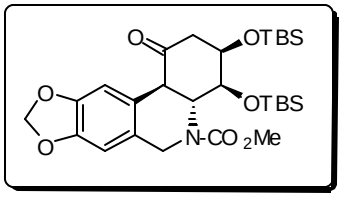


To a solution of **140** (3.17 g, 15.17 mmol), HMPA (5 mL) in dry THF (40 mL) was added *n*-BuLi (2.3 *M*, 6.6 mL, 15.17 mmol) at –78 ^{o}C. The mixture was stirred at same temperature for 0.5 h. A solution of **149** (4.5 g, 12.64 mmol) in dry THF (10 mL) was added drop wise to the reaction mixture and allowed to stir for additional 0.5 h followed by the addition of TBSCl (2.28 g, 15.17 mmol) in dry THF (10 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 (2:1, 2x100

mL). The combined organic extracts were washed successively with water (2x100 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 (98:2) as eluant to give **150** (8.15 g, 95 %) as a colorless gummy mass.

$[a]_D^{25}$	**:**	-54.1° (*c* 2, $CHCl_3$)
IR ($CHCl_3$)	**:**	1704, 1462, 1254 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 6.7 (m, 3H), 5.92 (s, 2H), 4.55- 4.25 (m, 3H), 3.90 - 3.6 (m, 6H), 2.15 (m, 2H), 0.93 (s, 9H), 0.87 (s, 18H), 0.2 – -0.1, (m, 18H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 156.8, 151.0, 147.5, 146.2, 120.0, 107.7, 107.6, 101.1, 100.6, 73.0, 68.9, 58.2, 52.0, 48.6, 36.2, 25.6, 25.3, 17.8, -4.7, -5.0, -5.1.
Mass *m/z* (%)	**:**	623 (M^+-56, 33), 548 (11), 289 (3), 200 (3), 136 (29), 73 (100).

17. Preparation of Methyl (3*R*,4*S*,4a*R*,10b*R*)-3,4-di-*O*-tertbutyldimethylsilyl-8,9-benzodioxol-3,4-dihydroxy-1-oxo-2,3,4,4a,6,10b-hexahydrophenanthridine-5(1*H*)-carboxylate 151:

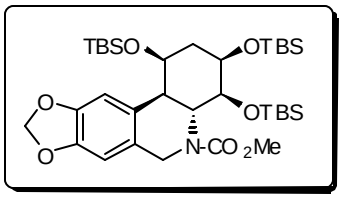


A solution of **150** (0.6 g, 0.88 mmol), 1,4-dicyanonaphthalene (DCN, 0.05 g, 0.28 mmol) in acetonitrile: water (24:1, 250 mL) was irradiated (pyrex filter, >280 nm, 450 W Hanovia medium pressure lamp) for 6 h. The solvent was concentrated under reduced pressure and residue was column chromatographed over silica gel using pet

ether: ethyl acetate (19:1) as eluant to give **151** (0.34 g, 68 %) as a single diastereomer.

$[a]_D^{25}$	**:**	+17.5° (*c* 2.1, $CHCl_3$)
IR ($CHCl_3$)	**:**	1717, 1695, 1215 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 6.65 (s, 1H), 6.48 (s, 1H), 5.94 (s, 2H), 4.87 (bd, *J* = 17.9 Hz, 2H), 4.25- 3.60 (complex multiplet, 7H), 2.50 (m, 2H), 0.90 (s, 18H), 0.10 (s, 12H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 206.7, 156.0, 146.9, 126.2, 107.2, 106.4, 100.9, 70.6, 70.3, 52.4, 51.3, 45.3, 43.2, 29.4, 25.4, 17.8, 17.6, -3.8, -4.6, -5.0, -5.2.
Mass *m/z* (%)	**:**	563 (M^+, 2), 548 (2), 506 (93), 374 (4), 232 (19), 147 (57), 73 (100).

18. Preparation of (1*S*,3*R*,4*S*,4a*R*,11b*R*)-1,3,4-Tri-*O*-tertbutyldimethylsilyl-2,3,4,4a,6,11b-hexahydro-1*H*-[1,3]dioxolo[4,5-*j*]phenanthridine-5-carboxylic acid methyl ester 152:



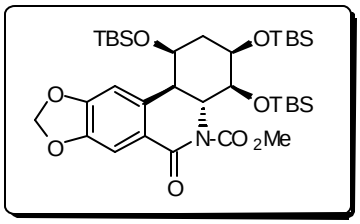
To a solution of **151** (0.1 g, 0.18 mmol) in isopropyl alcohol (1 mL) was added sodium borohydride (0.014 g, 0.36 mmol) at 0 °C. The resulting mixture was allowed to stir at room temperature for 12 h. Saturated sodium chloride solution (1 mL) was added and the stirring was continued for another 12 h. The reaction mixture was extracted with ethyl acetate (3x10 mL). The combined organic extracts were washed successively with water (2x10mL), brine (1x10 mL), dried over Na_2SO_4 and

concentrated under reduced pressure. The crude mixture was subjected to TBS protection without further purification.

To a solution of the above crude product, imidazole (0.018 g, 0.27 mmol), DMAP (one crystal) in dry DMF (1 mL) was added a solution of TBSCl in dry DCM (1 mL) at 0 ^{o}C. The resulting mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with water (2 mL) and the mixture was extracted with pet ether: ethyl acetate (1:1, 2x5 mL). The combined organic extracts were washed with water (2x5 mL), brine (1x5 mL), dried over sodium sulphate and concentrated. The residue was column chromatographed over silica gel using pet ether: ethyl acetate (98:2) as eluant to give **152** (0.103 g, 85 % yield over two steps) as a colorless pasty mass.

$[a]_D^{25}$	**:**	+27.0^{o} (*c* 0.75, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 6.74 (s, 1H), 6.65 (s, 1H), 5.90 (s, 2H), 4.97 (d, *J* = 16 Hz, 1H), 3.93 (d, *J* = 16.0 Hz, 1H), 3.80- 3.47 (m, 7H), 2.95 (dd, *J* = 10.3, 6.3 Hz, 1H), 2.10 (dd, *J* = 24,12.3 Hz, 1H), 1.75 (m, 1H), 0.95 (s, 9H), 0.90 (s, 9H), 0.80 (s, 9H), 0.15 (s, 6H), 0.05 (s, 6H), -0.25 (s, 3H), -0.45 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$)	**:**	δ 156.9, 146.5, 146.0, 131.0, 127.8, 111.2, 106.6, 100.5, 72.0, 70.3, 68.6, 58.0, 52.7, 45.9, 44.0, 36.2, 26.0 (multiple peaks), 18.0 (multiple peaks), -4.5, -5.0, -5.3, -6.0.
Mass *m/z* (%)	**:**	623 (M^{+}- 57, 17), 390 (7), 232 (4), 147 (23), 73 (100).

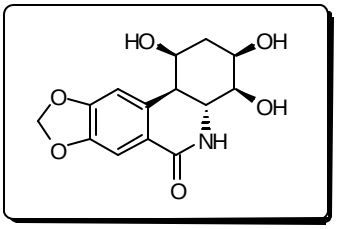
19. Preparation of (1*S*,3*R*,4*S*,4a*R*,11b*R*)-1,3,4-Tri-*O*-tertbutyldimethylsilyl-6-oxo-2,3,4,4a,6,11b-hexahydro-1*H*-[1,3]dioxolo[4,5-*j*]phenanthridine-5-carboxylic acid methyl ester 153:



To a stirred solution of sodium metaperiodate (0.047 g, 0.22 mmol) in degassed water (1 mL) was added ruthenium (IV) oxide (catalytic, 5 mg) at room temperature. The stirring was continued for 10 minutes. To this yellow solution, was added a solution of **152** (0.09 g, 0.15 mmol) in 1 mL of ethyl acetate and the stirring was continued for further 30 minutes. After the reaction was over, the reaction mixture was quenched with isopropyl alcohol and passed through a pad of Celite. The filtrate was concentrated under reduced pressure and residue was column chromatographed over silica gel using pet ether: ethyl acetate (19:1) as eluant to give **153** (0.09 g, 88 %) as a pasty mass.

$[a]_D^{25}$	**:**	+75.0° (*c* 0.2, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 7.52 (s, 1H), 6.74 (s, 1H), 6.0 (s, 2H), 4.2- 3.75 (complex multiplet, 7H), 3.65 (m, 1H), 2.95 (dd, *J* = 10.3, 3.7 Hz, 1H), 2.0, (m, 2H), 0.93 (s, 9H), 0.90 (s, 9H), 0.80 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.04 (s, 6H), -0.25 (s, 3H), -0.52 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$)	**:**	δ 163.5, 155.0, 151.5, 147.2, 136.5, 120.4, 111.5, 108.6, 102.4, 70.0, 69.5, 67.4, 60.4, 54.5, 42.7, 38.2, 26.0 (multiple peaks), 18.0 (multiple peaks), 14.0, -4.6, -4.7, -4.9, -5.1, -5.8.
Mass *m/z* (%)	**:**	636 (M^+- 57, 59), 389 (16), 248 (20), 189 (13), 147 (100).

20. Preparation of 2,7-dideoxypancratistatin 131:

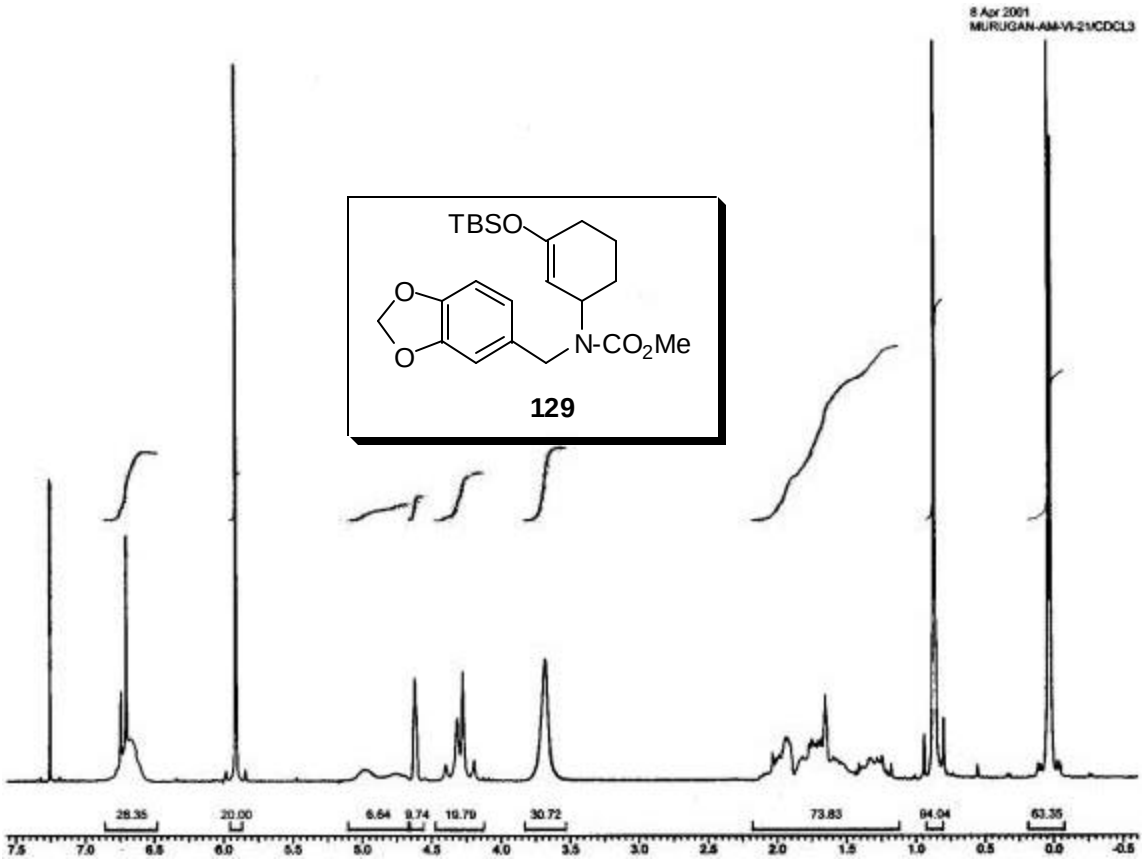


To a solution of **153** (0.09 g, 0.13 mmol) in dry methanol (1 mL) was added sodium methoxide solution (0.15 mL, 1*M*, 0.15 mmol) and the mixture was refluxed for 30 minutes. The mixture was diluted with water (1 mL) and extracted with ethyl acetate (2x5mL). The combined organic extracts were washed successively with water (2x5 mL), brine (1x5 mL), dried over sodium sulphate and concentrated under reduced pressure.

To solution of the above crude product in dry THF was added a solution of TBAF in THF (0.4 mL, 1*M*, 0.4 mmol) at 0 ^{o}C. The resulting mixture was allowed to stir for 10 h before quenching with water (1 mL). The mixture evaporated to dryness and the residue was column chromatographed over silica gel using ethyl acetate; methanol (9:1) as eluant to give **131** (0.034 g, 90 % over two steps) as a white solid.

$[a]_D^{25}$	**:**	+90.9^{o} (*c* 0.06, MeOH)
^{1}H NMR (200 MHz CD_3OD)	**:**	δ 7.38 (s, 1H), 6.86 (s, 1H), 6.05 (bs, 2H), 4.03- 3.92 (m, 3H), 3.63 (m, 1H), 2.74 (dd, *J* = 10.4, 3.4 Hz, 1H), 1.92 (m, 2H).
^{13}C NMR (125 MHz, CD_3OD)	**:**	δ 166.3, 150.3, 147.1, 136.7, 121.3, 109.3, 106.3, 101.4, 69.0, 68.4, 66.4, 55.6, 42.3, 35.7.
Mass *m/z* (%)	**:**	293 (M^+, 7), 239 (9), 190 (100), 172 (16), 132 (6), 85 (29), 69 (50), 57 (92).

SPECTRA


8 Apr 2001
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20.00
6.64
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19.79
30.72
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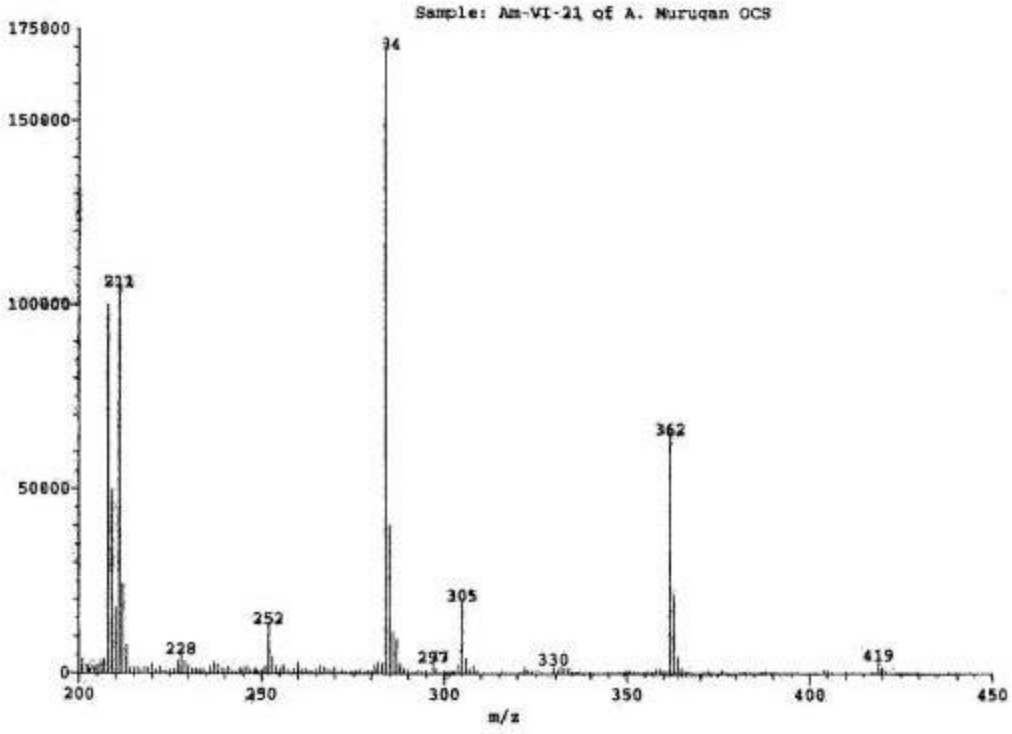
63.35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200
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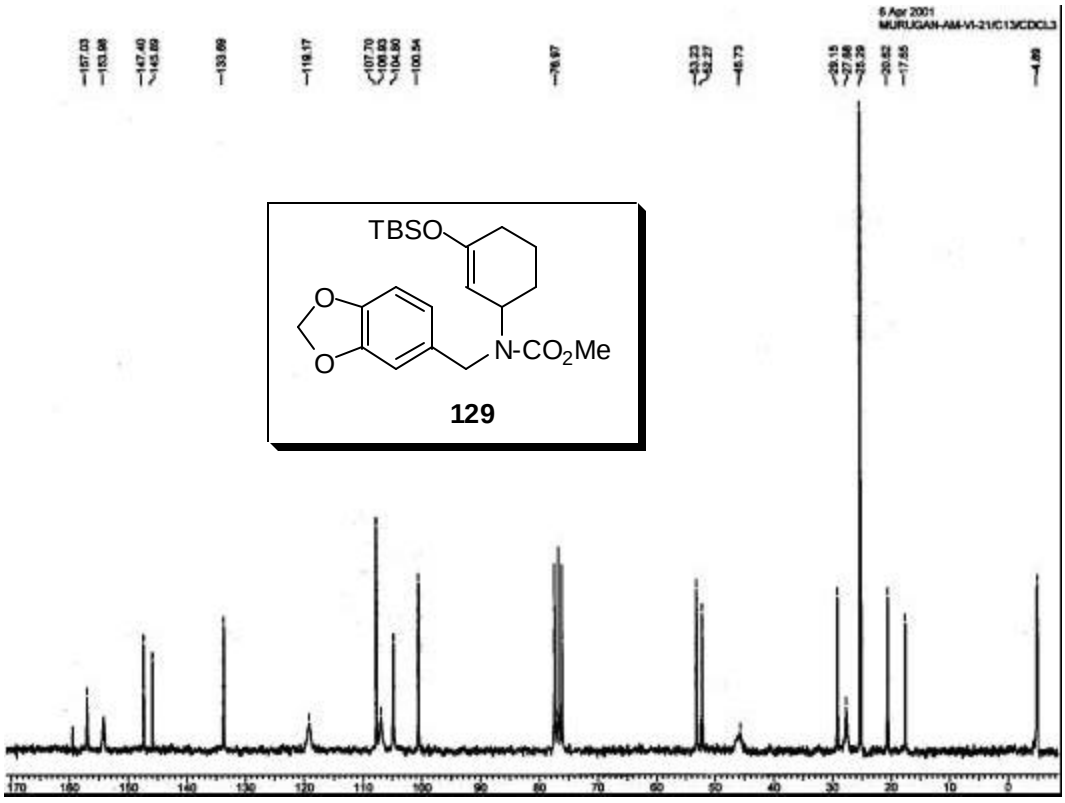
m/z


6 Apr 2001
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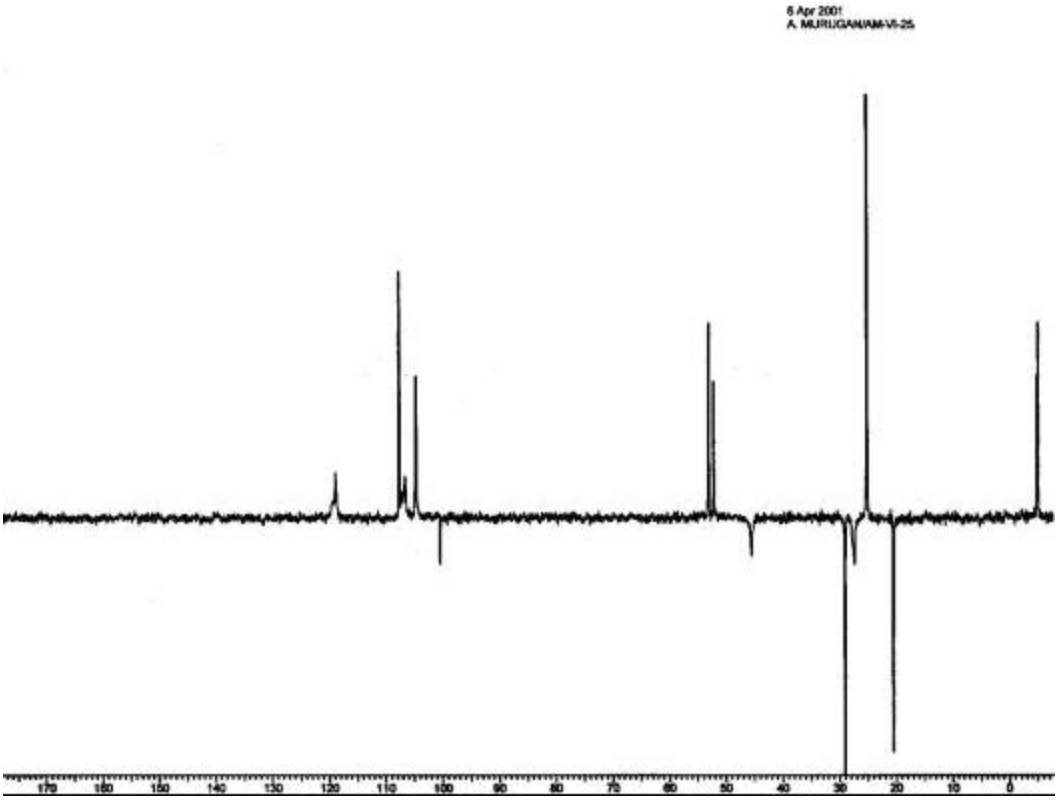
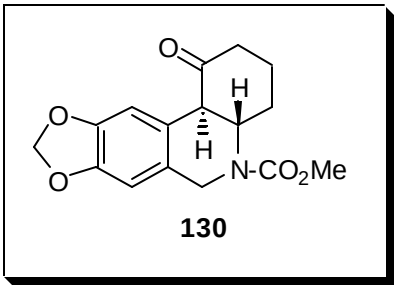
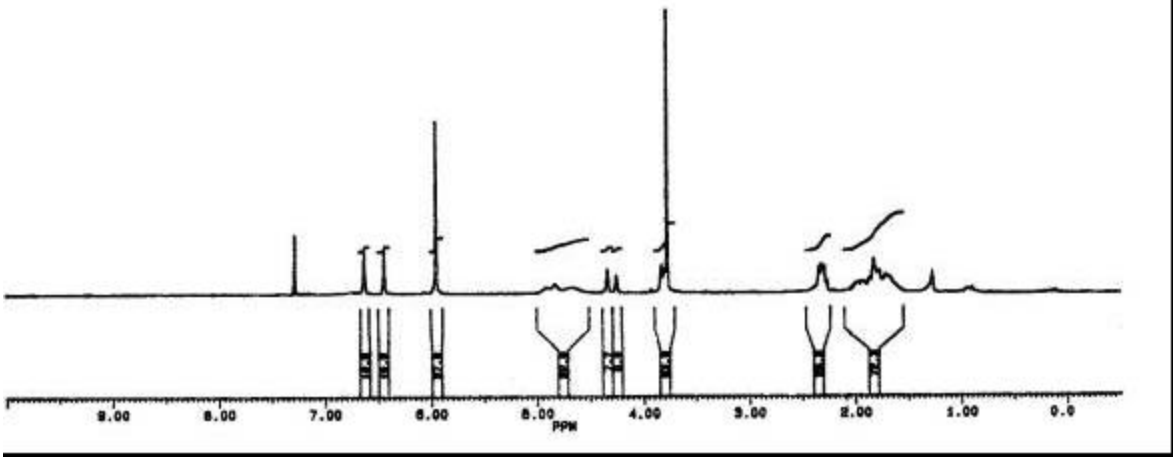
129


