# Novel methods and intermediates for the preparation of cyclitols & their derivatives- An approach towards the synthesis of phosphoinositols

THESIS

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**BY**

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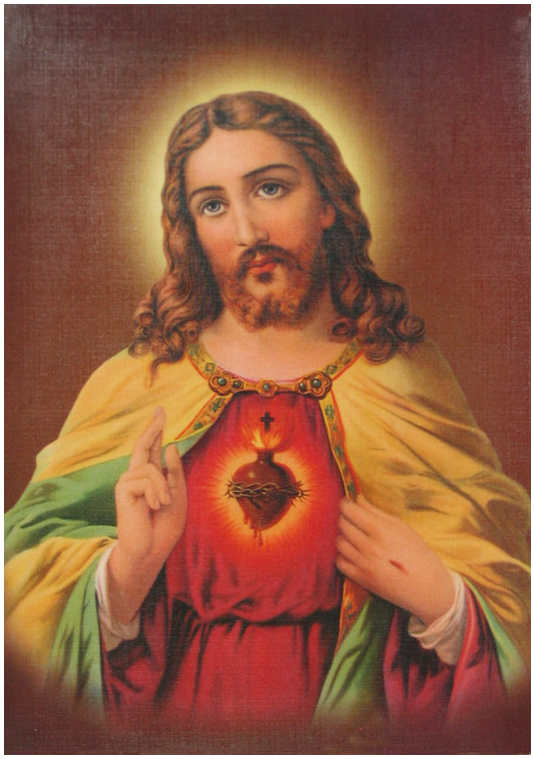
# "Gift of God" Dedicated to my Family



# CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "Novel methods and intermediates for the preparation of cyclitols & their derivatives- An approach towards the synthesis of phosphoinositols" submitted by **Alson Mart** was carried out by him under my supervision at the National Chemical Laboratory, Pune, India. Such materials, obtained from other sources have been duly acknowledged in the thesis.

Date: /02/2016

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## DECLARATION

I hereby declare that the thesis entitled **"Novel methods and intermediates for the preparation of cyclitols & their derivatives- An approach towards the synthesis of phosphoinositols"** submitted for Ph.D. degree to the Savitribai Phule Pune University has been carried out at National Chemical Laboratory, under the supervision of **Dr. M. S. Shashidhar**. This work is original and has not been submitted in part or full by me for any degree or diploma to any university.

Date: /02/2016

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**(ALSON MART)**

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# CONTENTS

## Chapter 3. Synthesis of biologically and synthetically important inositol derivatives.

# Abbreviations

| | |
|---|---|
| Ac | Acetyl |
| $Ac_2O$ | Acetic anhydride |
| AcCl | Acetyl chloride |
| All | Allyl |
| AllBr | Allyl bromide |
| Anhd. | Anhydrous |
| aq. | Aqueous |
| Bn | Benzyl |
| BnBr | Benzyl bromide |
| BOM | Benzyloxy methyl |
| $^t$BuOH | Tert-Butanol |
| Bz | Benzoyl |
| BzCl | Benzoyl chloride |
| Calcd | Calculated |
| Cat. | Catalytic |
| Concd | Concentration |
| CSA | Camphorsulfonic acid |
| DAG | Diacyl glycerol |
| DCC | N,N'-Dicyclohexylcarbodiimide |
| DCM | Dichloromethane |
| DDQ | 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone |
| $D_2O$ | Deuterium Oxide |
| DIBAL-H | Diisobutyl aluminium Hydride |
| dil. | Dilute |
| DIPEA | Di-isopropyl ethyl amine |
| DMAP | *N, N*-dimethylamino pyridine |
| DMF | *N, N*-Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| eq. | Equivalent |
| $Et_3N$ | Triethylamine |
| EtOH | Ethanol |

| | |
|---|---|
| g | Gram |
| GPI | Glycophosphatidylinositol |
| h | Hour (s) |
| HRMS | High resolution mass spectrometry |
| Hz | Hertz |
| ICP | Inductively coupled plasma analysis |
| $IP_6$ | Inositol hexakis phosphate |
| IR | Infrared |
| LC-MS | Liquid chromatography-mass spectrometry |
| *m*CPBA | 3-Chloroperbenzoic acid |
| Me | Methyl |
| MeOH | Methanol |
| MeI | Methyliodide |
| MeCN | Acetonitrile |
| mg | Milli gram |
| min. | Minute(s) |
| mL | Milliliter |
| mmol | Milli moles |
| MsCl | Methane sulfonyl chloride |
| Mp | Melting point |
| NaOMe | Sodium methoxide |
| NMR | Nuclear magnetic Resonance |
| PBB | 4-Bromo benzyl |
| Ph | Phenyl |
| $PIP_3$ | Phosphatidylinositol-3,4,5-tris-phosphate |
| PI-PLC | Phosphatidylinositol-specific phospholipase C |
| PMB | 4-Methoxy benzyl |
| PNB | 4-Nitro benzyl |
| $^{i}$PrOH | 2-Propanol |
| Py | Pyridine |
| *rac*- | Racemic |
| ref | Reference |

| | |
|---|---|
| rt | Room temperature (23–30 $^{o}$C) |
| sn | Stereospecific numbering |
| TBDMS | *tert*-Butyldimethylsilyl |
| TES | Triethylsilyl |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| TIPS | Triisopropylsilyl |
| TLC | Thin layer chromatography |
| TMS | Trimethylsilyl |
| Tr | Trityl |
| TsCl | 4-Toluene sulfonyl chloride |
| TsOH | 4-Toluene sulfonic acid |
| XPS | X-ray photoelectron spectroscopy |

## Synopsis of the thesis

The thesis entitled **"Novel methods and intermediates for the preparation of cyclitols & their derivatives- An approach towards the synthesis of phosphoinositols"** presents results pertaining to the development of $Pd(OH)_2/C$ as a selective ether cleaving agent and its use in the synthesis of inositol derivatives, in three chapters. Since syntheses involving inositols require extensive protection – deprotection strategy, it is well suited to illustrate the potential of $Pd(OH)_2/C$ as a selective ether cleaving agent.

**Chapter 1: Palladium in organic transformations– a brief literature survey.** This chapter is a brief review of the literature on selected uncommon reactions brought about by palladium(II) compounds and unligated Pd(0).

**Chapter 2: Potential of $Pd(OH)_2/C$ as a selective ether cleaving agent.** This chapter consists of four sections; **Section 2A** illustrates the selective and catalytic allyl ether cleaving ability of $Pd(OH)_2/C$. **Section 2B** demonstrates the ability of $Pd(OH)_2/C$ to cleave benzyl and substituted benzyl ethers. **Section 2C** presents results on miscellaneous cleavage experiments. **Section 2D** describes studies directed towards delineating the mechanism of the ether cleavage reactions.

**Chapter 3:** The final chapter presents results on the use of $Pd(OH)_2/C$ for the synthesis of inositol derivatives of contemporary significance.

Brief summary of the results that constitute each of the three chapters is given below.

### Chapter 1. Palladium in organic transformations– a brief literature survey.

Two kinds of palladium reagents namely, Pd(II) and Pd(0) are commonly used for the mediation of organic reactions. Among these Pd(0) complexes are exclusively used as catalysts whereas Pd(II) reagents are either used as stoichiometric oxidizing agents or as precursor for Pd(0). Among the palladium reagents, solid supported reagents are attractive because these reagents can be removed at the end of the reaction by filtration, allowing easy access to the required products, as well as recovery and possible recycling of the palladium reagent. Palladium salts [$Pd(OAc)_2$, $PdCl_2$] and complexes [Pd(0), Pd(II)] are well known for the coupling and oxidation reactions.[1] Palladium salts as well as Pd/C bring about cleavage of acetals and ethers such as silyl

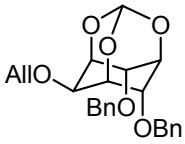
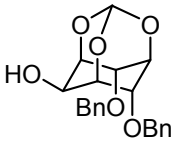
ethers and allyl ethers.[2] Pearlman's catalyst- $Pd(OH)_2/C$- is known to be a highly active catalyst for various coupling reactions and is reported to be more efficient than Pd/C for the hydrogenolysis of benzyl ethers.[4] However, its utility in organic chemistry is not well explored. The subsequent chapters explore the scope of the $Pd(OH)_2/C$ as a selective ether cleaving agent and its use for the synthesis of inositol derivatives.

**Chapter 2, Section A: Selective cleavage of allyl ethers with $Pd(OH)_2/C$.**

Taking cue from our earlier report[5] on the nonhydrogenolytic cleavage of benzyl ethers by $Pd(OH)_2/C$ we investigated the ability of $Pd(OH)_2/C$ to cleave ethers selectively. Preliminary experiments suggested that allyl ethers are more labile to $Pd(OH)_2/C$ than benzyl ethers. Hence we subjected several allyl ethers containing other hydroxyl protecting groups to cleavage conditions with $Pd(OH)_2/C$ and the results are shown in Table 2.1.

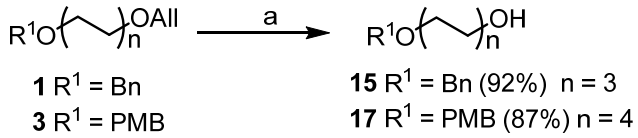
**Table 2.1** Cleavage of allyl ethers by $Pd(OH)_2/C$ in the presence of other hydroxyl protecting groups.

| Entry | Substrate | Conditions[a], h | Product/s (% yield) |
|---|---|---|---|
| 1 | | A, 50 | **14** $HO(CH_2)_6OH$ (76) |
| 2 | **1** $BnO(CH_2)_6OAll$ | B, 1.5 | **15** $BnO(CH_2)_6OH$ (94) |
| 3 | **2** $PBBO(CH_2)_8OAll$ | B, 1.5 | **16** $PBBO(CH_2)_8OH$ (84) |
| 4 | **3** $PMBO(CH_2)_8OAll$ | B, 1.25 | **17** $PMBO(CH_2)_8OH$ (88) |
| 5 | **4** $PNBO(CH_2)_8OAll$ | B, 1.5 | **18** $PNBO(CH_2)_8OH$ (91) |
| 6 | **5** $TsO(CH_2)_8OAll$ | B, 1.5 | **19** $TsO(CH_2)_8OH$ (87) |
| 7 | **6**$AcO(CH_2)_8OAll$ | B, 1.5 | **20** $AcO(CH_2)_8OH$ (92) |
| 8 | **7** $BzO(CH_2)_8OAll$ | B, 1.5 | **21** $BzO(CH_2)_8OH$ (91) |
| 9 | **8** $TrO(CH_2)_8OAll$ | B, 1.5 | **22** $TrO(CH_2)_8OH$ (58) |
| 10 | **8** $TrO(CH_2)_8OAll$ | C, 1 | **23** $TrO(CH_2)_8OH$ (66) |
| 11 | **9** PropargylO-$(CH_2)_8OAll$ | B, 2 | **24** $HO(CH_2)_8OAll$ (36)<br>**25** $HO(CH_2)_8OH$ (54) |
| 12 | **10** TBDMSO-$(CH_2)_8OAll$ | B, 1.5 | **25** $HO(CH_2)_8OH$ (78) |
| 13 | **11** $CH_2=CHCH_2OPh$ | A, 3 | **26** PhOH (70) |
| 14 | **12** $CH_2=CHCH_2OOCPh$ | D 8 | **27** PhCOOH (82) |

| | | | | |
|---|---|---|---|---|
| 15 |  **13** | B, 1.5 |  **28** | (78) |

[a]In all the experiments $Pd(OH)_2/C$ (20% by weight) was used in the proportion mentioned below. Conditions: A, 100 mol%, methanol, reflux; B, 50 mol%, $^{i}$PrOH, reflux; C, 50 mol%, $^{t}$BuOH, reflux; D, 70 mol%, methanol, reflux ; E, 150 mol%, methanol, reflux

The allyl ether cleavage reaction conditions are compatible with several functional groups including C=C and acid sensitive groups such as trityl and orthoester moiety. In some of the allyl ether cleavage experiments we observed the isomerization of the allyl ether to the corresponding propen-1-yl ether. Hence we postulated that the Pd(0) initially generated from Pd(II) during the ether cleavage reaction could be bringing about this isomerization. Isomerization of allyl ethers to the corresponding propenyl ether has earlier been reported.[6] Hence we used a mixture of $Pd(OH)_2/C$ and Pd/C which made the allyl ether cleavage reaction catalytic with respect to palladium (Scheme 2.1).




**Scheme 2.1**. Deallylation using catalytic amount of palladium reagents. (a) $Pd(OH)_2/C$ and Pd/C (10 mol% each), $^{i}$PrOH, reflux, 30 min.

**Chapter 2, Section B: Cleavage of benzyl ethers with $Pd(OH)_2/C$.**

We also investigated the relative ease of cleavage of benzyl ether and substituted benzyl ethers with $Pd(OH)_2/C$. Table 2.2 shows the results of attempts to discriminate the cleavage of different types of benzyloxy groups by $Pd(OH)_2/C$.

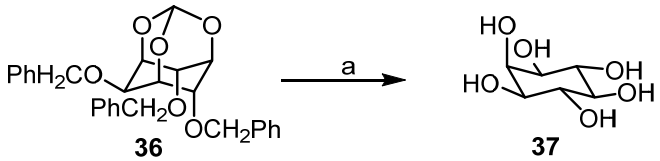
**Table 2.2** Cleavage of benzyl ether and substituted benzyl ethers by $Pd(OH)_2/C$.

| Entry | Substrate | Conditions[a], h | Product/s (% yield) |
|---|---|---|---|
| 1 | **29** $BnO(CH_2)_8OBn$ | A, 5 | **25** (96) |
| 2 | **30** $BnO(CH_2)_8OPNB$ | B, 3 | **18** $HO(CH_2)_8OPNB$ (77) |
| 3 | **31** $PMBO(CH_2)_8OPMB$ | A, 5 | **25** $HO(CH_2)_8OH$ (46) |
| | | | **17** $HO(CH_2)_8OPMB$ (24) |
| 4 | **32** $BnO(CH_2)_8OPMB$ | B, 3 | **17** $HO(CH_2)_8OPMB$ (49) |

| | | | |
|---|---|---|---|
| | | | **25** $HO(CH_2)_8OH$ (47) |
| 5 | **33** $PBBO(CH_2)_8OPBB$ | A, 5 | No reaction |
| 6 | **34** $PhCH_2OPh$ | D, 90 | No reaction |
| 7 | **35** $PhCH_2OOCPh$ | C, 24 | No reaction |

[a] $Pd(OH)_2/C$ (20% by weight) was used in all the experiments in the proportion mentioned below. Conditions: A, 100 mol%, methanol, reflux; B, 50 mol%, $^{i}$PrOH, reflux; C, 50 mol%, methanol, reflux; D, 70 mol%, methanol, reflux.

Competition experiments with benzyl ether and substituted benzyl ethers showed that benzyl ether can be cleaved in preference to *p*-nitrobenzyl ether. Although benzyl ether could be cleaved in preference to *p*-methoxy benzyl ether, the selectivity was modest. A comparison of the results on the cleavage of benzyl ether **11** and *p*-bromobenzyl ether **13** suggested that these two ethers can be discriminated. These results are in contrast to the preference in the cleavage of benzyl ether and *p*-methoxy benzyl ether by DDQ[7] (wherein PMB ether is more labile) and Buchwald's method[8] (wherein *p*-halobenzyl ethers are cleaved in preference to benzyl ether). It is also pertinent to note that although alkyl-benzyl ethers can be cleaved with $Pd(OH)_2/C$, aryl benzyl ethers and benzyl esters are stable. We also observed that cleavage of more benzyl ethers per molecule of the substrate required proportionately more of the palladium reagent and longer reaction time; however yield was not compromised (Scheme 2.2 below).

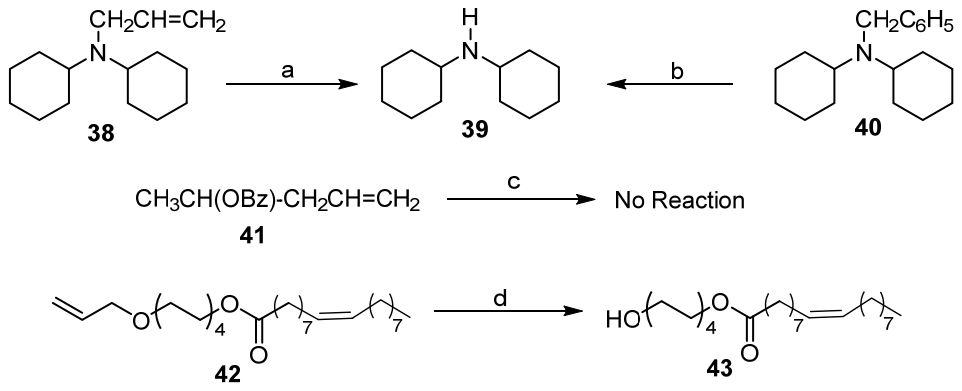



**36** **37**

**Scheme 2.2**: a) $Pd(OH)_2/C$ (150 mol%), MeOH, reflux, 72 h, 94%.

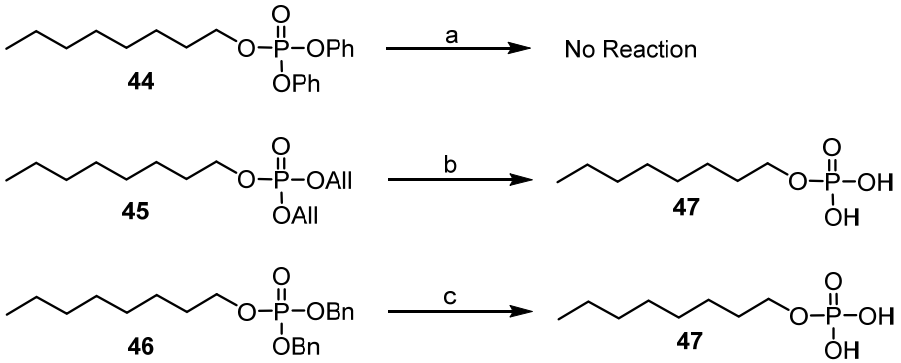
**Section 2C: Miscellaneous cleavage experiments.**

We subjected allyl and benzyl amines **38** and **40** respectively, to cleavage by $Pd(OH)_2/C$ and obtained the corresponding secondary amine **89** in good yield (Scheme 2.3). As seen during the cleavage of ethers, allyl amine was cleaved faster than the corresponding benzyl amine and required lesser quantity of $Pd(OH)_2/C$.




**Scheme 2.3**: a) 50 mol% $Pd(OH)_2/C$, methanol, reflux, 1 h, 69%; b) 100 mol% $Pd(OH)_2/C$, methanol, reflux, 8 h, 62%; c) 50 mol% $Pd(OH)_2/C$, methanol, reflux, 6 h; d) $Pd(OH)_2/C$ (20 mol%) + Pd/C (10 mol%), $^{i}$PrOH: THF (4:1), reflux, 10 h, 84%.

The benzoate and the C=C bond in **41** and **42** remained unaffected on treatment with $Pd(OH)_2/C$ showing that normal C-C double bonds are unaffected under the conditions of allyl ether cleavage. We used $^{i}$PrOH:THF mixture as the solvent for the allyl ether cleavage in compound **42** to increase the solubility of the substrate. This experiment also indicated that although allyl esters can be cleaved with $Pd(OH)_2/C$ (Table 2.1, entry 14) alkyl esters are stable. These results are of significance since they could be useful in the synthesis of natural lipids, which contain unsaturated fatty acids. Hence we also tested the susceptibility of allyl and benzyl phosphates to $Pd(OH)_2/C$ (Scheme 2.4).



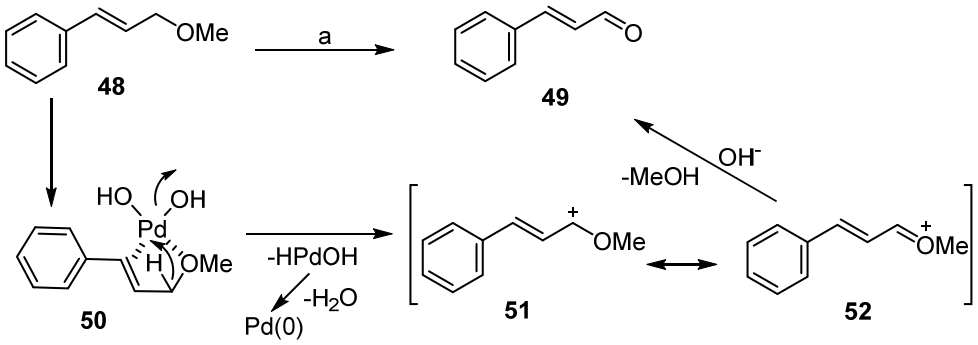

**Scheme 2.4**: a) $Pd(OH)_2/C$, MeOH, reflux, 24 h; b) $Pd(OH)_2/C$ + Pd/C, $^{i}$PrOH, reflux, 2 h, 97%; c) $Pd(OH)_2/C$, MeOH, reflux, 3.5 h, 99%.

These experiments showed that the facility of the cleavage of allyl and benzyl phosphates is more than that of the corresponding ethers. The allyl phosphates are more labile than benzyl phosphates under the reaction conditions shown in Scheme

2.4, but the phenyl phosphate was intact even after prolonged treatment with $Pd(OH)_2/C$. These procedures could be useful for the development of efficient synthetic routes for compounds containing phosphate groups, such as phospholipids. This is especially since the cleavage reaction is carried out more or less under neutral conditions and there are reports showing the propensity of the acid catalyzed migration of phosphate groups between hydroxyl groups.[9]

**Section 2D: Studies directed towards delineating the mechanism of the ether cleavage reactions with $Pd(OH)_2/C$.**

We subjected the cinnamyl ether **48** (Scheme 2.5) to cleavage with $Pd(OH)_2/C$ to see the fate of the (substituted)allyl group after ether cleavage. Formation of the aldehyde **49** in this reaction suggested that cleavage of allyl ethers by $Pd(OH)_2/C$ could be an oxidative process. A plausible route for the formation of the aldehyde **49** is depicted in Scheme 2.5. The modest isolated yield of the aldehyde **49** could be due to its tendency to polymerize easily.




**Scheme 2.5**: a) $Pd(OH)_2/C$, $^{i}PrOH$ , reflux, 6 h, 40%.

A comparison of the XPS data (Figure 2.1) of the palladium reagent before and after the cleavage of 1-allyloxy-6-benzyloxy hexane showed that Pd(II) had been converted into Pd(0). This data also supports the cleavage of allyl ethers by an oxidative process. There are literature precedents supporting such $H^-$ transfer followed by oxidation[11]

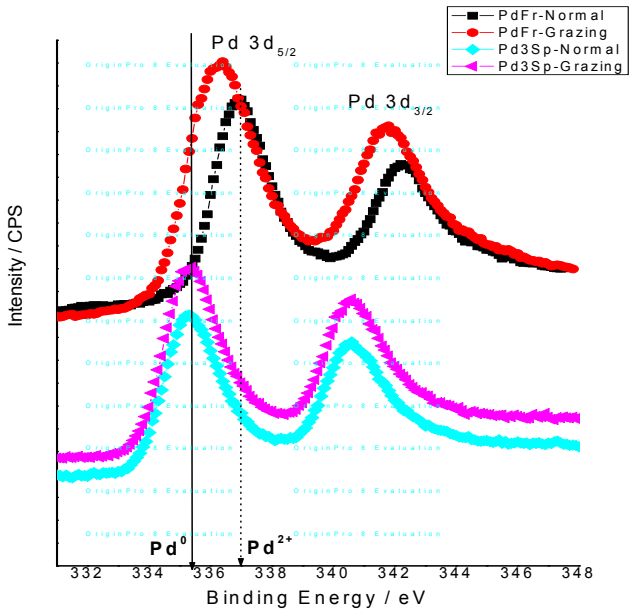
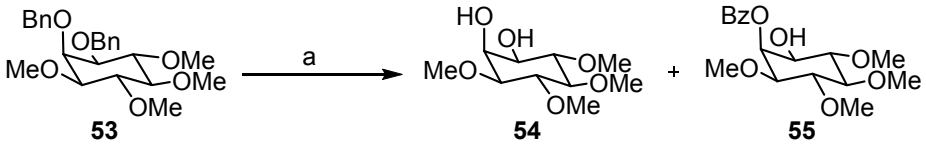



**Figure 2.1**: XPS spectra of the palladium reagent before and after the cleavage of 1-allyloxy-6-benzyloxy hexane. The upper and lower graphs indicate the oxidation state of palladium before and after the ether cleavage.

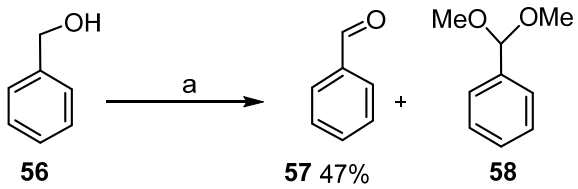
Oxidative cleavage of ethers by $Pd(OH)_2/C$ was also suggested by another experiment. Reaction of *myo*-inositol derived dibenzyl ether racemic **53** (Scheme 2.6) with $Pd(OH)_2/C$ in methanol or *iso*-propanol, although led largely to the complete cleavage of both the benzyl ethers to yield the corresponding racemic diol **54**, also yielded the racemic benzoate **55** as a minor product.




| ROH | Time (h) | Yield (%) 54 | 55 |
|---|---|---|---|
| Dry methanol | 40 | 80 | 14 |
| Dry 2-propanol | 40 | 71 | 27 |
| 2-propanol | 60 | 72 | 23 |

**Scheme 2.6**: Cleavage of *myo*-inositol derived benzyl ethers. a) $Pd(OH)_2/C$, ROH, reflux.

The $^1$H NMR spectrum of the crude product obtained after the cleavage of benzyl group in benzyloxy octane clearly showed the formation of benzaldehyde, which emphasizes the oxidative cleavage of benzyl ether. We theorized that if $Pd(OH)_2/C$ is capable of oxidatively cleaving a benzyl ether, it should also oxidize benzyl alcohol. Hence we subjected benzyl alcohol to ether cleavage conditions mediated by $Pd(OH)_2/C$. Analysis of the mixture of products showed the formation of benzaldehyde and its dimethyl acetal (Scheme 2.7).




**56** **57** 47% **58**

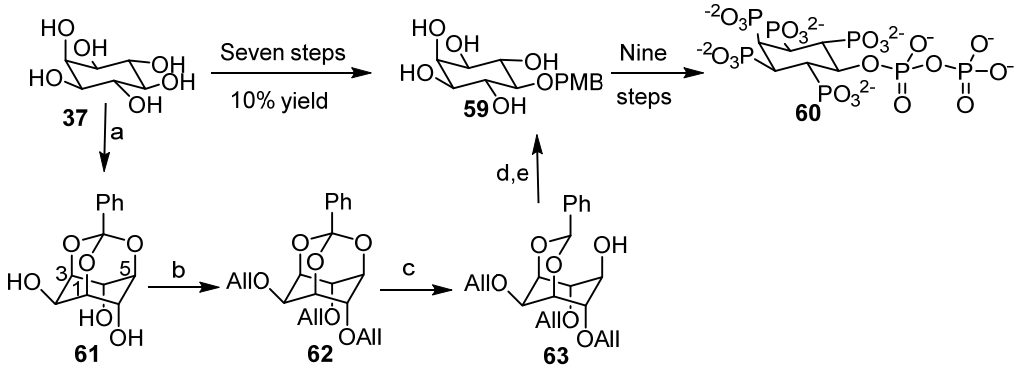
**Scheme 2.7**: $Pd(OH)_2/C$, MeOH, reflux, 30 min. The yield is based on $^1$H NMR spectrum of the mixture of products, estimated using dibromo methane as an internal standard.

In summary, the results presented in this chapter show that the ease of cleavage of ethers with $Pd(OH)_2/C$ can be tuned to the order: alkyl ether, PBB < PMB < Bn < allyl < propargyl ether, by varying any one or more of the following parameters; a) ratio of substrate/$Pd(OH)_2/C$; b) the reaction time; c) solvent of the reaction.

**Chapter 3: Synthesis of inositol derivatives of contemporary significance**

Availability of selective and facile methods for the cleavage of ethers is essential for the synthesis of cyclitols and their derivatives, as these synthetic protocols involve extensive protection and deprotection of hydroxyl groups. Novel methods for the deallylation and debenzylation developed in the previous chapter were used for the synthesis of inositol derivatives, to demonstrate the potential of $Pd(OH)_2/C$ as an ether cleaving agent.

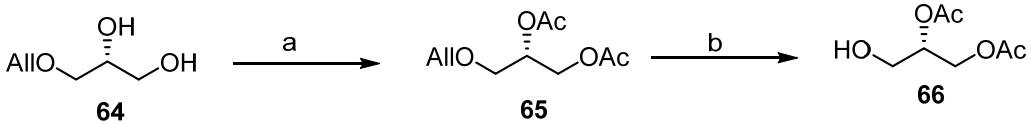
*myo*-Inositol pyrophosphates have been implicated in the control of several cellular processes such as endocytosis, chemotaxis, signal transduction, insulin secretion, cell death, and non enzymatic phosphorylation of proteins. Prestwich *et al* synthesized[10] the inositol pyrophosphate ($IP_7$) from *myo*-inositol through the key intermediate, 5-O-*p*-methoxybenzyl-*myo*-inositol (Scheme 3.1). We synthesized the same key intermediate with an overall yield of 45% in 5 steps, using $Pd(OH)_2/C$ to cleave allyl ethers and the benzylidene acetal in a single step.




**Scheme 3.1**: a) $(MeO)_3CPh$, CSA, DMSO, 80 $^oC$, 5 h, 89 %; b) NaH, AllBr, DMF, rt, 3 h, 94%; c) DIBAL-H, DCM, rt, 2 h, 69%; d) NaH, PMBCl, DMF, rt, 2 h; e) $Pd(OH)_2/C$, $^iPrOH$, reflux, 2 h, 78%. Overall yield 45%.

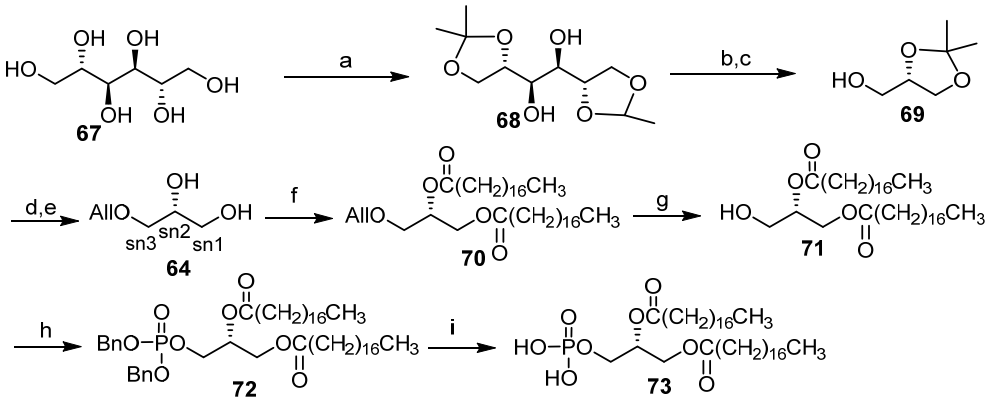
Inositol phospholipids are known to play a pivotal role in the cellular signal transduction pathways. The major challenges faced in the synthesis of naturally occurring inositol lipids are (a) the availability of suitably protected *myo*-inositol derivative with high enantiomeric purity, (b) preparation of the phosphodiester, (c) mild deprotection of the hydroxyl groups and the phosphate group without causing migration of the acyl groups and without affecting the C=C double bond of the fatty acid.

Results obtained in Chapter 2, suggested that neither C=C bonds nor ester groups are affected during the cleavage of allyl ethers by $Pd(OH)_2/C$. Furthermore the experiment shown in Scheme 3.2 showed that allyl ether cleavage with $Pd(OH)_2/C$ is not accompanied by migration of the acyl group in polyols (based on the $^1H$ NMR spectrum of the crude product).



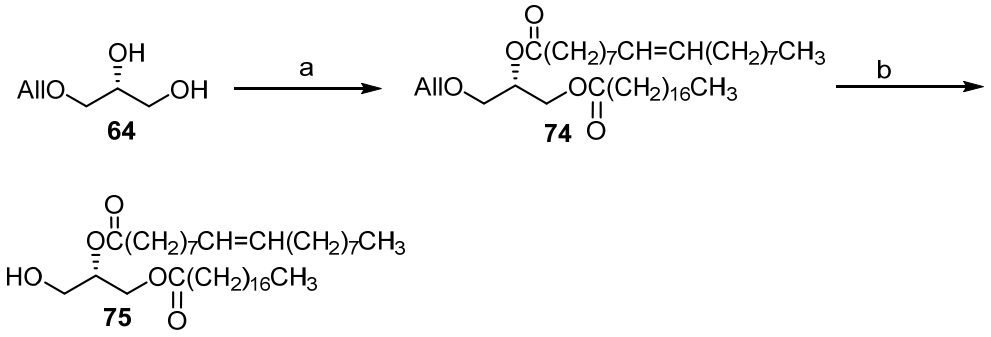

**Scheme 3.2**: a) $Ac_2O$, pyridine, DMAP, rt, overnight, 85%; b) $Pd(OH)_2/C$+Pd/C, MeOH, reflux, 9 h, 97%.

Hence we were able to prepare the phosphatidic acid as shown in Scheme 3.3.



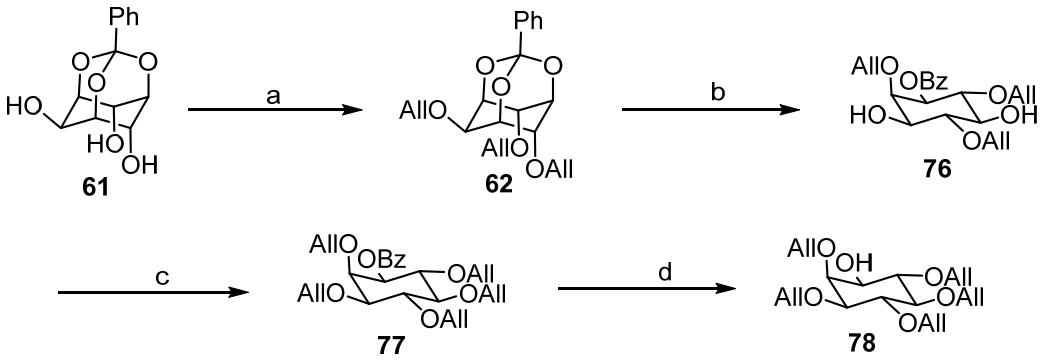
**Scheme 3.3**: a) 2,2-Dimethoxy propane, TsOH, DMSO, rt, 16 h, 67%; b) $NaIO_4$/silica, DCM, rt, 1 h; c) $NaBH_4$, MeOH, rt, 5 h, 81%; d) NaH, AllBr, DMF, rt, 3 h; e) TsOH, MeOH, reflux, 3 h, 88%. f) stearic acid, DMAP, DCC, DCM, rt, 10 h, 76%; g) $Pd(OH)_2$/C, MeOH, reflux, 3 h, 94%; h) 1H-tetrazole, $(BnO)_2$-P-N($i$pr)$_2$, $m$CPBA, DCM, rt, 4 h, 93%; i) $Pd(OH)_2$/C, 2-PrOH, reflux, 74 h, 82%.

Using a similar procedure we could obtain the differentially substituted diacyl glycerol (containing unsaturated fatty acid at sn2 position) as shown in scheme 3.4.



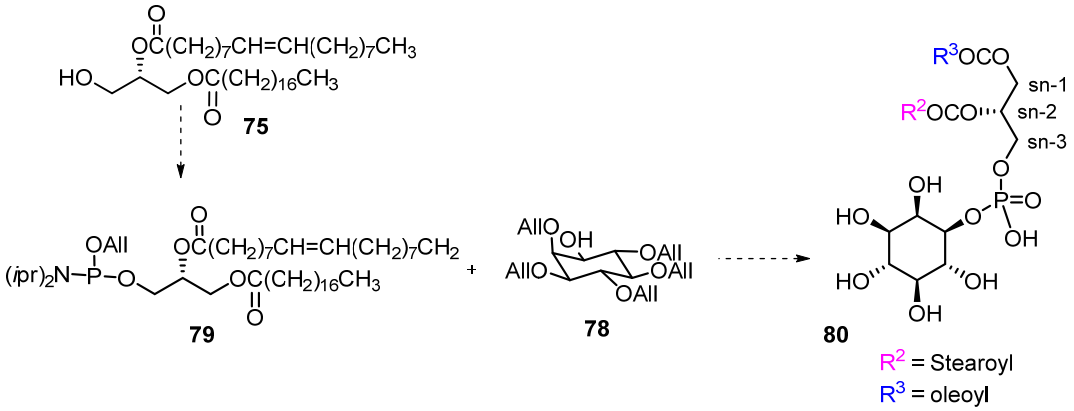
**Scheme 3.4**: a) i) Stearic acid, DCC, DMAP, DCM, -5 $^oC$, 1 h; ii) Oleic acid, DCC, DMAP, DCM, rt, 2 h, 88%; b) $Pd(OH)_2$/C, $^i$PrOH, 60 $^oC$, 17 h, 90%.

The racemic penta allyl ether of *myo*-inositol in which the C1-hydroxyl group is free, was prepared as shown in the scheme 3.5.




**Scheme 3.5**: a) NaH, AllBr, DMF, rt, 2 h, 88%; b) TFA:Water (3:1), 100 $^{o}$C, 5 h, 89%; c) $Ag_2O$, AllBr, DMF, 32 h, rt, 76%; d) KOH, MeOH, rt, 2 h, 94%.

Coupling of the pentaallyl ether and the diacyl glycerol (Scheme 3.6) to obtain phosphatidylinositol (mixture of diastereomers) is in progress.




**Scheme 3.6.**

**References:**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**Note**: Compound numbers in the synopsis of the thesis are different from those in the thesis and references are included separately for each chapter.

## List of Publications

1. **Mart, A**.; Shashidhar, M. S. 'Elaboration of the ether cleaving ability and selectivity of the classical Pearlman's catalyst [Pd(OH)2/C]: concise synthesis of a precursor for a myo-inositol Pyrophosphate,' *Tetrahedron*., **2012**,*68*, 9769–9776.

2. **Mart, A**.; Shashidhar, M. S. 'Pearlman's catalyst for the cleavage of phosphate protecting groups; A novel route for the synthesis of natural inositol lipids and it analogs' (Manuscript to be communicated)

3. **Mart, A**.; Shashidhar, M. S. 'A review on the unusual reactions by simple palladium salts and unligated Pd(0)' (Manuscript to be communicated)

## Poster presentations

1. **Alson Mart**, Mysore S. Shashidhar, Poster presentation, 'Pearlman's Catalyst as an ether cleaving agent: Is the active species Pd(II) or Pd(0) or combination of both' *National Science Day at NCL, 2012.*

2. **Alson Mart**, Mysore S. Shashidhar, Poster presentation, 'Pearlman's Catalyst as an ether cleaving agent: Reduces the milestones to inositol phospholipids' *National Science Day at NCL, 2013.*

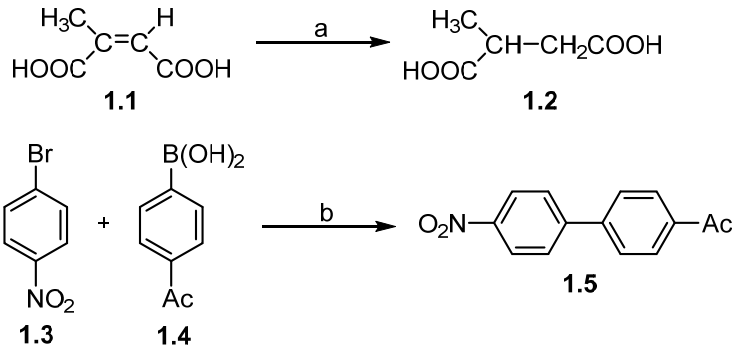
# Chapter 1

# Palladium in organic transformations – a brief literature survey.

## 1.1 Introduction

Palladium (Pd) is a noble metal discovered by William Hyde Wollaston in 1803. Wollaston derived its name from the name of an asteroid, 'Pallas'. An excellent functional group tolerance, reactivity and selectivity have given palladium reagents a pivotal role in organic synthesis. A revolutionary change has happened in synthetic organic chemistry due to the recent advances in the transition metal catalysis.[1] The vast utility and versatility of this transition metal (Palladium) was acknowledged by the award of 2010 Nobel prizes to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their work on Palladium catalyzed coupling reactions.[2] Two kinds of palladium reagents namely, Pd(II) and Pd(0) are commonly used for the mediation of organic reactions. Among these Pd(0) complexes are exclusively used as catalysts whereas Pd(II) reagents are either used as stoichiometric oxidizing agents or as precursors for Pd(0). Among the palladium reagents, solid supported reagents are attractive because these reagents can be removed at the end of the reaction by filtration, allowing easy access to the required products, as well as recovery and possible recycling of the palladium reagent. Although palladium chemistry has been practiced for several decades, efforts are continuing to develop new green and eco-friendly palladium mediated reactions; for example, solvent free $Pd/SiO_2$ catalyzed hydrogenation[3] and Pd/C catalyzed Suzuki-Miyaura reaction (Scheme 1.1).[4]

Palladium and its salts are extensively used as catalysts for the hydrogenation and hydrogenolysis of a variety of organic compounds and for the formation of carbon-carbon bonds (Heck, Suzuki, Buchwald and Sonogashira coupling reactions).[4] A survey of the literature reveals that Pd(0) and Pd(II) reagents have also been

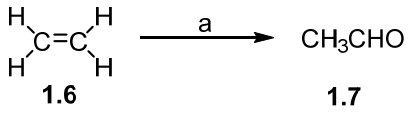



**Scheme1.1**: a) $H_2$, $Pd/SiO_2$, rt, 48 h, 94%; b) Pd/C (10%), $Cs_2CO_3$, 100 $^oC$, 24 h, 100%.

sporadically reported to be capable of bringing about several other kinds of reactions. The aim of the work presented in this thesis was to examine the utility of palladium hydroxide for the preparation of inositol derivatives since earlier work in our laboratory had suggested that palladium hydroxide is capable of cleaving benzyl ethers in the absence of hydrogen.[5] Accordingly, the current chapter presents selected uncommon reactions brought about by palladium(II) compounds and unligated Pd(0). This chapter illustrates the versatility of these reagents and places the rest of the work described in this thesis in proper perspective.

### 1.2. Palladium mediated organic transformations: Illustrative examples

The discovery of Wacker process (Scheme 1.2)[6] became an important milestone in palladium catalyzed oxidation reactions. This process drew attention of many research groups for exploring the utility of palladium reagents in various kinds of oxidation reactions.

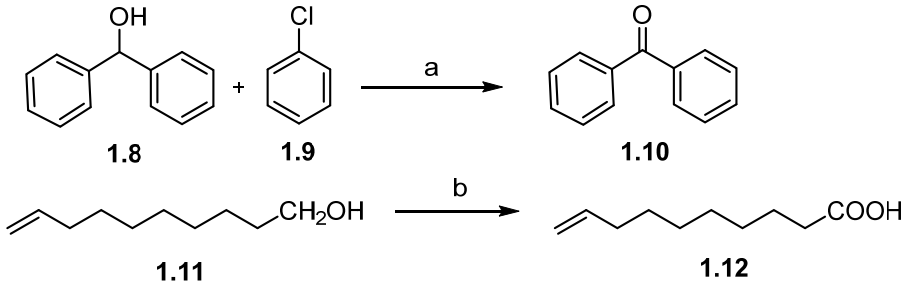



**1.6** **1.7**

**Scheme 1.2**: a) $PdCl_2$, $CuCl_2$, $O_2$, $H_2O$.

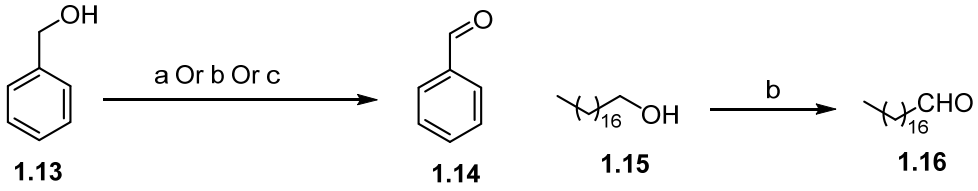
The oxidation of an alcohol to the corresponding aldehyde or ketone is an important and ubiquitous transformation in synthetic organic chemistry. Many of these methods use stoichiometric amount of metallic reagents which are hazardous to the ecosystem. The first use of palladium for the oxidation of alcohol was perhaps by Berzelius in 1828.[7] He reported the oxidation of alcohol with potassium tetrachloro palladate in aqueous ethanolic solution. Several groups in the recent past have introduced modifications to make the oxidation reactions selective and catalytic in palladium. Mainly Pd(II) (see below) or Pd(0) reagents[8] (to a lesser extent) have been used for the oxidation reactions.

In fact the Pd(0) catalysis (Scheme 1.3) is a dehydrogenation reaction through a palladium hydride intermediate.[9] In a few cases the oxidation of primary alcohols with supported Pd(0) reagents under basic condition progressed to the corresponding acid.[10]



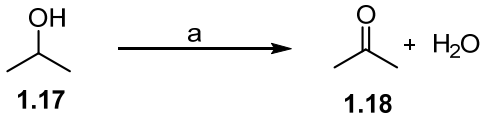

**Scheme 1.3**: a) Pd/C, KOH, $CH_3OH$:$H_2O$ (5:1), 60 $^oC$, 1 h, 91%; b) Pd/C, $O_2$, dioxane-water, 50 $^oC$, pH = 8.

Peterson and Larock[11] used palladium(II) acetate for the oxidation of benzyl alcohol (**1.13**) in DMSO solution (Scheme 1.4). Later Uemura and co workers[12] varied the conditions of the palladium(II) acetate mediated reactions to improve the selectivity and reduced the number of additives. They also explored the extension of these methods for the oxidation of aliphatic alcohols other than benzylic alcohols[13]




**Scheme 1.4**: (a) $Pd(OAc)_2$, $NaHCO_3$, $O_2$, DMSO, 80 $^oC$, 2 h, 90%;[11] (b) $Pd(OAc)_2$, pyridine, MS 3A, toluene, $O_2$, 80 $^oC$, 2 h, 95%; [13] (c) Pd(II)-hydrotalcite, air (1 atm), pyridine, toluene, 65 $^oC$, 3 h, 98%.[12a]

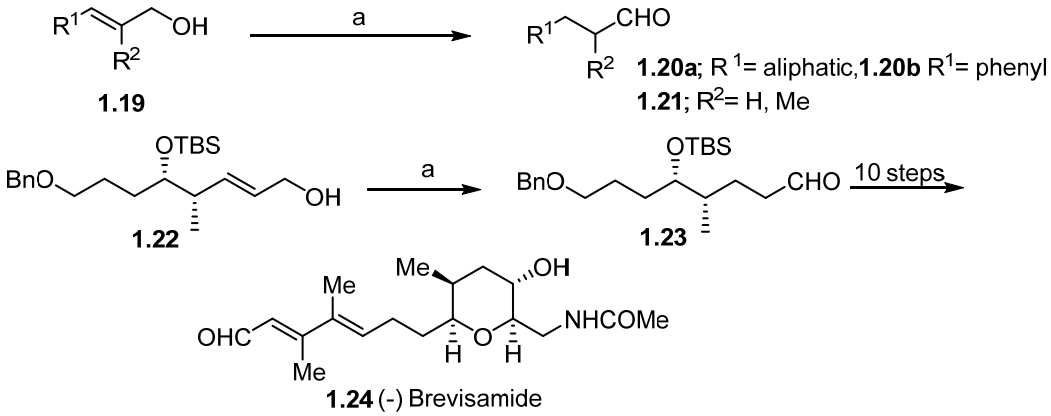
Palladium mediated oxidation reactions generally require an additional oxidant to maintain the Pd(II)/Pd(0) cycle. A number of conventional and unconventional oxidizing agents such as hydrogen peroxide, *tert*-butyl hydroperoxide, potasium periodate, N-halosuccinimides, copper salts, aryl halides, tetrachloro methane, as well as molecular oxygen have been used.




**Scheme 1.5**: a) $PdCl_2$-NaOAc, ethylene carbonate, $O_2$, 38 $^oC$, 100 h, 92%.

The use of oxygen as an oxidant in the palladium mediated oxidation of alcohols (Scheme 1.5) was first reported by Blackburn and Schwartz.[14]

Yadav *et al.,*[15] observed the isomerization of allylic alcohol to the corresponding aldehyde at room temperature in the presence of hydrogen pre-treated palladium catalyst (Scheme 1.6). This is the first report on the isomerization of allylic alcohol to the corresponding aldehyde at room temperature.

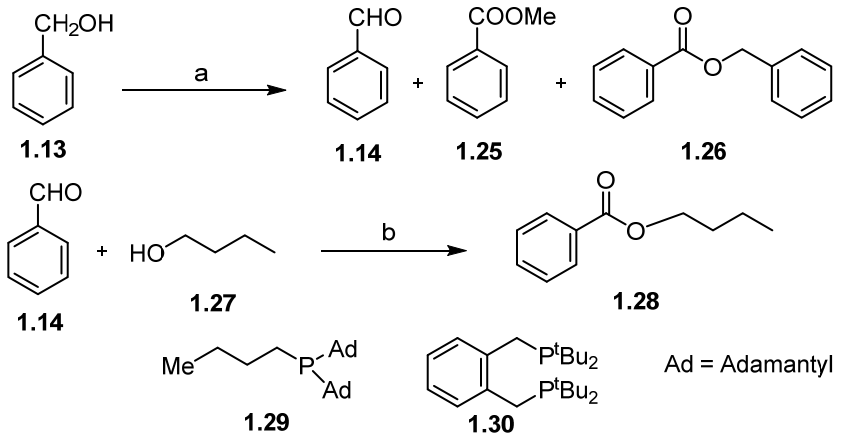



**Scheme 1.6**: a) Benzene, $Pd(OH)_2/C$ pre activated with hydrogen, rt, 10 min.

They optimized the isomerization reaction by varying the solvent and the palladium reagent (Pd/C or $Pd(OH)_2/C$ with and without pre-activation with gaseous hydrogen). The use of pre-activated $Pd(OH)_2/C$ in benzene gave the highest yield in the shortest time. The use of hydrogen gas during the reaction gave the saturated alcohol as a side product. This methodology was utilized for the formal synthesis of (-)-brevisamide.

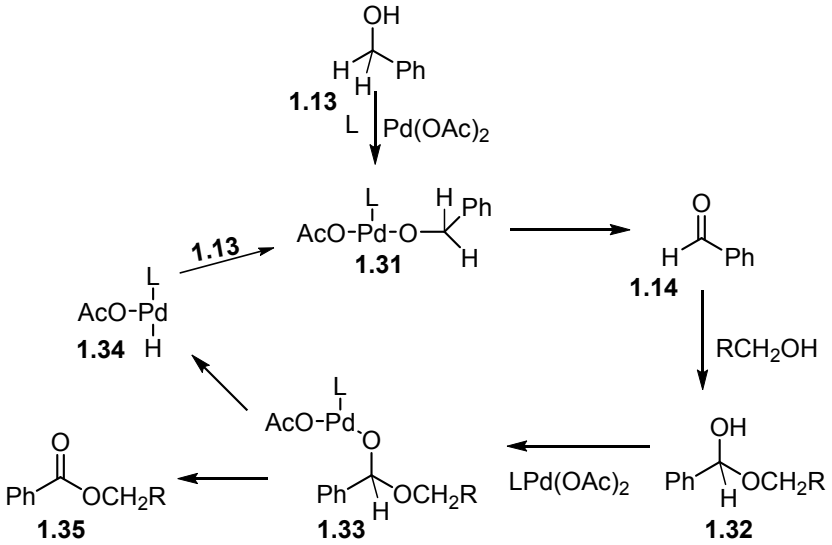
The esterification of alcohols with carboxylic acids and their derivatives is a ubiquitous reaction. But the oxidative esterification of alcohols and aldehydes is relatively rare and this reaction can be realized by using oxone,[16a] ruthenium pincer complexes,[16b] hypervalent iodine,[16c] or gold.[16d] Beller *et al.,*[17] reported an unusual palladium catalysed oxidative esterification of benzyl alcohol and its ring substituted derivatives. They observed the formation of methyl benzoate and benzyl benzoate from a methanolic solution of benzyl alcohol in a single step in the presence of palladium acetate and potassium carbonate (Scheme 1.7). Among the various ligands and silver additives used to improve the selectivity of the reaction, the ligand **1.30** and

toluene (as the solvent instead of methanol) resulted in considerable increase in the yield (85%) of benzyl benzoate. A similar palladium catalysed oxidative esterification of benzaldehyde to the corresponding benzoate was reported by Lei *et al*.[18]




**Scheme 1.7**: a) $Pd(OAc)_2$, $O_2$, **1.29/1.30**, MeOH, $K_2CO_3$; b) $PdCl_2(PPh_3)_2$, $K_2CO_3$, BnCl, THF, 60 $^oC$, 20 h, 96%.

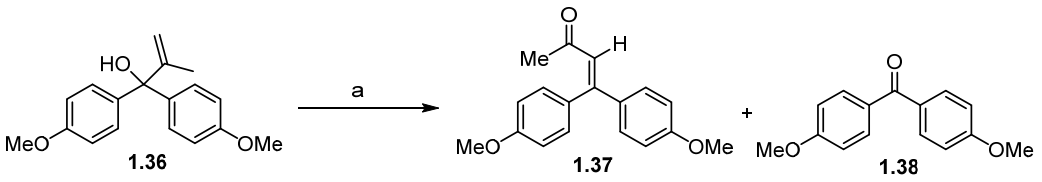
An advantage of this methodology was that molecular oxygen could be used as the oxidant to regenerate palladium(II). The reaction mechanism proposed (Scheme 1.8) involved the coordination of benzyl alcohol to Pd(II) followed by a β-H (with respect to Pd) elimination to generate the aldehyde **1.14**, which was then attacked by another




**Scheme 1.8**: Plausible mechanism for the oxidative esterification of alcohols with $Pd(OAc)_2$.

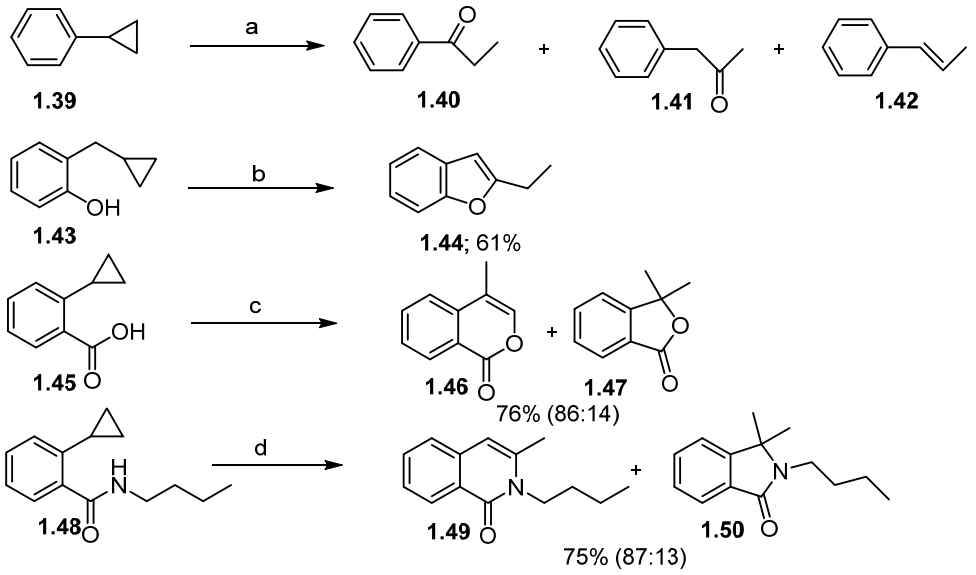
alcohol to give a hemiacetal **1.32**. The hemiacetal underwent further β-H elimination and gave the ester **1.35**. The eliminated palladium complex **1.34** was recycled to maintain the catalytic cycle.

Rosa and Orellana[19] reported an unusual palladium catalysed oxidation of diaryl alkenyl carbinol **1.36** (Scheme 1.9) into β,β-diaryl-α,β unsaturated ketone **1.37** by using molecular oxygen as the terminal oxidant. This reaction involved reorganization in the carbon framework of the allyl alcoholic part from a branched chain to a straight chain. The optimization experiments showed that the reaction worked best when dimethyl acetamide (DMA, as the solvent), CsOAc (as the base) and Palladium(II) chloride (as the oxidant) were used for the reaction. The use of DMA:MeCN mixture as the solvent minimized the formation of the diaryl ketone **1.38**.



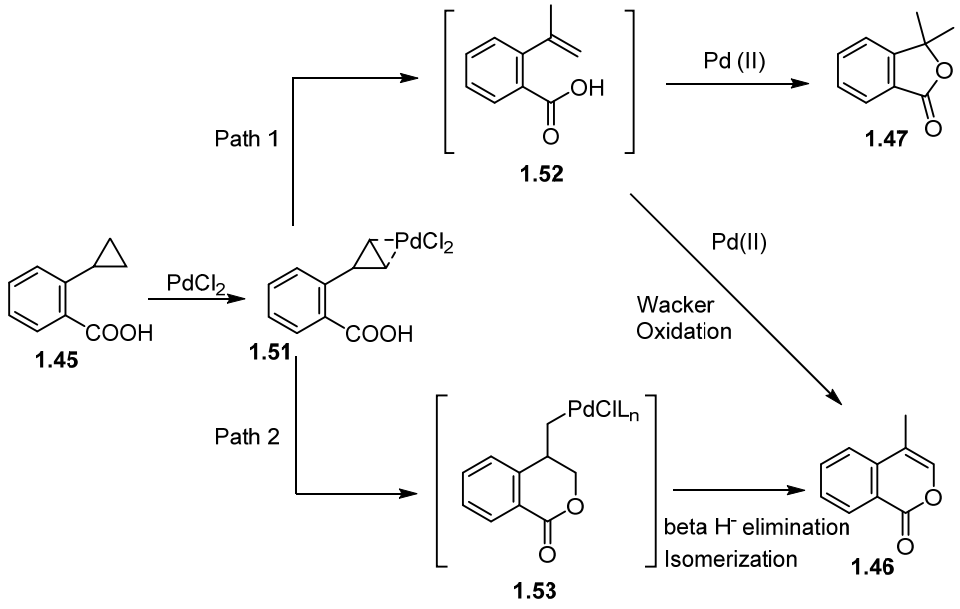

**Scheme 1.9**: a) $PdCl_2$, $O_2$ (balloon), CsOAc, DMA:MeCN (3:1), 80 $^oC$, 80%, 98:1 (**1.37:1.38**)

Cyclopropane rings are known to undergo oxidative cleavage with palladium reagents. Ouellette and Levin[20] observed the formation of ketones **1.40** and **1.41** from phenyl cyclopropane **1.39** (Scheme 1.10) in 60% and 35% isolated yield respectively. Formation of minor amount of *trans* propenyl benzene (**1.42**) was also observed. The exclusive transformation of **1.42** to phenyl acetone **1.41** under the same reaction conditions suggests that **1.42** could be the intermediate during the formation of the ketone **1.41** from phenyl cyclopropane. Similar reactions involving cyclopropane ring opening followed by the formation of heterocyclic ring systems has also been reported (Scheme 1.10).[21] The formation of ethers and lactones could be explained to occur *via* the isomerization of the cyclopropane to the substituted olefin followed by Wacker oxidation or *via* the carboxy palladation followed by β-H elimination as shown in Scheme 1.11.



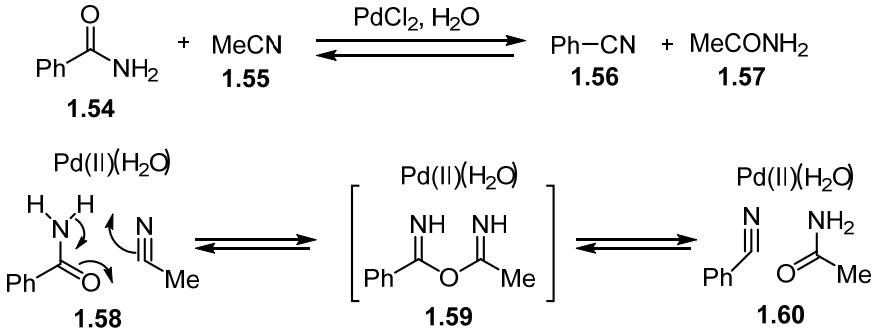

**Scheme 1.10**: a) $PdCl_2$, $H_2O$, 75 °C, 2 h; b) $PdCl_2$, $CuCl_2$, dioxane, 100 °C, 24 h; c) $PdCl_2$, $CuCl_2$, dioxane; d) $PdCl_2(MeCN)_2$, benzoquinone, dioxane, 80 °C, 12 h.

But interestingly a different regioselectivity was observed during the formation of lactams from amides, which is in contrast to the proposed mechanistic pathways.



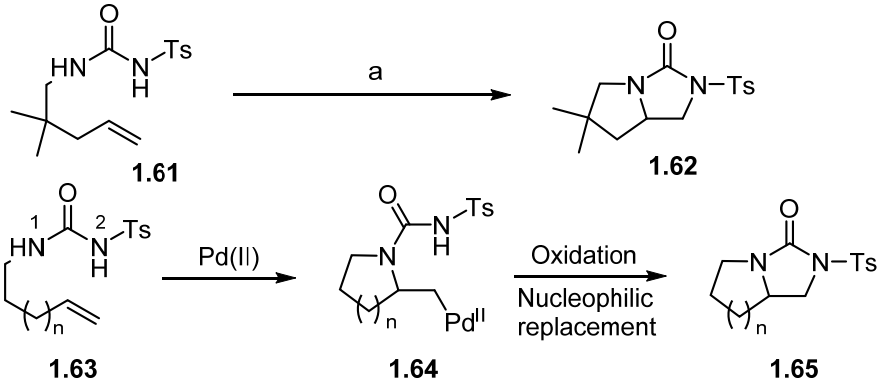

**Scheme 1.11**: Plausible routes for the cyclisation reactions shown in Scheme 1.10.

Palladium chloride is known to effect the reversible dehydration of primary amides in 1:1 aqueous acetonitrile.[22] Hydrolysis of nitriles to amides in the presence of palladium was however known previously (Scheme 1.12).[23]




**Scheme 1.12:** Dehydration of primary amides by palladium chloride.

Further investigations showed that the reaction was not feasible either in acetonitrile or in water as the only solvent. Although the reaction required both the solvents, their ratio could be varied depending on the solubility of the substrate. In fact this process is a reversible transfer of a water molecule between an amide and a nitrile. The reaction of benzonitrile with acetamide in the presence of palladium chloride in aqueous THF proceeded to give benzamide and acetonitrile indicating that the source of water for the conversion of benzonirile to the benzamide was acetamide and not water from the solvent. Involvement of a palladium(II) complex was hypothesized to account for the reversibility of the reaction (Scheme 1.12).

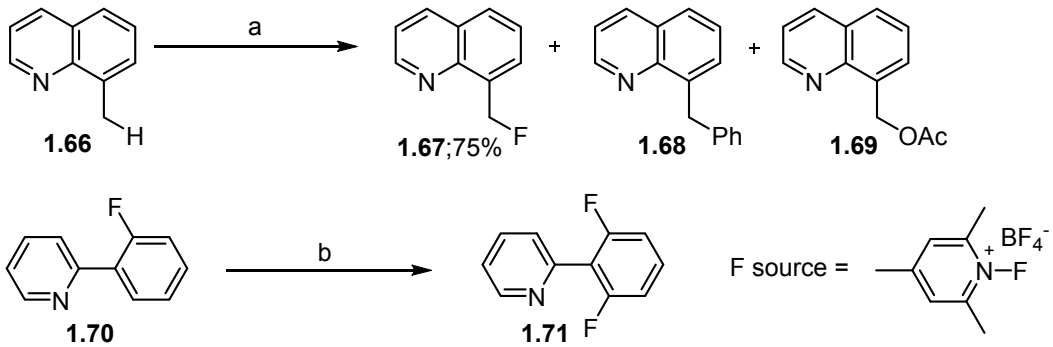



**Scheme 1.13**: a) DCM, $Pd(OAc)_2$, $PhI(OAc)_2$, $Me_4NCl$, NaOAc, rt, 12 h, 92%.

The first palladium mediated diamination of an unfunctionalised alkene was reported by Muñis *et al* (Scheme 1.13).[24] This cyclisation was mediated by a Pd(II)/Pd(IV) cycle, where diacetoxyiodo benzene was used as the oxidant. Coordination of a nitrogen (N1 in **1.63**) followed by a palladacycle formation converts Pd(II) into a higher oxidation state. Subsequent attack of the second NH group (N2) regenerates the Pd(II) followed by formation of the cyclised product **1.65**. Several reports on amino hydroxylation,[25a] hydroamination[25b]and allylic amination[25c] without the use of palladium reagents have also been reported in the recent past.

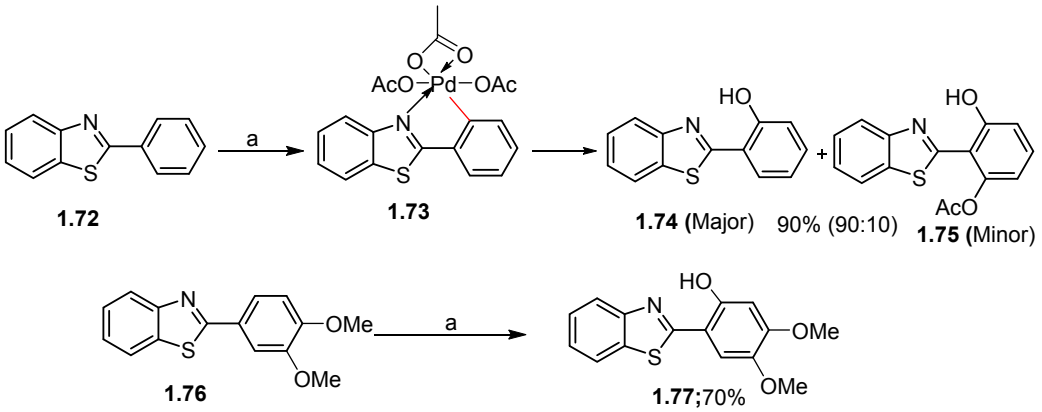
C-H activation reaction implies the replacement of a C-H bond by a new C-heteroatom bond. The first C-H activation reaction was reported by Joseph Chatt in 1965[26] by the insertion of ruthenium into the C-H bond at the 2nd position of naphthalene. Molecules containing C-F bonds have a wide range of applications such as imaging agents, pharmaceuticals, fine chemicals etc, however few reports deal with the fluorination of C-H bonds. Hull *et al.,*[27] reported the first Pd catalysed aromatic and benzylic fluorination by using an electrophilic fluorinating agent under microwave irradiation (Scheme 1.14). The fluorination reaction took longer time and was low yielding under thermal conditions. The fluorination reaction progressed through Pd(II)/Pd(IV) cycle rather than the usual Pd(II)/Pd(0) cycle.

Lyons *et al* have recently reviewed the C-H activation reactions in detail.[28a] Recent



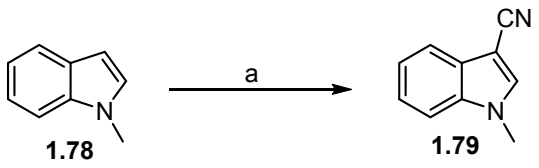

**Scheme 1.14**: a) $Pd(OAc)_2$, Flourine source, (1.5 eq.) benzene, 110 $^oC$, 1 h, 200 W; b) $Pd(OAc)_2$, F source, 0.5 mL $CH_3CN$ in $CF_3C_6H_5$, μ wave, 150 $^oC$, 1.5 h, 69%.

advances[28b] in the palladium catalysed C-H activation reveals that there is no requirement of any acid/base and ligands for this reaction. The C-H functionalisation reactions of the substrates with hetero atoms were facile as they assisted the cyclometallation step easily (as shown in scheme 1.15) and the subsequent C-H activation. Palladium catalysed C-O bond forming reactions of aryl pyrimidines are well explored, especially hydroxylations and acetoxylations. Banerjee *et al* reported[29] the C-H activation in 2-arylbenzothiazole (another substrate which can chelate with the metal and assist the C-H activation) using palladium acetate. Regioselective hydroxylation occurred at the less sterically hindered position of the phenyl ring as the competition comes between two positions.




**Scheme 1.15**: a) $Pd(OAc)_2$, AcOH, diacetoxy iodobenzene, (DIB) 5-7 h.

Recent reports[30]show that cyanation of a CH bond can be accomplished (in the absence of palladium reagents) with several metal cyanides or with $K_3(FeCN)_6$. But the applicability of these methods is limited due to the toxic nature of these cyanides. Palladium(II) mediated cyanation reaction by using ammonium hydrogen carbonate and DMSO as the CN source appears to provide an alternate safer procedure (Scheme 1.16).[31] No reaction was observed in the absence of palladium chloride.

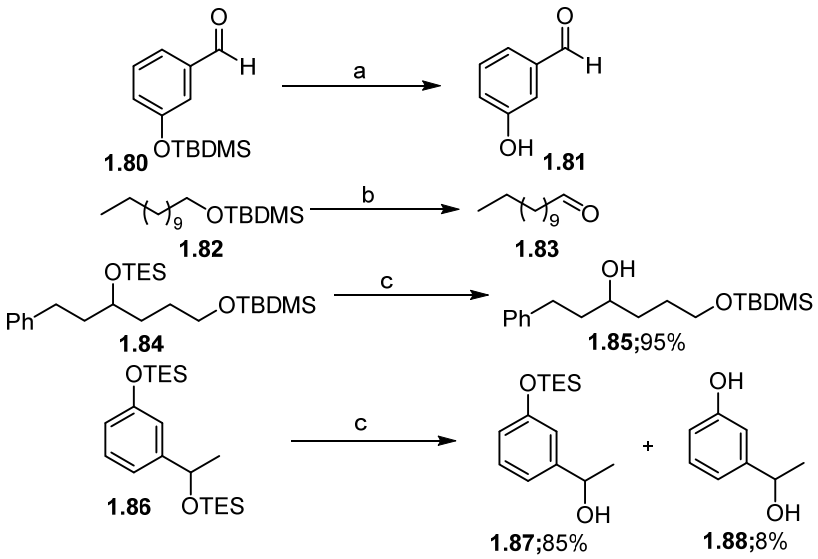



**Scheme 1.16**: a) $PdCl_2$, $Cu(OAc)_2$, $NH_4HCO_3$, DMSO, $O_2$, 140 $^oC$, 6 h, 85%.

Copper acetate worked best among the various oxidizing agents used. This cyanation reaction also worked when DMF was used instead of DMSO, but the yield was low (35%). However the mode of generation of -CN from ammonium hydrogen carbonate and DMSO or DMF is not clear.

### 1.3. Cleavage of ethers by Pd(0) and Pd(II) reagents

There are several reports on the use of palladium reagents for the cleavage of acetals, ethers and silyl ethers etc. in the recent past. Most of these methods use Pd(0)[32] complexes while relatively less reports pertain to the use of unligated Pd(0) and Pd(II) salts.[33,34] The ability of $PdCl_2(CH_3CN)_2$ to cleave TBDMS ethers was noticed by Lipshutz

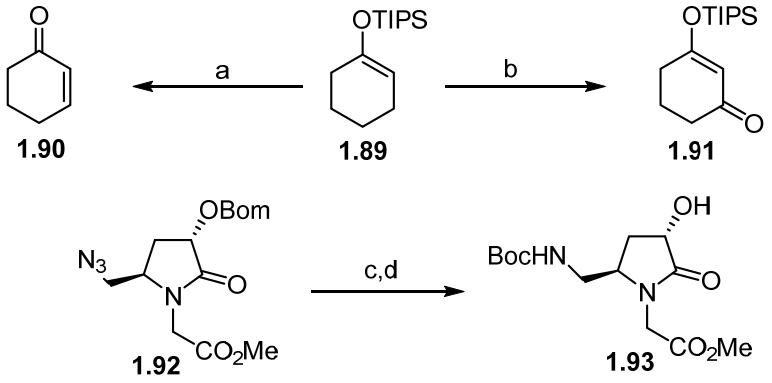



**Scheme 1.17**: a) $PdCl_2(CH_3CN)_2$, acetone, water, 75 $^oC$, 16 h, 76%; b) $PdCl_2(CH_3CN)_2$, acetone:DMF (1:1), water, 20 h, 75 $^oC$, 78%; c) Pd/C (10 wt%), MeOH, rt, 5 h.

*et al.,*[33b] and later Wilson and Keay[34b] extended this protocol for the cleavage of phenolic silyl ethers ( **1.80** in Scheme 1.17) They also showed that their method had a good functional group tolerance and was useful for the cleavage of other silyl ethers such as TMS,TES etc, whereas the TIPS and TBDPS ethers were stable under these reaction conditions (not shown in scheme 1.17). The same group reported the desilylation and subsequent oxidation of the alcohol generated, in a single step using $PdCl_2(CH_3CN)_2$ (**1.82** in scheme 1.17)[35] Pd/C in alcoholic solvents is known to

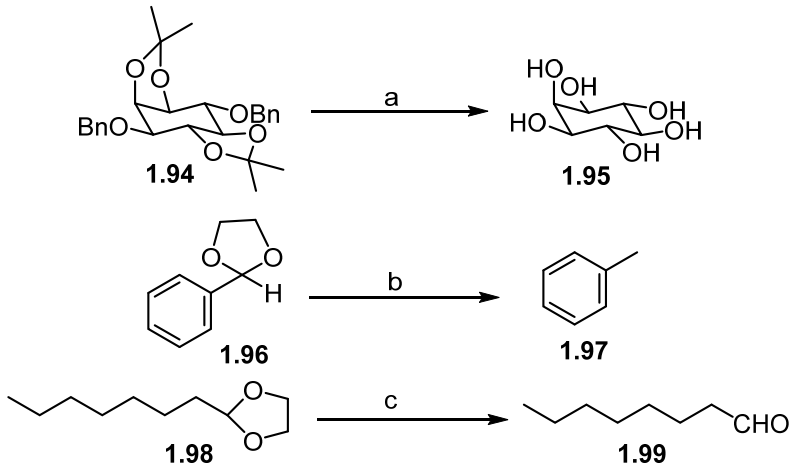
selectively cleave aliphatic triethylsilyl (TES) ethers in the presence of aromatic TES ethers and TBDMS ethers (compounds **1.86** and **1.84** respectively).[36]

Pearlman's catalyst has also been used for the oxidative cleavage of silyl ethers[37] and the benzyloxymethyl group (Scheme 1.18)[38]




**Scheme 1.18**: a) $Pd(OH)_2$, *t*-BuOOH, $Na_2HPO_4$, $CH_2Cl_2$, 24 $^oC$, 42 h, 73%; b) $Pd(OH)_2$, *t*-BuOOH, $CsCO_3$, $CH_2Cl_2$, 4 $^oC$, 38 h, 75%; c) $H_2$, Pd/C, $Boc_2O$, AcOEt, 89%; d) $H_2$, $Pd(OH)_2$/C, MeOH, 94%.

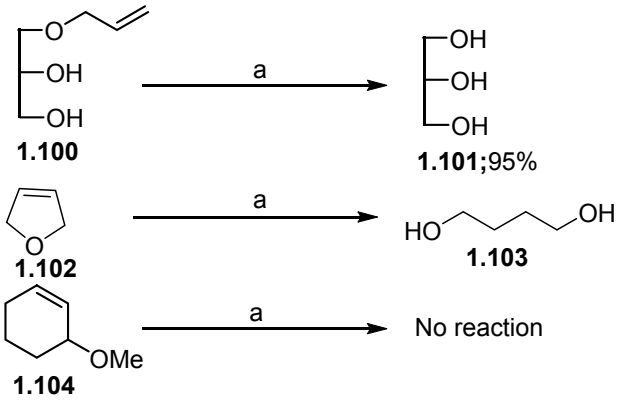
Lipshutz[33b] described the cleavage of acetals with $PdCl_2(CH_3CN)_2$. This reagent was highly selective with respect to the commonly used alcohol protecting groups except TBDMS group. Murali reported[5] a mild method for the deprotection of the acetals using $Pd(OH)_2$/C (Scheme 1.19). The same catalyst could be recycled for the cleavage




**Scheme 1.19**: a) $Pd(OH)_2$, MeOH, reflux, 8-22 h, 95-97%; b) $PdCl_2$, $Et_3SiH$, EtOH, reflux, 30 min, 96%; c) $PdCl_2(CH_3CN)_2$, acetone, rt, 45 min, 82%.

