Studies Towards Total Synthesis of Pachastrissamine, Cephalosporolide E/F and Their Analogs and Some Metal Mediated Reactions on Sugar Templates

A THESIS
SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

TO

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BY

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(Research Guide)

ORGANIC CHEMISTRY DIVISION
NATIONAL CHEMICAL LABORATORY
PUNE–411008

April–2009

DEDICATED
TO
MY FAMILY

DECLARATION

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. C. V. Ramana**, Organic Chemistry Division, National Chemical Laboratory, Pune – 411 008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other University.

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CERTIFICATE

The research work presented in thesis entitled **"Studies Towards Total Synthesis of Pachastrissamine, Cephalosporolide E/F and Their Analogs and Some Metal Mediated Reactions on Sugar Templates"** has been carried out under my supervision and is a bonafide work of **Mr. Sharad B. Suryawanshi**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune – 411008
April 2009

Dr. C. V. Ramana
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Sharad B. Suryawanshi

DEFINATIONS AND ABBREVIATIONS

Ac	–	Acetyl
Ac_2O	–	Acetic anhydride
AIBN	–	2,2'-Azobisisobutyronitrile
aq.	–	Aqueous
Bn	–	Benzyl
BnBr	–	Benzyl bromide
$BF_3{\cdot}Et_2O$	–	Boron trifluoride diethyl ether complex
Boc	–	*Tert*-Butoxy carbonyl
BSA	–	*N,O*-bis(trimethylsilyl)acetamide
n-BuLi	–	*n*-Butyl lithium
Bu_3SnH	–	Tributyltin hydride
Cat.	–	Catalytic/catalyst
Cbz	–	Benzyloxycarbonyl
Conc.	–	Concentrated
m-CPBA	–	*m*-Chloroperbenzoic acid
DMF	–	*N,N*-Dimethylformamide
DMAP	–	*N,N'*-Dimethylaminopyridine
DMSO	–	Dimethyl sulfoxide
EtOH	–	Ethanol
Et_2O	–	Diethyl ether
EtOAc	–	Ethyl acetate
Et_3N	–	Triethylamine
HMPA	–	Hexamethylphosphoramide
Im	–	Imidazole
LAH	–	Lithium aluminium hydride
LiN_3	–	Lithium azide
Ms/Mesyl	–	Methanesulfonyl
Me	–	Methyl
MTPA	–	α-Methoxytrifluorophenylacetic acid
NOESY	–	Nuclear overhauser effect spectroscopy

ORTEP	–	Oak Ridge Thermal Ellipsoid Plot
Pd/C	–	Palladium on Carbon
Ph	–	Phenyl
Py	–	Pyridine
PTSA	–	*Para*-Toluenesulfonic acid
rt.	–	Room temperature
sat.	–	Saturated
TBAF	–	Tetra-*n*-butylammonium fluoride
TBSCl	–	*Tert*-Butyldimethylsilyl chloride
TFA	–	Trifluoro acetic acid
Tf_2O	–	Trifluoromethanesulphonic anhydride
THF	–	Tetrahydrofuran
TMSOTf	–	Trimethylsilyl trifluoromethanesulphonate
TPP/PPh_3	–	Triphenylphosphine
TsCl	–	*Para*-Toluenesulphonyl chloride

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AV–200 MHz, AV–400 MHz, and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AV–50 MHz, AV–100 MHz, and DRX–125 MHz spectrometer.
- EI Mass spectra were recorded on Finngan MAT–1020 spectrometer at 70 *eV* using a direct inlet system.
- The X-Ray Crystal data were collected on *Bruker SMART APEX* CCD diffractometer using Mo K_{α} radiation with fine focus tube with 50 kV and 30 mA.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I_2, and anisaldehyde in ethanol as developing agents.
- All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 45 °C unless otherwise specified.
- Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.

CONTENTS

ABSTRACT

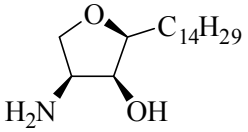
ABSTRACT

The thesis entitled "**Studies Towards Total Synthesis of Pachastrissamine, Cephalosporolide E/F and Their Analogs and Some Metal Mediated Reactions on Sugar Templates**" has been divided into two chapters. Each chapter again sub-divided into two sections. Chapter I, Section I describes the total synthesis of (–)-Pachastrissamine (Jaspine B) from D-glucose. Section II describes the total synthesis of Cephalosporolides E & F. Chapter II, Section I deals with the [2+2+2]-cyclotrimerization approach for the synthesis of enantiopure isochromans and spiroannulation of dihydroisobenzofuran on carbohydrate templates. A facile synthesis of modified nucleosides from the above [2+2+2]-cyclotrimerization products form the Section II of chapter II.

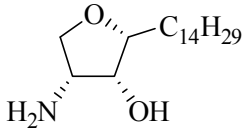
Chapter 1

Section I: Total synthesis of (–)-pachastrissamine (jaspine B) from D-glucose

Pachastrissamine (**1A.1**, Fig. 1), isolated and characterized by Higa and co-workers in 2002 from the Okinawa marine sponge *Pachastrissa sp*. (family Calthropellidae) is a novel anhydrophytosphingosine with important bioactivity. It was later (in 2003) isolated from another marine sponge, genus *Jaspis* by Debitus and co-workers and named as jaspine B. The structure of **1A.1** and the all *cis* geometry of the THF ring was assigned by spectroscopy, largely NMR, and the (2*S*,3*S*,4*S*) configuration of the ring carbon atoms was determined on the basis of (*S*)- and (*R*)-MTPA derivatization on the *N*-monoacetylated pachastrissamine. This was reported to exhibit promising cytotoxic activity in the submicromolar range against P388, A549, HT29, and MEL28 (IC_{50} = 0.001 μg/mL) cell lines. Its simple structure and this promising biological activity have stimulated substantial synthetic work, culminating in several total syntheses. We wish to synthesize both of **1A.1** and its antipode **1A.54** starting from D-glucose with enough flexibility to synthesize their analogues.



(+)-Pachastrissamine (**1A.1**)



(−)-Pachastrissamine (**1A.54**)

Figure 1

Retro Synthetic Strategy:

As shown in figure 2, our intended strategy exploit the pseudosymmetry present in pentodialdo-1,4-furanose **1A.56** to derive enantiomeric azidoalkynes **1A.62** and **1A.58**, which upon alkylation and hydrogenation should result in the synthesis of **1A.1** and **1A.54**, respectively. We synthesized tetrahydrofuran system **1A.57** by employing Ohira-Bestmann alkynylation at C(5) of **1A.56**.

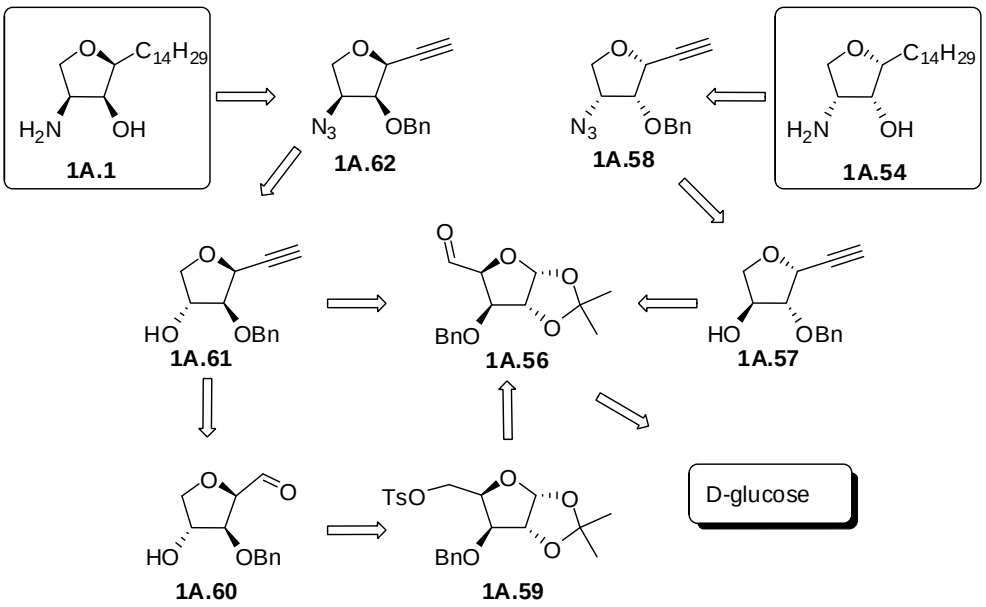
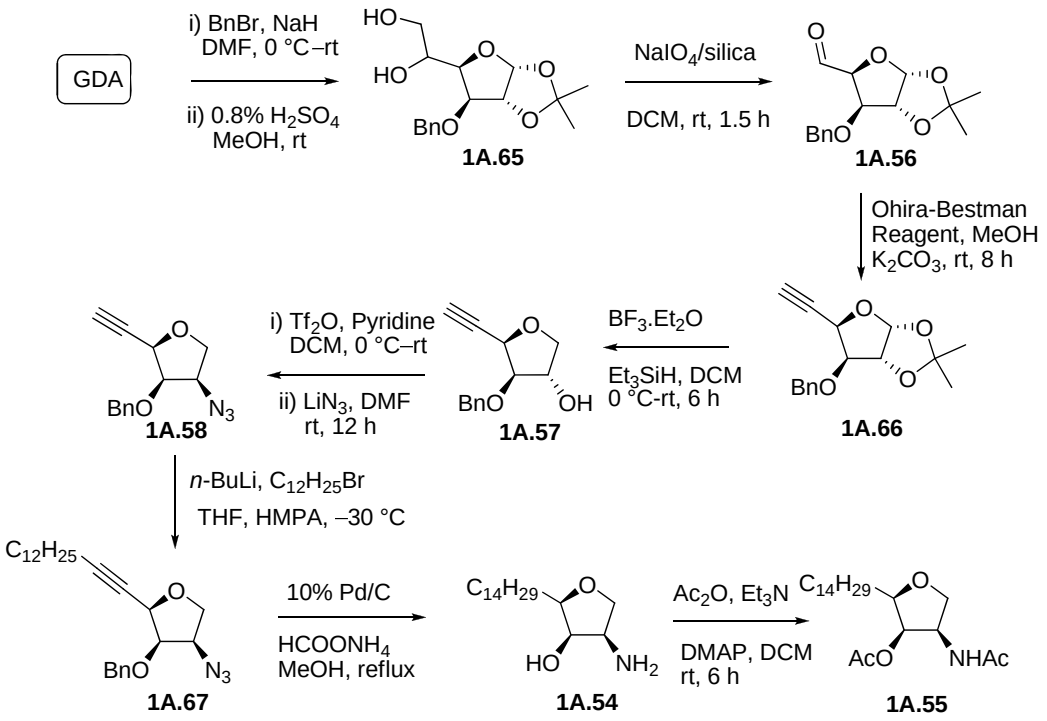


Figure 2

Free hydroxyl group of 1,2;5,6-Di-*O*-isopropylidine-α-D-glucofuranose (prepared from D-glucose) was protected as its benzyl ether and by selective deprotection of 5,6-acetonide using 0.8% H_2SO_4 in methanol at room temperature gave diol **1A.65**. Diol **1A.65** was oxidatively cleaved with sodium periodate to obtain the aldehyde **1A.56** which upon reaction with Ohira Bestman reagent afforded the alkyne **1A.66**. Reductive deketalization of alkyne **1A.66** using excess triethylsilane in the presence of $BF_3{\cdot}Et_2O$ gave alkynol **1A.57**. Compound **1A.57** was transformed to the corresponding azidoalkyne **1A.58** by treatment with Tf_2O in pyridine followed by reacting the intermediate triflate with LiN_3 in DMF. The alkylation of azidoalkyne **1A.58** with 1-bromododecane was facile using *n*-BuLi in THF-HMPA and the alkylated product **1A.67** was obtained in good yields. Transfer hydrogenolysis of **1A.67** with catalytic 10% Pd/C and excess ammonium formate in refluxing methanol

furnished the target compound **1A.54**. Further (–)-pachastrissamine **1A.54** was characterized as its diacetate derivative **1A.55**.



Scheme 1

In summary we have executed a simple chiral pool strategy for the first total synthesis of pachastrissamine enantiomer starting with D-glucose. The synthesis is sufficiently flexible to allow substitution or variation in the length of the side chain for accessing related analogues.

Section II: Pd(II)-Mediated alkynediol spiroketalization: First total synthesis of (–)-cephalosporolide E and (+)-cephalosporolide F

Cephalosporolides E (**1B.09**) and F (**1B.10**) were first isolated in 1985, by Hanson and co-workers from industrial fermentation of the fungus *Cephalosporium aphidcola* grown under sulfur limiting conditions. Later in 2004, by Rakachaisirikul and co-workers from the entomopathogenic fungus *Cordyceps militaris* BCC 2816. The relative configuration of **1B.09** and **1B.10** were elucidated by the extensive NMR studies and by single crystal X-ray analysis of **1B.09**. Cephalosporolides E and F are characterized by a 1,6-dioxaspiro[4.4]nonane in which one of the furan ring is fused with a γ-lactone ring. During their isolation of bassianolone (**1B.11**), Oltra and co-

workers noticed that compound **1B.11** can be transformed into a mixture of **1B.09** and **1B.10** by a silica gel promoted spirocyclization and concluded that **1B.09** and **1B.10** are artifacts during the isolation procedures. However, the recent isolation of several other natural products like ascospiroketals A (**1B.12**) and B (**1B.13**), cephalosporolides H (**1B.14**) and I (**1B.15**) having the central tricyclic core of **1B.09** and **1B.10**, establish this tricyclic structural core as unprecedented and of natural origin (Figure 3).

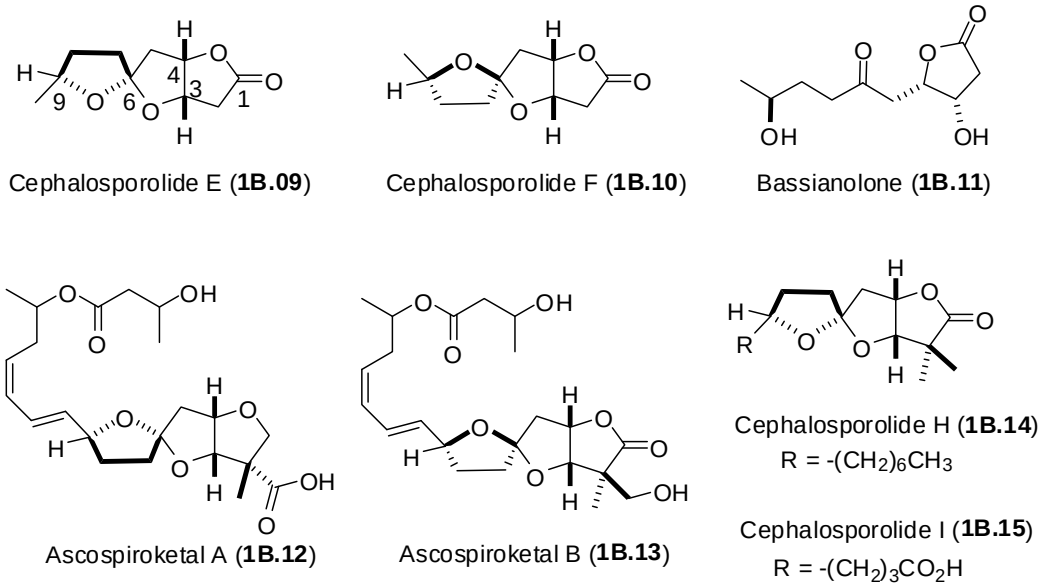


Figure 3

Despite the fact that the absolute configuration of all the natural products isolated unsettled, however not synthetic efforts were documented and this promoted us to undertake the synthesis of **1B.09** and **1B.10**.

Retro Synthetic Strategy:

As out lined in the Figure 4, considering the alkynol cycloisomerization as the key reaction and our earlier studies on influence of the electronic factors over the Pd-mediated cycloisomerization reactions, the alkyne unit has been placed between C(5)–C(6) and the central carbon chain of **1B.09** and **1B.10** has been disconnected between C(6)–C(7) (Figure 4).

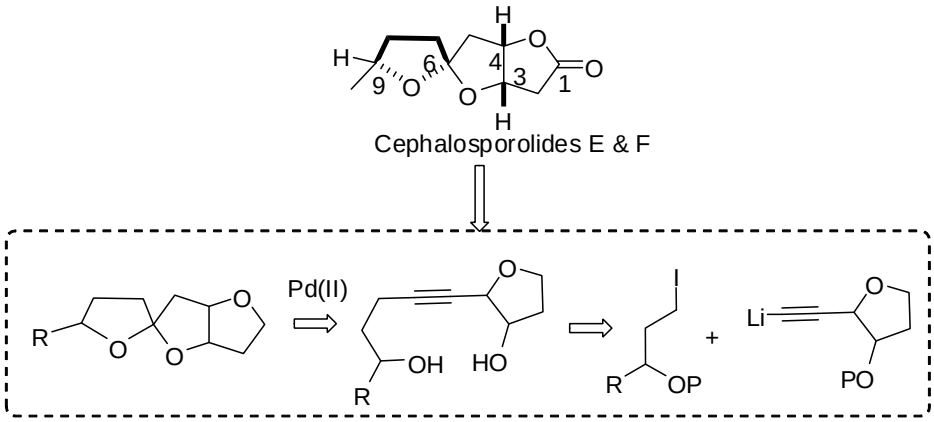
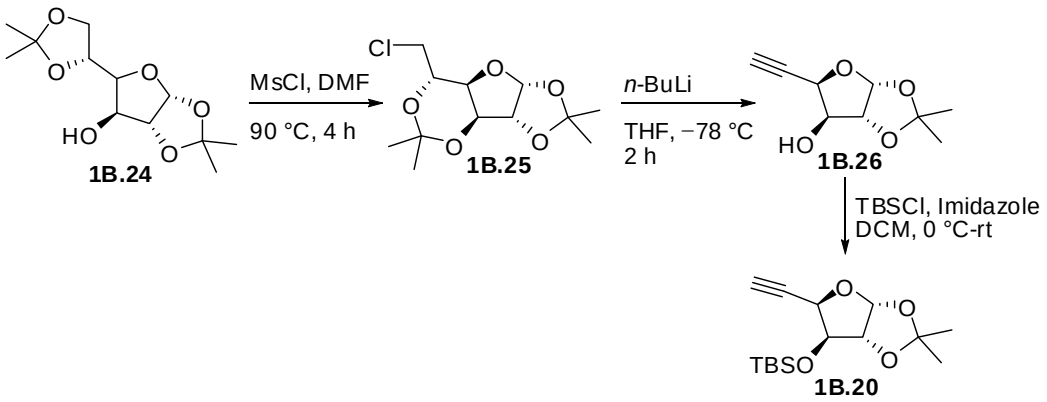


Figure 4

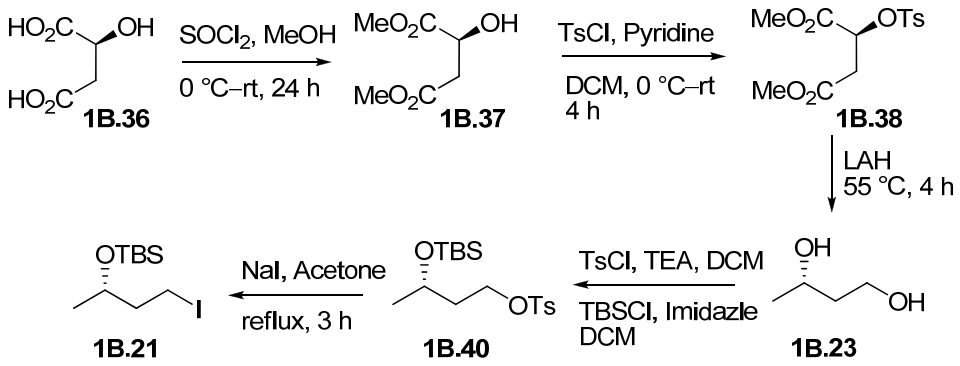
Synthesis of alkyne 1B.20 (Scheme 2)**:** The 6-chloro compound **1B.25** was prepared by treating glucose diacetonide with mesyl chloride in DMF at 90 °C, which on reaction with excess of *n*-BuLi at −78 °C gave the alkynol **1B.26**. Free hydroxyl group of **1B.26** was protected as its TBS ether to afford the alkyne fragment **1B.20**.



Scheme 2

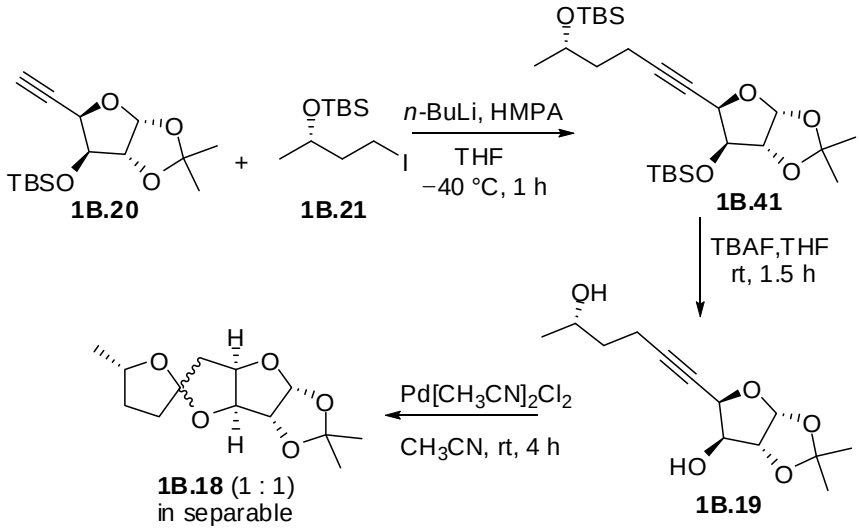
Synthesis of iodo compound 1B.21 (Scheme 3)**:** Synthesis was started with dimethyl ester **1B.37** of L-malic acid prepared by addition of thionyl chloride at 0 °C to malic acid **1B.36** in methanol and stirred at room temperature for 24 hours. Free hydroxyl was converted to its tosylate **1B.38** by treating it with tosyl chloride in pyridine and DCM at rt. Tosylate **1B.38** on reduction with 5 equivalents of LAH at 55 °C gave (*S*)-butane-1,3-diol (**1B.23**) in 47% yield. Primary hydroxyl group of **1B.23** was converted to its tosylate and then the secondary hydroxyl as its TBS ether to afford

compound **1B.40**. Compound **1B.40** on refluxing with sodium iodide in acetone gave the iodo compound **1B.21**.



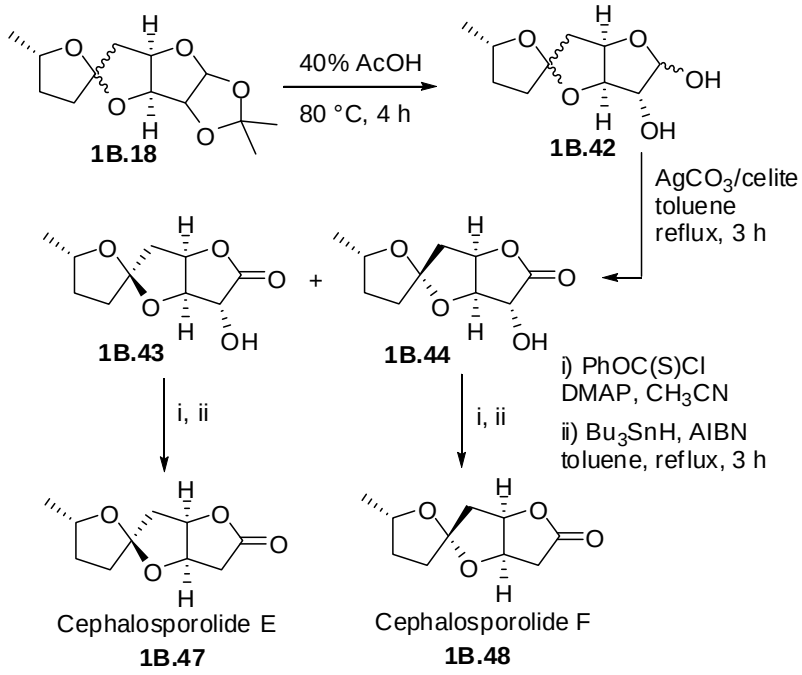
Scheme 3

Synthesis of alkynediol 1B.19 and its cycloisomerization (Scheme 4)**:** The alkyne **1B.20** synthesized from D-glucose and the iodo compound **1B.21** from L-malic acid were coupled by employing *n*-BuLi and HMPA in THF at −40 °C to afford **1B.41**. On TBS deprotection of **1B.41** by *tetra*-*n*-butyl ammonium fluoride afforded the key alkynediol **1B.19**. Alkynediol **1B.19** was subjected to the key palladium catalyzed cycloisomarization reaction to afford a 1:1 mixture of spiro tricyclic compounds **1B.18**.



Scheme 4

Synthesis of (–)-cephalosporolide E and (+)-cephalosporolide F (Scheme 5)**:** The 1,2-acetonide deprotection of **1B.18** was achieved by heating it in 40% acetic acid at 80 °C (oil bath temperature) for 4 to 5 hours to get a mixture of four lactols **1B.42**. The lactols **1B.42** were subjected for chemoselective oxidation employing either $Br_2/Ba(CO_3)$ or under Fetizon's conditions to afford the corresponding lactones **1B.43** and **1B.44**. The resulting lactones **1B.43** and **1B.44** were separated by silica gel column chromatography and characterized by NMR studies and by single crystal X-ray analysis of **1B.43**.



Scheme 5

Treatment of Lactones **1B.43** and **1B.44** with phenyl chlorothinoformate and DMAP in acetonitrile gave the corresponding xanthates, which were transferred to cephalosporolides E and F on radical deoxygenation by tributyl tin hydride and AIBN in toluene at reflux. Correlating the X-ray, NMR analysis spectrums of reported compounds and optical rotation, we have successfully determined absolute configuration of cephalosporolide E, cephalosporolide F and bassianolone.

In conclusion first total synthesis of cephalsporolides E and F were achieved using palladium catalyzed cycloisomarization reaction as the key step and successfully determined their absolute configuration.

Chapter 2

Section I: [2+2+2]-Cyclotrimerization approach for the synthesis of enantiopure isochromans and spiroannulation of dihydroisobenzofuran

Designing effective routes to construct complex cyclic structures through organo transition-metal catalyzed reactions have been recognized as an attractive strategy for delivering molecular diversity. Integrated with transition metal catalyzed reactions, sugar templates have been well deployed to address the synthesis of a variety of complex natural product skeletons. Amongst the many other metal catalyzed reactions which have been explored on sugar templates, catalytic [2+2+2]-alkyne cyclotrimerization is important as it delivers highly functionalized aromatic rings appended with a sugar ring. Herein, we describe the synthesis of enantomeric tricyclic molecular skeletons consisting of isochroman unit (Figure 5) and also the spiroannulation of dihydroisobenzofuran ring on carbohydrate templates (Figure 6) by employing cyclotrimerization as the key reaction.

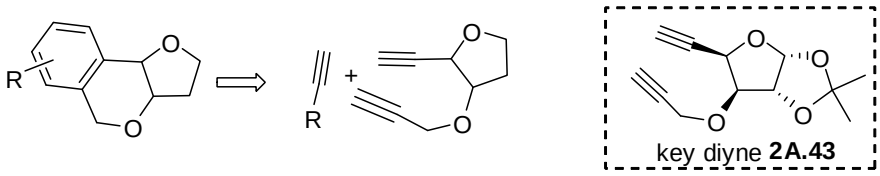


Figure 5: Key [2+2+2]-Cyclotrimerization approach for enantiopure isochromans

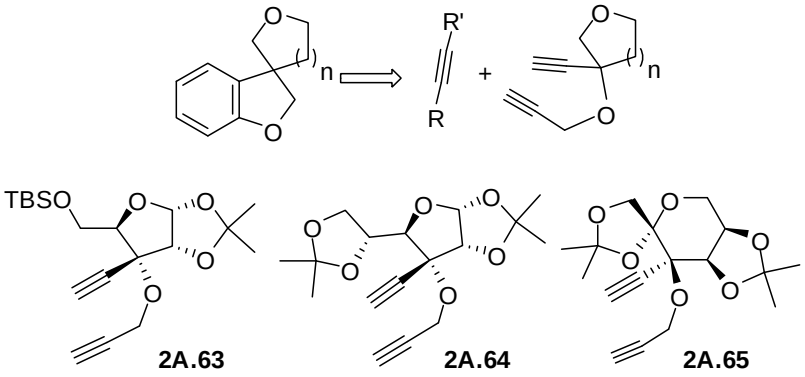
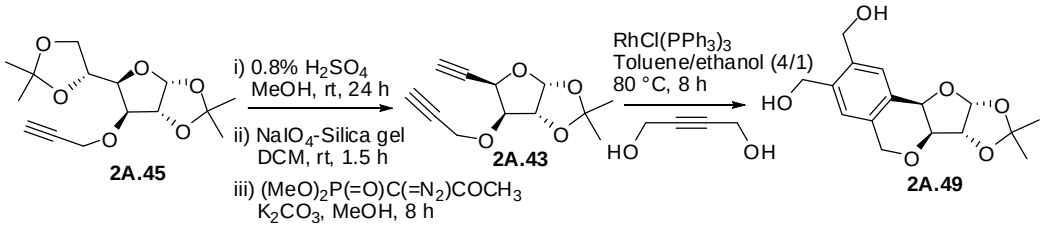


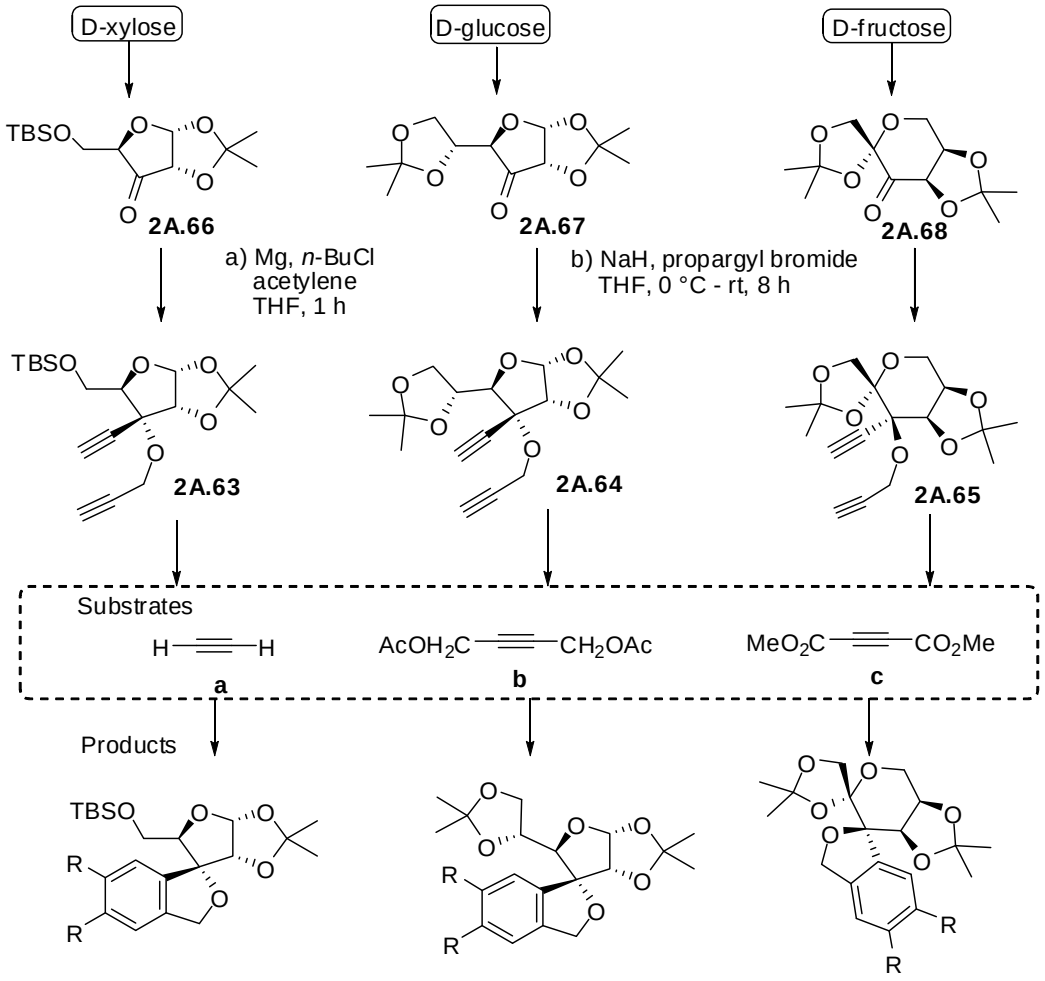
Figure 6: key [2+2+2]-Cyclotrimerization approach for spiroannulation of dihydroisobenzofuran and selected sugar diynes

The synthesis of the key diyne **2A.43** started with the propargylation of D-glucose diacetonide to procure the propargyl ether **2A.45**. Selective monoacetonide hydrolysis of **2A.45** followed by sodium periodate mediated cleavage and subsequent Ohira-Bestmann alkynylation of the intermediate aldehyde gave the diyne **2A.43** in 40% overall yield. Cyclotrimerization of **2A.43** was optimized with 2-butyne-1,4-diol using Wilkinson's catalyst and afforded the tricyclic derivative **2A.49** in good yield (Scheme 6). To illustrate the flexibility of our strategy, various symmetrical and unsymmetrical alkynes were employed. With unsymmetrical alkynes, the [2+2+2]-cyclotrimerization gave inseparable regiomeric mixtures in moderate to good yields.



Scheme 6

The synthesis of the key diyne substrates (**2A.63−2A.65**) of spiro-annulation protocols were started with addition of ethynylmagnesium bromide to the ketones **2A.66−2A.68**. Subsequent propargylation of 3°-hydroxyl of the resulting alkynes gave key diyne intermediates **2A.63−2A.65** (Scheme 7). Cyclotrimerization was carried out with diacetate of 2-butyne-1,4-diol using Wilkinson's catalyst to afford the tricyclic derivatives **2A.77**, **2A.86**, **2A.90** in good yields to optimize the reaction.



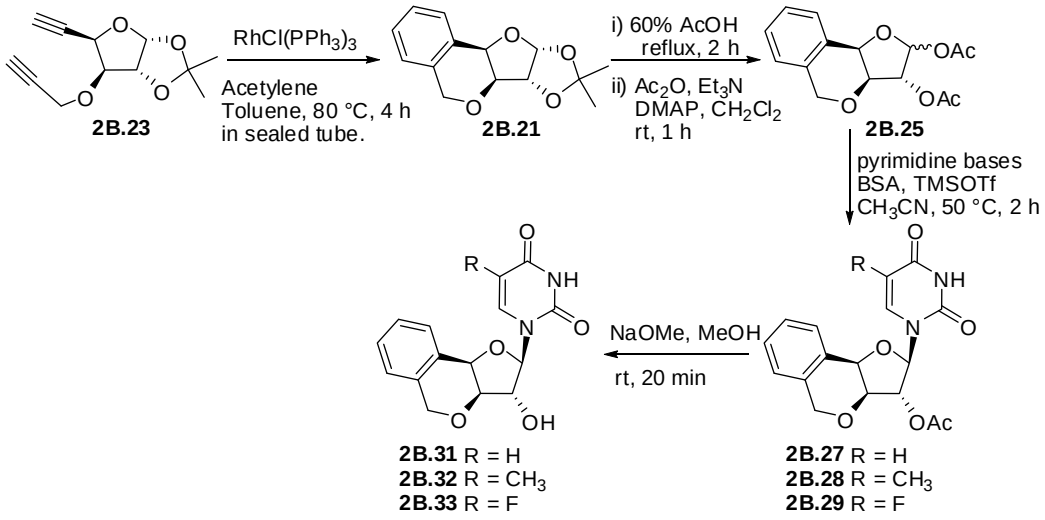
Scheme 7

With symmetrical alkyne substrates acetylene and dimethyl acetylene dicarboxylate the cyclotrimerization reaction proceeded effectively at 80 °C in a sealed tube to afford the corresponding spirocyclic products. The cyclotrimerization reactions of **2A.63**–**2A.65** with phenyl acetylene and of **2A.64** with propargyl alcohol, 1-hexadecyne, and *N*-propargyl phthalimide were executed under similar conditions. However, the trimerization with these substrates are not regioselective and gave inseparable regiomeric mixtures.

In summary, a general synthesis of enantiomeric tricyclic molecular skeletons consisting chiral isochroman & spirodihydroisobenzofuran units has been achieved via [2+2+2]-cyclotrimerization reaction on sugar templates.

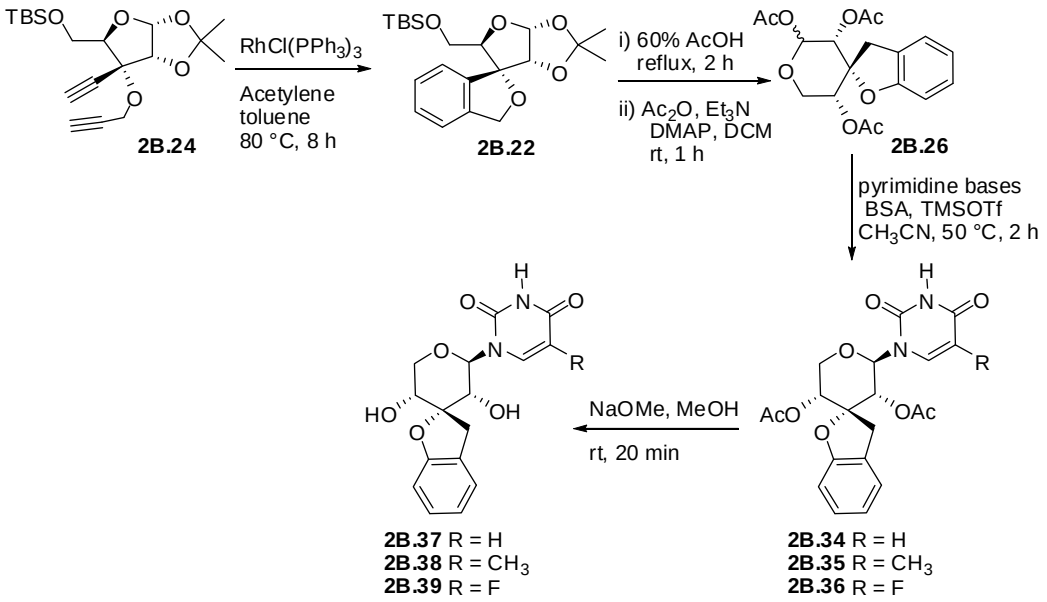
Section II: Synthesis of modified tricyclic nucleosides

Having provided an easy access to tricyclic sugar scaffolds herein, we extend their application in the synthesis of modified nucleosides by employing the two tricyclic compounds **2B.21** and **2B.22**. Compound **2B.21** was subjected to acid catalysed acetonide hydrolysis using 60% acetic acid followed by acetylation in Et_3N, acetic anhydride and dichloromethane to afford a 1:1 anomeric mixture of **2B.25**. Treatment of **2B.25** with pyrimidine bases such as uracil, thymine, 5-flurouracil and Cbz-cytosine under modified Vorbrüggen conditions afforded the respective protected nucleosides **2B.27–2B.30**. Compounds **2B.27–2B.29** upon Zemplen's deacetylation gave the tricyclic nucleosides **2B.31–2B.33** (Scheme 8). The structures of **2B.27** & **2B.32** were established with the help of X-ray crystallography that confirmed the assigned β-configuration.



Scheme 8

In a similar fashion, **2B.22** was subjected for acid catalysed acetonide hydrolysis followed by acetylation to afford a anomeric mixture of **2B.26** as its pyranoside of ribose core (Scheme 9).



Scheme 9

Treating the anomeric mixture **2B.26** with uracil, thymine and 5-flurouracil under modified Vorbrüggen conditions afforded the protected nucleosides **2B.34**–**2B.36**, respectively. Subjecting **2B.34**–**2B.36** to Zemplen's deacetylation afforded the tricyclic nucleosides **2B.37**–**2B.39** (scheme 9). The structural integrity of compound **2B.34** was established with the help of X-ray crystallography.

CHAPTER-I

Section I: Total synthesis of (−)-pachastrissamine (jaspine B) from D-glucose

1A.1. Introduction:

Phytosphingosines **1A.03–1A.06** are a sub-class of the sphingoid bases and consist of a 1,3,4-trihydroxy-2-amino unit at the head of a long hydrocarbon chain. By far, the most abundant phytosphingosine is D-*ribo*-phytosphingosine **1A.03**, with 18 carbon atoms in the hydrocarbon chain. Sphingolipids are essential components of eukaryotic cells[1] and phytosphingolipids exhibit important physiological properties.[2] Pachastrissamine **1A.01**, also known as Jaspine B was the first naturally occurring anhydrophytosphingosine isolated,[2,3] which also displays potent biological activity. Since its isolation in 2002, there has been a great deal of interest from synthetic chemists concerning the total synthesis of Pachastrissamine **1A.01**, its C(2)-epimer (2-*epi*-jaspine B **1A.02**) and their analogues (Figure 1A.1).

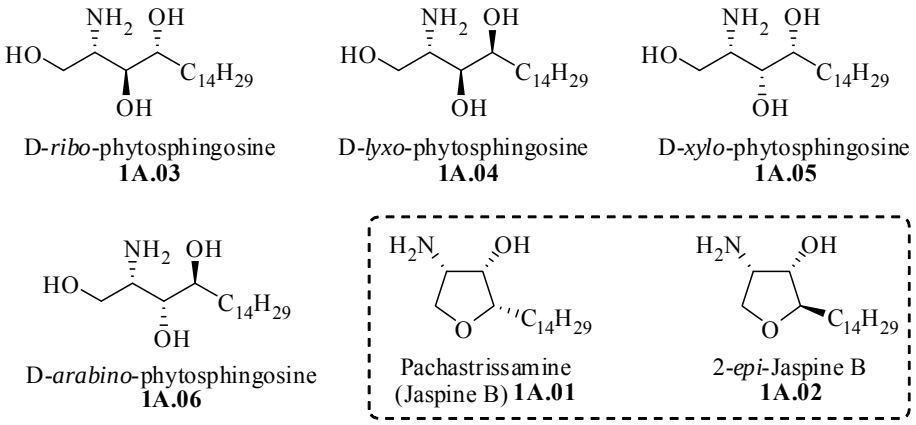
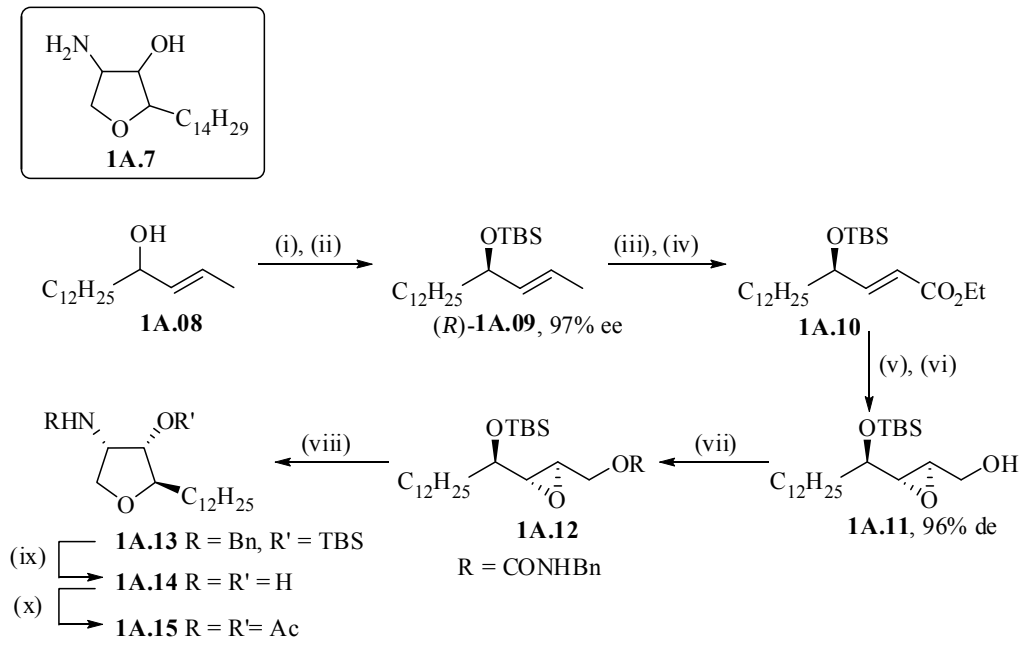


Figure 1A.1: Structures of C_{18} phytosphingosines **1A.03–1A.06** and anhydro-phytosphingosine jaspine B (**1A.01**) and 2-*epi*-jaspine B (**1A.02**).

1A.1.1 Synthesis of anhydrophytosphingosines prior to the isolation of jaspine B:

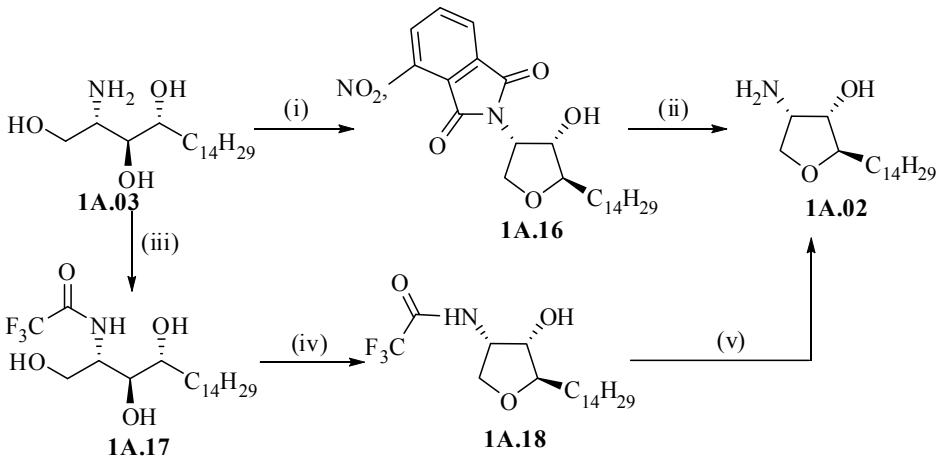
In 1959 the first report of an anhydrophytosphingosine **1A.07** appeared, although a stereochemical assignment was not given.[4] Subsequently, its structure and relative configuration were assigned by analogy with the 'truncated' analogue **1A.14**, bearing a $C_{12}H_{25}$ side chain. In this synthesis, allylic alcohol **1A.08** was kinetically resolved under Sharpless asymmetric epoxidation conditions with (+)-DIPT to afford an enantioenriched sample,[5] which upon *O*-silylation afforded (*R*)- **1A.09** of 97% ee. Ozonolysis of (*R*)- **1A.09** followed by Horner-Wadsworth-Emmons olefination gave **1A.10**. Reduction of the ester functionality of **1A.10** was achieved with DIBAL-H,

which was oxidised under Sharpless asymmetric epoxidation conditions with (–)-DIPT to give epoxide **1A.11**. Treatment of **1A.11** with benzylisocyanate gave urethane **1A.12**, and subsequent base-mediated epoxide opening gave tetrahydrofuran derivative **1A.13**. The configuration of **1A.15** (2*R*,3*S*,4*S*) was determined by ^{1}H NMR NOE studies on *N*,*O*-diacetyl derivative **1A.15** (Scheme 1A.1).[6]



Scheme 1A.1: *Reagents and conditions*: (i) $Ti(O^iPr)_4$, (+)-DIPT, $^tBuO_2H$, CH_2Cl_2, −20 °C, 15 h; (ii) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 12 h, 41% for two steps; (iii) O_3, CH_2Cl_2, −78 °C then Me_2S, −78 °C to rt; (iv) $(EtO)_2P(O)CH_2CO_2Et$, NaH, C_6H_6, 60 °C to rt, 15 min, 60% for two steps; (v) DIBAL-H, hexane, 0 °C to rt, 12 h, 90%; (vi) $Ti(O^iPr)_4$, (–)-DIPT, $^tBuO_2H$, CH_2Cl_2, −20 °C, 21 h, 97%; (vii) BnNCO, Et_3N, CH_2Cl_2, rt, 12 h, 98%; (viii) NaH, THF, rt, 12 h, 67%; (ix) HF, H_2O, MeCN, 70 °C, 2 h then Pd/C, cyc1ohexene, aq 1 M HCl, MeOH, reflux, 2 h, 78%; (x) Ac_2O, pyridine, 70 °C, 1.5 h, 96%.

Recently (in 2001), the synthesis of an authentic sample of 2-*epi*-jaspine B **1A.02** was reported by Kim *et al*., starting from D-*ribo*-phytosphingosine **1A.03**. Initial treatment of **1A.03** with 3-nitrophthalic acid at reflux under Dean-Stark conditions is reported to give tetrahydrofuran derivative **1A.16**, which on hydrazine-mediated *N*-deprotection afforded **1A.02**. Kim *et al*. also report that treatment of *N*-trifluoroacetyl D-*ribo*-phytosphingosine **1A.17** with TsCl in pyridine effected cyclisation to tetrahydrofuran derivative **1A.18**, which upon deprotection also gave **1A.02**, with identical spectroscopic data (Scheme 1A.2).[7]



Scheme 1A.2: *Reagents and conditions*: (i) 3-nitrophthalic acid, PhMe, reflux, 3 h, 67%; (ii) NH_2NH_2, H_2O, EtOH reflux, 2 h, 62%; (iii) F_3CCO_2Et, EtOH, 25 °C, 16 h; (iv) TsCl, pyridine, 25 °C, 16 h, 75%; (v) K_2CO_3, MeOH, 25 °C, 16 h, 67%.

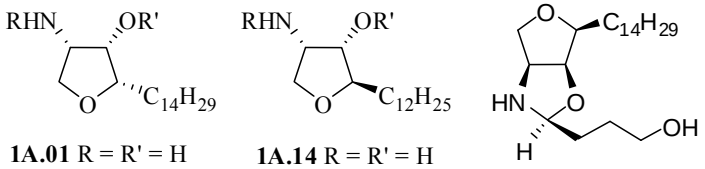
1A.1.2. Isolation of pachastrissamine (jaspine B):

In 2002, studies on the marine sponge *Pachastrissa* sp. by Higa and co-workers[2] led to the isolation of an anhydrophytosphingosine derivative which they named pachastrissamine (**1A.01**) (Figure 1A.2). Shortly after, in an independent study, Debitus and co-workers reported the isolation of two anhydrophytosphingosines from the marine sponge *Jaspis* sp.,[3] which they named jaspines A (**1A.19**) and B (**1A.01**); pachastrissamine and jaspine B being identical (Figure 1A.2). Both jaspines A (**1A.19**) and B (**1A.01**) display biological activity;[2] jaspine B (**1A.01**) in particular being the most potent compound isolated from the *Jaspis* genus to date against the A549 human lung carcinoma cell line.

Stereochemical assignment:

Higa *et al*. determined the relative configuration of pachastrissamine (**1A.01**) after the conversion of **1A.01** to the corresponding *N*-acetyl and *N*,*O*-diacetyl derivatives **1A.20** and **1A.21**, by ^{1}H NMR NOE analysis of the *N*,*O*-diacetyl derivative **1A.21**, which indicated the all-*cis* relationship of the substituents around the tetrahydrofuran ring. The (2*S*,3*S*,4*S*)–absolute configuration of the natural product was then established using the Mosher method, by conversion of *N*-acetyl pachastrissamine (**1A.20**) to the corresponding (*R*)- and (*S*)-2-methoxy-2-trifluoromethylphenyl acetyl (MTPA) derivatives.[8] In their independent study, Debitus *et al*. also converted jaspine B (**1A.01**) to the corresponding *N*-acetyl and *N*,*O*-diacetyl derivatives **1A.20** and **1A.21**, and compared the ^{1}H and ^{13}C NMR data

with that of the known $C_{12}H_{25}$ side-chain *N*,*O*-diacetyl derivative **1A.15**,[7] which also indicated an all-*cis* relationship of the substituents around the tetrahydrofuran ring. The absolute configuration of the natural product was then determined, also by the Mosher method, as (2*S*,3*S*,4*S*) (Figure 1A.2).



1A.01 R = R' = H
1A.20 R = Ac, R' = H
1A.21 R = R' = Ac

1A.14 R = R' = H
1A.15 R = R' = Ac

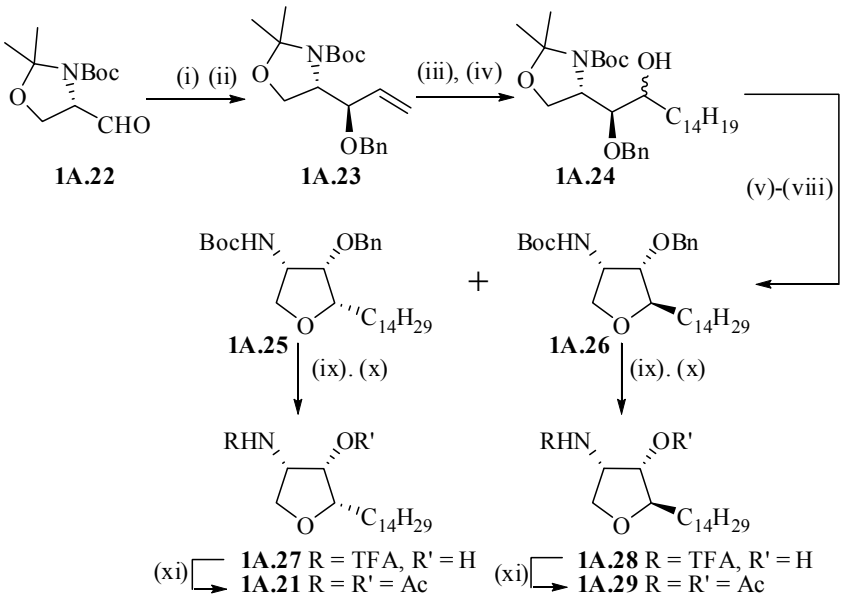
1A.19 Jaspine A

Figure 1A.2: Structures of jaspines A (**1A.19**)/B (**1A.01**), the 'truncated' $C_{12}H_{25}$ side-chain analogue **1A.14** and their corresponding acetate derivatives

1A.1.3. Synthesis of pachastrissamine (jaspine B)

1A.1.3.1. B. Venkateswara Rao *et al.* [9]

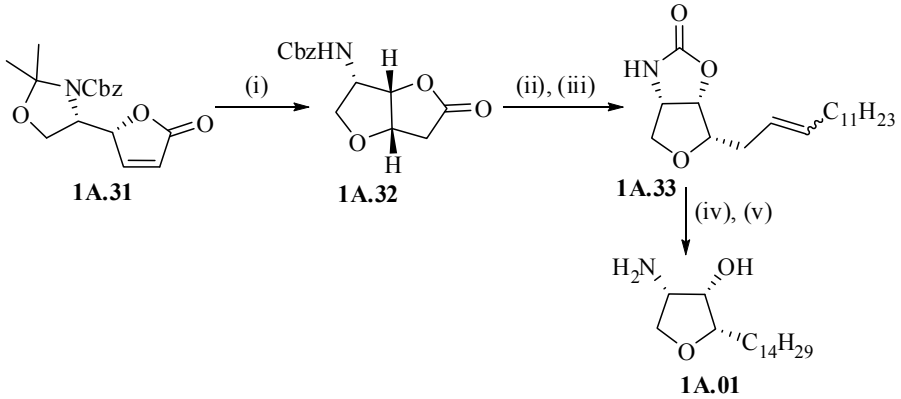
The first total synthesis of pachastrissamine **1A.01** reported by Rao and co-workers used L-serine derived Garner's aldehyde **1A.22**. Addition of vinylmagnesium bromide to **1A.22** gave a separable 86:14 mixture of diastereoisomeric alcohols in accordance with the well-known modified Felkin-Ahn selectivity for addition.[10] The major diastereoisomer was protected as the corresponding benzyl ether to give **1A.23**. Ozonolysis of **1A.23** was followed by addition of tetradecylmagnesium bromide to give an inseparable 70:30 mixture of the diastereoisomeric alcohols **1A.24**. Protection and deprotection manipulations follwed by mesylation and treatment of the mesylates with TBAF promoted desilylation and concomitant cyc1isation to a separable 70:30 mixture of tetrahydrofurans, from which the all-*cis* diastereoisomer **1A.25** and its C(2)-epimer **1A.26** was isolated. Subsequent debenzylation and diacetylation of **1A.25** and **1A.26** gave *N*,*O*-diacetyl jaspine B (**1A.21**) and *N*,*O*-diacetyl 2-*epi*-jaspine B (**1A.29**) respectively (Scheme 1A.3).



Scheme1A.3: *Reagents and conditions*: (i) viny1magnesiumbromide, THF, 0 °C to rt, 12h; (ii) BnBr, THF, NaH, 0 °C to rt, 12h, 92%; (iii) O_3, CH_2Cl_2, −78 °C, 1 h, Me_2S; (iv) $C_{14}H_{29}MgBr$, THF, 12 h, rt, 83% for two steps; (v) 80% AcOH, 0 °C to rt, 12 h, 91%; (vi) TBSCl, imidazole, CH_2Cl_2, DMAP, 0 °C to rt, 12 h, 86%; (vii) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt 2 h; (viii) TBAF, THF, rt, 2 h, 88% for two steps; (ix) Na, NH_3, THF, −78 °C, 30 min, 96%; (x) TFA:CH_2Cl_2 (1:1), rt, 6 h, 87%; (xi) Et_3N, AC_2O, CH_2Cl_2, 0 °C to rt, 4h, 94%.

1A.1.3.2. Apurba Datta *et al.*[11]

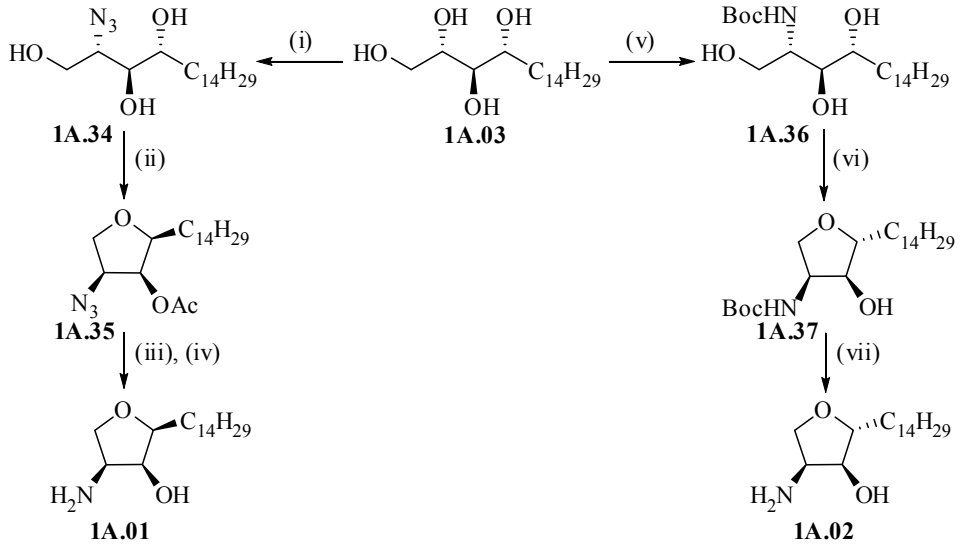
They have communicated their purported synthesis of jaspine B (**1A.01**), in this synthesis, L-serine was converted into butenolide **1A.31**. Treatment of **1A.31** with formic acid enabled deprotection of the acetonide, with subsequent Michael addition of the free hydroxyl group giving *cis*-fused bicycle **1A.32**. Subsequent reduction of **1A.32** with DIBAL-H and Wittig olefination gave **1A.33**. Hydrogenation and cleavage of the resultant oxazolidinone of **1A.33** afforded jaspine B (**1A.01**) (Scheme 1A.4).



Scheme 1A.4: *Reagents and conditions*: (i) HCO_2H, CH_2Cl_2, 0 °C then EtOAc, satd aq $NaHCO_3$, 79%; (ii) DIBAL-H, −78 °C, 83%; (iii) $C_{12}H_{25}Ph_3P^+Br^-$, *n*-BuLi, THF, −78 °C to rt, 81%; (iv) H_2, Pd/C, EtOAc, rt, 90%; (v) aq KOH, EtOH, reflux, 77%.

1A.1.3.3. Herman S. Overkleeft *et al.*[12]

Synthesis of pachastrissamine (**1A.01**) and 2-*epi*-pachastrissamine (**1A.02**), have reported by Overkleeft *et al*. by employing manipulation of D-*ribo*-phytosphingosine. Treatment of **1A.03** with TfN_3 resulted in azide **1A.34**. Subsequent Lewis acid-promoted cyclisation upon treatment with $BF_3{\cdot}EtO_2$ and trimethylorthoacetate (TMOA) gave tetrahydrofuran derivative **1A.35**. Removal of the acetate group followed by Staudinger reduction of the azide group gave pachastrissamine (**1A.01**) (Scheme 1A.5). The synthesis of 2-*epi*-pachastrissmine (**1A.02**) from **1A.03** was achieved *via* initial *N*-Boc protection, followed by selective tosylation of the primary hydroxyl and concomitant cyclisation to give **1A.37**, which on *N*-Boc deprotection gave 2-*epi*-jaspine B **1A.02** (Scheme 1A.5).

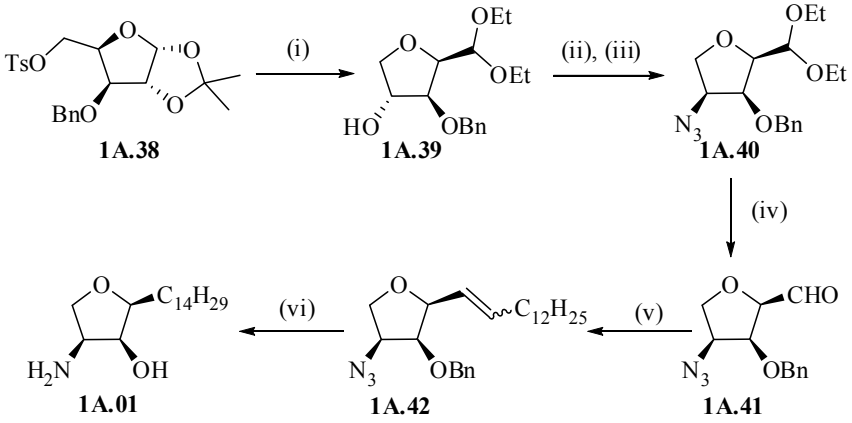


Scheme 1A.5: *Reagents and conditions*: (i) TfN_3, Na_2CO_3, $CuSO_4$, CH_2Cl_2, MeOH, H_2O, rt, 16 h, 96%; (ii) TMOA, $BF_3{\cdot}Et_2O$ (cat.), CH_2Cl_2, 0 °C to rt, 16 h, 92%; (iii) KO^{t}Bu, MeOH; (iv) Me_3P, PhMe/H_2O (24:1), rt, 16 h, 82% for two steps; (v) Boc_2O, Et_3N, THF, rt, 30 min, 92%; (vi) TsCl, pyridine/CH_2Cl_2 (1:1), rt, 16h, 83%; (vii) TFA, CH_2Cl_2, rt, 3 h, 95%.

1A.1.3.4. Yuguo Du *et al.*[13]

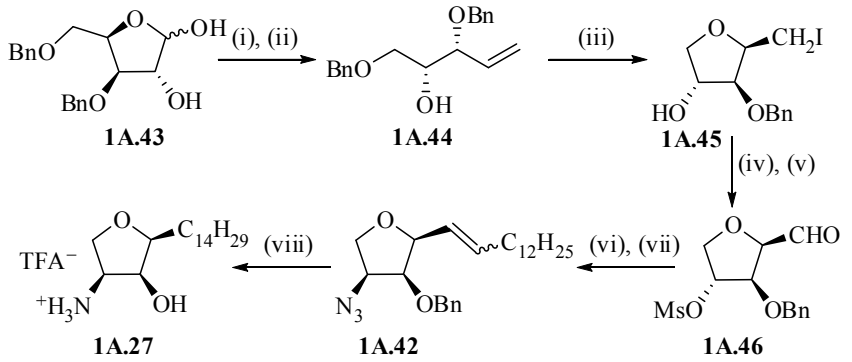
Tosylate **1A.38** was prepared from D-xylose in three steps. Subsequent treatment with HCl in EtOH gave **1A.39**, then mesylation and exposure to NaN_3 generated azide derivative **1A.40**. Hydrolysis of **1A.40** with aqueous TFA afforded

aldehyde **1A.41**, which was then subjected to Wittig olefination giving an inseparable mixture (*E*)- and (*Z*)-isomers of olefin **1A.42**. Finally, **1A.42** was hydrogenated to give pachastrissamine (**1A.01**) (Scheme 1A.6).



Scheme 1A.6: *Reagents and conditions*: (i) 5% HCl in EtOH (v/v), reflux, 3 h, 89%; (ii) MsCl, pyridine, rt, 4 h; (iii) NaN_3, NH_4Cl, DMF, 120 °C, 20 h, 71% for two steps; (iv) TFA (50% aq), CH_2Cl_2, rt, 30 min, 90%; (v) $C_{13}H_{27}Ph_3P^+Br^-$, *n*-BuLi, THF, −40 °C, 86%; (vi) H_2, $Pd(OH)_2/C$, MeOH/EtOAc, 5 h, 92%.

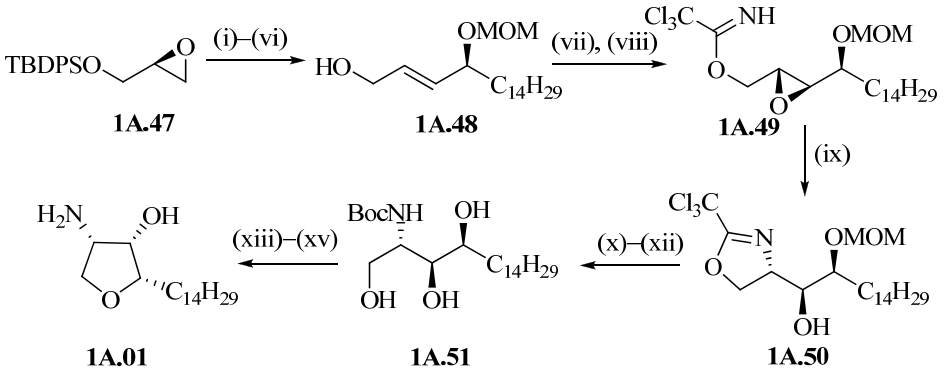
Subsequently, an improved and scaleable synthesis was reported by Du *et al*.,[13b] and it was also starting from D-xylose. In this approach, protected D-xylose derivative **1A.43** was treated with $NaIO_4$ followed by Wittig reaction gave **1A.44**. Iodine-promoted cyclofunctionalisation/debenzylation of **1A.44** afforded iodide **1A.45**, and subsequent oxidation of the iodomethyl group followed by treatment with MsCl gave mesylate **1A.46**. Wittig olefination of **1A.46**, followed by treatment of NaN_3 gave **1A.42**. Hydrogenation of **1A.42** in MeOH containing 1% TFA furnished target molecule, pachastrissamine **1A.27**, in a salt form (Scheme 1A.7).



Scheme 1A.7: *Reagents and conditions*: (i) $NaIO_4$, MeOH, H_2O; (ii) $CH_3Ph_3P^+Br^-$, *n*-BuLi, THF, −40 °C to rt, 82% for two steps; (iii) I_2, $NaHCO_3$, CH_3CN, 80%; (iv) $NaHCO_3$, DMSO, 150 °C, 6 min; (v) MsCl, pyridine, rt, 30 min, 74% for two steps; (vi) $C_{13}H_{27}Ph_3P^+Br^-$, *n*-BuLi, THF, −40 °C to rt, 90%, *Z*/*E* ratio 10/1; (vii) NaN_3, NH_4Cl, DMF, 120 °C, 20 h, 80%; (viii) H_2, Pd/C, MeOH, TFA, 5 h, 95%.

1A.1.3.5. J. A. Marco *et al.*[14]

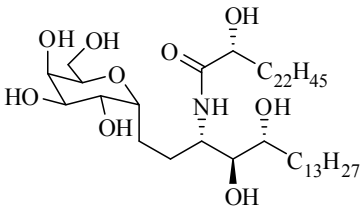
Marco and co-workers reported an enantiospecific synthesis of jaspine B (**1A.01**) from (*R*)-glycidol. *O*-TBDPS protected (*R*)-glycidol **1A.47** was initially treated with tridecylmagnesium bromide in the presence of CuI to afford the corresponding alcohol, which was then protected as its *O*-MOM derivative followed by desilylation, Swern oxidation, olefination and ester reduction gave allylic alcohol **1A.48**. Allylic alcohol **1A.48** was treated under Sharpless asymmetric epoxidation conditions, with (–)-DET, and then with trichloroacetonitrile in the presence of DBU to give imino ester derivative **1A.49**. Compound **1A.49** was then reacted with Et_2AlCl to generate oxazoline **1A.50**, subsequent hydrolysis, *N*-Boc protection and MOM deprotection gave triol **1A.51**. Triol **1A.51** was treated with TsCl, followed by K_2CO_3 in MeOH to induce cyclisation to give tetrahydrofuran derivative which on *N*-Boc deprotection gave pachastrissamine **1A.01** (Scheme 1A.8).



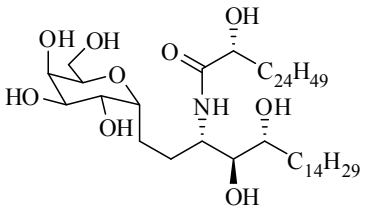
Scheme 1A.8: *Reagents and conditions*: (i) $C_{13}H_{27}MgBr$, CuI, THF, –10 to 0 °C, 82%; (ii) MOMCl, EtN^iPr_2, CH_2Cl_2, rt, 24 h, 94%; (iii) TBAF, THF, rt, 3 h, 94%; (iv) $COCl_2$, DMSO, Et_3N, CH_2Cl_2, –78 to –46 °C, 3 h; (v) $(^iPrO)_2P(O)CH_2CO_2Et$, LiBr, Et_3N, THF, rt; (vi) DIBAL-H, hexane, 0 °C, 2.5 h, 81% for three steps; (vii) (–)-DET, $Ti(O^iPr)_4$, $^tBuO_2H$, CH_2Cl_2 0 to 20 °C, 24 h, 89%; (viii) Cl_3CCN, DBD, CH_2Cl_2, 0 °C, 30 min; (ix) Et_2AlCl, CH_2Cl_2, 0 °C to rt, 5 h, 72% for two steps; (x) aq 1 M HCl, THF, rt, 5 h; (xi) Boc_2O, $NaHCO_3$, THF, rt, 16 h, 96% for two steps; (xii) TMSBr, CH_2Cl_2, –78 °C, 30 min, 75%; (xiii) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 20 min; (xiv) K_2CO_3, MeOH, rt, 16 h, 70% for two steps; (xv) TFA, CH_2Cl_2, 0 °C to rt, 45 min, then NaOH, MeOH, 5 min, 75%.

1A.2. Present Work:

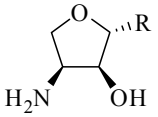
Spingolipids are ubiquitous as components of cell membranes. Some unusual spingolipids have been described from marine organisms. An example is a series of α-galactoceramides, agelasphins (e.g. **1A.52**), exhibiting potent in *vivo* antitumor activity but no in *vitro* cytotoxicity, from the sponge *Agelas mauritianus*.[15] This discovery led Natori and co-workers to the development of a synthetic anticancer agent (coded KRN7000, **1A.53**), which is now under clinical trial.[16] Studies on the marine sponge *Pachastrissa* sp. by Higa and co-workers in 2002, led to the isolation of a cyclic anhydrophytosphingosine, which they named as pachastrissamine (**1A.01**).[2] Shortly after (in 2003), Debitus and co-workers[3] reported the isolation of two anhydrophytosphighosines from the marine sponge *Jaspis* sp. and named as jaspine A (**1A.19**) and jaspine B (**1A.01**); pachastrissamine and jaspine B being identical. Jaspine B was reported to exhibit promising cytotoxic activity in the submicromolar range against P388, A549, HT29 and MEL28 (IC_{50} = 0.001 μg/mL) cancer cell lines. An analogous anhydrophytosphingosine 2-*epi*-jaspine B (**1A.02**) has been reported without stereochemistry as derivative of a plant metabolite.[4] Later its absolute structure was assigned by asymmetric synthesis of a compound **1A.14** having a shorter side chain.[6] In a recent report on the early synthesis of jaspine B has indeed revealed that the synthetic samples data given was matching with **1A.02**. This proposed an unwarranted synthesis of anhydrosphytosphingosine **1A.02**.[7]



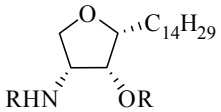
1A.52 Agelasphin 9a



1A.53 KRN7000



1A.02 R = $C_{14}H_{29}$
1A.14 R = $C_{12}H_{25}$



1A.54 R = H
1A.55 R = Ac

Figure 1A.3

The promising biological activity and novel structural features of jaspine B (**1A.01**) have encouraged us to undertake a synthetic work. In order to gain rapid access to products of biological interests, we have initiated a program to synthesize the jaspine enantiomer (**1A.54**) with a flexibility in placing the side chain, so as to synthesize a collection of the jaspine like small molecules (Figure 1A.3).

1A.2.1. Retrosynthesis

Our intended strategy (Figure 1A.4), exploit the pseudosymmetry present in pentodialdo-1,4-furanose **1A.56** to derive enantiomeric azidoalkynes **1A.62** and **1A.58**, which upon alkylation and hydrogenation should result in the synthesis of **1A.01** and **1A.54**, respectively. Alkyne functionality of azidoalkyne could be used for coupling reactions, and substitution of various alkyl halides to synthesize different analogues of pachastrissamine.

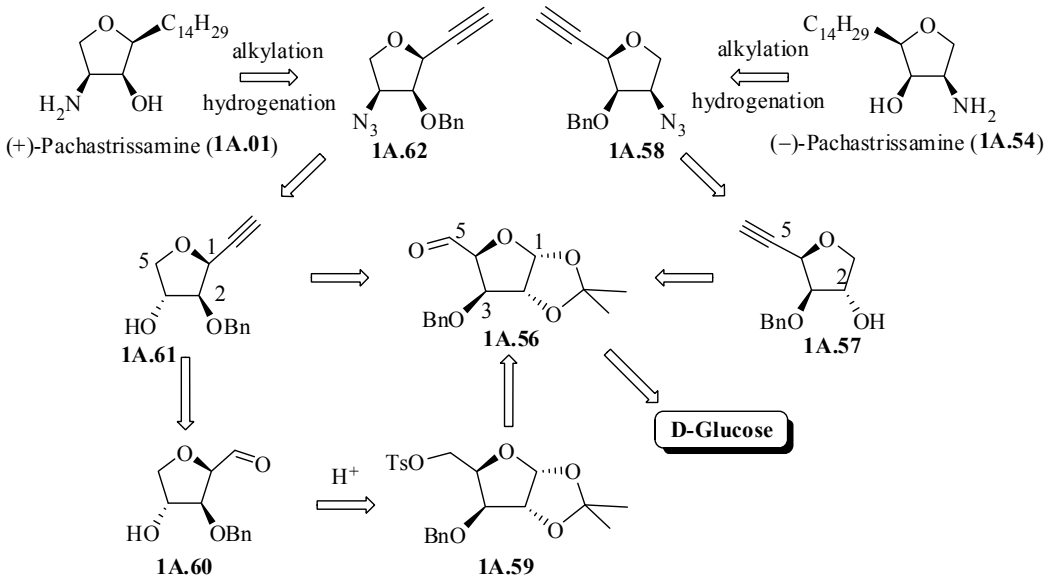


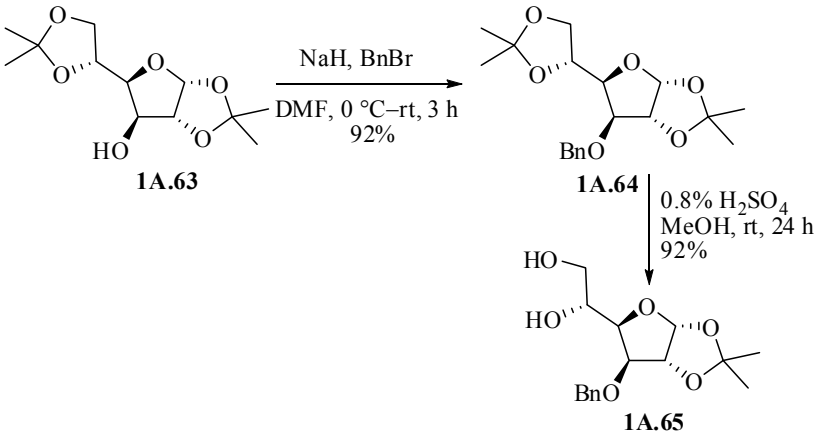
Figure 1A.4: Pseododesymmetrization strategy for (+)- and (–)-pachastrissamine

Azidoalkyne **1A.58** could be prepared from the alkynol **1A.57** with inversion of configuration at C(2) by azide displacement. We anticipated that the two enantiomeric furan systems **1A.57** and **1A.61** could be fashioned efficiently by employing selective Ohira-Bestmann alkynylation at either end of **1A.56**. The Bestmann alkynylation at C(5) is a direct proposition. Whereas for the Ohira-

Bestmann alkynylation at C(1), we are interested to bring the acid mediated ring isomerisation of **1A.59**.

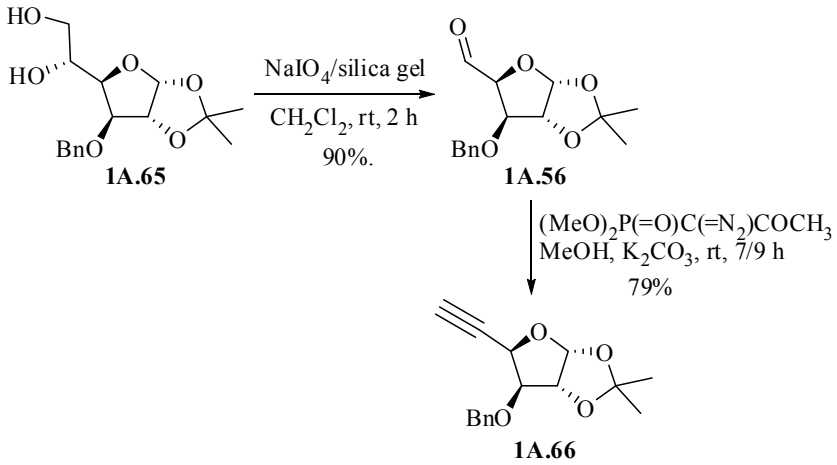
1A.2.2. Synthesis of Azidoalkyne 1A.58

As intended, the synthesis of azidoalkyne **1A.58** was initiated from D-glucose diacetonide **1A.63** (prepared from D-glucose by treating it with conc. H_2SO_4, anhydrous $CuSO_4$, in acetone.) Free hydroxyl (C3–OH), was protected as its benzyl ether by treating it with benzyl bromide and sodium hydride as base in DMF to obtain compound **1A.64**. Selective deprotection of 5,6-isopropylidene group by using 0.8% H_2SO_4 in methanol gave diol **1A.65** (Scheme 1A.9).



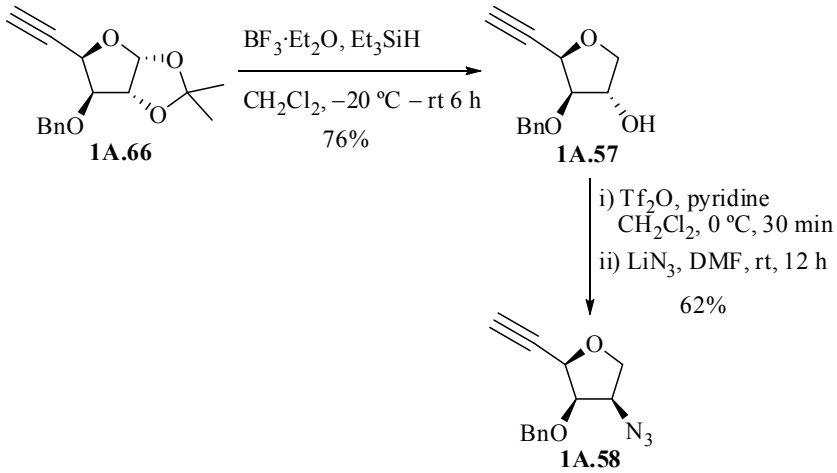
Scheme 1A.9: Synthesis of diol **1A.65**

Diol **1A.65** on oxidative cleavage by $NaIO_4$ adsorbed on silica gel, in DCM afforded the aldehyde **1A.56**, which was advanced to the next step without any purification/characterization. Treatment of **1A.56** with Ohira-Bestman reagent[17] in MeOH/K_2CO_3 gave the alkyne **1A.66** (Scheme 1A.10). In the ^1H spectum of alkyne **1A.66**, the acetylenic proton resonated at δ 2.61 as a doublet with J = 2.3 Hz. The ^{13}C spectrum revealed alkyne functionality at 76.5 ppm, (d) and 77.6 ppm, (s) and the IR spectrum showed acetylenic C–H stretching at 3305 cm^{-1} and alkyne C≡C stretching at 2135 cm^{-1}.



Scheme 1A.10: Synthesis of alkyne **1A.66**

Reductive deketalization of the alkyne **1A.66** using excess triethylsilane in the presence of $BF_3{\cdot}Et_2O$ in DCM afforded the alkynol **1A.57**.[18] The structure of compound **1A.57** was established with the help of spectral and analytical data. In the ^1H NMR spectrum of alkynol **1A.57**, the signal corresponding to the anomeric–H (doublet at δ 5.96 of **1A.66**) was absent. Two new dds corresponding to the C(1)–H_2 were resonated at δ 3.69 (J = 2.2, 9.7 Hz, 1H), and at δ 4.20 (J = 4.7, 9.8 Hz, 1H). This was further substantiated by the appearance of O–CH_2 resonance at 73.1(t) ppm, in the ^{13}C NMR specrum of **1A.57**. IR spectrum showed O–H stretching at 3424 cm^{-1} and the mass spectrum, elemental analysis further confirmed the assigned structure.



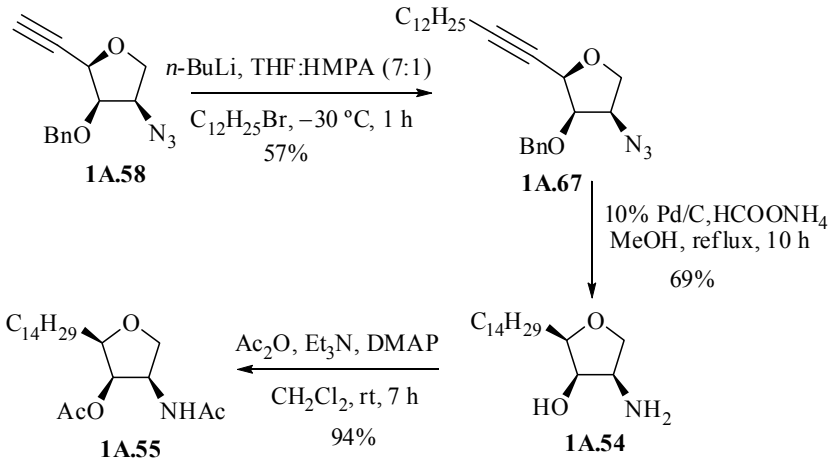
Scheme 1A.11: Synthesis of azidoalkyne **1A.58**

After having established an easy protocol for the preparation of the alkynol **1A.57**, our next concern was the synthesis of the advanced azidoalkyne **1A.58** and its further elaboration into enatiomer of pachastrissamine. Various leaving groups at C(3)–O such as mesyl, tosyl, and triflyl have been explored for the azide displacment reaction, amongst which, the reaction with triflate was found to be proceeding at rt. Thus the alkynol **1A.57** was transformed to the corresponding azidoalkyne **1A.58** by treatment with Tf_2O in pyridine followed by reacting the intermediate triflate with LiN_3 in DMF at room temperature (Scheme 1A.11). The spectral and analytical data of **1A.58** were in well agreement with the proposed structure. In the ^{1}H NMR spectrum, acetylenic proton showed doublet at 2.65 with J = 2.3 Hz and The ^{13}C NMR spectrum showed doublet at 59.9 ppm for C(2) carbon atom, alkyne carbon showed peaks at 78.8 ppm as singlet and 79.4 ppm as doublet. In the IR spectrum absorption peaks at 2109 and 2401 cm^{-1} indicated presence of alkyne and azide functionality respectively.

1A.2.3. Synthesis of (–)-pachastrissamine

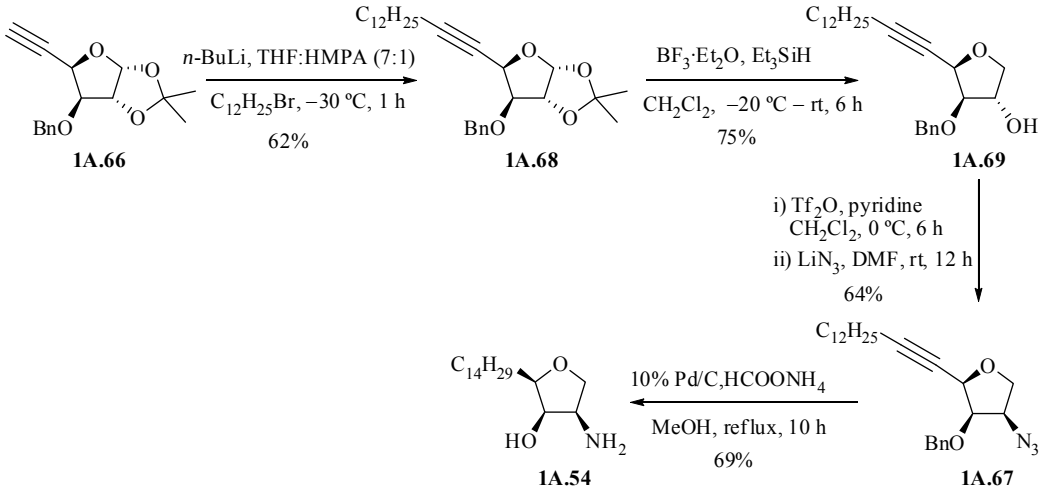
After examining a set of bases and reaction conditions, we concluded that the alkylation of azidoalkyne **1A.58** with 1-bromododecane was facile using *n*-BuLi in THF-HMPA and the alkylated product **1A.67** was obtained in 57% yield.[19] The structural integrity of the alkylated product **1A.67** was established with the help of NMR and mass spectral analyses. In the ^{1}H NMR spectrum, nine long chain methylene protons showed broad singlet at δ 1.23, terminal methyl group showed triplet at δ 0.87 with coupling constant 6.7 Hz, mass spectrum showed peaks at 429.3 (100%, $[M+NH_4]^+$), 434.3 (39%, $[M+Na]^+$). Hydrogenolysis of **1A.67** was effected by refluxing in methanol in the presence of ammonium formate and cat. 10% Pd/C to afford (–)-pachastrissamine **1A.54** as a white powder. The requisite (–)-pachastrissamine **1A.54** was characterized after chromatographic purification. The spectral and analytical data of synthetic **1A.54** were in agreement with the data reported for the natural pachastrissamine (**1A.01**) (Table1A.1). Specific rotation of the synthesized (–)-pachastrissamine **1A.54** was $[\alpha]_D^{25}$ –8.61° (*c* 0.6, MeOH) [lit. $[\alpha]_D^{25}$ +18° (*c* 0.1, EtOH),[2] and $[\alpha]_D^{20}$ +7° (*c* 0.1, $CHCl_3$)[3]]. In IR spectrum, broad peak at 3341 cm^{-1} indicated presence of free hydroxyl and amine groups. Further it was characterized by *N*,*O*-diacetate derivative **1A.55** prepared by treatment of (–)-pachastrissamine **1A.54** with acetic anhydride and triethyl amine in DCM (Scheme

1A.12). The ^{1}H NMR spectrum showed two singlets at δ 1.97 and 2.15, revealed the presence of two acetate groups, and other peaks in ^{1}H, ^{13}C NMR were well comparable with reported data. The ^{13}C NMR spectrum showed two singlets at 169.6 and 169.7 ppm for carbonyl carbons of two acetates. Other analytical data such as IR (1741 cm^{-1}), mass (*m/z* 384.4 (24%, $[M+H]^+$), 406.5 (100%, $[M+Na]^+$), 422.3 (14%, $[M+K]^+$), and microanalysis were in well agreement with the assigned diacetate derivative **1A.55**.



Scheme 1A.12: Synthesis of (–)-pachastrissamine (**1A.54**)

Alternatively by changing the series of reaction sequence we have synthesized our target (–)-pachastrissamine (**1A.54**). Alkyne **1A.66** was alkylated under standard alkylation condition with 1-bromododecane using *n*-BuLi in THF-HMPA to get alkylated compound **1A.68**. Compound **1A.68** under reductive deketalization using excess triethylsilane in the presence of $BF_3{\cdot}Et_2O$ in DCM gave alkynol **1A.69** in 75% yield. In the ^{1}H NMR spectrum of **1A.69** two singlets of acetonide protection in **1A.68** at δ 1.28 and 1.45 were disappeared. In the ^{13}C NMR spectrum two triplets were appeared at 72.4 and 72.8 ppm for C(1) and benzylic methylene carbons and IR spectrum showed absorption at 3429 cm^{-1} of free hydroxyl group. Alkynol **1A.69** was transformed to the azidoalkyne **1A.67** by treatment with Tf_2O in pyridine followed by reacting the intermediate triflate with LiN_3 in DMF at room temperature in good yield. Hydrogenolysis of **1A.67** was effected by refluxing in methanol in the presence of ammonium formate and cat. 10% Pd/C to afford (–)-pachastrissamine **1A.54** (Scheme 1A.13).



Scheme 1A.13: Synthesis of (–)-pachastrisamine (**1A.54**).

Table 1A.1: ^{1}H NMR ($CDCl_3$, 500 MHz), ^{13}C NMR ($CDCl_3$, 125 MHz) data of natural jaspine B (**1A.01**) and ^{1}H NMR ($CDCl_3$, 200 MHz), ^{13}C NMR ($CDCl_3$ + DMSO-D_6, 50 MHz) data of synthetic (–)-jaspine B (**1A.54**).

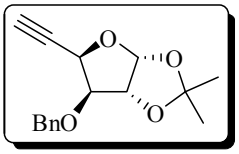
	Natural pachastrissamine		(–)-pachastrissamine	
	^{13}C	^{1}H	^{13}C	^{1}H
1a	72.2	3.51 (1H, dd, *J* = 7.0, 8.5 Hz)	70.4	3.51 (1H, dd, *J* = 7.3, 8.3 Hz,)
1b	72.2	3.95 (1H, dd, *J* = 7.0, 8.5 Hz)	70.4	3.91 (1H, dd, *J* = 7.3, 8.5 Hz)
2	54.2	3.68 (1H, dt, *J* = 5.0, 7.0 Hz)	54.3	3.61−3.66 (m, 1H)
3	71.6	3.88 (1H, dd, *J* = 3.5, 5.0 Hz)	71.0	3.86 (1H, dd, *J* = 3.6, 4.3 Hz)
4	83.1	3.75 (1H, ddd, *J* = 3.5, 7.0, 7.5 Hz)	82.5	3.70−3.74 (m, 1H)
5	29.3	1.71 (2H, m)	29.4	1.61−1.68 (2H, m)
6-17	22.0-31.0	1.20-1.70 (24H, m)	22.2-31.4	1.24 (24H, m)
CH_3	14.0	0.87 (3H, t, *J* = 6.5 Hz)	13.8	0.87 (3H, t, *J* = 7.0 Hz)
OH,		2.10 (bs)		1.79 (bs)
NH_2		2.10 (bs)		1.79 (bs)

Conclusion

A simple chiral pool strategy for the synthesis of pachastrissamine has been developed. Starting from the known and easily available glucose diacetonide, pachastrissamine enantiomer has been synthesized in six linear steps with an overall yield of 13.2%. As we have added the side chain at the penultimate step, our strategy is endowed with sufficient flexibility for the synthesis of pachastrissamine analogues with variation of side chain or alteration of its length.

1A.3. Experimental:

1,2-*O*-Isopropylidene-5,5,6,6-tetradehydro-5,6-dideoxy-3-*O*-benzyl-α-D-*xylo*-hexofuranose (1A.66)



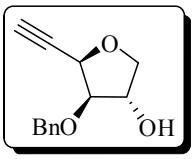
To a solution of the diol **1A.65** (856 mg, 2.76 mmol) in methanol (20 mL) and water (1.5 mL), $NaIO_4$ (708 mg, 3.31 mmol) was added and stirred for 30 min at rt. The mixture was filtered through *Celite* and the *Celite* pad was washed with methanol. The combined filtrates were concentrated under reduced pressure in order to remove methanol. The residue was extracted in ethyl acetate, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the aldehyde **1A.56** (690 mg, 90 %) as a colorless oil.

A suspension of aldehyde **1A.56** (690 mg, 2.48 mmol) and K_2CO_3 (411 mg, 2.99 mmol) in methanol (12 mL) was treated with Ohira-Bestmann reagent (572 mg, 2.99 mmol) and stirred for 8 h at rt. The reaction mixture was concentrated under reduced pressure and the residue was partitioned in water and ethyl acetate. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (5% ethyl acetate in petroleum ether) gave the alkyne **1A.66** (553 mg, 79% yield) as a colorless oil.

Mol. Formula	: $C_{16}H_{18}O_4$
$[\alpha]_D^{25}$	: +3.1 (*c* 1.1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3307, 3063, 2985, 2864, 2135, 1605, 1497, 1455, 1360, 1248, 1217, 1162, 1078 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.29 (s, 3H), 1.46 (s, 3H), 2.61 (d, *J* = 2.3 Hz, 1H), 3.99 (d, *J* = 3.0 Hz, 1H), 4.58 (d, *J* = 3.7 Hz, 1H), 4.73 (d, *J* = 12.2 Hz, 1H), 4.81 (d, *J* = 12.2 Hz, 1H), 4.82 (d, *J* = 2.3 Hz, 1H), 5.96 (d, *J* = 3.7 Hz, 1H), 7.28−7.41 (m, 5H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 26.1 (q), 26.7 (q), 70.6 (d), 72.6 (t), 76.5 (d), 77.6 (s), 82.4 (d), 82.8 (d), 104.7 (d), 111.9 (s), 127.7 (d, 2C), 127.9 (d), 128.4 (d, 2C), 137.3 (s) ppm.
ESI-MS (*m/z*)	: 275.5 (2%, $[M+H]^+$), 292.6 (17%, $[M+NH_4]^+$), 297.6

	(100%, $[M+Na]^+$).
Elemental	Calcd.: C, 70.06; H, 6.61%.
Analysis	Found: C, 70.17; H, 6.49%.