6 Apr 2001
A. MURUGAN/AM-VI-25



130



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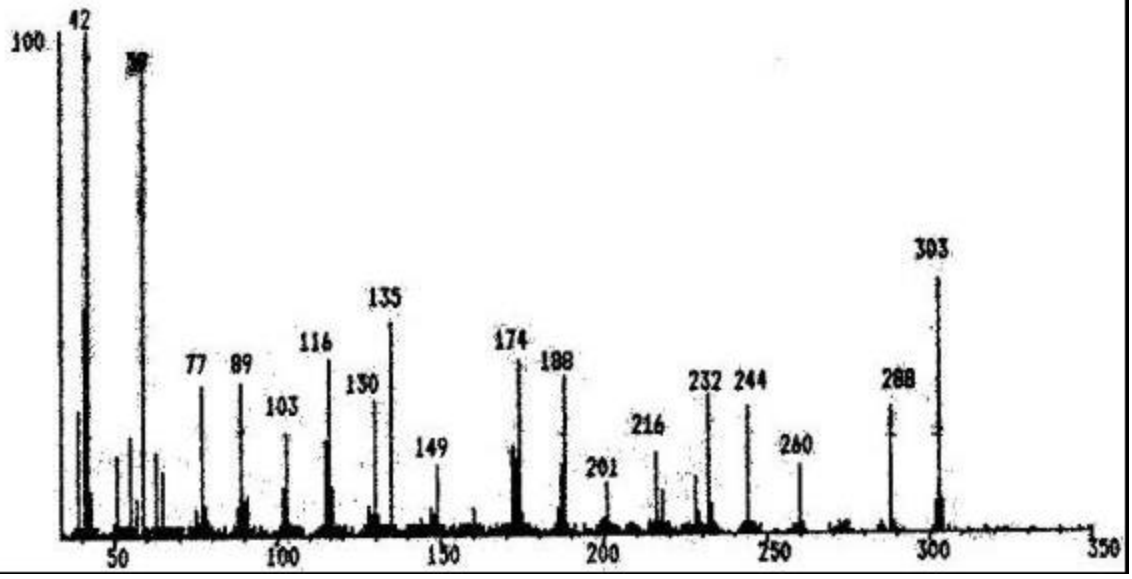
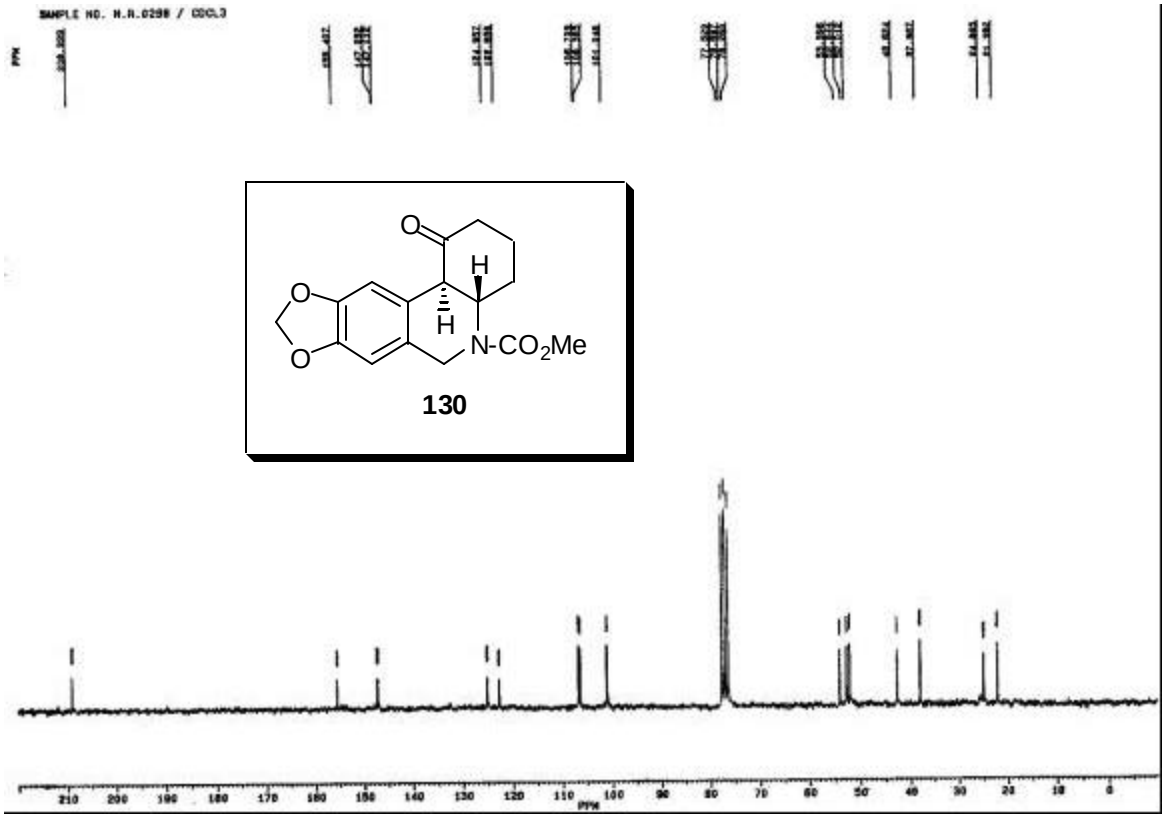
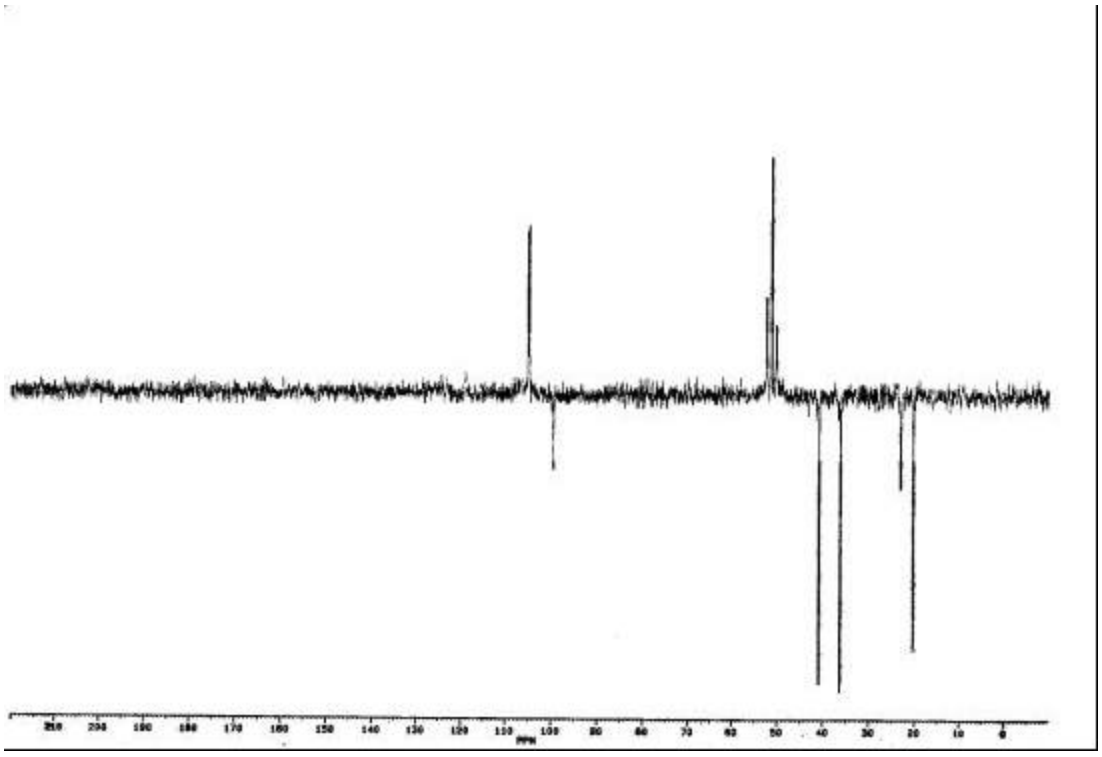
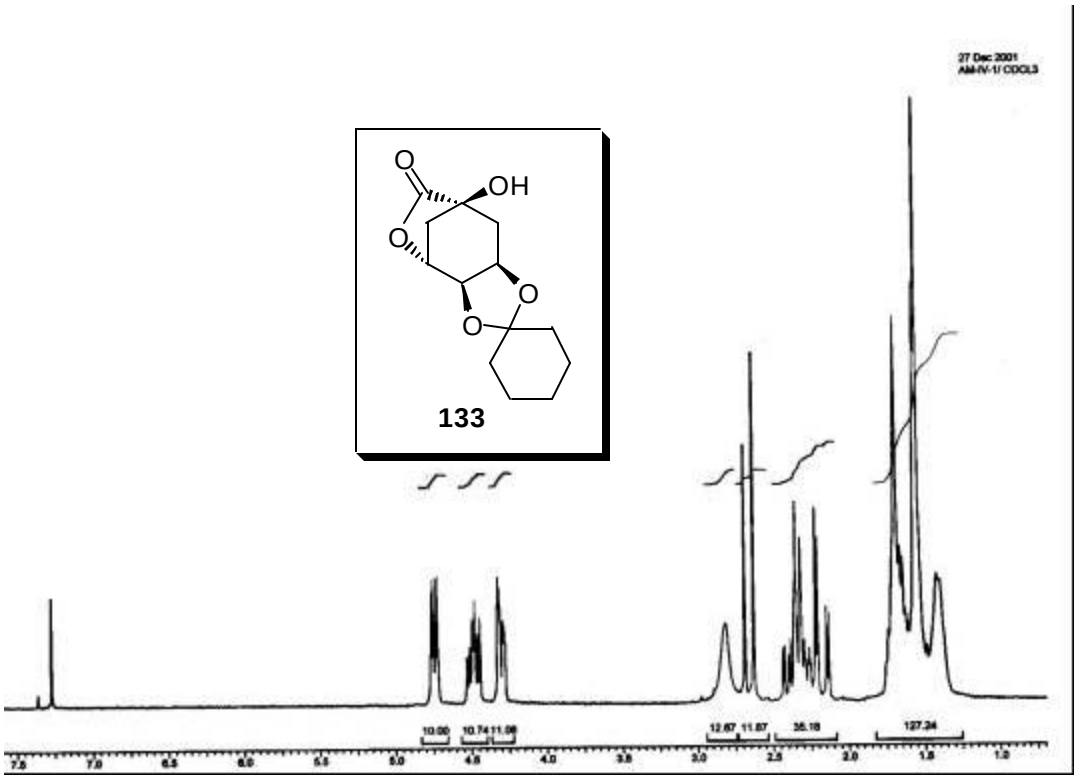
Date run : 11-06-1998(11:31:02) Instr. : VG 70-70H
Y CENTRE

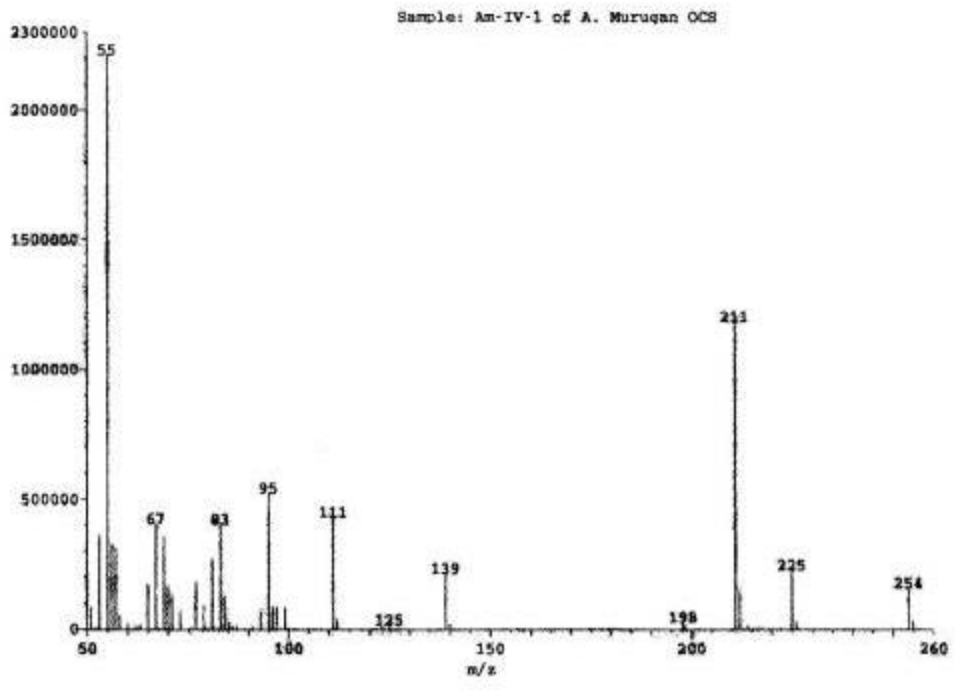


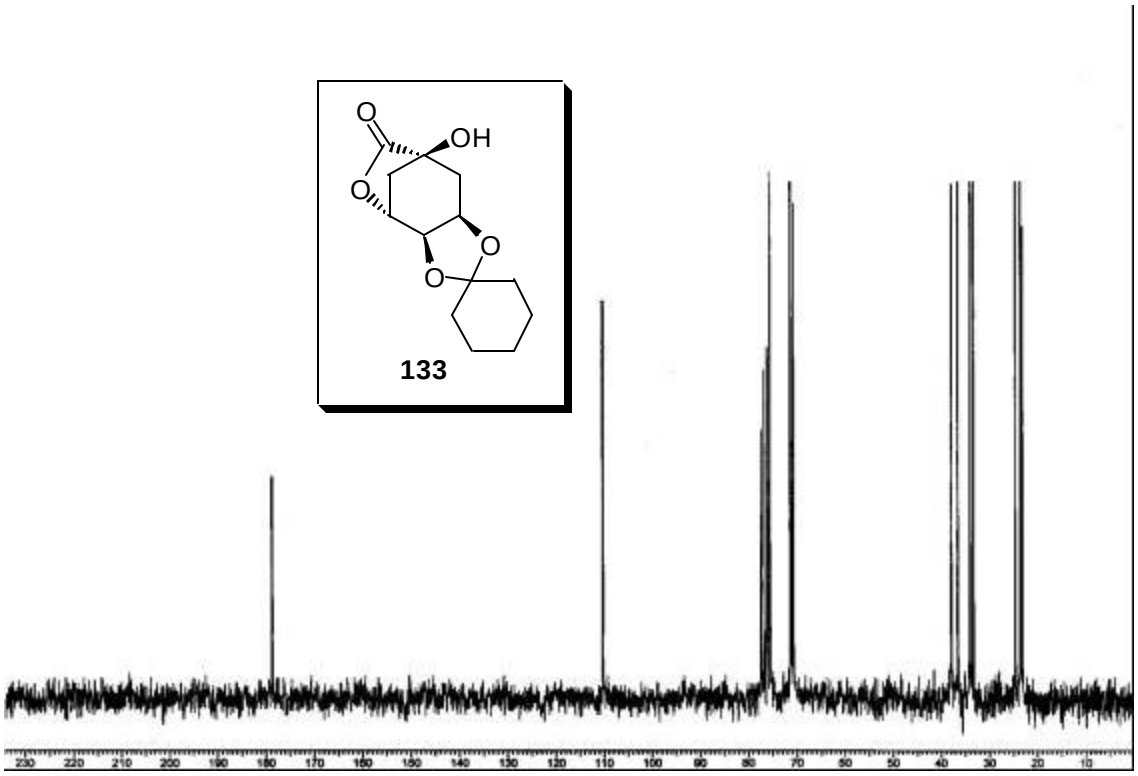

SAMPLE NO. N.R.0298 / CDCL3
PPM
O
H
O
H
O
N-CO2Me
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM

130

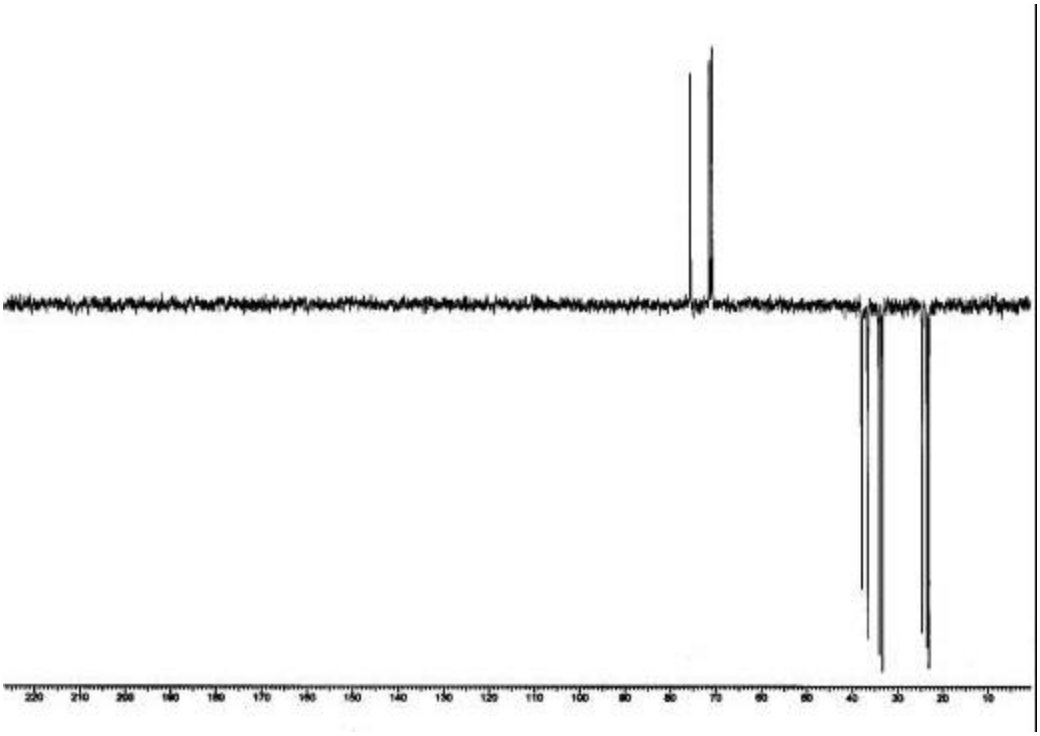

PPM

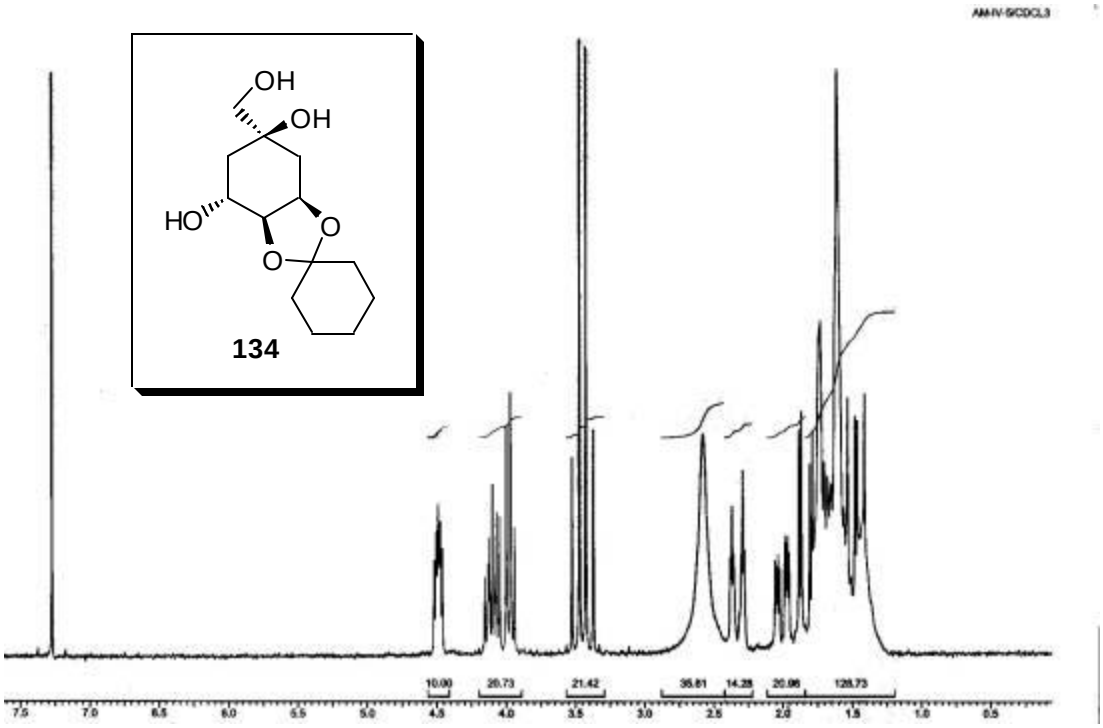

27 Dec 2001
O
OH
O
O
O
133

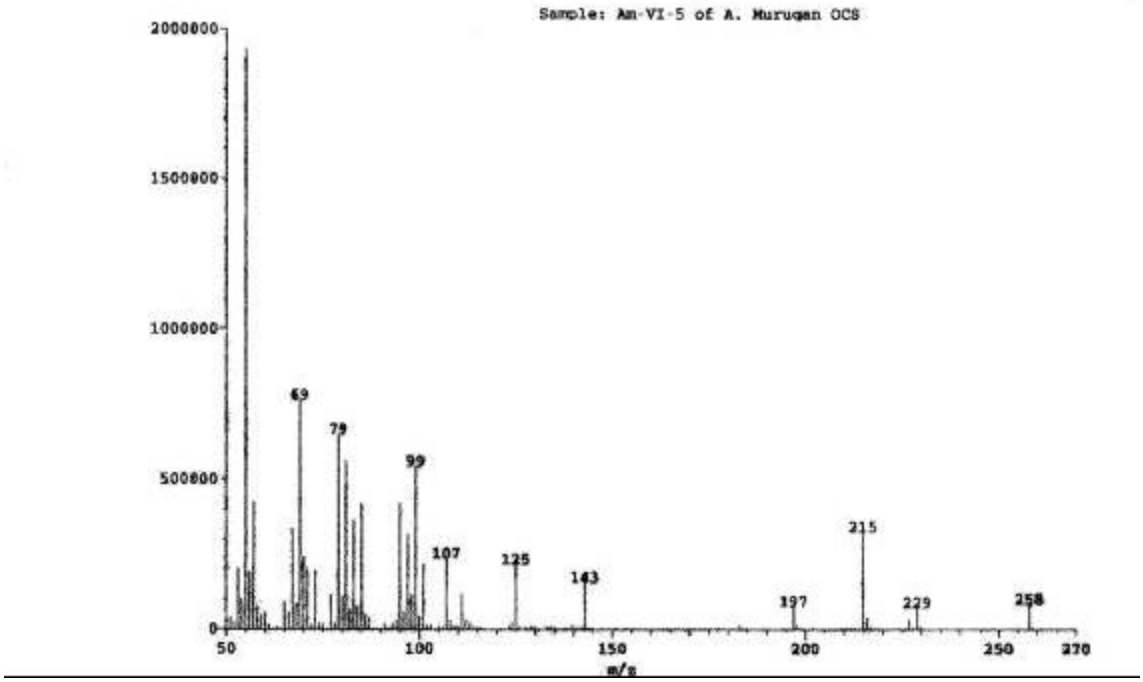

Sample: Am-IV-1 of A. Muruqan OCS
2300000
2000000
1500000
1000000
500000
0
55
67
83
95
111
139
211
225
254
50
100
150
200
250
m/z