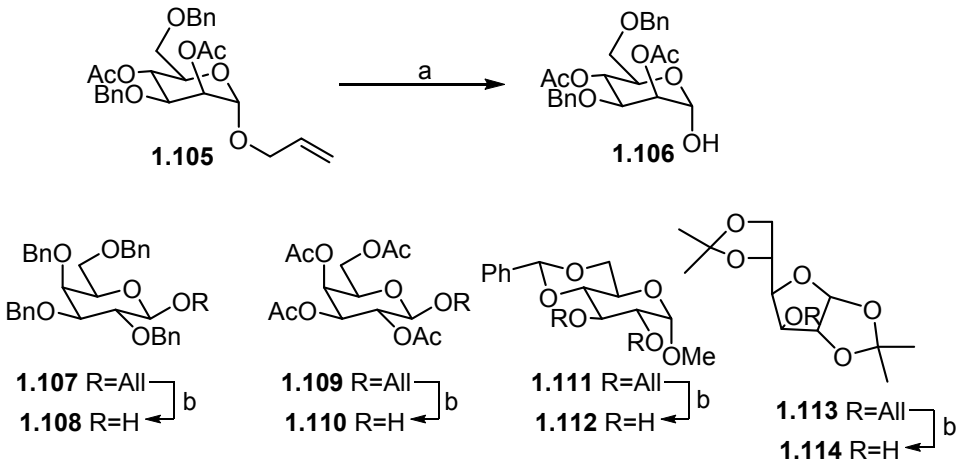
of 10 batches of the acetal substrate. Palladium chloride catalyses the reductive cleavage of acetals to the corresponding alkane with triethyl silane.[39]

Usual experimental protocol for the cleavage of allyl ethers typically involves two steps; isomerization of the allyl group to the prop-1-enyl system followed by acid catalysed hydrolysis.[40] A convenient alternative to this two step experimental protocol for the cleavage of allyl ethers using Pd/C and an acid (either *p*-TsOH or a mineral acid) was developed by Boss and Scheffold (Scheme 1.20).[41] The cleavage of the allyl ether was envisioned to have happened through the isomerization of the allylic group to the corresponding enol ether followed by hydrolysis. A *cisoid* conformation of the O-allyl group and the double bond is a requisite criterion for the isomerization to happen, as illustrated (compounds **1.102** & **1.104**) in the below scheme. However, it is not clear as to what led to the reduction of the double bond, during the formation of the diol **1.103**.




**Scheme 1.20**: a) Pd/C, MeOH/water, *p*-TsOH, reflux, 6 h.

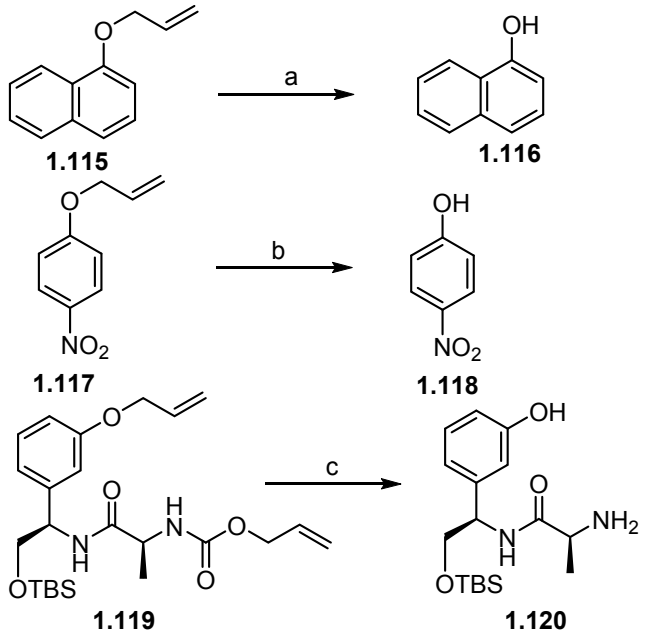
Ogawa *et al*.,[42a] used $PdCl_2$ in acetic acid for the deallylation of a sugar derivative; yield was moderate. A simpler and facile acid free deallylation was reported by Mereyala and Guntha.[42b] They carried out the deallylation of several carbohydrate derived allyl ethers (Scheme 1.21) which contained other protecting groups (such as benzyl, acetyl, acetal etc). The catalytic recycling of palladium(II) could be attained by the use of copper salts in aqueous DMF. However, it is surprising to note that the acetal moieties remained intact during the cleavage of allyl ethers




**Scheme 1.21**: a) $PdCl_2$, NaOAc, AcOH:$H_2O$ (20:1), 20 $^oC$, 14 h, 64%; b) $PdCl_2$, CuCl, DMF:$H_2O$ (10:1), rt, 1-6 h, 90-92%.

in some of these sugar derivatives, since palladium chloride had earlier been used for the cleavage of acetals at ambient temperatures (Scheme 1.19). No explanation or rationalization was offered for these contrasting observations.

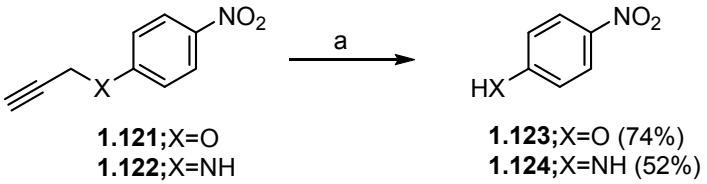
Phosphine coordinated palladium complexes were also widely used for the allyl ether cleavage. Vutukuri *et al*.,[43] developed a new method for the synthesis of dendrimers through a palladium complex catalysed deallylation in basic medium.




**Scheme 1.22**: a) $Pd(PPh_3)_4$, $K_2CO_3$, MeOH, rt, 2 h, 97%; b) $Pd(PPh_3)_4$, $NaBH_4$, THF, 1 h, 94%; c) $Pd(PPh_3)_4$, $LiBH_4$, THF, rt.

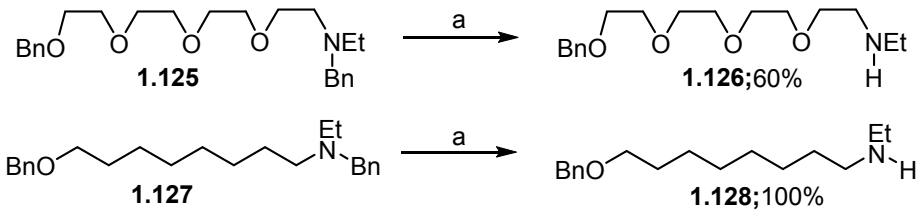
There are few reports on the use of $Pd(PPh_3)_4$ along with sodium borohydride,[44a] $LiBH_4$,[44b] sulphinic acids or corresponding sodium salts[44c] for the cleavage of allyl ethers.

Honda *et al*.,[40e] extended their method of deallylation to a number of substrates including allyl amines, allyl esters, allyl carbamates etc (Scheme 1.22). Palladium reagents are also known to cleave aryl O/N-propargyl groups[45] as illustrated in Scheme 1.23.




**Scheme 1.23**: $(Ph_3P)_2PdCl_2$, $Et_3N$, DMF-water, 80 $^oC$, 2-3 h.

Use of benzyl protecting group is common in synthetic organic chemistry due to the ease in the O-benzylation reaction and stability of the benzyloxy group under a variety of reaction conditions. Pd/C[46] as well as $Pd(OH)_2/C$ work well for the debenzylation under hydrogenolytic conditions[46b,47] and the latter reagent is known to cleave benzyl ethers under non-hydrogenolytic conditions as well.[5] The cleavage of benzyl ethers by transfer hydrogenation in the presence of Pd/C using cyclohexene,[48a] cyclohexadiene,[48b] formic acid,[48c] ammonium formate[48d] and isopropyl alcohol[48e] as a source of hydrogen has also been well studied. Since hydrogenolysis of benzyl ethers has received much attention in the literature, they will not be discussed here. However, a few unusual and interesting examples of cleavage of benzyl ethers have been included below.

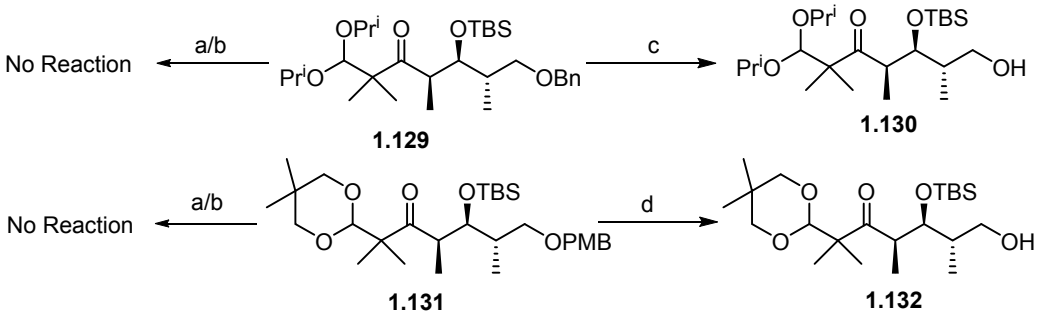



**Scheme 1.24**: a) Pd/C, $H_2$, EtOH, rt, 20-24 h.

Although generally, cleavage of the benzyl ether is faster than cleavage of the N-benzyl group (under hydrogenolytic conditions) complete inhibition of the cleavage

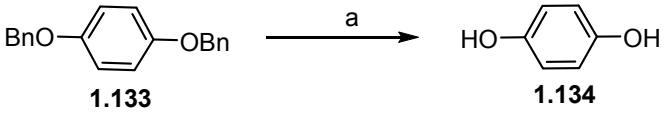
of the O-benzyl group due to the presence of N-benzyl group in the same molecule is reported.[49] Interestingly, unexpected selective cleavage of an N-benzyl group in the presence of a benzyl ether under hydrogenolytic conditions is also reported (Scheme 1.24).

Use of a mixture of Pd/C and $Pd(OH)_2/C$ as catalyst for the hydrogenolysis of benzyl ethers to attain better yields[50] when these catalysts failed to give a product when used separately for the same reaction, is known. This catalytic mixture of Pd/C and $Pd(OH)_2/C$ worked well for the cleavage of the OPMB groups (Scheme 1.25) also.




**Scheme 1.25**: a) Pd/C (30%), $H_2$, THF:*i*PrOH (3:1), rt, 48 h; b) $Pd(OH)_2$ (30%), $H_2$, THF:*i*PrOH (3:1), rt, 48 h; c) Pd/C (15%) + $Pd(OH)_2$ (15%), $H_2$, THF:*i*PrOH (3:1), rt, 48 h, 85%; d) as in c) 8 h, 85%.

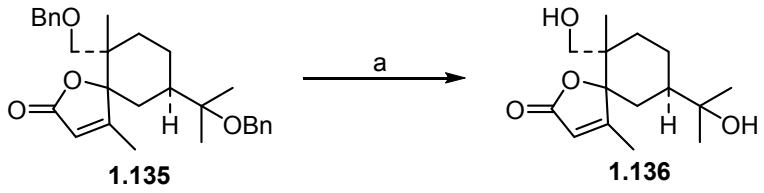
Recently attempts[51] have been made to cleave benzyl ethers in supercritical $CO_2$ (using very little amount of THF) in an attempt to develop greener conditions by limiting the use of organic solvents (Scheme 1.26)




**Scheme 1.26**: a) Pd, $H_2$, super critical $CO_2$, THF, 80-120 $^oC$.

The main disadvantage of the catalytic hydrogenolytic cleavage of benzyl ethers is the intolerance of the unsaturation (C-C multiple bonds) to these reaction conditions. Due to this restriction in the use of benzyl ether protecting groups, alternate methods for the cleavage of benzyl ethers are being sought. However,

isolated example of hydrogenolysis of benzyl ether without affecting a C-C double bond is reported. Caine and Smith[52] used Pd/C for the hydrogenolysis of a benzyl ether substrate containing a conjugated double bond, and surprisingly isolated the debenzylated derivative with the conjugated double bond intact, in quantitative yield (Scheme 1.27).

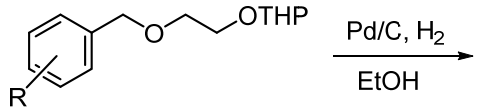


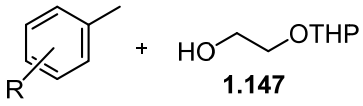

**1.135** **1.136**

**Scheme 1.27**: a) Pd/C, $H_2$, ethanol.

The importance of orthogonal protection strategies in the synthesis of multifunctional molecules prompted Spencer and coworkers[53] to investigate the influence of substitution on the benzyl group in hydrogenolytic cleavage of benzyl ethers. Knowledge of the reaction kinetics was required to understand the electronic effects of the substituents which could aid the development of orthogonal protection strategy using benzyl/substituted benzyl groups. Their observations summarized in Table 1.1 indicate clearly that electron withdrawing groups retard the rate of hydrogenolytic cleavage of the benzyl ethers.

**Table 1.1**: Effect of substitution on the rate of hydrogenolysis of benzyl ethers.



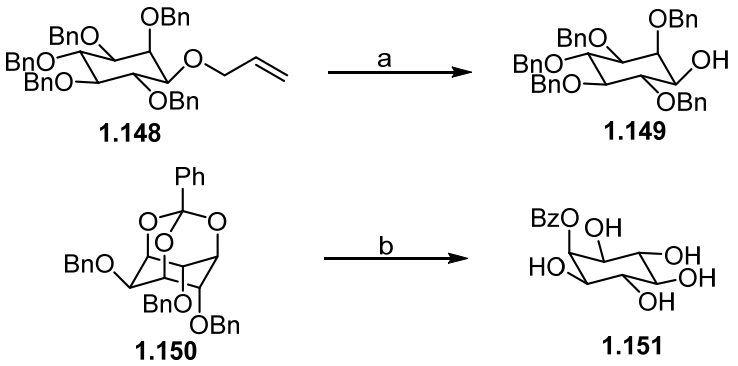

**1.147**

| | K ($Ms^{-1}$) × $10^{-6}$ | | Relative Rate |
|---|---|---|---|
| **1.137** R = 4-$CF_3$ | 0.080 ± 0.002 | **1.142** R = 4-$CF_3$ | 0.205 |
| **1.138** R = H | 0.390 ± 0.008 | **1.143** R = H | 1.00 |
| **1.139** R = 4-Me | 3.07 ± 0.12 | **1.144** R = 4-Me | 7.94 |
| **1.140** R = 3,5-di Me | 4.30 ± 0.22 | **1.145** R = 3,5-di Me | 11.01 |
| **1.141** R = tBu | 9.58 ± 0.78 | **1.146** R = tBu | 24.78 |

The utility and the catalytic nature of the classical Pearlman's catalyst are not yet explored well when compared to other palladium salts. But Pearlman's catalyst is known to be a highly active catalyst for various coupling reactions.[54] Palladium

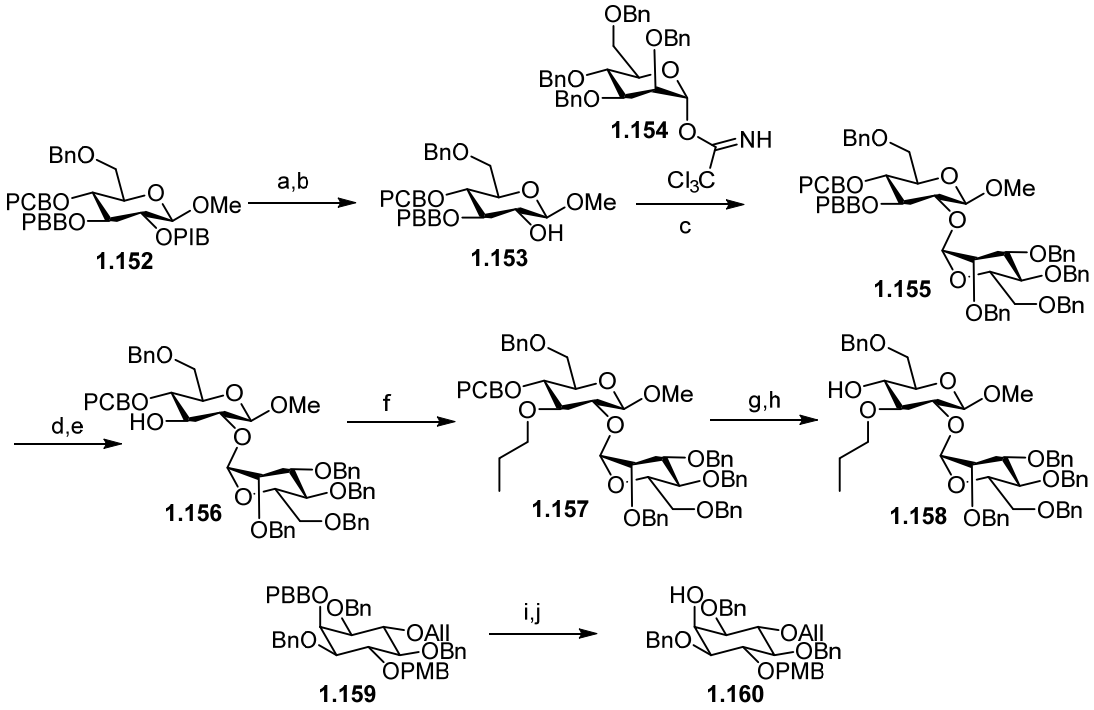
hydroxide is reported to be more efficient than Pd/C for the hydrogenolysis of benzyl ethers.[55]

Orthogonal protection-deprotection strategies are very essential for the synthesis of sugar and inositol derivatives. There are few reports on the usage of palladium




**Scheme 1.28**: a) $PdCl_2$, CuCl, DMF:$H_2O$ (10:1), rt, 1-6 h, 90-92%; (b) $Pd(OH)_2$/C, MeOH, reflux, 12 h, 92%.

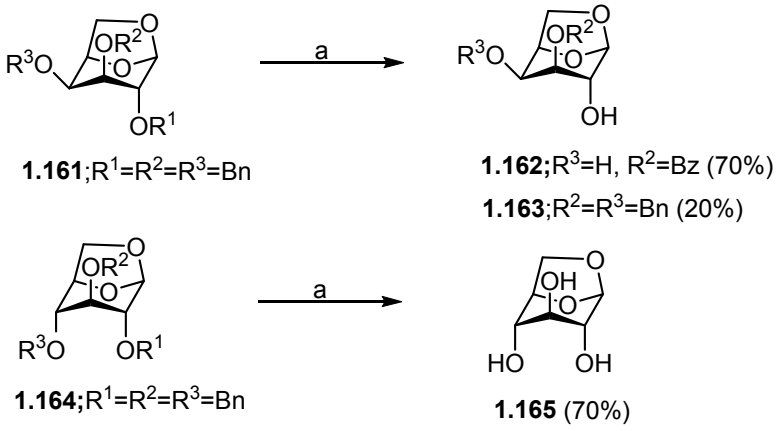
reagents for the cleavage of inositol derived ethers. Mereyala *et al.,*[42b] used $PdCl_2$ for the selective cleavage of allyl groups in inositol derivatives and Murali *et al.,*[5] used



**Scheme 1.29**: a) $Pd_2dba_3$, $NaO^tBu$, $L^1$, PhN(H)Me, rt, 4 h; b) $Cl_2HCCO_2H$, 84%; c)TMSOTf, rt, 88%; d) $Pd_2dba_3$, $NaO^tBu$, $L^2$, PhN(H)Me, 80 $^oC$; e) $SnCl_2$, 82%; f) NaH, propyl iodide, DMF, 99%; g) $Pd_2dba_3$, $NaO^tBu$, $L^2$, PhN(H)Me, rt; h) $SnCl_4$, 91%; i) $Pd(dba)_2$, $NaO^tBu$, (O-biph)P($t$Bu)$_2$, PhN(H)Me, $PhCH_3$,100 $^oC$; j) $CH_2Cl_2$, $ZnCl_2$, 0 $^oC$-rt; $L^1$ = 1-(*N,N*-dimethylamino)-1$^I$-(dicyclohexylphosphino)biphenyl, $L^2$ = (*o*-biphenyl)P(tBu)$_2$.

$Pd(OH)_2/C$ for the global deprotection of several inositol derivatives (Scheme 1.28).Orthogonal deprotection of halo substituted benzyl ethers in sugar derivatives using a single palladium reagent ($Pd_2dba_3$) was reported by Plante *et al*.[56] Our group has applied this orthogonal deprotection strategy for the synthesis of inositol derivatives (Scheme 1.29).[57]

In 1986 del Carmen and Martin-Lomas[48e] observed an unusual oxidation of benzyl ether to the corresponding benzoate by treatment with Pd/C in certain sugar derivatives (Scheme 1.30). They isolated an oxidized product (benzoate **1.162**, 70%) along with minor amount of a partially debenzylated product (**1.163)** after refluxing the tribenzyl ether **1.161** with Pd/C in *iso*-propanol. However, no oxidation products were observed when compound **1.164** was subjected to similar reaction conditions. These reactions gave a clue about the geometrical requirement of the substrate for the oxidation (of the benzyl ether to benzoate) to occur. Oxidation of a benzyl ether occurred only when there was a *cis* disposed protected hydroxyl group adjacent to the benzyl ether group at the 2$^{nd}$ position.




**Scheme 1.30**: a) 10% Pd/C, *i*PrOH, reflux, 3-5 h.

## 1.4. Conclusions

The palladium mediated reactions presented in this chapter have been selected out of a vast majority of reports in the literature pertaining to the use of palladium in the reactions of small organic molecules. These examples illustrate the fact that although palladium hydroxide is known to bring about several interesting organic transformations, its potential utility has not been fully explored. The reaction that is most relevant to us is the ability of palladium hydroxide to cleave ethers, particularly allyl and benzyl ethers; the former in a single step and the latter in the absence of hydrogen. These could be of significant utility during the synthesis of inositol derivatives as well as other polyols such as carbohydrates. However a survey of the literature shows that this aspect has not been examined systematically and hence is an open ended question. Accordingly we have investigated the ability of palladium hydroxide to cleave ethers selectively. Presentation of the results we have obtained in our efforts to demonstrate the selective cleavage of commonly used ether protecting groups, the application of the results obtained in the synthesis of inositol derivatives and investigation of the mechanism of a few of these reactions forms the subject of the subsequent chapters of this thesis.

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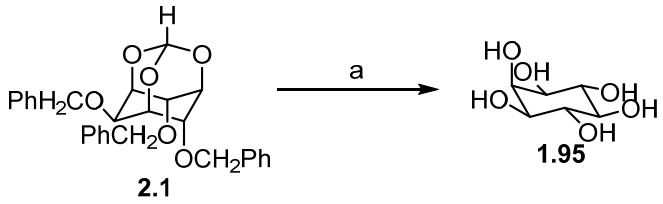
# Chapter 2

# Potential of $Pd(OH)_2/C$ as a selective ether cleaving agent.

## 2.1 Introduction

Pearlman's catalyst, palladium hydroxide supported on charcoal, is routinely used as a catalyst for the hydrogenation and hydrogenolysis reactions and for certain coupling reactions such as Fukuyama, Sonogashira, Suzuki coupling etc.[1] This palladium reagent is convenient for use and recycling because it can be removed at the end of the reaction by filtration. We had realized earlier[2] that $Pd(OH)_2/C$ is capable of cleaving benzyl ether (in the absence of hydrogen) as well as the orthoformate (Scheme 2.1).




**Scheme 2.1**: a) 20% $Pd(OH)_2/C$, MeOH, reflux, 72 h, 96%.

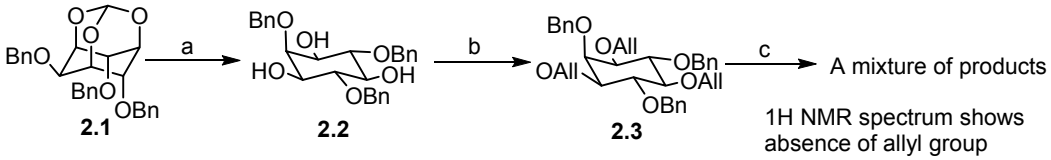
Analysis of the $^1H$ NMR spectrum of the mixture of products obtained (after the cleavage of benzyl ethers) suggested the presence of both benzaldehyde and methyl benzoate indicating that debenzylation as shown in Scheme 2.1, could be an oxidative process. Analysis of the XPS spectrum of the spent palladium hydroxide reagent which showed the conversion of Pd(II) to Pd(0) gave additional support to this possibility. Since the non-hydrogenolytic cleavage of benzyl ethers by $Pd(OH)_2/C$ was a clean reaction and the isolation of products was easy, we investigated the ability of $Pd(OH)_2/C$ to cleave ethers selectively. We herein present experimental results, which show that ether cleaving ability of $Pd(OH)_2/C$ can be tuned to achieve selective cleavage of certain ethers in preference to others and hence $Pd(OH)_2/C$ has the potential for use in the synthesis of complex organic molecules where protection-deprotection protocols are unavoidable.

## 2.2 Results and Discussion

### 2.2.1 Selective cleavage of allyl ethers with $Pd(OH)_2/C$.

As illustrated in the first chapter, since palladium reagents are capable of cleaving allyl ethers, we tested the relative ease of cleavage of allyl ether by $Pd(OH)_2/C$ in the presence of benzyl ethers. The *myo*-inositol hexa-ether **2.3** was prepared as shown in

Scheme 2.2 and subjected to ether cleavage by $Pd(OH)_2/C$ in refluxing methanol. The $^1H$ NMR spectrum of the crude product indicated the presence of more than one product and complete absence of allyl groups. This indicated that the cleavage of allyl ether by $Pd(OH)_2/C$ is more facile than the cleavage of benzyl ether.




**Scheme 2.2**: a) HCl/MeOH, reflux, 20 min, 86%. b) NaH, AllBr, rt, 3 h, 94%. c) $Pd(OH)_2/C$, MeOH, reflux, 80 h. See Appendix1 (page 69) for the $^1H$ NMR spectrum of the mixture of products.

Hence we subjected several allyl ethers containing other hydroxyl protecting groups to cleavage conditions with $Pd(OH)_2/C$ and the results are shown in Table 2.1.

**Table 2.1.** Cleavage of allyl ethers by $Pd(OH)_2/C$ in the presence of other hydroxyl protecting groups.

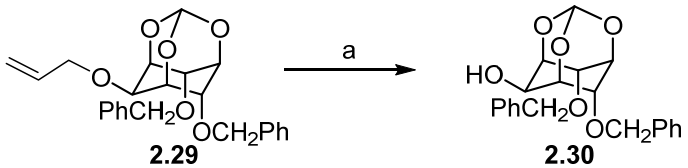
| Entry | Substrate | Conditions[a], h | Product/s (% yield) |
|---|---|---|---|
| 1 | **2.4** $BnO(CH_2)_6OAll$ | A, 50 | **2.16** $HO(CH_2)_6OH$ (76) |
| 2 | **2.4** $BnO(CH_2)_6OAll$ | B, 1.5 | **2.17** $BnO(CH_2)_6OH$ (94) |
| 3 | **2.5** $PBBO(CH_2)_8OAll$ | B, 1.5 | **2.18** $PBBO(CH_2)_8OH$ (84) |
| 4 | **2.6** $PMBO(CH_2)_8OAll$ | B, 1.25 | **2.19** $PMBO(CH_2)_8OH$ (88) |
| 5 | **2.7** $PNBO(CH_2)_8OAll$ | B, 1.5 | **2.20** $PNBO(CH_2)_8OH$ (91) |
| 6 | **2.8** $TsO(CH_2)_8OAll$ | B, 1.5 | **2.21** $TsO(CH_2)_8OH$ (87) |
| 7 | **2.9** $AcO(CH_2)_8OAll$ | B, 1.5 | **2.22** $AcO(CH_2)_8OH$ (92) |
| 8 | **2.10** $BzO(CH_2)_8OAll$ | B, 1.5 | **2.23** $BzO(CH_2)_8OH$ (91) |
| 9 | **2.11** $TrO(CH_2)_8OAll$ | B, 1.5 | **2.24** $TrO(CH_2)_8OH$ (58) |
| 10 | **2.11** $TrO(CH_2)_8OAll$ | C, 1 | **2.24** $TrO(CH_2)_8OH$ (66) |
| 11 | **2.12** PropargylO-$(CH_2)_8OAll$ | B, 2 | **2.25** $HO(CH_2)_8OAll$ (36)<br>**2.26** $HO(CH_2)_8OH$ (54) |

| | | | |
|---|---|---|---|
| 12 | **2.13** TBDMSO-$(CH_2)_8$OAll | B, 1.5 | **2.26** HO$(CH_2)_8$OH (78) |
| 13 | **2.14** $CH_2$=$CHCH_2$OPh | A, 3 | **2.27** PhOH (70) |
| 14 | **2.15** $CH_2$=$CHCH_2$OOCPh | D 8 | **2.28** PhCOOH (82) |

[a] $Pd(OH)_2/C$ (20% by weight) was used in all the experiments, in the proportion mentioned below. Conditions: A, 100 mol%, methanol, reflux; B, 50 mol%, $^{i}$PrOH, reflux; C, 50 mol%, $^{t}$BuOH, reflux; D, 70 mol%, methanol, reflux.

As is evident from Table 2.1, $Pd(OH)_2/C$ mediated allyl ether cleaving conditions are tolerated by several other hydroxyl protecting groups. Even the normally labile trityl ether is quite stable to $Pd(OH)_2/C$ (entry 10). The propargyl ether on the other hand was more labile than the allyl ether (entry 11), while silyl ether was as labile as the allyl ether (entry 12). Allyl phenyl ether (entry 13) as well as allyl ester (entry 14) could also be efficiently cleaved with $Pd(OH)_2/C$ in methanol. It is interesting to note that allyl ethers can be cleaved in one step, while the previously known methods required isomerization of the allyl ether to the corresponding enol ether followed by hydrolysis of the latter with protic acids.[3] These reaction conditions for the cleavage of allyl ethers are not compatible with other acid sensitive groups. But data in Table 1 clearly showed that the allyl ether can be cleaved with $Pd(OH)_2/C$ in the presence of acid sensitive group such as the trityl group (entry 10).

The results described so far shows that allyl ethers are more labile than benzyl ethers to cleavage conditions in the presence of $Pd(OH)_2/C$. The results shown in Scheme 2.1, reveals that the orthoformate does not survive benzyl ether cleavage conditions by $Pd(OH)_2/C$. Hence we wondered whether we could arrive at experimental conditions which cleave the allyl ether while leaving the orthoformate undisturbed. To realize this selectivity, we prepared the orthoformate **2.30** (Scheme 2.3) containing




**2.29** **2.30**

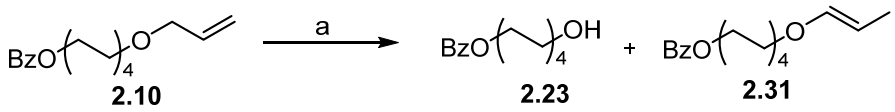
**Scheme 2.3**: a) $Pd(OH)_2/C$, $^{i}$PrOH, reflux, 1.5 h, 78%.

both benzyl and allyl ethers and subjected it to cleavage by $Pd(OH)_2/C$ in isopropanol. Indeed, we could isolate the deallylated orthoformate **2.30** in very good yield. Initial

experiments showed that a better selectivity can be achieved by using a bulkier alcohol as the solvent (entries 9&10 in Table 2.1). The extent of selectivity realized by the current method of cleavage of allyl ethers cannot be attained by the conventional two step procedure since it involves the use of protic acid (for the hydrolysis of the propenyl ether) to which orthoformate is quite labile. In contrast, $Pd(OH)_2/C$ ether cleavage conditions are essentially neutral.

**Cleavage of allyl ethers using catalytic amount of $Pd(OH)_2/C$.**

In some of the allyl ether cleavage experiments we observed the isomerization of the allyl ether to the corresponding propen-1-yl ether. Hence we postulated that the Pd(0) initially generated from Pd(II) during the ether cleavage reaction could be bringing about this isomerization.




**Scheme 2.4**: a) Pd/C, $^{i}$PrOH, reflux, 1h.

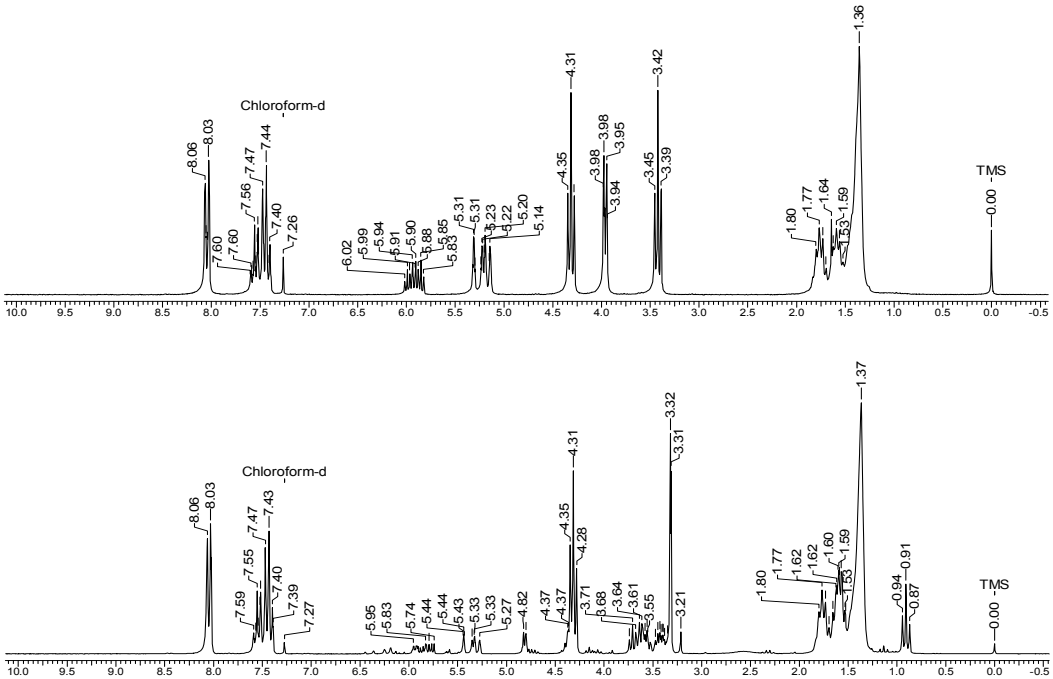
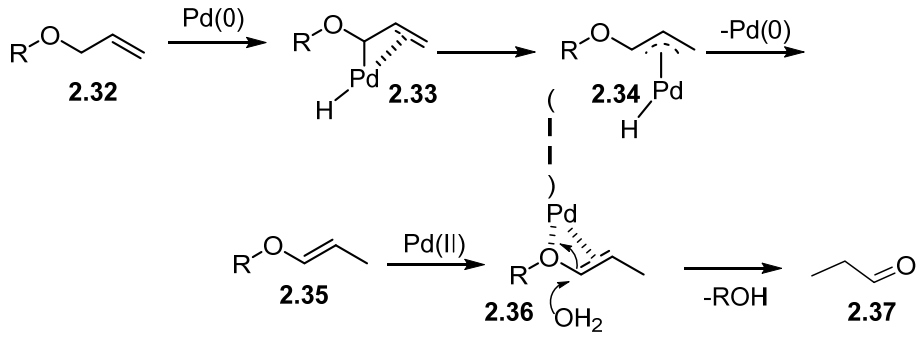



**Figure 2.2**: Comparison of the $^{1}$H NMR spectra of the compound **2.10** before (top) and after the treatment (bottom) with Pd/C under the conditions shown in Scheme 2.4.

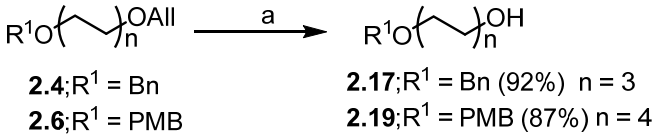
Isomerization of allyl ethers to the corresponding propenyl ether in the presence of Pd(0) has earlier been reported.[4] Treatment of 8-(allyloxy)octyl benzoate with Pd/C (10 mol %) indeed showed the isomerization of the allyl group (Scheme 2.4).

A comparison of the $^1$H NMR spectra of the starting material and the crude product obtained after refluxing one hour with Pd/C is given in Figure 2.2. The peaks at δ 4.82 and δ 6.2 indicate isomerization of the allyl ether. Hence it appears that once a considerable amount of Pd(0) gets accumulated in the reaction mixture, the cleavage of the allyl ether proceeds in parallel by oxidation with $Pd(OH)_2/C$ (see below, Scheme 2.9) as well as isomerization (by Pd(0)) and subsequent cleavage of the propen-1-yl ether by $Pd(OH)_2/C$. The latter process is a non-oxidative process (Scheme 2.5). Previous work in our laboratory had shown that $Pd(OH)_2/C$ is capable of cleaving acetals[2] and isomerization of the allyl ether to the corresponding propenyl ether by Pd(0) has earlier been reported.[3f]




**Scheme 2.5**: A plausible mechanism for the cleavage of allyl of ether *via* isomerization in the presence of Pd(0) and Pd(II).

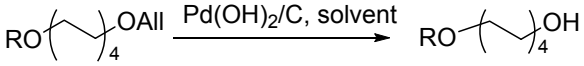
These observations in fact helped us to develop a procedure for the cleavage of allyl ethers wherein the palladium reagents could be used in catalytic amounts (Scheme 2.6).




**Scheme 2.6**: Deallylation using catalytic amount of palladium reagents.(a) $Pd(OH)_2/C$ and Pd/C (10 mol% each), $^i$PrOH, reflux, 30 min.

The recovered catalyst could be used for the cleavage of a second batch of the substrate. These results further enhance the synthetic utility of the method of allyl ether cleavage using $Pd(OH)_2/C$.

**Table 2.2**: Attempted experiments for the deallylation of allyl ethers with $Pd(OH)_2/C$ in the presence of oxidants.




**2.10**;R=Bz
**2.38**;R=Bn

**2.23**;R=Bz
**2.39**;R=Bn

| Entry | **Substrate**, Solvent, reaction conditions | **Product** (% Yield) |
|---|---|---|
| 1 | **2.38**, $Pd(OH)_2/C$ (50 mol%), methanol, rt, 24 h. | No reaction |
| 2 | **2.38**, $Pd(OH)_2/C$ (50 mol%), methanol, reflux, 1.5 h | **2.39** (78)[a] |
| 3 | **2.38**, $Pd(OH)_2/C$ (50 mol%), $^{i}$PrOH, reflux, 1.5 h | **2.39** (94) |
| 4 | **2.38**, $Pd(OH)_2/C$ (50 mol%), $^{i}$PrOH:DMSO (5:1), reflux, 3 h | No reaction |
| 5 | **2.38**, $Pd(OH)_2/C$ (50 mol%), $^{i}$PrOH:$H_2O$ (4:1), reflux, 2 h | Complete reaction [b] |
| 6 | **2.38**, $Pd(OH)_2/C$ (50 mol%), toluene, rt, 24 | No reaction |
| 7 | **2.38**, $Pd(OH)_2/C$ (50 mol%), toluene, reflux, 5 h | No reaction |
| 8 | **2.38**, $^{i}$PrOH, 20% $Pd(OH)_2/C$ (10 mol %), reflux, 13 h. | Complete reaction [b] |
| 9 | **2.10**, $^{i}$PrOH:$H_2O$ (2:1), 20% $Pd(OH)_2/C$ (20 mol%), $CuCl_2$, reflux, 1 h. | **2.23**(67%), **2.40**[c](26%)[d] |
| 10 | **2.10**, $^{i}$PrOH:$H_2O$ (2:1), 20% $Pd(OH)_2/C$ (20 mol%), CuCl, reflux, 5 h. | No reaction |

[a]TLC shows diol as a minor product – not isolated; [b]by TLC analysis ; [c]**2.40** is $BzO(CH_2)_8OCH_2COCH_3$; [d]Yield after column chromatography.

Prior to developing the allyl ether cleavage conditions shown in Scheme 2.6 we attempted to make the deallylation process catalytic by the use of oxidants capable of oxidizing Pd(0) to Pd(II) as is usually done in Pd(II) mediated reactions (See Chapter 1, page 16). We also carried out ether cleavage experiments in different solvents (Table 2.2 entries 2,3,4,5 and 6) to arrive at best allyl ether cleaving conditions so that an oxidant could be included later. Use of copper salts to regenerate Pd(II) were unsuccessful owing to the formation of Wacker oxidation type of products. Results of such attempts are shown in Table 2.2.

### 2.2.2 Cleavage of benzyl ethers

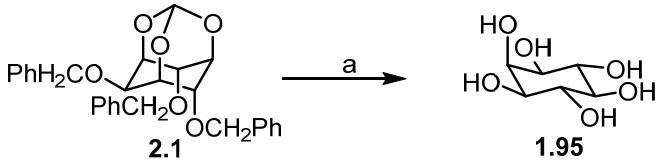
We also investigated the relative ease of cleavage of benzyl ether and substituted benzyl ethers with $Pd(OH)_2/C$, since the work described so far had clarified that allyl ethers, orthoesters, and acetals are more labile than the benzyl ether. Table 2.3 shows the results of attempts to discriminate between the cleavage of different types of benzyloxy groups by $Pd(OH)_2/C$.

**Table 2.3** Cleavage of benzyl ether and substituted benzyl ethers by $Pd(OH)_2/C$.

| Entry | Substrate | Conditions[a], h | Product/s (% yield) |
|---|---|---|---|
| 1 | **2.41** $BnO(CH_2)_8OBn$ | A, 5 | **2.26** $HO(CH_2)_8OH$ (96) |
| 2 | **2.42** $BnO(CH_2)_8OPNB$ | B, 3 | **2.20** $HO(CH_2)_8OPNB$ (77) |
| 3 | **2.43** $PMBO(CH_2)_8OPMB$ | A, 5 | **2.26** $HO(CH_2)_8OH$ (46) |
| | | | **2.19** $HO(CH_2)_8OPMB$ (24) |
| 4 | **2.44** $BnO(CH_2)_8OPMB$ | B, 3 | **2.19** $HO(CH_2)_8OPMB$ (49) |
| | | | **2.26** $HO(CH_2)_8OH$ (47) |
| 5 | **2.45** $PBBO(CH_2)_8OPBB$ | A, 5 | No reaction |
| 6 | **2.46** $PhCH_2OPh$ | D, 90 | No reaction |
| 7 | **2.47** $PhCH_2OOCPh$ | C, 24 | No reaction |

[a] $Pd(OH)_2/C$ (20% by weight) was used in all the experiments in the proportion mentioned below. Conditions: A, 100 mol%, methanol, reflux; B, 50 mol%, $^i$PrOH, reflux; C, 50 mol%, methanol, reflux; D, 70 mol%, methanol, reflux.

Competition experiments with benzyl ether and substituted benzyl ethers showed that benzyl ether can be cleaved in preference to *p*-nitrobenzyl ether. Although benzyl ether could be cleaved in preference to *p*-methoxy benzyl ether, the selectivity was modest. A comparison of the results on the cleavage of benzyl ether **2.41** and *p*-bromobenzyl ether **2.45** suggested that these two ethers can be discriminated. These results are in contrast to the preference in the cleavage of benzyl ether and *p*-methoxy benzyl ether by DDQ (wherein PMB ether is more labile)[5] and Buchwald's method (wherein *p*-halobenzyl ethers are cleaved in preference to benzyl ether).[6] It is also pertinent to note that although alkyl-benzyl ethers can be cleaved with $Pd(OH)_2/C$, aryl benzyl ethers and benzyl esters are stable. We also observed that cleavage of more benzyl ethers per molecule of the substrate required proportionately more of the palladium reagent and longer reaction time; however yield was not compromised (Scheme 2.7 below).




**2.1** **1.95**

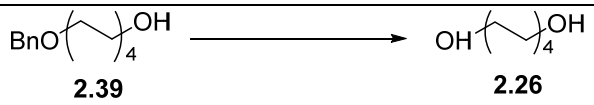
**Scheme 2.7**: a) $Pd(OH)_2/C$, MeOH, reflux, 72 h, 94%. (The molar ratio of compound 2.1: $Pd(OH)_2$ is 1: 1.5)

It is interesting to note that trityl ether is relatively stable to cleavage conditions with $Pd(OH)_2/C$, although they are (substituted)benzylic ethers in nature (entry 10, Table 2.1).

**Recycling of $Pd(OH)_2/C$ for the cleavage of benzyl ether.**

The debenzylation method using Pearlman's catalyst (Table 2.3 and Scheme 2.7) had certain limitations, such as the stoichiometric use of $Pd(OH)_2$. Hence we attempted several experiments to arrive at catalytic reaction conditions for the cleavage of benzyl ether. Results of such experiments are shown in the Table 2.4; but our attempts were not successful. We also carried out ether cleavage experiments in different solvents as control reactions (Table 2.4 entries 2-7).

**Table 2.4**: Attempted debenzylation of benzyl ethers using sub-stoichiometric amount of $Pd(OH)_2/C$.



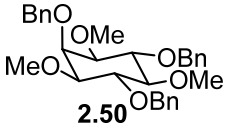
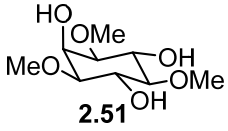

**2.39** **2.26**

| Entry | Reagents and reaction conditions | Yield (%) |
|---|---|---|
| 1 | $Pd(OH)_2/C$ (50 mol%), MeOH, rt, 24 h. | No reaction |
| 2 | $Pd(OH)_2/C$ (50 mol%), MeOH, reflux, 4 h | 86 |
| 3 | $Pd(OH)_2/C$(50 mol%), MeOH:DMSO (4:1), reflux, 10 h | Incomplete reaction |
| 4 | $Pd(OH)_2/C$ (50 mol%), THF, reflux, 10 h | No reaction |
| 5 | $Pd(OH)_2/C$ (50 mol%), MeOH:THF (4:1), reflux, 6 h | Complete reaction (by TLC) |
| 6 | $Pd(OH)_2/C$ (50 mol%), $CHCl_3$, reflux, 10 h | No reaction |
| 7 | $Pd(OH)_2/C$ (50 mol%), MeOH:$CHCl_3$ (4:1), reflux, 6 h | Complete reaction (by TLC) |
| 8 | $Pd(OH)_2/C$, 10% Pd/C (25mol% each), MeOH, reflux, 7 h | Complete reaction (by TLC) |
| 9 | $Pd(OH)_2/C$ + $CuCl_2$, MeOH, reflux, 10 h | No reaction |
| 10 | $Pd(OH)_2/C^a$, MeOH, reflux, 10 h | No reaction |
| 11 | $Pd(OH)_2/C^b$, MeOH, reflux,10 h | No reaction |

[a]Spent $Pd(OH)_2/C$ (after cleavage of one sample of benzyl ether **2.39**) was stirred with $CuCl_2$ in methanol:$H_2O$ for 5 h at rt and used. [b]Spent $Pd(OH)_2/C$ (after cleavage of one sample of benzyl ether **2.39**) was stirred with $CuCl_2$ in $O_2$ atmosphere in methanol:$H_2O$ for 5 h at rt and used.

We next attempted to recycle the spent palladium(II) reagent for the cleavage of fresh samples of a benzyl ether. The solvent containing the product was removed from the reaction mixture by decantation and the palladium reagent was washed (three times) with methanol and used for the cleavage of a fresh sample of the benzyl ether. This procedure could be used for the efficient cleavage of the benzyl ether. The aggregate yield obtained after the cleavage of four batches of the substrate indicated excellent recycling efficiency. The results of such experiments are shown in Table 2.5.

**Table 2.5**: Recycling of the palladium reagent for the cleavage of benzyl ethers in refluxing methanol.

| Entry | Benzyl ether | Reagents and conditions | Product (Yield %)[a] |
|---|---|---|---|
| 1 | **2.48** $BnO(CH_2)_7CH_3$ | $Pd(OH)_2/C$, 15 mol %. | **2.49** $HO(CH_2)_7CH_3$ (89) |
| 2 | **2.39** $BnO(CH_2)_8OH$ | $Pd(OH)_2/C$, 20 mol%. | **2.26** $HO(CH_2)_8OH$ (92) |
| 3 |  **2.50** | $Pd(OH)_2/C$, 120 mol%. |  **2.51** (96) |

[a] Aggregate yield after 4 cycles of ether cleavage with the same sample of palladium(II) reagent.

However, the reaction time for the subsequent batch of the benzyl ether increased. A comparison of the progress of the cleavage of 1-benzyloxy octane **2.48** in three successive batches is shown in the Figure 2.3. The reaction was monitored by $^1$H-NMR spectroscopy (see appendix 1 for spectra). The maximum recycling of the palladium reagent attempted was eight times. However, this does not imply that the palladium reagent cannot be recycled further. But it was rather surprising to see that the spent catalyst could be reused after washing with liberal volume of methanol. At present it is not clear how the palladium(II) reagent is regenerated. It is possible that the palladium (II) reagent was being regenerated by the areal oxidation perhaps due to thorough cleaning of the palladium reagent from the adsorbed organic material.[7a] Alternately, the results of the experiments shown in Table 2.5 could be due to the

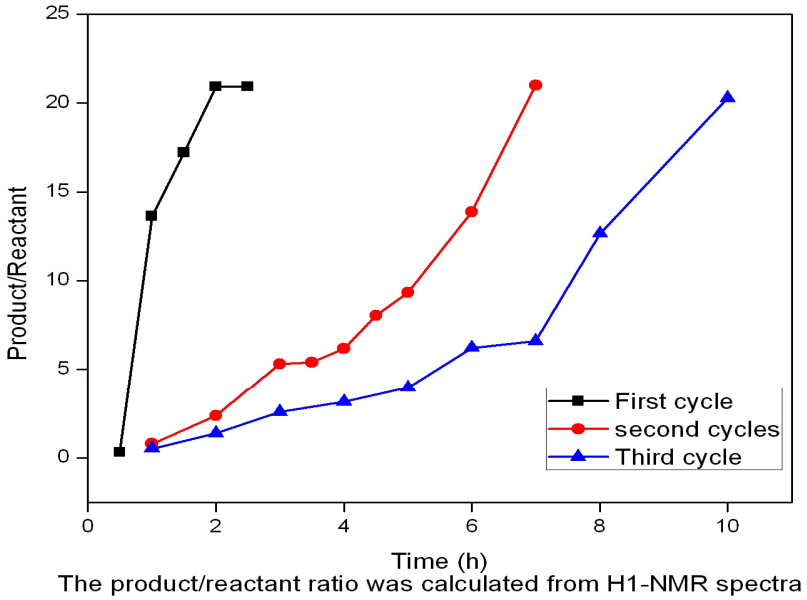
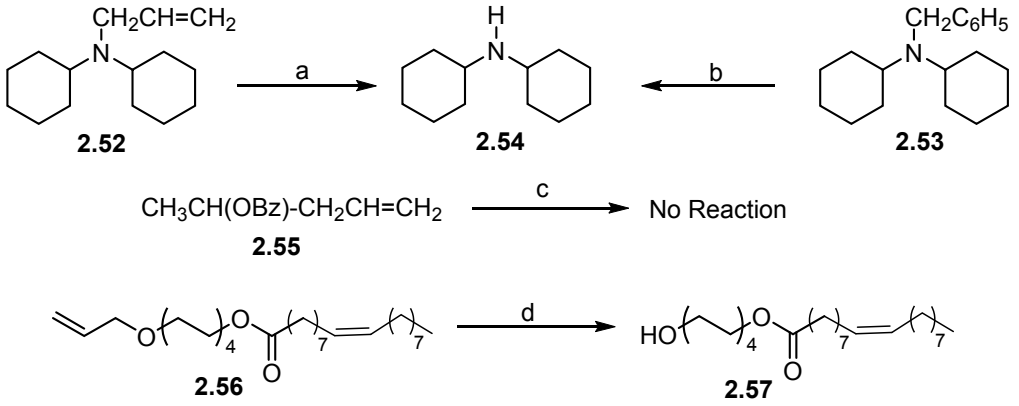



**Figure 2.3**: Comparison of the progress of debenzylation of three batches of the benzyl ether **2.48** with the same sample of $Pd(OH)_2/C$. The molar ratio of **2.48**: $Pd(OH)_2$ in each experiment was 1: 0.2.

influence of the subsurface.[7b] See reference 7b for a discussion on the influence of sub-surfaces.

### 2.2.3 Miscellaneous cleavage experiments

We subjected allyl and benzyl amines **2.52** and **2.53** respectively, to cleavage by $Pd(OH)_2/C$ and obtained the corresponding secondary amine **2.54** in good yield (Scheme 2.8). As seen during the cleavage of ethers, allyl amine was cleaved faster than the corresponding benzyl amine and required lesser quantity of $Pd(OH)_2/C$. The benzoate and the C=C bond in **2.55** and **2.56** remained unaffected on treatment with $Pd(OH)_2/C$ showing that normal C-C double bonds are unaffected under the conditions of allyl ether cleavage. We used $^{i}$PrOH:THF mixture as the solvent for the allyl ether cleavage in compound **2.56** to increase the solubility of the substrate. Unlike other allyl ethers (see Table 2.1) the cleavage of **2.56** went to completion after10 h. This experiment also indicated that although alkyl esters are stable to $Pd(OH)_2/C$ allyl esters can be cleaved. This is analogous to the ease of cleavage of

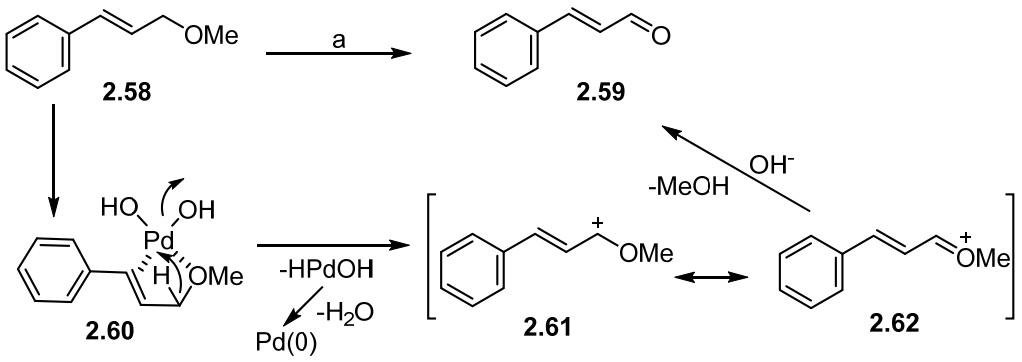



**Scheme 2.8**: a) 50 mol% $Pd(OH)_2/C$, methanol, reflux, 1 h, 69%; b) 100 mol% $Pd(OH)_2/C$, methanol, reflux, 8 h, 62%; c) 50 mol% $Pd(OH)_2/C$, methanol, reflux, 6 h; d) $Pd(OH)_2/C$ (20 mol%) + Pd/C (10 mol%), $^{i}$PrOH: THF (4:1), reflux, 10 h, 84%.

alkyl and allylethers (Table 2.1). These results are of significance since they could be useful in the synthesis of natural lipids, which contain unsaturated fatty acid moieties. Hence we also tested the susceptibility of allyl and benzyl phosphates to cleavage with $Pd(OH)_2/C$ (See Chapter 3).

### 2.2.4 Studies directed towards delineating the mechanism of the $Pd(OH)_2/C$ mediated ether cleavage reactions.

We subjected the cinnamyl ether **2.58** to cleavage with $Pd(OH)_2/C$ to see the fate of the (substituted) allyl group, after ether cleavage. Formation of the aldehyde **2.59** in




**Scheme 2.9**: a) $Pd(OH)_2/C$, $^{i}$PrOH , reflux, 6 h, 40%.

this reaction suggested that cleavage of allyl ethers by $Pd(OH)_2/C$ could be an oxidative process. A plausible route for the formation of the aldehyde **2.59** is depicted in Scheme 2.9. The modest isolated yield of the aldehyde **2.59** could be due to the tendency of the aldehyde **2.59** to polymerize easily.

A comparison of the XPS data (Figure 2.4) of the palladium reagent before and after the cleavage of 1-allyloxy-6-benzyloxy hexane (**2.4**) showed that Pd(II) had been converted into Pd(0). This data also supports the cleavage of allyl ethers by an oxidative process.

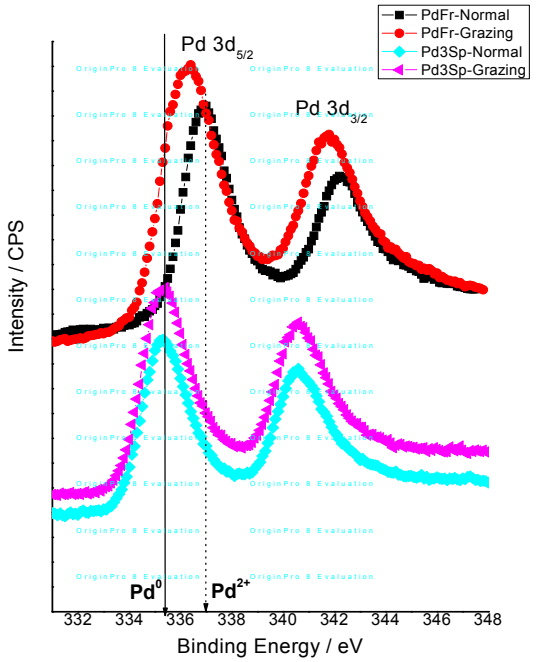
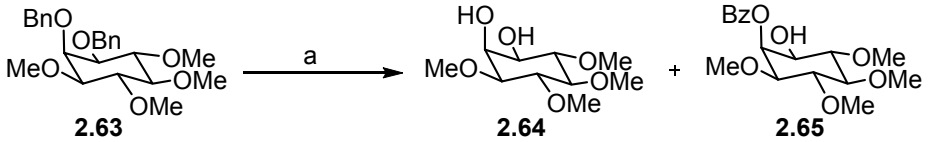



**Figure 2.4**: XPS spectra of the palladium reagent before and after the cleavage of 1-allyloxy-6-benzyloxy hexane (**2.4**). The upper and lower set of graphs indicate the oxidation state of palladium before and after the ether cleavage respectively.

There are literature precedents supporting such $H^-$ transfer (as shown in scheme 2.9) followed by oxidation.[8]

Oxidative cleavage of ethers by $Pd(OH)_2/C$ was also suggested by another experiment. Reaction of *myo*-inositol derived dibenzyl ether, racemic **2.63** with $Pd(OH)_2/C$ in methanol or *iso*-propanol, although led largely to the complete cleavage

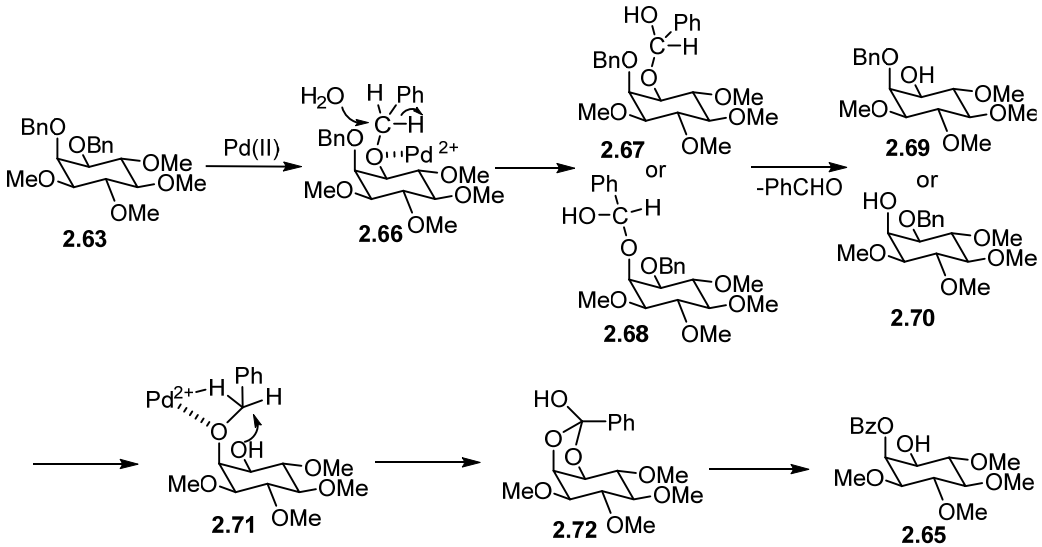
of both the benzyl ethers to yield the corresponding racemic diol **2.64**, also yielded the racemic benzoate **2.65** as a minor product (Scheme 2.10).




| ROH | Time (h) | Yield (%) | |
|---|---|---|---|
| | | **2.64** | **2.65** |
| Dry methanol | 40 | 80 | 14 |
| Dry 2-propanol | 40 | 71 | 27 |
| 2-propanol | 60 | 72 | 23 |

**Scheme 2.10**: Cleavage of *myo*-inositol derived benzyl ether **2.63**. a) $Pd(OH)_2/C$, ROH, reflux.

The racemic benzoate **2.65** could arise due to the intramolecular participation of the neighboring *cis*-hydroxyl group (Scheme 2.11) which leads to the formation of a cyclic orthobenzoate, hydrolysis of which yields the benzoate ester. Hydrolysis of the cyclic orthoester of a *cis*-cyclohexane-1,2-diol is known to lead to the formation of the axial benzoate predominantly.[9] Although relative ease of cleavage of the two benzyl ethers (axial vs equatorial) in racemic **2.63** is not known, the same




**Scheme 2.11**: Plausible route for the formation of the benzoate **2.65** during the cleavage of benzyl ethers by $Pd(OH)_2/C$.

intermediate (**2.72**) can form from both the monobenzyl ethers (**2.69** and **2.70**) that are possible to arise from the cleavage of one of the two benzyl groups in the racemic dibenzyl ether **2.63**.

In1986, del Carmen Cruzado *et al.,*[10] reported the oxidation of benzyl ether located adjacent to a *cis*-oxygen, to the corresponding benzoate ester in pyranose derivatives, on reaction with Pd/C (See chapter 1, pages 23-24). We are of the opinion that the Pd(II) species present in Pd/C they used, was responsible for the observed oxidation. We had earlier shown[2] that commercial samples of Pd/C contains considerable amount of Pd(II) species as revealed by their XPS data (Figure 2.5).

A comparison of the XPS of the Pd 3d core level of $Pd(OH)_2/C$ (curve 1), commercial sample of Pd/C (curve 2) and the spent $Pd(OH)_2/C$-recovered after the cleavage of cyclohexyl benzyl ether (curve 3) clearly showed (i) that the spent palladium recovered after the reaction did not contain Pd(II) species and (ii) the presence of a considerable amount of Pd(II) species in the commercial sample of Pd(0)/C (reproduced from reference 2).

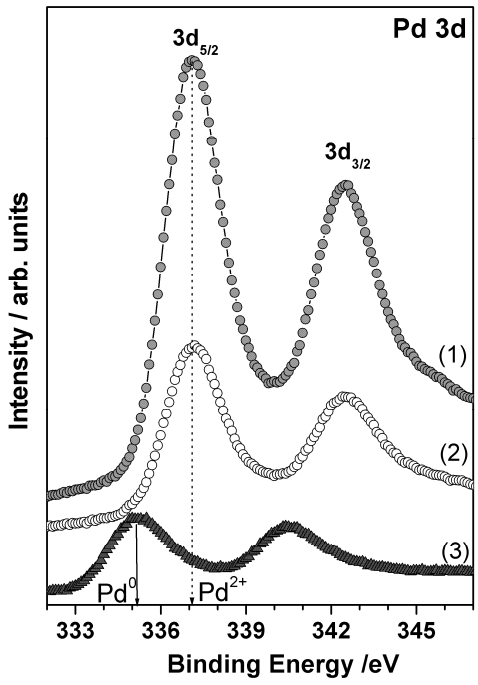
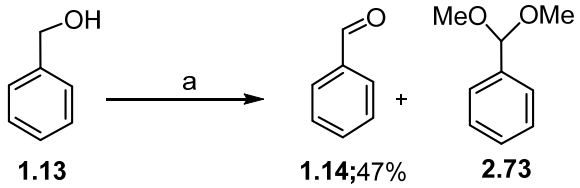



**Figure 2.5**:

These results also support our suggestion that $Pd(OH)_2/C$ cleaves ether by an oxidative process. Stability of trityl ethers to cleavage by $Pd(OH)_2/C$ also supports an

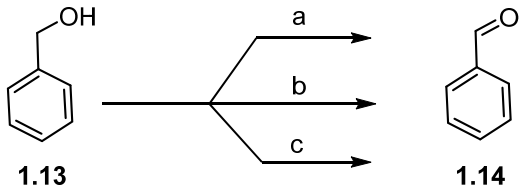
oxidative process for the cleavage of benzyl ethers. This is because, trityl ether, being a substituted benzyl ether, lacks hydrogen atoms on the benzylic carbon and hence is resistant to oxidative cleavage.

The $^1$H NMR spectra of the crude product obtained after the cleavage of benzyl group in benzyloxy octane clearly shows the formation of benzaldehyde, which emphasizes the oxidative cleavage of benzyl ether (appendix1 page number 90). We theorized that if $Pd(OH)_2/C$ is capable of oxidatively cleaving a benzyl ether, it should also oxidize benzyl alcohol. Hence we subjected benzyl alcohol to ether cleavage conditions mediated by $Pd(OH)_2/C$. Analysis of the mixture of products showed the formation of benzaldehyde and its dimethyl acetal (Scheme 2.12). Oxidation of benzylic alcohols by palladium reagents (other than $Pd(OH)_2/C$) have earlier been reported[11]




**Scheme 2.12**: $Pd(OH)_2/C$, MeOH, reflux, 30 min. The yield indicated was estimated by $^1$H NMR spectroscopy using dibromomethane as the internal standard.

However, we are not sure about the course of the reaction, i.e., whether the aldehyde **1.14** or the acetal **2.73** is formed first. Use of toluene instead of methanol as the solvent for the reaction yielded benzaldehyde as the only product (Scheme 2.13). It is of significance to note that among the three palladium(II) reagents used, $Pd(OH)_2$ gave the highest yield of bnezaldehyde.




**Scheme 2.13**: a) $Pd(OAc)_2$, toluene, 80 $^oC$, 3 h, 50% ; b) $PdCl_2$, toluene, 80 $^oC$, 3 h, no reaction; c) $Pd(OH)_2/C$, toluene, 80 $^oC$, 3 h, 70%.

## 2.3 Conclusions

The results presented in this chapter show that the ease of cleavage of ethers with $Pd(OH)_2/C$ can be tuned to the order: alkyl ether, PBB < PMB < Bn < allyl < propargyl ether by varying any one or more of the following parameters; a) ratio of substrate/$Pd(OH)_2/C$; b) the reaction time; c) solvent of the reaction. It is interesting to note that all these selectivities in ether cleavage can be achieved by using the same reagent ($Pd(OH)_2/C$) but under different reaction conditions, which is in contrast compared to the methods that use different reagents to achieve the selective cleavage of ethers. The advantage of the former approach is that in case global cleavage of all the ethers becomes necessary, it can be achieved in a single step rather than in a step-wise manner. An investigation into the mechanism of the ether cleavage reaction by $Pd(OH)_2/C$ aided us to arrive at reaction conditions that allow the use of catalytic amounts of the palladium reagent or recycling of the same reagent for the cleavage of several batches of allyl or benzyl ethers. Application of this method of ether cleavage for the synthesis of inositol derivatives is described in the next chapter.

## 2.4 Experimental Section

***General Procedures*:**

All the solvents were purified according to the literature procedures[12] before use. All air or moisture sensitive reactions were carried out in an atmosphere of argon or nitrogen. 60% dispersion of sodium hydride in mineral oil was used for O-substitution reactions. 'Work up' implies - washing of the organic layer successively with water, brine and drying over anhy. sodium sulphate. Thin Layer Chromatography was performed over E. Merck pre-coated 60 $F_{254}$ plates and the spots were rendered visible either by shining UV light or by charring the plates with chromic acid solution. Column chromatographic separations were carried out on silica gel (100-200 mesh and 230-400 mesh for flash chromatographic separations) with solvent system as mentioned in experimental procedures. Yields refer to chromatographically and spectroscopically pure compounds. Compounds previously reported in the literature were characterized by comparison of their melting points and/or $^1$H NMR spectra with the reported data. IR spectra were recorded (in $CHCl_3$ solution or as a Nujol mull or as a neat film) with a Shimadzu FTIR 8400 or Perkin-Elmer spectrophotometer. NMR spectra (200 MHz for $^1$H and 50.3 MHz for $^{13}$C) were recorded with a Bruker ACF 200 spectrometer unless otherwise mentioned. Chemical shifts (δ, ppm) reported are referred to internal tetramethylsilane (0 ppm for $^1$H NMR spectra), chloroform (77 ppm for $^{13}$C NMR spectra) and $H_3PO_4$ (0 ppm for $^{31}$P NMR spectra). Micro analytical data were obtained using a Carlo-Erba CHNS-0 EA 1108 elemental analyzer. All the melting points reported were recorded using a Büchi B-540 electro-thermal melting point apparatus. Optical rotation was recorded using JASCO P-1020 Polarimeter (in the solvents mentioned in individual experimental procedures). HRMS was recorded by Thermo Scientific Q exactive mass spectrometer.

***Experimental Procedures***

**Racemic 2,4,6-tri-*O*-benzyl-1,3,5-tri-*O*-allyl-*myo*-inositol (2.3)**

To an ice cold solution of 2,4,6-tri-*O*-benzyl-*myo*-inositol[13] (0.30 g, 0.66 mmol) in dry DMF (8 mL) sodium hydride (0.26 g, 6.6 mmol) was added and stirred it for 10 min. Then allyl bromide (0.57 mL, 6.6 mmol) was added drop-wise to the above mixture and the stirring continued for overnight at room temperature. Solvents were

removed under reduced pressure and the crude reaction mixture was worked up with ethyl acetate. The gummy product obtained was purified by column chromatography (eluent: 20% ethyl acetate/light petroleum) to afford **2.3** as a colorless oil (0.36 g, 95%). **$^1$H NMR** ($CDCl_3$, 200.13 MHz) δ: 7.20–7.50 (m, 15 H, ArH), 5.77–6.12 (m, 3H, allylic CH), 5.12–5.36 (m, 6H, allylic $CH_2$), 4.75–4.92 (m, 6H, 3×$OCH_2$), 4.27–4.40 (m, 2H, $OCH_2$), 3.88–4.15 (m, 7H, 2×$OCH_2$, InsH), 3.13–3.36 (m, 3H, InsH) ppm. **$^{13}$C NMR** ($CDCl_3$, 100.53 MHz) δ: 139.0 ($C_{arom}$), 138.9 ($C_{arom}$), 135.4 (allylic CH), 134.9 (allylic CH), 128.3 ($C_{arom}$), 128.2 ($C_{arom}$), 128.1 ($C_{arom}$), 127.8 ($C_{arom}$), 127.6 ($C_{arom}$), 127.3 ($C_{arom}$), 116.6 (=$CH_2$), 116.5 (=$CH_2$), 83.2 (InsC), 81.6 (InsC), 80.5 (InsC), 75.9 ($OCH_2$), 74.6 ($OCH_2$), 74.2 (InsC), 74.0 ($OCH_2$), 71.7 ($OCH_2$) ppm. **Elemental analysis** calcd for $C_{36}H_{42}O_6$: C, 75.76; H, 7.42; Found: C, 75.40; H, 7.65 %.

**Reaction of racemic-2,4,6-tri-*O*-benzyl-1,3,5-tri-*O*-allyl-*myo*-inositol (2.3) with $Pd(OH)_2$/C in methanol**

A mixture of **2.3** (0.20 g, 0.35 mmol) and $Pd(OH)_2$/C (0.51 g) was refluxed in methanol for 80 h. The reaction mixture was filtered through a short bed of Celite and the filtrate concentrated under reduced pressure. The crude product obtained was analyzed by NMR spectroscopy. The NMR spectrum showed the preferential cleavage of allyl group in presence of benzyl groups.

**((6-(Allyloxy)hexyloxy)methyl)benzene (2.4)**

Sodium hydride (0.10 g, 2.40 mmol) was added to a solution of **2.17**[14] (0.25 g, 1.20 mmol) in dry DMF (5 mL) at 0 $^oC$ and stirred for 15 min. Allyl bromide (0.20 mL, 2.40 mmol) was added drop-wise to the reaction mixture in cold condition and stirred at rt for 3 h. The reaction mixture was concentrated under reduced pressure and the gum obtained was worked up with ethyl acetate followed by drying over anhy. sodium sulphate. The crude product was purified by column chromatography (eluent: 10 % ethyl acetate/ light petroleum) to afford **2.4** as a colorless oil[15] (0.27 g, 90 %)**.**

**(1-(8-(Allyloxy)octyloxy)methyl)-4-bromobenzene (2.5)**

Sodium hydride (0.08 g, 2.01 mmol) was added to a solution of **2.25**[16] (0.25 g, 1.34 mmol) in dry DMF (6 mL) at 0 $^oC$ and the mixture stirred for 15 min. To this mixture *p*-bromobenzyl bromide (0.44 g, 1.70 mmol) was added and stirring continued for 4 h.

The reaction mixture was concentrated under reduced pressure and the residue worked up with ethyl acetate followed by drying over anhy. sodium sulphate. Purification of the crude product by column chromatography (eluent: 15 % ethyl acetate/ light petroleum) gave **2.5** as a colorless oil (0.40 g, 83 %). **IR** (neat): $\bar{\nu}$ 1010 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 200 MHz): δ 7.41–7.50 (m, 2H, ArH), 7.16–7.24 (m, 2H, ArH), 5.79–6.03 (m, 1H, =CH), 5.10– 5.33 (m, 2H, $=CH_2$), 4.43 (s, 2 H, $PhCH_2$), 3.95 (dt, 2H, *J* = 5.7, 1.4 Hz, $OCH_2$), 3.36– 3.48(m, 4H, $OCH_2$), 1.50–1.66 (m, 4H, $CH_2$), 1.25–1.39 (m, 8H, $CH_2$) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 137.8 ($C_{arom}$), 135.1 (allylic CH), 131.5 ($C_{arom}$), 129.2 ($C_{arom}$), 121.3 ($C_{arom}$), 116.7 (allylic $=CH_2$), 72.1 ($OCH_2$), 71.8 ($OCH_2$), 70.6 ($OCH_2$), 70.5 ($OCH_2$), 29.8 ($CH_2$), 29.7 ($CH_2$), 29.4 ($CH_2$), 26.1 ($CH_2$) ppm. **Elemental analysis** calcd for $C_{18}H_{27}O_2Br$: C, 60.85; H, 7.66; Found: C, 61.15; H, 8.01 %.

