SYNTHETIC STUDIES TOWARDS *AMARYLLIDACEAE* ALKALOIDS: AN INTRAMOLECULAR AZA-MICHAEL ADDITION APPROACH

THESIS

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By

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To My Beloved
MASTER

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Synthetic Studies towards *Amaryllidaceae* Alkaloids: An Intramolecular Aza-Michael Addition Approach**" which is being submitted to the **University of Pune** for the award of **Doctor of Philosophy in Chemistry** by **Mr. M. Balakrishnan** was carried out by him under my supervision at the **National Chemical Laboratory**, **Pune**. A material that has been obtained from other sources has been duly acknowledged in the thesis.

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DECLARATION

I hereby declare that the work presented in the thesis entitled **"Synthetic Studies towards *Amaryllidaceae* Alkaloids: An Intramolecular Aza-Michael Addition Approach"** submitted for Ph. D. Degree to the **University of Pune**, has been carried out by me at the **National Chemical Laboratory**, **Pune**, under the supervision of **Dr. Ganesh Pandey**. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University/Institute.

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Bala…

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Abbreviations

aq.	aqueous	MS	Mass spectrum
bp	boiling point	mL	Milliliter
Bn	Benzyl	mmol	Millimole
Boc	*tert*-Butoxycarbonyl	MOM	Methoxymethyl
Cbz	Benzyloxycarbonyl	mp	Melting point
COSY	Correlation spectroscopy	N	Normality
CSA	Camphorsulfonic acid	NMR	Nuclear magnetic resonance
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene	NOE	Nuclear overhauser effect/enhancement
DCM	Dichloromethane	NOESY	Nuclear overhauser enhancement spectroscopy
DEPT	Distortionless enhancement by polarization transfer	ORTEP	Orthogonal thermal ellipsoid plots
DIPEA	*N*,*N*-Diisopropylethylamine	PDC	Pyridinium dichromate
DMAP	*N*,*N*-Dimethylaminopyridine	*p*-TSA	*p*-Toluenesulfonic acid
DMF	*N*,*N*-dimethylformamide	py	Pyridine
DMSO	Dimethylsulfoxide	rt	Room temperature
g	gram	TBAHS	Tetrabutylammonium hydrogensulfate
GC	Gas chromatography	TBS	*tert*-Butyldimethylsilyl
GI	Growth inhibition	TEA	Triethylamine
h	hour	TFA	Trifluoroacetic acid
HMPA	Hexamethylphosphoramide	THF	Tetrahydrofuran
Hz	Hertz	TLC	Thin layer chromatography
Im	Imidazole	TMS	Trimethylsilyl
LAH	Lithium aluminum hydride		
LDA	Lithium diisopropylamide		
M	Molarity (molar)		
μg	Microgram		
mg	Milligram		
min	Minute(s)		

General Remarks

- All the solvents were purified according to literature procedure.[1]
- Petroleum ether used in the experiments was of 60–80 ^{o}C boiling range.
- Column chromatographic separations were carried out by gradient elution with suitable combination of two solvents and silica gel (60–120 mesh/100–200 mesh/230–400 mesh).
- Reaction progress was monitored by TLC or GC. TLC was performed on manually prepared silica gel plates and E-Merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, Iodine, phosphomolibdic acid, *o*-Anisol, $KMnO_4$. GC analysis was performed on Perkin Elmer 8700 and Varian CP 3800 GCs using SGE BP1, BP20 and Varian Chromopack CP-Sil-5CB columns.
- IR spectra were recorded on FTIR instrument, for solid either as nujol mull, neat in case of liquid compounds or their solution in chloroform.
- NMR spectra were recorded on Bruker AV 200 (200 MHz ^{1}H NMR and 50 MHz ^{13}C NMR), Bruker AV 400 (400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR) and Bruker DRX 500 (500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR). ^{13}C peak multiplicity assignments were made based on DEPT data.
- Mass spectra were recorded on PE SCIEX API QSTAR pulser (LC-MS) and Shimadzu QP 5000 GC/MS coupled to Shimadzu 17A GC using a DBI column.
- Microanalysis data were obtained using a Carlo-Erba CHNS-O EA 1108 Elemental Analyser. Elemental analyses observed for all the newly synthesized compounds were within the limit of accuracy (± 0.4 %).
- All the melting points recorded are uncorrected and were recorded using electrothermal melting point apparatus.
- Starting materials were obtained from commercial sources.
- **Numbering of compounds, schemes, tables, referencing and figures for each chapter as well as abstract are independent.**

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

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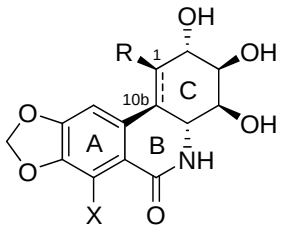
THESIS ABSTRACT

The present dissertation is divided into three chapters.

Chapter 1

An overview on pancratistatin class of *Amaryllidaceae* alkaloids

This chapter starts with the brief account on isolation and biological significance of few important *Amaryllidaceae* constituents (Figure I). Literature reports on the synthetic methodologies concerning with natural as well as synthetic analogues of pancratistatins have been summarized. This part of the dissertation also provides the current understanding of the scientific community regarding the essential and variable pharmacophores of pancratistatin, responsible for biological activities, through structure activity relationship (SAR) studies.



1 X = R = OH — Pancratistatin
2 X = H; R = OH — 7-deoxypancratistatin
3 X = OH; R = H — *trans*-dihydronarciclasine
4 X = R = H — *trans*-dihydrolycoricidine
5 X = OH; R = H; C_1–C_{10b} = double bond — Narciclasine
6 X = R = H; C_1–C_{10b} = double bond — Lycoricidine

Figure I. *Few representatives of Amaryllidaceae constituents*

Chapter 2

An Intramolecular aza-Michael addition approach towards the syntheses of pancratistatins

Main challenges associated with the synthesis of pancratistatin are the controlled installations of five to six contiguous stereogenic centers around the perimeter of C-ring and the elaboration of *trans*-fused BC-ring junction. Most of the documented synthetic reports of this molecule emphasized a convergent approach of formation of B-ring from the pre-constructed A and C-rings for the more practical synthesis of pancratistatin. Amongst various reported B-ring cyclizations, it was surprising to note that an aza-Michael addition mediated cyclization has not been explored even though it may offer an attractive, practical synthesis of this molecule. In this context, an approach based on intramolecular aza-Michael addition has been envisioned for phenanthridones (**1**–**6**) as depicted retrosynthetically in the Figure II.

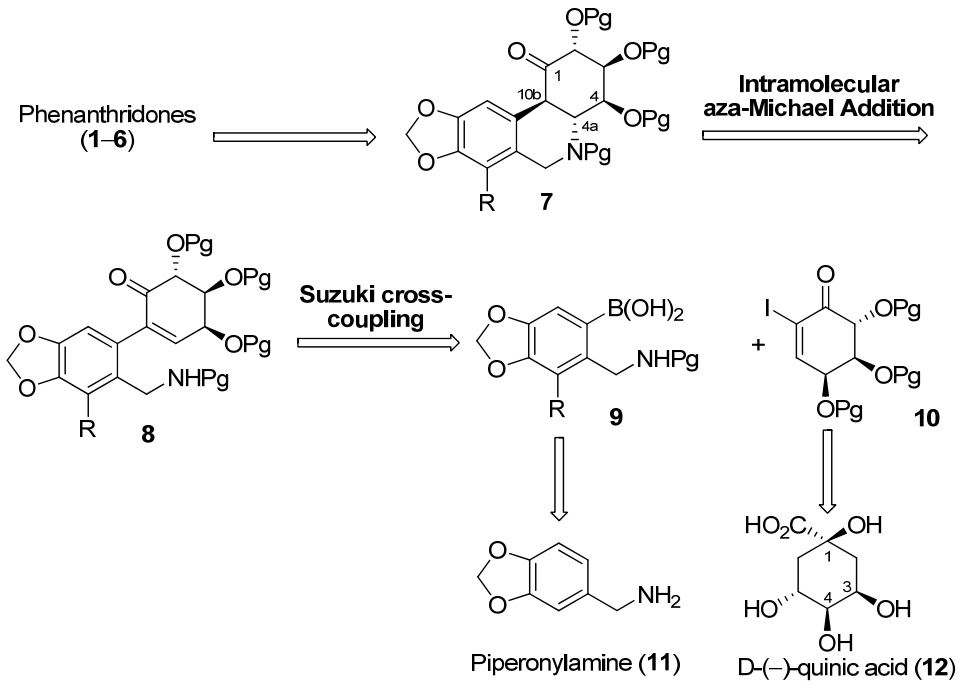
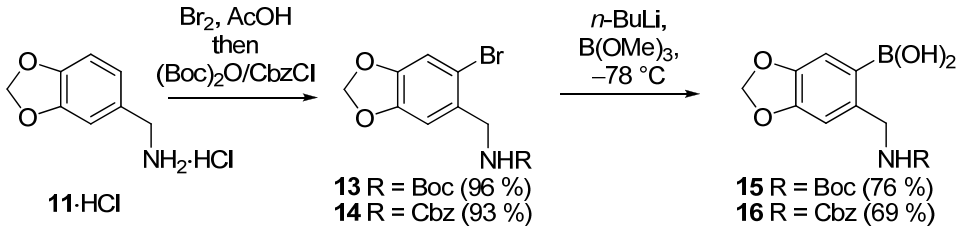


Figure II. *A retrosynthetic plan for phenanthridones*

In order to realize the designed strategy, the synthesis of requisite boronic acid **9** was planned from commercially available piperonyl amine (**11**) using two-stage bromination-boronation sequence (Scheme I). Boronic acids possessing different *N*-

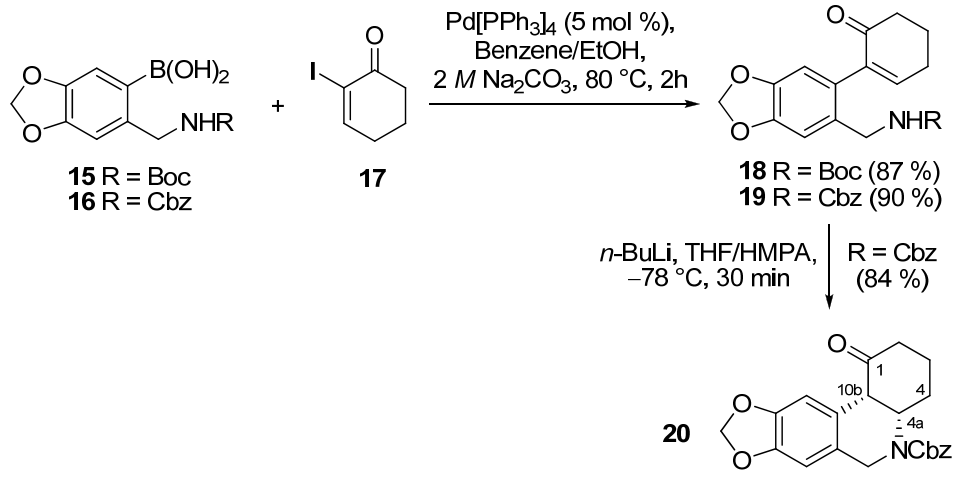
protecting groups (**15** & **16**) have been synthesized to study the nucleophilicities of carbamates during intramolecular aza-Michael addition.

Scheme I. *Syntheses of requisite boronic acids*



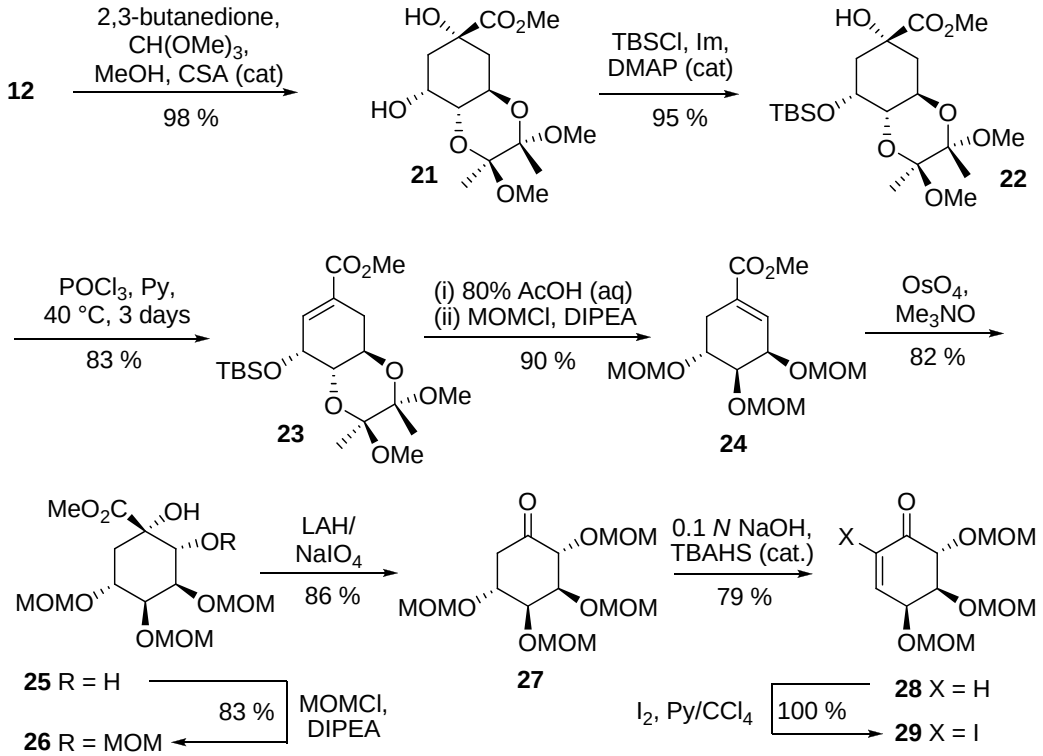
The validity of the proposed strategy was quickly checked through its application to synthesis of phenanthridone skeleton (**20**) as illustrated in scheme II. Suzuki cross-coupling of carbamates **15** and **16** with 2-iodoyclohexenone (**17**) produced the aza-Michael addition precursors **18** as well as **19** respectively. It was noticed that the benzyl carbamate **19** underwent smooth cyclization after *N*-lithiation with the aid of *n*-BuLi in THF/HMPA at −78 °C to afford *cis*-fused phenanthridone **20**.

Scheme II. *Synthesis of phenanthridone skeleton* (**20**)



After the successful preparation of **20**, we went ahead to synthesize the original target natural product with the hope that the *cis*-fused phenanthridone could be easily epimerized at C_{10b} in due course to produce the required *trans*-fused isomer. The suitably substituted chiral *α*-iodoenone **29** for the Suzuki cross-coupling reaction was synthesized from naturally abundant D-(−)-quinic acid (**12**) as shown in the Scheme III.

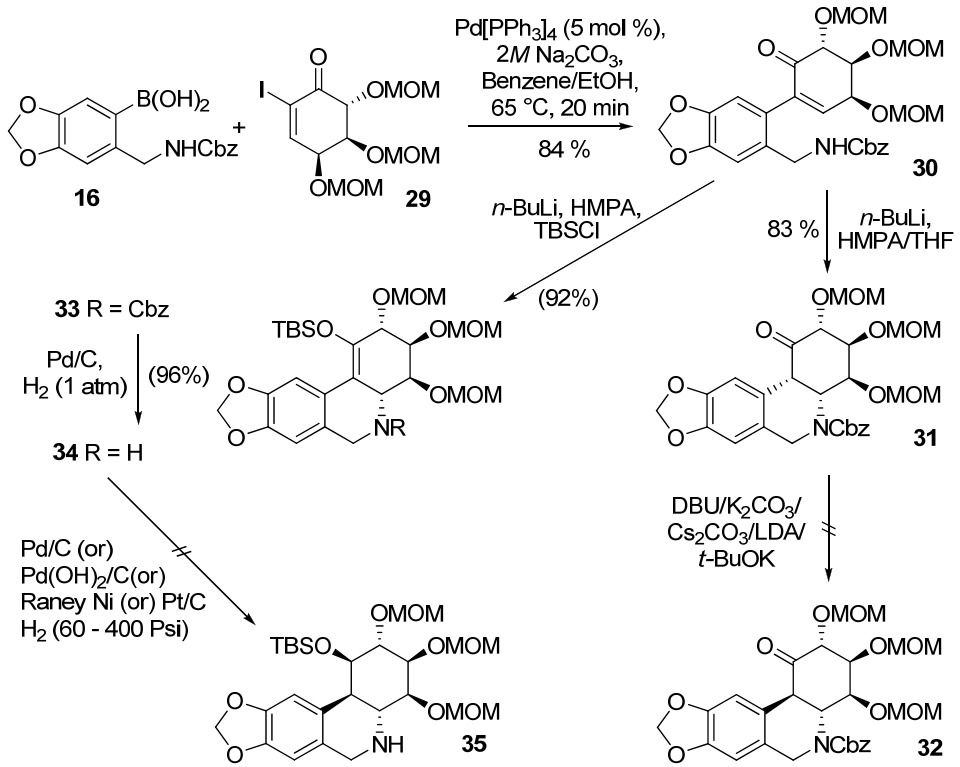
Scheme III. *Synthesis of α-iodoenone* **29**



As planned earlier, cross-coupling reactions of two subunits **16** and **29** provided the key precursor **30** for the intramolecular aza-Michael reaction. *N*-lithiation of **30** in the presence of *n*-BuLi at −78 °C gave phenanthridone **31** as a single diastereomer in 83 % isolated yield (Scheme IV). The stereochemistry of BC-ring fusion was found to be *cis* based on ^{1}H NMR spectral analysis. Attempts on the epimerization of **31** to the *trans*-fused phenanthridone **32** under various bases remained unsuccessful. Under more enforcing conditions, C-ring moiety of **31** underwent an aromatization reaction *via* retro-Michael reactions of both N and O functionalities at *β*-position of the carbonyl group.

An indirect epimerization of **31** was planned to overcome the above problem, where the TBS enol ether **33**, derived from **30**, was debenzyloxycarbonylated to give *sec*-amine **34**. This compound under stereoselective hydrogenation (*via* haptophilicity) was expected to produce required stereocenters at both C_1 and C_{10b}. However, hydrogenation of the sterically more congested tetra-substituted double bond of **34** was not rewarding under different catalysis listed in Scheme IV at various pressures ranging from 60–400 Psi.

Scheme IV. *Intramolecular aza-Michael addition and the haptophilicity*

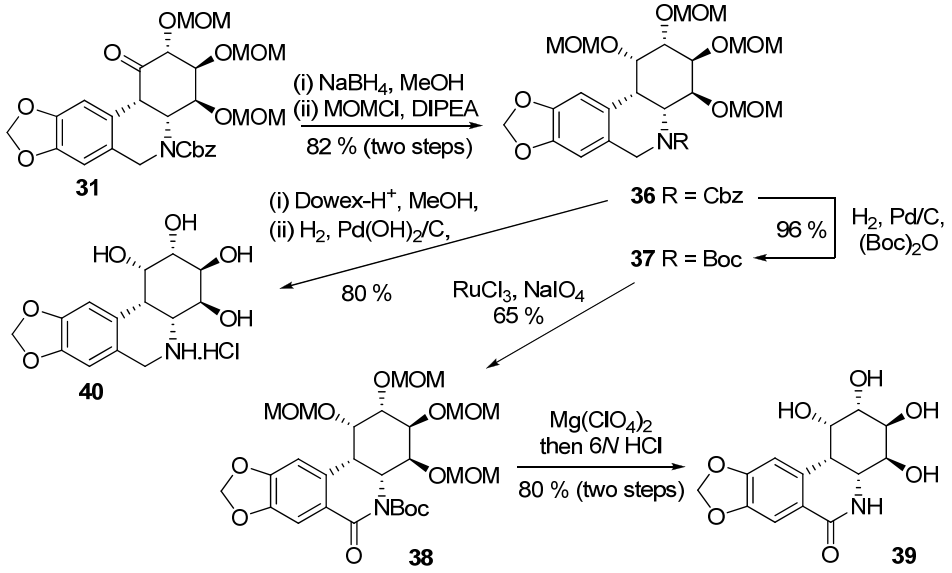


As the efforts on both direct and indirect epimerization trials at C_{10b} were not fruitful, we proceed with the planned synthetic sequence to achieve the syntheses of *cis*-analogues of 7-deoxypancratistain (Scheme V). The stereoselective reduction of **31** using $NaBH_4$, followed by methoxymethylation of the resulting alcohol afforded **36**. Since the RuO_4 mediated oxidation of **36** produced a more complicated mixture, the benzyl carbamate of **36** was interchanged with the *tert*-butyl carbamate (**37**) which was more compatible for the bezylic oxidation to produce **38** in 65 % yield. A two-stage deprotection strategy apllied to **38** produced 1,10b-*epi*-7-deoxypancratistatin (**39**) {mp 298–304 ºC; $[\alpha]^{27}_{D}$ +88.3 (*c* 0.35, DMSO)} in 80 % combined yield. All newly generated stereocenters of this molecule **39** were unambiguously confirmed with the help of single crystal X-ray crystallography.

For the purpose of evaluating biological profile of *cis*-analogues of pancratistatin, compound **40** {mp 214–218 ºC (with decomposition); $[\alpha]^{27}_{D}$ +40.8 (*c* 0.5, H_2O)} was also synthesized by the deprotection of N, O functionalities of **36**.

The compounds synthesized (**39** and **40**) were screened for their cytotoxicities against murine P388 lymphocytic leukemia and two other human cancerous cell lines MCF-7 (breast adenocarcinoma) and THP-1 (promonocytic leukemia).

Scheme V. *Synthesis of 1,10b-epi-7-deoxypancratistatin and its amine analogue*



In summary, a new synthetic strategy has been developed for the syntheses of phenanthridone class of alkaloids employing Suzuki cross coupling/Intramolecular aza-Michael reaction sequence. Compound **40** has shown some activity against THP-1 monocytic cells raising the hope that subtle variation in its structure may enhance the possibility of developing this molecule as therapeutic agents.

Experimental section provides detailed experimental procedures, tabulated spectral data for all new compounds, cancer cell growth inhibition assay general procedure and inhibition plots. ^{1}H & ^{13}C NMR spectra of all new compounds have been presented at the end of the experimental section.

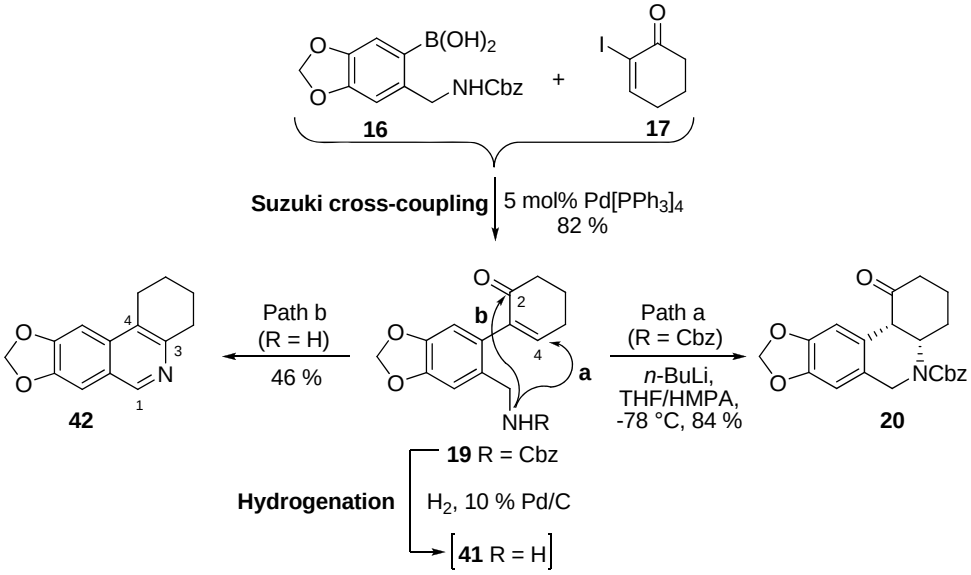
Chapter 3

Syntheses of pancratistatin-like isoquinolines: Development of new mild strategy for [*c*]annulated isoquinolines

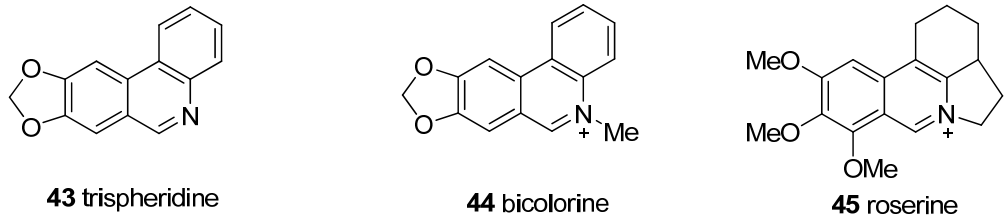
This chapter presents an account on our unexpected results while exploring intramolecular aza-Michael addition of substrate **19** in detail. As the previous chapter explored the scope and limitations of *cis*-fused phenanthridone **20**, the resultant when **19** was treated with *n*-BuLi, THF/HMPA at −78 °C (Scheme VI, *path a*), the current

chapter investigates the mode of interaction of the corresponding free amine (**41**). Thus, when reductive removal of benzyl carbamate of **19** was carried out by using 10 % Pd on charcoal at 1 atm pressure of H_2, to our surprise, the product obtained was an entirely unexpected product **42** (*path b*). The resultant product was thoroughly analyzed by all spectroscopic means to confirm that to be an [*c*]annulated isoquinoline. The introduction part also deals with some classical as well as novel isoquinoline syntheses which have been documented earlier in the literature.

Scheme VI. *Two different modes of aza-interactions*



[*c*]Annulated isoquinolines of type **42** are valuable synthetic precursor in the synthesis of trispheridine (**43**), a naturally occurring phenanthridine alkaloid from the *Amaryllidaceae* plant family (Figure III). Compound **33** also shares the close structural relationship with other alkaloids such as bicolorine (**44**) and roserine (**45**).



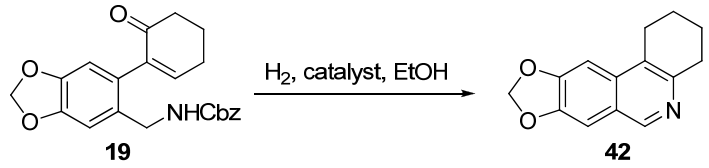
43 trispheridine **44** bicolorine **45** roserine

Figure III. *Few naturally occurring [c]annulated isoquinolines*

As we realized the potentiality of the product obtained (**42**) from above two-step sequence, we optimized the reductive removal of the benzyloxycarbonyl moiety of **19** to obtain the maximum yield of **42**. The result of the optimization studies

recommended the use of catalytic 20 % $Pd(OH)_2/C$ for the complete conversion of **19** at atmospheric pressure of the hydrogen to afford **42** (Table I, entry 5).

Table I. *Optimization of conditions for reductive debenzyloxycarbonylation*

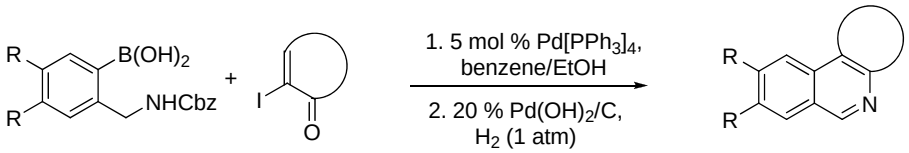


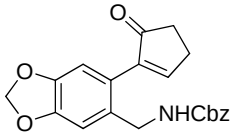
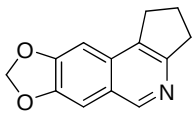
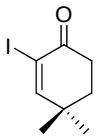
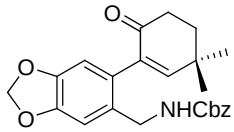
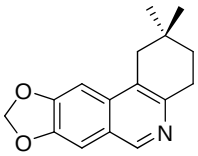
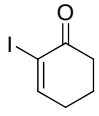
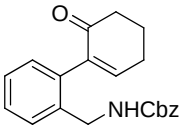
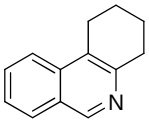
19 **42**

entry	catalyst	pressure (atm)	time (h)	yield (%)
1	10 % Pd/C	1	28	46
2	10 % Pd/C	4	12	52
3	W-2 Raney Ni	1	12	no rxn
4	W-2 Raney Ni	15	12	39
5	20 % $Pd(OH)_2/C$	1	8	96

The generality this methodology was evaluated by synthesizing various [*c*]annulated isoquinolines as summarized in Table II.

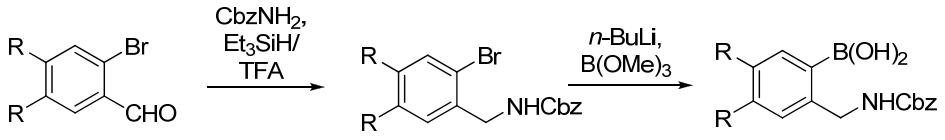
Table II. *Syntheses of isoquinolines using the two-step sequence*



entry	boronic acid	iodoenone	coupling product (yield)	isoquinoline (yield)
1	**16** (R=OCH_2O)	 **46**	 **47** (76 %)	 **48** (85 %)
2	**16**	 **49**	 **50** (87 %)	 **51** (92 %)
3	**52** (R=H)	 **17**	 **53** (75 %)	 **54** (82 %)

The requisite boronic acids of the Suzuki cross-coupling reactions (**16**, **52**, Scheme VII) were synthesized from the corresponding bromo analogues (**14**, **57**) using lithiation/boronation protocol, where as, bromides themselves were synthesized from corresponding aldehydes (**55**, **56**) and benzyl carbamate by the reductive *N*-alkylation of carbamates strategy.

Scheme VII. *Synthesis of boronic acids*



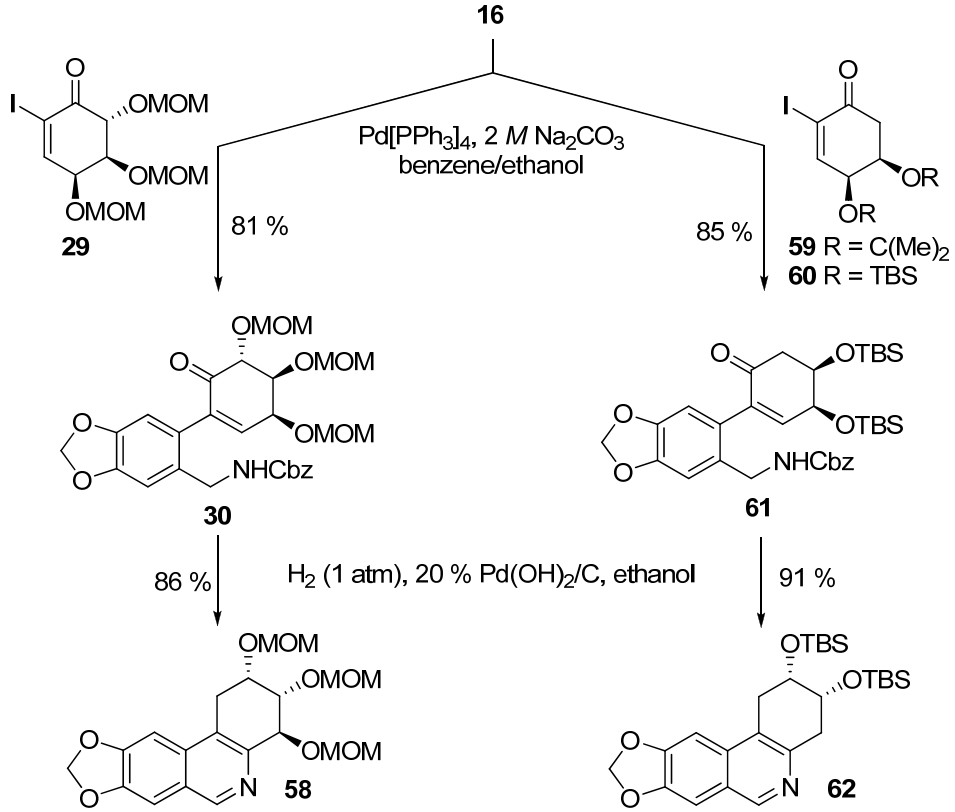
55 R = OCH_2O
56 R = H

14 R = OCH_2O (95 %)
57 R = H (92 %)

16 R = OCH_2O (69 %)
52 R = H (65 %)

The efficacy of Suzuki cross-coupling/reductive debenzyloxycarbonylation sequence was explored to the syntheses of few chiral alkoxylated isoquinolines (Scheme VIII). The requisite chiral *α*-iodoenones (**29**, **59** and **60**) were synthesized from D-(−)-quinic acid (**12**).

Scheme VIII. *Syntheses of alkoxylated isoquinolines*



Removal of the protecting groups from **58** as well as **62** using 6 *N* HCl in MeOH afforded isoquinolines **63** {87 %, mp 239–241 °C, $[\alpha]_D^{27}$ +48.5 (*c* 0.5, DMF)} and **64** {91 %, mp 286–291 °C, $[\alpha]_D^{27}$ –43.1 (*c* 0.5, DMF)}, respectively (Figure IV). Since these hydroxyl isoquinolines bear considerable structural similarity with naturally occurring 7-deoxypancratistatin (**2**), one can expect these compounds to possess interesting biological profiles like anti-cancer and anti-viral properties. Therefore, the isoquinolines **63** and **64** were screened against murine P388 lymphocytic leukemia and two other human cancerous cell lines MCF-7 (breast adenocarcinoma) and THP-1 (promonocytic leukemia). However, they exhibited >100 fold less activity (GI_{50} values are in the order of >40 μg/mL) in these cell lines in comparison to natural **2**.

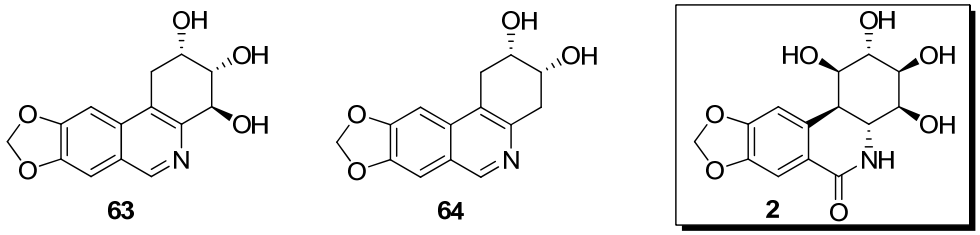


Figure IV. *Pancratistatin-like isoquinolines*

Experimental section at the end of this chapter provides detailed experimental procedures, tabulated spectral data, cancer cell growth inhibition plots for the compounds **63** as well as **64** and copies of ^1H & ^{13}C NMR spectra of all new compounds.

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

Chapter 1

An overview on pancratistatin class of *Amaryllidaceae* alkaloids

1.1. Introduction

The *Amaryllidaceae* alkaloids constitute an important class of naturally occurring compounds.[1] Medicinal history of these alkaloids dates back to at least the fourth century and they have been the subject of active chemical investigation for nearly 200 years.[2] Lycorine was the first alkaloid of these family to be isolated in 1877 from *Narcissus pseudonarcissus*[3] and was shown to have the characteristic galanthan ring system. Since then, more than hundred structurally diverse alkaloids have been isolated from various *Amaryllidaceae* species (Figure 1). In 1958, lycorine (**1**) was shown to possess antitumor activity.[4] Stimulated by the need for more potent antitumor agents, the search led to isolations of pancratistatin subclass of compounds. Lycoricidine (**2**) and narciclasine (**3**) were extracted from different bulbs of narcissi and daffodils.[5] The more oxygenated analogue, pancratistatin (**4**) was first isolated in 1984 by Pettit and co-workers from the Hawaiian plant *Hymenocallis littorale* (previously recognized as *Pancratium littorale*).[6] This particular compound attracted considerable attention because of its spectrum of antineoplastic activities.[7] Constituents **3** and **4** are the most potent anticancer agents, tested against human cancer cell lines and P388 lymphocytic leukemia (GI_{50} values on the order of 0.02 μg/mL).[7] Later, 7-deoxypancratistatin (**5**), isolated from *Haemanthus kalbreyeri* by Ghosal and coworkers[8] has been shown in vitro antiviral assays to exhibit a better therapeutic index than **4** due to decreased toxicity.[9] Pettit and co-workers isolated yet another constituent, *trans*-dihydronarciclasine (**6**) from the Chinese medicinal plant *Zephyranthes candida* in 1990,[10] and it exhibited even higher potency (two to ten fold higher) than pancratistatin against selected human cancer cell lines.[11]

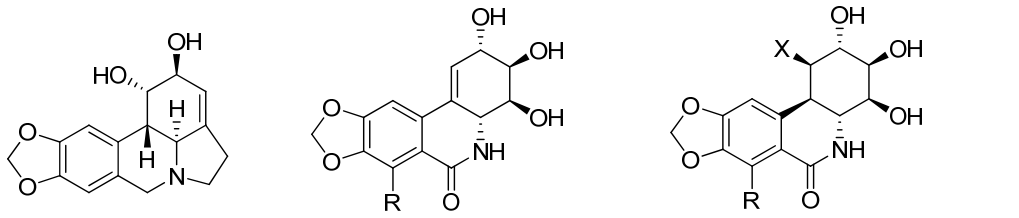


Figure 1. *Few representatives of Amaryllidaceae alkaloids*

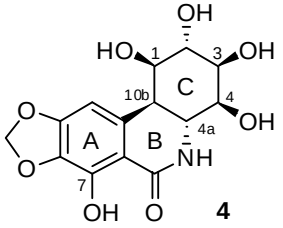
The cytotoxic effects are ascribed to the capacity of these compounds (**2**–**6**) to inhibit protein synthesis in eukaryotic ribosomes.[12] In the case of **3**, this effect is exerted by blocking of peptide bond formation on the 60-S ribosome unit.[12a] Recent studies in this area have revealed that pancratistatin (**4**) induces apoptosis, or programmed cell death, selectively in cancer cells, with minimal effect on normal cells, and that the mitochondria in cancerous cells are the site of action.[13] In addition to the antitumor activity, pancratistatin (**4**) also displays a reasonable antiviral profile,[7] most likely because of its aminoinositol moiety, which would effectively serve to act as an inhibitor of common glucosidases. Although the mode of action of these compounds remains to be elucidated, they are being the subject of preclinical development studies as agents for the treatment of certain cancers. These alkaloids are available only in minute quantities from natural sources (0.0028 % yield in isolation),[2,14] and their future as therapeutic agents depends on their availability.

The above problem has been addressed by various research groups in two different dimensions over two decades. One of the dimensions has been dealing with the quest for short, high yielding synthesis of the naturally occurring pancratistatins. The task promoted the screening and development of great number of existing and new methodologies[15–30] for their capabilities. The other dimension is looking for the potential and more bioavailable derivatives to substitute pancratistatin in all respects. This particular search resulted in the syntheses of various truncated and unnatural derivatives,[31–39] through which the scientific community has been enlighten with substantial amount of information regarding essential and variable pharmacophores of the molecule. The mile stones crossed in this area have been extensively reviewed in many different occasions.[40]

The promising biological activities, interesting structural features and extreme low natural abundance of these alkaloids have generated considerable attention from the synthetic community. The main challenges concerning the synthesis of these alkaloids include the elaboration of the *trans*-fused BC-ring juncture and the stereocontrolled installation of the contiguous hydroxyl functionalities located around the perimeter of the C-ring. The foregoing discussion would mainly focus on the methodologies involved in the literature reported syntheses of pancratistatin analogues (**2**–**6**) and structurally related synthetic analogues.

1.2. Synthetic methodologies concerning with natural as well as synthetic analogues of pancratistatin

Since the detailed discussion of all the literature reported syntheses have already been reviewed by many others[40] and also it would be beyond the scope of this dissertation, the important key features of these syntheses are highlighted in this section. In order to simplify the task of summarization, the existing methodologies are categorized into constructions of three rings A, B and C of **2**–**6**.

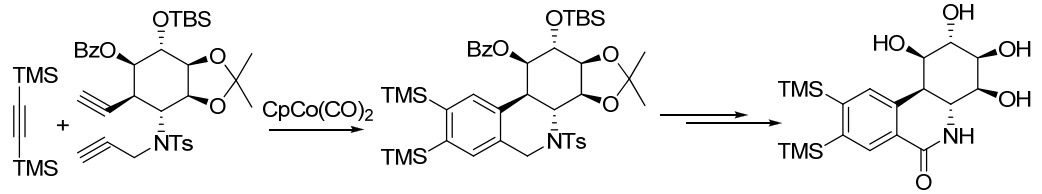


4

1.2A. Towards the construction of ring A

Being aromatic in nature, the ring A has been perhaps given the least preference of its construction. However, the derivative **10** of pancratistatin having no oxygen functionalities in the aromatic ring was synthesized by strategy based on the cobalt catalyzed cyclotrimerization of acetylenes **7** and **8** by Hudlicky *et al.* [41] (Scheme 1)

Scheme 1. *Cyclotrimerization approach*



7 **8** **9** **10** Deoxygenated Pancratistatin

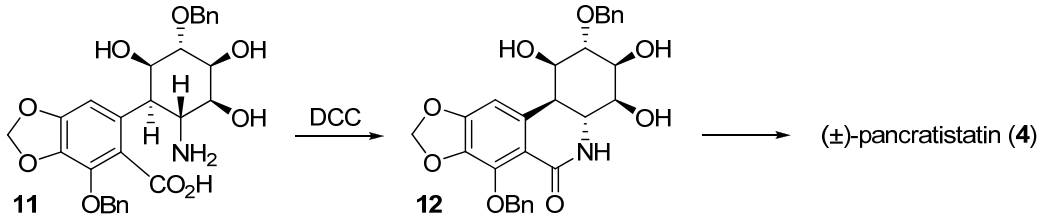
1.2B. Towards the construction of ring B

Heterocyclic nature of ring initiated screening of large number of methodologies to explore their capabilities in the construction of ring B.

1.2B.1. Lactamization and Transamidation

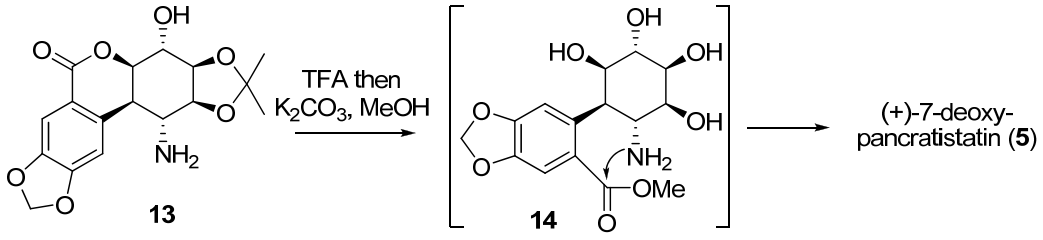
The simplest method envisioned was disconnection at amide bond. An intramolecular lactamization of amino acid **11** using DCC, demonstrated by Danishefsky, set the first total synthesis of pancratistatin (**4**) in 1989 (Scheme 2).[16]

Scheme 2. *Lactamization*



Later, a number of syntheses of these natural products had utilized the lactone-lactam conversion in which intramolecular amidation of **13**, most probably involved nucleophilic attack of primary amine to the *in situ* generated methyl ester (**14**) as shown in Scheme 3.[18,23]

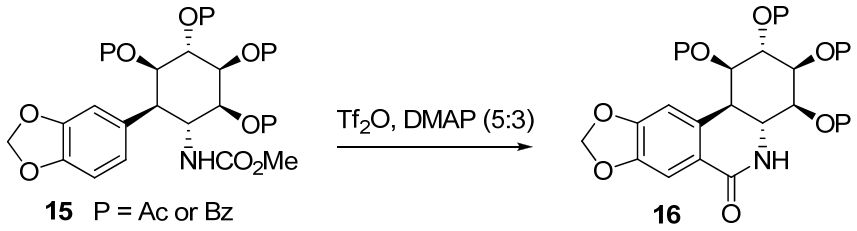
Scheme 3. *Transamidation*



1.2B.2. Modified Bischler-Napieralski reaction

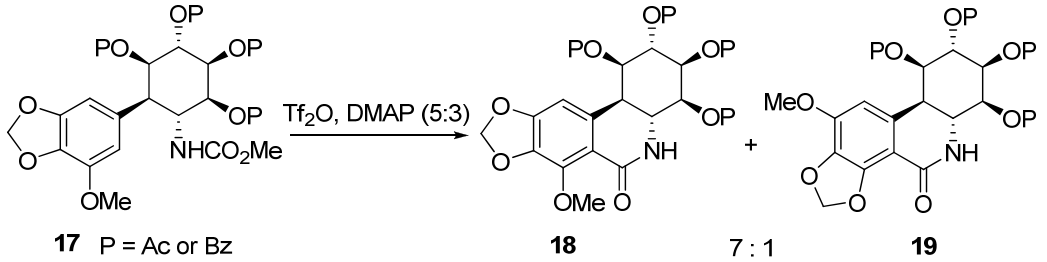
Another facile B-ring construction was based on modified Bischler-Napieralski cyclization which used the combination of Tf_2O/DMAP in particular ratio (5:3) to effect the cyclization between carbamate and electron rich arene to afford **16**. The crucial empirical ratio of reagents was optimized by Banwell (Scheme 4).[42]

Scheme 4. *Bischler-Napieralski cyclization*



Although, the reaction produced exclusively the required targets in the case of 7-deoxy analogues (**15**), the pancratistatin series (**17**) produced mixture of regioisomers (**18** and **19**) in 7:1 ratio with the required **18** as the major product (Scheme 5).

Scheme 5. *B-N cyclization of pancratistatin series*



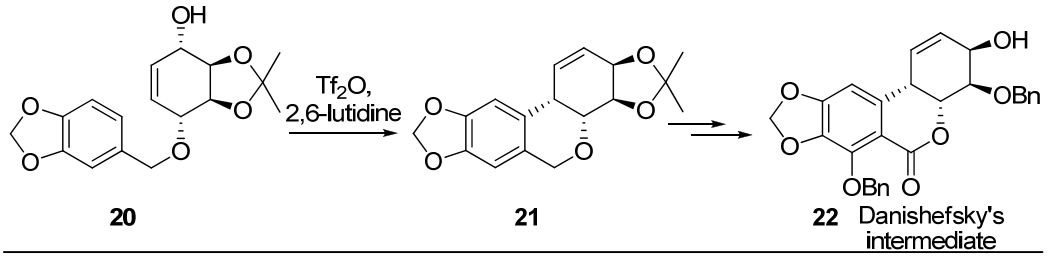
1.2B.3. Lewis acid mediated ring closure

The electron richness of aromatic ring in these natural products was exploited in the construction of ring B as shown by the couple of examples below.

1.2B.3a. Arene-allyl triflate coupling

The piperonylated conduritol **20** was converted to a late-stage intermediate **22** of Danishefsky's pancratistatin synthesis *via* Tf_2O induced intramolecular electrophilic aromatic substitution (Scheme 6).[20]

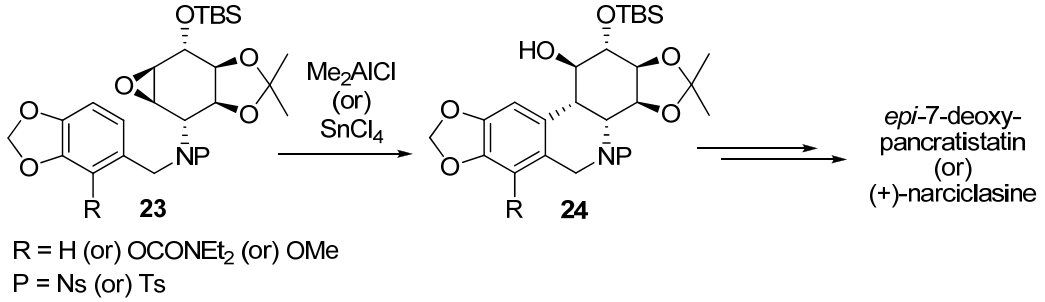
Scheme 6. *Allyl triflate mediated cyclization*



1.2B.3b. Arene-epoxide coupling

An intramolecular Lewis acid catalyzed cyclization onto an epoxy conduramine was demonstrated to produce *cis*-fused phenanthridine by Hudlicky[33] and Yan[27] independently. These *cis*-intermediates were further elaborated to either 10b-*epi*-7-deoxypancratistatin or (+)-narciclasine (Scheme 7).

Scheme 7. *Epoxide ring opening*

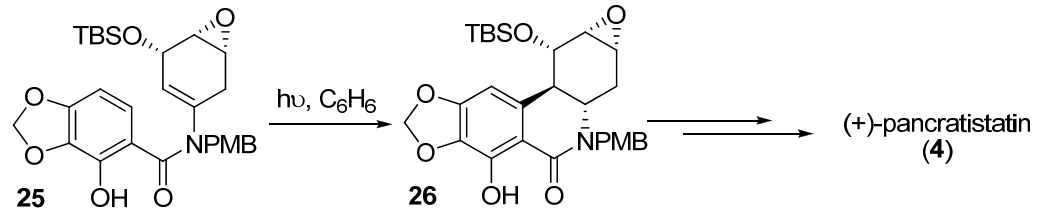


1.2B.4. Photocyclizations

1.2B.4a. Aryl enamide cyclization

This methodology features a stereo- and regiocontrolled aryl-enamide photocyclization to construct advanced intermediate **26** possessing a *trans*-fused BC ring junction (Scheme 8).[22] The hydrogen bonding between the phenolic alcohol and the amide carbonyl oxygen in **25** was claimed to be essential in order to control the regoichemical course of the B ring forming event by restricting the rotation around the aryl-amide carbonyl bond. Routine functional group transformation from **26** led to the synthesis of (+)-pancratistatin (**4**).

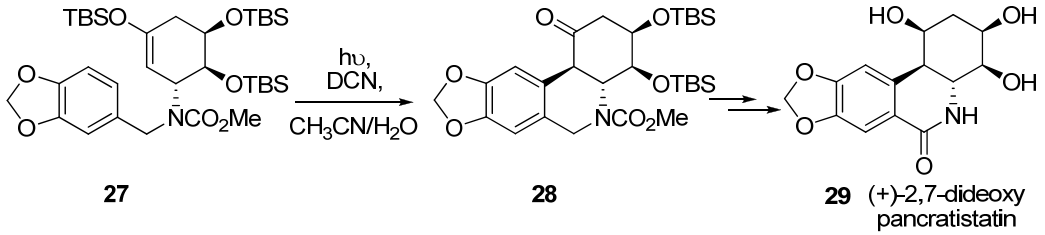
Scheme 8. *Aryl-enamide photocyclization*



1.2B.4b. Photoinduced Electron Transfer (PET) cyclization

Few years ago, our group had demonstrated the synthesis of (+)-2,7-dideoxypancratistatin (**29**, Scheme 9).[43] The key features of our synthetic strategy involved, (i) crucial B-ring cyclization *via* Photoinduced Electron Transfer (PET) initiated carbocyclization of silylenol ether to an electron rich aromatic ring in **27** to give *trans*-fused phenanthridone **28**, (ii) making use of naturally abundant D-(–)-quinic acid as chiral source to build the highly oxygenated C-ring system of **29**.

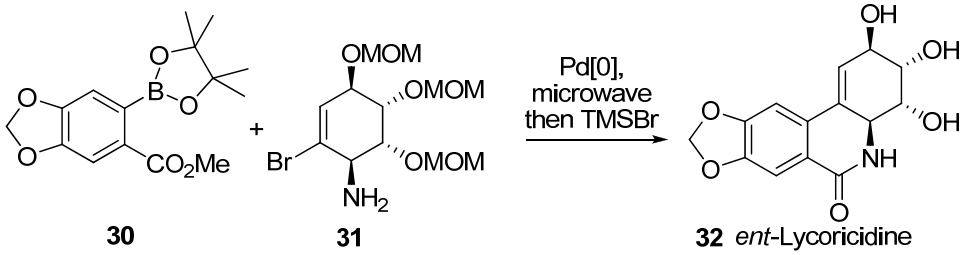
Scheme 9. *PET initiated carbocyclization*



1.2B.5. Tandem Suzuki cross-coupling/transamidation

Another cyclization of ring B, established by Banwell *et al.*[44], featured the microwave mediated, successive C–C, C–N bond formations through the sequential Suzuki cross-coupling/transamidation reactions for the syntheses of the analogues of the lycoricidine (**32**, Scheme 10). The chiral allyl amine (**31**) was synthesized from microbially derived, enantiomerically pure *cis*-1,2-dihydrocatechol.

Scheme 10. *Sequential Suzuki cross-coupling/transamidation reaction*



1.2C. Towards the construction of ring C

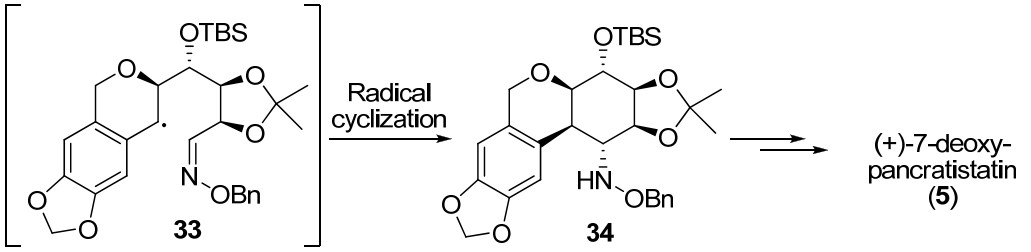
Since the perimeter of ring C is densely functionalized with all the stereocenters of the molecule, the challenge rendered in the construction of this particular ring is considered to be paramount. However, a number of synthetic methodologies had efficiently tackled the hurdles in stereocontrolled installations of functional groups around C-ring.

1.2C.1. Radical cyclization

Keck *et al.*[18] had established a 6-*exo* radical cyclization strategy for the diastereoselective construction of ring C, in which the benzylic radical underwent cyclization to *O*-benzyloxime ether in **33** to establish the C_{4a}–C_{10b} bond in **34**.

Advanced intermediate was then converted to naturally occurring 7-deoxypancratistatin (**5**, Scheme 11).

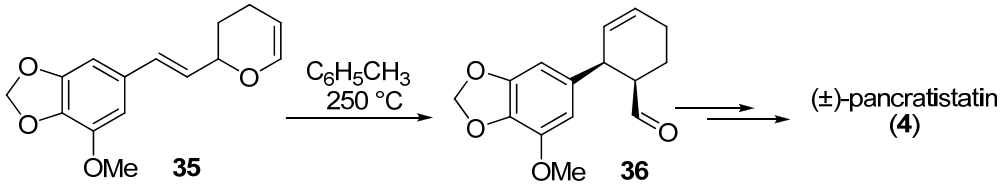
Scheme 11. *Radical cyclization of oxime ether*



1.2C.2. Claisen rearrangement

Racemic dihydropyranethylene **35** was subjected to Claisen rearrangement at 250 °C for 20 h to construct carbocyclic framework (**36**, Scheme 12).[25] Later, functional group manipulations of **36**, like iodolactonization, modified Curtius rearrangement and successive oxygenations produced completely functionalized C-ring of **4**. The chiral synthesis of pancratistatin (**4**) was also realized using Claisen-Ireland rearrangement.[26]

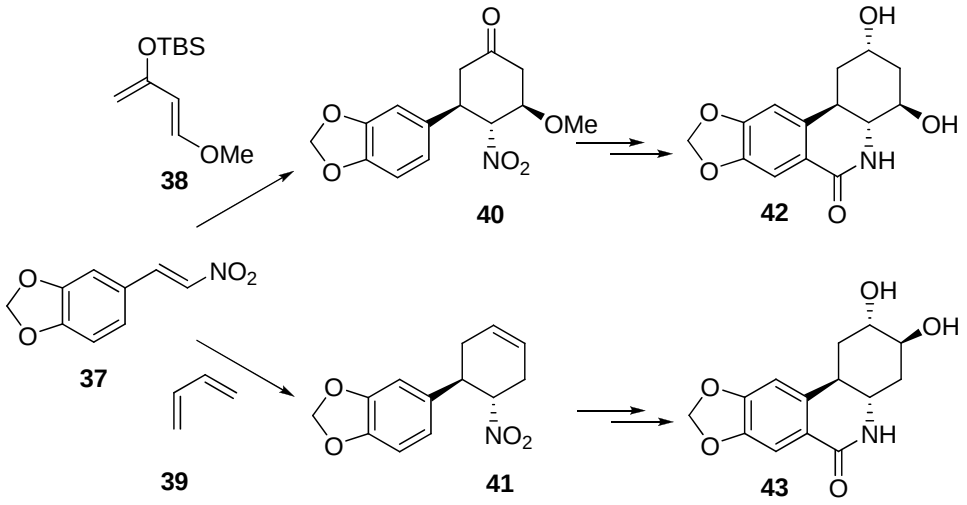
Scheme 12. *Claisen rearrangement of dihydropyran*



1.2C.3. Diels-Alder cycloaddition

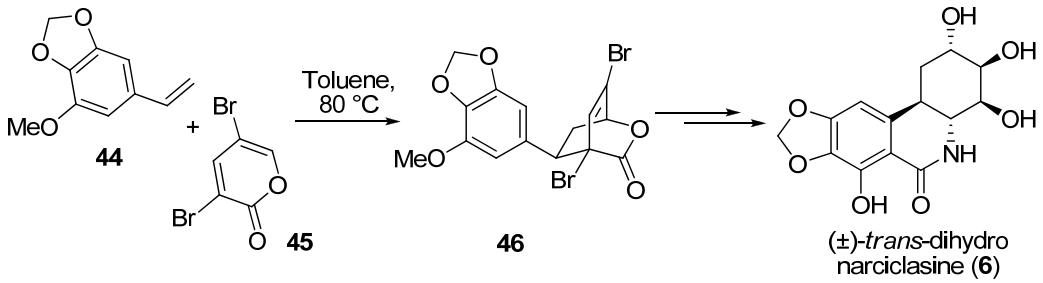
McNulty *et al.*[32,37] came up with the strategy for the construction of C-ring with limited number of hydroxyl functionalities for their structure-activity studies. The strategy involved Diels-Alder reaction of nitroalkene **37** with various dienes like Danishefsky's diene (**38**) and 1,3-butadiene (**39**) to afford cycloadducts **40** and **41** (Scheme 13). These adducts (**40** and **41**), upon further functionalizations on C-ring and Bischler-Napieralski ring closure reaction completed the syntheses of 1,3,7- as well as 1,4,7-trideoxypancratistatins (**42** and **43**).

Scheme 13. *Diels-Alder cycloaddition of nitroalkene*



In another Diels-Alder reaction[30] based strategy, a mixture of styrene **44** and 3,5-dibromo-2-pyrone **45** was heated in toluene at 80 °C (Scheme 14). A readily separable *endo*/*exo* mixture of cycloadducts was produced in the ratio of 98:2. The isolated *endo* adduct **46** was then subjected to series of functional group transformations to produce *trans*-dihydronarciclasine (**6**), a naturally occurring pancratistatin class of alkaloid.

Scheme 14. *Diels-Alder cycloaddition of 3,5-dibromo-2-pyrone*

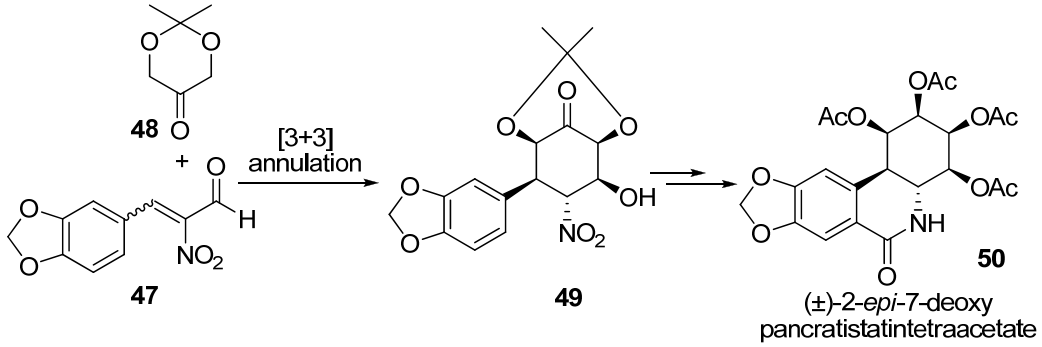


1.2C.4. Formal [3+3]- annulation

A highly stereocontrolled approach for the construction of C-ring was developed based on formal [3+3]-annulation of *β*-aryl-*α*-nitro-*α*,*β*-enal (**47**) with the enamine derived from 2,2-dimethyl-1,3-dioxan-5-one (**48**) and pyrrolidine by Alonso *et al.*[45] (Scheme 15). The key step produced a protected nitrocyclitol (**49**) with five

newly created stereocenters which led to the short, gram-scale synthesis of (±)-2-*epi*-7-deoxypancratistatin (**50**).

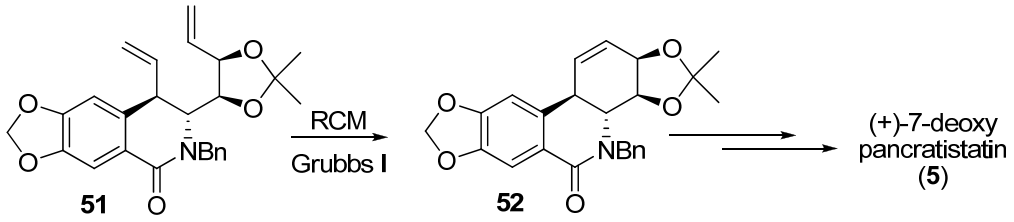
Scheme 15. *Stereocontrolled formal [3+3] annulation*



1.2C.5. RCM approach

The utility of olefin metathesis was explored in the elaboration of C-ring of 7-deoxypancratistatin by Madsen *et al.* [28] (Scheme 16). In their synthesis, the diene **51** was submitted to metathesis with Grubbs' first-generation catalyst to afford cyclohexene **52**, which was oxygenated to complete the synthesis of the natural product. The derivation of chiral diene **51** from D-ribose included zinc mediated tandem reactions.

Scheme 16. *Olefin metathesis*



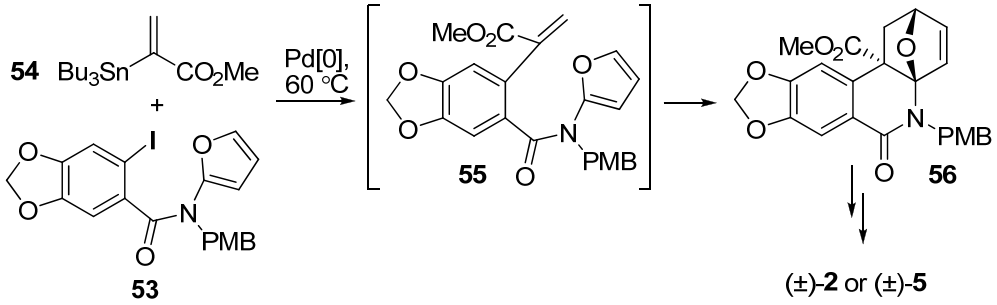
1.2D. Methods towards the one-pot constructions of B and C-rings

1.2D.1. Stille-IMDAF cycloaddition cascade

Padwa and Zhang demonstrated an elegant tandem cascade sequence consisting of Stille coupling followed by spontaneous intramolecular [4+2] cycloaddition of an amidofuran (IMDAF) for the syntheses of pancratistatin class of *Amaryllidaceae* alkaloids (Scheme 17).[29] Amidofuran **53** and methyl stannylacrylate

54 upon Stille coupling, gave expected cross-coupled amidofuran (**55**) spontaneously which underwent an intramolecular [4+2] cycloaddition to furnish phenanthridone skeleton (**56**) with essential ABC-fused rings. This rapid construction of phenanthridone frame work led to the synthesis of not only lycoricidine (**2**) but also highly oxygenated analogue, 7-deoxypancratistatin (**5**).

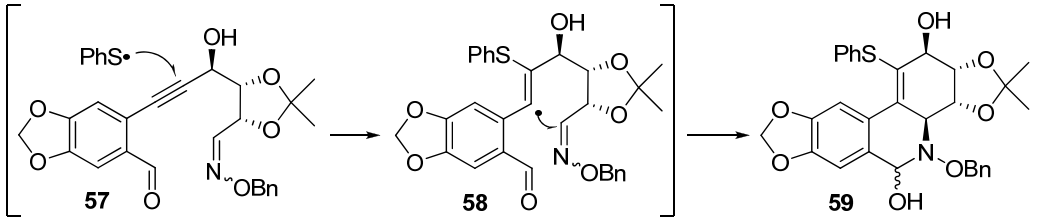
Scheme 17. *Intramolecular [4+2] cycloaddition of an amidofuran (IMDAF)*



1.2D.2. Thiyl radical addition-cyclization sequence

In another approach, Keck[46] showed the sequential constructions of B and C rings based on thiyl radical addition-cyclization cascade (Scheme 18). The methodology insisted upon the addition of photochemically generated thiyl radical, to the alkyne moiety in substrate **57**, followed by cyclization of the resulting vinyl radical (**58**) onto the suitably placed benzyl ether of oxime. This one electron cyclization was subsequently followed by two electron cyclization i.e. nucleophilic addition of resulting amine to aldehyde to afford aminol (**59**). However, elaboration of **59** to *ent*-lycoricidine framework was hampered by reduced yields in benzylic oxidation reaction.

Scheme 18. *Thiyl radical addition-cyclization cascade*



The successful executions of several retro-synthetic disconnections to date, acknowledges the rich synthetic background of these natural products. Despite

numerous synthetic approaches for the synthesis of pancratistatin class of *Amaryllidaceae* alkaloids, the interesting structural features still continue to fuel the innovative ideas in their efficient construction. Especially the heterocyclic framework provides a means to demonstrate the utility of new synthetic strategies.

1.3. Understanding of essential and variable pharmacophores of pancratistatin

The detailed understanding about the chemical-biology of these alkaloids has been mostly hampered by the limited supply from natural sources. A study conducted with relatively more abundant narciclasine (**3**) indicated that the mode of action may be connected to the inhibition of protein synthesis by interference with RNA transcription at the ribosomal level.[12a,b] Structural similarity of pancratistatin (**4**) with narciclasine (**3**) has led to the suggestion that the former also inhibits protein synthesis by the same mechanism. Although little is known about the precise mode of action of these compounds, a great deal of effort has been expended by various research groups for the structurally simpler, biologically active, synthetically accessible derivative or potential prodrug. The SAR based endeavors in search of more bioavailable derivatives and attempts to identify the pharmacophores of pancratistatin (**4**) led to the preparation and biological evaluation of a number of truncated as well as unnatural derivatives in these series.

