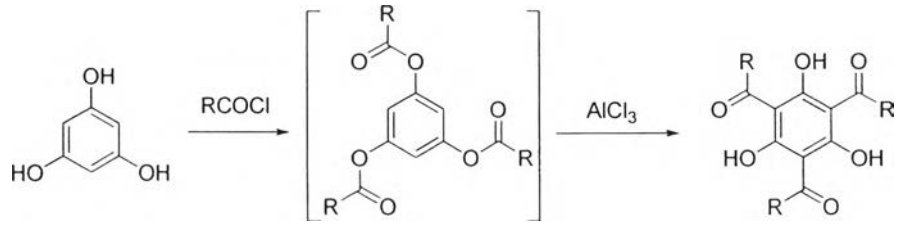
CHAPTER III

RESULTS AND DISCUSSION

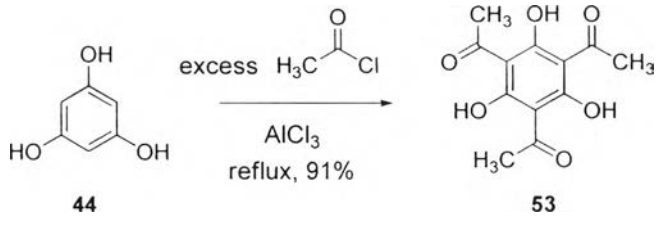
3.1 Synthesis of hexasubstituted benzene derivatives

The synthesis of 1,3,5-triacyl-2,4,6-trihydroxybenzene had been successfully performed using phloroglucinol dihydrate as the starting material reacting with various acid chlorides (RCOCl; R = CH_3, Ph and C_7H_{15}) as the electrophilic reagent and medium [80]. The desired products were obtained presumably through triple *O*-acylations and then underwent Fries rearrangement to *ortho* or *para*-positions to become tris(hydroxyacyl)aromatic molecules upon treatment with $AlCl_3$ (**Scheme 3.1**, also see **Section 1.3.2.4**).



Scheme 3.1 The general syntheses of 1,3,5-triacyl-2,4,6-trihydroxybenzene

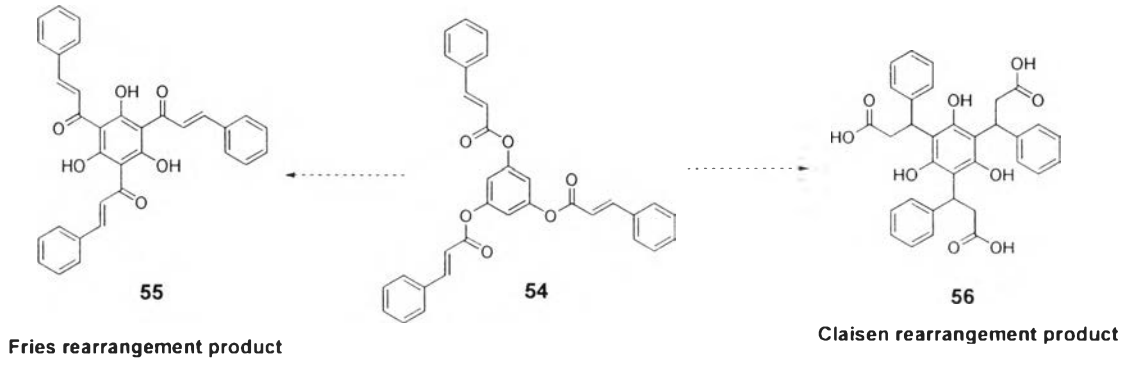
1,3,5-Triacetyl-2,4,6-trihydroxybenzene (**53**) was synthesized in one-pot, one step process by dissolving phloroglucinol dihydrate **(44)** in excess of acetyl chloride and adding 5 mole equivalents of anhydrous $AlCl_3$ into reaction mixture. The reaction was heated at reflux for an hour and then quenched with water. The mixture was filtered and the precipitate was collected. The crude product was recrystalized in ethanol to give colorless needle crystals in excellent yield (91%) (**Scheme 3.2**).



