STUDIES TOWARD THE SYNTHESES OF HIGHLY FUNCTIONALISED CYCLOHEXANES VIA ASYMMETRIC DESYMMETRIZATION APPROACH

THESIS

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By

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Studies Toward the Syntheses of Highly Functionalised Cyclohexanes via Asymmetric Desymmetrization Approach"** which is being submitted to the **University of Pune** for the award of **Doctor of Philosophy in Chemistry** by **Mr. Salla Rajender** was carried out by him under my supervision at the **National Chemical Laboratory, Pune**. A material that has been obtained from other sources has been duly acknowledged in the thesis.

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DECLARATION

I hereby declare that the work presented in the thesis entitled **"Studies Toward the Syntheses of Highly Functionalised Cyclohexanes via Asymmetric Desymmetrization 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.

Date: (Salla Rajender)

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Salla Rajender

CONTENTS

Abbreviations

aq.	aqueous	NMR	Nuclear magnetic resonance
bp	boiling point	NOE	Nuclear Overhauser effect/enhancement
Bn	Benzyl	NOESY	Nuclear Overhauser Enhancement Spectroscopy
Boc	*t*-Butoxycarbonyl	ORTEP	Orthogonal thermal ellipsoid plots
DCM	Dichloromethane	PDC	Pyridinium dichromate
DEPT	Distortionless enhancement by polarization transfer	*p*-TSA	*p*-Toluenesulfonic acid
DMF	N, N-dimethyl formamide	py	Pyridine
DMSO	dimethylsulfoxide	rt	Room temperature
COSY	correlated spectroscopy	TBS	*t*-Butyldimethylsilyl
g	gram	TEA	Triethyl amine
GC	Gas Chromatography	TFA	Trifluoroacetic acid
h	hour	THF	Tetrahydrofuran
Hz	Hertz	TLC	Thin layer chromatography
K*i*	Inhibition constant	TMS	Trimethylsilyl
M	Molarity (molar)	α-Glu	α-Glucosidase
Mg	Milligram	β-Glu	β-Glucosidase
Min	Minute(s)	α-Man	α-Mannosidase
mL	Milliliter	β-Man	β-Mannosidase
mmol	Millimole		
mp	Melting Point		
N	Normality		
MS	Mass Spectrum		
MsCl	Methanesulfonyl chloride		

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 AC 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 and in abstract are independent.**

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

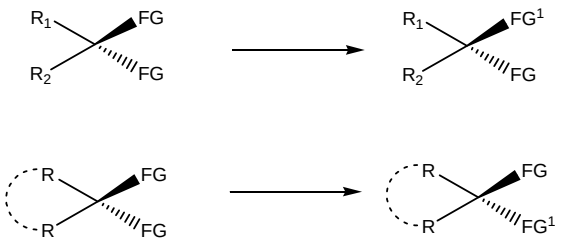
Thesis Abstract

Studies Toward the Syntheses of Highly Functionalised Cyclohexanes via Asymmetric Desymmetrization Approach

Chapter 1: This chapter describes an overview of desymmetrization concept, importance of 7-azabicyclic system and few selected literature reports.

Section-A: A brief account of desymmetrization concept and few literature reports on desymmetrization.

Asymmetric desymmetrization of *meso* compounds to synthesize optically active templates has proved to be a powerful tool in asymmetric synthesis since it allows formation of multiple stereogenic centers in one symmetry-breaking operation. Although, there have been elegant approaches known in asymmetric synthesis, desymmetrization has emerged as an attractive alternative strategy because of its significant contribution in the synthesis of either enantiomer of the desired product in a theoretical yield of up to 100%. In general, desymmetrization can be simply defined as differentiation between two enantiotopic functional groups / faces by breaking the symmetry using a chiral reagent or catalyst.

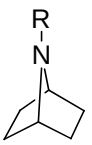


FG, FG^1 = Functional Groups

Figure 1.

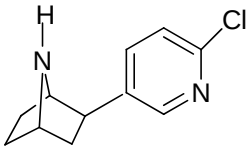
Section-B: Importance of 7-azabicyclo[2.2.1]heptane framework and known approaches for the construction of 7-azabicyclic system.

The synthesis of the 7-azabicyclo[2.2.1]heptane system (**1**) has been the subject of numerous synthetic studies which have resulted in the development of several methods for the construction of these novel structures. For sometimes, the interest in the synthesis of these systems were only a matter of academic interest since no naturally occurring compound was known at that time to contain these ring systems. However, in 1992 Daly *et al.*[14] reported the discovery and structural elucidation of (-)-epibatidine (**2**), a new alkaloid isolated from Ecuadorian poison frog, *Epipedobates tricolor,* featuring the 7-azabicyclo[2.2.1]heptane ring system with an *exo* oriented 5-(2-chloropyridyl) moiety (Figure 2). Due to the novel biological activity associated with epibatidine and its paucity in nature (1 mg isolated from 750 frogs), the total synthesis of compound had aroused the interest of organic chemist around the world.



1

7-azabicyclo[2.2.1]heptane

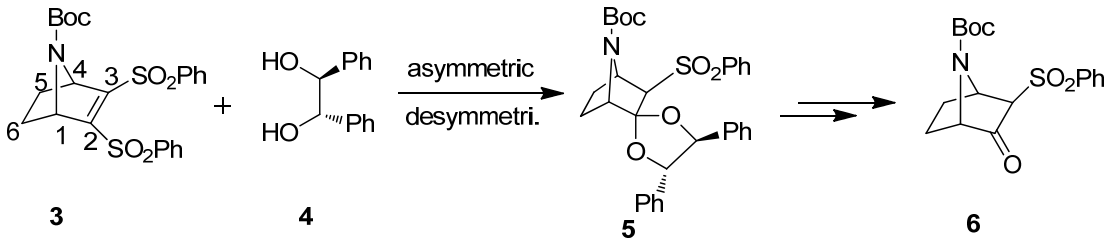


2

Epibatidine

Figure 2.

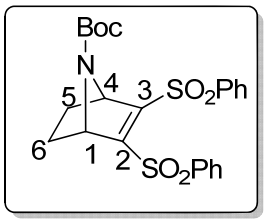
Visualizing the importance of 7-azabicyclo[2.2.1]heptanes system and our continuing efforts directed towards the development of novel methodologies for the construction of enantiopure 7-azanorbornene frame works, we have developed earlier a conceptually new and efficient route *via* asymmetric desymmetrization of *meso*-**3** using chiral diolate of **4** to produce optically pure 7-azabicyclic frame **5** with excellent diastereoselectivity and yield (99% *de*, 82% yield)[3] as outlined in Scheme 1 which was later elaborated for the total synthesis of various conduramines and substituted cyclohexane derivatives.



3 **4** **5** **6**

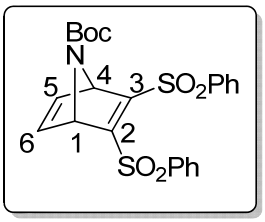
Scheme 1.

While working on the above approach, we envisaged the importance of *meso*-**7,** for further synthetic explorations owing to the possibility of introducing additional functionality through C5-C6 olefinic bond.



3

Previously used *meso*-precursor



7

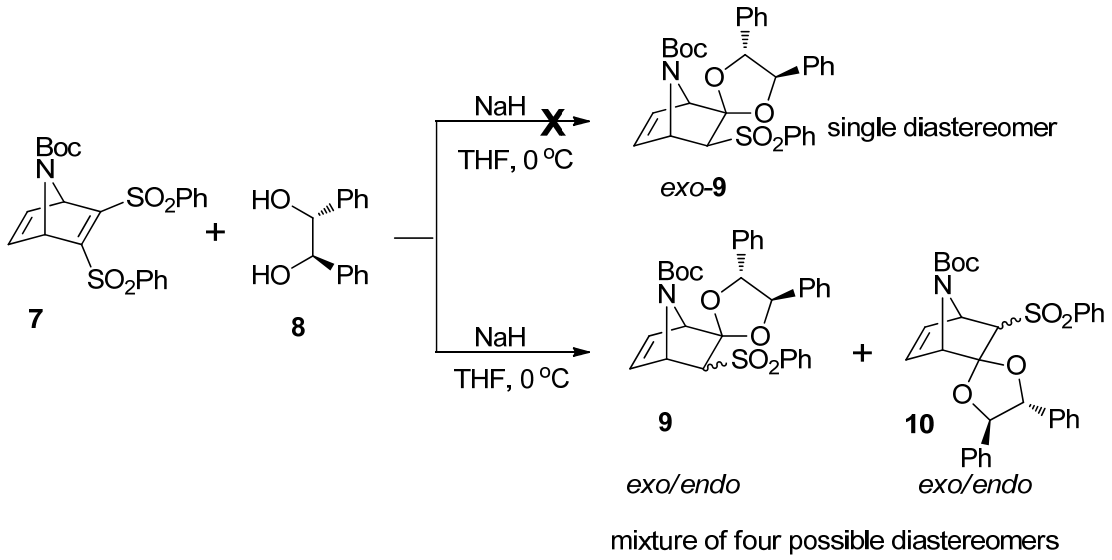
Present *meso*-precursor

Figure 3.

Chapter-2: This chapter illustrates the development of temperature guided desymmetrization of *meso*-7-azabicyclic frame work, structural conformation and mechanistic rationale.

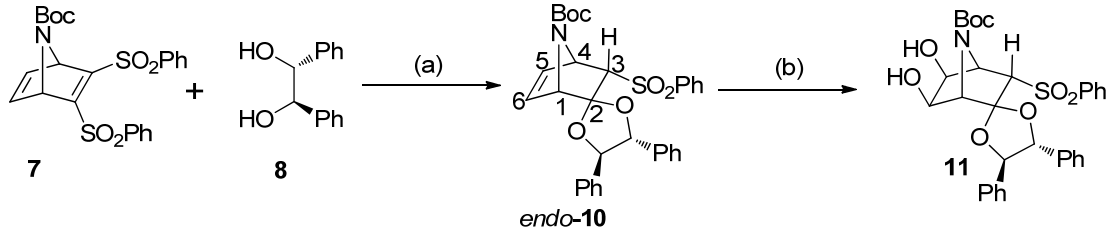
Temperature dependent desymmetrization of *meso*-7-azabicyclic frame work.

As per the protocol established by us earlier,[1] desymmetrization of **7** was carried out by stirring (2 h) with an equivalent amount of the disodium salt of (+)-hydrobenzoin **8** in anhydrous THF at 0 °C, however, it provided all four possible diastereomeric mixture of corresponding desymmetrized ketals in 2:2:6:1 ratio which was confirmed by HPLC analysis. This observation was in sharp contrast and surprising to our earlier observation (Scheme 2).



Scheme 2.

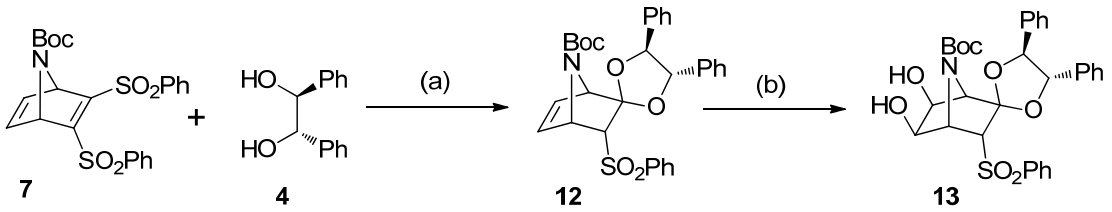
Therefore, it occurred to us to perform the same reaction at lower temperature with the hope that it might produce the expected desymmetrization *exo*-**9** in high diastereoselectivity. Thus, desymmetrization of **7** was performed at -100 °C and indeed, it produced desymmetrized *endo*-**10** as a white solid in 99% *de* and 89% yield (Scheme 5). ^{1}H NMR of *endo*-**10** displayed a singlet for H-3 at δ 4.06. Absolute configuration of *endo*-**10** was confirmed by X-ray crystal analysis of its corresponding dihydroxylated derivative **11**.



Scheme 3.

Reagents and Conditions : (a) NaH, THF, -100 °C, 3 h, 89% (b) OsO_4, NMO, Acetone:H_2O (9:1), 2 h, 91%

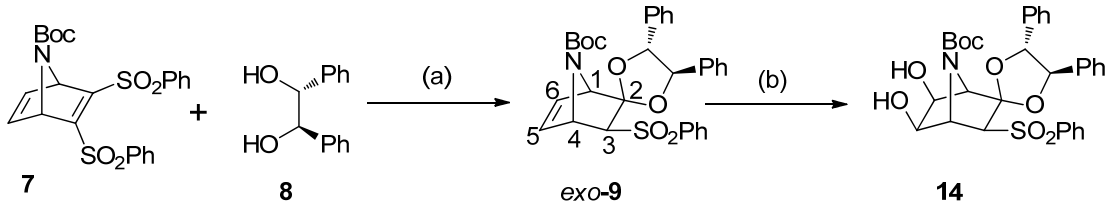
To compare this observation, desymmetrization of *meso*-**7** was also performed with opposite enantiomer of the chiral diolate (-)-**4** which gave expected diasteromer as evidenced from the X-ray analysis of corresponding **13**.



Scheme 4.

Reagents and Conditions : (a) NaH, THF, -100 °C, 3 h, 86% (c) OsO_4, NMO, Acetone:H_2O (9:1), 2 h, 88%

To probe further the role of the temperature on the diastereoselectivity, desymmetrization of *meso*-**7** was investigated using the diolate of **8** at temperature range from -100 °C to 50 °C. After several attempts of temperature screening, 35 °C was found to be optimum temperature to obtain *exo*-**9** with 92% diastereoselectivity as a white solid in 76% yield which was further confirmed by HPLC analysis. Absolute configuration of *exo*-**9** was also confirmed by X-ray analysis of its corresponding **14**.

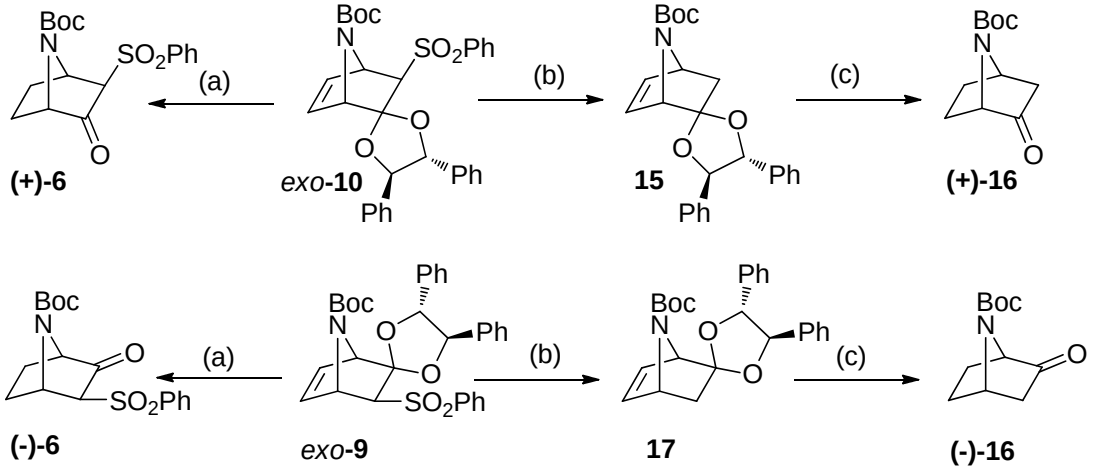


Scheme 5.

Reagents and Conditions : (a) NaH, THF, 40 °C, 2 h, 76% (c) OsO_4, NMO, Acetone:H_2O (9:1), 2 h, 84%

Structural confirmation of *exo*-10 and *exo*-9 by transforming in to known (+)- and (-)- enantiomeric pairs of various 7-azabicyclic ketones.

To provide conclusive proof to the structures of *exo*-**10** and *exo*-**9** as enantiomeric pair, these were hydrogenated in acetic acid at 60 psi using Pd/C as catalyst which furnished enantiomerically pure (+)-**6** ($[\alpha]_D$ +57.1 (c 0.60, $CHCl_3$), lit. = +57.9) and (-)-**6** ($[\alpha]_D$ +57.1 (c 0.75, $CHCl_3$)), respectively (Scheme 6).



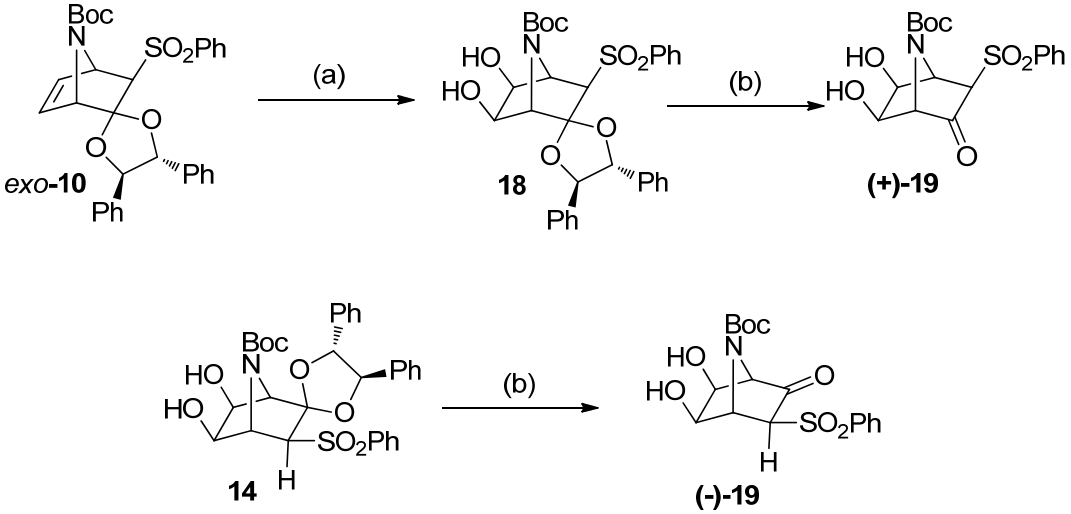
Scheme 6.

Reagents and Conditions : (a) H_2, Pd/C, AcOH, 60 psi, 24 h, 67% (b) Na-Hg 7%, Na_2HPO_4, THF-MeOH (1:1) (c) H_2, Pd/C, MeOH, 1 atm, 4 h

Furthermore, desulfonylation, using Na-Hg 6% in THF-MeOH (1:1), of these diastereomeric pair of compounds produced corresponding **15** and **17** in 82% and 85% yield, respectively, which on usual hydrogenation produced corresponding (+)- and (-)-7-azabicyclic ketone ((+)-**16** $[\alpha]^{27}_D$ +77.8 (*c* 1.0, $CHCl_3$) and (-)-**16** $[\alpha]^{27}_D$ -76.9 (*c* 1.0, $CHCl_3$) in 90% and 92% yield, respectively (Scheme 6). These optical rotation values were found to be in complete agreement with those reported in literature.

To provide further support to the fact that *exo*-**10** and *exo*-**9** are diastereomers, *exo*-**10** was converted to its corresponding dihydroxylated derivative **18** using OsO_4. Dihydroxylated **18** and **14** were hydrogenated to produce corresponding enantiopure

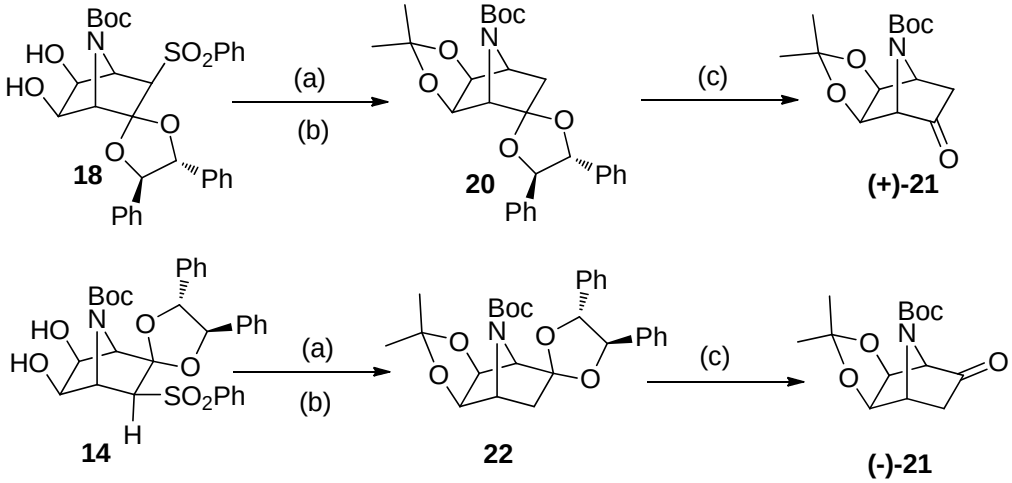
dihydroxylated 7-azabicyclic ketone (+)-**19** ($[\alpha]_D$ +38.7 (*c* 0.50, $CHCl_3$)) and (-)-**19** ($[\alpha]_D$ -41.4 (*c* 0.50, $CHCl_3$)) as white solids in 75% and 73%, respectively (Scheme 7).



Scheme 7.

Reagents and Conditions: (a) OsO_4, NMO, Acetone:H_2O (9:1), 2 h (b) H_2, Pd/C, AcOH, 60 psi, 24 h

The additional support to the observation that **18** and **14** produce opposite pairs of enantiomers of **19** they were further transformed in to their known derivatives of (+)-**21** $[\alpha]^{27}_D$ +48.1 (*c* 0.65, $CHCl_3$) and ((-)-**21** $[\alpha]^{27}_D$ -50.8 (*c* 0.65, $CHCl_3$)) (Scheme 8).



Scheme 8.

Reagents and Conditions : (a) 2,2-DMP, *p*-TSA, Acetone (b) Na-Hg 7%, Na_2HPO_4, THF-MeOH (1:1) (c) H_2, Pd/C, MeOH, 1 atm, 3 h

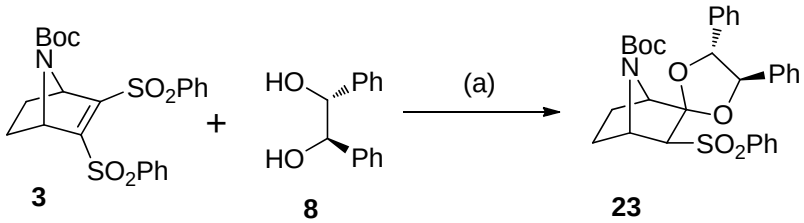
Mechanistic rationale for the inversion of diastereoselectivity.

From above observations, it was intriguing to note that in spite of skeletal similarities between *meso*-**3** and *meso*-**7**, desymmetrization of later was found to be temperature dependent. A closer evaluation indicates that *meso*-**7** differs with **3** only by having an electron rich double bond at C5-C6 position which appears to be playing role during desymmetrization.

present *meso* precursor **previously used *meso* precursor**

Figure 4.

Therefore, to probe the role of the double bond, desymmetrization of *meso*-**3** was evaluated at varying temperatures (-100 °C to 35 °C, Scheme 9) and it provided invariably the same single diastereomer irrespective of the temperature used. This experiment strongly supported the role of double bond in the observed diastereoselectivity switch during the desymmetrization of **7**.



Scheme 9.

Reagent and Condition: (a) NaH, THF, -78 °C, 7 h

Thus, it became apparent that reversal in diastereoselectivity during desymmetrization can only occur if the nucleophile approaches from the two different

faces of this bicyclic structure at different temperatures. Based on all the above observations, we have proposed two plausible transition states **A** and **B** depending upon the approach of the nucleophile to *meso*-**7**. According to the free energy equation *(*$\Delta G = \Delta H - T\Delta S$), at -100 ^{o}C, lowering of entropy might be compensated by enthalpic stabilization because of the intermolecular interactions producing **24** by favoring the transition state **A.** On the other hand, with rise in temperature, value of $T\Delta S$ (*Eyring Plots*)[6a,9] term increases towards the free energy change because of weaker molecular interactions, there by favouring the transition state **B** where nucleophile approaches from the above face of the *meso* bicyclic skeleton **7** due to steric crowding producing **25** as a predominant diastereomer.

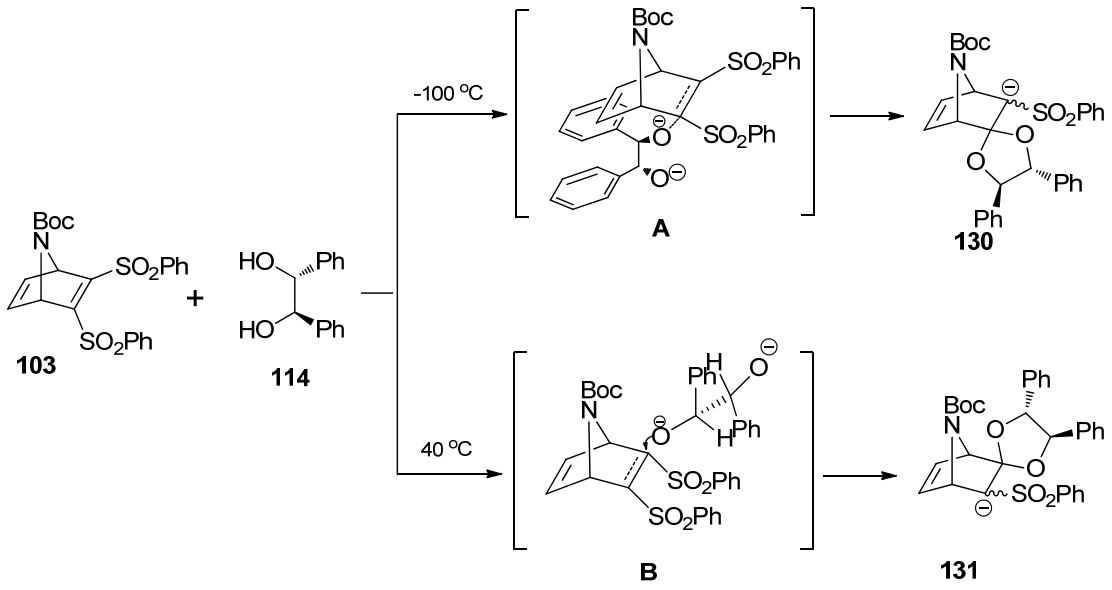


Figure 5.

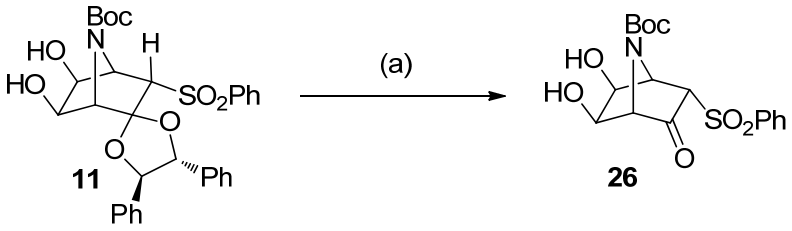
Chapter-3: This chapter illustrates the utility of the above methodology towards the synthesis of aminocyclitols.

Section-A: A brief account on aminocarbasugars and few selected known approaches for their synthesis.

Section-B: Application of temperature dependent desymmetrization concept towards the synthesis of aminocyclitols.

Synthesis of 1-*neo*-Inosamine:

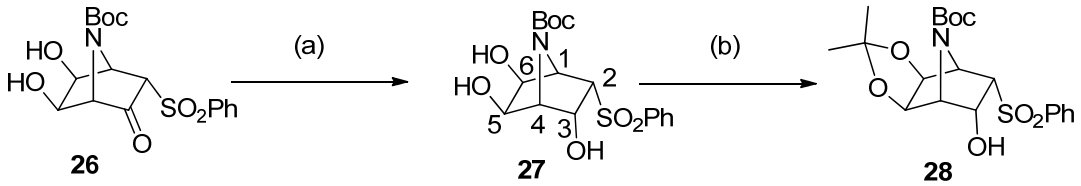
Towards executing our synthetic strategy, a suitable ketone precursor **26** ($[\alpha]^{25}_{D}$ +14.4 (*c* 1.0 $CHCl_3$)) was obtained in 71% yield by carrying out hydrogenation of the dihydroxylated compound **11** using Pd/C in the usual manner (Scheme 10). With stereodefined ketone **26** in hand, we focused our attention on its stereoselective reduction to obtain corresponding –OH functionality in *endo* fashion, which was necessary for further establishment of 1,2-*trans* amino alcohol core on cyclohexane ring system.



Scheme 10.

Reagent and Condition: (a) H_2, Pd/C, AcOH, 60 psi, 20 h, 71%

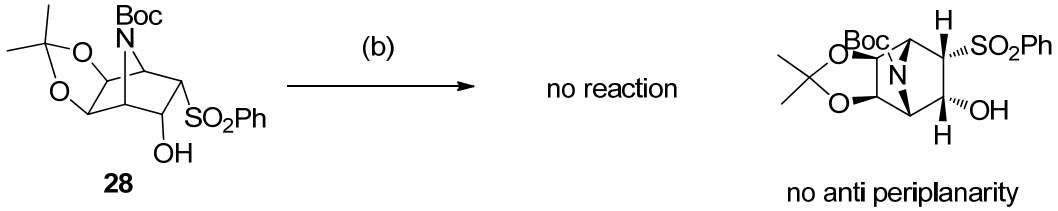
Reduction of **26** at -78 °C produced alcohol **27** ($[\alpha]^{25}_{D}$ + 9.25 (*c* 1.0 MeOH)) exclusively in 77% yield (Scheme 11). The configuration of *endo*-alcohol was unambiguously deduced from its ^{1}H NMR spectrum.



Scheme 11.

Reagents and Conditions : (a) $LiBH_4$, THF, -78 °C, 3.5 h, 77% (b) 2,2-dimethoxy propane, *p*-TSA, Acetone, 45 min.

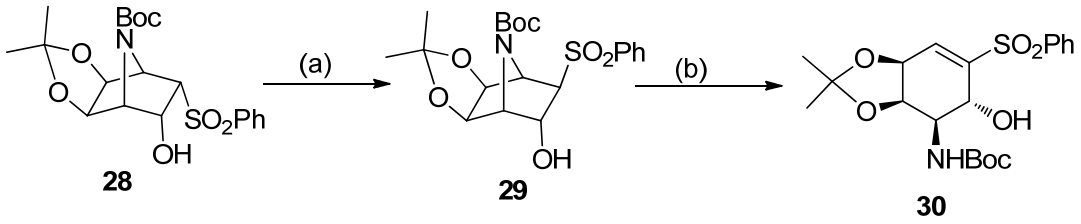
Compound **27** was further transformed to corresponding acetonide protected derivative **28**, using 2,2-dimethoxy propane in the presence of catalytic amount of *p*-TSA, before carrying out anionic rearrangement to avoid any complications. Initially, we attempted to carry out the ring opening rearrangement of **28** using excess of methyl magnesium bromide, however, reaction failed to give any product (Scheme 12). This failure led us to look at the structure of **28** more closely which indicated that the orientation of sulfone moiety is *endo* and rearrangement requires antiperiplanarity between the bonds to be cleaved (Scheme 12). Therefore, phenylsulfonyl moiety was



Scheme 12.

Reagent and Condition: (a) MeMgBr, THF, rt, 3 h

epimerized using KO^{t}Bu to its corresponding epimer **29** ($[\alpha]^{26}_D$ -5.71 (*c* 1.0 $CHCl_3$)) (Scheme 13). The structure of **29** was confirmed on the basis of ^{1}H NMR. Reaction of **29** with excess of methyl magnesium bromide in a THF solution at 0 °C produced **30** in 68%

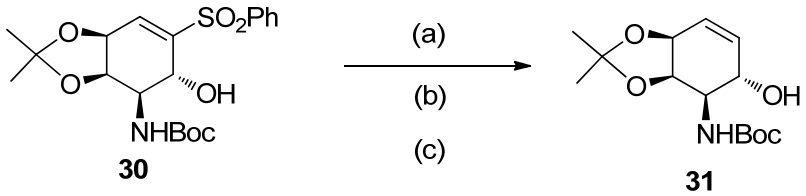


Scheme 13.

Reagents and Conditions : (a) K^{t}OBu, THF, 0 ^{o}C (b) MeMgBr, THF, rt, 2 h, 73%

overall yield from **28** (Scheme 13). The rearrangement of **28** to **29** was supported by NOESY interactions.

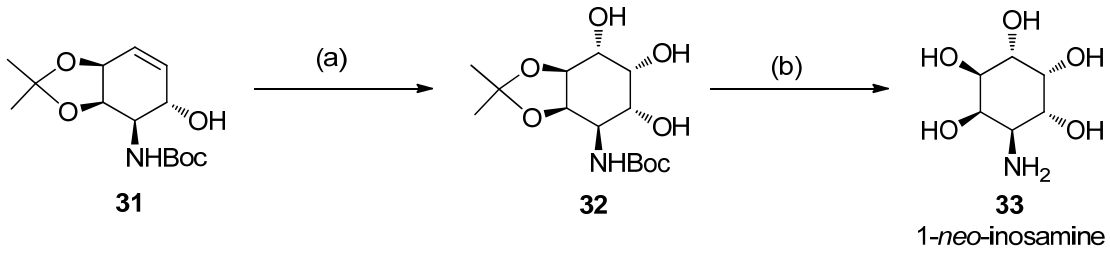
Initially desulfonylation of **30** was attempted using Na-Hg (6%) in a mixture of THF: MeOH (1:1) solvent but it was unsuccessful possibly due to the presence of adjacent acetonide group. Therefore, the same reaction was tried again with acetonide deprotected **30** and pleasingly it was desulfonylated successfully. The crude desulfonylated product was further protected and purified as **31** in 67% overall yield ($[\alpha]^{27}_D$ +14.77 (*c* 0.5 $CHCl_3$)) (Scheme 14).



Scheme 14.

Reagents and Conditions : (a) 1*N* HCl, MeOH, rt (b) 6% Na-Hg, THF-MeOH (c) 2,2-dimethoxypropane, *p*-TSA, 67% over 3 steps

Dihydroxylation of **31** using OsO_4 (50% aqueous NMO, acetone:water (9:1) produced **32** in 61% yield ($[\alpha]^{26}_D$ +5.12 (*c* 0.5 MeOH)). Deprotection of the acetonide as



Scheme 15.

Reagents and Conditions : (a) OsO4, NMO, rt, 10h, 61% (b) HCl, dioxane

well as *N*-Boc moiety of **32** by refluxing with 10*N* HCl in dioxane solvent delivered aminocyclitol (1-*neo*-inosamine **33**), however, due to its high polarity and solubility in water it was characterized as **32** only (Scheme 15).

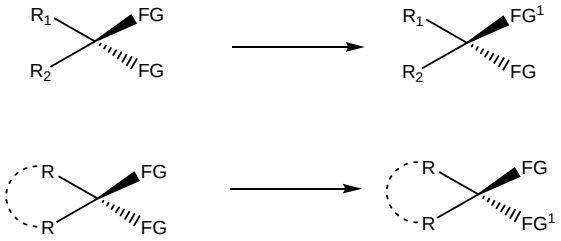
Chapter-1

Introduction of Aminocyclitols and 7-azabicyclic skeletons

Section-A

1A.1. Introduction

Asymmetric desymmetrization of *meso* compounds to synthesize optically active templates has proved to be a powerful tool in asymmetric synthesis since it allows formation of multiple stereogenic centers in one symmetry-breaking operation. Although, there have been elegant approaches known in asymmetric synthesis, desymmetrization has emerged as an attractive alternative strategy because of its significant contribution in the synthesis of either enantiomer of the desired product in a theoretical yield of up to 100%. In general, desymmetrization can be simply defined as differentiation between two enantiotopic functional groups / faces by breaking the symmetry using a chiral reagent or catalyst.



FG, FG^1 = Functional Groups

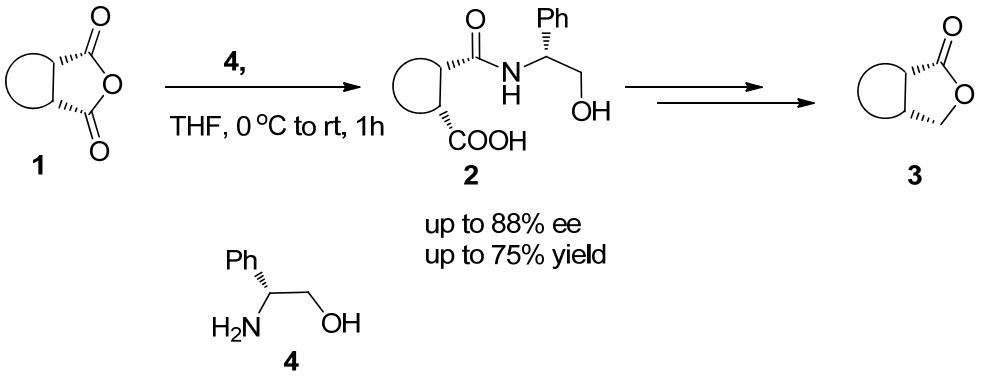
Figure 1.

Since first nonenzymatic desymmetrization reaction of β-phenylglutaric anhydride with L-α-phenethylamine reported by Schwartz *et al.*[1] in 1954, almost three decades later in 1981, Hazama *et al.*[2] reported the desymmetrization of anhydrides with significant improvement in the yield and selectivity utilizing various chiral secondary amines. In the later years, there has been continuous efforts devoted towards the development of new chiral enantiodiscriminating agents as well as modified *meso* starting precursors, owing to their importance in the organic synthesis and the same

concept has been successfully being applied till date in the synthesis of various important intermediates and biologically active molecules. Although, there are numerous literatures available on this concept, we would like to restrict our discussion by describing few of the more important examples as follows:

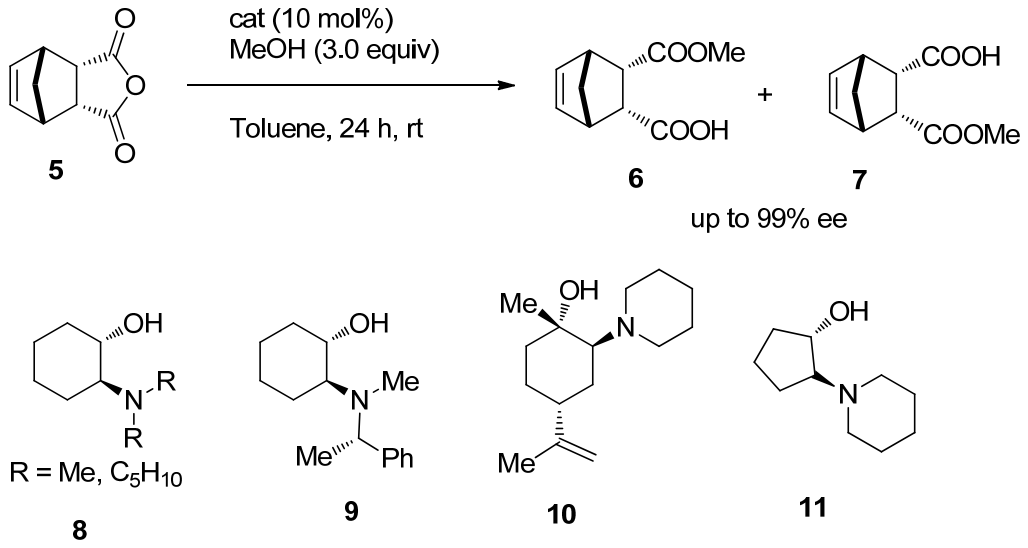
1A.2. Desymmetrization of Anhydrides

In 1983, Mukaiyama *et al.*[3] developed a protocol for the desymmetrization of several bicyclic anhydrides with (*R*)-2-amino-2-phenylethanol (**4**) followed by conversion of the amide **2** into their corresponding lactones **3** (Scheme 1) with moderate to good enantioselectivities (58-88% *ee*) in good overall yields (60-75%).



Scheme 1.

In 2010, Bolm and co-workers[4] also developed a protocol for highly enantioselective desymmetrization of cyclic *meso*-anhydride **5** employing alcohols as nucleophiles using several low molecular weight *trans*-cyclohexane-based β-aminoalcohol derivatives as organocatalysts e.g. **8, 9, 10** and **11** to furnish the corresponding products **6** and **7** with up to 99% *ee* in almost quantitative yields (Scheme 2).

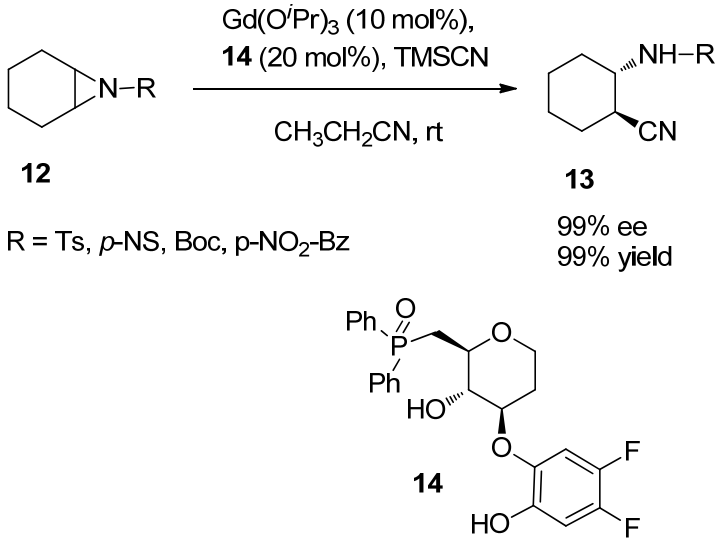


5 6 7 8 9 10 11

Scheme 2.

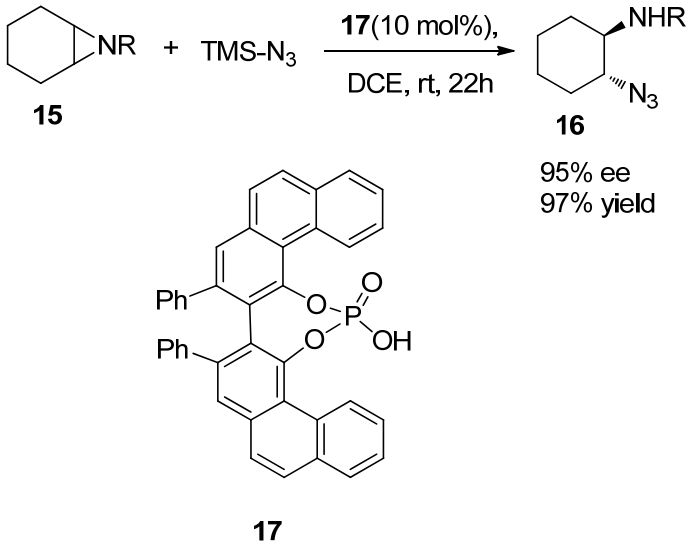
1A.3. Aziridine desymmetrization

Shibasaki and co-workers[5] developed a catalytic enantioselective desymmetrization route to synthesize *β*-amino acid derivatives of **13** with up to 99% *ee* and 99% yield from *meso*-*N*-acylaziridines **12** using trimethylcyanide as a nucleophile in the presence of Gadolinium complex of **14** as a catalyst (Scheme 3). These derivatives of **13** can be efficiently transformed into β-amino acids, an important chiral building blocks for the synthesis of various natural products and pharmaceuticals.



Scheme 3.

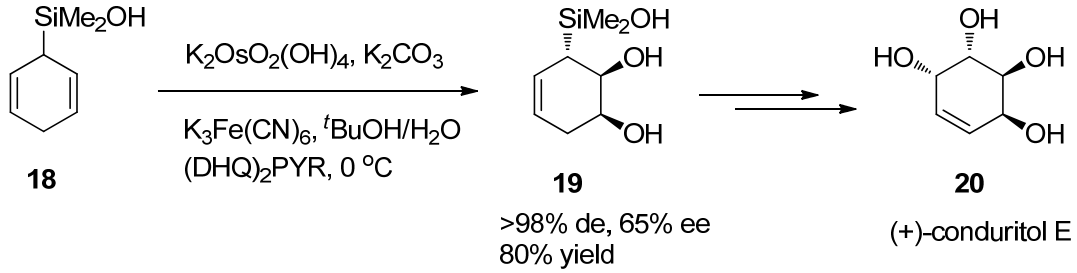
Rowland *et al.*[6] developed a protocol for synthesizing vicinal diamine structural frame work **16** (95% *ee*, 97% yield) *via* Bronsted acid **17** catalyzed desymmetrization of *meso* aziridines **15** using trimethylsilyl azide (Scheme 4) as the nucleophile. These diamines **16** have been extensively used in organic synthesis as chiral auxilaries, ligands and were also found in anticancer agents and anti-influenza drugs as well as in many biologically active compounds.



Scheme 4.

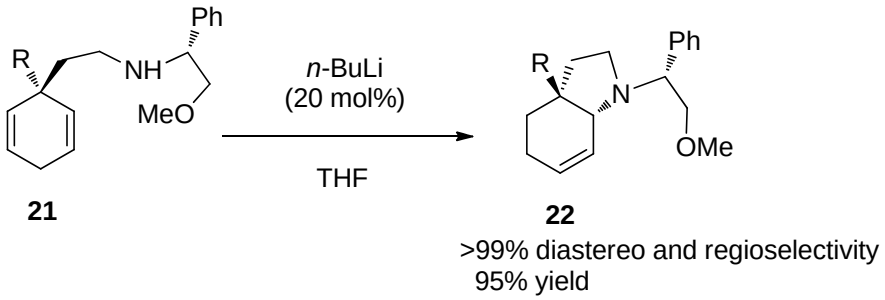
1A.4. Diene desymmetrization

The use of Sharpless asymmetric dihydroxylation (AD) is another important reaction to perform the desymmetrization of *meso* dienes. The synthesis of (+)-conduritol E **(20)** has been reported by Landais *et al*.[7] by employing the asymmetric dihydroxylation of silyl-substituted cyclohexadiene **18**. The treatment of *meso* diene **18** under modified AD conditions produced diol **19** (Scheme 5) in good yield and selectivity (80% yield and 65% *ee*). The enantiomerically enriched diol **19** was advanced to obtain (+)-Conduritol E (**20**).



Scheme 5.

Raphael *et al*.[8] reported diastereoselective hydroamination of cyclohexa-2,5-dienes **21** to obtain corresponding bicyclic allylic amines **22** in high selectivity (>99% diastereo and regio selectivity) and yields (95%) through desymmetrization. Mechanistically, desymmetrization results from the diastereoselective protonation of pentadienyl anion, resulted by the addition of a lithium amide across the double bond followed by highly regioselective protonation (Scheme 6).



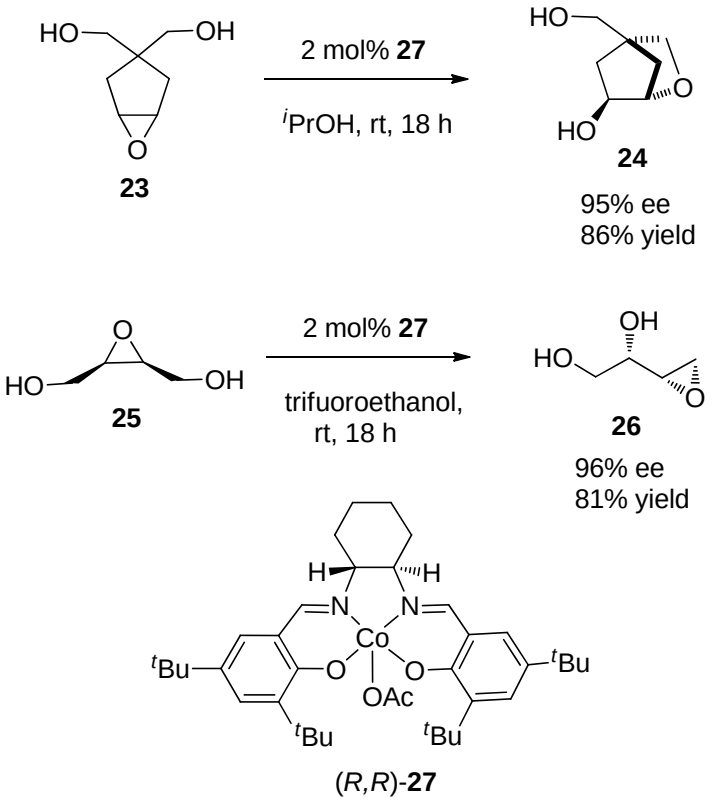
21 **22**

>99% diastereo and regioselectivity
95% yield

Scheme 6.

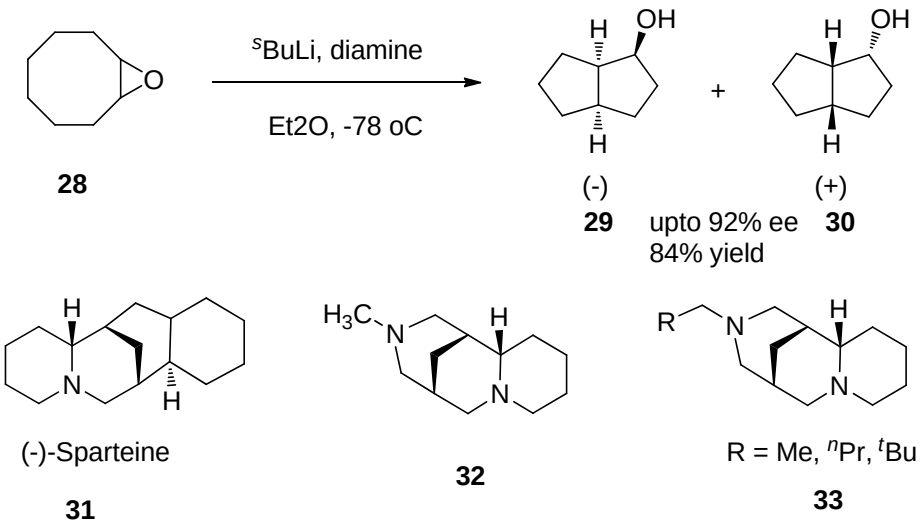
1A.5. Epoxide desymmetrization

Jacobsen *et al*.[9] discovered an intramolecular ring-opening reaction of epoxides with oxygen nucleophiles, catalyzed by the Co(salen)OAc catalyst **27**. The intramolecular opening of *meso*-epoxy diol **23** provided novel bicyclic product **24** with excellent yield and enantiomeric excess (>95% *ee*, 86% yield). Complex **27** also catalyzed an asymmetric Pyne rearrangement of the *meso*-epoxy diol **25** to afford the enantio enriched building block **26** in 81% yield and 96% *ee* (Scheme 7).