1.3.1. Truncated derivatives

Chapleur[47] prepared some flexible *seco*-derivatives (**60**, ***epi*-60**, **61**, ***epi*-61**) in which the B-ring is not closed for the evaluation of biological activities in early ninties. These derivatives incorporated the oxygenated C-ring anchored to different aromatic rings by an amide bond as shown in Figure 2. Even though these compounds possessed the structural features of narciclasine (**3**), except C_{10a}–C_{10b} bond, none of them showed significant antitumor activities against leukemia strain L1210. It is likely that these molecules adopt an extended conformation, more or less stabilized, that cannot assume a correct binding to ribosome. No antiviral activity particularly against HIV has been detected for these amides.

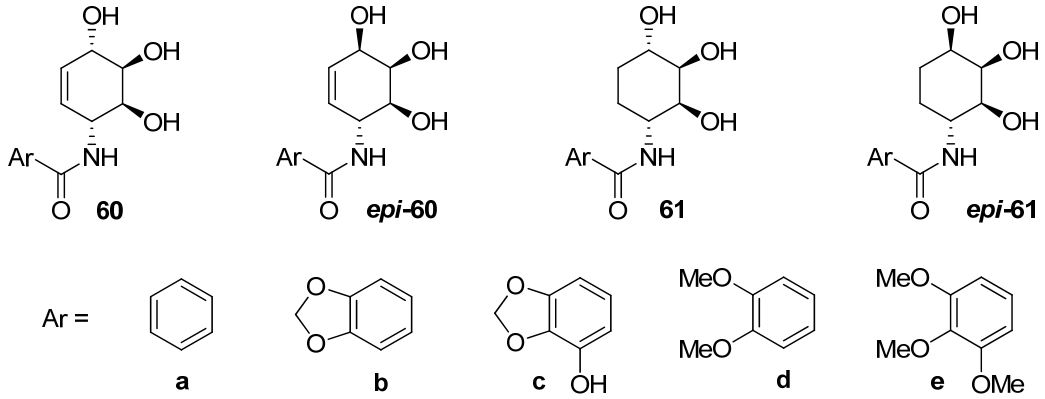


Figure 2. *Chapleur's flexible seco-derivatives*

McNulty[39] came up with another interesting *seco*-analogue such as *seco*-**62**, containing opened form of lactam ring B as well as cyclohexane ring C (Figure 3). Such derivatives (**62** and **63**) were considered to be more helpful in further understanding about the conformational requirements of the natural analogues. The cytotoxicity studies indicated, neither **62** nor the acetonide protected derivative **63** exhibited toxicity to human breast cell carcinoma (MCF-7) cells even at the highest concentrations. The results provided valuable information that the conformational restraints imposed by the lactam ring and cyclohexane appear to be critical for the correct positioning of the pharmacophoric elements in binding.

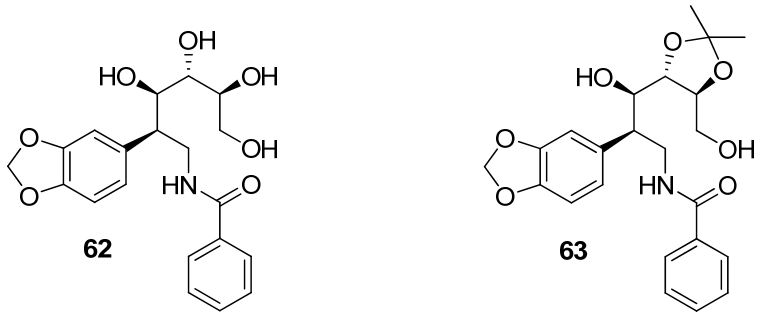


Figure 3. *McNulty's seco-analogues*

1.3.2. Unnatural derivatives

McNulty[32,37] investigated a systematic structure-based approach to unravel the cytotoxic pharmacophore of pancratistatin in order to define the minimum structural requirements for potent cytoxicity. Naturally occurring pancratistatin (**4**)

and *trans*-dihydrolycoricidine (**64**, Figure 4) shared a similar potency and profile of cytotoxicity against human tumor cell lines, indicating that the C_1 and C_7 hydroxyl substituents are not very essential pharmacophores. So, compound **64** is the structurally simplest natural analogue that exhibits potent cytotoxicity.

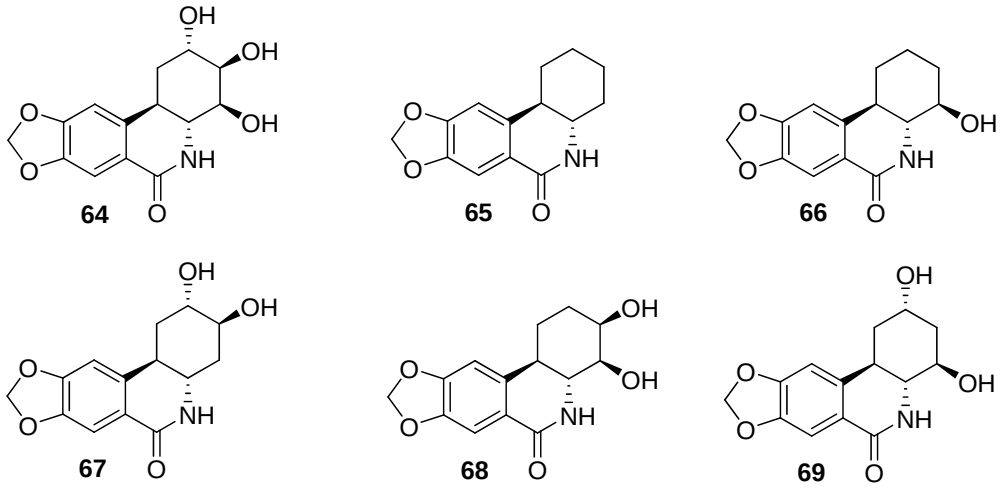


Figure 4. *McNulty's structures with minimum cytotoxic pharmacophore*

Theoretically, seven possible unnatural structures could embody the overall minimum cytotoxic pharmacophore as depicted in Figure 4; the fully deoxygenated cyclohexane derivative (**65**), three monoalcohols {2α; 3β; or 4β (**66**)} and three diols {2α,3β (**67**); 3β,4β (**68**) or 2α,4β (**69**)}. Among these, **66** and **67** were considered to be complementary to each other and collectively accounts for all the three monoalcohols. All of these unnatural analogues (**65-69**) were synthesized via the Diels-Alder strategy and found none of them were potent when subjected to cytotoxicity studies. It was concluded that natural **64** was the simplest analogue known so far possessing minimum pharmacophore for potent cytoxicity.

In the meantime, Fessner[48] suggested a hypothetical minimum structure (**70**, Figure 5), where he had reasoned that replacement of the cyclitol moiety by a carbohydrate ring structure might be a permissible structural variation due to the fact that most hexoaldoses and ketoses preferentially adopt a cyclic pyranoid structure in aqueous solution. In addition to the anomeric hydroxy group, which would mimic the C_2 –OH group of pancratistatin, a ketose unit as in **70** would further offer the possibility that the primary CH_2OH moiety may be positioned in a way to replace

hydrophilic contacts made by the extra C_1 –OH in **4** upon effective binding. Although, an account of the synthesis of the above lactone analogue **70** containing a carbohydrate motif was reported but no biological activities of the compound was evaluated.

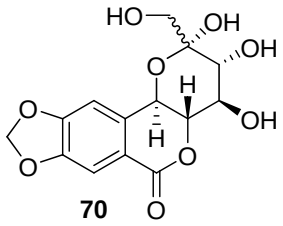


Figure 5. *Analogue with carbohydrate motif*

In 2004, Chapleur[36] synthesized lactone analogues of narciclasine and lycoricidine and *epi* derivatives (**71** and **72**) using the *o*-toluamide anion condensation onto gluonolactone strategy (Figure 6). These derivatives differ from the natural products only by the replacement of lactams by lactones in their core structure. Compounds **71** as well as **72** proved to be highly inactive to human cancer cells when screened for their antitumor activities, indicating the essentiality of amide for biological actions.

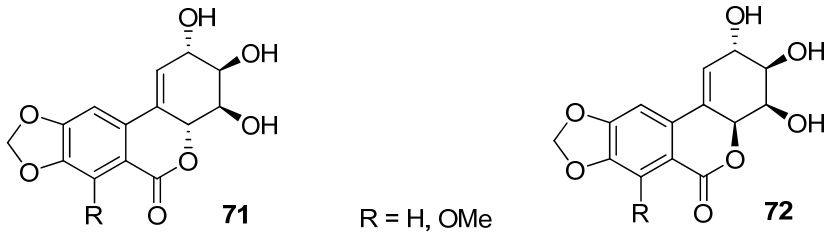


Figure 6. *Chapleur's lactone analogues*

Hudlicky has contributed significantly in the area of pancratistatin class of *Amaryllidaceae* alkaloids by synthesizing both natural[19,49] and unnatural[33–35,41,50] analogues of these alkaloids. His strategy stems upon regio- and stereoselective aziridine ring opening reactions with aromatic nucleophiles. The chirality of his molecules originated from toluene dioxygenase-mediated *cis*-dihydroxylation of halobenzenes to produce chiral diols. During the course of his explorations towards natural pancratistatins (**2**–**6**), he came across a number of unnatural derivatives

including enantiomer **73**,[50a] positional isomer **74**,[50b] 10b-epimer **75**,[33] few other truncated derivatives (**76a**–**d**)[50b] of **5** and very recently, carboxylic derivatives **77a**–**b** (Figure 7).[50e]

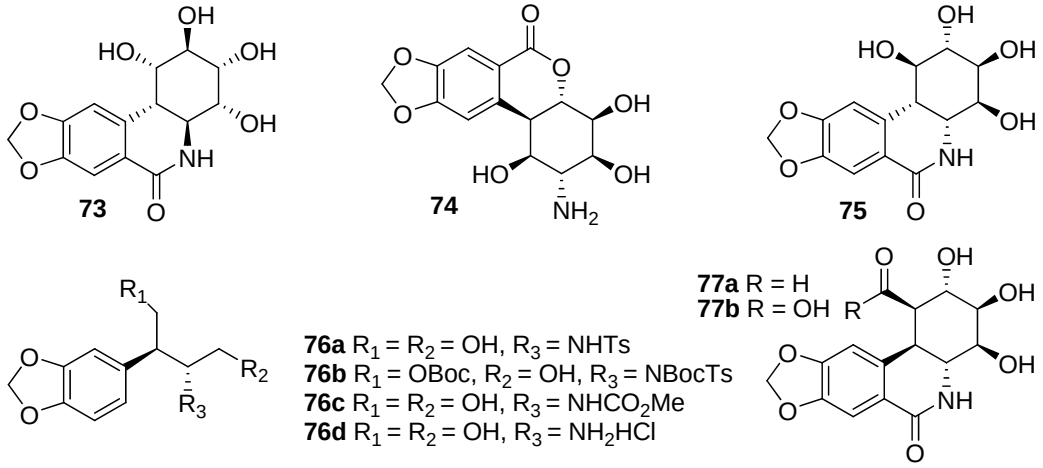


Figure 7. *Hudlicky's unnatural analogues*

Cancerous cell growth inhibition studies were made for most of these analogues (**73**–**76**) against mini panel of human cancer cells. The results revealed that *ent*-7-deoxypancratistatin (**73**) was about 10-fold less active than the natural **5**. The positional isomer **74** and *cis*-7-deoxypancratistatin (**75**) were found to be inactive to almost all cell lines. Among the truncated substances, only alcohol **76b** gave any indication of cancer cell line inhibition against some selective cells. Only syntheses of compounds **77a** and **77b** were reported and their biological activities are yet to be revealed. These studies are interesting from the viewpoint of providing useful information about the precise stereochemical requirements of the compounds to be biologically active.

Pancratistatin (**4**) and narciclasine (**3**) contain a free hydroxyl group that is the part of the enolized *β*-ketoamide function. It is this functional group that accounts for the greater (10-fold or more) activity of these compounds compared to that of their congeners 7-deoxypancratistatin (**5**) and lycoricidine (**2**), which lack the phenol group. Hudlicky speculated that the potency of **4** may in part be due to the hydrogen-bonding donor–acceptor pairing (**78**) of the *β*-ketoamide motifs present in these compounds but absent from the 7-deoxycongener (**5**, Figure 8).[34] This concept was proved by the synthesis and biological evaluation of **79** in which the piperonyl residue

of pancratistatin was replaced by anisole residue. Compound **79** inhibited cancer cell line growth activity 10-fold less than **5** (100-fold less than **4**).[35]

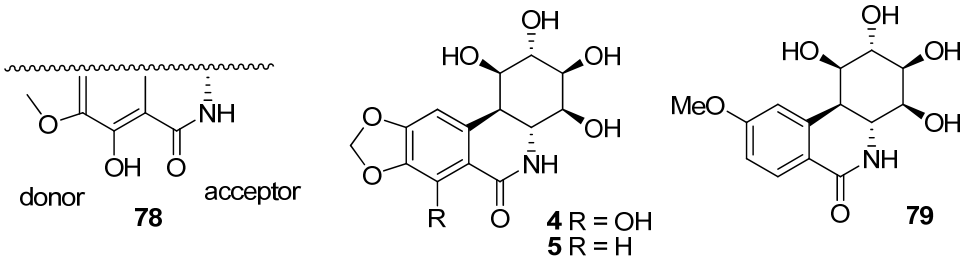


Figure 8. *Donor–acceptor pairing in pancratistatin*

Extending the above hydrogen-bonding donor-acceptor pairing concept, Hudlicky proposed another model (**80**), *β*-carboline-1-one analogue of **4**, compound **81**, in which such donor-acceptor pairing was extended through the vinyl indole ring, as shown in Figure 9.[34] The steric and, to some degree, the electronic properties of **4** and **81** were considered to be similar. The *β*-carboline-1-one analogue **81** was synthesized by silica gel mediated aziridine ring opening by indole aromatics. But, this compound was found to be 40-fold less potent in comparison with 7-deoxypancratistatin (**5**) against murine P388 lymphocytic leukemia assay.

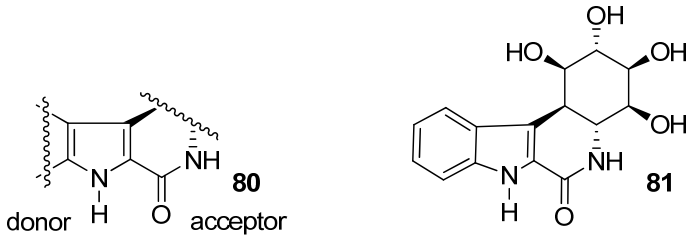


Figure 9. *β-carboline-1-one mimic of pancratistatin*

Pettit[52] devoted considerable effort to the syntheses of pancratistatin-based prodrugs[51] and more bioavailable analogues as well as the chemical conversion of narciclasine (**3**) into pancratistatin (**4**).[24] He believed that solution to the preclinical supply problems associated to **4** would be a high yield partial synthesis from the more abundant **3**. Towards this end, oxygenation of **3** was carried out through dihydroxylation using Sharpless protocol to obtain 10b-(*R*)-hydroxy-pancratistatin (**82**, Figure 10).[31] Further, selective deoxygenation of benzylic-hydroxyl group of **82**

using Barton's protocol, yielded, unfortunately, unnatural 10b-*epi*-pancratistatin (**83**).[38] Evaluation of these compounds (**82** and **83**) against the P388 lymphocytic leukemia cell line and minipanel of human cancer cell lines showed that the additional hydroxyl group and the *cis*-fused ring junction of **82** developed the impotency, whereas *cis*-fusion in **83** reduced the activity by the factor of 10.

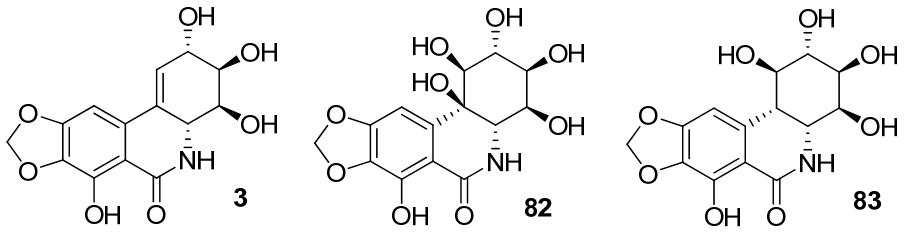


Figure 10. *Pettit's narciclasine derived unnatural analogues*

1.3.3. Inference from SAR based endeavors

The syntheses and biological screening of many unnatural derivatives discussed above resulted in the understanding of essential information about some of the functional groups required for activity. Those regions that are crucial for maintaining the activity of pancratistatin are indicated in Figure 11.

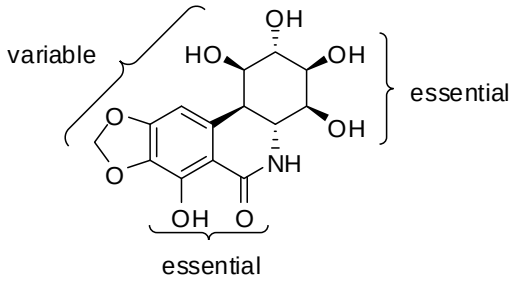


Figure 11. *Essential and variable pharmacophores of pancratistatin*

The following conclusions are drawn out from the systematic syntheses and biological screening of unnatural analogues:

- The presence of phenol and phenanthridone functionalities as a potential donor-acceptor pair is essential. The absence of phenolic hydroxyl, as in 7-deoxypancratistatin, leads to 8- to 32-fold decrease in activity in those cell lines against which both pancratistatin and 7-deoxypancratistatin were tested.

- Compounds lacking the amide functionality are inactive, as has been demonstrated with lactone analogues of lycoricidine and pancratistatin.
- Changes in the substitution patterns or functionalities elsewhere in the aromatic core lead to compounds with decreased activity, as has been shown with anisole and indole-containing mimic of **4**.
- The aminoinositol moiety must remain essentially intact, except for variations of substituents, functionalities, and configuration at C_1.
- The *trans*-fused BC-ring junction is essential to activity; the *cis*-fused 7-deoxypancratistatin is inactive.

It is clear from the results of biological screening that none of the unnatural derivatives rival the potency of either pancratistatin or narciclasine. Nevertheless, continuing preparation of new compounds that resemble the structural motifs of the natural products represents an endeavor with the potential for discovery as well as the eventual deciphering of the mode of action for these compounds.

1.4. Aim of this dissertation

A number of creative new approaches[53] to the syntheses of *Amaryllidaceae* constituents continue to appear despite the fact that nineteen years elapsed since the first synthesis of pancratistatin. Several groups continue a multi-generational effort in syntheses of these compounds to this date. *Amaryllidaceae* constituents represent ideal targets on which synthetic design may be practiced in an aesthetic manner. Towards this end, we have taken up the challenge to develop a practical and conceptually new strategy for the syntheses of highly oxygenated phenanthridones **2**–**6**. The foregoing Chapters will discuss our explorations and progress in this endeavor.

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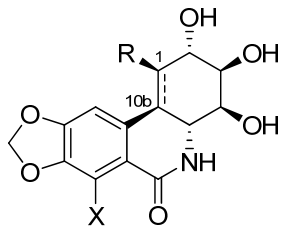
Chapter 2

An Intramolecular aza-Michael addition approach towards the syntheses of pancratistatins

2.1. Introduction

The highly oxygenated phenanthridones (**1**–**6**, Figure 1) of pancratistatin class, isolated from plants of *amaryllidaceae* species, have been the subject of several elegant total syntheses that centered on the major difficulty of a controlled installation of the five to six contiguous stereogenic centers, including the *trans*-fused BC-ring junction.



1 X = R = OH — Pancratistatin
2 X = H; R = OH — 7-deoxypancratistatin
3 X = OH; R = H — *trans*-dihydronarciclasine
4 X = R = H — *trans*-dihydrolycoricidine
5 X = OH; R = H; C_1-C_{10b} = double bond — Narciclasine
6 X = R = H; C_1-C_{10b} = double bond — Lycoricidine

Figure 1. *Few representatives of oxygenated phenanthridones*

From the synthetic point of view, two main approaches have been commonly practiced for these natural products. One of these approaches has dealt with a convergent route, constructing two fragments representing the A and C rings and finally coupling them together to form the B ring. This approach included the formation of the C_{10a}–C_{10b} bond as well as establishment of *trans*-fused BC-ring junction as the crucial points of the syntheses. An alternative synthetic route employed the formation of C-ring from a suitable precursor in which the elements required for the *trans*-fusion were already installed. The crucial points in these synthetic approaches were the stereocontrolled installations of oxygen functionalities around the C-ring. The literature survey of synthetic reports revealed that the more practical approach emphasized the first method i.e., cyclization of B-ring with the pre-constructed A and C-rings in convergent fashion. Different modes of cyclizations reported for the formation of B-ring included,

- C_6–N bond formation by lactamization[1] and transamidation[2,3] reactions
- C_6–C_{6a} bond formation using Banwell's modified Bischler-Napieralski[4–6] reaction
- C_{10a}–C_{10b} bond formation through either photocyclizations like PET[7], aryl enamide[8] or Lewis acid mediated coupling reactions of arene with allyl triflate[9] and epoxide[10]

- C_{4a}–C_{10b} bond formation *via* radical cyclization of oxime ether[2] and Diels-Alder cycloadditions[11]

The above methods of B-ring cyclizations are collectively depicted in Figure 2.

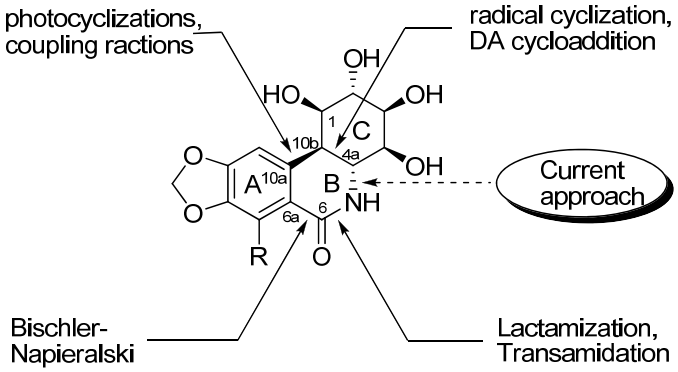


Figure 2. *Various cyclization strategies for B-ring closure*

2.2. Background concept and Retrosynthetic analysis

On careful scrutiny of these catalogued strategies of B-ring closure, it was noticed that the C_{4a}–N bond formation mediated cyclization has not been explored even though it may offer an attractive, practical and the general strategy for the syntheses of *Amaryllidaceae* constituents. In this context, we envisioned a retro-synthetic approach as shown in Figure 3. While designing above strategy, it was envisioned that an access to phenanthridones (**1**–**6**) could be realized easily from the *β*-amino carbonyl compound **7** which in turn could be obtained through an intramolecular aza-Michael[12] reaction of the potential precursor **8.** The stereochemical origin at C_{4a} of compound **7** was believed to be controlled by the adjacent stereocenter at C_4, which might direct the approach of the amine nucleophile to opposite face towards C_{4a} of the enone. The crucial *trans*-BC ring junction (C_{4a}, C_{10b}) was expected to arise through the resultant thermodynamically stable *trans*-perhydroquinoline like system. The key precursor **8** could be obtained by the Suzuki cross-coupling reaction[13] between two subunits **9** and **10** which were proposed to be obtained easily from commercially available piperonylamine (**11)** and D-(−)-quinic acid (**12).**

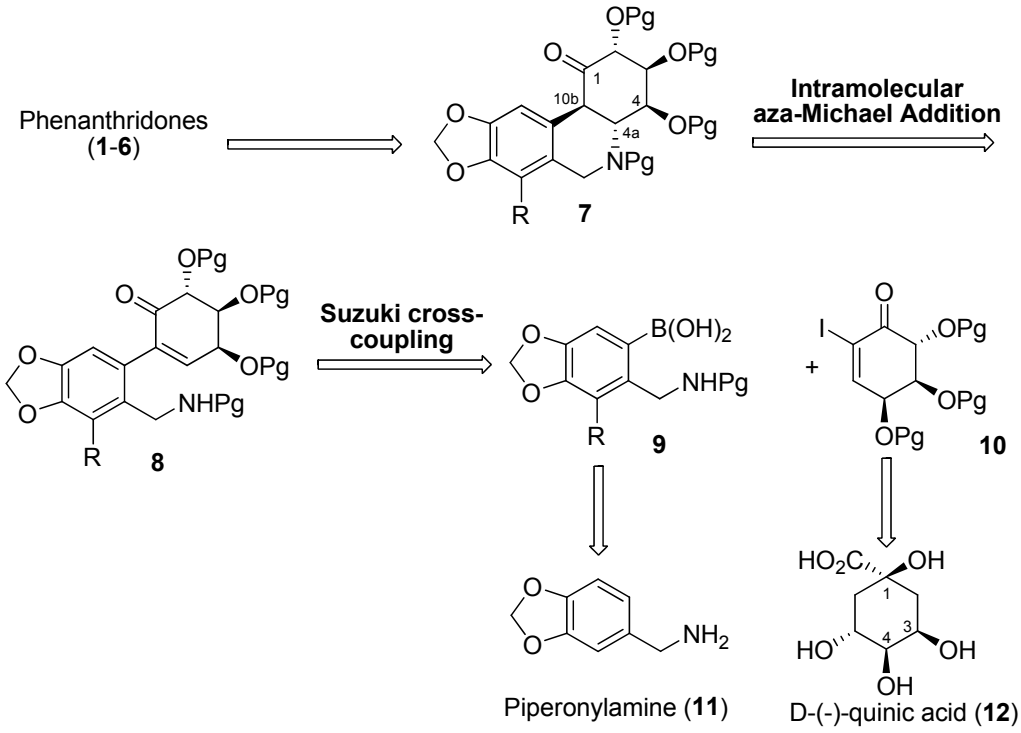


Figure 3. *A retrosynthetic plan for phenanthridones*

The selection of D-(−)-quinic acid (**12**) was made under following considerations,

- Its 3,4-*syn* dihydroxyl stereochemistry, akin to the stereocenters present in the C-ring of the alkaloid
- Ability of C_3, C_4 stereocenters to direct required functionalities at C_2 and C_{4a} stereoselectively
- Natural abundance

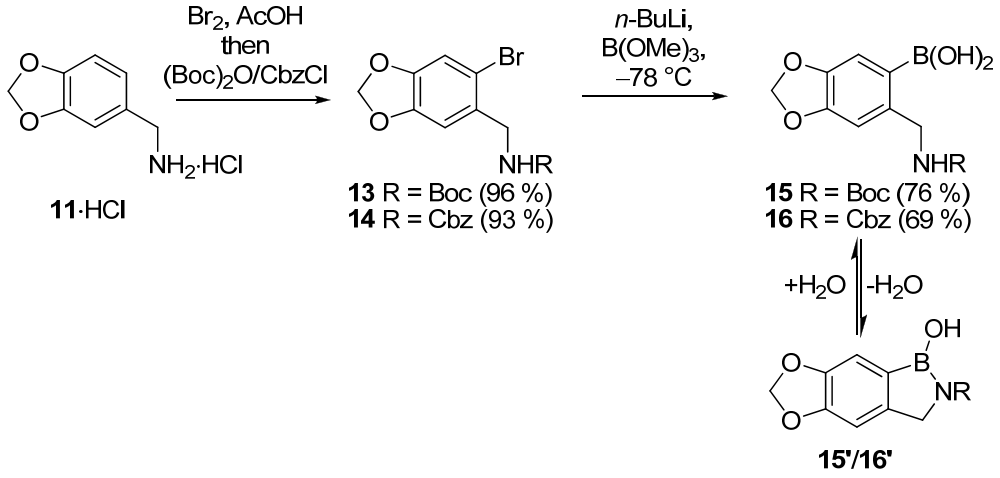
We describe herein the results of our studies in detail towards the synthesis of phenanthridone class of alkaloid.

2.3. Synthesis of arylboronic acids

The requisite boronic acid **9** was synthesized using two-stage bromination-boronation sequence. The aromatic bromination of the hydrochloride salt of piperonylamine (**11**·HCl) by following the analogous procedure used by Tietze *et al.*[14] gave corresponding 6-bromo derivative which upon basification followed by *tert*-butyl carbamate protection of the resultant free amine produced **13** in 96 % yield. To study the nucleophilicities of different carbamates during intramolecular aza-Michael addition, the corresponding benzyl carbamate **14** was also synthesized in 93 % yield.

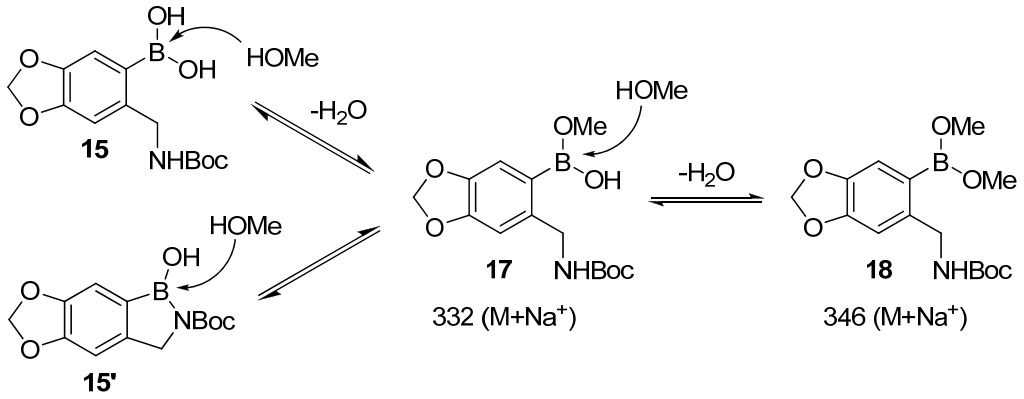
Lithium exchange of the bromides **13** and **14** using *n*-BuLi/THF at –78 °C followed by quenching with excess of trimethyl borate gave boronic acids **15** (76 %) as well as **16** (69 %), respectively (Scheme 1). It was surprising to observe that these boronic acids were exhibiting an equilibration between acyclic (**15**/**16**) and cyclic (**15'**/**16'**) forms in solution state. For illustration, when the ^{1}H NMR spectrum of **15** was recorded in $CDCl_3$, benzylic –CH_2 appeared at δ 4.33 (s, 1.32 H) and 4.19 (d, J = 6.4 Hz, 0.68 H), indicating the existence of both structural forms (**15** and **15'**). The splitting at δ 4.19 was caused by adjacent –N–H proton of acyclic substrate **15** where as the singlet at δ 4.33 was corresponding to **15'** in which the adjacent proton was absent. The ^{1}H NMR of **15** in DMSO-d_6 clearly indicated the complete acyclic nature by showing doublet at δ 4.18 (J = 6 Hz) for benzylic protons, characteristic –NH as well as –$B(OH)_2$ protons at δ 7.25 (bs, 1H) and δ 8.15 (s, 2H). It was also found that this nature was dependant on the polarity and hydrophilicity of the solvent of choice.

Scheme 1. *Syntheses of boronic acids*



Another interesting observation was made when methanol solutions of these compounds (**15** and **16**) were subjected to mass spectrometry. They underwent methanolysis when dissolved in methanol to produce both partial and fully methonolysed products (for example, intermediates **17** and **18** in the case of **15**, Scheme 2) which were detected during mass analysis.

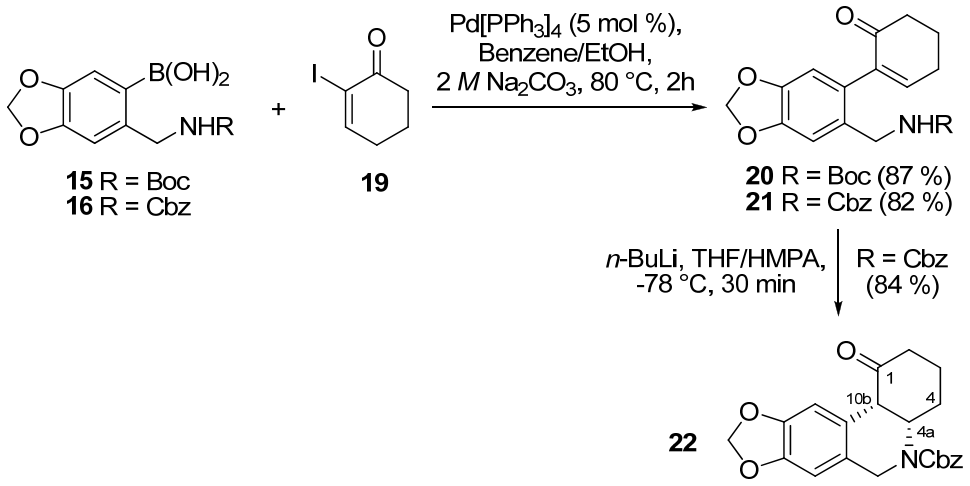
Scheme 2. *Methanolysis of boronic acid*



2.4. Intramolecular aza-Michael addition: A model study

Having the requisite boronic acids (**15** and **16**) in hand, a rapid check for the feasibility of the proposed aza-Michael addition concept was planned. For this purpose, a structurally simple analogue of phenanthridone **7** was targeted in which all chiral elements were absent. Eventually, one of the Suzuki cross-coupling partners of the retro-synthetic design turned out to be 2-iodocyclohexenone (**19**) for the current target. Compound **19** was synthesized from cyclohexenone using Johnson's iodination protocol (I_2, Py/CCl_4).[15] Suzuki cross-coupling reactions were carried out simultaneously with equimolar mixture of **15**/**16** and **19** in the presence of 5 mol % Pd[PPh_3]$_4$ to produce either **20** (87 %) or **21** (90 %), identified with the presence of characteristic olefin –CH in ^{1}H NMR at δ 6.90 (dd, J = 4.3, 4.0 Hz, 1H) and δ 6.40 (app t, J = 4.1 Hz, 1H) respectively. The syntheses of **20** as well as **21** set the stage for the intramolecular aza-Michael addition. In order to facilitate the key reaction, the carbamate (**20**/**21**) was *N*-lithiated with the aid of *n*-BuLi, in HMPA/THF (10:1) at –78 °C. It was surprising to note that only the benzyl carbamate **21** underwent the crucial Michael addition to produce the phenanthridone **22** in 84 % yields and the *tert*-butyl carbamate **20** was inert to the above reaction conditions. The failure of **20** to bring out the required reorganization could be probably due to the steric and electronic reasons associated with the *tert*-butyl carbamate.

Scheme 3. *Synthesis of phenanthridone skeleton* (**22**)



The resulting product **22** was fully characterized with all spectroscopic techniques. The ^{1}H NMR spectrum showed resonances at δ 4.68 (m, 1H) for C_{4a} proton and at δ 3.79 (d, J = 5.5 Hz, 1H) for the characteristic C_{10b} proton indicating the cyclization. This was further confirmed by ^{13}C NMR in which peaks at 54.0, 51.9 characterized for C_{4a} and $C_{10b,}$ respectively. However, it was disappointing to note the J value (5.5 Hz) H_{10b} revealing the *cis* relationship between H_{4a} and H_{10b}. Generally, for *trans*-BC ring junction, the coupling constant for H_{10b} should have been more than 10 Hz,[7,8] The final confirmation of *cis*-fused BC ring junction of **22** came from NOESY studies which clearly showed the spatial interaction of H_{4a} with H_{10b}. The most probable explanation to this observation could be offered by considering the protonation of the lithium enolate intermediate, formed during aza-Michael reaction, governed by the C_{4a}–N bond stereochemistry. At this stage, we decided to extend this strategy of intramolecular aza-Michael addition for the syntheses of natural pancratistatins, hoping the stereocenter at C_{10b} could be epimerized in due course to produce the *trans*-fused phenanthridone in the original synthesis.

2.5. Synthesis of chiral trialkoxylated iodoenone

The successful model study involving intramolecular aza-Michael addition for the synthesis of phenanthridone skeleton **22** prompted us to undertake the chiral synthesis of natural phenanthridones. A few functional group manipulations on naturally abundant D-(−)-quinic acid would allow the synthesis of suitably substituted chiral iodoenone **10** as summarized in Figure 4. The stereoselective oxygenation at C_2

would provide all the required stereocenters of the chiral enone **10**. While the α-hydroxyacid unit at C_1 could be easily converted to carbonyl functionality, elimination of C_5-hydroxyl group and *α*-iodination of the resultant enone should provide **10**.

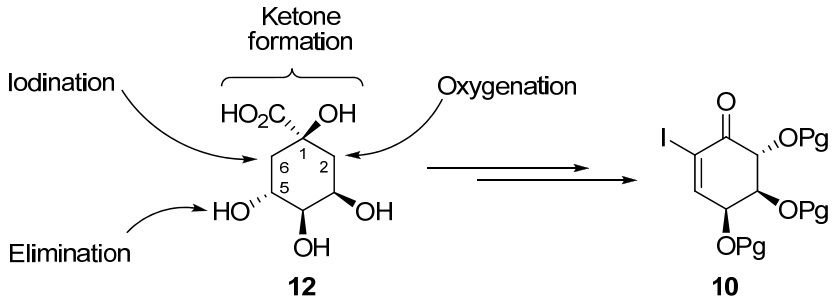


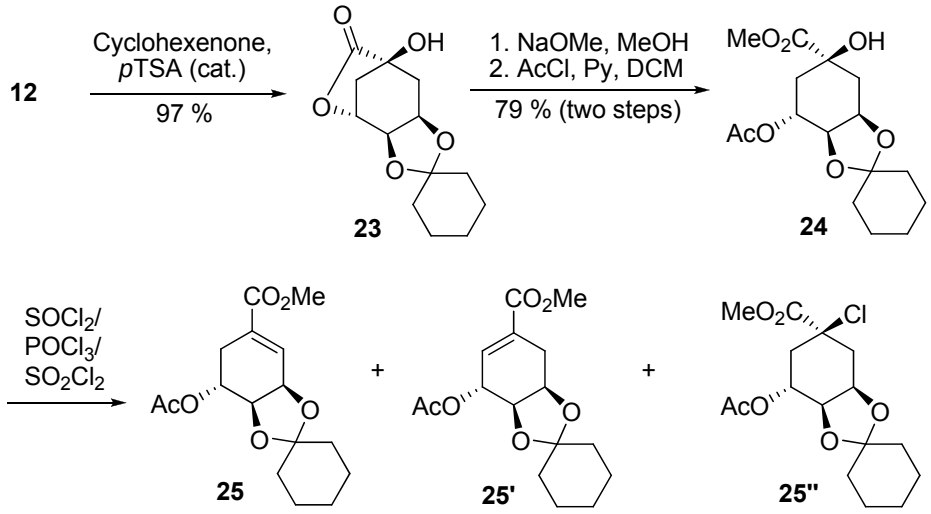
Figure 4. *Functionalization of Quinic acid*

2.5.1. Regioselective elimination studies

Stereoselective oxygenation at C_2 of **12** could be achieved by the regioselective elimination of C_1 hydroxyl group and *cis*-dihydroxylation of the resultant double bond. The procedure established by Grierson *et al.*[16] was followed to eliminate C_1 hydroxyl group of **12**, which used the cyclohexylidine derivative **24**, synthesized by three-step procedure in 77 % overall yield as shown in Scheme 4. However, in our hands elimination of **24** using $SOCl_2$/Py proved to be low yielding (36 % of **25**), because of the formation of unwanted regioisomer (**25'**) and chlorinated derivative (**25''**). The usage of several other reagent combinations, including $POCl_3$/Py, SO_2Cl_2/Py, NBS/SO_2/Py were not rewarding as the yields of the required regiomer (**25**) were never more than 40 %.

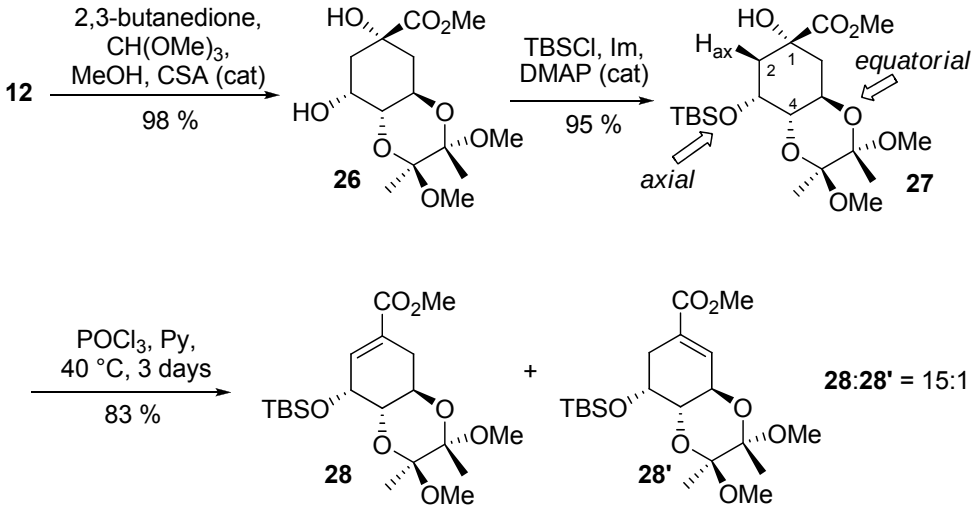
In the mean time, another sequence of reactions reported by Whitehead *et al.*[17] for the C_1 hydroxyl elimination of **12**, claimed to be regioselective and high yielding (Scheme 5) was evaluated. The 4,5-*trans*-diols of **12** were selectively protected as butane diacetal with concomitant methyl ester formation to afford **26** in 98 % yield. The *sec*-hydroxyl group of **26** was subjected to selective silylation to produce **27**. $POCl_3$/Py mediated elimination of **27** at 40 °C for 3 days afforded the mixture of **28** and **28'** in the ratio of 15:1. The observed regioselectivity was reasoned with the butane diacetal protecting group enforcing silyloxy group at C_3 to the axial

Scheme 4. *Regioselective elimination-cyclohexylidine derivative*



orientation. This axially disposed silyloxy group enhanced the acidity of C_2–H_{ax} due to the antiperiplanar arrangements.

Scheme 5. *Regioselective elimination-butane diacetal derivative*

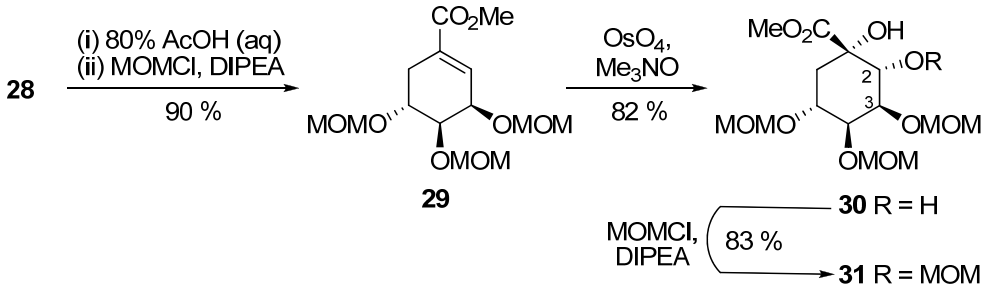


2.5.2. Oxygenation at C_2 of Quinic acid derivative

After identifying the suitable procedure for multi-gram scale synthesis of **28**, *cis*-dihydroxylation of the electron deficient olefin was planned. However, to avoid

unforeseen complications during the advanced stage of synthesis, the butane diacetal and silyl protections were removed by heating **28** with 80 % aqueous acetic acid at 80 °C and re-protected the free hydroxyls as their corresponding methoxymethyl ethers **29** using MOMCl/DIPEA in 90 % overall yield (Scheme 6). Subsequently, catalytic osmylation of the olefinic double bond of **29,** carried out in *tert*-BuOH/Py/H_2O (15:1:1) system and using trimethylamine *N*-oxide as co-oxidant at 80 °C gave **30** in 82 % isolated yield. The complete disappearance of vinyl proton and appearance of four –CH protons at δ 4.20, 4.08, 4.01, 3.92 in the ^{1}H NMR of **30** clearly indicated the formation of dihydroxylated product. Moreover, the higher coupling constant of the doublet at δ 4.20 (J = 10.0 Hz, 1H) unambiguously confirmed *trans*-relationship between H_2 and H_3, and established the correct stereochemistry at C_2. Selective monoprotection of **30** using MOMCl/DIPEA combination in DCM at high dilution gave **31** in 83 % yield. The resonances at δ 78.6, 76.8, 74.5 and 74.4 in the ^{13}C NMR spectrum of **31** supported the molecular structure as shown in Scheme 6.

Scheme 6. *Oxygenation at C_2*

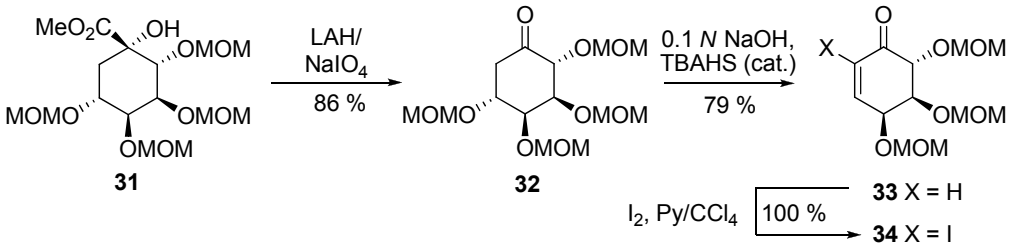


2.5.3. Synthesis of iodoenone 34

The reduction of the ester moiety of **31** by LAH/THF at 50 ºC produced corresponding diol which upon sodium periodate cleavage gave **32** in 86% yield. The IR spectrum of **32** showed a strong absorption band at 1732 cm^{-1} confirming the presence of carbonyl functionality in the molecule. This functionality was further confirmed by observing a peak at δ 204.4 in the ^{13}C NMR spectrum of the molecule. The diastereotropic methylene protons appeared at δ 2.91–2.80 (dd, J = 14.3, 3.3 Hz, 1H) and 2.64–2.52 (ddd, J = 14.3, 3.3, 1.1 Hz, 1H) in the ^{1}H NMR of **32**. Next, we attempted eliminating C_5-methoxymethoxyl group using Cs_2CO_3, *tert*-BuOK and DBU to obtain corresponding enone **33**, however, these reactions produced complex

mixture. Luckily, reaction of **32** with 0.1 *M* aqueous NaOH in the presence of catalytic amount of tetrabutylammonium hydrogensulfate (TBAHS) in DCM cleanly produced **33** in 79 % yield. The appearance of the doublet of doublet (J = 10.2, 4.5 Hz) at δ 6.90 and doublet (J = 10.2 Hz) at δ 6.05 in the ^{1}H NMR of **33** clearly indicated the presence of α,β-unsaturated carbonyl functionality in the molecule. At the same time, the doublet (J = 8.7 Hz) at δ 4.46 confirmed once again the *trans*-relationship of C_2, C_3 functionalities. The IR spectrum showed an absorption at 1703 cm^{-1} for the carbonyl group with α,β-unsaturation. Compound **33** was converted to the target precursor **34** quantitatively by following the Johnson's iodination protocol (I_2, Py/CCl_4).[15] The ^{1}H NMR spectrum of **34** displayed a peak at δ 7.67 (d, J = 4.6 Hz, 1H) for the vinyl proton of the molecule.

Scheme 7. *Synthesis of* **34**

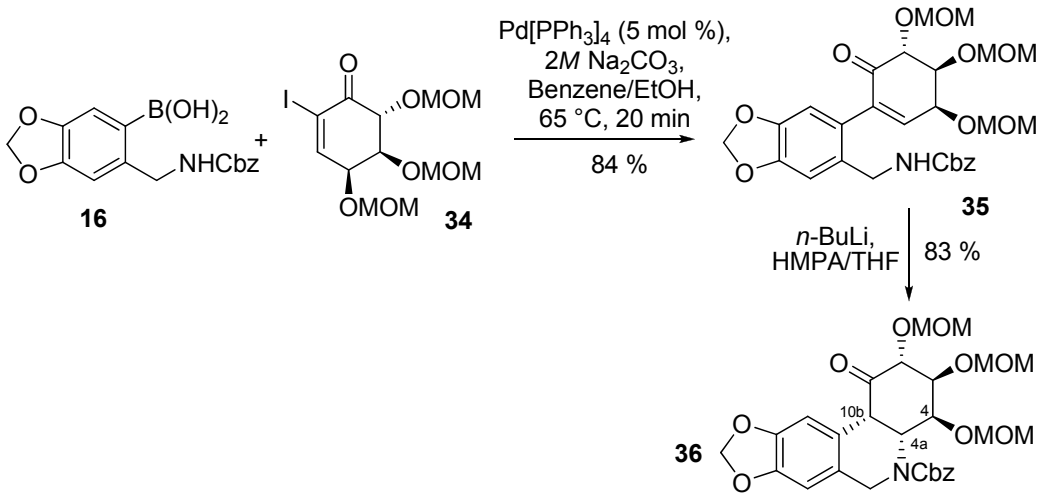


2.6. Suzuki cross-coupling/intramolecular aza-Michael addition

The easy accessibility of both the coupling partners **16** as well as **34** guided us to carry out Suzuki cross-coupling reaction to obtain aza-Michael precursor **35**. In this context, refluxing (20 min) an equimolar mixture of **16** and **34** along with 5 mol % $Pd[PPh_3]_4$ in benzene/ethanol (2:1) produced **35** in 84 % yield (Scheme 8). The characteristic doublet at δ 6.81 (J = 3.7 Hz) in the ^{1}H NMR and an olefinic –CH at δ 145.1 in ^{13}C NMR of **20** confirmed its structure.

The crucial intramolecular aza-Michael addition of **35** carried out using *n*-BuLi in HMPA/THF (10:1) at −78 °C provided cyclized product **36** as a single diastereomer in 83 % yield. The role of HMPA was very crucial in this key reaction, as without HMPA the reaction failed to bring about the required reorganization. Compound **36** was fully characterized by ^{1}H NMR, ^{13}C NMR and mass spectrometry (Scheme 8).

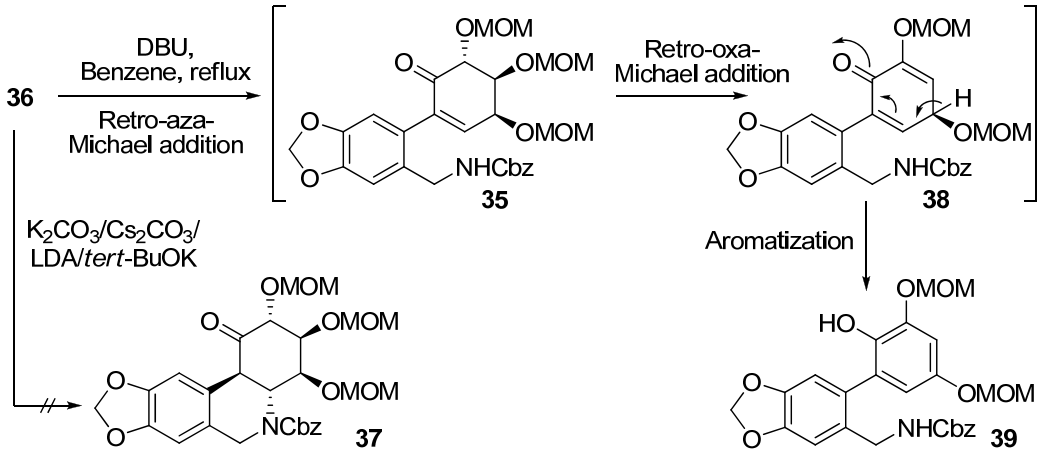
Scheme 8. *Suzuki cross-coupling/intramolecular aza-Michael addition sequence*



The relative stereochemistry of the newly formed C_{4a} and C_{10b} centers (BC-ring junction) was deduced by carefully examining the coupling constants between the attached protons (H_{4a}, H_{10b}) in the ^{1}H NMR spectrum of **36**. For example, H_{10b} appeared as a doublet (J = 6.8 Hz) at δ 4.02 coupling only with H_{4a} at δ 3.97 (dd, J = 6.8 Hz, 9.3 Hz). Once again, the lower value (6.8 Hz) of observed coupling constant for H_{10b} indicated *cis*-relationship between H_{4a} and H_{10b}. The additional coupling constant (J = 9.3 Hz) of H_{4a} was accounted for the coupling of H_{4a} with H_4. The observed higher J value between H_4 and H_{4a} clearly confirmed the *trans*-diaxial coupling establishing the *trans*-relationship for H_{4a}, H_4. These particular coupling constants (J = 6.8, 9.3 Hz) indicated that the amine nucleophile approached C_{4a} on the opposite face of C_4 alkoxyl group producing C_{4a}–N bond with required configuration at C_{4a}.

We also attempted inverting stereochemistry at C_{10b} of **36** through epimerization using several bases (K_2CO_3, Cs_2CO_3, LDA, *tert*-BuOK), however, it remained unsuccessful. It was surprising to note that our effort of epimerizing C_{10b} using DBU in boiling benzene led to retro-Michael reaction (**35**, **38**) and aromatization (**39**) of C-ring *via* β-elimination of methoxymethoxyl group at C_3. The results from the above studies support the thermodynamic stability of *cis*-fused ring junction in these phenanthridones.[8,18,19]

Scheme 9. *Epimerization trials on* **36**



2.7. The concept of haptophilicity

In order to bring the required stereochemistry at C_{10b}, an indirect protonation approach was visualized where the stereoselective hydrogenation of the tetra-substituted olefin of **41** was thought to be reduced to give **40** (Figure 5). It has been documented in literature that the free hydroxyl or amine functionalities of the molecule efficiently direct the hydrogen addition during hydrogenation. This phenomenon is identified as "haptophilicity" where the directing group existing in the molecule coordinates to catalyst and delivers the hydrogen in the same face. The free *sec*-amine functionality of **41**, was expected to direct the incoming hydrogen to *α*-face to fix both the stereocenters at C_1, C_{10b}.

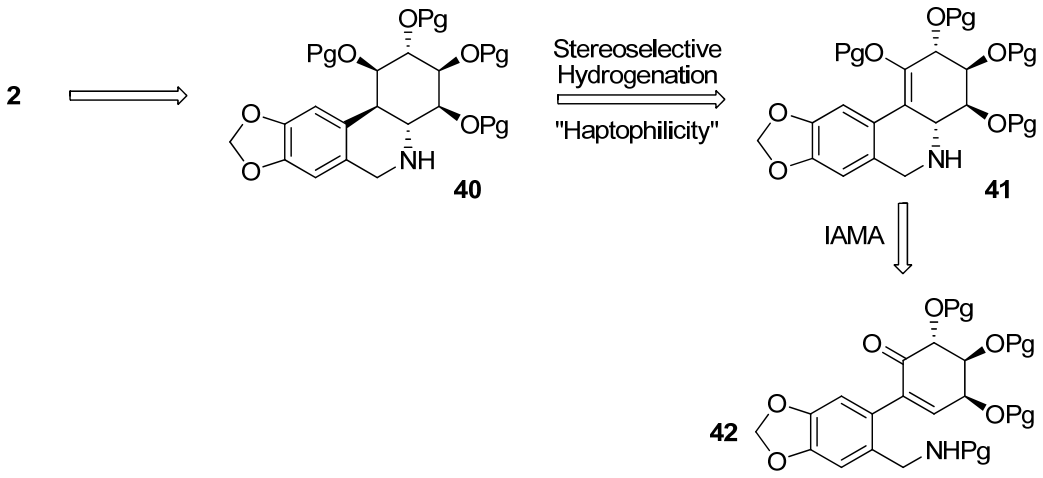
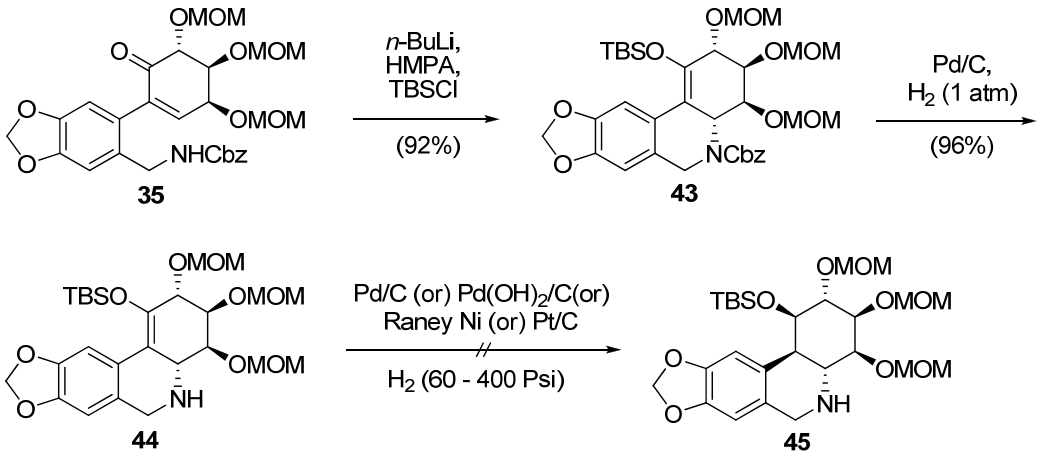


Figure 5. *Retrosynthesis based on haptophilicity*

In order to realize the proposed concept, intramolecular aza-Michael addition of **35** and *in situ* trapping the enolate as the TBS enol ether produced **43** in 92 % yield as depicted in Scheme 10. It is appropriate to mention here that the corresponding TMS enol ether of **43** was unstable to be isolated through column chromatography. The reductive debenzyloxycarbonylation of **43** using 10 % Pd on charcoal mediated hydrogenation at atmospheric pressure yielded the expected free amine **44**. Having this key precursor in hand, the reduction of the double bond was carried out in the presence of various catalysts (Pd/C (or) $Pd(OH)_2/C$ (or) Raney Ni (or) Pt/C) at different pressures (60–400 Psi) as summarized in Scheme 10.

Scheme 10. *Hydrogenation of silylenol ether* **44**



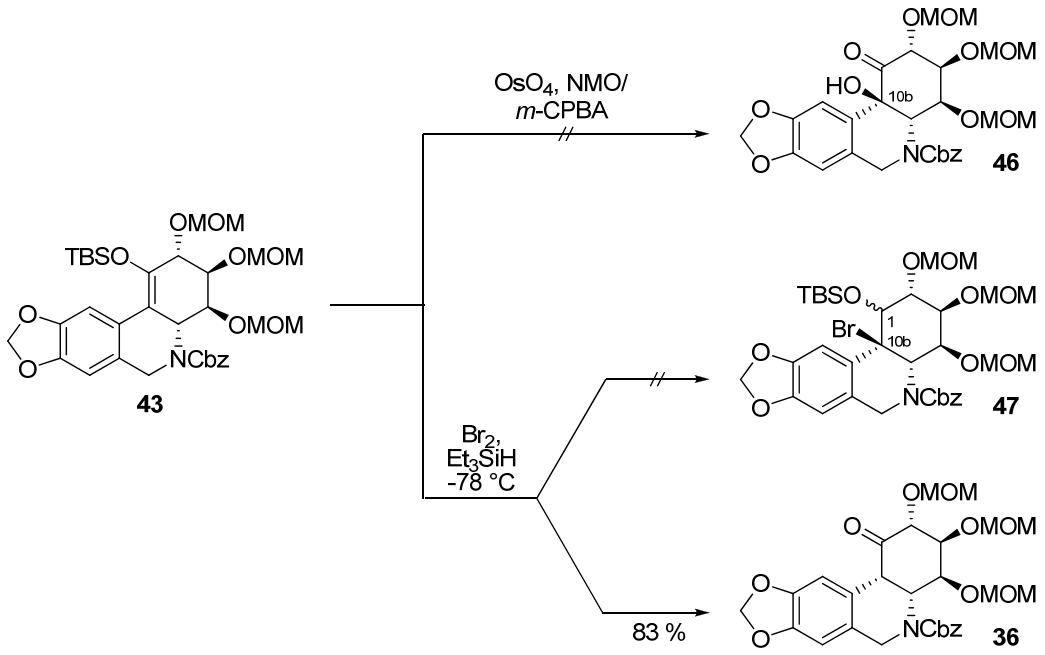
However, none of the reaction conditions was found to be rewarding towards the synthesis of **45**. The sterically crowded tetra-substituted double bond of the starting material was left untouched under almost all the conditions.

2.8. Functionalization of silylenol ether

The highly substituted olefin of silylenol ether **43** was examined for its reactivity towards oxygenation reactions like dihydroxylation (OsO_4, NMO, acetone, 60 °C) and epoxidation (*m*-CPBA, DCM, 0 °C–RT) with the hope that the resulting benzylic alcohol **46** could be epimerized at C_{10b} by S_N2 type reaction with hydride source at later stages of the synthesis (Scheme 11). However, the substrate **43** proved to be inert to the above reaction conditions and led to the complete recovery of **43** at the end of the reaction. A strong electrophile like bromine to activate the double bond with concomitant hydride reduction was thought to afford **47**, from which one can

easily derive the required stereocenters at C_1 as well as C_{10b}. The reaction of **43** with Br_2 in presence of excess of Et_3SiH at lower temperatures (–78 °C to 0 °C) surprisingly produced the previously synthesized **36** in 83 % yield, proving once

Scheme 11. *Functionalization of* **43**



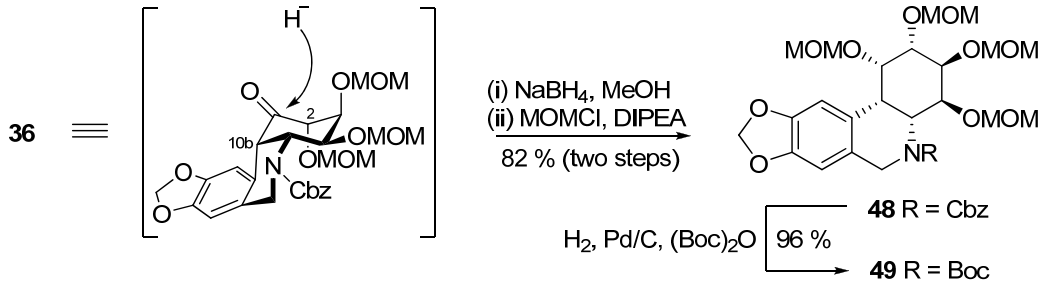
again that the *cis*-fused phenanthridone is thermodynamically more stable. The outcome of the above reaction could be rationalized by considering the Lewis acidity of bromine to activate silylenol ether of **43**, followed by the hydrolytic cleavage during aqueous work up.

2.9. Synthesis of 1,10b-*epi*-7-deoxypancratistatin

Although, the approach based on intramolecular aza-Michael addition produced the *cis*-fused phenanthridone and the efforts on both direct and indirect epimerization trials at C_{10b} were not fruitful, we proceeded with planned synthetic sequence to achieve the *cis*-analogues of 7-deoxypancratistatin. Sodium borohydride reduction of **36** in MeOH at 0 ºC afforded corresponding C_1 hydroxylated molecule. This reaction sequence completed the installation of all the hydroxyl functionalities at the periphery of C-ring (Scheme 12). At this stage, the stereochemistry of this newly created center (C_1) could not be established as the coupling constants were not well defined probably due to bent conformation of the *cis*-fused ring. However, one can anticipate that the α-orientations of both C_2, C_{10b} stereocenters would direct hydride

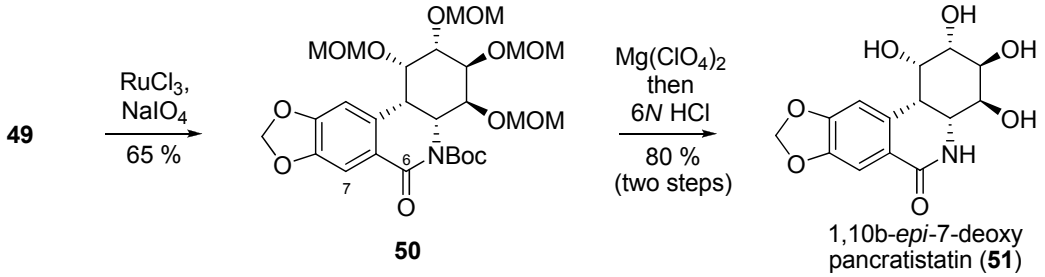
addition to the *β*-face to establish *syn-syn* relationship between C_{10b}, C_1, C_2. In order to complete the total synthesis of **25** along with the hope that C_6-benzylic oxidation may result a crystalline solid for X-ray analysis to confirm all newly generated stereocenters, we proceeded for the benzylic oxidation. However, this step required prior protection of the C_1 hydroxyl group and thus, it was protected as methoxymethyl ether (**48**, 82 % combined yield). The presence of six methyne protons (–CH) in the molecule was clearly confirmed by the appearance of peaks at *δ* 76.8, 75.6, 74.5, 71.2, 50.5, 39.2 in ^{13}C NMR spectrum of **48**. The ESI mass spectrum of this compound once again confirmed the product with the base peak at 628 ($M+Na^+$). The splitting pattern of the methylenedioxy ($-OCH_2O-$) protons at 5.87 (dd, J = 5.2, 1.4 Hz, 2H) in the ^{1}H NMR spectrum indicated the bent conformation of the molecule (linear conformation is generally identified with the singlet).

Scheme 12. *Stereoselective reduction of* **36**



Stirring **48** with $RuCl_3/NaIO_4$ (*in situ* generation of RuO_4)[20] in $CCl_4/CH_3CN/H_2O$ (1:1:2) at room temperature produced a very complex reaction mixture, possibly due to the interference of more activated benzyl group of Cbz protecting group. Therefore, we replaced benzyl carbamate of **48** with the corresponding *tert*-butyl carbamate (**49**) by the one-pot hydrogenation protocol[21] (Scheme 12) in 96 % yield and subjected the resulting product **49** for oxidation as described above. We were pleased to note that it underwent smooth oxidation resulting **50** in 65 % yield (Scheme 13). The compound was identified with disappearance of the characteristic peaks for the benzylic position in both ^{1}H, ^{13}C NMR spectrums of **50**. Moreover, the aromatic proton attached with C_7 was shifted to downfield *δ* 7.57 (s, 1H) in comparison with starting material {**49**, *δ* 6.49 (s, 1H)}, probably due to the deshielding effect of C_6-carbonyl oxygen. The mass spectrum of **50** showed a base peak at 609 ($MH+Na^+$) which further confirmation its structure.