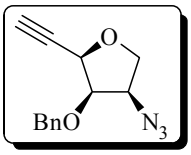
1,4-Anhydro-3-*O*-benzyl-5,5,6,6-tetradehydro-5,6-dideoxy-*xylo*-hexitol (1A.57)



To a solution of **1A.66** (800 mg, 2.92 mmol) in DCM (20 mL) at –20 °C was added triethylsilane (2.8 mL, 17.51 mmol) followed by freshly distilled $BF_3{\cdot}Et_2O$ (1.1 mL, 8.75 mmol). The reaction mixture was slowly brought to rt and stirred for 6 h. The reaction mixture was cooled and saturated solution of $NaHCO_3$ was added until it reached to neutral pH. The reaction mixture was partitioned between water and DCM. The organic phase was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (25% ethyl acetate in petroleum ether) to procure the alcohol **1A.57** (485 mg, 76% yield) as a colorless oil.

Mol. Formula	: $C_{13}H_{14}O_3$
$[\alpha]_D^{25}$	: +50.02 (*c* 0.9, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3424, 3305, 3016, 2939, 2124, 1604, 1398, 1216, 1097, 1047, 970, 923 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.99 (bs, 1H), 2.60 (d, *J* = 2.3 Hz, 1H), 3.69 (dd, *J* = 2.2, 9.7 Hz, 1H), 3.92 (dd, *J* = 2.4, 4.7 Hz, 1H), 4.20 (dd, *J* = 4.7, 9.8 Hz, 1H), 4.34−4.37 (m, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.79 (dd, *J* = 2.4, 4.7 Hz, 1H), 7.29−7.41 (m, 5H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 70.5 (d), 72.5 (t), 73.1 (t), 75.1 (d), 76.4 (d), 78.8 (s), 84.8 (d), 127.7 (d, 2C), 127.8 (d), 128.3 (d, 2C), 137.5 (s) ppm.
ESI-MS (*m/z*)	: 241.34 (100%, $[M+Na]^+$), 257.28 (25%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 71.54; H, 6.47%. Found: C, 71.40; H, 6.53%.

1,4-Anhydro-2-azido-3-*O*-benzyl-5,5,6,6-tetradehydro-2,5,6-trideoxy-*lyxo*-hexitol (1A.58)



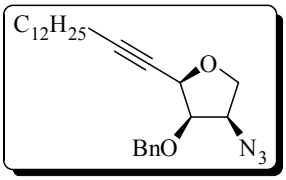
At –20 °C, a solution of **1A.57** (1.56 g, 7.15 mmol) and pyridine (1.7 mL, 21.46 mmol) in DCM (15 mL) was treated with triflic anhydride (1.4 mL, 8.58 mmol) and the reaction mixture was stirred for 30 min at rt. The mixture was neutralized with 1N HCl and extracted with DCM. The combined organic phase was washed with saturated $NaHCO_3$ and water, dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the intermediate triflate product as a colorless liquid (2.3 g).

The above triflate (2.3 g) was dissolved in DMF (10 mL) and cooled to 0 °C. Lithium azide (1.67 g, 34.2 mmol) was slowly added and stirred at rt for 12 h. The reaction mixture was diluted with ethyl acetate and washed with water (3 x 25 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (8% ethyl acetate in petroleum ether) gave azido alkyne **1A.58** (1.08 g, 62.3% yield) as a colorless oil.

Mol. Formula	: $C_{13}H_{13}N_3O_2$
$[\alpha]_D^{25}$	: +70.1 (*c* 1.3, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3306, 3019, 2401, 2109, 1728, 1608, 1455, 1385, 1215, 1127, 1068, 928 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.65 (d, *J* = 2.3 Hz, 1H), 3.88−3.95 (m, 1H), 3.95−4.04 (m, 2H), 4.16 (t, *J* = 5.6 Hz, 1H), 4.72 (dd, *J* = 2.3, 6.0 Hz, 1H), 4.74 (d, *J* = 11.9 Hz, 1H), 4.83 (d, *J* = 11.9 Hz, 1H), 7.33−7.41 (m, 5H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 59.9 (d), 69.4 (t), 69.7 (d), 73.2 (t), 76.9 (d), 78.8 (s), 79.4 (d), 127.9 (d, 2C), 128.1 (d), 128.5 (d, 2C), 137.0 (s) ppm.
ESI-MS (*m/z*)	: 266.34 (100%, $[M+Na]^+$), 282.39 (39%, $[M+K]^+$).

Elemental Analysis	Calcd.: C, 64.19; H, 5.39; N, 17.27%. Found: C, 64.03; H, 5.51; N, 17.19%.

6-*C*-Dodecyl-1,4-Anhydro-2-azido-3-*O*-benzyl-5,5,6,6-tetradehydro-2,5,6-trideoxy-*lyxo*-hexitol (1A.67)

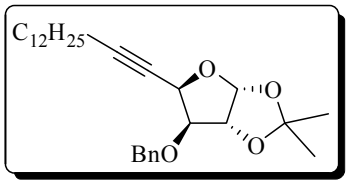


A solution of **1A.58** (0.5 g, 2.06 mmol) in THF (15 mL) and HMPA (3 mL) was cooled to –78 °C and treated with *n*-BuLi (1.4 mL, 1.6 M in hexanes, 2.62 mmol) was added drop-wise and stirred for 20 min. To this, dodecyl bromide (0.75 mL, 3.09 mmol) was introduced slowly and the reaction mixture was warmed to –30 °C and allowed to stirr for 1 h at this temperature. The reaction mixture was quenched by saturated aqueous solution of NH_4Cl and extracted with ethyl acetate. The combined organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (7% ethyl acetate in petroleum ether) to produce **1A.67** (0.48 g, 57% yield) as a colorless oil.

Mol. Formula	: $C_{25}H_{37}N_3O_2$
$[\alpha]_D^{25}$	: +59.8 (*c* 1.3, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3018, 2928, 2856, 2237, 2108, 1725, 1456, 1350, 1216, 1126, 1057, 927 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.87 (t, *J* = 6.7 Hz, 3H), 1.23 (bs, 18H), 1.51 (q, *J* = 7.1 Hz, 2H), 2.25 (dt, *J* = 2.0, 6.9 Hz, 2H), 3.86 (dt, *J* = 1.5, 5.7 Hz, 1H), 3.90−4.01 (m, 2H), 4.11 (t, *J* = 5.4 Hz, 1H), 4.68−4.73 (m, 1H), 4.73 (d, *J* = 11.9 Hz, 1H), 4.85 (d, *J* = 11.9 Hz, 1H), 7.29−7.45 (m, 5H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 14.0 (q), 18.9 (t), 22.6 (t), 28.4 (t), 28.8 (t), 29.1 (t), 29.3 (t), 29.4 (t), 29.6 (t, 3C), 31.8 (t), 60.0 (d), 68.8 (t), 70.5 (d), 73.0 (t), 74.6 (s), 79.6 (d), 89.9 (s), 127.7 (d, 2C), 127.8 (d), 128.3 (d, 2C), 137.3 (s) ppm.
ESI-MS (*m/z*)	: 429.32 (100%, $[M+NH_4]^+$), 434.27 (39%, $[M+Na]^+$).

Elemental Analysis	Calcd.: C, 72.95; H, 9.06; N, 10.21%. Found: C, 73.11; H, 9.20; N, 10.01%.

6-*C*-dodecyl-1,2-*O*-Isopropylidene-3-*O*-benzyl-5,5,6,6-tetradehydro-2,5,-dideoxy-α-D-*xylo*-hexofuranose (1A.68)

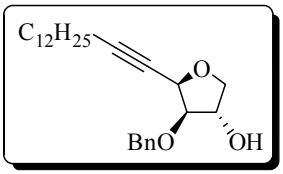


A solution of **1A.66** (0.5 g, 2.06 mmol) in THF (15 mL) and HMPA (3 mL) was cooled to –78 °C and treated with *n*-BuLi (1.4 mL, 1.6 M in hexanes, 2.62 mmol) and stirred for 20 min. To this, dodecyl bromide (0.75 mL, 3.085 mmol) was added dropwise and the reaction mixture was warmed to –30 °C and allowed to stirr for 1 h at this temperature. The reaction mixture was quenched by saturated aqueous solution of NH_4Cl and extracted with ethyl acetate. The combined organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (4% ethyl acetate in petroleum ether) to produce **1A.68** (0.5 g, 62% yield) as a colorless oil.

Mol. Formula	: $C_{28}H_{42}O_4$
$[\alpha]_D^{25}$	: +10.1 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3019, 2927, 2855, 2244, 1609, 1497, 1251, 1165, 1076, 1023 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.87 (t, *J* = 6.7 Hz, 3H), 1.24 (bs, 18H), 1.28 (s, 3H), 1.45 (s, 3H), 1.49–1.58 (m, 2H), 2.26 (dt, *J* = 2.0, 7.0 Hz, 2H), 3.92 (d, *J* = 2.9 Hz, 1H), 4.56 (d, *J* = 3.9 Hz, 1H), 4.73 (d, *J* = 12.1 Hz, 1H), 4.82 (d, *J* = 12.1 Hz, 1H), 4.81–4.83 (m, 1H), 5.95 (d, *J* = 3.9 Hz, 1H), 7.29–7.37 (m, 5H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 14.0 (q), 18.9 (t), 22.6 (t), 26.1 (q), 26.7 (q), 28.4 (t), 28.9 (t), 29.1 (t), 29.3 (t), 29.5 (t), 29.6 (t, 3C), 31.9 (t), 71.1 (d), 72.5 (t), 73.7 (s), 82.7 (d), 83.0 (d), 89.3 (s), 104.5 (d), 111.7 (s), 127.6 (d, 2C), 127.7 (d), 128.3 (d, 2C), 137.7 (s) ppm.
ESI-MS (*m/z*)	: 460.44 (48%, $[M+NH_4]^+$), 465.37 (100%, $[M+Na]^+$).

Elemental Analysis	Calcd.: C, 75.98; H, 9.56%. Found: C, 75.82; H, 9.61%.

6-*C*-dodecyl-1,4-Anhydro-3-*O*-benzyl-5,5,6,6-tetradehydro-5,6-dideoxy-*xylo*-hexitol (1A.69)

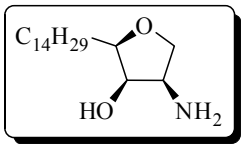


To a solution of **1A.68** (700 mg, 1.58 mmol), in DCM (18 ml), at –20 °C was added triethylsilane (1.5 mL, 9.49 mmol), followed by freshly distilled $BF_3{\cdot}Et_2O$ (0.6 mL, 4.76 mmol). Reaction mixture was slowly brought to room temperature and stirred for 6 h. Reaction mixture was cooled and saturated solution of $NaHCO_3$ was added until neutral pH. Aqueous phase was extracted with DCM. The combined extracts were washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The purification of residue by silica gel chromatography (25% ethyl acetate in petroleum ether) gave **1A.69** (458 mg, 75% yield) as a colorless oil.

Mol. Formula	: $C_{25}H_{38}O_3$
$[\alpha]_D^{25}$	: +58.59 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3429, 3014, 2927, 2855, 2234, 1604, 1497, 1455, 1216, 1158, 1098, 1029, 973 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.87 (t, *J* = 6.7 Hz, 3H), 1.23 (bs, 18H), 1.48–1.58 (m, 2H), 1.89 (bs, 1H), 2.25 (dt, *J* = 2.0, 7.0 Hz, 2H), 3.65 (dd, *J* = 2.3, 9.7 Hz, 1H), 3.86 (q, *J* = 2.2 Hz, 1H), 4.21 (dd, *J* = 4.9, 9.7 Hz, 1H), 4.34–4.39 (m, 1H), 4.65 (d, *J* = 12.1 Hz, 1H), 4.76–4.80 (m, 1H), 4.80 (d, *J* = 12.1 Hz, 1H), 7.30–7.41 (m, 5H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 14.0 (q), 18.9 (t), 22.6 (t), 28.4 (t), 28.9 (t), 29.1 (t), 29.3 (t), 29.4 (t), 29.6 (t, 3C), 31.8 (t), 71.0 (d), 72.4 (t), 72.8 (t), 74.7 (s), 75.5 (d), 85.1 (d), 89.1 (s), 127.6 (d, 2C), 127.7 (d), 128.3 (d, 2C), 137.8 (s) ppm.
ESI-MS (*m/z*)	: 387.5 (4%, $[M+H]^+$), 404.5 (29%, $[M+NH_4]^+$), 409.4 (100%, $[M+Na]^+$).

Elemental Analysis	Calcd.: C, 77.68; H, 9.91%. Found: C, 77.53; H, 9.84%.

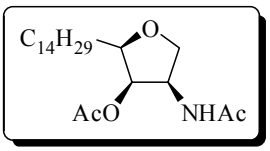
(–)-Pachastrissamine (1A.54)



To a suspension of **1A.67** (150 mg, 0.36 mmol) and ammonium formate $HCOONH_4$ (250 mg, 3.96 mmol) in methanol (4 mL), was added Pd/C (10% content, 15 mg) and refluxed for 10 h. The reaction mixture was cooled and filtered through *celite* and *celite* pad was washed with methanol. The combined filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1:4:95, aq ammonium hydroxide/methanol/chloroform) to obtain (–)- pachastrissamine (jaspine B) **1A.54** (75 mg, 69% yield) as white solid.

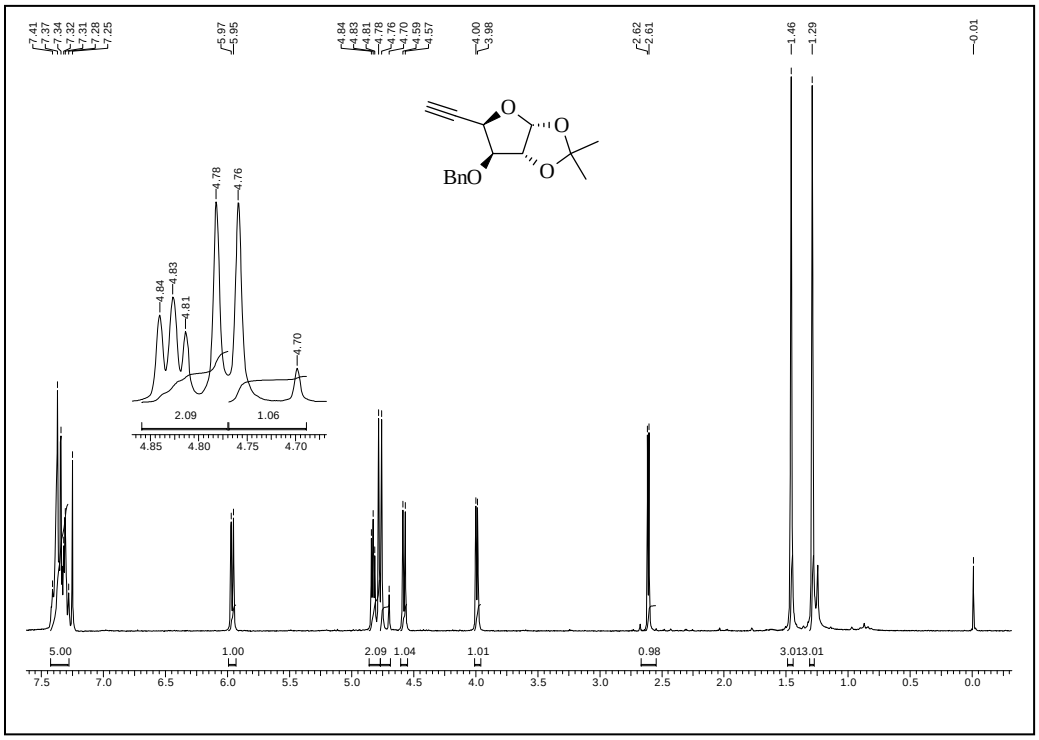
Mol. Formula	: $C_{18}H_{37}NO_2$
M. P.	: 95.8 – 96.6 °C
$[\alpha]_D^{25}$	: –8.6 (*c* 0.6, MeOH).
IR ($CHCl_3$) $\tilde{\nu}$	: 3341, 2923, 2850, 1470, 1216, 1070, 1036, 988 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.24 (m, 24H), 1.61–1.68 (m, 2H), 1.79 (bs, 3H), 3.51 (dd, *J* = 7.3, 8.3 Hz, 1H), 3.61–3.66 (m, 1H), 3.70–3.74 (m, 1H), 3.86 (dd, *J* = 3.6, 4.3 Hz, 1H), 3.91 (dd, *J* = 7.3, 8.5 Hz, 1H).
^{13}C NMR ($CDCl_3$,DMSO-D_6, 50 MHz)	: 13.8 (q), 22.2 (t, 2C), 25.7 (t), 28.8 (t), 28.9 (t), 29.1 (t, 2C), 29.2 (t, 3C), 29.4 (t), 29.5 (t), 31.4 (t), 54.3 (d), 70.4 (t), 71.0 (d), 82.5 (d) ppm.
ESI-MS (*m/z*)	: 300.0 (100%, $[M+1]^+$), 322.0 (10%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 72.19; H, 12.45; N, 4.68%. Found: C, 72.10; H, 12.51; N, 4.73%.

***N,O*-Diacetyl pachastrissamine (1A.55)**

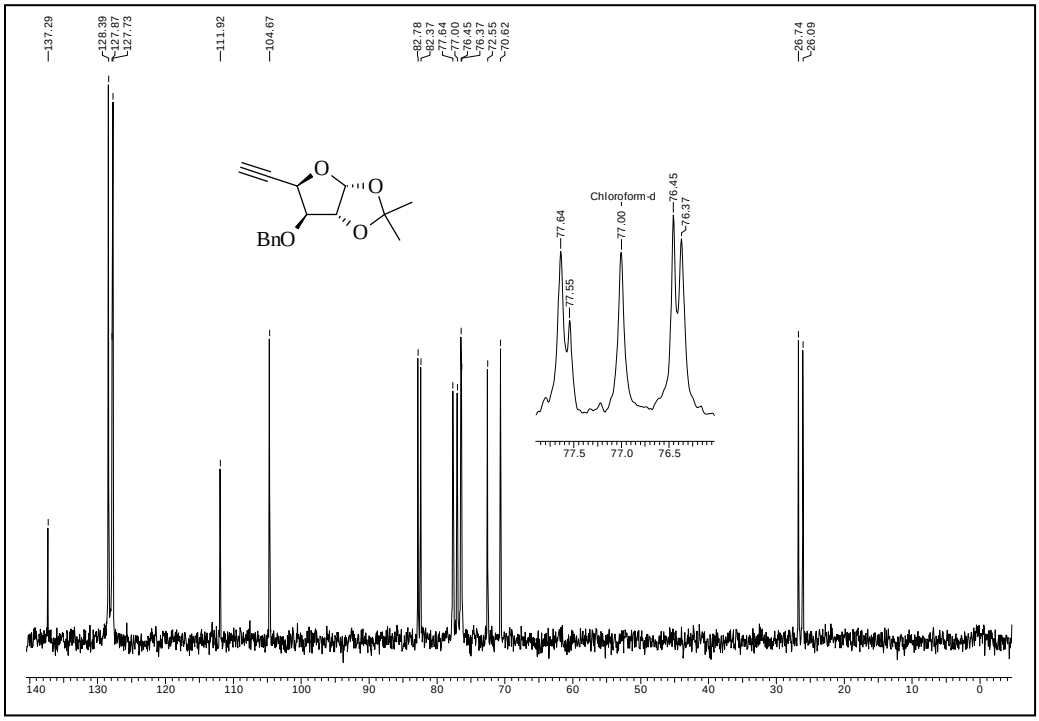


To a solution of **1A.54** (30 mg, 0.1 mmol) in pyridine (1.5 mL) was added acetic anhydride (0.5 ml, 5 mmol). The reaction mixture was stirred for 7 h at rt. Pyridine was removed under reduced pressure and the crude was purified by silica gel chromatography (40% ethyl acetate in petroleum ether) to produce diacetate of (–)-pachastrissmine **1A.55** (36 mg, 94 %) as a white crystalline solid.

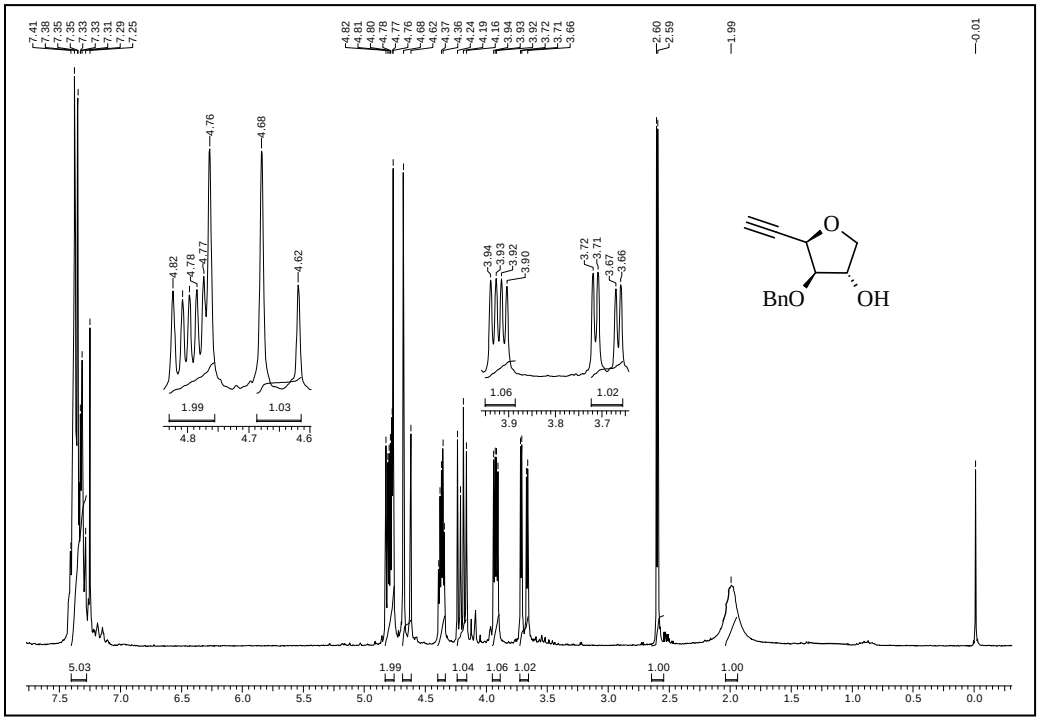
Mol. Formula	: $C_{22}H_{41}NO_4$
M. P.	: 93−96 °C
$[\alpha]_D^{25}$	: +27.6 (*c* 0.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 2927, 2855, 1741, 1671, 1512, 1466, 1216, 1051 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.87 (t, *J* = 6.8 Hz, 3H), 1.24 (bs, 26H), 1.58 (bs, 1H), 1.97 (s, 3H), 2.15 (s, 3H), 3.56 (dd, *J* = 7.7, 8.2 Hz, 1H), 4.05 (dd, *J* = 8.2, 8.5 Hz, 1H), 4.74–4.86 (m, 1H), 5.35 (dd, *J* = 3.4, 5.3 Hz, 1H), 5.55 (d, *J* = 8.3 Hz , 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 14.2 (q), 20.7 (q), 22.7 (t), 23.2 (q), 26.1 (t), 29.4 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.6 (t), 29.8 (t, 5C), 32.0 (t), 51.4 (d), 70.1 (t), 73.7 (d), 81.2 (d), 169.6 (s), 169.7 (s) ppm.
ESI-MS (*m/z*)	: 384.4 (24%, $[M+H]^+$), 406.5 (100%, $[M+Na]^+$), 422.3 (14%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 68.89; H, 10.77; N, 3.65%. Found: C, 68.74; H, 10.87; N, 3.78%.



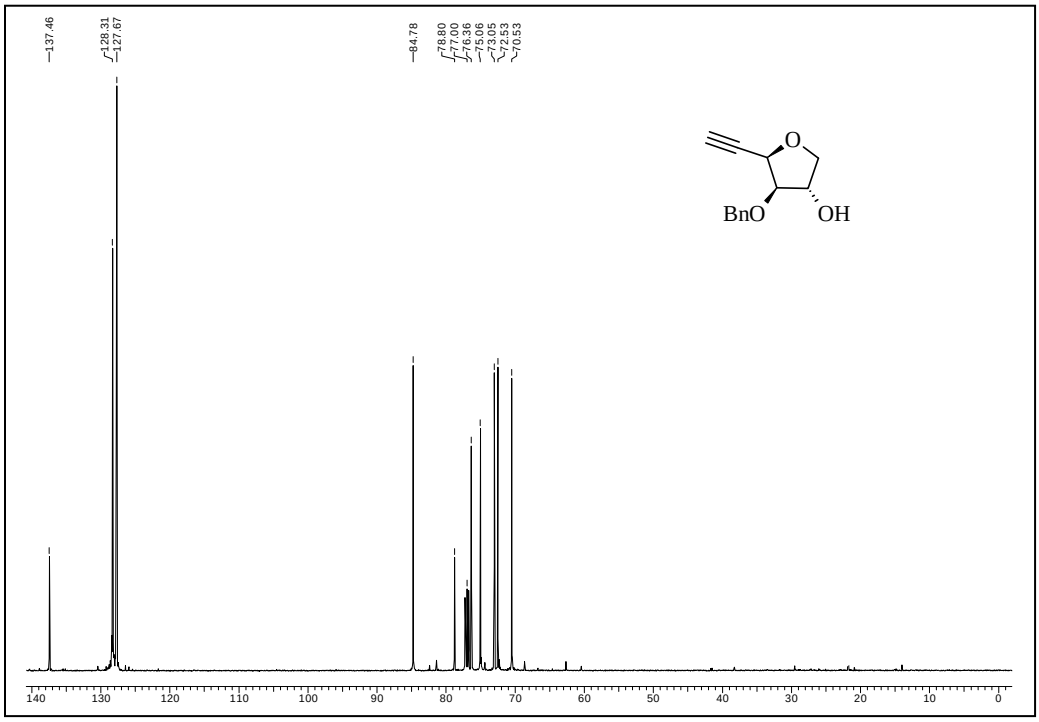
^{1}H NMR Spectrum of 1A.66 in $CDCl_3$



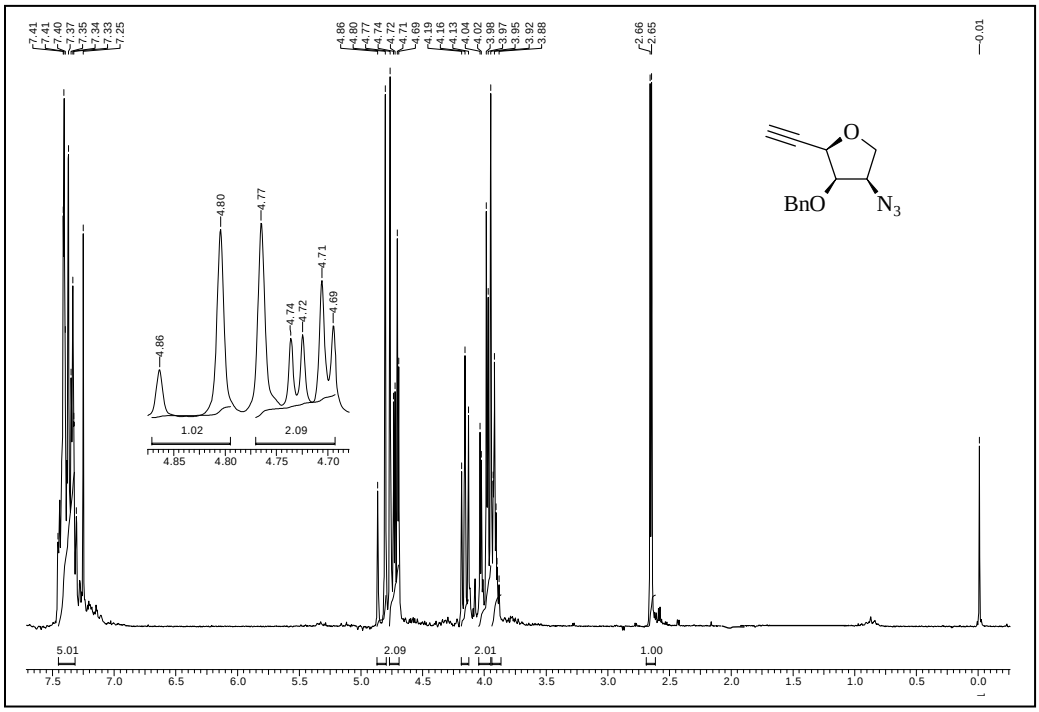
^{13}C NMR Spectrum of 1A.66 in $CDCl_3$



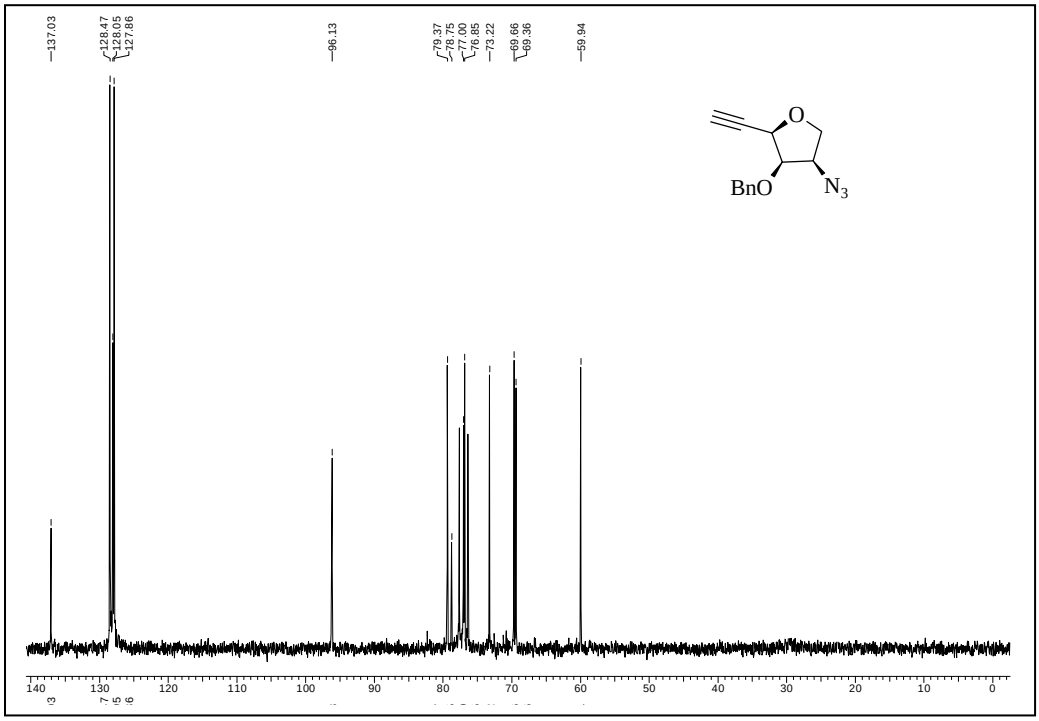
^{1}H NMR Spectrum of 1A.57 in $CDCl_3$



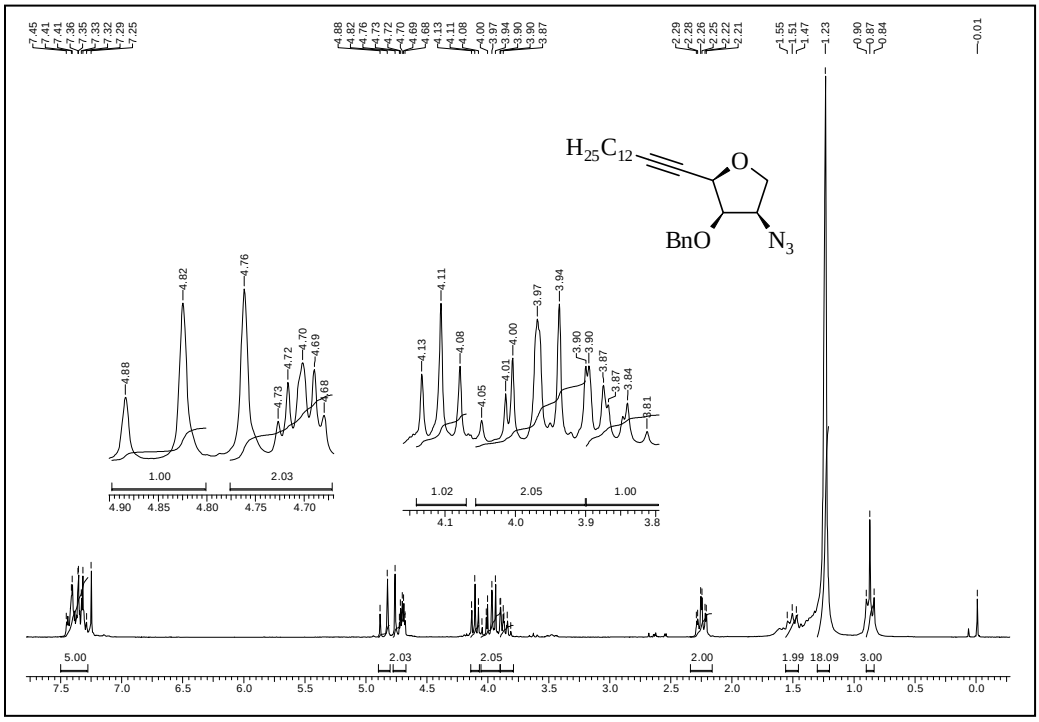
^{13}C NMR Spectrum of 1A.57 in $CDCl_3$



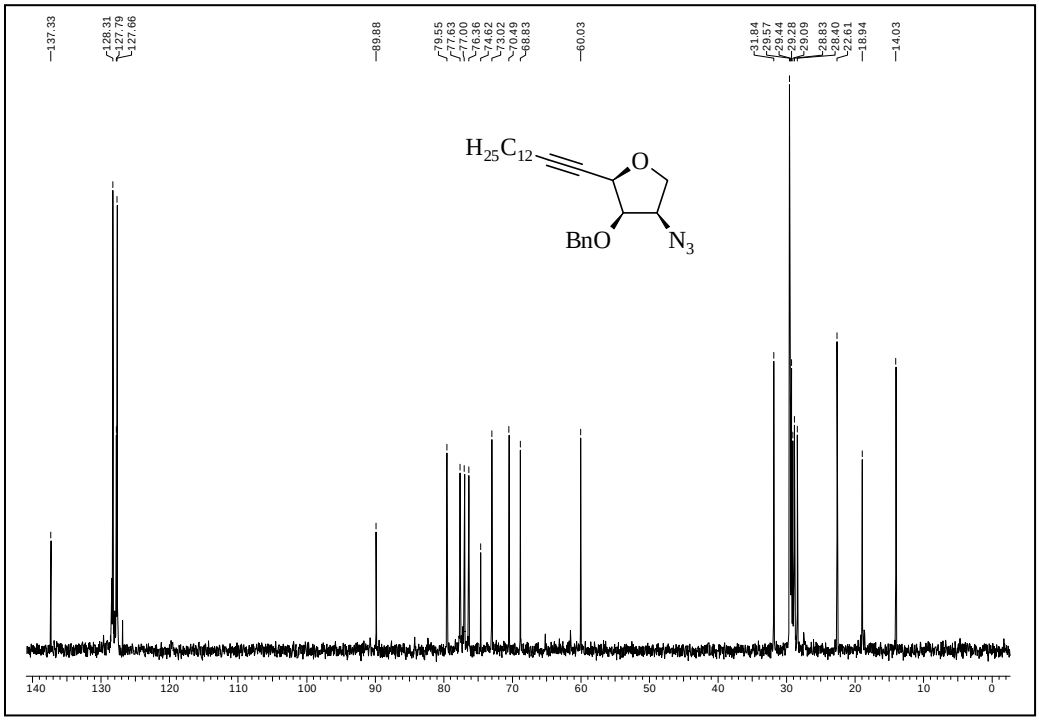
^{1}H NMR Spectrum of 1A.58 in $CDCl_3$



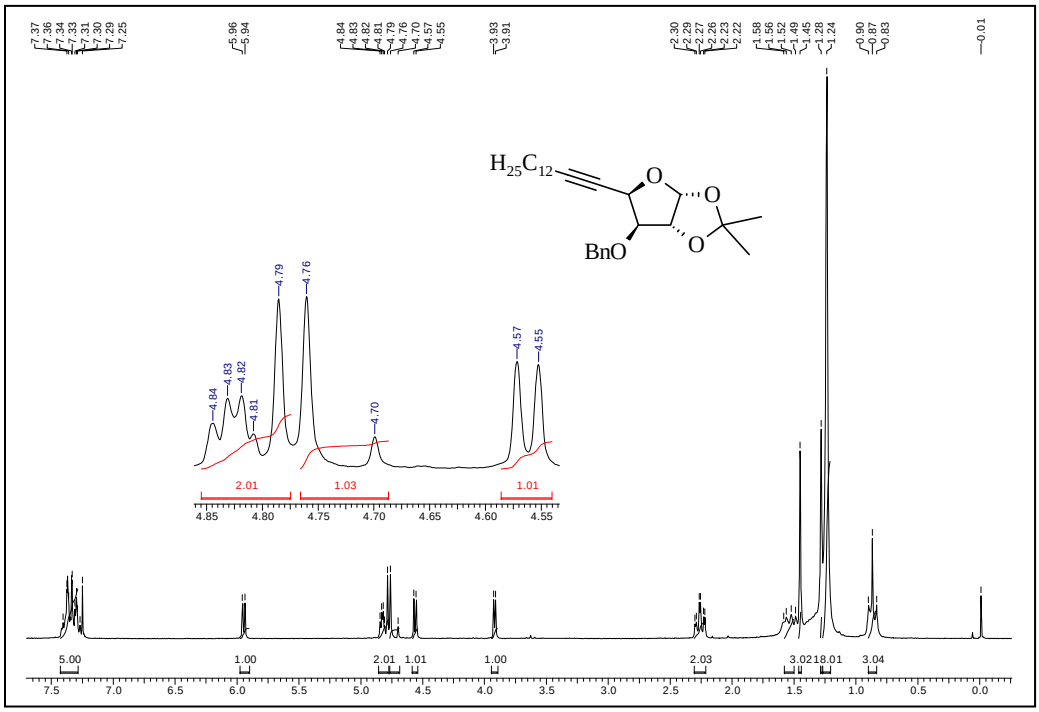
^{13}C NMR Spectrum of 1A.58 in $CDCl_3$



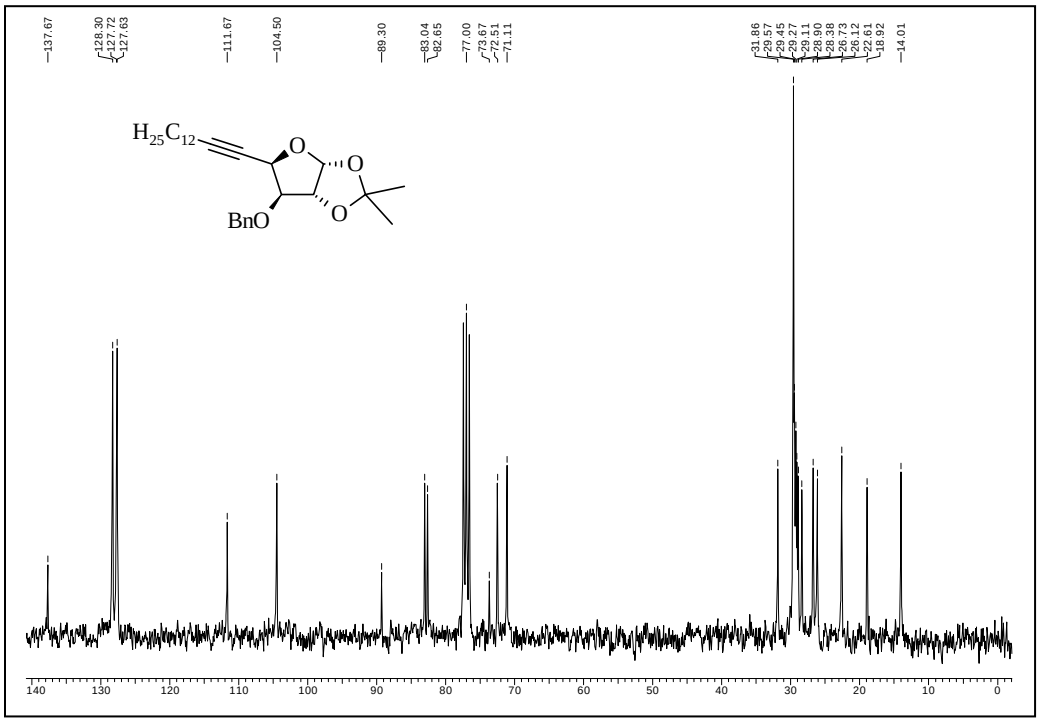
^{1}H NMR Spectrum of 1A.67 in $CDCl_3$



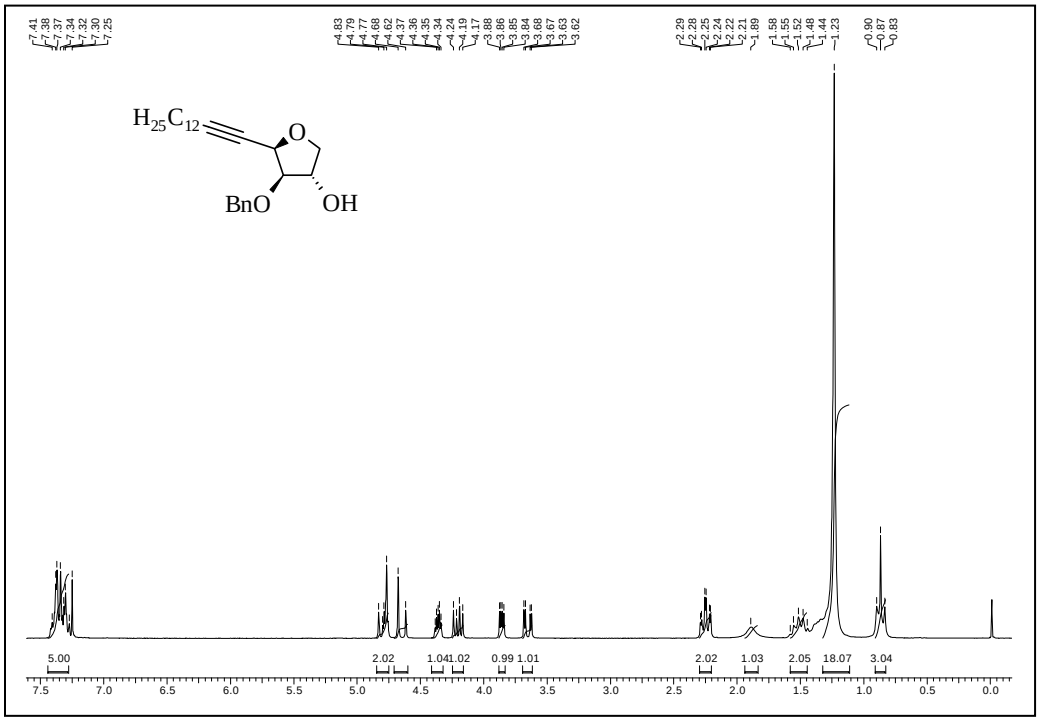
^{13}C NMR Spectrum of 1A.67 in $CDCl_3$



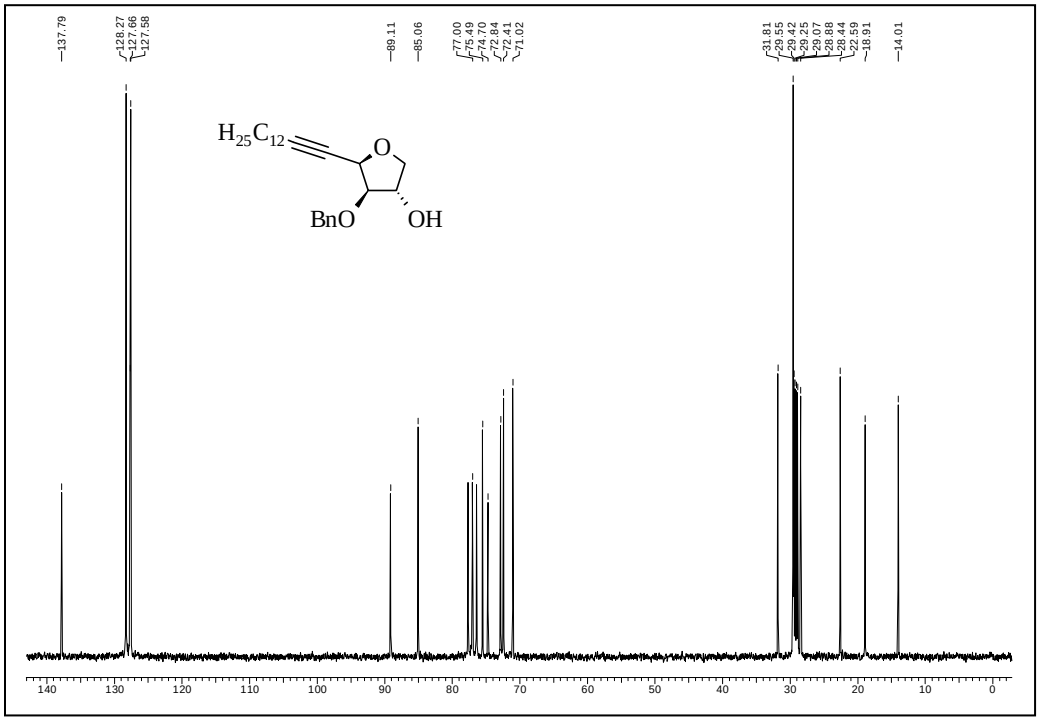
^{1}H NMR Spectrum of 1A.68 in $CDCl_3$



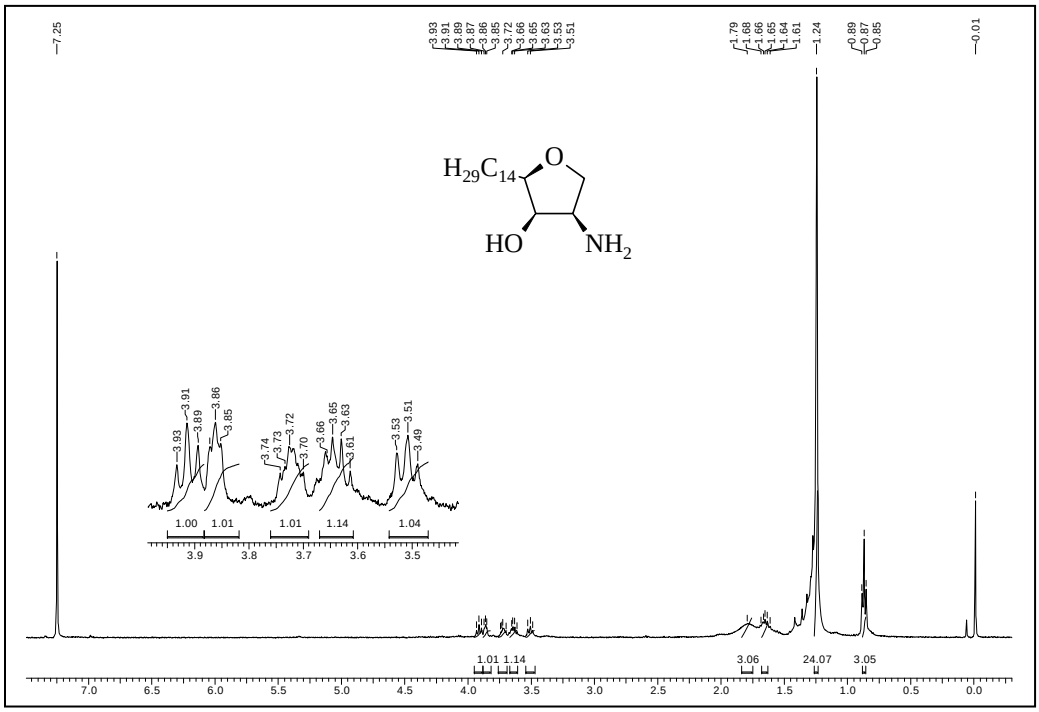
^{13}C NMR Spectrum of 1A.68 in $CDCl_3$



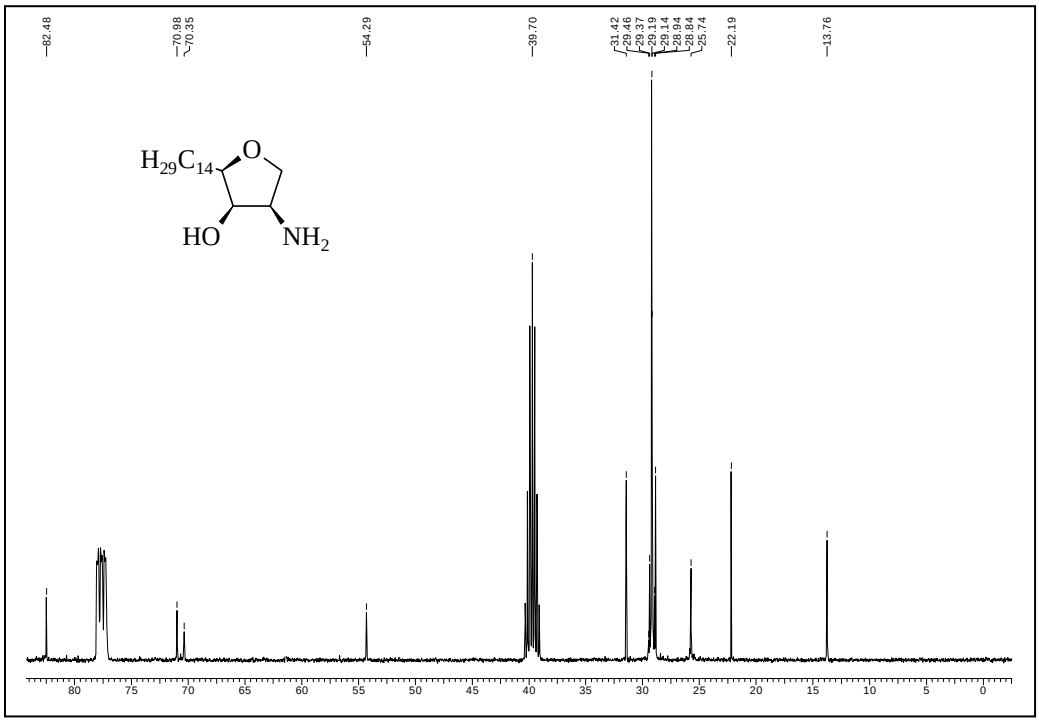
^{1}H NMR Spectrum of 1A.69 in $CDCl_3$



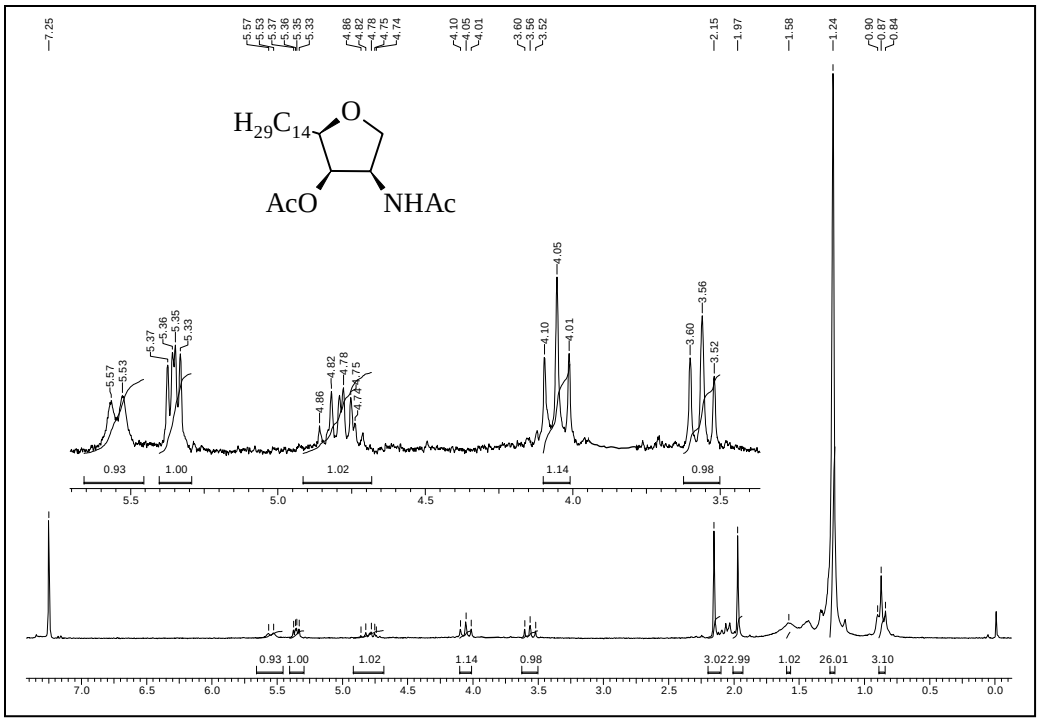
^{13}C NMR Spectrum of 1A.69 in $CDCl_3$



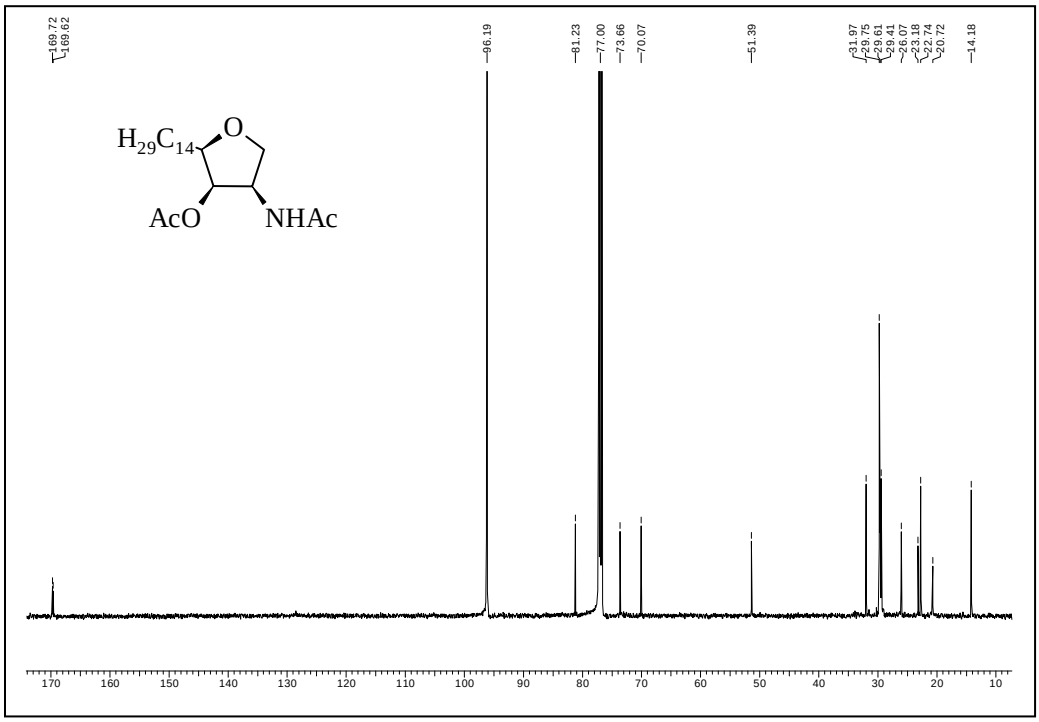
^{1}H NMR Spectrum of 1A.54 in $CDCl_3$



^{13}C NMR Spectrum of 1A.54 in $CDCl_3$+DMSO-D_6



^{1}H NMR Spectrum of 1A.55 in $CDCl_3$



^{13}C NMR Spectrum of 1A.55 in $CDCl_3$

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CHAPTER-I

Section II: Pd(II)-Mediated alkynediol spiroketalization: First total synthesis of (−)-cephalosporolide E and (+)-cephalosporolide F

1B.1. Introduction:

The characterization of many important natural products which exhibit a spiroacetal ring system in their structures has stimulated the development of several methodologies for the synthesis of this substructural unit.[1] The 1,6-dioxaspiro[4.4]nonane type of heterocyclic moiety is present in many natural products from different sources including insects, microbes, plants, fungi and marine organisms.[1,2] Among them, one can find simple structures, such as the volatile insect pheromone chalcogran (**1B.01**), an aggregation pheromone of Pityiogenes chalcographus[3] or more complex molecules, such as hippurin–1 (**1B.02**), isolated from the gorgonian Isis hippuris,[4] obtusin (**1B.03**), isolated from the red seaweed Laurrecia obtusa,[5] asperketal D (**1B.04**), isolated from the Caribbean sea whip Eunicea asperula[6] and chrisothane (**1B.05**), isolated from the Compositae Crisothamnus paniculatus[7] (Figure 1B.1).

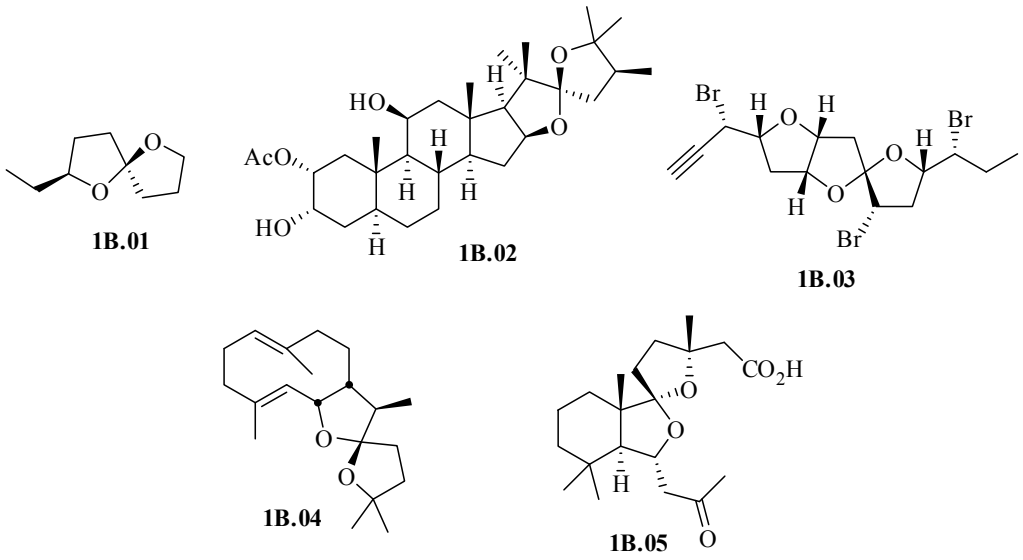
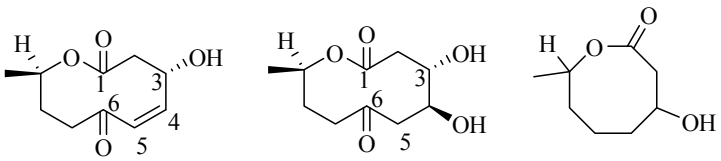


Figure 1B.1: 1,6-dioxaspiro[4.4]nonane moiety in natural products

The synthesis of several of these natural products and analogues have been achieved and during these studies very interesting methodologies have been brought to light.[8] Some research groups have developed preparation of substituted 1,6-dioxaspiro[4.4]nonane units in order to apply the same to synthesize complex natural products.[9]

In 1985, Hanson and co-workers isolated and characterized cephalosporolides E (**1B.09**) and F (**1B.10**) containing 1,6-dioxaspiro[4.4]nonane unit in which one of the furan rings is fused with a γ-lactone ring along with cephalosporolides B–D,[10] (**1B.06–1B.08**) (Figure 1B.2). Later in 2004, Rakachaisirikul and co-workers[11] isolated **1B.09** and **1B.10** from the entomopathogenic fungus *Cordyceps militaris* BCC 2816.



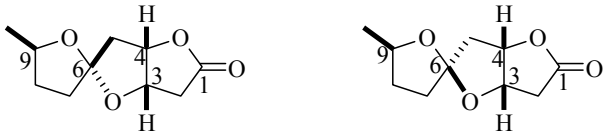
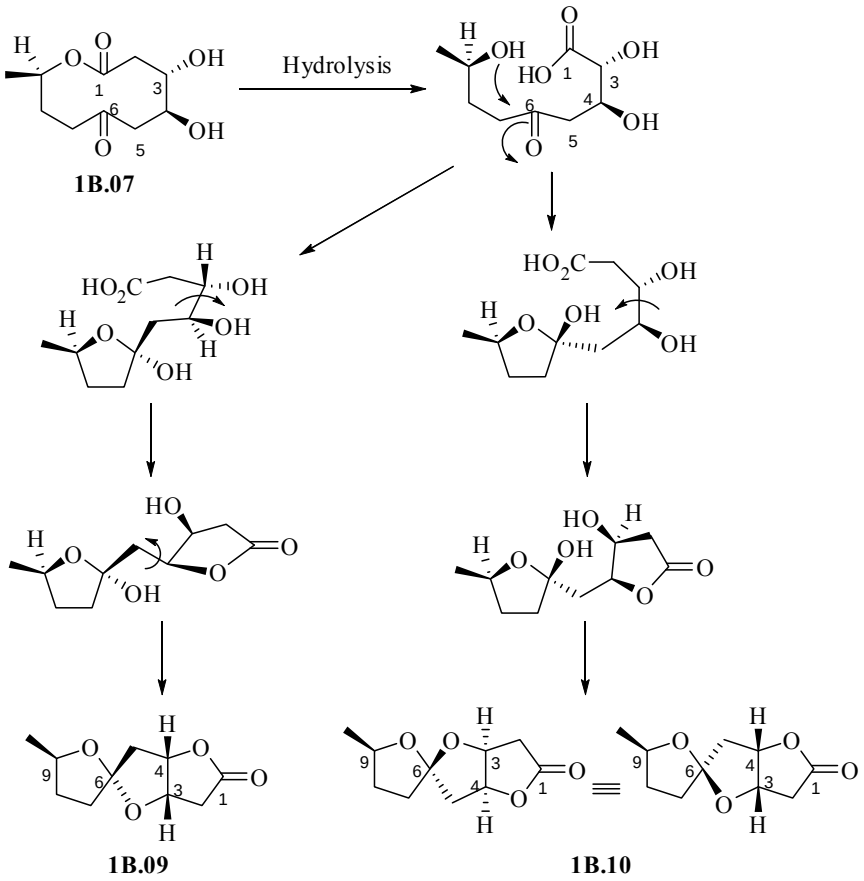


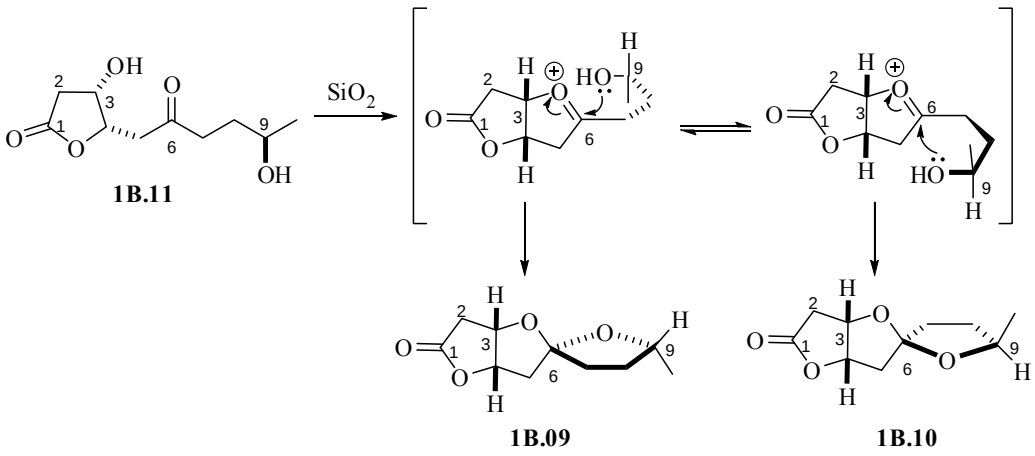
Figure 1B.2: Structures of cephalosporolides B–F, (**1B.6–1B.10**)

Hanson and co-workers established the chemical structure and relative configurations of **1B.09** and **1B.10** by extensive NMR studies and by single crystal X-ray analysis of **1B.09**. The authors suggested that cephalosporolides E (**1B.09**) and F (**1B.10**) might arise from cephalosporolide C (**1B.07**), via a process involving hydrolysis, relactonization and acetal formation (Scheme 1B.1).[10] Nevertheless, they could not mimic this process in the laboratory.

Oltra and co-workers (in 2004), isolated bassianolone **1B.11** from the entomoparastic fungus *Beauveria bassiana*.[12] Among the products, extracted from this fungus to the broth culture of a low-nitrogen medium, they unexpectedly found cephalosporolides E (**1B.09**) and F (**1B.10**). When they passed bassianolone (**1B.11**) through a pad of silica gel, they obtained a mixture of spiroketals **1B.09** and **1B.10**. In contrast with Hanson's proposal, Oltra stated that the bassianolone **1B.11** is the true chemical parent of cephalosporolides E (**1B.09**) and F (**1B.10**), which are possibly simple artifacts formed during the isolation process (Scheme 1B.2).[12]



Scheme 1B.1: Hanson's proposal of formation of cephalosporolides E (**1B.09**), and F (**1B.10**) from cephalosporolode C (**1B.07**)



Scheme 1B.2: Silica gel promoted spirocyclization of **1B.11**

In 2007, ascospiroketals A (**1B.12**) and B (**1B.13**) were isolated by Gabriele and co-workers from marine derived fungus *Ascochta salicorniae*.[13] Tricyclic core of ascospirokerals A (**1B.12**) and B (**1B.13**) bears some resemblance to cephalosporolides E (**1B.09**) and F (**1B.10**) (Figure 1B.3).

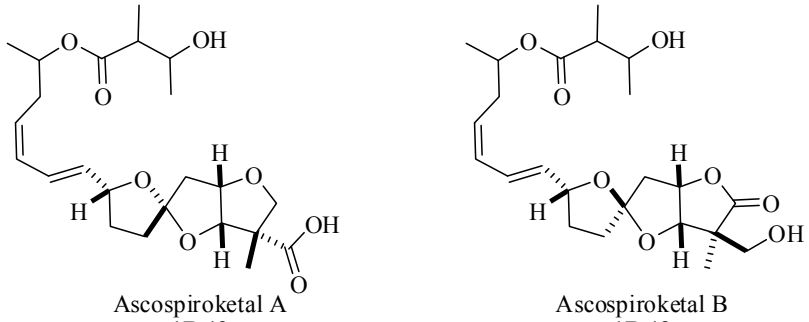


Figure 1B.3: Ascospiroketals A (**1B.12**) and B (**1B.13**)

Very recently, Xiang Li and co-workers isolated four lactone compounds, cephalosporolides H (**1B.14**), I (**1B.15**) from a lyophilized culture broth of the fungus *Penicillium* sp.[14a] and penisporolides A (**1B.16**), B (**1B.17**) from the marine-derived fungus *penicillium* sp.[14b] which bear the same tricyclic structural core of cephalosporolides E (**1B.09**) and F (**1B.10**) (Figure 1B.4). Structures of compounds **1B.12**−**1B.17** were elucidated on the basis of their HRESI-MS, ^{1}H- and ^{13}C-NMR, together with 2D-NMR spectroscopic analyses. Their relative stereochemistries were mainly accessed by NOESY analysis.[10–14]

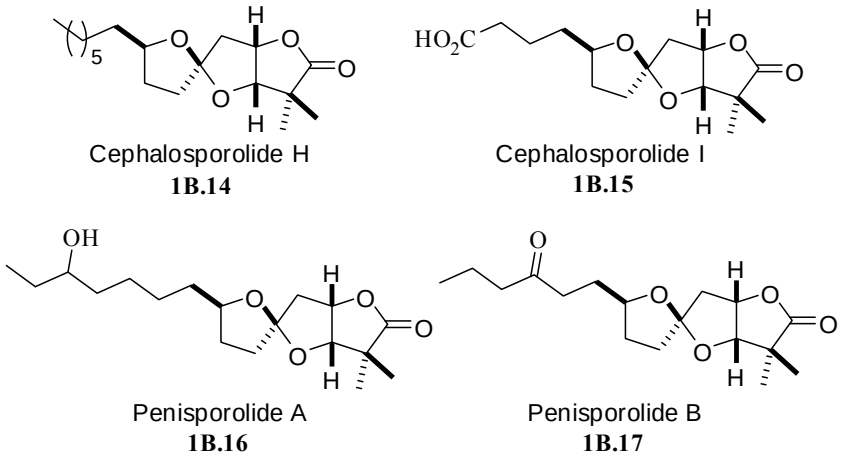


Figure 1B.4: Cephalosporolides H (**1B.14**)/ I (**1B.15**) and Penisporolides A (**1B.16**)/ B (**1B.17**)

Even with the aid of all the modern spectroscopic techniques, the isolation chemists find themselves in a position where they are unable to propose the complete structure. In most of the cases, absolute and relative stereochemistry for one or more chiral centers cannot be assigned. In case of all above natural compounds **1B.09**–**1B.17**, the relative configurations have been elucidated with the help of spectroscopic techniques and X-ray analysis of **1B.09**.[10]

Transition metal mediated cycloisomerization reaction is projected as a tool to synthesize oxygen containing heterocycles encompassing functionalized furan, pyran, benzopyran and bicyclicketal skeletons.[15–19] Various transition metals like palladium, platinum, tungsten, ruthenium, rhodium, gold and iridium have been explored as catalysts for cycloisomerization reactions.[16] Utimoto *et al*. have reported the first example for the construction of a spiro acetal unit through Pd-mediated alkyne diol spiro ketalization. This approach has seen little attention in total synthesis. Only recently, Trost group has accomplished the total synthesis of a couple of natural products having this structural unit. Our group has been currently engaged in finding out the mechanistic details of the Pd-mediated alkynol cycloisomerizations and its application in the total synthesis of small molecules and natural products having bridged bicyclic ketal unit. Considering the availability of various cephalosporolides E & F and related natural products with a common tricyclic core, we have interested to deliver a common strategy for the synthesis of these natural products by employing a Pd-mediated alkyne diol spiroketalization which forms the main content of the present chapter.

1B.2. Present Work:

The fungus, *Cephalosprium aphidicola* is a rich source of natural compounds especially containing macrolactones.[20] Hanson and co-workers were isolated and elucidated structures of a group of lactones cephalosporolide B–D, (**1B.06**)–(**1B.08**), thiobiscephalosporolide A produced by an industrial fermentation of the fungus *C. aphidicola* ACC 3490. Cephalosporolides E (**1B.09**) and F (**1B.10**) were first isolated in 1985, by the same group[10] from industrial fermentation of the same fungus *Cephalosporium aphidcola* grown under sulfur limiting conditions. The relative configuration of **1B.09** and **1B.10** were elucidated by extensive NMR studies and by single crystal X-ray analysis of **1B.09**.[10] Cephalosporolide E (**1B.09**) and cephalosporolide F (**1B.10**) are epimeric at spiro center C(6).

1B.2.1. Retrosynthesis:

The C(6)-epimeric tricyclic spiroketals **1B.18** were assumed to arise from cycloisomerization of alkyne diol **1B.19**. The spiroketals **1B.18** could be advanced to cephalosporolides E (**1B.09**) and F (**1B.10**) by oxidation of the C(1) lactol unit to lactone and the subsequent deoxygenation at C(2). By selecting a tentative 3*R*,4*R*,9*S* configuration for the targeted **1B.09** and **1B.10**, 3-alkyne-1,7-diol **1B.19** was identified as an advanced intermediate. The central carbon chain of **1B.18** has been disconnected between C(6)–C(7), identifying the alkyne **1B.20** and iodo compound **1B.21** or methyl vinyl ketone **1B.22** as the coupling units (Figure 1B.5).

Keeping the requisite absolute configurations at C(3), C(4) of alkyne **1B.20**, D-glucose was identified as an suitable chiral pool precursor. Configuration at C(9) could be generated by asymmetric reduction of ketone functionality after 1,4-addition of **1B.22** at terminal alkyne function of **1B.20**. Iodo compound **1B.21** could be elaborated from known (3*S*)-butane-1,3-diol **1B.23** by selective functional group manipulations, which in turn can readily be obtained from L-malic acid (see Figure 1B.5).

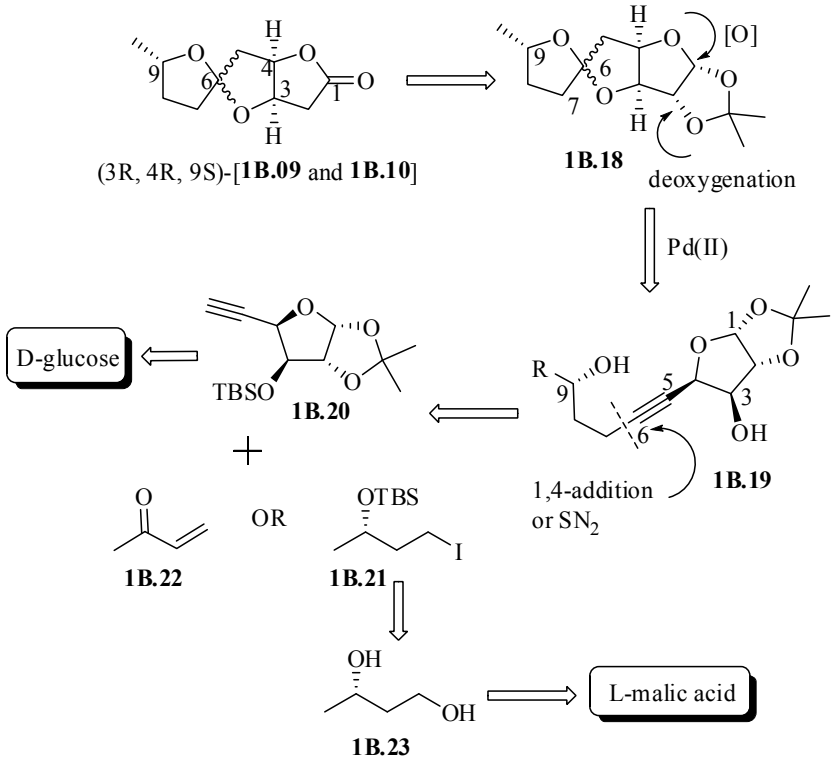
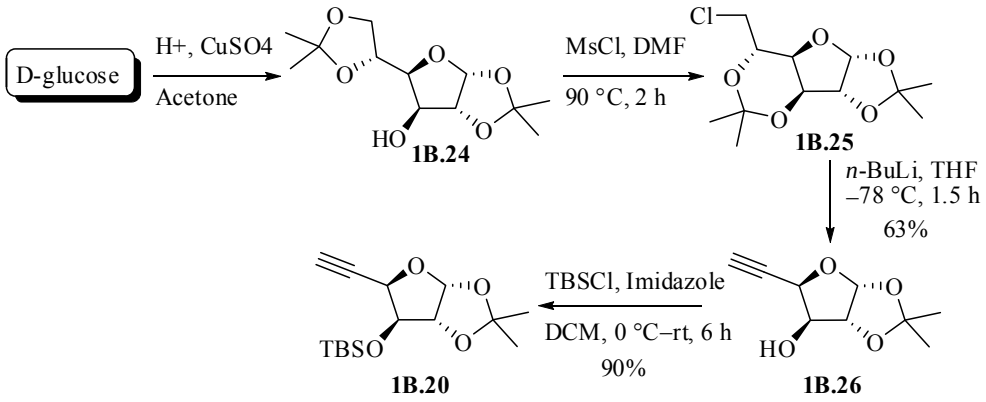


Figure 1B.5: Retrosynthetic strategy for cephalosporolides E (**1B.09**) and F (**1B.10**)

1B.2.2. Synthesis of Alkyne 1B.20

Synthesis was initiated with D-glucose diacetonide **1B.24**. According to the reported procedure, **1B.24** was treated with methanesulfonyl chloride (MsCl) in dry DMF at 90 °C to afford **1B.25** by a one-pot C(6)-chlorination and terminal acetonide migration.[22] The compound **1B.25** was then subjected to *n*-BuLi mediated double elimination[23] in THF at –78 °C to furnish the alkyne **1B.26**. The C(3)–hydroxyl group of **1B.26** was protected as its TBS ether by treating it with TBSCl and imidazole in DCM at rt to get the alkyne partener **1B.20** for the coupling reaction (Scheme 1B.3). The spectral and analytical data of alkyne **1B.20** were in accordance with the assigned structure. For example, the characteristic alkyne–H resonated as a doublet at δ 2.50 (J = 2.2 Hz) in the ^{1}H NMR spectrum of **1B.20**. The dioxolane ring protons i.e. H–1 and H–2 resonated as doublets at δ 5.95 and 4.39 ppm with a coupling of 3.6 Hz. In the ^{13}C NMR spectrum of **1B.20**, the alkyne carbons resonated at 76.1 (s), 85.1 (d) ppm and of the anomeric carbon at 104.7 ppm as a doublet. The resonances of the rest of the carbons are as expected. Mass spectrum showed peak at 299.1 $[M+H]^{+}$ and the IR

spectrum showed acetylinic C−H stretching frequency at 3313 cm^{-1} and C≡C stretching frequency at 2132 cm^{-1}.

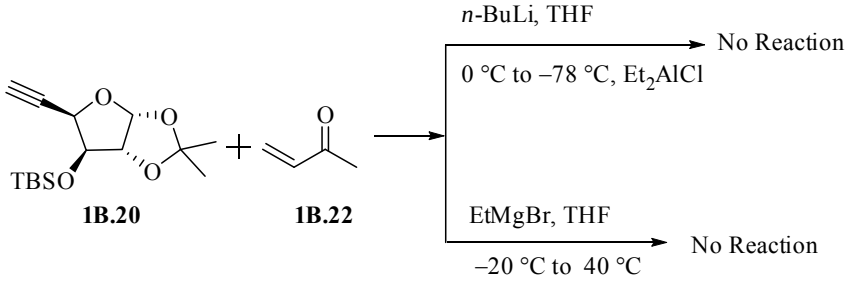


Scheme 1B.3: Synthesis of alkyne **1B.20**

1B.2.3. Attempted Coupling of alkyne 1B.20 with enones

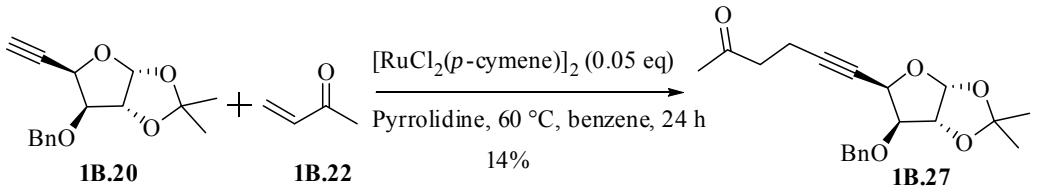
1B.2.3.1. 1,4-Addition of alkyne 1B.20 to MVK 1B.22

As given in figure 1B.5, we intended to synthesize the alkynediol intermediate **1B.19** by a conjugate addition of terminal alkyne **1B.20** with methyl vinyl ketone (MVK) **1B.22** followed by asymmetric reduction of resulting product. In order to get 1,4-addition product of alkyne **1B.20** and **1B.22**, we explored different protocols such as the addition of either the alkynyl lithium intermediate[24] (generated from the alkyne **1B.20** and *n*-BuLi in THF) or the alkynyl magnesium bromide[25] (prepared from **1B.20** by Grignard exchange with EtMgBr) to enone **1B.22** in different sovents and at different temperatures. Unfortunately in any of the attempted conditions, expected alkynone compound **1B.27** (Scheme 1B.4) was not obtained.



Scheme 1B.4

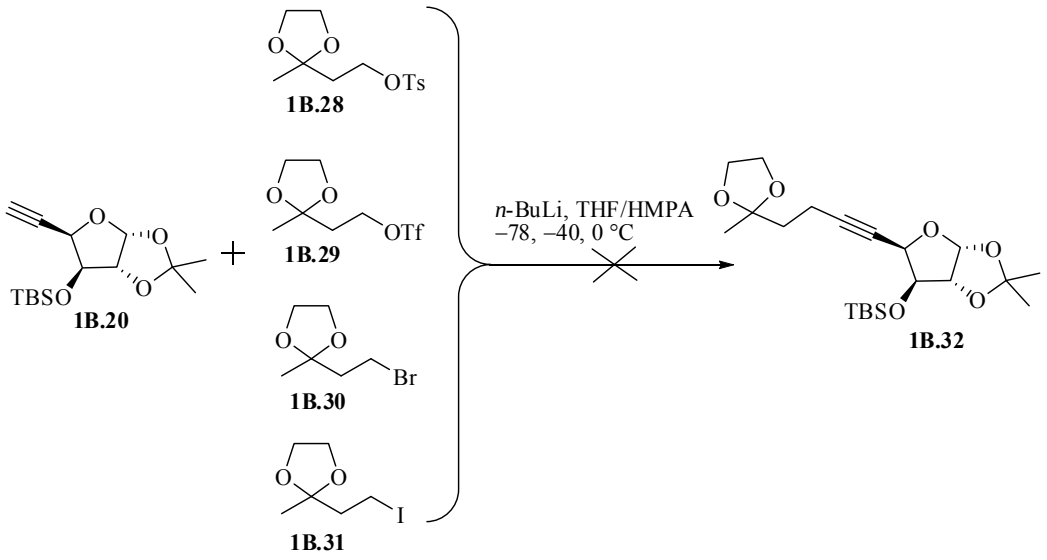
As our intended conjugate addition reaction has turned out to be a failure, we next explored a $[RuCl_2(p\text{-cymene})]_2$ complex catalyzed addition of alkynes to enones.[26] After exposing **1B.20** and **1B.22** for 2 days to catalytic $[RuCl_2(p\text{-cymene})]_2$, we could be able to procure the conjugate addition product **1B.27** in 14% yield (Scheme 1B.5). The structure of the compound **1B.27** was confirmed by spectroscopic and analytical data. In the ^1H NMR spectrum of the **1B.27** terminal acetylinic proton at δ 2.50 were disappeared and C(10) methyl proton showed singlet at δ 2.12 and four methylene protons showed peaks between δ 2.47 to 2.70. In the ^{13}C NMR spectrum, three tripets were appeared at 13.3, 42.0 and 72.4 ppm corresponding to C(7), C(8), and benzylic methylene carbon and three singlets were appeared at 206.0 ppm (carbonyl carbon) and at 74.2, 87.5 ppm (two alkyne carbons). In the IR spectrum, carbonyl stretching frequency observed at 1717 cm^{-1}. Mass and elemental analysis further assured the structure of the expected 1,4-addition product. However the yield 14% and the duration of conjugate reaction were not encouraging.



Scheme 1B.5: Ruthenium catalyzed 1,4-addition

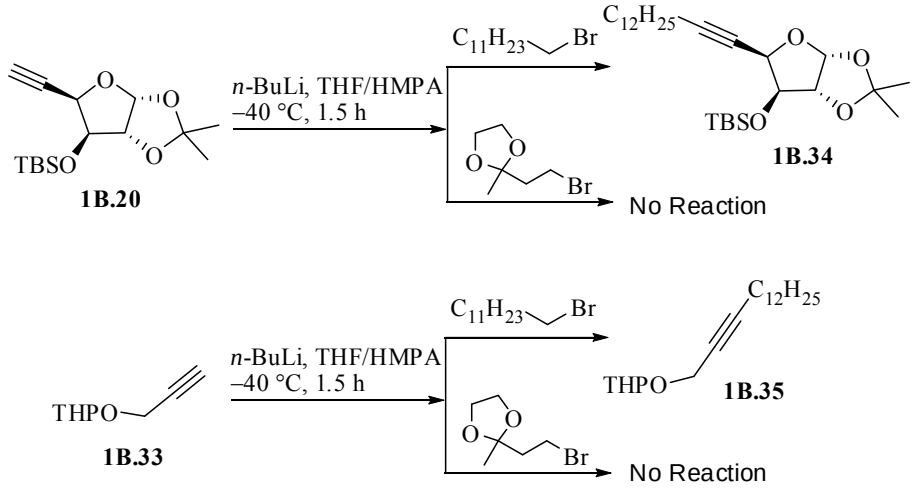
1B.2.4. SN_2 reactions with alkyne 1B.20

As the Ru(II)-mediated conjugate addition reaction also did not afford reasonable amounts of the requisite product, we have turned our attention to a nucleophilic substitution reaction[27] with **1B.20** employing tosylate **1B.28**, triflate **1B.29**, bromo **1B.30** and iodo **1B.31** derivatives to procure a masked ketone **1B.32**, which upon hydrolysis should provide the alkynone **1B.27** (Scheme 1B.6).



Scheme 1B.6: Displacement reaction of **1B.20** with **1B.28**−**1B.31**

Compounds **1B.28**–**1B.31** were prepared from ethyl aceto acetate by following the established sequence of reactions. However, all our attempts to bring the substitution reaction of **1B.28**–**1B.31** with alkyne **1B.20** were unsuccessful under various reaction conditions (Scheme 1B.6). In order to check feasibility, the alkylation of alkyne **1B.20** was attempted with the simple bromo compound (dodecyl bromide). Under optimized reaction conditions (Section 1, Scheme 1A.12, at –40 °C, using *n*-BuLi in THF/HMPA), the alkylated product **1B.34** was obtained in 67% yield.

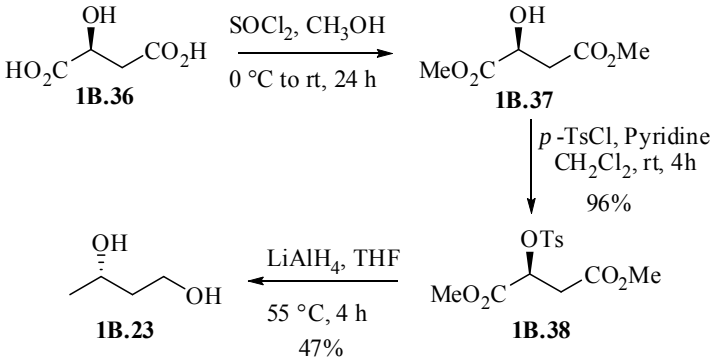


Scheme 1B.7: Feasibility of **1B.20** towards SN_2 reaction

However, under similar reaction conditions, the alkylation of alkyne **1B.33** with **1B.30** was not facile, where as alkylated product **1B.35** when dodecyl bromide was employed as an electrophile (Scheme 1B.7).

1B.2.5. Synthesis of iodo compound 1B.21

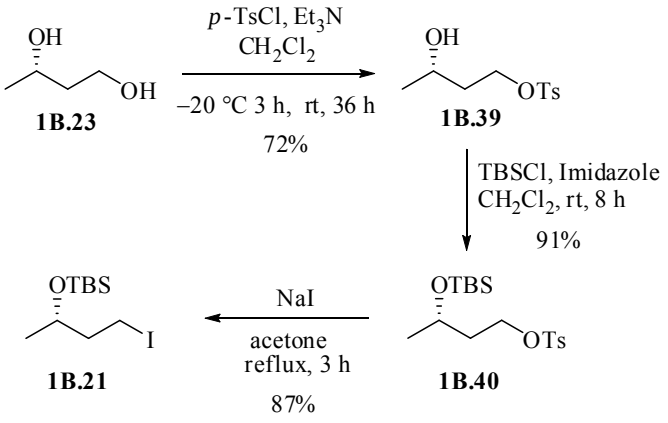
After successfully conducting the substitution reaction of alkyne **1B.20** with simple alkyl halide, we have turned our strategy by identifying the iodo compound **1B.21** having the requisite C(10) stereochemistry of the cephalosporolides E and F. Iodo compound **1B.21** was synthesized from (*S*)-butane-1,3-diol (**1B.23**), which in turn was prepared from L-malic acid[28] **1B.36**, (Scheme 1B.8). The synthesis of **1B.23** was started with the conversion of (*S*)-malic acid (**1B.36**) to the corresponding dimethyl ester **1B.37** by employing thionyl chloride in methanol at 0 °C.[29] The resulting dimethyl ester **1B.37** was treated with tosyl chloride in pyridine to afford the tosylate **1B.38** in 96% yield. Heating a suspension of tosylate **1B.38** with 5 equiv of lithium aluminum hydride (LAH) in THF at 55 °C for 4 h afforded the (+)-1,3-butanediol (**1B.23**) in 47% yield along with 1,4-butanediol (yield 10%). Comparison of the optical rotation of the obtained diol **1B.23** {$[\alpha]^{25}_{D}$ +26.2 (*c* 1.2 $CHCl_3$)} with that of known (+)-**1B.23** {$[\alpha]^{20}_{D}$ +30.0 (*c* 1.0 EtOH)}[28] confirmed its configuration as expected 3*S*.



Scheme 1B.8: Synthesis of (+)-1,3-butanediol **1B.23**

Selective monotosylation of 1,3-butanediol **1B.23** by addition of tosyl chloride to a solution of **1B.23** and triethyl amine in DCM at –20 °C over a period of 3 h, and stirring further for 36 h at rt to gave the tosylate **1B.39** in 72% yield. The ^{1}H NMR spectrum of **1B.39** showed doublet at δ 1.18 and one singlet at δ 2.44 for methyl

protons. In the ^{13}C NMR spectrum, two quartets were appeared at 21.4 and 23.3 ppm and two triplets at 37.6 and 67.8 ppm. The IR spectrum showed O–H stretching frequency at 3401 cm^{-1}. The secondory hydroxyl group of **1B.39** was protected as its TBS ether to get compound **1B.40** in 91% yield. Nucleophilic substitution of tosylate group of **1B.40** with sodium iodide[30] (acetone under reflux for 3 h) gave the iodo compound **1B.21** in 87% yield (Scheme 1B.9). In the ^{1}H NMR spectrum of **1B.21**, singlet of tosylate **1B.40** at δ 2.43 was disappeared and the ^{13}C spectrum showed two triplets at 3.4 and 43.2 ppm. Further mass spectrum and elemental analysis confirmed the proposed constitution of **1B.21**.

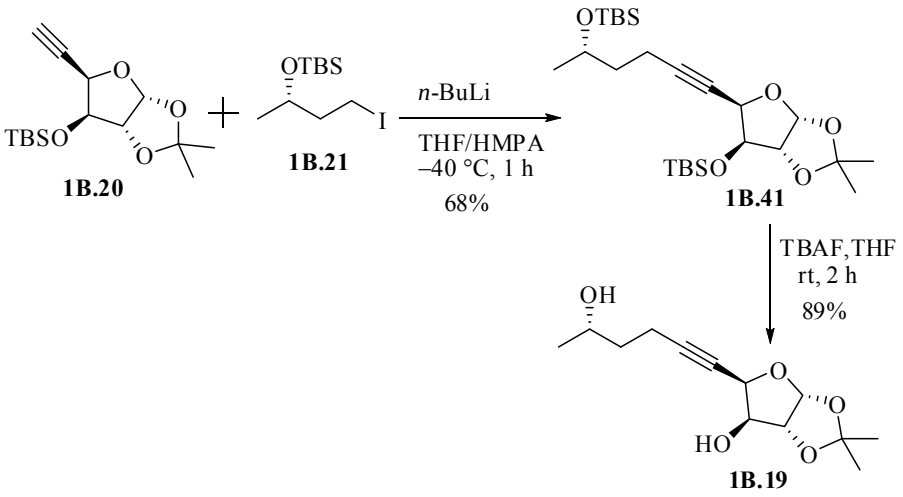


Scheme 1B.9: Synthesis of iodo compound **1B.21**

1B.2.6. Synthesis of Cephalosporolides E (1B.09) and F (1B.10)

Having synthesized the alkyne **1B.20** and the iodo compound **1B.21**, our next concern was the synthesis of the key cycloisomerization substrate **1B.19**. Using *n*-BuLi as base, several combinations of THF-HMPA were explored to bring about the alkylation of compound **1B.20** with iodo derivative **1B.21** and under optimized conditions the di-TBS protected alkynediol **1B.41** was obtained in 68% yield.[31] Spectral and analytical data of di-TBS compound **1B.41** were in well agreement with the proposed structure. In the ^{1}H NMR spectrum of **1B.41**, 24 protons of two TBS groups were resonated between δ 0.03 to 0.91 ppm. The C(10)–methyl group showed a doublet at δ 1.10 with J = 6.1 Hz and four methylene protons showed peaks at δ 1.60 (dd), 1.62 (d), 2.22 (ddt), 2.31 (ddt). The C(1)–H and C(2)–H resonated as doublets at δ 5.93 and 4.37 respectively with $J_{1,2}$ = 3.6 Hz. The ^{13}C NMR spectrum showed two methylene carbon atoms at 15.2 and 38.0 ppm and two acetylinic carbons

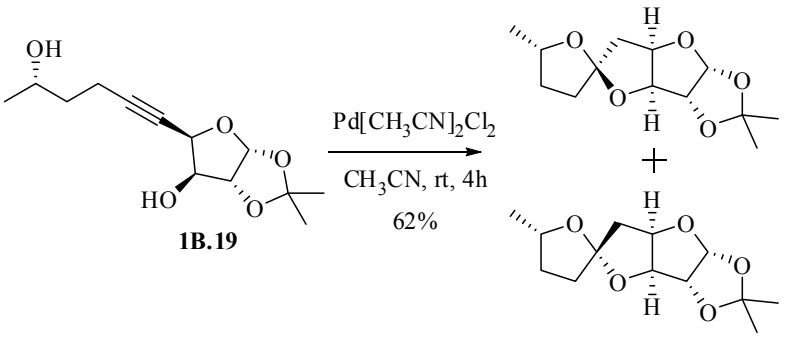
resonated as singlets at 74.1 and 88.7 ppm. Mass spectrum was in accordance with the proposed coupling product.