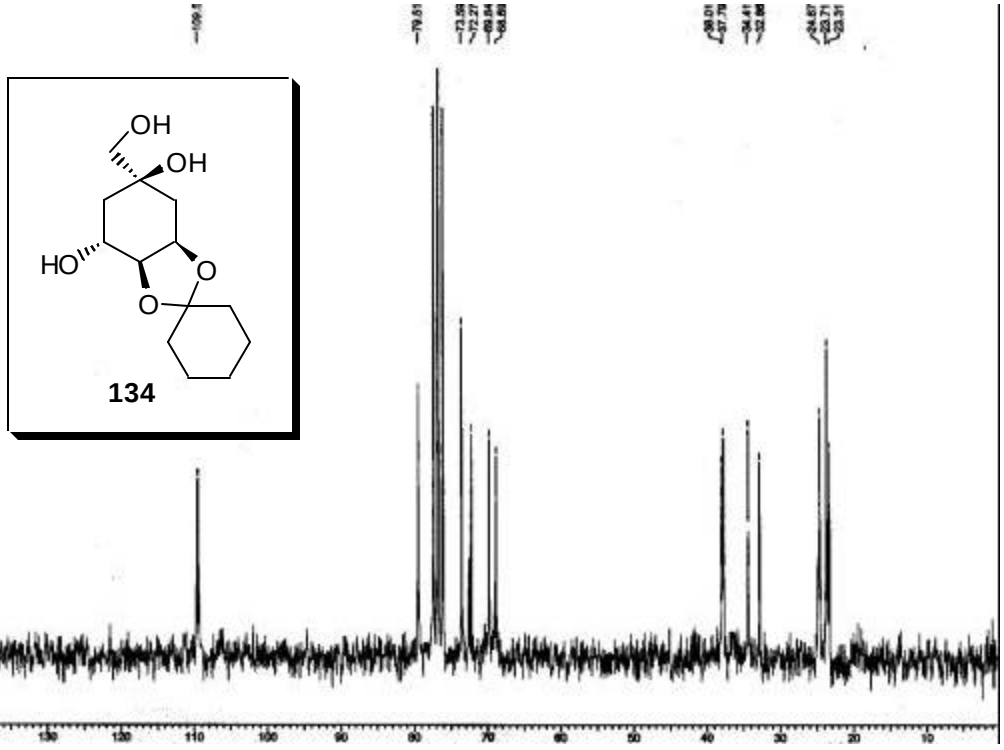


133

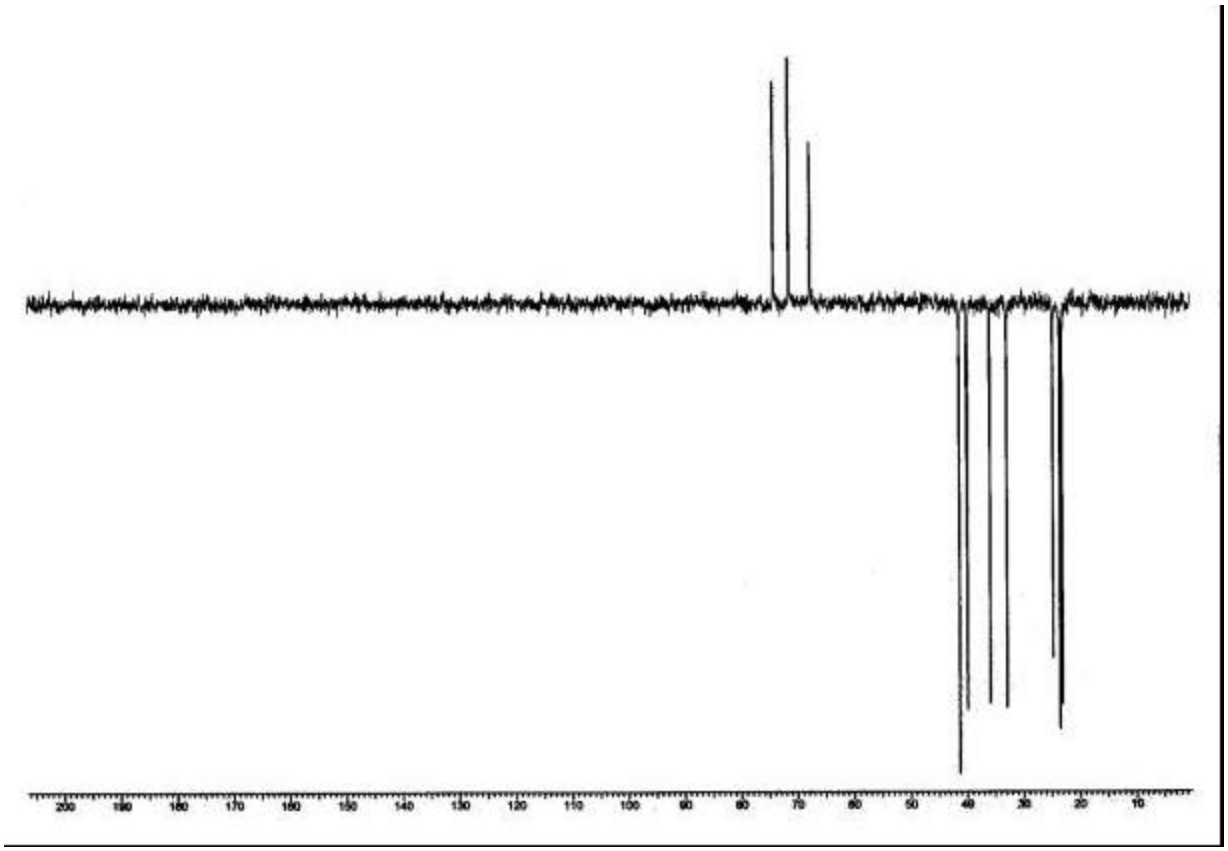


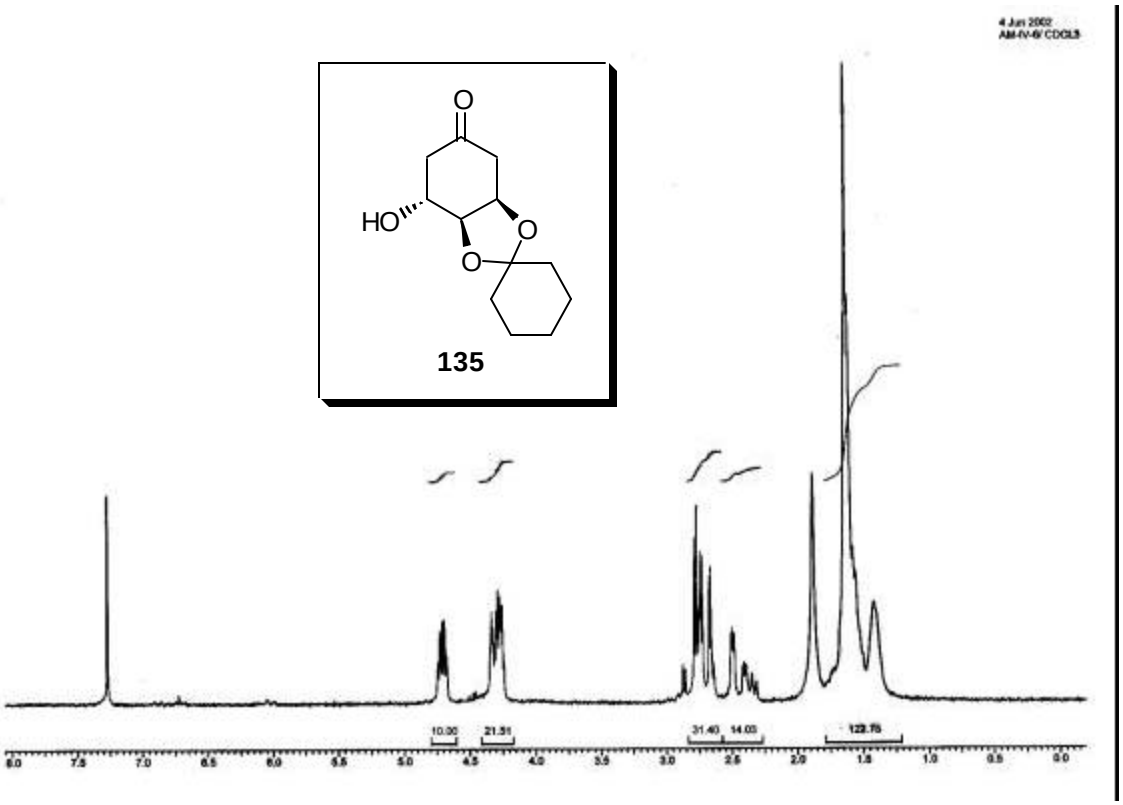

OH
OH
HO
O
O
134

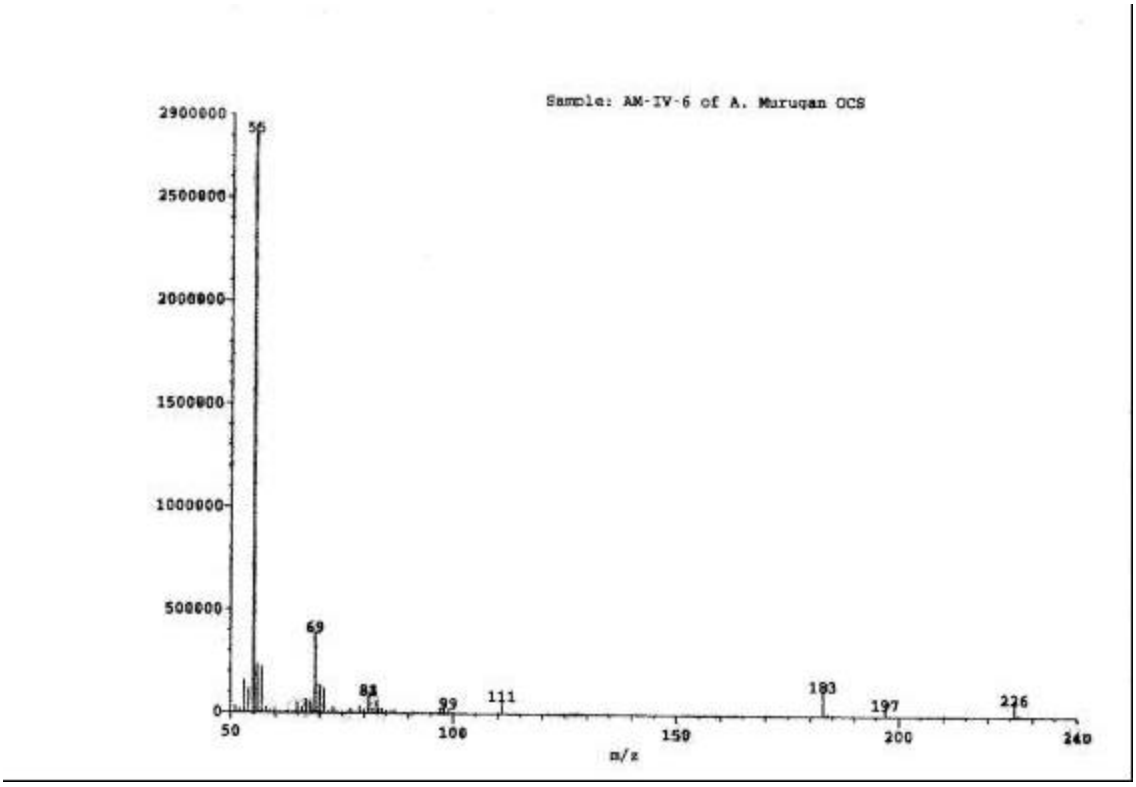

Sample: Am-VI-5 of A. Muruqan OCS
2000000
1500000
1000000
500000
0
69
79
99
107
125
143
197
215
229
258
50
100
150
200
250
270
m/z

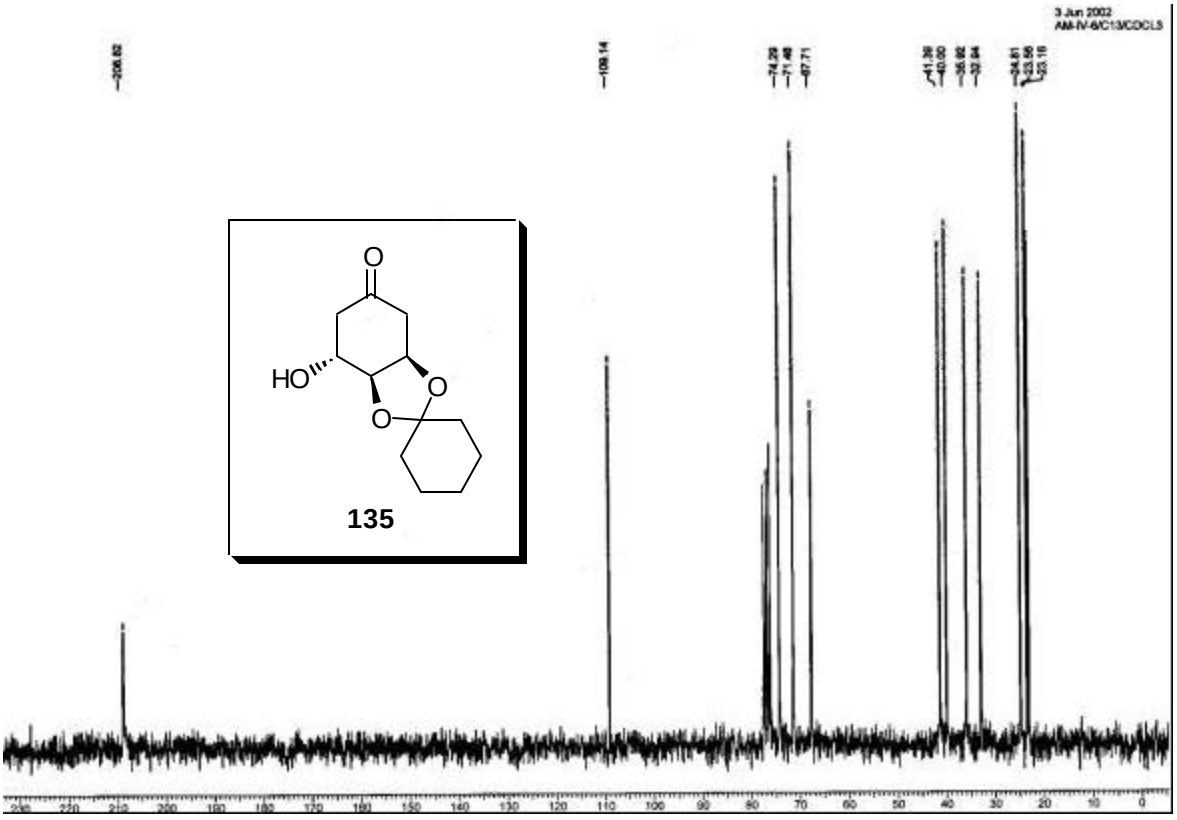


134

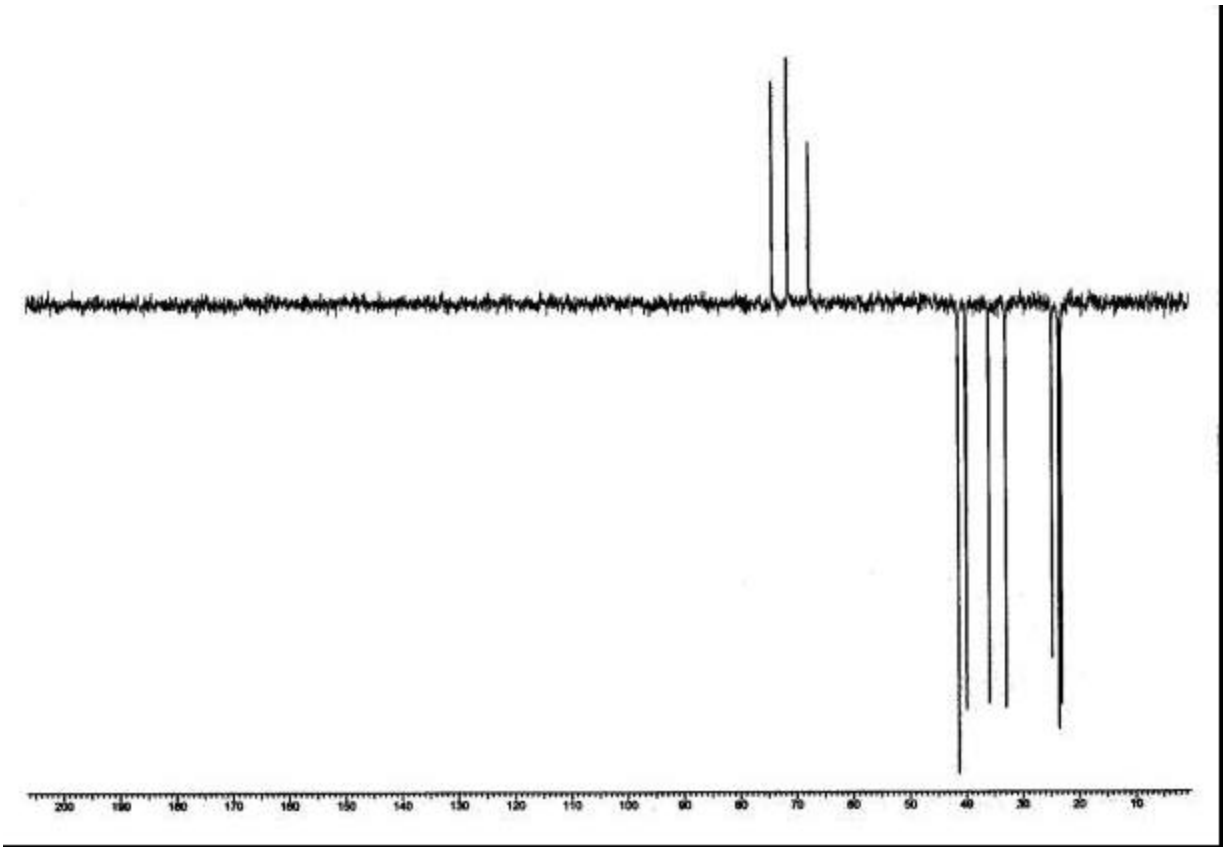


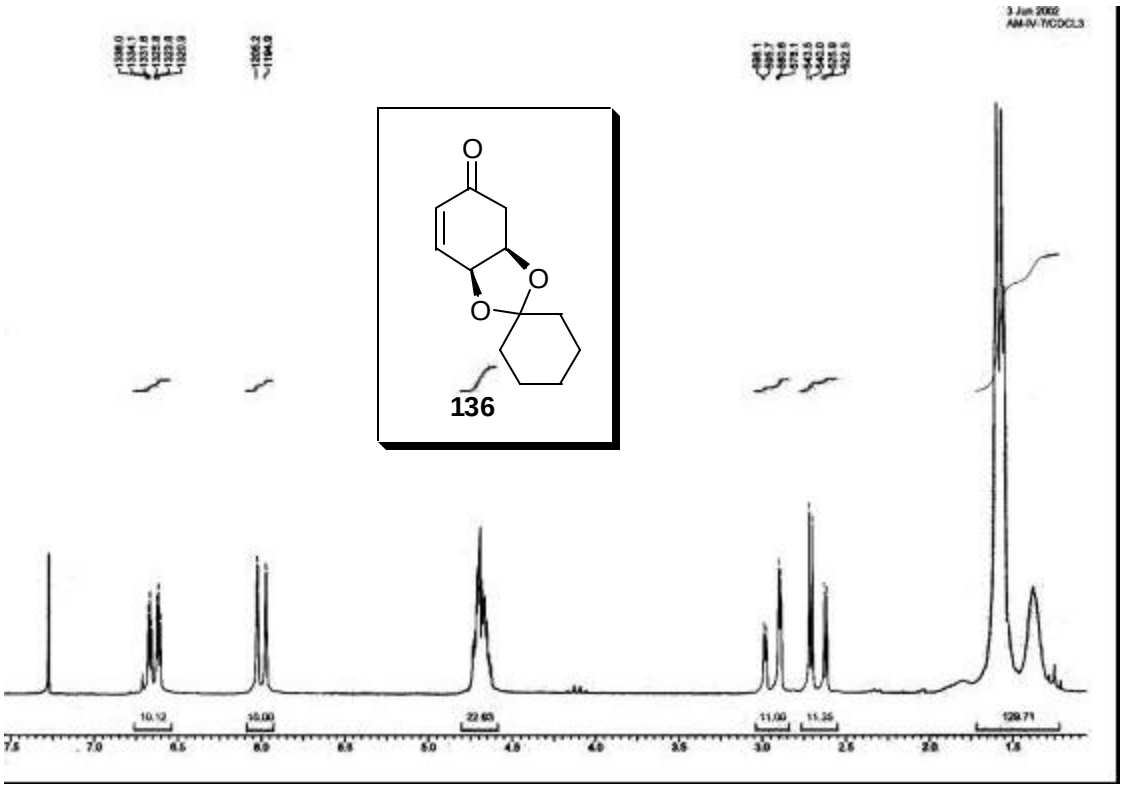

HO
O
O
O
135

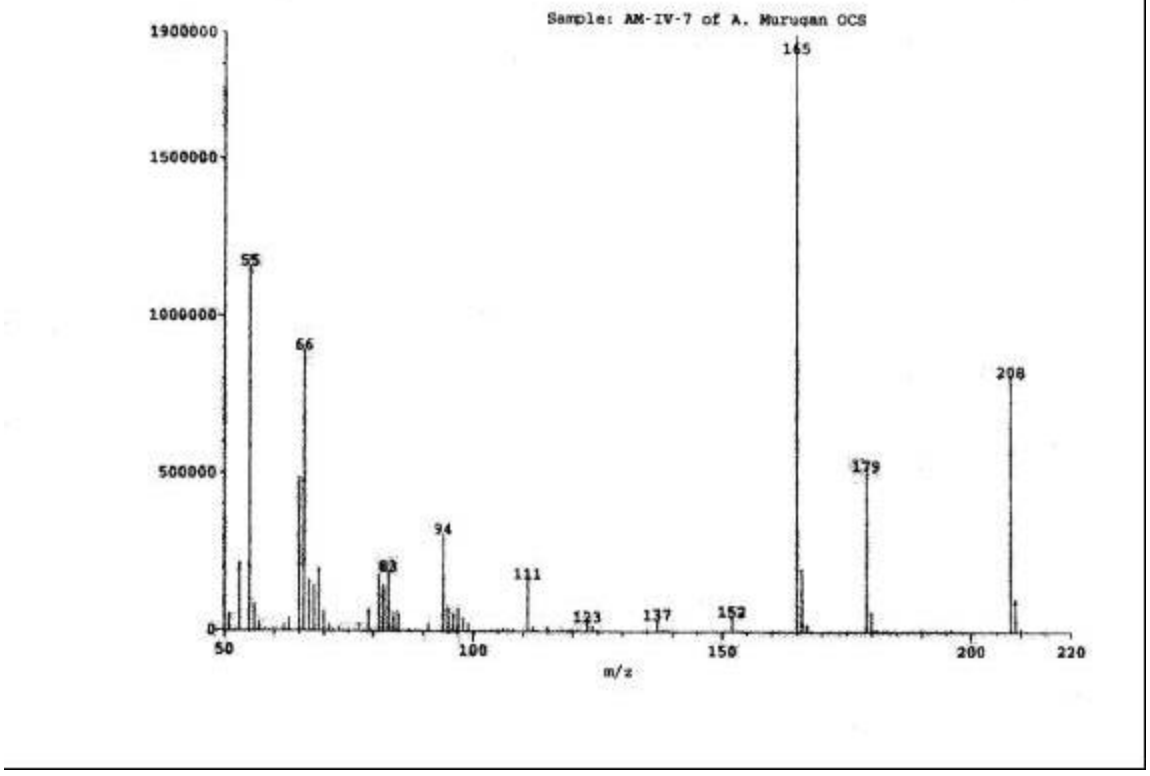

Sample: AM-IV-6 of A. Muruqan OCS
2900000
2500000
2000000
1500000
1000000
500000
0
55
69
81
99
111
183
197
226
50
100
150
200
m/z

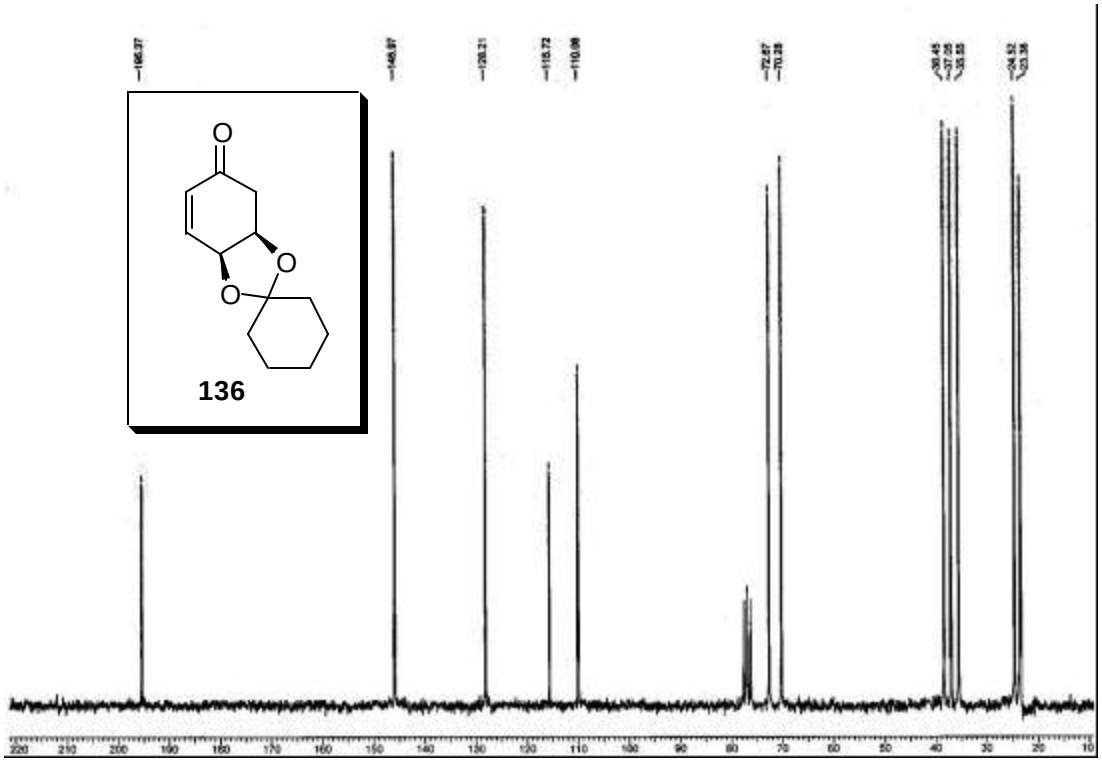

3 Jun 2002
AM-IV-6/C13/CDCL3
206.82
108.14
74.29
71.48
67.71
41.36
40.00
35.92
32.94
24.61
23.65
23.19
HO
O
O
O

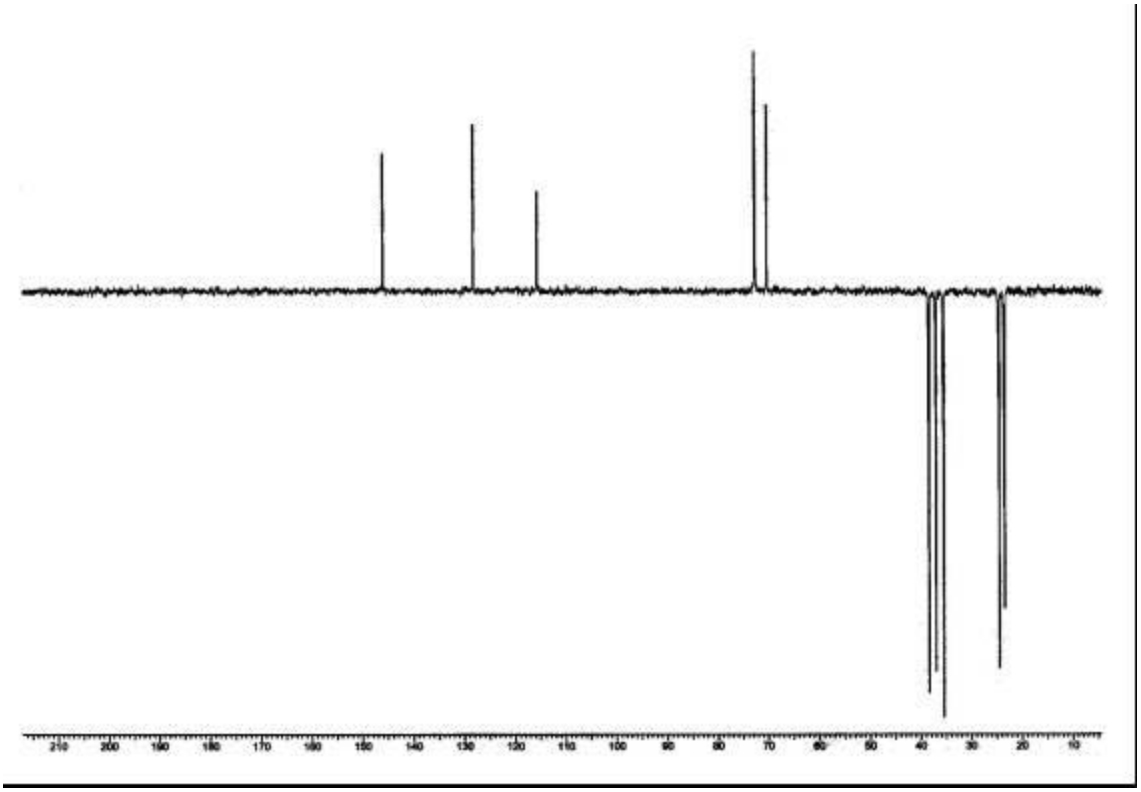
135

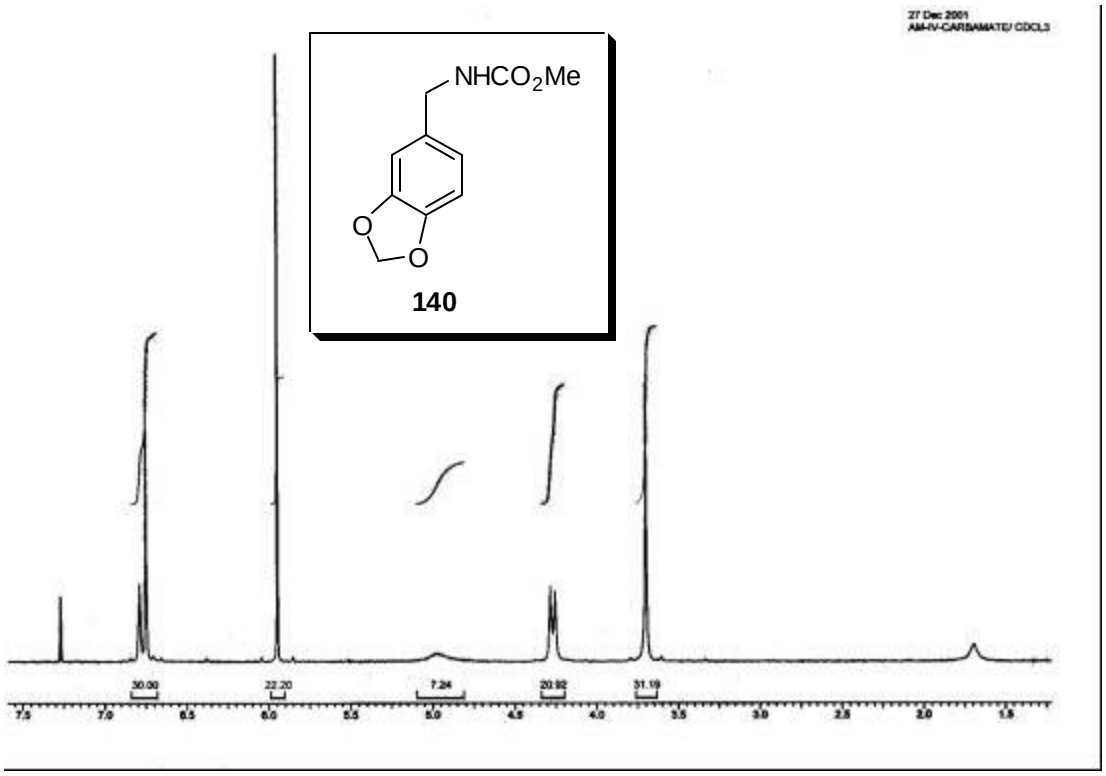


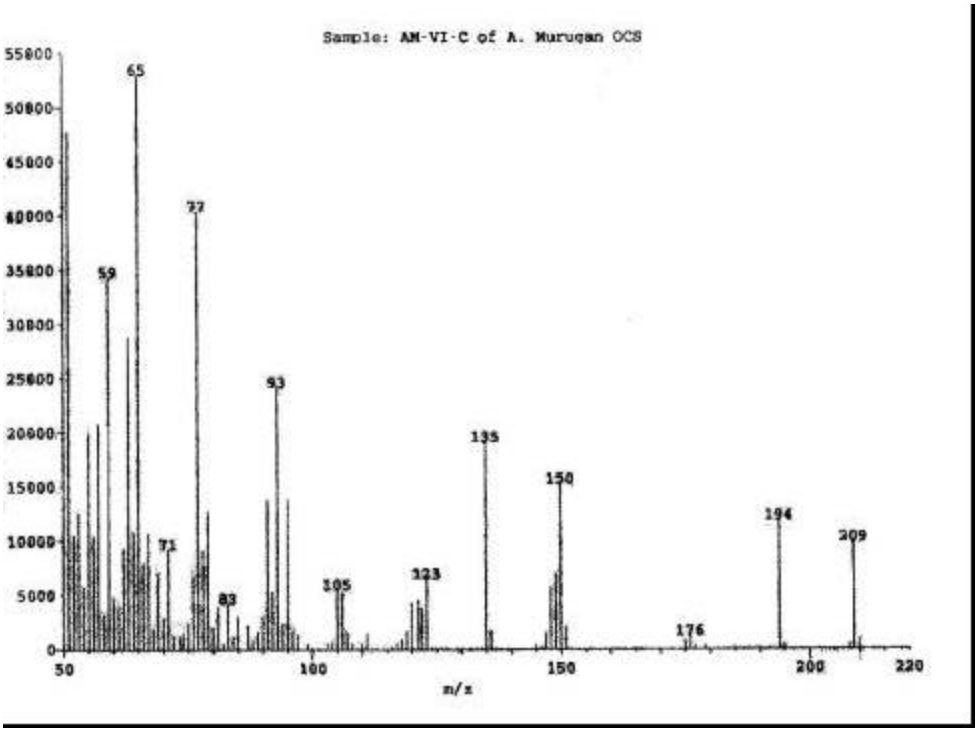

O
O
O
136

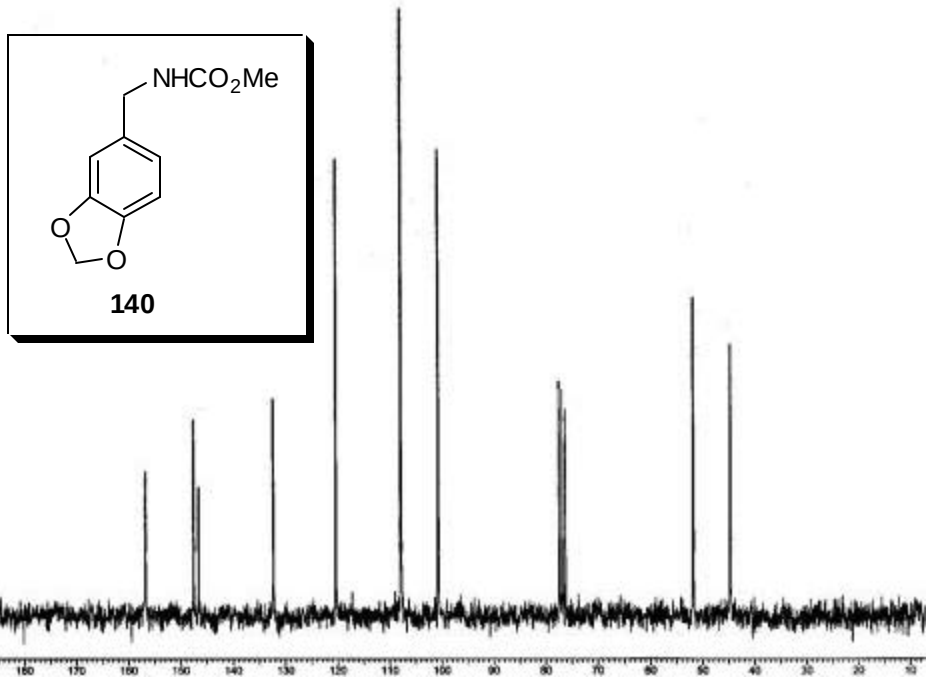

Sample: AM-IV-7 of A. Muruqan OCS
1900000
1500000
1000000
500000
0
55
66
83
94
111
123
137
152
165
179
208
50
100
150
200
220
m/z