Scheme 13. *Synthesis of epi-7-deoxypancratistain*



Since global deprotection of **50** gave mixture of partially deprotected products in variable yields, we adopted two stage deprotection strategy. Initially, removal of *tert*-butoxycarbonyl group of imide **50** selectively by using $[Mg(ClO_4)_2/CH_3CN]$,[22] followed by refluxing the resultant amide in HCl/methanol afforded 1,10b-*epi*-7-deoxypancratistatin (**51**) {mp 298–304 ºC; $[\alpha]^{27}_D$ +88.3 (*c* 0.35, DMSO)} in 80 % combined yield.

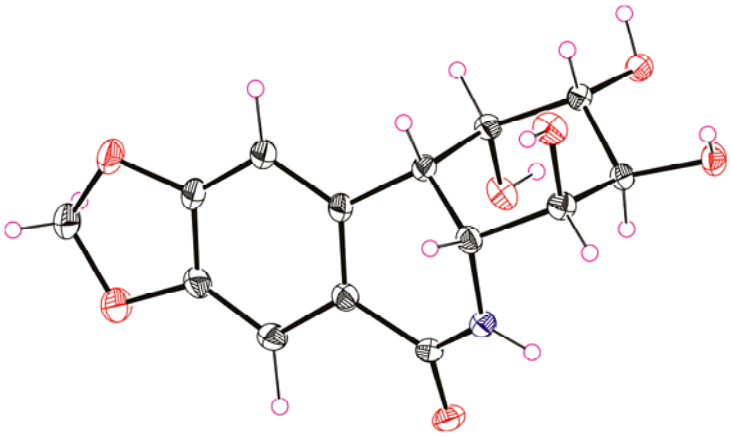


Figure 6. *ORTEP diagram of 1,10b-epi-7-deoxypancratistatin* (**51**).

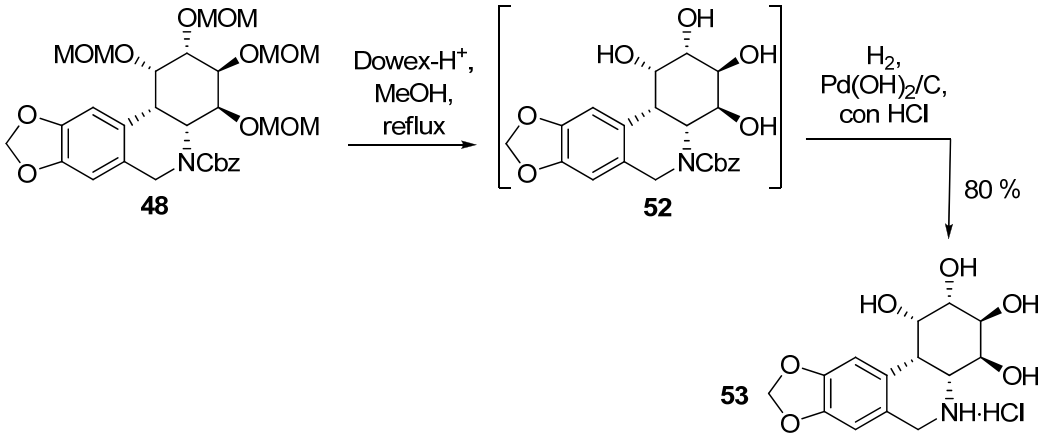
When the ^{1}H NMR of **51** was recorded in DMSO-d_6, broad peaks associated with –OH groups made the spectrum more complicated. However, addition of few drops of D_2O simplified the spectrum for the analysis. While the aromatic protons of **51** appeared at δ 7.22 and 6.89 as singlets, methylenedioxy ($-OCH_2O-$) protons resonated at δ 5.99 (apparent d, J = 5.3 Hz). Six methyne (–CH) protons of this molecule appeared at δ 3.95 (s, 1H), 3.80–3.62 (m, 4H), 2.99 (s, 1H). The ^{13}C NMR spectrum clearly confirmed the existence of six methyne carbons in the molecule by

showing peaks at δ 73.8, 70.6, 69.7, 67.0, 55.3, 38.4. The ESI mass spectrum of **51** displayed a peak at 332 ($M+Na^+$) confirming the structure of the final product. Finally the X-ray analysis of crystalline solid unambiguously confirmed all the stereocenters of **51** as shown in Figure 6.

2.10. Synthesis of amine hydrochloride of 1,10b-*epi*-7-deoxypancratistatin

For the purpose of evaluating biological profile of *cis*-analogues of pancratistatin, compound **53** {mp 214–218 ºC (with decomposition); $[\alpha]^{27}_D$ +40.8 (*c* 0.5, H_2O)} was also synthesized (Scheme 14) by refluxing **48** with equal amount of DOWEX-H^+ resin in MeOH, followed by hydrogenating the resulting tetrol **52** in acidic methanol (80 % yield). The ^{1}H NMR spectrum of **53** recorded in D_2O revealed, the aromatic as well as methylenedioxy protons appearing as singlets at δ 6.73, 6.60 and at δ 5. 85 (apparent d, J = 3.0 Hz), respectively. Benzylic protons of the molecule displayed two doublet of doublets at δ 3.93 (J = 10.3, 3.4 Hz, 1H), 3.88 (J = 10.3, 2.5 Hz, 1H) and the six –CH protons resonated at δ 4.28 (d, J = 7.5 Hz, 1H), 4.25 (dd, J = 3.1, 2.8 Hz, 1H), 4.09 (m, 2H), 3.62 (m, 1H), 3.20 (m, 1H). The ESI mass of **53** clearly emphasized the presence of the salt by showing the cationic part of **53** at 296 as a base peak.

Scheme 14. *Synthesis of amine hydrochloride* **53**

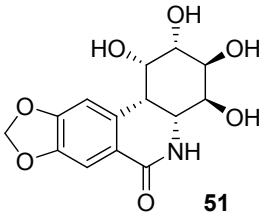
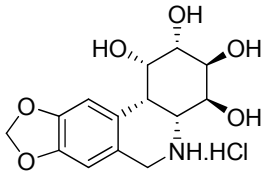
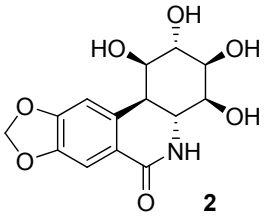


2.11. Evaluation of cytotoxicity of 51 and 53

Since, our synthesized compounds were new and no biological activity data were available, we decided to screen them against murine P388 lymphocytic leukemia and two other human cancerous cell lines MCF-7 (breast adenocarcinoma) and THP-1

(promonocytic leukemia), respectively. Compound **51** exhibited 100-fold less activity (GI_{50}= 44.5 μg/mL) in comparison with natural 7-deoxypancratistatin (**2**, 0.44 μg/mL) against murine P388. The analogue **53** also showed similar activity (50.0 μg/mL) in the murine P388 cell line. However, the inhibition of THP-1 monocytic cells with **53** was found to be 14.5 μg/mL in comparision to **51** (>100 μg/mL). In the breast cancerous MCF-7 cell line, both the analogues **51** as well as **53** displayed similar range of activity 74.6 and 85.3 μg/mL, respectively.

Table 1. *Cytotoxicity data[a] of cis-analogues of* **2***

Compound	Cancer cell lines		
	murine P388	THP-1	MCF-7
 **51**	44.5	>100	74.6
 **53**	50.0	14.48	85.34
 **2**	0.44[b]	–	–

[a]Data reported as IC_{50} in μg/mL; [b]Data has been reported earlier;[23] ***Detailed inhibition assay procedure is given in experimental section; –, means not known.***

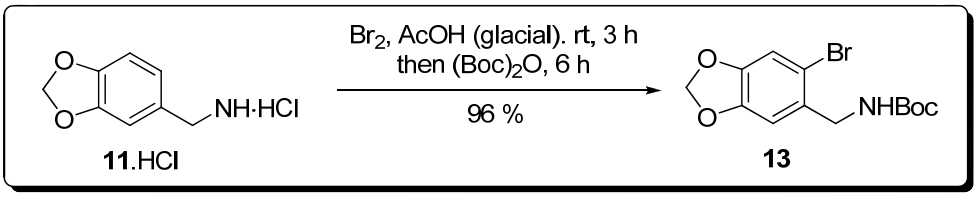
2.12. Conclusion

In summary, a new synthetic strategy has been developed for the syntheses of phenanthridone class of alkaloids employing Suzuki cross coupling/intramolecular aza-Michael reaction sequence. This approach also highlighted the use of cheaply available D-(−)-quinic acid as starting material for the most difficult C-ring

construction in the syntheses of this class of alkaloids. Although, intramolecular aza-Michael reaction for B-ring closure of the present synthesis produced an incorrect *cis*-fused phenanthridone, the potential of this stereoselective reaction could be more appropriately exploited for the total synthesis of other members of this family like γ-lycorane, fortucine and siculinine featuring *cis*-BC ring junction.[24,25] Compound **51** was found to exhibit moderate cyctotoxity against the studied cancer cell lines but **53** has shown good activity against THP-1 monocytic cells raising the hope that some subtle variation in its structure may enhance the possibility of developing this molecule as therapeutic agents.

2.13.I. Experimental section

1. *tert*-Butyl (6-bromobenzo[*d*][1,3]dioxol-5-yl)methylcarbamate (13):

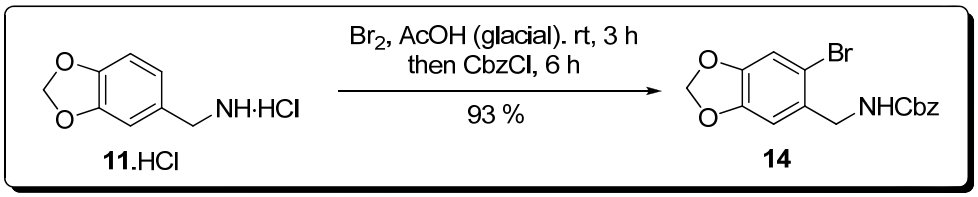


To a suspension of hydrochloride salt of piperonylamine (**11**.HCl, 5 g, 26.65 mmol) in glacial acetic acid (25 mL) was added bromine (2.73 mL, 53.30 mmol). The solids dissolved to form clear red solution, which was stirred at room temperature for 3 h. The saturated aqueous Na_2SO_3 was added until decolorization. It was cooled in an ice bath and made strongly basic with the help of 20 % aqueous NaOH solution. This reaction mixture was successively added with DCM (100 mL) and $(Boc)_2O$ (6.73 mL, 29.31 mmol) by maintaining the temperature at 0 °C. The biphasic solution was warmed to room temperature and stirred for further 6 h. The aqueous layer was extracted with DCM (2×50 mL). The combined organic extracts were washed with water (2×75 mL), brine (1×75 mL) and dried (Na_2SO_4). The solution was filtered, concentrated under reduced pressure and the residue was further purified by column chromatography (silica gel, elution with 10 % ethyl acetate/pet ether) to afford **13** (8.06 g, 96 %) as colorless oil.

Note: 13 *is unstable, undergoes debromination at room temperature within 48 h to produce tert-butoxycarbonyl protected piperonylamine.*

IR ν_{max} cm^{-1} (neat)	:	3350, 2978, 1693, 1504, 1250
^{1}H NMR (CDCl$_3$, 200 MHz) δ	:	6.96 (s, 1H), 6.86 (s, 1H), 5.94 (s, 2H), 4.99 (bs, 1H), 4.26 (d, *J* = 4.0 Hz, 2H), 1.43 (s, 9H)
^{13}C NMR (CDCl$_3$, 50 MHz) δ	:	155.7, 147.5, 147.4, 131.2, 113.6, 112.5, 109.5, 101.6, 79.5, 44.6, 28.3

2. Benzyl (6-bromobenzo[*d*][1,3]dioxol-5-yl)methylcarbamate (14):



The title compound (**14**) was prepared by adopting the same procedure as that of *tert*-butyl carbamate (**13**) except using benzyl chloroformate (4.2 mL, 29.31 mmol)

to protect the amine intermediate. The crude solid after workup, was purified by recrystallization from ethyl acetate/pet ether (1:9) to afford **14** (9 g, 93 %) as white crystals.

mp : 96–97 °C

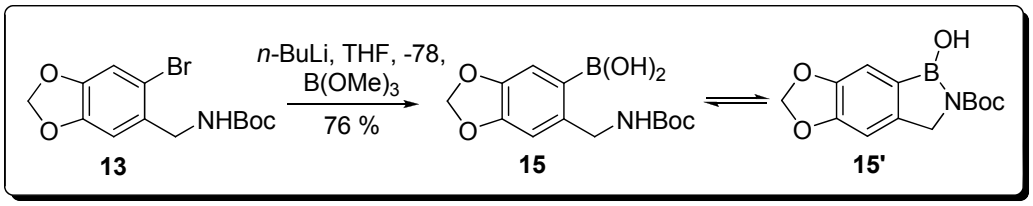
IR ν_{max} cm^{-1} ($CHCl_3$) : 3446, 3018, 1718, 1506, 1215

^{1}H NMR ($CDCl_3$, 200 MHz) δ : 7.34 (s, 5H), 6.98 (s, 1H), 6.90 (s, 1H), 5.95 (s, 2H), 5.27 (bs, 1H), 5.10 (s, 2H), 4.33 (d, *J* = 6.2 Hz, 2H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ : 156.2, 147.7, 147.4, 136.3, 130.7, 128.4, 128.0, 113.8, 112.6, 109.8, 101.7, 66.8, 45.2

Mass: m/z (%) : 388 ($M+2+Na^+$, 27), 386 ($M+Na^+$, 27), 343 (9), 301 (18), 264 (100)

3. 6-((*tert*-Butoxycarbonylamino)methyl)benzo[*d*][1,3]dioxol-5-ylboronic acid (15):



To a solution of **13** (5 g, 15.87 mmol) in dry THF (70 mL) was added *n*-BuLi (2 *M* hexane, 17.5 mL, 34.92 mmol) at –78 °C over a period of 10 min. The resultant dark yellow colored solution was stirred for 20 min. at the same temperature and trimethyl borate (18.0 mL, 158.73 mmol) was added rapidly in one portion. The solution became colorless and then it was stirred for further 30 min at –78 °C. The reaction mixture was warmed to room temperature over 2 h, before quenching with large excess of saturated aqueous NH_4Cl (50 mL). The heterogeneous mixture was stirred for an hour and extracted with ethyl acetate (3×60 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated by rotary-evaporation. The residue was purified using column chromatography (silica gel, elution with 35 % ethyl acetate-pet ether) to provide **15** (3.0 g, 76 %) as a white paste, which on storing in refrigerator became solid.

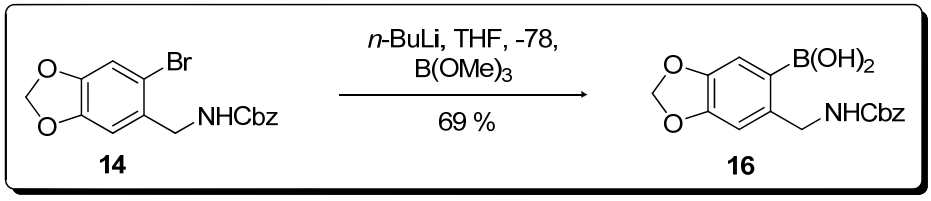
mp : 116–121 °C

IR ν_{max} cm^{-1} ($CHCl_3$) : 2979, 1682, 1504, 1255

^{1}H NMR ($CDCl_3$, 200 MHz) δ : 7.62 (bs, 0.4H), 7.12 (s, 0.34H), 7.10 (s, 0.66H), 6.77 (s, 0.66H), 6.70 (m, 0.34H), 5.57 (app t, *J* = 5.9 Hz, 0.3H), 5.98 (s, 1.32H),

		5.93 (s, 0.68), 4.33 (bs, 1.32H), 4.19 (d, *J* = 6.4 Hz, 0.68H), 1.54 (s, 5.94H), 1.38 (s, 3.06H)
^{1}H NMR (DMSO-d_6, 200 MHz) δ		8.15 (s, 2H), 7.25 (bs, 1H), 6.99 (s, 1H), 6.79 (s, 1H), 5.96 (s, 2H), 4.18 (d, *J* = 6.2 Hz, 2H), 1.37 (s, 9H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	157.2, 151.2, 147.3, 146.6, 144.1, 109.1, 103.4, 101.1, 50.4, 28.2
Mass: m/z (%)	:	346 (M+2MeOH-H_2O+Na^+, 100), 332 (M+MeOH+Na^+, 56), 292 (26), 236 (45)

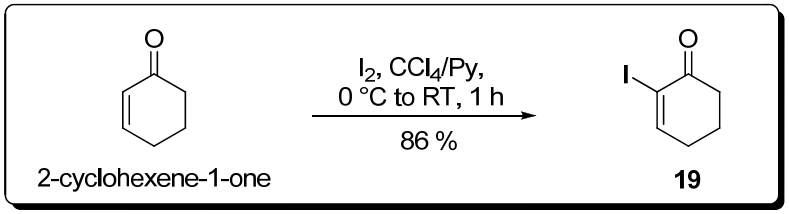
4. 6-((Benzyloxycarbonylamino)methyl)benzo[*d*][1,3]dioxol-5-ylboronic acid (16):



A similar procedure was used as described for the preparation of **15**, starting with **14** (5 g, 13.74 mmol). The crude boronic acid was purified using column chromatography (silica gel, elution with 45 % ethyl acetate-pet ether) to provide **16** (3.12 g, 69 %) as white amorphous solid.

mp	:	152–153 °C
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2926, 1693, 1462, 1250
^{1}H NMR (DMSO-d_6, 200 MHz) δ	:	8.15 (s, 2H), 7.67 (bs, 1H), 7.34 (s, 5H), 7.00 (s, 1H), 6.80 (s, 1H), 5.96 (s, 2H), 5.02 (s, 2H), 4.28 (d, *J* = 6.1 Hz, 2H)
^{13}C NMR (DMSO-d_6, 50 MHz) δ	:	157.1, 148.8, 145.9, 139.0, 137.4, 128.8, 128.2, 113.4, 108.4, 101.1, 66.0, 44.1
Mass: m/z (%)	:	380 (M+2MeOH-2H_2O+Na^+, 50), 326 (22), 188 (15), 156 (100)

5. 2-Iodocyclohex-2-enone (19):



Iodine (2.66 g, 10.49 mmol) dissolved in CCl_4/pyridine (1:1, 20 mL) was added drop-wise, under an atmosphere of argon to a solution of 2-cyclohexene-1-one (0.5 mL, 5.24 mmol) in CCl_4/pyridine (1:1, 20 mL) at 0 °C. The mixture was stirred

for 1 h during which time the temperature was allowed to warm to room temperature. The mixture was diluted with ethyl acetate (100 mL) and washed successively with 1 *N* HCl (4×20 mL), saturated aqueous solution of $NaHCO_3$ (40 mL), 20 % aqueous $Na_2S_2O_3$ (40 mL) and dried (Na_2SO_4). After filtration and concentration under reduced pressure, the residue was purified further by column chromatography (silica gel, 15 % ethyl acetate-pet ether) to afford **19** (1 g, 86 %) as white solid.

mp : 48–49 °C

IR ν_{max} cm^{-1} ($CHCl_3$) : 2951, 1682, 1585, 1315

^{1}H NMR ($CDCl_3$, 200 MHz) δ : 7.74 (t, *J* = 4.4 Hz, 1H), 2.63 (dd, *J* = 7.1, 6.3 Hz, 2H), 2.47–2.36 (td, *J* = 4.6, 5.9 Hz, 2H), 2.13–1.98 (m, 2H)

^{13}C NMR ($CDCl_3$, 50 MHz) δ : 192.0, 159.5, 103.5, 37.0, 29.7, 22.6

Mass: m/z (%) : 245 ($M+Na^+$, 100), 244 (50), 223 (31), 190 (17)

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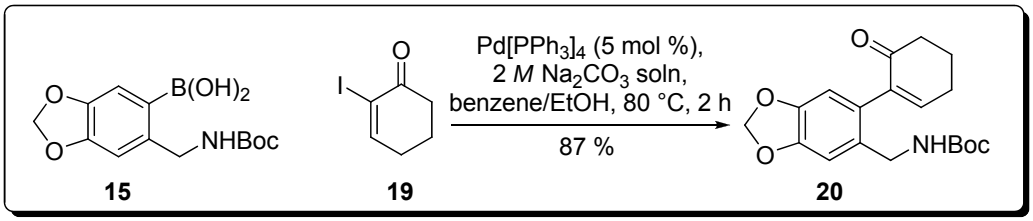
6. *tert*-Butyl (6-(6-oxocyclohex-1-enyl)benzo[*d*][1,3]dioxol-5-yl)methylcrbamate (20):



To a solution of **19** (0.5 g, 2.25 mmol) in distilled benzene (14 mL) was added a predissolved solution of **15** (0.66 g, 2.25 mmol) in ethanol (10 mL), aqueous 2 *M* Na_2CO_3 (5 mL) and catalytic amount of $Pd[PPh_3]_4$ (0.13 g, 0.11 mmol). The vigorously stirring yellow solution was heated in an oil bath set at 80 °C for 2 h. under an atmosphere of argon produced a dark reddish mixture. The reaction was cooled and diluted with water (15 mL), extracted with ethyl acetate (3×25 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, elution with 20 % ethyl acetate-pet ether) to yield the Suzuki cross-coupling product (**20**, 0.68 g, 87 %) as dark orange colored paste.

IR ν_{max} cm^{-1} ($CHCl_3$) : 2947, 1712, 1694, 1504

^{1}H NMR ($CDCl_3$, 400 MHz) δ : 6.90 (dd, *J* = 4.3, 4.0 Hz, 1H), 6.84 (s, 1H), 6.47 (s, 1H), 5.91 (s, 2H), 4.97 (bs, 1H), 3.94 (bs, 2H), 2.56 (dd, *J* = 6.8, 6.5 Hz, 2H),

2.50 (dd, *J* = 10.3, 5.8 Hz, 2H), 2.10 (quintet, *J* = 6.5 Hz, 2H), 1.42 (s, 9H)

^{13}C NMR (CDCl$_3$, 100 MHz) δ : 198.7, 155.8, 150.0, 147.6, 146.7, 140.4, 131.2, 129.3, 109.9, 108.9, 101.1, 79.1, 42.2, 38.5, 28.4, 26.4, 22.9

Mass: m/z (%) : 384 (M+K$^+$, 18), 368 (M+Na$^+$, 64), 360 (41), 344 (M-1$^+$, 44), 244 (100), 224 (48)

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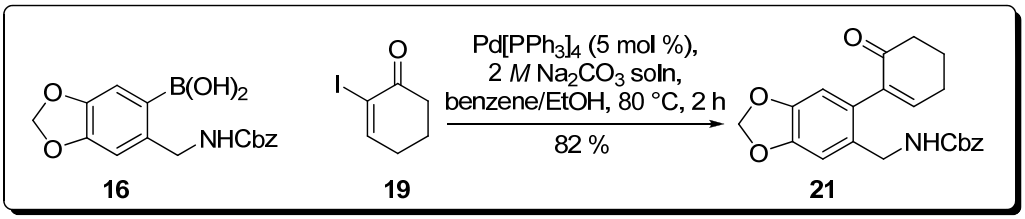
7. Benzyl (6-(6-oxocyclohex-1-enyl)benzo[*d*][1,3]dioxol-5-yl)methylcarbamate (21):



16 **19** **21**

An identical Suzuki cross coupling procedure was followed as that for **20**. The residue after workup was subjected to column chromatography (silica gel, elution with 25 % ethyl acetate-pet ether) to afford **21** (82 %) as yellow solid.

mp : 123–124 °C

IR ν_{max} cm^{-1} (CHCl$_3$) : 2947, 1712, 1694, 1504, 1230, 1040

^{1}H NMR (Benzene-d_6, 500 MHz) δ : 7.32 (s, 1H), 7.31 (s, 1H), 7.21–7.11 (m, 3H), 7.00 (s, 1H), 6.52 (s, 1H), 6.40 (t, J = 4.1 Hz, 1H), 5.54 (bs, 1H), 5.43 (s, 2H), 5.16 (s, 2H), 4.21 (bs, 2H), 2.24 (t, J = 6.4 Hz, 2H), 1.83 (m, 2H), 1.54 (quintet, J = 6.4 Hz, 2H)

^{13}C NMR (Benzene-d_6, 125 MHz) δ : 197.6, 156.5, 149.4, 148.0, 147.2, 140.6, 137.6, 131.7, 130.3, 128.5, 128.3, 127.9, 110.4, 109.4, 101.1, 66.5, 43.3, 38.6, 26.1, 22.8

Mass: m/z (%) : 402 (M+Na$^+$, 55), 272 (55), 258 (52), 244(100)

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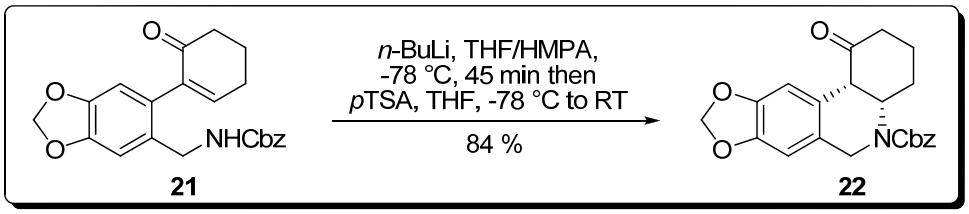
8. Benzyl 1-oxo-1,2,3,4,4a,10b-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-5(6*H*)-carboxylate (22):

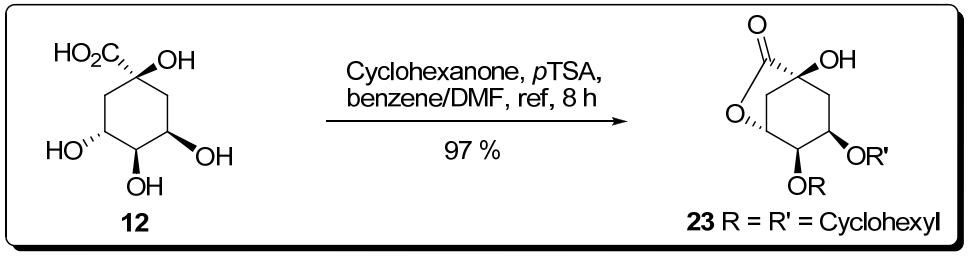
The Suzuki coupling product **21** (0.3 g, 0.79 mmol) was dissolved in a mixture of THF (8 mL) and HMPA (0.8 mL). The solution temperature was brought down to –78 °C with the aid of dry ice bath and *n*-BuLi (1.86 M in hexane, 0.51 mL, 0.95 mmol) was added over a period of 5 min. The resultant clear solution was stirred at the same temperature for 45 min. A solution of *p*-TSA (0.20 g, 1.05 mmol) in THF (2 mL) was added drop-wise and allowed to stir for further 10 min.



A saturated aqueous solution of $NaHCO_3$ (5 mL) was added after warming the reaction mixture to room temperature and extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was subjected to column chromatography (silica gel, elution with 20 % ethyl acetate-pet ether) to give **22** (0.25 g, 84 %) as pale yellow paste.

IR ν_{max} cm^{-1} (neat)	:	3018, 1713, 1695, 1504, 1217
^{1}H NMR (CDCl$_3$, 400 MHz) δ	:	7.38–7.28 (m, 5H), 6.58 (s, 1H), 6.41 (s, 1H), 5.91 (app q, *J* = 1.3 Hz, 2H), 5.17 (s, 1H), 4.86 (bs, 1H), 4.68 (bs, 1H), 4.29 (d, *J* = 17.3 Hz, 1H), 3.79 (d, *J* = 5.5 Hz, 1H), 2.28 (d, *J* = 5.3 Hz, 1H), 2.25 (d, *J* = 5.8 Hz, 1H), 1.95–1.87 (m, 2H), 1.77 (d, *J* = 12.8 Hz, 2H)
^{13}C NMR (CDCl$_3$, 100 MHz) δ	:	209.4, 154.8, 147.2, 147.1, 136.35, 128.5, 128.1, 128.0, 124.8, 122.5, 106.7, 106.5, 101.2, 67.5, 54.0, 51.9, 42.6, 37.9, 24.9, 22.0
Mass: m/z (%)	:	402 (M+Na+, 48), 284 (100), 242 (11)

9. 3, 4-*O*-cyclohexylidenequinic acid 1,5-lactone (23):

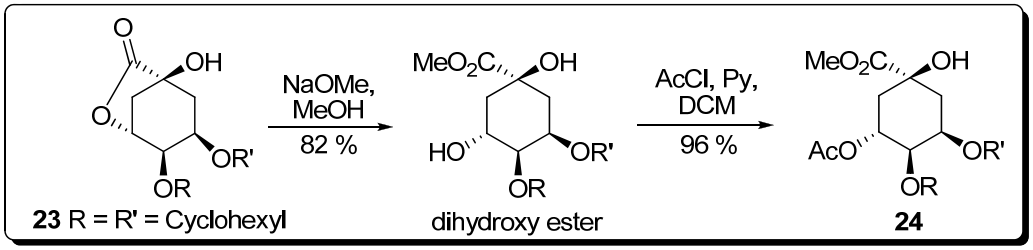


A suspension of D-(−)-quinic acid (**12**, 10 g, 52.08 mmol), *p*-toluenesulfonic acid (0.11 g, 0.60 mmol), cyclohexanone (15 mL), and *N*,*N*-dimethylformamide (20 mL) in benzene (150 mL) were stirred under reflux (Dean-Stark) until all the solids had dissolved (8 h). The reaction was cooled to room temperature and then diluted with ethyl acetate (300 mL), washed successively with saturated $NaHCO_3$ solution (1×50 mL), water (4×50 mL), brine (1×100 mL), dried (Na_2SO_4). The organic extract

was filtered and concentrated under reduced pressure. The solid residue was crystallized from pet ether/acetone mixture (9:1) to give white crystals (12.50 g, 95 % yield) of **23**.

mp	:	140–142 °C
$[\alpha]^{27}_D$	:	–33.5° (*c* 2.0, MeOH)
IR ν_{max} cm^{-1} (nujol)	:	3429, 3018, 1789,1215
^{1}H NMR ($CDCl_3$, 200 MHz) 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), 2.35 (ddd, *J* = 14.6, 7.0, 2.0 Hz, 1H), 2.28 (ddd, *J* = 11.8, 7.0, 1.2 Hz, 1H), 2.16 (dd, *J* = 14.6, 3.0 Hz, 1H), 1.72–1.20 (m, 10H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	178.6, 110.2, 75.6, 71.3, 71.2, 70.7, 37.9, 36.5, 34.0, 33.3, 24.6, 23.5, 23.1
Mass: m/z (%)	:	278 ($MH+Na^+$, 17), 277 ($M+Na^+$, 100), 272 ($M+NH_4^+$, 25), 255 (MH^+, 3), 243 (15)

10. Methyl 5-*O*-acetyl-3,4-*O*-cyclohexylidenequinate (24):



23 R = R' = Cyclohexyl dihydroxy ester **24**

Sodium methoxide generated *in situ* from freshly cut sodium (1.68 g, 73.04 mmol) in dry MeOH (65 mL) was added solid **23** (11.6 g, 45.67 mmol) in portions at room temperature. The stirring was continued for 6 h and then it was neutralized by the slow addition of glacial acetic acid (4.2 mL, 73.04 mmol). Evaporation of the solvent at reduced pressure gave a paste which was redissolved in ethyl acetate (250 mL), washed with water (2×30 mL), brine (1×100 mL), dried (Na_2SO_4). The rotary evaporation of the solvent gave a brown residue which was purified by column chromatography (silica gel, elution with 50 % ethyl acetate-pet ether) to afford recovered starting lactone (**23**, 1.50 g) and dihydroxy ester (10.45 g, 80 %) as white crystals.

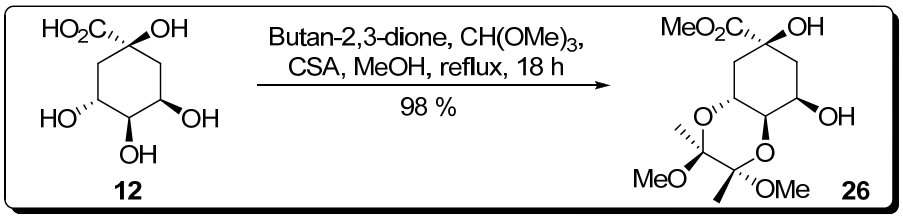
mp	:	79–80 °C
$[\alpha]^{27}_D$	:	–44.9 (*c* 1.8, MeOH)

IR ν_{max} cm^{-1} ($CHCl_3$)	:	3340, 1733
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	4.44 (ddd, *J* = 6.0, 3.9, 3.7 Hz, 1H), 4.09 (ddd, *J* = 10.9, 6.4, 4.3 Hz, 1H), 3.95 (dd, *J* = 6.4,6.0H z, 1H), 3.68 (s, 1H), 3.48 (s, 1H), 2.80 (bs, 1H), 2.30–2.20 (m, 2H), 2.06 (ddd, *J* = 13.6, 4.3, 1.6 Hz, 1H), 1.83 (dd, *J* = 13.6, 10.9 Hz, 1H), 1.75–1.30 (m, 10H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	176.1, 110.7, 80.1, 74.7, 73.8, 69.2, 53.7, 39.7, 38.7, 35.5, 35.4, 25.6, 24.7, 24.3
Mass: m/z (%)	:	304 ($M+NH_4^+$, 38), 288 ($M+2^+$, 19), 287 (MH^+, 100), 207 (11), 189 (22)

To a stirring solution of intermediate dihydroxy ester (5 g, 17.48 mmol) in dry DCM (50 mL) at 0 °C was added dry pyridine (1.61 mL, 20.10 mmol) and freshly distilled actyl chloride (1.49 mL, 20.98 mmol). The reaction was allowed for the gradual warming over a period of 12 h. The reaction mixture was then partitioned with water (75 mL) and extracted with DCM (2×75 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated to afford pure **24** (5.70 g, 100 %) as white crystals.

mp	:	140 °C
$[\alpha]^{27}_D$	:	–70.9 (*c* 2.0, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3340, 3020, 1737,1215
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	5.28 (ddd, *J* = 11.5, 7.2, 4.5 Hz, 1 H), 4.48 (ddd, *J* = 5.0, 4.3, 2.5 Hz, lH), 4.09 (dd, *J* = 7.2, 5.0 Hz, lH), 3.75 (s, 3H), 2.34 (dt, *J* = 15.6, 2.5 Hz, lH), 2.23 (dd, *J* = 15.6, 4.3 Hz, 1H), 2.15 (ddd, *J* = 13.3, 4.5, 2.5 Hz, 1H), 2.06 (s, 3 H), 1.90-1.20 (m, 12H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	174.6, 170.1, 110.4, 76.3, 74.0, 73.4, 71.0, 53.0, 37.8, 36.8, 35.1, 34.4, 25.0, 24.0, 23.7, 21.2
Mass: m/z (%)	:	351 ($M+Na^+$, 100), 346 ($M+NH_4^+$, 52), 329 (MH^+, 40), 243 (16), 231 (16)

11. (2'*S*, 3'*S*)- Methyl-4-*O*,5-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-quinate (26):

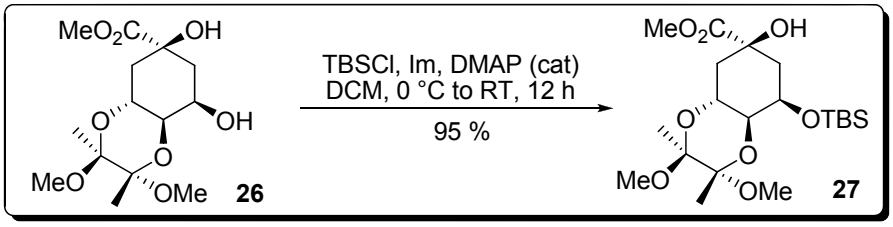


To a solution of D-(–)-quinic acid (**12**, 11.01 g, 57.30 mmol) and CSA (1.50 g, 6.50 mmol) in CH_3OH (250 mL) was added trimethylorthoformate (49 mL, 448.00

mmol) and butan-2,3-dione (11.8 mL, 134.00 mmol). The yellow solution was heated under reflux for 6 h, stirred at room temperature overnight and then heated under reflux for a further 6 h. After cooling to room temperature, Et_3N (15 mL, 108 mmol) was added and the solution was concentrated under reduced pressure to give the crude product as a brown solid. Decolorization of a solution of the crude product in EtOAc with activated charcoal followed by concentration and recrystallisation from hot EtOAc/pet ether (4:6) provided **26** (16.5 g, 98 %) as colorless crystals.

mp	:	135–136 °C
$[\alpha]^{27}_D$	:	+135.7 (*c* 2.0, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3471, 3016, 1736, 1215, 1134
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	4.26 (ddd, *J* = 12, 10.2, 4.8 Hz, 1H), 4.16 (q, *J* = 2.9 Hz, 1H), 3.75 (s, 3H), 3.56 (dd, *J* = 10.2, 2.9 Hz, 1H), 3.22 (s, 2 x 3H), 2.19 (ddd, *J* = 15.0, 3.0, 3.0 Hz, 1H), 2.10 (ddd, *J* = 12.0, 5.0, 3.0 Hz, 1H), 2.03 (dd, *J* = 5.0, 3.0 Hz, 1H), 1.92 (dd, *J* = 12.0, 12.0 Hz, 1H), 1.34 (s, 3H), 1.30 (s, 3H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	174.1, 100.2, 99.6, 75.7, 72.6, 69.0, 62.3, 52.8, 47.8, 38.5, 37.3, 17.7, 17.5
Mass: m/z (%)	:	343 ($M+Na^+$, 100), 338 ($M+NH_4^+$, 36), 288 (11)

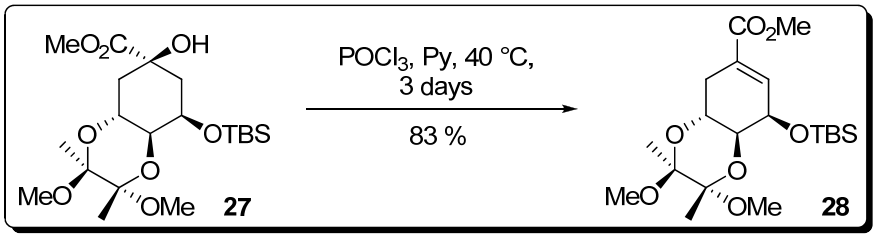
12. (2'*S*, 3'*S*)- Methyl-3-*O*-^{t}butyldimethylsilyl-4-*O*,5-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-quinate (27):



To a solution of **26** (16.21 g, 50.66 mmol) and imidazole (8.62 g, 126.64 mmol) in dry DMF (100 mL) at 0 °C was added solid TBSCl (15. 27 g, 101.31 mmol) in one portion. The resulting yellow solution was stirred at 0 °C for 2 h and then gradually warmed to room temperature. It was stirred overnight before quenching with water (100 mL) and the reaction mixture was extracted with mixture of ethyl acetate/pet ether (1:1) (2×150 mL). The combined organic extracts were washed with small portions of water (4×50 mL), brine (1×150 mL), dried (Na_2SO_4), filtered and concentrated in rotary evaporator to afford a brown solid. Purification by recrystallization from hot MeOH and H_2O gave **27** as colorless solid (20.8 g, 95 %).

mp	:	115–116 °C
$[\alpha]^{27}_D$	:	+101.6 (*c* 1.62, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3446, 3018, 2954, 1742, 1215, 1134
^1H NMR ($CDCl_3$, 200 MHz) δ	:	4.9 (bs, 1H), 4.31–4.20 (m, 2H), 3.76 (s, 3H), 3.48 (dd, *J* = 10.1, 2.5 Hz, 1H), 3.23 (s, 3H), 3.21 (s, 3H), 2.18 (dd, *J* = 12.8, 4.6 Hz, 1H), 2.09–2.05 (m, 2H), 1.86 (app t, *J* = 12.5 Hz, 1H), 1.28 (s, 3H), 1.26 (s, 3H), 0.90 (s, 9H), 0.17 (s, 3H), 0.11 (s, 3H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	173.5, 99.8, 99.2, 76.1, 72.6, 70.8, 62.3, 52.4, 47.6, 47.4, 39.3, 38.3, 25.5, 17.9, 17.7, 17.4, –4.9, –5.5
Mass: m/z (%)	:	458 ($MH+Na^+$, 100), 453 ($MH+NH_4^+$, 48), 435 (MH^+, 39), 403 (61)

13. (2'*S*, 3'*S*)- Methyl-3-*O*-^{t}butyldimethylsilyl-4-*O*,5-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-shikimate (28):



To a solution of **27** (15.8 g, 36.41 mmol) in freshly distilled pyridine (60 mL) at 0 °C was added $POCl_3$ (6.7 mL, 72.81 mmol) under an atmosphere of argon. The reaction mixture was warmed at 40 °C and maintained at the same temperature for 3 days. Then it was cooled to 0 °C and quenched by the careful addition of saturated aqueous solution of ammonium chloride (150 mL). The organic material was extracted into ethyl acetate (3×100 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford yellow crystals of crude product. Recrystallization from MeOH/H_2O afforded **28** (contaminated with approx. 6 % of regioisomer) as colorless crystals (12.27 g, 83 %).

mp	:	74–77 °C
$[\alpha]^{27}_D$	:	–17.2 (*c* 2.0, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2951, 1726, 1250, 1124
^1H NMR ($CDCl_3$, 200 MHz) δ	:	6.77 (dd, *J* = 5.5, 2.6 Hz, 1H), 4.31 (dd, *J* = 5.5, 3.9 Hz, 1H), 4.11 (ddd, *J* = 10.9, 10.4, 6.0 Hz, 1H), 3.75 (s, 3H), 3.48 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.24 (s, 3H), 3.23 (s, 3H), 2.80 (dd, *J* = 17.6, 6.0 Hz, 1H), 2.21 (ddd, *J* = 17.6, 10.4, 2.6 Hz, 1H), 1.29 (s, 3H),

1.28 (s, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H)

^{13}C NMR (CDCl$_3$, 50 MHz) δ : 167.0, 136.6, 129.7, 99.4, 98.6, 70.8, 65.9, 62.3, 51.9, 47.7, 47.5, 30.3, 25.7, 18.3, 17.8, 17.6, –4.8, –4.9

Mass: m/z (%) : 439 (M+Na$^+$, 70), 434 (M+NH$_4^+$, 78), 385 (96), 267 (100)

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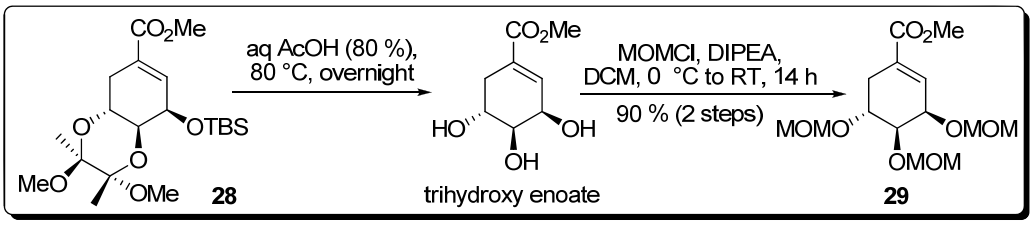
14. (3*R*,4*S*,5*R*)-Methyl 3,4,5-tris(methoxymethoxy)cyclohex-1-enecarboxylate (29):



A solution of methyl shikimate **28** (12 g, 28.85 mmol) in 80 % aqueous acetic acid was immersed in an oil bath set at 80 °C and stirred for overnight. Then the yellow solution was distilled at 50 °C applying high vacuum to remove volatile materials. The brown pasty residue was triturated with pet ether to facilitate the precipitation and then the solvent was decanted after settling. The process of trituration was repeated (approx. four times) to afford chalky powder (4.95 g, 91 %) after drying under vacuum. The trihydroxy enecarboxylate obtained was subjected to next step without further purification.

To a stirring solution of the above trihydroxy enoate intermediate (4.95 g, 26.33 mmol) in dry DCM (80 mL) was successively added DIPEA (16.51 mL, 94.79 mmol) and MOMCl (10 mL, 131.65 mmol) drop-wise at 0 °C. The yellow solution was warmed to room temperature and stirred for 14 h before adding water (100 mL). The aqueous layer was extracted with DCM (2×70 mL) and the organic layers were combined, dried (Na_2SO_4), filtered and concentrated to produce yellow oil. It was then purified using column chromatography (silica gel, elution with 20 % ethyl acetate-pet ether) to yield **29** (7.60 g, 90 %) as colorless oil.

$[\alpha]^{27}_D$: –82.8° (*c* 1.12, $CHCl_3$)

IR ν_{max} cm^{-1} (neat) : 2953, 1717, 1439, 1036

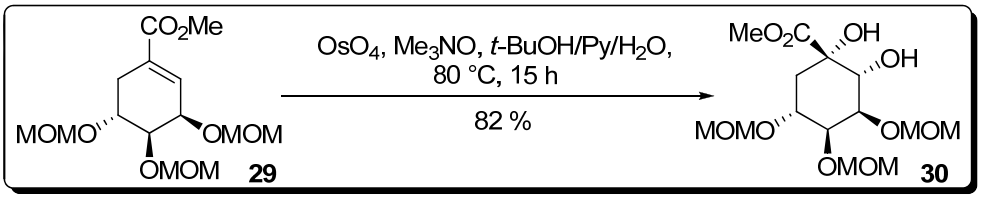
^{1}H NMR (CDCl$_3$, 200 MHz) δ : 6.85 (bs, 1H), 4.77 (d, *J* = 2.9 Hz, 2H), 4.74 (s, 2H), 4.69 (s, 2H), 4.50 (m, 1H), 4.11 (m, 1H), 3.95 (dd, *J* = 6.4, 3.8 Hz, 1H), 3.73 (s, 3H), 3.40 (s, 3H), 3.38 (s, 3H), 3.36 (s, 3H), 2.65–2.81 (tdd, *J* = 18.6, 4.7, 2.3 Hz, 1H), 2.33-2.48 (tdd, *J* = 18.6, 4.1, 1.5 Hz,

1H)

^{13}C NMR (CDCl$_3$, 50 MHz) δ : 166.6, 136.3, 129.2, 96.8, 96.0, 95.6, 74.2, 72.5, 70.8, 55.6, 55.5, 55.4, 51.7, 28.5

Mass: m/z (%) : 323 (100), 320 M^+, 7), 318 (43), 271 (17)

15. (1*S*,2*R*,3*R*,4*S*,5*R*)-Methyl 1,2-dihydroxy-3,4,5-tris(methoxymethoxy)cyclohexane carboxylate (30):



Trimethylamine *N*-oxide dihydrate (3.57 g, 32.12 mmol) was added to a solution of **29** (7.34 g, 22.94 mmol) in a mixture of *t*-BuOH (62 mL), pyridine (3.5 mL) and water (3.5 mL). The solution was stirred until all solids had dissolved and a crystal of OsO_4 was added at room temperature. The resulting yellow stirring solution was immersed in an oil bath set at 80 °C for 15 h. The reaction mixture was cooled and added with solid Na_2SO_3 (1 g) and allowed to stir for 30 min. The solvent was removed by rotary-evaporation, the residue was redissolved in ethyl acetate (150 mL) and partitioned with minimum amount of water (50 mL). The aqueous layer was extracted with ethyl acetate (2×75 mL), organic layers were combined, dried (Na_2SO_4) and purified by column chromatography (silica gel, elution with 60 % ethyl acetate-pet ether) to give **30** (6.66 g, 82 %) as white crystals.

mp : 83–84 °C

$[\alpha]^{27}_D$: –8.7° (*c* 1.62, $CHCl_3$)

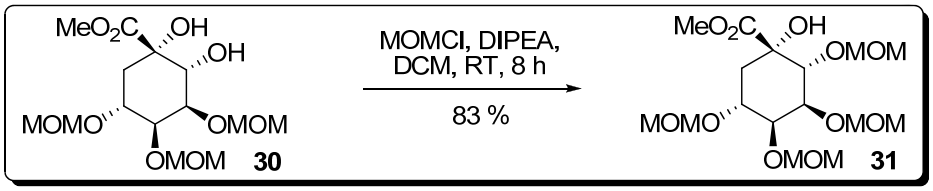
IR ν_{max} cm^{-1} ($CHCl_3$) : 3471, 2893, 1730, 1255, 1151

^{1}H NMR (CDCl$_3$, 200 MHz) δ : 4.83–4.62 (m, 6H), 4.20 (d, *J* = 10.0 Hz, 1H), 4.08 (m, 1H), 4.01 (dd, *J* = 6.2, 3.4 Hz, 1H), 3.92 (dd, *J* = 10, 2.8 Hz, 1H), 3.79 (s, 3H), 3.41 (s, 3H), 3.39 (s, 3H), 3.38 (s, 3H), 3.12 (bs, 1H), 2.38–2.26 (dd, *J* = 15.0, 3.5 Hz, 1H), 2.09–1.96 (ddd, *J* = 15.0, 2.3, 1.5 Hz, 1H)

^{13}C NMR (CDCl$_3$, 50 MHz) δ : 173.8, 96.9, 95.9, 76.3, 74.4, 71.4, 55.6, 55.5, 52.7, 32.2

Mass: m/z (%) : 377 (M+Na^+, 17), 372 (M+NH_4^+, 13), 355 (MH^+, 3), 279 (44), 246 (24), 218 (100), 190 (35), 156 (24)

16. (1*S*,2*R*,3*S*,4*S*,5*R*)-Methyl 1-hydroxy-2,3,4,5-tetrakis(methoxymethoxy) cyclohexanecarboxylate (31):



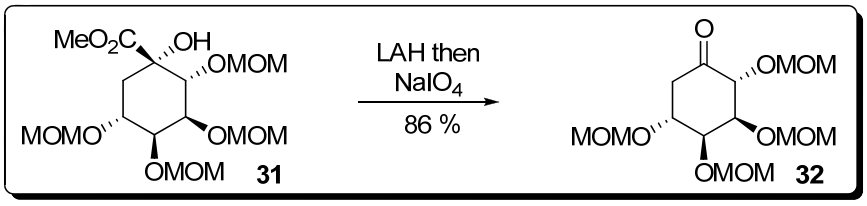
A solution of MOMCl (3.49 mL, 45.90 mmol) in dry DCM (35 mL) was added to the solution of **30** (6.5 g, 18.36 mmol) in dry DCM (60 mL) and DIPEA (6.40mL, 36.72 mmol) utilizing a syringe pump over a period of 2 h at room temperature. The reaction was stirred for further 6 h before the addition of water (80 mL). The aqueous layer was extracted with DCM (2×75 mL), combined organic extracts were dried (Na_2SO_4), filtered. Removal of the solvent by rotary evaporation gave a dark brown paste which was purified by column chromatography (silica gel, elution with 45 % ethyl acetae-pet ether) to give **31** (6.07 g, 83 %) as pale yellow paste.

$[\alpha]^{27}_D$	:	–51.0° (*c* 1.13, $CHCl_3$)
IR ν_{max} cm^{-1} (neat)	:	3460, 2895, 1745, 1443, 1244, 1150
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	4.89–4.56 (m, 8H), 4.19 (s, 1H), 4.17 (d, *J* = 2.2 Hz, 1H), 4.10 (m, 1H), 3.98 (dd, *J* = 6.7, 3.5 Hz, 1H), 3.78 (s, 3H), 3.67 (bs, 1H), 3.39 (s, 3H), 3.38 (s, 6H), 3.28 (s, 3H), 2.43–2.30 (dd, *J* = 14.9, 3.7 Hz, 1H), 2.03–1.90 (ddd, *J* = 14.9, 2.7. 1.3 Hz, 1H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	173.9, 98.3, 96.9, 96.5, 96.2, 78.6, 77.8, 76.8, 74.5, 74.4, 56.2, 55.7, 55.6, 55.5, 52.7, 33.1
Mass: m/z (%)	:	421 ($M+Na^+$, 30), 416 ($M+NH_4^+$, 13), 259 (100), 229 (19), 199 (28)

17. (2*R*,3*S*,4*S*,5*R*)-2,3,4,5-Tetrakis(methoxymethoxy)cyclohexanone (32):

A suspension of LAH (0.86 g, 22.61 mmol) in dry THF (25 mL) at 0 °C was cannulated drop-wise a solution of **31** (4.5 g, 11.30 mmol) dissolved in dry THF (40 mL) over a period of 30 min. The reaction mixture was warmed to room temperature and then stirred by maintaining the temperature at 50 °C in an oil bath for 18 h. The suspension was cooled to room temperature and poured *cautiously* by washing the flask with ethyl acetate into moisten Na_2SO_4 (approx. 50 g). It was mixed thoroughly and kept aside for 2 h. The milky white suspension was filtered on a Büchner funnel

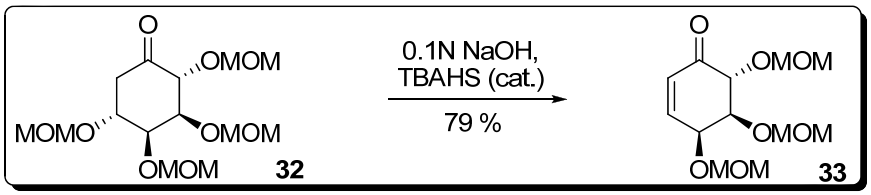
and the inorganic material was washed with ethyl acetate (150 mL). The filtrate was dried (Na_2SO_4), concentrated under reduced pressure gave crude diol (4.0 g) which was carried forward to the next step with out any further purification.



The crude diol (4.0 g) obtained above was dissolved in phosphate buffer (pH7, 35 mL) and cooled to 0 °C. Solid $NaIO_4$ (3.65 g, 17.04 mmol) was added in portions over a period of 10 min. maintaining the temperature 0–5 °C. The reaction mixture was stirred at the same temperature for additional 20 min. and extracted with ethyl acetate (3×50 mL), dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was subjected to column chromatography (silica gel, elution with 30 % ethyl acetate-pet ether) to produce **32** (3.29 g, 86 % for two steps) as colorless paste.

$[\alpha]^{27}_D$	:	–10.2° (*c* 1.02, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2895, 2359, 1732, 1030
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	4.90–4.59 (m, 8H), 4.52 (d, *J* = 10.1 Hz, 1H), 4.20–4.04 (m, 3H), 3.41 (s, 3H), 3.40 (s, 3H), 3.39 (s, 3H), 3.32 (s, 3H), 2.91–2.80 (dd, *J* = 14.3, 3.3 Hz, 1H), 2.64–2.52 (ddd, *J* = 14.3, 3.3, 1.1 Hz, 1H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	204.4, 97.2, 96.8, 96.5, 96.2, 80.1, 77.0, 76.2, 74.4, 55.7, 55.6, 55.4, 41.4
Mass: m/z (%)	:	377 ($M+K^+$, 14), 361 ($M+Na^+$,100), 123 (10)

18. (4*S*,5*S*,6*R*)-4,5,6-Tris(methoxymethoxy)cyclohex-2-enone (33):

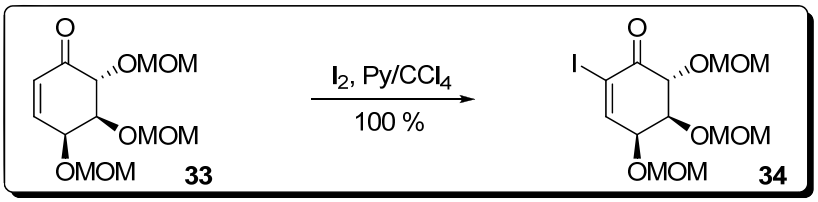


To a solution of **32** (3.00 g, 8.88 mmol) in distilled DCM (260 mL) was added an aqueous solution of NaOH (0.1 *N*, 65 mL) at 0 °C. The vigorously stirred biphasic solution was added catalylitic amount of tetrabutylammonium hydrogensulphate (TBAHS, 0.15 g, 0.44 mmol) and stirred at same temperature for the complete consumption of the starting material (GC monitoring). The reaction mixture was

portioned in a separatory funnel and the aqueous layer was extracted with DCM (2×50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent was distilled off under reduced pressure. The crude material was purified by column chromatography (silica gel, elution with 30 % ethyl acetate-pet ether to produce **33** (1.94 g, 79 %) as colorless oil.

$[\alpha]^{27}_D$	:	+113.1° (*c* 1.62, $CHCl_3$)
IR ν_{max} cm^{-1} (neat)	:	2951, 1703, 1441, 1113
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	6.90 (dd, *J* = 10.2, 4.5 Hz, 1H), 6.05 (d, *J* = 10.2 Hz, 1H), 4.86–4.71 (m, 6H), 4.53 (dd, *J* = 4.2, 4 Hz, 1H), 4.46 (d, *J* = 8.7 Hz, 1H), 4.10 (dd, *J* = 8.6, 3.4 Hz, 1H), 3.42 (s, 3H), 3.38 (s, 6H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	196.1, 145.7, 129.2, 96.9, 96.7, 76.9, 71.5, 55.9, 55.7, 55.6
Mass: m/z (%)	:	299 ($M+Na^+$, 100)

19. (4*S*,5*S*,6*R*)-2-Iodo-4,5,6-tris(methoxymethoxy)cyclohex-2-enone (34):



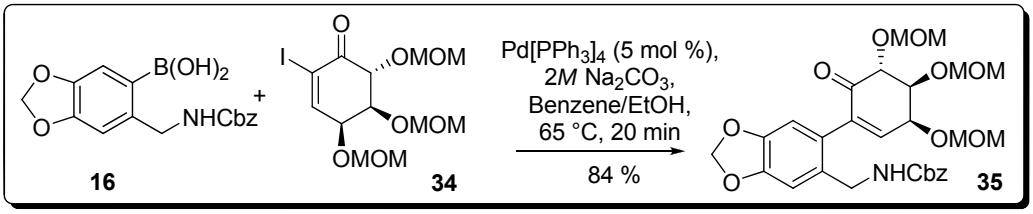
Iodine (4.05 g, 15.94 mmol) dissolved in CCl_4/pyridine (1:1, 20 mL) was added drop-wise, under an atmosphere of argon to a solution of **33** (1.76 g, 6.38 mmol) in CCl_4/pyridine (1:1, 20 mL) at 0 °C. The mixture was stirred for 1 h during which time the mixture was allowed to warm to room temperature. The mixture was diluted with ethyl acetae (100 mL) and washed successively with 1 *N* HCl (5×20 mL), aqueous saturated $NaHCO_3$ (1×30 mL), 20 % aqueous $Na_2S_2O_3$ (40 mL) and dried (Na_2SO_4). After filtration and concentration under reduced pressure, the residue was subjected to column chromatography (silica gel, elution with 25 % ethyl acetate-pet ether) to afford **34** (2.56 g, quantitative) as pale yellow oil.

$[\alpha]^{27}_D$	:	+85.9° (*c* 1.32, $CHCl_3$)
IR ν_{max} cm^{-1} (neat)	:	2895, 1693, 1443, 1034
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	7.67 (d, *J* = 4.6 Hz, 1H), 4.85–4.71 (m, 6H), 4.56 (d, *J* = 8.0 Hz, 1H), 4.51 (d, *J* = 4.4 Hz, 1H), 4.15 (dd, *J* = 8.0, 3.3 Hz, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 3.36 (s, 3H)
^{13}C NMR	:	190.0, 154.4, 103.8, 96.9, 96.7, 96.5, 76.7, 75.7, 73.4, 56.0,

($CDCl_3$, 50 MHz) δ 55.7, 55.6

Mass: m/z (%) : 441 ($M+K^+$, 7), 425 ($M+Na^+$, 100), 403 (MH^+, ≤1), 327 (5)

20. Benzyl (6-((3*S*,4*S*,5*R*)-3,4,5-tris(methoxymethoxy)-6-oxocyclohex-1-enyl)benzo[*d*] [1,3]dioxol-5-yl)methylcarbamate (35):



To a solution of **34** (1 g, 2.49 mmol) in distilled benzene (20 mL) was added a pre-dissolved solution of **16** (0.82 g, 2.49 mmol) in ethanol (14 mL), aqueous 2 *M* Na_2CO_3 (8 mL) and catalytic amount of $Pd[PPh_3]_4$ (0.14 g, 0.12 mmol). The vigorously stirring yellow solution was heated in an oil bath set at 65 °C for 20 min under an atmosphere of argon produced a dark brown mixture. The reaction was cooled and diluted with water (20 mL), extracted with ethyl acetate (3×75 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, elution with 30 % ethyl acetate-pet ether) to yield **35** (1.17 g, 84 %) as dark orange colored paste.

$[\alpha]^{27}_D$: +69.5° (*c* 1.16, $CHCl_3$)

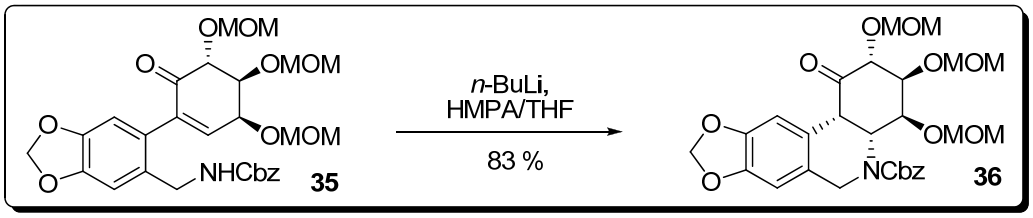
IR ν_{max} cm^{-1} (neat) : 2895, 1730, 1713, 1693, 1504, 1485, 1371, 1240, 1042

^{1}H NMR ($CDCl_3$, 200 MHz) δ : 7.32 (s, 5H), 6.90 (s, 1H), 6.81 (d, *J* = 3.7 Hz, 1H), 6.51 (s, 1H), 5.93 (s, 2H), 5.39 (bs, 1H), 5.07 (s, 2H), 4.86 (d, *J* = 7.0 Hz, 1H), 4.81–4.70 (m, 6H), 4.50 (d, *J* = 7.6 Hz, 1H), 4.27 (dd, *J* = 7.5, 2.9 Hz, 1H), 4.02 (bs, 2H), 3.41 (s, 3H), 3.40 (s, 3H), 3.37 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ : 194.8, 156.2, 147.9, 146.8, 145.1, 139.3, 136.6, 131.1, 128.2, 127.8, 127.5, 109.6, 109.3, 101.2, 96.9, 96.8, 96.4, 77.2, 76.9, 71.4, 66.5, 55.9, 55.6, 55.5, 42.7

Mass: m/z (%) : 583 ($MH+Na^+$, 29), 582 ($M+Na^+$, 100), 577 ($M+NH_4^+$, 12), 560 (13)

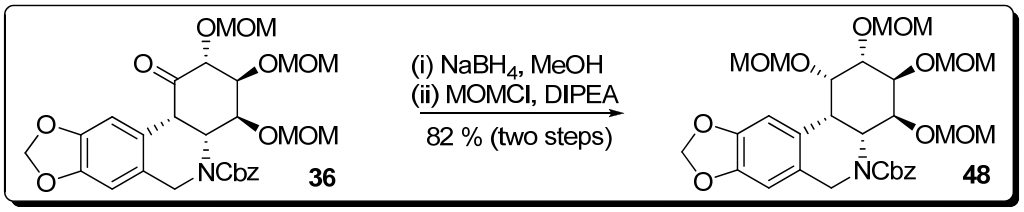
21. (2*R*,3*S*,4*S*,4a*R*,10b*S*)-Benzyl 2,3,4-tris(methoxymethoxy)-1-oxo-1,2,3,4,4a,10b-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-5(6*H*)-carboxylate (36):



To a stirred solution of coupling product **35** (0.7 g, 1.25 mmol) in dry THF (12 mL) was added HMPA (1.60 mL) at room temperature. The solution temperature was brought down to −78 °C with the aid of dry ice bath and *n*-BuLi (1.62 M in hexane, 1 mL, 1.62 mmol) was added over a period of 10 min. The resultant clear solution was stirred at the same temperature for 30 min. A solution of *p*-TSA (0.36 g, 1.88 mmol) in THF (3 mL) was added drop-wise and allowed to stir for further 10 min. A saturated aqueous solution of $NaHCO_3$ (10 mL) was added after warming the reaction mixture to room temperature and extracted with ethyl acetate (3×25 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was subjected to column chromatography (silica gel, elution with 25 % ethyl acetate-pet ether) to give **36** (0.57 g, 83 %) as pale yellow paste.

$[\alpha]^{27}_D$	:	+56.9° (*c* 0.64, $CHCl_3$)
IR ν_{max} cm^{-1} (neat)	:	2954, 1730, 1713, 1693, 1487, 1217, 1039
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	7.34 (m, 5H), 6.65 (s, 1H), 6.61 (s, 1H), 5.93 (dd, *J* = 4.6, 1.5 Hz, 2H), 5.24–5.03 (m, 3H), 5.98–4.80 (m, 2H), 4.80–4.61 (m, 6H), 4.59 (d, *J* = 3.3 Hz, 1H), 4.48 (dd, *J* = 6.7, 5.3 Hz, 1H), 4.02 (d, *J* = 6.8 Hz, 1H), 3.97 (dd, *J* = 9.3, 2.4 Hz, 1H), 3.65 (d, *J* = 15.8 Hz, 1H), 3.40 (d, *J* = 15.8 Hz, 1H), 3.35-3.32 (m, 7H)
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	205.3, 155.9, 147.0, 136.1, 128.5, 128.4, 128.2, 128.1, 128.0, 124.9, 108.5, 107.0, 101.1, 96.6, 96.5, 79.4, 75.5, 73.7, 67.7, 55.9, 55.8, 55.6, 54.8, 50.0, 44.4
Mass: m/z (%)	:	598 ($M+K^+$, 23), 582 ($M+Na^+$, 39), 560 (MH^+, 2), 361 (86), 331 (100)

22. (1*S*,2*S*,3*S*,4*S*,4a*R*,10b*S*)-Benzyl 1,2,3,4-tetrakis(methoxymethoxy)-1,2,3,4,4a,10b-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-5(6*H*)-carboxylate (48):

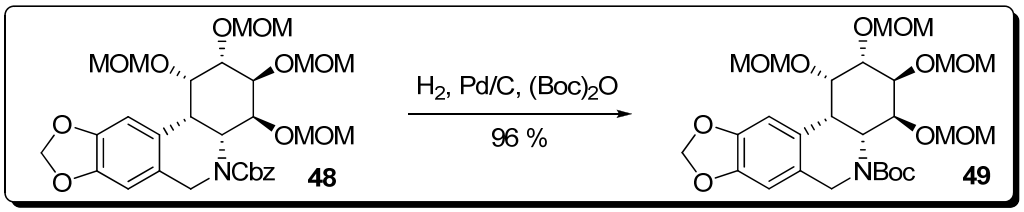


Sodium borohydride (0.1 g, 2.68 mmol) was added to a solution of **36** (0.5 g, 0.89 mmol) in dry methanol (10 mL). The resulting mixture was stirred for 12 h and then quenched by the addition of excess of saturated aqueous solution of NaCl. This brownish suspension was stirred overnight and extracted with ethyl aceteate (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was distilled off. The residue (0.44 g) was evaporated to dryness and used for the next step with out purification.