Scheme 1B.10: Synthesis of key alkynediol **1B.19**

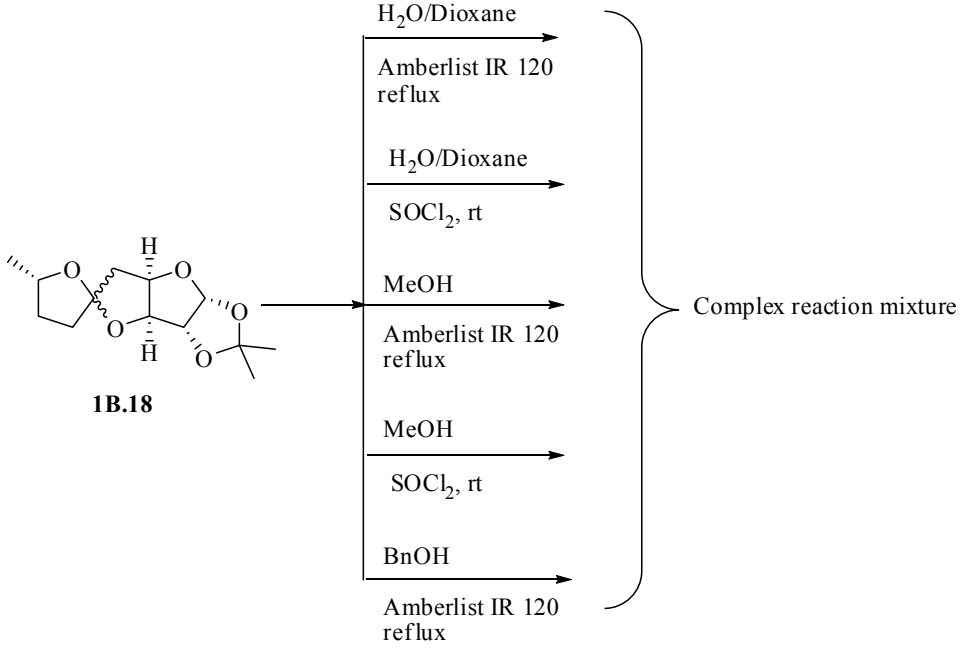
The desilylation of the compound **1B.41** was carried out by employing TBAF in THF to arrive at the key alkynediol **1B.19** (Scheme 1B.10). The ^{1}H NMR spectrum of **1B.19** showed doublet at δ 1.15 (J = 6.2 Hz), two singlets at δ 1.24 and 1.42 for the three methyl groups. In the ^{13}C NMR spectrum of **1B.19**, two singlets were appeared at 73.5 and 89.8 ppm corresponding to the alkyne carbon atoms, and the triplets of the two methylene carbons appeared at 15.3 and 36.7 ppm. The IR spectrum of **1B.19** showed C≡C stretching frequency at 2244 cm^{-1}.

The key cycloisomerization reaction of **1B.19** could be conducted smoothly with 10 mol% of $Pd[CH_3CN]_2Cl_2$ complex in acetonitrile at room temperature and the C(6) epimeric (1:1) spirocyclic ketals **1B.18** were obtained in 62% yield (Scheme 1B.11) as an inseparable mixture. The ^{1}H NMR spectrum of **1B.18** showed two doublets at δ 1.19 and 1.26 (J = 6.2 Hz, 3H) ppm, two singlets at δ 1.29 and 1.32 (3H) ppm, and two singlets at δ 1.45 and 1.46 (3H) ppm. In the ^{13}C NMR spectrum of **1B.18**, two singlets were appeared at 115.5 and 116.5 ppm for the spiroketal C(6). Mass spectrum and elemental analysis were in good agreement with proposed constitution.



Scheme 1B.11: Pd(II) catalyzed cyclisomarization of key alkynediol **1B.19**

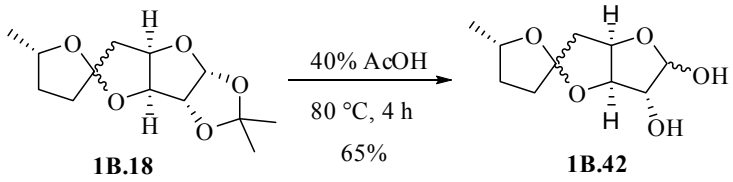
The deprotection of 1,2-acetonide of **1B.18** without affecting spiroketal unit, was turned out to be a critical reaction as in majority of the conditions attempted (Scheme 1B.12), the reactions led to a complex mixture, characterization of which was found to be a difficult task by spectroscopic analysis.



Scheme 1B.12: Attempts to 1,2-acetonide deprotection of **1B.18**

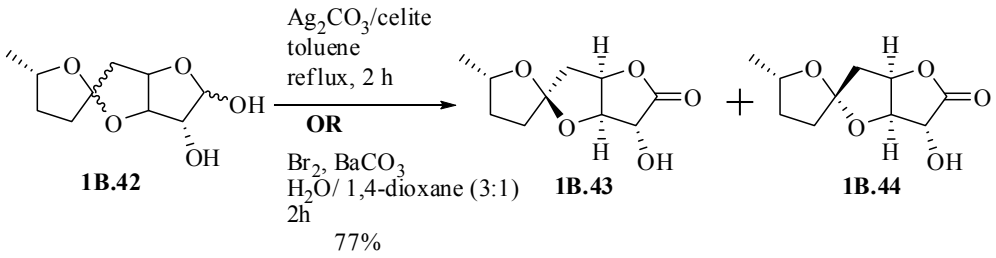
After a lot of experimentation, the deprotection of 1,2-acetonide of **1B.18** could be conducted successfully using 40% acetic acid at 80 °C (oil bath temperature) for 4 h to obtain a mixture of lactols **1B.42** in 65% yield along with recovery of 20% unreacted compound **1B.18 (**Scheme 1B.13). Prolonged heating or increasing

temperature higher than 80 °C lead to the opening of spiroketals resulting in a change of the ratio of the lactols. The constitution of the lactols **1B.42** was mainly checked by mass spectrum analysis.



Scheme 1B.13: 1,2-acetonide deprotection of **1B.18**

Selective oxidation of lactols **1B.42** under Fétizon's reaction conditions[32] employing Ag_2CO_3/*Celite* gave the lactones **1B.43** and **1B.44**. The epimeric lactones **1B.43** and **1B.44** were separated in 53% yield as white crystalline solid and 24% yield as colorless oil respectively. The selective anomeric oxidation of **1B.42** was also facile with bromine and barium carbonate[33] and gave the lactones **1B.43** and **1B.44** in a similar ratios as in Fétizon's reaction conditions (Scheme 1B.14). The relative configuration of the newly created spiro center in compounds **1B.43** and **1B.44** was assigned by comparing the multiplicity and coupling constants of H–C(4) and H–C(5) with the reported values of **1B.09**, **1B.10** and **1B.12** – **1B.15** (Table 1B.1).



Scheme 1B.14: Selective oxidation of lactols **1B.42** to lactones **1B.43** and **1B.44**

Table 1B.1: Chemical shift and coupling constants reported for H–C(4) and H–C(5) of **1B.09**, **1B.10**, **1B.12–1B.15**, **1B.18a**, **1B.18b**, **1B.47** and **1B.48**.

Entry	H–C(4)	Entry	H–C(4)
1B.09	5.09 (t, *J* = 6.0 Hz)	**1B.10**	5.05 (ddd, *J* = 2.0, 5.0, 7.0 Hz)
1B.43	5.23 (t, *J* = 6.2 Hz)	**1B.44**	5.26 (ddd, *J* = 2.8, 4.7, 6.7 Hz)
1B.18a	5.00 (t, *J* = 5.2 Hz)	**1B.18b**	4.87 (ddd, *J* = 1.5, 3.3, 5.2 Hz)
1B.47	5.09 (t, *J* = 5.8 Hz)	**1B.48**	5.02 (ddd, *J* = 2.1, 4.4, 6.6 Hz)
1B.12	4.73 (q, *J* = 3.5 Hz)	**1B.13**	5.10 (ddd, *J* = 2.2, 4.4, 6.9 Hz)
		1B.14	5.01 (m)
		1B.15	5.05 (dt, *J* = 5.4, 3.6 Hz)
Entry	**H–C(5)**	**Entry**	**H–C(5)**
1B.09	2.04 (dd, *J* = 6.0, 14 Hz) 2.33 (d, *J* = 14 Hz)	**1B.10**	2.27 (dd, *J* = 2.0, 15.0 Hz) 2.46 (dd, *J* = 7.0, 15.0 Hz)
1B.43	2.12 (dd, *J* = 6.5, 14.3 Hz) 2.39 (*J* = 14.3 Hz)	**1B.44**	2.27 (dd, *J* = 2.7, 14.8 Hz) 2.50 (dd, *J* = 6.8, 14.8 Hz)
1B.47	2.06 (dd, *J* = 6.1, 14.1 Hz) 2.38 (d, *J* = 14.3 Hz)	**1B.48**	2.27 (dd, *J* = 1.8, 14.9 Hz) 2.45 (dd, *J* = 6.8, 15.0 Hz)
1B.12	2.16 (d, *J* = 3.5 Hz)	**1B.13**	2.27 (dd, *J* = 2.2, 14.8 Hz) 2.58 (dd, *J* = 6.9, 14.8 Hz)
		1B.14	2.35 (d, *J* = 2.5 Hz) 2.52 (d, *J* = 6.3 Hz)
		1B.15	2.33 (d, *J* = 2.8) 2.50 (d, *J* = 6.0)

The assigned configuration of compound **1B.43** was further confirmed with the help of a single crystal X-ray analysis (Figure 1B.6).

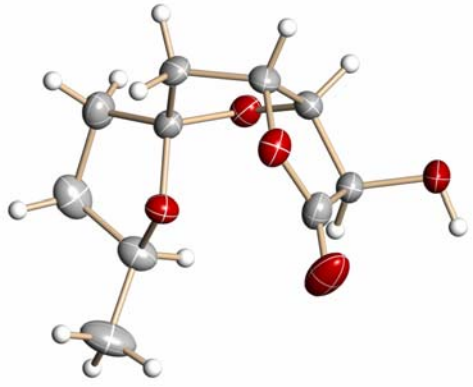
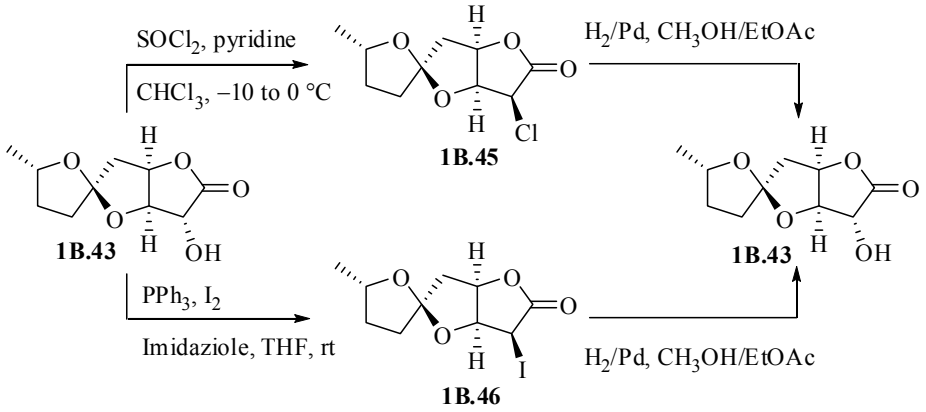


Figure 1B.6: *ORTEP* diagram of **1B.43**

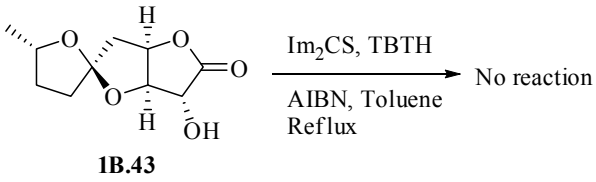
After having the complete frame work of cephalosporolides E and F, the task was set now for the deoxygenation at C(2). The α-hydroxy function of **1B.43** was subjected for deoxygenation under various reaction conditions. Initially, the deoxygenation was planned through the hydrogenolysis of the corresponding chloro-

and iodo-derivatives **1B.45**, **1B.46** respectively. The halogenations of **1B.43** was attempted under standard conditions and the resulting products were subjected for the dehalogenation (without any purification) under catalytic hydrogenolysis. However, isolation of the starting compound **1B.43** from these reactions has indicated that the halogenation of the lactones was not happened (Scheme 1B.15). This might be due to the steric hindrance for the halonucleophiles to displace the corresponding activated intermediates.



Scheme 1B.15

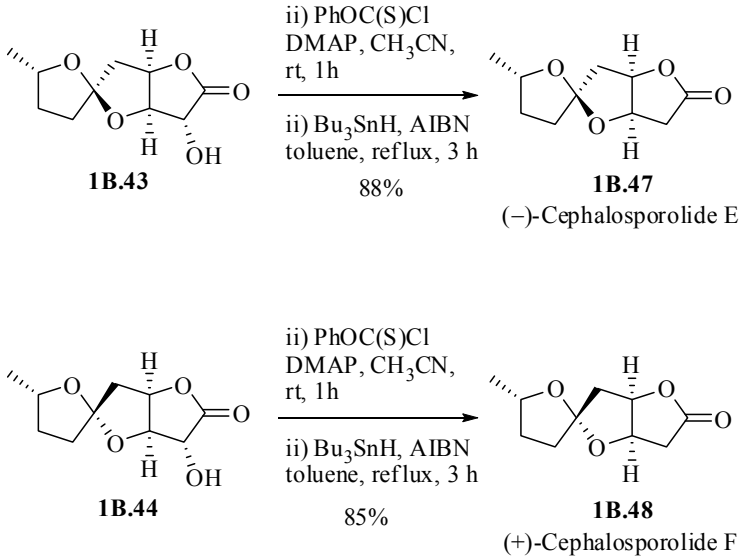
In similar lines, the attempted deoxygenation of **1B.43** under Barton-McCombie conditions by employing thiocarbony diimidazole, tributyl tin hydride (TBTH) and AIBN in toluene at reflux condition led exclusively (Scheme 1B.16) in recovering the starting material.



Scheme 1B.16

Finally, the Barton-McCombie deoxygenation[34] of **1B.43** and **1B.44** could be conducted successfully by employing the corresponding phenylthionocarbonate intermediates. Thus, the treatment of **1B.43** and **1B.44** with PhOC(=S)Cl in presence of DMAP followed by usual workup, quick chromatographic purification and

deoxygenation (AIBN, Bu_3SnH) gave **1B.47** in 88% yield as viscous oil and **1B.48** in 85% yield as colorless crystalline solid (Scheme 1B.17).



Scheme 1B.17: Synthesis of (–)-cephalosporolides E (**1B.47**) and (+)-cephalosporolides F (**1B.48**)

The spectral data of synthetic cephalosporolide E (**1B.47**) were in agreement with the reported data (Table 2) and the observed optical rotation $\{[\alpha]_D^{25} = -48.2$ (c = 0.50, $CHCl_3$), $^{Lit.}[\alpha]_D^{30} = +51.3$ (c = 0.42)[1]$\}$ indicated that enantiomer of the cephalosporolide E has been synthesized. Mass spectrum of **1B.47** showed m/z 199 (13%, $[M+H]^+$), 221(100%, $[M+Na]^+$), 237 (44%, $[M+K]^+$), IR spectrum showed absorption peak at 1780 cm^{-1} for the lactone carbonyl.

Whilst the spectral data for **1B.48** was found to be in excellent agreement with that for cephalosporolide F (Table 2B.1), the opposite sign and a large deviation in the magnitude of specific rotation $\{[\alpha]_D^{25\ Synthetic} +95.2$ (c 0.9, $CHCl_3$), $[\alpha]_D^{25\ Lit} = -33.3$ (c 0.79, $CHCl_3$)[2]$\}$ was noticed. The constitution and the relative stereochemistry of compound **1B.48** were further established by single crystal X-ray analysis (Figure 1B.7), which, along with the observed opposite sign of specific rotation, confirmed that it was the enantiomer of the natural cephalosporolide F.

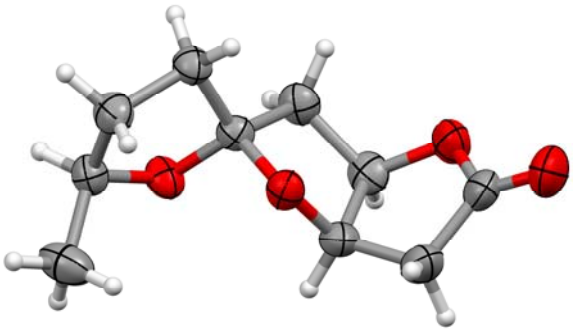


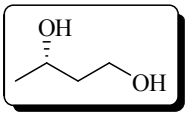
Figure 1B.7: *ORTEP* diagram of cephalosporlide F **1B.48**

Conclusion:

Herein we document the first total synthesis of the cephalosporolides E and F, the simplest members of the natural products having an unprecedent tricyclic core. A Pd-mediated alkynediol cycloisomerization has been executed to construct the central tricyclic core of cephalosporolides E/F. A concise synthesis of cephalosporolide E (**1B.47**) and cephalosporolide F (**1B.48**) has been executed, which established their absolute configurations as (3*S*,4*S*,6*S*,9*R*) and (3*S*,4*S*,6*R*,9*R*) respectively. As a result of convergence at an advanced stage and the late stage installation of the key spirocyclic core, the present approach leaves ample room for the synthesis of related natural products which is in progress.

1B.3. Experimental:

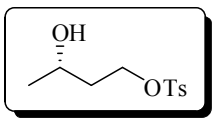
(*S*)-Butane-1,3-diol (1B.23)



To a suspension of lithium aluminum hydride (LAH) (14.5 g, 0.38 mol) in anhydrous THF (700 mL) was added dropwise a solution of **1B.38** (20 g, 63.3 mmol) in THF (50 mL). The reaction mixture was stirred at 55 °C for 4 h and then re-cooled to –10 °C. To the resultant mixture were added successively saturated aqueous solution of Na_2SO_4 (10 mL), ethyl acetate. The mixture was filtered though celite and the celite pad was washed with ethyl acetate. the combined filtrate was concentrated under reduced pressure. The residue was purifed by silica gel column chromatography (80% ethyl acetate in petroleum ether) to produce the diol **1B.23** (2.68 g, 47% yield) as a colorless oil.

Mol. Formula	: $C_4H_{10}O_2$
$[\alpha]_D^{25}$	: +26.2 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3412, 2932, 1585, 1337, 1170, 1250, 942, 893 cm^{-1}.
^{1}H NMR	: 1.20 (d, *J* = 6.2 Hz, 3H), 1.60–1.69 (m, 2H), 3.25 (brs, 2H),
($CDCl_3$, 200 MHz)	3.70–3.89 (m, 2H), 3.94–4.10 (m, 1H).
^{13}C NMR	: 23.5 (q), 40.1 (t), 60.6 (t), 67.1 (d) ppm.
($CDCl_3$, 50 MHz)	
ESI-MS (*m/z*)	: 91.2 (13%, $[M+H]^+$), 113.2 (100%, $[M+Na]^+$).
Elemental	Calcd.: C, 53.31; H, 11.18%.
Analysis	Found: C, 53.24; H, 11.32%.

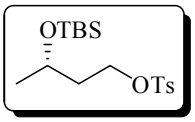
(*S*)-3-Hydroxybutyl 4-methylbenzenesulfonate (1B.39)



A solution of **1B.23** (3.3 g, 36.6 mmol) in DCM (40 mL) and Et_3N (6.6 mL, 47.7 mmol) was cooled to –20 °C. A Solution of tosyl chloride (6.99 g, 36.6 mmol) in DCM (40 mL) was added to the reaction mixture over the period of 2 h. After being stirred at –20 °C for 3 h, the mixture was allowed to warm and stirred for additional 36 h at rt. The reaction mixture was poured into 70 mL of water and extracted with DCM. The combined organic layers was washed successively with an aqueous solution of 2 N HCl (40 mL), a saturated aqueous solution of $NaHCO_3$ (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The purification of residue by silica gel column chromatography (40% ethyl acetate in petroleum ether) gave monotosylate **1B.39** (6.4 g, 72% yield) as a colorless oil.

Mol. Formula	: $C_{11}H_{16}O_4S$
$[\alpha]_D^{25}$	: –23.3 (*c* 1.4, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3401, 3009, 2970, 2928, 1599, 1455, 1355, 1097 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.18 (d, *J* = 6.2 Hz, 3H), 1.66–1.83 (m, 3H), 2.44 (s, 3H), 3.85–3.99 (m, 1H), 4.05–4.29 (m, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 21.4 (q), 23.3 (q), 37.6 (t), 63.7 (d), 67.8 (t), 127.6 (d, 2C), 129.8 (d, 2C), 132.5 (s), 144.8 (s) ppm.
ESI-MS (*m/z*)	: 245.2 (17%, $[M+H]^+$), 267.2 (100%, $[M+Na]^+$), 283.2 (18%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 54.08; H, 6.60%. Found: C, 53.92; H, 6.72%.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)butyl 4-methylbenzenesulfonate (1B.40)

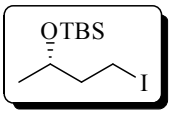


TBSCl (1.21 g, 8.04 mmol) was added to a cooled solution of tosylate **1B.39** (1.636 g, 6.68 mmol), imidazole (1.2 g, 16.72 mmol) and catalytic DMAP in anhydrous DCM (20 mL), portionwise and stirred for 8 h at rt. The reaction mixture was partionised in water and DCM. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica

gel column chromatography (15% ethyl acetate in petroleum ether) to obtain **1B.40** (2.18 g, 91% yield) as a colorless oil.

Mol. Formula	: $C_{17}H_{30}O_4SSi$
$[\alpha]_D^{25}$	: –33.3 (*c* 1.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3012, 2956, 2930, 2895, 1599, 1462, 1256, 1047 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ –0.05 (s, 3H), 0.00 (s, 3H), 0.79 (s, 9H), 1.09 (d, *J* = 6.1 Hz, 3H), 1.61–1.77 (m, 2H), 2.43 (s, 3H), 3.81–3.93 (m, 1H), 4.08 (dd, *J* = 6.2, 7.2, Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: –5.2 (q), –4.5 (q), 17.8 (s), 21.5 (q), 23.6 (q), 25.6 (q, 3C), 38.4 (t), 64.5 (d), 67.7 (t), 127.8 (d, 2C), 129.7 (d, 2C), 133.0 (s), 144.6 (s) ppm.
ESI-MS (*m/z*)	: 359.5 (9%, $[M+H]^+$), 381.6 (100%, $[M+Na]^+$), 397.5 (19%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 56.94; H, 8.43%. Found: C, 56.79; H, 8.58%.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-iodo-butane (1B.21)



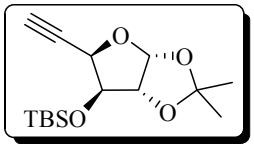
A suspension of tosylate **1B.40** (2.47 g, 6.89 mmol), NaI (10.32 g, 68.96 mmol) in anhydrous acetone (60 mL) was refluxed under nitrogen atmosphere for 3 h. Reaction mixture was filtered through *Celite* and concentrated under reduced pressure. The purification of residue by silica gel column chromatography (8% ethyl acetate in petroleum ether) gave iodo compound **1B.21** (1.88 g, 87% yield) as a colorless oil.

Mol. Formula	: $C_{10}H_{23}IOSi$
$[\alpha]_D^{25}$	: –9.3 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 2957, 2894, 2858, 1463, 1472, 1362, 1148, 967 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.07 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 1.14 (d, *J* = 6.1 Hz, 3H), 1.84–1.95 (m, 2H), 3.217–3.25 (m, 2H), 3.85–3.90

(Sextet, J = 6.2, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz)	: –4.6 (q), –4.2 (q), 3.4 (t), 17.8 (s), 23.4 (q), 25.8 (q, 3C), 43.2 (t), 68.2 (d) ppm.
ESI-MS (*m/z*)	: 315.3 (29%, $[M+H]^+$), 337.4 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 38.22; H, 7.38%. Found: C, 38.09; H, 7.50%.

5,5,6,6-Tetradehydro-5,6-dideoxi-3-*O*-(*tert*-butyldimethylsilyl)-1,2-isopropyledene-α-D-*xylo*-hexofuranose (1B.20)

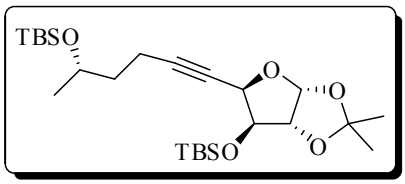


TBSCl (2.94 g, 19.57 mmol) was added to a cooled solution of **1B.26** (3.0 g, 16.3 mmol) and imidazole (2.22 g, 32.59 mmol) and catalytic DMAP in anhydrous DCM (20 mL), in portionwise and stirred for 6 h at rt. The reaction mixture was partitioned in water and DCM. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% ethyl acetate in petroleum ether) to give TBS protected alkynol **1B.20** (4.3 g, 90% yield) as a colorless oil.

Mol. Formula	: $C_{15}H_{26}O_4Si$
$[\alpha]_D^{25}$	: –50.3 (*c* 1.6, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3313, 3275, 2954, 2932, 2887, 2132, 1473, 1464, 1375, 1256, 1218, 1137, 1016 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.13, 0.14 (2s, 6H), 0.91 (s, 9H), 1.30 (s, 3H), 1.47 (s, 3H), 2.50 (d, J = 2.2 Hz, 1H), 4.19 (d, J = 2.6 Hz, 1H), 4.39 (d, J = 3.6 Hz, 1H), 4.78 (t, J = 2.5 Hz, 1H), 5.95 (d, J = 3.6 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: –5.0 (q), –4.8 (q), 18.2 (s), 25.7 (q, 3C), 26.2 (q), 26.8 (q), 72.1 (d), 76.1 (s), 77.2 (d), 78.1 (s), 85.1 (d), 104.7 (d), 111.8 (s) ppm.
ESI-MS (*m/z*)	: 299.1 (100%, $[M+H]^+$), 316.1 (84%, $[M+NH_4]^+$), 321.1 (95%, $[M+Na]^+$), 337.1 (9%, $[M+K]^+$).

Elemental Analysis Calcd.: C, 60.37; H, 8.78%.
Found: C, 60.25; H, 8.91%.

6-*C*-(3'(*S*)-*O*-(*tert*-Butyldimethylsilyl)-5,5,6,6-tetradehydro-5,6-dideoxi-3-*O*-(*tert*-butyldimethylsilyl)-1,2-isopropyledene-α-D-*xylo*-hexofuranose (1B.41)



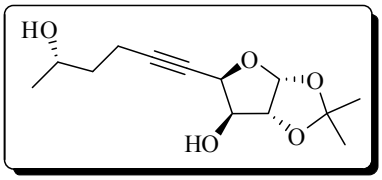
A solution of **1B.20** (1.6 g, 5.37 mmol) in THF (40 mL) and HMPA (5 mL) was cooled to –40 °C and treated with drop wise addition of *n*-BuLi (4 mL, 1.6 M in hexanes, 6.44 mmol) and stirred for 20 min. To this, iodo compound **1B.21** (2.0 g, 6.44 mmol,) was added dropwise, and stirred for 1 h at –40 °C. The reaction mixture was quenched by saturate aqueous solution of NH_4Cl and extracted with ethyl acetate. The combined organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (7% ethyl acetate in petroleum ether) to produce **1B.41** (1.77 g, 68% yield) as a colorless oil.

Mol. Formula	: $C_{25}H_{48}O_5Si_2$
$[\alpha]_D^{25}$	: +15.3 (*c* 1.7, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 2956, 2931, 2828, 2238, 1472, 1376, 1256, 1218, 1131, 1082, 1018, 838 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.03 (2s, 6H), 0.12, 0.13 (2s, 6H), 0.86 (s, 9H), 0.91 (s, 9H), 1.10 (d, *J* = 6.1 Hz, 3H), 1.29 (s, 3H), 1.46 (s, 3H), 1.60 (dd, *J* = 1.7, 5.9 Hz, 1H), 1.62 (d, *J* = 7.4 Hz, 1H), 2.22 (ddt, *J* = 2.0, 8.0, 16.8 Hz, 1H), 2.31 (ddt, *J* = 2.0, 7.2, 16.8 Hz, 1H), 3.86 (sextet, *J* = 6.1 Hz, 1H), 4.12 (d, *J* = 2.5 Hz, 1H), 4.37 (d, *J* = 3.6 Hz, 1H), 4.78 (dd, *J* = 2.1, 4.3 Hz, 1H), 5.93 (d, *J* = 3.6 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: –5.0 (q), –4.9 (q), –4.8 (q), –4.4 (q), 15.2 (t), 18.0 (s), 18.3 (s), 23.5 (q), 25.7 (q, 3C), 25.8 (q, 3C), 26.2 (q), 26.8 (q), 38.0 (t), 67.1 (d), 72.5 (d), 74.1 (s), 77.3 (d), 85.2 (d), 88.7

(s), 104.5 (d), 111.6 (s) ppm.

ESI-MS (*m/z*)	: 485.5 (6%, $[M+H]^+$), 502.6 (21%, $[M+NH_4]^+$), 507.6 (100%, $[M+Na]^+$), 523.6 (13%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 61.93; H, 9.98%. Found: C, 61.84; H, 10.03%.

6-*C*-(3'(*S*)-Butynol)- 5,5,6,6-tetradehydro-5,6-dideoxi-1,2-isopropyledene-α-D-*xylo*-hexofuranose (1B.19)

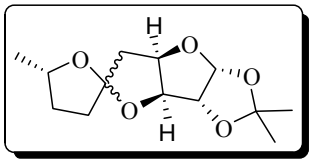


To a cooled solution of **1B.41** (1.22 g, 2.52 mmol) in THF (25 mL) was added *tetra*-butyl ammonium fluoride (1.65 g, 6.3 mmol) and stirred at rt for 2 h. The reaction mixture was partionized in water and ethyl acetate, aqueous layer was extracted with ethyl acetate. The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The purification of residue by silica gel column chromatography (45% ethyl acetate in petroleum ether) afforded alkyne diol **1B.19** (570 mg, 89% yield) as a colorless oil.

Mol. Formula	: $C_{13}H_{20}O_5$
$[\alpha]_D^{25}$	: –57.0 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3414, 2970, 2935, 2244, 1457, 1376, 1218, 1015, 952 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.15 (d, *J* = 6.2 Hz, 3H), 1.24 (s, 3H), 1.42 (s, 3H), 1.60 (t, *J* = 6.9 Hz, 2H), 2.29–2.40 (m, 2H), 2.98 (bs, 2H), 3.88 (sextet, *J* = 6.2 Hz, 1H), 4.06 (d, *J* = 2.6 Hz, 1H), 4.51 (d, *J* = 3.7 Hz, 1H), 4.77 (dd, *J* = 2.3, 4.2 Hz, 1H), 5.87 (d, *J* = 3.7 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 15.3 (t), 23.2 (q), 25.9 (q), 26.6 (q), 36.7 (t), 66.6 (d), 72.4 (d), 73.5 (s), 75.8 (d), 84.0 (d), 89.8 (s), 104.5 (d), 111.6 (s) ppm.
ESI-MS (*m/z*)	: 274.1 (19%, $[M+NH_4]^+$), 279.1 (100%, $[M+Na]^+$), 295.0 (4%, $[M+K]^+$).

Elemental Analysis	Calcd.: C, 60.92; H, 7.87%. Found: C, 60.79; H, 8.98%.

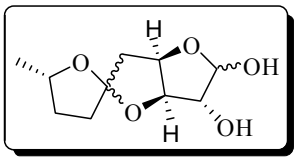
Tricyclic spiroketal (1B.18)



A solution of **1B.19** (200 mg, 0.78 mmol) and $PdCl_2(CH_3CN)_2$ (10.0 mg, 0.03 mmol) in dry CH_3CN (10 mL) was flushed with argon for 10 min and stirred at rt for 4 h under argon atmosphere. The reaction mixture was concentrated under reduced pressure and crude residue was purified by silica gel column chromatography (10% ethyl acetate in petroleum ether) to give mixture spiroketals **1B.18** (124 mg, 62% yield) as a viscous, colorless oil.

Mol. Formula	: $C_{13}H_{20}O_5$
IR ($CHCl_3$) $\tilde{\nu}$	: 2980, 1458, 1383, 1218, 1164, 1058, 891 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.19 (d, *J* = 6.2 Hz, 1.5H), 1.26 (d, *J* = 6.2 Hz, 1.5H), 1.29 (s, 1.5H), 1.32 (s, 1.5H), 1.45, 1.46 (2s, 3H), 1.66–1.76 (m, 0.5H), 1.84–2.16 (m, 4H), 2.22–2.37 (m, 1.5H), 4.05–4.21 (m, 1H), 4.52 (m, *J* = 3.6, 3.8 Hz, 2H), 4.87 (ddd, *J* = 1.5, 3.3, 4.7 Hz, 0.5H), 5.00 (t, *J* = 5.2 Hz, 0.5H), 5.88 (d, *J* = 3.8 Hz, 0.5H), 6.02 (d, *J* = 3.6 Hz, 0.5H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 21.0 (q), 22.7 (q), 26.6 (q), 27.1 (q, 2C), 27.7 (q,), 31.1 (t), 32.5 (t), 35.0 (t), 38.0 (t), 42.3 (t), 43.0 (t), 74.9 (d), 76.2 (d), 83.1 (d), 83.2 (d), 83.7 (d), 85.3 (d), 86.2 (d), 86.4 (d), 106.7 (d), 106.8 (d), 111.6 (s), 112.3 (s), 115.5 (s), 116.5 (s) ppm.
ESI-MS (*m/z*)	: 257.3 (19%, $[M+H]^+$), 279.1 (100%, $[M+Na]^+$), 295.1 (18%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 60.92; H, 7.87%. Found: C, 60.84; H, 7.94%.

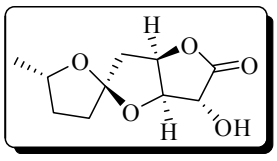
Mixture of lactols (1B.42)



A solution of **1B.18** (200 mg, 0.78 mmol) and 40% acetic acid (10 mL) was heated at 80 °C (oil bath) for 3 to 4 h. The reaction mixture was neutralized with solid K_2CO_3 and evaporated to dryness under reduced pressure. The residue was extracted with ethyl acetate, dried over Na_2SO_4, filtered, concentrated and purified by silica gel column chromatography (50% ethyl acetate in petroleum ether) to afford mixture of lactols **1B.42** (110 mg, 65% yield) as a colorless oil.

Mol. Formula	: $C_{10}H_{16}O_5$
IR ($CHCl_3$) $\tilde{\nu}$	: 3391, 2980, 2855, 1457, 1345, 1303, 1145, 954 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.18–1.24 (m, 3H), 1.37–2.28 (m, 1H), 1.96–2.28 4.51 (m, 4H), 2.48–2.56 (m, 1H), 2.24 (bs, 1H), 4.12–4.37 (m, 2H), 4.48 (d, *J* = 4.5 Hz, 1H), 4.48–4.96 (m, 1H), 5.18 (s, 0.60H), 5.43 (d, *J* = 3.9 Hz, 0.20H), 5.63 (d, *J* = 3.9 Hz, 0.20H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 21.0 (q, 3C), 21.1 (q), 30.8 (t), 31.1 (t), 32.3 (t), 32.4 (t), 36.0 (t, 2C), 36.7 (t), 37.1 (t), 42.4 (t), 42.6 (t), 43.8 (t, 2C), 74.9 (d), 75.6 (d), 75.7 (d), 76.5 (d), 78.5 (d), 80.3 (d), 80.6 (d), 81.3 (d, 2C), 83.6 (d), 84.1 (d), 85.9 (d), 86.5 (d), 88.5 (d), 89.1 (d, 2C), 104.7 (d), 106.8 (d, 3C), 116.0 (s), 116.6 (s, 3C) ppm.
ESI-MS (*m/z*)	: 217.5 (4%, $[M+H]^+$), 239.5 (100%, $[M+Na]^+$), 255.5 (6%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 55.55; H, 7.46%. Found: C, 55.41; H, 7.58%.

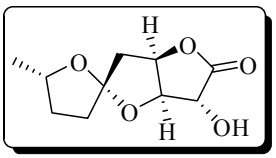
2-*C*-(*R*)-Hydroxy cephalosporolide E (1B.43)



Ag_2CO_3 impregnated on *Celite* (1.19 g, 2.08 mmol, contains 1 mmol of Ag_2CO_3 per 0.57 g of prepared reagent) was added to a solution of mixtures of lactols **1B.42** (150 mg, 0.69 mmol) in toluene (15 mL) under argon atmosphere and heated at reflux for 2 h. The reaction mixture was then cooled to room temperature and filtered through a pad of *Celite* and the *Celite* pad was washed with ethyl acetate. Combined filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (25% ethyl acetate in petroleum ether) to give **1B.43** (78 mg, 53%) as white crystalline solid and **1B.44** (36 mg, 24% yield) as a colorless viscous oil . (yields are with respect to starting mixture of lactols).

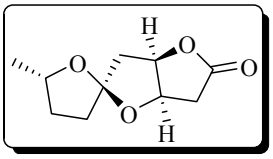
Mol. Formula	: $C_{10}H_{14}O_5$
M. P.	: 85–87 °C
$[\alpha]_D^{25}$	: +5.2 (*c* 0.5, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	: 3430, 2929, 1774, 1403, 1216, 1050, 970 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.17 (d, *J* = 6.2 Hz, 3H), 1.41–1.47 (m, 1H), 2.05–2.14 (m, 4H), 2.39 (d, *J* = 14.3 Hz, 1H), 3.06 (bs, 1H), 4.14 (sextet, *J* = 6.2 Hz, 1H), 4.35 (s, 1H), 4.71 (d, *J* = 6.2 Hz, 1H), 5.23 (t, *J* = 6.2 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 20.8 (q), 31.3 (t), 33.8 (t), 41.2 (t), 74.3 (d), 75.3 (d), 82.2 (d), 83.6 (d), 115.2 (s), 176.5 (s) ppm.
ESI-MS (*m/z*)	: 215.2 (40%, $[M+H]^+$), 237.2 (100%, $[M+Na]^+$), 253.2 (13%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 56.07; H, 6.59%. Found: C, 55.92; H, 6.70%.

2-*C*-(*R*)-Hydroxy cephalosporolide F (1B.44)



Mol. Formula	: $C_{10}H_{14}O_5$
$[\alpha]_D^{25}$	: +81.6 (*c* 0.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3436, 2930, 1775, 1403, 1216, 1051, 919 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.27 (d, *J* = 6.2 Hz, 3H), 1.69–1.74 (m, 1H), 1.95–2.01 (m, 1H), 2.05-2.12 (m, 2H), 2.27 (dd, *J* = 2.6, 14.7 Hz, 1H), 2.50 (dd, *J* = 6.7, 14.7 Hz, 1H), 3.28 (bs, 1H), 4.16–4.23 (m, 1H), 4.31 (s, 1H), 4.63 (d, *J* = 4.7 Hz, 1H), 5.25–5.28 (m, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 22.7 (q), 32.3 (t), 36.9 (t), 41. 5 (t), 72.8 (d), 77.1 (d), 81.9 (d), 83.0 (d), 115.7 (s), 176.2 (s) ppm.
ESI-MS (*m/z*)	: 215.2 (34%, $[M+H]^+$), 237.2 (100%, $[M+Na]^+$), 253.2 (30%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 56.07; H, 6.59%. Found: C, 56.13; H, 6.67%.

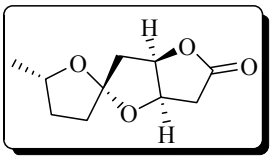
(–)-Cephalosporolide E (1B.47)



Phenyl chlorothionoformate (50 μL, 0.35 mmol) was added to a cooled solution of α-hydroxy lactone **1B.43** (50 mg, 0.23 mmol) and DMAP (57 mg, 0.47 mmol) in CH_3CN (5 mL) and stirred for 1 h at rt. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (10% ethyl acetate in petroleum ether) to obtain phenylthiocarbonate intermediate (77 mg). A solution of thiocarbonate intermediate (77 mg, 0.22 mmol), tri-butyl tinhydride (87 μL, 0.33 mmol) and AIBN (0.7 mg) in toluene (10 mL) was deoxygenated by purging argon for 20 min and refluxed for 3 h under argon atmosphere. Then the mixture was cooled to rt, concentrated under reduced pressure and purified by silica gel column chromatography (25% ethyl acetate in petroleum ether) to afford (–)-cephalosporolide E **1B.47** (41 mg, 88%) as colorless needles.

Mol. Formula	: $C_{10}H_{14}O_4$
M. P.	: 96−98 °C
$[\alpha]_D^{25}$	: – 48.2 (*c* 0.5, $CHCl_3$) {lit. $[\alpha]_D^{30}$ +51.3 (*c* 0.42, $CHCl_3$)}
IR ($CHCl_3$) $\tilde{\nu}$	: 2969, 1780, 1402, 1303, 1157, 1098, 1056, 918, 825 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.13 (d, *J* = 6.2 Hz, 3H), 1.36–1.39 (m, 1H), 1.98–2.08 (m, 4H), 2.38 (d, *J* = 14.3 Hz, 1H), 2.59 (d, *J* = 18.8 Hz, 1H), 2.68 (dd, *J* = 7.5, 18.8 Hz, 1H), 4.09–4.14 (m, 1H), 4.82 (t, *J* = 6.2 Hz, 1H), 5.09 (t, *J* = 5.8 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 20.9 (q), 31.3 (t), 34.2 (t), 37.6 (t), 41.6 (t), 75.1 (d), 77.2 (d), 83.4 (d), 115.1 (s), 175.8 (s) ppm.
ESI-MS (*m/z*)	:199 (13%, $[M+H]^+$), 221 (100%, $[M+Na]^+$), 237 (44%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 60.59; H, 7.12%. Found: C, 60.45; H, 7.19%.

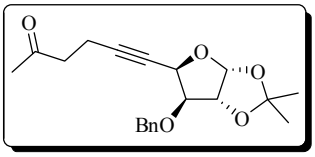
(+)-Cephalosporolide F (1B.48)



Phenyl chlorothionoformate (30 μL, 0.21 mmol) was added to a cooled solution of α-hydroxy lactone **1B.44** (30 mg, 0.14 mmol) and DMAP (34 mg, 0.28 mmol) in CH_3CN (4 mL) and stirred for 1 h at rt. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (10% ethyl acetate in petroleum ether) to give phenylthiocarbonate intermediate (47 mg). A solution of thiocarbonate intermediate (47 mg, 0.134 mmol) tri-butyl tinhydride (53 μL, 0.20 mmol) and AIBN (0.3 mg) in toluene was deoxygenated by purging argon for 20 min and refluxed for 3 h under argon atmosphere. Then the mixture was cooled to rt, concentrated under reduced pressure and purified by silica gel column chromatography (25% ethyl acetate in petroleum ether) to afford (+)-cephalosporolide F **1B.48** (24 mg, 85%) as crystalline solid.

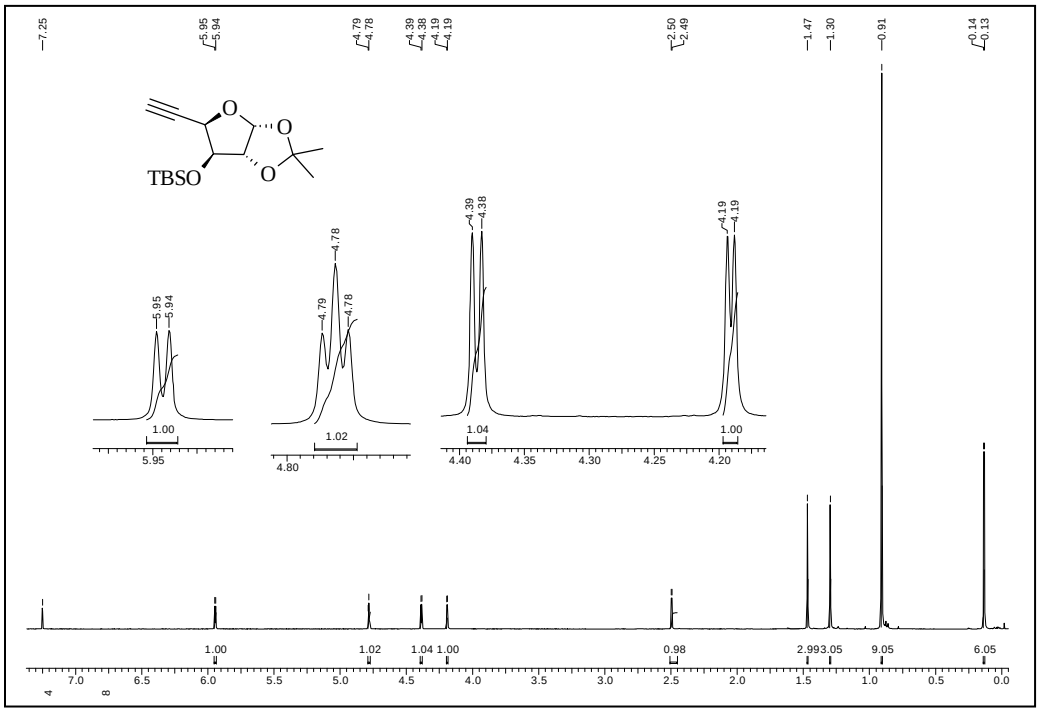
Mol. Formula	: $C_{10}H_{14}O_4$
M. P.	: 62–64 °C
$[\alpha]_D^{25}$	: +95.2 (*c* 0.9, $CHCl_3$) {lit. $[\alpha]_D^{25}$ –33.3 (*c* 0.79, $CHCl_3$)}
IR ($CHCl_3$) $\tilde{\nu}$	: 3020, 1781, 1403, 1216, 1167, 1096, 1061, 927 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.22 (d, *J* = 6.3 Hz, 3H), 1.64–1.69 (m, 1H), 1.93 (dd, *J* = 7.8, 12.3 Hz, 1H), 1.98–2.03 (m, 1H), 2.06–2.11 (m, 1H), 2.27 (dd, *J* = 1.8, 14.9 Hz, 1H), 2.45 (dd, *J* = 6.8, 15.0 Hz, 1H), 2.62 (d, *J* = 18.3 Hz, 1H), 2.68 (dd, *J* = 5.3, 18.3 Hz, 1H), 4.09-4.17 (m, 1H), 4.73 (t, *J* = 4.5 Hz, 1H), 5.02 (ddd, *J* = 2.1, 4.4, 6.6 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 22.8 (q), 32.4 (t), 36.0 (t), 36.9 (t), 42.1 (t), 76.5 (d), 76.9 (d), 83.8 (d), 115.5 (s), 175.6 (s) ppm.
ESI-MS (*m/z*)	: 199 (16%, $[M+H]^+$), 221 (100%, $[M+Na]^+$), 237 (46%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 60.59; H, 7.12%. Found: C, 60.51; H, 7.07%.

6-*C*-(3'Butynone)- 5,5,6,6-tetradehydro-5,6-dideoxi-3-*O*-benzyl-1,2-isopropyledene-α-D-*xylo*-hexofuranose (1B.27)

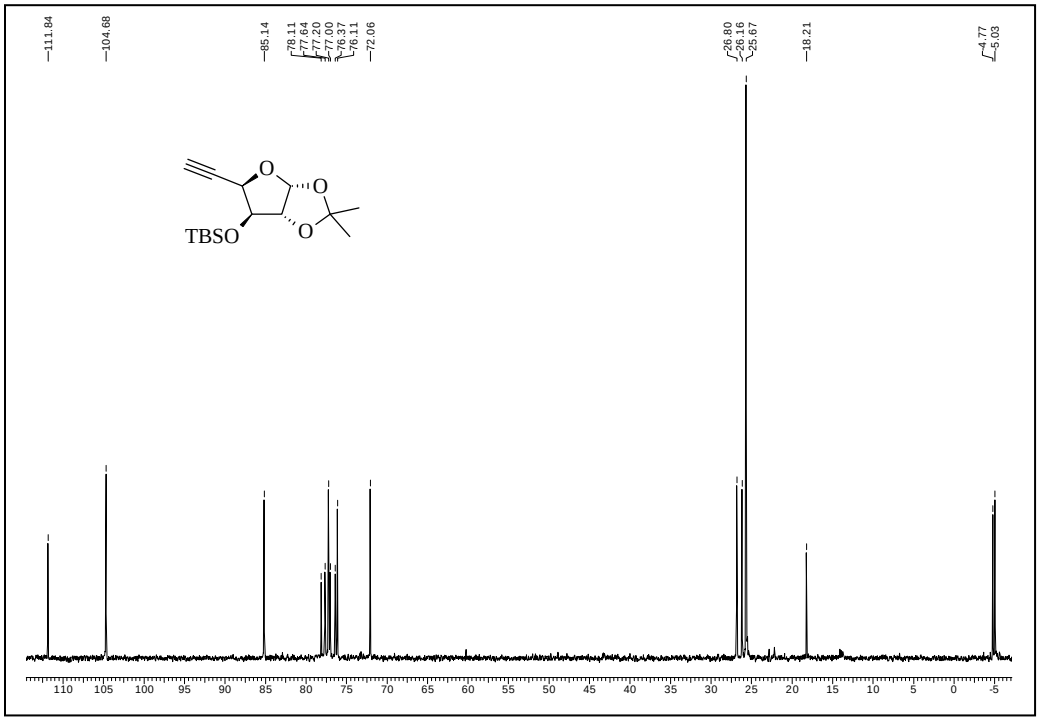


To a stirred solution of $[RuCl_2$-(*p*-cymene)$]_2$ (16 mg, 0.027 mmol) in benzene (5 mL) was added pyrrolidine (0.01 mL, 0.11 mmol), and the mixture was stirred for 15 min at room temperature followed by the addition of alkyne **1B.20** (150 mg, 0.55 mmol) and methyl vinyl ketone **1B.22** (0.14 mg, 1.64 mmol). Then after reaction mixture was stirred for 24 h at 60 °C, re-cooled to rt and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (12% ethyl acetate in petroleum ether) to afford 1,4-addition product **1B.27** (25 mg, 14.5% yield) as colorless oil.

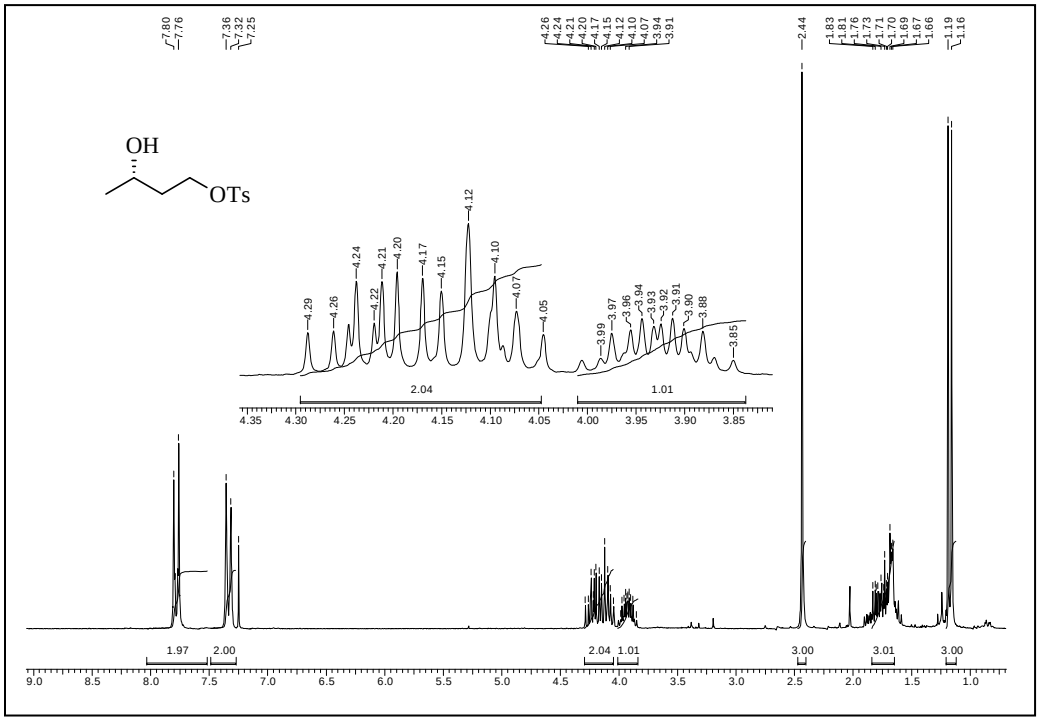
Mol. Formula	: $C_{20}H_{24}O_5$
IR ($CHCl_3$) $\tilde{\nu}$	: 3020, 2933, 2401, 1717, 1385, 1216, 1164, 1077, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.29 (s, 3H), 1.45 (s, 3H), 2.12 (s, 3H), 2.47–2.55 (m, 2H), 2.62–2.70 (m, 2H), 3.92 (d, *J* = 2.8 Hz, 1H), 4.56 (d, *J* = 3.7 Hz, 1H), 4.72 (d, *J* = 12.2 Hz, 1H), 4.78 (d, *J* = 12.2 Hz, 1H), 4.79 (d, *J* = 2.8 Hz, 1H), 5.93 (d, *J* = 3.7 Hz, 1H), 7.31–7.40 (m, 5H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 13.3 (t), 26.2 (q), 26.8 (q), 29.7 (q), 42.0 (t), 71.0 (d), 72.4 (t), 74.2 (s), 82.5 (d), 82.9 (d), 87.5 (s), 104.5 (d), 111.7 (s), 127.6 (d), 127.8 (d), 128.4 (d), 137.5 (s), 206.0 (s) ppm.
ESI-MS (*m/z*)	: 345.2 (8%, $[M+H]^+$), 362.2 (100%, $[M+NH_4]^+$), 367.2 (88%, $[M+Na]^+$), 383.2 (32%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 69.75; H, 7.02%. Found: C, 69.59; H, 6.92%.



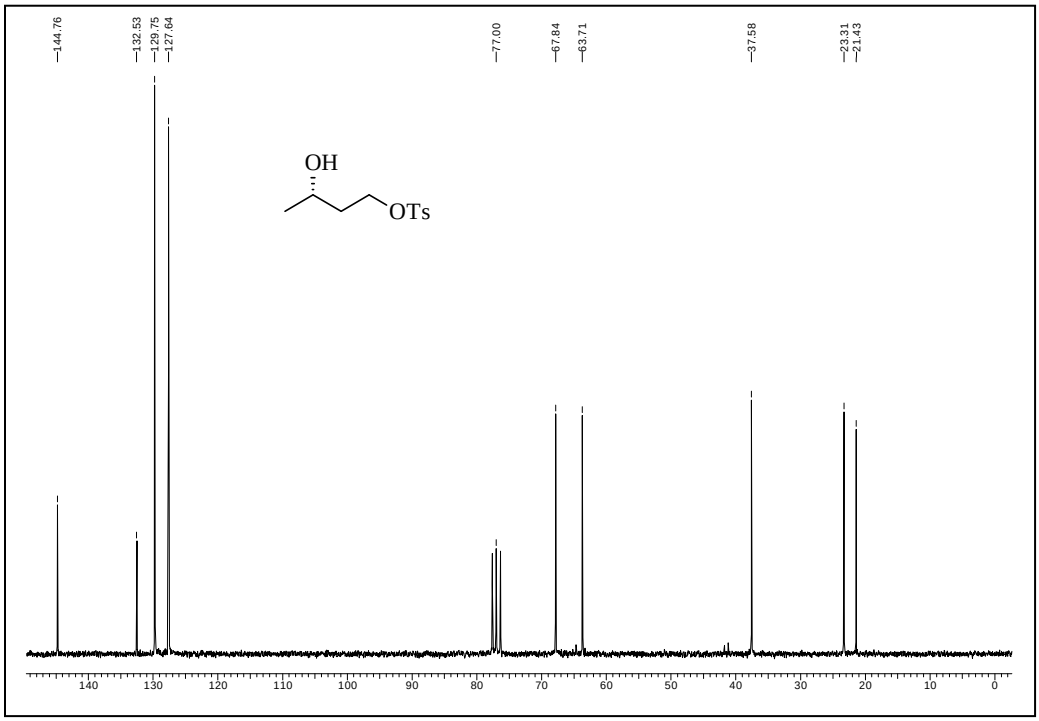
^{1}H NMR Spectrum of 1B.20 in $CDCl_3$



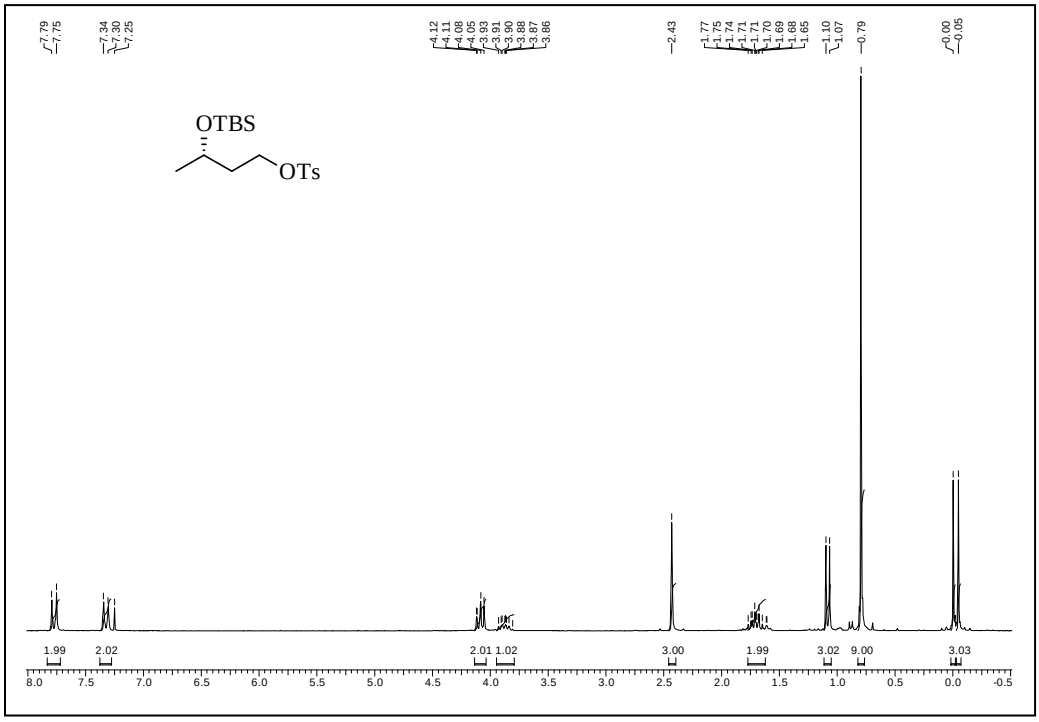
^{13}C NMR Spectrum of 1B.20 in $CDCl_3$



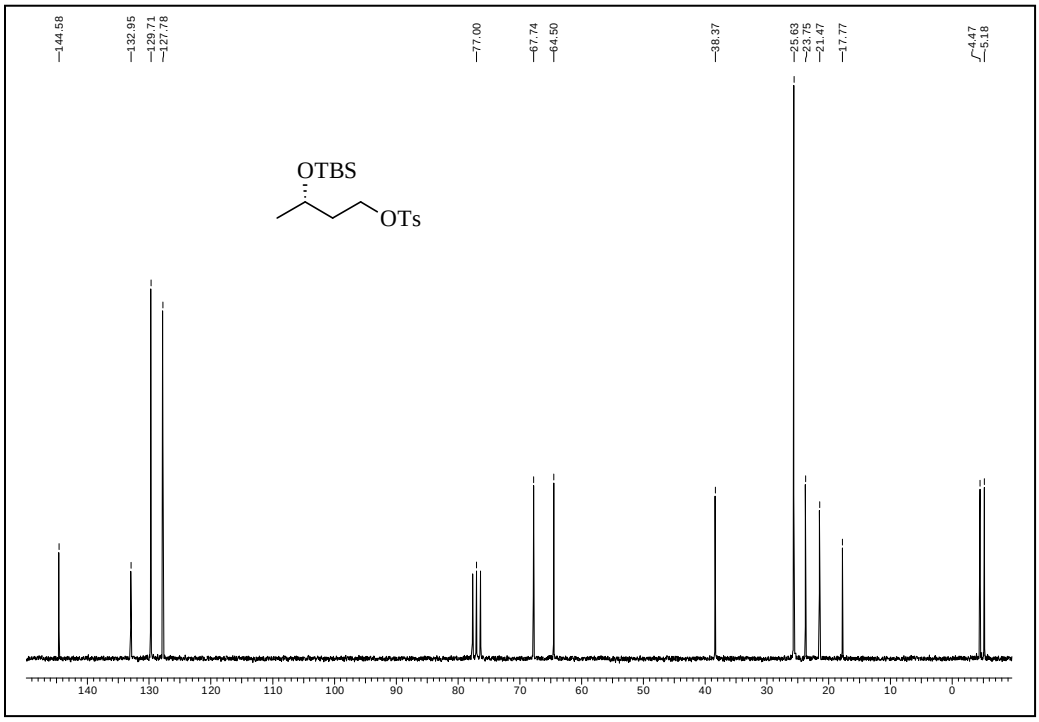
^{1}H NMR Spectrum of 1B.39 in $CDCl_3$



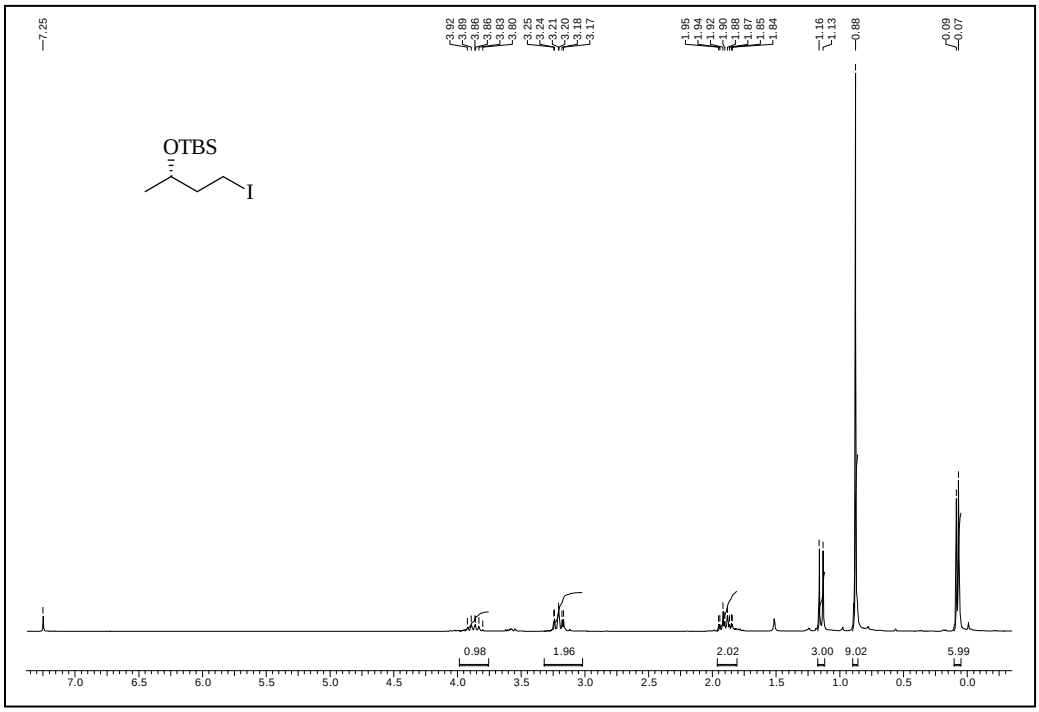
^{13}C NMR Spectrum of 1B.39 in $CDCl_3$



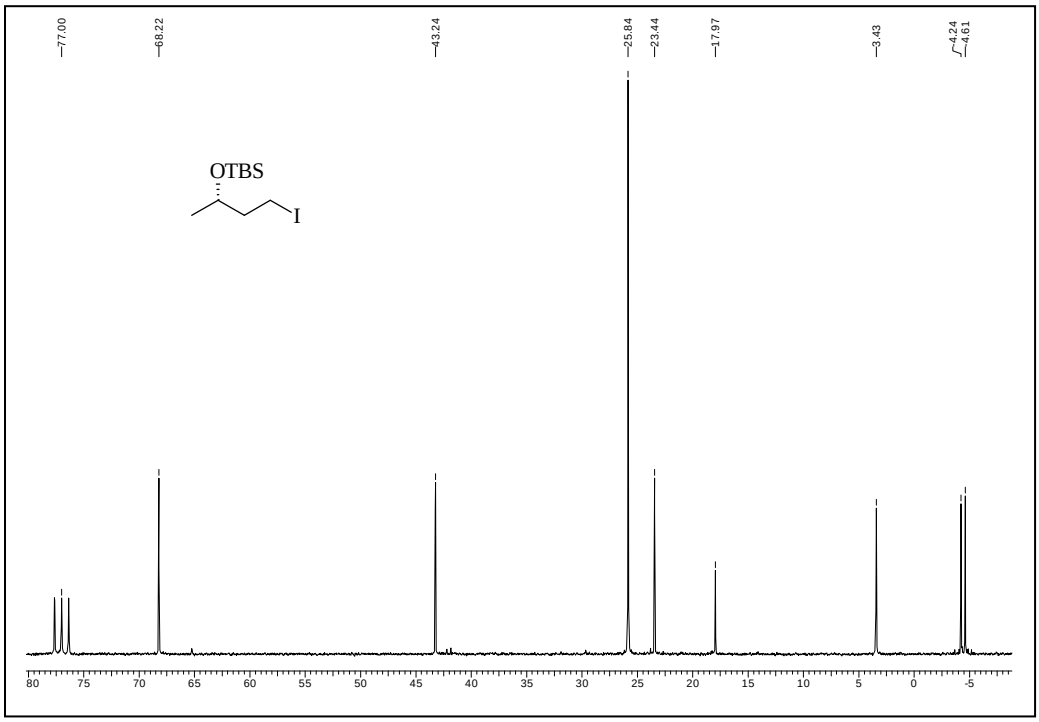
^{1}H NMR Spectrum of 1B.40 in $CDCl_3$



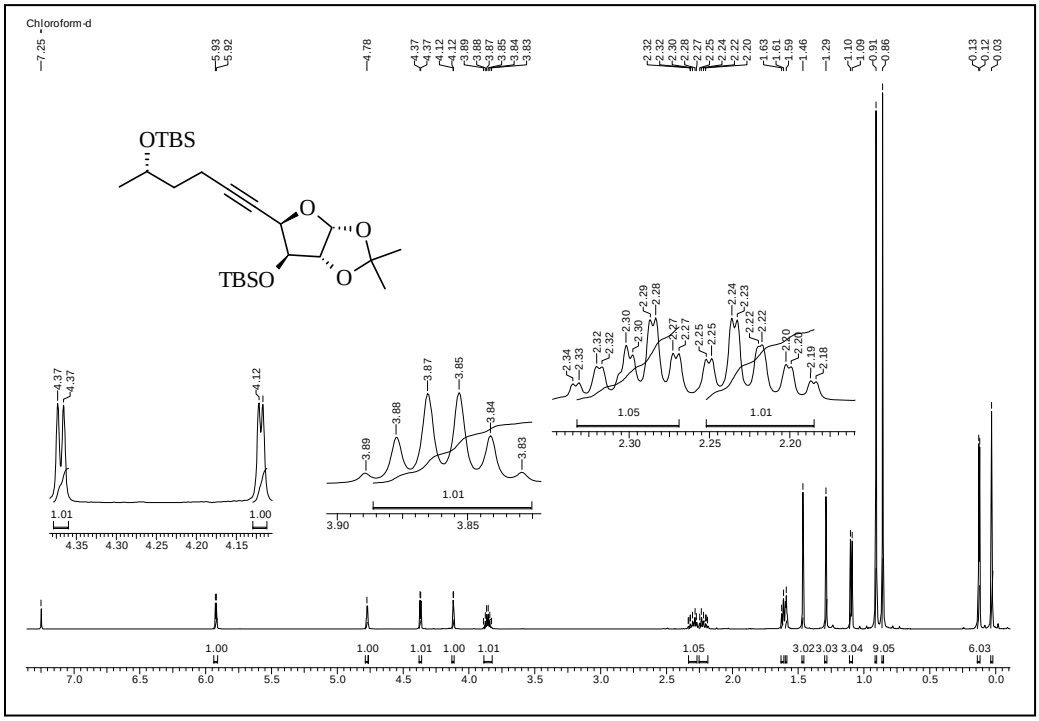
^{13}C NMR Spectrum of 1B.40 in $CDCl_3$



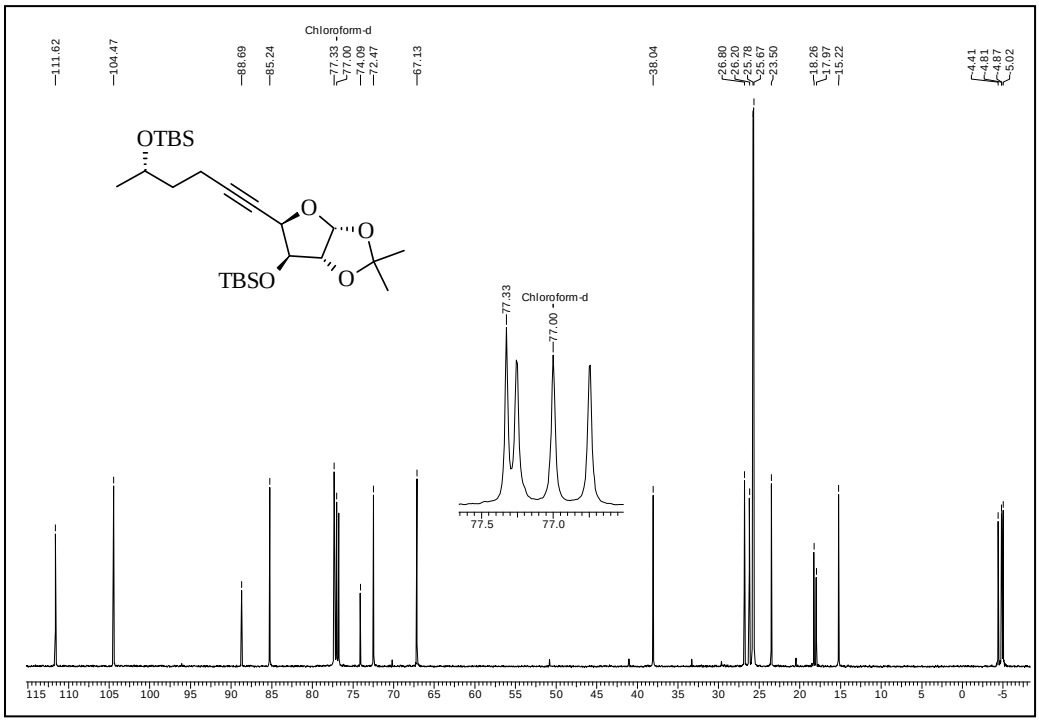
^{1}H NMR Spectrum of 1B.21 in $CDCl_3$



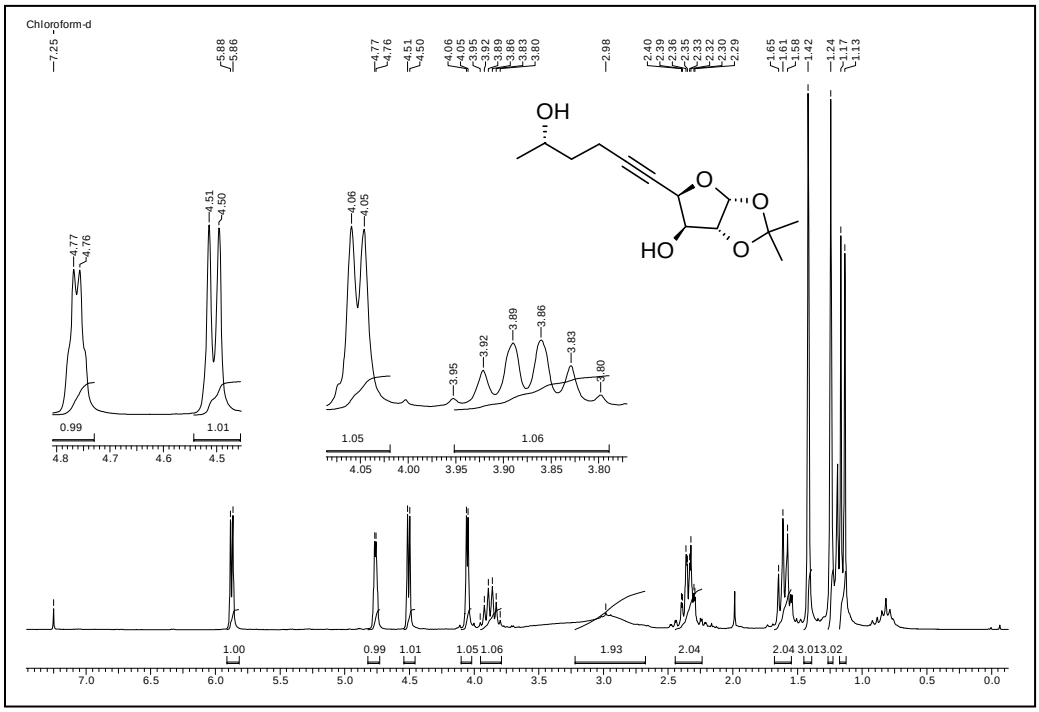
^{13}C NMR Spectrum of 1B.21 in $CDCl_3$



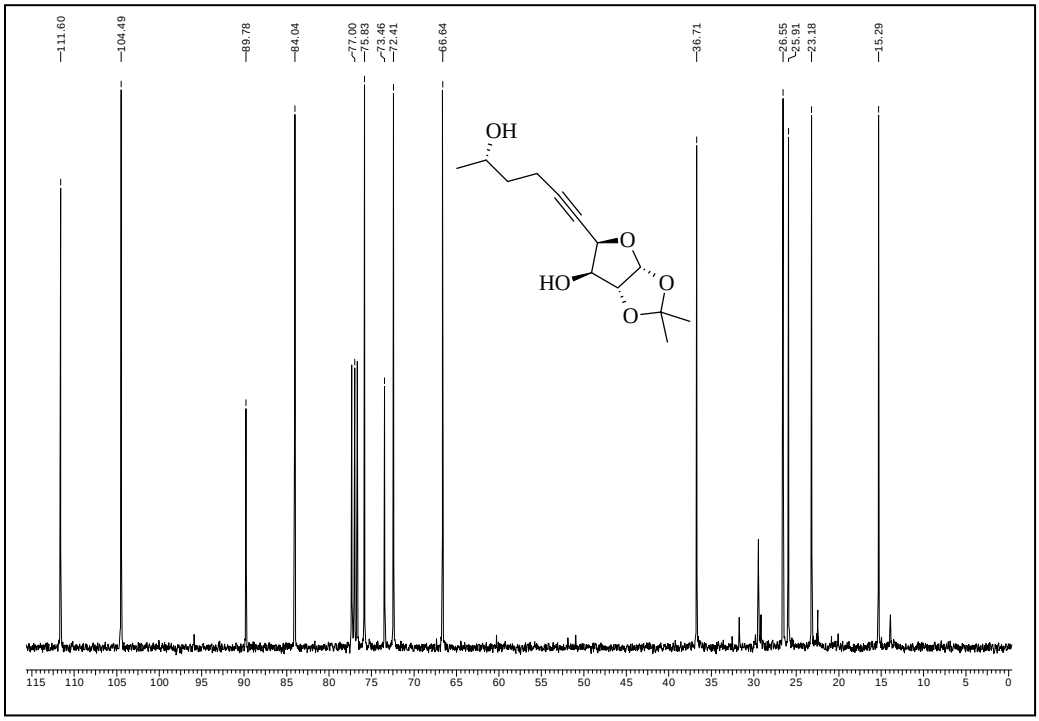
^{1}H NMR Spectrum of 1B.41 in $CDCl_3$



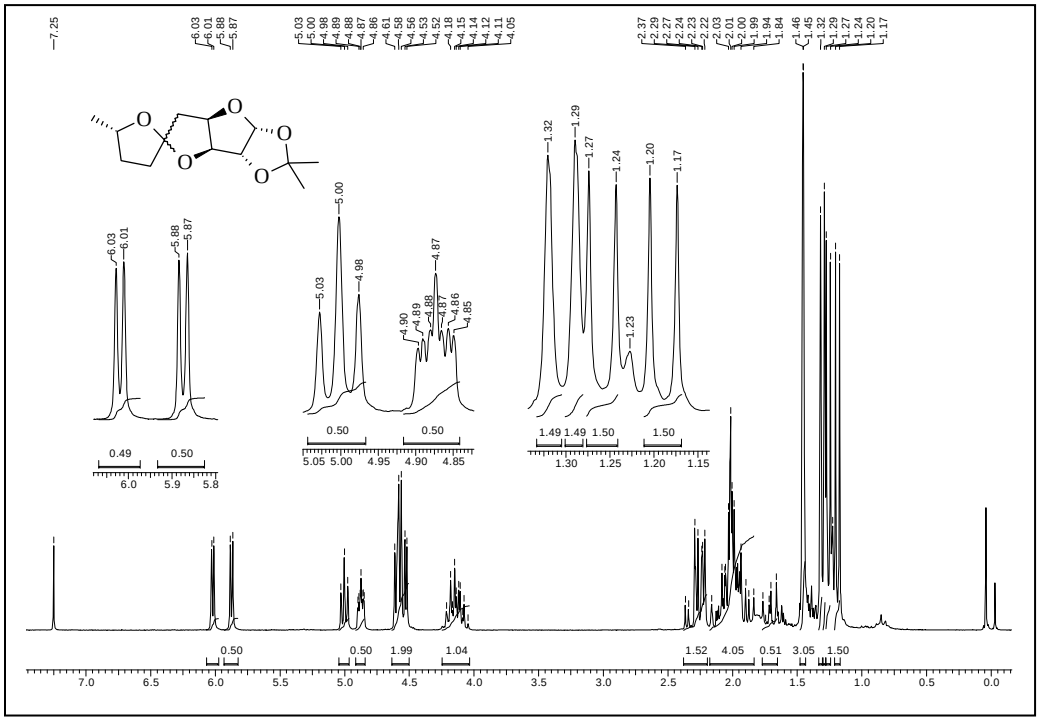
^{13}C NMR Spectrum of 1B.41 in $CDCl_3$



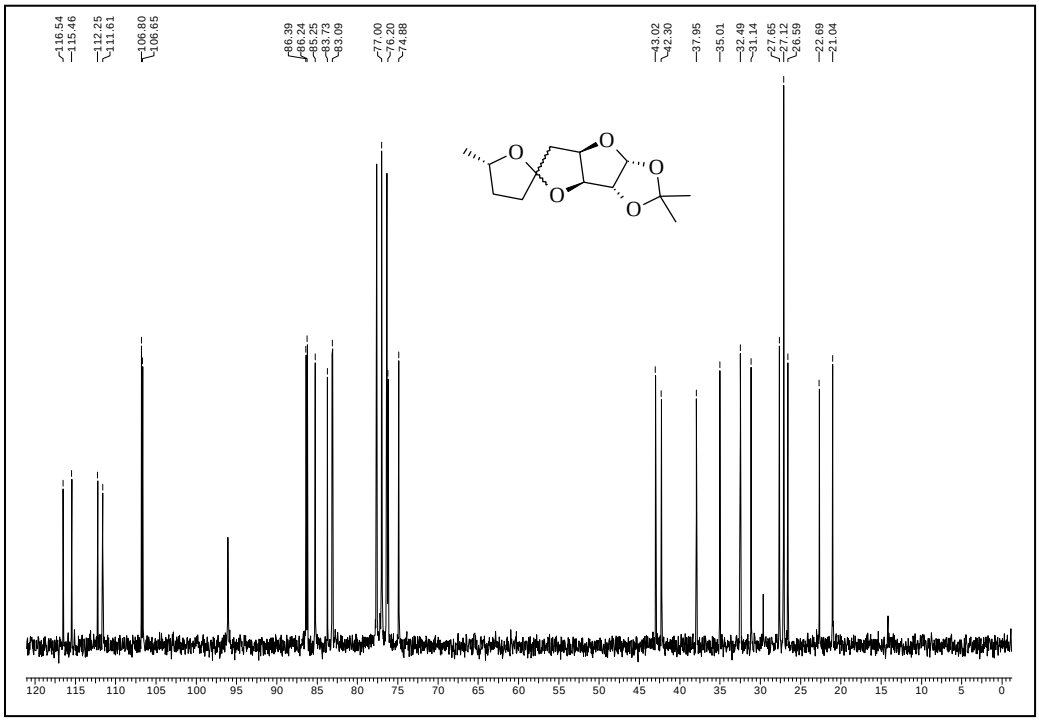
^{1}H NMR Spectrum of 1B.19 in $CDCl_3$



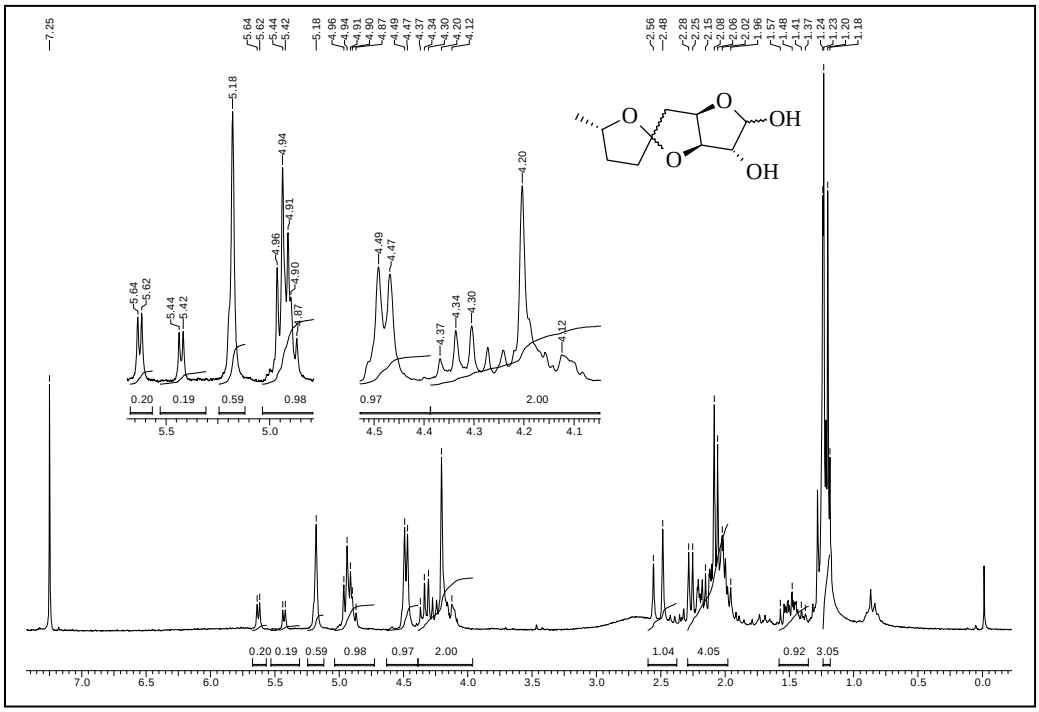
^{13}C NMR Spectrum of 1B.19 in $CDCl_3$



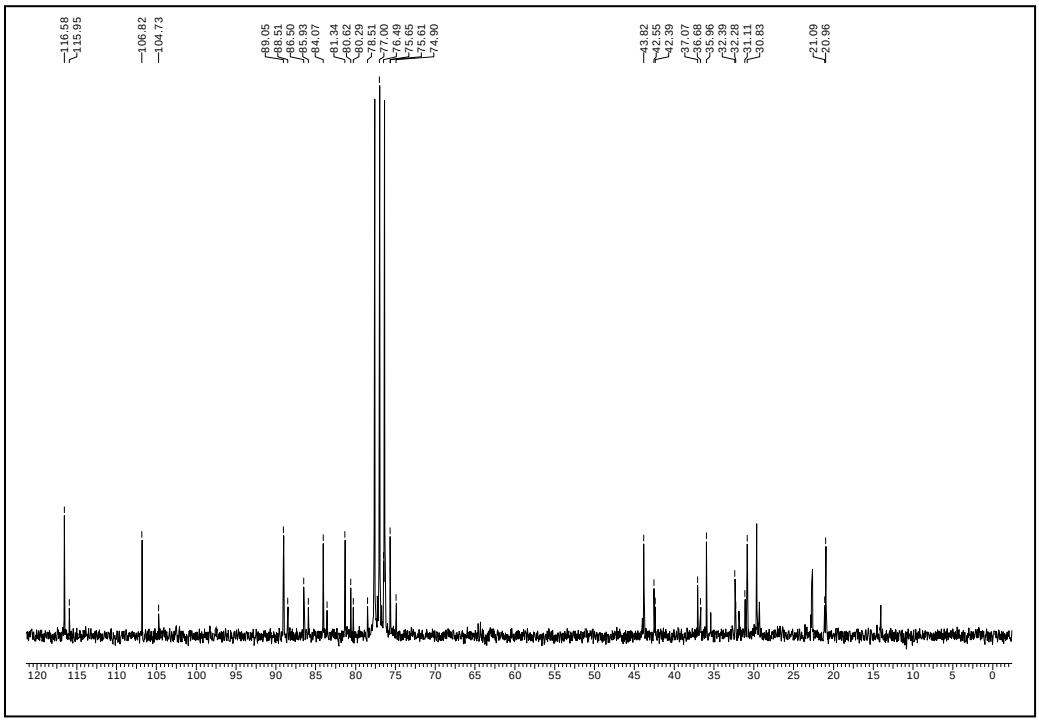
^{1}H NMR Spectrum of 1B.18 in $CDCl_3$



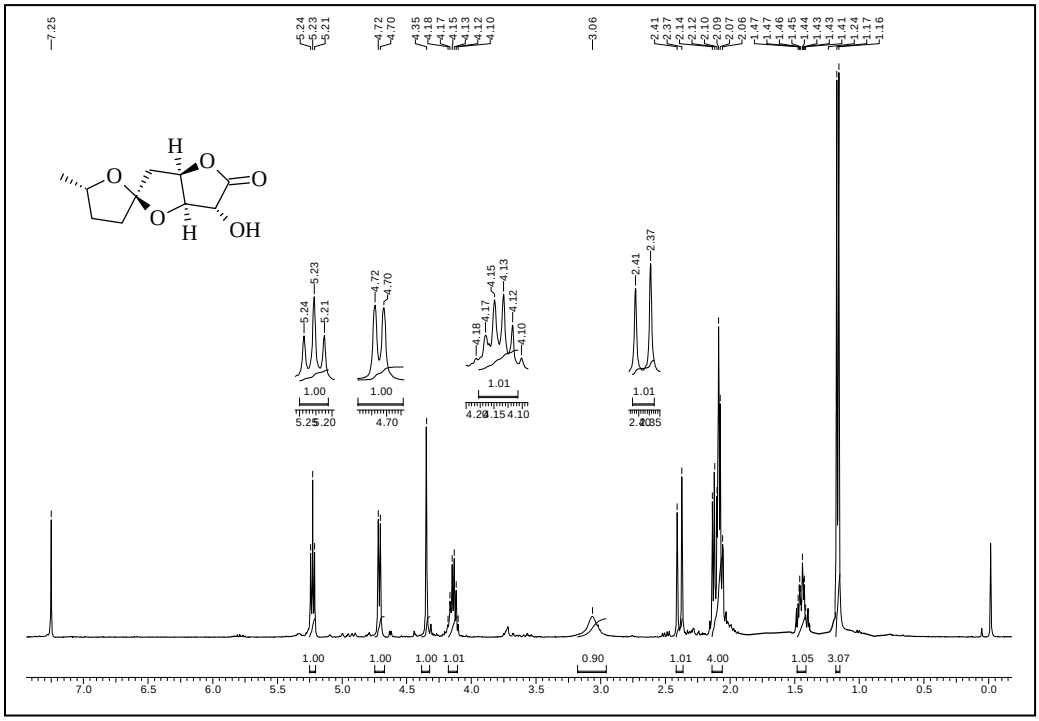
^{13}C NMR Spectrum of 1B.18 in $CDCl_3$



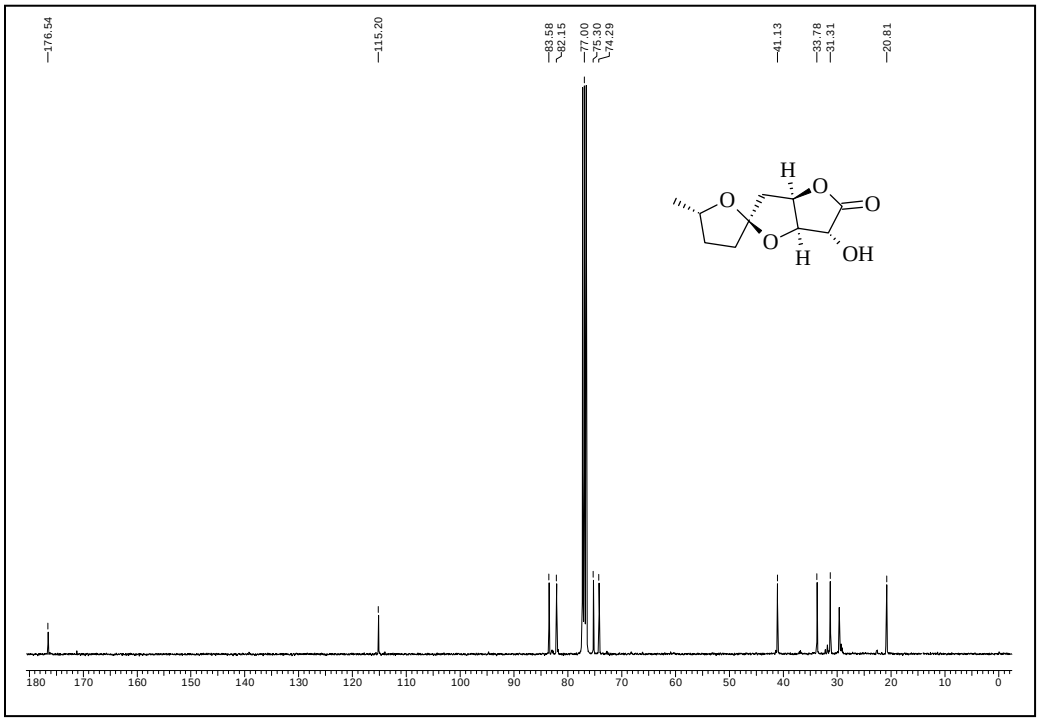
^{1}H NMR Spectrum of 1B.42 in $CDCl_3$



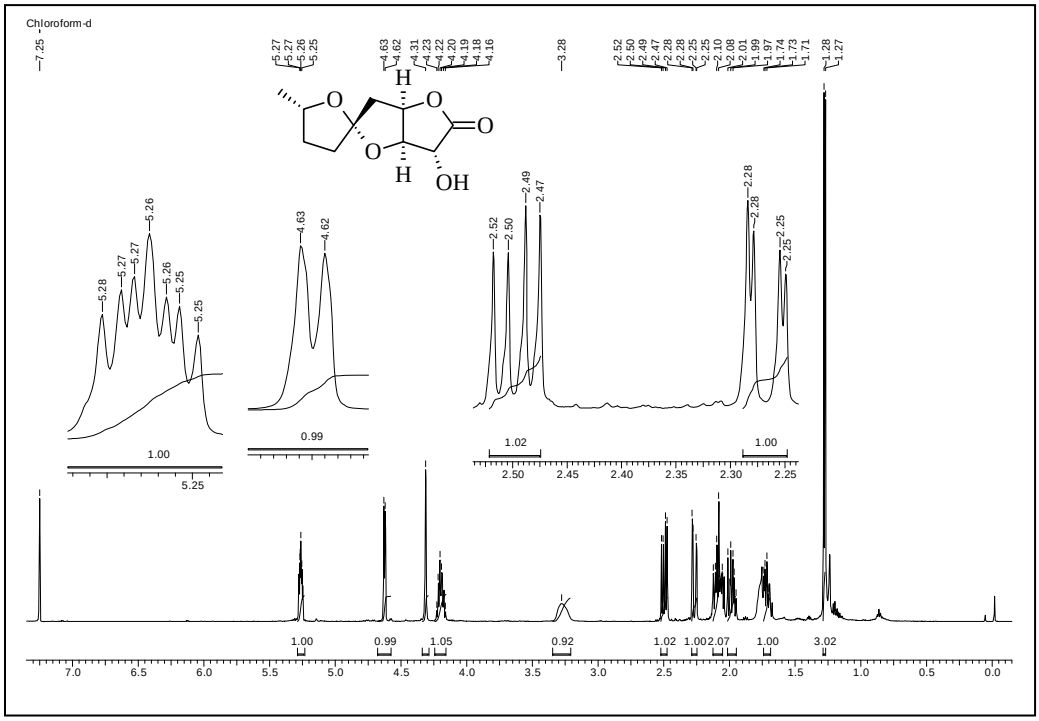
^{13}C NMR Spectrum of 1B.42 in $CDCl_3$



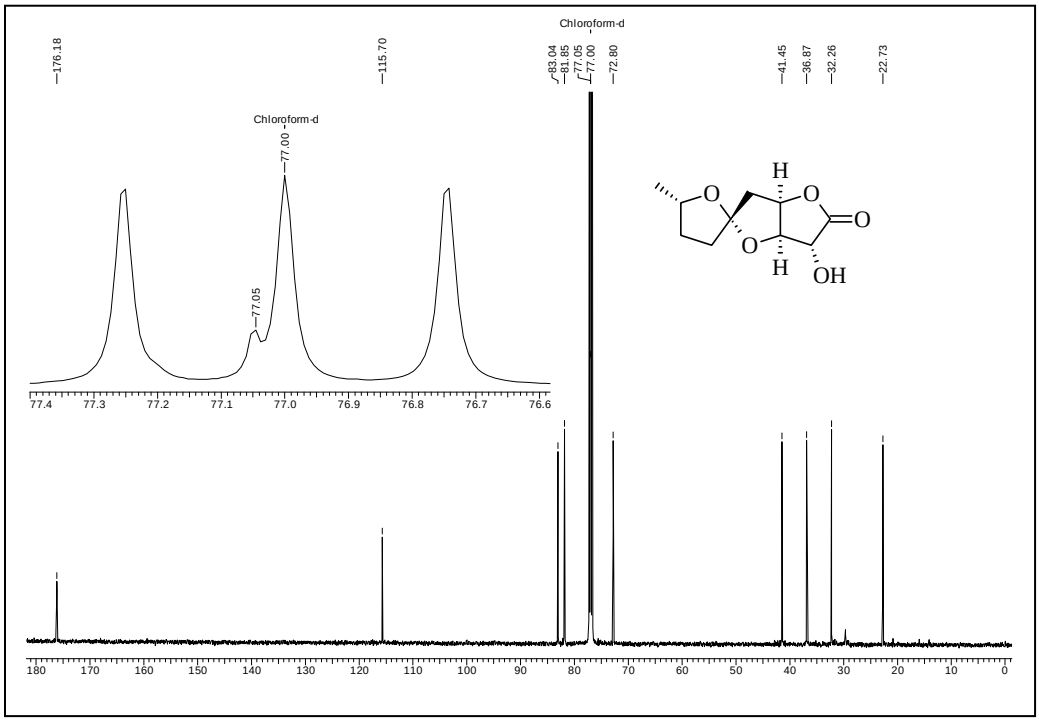
^{1}H NMR Spectrum of 1B.43 in $CDCl_3$



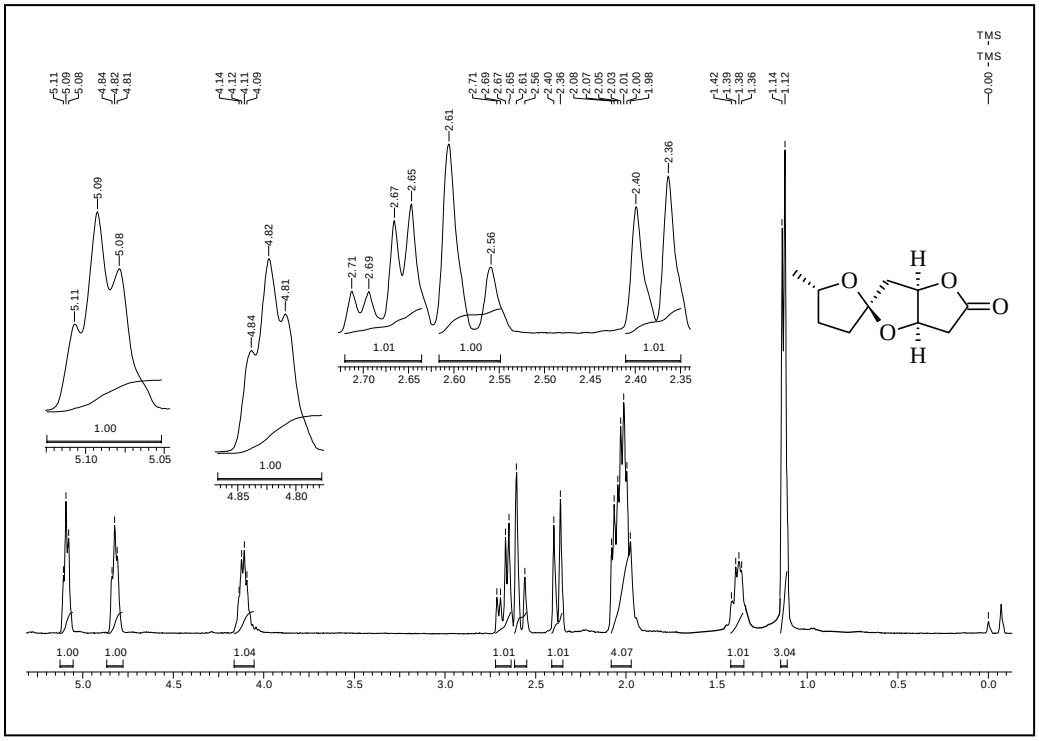
^{13}C NMR Spectrum of 1B.43 in $CDCl_3$