Scheme 7.

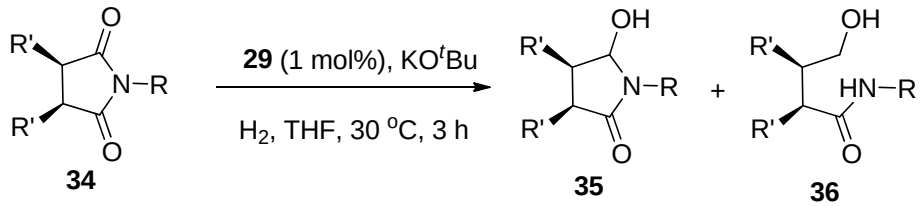
Dearden *et al.*[10] reported evaluation of spartiene-like diamines for the asymmetric desymmetrization of the cyclooctene epoxide **28** to produce bicyclic alcohols **29** and **30** with good enantioselectivites (92% *ee*) and yield (84%) (Scheme 8). Products **29** and **30** are the key intermediates for the synthesis of various biologically active compounds.

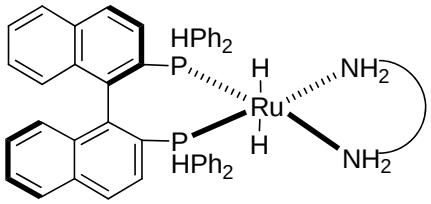


Scheme 8.

1A.6. Cyclicimide desymmetrization

Takebayashi *et al.*[11] reported first enantioselective desymmetrization of *meso* cyclic imides **34** by monohydrogenation to form hydroxyl lactams **35** and their derivatives **36** using ruthenium catalyst **37** with high selectivities and yields (97% *ee* and 99% yield) (Scheme 9). These hydroxyl lactams are versatile building blocks that have been used to prepare numerous heterocyclic compounds including vitamins, antibiotics, ACE inhibitors, and anticancer drugs such as (+)-biotin, loracarbef, (-)-A58365A, and swainsonine.



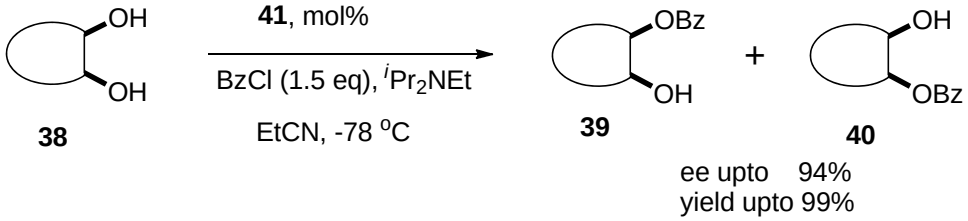


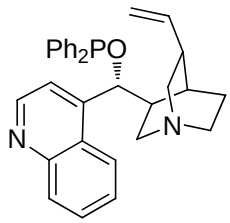
37

Scheme 9.

1A.7. Desymmetrization of 1,2-diols

Fujimoto and co-workers[12] developed an efficient protocol for direct desymmetrization of *meso*-1,2-diols **38** in the presence of phosphinite derivative of cinchona alkaloid **41** as a catalyst to produce **39** (Scheme 10) with excellent enantio selectivity and yields (94% *ee*, 99% yield).



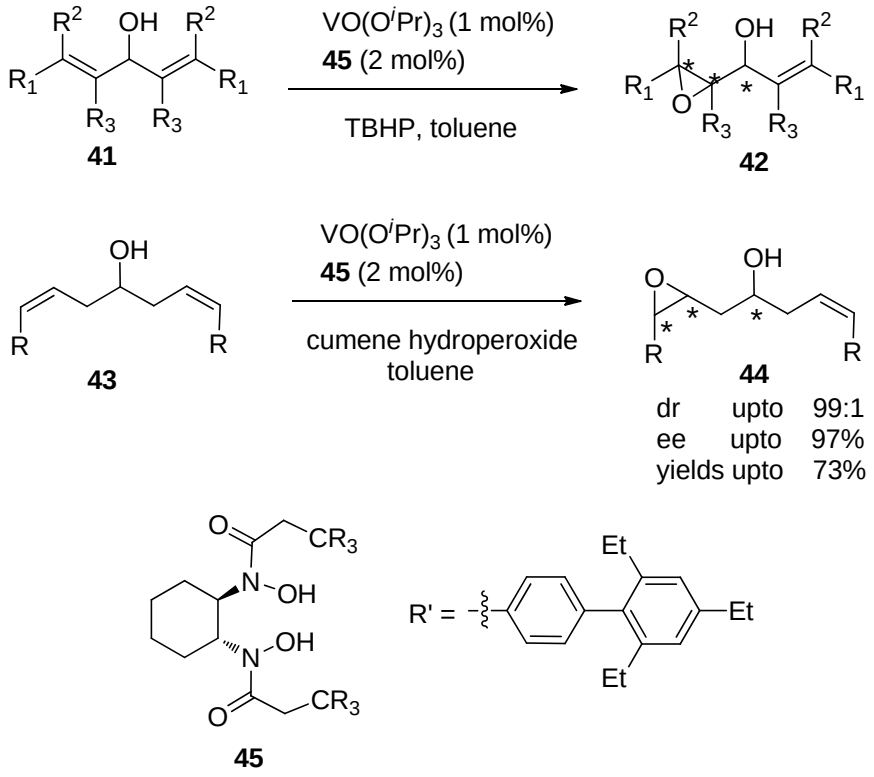


41

Scheme 10.

1A.8. Desymmetrization of allylic and homoallylic alcohols

Yamamoto and co-workers[13] developed a straight forward protocol for asymmetric desymmetrization of *meso* secondary allylic alcohol **41** and homoallylic alcohols **43** using vanadium catalytic **45** for epoxidation to produce corresponding desymmetrized derivatives **41** and **43** respectively (Scheme 11) with excellent diastereo, enantio selectivities and good yields (97% *ee*, 99:1 *dr*, 73% yield).

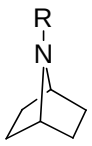


Scheme 11.

Section-B

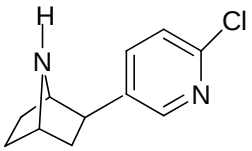
1B.1. Importance of 7-azabicyclo[2.2.1]heptane framework

The synthesis of the 7-azabicyclo[2.2.1]heptane system (**46**) has been the subject of numerous synthetic studies which have resulted in the development of several methods for the construction of these novel structures. For sometimes, the interest in the synthesis of these systems were only a matter of academic interest since no naturally occurring compound was known at that time to contain these ring systems. However, in 1992 Daly *et al.*[14] reported the discovery and structural elucidation of (-)-epibatidine (**47**), a new alkaloid isolated from Ecuadorian poison frog, *Epipedobates tricolor,* featuring the 7-azabicyclo[2.2.1]heptane ring system with an *exo* oriented 5-(2-chloropyridyl) moiety (Figure 2). Due to the novel biological activity associated with epibatidine and its paucity in nature (1 mg isolated from 750 frogs), the total synthesis of compound had aroused the interest of organic chemist around the world.



46

7-azabicyclo[2.2.1]heptane



47

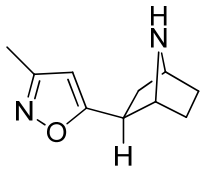
Epibatidine

Figure 2.

The extraordinary pharmacology[15] of **47** had indicated its potential for nicotinic acetylcholine receptor (nAChR) ligands for serving as a new therapeutic class of host of CNS disorders. Many of such ligands are natural products, or analogues thereof, which represent a significant challenge to the synthetic chemist.

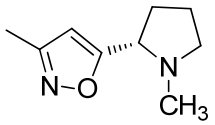
The chance of epibatidine ever being used as a medicinal agent became quite low because of its high toxicity, however, in order to cope up with toxicity, several analogues

of epibatidine have been designed and synthesized by altering the side chain as well as bicyclic skeleton. One of the interesting analogue is epiboxidine[16] (**48**), a hybrid of epibatidine and ABT-418 (**49**) which is an isosteric analogue of nicotine, where chloropyridine ring has been replaced by methylisoxzole (Figure 3). Although, not as potent as epibatidine, epiboxidine (**48**) has higher affinity than nicotine and has been found 20 fold less toxic than epibatidine.



48

Epiboxidine

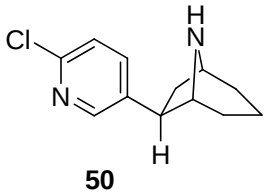


49

ABT-418

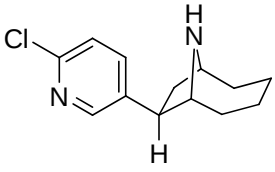
Figure 3.

One other class of the epibatidine analogue in which the azabicycloheptane ring is altered, has been synthesized and tested, includes homoepibatidine (**50**), *bis* homoepibatidine[17] (**51**) and diazabicyclopyrazine DBO-83[18] (**52**) (Figure 4).



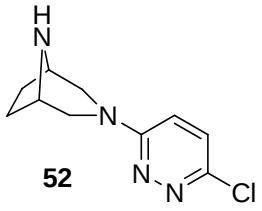
50

homoepibatidine



51

bis- homoepibatidine

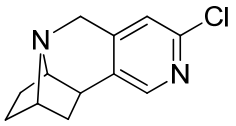


52

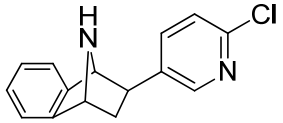
DBO -83

Figure 4.

In search for better selectivity, conformationally restricted analogue **53** as well as fused analogue **54** has also been synthesized[19] and screened (Figure 5). Although, these analogues show low affinity and do not encompass the ideal conformation for the high affinity, they provide valuable information concerning the pharmacophore studies.



53



54

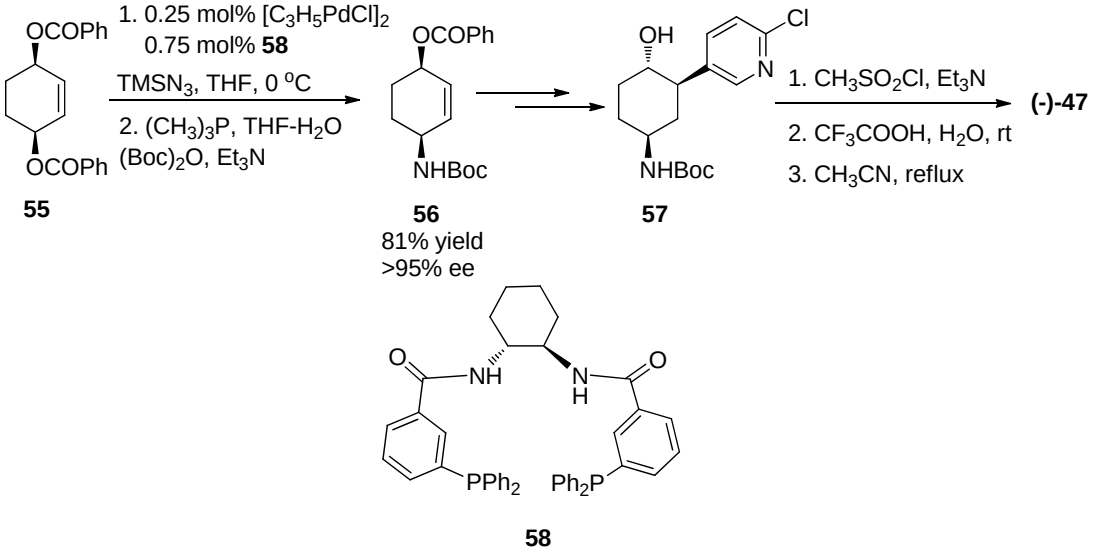
Figure 5.

Despite significant progress in the research dealing with the chemistry of 7-azabicyclo[2.2.1]heptane ring system, most of these novel structures have been used in the synthesis of epibatidine and its analogues. Because of the importance of 7-azabicyclic frame work in general and epibatidine in particular, various groups have developed different approaches for the construction of 7-azabicyclo[2.2.1]heptane ring system. However, before discussing our contribution in this field, it would be appropriate to describe some of the selected examples used for the synthesis of 7-azabicyclo[2.2.1]heptane frame work from the literature.

1B.2. Known approaches for the construction of 7-azabicyclic system

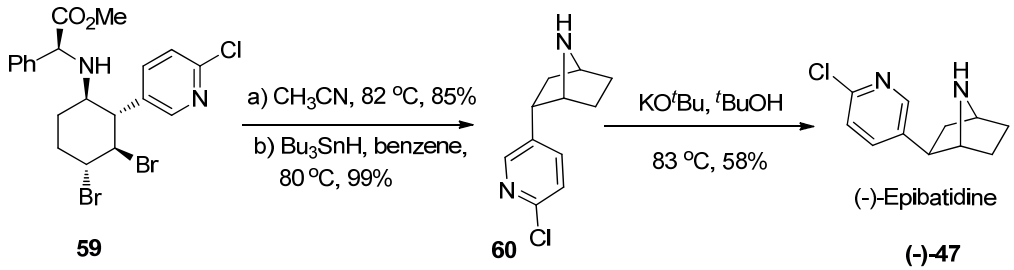
1B.2a *trans*-Annular cyclization

Trost *et al*.[20] reported the first asymmetric synthesis of (-)-epibatidine (**47)** using Pd-catalyzed desymmetrization of *meso*-**55** to produce **56** which was later converted into a key precursor **57**. The intermediate **57** was subjected to *trans*-annular cyclization to construct 7-azabicyclic system producing (-)-**47** with 81% yield and >95% *ee* as depicted in Scheme 12.



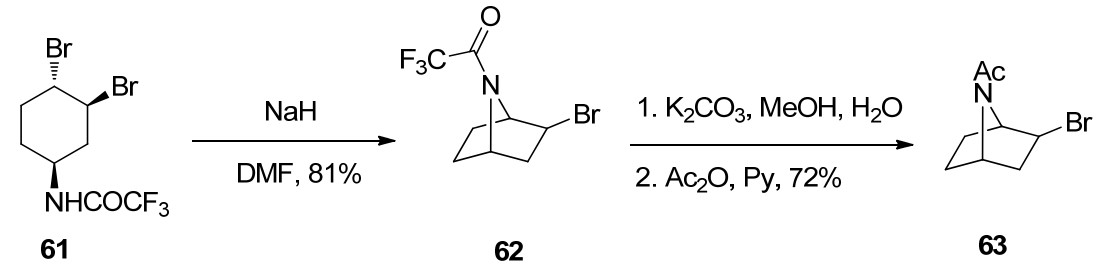
Scheme 12.

Lee *et al.*[21] developed a short and straightforward practical procedure for the gram-scale synthesis of **47** by intramolecular cyclization of **59** followed by the radical dehalogenation to provide **60** as a sole product which was further epimerized to (-)-**47** as shown in Scheme 13.



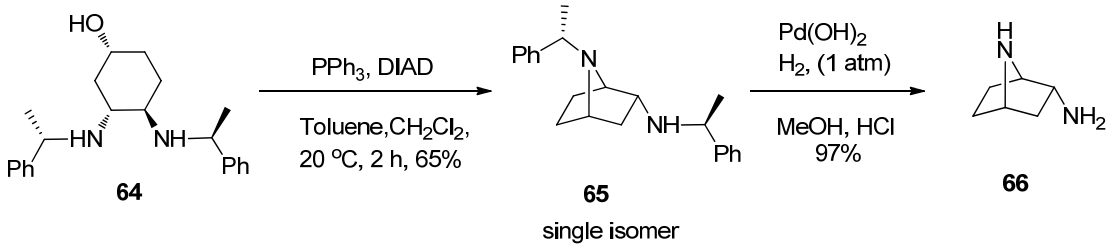
Scheme 13.

Sanchez and co-workers reported[22] NaH/DMF-promoted heterocyclization reaction of *N*-(3-*cis*,4-*trans*-dibromocyclohex-1-yl)-2,2,2-trifluoroacetamide **61** to afford 7-azabicyclo [2.2.1] heptane derivative **62** in good yield (81%) which on basic hydrolysis followed by acetylation gave **63** in 72% yield (Scheme 14).



Scheme 14.

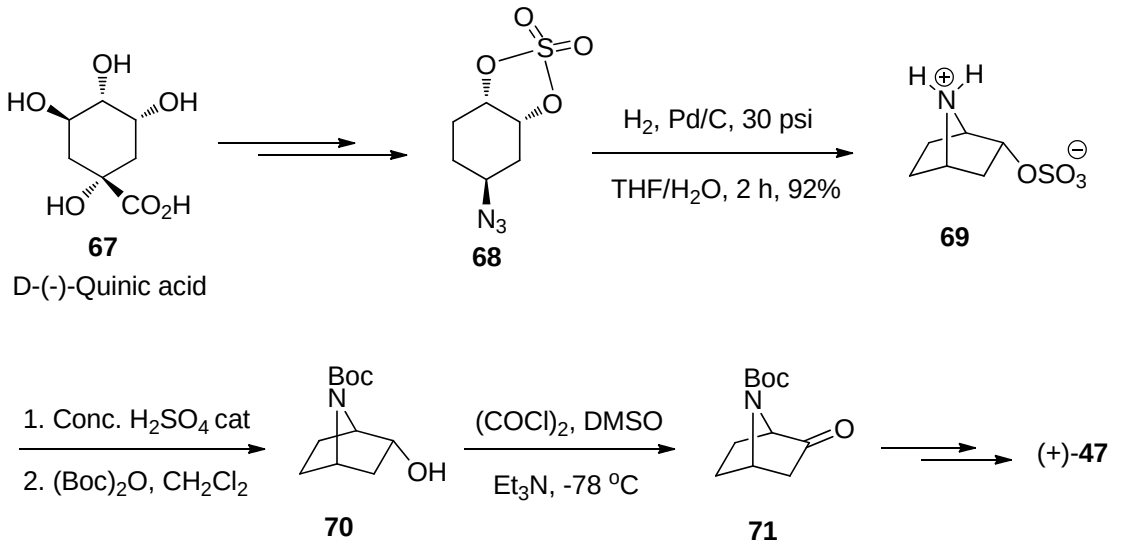
Savoia *et al.*[23] developed a simple and efficient protocol for the synthesis of optically pure *endo*-7-azabicyclo[2.2.1]heptane **65** by the cyclization of **64** using Mitsunobu protocol. Subsequent removal of benzylic substituents by reductive hydrogenation in the presence of palladium hydroxide in methanol in the presence of 2.5 eq HCl/MeOH produced *endo*-**7**-azabicyclo[2.2.1]heptan-2-amine **66** as a single isomer in 97% yield (Scheme 15).



Scheme 15.

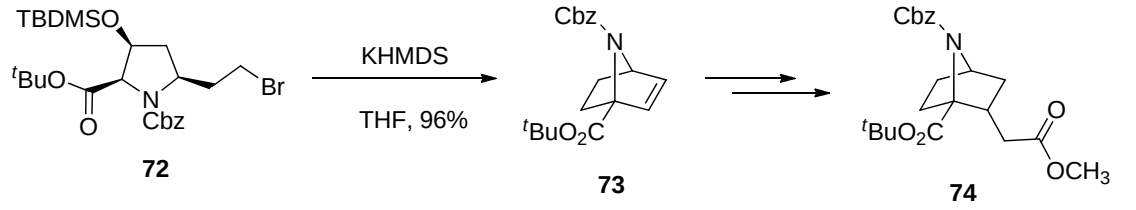
1B.2b Intramolecular cyclization

Albertini *et al.*[24] have reported conceptually attractive strategy for the enantioselective construction of 7-azabicyclo[2.2.1]heptane skeleton **69** in high yield (92%), employing a facial and regio-selective intramolecular nucleophilic ring opening of a chiral cyclic sulfate **68** derived from D-(-)-quinic acid **67** as shown in Scheme 16. Intermediate salt **69** was further transformed to 7-azabicyclic ketone **71** for the synthesis of (-)-epibatidine.



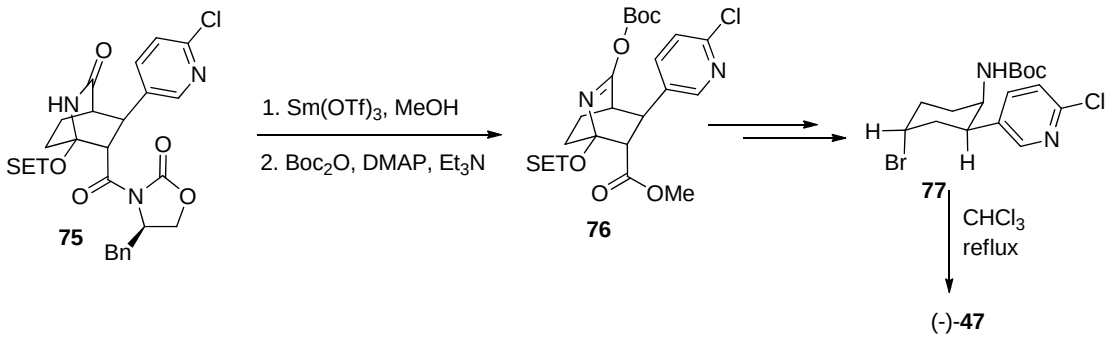
Scheme 16.

Barry *et al*.[25] reported the synthesis of 7-azabicyclic ring system **73** in excellent yield (96%) involving β-elimination of silyl ether of **72** followed by cyclization to afford **73.** Intermediate **73** was further converted into 2-substituted 7-azabicyclo[2.2.1]heptane glutamic acid analogue **74** employing simple transformations (Scheme 17).



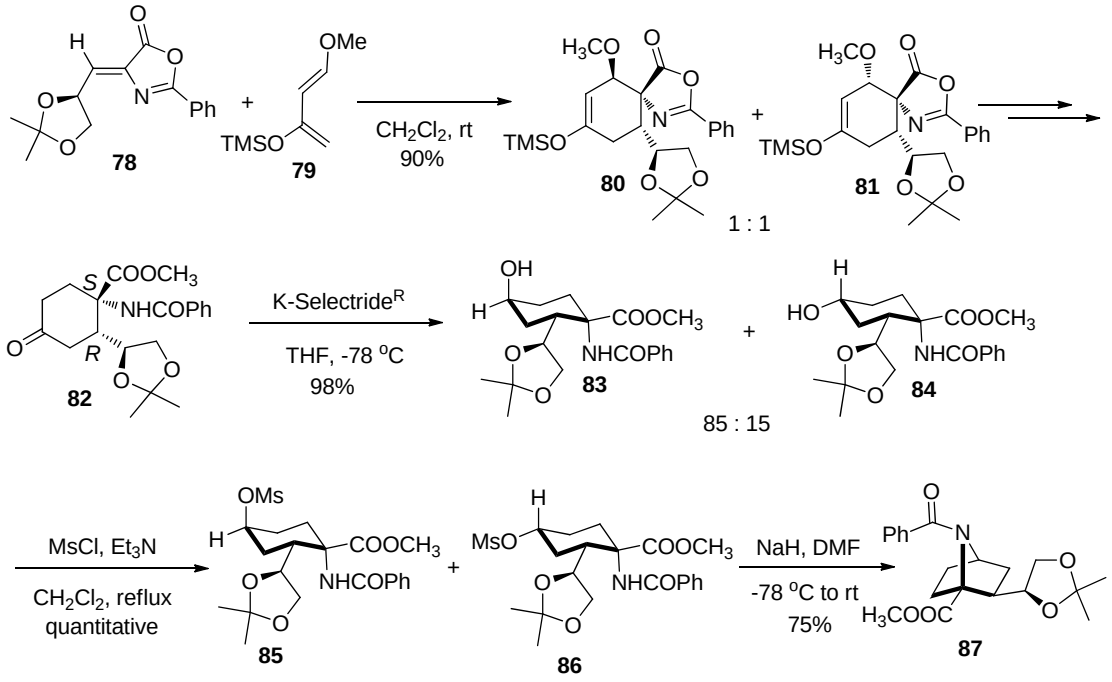
Scheme 17.

Evans *et al*.[26] reported asymmetric hetero Diels-Alder reaction as a key step for the synthesis of (-)-epibatidine. The key intermediate **77** was obtained in high yield and selectivity from **76**, a product derived from an asymmetric Diels-Alder cycloadduct **75**. The precursor **77** was further converted to (-)-**47** by intramolecular cyclization as shown in Scheme 18.



Scheme 18.

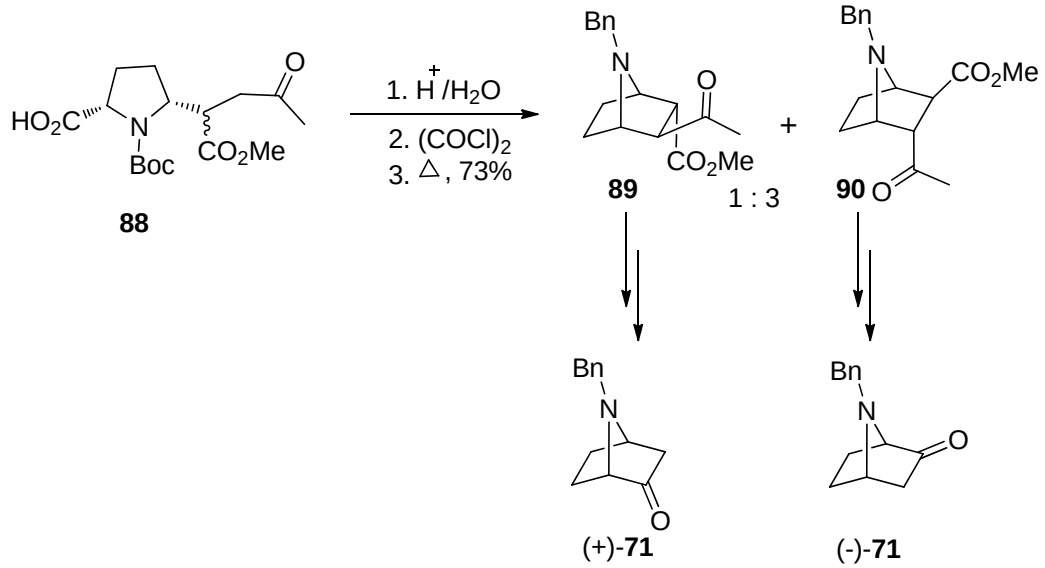
Elena and co-workers [27] developed a protocol for the synthesis of 7-azabicyclic system **87** by intramolecular cyclization of a mixture of **85** and **86** which in turn was obtained by the cyclization of **82**. The key intermediate **82** was obtained by Diels-Alder reaction of (*Z*)-2-phenyl-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethylene]-5-oxazolone **78** and Danishefsky's diene **79** (Scheme 19).



Scheme 19.

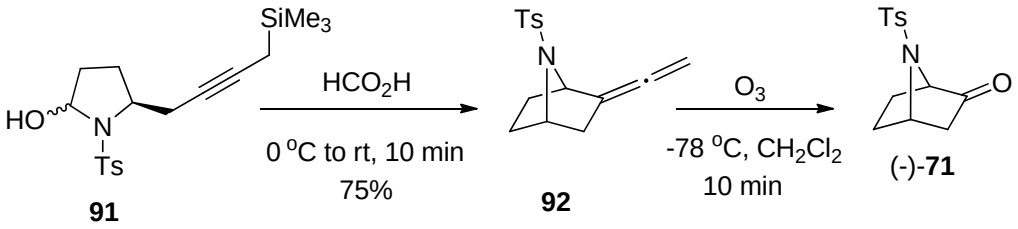
1B.2c. Intramolecular iminium cyclization

Rapoport *et al*.[28] have introduced a novel "Chiron" concept of decarbonylation/intramolecular iminium-ion cyclization of **88**, for the construction of enantiopure *trans*-2,3-disubstituted-7-azabicyclo[2.2.1]heptanes **89** and **90** in 1:3 ratio, those were further converted into (+)-**71** and (-)-**71** respectively, *via* single chemical manipulation as shown in Scheme 20.



Scheme 20.

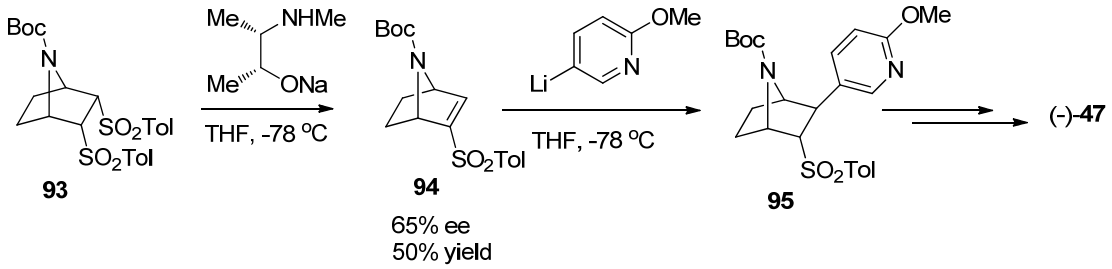
Karsten *et al*.[29] developed a method for the construction of enantiopure 7-azabicyclo[2.2.1]heptanes skeleton **92** in 75% yield by intramolecular *N*-acyliminium ion cyclization of **91** followed by ozonolysis of **92** to produce a key precursor (-)-**71** for (+)-epibatidine (Scheme 21) synthesis.



Scheme 21.

1B.2d Asymmetric elimination

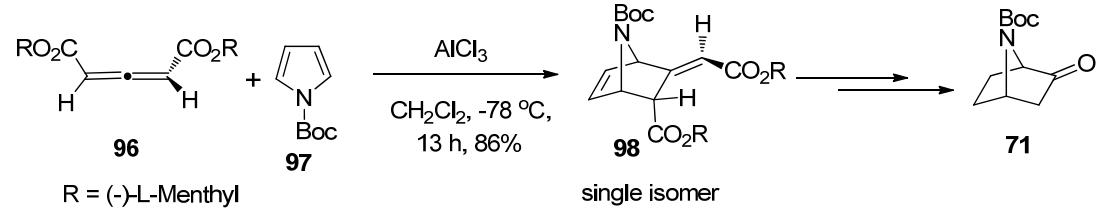
Simpkins *et al*.[30] have reported an unique approach for the total synthesis of (-)-epibatidine (**47)**, utilizing asymmetric elimination of a sulfone group from a vicinal *bis*-sulfone having the 7-azabicyclo[2.2.1]heptanes skeleton **93** by the sodium alkoxide derivative of (*1R,2S*)-ephedrine. Key precursor **95** was further converted in to (-)-**47** by simple chemical transformation (Scheme 22).



Scheme 22.

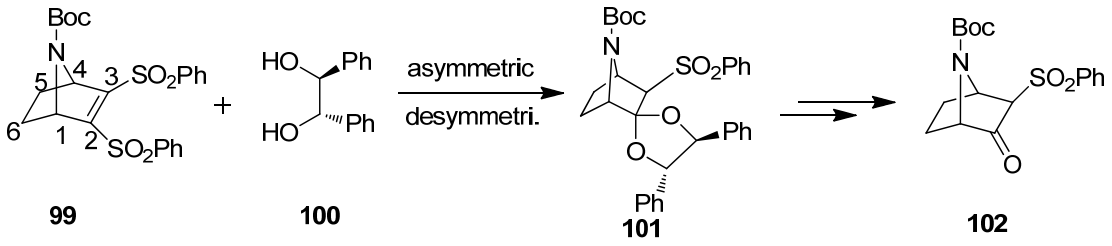
1B.2e Asymmetric Diels-Alder cycloaddition

A very interesting approach has been adopted by Node and co-workers[31] for the construction of enantiopure 7-azabicyclo[2.2.1]heptanes system **98** (86 %) as a sole product utilizing asymmetric Diels-Alder reaction of di-L-(2)-menthyl allene-1,3-dicarboxylate (*R*)-**96** with *N*-Boc-pyrrole **97** in the presence of $AlCl_3$ in CH_2Cl_2 at -78 °C. Compound **98** was subsequently converted into a synthetic precursor **71** for the synthesis of (-)-epibatidine (Scheme 23).



Scheme 23.

Visualizing the importance of 7-azabicyclo[2.2.1]heptanes system and our continuing efforts directed towards the development of novel methodologies[32] for the construction of enantiopure 7-azanorbornene frame works, we have developed earlier a conceptually new and efficient route *via* asymmetric desymmetrization of *meso*-**99** using chiral diolate of **100** to produce optically pure 7-azabicyclic frame **101** with excellent diastereoselectivity and yield (99% *de*, 82% yield)[33] as outlined in Scheme 24 which was later elaborated for the total synthesis of various conduramines and substituted cyclohexane derivatives.

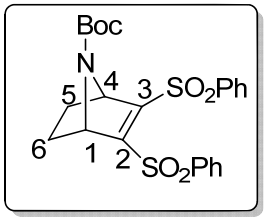


99 **100** **101** **102**

Scheme 24.

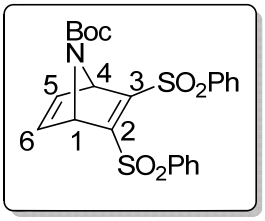
1B.3. Objectives and aims of the present dissertation

While working on the above approach, we envisaged the importance of *meso*-**103,** for further synthetic explorations owing to the possibility of introducing additional functionality through C5-C6 olefinic bond.



99

Previously used *meso*-precursor



103

Present *meso*-precursor

In this context, we have explored the desymmetrization of *meso*-**103** for the synthesis of highly functionalized 7-azabicyclic frameworks and their application towards the synthesis of aminocyclitols and this would be the present aim of our dissertation. The proceeding chapter would describe our exploration and progress in this endeavor.

1B.4. References:

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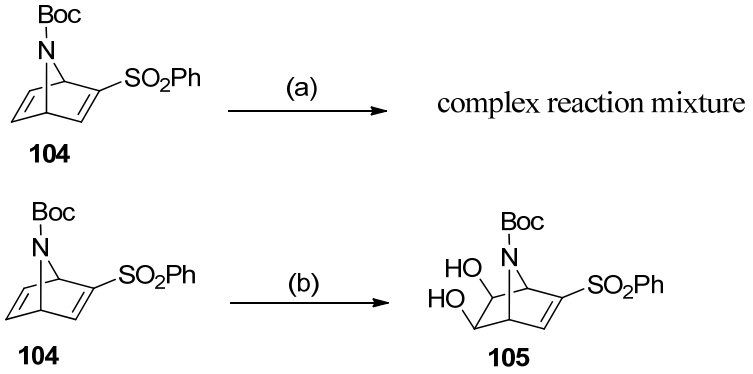
Chapter-2

Desymmetrization of meso-7-azabicyclo[2.2.1]heptadiene system

In order to explore the application of desymmetrization protocol in the total synthesis of various aminocyclitols (natural and unnatural), we began our research by developing a strategy to prepare *meso*-**103** which is described as follows:

2A.1. Attempts towards synthesizing meso-103

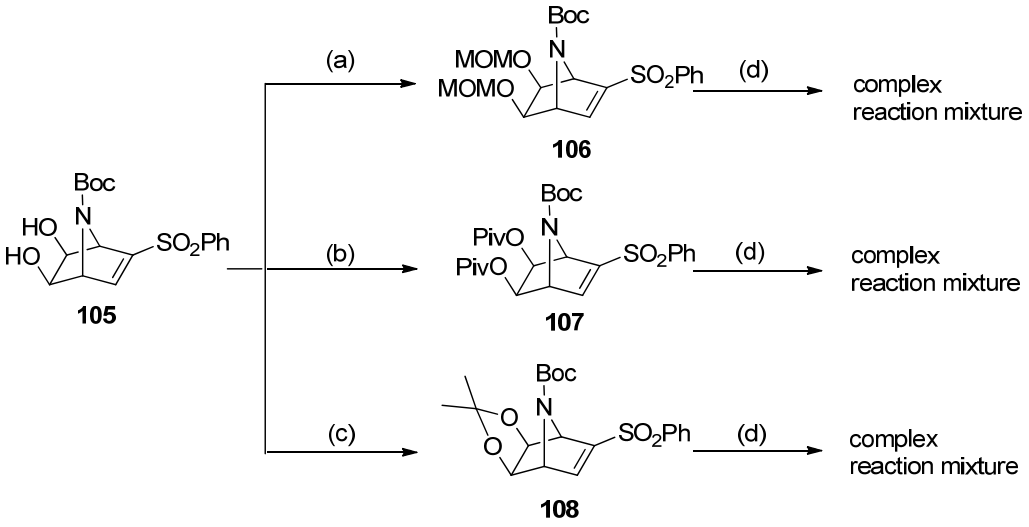
Initially, we attempted the synthesis of **103** by following our earlier protocol[1] by lithiating vinylic proton of **104** using *n*-BuLi / THF at -78 °C followed by quenching with $PhSO_2F$. However, this reaction did not provide required *meso*-**103**, instead, produced complex reaction mixture. This unexpected result was initially interpreted due to the presence of C5-C6 double bond and therefore, it was dihydroxylated to **105** using OsO_4 in *t*-BuOH in order to inhibit its possible role in the above reaction.



Scheme 1.

Reagent and Condition: (a) n-BuLi, $PhSO_2F$, THF, -78 ^oC (b) OsO_4, NMO, Acetone : H_2O (9:1), 2 h, 92%

Unfortunately, another attempt of sulphonylation with corresponding -OMOM protected **106** also produced a complex reaction mixture. Subsequently, we also evaluated sulphonylation reaction with variously protected **105** using identical reaction condition, but to our disappointment none of these attempts delivered the required *meso* precursor for desymmetrization.



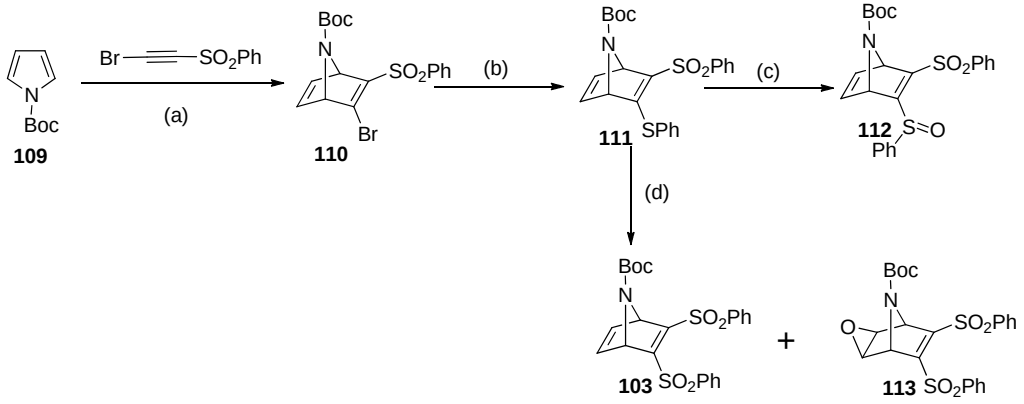
Scheme 2.

Reagent and Condition : (a) MOMCl, Et_3N, DCM, 77% (b) PivCl, Et_3N, DCM, 72 (c) 2,2-dimethoxy propane, *p*-TSA, Acetone, 86% (d) *n*-BuLi, $PhSO_2F$, THF, -78 ^oC

Since all our above efforts failed to bring about desired *meso*-**103** (or equivalent), we ultimately modified our strategy which is described as follows:

2A.2. Synthesis of *meso*-103

Cycloadduct **110,** readily prepared in 76% yield by heating (90 °C) a mixture of 2-bromoethynyl phenyl sulfone and *N-tert*-butoxy pyrrole carbamte **109** for 24 h (Scheme 3)[2], was treated with freshly prepared thiophenol sodium salt in THF at room temperature to obtain **111** in quantitative yield.



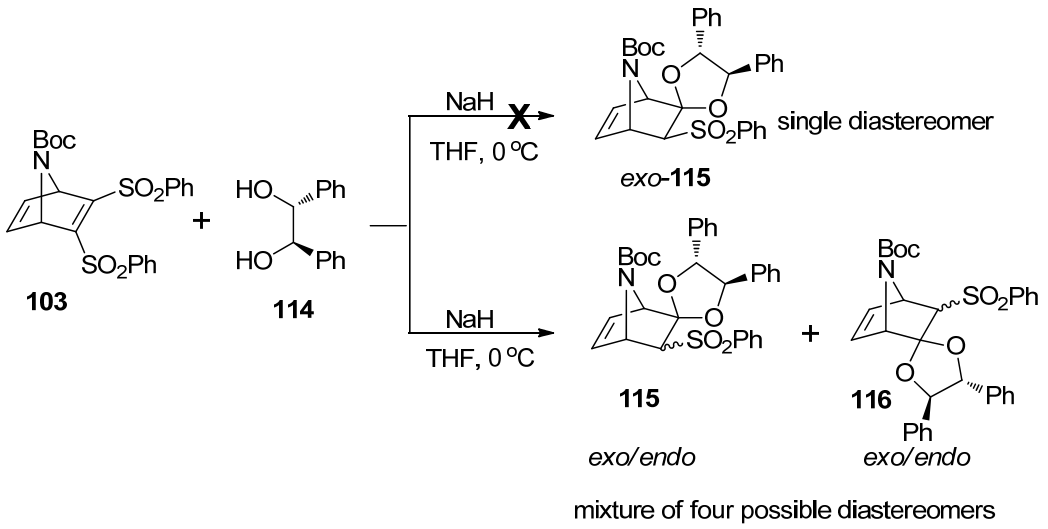
Scheme 3.

Reagent and Condition : (a) Toluene, 90 °C, 24 h, 76% (b) NaH, PhSH, THF, rt, 0.5 h, quant (c) TEBA-OXONE, DCM, few weeks (d) *m*-CPBA, DCM, 0 °C→rt, 72%

Initially oxidation of **111** was evaluated using mild oxidizing agent such as TEBA-OXONE to selectively oxidize the -SPh group to corresponding sulphone in the presence of C5-C6 double bond, however, even after prolonged reaction time and excess of the reagent, only sulfoxide **112** could be obtained.[3] Ultimately, *meso*-**103** was prepared in good yield (72%) by oxidizing **111** using *m*-CPBA (2.1 equiv.) as the oxidizing agent. During the optimization of this oxidation reaction, trace amount of over oxidized product **113** was also isolated (Scheme 3). In the ^{1}H NMR spectrum of **103**, ten aromatic protons appeared as two multiplets between δ 7.54 and 8.07. A singlet at δ 6.83, integrating for two protons, was assigned to the two olefinic protons and another singlet at δ 5.52, integrating for two protons, was assigned to the two bridgehead protons. The mass spectrum of compound **103** showed molecular ion peak at 474 (M^+ +H).

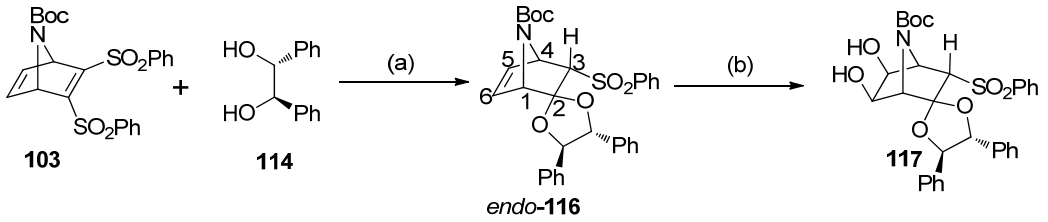
2A.3. Desymmetrization of *meso*-7-azabicyclic frame work (103)

As per the protocol established by us earlier,[1] desymmetrization of **103** was carried out by stirring (2 h) with an equivalent amount of the disodium salt of (+)-hydrobenzoin **114** in anhydrous THF at 0 °C, however, it provided all four possible diastereomeric mixture of corresponding desymmetrized ketals in 2:2:6:1 ratio (HPLC analysis [Merck Purospher (250x 4.6mm) CH_3CN:H_2O (60:40) isocratic, flow rate 1.0 ml/min]. This observation was in sharp contrast and surprising to our earlier observation (Scheme 4).



Scheme 4.

Therefore, it occurred to us to perform the same reaction at lower temperature with the hope that it might produce the expected desymmetrization *exo*-**115** in high diastereoselectivity. Thus, desymmetrization of **103** was performed at -100 °C and indeed, it produced desymmetrized *endo*-**116** as a white solid in 99% *de* and 89% yield (Scheme 5). ^{1}H NMR of *endo*-**116** displayed a singlet for H-3 at δ 4.06. Multiplets appearing in between δ 7.42-7.96, integrating for fifteen protons, were attributed to the aromatic protons. Two broad singlets at δ 6.76 and δ 6.64, integrating for one proton each, were assigned to the olefinic protons. A doublet at δ 5.10 (d, J = 8.85 Hz) integrating for one proton, could be assigned to either one of the benzylic protons. Another multiplet appearing between δ 4.80-4.91, integrating for two protons, one of them may be attributed to benzylic and another one to bridgehead proton. A singlet at δ 4.41, equivalent to one proton, was assigned to another bridgehead proton. The mass spectrum of *endo*-**116** showed molecular ion peak at 546 (M+H).



Scheme 5.

Reagents and Conditions : (a) NaH, THF, -100 °C, 3 h, 89% (b) OsO_4, NMO, Acetone:H_2O (9:1), 2 h, 91%

Based on NOESY experiment, the stereochemistry of H-3 was assigned as *exo* because of the intense interactions observed with the adjacent bridgehead H-4 as is known in the 7-azabicyclo[2.2.1.]alkane skeleton due to the dihedral angle being less than 60° between them. The *endo* orientation of the phenylsulfonyl group was also evidenced from the characteristic interactions observed between *ortho* protons of phenylsulfonyl group at δ 7.95 and the olefinic protons at δ 6.76 and δ 6.64. Although, *endo*-**116** was crystalline, it did not diffract properly for X-ray analysis. Therefore, it was dihydroxylated using OsO_4 in the presence of *N*-methymorpholine-*N*-Oxide to obtain corresponding **117** as a crystalline solid (mp 199 °C) in 91% yield (Scheme 5). The X-ray confirmed its structure as shown in Fig. 1.[1]

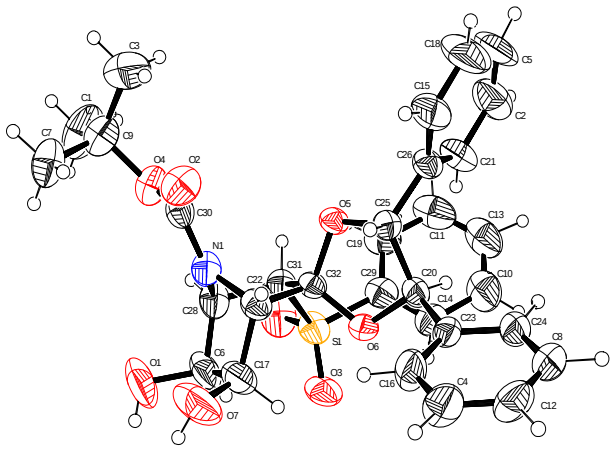
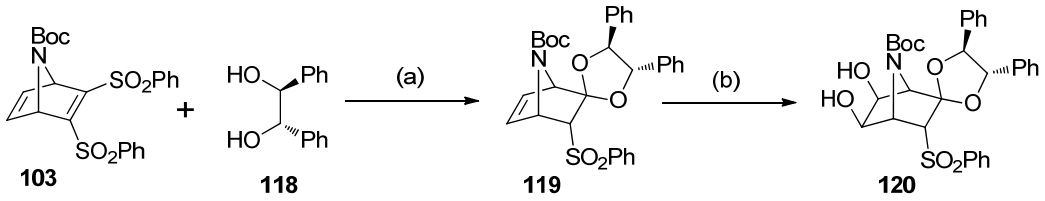


Figure 1. ORTEP diagram of **117**

To compare this observation, desymmetrization of *meso*-**103** was also performed with opposite enantiomer of the chiral diolate (-)-**118** which gave expected diasteromer as evidenced from the X-ray analysis of corresponding **120** (Figure 2).



Scheme 6.

Reagents and Conditions : (a) NaH, THF, -100 °C, 3 h, 86% (c) OsO_4, NMO, Acetone:H_2O (9:1), 2 h, 88%

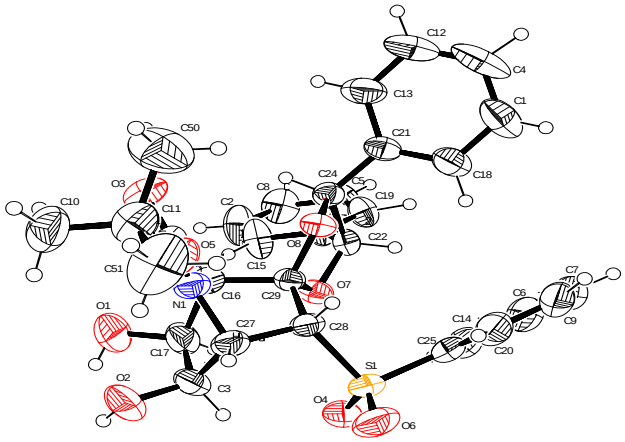
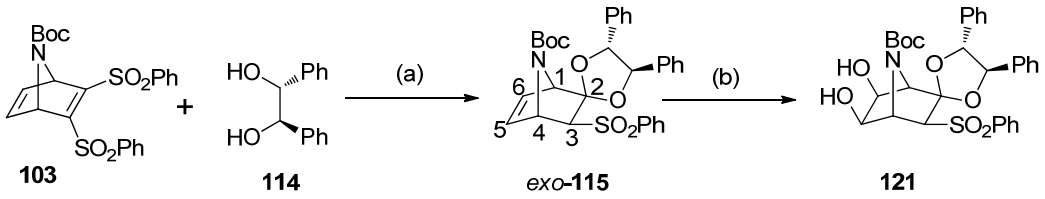


Figure 2. ORTEP diagram of **120**

To probe further the role of the temperature on the diastereoselectivity, desymmetrization of *meso*-**103** was investigated using the diolate of **114** at temperature range from -100 °C to 50 °C. The results are presented in Table-1. After several attempts of temperature screening, 35 °C was found to be optimum temperature to obtain *exo*-**115** with 92% diastereoselectivity as a white solid in 76% yield which was further confirmed by HPLC analysis [Merck Purospher (250 x 4.6 mm) CH_3CN:H_2O (60:40) isocratic, flow rate 1.0 ml/min]. Although

diastereoselectivity obtained was very high (99%) at 50 °C, yield obtained (28%) was low to proceed further. After single recrystallization, ^{1}H NMR spectrum of *exo*-**115** displayed one singlet for H-3 proton at δ 3.58 indicating it to be a single diastereomer.



Scheme 7.