To a solution of crude alcohol (0.44 g, 0.78 mmol) in dry DCM (8 mL) was successively added DIPEA (0.68 mL, 3.92 mmol) and MOMCl (0.6 mL, 7.84 mmol) drop-wise at 0 °C. The yellow solution was warmed to room temperature and stirred for 12 h before adding water (10 mL). The aqueous layer was extracted with DCM (2×7 mL) and the organic layers were combined, dried (Na_2SO_4), filtered and concentrated to produce an orange colored paste. It was then purified using column chromatography (silica gel, elution with 30 % ethyl acetate-pet ether) to yield **48** (0.44 g, 82 % for two steps) as colorless paste.

$[\alpha]^{27}_D$	:	-17.1° (*c* 1.24, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2891, 1693, 1487, 1217, 1035
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	7.72 (bs, 1H), 6.50 (bs, 1H), 5.87 (dd, *J* = 5.2, 1.4 Hz, 2H), 5.35–5.02 (m, 2H), 4.90-4.60 (m, 8H), 4.53–4.20 (m, 4H), 4.09 (app s, 1H), 4.00–3.81 (m, 2H), 3.58 (bs, 1H), 3.39 (s, 2x3H), 3.29 (s, 3H), 3.22 (s, 3H)
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	156.0, 145.6, 137.0, 136.6, 128.4, 128.2, 128.0, 127.5, 124.7, 109.7, 105.2, 100.5, 97.6, 97.1, 96.4, 95.4, 76.8, 75.6, 74.5, 71.2, 67.2, 66.8, 55.9, 55.7, 55.6, 55.4, 50.5, 42.9, 39.2
Mass: m/z (%)	:	628 ($M+Na^+$, 100)

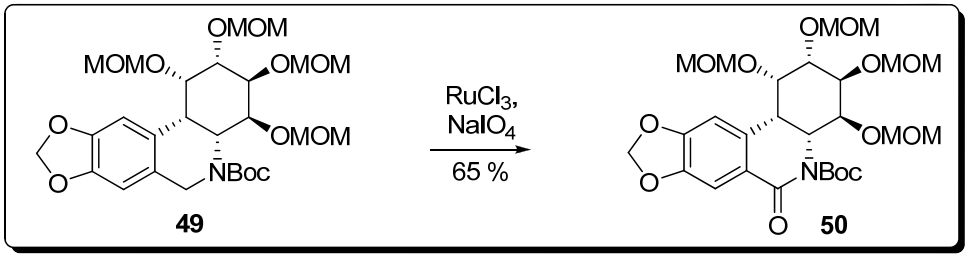
23. (1*S*,2*S*,3*S*,4*S*,4a*R*,10b*S*)-tert-Butyl 1,2,3,4-tetrakis(methoxymethoxy)-1,2,3,4,4a,10b-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-5(6*H*)-carboxylate (49):



A mixture of **48** (0.4 g, 0.66 mmol) and $(Boc)_2O$ (0.2 mL, 0.86 mmol) in distilled methanol (12 mL) was hydrogenated for 7 h at atmospheric pressure in the presence of 10 % Pd on charcoal (40 mg). The reaction mixture was passed through a short pad of Celite and the solvent was removed by rotary-evaporation. The residue was purified by column chromatography (silica gel, elution with 25 % ethyl acetate-pet ether) to afford **49** (0.36 g, 96 %) as colorless gum.

$[\alpha]^{27}_D$	:	−18.5° (*c* 0.80, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2891, 1695, 1485, 1365, 1151, 1037
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	7.71 (bs, 1H), 6.49 (s, 1H), 5.86 (dd, *J* = 5.2, 1.4 Hz, 2H), 4.90–4.60 (m, 8H), 4.52 (bs, 1H), 4.42–4.28 (m, 2H), 4.28–4.00 (m, 2H), 3.95–3.75 (m, 2H), 3.55 (bs, 1H), 3.40 (s, 2x3H), 3.36 (s, 3H), 3.21 (s, 3H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	145.5, 127.5, 125.0, 109.7, 105.2, 100.4, 96.3, 95.2, 79.7, 77.2, 76.8, 75.6, 74.2, 71.1, 55.6, 55.4, 50.4, 42.9, 39.0, 28.3
Mass: m/z (%)	:	594 ($M+Na^+$, 100)

24. (1*S*,2*S*,3*S*,4*S*,4a*R*,10b*S*)-tert-Butyl 1,2,3,4-tetrakis(methoxymethoxy)-6-oxo-1,2,3,4,4a,10b-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-5(6*H*)-carboxylate (50):

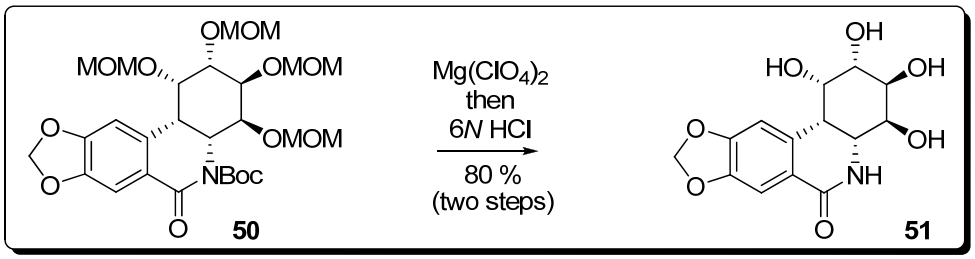


To a vigorously stirred solution of **49** (0.24 g, 0.42 mmol) in distilled CH_3CN/CCl_4 (1:1, 20 mL) was added an aqueous solution of $NaIO_4$ (0.27 g in 15 mL

H_2O) and $RuCl_3$ (24 mg). After being stirred for 3 h. the reaction mixture was diluted with DCM (30 mL), the aqueous phase was extracted with DCM (3×15 mL) and EtOAc (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was diluted with ether (20 mL), filtered through a pad of Celite and concentrated. The residue was purified by column chromatography (silica gel, elution with 40 % ethyl acetate-pet ether) to give **50** (0.16 g, 65 %) as colorless paste.

$[\alpha]^{27}_D$	:	+27.2° (*c* 1.25, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2895, 1764, 1693, 1483, 1242, 1151, 1038
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	7.74 (s, 1H), 7.57 (s, 1H), 5.98 (d, *J* = 12.1 Hz, 2H), 5.01 (dd, *J* = 11.1, 4.8 Hz, 1H), 4.81 (s, 2H), 4.78 (d, *J* = 7.1 Hz, 1H), 4.72 (d, *J* = 7.1 Hz, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.58 (d, *J* = 7.1 Hz, 1H), 4.46 (dd, *J* = 7.6, 7.1 Hz, 2H), 4.38 (dd, *J* = 5.1, 3 Hz, 1H), 4.10 (app s, 1H), 3.94 (s, 1H), 3.92 (app s, 1H), 3.89 (t, *J* = 5.1 Hz, 1H), 3.42 (s, 3H), 3.40 (s, 3H), 3.30 (s, 3H), 3.24 (s, 3H)
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	162.2, 152.4, 150.8, 146.5, 135.3, 123.2, 109.4, 108.3, 101.4, 97.5, 96.6, 95.7, 82.8, 77.2, 77.1, 75.3, 74.9, 72.0, 55.9, 55.8, 55.7, 53.1, 39.4, 28.0
Mass: m/z (%)	:	609 ($MH+Na^+$, 100), 586 (MH^+, 7), 508 (19), 486 (15)

25. 1,10b-*Epi*-7-deoxypancratistatin (51):

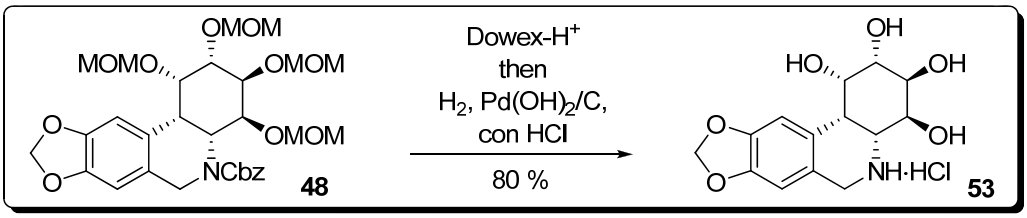


To a solution of **50** (0.1 g, 0.17 mmol) in dry CH_3CN (1 mL) was added catalytic amount of solid $Mg(ClO_4)_2$ (8 mg, 0.036 mmol) at room temperature. The stirring reaction mixture was heated with aid of oil bath set at 50 °C for 1.5 h. It was then cooled to room temperature, partitioned between ethyl acetate (10 mL) and water (5 mL) in a separating funnel. The aqueous layer was extracted with ethyl acetate (2×5 mL), the organic extracts were combined, dried (Na_2SO_4), filtered and subjected to rotary evaporation to afford spectroscopically pure amide (75 mg, 90 %) as white solid, which was forwarded to the next step.

To a solution of pure amide (75 mg, 0.15 mmol) in dioxane/methanol (2:1, 4 mL) was added 6 *N* HCl (2 mL) and the reaction mixture was refluxed for 18 h. The solvent was evaporated to dryness to afford a brown solid which was triturated with distilled MeOH (2 mL), allowed to settle, and the solvent was decanted. The trituration was repeated once again and removal of the solvent afforded **51** (42 mg, 89 %) as half white solid.

mp	:	298–305 °C
$[\alpha]^{27}_D$	:	+88.3 (*c* 0.35, DMSO)
^{1}H NMR (DMSO-d_6, drops of D_2O, 400 MHz) δ	:	7.22 (s, 1H), 6.89 (s, 1H), 5.99 (d, *J* = 5.3 Hz, 2H), 3.95 (s, 1H), 3.80–3.62 (m, 4H), 2.99 (s, 1H)
^{13}C NMR (DMSO-d_6, 100 MHz) δ	:	164.6, 149.9, 146.3, 135.7, 125.8, 107.4, 106.2, 101.4, 73.8, 70.6, 69.7, 67.0, 55.3, 38.4
Mass: m/z (%)	:	332 ($M+Na^+$, 16), 310 (MH^+, 20), 301 (21), 295 (100), 253 (98)

26. Amine analogue of 1,10b-*epi*-7-deoxypancratistatin (53):



A solution of **48** (70 mg, 0.116 mmol) in methanol (2 mL) was added with pre activated Dowex 50WX2-400 resin (90 mg). The heterogeneous mixture was refluxed with stirring for 14 h. the mixture was cooled, filtered through a short pad of Celite, and concentrated by rotary-evaporation to afford a brown residue, which was then purified by column chromatography (silica gel, elution with 5 % methanol-chloroform) to produce the tetrol (40 mg, 80 %) as amorphous white solid.

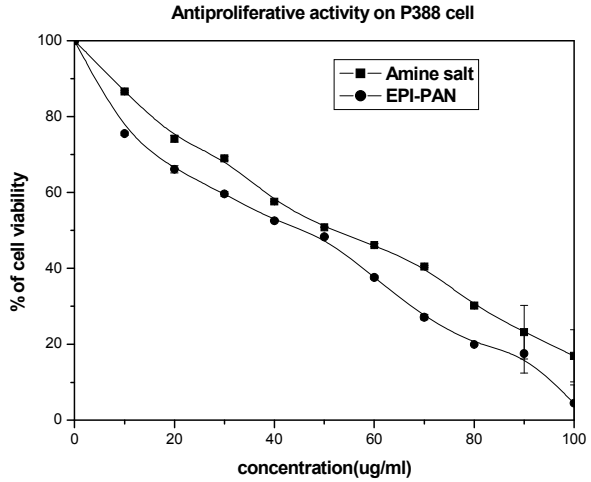
To a solution of the above tetrol (40 mg, 0.093 mmol) in distilled methanol (2 mL) was added conc. HCl (2 drops), and hydrogenated in the presence of 20 % $Pd(0H)_2$ on carbon (8 mg) under atmospheric pressure for 12 h. After passing through a pad of Celite, the solvent evaporated off to dryness to afford **53** (31 mg, ~100 %) as pale yellow solid.

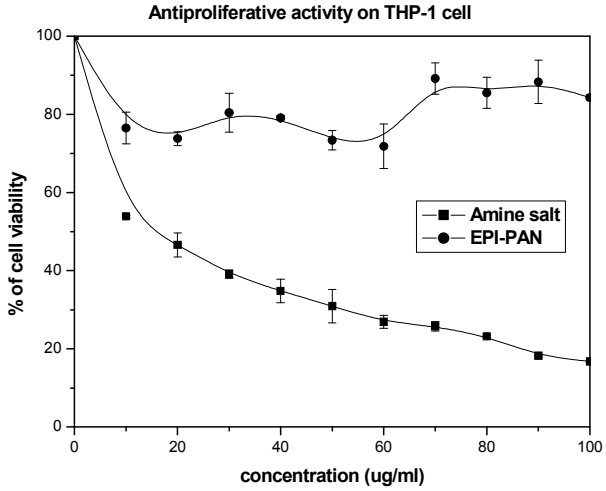
mp	:	214.2–216.4 °C (complete decomposition at 253.9 °C)
$[\alpha]^{27}_D$	:	+40.8 (*c* 0.5, H_2O)
^{1}H NMR (D_2O, 500 MHz) δ	:	6.73 (s, 1H), 6.60 (s, 1H), 5. 85 (d, *J* = 3.0 Hz, 2H), 4.28 (d, *J* = 7.5 Hz, 1H), 4.25 (dd, *J* = 3.1, 2.8 Hz, 1H), 4.09 (m, 2H), 3.93 (dd, *J* = 10.3, 3.4 Hz, 1H), 3.88 (dd, *J* = 10.3, 2.5 Hz, 1H), 3.62 (m, 1H), 3.20 (m, 1H)
^{13}C NMR (D_2O, 125 MHz) δ	:	147.1, 146.7, 125.0, 121.5, 107.8, 105.6, 101.2, 74.7, 69.6, 68.7, 66.6, 57.4, 45.5, 35.1
Mass: m/z (%)	:	296 (MH^+, 100)

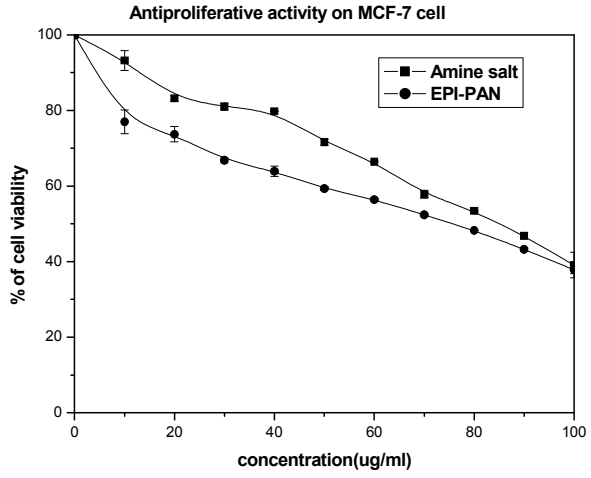
2.13.II. Cytotxicity studies

Murine P388, THP-1 and MCF-7 cells were seeded with 10,000 cells per well in 96-well tissue culture plates. Cells were allowed to adhere for 24 h at 37 ºC and then treated with various concentrations (10, 20, 30,.....100 μg/mL) of compounds (**51**, **53**) diluted in culture medium and again incubated for additional 72 h. In control wells, a culture medium consisting of corresponding concentration of DMSO only was added.

After above incubation, proliferation of compound treated cells were assessed by adding 10 μL medium containing 5 mg/mL MTT to each well and subsequently incubated for another 1 h at 37 ºC. The formazan crystals formed due to the reduction of the dye within the cells were solublized by incubating for another 4 h in presence of 200 μL of isopropanol. The optical density was read on SpectraMax 384 plate reader at 490 nm against a blank prepared from cell-free wells. Absorbance given by cells treated with the carrier DMSO alone was taken as 100 % cell growth. All assays were performed in triplicate.


Antiproliferative activity on P388 cell
Amine salt
EPI-PAN
% of cell viability
concentration(ug/ml)
0
20
40
60
80
100


Antiproliferative activity on THP-1 cell
Amine salt
EPI-PAN
% of cell viability
concentration (ug/ml)
0
20
40
60
80
100


Antiproliferative activity on MCF-7 cell
Amine salt
EPI-PAN
% of cell viability
concentration(ug/ml)
0
20
40
60
80
100

2.14. References

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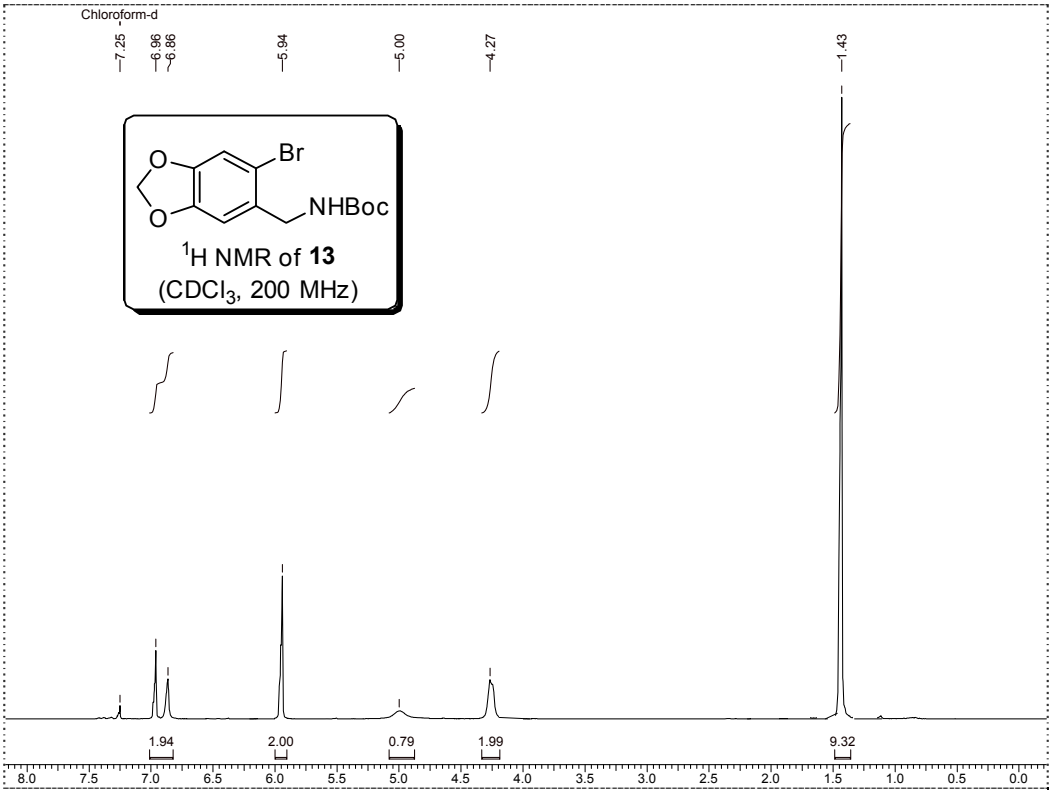
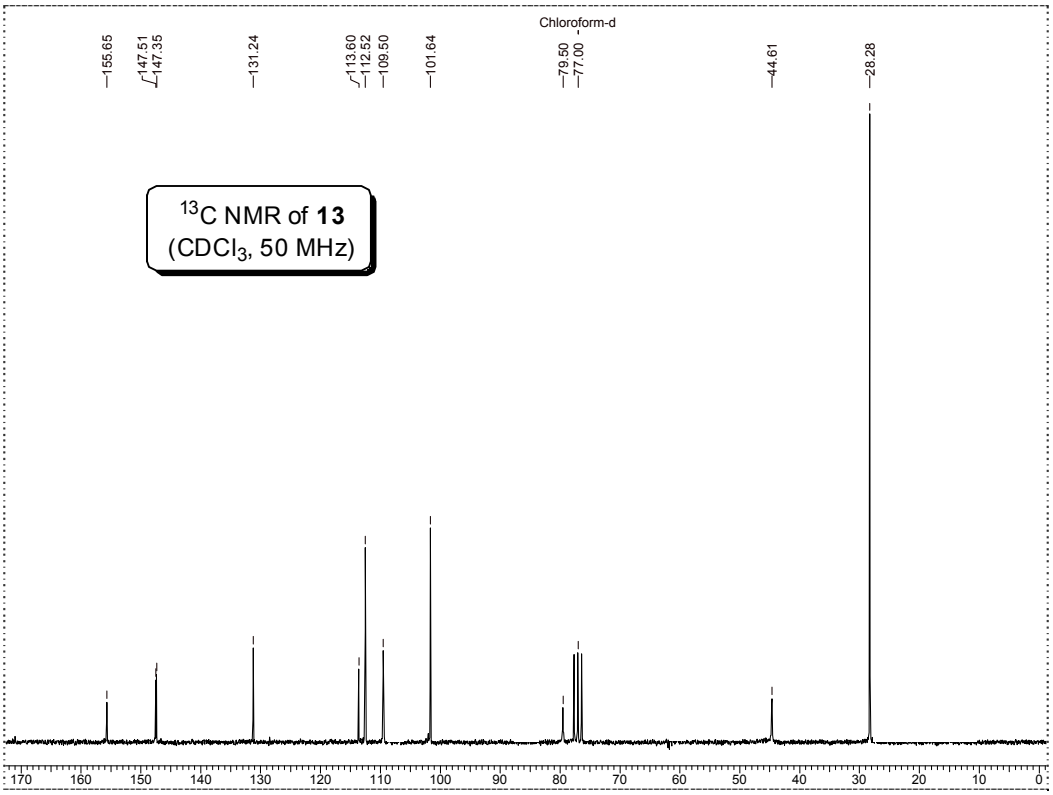
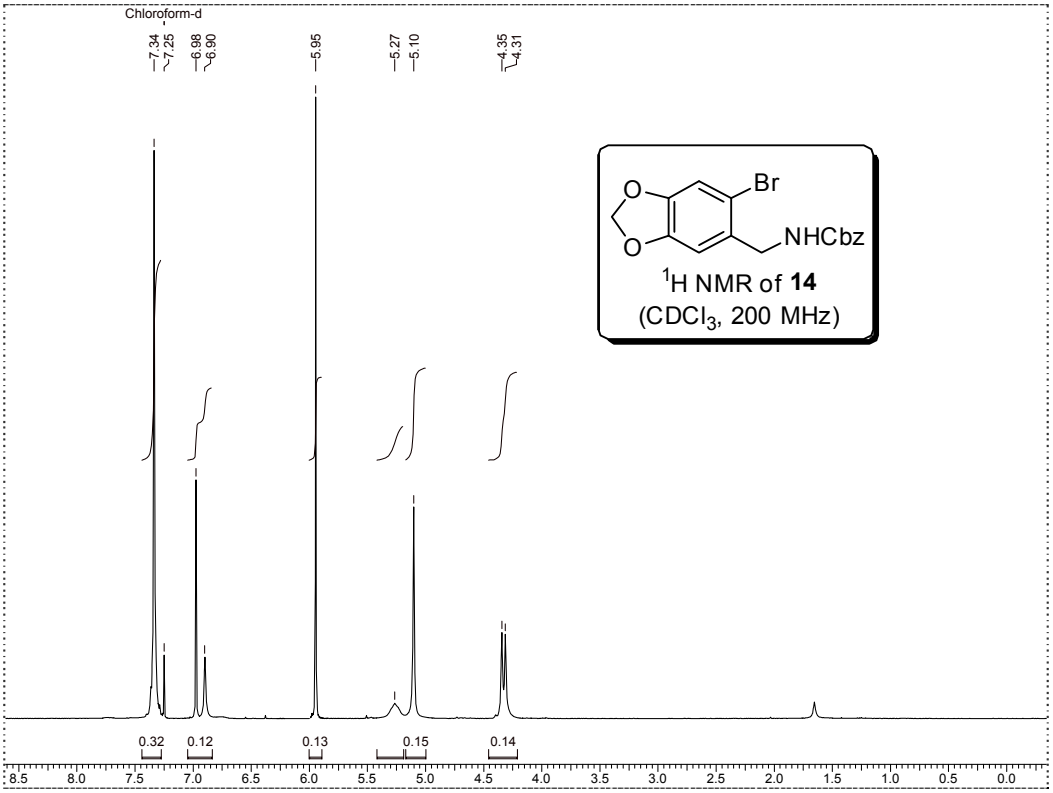
2.15. Spectra of all new compounds

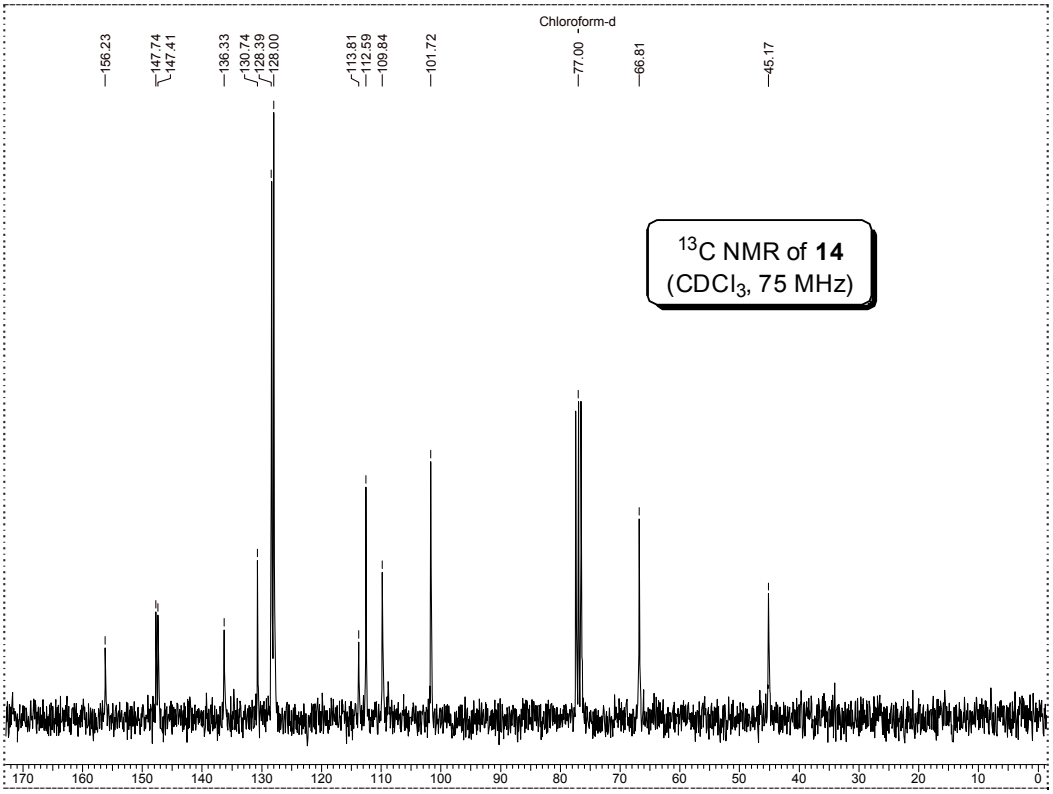
1. *tert*-Butyl (6-bromobenzo[*d*][1,3]dioxol-5-yl)methylcarbamate (13):



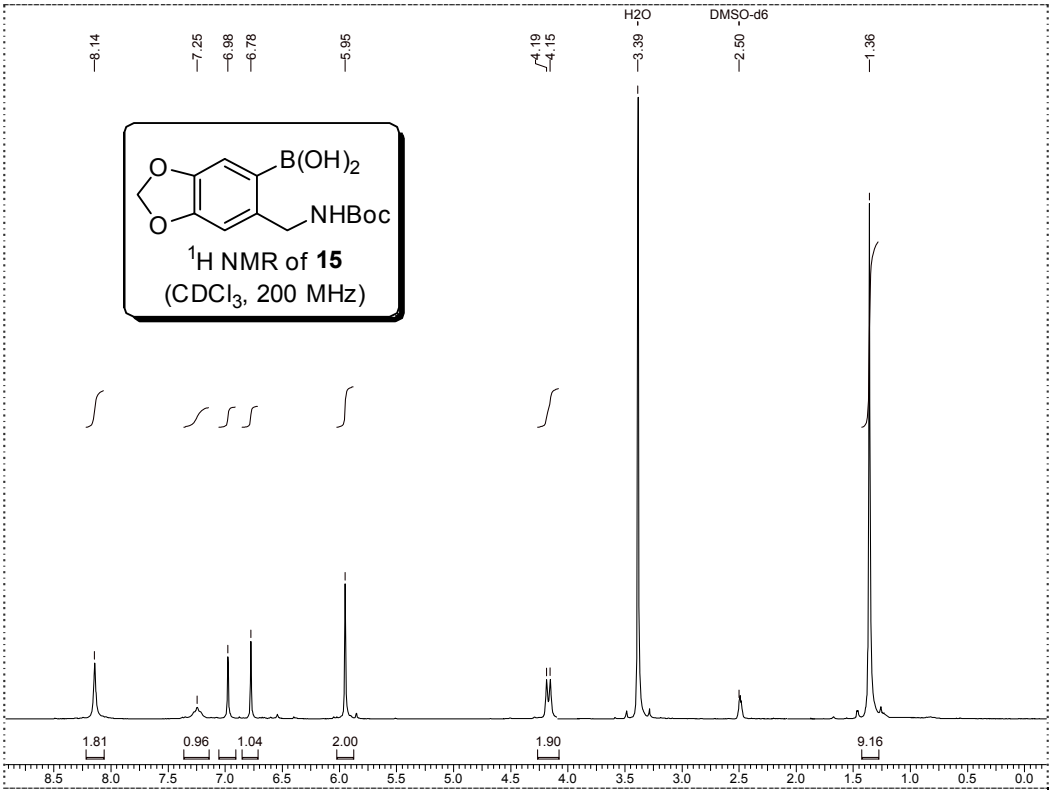


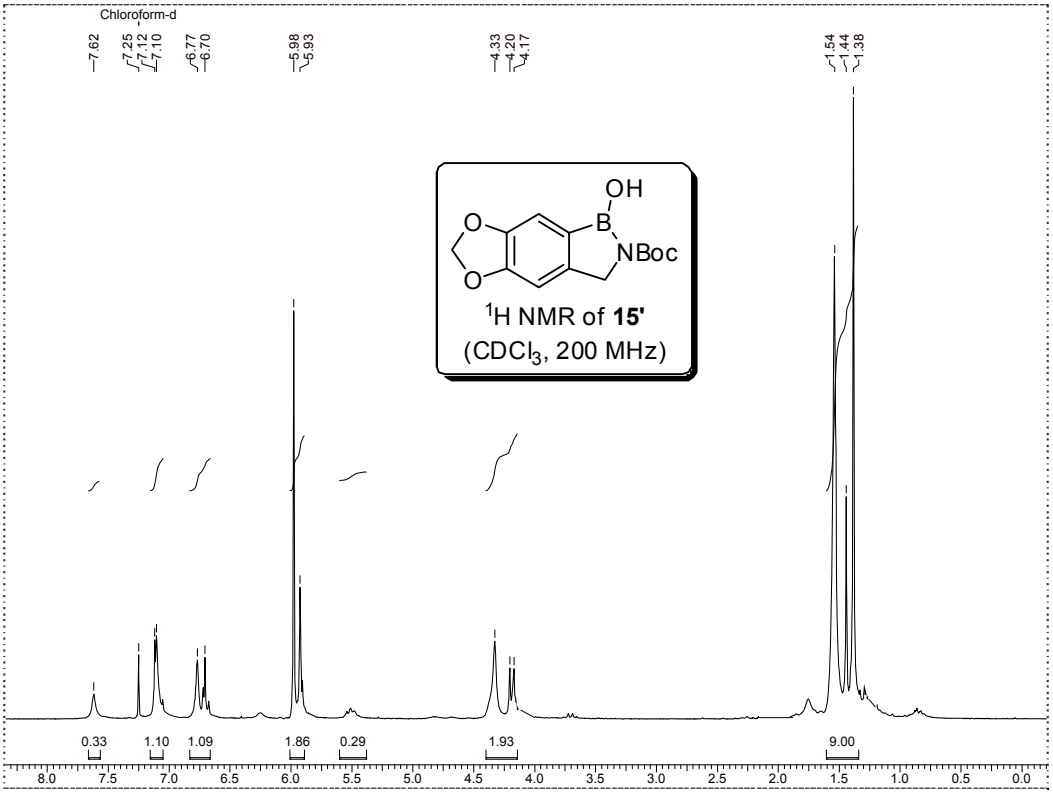
2. Benzyl (6-bromobenzo[*d*][1,3]dioxol-5-yl)methylcarbamate (14):

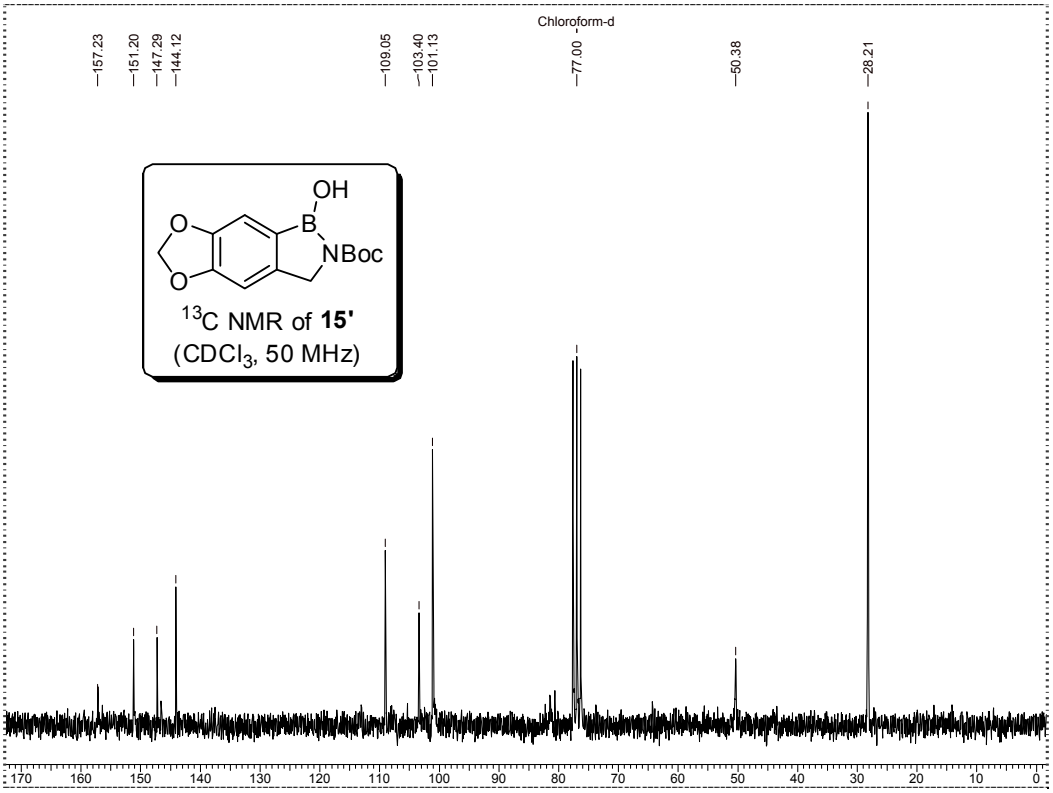


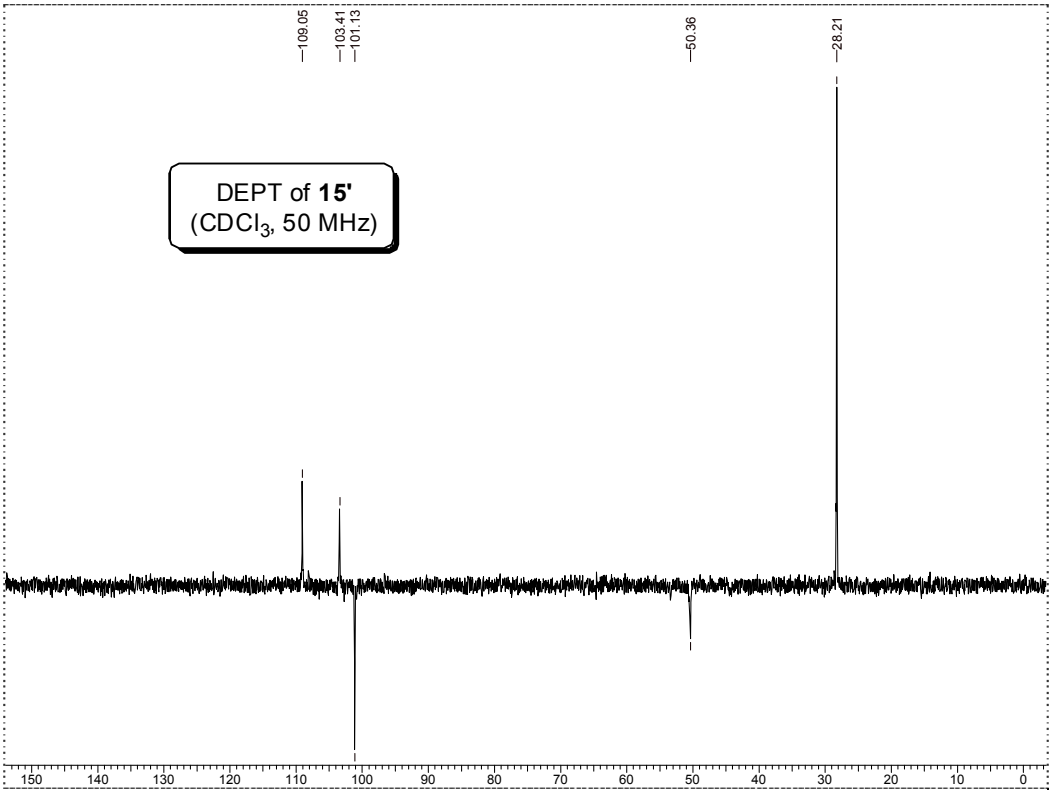


3. 6-((*tert*-Butoxycarbonylamino)methyl)benzo[*d*][1,3]dioxol-5-ylboronic acid (15):

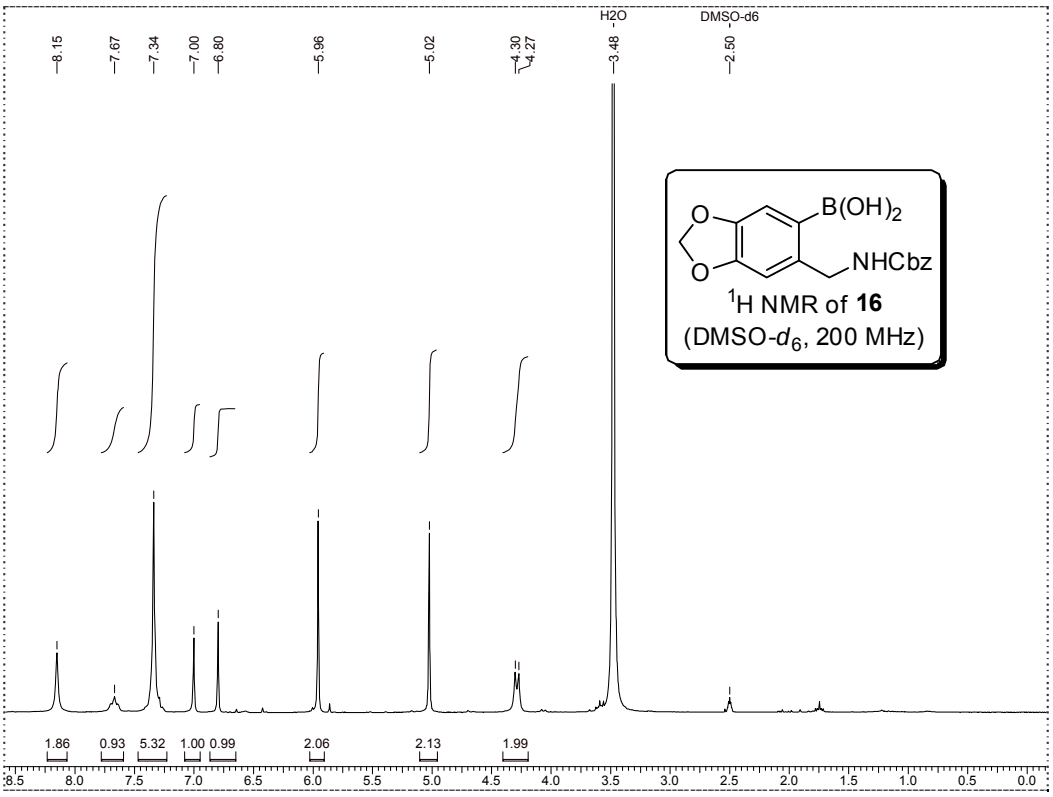


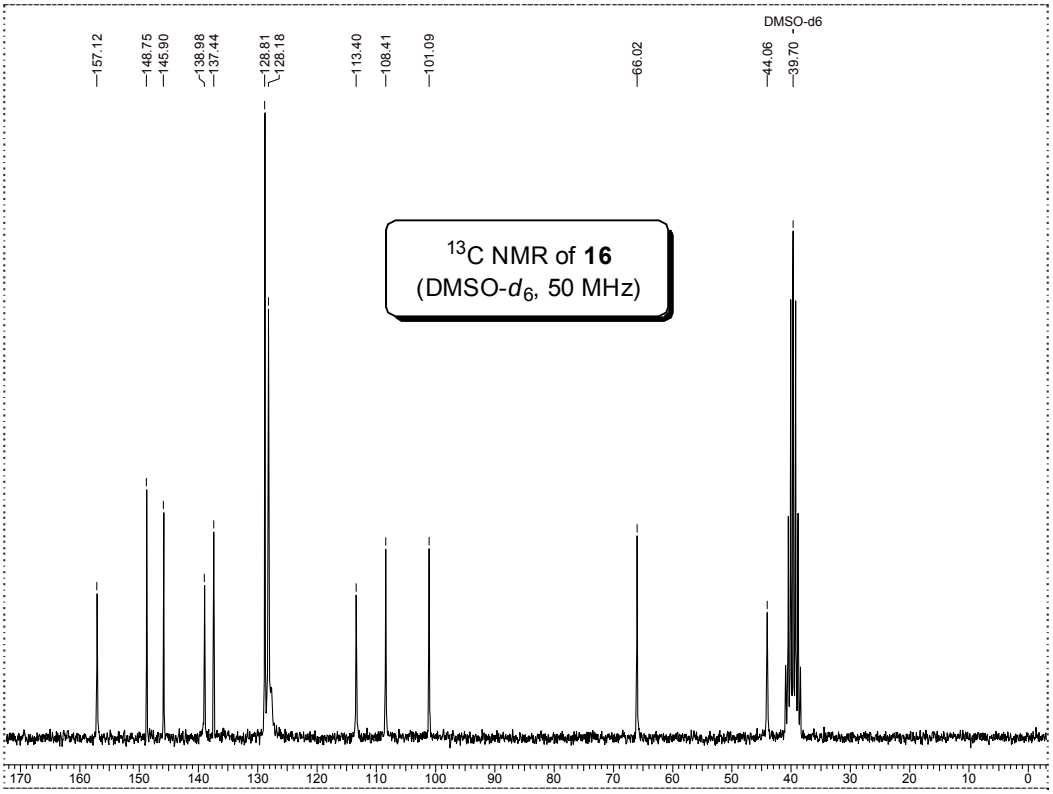



Chloroform-d
157.23
151.20
147.29
144.12
109.05
103.40
101.13
77.00
50.38
28.21
OH
B
O
O
NBoc
^{13}C NMR of **15'**
($CDCl_3$, 50 MHz)

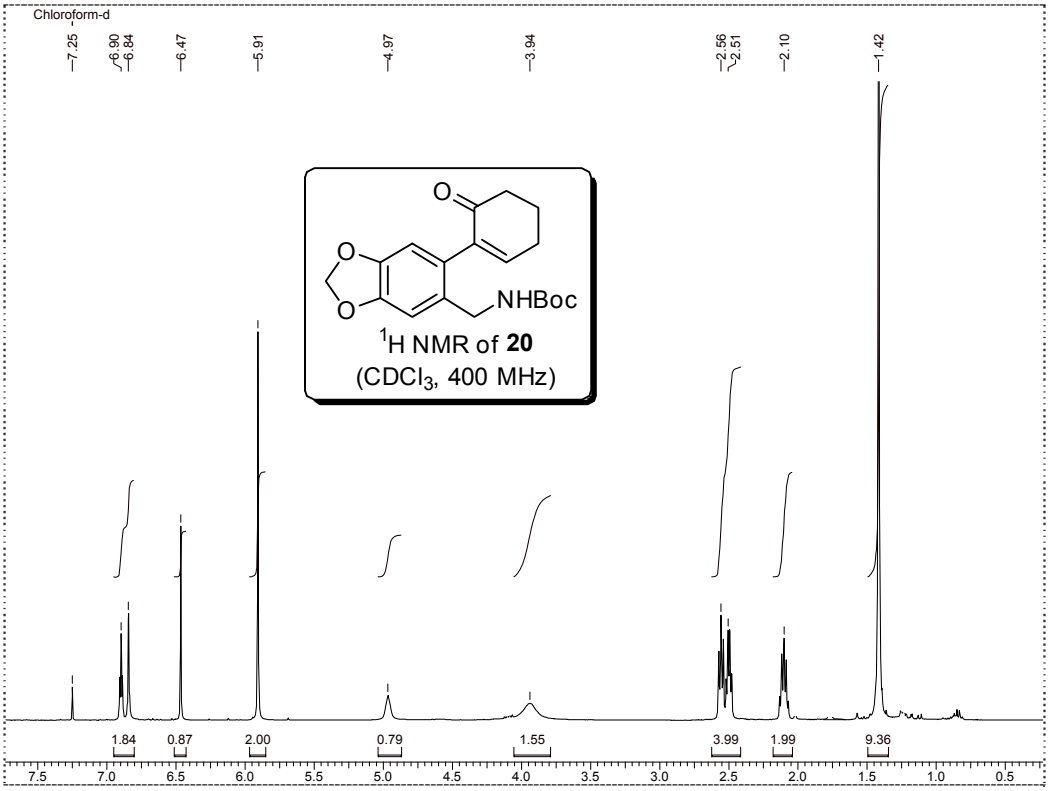

109.05
103.41
101.13
50.36
28.21
DEPT of **15'**
($CDCl_3$, 50 MHz)

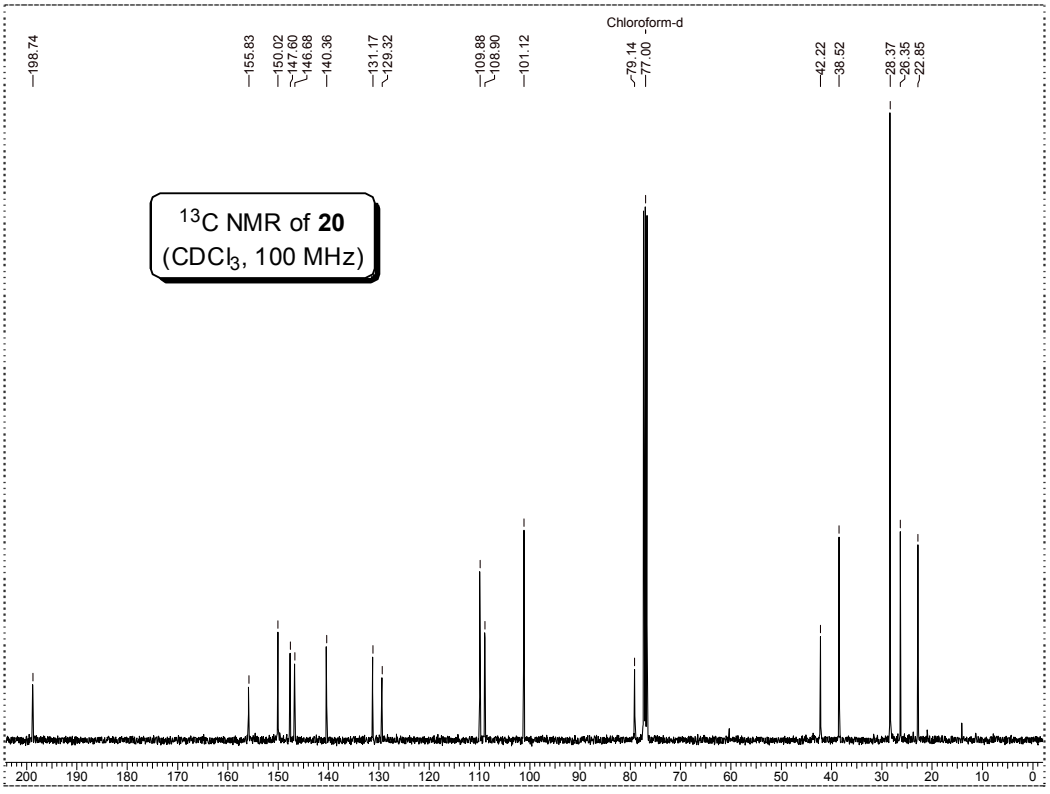
4. 6-((Benzyloxycarbonylamino)methyl)benzo[*d*][1,3]dioxol-5-ylboronic acid (16):



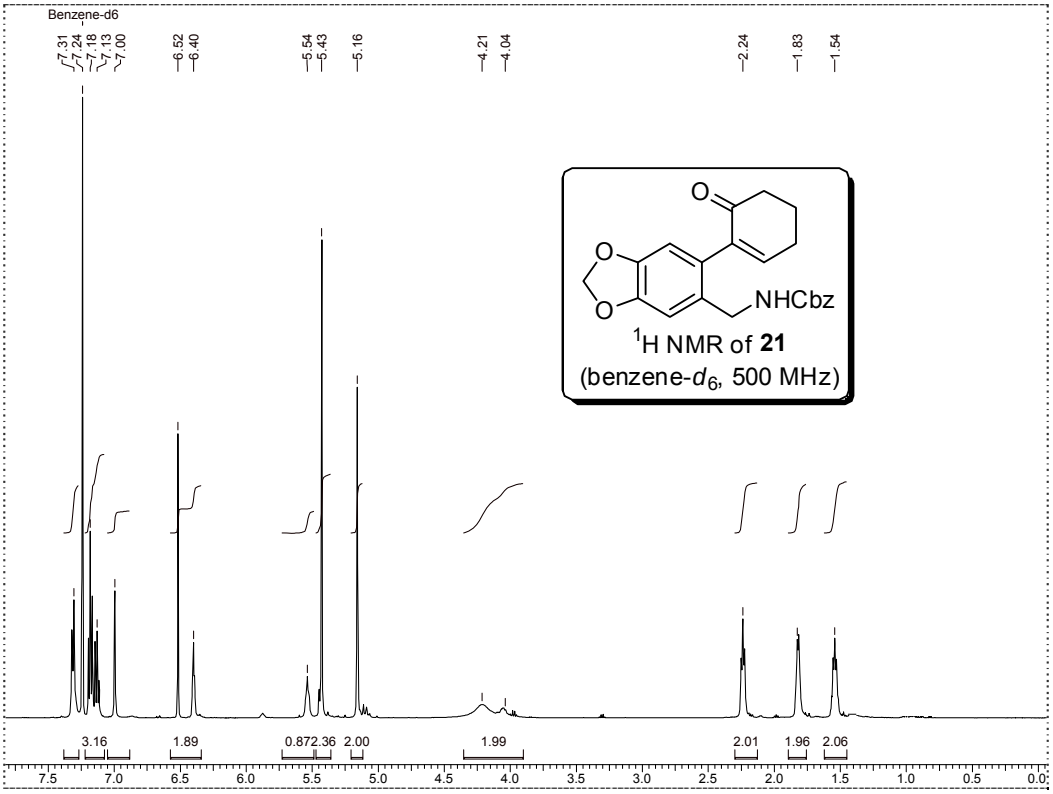


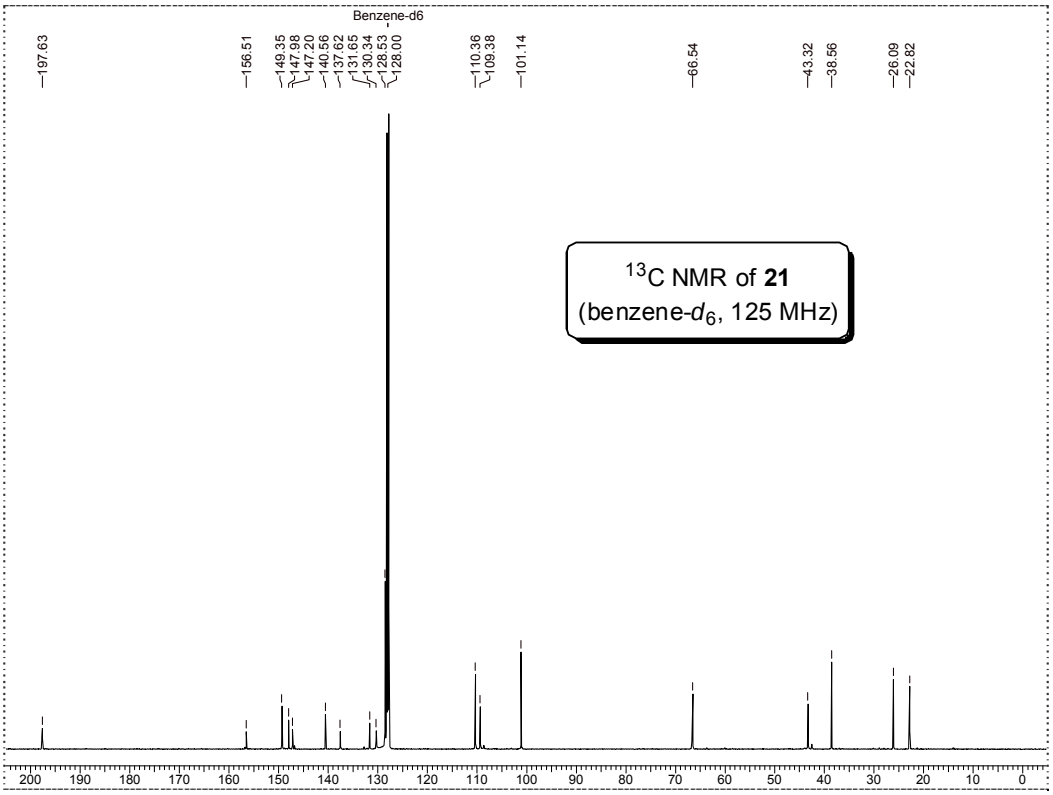
5. *tert*-Butyl (6-(6-oxocyclohex-1-enyl)benzo[*d*][1,3]dioxol-5-yl)methylcrbamate (20):



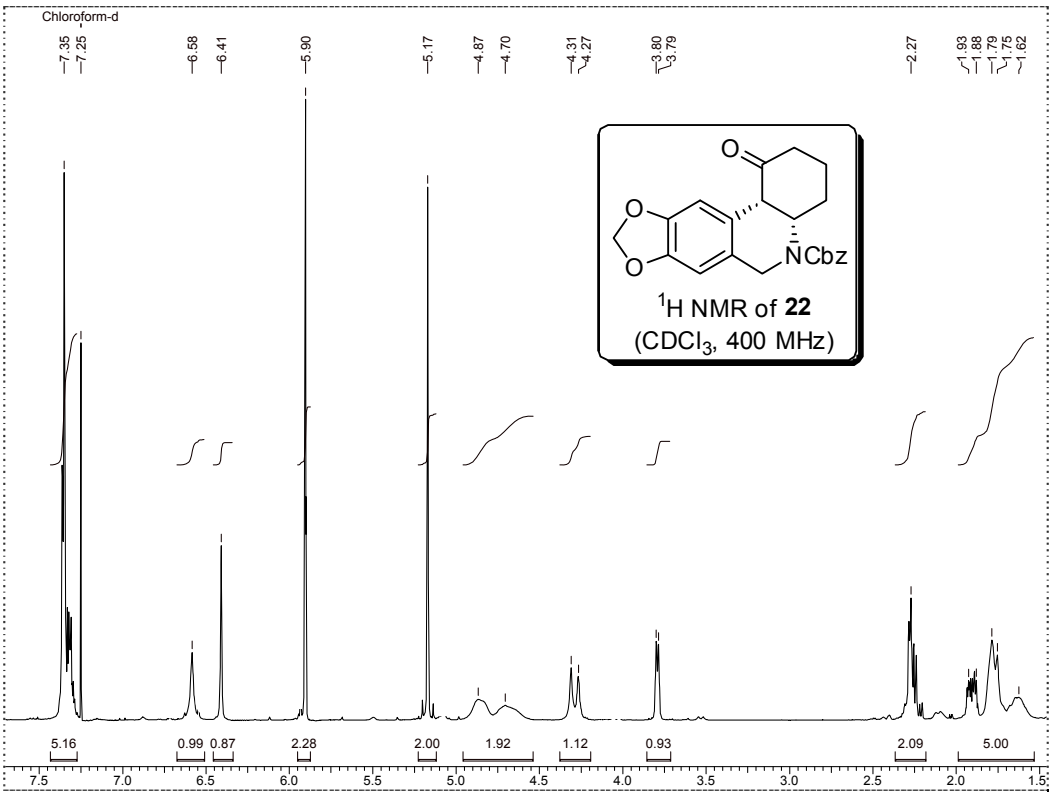


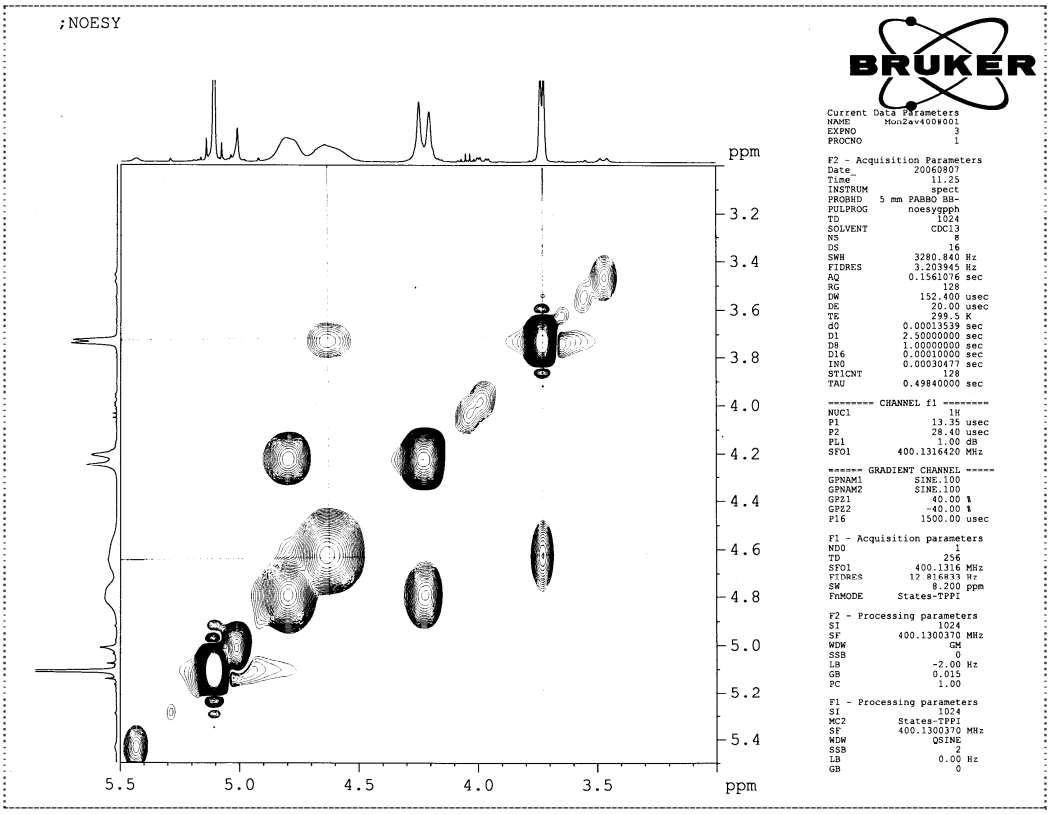
6. Benzyl (6-(6-oxocyclohex-1-enyl)benzo[*d*][1,3]dioxol-5-yl)methylcarbamate (21):

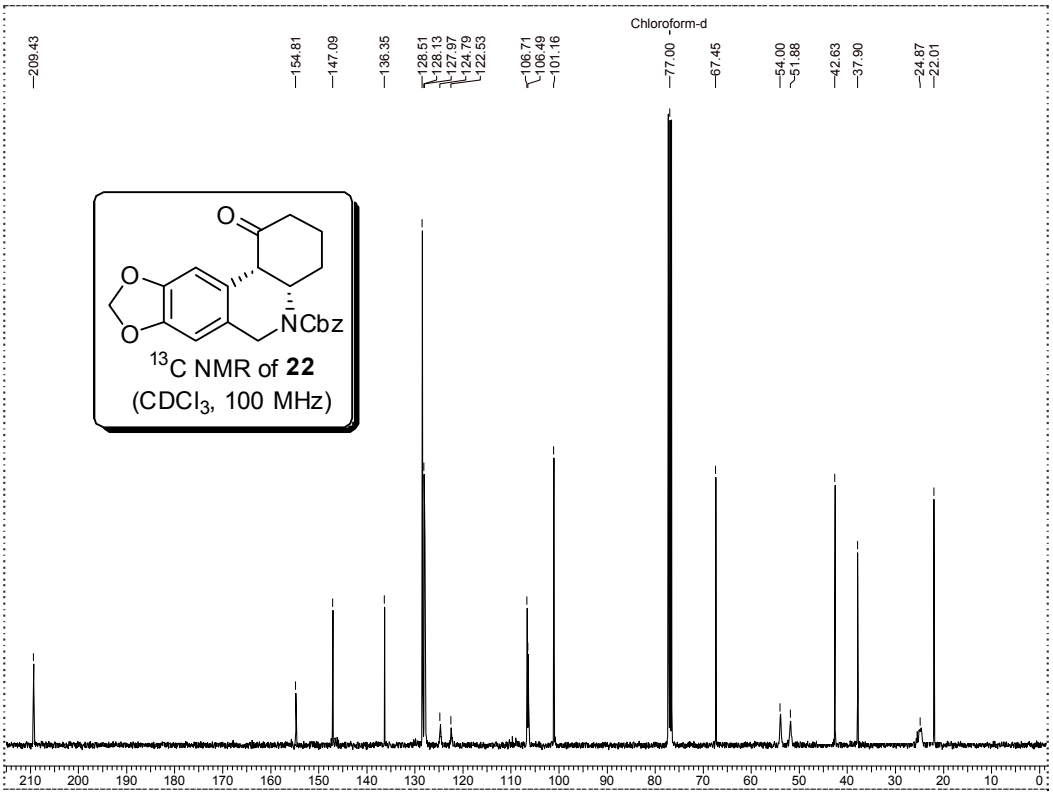


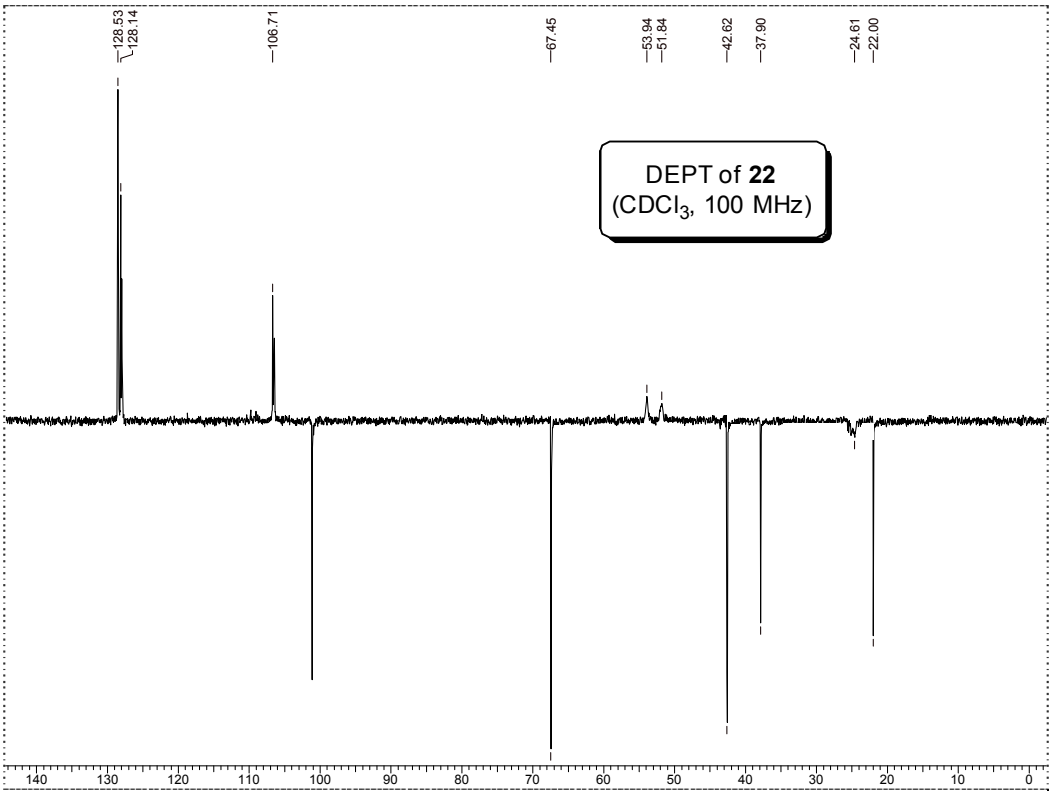


7. Benzyl 1-oxo-1,2,3,4,4a,10b-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-5(6*H*)-carboxylate (22):

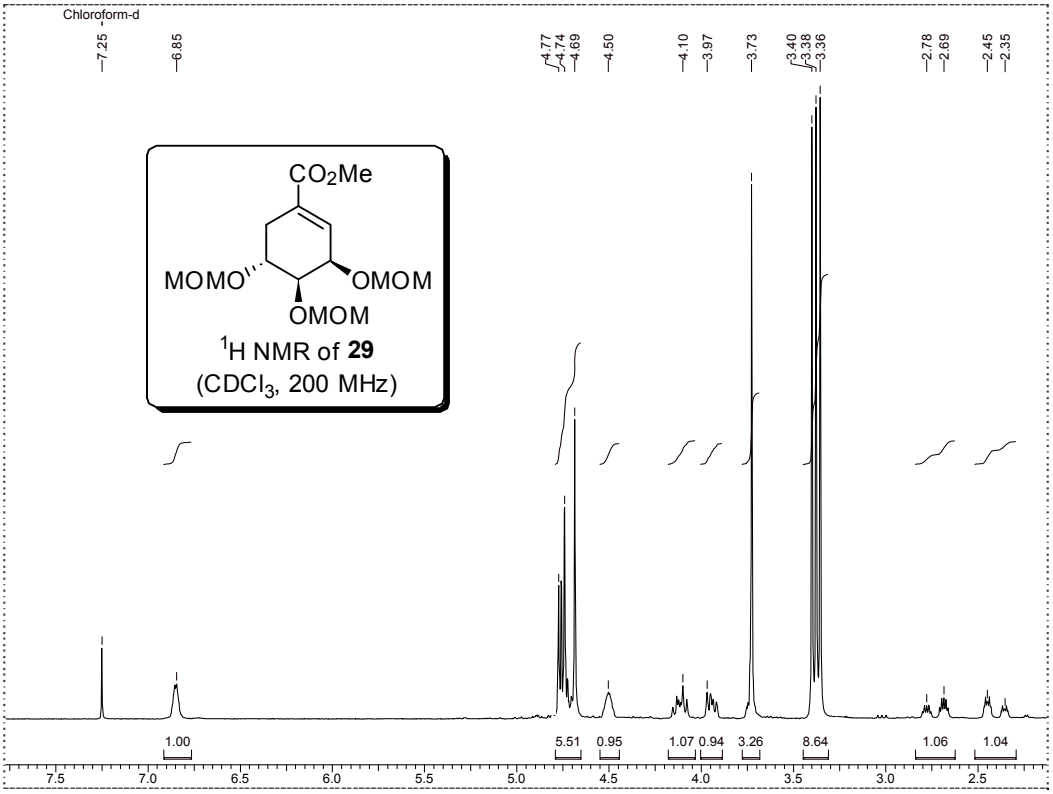


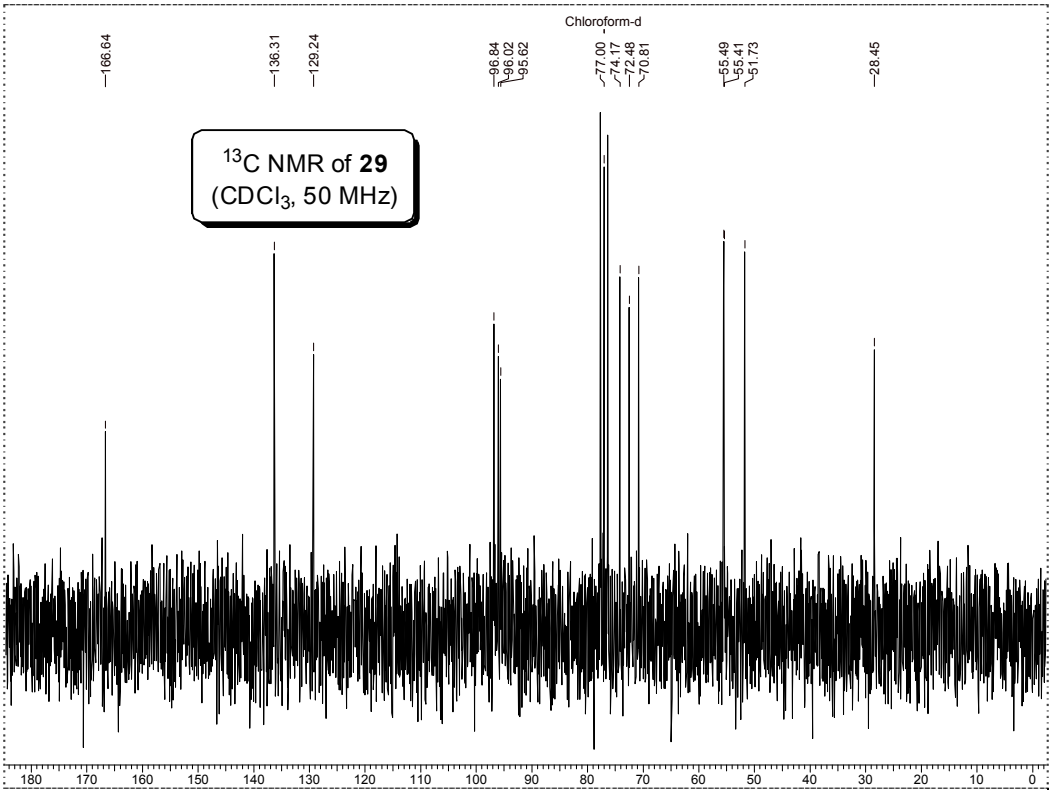



Chloroform-d
209.43
154.81
147.09
136.35
128.51
128.13
127.97
124.79
122.53
106.71
106.49
101.16
77.00
67.45
54.00
51.88
42.63
37.90
24.87
22.01
O
O
O
NCbz
^{13}C NMR of **22**
($CDCl_3$, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