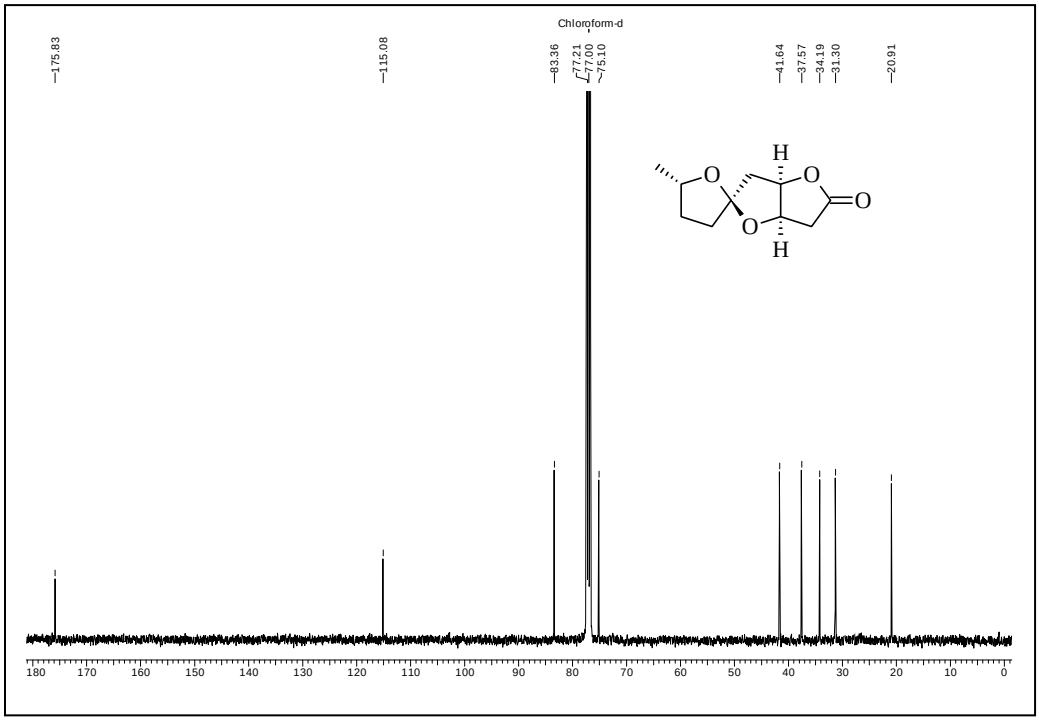
^{1}H NMR Spectrum of 1B.44 in $CDCl_3$



^{13}C NMR Spectrum of 1B.44 in $CDCl_3$



^{1}H NMR Spectrum of 1B.47 in $CDCl_3$



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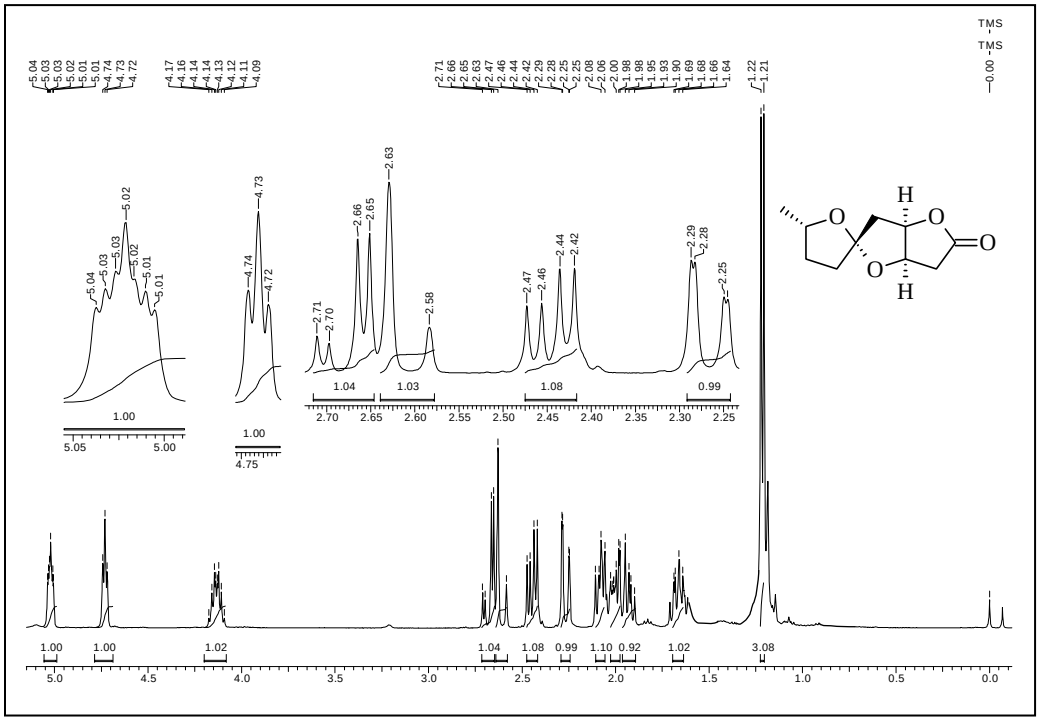

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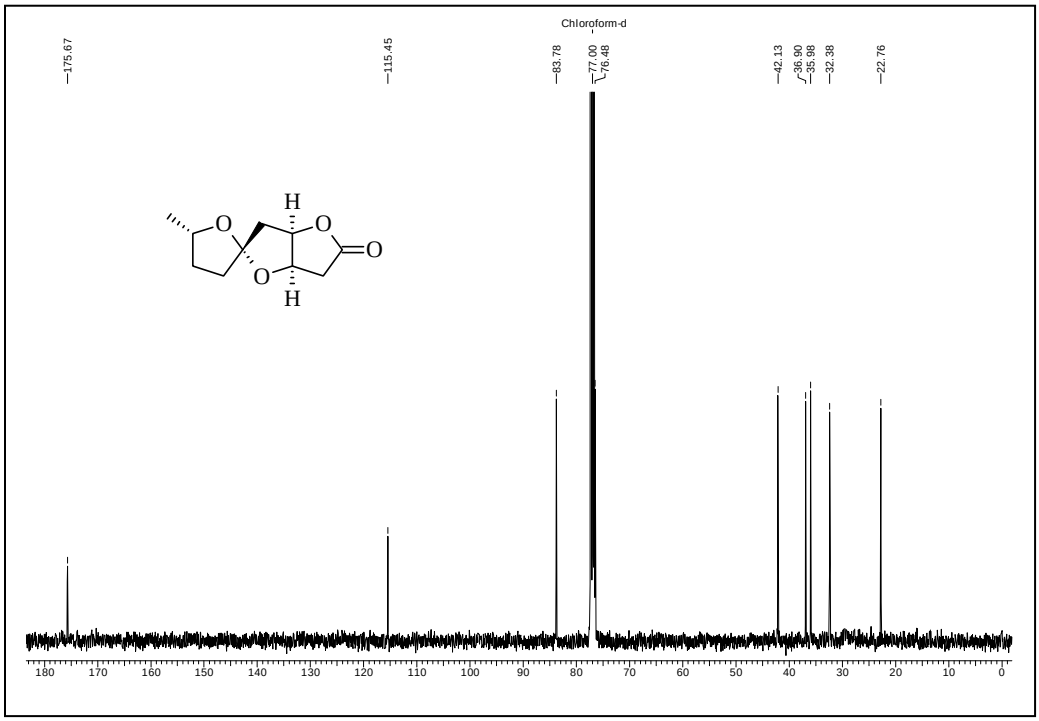

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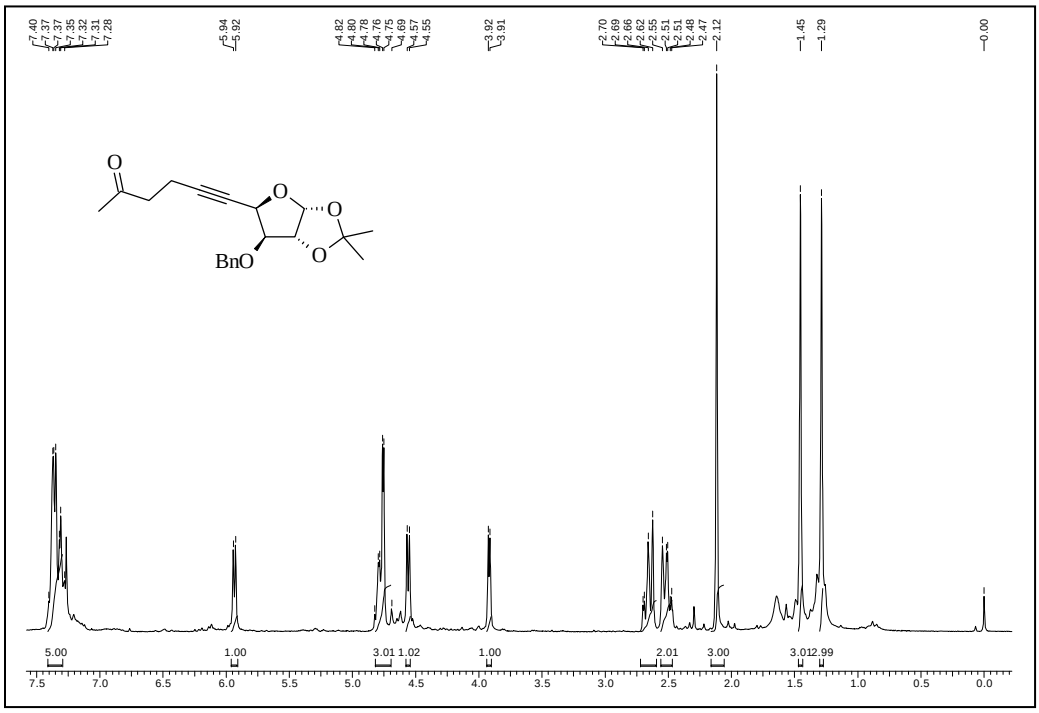
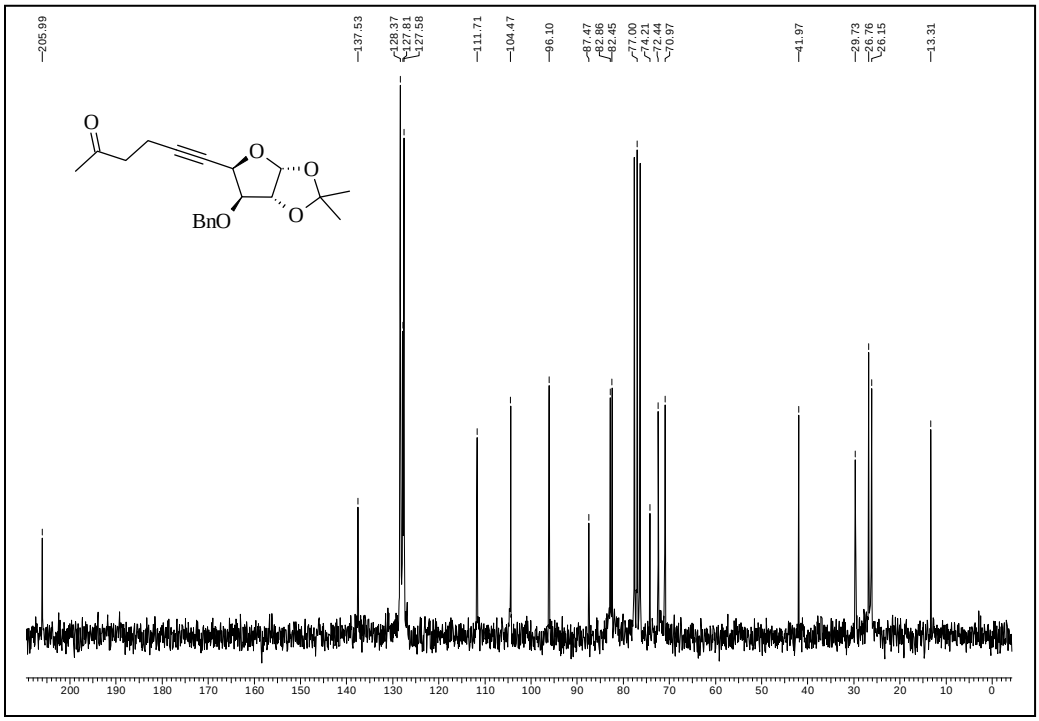


^{1}H NMR Spectrum of 1B.27 in $CDCl_3$



^{13}C NMR Spectrum of 1B.27 in $CDCl_3$

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CHAPTER-II

Section I: [2+2+2]-cyclotrimerization approach for the synthesis of enantiopure isochromans and spiroannulation of dihydroisobenzofuran

2A.1. Introduction to Cyclotrimerization:

Designing effective routes to construct complex cyclic structures through organo transition-metal catalyzed reactions has been recognized as an attractive strategy for delivering molecular diversity.[1] More specifically, the use of carbon-carbon bond formation reactions to generate new ring systems is an ever demanding task in organic synthesis. In this respect, cycloaddition reactions are considered to be strategically useful where more than one carbon-carbon or carbon-heteroatom bonds are formed. With this as a goal, several researchers have developed new reaction pathways aimed towards the synthesis of complex organic molecules with cycloaddition reaction as the key skeletal construct. Novel catalysts and new reaction conditions addressing the chemo- and regioselectivity aspects of various types cycloaddition reactions have been disclosed.

The [2+2+2]-cycloaddition involving alkynes to generate annulated benzene derivatives is one of the more elegant methods for the construction of aromatic ring. The transition metal catalyzed cyclotrimerization of acetylenes to benzene derivatives was first reported by Reppe *et al*. employing Ni catalyst.[2] Since then, cyclotrimerization reaction has attracted considerable attention by virtue of its intrinsic atom economy, as well as the importance of substituted and annulated benzenes as synthetic intermediates. Various transition metal catalysts based on Ni, Co, Pd, Cr, Rh, Fe, Zr, Nb, Ir, and Ta have been developed for the trimerization reaction involving alkynes. In addition to the alkynes, other unsaturated functional groups such as nitriles, isocyanates, olefins, carbonyl compounds, imines, and diimides have been shown to participate in cyclotrimerizations with alkynes to deliver useful heterocyclic end-products.[3,4]

Cyclotrimerization of alkynes can be classified into three types, i.e., two intermolecular reactions (types I and II) and an intramolecular reaction (type III, Scheme 2A.1), giving substituted benzene derivatives **2A.1**–**2A.3** respectively.

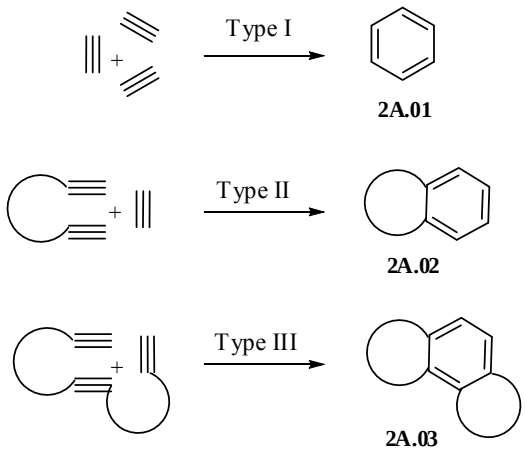
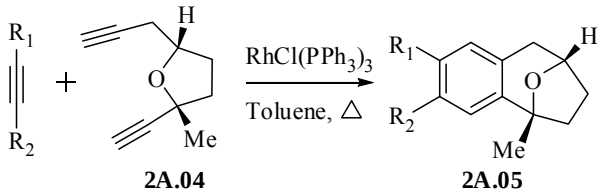


Figure 2A.1: Cyclotrimerization of alkynes

In general, these reactions can be performed in common organic solvents at temperatures ranging from room temperature upwards. Due to its operational simplicity, and ability to provide complex molecular structures, the transition metal catalyzed [2+2+2]-alkyne cyclotrimerization has become an integral component in the armory of organic synthetic methods.[3,5] For a long time, the regioselectivity was a primary concern for this type of reactions,[4] but little success was achieved despite enormous efforts to control regioselectivity.

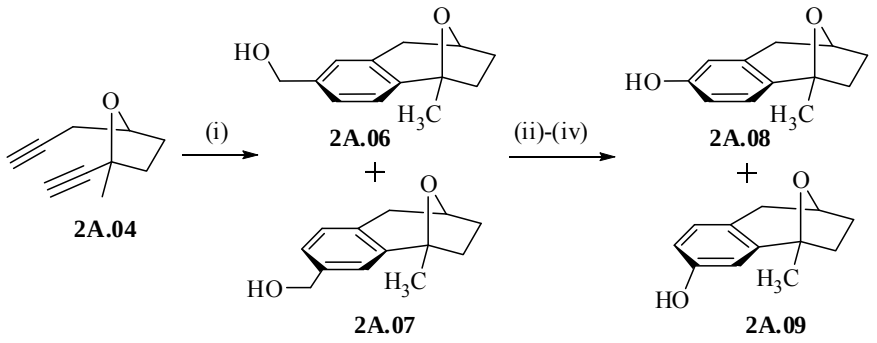
[2+2+2]-Cyclotrimerization for bridged bicyclic systems

Our group has reported for the first time, a new entry to benzannulated 8-oxabicylo[3.2.1] systems by cross alkyne cyclotrimerization (Scheme 2A.1).[6] Dialkyne **2A.04** (synthesized from geraniol diacetate) subjected to [2+2+2]-cyclotrimerisation with symmetrical and unsymmetrical alkynes using different metal catalysts and concluded that the Wilkinson's catalyst [$RhCl(PPh_3)_3$] bring the cyclotrimerization reaction effectively above 80 °C yielding good yields.



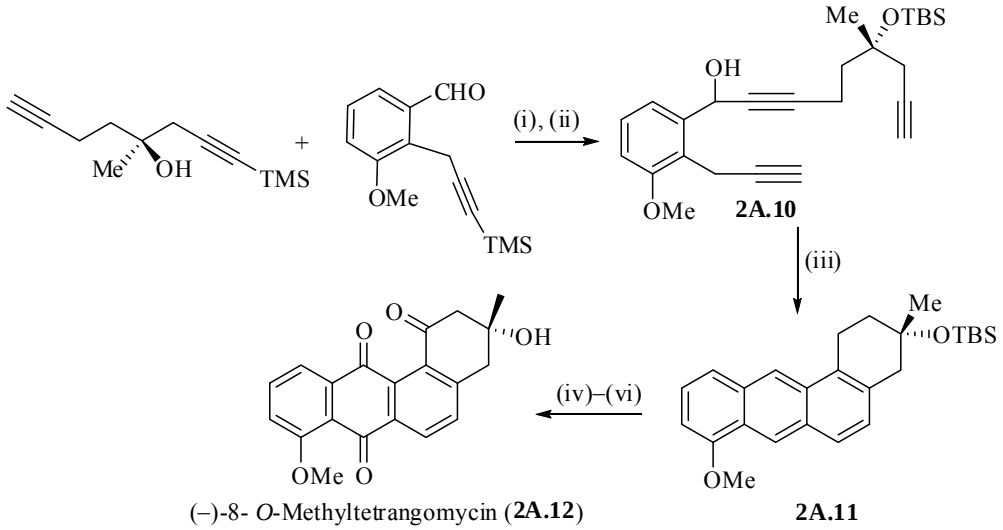
Scheme 2A.1: construction of benzannulated-8-oxa-bicyclo[3.2.1]octane

After complete standardization of [2+2+2]-cyclotrimerisation reaction towards benzannulated-8-oxa-bicyclo[3.2.1]octanes, we applied it to the first total synthesis of (–)-bruguierol-A (Scheme 2A.2). Oxidation of mixture of compounds **2A.06/2A.07** (prepared by employing trimerization reaction between diyne **2A.4** and propargyl alcohol) with MnO_2 followed by treatment with *m*-CPBA provided bruguierol A (**2A.08**) and and its regioisomer **2A.09**.



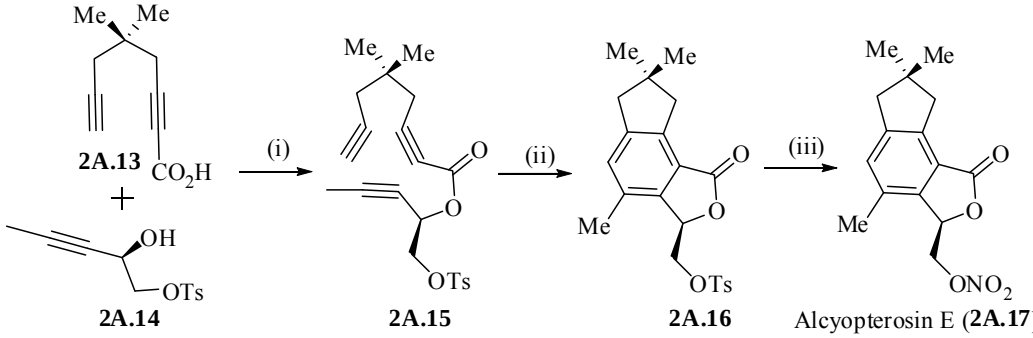
Scheme 2A.2: *reagents and reaction conditions*: (i) propargyl alcohol, $RhCl(PPh_3)_3$, Toluene, 80 °C, 67%. (ii) MnO_2, CH_2Cl_2, rt, 5h. (iii) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 4h. (iiv) aq. NaOH, THF, 2h (33% yield for three steps).

Groth and co-workers reported the stereoselective total synthesis of the natural antibiotic (–)-8-*O*-methyltetrangomycin (MM 47755) (**2A.12**).[7] The cobalt-mediated [2+2+2]-cyclotrimerization reaction of the triyne **2A.10** led to a benz[a]anthracene system **2A.11** (Scheme 2A.3), which was oxidized with $Ag(Py)_2MnO_4$ to a benz[a]anthraquinone. Deprotection with aq. HF in acetonitrile and photooxidation afforded the desired natural product **2A.12**.



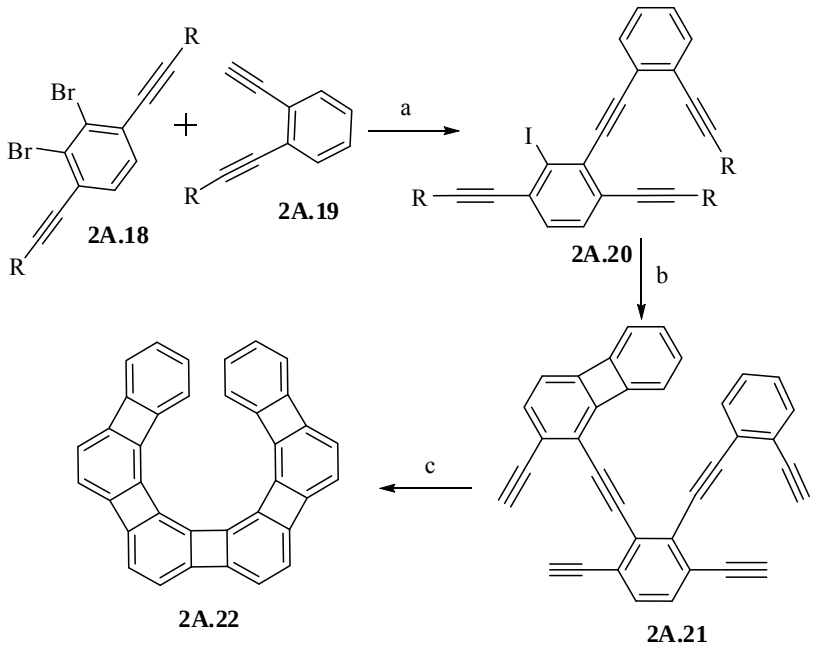
Scheme 2A.3: *Reagents and conditions:* (i) *n*-BuLi, Et_2O, –78 °C, 3 h, $BF_3.Et_2O$, Et_2O, –78 °C, 2 h, 70%. (ii) K_2CO_3, MeOH, rt., 6 h, 90%. (iii) $CpCo(C_2H_4)_2$, Et_2O, –78 °C to rt., 4 h, then cat. AcOH, 80%. (iv) $Ag(Py)_2MnO_4$, SiO_2, CH_2Cl_2, rt., 7 h, 65%. (v) aq. HF, CH_3CN, 50 °C, 5 h, 98%. (vi) hν, air, $CHCl_3$, rt., 1 h, 58%.

The first synthesis of the marine illudalane sesquiterpenoid alcyopterosin E (**2A.17**) was reported by Witulski and co-workers through a concise ABC ring-formation using an intramolecular alkyne cyclotrimerisation.[8] The DCC mediated coupling of **2A.13** and **2A.14** provided the triyne ester **2A.15**. Treatment of **2A.15** with 10 mol% $RhCl(PPh_3)_3$ in DCM at 40 °C gave **2A.16** as a single product in 72% yield. Finally, the first synthesis of alcyopterosin E (**2A.17**) was completed by nucleophilic displacement of the tosyl protective group to provide the nitrate ester functionality of **2A.17** (Scheme 2A.4).



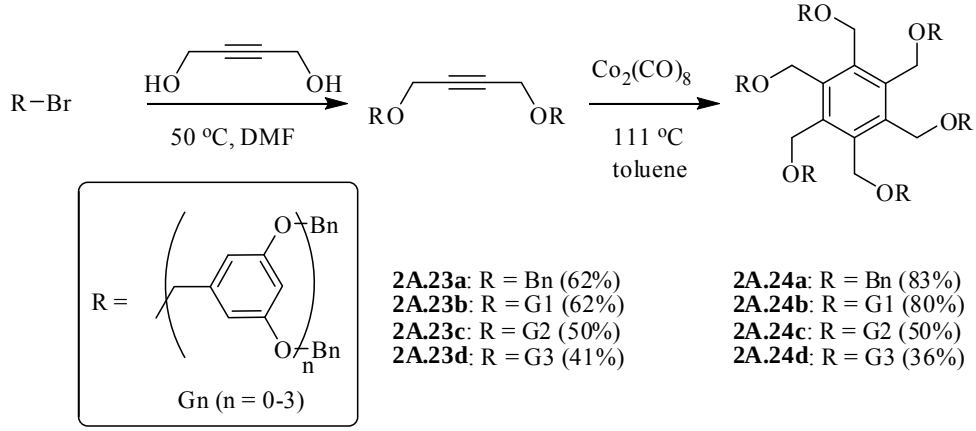
Scheme 2A.4: *Reagents and conditions:* i) DCC, DMAP, CH_2Cl_2, –78 °C to r.t., 70%. ii) 10 mol% $RhCl(PPh_3)_3$, CH_2Cl_2, 40 °C, 72%. iii) $NaNO_3$ (10 equiv.), Bu_4NNO_3, toluene, 110 °C, 69%.

Vollhardt and co-workers reported total syntheses and structures of angular [6]- and [7]-phenylene (heliphenes).[9] The synthesis started with Pd-catalyzed alkynylation of readily available dibromo compound **2A.18** with alkyne **2A.19** followed by replacement of bromo with iodo to furnish **2A.20**. A second alkynylation with 1-ethynyl-2-(2-DMTS-ethynyl)biphenylene followed by global silyl deprotection gave hexayne **2A.21**. Finally, cobalt-catalyzed intramolecular cyclotrimerization of **2A.21** in refluxing xylene photochemical irradiation furnished **2A.22** (Scheme 2A.5).



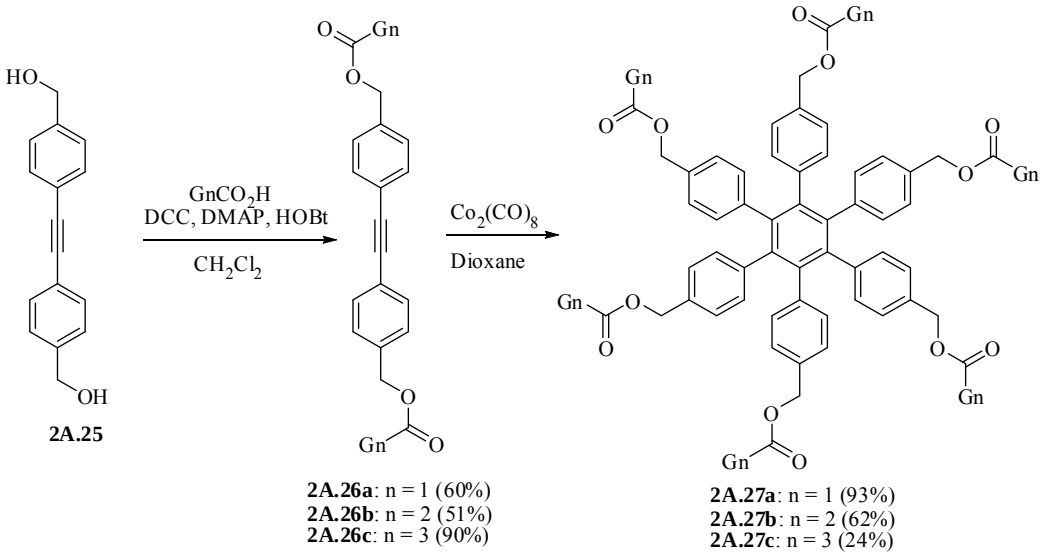
Scheme 2A.5: *Reagents and conditions:* (a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 70–85 °C, 14 h. (b) i. *n*-BuLi, Et_2O, –78 °C; ii. I_2, Et_2O, –78 °C, 54%; iii. 1-ethynyl-2-(2-DMTS-ethynyl)biphenylene, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 85 °C, 22 h; iv. $Bu_4N^+F^-$, THF, 23 °C, 40 min, 58%. (c) $CpCo(CO)_2$, *m*-xylene, hν, Δ, 30 min, 12%.

Frechet and co-workers reported synthesis of novel benzene-core dendrimers *via* alkyne cyclotrimerization.[10] The substituted alkynes **2A.23a–2A.23d** were synthesized by the Williamson ether coupling of 2-butyne-1,4-diol with appropriate polybenzyl ether-type dendritic bromides. The trimerization reaction of **2A.23a–2A.23d** was carried out in refluxing toluene using dicobalt octacarbonyl as the catalyst to afford novel structures **2A.24a–2A.24d** (Scheme 2A.6).



Scheme 2A.6: Synthesis of dendritic assemblies

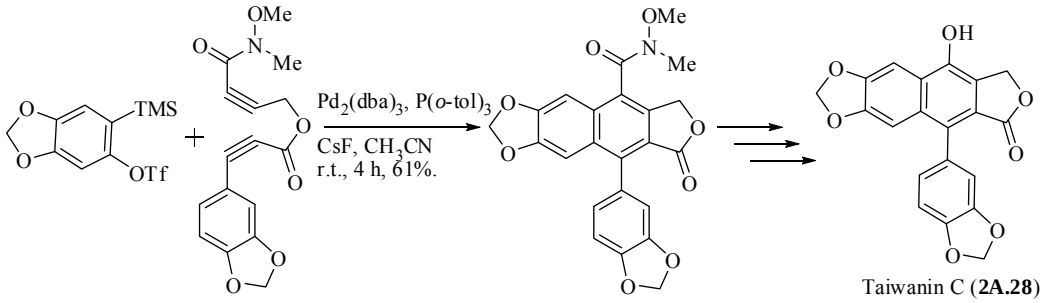
Nierengarten and co-workers[11a] recently reported an efficient synthesis of fullerodendrimers **2A.27a–2A.27c** with hexaphenylbenzene cores and peripheral C_{60} units were prepared by metal-catalyzed cyclotrimerization of the corresponding dendritic *bis*-(aryl)alkyne. The alkyne precursors **2A.26a–2A.26c** were obtained by reaction of diol **2A.25** with fullerodendron $G1CO_2H$, $G2CO_2H$, and $G3CO_2H$, respectively under esterification condition.[11b] Treatment of **2A.26a** with catalytic amount of $Co_2(CO)_8$ in dioxane at rt. for 24 h afforded **2A.27a** in 93% yield (Scheme 2A.7).



Scheme 2A.7: Synthesis of fullerodendrimers

The reaction of the second-generation derivative **2A.26b** was finished after one day and compound **2A.27b** was isolated in 62% yield. In contrast, the reaction of the higher generation precursor **2A.26c** was very slow, most probably as a result of steric crowding and the product **2A.27c** was isolated in 24% yield after 5 days (Scheme 2A.7).

Only the first occurrence by Soto and Mori *et al*. developed a novel method for the construction of arylnaphthalene skeletons through a Pd°-catalyzed [2+2+2] cocyclization of diynes and arynes.[12] The cocyclization was the key step in the total synthesis of taiwanin C (**2A.28**) (Scheme 2A.8).



Scheme 2A.8: Synthesis of taiwanin C (2A.28)

2A.1.1. [2+2+2]-Cyclotrimerozation on sugar templates:

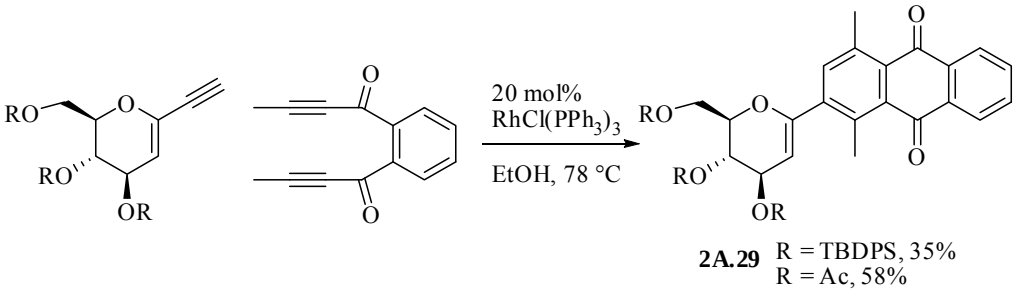
Besides the above selected examples, cyclotrimerizations on sugar derived templates deserves a special mention, which is rather a remote area. Integrated with the transition metal catalyzed reactions, the sugar templates have been well deployed to address the synthesis of a variety of complex natural products skeletons.[13] Amongst the many other metal catalyzed reactions which have been explored on the sugar templates, catalytic [2+2+2] alkyne cyclotrimerization occupies a special mention because it delivers highly functionalized aromatic rings appended with sugar rings.

2A.1.1.1. [2+2+2]-Cyclotrimerozation in Synthesis of *C*-arylglycosides:

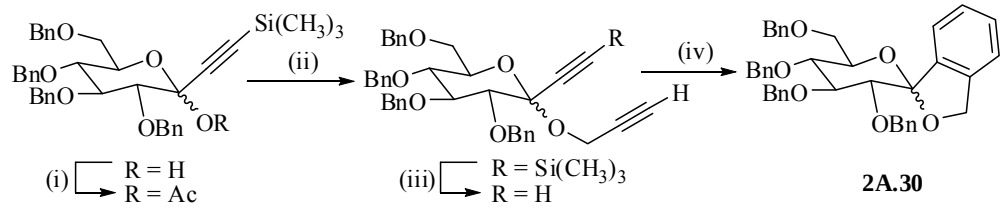
The synthesis of *C*-glycosides, in which the glycosidic oxygen is replaced by a carbon atom, has been an area of intense study in bioorganic and synthetic chemistry. This is because *C*-glycosides are stable toward enzymatic and chemical hydrolysis, and therefore, they are potent inhibitors for glycosidases and glycosyltransferases.[14] Frequently encountered *C*-glycoside motifs in nature are *C*-arylglycosides. *C*-Arylglycoside frameworks are generally obtained by the direct arylation of appropriate carbohydrate precursors.[15] However, the control of regiochemistry is a crucial problem when a highly substituted aromatic precursor is employed for this purpose. The [2+2+2]-cycloaddition of α,ω-diynes with *C*-alkynylglycosides is a convergent and atom economical approach.

McDonald and co-workers have realized this method for the first time in the synthesis of anthraquinone *C*-glycosides **2A.29** (Scheme 2A.9) and *C*-aryl spiroglycosides **2A.30** (Scheme 2A.10).[16] They used Wilkinson catalyst, $RhCl(PPh_3)_3$,

in EtOH at 78 °C to achieve the cycloaddition of a diketodiynewith protected alkynylglycals.

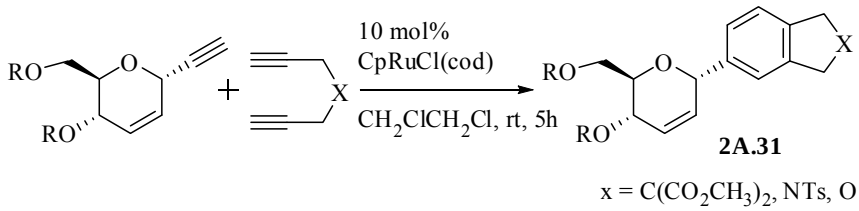


Scheme 2A.9: Synthesis of anthraquinone *C*-glycosides



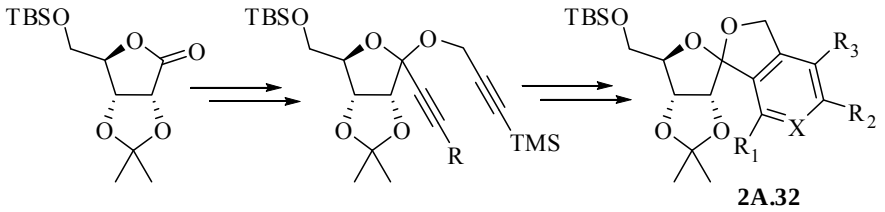
Scheme 2A.10: *Reagents and conditions:* (i) Ac_2O, pyridine, 20 mol % DMAP, CH_2Cl_2, 57% (2.6:1 mixture). (ii) $TMSOCH_2C{\equiv}CH$, 10 mol % $SnCl_4$, 10 mol % $AgClO_4$, CH_2Cl_2. (iii) 50% aqueous NaOH, 20 mol % $BnNEt_3Cl$, CH_3CN, 67% (two steps, 2.2: 1 mixture). (iv) saturated $HC{\equiv}CH$ in EtOH, 10 mol % $RhCl(PPh_3)_3$, 0 °C, 89%.

Yamamoto *et al.* synthesized the *C*-arylglycosides **2A.31** by employing ruthenium-catalyzed cycloaddition reaction on *C*-alkynylglycoside of different sugar derivatives with diynes having hetero atoms[17] (Scheme 2A.11).



Scheme 2A.11

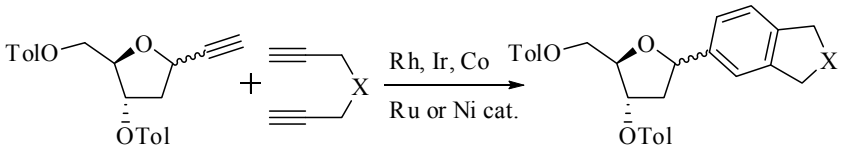
Later in 2006, Yamamoto and co-workers synthesized spirocyclic *C*-ribosides **2A.32** from the known γ-ribonolactone derivative.[18] The lithium acetalide addition followed by glycosylation with 3-(trimethylsilyl)propargyl alcohol converted the ribonolactone to silylated diynes. After desilylation or iodination, subsequent ruthenium catalyzed cyclotrimerization of resultant diynes with alkynes or chloroacetonitrile gave spirocyclic *C*-arylribosides (Scheme 2A.12).



2A.32

Scheme 2A.12

Martin Kotora *et al.* employed various transition metal complexes (Rh, Ir, Co, Ru, and Ni) for the [2+2+2]-cyclotrimerozation reaction of *C*-alkynyldeoxiriboside **2A.33** with a variety of substituted 1,6-heptadiynes **2A.34** to the corresponding *C*-aryldeoxyribosides **2A.35** (Scheme 2.13).[19] They concluded that the Wikinson's catalyst $RhCl(PPh_3)_3$ could catalyze most of the cyclotrimerizations in high yields (52–95%).



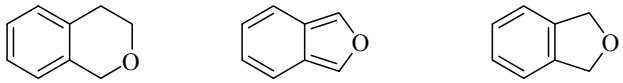
2A.33 **2A.34** **2A.35**

X = $C(CO_2Et)_2$, $C(COCH_3)_2$, $C(CO_2Et)COCH_3$, $C(CO_2Et)CN$, NTs, O.
Cat. Used: $RhCl(PPh_3)_3$, $[Ir(COD)Cl]_2$, $NiBr_2(dppe)$, $Ni(cod)_2/2PPh_3$, $CpRuCl(cod)$, $Co(PPh_3)_3Br$

Scheme 2A.13

2A.2. Present Work:

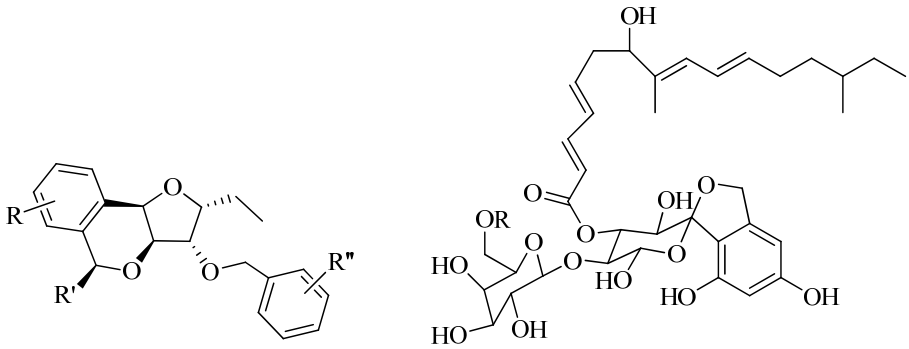
The isochroman **2A.36**, isobenzofuran **2A.37** and 1,3-dihydro-isobenzofuran **2A.38** are integral part of many naturally occurring substances, commercially available drugs and cosmetics[20] (Figure 2A.2). Several synthetic 6,7-dimethoxyisochromans and their 1-arylated analogues have been disclosed as new investigational drugs with a wide range of activities such as analgesic, muscle relaxant, antidepressant, antiinflammatory, antihistaminic, anticoagulant and antihypertensive.[21]



Isochroman **2A.36** | Isobenzofuran **2A.37** | 1,3-Dihydro-isobenzofuran **2A.38**

Figure 2A.2

For example, a series of tricyclic isochroman derivatives **2A.39** have been prepared from D-glucose and evaluated for their herbicidal activities (Figure 2A.3).[22] The papulacandins **2A.40**, are a group of antifungal agents from *Papularia Spherosperma* which exhibit potent in *vitro* activity against *Candida albicans* and related microorganisms,[23] and the 1,3-dihydrospiro-isobenzofuran is the core part of these molecules (Figure 2A.3).



Investigational herbicide **2A.39**

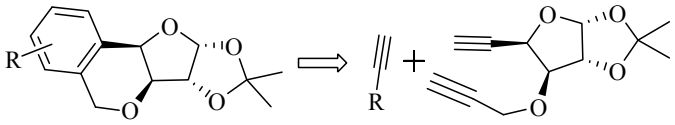
Populacandins **2A.40**

Figure 2A.3: Biologicaly active compounds containing isochromane and 1,3-dihydrospiroisobezofuran core system

A number of synthetic methods involving electrophilic reactions mediated by Lewis acids, radical and carbanion–mediated annulations, and cycloadditions have been reported for the synthesis of isochroman units.[24] The oxa-Pictet-Spengler condensation is a widely used method for the preparation of isochroman units.[23b] An expedient approach for sugar annulated isochromans by Martin *et al.* using intramolecular Friedel-Craft cyclization has been reported. Recently, Kaliappan and co-workers reported an intramolecular enyne-metathesis and subsequent trapping of the resulting dienes by various quinines for the synthesis of tetracyclic derivatives containing isochroman ring.[25] Similarly, several excellent protocols for the spiroannulation of furan/isobenzofuran ring on sugar templates have been reported.[26,27]

Amongst the available methods in this context, catalytic [2+2+2]-alkyne cyclotrimerizations are important as they address the substituent flexibility on the appended aromatic ring. An early example in this regard, is the expedient synthesis of the spirocyclic *C*-arylglycoside framework closely related to the papulacandins by McDonald and co-workers utilizing a rhodium(I)-catalyzed [2+2+2]-cyclotrimerization.

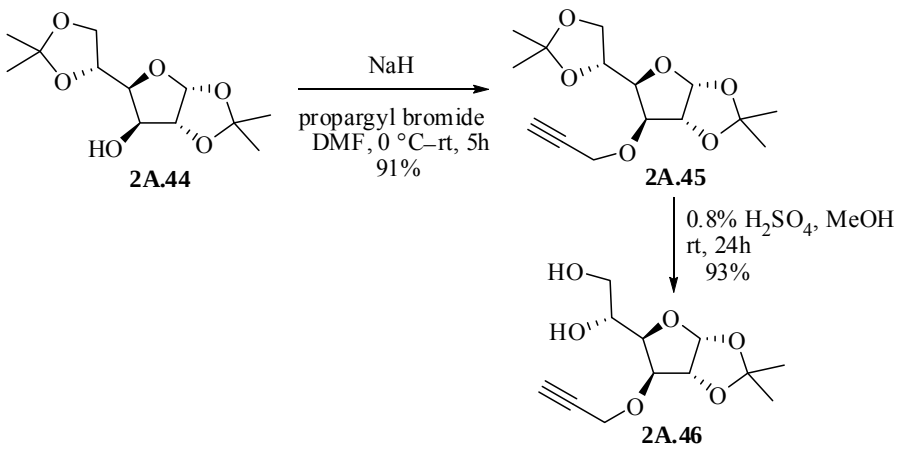
The strategy we intended for the synthesis of enantiopure isochromans is described in Figure 2A.4. Tricyclic derivative containing isochroman core **2A.41** can be easily obtained by using [2+2+2]-cyclotrimerization reaction between dialkyne **2A.43** and alkyne **2A.42**.



2A.41 **2A.42** **2A.43**

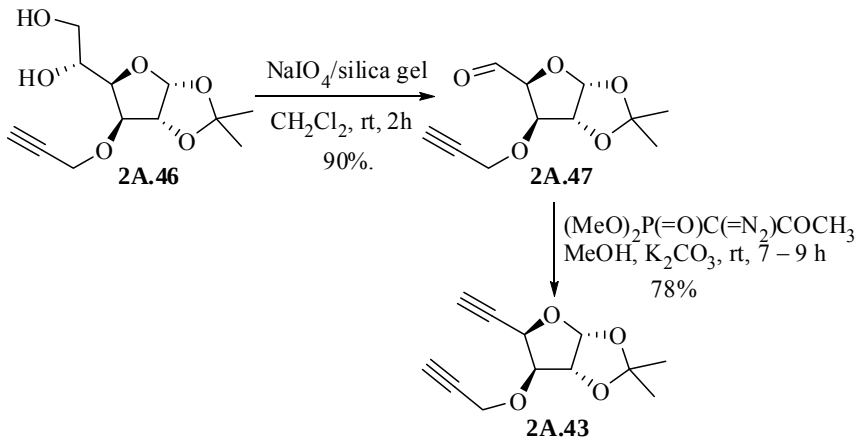
Figure 2A.4: [2+2+2]-cyclotrimerization approach for enantiopure isochromans

The synthesis of the key diyne **2A.43** was started with glucose diacetonide **2A.44** prepared from D-glucose by treating it with conc. H_2SO_4, anhydrous $CuSO_4$ in acetone. Propargylation of glucose diacetonide **2A.44** by using propargyl bromide and sodium hydride in DMF to procure the propargyl ether **2A.45**. Selective deprotection of 5,6-isopropylidene by using 0.8% H_2SO_4 in methanol gave diol **2A.46** in 93% yield (Scheme 2A.14).



Scheme 2A.14: Synthesis of diol **2A.46**

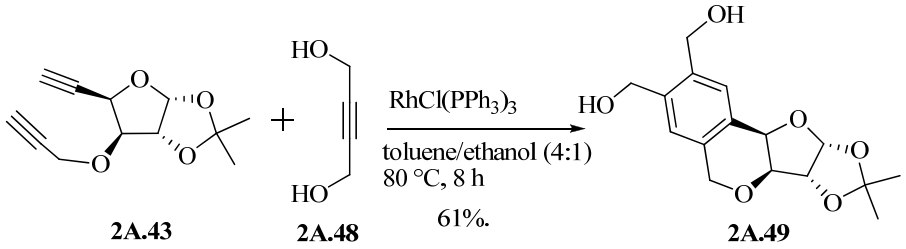
Diol **2A.46** on oxidative cleavage by $NaIO_4$ adsorbed on silica gel in DCM afforded the aldehyde **2A.47**, which upon treatment with Ohira-Bestman reagent[28] in presence of potassium carbonate in methanol gave the diyne **2A.43** in 78% yield (Scheme 2A.15). The diyne **2A.43** was fully characterized by spectroscopic and analytical data. In the ^{1}H NMR spectrum, the two acetylenic protons resonated at δ 2.46 as a triplet (J = 2.4 Hz), and at δ 2.55 as a doublet (J = 2.3 Hz). The ^{13}C NMR spectrum showed peaks at 75.4, 76.5, 77.1, 78.8 ppm for the carbon atoms of the two alkyne units. The IR spectrum showed acetylenic C–H stretching frequency at 3291 cm^{-1} and alkyne C≡C stretching at 2120 cm^{-1}.



Scheme 2A.15: Synthesis of diyne **2A.43**

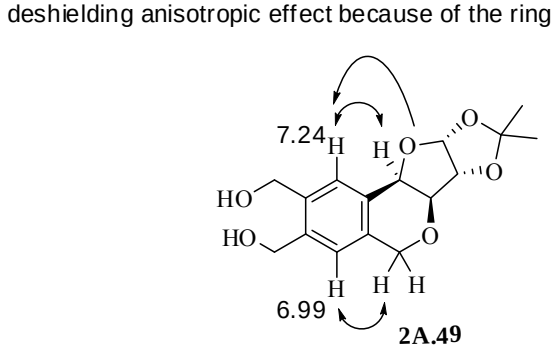
With the fully elaborated diyne framework **2A.43** in place, cyclotrimerization was attempted with 2-butyne-1,4-diol (**2A.48**) employing some commonly used

trimerization catalysts amongst which, the reactions with Wilkinson's catalyst[19] are smooth and yielded the tricyclic compound in good yields. The optimized conditions for this reaction involve the heating of the diyne with the diol in toluene/ethanol (4:1) at 80 °C and resulted with the tricyclic derivative **2A.49** in 61% yield (Scheme 2A.16). The spectral and analytical data of **2A.49** were in accordance with the assigned structure. For example, in the ^{1}H NMR spectrum of **2A.49**, the two aromatic–H appeared as singlets at δ 6.99 and δ 7.24. The characteristic C(1)–H and C(2)–H of the furanose ring appeared as doublets at δ 5.93 and 4.70 ppm ($J_{1,2}$ = 3.8 Hz), respectively. The C(4)–H appeared downfield (δ 4.89) as a doublet with J = 2.3 Hz.



Scheme 2A.16

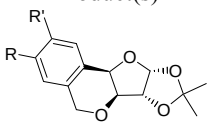
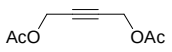
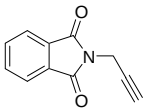
In the NOESY spectrum, the observed cross peaks between C(4)–H and the aromatic ring proton at δ 7.24 were indicative of a possible anisotropic effect of the furanose ring oxygen. This observation has helped in assigning the ratios of the regiomeric compounds resulting from unsymmetric alkynes (Table 2A.1). The presence of two methyleneoxy groups at 62.7 and 67.0 ppm in the ^{13}C NMR further confirmed the assigned structure.



To show the flexibility of our strategy, diyne **2A.43** was subjected to the [2+2+2]-cyclotrimerization employing symmetric and unsymmetric alkynes that are easily available and the results are summarized in Table 2A.1. With acetylene and

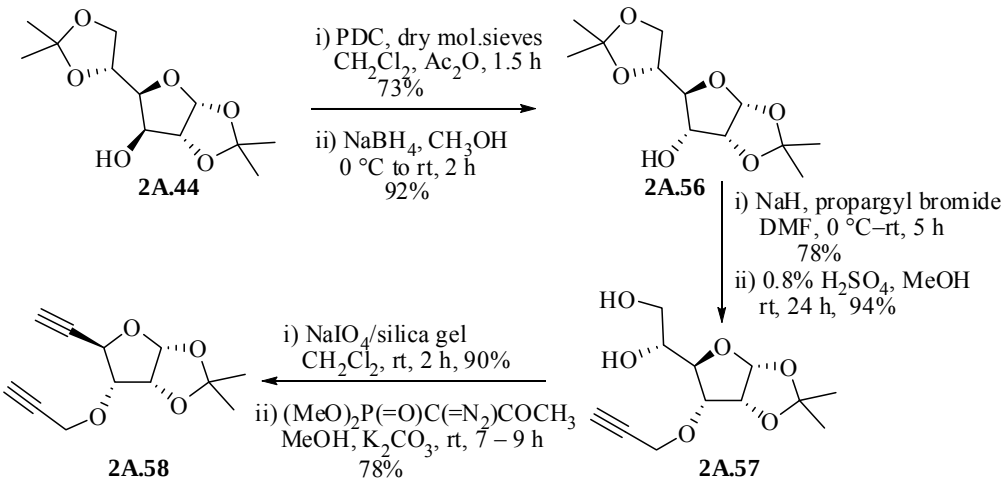
dimethyl acetylene dicarboxylate, the cyclotrimerization reaction proceeded effectively at 80 °C in a sealed tube to afford **2A.50** and **2A.52** in 65% and 45% yields respectively. Interestingly, the reaction of **2A.43** with dimethyl acetylene dicarboxylate did not proceed at different temperatures under atmospheric pressure. Unsymmetrical alkynes such as phenylacetylene and hexadec-1-yne gave inseparable regiomeric mixtures in moderate to good yields (Table 2A.1). In case of sterically crowded alkynes we did not observe any reaction even in sealed tube at various reaction temperature (Table 2A.1, entry 4–6).

Table 2A.1: [2+2+2]-cyclotrimerization reaction between diyne **2A.43** and various alkynes

Entry	alkyne	Product(s) 	Yield(%)
1		**2A.50** (R = R = H)	65%
2		**2A.51** (R = R' = CH_2OAc)	57%
3		**2A.52** (R = R' = CO_2Me)	45%
4		No reaction	–
5		No reaction	–
6		No reaction	–
7		**2A.53a** (R = Ph, R'= H) **2A.53b** (R = H, R'= Ph) (1:4)	72%
8		**2A.54a** (R = CH_2NPhth, R'= H) **2A.54b** (R = H, R' = CH_2NPhth) (1:3)	67%
9		**2A.55a** (R = *n*-C_4H_{29}, R' = H) **2A.55b** (R = H, R' = *n*-C_4H_{29}) (1:1)	49%

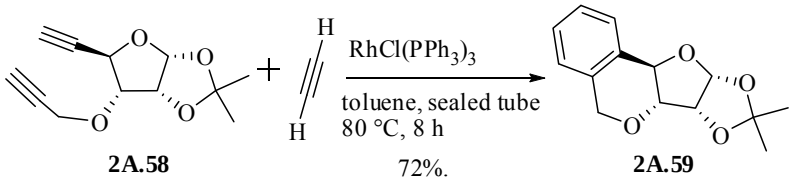
To examine the feasibility of the trimerization with *anti*-oriented diyne, we have synthesized the diyne **2A.58** with D-*ribo*-configuration from the glucose diacetonide **2A.44**, by following the reaction sequence i. PDC oxidation of free

hydroxyl to ketone, ii. reduction of ketone by sodium borohydride, iii. propargylation of free hydroxyl group of obtained alcohol with propargyl bromide, iv. selective 5,6-acetonide deprotection to get 5,6-diol **2A.57**. Oxidative cleavage of diol to aldehyde which was immediately subjected to Ohira-Bestman reaction gave diyne **2A.58** (Scheme 2A.17).



Scheme 2A.17: Synthesis of diyne **2A.58**

Diyne **2A.58** was subjected to [2+2+2]-cyclotrimerization reaction with acetylene in sealed tube at 80 °C to procure product **2A.59** in 72% yield (Scheme 2A.18). The structure of tricyclic derivative **2A.59** was confirmed by spectral and analytical data. In the ^{1}H NMR spectrum, C(3)–H showed double of doublet at δ 3.50 with J = 9.4 and 4.0 Hz, C(2)–H showed triplet at δ 4.78 with (J = 3.8 Hz). and benzylic protons showed doublets at δ 5.07 and 5.16 with a geminal coupling J = 14.9 Hz. In the ^{13}C NMR spectrum, triplet for benzylic carbon atom resonated at 70.3 ppm. Further, mass spectrum and elemental analysis were in agreement with proposed structure **2A.59**.



Scheme 2A.18

After having successfully synthesized tricyclic benzannulated sugar derivatives now we have turned out attention towards the synthesis of spiro tricyclic sugar derivatives through spiro-benzofurannulation by employing cyclotrimerization as the key skeleton construct.

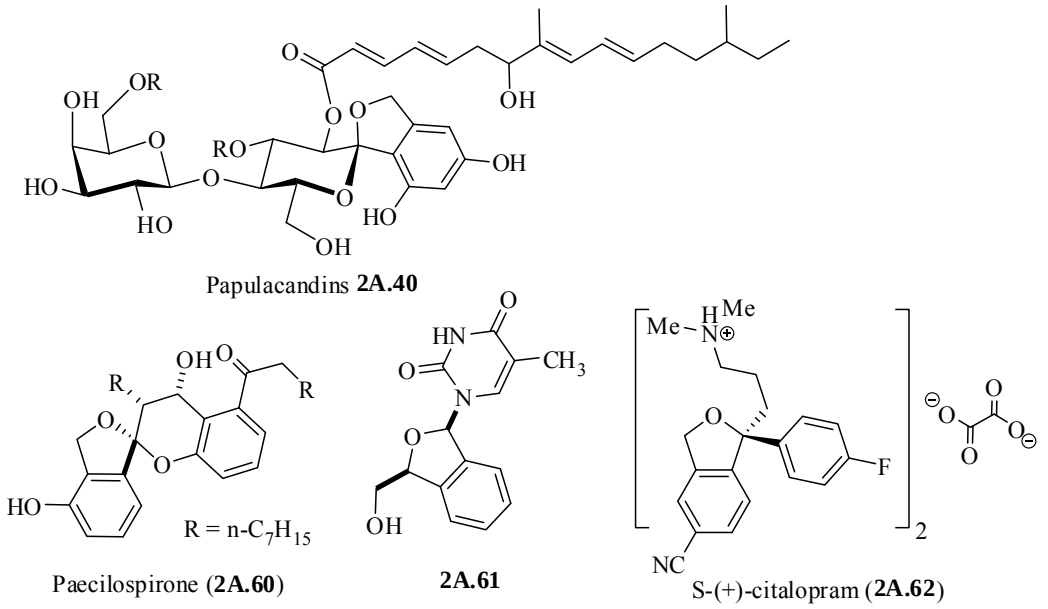


Figure 2A.5: Spirocyclic natural products containing dihydroisibenzofuran subunit

Spirocyclic subunits are present in a diverse range of bioactive natural products, thereby attracting considerable attention from synthetic chemists. Dihydroisobenzofuran is one of the commonly found structural units in many of the naturally occurring substances produced by a wide variety of microbes, insects, plants, fungi and microorganisms.[29] For example, *C*-arylglycosyl spiroacetal papulacandins **2A.40** were found to exhibit potent in vitro activity against *Candida albicans* and related microorganisms.[30] Paecilospirone **2A.60** isolated recently from a marine fungus *Paecilomyces* sp. was a promising inhibitor of microtubule assembly (Figure 2A.5).[31] Escitalopram (to treat depression) and isobenzofuran nucleoside (an investigational anti-viral drug) are some of the medicinally important agents containing the isobenzofuran unit.

In view of 1,3-dihydrobenzofuran importance, we have identified [2+2+2]-alkyne cyclotrimerization as a flexible skeletol construct for the spiroannulation of

isobenzofuran ring on carbohydrate templates. Our intended strategy is described in figure 2A.6.

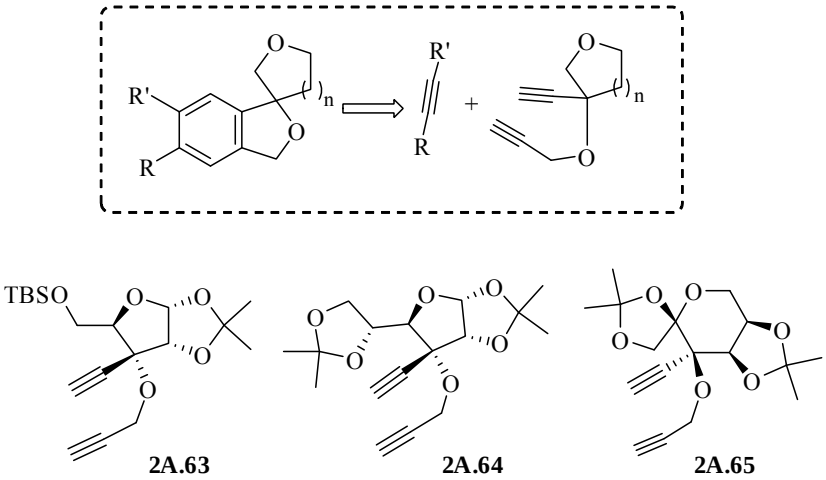
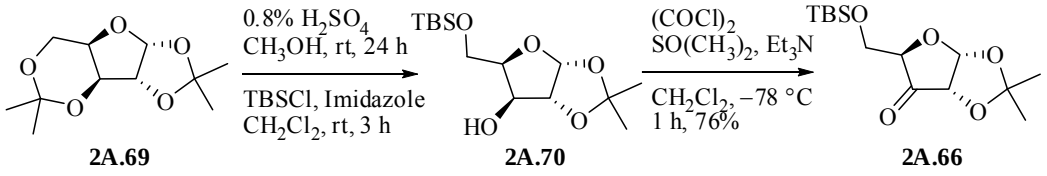


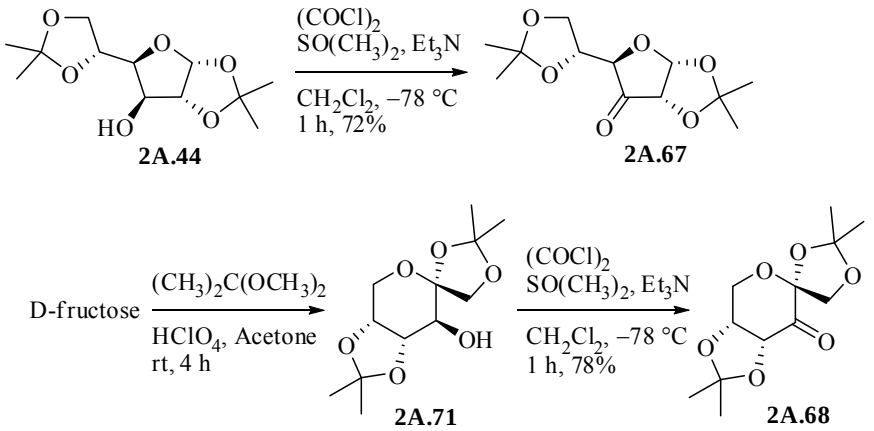
Figure 2A.6: Projected dihydroisobenzifuran spiro-annulation through [2+2+2]-Trimerization and selected diyne substrates

Ketones **2A.66**–**2A.68** were prepared from D-xylose, D-glucose and D-fructose respectively. Xylose diacetonide **2A.69** (prepared from D-xylose, under selective 3,5-isopropylidine deprotection using 0.8% H_2SO_4 in MeOH) followed by selective TBS protectection of pimary hydroxyl group using TBSCl and imidazole in DCM gave compound **2A.70**. Swern oxidation of of **2A.70** afforded ketone **2A.66** in 76% of yield (Scheme 2A.19).



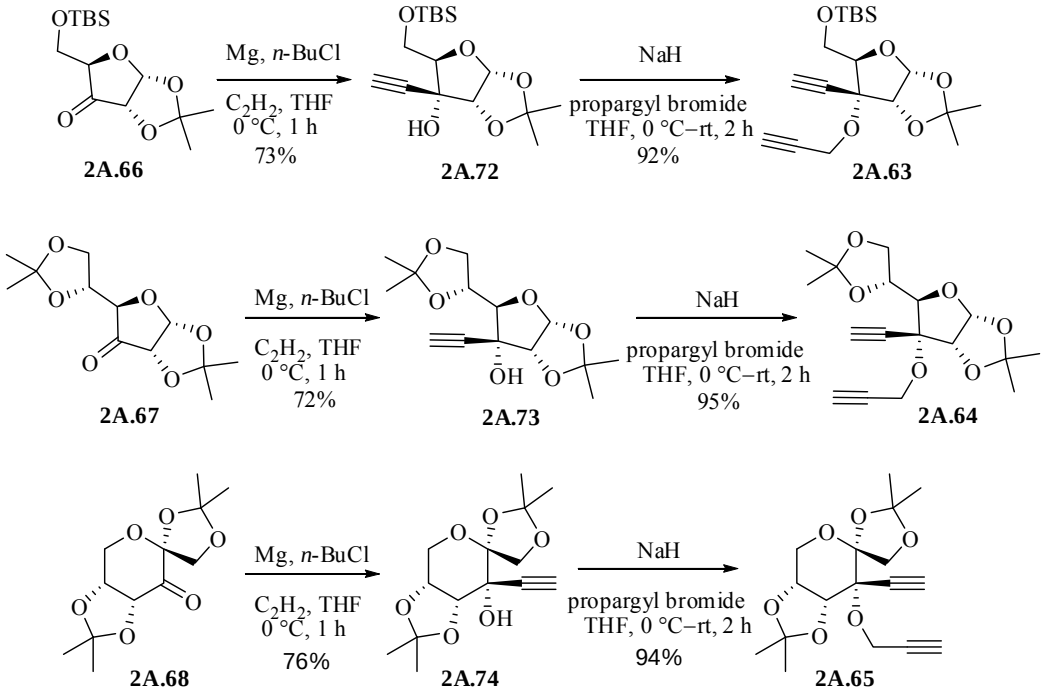
Scheme 2A.19: Synthesis of ketone **2A.66**

Glucose diacetonide **2A.44** was subjected under Swern oxidation conditions to afford ketone **2A.67** in 72% yield. Ketone **2A.68** was prepared under Swern oxidation condition of fructose diactetonide **2A.71** (obtained by treating D-fructose with 2,2-dimethoxy propane and 70% perchloric acid in acetone) in 78% yield (Scheme 2A.20).



Scheme 2A.20: Synthesis of ketones **2A.67** & **2A.68**

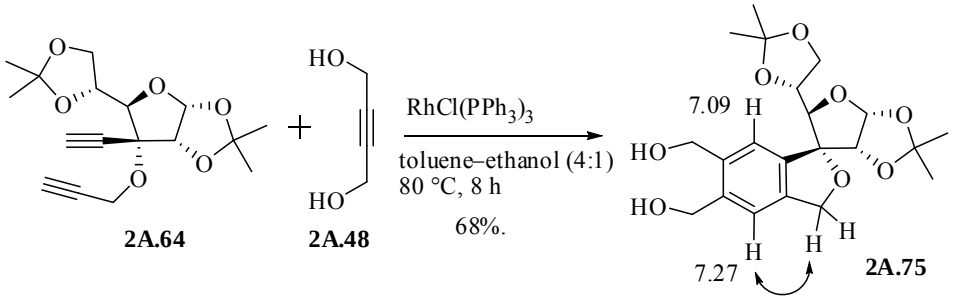
Addition of ethynylmagnesium chloride prepared by Grignard exchange with *n*-butylmagnesium chloride at 0 °C to the ketones[32] **2A.66**–**2A.68** and consequently propargylation of 3°-hydroxyl of obtained grignard products afforded diynes **2A.63**–**2A.65** respectively (Scheme 2A.21).



Scheme 2A.21: Syntheses of diynes **2A.63**–**2A.65**

Diynes **2A.63**–**2A.65** were fully characterized by spectral and analytical data. Compound **2A.63** showed alkyne protons at δ 2.44 as a triplet with J = 2.4 Hz and at δ 2.66 as a singlet in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum, alkyne carbons and quaternary carbon C(3) showed singlets at 74.5, 77.8, 79.4, 79.5 and 80.6 ppm. The acetylenic C–H stretching frequency was appeared at 3307 cm^{-1} and C≡C stretching frequency at 2110 cm^{-1} in the IR spectrum of compound **2A.63**. Compound **2A.64** showed alkyne protons at δ 2.41 as a triplet with J = 2.4 and at δ 2.75 as a singlet in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum, alkyne carbons and quaternary carbon C(3) showed singlets at 74.5, 78.2, 79.7, 80.4 and 81.0 ppm. The acetylenic C–H stretching frequency at 3306 cm^{-1} and C≡C stretching frequency at 2112 cm^{-1} were appeared in IR spectrum. Similarly, spectral and analytical data for compound **2A.65** were in well agreement with proposed structure.

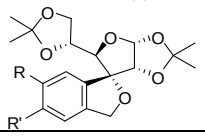
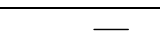
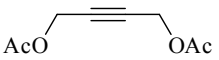
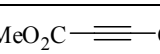
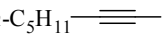
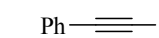
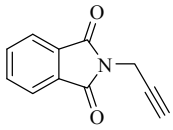
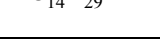
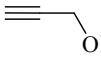
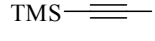
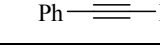
The diyne **2A.64** was subjected to cyclotrimerization with 2-butyne-1,4-diol (**2A.48**) using Wilkinson's catalyst in toluene/ethanol (4:1) at 80 °C giving the spirocyclic 1,3-dihydrobenzofuran derivative **2A.75** in 68% yield (Scheme 2A.22). The spectral and analytical data of **2A.75** were in accordance with the assigned structure. For example, in the ^{1}H NMR spectrum of **2A.75**, the two aromatic–H appeared as singlets at δ 7.09 and δ 7.27. The characteristic C(1')–H and C(2')–H of the furanose ring appeared as doublets at δ 5.99 and 4.39 ($J_{1,2}$ = 3.5 Hz) respectively. The C(4')–H appeared downfield (δ 4.27) as a doublet with J = 8.5 Hz. The observed cross peaks between benzylic CH_2 and the aromatic ring proton at δ 7.27 in the NOESY spectrum was helpful in assigning the ratios of the regiomeric compounds resulting from unsymmetric alkynes. The presence of four methyleneoxy groups at 63.4, 63.7, 67.4 and 73.3 ppm in the ^{13}C NMR further confirmed the assigned structure.



Scheme 2A.22

To illustrate the flexibility of our strategy, [2+2+2]-cyclotrimerization reaction of diyne **2A.64** was carried out with symmetrical alkynes such as acetylene, diacetate of 2-butyne-1,4-diol and with unsymmetrical alkynes like phenyl acetylene, propargyl alcohol, 1-hexadecyne, and *N*-propargyl phthalimide under similar conditions. With acetylene and dimethyl acetylene dicarboxylate the reaction proceeded effectively at 80 °C in a sealed tube to afford **2A.76** and **2A.78** in 76% and 52% yields respectively.

Table 2A.2: [2+2+2]-cyclotrimerization reaction between diyne **2A.64** and various alkynes

Entry	alkyne	Product(s) 	Yield
1		**2A.76** (R=R=H)	76%
2		**2A.77** (R=R'= CH_2OAc)	65%
3		**2A.78** (R=R'= CO_2Me)	52%
4		**2A.79** (R=R'= C_5H_{11})	43%
5		**2A.80a** (R = Ph, R'= H) **2A.80b** (R = H, R'= Ph) (1: 3)	69 %
6		**2A.81a** (R=CH_2NPhth, R'= H) **2A.81b** (R=H, R'= CH_2NPhth) (2:3)	72%
7		**2A.82a** (R = *n*-C_4H_{29}, R'= H) **2A.82b** (R = H, R'= *n*-C_4H_{29}) (1:1)	52%
8		**2A.83a** (R = CH_2OH, R'= H) **2A.83b** (R = H, R'= CH_2OH) (1:1)	78%
9		**2A.84**-Dimer of starting dialkyne	40%
10		**2A.84**-Dimer of starting dialkyne	

In case of sterically crowded alkynes like diphenyl acetylene and bis-(trimethylsilyl)acetylene we observed the dimerised products **2A.84** of diyne **2A.64**. Mass spectrum of dimers **2A.84** gave peaks at *m/z* 645.1 $[M+H]^+$ in 9%, 667.1 $[M+Na]^+$ in 100%, and elemental analysis was in agreement with calculated values for dimers **2A.84**. Reactions with unsymmetrical alkynes are not regioselective and gave inseparable regiomeric mixtures in good yields and the results are summarized in table 2A.2.

To generalize the [2+2+2]-cyclotrimerization reaction on sugar based diynes, we subjected diynes **2A.63** and **2A.65** to trimerization under standardized reaction condition with acetylene, diacetate of 2-butyne-1,4-diol, dimethyl acetylene dicarboxylate and 2,5-dimethylhex-3-yne-2,5-diol as symmetrical alkynes and phenyl acetylene as unsymmetrical alkyne. The obtained results are summarized in table 2A.3 and table 2A.4.

Table 2A.3: [2+2+2]-cyclotrimerization reaction between diyne **2A.63** and various alkynes

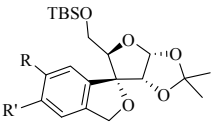
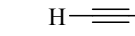
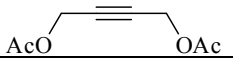
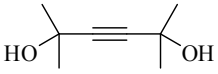
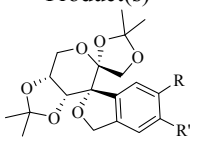
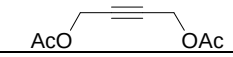
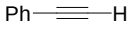
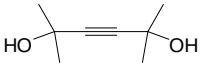
Entry	alkyne	Product(s) 	Yield
1		**2A.85** (R=R'=H)	71%
2		**2A.86** (R=R'= CH_2OAc)	60%
3		**2A.87** (R=R'= CO_2Me)	67%
4		**2A.88a** (R = Ph, R'= H) **2A.88b** (R = H, R'= Ph) (1:3)	78%
5		No Reaction	

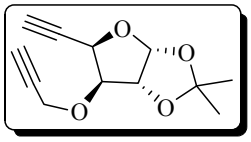
Table 2A.4: [2+2+2]-cyclotrimerization reaction between diyne **2A.65** and various alkynes

Entry	alkyne	Product(s) 	Yield
1		**2A.89** (R=R'=H)	73%
2		**2A.90** (R=R'= CH_2OAc)	65%
3		**2A.91** (R=R'= CO_2Me)	69%
4		**2A.92a** (R = Ph, R'= H) **2A.92b** (R = H, R'= Ph) (1:3)	75%
5		No reaction	

Conclusion: In conclusion, we have developed a simple protocol for the isobenzopyrannulation and spirodihydroisobenzofurannualtion on sugar templates by employing [2+2+2]-cyclotrimerization as the key reaction. Because of the easy availability of alkynes, the present method is characterized by the enormous flexibility to synthesize corresponding tricyclic compound libraries with an ease. Additionally, all these synthesized compounds have the potential to be extended further at the anomeric center either to prepare the oligosaccharides or nucleosides by employing appropriate glycosyl acceptos and suitable glycosidation protocols. To demonostrate this, in the next part of this chapter, we have used a couple of these intermediates to arrive at tricyclic nucleosides.

2A.3. Experimental:

1,2-*O*-Isopropylidene-5,5,6,6-tetradehydro-5,6-dideoxy-3-*O*-propargyl-α-D-*xylo*-hexofuranose (2A.43)



To a solution of the diol **2A.46** (1.5 g, 5.8 mmol) in methanol (25 mL) and water (2 mL), $NaIO_4$ (1.4 g, 7.0 mmol) was added and stirred for 30 min at rt. The mixture was filtered through celite and concentrated under reduced pressure. The residue was extracted with ethyl acetate, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford aldehyde **2A.47** (1.2 g, 90%).

To a mixture of the aldehyde **2A.47** (1.2 g, 5.3 mmol) and K_2CO_3 (95 mg, 6.9 mmol) in methanol (30 mL), Ohira-Bestmann reagent (1.22 g, 6.3 mmol) was added and stirred at rt for 6 h. The reaction mixture was concentrated under reduced pressure and the crude material was patronized between water and ethyl acetate. The organic phase was separared, dried over Na_2SO_4 and concentrated under reduced pressure. The purification of residue by silica gel column chromatography (7% ethyl acetate in petroleum ether) gave **2A.43** (920 mg, 78% yield) as a colorless oil.

Mol. Formula	: $C_{12}H_{14}O_4$
$[\alpha]_D^{25}$	: +33.7 (*c* 1.3, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3291, 2990, 2938, 2120, 1455, 1376, 1347, 1254, 1218, 1164, 1078, 1028, 952, 861, 758, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.30 (s, 3H), 1.47 (s, 3H), 2.46 (t, *J* = 2.4 Hz, 1H), 2.55 (d, *J* = 2.3 Hz, 1H), 4.17 (d, *J* = 3.0 Hz, 1H), 4.40 (t, *J* = 2.2 Hz, 2H), 4.60 (d, *J* = 3.8 Hz, 1H), 4.80 (t, *J* = 2.6 Hz, 1H), 5.91 (d, *J* = 3.8 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 26.1 (q), 26.7 (q), 58.0 (t), 70.2 (d), 75.4 (d), 76.5 (d), 77.1 (s), 78.8 (s), 81.8 (d), 82.7 (d), 104.5 (d), 111.9 (s) ppm.
ESI-MS (*m/z*)	: 223.2 (5%, $[M+H]^+$), 240.3 (15%, $[M+NH_4]^+$), 245.2 (100%, $[M+Na]^+$), 261.2 (6 %, $[M+K]^+$).

Elemental Analysis	Calcd.: C, 64.85; H, 6.35 %. Found: C, 64.82; H, 6.38 %.

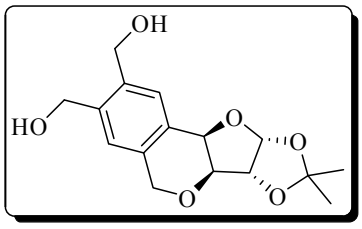
Representative procedures for [2+2+2]-cyclotrimerization:

Procedure A: A Solution of diyne **2A.43** (0.5 mmol) and alkyne (1.5 mmol) in toluene/ethanol (9/3 mL) was degassed with dry argon for 20 minutes, then Wilkinson's catalyst [$RhCl(PPh_3)_3$] (0.03 mmol) was introduced. The reaction mixture was heated at 80 °C for 6 hours and then allowed to cool to room temperature. Solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate in petroleum ether) to produce cyclotrimerized product.

Procedure B: A Solution of diyne **2A.43** (0.5 mmol) and alkyne (1.5 mmol) in toluene/ethanol (9/3 mL) in seal tube was degassed with dry argon for 20 minutes, then Wilkinson's catalyst [$RhCl(PPh_3)_3$] (0.03 mmol) was introduced. The reaction mixture was cooled to −78 °C and sealed by fusion. Sealed tube was transferred into a steel bomb, heated at 80 °C for 4 hours and then allowed to cool to room temperature. Tube was broken and mixture was transferred into RB and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate in petroleum ether) to give cyclotrimerized product.

Procedure C: A Solution of diyne **2A.43** (0.5 mmol) in toluene (10 mL) was degassed with dry acetylene for 20 minutes, then Wilkinson's catalyst [$RhCl(PPh_3)_3$] (0.03 mmol) was introduced. The reaction mixture was corked with septum and copper wire, cooled to −78 °C and acetylene gas was condensed by continuous bubbling for 25 min. The reaction was transferred into a steel bomb, heated at 80 °C for 4 hours and then allowed to cool to room temperature. Solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate in petroleum ether) to afford cyclotrimerized product.

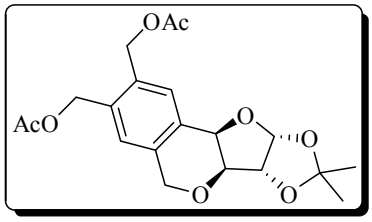
Compound (2A.49)



By following the procedure A, reaction mixture of diyne **2A.43** (120 mg, 0.54 mmol), diol **2A.48** (140 mg, 1.6 mmol) and $[RhCl(PPh_3)_3]$ (25 mg, 0.03 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 8 h. Purification of residue by column chromatography (60% ethyl acetate in petroleum ether) afforded **2A.49** (102 mg, 61%) as viscous oil.

Mol. Formula	: $C_{16}H_{20}O_6$
$[\alpha]_D^{25}$	: +28.0 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3401, 3016, 2932, 1624, 1438, 1216, 1080, 1017, 898 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.35 (s, 3H), 1.58 (s, 3H), 3.90 (bs, 2H), 4.09 (d, *J* = 2.3 Hz, 1H), 4.48–4.55 (m, *J* = 12.7 Hz, 3H), 4.58 (d, *J* = 15.1 Hz, 1H), 4.59 (d, *J* = 12.7 Hz, 1H), 4.67 (d, *J* = 3.8 Hz, 1H), 4.70 (d, *J* = 15.1 Hz, 1H), 4.90 (d, *J* = 2.3 Hz, 1H), 5.93 (d, *J* = 3.8 Hz, 1H), 6.99 (s, 1H), 7.24 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 26.1 (q), 26.7 (q), 62.7 (t, 2C), 67.0 (t), 73.1 (d), 79.8 (d), 84.4 (d), 104.9 (d), 111.7 (s), 124.6 (d), 128.4 (s), 130.9 (d), 134.4 (s), 138.2 (s), 140.2 (s) ppm.
ESI-MS (*m/z*)	: 309.4 (3%, $[M+H]^+$), 331.3 (100%, $[M+Na]^+$), 347.3 (4%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 62.33; H, 6.54 %. Found: C, 62.12; H, 6.68 %.

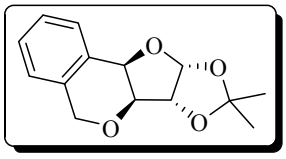
Compound (2A.51)



By following the procedure A, reaction mixture of diyne **2A.43** (100 mg, 0.45 mmol), diacetate of 2-butyne-1,4-diol (230 mg, 1.4 mmol) and $[RhCl(PPh_3)_3]$ (21 mg, 0.03 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 6 h. Purification of residue by column chromatography (30% ethyl acetate in petroleum ether) afforded **2A.51** (101 mg, 57%) as colorless oil.

Mol. Formula	: $C_{20}H_{24}O_8$
$[\alpha]_D^{25}$	: +6.8 (*c* 1.1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3020, 2932, 2854, 1740, 1614, 1454, 1244, 1064, 1118, 1104, 1081, 1022, 896 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.35 (s, 3H), 1.58 (s, 3H), 2.06 (s, 3H), 2.09 (s, 3H), 4.15 (d, *J* = 2.3 Hz, 1H), 4.65 (d, *J* = 15.2 Hz, 1H), 4.69 (d, *J* = 3.8 Hz, 1H), 4.79 (d, *J* = 15.2 Hz, 1H), 4.97 (d, *J* = 2.2 Hz, 1H), 5.14, 5.16 (2s, 4H), 5.97 (d, *J* = 3.8 Hz, 1H), 7.11 (s, 1H), 7.55 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 20.8 (q), 20.9 (q), 26.2 (q), 26.8 (q), 63.2 (t), 63.3 (t), 67.0 (t), 72.9 (d), 79.9 (d), 84.5 (d), 105.1 (d), 111.6 (s), 125.7 (d), 129.9 (s), 131.7 (d), 133.8 (s), 134.9 (s), 135.1 (s), 170.3 (s), 170.4 (s) ppm.
ESI-MS (*m/z*)	: 410.5 (37%, $[M+NH_4]^+$), 415.4 (100%, $[M+Na]^+$), 431.4 (5%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 61.22; H, 6.16 %. Found: C, 61.15; H, 6.29 %.

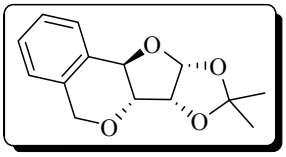
Compound (2A.50)



By following the procedure C, reaction mixture of diyne **2A.43** (150 mg, 0.68 mmol) in presence of catalyst $[RhCl(PPh_3)_3]$ (31 mg, 0.03 mmol) in toluene (10 mL) was heated at 80 °C for 4 h. Purification of residue by column chromatography (20% ethyl acetate in petroleum ether) gave **2A.50** (109 mg, 65%) as viscous oil.

Mol. Formula	: $C_{14}H_{16}O_4$
$[\alpha]_D^{25}$	: +21.6 (*c* 1.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3018, 2927, 1612, 1458, 1376, 1216, 1164, 1091, 1020, 920 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.28 (s, 3H), 1.50 (s, 3H), 4.07 (d, *J* = 2.4 Hz, 1H), 4.59 (d, *J* = 14.9 Hz, 1H), 4.60 (d, *J* = 3.8 Hz, 1H), 4.71 (d, *J* = 14.9 Hz, 1H), 4.88 (d, *J* = 2.4 Hz, 1H), 5.89 (d, *J* = 3.8 Hz, 1H), 6.94–6.99 (m, 1H), 7.17–7.23 (m, 2H), 7.35–7.42 (m, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 26.3 (q), 26.9 (q), 67.4 (t), 73.5 (d), 80.1 (d), 84.7 (d), 105.2 (d), 111.6 (s), 124.2 (d), 127.4 (d), 128.7 (d), 129.5 (s), 130.7 (d), 134.8 (s) ppm.
ESI-MS (*m/z*)	: 266.3 (36%, $[M+NH_4]^+$), 271.3 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 67.73; H, 6.50 %. Found: C, 67.88; H, 6.59 %.

Compound (2A.59)

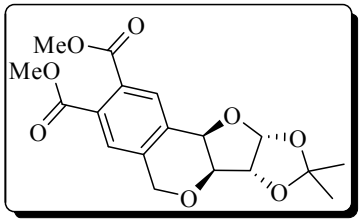


By following the procedure C, reaction mixture of diyne **2A.58** (130 mg, 0.59 mmol) in presence of catalyst $[RhCl(PPh_3)_3]$ (27 mg, 0.03 mmol) in toluene (10 mL) was heated at 80 °C for 4 h. Purification of residue by column chromatography (20% ethyl acetate in petroleum ether) afforded **2A.59** (106 mg, 72%) as viscous oil.

Mol. Formula	: $C_{14}H_{16}O_4$
$[\alpha]_D^{25}$	: +48.1 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3020, 2921, 1610, 1369, 1219, 1165, 1090, 922 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.41 (s, 3H), 1.65 (s, 3H), 3.50 (dd, *J* = 4.0, 9.4 Hz, 1H), 4.78 (t, *J* = 3.7 Hz, 1H), 5.01 (d, *J* = 9.2 Hz, 1H), 5.07 (d, *J* = 14.9 Hz, 1H), 5.16 (d, *J* = 14.9 Hz, 1H), 6.00 (d, *J* = 3.5 Hz, 1H), 7.03–7.10 (m, 1H), 7.22–7.31 (m, 2H), 7.42–7.46 (m, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz)	: 26.0 (q), 26.3 (q), 70.3 (t), 71.8 (d), 76.7 (d), 79.2 (d), 106.4 (d), 113.7 (s), 123.9 (d, 2C), 126.8 (d), 127.2 (d), 132.9 (s), 135.5 (s) ppm.
ESI-MS (*m/z*)	: 266.3 (43%, $[M+NH_4]^+$), 271.3 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 67.73; H, 6.50 %. Found: C, 67.58; H, 6.71 %.

Compound (2A.52)

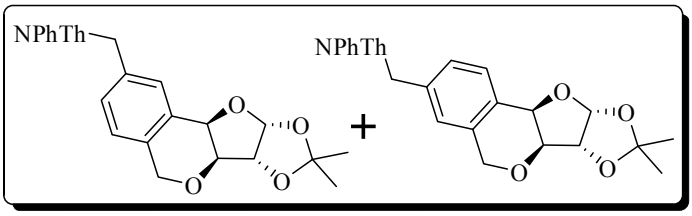


By following the procedure B, reaction mixture of diyne **2A.43** (120 mg, 0.54 mmol), dimethyl acetylene dicaboxylate (230 mg, 1.6 mmol) and $[RhCl(PPh_3)_3]$ (25 mg, 0.03 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 4 h. Purification of residue by column chromatography (25% ethyl acetate in petroleum ether) afforded **2A.52** (89 mg, 45%) as colorless oil.

Mol. Formula	: $C_{18}H_{20}O_8$
$[\alpha]_D^{25}$	: +8.7 (*c* 1.4, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3022, 2994, 2955, 2847, 1726, 1620, 1578, 1437, 1215, 1163, 1093, 1045, 895 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.35 (s, 3H), 1.56 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 4.16 (d, *J* = 2.4 Hz, 1H), 4.66 (d, *J* = 15.6 Hz, 1H), 4.68 (d, *J* = 3.8 Hz, 1H), 4.83 (d, *J* = 15.6 Hz, 1H), 4.95 (d, *J* = 2.4 Hz, 1H), 5.94 (d, *J* = 3.8 Hz, 1H), 7.38 (s, 1H), 7.91 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 26.2 (q), 26.8 (q), 52.5 (q), 52.7 (q), 66.8 (t), 72.5 (d), 79.9 (d), 84.5 (d), 105.2 (d), 111.8 (s), 124.8 (d), 130.4 (s), 131.6 (d), 132.5 (s), 132.6 (s), 138.3 (s), 166.8 (s), 167.6 (s) ppm.
ESI-MS (*m/z*)	: 365.4 (29%, $[M+H]^+$), 387.4 (100%, $[M+Na]^+$), 403.4 (11%, $[M+K]^+$).

Elemental Analysis	Calcd.: C, 59.34; H, 5.53 %. Found: C, 59.48; H, 5.70 %.

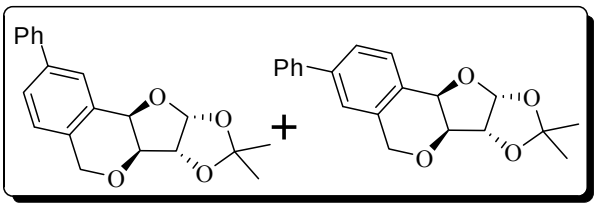
Compounds (2A.54a,b)



By following the procedure A, reaction mixture of diyne **2A.43** (130 mg, 0.59 mmol), propargyl phthalamide (325 mg, 1.8 mmol) and $[RhCl(PPh_3)_3]$ (27 mg, 0.03 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 8 h. Purification of residue by column chromatography (30% ethyl acetate in petroleum ether) afforded mixture of **2A.54a** and **2A.54b** (160 mg, 67%) as viscous oil.

Mol. Formula	: $C_{23}H_{21}NO_6$
IR ($CHCl_3$) $\tilde{\nu}$	: 3017, 2924, 2854, 1770, 1714, 1460, 1376, 1247, 1164, 1088, 1019, 947 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.26 (s, 3H), 1.48 (s, 3H), 4.02 (d, *J* = 2.2 Hz, 1H), 4.53 (d, *J* = 15.6 Hz, 1H), 4.56 (d, *J* = 3.6 Hz, 1H), 4.64–4.89 (m, *J* = 2.2, 15.6 Hz, 4H), 5.84, 5.86 (2d, *J* = 3.6 Hz, 1H), 6.90–7.05 (m, 1H), 7.27–7.44 (m, 2H), 7.59–7.65 (m, 2H), 7.72–7.76 (m, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 26.2 (q), 26.2 (q), 26.9 (q), 41.2 (t), 41.3 (t), 67.1 (t), 67.2 (t), 73.2 (d), 73.3 (d), 80.0 (d), 80.0 (d), 84.6 (d), 84.6 (d), 105.1 (d), 111.5 (s), 111.6 (s), 123.4 (d), 124.6 (d), 127.8 (d), 128.5 (d), 128.5 (d), 128.9 (d), 129.2 (d), 129.8 (s), 130.7 (d), 131.0 (d), 132.1 (s), 132.2 (s), 133.9 (d), 134.0 (d), 134.4 (s), 135.2 (s), 135.6 (s), 136.9 (s), 167.7 (s), 167.7 (s) ppm.
ESI-MS (*m/z*)	: 425.4 (15%, $[M+NH_4]^+$), 430.5 (100%, $[M+Na]^+$),
Elemental Analysis	Calcd.: C, 67.80; H, 5.20; N, 3.44 %. Found: C, 68.01; H, 5.43; N, 3.28 %.