Reagents and Conditions : (a) NaH, THF, 40 °C, 2 h, 76% (c) OsO_4, NMO, Acetone:H_2O (9:1), 2 h, 84%

At this stage, as it was very difficult to assign the position of chiral ketal moiety by NMR studies, because of undefined couplings between the all stereochemical protons, desymmetrized compound *exo*-**115** was converted in to its corresponding dihydroxylated derivative **121** by following the same procedure as described for **117** and recrystallized to provide **121** as a single diastereomer, (crystalline solid, mp 187 °C) in 84% yield (Scheme 7). Absolute configuration of **121** was unambiguously confirmed by X-ray analysis and it was surprising to note that it was opposite except the *exo*-orientation of the phenyl sulfonyl group compared to *endo*-**116** formed at -100 °C.

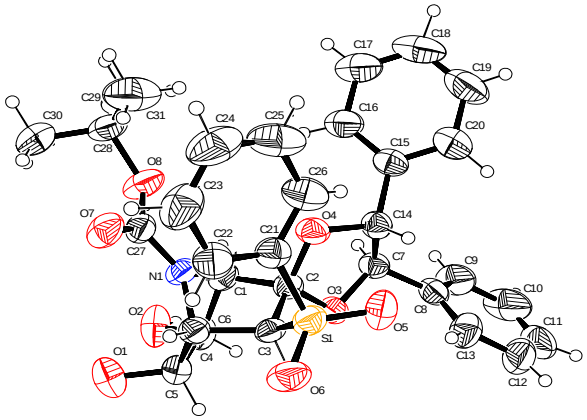


Figure 3. ORTEP diagram of **121**

From the formation of **117** and **121**, it was apparent that there is diastereoselectivity switch during the desymmetrization of *meso*-**103** from lower to higher temperature. Since temperature is also known to play significant role on stereoselectivity,[6] we probed this desymmetrization reaction in different solvents (toluene, dioxane and THF) at varying temperatures and results are given in Table 1.

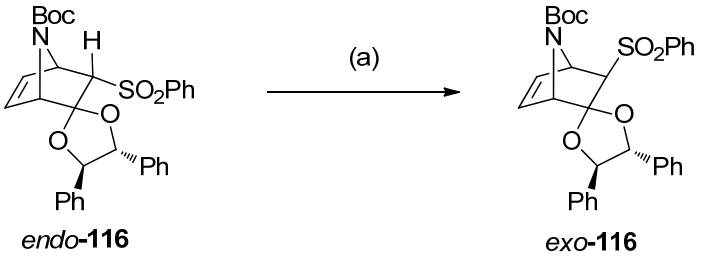
These results (Table 1) clearly demonstrate that solvent has no significant role in altering the diastereoselectivity, particulary in this case. From the above experiment results, it is obvious that temperature guides diastereoselectivity in the desymmetrization of *meso*-**103** and opposite pairs of diastereomers can be obtained with the same hydrobenzoin simply by altering the temperature.

Table 1. Temperature and solvent role in desymmetrization of *meso*-**103**

entry	solvent	temp (°C)	time (h)	yield (%)	**116**/**115** (*dr*)[a]
1	THF	-100	3.5	89	99:1
		-78	3.5	91	92:8
		0	2.0	85	diastereomeric mixture
		35	2.0	76	8:92
		50	2.0	28	1:99
2	toluene	-78	3.5	67	75:25
		35	2.0	48	20:80
3	Dioxane	35	2.0	62	15:85

[a] diastereomeric ratios were confirmed by HPLC analysis [XBridge RP-18 column, 250 x 4.6 mm, $CH_3CN:H_2O$ = 60:40].

At this juncture, we also visualized that *exo*-**116**, easily obtainable by epimerization of *endo*-**116**, and **115** would result enantiomeric pairs of 7-azabicyclic ketones (+) and (-)-**26** upon deketalization and should show opposite sign of optical rotation if, indeed, they are diastereomers.



endo-**116** *exo*-**116**

Scheme 8.

Reagents and Conditions: (a) KO^{t}Bu , THF, 0 °C, 3 min, 81%

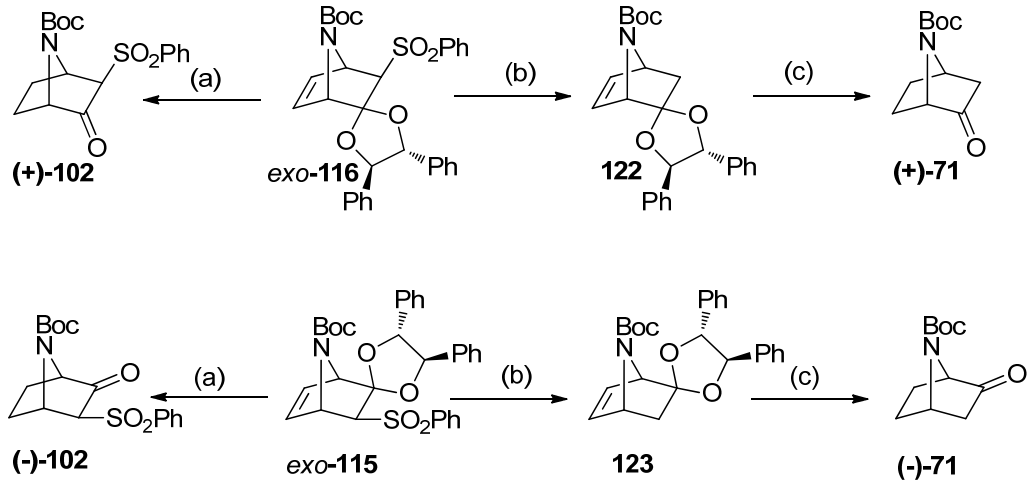
In this context, initially attempt was made to epimerize the *endo* sulfone moiety of **116** to *exo* sulfone using LiHMDS and KHMDS, however, it produced expected *exo*-**116** in poor yield. After few other experimentations, it was successfully epimerized using an equivalent amount of KO^{t}Bu at 0 °C → rt followed by quenching with dry methanol and obtained *exo*-**116** in 81% yield (Scheme 8). The stereochemistry of *exo*-**116** was confirmed on the basis of ^{1}H NMR and NOESY experiment analysis. In ^{1}H NMR of *exo*-**116**, H-3 at δ 3.75 appeared as a sharp singlet providing clear evidence for the successful transformation of *endo*-**116** to *exo*-**116** which was also confirmed by NOESY experiment.

2A.4. Structural confirmation of *exo*-116 and *exo*-115 by transforming in to known (+)- and (-)- enantiomeric pairs of 102 and 71

To provide conclusive proof to the structures of *exo*-**116** and *exo*-**115** as enantiomeric pair, these were hydrogenated in acetic acid at 60 psi using Pd/C as catalyst which furnished enantiomerically pure (+)-**102** ($[\alpha]_D$ +57.1 (c 0.60, $CHCl_3$), lit.[1] = +57.9) and (-)-**102** ($[\alpha]_D$ +57.1 (c 0.75, $CHCl_3$)), respectively (Scheme 9).

Compound **102** showed a strong absorption band at 1710 cm^{-1}, a characteristic peak of a carbonyl group. ^{1}H NMR spectrum displayed a multiplet between δ 8.00-7.86, attributable to the two *ortho* aromatic protons of the phenylsulfonyl group. The multiplets appearing between δ 7.67-7.48, integrating for three protons were assigned

to the remaining aromatic protons. The three other protons appearing at δ 4.95, δ 4.25 and δ 3.57 were assigned to two bridgehead protons and another proton adjacent to sulfonyl group. Mass spectrum of **102** showed molecular ion peak at 352 (M^++H).



Scheme 9.

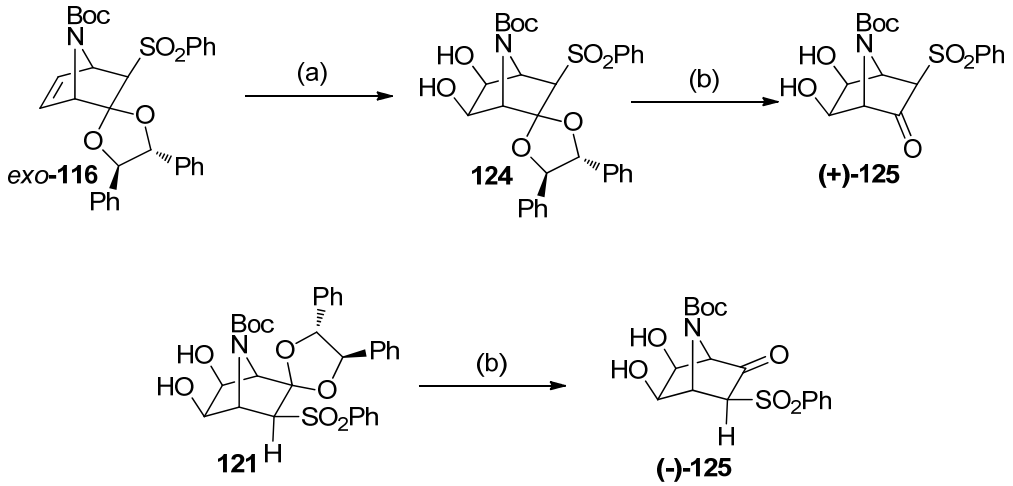
Reagent and Condition : (a) H_2, Pd/C, AcOH, 60 psi, 24 h, 67% (b) Na-Hg 7%, Na_2HPO_4, THF-MeOH (1:1) (c) H_2, Pd/C, MeOH, 1 atm, 4 h

Furthermore, desulfonylation, using Na-Hg 6% in THF-MeOH (1:1), of these diastereomeric pair of compounds produced corresponding **122** and **123** in 82% and 85% yield, respectively, which on usual hydrogenation produced corresponding (+)- and (-)-7-azabicyclic ketone ((+)-**71** $[\alpha]^{27}_D$ +77.8 (*c* 1.0, $CHCl_3$) and (-)-**71** $[\alpha]^{27}_D$ -76.9 (*c* 1.0, $CHCl_3$) in 90% and 92% yield, respectively (Scheme 9). These optical rotation values were found to be in complete agreement with those reported in literature.[1b,8]

2A.5. Synthesis of (+) and (-)-125

To provide further support to the fact that *exo*-**116** and *exo*-**115** are diastereomers, *exo*-**116** was converted to its corresponding dihydroxylated derivative **124** using OsO_4 in the presence of 50% aqueous NMO using acetone and water (9:1)

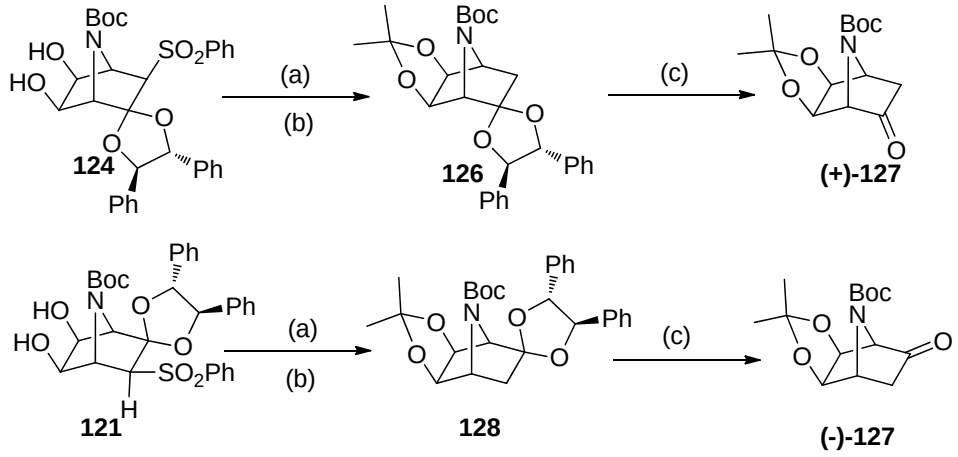
mixture as solvent. Dihydroxylated **124** and **121** were hydrogenated to produce corresponding enantiopure dihydroxylated 7-azabicyclic ketone (+)-**125** ($[\alpha]_D$ +38.7 (*c* 0.50, $CHCl_3$)) and (-)-**125** ($[\alpha]_D$ -41.4 (*c* 0.50, $CHCl_3$)) as white solids in 75% and 73%, respectively (Scheme 10).



Scheme 10.

Reagents and Conditions: (a) OsO_4, NMO, Acetone:H_2O (9:1), 2 h (b) H_2, Pd/C, AcOH, 60 psi, 24 h

The additional support to the observation that **124** and **121** produce opposite pairs of enantiomers of **125** they were further transformed in to their known derivatives of (+)-**127** $[\alpha]^{27}_D$ +48.1 (*c* 0.65, $CHCl_3$) and ((-)-**127** $[\alpha]^{27}_D$ -50.8 (*c* 0.65, $CHCl_3$)) (Scheme 11).



Scheme 11.

Reagents and Conditions : (a) 2,2-DMP, *p*-TSA, Acetone (b) Na-Hg 7%, Na_2HPO_4, THF-MeOH (1:1) (c) H_2, Pd/C, MeOH, 1 atm, 3 h

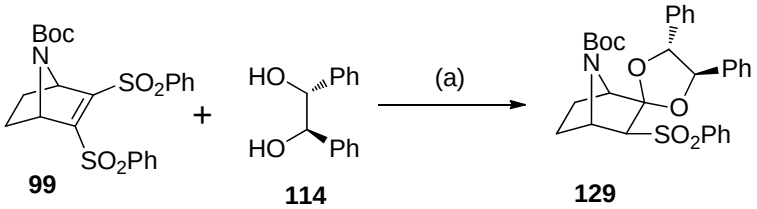
2A.6. Plausible Mechanistic Rationale for Observed Diastereoselectivity Reversal

From above observations, it was intriguing to note that in spite of skeletal similarities between *meso*-**99** and *meso*-**103**, desymmetrization of later was found to be temperature dependent. A closer evaluation indicates that *meso*-**103** differs with **99** only by having an electron rich double bond at C5-C6 position which appears to be playing role during desymmetrization.

present *meso* precursor **previously used *meso* precursor**

Figure 4.

Therefore, to probe the role of the double bond, desymmetrization of *meso*-**99** was evaluated at varying temperatures (-100 °C to 35 °C, Scheme 12) and it provided invariably the same single diastereomer irrespective of the temperature used. This experiment strongly supported the role of double bond in the observed diastereoselectivity switch during the desymmetrization of **103**.



Scheme 12.

Reagent and Condition: (a) NaH, THF, -78 °C, 7 h

Thus, it became apparent that reversal in diastereoselectivity during desymmetrization can only occur if the nucleophile approaches from the two different faces of this bicyclic structure at different temperatures. Based on all the above observations, we have proposed two plausible transition states **A** and **B** depending upon the approach of the nucleophile to *meso*-**103**. According to the free energy equation *(*$\Delta G = \Delta H - T\Delta S$), at -100 ^{o}C, lowering of entropy might be compensated by enthalpic stabilization because of the intermolecular interactions producing **130** by favoring the transition state **A.** On the other hand, with rise in temperature, value of $T\Delta S$ (*Eyring Plots*)[6a,9] term increases towards the free energy change because of weaker molecular interactions, there by favouring the transition state **B** where nucleophile approaches from the above face of the *meso* bicyclic skeleton **103** due to steric crowding producing **131** as a predominant diastereomer.

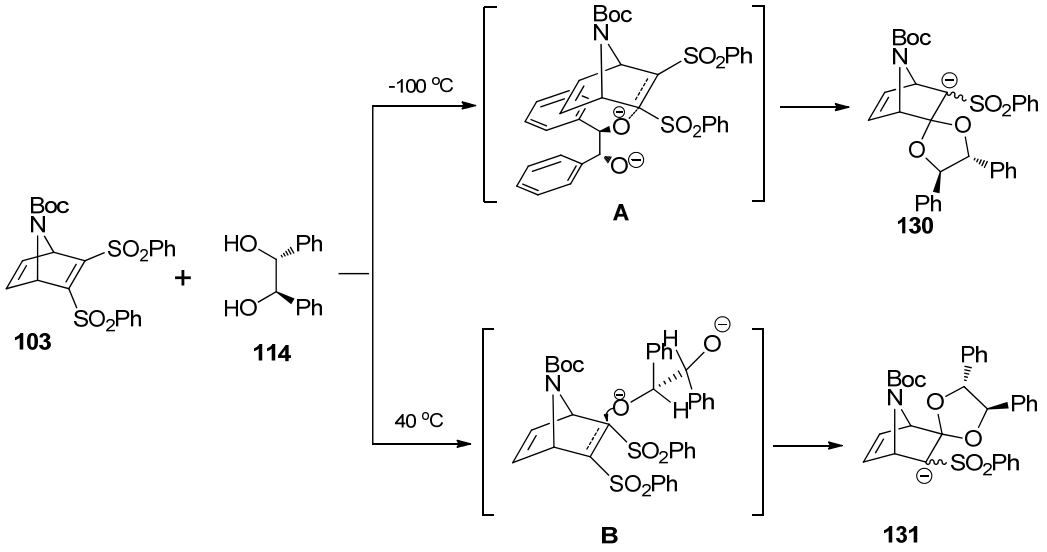


Figure 5.

Mechanistically, the formation of **116** requires nucleophilic attack of alcoholate anion onto the conjugated vinylic carbon atom from the below face of *meso*-**103** involving in the π- π interactions between aromatic ring and electron rich double bond. On the other hand, formation of **115** requires nucleophilic attack of chiral

diolate from above face of *meso* precursor which is least encumbered trajectory where phenyl group points upwards and alkyl to the side.

Utility and scope of the above temperature guided desymmetrization protocol was visualized in the synthesis of enantiomeric pairs of various highly functionalized cyclohexane and pyrrolidine rings as shown in figure 6.

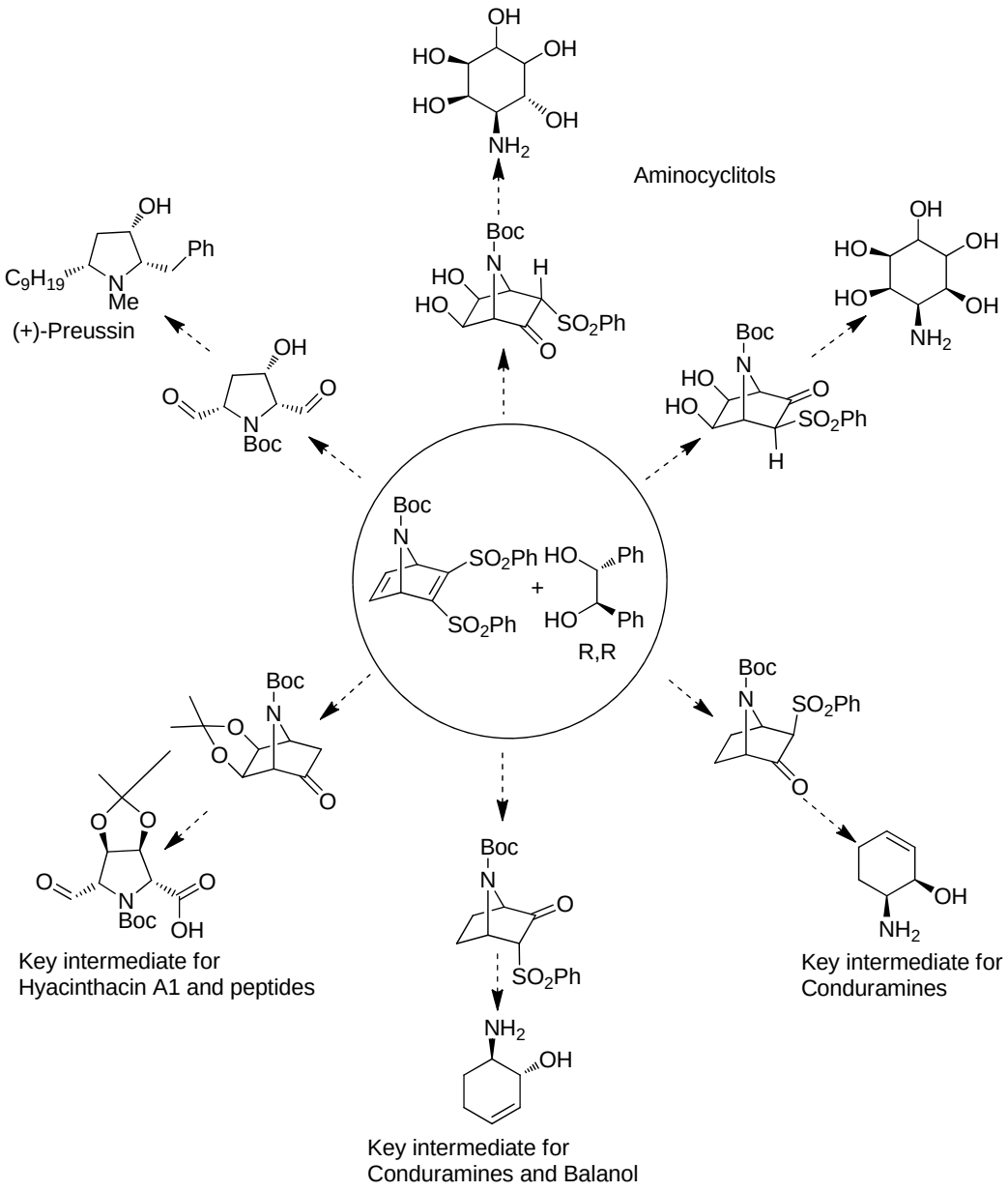


Figure 6

Summery: In conclusion, we have successfully optimized conditions for the reversal diastereoselective desymmetrization of **103.** Stuctural conformation was also illustrated by synthesizing known (+) and (-) enantiomeric pairs of various 7-azabicyclic ketone intermediates. Since, it is beyond the possibility of discussing the results of the synthetic applications of this methodology in one thesis, the foregoing chapter will discuss only our exploration and progress of temperature guided desymmetrization concept in the synthesis of aminocyclitols.

2A.7. References:

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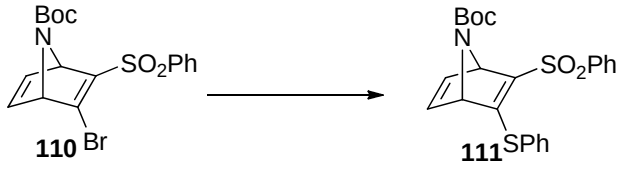
2A.8. Experimental Section:

(1*R*,4*S*)-*tert*-butyl 2-(phenylsulfonyl)-3-(phenylthio)-7-azabicyclo[2.2.1]hepta-2,5-diene-7-carboxylate (111):

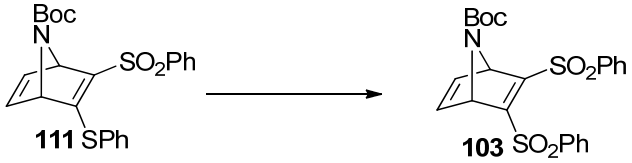


110 **111**

To an ice cooled suspension of NaH (0.117 g, 2.92 mmol, 60% suspension in mineral oil) in anhydrous THF (3 mL) was added a solution of PhSH (0.25 mL, 2.43 mmol) in anhydrous THF (6 mL) drop wise. After complete addition, the reaction mixture was stirred at room temperature for 15 min. A solution of **110** (1 g, 2.43 mmol) dissolved in anhydrous THF (6 mL) was added drop wise into the flask while stirring at 0 ^{o}C. The reaction mixture was further allowed to stir at room temperature for additional 1h. Completion of the reaction was monitored by silica gel TLC and after complete disappearance of **110**, the reaction mixture was quenched with brine (5 mL). Usual workup followed by column chromatography (SiO_2, ethyl acetate: pet ether, 1:5→2:5) provided **111** as a viscous liquid (1g, 96%). $\boldsymbol{R_f}$ = 0.3 (SiO_2, ethyl acetate-pet ether, 3:7);

IR υ_{max} cm^{-1} in $CHCl_3$	:	1725, 1690, 1627, 1308, 1290, 1121
^{1}H NMR (200 MHz, $CDCl_3$) δ	:	7.95-7.99 (m, 2H), 7.43-7.64 (m, 8H), 6.83 (br s, 1H), 6.63 (br s, 1H), 5.32 (br s, 1H), 4.79 (br s, 1H), 1.25 (s, 9H).
^{13}C NMR (50 MHz, $CDCl_3$) δ	:	153.6, 142.6, 140.3, 138.3, 135.7, 134.6, 133.6, 130.1, 129.7, 129.2, 127.2, 120.4, 81.4, 71.5, 69.4, 27.8.
Mass (ESI): *m/z*	:	442 (M $^+$+H).

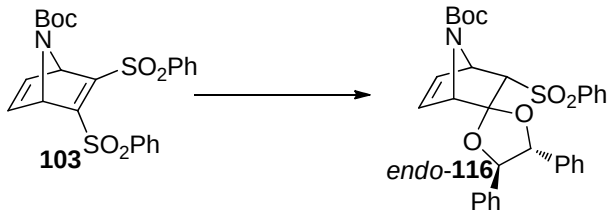
***meso-tert*-butyl 2,3-bis(phenylsulfonyl)-7-azabicyclo[2.2.1]hepta-2,5-diene-7-carboxylate (103):**



To an ice-cooled solution of **111** (1 g, 2.27 mmol) in DCM (9 mL) was added a solution of *m*-CPBA (1.174 g, 4.786 mmol) in DCM (9 mL) drop wise. After complete addition, the reaction mixture was allowed to stir at same temperature for 0.5 h and finally at room temperature for 1 h. Silica gel was added to the reaction mixture to absorb the crude product and purified by silica gel column chromatography with ethyl acetate : pet-ether (1:5→2:5) which gave **103** as a white solid (0.77 g, 72%). R_f = 0.3 (SiO_2, ethyl acetate-pet ether, 3:7);

m.p.	:	134-135 °C
IR υ_{max} cm^{-1} in $CHCl_3$	:	1710, 1640, 1610, 1330, 1272, 1080
^{1}H NMR (400 MHz, $CDCl_3$) δ	:	8.04-8.07 (m, 4H), 7.54-7.73 (m, 6H), 6.83 (s, 2H), 5.52 (s, 2H), 1.22 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	:	153.4, 141.1, 138.3, 134.6, 129.3, 128.9, 82.4, 72.0, 27.6.
Mass (ESI): *m/z*	:	474 (M^++H).

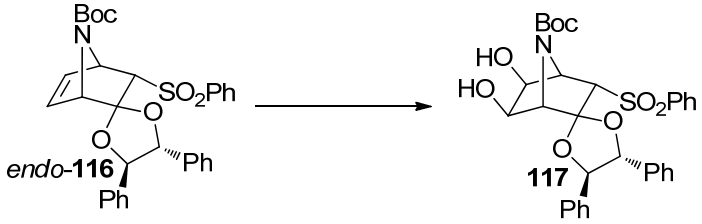
(1*S*,3*S*,4*R*,4'*R*,5'*R*)-*tert*-butyl-4',5'-diphenyl-3-(phenylsulfonyl)-7-azaspiro[bicyclo[2.2.1] hept [5]ene-2,2'-[1,3]dioxolane]-7-carboxylate (*endo*-116):



To an ice-cooled anhydrous THF (3 mL) solution containing suspension of NaH (0.172 g, 4.33 mmol, 60% suspension in mineral oil) was added a solution of (+)-hydrobenzoin (0.451 g, 2.11 mmol) dissolved in anhydrous THF (6 mL) dropwise. After complete addition, the reaction mixture was allowed to stir at room temperature for 0.5 h and then cooled to -100 ^{o}C. A solution of **103** (1g, 2.11 mmol) dissolved in anhydrous THF (8 mL) was added dropwise into the flask while stirring at -100 ^{o}C. The reaction mixture was further allowed to stir at the same temperature for an additional 3.5 h. After complete disappearance of **103**, the reaction was quenched at the same temperature with dropwise addition of methanol (2 mL). Usual work-up followed by silica gel flash column chromatography with ethyl acetate : pet ether (1:5→2:5) gave *endo*-**116** as a white solid (1.02 g, 89%). The diastereomeric purity was confirmed by HPLC analysis. $\boldsymbol{R_f}$ = 0.3 (SiO_2, ethyl acetate : pet ether, 3:7);

m.p.	:	167-168 °C
$[\alpha]^{25}_{D}$	:	+89.20 (*c* 1.0, $CHCl_3$)
IR υ_{max} cm^{-1} in $CHCl_3$	:	1705, 1670, 1300, 1150
^{1}H NMR (400 MHz, $CDCl_3$) δ	:	7.95-7.96 (d, 2H, *J* = 7.63 Hz), 7.67-7.70 (t, 1H, *J* = 7.33 Hz), 7.58-7.61 (t, 2H, *J* = 7.93 Hz), 7.28-7.42 (m, 10H), 6.76 (br s, 1H), 6.64 (br s, 1H), 5.10-5.12 (d, 1H, *J* = 8.85 Hz), 4.80-4.91 (m, 2H), 4.41 (s, 1H), 4.06 (br s), 1.39 (s, 9H).
^{13}C NMR (50 MHz, $CDCl_3$) δ	:	154.0, 140.0, 135.5, 135.1, 133.9, 133.8, 133.5, 129.5, 128.6, 128.4, 128.3, 128.3, 128.0, 127.6, 126.7, 115.8, 87.8, 85.7, 81.3, 71.7, 68.6, 61.0, 28.0.
Mass (ESI): *m/z*	:	546 (M^{+}+H).

(1*S*,3*S*,4*R*,4'*R*,5*S*,5'*R*,6*R*)-*tert*-butyl-5,6-dihydroxy-4',5'-diphenyl-3-(phenylsulfonyl)-7-azaspiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-7-carboxylate (117):



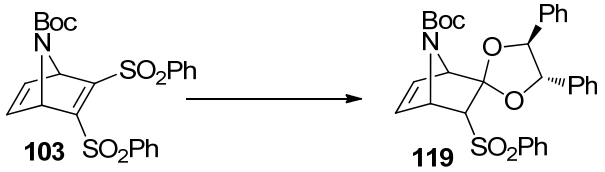
To a solution of *endo*-**116** (1.0 g, 1.83 mmol) in acetone/H_2O (9:1, 10 mL) was added *N*-methyl morpholine-*N*-oxide (50% aq. solution) (0.30 mL, 3.64 mmol) and osmium tetroxide (0.24 mL, 1% solution of OsO_4 in *t*-BuOH). The reaction mixture was stirred for 2 h. Completion of the reaction was monitored by TLC. Reaction was quenched with saturated aqueous solution of $NaHSO_3$. The crude reaction mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were dried over Na_2SO_4, solvent removed under reduced pressure, and the residue was purified by column chromatography (DCM/MeOH, 9:1 to 4:1) to afford pure **117** (0.96 g, 91%) as a white crystalline solid. $\boldsymbol{R_f}$ = 0.5 (SiO_2, methanol : dichloromethane, 1:9)

m.p.	:	199-200 °C
$[\alpha]^{26}_D$	:	+118.12 (*c* 1.0, $CHCl_3$)
IR υ_{max} cm^{-1} in $CHCl_3$	:	3620, 1702, 1302, 1147
^{1}H NMR (400 MHz, DMSO-d^6) δ	:	8.06-8.11 (m, 2H), 7.78-7.89 (m, 3H), 7.13-7.39 (m, 8H), 6.81-6.86 (m, 2H), 5.24-5.25 (d, 1H, J=3.26 Hz), 5.04-5.05 (d, 1H, *J* = 3.26Hz), 4.80-4.87 (m, 2H), 4.36 (b s), 4.15-4.26 (m, 2H), 4.04-4.05 (d, 1H, *J* = 4.5Hz), 3.94-3.97 (d, 0.2H, *J* = 9.03Hz), 3.90-3.92 (d, 0.8H, *J* = 9.03 Hz), 1.32-1.37 (s, 2H), 1.15-1.22 (s, 7H).
^{13}C NMR (50 MHz, $CDCl_3$) δ	:	155.4, 139.7, 135.2, 134.5, 133.9, 130.0, 129.1, 128.8, 128.6, 127.1, 110.9, 86.6, 83.2, 80.0, 70.6, 68.9, 67.7,

66.8, 64.3, 27.8.

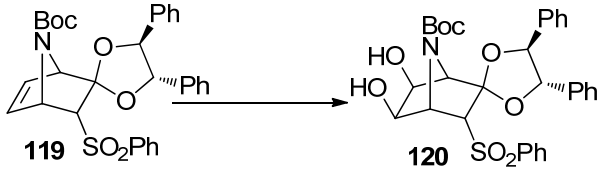
Mass (ESI): *m/z* : 580 (M^++H).

(1*R*,3*R*,4*S*,4'*S*,5'*S*)-*tert*-butyl-4',5'-diphenyl-3-(phenylsulfonyl)-7-azaspiro[bicyclo[2.2.1] hept[5]ene-2,2'-[1,3]dioxolane]-7-carboxylate (119):



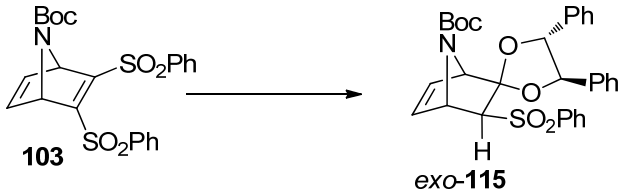
119 was prepared in the identical manner as described for *endo*-**116** using (-)-hydrobenzoin as enantio discriminating reagent. $[\alpha]^{25}_{D}$ = -90.71 (*c* 1.0, $CHCl_3$).

(1*R*,3*R*,4*S*,4'*S*,5*R*,5'*S*,6*S*)-*tert*-butyl-5,6-dihydroxy-4',5'-diphenyl-3-(phenylsulfonyl)-7-azaspiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-7-carboxylate (120):



120 was prepared in the identical manner as described for **117** from **119**. $[\alpha]^{25}_{D}$ = -117.24 (*c* 1.0, $CHCl_3$).

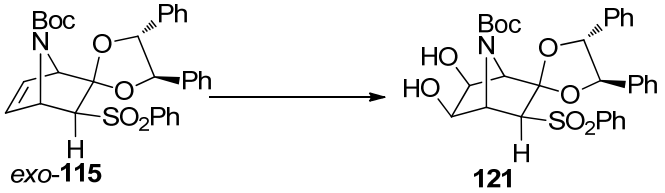
(1*R*,4*S*,4'*R*,5'*R*)-*tert*-butyl-4',5'-diphenyl-3-(phenylsulfonyl)-7-azaspiro[bicyclo[2.2.1]hept[5] ene-2,2'-[1,3]dioxolane]-7-carboxylate (*exo*-115):



To an ice-cooled suspension of NaH (0.184 g, 4.64 mmol, 60% suspension in mineral oil) in anhydrous THF (3 mL) was added a solution of (+)-hydrobenzoin (0.451 g, 2.11 mmol) dissolved in anhydrous THF (6 mL) dropwise. After complete addition, the reaction mixture was allowed to stir at room temperature for 0.5 h. A solution of **103** (1g, 2.11 mmol) dissolved in anhydrous THF (8 mL) was added dropwise into the flask while stirring at room temperature. The reaction mixture was further allowed to stir at the same temperature for additional 2.0 h. Completion of reaction was monitored by silica gel TLC and after complete disappearance of **103**, the reaction was quenched with methanol (2 mL). Usual work-up followed by silica gel flash column chromatography with ethyl acetate: pet-ether (1:5→2:5) gave *exo*-**115** as a white solid (0.97 g, 76%) in 92% diastereoslectivity. The diastereomeric purity was confirmed by HPLC analysis. $\boldsymbol{R_f}$ = 0.4 (SiO_2, ethyl acetate : pet ether, 3:7);

m.p.	:	173-174 °C
$[\alpha]^{25}_D$	:	+165.20 (*c* 1.0, $CHCl_3$)
IR υ_{max} cm^{-1} in $CHCl_3$	:	1700, 1635, 1315, 1159
^{1}H NMR (400 MHz, $CDCl_3$) (rotamers) δ	:	7.96-7.97 (m, 2H), 7.53-7.55 (m, 1H), 7.15-7.39 (m, 12H), 6.76 (br d, 1H), 6.48-6.60 (m, 2H), 5.16-5.36 (m, 2H), 4.48-4.64 (m, 2H), 3.52,3.58 (s, 1H), 1.31,1.37 (s, 9H).
^{13}C NMR (100 MHz, DMSO-d^6) δ	:	153.5, 139.9, 135.2, 135.0, 134.4, 134.3, 133.8, 129.9, 129.0, 128.8, 128.6, 128.5, 128.2, 127.6, 115.5, 86.0, 85.2, 80.5, 79.3, 70.8, 68.3, 60.8, 27.7.
Mass (ESI): *m/z*	:	546 (M^++H).

(1*R*,3*S*,4*S*,4'*R*,5*R*,5'*R*,6*S*)-*tert*-butyl-5,6-dihydroxy-4',5'-diphenyl-3-(phenylsulfonyl)-7-azaspiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-7-carboxylate (121):

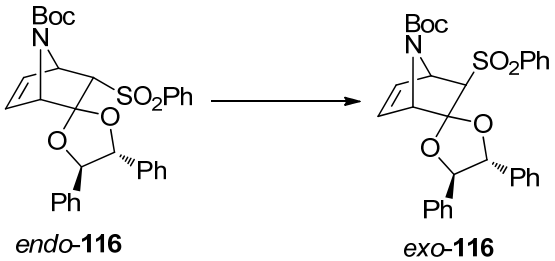


121 was prepared in the identical manner as described for **117** from *endo*-**117**.

White crystalline solid. R_f = 0.5 (SiO_2, methanol : dichloromethane, 1:9)

m.p.	:	187-188°C
$[\alpha]^{27}_D$	:	+149.52 (*c* 1.0, $CHCl_3$)
IR υ_{max} cm^{-1} in $CHCl_3$	:	3645, 1687, 1310, 1156
^{1}H NMR (500 MHz, DMSO-d^6) (rotamers)[1]	:	7.94-7.96 (d, 2H, *J* = 7.82 Hz), 7.73-7.76 (t, 1H, *J* = 7.58 Hz), 7.59-7.64 (m, 2H), 7.29-7.46 (m, 10H), 4.96-5.08 (m, 2H), 4.78-4.80 (d, 0.75H, *J* = 9.05 Hz), 4.73-4.75 (d, 0.37H, *J* = 9.05 Hz), 4.19-4.26 (m, 2H), 4.12-4.15 (m, 1H), 4.07 (br s, 1H), 4.02 (br s, 1H), 3.91-3.93 (t, 1H, *J* = 5.38 Hz), 1.40 (s, 6H), 1.29 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	:	28.2, 63.5, 64.4, 67.6, 68.3, 70.6, 71.7, 78.9, 85.1, 112.2, 127.3, 127.4, 127.8, 128.0, 128.5, 128.8, 129.0, 129.1, 129.4, 129.7, 134.1, 134.9, 139.5, 153.0.
Mass (ESI): *m/z*	:	580 (M^++H).

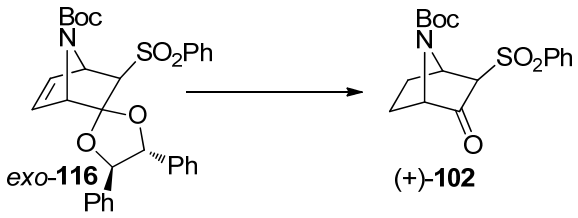
(1*S*,3*R*,4*R*,4'*R*,5'*R*)-*tert*-butyl-4',5'-diphenyl-3-(phenylsulfonyl)-7-azaspiro [bicyclo[2.2.1]hept[5]ene-2,2'-[1,3]dioxolane]-7-carboxylate (*exo*-116):



To a solution of K^{t}OBu (0.103 g, 0.917 mmol) in anhydrous THF (3 mL) was added *endo*-**116** (0.50 g, 0.917 mmol) dissolved in THF (10 mL) at 0 ^oC. The reaction mixture was stirred at the same temperature for 3 min and quenched by addition of methanol. Usual work-up followed by flash column chromatography on silica gel provided *exo*-**116** which on crystallization with ethyl acetate: pet ether gave analytically pure *exo*-**116** (0.405 g, 81%) as white crystals. $\boldsymbol{R_f}$ = 0.3 (SiO_2, ethyl acetate : pet ether, 3:7).

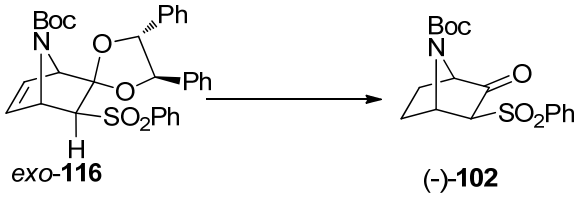
m.p.	:	170-171 °C
$[\alpha]^{26}_D$	:	+71.22 (*c* 1.0, $CHCl_3$)
IR υ_{max} cm^{-1} in $CHCl_3$	:	1700, 1677, 1303, 1149
^{1}H NMR (400 MHz, DMSO-d^6) δ	:	7.89-7.91 (d, 2H, *J* = 7.58 Hz), 7.65-7.68 (t, 1H, *J* = 7.34 Hz, 7.58 Hz), 7.33-7.55 (m, 10H), 7.24-7.25 (m, 2H), 6.65-6.77 (m, 2H), 5.06-5.08 (d, 1H, *J* = 9.05 Hz), 4.83-4.87 (m, 2H), 4.71 (s, 1H), 3.75 (s, 1H), 1.33 (s, 9H).
^{13}C NMR (50 MHz, DMSO-d^6) δ	:	154.6, 153.7, 139.1, 138.8, 137.4, 136.1, 135.1, 134.0, 133.9, 129.5, 129.2, 128.9, 128.6, 128.3, 127.3, 113.1, 112.2, 85.4, 85.0, 80.2, 72.7, 71.2, 67.0, 66.1, 63.1, 62.6, 27.9.
Mass (ESI): *m/z*	:	546 (M $^+$+H).

(1*S*,4*R*)-*tert*-butyl 2-oxo-3-(phenylsulfonyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate ((+)-102):



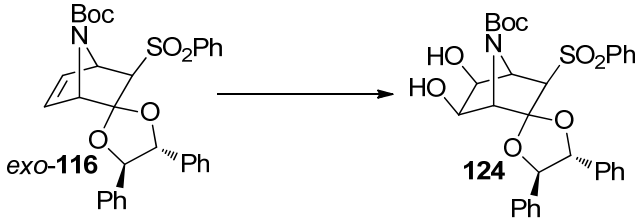
To a solution of *exo*-**116** (0.2 g, 0.345 mmol) in AcOH (1.5 mL) was added Pd/C (0.038 g, 10 mol% Pd on activated charcoal) and hydrogenated over Parr shaker at 60 Psi for 22 h. The reaction mixture was filtered using Whatmann filter paper and washed with excess of aqueous solution of $NaHCO_3$ in order to remove the acetic acid. The reaction mixture was extracted several times with the ethyl acetate and the combined organic layer was dried over Na_2SO_4. The products were isolated by column chromatography to give (+)-**102** as a white solid (0.092g, 72%). $[\alpha]^{27}_{D}$ = +57.1 (*c* 1.0, $CHCl_3$).

(1*R*,3*S*,4*S*)-*tert*-butyl 2-oxo-3-(phenylsulfonyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate ((-)-102):



(-)-**122** was prepared in the identical manner as described for (+)-**122** from **115**. Yield: 67%. $[\alpha]^{27}_{D}$ -54.5 (*c* 1.0 $CHCl_3$).

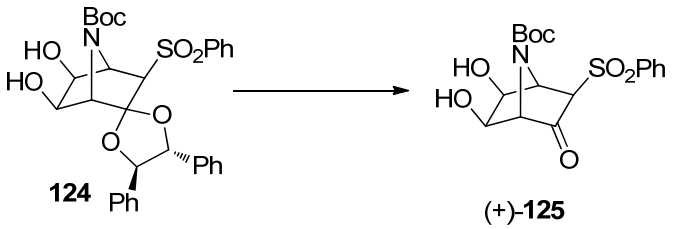
(1*S*,3*R*,4*R*,4'*R*,5*S*,5'*R*,6*R*)-*tert*-butyl-5,6-dihydroxy-4',5'-diphenyl-3-(phenylsulfonyl)-7-azaspiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-7-carboxylate (124):



126 was prepared in the identical manner as described for **117** except from *exo*-**116**. White crystalline solid. R_f = 0.5 (SiO_2, methanol-dichloromethane, 1:9)

m.p.	:	203-204 °C
$[\alpha]^{25}_D$	:	+97.44 (*c* 1.0, $CHCl_3$)
IR υ_{max} cm^{-1} in $CHCl_3$	:	3625, 1706, 1305, 1159
^1H NMR (400 MHz, DMSO-d^6) δ (rotamers)	:	8.00-8.02 (d, 2H, *J* = 7.79 Hz), 7.84-7.88 (t, 1H, *J* = 7.28 Hz), 7.73-7.77 (t, 2H, *J* = 7.53 Hz), 7.23-7.36 (m, 10H), 5.22-5.24 (d, 1H, *J* = 6.27 Hz), 5.11-5.13 (d, 0.9H, *J* = 9.04 Hz), 4.99-5.01 (d, 0.1H, *J* = 9.04 Hz), 4.89-4.91 (d, 1H, *J* = 6.53 Hz), 4.71-4.79 (m, 2H), 4.26-4.32 (m, 2H), 3.91-3.92 (d, 1H, *J* = 5.02 Hz), 3.62-3.64 (br d, 1H, *J* = 4.77 Hz), 1.26 (s, 9H).
^{13}C NMR (50 MHz, $CDCl_3$) δ	:	155.0, 139.8, 134.7, 134.2, 130.2, 129.1, 128.6, 127.6, 126.9, 112.0, 86.4, 84.5, 80.1, 71.7, 70.2, 68.2, 66.2, 64.4, 27.8.
Mass (ESI): *m/z*	:	580 (M^++H).

(1*R*,2*S*,3*R*,4*S*,6*R*)-*tert*-butyl-2,3-dihydroxy-5-oxo-6-(phenylsulfonyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate ((+)-125):



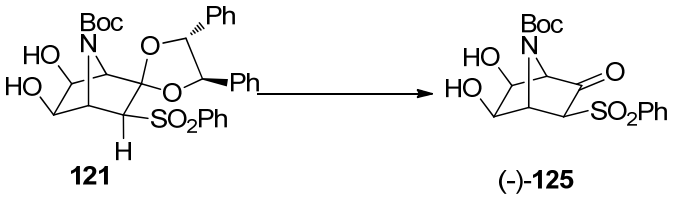
(+)-**125** was prepared in the identical manner as described for **102** except using **124**.

White solid (0.989 g, 75%). $\boldsymbol{R_f}$ = 0.5 (SiO_2, methanol : dichloromethane, 1:9);

m.p.	:	152-154 °C
$[\alpha]^{25}_D$	:	+ 38.7 (*c* 1.0, $CHCl_3$)
IR υ_{max} cm^{-1} in $CHCl_3$	:	3640, 1766, 1715, 1252, 1152

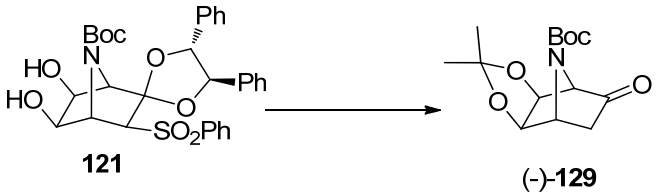
^{1}H NMR (400 MHz, $CDCl_3$) δ	:	7.88-7.95 (t, 2H, J = 6.44 Hz), 7.51-7.67 (m, 3H), 4.68 (br s, 1H), 4.15-4.35 (m, 2H), 3.91-3.99 (dd, 1H, $J_{1,2}$= 2.78 Hz, $J_{1,3}$ = 13.64 Hz), 3.69 (s, 2H), 3.11-3.33 (m, 1H), 1.34 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	:	201.0, 157.1, 136.9, 131.8, 131.4, 84.4, 73.7, 73.2, 64.1, 60.3, 54.8, 31.9, 28.2.
Mass (ESI): *m/z*	:	384 (M^++H).

(1*S*,2*R*,3*S*,4*R*,6*S*)-*tert*-butyl-2,3-dihydroxy-5-oxo-6-(phenylsulfonyl)-7-azabicyclo[2.2.1] heptane-7-carboxylate ((-)-125):



(-)-**125** was prepared in the same manner as described for **102** except starting with **121**. Yield: 73%. **[α]$^{26}_D$** -41.4 (*c* 1.0, $CHCl_3$).

(3a*S*,4*R*,7*R*,7a*R*)-*tert*-butyl-2,2-dimethyl-5-oxohexahydro-4,7-epiminobenzo [*d*][1,3]dioxole-8-carboxylate ((-)-127):

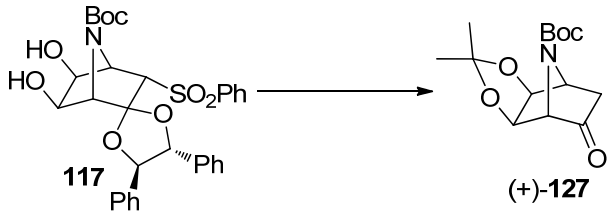


To a solution of **121** (0.73 g, 1.26 mmol) in dry acetone (6 mL) was added 2,2-dimethoxy propane (0.8 mL), *p*-TSA (18 mg) and stirred for 2 h. Reaction was monitored by TLC. After the complete disappearance of **121**, reaction was quenched using aqueous solution of $NaHCO_3$ and was extracted with ethyl acetate. Organic layer was concentrated under reduced pressure.

To a stirring solution of NaH_2PO_4 (0.75 g, 6.18 mmol) in anhydrous methanol (2 mL), above obtained crude product (0.77 g, 1.24 mmol) dissolved in methanol (7 mL) was added. The reaction mixture was cooled to -10 ^oC and sodium amalgam (2.1 g, 7%) was added portion wise (30 min) while stirring at the same temperature. The reaction mixture was allowed to stir for an additional 3 h at -10 ^oC. The progress of reaction was monitored by TLC and after the completion of the reaction; water (1 mL) was added drop wise. The solution was warmed to room temperature and was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over Na_2SO_4. Solvent was evaporated under reduced pressure and purified by column chromatography to obtain **128** as a white solid.