136

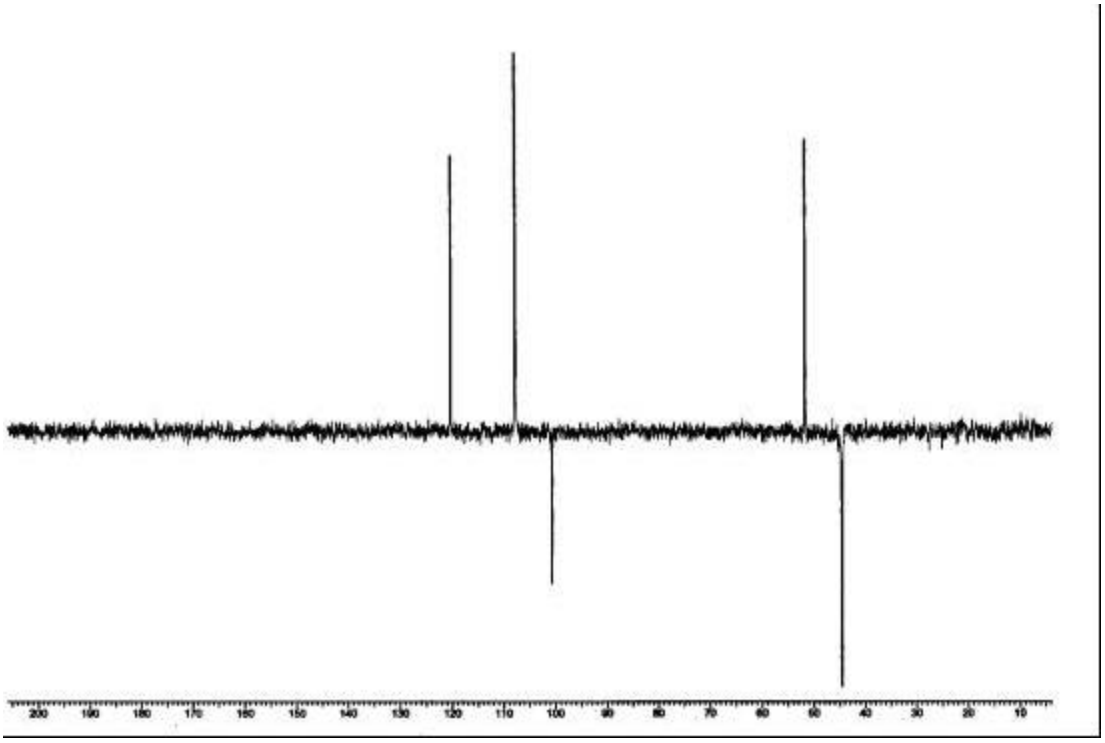


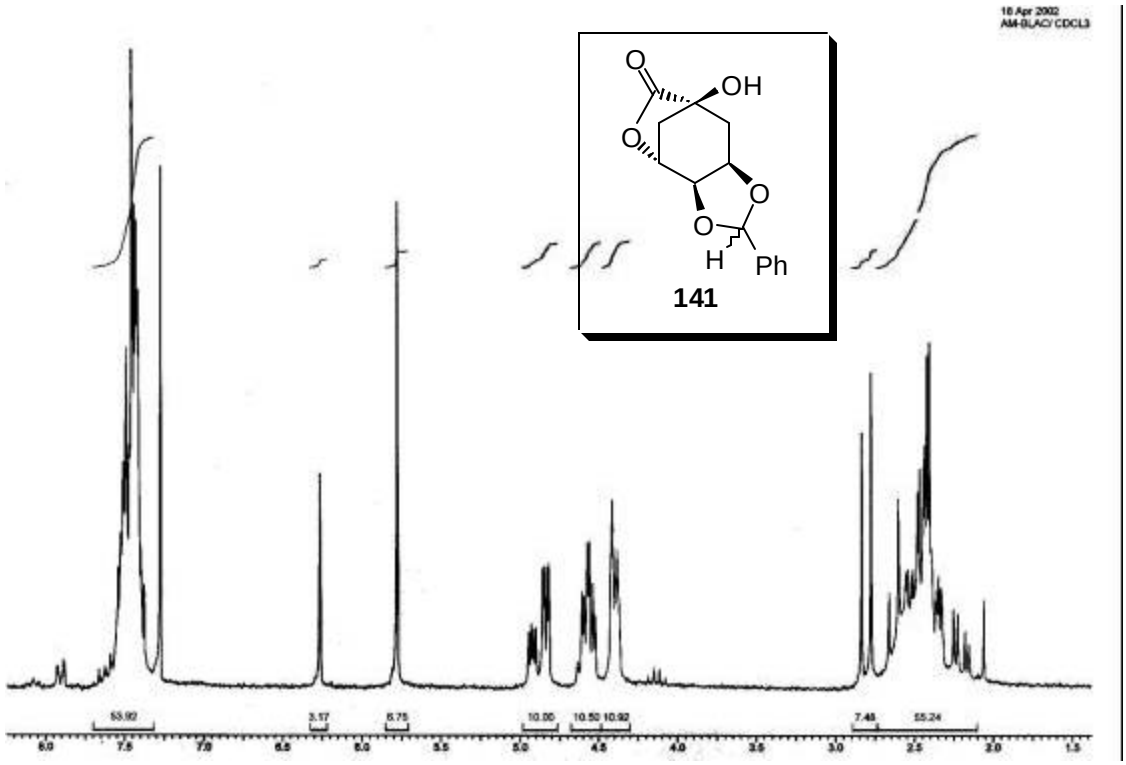

NHCO2Me
O
O
140

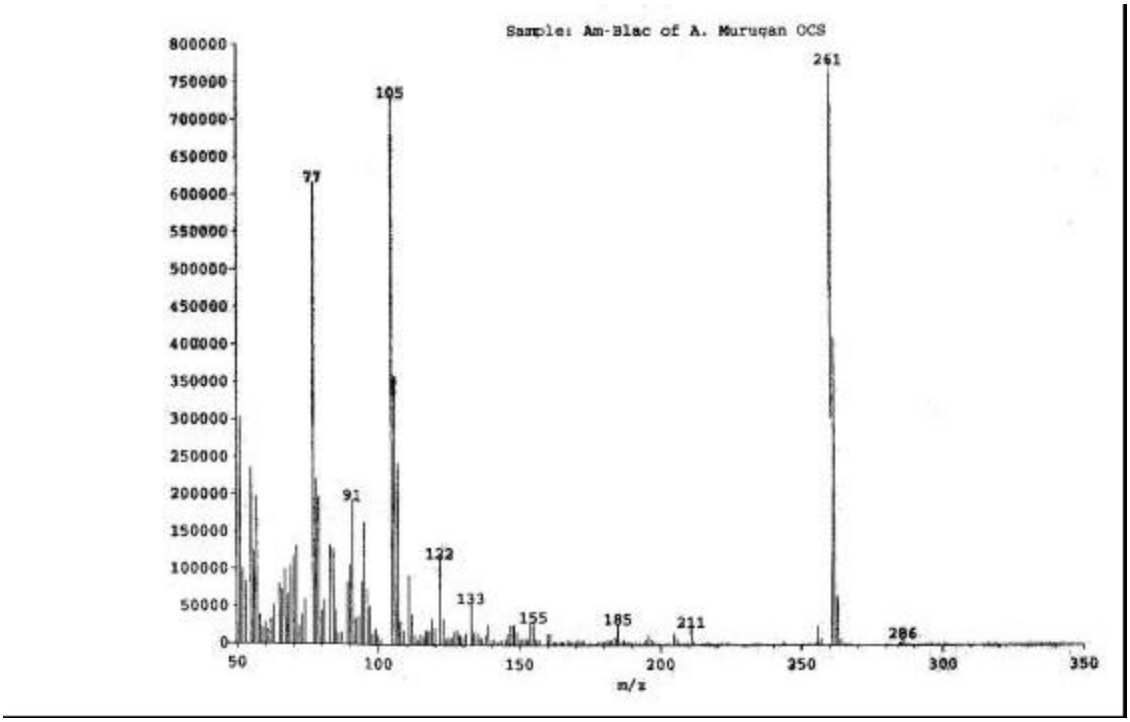

Sample: AM-VI-C of A. Muruqan OCS
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
65
77
59
93
135
150
194
209
71
105
123
83
176
50
100
150
200
220
m/z

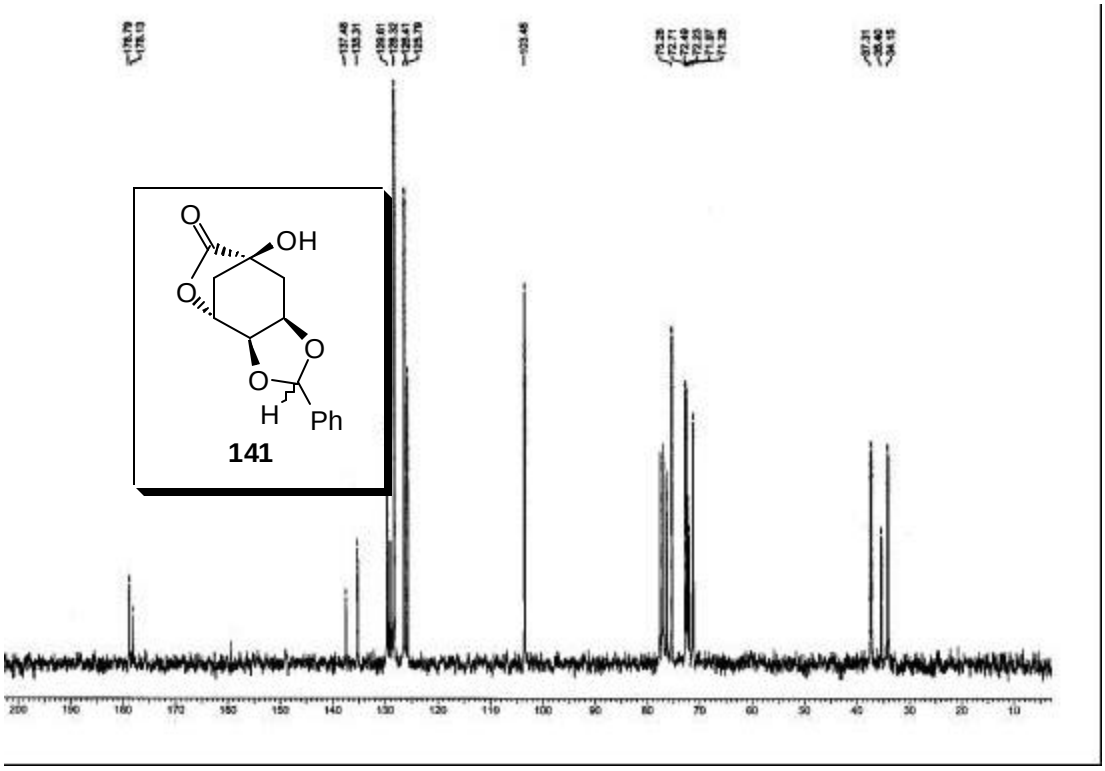


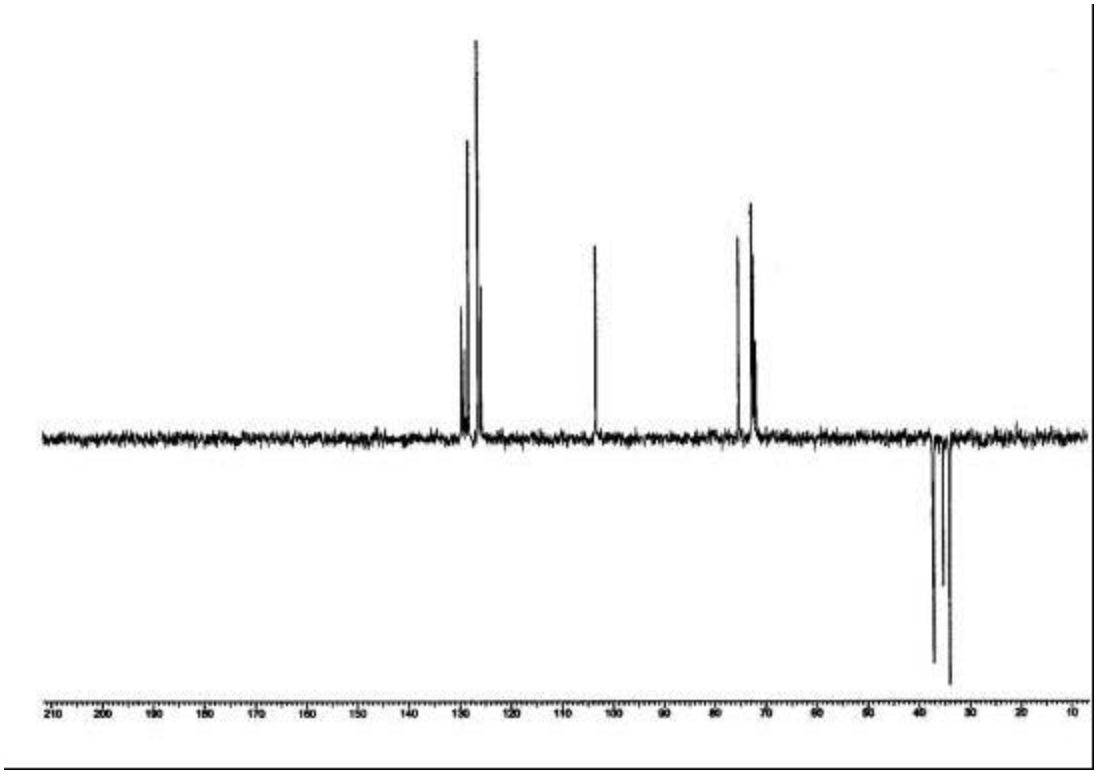
140

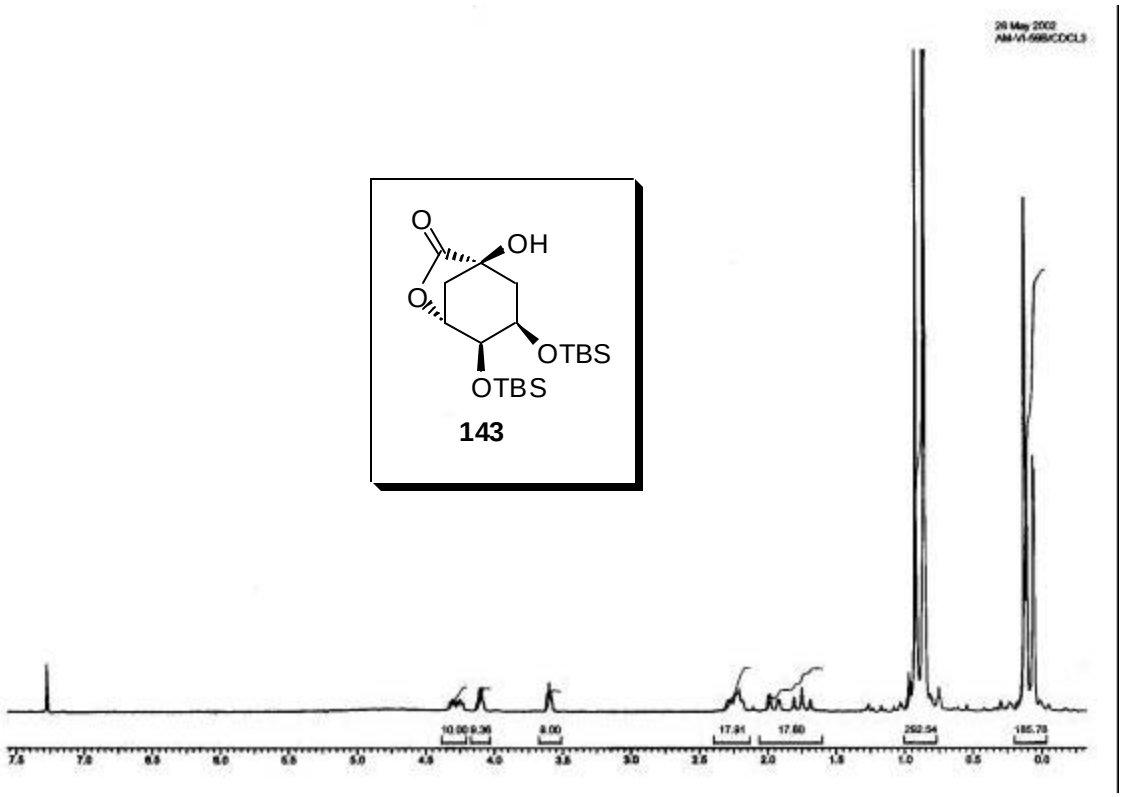



16 Apr 2002
AM-BLAC/ CDCL3
O
OH
O
O
O
H
Ph
141

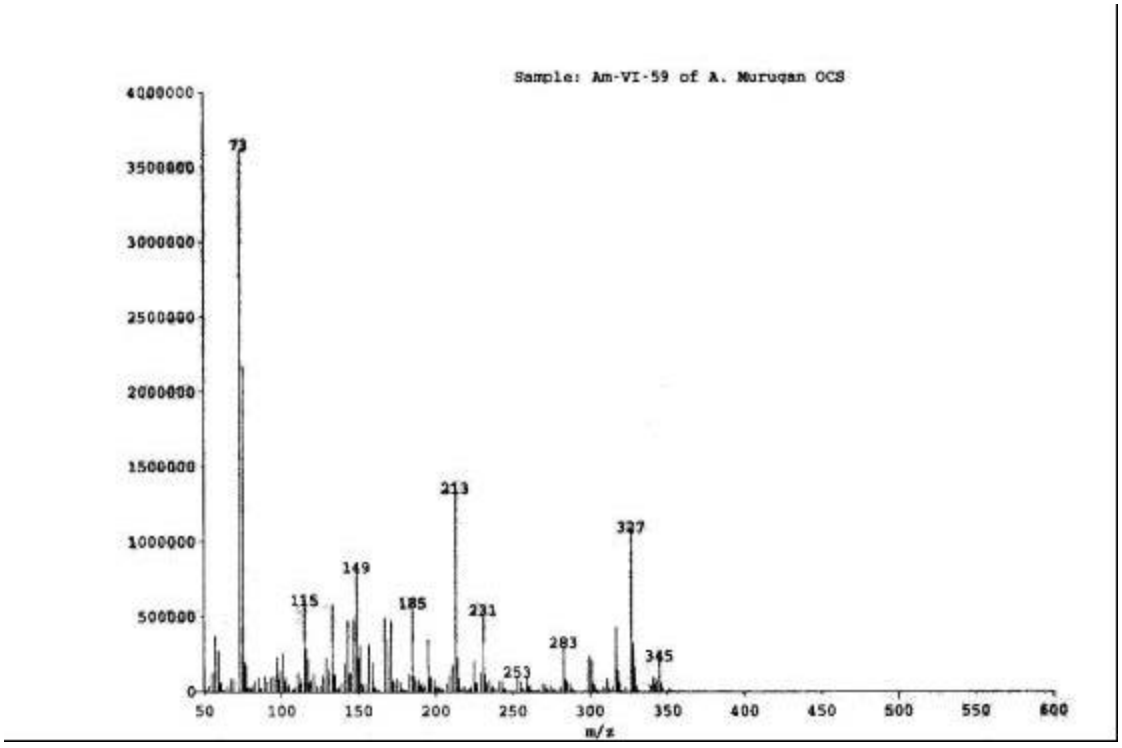

Sample: Am-Blac of A. Muruqan OCS
261
105
77
91
122
133
155
185
211
286
m/z

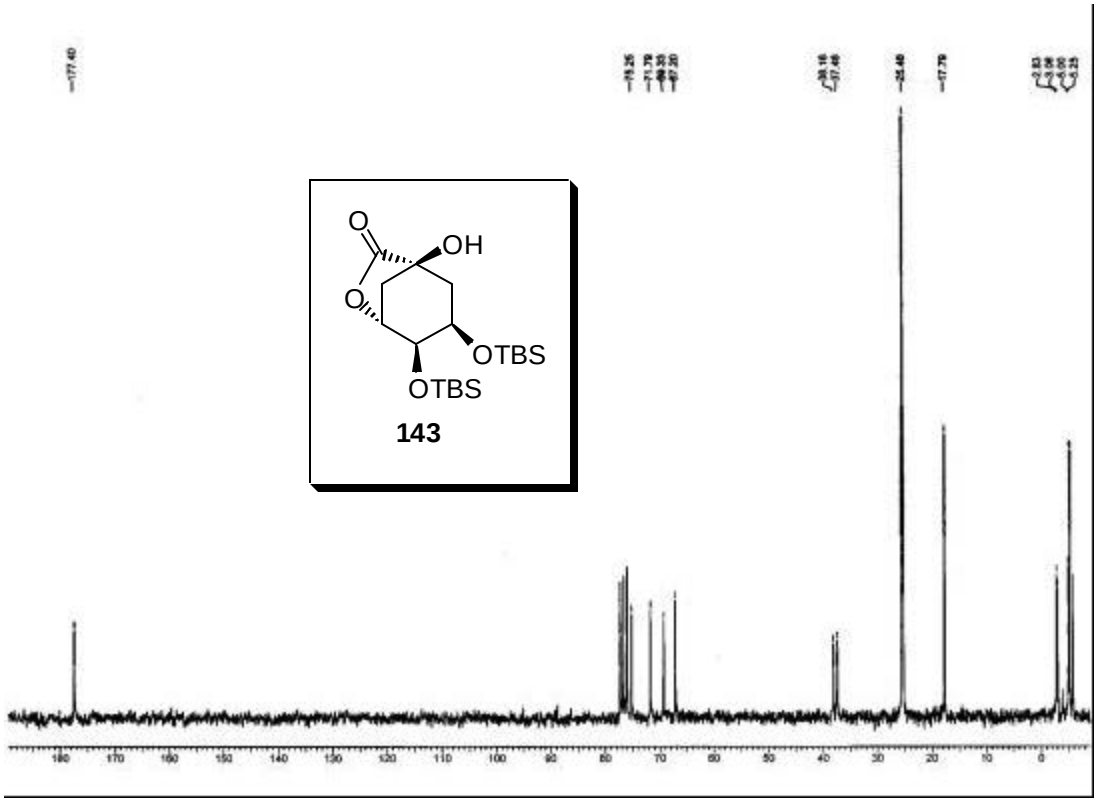

O
OH
O
O
O
H
Ph
141



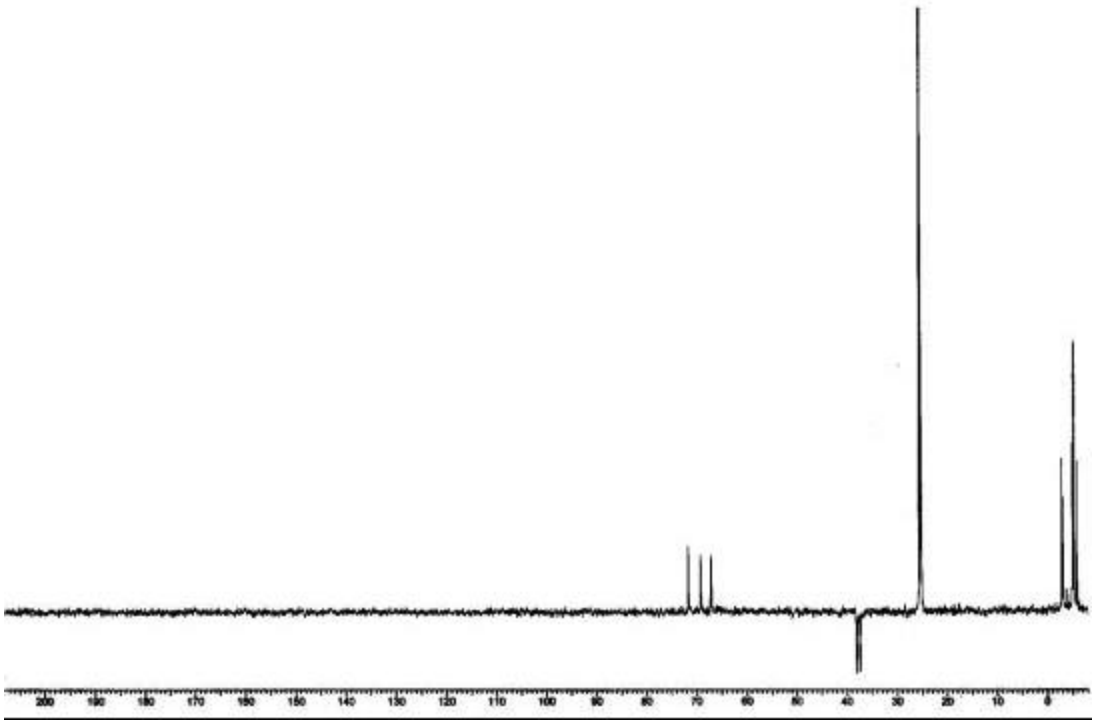

O
OH
O
OTBS
OTBS

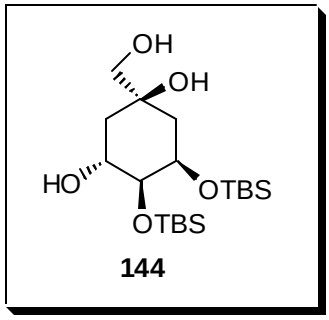
143


Sample: Am-VI-59 of A. Muruqan OCS
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
73
115
149
185
213
231
253
283
327
345
50
100
150
200
250
300
350
400
450
500
550
600
m/z