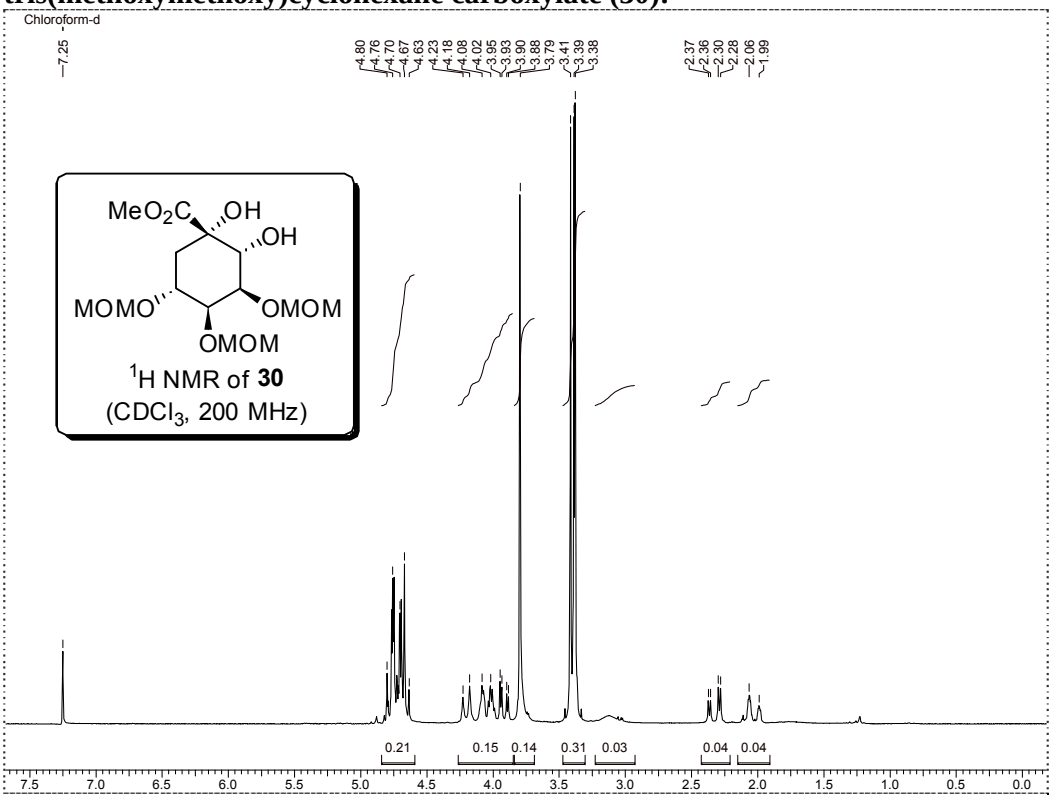

128.53
128.14
106.71
67.45
53.94
51.84
42.62
37.90
24.61
22.00
DEPT of **22**
($CDCl_3$, 100 MHz)
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

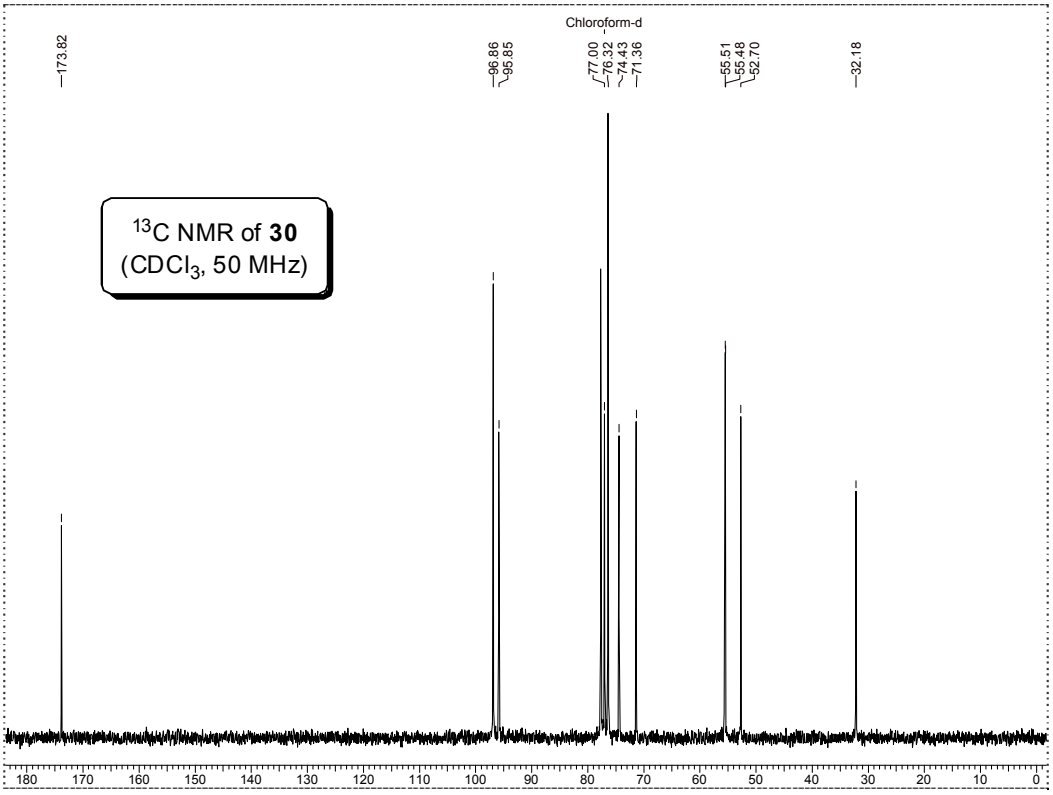
8. (3*R*,4*S*,5*R*)-Methyl 3,4,5-tris(methoxymethoxy)cyclohex-1-enecarboxylate (29):



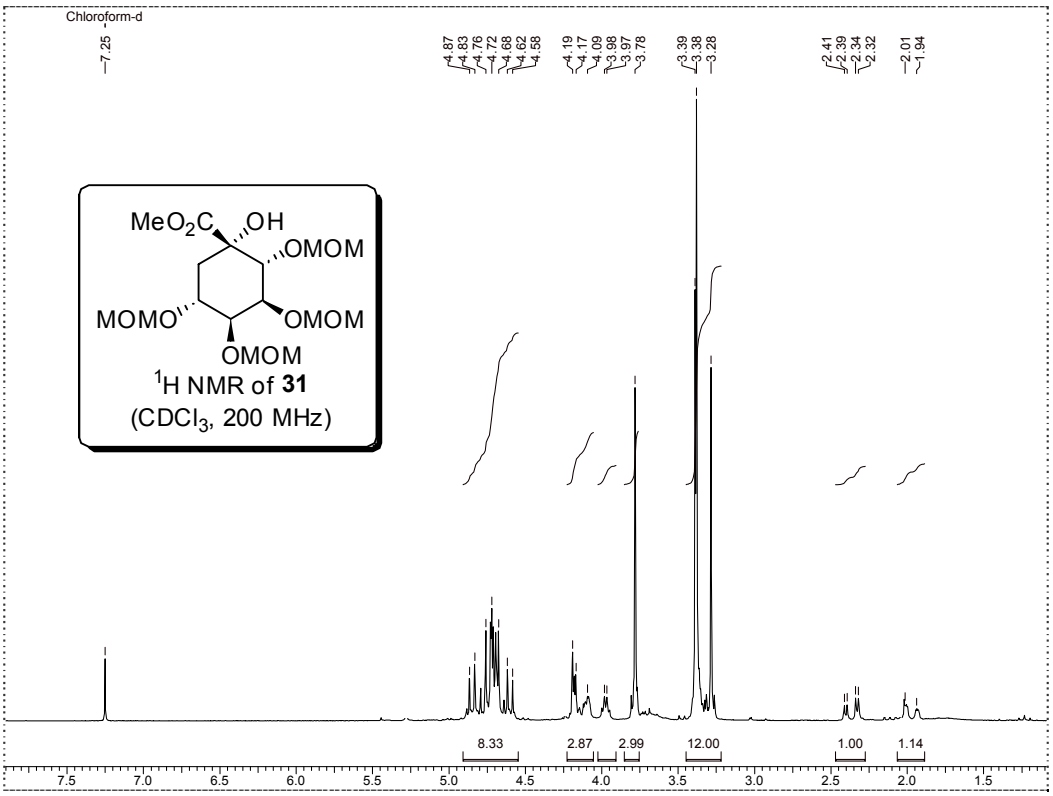


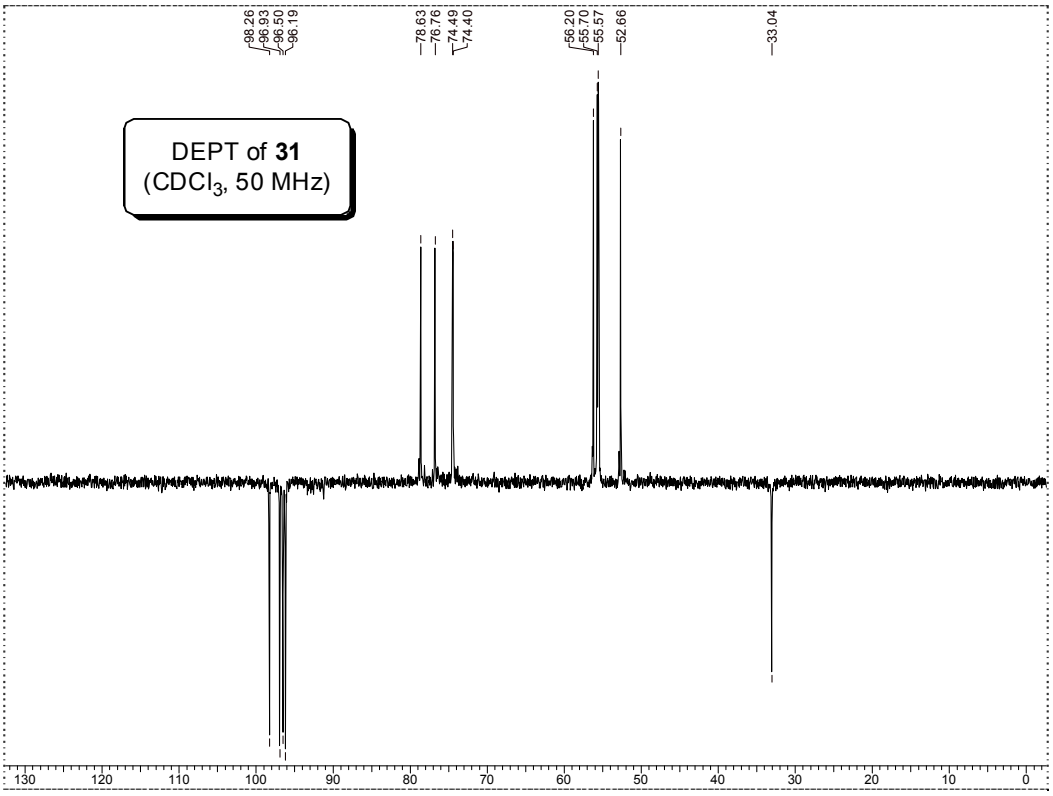
9. (1*S*,2*R*,3*R*,4*S*,5*R*)-Methyl 1,2-dihydroxy-3,4,5-tris(methoxymethoxy)cyclohexane carboxylate (30):



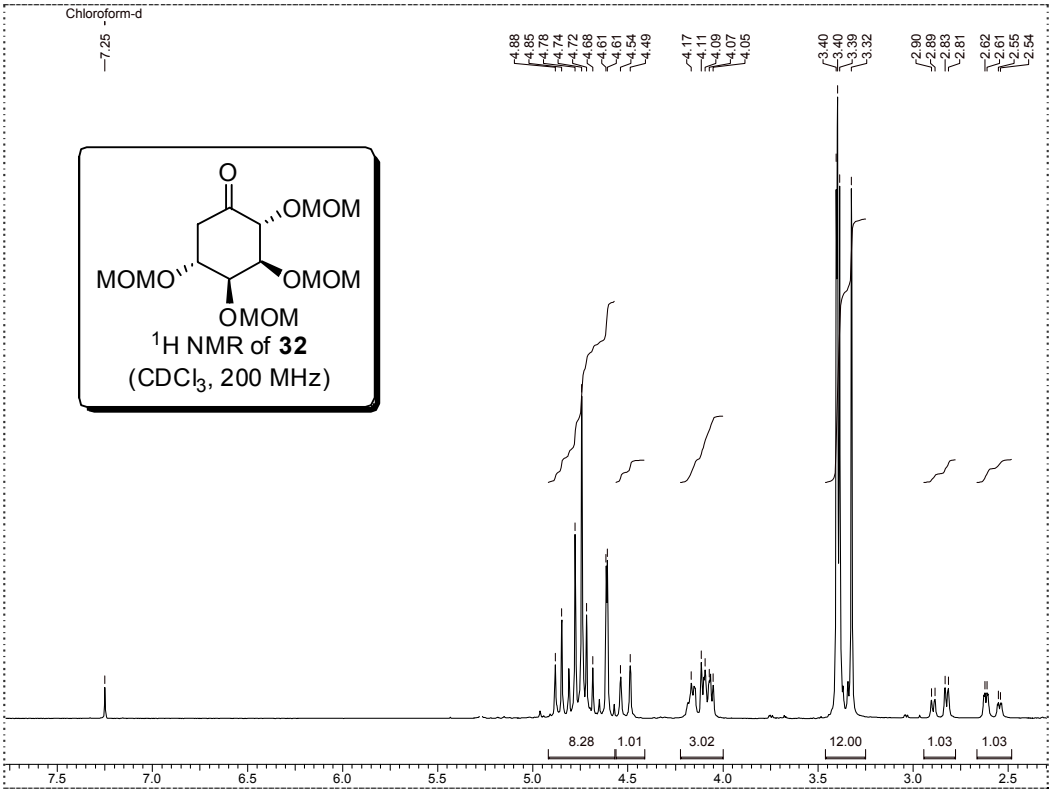


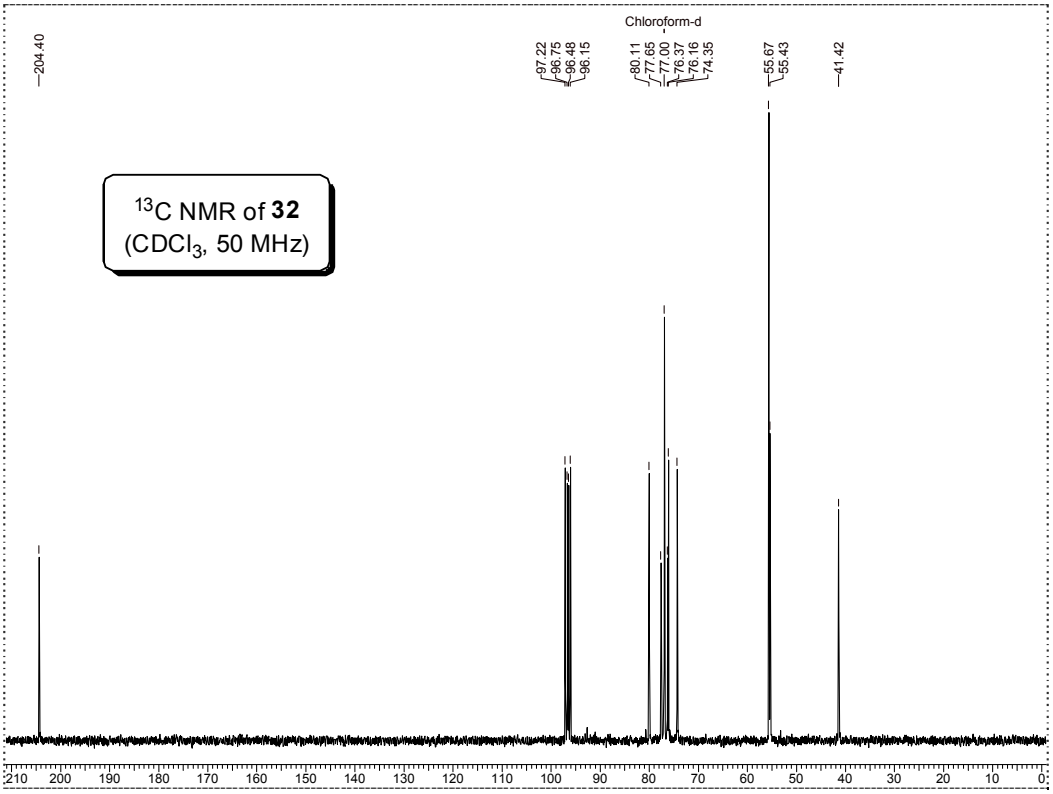
10. (1*S*,2*R*,3*S*,4*S*,5*R*)-Methyl 1-hydroxy-2,3,4,5-tetrakis(methoxymethoxy) cyclohexanecarboxylate (31):



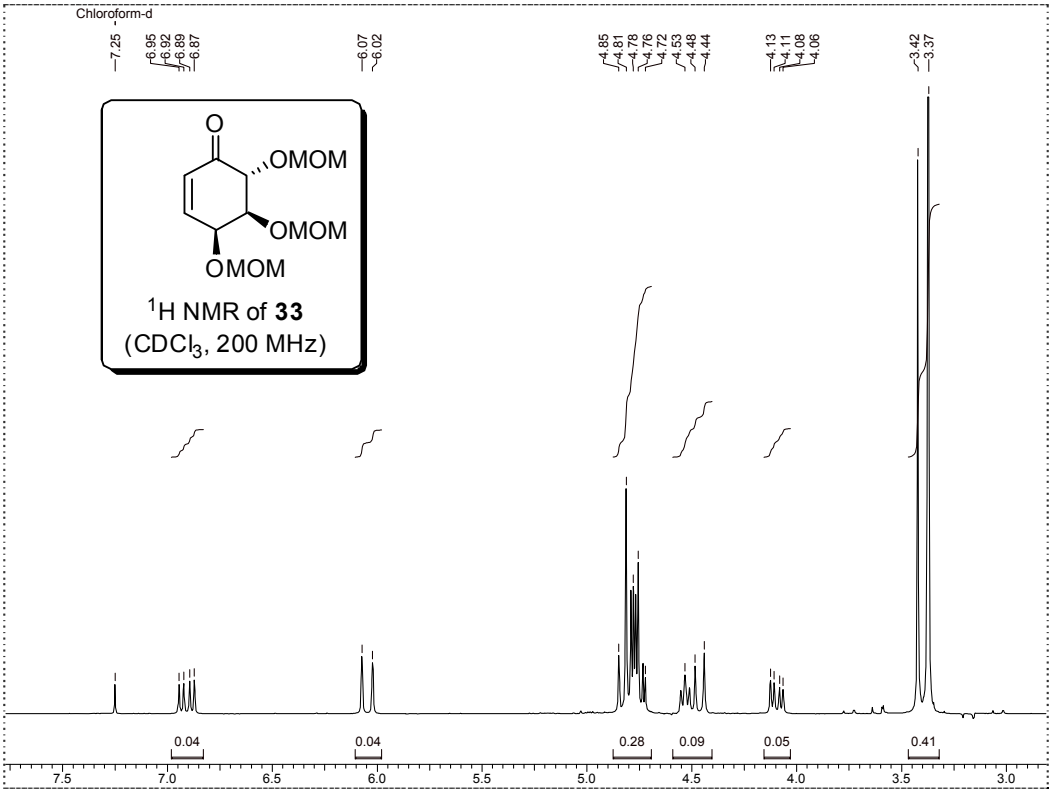


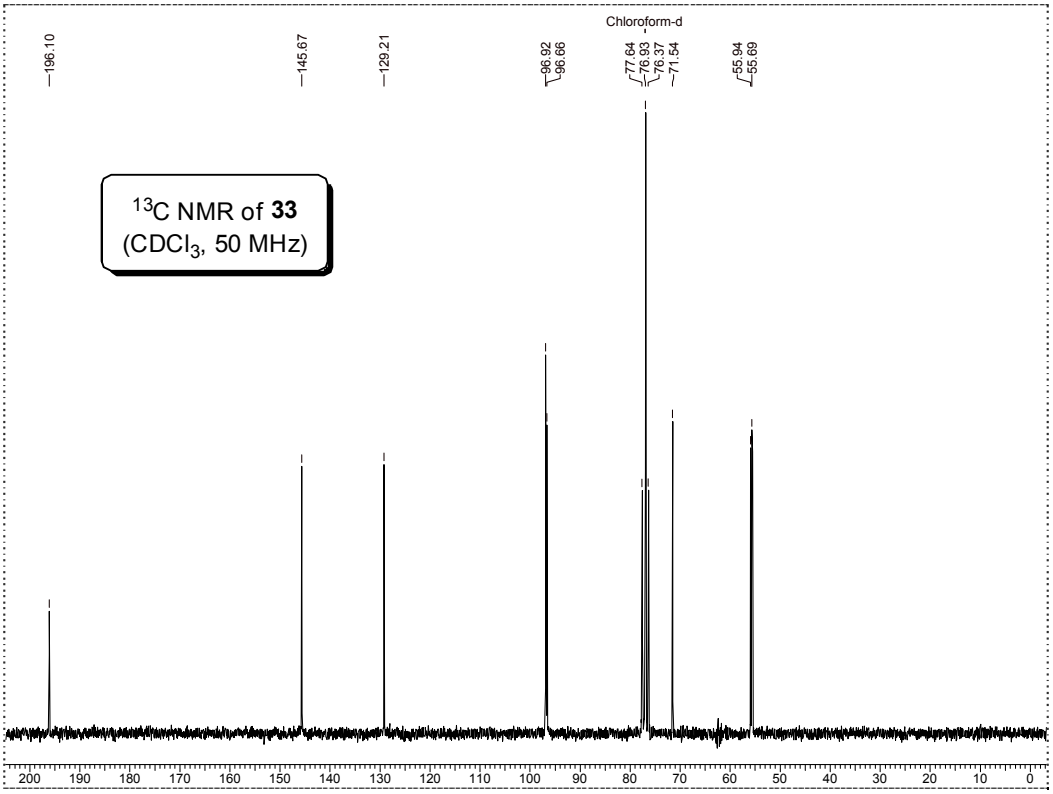
11. (2*R*,3*S*,4*S*,5*R*)-2,3,4,5-Tetrakis(methoxymethoxy)cyclohexanone (32):



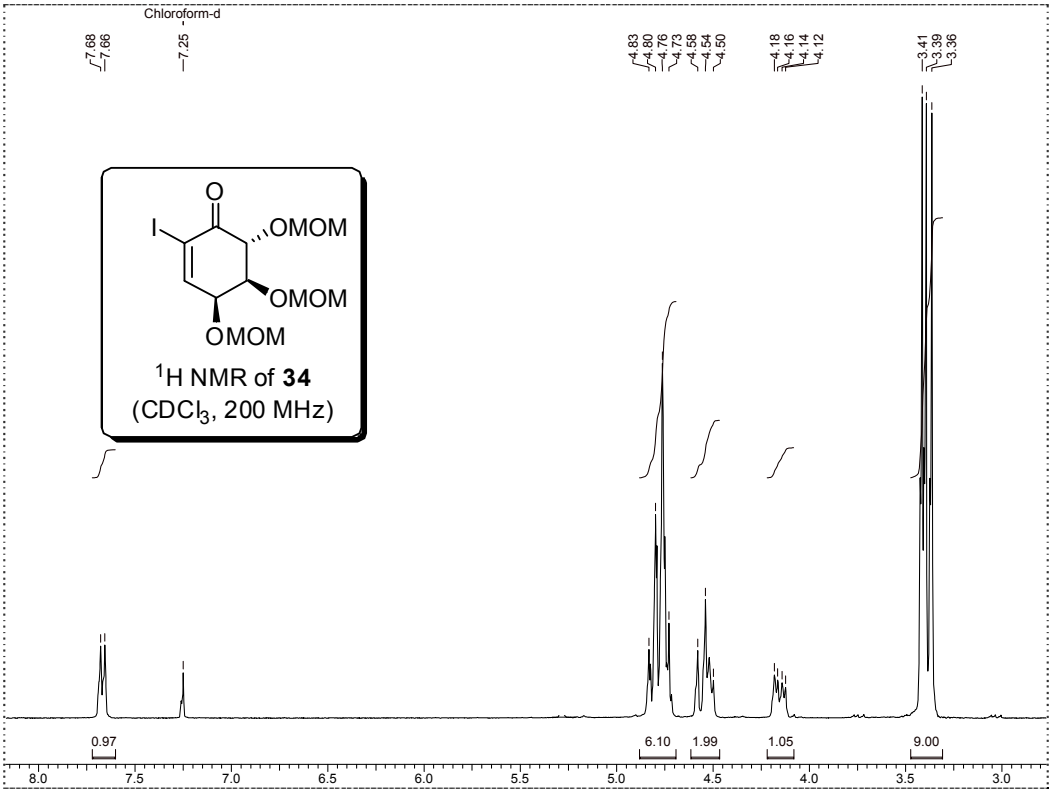


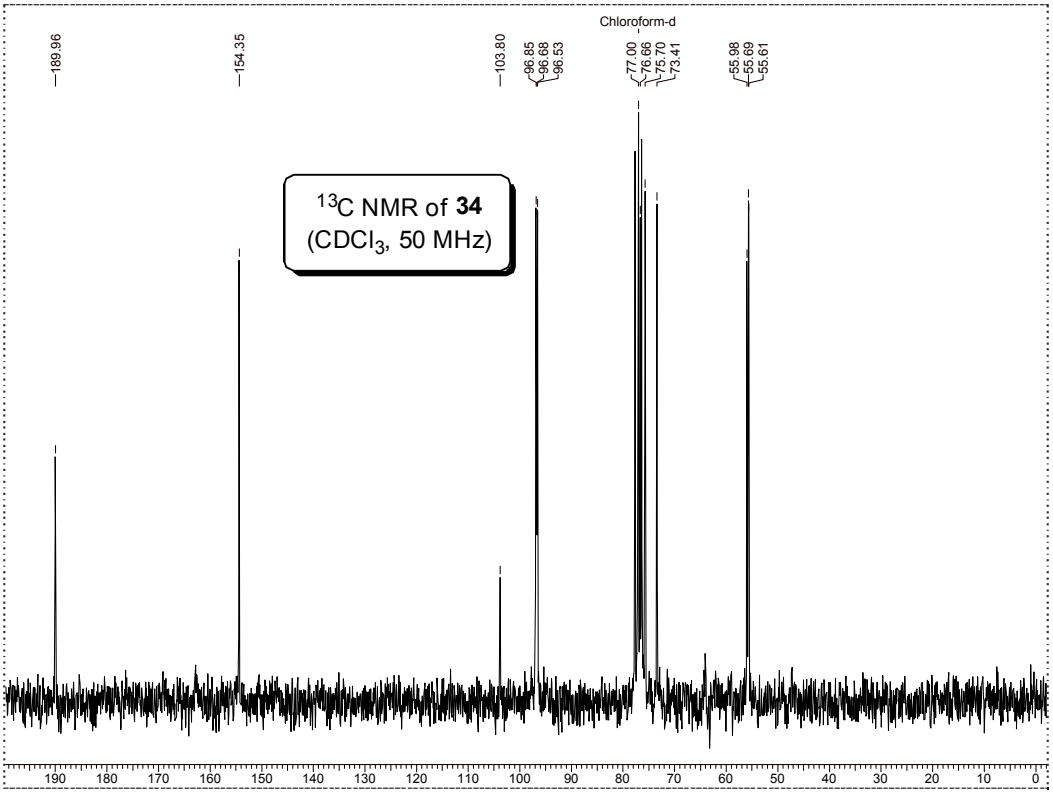
12. (4*S*,5*S*,6*R*)-4,5,6-Tris(methoxymethoxy)cyclohex-2-enone (33):



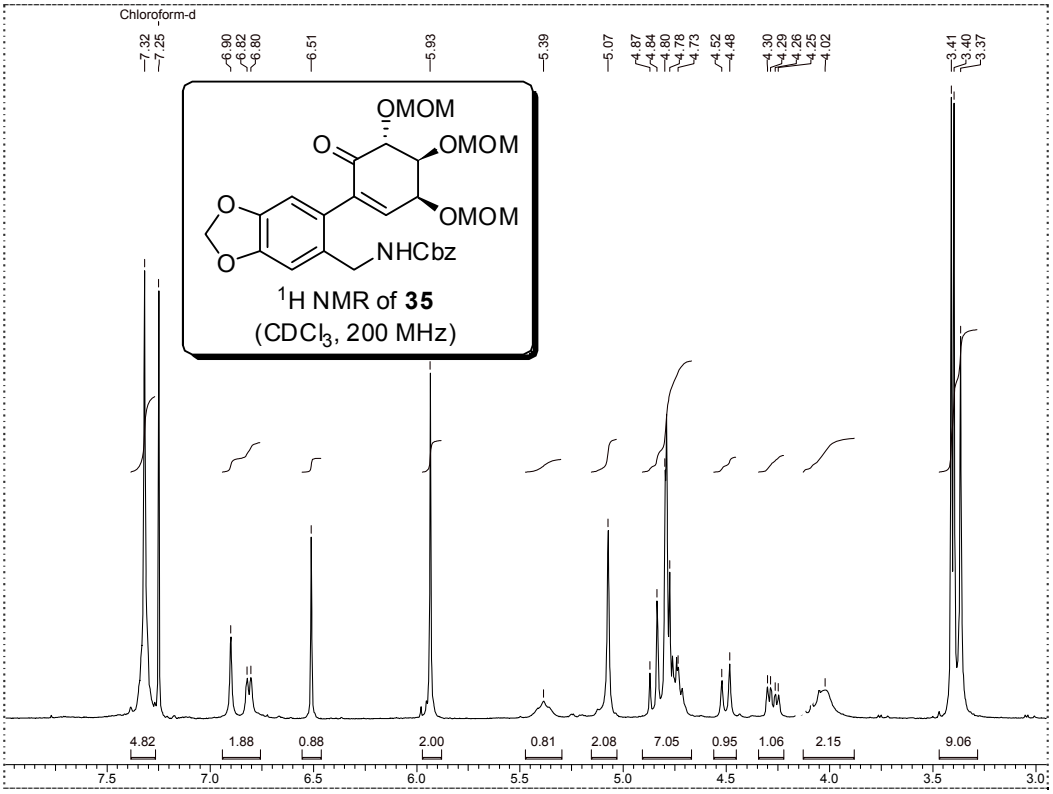


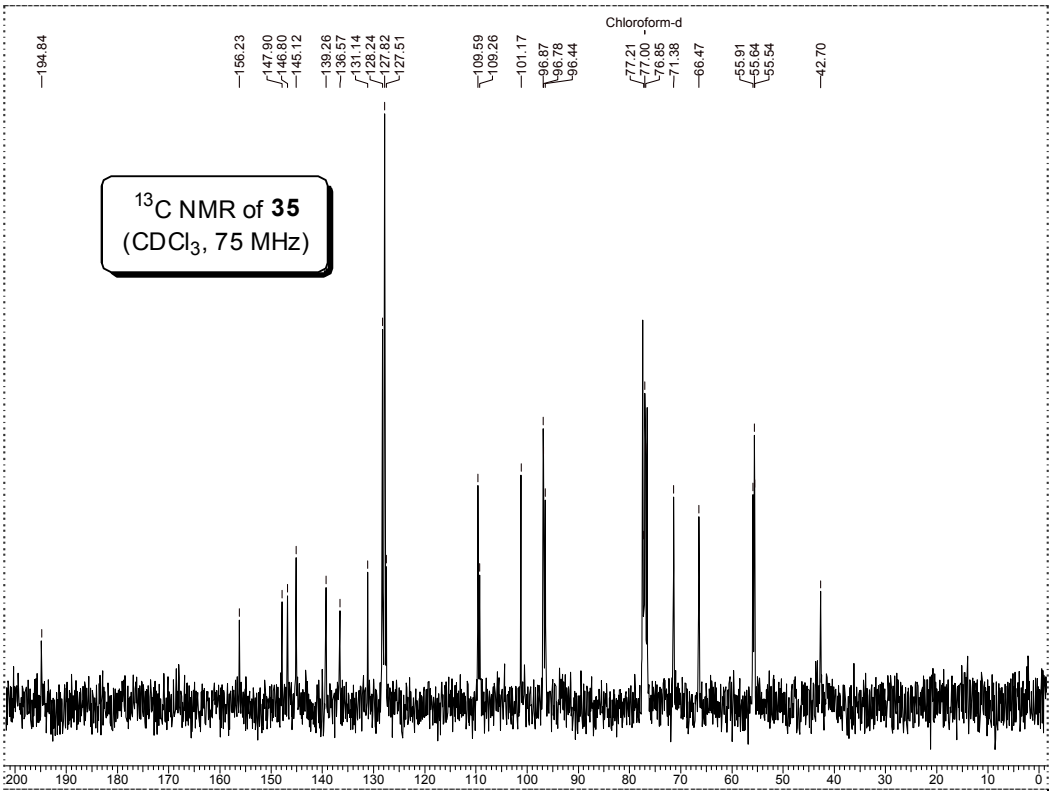
13. (4*S*,5*S*,6*R*)-2-Iodo-4,5,6-tris(methoxymethoxy)cyclohex-2-enone (34):

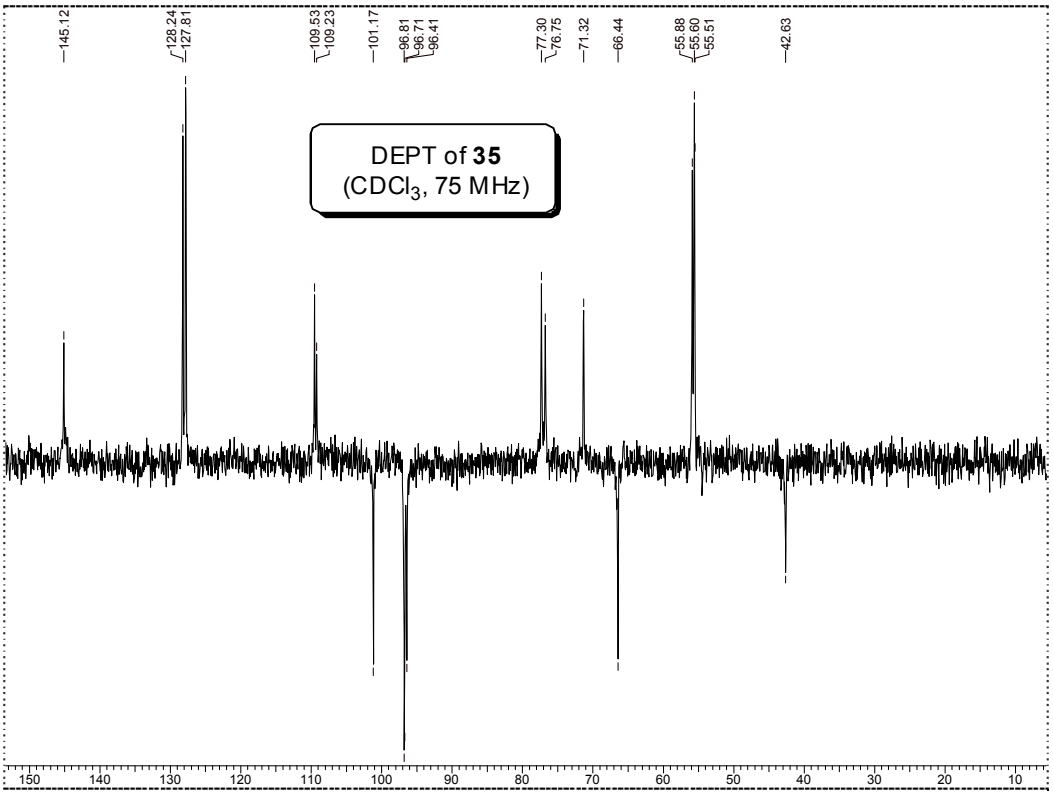




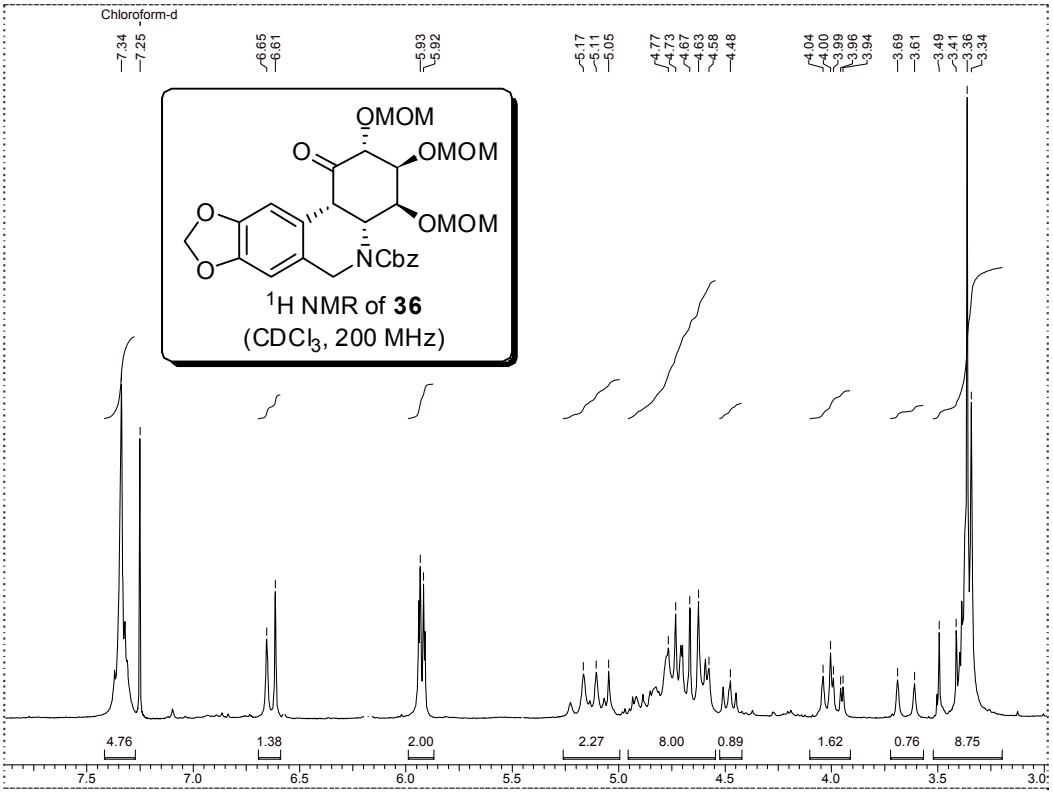
14. Benzyl (6-((3*S*,4*S*,5*R*)-3,4,5-tris(methoxymethoxy)-6-oxocyclohex-1-enyl)benzo[*d*] [1,3]dioxol-5-yl)methylcarbamate (35):

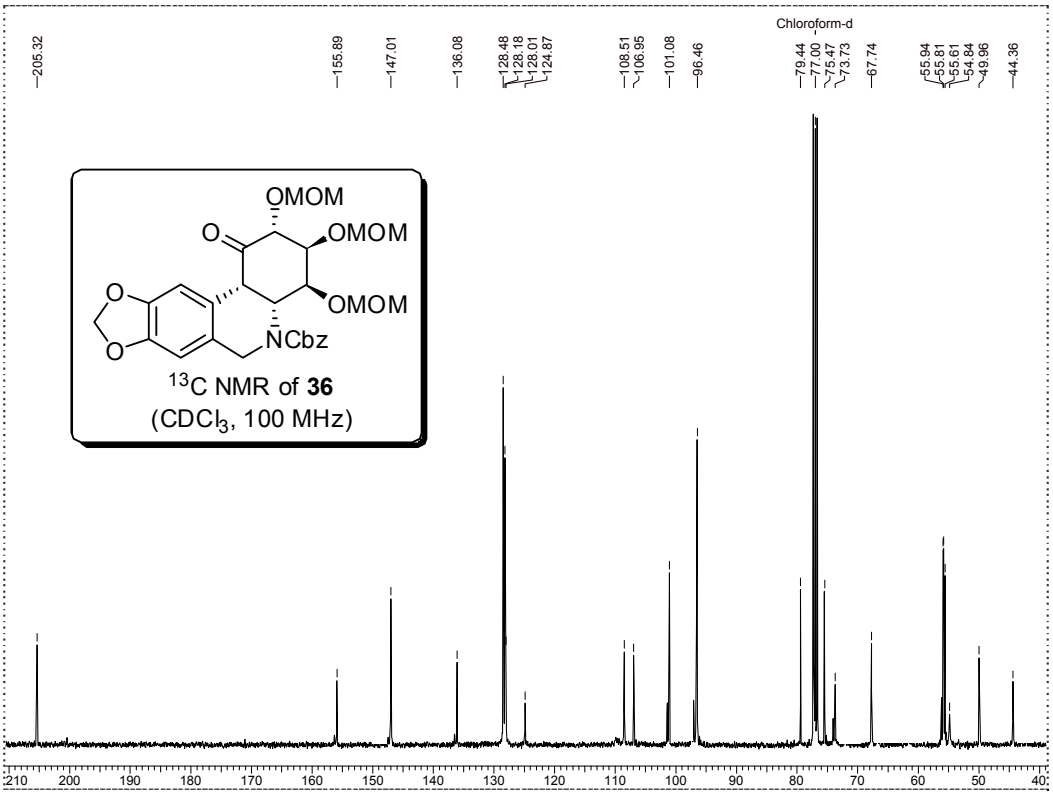


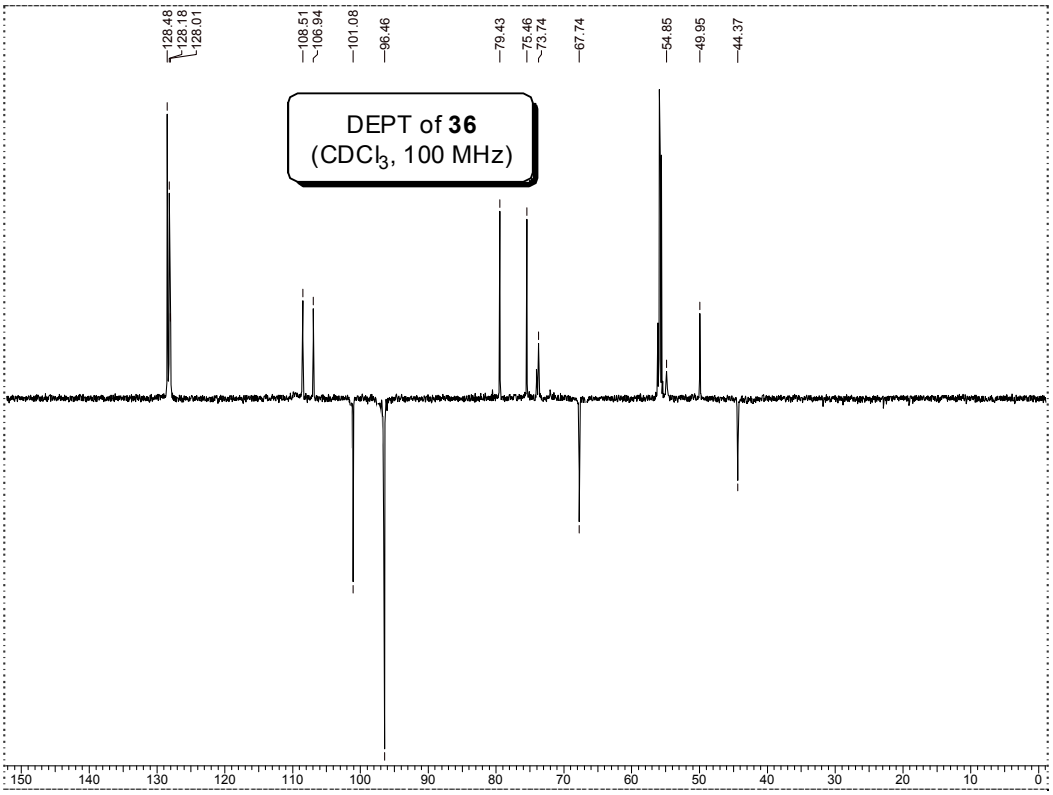




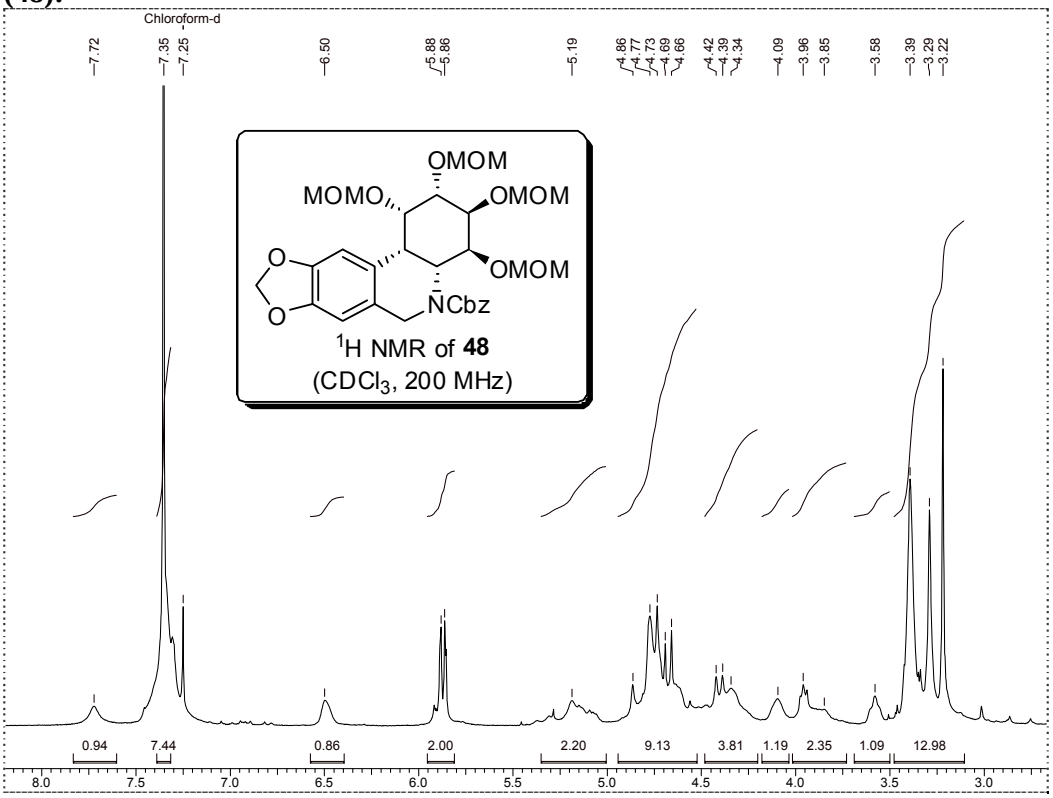
15. (2*R*,3*S*,4*S*,4a*R*,10b*S*)-Benzyl 2,3,4-tris(methoxymethoxy)-1-oxo-1,2,3,4,4a,10b-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-5(6*H*)-carboxylate (36):

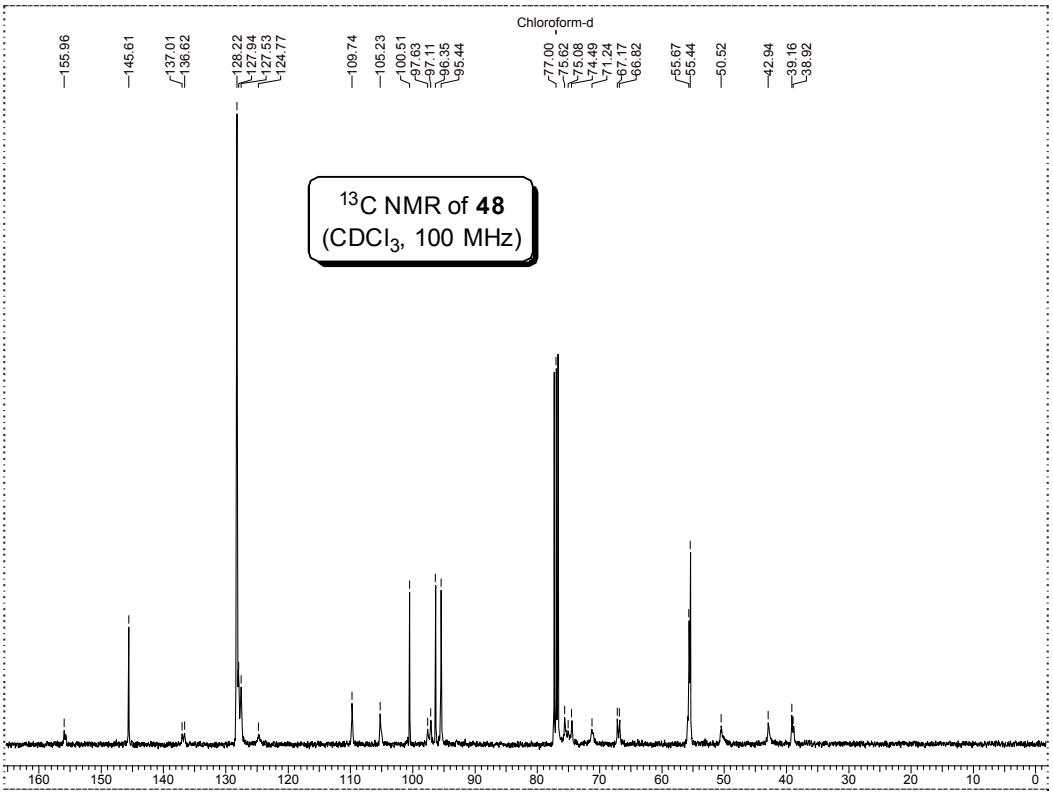



Chloroform-d
205.32
155.89
147.01
136.08
128.48
128.18
128.01
124.87
108.51
106.95
101.08
96.46
79.44
77.00
75.47
73.73
67.74
55.94
55.81
55.61
54.84
49.96
44.36
OMOM
O
OMOM
O
OMOM
O
NCbz
^{13}C NMR of **36**
($CDCl_3$, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40

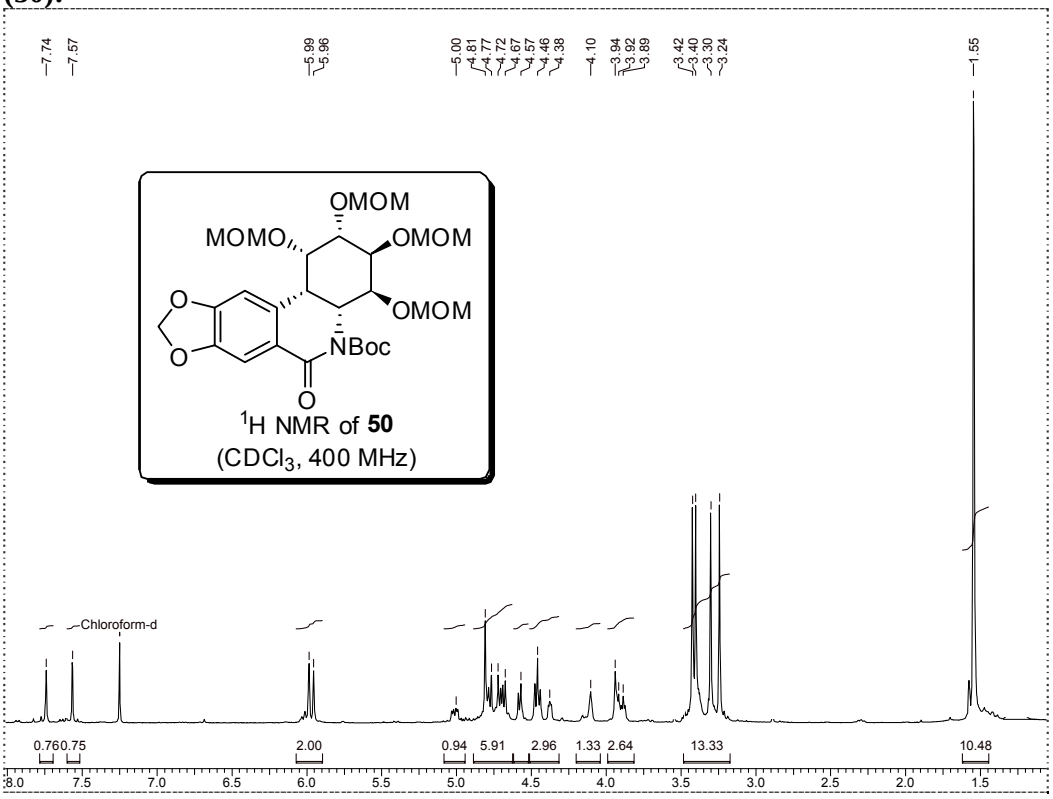

128.48
128.18
128.01
108.51
106.94
101.08
96.46
79.43
75.46
73.74
67.74
54.85
49.95
44.37
DEPT of **36**
($CDCl_3$, 100 MHz)
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

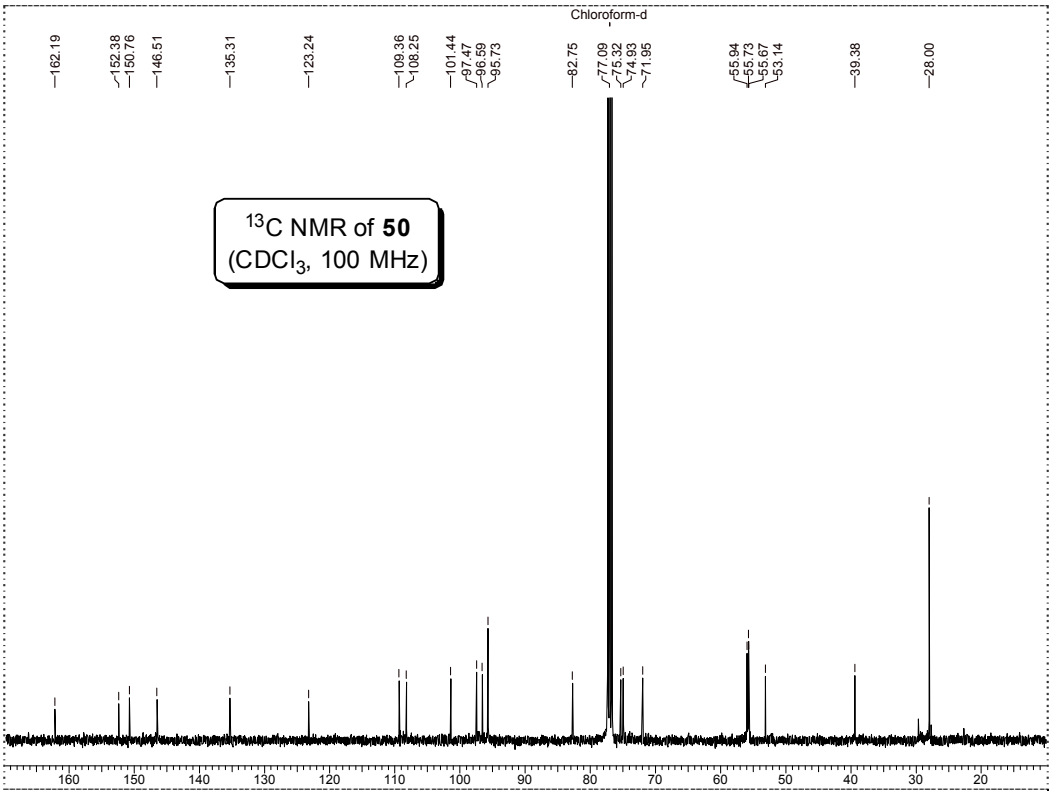
16. (1*S*,2*S*,3*S*,4*S*,4a*R*,10b*S*)-Benzyl 1,2,3,4-tetrakis(methoxymethoxy)-1,2,3,4,4a,10b-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-5(6*H*)-carboxylate (48):



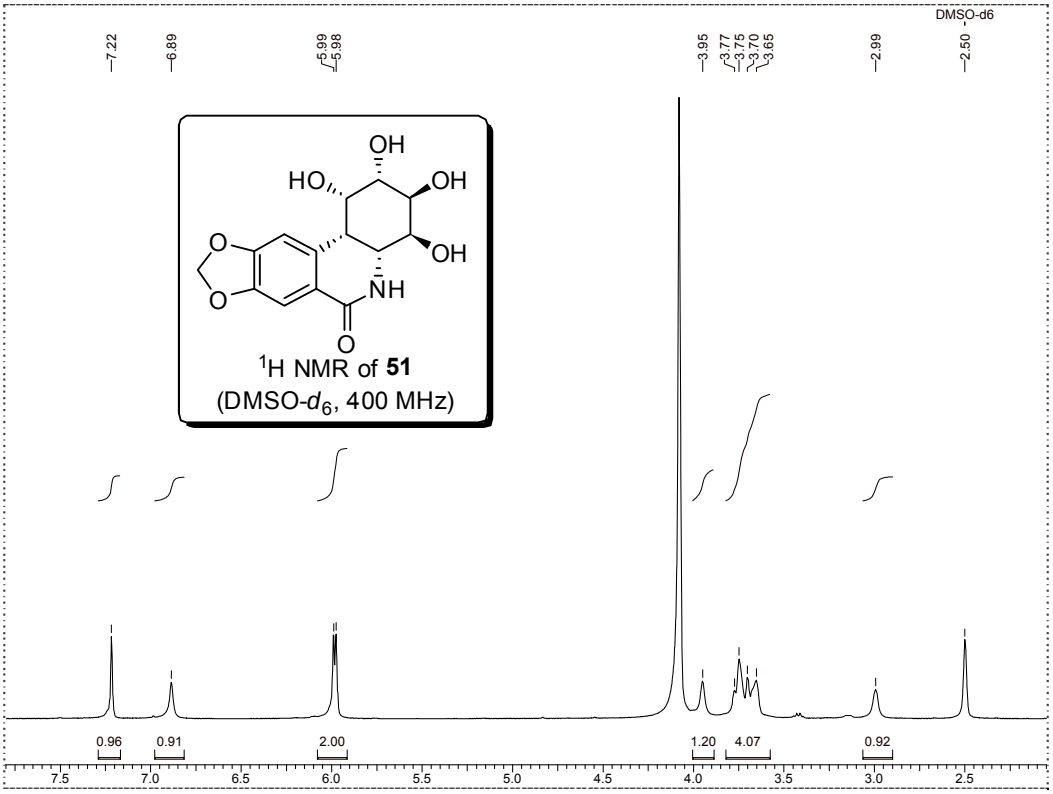


17. (1*S*,2*S*,3*S*,4*S*,4a*R*,10b*S*)-tert-Butyl 1,2,3,4-tetrakis(methoxymethoxy)-6-oxo-1,2,3,4,4a,10b-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-5(6*H*)-carboxylate (50):

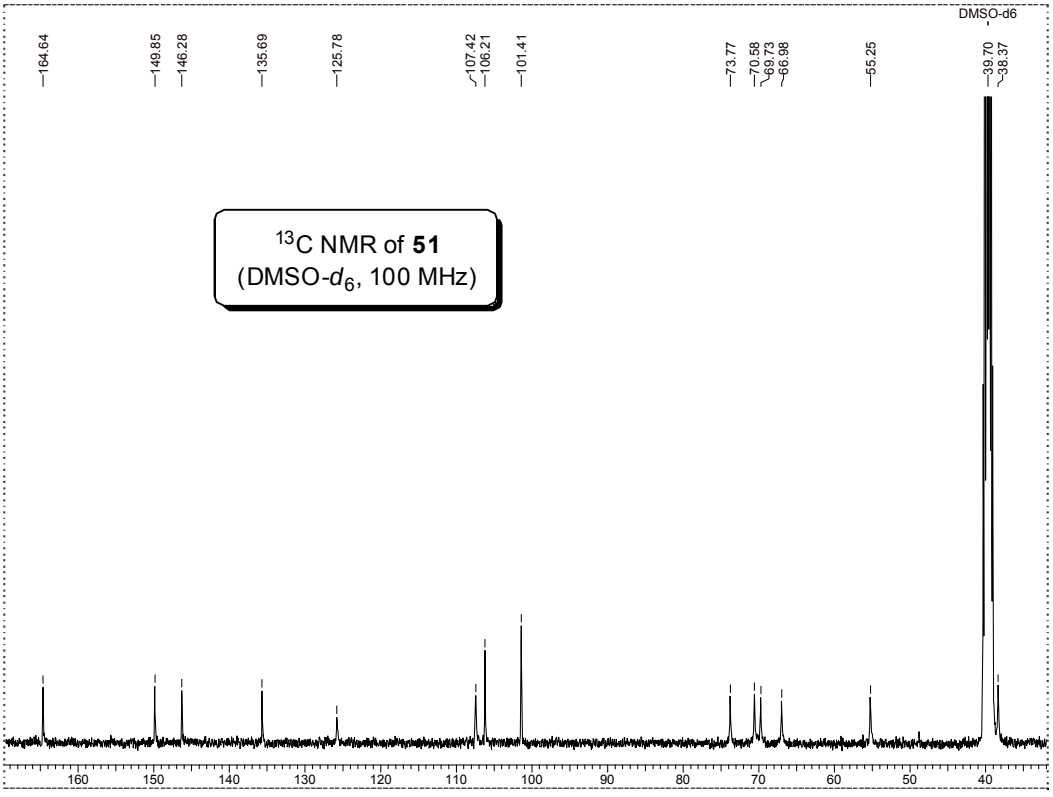




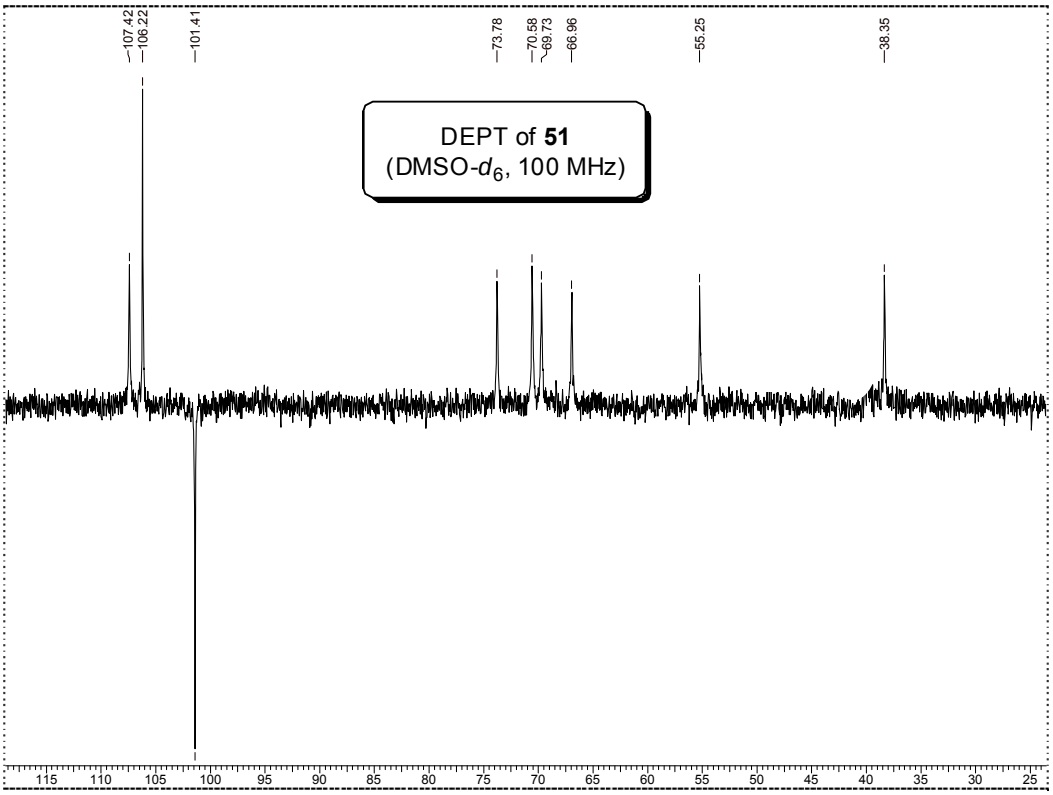
18. 1,10b-*Epi*-7-deoxypancratistatin (51):