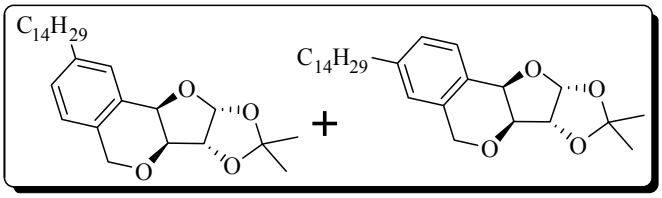
Compounds (2A.53a,b)



By following the procedure A, reaction mixture of diyne **2A.43** (120 mg, 0.54 mmol), phenyl acetylene (0.2 mL, 1.6 mmol) and $[RhCl(PPh_3)_3]$ (25 mg, 0.03 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 6 h. Purification of residue by column chromatography (25% ethyl acetate in petroleum ether) gave mixture of **2A.53a** and **2A.53b** (126 mg, 72%) as redish oil.

Mol. Formula	: $C_{20}H_{20}O_4$
IR ($CHCl_3$) $\tilde{\nu}$	: 3019, 2926, 1679, 1488, 1453, 1384, 1163, 1019 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.30 (s, 3H), 1.53 (s, 3H), 4.12 (d, *J* = 2.3 Hz, 1H), 4.62–4.82 (m, *J* = 3.8, 15.5 Hz, 3H), 4.94, 4.95 (2d, *J* = 2.3 Hz, 1H), 5.88 (d, *J* = 3.8 Hz, 0.20H), 5.92 (2d, *J* = 3.8 Hz, 0.80H), 7.18–7.53 (m, 8H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 26.2 (q), 26.8 (q), 67.2 (t), 67.4 (t), 73.3 (d), 73.6 (d), 80.0 (d), 80.1 (d), 84.6 (d), 104.7 (d), 105.1 (d), 111.5 (s), 111.9 (s), 122.9 (d), 124.7 (d), 126.2 (d), 127.0 (d), 127.1 (d), 127.4 (d), 127.5 (d), 128.3 (d), 128.4 (s), 128.4 (d) 128.8 (d), 129.2 (d), 129.8 (s), 130.9 (d), 131.6 (d), 133.6 (s), 135.1 (s), 140.3 (s), 140.4 (s), 140.5 (s), 141.7 (s) ppm.
ESI-MS (*m/z*)	: 347.4 (100%, $[M+Na]^+$), 363.4 (34%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 74.06; H, 6.21 %. Found: C, 73.93; H, 6.38 %.

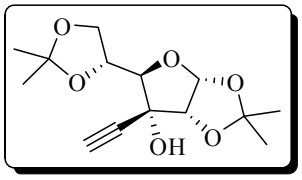
Compounds (2A.55a,b)



By following the procedure B, reaction mixture of diyne **2A.43** (100 mg, 0.45 mmol), 1-hexadecyne (300 mg, 1.4 mmol) and $[RhCl(PPh_3)_3]$ (21 mg, 0.03 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 6 h. Purification of residue by column chromatography (20% ethyl acetate in petroleum ether) afforded mixture of **2A.55a** and **2A.55b** (98 mg, 49%) as colorless oil.

Mol. Formula	: $C_{28}H_{44}O_4$
IR ($CHCl_3$) $\tilde{\nu}$	: 3017, 2926, 2854, 1619, 1465, 1375, 1245, 1090, 865 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.86 (t, *J* = 6.6 Hz, 3H), 1.25 (bs, 23H), 1.36 (s, 3H), 1.53–1.58 (m, 4H), 2.52–2.61 (m, *J* = 3.7, 7.3 Hz, 2H), 4.13 (d, *J* = 2.4 Hz, 1H), 4.64 (d, *J* = 15.1 Hz, 1H), 4.67 (d, *J* = 3.6 Hz, 1H), 4.76 (d, *J* = 15.1 Hz, 1H), 4.93 (d, *J* = 2.3 Hz, 1H), 5.97 (d, *J* = 3.7 Hz, 1H), 6.85–6.97 (m, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.30−7.39 (m, *J* = 1.5, 7.81 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 14.2 (q), 22.7 (t), 26.3 (q), 26.9 (q), 29.3 (t), 29.4 (t), 29.4 (t), 29.6 (t), 29.6 (t), 29.7 (t), 31.4 (t), 32.0 (t), 35.6 (t), 35.9 (t), 67.3 (t), 67.5 (t), 73.5 (d), 73.7 (d), 80.1 (d), 80.1 (d), 84.7 (d), 105.2 (d), 111.5 (s), 111.5 (s), 124.1 (d), 124.1 (d), 126.6 (s), 127.6 (d), 128.9 (d), 129.1 (s), 130.4 (d), 130.5 (d), 131.9 (s), 134.5 (s), 142.1 (s), 143.6 (s) ppm.
ESI-MS (*m/z*)	: 462.7 (27%, $[M+NH_4]^+$), 467.7 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 75.63; H, 9.97 %. Found: C, 75.80; H, 10.12 %.

1,2;5,6-*O*-Isopropylidene-3-*C*-ethynyl-α-D-allofuranose (2A.73)



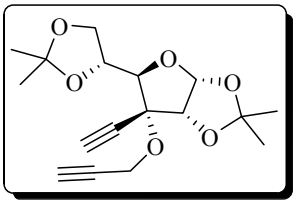
Grignard reaction (Procedure D):

Mg (4.65 g, 0.19 mol) was flame dried in a two neck R.B. flask fitted with a reflux condenser and cooled to room temperature in argon atmosphere. Dry THF (100

mL) was introduced followed by a few crystals of iodine. Half of the total volume of *n*-BuCl (20 mL, 0.19 mol) was added and the contents were refluxed till the generation of Grignard reagent. Heating was removed and rest of *n*-BuCl was added. Stirring was continued at room temperature till all the magnesium was consumed. Then the reaction mixture was cooled to 0 °C and acetylene gas was bubbled into it for 15 min. Ketone **2A.67** (10 g, 38.7 mmol) in THF (70 mL) was added at 0 °C and stirred for 30 min. The reaction was quenched with saturated NH_4Cl solution, diluted with water and extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4, concentrated and purified on silica gel chromatography (15% ethyl acetate in light petroleum) to give the alkynol **2A.73** (8 g, 72%) as a colorless oil.

Mol. Formula	: $C_{14}H_{20}O_6$
$[\alpha]_D^{25}$	: +8.0 (*c* 2.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3502, 3236, 2989, 2925, 2855, 2116, 1261, 1212, 1075 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: 1.35 (s, 6H), 1.44 (s, 3H), 1.58 (s, 3H), 2.63 (s, 1H), 3.07 (bs, 1H), 3.82 (d, *J* = 8.2 Hz, 1H), 4.01 (dd, *J* = 4.7, 8.8 Hz, 1H), 4.12 (dd, *J* = 8.8, 6.1 Hz, 1H), 4.40 (ddd, *J* = 4.8, 6.1, 8.2 Hz, 1H), 4.59 (d, *J* = 3.5 Hz, 1H), 5.78 (d, *J* = 3.5 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: 25.2 (q), 26.6 (q), 26.7 (q), 26.8 (q), 67.1 (t), 74.8 (d), 75.8 (s), 77.0 (s), 80.7 (d), 80.8 (s), 84.1 (d), 104.1 (d), 109.7 (s), 113.8 (s) ppm.
ESI-MS (*m/z*)	: 285.36 (11.76%, $[M+H]^+$), 302.39 (4.41%, $[M+NH_4]^+$), 307. 36 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 59.14; H, 7.09 %. Found: C, 59.01; H, 7.21 %.

1,2;5,6-*O*-Isopropylidene-3-*C*-ethynyl-3-*O*-propargyl-α-D-allofuranose (2A.64)

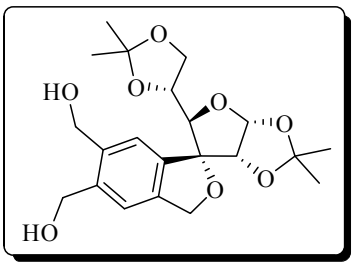


Propagylation of quaternary alcohol (procedure E):

To a suspension of alkynol **2A.73** (8.0 g, 28 mmol), NaH (1.7 g, 42 mmol) in DMF (60 mL), propargyl bromide (3 mL, 34 mmol) was added drop-wise at 0 °C, reaction mixture was allowed to warm to room temperature and stirred for 2 hours. Reaction mixture was quenched with slow addition of cold water at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with water, dried over Na_2SO_4, concentrated and purified by silica gel column chromatography (10% ethyl acetate in light petroleum) to give **2A.64** (8.5 g, 95%) as a colorless oil.

Mol. Formula	: $C_{17}H_{22}O_6$
$[\alpha]_D^{25}$	: +23.2 (*c* 2.3, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3306, 3018, 2991, 2937, 2112, 1456, 1384, 1309, 1217, 1166, 1135, 1076, 1030, 990, 844, 758 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.34 (s, 6H), 1.42 (s, 3H), 1.58 (s, 3H), 2.41 (t, *J* = 2.4 Hz, 1H), 2.75 (s, 1H), 4.04–4.11 (m, 3H), 4.31 (t, *J* = 5.8 Hz, 1H), 4.41 (dd, *J* = 2.4, 9.1 Hz, 2H), 4.62 (d, *J* = 3.5 Hz, 1H), 5.76 (d, *J* = 3.5 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 25.4 (q), 26.6 (q), 26.9 (q), 26.9 (q), 54.7 (t), 66.2 (t), 74.4 (d), 74.5 (s), 78.2 (s), 79.7 (s), 80.4 (s), 81.0 (s), 81.2 (d), 83.4 (d), 104.0 (d), 109.2 (s), 113.8 (s) ppm.
ESI-MS (*m/z*)	: 323.3 (6%, $[M+H]^+$), 340.4 (6%, $[M+NH_4]^+$), 335.4 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 63.34; H, 6.88 %. Found: C, 63.19; H, 7.01 %.

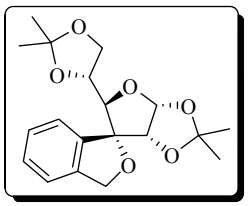
1',2';5',6'-Di-*O*-Isopropylidene-3'-didehydro-3'-deoxy-4,5-di(hydroxymethyl)-7*H*-spiro[isobenzofuran-2,3'-*C*-α-D-allofuranose] (2A.75)



By following the procedure A, reaction mixture of diyne **2A.64** (100 mg, 0.31 mmol), 2-butyne-1,4-diol (80 mg, 0.93 mmol) and $[RhCl(PPh_3)_3]$ (14 mg, 0.02 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 8 h. Purification of residue by column chromatography (60% ethyl acetate in petroleum ether) afforded **2A.75** (86 mg, 68%) as colorless oil.

Mol. Formula	: $C_{21}H_{28}O_8$
$[\alpha]_D^{25}$	: –4.8 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3412, 2989, 2935, 2875, 1438, 1374, 1330, 1217, 1123, 1074, 1022, 872, 842, 754, 724, 695, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$,200 MHz)	: δ 1.11 (s, 3H), 1.36 (s, 3H), 1.38 (s, 3H), 1.68 (s, 3H), 3.23 (bs, 2H), 3.55 (dt, *J* = 5.5, 8.5 Hz, 1H), 3.79 (dd, *J* = 5.9, 8.5 Hz, 1H), 3.93 (dd, *J* = 4.7, 8.6 Hz, 1H), 4.27 (d, *J* = 8.5 Hz, 1H), 4.39 (d, *J* = 3.5 Hz, 1H), 4.71 (d, *J* = 12.2 Hz, 1H), 4.73 (d, *J* = 12.2 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 2H), 5.16 (d, *J* = 12.3 Hz, 1H), 5.23 (d, *J* = 12.3 Hz, 1H), 5.99 (d, *J* = 3.5 Hz, 1H), 7.09 (s, 1H), 7.27 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 25.4 (q), 26.2 (q), 26.7 (q), 26.8 (q), 64.0 (t), 64.0 (t), 67.4 (t), 73.3 (t), 73.8 (d), 79.3 (d), 84.3 (d), 93.8 (s), 103.5 (d), 109.3 (s), 113.5 (s), 122.6 (d), 122.6 (d), 137.8 (s), 139.0 (s), 140.2 (s), 140.9 (s) ppm.
ESI-MS (*m/z*)	: 431.5 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 61.75; H, 6.91 %. Found: C, 61.87; H, 6.99 %.

1',2';5',6'-Di-*O*-Isopropylidene-3'-didehydro-3'-deoxy-7*H*-spiro[isobenzofuran-2,3'-*C*-α-D-allofuranose] (2A.76)

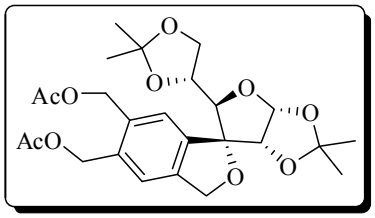


By following the procedure C, reaction mixture of diyne **2A.64** (120 mg, 0.37 mmol) in presence of catalyst $[RhCl(PPh_3)_3]$ (17 mg, 0.02mmol) in toluene (12 mL)

was heated at 80 °C for 4 h. Purification of residue by column chromatography (20% ethyl acetate in petroleum ether) afforded **2A.76** (99 mg, 76%) as viscous oil.

Mol. Formula	: $C_{19}H_{24}O_6$
$[\alpha]_D^{25}$	: +12.9 (*c* 1.9, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3019, 2939, 1461, 1375, 1216, 1165, 1074, 1034, 1017, 929, 845, 873, 757 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.03 (s, 3H), 1.29 (s, 3H), 1.31 (s, 3H), 1.61 (s, 3H), 3.47 (dt, *J* = 5.5, 8.3 Hz, 1H), 3.70 (dd, *J* = 5.8, 8.5 Hz, 1H), 3.84 (dd, *J* = 5.1, 8.5 Hz, 1H), 4.20 (d, *J* = 8.3 Hz, 1H), 4.32 (d, *J* = 3.5 Hz, 1H), 5.09 (d, *J* = 12.0 Hz, 1H), 5.18 (d, *J* = 12.0 Hz, 1H), 5.88 (d, *J* = 3.5 Hz, 1H), 7.02 (dd, *J* = 1.2, 7.7 Hz, 1H), 7.16–733 (m, *J* = 1.2, 7.7 Hz, 3H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 25.4 (q), 26.3 (q), 26.7 (q), 26.9 (q), 67.4 (t), 73.4 (t), 73.8 (d), 79.4 (d), 84.3 (d), 93.7 (s), 103.5 (d), 109.0 (s), 113.3 (s), 121.3 (d), 121.4 (d), 127.3 (d), 128.7 (d), 137.4 (s), 140.4 (s) ppm.
ESI-MS (*m/z*)	: 371.0 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 65.50; H, 6.94 %. Found: C, 65.37; H, 6.69 %.

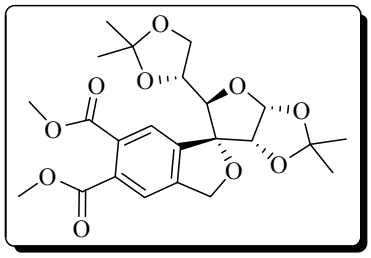
1',2';5',6'-Di-*O*-Isopropylidene-3'-didehydro-3'-deoxy-4,5-di(acetoxymethyl)-7*H*-spiro[isobenzofuran-2,3'-*C*-α-D-allofuranose] (2A.77)



By following the procedure A, reaction mixture of diyne **2A.64** (150 mg, 0.46 mmol), diacetate of 2-butyne-1,4-diol (237 mg, 1.4 mmol) and $[RhCl(PPh_3)_3]$ (21 mg, 0.03 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 8 h. Purification of residue by column chromatography (30% ethyl acetate in petroleum ether) gave **2A.77** (129 mg, 65%) as colorless oil.

Mol. Formula	: $C_{25}H_{32}O_{10}$
$[\alpha]_D^{25}$	: –8.4 (*c* 1.3, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3019, 2939, 1739, 1610, 1461, 1384, 1375, 1332, 1216, 1165, 1074, 1034, 1017, 929, 845, 757 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.10 (s, 3H), 1.34 (s, 3H), 1.36 (s, 3H), 1.66 (s, 3H), 2.08, 2.09 (2s, 6H), 3.50 (ddd, *J* = 4.6, 5.7, 8.5 Hz, 1H), 3.79 (dd, *J* = 4.7, 8.5 Hz, 1H), 3.91 (dd, *J* = 4.7, 8.5 Hz, 1H), 4.23 (d, *J* = 8.5 Hz, 1H), 4.34 (d, *J* = 3.6 Hz, 1H), 5.09–5.24 (3d, *J* = 12.1 Hz, 6H), 5.94 (d, *J* = 3.6 Hz, 1H), 7.08 (s, 1H), 7.29 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 20.9 (q, 2C), 25.5 (q), 26.4 (q), 26.8 (q), 26.9 (q), 63.4 (t), 63.7 (t), 67.4 (t), 73.3 (t), 73.8 (d), 79.2 (d), 84.3 (d), 93.8 (s), 103.4 (d), 109.2 (s), 113.5 (s), 122.6 (d), 123.0 (d), 133.9 (s), 135.6 (s), 138.2 (s), 141.3 (s), 170.3 (s, 2C) ppm.
ESI-MS (*m/z*)	: 493.3 (4%, $[M+H]^+$), 510.4 (20%, $[M+NH_4]^+$), 515.3 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 60.97; H, 6.55 %. Found: C, 60.82; H, 6.71 %.

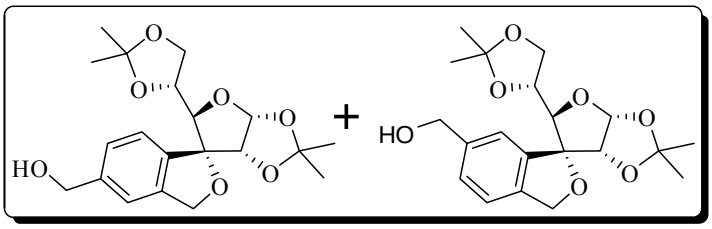
1',2';5',6'-Di-*O*-Isopropylidene-3'-didehydro-3'-deoxy-4,5-di(methoxycarbonyl)-7*H*-spiro[isobenzofuran-2,3'-*C*-α-D-allofuranose] (2A.78)



By following the procedure B, reaction mixture of diyne **2A.64** (150 mg, 0.46 mmol), dimethyl acetylene dicaboxylate (0.4 mL, 2.7 mmol) and $[RhCl(PPh_3)_3]$ (21 mg, 0.03 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 4 h. Purification of residue by column chromatography (30% ethyl acetate in petroleum ether) afforded **2A.78** (112 mg, 52%) as colorless oil.

Mol. Formula	: $C_{23}H_{28}O_{10}$
$[\alpha]_D^{25}$	: –10.2 (*c* 0.9, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3021, 2989, 2954, 1735, 1621, 1579, 1383, 1219, 1165, 1125, 1075, 1053, 985, 922, 843, 755 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.08 (s, 3H), 1.34, 1.36 (2s, 6H), 1.65 (s, 3H), 3.46 (ddd, *J* = 4.4, 5.5, 9.1 Hz, 1H), 3.82 (s, 2H), 3.89 (s, 6H), 4.19 (d, *J* = 9.1 Hz, 1H), 4.37 (d, *J* = 3.6 Hz, 1H), 5.15 (d, *J* = 12.9 Hz, 1H), 5.24 (d, *J* = 12.9 Hz, 1H), 5.97 (d, *J* = 3.6 Hz, 1H), 7.39 (s, 1H), 7.57 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 25.2 (q), 26.2 (q), 26.6 (q), 52.6 (q), 53.2 (q, 2C), 67.5 (t), 73.0 (t), 73.6 (d), 79.3 (d), 84.1 (d), 93.8 (s), 103.3 (d), 109.3 (s), 113.4 (s), 121.9 (d, 2C), 131.6 (s), 133.0 (s), 140.9 (s), 144.1 (s), 167.2 (s), 167.4 (s) ppm.
ESI-MS (*m/z*)	: 487.0 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 59.48; H, 6.08 %. Found: C, 59.59; H, 6.02 %.

Compounds (2A.83a,b)

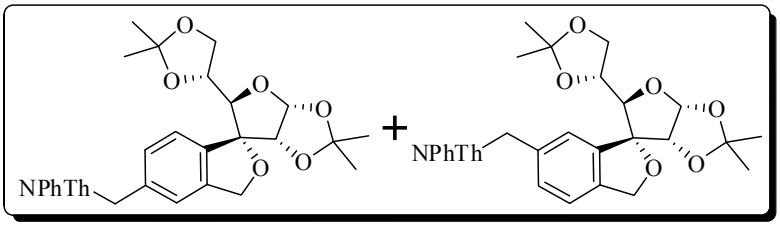


By following the procedure A, reaction mixture of diyne **2A.64** (100 mg, 0.31 mmol), propargyl alcohol (0.11 mL, 0.18 mmol) and $[RhCl(PPh_3)_3]$ (14 mg, 0.02 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 8 h. Purification of residue by column chromatography (50% ethyl acetate in petroleum ether) afforded mixture of **2A.83a** and **2A.83b** (92 mg, 78%) as colorless oil.

Mol. Formula	: $C_{20}H_{26}O_7$
IR ($CHCl_3$) $\tilde{\nu}$	: 3471, 3019, 2936, 1607, 1384, 1375, 1216, 1166, 1074, 1023, 873, 757 cm^{-1}.
^{1}H NMR	: δ 1.08 (s, 3H), 1.33, 1.36 (2s, 6H), 1.65 (s, 3H), 2.01 (bs,

($CDCl_3$, 200 MHz)	1H), 3.51 (ddd, *J* = 5.3, 8.4 Hz, 1H), 3.75 (2dd, *J* = 5.6, 8.4 Hz, 1H), 3.89 (2dd, *J* = 4.8, 8.5 Hz, 1H), 4.23 (d, *J* = 8.4 Hz, 1H), 4.33, 4.36 (2d, *J* = 3.6 Hz, 1H), 4.69 (s, 2H), 5.11 (d, *J* = 12.0 Hz, 1H), 5.20 (d, *J* = 12.0 Hz, 1H), 5.92, 5.95 (2d, *J* = 3.6 Hz, 1H), 7.03 (2d, *J* = 8.4 Hz, 1H), 7.18−7.33 (m, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 25.4 (q), 26.3 (q), 26.6 (q), 26.7 (q), 26.9 (q), 26.9 (q), 64.6 (t), 67.3 (t), 73.2 (t), 73.3 (t), 73.8 (d), 79.3 (d), 79.4 (d), 84.3 (d), 84.3 (d), 93.6 (s), 93.6 (s), 103.4 (d), 103.5 (d), 109.1 (s), 113.3 (s), 113.3 (s), 119.7 (d), 119.8 (d), 121.3 (d), 121.4 (d), 126.1 (d), 127.5 (d), 136.7 (s), 137.9 (s), 139.7 (s), 140.6 (s), 140.9 (s), 141.9 (s) ppm.
ESI-MS (*m/z*)	: 401.2 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd: C, 63.48; H, 6.93 %. Found: C, 63.42; H, 7.02 %.

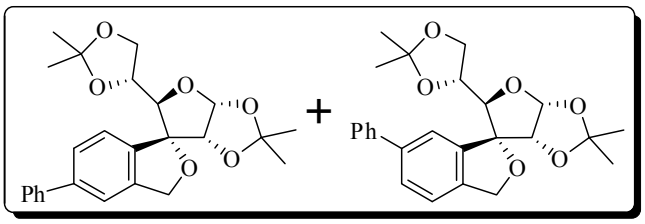
Compounds (2A.81a,b)



By following the procedure A, reaction mixture of diyne **2A.64** (130 mg, 0.4 mmol), propargyl phthalamide (224 mg, 1.2 mmol) and $[RhCl(PPh_3)_3]$ (18 mg, 0.02 mmol) in toluene/ethanol (10/3 mL) was heated at 80 °C for 7 h. Purification of residue by column chromatography (40% ethyl acetate in petroleum ether) afforded mixture of **2A.81a** and **2A.81b** (147 mg, 72%) as viscous oil.

Mol. Formula	: $C_{28}H_{29}NO_8$
IR ($CHCl_3$) $\tilde{\nu}$	: 3020, 2991, 2936, 1771, 1716, 1395, 1216, 1074, 1024 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.07 (s, 3H), 1.31, 1.35 (2s, 6H), 1.64, 1.66 (2s, 3H), 3.45−3.55 (m, 1H), 3.72−3.80 (m, 1H), 3.84−3.93 (m, 1H), 4.22 (dd, *J* = 3.4, 8.4 Hz, 1H), 4.32 (dd, *J* = 3.5, 9.6 Hz, 1H), 4.85 (s, 2H), 5.09 (d, *J* = 12.1 Hz, 1H), 5.18 (d, *J* = 12.1 Hz, 1H), 5.88, 5.98 (2d, *J* = 3.6 Hz, 1H), 7.00−7.30 (m, 2H), 7.34−7.42 (m, 1H), 7.68−7.75 (m, 2H), 7.80−7.87 (m, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 25.4 (q), 26.3 (q), 26.4 (q), 26.7 (q), 26.9 (q), 26.9 (q), 41.2 (t), 41.4 (t), 67.3 (t), 67.4 (t), 73.2 (t), 73.8 (d), 73.8 (d), 79.2 (d), 79.3 (d), 84.3 (d), 93.6 (s), 93.7 (s), 103.4 (d), 103.5 (d), 109.0 (s), 109.1 (s), 113.3 (s), 121.6 (d), 121.6 (d), 122.1 (d), 123.4 (d), 128.0 (d), 129.2 (d), 132.0 (s), 134.0 (d), 135.8 (s), 137.1 (s), 137.2 (s), 138.1 (s), 140.2 (s), 141.2 (s), 167.7 (s) ppm.
ESI-MS (*m/z*)	: 508.4 (7%, $[M+H]^+$), 525.4 (27%, $[M+NH_4]^+$), 530.3 (100% , $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 66.26; H, 5.76; N, 2.76 %. Found : C, 66.30; H, 5.82; N, 2.70 %.

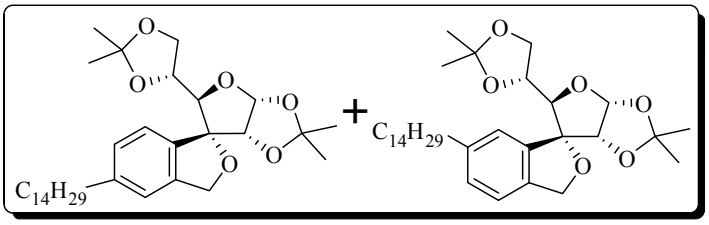
Compounds (2A.80a,b)



By following the procedure A, reaction mixture of diyne **2A.64** (110 mg, 0.33 mmol), phenyl acetylene (0.2 mL, 1.9 mmol) and $[RhCl(PPh_3)_3]$ (16 mg, 0.02 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 6 h. Purification of residue by column chromatography (20% ethyl acetate in petroleum ether) afforded mixture of **2A.80a** and **2A.80b** (100 mg, 69%) as redish oil.

Mol. Formula	: $C_{25}H_{28}O_6$
IR ($CHCl_3$) $\tilde{\nu}$	: 3020, 2991, 2936, 1620, 1375, 1215, 1165, 1974, 1044, 1028, 873, 843 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.13 (s, 3H), 1.38 (s, 3H), 1.40 (s, 3H), 1.69 (s, 3H), 3.56−3.68 (m, 1H), 3.82 (2dd, *J* = 5.7, 8.5 Hz, 1H), 3.95 (dd, *J* = 8.5, 4.9 Hz, 1H), 4.31 (2d, *J* = 8.3 Hz, 1H), 4.43 (2d, *J* = 3.6, 4.2 Hz, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 5.29 (d, *J* = 12.1 Hz, 1H), 5.99 (2d, *J* = 3.6 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.29−7.60 (m, 7H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 25.5 (q), 26.3 (q), 26.7 (q), 26.9 (q), 67.3 (t), 67.4 (t), 73.3 (t), 73.4 (t), 73.9 (d), 79.4 (d), 84.4 (d), 93.7 (s), 93.7 (s), 103.5 (d), 103.5 (d), 109.1 (s), 113.3 (s), 113.3 (s), 120.0 (d), 120.0 (d), 121.6 (d), 121.7 (d), 126.6 (d), 127.1 (d), 127.6 (d), 127.9 (d), 128.8 (d), 128.8 (d), 136.5 (s), 138.4 (s), 139.5 (s), 140.5 (s), 140.5 (s), 141.0 (s), 141.3 (s), 142.1 (s) ppm.
ESI-MS (*m/z*)	: 447.8 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd: C, 70.74; H, 6.65 %. Found: C, 70.79; H, 6.82 %.

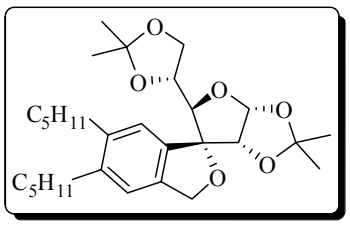
Compounds (2A.82a,b)



By following the procedure A, reaction mixture of diyne **2A.64** (120 mg, 0.37 mmol), 1-hexadecyne (248 mg, 1.1 mmol) and $[RhCl(PPh_3)_3]$ (17 mg, 0.02 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 4 h. Purification of residue by column chromatography (20% ethyl acetate in petroleum ether) afforded mixture of **2A.82a** and **2A.82b** (105 mg, 52%) as colorless oil.

Mol. Formula	: $C_{33}H_{52}O_6$
IR ($CHCl_3$) $\tilde{\nu}$	: 3019, 2987, 2927, 2855, 1618, 1458, 1373, 1249, 1217, 1167, 1074, 1025, 873 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.87 (t, *J* = 6.4 Hz, 3H), 1.10 (s, 3H), 1.24 (bs, 20H), 1.34−1.36 (m, 7H), 1.53−1.59 (m, 3H), 1.67 (s, 3H), 2.61 (t, *J* = 7.6 Hz, 2H), 3.54 (2d, *J* = 5.4, 7.9 Hz, 1H), 3.72 (2dd, *J* = 5.8, 8.4 Hz, 1H), 3.88 (2dd, *J* = 5.2, 8.4 Hz, 1H), 4.26, 4.27 (2d, *J* = 7.9 Hz, 1H), 4.36, 4.37 (2d, *J* = 3.6 Hz, 1H), 5.10 (d, *J* = 11.8 Hz, 1H), 5.19 (d, *J* = 11.8 Hz, 1H), 5.92, 5.95 (2d, *J* = 3.6 Hz, 1H), 6.83, 7.03 (2s, 1H), 6.95, 7.07 (2d, *J* = 7.7 Hz, 1H), 7.09−0.13 (2d, *J* = 7.8 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 14.1 (q) 22.7 (t), 25.5 (q), 26.4 (q), 26.7 (q), 27.0 (q), 29.3 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.7 (t), 31.6 (t), 31.8 (t), 32.0 (t), 35.9 (t), 67.2 (t), 67.3 (t), 73.4 (t), 73.4 (t), 73.9 (d), 79.5 (d), 79.5 (d), 84.4 (d), 84.4 (d), 93.6 (s), 93.6 (s), 103.5 (d), 103.6 (d), 109.0 (s), 113.3 (s), 121.1 (d), 121.2 (d), 121.2 (d), 121.2 (d), 127.7 (d), 129.0 (d), 134.8 (s), 137.7 (s), 137.8 (s), 140.7 (s), 142.4 (s), 143.7 (s) ppm.
ESI-MS (*m/z*)	: 567.1 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 72.76; H, 9.62 %. Found : C, 72.59; H, 9.78 %.

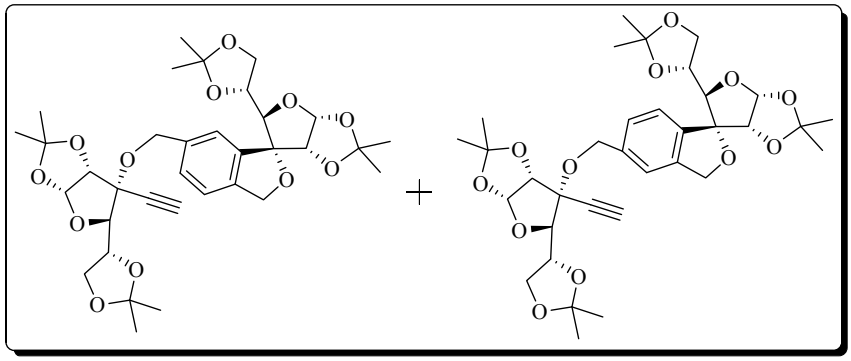
1',2';5',6'-Di-*O*-Isopropylidene-3'-didehydro-3'-deoxy-4,5-di(*n*-pentyl)-7*H*-spiro[isobenzofuran-2,3'-*C*-α-D-allofuranose] (2A.79)



By following the procedure B, reaction mixture of diyne **2A.64** (130 mg, 0.4 mmol), 6-dodecyne (0.34 mL, 1.6 mmol) and $[RhCl(PPh_3)_3]$ (18 mg, 0.02 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 4 h. Purification of residue by column chromatography (20% ethyl acetate in petroleum ether) afforded mixture of **2A.79** (84 mg, 43%) as colorless oil.

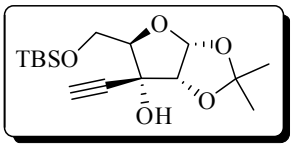
Mol. Formula	: $C_{29}H_{44}O_6$
$[\alpha]_D^{25}$	: +18.7 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 2986, 2930, 2859, 1620, 1331, 1249, 1218, 1075, 873 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.89 (2t, *J* = 6.7 Hz, 6H), 1.11 (s, 3H), 1.24−1.38 (m, 15H), 1.58 (s, 3H), 1.67 (s, 3H), 2.11 (t, *J* = 7.6 Hz, 4H), 3.48−3.59 (m, 1H), 3.76 (dd, *J* = 5.8, 8.4 Hz, 1H), 3.91 (ddd, *J* = 4.6, 6.2, 8.4 Hz, 1H), 4.22 (d, *J* = 8.4 Hz, 1H), 4.33 (d, *J* = 3.6 Hz, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 5.21 (d, *J* = 12.0 Hz, 1H), 5.82 (d, *J* = 3.6 Hz, 1H), 7.09 (s, 1H), 7.31 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 14.0 (q, 2C), 22.5 (t), 22.5 (t), 25.4 (q), 25.5 (q), 26.6 (q), 26.7 (q), 28.0 (t), 28.3 (t), 28.8 (t), 30.3 (t), 31.2 (t), 31.5 (t), 67.3 (t), 73.3 (t), 73.8 (d), 83.3 (d), 84.4 (d), 93.7 (s), 103.4 (d), 109.1 (s), 113.3 (s), 120.9,(d), 120.9 (d), 121.6 (s), 137.9 (s), 139.3 (s), 139.7 (s) ppm.
ESI-MS (*m/z*)	: 511.2 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 71.28; H, 9.08 %. Found : C, 71.40; H, 9.26 %.

Dimers (2A.84)



Mol. Formula	: $C_{34}H_{44}O_{12}$
IR ($CHCl_3$) $\tilde{\nu}$	: 3302, 2989, 2934, 2109, 1619, 1455, 1074, 1025, 873 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.05 (s, 3H), 1.29−1.32 (m, 15H), 1.52 (s, 3H), 1.61 (s, 3H), 2.67 (d, *J* = 1.4 Hz, 1H), 3.47 (2dd, *J* = 5.3, 8.3 Hz, 1H), 3.65−3.73 (m, 1H), 3.81−3.88 (m, 1H), 4.02−4.11 (m, 3H), 4.20 (dd, *J* = 8.3, 8.4 Hz, 1H), 4.27−4.38 (m, 2H), 4.62 (dd, *J* = 3.3, 8.3 Hz, 2H), 4.79−4.84 (m, 1H), 5.07 (d, *J* = 12.0 Hz, 1H), 5.15 (d, *J* = 12.0 Hz, 1H), 5.78 (d, *J* = 3.6 Hz, 1H), 5.88 (t, *J* = 3.5 Hz, 1H), 6.94−7.36 (m, 3H).
ESI-MS (*m/z*)	: 645.1 (9%, $[M+H]^+$), 662.2 (22%, $[M+NH_4]^+$), 667.1 (100 %, $[M+Na]^+$)
Elemental Analysis	Calcd.: C, 63.34; H, 6.88 %. Found : C, 63.18; H, 6.97 %.

1,2-*O*-Isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-3-*C*-ethynyl-α-D-ribofuranose (2A.72)

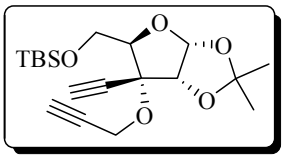


By following the procedures D ketone **2A.66** (4 g, 13.2 mmol) was transformed to diyne **2A.72** (3.2 g, 73%) as colorless solid.

Mol. Formula	: $C_{16}H_{28}O_5Si$
M. P.	: 65−67 °C
$[\alpha]_D^{25}$	: +10.5 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3306, 3019, 2958, 2930, 2882, 2401, 1519, 1376, 1255, 1163, 1050, 877 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.08, 0.09 (2s, 6H), 0.89 (s, 9H), 1.36 (s, 3H), 1.59 (s, 3H), 2.57 (s, 1H), 3.11 (s, 1H), 3.93−4.05 (m, 3H), 4.57 (d, *J* = 3.7 Hz, 1H), 5.84 (d, *J* = 3.7 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	-5.6 (q), -5.5 (q), 18.1 (s), 25.8 (q, 3C), 26.5 (q), 26.6 (q), 62.7 (t), 75.3 (s), 76.1 (d), 80.4 (s), 80.7 (d), 83.8 (d), 104.1 (d), 113.4 (s) ppm.

ESI-MS (*m/z*)	: 329.5 (100%, $[M+H]^+$), 389.5 (42%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 58.50; H, 8.59%.
	Found: C, 58.67; H, 8.42%.

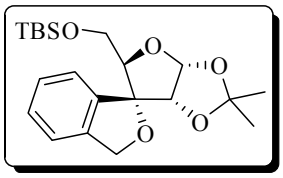
1,2-*O*-Isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-3-*C*-ethynyl-3-*O*-propargyl-α-D-ribofuranose (2A.63)



By following the procedures E alkynol **2A.72** (3.2 g, 9.7 mmol) was transformed to diyne **2A.63** (3.3 g, in 92%) as white solide.

Mol. Formula	: $C_{19}H_{30}O_5Si$
M. P.	: 105−110 °C
$[\alpha]_D^{25}$	: +40.6 (*c* 1.1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3307, 2955, 2931, 2885, 2858, 2110, 1473, 1375, 1254, 1132, 1047, 876 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.06 (s, 6H), 0.88 (s, 9H), 1.33 (s, 3H), 1.57 (s, 3H), 2.44 (t, *J* = 2.4 Hz, 1H), 2.66 (s, 1H), 3.81−3.97 (2dd, *J* = 3.9, 11.2 Hz, 2H), 4.15 (dd, *J* = 3.9, 6.7 Hz, 1H), 4.32 (dd, *J* = 2.4, 14.6 Hz, 1H), 4.45 (dd, *J* = 2.4, 14.6 Hz, 1H), 4.59 (d, *J* = 3.6 Hz, 1H), 5.82 (d, *J* = 3.6 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: −5.4 (q), −5.2 (q), 18.3 (s), 25.9 (q, 3C), 26.8 (q), 26.9 (q), 54.5 (t), 63.0 (t), 74.5 (d), 77.8 (d), 79.4 (s), 79.5 (s), 80.6 (s), 81.7 (d), 82.8 (d), 104.3 (d), 113.6 (s) ppm.
ESI-MS (*m/z*)	: 367.5 (5%, $[M+H]^+$), 389.5 (100%, $[M+Na]^+$), 405.5 (67%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 62.26; H, 8.25%.
	Found: C, 62.12; H, 8.37%.

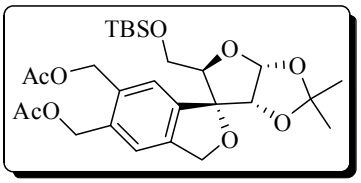
1',2'-*O*-Isopropylidene-5'-*O*-(*tert*-butyldimethylsilyl)-3'-didehydro-3'-deoxy-7*H*-spiro[isobenzofuran-2,3'-*C*-α-D-ribofuranose] (2A.85)



By following the procedure C, reaction mixture of diyne **2A.63** (200 mg, 0.55 mmol) and $[RhCl(PPh_3)_3]$ (25 mg, 0.03 mmol) in toluene (20 mL) was heated at 80 °C for 4 h. Purification of residue by column chromatography (15% ethyl acetate in petroleum ether) afforded **2A.85** (152 mg, 71%) as colorless oil.

Mol. Formula	: $C_{21}H_{32}O_5Si$
$[\alpha]_D^{25}$	: +36.4 (*c* 1.1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3077, 3019, 2955, 2930, 2858, 1608, 1462, 1383, 1255, 1167, 1087, 1049, 939 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ −0.09, −0.08 (2s, 6H), 0.80 (s, 9H), 1.36 (s, 3H), 1.69 (s, 3H), 3.30 (dd, *J* = 5.2, 11.1 Hz, 1H), 3.54 (dd, *J* = 6.5, 11.1 Hz, 1H), 4.35 (d, *J* = 3.6 Hz, 1H), 4.46 (dd, *J* = 5.2, 6.5 Hz, 1H), 5.17 (d, *J* = 12.5 Hz, 1H), 5.23 (d, *J* = 12.5 Hz, 1H), 5.99 (d, *J* = 3.6 Hz, 1H), 7.16 (dd, *J* = 1.6, 7.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.29−7.40 (m, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: −5.9 (q), −5.8 (q), 17.9 (s), 25.5 (q, 3C), 26.1 (q), 26.6 (q), 61.9 (t), 73.0 (t), 79.8 (d), 83.6 (d), 93.1 (s), 103.4 (d), 112.9 (s), 121.0 (d), 121.4 (d), 127.3 (d), 128.4 (d), 136.9 (s), 139.4 (s) ppm.
ESI-MS (*m/z*)	: 410.7 (47%, $[M+NH_4]^+$), 415.3 (100%, $[M+Na]^+$), 431.3 (67%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 64.25; H, 8.22 %. Found: C, 64.32; H, 8.14 %.

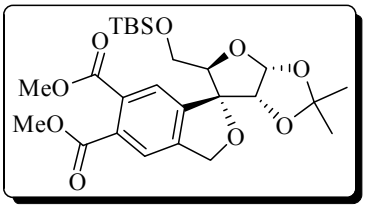
1',2'-*O*-Isopropylidene-5'-*O*-(*tert*-butyldimethylsilyl)-3'-didehydro-3'-deoxy-4,5-di(acetoxymethyl)-7*H*-spiro[isobenzofuran-2,3'-*C*-α-D-ribofuranose] (2A.86)



By following the procedure A, reaction mixture of diyne **2A.63** (150 mg, 0.41 mmol), diacetate of 2-butyne-1,4-diol (209 mg, 1.2 mmol) and $[RhCl(PPh_3)_3]$ (19 mg, 0.02 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 7 h. Purification of residue by column chromatography (25% ethyl acetate in petroleum ether) afforded **2A.86** (132 mg, 60%) as colorless oil.

Mol. Formula	: $C_{27}H_{40}O_9Si$
$[\alpha]_D^{25}$	: +25.0 (*c* 2.6, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3020, 2930, 2857, 1745, 1626, 1472, 1375, 1221, 1078, 1023, 874, 838, 756, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ −0.11, −0.10 (2s, 6H), 0.76 (s, 9H), 1.34 (s, 3H), 1.66 (s, 3H), 2.07, 2.08 (2s, 6H), 3.27 (dd, *J* = 5.2, 11.0 Hz, 1H), 3.53 (dd, *J* = 6.6, 11.0 Hz, 1H), 4.31 (d, *J* = 3.6 Hz, 1H), 4.42 (dd, *J* = 5.2, 6.5 Hz, 1H), 5.09−5.22 (m, 6H), 5.97 (d, *J* = 3.6 Hz, 1H), 7.17 (s, 1H), 7.28 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: −5.7 (q), −5.6 (q), 18.2 (s), 20.8 (q), 25.7 (q, 2C), 25.8 (q), 26.3 (q), 26.7 (q), 61.9 (t), 63.3 (t), 63.5 (t), 73.0 (t), 79.7 (d), 83.6 (d), 93.3 (s), 103.5 (d), 113.3 (s), 122.5 (d), 123.2 (d), 134.1 (s), 135.5 (s), 137.8 (s), 140.4 (s), 170.4 (s), 170.4 (s) ppm.
ESI-MS (*m/z*)	: 554.6 (36%, $[M+NH_4]^+$), 559.5 (100%, $[M+Na]^+$), 575.5 (35%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 60.42; H, 7.51 %. Found: C, 60.29; H, 7.67 %.

1',2'-*O*-Isopropylidene-5'-*O*-(*tert*-butyldimethylsilyl)-3'-didehydro-3'-deoxy-4,5-di(methoxycarbonyl)-7*H*-spiro[isobenzofuran-2,3'-*C*-α-D-ribofuranose] (2A.87)

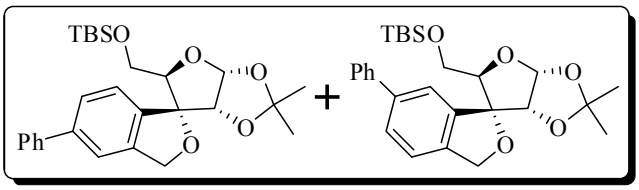


By following the procedure B, reaction mixture of diyne **2A.63** (130 mg, 0.36 mmol), dimethyl acetylene dicaboxylate (0.13 mL, 1.1 mmol) and $[RhCl(PPh_3)_3]$ (16 mg, 0.02 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 4 h. Purification

of residue by column chromatography (30% ethyl acetate in petroleum ether) afforded **2A.87** (121 mg, 67%) as colorless oil.

Mol. Formula	: $C_{25}H_{36}O_9Si$
$[\alpha]_D^{25}$	: +6.6 (*c* 0.7, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3021, 2955, 2858, 1730, 1621, 1271, 1216, 1022 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ −0.12, −0.10 (2s, 6H), 0.76 (s, 9H), 1.33 (s, 3H), 1.66 (s, 3H), 3.25 (dd, *J* = 5.7, 11.1 Hz, 1H), 3.57 (dd, *J* = 6.2, 11.0 Hz, 1H), 3.89 (2s, 6H), 4.33 (d, *J* = 3.7 Hz, 1H), 4.41 (t, *J* = 5.9 Hz, 1H), 5.20 (s, 2H), (d, *J* = 3.7 Hz, 1H), 7.49 (s, 1H), 7.55 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: −5.7 (q), −5.6 (q), 18.2 (s), 25.7 (q, 2C), 26.3 (q), 26.7 (q), 52.8 (q), 52.9 (q), 61.6 (t), 72.9 (t), 79.5 (d), 83.5 (d), 93.5 (s), 103.5 (d), 113.5 (s), 121.9 (d), 122.5 (d), 131.7 (s), 133.2 (s), 140.6 (s), 143.4 (s), 167.2 (s), 167.7 (s) ppm.
ESI-MS (*m/z*)	: 509.5 (11%, $[M+H]^+$), 526.6 (30%, $[M+NH_4]^+$), 531.5 (100%, $[M+Na]^+$), 547.5 (9%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 59.03; H, 7.13 %. Found: C, 58.91; H, 7.20 %.

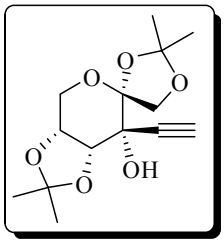
Compounds (2A.88a,b)



By following the procedure A, reaction mixture of diyne **2A.63** (130 mg, 0.36 mmol), phenyl acetylene (0.2 mL, 1.8 mmol) and $[RhCl(PPh_3)_3]$ (16 mg, 0.02 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 8 h. Purification of residue by column chromatography (20% ethyl acetate in petroleum ether) afforded mixture of **2A.88a** and **2A.88b** (130 mg, 78%) as redish viscous oil.

Mol. Formula	: $C_{27}H_{36}O_5Si$
IR ($CHCl_3$) $\tilde{\nu}$	: 3019, 2955, 2857, 1600, 1472, 1255, 1085, 1016, 837 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ −0.15, −0.14 (2s, 6H), 0.72 (s, 9H), 1.29, 1.30 (2s, 3H), 1.62 (s, 3H), 3.27−3.32 (2dd, *J* = 5.2, 11.0 Hz, 1H), 3.51-3.57 (2dd, *J* = 6.6, 11.0 Hz, 1H), 4.32, 4.33 (2d, *J* = 3.6 Hz, 1H), 4.40−4.43 (m, 1H), 5.13−5.19 (m, *J* = 13 Hz, 2H), 5.94, 5.95 (2d, *J* = 3.6 Hz, 1H), 7.14−7.31 (m, 2H), 7.36−7.50 (m, 6H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: −5.7 (q), −5.5 (q), 18.2 (s), 25.8 (q), 26.3 (q), 26.8 (q), 62.1 (t), 62.1 (d), 73.1 (t), 73.2 (t), 79.9 (d), 83.8 (d), 93.3 (s), 93.4 (s), 103.6 (d), 103.6 (d), 113.2 (s), 113.2 (s), 119.9 (d), 120.3 (d), 121.5 (d), 121.9 (d), 126.8 (d), 127.1 (d), 127.5 (d), 127.9 (d), 128.8 (d), 136.2 (s), 138.0 (s), 138.8 (s), 140.5 (s), 140.5 (s), 141.1 (s), 142.1 (s) ppm.
ESI-MS (*m/z*)	: 492.0 (100%, $[M+Na]^+$), 508.0 (25%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 69.20; H, 7.74 %. Found: C, 69.12; H, 7.81 %.

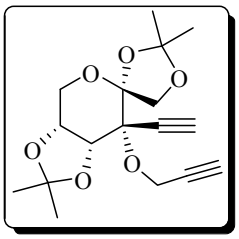
1,2;4,5-Di-*O*-isopropylidene-3-*C*-ethynyl-α-D-psicopyranose (2A.74)



By following the procedures D ketone **2A.68** (4 g, 15.5 mmol) was transformed to alkynol **2A.74** (3.3 g, 76% yield) as white solid.

Mol. Formula	: $C_{14}H_{20}O_6$
M. P.	: 155−157 °C
$[\alpha]_D^{25}$	: −184.8 (*c* 1.6, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3479, 3270, 2989, 2940, 2117, 1458, 1384, 1213, 1089, 986, cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.38 (s, 3H), 1.44 (s, 3H), 1.49 (s, 3H), 1.60 (s, 3H), 2.49 (s, 1H), 2.85 (s, 1H), 4.06−4.11 (m, 1H), 4.14−4.26 (m, 3H), 4.41−4.46 (m, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	25.0 (q), 25.6 (q), 25.8 (q), 26.5 (q), 59.6 (t), 69.0 (s), 70.6 (d), 72.9 (t), 73.2 (d), 76.0 (d), 82.6 (s), 105.1 (s), 109.4 (s), 113.2 (s) ppm.
ESI-MS (*m/z*)	: 285.3 (11%, $[M+H]^+$), 307.3 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 59.14; H, 7.09%. Found: C, 58.97; H, 7.28%.

1,2;4,5-Di-*O*-isopropylidene-3-*C*-ethynyl-3-*O*-propargyl-α-D-psicopyranose (2A.65)

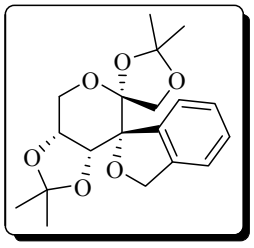


By following the procedures alkynol **2A.74** (3.3 g, 11.6 mmol) was transformed to diyne **2A.65** (3.5 g, in 94%) as a white solid.

Mol. Formula	: $C_{17}H_{22}O_6$
M. P.	: 104−106 °C
$[\alpha]_D^{25}$	: −139.5 (*c* 1.6, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	: 3271, 2989, 2939, 2114, 1458, 1255, 1094, 1015, 981 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.34 (s, 3H), 1.44 (s, 3H), 1.48 (s, 3H), 1.55 (s, 3H), 2.41 (t, *J* = 2.4 Hz, 1H), 2.73 (s, 1H), 3.97−4.08 (m, 2H), 4.19−4.28 (m, 2H), 4.43 (d, *J* = 9.3 Hz, 1H), 4.48 (d, *J* = 6.2 Hz, 1H), 4.53 (d, *J* = 2.4 Hz, 2H).
^{13}C NMR	: 25.2 (q), 25.9 (q), 26.2 (q), 26.2 (q), 56.3 (t), 61.2 (t), 71.3

($CDCl_3$, 50 MHz)	(d), 73.0 (t), 74.5 (d), 74.9 (s), 77.6 (d), 77.6 (s), 79.0 (d), 80.3 (d), 105.5 (s), 109.9 (s), 112.2 (s) ppm.
ESI-MS (*m/z*)	: 345.3 (100%, $[M+Na]^+$), 361.3 (73%, $[M+K]^+$).
Elemental	Calcd.: C, 63.34; H, 6.88 %.
Analysis	Found: C, 63.19; H, 6.97 %.

1',2';4',5'-Di-*O*-isopropylidene-3'-didehydro-3'-deoxy-7*H*-spiro[isobenzofuran-2,3'-*C*-α-D-psicopyranoside] (2A.89)

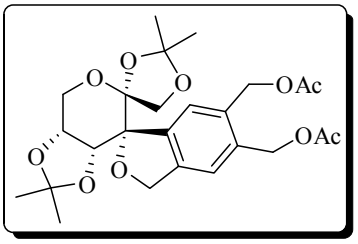


By following the procedure C, reaction mixture of diyne **2A.65** (150 mg, 0.47 mmol) and $[RhCl(PPh_3)_3]$ (22 mg, 0.02 mmol) in toluene (20 mL) was heated at 80 °C for 4 h. Purification of residue by column chromatography (15% ethyl acetate in petroleum ether) afforded **2A.89** (118 mg, 73%) as crystalline solid.

Mol. Formula	: $C_{19}H_{24}O_6$
M. P.	: 91−94 °C
$[\alpha]_D^{25}$	: −183.5 (*c* 1.3, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	: 3077, 3016, 2987, 2935, 2867, 1609, 1460, 1380, 1247, 1090, 1064, 979, 885 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.32 (s, 6H), 1.52 (s, 3H), 1.59 (s, 3H), 3.46 (d, *J* = 9.0 Hz, 1H), 4.08 (d, *J* = 9.0 Hz, 1H), 4.25−4.29 (m, 3H), 4.48 (d, *J* = 5.3 Hz, 1H), 5.11 (d, *J* = 12.3 Hz, 1H), 5.23 (d, *J* = 12.3 Hz, 1H), 7.19 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.27−7.41 (m, 3H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 25.6 (q), 25.7 (q), 26.1 (q), 26.6 (q), 59.8 (t), 71.1 (d), 72.5 (t), 73.7 (t), 76.6 (d), 86.7 (s), 106.6 (s), 109.3 (s), 112.8 (s), 120.5 (d), 123.5 (d), 127.3 (d), 128.7 (d), 138.2 (s), 140.7 (s) ppm.
ESI-MS (*m/z*)	: 349.2 (9%, $[M+H]^+$), 366.2 (100%, $[M+NH_4]^+$), 371.2 (12%, $[M+Na]^+$), 387.2 (17%, $[M+K]^+$).

Elemental Analysis	Calcd.: C, 65.50; H, 6.94 %. Found: C, 65.62; H, 7.03 %.

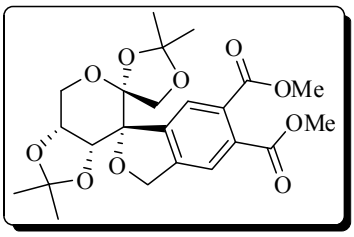
1',2';4',5'-Di-*O*-isopropylidene-3'-didehydro-3'-deoxy-4,5-di(acetoxymethyl)-7*H*-spiro[isobenzofuran-2,3'-*C*-α-D-psicopyranoside] (2A.90)



By following the procedure A, reaction mixture of diyne **2A.65** (130 mg, 0.4 mmol), diacetate of 2-butyne-1,4-diol (206 mg, 1.2 mmol) and $[RhCl(PPh_3)_3]$ (19 mg, 0.02 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 7 h. Purification of residue by column chromatography (30% ethyl acetate in petroleum ether) afforded **2A.90** (130 mg, 65%) as viscous oil.

Mol. Formula	: $C_{25}H_{32}O_{10}$
$[\alpha]_D^{25}$	: −111.43 (*c* 1.4, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3020, 2989, 2937, 1736, 1600, 1381, 1090, 980 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.29 (s, 3H), 1.33 (s, 3H), 1.49 (s, 3H), 1.55 (s, 3H), 2.03 (s, 3H), 2.06 (s, 3H), 3.44 (d, *J* = 9.0 Hz, 1H), 4.03 (d, *J* = 9.0 Hz, 1H), 4.24−4.26 (m, 3H), 4.45 (d, *J* = 5.3 Hz, 1H), 5.07−5.21 (m, *J* = 12.5, 12.8 Hz, 6H), 7.23 (s, 1H), 7.42 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 20.7 (q), 20.8 (q), 25.5 (q), 25.6 (q), 26.0 (q), 26.3 (q), 59.8 (t), 63.4 (t), 63.4 (t), 71.0 (d), 72.6 (t), 73.5 (t), 76.5 (d), 86.7 (s), 106.5 (s), 109.4 (s), 112.8 (s), 122.1 (d), 124.9 (d), 134.0 (s), 135.3 (s), 139.1 (s), 141.0 (s), 170.4 (s), 170.5 (s) ppm.
ESI-MS (*m/z*)	: 510.8 (43%, $[M+NH_4]^+$), 515.7 (100%, $[M+Na]^+$), 531.7 (17%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 60.97; H, 6.55 %. Found: C, 60.82; H, 6.68 %.

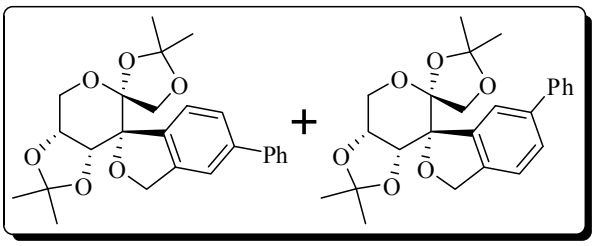
1',2';4',5'-Di-*O*-isopropylidene-3'-didehydro-3'-deoxy-4,5-di(methoxycarbonyl)-7*H*-spiro[isobenzofuran-2,3'-*C*-α-D-psicopyranoside] (2A.91)



By following the procedure B, reaction mixture of diyne **2A.65** (130 mg, 0.4 mmol), dimethyl acetylene dicaboxylate (0.15 mL, 1.2 mmol) and $[RhCl(PPh_3)_3]$ (19 mg, 0.02 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 4 h. Purification of residue by column chromatography (30% ethyl acetate in petroleum ether) afforded **2A.91** (129 mg, 69%) as white solid.

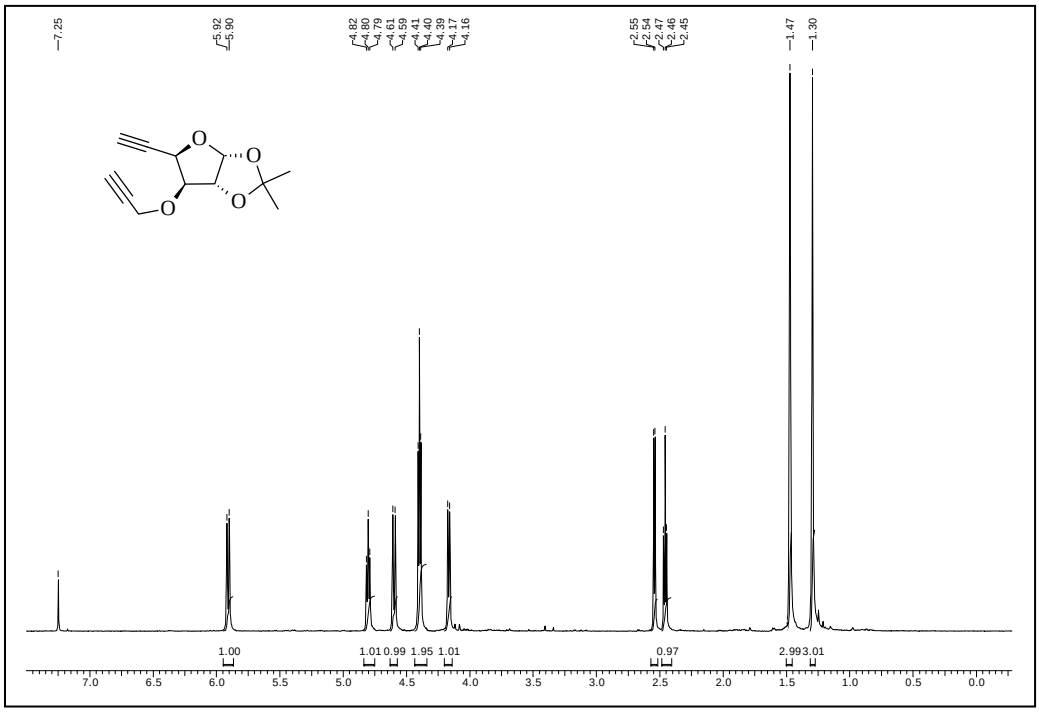
Mol. Formula	: $C_{23}H_{28}O_{10}$
M. P.	: 78−81 °C
$[\alpha]_D^{25}$	: −136.5 (*c* 0.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3019, 2990, 2938, 2874, 1779, 1730, 1622, 1437, 1383, 1216, 1091, 980, 877, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.30 (s, 3H), 1.35 (s, 3H), 1.50 (s, 3H), 1.57 (s, 3H), 3.41(d, *J* = 9.1 Hz, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.06 (d, *J* = 9.1 Hz, 1H), 4.25−4.28 (m, 3H), 4.45 (d, *J* = 5.3 Hz, 1H), 5.14 (d, *J* = 13.1 Hz, 1H), 5.26 (d, *J* = 13.1 Hz, 1H), 7.49 (s, 1H), 7.82 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 25.4 (q), 25.6 (q), 25.8 (q), 26.2 (q), 52.6 (q), 52.7 (q), 59.8 (t), 70.8 (d), 72.5 (t), 73.5 (t), 76.5 (d), 86.7 (s), 106.1 (s), 109.5 (s), 113.0 (s), 121.1 (d), 124.8 (d), 130.9 (s), 133.5 (s), 141.6 (s), 144.0 (s), 167.1 (s), 168.0 (s) ppm.
ESI-MS (*m/z*)	: 465.5 (14%, $[M+H]^+$), 487.5(100%, $[M+Na]^+$), 503.5 (33%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 59.48; H, 6.08 %. Found: C, 59.69; H, 6.14 %.

Compounds (2A.92a,b)

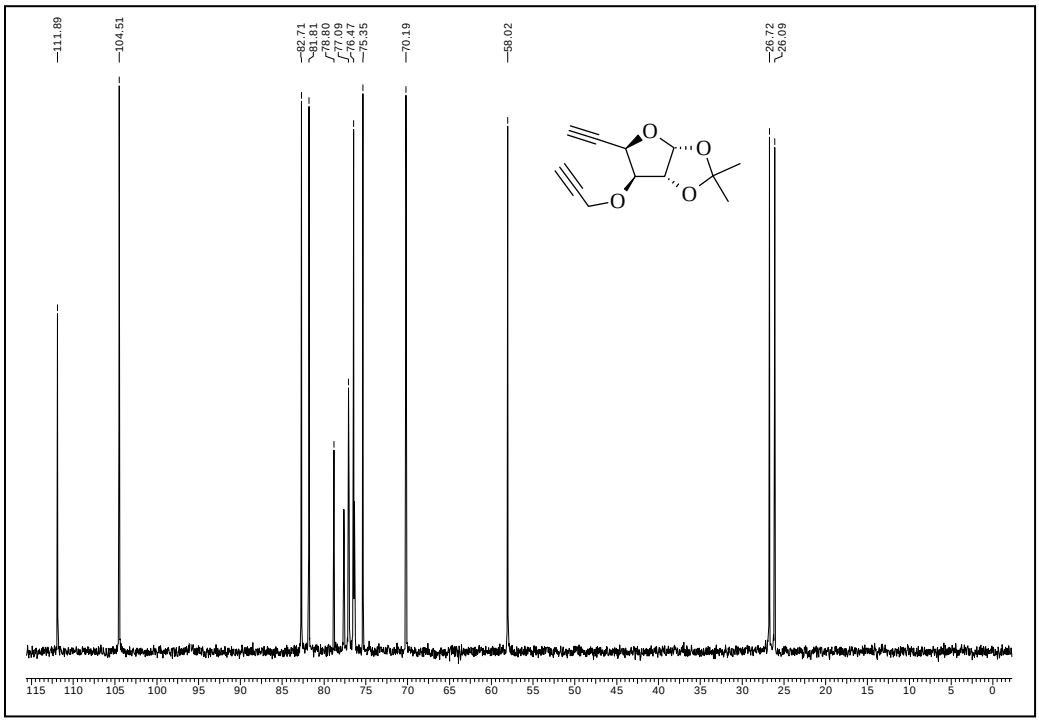


By following the procedure A, reaction mixture of diyne **2A.65** (140 mg, 0.43 mmol), phenyl acetylene (0.2 mL, 1.7 mmol) and $[RhCl(PPh_3)_3]$ (20 mg, 0.02 mmol) in toluene/ethanol (9/3 mL) was heated at 80 °C for 8 h. Purification of residue by column chromatography (20% ethyl acetate in petroleum ether) afforded mixture of **2A.92a** and **2A.92b** (138 mg, 75%) as amorphous solid.

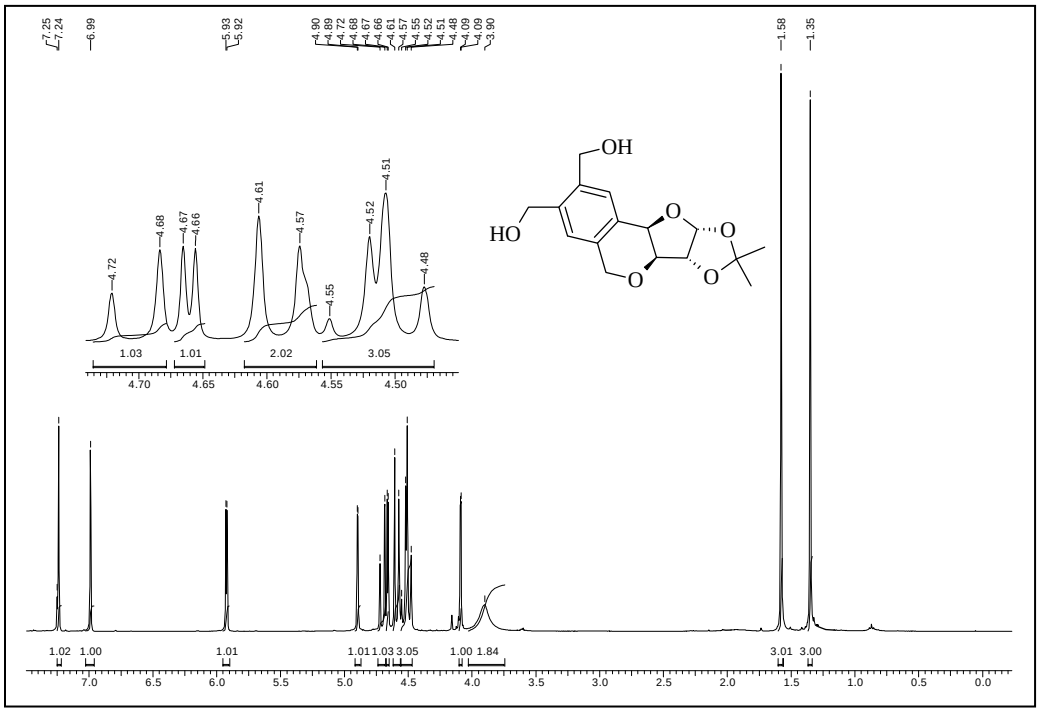
Mol. Formula	: $C_{25}H_{28}O_6$
M. P.	: 71−73 °C
IR ($CHCl_3$) $\tilde{\nu}$	: 3019, 2935, 1601, 1382, 1133, 1091, 879 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.27, 1.28, 1.31 (3s, 6H), 1.48 (s, 3H), 1.56 (s, 3H), 3.49 (2d, *J* = 9.0 Hz, 1H), 4.08 (2d, *J* = 9.0 Hz, 1H), 4.22−4.28 (m, 3H), 4.46, 4.49 (2d, *J* = 5.3 Hz, 1H), 5.10, 5.11 (2d, *J* = 12.2, 12.3 Hz, 1H), 5.19, 5.24 (2d, *J* = 12.3 Hz, 1H), 7.19−7.39 (m, 5H), 7.44−7.53 (m, 3H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 25.6 (q), 25.7 (q), 26.2 (q), 26.3 (q), 26.5 (q), 26.6 (q), 59.7 (t), 59.8 (t), 71.1 (d), 72.6 (t), 73.6 (t), 73.7 (t), 76.6 (d), 86.6 (s), 86.7 (s), 106.7 (s), 109.4 (s), 112.8 (s), 119.4 (d), 120.9 (d), 122.3 (d), 123.8 (d), 126.8 (d), 126.9 (d), 127.2 (d), 127.3 (d), 128.1 (d), 128.7 (d), 137.3 (s), 139.1 (s), 139.4 (s), 140.7 (s), 140.8 (s), 141.0 (s), 142.2 (s) ppm.
ESI-MS (*m/z*)	: 425.7 (9%, $[M+H]^+$), 442.7 (53%, $[M+NH_4]^+$), 447.7 (100%, $[M+Na]^+$), 463.7 (16%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 70.74; H, 6.65 %. Found: C, 70.52; H, 6.79 %.



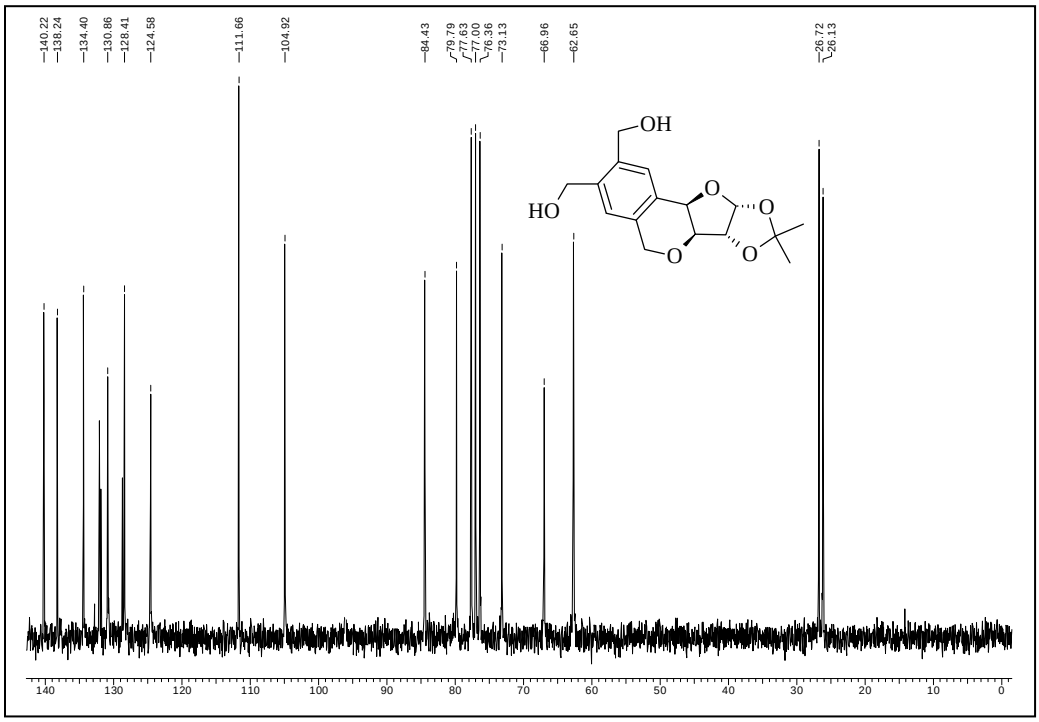
^{1}H NMR Spectrum of 2A.43 in $CDCl_3$



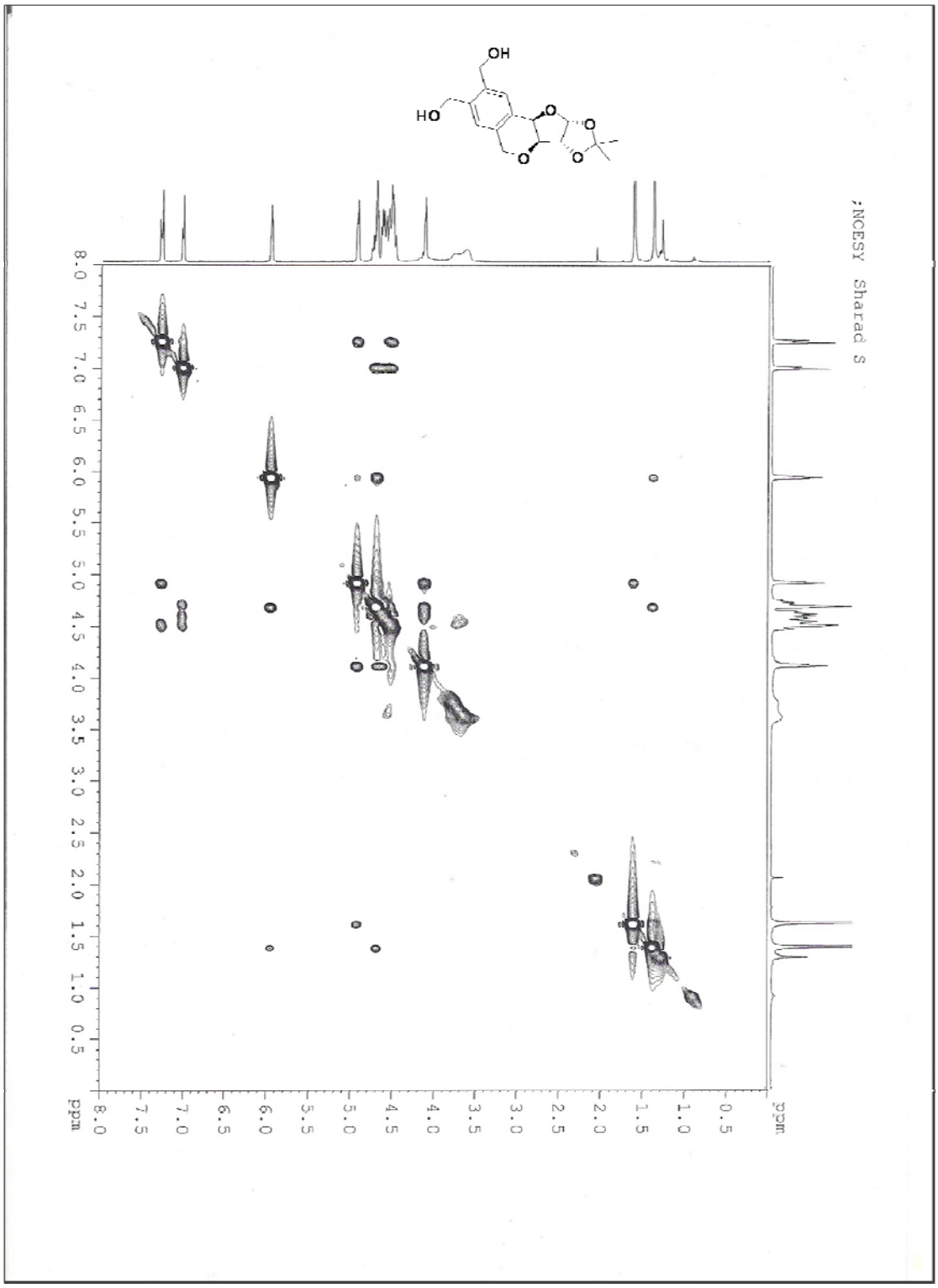
^{13}C NMR Spectrum of 2A.43 in $CDCl_3$

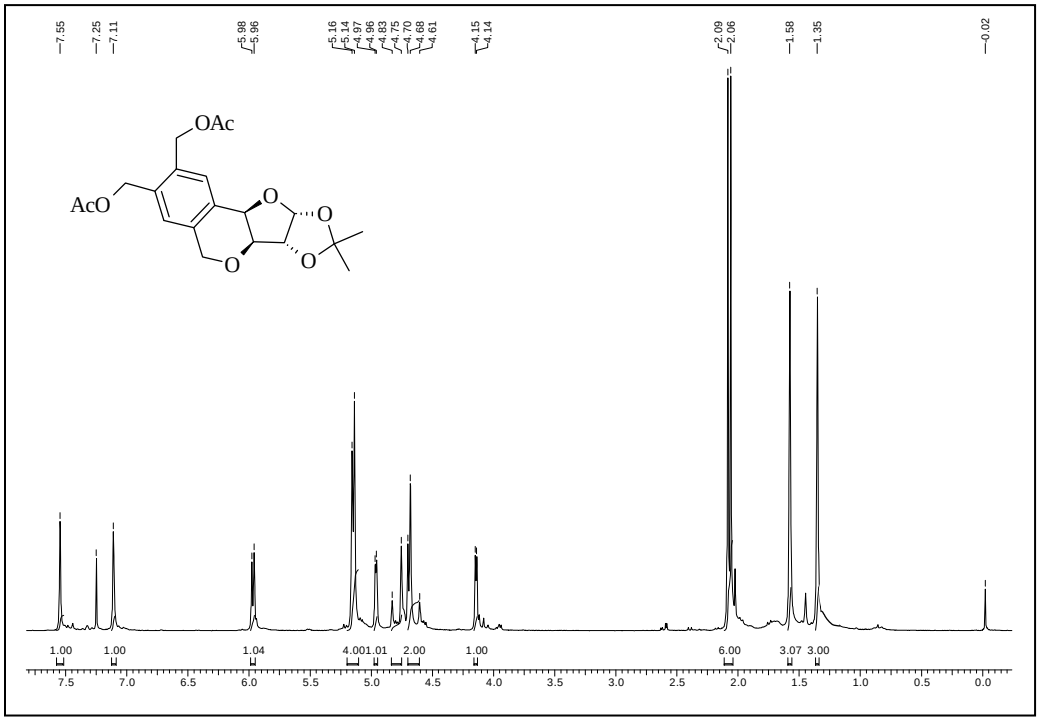


^{1}H NMR Spectrum of 2A.49 in $CDCl_3$

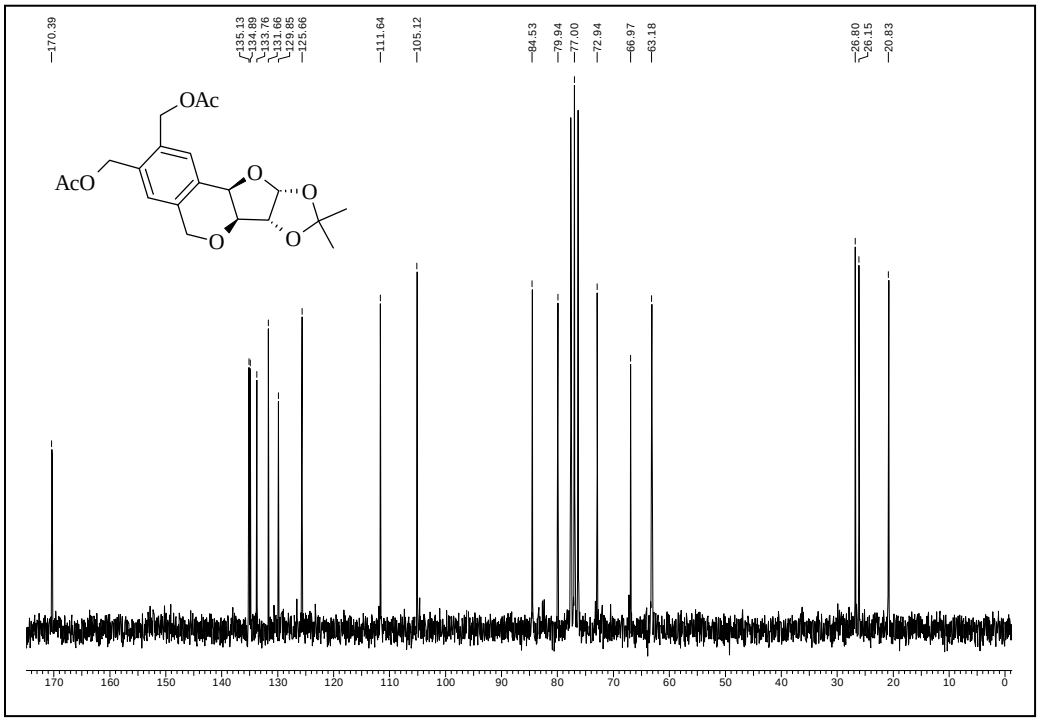


^{13}C NMR Spectrum of 2A.49 in $CDCl_3$

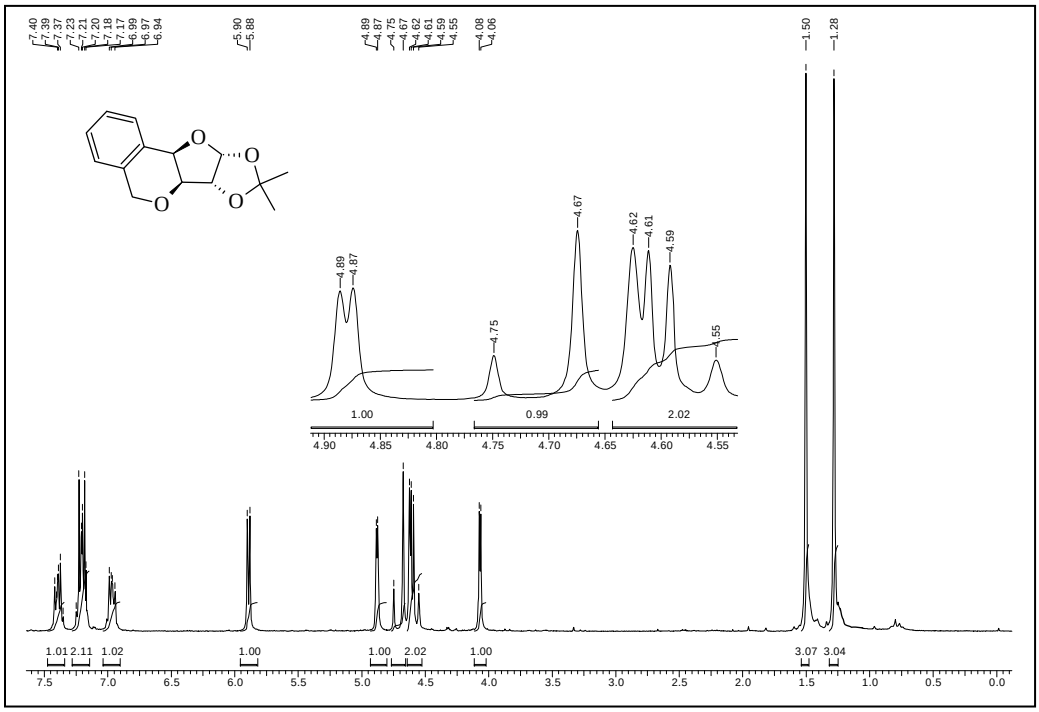

OH
HO
O
O
O
O
NCESY Sharad S
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm



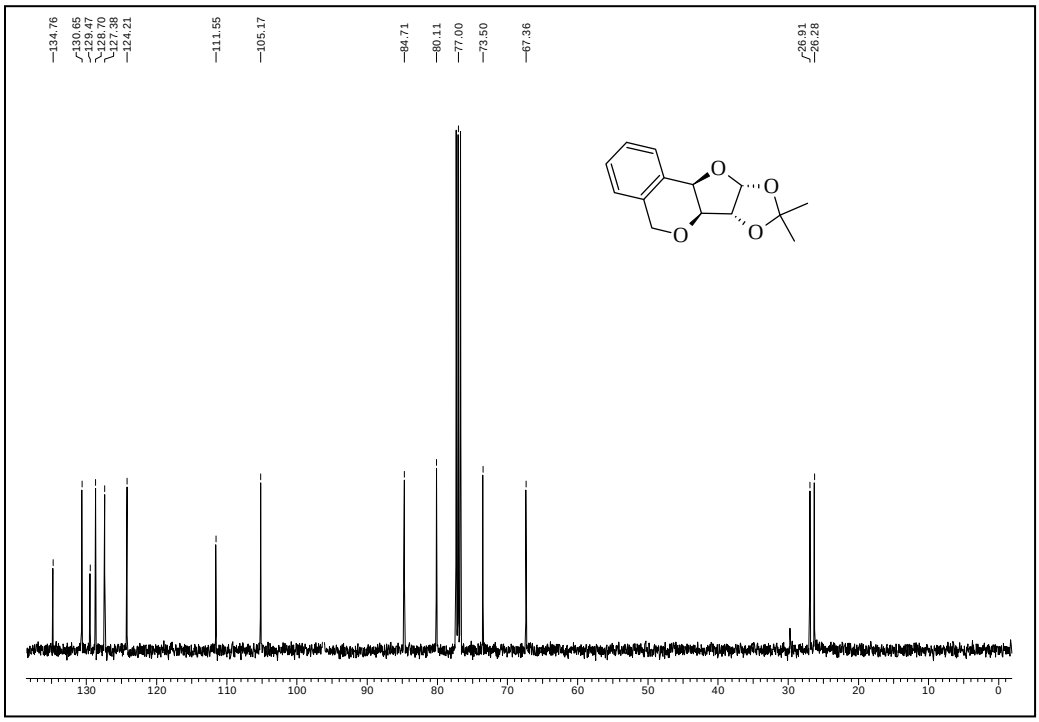
^{1}H NMR Spectrum of 2A.51 in $CDCl_3$



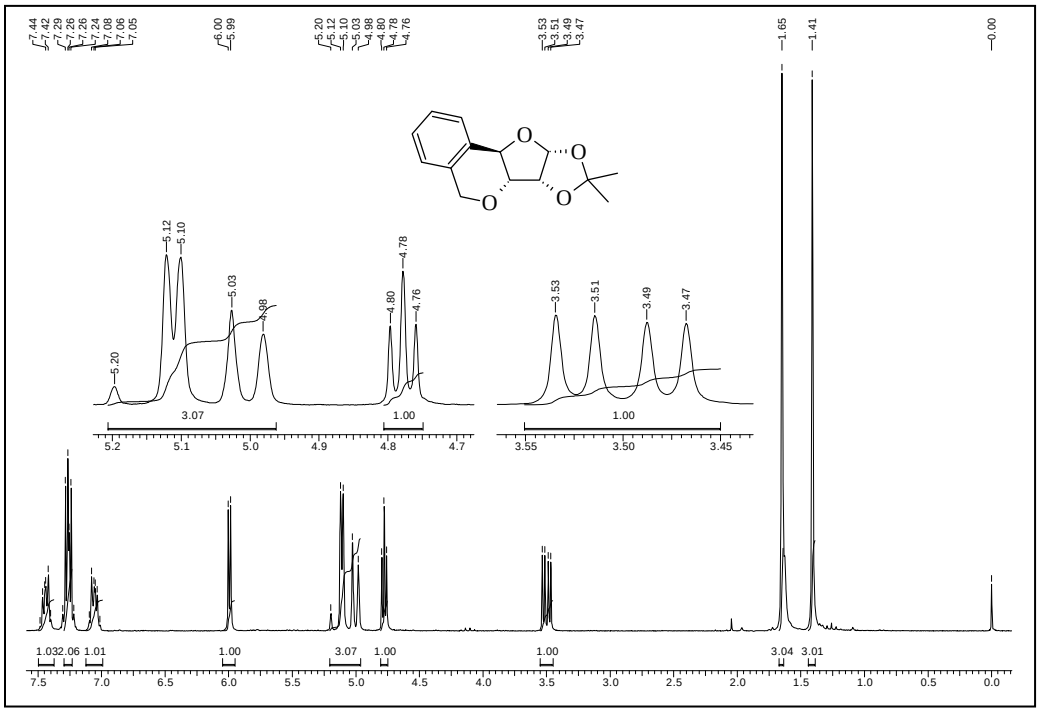
^{13}C NMR Spectrum of 2A.51 in $CDCl_3$



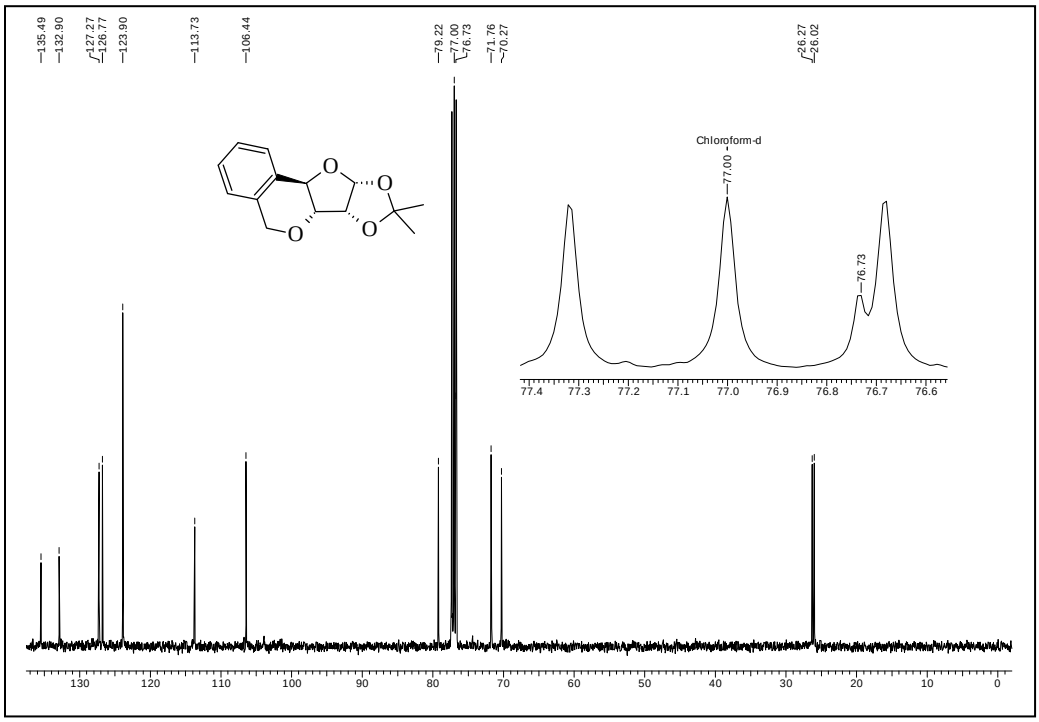
^{1}H NMR Spectrum of 2A.50 in $CDCl_3$



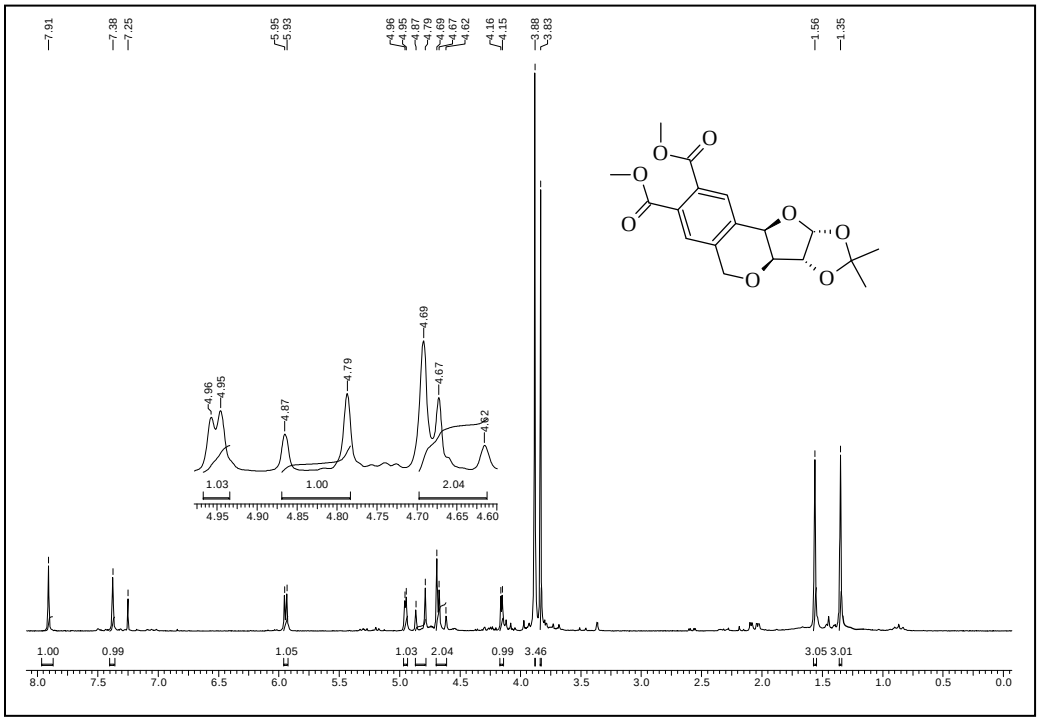
^{13}C NMR Spectrum of 2A.50 in $CDCl_3$