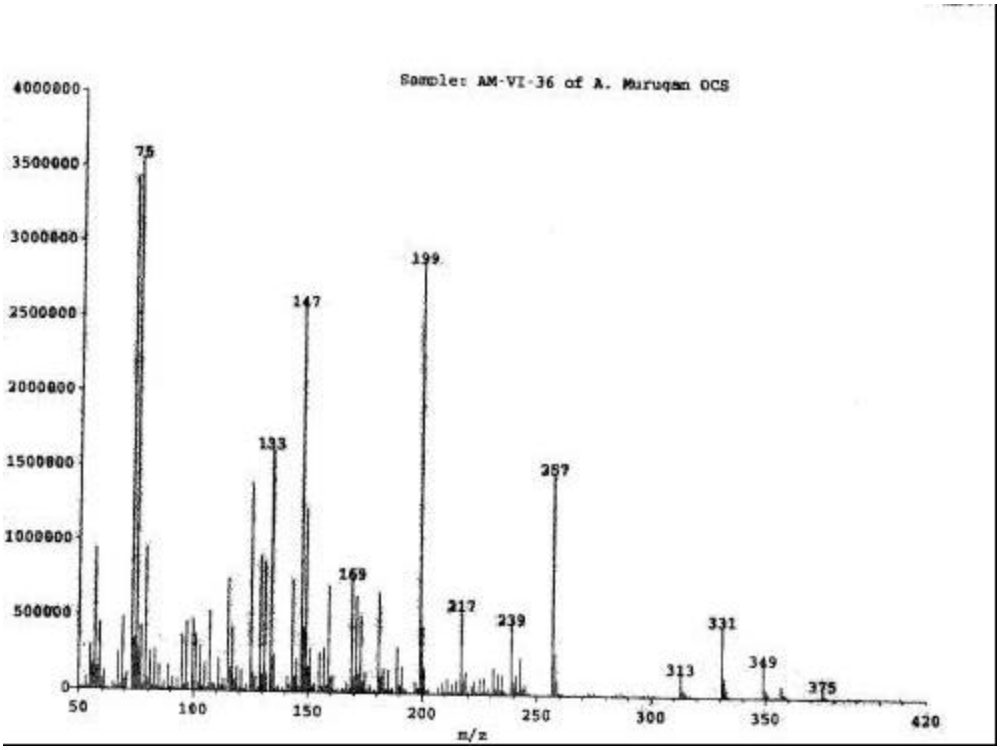


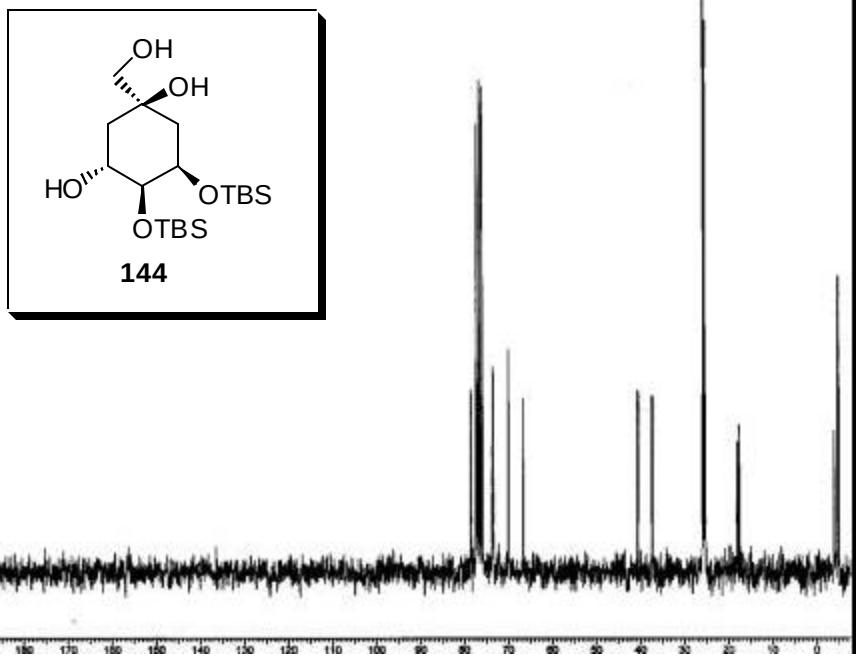
143



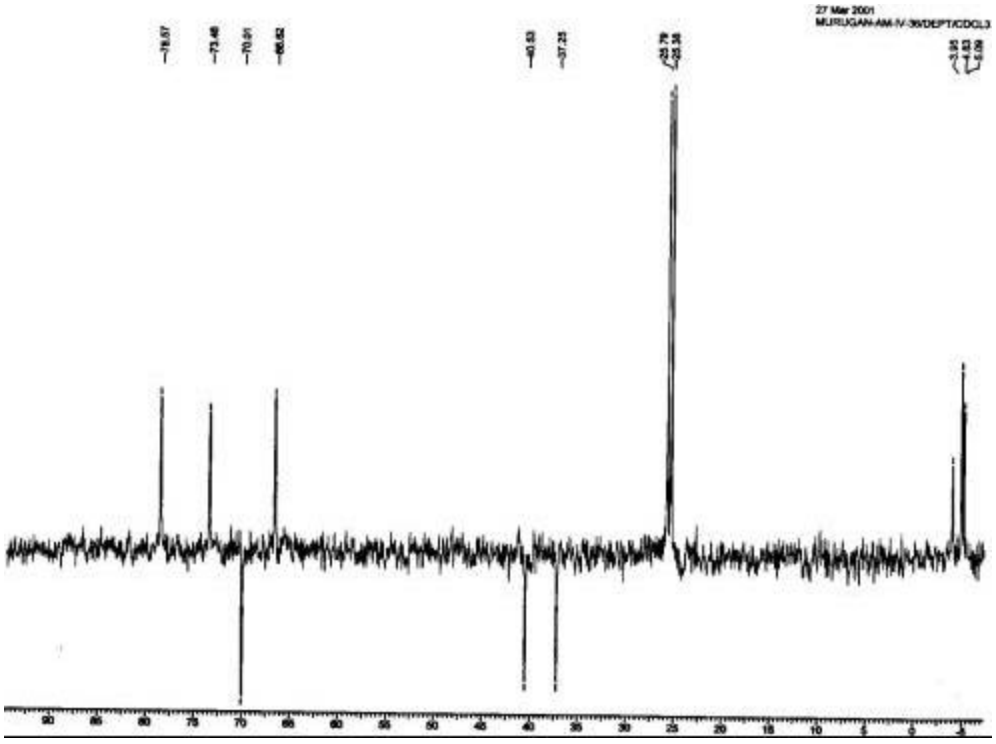

OH
OH
HO
OTBS
OTBS

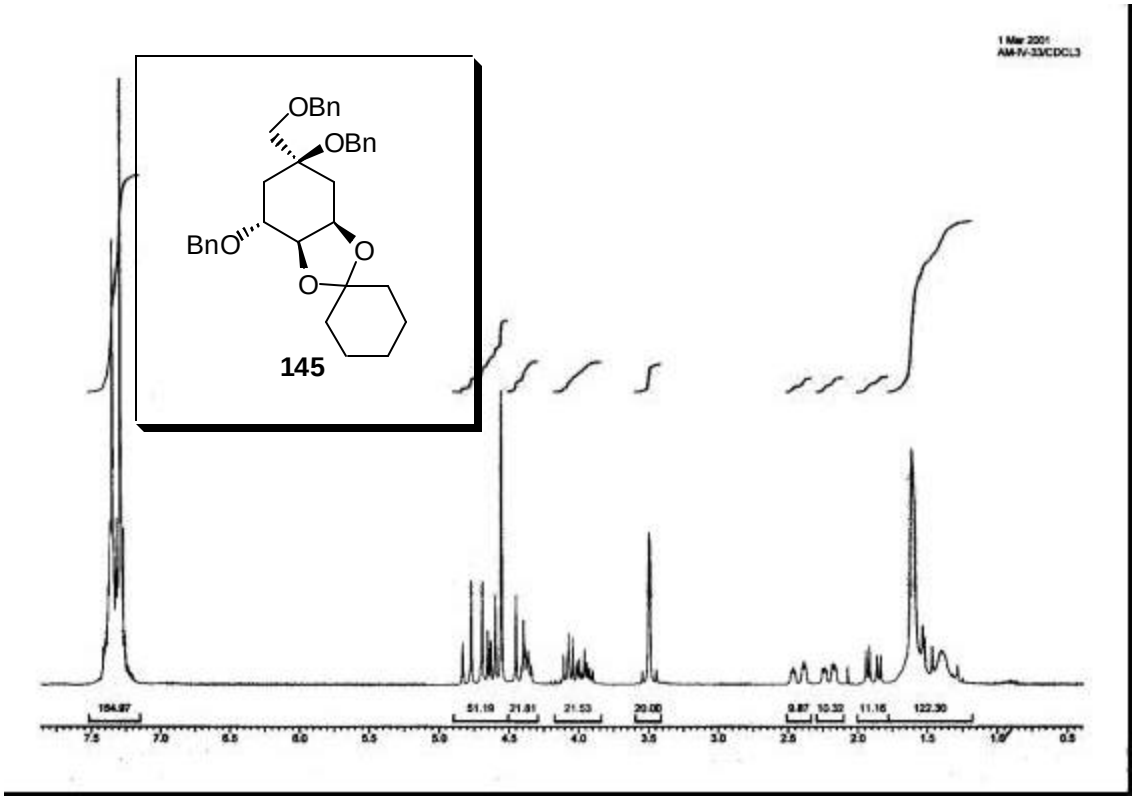
144

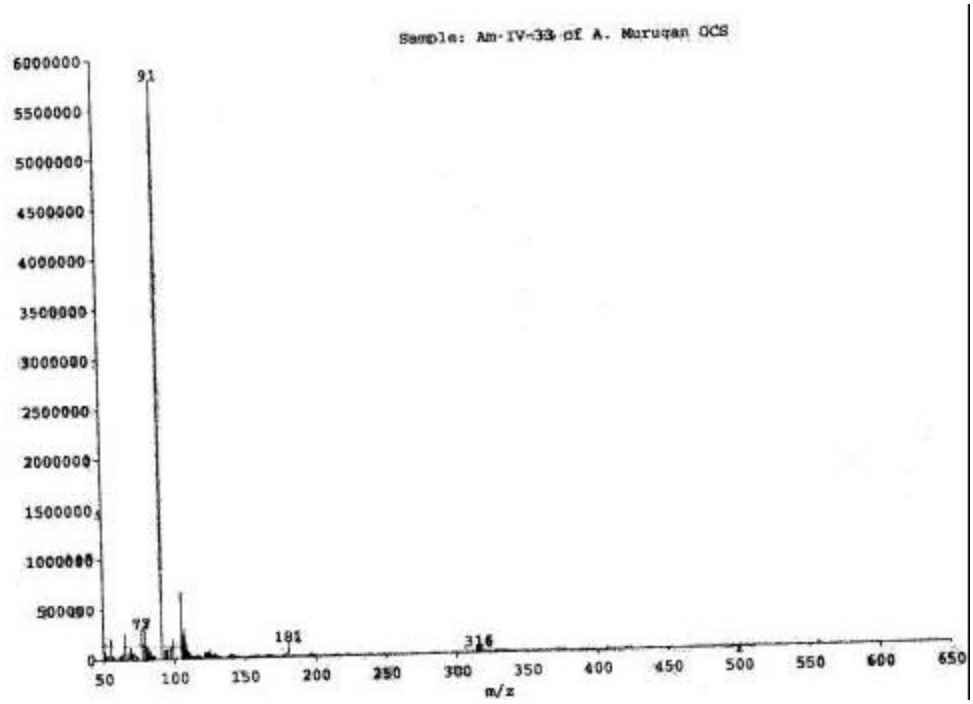

Sample: AM-VI-36 of A. Muruqan OCS
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
75
147
133
199
169
217
239
257
313
331
349
375
50
100
150
200
250
300
350
420
m/z