**(1-((Allyloxy)octyloxy)methyl)4-methoxy benzene (2.6)**

Sodium hydride (0.15 g, 3.65 mmol) was added to a cooled solution of **2.25** (0.4 g, 2.15 mmol) in dry DMF (7 mL) and stirred for 15 min. PMBCl (0.44 mL, 3.23 mmol) was added to this mixture drop-wise by maintaining the temperature at 0 $^oC$ and stirring was continued for 3 h at rt. The reaction mixture was concentrated under reduced pressure and the residue was worked up with ethyl acetate followed by drying over anhy. sodium sulphate. The crude product was purified by column chromatography (eluent: 15 % ethyl acetate/ light petroleum) to obtain **2.6** as a colorless oil (0.53 g, 80 %). **$^1$H NMR** ($CDCl_3$, 200 MHz): 7.22–7.30 (m, 2H, ArH), 6.83–6.92 (m, 2H, ArH), 6.80–6.02 (m, 1H, HC=C), 5.11–5.33 (m, 2H, $=CH_2$), 4.42 (s, 2H, $PhCH_2$), 3.96 (dt, 2H, *J* = 5.5, 1.4 Hz, $OCH_2$), 3.79 (s, 3H, $OCH_3$), 3.37–3.47 (m, 4H, 2×$OCH_2$), 1.50–1.66 (m, 4H, 2×$CH_2$), 1.24–1.38 (m, 8H, 4×$CH_2$) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 159.1 ($C_{arom}$), 135.1 (allylic CH=), 130.8 ($C_{arom}$), 129.3 ($C_{arom}$), 116.7 (allylic $=CH_2$), 113.7 ($C_{arom}$), 72.5 ($OCH_2$), 71.8 ($OCH_2$), 70.5 ($OCH_2$), 70.2 ($OCH_2$), 55.3 ($OCH_3$), 29.8 ($CH_2$), 29.5 ($CH_2$), 26.2 ($CH_2$) ppm. **Elemental analysis** calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87; Found: C, 74.38; H, 10.23 %.

**(1-((8-Allyloxy)octyloxy)methyl)-4-nitrobenzene (2.7)**

The 4-nitrobenzyl ether **2.7** was prepared by using 4-nitrobenzyl alcohol and the allyl ether **2.25** as a pale yellow liquid (0.17 g, 50 %) by adopting a reported procedure.[17]

**IR** ($CHCl_3$): $\bar{\nu}$ 1522 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 200 MHz): δ 8.21 (d, 2H, *J* = 8.6 Hz, ArH), 7.51 (d, 2H, *J* = 8.6 Hz, ArH), 5.80–6.05 (m, 1H, CH), 5.11–5.35 (m, 2H, $=CH_2$), 4.60 (s, 2H, $CH_2Ph$), 3.96 (d, 2H, *J* = 5.6 Hz, $OCH_2$), 3.51 (t, 2H, 6.6 Hz, $OCH_2$), 3.42 (t, 2H, *J* = 5.6 Hz, $OCH_2$) 1.52– 1.71 (m, 4H, 2×$CH_2$), 1.26–1.42 (m, 8H, 4×$CH_2$) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 147.3 ($C_{arom}$), 146.5 ($C_{arom}$), 135.1 (allylic CH=), 127.6 ($C_{arom}$), 123.6 ($C_{arom}$), 116.7 (allylic $=CH_2$), 71.8 ($OCH_2$), 71.6 ($OCH_2$), 71.2 ($OCH_2$), 70.5 ($OCH_2$), 29.8 ($CH_2$), 29.7 ($CH_2$), 29.4 ($CH_2$), 29.4 ($CH_2$), 26.14 ($CH_2$), 26.11 ($CH_2$) ppm.**Elemental analysis** calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36; Found: C, 67.07; H, 8.64; N, 4.06 %.

### 8-(Allyloxy)octyl tosylate (2.8)

Tosyl chloride (0.45 g, 2.35 mmol) was added to a solution of **2.25** (0.20 g, 1.07 mmol) in dry pyridine (8 mL) at 0 $^oC$ and the mixture stirred for 1 h at rt. The reaction mixture was concentrated under reduced pressure and worked up with ethyl acetate. The residue obtained was purified by column chromatography (eluent; 20 % ethyl acetate/ light petroleum) to afford **2.8** as a gum (0.24 g, 67 %). **$^1$H NMR** ($CDCl_3$, 200MHz): δ 7.79 (d, 2H, *J* = 8.2 Hz, ArH), 7.35 (d, 2H, *J* = 8.1 Hz, ArH), 5.79–6.05 (m, 1H, HC=C),5.11–5.34 (m, 2H, $=CH_2$), 3.92–4.06 (m, 4H, 2×$OCH_2$), 3.40 (t, 2H, *J* = 6.6 Hz, $OCH_2$), 2.45 (s, 3H, $CH_3$), 1.47–1.70 (m, 4H, 2×$CH_2$), 1.20–1.36 (m, 8H, 4×$CH_2$) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 144.7 ($C_{arom}$)**,** 135.1 (O-C-CH=C), 133.2 ($C_{arom}$), 129.8 ($C_{arom}$), 127.9 ($C_{arom}$), 116.7 ($C=CH_2$), 71.8 ($OCH_2$), 70.7 ($OCH_2$), 70.4 ($OCH_2$), 29.7 ($CH_2$), 29.2 ($CH_2$), 28.8 ($CH_2$), 28.8 ($CH_2$), 26.0 ($CH_2$), 25.3 ($CH_2$), 21.6 ($CH_3$) ppm; **Elemental analysis** calcd for $C_{18}H_{28}O_4S$: C, 63.50; H, 8.29; Found: C, 63.59; H, 8.16 %.

### 8-(Allyloxy)octyl acetate (2.9)

Acetic anhydride (0.30 mL, 3.22 mmol) was added drop-wise to a solution of **2.25** (0.50 g, 2.69 mmol) in dry pyridine (8 mL) followed by catalytic amount of N, N-dimethylamino pyridine (DMAP) at 0 $^oC$ and the mixture stirred for 4 h at rt. The reaction mixture was concentrated under reduced pressure and the residue was worked up with ethyl acetate and dried over anhy sodium sulphate. The crude product obtained was purified by column chromatography (eluent: 20 % ethyl acetate/ light petroleum) to afford **2.9** as a gum (0.51 g, 84 %). **IR** (neat): $\bar{\nu}$ 1741 $cm^{-1}$; **$^1$H NMR**

($CDCl_3$, 200 MHz): δ 5.79–6.03 (m, 1H, HC=C), 5.11–5.33 (m, 2H, $=CH_2$), 4.05 (t, 2H, *J* = 6.7 Hz, $OCH_2$), 3.96 (dt, 2H, *J* = 5.6, 1.3 Hz, $OCH_2$), 3.42 (t, 2H, *J* = 6.6 Hz, $OCH_2$), 2.05 (s, 3H, $CH_3$), 1.50–1.68 (m, 4H, 2×$CH_2$), 1.26–1.40 (m, 8H, 4×$CH_2$) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 171.23 (C=O), 135.1 (allylic CH= ), 116.2 (allylic $=CH_2$), 71.8 ($OCH_2$), 70.4 ($OCH_2$), 64.6 ($OCH_2$), 29.7 ($CH_2$), 29.3 ($CH_2$), 29.2 ($CH_2$), 28.6 ($CH_2$), 26.1 ($CH_2$), 25.8 ($CH_2$), 21.0 ($CH_3$) ppm. **Elemental analysis** calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59; Found: C, 68.59; H, 10.56 %.

**8-(Allyloxy)octyl benzoate (2.10)**

Benzoyl chloride (0.29 mL, 2.58 mmol) was added drop-wise to a solution of **2.25** (0.40 g, 2.15 mmol) in dry pyridine (10 mL) at 0 $^oC$ and stirred overnight at ambient temperature. The reaction mixture was concentrated under reduced pressure and the residue worked up with ethyl acetate followed by drying over anhy sodium sulphate. The yellow colored crude product was purified by column chromatography (eluent, 10 % ethyl acetate/ light petroleum) to afford **2.10** as colorless oil (0.52 g, 84 %). **IR** (neat): $\bar{\nu}$ 1720 $cm^{-1}$ ; **$^1$H NMR** ($CDCl_3$, 200MHz): δ 8.00–8.13(m, 2H, ArH), 7.38–7.63 (m, 3 H, ArH), 5.80–6.06 (m, 1H, HC=), 5.11–5.35 (m, 2H, $=CH_2$), 4.31 (t, 2 H, *J* = 6.6 Hz, $OCH_2$), 3.96 (dt, 2H, *J* = 5.7, 1.3 Hz, $OCH_2$), 3.42 (t, 2 H, 6.6 Hz, $OCH_2$), 1.25–1.86 (m, 12H, 6×$CH_2$) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 166.7 (C=O), 135.1 (CH=), 132.8 ($C_{arom}$), 130.5 ($C_{arom}$), 129.6 ($C_{arom}$), 128.3 ($C_{arom}$), 116.7 ($=CH_2$), 71.8 ($OCH_2$), 70.5 ($OCH_2$), 65.1 ($OCH_2$), 29.8 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 28.7 ($CH_2$), 26.1 ($CH_2$), 26.0 ($CH_2$) ppm; **Elemental analysis** calcd. for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02; Found: C, 74.22; H, 9.33 %.

**1-Allyloxy-8-trityloxyoctane (2.11)**

To a solution of **2.25** (0.30 g, 1.61 mmol) in dry dichloromethane (8 mL), triethyl amine (0.40 mL, 2.73 mmol) was added at 0 $^oC$ followed by trityl chloride (0.54 g, 1.93 mmol). Catalytic amount of dimethylamino pyridine (DMAP) was then added and the mixture was stirred for 2 h at rt. The reaction mixture was concentrated under reduced pressure and the residue worked up with dichloromethane followed by drying over anhy. sodium sulphate. The crude product was purified by column chromatography [eluent: 10 % ethyl acetate/ light petroleum; silica gel was pre-eluted with of 1% triethylamine in light petroleum (3×50 mL)] to afford **2.11** as a colorless

oil (0.54 g, 79 %). **$^1$H NMR** ($CDCl_3$, 200 MHz): δ 7.17–7.50 (m, 15H, ArH), 5.78–6.05 (m, 1H, =CH), 5.11–5.33 (m, 2H, $=CH_2$), 3.96 (dt, 2H, *J* = 5.7, 1.4 Hz, $OCH_2$), 3.41 (t, 2H, *J* = 6.6 Hz, $OCH_2$), 3.03 (t, 2H, *J* = 6.6 Hz, $OCH_2$), 1.50–1.66 (m, 4H, 2×$CH_2$), 1.21–1.39 (m, 8H, 4×$CH_2$) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 144.6 ($C_{arom}$), 135.1 (allylic CH), 128.7 ($C_{arom}$), 127.7 ($C_{arom}$), 126.8 ($C_{arom}$), 116.8 ($=CH_2$), 86.3 (quarternary C), 71.9 ($OCH_2$), 70.5 ($OCH_2$), 63.7 ($OCH_2$), 30.0 ($CH_2$), 29.8 ($CH_2$), 29.5 ($CH_2$), 26.3 ($CH_2$), 26.2 ($CH_2$) ppm. **Elemental analysis** calcd for $C_{30}H_{36}O_2$: C, 84.07; H, 8.47; Found: C, 83.78; H, 8.38 %.

**1-(Allyloxy)-8-(prop-2-yn-1-yloxy)octane (2.12)**

Sodium hydride (0.10 g, 3.22 mmol) was added to a solution of **2.25** (0.40 g, 2.16 mmol) in dry DMF (8 mL) at 0 $^oC$ and the mixture stirred for 15 min. Propargyl bromide (80 % solution in toluene, 0.29 mL, 2.58 mmol) was added drop-wise to the reaction mixture and stirred for 3 h at ambient temperature. The reaction mixture was concentrated under reduced pressure and the residue worked up with diethyl ether. The crude product obtained was purified by column chromatography (eluent: 8 % ethyl acetate in light petroleum) to afford **2.12** as a pale yellow liquid[18] (0.29 g, 63 %).

**(1-(Allyloxy)(8-(tert-butyl)dimethylsiloxy)octane (2.13)**

Imidazole (0.40 g, 5.91 mmol) was added to a solution of **2.25** (0.50 g, 2.69 mmol) in dry DMF (8 mL) at 0 $^oC$ and stirred for 10 min. TBDMSCl (0.81 g, 5.38 mmol) was added to the reaction mixture and stirred overnight at ambient temperature. The reaction mixture was concentrated and worked up with ethyl acetate followed by drying over anhy sodium sulphate. The crude product was purified by column chromatography (eluent: 10 % ethyl acetate/ light petroleum) to afford **2.13** as a colorless oil (0.71 g, 88 %).**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 5.87–5.97 (m, 1H, CH), 5.23–5.30 (m, 1H, =CH), 5.14–5.19 (m, 1H, =CH), 3.96 (dt, 2H, *J* = 5.5, 1.5 Hz, $OCH_2$), 3.59 (t, 2H, *J* = 6.7 Hz, $OCH_2$), 3.42 (t, 2H, *J* = 6.7 Hz, $OCH_2$), 1.55–1.61 (m, 2H, $CH_2$), 1.47–1.53 (m, 2H, $CH_2$), 1.28–1.34 (m, 8H, 4×$CH_2$), 0.89 (s, 9H, $C(CH_3)_3$), 0.05 (s, 6H, 2×$CH_3$) ppm. **$^{13}$C NMR** ($CDCl_3$, 125.76 MHz) δ 135.0 (allylic CH=), 116.6 ($=CH_2$), 71.8 ($OCH_2$), 70.5 ($OCH_2$), 63.3 ($OCH_2$), 32.8 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 26.1 ($CH_2$), 25.7 ($CH_2$), 26.0 ($C(\mathit{C}H_3)_3$), 18.4

(quarternary C), -5.3 ($CH_3$) ppm. **Elemental analysis** calcd for $C_{17}H_{36}O_2Si$: C, 67.94; H, 12.07; Found: C, 67.87; H, 12.64 %.

**General procedure for the cleavage of ethers (conditions A–D)**

The required ether was dissolved in alcohol (methanol or 2-propanol or *tert*-butanol) and refluxed after the addition of $Pd(OH)_2/C$ (20 wt %, 0.35 g – 1.05 g / mmol of the substrate). The reaction mixture was filtered through a short bed of Celite and Celite washed with a suitable solvent (ethyl acetate, methanol, DCM, water). The filtrate was concentrated and the products were isolated by column chromatography over silica gel

**Reaction of ((6-(Allyloxy)hexyloxy)methyl)benzene (2.4) with $Pd(OH)_2/C$ in methanol.**

The allyl ether **2.4** (0.20 g, 0.81 mmol) was cleaved in methanol (3 mL) with $Pd(OH)_2/C$ (0.56 g) to obtain **2.16** as a gum (0.08 g, 76 %). Column chromatographic purification was carried out with 20 % methanol/ ethyl acetate as the eluent.

**Reaction of ((6-(Allyloxy)hexyloxy)methyl)benzene (2.4) with $Pd(OH)_2/C$ in 2-Propanol**

The allyl ether **2.4** (0.20 g, 0.81 mmol) was cleaved in 2- propanol (3 mL) with $Pd(OH)_2/C$ (0.28 g) to obtain **2.17** as a colorless oil[14] (0.16 g, 94 %). Column chromatographic purification was carried out with 60 % ethyl acetate/ light petroleum as the eluent.

**Reaction of (1-(8-(Allyloxy)octyloxy)methyl)-4-bromobenzene (2.5) with $Pd(OH)_2/C$ in 2-propanol**

The allyl ether **2.5** (0.31 g, 0.87 mmol) was cleaved in 2-propanol (3 mL) with $Pd(OH)_2/C$ (0.30 g) to obtain **2.18** as a colorless oil (0.23 g, 84 %). Column chromatographic purification was carried out with 50 % ethyl acetate/ light petroleum as the eluent. **IR** (neat): $\bar{\nu}$ 3103–3628 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 200 MHz): δ 7.46 (d, 2H, *J* = 8.3 Hz, ArH), 7.21 (d, 2H, *J* = 8.3 Hz, ArH), 4.44 (s, 2H, $OCH_2$), 3.62 (t, 2H, *J* = 6.6 Hz, $OCH_2$,), 3.44 (t, 2H, *J* = 6.6 Hz, $OCH_2$,), 1.48–1.75 (m, 5H, 2×$CH_2$, OH), 1.25-1.41 (m, 8H, 4×$CH_2$) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 137.7 ($C_{arom}$), 131.5 ($C_{arom}$), 129.3 ($C_{arom}$), 121.3 ($C_{arom}$), 72.1 ($OCH_2$), 70.6 ($OCH_2$), 63.0 ($OCH_2$), 32.8

($CH_2$), 29.7 ($CH_2$), 29.4 ($CH_2$), 29.4 ($CH_2$), 26.1 ($CH_2$), 25.7 ($CH_2$) ppm. **Elemental analysis** calcd for $C_{15}H_{23}O_2Br$: C, 57.15; H, 7.35; Found: C, 57.26; H, 7.25 %.

### Reaction of (1-((Allyloxy)octyloxy)methyl)4-methoxy benzene (2.6) with $Pd(OH)_2/C$ in 2-propanol

The allyl ether **2.6** (0.33 g, 1.07 mmol) was cleaved in 2-propanol (3 mL) with $Pd(OH)_2/C$ (0.37 g) to obtain **2.19** as a colorless oil (0.25 g, 88 %). Column chromatographic purification was carried out with 50 % ethyl acetate/ light petroleum as the eluent. **IR** (neat): $\bar{\nu}$ 3113–3630 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 200 MHz): δ 7.21–7.30 (m, 2H, ArH), 6.82–6.93 (m, 2H, ArH), 4.43 (s, 2H, $OCH_2$), 3.80 (s, 3H, $OCH_3$), 3.60 (t, 2H, $J$ = 6.6 Hz, $OCH_2$), 3.43 (t, 2H, $J$ = 6.6 Hz, $OCH_2$), 1.77 (br s, 1H, OH), 1.46–1.67 (m, 4H, 2×$CH_2$), 1.25-1.40 (m, 8H, 4×$CH_2$) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 159.1 ($C_{arom}$), 130.8 ($C_{arom}$), 129.3 ($C_{arom}$), 113.8 ($C_{arom}$), 72.5 ($OCH_2$), 70.2 ($OCH_2$), 62.9 ($OCH_2$), 55.3 ($OCH_3$), 32.8 ($CH_2$), 29.7 ($CH_2$), 29.4 ($CH_2$), 29.4 ($CH_2$), 26.1 ($CH_2$), 25.7 ($CH_2$) ppm. **Elemental analysis** calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84; Found: C, 72.47; H, 10.15 %.

### Reaction of (1-((8-Allyloxy)octyloxy)methyl)-4-nitrobenzene (2.7) with $Pd(OH)_2/C$ in 2-propanol

The allyl ether **2.7** (0.10 g, 0.31 mmol) was cleaved in 2-propanol (3 mL) with $Pd(OH)_2/C$ (0.11 g) to obtain **2.20** as a pale yellow oil (0.08 g, 91 %). Column chromatographic purification was carried out with 40 % ethyl acetate/ light petroleum as the eluent. **IR** (neat): $\bar{\nu}$ 3132–3624 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 200 MHz): δ 8.12–8.27 (m, 2H, ArH), 7.50 (d, 2H, $J$ = 8.7 Hz, ArH), 4.60 (s, 2H, $OCH_2$), 3.64 (t, 2H, $J$ = 6.6 Hz, $OCH_2$), 3.52 (t, 2H, $J$ = 6.6 Hz, $OCH_2$), 1.48–1.74 (m, 5H, 2×$CH_2$, OH), 1.25–1.45 (m, 8H, 4×$CH_2$) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 147.2 ($C_{arom}$), 146.4 ($C_{arom}$), 127.6($C_{arom}$), 123.5 ($C_{arom}$), 71.5 ($OCH_2$), 71.1 ($OCH_2$), 62.9 ($OCH_2$), 32.6 ($CH_2$), 29.6 ($CH_2$), 29.31 ($CH_2$), 29.26 ($CH_2$), 26.0 ($CH_2$), 25.6 ($CH_2$) ppm. **Elemental analysis** calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98; Found: C, 64.22; H, 8.41; N, 4.64 %.

### Reaction of 8-(Allyloxy)octyl tosylate (2.8) with $Pd(OH)_2/C$ in 2-propanol

The allyl ether **2.8** (0.15 g, 0.44 mmol) was cleaved in 2-propanol (2 mL) with $Pd(OH)_2/C$ (0.15 g) to obtain **2.21** as a colorless oil[19] (0.12 g, 87 %). Column chromatographic purification was carried out with 45 % ethyl acetate/ light petroleum as the eluent.

**Reaction of 8-(Allyloxy)octyl acetate (2.9) with $Pd(OH)_2/C$ in 2-propanol**

The allyl ether **2.9** (0.20 g, 0.88 mmol) was cleaved in 2-propanol (3 mL) with $Pd(OH)_2/C$ (0.30 g) to obtain **2.22** as a colorless oil (0.15 g, 92 %). Column chromatographic purification was carried out with 35 % ethyl acetate/ light petroleum as the eluent.

**Reaction of 8-(Allyloxy)octyl benzoate (2.10) with $Pd(OH)_2/C$ in 2-propanol**

The allyl ether **2.10** (0.19 g, 0.64 mmol) was cleaved in 2-propanol (3 mL) with $Pd(OH)_2/C$ (0.22 g) to obtain **2.23** as a colorless oil (0.14 g, 91 %). Column chromatographic purification was carried out with 40 % ethyl acetate/ light petroleum as the eluent.

**Reaction of 1-Allyloxy-8-trityloxyoctane (2.11) with $Pd(OH)_2/C$ in *tert*-butanol**

The allyl ether **2.11** (0.20 g, 0.47 mmol) was cleaved in *tert*-butanol (3 mL) with $Pd(OH)_2/C$ (0.16 g) to obtain **2.24** as a colorless oil[18] (0.12 g, 66 %). Column chromatographic purification was carried out with 25 % ethyl acetate/ light petroleum as the eluent. The yield of the same cleavage reaction in 2-propanol was relatively less (58%).

**Reaction of 1-(Allyloxy)-8-(prop-2-yn-1-yloxy)octane (2.12) with $Pd(OH)_2/C$ in 2-propanol**

The allyl ether **2.12** (0.20 g, 0.89 mmol) was cleaved in 2-propanol (3 mL) with $Pd(OH)_2/C$ (0.31 g) to obtain **2.26** (0.07 g, 54 %) as a colorless solid and **2.25** (0.06 g, 36 %) as a colorless oil. Column chromatography was carried out with 40 % ethyl acetate/ light petroleum and 20 % methanol/ ethyl acetate as eluent for **2.25** and **2.26** respectively.

**Reaction of (1-(Allyloxy)(8-(tert-butyl)dimethylsiloxy)octane (2.13) with $Pd(OH)_2/C$ in 2-propanol**

The allyl ether **2.13** (0.30 g, 1.00 mmol) was cleaved in 2-propanol (3 mL) with $Pd(OH)_2/C$ (0.35 g) to obtain **2.26** as a colorless solid (0.12 g, 78 %). Column chromatographic purification was carried out with 20 % methanol/ ethyl acetate as the eluent.

**Reaction of allyloxy benzene (2.14) with $Pd(OH)_2/C$ in methanol**

The allyl ether **2.14** (0.15 g, 1.11 mmol) was cleaved in methanol (4 mL) with $Pd(OH)_2/C$ (0.78 g) to obtain phenol (**2.27**) as a colorless oil (0.07 g, 70 %). Column chromatographic purification was carried out with 15 % ethyl acetate/ light petroleum as the eluent.

**Reaction of allyl benzoate (2.15) with $Pd(OH)_2/C$ in methanol**

The allyl ester **2.15** (0.15 g, 0.92 mmol) was cleaved in methanol (3 mL) with $Pd(OH)_2/C$ (0.45 g) to obtain benzoic acid (**2.28**) as a colorless solid (0.09 g, 82 %). Column chromatographic purification was carried out with 25% ethyl acetate/ light petroleum as the eluent. **Mp.** = 118–120.4 $^oC$ Lit[19] mp. 122.4 $^oC$

**2-O-Allyl-4,6-di-O-benzyl-*myo*-inositol-1,3,5orthoformate (2.29)**

Sodium hydride (0.09 g, 2.23 mmol) was added to a solution of **2.30**[20] (0.70 g, 1.89 mmol) in dry DMF (6 mL) at 0 $^oC$ with stirring. Then allyl bromide (0.19 mL, 2.07 mmol) was added drop-wise to the reaction mixture and the stirring continued for 3 h at rt. The reaction mixture was concentrated under reduced pressure and the residue worked up with ethyl acetate followed by drying over anhy. sodium sulphate. The crude product was purified by column chromatography (eluent: 30 % ethyl acetate/ light petroleum) to afford **2.29** as a colorless oil (0.60 g, 78 %).**$^1$H NMR** ($CDCl_3$, 200 MHz): δ 7.22–7.38 (m,10H, ArH), 5.85–6.08 (m, 1H, HC=C), 5.52 (d, 1H, $J$ = 1.3 Hz, $HCO_3$), 5.15–5.36 (m, 2H, $=CH_2$), 4.68 (d, 2H, $J$ = 11.6 Hz, $OCH_2$), 4.55 (d, 2H, $J$ = 11.6 Hz, $OCH_2$), 4.42–4.49 (m, 1H, InsH), 4.28–4.40 (m, 4H, Ins H), 4.10 (dt, 2H, $J$ = 5.7, 1.39 Hz, $OCH_2$), 3.99 (q, 1H, $J$ = 1.5 Hz, Ins H) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 137.7 ($C_{arom}$), 134.6 (allylic CH=), 128.5 ($C_{arom}$), 128.0 ($C_{arom}$), 127.7 ($C_{arom}$), 117.8 (allylic $=CH_2$), 103.3 ($HCO_3$), 74.1 (Ins C), 71.8 ($OCH_2$), 70.6 ($OCH_2$), 70.6

(Ins C), 68.1 (Ins C), 67.5 (Ins C) ppm. **Elemental analysis** calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.38; Found: C, 70.27; H, 6.71 %.

**Reaction of 2-O-Allyl-4,6-di-O-benzyl-*myo*-inositol 1,3,5orthoformate (2.29) with $Pd(OH)_2/C$ in 2-propanol**

The allyl ether **2.29** (0.10 g, 0.24 mmol) was cleaved in 2-propanol (2 mL) with $Pd(OH)_2/C$ (0.08 g) to obtain **2.30** as a colorless solid with **Mp**.=119-121 $^oC$ (0.07 g, 78 %). Column chromatographic purification was carried out with 40 % ethyl acetate/ light petroleum as the eluent. Lit[20] **Mp. =** 120–122 $^oC$.

**Reaction of ((6-(Allyloxy)hexyloxy)methyl)benzene (2.4) with a mixture of $Pd(OH)_2/C$ and Pd/C**

A solution of **2.4** (0.05 g, 0.20 mmol) in 2-propanol (1 mL) was refluxed with $Pd(OH)_2/C$ (0.014 g, 0.02 mmol) and Pd/C (0.021 g, 0.02 mmol) for 30 min to obtain **2.17** (0.038 g, 92%) as an oil. The recovered catalyst could be used to cleave a second batch of **2.4**.

**Reaction of (1-((Allyloxy)octyloxy)methyl)4-methoxy benzene (2.6) with a mixture of $Pd(OH)_2/C$ and Pd/C**

A solution of **2.6** (0.05 g, 0.16 mmol) in 2-propanol (1 mL) was refluxed with $Pd(OH)_2/C$ (0.011 g) and Pd/C (0.017 g) for 30 min to obtain **2.19** (0.037 g, 87%) as an oil.

**Reaction of 8-(Allyloxy)octyl benzoate (2.10) with $Pd(OH)_2/C$ in presence of $CuCl_2$ as a re oxidant**

To a solution of **2.10** (0.09 g, 0.30 mmol) in 2-propanol:$H_2O$ mixture (2:1) as solvent (3 mL) $Pd(OH)_2/C$ (0.04 g) and $CuCl_2$ (0.05 g, 0.30 mmol) were added and reluxed it for 1 h. The reaction mixture was filtered through a short bed of Celite and the filtrate concentrated under reduced pressure. The crude product was purified and separated by column chromatography, 20% and 40 % ethyl acetate/light petroleum respectively used to obtain **2.40** (0.02 g, 27%) and **2.23** (0.05g, 67%). Data of **2.40**: **$^1$H NMR**($CDCl_3$,200 MHz): δ 7.98–8.11 (m, 2H, ArH), 7.38–7.60 (m, 3H, ArH), 4.32 (t, 2H, $OCH_2$, $J$ = 6.6 Hz), 4.02 (s, 2H, $OCH_2$), 3.48 (t, 2H, $OCH_2$, $J$ = 6.6 Hz), 2.16 (s, 3H, $COCH_3$), 1.60–1.80 (m, 4H, 2×$CH_2$), 1.30–1.47 (m, 8H, 4×$CH_2$) ppm. **$^{13}$C NMR**

($CDCl_3$, 50.3 MHz): δ 207.4 (CO), 166.7 (CO), 132.8 ($C_{arom}$), 129.5 ($C_{arom}$), 128.3 ($C_{arom}$), 76.4, 71.8, 65.0, 29.5, 29.3, 29.2, 28.6 ($CH_2$), 26.3 ($CH_3$), 25.9 ($CH_2$) ppm. **Elemental analysis** calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27; Found: C, 69.77; H, 8.32 %.

**1,8-Bis(benzyloxy)octane (2.41)**

Sodium hydride (0.44 g, 10.94 mmol) was added to a solution of octane diol (0.50 g, 3.42 mmol) in dry DMF (12 mL) at 0 $^oC$ and stirred for 15 min. Benzyl bromide (1.09 mL, 9.23 mmol) was added drop-wise to the reaction mixture in cold condition and stirring continued for 3 h at rt. The solvents were evaporated under reduced pressure and the residue worked up with ethyl acetate followed by drying over anhy. sodium sulphate. Purification of the crude product by column chromatography (eluent: 8 % ethyl acetate/ light petroleum) afforded **2.41** as a colorless oil (1.08 g, 97 %). **$^1$H NMR** ($CDCl_3$, 200 MHz): δ 7.12–7.41 (m, 10H, ArH), 4.48 (s, 4H, $PhCH_2$), 3.44 (t, 4H, $J$ = 6.5 Hz, 2×$OCH_2$), 1.50–1.70 (m, 4H, 2×$CH_2$), 1.30 (br s, 8H, 4×$CH_2$) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 138.8 ($C_{arom}$), 128.4 ($C_{arom}$), 127.7 ($C_{arom}$), 127.6 ($C_{arom}$), 72.9 ($OCH_2$), 70.6 ($OCH_2$), 29.9 ($CH_2$), 29.5 ($CH_2$), 26.2 ($CH_2$) ppm. **Elemental analysis** calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26; Found: C, 80.89; H, 9.14 %.

**(1-((8-Benzyloxy)octyloxy)methyl)-4-nitrobenzene (2.42)**

The 4-nitro derivative **2.42** was prepared by using 4-nitrobenzyl alcohol and the 8-benzyloxy octan-1-ol as a pale yellow solid (0.12 g, 44 %) by adopting a reported procedure.[17] ( **Mp**. = 41.6–43.6 $^oC$, **IR** ($CDCl_3$): $\bar{\nu}$ 2924, 1345 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 200 MHz): δ 8.15–8.27 (m, 2H, ArH), 7.44–7.57 (m, 2H, ArH), 7.22–7.41 (m, 5H, ArH), 4.59 (s, 2H, $OCH_2$), 4.50 (s, 2H, $OCH_2$), 3.41–3.56 (m, 4H, 2×$OCH_2$), 1.56–1.66 (m, 4H, 2×$CH_2$), 1.27–1.45 (m, 8H, 4×$CH_2$) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 147.3 ($C_{arom}$), 146.5 ($C_{arom}$), 138.7 ($C_{arom}$), 128.4 ($C_{arom}$), 127.7 ($C_{arom}$), 127.5 ($C_{arom}$), 123.6 ($C_{arom}$), 72.9 ($OCH_2$), 71.6 ($OCH_2$), 71.2 ($OCH_2$), 70.5 ($OCH_2$), 29.8 ($CH_2$), 29.7 ($CH_2$), 29.4 ($CH_2$), 26.2 ($CH_2$) ppm. **Elemental analysis** calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77; Found: C, 70.80; H, 8.11; N, 3.50 %.

**1,8-Bis(4-methoxybenzyloxy)octane (2.43)**

Sodium hydride (0.44 g, 10.94 mmol) was added to a solution of octane 1,8-diol (0.50 g, 3.42 mmol) in dry DMF (12 mL) at 0 $^{o}$C and stirred for 15 min. PMBCl (1.25 mL, 9.23 mmol) was added drop-wise to the reaction mixture (0-5 $^{o}$C) and stirred for 3 h at rt. The reaction mixture was concentrated under reduced pressure and the residue worked up with ethyl acetate followed by drying over anhy. sodium sulphate. Purification of the crude product by column chromatography (eluent: 12 % ethyl acetate/ light petroleum) afforded **2.43** as a colorless oil (1.12 g, 89%) which turned into solid. **Mp**. = 31.7–33.3 $^{o}$C; **$^{1}$H NMR** ($CDCl_3$, 200 MHz): δ 7.20–7.32 (m, 4H, ArH), 6.82–6.93 (m, 4H, ArH), 4.43 (s, 4H, $PhCH_2$), 3.80 (s, 6H, 2×$OCH_3$), 3.42 (t, 4H, *J* = 6.7 Hz, 2×$OCH_2$,), 1.50–1.67 (m, 4H, 2×$CH_2$), 1.29 (br s, 8H, 4×$CH_2$) ppm;**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): 159.1 ($C_{arom}$), 130.8 ($C_{arom}$), 129.3 ($C_{arom}$), 113.8 ($C_{arom}$), 72.5 ($OCH_2$), 70.2 ($OCH_2$), 55.3 ($OCH_3$), 29.8 ($CH_2$), 29.5 ($CH_2$), 26.2 ($CH_2$) ppm. **Elemental analysis** calcd for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87; Found: C, 74.20; H, 9.04 %.

**1-((8-Benzyloxy)octyloxy)methyl)-4-methoxybenzene (2.44)**

Sodium hydride (0.13 g, 3.33 mmol) was added to a solution of 8-benzyloxyoctan-1-ol (0.53 g, 2.20 mmol) in dry DMF (10 mL) at 0 $^{o}$C and stirred for 15 min. PMBCl (0.39 mL, 2.86 mmol) was added drop-wise to the reaction mixture (0-5 $^{o}$C) and the mixture stirred for 4 h at rt. The reaction mixture was concentrated under reduced pressure and the residue worked up with ethyl acetate. The crude product was purified by column chromatography (eluent: 7 % ethyl acetate/ light petroleum) to afford **2.44** as a colorless oil (0.64 g, 81 %). **$^{1}$H NMR** ($CDCl_3$, 200 MHZ): δ 7.20–7.38 (m, 7H, ArH), 6.83–6.92 (m, 2H, ArH), 4.49 (s, 2H, $OCH_2$), 4.42 (s, 2H, $OCH_2$), 3.79 (s, 3H, $OCH_3$), 3.44 (q, 4 H, *J* = 6.5 Hz, 2×$OCH_2$), 1.50–1.72 (m, 4H, 2×$CH_2$), 1.19–1.46 (m, 8H, 4×$CH_2$) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): 159.1 ($C_{arom}$), 138.7 ($C_{arom}$), 130.8 ($C_{arom}$), 129.3 ($C_{arom}$), 128.4 ($C_{arom}$), 127.7 ($C_{arom}$), 127.5 ($C_{arom}$), 113.8 ($C_{arom}$), 72.9 ($OCH_2$), 72.5 ($OCH_2$), 70.5 ($OCH_2$), 70.2 ($OCH_2$), 55.3 ($OCH_3$), 29.8 ($CH_2$), 29.5 ($CH_2$), 26.2 ($CH_2$) ppm. **Elemental analysis** calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05; Found: C, 77.17; H, 9.05 %.

**1,8-Bis(4-bromobenzyloxy)octane (2.45)**

Sodium hydride (0.66 g, 16.40 mmol) was added to a solution of octane-1,8-diol (1.00 g, 6.84 mmol) in dry DMF (20 mL) at 0 $^{o}$C and stirred for 15 min. *p*-bromobenzyl bromide (3.4 g, 13.68 mmol) was added to the reaction mixture (0-5 $^{o}$C) and stirring continued for 3 h at rt. The reaction mixture was concentrated under reduced pressure and the residue worked up with ethyl acetate followed by drying over anhy. sodium sulphate. Purification of the crude product by column chromatography (eluent: 16 % ethyl acetate/ light petroleum) afforded **2.45** as a colorless solid (3.08 g, 93%). **Mp**. = 44–46.5 $^{o}$C; **$^{1}$H NMR** ($CDCl_3$, 200 MHz): δ 7.41–7.52 (m, 4H, ArH), 7.17–7.25 (m, 4H, ArH), 4.44 (s, 4H, $PhCH_2$), 3.44 (t, 4H, *J* = 6.6 Hz, 2×$OCH_2$), 1.52–1.67 (m, 4H, 2×$CH_2$), 1.20–1.42 (m, 8H, 4×$CH_2$) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 137.8 ($C_{arom}$), 131.5 ($C_{arom}$), 129.2 ($C_{arom}$), 121.3 ($C_{arom}$), 72.1 ($OCH_2$), 70.6 ($OCH_2$), 29.7 ($CH_2$), 29.4 ($CH_2$), 26.1 ($CH_2$) ppm. **Elemental analysis** calcd for $C_{22}H_{28}Br_2O_2$: C, 54.56; H, 5.83; Found: C, 54.59; H, 5.77 %.

**Reaction of 1,8-Bis(benzyloxy)octane (2.41) with $Pd(OH)_2$/C in methanol**

A mixture of **2.41** (0.20 g, 0.61 mmol) and $Pd(OH)_2$/C (0.43 g) was refluxed in methanol (3 mL) for 5 h. The reaction mixture was filtered through a short bed of Celite and the Celite washed with several portions of ethyl acetate followed by methanol. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (eluent: 20 % methanol/ ethyl acetate) to afford **2.26** as a colorless solid (0.19 g, 96 %).

**Reaction of (1-((8-Benzyloxy)octyloxy)methyl)-4-nitrobenzene (2.42) with $Pd(OH)_2$/C in 2-propanol**

A mixture of **2.42** (0.09 g, 0.23 mmol) and $Pd(OH)_2$/C (0.08 g) was refluxed in 2-propanol (3 mL) for 3 h. The reaction mixture was filtered through a short bed of Celite and the Celite washed with several portions of ethyl acetate followed by methanol. The reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: 40 % ethyl acetate/ light petroleum) to afford **2.20** (0.05 g, 77 %) as a pale yellow oil and the starting material **2.42** (0.02 g, 20 %).

**Reaction of 1,8-Bis(4-methoxybenzyloxy)octane (2.43) with $Pd(OH)_2/C$ in methanol**

A mixture of **2.43** (0.20 g, 0.53 mmol) and $Pd(OH)_2/C$ (0.37 g) was refluxed in methanol (3 mL) for 5 h. The reaction mixture was filtered through a short bed of Celite and the Celite washed with several portions of ethyl acetate followed by methanol. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (eluent : 50 % ethyl acetate/ light petroleum) to obtain **2.19**(0.03 g, 24 %) as a colorless oil, **2.26** (0.35 g, 46 %) as a colorless solid and the starting material **2.43** (0.03 g, 15 %).

**Reaction of 1-((8-Benzyloxy)octyloxy)methyl)-4-methoxybenzene (2.44) with $Pd(OH)_2/C$ in 2-propanol**

A mixture of **2.44** (0.23 g, 0.64 mmol) and $Pd(OH)_2/C$ (0.22 g) was refluxed in 2-propanol (3 mL) for 3 h. The reaction mixture was filtered through a short bed of Celite and the Celite was washed with several portions of ethyl acetate followed by methanol. The filtrate was evaporated under reduced pressure and the residue was subjected to column chromatography (gradient elution, 30 % ethyl acetate/ light petroleum to 20 % methanol/ ethyl acetate) to afford **2.19** (0.08 g, 49 %) as a colorless oil and **2.26** (0.043 g, 47 %) as a colorless solid.

**Reaction of 2,4,6-tri-*O*-benzyl-*myo*-inositol orthoformate (2.1) with $Pd(OH)_2/C$ in methanol**

The tribenzyl ether **2.1** (0.23 g, 0.50 mmol) was refluxed with $Pd(OH)_2/C$ (0.53 g) in methanol (10 mL) and filtered. The filtrate was concentrated under reduced pressure and the crude product was acylated[21] to obtain the hexaacetyl derivative of **1.95** as a colorless solid (0.09 g, 89% for two steps) after column chromatography (silica gel, 230-400 mesh, eluent: 35 % ethyl acetate/ light petroleum). **Mp.** = 209– 212 $^oC$ (Lit[21] Mp. = 211– 212 $^oC$)

**Recycling of the catalyst- general procedure**

A mixture of the benzyl ether and 20% $Pd(OH)_2/C$ was refluxed in MeOH (2 mL) for the time indicated in the table 2.5. Then the palladium reagent was separated by decantation and washed with methanol (3×3 mL). The recovered reagent was used for

the cleavage of another sample of the benzyl ether. After four cycles the combined methanol solution was evaporated under reduced pressure to obtain the product. The maximum number of times the palladium reagent could be recycled was eight.

**Synthesis of 1,3,5-tri-O-methyl-2,4,6-tri-O-benzyl-*myo*-inositol (2.50)**

To a solution of 2,4,6-tri-O-benzyl *myo*-inositol (0.51 g, 1.13 mmol) in DMF (5 mL) sodium hydride (0.23 g, 5.66 mmol) was added at 0 $^{o}$C and stirred for 10 min. Methyl iodide (0.45 mL, 4.53 mmol) was added drop wise to the above mixture and stirred for further 4 h. The solvents were evaporated under reduced pressure and the crude reaction mixture was worked up with ethyl acetate and the organic layer was dried using anhy. sodium sulphate. The organic layer was concentrated under reduced pressure and the residue purified by column chromatography (100-200 mesh, 25% ethyl acetate/light petroleum) to obtain 1,3,5-tri-O-methyl-2,4,6-tri-O-benzyl- *myo*-inositol (0.52 g, 92%) as a colorless solid (mp. = 93.6-96.5 $^{o}$C). **$^{1}$H NMR** ($CDCl_3$, 200 MHz): δ 7.20–7.48 (m, 15H, ArH), 4.74–4.90 (m, 6H, 3×$CH_2$), 4.10 (t, 1H, InsH, *J*= 2.3 Hz), 3.87 (t, 2H, InsH, *J* = 9.5 Hz), 3.65 (s, 3H, $OCH_3$), 3.45 (s, 6H, 2×$CH_3$), 3.00–3.21 (m, 3H, InsH) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 139.1 ($C_{arom}$), 139.0 ($C_{arom}$), 128.3 ($C_{arom}$), 128.1 ($C_{arom}$), 127.6 ($C_{arom}$), 127.5 ($C_{arom}$), 127.3 ($C_{arom}$), 85.4 (InsC), 82.9 (InsC), 81.7 (InsC), 75.6 ($OCH_2$), 74.0 ($OCH_2$), 72.8 (InsC), 61.4 ($OCH_3$), 58.5 ($OCH_3$) ppm; **HRMS** calcd for $[C_{30}H_{36}O_6+Na]^+$ is 515.2404; Found: 515.2407.

**Debenzylation of 1,3,5-tri-O-methyl-2,4,6-tri-O-benzyl-*myo*-inositol (2.50)**

A solution of **2.50** (0.05 g, 0.10 mmol) was refluxed with $Pd(OH)_2/C$ (20 wt%, 0.084 g) in methanol (2 mL) for 24 h. The reaction mixture was decanted once the TLC analysis indicated the complete consumption of the starting material. The spent catalyst was washed 3 times with 3 mL portions of methanol and this catalyst used for the next batch of the substrate (0.05 g). The same procedure was repeated for the further cycles. The reaction time increased after each cycle. After 4 cycles the catalyst was filtered through a short bed of Celite and the Celite bed was washed with methanol (5 mL) and the combined filtrate and washings were evaporated under reduced pressure to obtain the debenzylated product **2.51** (0.086 g, 96%) as a colorless solid (mp. = 136.3–138.3 $^{o}$C).

**Procedure to determine the time course of the debenzylation reaction**

**Trial 1.** 1-Benzyloxy octane (0.05 g, 0.22 mmol) was refluxed with $Pd(OH)_2/C$ (20 wt%, 0.08 g) in methanol (3 mL) for 2.5 h. Samples of the reaction mixture (0.5 mL) were withdrawn at the end of 30 min, 1 h, 1.5 h, 2 h and 2.5 h. The refluxing was stopped (2-3 min) and the solids were allowed to settle before withdrawing each sample. Each sample was evaporated under reduced pressure and the residue was analyzed by $^1H$ NMR spectroscopy in $CDCl_3$ solution. The relative ratio of 1-octanol and 1-benzyloxy octane was estimated by integrals of the peaks at $\delta$ 3.64 (triplet) and $\delta$ 4.50 (singlet) respectively (squares in Figure 2.3). The palladium reagent was recovered by decantation and washed with methanol (3×3 mL). The washings were rejected.

**Trial 2.** The palladium reagent (recovered as above) was used in this experiment to cleave 1-benzyloxy octane as above. The samples were withdrawn at 1 h, 2 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 6 h, 7 h and the relative ratio of 1-octanol and 1-benzyloxy octane was estimated as above (circles in Figure 2.3).

**Trial 3.** The palladium reagent (recovered in trial 2) was used in this experiment to cleave 1-benzyloxy octane as above. The samples were withdrawn at 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 10 h and the relative ratio of 1-octanol and 1-benzyloxy octane was estimated as above (triangles in Figure 2.3). A plot of the results is shown in Figure 2.3.

**Reaction of N-allyl-N, N-dicyclohexyl amine (2.52) with $Pd(OH)_2/C$ in methanol**

The N-allyl amine **2.52** (0.10 g, 0.45 mmol) was cleaved in methanol (2 mL) with $Pd(OH)_2/C$ (0.16 g) to obtain **2.54** as a pale yellow oil (0.06 g, 69 %). Column chromatographic purification was carried out with a mixture of DCM:Methanol:$NH_4OH$ (98:2:0.30 v/v) as the eluent.

**Reaction of N-benzyl-N, N-dicyclohexyl amine (2.53) with $Pd(OH)_2/C$ in methanol**

The N-benzyl amine **2.53** (0.20 g, 0.74 mmol) was cleaved in methanol (3 mL) with $Pd(OH)_2/C$ (0.52 g) to obtain **2.54** as a pale yellow oil (0.08 g, 62 %). Column chromatographic purification was carried out with a mixture of

DCM:Methanol:$NH_4OH$ (98:2:0.30 v/v) as the eluent.

**Pent-4-en-2-yl benzoate (2.55)**

Benzoyl chloride (1.62 mL, 13.94 mmol) was added drop-wise to a solution of pent-4-en-2-ol (1.19 mL, 11.62 mmol) in dry pyridine (25 mL) at 0 $^oC$ and stirred overnight at rt. The reaction mixture was concentrated under reduced pressure and worked up with ethyl acetate followed by drying over anhy sodium sulphate. Purification of the crude product by column chromatography (eluent: 8 % ethyl acetate/ light petroleum) afforded **2.55** as a colorless oil.[22]

**8-(allyloxy)octyl octadec-9-enoate. (2.56)**

To a solution of **2.25** (0.27 g, 1.45 mmol) in dry DCM (6 mL) triethyl amine (0.40 mL, 2.90 mmol) and oleoyl chloride (0.58 mL, 1.74 mmol) were added at 0 $^oC$ followed by catalytic amount of DMAP. The reaction mixture was strirred at rt for 2 h. The solvents were evaporated under reduced pressure. The residue obtained was purified by column chromatography (100–200 mesh, 4 % ethyl acetate/light petroleum) to afford **2.56** (0.57 g, 87%) as a pale yellow liquid. $R_f$ = 0.34 (5% ethyl acetate/light petroleum)

**IR** (neat): $\bar{\nu}$ 1738 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 200 MHz): δ 5.80–6.04 (m, 1H, HC=), 5.13–5.38 (m, 4H, $=CH_2$, HC=CH), 4.05 (t, 2H, $OCH_2$, $J$ = 6.7 Hz), 3.96 (dt, 2H, $=CH_2$, $J$ = 5.7, 1.4 Hz), 3.42 (t, 2H, $OCH_2$, $J$ = 6.6 Hz), 2.29 (t, 2H, $COCH_2$, $J$ = 7.7 Hz), 1.95–2.07 (m, 4H, $CH_2$), 1.51–1.71 (m, 6H, 3× $CH_2$), 1.25–1.35 (m, 28 H, 14 × $CH_2$), 0.88 (t, 3H, $J$ = 6.8 Hz, $CH_3$) ppm. **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 174.0 (CO), 135.0 (HC=), 129.9 (CH), 129.7 (CH), 116.7 ($=CH_2$), 71.8 ($OCH_2$), 70.4 ($OCH_2$), 64.3 ($OCH_2$), 34.3 ($CH_2$), 31.9 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 29.14 ($CH_2$), 29.09 ($CH_2$), 28.6 ($CH_2$), 27.2 ($CH_2$), 27.1 ($CH_2$), 26.1 ($CH_2$), 25.8 ($CH_2$), 25.0 ($CH_2$), 22.6 ($CH_2$), 14.1 ($CH_3$) ppm. **Elemental analysis** calcd for $C_{29}H_{54}O_3$: C,77.28; H, 12.08; Found: C, 77.35; H, 12.39 %.

**Reaction of 8-(allyloxy)octyl octadec-9-enoate (2.56) with $Pd(OH)_2/C$**

A mixture of **2.56** (0.20 g, 0.44 mmol) and $Pd(OH)_2/C$ (0.06 g) and Pd/C (0.05 g) in 2- propanol:THF (4:1, 2 mL) was refluxed for 10 h. then the solid was filtered off through a short bed of Celite . The Celite was washed with ethyl acetate. The

combined filtrate and washings was evaporated under reduced pressure to get **2.57** (0.15 g, 84 %) as colorless oil. $R_f$ = 0.20 (10% ethyl acetate/light petroleum)

**IR** (neat): $\bar{\nu}$ 1736 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 200MHz): δ 5.24–5.44 (m, 2H, 2 × CH), 4.06 (t, 2H, $OCH_2$, *J* = 6.7 Hz), 3.64 (t, 2H, $OCH_2$, *J* = 6.6 Hz), 2.29 (t, 2H, -$OCOCH_2$, *J* = 7.7 Hz), 1.87–2.15 (m, 4H, $CH_2$), 1.45–1.67 (m, 7H, 3 × $CH_2$, OH), 1.22–1.39 (m, 28H, 14 × $CH_2$), 0.88 (t, 3H, $CH_3$, 6.7 Hz) ppm. **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 174.0 (CO), 130.0 (CH), 129.7 (CH), 64.3 ($OCH_2$), 63.0 ($OCH_2$), 34.4 ($CH_2$), 32.7 ($CH_2$), 31.9 ($CH_2$), 29.8 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 29.2 ($CH_2$), 29.1 ($CH_2$), 28.6 ($CH_2$), 27.20 ($CH_2$), 27.15 ($CH_2$), 25.8 ($CH_2$), 25.6 ($CH_2$), 25.0 ($CH_2$), 22.7 ($CH_2$), 14.1 ($CH_3$) ppm. **Elemental analysis** calcd for $C_{26}H_{50}O_3$: C, 76.04; H, 12.27; Found: 75.79; H, 12.57 %.

**Reaction of methyl cinnamyl ether (2.58) with $Pd(OH)_2$/C in 2-propanol**

The cinnamyl ether **2.58** (0.30 g, 2.02 mmol) was cleaved in 2-propanol (3 mL) with $Pd(OH)_2$/C (0.70 g) to obtain **2.59** as a colorless oil (0.11 g, 40 %). Column chromatographic purification was carried out with 10 % ethyl acetate/ light petroleum as the eluent.

**Racemic 1,2-di-O-benzyl-3,4,5,6-tetra-O-methyl-*myo*-inositol (2.63)**

Sodium hydride (1.25 g, 31.05 mmol) was added to a solution of the diol **2.64** (1.65 g, 6.90 mmol) in dry DMF (20 mL) at 0 $^oC$ and stirred for 15 min. Benzyl bromide (3.3 mL, 27.6 mmol) was added drop-wise to the reaction mixture and stirred for 4 h. After quenching the excess sodium hydride by the addition of ice, the solvents were evaporated under reduced pressure. The residue obtained was worked up with ethyl acetate. The crude product was purified by column chromatography (eluent: 25 % ethyl acetate/ light petroleum) to afford **2.63** as a colorless gum (2.50 g, 87 %). **$^1$H NMR** ($CDCl_3$, 200 MHz): δ 7.22-7.43 (m, 10 H, ArH), 4.83 (q, 2H, *J* = 12.1 Hz, $OCH_2$), 4.64 (q, 2H, *J* = 11.9 Hz, $OCH_2$), 4.01 (t, 1H, *J* = 2.3 Hz, Ins H), 3.50- 3.70 (m, 11H, 3× $OCH_3$, 2 Ins H), 3.37 (s, 3H, $OCH_3$), 3.20 (dd, 1H, *J* = 9.9, 2.4 Hz, Ins H), 2.88-3.04 (m, 2H, Ins H) ppm. **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 138.9 ($C_{arom}$), 138.6 ($C_{arom}$), 128.3 ($C_{arom}$), 128.0 ($C_{arom}$), 127.6 ($C_{arom}$), 127.5 ($C_{arom}$), 127.3 ($C_{arom}$), 127.2 ($C_{arom}$), 85.6 (Ins C), 83.4 (Ins C), 83.0 (Ins C), 82.5 (Ins C), 80.7 (Ins C), 73.8

($OCH_2$), 73.5 (Ins C), 72.8 ($OCH_2$), 61.2 ($OCH_3$), 60.9 ($OCH_3$), 58.3 ($OCH_3$) ppm. **Elemental analysis** calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74; Found: C, 68.86; H, 7.94 %.

**Reaction of Racemic 1,2-di-O-benzyl-3,4,5,6-tetra-O-methyl-*myo*-inositol (2.63) with $Pd(OH)_2/C$ in 2-propanol**

A mixture of **2.63** (1.0 g, 2.40 mmol) and $Pd(OH)_2/C$ (20 wt %, 2.20 g) was refluxed in 2-propanol for 60 h. The reaction mixture was filtered through a short bed of Celite and the Celite washed with methanol followed by ethyl acetate. The combined washings were evaporated under reduced pressure and the residue was purified by column chromatography (eluent: 50 % ethyl acetate in light petroleum) to afford **2.65** as a colorless oil (0.18 g, 23 %) and **2.64**[23] (eluent:15 % methanol/ethyl acetate) as a colorless solid (0.41 g, 74 %). **Mp.** = 97–99.3 $^oC$ (lit.[23] Mp. 105–106 $^oC$). Data for **2.65: IR** ($CHCl_3$): $\bar{\nu}$ 3120–3660, 1724 $cm^{-1}$. **$^1$H NMR** ($CDCl_3$, 200 MHz): δ 8.03–8.09 (m, 2H, ArH), 7.55–7.61 (m, 1H, ArH), 7.43–7.51 (m, 2H, ArH), 5.89 (t, 1H, $J$ = 2.8 Hz, InsH), 3.69 (s, 3H, $OCH_3$), 3.67 (s, 3H, $OCH_3$), 3.61-3.65 (m, 4H, $OCH_3$, InsH), 3.49–3.60 (m, 3H, Ins H), 3.45 (s, 3H, $OCH_3$), 3.09–3.26 (m, 2H, Ins H, OH) ppm.**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 166.0, 133.1, 130.0, 129.9, 128.4, 85.3, 83.7, 83.3, 80.5, 70.2, 69.5, 61.2, 61.1, 61.0, 58.0 ppm. **Elemental analysis** calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11; Found: C, 60.30; H, 7.54 %.

**Reaction of bezyl alcohol (1.13) with $Pd(OH)_2/C$ in methanol**

A mixture of **1.13** (0.10 g, 0.93 mmol) and $Pd(OH)_2/C$ (0.06 g) was refluxed in methanol (3 mL) for 30 min. The reaction mixture was filtered through a short bed of Celite and the crude product submitted for nmr analysis using dibromomethane as the internal standard which indicated 47% of benzaldehyde is present in the mixture. The products were separated by column chromatography to obtain benzaldehyde **1.14** (0.035 g, 36 %) and benzaldehyde dimethyl acetal **2.73** (0.034 g, 27 %). See page 96 for $^1$H NMR spectra.

**Reaction of bezyl alcohol (1.13) with $Pd(OH)_2/C$ in toluene.**

A mixture of **1.13** (0.10 g, 0.92 mmol) and $Pd(OH)_2/C$ (0.06 g) was refluxed in toluene (3 mL) for 3 h. The reaction mixture was filtered through a short bed of Celite

and the nmr analysis of the crude product using dibromomethane as internal standard shows 70 % yield of benzaldehyde

**Reaction of bezyl alcohol (1.13) with $Pd(OAc)_2$ in toluene.**

Reaction was conducted as above to obtain benzaldehyde (yield 50%, estimated by $^1H$ NMR spectroscopy).

**Reaction of bezyl alcohol (1.13) with $PdCl_2$ in toluene.**

Reaction was conducted as above to obtain benzaldehyde. However the reaction didn't progress after 3 h.

## 2.5 References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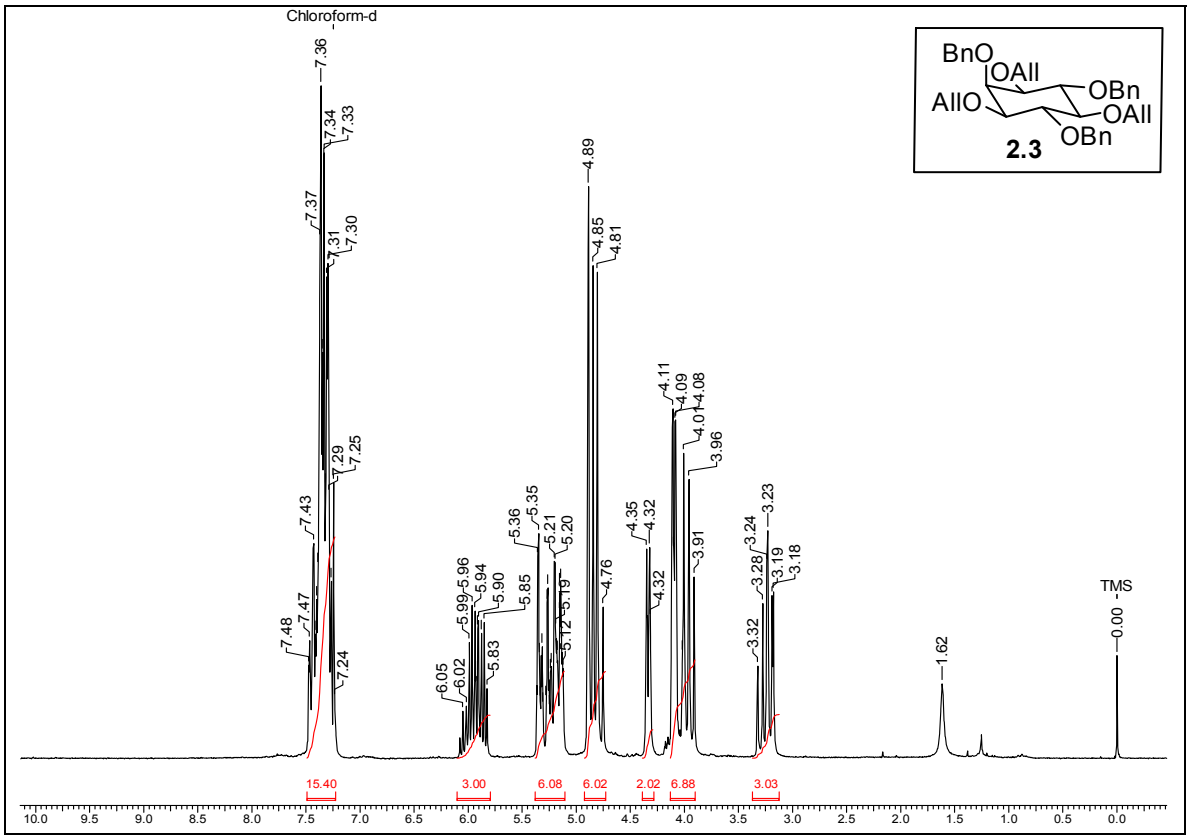
## 2.6. Appendix I

### Appendix 1 Index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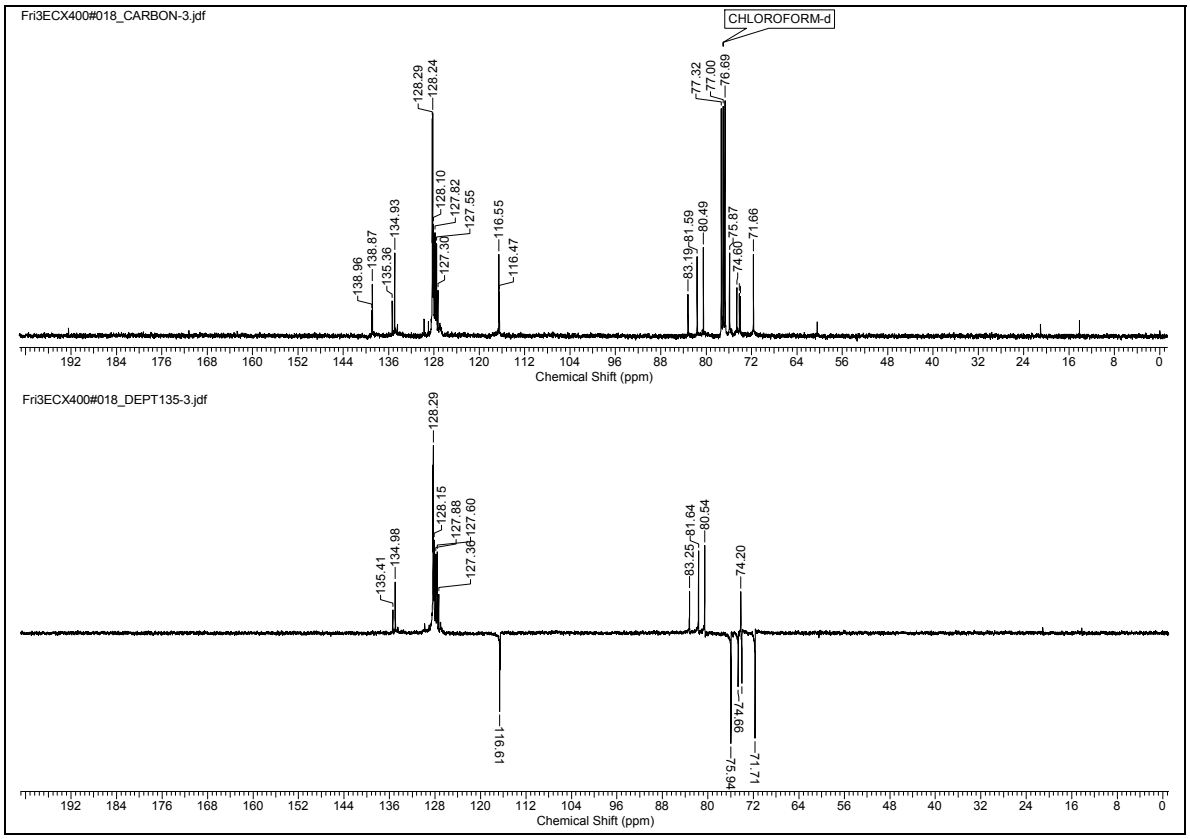
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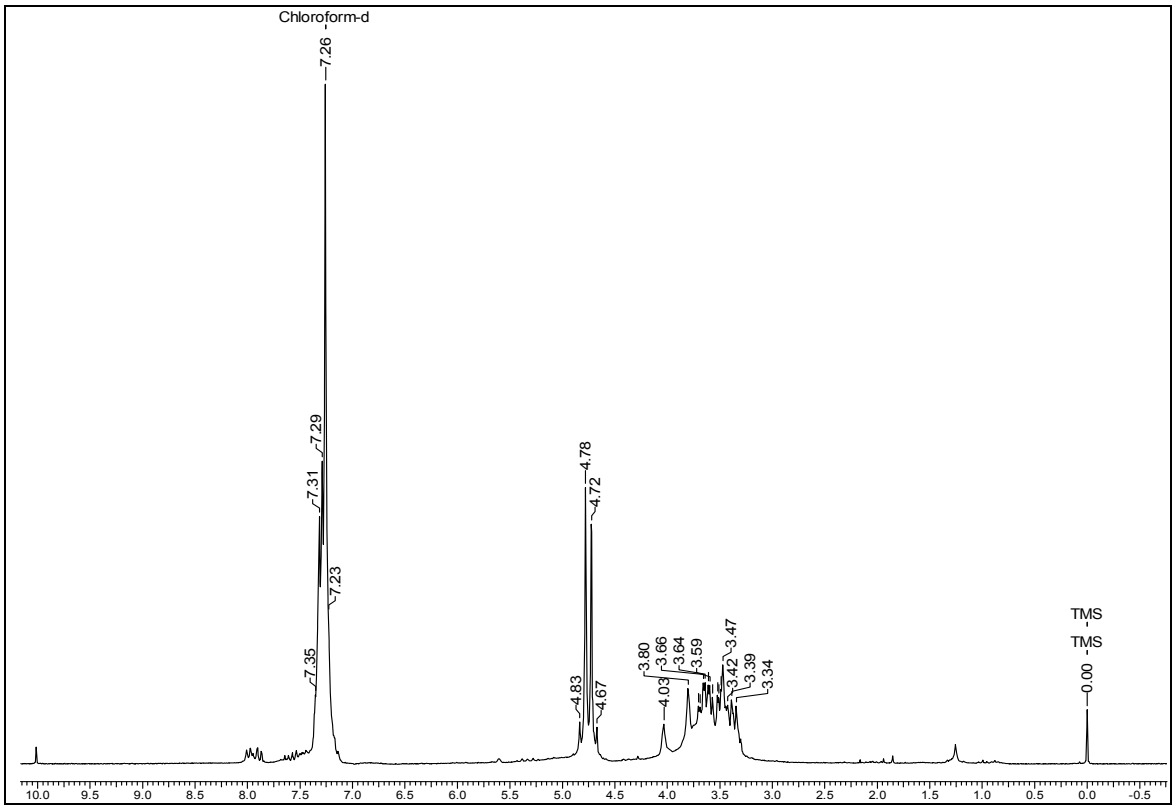
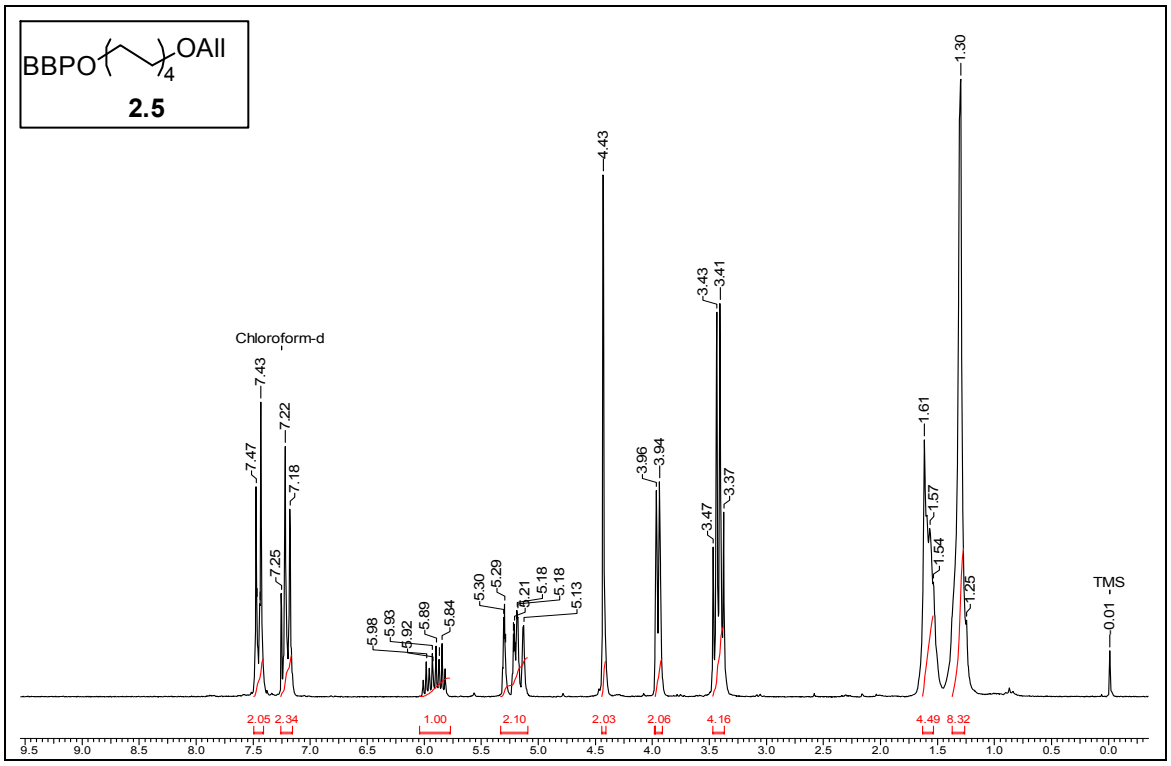
**NMR Spectrum of the crude product obtained in the reaction of 2.3 with $Pd(OH)_2/C$**