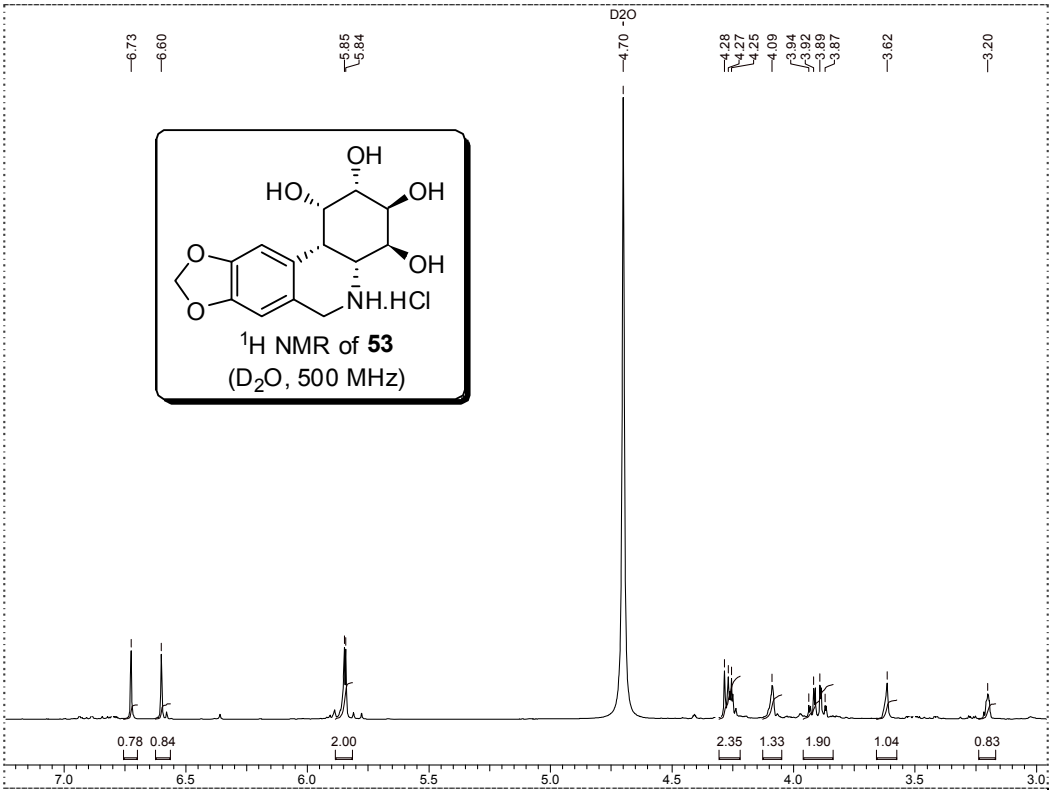
^{1}H NMR of **51**
(DMSO-d_6, 400 MHz)

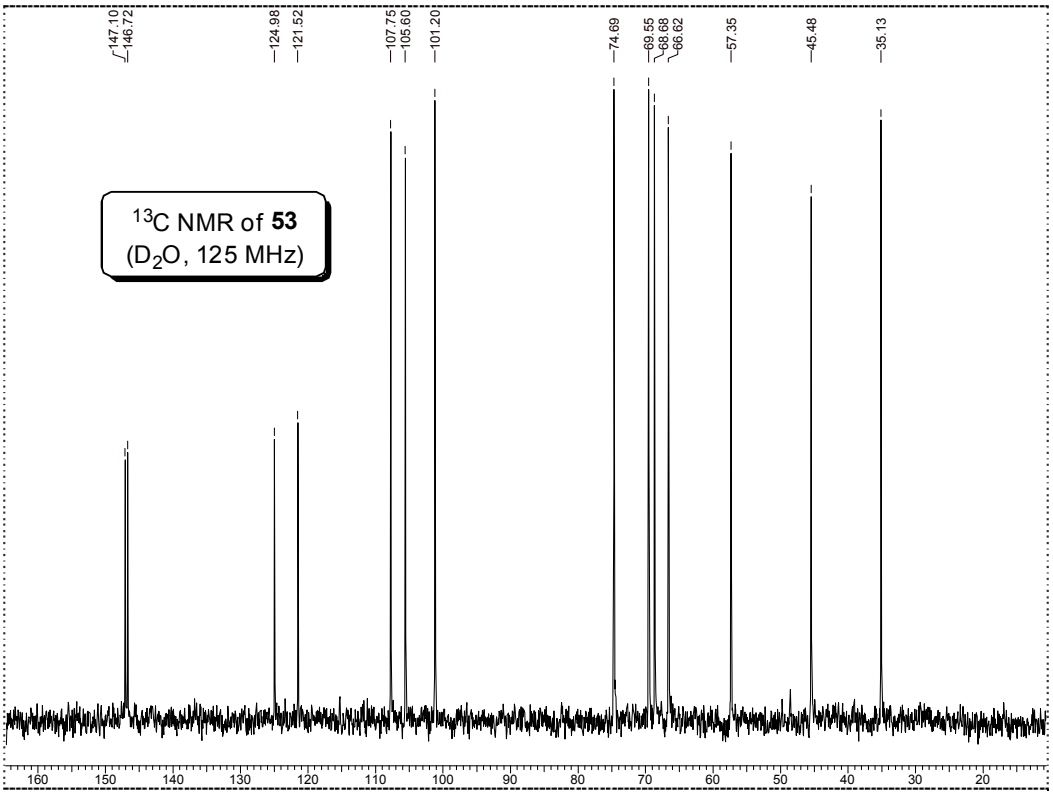


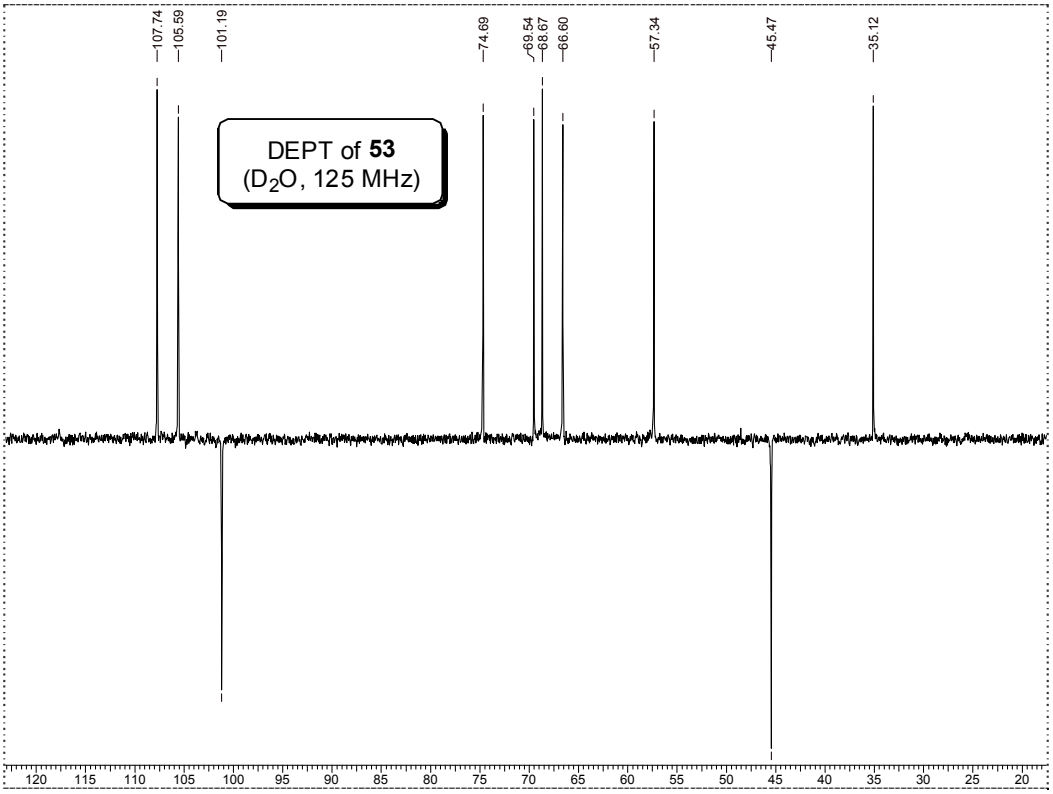
^{13}C NMR of **51**
(DMSO-d_6, 100 MHz)



19. Amine analogue of 1,10b-*epi*-7-deoxypancratistatin (53):




147.10
146.72
124.98
121.52
107.75
105.60
101.20
74.69
69.55
68.68
66.62
57.35
45.48
35.13
^{13}C NMR of **53**
(D_2O, 125 MHz)
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20


107.74
105.59
101.19
74.69
69.54
68.67
66.60
57.34
45.47
35.12
DEPT of **53**
(D_2O, 125 MHz)
120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20

Chapter 3

Syntheses of pancratistatin-like isoquinolines: Development of new mild strategy for [*c*]annulated isoquinolines

3.1. Introduction

Isoquinolines, their dihydro and tetrahydro derivatives are the structural component of several biologically active natural alkaloids.[1] Especially, functionalized isoquinolines possess important pharmacological properties such as antitumor, analgesic, antihistaminic, and antifertility activity.[2] Furthermore, these compounds are useful ligands in phosphorescent emitters for organic light-emitting diodes.[3] They are also known to serve as important molecular scaffolds for the syntheses of complex natural products.[4] Common approaches to assemble these ring systems are highly dependent on few classical reactions summarized in Figure 1.

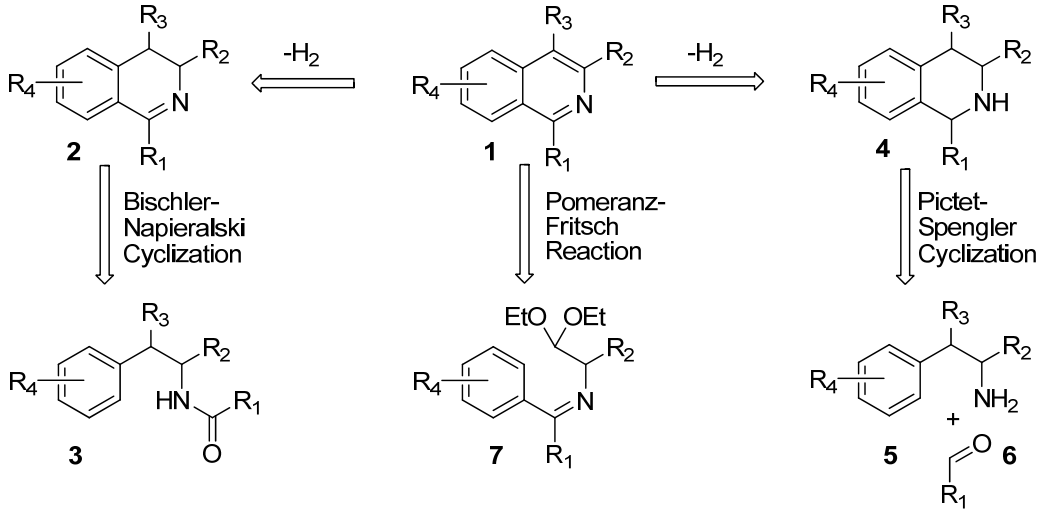


Figure 1. *Classical approaches of isoquinolines*

3.1.1. Bischler-Napieralski reaction[5a]

This reaction involves the cyclization of phenethylamides **3** in the presence of dehydrating agents such as P_2O_5, $POCl_3$ to afford 3,4-dihydroisoquinoline derivatives **2**. Dehydrogenation of **2** normally leads to the synthesis of the target heterocycle **1**. This reaction is one of the most classically employed and versatile methods for the synthesis of isoquinoline system.

3.1.2. Pictet-Spengler reaction[5b]

The condensation reaction between *β*-arylethylamine **5** with an aldehyde **6**/ketone/1,2-dicarbonyl compound to give the corresponding tetrahydroisoquinoline **4** constitute this particular name reaction. Usually an acidic catalyst is employed and the reaction mixture is heated in these reactions. Aromatic compounds containing electron donating substituents are the most reactive substrates towards this reaction.

3.1.3. Pomeranz-Fritsch reaction[5c]

This reaction involves the preparation of isoquinolines **1** *via* the acid mediated cyclization of the appropriate imineacetal intermediate **7**. The best yields of these reactions are usually obtained with electron rich aromatic ring systems.

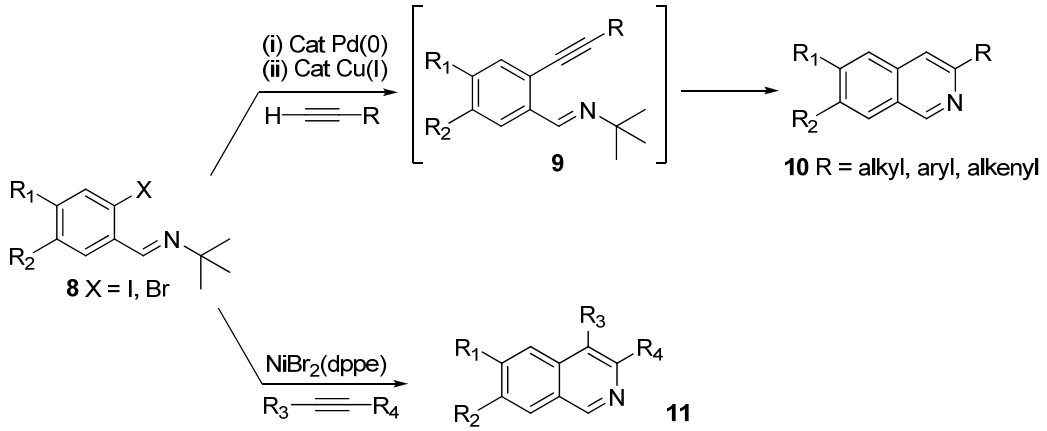
3.2. Reports on the novel syntheses of isoquinolines

The above discussed classical methods normally require harsh conditions (the presence of strong acid), which prevent the elaboration of sensitive isoquinolines. Over the last two decades, there has been growing interest to develop mild and efficient syntheses of isoquinolines against these tedious and conventional approaches. Research towards this end promoted exploration of transition metal mediated isoquinoline syntheses, especially the use of palladium has been documented widely in the literature.

3.2.1. Palladium and Nickel catalysis

Initially, heteroannulation of stoichiometric palladacycles of aldimines with internal alkynes were shown to be efficient but expensive in the construction of 3,4-disubstituted isoquinolines.[6] Later, the process was made more accessible through development of the catalytic version of the above reaction in which *ortho*-iodobenzaldimines **8** were annulated with internal alkynes (Scheme 1).[7a]

Scheme 1. *Heteroannulation of aldimines with alkynes*



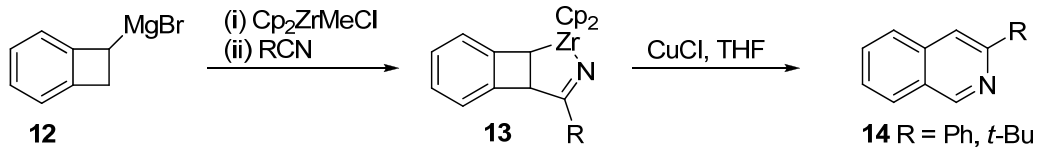
This particular palladium catalysis led to the production of diverse array of isoquinolines, substituted with aryl,[7b,c,d] alkyl,[7b,c,d] aroyl,[7e] alkenyl[7f] and fluoroalkyl[7g] at 3, 4-positions. Furthermore, the nickel-catalyzed annulations of the same starting

materials claimed the process to be more efficient, mild and highly regioselective when unsymmetrical alkynes were used as annulation partner.[8]

3.2.2. Zirconium, Rhodium and Copper catalysis

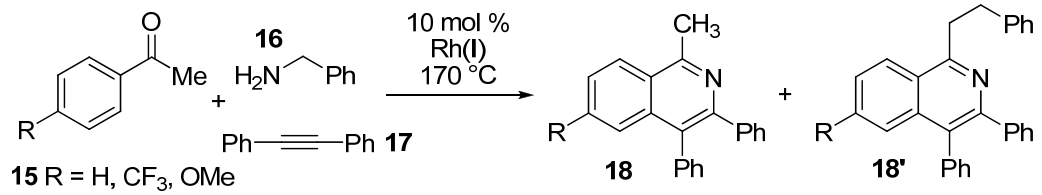
The transition metal chemistry focusing isoquinoline syntheses was further expanded by exploring other elements of this series for their usefulness. The commercially available 1-bromobenzocyclobutene was readily converted into Cp_2Zr(benzocyclobutadiene), which gave fused benzocyclobutane zirconocycle (**13**) on coupling with a nitrile. Further transmetalation of **13** with copper (I) chloride afforded 3-substituted isoquinoline **14** in moderate yield as depicted in Scheme 2.[9]

Scheme 2. *Isoquinolines from zirconocycles*



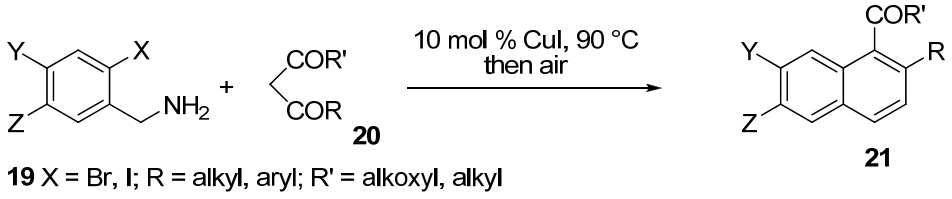
At the same period of time, an application of Rh(I)-catalyzed direct *ortho*-alkenylation of aromatic ketimines with alkynes was demonstrated to set the synthetic protocol of isoquinoline derivatives (**18**, **18'**, Scheme 3).[10] This efficient single-step synthesis of isoquinoline derivatives involved three-component reaction of aromatic ketone **15** with benzylamine (**16**) and alkyne **17** without any use of *ortho*-functionalized aromatic compounds.

Scheme 3. *Isoquinolines from Rh(I) catalysis*



Very recently, synthesis of 1,2-dihydroisoquinolines, which underwent smooth dehydrogenation under air atmosphere to afford 3,4-substituted isoquinolines (**21**, Scheme 4) is reported[11] by CuI-catalyzed coupling/cyclization reaction of *β*-keto esters **20** and 2-halobenzylamines **19**.

Scheme 4. *Isoquinolines from Cu(I) catalysis*

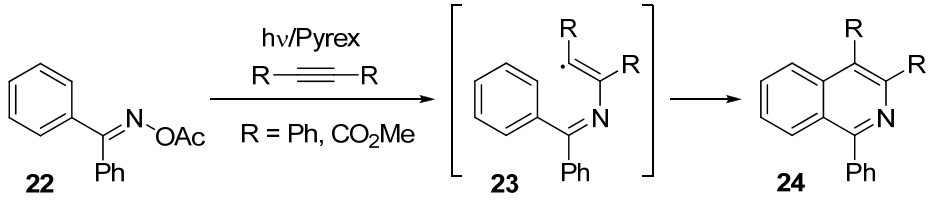


19 X = Br, I; R = alkyl, aryl; R' = alkoxyl, alkyl

3.2.3. Photochemical synthesis

Many other strategies have also been developed for the synthesis of isoquinolines. One such important approach relates with the photochemical generation of iminyl radical from acyloximes **22** which on intermolecular addition to acetylenic compound followed by cyclization of intermediate radical species **23** produces substituted isoquinolines (Scheme 5).[12]

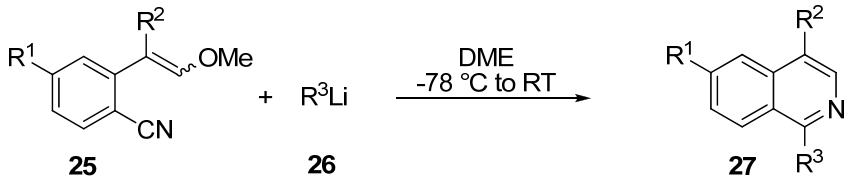
Scheme 5. *Photochemical heteroannulation*



3.2.4. Organolithium mediated synthesis

Another strategy for the synthesis of isoquinoline was initiated by the addition of the organolithiums **26** to nitrile carbon of 2-(2-methoxy-ethenyl)benzonitrile (**25**) as shown in Scheme 6. This method has been successfully extended to the syntheses of various 3,4-dihydroisoquinolines and 1-isoquinolinamines.[13]

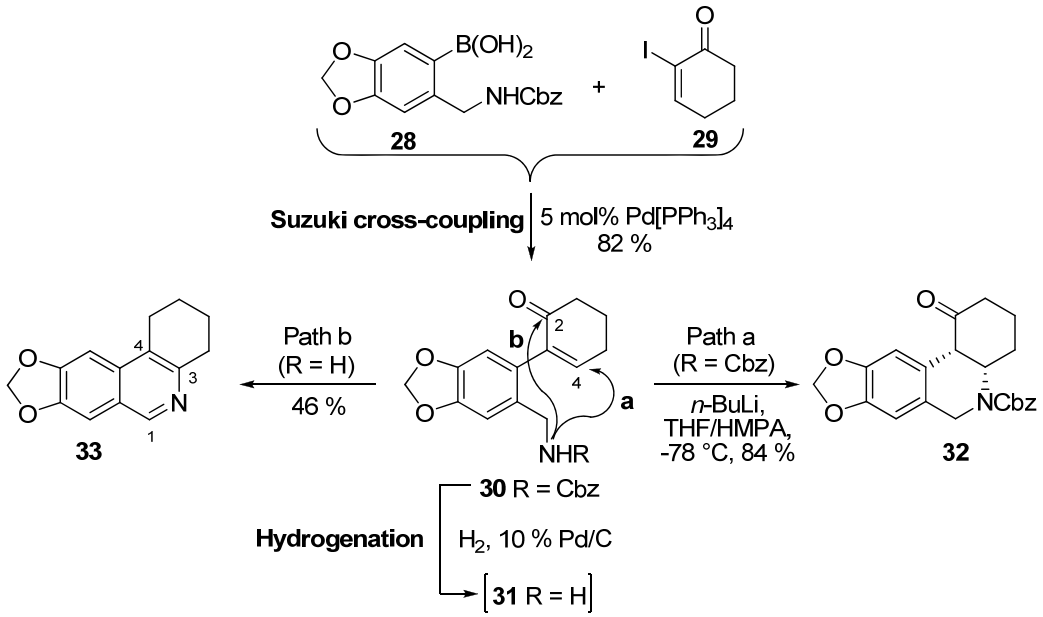
Scheme 6. *Organolithium addition to nitriles*



3.3. Background and concept of the present work

We had explored the intramolecular aza-Michael addition reaction of aza-tethered enone **30,** obtained from Suzuki cross-coupling reaction[14] of **28** and **29**, for the construction of phenanthridone structural framework as described in the previous chapter of this dissertation. A *cis*-fused phenanthridone **32** resulted when precursor **30** was treated with *n*-BuLi, THF/HMPA at −78 °C (Scheme 7, *path a*). This strategy was further explored for the synthesis of *epi*-7-deoxypacratistatin. Eventually, we became interested to investigate the mode of interaction of the corresponding free amine (**31**). Thus, when reductive removal of benzyl carbamate of **30** was carried out by using 10 % Pd on charcoal at 1 atm pressure of H_2, to our surprise, the product obtained was an entirely new product **33** in 46 % yield (*path b*).

Scheme 7. *Two different modes of aza-interactions*



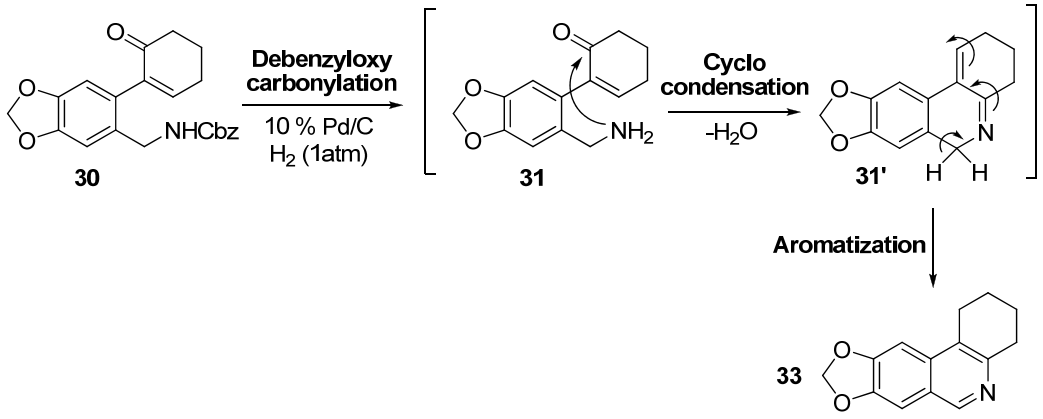
The resultant product was thoroughly analyzed by all spectroscopic means to confirm that to be an [*c*]annulated isoquinoline. The ^{1}H NMR of this product showed three singlets at δ 8.73 (1H), 7.07 (2H), 6.02 (2H) corresponding to H_1, aromatic protons and methylenedioxy protons, respectively. ^{13}CMR of the product showed aromatic carbons appearing at δ 150.8, 149.2, 147.7, 147.0, 133.6, 124.2, 123.8, 103.5, 98.5 and the methylene carbons at δ 32.5, 25.1, 23.0, 22.7. ESI mass spectrum of **33** clearly indicated the presence of the expected molecular structure by showing the base peak

at 250 ($M+Na^+$). All these detailed spectroscopic data confirmed the [*c*]annulated isoquinoline structure for **33**.

3.4. Mechanism of isoquinoline formation

A plausible mechanism for this observation was explained by considering the initial formation of intermediate **31** through Pd/C mediated reductive debenzyloxycarbonylation of **30** (Scheme 8). The *in situ* generated **31** undergoes cyclocondensation to produce the cyclic **31'**. Solvent mediated aromatization *via* reorganization of the benzylic proton of **31'** eventually leads to the generation of isoquinoline **33**.

Scheme 8. *Plausible mechanism*



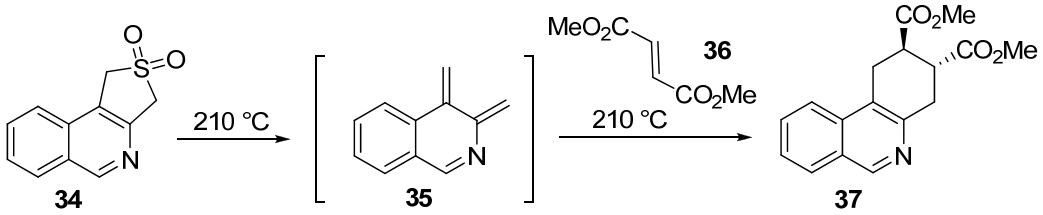
3.5. Literature precedence for [*c*]annulated isoquinolines

There are only few methods reported for the syntheses of cycloalkene fused isoquinolines. None of these reported methods are general as they are very specific to the particular substrates which are described as follows:

3.5.1. Diels-Alder Cycloaddition of isoquinoline-*o*-quinodimethane[15]

The pyrolysis of isoquinoline-3-sulfolene **34** at 210 °C provides an easy entry to the corresponding isoquinoline-*o*-quinodimethane (**35**) which on *in situ* Diels-Alder cycloaddition with dimethyl fumarate (**36**) produces substituted cyclohexene fused isoquinoline **37** (Scheme 9). However, this method suffers from the lengthy route required for the preparation of the starting sulfate **34** and also the restricted accessibility of various substituted quinodimethanes **35**.

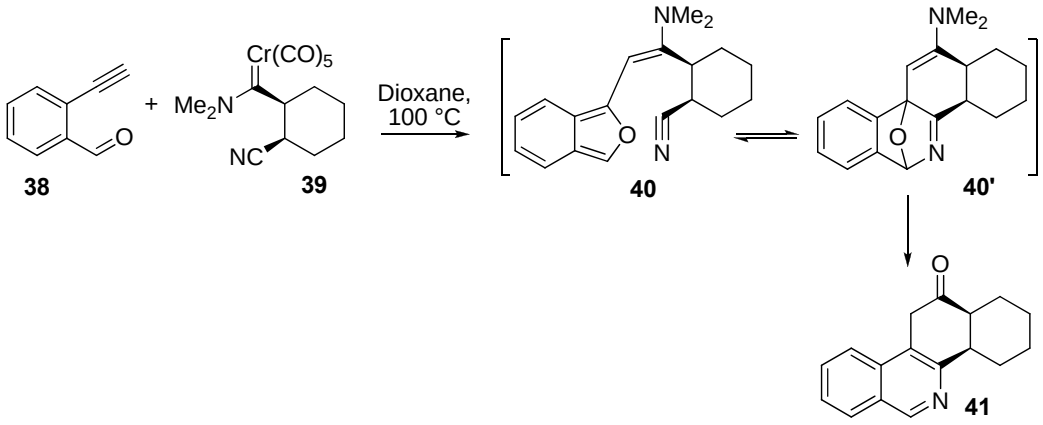
Scheme 9. *DA cycloaddition of quinodimethanes*



3.5.2. Isobenzofuran-nitrile DA cycloaddition[16]

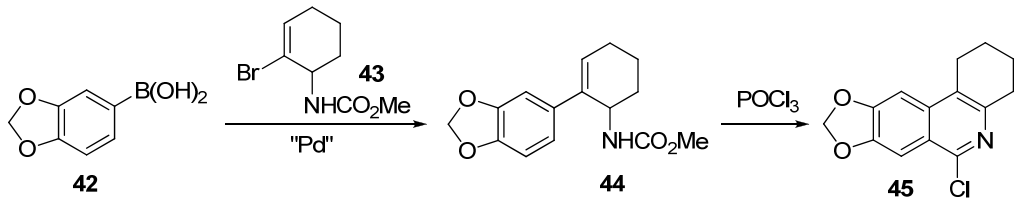
Another report for the synthesis of fused isoquinoline involved intramolecualr DA cycloaddition of isobenzofuran **40**, obtained by the coupling of 2-alkynylbenzaldehyde (**38**) with *β*-cyanocarbene complex **39** as depicted in Scheme 10. The cycloadduct **40'** upon deoxygenation produces isoquinoline **41**.

Scheme 10. *Isobenzofuran mediated isoquinoline synthesis*



3.5.3. Bischler-Napieralski cyclization[17]

Scheme 11. *Bischeler-Napieralski cyclization*

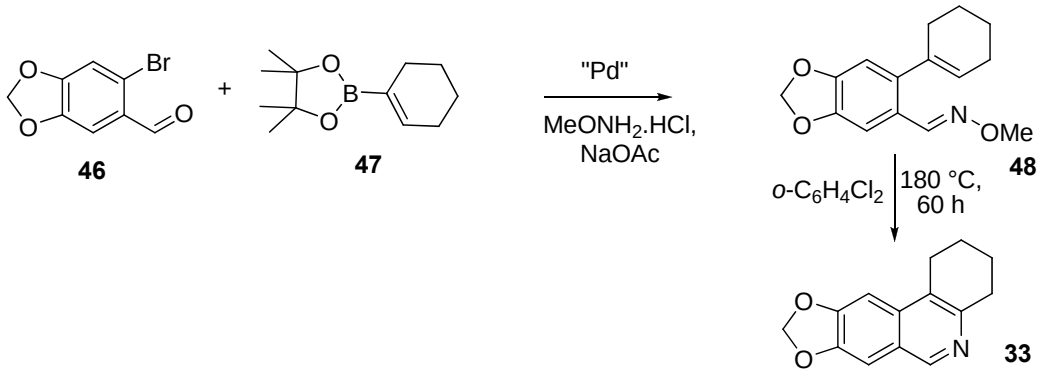


Suzuki cross-coupling product **44** upon reacting with $POCl_3$ (Bischeler-Napieralski cyclization protocol) afforded 1-chloro substituted isoquinoline **45** as shown in Scheme 11). The main drawback of the strategy is that this reaction required heating the mixture of **44** and $POCl_3$ at 120 °C for 12 h in a sealed tube.

3.5.4. Thermal electrocyclization[18]

In another strategy reported for the synthesis of annulated isoquinoline **33** employed thermal aza-6π-electrocyclization of 6-cyclohexenyl piperonal *O*-methyl oxime (**48**) in refluxing *o*-dichlorobenzene at 180 °C for 60 h as shown in Scheme 12. The same reaction has also been studied under μ-wave reaction conditions to optimize the yields. The precursor **48** was obtained using Suzuki cross-coupling reaction between **46** and **47**, followed by the formation of *O*-methyl oxime.

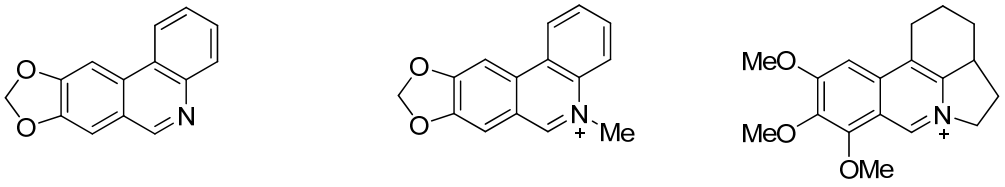
Scheme 12. *Isoquinoline via electrocyclization*



3.6. Synthesis of [*c*]annulated isoquinolines

Our unexpected observation of isoquinoline **33** formation (Scheme 8) during the reductive debenzyloxycarbonylation of **30**, led us to explore the utility of this reaction for the syntheses of [*c*]annulated isoquinilines, as to the best of our knowledge, there was no straightforward and general approach to access these isoquinolines. [*c*]Annulated isoquinolines of type **33** are valuable synthetic precursor in the synthesis of trispheridine (**49**),[19] a naturally occurring phenanthridine alkaloid from the *Amaryllidaceae* plant family (Figure 2). Palladium catalyzed dehydrogenation of **33** in refluxing xylene have been reported for the efficient access to **49**[18] in shortest possible steps. Compound **33** also shares the close structural relationship with other alkaloids such as bicolorine (**50**)[20] and roserine (**51**).[21] The

foregoing sections of this dissertation would discuss the development of mild two-step syntheses of [*c*]annulated isoquinolines involving Suzuki cross-coupling/reductive debenzyloxycarbonylation sequence and the application to the pancratistatin-like isoquinolines.



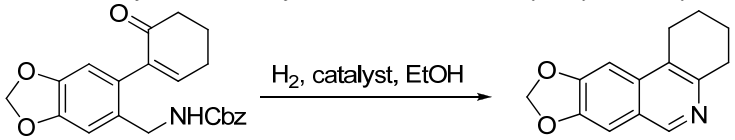
49 trispheridine **50** bicolorine **51** roserine

Figure 2. *Few naturally occurring [c]annulated isoquinolines*

3.6.1. Optimization of Reductive Debenzyloxycarbonylation reaction

Driven by the easy access of annulated isoquinoline **33** through the above route, we examined the *in situ* generation of free amine by the reductive removal of the benzyloxycarbonyl moiety of **30** to obtain the maximum yield of **33**. The results of the optimization studies are listed in Table 1.

Table 1. *Optimization of conditions for reductive debenzyloxycarbonylation*



30 **33**

entry	catalyst[a]	pressure (atm)	time (h)	yield (%)
1	10 % Pd/C	1	28	46[b]
2	10 % Pd/C	4	12	52
3	W-2 Raney Ni	1	12	no rxn
4	W-2 Raney Ni	15[c]	12	39
5	20 % $Pd(OH)_2$/C	1	8	96

[a]*All hydrogenations were performed with 20 mol % of the catalysts consistently.* [b]**30** *was recovered in 48 % yield.* [c]*Hydrogenation was conducted in par reactor.*

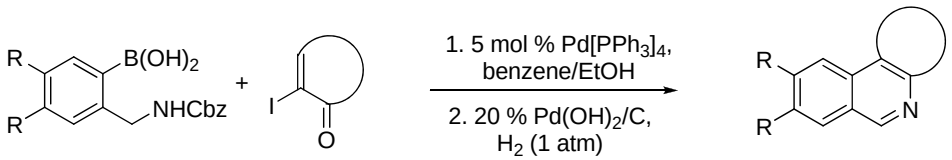
During the course of the hydrogenation, the conversion of **30** was observed to be incomplete in the presence of catalytic 10 % Pd/C under 1atm of hydrogen pressure and gave only 46 % isolated yield of **33** even after 28 h of the reaction. Therefore, we raised the hydrogen pressure to 4 atm which, though, completed the reaction in 12 h, the yield of **33** did not improve significantly due to the formation of several undesired products. It was also noticed that **30** remained inactive to Raney Ni mediated hydrogenation at 1 atm pressure of hydrogen, but produced complex reaction mixture along with required isoquinoline **33** in small amounts (39 %, entry 4) when the reaction was conducted at high pressure (15 atm). Pleasingly, the use of catalytic 20 % $Pd(OH)_2/C$ cleanly effected complete conversion of **30** at atmospheric pressure of the hydrogen and afforded **33** in 96 % yield (8 h, entry 5).

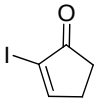
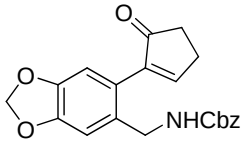
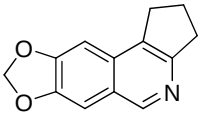
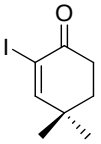
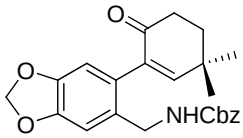
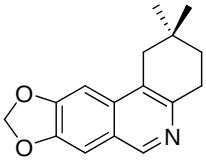
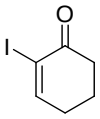
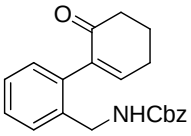
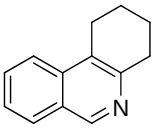
3.6.2. Generalization of the methodology for the synthesis of [*c*]annulated isoquinolines

The generality of the Suzuki cross-coupling/reductive debenzyloxycarbonylation sequence was evaluated by synthesizing isoquinolines **54**, **57** and **60**. The corresponding coupling partners (**28**, **29**, **52**, **55** and **58**), coupling products (**53**, **56** and **59**) and respective yields of these reactions are summarized in Table 2.

Coupling products of the devised synthetic sequence were prepared by using standard Suzuki cross-coupling conditions (5 mol % $Pd[PPh_3]_4$, 2 *M* Na_2CO_3, benzene/EtOH) in 75–87 % yields. These compounds were identified with their olefinic –CH which appeared around δ 5.50 in ^{1}H NMR spectrums and around δ 160.0 in ^{13}C NMR spectrums. Reductive denzyloxycarbonylations were carried out with the freshly purified coupling products (**53**, **56** and **59**) by the optimized hydrogenation conditions ($Pd(OH)_2/C$, H_2 (1 atm), EtOH) to afford isoquinolines **54**, **57** and **60** in 82–92 % yields. The newly generated aromatic proton (adjacent to N) of electron rich isoquinolines (**54**, **57**) appeared in the ^{1}H NMR spectrums at δ 8.75 where as, for isoquinoline **60**, the same aromatic proton appeared at δ 9.03, revealing the electron deficient nature of isoquinoline ring in comparison to **54** and **57**. The ^{13}C NMR spectrum of all these compounds invariably showed nine separate signals to confirm the existence of isoquinoline ring system in the molecule.

Table 2. *Syntheses of isoquinolines using Suzuki cross-coupling[a]/reductive debenzyloxycarbonylation[b] sequence*



entry	boronic acid	iodoenone	coupling product (yield)[c]	isoquinoline (yield)[c]
1	**28** (R=OCH_2O)	 **52**	 **53** (76 %)	 **54** (85 %)
2	**28**	 **55**	 **56** (87 %)	 **57** (92 %)
3	**58** (R=H)	 **29**	 **59** (75 %)	 **60** (82 %)

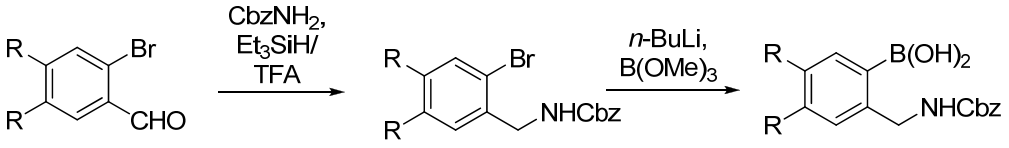
[a]*Suzuki cross-coupling reactions were carried out by refluxing (80 °C) mixture of* **28/58** *(1.0 mmol) and* **29/52/55** *(1.0 mmol) along with 5 mol % of* $Pd[PPh_3]_4$ *in benzene/ethanol (2:1, 15 mL) for 1–2 h.* [b]*Freshly purified* **53/56/59** *were reduced in ethanol using optimized hydrogenation conditions defined in entry 5, Table 1.* [c]*Isolated yield. Compound* **60** *is previously known.*[22]

3.6.3. Syntheses of reaction partners for the two-step strategy

The requisite starting materials required for this reaction sequence were easily obtained through established procedures. The *α*-iodoenones (**29**, **52**, **55**) employed for Suzuki cross-coupling reaction were readily obtained using Johnson's iodination protocol (I_2, CCl_4/Py).[23] The improved version of this protocol {I_2, K_2CO_3, DMAP (cat), THF/H_2O (1:1)} had also been utilized in the case of inactive enones (for

example, **55**). Synthesized iodoenones were completely characterized by all spectroscopic means. Normally, they were identified with their characteristic olefin (–CH) functionality with the proton appearing in the range of δ 7.44–8.00 in ^{1}H NMR spectroscopy. The corresponding olefinic carbon appeared at δ 159.5, 169.7 and 167.9 in ^{13}C NMR spectrums of **29**, **52** and **55,** respectively. α,β-Unsaturated carbonyl functionality of these iodoenones vibrated in the frequency range of 1680–1690 cm^{-1}. The other coupling partners (**28**, **58**, Scheme 13) were synthesized from the corresponding bromo analogues (**63**, **64**) using lithiation/boronation protocol as discussed in the previous chapter of this dissertation. Both of these (**28**, **58**) compounds showed distinctive boronic acid protons at δ 8.15–8.20 (s, 2H) and a broad singlet at δ 7.67 for –NH proton. The property of methonolysis associated with **28**, while recording the ESI mass spectrum in methanol (detailed in second chapter) was also observed with **58**. Although, compound **63** had been synthesized from piperonylamine (compound **11** of chapter 2), we looked for a more general and easily accessible method of synthesizing these bromides (**63**, **64**). Towards this end, we identified a strategy based on reductive *N*-alkylation of carbamates reported by Dubé, where bromides **63**, **64** could be synthesized from the corresponding aldehydes (**61**, **62**).[24] These bromides were unambiguously confirmed by usual spectroscopical techniques, especially, the ESI mass spectrums of **63** and **64** showed the characteristic isotopic peaks (M+Na^{+}, M+2+Na^{+}) of equal intensity. It should be noticed that most of the *ortho*-bromo aldehydes are commercially available for the syntheses of various aromatic substituted boronic acids.

Scheme 13. *Synthesis of boronic acids*



61 R = OCH_2O
62 R = H

63 R = OCH_2O (95 %)
64 R = H (92 %)

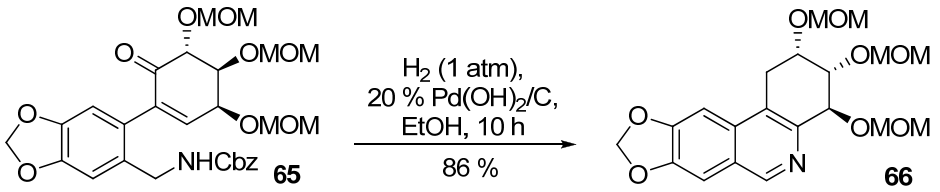
28 R = OCH_2O (69 %)
58 R = H (65 %)

3.7. Synthesis of highly oxygenated isoquinolines

Since, the success of any methodology is defined by its application to the syntheses of complex molecule, we investigated the efficacy of this reaction sequence

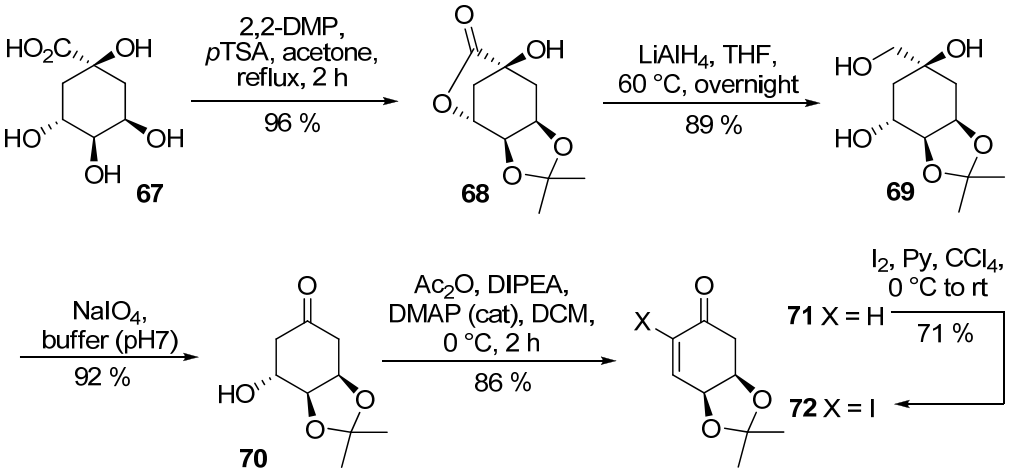
for the synthesis of **66**. Highly oxygenated Suzuki coupled product **65**, which had been previously derived in 24 % overall yield from the commercially available D-(−)-quinic acid (chapter 2) was hydrogenated to afford trialkoxycyclohexene annulated isoquinoline {**66**, 86 %, $[\alpha]^{27}_{D}$ +118.1 (*c* 1.1, $CHCl_3$), Scheme 14}. Aromatic protons of **66** appeared as singlets at δ 8.88, 7.21, 7.15. An apparent doublet (J = 2.3 Hz) appearing at δ 6.08 was correlated to methylenedioxy protons in the ^{1}H NMR spectrum. Methine protons of the molecule were observed at δ 4.73 (d, J = 6.8 Hz, 1H), 4.50–4.40 (m, 2H). Very importantly, the newly generated methylene protons of the fused cyclohexene ring showed diastereotropic nature by displaying two doublet of doublets at δ 3.32 (J = 16.0, 6.3 Hz, 1H), 3.15 (J = 16.0, 10 Hz, 1H). The assigned structure of **66** was undoubtedly supported by the DEPT spectrum, as aromatic and aliphatic –CH carbons appeared at δ 149.4, 103.7, 99.3, and at δ 78.8, 75.4, 71.3 respectively. Methylene carbons of **66** displayed signals at δ 101.7 (methylenedioxy) and at δ 27.6 (newly generated). It should be mentioned that oxygenated isoquinoline of this type has not been synthesized previously and would be difficult to obtain *via* classical approaches, as known approaches utilized normally strong acidic conditions.

Scheme 14. *Synthesis of trialkoxylated isoquinoline* (**66**)



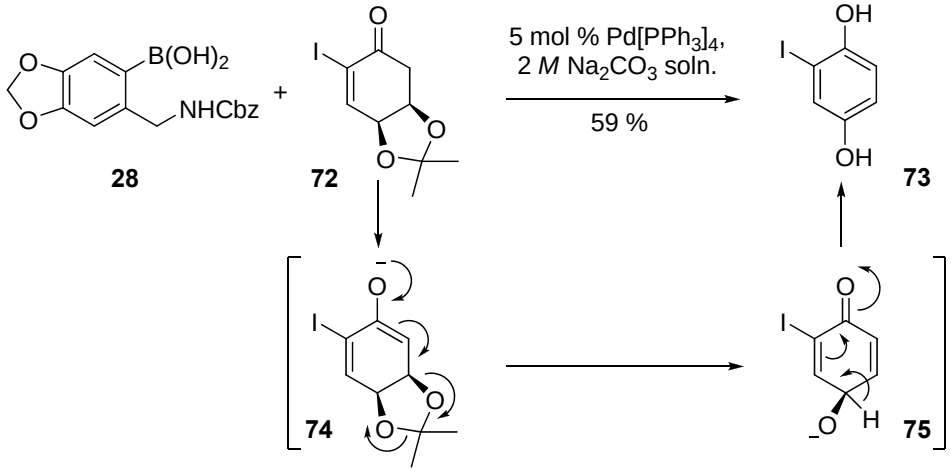
In order to demonstrate further application of this methodology, the synthesis of lower analogue of this isoquiniline series (dialkoxylated) was targeted. We had synthesized the requisite α-iodoenone **72** from D-(−)-quinic acid (**67**) by following the known procedure[25] in 48 % overall yield as illustrated in Scheme 15.

Scheme 15. *Synthesis of iodoenone* **72**



Initially, preparation of required hydrogenation precursor was attempted by coupling iodoenone **72** with boronic acid **28** (Scheme 16). However, it was disappointing to note that it did not produce the expected coupling product and gave some completely aromatized product **73** in 59 % isolated yield, possibly by *β*-alkoxy elimination (**74**) followed by aromatization (**75**) under the basic reaction conditions (2 *M* Na_2CO_3).

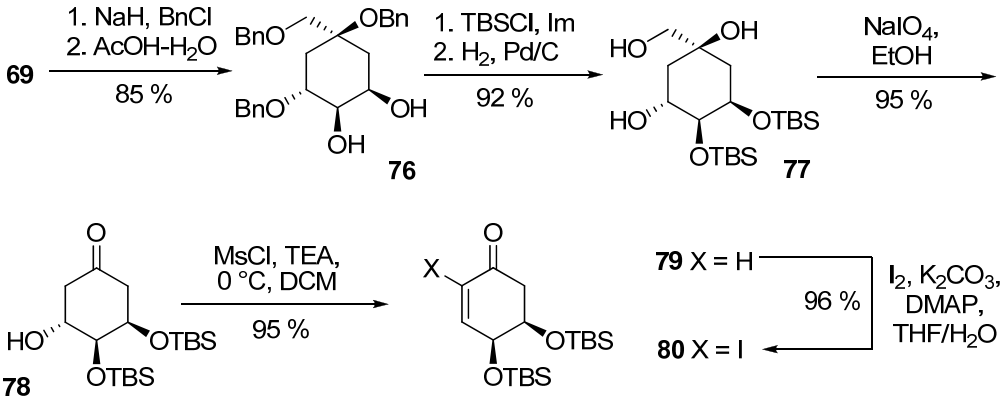
Scheme 16. *Suzuki cross-coupling of* **28** *and* **72**



Therefore, we employed corresponding silyl protected enone **79** (Scheme 17) which had already been synthesized (60 % overall yield from **67**) by our group as an important intermediate for the synthesis of 2,7-dideoxypancratistatin.[26] Enone **79** was

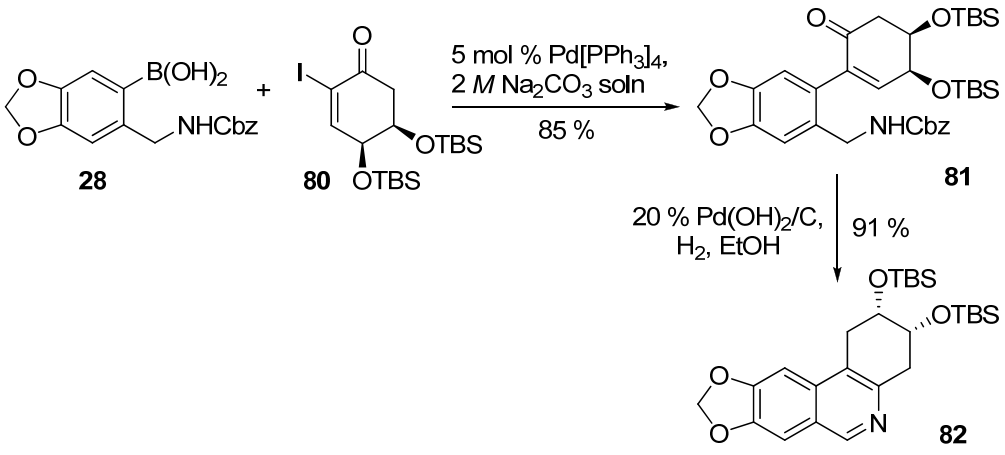
subjected to improved version of Johnson's iodination protocol (I_2, K_2CO_3, DMAP, THF/H_2O) to afford **80** in 96 % yield.

Scheme 17. *Synthesis of iodoenone* **80**



This α-iodoenone (**80**) suited well to the devised two-step synthetic sequence to obtain **81** as well as isoquinoline **82** {77 % combined yield, mp 137–138 °C; $[\alpha]^{27}_D$ –20.6 (*c* 1.0, $CHCl_3$)} as described in Scheme 18.

Scheme 18. *Synthesis of dialkoxylated isoquinoline* (**82**)



The ^{1}H NMR spectrum of **82** revealed that the aromatic protons of the molecule displayed singlets at δ 8.79 (1H), 7.13 (2H) and the peak at δ 6.06 (s, 2H) represented the methylenedioxy (–OCH_2O–) protons. While two methine (–CH) protons appeared together at δ 4.16 (m, 2H), methylene (–CH_2) protons of the molecule appeared at δ 3.10 (m, 4H). The molecular structure of **82** was confirmed with DEPT spectrum,

accounting for the five signals at δ 148.3, 103.6, 98.7, 70.8, 70.6 for –CH carbons and three signals at δ 101.5, 39.1, 31.5 for $-CH_2$ carbons of the molecule.

Removal of the protecting groups from **66** as well as **82** using 6 *N* HCl in MeOH afforded isoquinolines **83** {87 %, mp 239–241 °C, $[\alpha]_D^{27}$ +48.5 (*c* 0.5, DMF)} and **84** {91 %, mp 286–291 °C, $[\alpha]_D^{27}$ –43.1 (*c* 0.5, DMF)}, respectively (Figure 3). Hydroxy isoquinolines (**83** and **84**) were fully characterized with ^1H, ^{13}C NMR spectroscopic techniques to confirm their molecular structures. Finally, compounds **83** and **84** were confirmed with ESI mass spectrums, showing the corresponding MH^+ ions as their base peaks at 276 and 260, respectively. Since these hydroxyl isoquinolines bear considerable structural similarity with naturally occurring 7-deoxypancratistatin (**85**),[27] one can expect these compounds to possess interesting biological profiles like anti-cancer and anti-viral properties.

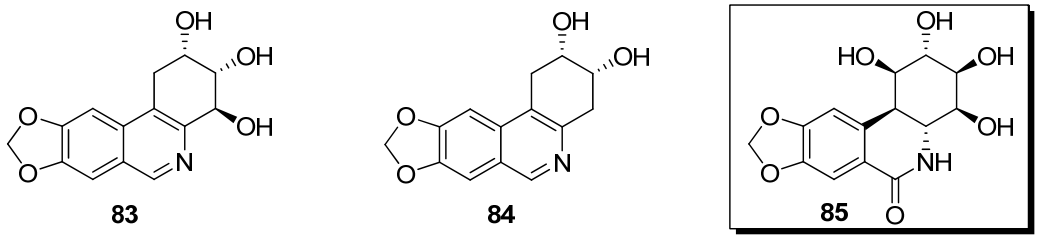
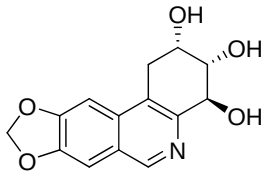
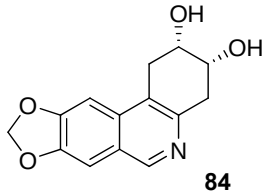
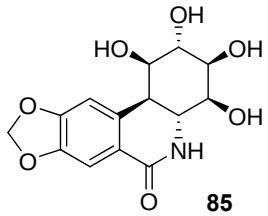


Figure 3. *Pancratistatin-like isoquinolines*

3.8. Evaluation of cytotoxicity of 83 and 84

The synthesized hydroxyl isoquinolines (**83** and **84**) were screened against murine P388 lymphocytic leukemia and two other human cancerous cell lines MCF-7 (breast adenocarcinoma) and THP-1 (promonocytic leukemia). The result of these studies is summarized in Table 3. Both of these compounds **83** as well as **84** exhibited 100–130 fold less activity (GI_{50}= 41.1–57.4 μg/mL) in comparison with natural 7-deoxypancratistatin (**85**, 0.44 μg/mL) against murine P388. Against the other cell lines (THP-1 and MCF-7), isoquinolines **83** and **84** showed similar activities where GI_{50} values ranging from 80–100 μg/mL, indicating the lack of cytotoxicity.

Table 3. *Cytotoxicity data[a] of pancratistatin-like isoquinolines**

Compound	Cancer cell lines		
	murine P388	THP-1	MCF-7
 **83**	57.4	>100	83.6
 **84**	41.1	79.3	81.3
 **85**	0.44[b]	–	–

*[a]Data reported as IC_{50} in μg/mL; [b]Data has been reported earlier;[23] *Detailed inhibition assay procedure is given in experimental section; –, means not known.*

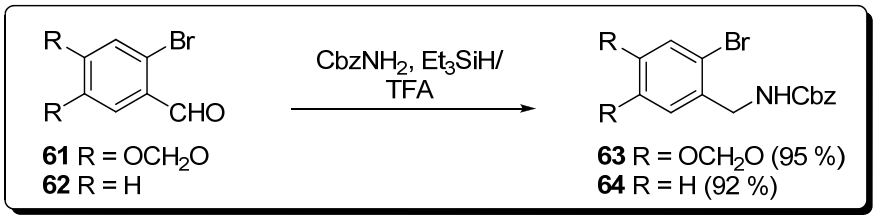
3.9. Conclusion

In summary, we have developed a mild, two-step strategy to synthesize [*c*]annulated isoquinolines involving Suzuki cross-coupling/reductive debenzyloxycarbonylation sequence. The practical viability of the strategy for isoquinoline synthesis is appropriately acknowledged by the catalytic nature and operational simplicity of both the steps involved and also by the easy accessibility of starting materials. The method was successfully applied to the syntheses of range of both substituted and unsubstituted cycloalkene fused isoquinolines.

3.10.I. Experimental section

I. General procedure for syntheses of boronic acids (28 & 58):

(a) Syntheses of bromides (63 & 64):

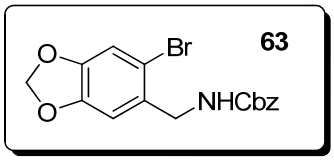


61 R = OCH_2O
62 R = H

63 R = OCH_2O (95 %)
64 R = H (92 %)

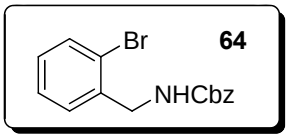
A solution of aromatic aldehyde (**61**/**62**, 10 mmol), benzylcarbamate (30 mmol), Et_3SiH (30 mmol) and TFA (20 mmol) in CH_3CN (40 mL) was stirred at 25 °C for 18 h, The mixture was diluted with EtOAc (100 mL), washed successively with $NaHCO_3$ solution (40 mL) and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography to yield pure solids (**63** & **64**).

1. Benzyl (6-bromobenzo[*d*][1,3]dioxol-5-yl)methylcarbamate (63).



Yield	:	95 %
mp	:	96–97 °C
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3446, 3018, 1718, 1506, 1215
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	7.34 (s, 5H), 6.98 (s, 1H), 6.90 (s, 1H), 5.95 (s, 2H), 5.27 (bs, 1H), 5.10 (s, 2H), 4.33 (d, *J* = 6.2 Hz, 2H)
^{13}C NMR ($CDCl_3$, 75 MHz) δ	:	156.2, 147.7, 147.4, 136.3, 130.7, 128.4, 128.0, 113.8, 112.6, 109.8, 101.7, 66.8, 45.2
Mass: m/z (%)	:	388 ($M+2+Na^+$, 27), 386 ($M+Na^+$, 27), 343 (9), 301 (18), 264 (100)

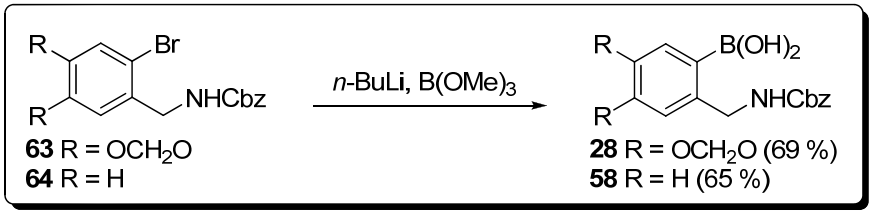
2. Benzyl 2-bromobenzylcarbamate (64).



Yield	:	92 %
mp	:	69–70 °C

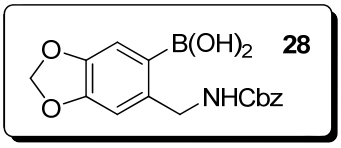
IR ν_{max} cm^{-1} ($CHCl_3$)	:	1714, 1503, 1217
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	7.57–7.10 (m, 9H), 5.32 (bs, 1H), 5.11 (s, 2H), 4.44 (d, *J* = 6.3 Hz, 2H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	156.2, 137.4, 136.2, 132.6, 129.8, 129.0, 128.4, 128.1, 127.6, 123.4, 66.8, 45.2
Mass: m/z (%)	:	344 (M+2+Na^+, 100), 342 (M+Na^+, 100), 278 (66), 276 (66), 256 (25)

(b) Syntheses of boronic acids (28 & 58):



To a solution of bromide (**63/64**, 10 mmol) in dry THF (50 mL) was added *n*-BuLi (2 *M* hexane, 21 mmol) at −78 °C over a period of 10 min. The resultant dark yellow solution was stirred for 20 min at the same temperature and trimethyl borate (50 mmol) was added rapidly in one portion. The solution became colorless and stirred for further 30 min at −78 °C. The reaction mixture was warmed to room temperature over 2 h, before quenching with large excess of saturated aqueous NH_4Cl (50 mL). The heterogeneous mixture was stirred for an hour and extracted with ethyl acetate (3 x 60 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated by rotary-evaporation. The residue was purified using column chromatography (silica gel, elution with 30–40 % ethyl acetate-pet ether) to provide **28/58** as colorless solids.

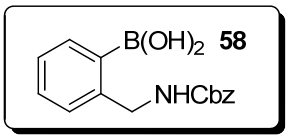
1. 6-((Benzyloxycarbonylamino)methyl)benzo[*d*][1,3]dioxol-5-ylboronic acid (28).



Yield	:	69 %
mp	:	152–153 °C
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2926, 1693, 1462, 1250
^{1}H NMR (DMSO-d_6, 200 MHz) δ	:	8.15 (s, 2H), 7.67 (bs, 1H), 7.34 (s, 5H), 7.00 (s, 1H), 6.80 (s, 1H), 5.96 (s, 2H), 5.02 (s, 2H), 4.28 (d, *J* = 6.1 Hz, 2H)
^{13}C NMR (DMSO-d_6,	:	157.1, 148.8, 145.9, 139.0, 137.4, 128.8, 128.2, 113.4, 108.4,

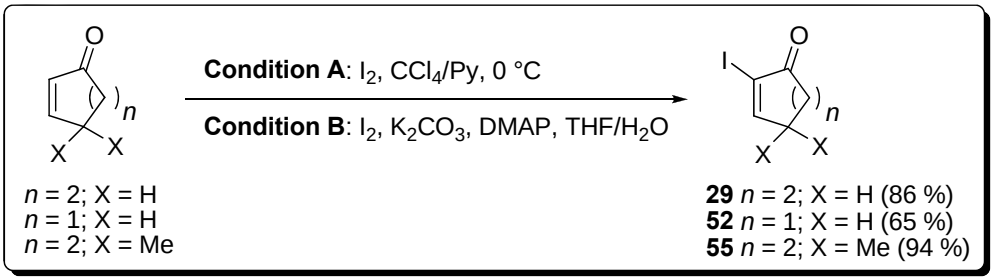
50 MHz) δ		101.1, 66.0, 44.1
Mass: m/z (%)	:	380 (M+2MeOH-2H_2O+Na^+, 50), 326 (22), 188 (15), 156 (100)

2. 2-((Benzyloxycarbonylamino)methyl)phenylboronic acid (58).