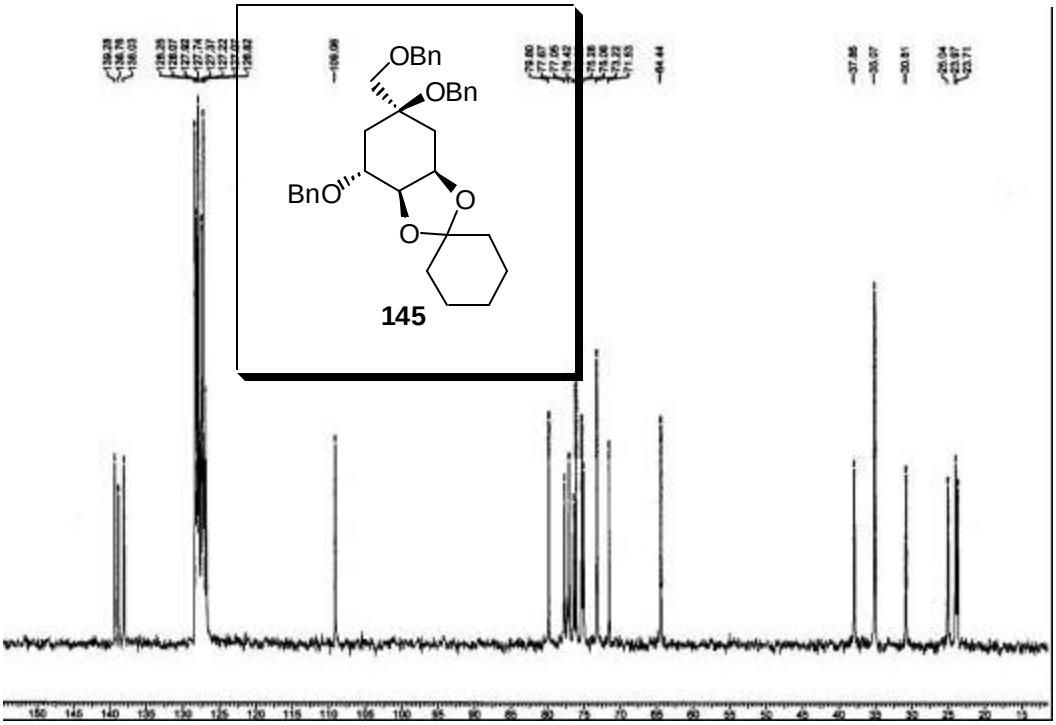


144

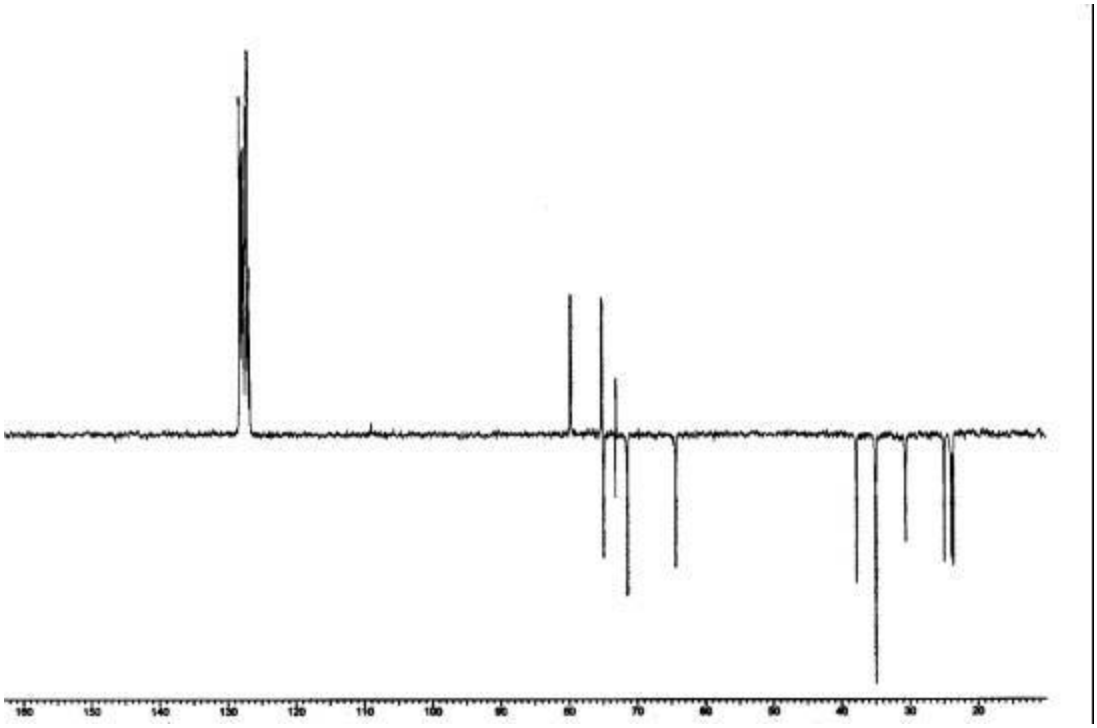


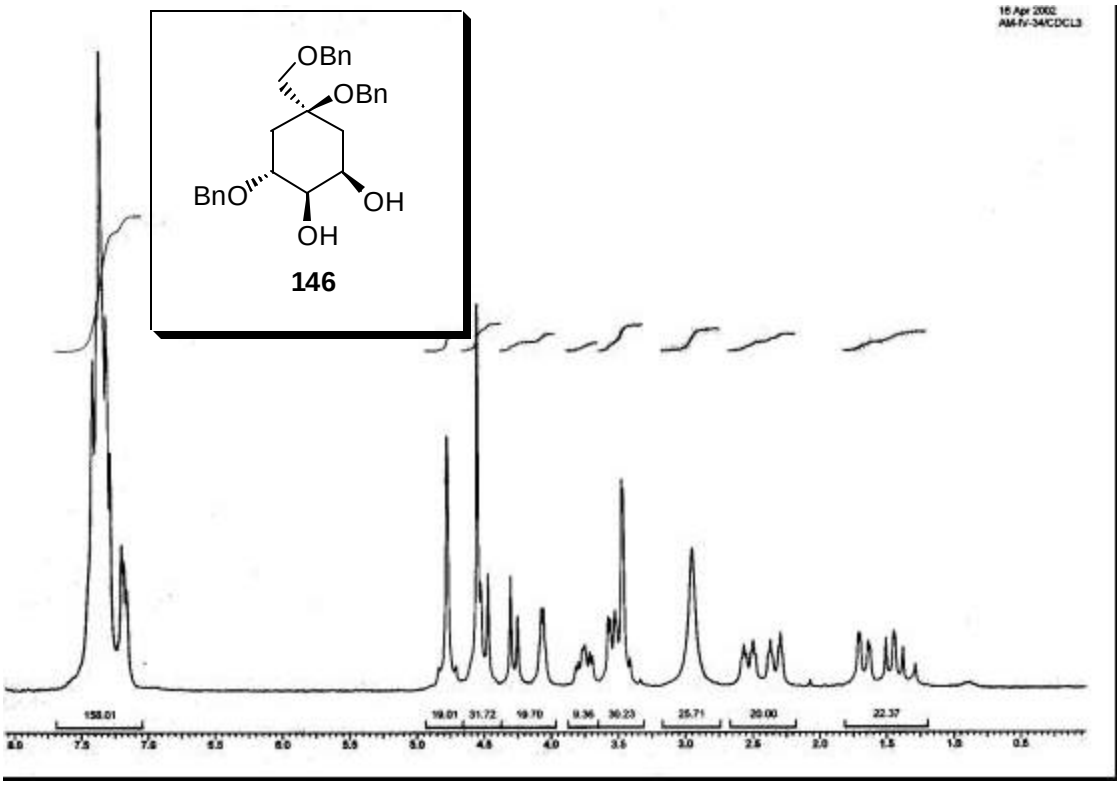

OBn
OBn
BnO
O
O
145


Sample: Am-IV-33 of A. Muruqan OCS
91
77
181
316
m/z

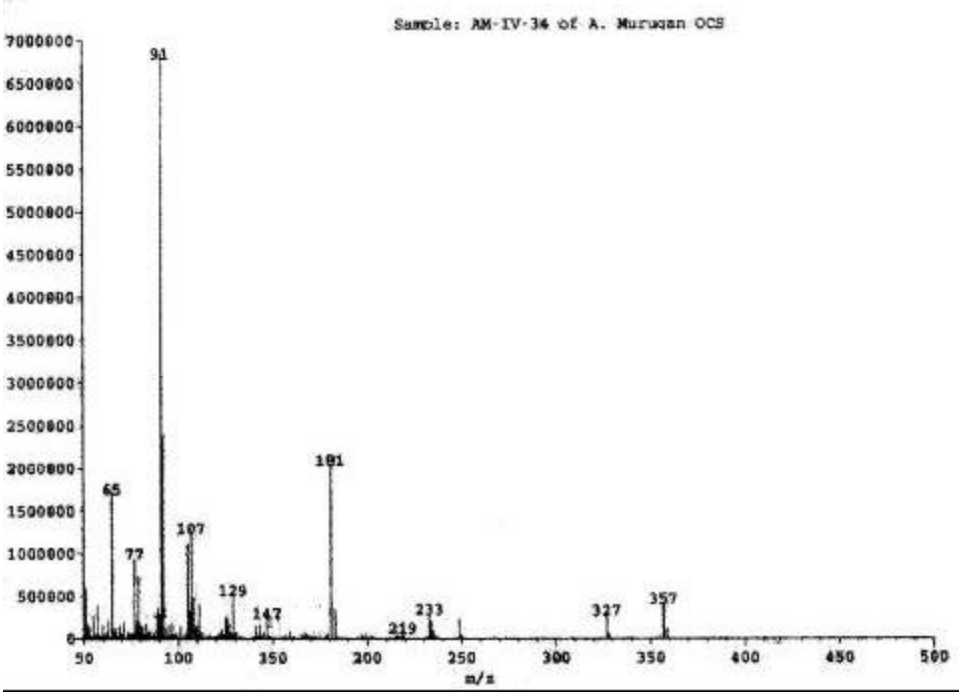


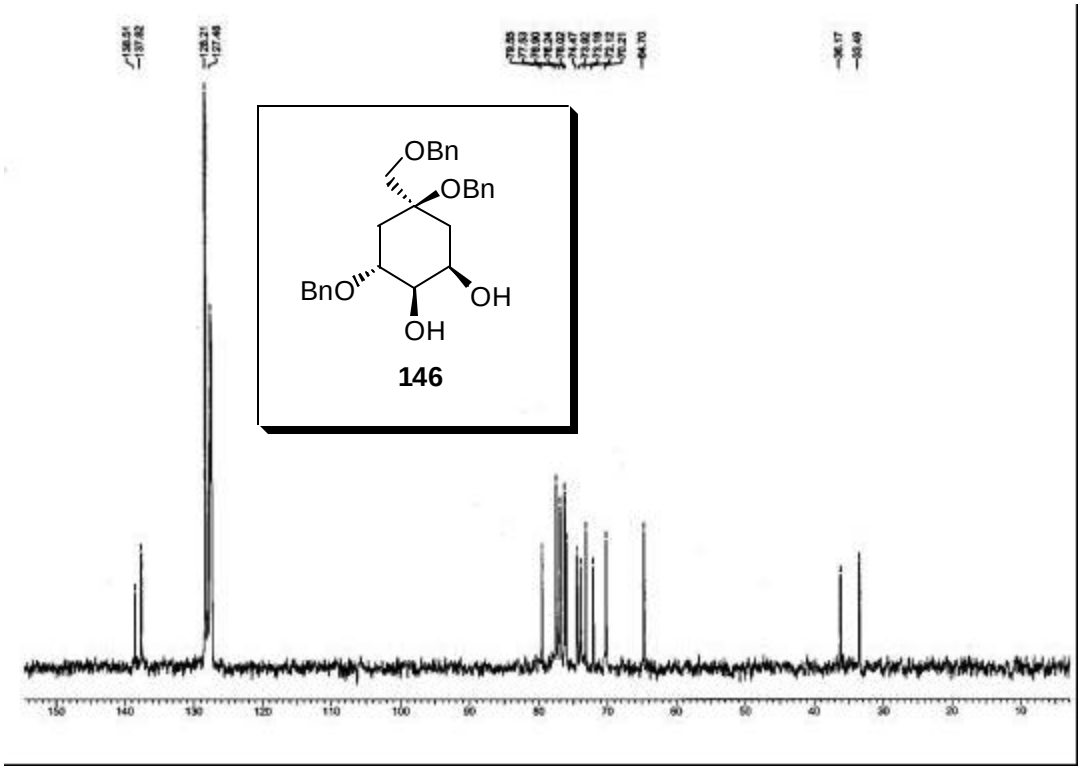
145



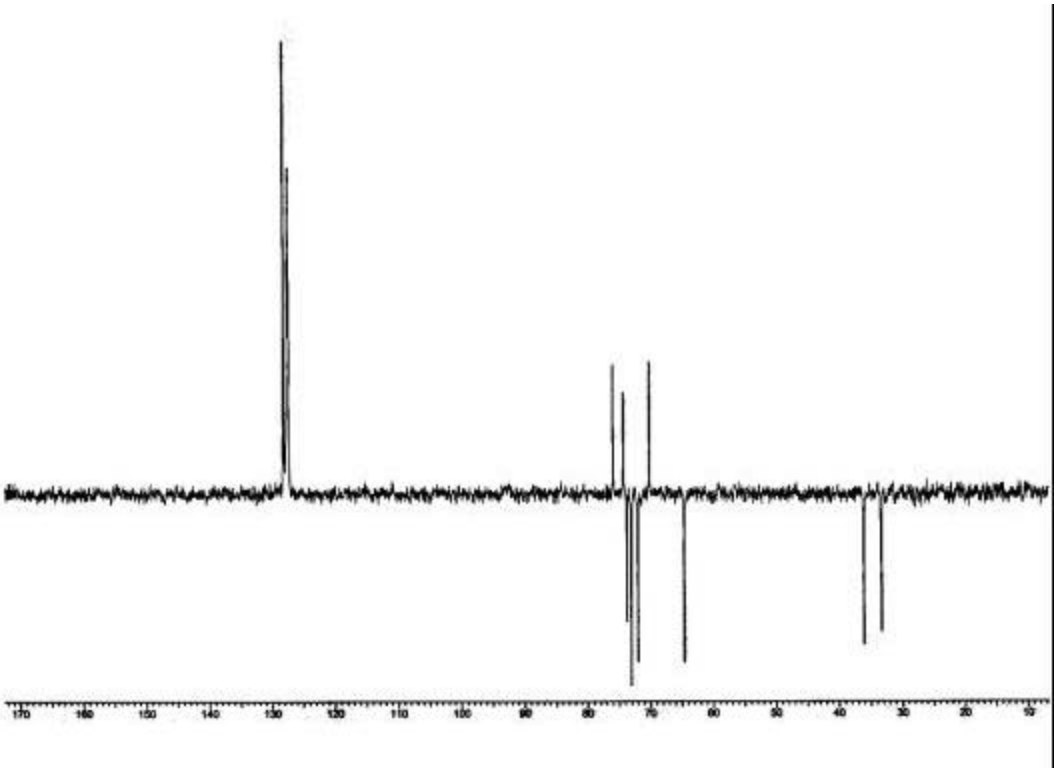

OBn
OBn
BnO
OH
OH

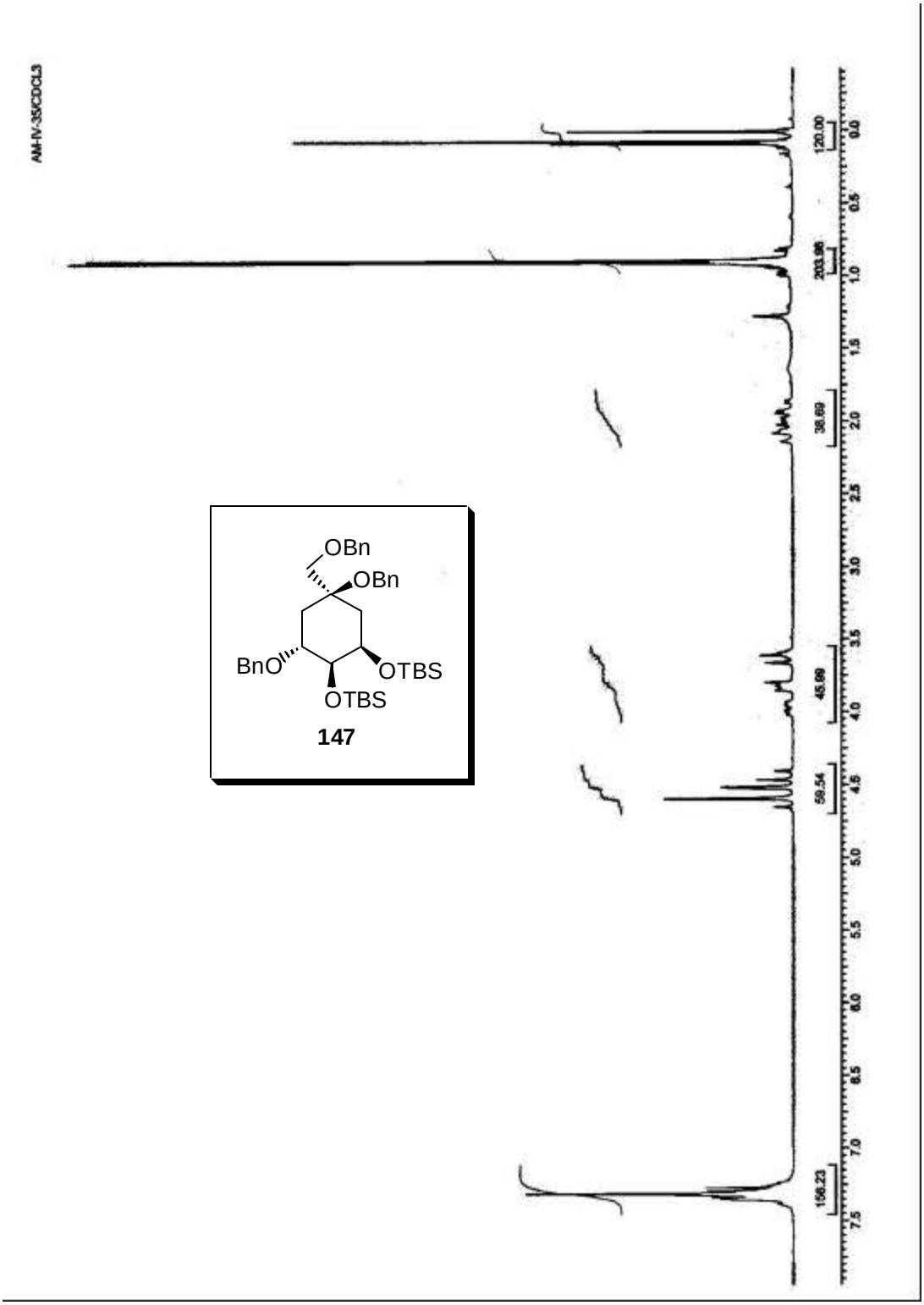
146

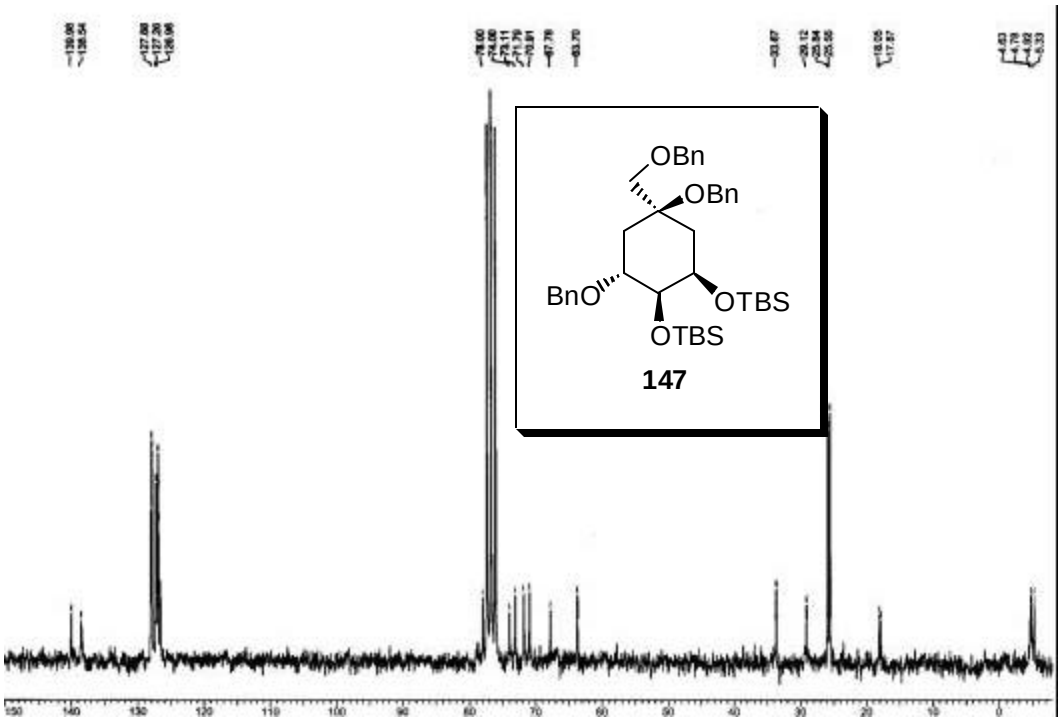

Sample: AM-IV-34 of A. Muruqan OCS
91
181
65
107
77
129
147
233
219
327
357
m/z



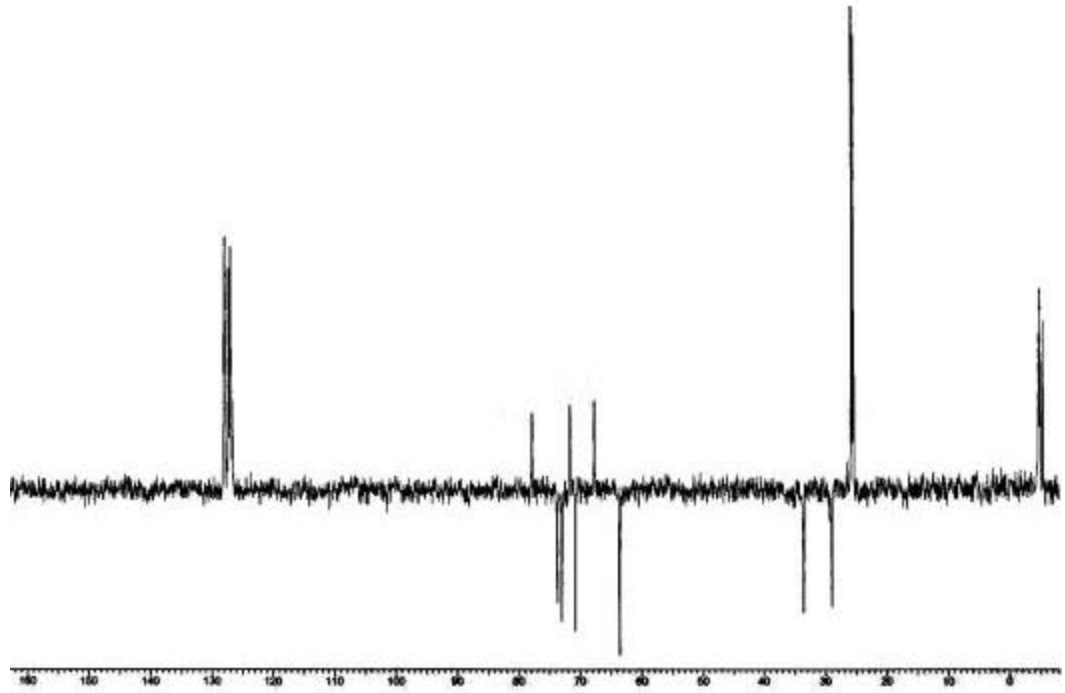
146

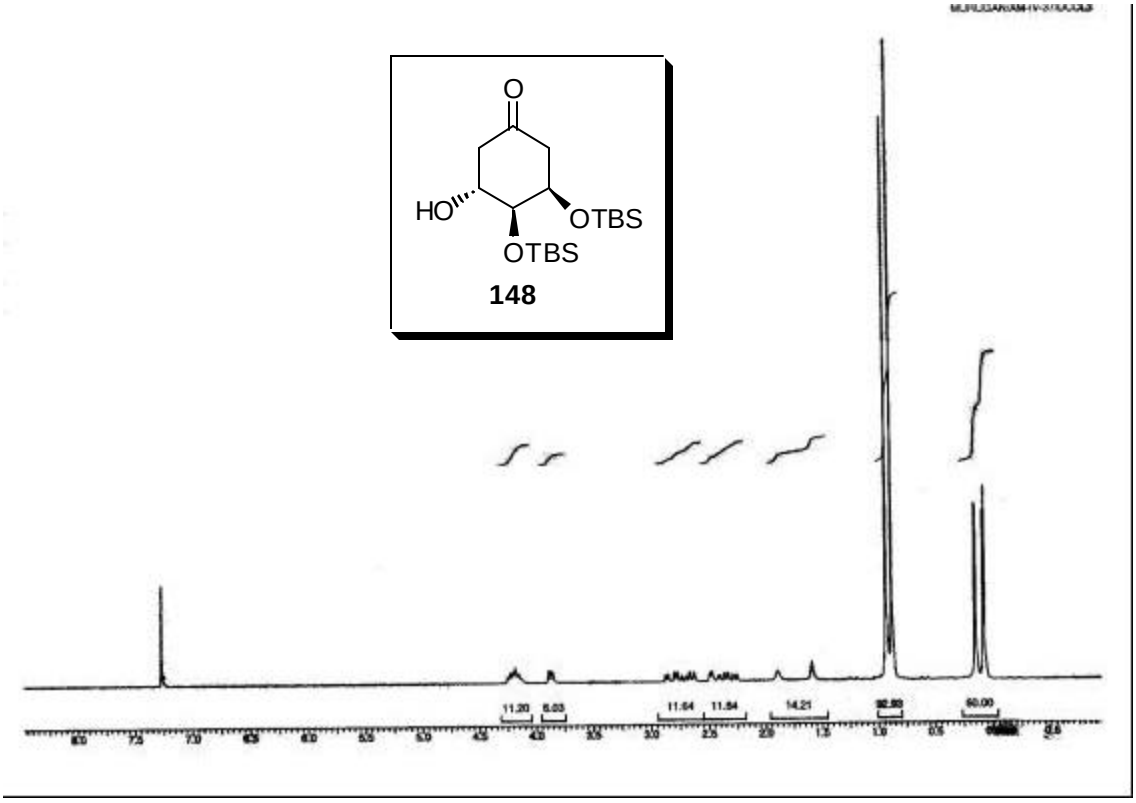


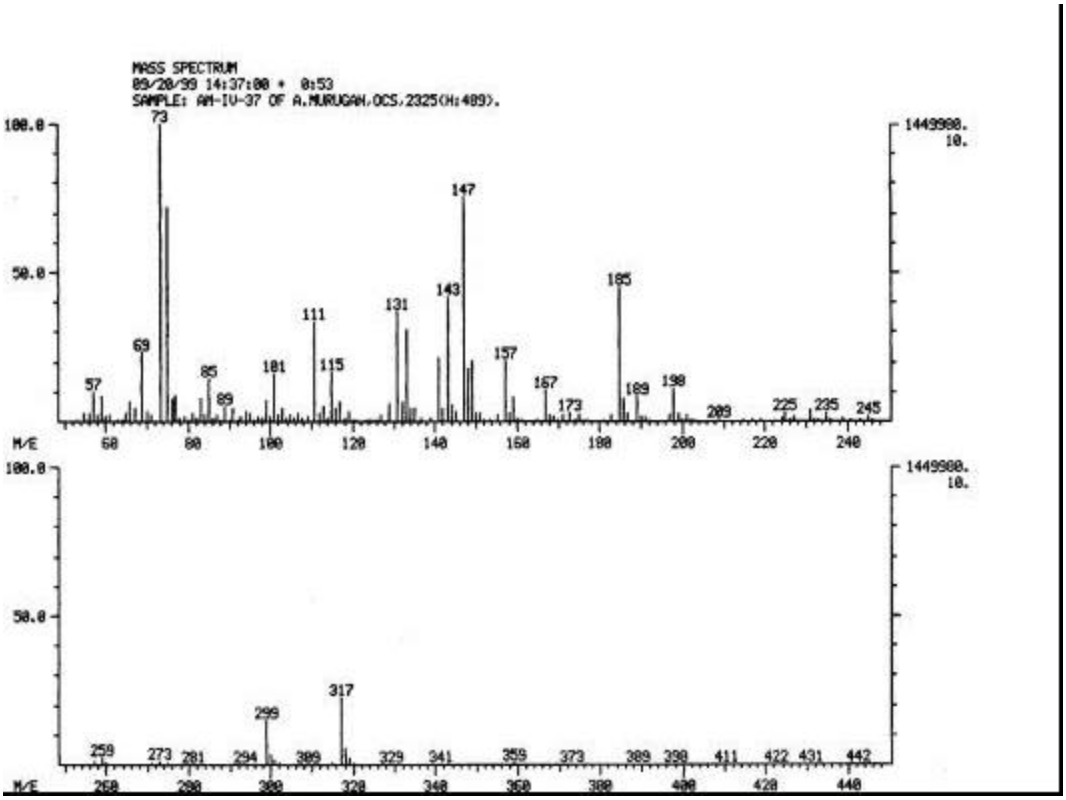

AM-IV-35/CDCL3
OBn
OBn
BnO
OTBS
OTBS
147

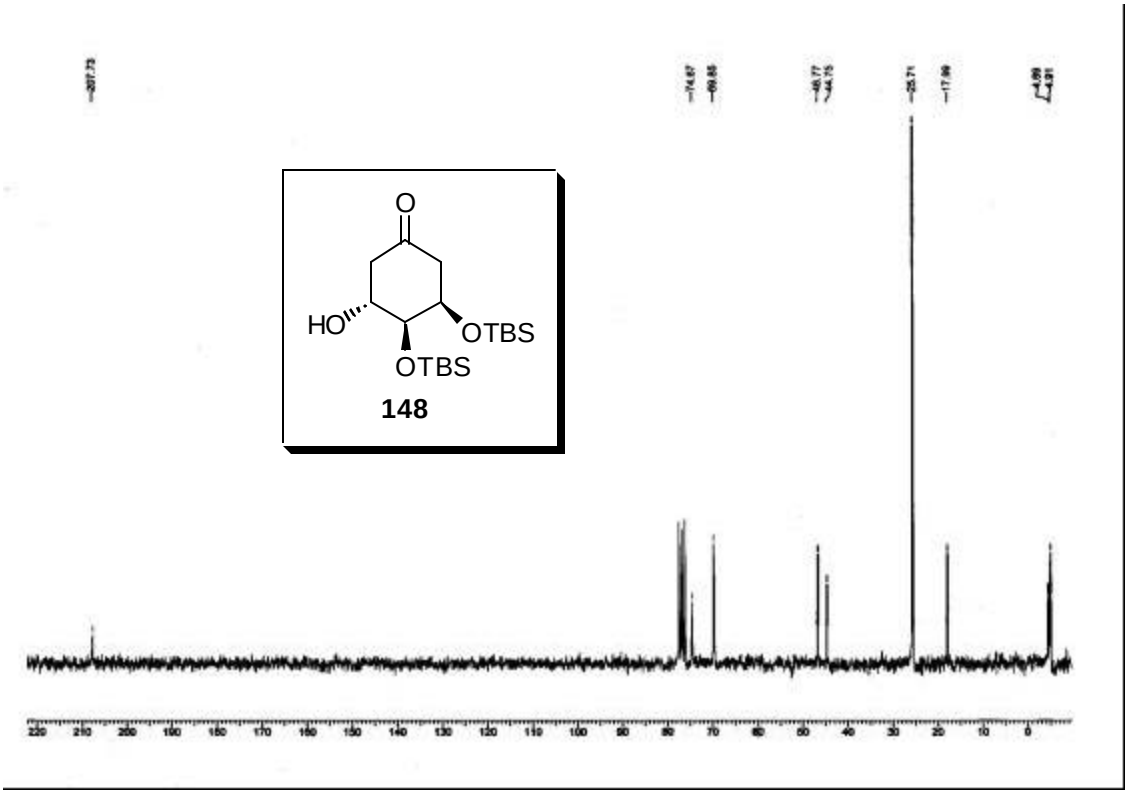


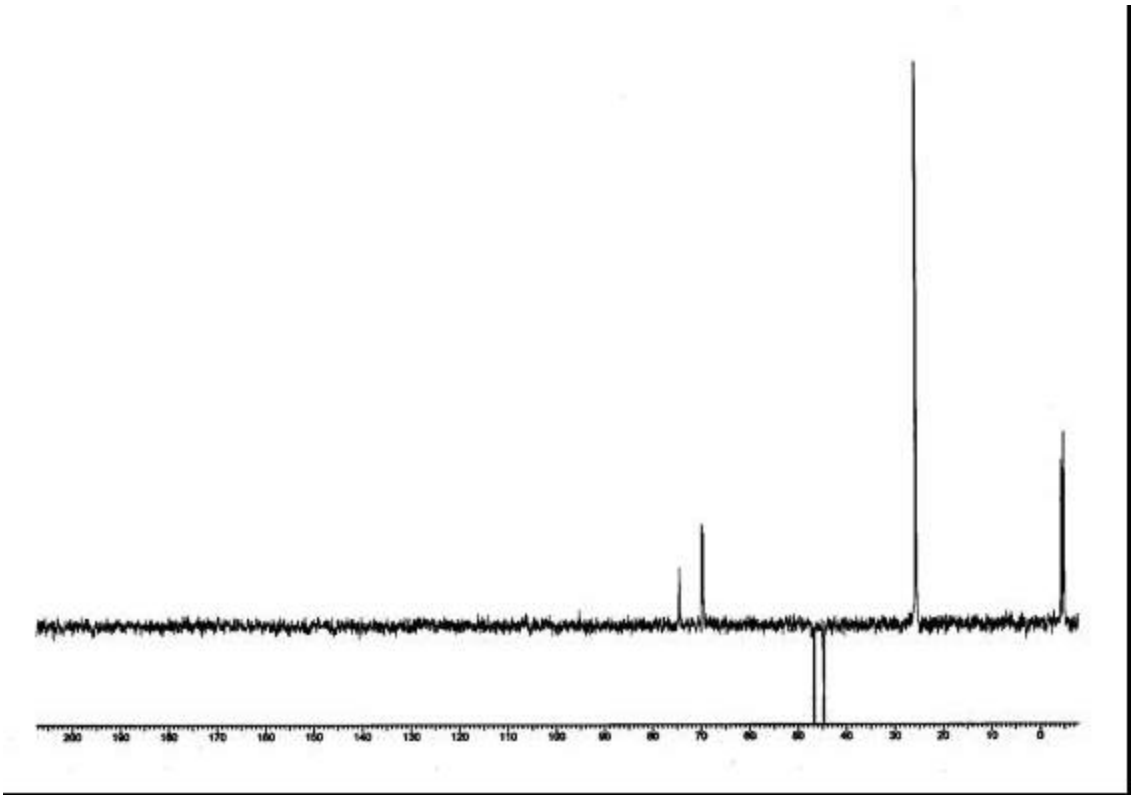
147

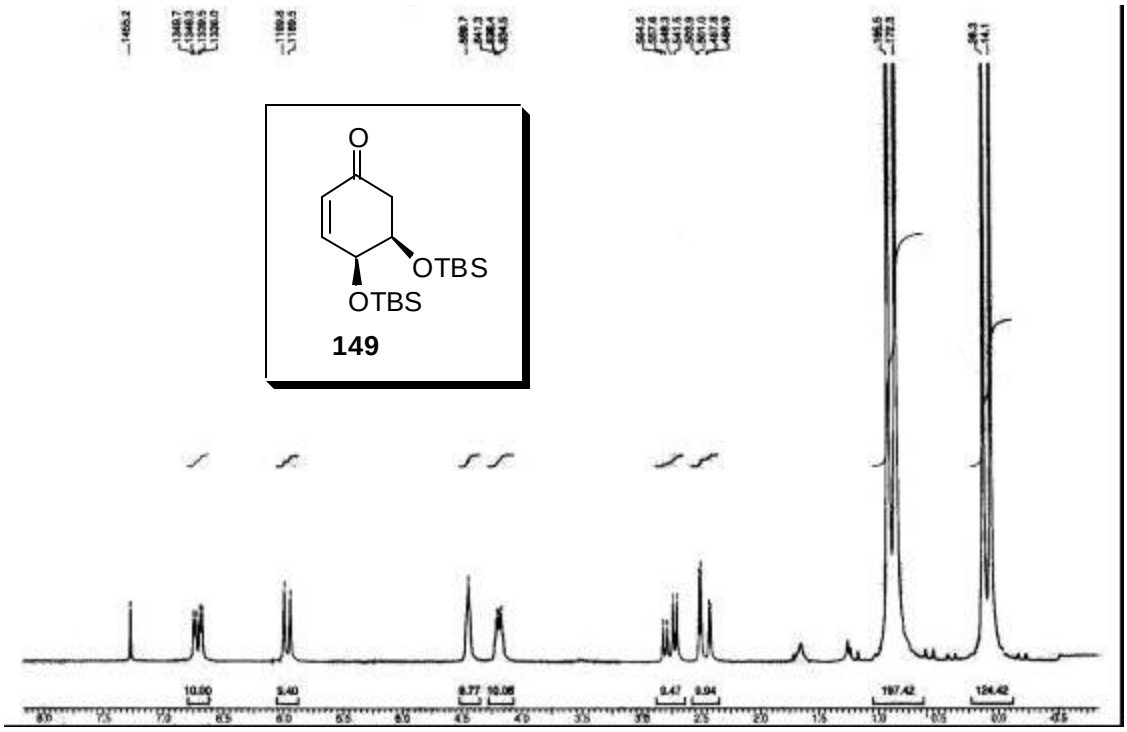


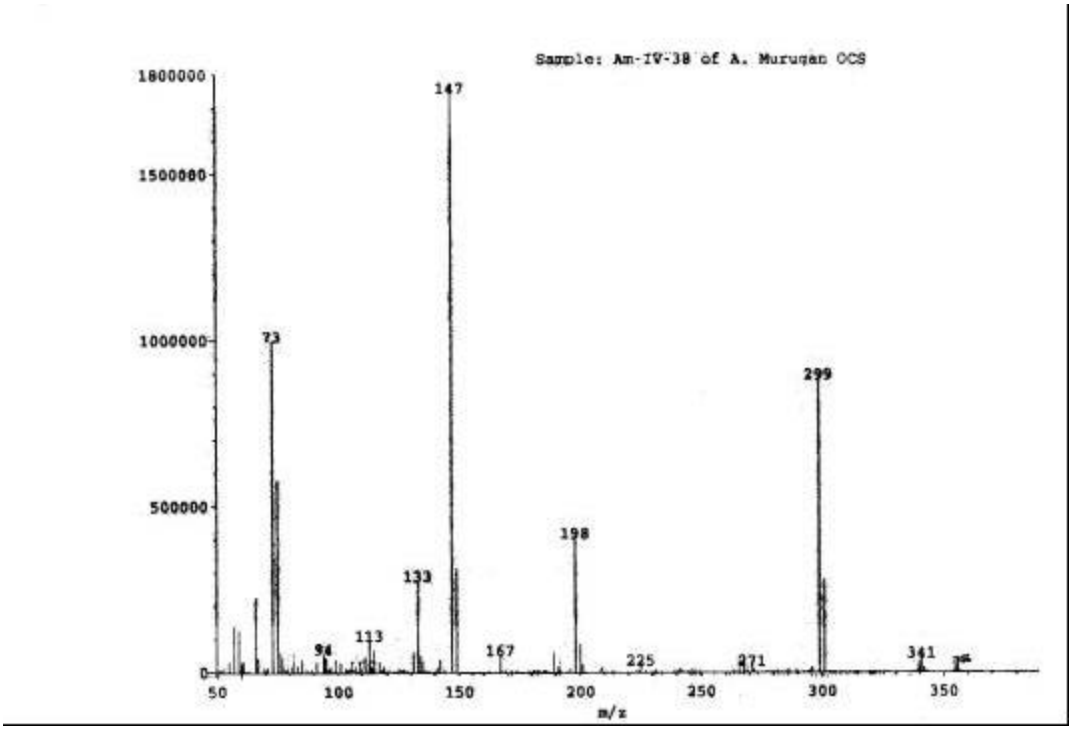

O
HO
OTBS
OTBS
148

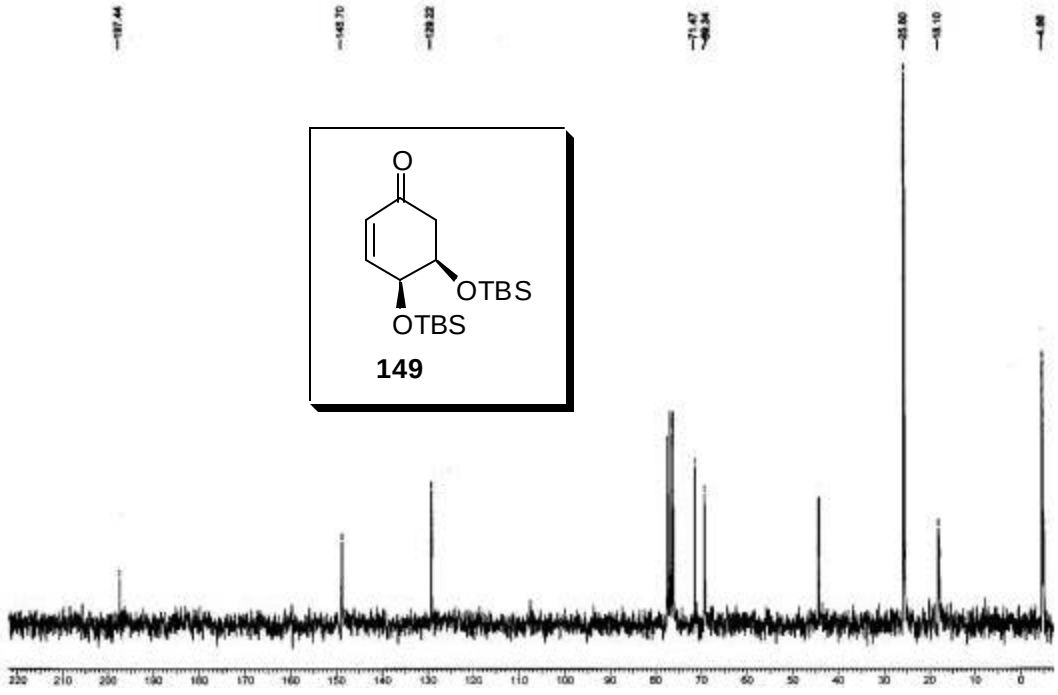

MASS SPECTRUM
09/20/99 14:37:00 + 0:53
SAMPLE: AM-IV-37 OF A.MURUGAN,OCS,2325(H:489).
100.0
50.0
M/E
1449900.
10.
73
147
185
143
131
111
69
157
57
85
89
101
115
167
173
189
198
209
225
235
245
317
299