44 **53**

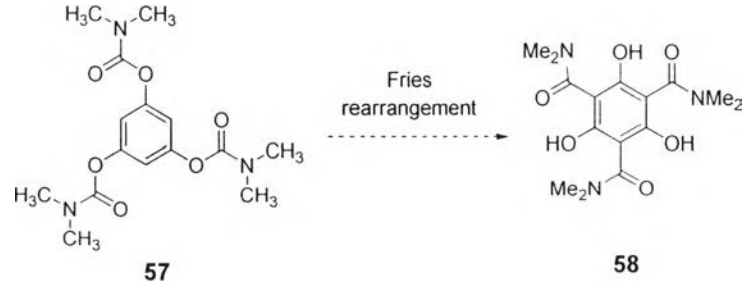
Scheme 3.2 Synthesis of 1,3,5-triacetyl-2,4,6-trihydroxybenzene **(53)**

The synthetic method has been extended to use other acid chlorides as electrophile such as cinnamoyl chloride, *N,N*-dimethylcarbamoyl chloride and chloroacetyl chloride. The triple *O*-acylated products **(54** and **57)** were found as a major product in the cases of cinnamoyl chloride and *N,N*-dimethylcarbamoyl chloride, respectively. Tris-cinnamate ester **54** was subjected to either Fries rearrangement of the acyl groups or Claisen rearrangement to generate hexasubstituted benzenes **55** and **56** respectively in the presence or absence of $AlCl_3$ (**Scheme 3.3**). Unfortunately, the desired products were not found in none of these conditions. Only the starting material was recovered together with some unidentifiable polymeric solids.



Scheme 3.3 The possible rearranged products from tris-cinnamate **54**

The tris-carbamate **57** had also been subjected to Fries rearrangement to tris-amide **58** (**Scheme 3.4**) using *N,N*-dimethylcarbamoyl chloride as medium.



Scheme 3.4 The desired rearranged product from tris-carbamate **57**

After an extraction of the resulted crude product, the ^{1}H-NMR spectrum of the obtained mixture from the organic phase showed unexpected singlet signals of

aromatic protons and complicated proton signals of many types of *N*-CH_3 groups (**Figure 3.1**). Mass spectrum showed the presence of many products, though the desired product was excluded (**Figure 3.2**). Some possible products or MS fragments were shown in **Figure 3.3**. The aqueous extract was also examined. The highly polar solid compound obtained from this phase could not be dissolved in any organic solvents except aqueous hydroxide or strong acid solution, with the unpleasant scent of probably dimethylamine released as byproduct. The polar solid was assumed to be the tricarboxylic acid **59**.