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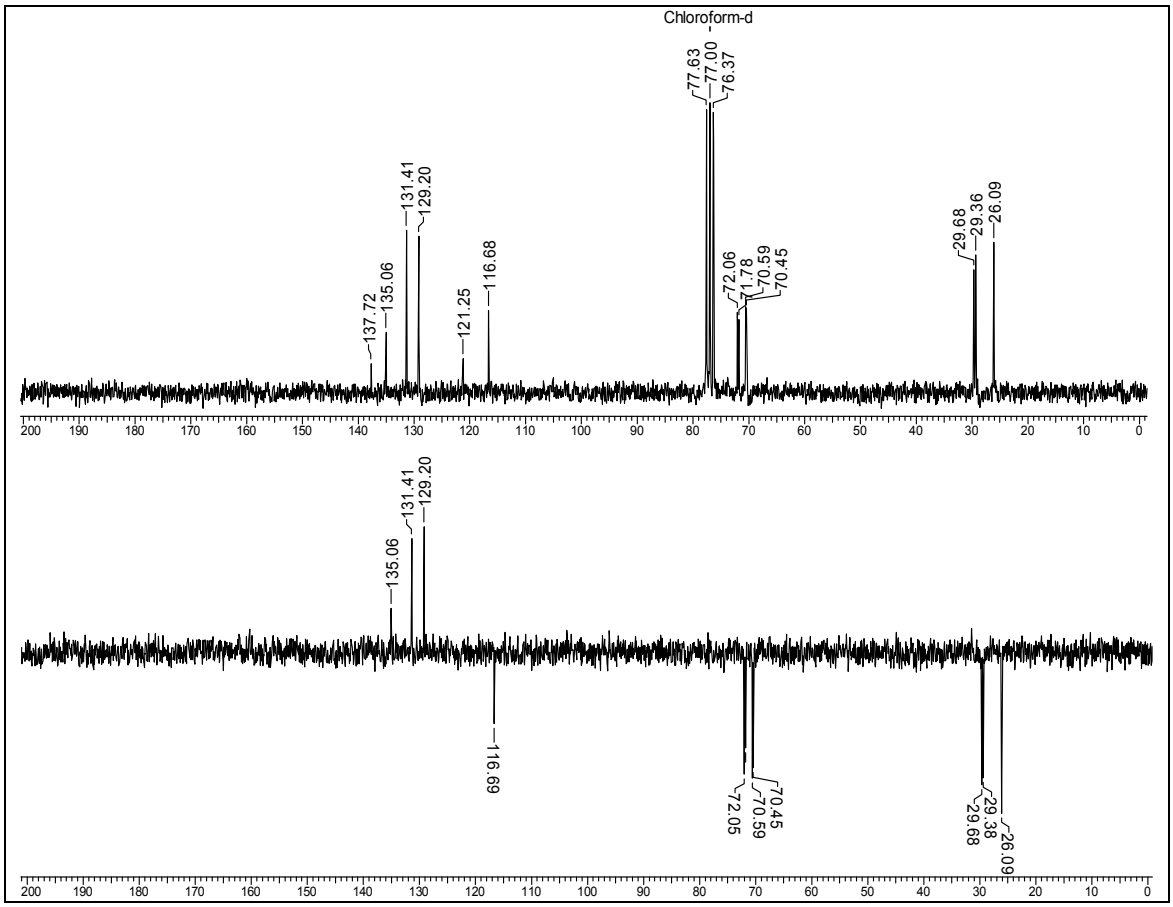
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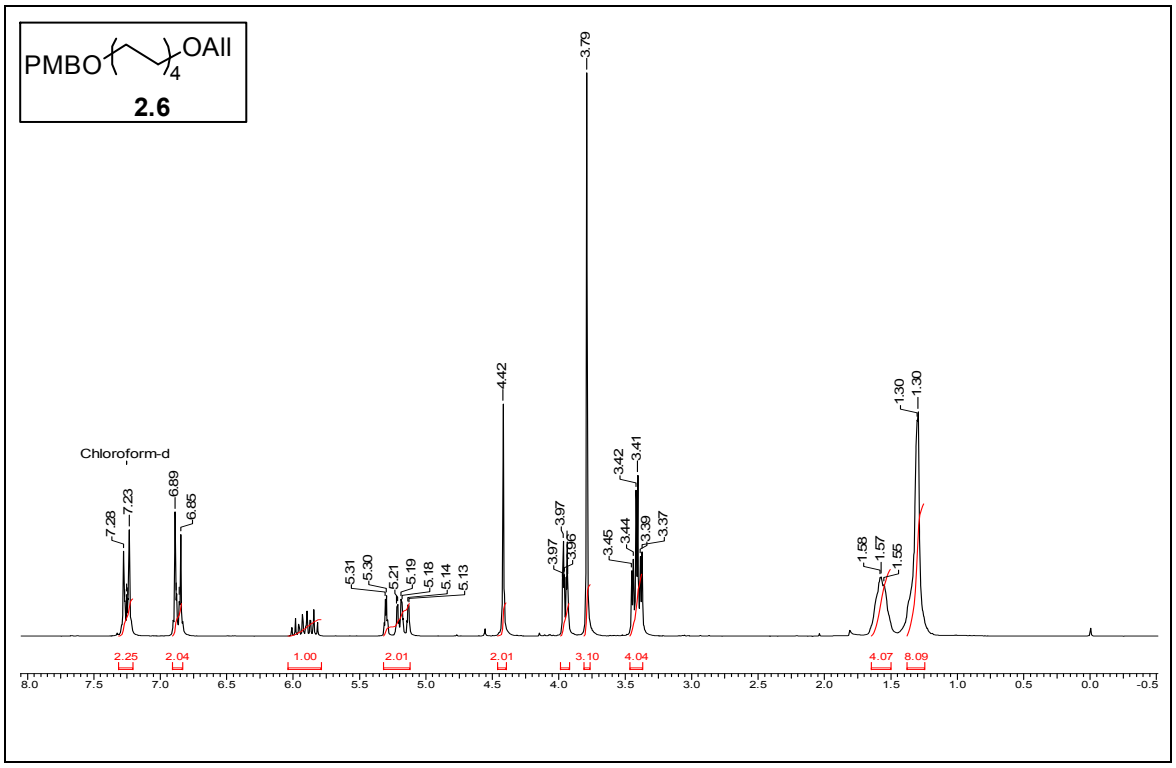
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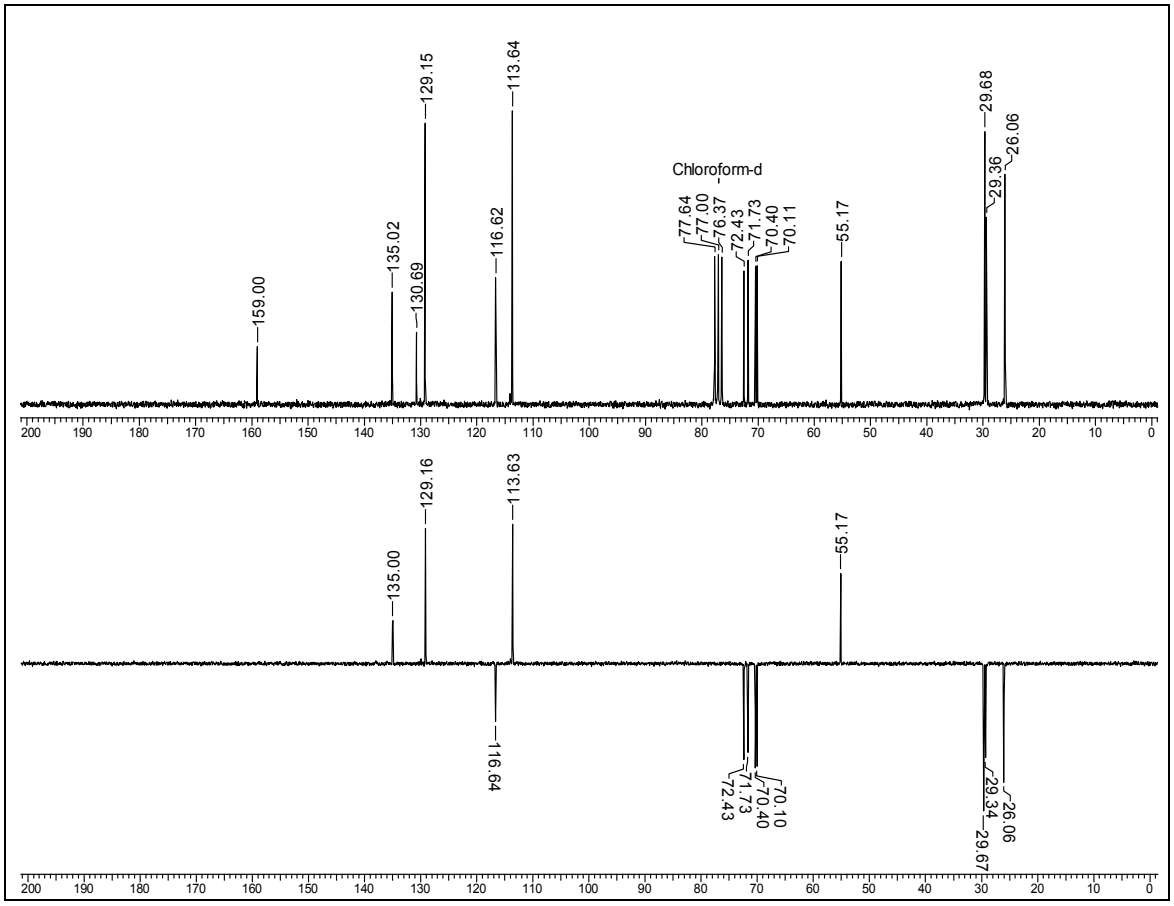
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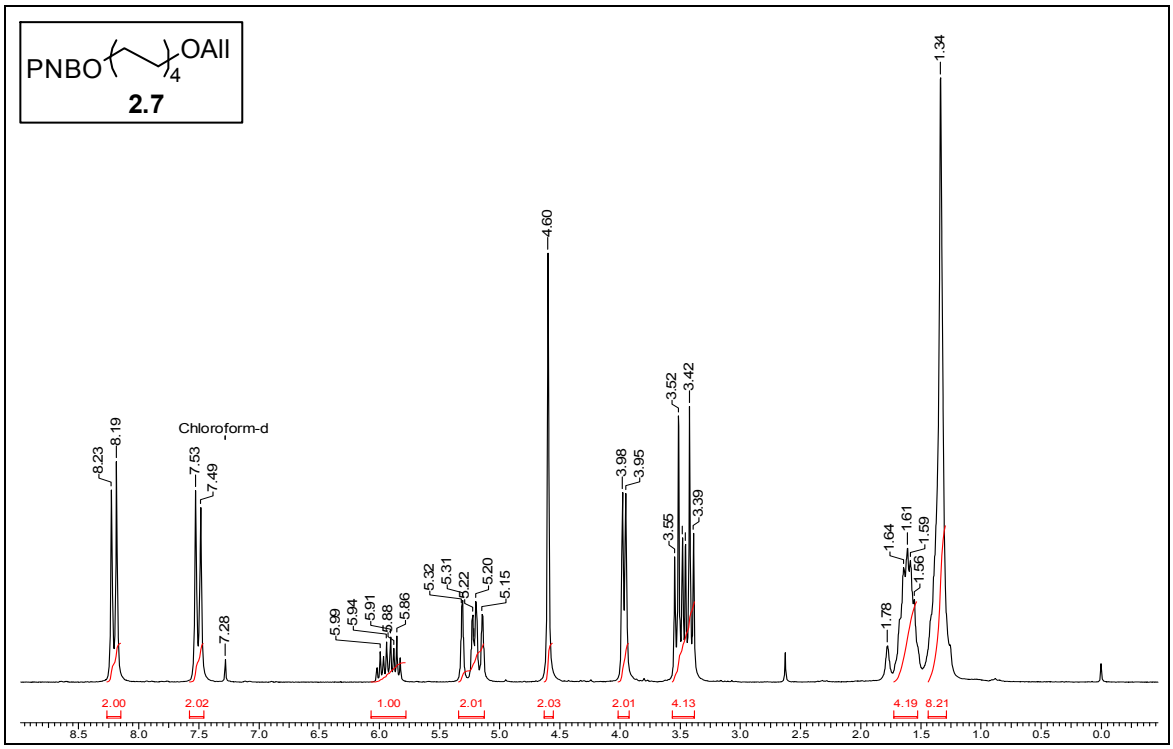
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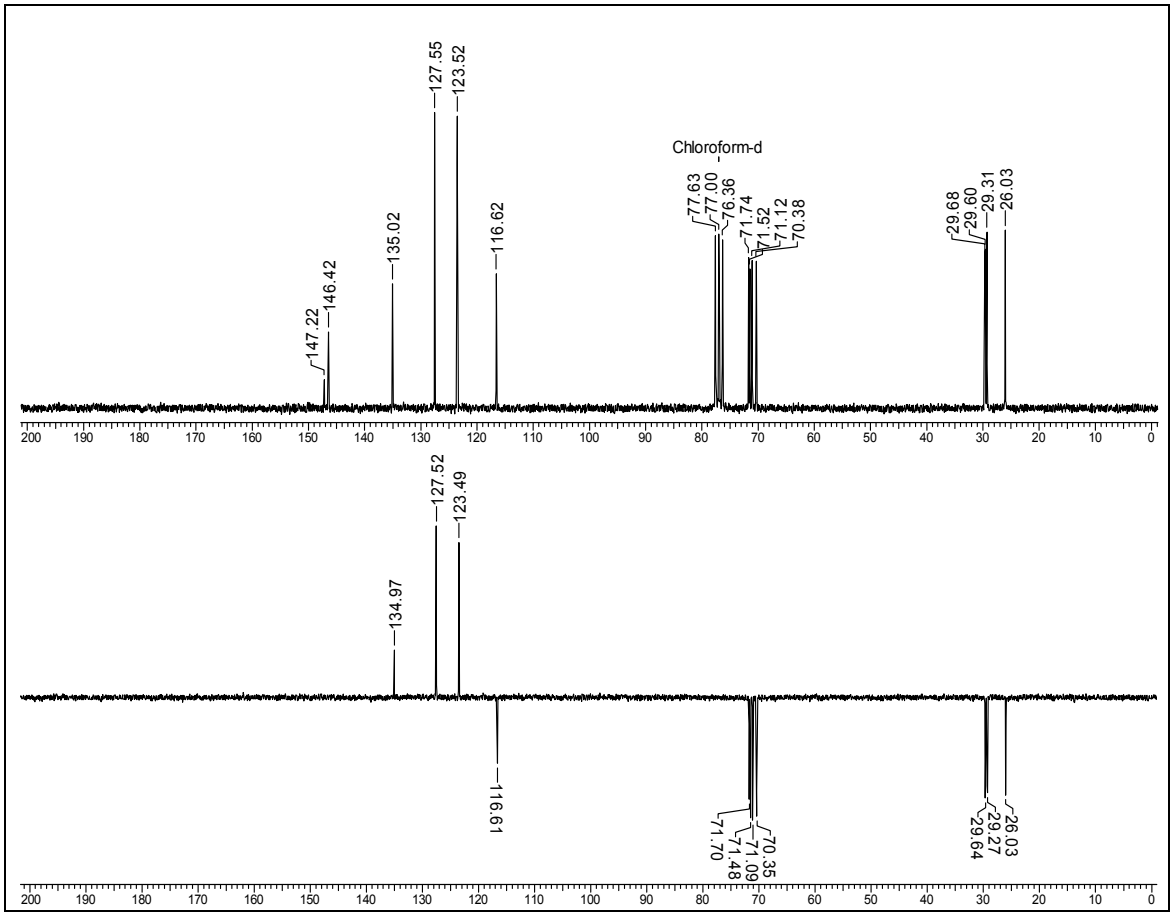
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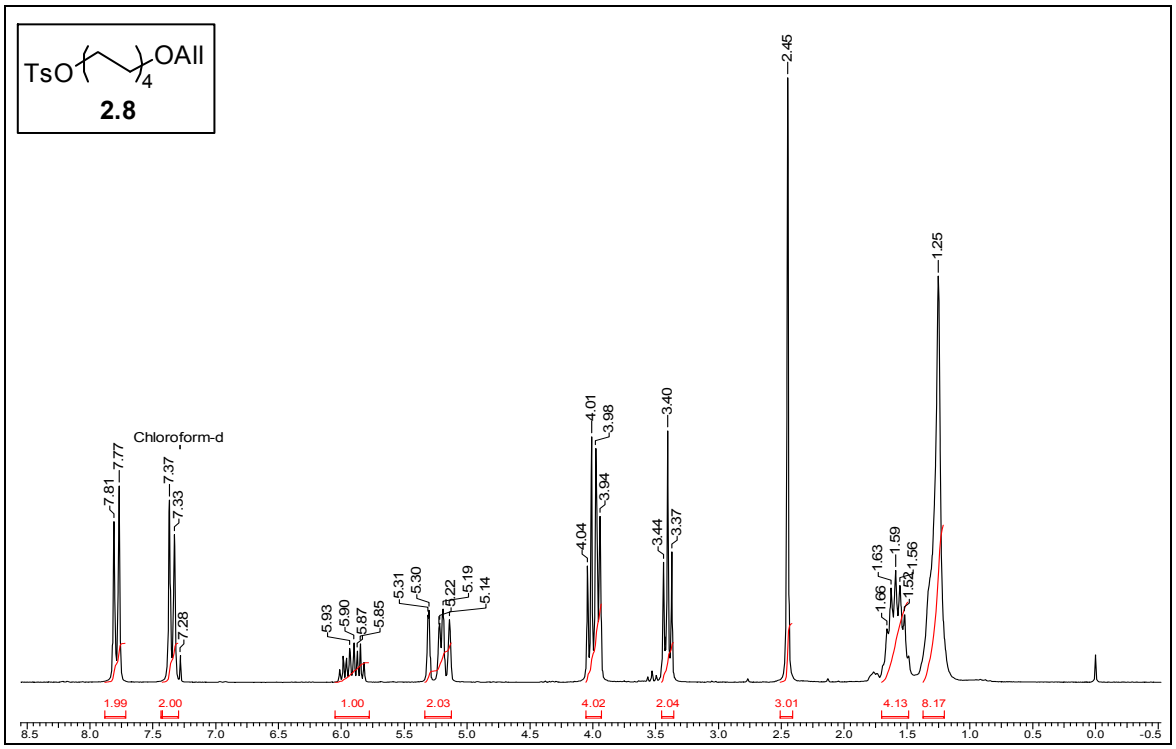
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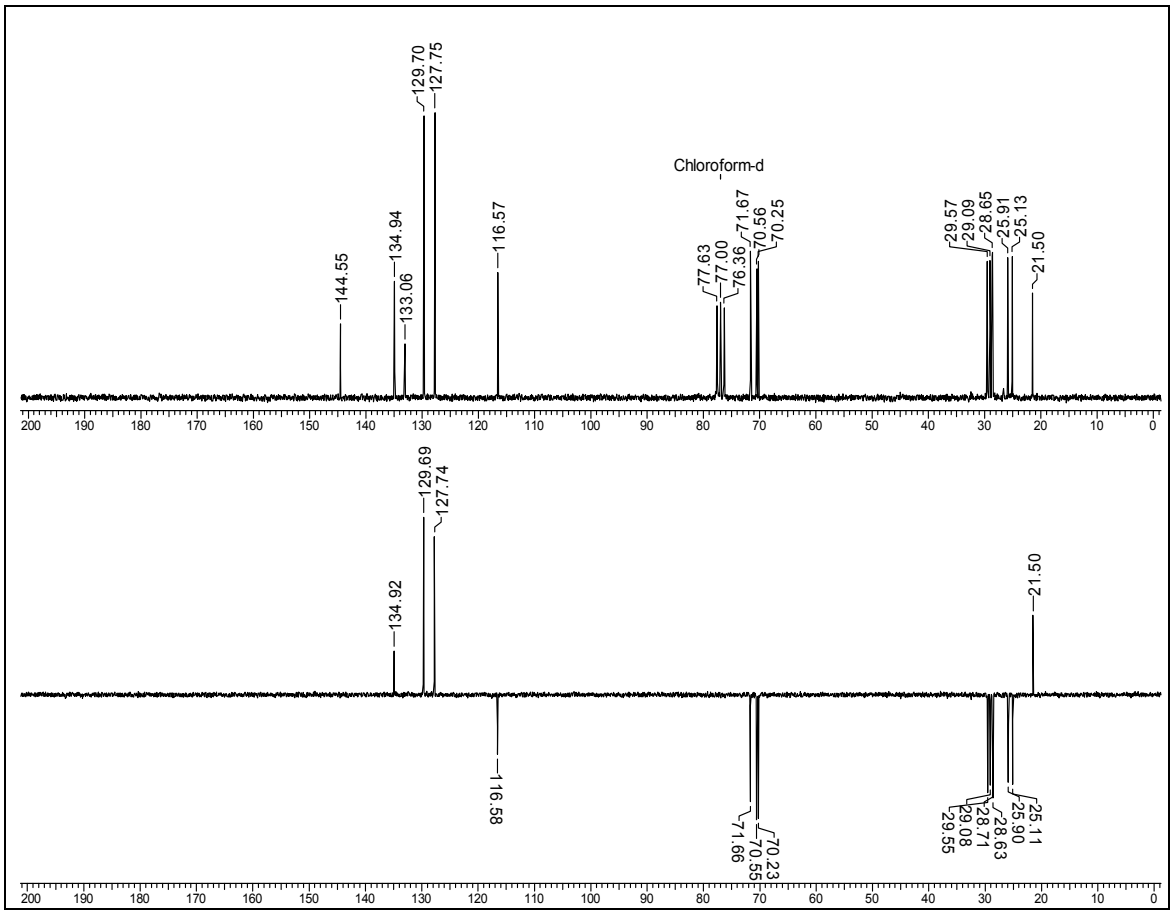
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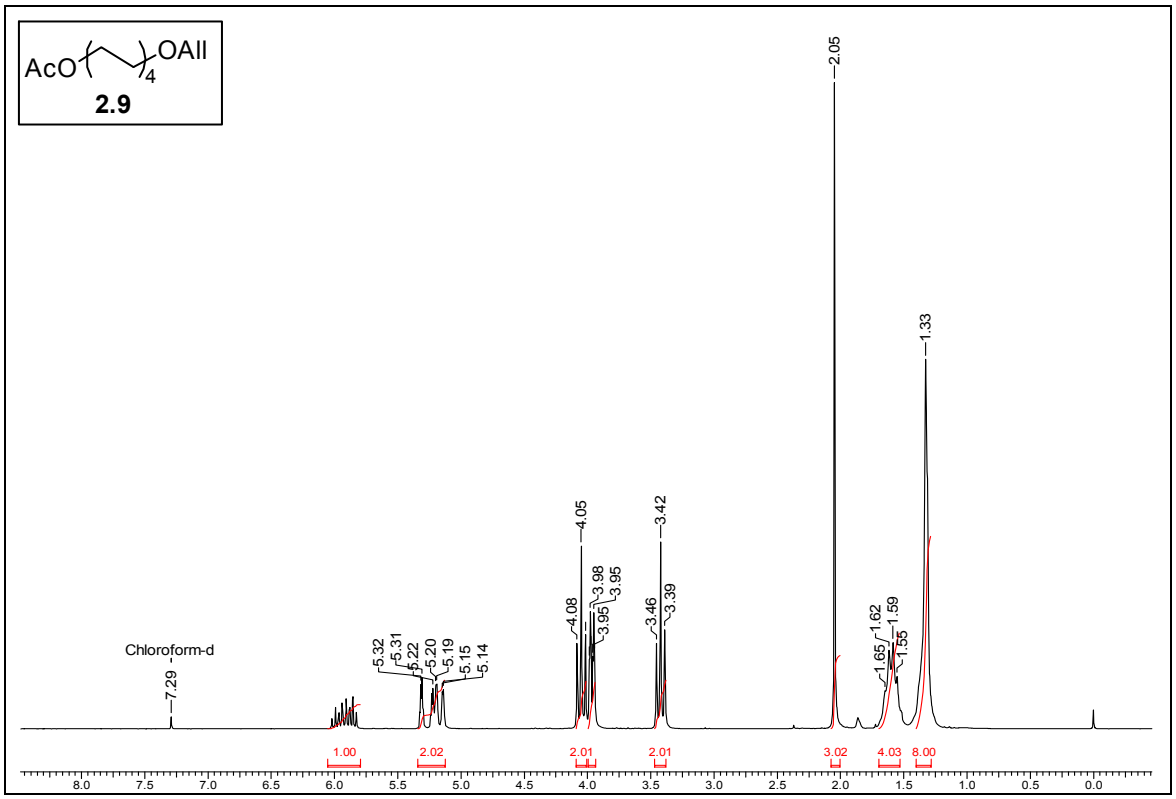
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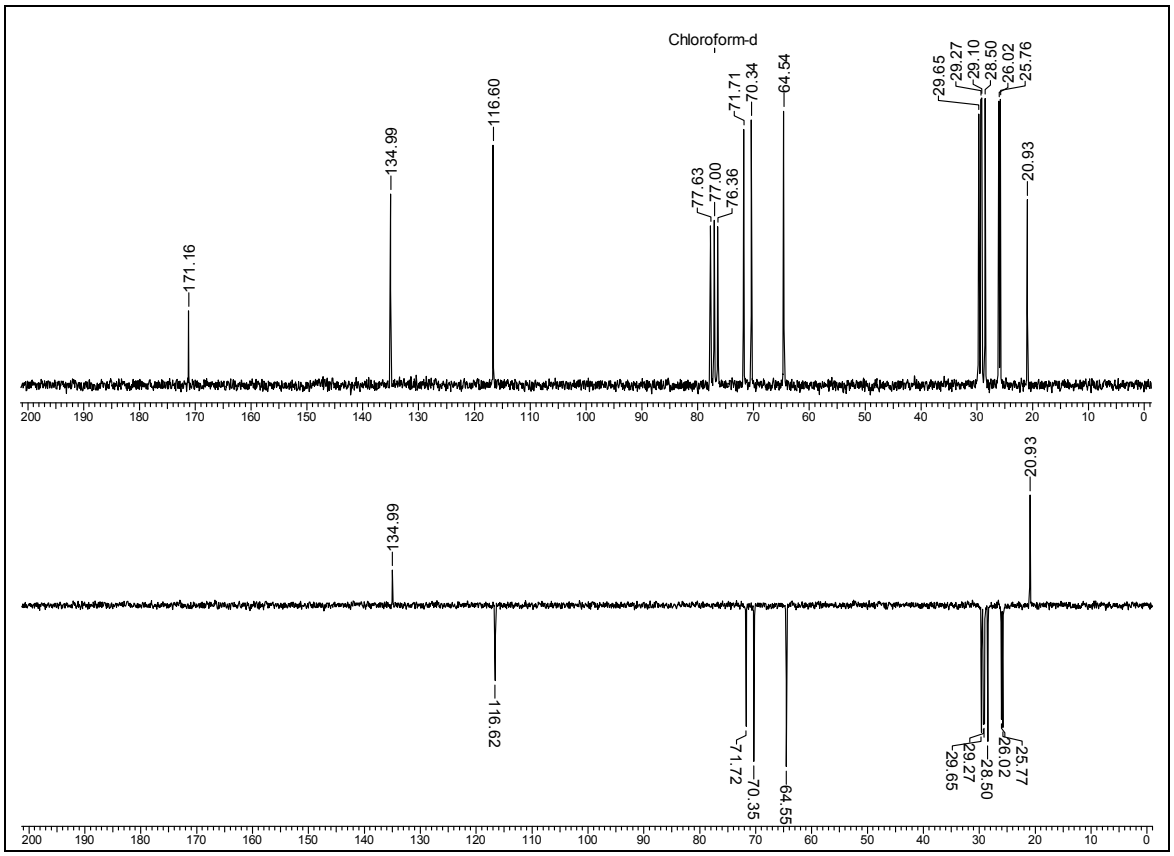
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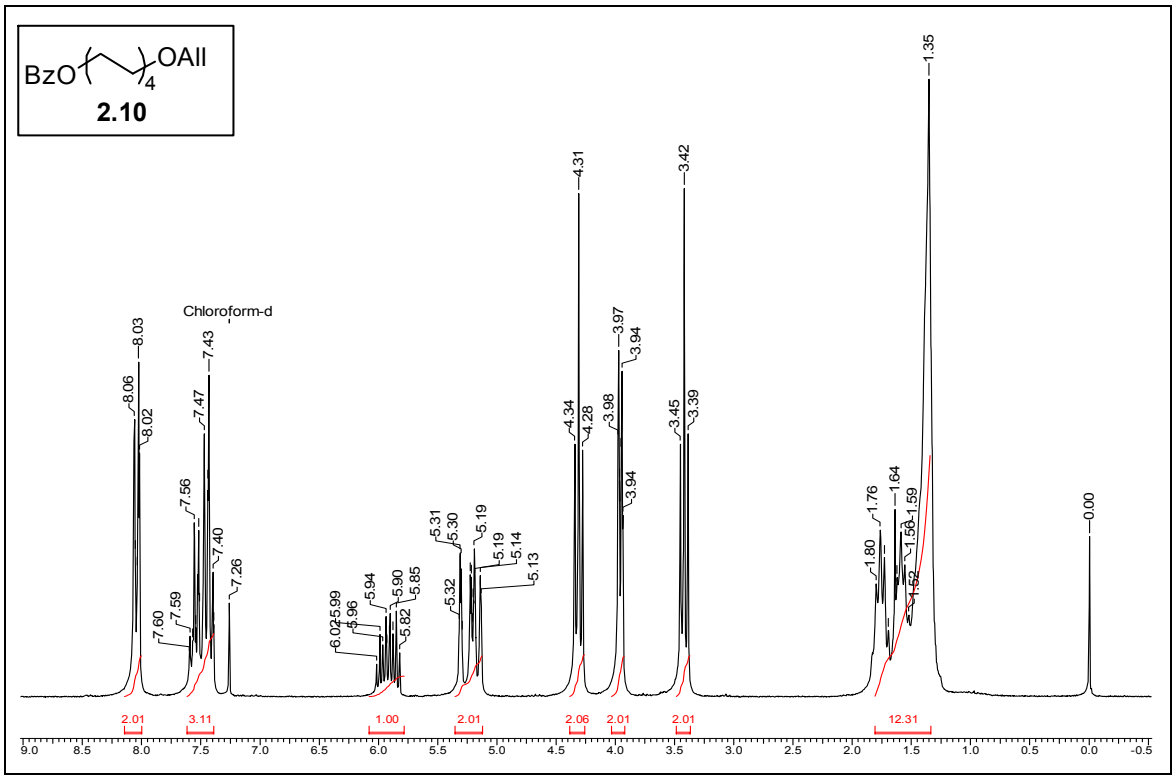
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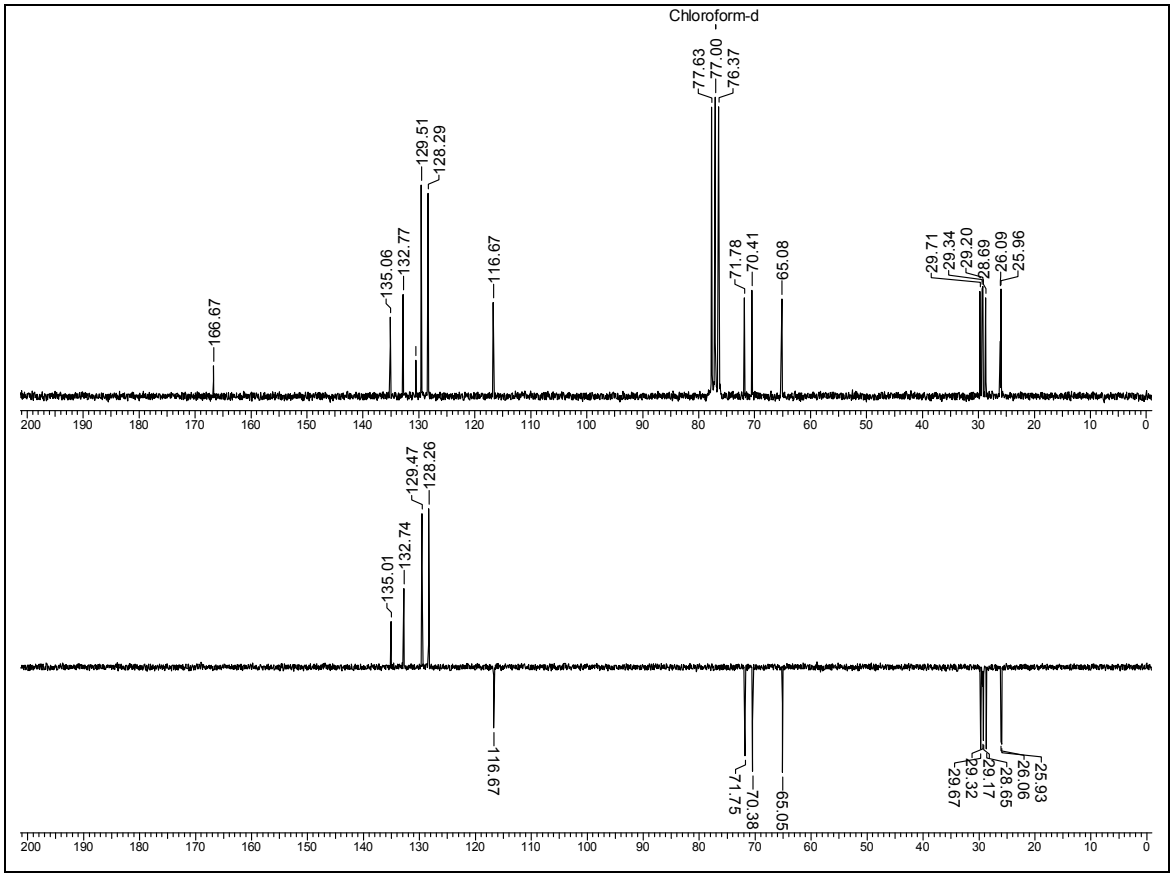
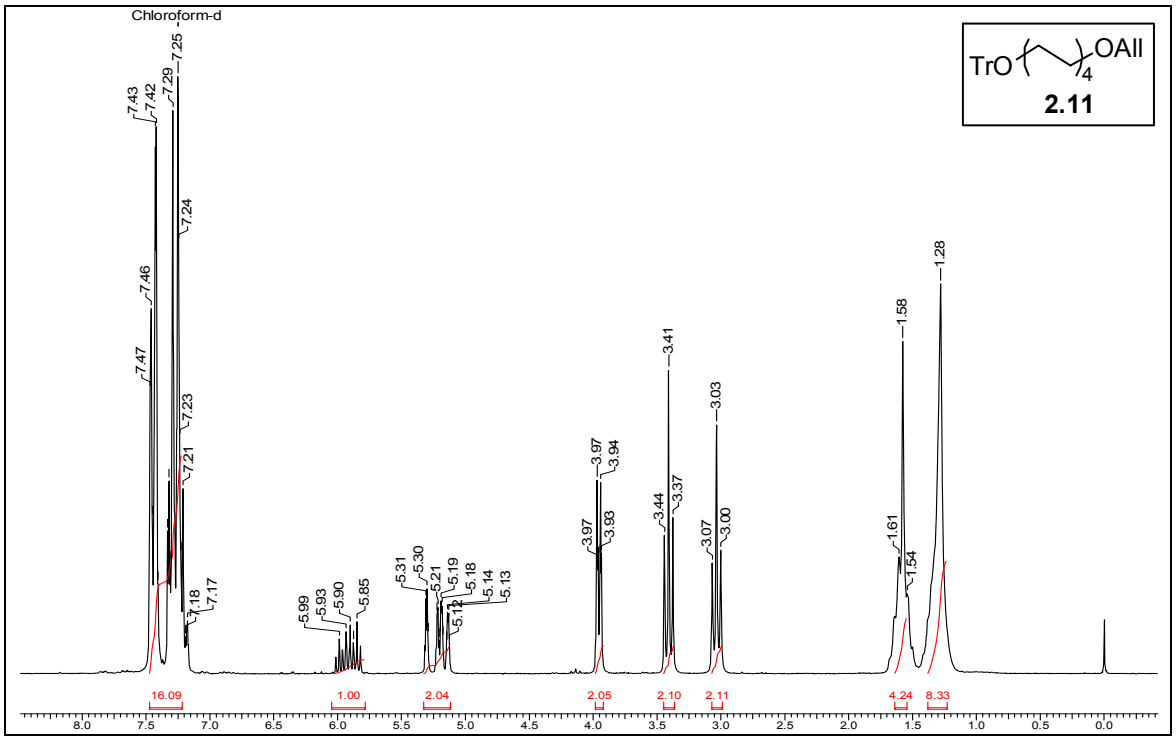
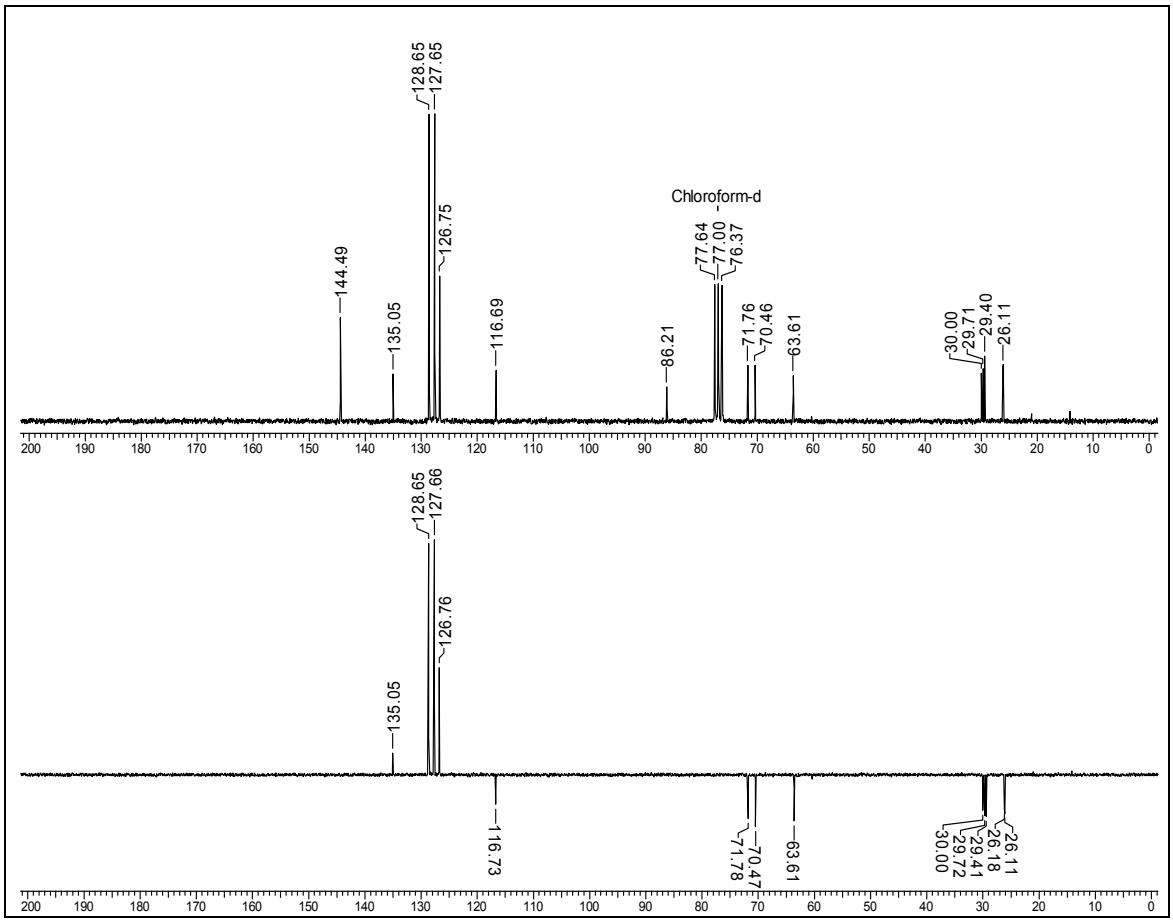
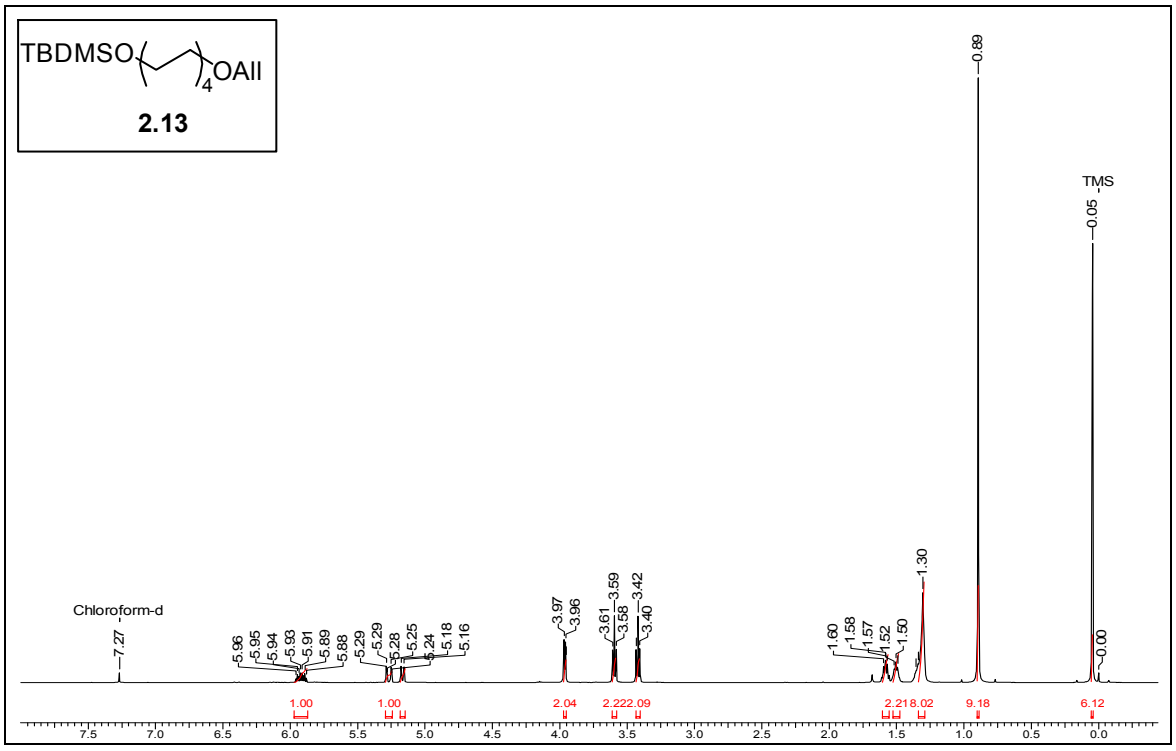
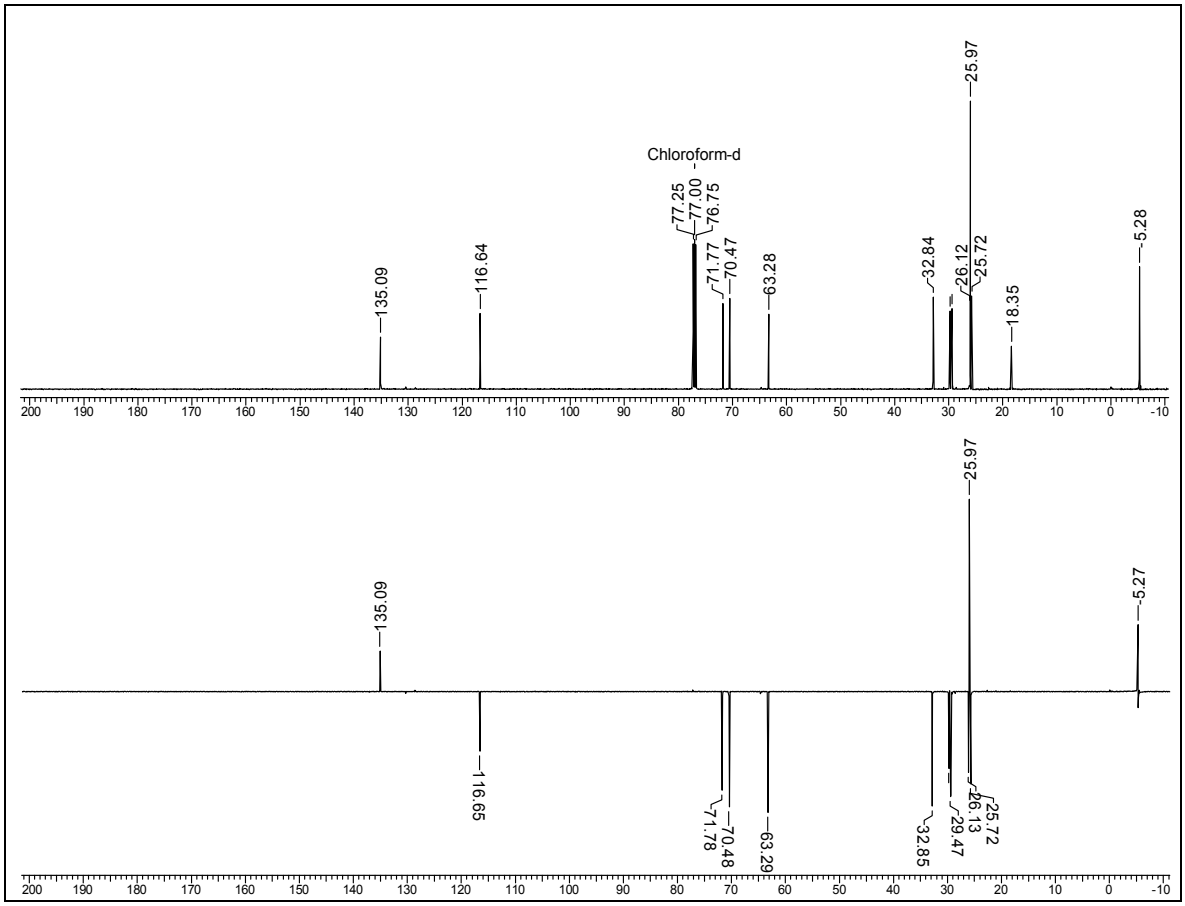
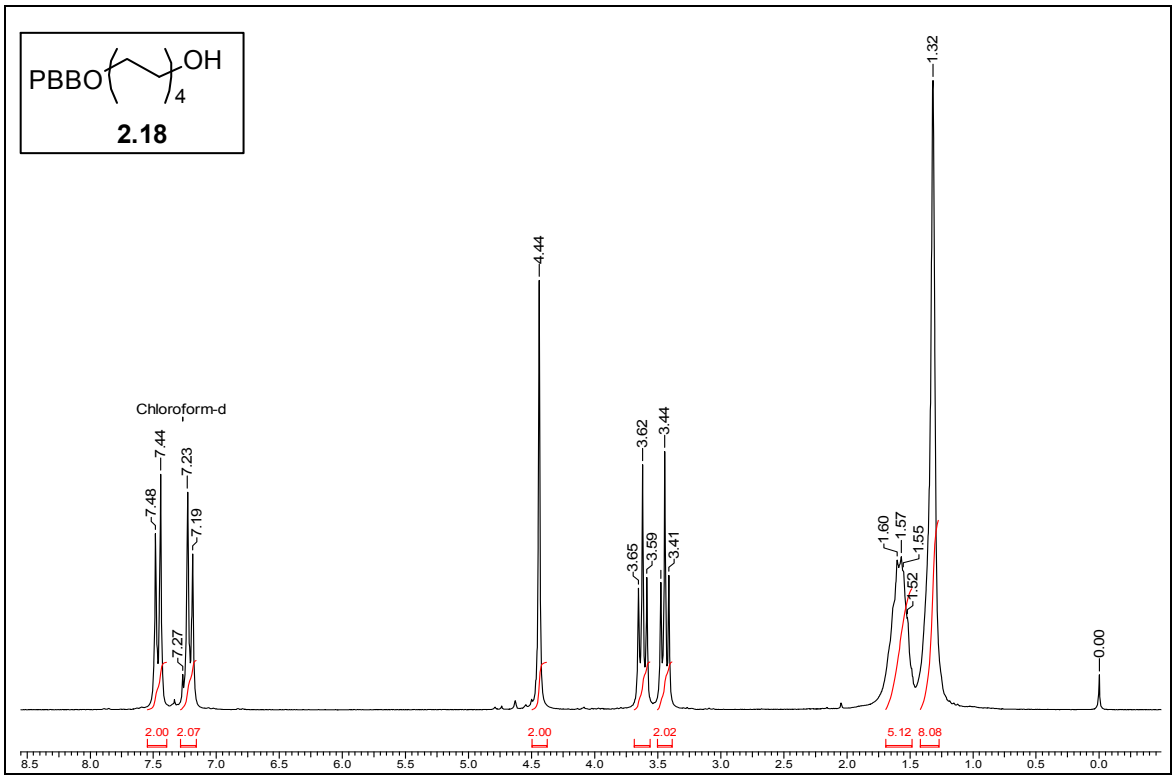

Chloroform-d
77.63
77.00
76.37
129.51
128.29
135.06
132.77
116.67
166.67
71.78
70.41
65.08
29.71
29.34
29.20
28.69
26.09
25.96
129.47
128.26
135.01
132.74
116.67
71.75
70.38
65.05
29.67
29.32
29.17
28.65
26.06
25.93

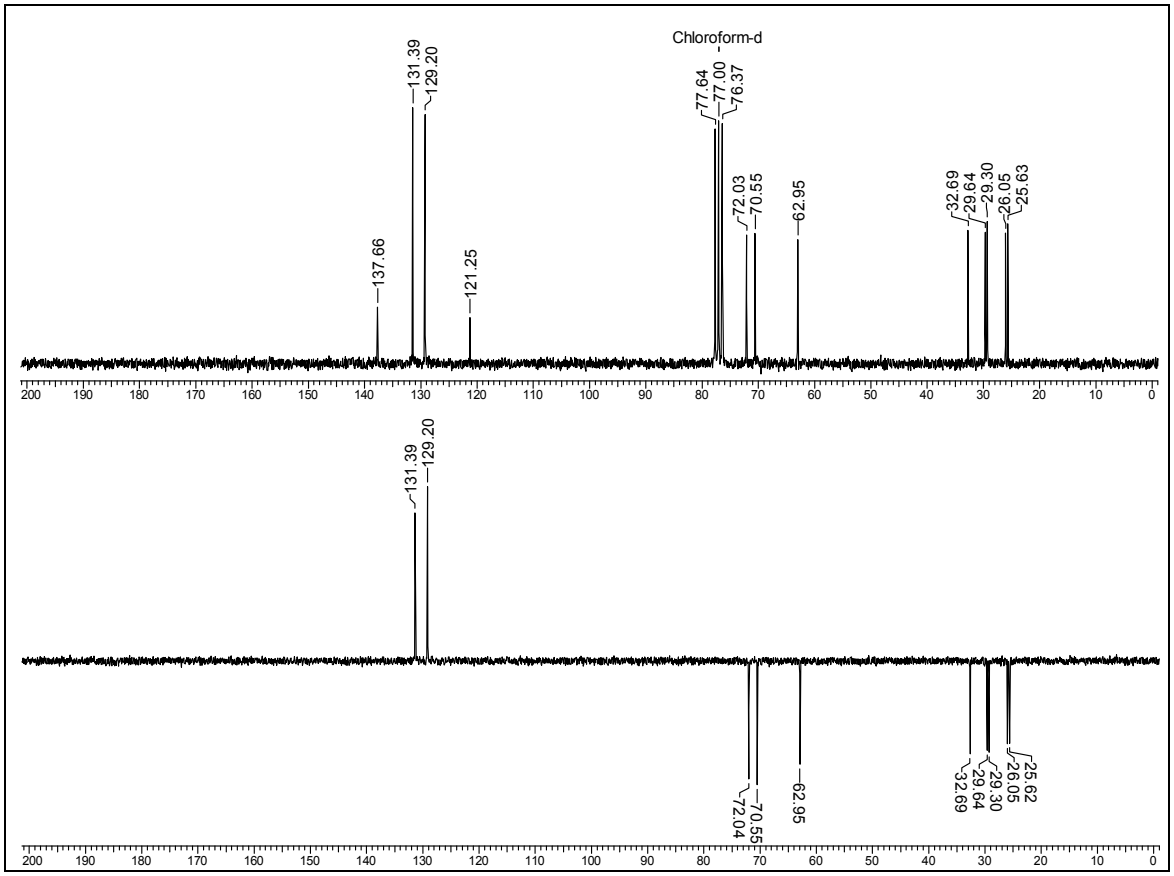

Chloroform-d
TrO
OAll
4
2.11
7.43
7.42
7.29
7.25
7.24
7.46
7.47
7.23
7.21
7.18
7.17
5.99
5.93
5.90
5.85
5.31
5.30
5.21
5.19
5.18
5.14
5.13
3.97
3.94
3.93
3.44
3.41
3.37
3.07
3.03
3.00
1.61
1.58
1.54
1.28
16.09
1.00
2.04
2.05
2.10
2.11
4.24
8.33

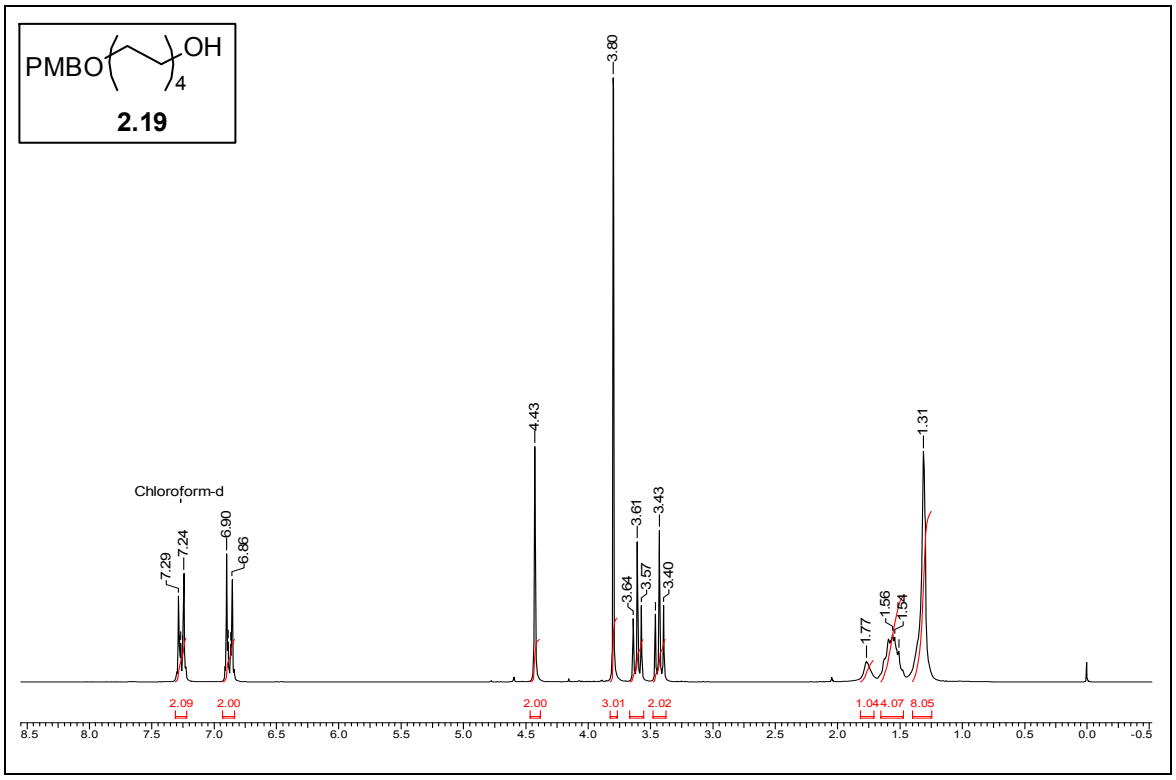

128.65
127.65
126.75
144.49
135.05
116.69
Chloroform-d
77.64
77.00
76.37
86.21
71.76
70.46
63.61
30.00
29.71
29.40
26.11
128.65
127.66
126.76
135.05
116.73
71.78
70.47
63.61
30.00
29.72
29.41
26.18
26.11

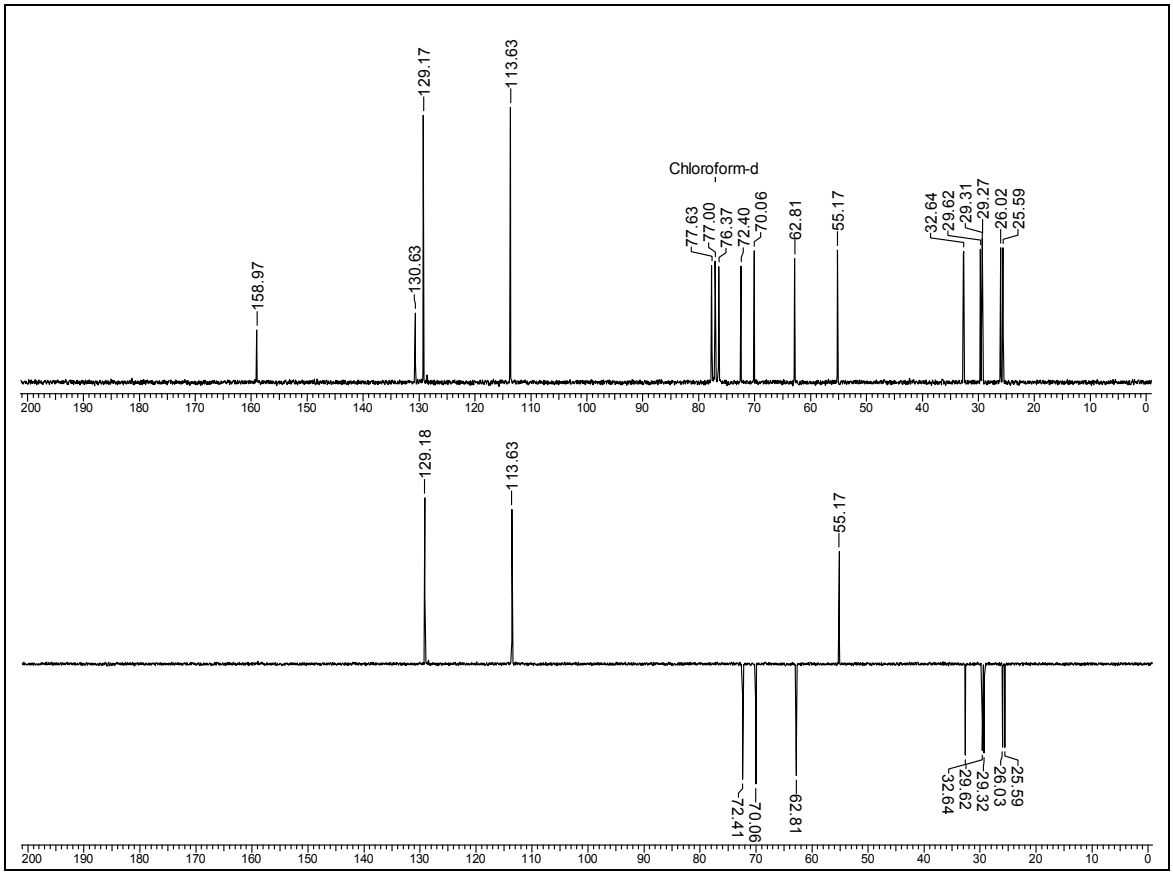

TBDMSO
4
OAll
2.13
Chloroform-d
TMS
7.27
5.96
5.95
5.94
5.93
5.91
5.89
5.88
5.29
5.28
5.25
5.24
5.18
5.16
3.97
3.96
3.61
3.59
3.58
3.42
3.40
1.60
1.58
1.57
1.52
1.50
1.30
0.89
0.05
0.00
1.00
1.00
2.04
2.22
2.09
2.21
8.02
9.18
6.12

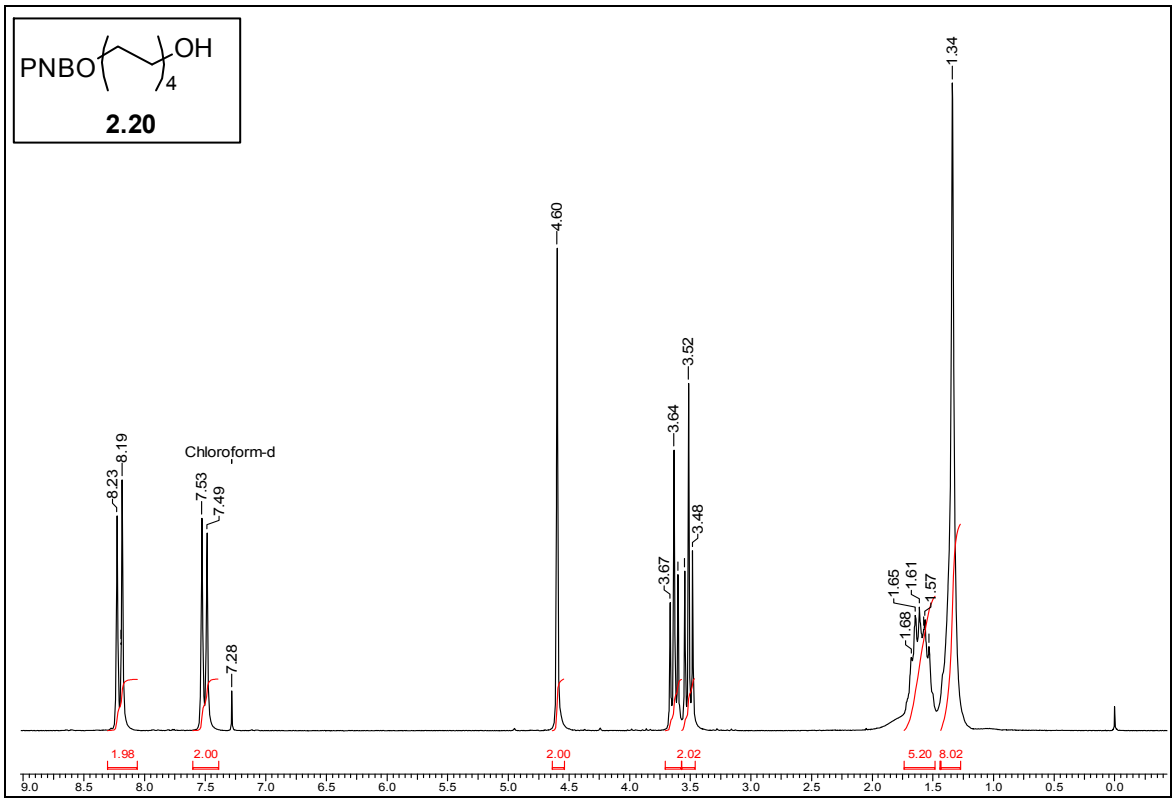

Chloroform-d
135.09
116.64
77.25
77.00
76.75
71.77
70.47
63.28
32.84
26.12
25.97
25.72
18.35
5.28
135.09
116.65
71.78
70.48
63.29
32.85
29.47
26.13
25.97
25.72
5.27

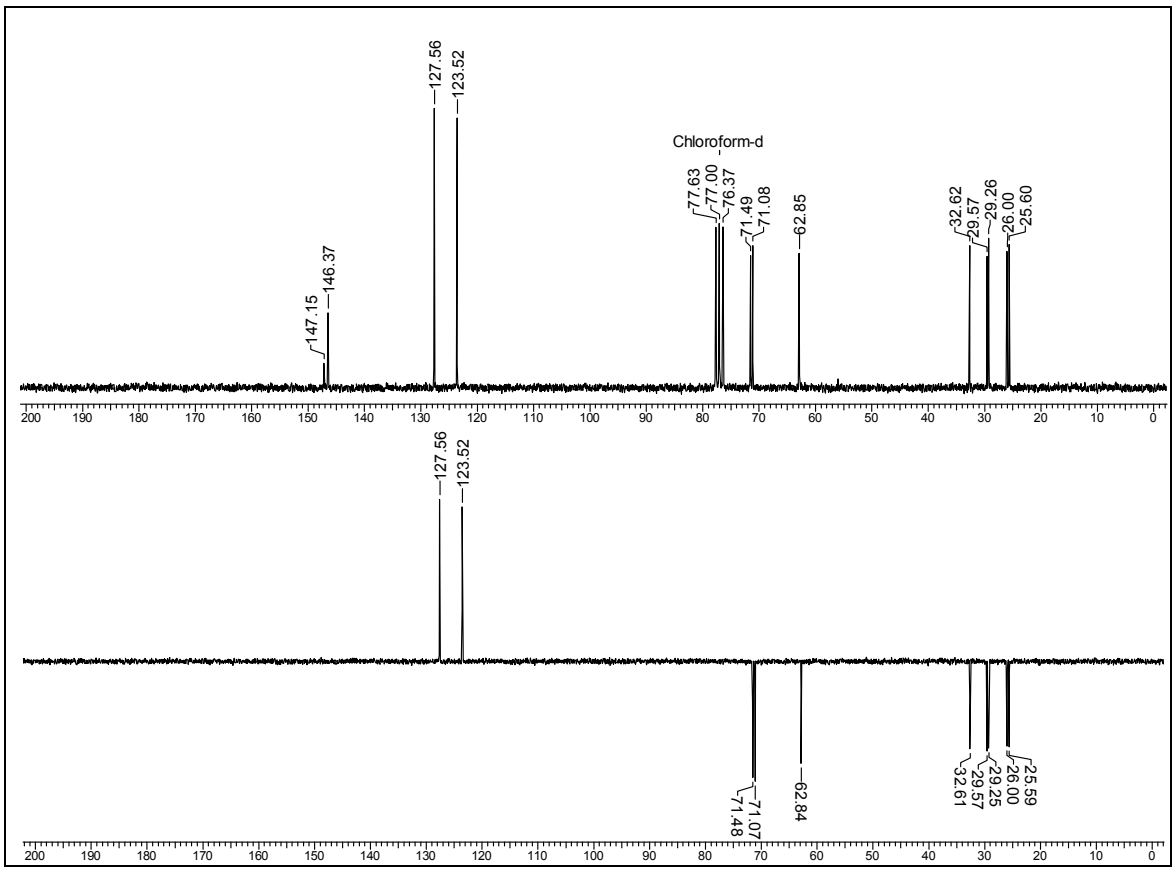

PBBO
OH
4
2.18
Chloroform-d
7.48
7.44
7.27
7.23
7.19
4.44
3.65
3.62
3.59
3.44
3.41
1.60
1.57
1.55
1.52
1.32
0.00
2.00
2.07
2.00
2.02
5.12
8.08

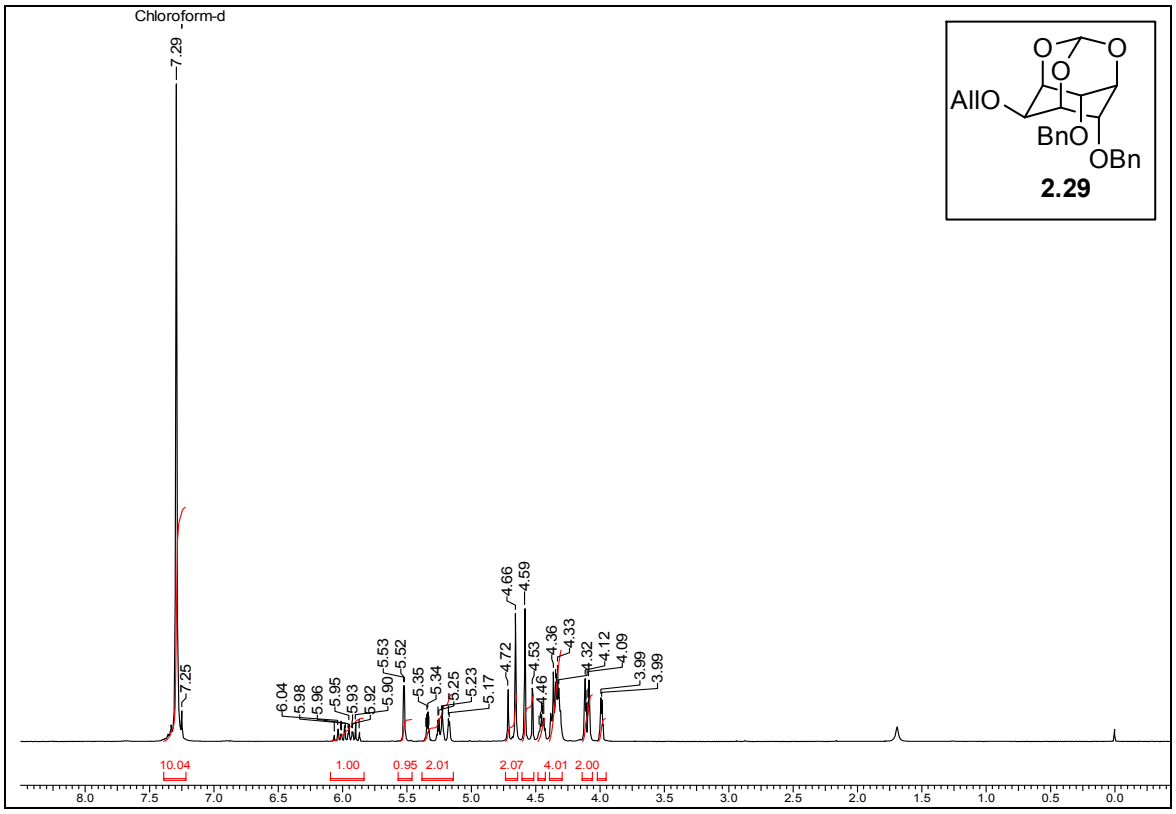

Chloroform-d
137.66
131.39
129.20
121.25
77.64
77.00
76.37
72.03
70.55
62.95
32.69
29.64
29.30
26.05
25.63
131.39
129.20
72.04
70.55
62.95
32.69
29.64
29.30
26.05
25.62

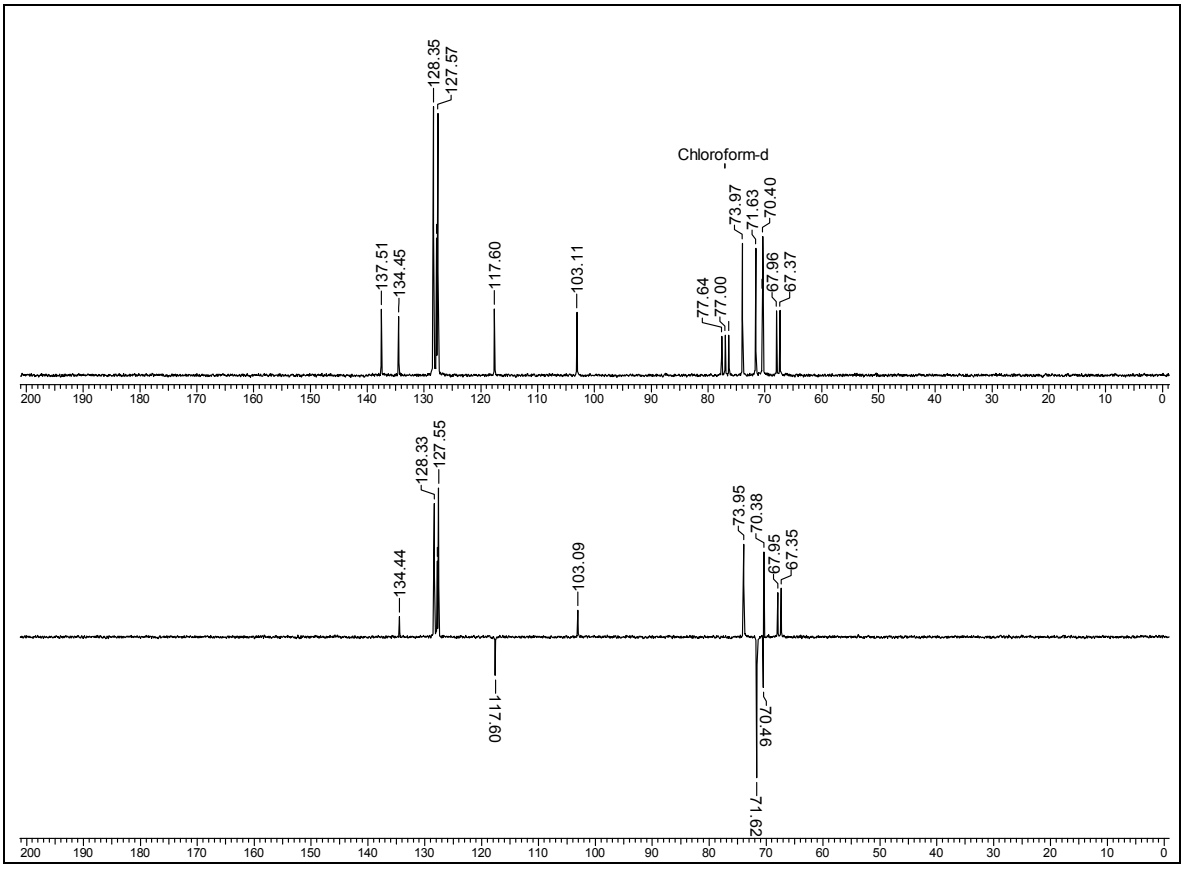

PMBO
OH
4
2.19
Chloroform-d
7.29
7.24
6.90
6.86
4.43
3.80
3.64
3.61
3.57
3.43
3.40
1.77
1.56
1.54
1.31
2.09
2.00
2.00
3.01
2.02
1.04
4.07
8.05

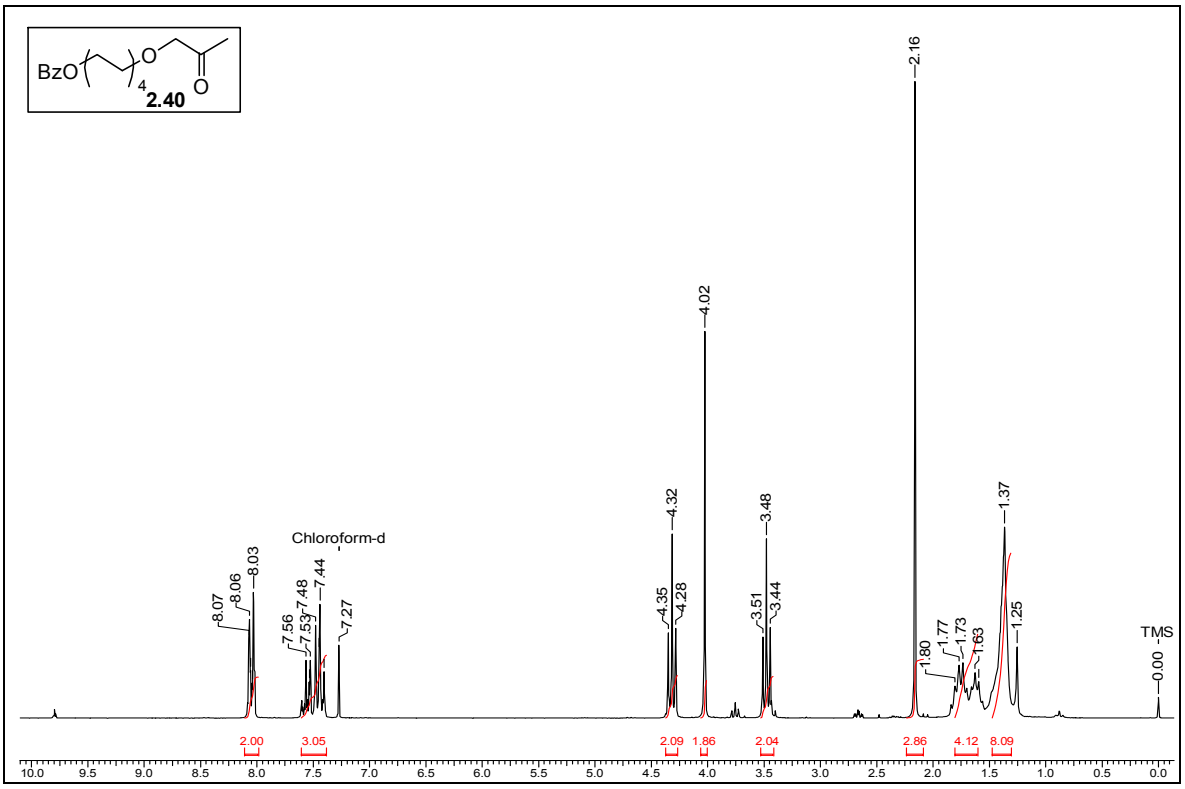

158.97
130.63
129.17
113.63
Chloroform-d
77.63
77.00
76.37
72.40
70.06
62.81
55.17
32.64
29.62
29.31
29.27
26.02
25.59
129.18
113.63
55.17
72.41
70.06
62.81
32.64
29.62
29.32
26.03
25.59

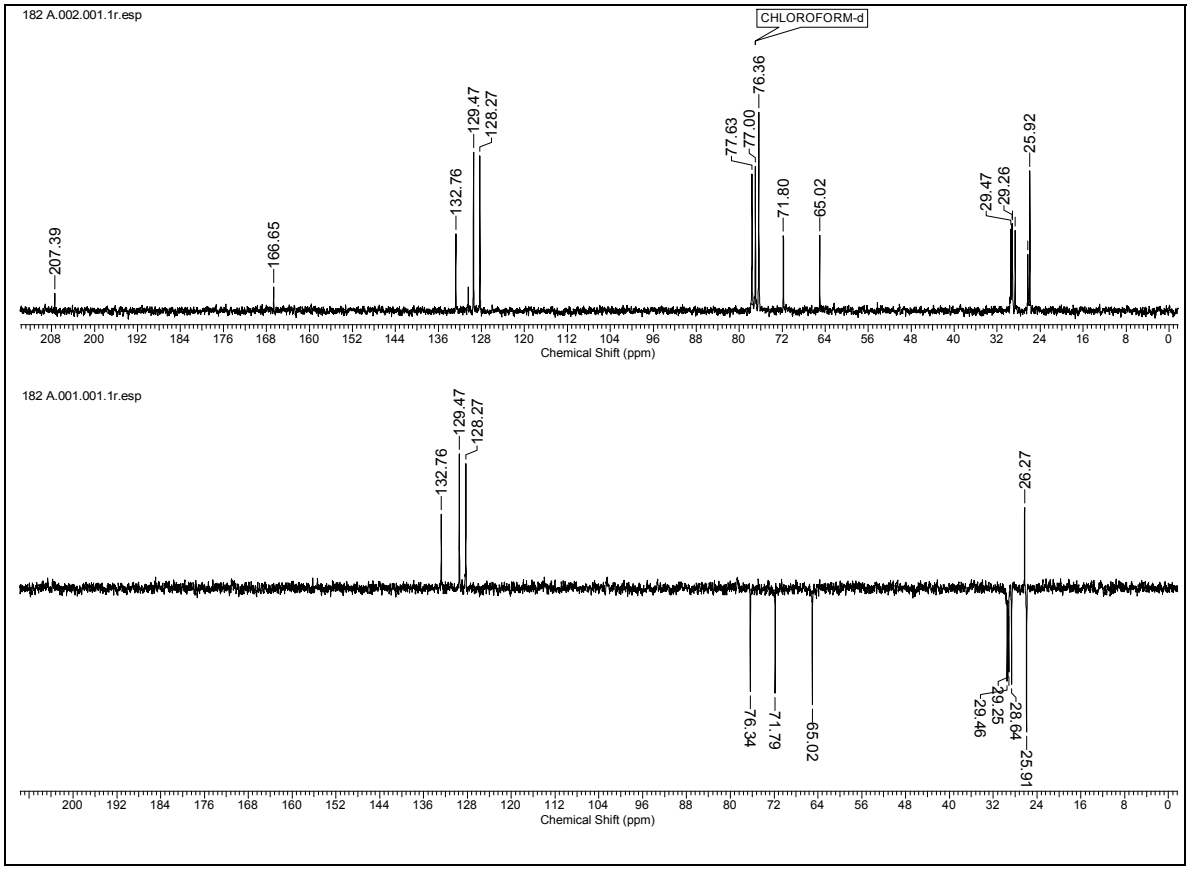

PNBO
OH
4
2.20
Chloroform-d
8.23
8.19
7.53
7.49
7.28
4.60
3.64
3.52
3.48
3.67
1.65
1.61
1.57
1.68
1.34
1.98
2.00
2.00
2.02
5.20
8.02

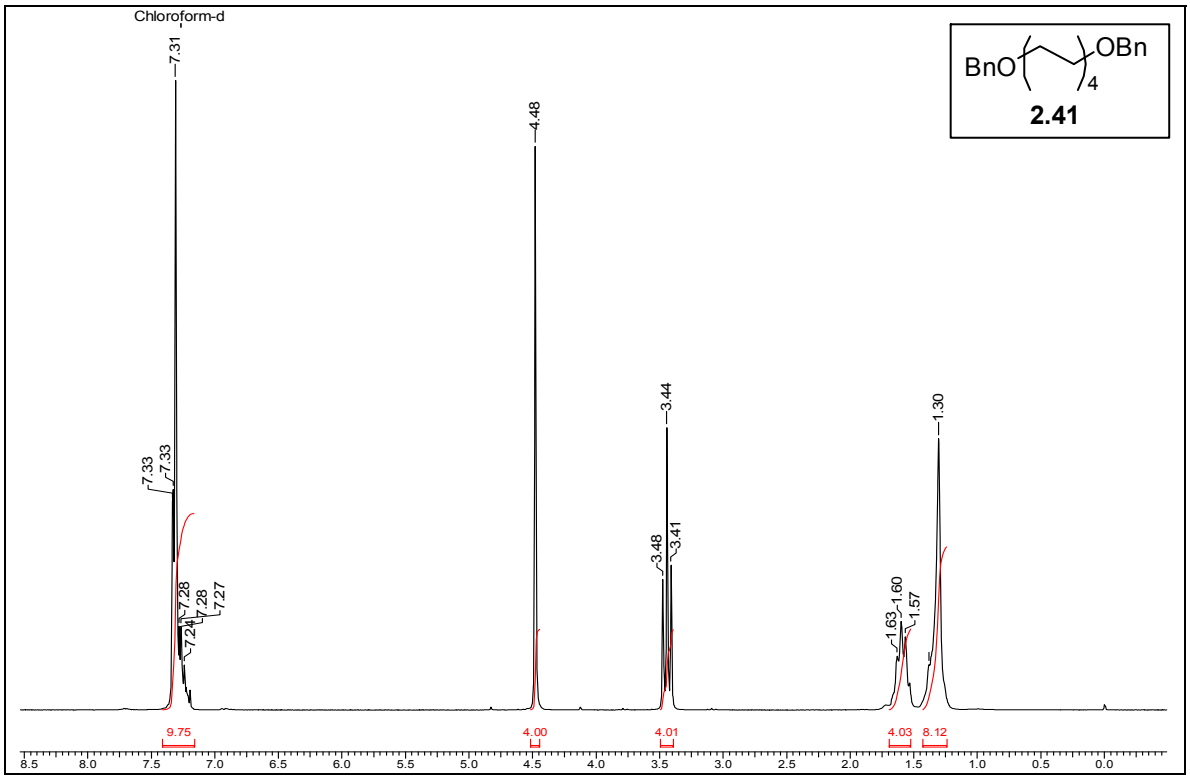

127.56
123.52
Chloroform-d
77.63
77.00
76.37
71.49
71.08
62.85
32.62
29.57
29.26
26.00
25.60
147.15
146.37
127.56
123.52
71.48
71.07
62.84
32.61
29.57
29.25
26.00
25.59