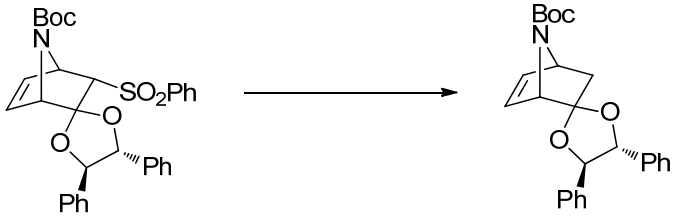
To the solution of above purified product (0.42 g, 0.88 mmol) in MeOH (4 mL) was added Pd/C (0.10 g, 10 mol% Pd on activated charcoal) and hydrogenated in the presence of $NaHCO_3$ at 1 atm for 3 h. The reaction mixture was filtered by a Whatmann filter paper. Solvent was evaporated and product was isolated by column chromatography [ethyl acetate: pet ether (1:5→2:5)] to give (-)-**127** (0.22 g, 64 % overall). $[\alpha]^{27}_D$ -50.8 (*c* 0.65, $CHCl_3$).

(3a*R*,4*S*,7*S*,7a*S*)-*tert*-butyl-2,2-dimethyl-5-oxohexahydro-4,7-epiminobenzo [*d*][1,3]dioxole-8-carboxylate ((+)-127):



(+)-**127** was prepared (0.23 g, 67% overall yield) in the same manner as described for (-)-**127** except that **117** was used. $[\alpha]^{27}_D$ +48.1 (*c* 0.65, $CHCl_3$).

(1*S*,4*S*,4'*R*,5'*R*)-*tert*-butyl 4',5'-diphenyl-7-azaspiro[bicyclo[2.2.1]hept[5]ene-2,2'-[1,3]dioxolane]-7-carboxylate (122):

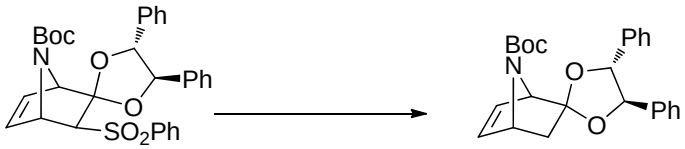


exo-**116** **122**

To a stirring solution of NaH_2PO_4 (0.6589 g, 5.44 mmol) in anhydrous methanol (10 mL), *exo*-**116** (0.550 g, 1.08 mmol) dissolved in methanol (5 mL) was added. The reaction mixture was cooled to 0 ^oC and sodium amalgam (2.0 g, 6%) was added portionwise (30 min.) while stirring at the same temperature. The reaction mixture was allowed to stir for an additional 3 h at 0 ^oC. The progress of reaction was monitored by TLC and after the completion of the reaction water (1 mL) was added dropwise. The solution was warmed to room temperature and was extracted with ethyl acetate several times. The combined organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvent and silica gel column chromatography purification of the obtained residue using ethyl acetate : pet.ether as eluent afforded **122** (0.347 g, 85%) as a white solid.

m.p.	:	93-94 ^oC
$[\alpha]^{25}_D$	:	+67.5 (*c* 1.0, $CHCl_3$)
^{1}H NMR (400 MHz, $CDCl_3$) δ		7.18-7.35 (m, 10H), 6.45-6.61 (m, 2H), 4.85-4.96 (m, 1H), 4.61-4.70 (m, 2H), 4.39-4.41 (m, 1H), 2.24-2.33 (m, 1H), 1.69-1.72 (d, *J* = 12.05, 1H), 1.35, 1.28 (s, 9H).
^{13}C NMR (50 MHz, $CDCl_3$) δ	:	154.7, 139.6, 136.6, 135.7, 133.4, 128.9, 128.7, 127.2, 115.8, 114.8, 85.3, 84.4, 79.5, 85.8, 56.3, 28.1, 18.8.
Mass (ESI): *m/z*	:	428 (M^++Na).
	:	

(1*R*,4*R*,4'*R*,5'*R*)-*tert*-butyl 4',5'-diphenyl-7-azaspiro[bicyclo[2.2.1]hept[5]ene-2,2'-[1,3]dioxolane]-7-carboxylate (123):

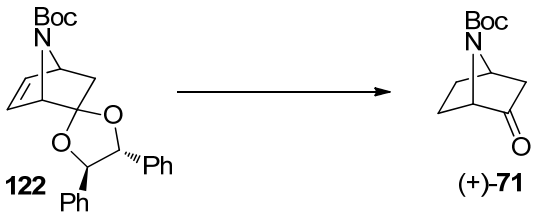


exo-**115** **123**

123 was prepared (0.23 g, 67% overall yield) in the same manner as described for **122** except that *exo*-**115** was used.

m.p.	:	101-102 ^{o}C
$[\alpha]^{25}_{D}$	:	+73.2 (*c* 1.0, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$) δ		7.18-7.37 (m, 10H), 6.42-6.59 (m, 2H), 4.92-4.93 (m, 1H), 4.81-4.83 (m, 1H), 4.64-4.70 (m, 2H), 2.22-2.29 (m, 1H), 1.69-1.72 (d, *J* = 12.05, 1H), 1.33, 1.37 (s, 9H).
^{13}C NMR (50 MHz, $CDCl_3$) δ	:	154.3, 139.5, 139.1, 137.0, 136.2, 133.2, 128.8, 127.2, 115.7, 85.1, 84.8, 66.4, 56.3, 28.1, 18.8.
Mass (ESI): *m/z*	:	428 (M^{+}+Na).
	:	

Preparation of (1*S*,4*R*)-tert-butyl 2-oxo-7-azabicyclo[2.2.1]heptane-7-carboxylate (25)

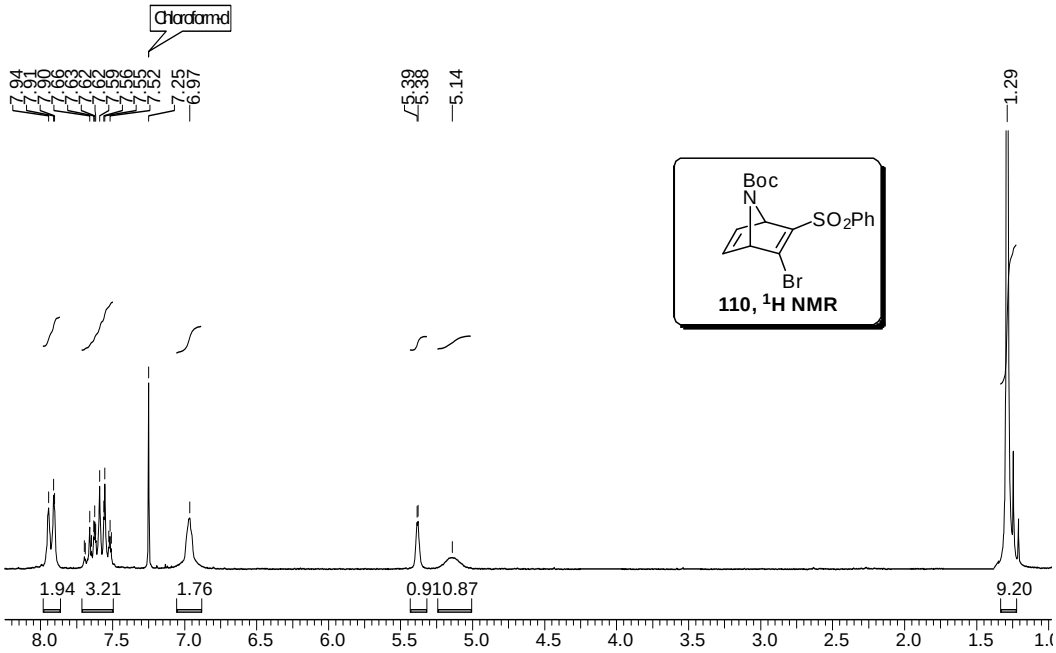


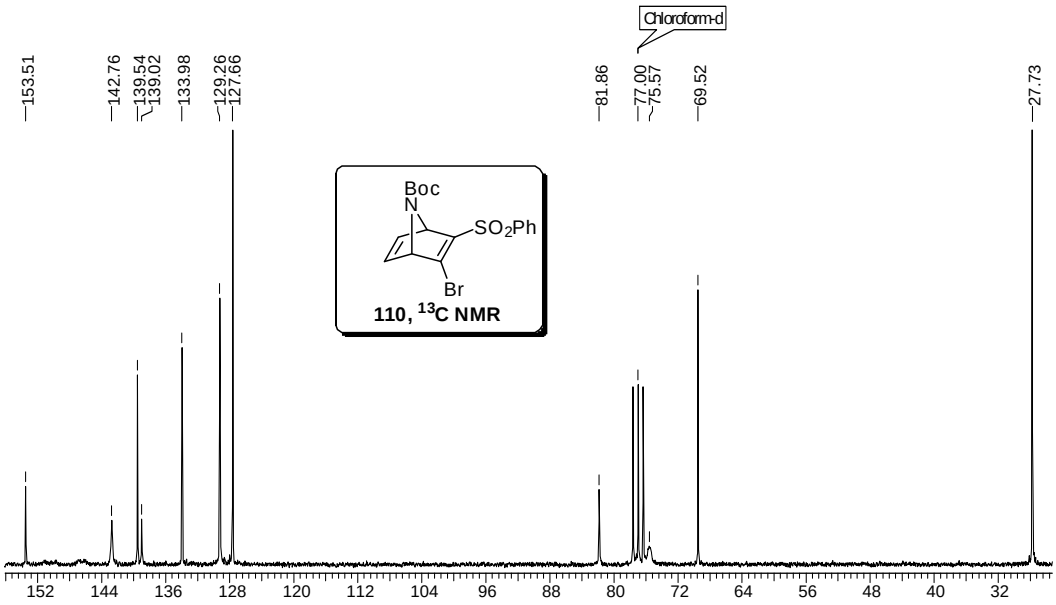
A solution of **122** (0.050 g, 0.122 mmol) in methanol (3 mL) with Pd/C (0.006 g, 10% Pd on activated charcoal) was hydrogenated at 1 atm pressure of hydrogen for 20 h. After the completion of the reaction, the reaction mixture was filtered off and

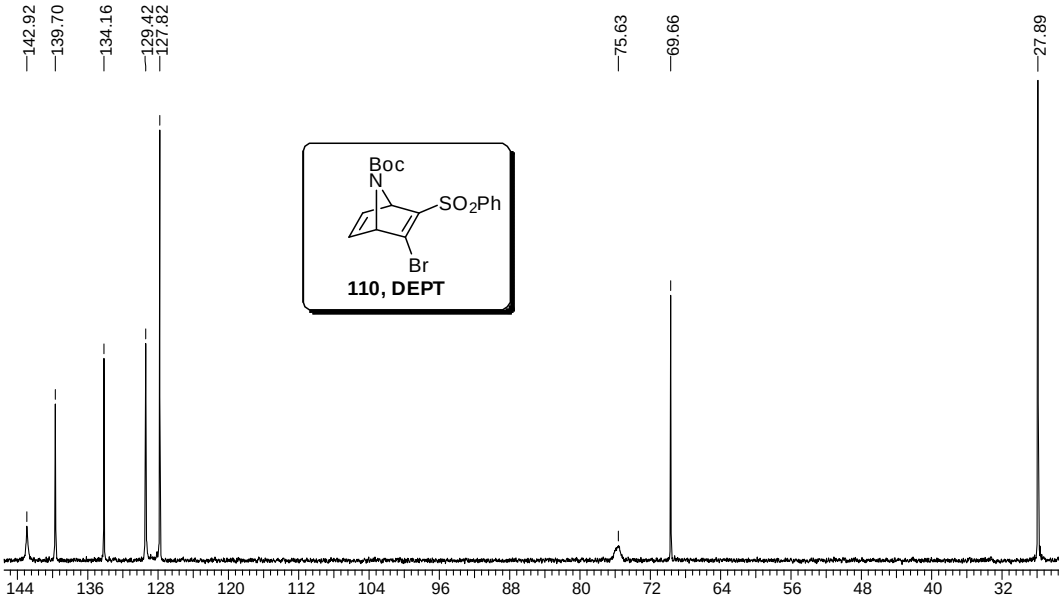
solvent was removed under reduced pressure. The residue was column chromatographed over silica gel eluting with ethyl acetate : pet. ether to afford (+)-**71**(0.023 g, 90%) as a colourless liquid.

$[\alpha]^{29}_{D}$	:	+77.3 (*c* 1.0, $CHCl_3$)
IR υ_{max} cm^{-1} in $CHCl_3$	:	1764, 1699
^{1}H NMR (400 MHz, $CDCl_3$) δ	:	4.55 (t, *J* = 4.64 Hz, 1H), 4.23 (d, J = 4.68 Hz, 1H), 2.46 (dd, *J* = 17.56, 5.50 Hz, 1H), 2.05-1.94 (m, 3H), 1.63-1.57 (m, 2H), 1.44 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	:	209.5, 155.0, 80.7, 63.8, 56.0, 45.1, 28.1, 27.5, 24.3.
Mass (ESI): *m/z*	:	212 (M^++H), 234 (M^++Na).

2A.9. Spectral Data:



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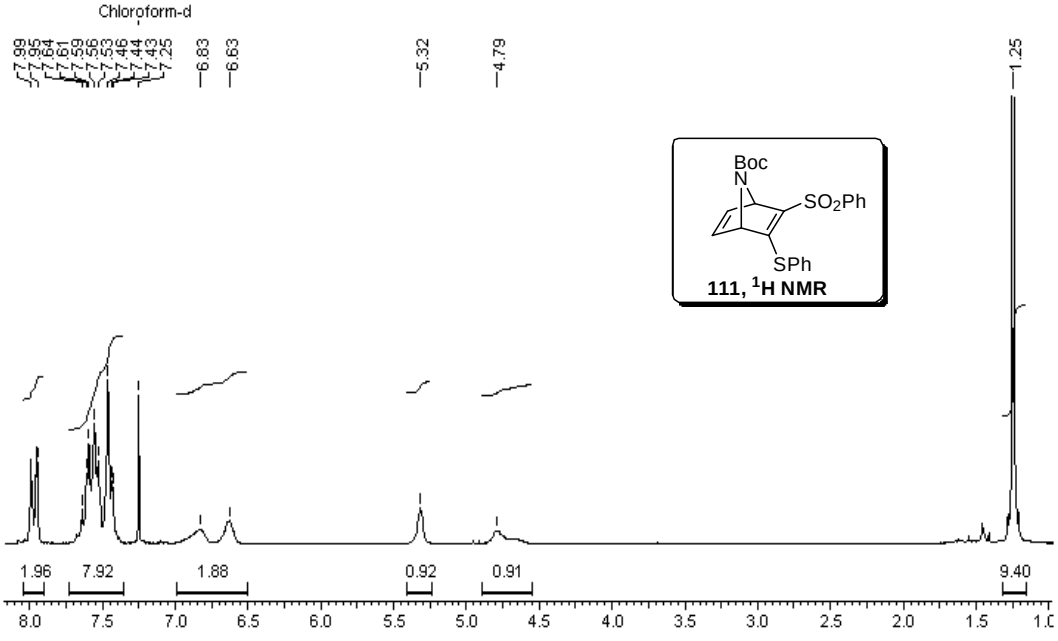
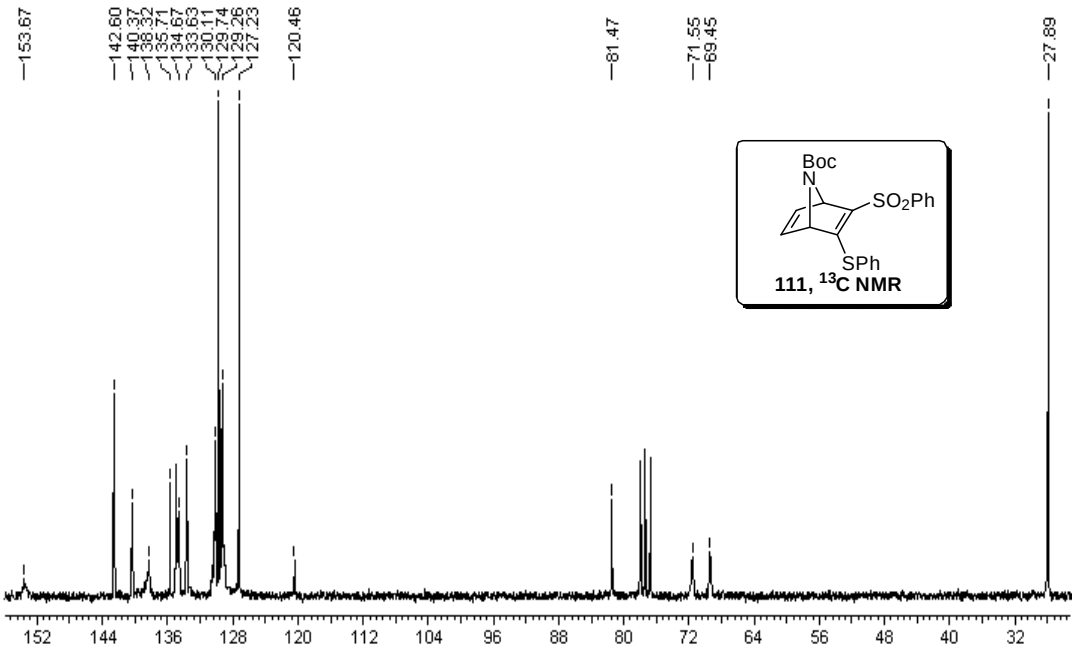
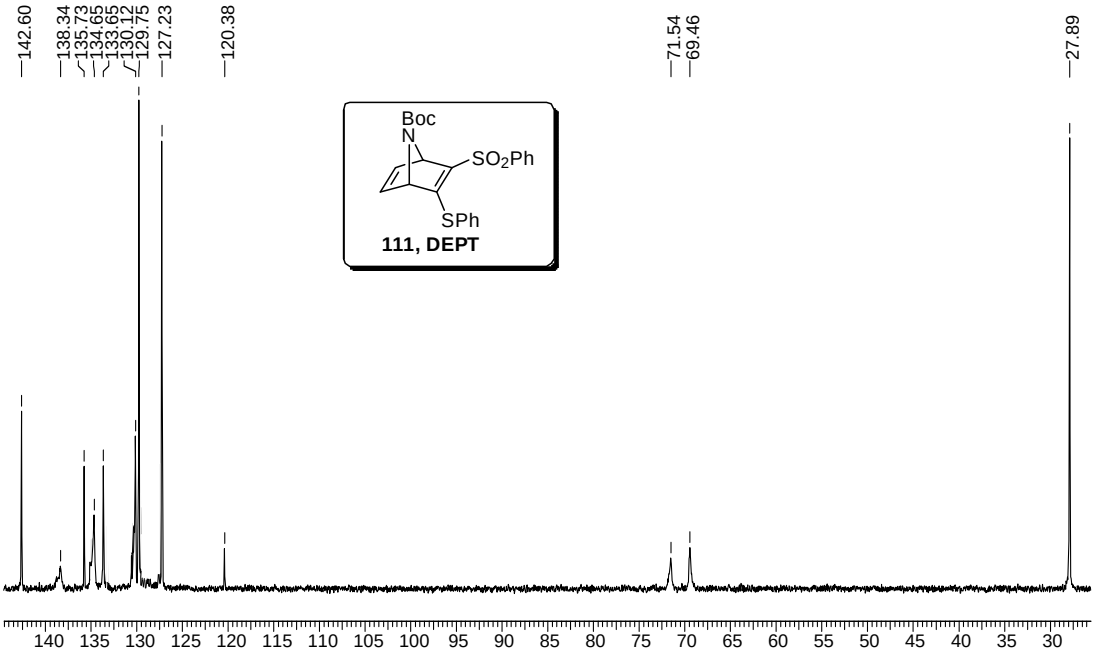
139.70
134.16
129.42
127.82
75.63
69.66
27.89
Boc
N
SO2Ph
Br
110, DEPT


Chloroform-d
7.99
7.95
7.64
7.61
7.59
7.56
7.53
7.46
7.44
7.43
7.25
6.83
6.63
5.32
4.79
1.25
Boc
N
SO2Ph
SPh
111, 1H NMR
1.96
7.92
1.88
0.92
0.91
9.40


153.67
142.60
140.37
138.32
135.71
134.67
133.63
130.11
129.74
129.26
127.23
120.46
81.47
71.55
69.45
27.89
Boc
N
SO2Ph
SPh
111, 13C NMR
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32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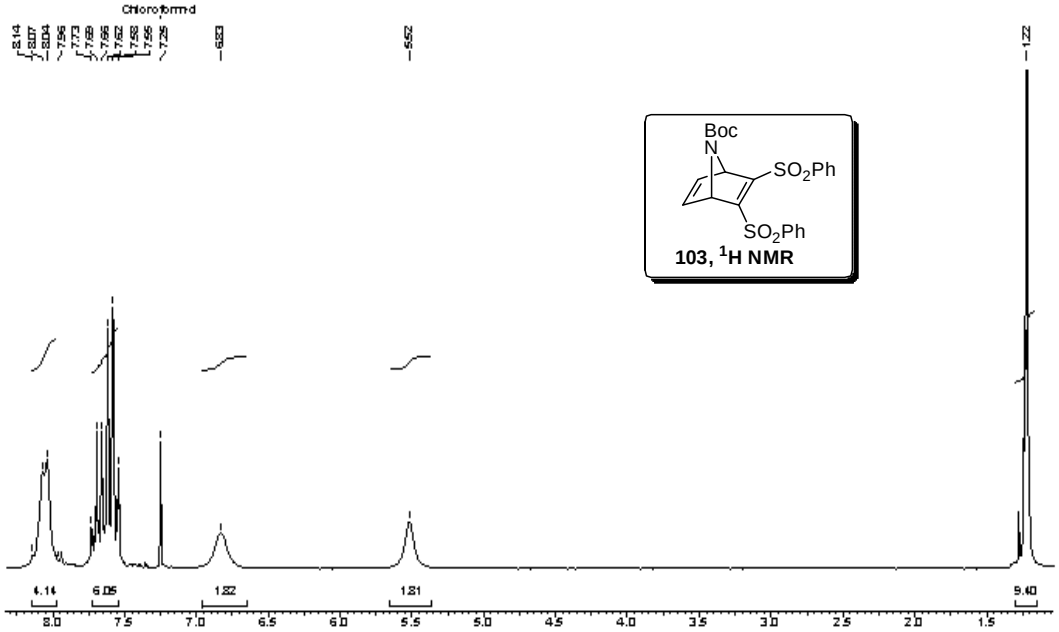
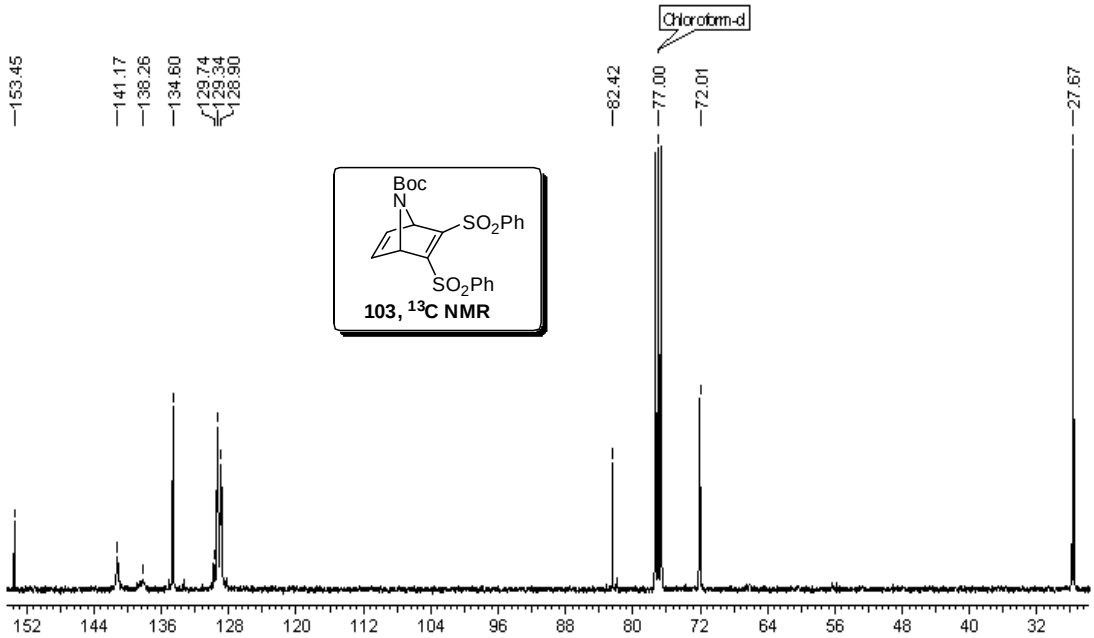
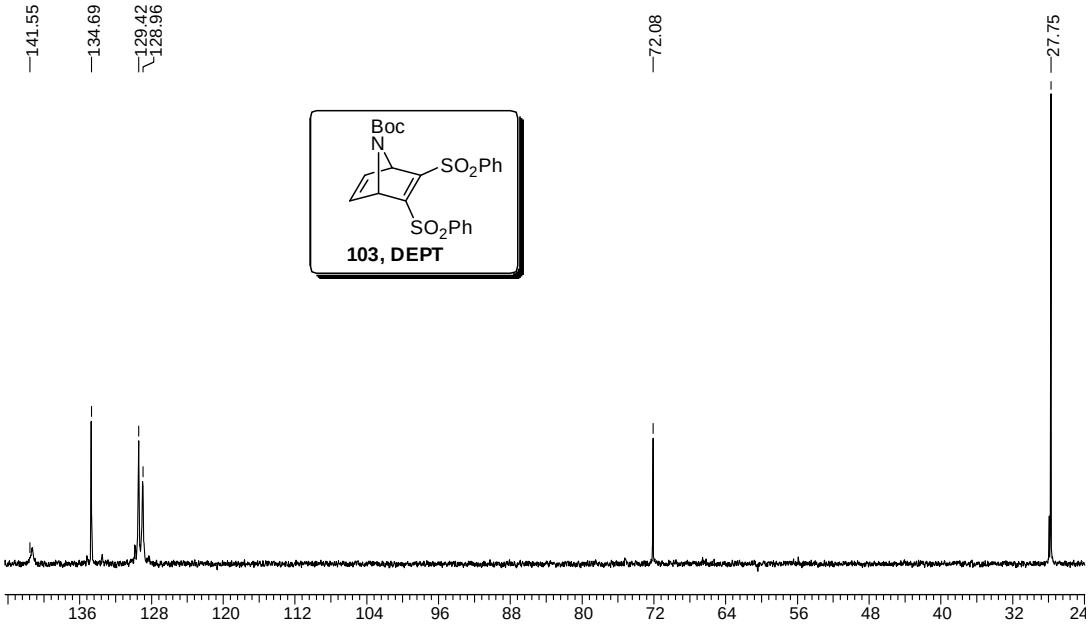
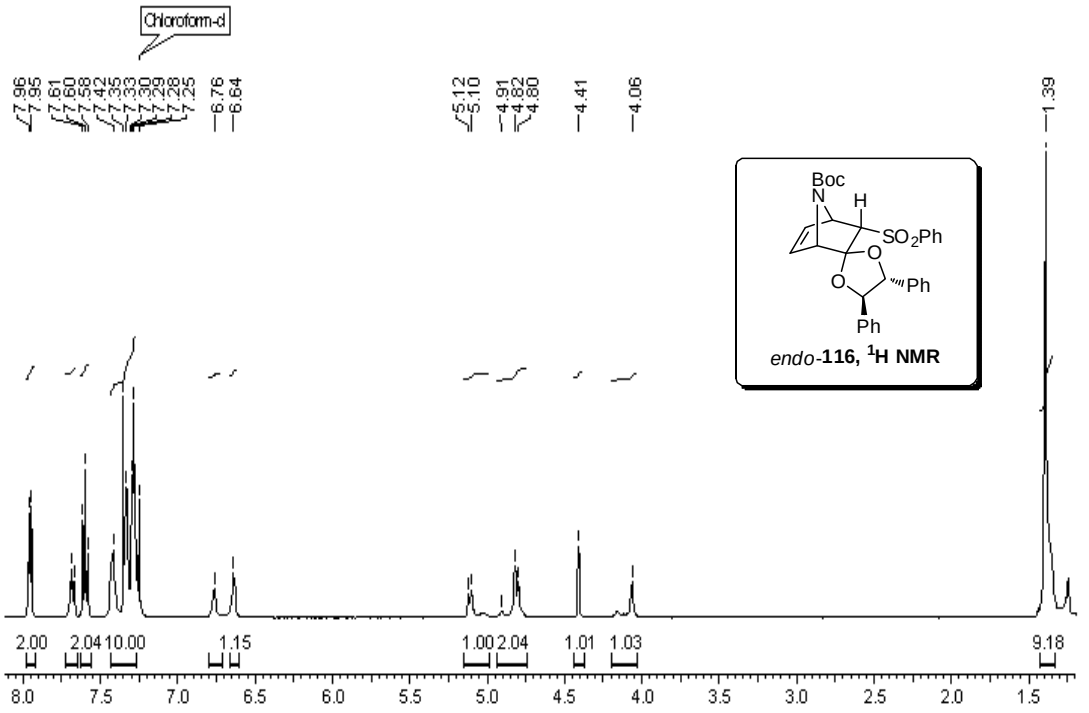
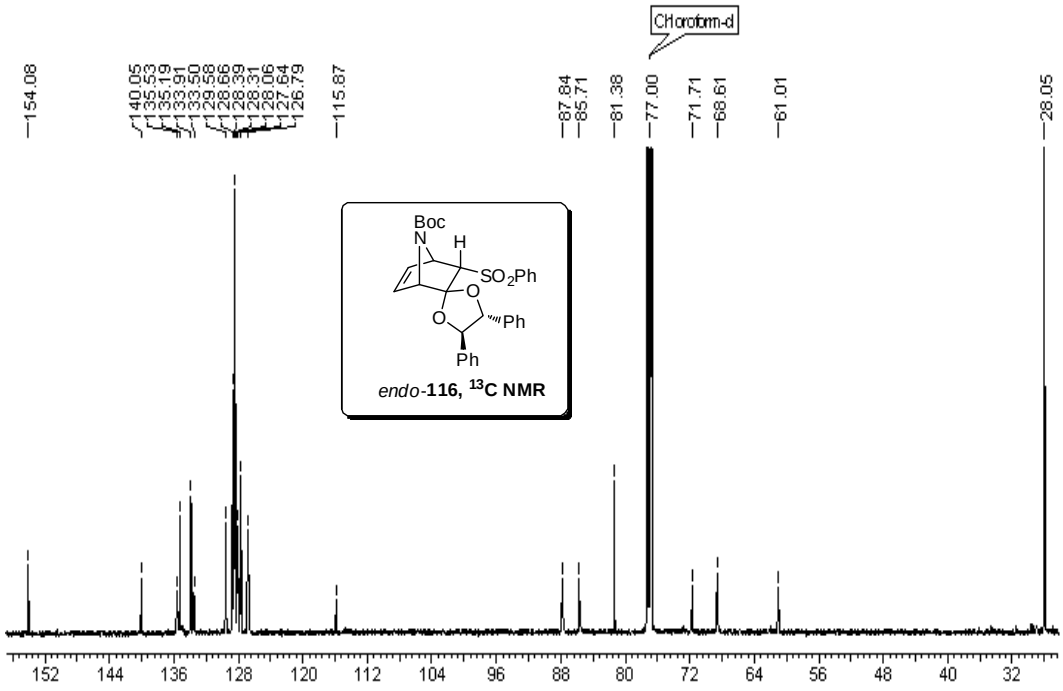
138.34
135.73
134.65
133.65
130.12
129.75
127.23
120.38
71.54
69.46
27.89
Boc
N
SO2Ph
SPh
111, DEPT
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30


Chloroform-d
8.14
8.07
8.04
7.96
7.73
7.69
7.66
7.62
7.58
7.56
7.25
6.83
5.52
1.22
Boc
N
SO2Ph
SO2Ph
103, 1H NMR
4.14
6.05
1.82
1.81
9.40
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

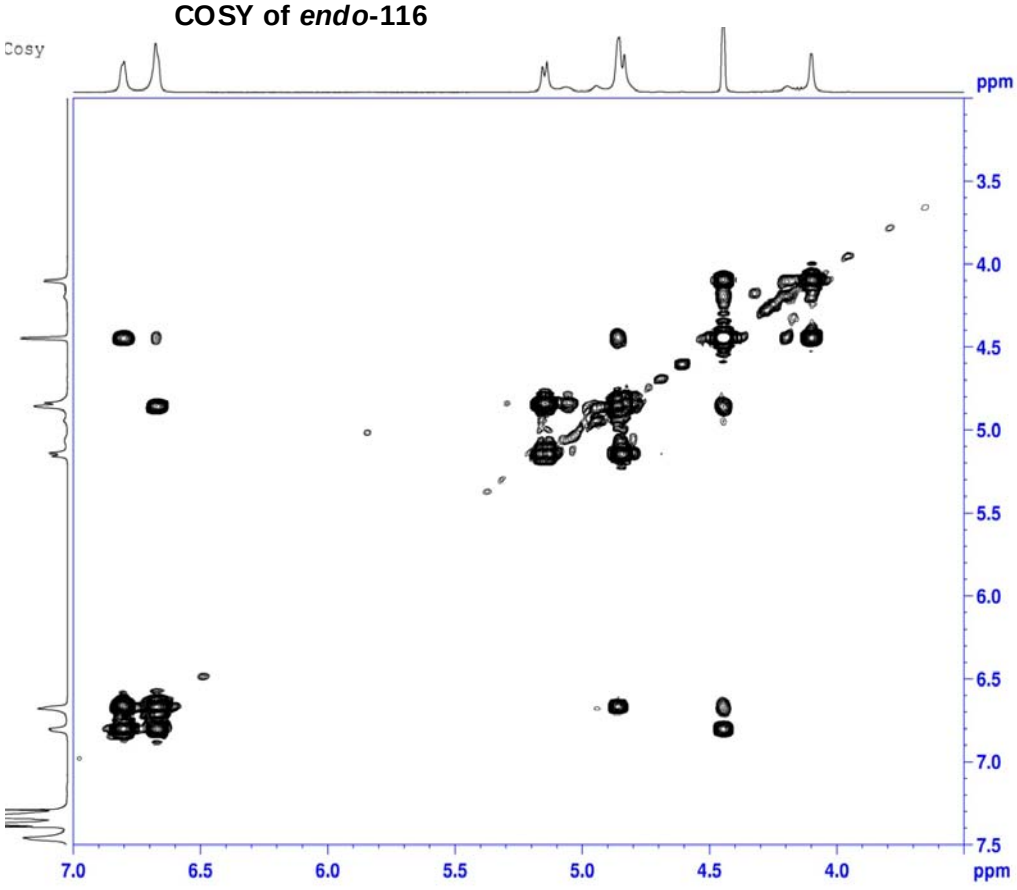

153.45
141.17
136.26
134.60
129.74
129.34
128.90
82.42
77.00
72.01
27.67
Chloroform-d
Boc
N
SO2Ph
SO2Ph
103, 13C NMR
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32


141.55
134.69
129.42
128.96
72.08
27.75
Boc
N
SO2Ph
SO2Ph
103, DEPT
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24

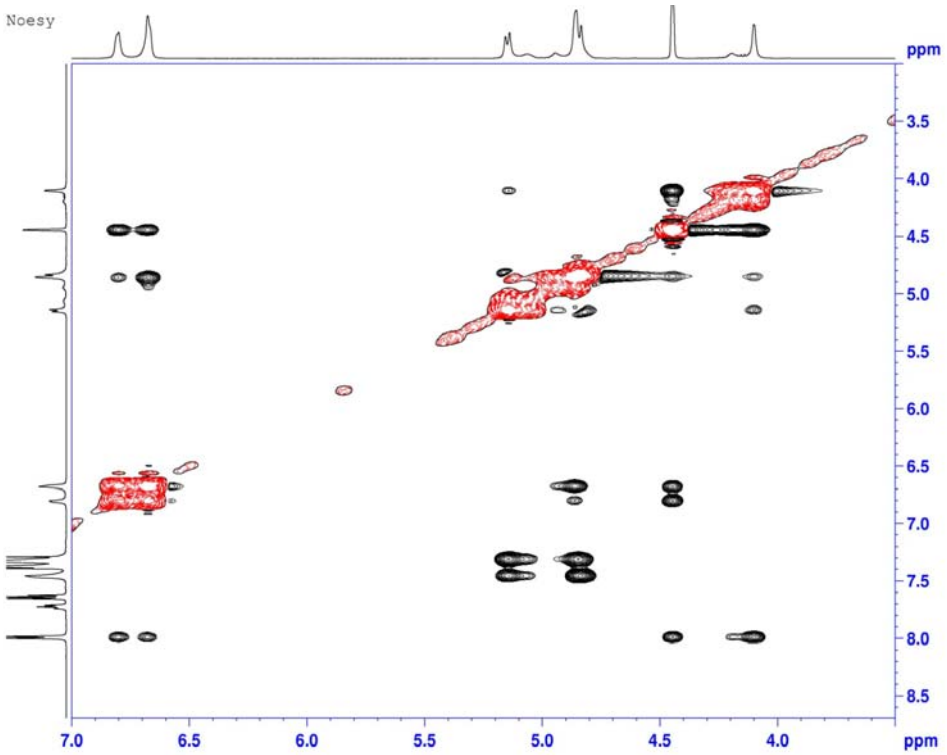

Chloroform-d
7.96
7.95
7.61
7.60
7.58
7.42
7.35
7.33
7.30
7.29
7.28
7.25
6.76
6.64
5.12
5.10
4.91
4.82
4.80
4.41
4.06
1.39
Boc
N
H
SO2Ph
O
O
Ph
Ph
endo-116, 1H NMR
2.00
2.04
10.00
1.15
1.00
2.04
1.01
1.03
9.18
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5



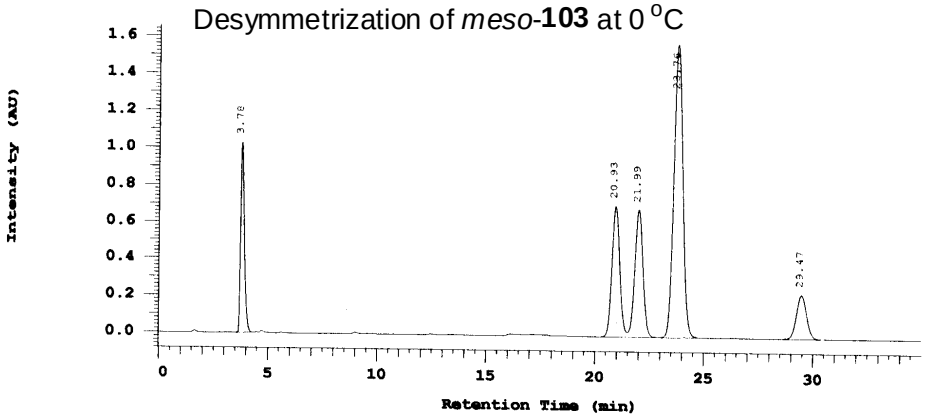
COSY of *endo*-116



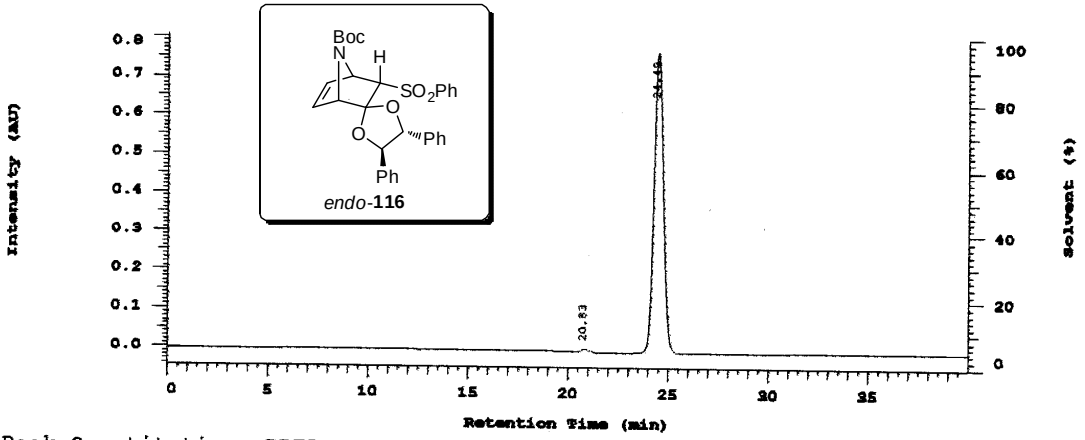
NOESY of *endo*-116



Desymmetrization of *meso*-**103** at 0 °C



No.	RT	Area	Conc 1	BC
1	3.78	5917935	11.928	BB
2	20.93	8676488	17.488	BV
3	21.99	8902512	17.944	VB
4	23.76	22349305	45.047	BB
5	29.47	3767002	7.593	BB
		49613242	100.000	



Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Height	Area	Area %
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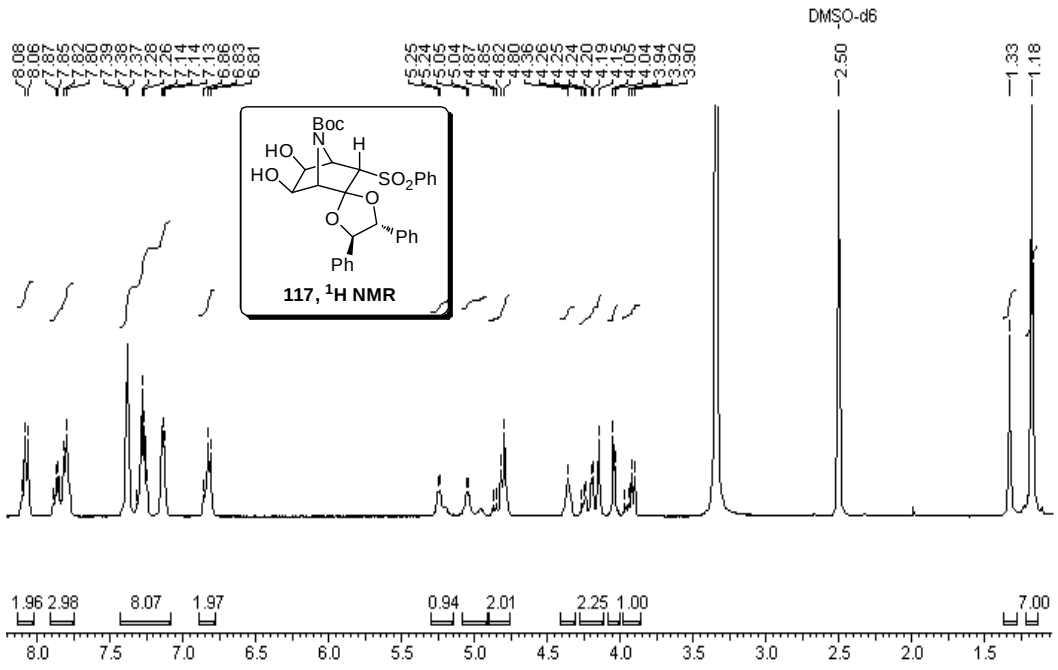
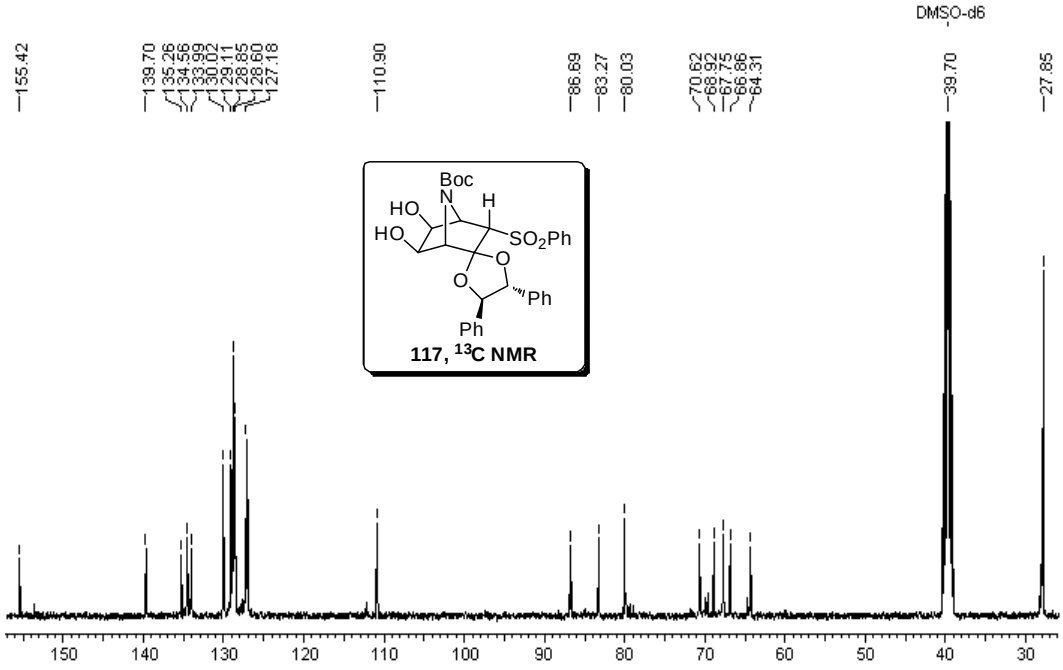
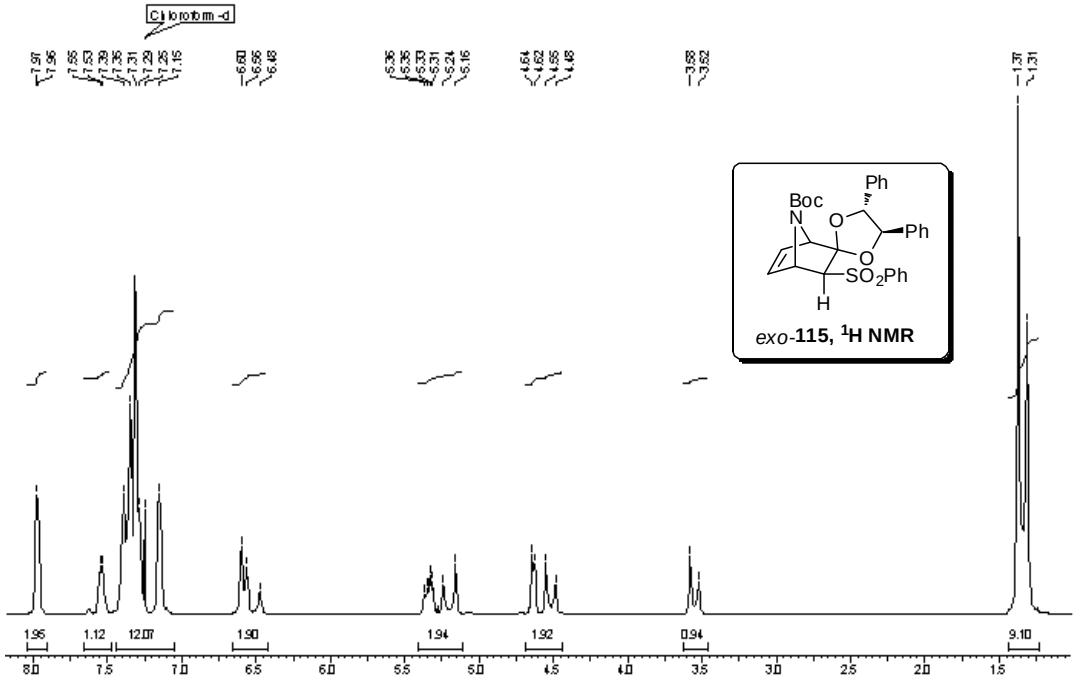
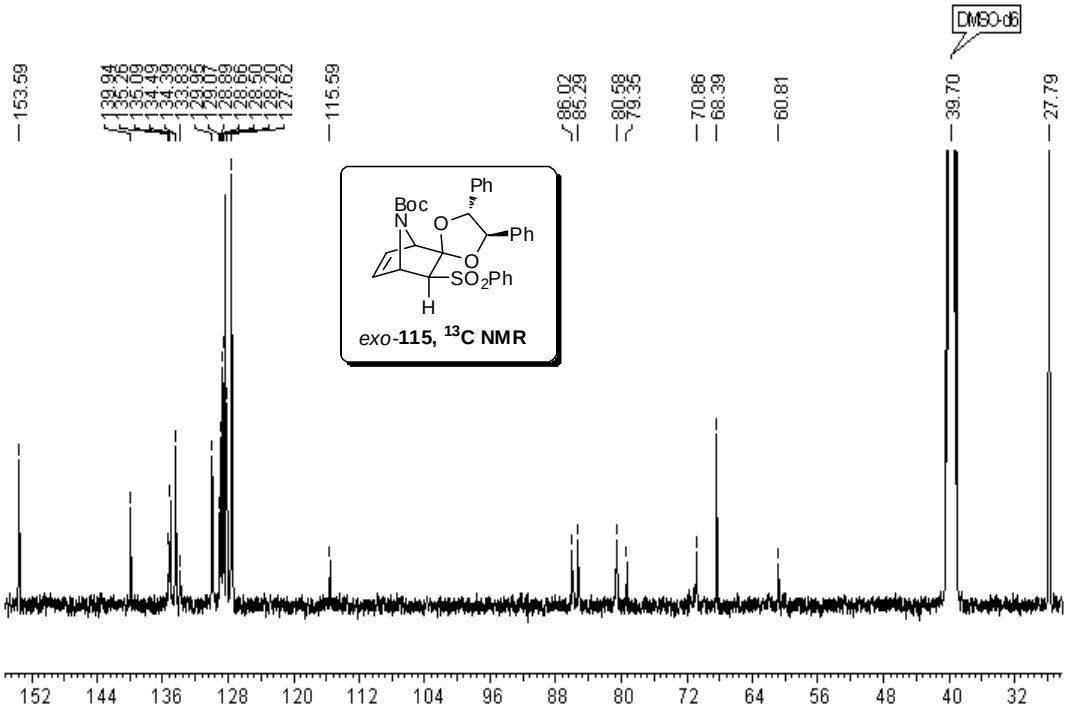
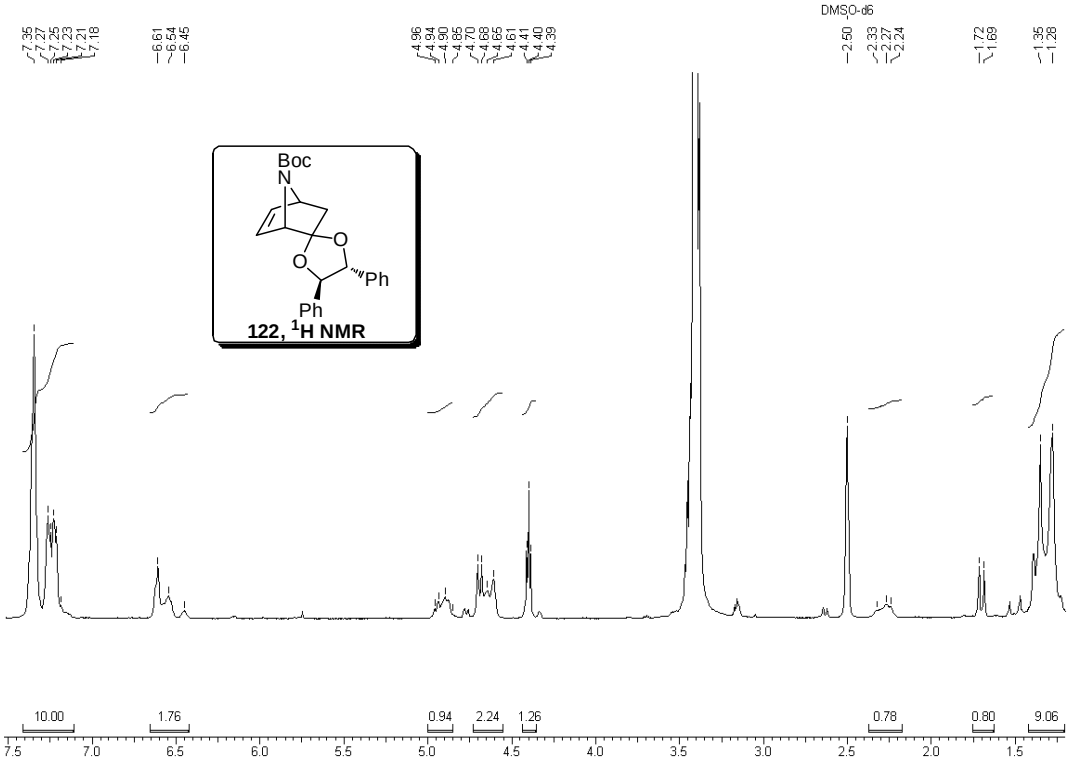
2	24.49	384181	12148901	99.730
		386225	12181825	100.000