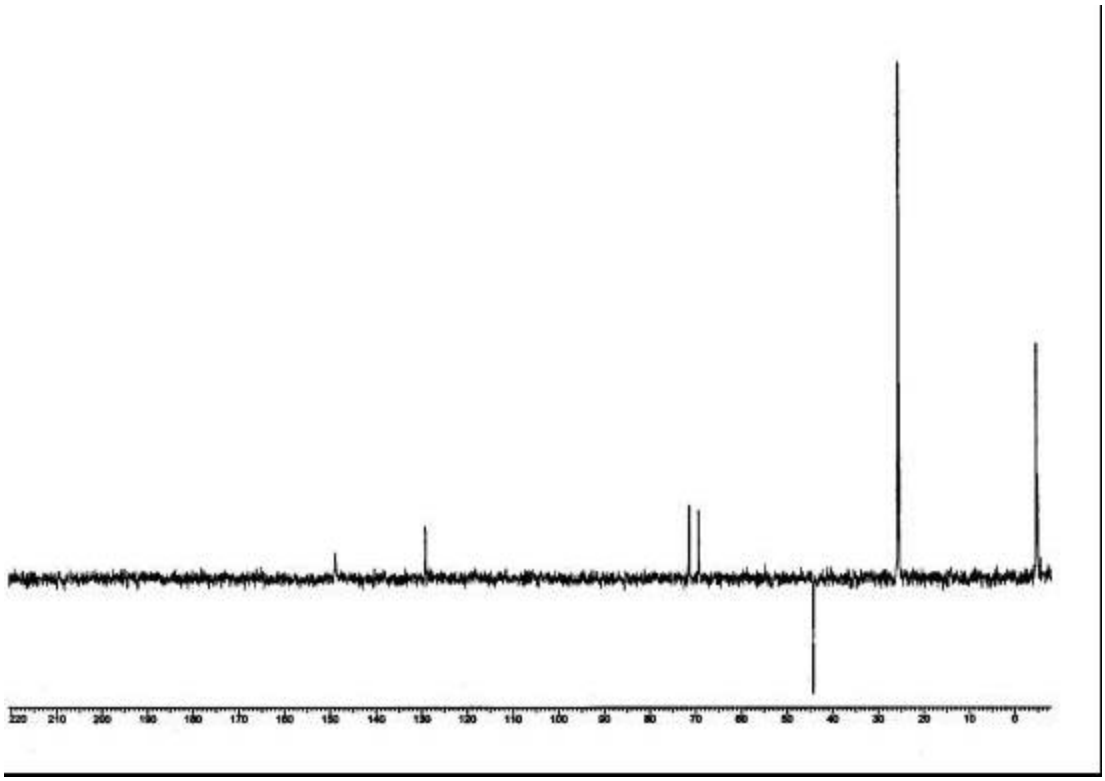

O
HO
OTBS
OTBS
148

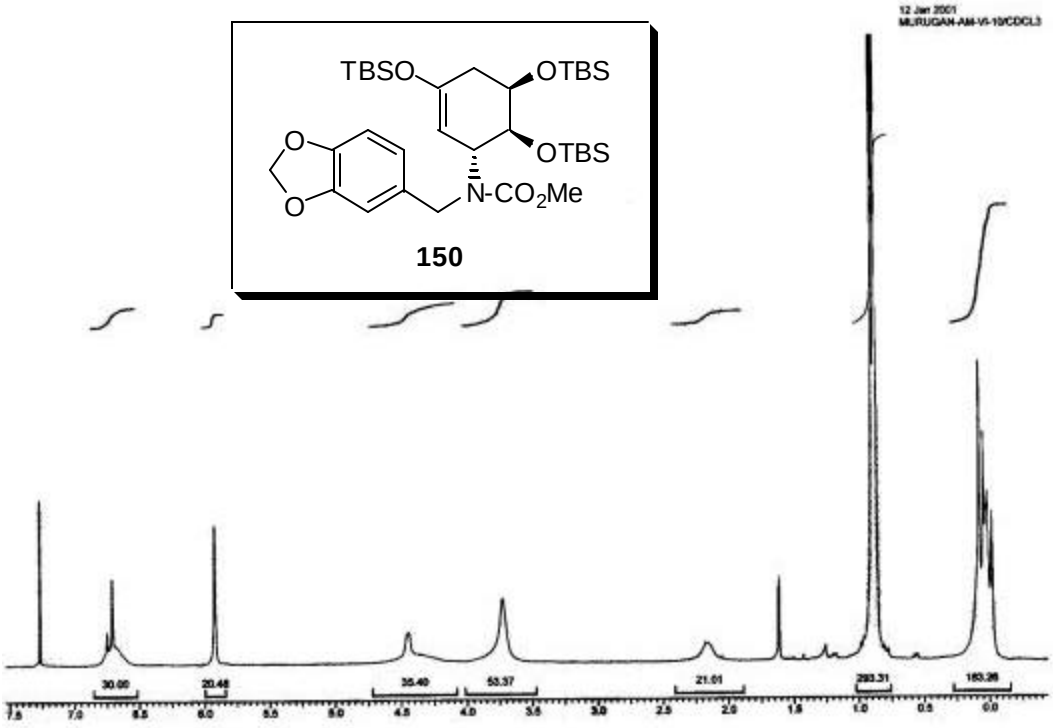


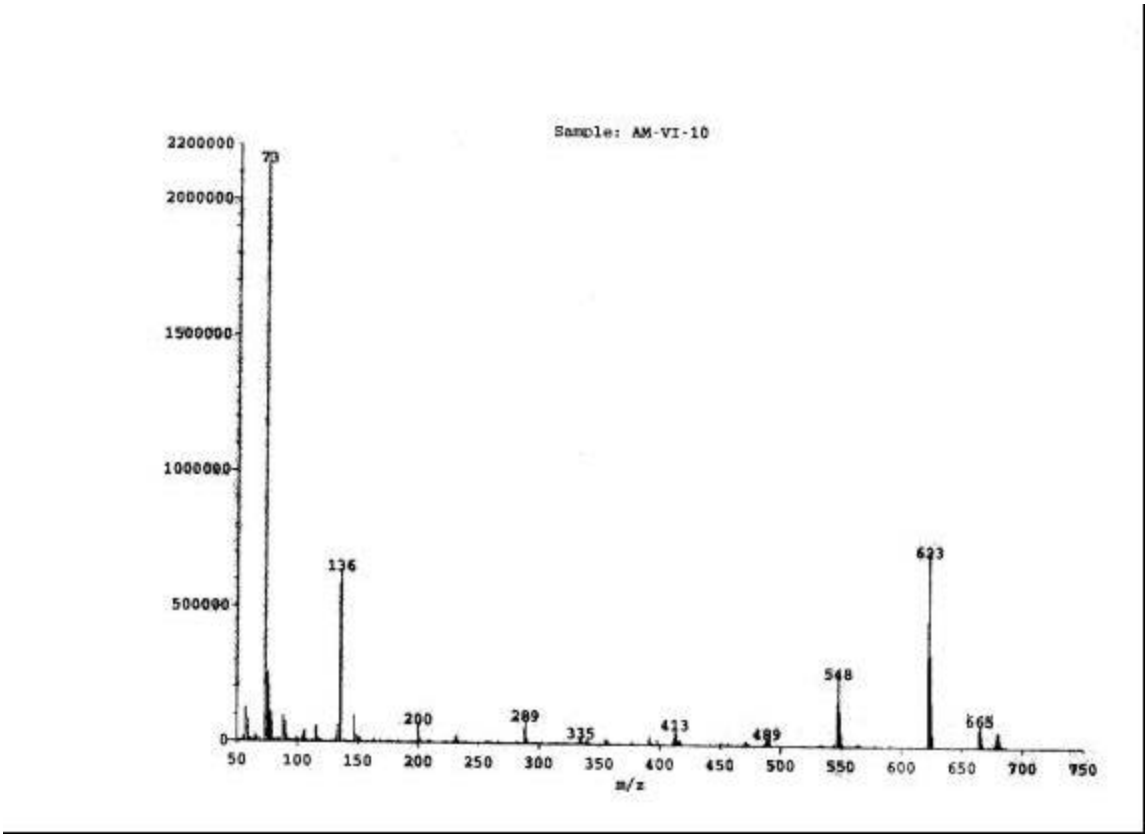

O
OTBS
OTBS
149

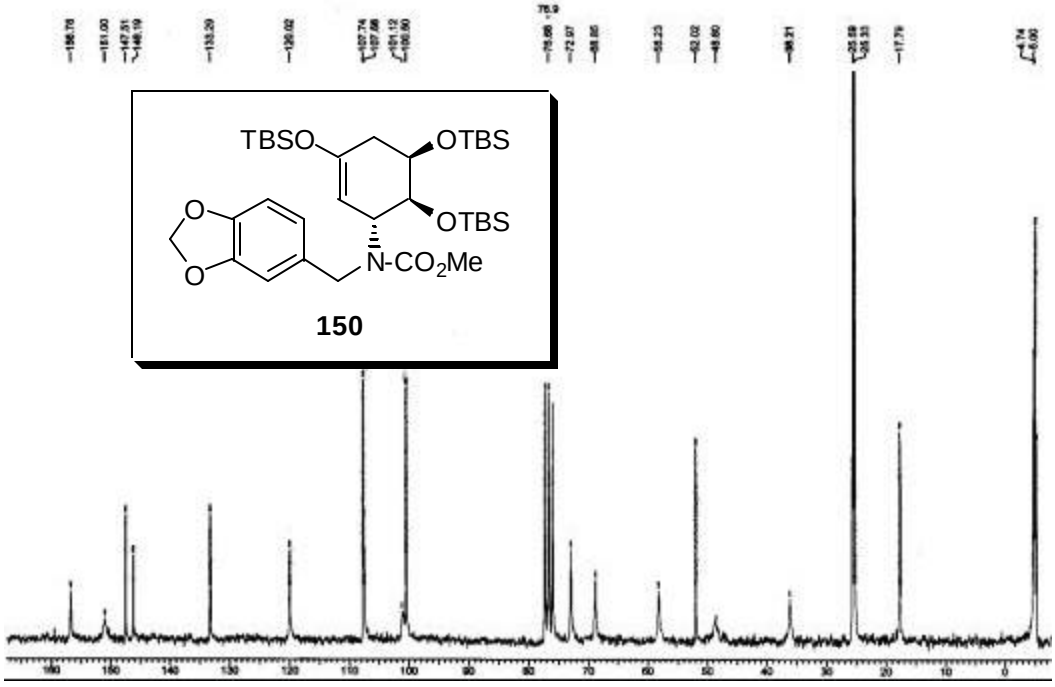

Sample: Am-IV-38 of A. Muruqan OCS
1800000
1500000
1000000
500000
0
147
73
299
198
133
113
94
167
225
271
341
50
100
150
200
250
300
350
m/z


O
OTBS
OTBS
149

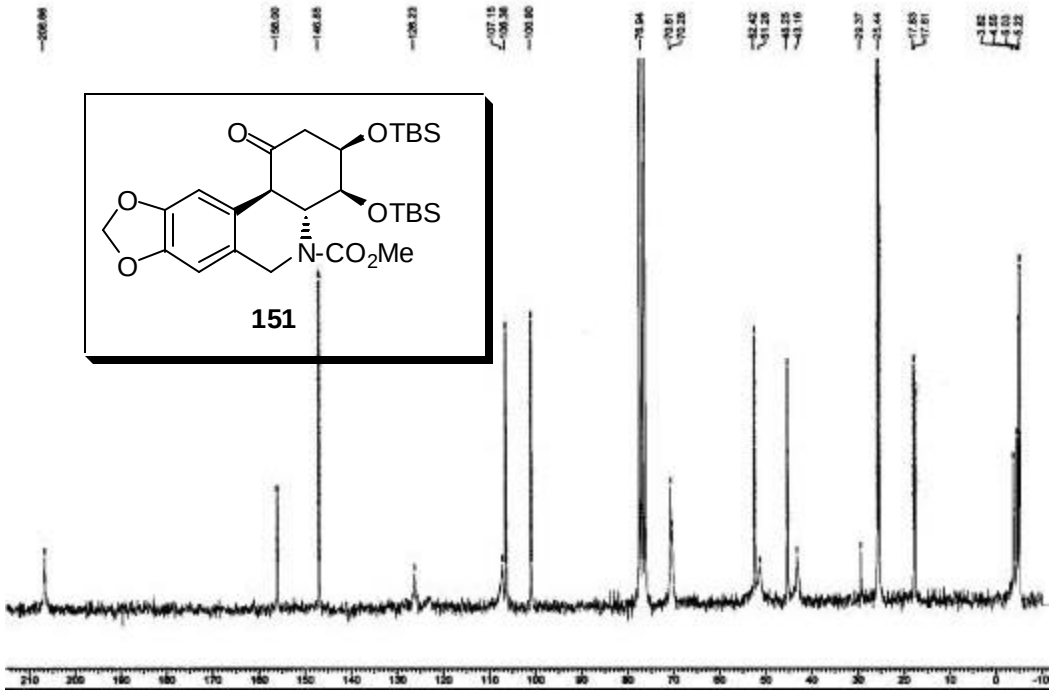



TBSO
OTBS
OTBS
O
O
N-CO2Me
150

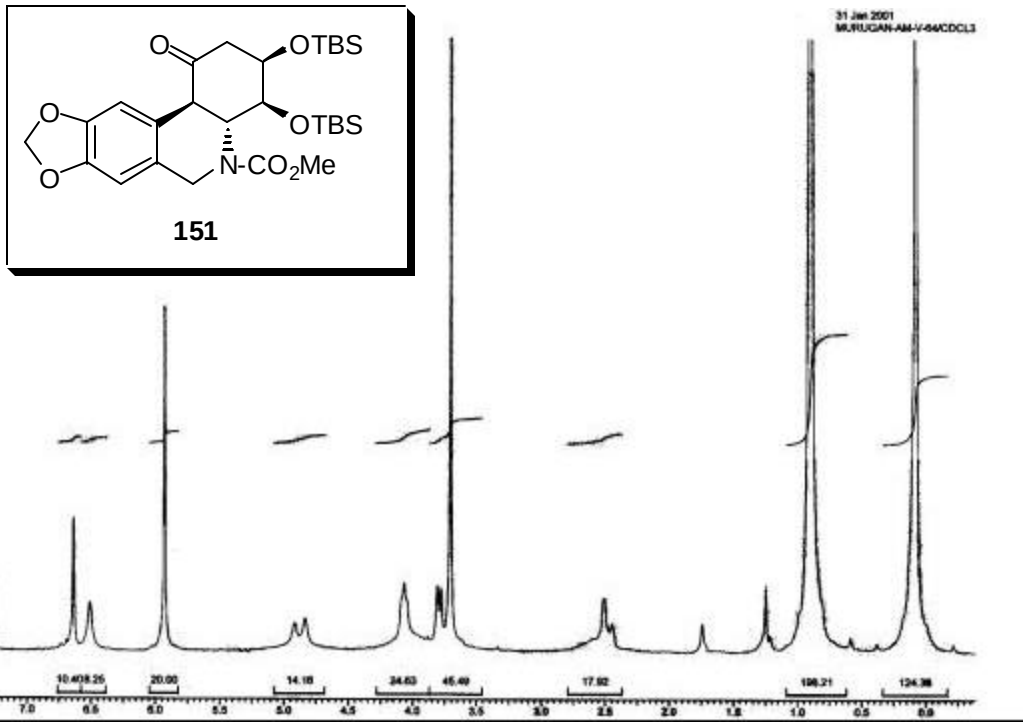

Sample: AM-VI-10
2200000
2000000
1500000
1000000
500000
0
73
136
200
289
335
413
489
548
623
668
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
m/z