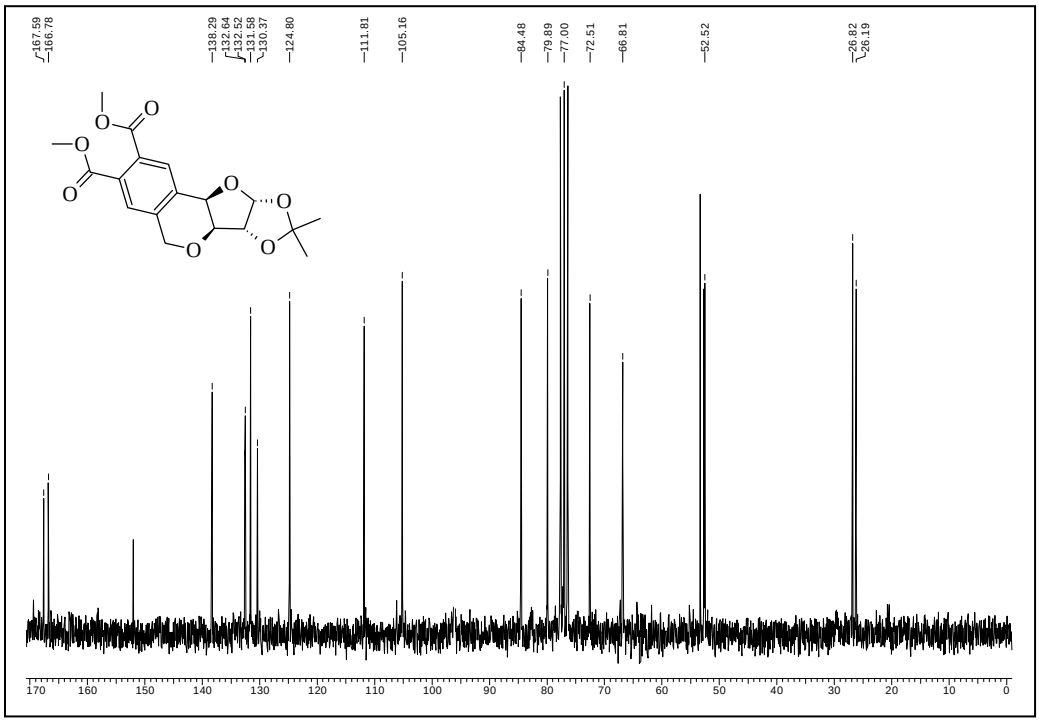
^{1}H NMR Spectrum of 2A.59 in $CDCl_3$



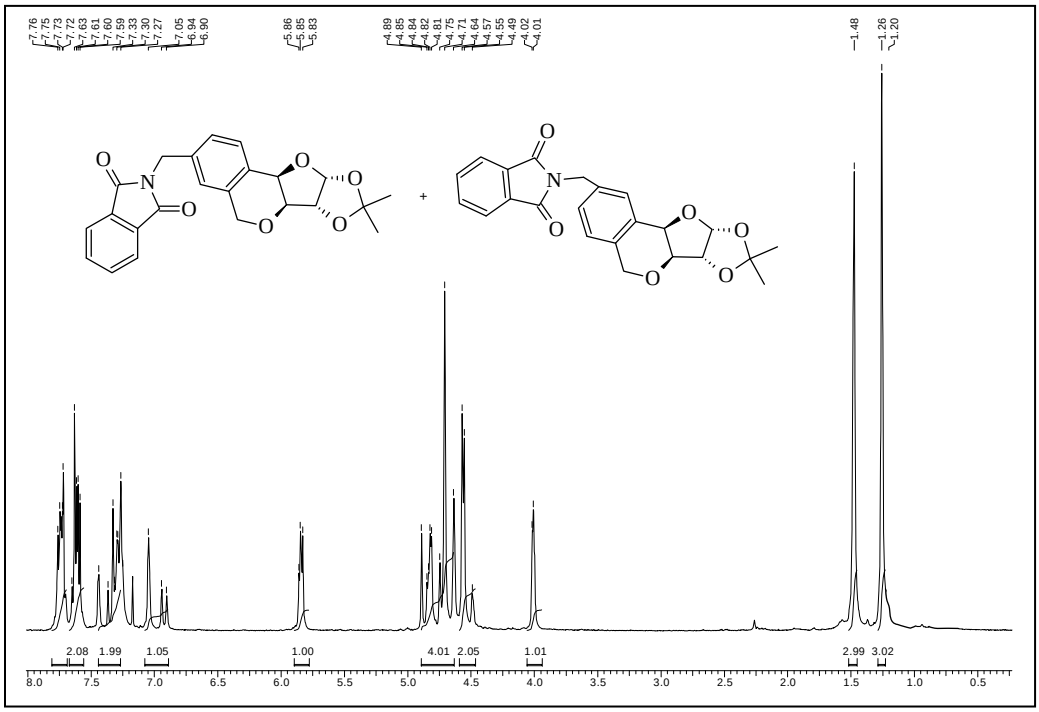
^{13}C NMR Spectrum of 2A.59 in $CDCl_3$



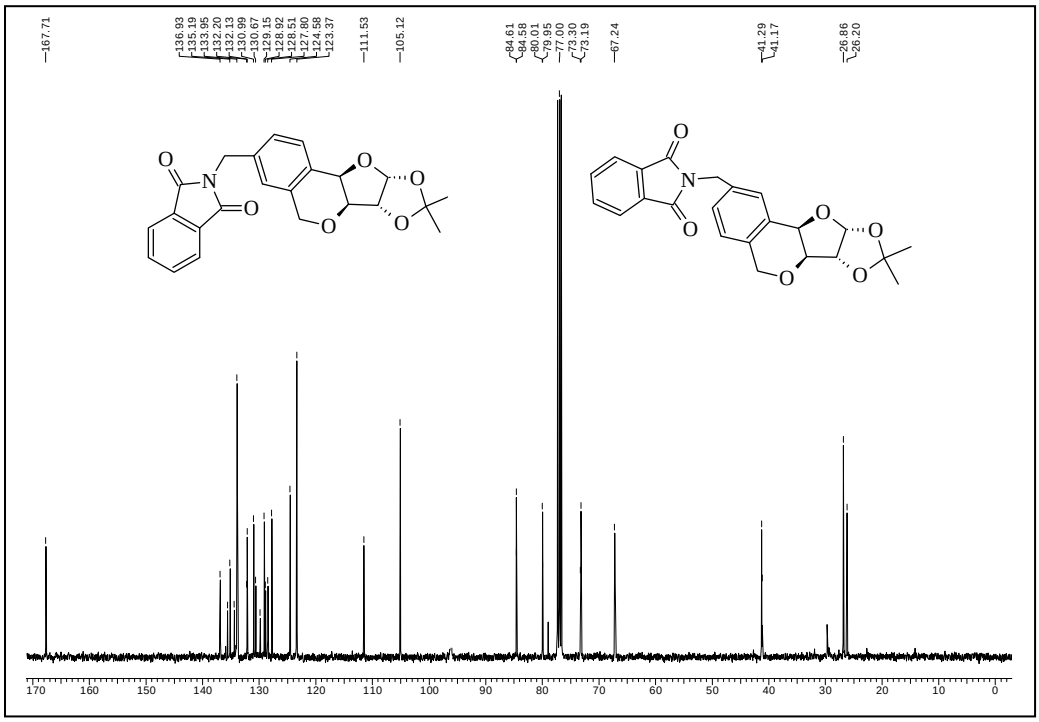
^{1}H NMR Spectrum of 2A.52 in $CDCl_3$



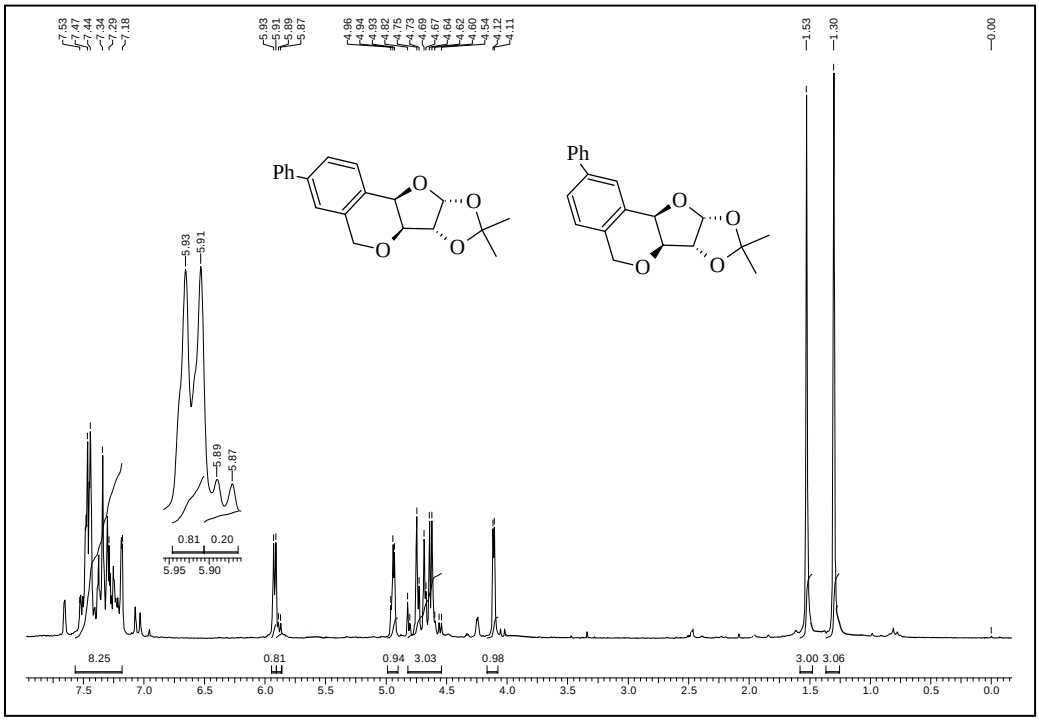
^{13}C NMR Spectrum of 2A.52 in $CDCl_3$



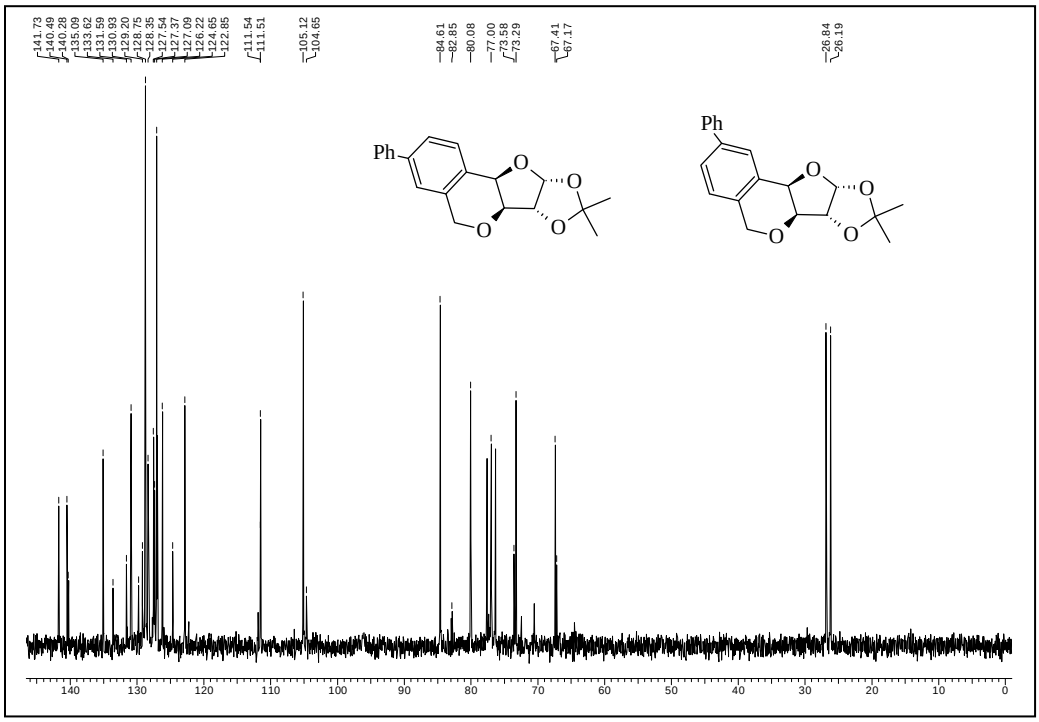
^{1}H NMR Spectrum of 2A.54a/2A.54b in $CDCl_3$



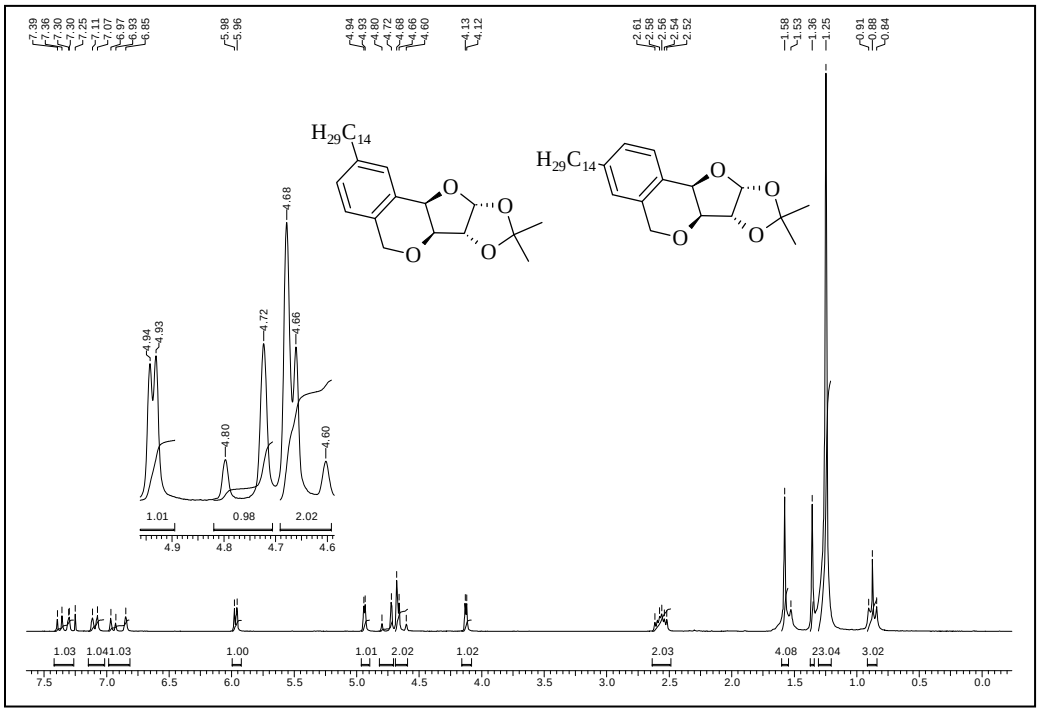
^{13}C NMR Spectrum of 2A.54a/2A.54b in $CDCl_3$



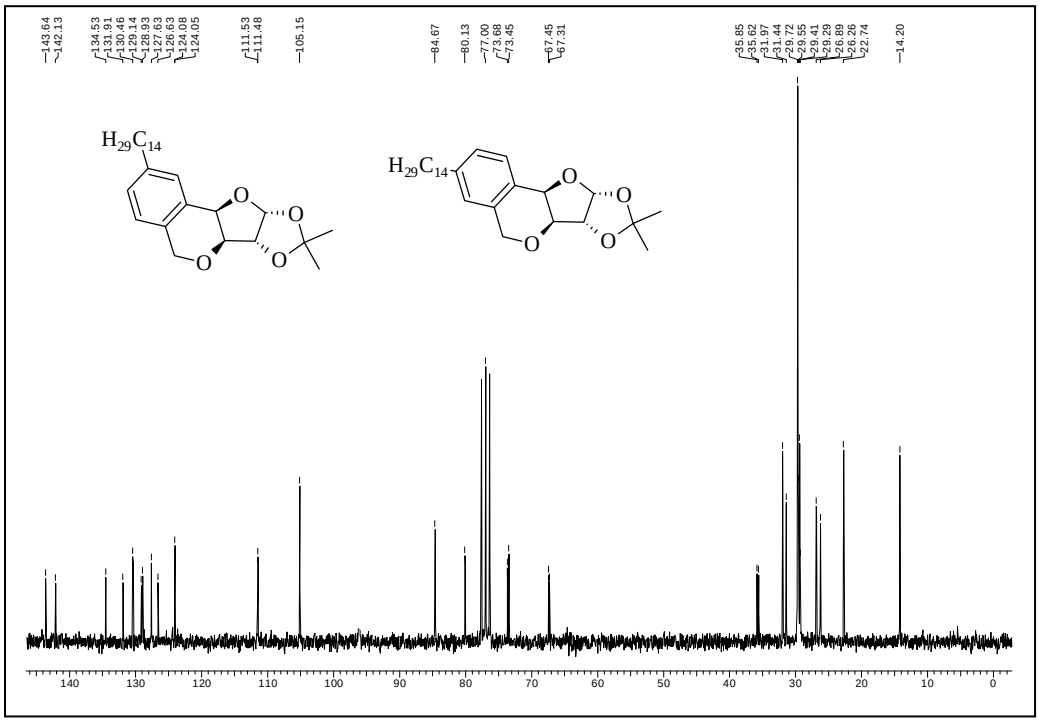
^{1}H NMR Spectrum of 2A.53a/2A.53b in $CDCl_3$



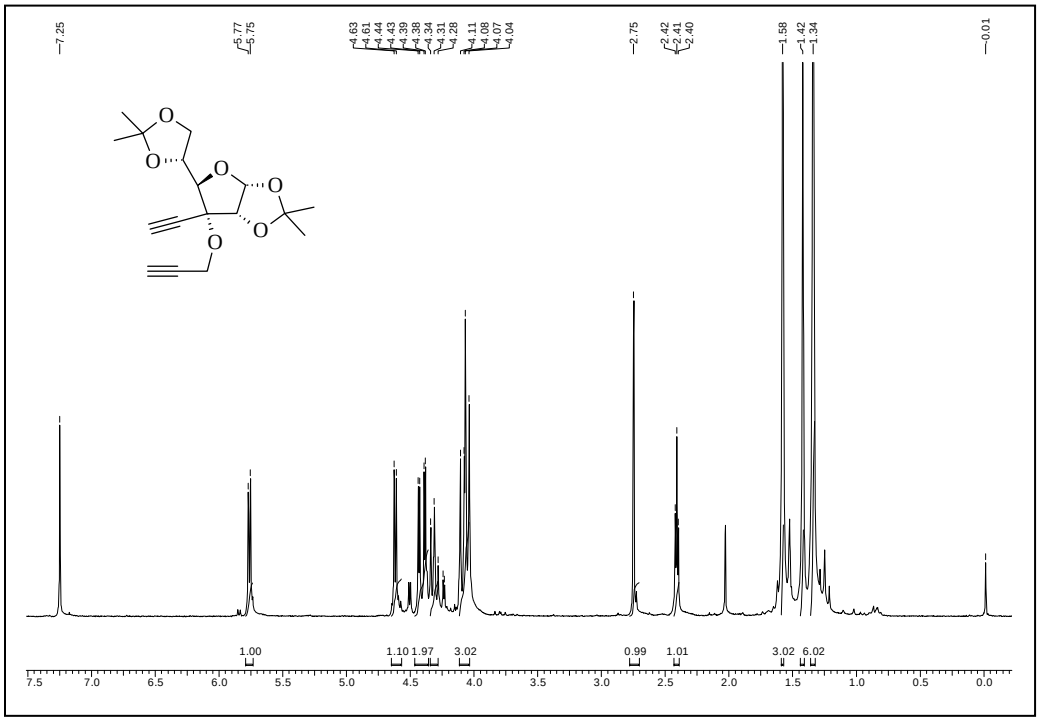
^{13}C NMR Spectrum of 2A.53a/2A.53b in $CDCl_3$



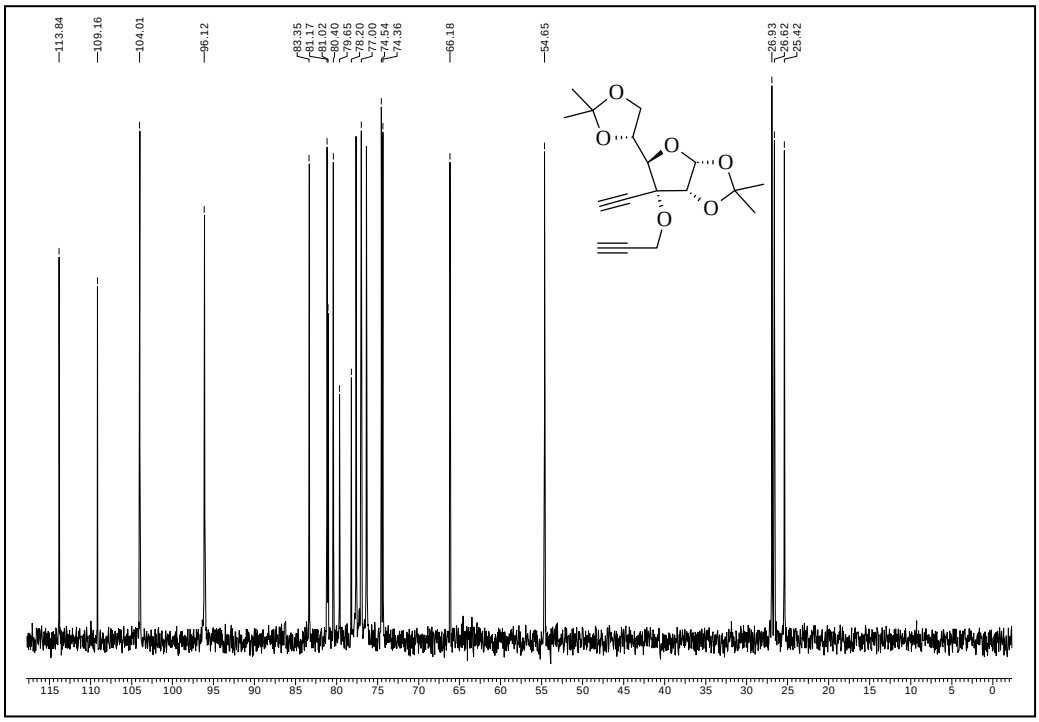
^{1}H NMR Spectrum of 2A.55a/2A.55b in $CDCl_3$



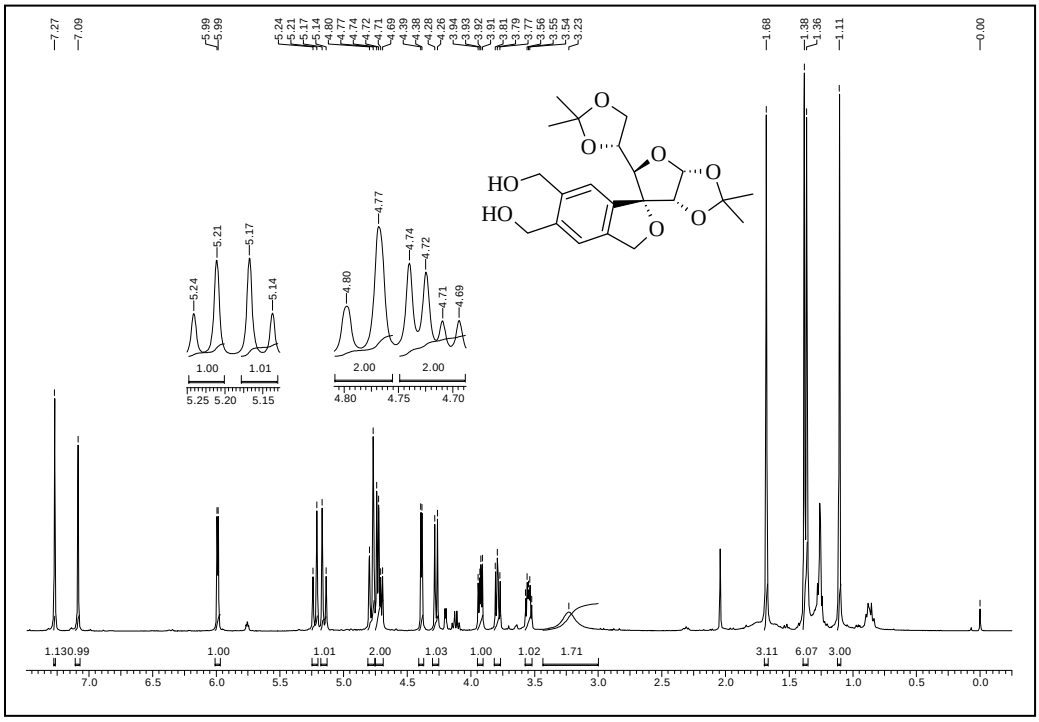
^{13}C NMR Spectrum of 2A.55a/2A.55b in $CDCl_3$



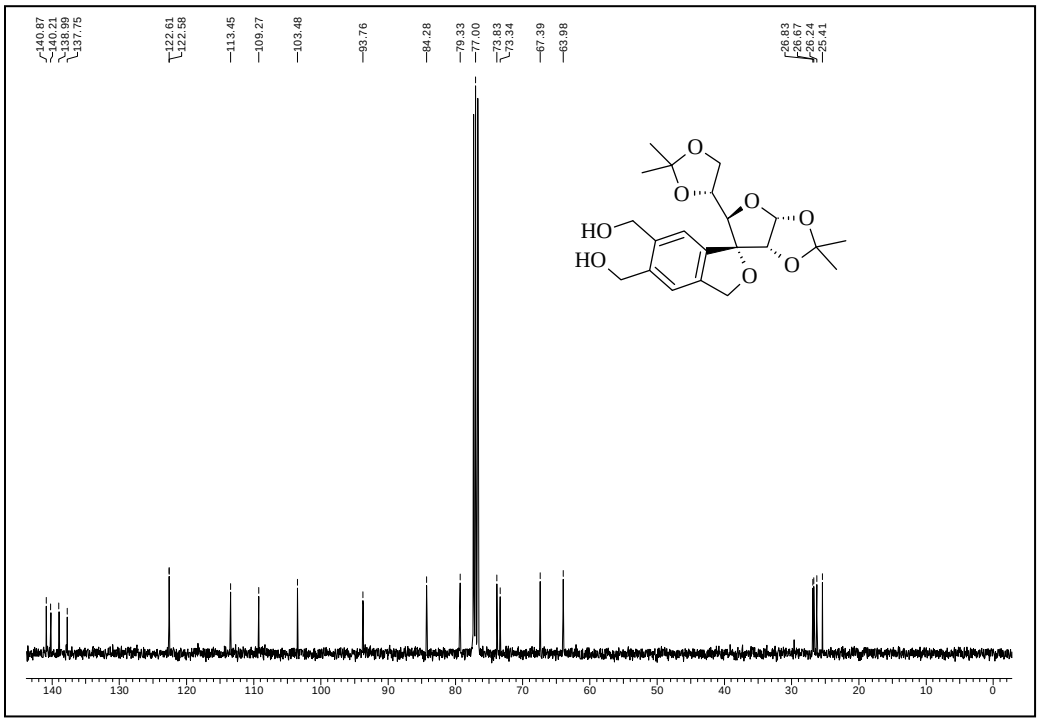
^{1}H NMR Spectrum of 2A.64 in $CDCl_3$



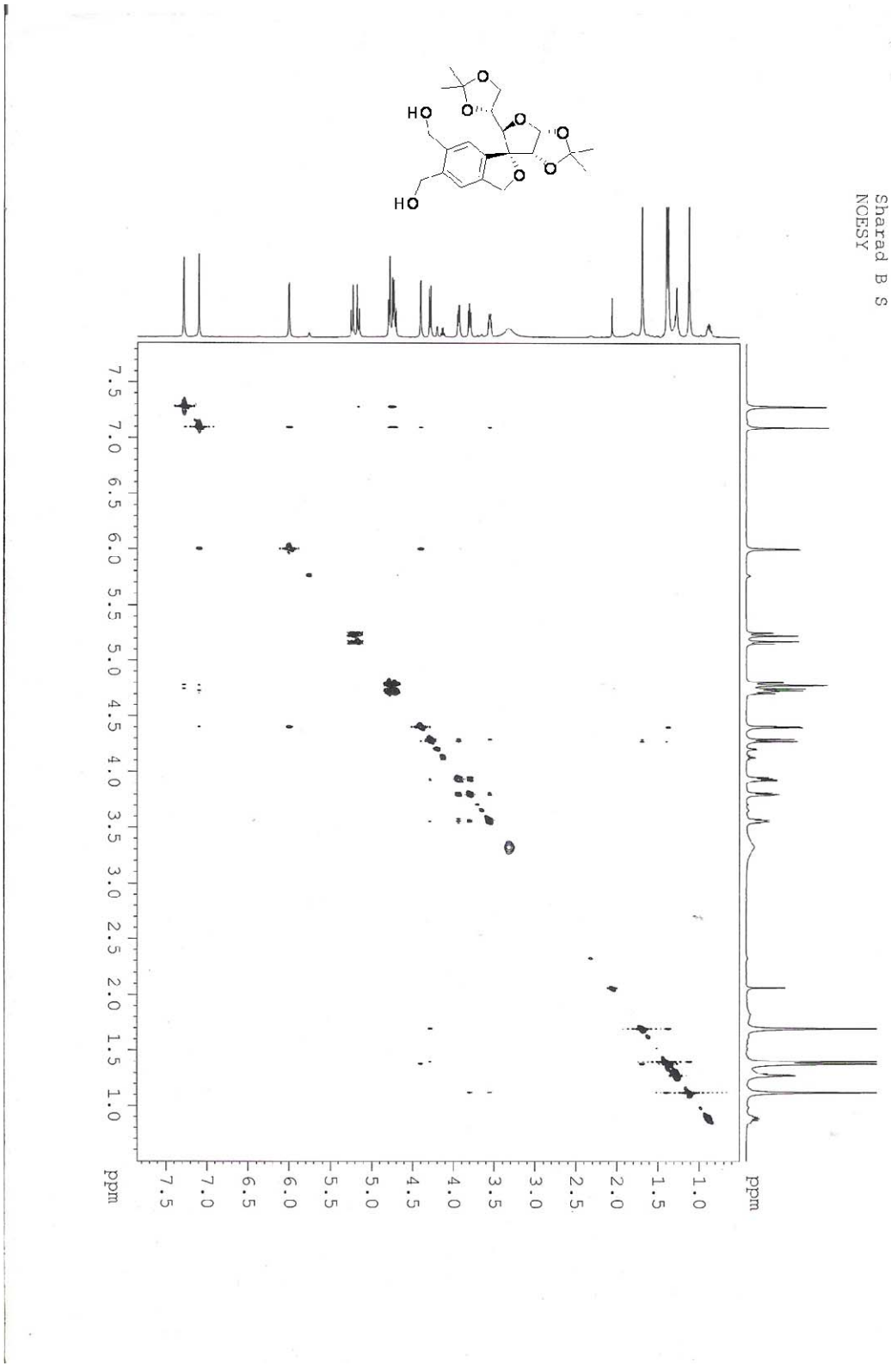
^{13}C NMR Spectrum of 2A.64 in $CDCl_3$

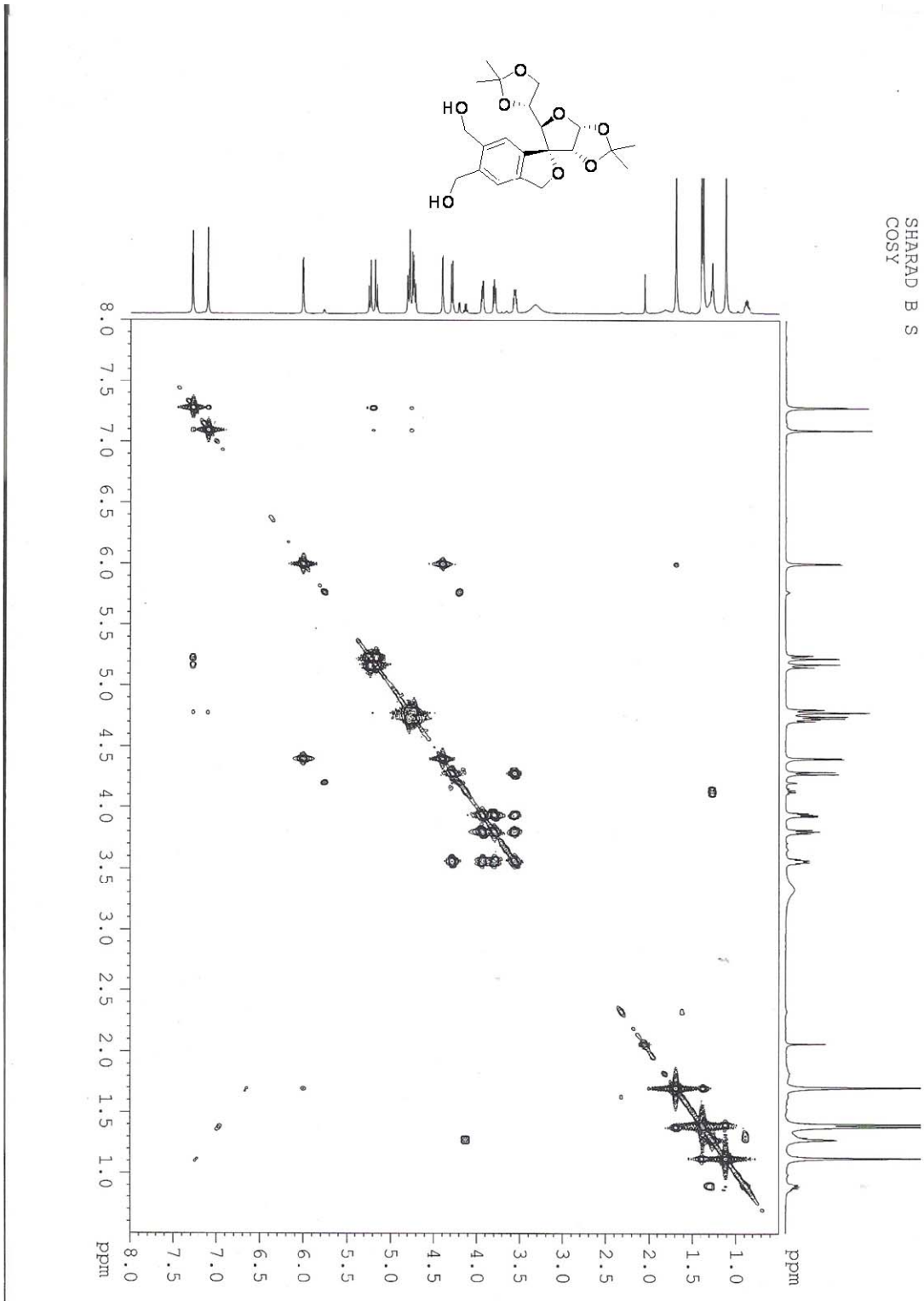


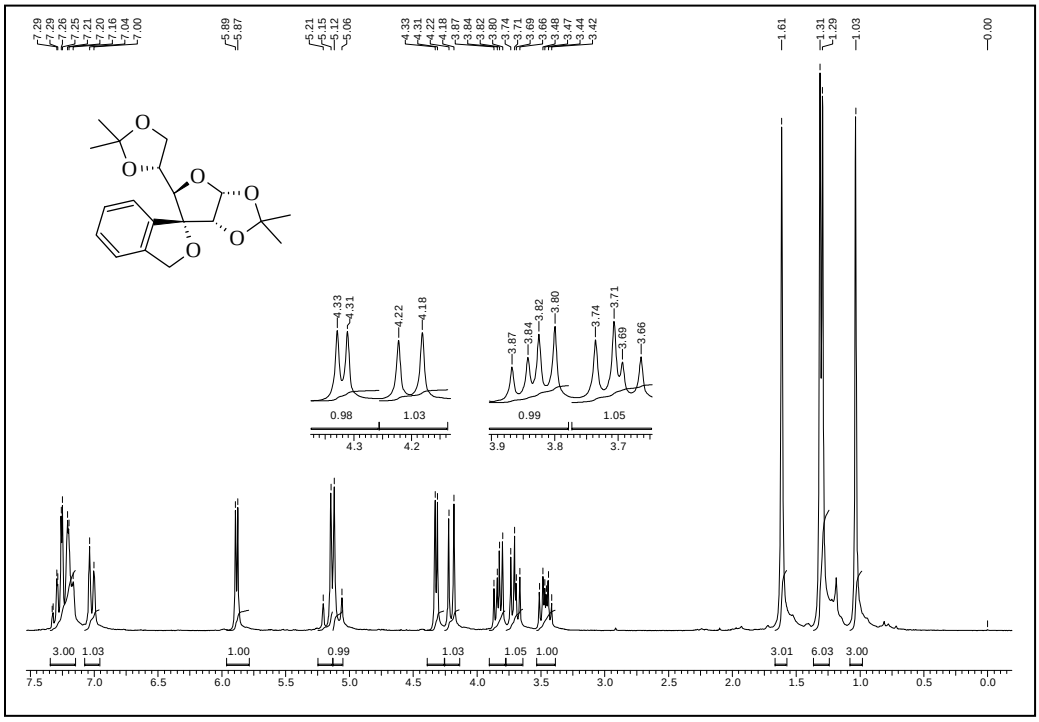
^{1}H NMR Spectrum of 2A.75 in $CDCl_3$



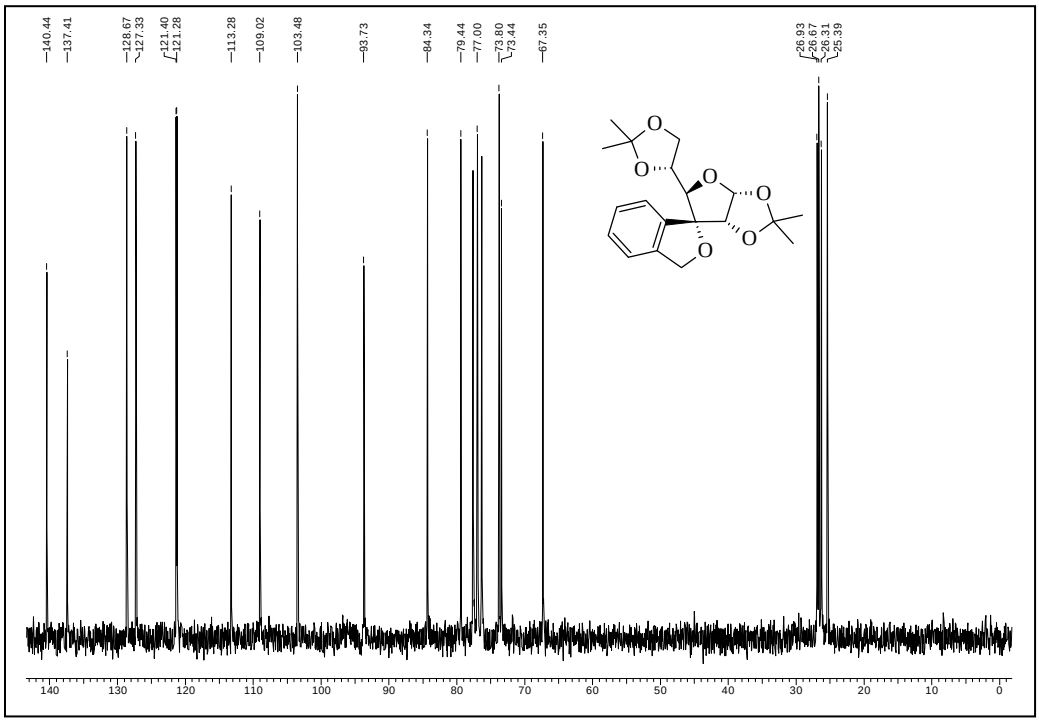
^{13}C NMR Spectrum of 2A.75 in $CDCl_3$


Sharad B S
NOESY
HO
HO
O
O
O
O
O
O
O
O
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
ppm
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
ppm

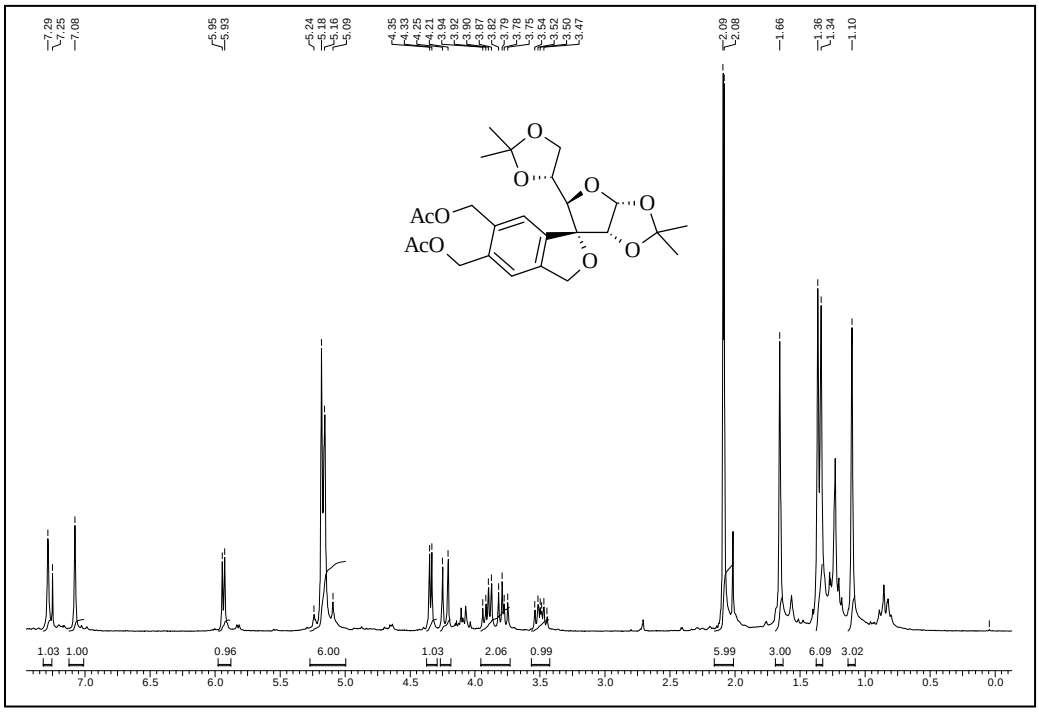

SHARAD B S
COSY
HO
HO
O
O
O
O
O
O
O
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm



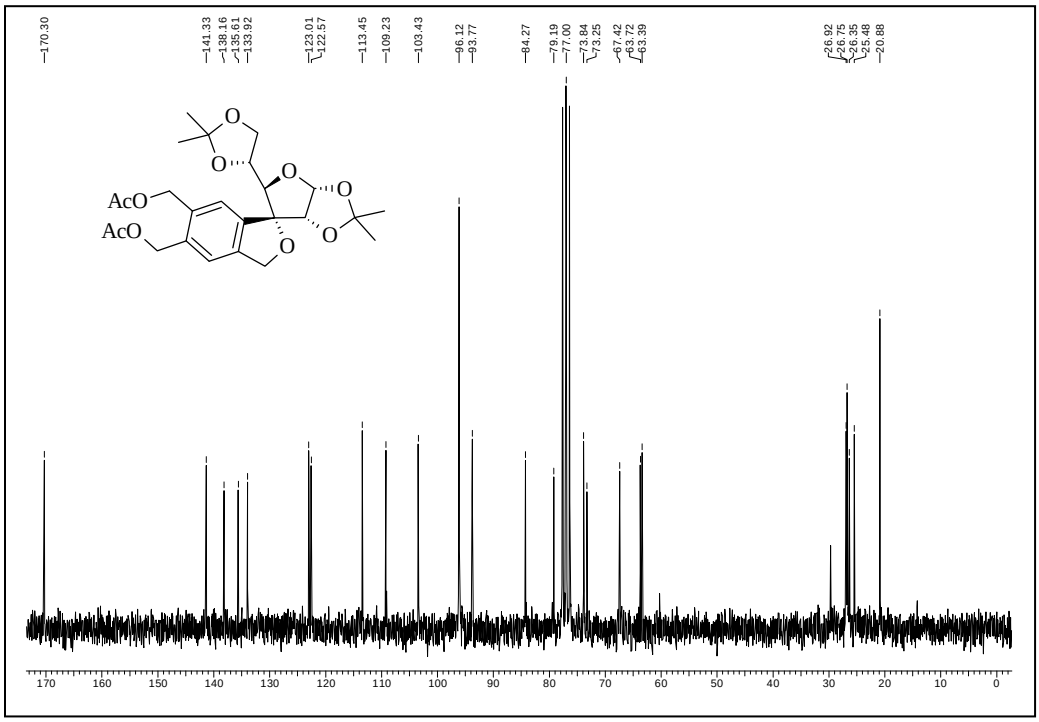
^{1}H NMR Spectrum of 2A.76 in $CDCl_3$



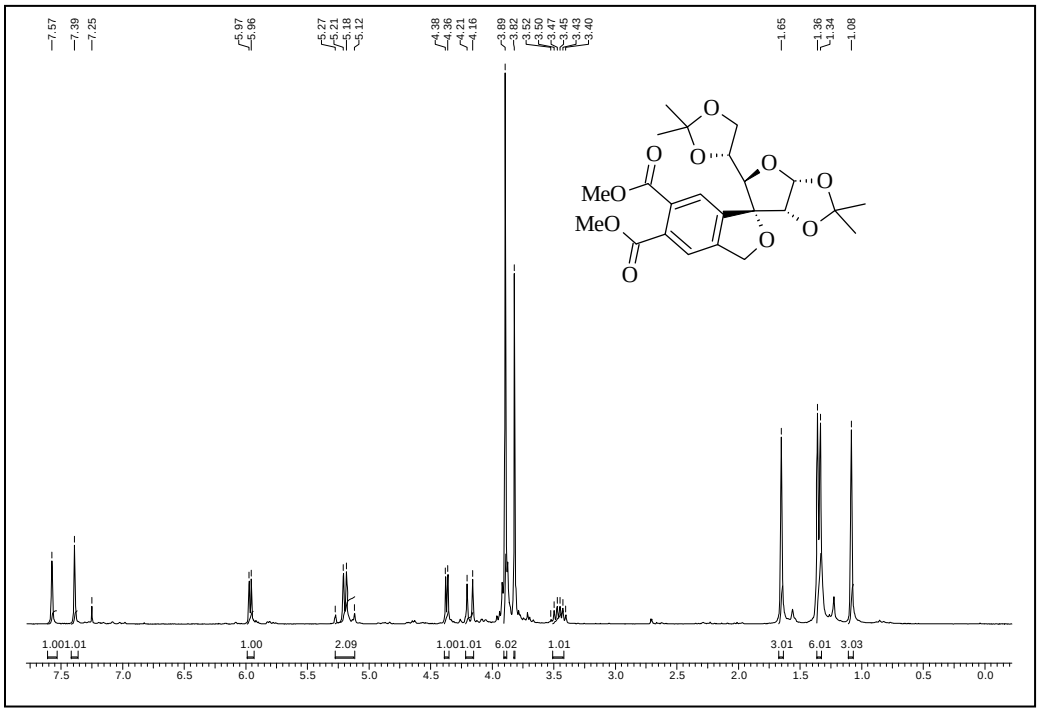
^{13}C NMR Spectrum of 2A.76 in $CDCl_3$



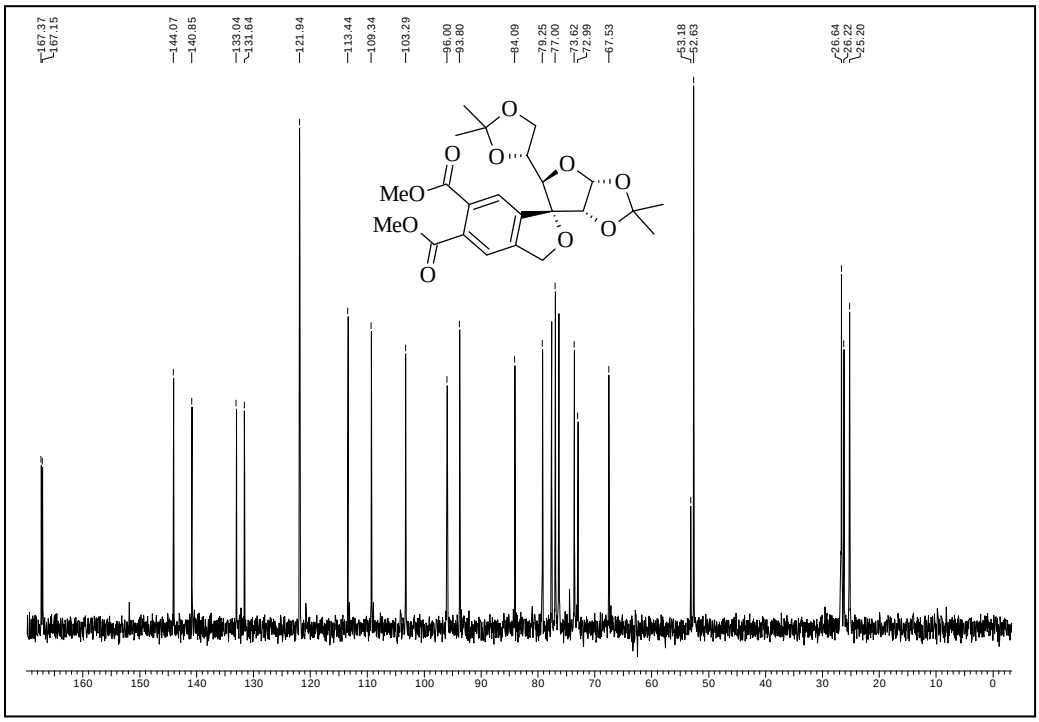
^{1}H NMR Spectrum of 2A.77 in $CDCl_3$



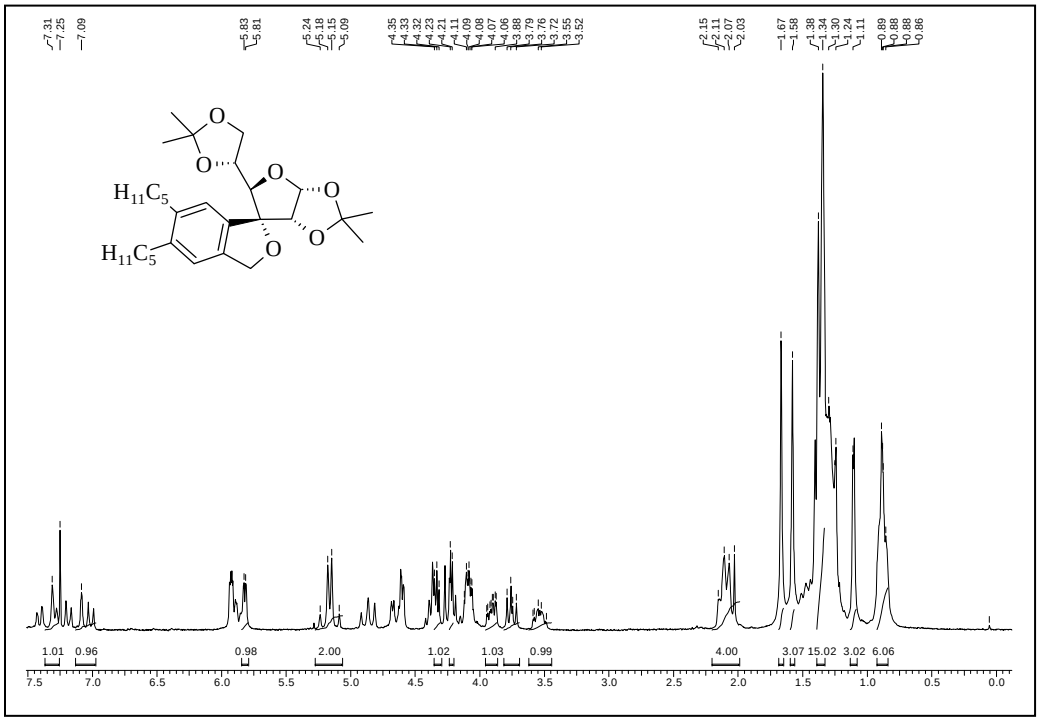
^{13}C NMR Spectrum of 2A.77 in $CDCl_3$



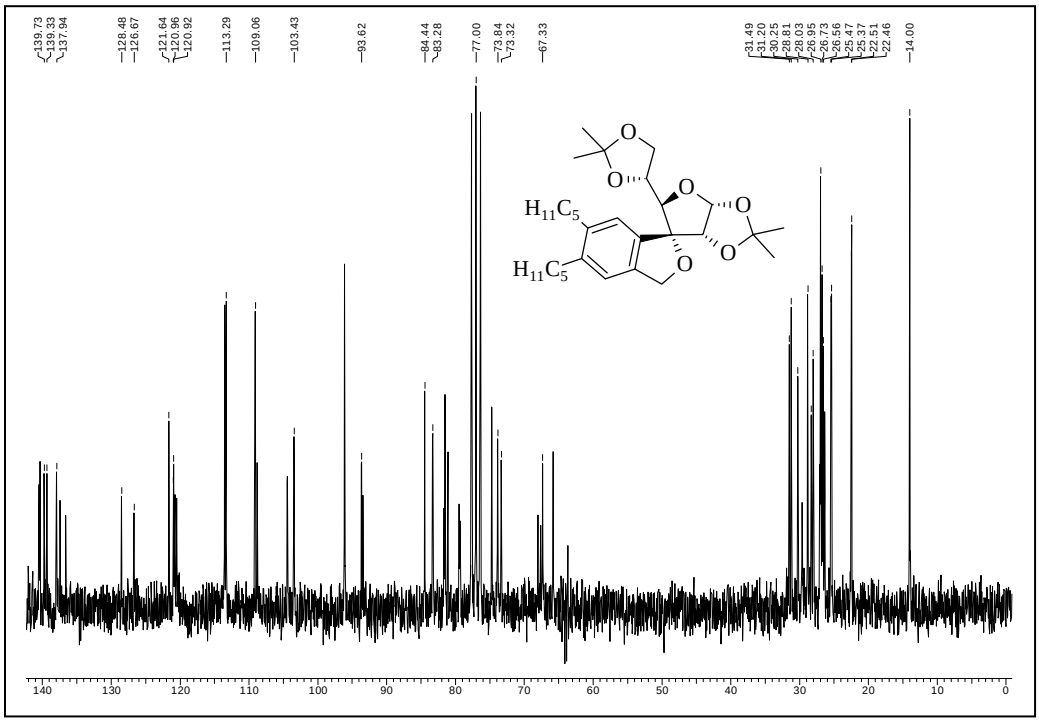
^{1}H NMR Spectrum of 2A.78 in $CDCl_3$



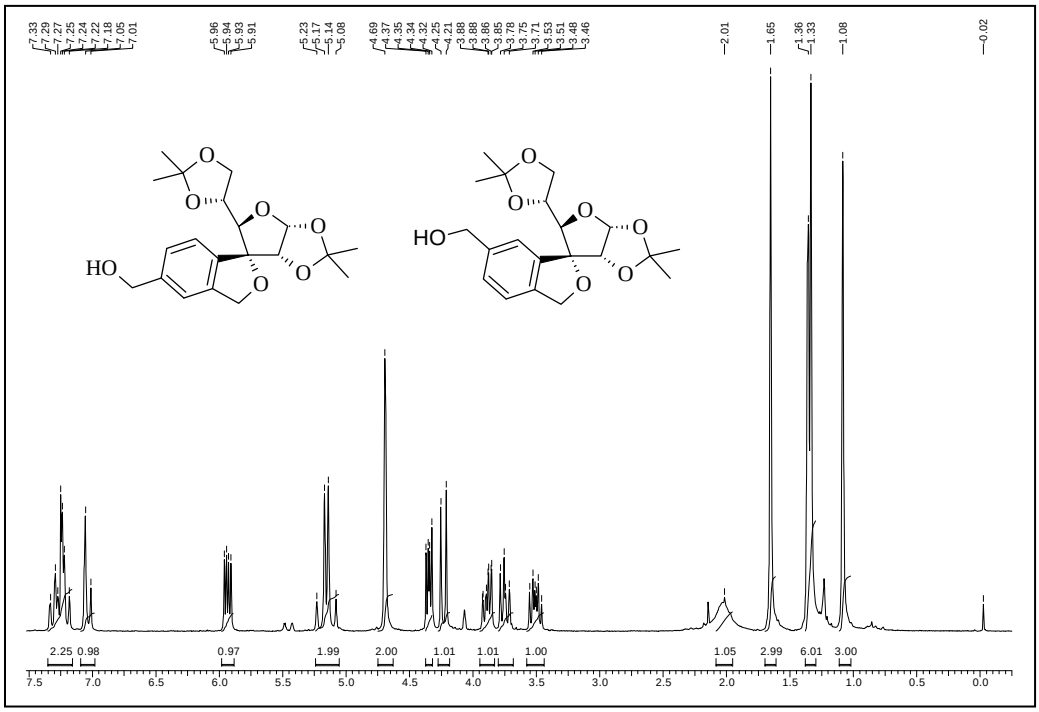
^{13}C NMR Spectrum of 2A.78 in $CDCl_3$



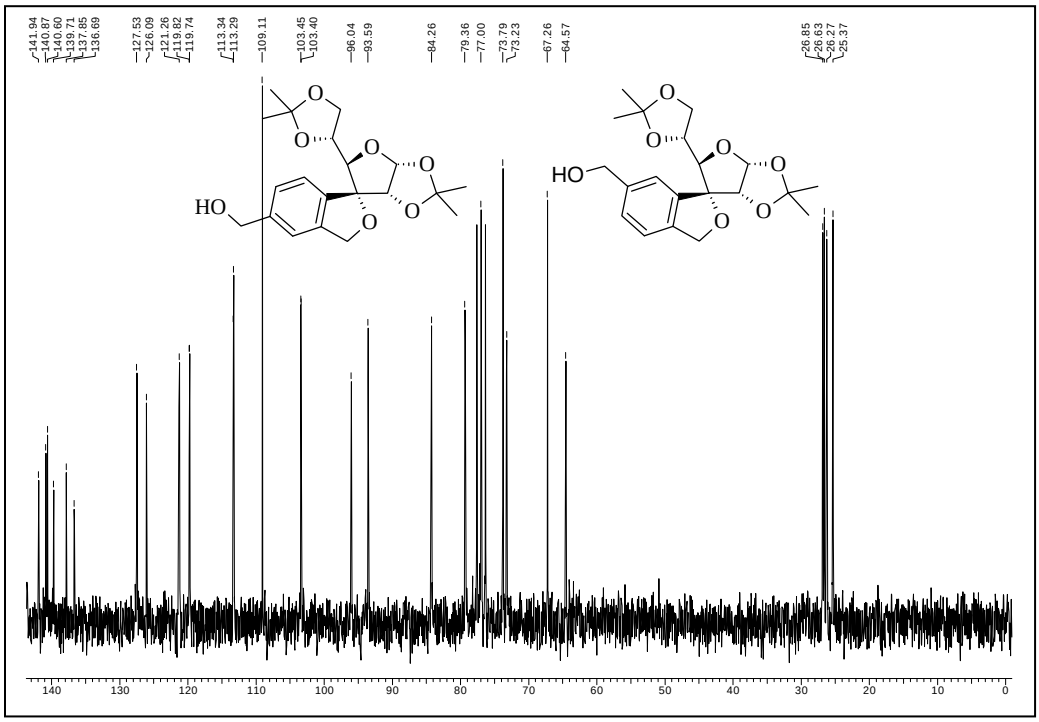
^{1}H NMR Spectrum of 2A.79 in $CDCl_3$



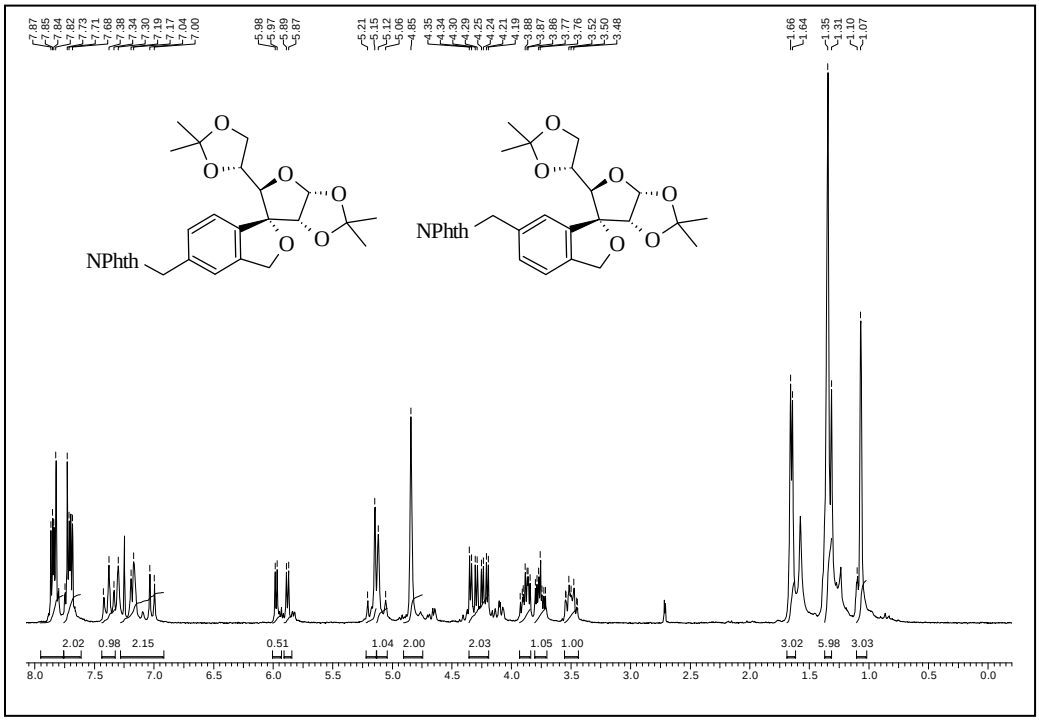
^{13}C NMR Spectrum of 2A.79 in $CDCl_3$



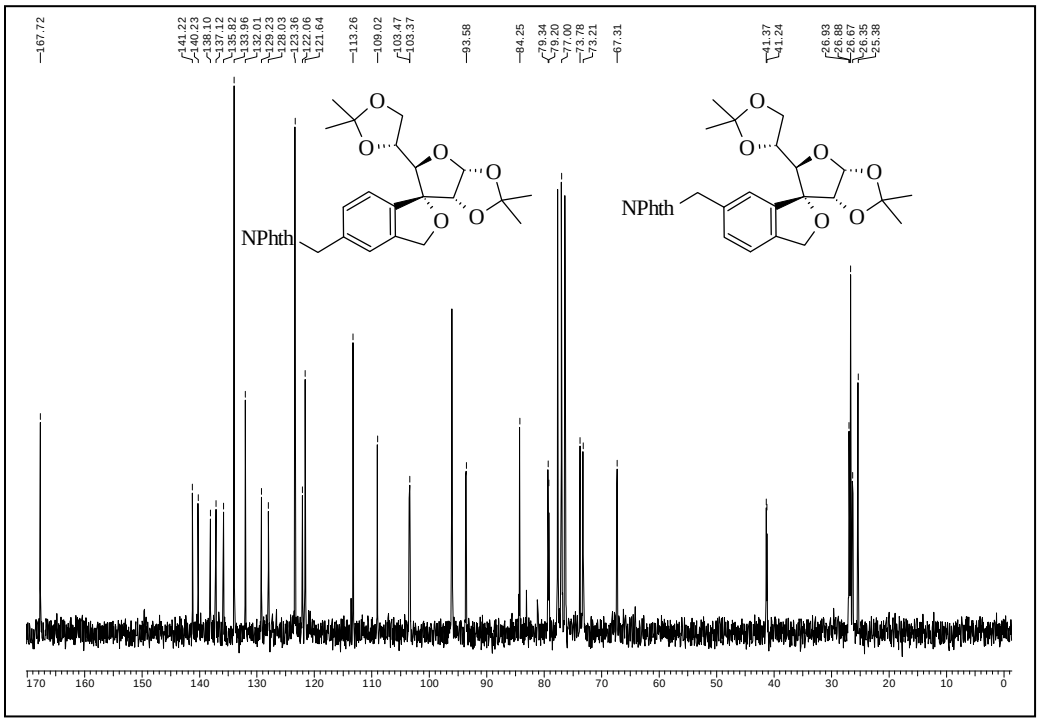
^{1}H NMR Spectrum of 2A.83a/2A.83b in $CDCl_3$



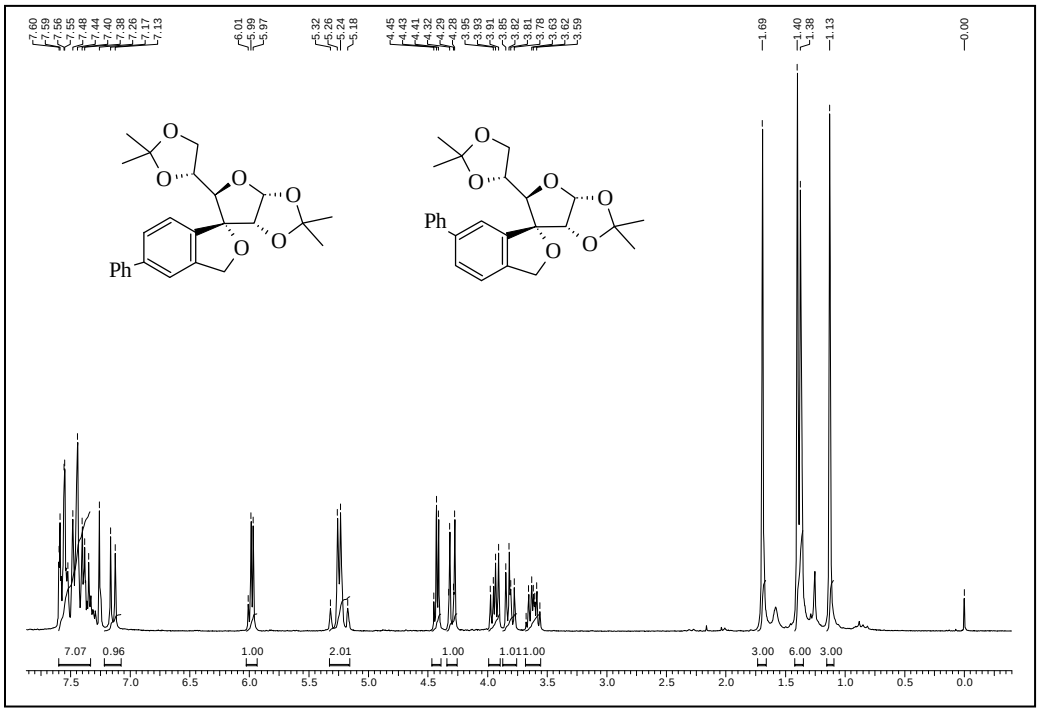
^{13}C NMR Spectrum of 2A.83a/2A.83b in $CDCl_3$



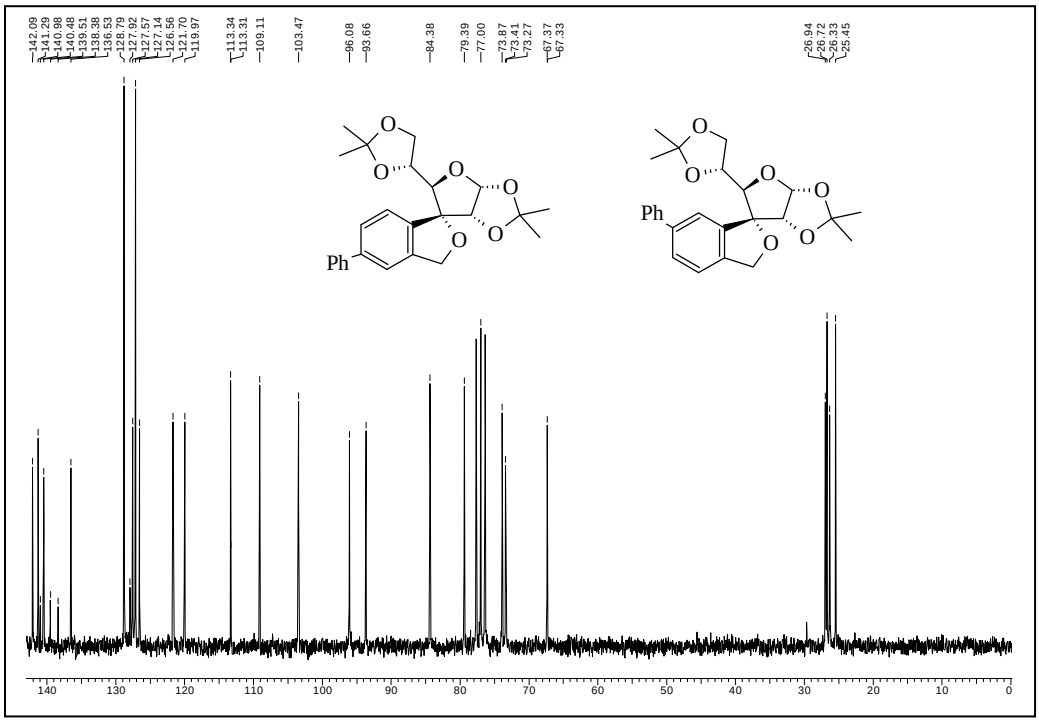
^{1}H NMR Spectrum of 2A.81a/2A.81b in $CDCl_3$



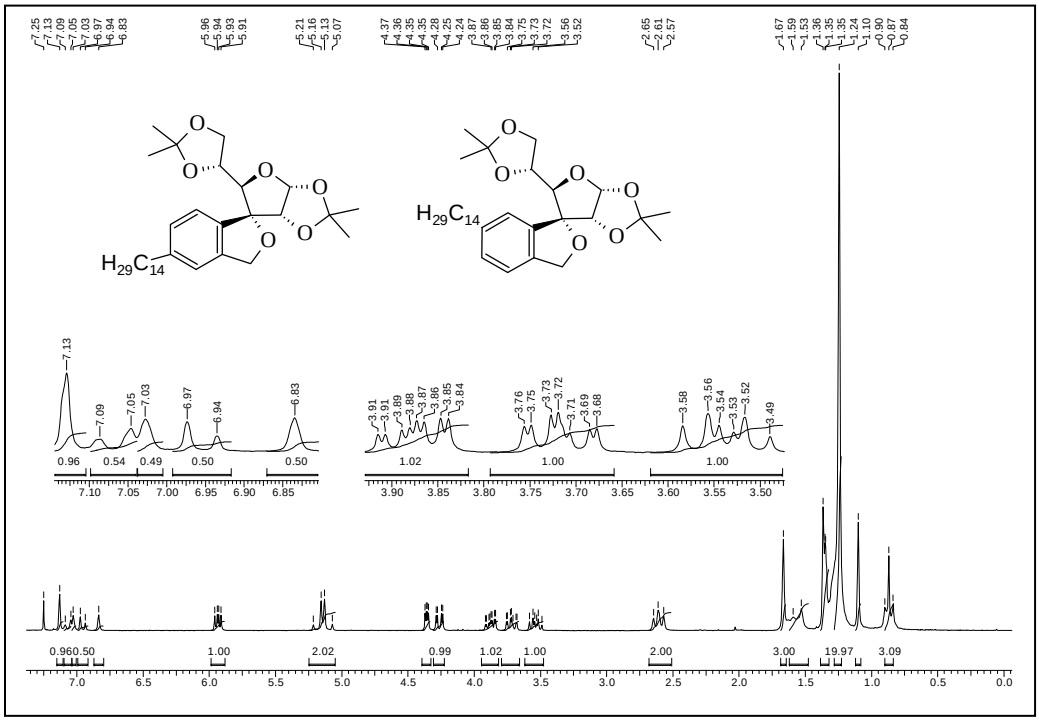
^{13}C NMR Spectrum of 2A.81a/2A.81b in $CDCl_3$



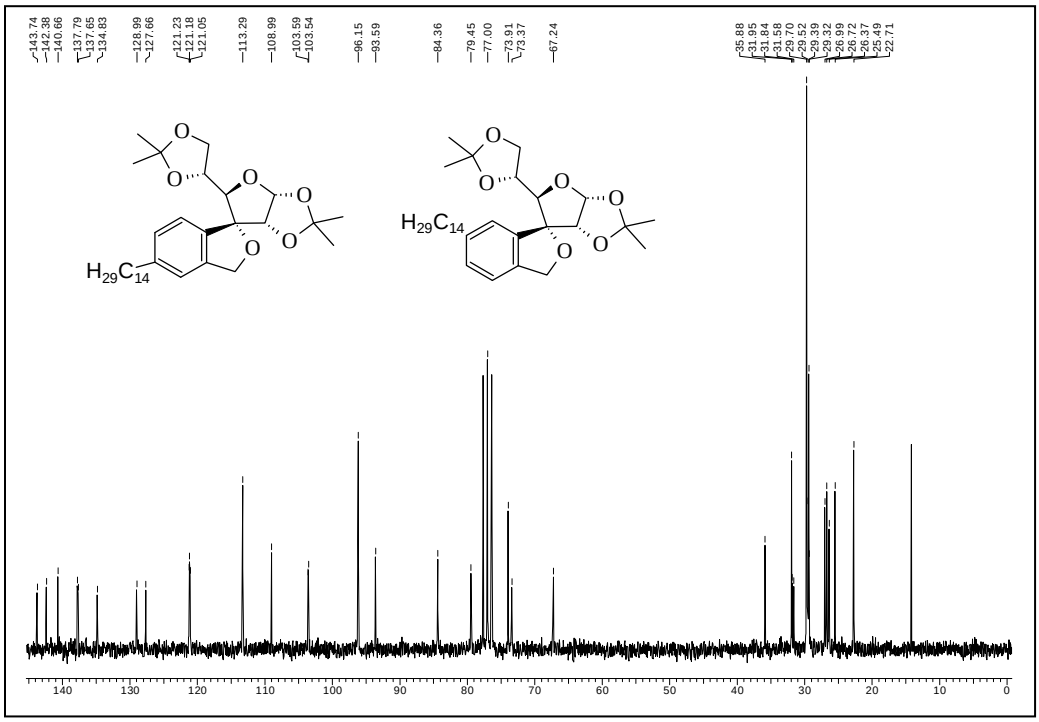
^{1}H NMR Spectrum of 2A.80a/2A.80b in $CDCl_3$



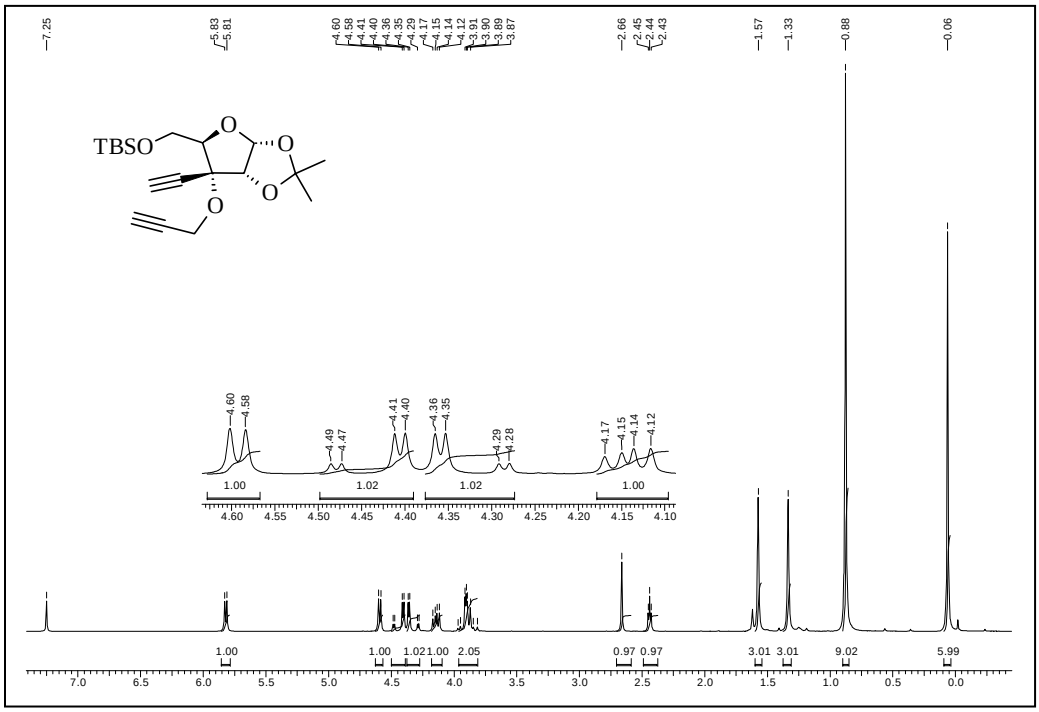
^{13}C NMR Spectrum of 2A.80a/2A.80b in $CDCl_3$



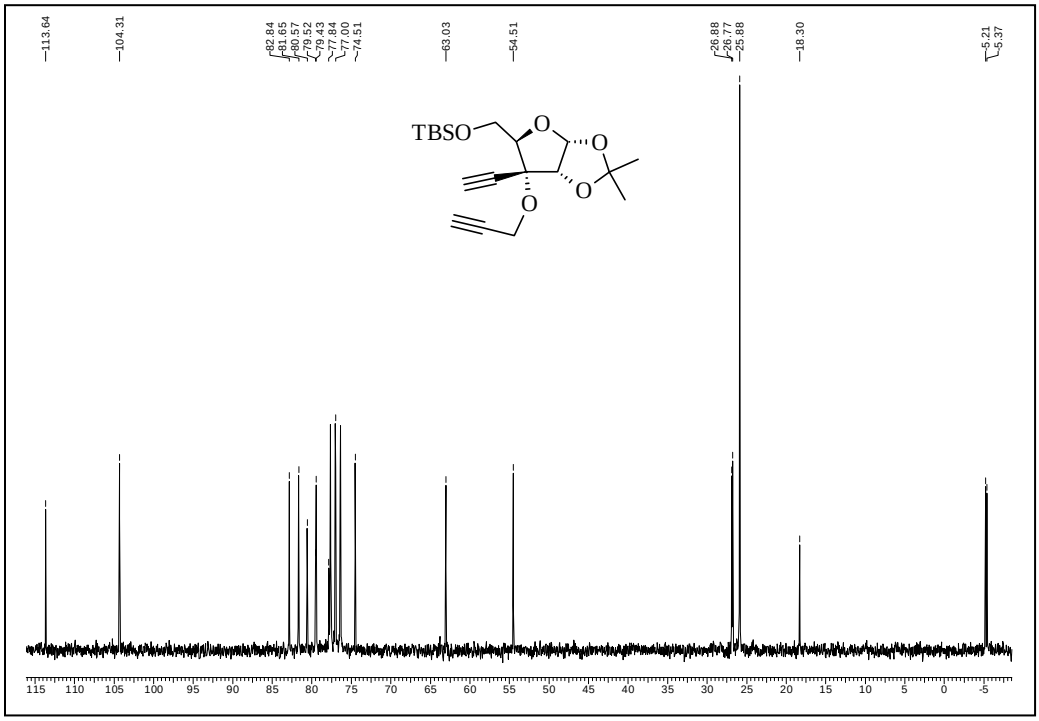
^{1}H NMR Spectrum of 2A.82a/2A.82b in $CDCl_3$



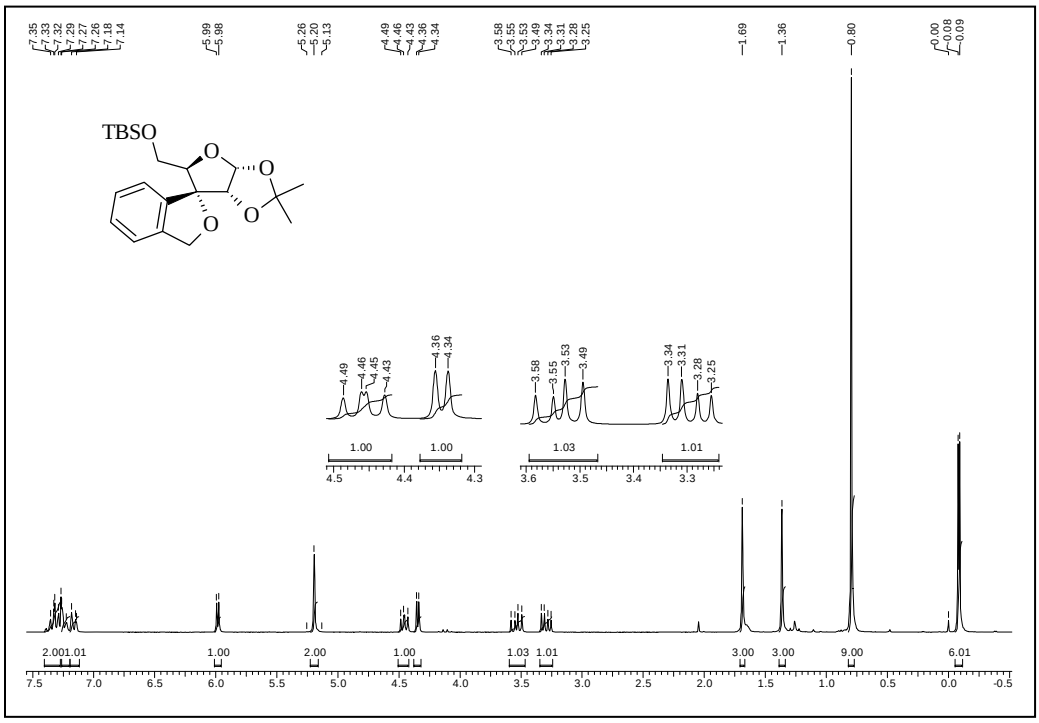
^{13}C NMR Spectrum of 2A.82a/2A.82b in $CDCl_3$



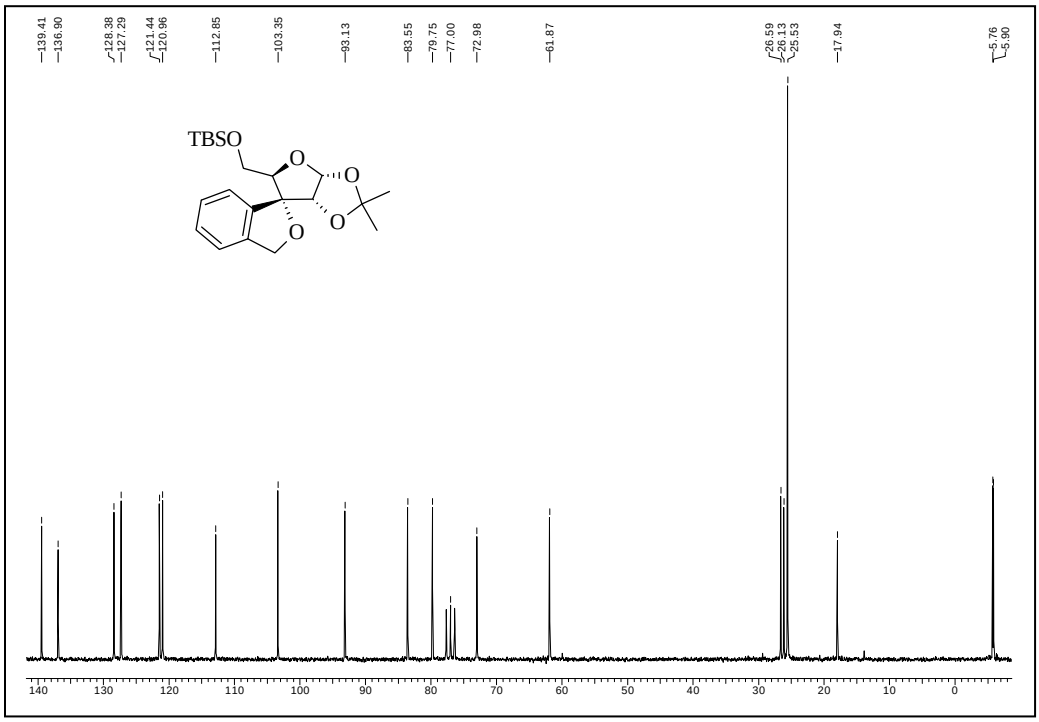
^{1}H NMR Spectrum of 2A.63 in $CDCl_3$



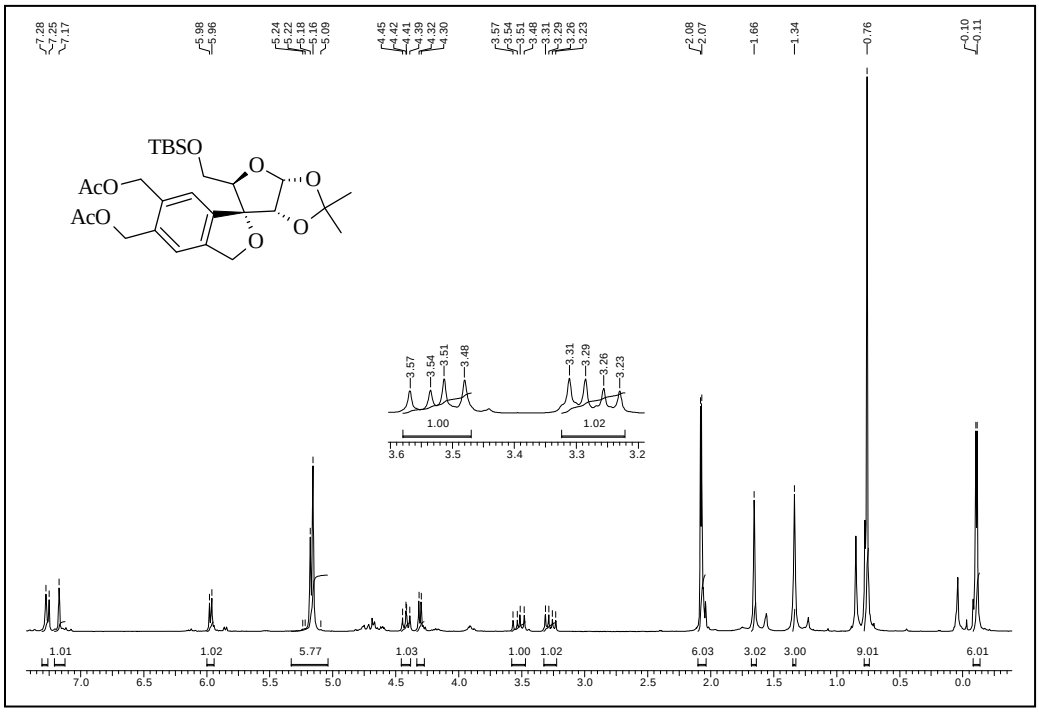
^{13}C NMR Spectrum of 2A.63 in $CDCl_3$



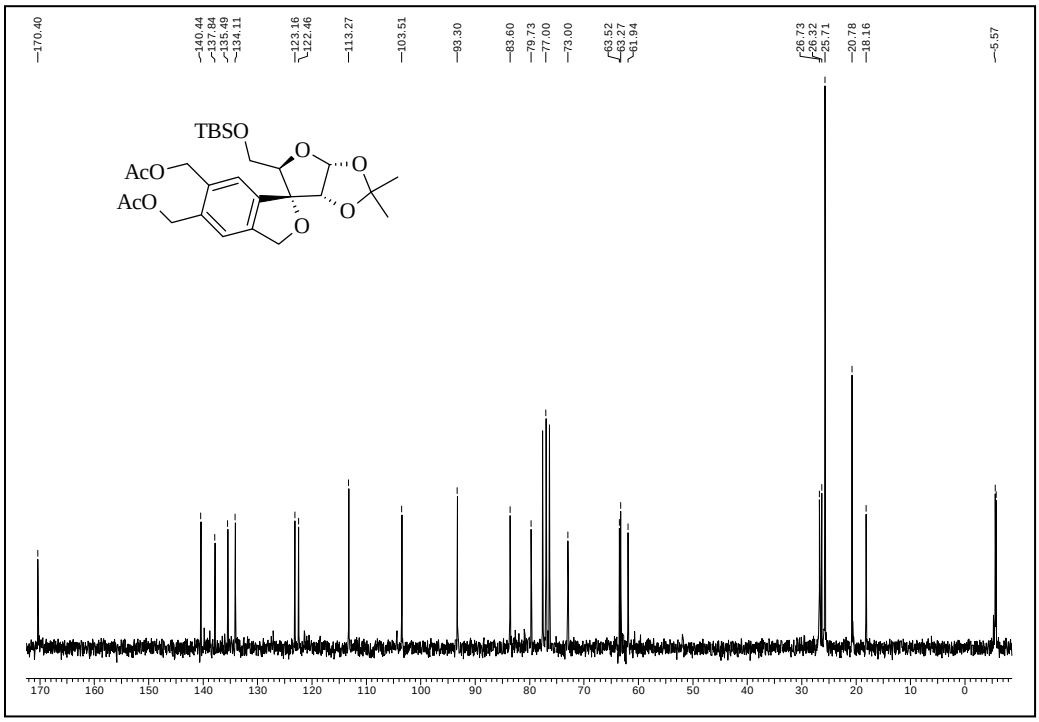
^{1}H NMR Spectrum of 2A.85 in $CDCl_3$



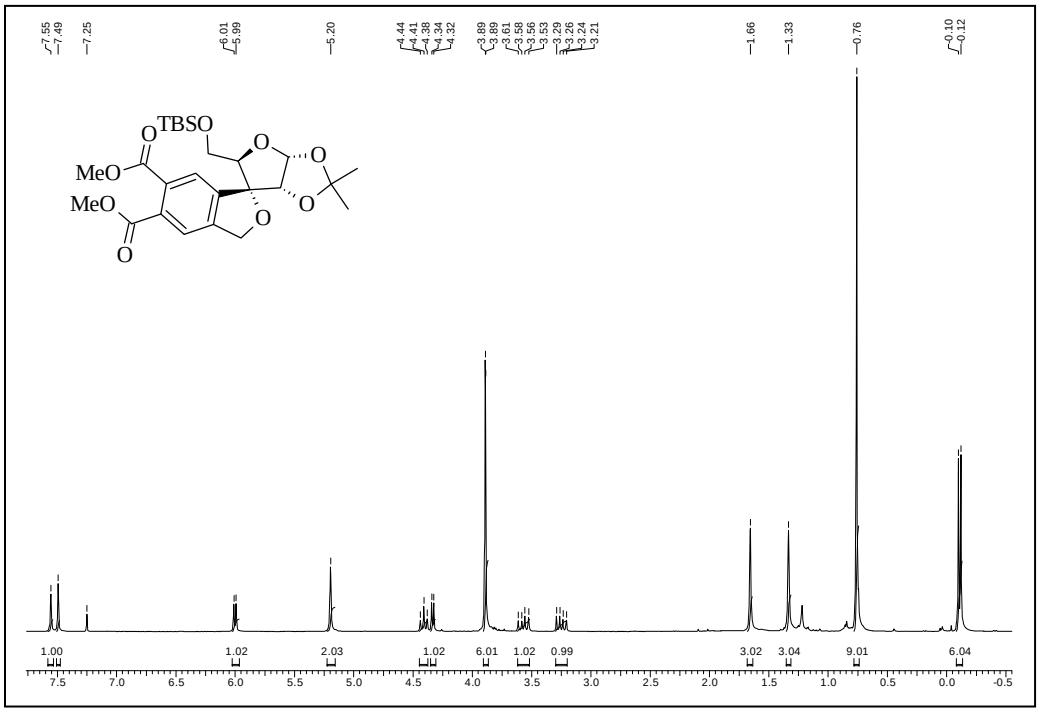
^{13}C NMR Spectrum of 2A.85 in $CDCl_3$



^{1}H NMR Spectrum of 2A.86 in $CDCl_3$



^{13}C NMR Spectrum of 2A.86 in $CDCl_3$



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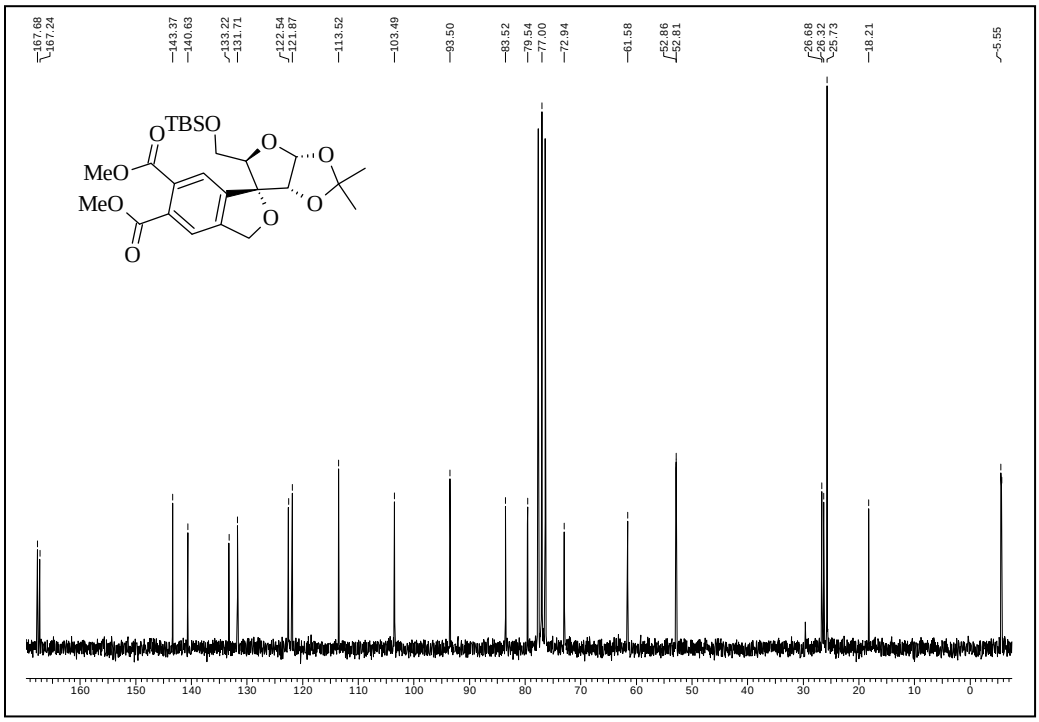
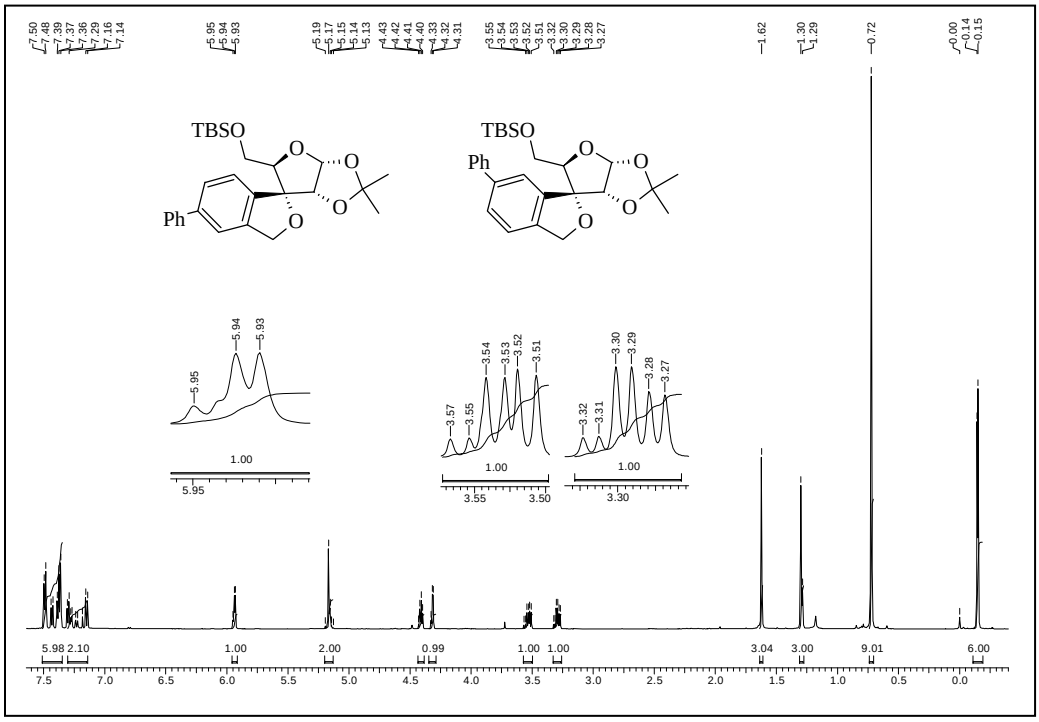