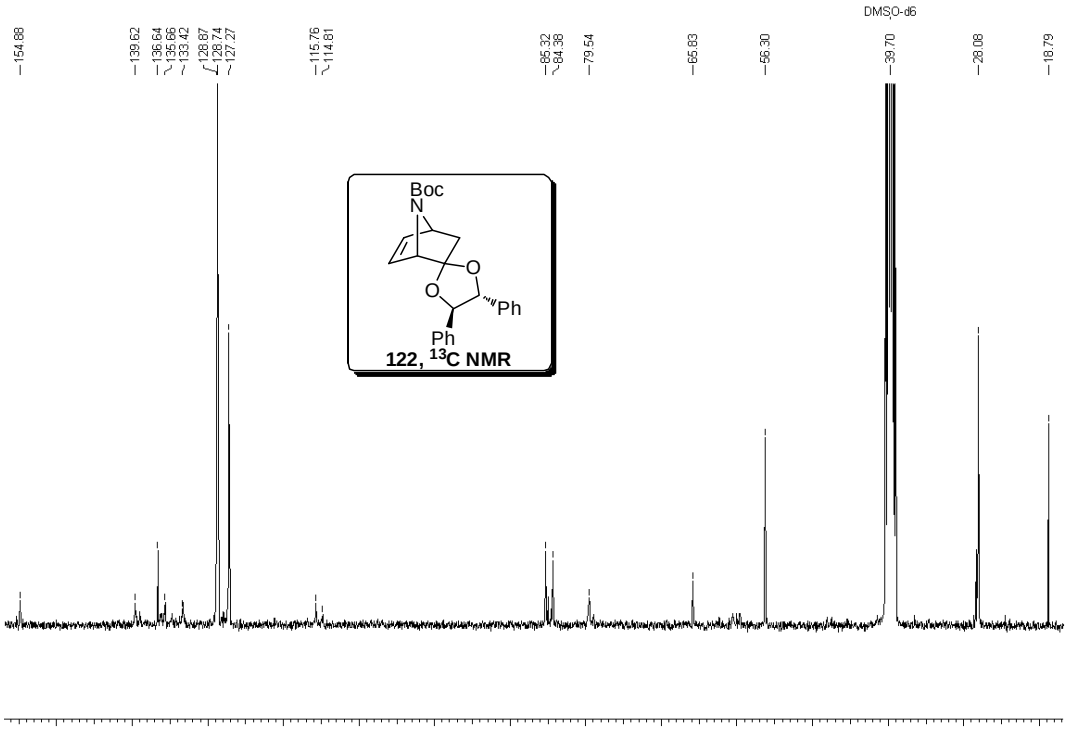


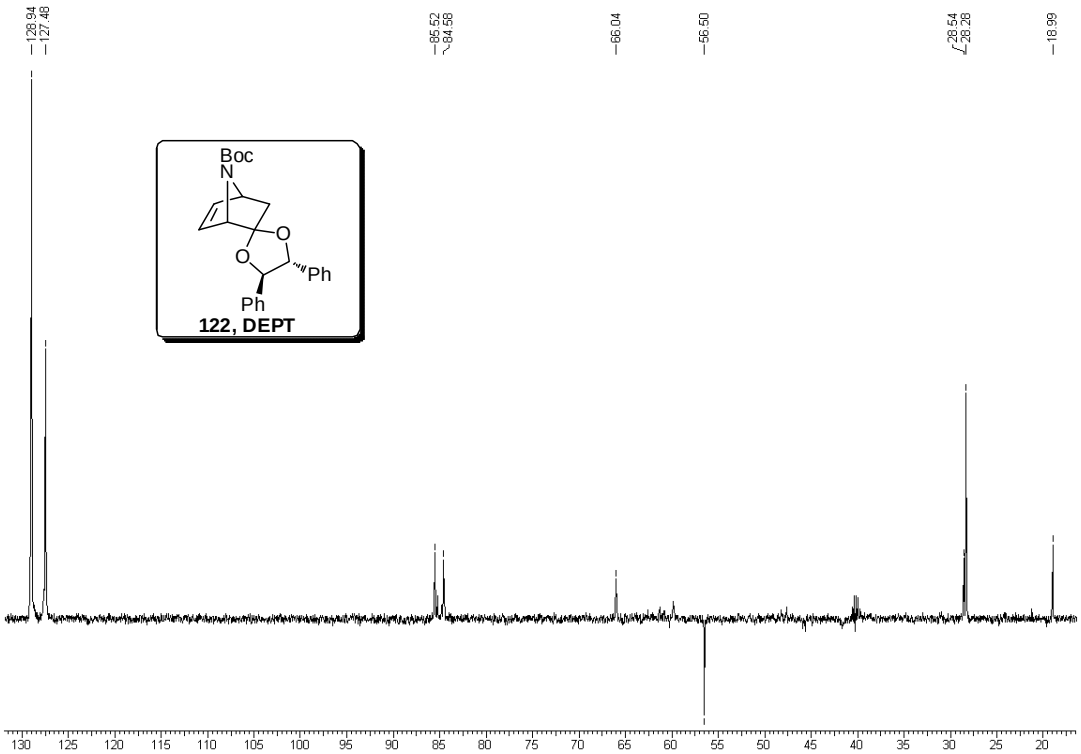

DMSO-d6
155.42
139.70
135.26
134.56
133.89
130.02
129.11
128.85
128.60
127.18
110.90
86.69
83.27
80.03
70.62
68.92
67.75
66.86
64.31
39.70
27.85
Boc
N
H
HO
HO
SO2Ph
O
O
Ph
Ph
117, 13C NMR

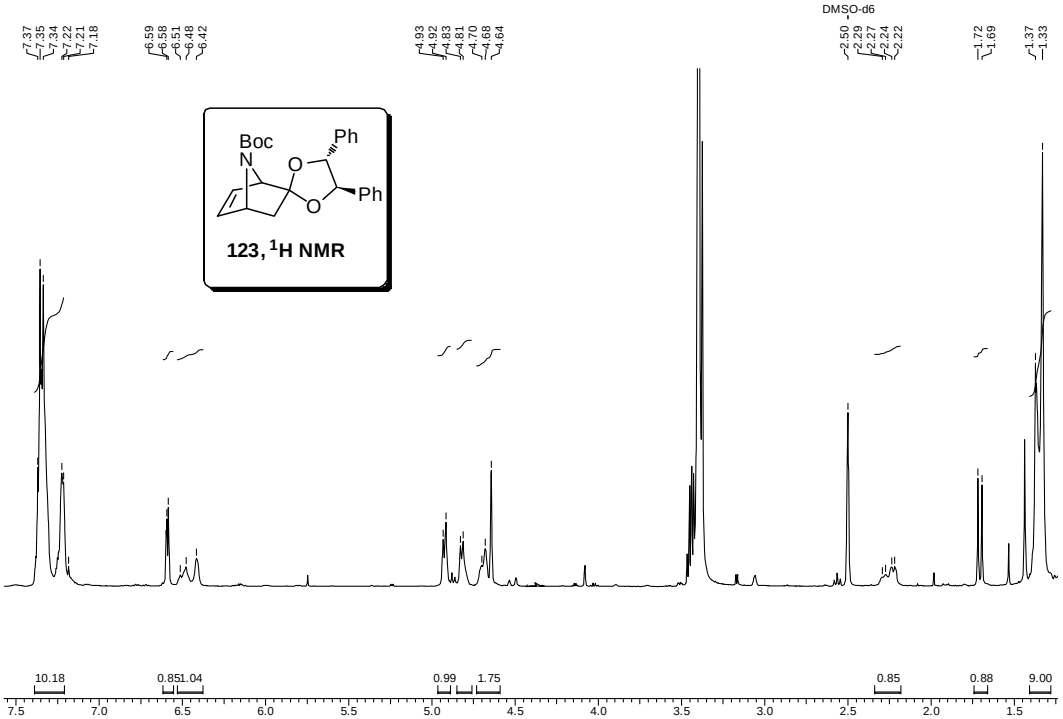

Chloroform-d
7.97
7.96
7.55
7.53
7.39
7.36
7.31
7.29
7.25
7.15
6.60
6.56
6.48
5.36
5.35
5.33
5.31
5.24
5.16
4.64
4.62
4.55
4.48
3.58
3.52
1.37
1.31
Boc
N
O
Ph
Ph
O
SO2Ph
H
exo-115, 1H NMR
1.96
1.12
12.07
1.90
1.94
1.92
0.94
9.10

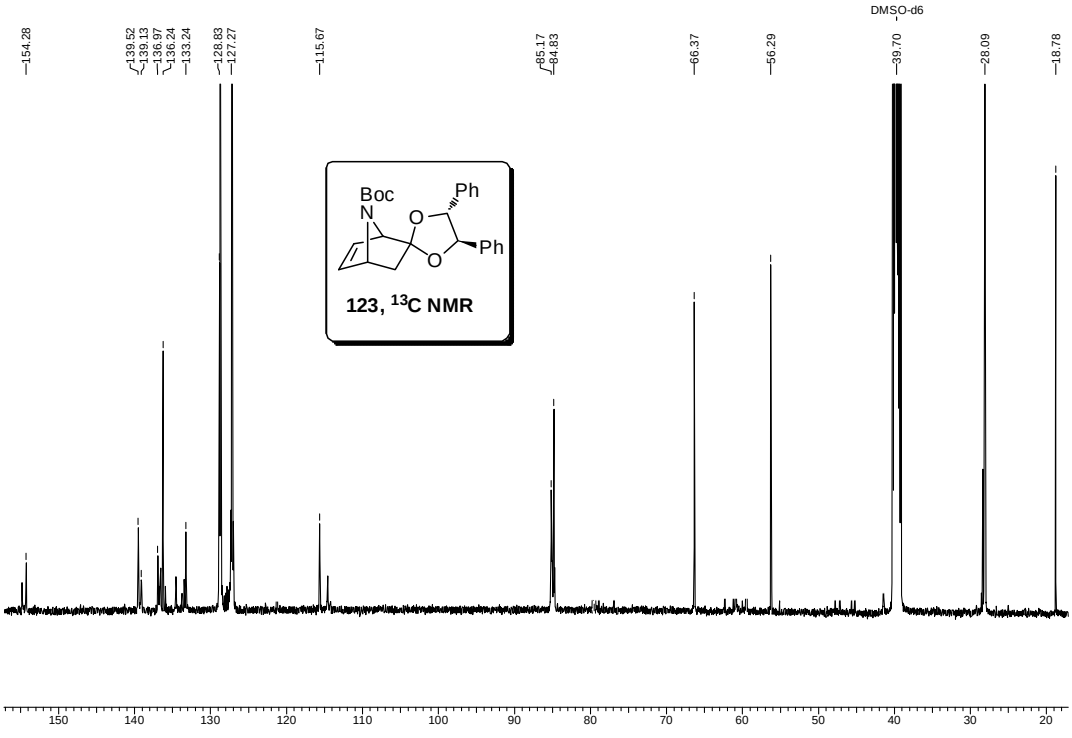

DMSO-d6
153.59
139.94
136.26
135.09
134.49
134.39
133.83
129.07
128.89
128.66
128.50
128.20
127.62
115.59
86.02
85.29
80.58
79.35
70.86
68.39
60.81
39.70
27.79
Boc
N
O
Ph
Ph
O
SO2Ph
H
exo-115, 13C NMR
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32

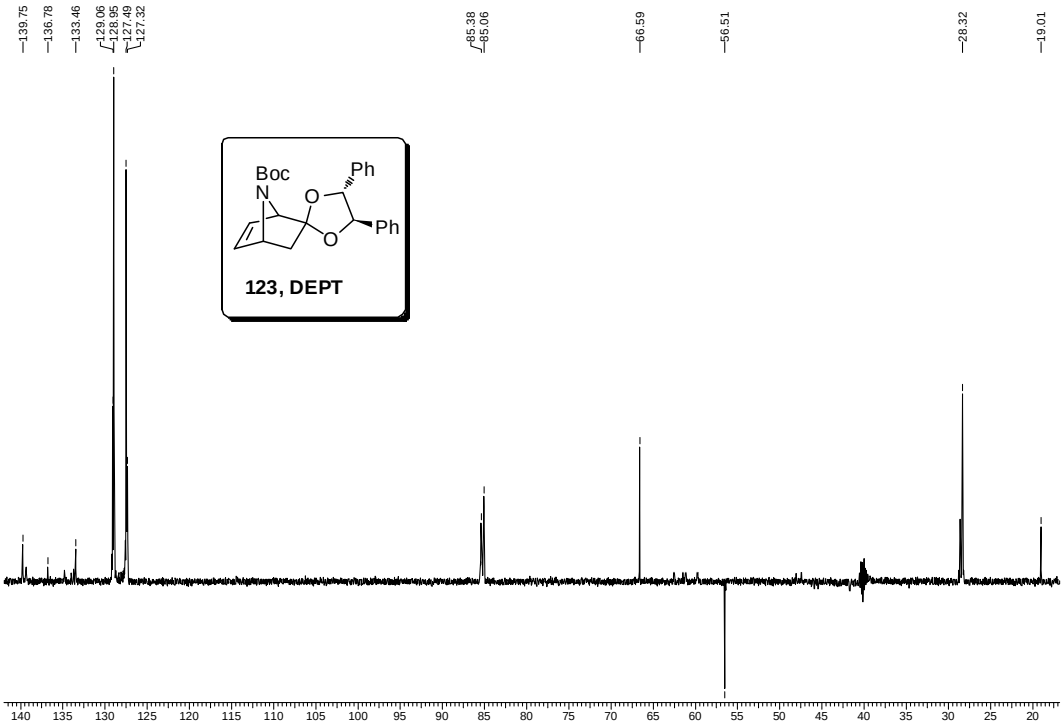

DMSO-d6
7.35
7.27
7.26
7.23
7.21
7.18
6.61
6.54
6.45
4.96
4.94
4.90
4.85
4.70
4.68
4.65
4.61
4.41
4.40
4.39
2.50
2.33
2.27
2.24
1.72
1.69
1.35
1.28
Boc
N
O
O
Ph
Ph
122, 1H NMR
10.00
1.76
0.94
2.24
1.26
0.78
0.80
9.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

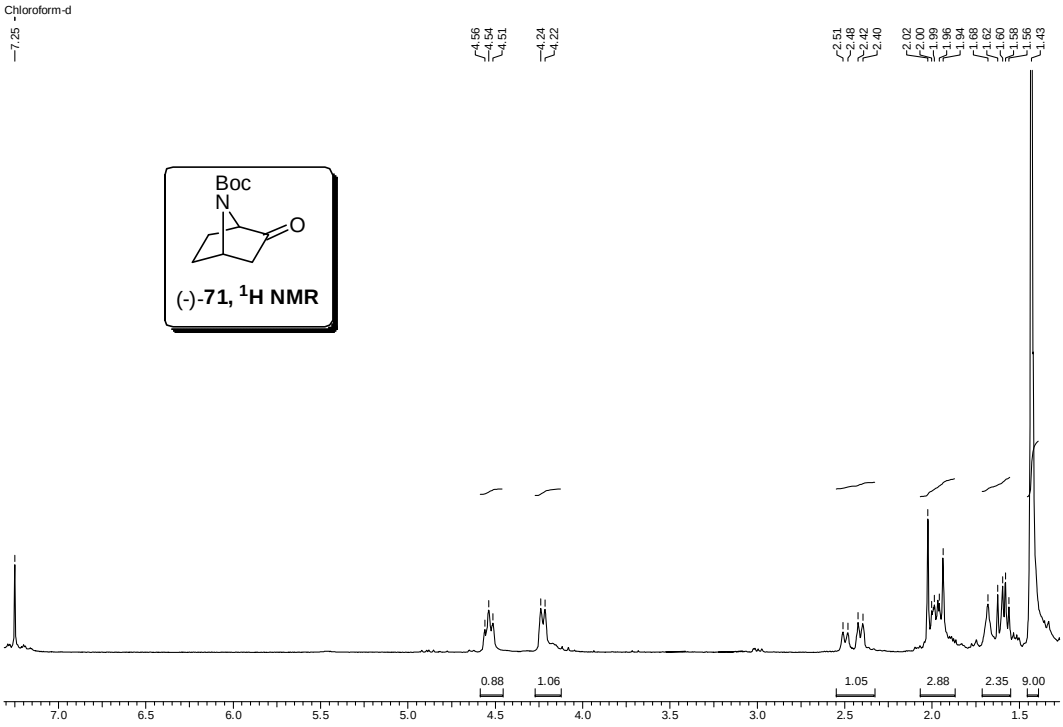

154.88
139.62
136.64
135.66
133.42
128.87
128.74
127.27
115.76
114.81
85.32
84.38
79.54
65.83
56.30
DMSO-d6
39.70
28.08
18.79
Boc
N
O
O
Ph
Ph
122, 13C NMR

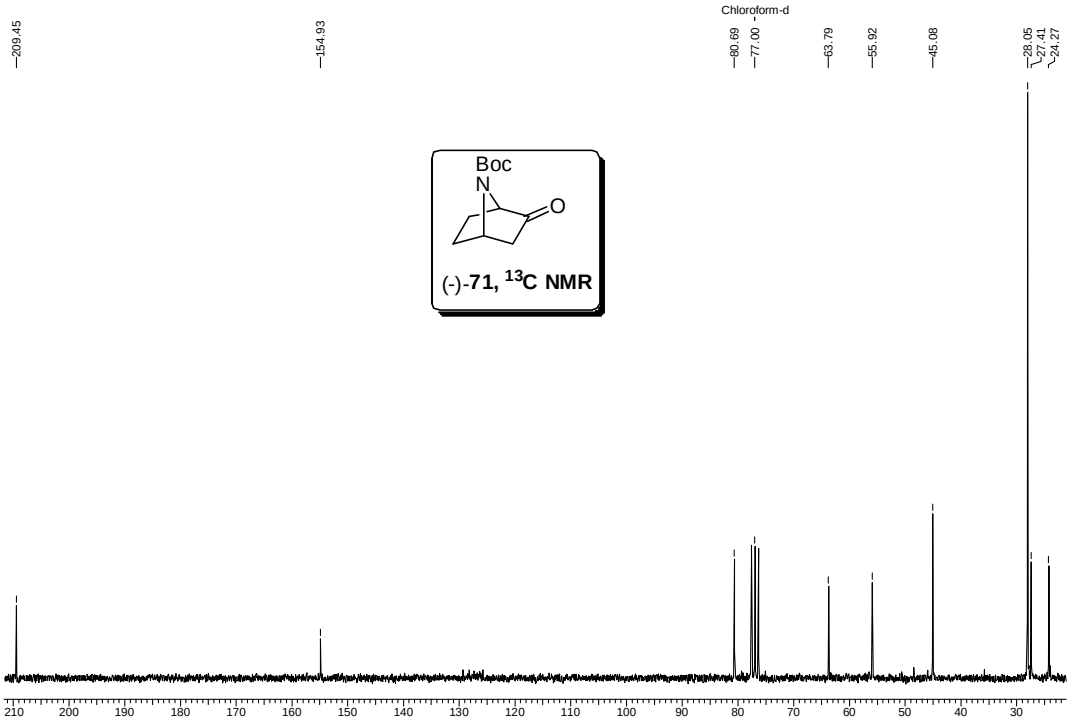

129.94
127.48
85.52
84.56
66.04
56.50
28.54
28.28
18.99
Boc
N
O
O
Ph
Ph
122, DEPT
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20

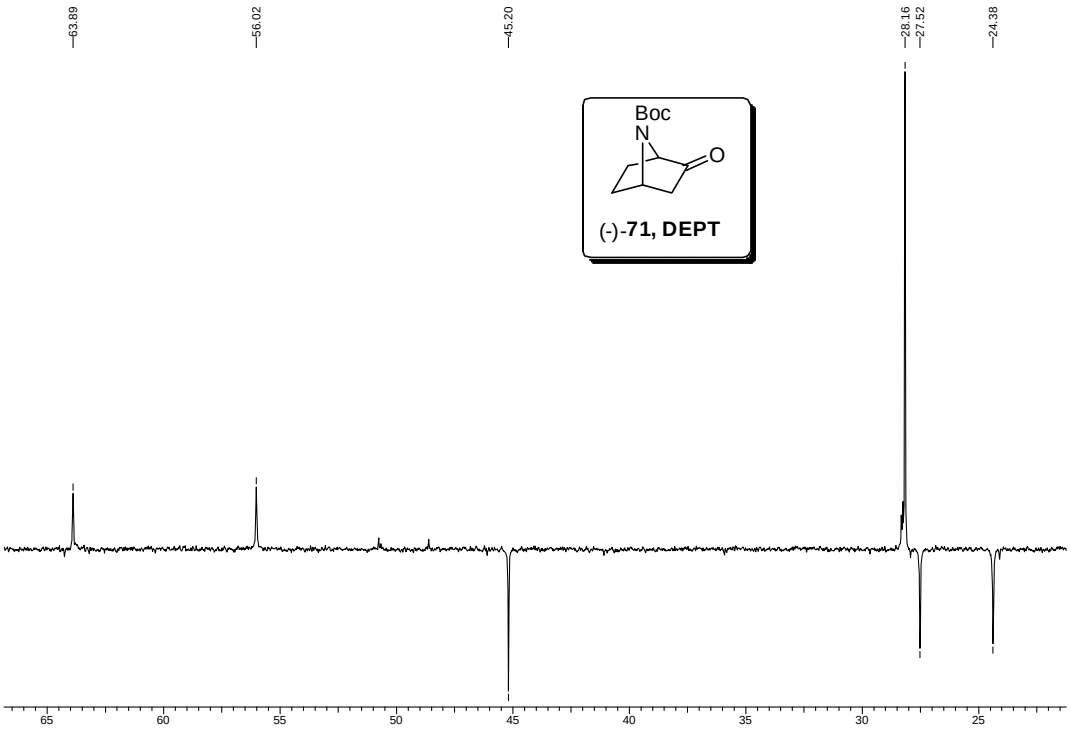

DMSO-d6
7.37
7.35
7.34
7.22
7.21
7.18
6.59
6.58
6.51
6.48
6.42
4.93
4.92
4.83
4.81
4.70
4.68
4.64
2.50
2.29
2.27
2.24
2.22
1.72
1.69
1.37
1.33
Boc
N
O
O
Ph
Ph
123, 1H NMR
10.18
0.85
1.04
0.99
1.75
0.85
0.88
9.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5


DMSO-d6
154.28
139.52
139.13
136.97
136.24
133.24
128.83
127.27
115.67
85.17
84.83
66.37
56.29
39.70
28.09
18.78
Boc
N
O
O
Ph
Ph
123, 13C NMR
150
140
130
120
110
100
90
80
70
60
50
40
30
20

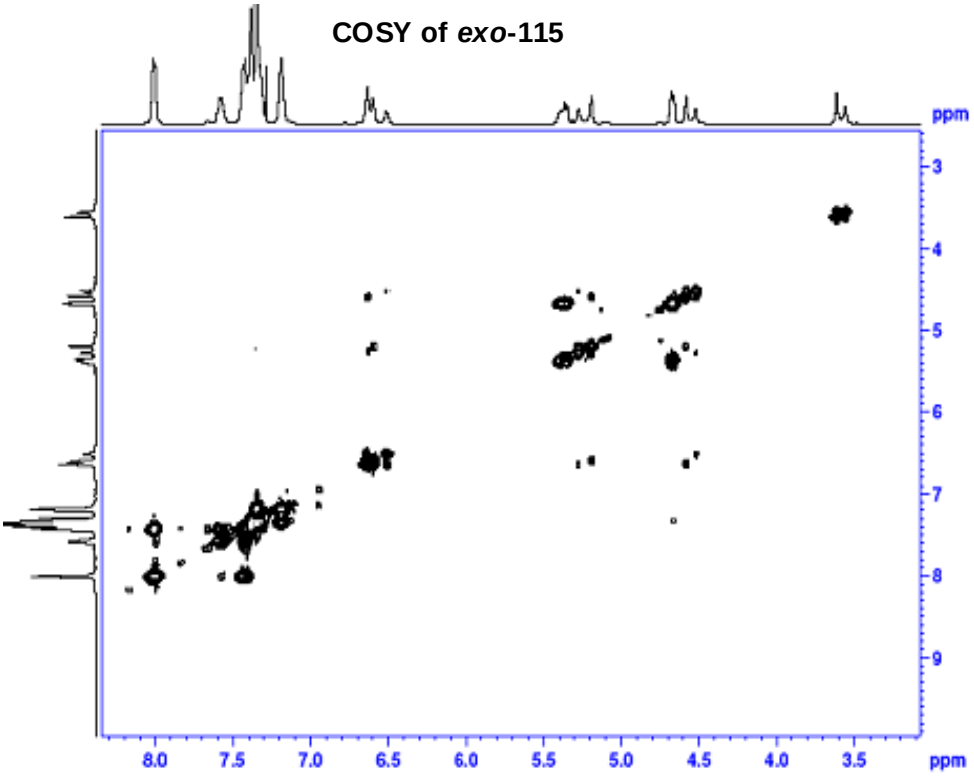

139.75
136.78
133.46
129.06
128.95
127.49
127.32
85.38
85.06
66.59
56.51
28.32
19.01
Boc
N
O
O
Ph
Ph
123, DEPT


Chloroform-d
7.25
4.56
4.54
4.51
4.24
4.22
2.51
2.48
2.42
2.40
2.02
2.00
1.99
1.96
1.94
1.68
1.62
1.60
1.58
1.56
1.43
Boc
N
O
(-)-71, 1H NMR
0.88
1.06
1.05
2.88
2.35
9.00

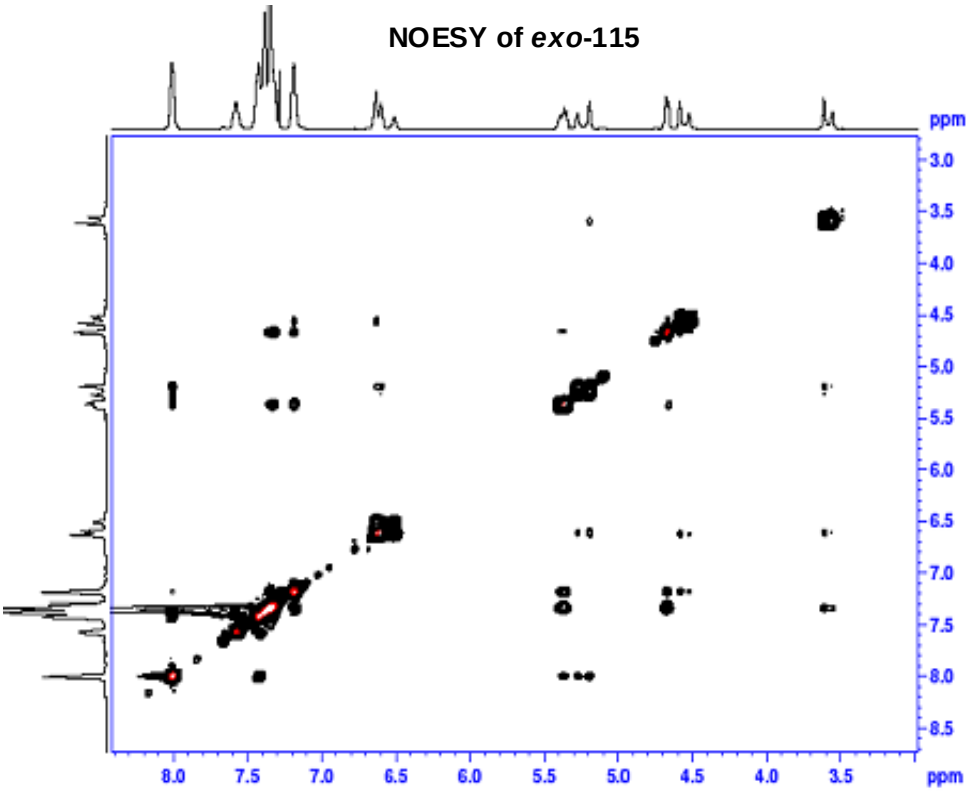

Chloroform-d
209.45
154.93
80.69
77.00
63.79
55.92
45.08
28.05
27.41
24.27
Boc
N
O
(-)-71, 13C NMR
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30

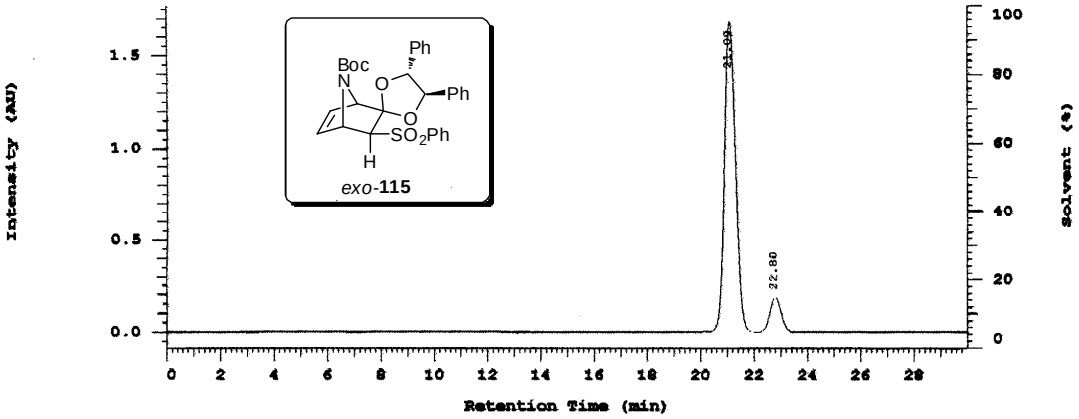

63.89
56.02
45.20
28.16
27.52
24.38
Boc
N
O
(-)-71, DEPT
65
60
55
50
45
40
35
30
25

COSY of *exo*-115



NOESY of *exo*-115





Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Height	Area	Area %
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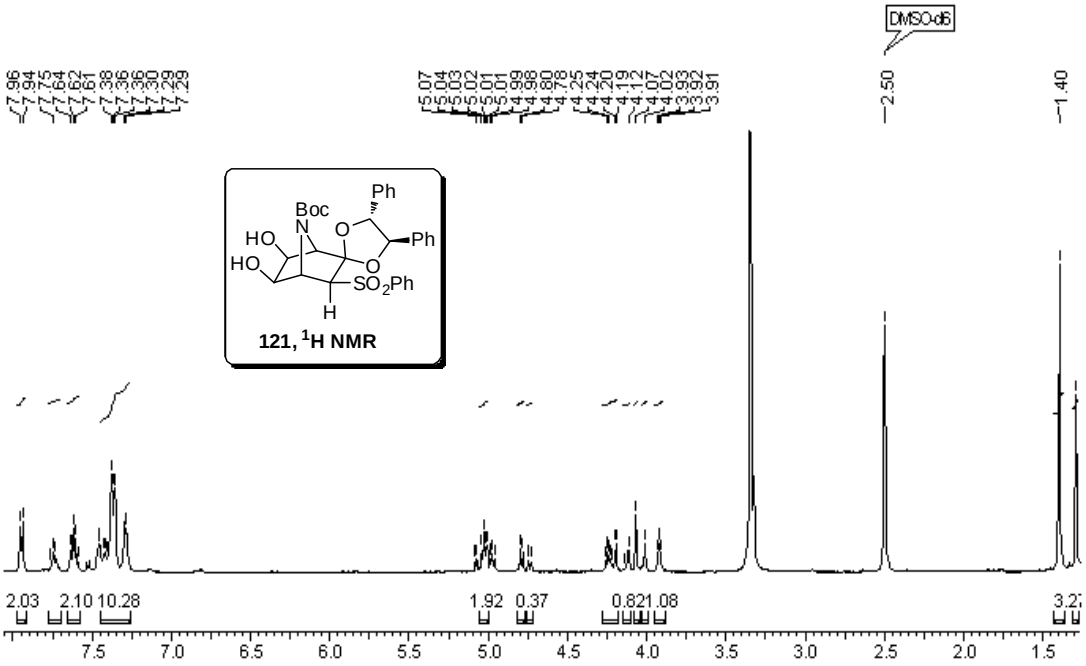
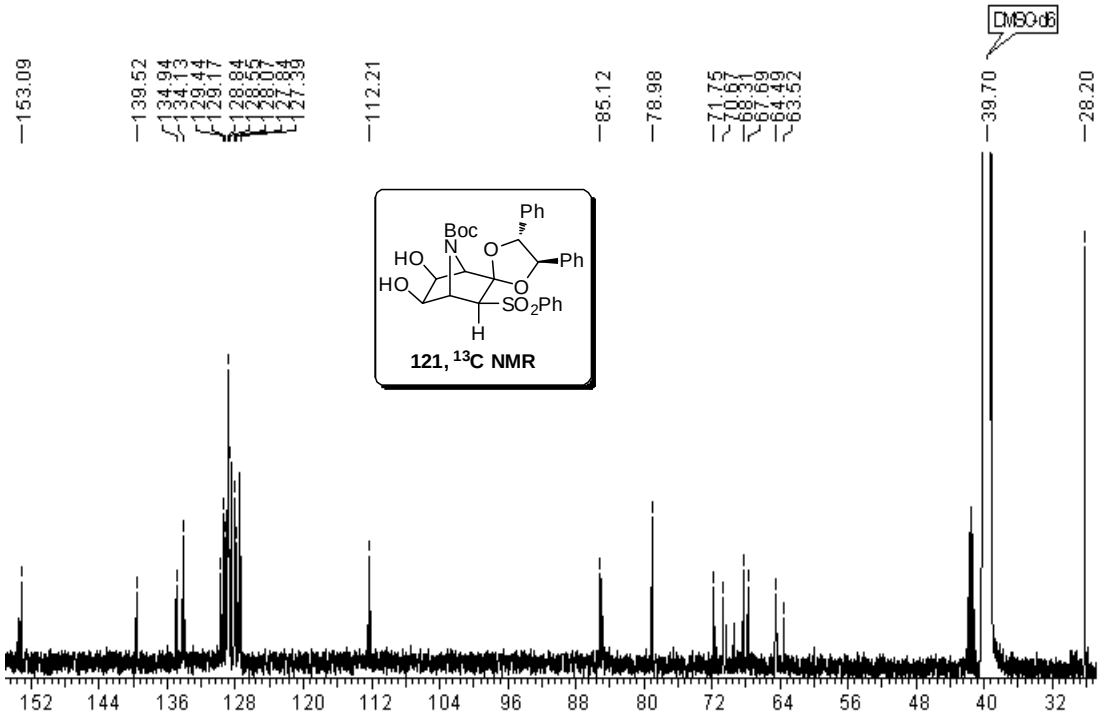
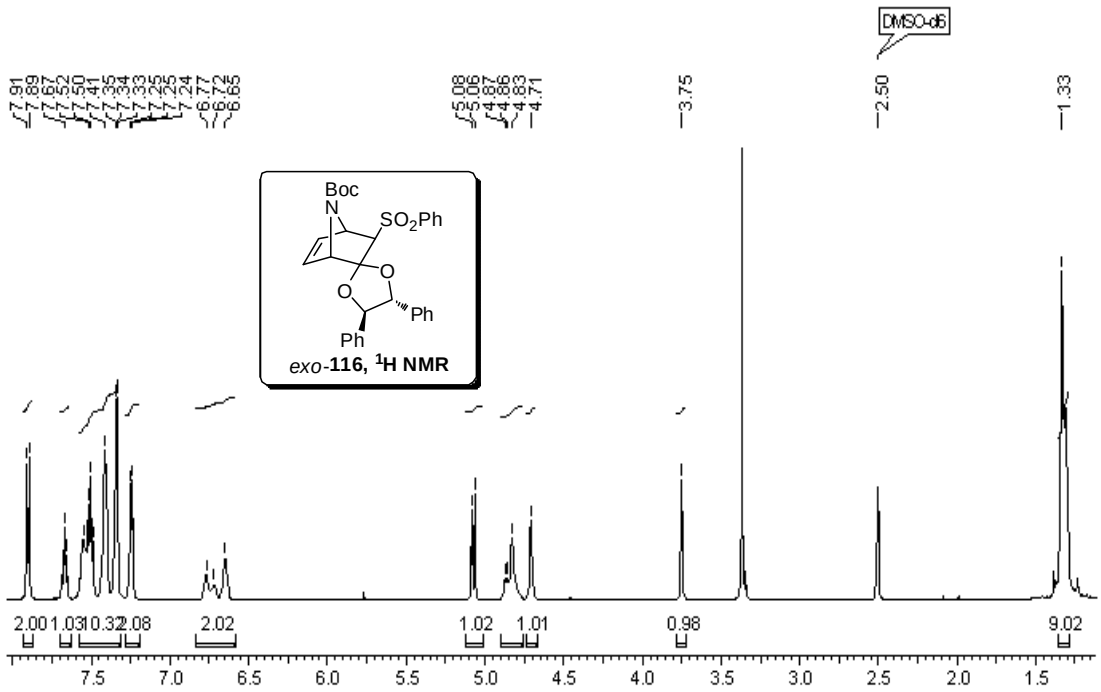
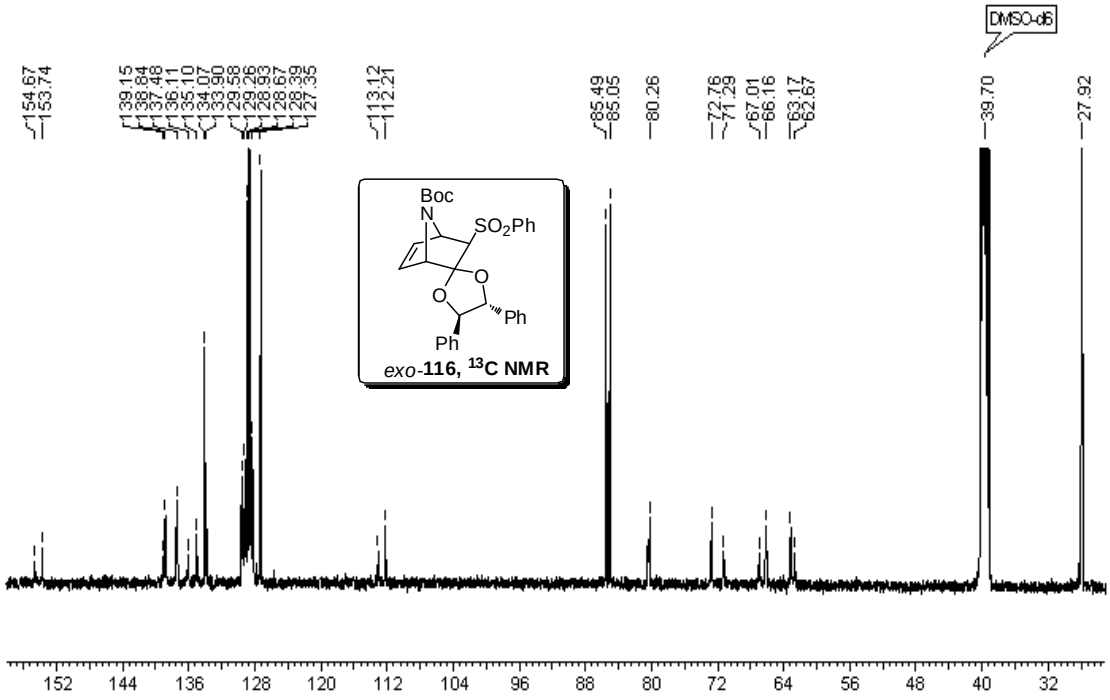
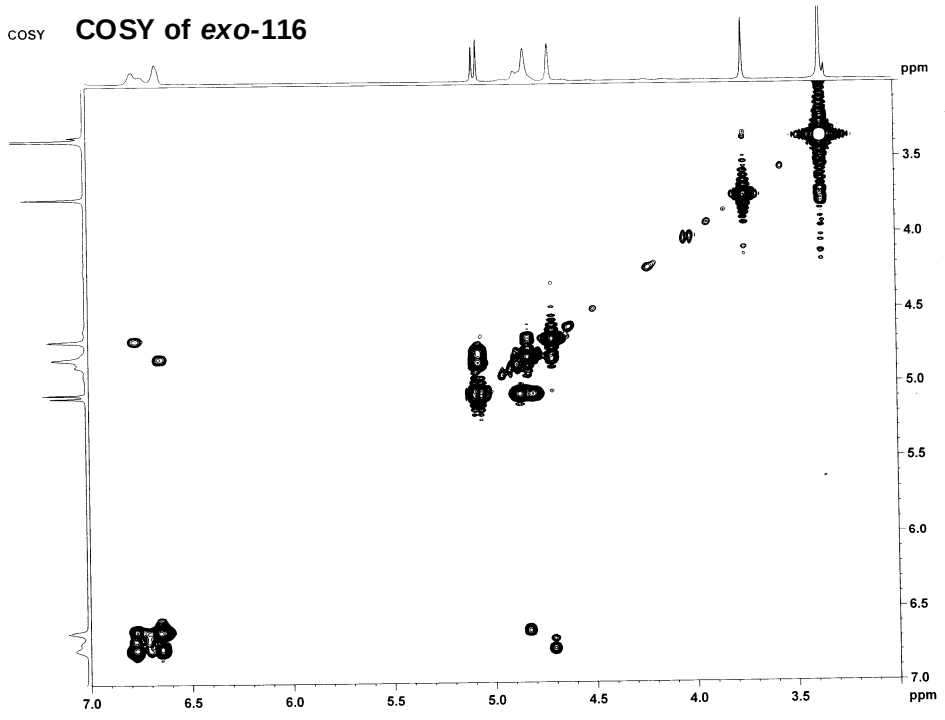
2	22.80	44008	1335657	8.177
		508165	16333653	100.000




DMSO-d6
153.09
139.52
134.94
134.13
129.44
129.17
128.84
128.05
127.84
127.39
112.21
85.12
78.98
71.75
70.67
68.31
67.69
64.49
63.52
39.70
28.20
Boc
N
Ph
O
HO
HO
Ph
O
SO2Ph
H
121, 13C NMR
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32


DMSO-d6
7.91
7.89
7.67
7.52
7.50
7.41
7.35
7.34
7.33
7.25
7.24
6.77
6.72
6.65
5.08
5.06
4.87
4.86
4.83
4.71
3.75
2.50
1.33
Boc
N
SO2Ph
O
O
Ph
Ph
exo-116, 1H NMR
2.00
1.03
0.32
2.08
2.02
1.02
1.01
0.98
9.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5