Yield	:	65 %
mp	:	146–148 °C
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2932, 1696, 1453, 1250
^{1}H NMR (DMSO-d_6, 200 MHz) δ	:	8.20 (s, 2H), 7.68 (bs, 1H), 7.51 (d, *J* = 6.3 Hz, 1H), 7.35 (s, 5H), 7.30–7.15 (m, 3H), 5.04 (s, 2H), 4.37 (d, *J* = 6.1 Hz, 2H)
^{13}C NMR (DMSO-d_6, 50 MHz) δ	:	156.8, 143.4, 137.4, 133.8, 129.3, 128.6, 128.0, 127.9, 126.8, 126.0, 65.7, 44.3
Mass: m/z (%)	:	336 (M+2MeOH-2H_2O+Na^+, 100), 322 (M+MeOH-H_2O+Na^+, 54)

II. General procedure for preparation of α-iodoenones (29/52/55):



n = 2; X = H
n = 1; X = H
n = 2; X = Me

29 *n* = 2; X = H (86 %)
52 *n* = 1; X = H (65 %)
55 *n* = 2; X = Me (94 %)

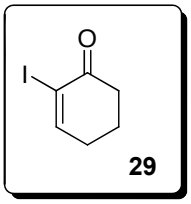
Condition A: Iodine (10 mmol) dissolved in CCl_4/pyridine (1:1, 20 mL) was added drop-wise, under an atmosphere of argon to a solution of cycloalkenone (5 mmol) in CCl_4/pyridine (1:1, 20 mL) at 0 °C. The mixture was stirred for 2 h during which time the temperature was allowed to warm to room temperature. The mixture was diluted with ethyl acetate (100 mL) and washed successively with 1 *N* HCl (4 x 20 mL), saturated aqueous solution of $NaHCO_3$ (40 mL), 20 % aqueous $Na_2S_2O_3$ (40 mL) and dried (Na_2SO_4). After filtration and concentration under reduced pressure, the residue was either purified further by column chromatography or used as such for the next step.

Condition B: To a stirred solution of cycloalkenone (5 mmol) in THF/H_2O (1:1, 16 mL) was added DMAP (1 mmol) and K_2CO_3 (7.5 mmol). The resulting solution was stirred for 5 min, before iodine crystals (7.5 mmol) were added and the reaction was

monitored for the complete consumption of starting material (TLC analysis). The reaction was diluted with EtOAc (50 mL) and the organic phase was washed successively with saturated aqueous solution of $Na_2S_2O_3$ (30 mL), brine (30 mL) and dried (Na_2SO_4). The solution was filtered and evaporated to produce a residue which was either purified further by column chromatography or used for the next step with out purification.

Note: *The α-iodoenones prepared were light and temperature sensitive, so they were refrigerated at below room temperature in dark to prevent decomposition*.

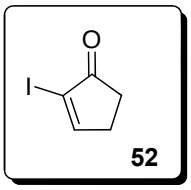
1. 2-iodocyclohex-2-enone (29):



The title compound was prepared using condition A, column chromatographed (silica gel, elution with 10 % ethyl acetate/pet ether) to provide **29** as yellow solid.

Yield	:	86 %
mp	:	48–49 °C
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2951, 1682, 1585, 1315
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	7.74 (t, *J* = 4.4 Hz, 1H), 2.63 (dd, *J* = 7.1, 6.3 Hz, 2H), 2.47–2.36 (td, *J* = 4.6, 5.9 Hz, 2H), 2.13–1.98 (m, 2H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	192.0, 159.5, 103.5, 37.0, 29.7, 22.6
Mass: m/z (%)	:	245 ($M+Na^+$, 100), 244 (50), 223 (31), 190 (17)

2. 2-iodocyclopent-2-enone (52):

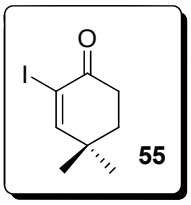


The title compound was prepared using condition A, column chromatographed (silica gel, elution with 15 % ethyl acetate/pet ether) to provide **52** as yellow solid.

Yield	:	65 %
mp	:	71–72 °C
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2951, 1683, 1580, 1314

^{1}H NMR (CDCl$_3$, 200 MHz) δ	:	8.00 (dt, *J* = 3.0, 0.9 Hz, 1H), 2.78–2.74 (m, 2H), 2.50–2.46 (m, 2H)
^{13}C NMR (CDCl$_3$, 50 MHz) δ	:	204.1, 169.7, 102.9, 31.3, 31.0
Mass: m/z (%)	:	231 (M+Na$^+$, 100), 209 (MH$^+$, 18), 147 (79)

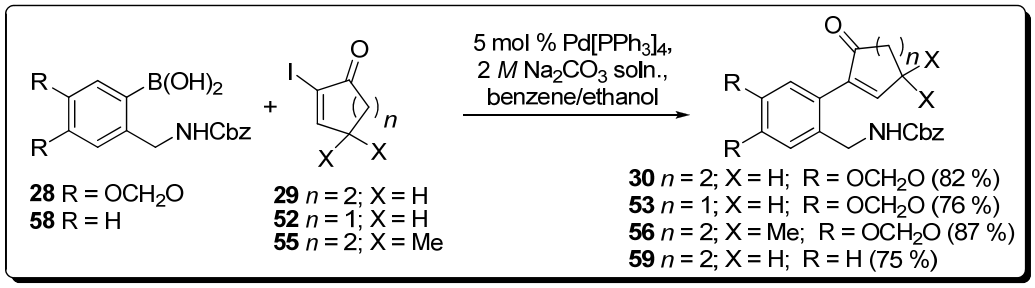
3. 2-iodo-4,4-dimethylcyclohex-2-enone (55):



Prepared using condition B, the yellow oil after workup was sufficiently pure enough to proceed for the next step (94 % yield).

Yield	:	94 %
IR ν_{max} cm^{-1} (CHCl$_3$)	:	2962, 1693, 1583
^{1}H NMR (CDCl$_3$, 200 MHz) δ	:	7.44 (s, 1H), 2.66 (dd, *J* = 7.1, 6.6 Hz, 2H), 1.91 (dd, *J* = 7.5, 6.2 Hz, 2H), 1.17 (s, 6H)
^{13}C NMR (CDCl$_3$, 50 MHz) δ	:	191.7, 167.9, 101.6, 37.8, 35.7, 33.1, 27.1
Mass: m/z (%)	:	273 (M+Na$^+$, 100), 251 (MH$^+$, 13), 214 (38), 122 (100)

III. General procedure for Suzuki cross-coupling reactions:



28 R = OCH_2O
58 R = H

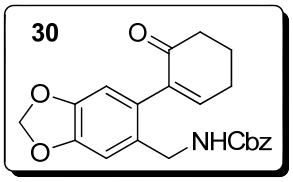
29 *n* = 2; X = H
52 *n* = 1; X = H
55 *n* = 2; X = Me

30 *n* = 2; X = H; R = OCH_2O (82 %)
53 *n* = 1; X = H; R = OCH_2O (76 %)
56 *n* = 2; X = Me; R = OCH_2O (87 %)
59 *n* = 2; X = H; R = H (75 %)

To a solution of iodoenone (**29/52/55**, 2 mmol) in benzene (20 mL) was added a solution of boronic acid (**28/58**, 2 mmol) in ethanol (10 mL), aqueous 2 *M* Na_2CO_3 (5 mL) and catalytic amount of $Pd[PPh_3]_4$ (0.1 mmol). The vigorously stirring yellow solution was heated in an oil bath set at 65–80 °C for 20 min–2 h under an atmosphere of argon. The dark reddish mixture produced was cooled and diluted with water (15 mL), extracted with EtOAc (3 x 25 mL). The combined organic extracts

were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue obtained was purified by column chromatography to afford **30/53/56/59**.

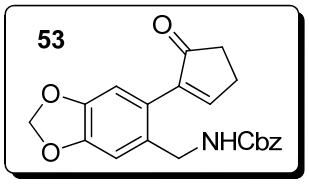
1. Benzyl (6-(6-oxocyclohex-1-enyl)benzo[*d*][1,3]dioxol-5-yl)methylcarbamate (30).



Purification by column chromatography (silica gel, elution with 25 % ethyl acetate-pet ether) afforded **30** as yellow paste.

Yield	:	82 %
mp	:	123–124 °C
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2947, 1712, 1694, 1504, 1230, 1040
^{1}H NMR (Benzene-d_6, 500 MHz) δ	:	7.32 (s, 1H), 7.31 (s, 1H), 7.21–7.11 (m, 3H), 7.00 (s, 1H), 6.52 (s, 1H), 6.40 (t, J = 4.1 Hz, 1H), 5.54 (bs, 1H), 5.43 (s, 2H), 5.16 (s, 2H), 4.21 (bs, 2H), 2.24 (t, J = 6.4 Hz, 2H), 1.83 (m, 2H), 1.54 (quintet, J = 6.4 Hz, 2H)
^{13}C NMR (Benzene-d_6, 125 MHz) δ	:	197.6, 156.5, 149.4, 148.0, 147.2, 140.6, 137.6, 131.7, 130.3, 128.5, 128.3, 127.9, 110.4, 109.4, 101.1, 66.5, 43.3, 38.6, 26.1, 22.8
Mass: m/z (%)	:	402 (M+Na^+, 55), 272 (55), 258 (52), 244(100)

2. Benzyl (6-(5-oxocyclopent-1-enyl)benzo[*d*][1,3]dioxol-5-yl)methylcarbamate (53).



Purification by column chromatography (silica gel, elution with 25 % ethyl acetate-pet ether) afforded **53** as yellow paste.

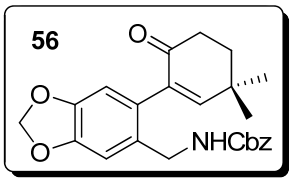
Yield	:	76 %
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3053, 1701, 1485, 1265
^{1}H NMR (Benzene-d_6, 400 MHz) δ	:	7.34–7.10 (m, 6H), 6.89 (s, 1H), 6.58 (s, 1H), 5.81 (bs, 1H), 5.40 (s, 2H), 5.16 (s, 2H), 4.23 (d, *J* = 6 Hz, 2H), 2.03 (m, 2H),

1.91 (m, 2H)

^{13}C NMR (Benzene-d_6, 100 MHz) δ : 207.2, 161.5, 156.7, 148.5, 147.4, 145.6, 137.6, 132.2, 128.6, 125.4, 109.9, 109.8, 101.3, 66.6, 43.2, 34.6, 26.6

Mass: m/z (%) : 404 ($M+K^+$, 22), 388 ($M+Na^+$, 100), 383 ($M+NH_4^+$, 22), 366 (MH^+, 18), 215 (35)

3. Benzyl (6-(3,3-dimethyl-6-oxocyclohex-1-enyl)benzo[*d*][1,3]dioxol-5-yl)methylcarbamate (56).



Purification by column chromatography (silica gel, elution with 20 % ethyl acetate-pet ether) afforded **56** as yellow paste.

Yield : 87 %

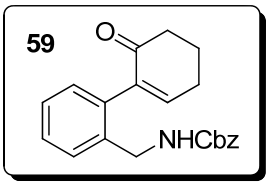
IR ν_{max} cm^{-1} ($CHCl_3$) : 3053, 1710, 1265

^{1}H NMR ($CDCl_3$, 200 MHz) δ : 7.37–7.28 (m, 5H), 6.85 (s, 1H), 6.59 (s, 1H), 6.46 (s, 1H), 5.95 (s, 2H), 5.22 (bs, 1H), 5.09 (s, 2H), 4.01(bs, 2H), 2.57 (dd, *J* = 7.2, 6.4 Hz, 2H), 1.93 (dd, *J* = 7, 6.6 Hz, 2H), 1.22 (s, 6H)

^{13}C NMR ($CDCl_3$, 50 MHz) δ : 198.7, 159.3, 156.2, 147.6, 146.8, 137.2, 136.5, 130.5, 129.3, 128.4, 128.0, 127.9, 110.0, 109.1, 101.2, 66.5, 42.8, 35.8, 34.7, 33.4, 27.7

Mass: m/z (%) : 430 ($M+Na^+$, 100), 425 ($M+NH_4^+$, 30), 408 (MH^+, 22), 257 (44), 184 (50)

4. Benzyl 2-(6-oxocyclohex-1-enyl)benzylcarbamate (59).



Purification by column chromatography (silica gel, elution with 20 % ethyl acetate-pet ether) afforded **59** as colorless paste.

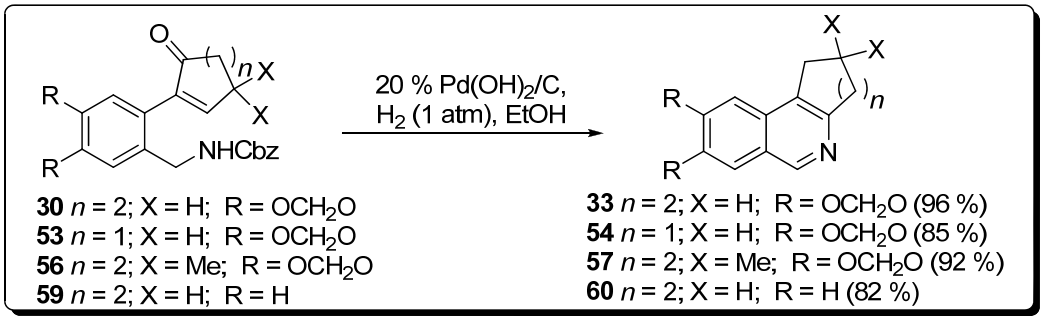
Yield : 75 %

IR ν_{max} cm^{-1} ($CHCl_3$) : 3055, 2927, 2358, 1714, 1514, 1265

^{1}H NMR ($CDCl_3$, 200 MHz) δ : 7.42–7.20 (m, 8H), 7.02 (m, 1H), 6.94 (t, *J* = 4.2 Hz, 1H), 5.29 (bs, 1H), 5.10 (s, 2H), 4.14 (bs, 2H), 2.52 (m, 4H), 2.09 (m, 2H)

^{13}C NMR	:	198.7, 156.2, 150.0, 140.5, 136.8, 136.5, 136.2, 129.9, 128.8,
($CDCl_3$, 50 MHz) δ		128.3, 127.9, 127.5, 66.4, 42.9, 38.4, 26.2, 22.8
Mass: m/z (%)	:	358 ($M+Na^+$, 100), 353 ($M+NH_4^+$, 38), 336 (MH^+, 50), 292 (25)

IV. General procedure for syntheses of isoquinolines:

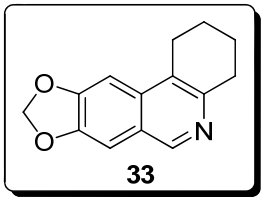


30 *n* = 2; X = H; R = OCH_2O
53 *n* = 1; X = H; R = OCH_2O
56 *n* = 2; X = Me; R = OCH_2O
59 *n* = 2; X = H; R = H

33 *n* = 2; X = H; R = OCH_2O (96 %)
54 *n* = 1; X = H; R = OCH_2O (85 %)
57 *n* = 2; X = Me; R = OCH_2O (92 %)
60 *n* = 2; X = H; R = H (82 %)

A solution of Suzuki cross coupling product (**30/53/56/59**, 0.5 mmol) in ethanol (25 mL) was hydrogenated at atmospheric pressure in the presence of 20 % $Pd(OH)_2$ on charcoal (50 mg). The reaction was monitored for its starting material consumption (TLC analysis, approx. 9–14 h). After complete disappearance of starting material, the reaction mixture was passed through a short pad of Celite. The solvent was removed by rotary evaporation and the residue was purified by column chromatography to produce **33/54/57/60**.

1. 1,2,3,4-Tetrahydro-[1,3]dioxolo[4,5-*j*]phenanthridine (33).

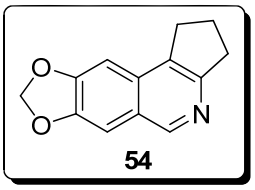


33

Purified by column chromatography (silica gel, elution with 45 % ethyl acetate-pet ether) to provide **33** as white solid.

Yield	:	96 %
mp	:	89–91 °C
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3053, 2306, 1460, 1265
^{1}H NMR	:	8.73 (s, 1H), 7.07 (s, 2H), 6.02 (s, 2H), 2.98 (s, 2H), 2.87 (s,
($CDCl_3$, 400 MHz) δ		2H), 1.88 (m, 4H)
^{13}C NMR	:	150.8, 149.2, 147.7, 147.0, 133.6, 124.2, 123.8, 103.5, 101.3,
($CDCl_3$, 100 MHz) δ		98.5, 32.5, 25.1, 23.0, 22.7
Mass: m/z (%)	:	250 ($M+Na^+$, 100)

2. 2,3-Tihydro-1*H*-cyclopenta[*c*][1,3]dioxolo[4,5-*g*]isoquinoline (54).

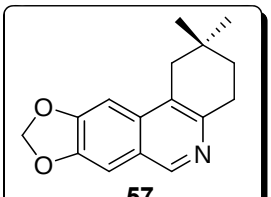


54

The isoquinoline **54** was purified by column chromatography (silica gel, elution with 50 % ethyl acetate-pet ether) to give the white solid.

Yield	:	85 %
mp	:	133–135 °C
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3053, 2358, 1461, 1265
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	8.76 (s, 1H), 7.16 (s, 1H), 6.94 (s, 1H), 6.05 (s, 2H), 3.18-3.06 (m, 4H), 2.22 (quintet, *J* = 7.5 Hz, 2H)
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	156.9, 150.8, 149.0, 147.3, 31.8, 129.9, 124.2, 103.7, 101.4, 99.5, 34.4, 29.1, 22.4
Mass: m/z (%)	:	214 (MH^+, 100)

3. 2,2-Dimethyl-1,2,3,4-tetrahydro-[1,3]dioxolo[4,5-*j*]phenanthridine (57).

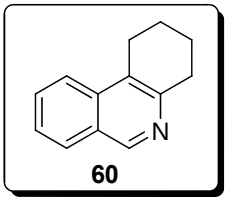


57

Purified by column chromatography (silica gel, elution with 45 % ethyl acetate-pet ether) to afford **57** as white solid.

Yield	:	92 %
mp	:	173–174 °C
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3055, 2360, 1460, 1265
^{1}H NMR ($CDCl_3$, 200 MHz) δ	:	8.78 (s, 1H), 7.14 (s, 1H), 7.12 (s, 1H), 6.05 (s, 2H), 3.03 (t, *J* = 6.7 Hz, 2H), 2.69 (s, 2H), 1.6 (t, *J* = 6.7 Hz, 2H), 1.06 (s, 6H)
^{13}C NMR ($CDCl_3$, 50 MHz) δ	:	150.8, 147.9, 147.8, 147.0, 133.8, 123.8, 123.3, 103.5, 101.3, 98.5, 39.0, 35.4, 29.5, 29.2, 28.3
Mass: m/z (%)	:	278 ($M+Na^+$, 16), 257 ($M+2^+$, 24), 256 (MH^+, 100)

4. 1,2,3,4-Tetrahydrophenanthridine (60).

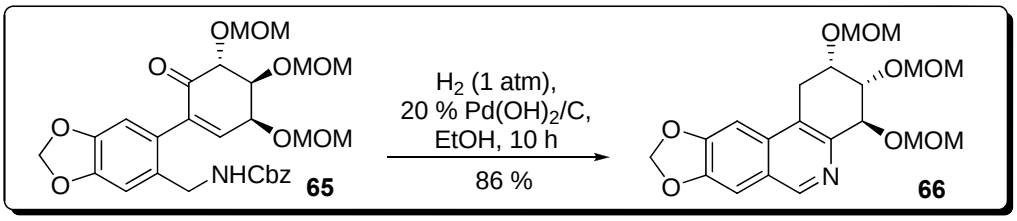


Purified by column chromatography (silica gel, elution with 40 % ethyl acetate-pet ether) to give the isoquinoline **60** as colorless oil.

Yield	:	82 %
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3055, 2931, 2358, 2341, 1622, 1577
^{1}H NMR	:	9.03 (s,1H), 7.90 (m, 1H), 7.86 (m, 1H), 7.67 (m, 1H), 7.50 (m,
($CDCl_3$, 200 MHz) δ		1H), 3.06 (m, 4H), 1.94 (m, 4H)
^{13}C NMR	:	149.9, 135.2, 130.0, 128.0, 126.7, 125.7, 124.5, 121.8, 32.6,
($CDCl_3$, 50 MHz) δ		24.7, 22.9, 22.5
Mass: m/z (%)	:	206 ($M+Na^+$, 11), 184 (MH^+, 100)

V. Syntheses of pancratistatin-like isoquinolines:

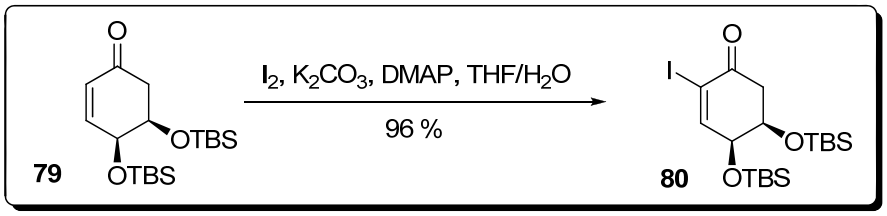
1. (2*S*,3*S*,4*S*)-2,3,4-Tris(methoxymethoxy)-1,2,3,4-tetrahydro-[1,3]dioxolo[4,5-*j*]phenanthridine (66).



General synthesis of isoquinoline procedure was applied to **65** to produce **66** after column chromatography (silica gel, elution with 60 % ethyl acetate-hexanes).

Yield	:	86 %
$[\alpha]^{27}_D$	:	+118.1 (*c* 1.1, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3433, 2360, 1643,
^{1}H NMR	:	8.88 (s, 1H), 7.21 (s, 1H), 7.15 (s, 1H), 6.08 (d, *J* = 2.3 Hz, 2H),
($CDCl_3$, 400 MHz) δ		5.12 (d, *J* = 6.8 Hz, 1H), 4.92 (d, *J* = 3.5 Hz, 1H), 4.90–4.78 (m 4H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.50–4.40 (m, 2H), 3.47 (s, 3H), 3.46 (s, 3H), 3.32 (dd, *J* = 16.0, 6.3 Hz, 1H), 3.30 (s, 3H), 3.15 (dd, *J* = 16.0, 10 Hz, 1H)
^{13}C NMR	:	151.3, 149.4, 148.2, 144.7, 133.1, 125.1, 123.9, 103.7, 101.7,
($CDCl_3$, 100 MHz) δ		99.3, 97.2, 96.6, 95.4, 78.8, 75.4, 71.3, 55.9, 55.5, 55.54, 27.6
Mass: m/z (%)	:	408 (MH^+, 100), 228 (68), 214 (66)

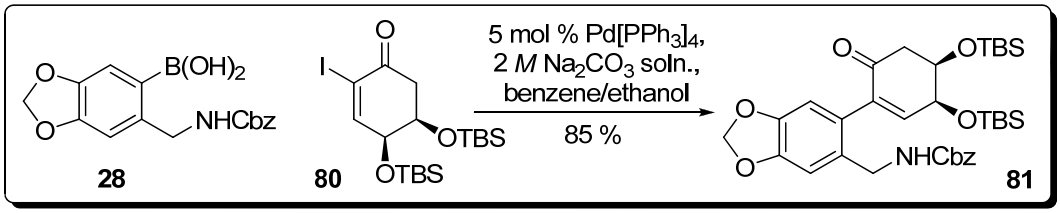
2. (4*S*,5*R*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-2-iodocyclohex-2-enone (80).



Prepared using general procedure for α-iodoenones (condition B), the residue was subjected to column chromatography (silica gel, elution with 4 % ethyl acetate-pet ether) to give **80** as a white solid.

Yield	:	96 %
$[\alpha]^{27}_D$	:	+70.2 (*c* 1.0, $CHCl_3$)
mp	:	71–72 °C
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3053, 2956, 1697, 1421, 1265
^{1}H NMR ($CDCl_3$, 400 MHz) δ	:	7.46 (d, *J* = 3.0 Hz, 1H), 4.39 (s, 1H), 4.18 (dd, *J* = 3.3, 3.0 Hz, 1H), 2.94 (dd, *J* = 16.1, 7.0 Hz, 1H), 2.62 (dd, *J* = 16.1, 2.8 Hz, 1H), 0.90 (s, 9H), 0.82 (s, 9H), 0.11 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H)
^{13}C NMR ($CDCl_3$, 100 MHz) δ	:	190.7, 157.5, 71.9, 71.4, 42.7, 25.8, 25.7, 18.2, 18.0, –4.5, –4.7, –4.8
Mass: m/z (%)	:	521 ($M+K^+$, 28), 505 ($M+Na^+$, 25), 500 ($M+NH_4^+$, 100), 483 (MH^+, 23), 376 (20), 238 (22), 216 (33)

3. Benzyl (6-((3*S*,4*R*)-3,4-bis(*tert*-butyldimethylsilyloxy)-6-oxocyclohex-1-enyl)benzo[*d*][1,3]dioxol-5-yl)methylcarbamate (81).

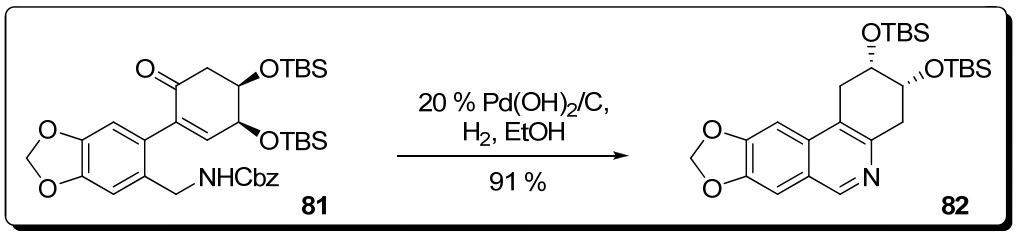


General Suzuki cross-coupling procedure was applied to precursors **28** and **80**, purified by column chromatography (silica gel, elution with 10 % ethyl acetate-pet ether) to obtain **81**.

Yield	:	85 %
$[\alpha]^{27}_D$	:	+60.6 (*c* 1.46, $CHCl_3$)
IR ν_{max} cm^{-1} ($CHCl_3$)	:	2930, 2358, 1720, 1504, 1265

^{1}H NMR	:	7.32 (m, 5H), 6.92 (s, 1H), 6.57 (s, 1H), 6.47 (s, 1H), 5.94 (s,
($CDCl_3$, 200 MHz) δ		2H), 5.30 (bs, 1H), 5.08 (s, 2H), 4.62 (bs, 1H), 4.32 (bs, 1H), 4.02 (bs, 2H), 2.84 (dd, *J* = 16.4, 5.4 Hz, 1H), 2.60 (dd, *J* = 16.2, 2.0, 1H), 0.92 (s, 9H), 0.84 (s, 9H), 0.14 (s, 3H), 0.13 (s,3H), 0.08 (s, 6H)
^{13}C NMR	:	196.9, 156.4, 149.2, 147.8, 146.8, 139.5, 136.6, 128.4, 127.9,
($CDCl_3$, 50 MHz) δ		109.6, 101.2, 72.4, 70.5, 66.5, 45.4, 42.7, 25.9, 25.7, 18.3, 18.1, –4.5, –4.8, –5.0
Mass: m/z (%)	:	662 ($M+Na^+$, 100), 657 ($M+NH_4^+$, 25), 640 (MH^+, 13)

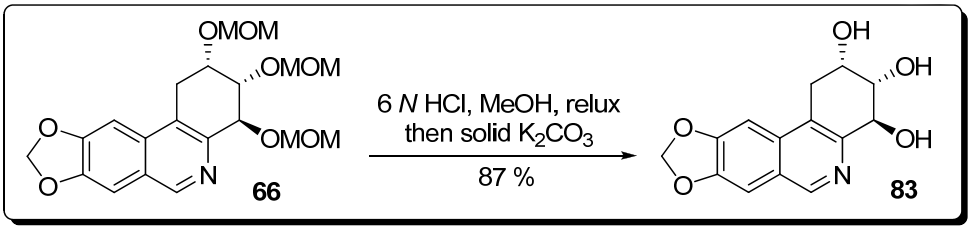
4. (2*S*,3*R*)-2,3-Bis(*tert*-butyldimethylsilyloxy)-1,2,3,4-tetrahydro-[1,3]dioxolo[4,5-*j*]phenanthridine (82).



General isoquinoline synthesis procedure was applied to **81** to produce **82** after column chromatography (silica gel, elution with 25 % ethyl acetate-pet ether).

Yield	:	91 %
$[\alpha]^{27}_D$	:	–20.6 (*c* 1.0, $CHCl_3$)
mp	:	137–138 °C
IR ν_{max} cm^{-1} ($CHCl_3$)	:	3050, 2359, 1472, 1265
^{1}H NMR	:	8.79 (s, 1H), 7.13 (s, 2H), 6.06 (s, 2H), 4.16 (m, 2H), 3.10 (m,
($CDCl_3$, 200 MHz) δ		4H), 0.86 (s, 9H), 0.83 (s, 9H), 0.12 (s, 3H), 0.10 (s, 6H), 0.07 (s, 3H)
^{13}C NMR	:	151.0, 148.3, 147.2, 146.5, 133.4, 123.9, 121.8, 103.6, 101.5,
($CDCl_3$, 50 MHz) δ		98.7, 70.8, 70.6, 39.1, 31.5, 25.9, 25.8, 18.2, –4.4, –4.5, –4.7
Mass: m/z (%)	:	511 ($M+Na^+$, 16), 489 (MH^+, 100)

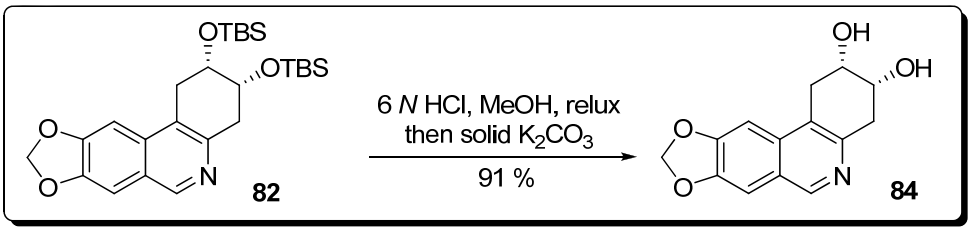
5. (2*S*,3*S*,4*S*)-1,2,3,4-tetrahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-2,3,4-triol (83).



To a solution of **66** (75 mg, 0.18 mmol) in methanol (5 mL) was added 6 *N* HCl (2 mL) and the reaction mixture was refluxed for 18 h. Reaction mixture was cooled, basified with excess of solid K_2CO_3 and stirred for further 3 h. Solvents were evaporated to dryness and the residue was subjected to column chromatography (silica gel, elution with 15 % $CHCl_3$-methanol) to afford **83** as white solid.

Yield	:	87 %
$[\alpha]^{27}_D$	:	+48.5 (*c* 0.5, DMF)
mp	:	240–241 °C
^{1}H NMR (DMSO-d_6, 500 MHz) δ	:	8.80 (s, 1H), 7.41 (s, 1H), 7.28 (s, 1H), 6.10 (s, 2H), 4.81 (d, *J* = 4.4 Hz, 1H), 4.78 (d, *J* = 4.2 Hz, 1H), 4.03 (d, *J* = 4.7 Hz, 1H), 3.97 (d, *J* = 4.7 Hz, 1H), 3.01 (m, 4H)
^{13}C NMR (DMSO-d_6, 125 MHz) δ	:	151.0, 148.3, 148.2, 147.7, 132.6, 124.5, 123.1, 103.4, 102.0, 99.2, 73.6, 73.5, 65.4, 29.4
Mass: m/z (%)	:	298 ($M+Na^+$, 38), 276 (MH^+, 100), 214 (42)

6. (2*S*,3*R*)-1,2,3,4-Tetrahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-2,3-diol (84).

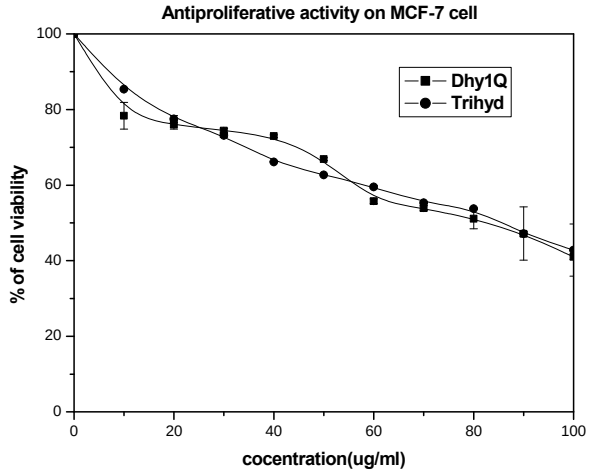


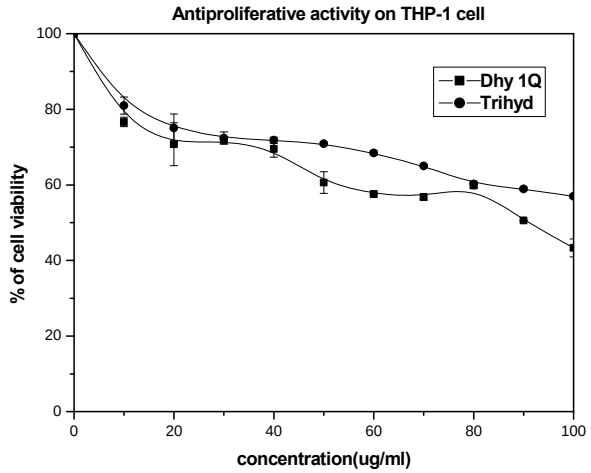
Compound **82** was subjected to the above deprotection procedure and column chromatographed (silica gel, elution with 7 % $CHCl_3$-methanol) to afford **84** as white solid.

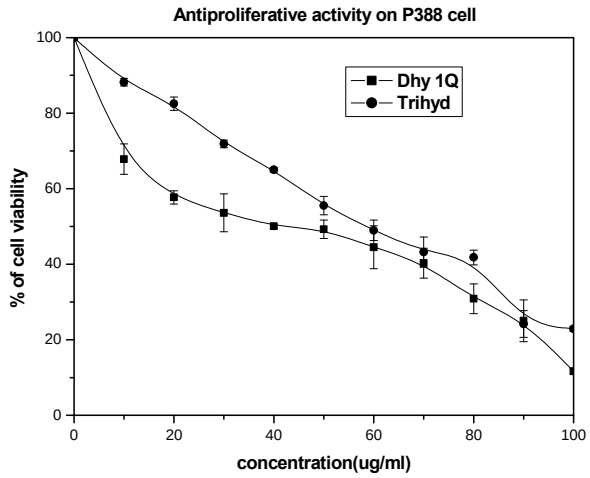
Yield	:	91 %
$[\alpha]^{27}_D$	:	–43.1 (*c* 0.5, DMF)
mp	:	287–289 °C
^{1}H NMR (DMSO-d_6, 500 MHz) δ	:	8.80 (s, 1H), 7.41 (s, 1H), 7.28 (s, 1H), 6.10 (s, 2H), 4.81 (d, *J* = 4.4 Hz, 1H), 4.78 (d, *J* = 4.2 Hz, 1H), 4.03 (d, *J* = 4.7 Hz, 1H), 3.97 (d, *J* = 4.7 Hz, 1H), 3.01 (m, 4H)
^{13}C NMR (DMSO-d_6, 125 MHz) δ	:	150.9, 148.0, 147.2, 146.8, 133.0, 123.9, 121.8, 103.5, 101.9, 98.7, 68.4, 68.0, 38.0, 30.6
Mass: m/z (%)	:	282 ($M+Na^+$, 19), 260 (MH^+, 100)

3.10.II. Cytotxicity studies

The general procedure for growth inhibition assay discussed in the second chapter of this dissertation was followed to evaluate cytotoxicities of compounds **83** and **84**. The growth inhibition plots for three cells are given below.






Antiproliferative activity on P388 cell
Dhy 1Q
Trihyd
% of cell viability
concentration(ug/ml)
0
20
40
60
80
100

3.11. References

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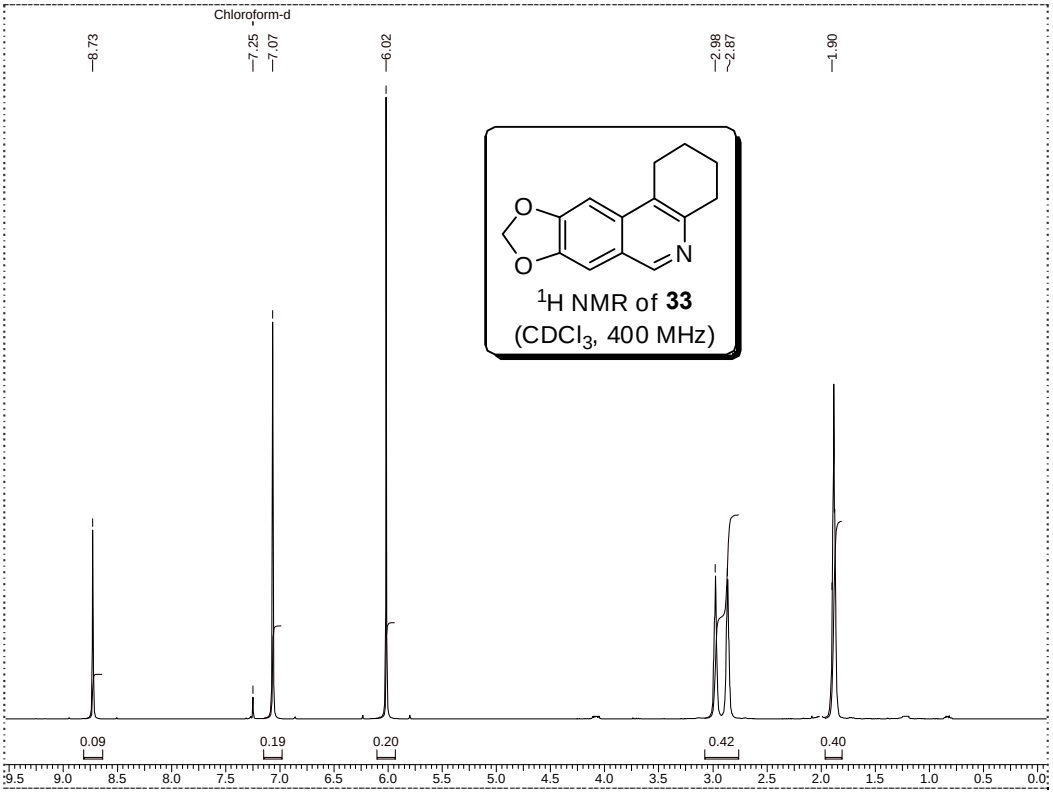
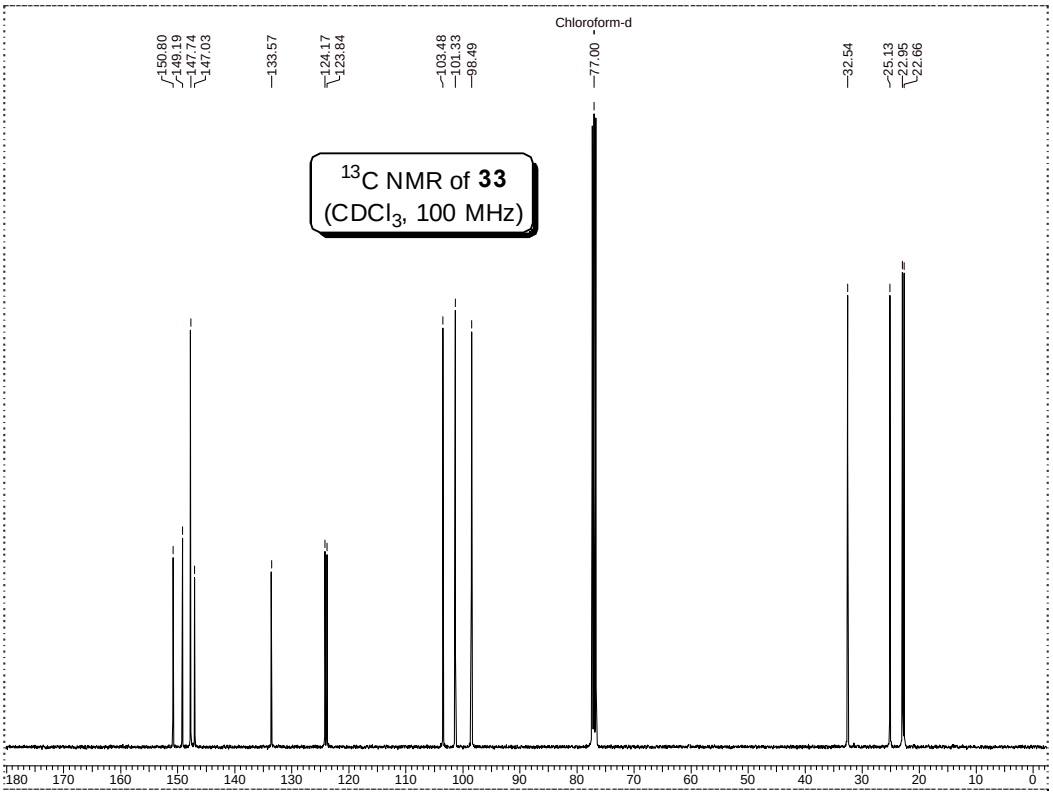
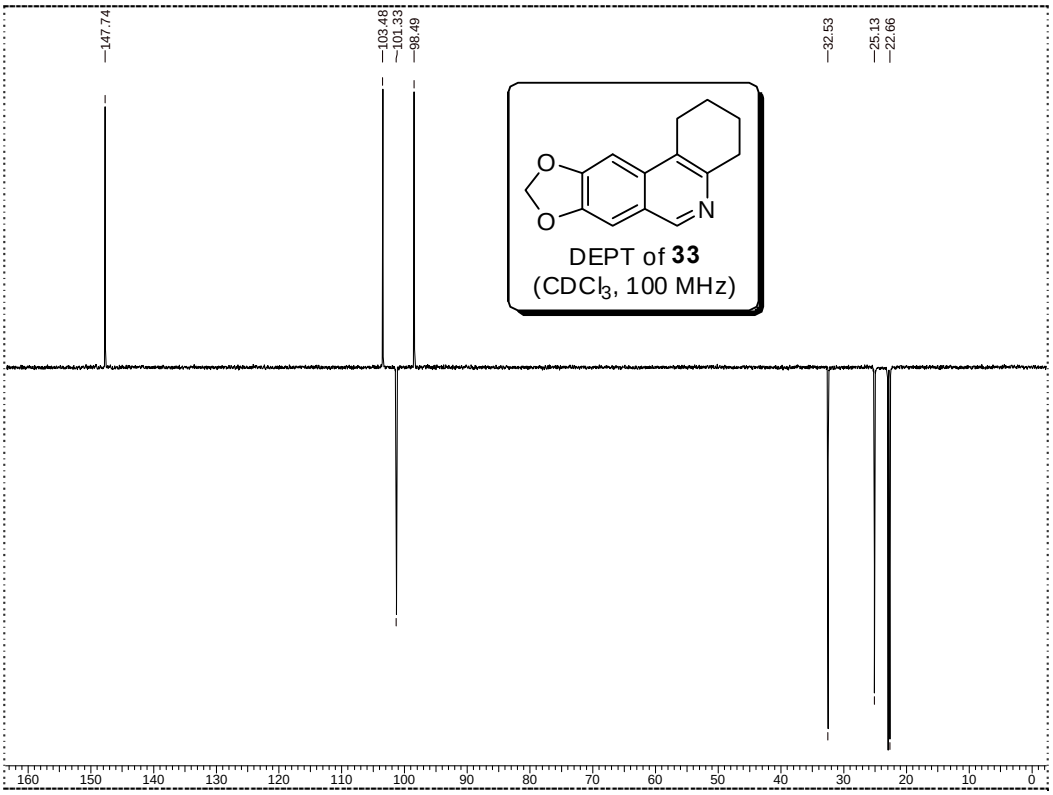
3.12. Spectra of all new compounds

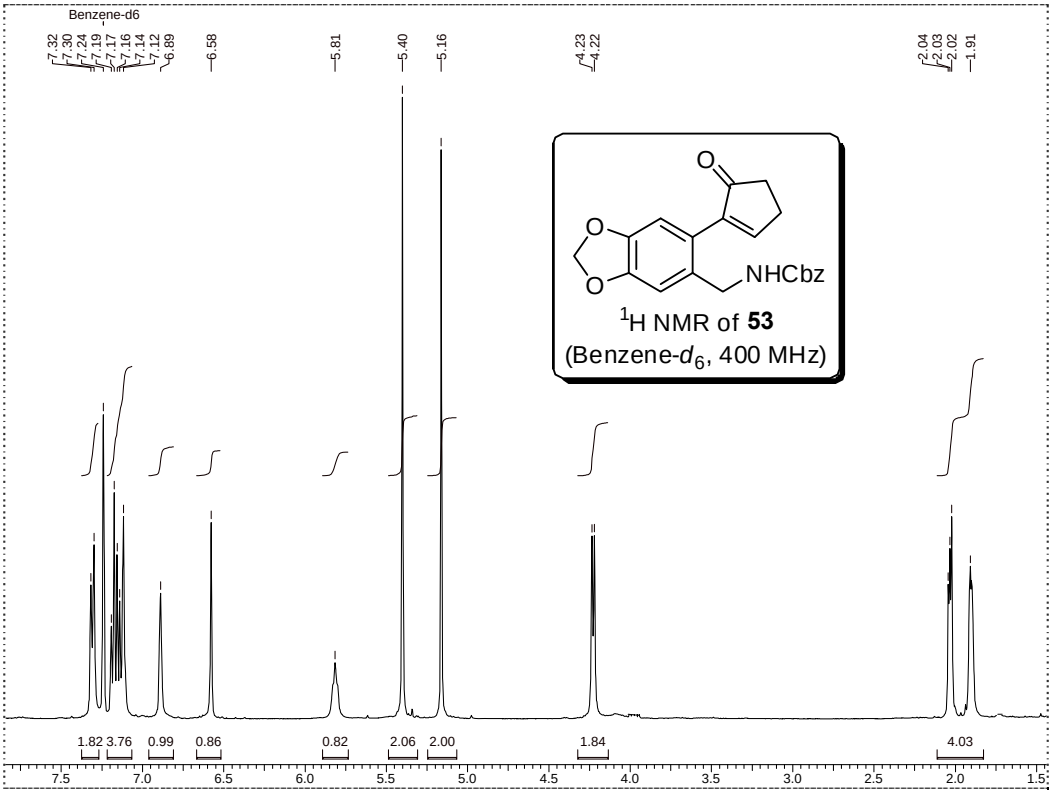
1. 1,2,3,4-Tetrahydro-[1,3]dioxolo[4,5-*j*]phenanthridine (33).

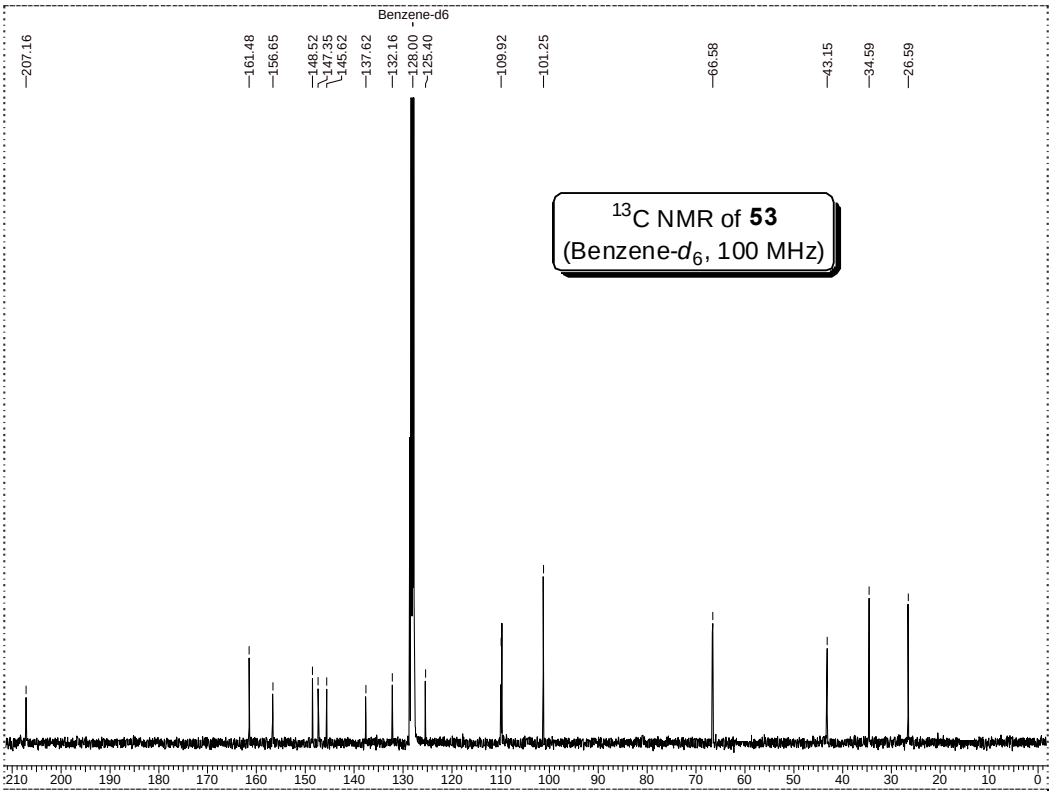




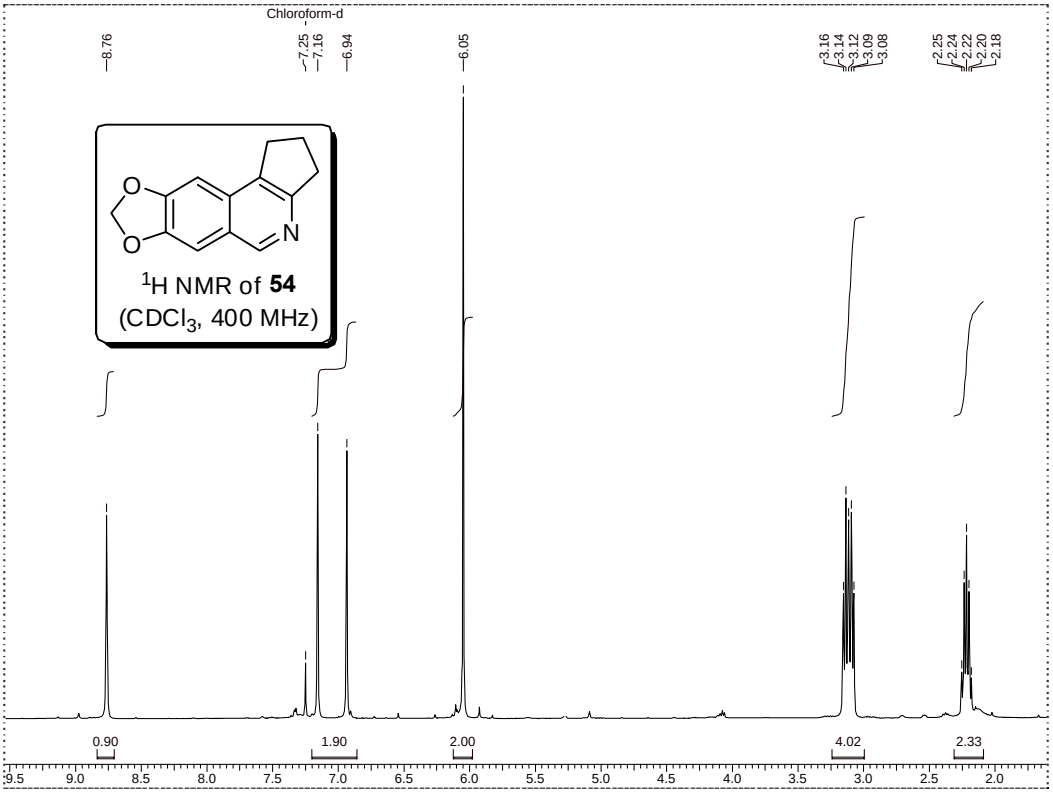

147.74
103.48
101.33
98.49
32.53
25.13
22.66
O
O
N
DEPT of **33**
($CDCl_3$, 100 MHz)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

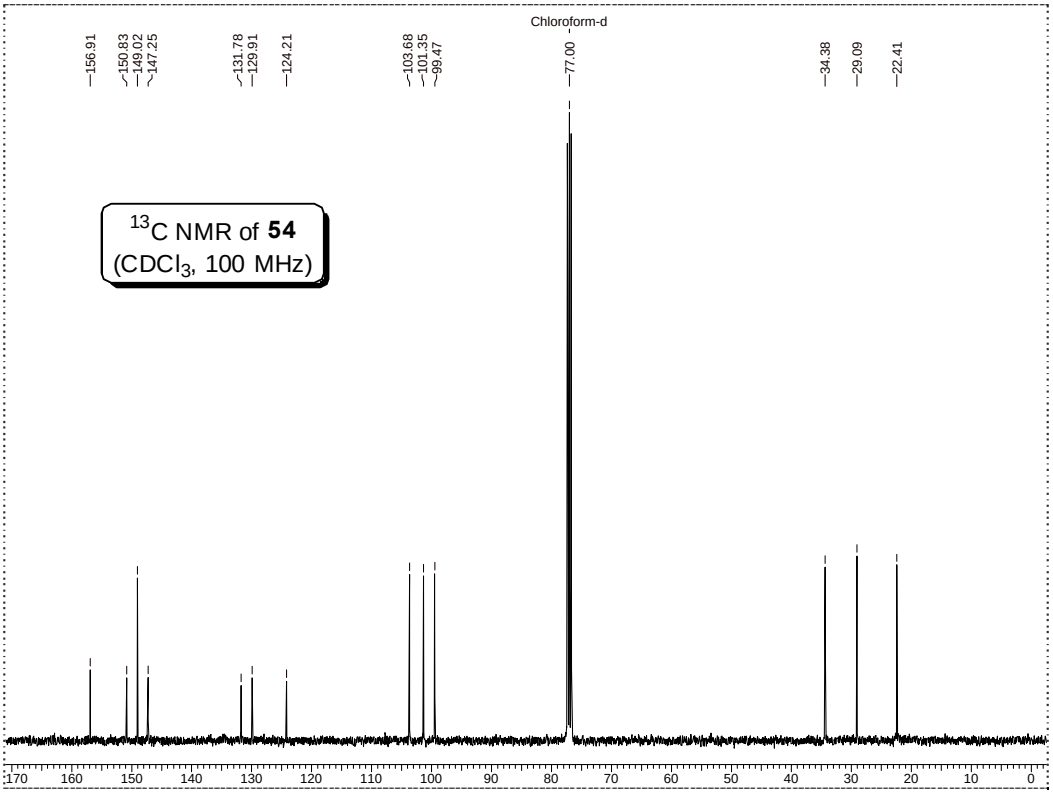
2. Benzyl (6-(5-oxocyclopent-1-enyl)benzo[*d*][1,3]dioxol-5-yl)methylcarbamate (53).



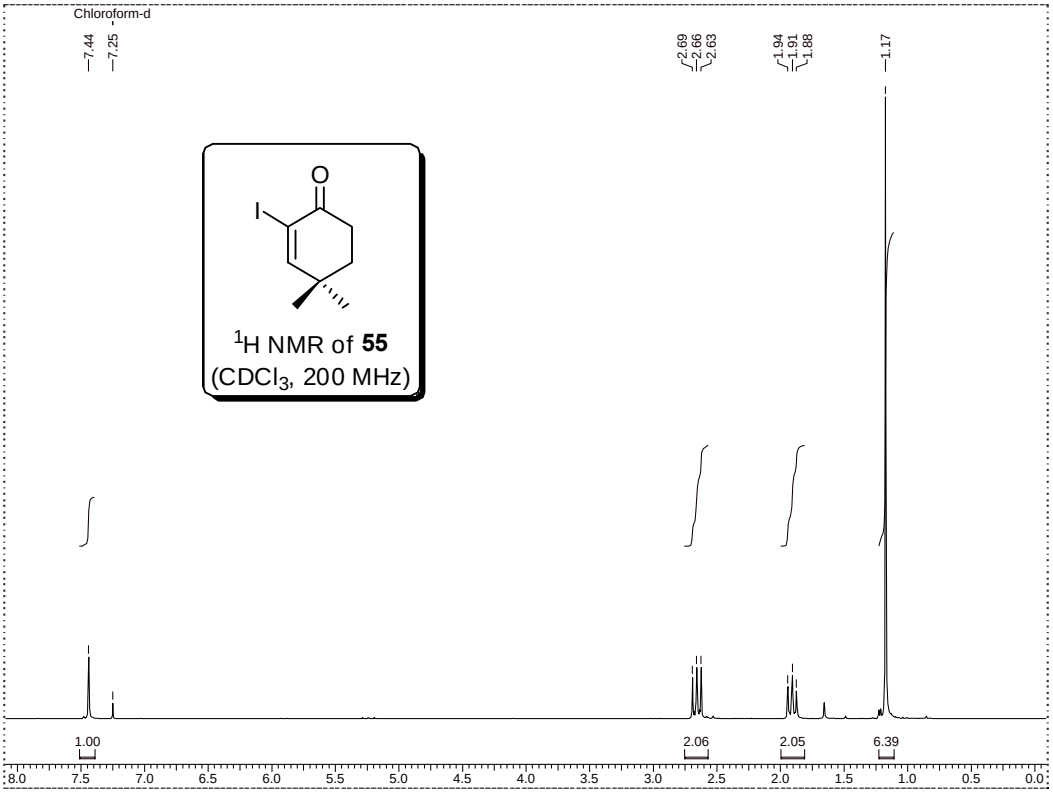


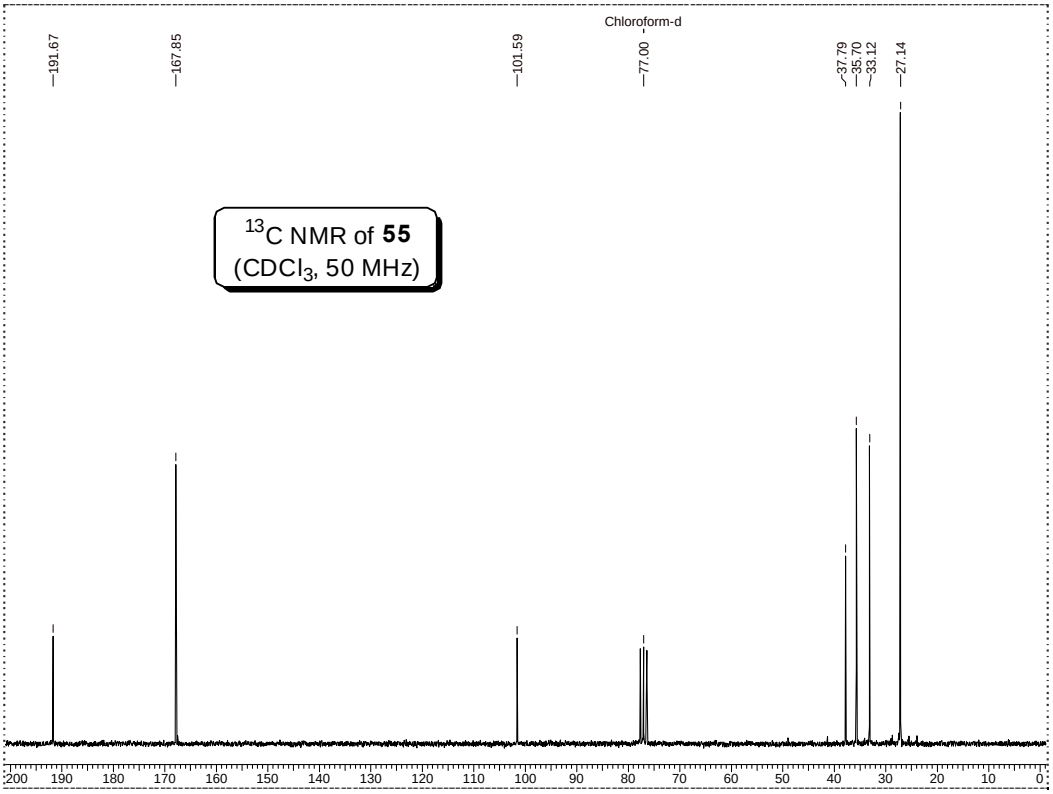
3. 2,3-Tihydro-1*H*-cyclopenta[*c*][1,3]dioxolo[4,5-*g*]isoquinoline (54).



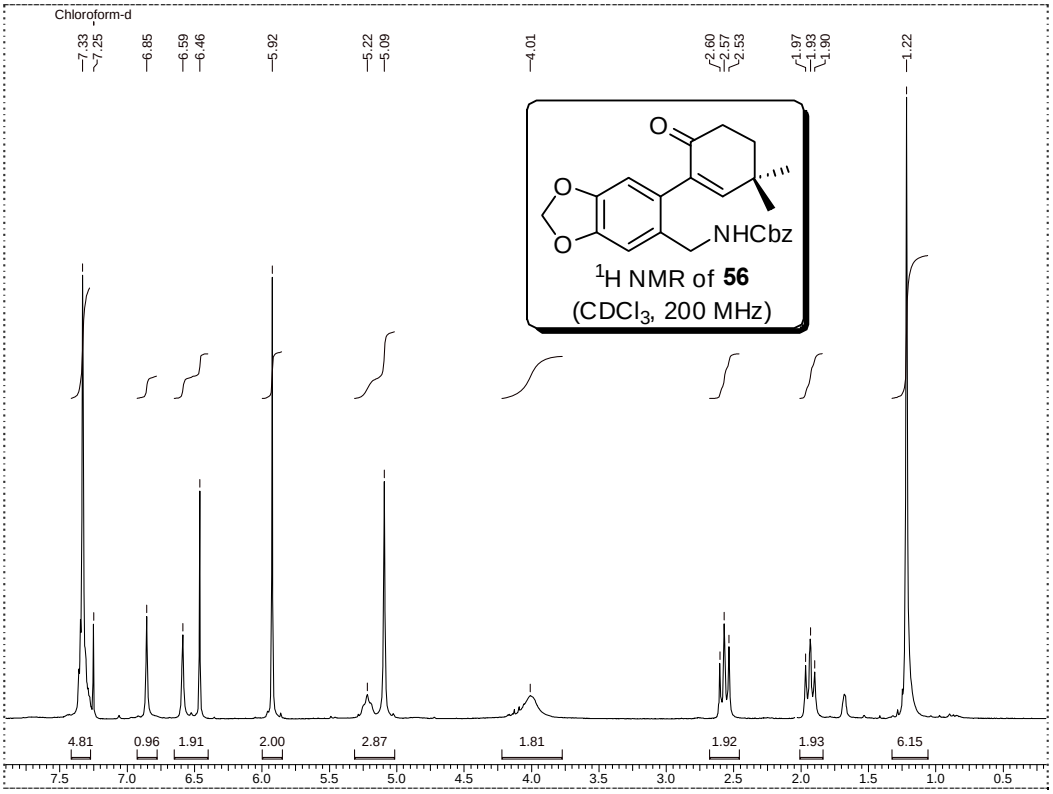


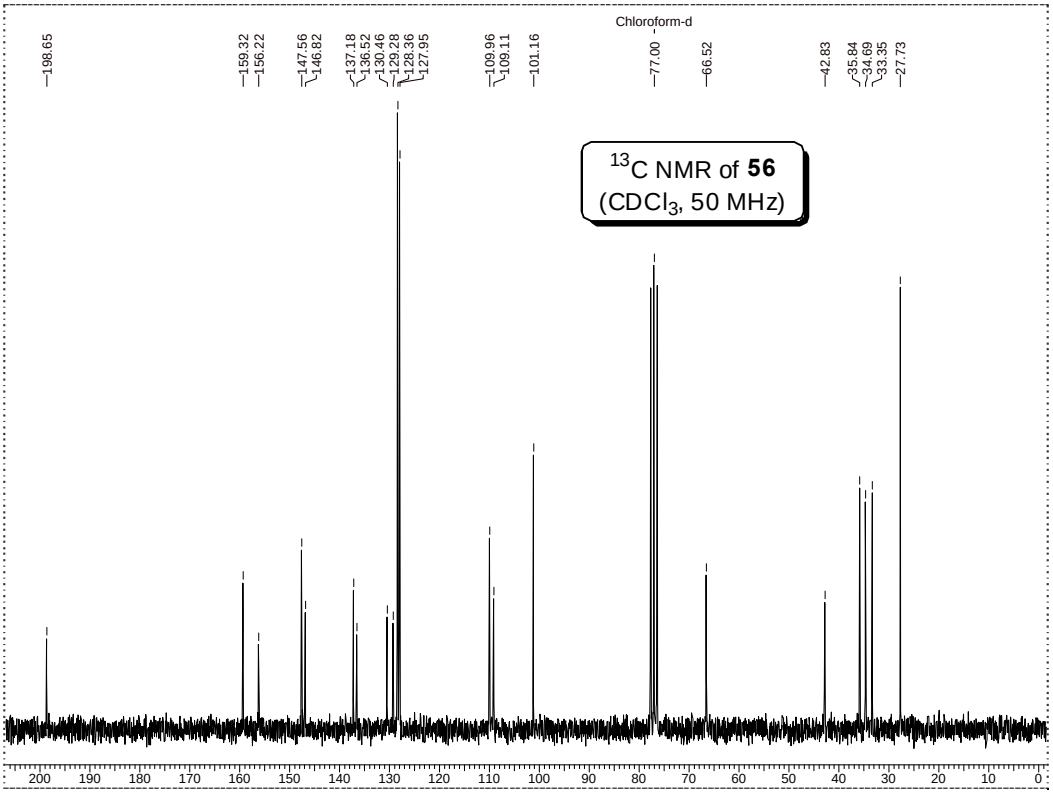
4. 2-iodo-4,4-dimethylcyclohex-2-enone (55):



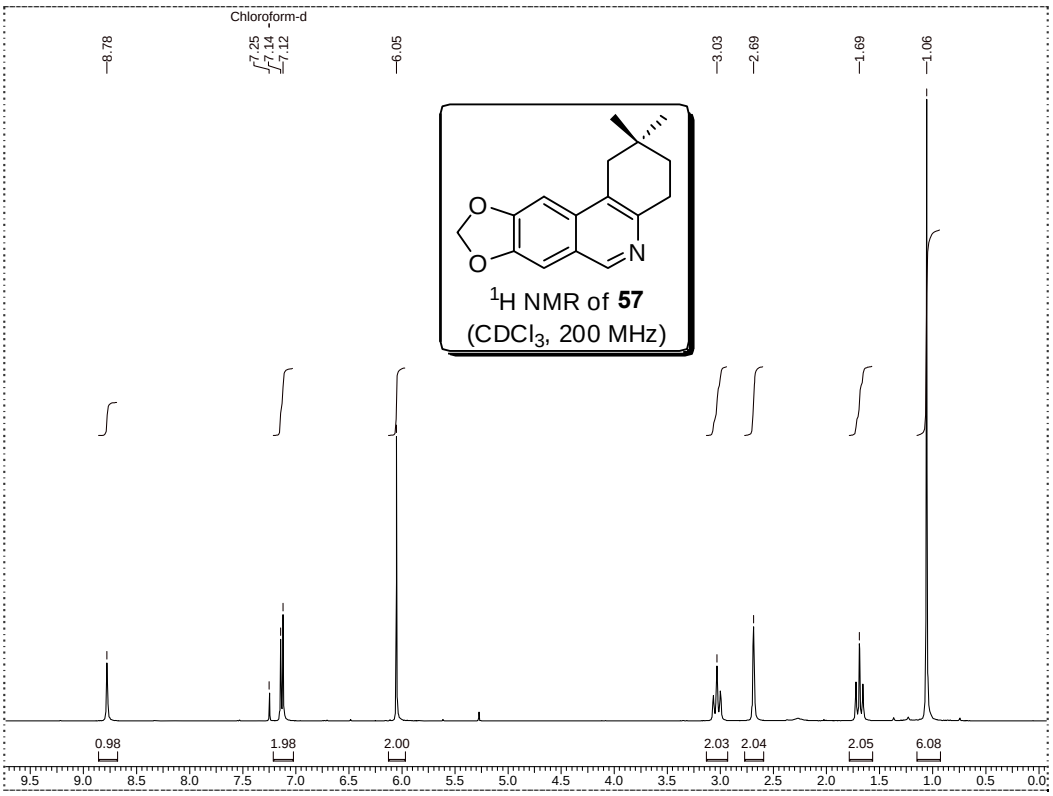


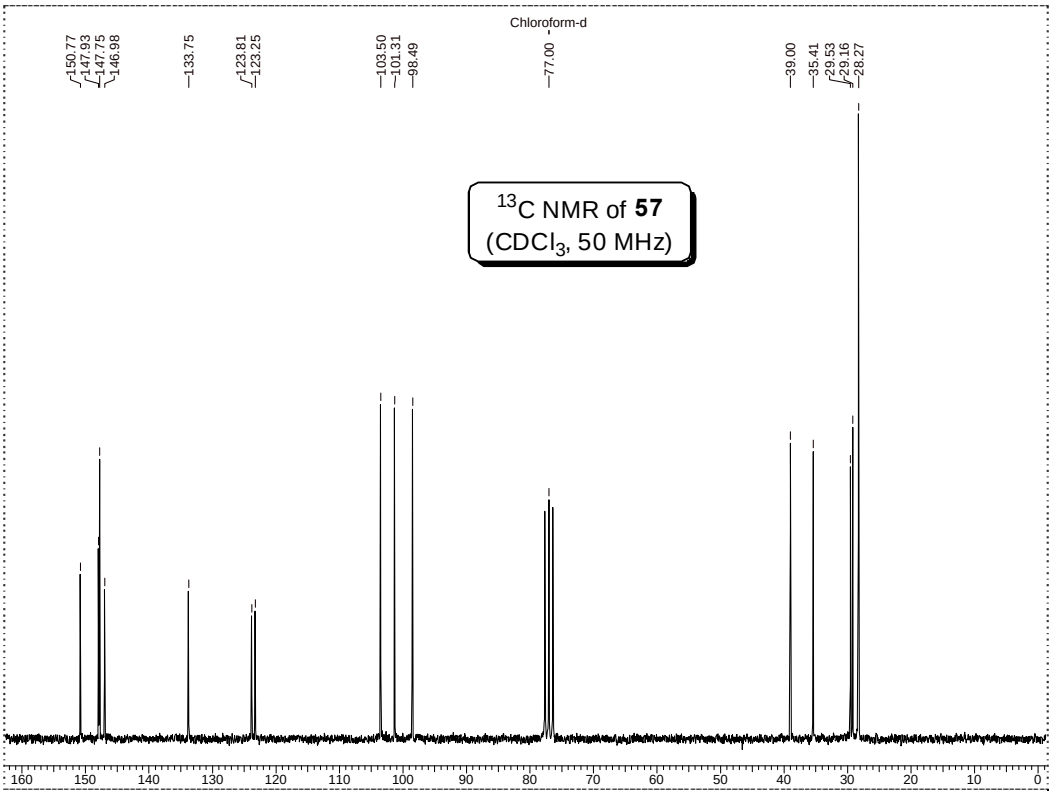
5. Benzyl (6-(3,3-dimethyl-6-oxocyclohex-1-enyl)benzo[*d*][1,3]dioxol-5-yl)methylcarbamate (56).