^{13}C NMR Spectrum of 2A.87 in $CDCl_3$



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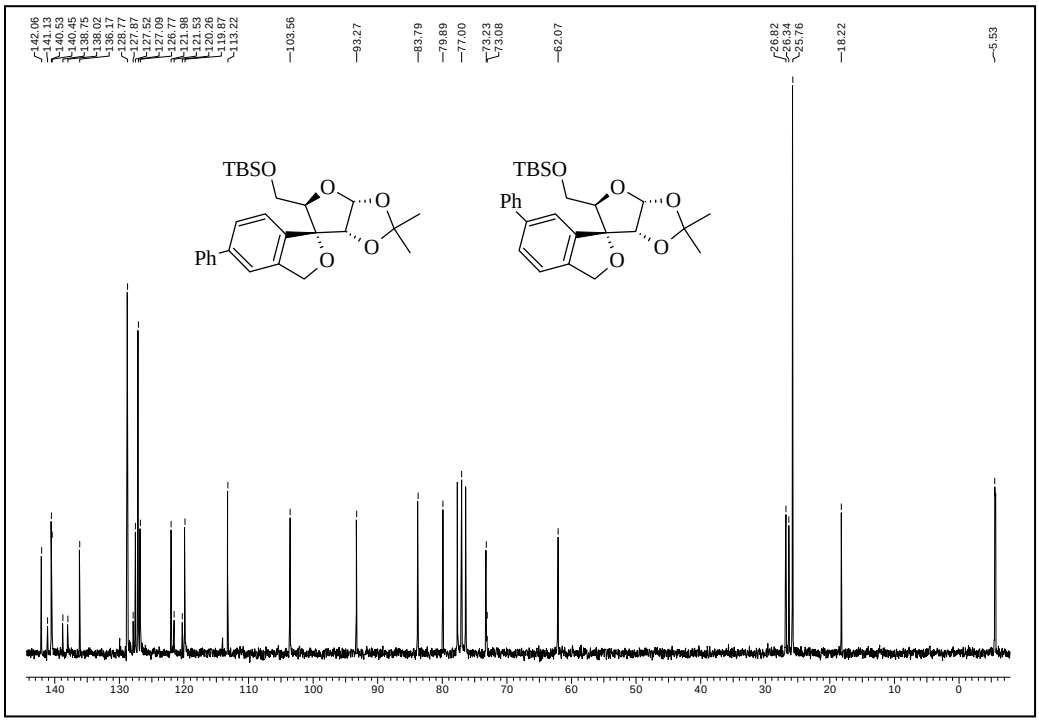
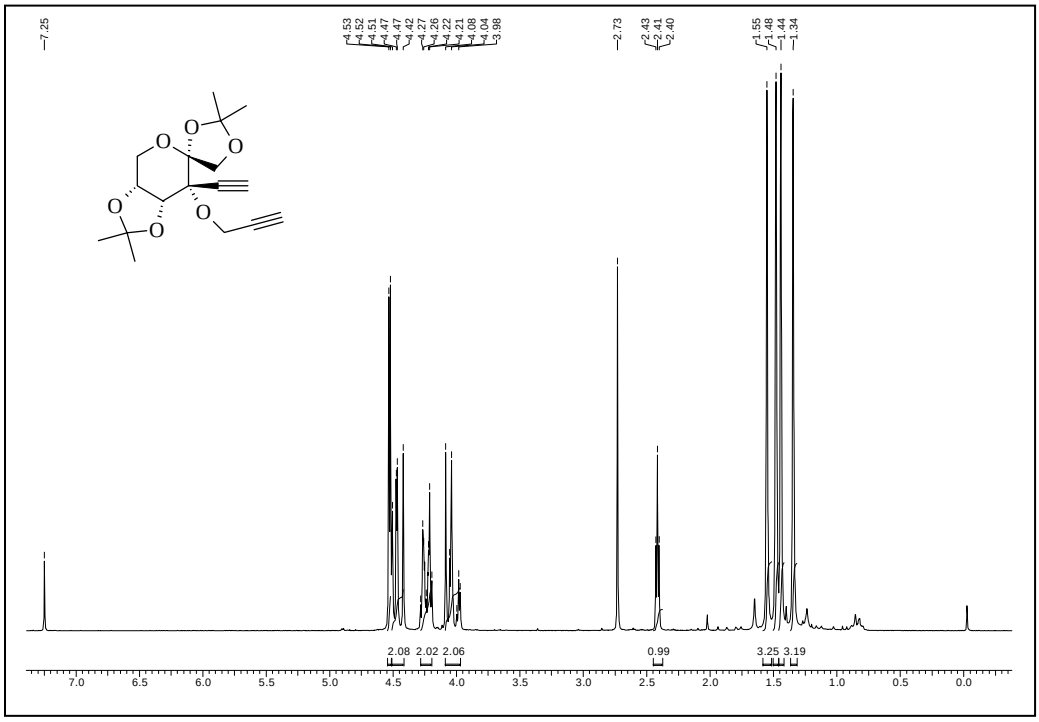


^{13}C NMR Spectrum of 2A.88a/2A.88b in $CDCl_3$



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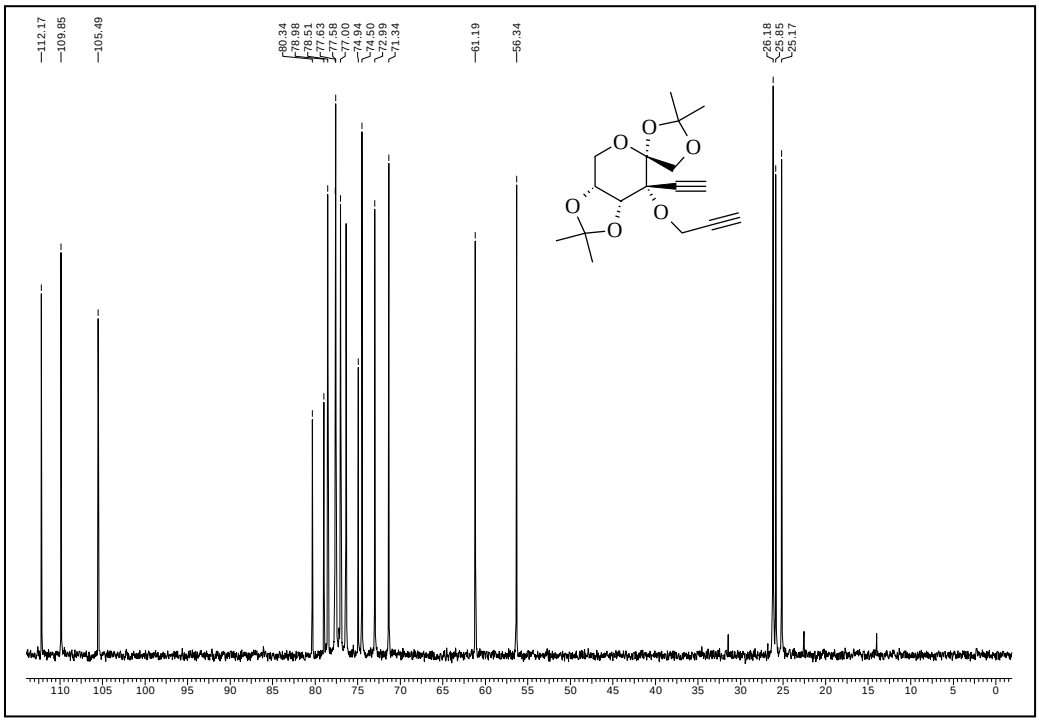

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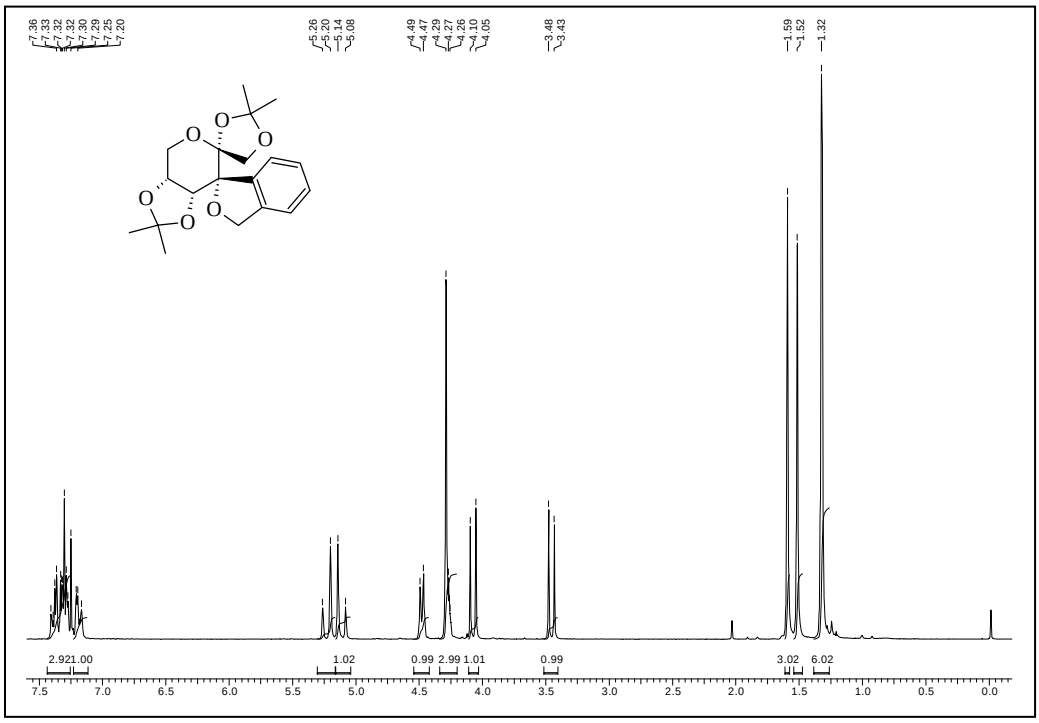

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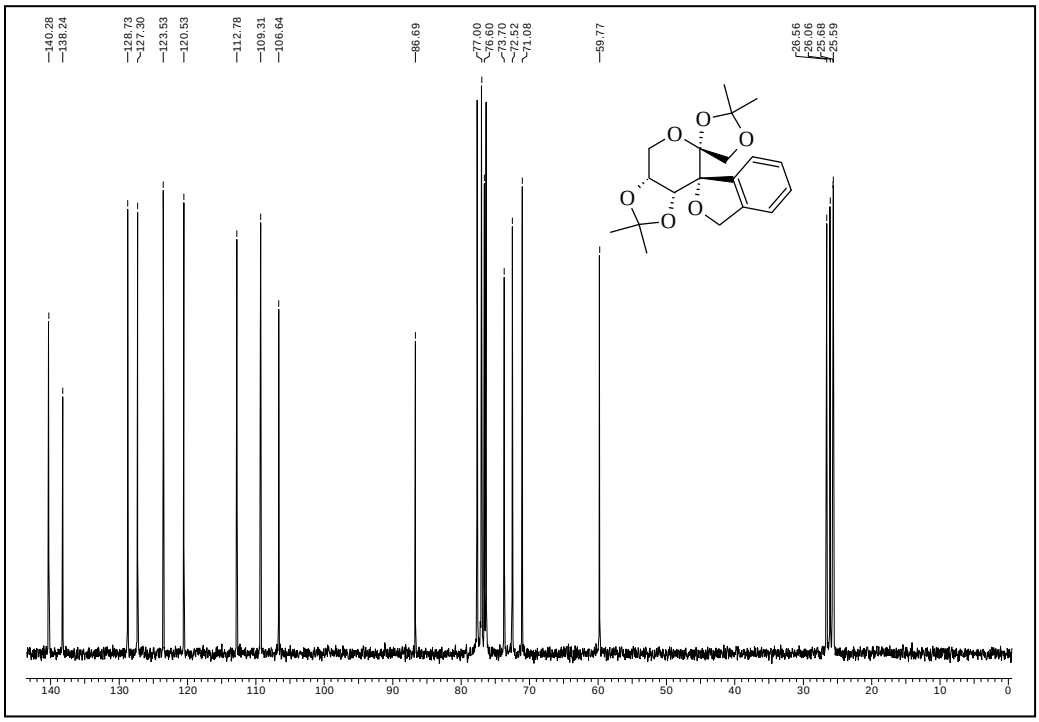

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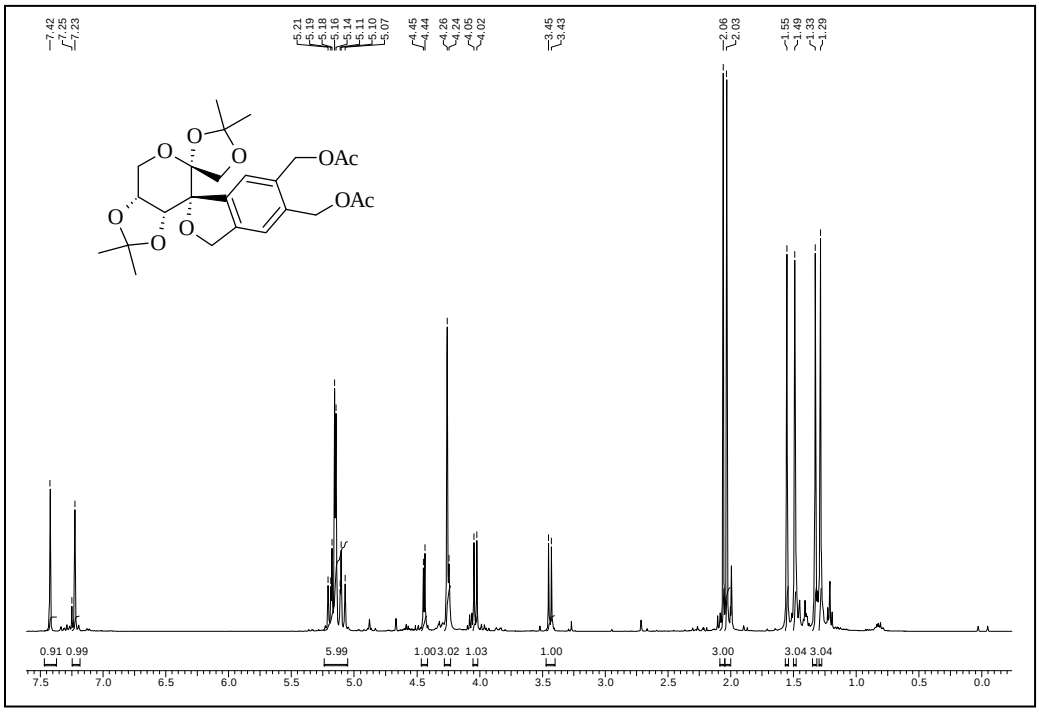

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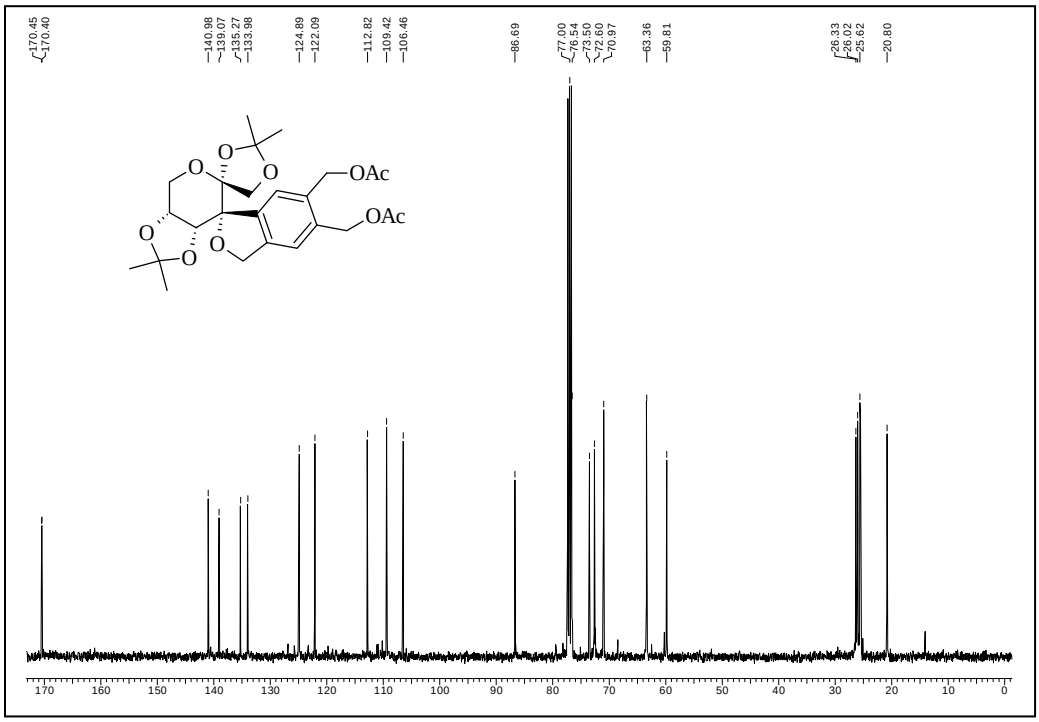

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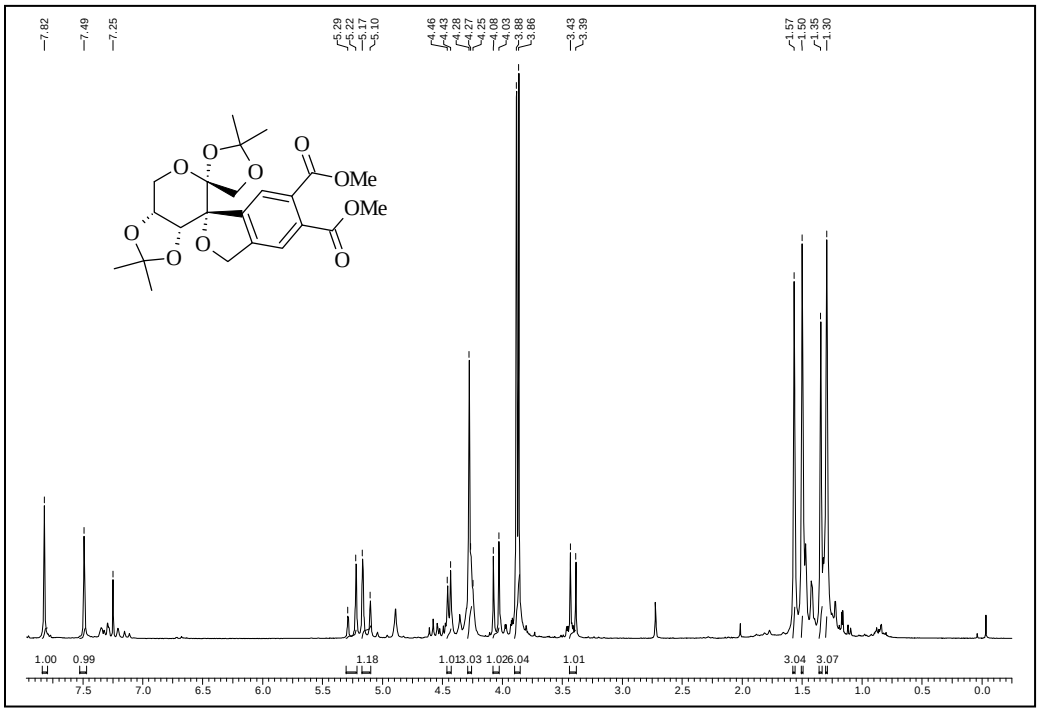

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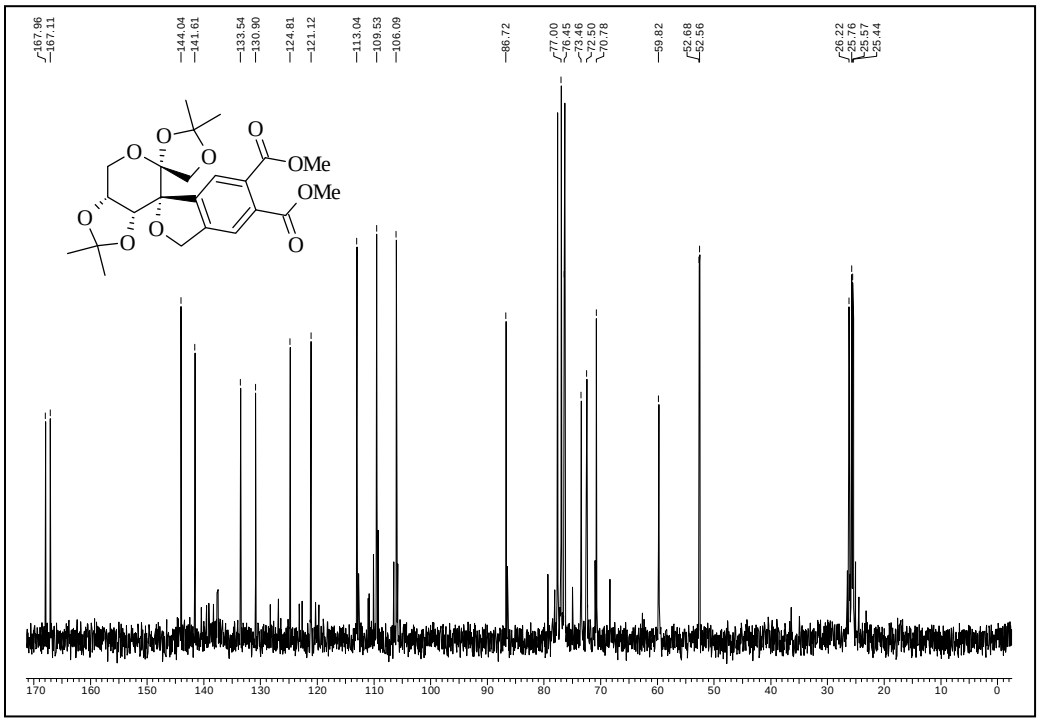

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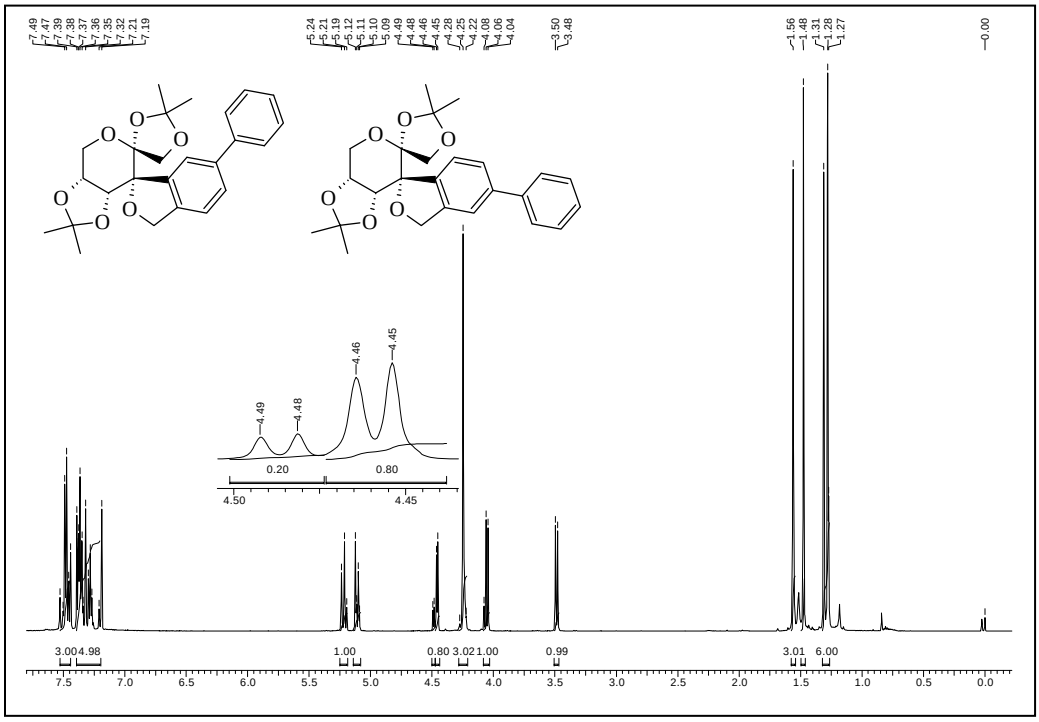
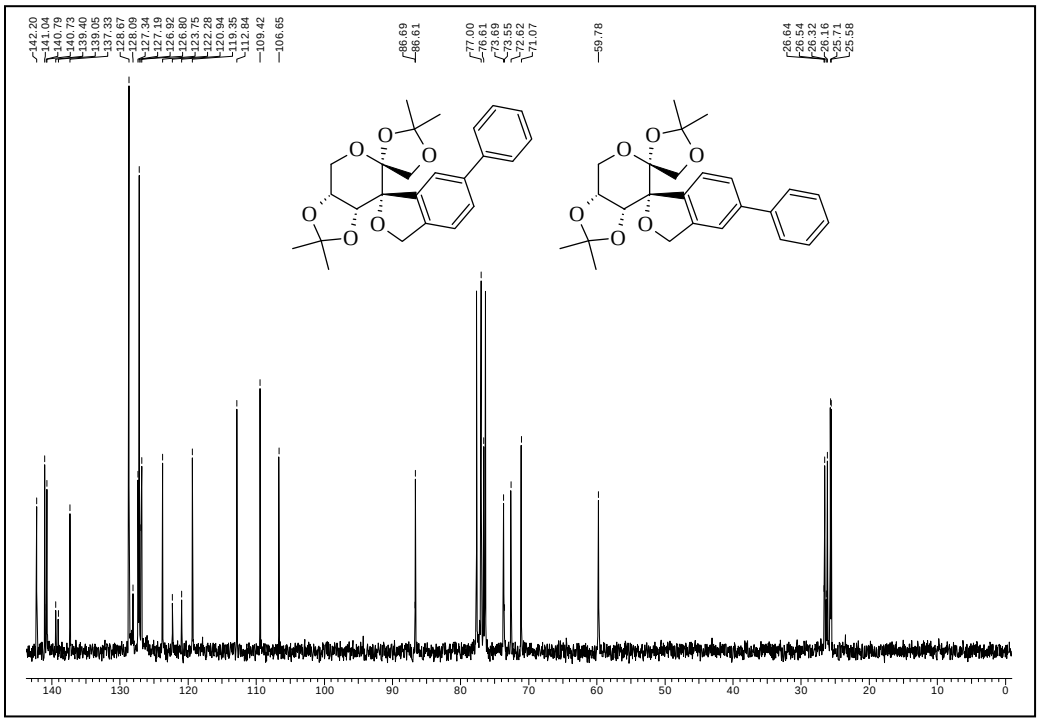


^{1}H NMR Spectrum of 2A.92a/2A.92b in $CDCl_3$



^{13}C NMR Spectrum of 2A.92a/2A.92b in $CDCl_3$

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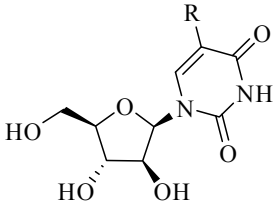
CHAPTER-II

Section II: Synthesis of modified tricyclic nucleosides

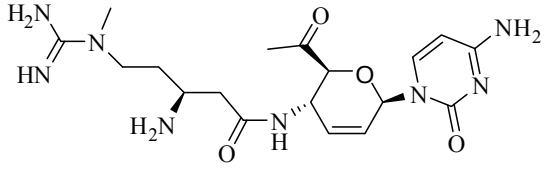
2B.1. Introduction:

Nucleosides are glycosylamines consisting of a nucleobase bonded to a ribose or deoxyribose sugar. Nucleosides can be phosphorylated by specific kinases in the cell on the sugar's primary alcohol group, producing nucleotides, which are the molecular building block of DNA and RNA. In medicine several natural nucleosides and their analogs are used as antiviral or anticancer agents.

Natural nucleosides are of great biological importance in metabolic pathways.[1] For many years, the typical structure of nucleosides was described by scientists as two molecular fragments: D-ribose or D-deoxyribose as the sugar moiety connected by a β-glycosyl linkage to different heterocyclic bases such as thymine, uracil, cytosine, adenine and guanine. This dogma disappeared when different groups reported the isolation of natural nucleosides having D-arabinose instead of the D-ribose part (Figure 2B.1). In 1950, Bergmann *et al*. reported the isolation of spongouridine **2B.01** and spongothymidine **2B.02** from marine Caribbean sponges *Cryptotheca crypta*, which had D-arabinose as the sugar moiety.[2] In 1958, Y. Yonehara *et al*. reported the discovery of a metabolite of Streptomyces griseochromogenes, Blasticidin S (**2B.03**),[3] which controls rice blast Pyricularia oryzae.[4] In 1978, K. Suetomi *et al*. reported the isolation of antifungal mildiomycin from a culture of Streptoverticillium rimofaciens.[5]



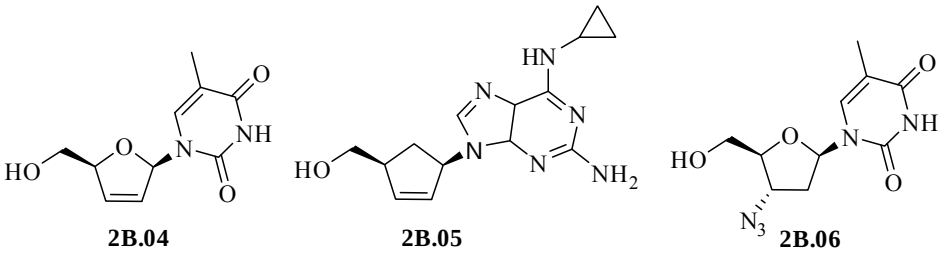
2B.01 R = H
2B.02 R = CH_3



2B.03

Figure 2B.1: Natural nucleosides having other than *ribo* sugar part

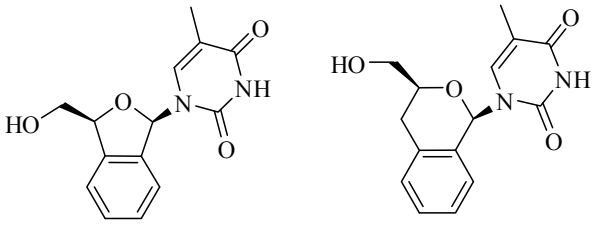
These discoveries led to a large number of nucleoside analogues that were tested for the treatment of viral diseases.[6] Among the US FDA approved compounds used in the treatment of acquired immunodeficiency syndrome (AIDS), the 2',3'-didehydro-3'-deoxythymidine d4T (**2B.04**),[7–9] the carbocyclic 2-amino-6-cyclopropylaminopurine analogue abacavir (**2B.05**)[10,11] and AZT (**2B.06**) and showed potent anti-human immunodeficiency virus (HIV) activity (Figure. 2B.2).



2B.04 **2B.05** **2B.06**

Figure 2B.02: Stavudine **2B.04**, abacavir **2B.05** and AZT **2B.06**

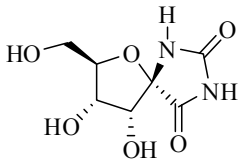
However, side effects and drug-resistant variants remained a problem with these antiviral agents.[12–14] Moreover, the introduction of the 2',3'-double bond in compound **2B.04** resulted in an increased lipophilicity compared to the corresponding natural and saturated 2',3'-dideoxynucleoside series but decreased the chemical stability in acidic medium. In the course of the search for new antiviral agents with a higher therapeutic index, the obvious emphasis was on the design of drugs with potent activity, high stability, low cytotoxicity and minimal side effects. Christophe Len and co-workers reported the synthesis of pyrimidine nucleoside analogues of d4T based on the 1,3-dihydrobenzo[c]furan core **2B.07** (Figure 2B.3).[15,16] This class of nucleoside with a modified glycon part was attractive because: (i) it retained the phosphorylation site; (ii) the presence of the benzene ring as electron-withdrawing group stabilized the glycosidic bond compared to the olefinic analogue: 2',3'-didehydro-2',3'-dideoxynucleoside; (iii) the introduction of the aromatic residue increased the lipophilicity compared to d4T.[17] In an attempt to expand the variety of nucleoside antiviral drugs, a novel range of unsaturated nucleoside analogues of d4T **2B.08** were synthesized to explore their potential as antiviral drugs.



2B.07 **2B.08**

Figure 2B.3: Isobenzofuran and isochroman derivatives **2B.07** and **2B.08**

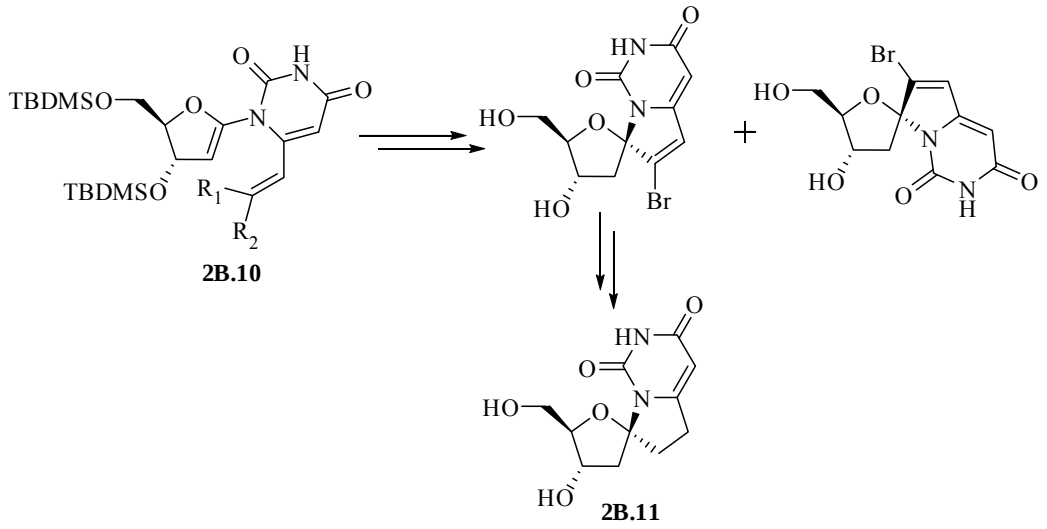
The synthesis of structurally modified nucleosides has been emerging as an important area of research because some members show biological activities of medicinal interest.[18] The term spironucleoside was introduced in 1990 to designate a class of spiranic sugar derivatives in which the anomeric carbon belongs to both the sugar ring and to a heterocyclic base. Data on this type of compound were reported before 1990, but only recently the term spironucleoside has been used. Of the different classes of nucleosides, the spironucleosides are probably the least well known. However, the isolation from *Streptomyces hygroscopicus*, in 1991, of (+)-hydantocidin,[19] (**2B.09**) the first natural spironucleoside, and later the discovery of its potent herbicidal and regulatory plant growth activities[20] and its low mammalian toxicity, have resulted in great interest in the chemistry of spironucleosides (Figure 2B.4). Since then, there have been notable contributions from Miyasaka's and Paquette's groups in addition to others, to synthesize C(1')-spiro-, C(2')-spiro-, C(3')-spiro- and C(4')-spironucleoside derivatives as conformationally restricted analogues.



2B.09

Figure 2B.4: Naturally occurring spironucleoside hydantocidin

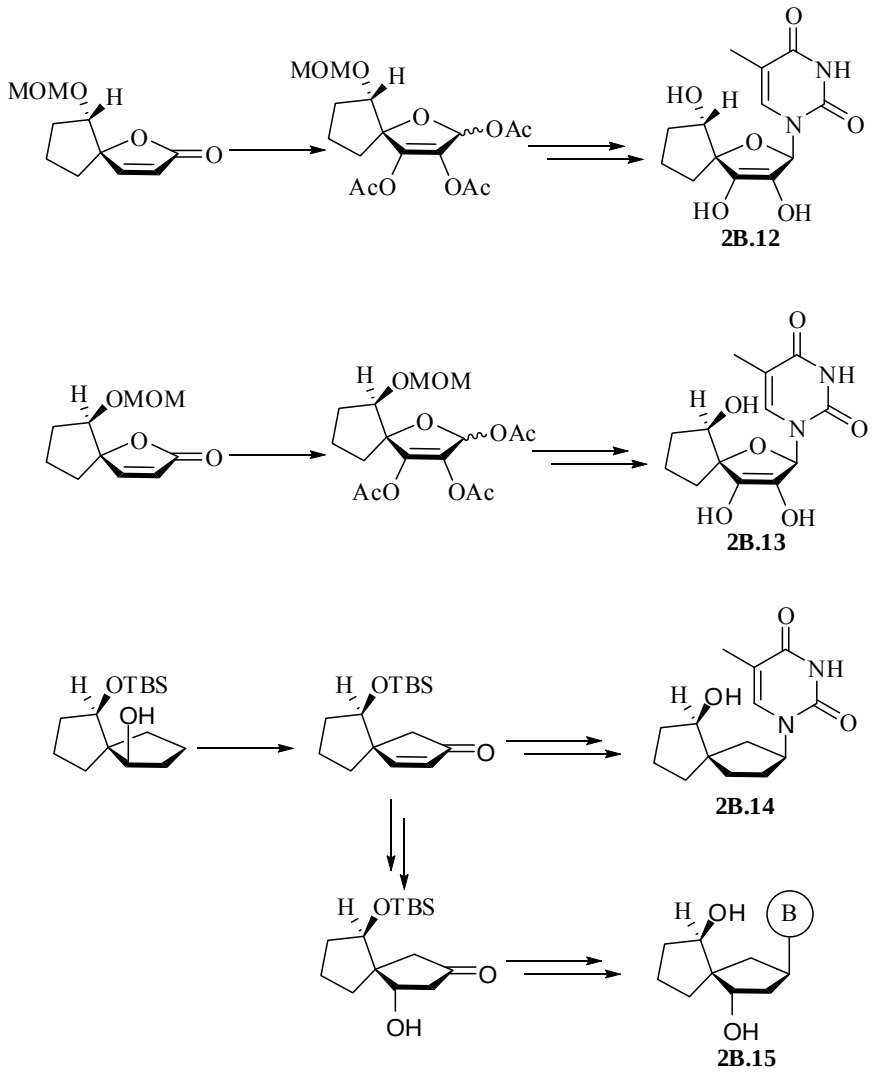
The isolation of hydantocidin **2B.09** stimulated the synthesis of anomeric spiro nucleosides. Hiromichi Tanaka[21] prepared 6-bromovinyl derivatives of 1-(2-deoxy-D-erythro-pent-1-enofuranosyl)uracils **2B.10** and developed new method for the synthesis of anomeric spiro nucleosides **2B.11** by vinyl radical-mediated reactions (Scheme 2B.1). Later, various groups have synthesized anomeric spiro nucleosides by using radical intermediate cyclizations.[22]



Scheme 2B.1: Synthesis of anomeric spironucleosides

To impart some degree of conformational restriction to the natural nucleosides, several possibilities have been suggested. These include (i) synthesis of locked bicyclic and tricyclic nucleoside analogues by inserting an extra ring fused to the furanose moiety, (ii) synthesis of spironucleosides and (iii) synthesis of nucleosides of varied ring structures. Mainly researchers have reported the synthesis of fused bicyclic, tricyclic nucleosides and C(4')- spiroannulated nucleosides, but the synthesis of C(3')- spiroannulated nucleosides has attempted only by Nielsen and co-workers in 1996.[23] We have therefore taken up a project to synthesize new classes of tricyclic nucleosides containing isochroman annulated unit and *C*-(3') spiroannulated nucleosides.

Paquette and co-workers developed spirocyclic nucleosides with different modifications on sugar ring. In 2001 he reported the synthesis of *syn*- and *anti*-oxaspiro[4.4]nonalyl mimics (**2B.12**),[24] (**2B.13**)[25] respectively and later in a couple of years he made their carbocyclic analogues (**2B.14**),[26] (**2B.15**)[27] (Scheme 2B.2).



Scheme 2B.2: Synthesis of *syn*-, *anti*-oxaspiro[4.4]nonalyl mimic and carbaspironucleosides.

Recently, attention has turned towards the synthesis of C(4')-spiroalkylated nucleosides having sulfur and nitrogen incorporated. The rapidity with which 2',3'-dideoxy-3'-thiacytidine was adopted for clinical use in the treatment of AIDS,[28] and the high-level antiviral and anticancer potency of several sulfur mimics having the heteroatom at the apex position[29] has ignited research in this area from several directions. Paquette's and Mandal's groups reported new sulfur containing derivatives of spironucleosides (Figure 2B.5).

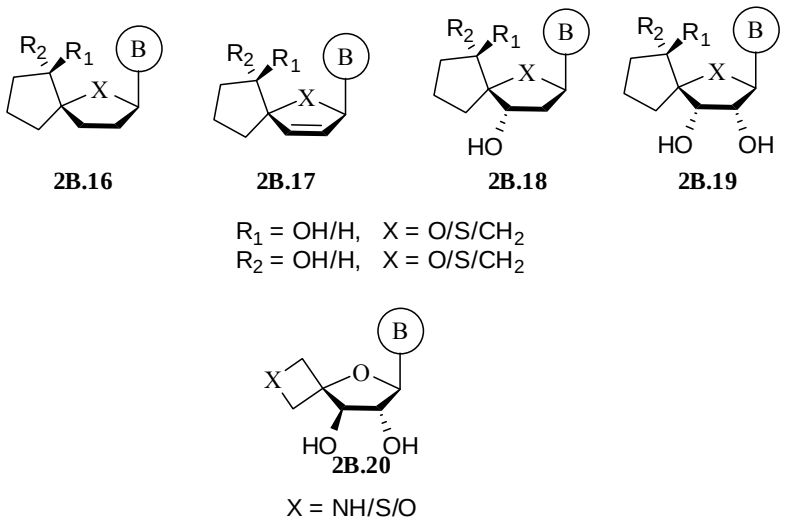


Figure 2B.5: Some structurally unique spironucleosides

Jesper Wangel and co-workers in 2003 first time reported the synthesis of bicyclic C(2')- spiro ribo and arabinonucleosides via C(2')- allyl nucleosides as key intermediates.[30] As per our knowledge, except Nielsen in 1996, no report is available towards the synthesis of C(3')- spiro nucleosides. An attempt to expand the variety of nucleoside as an antiviral drugs, a novel range of unsaturated, conformationally restricted, tricyclic nucleosides containing isochroman unit and C(3')-spironucleosides containing dihydroisobenzofuran system were synthesized to explore their potential as antiviral drugs.

2B.2. Present Work:

We have standardized the [2+2+2]-cyclotrimerization reaction on sugar derived dialkynes to synthesize enantiopure isochromans and spiroannulated dihydroisobenzofurans. As reported (in section 1, Scheme 2A.16, table 2A.1, entry 1) tricyclic compounds **2B.21** having *xylo*-configuration was synthesized by applying cyclotrimerization reaction on diyne **2B.23** and acetylene in sealed tube at 80 °C in 4 to 5 hours. The spirocyclic compound **2B.22** was synthesized under similar reaction conditions from diyne **2B.24** (Scheme 2B.3).

Considering the importance of the modified nucleosides in the area of anti-viral and anti-cancer drug discovery programs and as a part of our program to provide flexible methods for the synthesis of biologically active small molecules, we have identified that cyclotrimerization on sugar templates and glycosidation could be combined effectively to address the synthesis of either conformationally restricted or spiroannulated nucleosides libraries rapidly. Figure 2B.6 describes our intended approach.

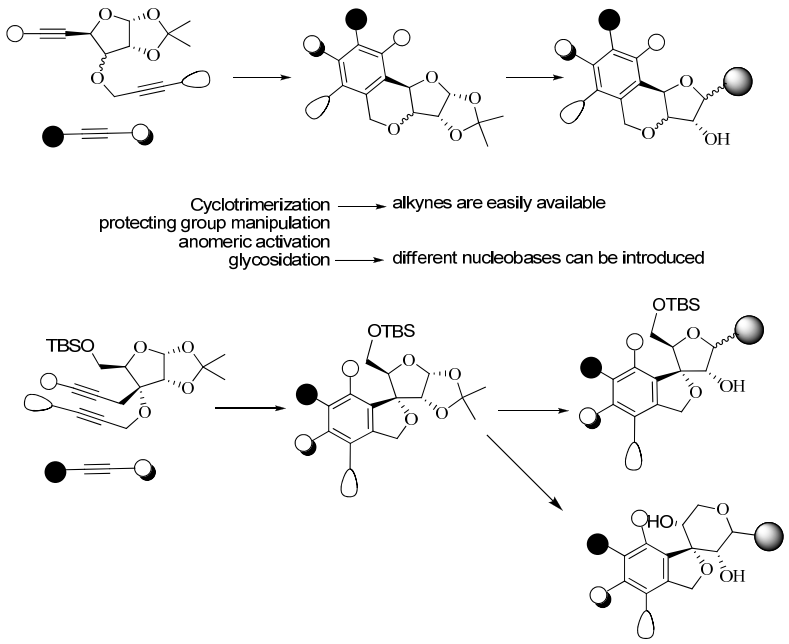
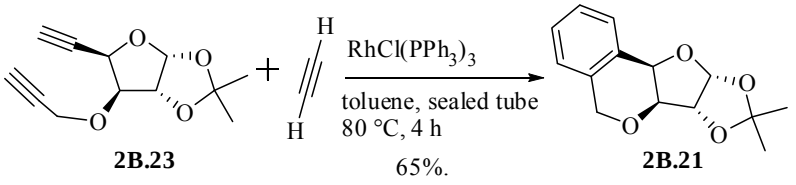


Figure 2B.6

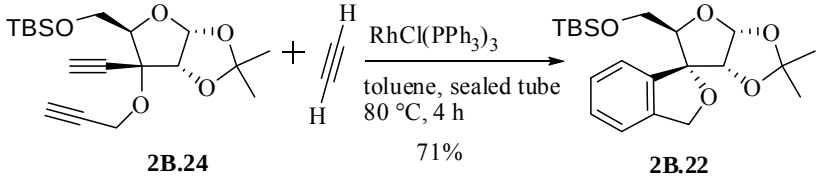
As indicated in Figure 2B.6, one could have flexibility in terms of the employing substrates at both the stages i.e., trimerization (in the form commercial availability of hundres of alkynes and through easy synthesis) also at the glycosidation (apart from the 5 parent nucleobases several of their analogues and

various other nitrogen containing hetercycles could be employed as glycosyl acceptors). In order to demonstrate the efficacy of our two stage flexible strategy, we have identified the simple acetylene co-trimerization product **2B.21** as a precursor for the conformationally restricted tricyclic nucleosides and the spirocyclic sugar **2B.22** as the starting point precursor for C(3')-spiroannulated ribofuranosyl or pyranosyl nucleosides.

As described in the previous part, requisite tricyclic precursors **2B.21** and **2B.22** were synthesized from the corresponding diynes by following the established trimerization protocol employing acetylene as the partner. The reactions were performed on above 1 g scale to prepare the tricyclic derivatives in good amounts.



2B.23 **2B.21**



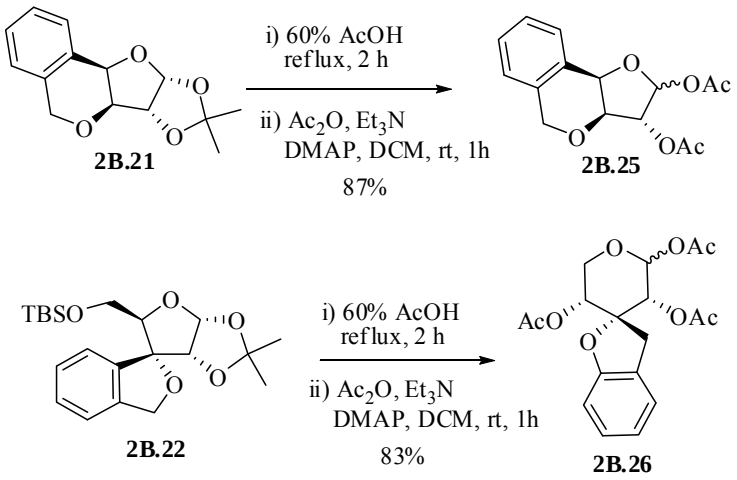
2B.24 **2B.22**

Scheme 2B.3: Synthesis of tricyclic compounds **2B.21**and **2B.22** by employing Rh-catalyzed [2+2+2]-cyclotrimerization reaction

Synthesis of glycosyl donors

The tricyclic sugar derivative **2B.21** and **2B.22** were subjected to acid catalyzed acetonide hydrolysis to deprotect the acetonide and TBS groups. Thus heating compound **2B.21** or **2B.22** in 60% acetic acid at reflux temperature for two hours gave the corresponding lactols. Acetylation of these lactols by using acetic anhydride and Et_3N in dichloromethane afforded anomeric mixture of diacetates **2B.25** (inseparable on silica gel column) and the pyranosyl triacetate **2B.26** (separable

on silica gel column) derivatives in 87% and 83% yields over two steps respectively (Scheme 2B.4).

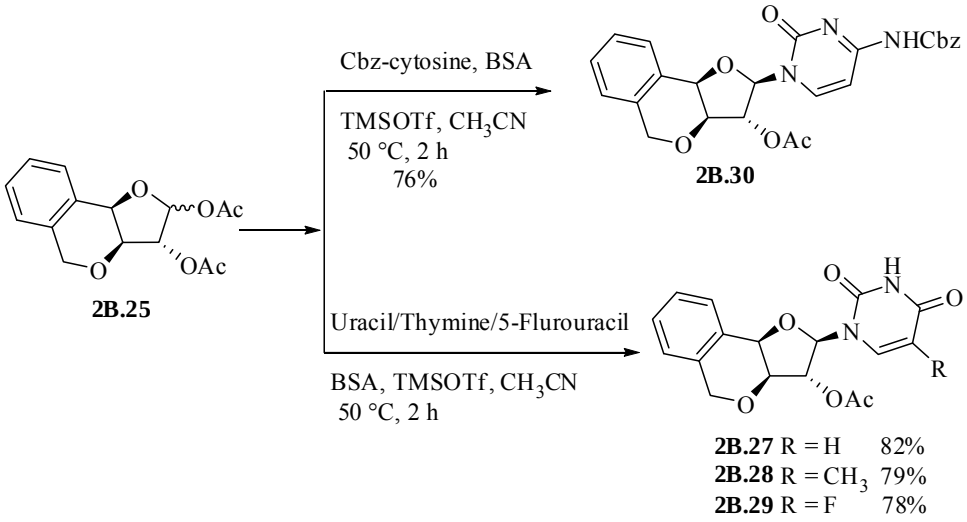


Scheme 2B.4

Mixture of diacetate **2B.25** and triacetate **2B.26** derivatives were characterized by spectral and analytical data. The ^{1}H NMR spectrum of **2B.25** showed two peaks for anomeric proton at δ 6.16 as singlet and at δ 6.53 as doublet with 4.7 Hz coupling constant in 3:7 ratio. Two benzylic protons were resonated at δ 4.61 as two doublets and at δ 4.79, 4.84 as two doublets with 14.5 Hz coupling constant. By comparing the integrations for two isomers, α:β ratio of diacetates is 7:3. In the ^{13}C NMR spectrum of **2B.25** four carbonyl carbons resonated at 168.9, 169.1, 169.2 and 169.4 ppm and fout methyl carbons resonated at 20.4, 20.7, 20.9 and 2.16 ppm. Carbonyl stretching frequency of acetates gave strong absorption peak at 1751 cm^{-1} in IR spectrum. The ^{1}H NMR spectrum of α isomer of **2B.26** showed two peaks for anomeric proton at δ 6.04 as a doublet with 8.5 Hz coupling constant, two C(5)–H showed two doublets at δ 4.01 (J = 8.1 Hz), two benzylic protons resonated at δ 5.19, 5.22 as doublets with coupling constant J = 12.0 Hz. Observation of large coupling constants indicated the formation of pyranoside framework after hydrolysis of 1,2-acetonide and deprotection of TBS ether of compound **2B.22**. Three acetates were showed peaks at 20.1, 20.3 and 20.9 ppm for methyl carbons, and 169.0, 169.3 and 169.4 ppm for carbonyl carbons in the ^{13}C NMR spectrum of α isomer of **2B.26**.

Treatment of anomeric mixture of diacetate **2B.25** with uracil, thymine, 5-flurouracil and Cbz protected cytosine under modified Vorbrüggen[31] conditions

[refluxing the diacetate with BSA *N*,*O*-bis(trimethylsilyl)acetamide and base in acetonitrile, then after, adition of TMSOTf and heating at 50 °C for 2 h] afforded the protected nucleosides **2B.27**–**2B.30** respectively (Scheme 2B.5).



Scheme 2B.5: Synthesis of protected nucleosides

Synthesized protected nucleosides **2B.27**–**2B.30** were characterized by extensive NMR spectroscopy. The anomeric proton of **2B.27** resonated at δ 6.16 with coupling constant J = 1.6 Hz in the ^{1}H NMR spectrum. The C(2)–H showed doublet at 5.22 (J = 1.6 Hz), olefinic 3' proton of uracil displayed double of doublet at δ 5.60 with J = 2.1, 8.2 Hz and 2' proton resonated at down field δ 7.11 with J = 2.1, 8.2 Hz. The amide hydrogen of **2B.27** showed broad singlet at δ 9.21. Olefinic 3' carbon resonated at 102.5 ppm and 2' carbon resonated at 140.5 ppm in the ^{13}C NMR spectrum of compound **2B.27**. β-configuration of glycosidic linkage was further confirmed by single crystal X-ray analysis of **2B.27** (Figure 2B.7).

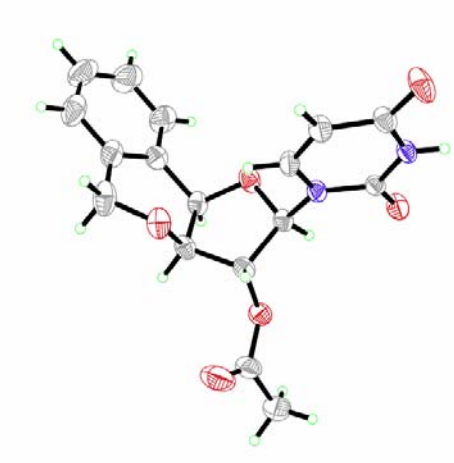
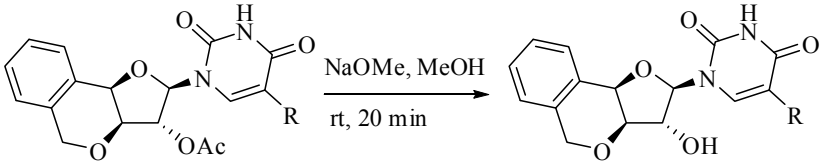


Figure 2B.7: *ORTEP* structure of compound **2B.27**

Subjecting **2B.27**–**2B.29** to Zemplen's deacetylation afforded the tricyclic nucleosides **2B.31**–**2B.33** (Scheme 2B.6). The structural integrity and β-configuration of compound **2B.31** was established with the help of COSY and NOESY. For example, in the ^{1}H NMR spectrum of **2B.31**, the characteristic C(1)–H and C(2)–H of the furanose ring appeared at δ 5.89 (s) and 4.52 (s) respectively. The C(2)–OH resonated as a broad singlet at δ 5.65 and C(4)–H, C(3)–H appeared as doublets respectively at δ 5.24, δ 4.22 with J = 1.9 Hz. The olefinic protons of uracil unit resonated as doublets at δ 5.48 and 7.15 with coupling constant J = 8.0 Hz. In the NOESY spectrum of **2B.31**, C(2)–OH showed spatial interaction with C(1)–H and C(4)–H showed spatial interaction with C(3)–H as well as with C(1)–H. A similar β-configuration was assigned for **2B.32** and **2B.33** by comparing their chemical shifts and coupling constants with that of **2B.31** (Table 2B.1). Further it was confirmed with the help of single crystal X-ray analysis of **2B.32** (Figure 2B.8).



2B.27 R = H
2B.28 R = CH_3
2B.29 R = F

2B.31 R = H 96%
2B.32 R = CH_3 95%
2B.33 R = F 92%

Scheme 2B.6

Table 2B.1: Chemical Shifts and coupling constants of **2B.31–2B.33**

Entry	H–C(1)	H–C(2)	H–C(3)	H–C(4)	C–1 (ppm)
2B.31	5.89 (s)	4.52 (s)	4.22 (d, *J* = 1.9 Hz)	5.24 (d, *J* = 1.9 Hz)	94.2
2B.32	5.93 (s)	4.52 (s)	4.25 (d, *J* = 2.6 Hz)	5.23 (d, *J* = 2.6 Hz)	93.8
2B.33	5.87 (d, *J* = 1.0 Hz)	4.52 (s)	4.26 (d, *J* = 2.6 Hz)	5.24 (d, *J* = 2.6 Hz)	92.9

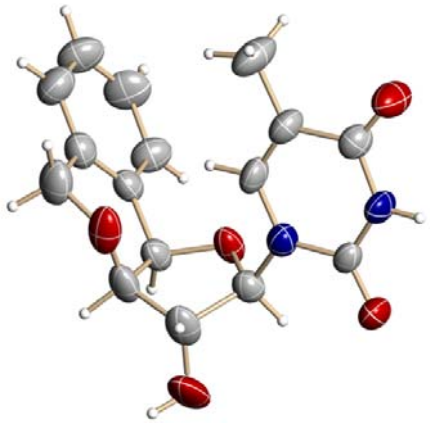
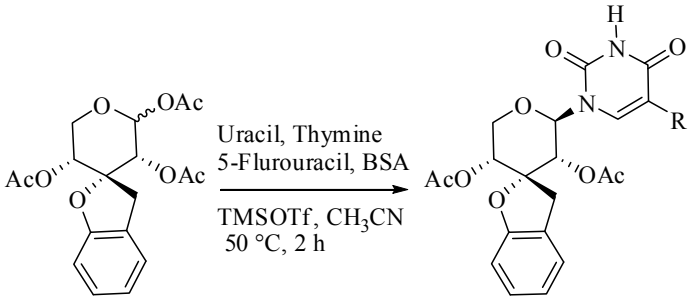


Figure 2B.8: *ORTEP* structure of compound **2B.32**

Treatment of anomeric mixture of triacetates **2B.26** with uracil, thymine and 5-flurouracil under modified Vorbrüggen[31] conditions [refluxing the diacetate with *N*,*O*-bis(trimethil silyl)cetamide and base in acetonitrile followed by the addition of TMSOTf and heating at 50 °C for 2 h] afforded the protected nucleosides **2B.34–2B.36** respectively (Scheme 2B.7).



2B.26

2B.34 R = H 84%
2B.35 R = CH_3 76%
2B.36 R = F 77%

Scheme 2B.7

Diacetate derivatives of nucleosides **2B.34–2B.36** were characterized by spectroscopic and analytical data. Methyl protons of thymine resonated at δ 2.91 as a singlet, anomeric proton and C(2)–H resonated at δ 6.18 and 5.35 with coupling constant 9.5 Hz in the ^{1}H NMR spectrum of **2B.35**. Two benzylic protons of pyranose ring showed two doublet of doublets at δ 4.05 and 5.33 (J = 7.3, 9.1 Hz). The two benzylic protons of isobenzofuran core resonated as doublets at δ 5.19 and 5.25 with coupling constant (J = 12.1 Hz). In ^{13}C NMR spectrum of **2B.35**, two triplets for methylene carbon atoms were resonated at 64.5 and 74.2 ppm. Mass spectrum and elemental analysis were in well agreement with proposed structure. The β-configuration of compound **2B.34** was further confirmed with the help of single crystal X-ray analysis (Figure 2B.9).

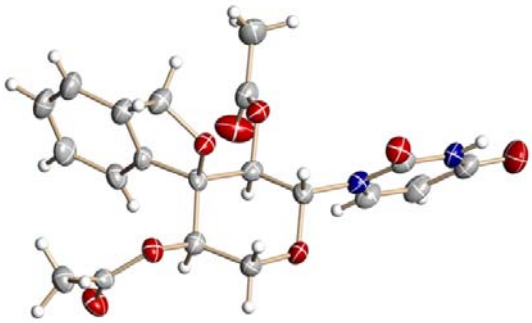
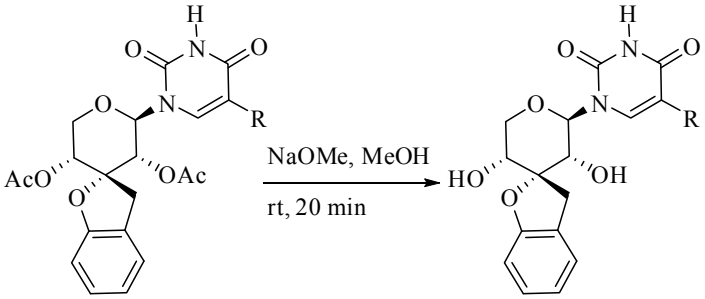


Figure 2B.9: *ORTEP* structure of compound **2B.34**

Subjecting **2B.34**–**2B.36** to Zemplen's deacetylation afforded the tricyclic spironucleosides **2B.37**–**2B.39** (Scheme 2B.8). The structural integrity and β-

configuration of compound **2B.38** was established with the help of COSY and NOESY. For example, in the ^{1}H NMR spectrum of **2B.38**, the thymine C(6')–H appeared as a quartet at δ 7.63 ppm (J = 1.1 Hz). The characteristic C(1)–H and C(2)–H of the furanose ring appeared at δ 5.90 (d) and 4.23 (t) respectively with $J_{1,2}$ = 9.5 Hz. The C(2)–OH resonated as a doublet at 4.17 ppm (J = 9.2 Hz) indicating a strong intramolecular hydrogen bonding and C(4)–H appeared as a dd (δ 4.07 ppm, J = 10.9, 5.5 Hz). In the NOESY spectrum of **2B.38**, C(1)–H showed through spatial interaction with C(4)–H and C(2)–OH thus confirming the assigned β-configuration. A similar β-configuration was assigned for **2B.37** and **2B.39** by comparing their chemical shifts and coupling constants with that of **2B.38** (Table 2B.2).



2B.34 R = H
2B.35 R = CH_3
2B.36 R = F

2B.37 R = H 95%
2B.38 R = CH_3 90%
2B.39 R = F 93%

Scheme 2B.8

Table 2B.2: Chemical shifts and coupling constants of **2B.37–2B.39**

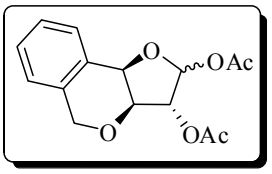
Entry	H–C(1)	H–C(2)	H–C(3)	H–C(5')
2B.37	5.86 (d, J = 9.5 Hz)	4.06 (d, J = 9.5 Hz)	3.94 (dd, J = 5.4, 10.8 Hz)	3.85 (d, J = 10.8 Hz)
2B.38	5.90 (d, J = 9.5 Hz)	4.23 (dd, J = 8.8, 9.5 Hz)	3.93 (dd, J = 5.5, 10.7 Hz)	3.83 (d, J = 10.7 Hz)
2B.39	5.84 (dd, J = 1.5, 9.5 Hz)	4.02 (d, J = 9.5 Hz)	3.95(dd, J = 5.3, 10.7 Hz)	3.85 (d, J = 10.9 Hz)

Conclusion:

To conclude, a simple approach for the synthesis of linear tricyclic and spiro-tricyclic nucleosides through the [2+2+2]-cyclotrimerization on sugar templates has been developed. When compared with the other protocols available for spironucleosides, our approach is characterized by the enormous flexibility at two stages. Considering the importance of modified nucleosides as antiviral and anti-cancer agents and as potential antisense therapeutic and diagnostic agents, the results from the present investigation could be further explored for a strategic construction of these molecular skeletons. Work in this direction is ongoing in our laboratory. Also, incorporation of the spirocyclic nucleoside monomers into oligodeoxynucleosides and their biological evaluation is presently progressing in our lab.

2B.3. Experimental:

Diacetetes (2B.25)



Procedure A:

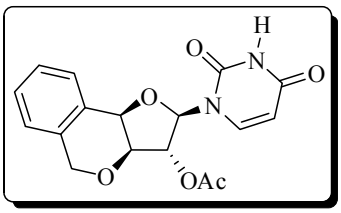
Compound **2B.21** (700 mg, 2.82 mmol) in 60% acetic acid (20 mL) was heated under reflux temperature for 2 h. The reaction mixture was neutralized by slow addition of solid K_2CO_3 and extracted in ethyl acetate. Combined ethyl acetate extracts were dried (Na_2SO_4) and concentrated under reduced pressure.

At 0 °C, a solution of above lactols (570 mg, 3.5 mmol), TEA (5 mL) and catalytic DMAP in dry DCM (15 mL) was treated with acetic anhydride (0.77 mL, 8.22 mmol) and stirred at rt for 1 h. The reaction mixture was cooled to 0 °C and quenched with 2N HCl and extracted in DCM. Combined organic phase was washed with sat. $NaHCO_3$ and water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (15% ethyl acetate in petroleum ether) gave a mixture of diacetates **2B.25** (717 mg, 87% yield) as colorless oil.

Mol. Formula	: $C_{15}H_{16}O_6$
IR ($CHCl_3$) $\tilde{\nu}$	: 3032, 2903, 1751, 1638, 1432, 1374, 1242, 1219, 1087, 1012, 925, 909 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.94, 2.12, 2.13, 2.16 (4s, 6H), 4.26 (d, *J* = 3.9 Hz, 0.3H), 4.42 (dd, *J* = 2.4, 4.3 Hz, 0.7H), 4.61 (2d, *J* = 14.5 Hz, 1H), 4.79, 4.84 (2d, *J* = 14.5 Hz, 1H), 5.03 (t, *J* = 4.3 Hz, 1H), 5.30 (s, 0.3H), 5.36 (dd, *J* = 2.4, 4.6 Hz, 0.7H), 6.16 (s, 0.3H), 6.52 (d, *J* = 4.7 Hz, 0.7H), 7.06−7.13 (m, 1H), 7.26−7.32 (m, 2H), 7.42−7.50 (m, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 20.4 (q), 20.7 (q), 20.9 (q), 21.0 (q), 66.5 (t), 66.9 (t), 72.7 (d), 75.7 (d), 77.7 (d), 78.8 (d), 79.2 (d), 81.6 (d), 94.4 (d), 99.6 (d), 124.2 (d), 124.4 (d), 127.6 (d), 128.4 (d), 128.6 (d), 129.5 (s), 129.9 (d, 2C), 130.0 (d), 130.3 (s), 134.3 (s), 134.8 (s), 168.9 (s), 169.1 (s), 169.2 (s), 169.4 (s) ppm.

ESI–MS (*m/z*)	: 315.0 (100%, $[M+Na]^+$), 331.1 (10%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 61.64; H, 5.52%. Found: C, 61.50; H, 5.67%.

(2*R*,3*R*,3a*S*,9b*R*)-2-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-c]isochromen-3-yl acetate (2B.27)



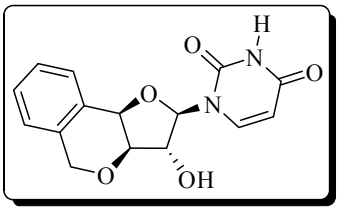
Procedure B:

A solution of acetates **2B.25** (100 mg, 0.34 mmol), uracil (77 mg, 0.68 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (0.42 mL, 1.71 mmol) in anhydrous CH_3CN (5 mL) was heated to reflux for 15 min. The reaction mixture was cooled to 0 °C and TMSOTf (0.12 mL, 0.68 mmol) was added. The reaction mixture was stirred at 50 °C for 2 h, quenched with cold aq. $NaHCO_3$ and extracted with EtOAc. The combined organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (45% ethyl acetate in petroleum ether) afforded the nuleoside **2B.27** (97 mg, 82% yield) as crystalline solid.

Mol. Formula	: $C_{17}H_{16}N_2O_6$
M. P.	: 214−216 °C
$[\alpha]_D^{25}$	: −8.6 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3241, 3032, 2927, 2253, 1750, 1686, 1461, 1371, 1320, 1268, 1225, 1108, 1066, 909 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.17 (s, 3H), 4.19 (d, *J* = 2.6 Hz, 1H), 4.72 (d, *J* = 15.2 Hz, 1H), 4.87 (d, *J* = 15.2 Hz, 1H), 4.96 (d, *J* = 2.6 Hz, 1H), 5.22 (d, *J* = 1.6 Hz, 1H), 5.60 (dd, *J* = 2.1, 8.2 Hz, 1H), 6.16 (d, *J* = 1.6 Hz, 1H), 7.11 (dd, *J* = 2.1, 8.2 Hz, 1H), 7.32-7.48 (m, 4H), 9.21 (bs, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 20.7 (q), 67.3 (t), 75.4 (d), 78.8 (d), 81.7 (d), 89.3 (d), 102.5 (d), 124.4 (d), 127.8 (d), 127.9 (s), 129.4 (d), 130.6 (d), 134.1 (s), 140.5 (d), 150.2 (s), 163.1 (s), 169.2 (s) ppm.

ESI-MS (*m/z*)	: 345.1 (6%, $[M+H]^+$), 367.0 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 59.30; H, 4.68; N, 8.14 %. Found: C, 59.09; H, 4.80; N, 8.26 %.

1-((2*R*,3*R*,3a*R*,9b*R*)-3-Hydroxy-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-c]isochromen-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (2B.31)

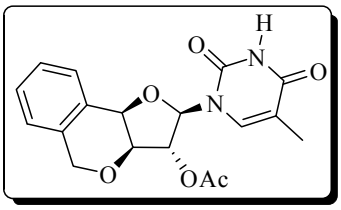


Procedure C:

A solution of **2B.27** (80 mg, 0.36 mmol) and catalytic NaOMe in methanol (2 mL) was stirred at rt for 20 min. Reaction mixture was concentrated under reduced pressure and the crude was purified by silica gel column chromatography to afford tricyclic nucleoside **2B.31** (67 mg, 96% yield) as white solid.

Mol. Formula	: $C_{15}H_{14}N_2O_5$
M. P.	: 140−143 °C
$[\alpha]_D^{25}$	: +60.4 (*c* 1.9, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3383, 3218, 3108, 3068, 2923, 2844, 2252, 1775, 1695, 1464, 1393, 1322, 1265, 1114, 1097, 1059, 999 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 4.22 (d, *J* = 1.9 Hz, 1H), 4.52 (s, 1H), 4.64 (d, *J* = 15.1 Hz, 1H), 4.72 (d, *J* = 15.1 Hz, 1H), 5.24 (d, *J* = 1.9 Hz, 1H), 5.48 (d, *J* = 8.0 Hz, 1H), 5.65 (bs, 1H), 5.89 (s, 1H), 7.10 (dd, *J* = 2.3, 8.1 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.34-7.36 (m, 2H), 7.51 (dd, *J* = 2.3, 8.1 Hz, 1H), 10.61 (bs, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 66.9 (t), 77.1 (d), 80.1 (d), 80.7 (d), 94.2 (d), 101.1 (d), 124.3 (d), 127.8 (d), 128.8 (s), 129.2 (d), 130.8 (d), 134.3 (s), 140.7 (d), 151.1 (s), 164.2 (s) ppm.
ESI-MS (*m/z*)	: 325.0 (100%, $[M+Na]^+$), 341.0 (7%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 59.60; H, 4.67; N, 9.27 %. Found: C, 59.52; H, 4.76; N, 9.18 %.

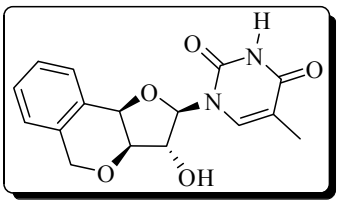
(2*R*,3*R*,3a*S*,9b*R*)-2-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-c]isochromen-3-yl acetate (2B.28)



By following procedure B, acetates **2B.25** (100 mg, 0.34 mmol) was subjected to glycosidation under Vorbruggen conditions with thymine (86 mg, 0.68 mmol). After usual workup and purification, the tricyclic nuleoside **2B.28** (97 mg, 79% yield) was obtained as white solid.

Mol. Formula	: $C_{18}H_{18}N_2O_6$
M. P.	: 192–194 °C
$[\alpha]_D^{25}$	: −18.9 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3196, 3019, 2927, 2851, 1752, 1697, 1466, 1372, 1270, 1228, 1110, 1061, 875 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.77 (d, *J* = 1.1 Hz, 3H), 2.16 (s, 3H), 4.20 (d, *J* = 2.7 Hz, 1H), 4.74 (d, *J* = 15.2 Hz, 1H), 4.89 (d, *J* = 15.2 Hz, 1H), 4.92 (d, *J* = 2.1 Hz, 1H), 5.22 (d, *J* = 2.0 Hz, 1H), 6.21 (d, *J* = 2.1 Hz, 1H), 7.13 (dd, *J* = 2.5, 7.3 Hz, 1H), 7.22 (d, *J* = 1.1 Hz, 1H), 7.32–7.38 (m, 2H), 7.46 (dd, *J* = 2.5, 7.2 Hz, 1H), 9.03 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 12.5 (q), 20.6 (q), 67.2 (t), 74.7 (d), 78.9 (d), 81.6 (d), 88.9 (d), 111.0 (s), 124.2 (d), 127.7 (d), 127.9 (s), 129.2 (d), 130.4 (d), 134.1 (s), 136.3 (d), 150.4 (s), 163.9 (s), 169.4 (s) ppm.
ESI-MS (*m/z*)	: 359.3 (19%, $[M+H]^+$), 381.2 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 60.33; H, 5.06; N, 7.82 %. Found: C, 60.26; H, 4.98; N, 7.76 %.

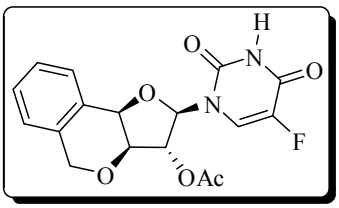
1-((2*R*,3*R*,3a*R*,9b*R*)-3-Hydroxy-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-c]isochromen-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (2B.32)



By following procedure C, **2B.28** (70 mg, 0.2 mmol) was subjected to Zemplen's deacetylation reaction to give nucleoside **2B.32** (57 mg, 95% yield) as crystalline solid.

Mol. Formula	: $C_{16}H_{16}N_2O_5$
M. P.	: 177–179 °C
$[\alpha]_D^{25}$	: +40.0 (*c* 1.0, MeOH).
IR (Nujol) $\tilde{\nu}$	: 3392, 3220, 3065, 2924, 2854, 1668, 1462, 1377, 1270, 1099, 1062, 916 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.61 (d, *J* = 1.0 Hz, 3H), 4.25 (d, *J* = 2.6 Hz, 1H), 4.52 (s, 1H), 4.64 (d, *J* = 15.2 Hz, 1H), 4.74 (d, *J* = 15.2 Hz, 1H), 5.23 (d, *J* = 2.6 Hz, 1H), 5.78 (bs, 1H), 5.93 (s, 1H), 6.97 (d, *J* = 1.1 Hz, 1H), 7.08–7.13 (m, 1H), 7.33–7.38 (m, 2H), 7.47–7.54 (m, 1H), 10.62 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 12.4 (q), 66.8 (t), 76.8 (d), 80.2 (d), 80.8 (d), 93.8 (d), 109.2 (s), 124.2 (d), 127.8 (d), 128.9 (s), 129.1 (d), 130.7 (d), 134.3 (s), 137.0 (d), 151.0 (s), 164.7 (s) ppm.
ESI-MS (*m/z*)	: 339.1 (100%, $[M+Na]^+$), 355.1 (13%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 60.75; H, 5.10; N, 8.86 %. Found: C, 60.59; H, 4.97; N, 8.98 %.

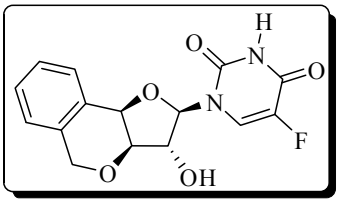
(2*R*,3*R*,3a*S*,9b*R*)-2-(5-Fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-c]isochromen-3-yl acetate (2B.29)



By following the procedure B, subjecting acetates **2B.25** (100 mg, 0.34 mmol) and 5-flurouracil (89 mg, 0.68 mmol) to Vorbruggen modified glycosidation conditions gave the nuleoside **2B.29** (96 mg, 78% yield) as a white solid.

Mol. Formula	: $C_{17}H_{15}FN_2O_6$
M. P.	: 194–196 °C
$[\alpha]_D^{25}$	: +2.2 (*c* 1.1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3239, 3109, 3078, 3024, 2925, 2894, 2853, 1752, 1715, 1466, 1373, 1345, 1268, 1224, 1091, 1072, 879 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.17 (s, 3H), 4.20 (d, *J* = 2.5 Hz, 1H), 4.73 (d, *J* = 15.2 Hz, 1H), 4.90 (d, *J* = 15.2 Hz, 1H), 4.97 (d, *J* = 2.5 Hz, 1H), 5.22 (d, *J* = 1.4 Hz, 1H), 6.15 (t, *J* = 1.6 Hz, 1H), 7.13 (dd, *J* = 2.3, 6.4 Hz, 1H), 7.33–7.39 (m, 2H), 7.42–7.46 (m, 1H), 7.50 (d, *J* = 6.32 Hz, 1H), 9.65 (bs, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 20.5 (q), 67.1 (t), 75.4 (d), 78.4 (d), 81.5 (d), 89.4 (d), 124.4 (d), 124.5(d), 125.2 (d), 127.5 (s), 127.7 (d), 129.4 (d), 130.5 (d), 133.9 (s), 137.9 (s), 142.6 (s), 149.0 (s), 156.7 (s), 157.2 (s), 169.4 (s) ppm.
ESI-MS (*m/z*)	: 385.2 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 56.36; H, 4.17; N, 7.73 %. Found: C, 56.25; H, 4.29; N, 7.60 %.

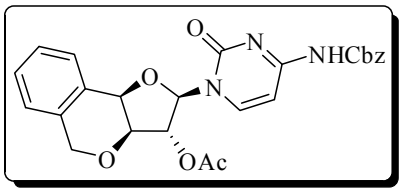
5-Fluoro-1-((2*R*,3*R*,3a*R*,9b*R*)-3-hydroxy-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-c]isochromen-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (2B.33)



By following procedure C, **2B.29** (85 mg, 0.23 mmol) was subjected to Zemplen's deacetylation to procure nucleoside **2B.33** (70 mg, 92% yield) as crystalline solid.

Mol. Formula	: $C_{15}H_{13}FN_2O_5$
M. P.	: 142–144 °C
$[\alpha]_D^{25}$	: +58.5 (*c* 1.3, MeOH).
IR (Nujol) $\tilde{\nu}$	: 3400, 3217, 3067, 2924, 2854, 1712, 1461, 1377, 1256, 1081, 964, 909, 761 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 4.26 (d, *J* = 2.6 Hz, 1H), 4.52 (s, 1H), 4.65 (d, *J* = 15.1 Hz, 1H), 4.76 (d, *J* = 15.1 Hz, 1H), 5.24 (d, *J* = 2.6 Hz, 1H), 5.48 (bs, 1H), 5.87 (d, *J* = 1.0 Hz, 1H), 7.11 (dd, *J* = 2.2, 6.8 Hz, 1H), 7.22 (d, *J* = 6.3 Hz, 1H), 7.31−7.41 (m, 2H), 7.50 (dd, *J* = 2.2, 6.3 Hz, 1H), 10.84 (d, *J* = 3.5 Hz, 1H).
^{13}C NMR ($CDCl_3$+Methanol −D_4, 50 MHz)	: 66.7 (t), 76.4 (d), 80.1 (d), 92.9 (d), 124.1 (d), 124.9 (d), 125.3 (d), 127.5 (d), 128.1 (s), 129.0 (d), 130.3 (d), 133.9 (s), 138.4 (s), 140.7 (s), 149.1 (s) ppm.
ESI-MS (*m/z*)	: 321.1 (4%, $[M+H]^+$), 343.1 (100%, $[M+Na]^+$), 359.0 (13 %, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 56.25; H, 4.09; N, 7.75 %. Found: C, 56.37; H, 4.18; N, 7.83 %.

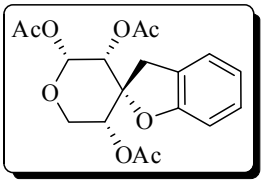
(2*R*,3*R*,3a*S*,9b*R*)-2-(4-(Benzyloxycarbonylamino)-2-oxopyrimidin-1(2*H*)-yl)-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-c]isochromen-3-yl acetate (2B.30)



By following procedure B, employing acetates **2B.25** (80 mg, 0.27 mmol) and Cbz-cytosine (134 mg, 0.55 mmol) to Vorbruggen conditions, gave the protected nuleoside **2B.30** (99 mg, 76% yield) as gummy solid.

Mol. Formula	: $C_{25}H_{23}N_3O_7$
$[\alpha]_D^{25}$	: +40.4 (*c* 1.3, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3145, 3015, 2926, 2851, 1752, 1665, 1624, 1555, 1498, 1373, 1328, 1268, 1219, 1105, 1073, 995, 750 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.17 (s, 3H), 4.19 (d, *J* = 2.7 Hz, 1H), 4.63 (d, *J* = 15.2 Hz, 1H), 4.76 (d, *J* = 15.2 Hz, 1H), 5.11 (d, *J* = 2.3 Hz, 1H), 5.16 (2s, 2H), 5.34 (s, 1H), 6.16 (s, 1H), 7.00–7.14 (m, 2H), 7.34–7.40 (m, 7H), 7.50–7.55 (m, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 20.7 (q), 66.9 (t), 67.6 (t), 76.4 (d), 78.2 (d), 81.1 (d), 91.0 (d), 124.3 (d), 127.7 (d), 128.0 (d), 128.1 (s), 128.3 (d), 128.4 (d), 129.3 (d), 130.5 (d), 134.0 (s), 135.0 (s), 144.7 (d), 152.3 (s), 154.7 (s), 162.4 (s), 169.1 (s) ppm.
ESI-MS (*m/z*)	: 478.3 (18%, $[M+H]^+$), 500.3 (100%, $[M+Na]^+$), 516.3 (14%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 59.79; H, 5.02; N, 13.95 %. Found: C, 56.67; H, 4.96; N, 14.04 %.

Triacetates (2B.26)



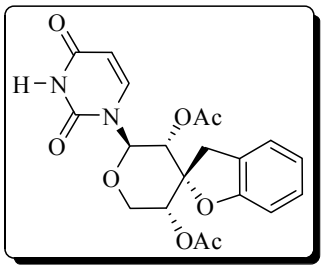
By following procedure A, compound **2B.22** (600 mg, 1.53 mmol) was hydrolyzed to triol and subsequent acetylation by treating it with acetic anhydride gave triacetates **2B.26** (462 mg, 83% yield) as colorless oil.

Mol. Formula	: $C_{18}H_{20}O_8$
IR ($CHCl_3$) $\tilde{\nu}$	: 3025, 2952, 2872, 1751, 1611, 1463, 1371, 1265, 1070, 1039, 941, 755 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: 1.70 (s, 3H), 1.74 (s, 3H), 2.09 (s, 3H), 4.01 (d, *J* = 8.1 Hz, 2H), 5.19 (d, *J* = 12.0 Hz, 1H), 5.22 (d, *J* = 12.0 Hz, 1H), 5.31 (d, *J* = 8.5 Hz, 1H), 5.33 (t, *J* = 8.4 Hz, 1H), 6.04 (d, *J* =

8.5 Hz, 1H), 7.19 (d, *J* = 7.87 Hz, 1H), 7.23−7.33 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz)	: 20.1 (q), 20.3 (q), 20.9 (q), 63.1 (t), 70.2 (d), 71.9 (d), 74.2 (t), 90.0 (s), 91.8 (d), 120.3 (d), 122.0 (d), 127.7 (d), 128.9 (d), 134.7 (s), 140.6 (s), 169.0 (s), 169.3 (s), 169.4 (s) ppm.
ESI-MS (*m/z*)	: 387.2 (100%, $[M+Na]^+$), 403.2 (12%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 59.34; H, 5.53 %. Found: C, 59.22; H, 5.60 %.

(2*R*,2'*R*,3'*R*,5'*R*)-2'-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2',3',5',6'-tetrahydro-3*H*-spiro[benzofuran-2,4'-pyran]-3',5'-diyl diacetate (2B.34)

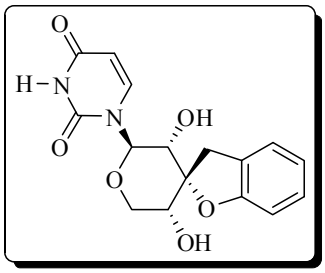


According to procedure B, the glycosidation of triacetates **2B.26** (120 mg, 0.33 mmol) with uracil (74 mg, 0.66 mmol) under Vorbruggen conditions gave the nuleoside **2B.34** (115 mg, 84% yield) as crystalline solid.

Mol. Formula	: $C_{20}H_{20}N_2O_8$
M. P.	: 213–215 °C
$[\alpha]_D^{25}$	: +52.7 (*c* 1.1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3214, 3021, 2962, 2928, 2873, 1754, 1695, 1634, 1456, 1373, 1219, 1071, 1041, 810, 765 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.57 (s, 3H), 1.70 (s, 3H), 4.01 (d, *J* = 8.1 Hz, 2H), 5.14 (d, *J* = 12.3 Hz, 1H), 5.22 (d, *J* = 12.3 Hz, 1H), 5.25–5.33 (m, 2H), 5.72 (d, *J* = 8.2 Hz, 1H), 6.15 (d, *J* = 9.4 Hz, 1H), 7.12–7.27 (m, 4H), 7.39 (d, *J* = 8.2 Hz, 1H), 9.10 (bs, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 19.8 (q), 20.2 (q), 64.4 (t), 69.8 (d), 71.2 (d), 74.2 (t), 79.5 (d), 89.6 (s), 103.1 (d), 120.5 (d), 121.4 (d), 127.7 (d), 129.0 (d), 134.3 (s), 139.7 (d), 140.6 (s), 150.5 (s), 163.0 (s), 169.3 (s), 169.6 (s) ppm.

ESI-MS (*m/z*)	: 417.5 (40%, $[M+H]^+$), 439.5 (100%, $[M+Na]^+$), 455.5 (19%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 57.69; H, 4.84; N, 6.73 %. Found: C, 57.56; H, 4.94; N, 6.86 %.

1-((2*R*,2'*R*,3'*R*,5'*R*)-3',5'-Dihydroxy-2',3',5',6'-tetrahydro-3*H*-spiro[benzofuran-2,4'-pyran]-2'-yl)pyrimidine-2,4(1*H*,3*H*)-dione (2B.37)

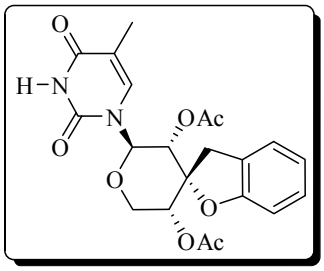


By following procedure C, **2B.34** (90 mg, 0.22 mmol) was subjected to Zemplen's deacetylation to afford nucleoside **2B.37** (68 mg, 95% yield) as white solid.

Mol. Formula	: $C_{16}H_{16}N_2O_6$
M. P.	: 138–140 °C
$[\alpha]_D^{25}$	: +56.5 (*c* 0.4, MeOH).
IR (nujol) $\tilde{\nu}$	: 3393, 3018, 2961, 2854, 1679, 1459, 1377, 1243, 1062 cm^{-1}.
^{1}H NMR (Methanol−D_4, 200 MHz)	: δ 3.85 (t, *J* = 10.8 Hz, 1H), 3.94 (dd, *J* = 5.4, 10.8 Hz, 1H), 4.03 (dd, *J* = 5.4, 10.8 Hz, 1H), 4.06 (d, *J* = 9.5 Hz, 1H), 5.22 (d, *J* = 11.8 Hz, 1H), 5.27 (d, *J* = 11.8 Hz, 1H), 5.73 (d, *J* = 8.1 Hz, 1H), 5.86 (d, *J* = 9.5 Hz, 1H), 7.25 (dd, *J* = 6.1, 1.55 Hz, 1H), 7.30–7.35 (m, 2H), 7.38–7.40 (m, 1H), 7.79 (d, *J* = 8.1 Hz, 1H).
^{13}C NMR (Methanol−D_4, 50 MHz)	: 68.8 (t), 71.4 (d), 72.7 (d), 75.8 (t), 83.7 (d), 93.9 (s), 103.2 (d), 121.8 (d), 122.3 (d), 128.6 (d), 129.4 (d), 139.5 (s), 142.9 (d), 143.0 (s), 152.9 (s), 166.1 (s) ppm.
ESI-MS (*m/z*)	: 333.60 (19.12%, $[M+1]^+$), 355.60 (100%, $[M+Na]^+$), 371.57 (11.03%, $[M+K]^+$).

Elemental Analysis	Calcd.: C, 57.83; H, 4.85; N, 8.43 %. Found: C, 57.95; H, 4.98; N, 8.56 %.

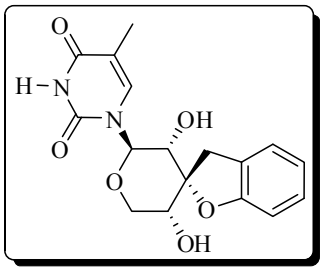
(2*R*,2'*R*,3'*R*,5'*R*)-2'-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2',3',5',6'-tetrahydro-3*H*-spiro[benzofuran-2,4'-pyran]-3',5'-diyl diacetate (2B.35)



By following procedure B, glycosidation of triacetates **2B.26** (110 mg, 0.30 mmol) with thymine (76 mg, 0.60 mmol) under Vorbruggen conditions gave the nuleoside **2B.35** (99 mg, 76% yield) as crystalline solid.

Mol. Formula	: $C_{21}H_{22}N_2O_8$
M. P.	: 158–160 °C
$[\alpha]_D^{25}$	: +20.0 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3389, 3020, 2874, 1745, 1686, 1461, 1373, 1216, 1150, 1071, 1042, 985 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.61 (s, 3H), 1.74 (s, 3H), 1.91 (s, 3H), 4.05 (dd, *J* = 7.3, 9.1 Hz, 2H), 5.19 (d, *J* = 12.1 Hz, 1H), 5.25 (d, *J* = 12.1 Hz, 1H), 5.33 (dd, *J* = 7.3, 9.1 Hz, 1H), 5.35 (d, *J* = 9.5 Hz, 1H), 6.18 (d, *J* = 9.5 Hz, 1H), 7.19–7.23 (m, 2H), 7.26–7.32 (m, 3H), 9.37 (bs, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 12.4 (q), 19.9 (q), 20.2 (q), 64.5 (t), 69.9 (d), 71.3 (d), 74.2 (t), 79.5 (d), 89.7 (s), 111.5 (s), 120.5 (d), 121.5 (d), 127.7 (d), 129.1 (d), 134.5 (s), 135.3 (d), 140.7 (s), 150.6 (s), 163.7 (s), 169.3 (s), 169.6 (s) ppm.
ESI-MS (*m/z*)	: 431.2 (10%, $[M+H]^+$), 453.3 (100%, $[M+Na]^+$), 469.3 (8%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 58.60; H, 5.15; N, 6.51 %. Found: C, 58.76; H, 4.99; N, 6.63 %.

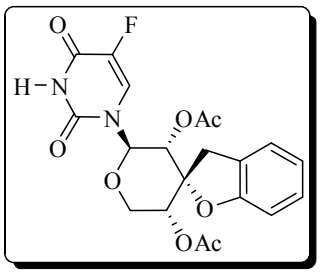
1-((2*R*,2'*R*,3'*R*,5'*R*)-3',5'-Dihydroxy-2',3',5',6'-tetrahydro-3*H*-spiro[benzofuran-2,4'-pyran]-2'-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (2B.38)



By following procedure C, compound **2B.35** (80 mg, 0.19 mmol) was subjected to Zemplen's deacetylation to afford nucleoside **3B.38** (58 mg, 90% yield) as crystalline solid.

Mol. Formula	: $C_{17}H_{18}N_2O_6$
M. P.	: 116–118 °C
$[\alpha]_D^{25}$	: +30.0 (*c* 0.8, MeOH).
IR (nujol) $\tilde{\nu}$	: 3371, 3017, 2925, 2855, 1653, 1463, 1377, 1064, 762 cm^{-1}.
^{1}H NMR (Acetone−D_6, 200 MHz)	: δ 1.85 (d, *J* = 1.07 Hz, 3H), 3.83 (t, *J* = 10.7 Hz, 1H), 3.91 (m, 1H), 3.93 (dd, *J* = 5.5, 10.7 Hz, 1H), 4.05−4.11 (m, 1H), 4.17 (d, *J* = 9.1 Hz, 1H), 4.23 (dd, *J* = 8.8, 9.5 Hz, 1H), 5.24 (d, *J* = 11.7 Hz, 1H), 5.29 (d, *J* = 11.7 Hz, 1H), 5.90 (d, *J* = 9.5 Hz, 1H), 7.27–7.28 (m, 1H), 7.30−7.35 (m, 2H), 7.40–7.42 (m, 1H), 7.63 (q, *J* = 1.1 Hz, 1H), 10.12 (bs, 1H).
^{13}C NMR (Acetone−D_6, 50 MHz)	: 12.3 (q), 68.5 (t), 71.1 (d), 72.2 (d), 75.3 (t), 82.8 (d), 93.5 (s), 110.8 (s), 121.4 (d), 122.0 (d), 127.9 (d), 128.7 (d), 137.1 (d), 139.7 (s), 142.5 (s), 152.0 (s), 164.2 (s) ppm.
ESI-MS (*m/z*)	: 369.1 (100%, $[M+Na]^+$), 385.2 (6%, $[M+K]^+$).
Elemental Analysis	Calcd.: C, 58.96; H, 5.24; N, 8.09 %. Found: C, 59.10; H, 5.06; N, 7.97 %.

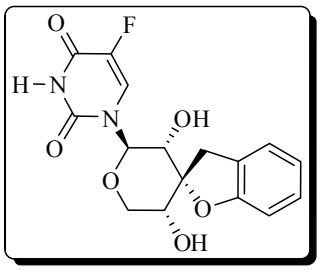
(2*R*,2'*R*,3'*R*,5'*R*)-2'-(5-Fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2',3',5',6'-tetrahydro-3*H*-spiro[benzofuran-2,4'-pyran]-3',5'-diyl diacetate (2B.36)



By following procedure B, triacetates **2B.26** (120 mg, 0.33 mmol) were subjected to glycosidation with 5-flurouracil (86 mg, 0.66 mmol) under Vorbruggen conditions to provide nuleoside **2B.36** (110 mg, 77% yield) as white solid.