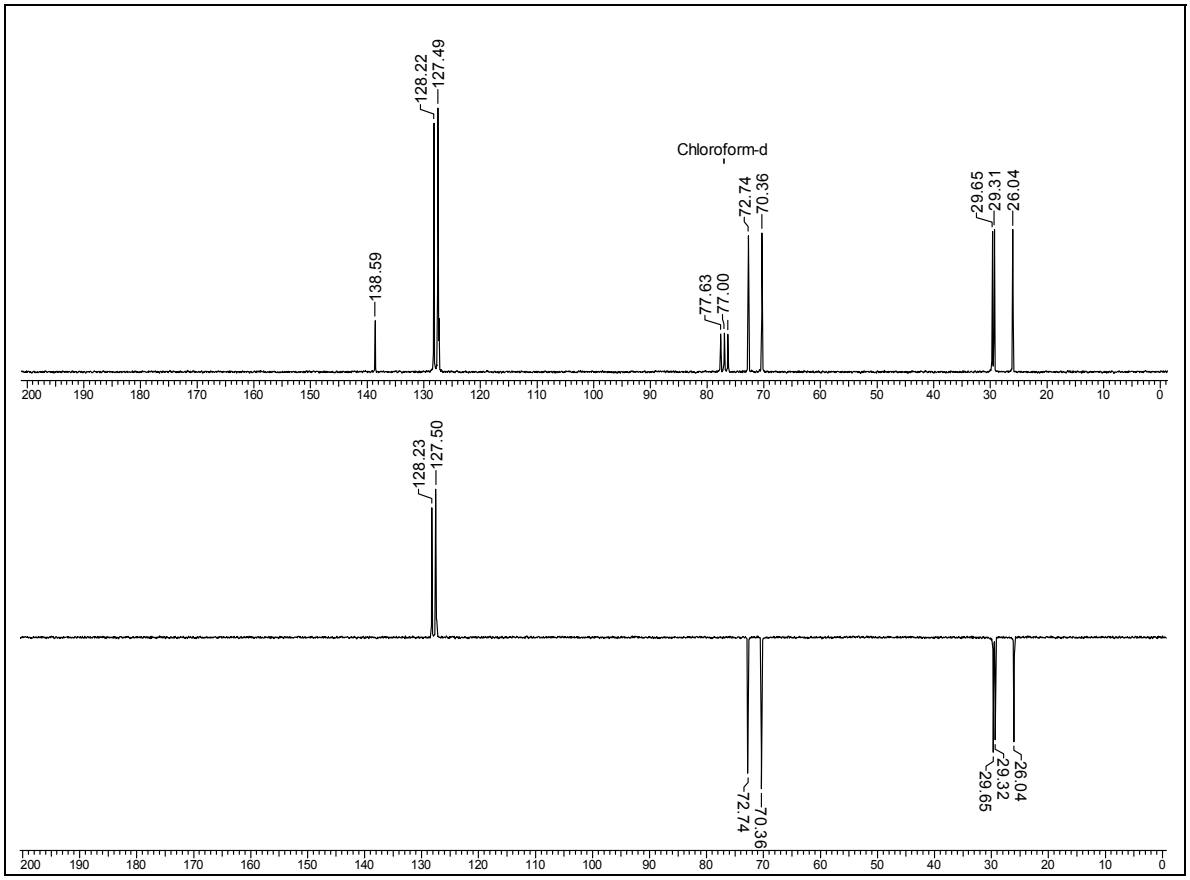

Chloroform-d
7.29
7.25
6.04
5.98
5.96
5.95
5.93
5.92
5.90
5.53
5.52
5.35
5.34
5.25
5.23
5.17
4.72
4.66
4.59
4.53
4.46
4.36
4.33
4.32
4.12
4.09
3.99
3.99
10.04
1.00
0.95
2.01
2.07
4.01
2.00
AllO
BnO
OBn
2.29

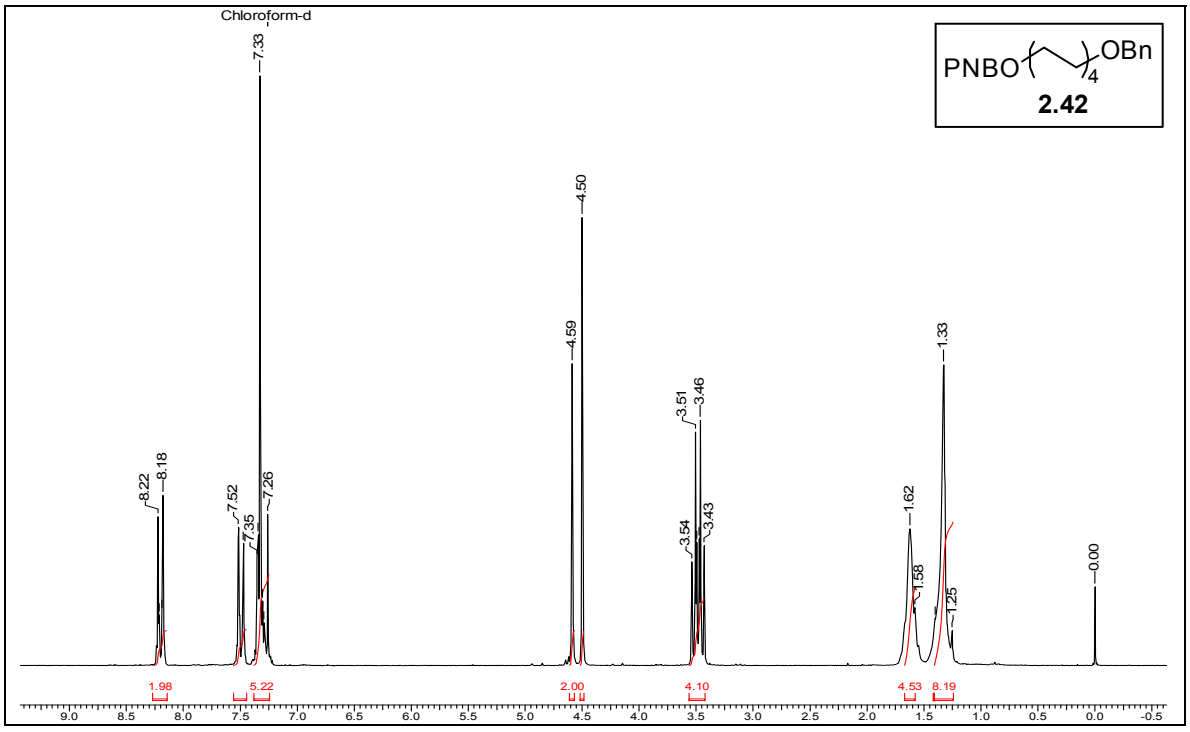

128.35
127.57
Chloroform-d
137.51
134.45
117.60
103.11
77.64
77.00
73.97
71.63
70.40
67.96
67.37
128.33
127.55
134.44
103.09
73.95
70.38
67.95
67.35
117.60
70.46
71.62

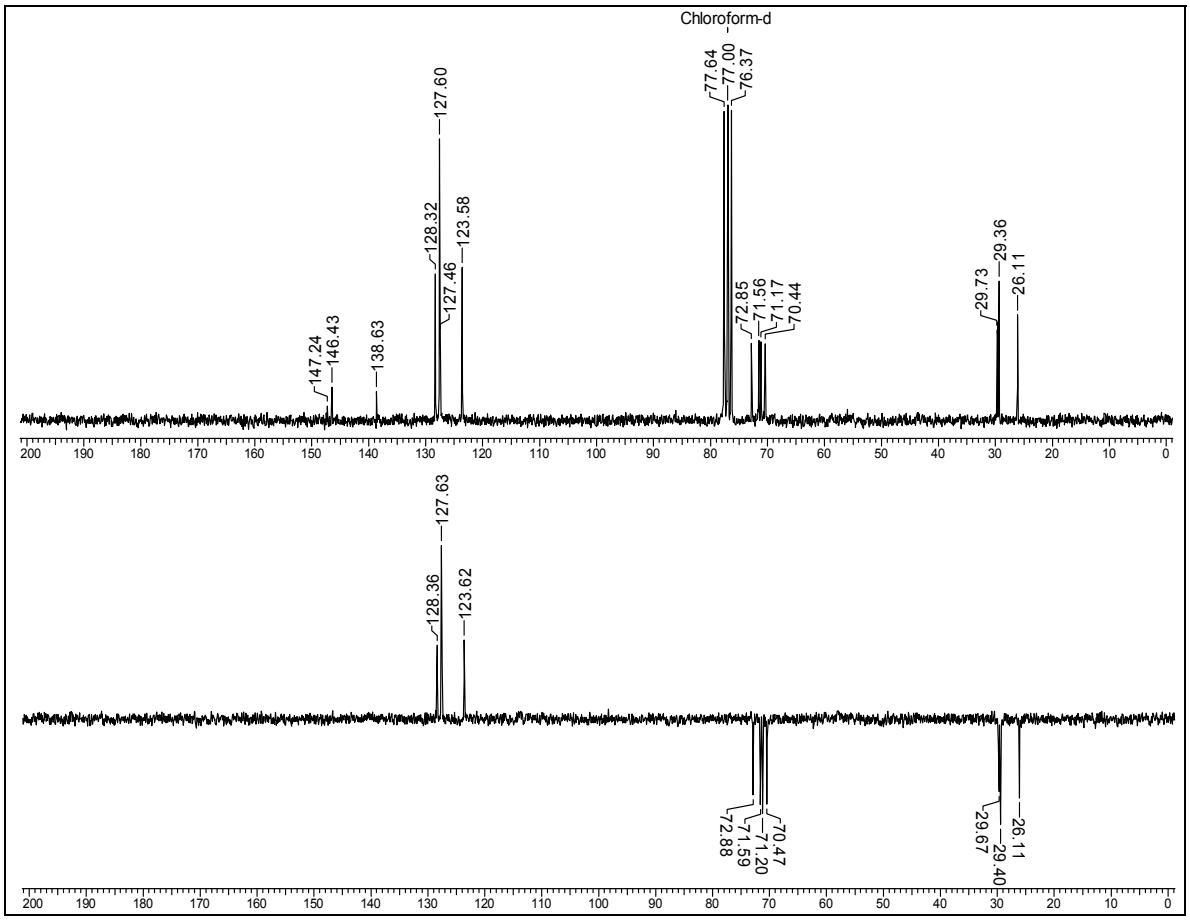

BzO
O
4
O
2.40
Chloroform-d
TMS
2.16
4.02
4.32
3.48
1.37
8.07
8.06
8.03
7.56
7.53
7.48
7.44
7.27
4.35
4.28
3.51
3.44
1.80
1.77
1.73
1.63
1.25
0.00
2.00
3.05
2.09
1.86
2.04
2.86
4.12
8.09

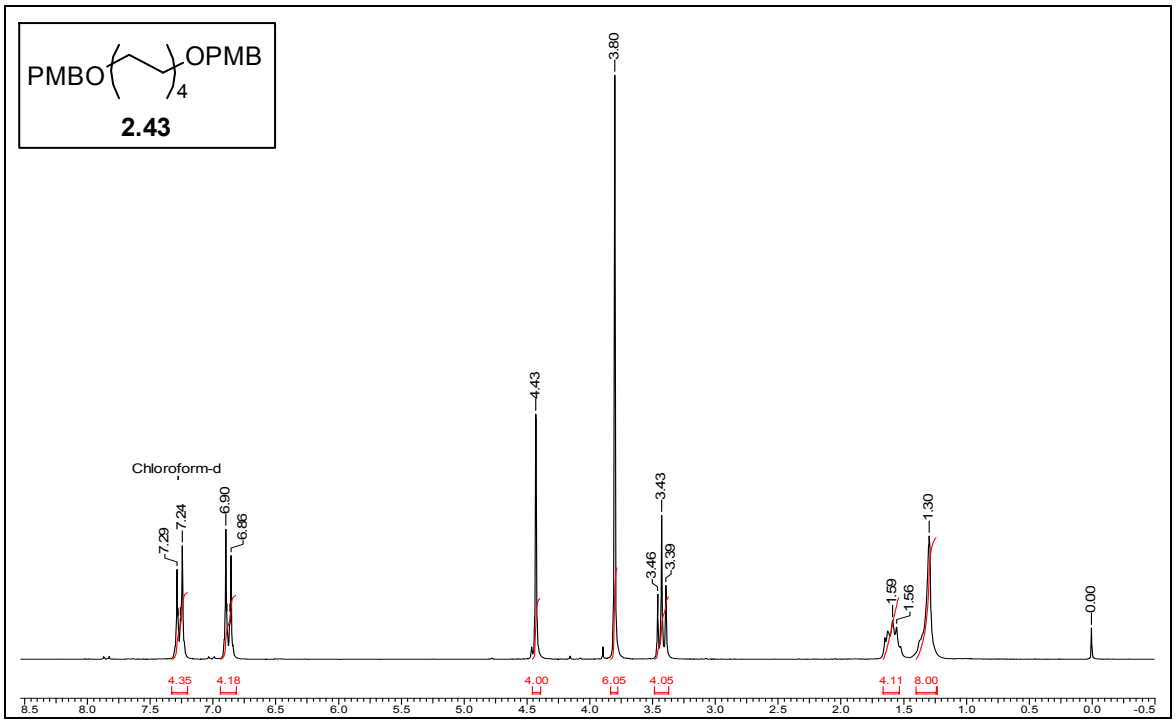

182 A.002.001.1r.esp
CHLOROFORM-d
207.39
166.65
132.76
129.47
128.27
77.63
77.00
76.36
71.80
65.02
29.47
29.26
25.92
Chemical Shift (ppm)
182 A.001.001.1r.esp
132.76
129.47
128.27
26.27
76.34
71.79
65.02
29.46
29.25
28.94
25.91
Chemical Shift (ppm)

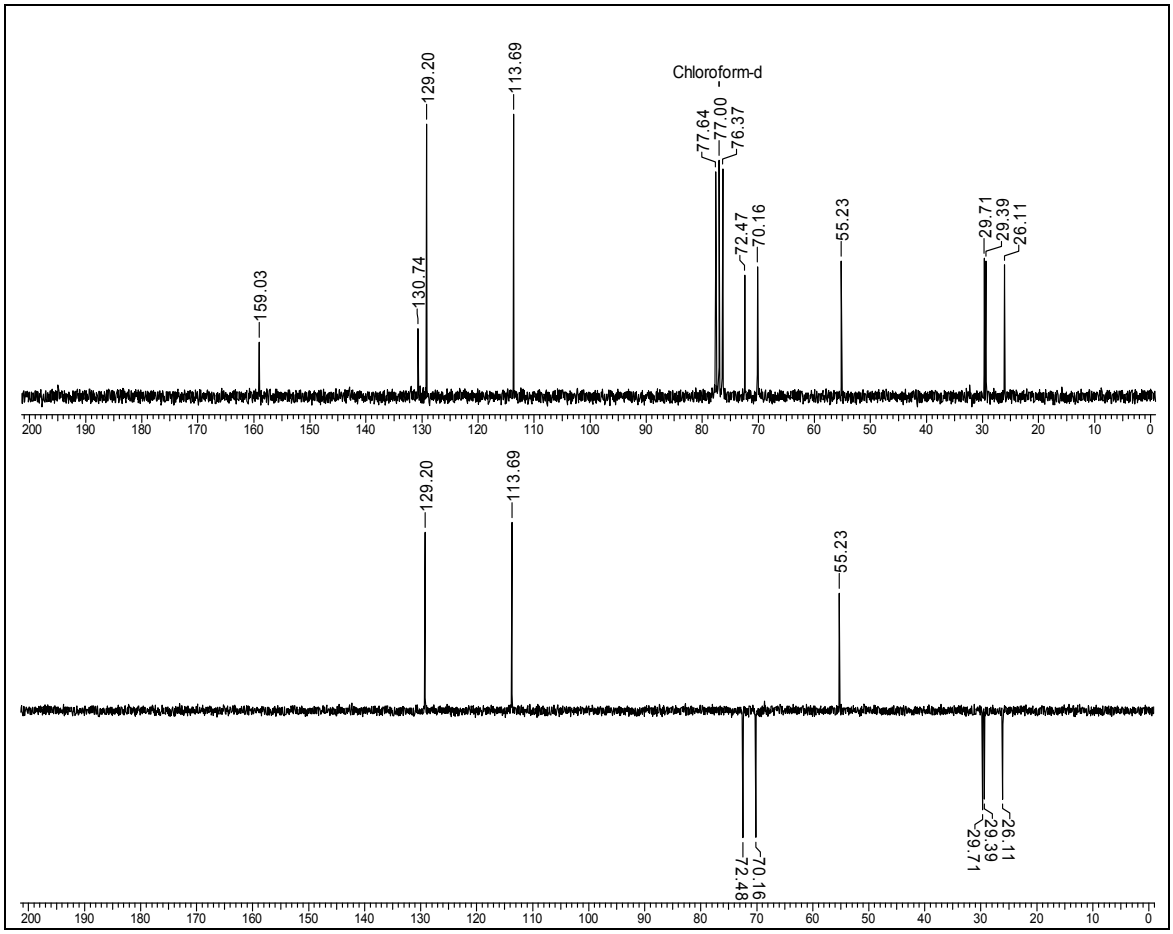

Chloroform-d
7.31
4.48
3.44
1.30
7.33
7.33
3.48
3.41
7.28
7.28
7.27
7.24
1.63
1.60
1.57
BnO
OBn
4
2.41
9.75
4.00
4.01
4.03
8.12

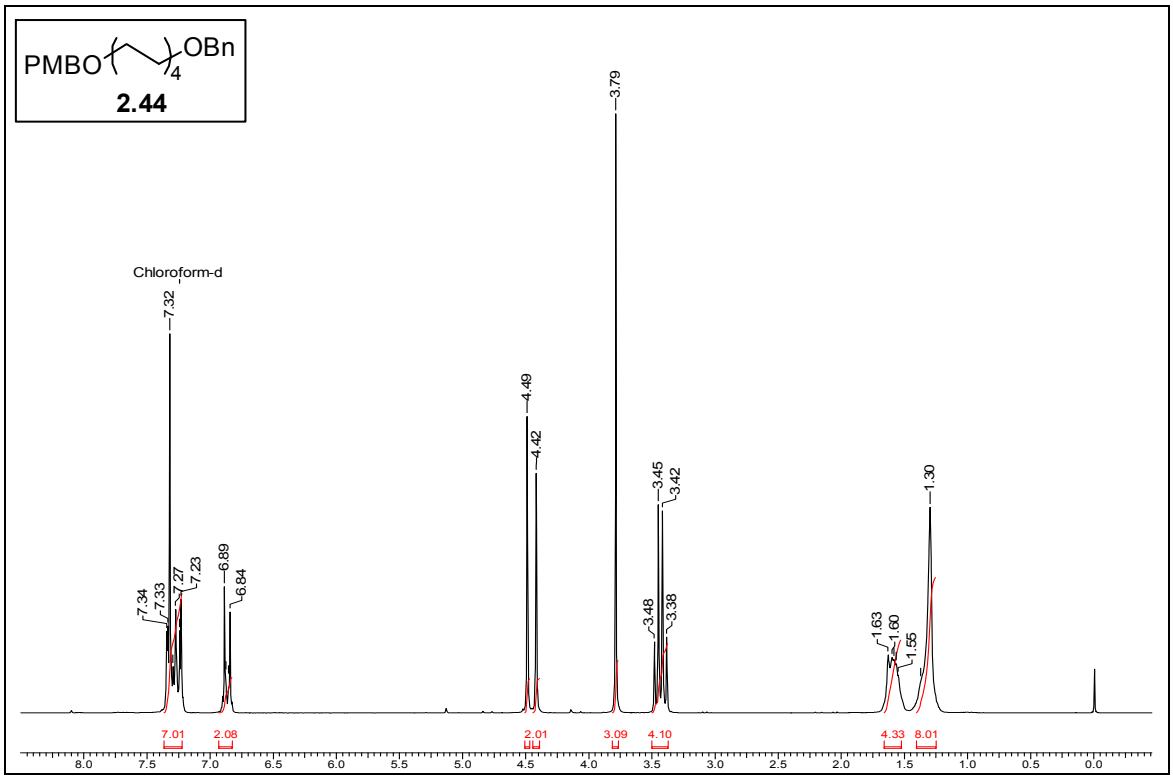

128.22
127.49
Chloroform-d
72.74
70.36
29.65
29.31
26.04
138.59
77.63
77.00
128.23
127.50
72.74
70.36
29.65
29.32
26.04

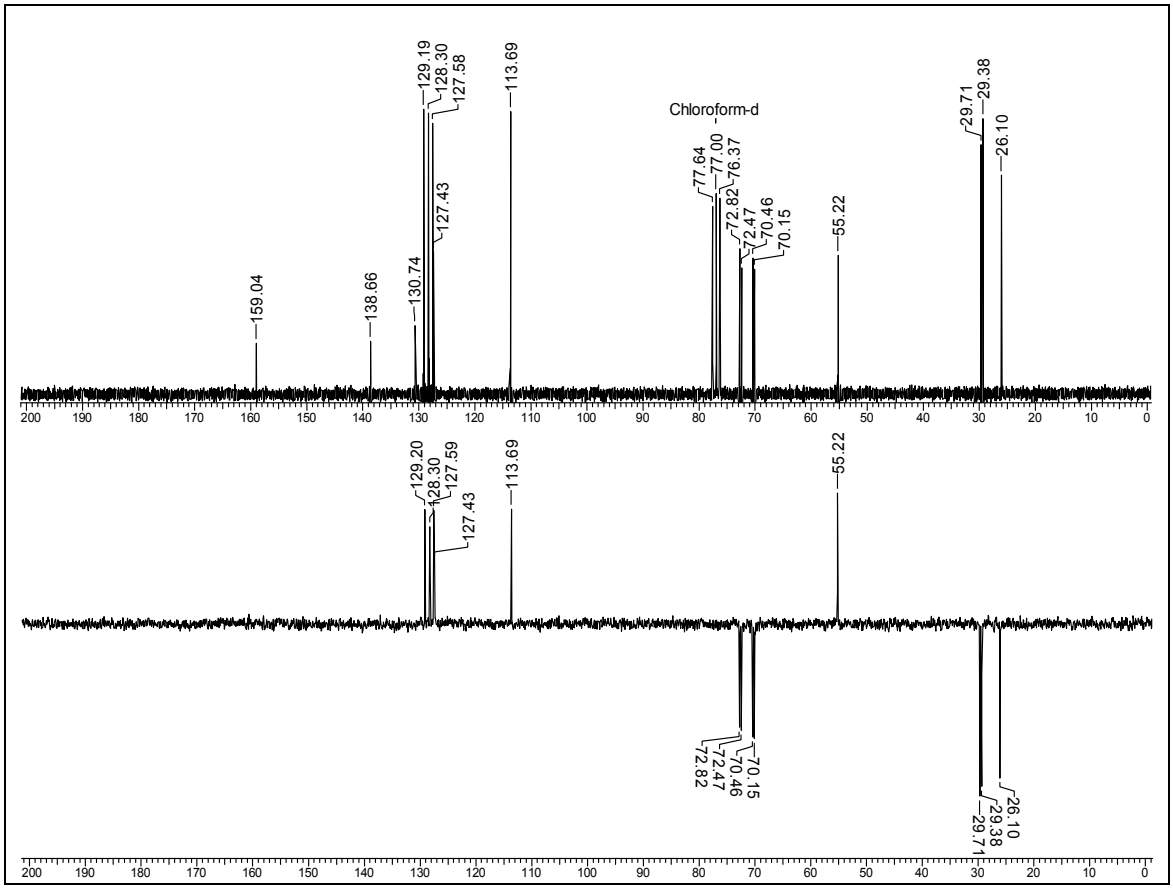

Chloroform-d
PNBO
OBn
4
2.42
8.22
8.18
7.52
7.35
7.33
7.26
4.59
4.50
3.54
3.51
3.46
3.43
1.62
1.58
1.33
1.25
0.00
1.98
5.22
2.00
4.10
4.53
8.19

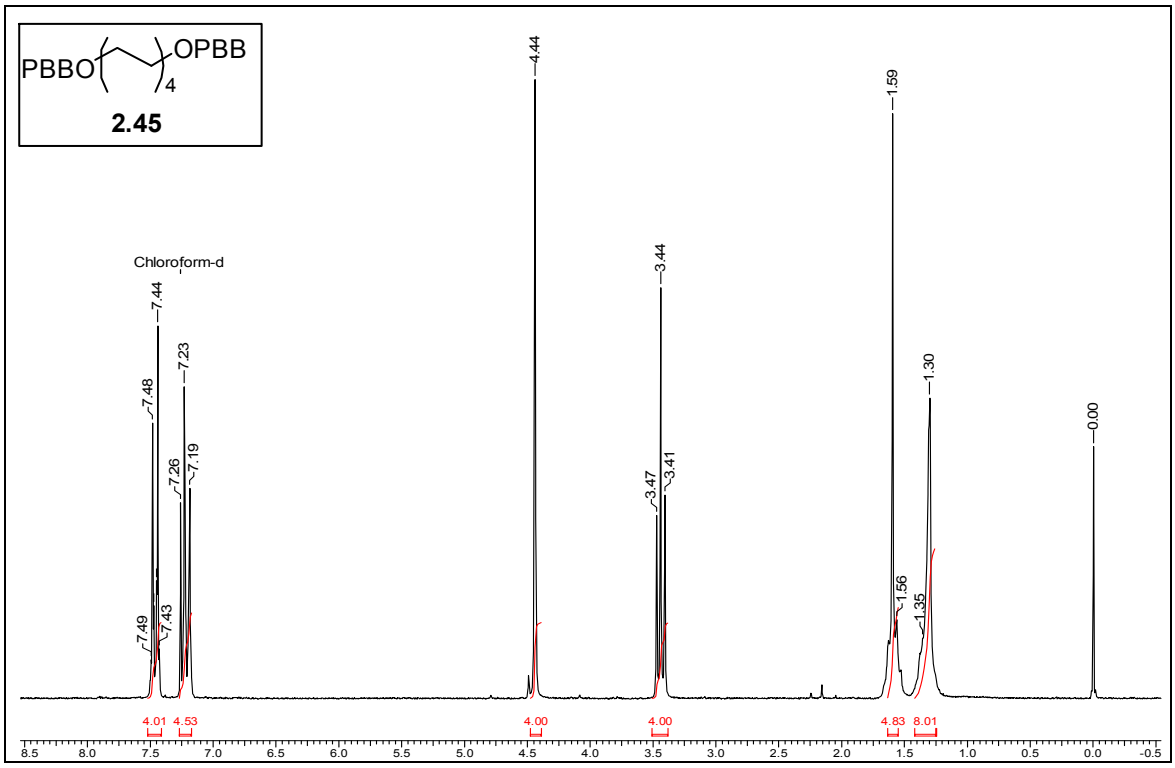

Chloroform-d
147.24
146.43
138.63
128.32
127.60
127.46
123.58
77.64
77.00
76.37
72.85
71.56
71.17
70.44
29.73
29.36
26.11
128.36
127.63
123.62
72.88
71.59
71.20
70.47
29.67
29.40
26.11

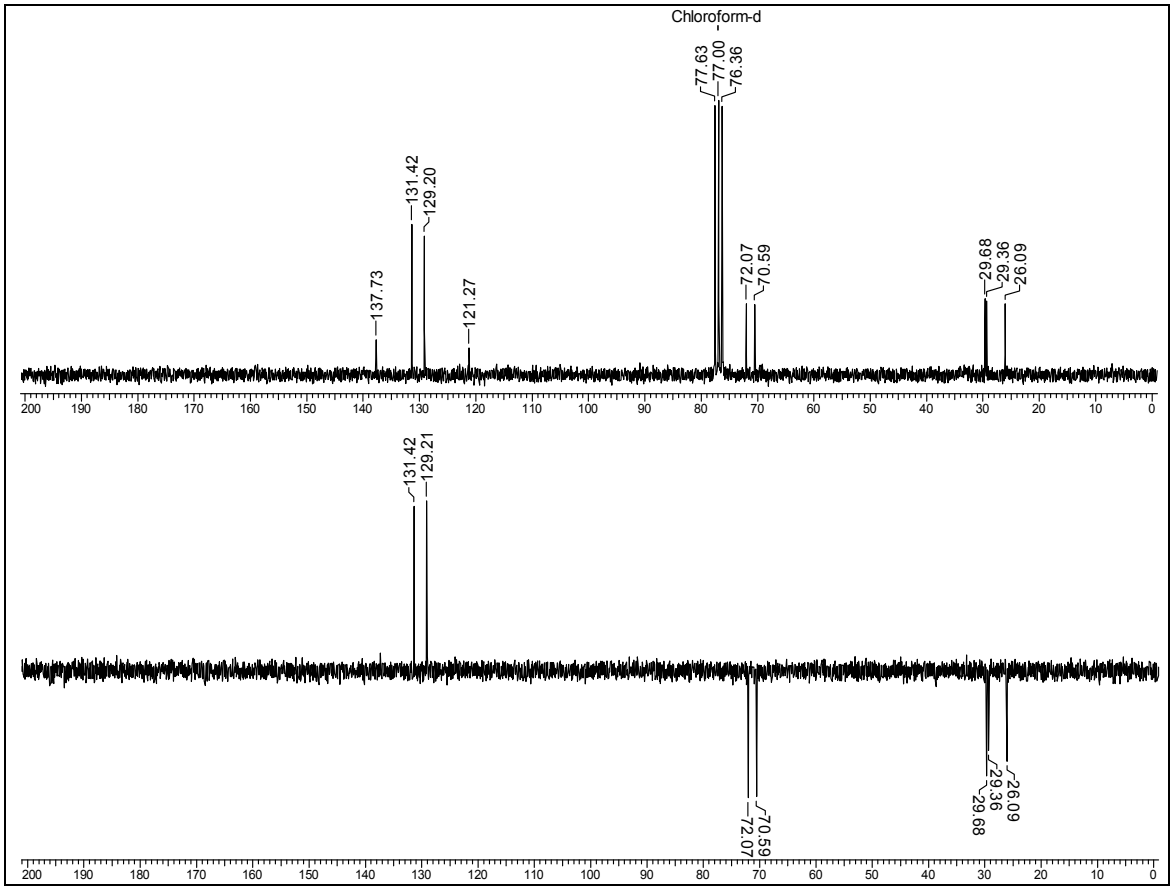

PMBO
OPMB
4
2.43
Chloroform-d
7.29
7.24
6.90
6.86
4.43
3.80
3.46
3.43
3.39
1.59
1.56
1.30
0.00
4.35
4.18
4.00
6.05
4.05
4.11
8.00

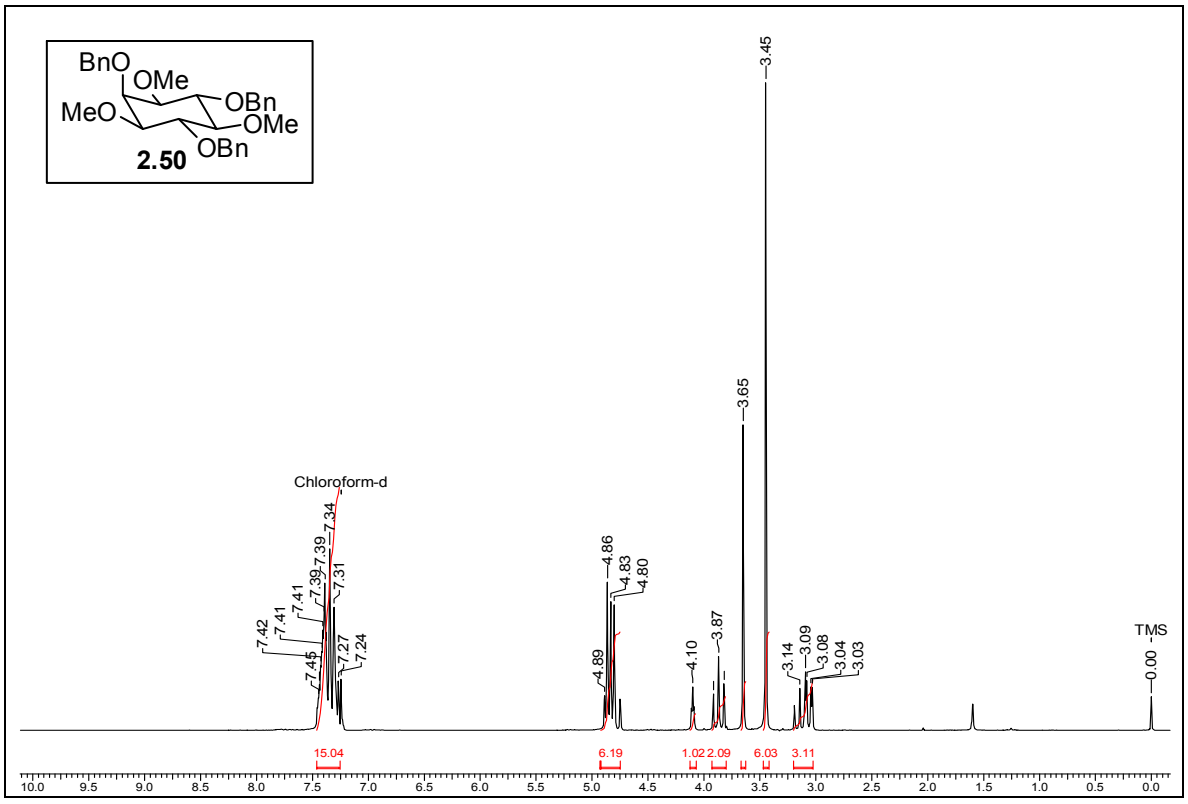

Chloroform-d
159.03
130.74
129.20
113.69
77.64
77.00
76.37
72.47
70.16
55.23
29.71
29.39
26.11
129.20
113.69
55.23
72.48
70.16
29.71
29.39
26.11

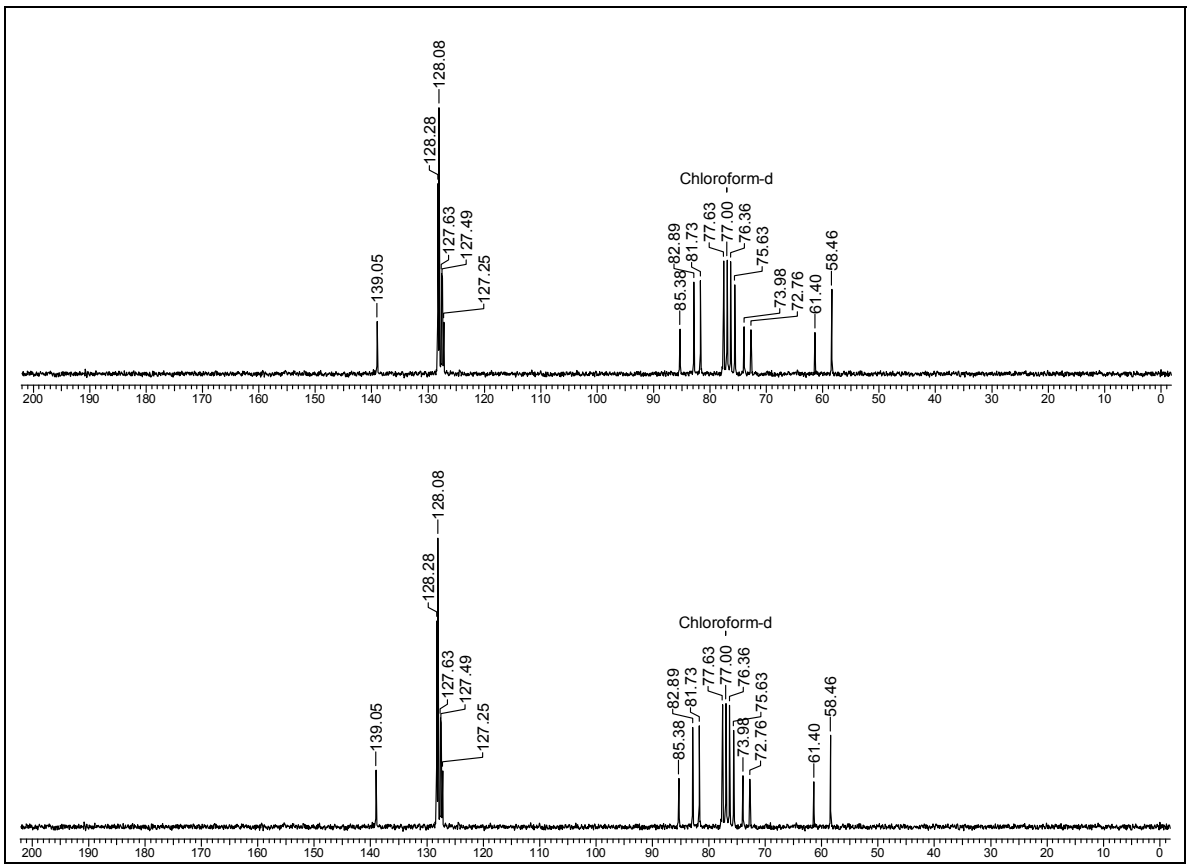

PMBO
OBn
4
2.44
Chloroform-d
7.32
7.34
7.33
7.27
7.23
6.89
6.84
4.49
4.42
3.79
3.45
3.42
3.48
3.38
1.30
1.63
1.60
1.55
7.01
2.08
2.01
3.09
4.10
4.33
8.01

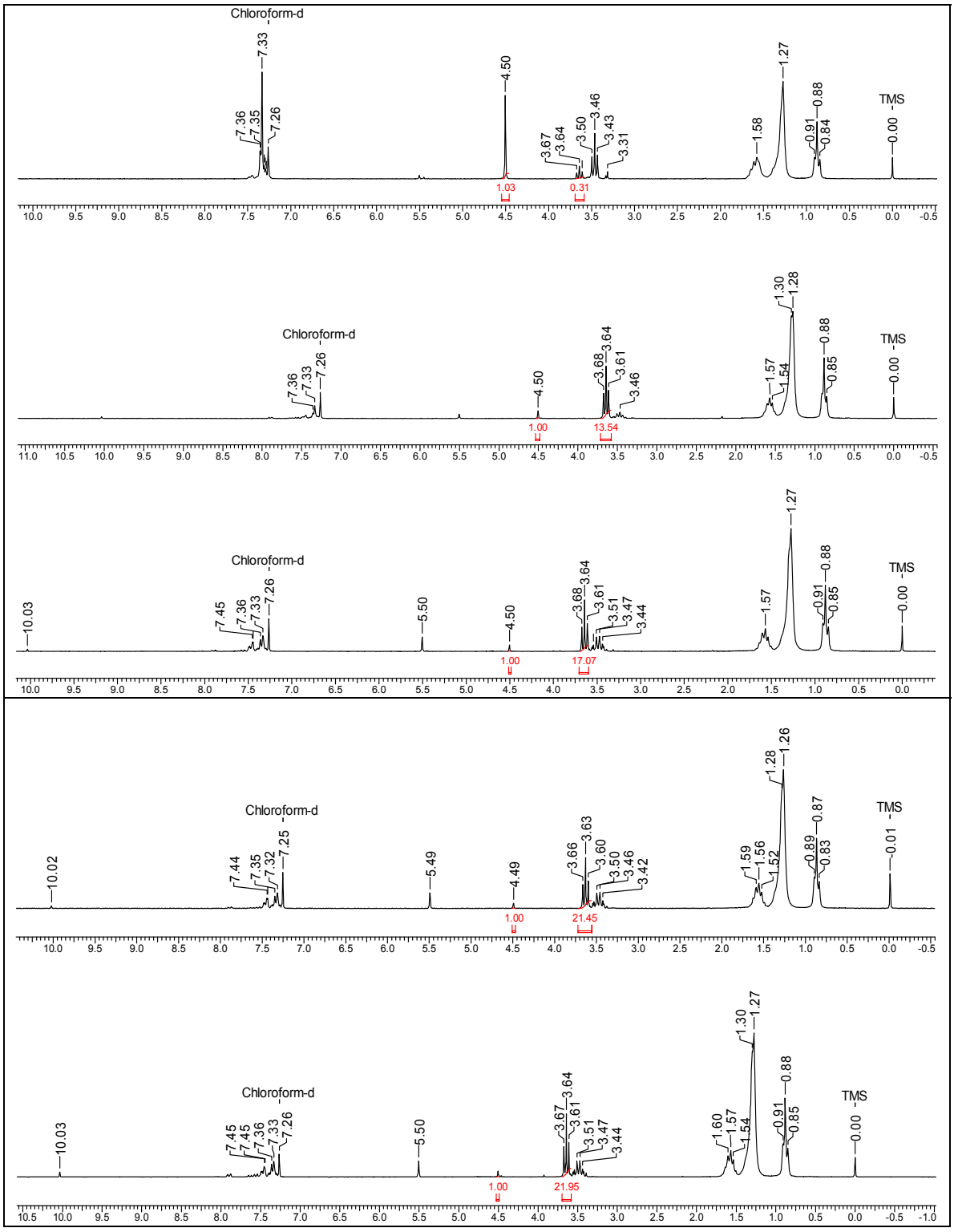

129.19
128.30
127.58
113.69
127.43
159.04
138.66
130.74
Chloroform-d
77.64
77.00
76.37
72.82
72.47
70.46
70.15
55.22
29.71
29.38
26.10
129.20
128.30
127.59
127.43
113.69
55.22
72.82
72.47
70.46
70.15
29.71
29.38
26.10


PBBO
OPBB
4
2.45
Chloroform-d
7.44
7.48
7.23
7.26
7.19
7.49
7.43
4.44
3.44
3.47
3.41
1.59
1.30
1.56
1.35
0.00
4.01
4.53
4.00
4.00
4.83
8.01

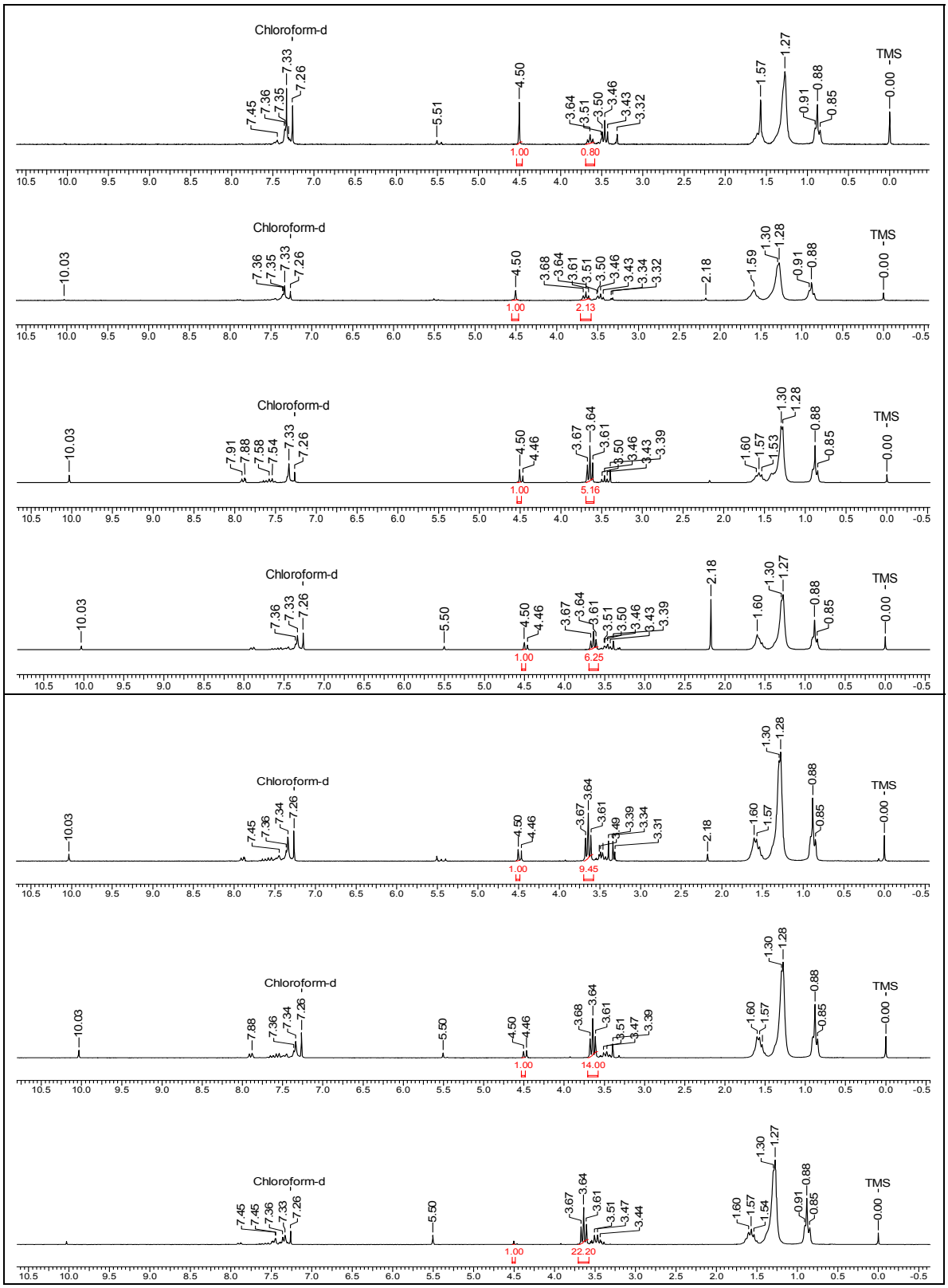

Chloroform-d
77.63
77.00
76.36
131.42
129.20
137.73
121.27
72.07
70.59
29.68
29.36
26.09
131.42
129.21
72.07
70.59
29.68
29.36
26.09


BnO
OMe
MeO
OBn
OMe
OBn
2.50
Chloroform-d
TMS
15.04
6.19
1.02
2.09
6.03
3.11

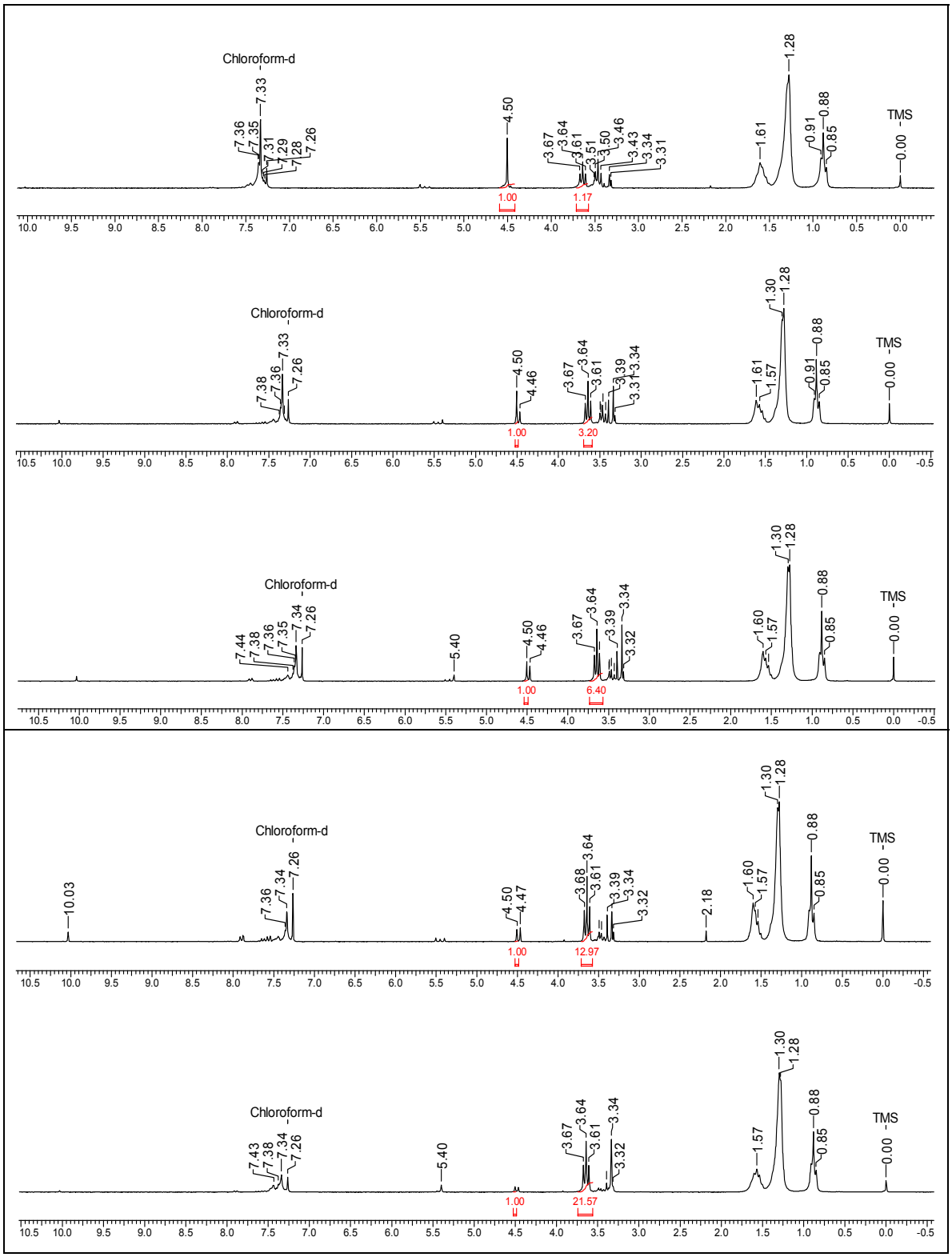

Chloroform-d
Chloroform-d



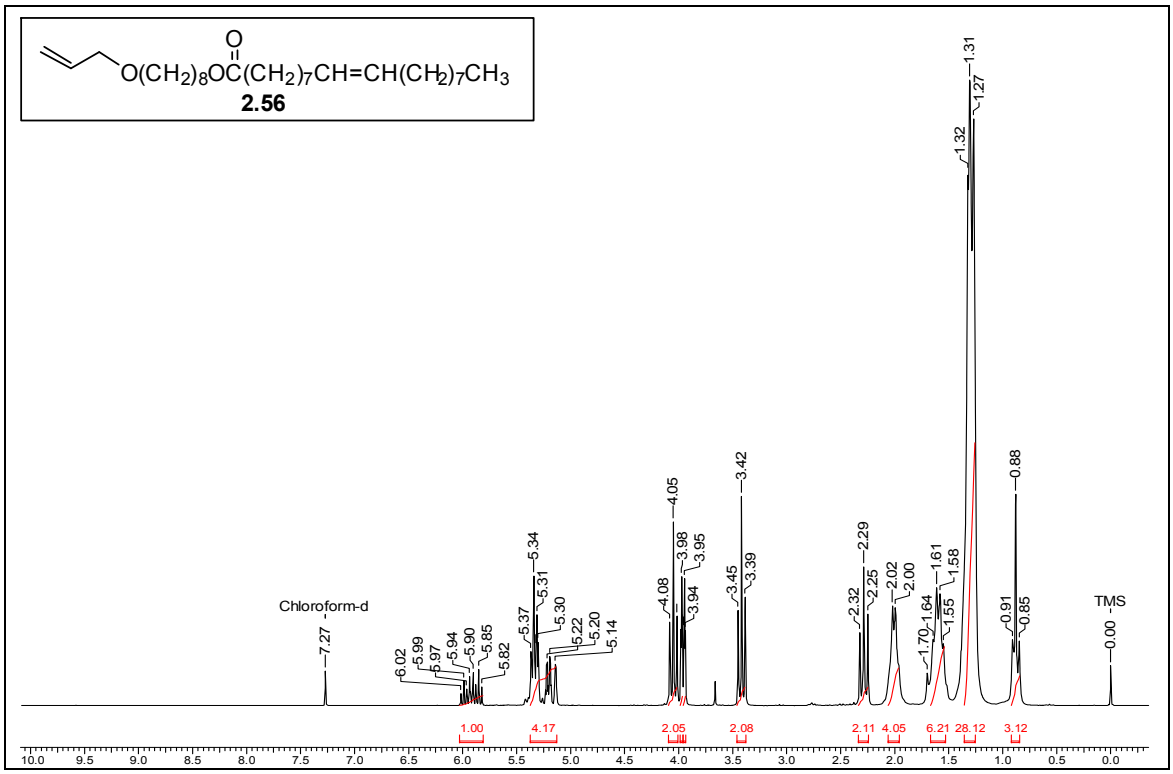

H1 NMR spectra of crude reaction mixture after the debenzylation of 1st batch of compound **2.48** with $Pd(OH)_2/C$. The spectra from top to bottom are taken at reaction timing 0.5, 1, 1.5, 2, 2.5 hrs respectivetly.




2nd Batch of **2.48** with the recovered catalyst, Specra from top to bottom are of crude reaction mixture at timing 1,2,3,4,5,6 and 7 hrs respectively.




3rd Batch of **2.48** with the recovered catalyst, Specra from top to bottom are of crude reaction mixture at timing 2,4,6,8,and 10 hrs respectively.


O(CH2)8OC(CH2)7CH=CH(CH2)7CH3
2.56
Chloroform-d
TMS
7.27
6.02
5.99
5.97
5.94
5.90
5.85
5.82
5.37
5.34
5.31
5.30
5.22
5.20
5.14
4.08
4.05
3.98
3.95
3.94
3.45
3.42
3.39
2.32
2.29
2.25
2.02
2.00
1.70
1.64
1.61
1.58
1.55
1.32
1.31
1.27
0.91
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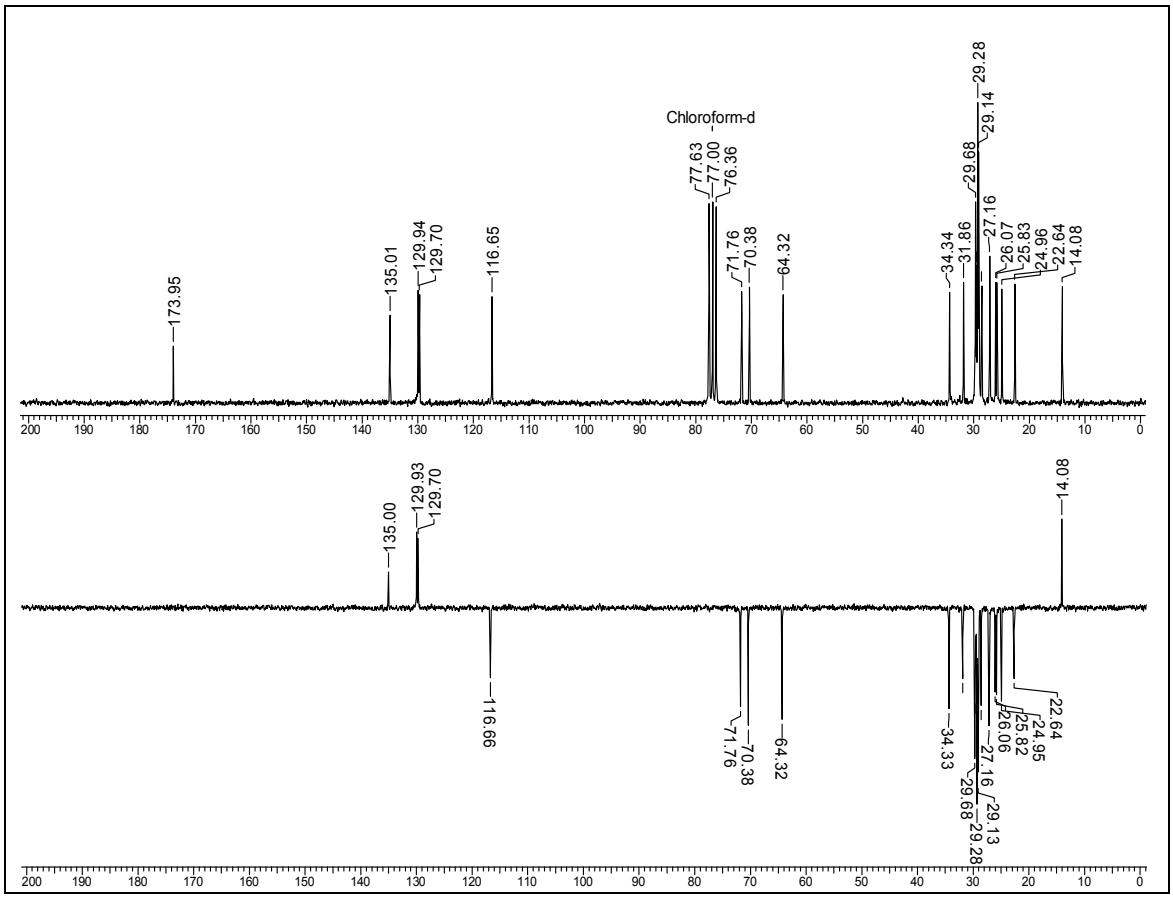
1.00
4.17
2.05
2.08
2.11
4.05
6.21
28.12
3.12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129.94
129.70
116.65
77.63
77.00
76.36
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34.34
31.86
29.68
29.28
29.14
27.16
26.07
25.83
24.96
22.64
14.08
135.00
129.93
129.70
116.66
71.76
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27.16
26.06
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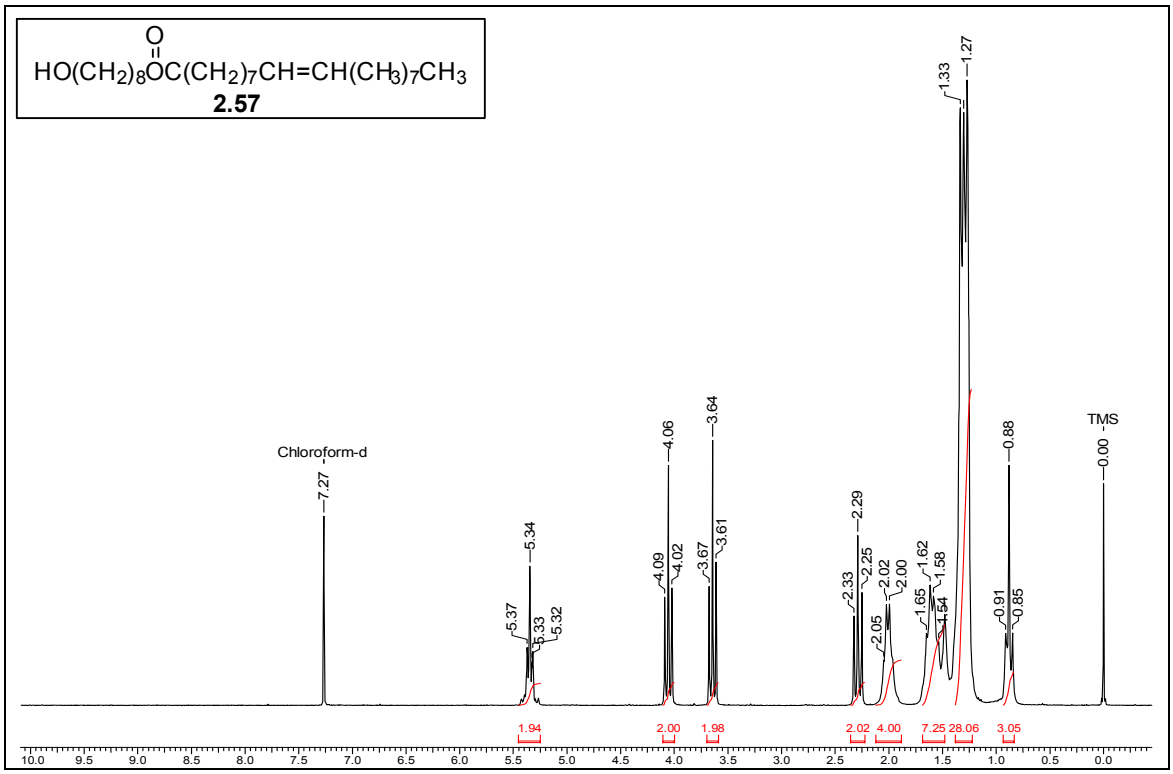
24.95
22.64
14.08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Chloroform-d
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5.34
5.33
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4.09
4.06
4.02
3.67
3.64
3.61
2.33
2.29
2.25
2.05
2.02
2.00
1.65
1.62
1.58
1.54
1.33
1.27
0.91
0.88
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2.02
4.00
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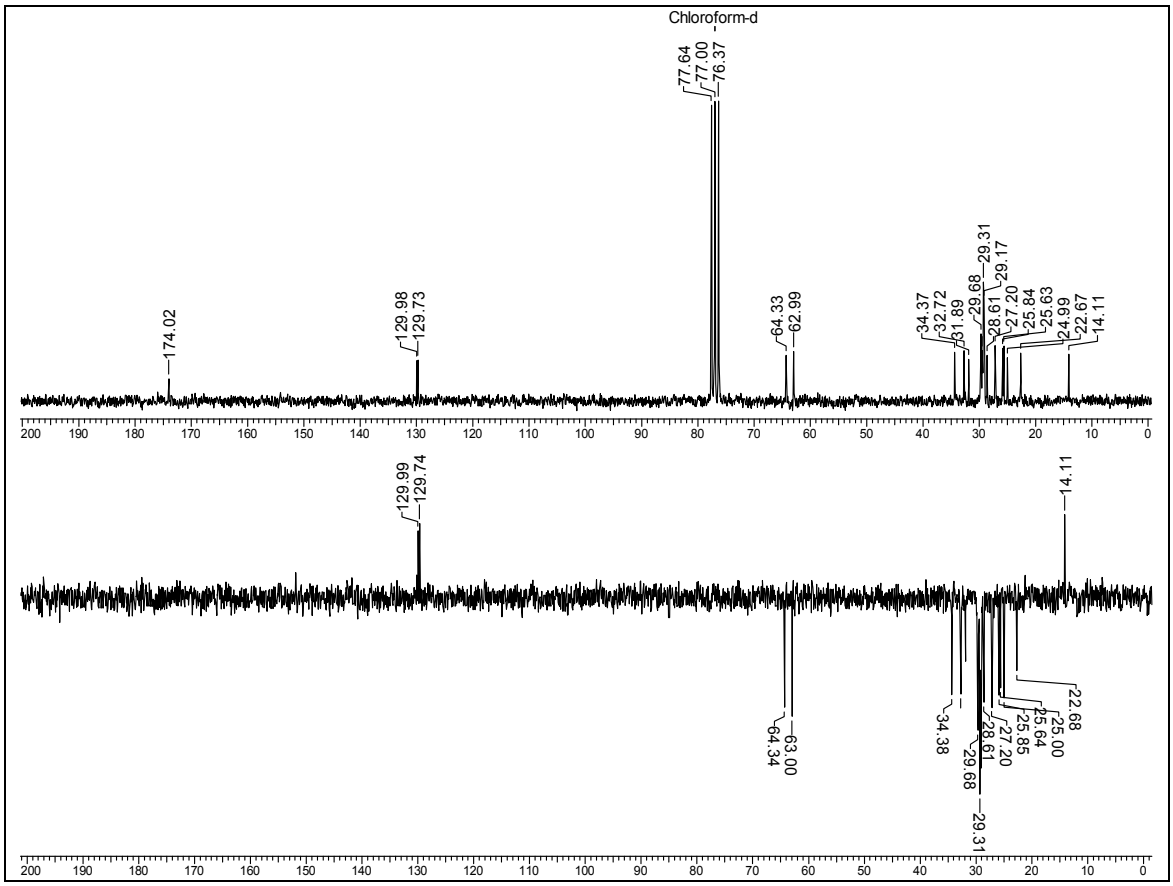
3.05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29.31
29.17
28.61
27.20
25.84
25.63
24.99
22.67
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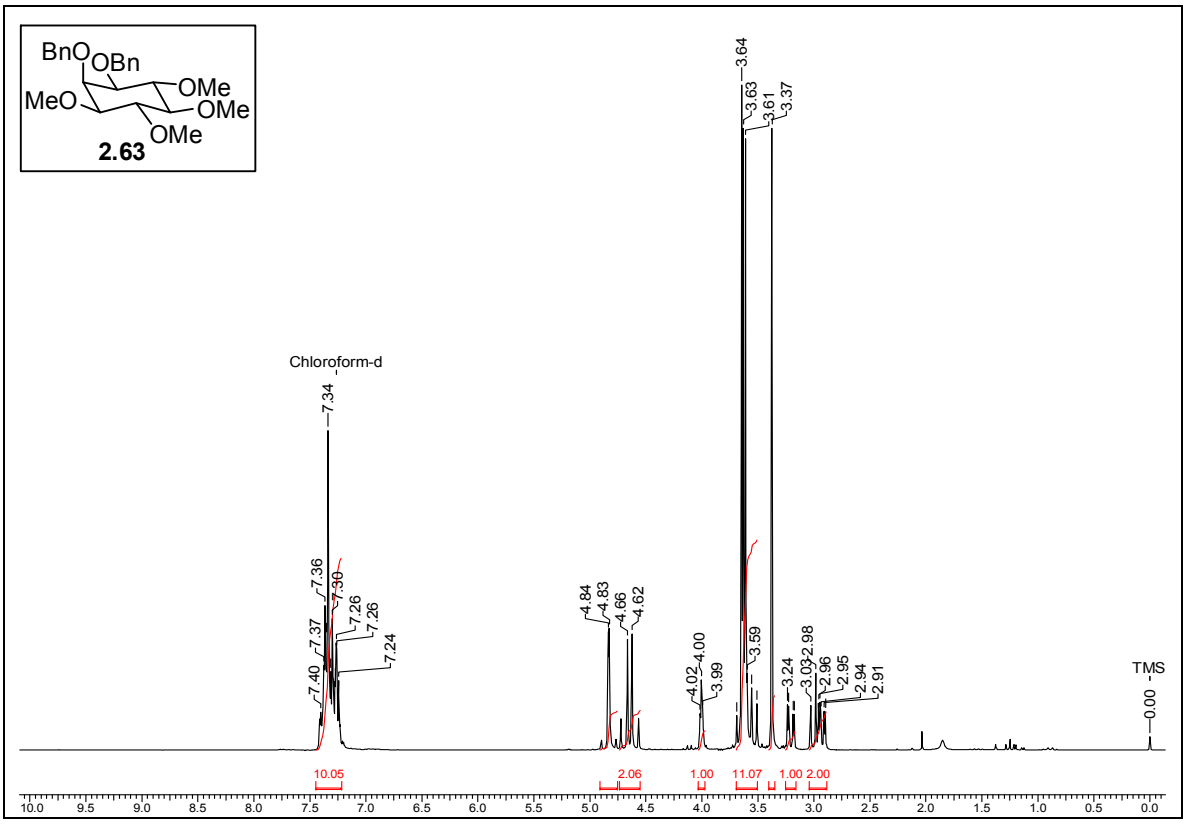
25.00
22.68
14.11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MeO
OMe
OMe
OMe
2.63
Chloroform-d
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7.26
7.24
4.84
4.83
4.66
4.62
4.02
4.00
3.99
3.64
3.63
3.61
3.59
3.37
3.24
3.03
2.98
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2.94
2.91
TMS
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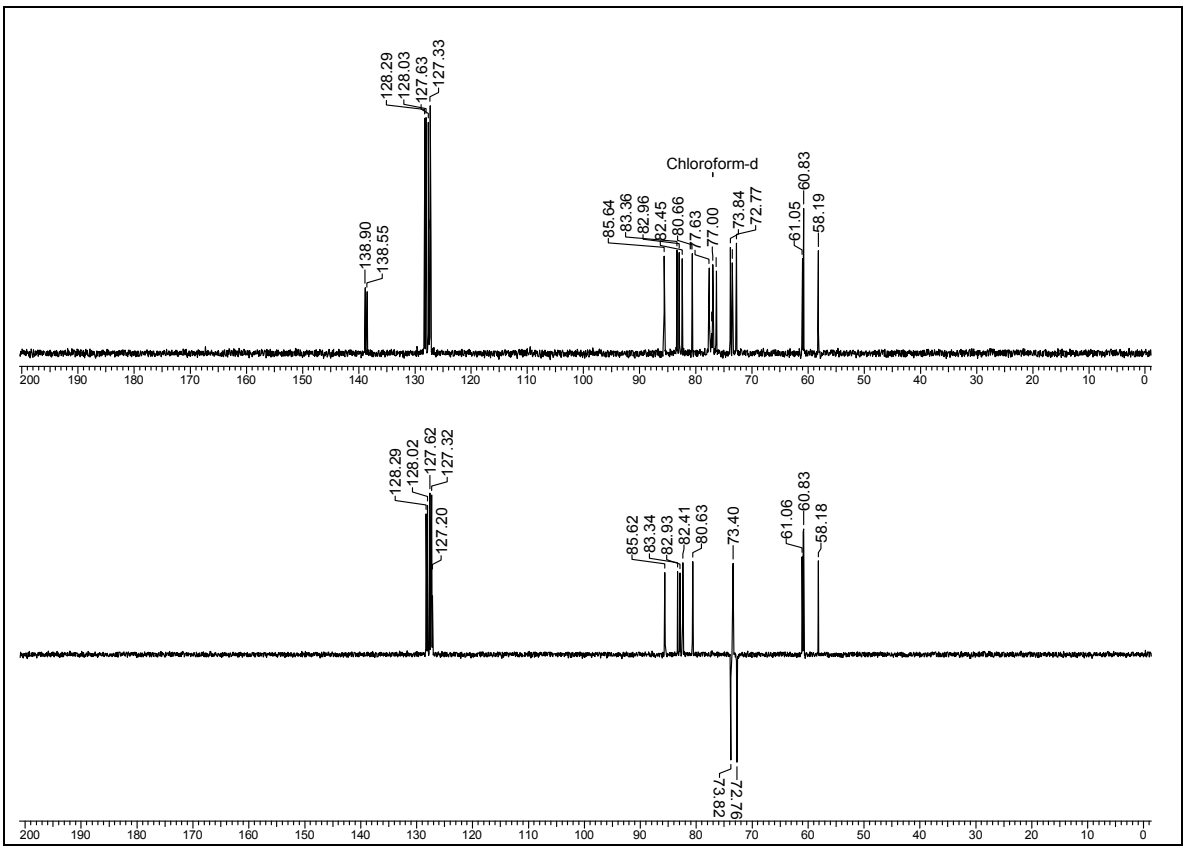
2.00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Chloroform-d
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127.32
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61.06
60.83
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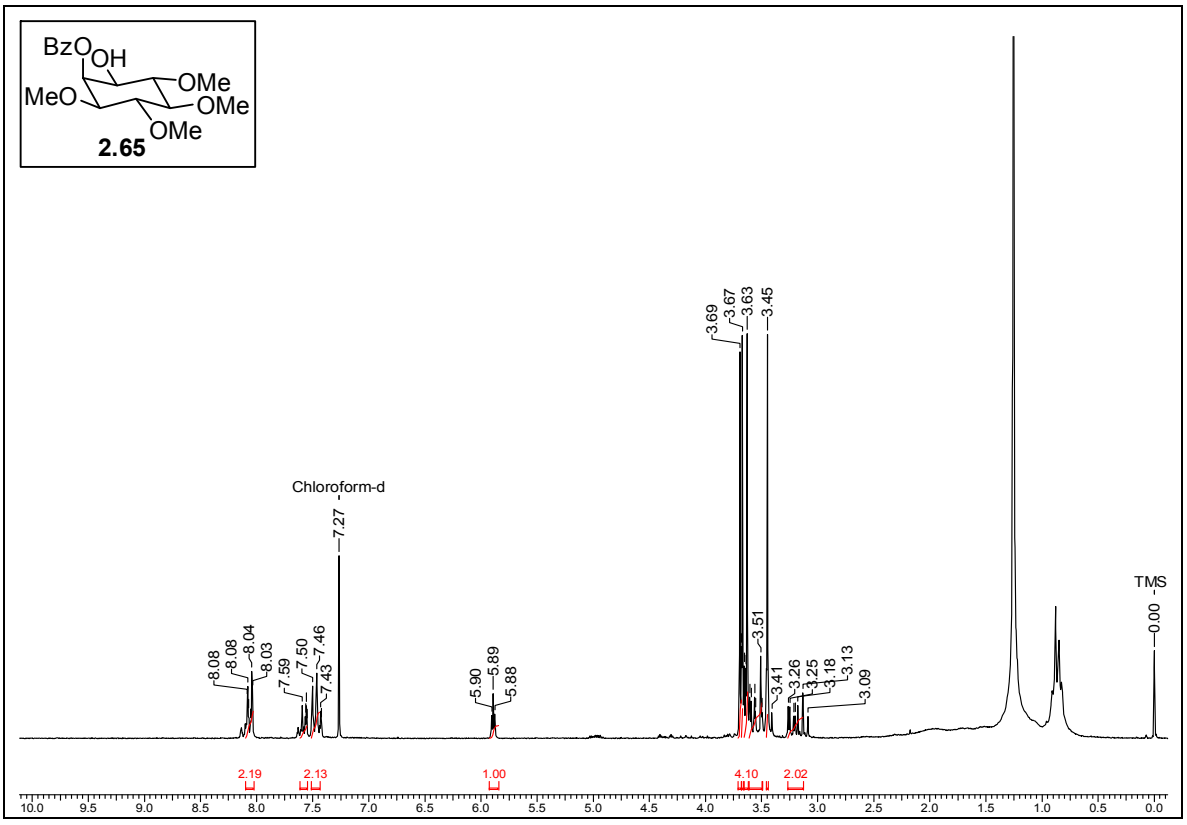
73.82
72.76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OMe
OMe
OMe
2.65
Chloroform-d
TMS
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8.08
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7.59
7.50
7.46
7.43
7.27
5.90
5.89
5.88
3.69
3.67
3.63
3.51
3.45
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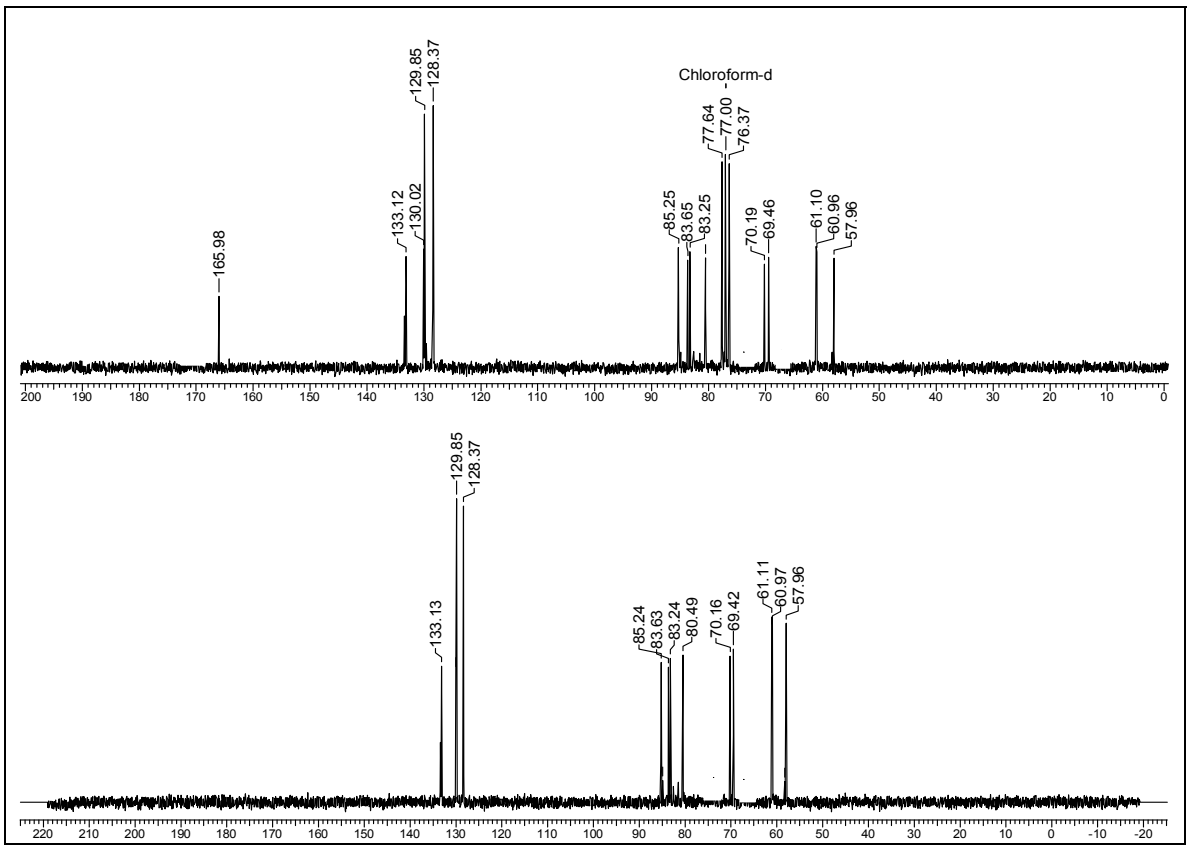
2.02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76.37
70.19
69.46
61.10
60.96
57.96
133.13
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83.24
80.49
70.16
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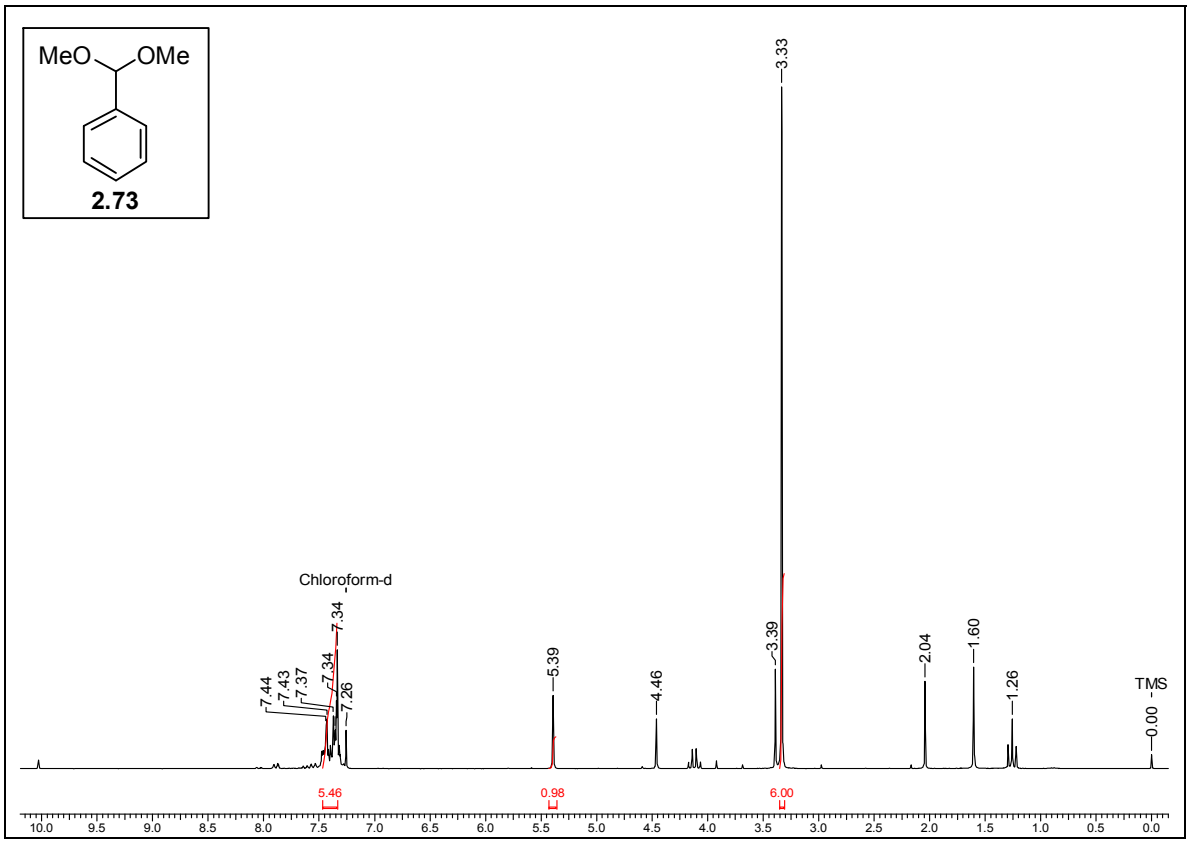
61.11
60.97
57.96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7.34
7.34
7.26
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TMS
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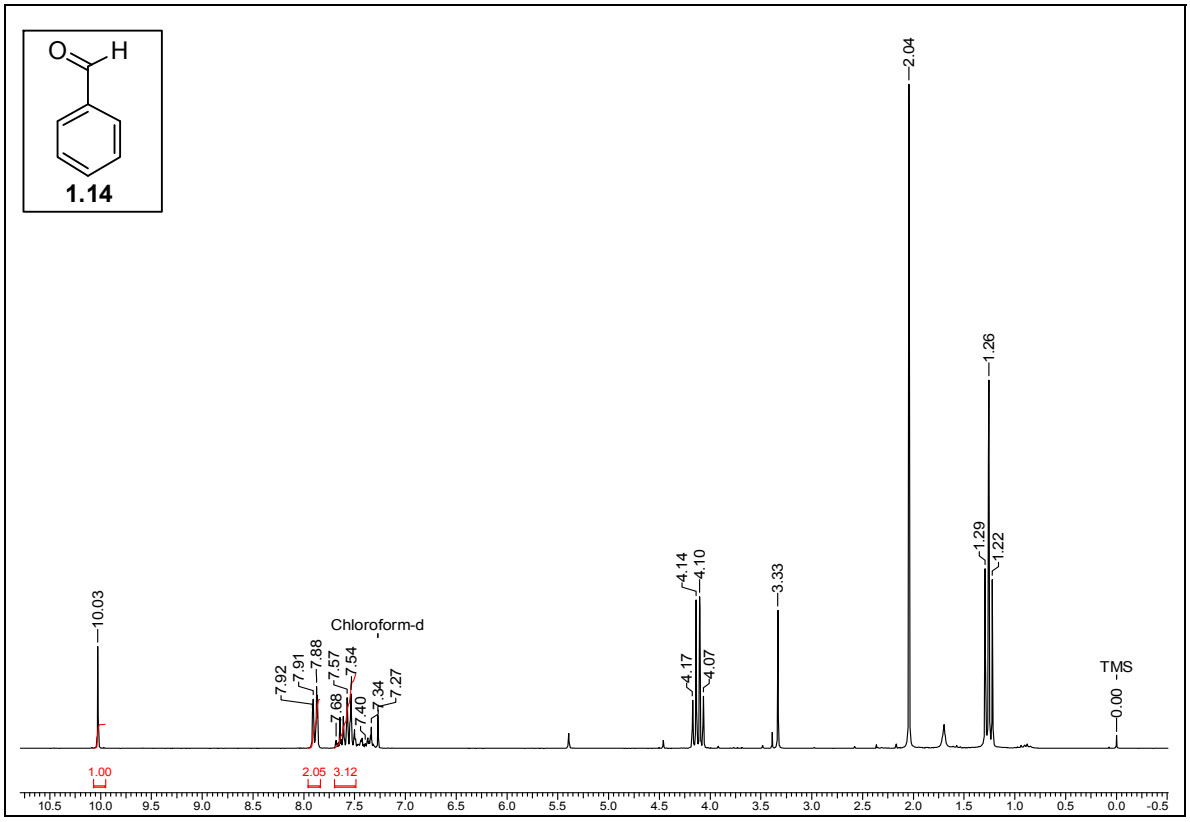
6.00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7.27
4.14
4.10
4.17
4.07
3.33
2.04
1.26
1.29
1.22
TMS
0.00
1.00
2.05
3.12

# Chapter 3

# Synthesis of biologically and synthetically important inositol derivatives.

## 3.1 Introduction

In the previous chapter, palladium(II) hydroxide mediated methods for the selective cleavage of ethers that are routinely used to mask hydroxyl groups during the synthesis of multifunctional organic compounds were developed. Comparison of these methods with previously reported methods for similar cleavage reactions indicated the possibility of the current method being more efficient and selective. Hence we proceeded to test the applicability of the palladium(II) hydroxide mediated ether cleavage reactions by actually using these conditions during the synthesis of certain inositol derivatives. Inositols carry six secondary hydroxyl groups which have more or less same reactivity and any synthesis starting from the commercially available *myo*-inositol requires extensive and selective protection – deprotection of the six hydroxyl groups. Hence synthesis of inositol derivatives is a good test to check the utility of the palladium(II) hydroxide mediated ether cleaving methods described in the previous chapter. A brief introduction to *myo*-inositol and its phosphorylated derivatives is given below to emphasize reasons for their resurrection in the contemporary literature.