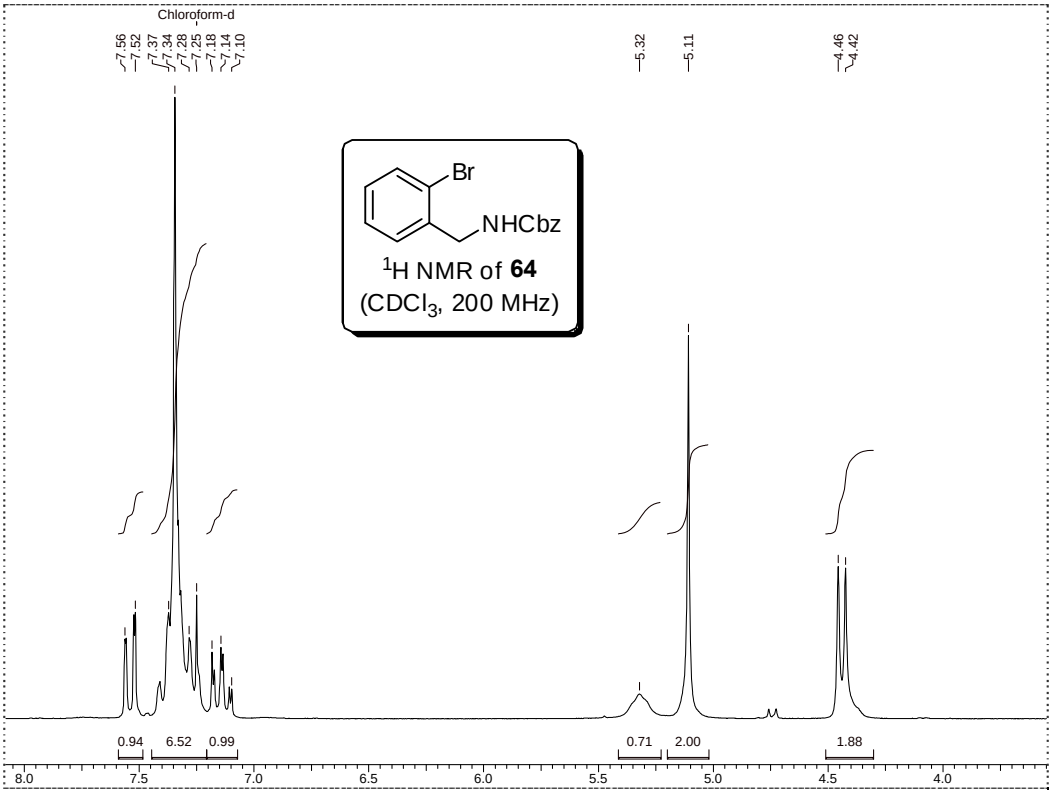


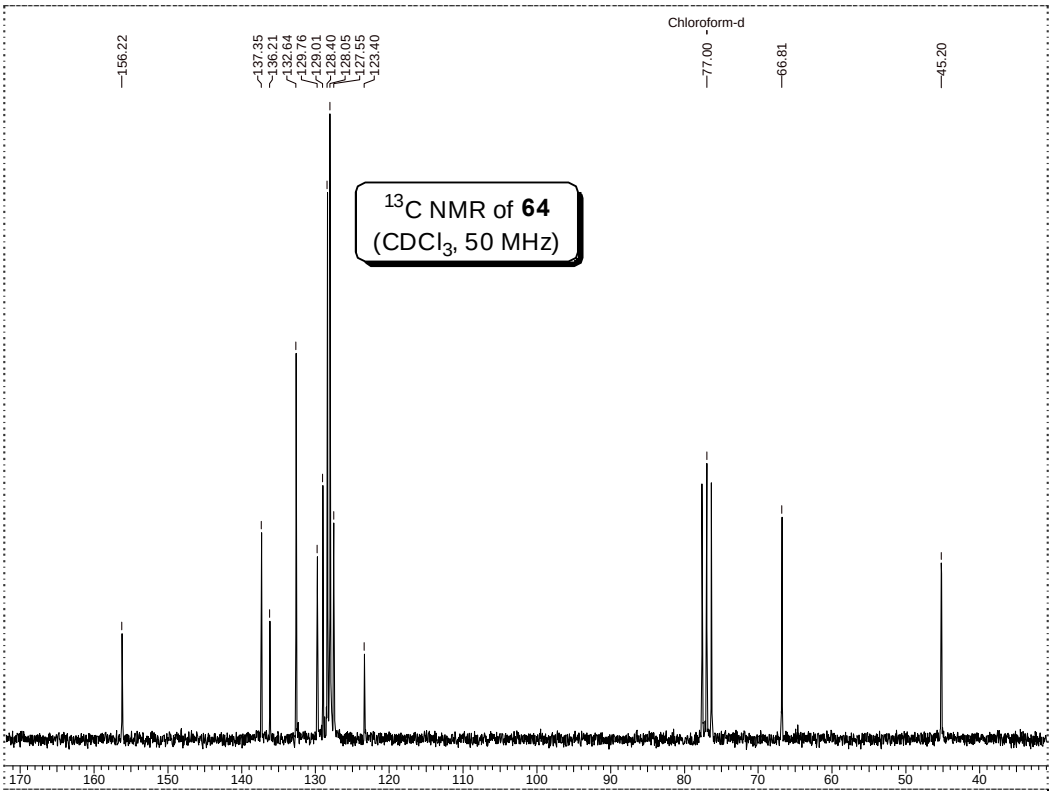
6. 2,2-Dimethyl-1,2,3,4-tetrahydro-[1,3]dioxolo[4,5-*j*]phenanthridine (57).



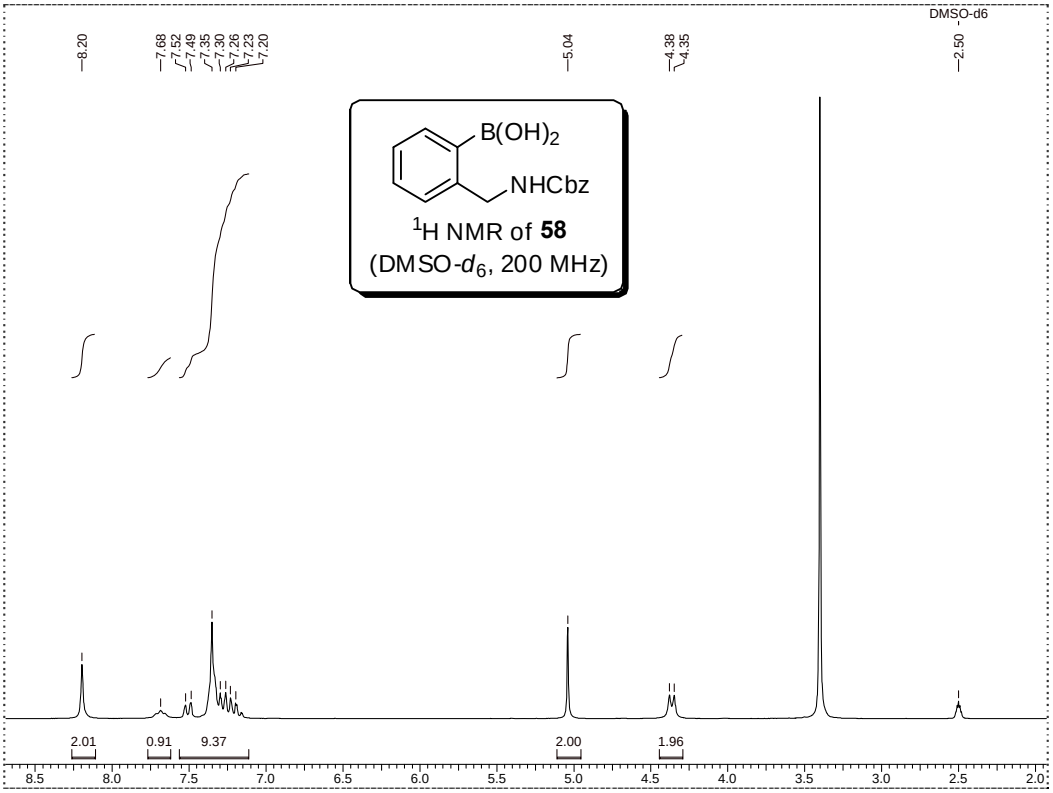


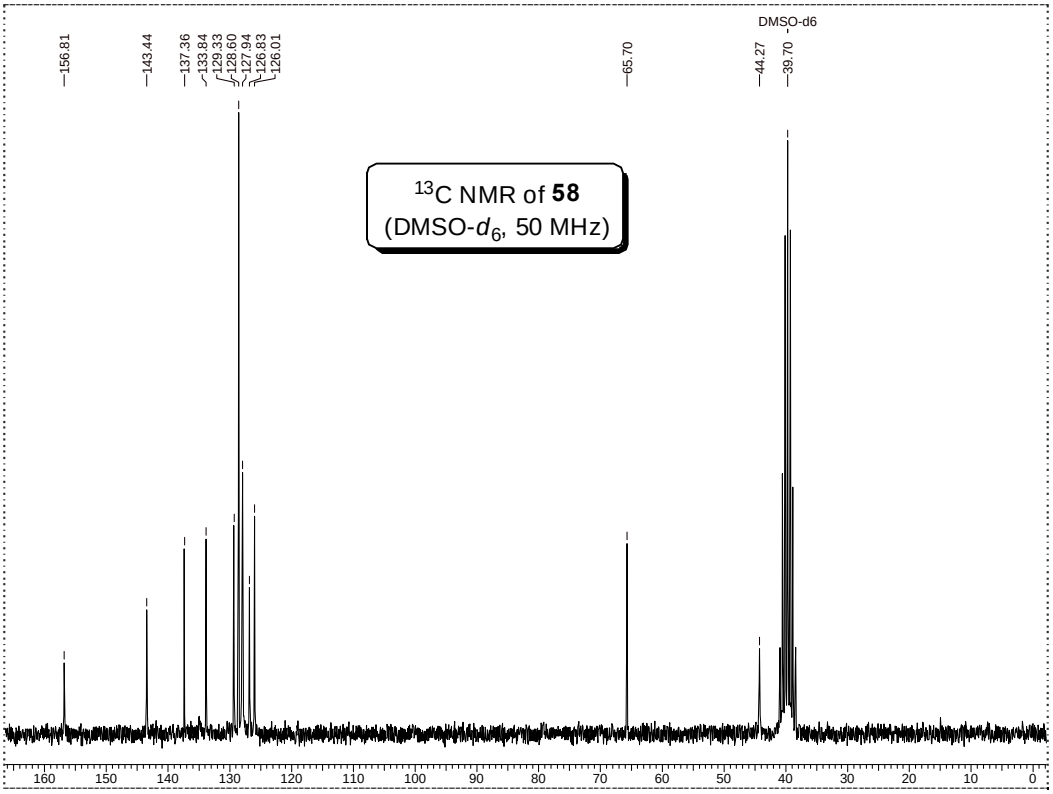
7. Benzyl 2-bromobenzylcarbamate (64).



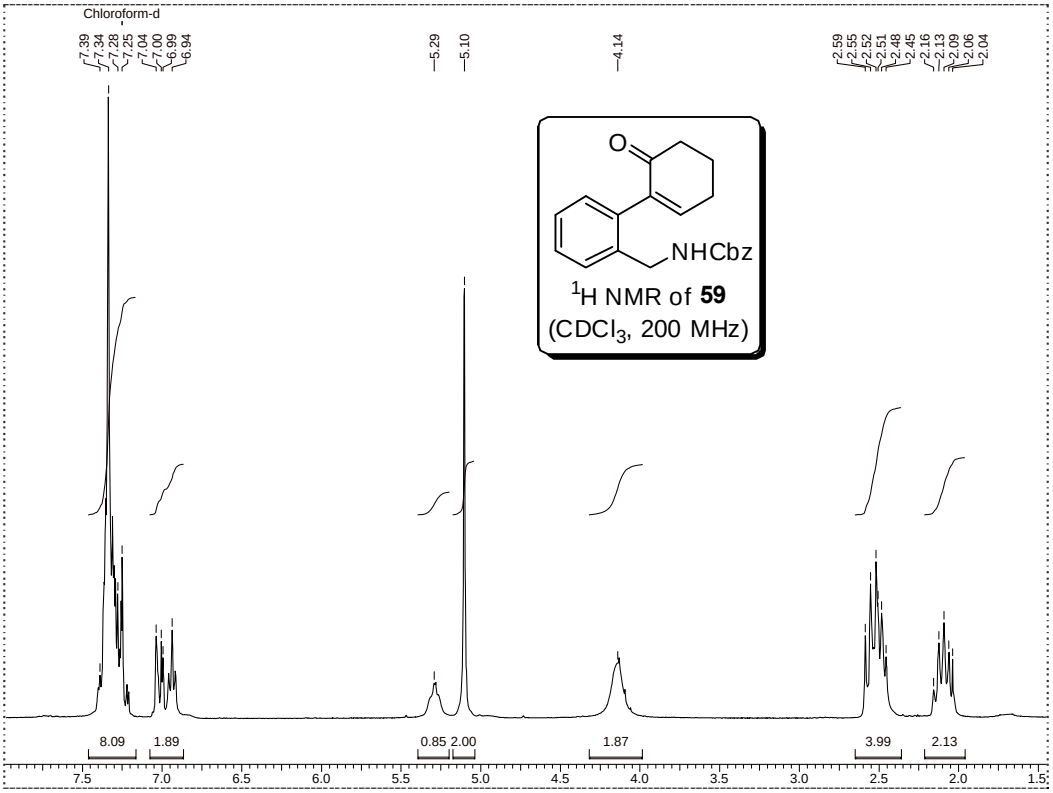


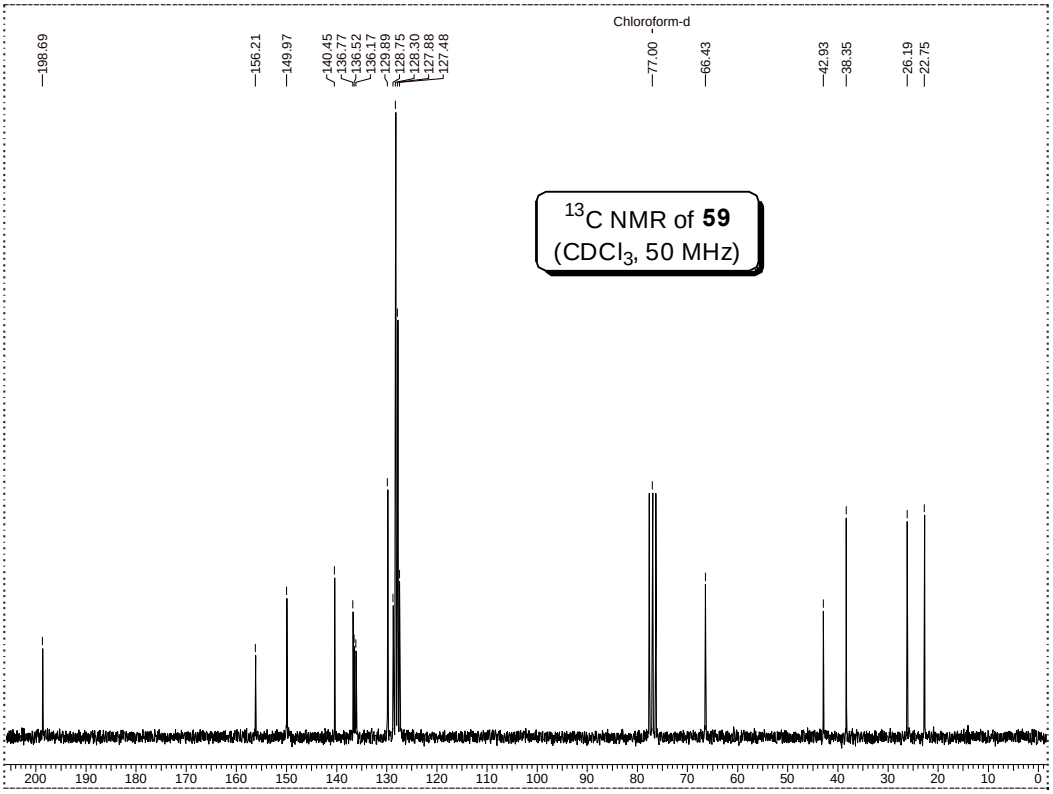
8. 2-((Benzyloxycarbonylamino)methyl)phenylboronic acid (58).



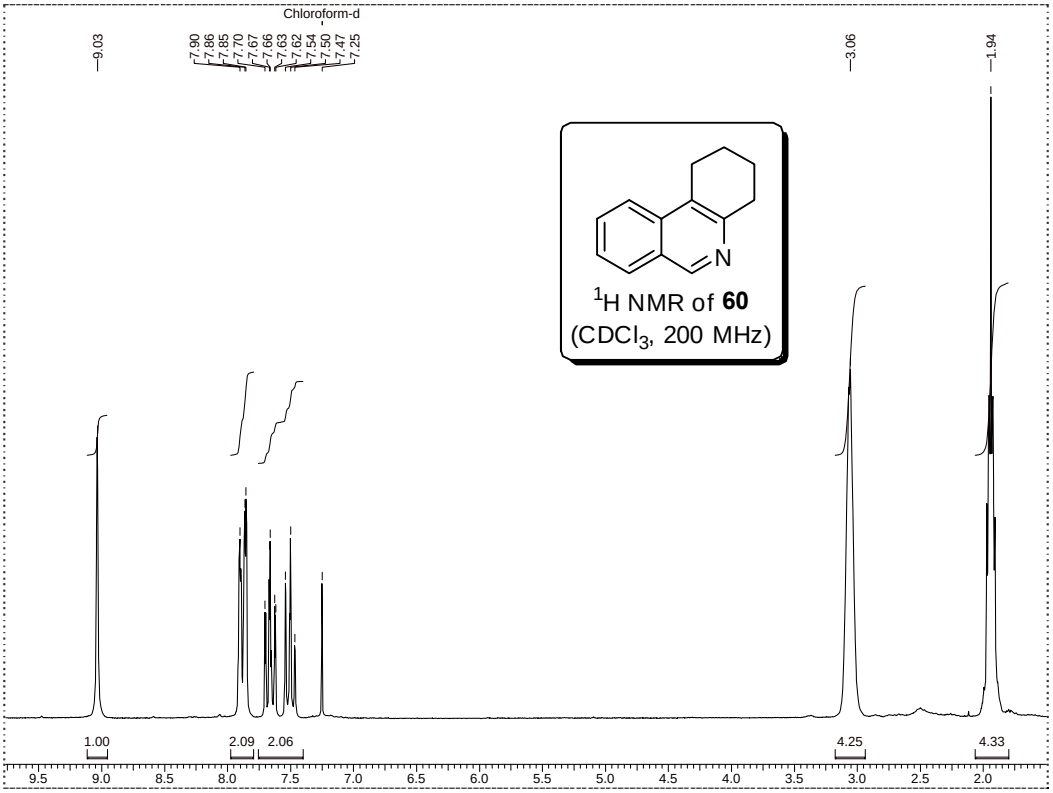


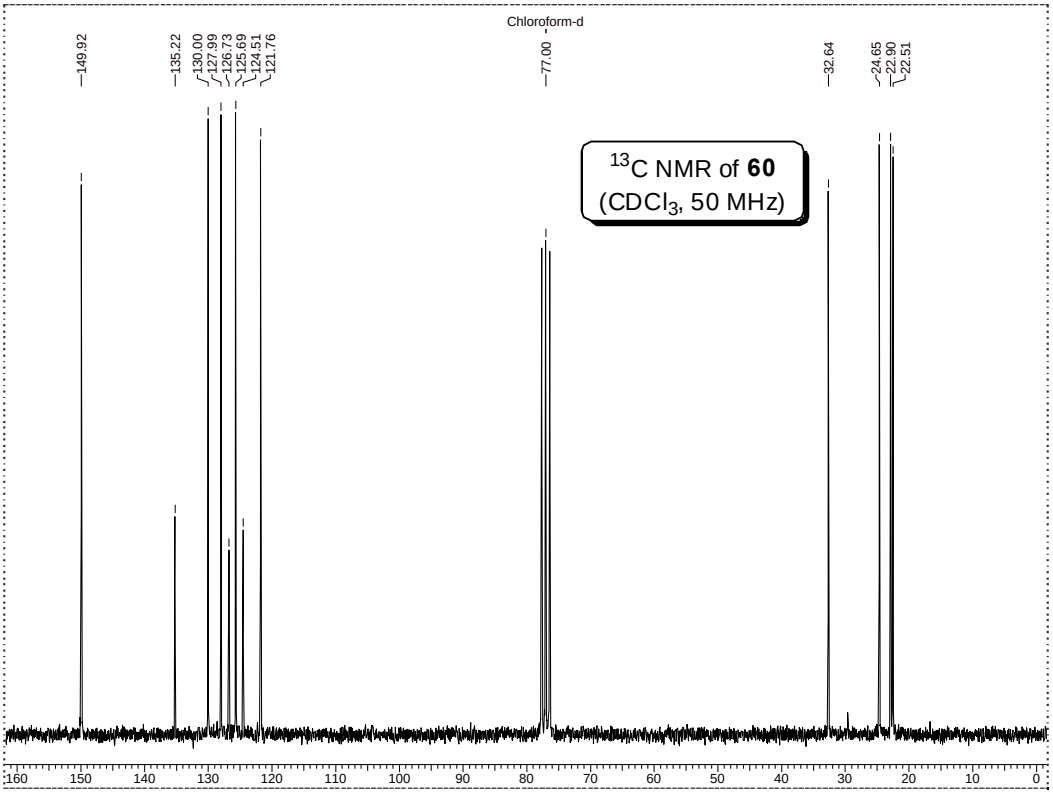
9. Benzyl 2-(6-oxocyclohex-1-enyl)benzylcarbamate (59).



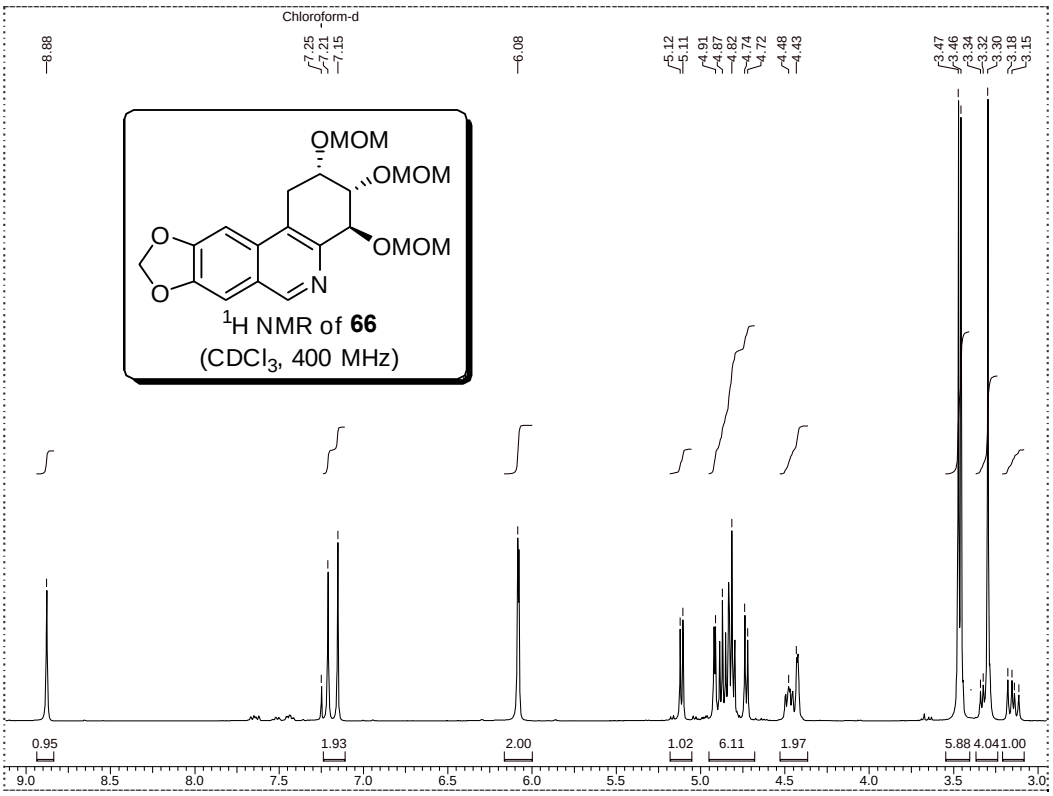


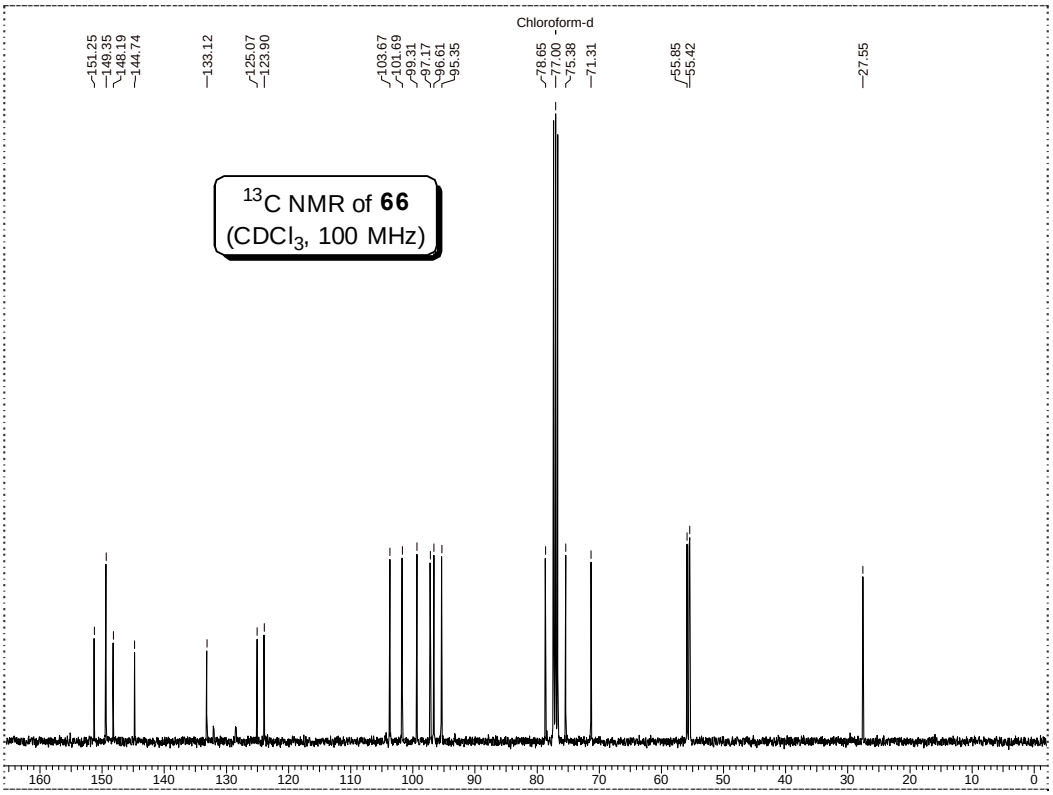
10. 1,2,3,4-Tetrahydrophenanthridine (60).



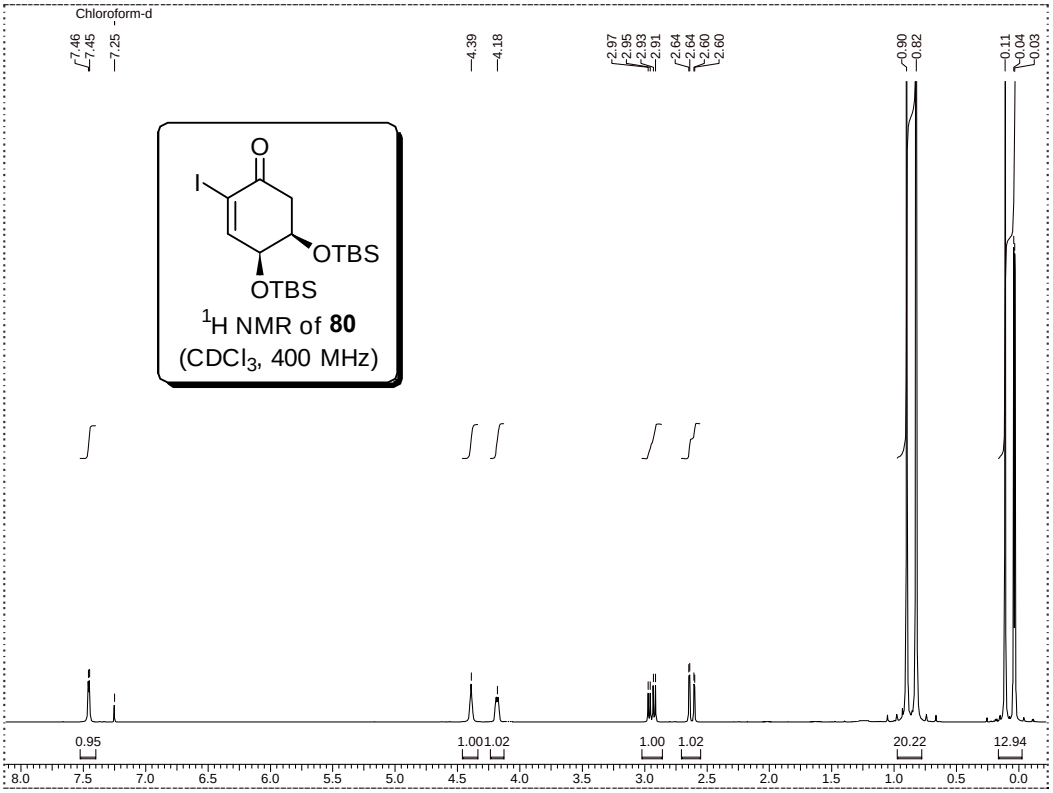


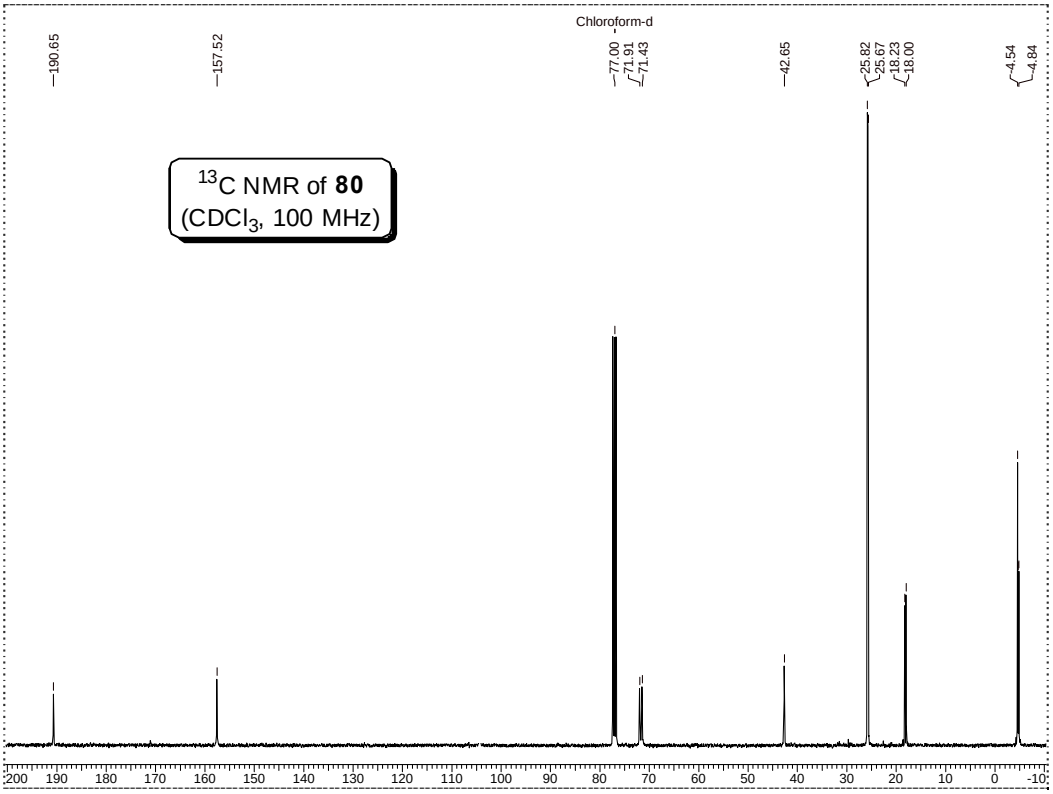
11. (2*S*,3*S*,4*S*)-2,3,4-Tris(methoxymethoxy)-1,2,3,4-tetrahydro-[1,3]dioxolo[4,5-*j*]phenanthridine (66).



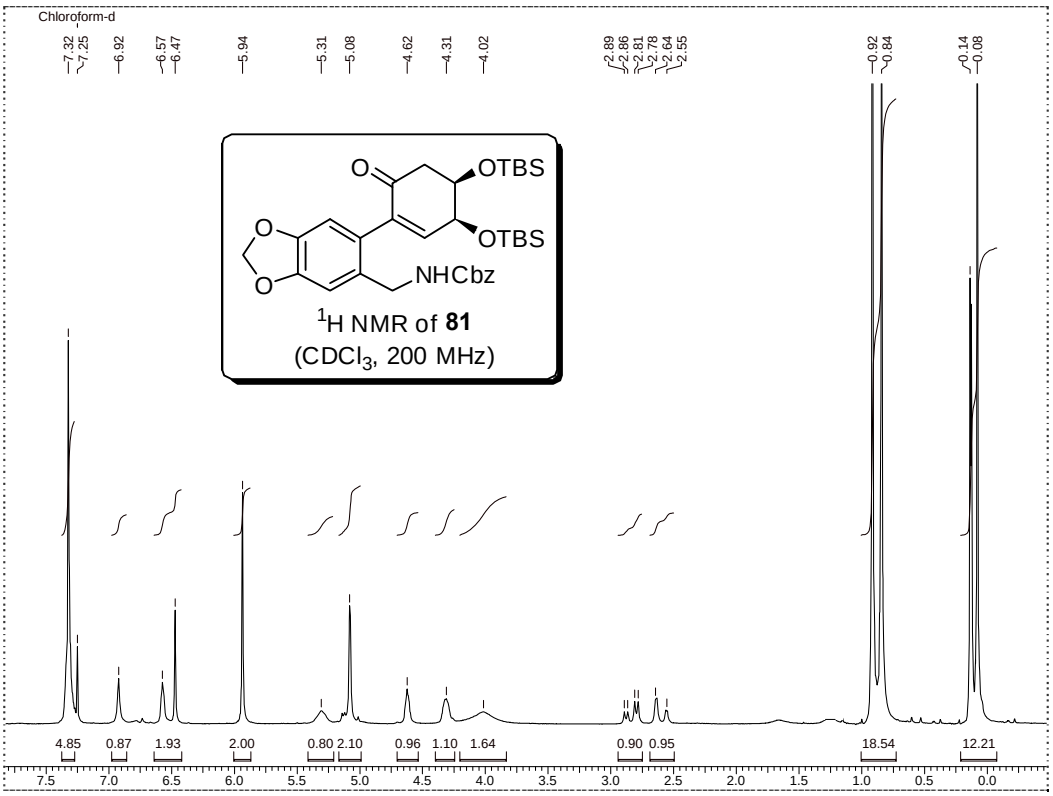


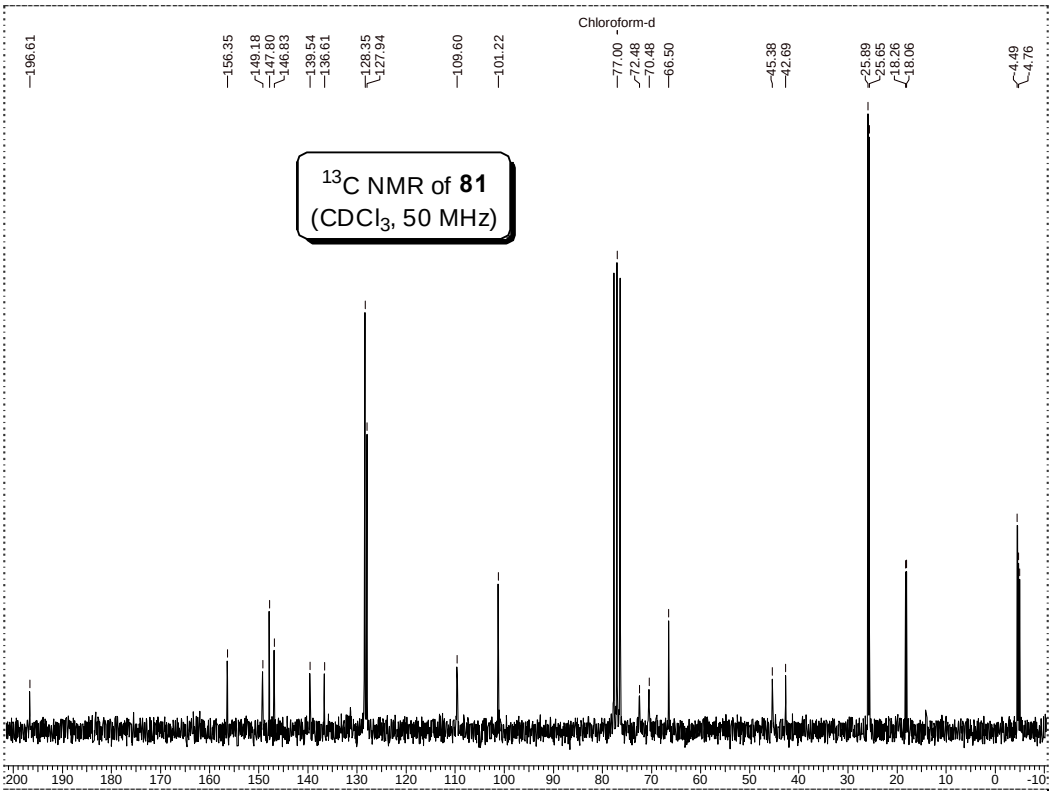
12. (4*S*,5*R*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-2-iodocyclohex-2-enone (80).



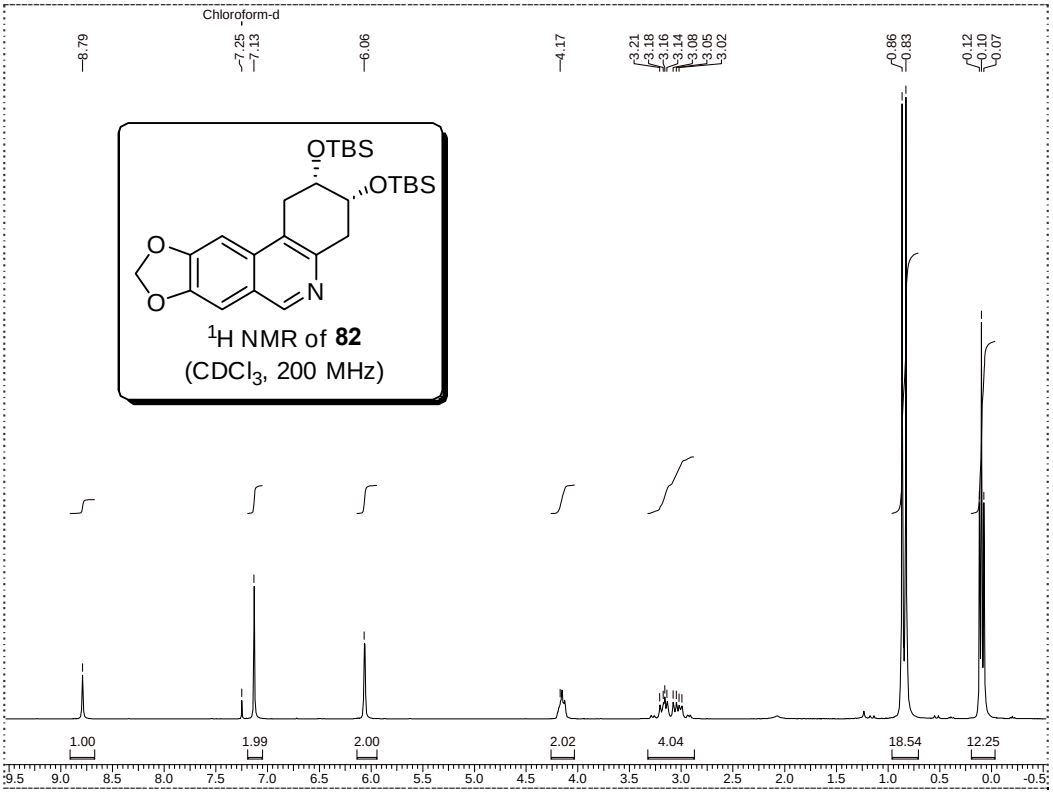


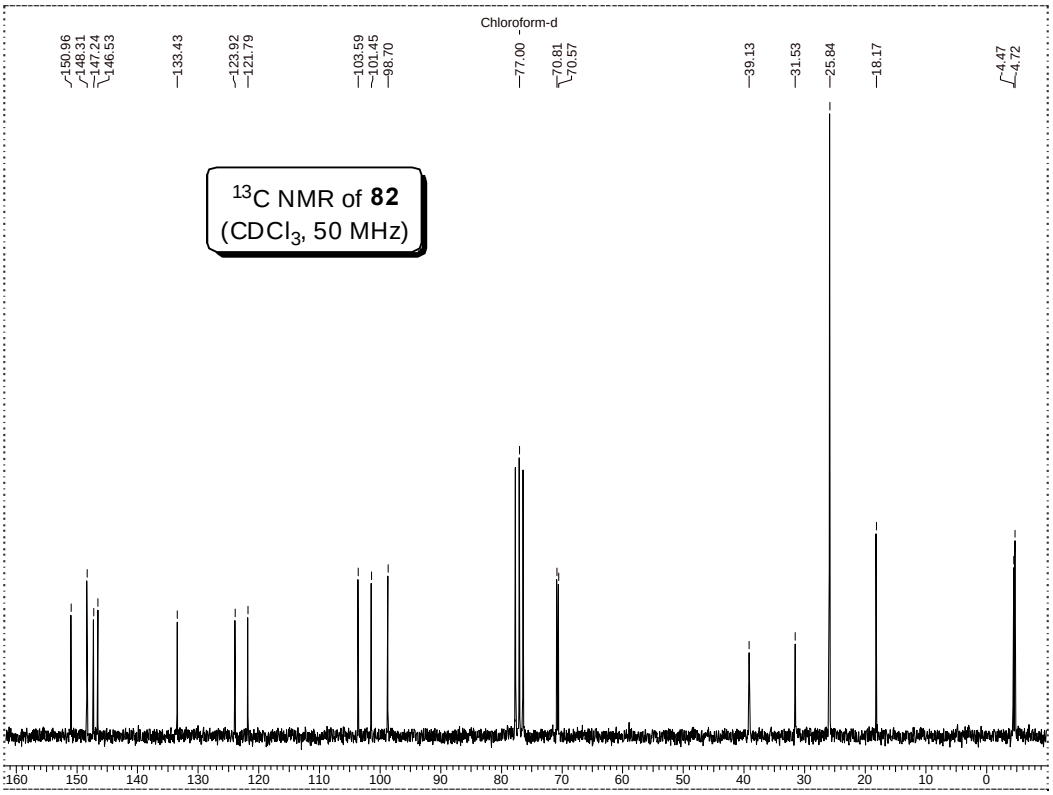
13. Benzyl (6-((3*S*,4*R*)-3,4-bis(*tert*-butyldimethylsilyloxy)-6-oxocyclohex-1-enyl)benzo[*d*][1,3]dioxol-5-yl)methylcarbamate (81).



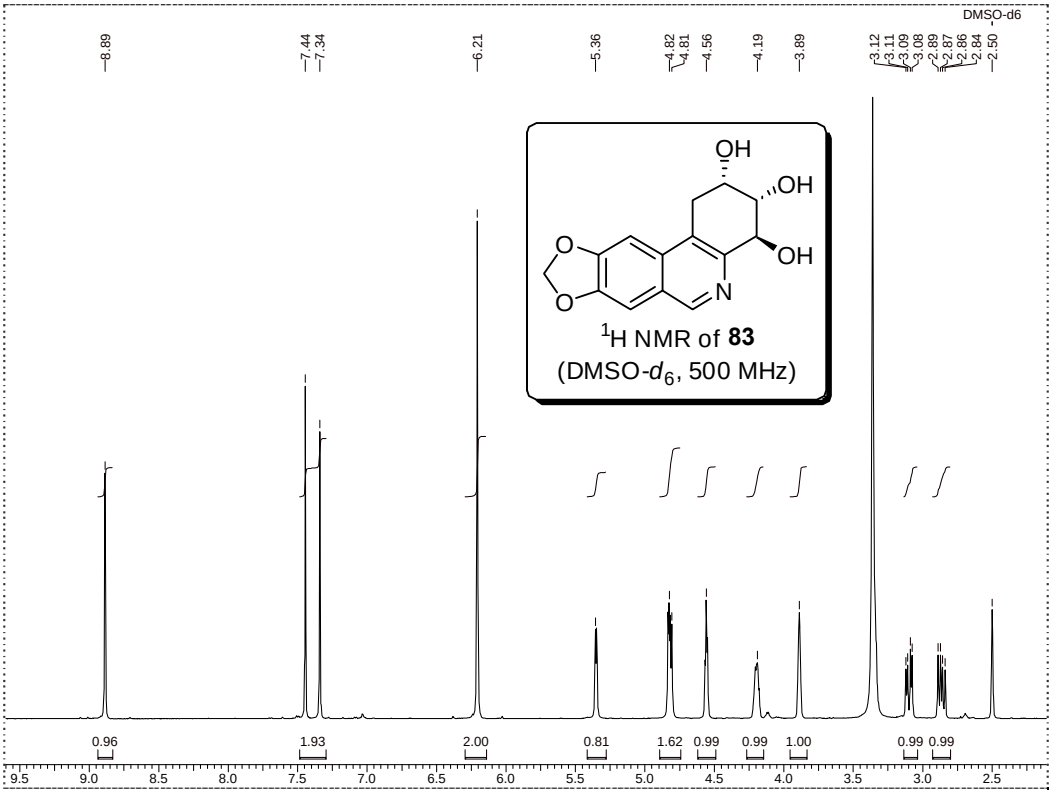


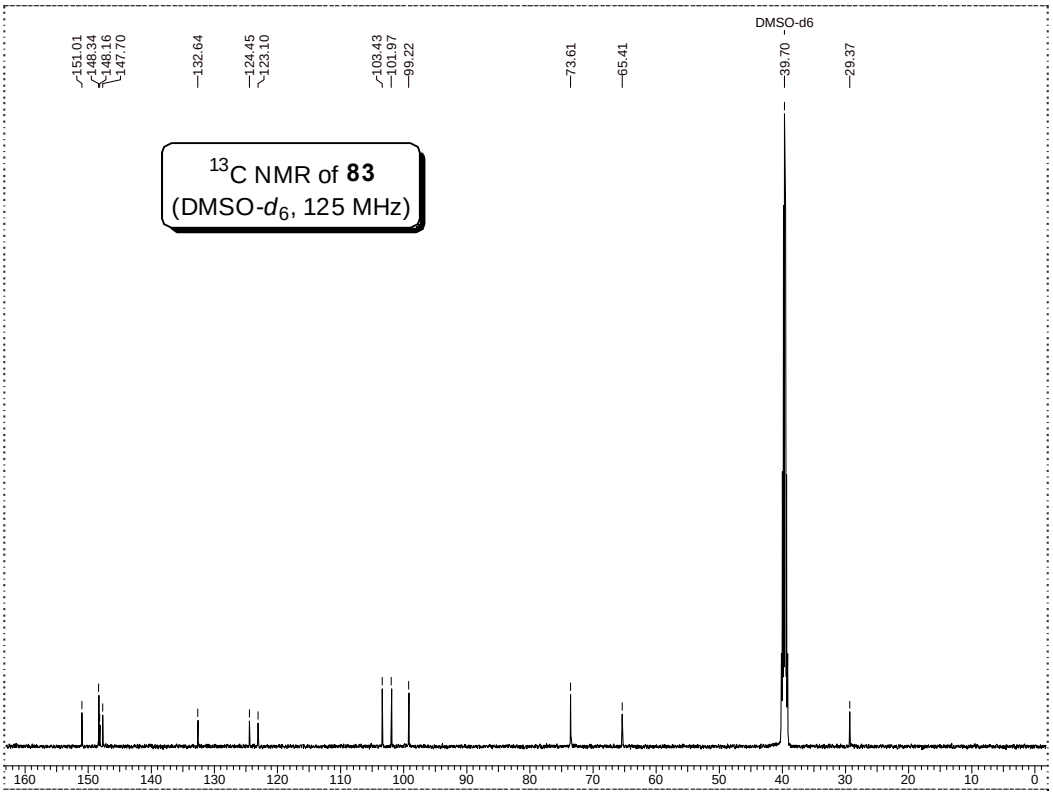
14. (2*S*,3*R*)-2,3-Bis(*tert*-butyldimethylsilyloxy)-1,2,3,4-tetrahydro-[1,3]dioxolo[4,5-*j*]phenanthridine (82).

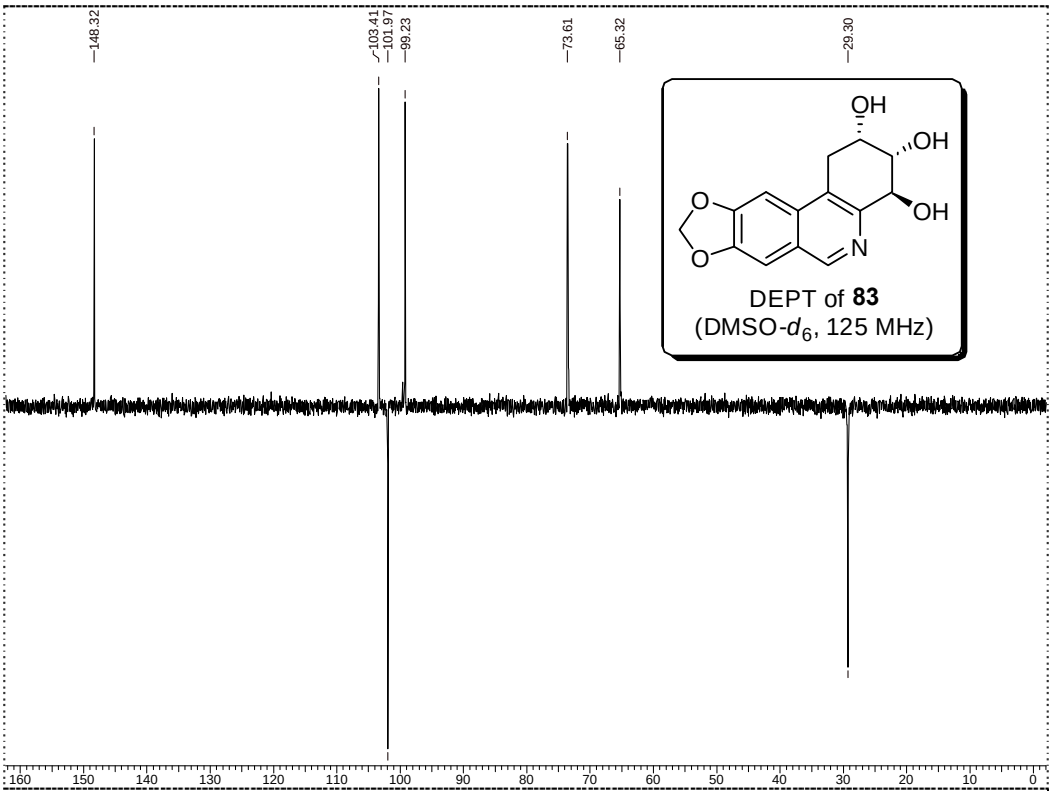




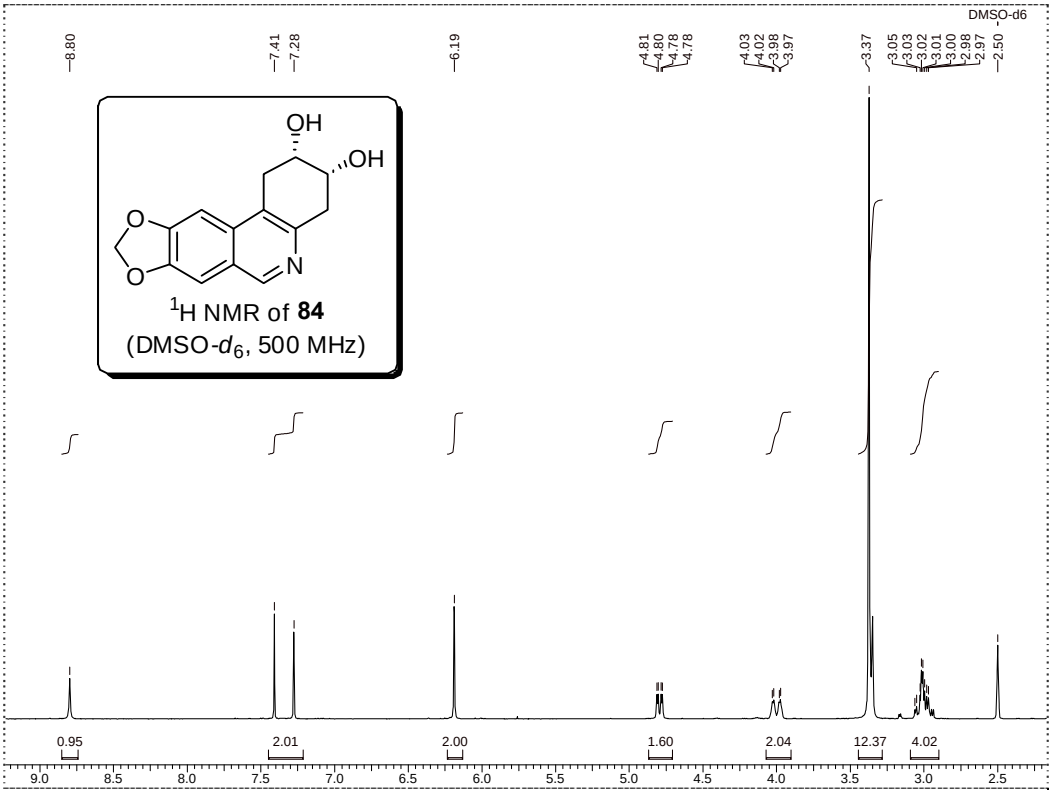
15. (2*S*,3*S*,4*S*)-1,2,3,4-tetrahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-2,3,4-triol (83).

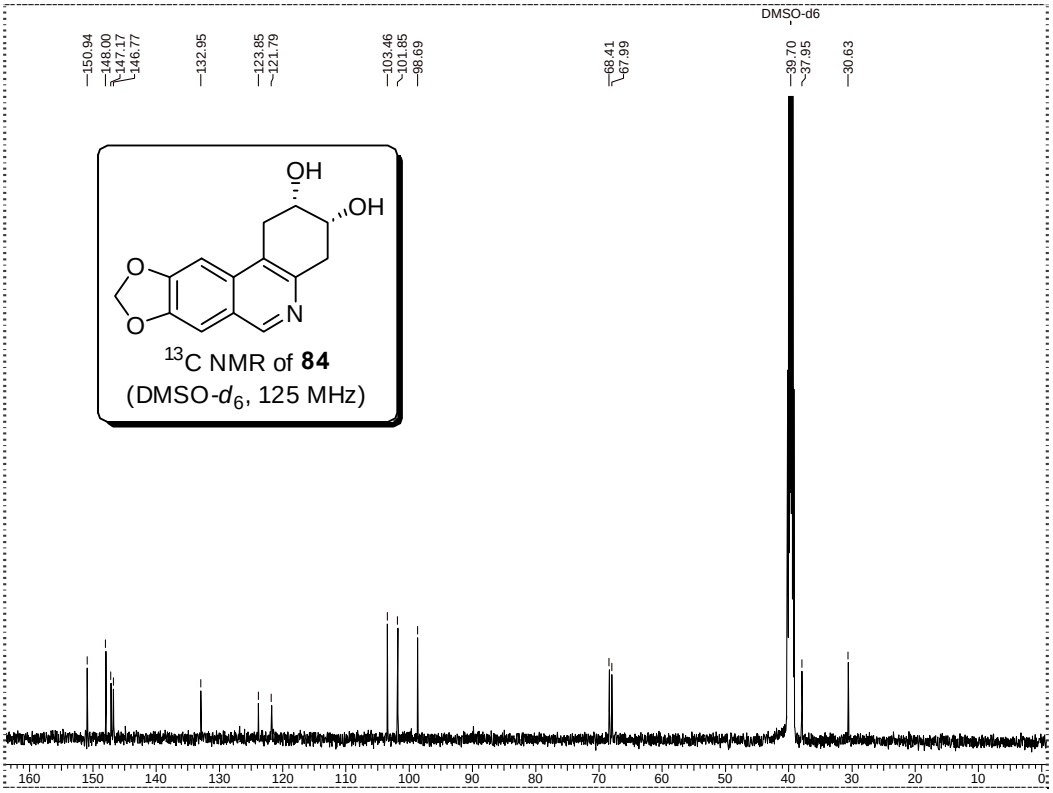


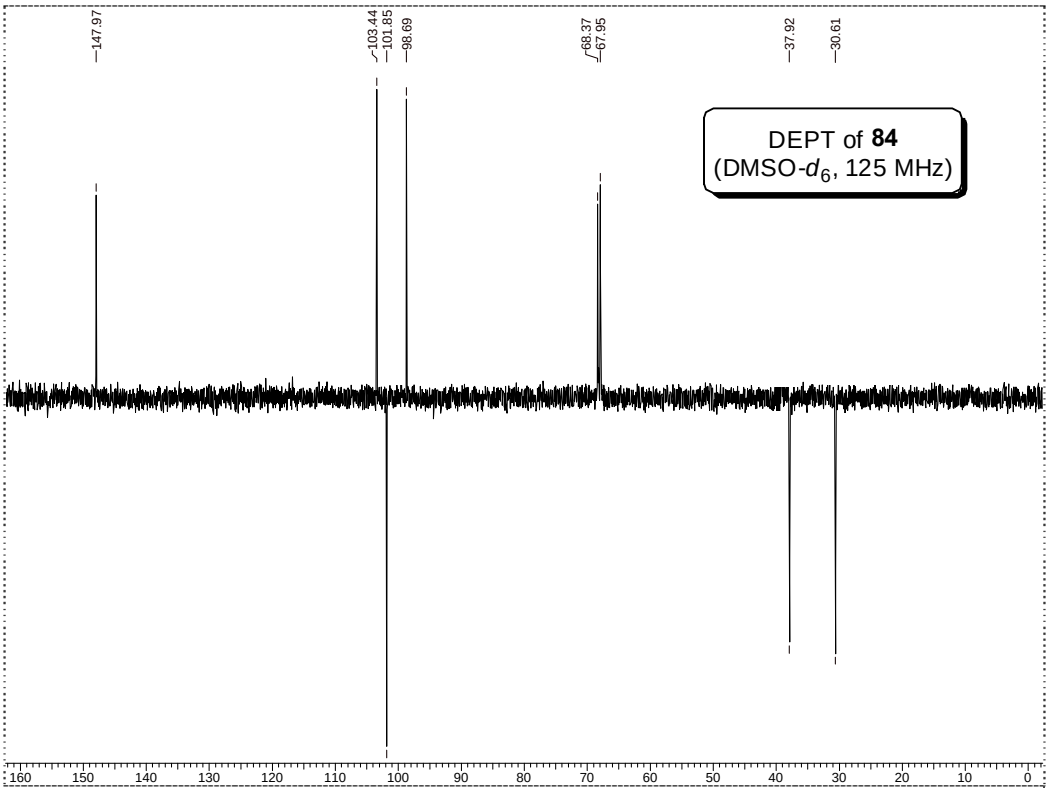




16. (2*S*,3*R*)-1,2,3,4-Tetrahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-2,3-diol (84).




DMSO-d6
150.94
148.00
147.17
146.77
132.95
123.85
121.79
103.46
101.85
98.69
68.41
67.99
39.70
37.95
30.63
OH
OH
O
O
N
^{13}C NMR of **84**
(DMSO-d_6, 125 MHz)


147.97
103.44
101.85
98.69
68.37
67.95
37.92
30.61
DEPT of **84**
(DMSO-d_6, 125 MHz)

List of Publications

1. A new strategy towards the total synthesis of phenanthridone alkaloids: synthesis of (+)-2,7-dideoxypancratistatin as a model study

   Pandey, G.; Murugan, A.; Balakrishnan, M. *Chem. Commun*. **2002**, 624-625.

2. Suzuki cross-coupling and intramolecular aza-Michael addition sequence towards the syntheses of 1,10b-*epi*-7-deoxypancratistatins and their cytotoxicity studies

   Pandey, G.; Balakrishnan, M.; Swaroop, P. S. *Eur. J. Org. Chem*. **2008** (article in press).

3. Suzuki cross-coupling/reductive debenzyloxycarbonylation sequence for the syntheses of [*c*]annulated isoquinolines: application for the syntheses of pancratistatin-like isoquinolines

   Pandey, G.; Balakrishnan, M. *J. Org. Chem*. **2008** (article in press).

Erratum