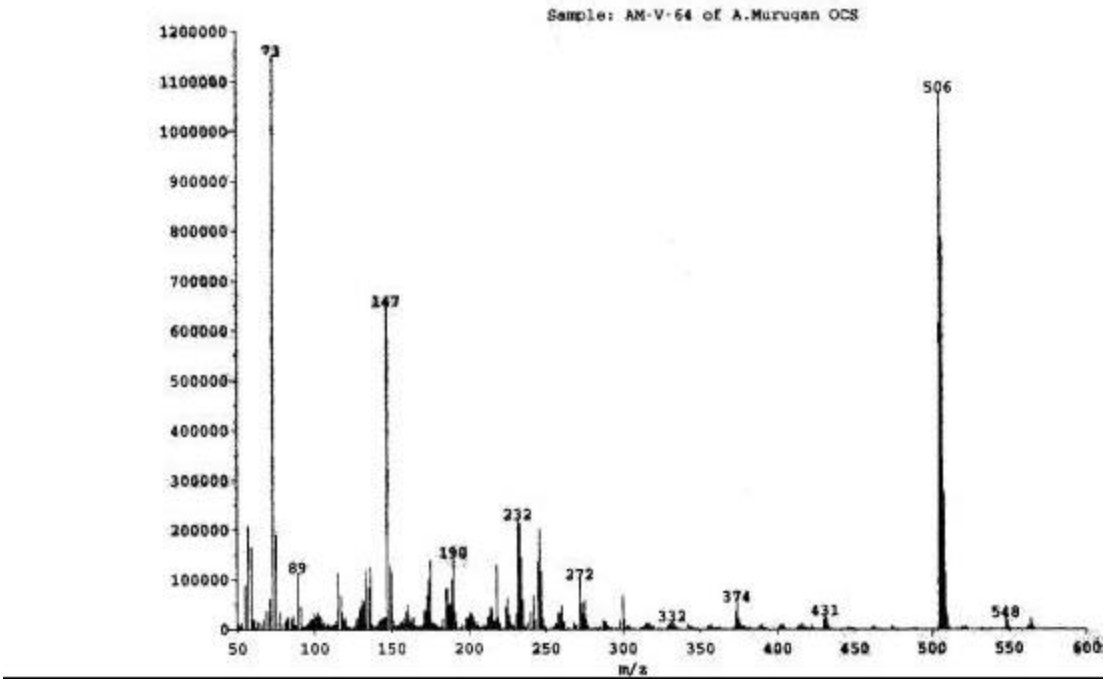
150

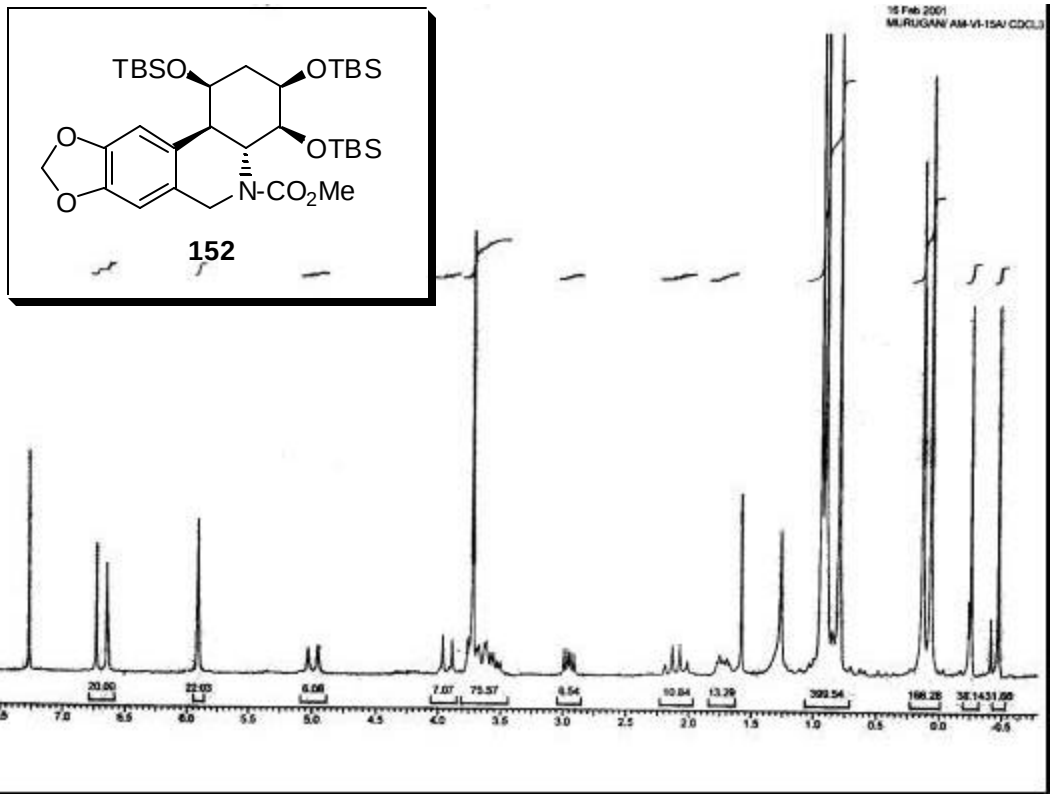


151

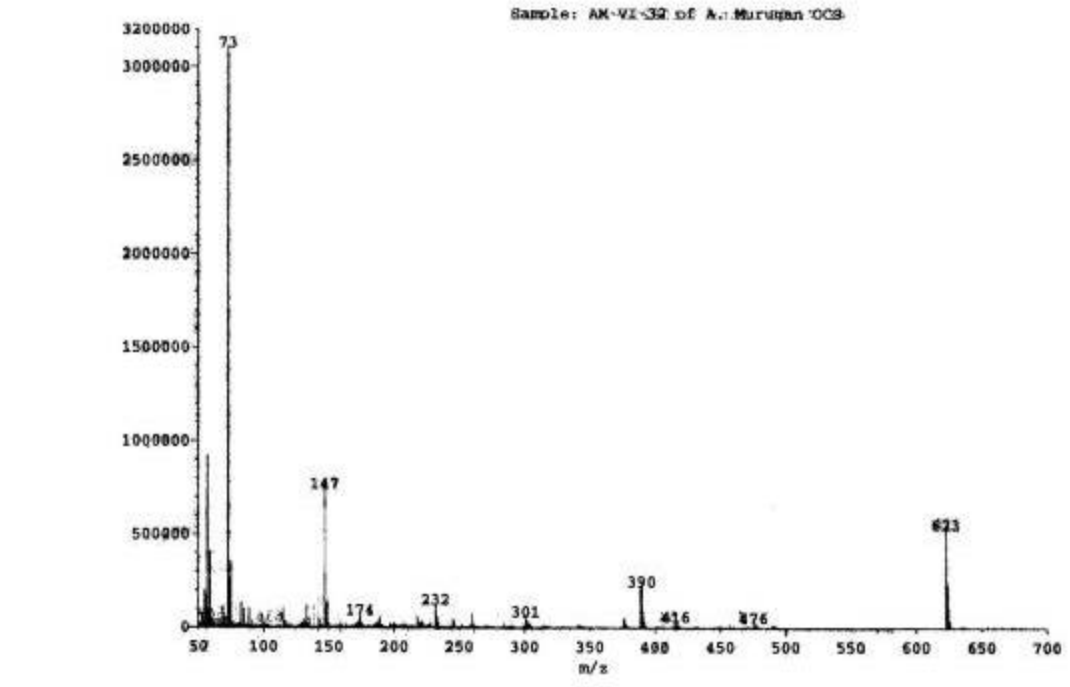

O
OTBS
OTBS
O
O
N-CO2Me

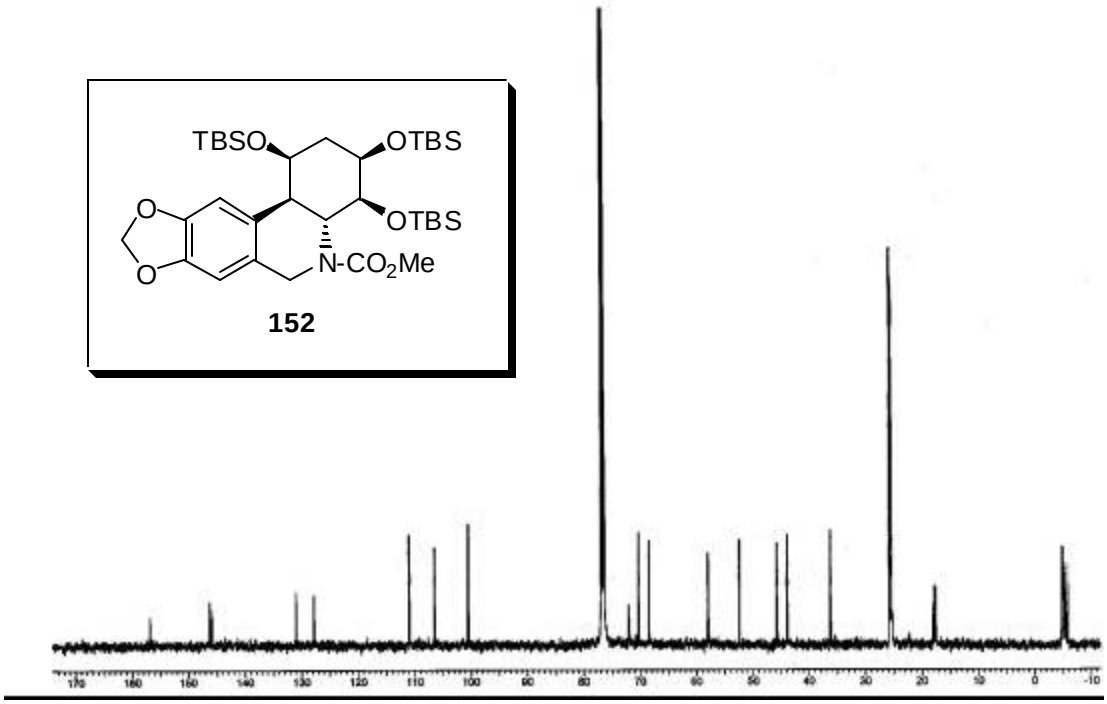
151


Sample: AM-V-64 of A.Muruqan OCS
73
147
89
190
232
272
333
374
431
506
548
m/z

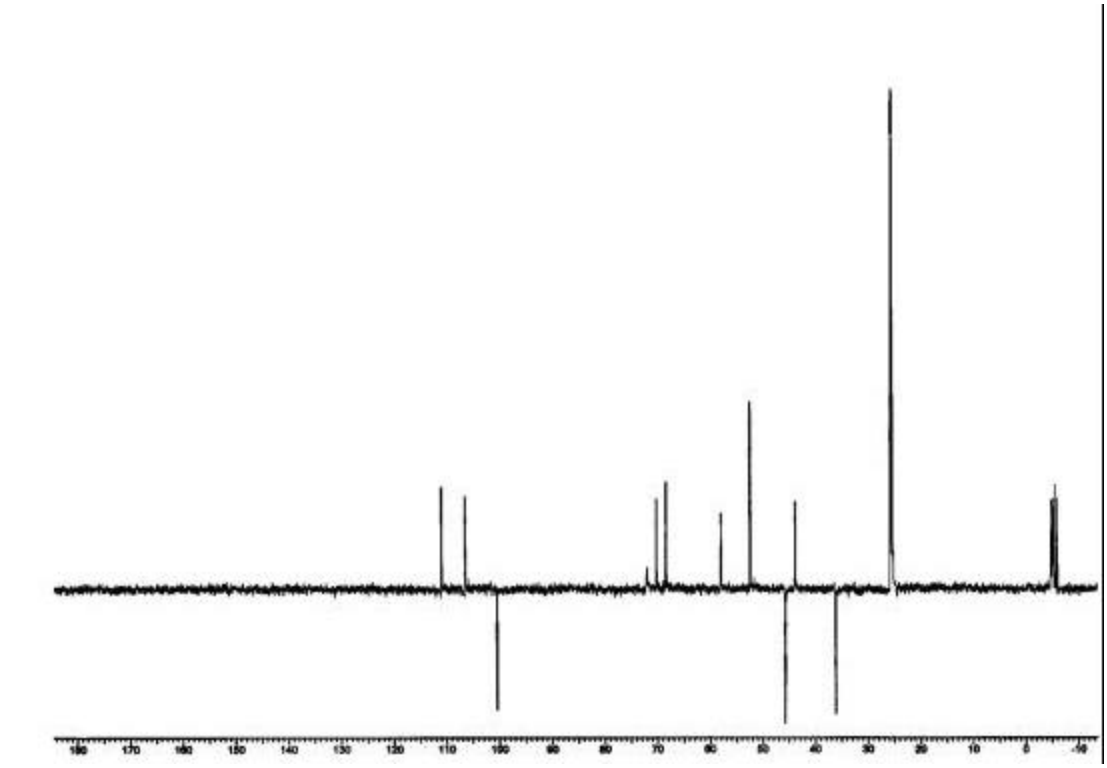

TBSO
OTBS
OTBS
O
O
N-CO2Me

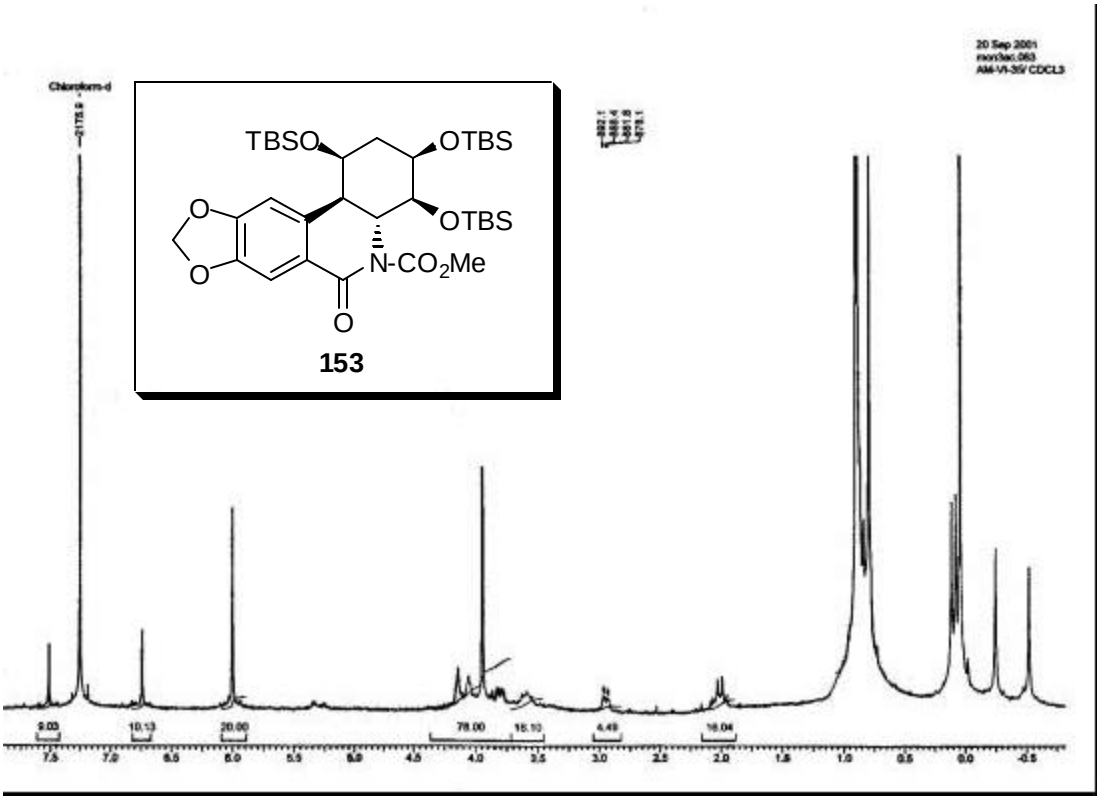
152

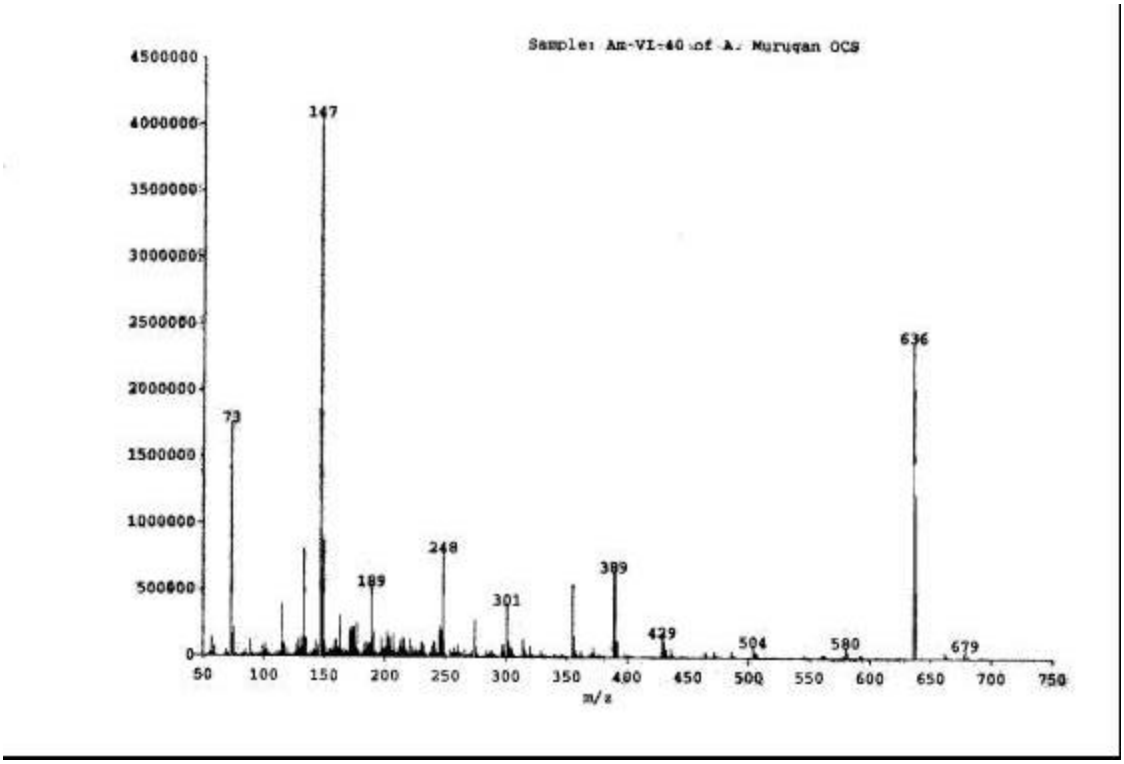

Sample: AK-VI-32 of A. Murugan OCS
3200000
3000000
2500000
2000000
1500000
1000000
500000
0
73
147
174
232
301
390
416
476
623
50
100
150
200
250
300
350
400
450
500
550
600
650
700
m/z

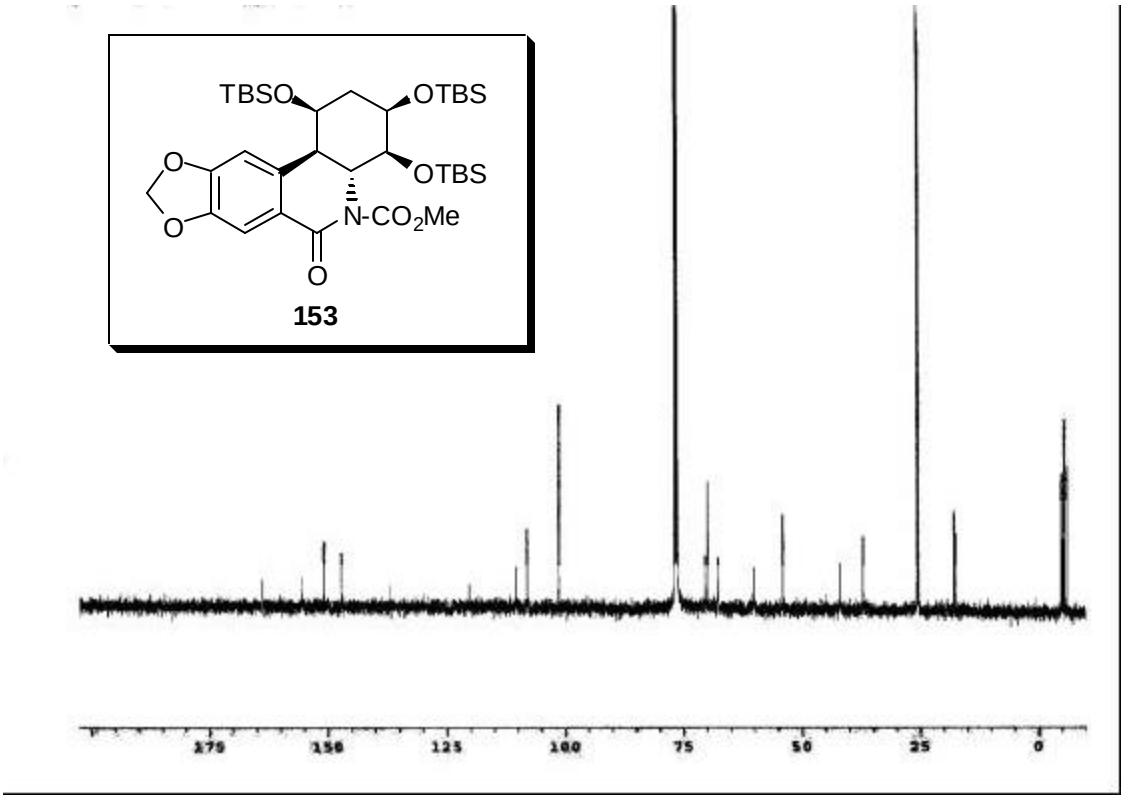


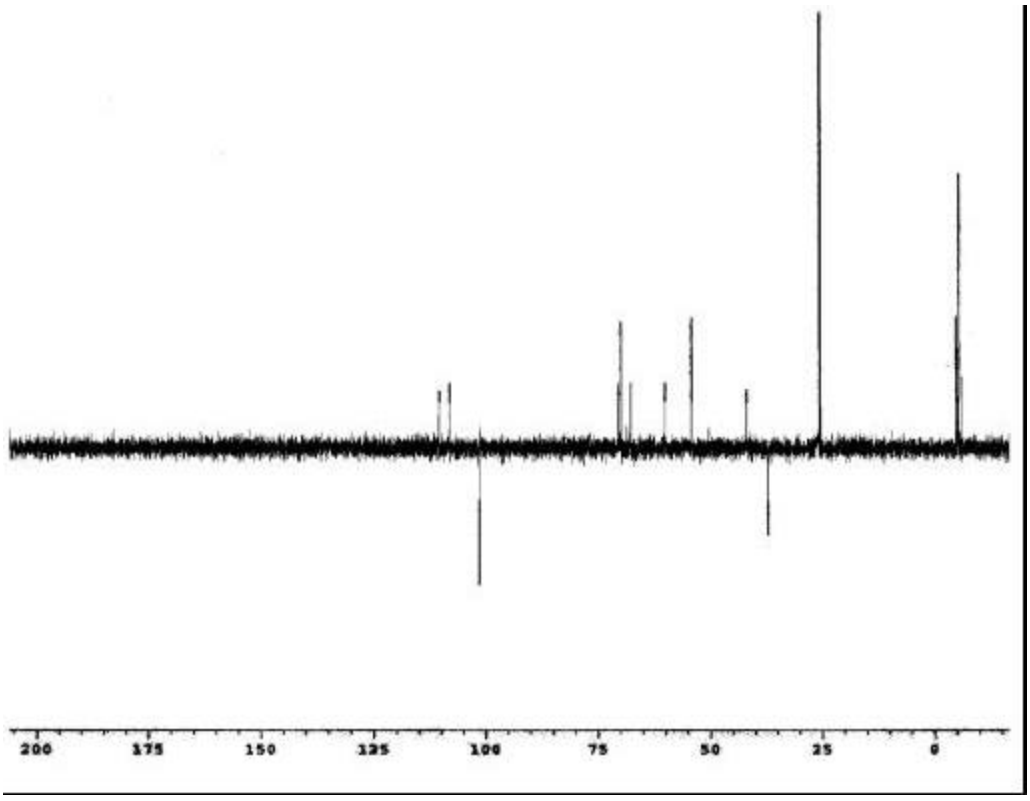
152

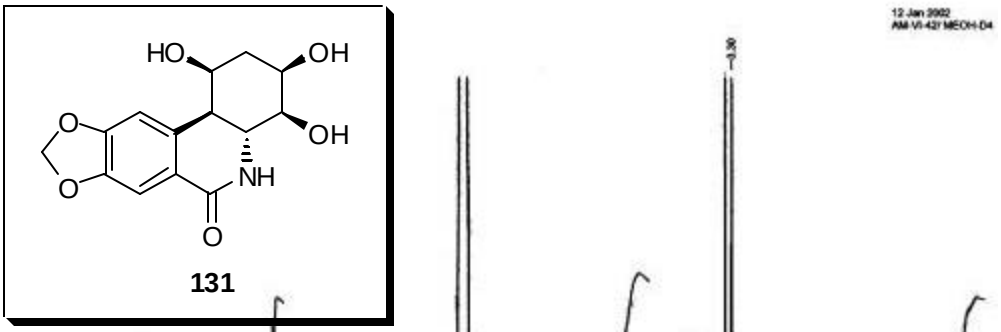



TBSO
OTBS
OTBS
O
O
N-CO2Me
O
153

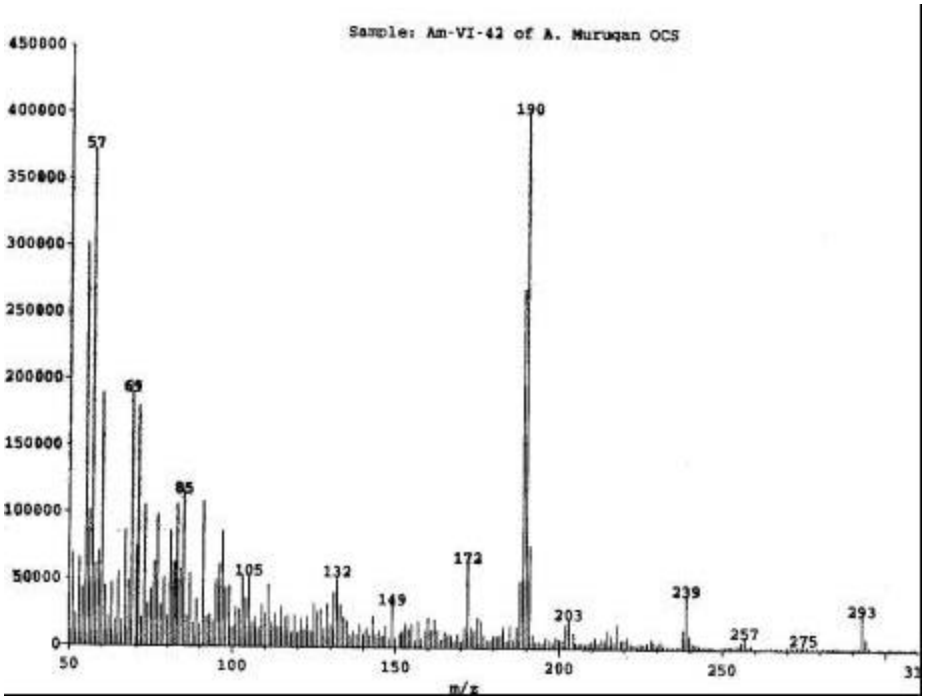

Sample: Am-VI-40 of A. Muruqan OCS
m/z
147
73
636
248
189
389
301
429
504
580
679

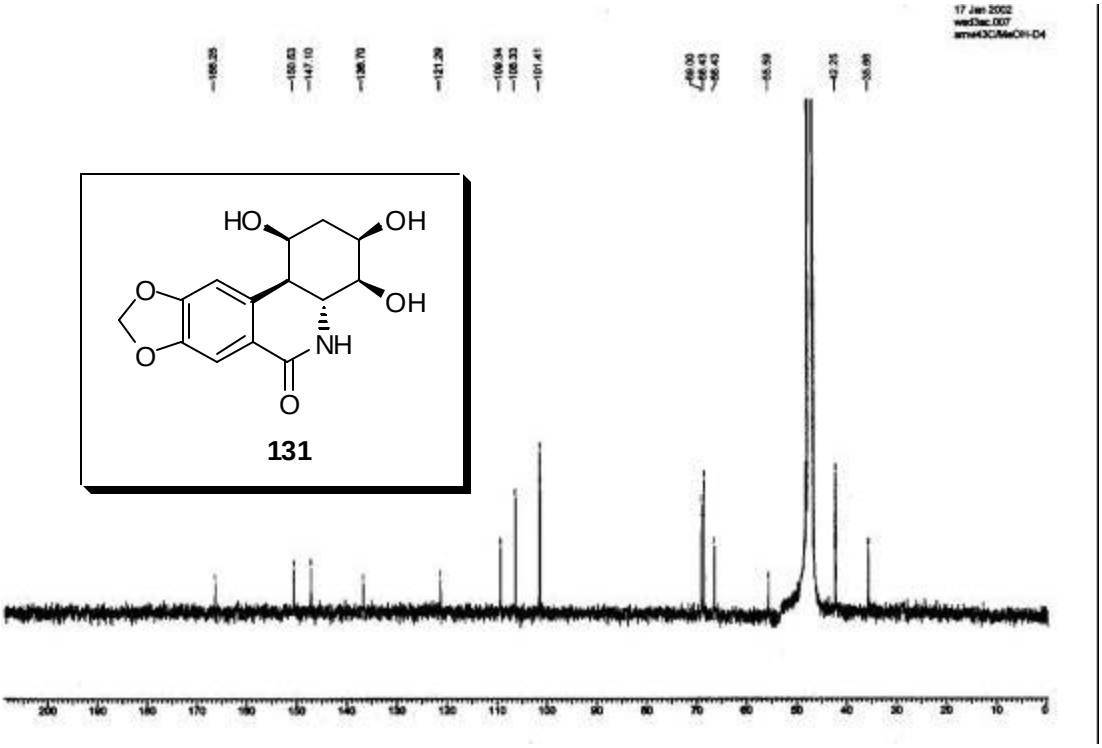

TBSO
OTBS
OTBS
O
O
N-CO2Me
O
153
175
150
125
100
75
50
25
0


200
175
150
125
100
75
50
25
0

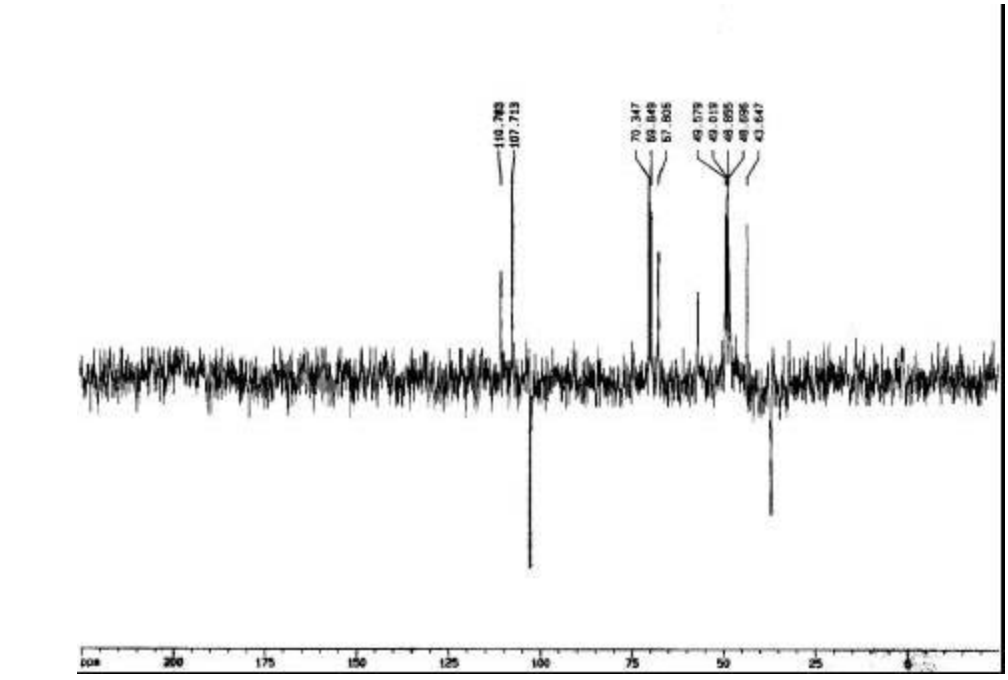

HO
OH
OH
O
O
NH
O

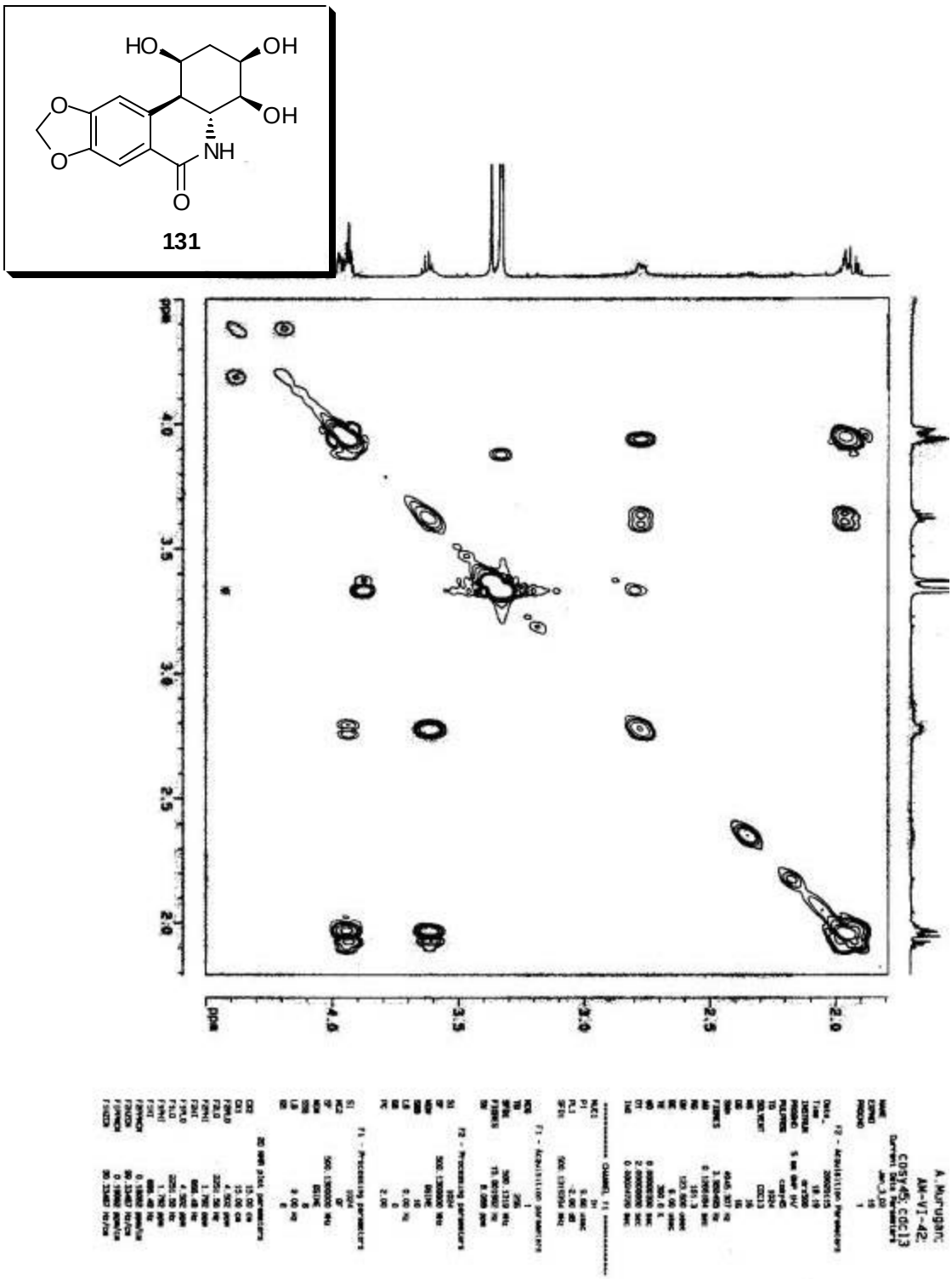
131


Sample: Am-VI-42 of A. Muruqan OCS
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
57
69
85
105
132
149
172
190
203
239
257
275
293
50
100
150
200
250
m/z



131




HO
OH
OH
O
O
NH
O
131
ppm
4.0
3.5
3.0
2.5
2.0