### Inositols and phosphoinositols

Inositols are cyclohexane hexols. Nine isomers are known in the literature (Chart 3.1), among these *myo*-, *scyllo*- and *chiro*-isomers or their derivatives occur in nature, the *myo*-isomer (and its derivatives) being the most abundant. *myo*-Inositol **1.95** has one axial and five equatorial hydroxyl groups, in its most stable conformation. The carbon bearing the axial hydroxyl group is designated as C2 and the other ring carbons can be numbered from C1 to C6 starting from a C1 atom and proceeding around the ring in clockwise or anticlockwise fashion. According to convention, an anticlockwise numbering in asymmetrically substituted *myo*-inositol leads to the configuration with D-prefix and the clockwise numbering gives the substituted *myo*-inositol an L-prefix.

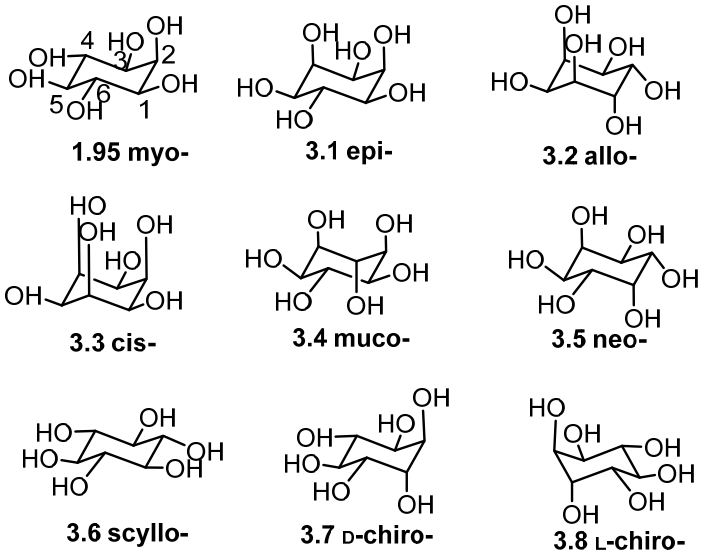



**Chart 3.1**

An IUBAC recommendation allowing all the biologically relevant compounds to be denoted as D-isomers has also been proposed[1] (Figure 3.1).

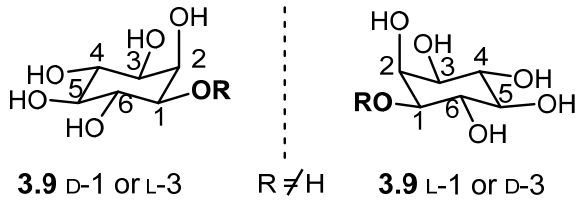



**Figure 3.1**: Ring atom numbering in unsymmetrical *myo*-inositol derivatives.

Although, many of the unsymmetrically substituted *myo*-inositol derivatives reported in this thesis are racemic, for clarity and simplicity they are represented in schemes by only one enantiomer. Optically inactive (racemic, *meso*) synthetic derivatives of inositol (other than phosphates) are numbered without prefixes, while optically active derivatives are numbered with a suitable prefix (**D**, **L**).

The presence of inositol in a plant lipid, soybean oil, was first reported by Klenk and Sakai in 1939[2] and plants were known to contain phytic acid (*myo*-inositol hexakisphosphate) prior to this discovery.[3] Inositol phospholipids are known to play a pivotal role in the cellular signal transduction pathways.[4] It is thought that perturbations in this signaling system might lead to diseases such as cancer, diabetes

etc.[5] An illustrative diagram depicting the various steps involved in the *myo*-inositol cycle is given in Figure 3.2.

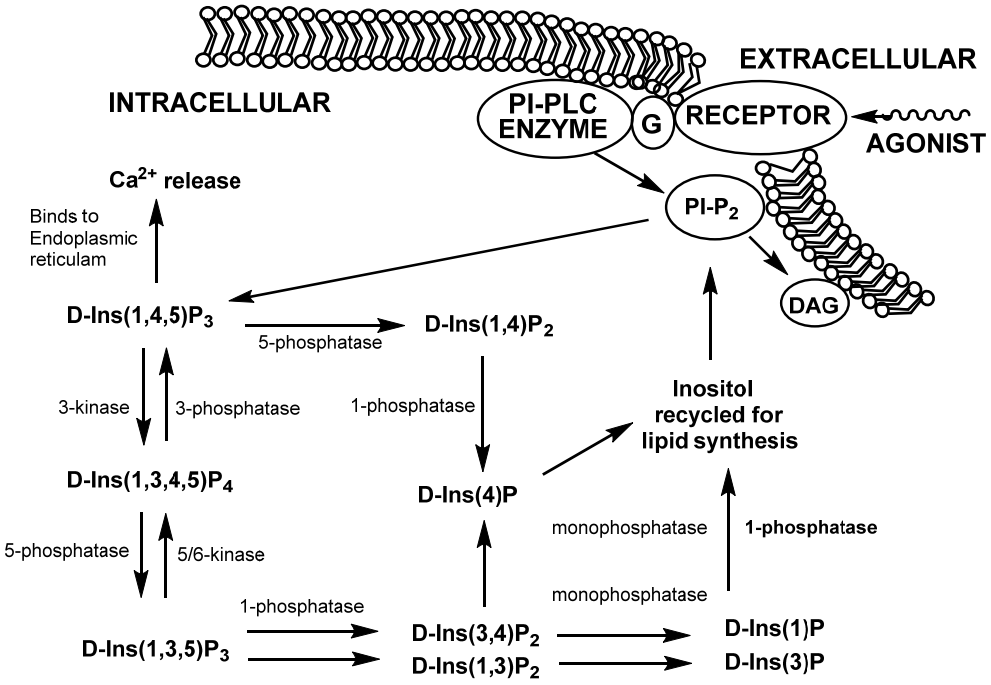
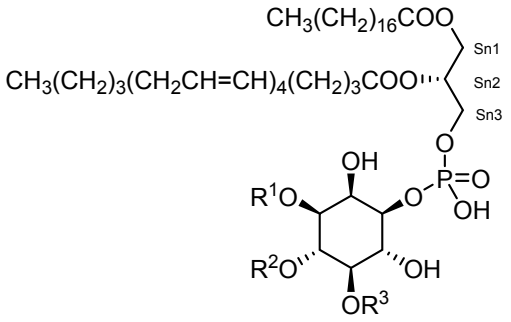



**Figure 3.2**: Transmembrane signaling by *myo*-inositol lipids and the *myo*-inositol cycle.

Activation of the membrane bound G protein due to an external stimulus (*via* membrane receptors) leads to hydrolysis of PtdIns(4,5)$P_2$ catalyzed by PtdIns(4,5)$P_2$-specific phospholipase C. This generates second messengers, D-Ins(1,4,5)$P_3$ (released to the cytosol) and the corresponding diacylglycerol (retained in the membrane) in the cell. The former component activates receptors on the endoplasmic reticulum resulting in the release of $Ca^{2+}$ ions. D-Ins(1,4,5)$P_3$ subsequently undergoes a series of metabolic steps to *myo*-inositol, which in turn is utilized for the synthesis of PtdIns (Figure 3.2).

Eight inositol lipids are recognized so far having specific role in the cellular signal transduction pathways (Figure 3.3). Most of these lipids are not available in sufficient quantities, for isolation from natural sources. Hence in order to aid a deep insight about the biological functions of inositol lipids, efficient synthetic methods for natural

lipids as well as their synthetic analogs have to be developed. Synthetic analogs could also be useful for the pharmacological intervention of the *myo*-inositol cycle.

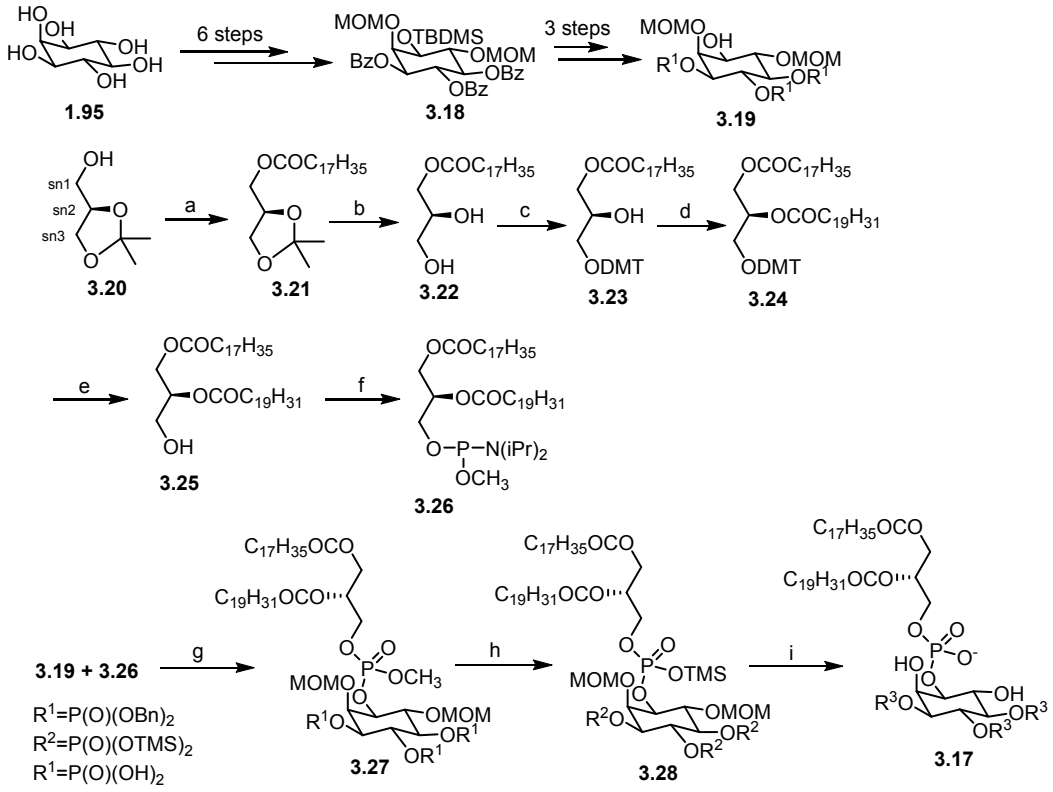



**3.10**; $R^1=R^2=R^3=H$; PI
**3.11;** $R^1=PO_3^{2-}$, $R^2=R^3=H$; PI-3-P
**3.12**; $R^2=PO_3^{2-}$, $R^1=R^3=H$; PI-4-P
**3.13**; $R^3=PO_3^{2-}$, $R^1=R^2=H$; PI-5-P
**3.14**; $R^1=R^2=PO_3^{2-}$, $R^3=H$; PI-3,4-$P_2$
**3.15**; $R^1=R^3=PO_3^{2-}$, $R^2=H$; PI-3,5-$P_2$
**3.16**; $R^2=R^3=PO_3^{2-}$, $R^1=H$; PI-4,5-$P_2$
**3.17;** $R^1=R^2=R^3=PO_3^{2-}$; PI-3,4,5-$P_3$

**Figure 3.3**: Inositol lipids involved in the cellular signal transduction pathways.

Davies and Malkin reported the first chemical synthesis of an inositol phospholipid, racemic 2,3-distearyl-glyceryl 2-*myo* inosityl phosphate.[6] Most of the earlier literature reports[7] pertain to the synthesis of inositol lipids containing saturated fatty acids; synthesis of naturally occurring inositol lipids was developed relatively recently.[8] This could be because synthesis of inositol containing phospholipids use benzyl protected phosphorylating agents which required their cleavage by catalytic hydrogenolysis, to generate the required phosphodiester. Carbon – carbon double bonds present in naturally occurring phospholipids do not tolerate catalytic hydrogenolytic conditions. Although non-hydrogenolytic cleavage of benzyl phosphates is known,[9] these are often not tolerant to other groups present in the head group of the lipids, especially in PIs and glycolipids. Another way of circumventing hydrogenolysis is the use of phenyl phosphates, from which free phosphate can be released under basic conditions. However carboxylic acid esters are not stable to these conditions and hence this procedure only allows the synthesis of ether lipids. Use of non-hydrogenolytic deprotection methods also require elaborate purification procedures to isolate the phospholipids, which compromises the yield (Scheme 3.1).

The major challenges faced in the synthesis of phosphoinositols are (i) regioselective protection of inositol hydroxyl groups; (ii) preparation of the required protected inositol derivative with high enantiomeric purity; (iii) selective deprotection




**Scheme 3.1**: a) stearic acid, DCC, DMAP; b) amberlyst-$H^+$, MeOH; c) DMT-Cl, pyridine; d) arachidonic acid, DCC, DMAP; e) TFA, pyrrole; f) Cl-P(OMe)(N*i*Pr$_2$), EtN*i*Pr$_2$; g) tetrazole, $Bu_4N^+ IO_4^-$ , DCM; h) $Me_3SiBr$ i) i) MeOH, ii) EtSH.

methods; (iv) efficient phosphorylation methods; (v) facile methods for the deprotection of phosphates and (vi) during the synthesis of inositol lipids, deprotection methods which leave the double bond and ester groups in the diacyl glycerol part, unaltered. Progress in the chemistry of inositols in the last three decades has helped achieve most of these requirements.[10] We are working on the last two synthetic aspects mentioned above. The method for the cleavage of ethers described in the previous chapter, circumvents such limitations since carbon – carbon double bonds (except O-allyl groups) and esters remained intact during ether cleavage with $Pd(OH)_2/C$. Hence we attempted to adopt the conditions of $Pd(OH)_2/C$ mediated cleavage of ethers for the cleavage of phosphate protecting groups and develop a methodology for synthetic access to naturally occurring phospholipids and phosphoinositols. Results of these experiments are presented below.

Cyclitols have also been used as starting materials for the synthesis of natural products and their analogs (other than phosphoinositols) having interesting biological and medicinal properties (Figure 3.4) Hence results described in this thesis are also useful during the synthesis of cyclitol based natural products and their analogs.

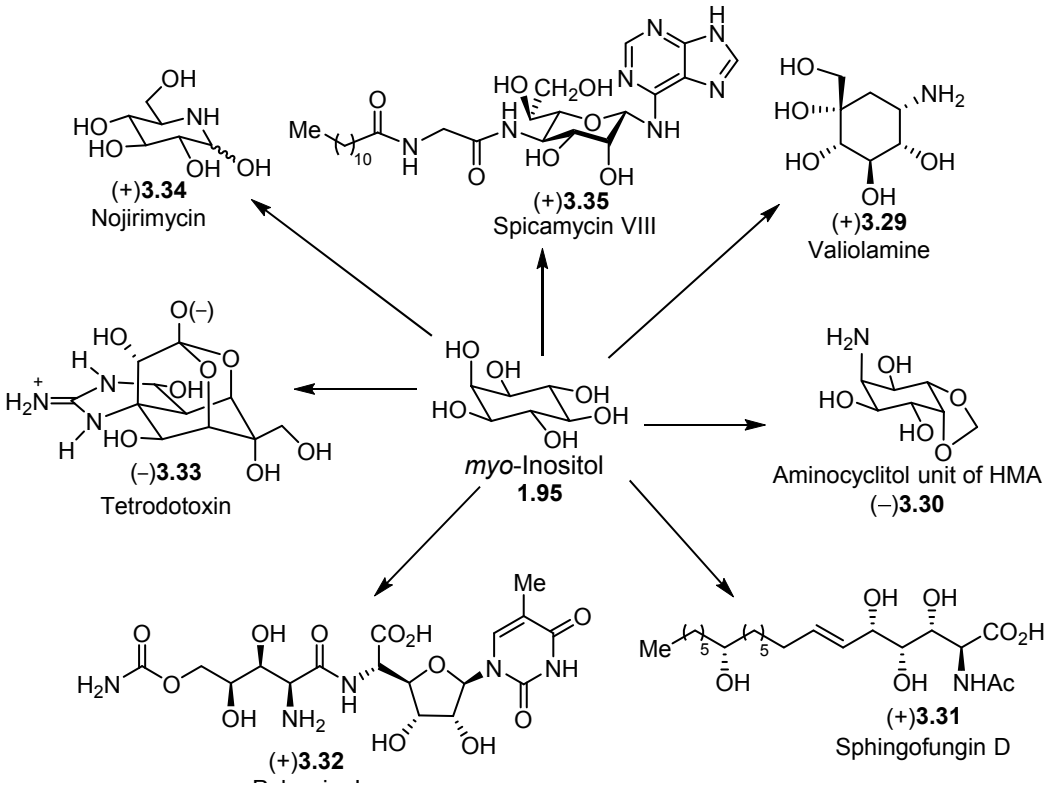


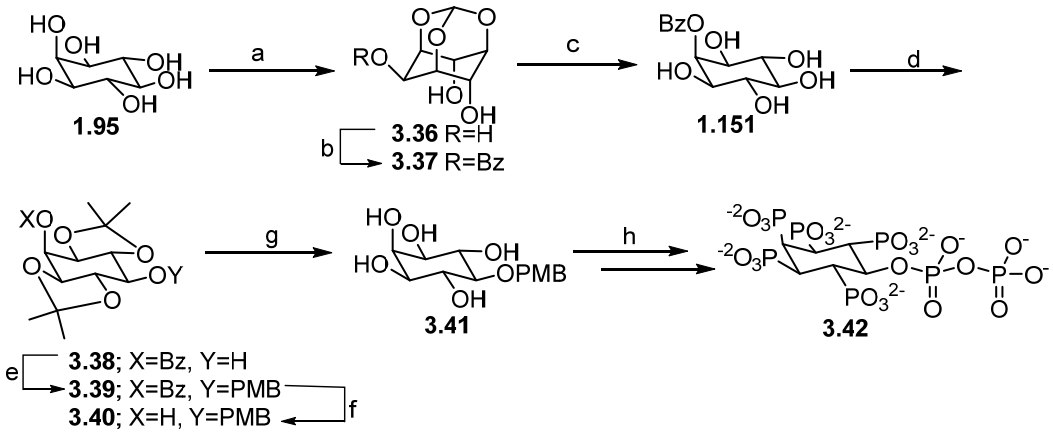

**Figure 3.4** Selected natural products synthesized from *myo*-inositol

## 3.2. Results and Discussions

### 3.2.1 Use of Pearlman's catalyst for the synthesis of a precursor for *myo*-inositol pyrophosphate.

Inositol pyrophosphates are well distinguished molecules due to the presence of high energy pyrophosphate bond which is capable of bringing about non-enzymatic phosphate transfer reactions. The biosynthesis of inositol pyrophosphates happens in eukaryotic cells by the action of several inositol hexakisphosphate kinases on *myo*-inositol hexakisphosphate. *myo*-Inositol pyrophosphates have been implicated in the control of several cellular processes such as endocytosis, chemotaxis, signal

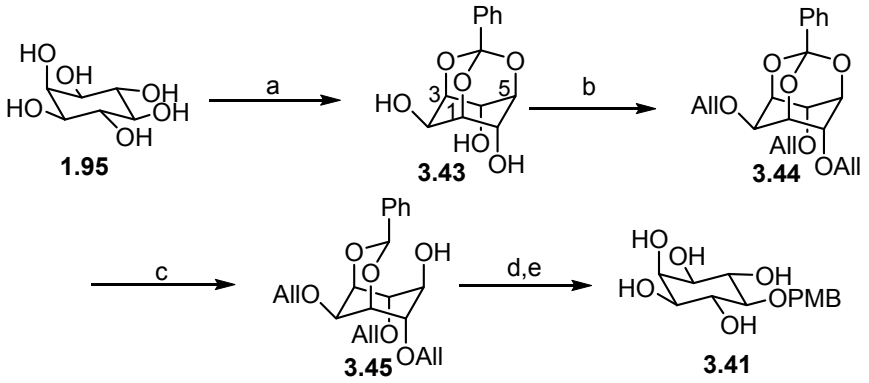
transduction,[11] insulin secretion,[12] cell death[13] and non enzymatic phosphorylation of proteins.[14] Recent studies revealed a relationship between the intracellular $IP_7$ (**3.42**, Scheme 3.2) content and insulin activity. This wide range of cellular functions underline the importance of the upcoming new efficient methods for the synthesis of inositol pyrophosphates. Prestwich *et al*[11b] synthesized the inositol pyrophosphate ($IP_7$) from *myo*-inositol through an intermediate, 5-O-*p*-methoxybenzyl-*myo*-inositol (**3.41**, Scheme 3.2).




**Scheme 3.2**: a) $HC(OMe)_3$, *p*-TsOH, DMF, 49%; b) BzCl, pyridine, 92%; c) HCl, MeOH, 100%; d) 2-methoxy propene, *p*-TsOH, DMF, 41%; e) PMBBr, BEMP, $CH_3CN$, 84%; f) NaOMe, MeOH, 82%; g) *p*-TsOH, acetone, $H_2O$, 79%; h) reported in Ref: 11b

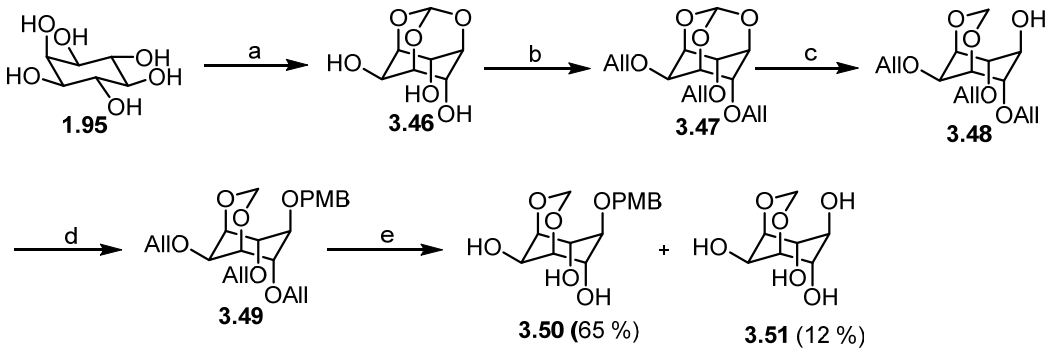
We utilized our methodology for the selective cleavage of ethers, for convenient access to the precursor **3.41** (Scheme 3.2) for *myo*-inositol pyrophosphate derivative **3.42** We had earlier shown that *myo*-inositol orthoesters and the *myo*-inositol-1,3-acetals are very good early intermediates for the synthesis of cycltiol derivatives.[15] Hence our synthesis started from *myo*-inositol orthobenzoate (Scheme 3.3). The triol **3.43** was allylated and the orthobenzoate moiety in **3.44** was cleaved selectively with DIBAL-H to release the C5-hydroxyl group.[16] *p*-Methoxybenzylation of the C-5 hydroxyl group in **3.45** followed by treatment of the ensuing PMB ether with $Pd(OH)_2/C$ in *iso*-propanol under reflux resulted in the release of all the hydroxyl groups, except the C5-hydroxyl group. The pentol **3.41** was obtained in an overall

yield of 45%. The earlier reported method[11b] provided the same precursor in a yield of 10% in 7 steps from *myo*-inositol.




**Scheme 3.3**: a) $(MeO)_3CPh$, CSA, DMSO, 80 $^oC$, 5 h, 89%; b) NaH, AllBr, DMF, rt, 3 h, 94%; c) DIBAL-H, DCM, rt, 2 h, 69%; d) NaH, PMBCl, DMF, rt, 2 h; e) $Pd(OH)_2/C$, $^iPrOH$, reflux, 2 h, 78% (aggregate yield for two steps).

We initially tried to synthesize the PMB ether **3.41** *via myo*-inositol orthoformate**3.46**.

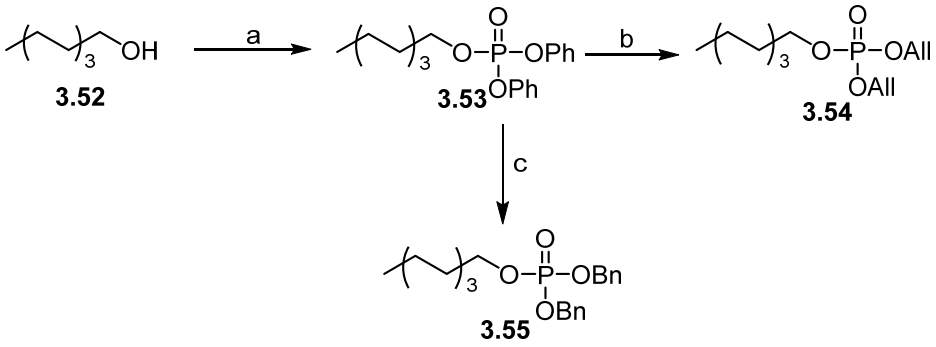



**Scheme 3.4**: (a) $(EtO)_3CH$, TsOH, DMF, 110 $^oC$, 4 h, 88%. (b) NaH, AllBr, DMF, rt, 2 h, 86%. (c) DIBAL-H, DCM, 2 h, 86%. (d) NaH, PMBCl, DMF, rt, 2 h, 92%. (e) $Pd(OH)_2/C$, 2-PrOH, reflux, 3 h.

But the methylidine 1,3-acetal obtained after the DIBAL-H cleavage of the orthoformate was rather stable under the $Pd(OH)_2/C$ cleavage conditions. We observed preferential cleavage of the allyl ethers and partial cleavage of the PMB ether (in **3.49**) rather than the desired cleavage of the methylidine 1,3-acetal. This methylidine acetal appears to be unusually stable in spite of the fact that the inositol ring in **3.49** does not have the normal (equatorial rich) chair conformation.[17]

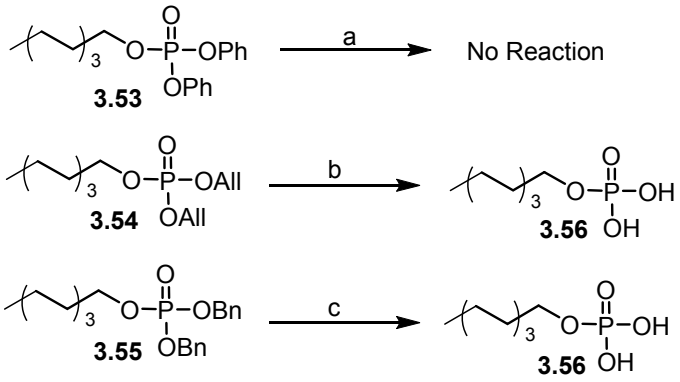
### 3.2.2. Use of Pearlman's catalyst for the synthesis of phospholipids

The utility of results described in the previous chapter was demonstrated by the efficient synthesis of a precursor for *myo*-inositol pyrophosphate. In light of these results we wondered whether Pearlman's catalyst is capable of cleaving alkyl phosphates. We postulated that the ability or inability of the Pearlman's catalyst to cleave alkyl phosphates could be exploited for the synthesis of phospholipids, as carboxylic acid esters were stable to the ether cleavage conditions (as discussed in Chapter 2). With this line of thought, we tested the ability of Pearlman's catalyst to cleave a few phosphotriesters, relevant to phospholipid synthesis.




**Scheme 3.5**: a) $(PhO)_2POCl$, pyridine, rt, overnight, 89%; b) NaH, AllOH, DMF, rt, overnight, 62%; c) NaH, BnOH, DMF, rt, overnight, 60%.

The phosphates **3.54** and **3.55** were prepared from the diphenyl phosphate **3.53** by nucleophilic substitution of the phenoxy group with allyl and benzyl alcohols

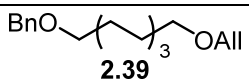
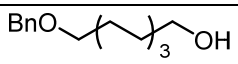
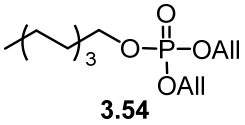
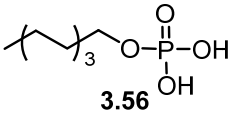
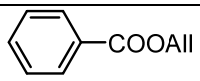
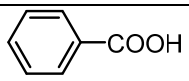
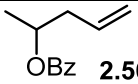
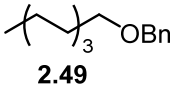
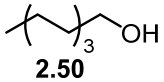


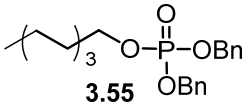
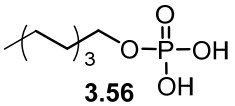

**Scheme 3.6**: a) $Pd(OH)_2/C$, MeOH, reflux, 24 h; b) $Pd(OH)_2/C$ + Pd/C, $^{i}$PrOH, reflux, 2 h, 97%; c) $Pd(OH)_2/C$, MeOH, reflux, 3.5 h, 99%.

respectively. The yields were moderately good. The products obtained, after chromatographic purification as well as the diphenyl phosphate **3.53** were subjected to cleavage by $Pd(OH)_2/C$ (Scheme 3.6) in separate experiments.

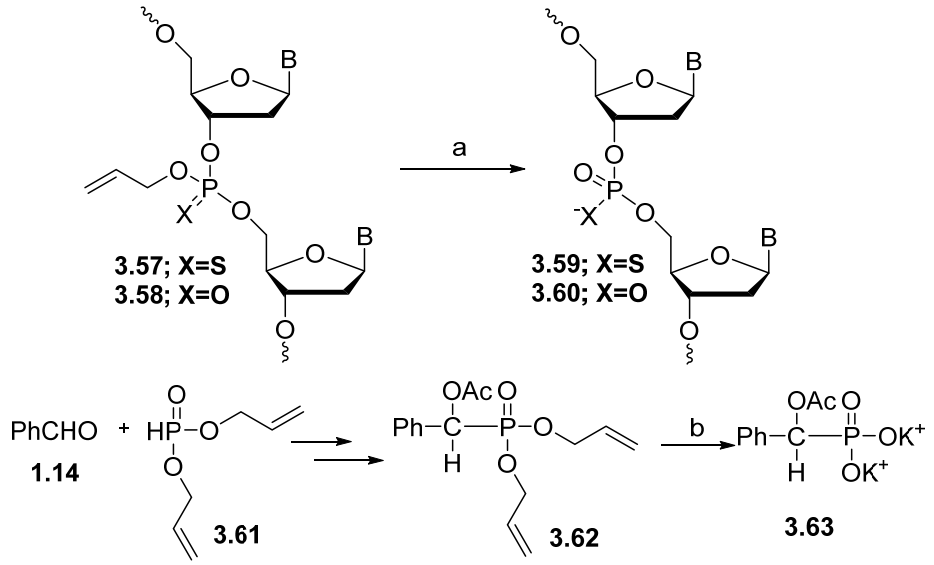
These experiments revealed that the facility of cleavage of allyl and benzyl phosphates with $Pd(OH)_2/C$ is as good as that of the corresponding ethers. A mixture of $Pd(OH)_2/C$ and Pd/C was used for the cleavage of the allyl phosphate since this mixture allowed the use of catalytic amounts of palladium reagent, as discussed earlier (see chapter 2). The allyl phosphate is more labile than benzyl phosphate under the reaction conditions shown in Scheme 3.6, but the phenyl phosphate (in **3.53**) was intact even after treating with $Pd(OH)_2/C$ for a long time under comparable conditions.

**Table 3.1**: A Comparison of $Pd(OH)_2/C$ mediated ether / phosphotriester cleavage conditions relevant to phospholipid synthesis.

| Entry | Substrate | Reaction Conditions | Product (Yied %) |
|---|---|---|---|
| 1 |  **2.39** | Catalytic Pd, $^{i}$PrOH, reflux, 30 min |  **2.40** (92%) |
| 2 |  **3.54** | Catalytic Pd, $^{i}$PrOH, reflux, 2 h |  **3.56** (97%) |
| 3 |  **2.16** | $Pd(OH)_2/C$ (70 mol%), MeOH, reflux, 8 h. |  **2.29** (82%) |
| 4 |  **2.56** | $Pd(OH)_2/C$ (50 mol%), methanol, relux, 6 h | No reaction |
| 5 |  **2.49** | $Pd(OH)_2/C$ (50 mol%), MeOH, reflux, 3h |  **2.50** (90%) |

| | | | |
|---|---|---|---|
| 6 |  **3.55** | $Pd(OH)_2/C$ (90 mol%), MeOH, reflux, 3.5 h |  **3.56** (99%) |

Hence, these procedures could be useful for the development of efficient synthetic routes for compounds containing phosphate groups, such as phospholipids and glycolipids. This is especially since the cleavage reaction is carried out more or less




**Scheme 3.7**: a) 2% $HOCH_2CH_2SH$, conc $NH_4OH$; b) 3% $Pd(PPh_3)_4$, 4-5% $PPh_3$, potassium 2-ethyl hexanoate, ethyl acetate.

under neutral conditions and there are reports showing the propensity of the acid catalyzed migration of phosphate groups between hydroxyl groups.[18] Although the use of benzyl group for the protection of phosphates is frequently encountered during the synthesis of organo-phosphates,[7a,8a] there are reports on the use of allyl group for the protection of phosphates during the synthesis of α-acetoxy phosphonates and oligonucleotides. (scheme 3.7)[19]

The purity of the product is an important aspect in organic synthesis especially in pharmaceutical industry. To ensure that there is not much metal contamination in the products after the $Pd(OH)_2/C$ catalyzed ether cleavage, we carried out the ICP analysis of few crude samples after the deprotection (Table 3.2). Owing to the simple work up procedure of filtration of the sample, there are more chances of the product to

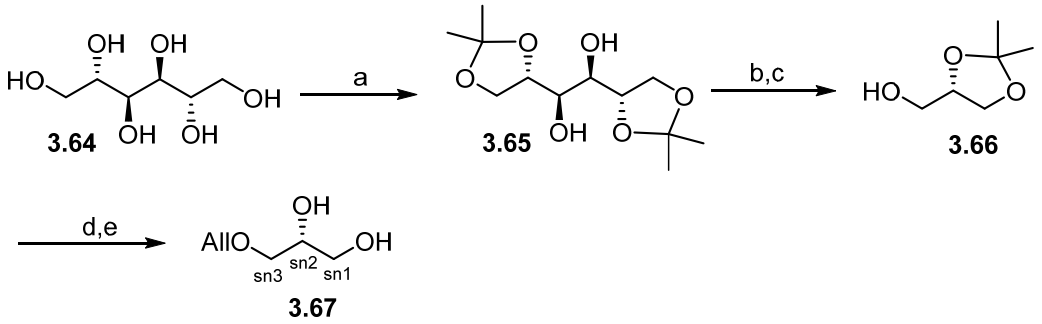
get contaminated with the metal. However, the results obtained indicated that the amount of palladium leached out even after the use of 50 mol% $Pd(OH)_2/C$ was about 1 ppm or less.

**Table 3.2**: ICP analysis of the product samples after the cleavage of ethers by $Pd(OH)_2/C$.

| **Reaction** | **Reagent used** | **Leached Pd (ppm)** |
|---|---|---|
| $HO(CH_2)_8OBn \longrightarrow OH(CH_2)_8OH$ **2.40** **2.27** | 50 mol% $Pd(OH)_2/C$ | 1.01 |
| $CH_3(CH_2)_7OPO(OAll)_2 \longrightarrow CH_3(CH_2)_7OPO(OH)_2$ **3.54** **3.56** | 10 mol% Pd/C+10 mol%$Pd(OH)_2/C$ | 0.09 |

**Preparation of diacylglycerols**

There are several literature reports on the use of benzyl or *p*-methoxybenzyl groups during the synthesis of diacyl glycerols.[20] But we used the allyl group for the protection of the glycerol hydroxyl group during the preparation of diacylglycerol (Scheme 3.8), since our earlier experiments had shown (Table 3.1) that allyl ethers are

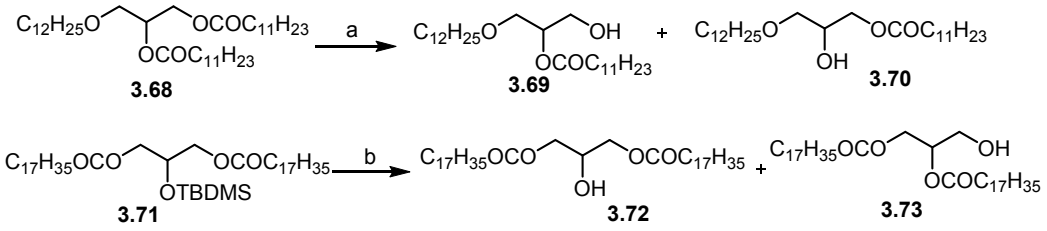



**Scheme 3.8**: a) 2,2-dimethoxy propane, TsOH, DMSO, rt, 16 h, 67%; b) $NaIO_4$/silica, DCM, rt, 1 h; c) $NaBH_4$, MeOH, rt, 5 h, 81%; d) NaH, AllBr, DMF, rt, 3 h; e) TsOH, MeOH, reflux, 3 h, 88%.

more labile than benzyl ethers and substituted benzyl ethers for cleavage with $Pd(OH)_2/C$.

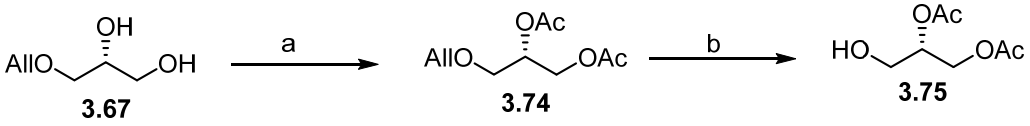
S(+)-1,2-isopropylideneglycerol (**3.66**) commonly known as Solketal was synthesized by the oxidative cleavage of mannitol diacetonide **3.65** and subsequent sodium borohydride reduction of the aldehyde obtained. O-allylation of 1,2-isopropylideneglycerol followed by deprotection of the ketal resulted in 3-O-allyl-*sn*-glycerol (**3.67**), which could be used for the preparation of diacylglycerol.

Before proceeding with the preparation of diacylglycerol, we wanted to make sure that the acyl groups in diacylglycerol do not migrate under the conditions of $Pd(OH)_2/C$ mediated ether cleavage. There are instances of the ester group migration under acidic as well as in basic conditions (Scheme 3.9).[21]




**Scheme 3.9**: a) TRIS buffer (pH=8), lipase, $CaCl_2$, Na-deoxycholate, 2h, 40 $^oC$, purification by chromatography over silica; b) $nBu_4NF$,THF, rt, 10 min.

Lipase catalyzed hydrolysis of the diester **3.68** resulted in the formation of only the primary alcohol **3.69**. Subsequent purification of this diacylglycerol by silica gel chromatography resulted in the formation of a mixture of both the possible diacylglycerols (**3.69** and **3.70**). This showed that acyl migration between the vicinal OH groups of glycerol is feasible even in the presence of silica (a very weak acid). Hence we prepared the diacetate **3.74** and subjected it to allyl ether cleavage with $Pd(OH)_2/C$ and obtained the diacetate **3.75** (Scheme 3.10).




**Scheme 3.10**: a) $Ac_2O$, pyridine, DMAP, rt, overnight, 85%; b) $Pd(OH)_2/C$+Pd/C, MeOH, reflux, 9 h, 97%.

A comparison of the $^{1}$H NMR spectra (Figure 3.5) of **3.74** and **3.75**(even after several hours of heating with $Pd(OH)_2/C$ and Pd/C mixture) did not indicate migration of the acetyl groups. This is confirmed by the comparison of the $^{1}$H spectra of **3.75** with that of 1,3- diacetyl glycerol reported by Magnusson and Haraldsson, where the acetyl

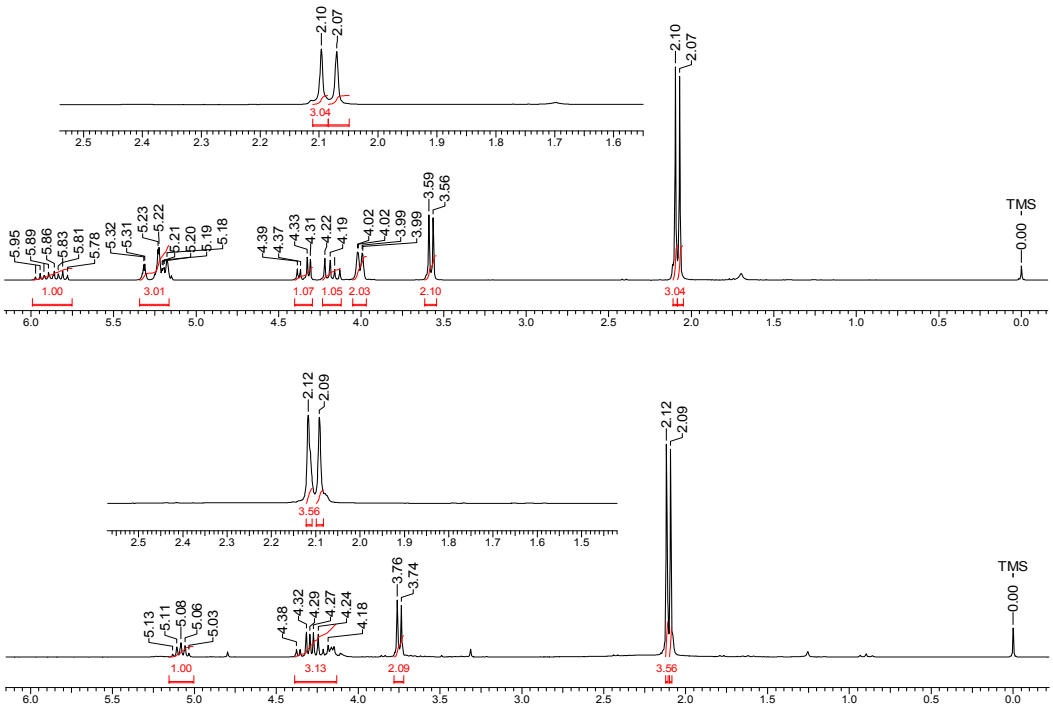
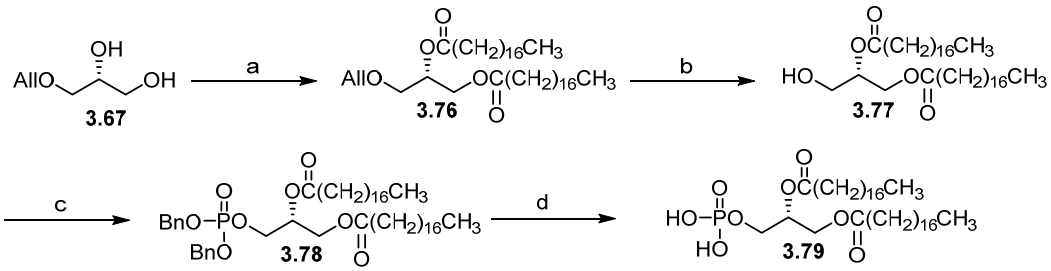



**Figure 3.5**: Comparison of the $^{1}$H NMR spectra of **3.75** and **3.76** (obtained under conditions b as in scheme 3.10).

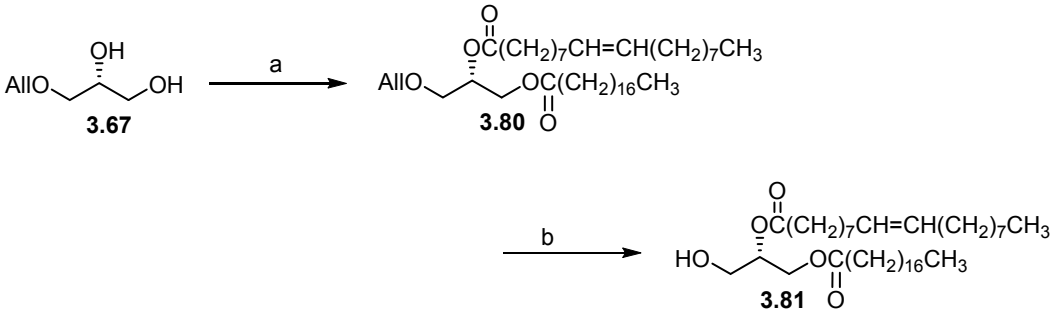
protons show a singlet at δ 2.10.[22] The ratio of integrals of the aetyl methyl group in **3.74** and **3.75** was 1:0.96 and 1: 0.92 respectively. Had there been migration of the acetyl group, this ratio would not have remained unaltered. Since the acetyl groups do not migrate in the presence of $Pd(OH)_2/C$, it is unlikely that $Pd(OH)_2/C$ brings about migration of the larger fatty acyl groups during the synthesis of lipids. The O-allyl glycerol **3.67** was acylated with stearic acid in the presence of DCC to obtain the distearate **3.74**. The allyl ether in **3.74** was cleaved using $Pd(OH)_2/C$ in methanol to obtain the diacyl glycerol **3.75**. Phosphorylation of **3.75** was achieved using dibenzyl(N,N-diisopropyl) phosphoramidite followed by oxidation with *m*CPBA. The dibenzyl phosphate was subjected to debenzylation conditions with $Pd(OH)_2/C$ to

ensure the adaptability of this ether cleaving method for the synthesis of phospholipids. Although we could obtain the phosphatidic acid **3.77** in good yield, the cleavage of benzyl phosphate in **3.78** took longer than anticipated.



**Scheme 3.11**: a) stearic acid, DMAP, DCC, DCM, rt, 10 h, 76%; b) $Pd(OH)_2/C$, MeOH, reflux, 3 h, 94%; c) (i) 1H-tetrazole, $(BnO)_2$-P-N(*i*pr)$_2$; (ii) *m*CPBA, DCM, rt, 4 h, 93%; d) $Pd(OH)_2/C$, 2-PrOH, reflux, 74 h, 82%.

This result gave us confidence to proceed with the synthesis of phospholipids containing unsaturated fatty acyl group at the sn-2 position, as in naturally occurring lipids (Scheme 3.1). The sequential acylation at positions 1 and 2 (of *sn*-3-glycerol) was achieved by the O-acylation of the allyl glycerol **3.67** with stearic acid and oleic acid in succession, using DCC as the coupling agent (Scheme 3.12). It was important to ensure a gradual increase in temperature from -5 $^oC$ to room temperature to achieve good selectivity as per the reported procedure.[20b] The allyl ether in **3.80** was cleaved using $Pd(OH)_2/C$ to obtain the diacylglycerol **3.81**. Although the allyl ether in **3.80** could be cleaved completely in 12 h in refluxing *iso*-propanol (81 $^oC$), it gave rise to another unidentified product. Hence the step 'b' in scheme 3.12 was carried out at a

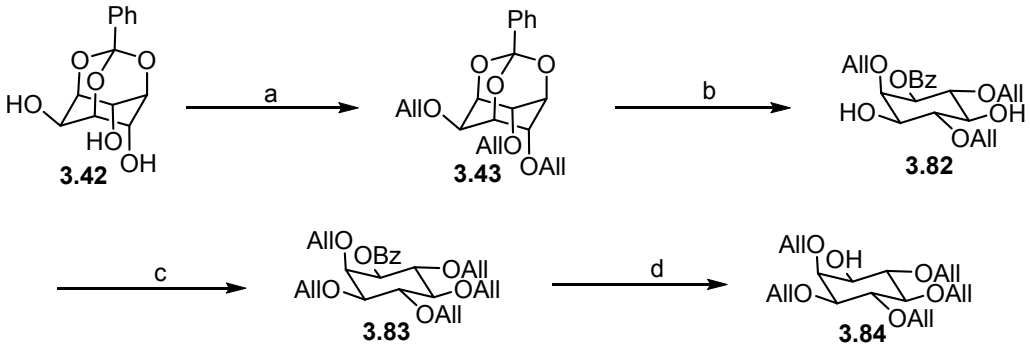


**Scheme 3.12**: a) i) Stearic acid, DCC, DMAP, DCM, -5 $^oC$, 1 h; ii) Oleic acid, DCC, DMAP, DCM, rt, 2 h, 88%; b) $Pd(OH)_2/C$, 2-PrOH, 60 $^oC$, 17 h, 90%.

lower temperature (60 $^{o}$C) to obtain **3.81** as a single product (although this led to increase in the reaction time).

**Preparation of a penta-allyl ether of *myo*-inositol.**

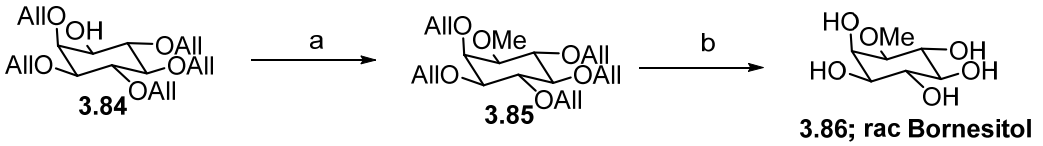
The racemic penta-allyl ether **3.84** of *myo*-inositol, having the C1-hyroxyl group free was prepared from the orthobenzoate **3.42** (Scheme 3.13). The triol **3.42** was O-allylated and the orthobenzoate moiety in the resulting triether was hydrolyzed using aqueous TFA to obtain the corresponding racemic C1-benzoate **3.82** of *myo*-inositol. Exclusive formation of the C1-benzoate on hydrolysis of *myo*-inositol orthobenzoate is reported earlier.[23]The diol **3.82** was allylated in the presence of silver(I) oxide to obtain the corresponding penta ether **3.83**. Alkaline hydrolysis of the benzoate in **3.83** provided the racemic penta-allyl ether **3.84** required for phosphatidylinositol synthesis.




**Scheme 3.13**: a) NaH, AllBr, DMF, rt, 2 h, 88%; b) TFA:Water (3:1), 100 $^{o}$C, 5 h, 89%; c) $Ag_2O$, AllBr, DMF, 32 h, rt, 76%; KOH, MeOH, rt, 2 h, 94%.

We prepared racemic bornesitol (1-*O*-methyl inositol, **3.86**) from the penta allyl inositol **3.84**, to make sure that all the five allyl ethers in an inositol derivative can be cleaved without a hitch. This is because, release of five hydroxyl groups in an inositol derivative converts a completely hydrophobic molecule (such as **3.85**) to a hydrophilic molecule (such as **3.86**). Hence the starting allyl ether and the resulting polyol end product have opposite solubility characteristics. Furthermore, the intermediates involved in this reaction could have intermediate hydrophobicity or hydrophilicity (and hence a range of solubility) as compared to the starting material and the product. These factors could affect the facility and efficiency of the

(penta)ether cleavage reaction under heterogeneous conditions (especially if any of the intermediate or the products precipitate out of the reaction mixture). However, smooth conversion of **3.85** to **3.86** illustrates that concerns as above might not limit the utility of Pearlman's Catalyst for the synthesis of inositol lipids.




**Scheme 3.14**: a) NaH, MeI, DMF, rt, 3 h, 82%; b) $Pd(OH)_2/C$+Pd/C, MeOH, reflux, 26 h, 97%

Various research groups[24] have solved the problem in getting the differentially protected enantiomerically pure inositol using different approaches such as either by using enantio-pure natural precursors such as D-glucose, quinic acid etc or by the separation of diastereomers of inositol conjugates with chiral auxiliaries. So for the synthesis of enantiomerically pure natural lipid one can follow any of these procedures. But in our synthesis we didn't give much focus on the preparation of optically active inositol. Hence for the demonstration of our method we synthesized a racemic inositol derivative **3.85** in which all the five hydroxyl groups except the C1-hydroxyl group are protected with allyl groups as shown in the scheme 3.13.

To synthesize PI s from the synthons we made (**3.81**, **3.84**), one can follow the same procedure as in Scheme 3.1 (steps f & g). Then the protected PIs can be deprotected in a single step by using our deprotection strategy.

### 3.3. Conclusions

We prepared the two synthons (racemic 2,3,4,5,6-penta-O-allyl-*myo*-inositol and enantiomeric *sn3*-diacyl glycerol) essential for the preparation of phosphatidylinositol. During the course of these syntheses the ether cleaving (elaborated in previous chapters) and (benzyl and allyl) phosphate cleaving ability of palladium(II) hydroxide was exploited. Control reactions performed with the two synthons illustrate that the ligation of these two synthons *via* a phosphodiester linkage

to complete the synthesis of phosphatidylinositol is possible. Unfortunately, we could not complete this step due to paucity of time. However, the results presented in this chapter do enable other chemists to utilize these reactions for the synthesis of phospholipids.

## 3.4. Experimental

### 2,4,6-tri-*O*-allyl-*myo*-inositol-1,3,5-orthobenzoate (3.44)

Sodium hydride (0.53 g, 13.15 mmol) was added to a solution of **3.43**[25] (0.70 g, 2.63 mmol) in dry DMF (10 mL) at 0 $^{o}$C and stirred for 15 min. Allyl bromide (0.80 mL, 9.20 mmol) was added drop wise to the reaction mixture under inert atmosphere then the reaction mixture was allowed to warm up to ambient temperature and the mixture stirred for 3 h. The reaction mixture was concentrated under reduced pressure and the residue obtained was worked up with ethyl acetate. The crude product was purified by column chromatography (eluent: 14 % ethyl acetate in light petroleum) to afford **3.44** as a colorless solid (0.95 g, 94 %).

**Mp.** = 55.3-57.3 $^{o}$C; **$^{1}$H NMR** ($CDCl_3$, 200 MHz): δ 7.60-7.71 (m, 2H, Ar H), 7.29-7.39 (m, 3H, Ar H), 5.81-6.12 (m, 3H, allylic CH=C), 5.16- 5.42 (m, 6 H, 3× allylic $=CH_2$), 4.48- 4.57 (m, 3H, Ins H), 4.36-4.44 (m, 2H, Ins H), 4.08- 4.25 (m, 6H, 3× allylic $OCH_2$), 3.94- 4.00 (m, 1H, Ins H) ppm; 137.23 ($C_{arom}$), 134.87 (allylic CH=), 134.24 (allylic CH=), 129.41 ($C_{arom}$), 127.96 ($C_{arom}$), 125.44 ($C_{arom}$), 117.53 (allylic $=CH_2$), 73.77 (Ins C), 72.04 (Ins C), 70.73 (allylic $OCH_2$), 70.51 (allylic $OCH_2$), 69.00 (Ins C), 66.50 (Ins C) ppm. **Elemental analysis** calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78; Found: C, 68.50; H, 6.42 %.

### 1,3-*O*-benzylidene-2,4,6-tri-*O*-allyl-*myo*-inositol (3.45)

DIBAL-H (8.54 mL of a 1M solution in toluene, 8.54 mmol) was added to a solution of **3.44** (1.5 g, 3.88 mmol) in dry DCM (15 mL) at 0 $^{o}$C under argon atmosphere. The mixture was stirred at rt for 2 h, poured into a rapidly stirred cooled solution of sodium potassium tartrate (40 g in 75 mL of $H_2O$) and saturated aq. $NH_4Cl$ (60 mL). Excess DCM (150 mL) was added and stirred overnight and the aqueous layer was then separated and extracted with DCM, organic layers were combined and dried over anhy. sodium sulphate. The solvent was evaporated under reduced pressure and the crude product purified by flash column chromatography (eluent: 16 % ethyl acetate in light petroleum) to afford **3.45** as a colorless crystalline solid (69 %).

**Mp.** = 45.5–47.5 $^{o}$C; **IR** ($CDCl_3$): $\bar{\nu}$ 3196–3622 cm$^{-1}$; **$^{1}$H NMR** ($CDCl_3$, 200 MHz): δ 7.46-7.60 (m, 2H, Ar H), 7.29-7.45 (m, 3H, Ar H), 5.80-6.15 (m, 3H, 3× allylic

CH=), 5.73 (s, 1H, $PhHCO_2$), 5.15-5.47 (m,6H, 3× allylic $=CH_2$), 4.05-4.34 (m, 10H, 3× allylic $OCH_2$, 2× Ins H), 3.96 (d, 2H, 2× Ins H, *J* = 8.46 Hz), 3.68-3.81 (m, 1H, Ins H), 3.53 (t, 1H, Ins H, *J* = 2.4 Hz), 2.73 (d, 1H, OH, *J* = 2.27 Hz) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): 137.94 ($C_{arom}$), 134.55 (allylic CH=), 133.98 (allylic CH=), 129.42 ($C_{arom}$), 128.43 ($C_{arom}$), 126.56 ($C_{arom}$), 118.14 (allylic $=CH_2$), 117.50 (allylic $=CH_2$), 92.85 (PhCH), 81.33 (Ins C), 73.63 (Ins C), 73.51 (Ins C), 70.73 (allylic $OCH_2$), 69.92 (allylic $OCH_2$), 67.98 (Ins C) ppm.**Elemental analysis** calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27; Found: C, 67.81; H, 6.90 %.

**5-*O*-(4-methoxy)benzyl *myo* inositol (3.41)**

Sodium hydride (0.047 g, 1.20 mmol) was added to a cooled (0 $^oC$) solution of **3.45** (0.31 g, 0.80 mmol) in dry DMF (3 mL) and stirred for 15 min. PMBCl (0.13 mL, 0.96 mmol) was added drop wise to the stirred solution and stirring continued for 2 h. The reaction mixture was worked up using ethyl acetate. The gummy crude product obtained after the evaporation of ethyl acetate was used for next step without purification.

The crude product obtained above (0.25g) and $Pd(OH)_2/C$ (20 wt %, 0.55 g) were refluxed in 2-propanol (3 mL) for 1.5 h. The reaction mixture was filtered through a short bed of Celite and the Celite washed with several portions of 1:1 mixture of $H_2O$ and methanol. The combined washings was evaporated under reduced pressure. Repeated washing of the residue with ethyl acetate (3×5 mL) afforded **3.41** as a colorless solid (0.12 g, 78 %). **Mp**. = 238–241 $^oC$.

**1,3-*O*-Methylidene-2,4,6-tri-*O*-allyl-*myo*-inositol (3.48)**

DIBAL-H (4.82 mL of a 1M solution in toluene, 4.82 mmol) was added to a solution of **3.47**[26] (0.60 g, 1.93 mmol) in dry DCM (15 mL) at 0 $^oC$ under argon atmosphere. The mixture was stirred at rt for 2 h, poured into a rapidly stirred cooled solution of sodium potassium tartrate (15 g in 25 mL of $H_2O$) and saturated aq. $NH_4Cl$ (20 mL). Excess DCM (60 mL) was added and stirred overnight and the aqueous layer was then separated and extracted with DCM, organic layers were combined and dried over anhy. sodium sulphate. The solvent was evaporated under reduced pressure and the

crude product purified by flash column chromatography (eluent: 40 % ethyl acetate in light petroleum) to afford **3.48** as a gum (0.52 g, 86%).

**$^1$H NMR** ($CDCl_3$, 200 MHz): δ 5.77–6.06 (m, 3H, allylic CH), 5.49 (d, 1H, C*H*$HO_2$, *J* =4.9 Hz), 5.15–5.40 (m, 6H, =$CH_2$), 4.69 (d, 1H, CH*H*$O_2$, *J* =4.9 Hz), 4.33–4.42 (m, 2H, Ins H), 4.05–4.20 (m, 7H, $OCH_2$, Ins H), 3.93 (t, 2H, Ins H, *J* =3.0 Hz), 3.79–3.87 (m, 1H, InsH), 2.99 (d, 1H, OH, *J*= 9.6 Hz) ppm.

**5-*O*-(4-methoxy)benzyl-1,3-*O*-Methylidene-2,4,6-tri-*O*-allyl-*myo*-inositol (3.49)**

To a solution of **3.48** (0.20 g, 0.64 mmol) in dry DMF (5 mL) sodium hydride (0.04 g, 0.96 mmol) was added at 0 $^oC$ and stirred it for 10 min. *p*-Methoxy benzyl chloride (0.11 mL, 0.77 mmol) was added drop wise to the reaction mixture under cold condition, stirred it for 2 h at rt. The solvents were evaporated under reduced pressure and the crude reaction mixture was worked up with ethyl acetate. The organic layer was dried over anhy. sodium sulphate and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Eluent: 20 % ethyl acetate in light petroleum) to afford **3.49** (0.25 g, 92%) as a colorless oil.

**$^1$H NMR** ($CDCl_3$, 200 MHz): δ 7.25–7.35 (m, 2H, Ar H), 6.84–6.92 (m, 2H, Ar H), 5.80–6.09 (m, 3H, allylic CH), 5.16–5.39 (m, 6H, =$CH_2$), 5.09 (d, 1H, C*H*$HO_2$, *J* =5.8 Hz), 4.84 (d, 1H, C*H*$HO_2$, *J* =5.8 Hz), 4.68 (s, 2H, $OCH_2$), 3.99–4.19 (m, 8H, $OCH_2$, Ins H), 3.83–3.89 (m, 2H, Ins H), 3.81 (s, 3H, $OCH_3$), 3.66 (t, 1H, Ins H, *J* = 2.0 Hz), 3.48–3.58 (m, 1H, Ins H) ppm.

**Reaction of 3.49 with $Pd(OH)_2$/C**

A solution of **3.49** (0.19 g, 0.44 mmol) in 2-propanol (5 mL) was refluxed with $Pd(OH)_2$/C (0.67 g) for 2 hrs. The reaction mixture was filtered through a short bed of Celite. The Celite bed was washed with excess methanol and the filtrate was concentrated under reduced pressure. The products obtained were separated by gradient elution to obtain **3.50** (0.09 g, 65%; eluent: 80% ethyl acetate in light petroleum) and **3.51** (0.01 g, 12%; eluent: 5% methanol in ethyl acetate) respectively.

Data of **3.50 :** $^1$H **NMR** ($CD_3OD$, 200 MHz): δ 7.28–7.40 (m, 2H, Ar H), 6.84–6.95 (m, 2H, Ar H), 4.95 (d, 1H, d, 1H, C*H*$HO_2$, *J* =6.2 Hz), 4.73 (s, 2H, $OCH_2$), 4.03–4.11

(m, 2H, Ins H), 3.84–3.94 (m, 3H, Ins H), 3.78 (s, 3H, $OCH_3$), 3.42 (t, 1H, Ins H, $J$ = 6.1 Hz) ppm.

Data of **3.51:** $^1$H **NMR** ($CD_3OD$, 200 MHz): δ 5.03 (d, 1H, d, 1H, C*H*$HO_2$, $J$ =6.1 Hz), 4.84 (d, 1H, d, 1H, CH*H*$O_2$, $J$ =6.2 Hz), 3.84–4.04 (m, 5H, Ins H), 3.46 (t, 1H, Ins H, $J$ = 6.6 Hz) ppm.

**Octyl diphenyl phospate (3.53)**

To a solution of 1-Octanol (0.50 g, 3.80 mmol) in pyridine (10 mL) diphenyl phosphoro chloridate (1.20 mL, 5.76 mmol) was added drop-wise at 0 $^oC$ over a period of 10 min. The reaction mixture was stirred at rt overnight. The solvent was evaporated under reduced pressure and the residue worked up with ethyl acetate. The organic layer was dried over anhy. sodium sulphate and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Eluent: 8 % ethyl acetate in light petroleum) to afford **3.53** (1.24 g, 89 %) as a colorless oil. $R_f$ = 0.35 (10% ethyl acetate/light petroleum)

**$^1$H NMR** ($CDCl_3$, 200 MHz): δ 7.02–7.50 (m, 10 H, ArH), 4.17–4.32 (m, 2H, $OCH_2$), 1.60–1.78 (m, 2H, $CH_2$), 1.17–1.40 (m, 10H, 5 × $CH_2$), 0.88 (t, 3H, $CH_3$, $J$ = 6.8 Hz) ppm. **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 150.6 ($C_{arom}$), 150.4 ($C_{arom}$), 129.7 ($C_{arom}$), 125.2 ($C_{arom}$), 120.0 ($C_{arom}$), 119.9 ($C_{arom}$), 69.4 ($CH_2$), 69.3 ($CH_2$), 31.6 ($CH_2$), 30.0 ($CH_2$), 29.0 ($CH_2$), 28.9 ($CH_2$), 25.2 ($CH_2$), 22.5 ($CH_2$), 14.0 ($CH_3$) ppm. **$^{31}$P NMR** ($CDCl_3$, 161.98 MHz, Ref: $H_3PO_4$):δ -11.2 ppm. **Elemental analysis** calcd for $C_{20}H_{27}O_2P$: C, 66.26; H, 7.51; Found: C, 66.48; H, 7.68 %.

**Diallyl octyl Phosphate (3.54)**

To a solution of allyl alcohol (0.13 mL, 1.90 mmol) in dry DMF (5 mL) sodium hydride (0.08 g, 2.07 mmol) was added at 0 $^oC$ and the suspension was stirred for 10 min. **3.53** (0.3 g, 0.82 mmol) was added drop-wise to the above mixture and stirred overnight at rt. The solvents were evaporated under reduced pressure and the residue was worked up with ethyl acetate. The purification of the crude product by column chromatography (100-200 mesh, 15% ethyl acetate/light petroleum) afforded **3.54** (0.15 g, 62.5%) as a colorless gum. $R_f$ = 0.43 (20% ethyl acetate/light petroleum)

**$^{1}$H NMR** ($CDCl_3$, 200 MHz): δ 5.83–6.07 (m, 2H, allylic CH), 5.20–5.44 (m, 4H, allylic $CH_2$), 4.49–4.59 (m, 4H, $OCH_2$), 4.05 (quartet, 2H, $OCH_2$, $J$ = 6.7 Hz), 1.63–1.73 (m, 2H, $CH_2$), 1.23–1.40 (m, 10H, $CH_2$), 0.88 (t, 3H, $CH_3$, $J$ = 6.7 Hz) ppm.**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 132.6 (HC=),132.5 (HC=), 118.1 (=$CH_2$), 68.1 ($OCH_2$), 68.0 ($OCH_2$), 31.7 ($CH_2$), 30.3 ($CH_2$), 30.2 ($CH_2$), 29.2 ($CH_2$), 29.05 ($CH_2$), 25.4 ($CH_2$), 22.6 ($CH_2$), 14.1($CH_3$) ppm; **$^{31}$P NMR** ($CDCl_3$, 202.46 MHz, Ref: $H_3PO_4$): δ 0.22 ppm; **HRMS**: calcd. for [$C_{14}H_{28}O_4P$] 291.1720, Found 291.1720.

**Dibenzyl octyl phospate (3.55)**

To a solution of benzyl alcohol (0.26 mL, 2.53 mmol) in dry DMF (6 mL) sodium hydride (0.11 g, 2.75 mmol) was added at 0 $^{o}$C and the suspension stirred for 10 min. **3.53** (0.40 g, 1.10 mmol) was added drop-wise to the above mixture and stirred overnight at rt. The solvents were evaporated under reduced pressure and the residue was worked up with ethyl acetate. Purification of the crude product by column chromatography (100-200 mesh, 20% ethyl acetate/light petroleum) afforded **3.55** (0.70 g, 60.0%) as a colorless gum. $R_f$ = 0.29 (20% ethyl acetate/light petroleum).

**$^{1}$H NMR** ($CDCl_3$, 200 MHz): δ 7.28–7.42 (m, 10H, ArH), 4.94–5.14 (m, 4H, 2×$OCH_2$), 3.92–4.04 (m, 2H, $OCH_2$), 1.52–1.66 (m, 2H, $CH_2$), 1.17–1.34 (m, 10H, 5×$CH_2$), 0.88 (t, 3H, $CH_3$, $J$ = 6.7 Hz) ppm. **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 136.0 ($C_{arom}$), 135.9 ($C_{arom}$), 128.5 ($C_{arom}$), 128.4 ($C_{arom}$), 127.9 ($C_{arom}$), 69.1, 69.0 ($OCH_2$), 68.1, 68.0 ($OCH_2$), 31.7 ($CH_2$), 30.2, 30.1 ($CH_2$), 29.1, 29.0 ($CH_2$), 25.3 ($CH_2$), 22.6 ($CH_2$), 14.0 ($CH_3$) ppm. **$^{31}$P NMR** ($CDCl_3$, 202.46 MHz, Ref: $H_3PO_4$): δ -0.34 ppm. **HRMS**: calcd. for [$C_{22}H_{32}O_4P$] 391.2033, Found 391.2028.