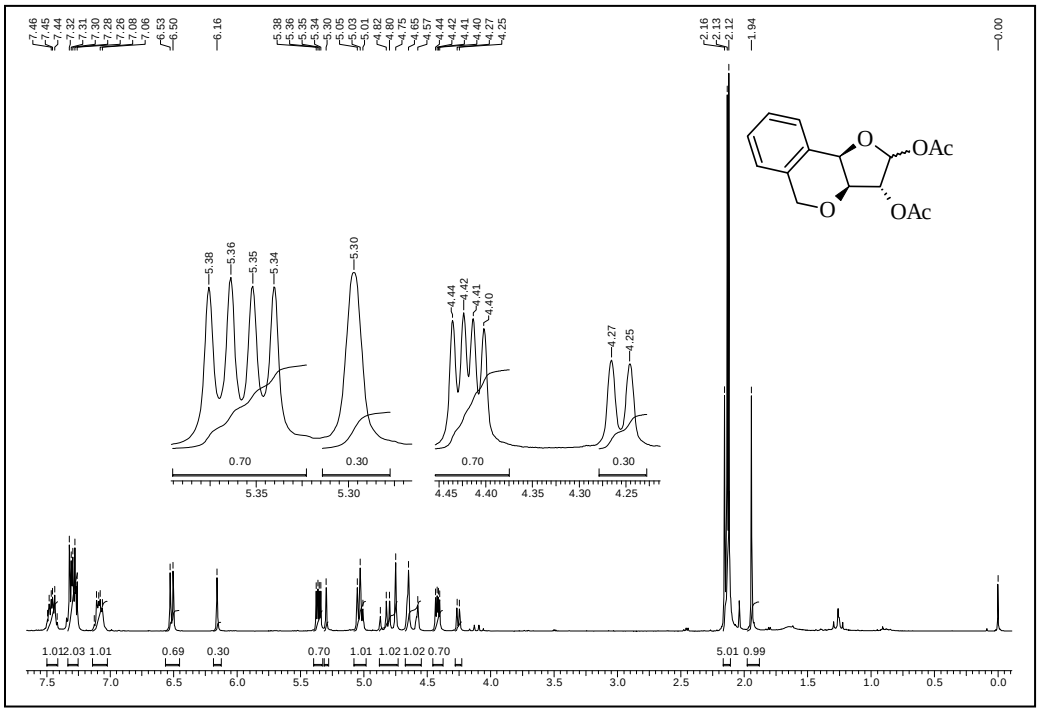
Mol. Formula	: $C_{20}H_{19}FN_2O_8$
M. P.	: 216−218 °C
$[\alpha]_D^{25}$	: +38.7 (*c* 1.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3217, 3084, 3023, 2930, 2874, 1732, 1673, 1463, 1373, 1219, 1072, 1043, 904 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.58 (s, 3H), 1.71 (s, 3H), 4.03 (d, *J* = 8.2 Hz, 2H), 5.15 (d, *J* = 12.1 Hz, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 5.32 (d, *J* = 9.3 Hz, 1H), 5.38 (t, *J* = 8.2 Hz, 1H), 6.12 (d, *J* = 9.3 Hz, 1H), 7.12–7.21 (m, 3H), 7.24–7.28 (m, 1H), 7.53 (d, *J* = 6.0 Hz, 1H), 9.81 (bs, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 19.8 (q), 20.2 (q), 64.4 (t), 69.7 (d), 71.3 (d), 74.2 (t), 80.0 (d), 89.6 (s), 120.5 (d), 121.3 (d), 124.0 (d), 124.4 (d), 127.7 (d), 129.1 (d), 134.3 (s), 139.3 (s), 140.6 (s), 141.6 (s), 149.2 (s), 156.6 (s), 156.9 (s), 169.5 (s), 169.8 (s) ppm.
ESI-MS (*m/z*)	: 435.4 (20%, $[M+H]^+$), 452.47 (35%, $[M+NH_4]^+$), 457.44 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 55.30; H, 4.41; N, 6.45 %. Found: C, 55.21; H, 4.50; N, 6.51 %.

1-((2*R*,2'*R*,3'*R*,5'*R*)-3',5'-Dihydroxy-2',3',5',6'-tetrahydro-3*H*-spiro[benzofuran-2,4'-pyran]-2'-yl)-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione (2B.39)

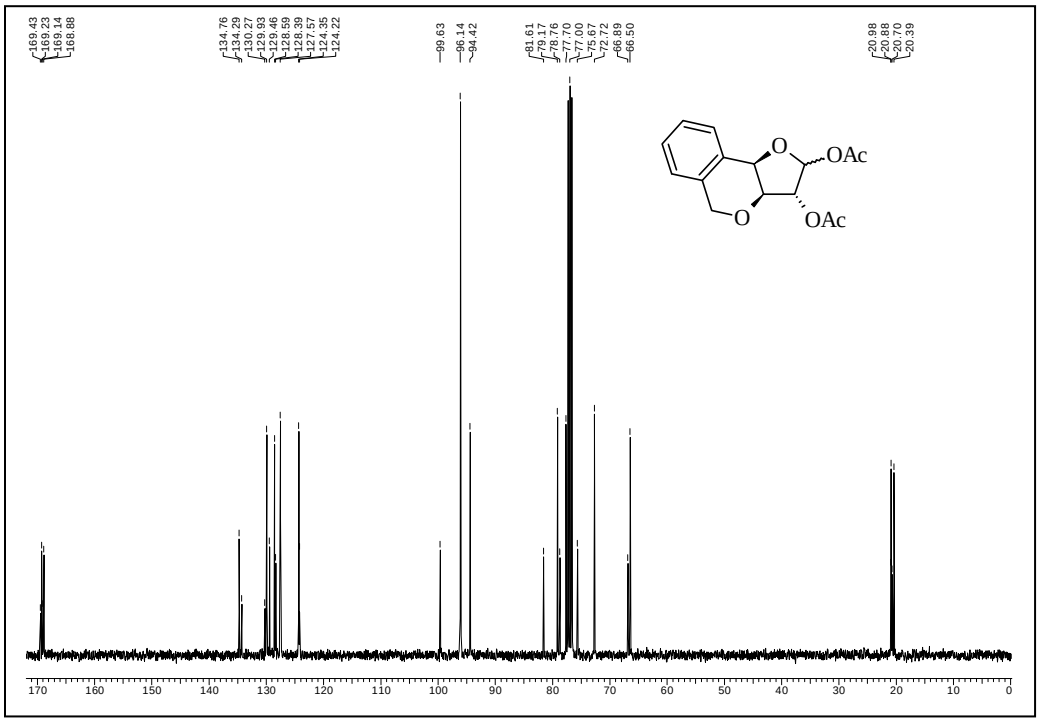


By following procedure C, **2B.36** (90 mg, 0.21 mmol) was subjected to Zemplen's deacetylation to afford nucleoside **2B.39** (67 mg, 93% yield) as crystalline solid.

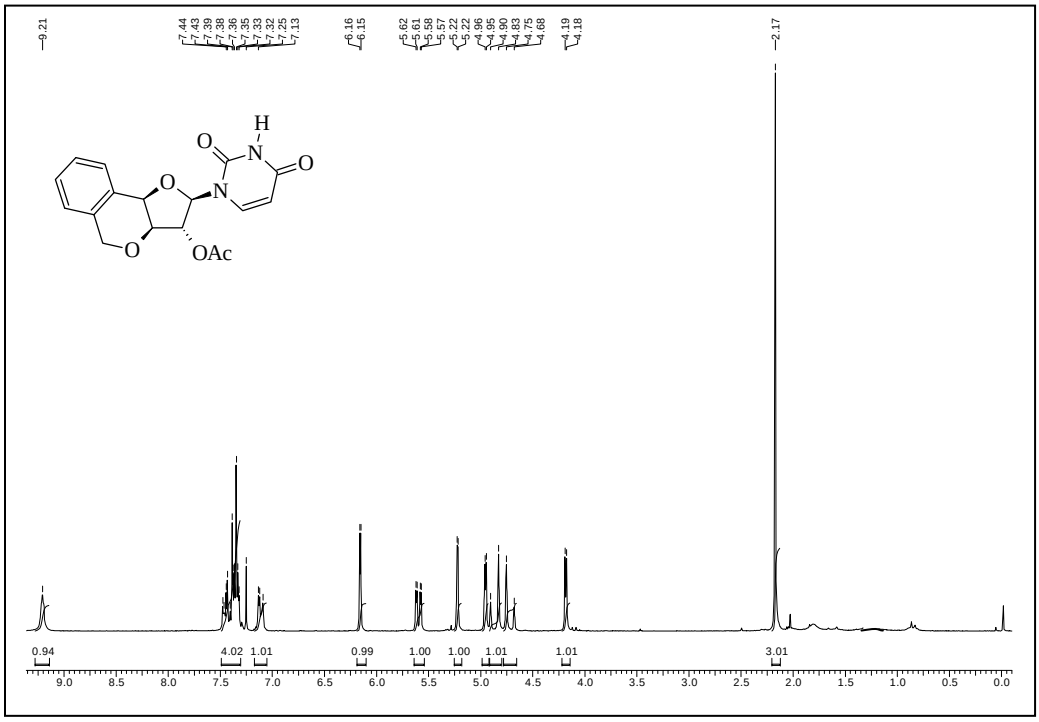
Mol. Formula	: $C_{16}H_{15}FN_2O_6$
M. P.	: 153–155 °C
$[\alpha]_D^{25}$	: +44.0 (*c* 0.7, MeOH).
IR (nujol) $\tilde{\nu}$	: 3387, 3021, 2920, 2854, 1698, 1666, 1461, 1377, 1284, 1245, 1063, 914, 756 cm^{-1}.
^{1}H NMR (Methanol−D_4, 200 MHz)	: δ 3.85 (t, *J* = 10.9 Hz, 1H), 3.95 (dd, *J* = 5.3, 10.7 Hz, 1H), 3.99–4.04 (m, 2H), 5.22 (d, *J* = 11.9 Hz, 1H), 5.26 (d, *J* = 11.9 Hz, 1H), 5.84 (dd, *J* = 1.5, 9.5 Hz, 1H), 7.23−7.25 (m, 1H), 7.29–7.38 (m, 3H), 7.94 (d, *J* = 6.5 Hz, 1H).
^{13}C NMR (Methanol−D_4, 50 MHz)	: 68.5 (t), 71.0 (d), 72.5 (d), 75.6 (t), 83.6 (d), 93.5 (s), 121.6 (d), 121.9 (d), 126.1 (d), 126.5 (d), 128.4 (d), 129.2 (d), 139.0 (s), 142.5 (s), 151.2 (s), 159.0 (s), 159.2 (s) ppm.
ESI-MS (*m/z*)	: 351.5 (18%, $[M+H]^+$), 373.5 (100%, $[M+Na]^+$).
Elemental Analysis	Calcd.: C, 54.86; H, 4.32; N, 8.00 %. Found: C, 54.71; H, 4.48; N, 8.13 %.



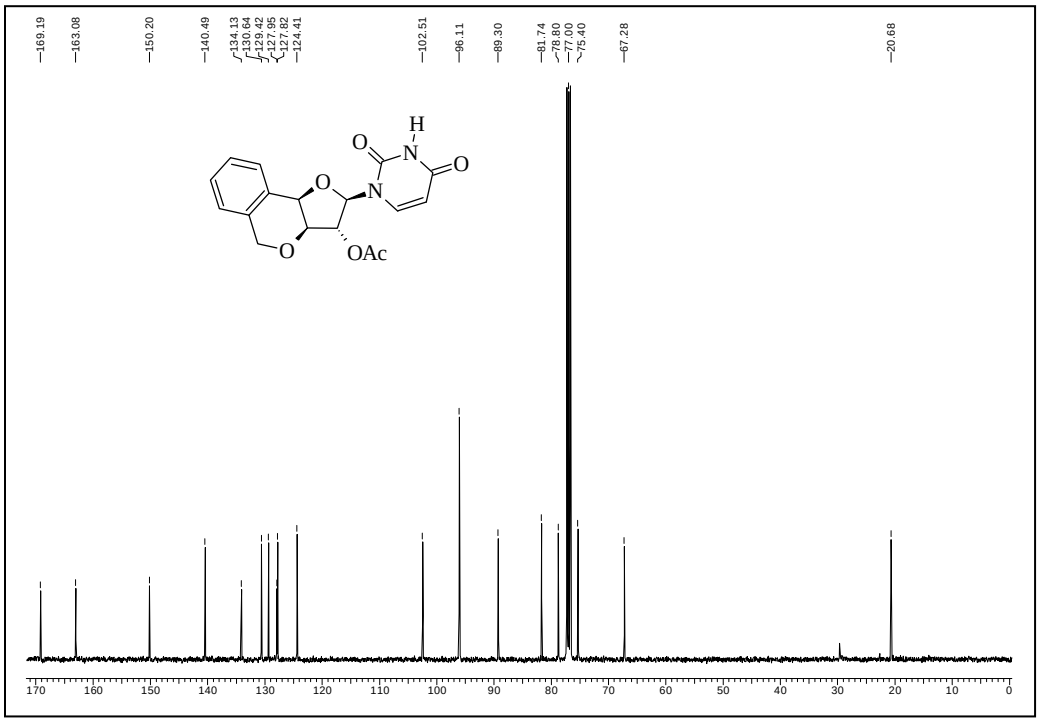
^{1}H NMR Spectrum of 2B.25 in $CDCl_3$



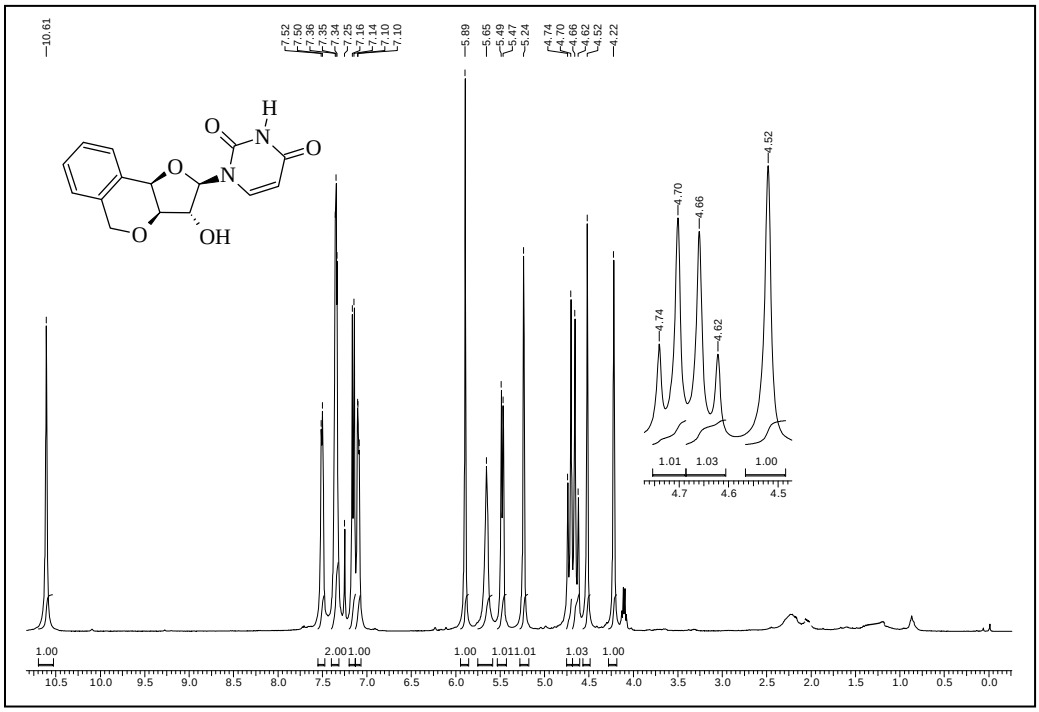
^{13}C NMR Spectrum of 2B.25 in $CDCl_3$



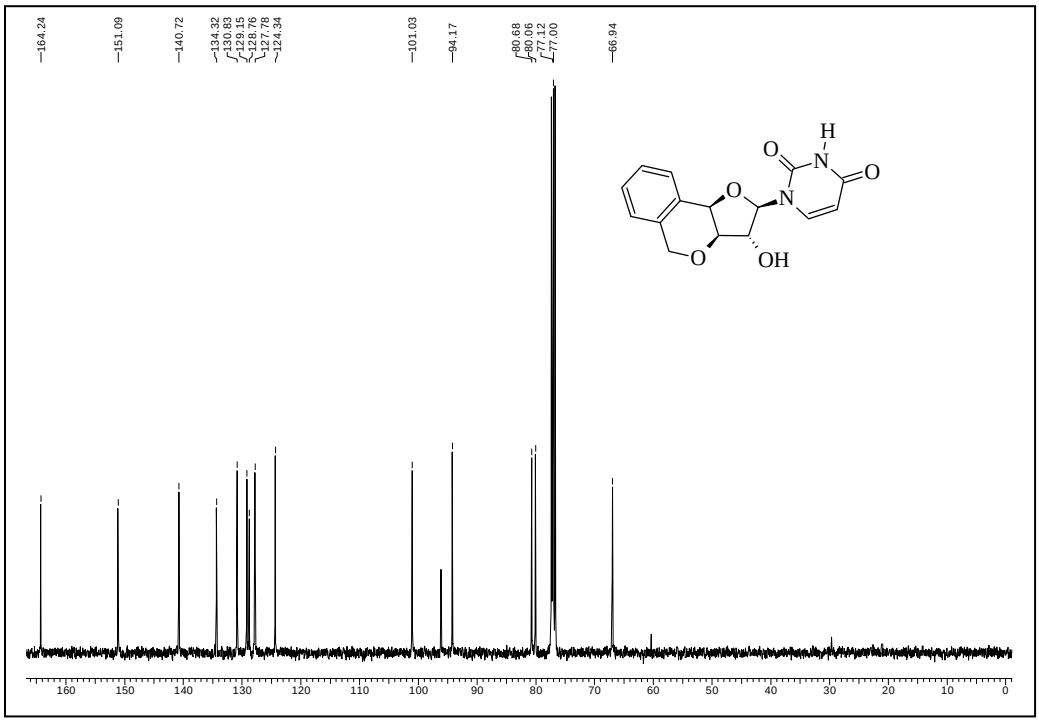
^{1}H NMR Spectrum of 2B.27 in $CDCl_3$



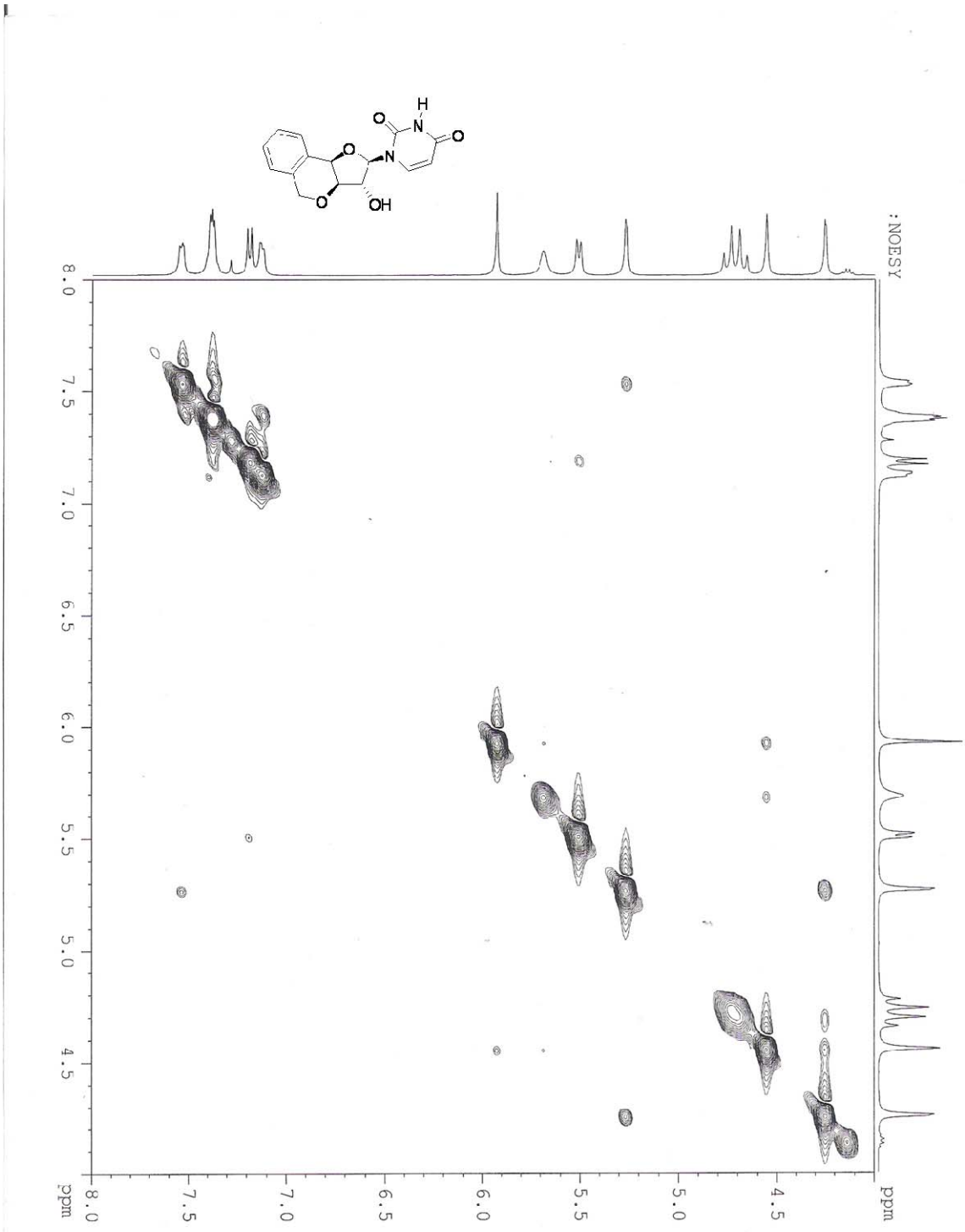
^{13}C NMR Spectrum of 2B.27 in $CDCl_3$



^{1}H NMR Spectrum of 2B.31 in $CDCl_3$



^{13}C NMR Spectrum of 2B.31 in $CDCl_3$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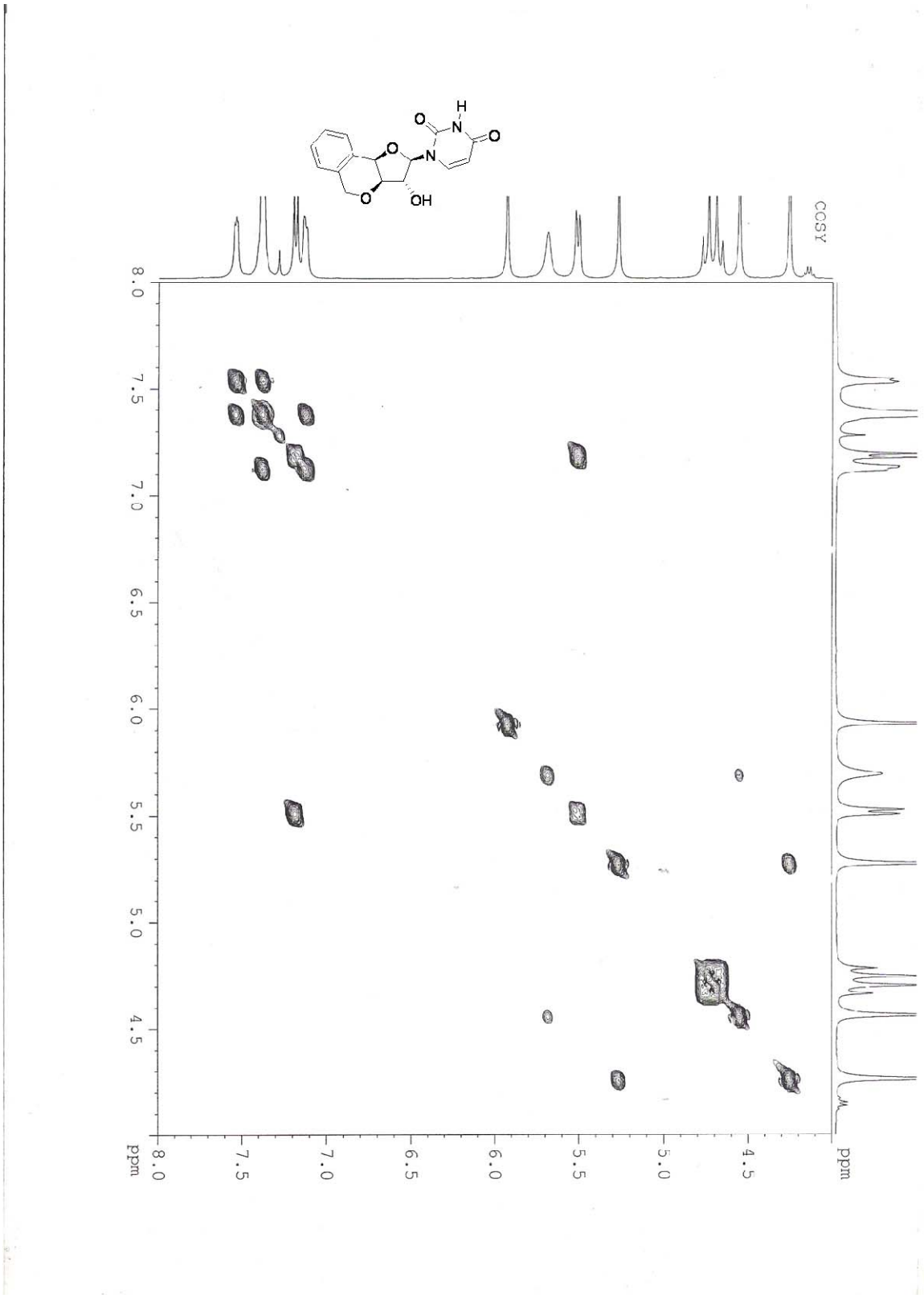
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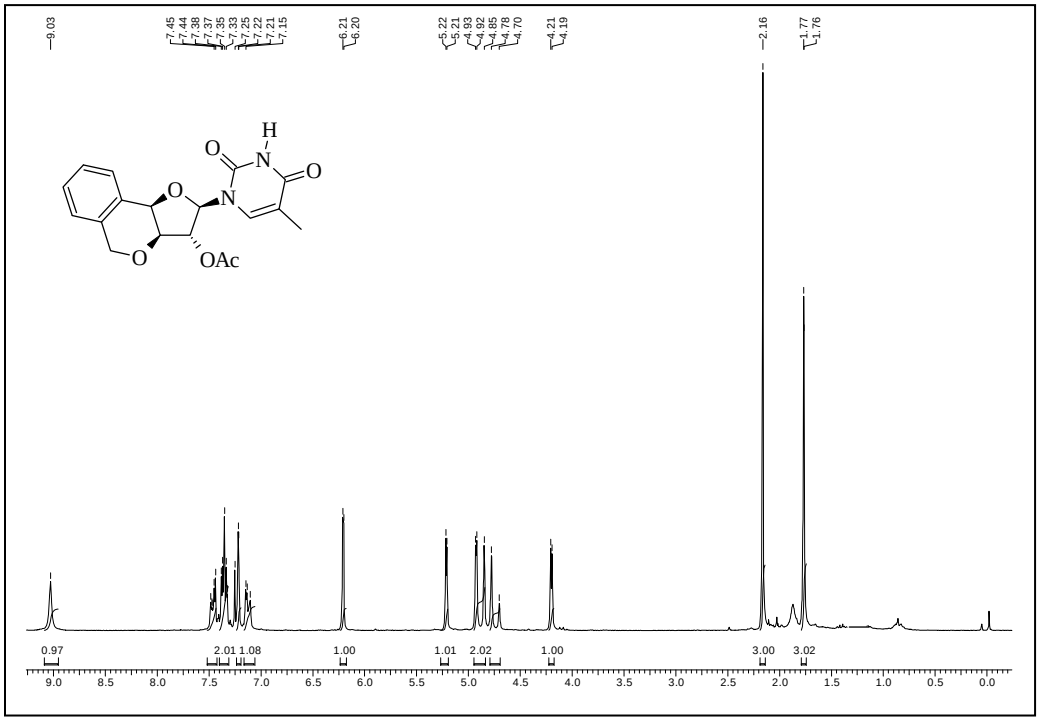
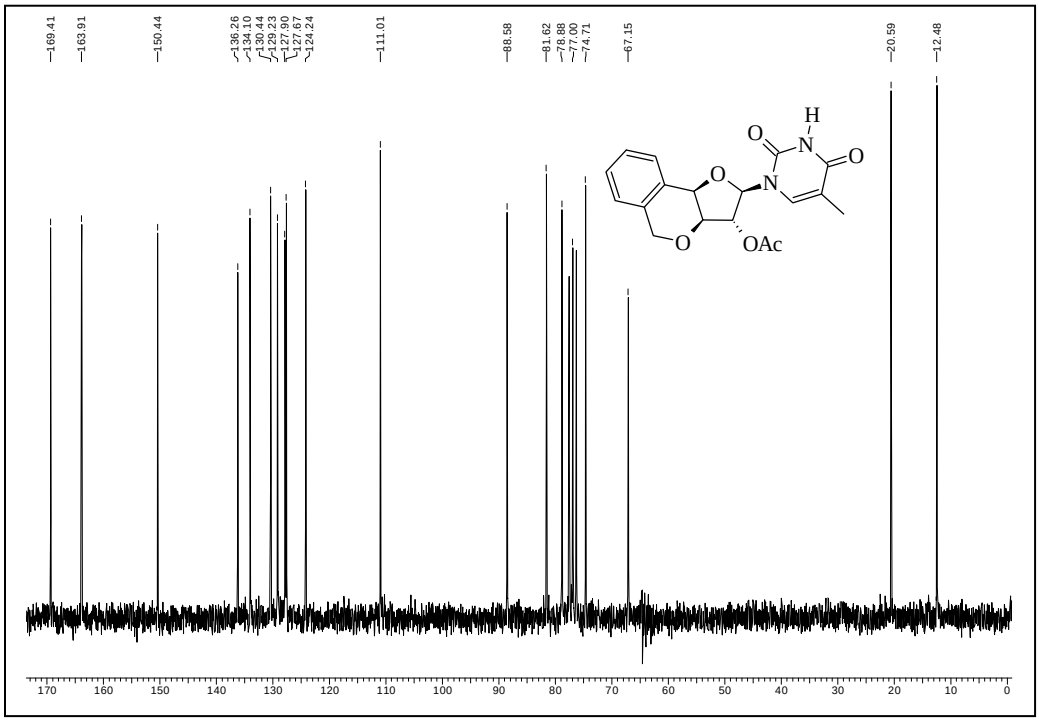
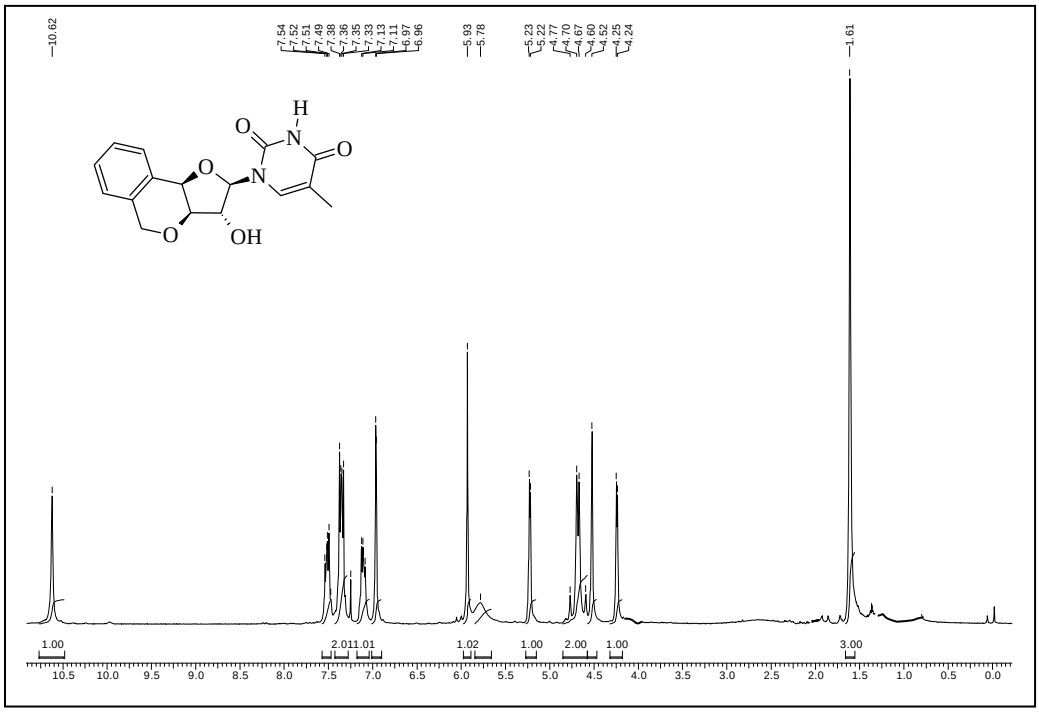


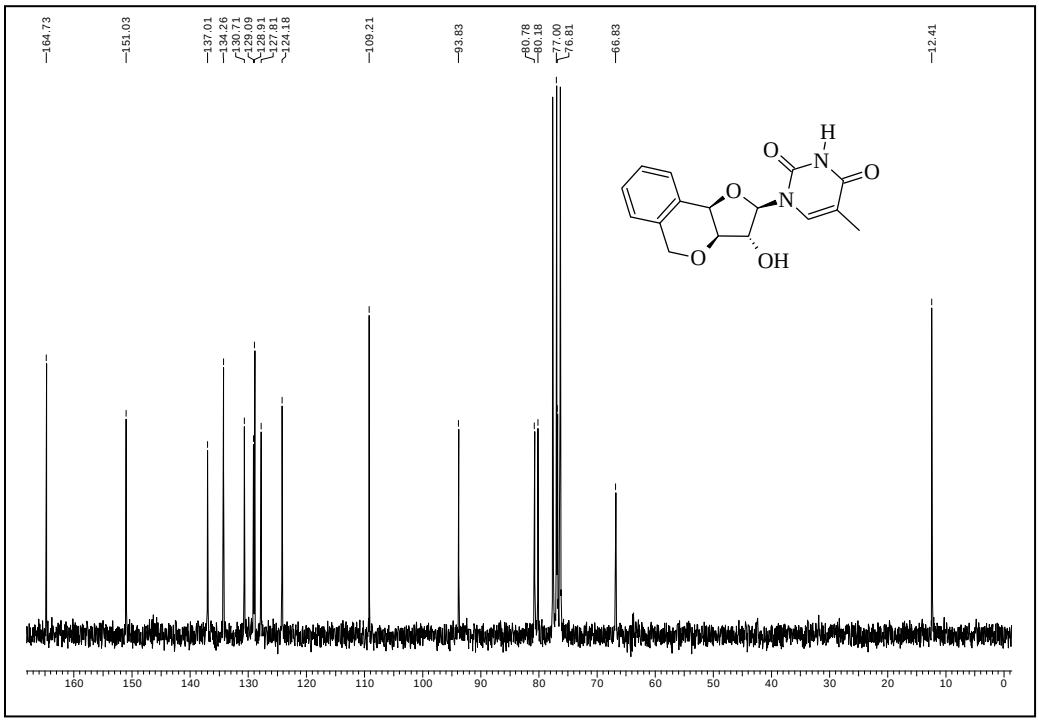
^{1}H NMR Spectrum of 2B.28 in $CDCl_3$



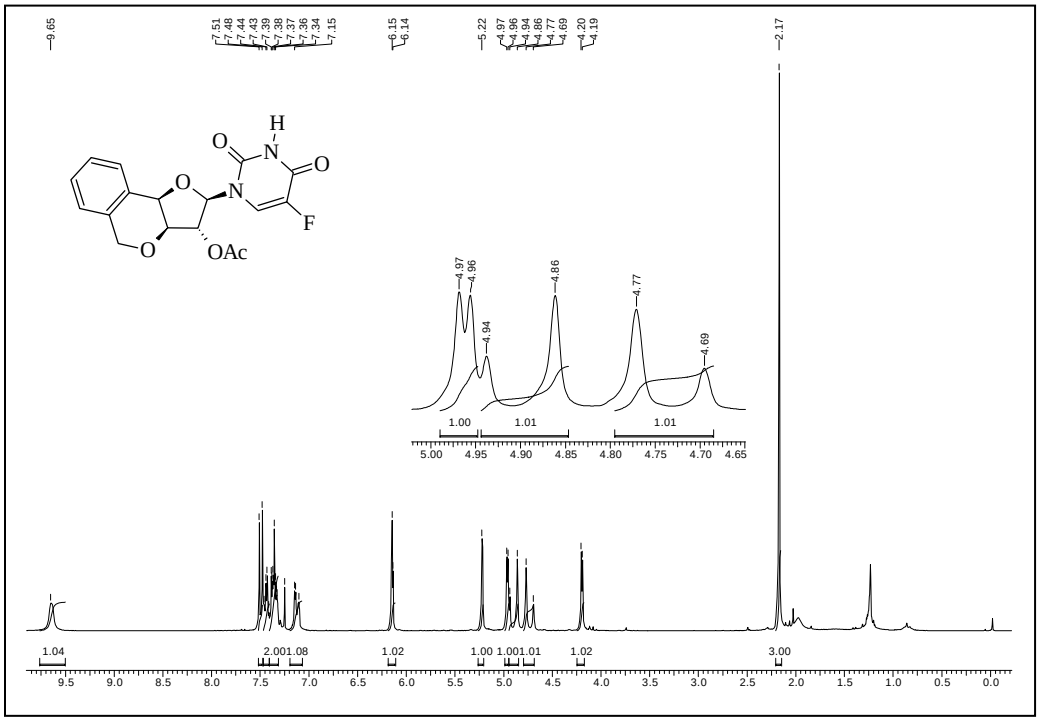
^{13}C NMR Spectrum of 2B.28 in $CDCl_3$



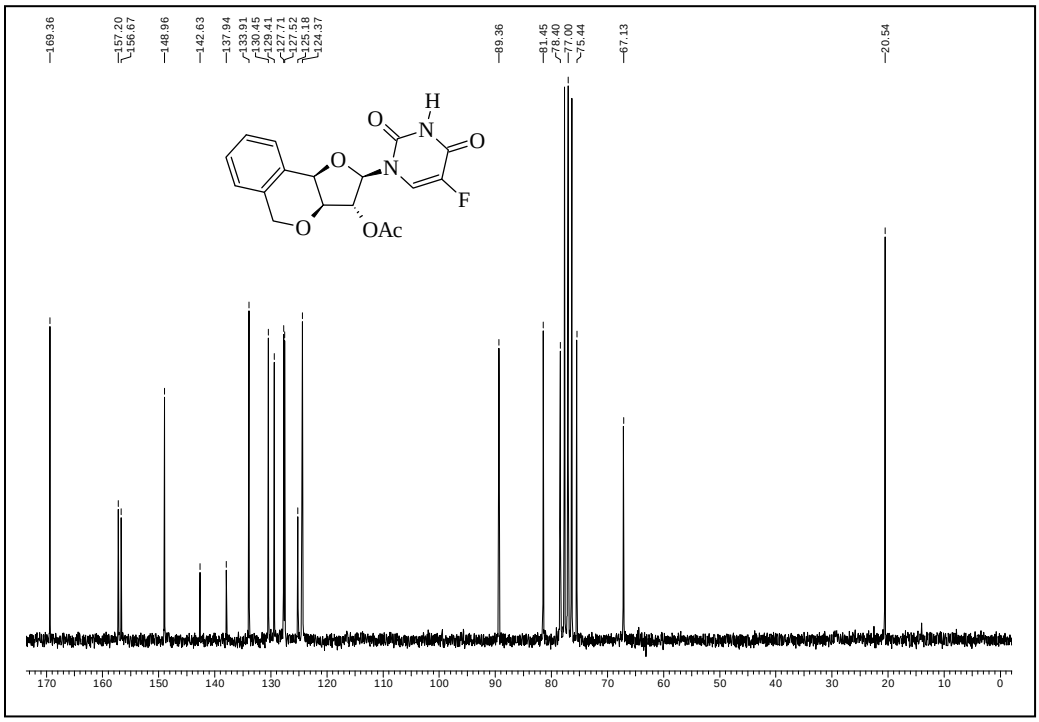
^{1}H NMR Spectrum of 2B.32 in $CDCl_3$



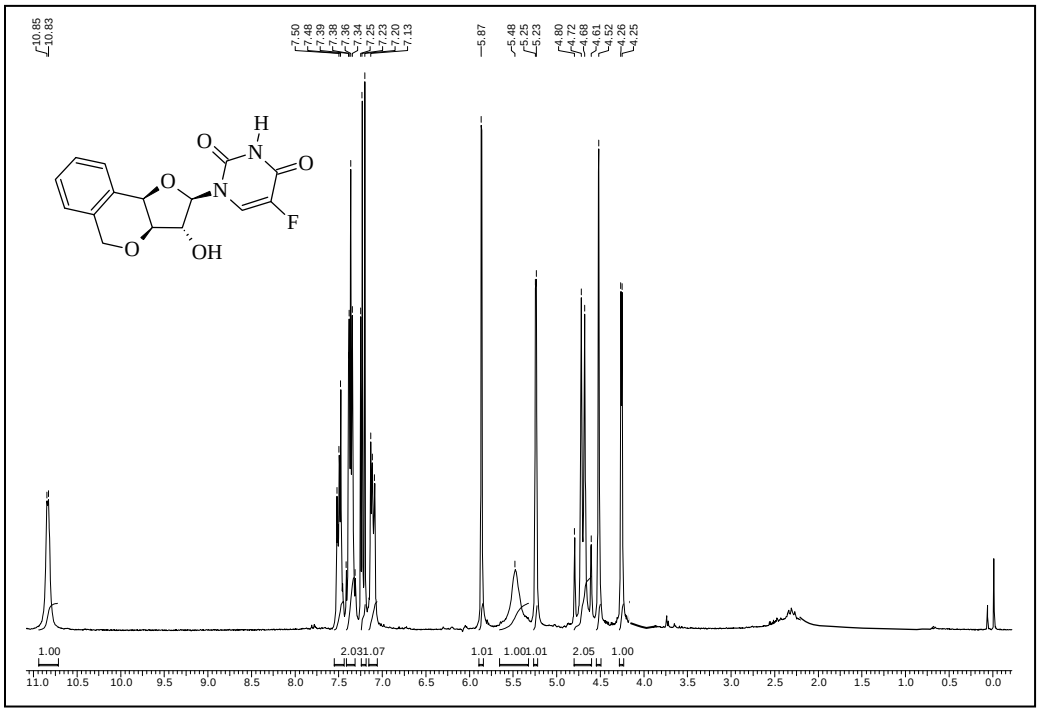
^{13}C NMR Spectrum of 2B.32 in $CDCl_3$



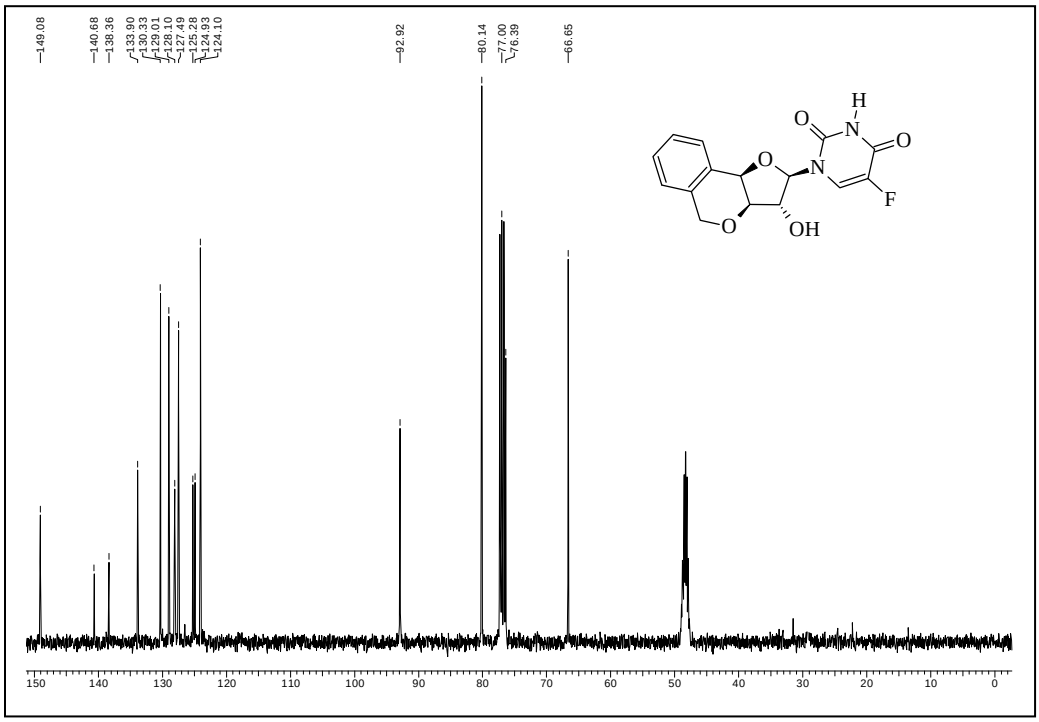
^{1}H NMR Spectrum of 2B.29 in $CDCl_3$



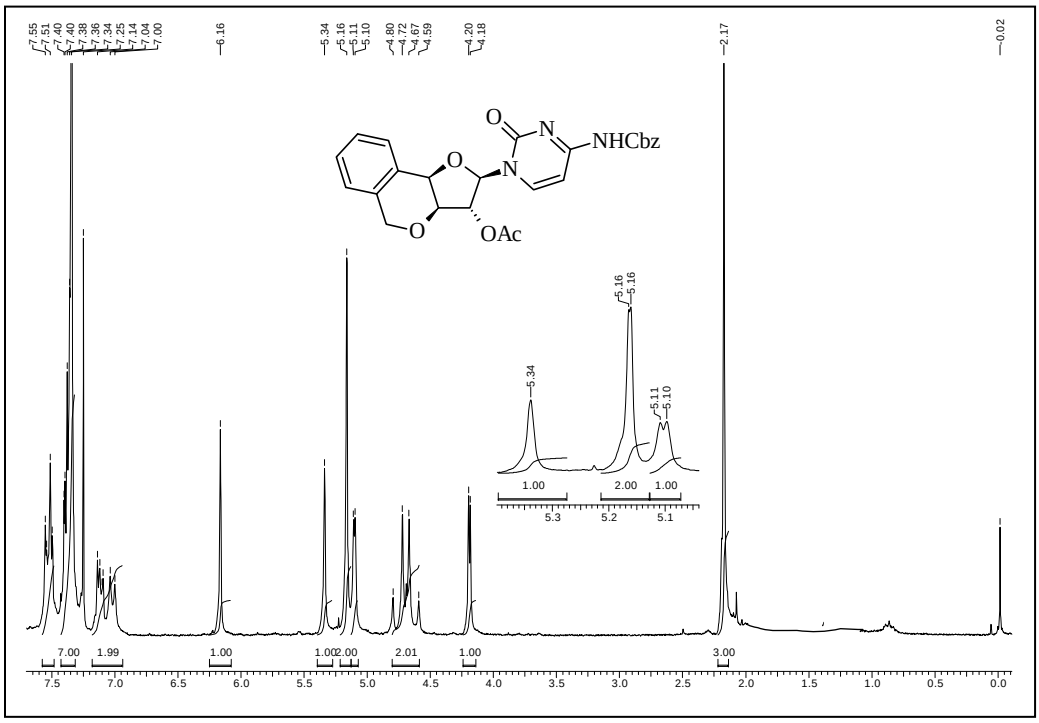
^{13}C NMR Spectrum of 2B.29 in $CDCl_3$



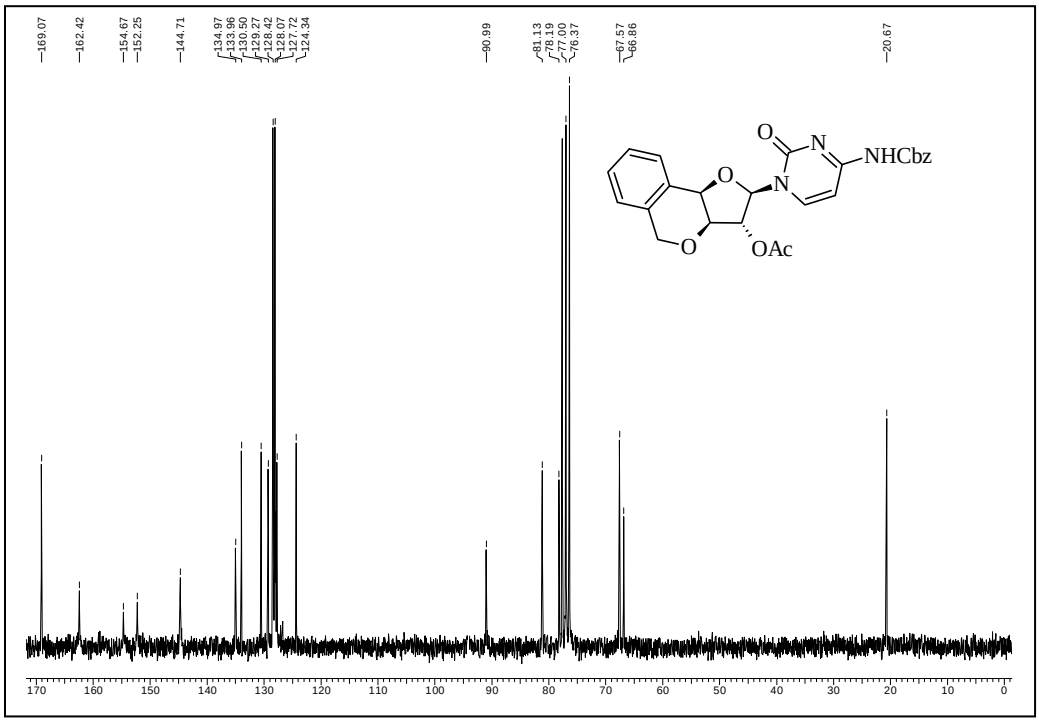
^{1}H NMR Spectrum of 2B.33 in $CDCl_3$



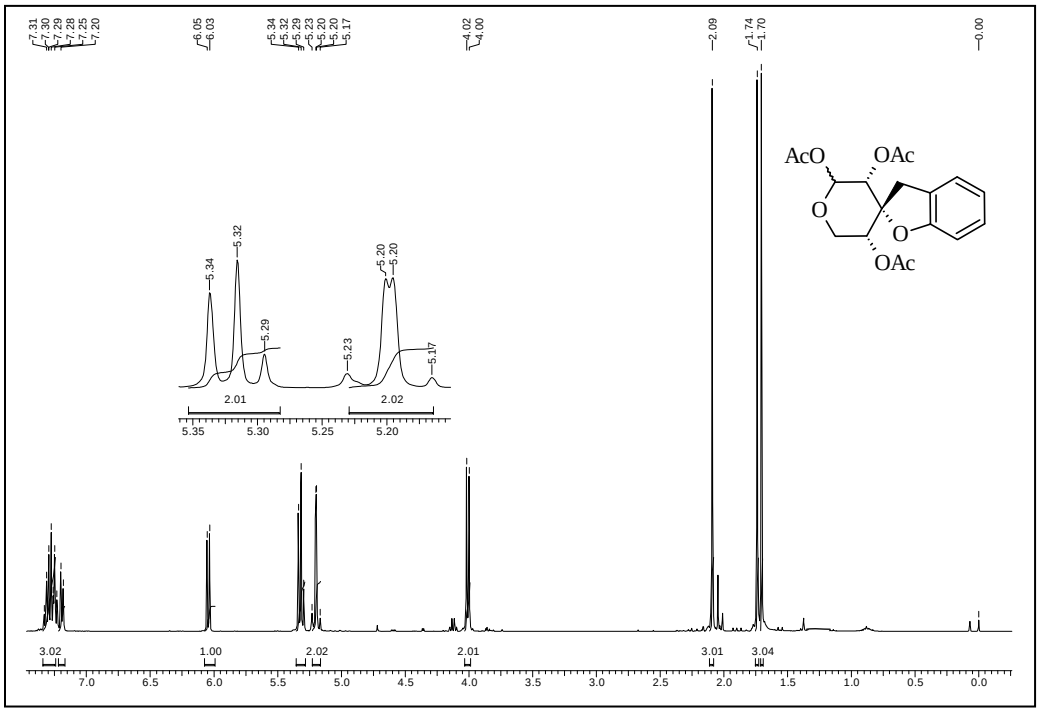
^{13}C NMR Spectrum of 2B.33 in $CDCl_3$+Methanol-D_4



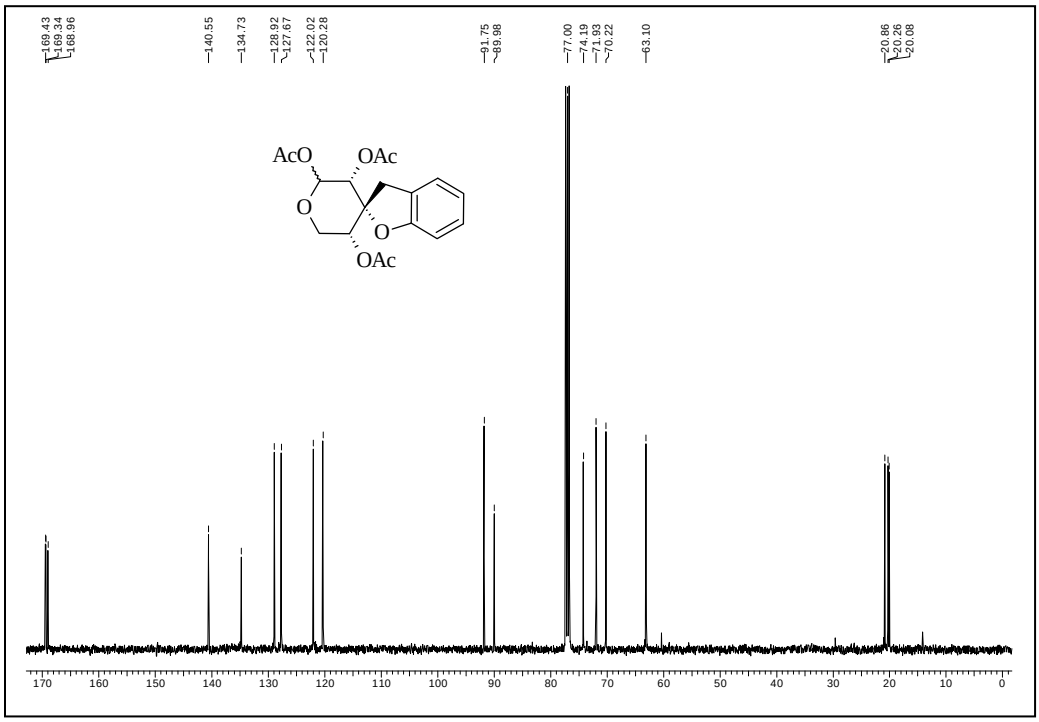
^{1}H NMR Spectrum of 2B.30 in $CDCl_3$



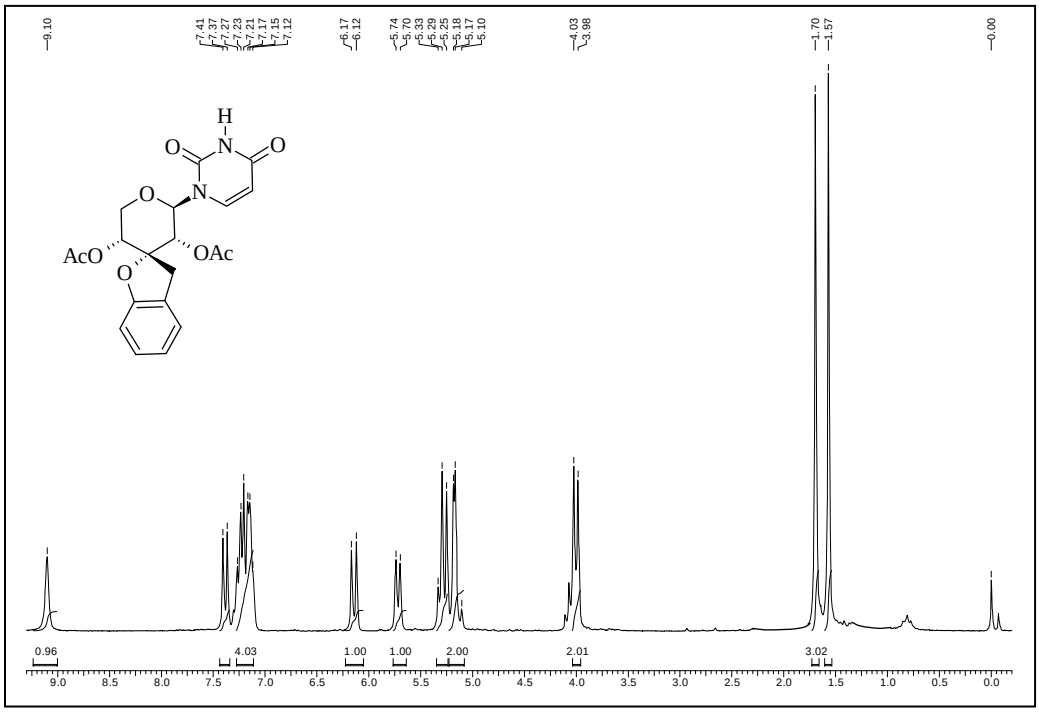
^{13}C NMR Spectrum of 2B.30 in $CDCl_3$



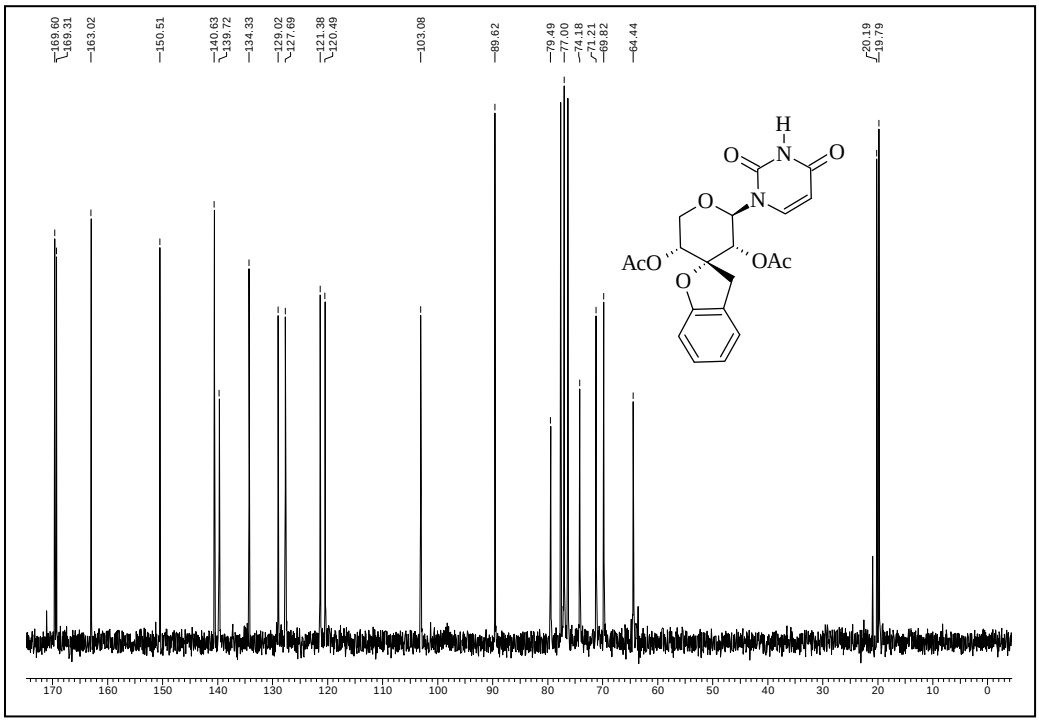
^{1}H NMR Spectrum of 2B.26 in $CDCl_3$



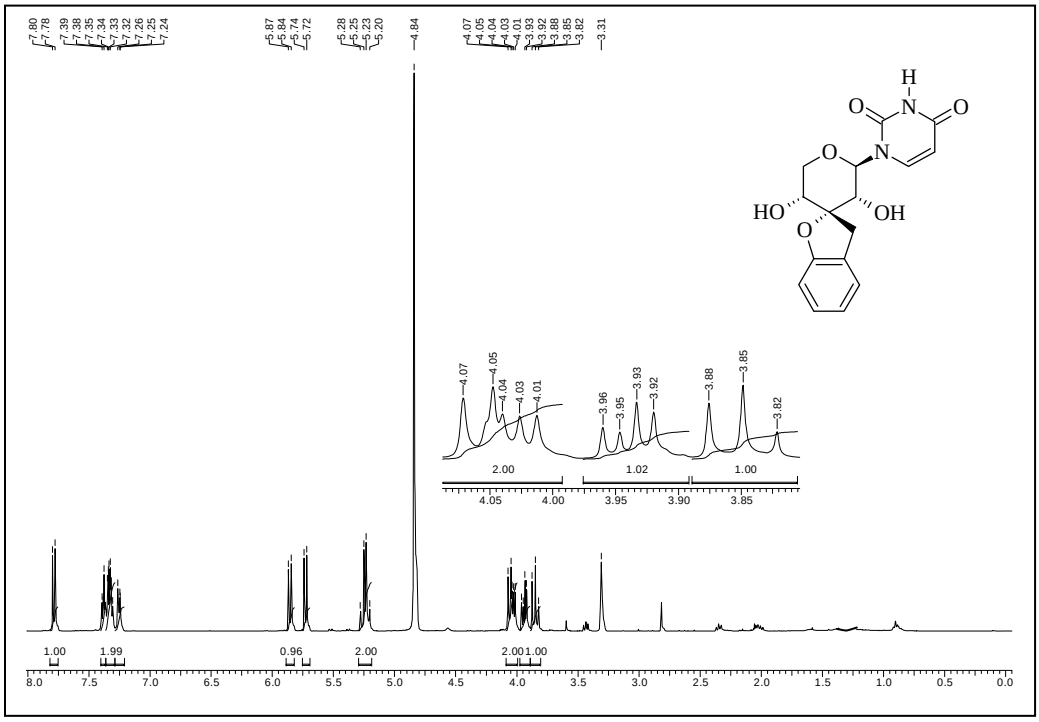
^{13}C NMR Spectrum of 2B.26 in $CDCl_3$



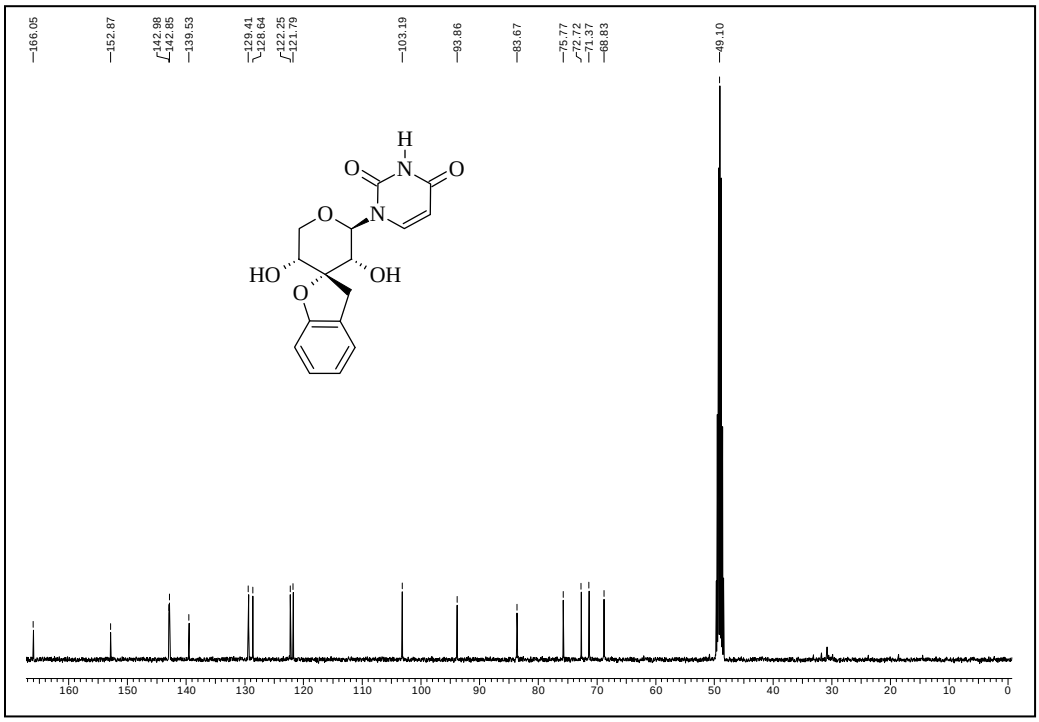
^{1}H NMR Spectrum of 2B.34 in $CDCl_3$



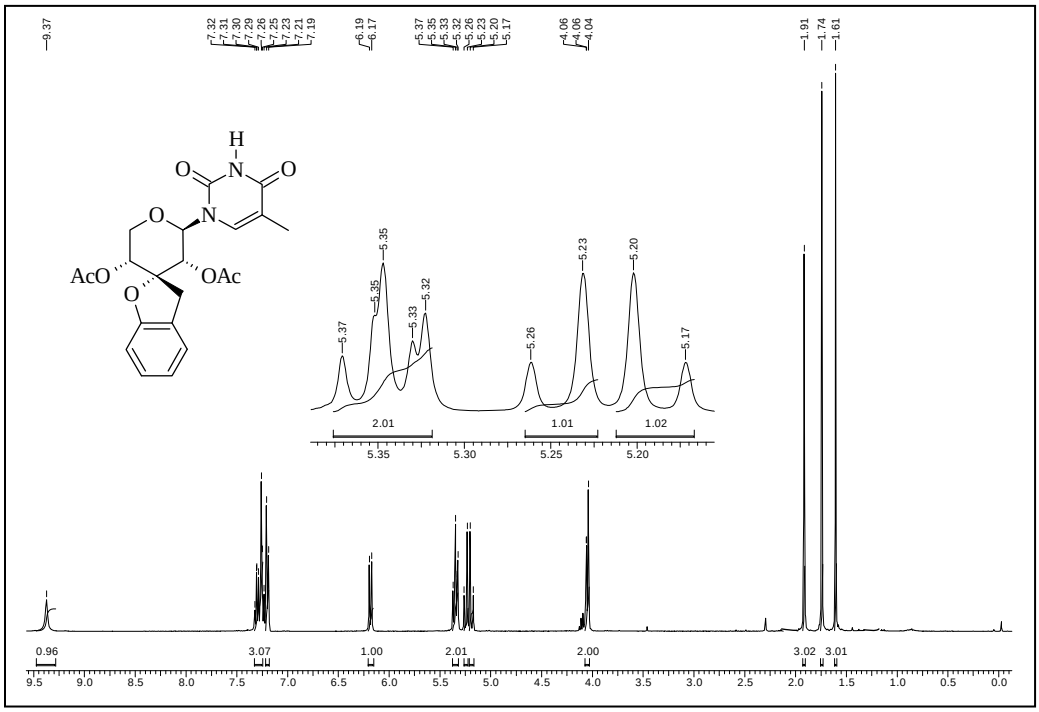
^{13}C NMR Spectrum of 2B.34 in $CDCl_3$



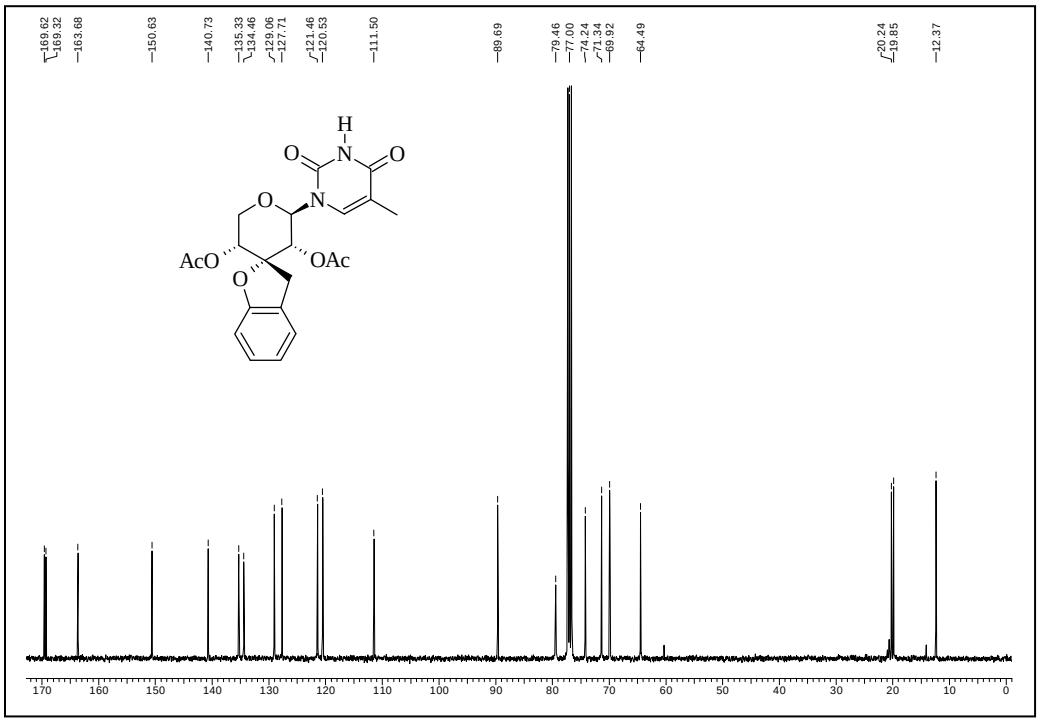
^{1}H NMR Spectrum of 2B.37 in Methanol-D_4



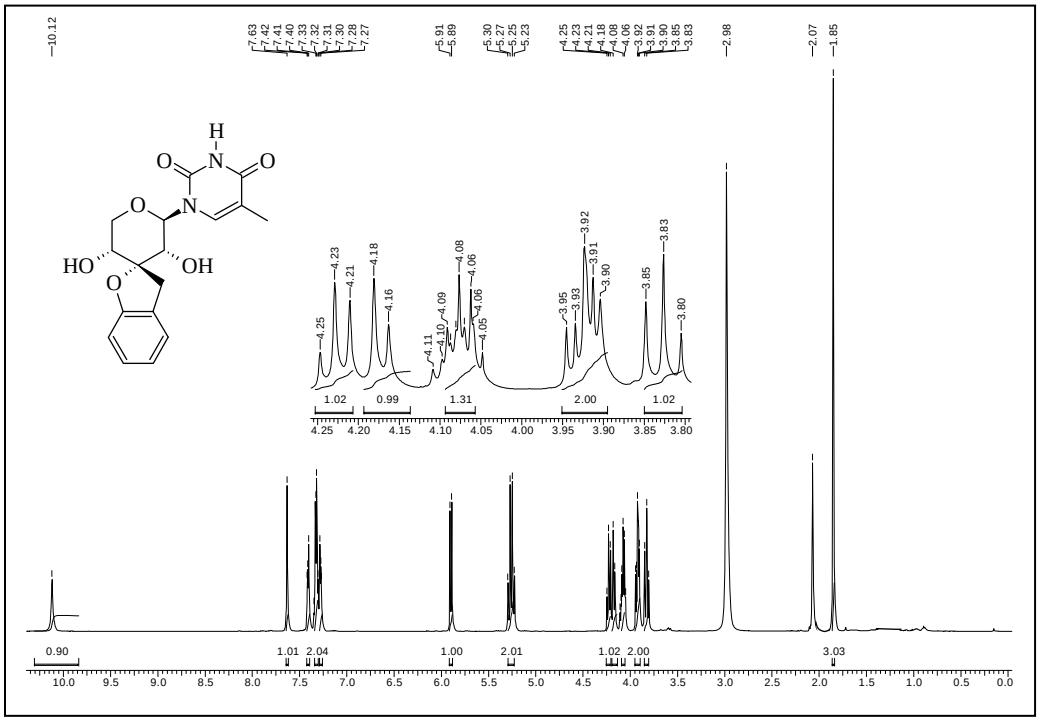
^{13}C NMR Spectrum of 2B.37 in Methanol-D_4



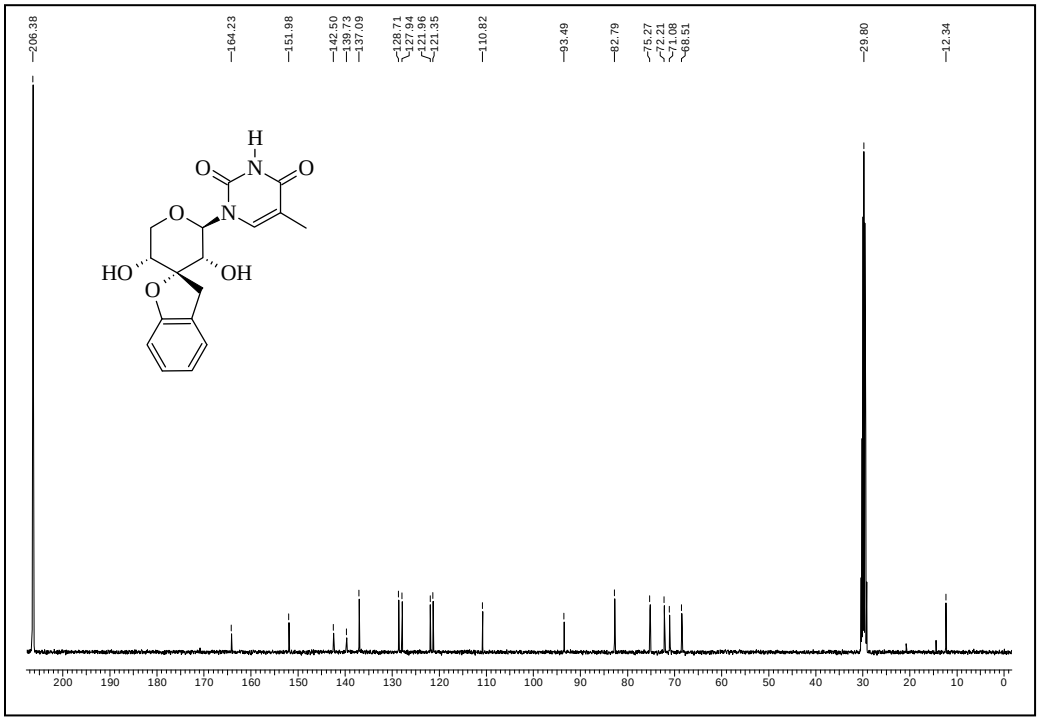
^{1}H NMR Spectrum of 2B.35 in $CDCl_3$



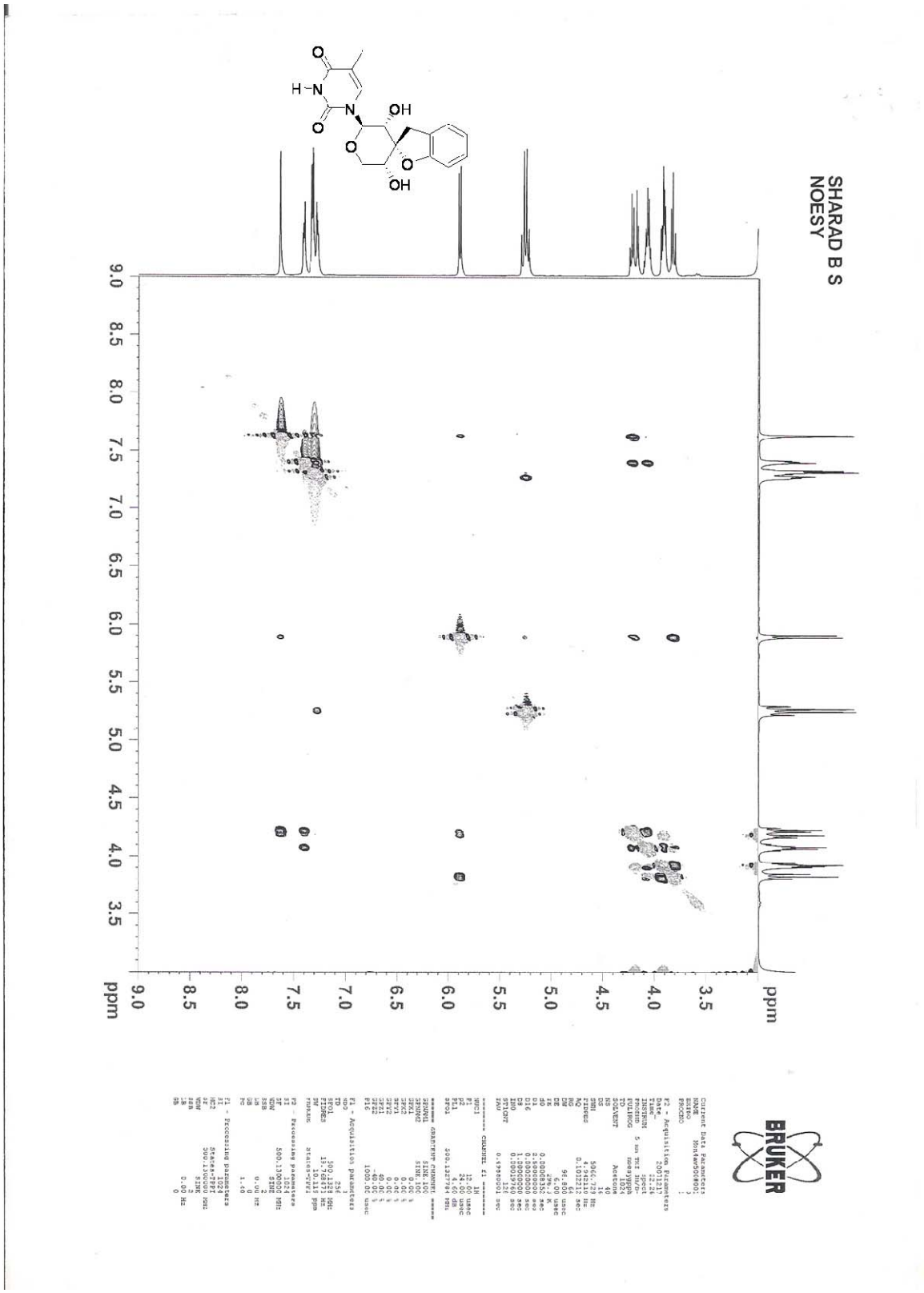
^{13}C NMR Spectrum of 2B.35 in $CDCl_3$



^{1}H NMR Spectrum of 2B.38 in Acetone-D$_6$



^{13}C NMR Spectrum of 2B.38 in Acetone-D$_6$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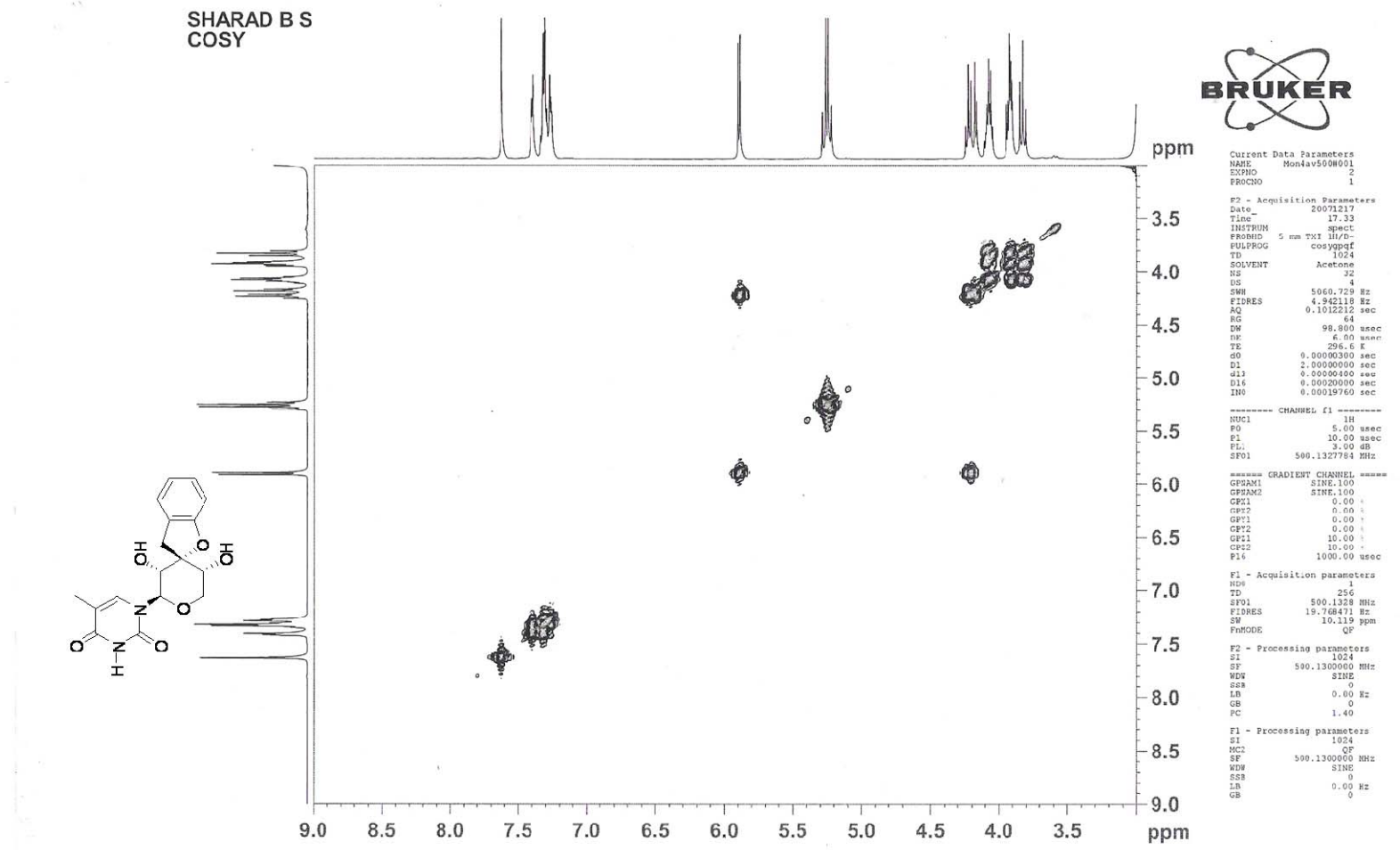
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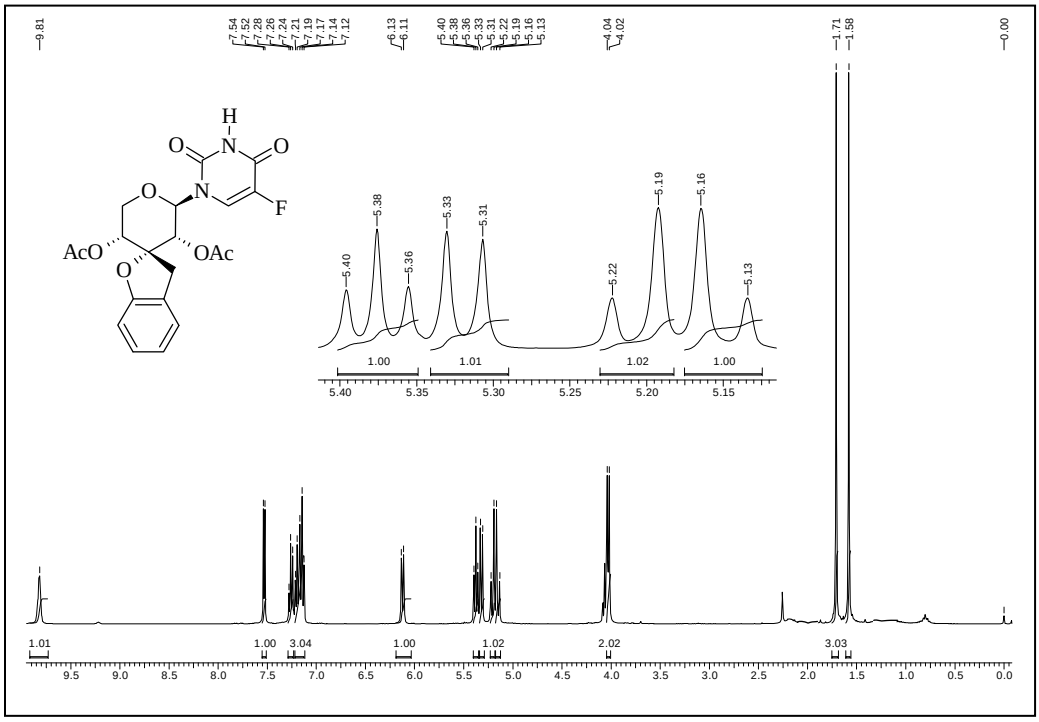
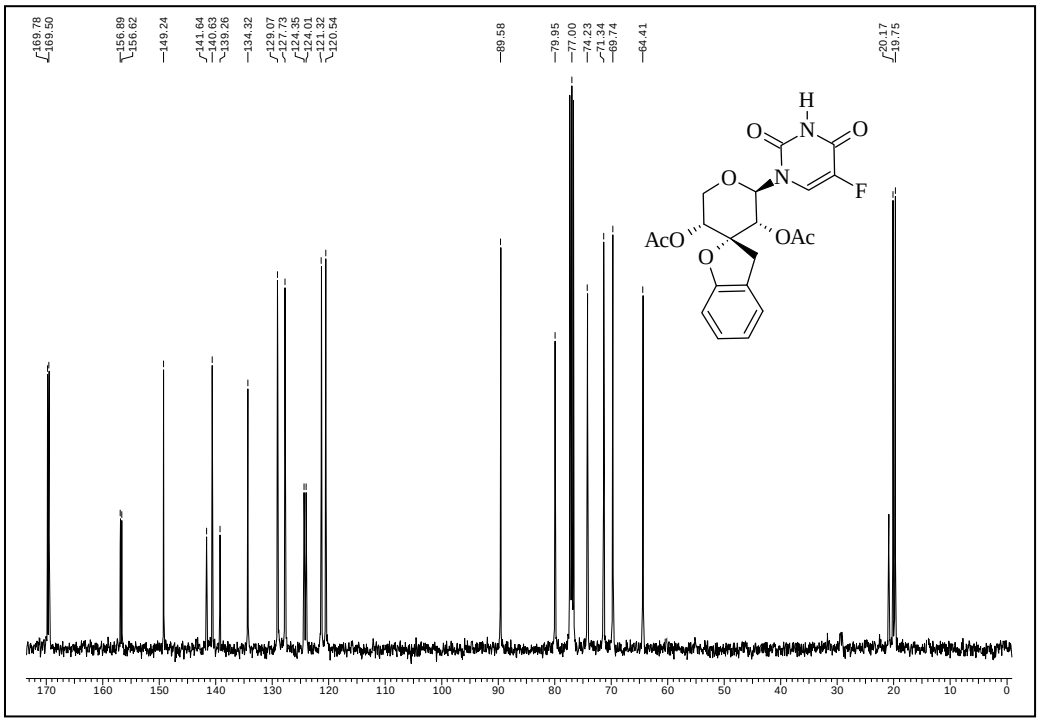
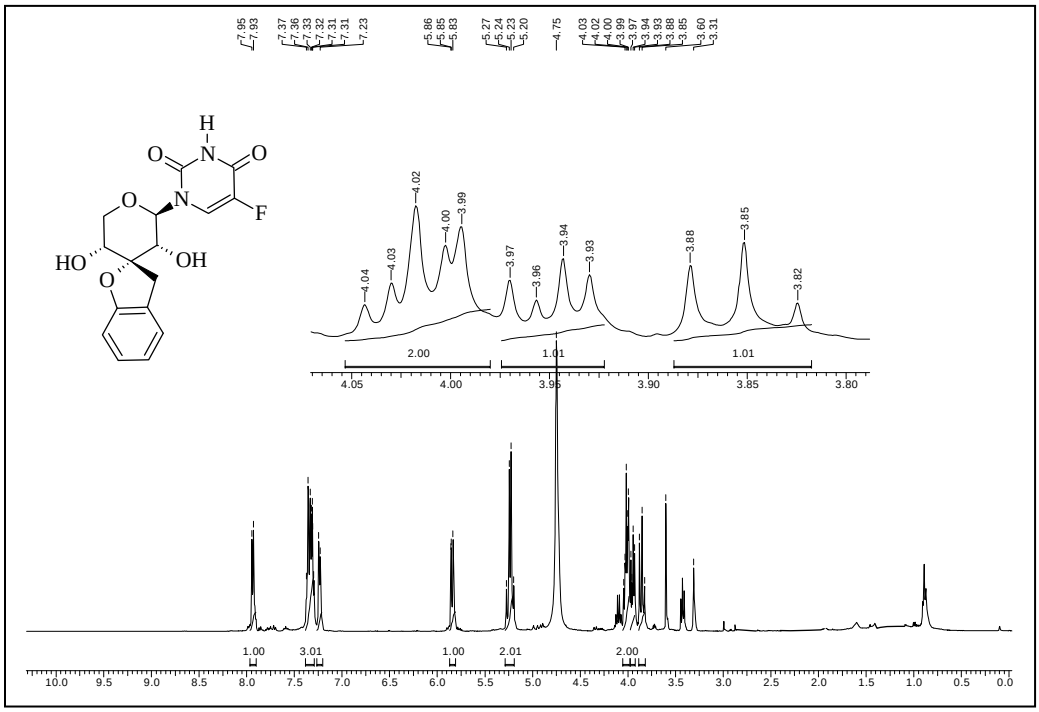
OH
O
O
N
N
H
O
O
Current Data Parameters
NAME Mon4av500H001
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20071217
Time 17.33
INSTRUM spect
PROBHD 5 mm TXI 1H/D-
PULPROG cosygpqf
TD 1024
SOLVENT Acetone
NS 32
DS 4
SWH 5060.729 Hz
FIDRES 4.942118 Hz
AQ 0.1012212 sec
RG 64
DW 98.800 usec
DE 6.00 usec
TE 296.6 K
d0 0.00000300 sec
D1 2.00000000 sec
d13 0.00000400 sec
D16 0.00020000 sec
IN0 0.00019760 sec
======== CHANNEL f1 ========
NUC1 1H
P0 5.00 usec
P1 10.00 usec
PL1 3.00 dB
SFO1 500.1327784 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPY2 0.00 %
GPZ1 0.00 %
GPY2 0.00 %
GPZ1 10.00 %
GPZ2 10.00 %
P16 1000.00 usec
F1 - Acquisition parameters
ND0 1
TD 256
SFO1 500.1328 MHz
FIDRES 19.768471 Hz
SW 10.119 ppm
FnMODE QF
F2 - Processing parameters
SI 1024
SF 500.1300000 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 1024
MC2 QF
SF 500.1300000 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0



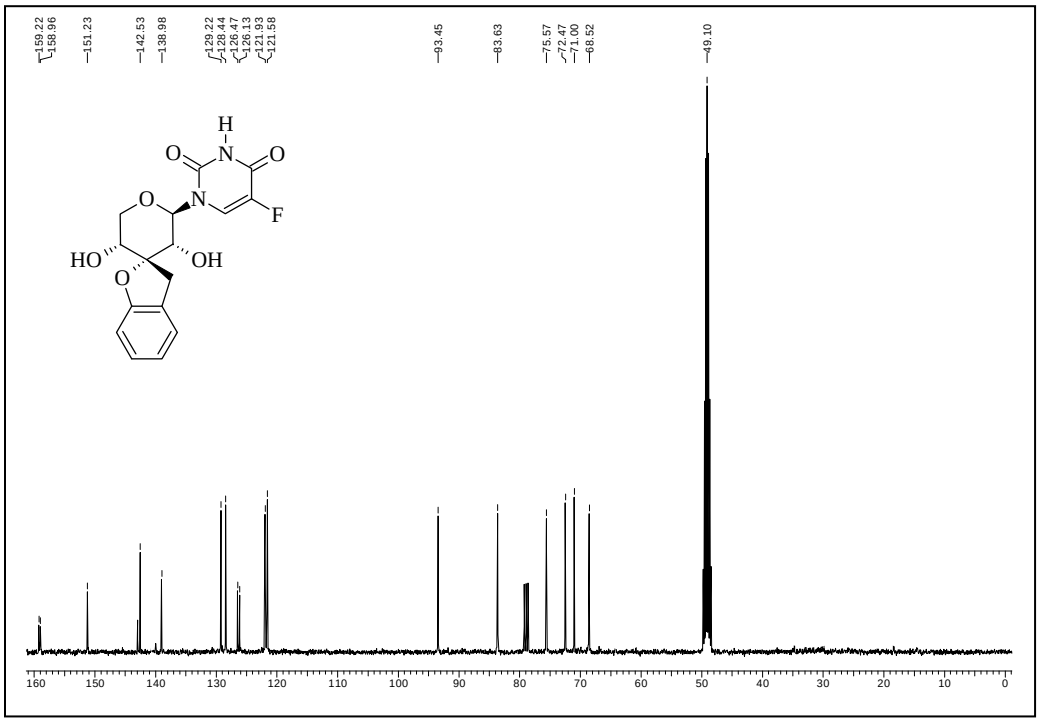
^{1}H NMR Spectrum of 2B.36 in $CDCl_3$



^{13}C NMR Spectrum of 2B.36 in $CDCl_3$



^{1}H NMR Spectrum of 2B.39 in $CDCl_3$+Methanol-D_4



^{13}C NMR Spectrum of 2B.39 in $CDCl_3$+Methanol-D_4

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LIST OF PUBLICATIONS

1. "Total synthesis of pachastrissamine (jaspine B) enantiomers from D-glucose" C. V. Ramana, Awadut G. Giri, **Sharad B. Suryawanshi** and Rajesh G. Gonnade. *Tetrahedron Letters* **2007**, *48*, 265−268.
2. "A [2+2+2]-cyclotrimerization approach for the synthesis of enantiopure isochromans using a carbohydrate derived dialkyne template" C. V. Ramana, **Sharad B. Suryawanshi** *Tetrahedron Letters* **2008**, *49*, 445−448.
3. "Pd(II)-Mediated Alkynediol Spiroketalization: First Total Synthesis of (–)-Cephalosporolide E and (+)-Cephalosporolide F" C. V. Ramana, **Sharad B. Suryawanshi** and Rajesh G. Gonnade *J. Org. Chem.* **2009**, *74*, 2842–2845**.**
4. "Flexibility Oriented Synthesis of *C*–3' Spiroannulated Nucleosides" C. V. Ramana, Mangesh G. Dushing and **Sharad B. Suryawanshi** (*communicated*).
5. *A [2+2+2]-cyclotrimerization approach for spiroannulation of 1,3-dihydroisobenzofuran ring on carbohydrate templates* C. V. Ramana, and **Sharad B. Suryawanshi** (*to be communicated*).

POSTER PRESENTATIONS

1. Total synthesis of pachastrissamine enantiomers (jaspine B) from D-glucose (*National Science Day* celebration at NCL – **2007**).
2. A [2+2+2]-cyclotrimerization approach for synthesis of Tri-/Spriocyclic Nucleosides (Best Poster Award on *National Science Day* celebration at NCL – **2008**).
3. First Total Synthesis of Cephalosporolides E & F (Best Poster Award on *National Science Day* celebration at NCL – **2009**).

Erratum