DMSO-d6
154.67
153.74
139.15
138.84
137.48
136.11
135.10
134.07
133.90
129.58
129.26
128.93
128.67
128.39
127.35
113.12
112.21
85.49
85.05
80.26
72.76
71.29
67.01
66.16
63.17
62.67
39.70
27.92
Boc
N
SO2Ph
O
O
Ph
Ph
exo-116, 13C NMR
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32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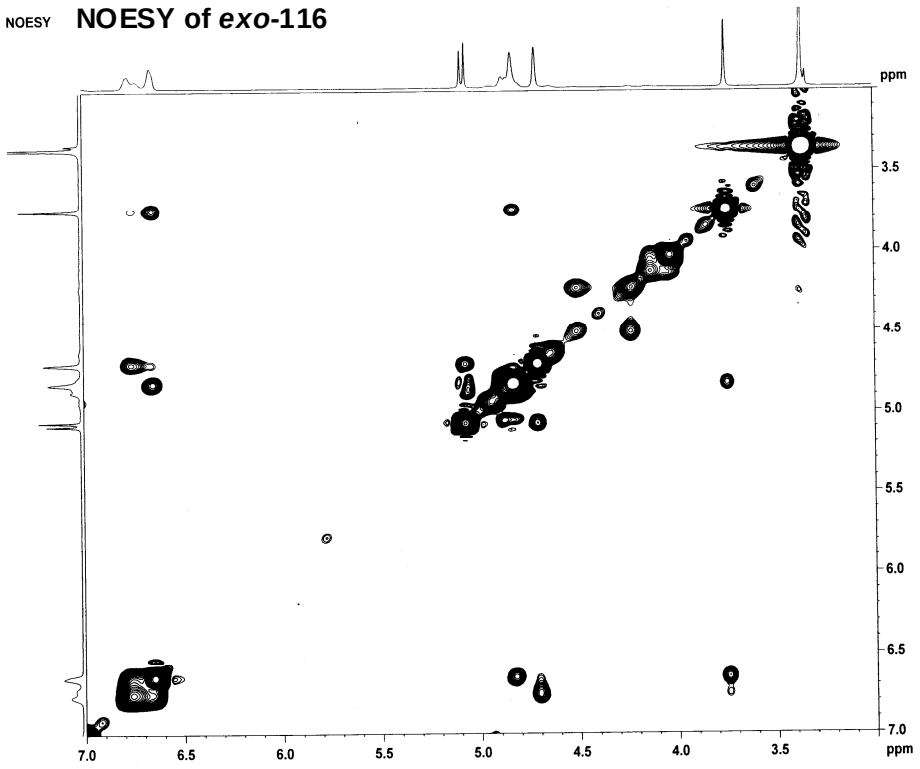
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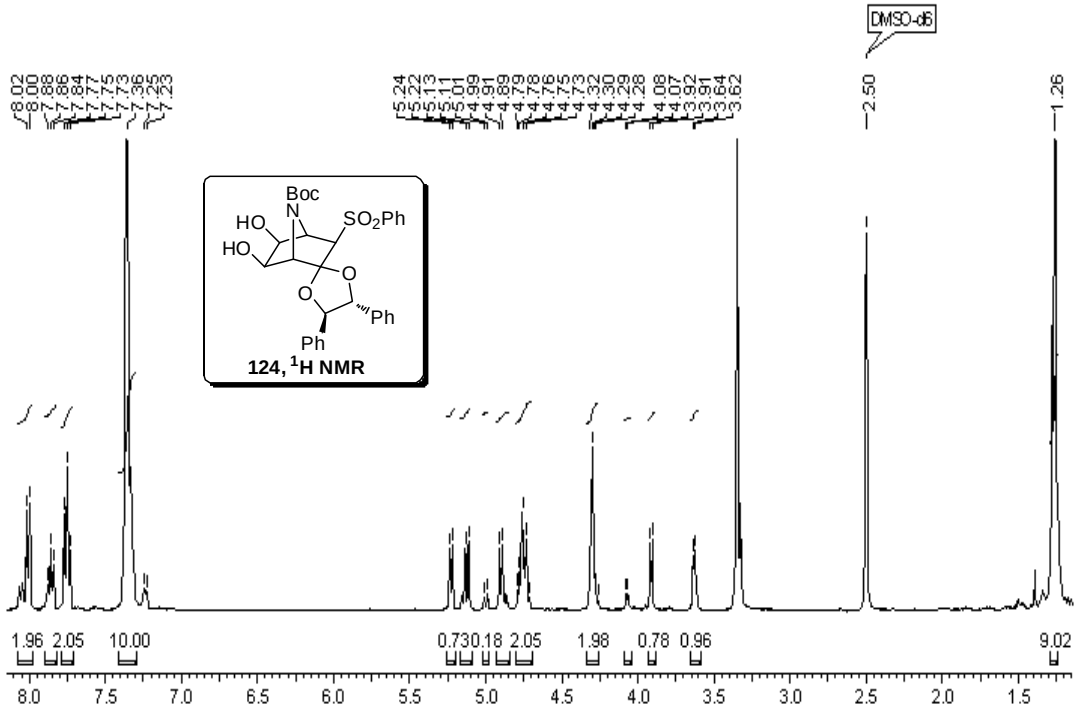
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Boc
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SO2Ph
O
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Ph
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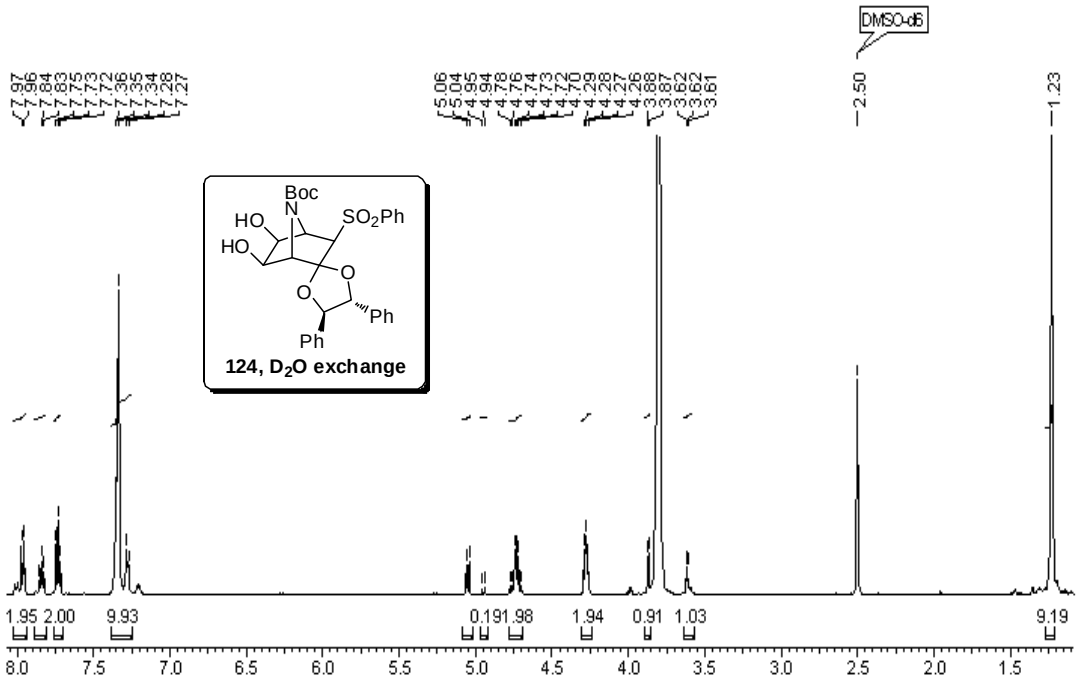
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4.70
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4.28
4.27
4.26
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3.87
3.62
3.61
2.50
1.23
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HO
HO
SO2Ph
O
O
Ph
Ph
124, D2O exchange
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2.00
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0.19
1.98
1.94
0.91
1.03
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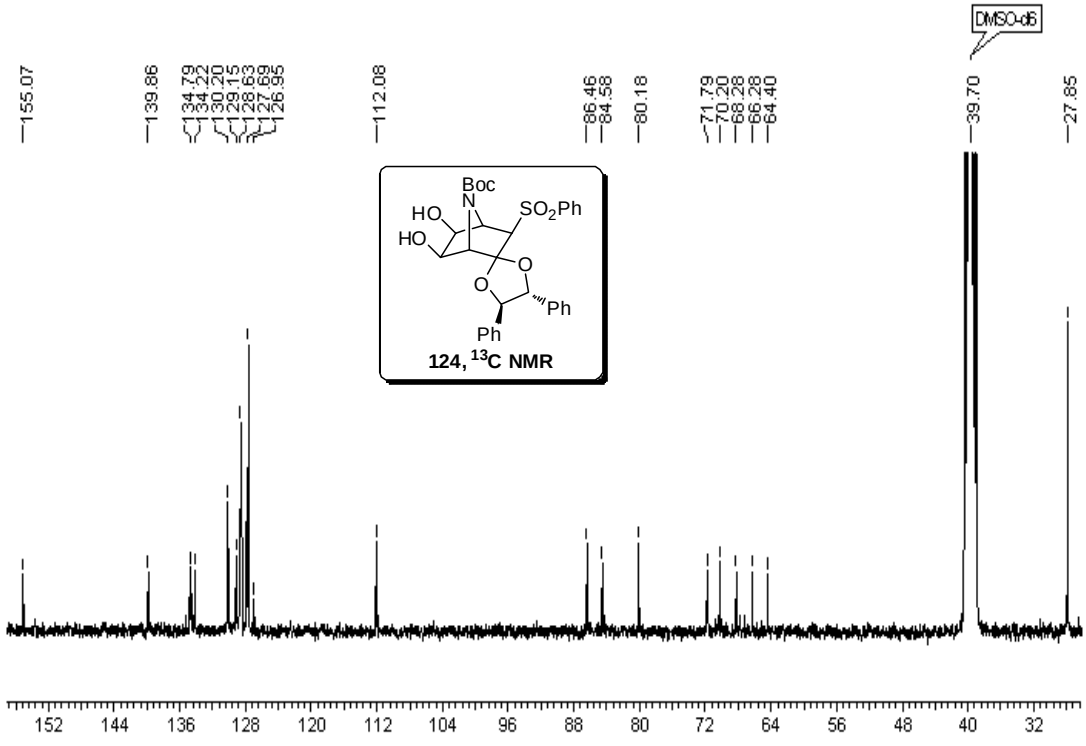
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71.79
70.20
68.28
66.28
64.40
39.70
27.85
Boc
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HO
HO
SO2Ph
O
O
Ph
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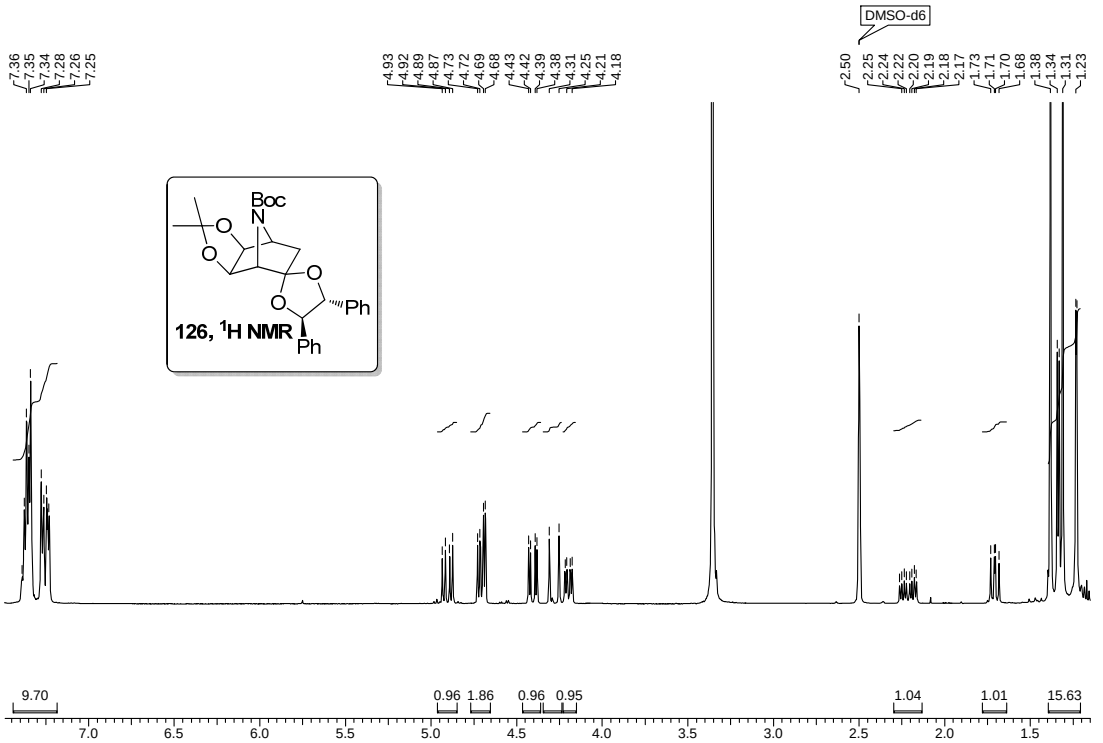
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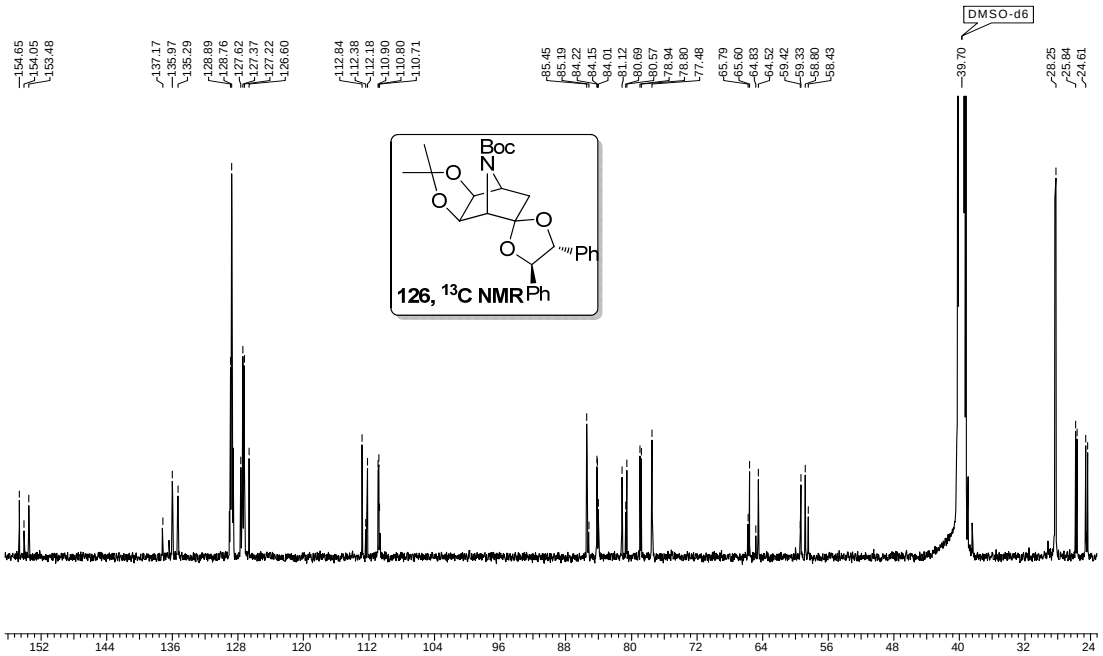
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O
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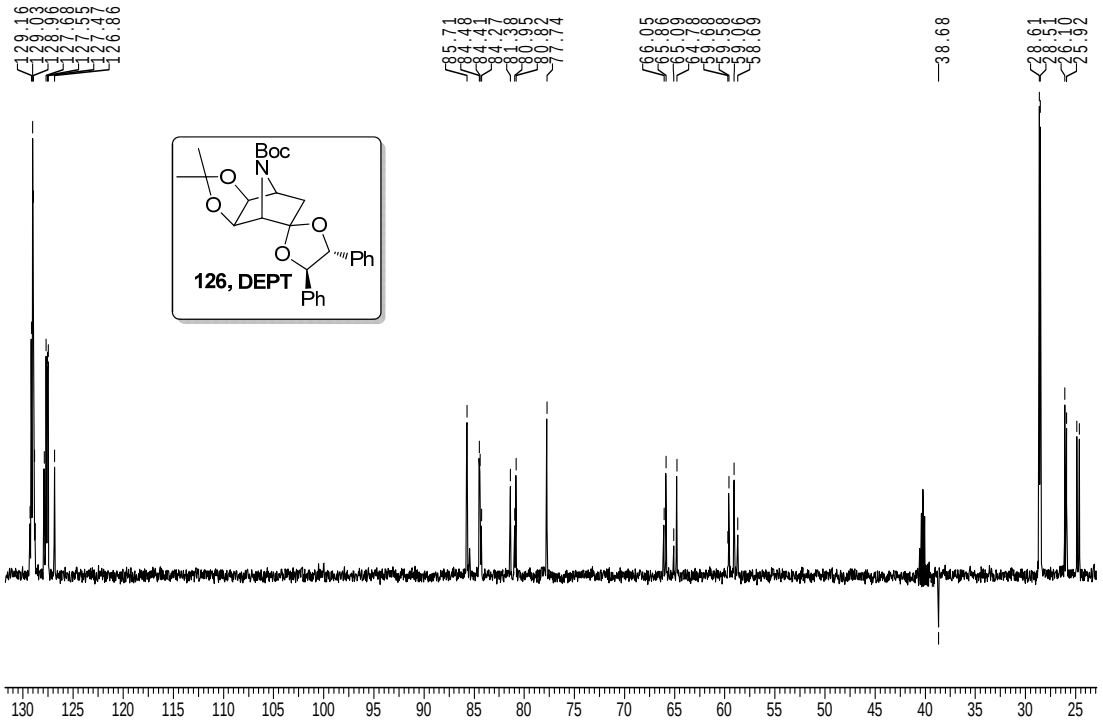
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26.10
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Boc
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O
O
O
Ph
Ph
126, DEPT
130
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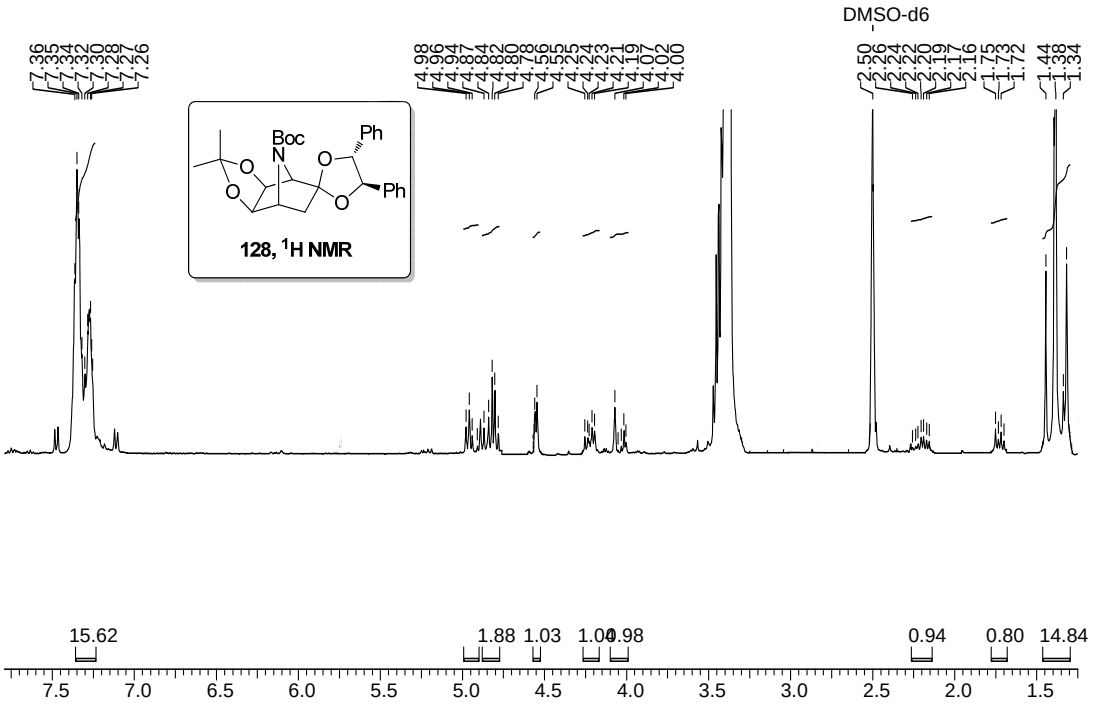
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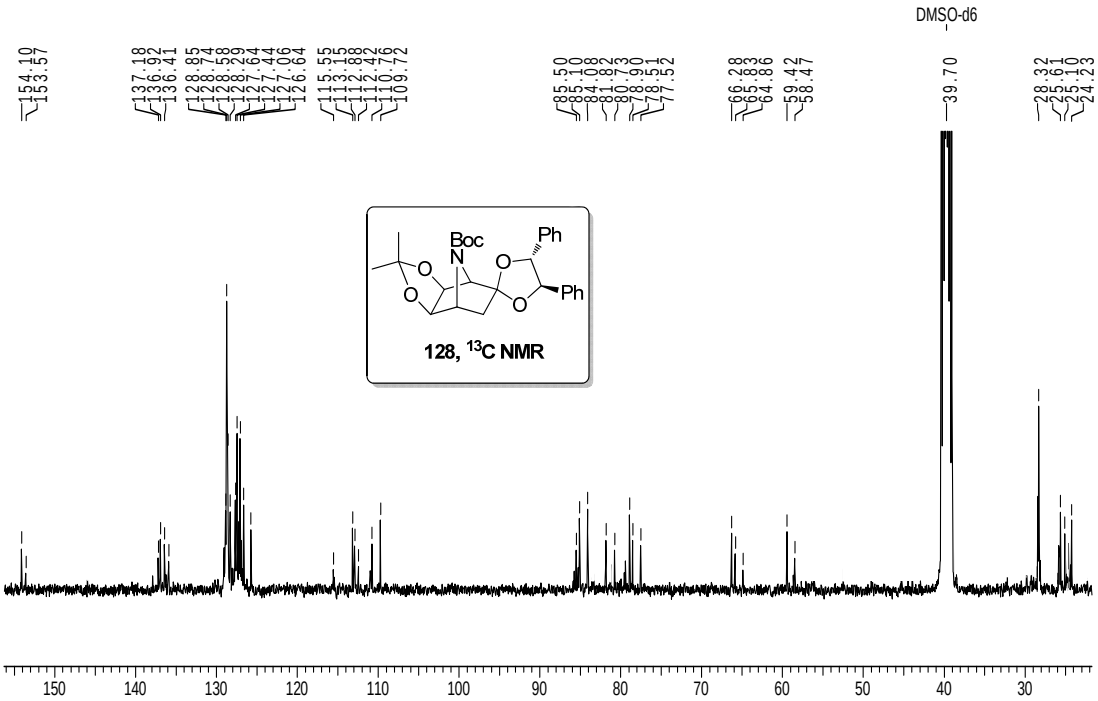
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100
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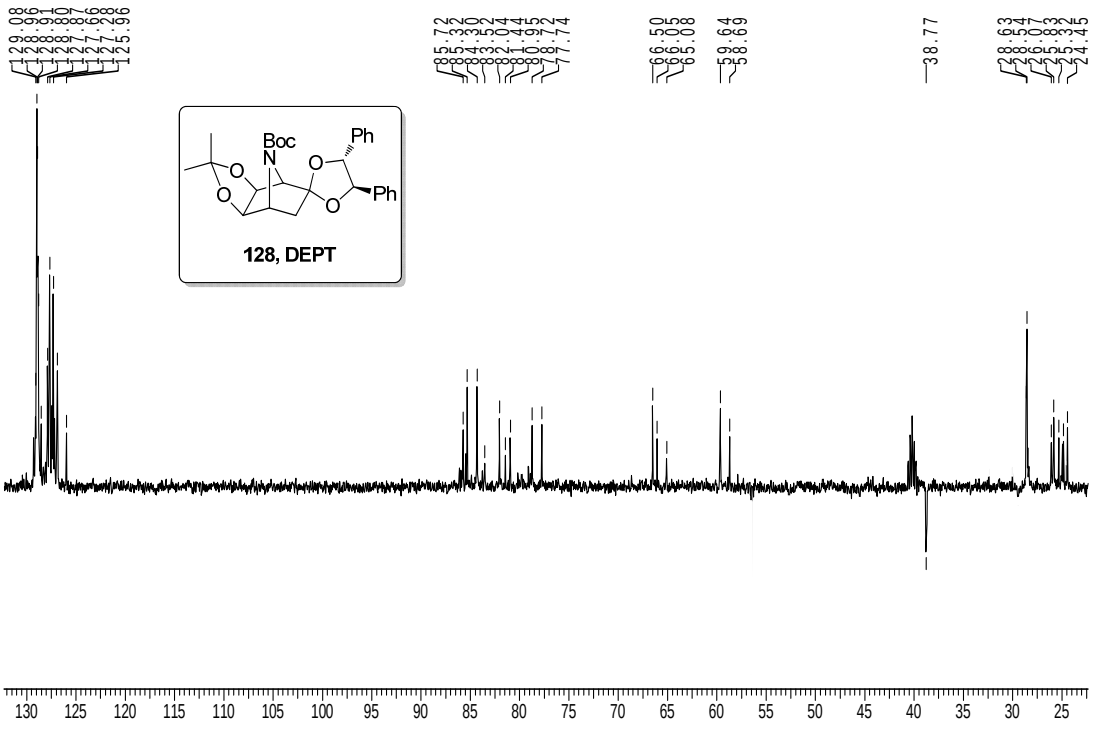
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38.77
28.63
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Ph
Ph
128, DEPT
130
125
120
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110
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100
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85
80
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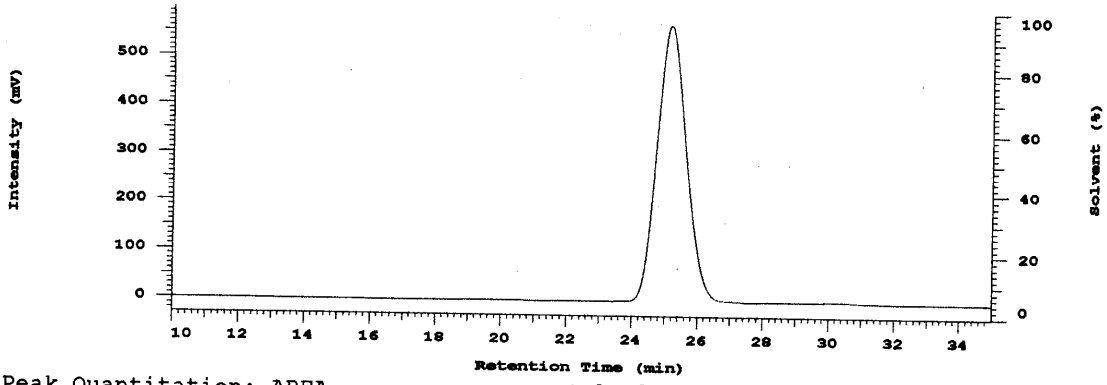
30
25

Desymmetrization of *meso*-**99** screening the temperature from -100 ^{o}C to 35 ^{o}C



Peak Quantitation: AREA Calculation Method: AREA%

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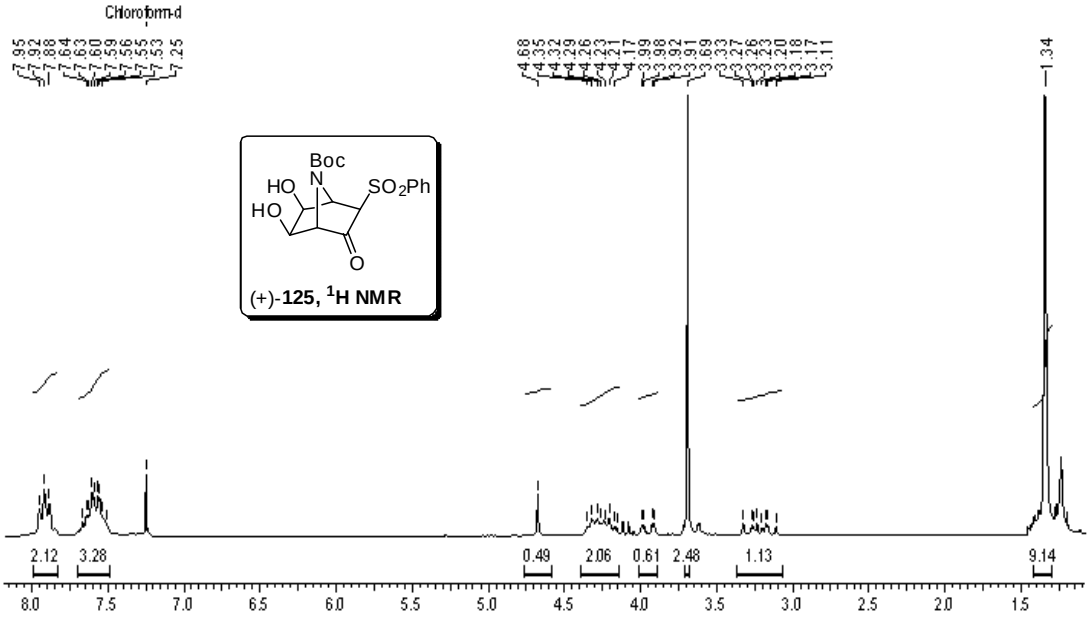

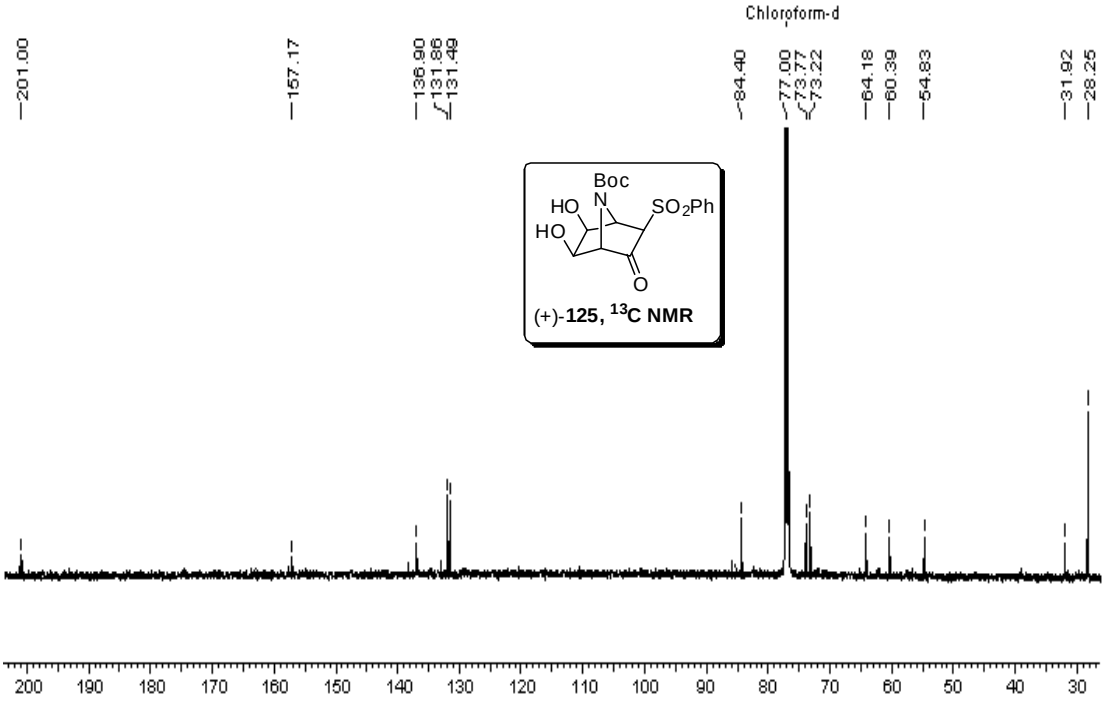
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131.49
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28.25
Boc
N
HO
HO
SO2Ph
O
(+)-125, 13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30

Chapter-3

Synthesis of 1-neo-Inosamine

Section-A

3A.1. Aminocarbasugars introduction:

Recently a great deal of attention has been focused towards the design and synthesis of glycosidase inhibitors under the premise that glycoconjugates such as oligosaccharides, glycolipids, and glycoproteins play pivotal roles in living systems. Glycosidase inhibitors possess interesting enzyme specific inhibitory activities, therefore, they are expected not only to be tools to elucidate the mechanisms of a living systems, manipulated by the glycoconjugates but also potential clinical drugs for obesity, diabetics, fungal, and viral diseases including human immunodeficiency viruses (HIV). Most of the glycosidase inhibitors are isolated from natural sources and they possess interesting structures. Some of them possess highly functionalized and oxygenated cyclohexane or cyclopentane moieties. Aminocyclitols are a group of natural products of significant relevance in medicinal chemistry as they are the structural component of a variety of antibiotics[1], glycosidase inhibitors[2] and other families of biologically active compounds[3]. From a structural point of view, aminocyclitols are cycloalkanes containing at least one free or substituted amino group and three additional hydroxyl groups on the ring. Because of their close structural relationship with sugars, aminocyclitols are also regarded as aminocarbasugars[4].

Biochemically, carbasugars and cylitols themselves are recognized as the pseudo-sugars in a living system, and they show interesting biological activities based on the structural similarity to sugars. The most interesting and significant points for the synthesis of glycosidase inhibitors possessing cyclitols are how one can form the frameworks of the cyclitols and how can the functional groups essential to generate their specific and interesting biological activities be introduced.

Natural aminocyclitols are secondary metabolites found as structural subunits in some complex natural products, such as validamycins, a family of antibiotics isolated

from the fermentation culture of *Streptomyces hygroscopius*[5]. A validamycin **133** is composed of one valienamine unit, together with an additional unit of validamine, valiolamine or hydroxyvalidamine. The α-amylase inhibitor acarbose **132** is another complex natural product containing an aminocyclitol unit valienamine linked with a trisaccharide (Figure 1).

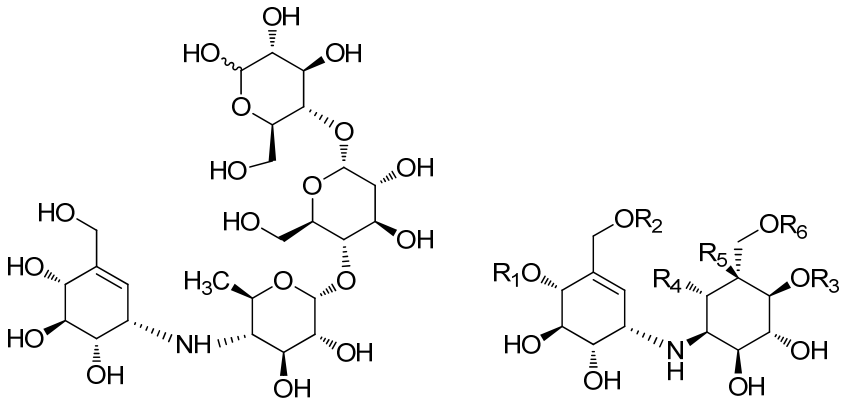


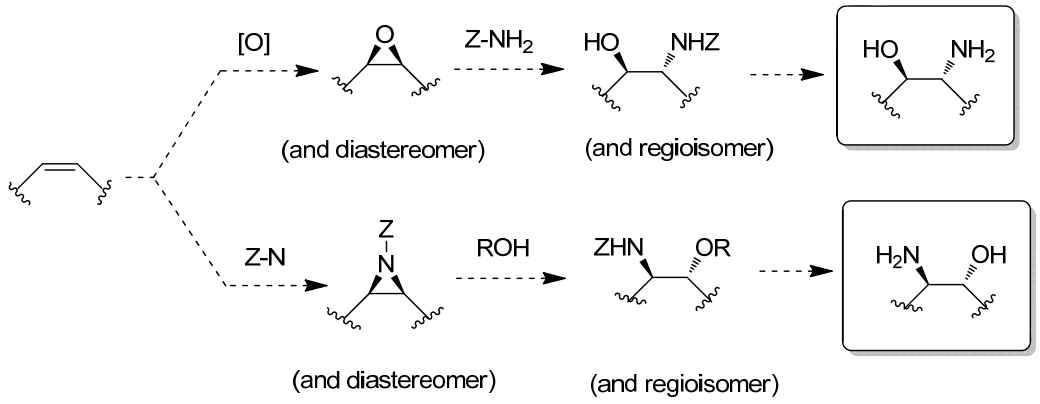
Figure 1. Acarbose and validamycin

Owing to the protonation of their amino group at physiological pH, these aminocyclitols are believed to mimic the transition state in the enzymatic glycoside hydrolysis. In parallel, hundreds of analogs have been synthesized and tested as inhibitors of glycosidases enzymes besides being used as biosynthetic building blocks in many antibiotics.

Compounds with obvious structural similarity to a carbohydrate skeleton are a new class of inhibitors and the elucidation of their mechanism of action may add new insights in the search for new therapeutic agents. Conduramines as well as aminocarbasugars, due to their structural similarity, are a family of carbohydrate mimics which have attracted a great deal of attention among organic and medicinal chemists due to their profound biological activities towards glycosidases. The polyhydroxy glycosidase inhibitors are a widely diverse class of compounds often isolated from plants and microorganisms and they have significant therapeutic use or

potential. Current interest in these compounds has been extended to a diverse range of diseases including lysosomal storage disorders and cancer, and special attention has been given to those compounds with anti-HIV activity. Isolation of suitable glucosidase inhibitors from natural sources or their chemical synthesis provides biochemical tools for the elucidation of the mechanistic activity of enzyme through the use of kinetic data combined with variations in potential inhibitor structural information. Such knowledge is fundamental to the discovery of lead compounds, because of their promising therapeutic potential.

Aminocyclitols and diaminocyclitols, derived from conduramines and their analogues, comprise parts of aminoglycoside antibiotics which are among the oldest known antibiotics. These compounds possess arrays of hydroxyl and amino groups and are potentially interesting systems, as they can target pivotal RNA sites, and are thus candidates for drug discovery[6]. Apart from, due to their glycosidase inhibitory activities, they can act as potential anticancer or antiviral agents[7]. Given the importance of conduramines as synthetic building blocks, it is not surprising that so much effort has been devoted to the development of useful preparative routes to these compounds and their derivatives.



Scheme 1. Synthesis of *trans* vicinal amino alcohol by attack of external nucleophile

A characteristic functionality identified in these aminocyclitols is the *trans*-vicinal amino alcohol functionality which is relatively more complicated. The only

general approach known in the literature is ring opening of epoxide by a nitrogen nucleophile or ring opening of an aziridine by an oxygen nucleophile as shown in Scheme 1. However, site and face differentiation remains the matter of concern in this approach.

Aminocarbasugars, such as valienamine **136**, validamine **134**, hydroxyvalidamine **135** and valiolamine **137** (Figure 2) are secondary metabolites which are exclusively produced by microorganisms. These aminocarbasugars appeared to be active against several sugar hydrolases but valiolamine is found to be a more potent α-glucosidase inhibitor against porcine intestinal sucrase, maltase, and isomaltase than the rest of the aminocarbasugars.

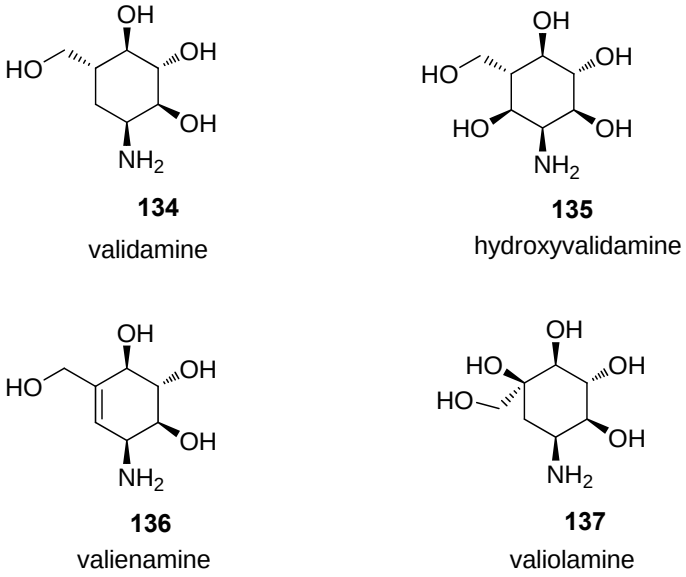


Figure 2.

To know the kind of inhibitory activity a molecule can exhibit, it is customary to understand the structural resemblance with sugar molecule. Fig. 3 shows the structural resemblance of valiolamine with different sugars[3]. Since valiolamine resembles with α-D-glucose, it is expected to be a potent glucosidase inhibitor.

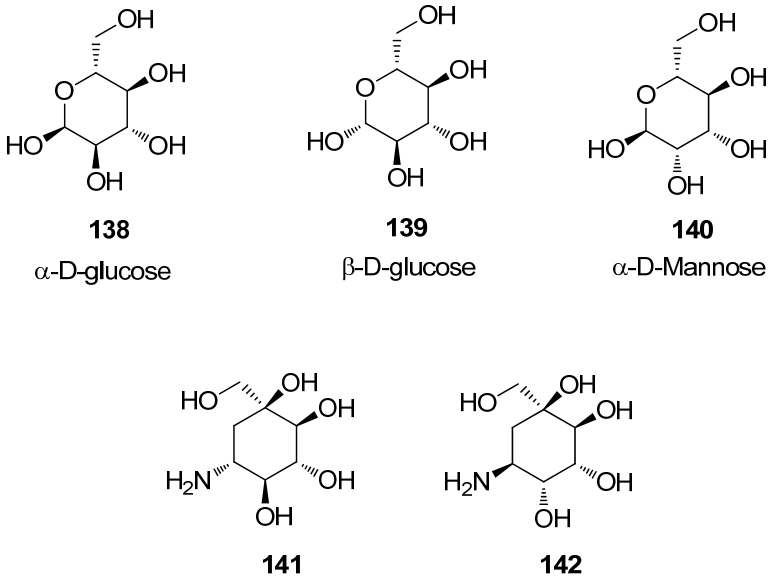


Figure 3.

In search for better glycosidase inhibitory activities, several chemically modified analogues of aminocarbasugars like **143** and **144** (Figure 4) have been synthesized and evaluated[4]. Although, these modifications did not enhance inhibitory activity much against the targeted enzyme, it provided information to understand better structure activity relationship.

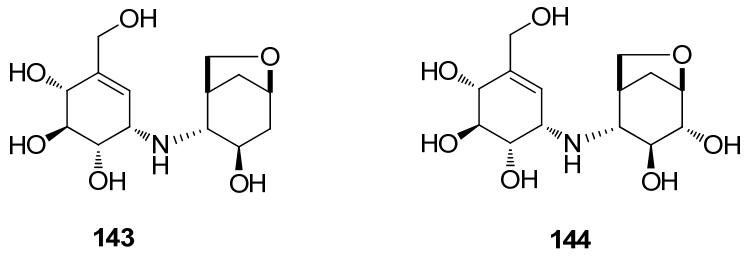


Figure 4.

More recently, the abilities of some aminocyclitols to interfere with sphingolipid metabolism[8] have paved the way for research into new potential therapeutic applications for this class of compounds. This is the case with *N*-octylvalienamine (NOV) **145**, currently under study for chemical chaperone therapy

for the treatment of Gaucher's disease[9]. In addition, several carbocyclic analogues of glycosylceramide such as **146** and **147** have been synthesized by replacing the sugar residue with either saturated or unsaturated aminocarbasugars[10] (Figure 5) and have been found to be very potent and specific inhibitors for gluco- and galactocerebrosidase.

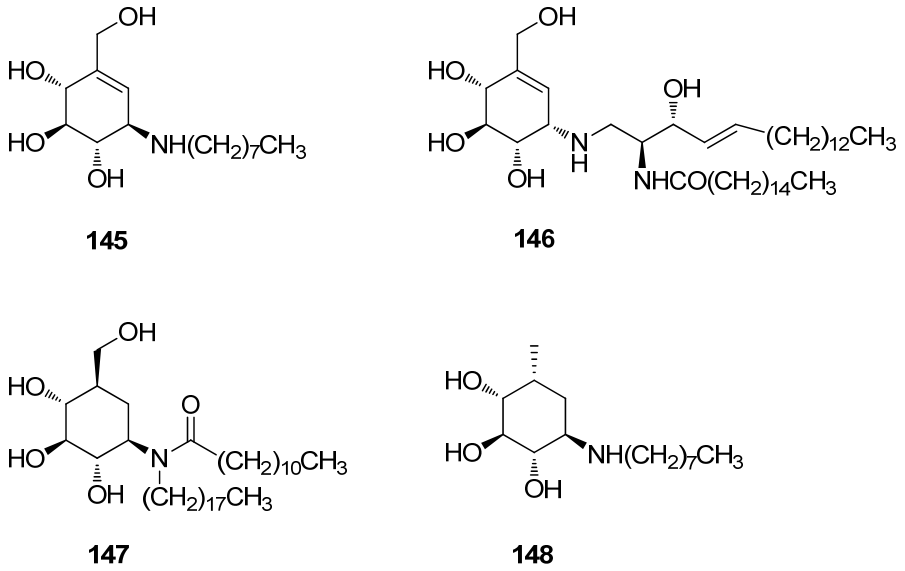
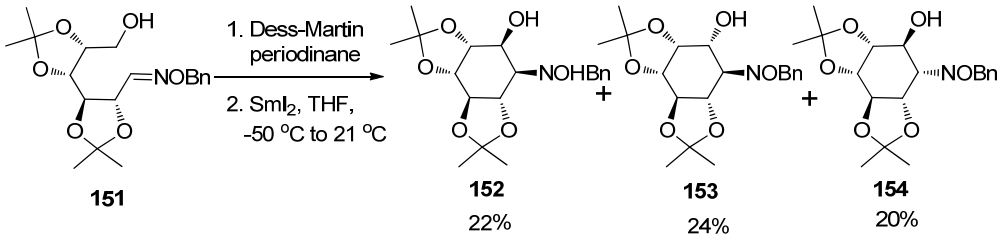


Figure 5.

In continuation of the structural modification of aminocarbasugars, molecule like **148** have been prepared by replacing hydroxymethyl group with methyl group and incorporating alkyl side chain into the amino function of aminocyclitol (Fig. 5). These all modifications have led to increase the inhibitory activities more than the parent molecule.[11] Aminocyclitols or amino glycosides possessing either 1,2-*trans* or 1,2-*cis*-vicinal amino alcohol represent important class of antibiotics having significant relevance in the medicinal chemistry. Owing to their prominent biological role and structural importance, there has been considerable interest in designing as well as developing new strategies for the synthesis of aminocyclitols. In this context it would be quite logical to discuss some of the important approaches reported in the literature.

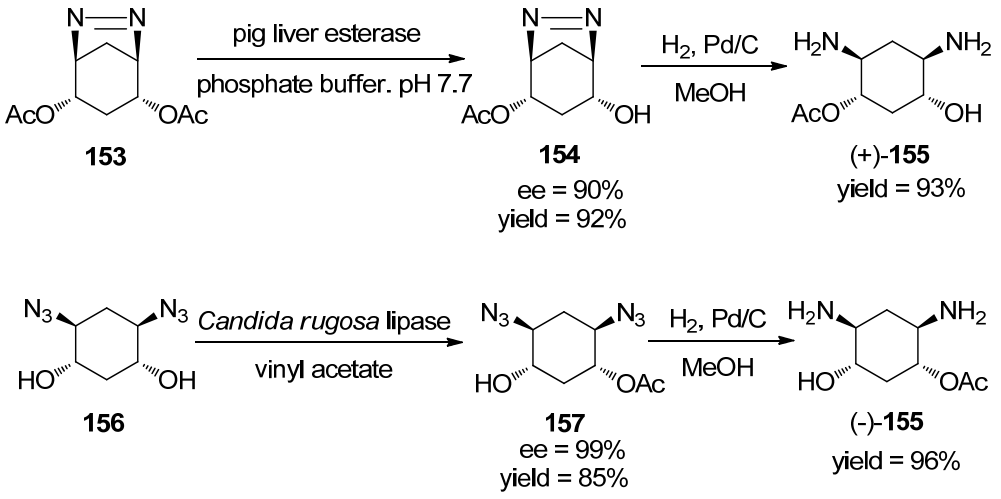
3A.2. Selected known Syntheses of Aminocyclitols:

Marco-Contelles *et al.*[18] reported a samarium diiodide mediated cyclization strategy of sugar-derived oxime ethers with an ε-aldehyde group **150** to synthesize aminocyclitols **150**, **151** and **152** in good overall yield with 22%, 24% and 20% diastereoselectivities, respectively (Scheme 2). However, in this approach 1, 2–*trans*-amino alcohol stereochemistry was not very selective.



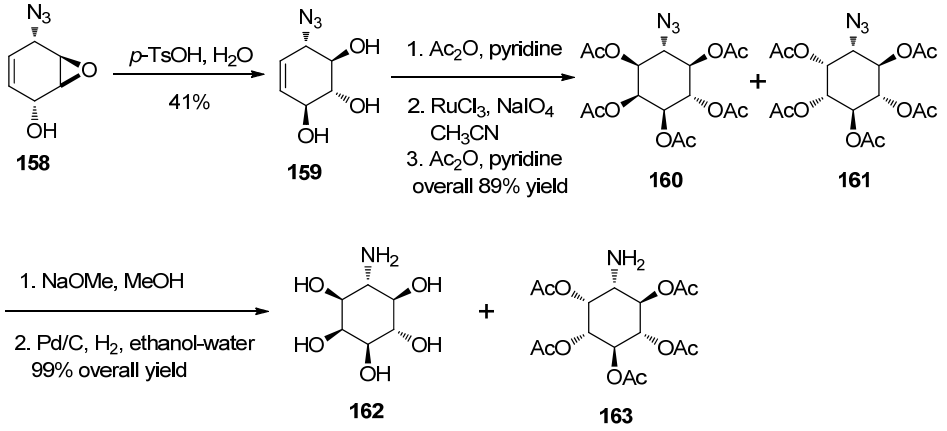
Scheme 2.

1,2-*trans* amino alcohol stereochemistry in the synthesis of the both enantiomeric pairs of the aminocyclitols **155** was achieved by Chenevert et al.[19] through enzymatic desymmetrization of 2, 5-dideoxystreptamine precursors **153** and **156** either through pig liver esterase hydrolysis or *Candida rugosa* lipase mediated acylation**,** respectively (Scheme 3).



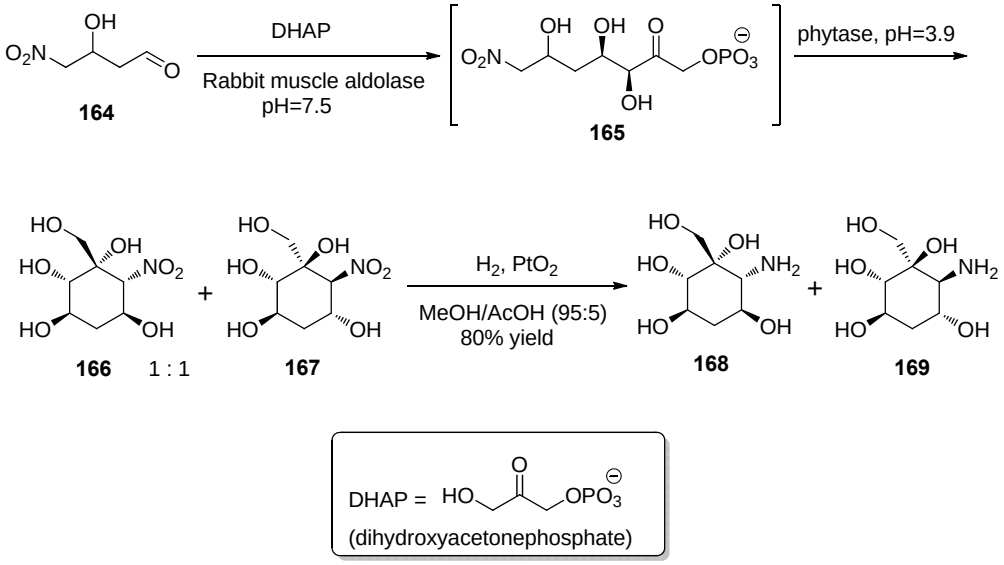
Scheme 3.

Podeschwa et al.[26] reported stereoselective synthesis of different 1, 2- *trans*-aminocyclitols by acid catalyzed ring opening of *alpha*-azido epoxide **158** followed by its transformation to aminocyclitols **162** and **163** (99% , 6 : 4 *dr*) as shown in Scheme 4.



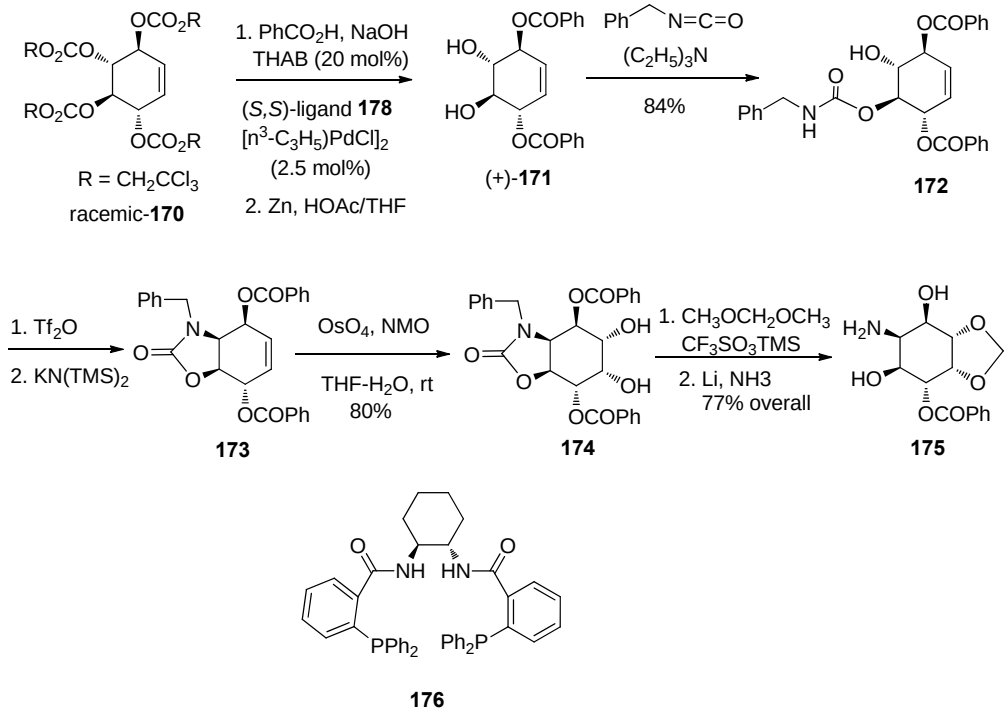
Scheme 4.

A straight forward chemo-enzymatic strategy is reported[27] for the synthesis of aminocyclitols and analogues of valiolamine. For Illustration, enzymatic aldol reaction of **164** with DHP followed by highly stereoselective intramolecular Henry reaction of resultant **165** gave two separable nitrocyclitols **166** and **167** in 1:1 ratio which was further reduced to produce aminocyclitols **168** and **169**, respectively (Scheme 5).