**Reaction of Octyl diphenyl phosphate (3.53) with $Pd(OH)_2$/C**

A mixture of **3.53** (0.15 g, 0.41 mmol) and Pd $(OH)_2$/C (0.29 g) was refluxed in 2-propanol (2 mL) for 24 h. The reaction mixture was filtered through a short bed of Celite and the Celite washed with successively with ethyl acetate (3×3 mL).The combined washings were concentrated under reduced pressure to recover the starting material.

**Reaction of Diallyl octyl Phosphate (3.54) with $Pd(OH)_2/C$**

**14** (0.12 g, 0.41 mmol) was refluxed with a mixture of $Pd(OH)_2/C$ (0.03 g) and Pd/C (0.04 g) in methanol (3 mL) for 1 h and the reaction mixture filtered through a short bed of Celite and the Celite bed was washed with methanol and ethyl acetate successively. The combined filtrate and washings were concentrated under reduced pressure to give **3.56** (0.08 g, 97%) as a colorless oil.

**$^1$H NMR** ($CDCl_3$, 200 MHz): δ 3.85–4.25 (m, 2H, $OCH_2$), 1.55–1.78 (m, 2H, $CH_2$), 1.21–1.42 (m, 10H, 5×$CH_2$), 0.88 (t, 3H, $CH_3$, $J$ = 6.3 Hz) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 68.0 ($CH_2$), 31.8 ($CH_2$), 30.2 ($CH_2$), 29.2 ($CH_2$), 25.4 ($CH_2$), 22.6 ($CH_2$), 14.0 ($CH_3$) ppm; **$^{31}$P NMR** ($CDCl_3$, 161.98 MHz, Ref: $H_3PO_4$): δ 9.33 ppm. **HRMS**: calcd. for $[C_8H_{19}O_4+Na]^+$ 233.0913, Found 233.0913.

**Reaction of Dibenzyl octyl phospate (3.55) with $Pd(OH)_2/C$**

**3.55** (0.15 g, 3.97 mmol) was refluxed with $Pd(OH)_2/C$ (0.25 g, 3.46 mmol) in methanol (5 mL) for 3.5 h. The reaction mixture was filtered through a short bed of Celite and the Celite was washed with methanol (3 mL) and ethyl acetate (5 mL) successively. The filtrate was evaporated under reduced pressure to give **3.56** (0.08 g, 99%) as a colorless oil.

**Mannitol- 1,2,5,6-diacetonide (3.65)**

**3.65** was prepared as per the procedure reported in Ref: 27

**(*S*)- Glycerol acetonide (3.66)**

To a solution of mannitol diacetonide (0.40 g, 1.52 mmol) in dry DCM (15 mL) $NaIO_4$/silica (3.42 g, 5.34 mmol) was added at rt and stirred for 15 min. A second batch of $NaIO_4$/silica (3.42 g, 5.34 mmol) was added and the stirring continued for 45 min. The reaction mixture was filtered and the filtrate was concentrated to get the crude aldehyde. To the crude aldehyde obtained above (0.35 g, 2.69 mmol) in MeOH (7 mL) $NaBH_4$ (0.24 g, 6.30 mmol) was added at 0 $^oC$ over 10 min. The reaction mixture was stirred overnight at rt. Excess sodium borohydride was quenched by adding $NH_4Cl$ solution, the solvents were evaporated under reduced pressure and the crude product was purified by column chromatography (100-200 mesh, 40 % ethyl

acetate/light petroleum) to afford **3.66**[28] (0.33 g, 81.6%) as a colorless oil. $[\alpha]_D$ = +11.33 (1, $CHCl_3$) (lit.[31] $[\alpha]_D$ = +13.6).

**3-allyl *sn* glycerol (3.67)**

To a solution of the acetonide (0.25 g, 1.89 mmol)in THF (5 mL) sodium hydride (0.11g, 2.84 mmol) was added at 0 $^oC$ and stirred for 10 min. To the above mixture allyl bromide (0.20 mL, 2.27 mmol) was added dropwise and stirred for 6 h. The solvents were evaporated under reduced pressure and the residue was worked up with DCM. The organic layer was concentrated , the residue obtained was dissolved in methanol (5 mL) and refluxed with *p*-toluene sulphonic acid (0.05 g) for 3 h. The solvents were evaporated under reduced pressure and the crude product was purified by column chromatography (100–200 mesh, 5% MeOH/Ethyl acetate) to afford **3.67** (0.22 g, 88%) as a colorless oil.[29]

**1,2-diacyl-3-allyl-*sn*-glycerol (3.74)**

To a solution of **3.67** (0.14 g, 1.06 mmol) in pyridine (5 mL) acetic anhydride (0.35 mL, 3.71 mmol) was added dropwise at 0 $^oC$ followed by catalytic amount of DMAP and stirred overnight at rt. Then solvent was evaporated under reduced pressure, the residue was dissolved in ethyl acetate washed with saturated solution of ammonium chloride. After the usual work up the crude product was purified by column chromatography (100-200 mesh, 30% ethyl acetate/light petroleum) to afford **3.74** as a colorless oil (0.20 g, 85 %). $R_f$ = 0.42 (20% ethyl acetate/light petroleum).

**IR** ($CHCl_3$): $\bar{\nu}$ 1742 $cm^{-1}$; **1H NMR** ($CDCl_3$): δ 5.75–6.00 (m, 1H, CH), 5.14–5.35 (m, 3H, $CH_2$ and CH), 4.30–4.40 (m, 1H, OCH), 4.12–4.23 (m, 1H, OCH), 4.01 (dd, 2H, $OCH_2$, *J* = 5.4, 0.8 Hz), 3.58 (d, 2H, $OCH_2$, *J* = 5.2 Hz), 2.10 (s, 3H, $CH_3$), 2.07 (s, 3H, $CH_3$) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 170.6 (CO), 170.3 (CO), 134.1 (CH), 117.4 ($CH_2$), 72.2 ($OCH_2$), 70.2 (OCH), 68.1 ($OCH_2$), 62.9 ($OCH_2$), 21.0 ($CH_3$), 20.7 ($CH_3$) ppm; **HRMS** : calcd. for $[C_{10}H_{16}O_5+Na]^+$ 239.0890, Found 239.0887.

**Deallylation of 3.74**

**3.74** (0.14 g, 0.64 mmol) was refluxed with $Pd(OH)_2/C$ (0.09 g) and Pd/C (0.08 g) in MeOH (2 mL) for 9 h, the TLC analysis indicated the complete consumption of the starting material. Refluxing was continued for 5h to check whether the acyl migration occurs. Then the reaction mixture was filtered through a short bed of Celite and the Celite was washed with with MeOH (3 mL) as well as ethyl acetate (3 mL). **3.75**[30] (0.11 g, 97%) was obtained after the evaporation of the solvents under reduced pressure.

**3-Allyl–1,2-di-stearoyl-*sn*-glycerol (3.76)**

To a solution of 3-O-allyl-*sn*-glycerol (0.16 g, 1.2 mmol), DMAP (0.016 g, 0.13 mmol) and stearic acid (0.86 g, 3.03 mmol) in dry DCM (9 mL) at rt was added drop-wise a solution of DCC (0.75 g, 3.63 mmol) in dry DCM (6 mL) over 30 min. and the resulting mixture was stirred for 10 h at rt. The solid was removed by filtration through a celite bed. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (eluent: 4% ethyl acetate/light petroleum) to obtain **3.76** (0.61 g, 76%) as a colorless solid (mp. = 48.3–49.4 $^oC$). $[\alpha]_D$ = +5.01 (2, $CHCl_3$); **IR** ($CHCl_3$): $\bar{\nu}$ 1737 $cm^{-1}$; **$^1$HNMR** ($CDCl_3$, 200 MHz): δ 5.76–5.98 (m, 1H, allylic CH), 5.14–5.34 (m, 3H, OCH and $=CH_2$), 5.33 (dd, 1H, OC*H*H, *J* = 3.9, 11.9 Hz), 4.17 (dd, 1H, OCH*H*, *J* = 6.4, 11.9 Hz), 3.97–4.03 (m, 2H, $OCH_2$), 3.56 (d, 2H, $OCH_2$, *J* = 5.2 Hz), 2.25-2.37 (m, 4H, 2×$CH_2$), 1.58–1.66 (m, 4H, 2×$CH_2$), 1.17–1.37 (m, 56 H, 28× $CH_2$), 0.88 (t, 6H, 2×$CH_3$, *J* = 6.7 Hz) ppm. **$^{13}$C NMR** ($CDCl_3$, 56.3 MHz): δ 173.5 (CO), 173.2 (CO), 134.2 (=CH), 117.4 ($=CH_2$), 72.3 ($CH_2$), 70.0 (CH), 68.2 ($CH_2$), 62.7 ($CH_2$), 34.3 ($CH_2$), 34.1 ($CH_2$), 31.9 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 29.11 ($CH_2$), 29.07 ($CH_2$), 24.94 ($CH_2$), 24.88 ($CH_2$), 22.7 ($CH_2$), 14.1 ($CH_3$) ppm. **Elemental analysis** calcd for $C_{42}H_{80}O_5$: C, 75.85; H, 12.12; Found: C, 75.83; H, 11.81 %.

**1,2-di-stearoyl-*sn*-glycerol (3.77)**

To a suspension of **3.76** (0.05 g, 0.08 mmol) in MeOH (3 mL), $Pd(OH)_2/C$ (0.05 g) was added and refluxed for 3 h. The reaction mixture was cooled to rt and filtered

through a short bed of Celite. The Celite bed was washed with methanol (3×5 mL), the combined filtrate and washings was evaporated under reduced pressure to obtain **3.77** (0.044 g, 94%) as a colorless solid.[31] Mp. = 71.3–72.4 $^{o}$C (lit[34]. mp. = 73.0– 74.5 $^{o}$C) **,** $[\alpha]_D$ = -2.3 (1, $CHCl_3$), lit $[\alpha]_D$ = -2.6 (1, $CHCl_3$)

**(*R*)-3-((bis(benzyloxy)phosphoryl)oxy)propane-1,2-diyl distearate (3.78)**

1H-tetrazole (3.20 mL of 0.45M solution in toluene, 1.44 mmol) and dibenzyl N, N-diisopropyl phosphoramidite (0.24 mL, 0.72 mmol) were taken in dry DCM (5 mL) and stirred for 0.5 hour. **3.77** (0.24 g, 0.36 mmol) was added in one lot to the above mixtureand the stirring continued for 2 hours. Then *m*CPBA (0.25 g, 1.44 mmol) was added in two portions at -40 $^{o}$C and the reaction mixture brought into room temperature over half an hour and stirring continued for 4h. The solvent was evaporated under reduced pressure and the residue was washed successively with 10% $Na_2SO_3$ and 10% $NaHCO_3$ solutions. The organic layer was dried over anhy sodium sulphate and concentrated. The crude product was purified by flash column chromatography (22% ethyl acetate/light petroleum) to obtain **3.78** (0.32 g, 93%) as a colorless solid.

**Mp. =** 52.7–54.4 $^{o}$C; $[\alpha]_D$ = +2.10 (1, $CHCl_3$); **IR** ($CHCl_3$): $\bar{\nu}$ 1745 $cm^{-1}$. **$^{1}$HNMR** ($CDCl_3$, 400 MHz) δ: 7.31–7.38 (m, 10H, ArH), 5.11–5.20 (m, 1H, CH), 5.01–5.08 (m, 4H, 2× $OCH_2$), 4.25 (m, 1H, OC*H*H), 4.01–4.16 (m, 3H, OCH*H*, $OCH_2$), 2.23–2.32 (m, 4H, $CH_2$), 1.53–1.62 (m, 4H, $CH_2$), 1.22–1.28 (m, 56H, $CH_2$), 0.88 (t, 6H, *J* = 7.03 Hz, $CH_3$) ppm. **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ: 173.2 (CO), 172.8 (CO), 135.6 ($C_{arom}$), 128.6 ($C_{arom}$), 128.0 ($C_{arom}$), 69.54, 69.48 ($CH_2$), 69.33, 69.25 (CH), 65.4, 65.3 ($CH_2$), 61.6 ($CH_2$), 34.1 ($CH_2$), 34.0 ($CH_2$), 31.9 ($CH_2$), 29.7 ($CH_2$), 29.50 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 29.1 ($CH_2$), 29.06 ($CH_2$), 24.8 ($CH_2$), 22.7 ($CH_2$), 14.1 ($CH_3$) ppm. **$^{31}$P NMR** ($CDCl_3$, 161.98 MHz, Ref: $H_3PO_4$) δ: -0.45 ppm. **Elemental analysis** calcd for $C_{53}H_{89}O_8P$: C, 71.91; H, 10.13; Found: C, 71.58; H, 9.73%.

**Debenzylation of 3.78 with $Pd(OH)_2$/C**

Compound **3.78** (0.12 g, 0.14 mmol) was refluxed with $Pd(OH)_2$/C (0.05 g, 0.07 mmol) in 2-propanol (2 mL) for 72 h. The reaction mixture was filtered over a short bed of Celite and the Celite was washed with successive portions of methanol and

DCM. The filtrate was concentrated under rduced pressure to obtain **3.79** (0.08 g, 82%) as a colorless gum.

**$^1$HNMR** ($CD_3OD$ + $CD_2Cl_2$, 200 MHz): δ 5.10–5.14 (m, 1H, OCH), 3.50–3.70 (m, 4H, $OCH_2$), 2.00–2.15 (m, 4H, $CH_2$), 1.32–1.47 (m, 4H, $CH_2$), 0.95–1.17 (m, 56 H, $CH_2$), 0.66 (t, 6H, $CH_3$) ppm.

**3-Allyl–1-stearoyl-2-oleoyl-*sn*-glycerol (3.80)**

To a solution of **3.67** (0.19 g, 1.43 mmol), DMAP (0.01 g, o.07 mmol) and stearic acid (0.42 g, 1.46 mmol) in DCM (6 mL) a solution of DCC (0.36 g, 1.72 mmol) in DCM (3 mL) was added dropwise at -5 $^oC$ over 1h and stirred further for 1h. The reaction mixture was filtered throgh a short bed of Celite and the Celite washed with DCM (3 mL) and the filtrate was concentrated under reduced pressure. The residue (0.62 g) was redissolved in DCM (15 mL). To this solution DMAP (0.01 g, 0.07 mmol) and oleic acid (0.546 mL, 1.72 mmol) were added and stirred at rt for 5 min. A solution of DCC (0.44 g, 2.14 mmol) in DCM (5 mL) was added dropwise to the reaction mixture over 30 min and stirred further for 2h. The reaction mixture was filtered through a short bed of Celite and the celite was washed with DCM (5 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (eluent: 7% ethyl acetate/light petroleum) to obtain **3.80** (0.83 g, 87.6%) as a gum.

**IR** (neat): $\bar{\nu}$ 1744 $cm^{-1}$; $[\alpha]_D$ = +4.75 (2, $CHCl_3$); **$^1$H NMR** ($CDCl_3$,200 MHz): δ 5.72–6.00 (m, 1H, =CH), 5.29–5.43 (m, 3H, OCH, $=CH_2$), 5.15–5.27 (m, 2H, 2×CH), 4.29–4.41 (m, 1H, OCH), 4.10–4.22 (m, 1H, OCH), 3.96–4.05 (m, 2H, $OCH_2$), 3.54–3.60 (m, 2H, $OCH_2$), 2.25–2.38 (m, 4H, 2×$CH_2$), 1.95–2.08 (m, 4H, 2×$CH_2$), 1.58–1.62 (m, 4H, 2×$CH_2$), 1.21–1.38 (m, 48H, 24×$CH_2$), 0.88 (t, 6H, 2×$CH_3$, $J$ = 6.6 Hz) ppm; **$^{13}$C NMR** ($CDCl_3$, 100.61 MHz): δ 173.4 (CO), 173.1 (CO), 134.2 (CH), 130.0 (CH), 129.7 (CH), 117.4 ($=CH_2$), 72.3 ($OCH_2$), 70.0 (OCH), 68.2 ($OCH_2$), 62.7 ($OCH_2$), 34.3, 31.9, 29.8, 29.7, 29.5, 29.3, 29.2, 29.1, 29.0, 27.20, 27.16, 24.93, 24.87, 22.7 ($CH_2$), 14.1 ($CH_3$) ppm; **Elemental analysis** calcd. for $C_{42}H_{78}O_5$: C, 76.08; H, 11.86; Found: C, 76.14; H, 11.80%.

**Deallylation of 3.80 with $Pd(OH)_2/C$**

Compound **3.80** (0.16 g, 0.24 mmol) was stirred with $Pd(OH)_2/C$ (0.15 g, 0.21 mmol) in 2-propanol at 60 $^oC$ for 17 hrs. The reaction mixture was filtered through a short bed of Celite at hot condition. The Celite was washed with hot methanol (5 mL). The filtrate was evaporated to obtain the deallylated product **3.81** (0.14 g, 90%) as a gum.[32]

**Racemic 1-*O*-benzoyl-2,4,6-tri-*O*-allyl-*myo*-inositol (3.82)**

To a solution of *myo* inositol-1,3,5-orthobenzoate triol **3.42** (0.50 g, 1.87 mmol) in dry DMF (10 mL) sodium hydride (0.32 g, 7.89 mmol) was added at 0 $^oC$ and stirred for 10 min. Allyl bromide (0.57 mL, 6.57 mmol) was added drop-wise to the reaction mixture and it was warmed to rt. and stirred it for 2h. The solvents were evaporated under reduced pressure and the residue was worked up with ethyl acetate. The organic layer was dried over anhyd sodium sulphate and evaporated under reduced pressure and the crude product (0.63 g) was refluxed in TFA:$H_2O$ (1:1, 5 mL) for 5 h. The reaction mixture was neutralized by the addition of triethyl amine (0.3 mL) and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography (100-200 mesh, 40% ethyl acetate/light petroleum) to afford **3.82** (0.56 g, 86.2%) as a gum.

**IR** ($CHCl_3$) $\bar{\nu}$ 3200-3600, 1721 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$, 200 MHz): δ 8.03–8.13 (m, 2H, ArH), 7.56–7.67 (m, 1H, ArH), 7.43–7.54 (m, 2H, ArH), 5.71–6.13 (m, 3H, allylic CH), 4.99–5.39 (m, 7H, Allylic $CH_2$, InsH), 4.12–4.50 (m, 6H, $OCH_2$), 4.07 (t, 1H, InsH, $J$ = 2.4 Hz), 3.84–3.95 (m, 1H, InsH), 3.51–3.69 (m, 3H, InsH), 2.26 (br s, 2H, 2×OH, $D_2O$ exchangable) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 165.6 (CO), 135.1 (=CH), 134.7 ($C_{arom}$), 134.6 (=CH), 133.3 (=CH), 129.7 ($C_{arom}$), 128.6 ($C_{arom}$), 117.2 (=$CH_2$), 117.1 (=$CH_2$), 81.2 (InsC), 79.2 (InsC), 77.5 (InsC), 74.6 (InsC), 74.4 (InsC), 74.3 ($OCH_2$), 74.1 ($OCH_2$), 74.0 ($OCH_2$), 71.7 (InsC) ppm; **HRMS**: calcd. for $[C_{22}H_{28}O_7+H]^+$ 405.1908, Found 405.1898.

**Racemic-1-O-benzoyl-2,3,4,5,6-penta-O-allyl-*myo*-inositol (3.83)**

The diol **3.82** (0.40 g, 0.99 mmol) and allyl bromide (0.26 mL, 2.97 mmol) were taken in dry DMF (5 mL) and freshly prepared silver(I) oxide (1.37 g, 5.94 mmol) was added in portions over a period of 10 min with vigorous stirring and external cooling with ice. Stirring was continued till the starting material disappeared on TLC. The solid was allowed to settle and the supernatant liquid was decanted. The residue was washed successively with DMF and chloroform. The organic layer was washed with sodium cyanide solution (1%) and the aqueous layer was extracted with chloroform. The combined chloroform extract was washed with water and dried over anhy sodium sulphate. Purification of the residue obtained on evaporation of the solvent by flash column chromatography (eluent: 18% ethyl acetate/light petroleum) afforded **3.83** (0.36 g,76%) as a colorless oil.

**$^1$H NMR** ($CDCl_3$, 200 MHz): δ 8.04–8.13 (m, 2H, ArH), 7.41–7.67 (m, 3H, ArH), 5.70–6.10 (m, 5H, Allylic CH), 4.98–5.37 (m, 10H, allylic $CH_2$), 4.90 (dd, 1H, InsH, *J* = 10.2, 2.5 Hz), 4.01–4.42 (m, 11H, 5×$OCH_2$, InsH), 3.94 (t, 1H, InsH, *J* = 10.2 Hz), 3.76 (t, 1H, InsH, *J* = 9.6 Hz), 3.24–3.38 (m, 2H, InsH) ppm; **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 165.9 (CO), 135.4, 135.3, 135.1, 134.7, 133.2 (CH of allylic group), 129.9 ( $C_{arom}$), 129.7 ($C_{arom}$), 128.5 ($C_{arom}$), 116.8, 116.7, 116.5 (=$CH_2$), 82.9 (Ins C), 81.1 (Ins C), 79.8 (Ins C), 79.0 (Ins C), 74.9 (Ins C), 74.6 ($OCH_2$), 74.57 ($OCH_2$), 74.4 ($OCH_2$), 74.2 (Ins C), 73.8 ($OCH_2$), 71.8 ($OCH_2$) ppm. **HRMS** calcd for $[C_{28}H_{36}O_7+H]^+$ 485.2534, Found 485.2535.

**Racemic-2,3,4,5,6-penta-O-allyl-*myo*-inositol (3.84)**

To a solution of **3.83** (0.25 g, 0.52 mmol) in methanol (3 mL) potassium hydroxide (1 pellet) was added and stirred for 2 h at rt. Solvents were evaporated under reduced pressure and the residue was worked up with ethyl acetate. The crude product was purified by column chromatography (60-120 mesh, 30% ethyl acetate/light petroleum) to afford **3.84** (0.18 g, 94% ) as a colorless oil.

**$^1$H NMR** ($CDCl_3$, 200 MHz):δ 5.79–6.10 (m, 5H, allylic CH), 5.10–5.37 (m, 10H, =$CH_2$), 4.10–4.48 (m, 10H, $OCH_2$), 3.90 (t, 1H, Ins H, *J* = 2.6 MHz), 3.63–3.75 (m, 1H, Ins H), 3.47–3.59 (m, 1H, InsH), 3.32–3.45 (m, 1H, Ins H), 3.11–3.26 (m, 2H, Ins

H), 2.35 (br s, 1H, OH, $D_2O$ exchangable); **$^{13}$C NMR** ($CDCl_3$, 50.3 MHz): δ 135.4 (=CH), 135.3 (=CH), 135.24 (=CH), 135 (=CH).15 (=CH), 134.8 (=CH), 117.0 ($=CH_2$), 116.7 ($=CH_2$), 116.6 ($=CH_2$), 116.5 ($=CH_2$), 83.1 (Ins C), 81.6 (Ins C), 81.4 (Ins C), 80.5 (Ins C), 76.6 (Ins C), 74.5 ($OCH_2$), 74.4 ($OCH_2$), 74.3 ($OCH_2$), 73.6 ($OCH_2$), 71.9 (Ins C), 71.8 ($OCH_2$) ppm. **HRMS** calcd for $[C_{21}H_{32}O_6+Na]^+$ 403.2097, Found 403.2086.

**Racemic-1-O-methyl-2,3,4,5,6-penta-O-allyl-*myo*-inositol (3.85)**

To a solution of **3.84** (0.11 g, 0.29 mmol) in dry DMF (3 mL) sodium hydride (0.02 g, 0.38 mmol) was added at 0 $^oC$ and stirred it for 10 min. Methyl iodide (0.22 mL, 0.35 mmol) was added dropwise to the reaction mixture under cold condition and stirred it for 3 h at rt. The solvents were evaporated under reduced pressure and the crude reaction mixture was worked up with ethyl acetate followed by drying over anhy. sodium sulphate. The organic layer was concentrated under reduced pressure and the crude product obtained was purified by column chromatography (silica 100-200, eluent: 20 % ethyl acetate in light petroleum) to obtain **3.85** (0.09 g, 82%) as a colorless oil.

**$^1$H NMR** ($CDCl_3$, 200 MHz):δ 5.80–6.10 (m, 5H, allylic CH), 5.09–5.36 (m, 10H, allylic $=CH_2$), 4.23–4.35 (m, 8H, $OCH_2$), 4.10–4.17 (m, 2H, $OCH_2$), 3.95 (t, 1H, Ins H, *J* =2.4 Hz), 3.61–3.77 (m, 2H, Ins H), 3.45 (s, 3H, $OCH_3$), 3.07–3.22 (m, 2H, Ins H), 2.92–3.01 (m, 1H, Ins H) ppm.

**Deallylation of 3.85 to obtain racemic Bornesitol**

A solution of **3.85** (0.07 g, 0.16 mmol) in MeOH (2 mL) was refluxed with a mixture of $Pd(OH)_2/C$ (0.028 g) and Pd/C (0.025 g) for 26 h. The reaction mixture was filtered through a short bed of Celite and the Celite was washed with hot MeOH. The filtrate was evaporated under reduced pressure and the crude product obtained was washed with ether (2 × 2 mL). The resultant compound obtained **3.86** (0.031 g, 97%) was used for characterization.[33]

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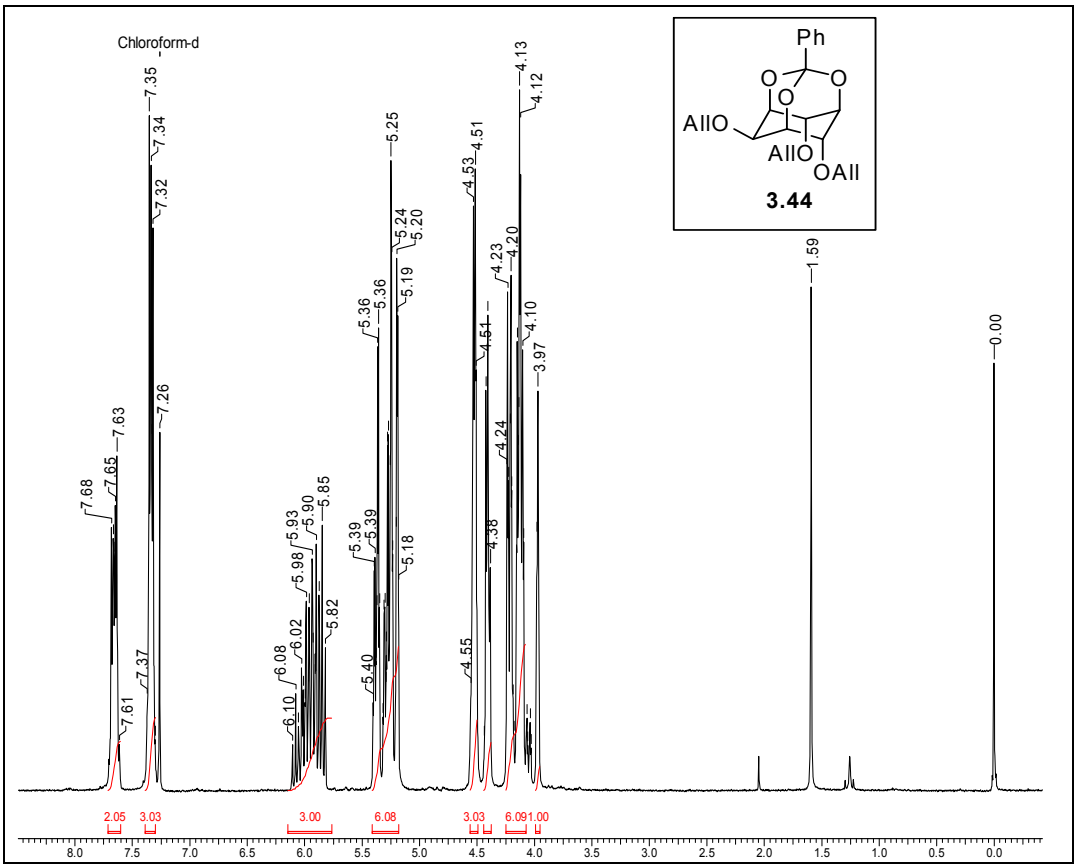
## 3.6. Appendix II

**Appendix II Index**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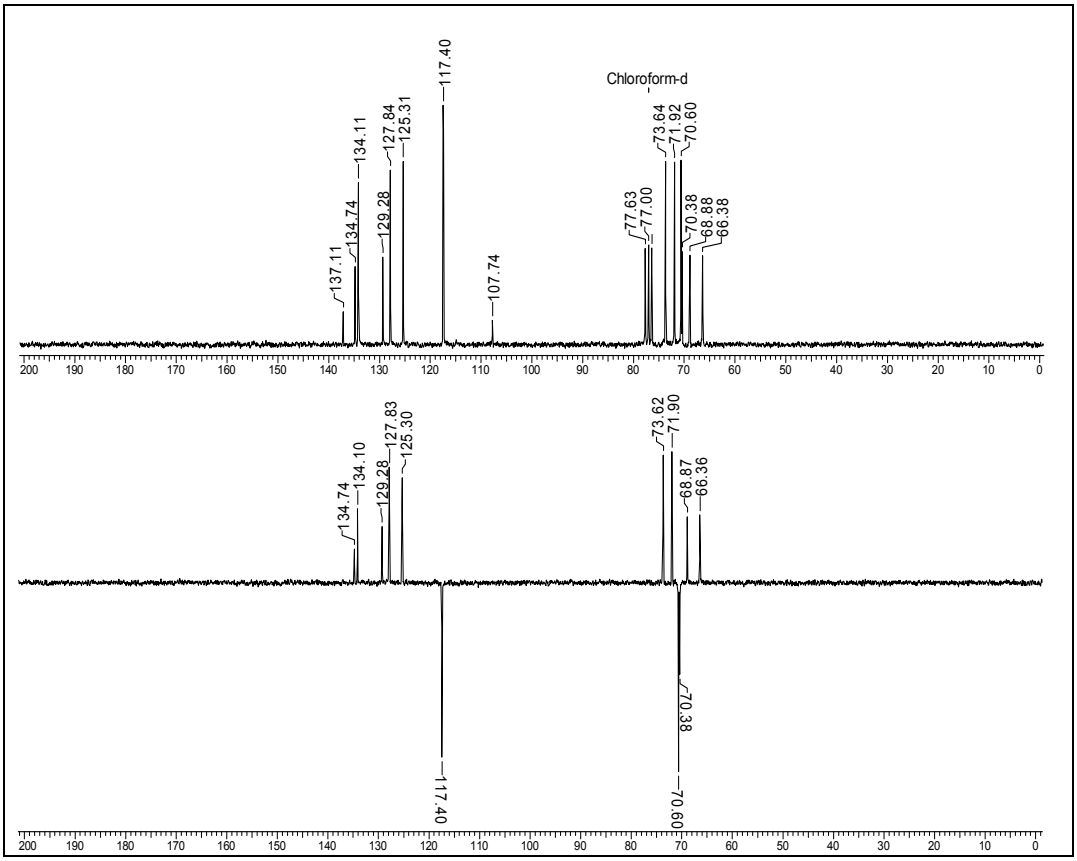
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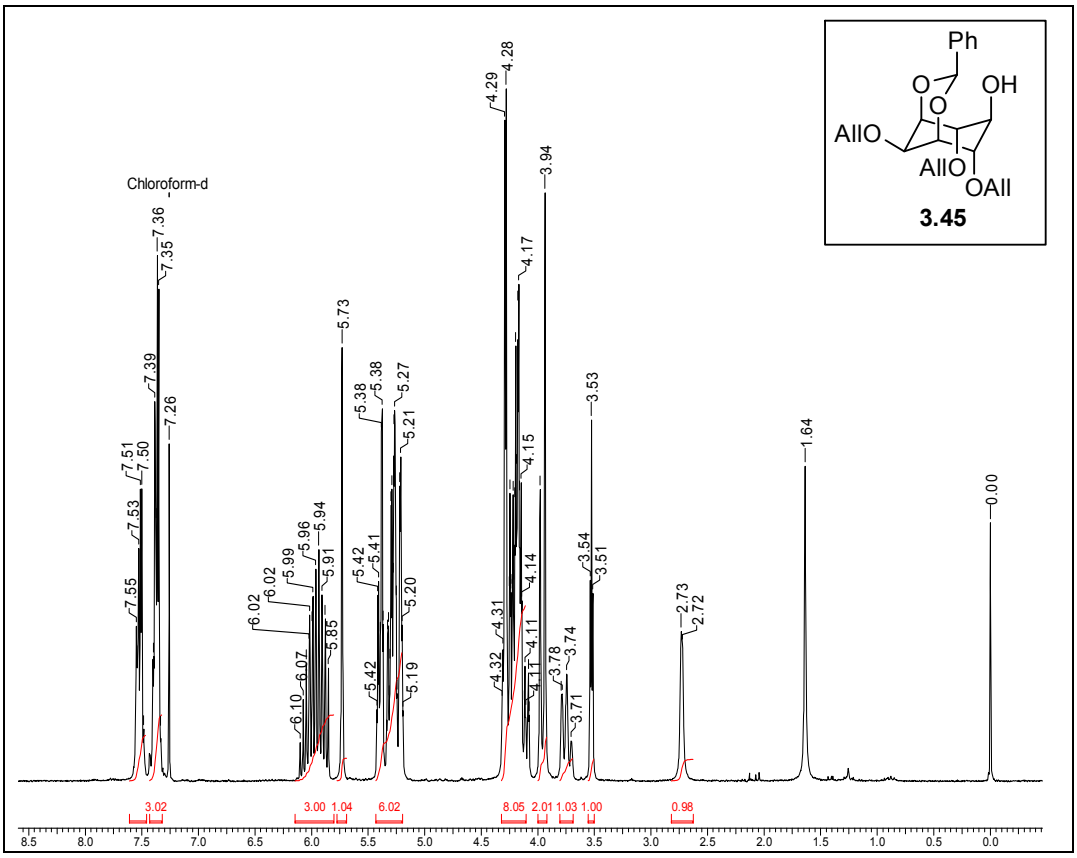
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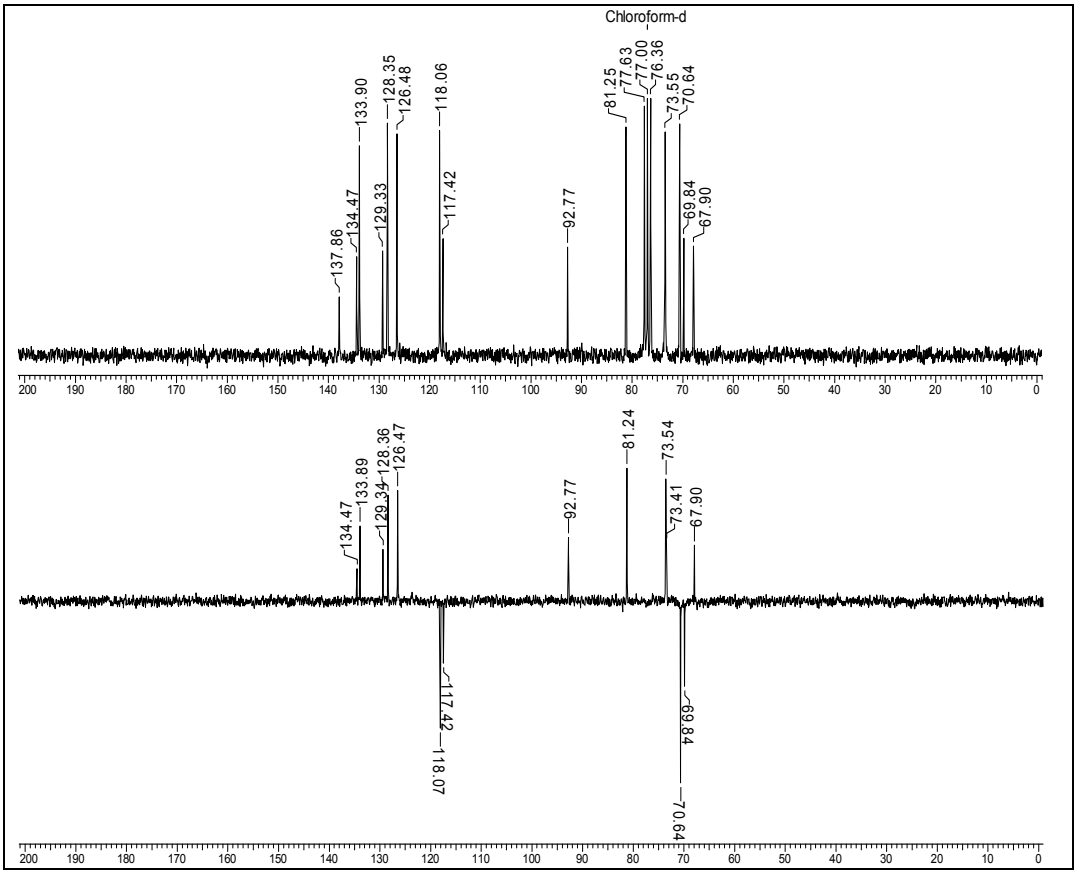
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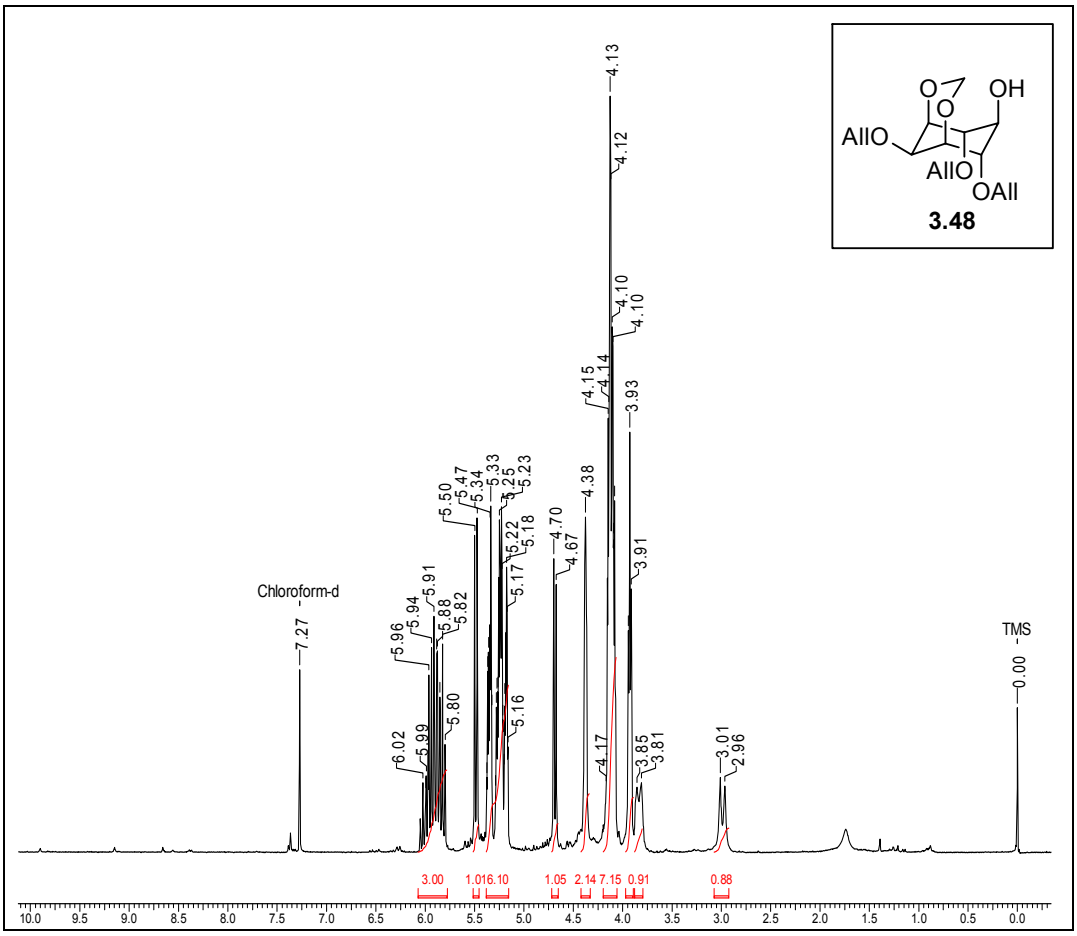
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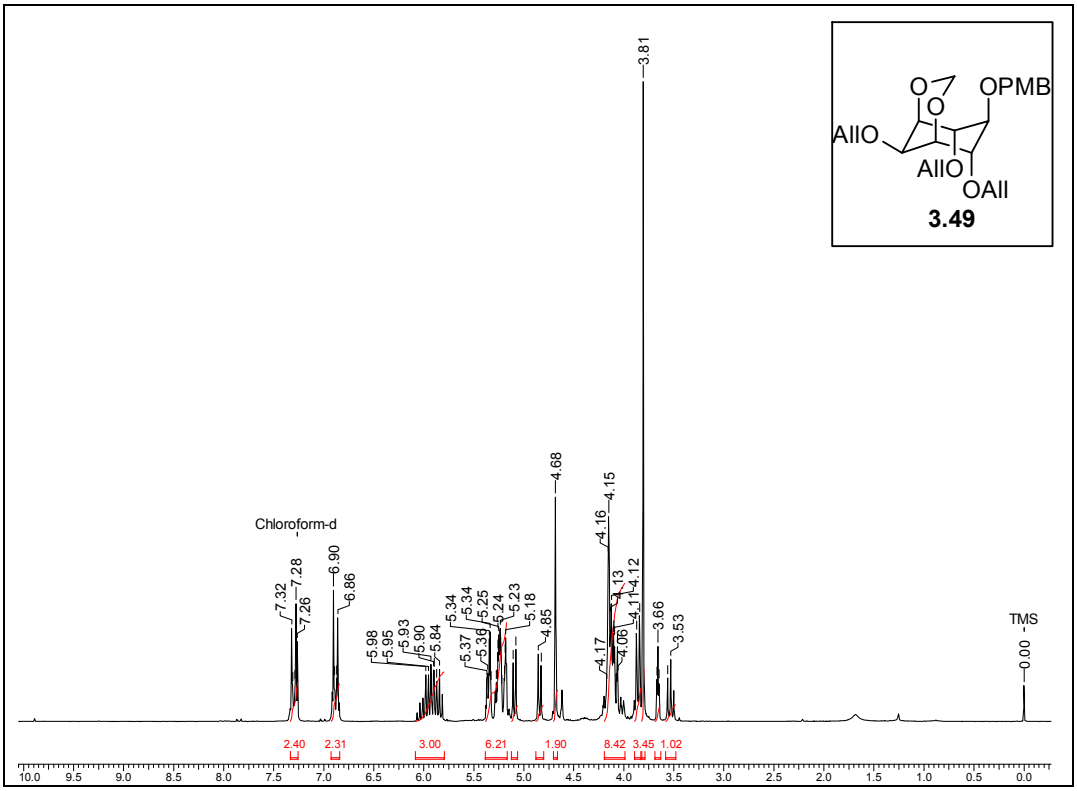
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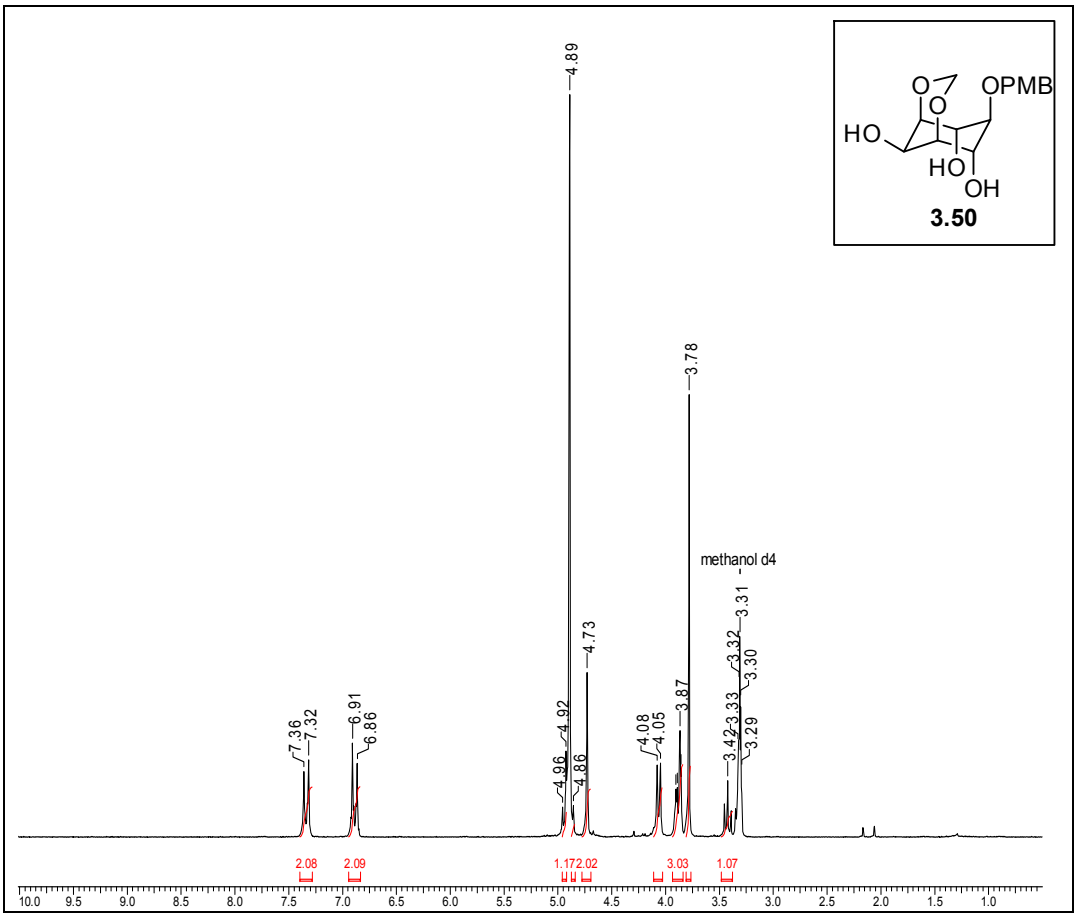
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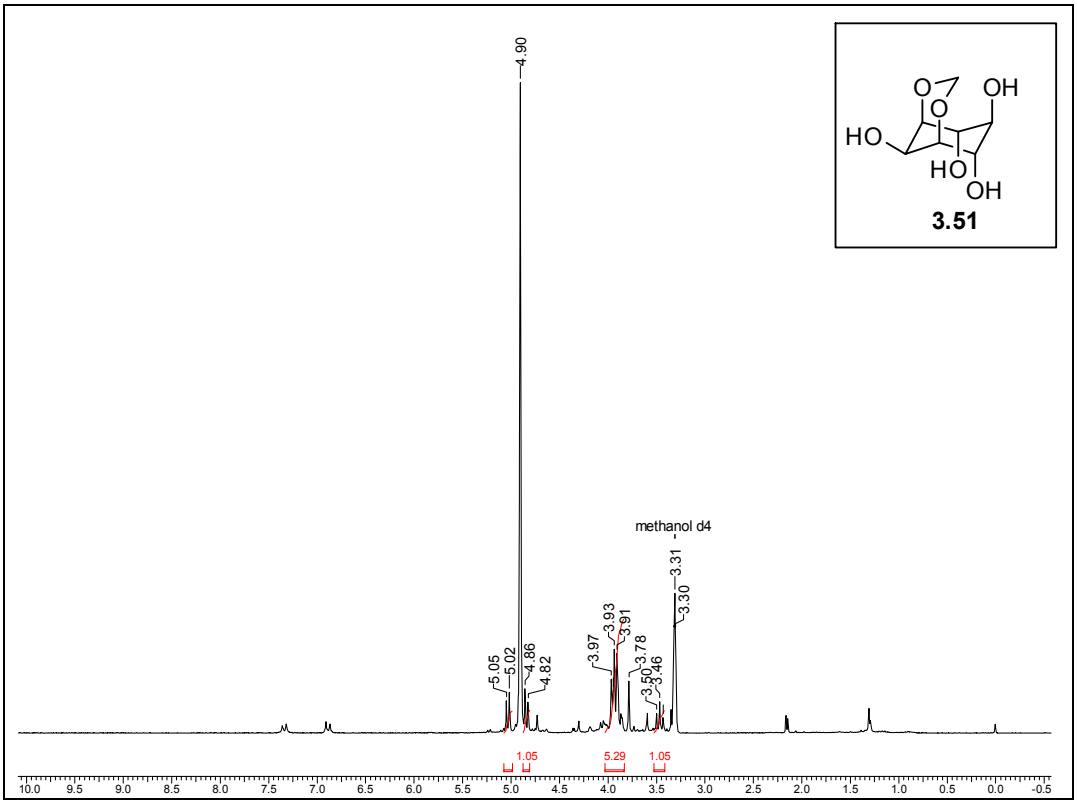
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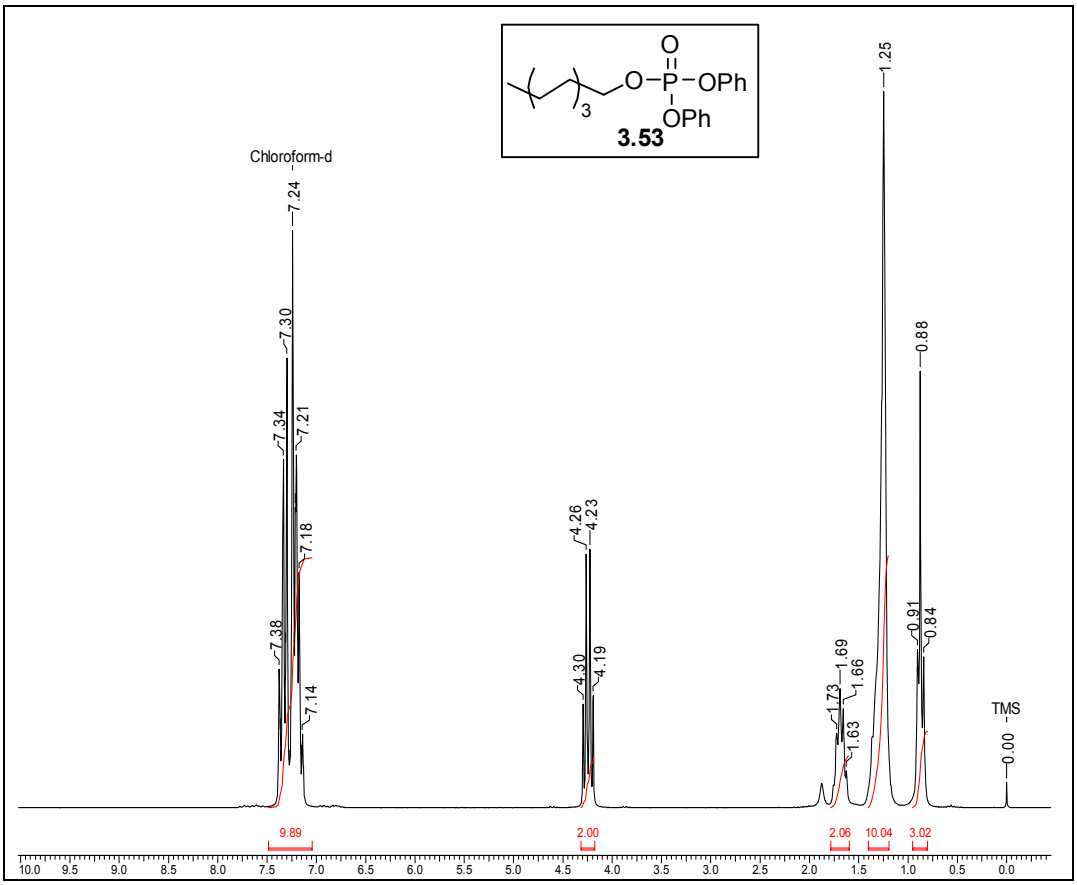
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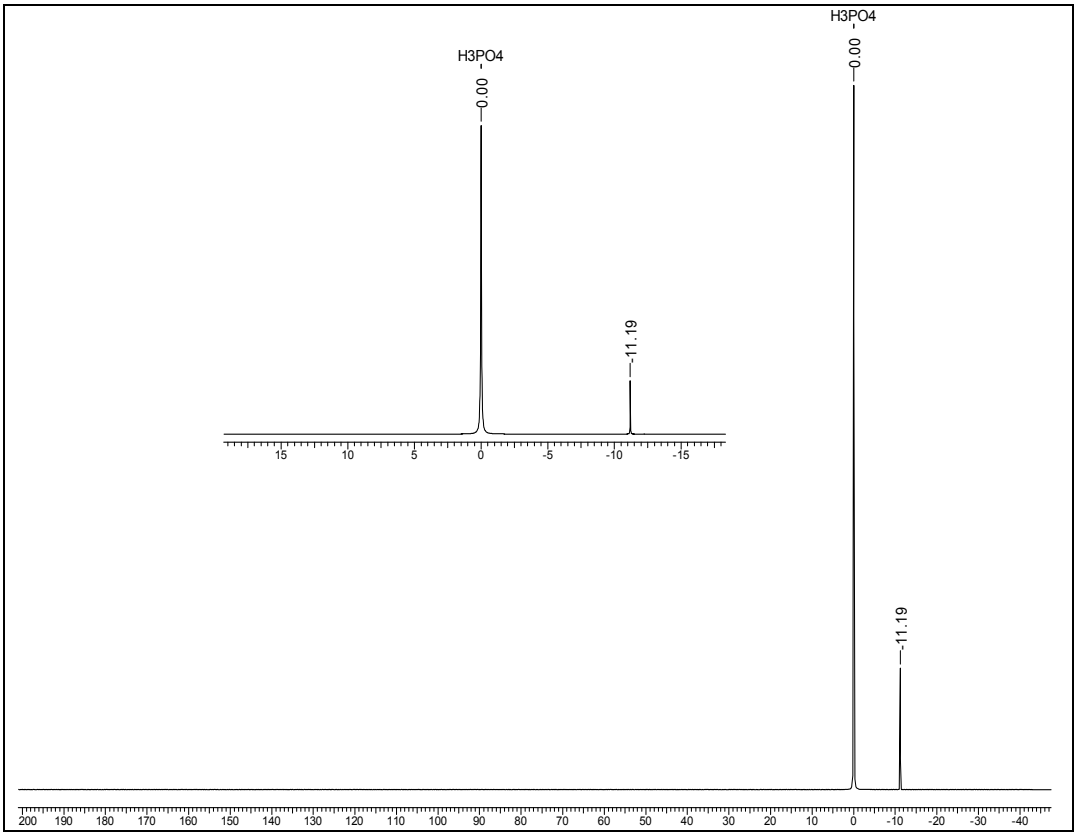
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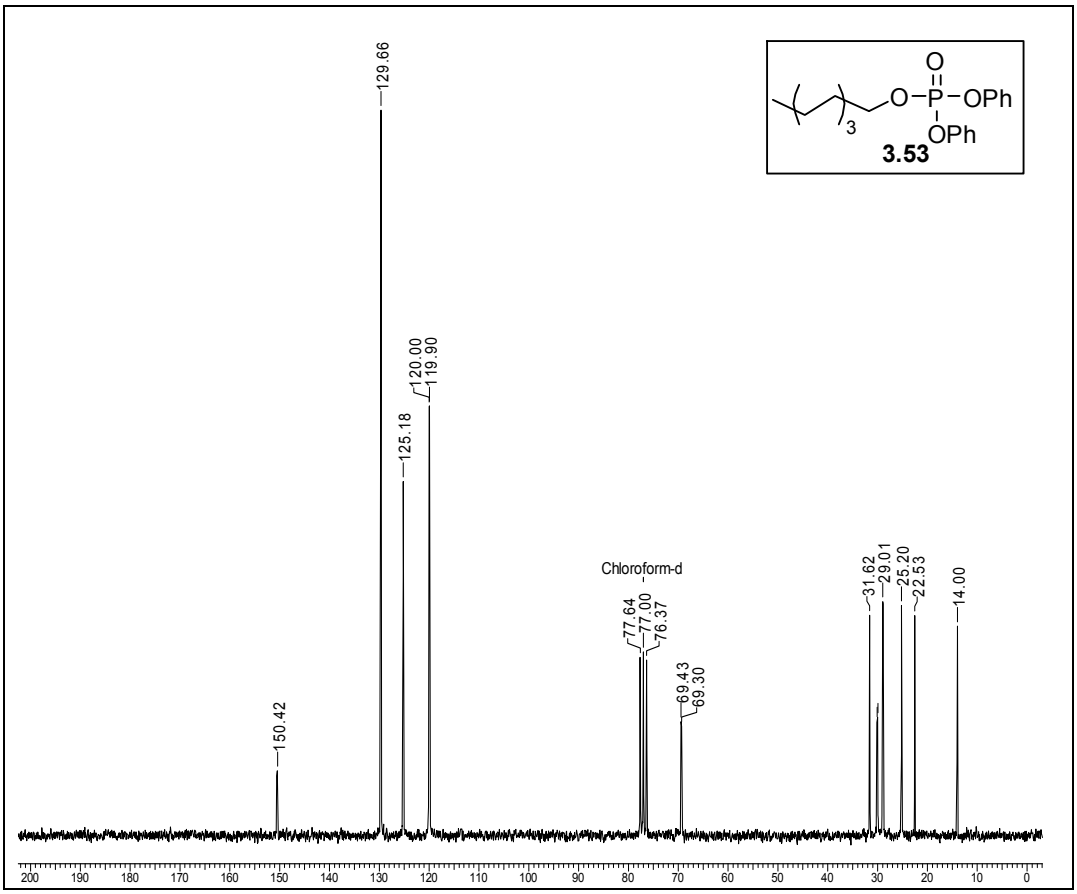
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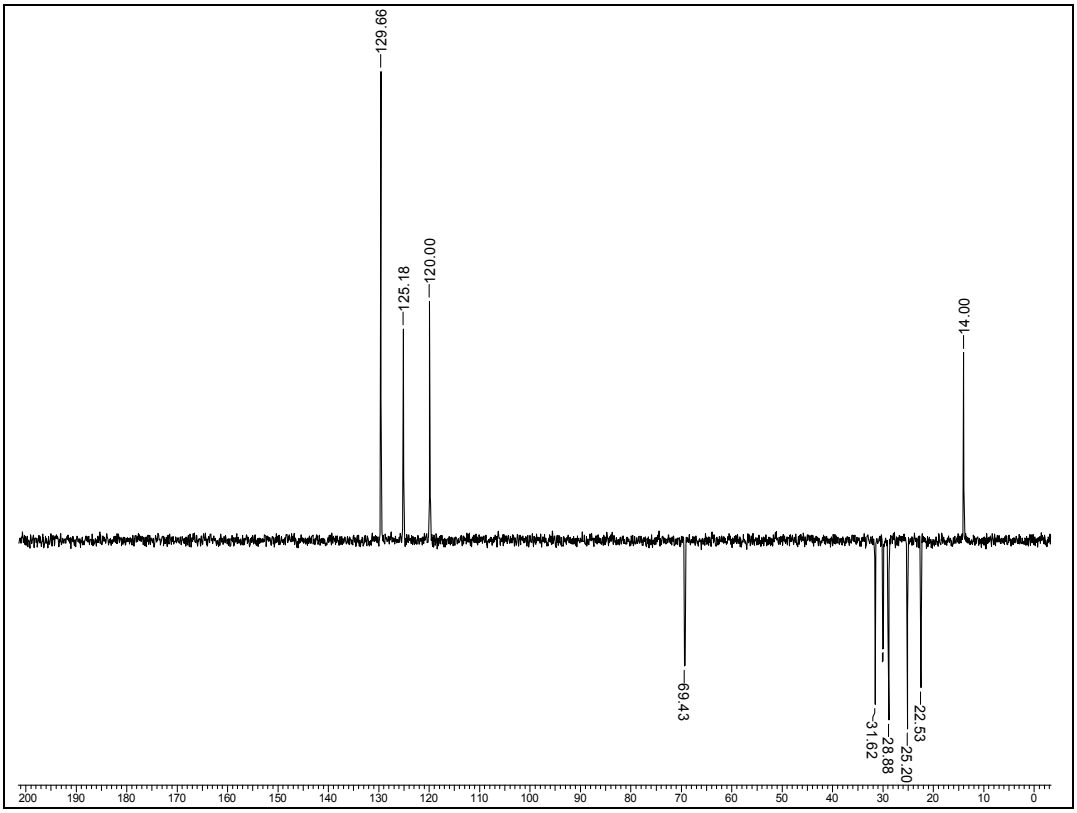
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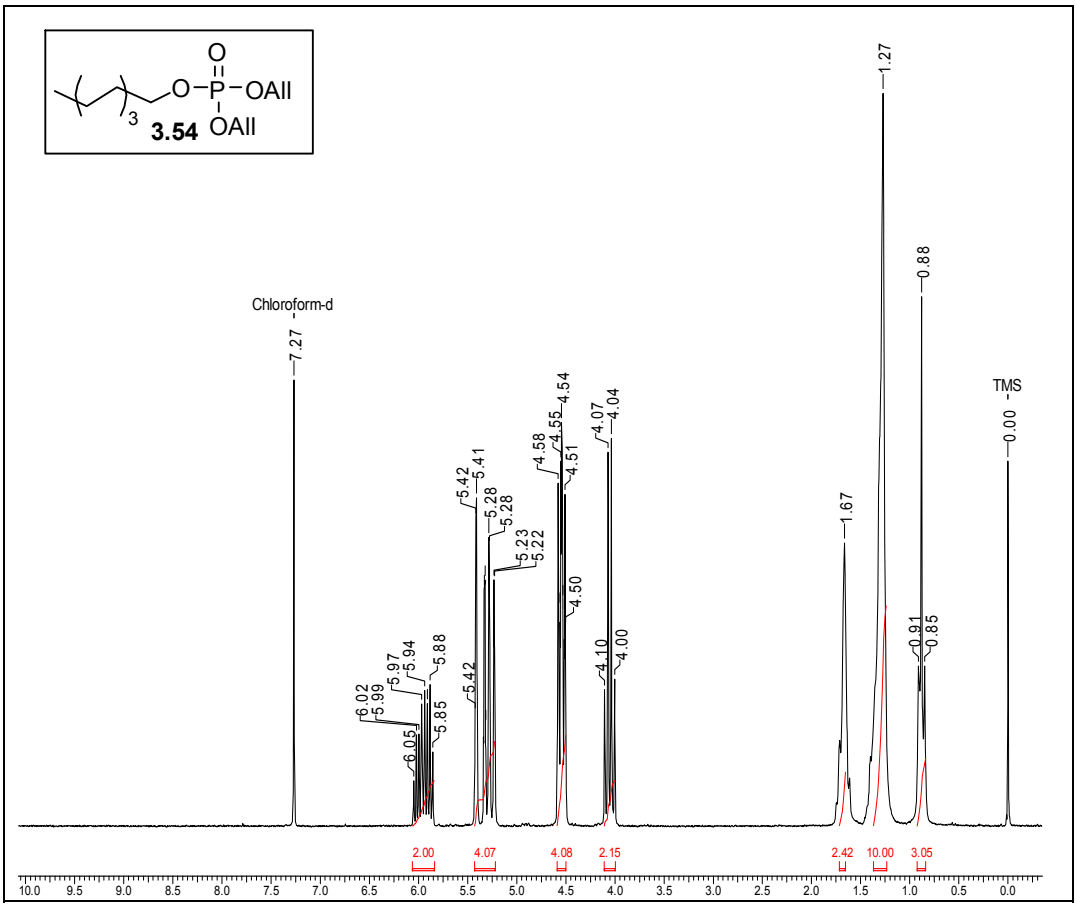
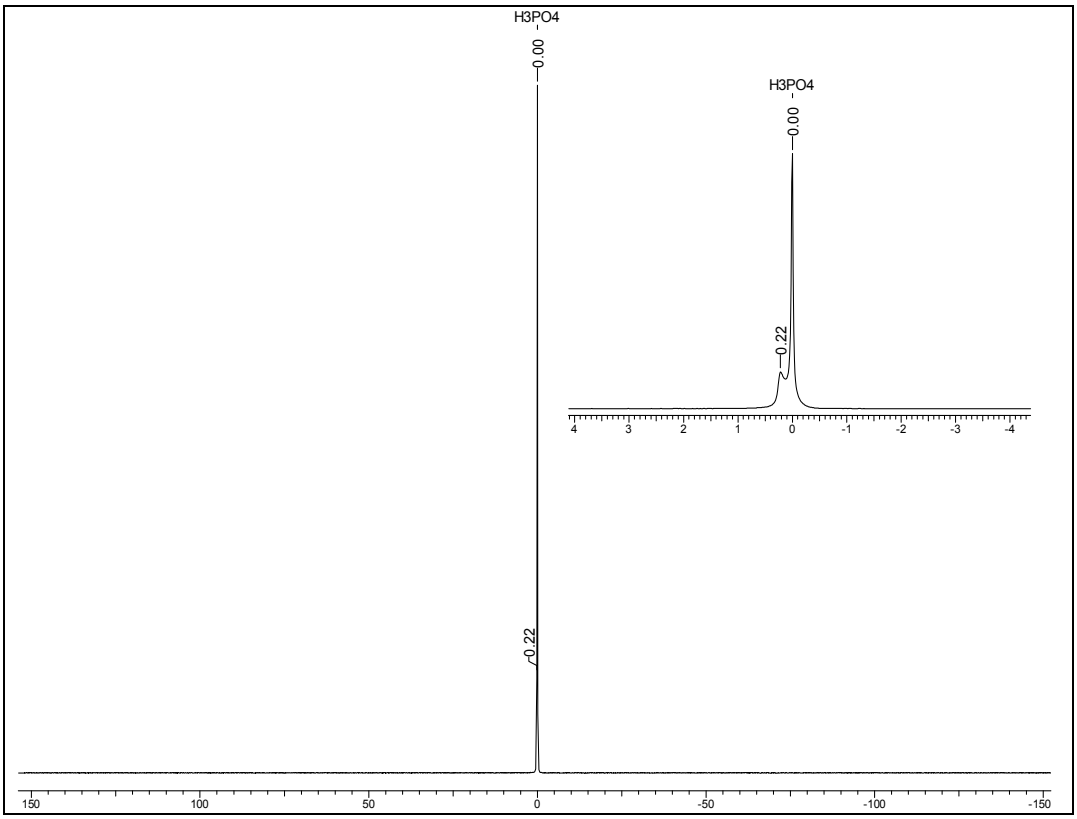
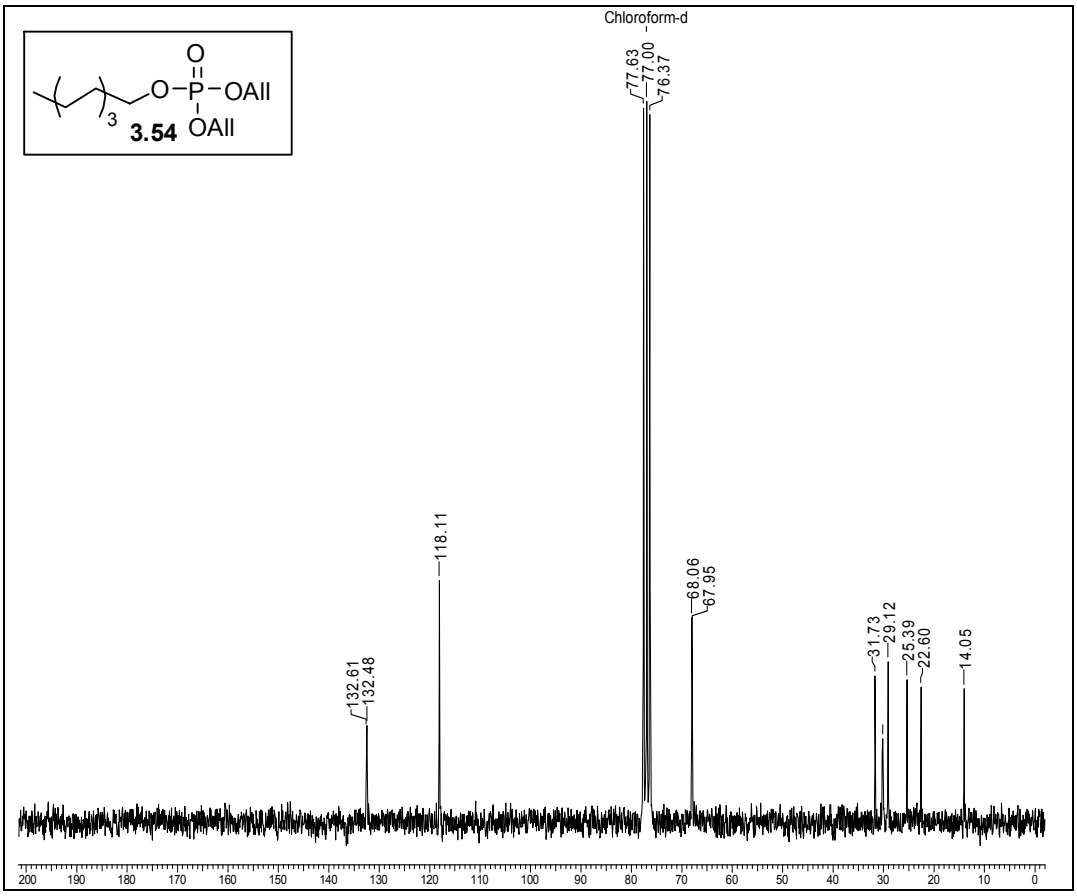
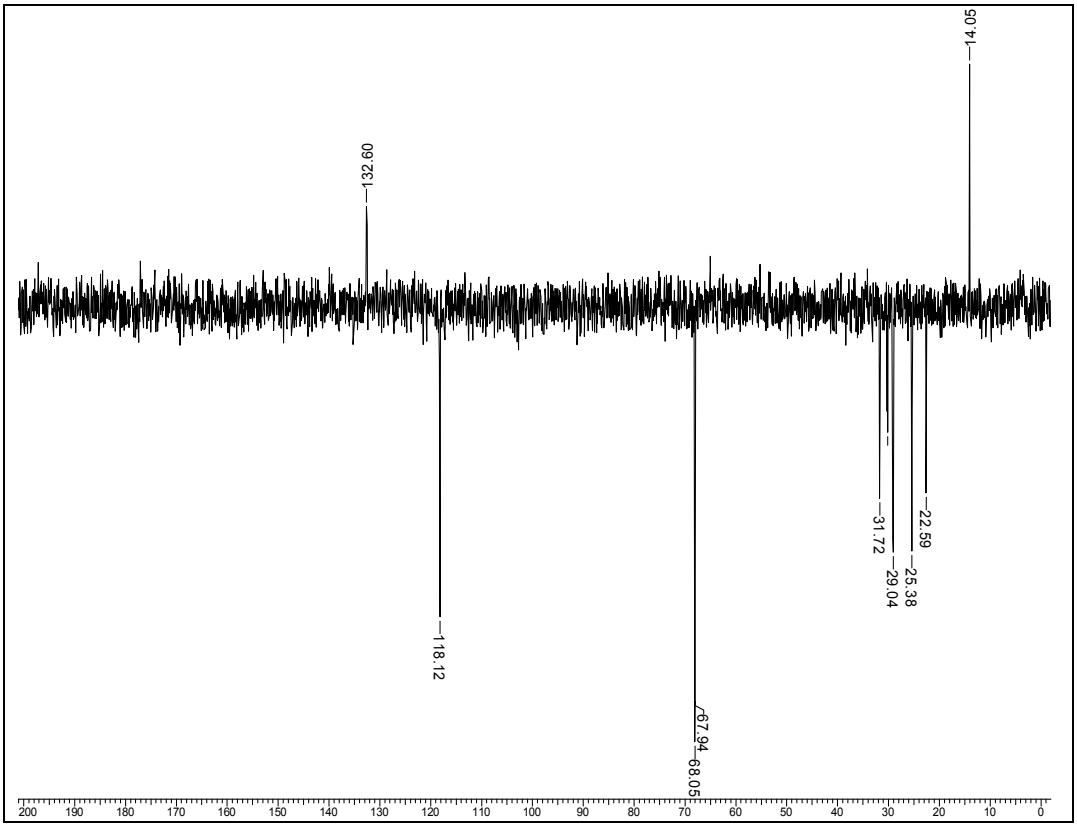
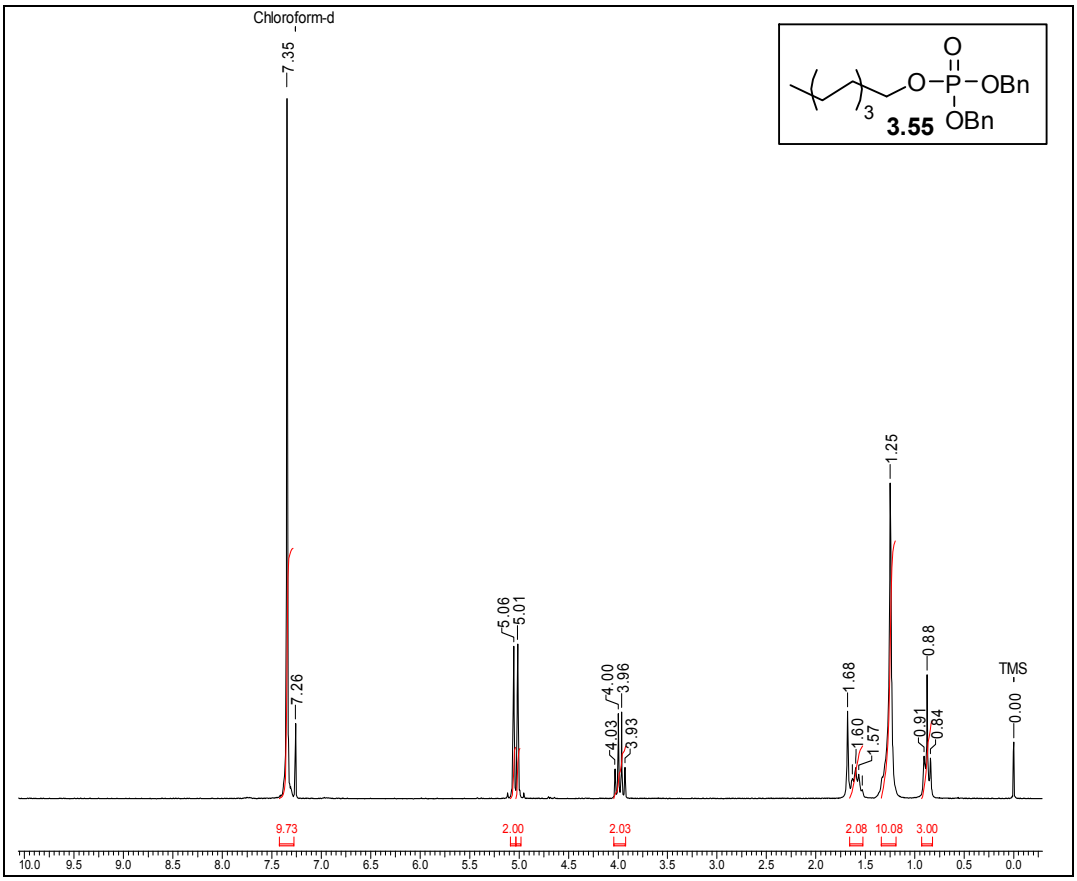
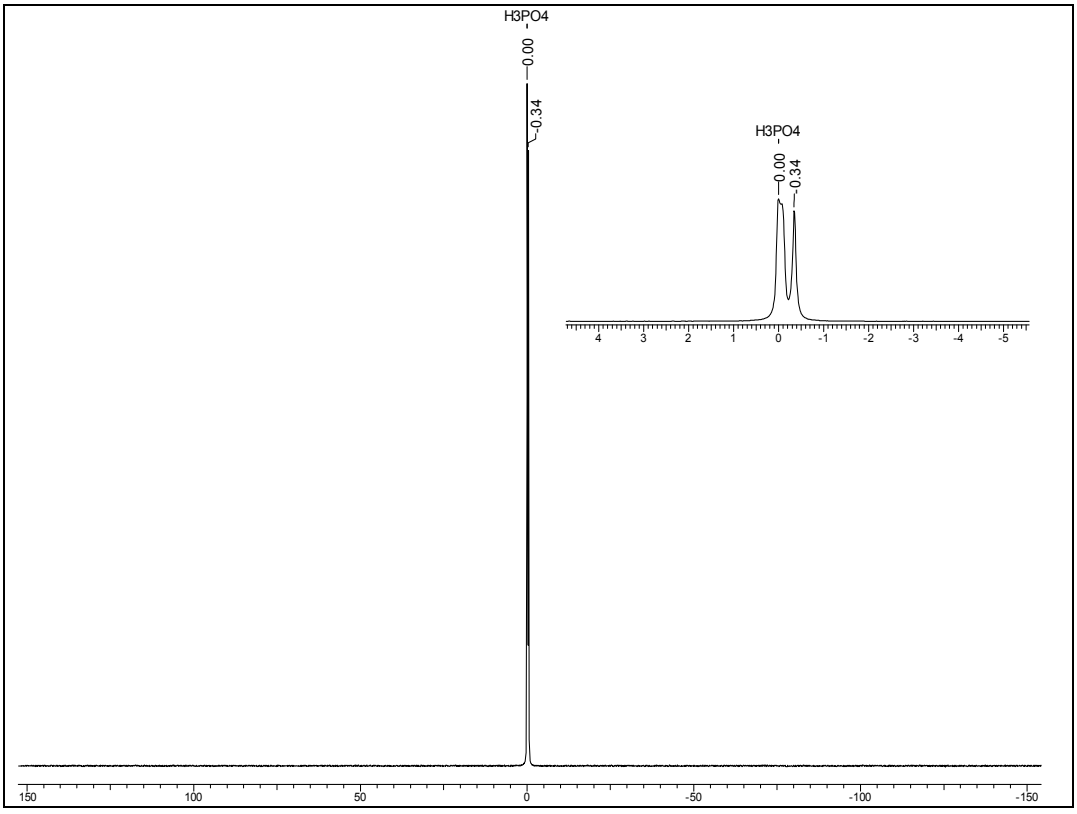

O
O–P–OAll
3
OAll
3.54
Chloroform-d
7.27
1.27
0.88
TMS
0.00
1.67
0.91
0.85
5.42
5.41
5.28
5.28
5.23
5.22
4.58
4.55
4.54
4.51
4.50
4.07
4.04
4.10
4.00
6.02
5.99
5.97
5.94
5.88
5.85
6.05
2.00
4.07
4.08
2.15
2.42
10.00
3.05

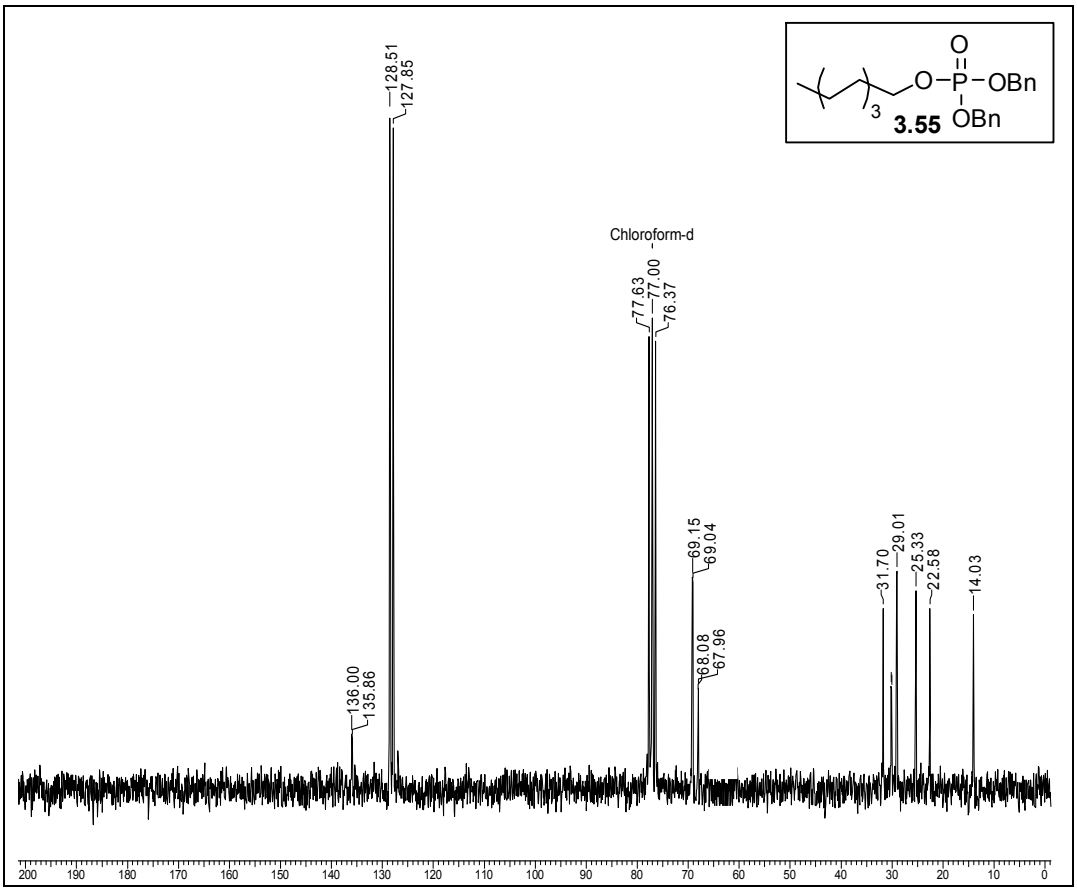

H3PO4
0.00
0.22
H3PO4
0.00
0.22

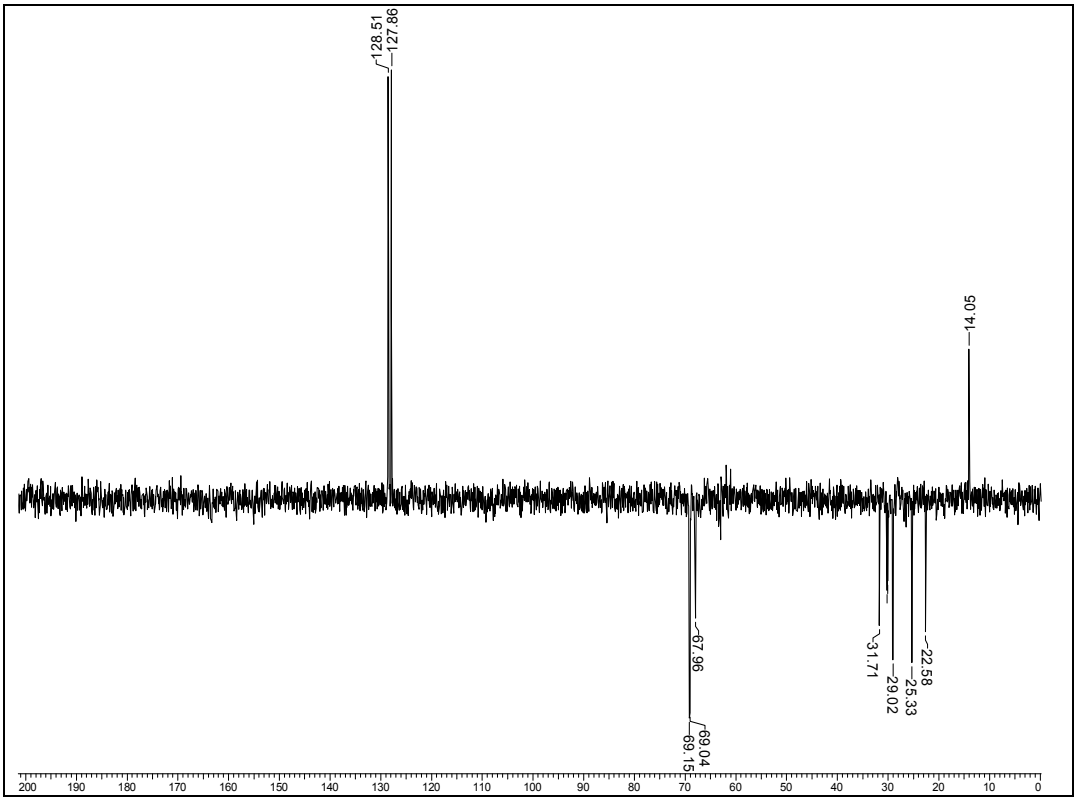

Chloroform-d
77.63
77.00
76.37
118.11
68.06
67.95
132.61
132.48
31.73
29.12
25.39
22.60
14.05
O
O–P–OAll
3
3.54 OAll

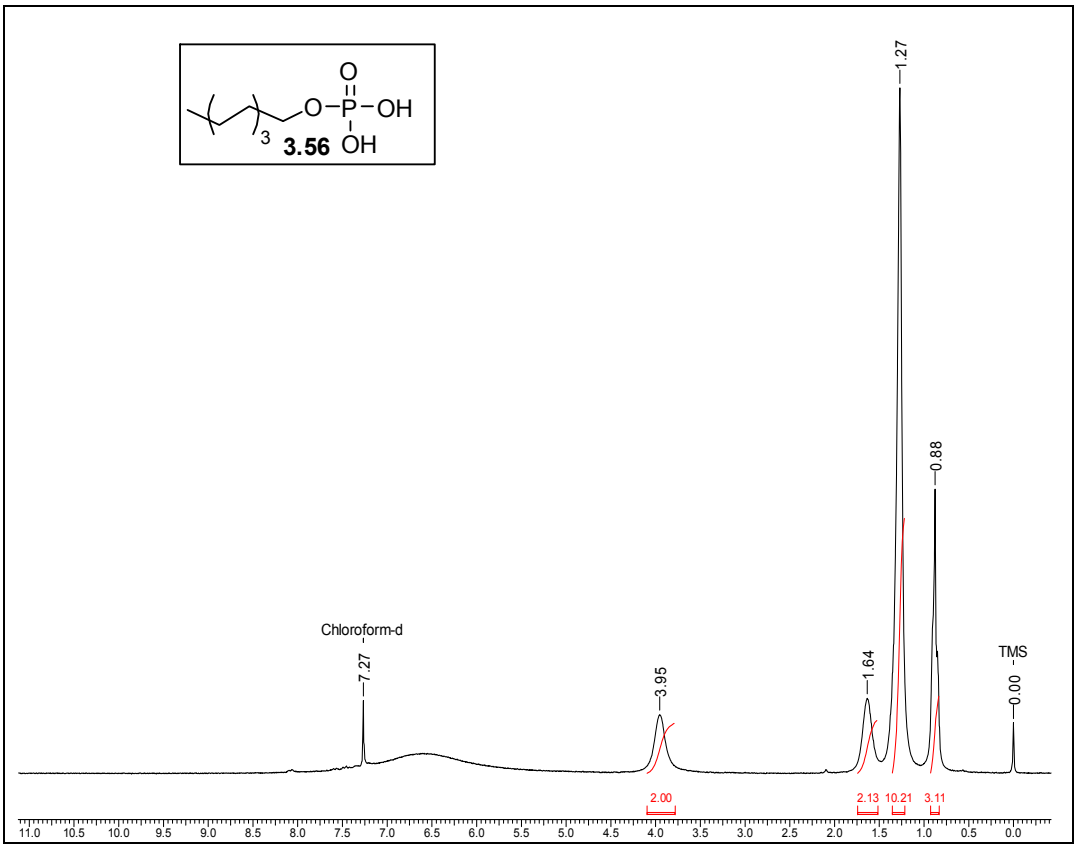

14.05
132.60
31.72
29.04
25.38
22.59
118.12
67.94
68.05

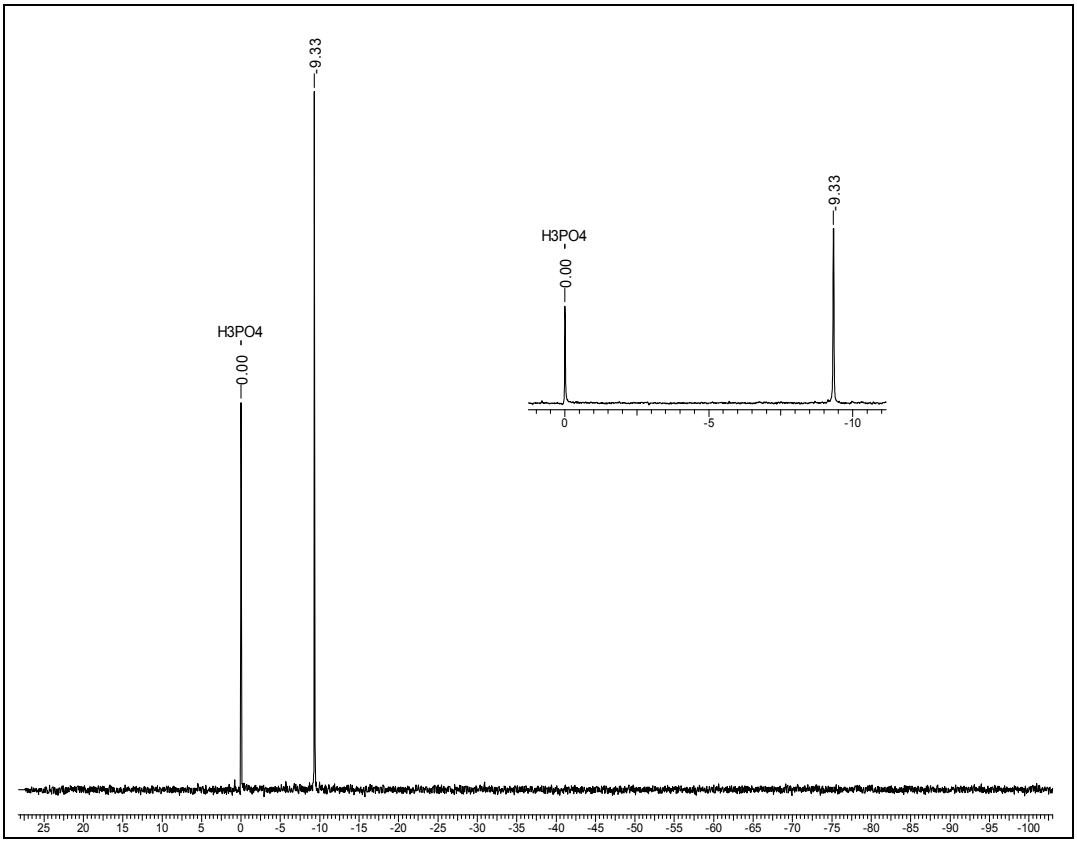

Chloroform-d
7.35
7.26
5.06
5.01
4.03
4.00
3.96
3.93
1.68
1.60
1.57
1.25
0.91
0.88
0.84
TMS
0.00
9.73
2.00
2.03
2.08
10.08
3.00
3.55
OBn
OBn

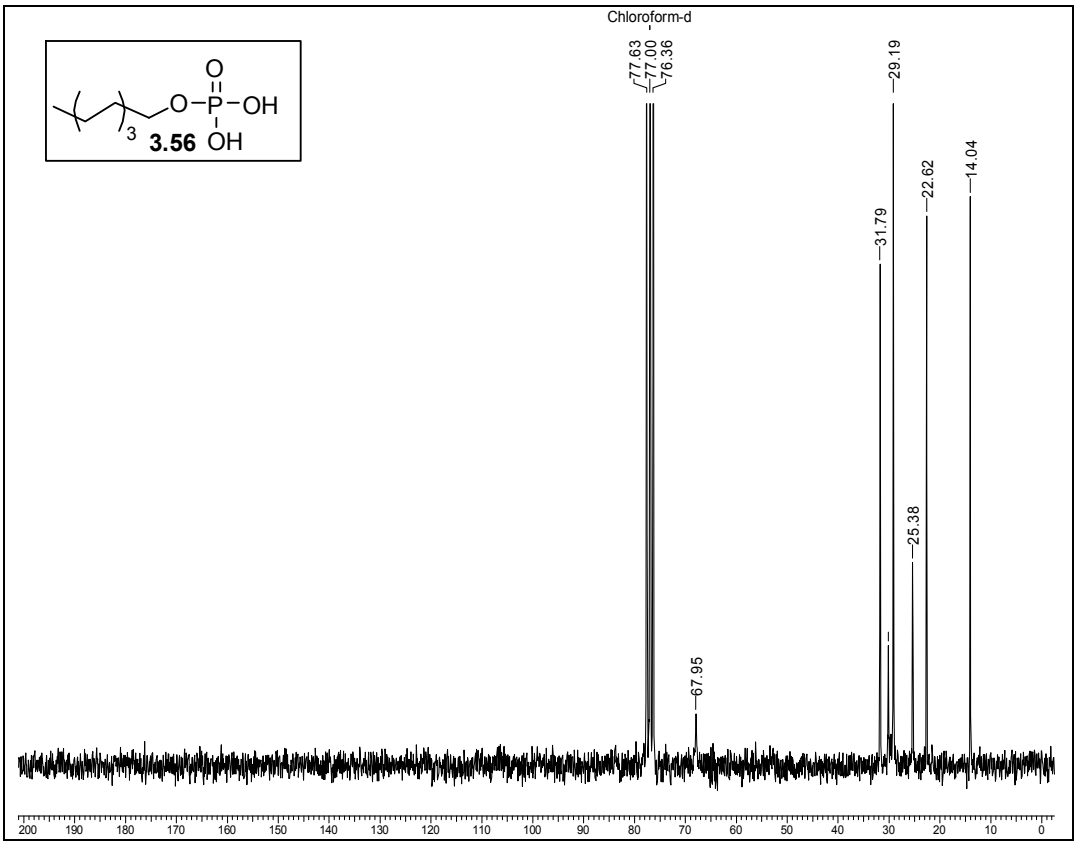

H3PO4
0.00
-0.34
H3PO4
0.00
-0.34

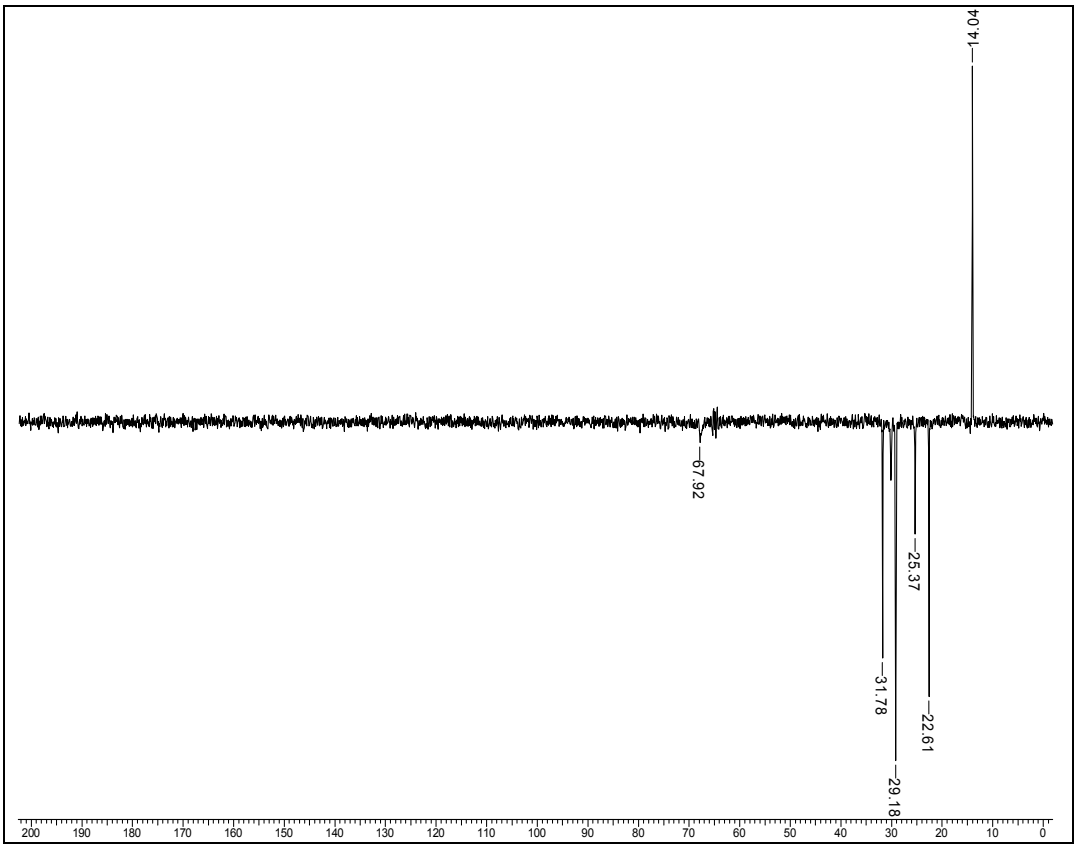

O
O–P–OBn
3
OBn
3.55
128.51
127.85
Chloroform-d
77.63
77.00
76.37
69.15
69.04
68.08
67.96
136.00
135.86
31.70
29.01
25.33
22.58
14.03

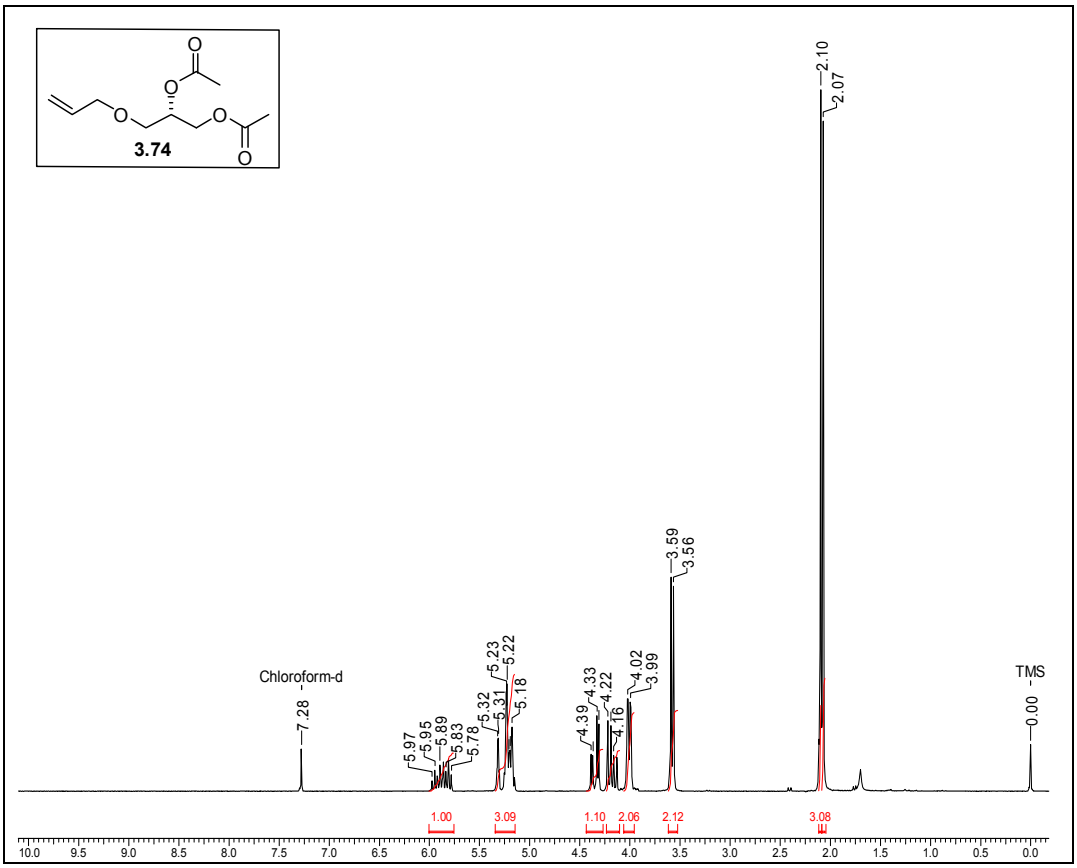

128.51
127.86
14.05
67.96
69.04
69.15
31.71
29.02
25.33
22.58

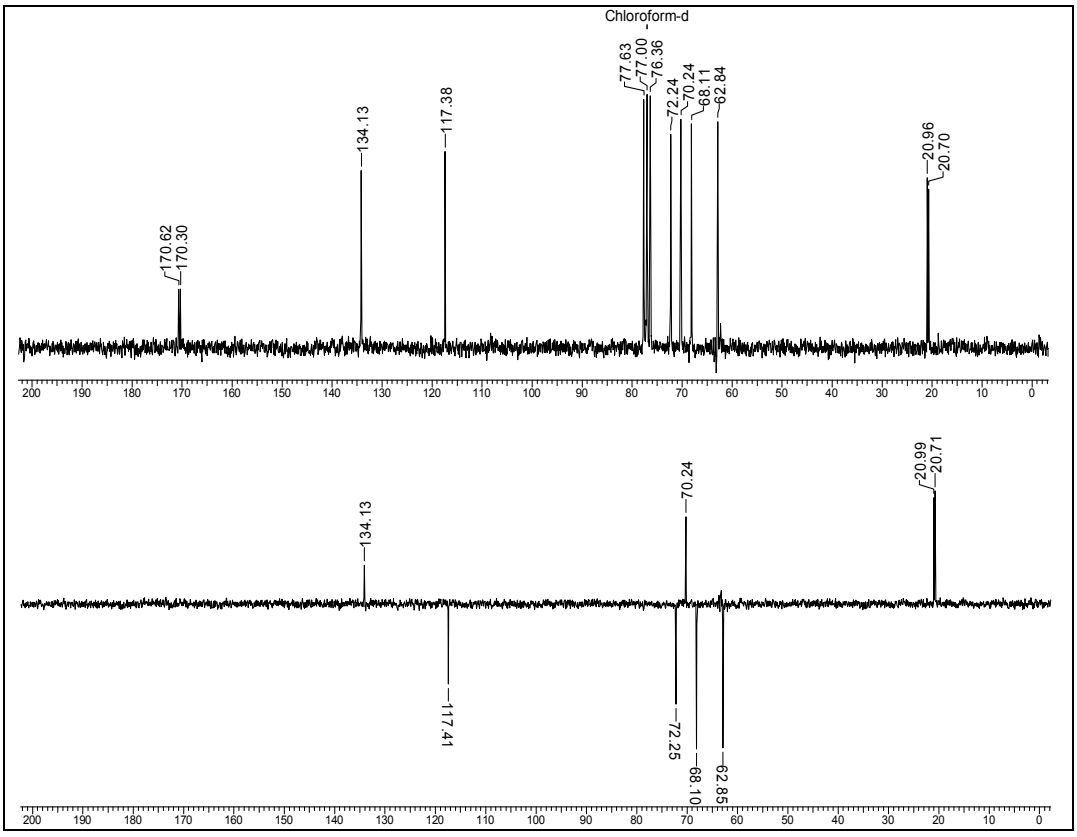

3.56
Chloroform-d
7.27
3.95
1.64
1.27
0.88
TMS
0.00
2.00
2.13
10.21
3.11


H3PO4
0.00
9.33
H3PO4
0.00
9.33


Chloroform-d
77.63
77.00
76.36
29.19
31.79
25.38
22.62
14.04
67.95
3.56 OH
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


14.04
67.92
25.37
31.78
22.61
29.18
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


3.74
Chloroform-d
7.28
5.97
5.95
5.89
5.83
5.78
5.32
5.31
5.23
5.22
5.18
4.39
4.33
4.22
4.16
4.02
3.99
3.59
3.56
2.10
2.07
TMS
0.00
1.00
3.09
1.10
2.06
2.12
3.08


Chloroform-d
170.62
170.30
134.13
117.38
77.63
77.00
76.36
72.24
70.24
68.11
62.84
20.96
20.70
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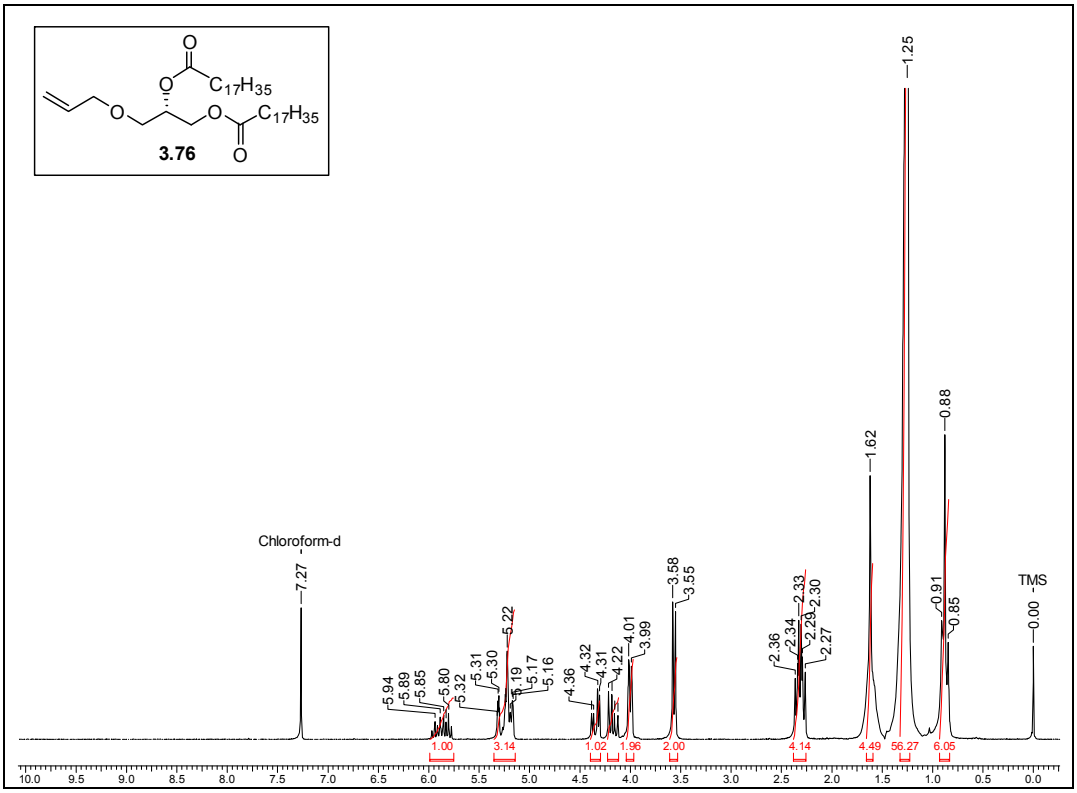
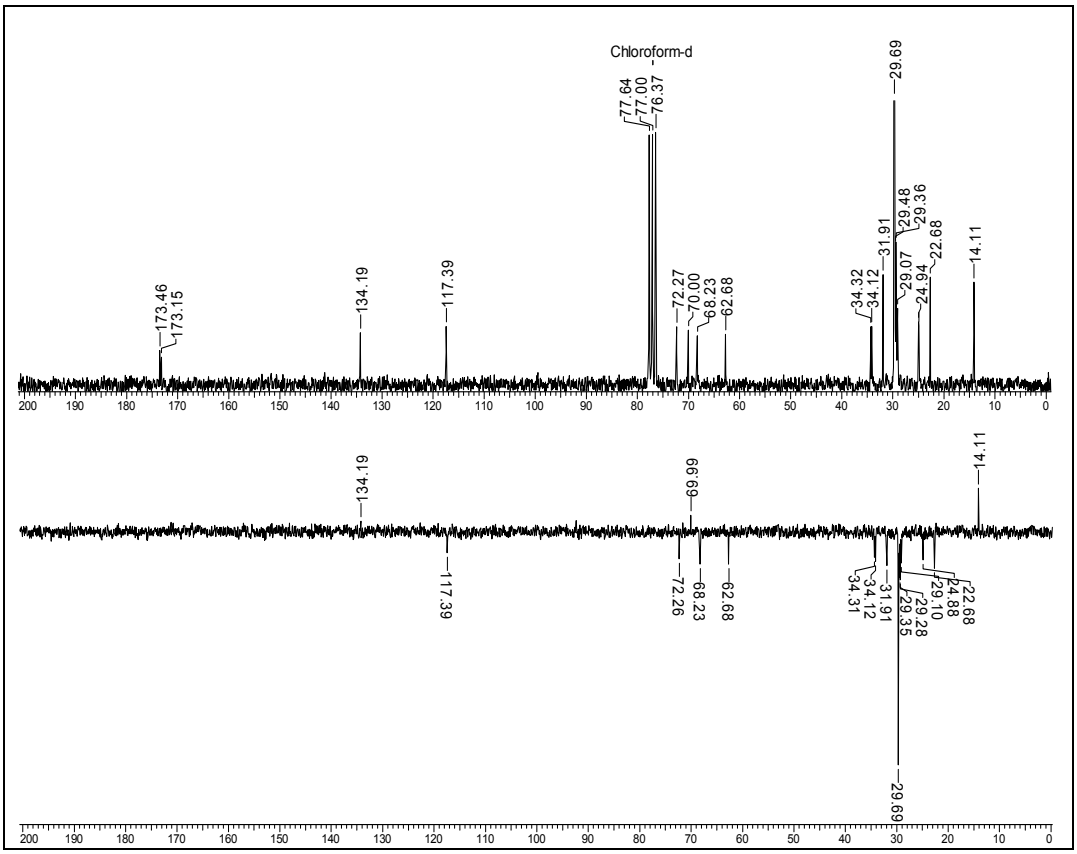
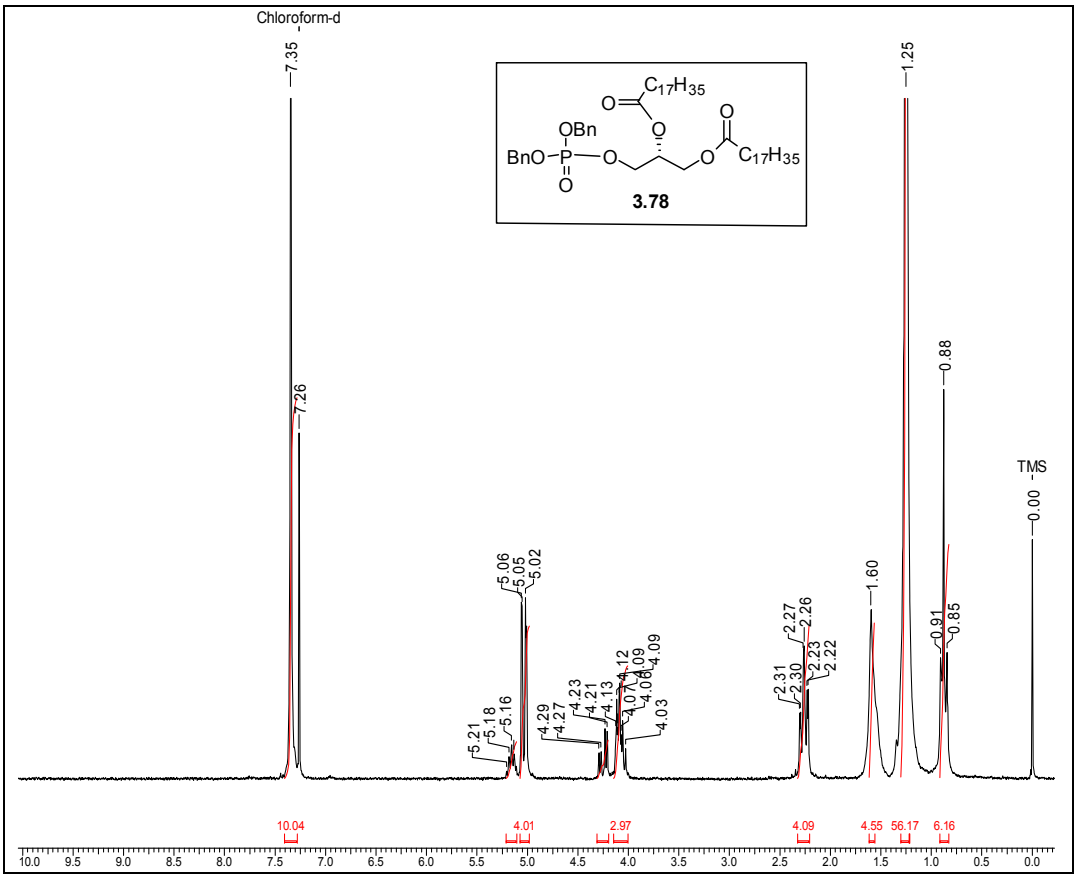
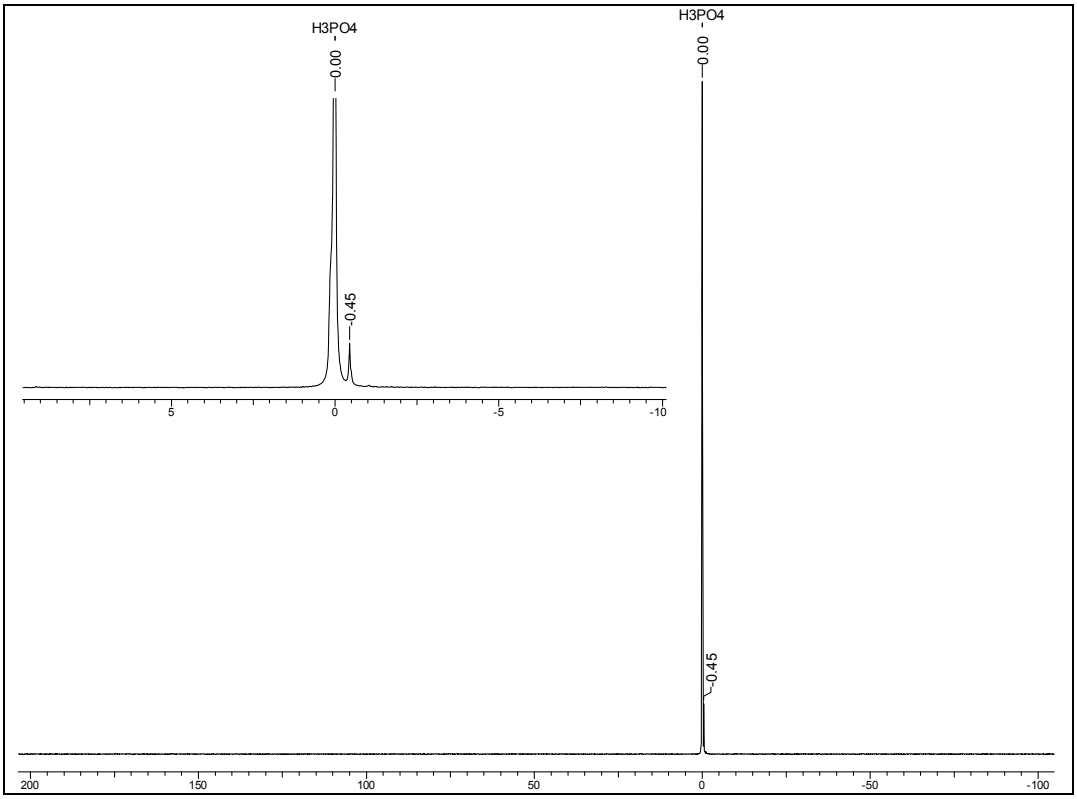
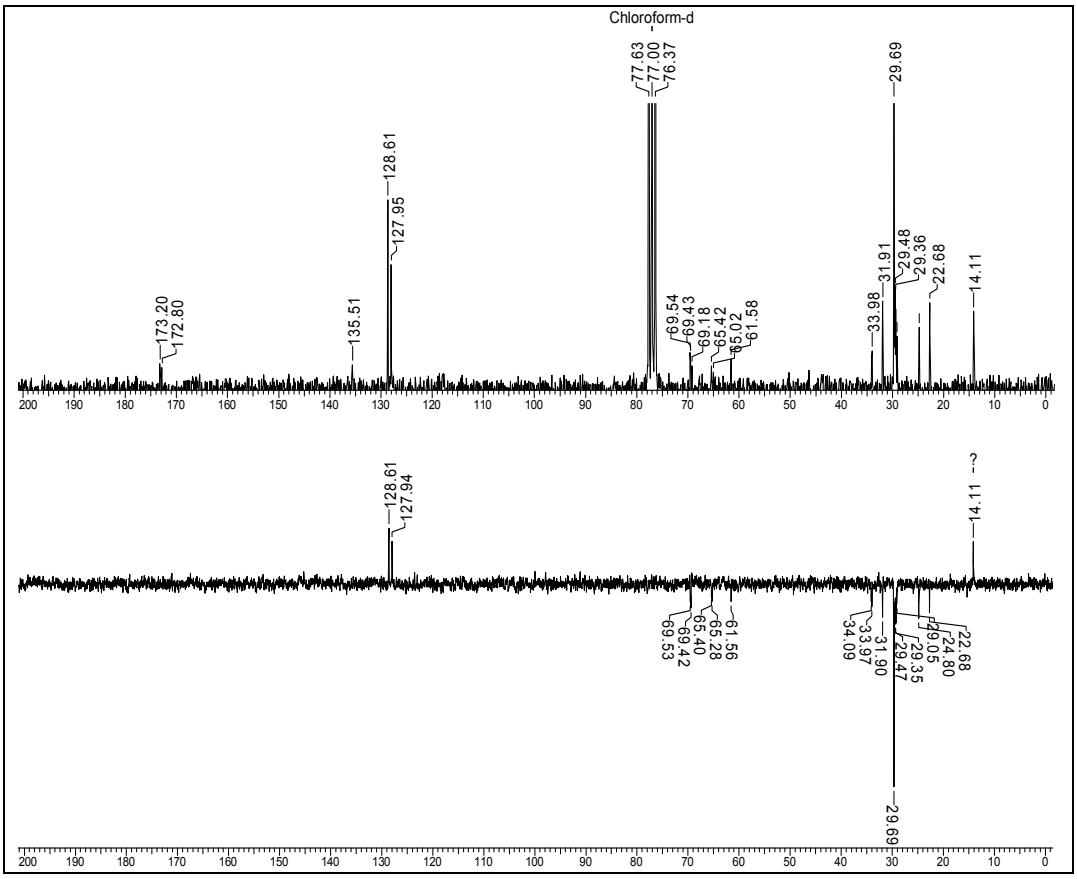
117.41
70.24
72.25
68.10
62.88
20.99
20.71

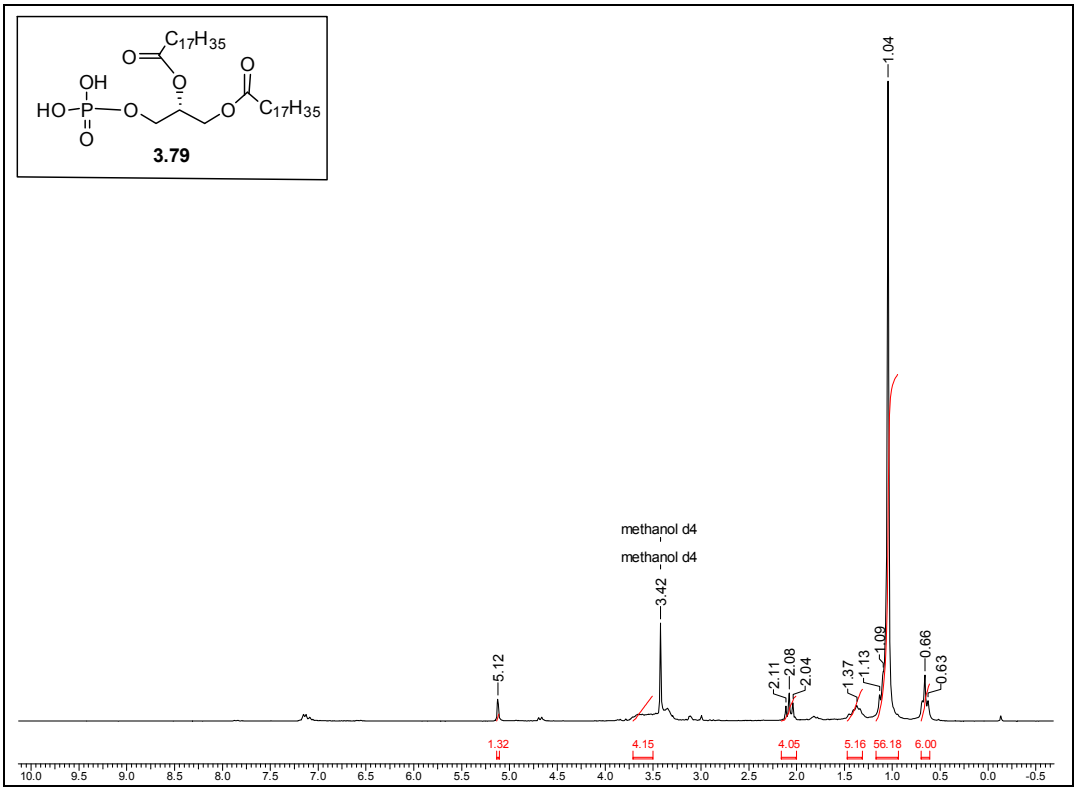

3.76
Chloroform-d
7.27
5.94
5.89
5.85
5.80
5.32
5.31
5.30
5.22
5.19
5.17
5.16
4.36
4.32
4.31
4.22
4.01
3.99
3.58
3.55
2.36
2.34
2.33
2.30
2.29
2.27
1.62
1.25
0.91
0.88
0.85
TMS
0.00
1.00
3.14
1.02
1.96
2.00
4.14
4.49
56.27
6.05

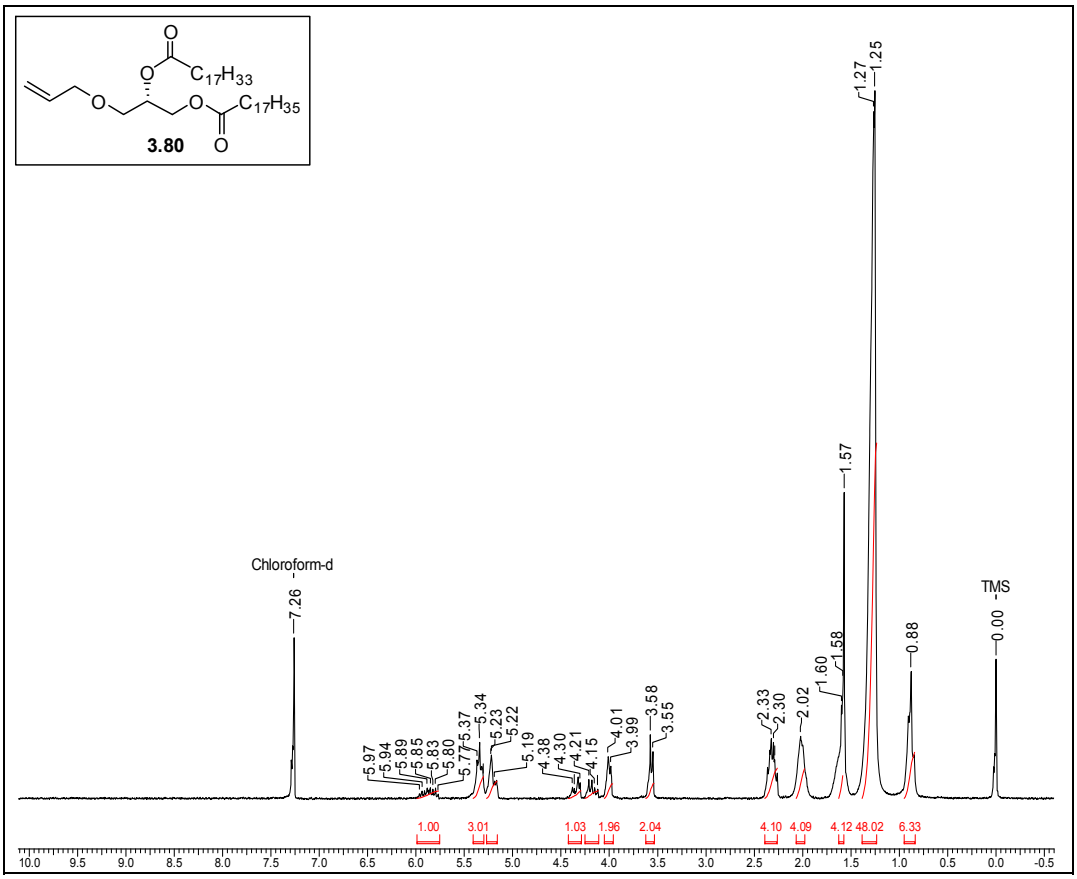

Chloroform-d
77.64
77.00
76.37
173.46
173.15
134.19
117.39
72.27
70.00
68.23
62.68
34.32
34.12
31.91
29.69
29.48
29.36
29.07
24.94
22.68
14.11
134.19
117.39
69.99
72.26
68.23
62.68
14.11
34.31
34.12
31.91
29.35
29.28
29.10
24.88
22.68
29.69

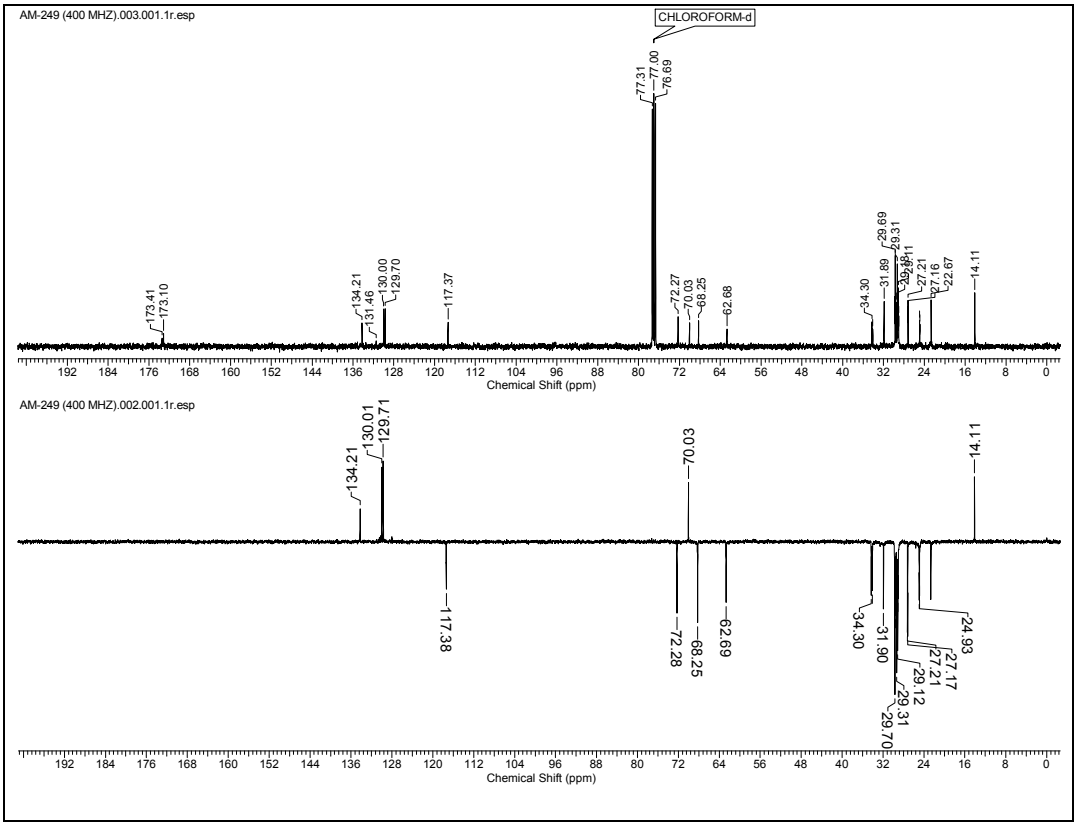

Chloroform-d
7.35
7.26
1.25
0.88
TMS
0.00
1.60
0.91
0.85
5.06
5.05
5.02
5.21
5.18
5.16
4.29
4.27
4.23
4.21
4.13
4.12
4.09
4.08
4.07
4.03
2.31
2.30
2.27
2.26
2.23
2.22
10.04
4.01
2.97
4.09
4.55
56.17
6.16
3.78

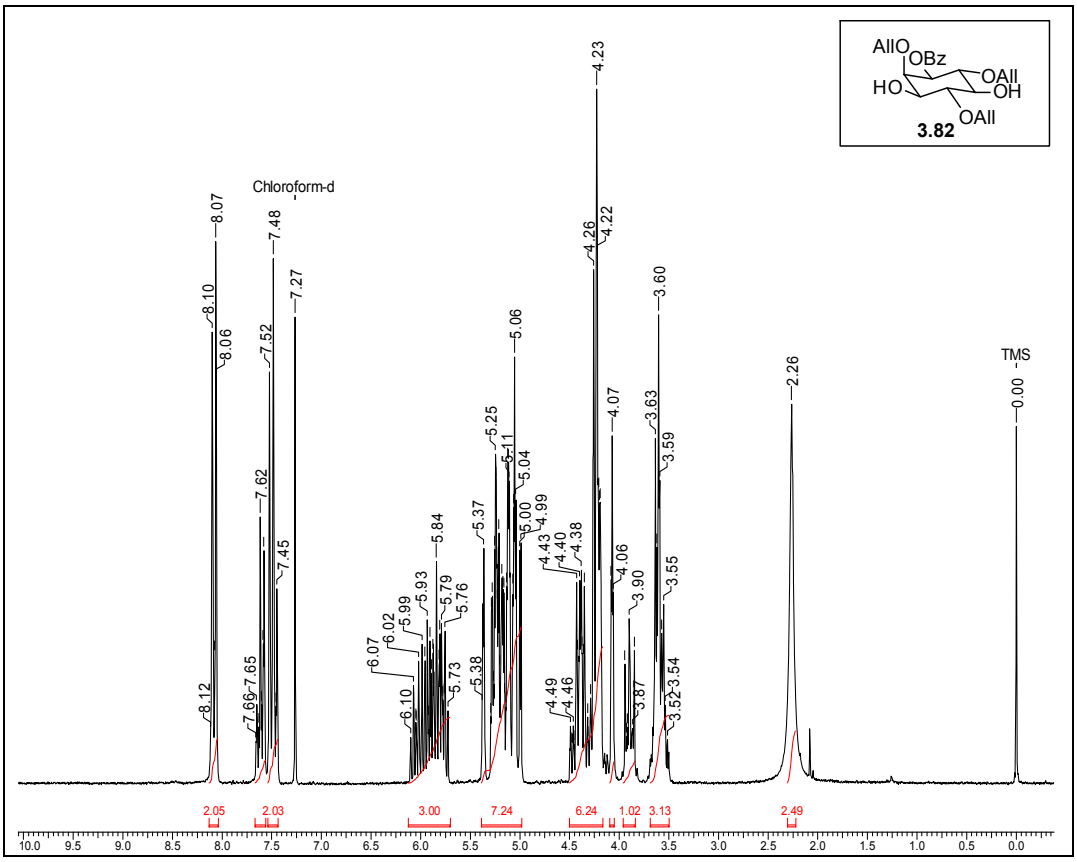

H3PO4
0.00
0.45
H3PO4
0.00
0.45

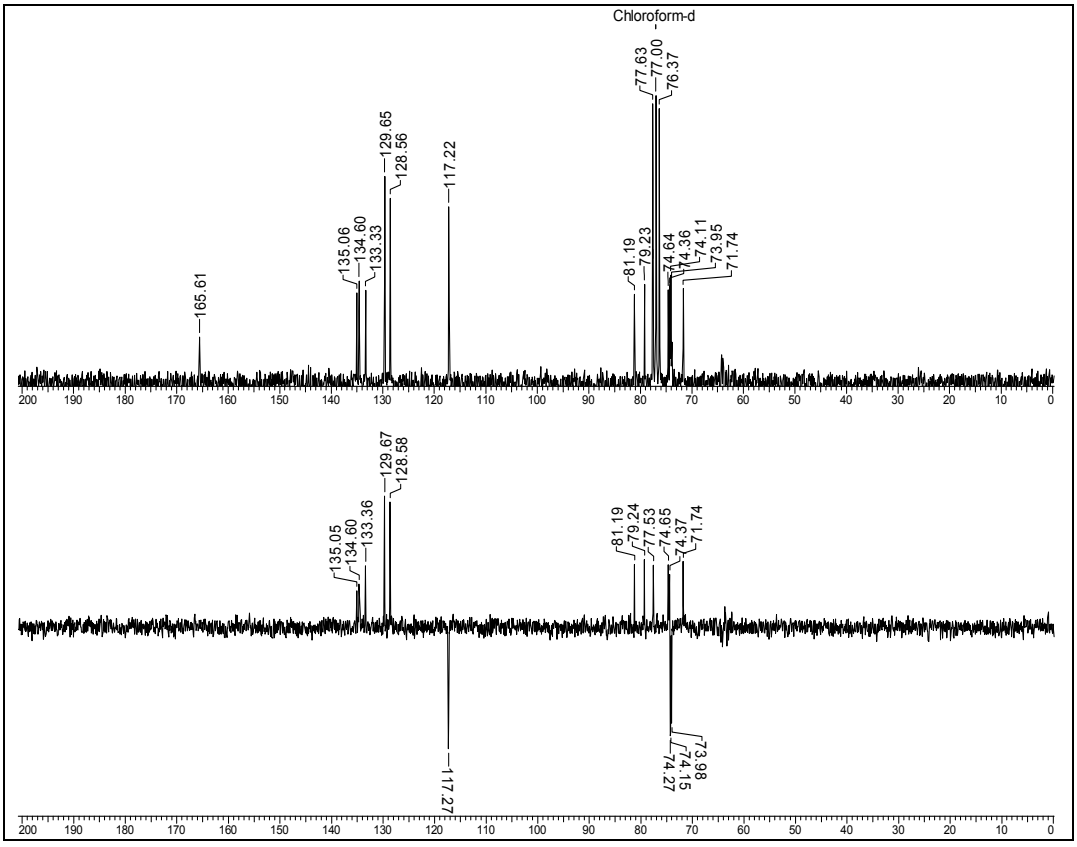

Chloroform-d
77.63
77.00
76.37
29.69
128.61
127.95
173.20
172.80
135.51
69.54
69.43
69.18
65.42
65.02
61.58
33.98
31.91
29.48
29.36
22.88
14.11
128.61
127.94
14.11
69.53
69.42
65.40
65.28
61.96
34.09
33.97
31.90
29.47
29.35
29.05
24.80
22.68
29.69

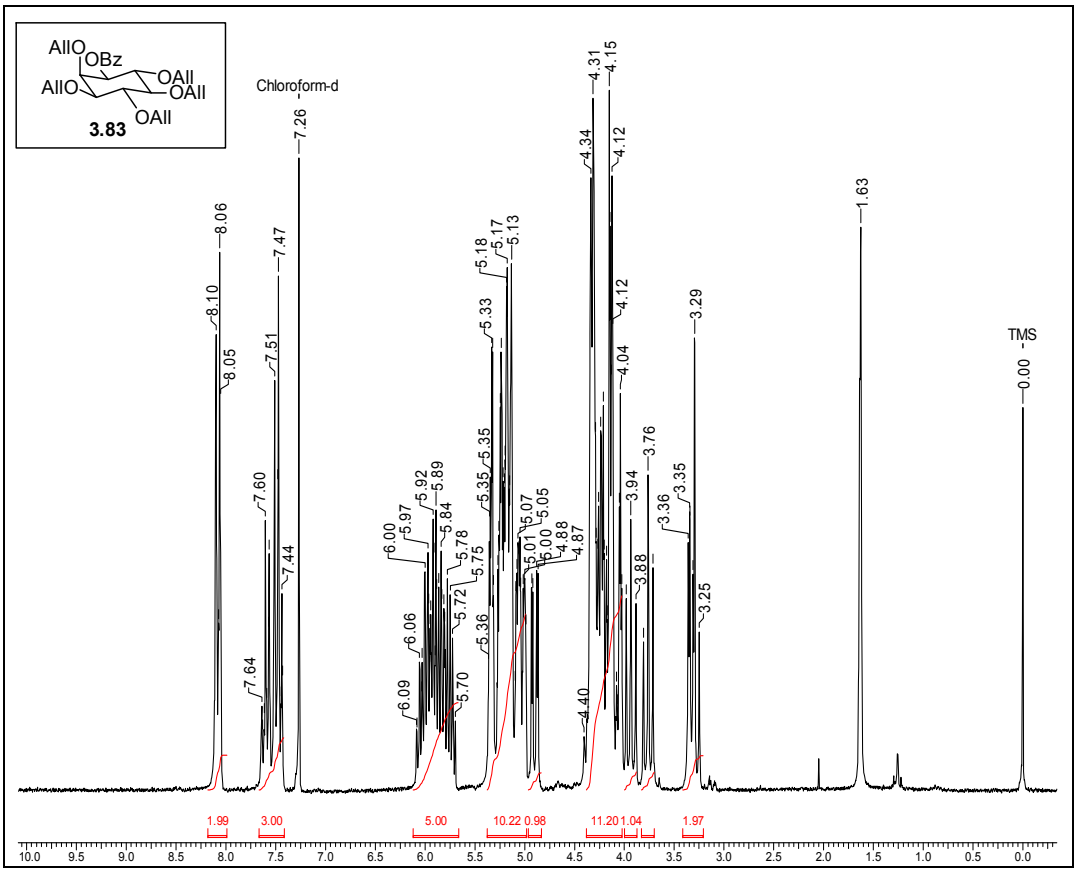

$C_{17}H_{35}$
OH
HO
P
O
$C_{17}H_{35}$
3.79
1.04
methanol d4
methanol d4
3.42
5.12
2.11
2.08
2.04
1.37
1.13
1.09
0.66
0.63
1.32
4.15
4.05
5.16
56.18
6.00

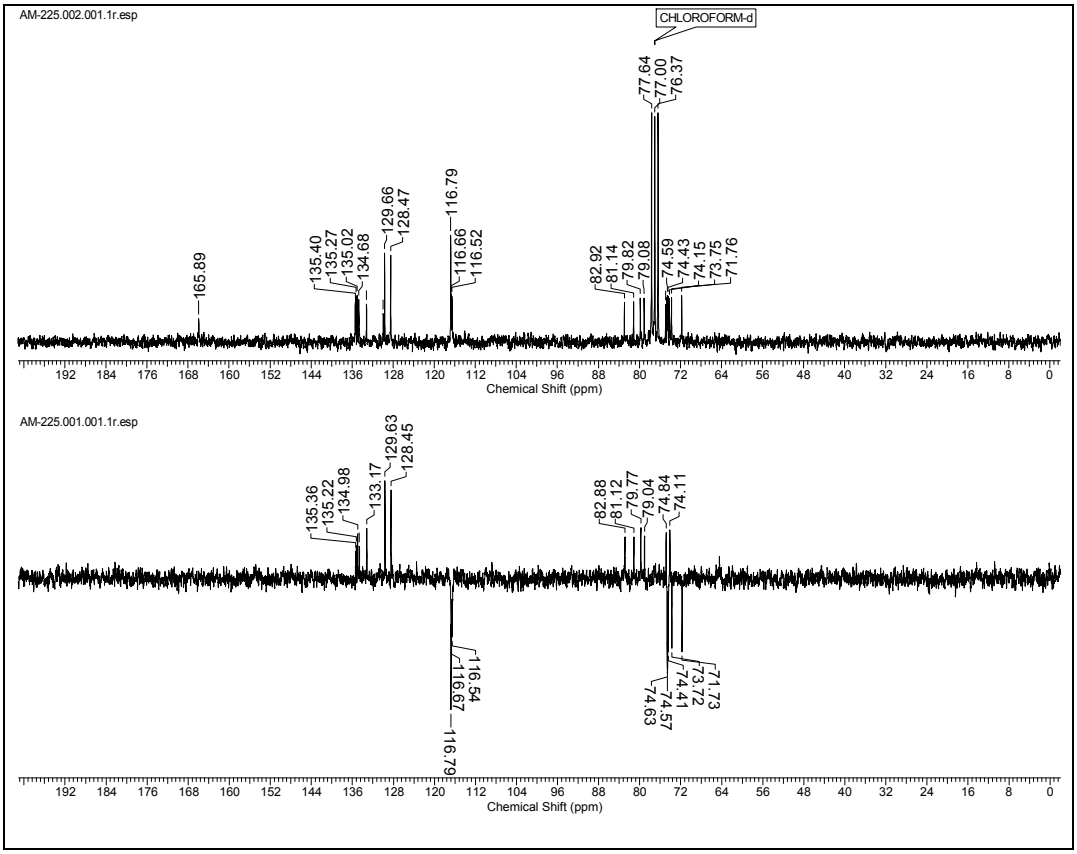

3.80
Chloroform-d
TMS
7.26
0.00
1.27
1.25
1.57
1.60
1.58
0.88
2.33
2.30
2.02
5.97
5.94
5.89
5.85
5.83
5.80
5.77
5.37
5.34
5.23
5.22
5.19
4.38
4.30
4.21
4.15
4.01
3.99
3.58
3.55
1.00
3.01
1.03
1.96
2.04
4.10
4.09
4.12
48.02
6.33

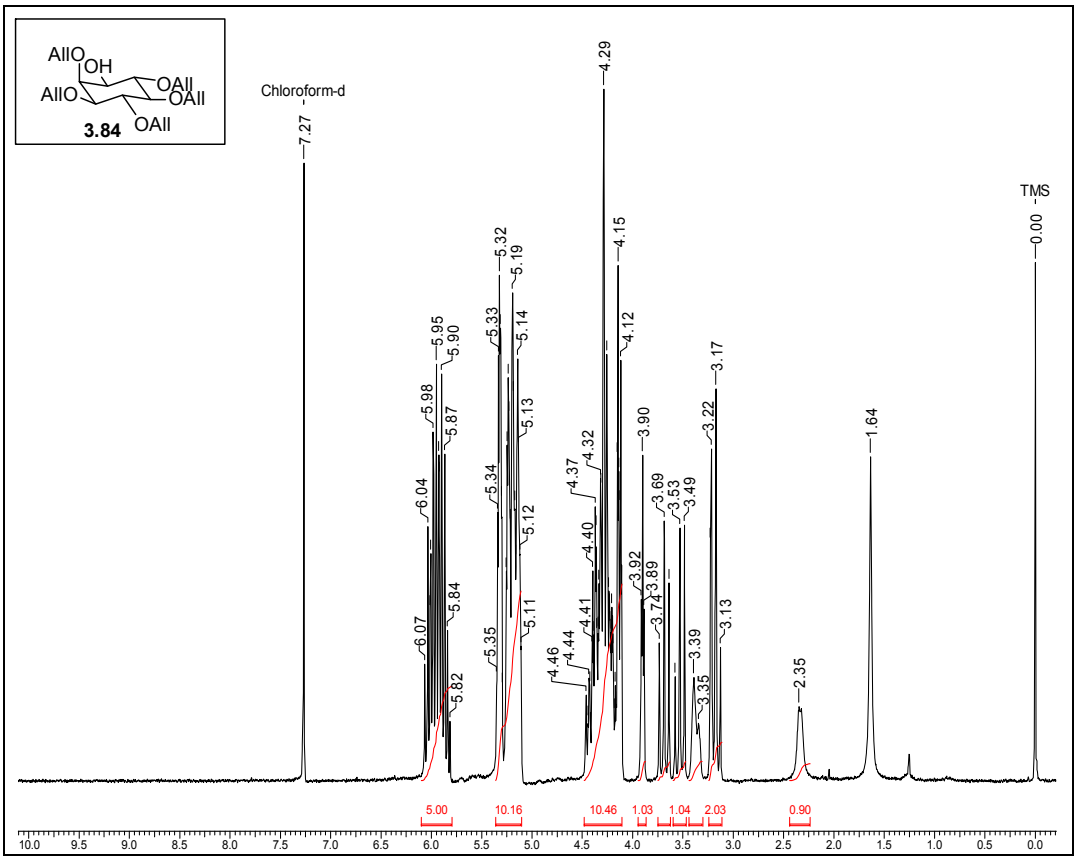

AM-249 (400 MHZ).003.001.1r.esp
CHLOROFORM-d
77.31
77.00
76.69
173.41
173.10
134.21
131.46
130.00
129.70
117.37
72.27
70.03
68.25
62.68
34.30
31.89
29.69
29.31
29.12
29.11
27.21
27.16
22.67
14.11
Chemical Shift (ppm)
AM-249 (400 MHZ).002.001.1r.esp
134.21
130.01
129.71
70.03
14.11
117.38
72.28
68.25
62.69
34.30
31.90
29.12
29.31
29.70
24.93
27.17
27.21
Chemical Shift (ppm)

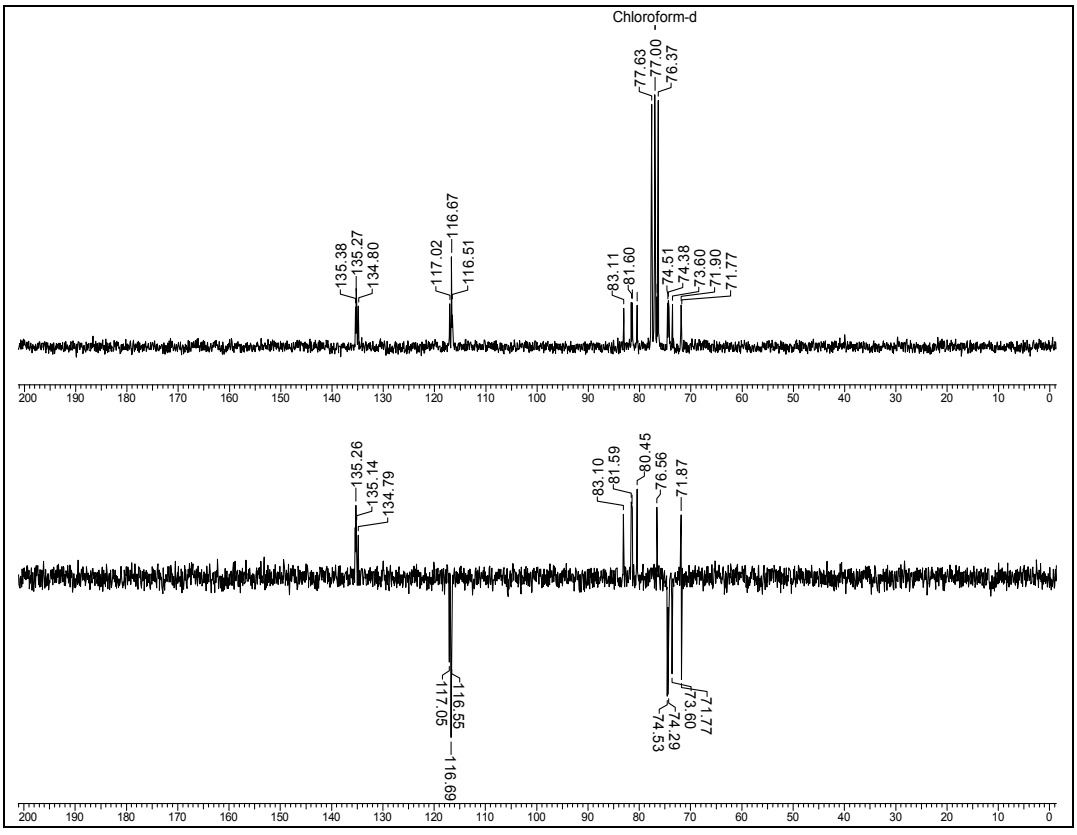

AllO
OBz
HO
OAll
OH
OAll
3.82
Chloroform-d
TMS
8.07
8.10
8.06
7.48
7.52
7.27
7.62
7.45
8.12
7.66
7.65
4.23
4.26
4.22
3.60
5.06
5.25
5.11
5.04
5.00
4.99
5.37
5.84
4.43
4.40
4.38
4.07
3.63
3.59
2.26
0.00
6.07
6.02
5.99
5.93
5.79
5.76
5.38
5.73
6.10
4.49
4.46
4.06
3.90
3.55
3.87
3.54
3.52
2.05
2.03
3.00
7.24
6.24
1.02
3.13
2.49

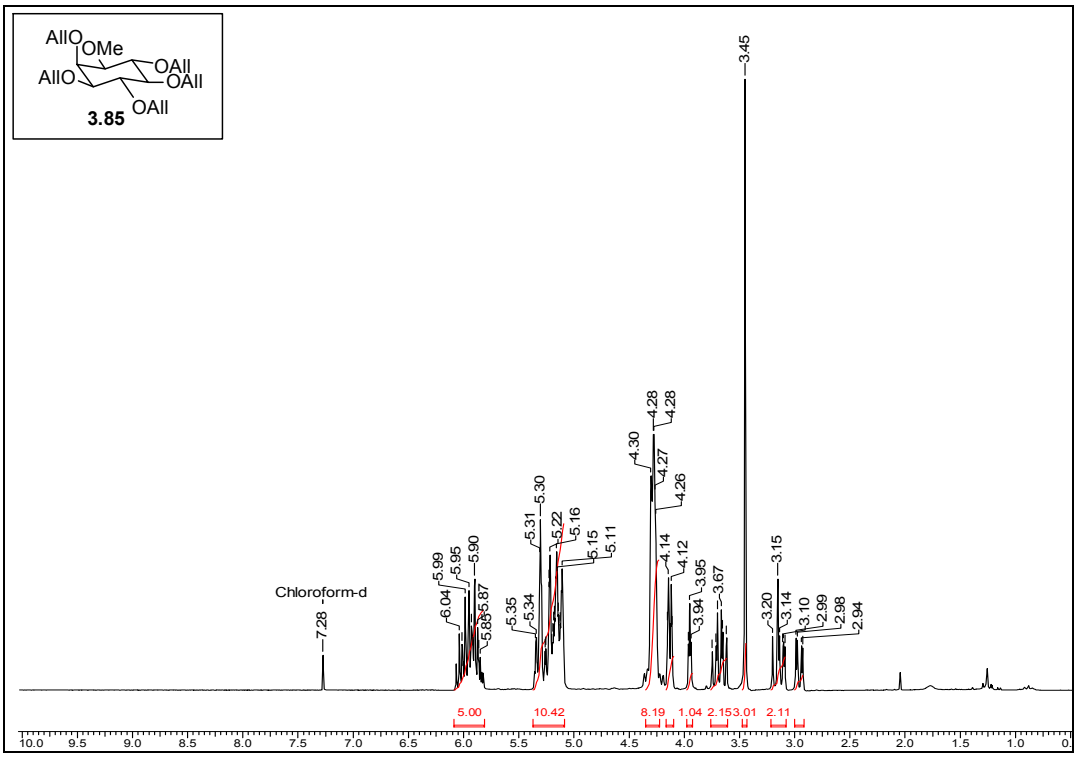

Chloroform-d
77.63
77.00
76.37
129.65
128.56
117.22
135.06
134.60
133.33
165.61
81.19
79.23
74.64
74.36
74.11
73.95
71.74
129.67
128.58
135.05
134.60
133.36
81.19
79.24
77.53
74.65
74.37
71.74
117.27
73.98
74.15
74.27


AllO
OBz
AllO
OAll
OAll
OAll
3.83
Chloroform-d
TMS


AM-225.002.001.1r.esp
CHLOROFORM-d
Chemical Shift (ppm)
AM-225.001.001.1r.esp
Chemical Shift (ppm)


AllO
OH
AllO
OAll
OAll
OAll
3.84
Chloroform-d
7.27
4.29
4.15
4.12
3.90
3.17
3.22
1.64
TMS
0.00
5.32
5.19
5.33
5.14
5.95
5.90
5.98
5.87
5.13
6.04
5.34
5.12
4.37
4.32
4.40
3.92
3.89
3.74
3.69
3.53
3.49
6.07
5.84
5.11
4.41
4.44
4.46
5.35
5.82
3.39
3.35
3.13
2.35
5.00
10.16
10.46
1.03
1.04
2.03
0.90


Chloroform-d
77.63
77.00
76.37
135.38
135.27
134.80
117.02
116.67
116.51
83.11
81.60
74.51
74.38
73.60
71.90
71.77
135.26
135.14
134.79
83.10
81.59
80.45
76.56
71.87
117.05
116.55
116.69
74.63
74.29
74.00
71.77


AllO
OMe
OAll
AllO
OAll
OAll
3.85
Chloroform-d
7.28
5.99
5.95
5.90
6.04
5.87
5.85
5.35
5.34
5.31
5.30
5.22
5.16
5.15
5.11
4.30
4.28
4.28
4.27
4.26
4.14
4.12
3.95
3.94
3.67
3.45
3.20
3.15
3.14
3.10
2.99
2.98
2.94
5.00
10.42
8.19
1.04
2.15
3.01
2.11
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.