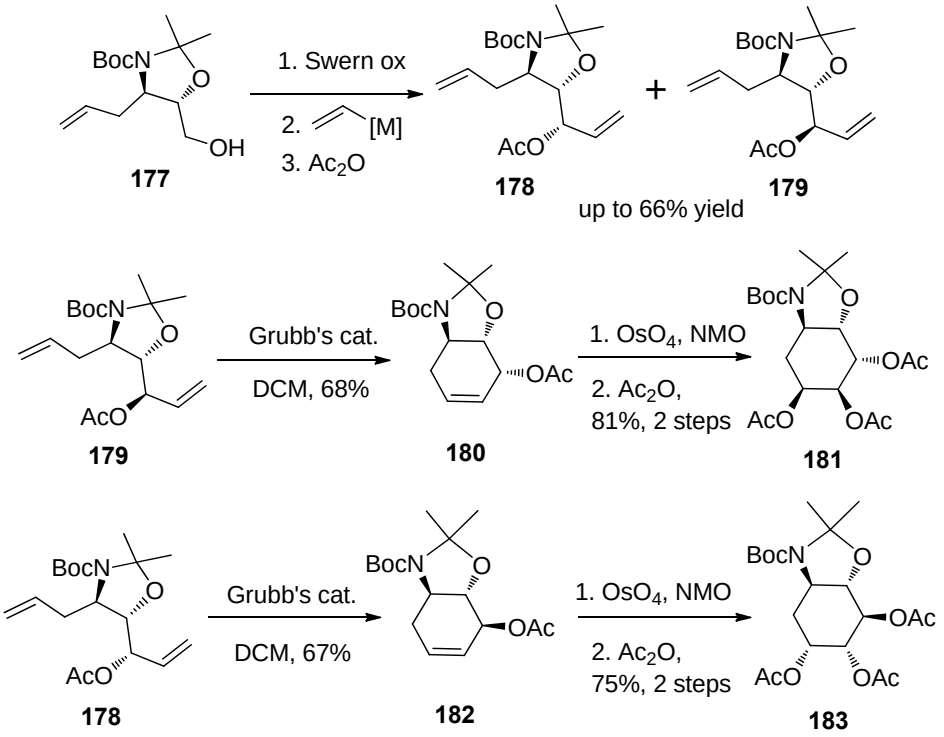
Scheme 5.

Trost *et al.*[28] reported the synthesis of aminocyclitol **175** of Hygromycin A by employing Pd-catalyzed kinetic resolution of racemic **170** as the key step to obtain optically pure (+)**-171** which was further transformed in to **175** *via* mono-carbamate **172** as shown in Scheme 6.



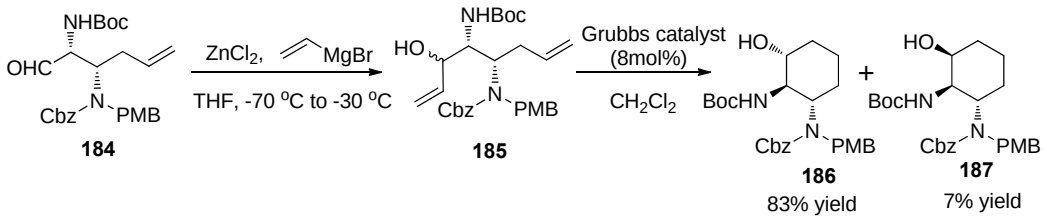
Scheme 6.

Two diastereomeric aminocyclitol skeleton **181** and **183** were constructed by Riera *et al.*[29] through RCM of corresponding **178** and **179** followed by dihydroxylation as depicted in Scheme 7.



Scheme 7.

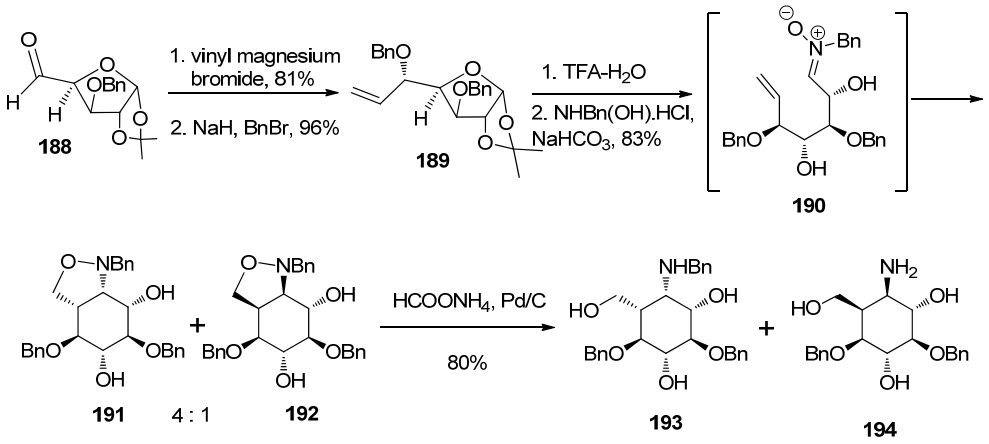
In another approach[20] RCM of the diastereomeric mixture **185** in DCM is reported to afford the separable cyclohexene derivatives **186** and **187** in 83% and 7% yield, respectively (Scheme 8).



Scheme 8.

Dhavale and co-workers have reported an intramolecular nitrone-olefine cycloaddition of **190** to obtain diastereomeric (4:1) mixtures of fused bicyclic isoxazolidines **191** and **192** in 83% yield with 4 : 1 ratio, respectively**.** The corresponding nitrone intermediate **190** was generated by the reaction of benzyl

hydroxylamine with D-glucose derived allylic alcohol **190**. Finally hydrogenation of isoxazolidines produced corresponding aminocyclitols **193** and **194** (Scheme 9).[30]



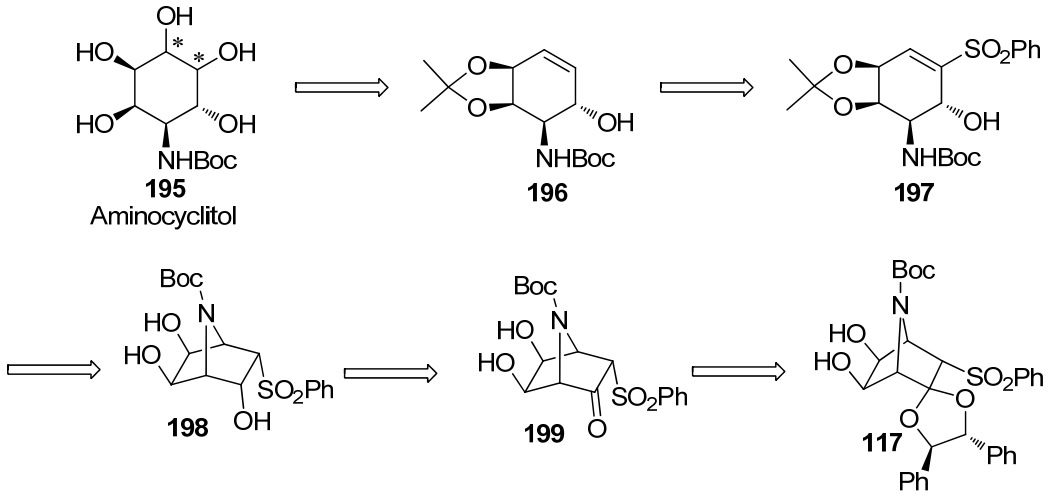
Scheme 9.

From the above discussion it is apparent that main challenge in this area lies in the stereoselective installation of 1,2-vicinal amino alcohol moiety, most importantly *trans*, in a functionalized cyclohexane moiety. Having established temperature-guided diastereoselectivity switch in the desymmetrization of *meso*-**103**, we turned our attention towards utilizing a desymmetrized chiral template **117** for the synthesis of aminocyclitols.

Section-B

3B.1. Retrosynthetic analysis:

A retrosynthetic analysis was worked out for the synthesis of aminocyclitol **195** as shown in Scheme 10. We considered that **198** could act as an advanced intermediate for the synthesis of **195** as its anionic rearrangement, as shown earlier from our group[23] was expected to produce **197** (Scheme 10).



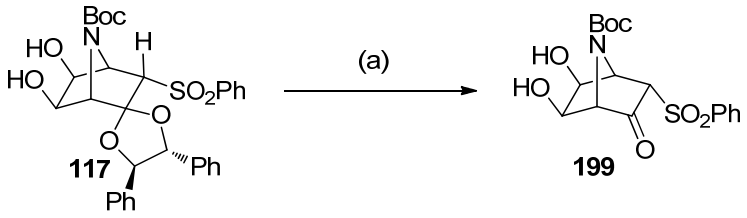
Scheme 10.

3B.2 Results and discussion

Towards executing our synthetic strategy, as perceived through retrosynthetic analysis, a suitable ketone precursor **199** ($[\alpha]^{25}_{D}$ +14.4 (*c* 1.0 $CHCl_3$)) was obtained in 71% yield by carrying out hydrogenation of the dihydroxylated compound **117** using Pd/C in the usual manner (Scheme 11). The IR spectrum of **199** showed a strong characteristic absorption band at 1710 cm^{-1}, indicating the presence of ketone functionality. Mass spectrum of **199** showed molecular ion peak at 384 (M^{+}+H).

With stereodefined ketone **199** in hand, we focused our attention on its stereoselective reduction to obtain corresponding –OH functionality in *endo* fashion,

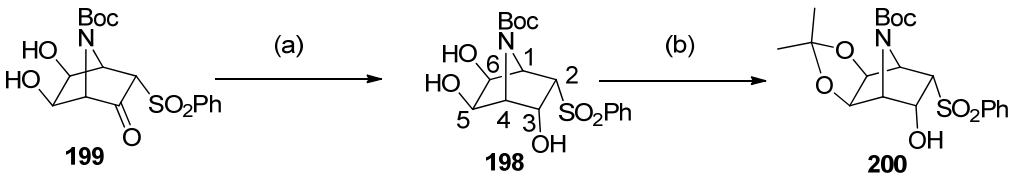
which was necessary for further establishment of 1,2-*trans* amino alcohol core on cyclohexane ring system.



Scheme 11.

Reagent and Condition: (a) H_2, Pd/C, AcOH, 60 psi, 20 h, 71%

Reduction of **199** at -78 °C produced alcohol **198** ($[\alpha]^{25}_{D}$ + 9.25 (*c* 1.0 MeOH)) exclusively in 77% yield (Scheme 12).[23] The configuration of *endo*-alcohol was unambiguously deduced from its ^{1}H NMR spectrum. For illustration, the H-2 proton in **198,** appeared as doublet of doublet (*J* = 9.3, 5.0 Hz) coupling with bridgehead H-1 and H-3 whereas H-3 appeared as doublet of doublet of doublet (*J* = 9.3, 7.1, 5.0 Hz) coupling with H-2, bridgehead H-4 and O-H proton, respectively. The coupling constant (J = 7.1 Hz) was confirmed due to coupling with –OH by recording ^{1}HNMR after D_2O exchange which simplified the coupling of H-3 to dd (*J* = 9.3, 5.0 Hz). Mass spectrum showed molecular ion peak at 408 (M^++Na).

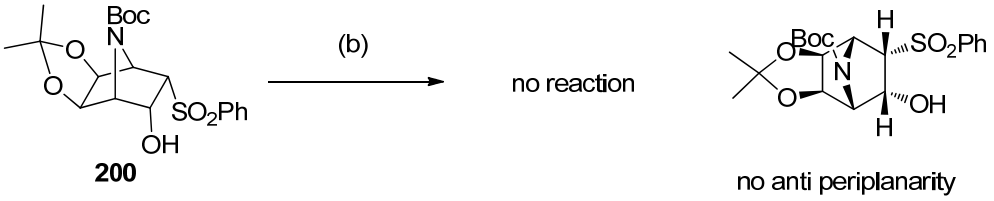


Scheme 12.

Reagents and Conditions : (a) $LiBH_4$, THF, -78 °C, 3.5 h, 77% (b) 2,2-dimethoxy propane, *p*-TSA, Acetone, 45 min.

Compound **198** was further transformed to corresponding acetonide protected derivative **200**, using 2,2-dimethoxy propane in the presence of catalytic amount of *p*-

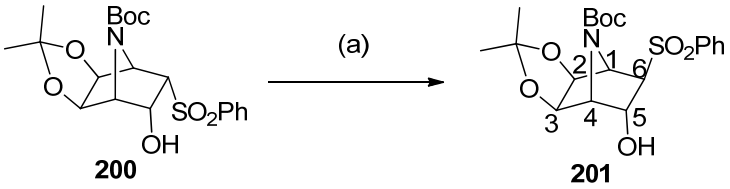
TSA, before carrying out anionic rearrangement to avoid any complications. Initially, we attempted to carry out the ring opening rearrangement of **200** using excess of methyl magnesium bromide, however, reaction failed to give any product (Scheme 13). This failure led us to look at the structure of **200** more closely which indicated that the orientation of sulfone moiety is *endo* and rearrangement requires antiperiplanarity between the bonds to be cleaved (Scheme 13). Therefore,



Scheme 13.

Reagent and Condition: (a) MeMgBr, THF, rt, 3 h

phenylsulfonyl moiety was epimerized using KO^{t}Bu to its corresponding epimer **201** ($[\alpha]^{26}_D$ -5.71 (*c* 1.0 $CHCl_3$)) (Scheme 14). The structure of **201** was confirmed on the basis of ^{1}H NMR in which characteristic H-6 proton at δ 3.12 appeared as doublet of doublet ($J_{1,2}$ = 4.30 Hz, $J_{1,3}$ = 13.21 Hz) and the intense interaction was found missing with H-1 in NOESY.

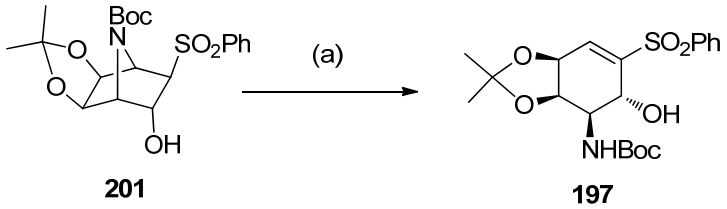


Scheme 14

Reagent and Condition: (a) K^{t}OBu, THF, 0 ^{o}C

Reaction of **201** with excess of methyl magnesium bromide in a THF solution at 0 °C produced **197** ($[\alpha]^{27}_D$ = +27.32 (*c* 1.0 $CHCl_3$)) in 68% overall yield from **200** (Scheme 15).[23] The rearrangement of **200** to **201** was supported by observing an

olefinic proton signal at δ 6.91 (d, 1H, *J* = 3.02 Hz) which was further confirmed by the molecular ion peak at 426 (M^+ +H) in the mass spectrum.

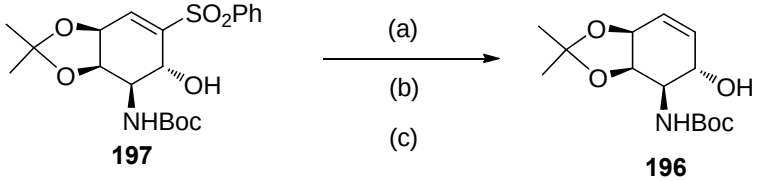


201 **197**

Scheme 15

Reagent and Condition: (a) MeMgBr, THF, rt, 2 h, 73%

Initially desulfonylation of **197** was attempted using Na-Hg (6%) in a mixture of THF: MeOH (1:1) solvent but it was unsuccessful possibly due to the presence of adjacent acetonide group.[24] Therefore, the same reaction was tried again with acetonide deprotected **197** and pleasingly it was desulfonylated successfully. The crude desuphonylated product was further protected and purified as **196** in 67% overall yield ($[\alpha]^{27}_D$ +14.77 (*c* 0.5 $CHCl_3$)) (Scheme 16). Structure of **196** was confirmed by observing two multiplets at δ 5.81 and δ 5.63 for olefinic protons in the ^{1}HNMR spectrum. The mass spectrum also showed molecular ion peak at 286 (M^+ +H).



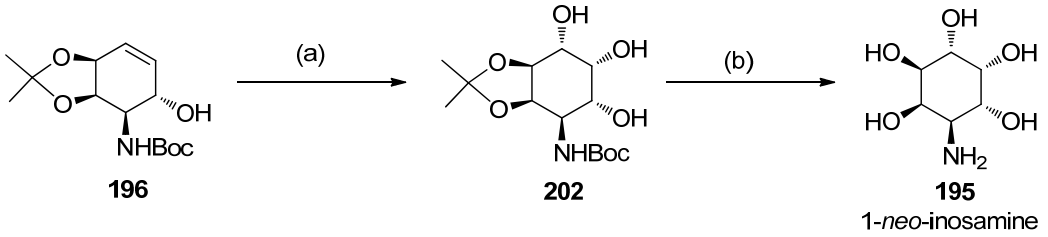
197 **196**

Scheme 16.

Reagents and Conditions : (a) 1*N* HCl, MeOH, rt (b) 6% Na-Hg, THF-MeOH (c) 2,2-dimethoxypropane, *p*-TSA, 67% over 3 steps

Dihydroxylation of **196** using OsO_4 (50% aqueous NMO, acetone:water (9:1) produced **202** in 61% yield ($[\alpha]^{26}_D$ +5.12 (*c* 0.5 MeOH)). In the ^{1}H NMR spectrum,

three multiplets, integrating each for one proton, appeared at δ 4.30, δ 4.05 and δ 3.96. Two doublet of doublets appearing at δ 3.68 ($J_{1,2}$ = 2.26 Hz, $J_{1,3}$ = 11.04 Hz) and δ 3.59 ($J_{1,2}$ = 2.01 Hz, $J_{1,3}$ = 8.28 Hz) also integrated for one proton each.



Scheme 17.

Reagents and Conditions : (a) OsO4, NMO, rt, 10h, 61% (b) HCl, dioxane

Deprotection of the acetonide as well as *N*-Boc moiety of **202** by refluxing with 10*N* HCl in dioxane solvent delivered aminocyclitol (1-*neo*-inosamine **195**), however, due to its high polarity and solubility in water it was characterized as **202** only (Scheme 17).[25]

3B.3. Conclusion and Future Outlook:

A conceptually new temperature guided desymmetrization of a *meso*-7-azabicyclic system and its application in the synthesis of 1-*neo*-inosamine is demonstrated. Since aminocyclitols constitute a large group of natural and synthetic products which are of great synthetic importance due to their potential biological activities as well as their synthetic usefulness in the synthesis of other natural or pharmaceutical compounds, this stereoselective approach for their syntheses will have great significance in synthesizing other aminocyclitols.

3B.4. Crystal data:

X-ray Crystal data for Compound 117

Single crystals of the compound were grown by slow evaporation of the solution mixture in pet. ether and ethyl acetate. Colourless crystal of approximate size 0.36 x 0.31 x 0.30 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50kV and 30mA.

Crystal data and structure refinement for **117**.

Emperical formula	C_{31} H_{33} N O_8 S
Formula weight	579.64
Temperature	298(2) K
Wavelength	0.71073
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 9.424(3) alpha = 90 deg
	b = 12.080(3) beta = 95 deg
	c = 13.222(4) gamma = 90 deg
Volume	1497.1(7)
Z	2
Calculated density	1.286 g/cc
Absorption coefficient	0.159 mm^-1
F(000)	612
Crystal size	0.36 x 0.31 x 0.30 mm
Theta range for data collection	1.55 to 25.30 deg
Reflections collected	7692
Completeness to theta = 25.30	
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4693 / 1 / 458
Goodness-of-fit on F^2	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0182, wR2 = 0.0291

X-ray Crystal data for Compound 120

Single crystals of the compound were grown by slow evaporation of the solution mixture in pet. ether and ethyl acetate. Colourless crystal of approximate size 0.38 x 0.32 x 0.30 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50kV and 30mA.

Crystal data and structure refinement for **120**.

Emperical formula	C_{31} H_{33} N O_8 S
Formula weight	579.64
Temperature	298(2) K
Wavelength	0.71073
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 9.4194(18) alpha = 90 deg
	b = 12.057(2) beta = 95 deg
	c = 13.214(3) gamma = 90 deg
Volume	1492.7(5)
Z	2
Calculated density	1.290 g/cc
Absorption coefficient	0.159 mm^-1
F(000)	612
Crystal size	0.38 x 0.32 x 0.30 mm
Theta range for data collection	1.55 to 25.25 deg
Reflections collected	10842
Completeness to theta = 25.25	
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5367 / 1 / 450
Goodness-of-fit on F^2	1.099
Final R indices [I>2sigma(I)]	R1 = 0.0278, wR2 = 0.0285

X-ray Crystal data for Compound 121

Single crystals of the compound were grown by slow evaporation of the solution mixture in pet. ether and ethyl acetate. Colourless crystal of approximate size 0.32 x 0.28 x 0.26 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50kV and 30mA.

Crystal data and structure refinement for **121**.

Emperical formula	C_{31} H_{33} N O_8 S
Formula weight	579.64
Temperature	298(2) K
Wavelength	0.71073
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 10.900(3) alpha = 90 deg
	b = 11.523(3) beta = 90 deg
	c = 24.278(7) gamma = 90 deg
Volume	3049.3(15)
Z	4
Calculated density	1.263 g/cc
Absorption coefficient	0.156 mm^-1
F(000)	1224
Crystal size	0.32 x 0.28 x 0.26 mm
Theta range for data collection	1.68 to 25.27 deg
Reflections collected	15750
Completeness to theta = 25.27	
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5512 / 0 / 466
Goodness-of-fit on F^2	0.985
Final R indices [I>2sigma(I)]	R1 = 0.0283, wR2 = 0.0407

3B.5. References:

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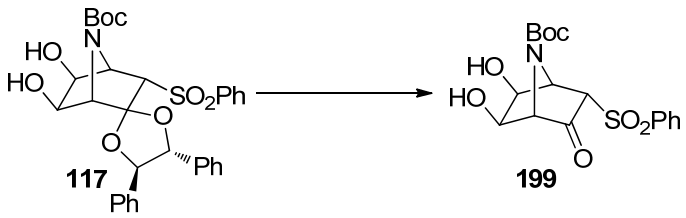
3B.6. Experimental section:

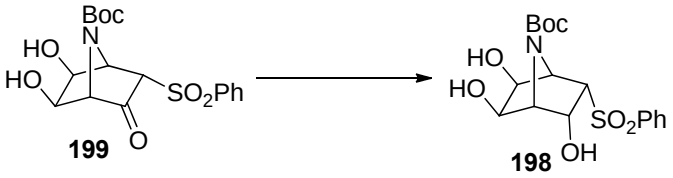
(1*R*,2*S*,3*R*,4*S*,6*S*)-*tert*-butyl 2,3-dihydroxy-5-oxo-6-(phenylsulfonyl)-7-azabicyclo [2.2.1] heptanes-7-carboxylate (199):



199 was prepared in the same manner as described for (+)-**102** except that **117** was used. Usual work-up followed by column chromatography on silica gel provided optically pure 17 as a white solid in71% yield. R_f = 0.5 (SiO_2, methanol : dichloromethane, 1:9).

m.p.	:	138-140 °C
$[\alpha]^{25}_D$	:	+14.4 (*c* 1.0 $CHCl_3$)
IR υ_{max} cm^{-1} in $CHCl_3$	:	3623, 1746, 1710, 1248, 1142
^{1}H NMR (400 MHz, $CDCl_3$) (rotamers)[1] δ	:	7.86-788 (d, 2H, *J* = 7.58 Hz), 7.70-7.73 (dd, 1H, $J_{1,2}$ = 7.33 Hz, $J_{1,3}$ = 7.58 Hz), 7.58-7.61 (t, 2H, *J* = 7.83 Hz), 4.84-4.85 (d, 1H, *J* = 7.33 Hz), 4.22 (br s, 1H), 3.94-4.01 (m, 1H), 3.65-3.74 (m, 3H), 3.47 (br s, 1H), 1.46 (s, 9H)
^{13}C NMR (100 MHz, $CDCl_3$) δ	:	199.7, 155.0, 134.7, 129.4, 129.0, 82.3, 72.1, 71.7, 62.1, 57.5, 53.3, 29.6
Mass (ESI): *m/z*	:	384 (M^++H)

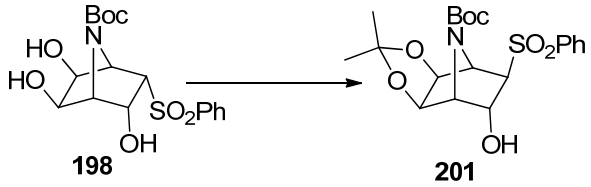
(1*R*,2*S*,3*R*,4*S*,5*R*,6*S*)-*tert*-butyl-2,3,5-trihydroxy-6-(phenylsulfonyl)-7-azabicyclo[2.2.1] heptane-7-carboxylate (198):



To a solution of **199** (1 g, 2.61 mmol) in anhydrous THF (15 mL) was added a solution of $LiBH_4$ (1.30 mL, 2.60 mmol, 2.0 M) at -78 ^oC. After stirring the mixture for 3 h, saturated aqueous solution of NH_4Cl was added and allowed to warm to room temperature while stirring. The solution was diluted with ethyl acetate, washed with water and brine and solvent was evaporated under reduced pressure. The resultant residue was purified by column chromatography (SiO_2, methanol : dichloromethane, 1:5→2:5) to obtain **198** (0.77 g, 77%) as a white solid. $\boldsymbol{R_f}$ = 0.3 (SiO_2, methanol : dichloromethane, 2:8)

m.p.	:	158-161 °C
$[\alpha]^{25}_D$	:	+9.25 (*c* 1.0 MeOH)
IR υ_{max} cm^{-1} in $CHCl_3$	:	3440, 2962, 1686, 1155
^{1}H NMR (500 MHz, $CDCl_3$) δ	:	7.94-7.95 (d, 2H, *J* = 7.43 Hz), 7.68-7.71 (t, 1H, *J* = 7.43 Hz), 7.59-7.62 (dd, 2H, *J* = 7.97 Hz, 7.43Hz), 5.03 (br s, 1H), 4.67-4.69 (dd, 1H, *J* = 5.78 Hz, 6.05 Hz), 4.48-4.63 (m, 1H), 4.29 (br s, 1H), 4.23-4.24 (d, 1H, *J* = 4.67 Hz), 3.67 (br s, 1H), 3.65-3.68 (dd, 1H, $J_{1,2}$ = 4.95 Hz, $J_{1,3}$ = 9.35 Hz), 3.12 (br s, 1H), 3.00 (br s, 1H), 1.39 (s, 9H)
^{13}C NMR (125 MHz, $CDCl_3$) δ	:	155.3, 139.6, 134.1, 129.5, 127.9, 81.4, 69.0, 68.6, 67.8, 66.9, 64.4, 63.8, 28.0
Mass (ESI): *m/z*	:	386 (M^++H)

(3a*R*,4*R*,5*R*,6*R*,7*R*,7a*S*)-*tert*-butyl-5-hydroxy-2,2-dimethyl-6-(phenylsulfonyl) hexahydro-4,7-epiminobenzo[*d*][1,3]dioxole-8-carboxylate (201):



To a solution of **198** (0.5 g, 1.29 mmol) in dry acetone (6 mL) was added 2,2-dimethoxy propane (0.7 mL), *p*-TSA (15 mg) and stirred for 30 min. After the completion of the reaction, it was basified using aqueous solution of $NaHCO_3$ and was extracted with ethyl acetate. Organic layer was concentrated under reduced pressure and further proceeded using the crude product.

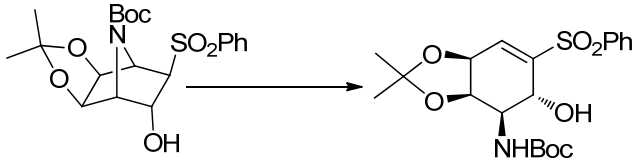
To a solution of KO^tBu (0.053 g, 0.47 mmol) in anhydrous THF (1 mL) was added to above extracted crude reaction mixture in THF (2 mL) at 0 ^oC. The reaction mixture was stirred at the same temperature for 3 min and quenched by adding 1*N* HCl followed by the addition of saturated $NaHCO_3$ solution. Usual work-up followed by column chromatography (SiO_2, ethyl acetate : pet ether, 2:5→3:5) yielded **201** (0.082 g, 68% overall) as a white solid. $\boldsymbol{R_f}$ = 0.3 (SiO_2, ethyl acetate : pet ether, 3:7)

m.p.	:	163-164 °C
$[\alpha]^{26}_D$	:	-5.71 (*c* 1.0 $CHCl_3$)
IR υ_{max} cm^{-1} in $CHCl_3$	:	3430, 1705, 1670, 1148
^{1}H NMR (500 MHz, DMSO-d^6) (rotamers)^1 δ	:	7.64-7.90 (m, 5H), 6.02-6.08 (m,1H), 4.63-4.65 (dd, 1H, $J_{1,2}$ = 5.5 Hz, 6.05 Hz), 4.32-4.44 (m, 2H), 4.22 (rotamers), 4.06-4.09 (m, 2H), 3.12-3.15 (dd, 1H, $J_{1,2}$ = 4.30 Hz, $J_{1,3}$ = 13.21 Hz), 1.16-1.37 (15H)
^{13}C NMR (100 MHz, DMSO-d^6) δ	:	152.6, 152.5, 137.9, 137.7, 134.5, 134.3, 129.8, 129.7, 128.8, 128.6, 110.5, 110.4, 80.4, 80.2, 79.1, 77.4, 77.0,

69.5, 68.9, 68.4, 68.1, 62.8, 61.9, 60.88, 60.0, 28.3, 28.2, 25.6, 25.5, 24.4, 24.34

Mass (ESI): *m/z* : 426 (M^++H)

***tert*-butyl-((3a*R*,4*R*,5*R*,7a*S*)-5-hydroxy-2,2-dimethyl-6-(phenylsulfonyl)-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl)carbamate (197):**



The solution of **201** (0.25 g, 0.588 mmol) in anhydrous THF (10 mL) was degassed by passing a slow stream of argon for 5-10 min. A THF-toluene solution of methyl magnesium bromide (2.10 mL, 2.94 mmol) was added slowly to the stirred solution of compound portion wise at 0 °C. The reaction mixture was further stirred for an additional 2 h. After the completion of the reaction, it was quenched with H_2O. After usual workup with ethyl acetate, the crude product was purified by column chromatography (SiO_2, ethyl acetate : pet ether, 2:3→1:1) to obtain **197** (0.182 g, 73%) as a solid. R_f = 0.3 (SiO_2, ethyl acetate : pet ether, 4:6)

m.p. : 156-157 °C

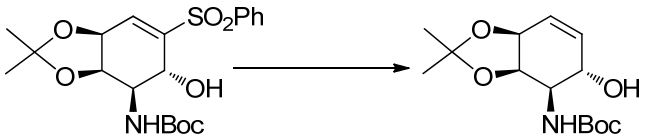
$[\alpha]^{27}_D$: +27.32 (*c* 1.0 $CHCl_3$)

IR υ_{max} cm^{-1} in $CHCl_3$: 3438, 1717, 1670, 1585, 1370, 1145

^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.90-7.91 (d, 2H, *J* = 7.43 Hz), 7.59-7.62 (dd, 1H, *J* = 7.15 Hz, 7.43Hz), 7.50-7.53 (t, 2H, *J* = 7.70 Hz), 6.91-6.92 (d, 1H, *J* = 3.02 Hz), 4.92-4.94 (d, 1H, *J* = 8.25 Hz), 4.73-4.77 (m, 1H), 4.42-4.44 (m, 1H), 3.97-4.00 (m, 1H), 3.31-3.32 (d, 1H, *J* = 4.13 Hz), 1.27-1.38 (15H)

^{13}C NMR (100 MHz, $CDCl_3$) δ	:	25.7, 27.1, 28.1, 53.5, 66.1, 71.6, 74.2, 80.2, 110.2, 128.2, 128.9, 133.4, 135.8, 139.5, 142.3, 156.0
Mass (ESI): *m/z*	:	426 (M^++H)

***tert*-butyl-((3a*R*,4*R*,5*S*,7a*S*)-5-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo [*d*][1,3] dioxol-4-yl)carbamate (196):**



A solution of **197** (0.2 g, 0.70 mmol) in THF and 1*N* HCl (0.3 mL) was first stirred at rt for 20 min. After complete disappearance of starting material solvent was removed and crude product was subjected to desulfonylation by following the identical experimental protocol as described for **122** except that THF : MeOH (1:1) was used as the solvent. Furthermore, to this crude desulfonylated crude compound dissolved in dry acetone (6 mL) was added 2,2-dimethoxy propane (excess), *p*-TSA (30 mg) and stirred for 1.5 h. After the completion of the reaction, it was basified using aqueous solution of $NaHCO_3$, extracted with ethyl acetate concentrated. The crude product was purified by column chromatography (SiO_2, ethyl acetate : pet ether, 3:7→2:3) to obtain **196** (0.089 g, 67% over all yield) as a solid. R_f = 0.5 (SiO_2, ethyl acetate : pet ether, 4:6).

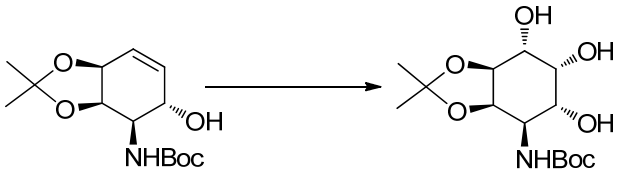
m.p.	:	163-164 °C
$[\alpha]^{27}_D$	:	+14.77 (*c* 0.5 $CHCl_3$)
IR υ_{max} cm^{-1} in $CHCl_3$	:	3610, 3093, 1638, 1572, 1240
^{1}H NMR (400 MHz, $CDCl_3$) δ	:	5.81-5.83 (m, 1H), 5.63-5.65 (m, 1H), 5.24 (br s, 1H), 4.62-4.63 (m, 1H), 4.36-4.38 (m, 1H), 4.21-4.24 (m, 1H)

3.71-3.75 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ : 157.2, 131.9, 130.7, 109.5, 80.5, 75.3, 73.1, 68.7, 55.6, 28.3, 27.4, 26.4

Mass (ESI): *m/z* : 286 (M^++H)

***tert*-butyl-((3a*R*,4*R*,5*R*,6*R*,7*R*,7a*S*)-5,6,7-trihydroxy-2,2-dimethyl-hexahydrobenzo[*d*][1,3] dioxol-4-yl)carbamate (202):**



196 **202**

202 was prepared from **196** by following the experimental protocol as described for **117** (0.047 g, 61% yield) solid. R_f = 0.4 (SiO_2, methanol : dichloromethane, 3:7)

m.p. : 247-248 °C

$[\alpha]^{26}_D$: +5.12 (*c* 0.5 MeOH)

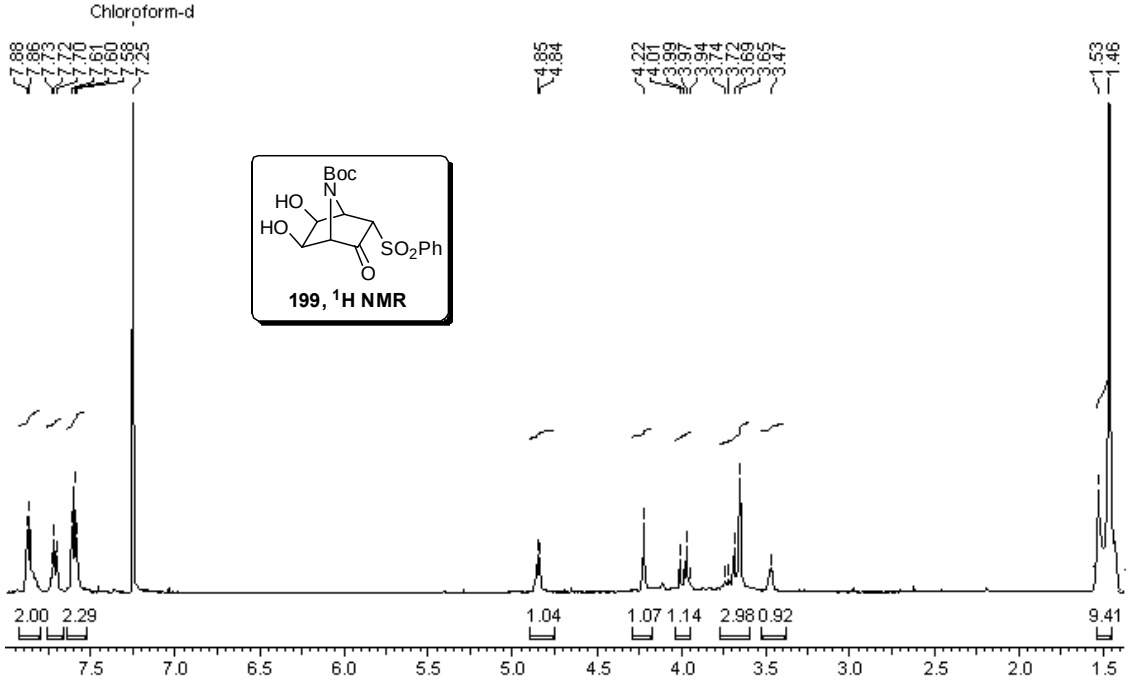
IR υ_{max} cm^{-1} : 3625, 3110, 1612, 1053

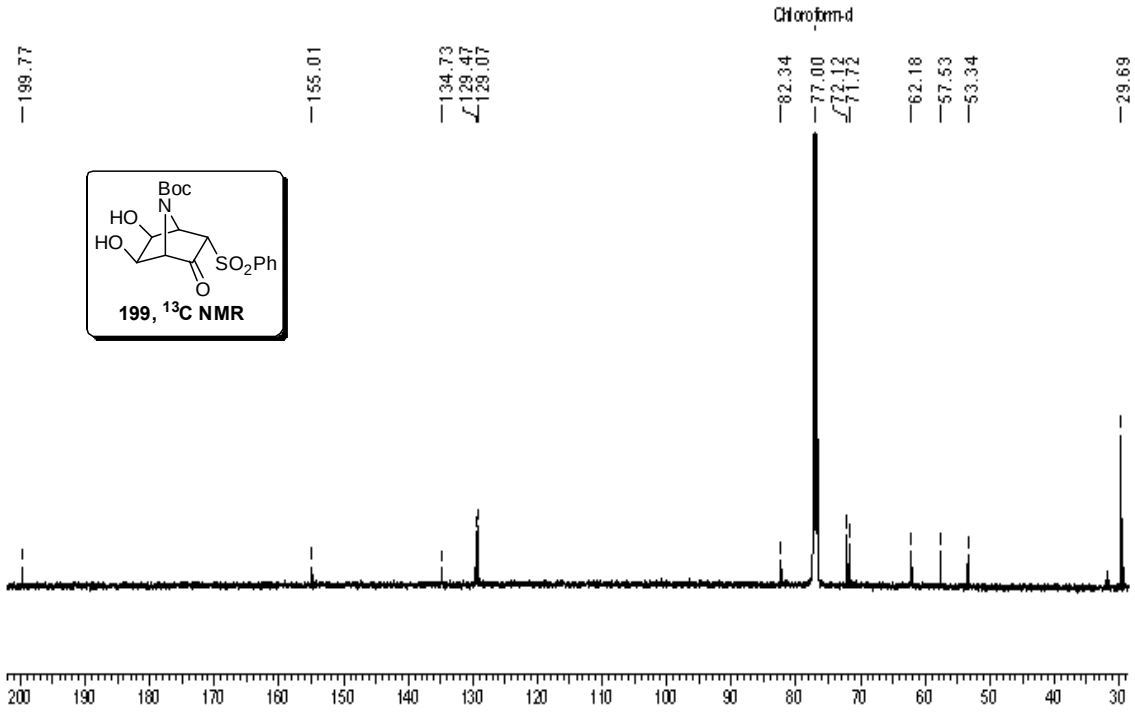
^{1}H NMR (500 MHz, D_2O) δ : 4.30-4.33 (m, 1H), 4.05-4.08 (m, 1H), 3.96-4.00 (m, 1H), 3.91 (br s, 1H), 3.68-3.71 (dd, 1H, $J_{1,2}$ = 2.26 Hz, $J_{1,3}$ = 11.04 Hz), 3.59-3.62 (dd, 1H, $J_{1,2}$ = 2.01 Hz, $J_{1,3}$ = 8.28 Hz), 1.38, 1.37, 1.32, 1.35 (15H)

^{13}C NMR (125 MHz, D_2O) δ : 160.2, 117.7, 100.1, 81.4, 73.3, 68.4, 63.1, 59,6, 52.7, 27.4, 25.1

Mass (ESI): *m/z* : 320 (M^++H)

3B.7. Spectra:


Chloroform-d
7.88
7.86
7.73
7.72
7.70
7.61
7.60
7.58
7.25
4.85
4.84
4.22
4.01
3.99
3.97
3.94
3.74
3.72
3.69
3.65
3.47
1.53
1.46
Boc
N
HO
HO
SO2Ph
O
199, 1H NMR
2.00
2.29
1.04
1.07
1.14
2.98
0.92
9.41
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5


Chloroform-d
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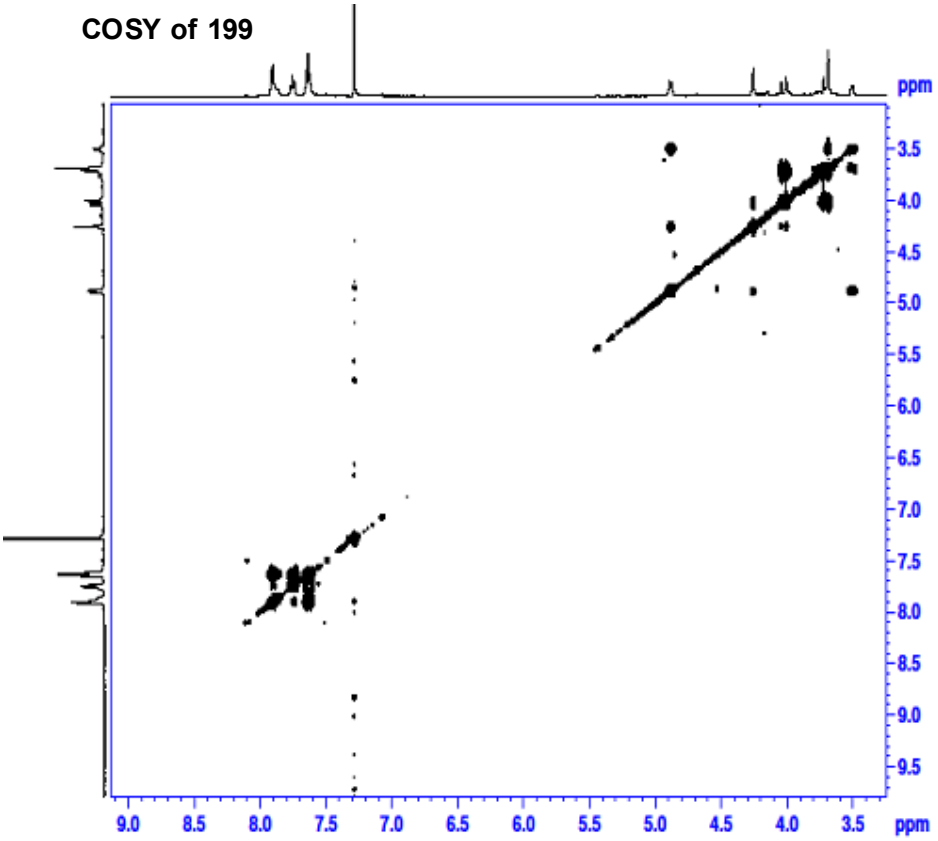
155.01
134.73
129.47
129.07
82.34
77.00
72.12
71.72
62.18
57.53
53.34
29.69
Boc
N
HO
HO
SO2Ph
O
199, 13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30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7.0
7.5
8.0
8.5
9.0
9.5
9.0
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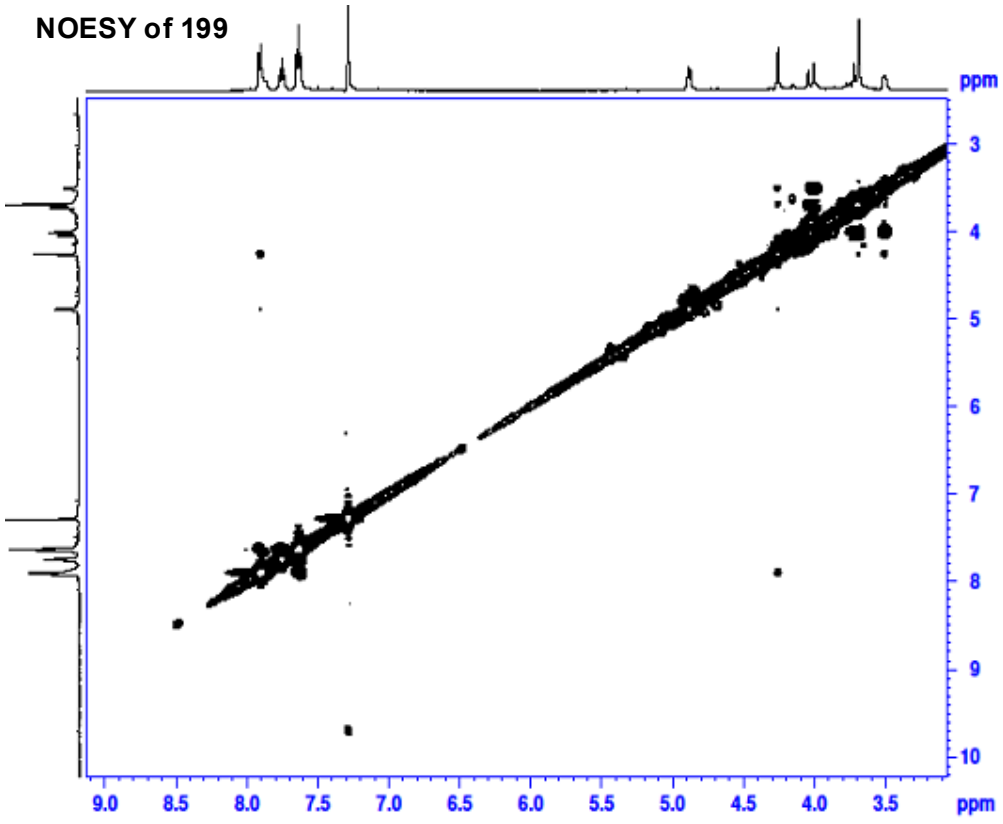
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm


NOESY of 199
ppm
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4
5
6
7
8
9
10
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8.5
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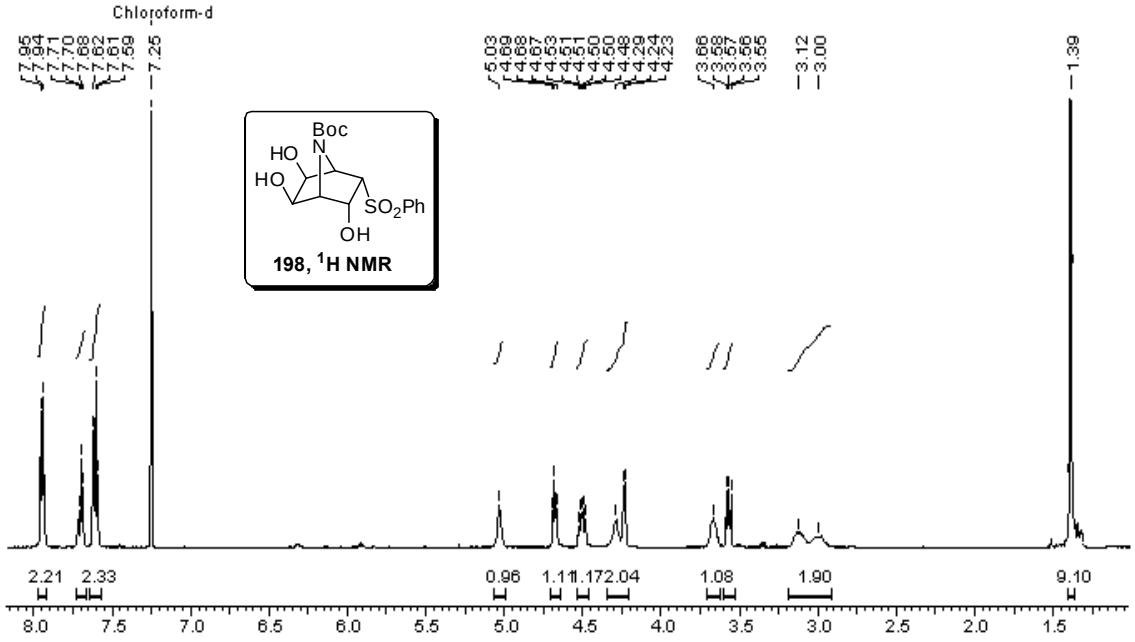
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm


Chloroform-d
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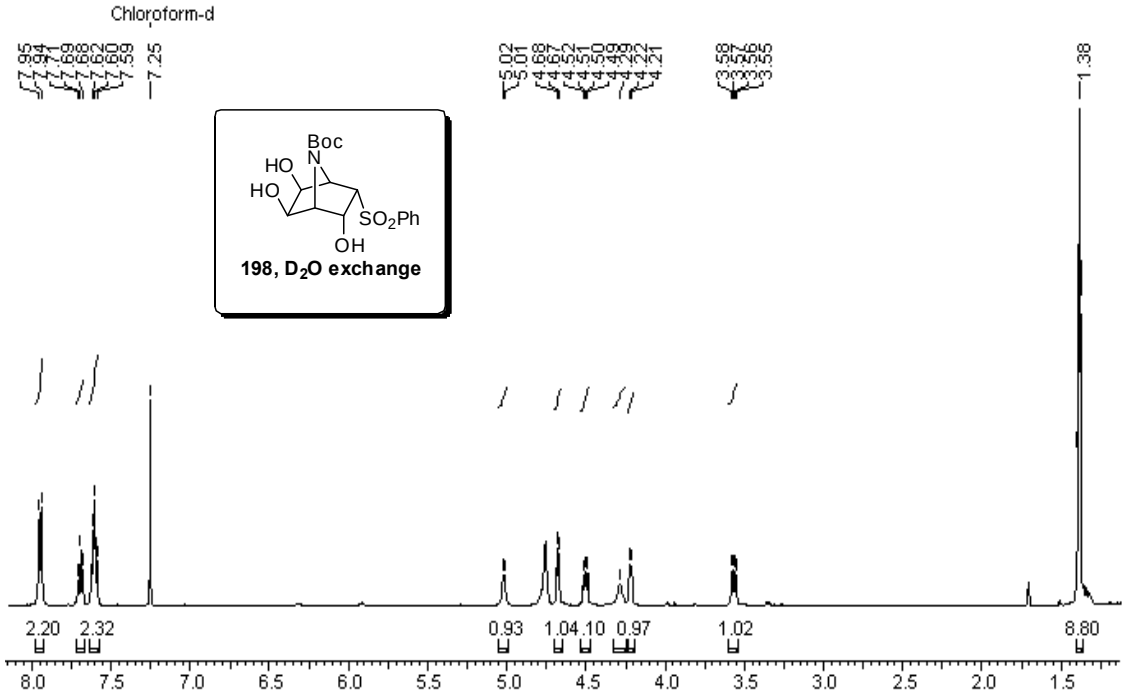
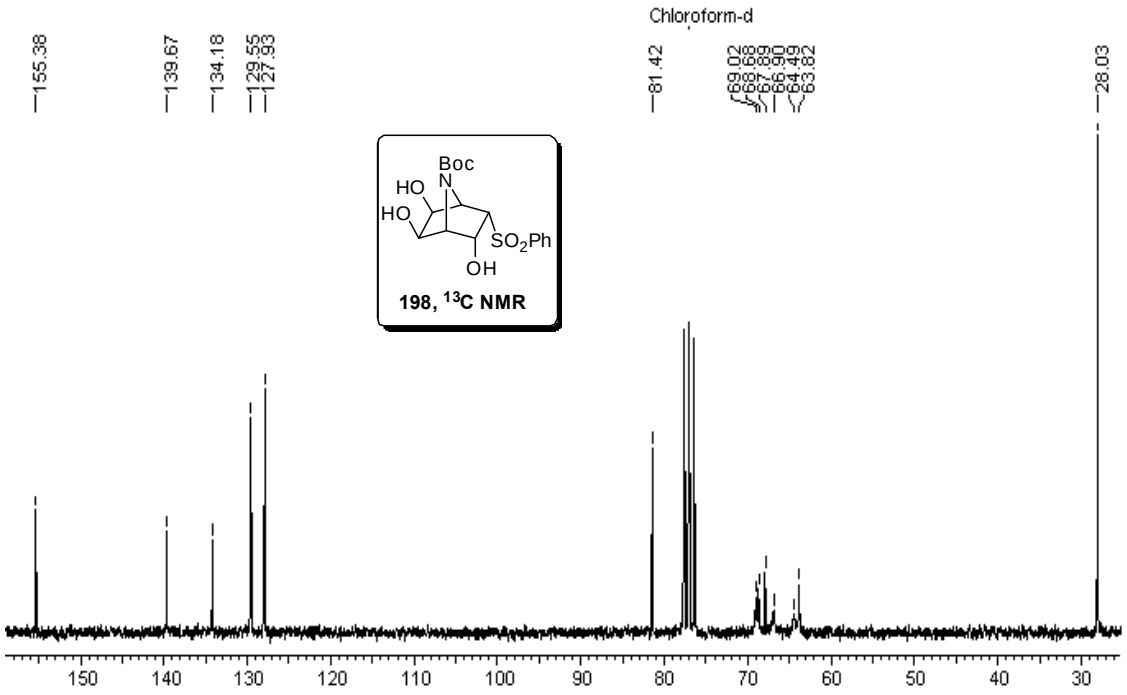
7.94
7.71
7.70
7.68
7.62
7.61
7.59
7.25
5.03
4.69
4.68
4.67
4.63
4.61
4.51
4.50
4.48
4.29
4.24
4.23
3.66
3.58
3.57
3.56
3.55
3.12
3.00
1.39
Boc
N
HO
HO
SO2Ph
OH
198, 1H NMR
2.21
2.33
0.96
1.11
1.17
2.04
1.08
1.90
9.10
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5


Chloroform-d
7.95
7.94
7.71
7.69
7.68
7.62
7.60
7.59
7.25
5.02
5.01
4.68
4.67
4.52
4.51
4.50
4.49
4.22
4.21
3.58
3.57
3.56
3.55
1.38
Boc
N
HO
HO
SO2Ph
OH
198, D2O exchange
2.20
2.32
0.93
1.04
1.10
0.97
1.02
8.80
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5


Chloroform-d
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139.67
134.18
129.55
127.93
81.42
69.02
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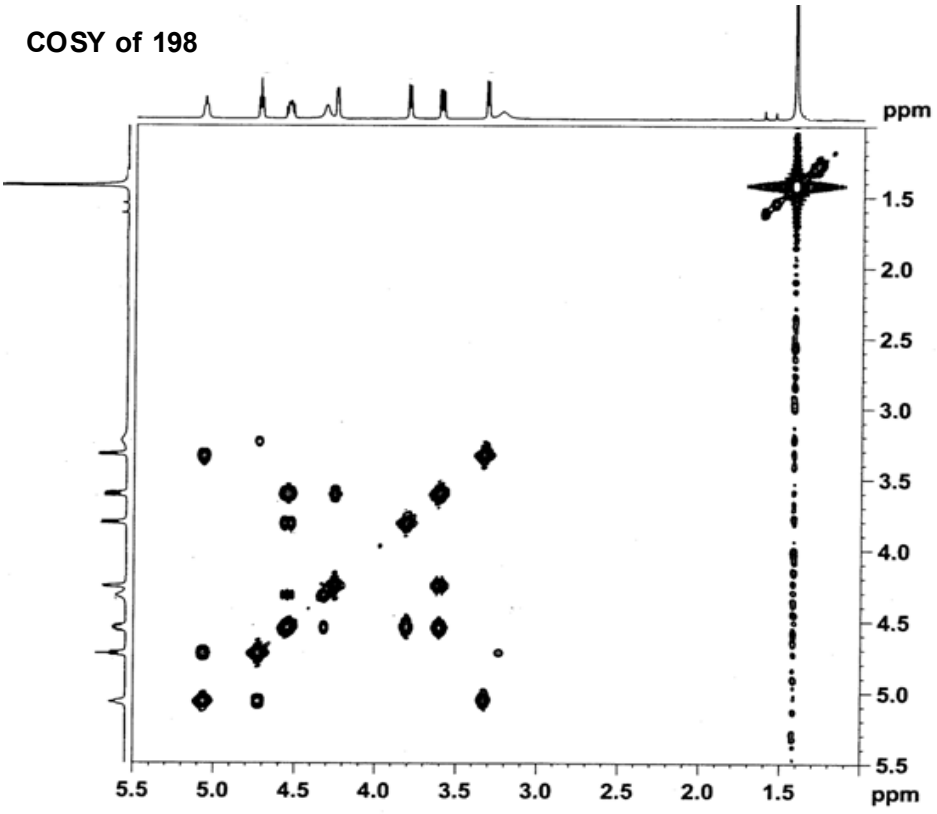
67.89
66.90
64.49
63.82
28.03
Boc
N
HO
HO
SO2Ph
OH
198, 13C NMR
150
140
130
120
110
100
90
80
70
60
50
40
30

COSY of 198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4.5
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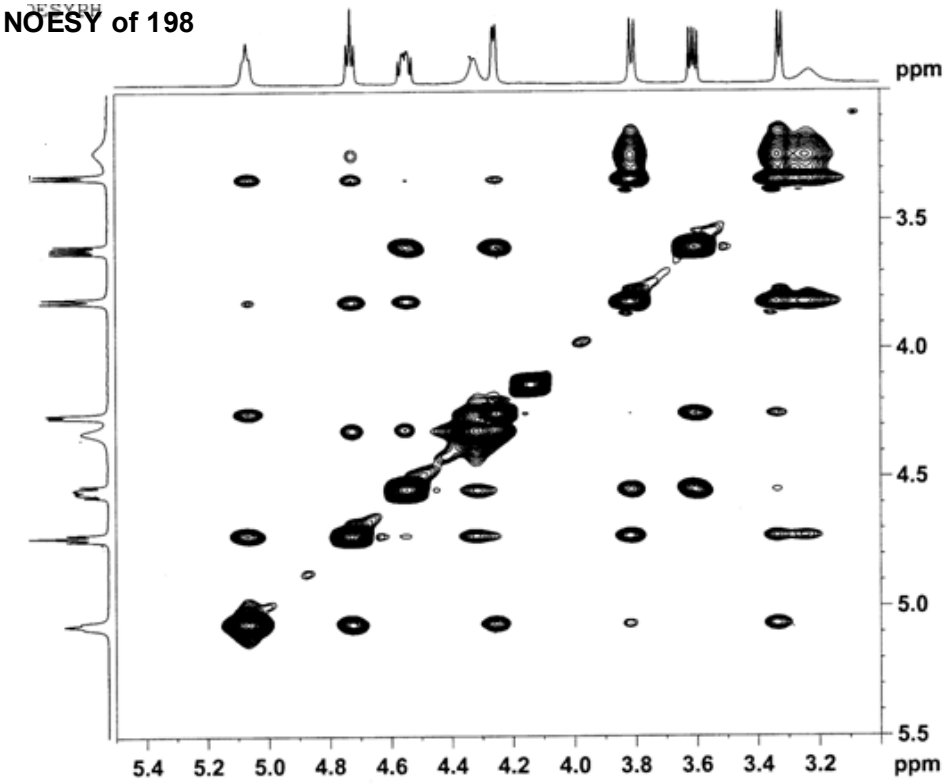
3.5
3.0
2.5
2.0
1.5
ppm

NOESY of 198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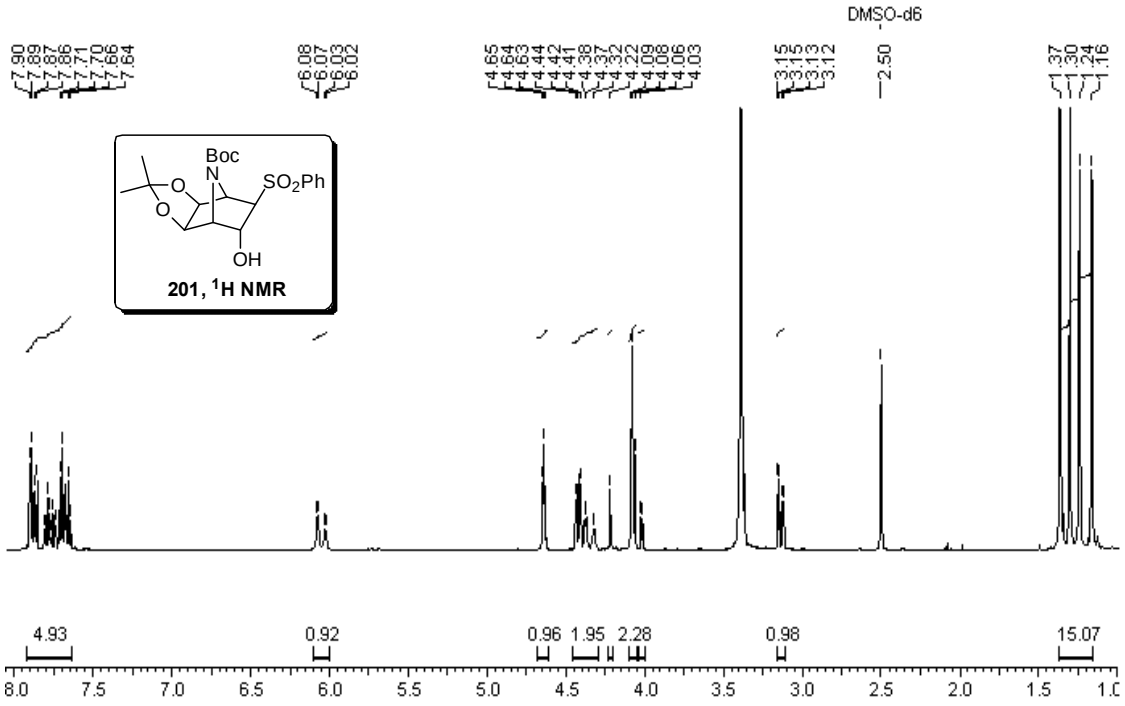
ppm


DMSO-d6
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7.86
7.71
7.70
7.66
7.64
6.08
6.07
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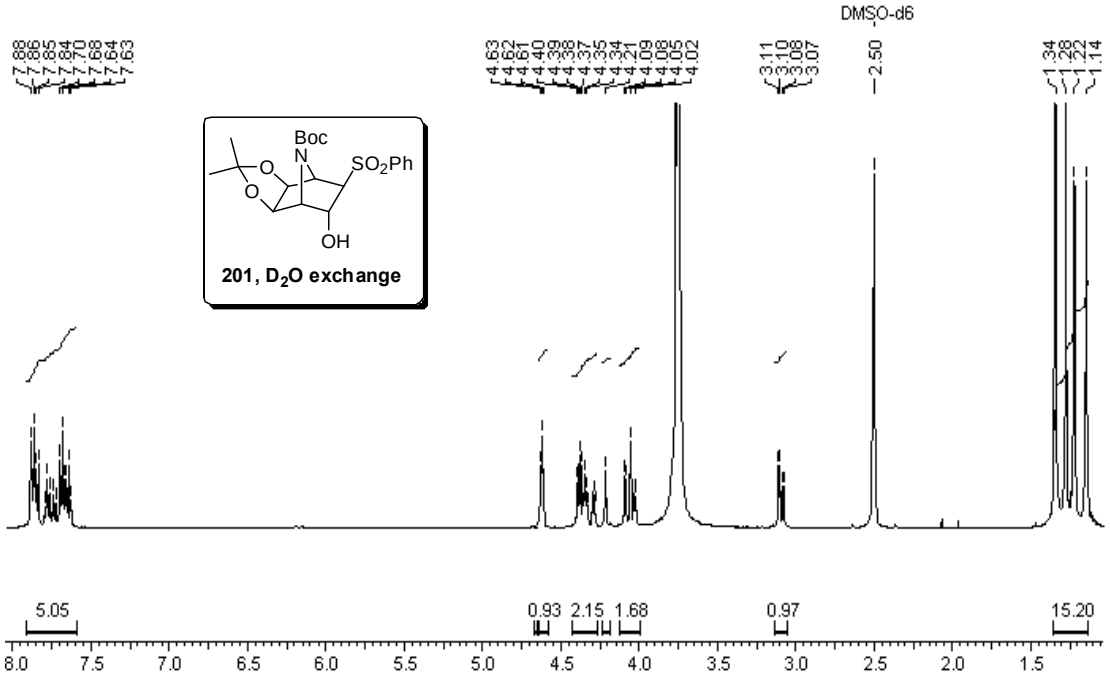
4.63
4.44
4.42
4.41
4.38
4.37
4.32
4.22
4.09
4.08
4.06
4.03
3.15
3.15
3.13
3.12
2.50
1.37
1.30
1.24
1.16
Boc
N
O
O
SO2Ph
OH
201, 1H NMR
4.93
0.92
0.96
1.95
2.28
0.98
15.07
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0


DMSO-d6
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7.86
7.85
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7.70
7.68
7.64
7.63
4.63
4.62
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4.39
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3.08
3.07
2.50
1.34
1.28
1.22
1.14
Boc
N
SO2Ph
O
O
OH
201, D2O exchange
5.05
0.93
2.15
1.68
0.97
15.20
8.0
7.5
7.0
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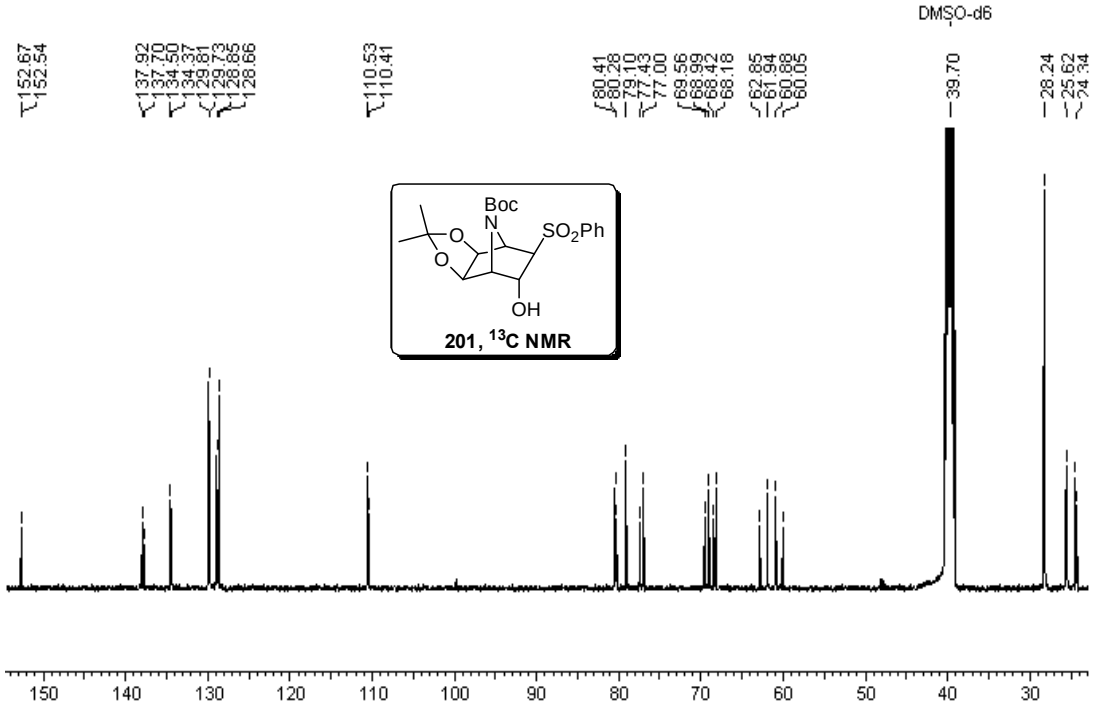
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5


DMSO-d6
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152.54
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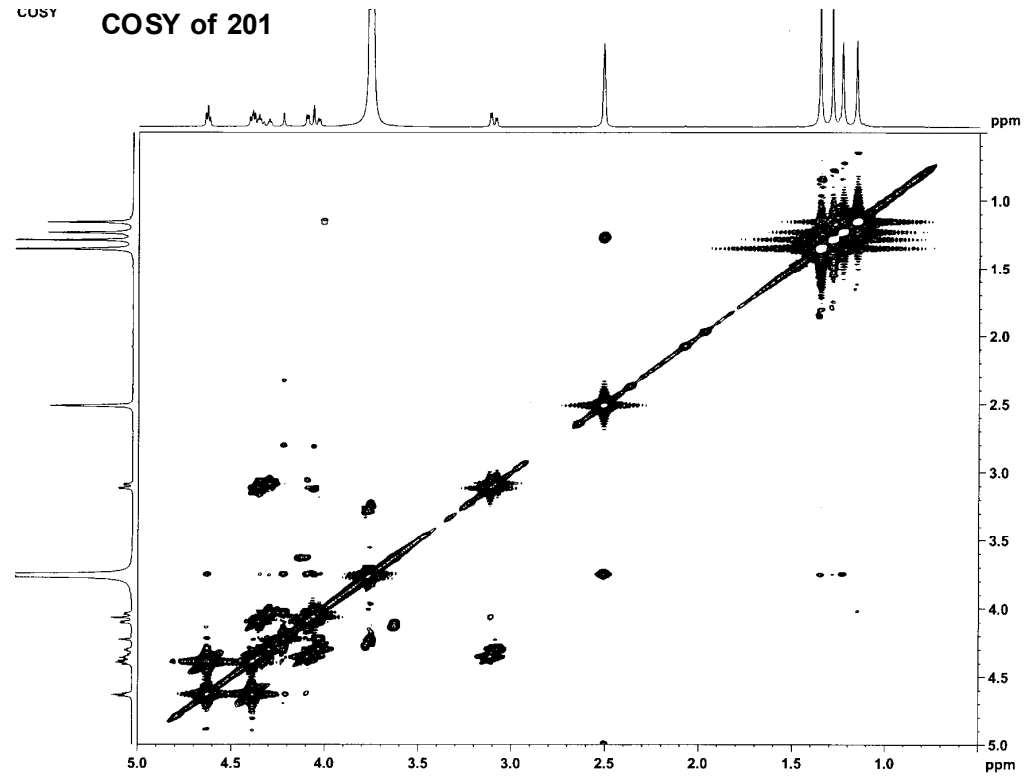
134.50
134.37
129.81
129.73
128.85
128.66
110.53
110.41
80.41
80.28
79.10
77.43
77.00
69.56
68.99
68.42
68.18
62.85
61.94
60.88
60.05
39.70
28.24
25.62
24.34
Boc
N
SO2Ph
O
O
OH
201, 13C NMR
150
140
130
120
110
100
90
80
70
60
50
40
30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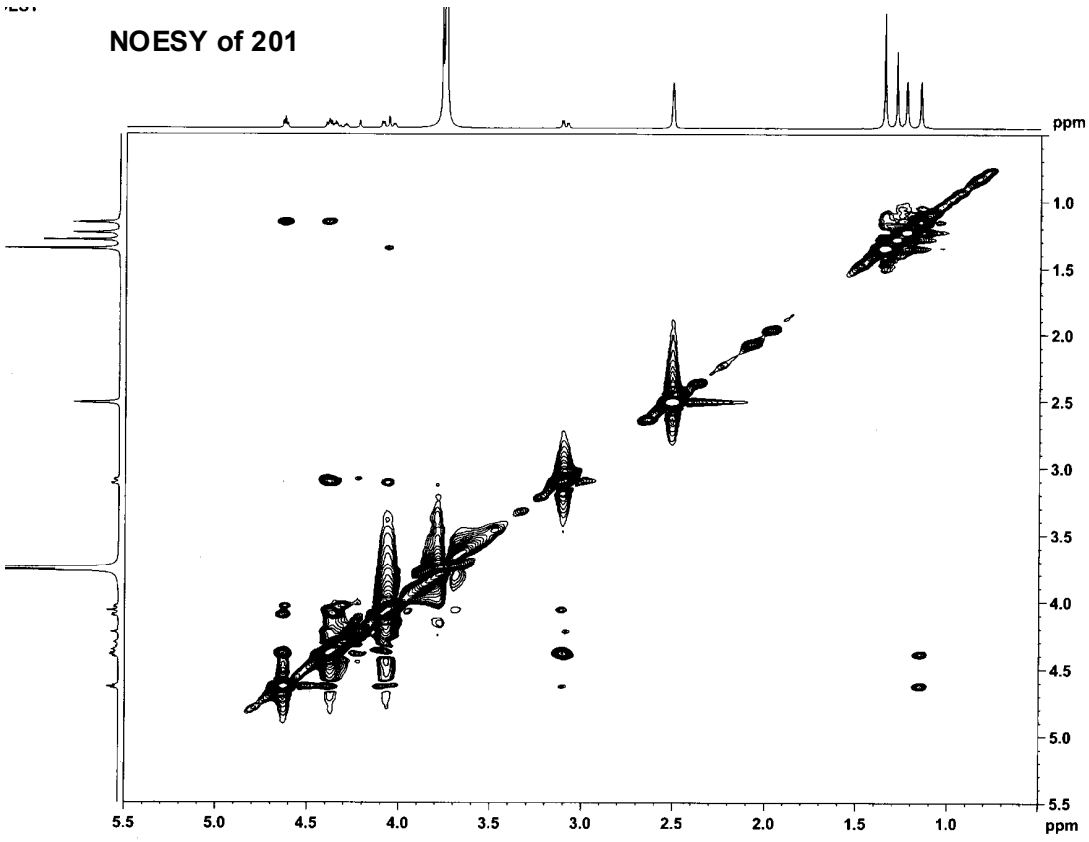
3.0
2.5
2.0
1.5
1.0
ppm


NOESY of 201
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2.5
3.0
3.5
4.0
4.5
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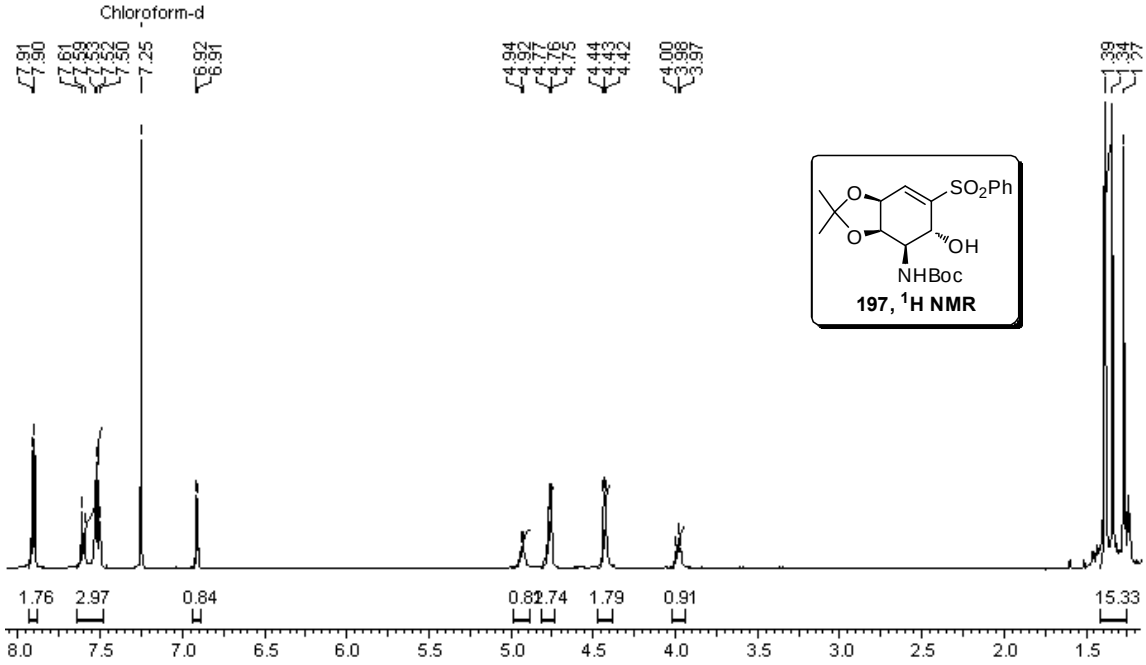
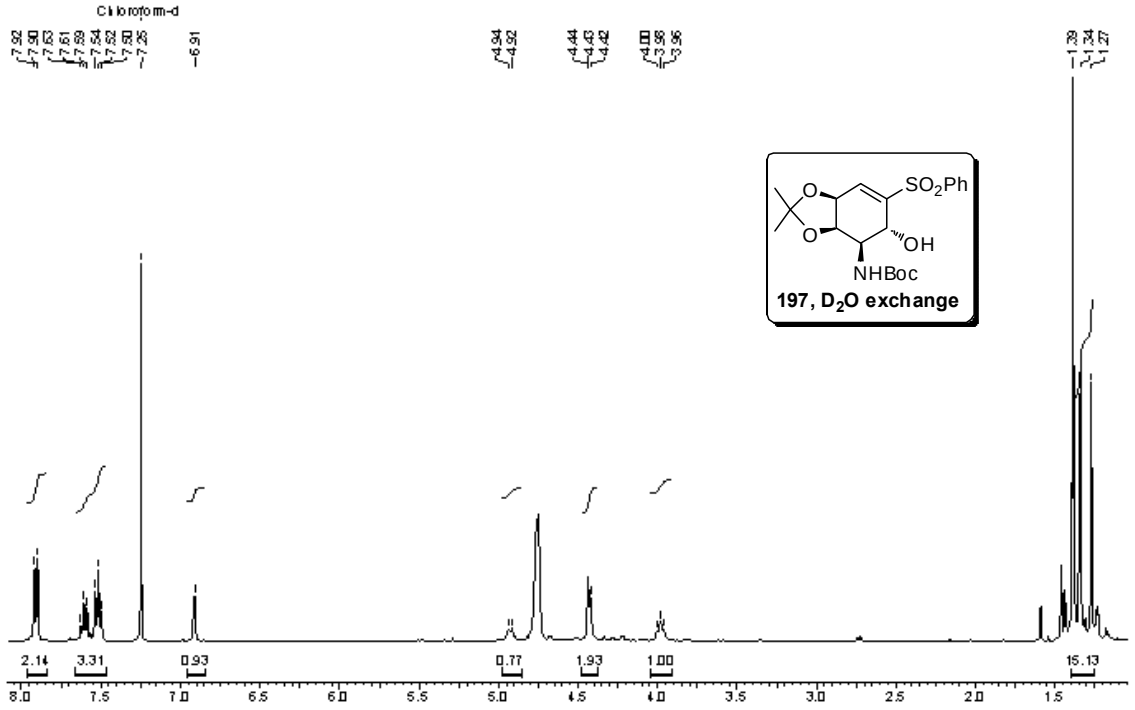
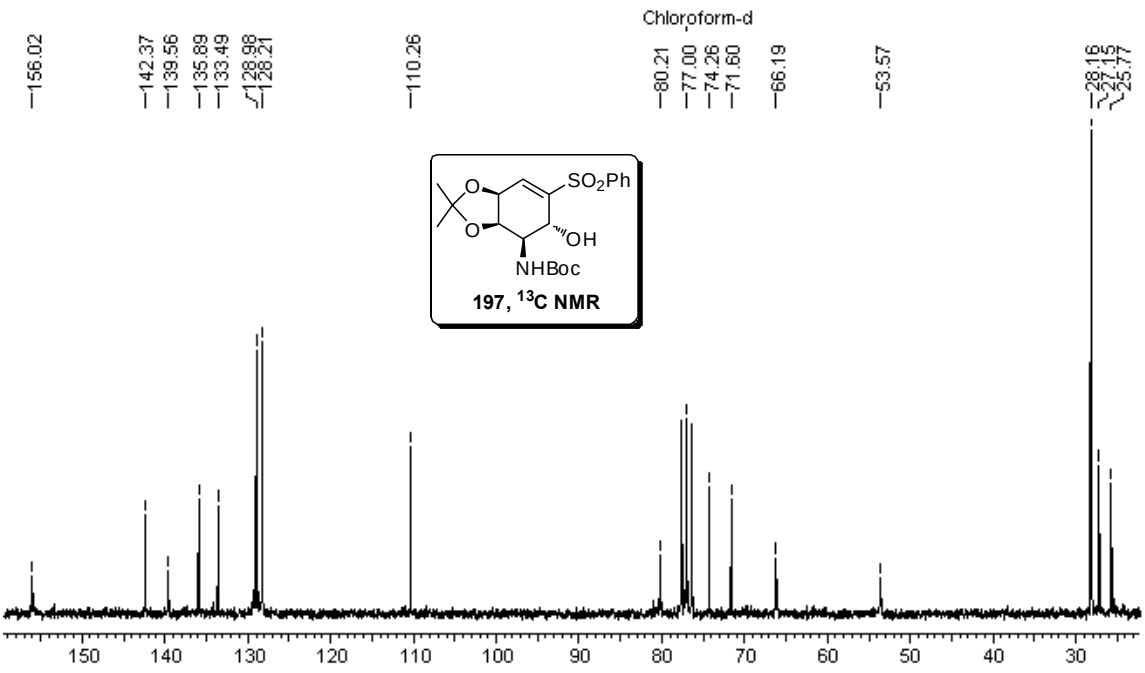
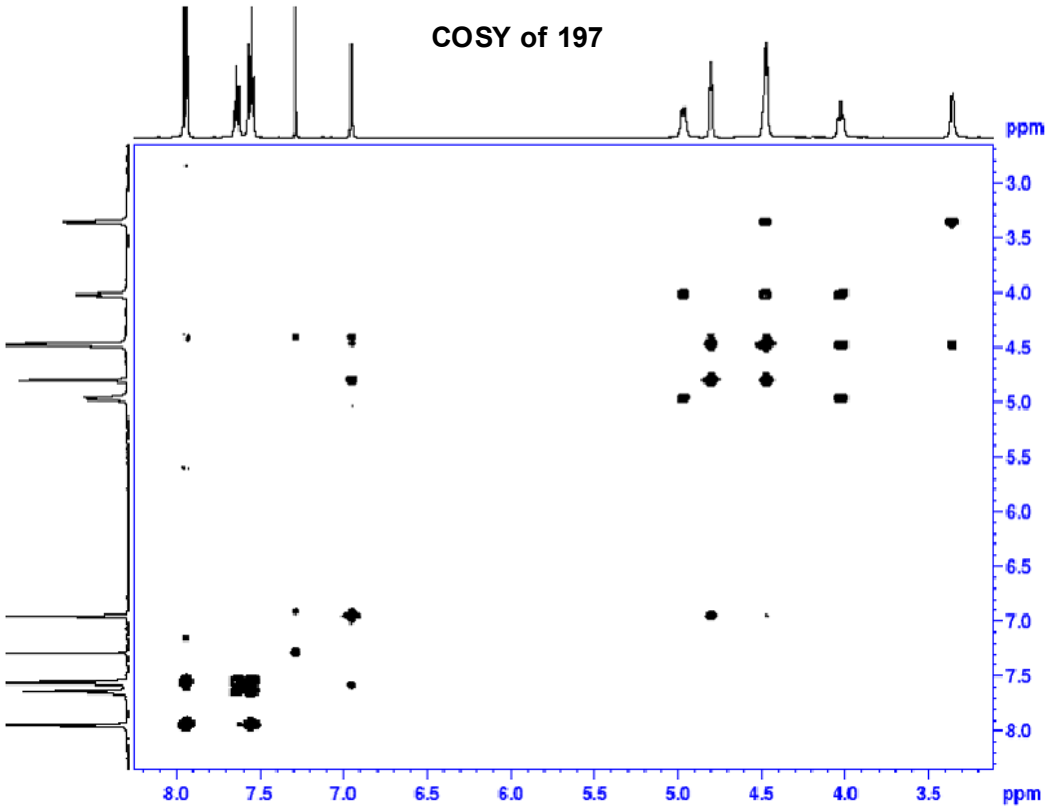
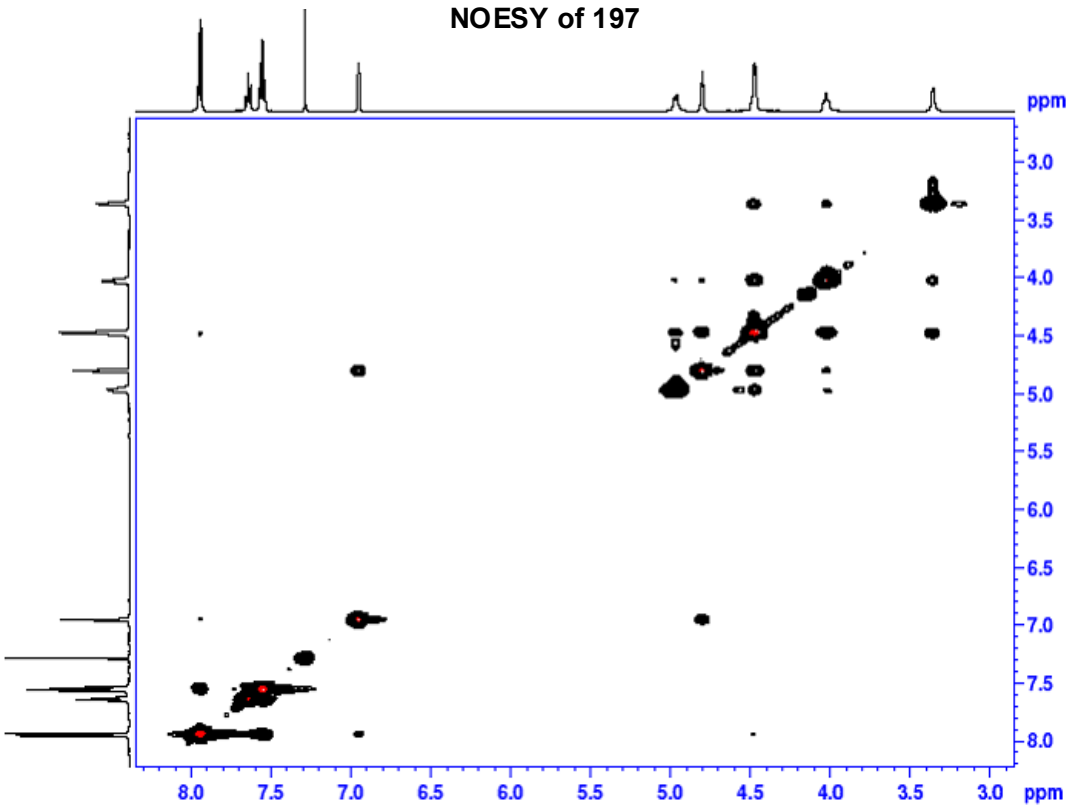
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

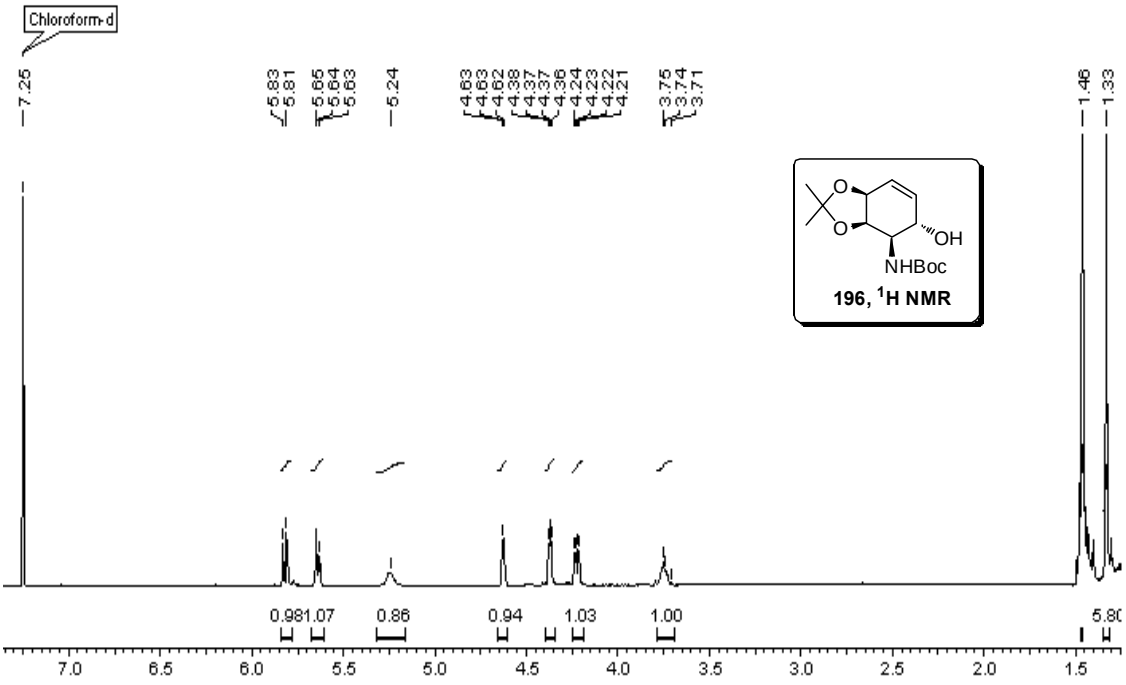

Chloroform-d
7.91
7.90
7.61
7.59
7.53
7.52
7.50
7.25
6.92
6.91
4.94
4.92
4.77
4.76
4.75
4.44
4.43
4.42
4.00
3.98
3.97
1.39
1.34
1.27
SO2Ph
O
O
OH
NHBoc
197, 1H NMR
1.76
2.97
0.84
0.82
2.74
1.79
0.91
15.33
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

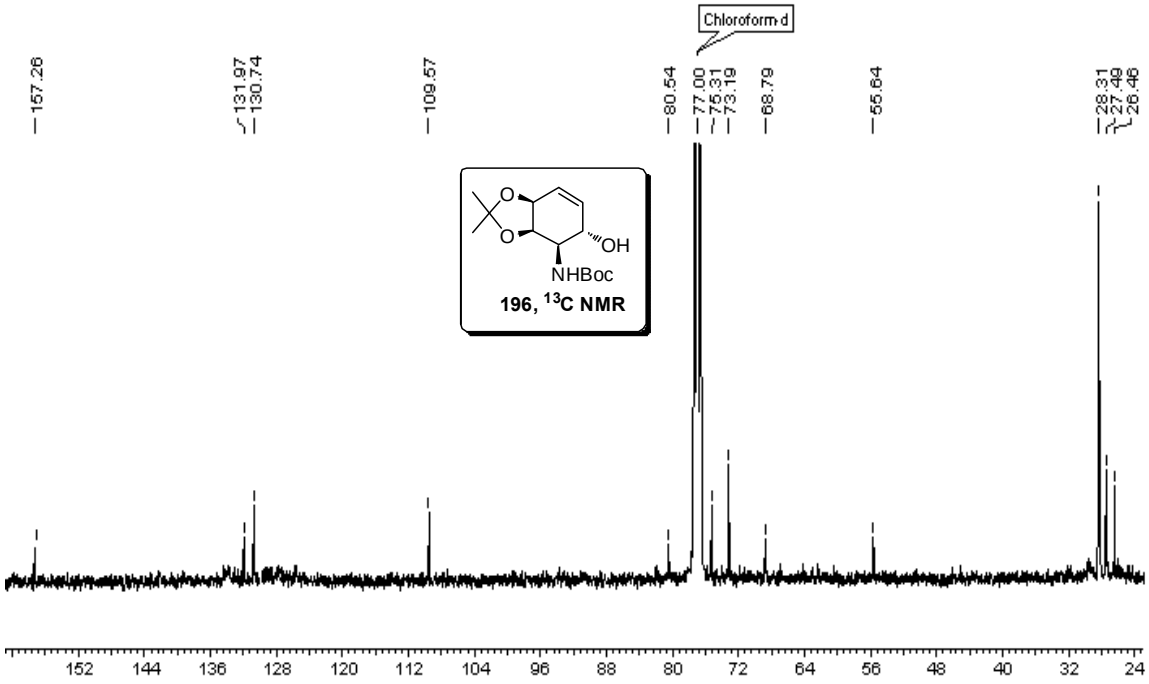

Chloroform-d
SO2Ph
O
O
OH
NHBoc
197, D2O exchange
2.14
3.31
0.93
0.77
1.93
1.00
15.13

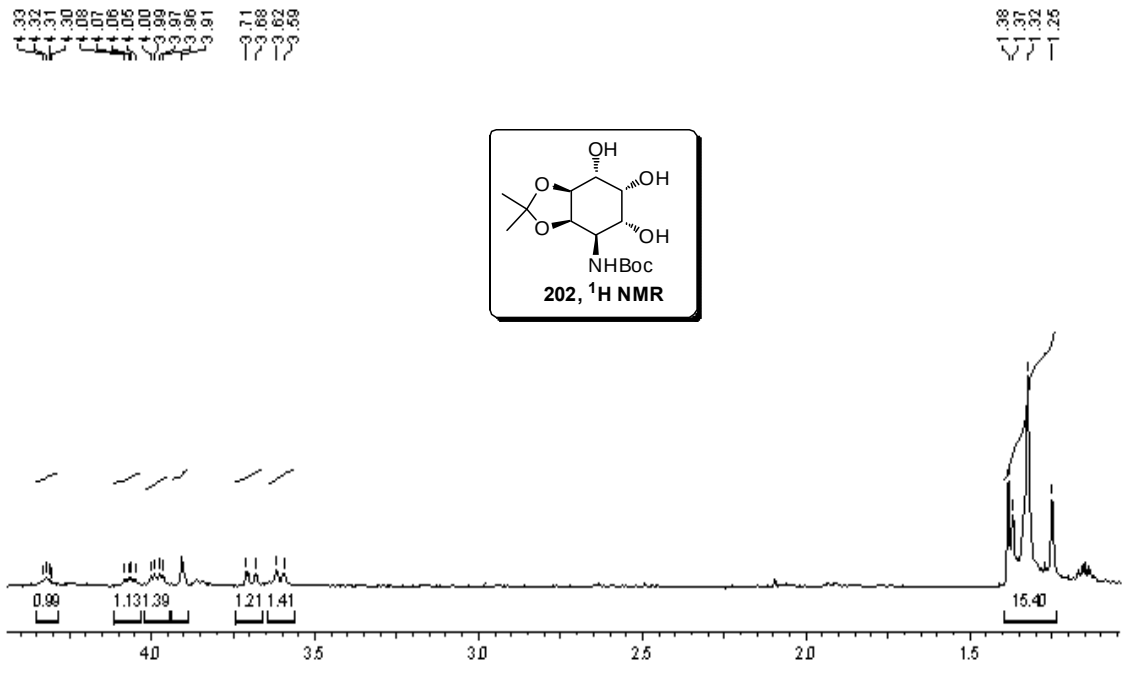

Chloroform-d
156.02
142.37
139.56
135.89
133.49
128.98
128.21
110.26
80.21
77.00
74.26
71.60
66.19
53.57
28.16
27.15
25.77
SO2Ph
OH
NHBoc
197, 13C NMR
150
140
130
120
110
100
90
80
70
60
50
40
30

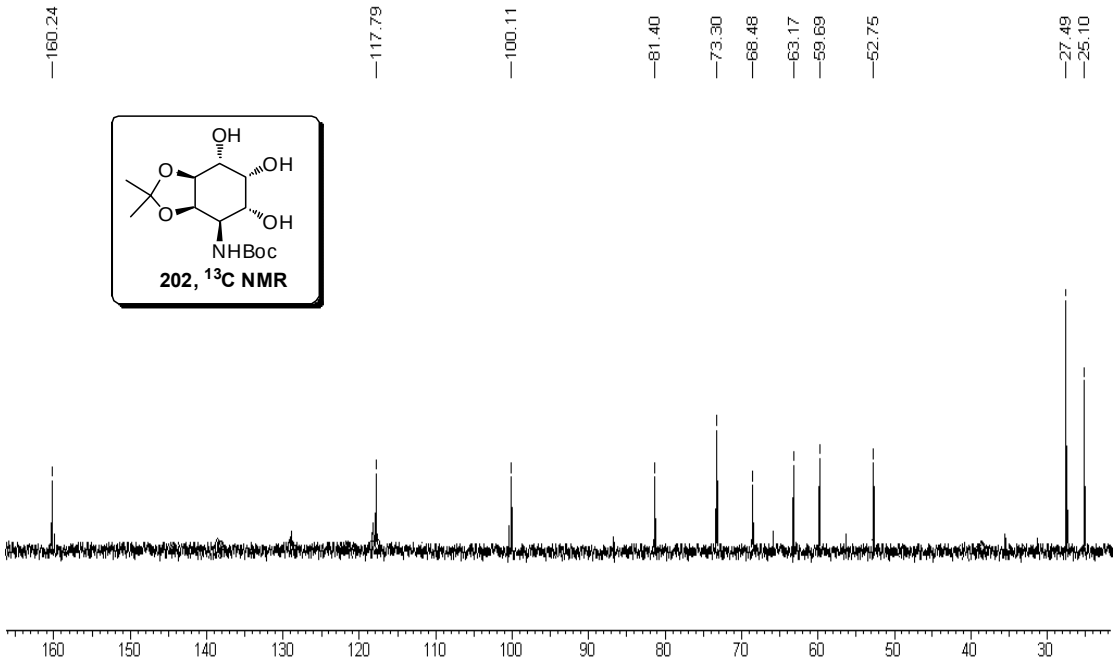

COSY of 197
ppm
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm


NOESY of 197
ppm
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 ppm


Chloroform-d
7.25
5.83
5.81
5.65
5.64
5.63
5.24
4.63
4.63
4.62
4.38
4.37
4.36
4.24
4.23
4.22
4.21
3.75
3.74
3.71
1.46
1.33
O
O
OH
NHBoc
196, 1H NMR
0.98
1.07
0.86
0.94
1.03
1.00
5.80
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5

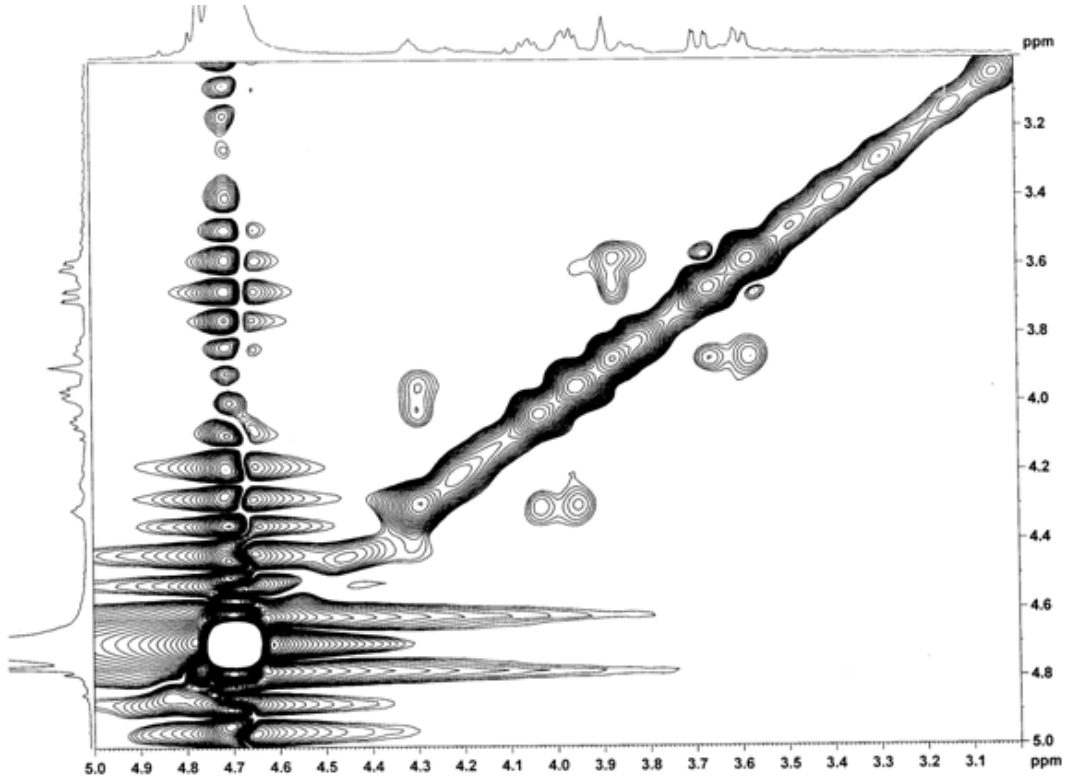

Chloroform-d
157.26
131.97
130.74
109.57
80.54
77.00
75.31
73.19
68.79
55.64
28.31
27.49
26.46
OH
NHBoc
196, ^{13}C NMR
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24


4.33
4.32
4.31
4.30
4.08
4.07
4.06
4.05
4.00
3.99
3.97
3.96
3.91
3.71
3.68
3.62
3.59
1.38
1.37
1.32
1.25
OH
OH
OH
NHBoc
202, ^{1}H NMR
0.99
1.13
1.39
1.21
1.41
15.40
4.0
3.5
3.0
2.5
2.0
1.5



202, ^{13}C NMR

NOESY of 202



List of Publications

1. Temperature Guided Diastereoselectivity Switch During Desymmetrization of *meso*-7-azabicyclo[2.2.1]heptadiene Structural Framework: Unusual Observation and New Strategy towards the Synthesis of Aminocyclitols.

Ganesh Pandey, **Salla Rajender** (**accepted for *Chem. A Eur. J.***)

2. An Efficient, Highly Enantioenriched Route to L-Carnitine and α-Lipoic Acid *via* Hydrolytic Kinetic Resolution

D. Subhas Bose, Liyakat Fatima, **Salla Rajender**, *Synthesis.* **2006**, *11*, 1863–1867.

Erratum