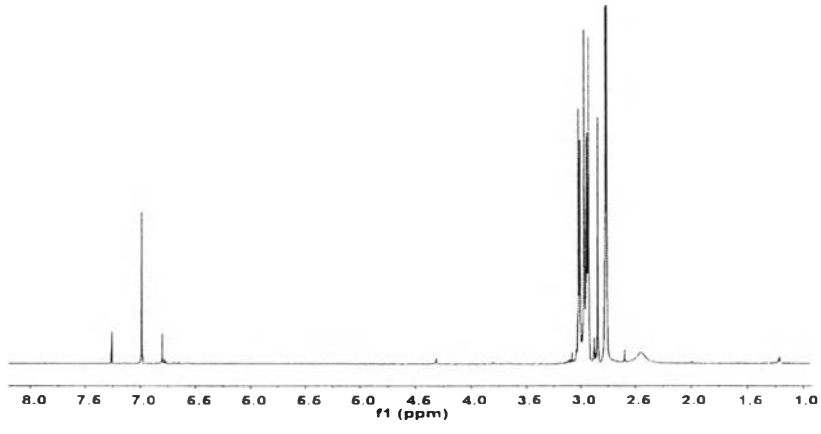


Figure 3.1 ^{1}H-NMR spectrum of the product from tris-carbamate **57**

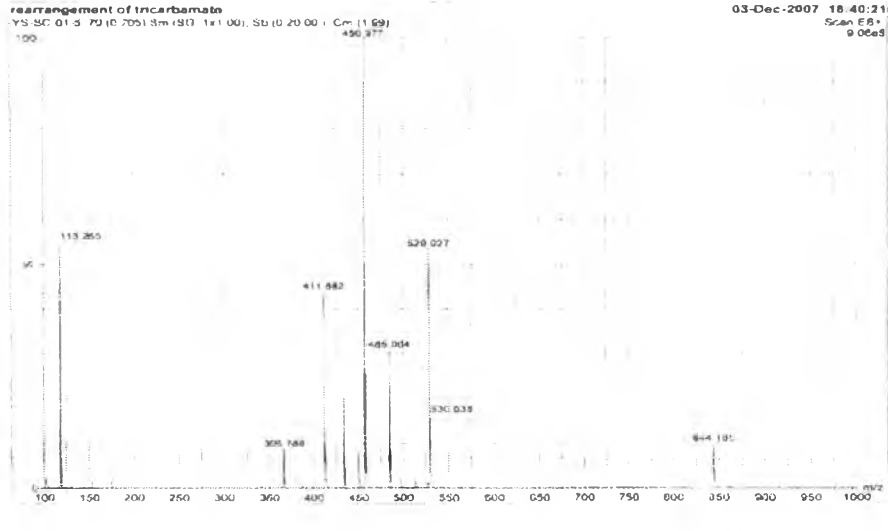


Figure 3.2 Mass spectra of the product from tris-carbamate **57**

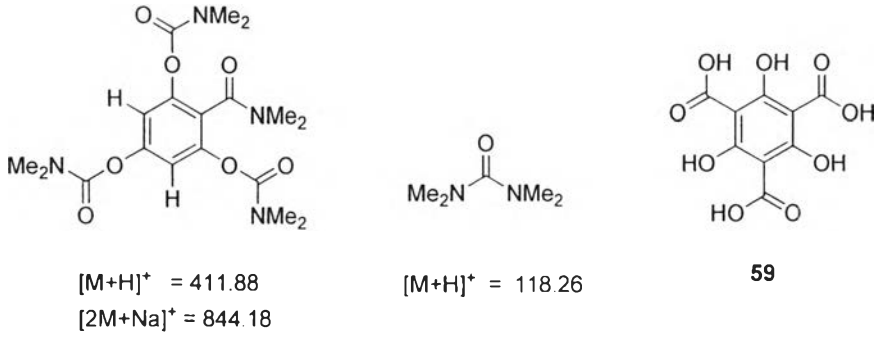
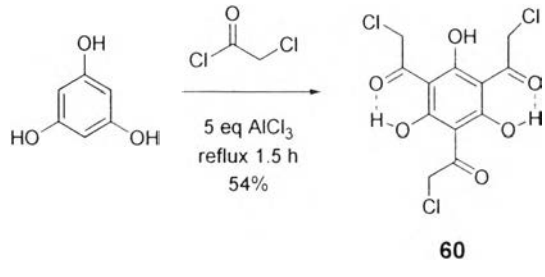


Figure 3.3 Some possible products or MS fragments from the reaction of tris-carbamate **57**

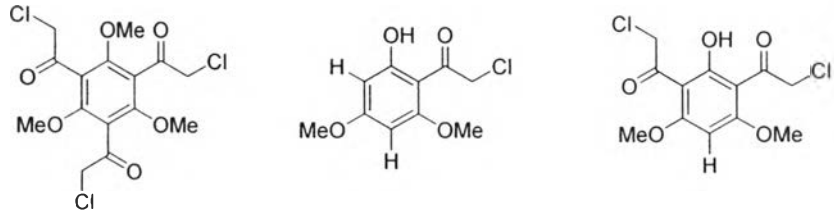
Next, chloroacetyl chloride was used as the electrophile to react with phloroglucinol to observe 1,3,5-tris(chloroacetyl)-2,4,6-trihydroxy benzene **(60)** (**Scheme 3.5**). The reaction gave the product in moderate yields. Although the characterization by ^{1}H-NMR spectroscopy (**Figure A.14**) showed the corresponding signals, the ratio of the peak area of phenolic hydroxy protons and methylene protons were observed to be approximately 1:3 rather than the expected 1:2. It was assumed that the integration of hydroxy protons might not be fully included.



Scheme 3.5 Synthesis of 1,3,5-tris(chloroacetyl)-2,4,6-trihydroxybenzene **(60)**

Alternatively, 1,3,5-trimethoxybenzene **(61)** was used as the starting material to generate 1,3,5-tris(chloroacetyl)-2,4,6-trimethoxybenzene **(62)** by direct *C*-acylations (Friedel-Craft acylation) (**Figure 3.4**). The reaction, however, gave the phenol derivatives **63** and **64** as the isolable products. Low nucleophilicity and the highly steric crowded of the starting material might hindered the reaction toward the electrophile. Moreover, the acidic condition could induce partial demethylation of the starting material, in which presumably compounds **63** and **64** were probably generated

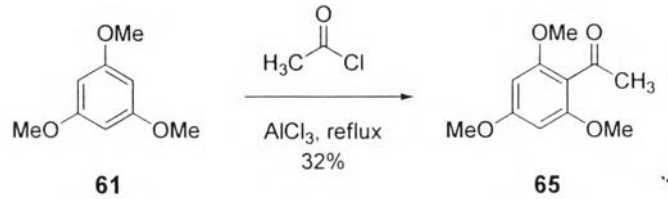
from this phenolic intermediate, through *O*-acylation and Fries rearrangement. The hexasubstituted product still was not observed even with prolonged reaction time.



62 **63** **64**

Figure 3.4 Structures of chloroacetylated compounds **62-64**

To confirm the above observation, compound **61** was also used as the starting material to synthesize hexasubstituted product, 1,3,5-triacetyl-2,4,6-trimethoxy benzene, upon treatment with acetyl chloride (**Scheme 3.6**). In this case, only compound **65** was observed in 32% yield. Prolonged reaction indicated that this highly congested starting material lost its methyl group as well and provided some other mono- and/or dimethylated byproducts.

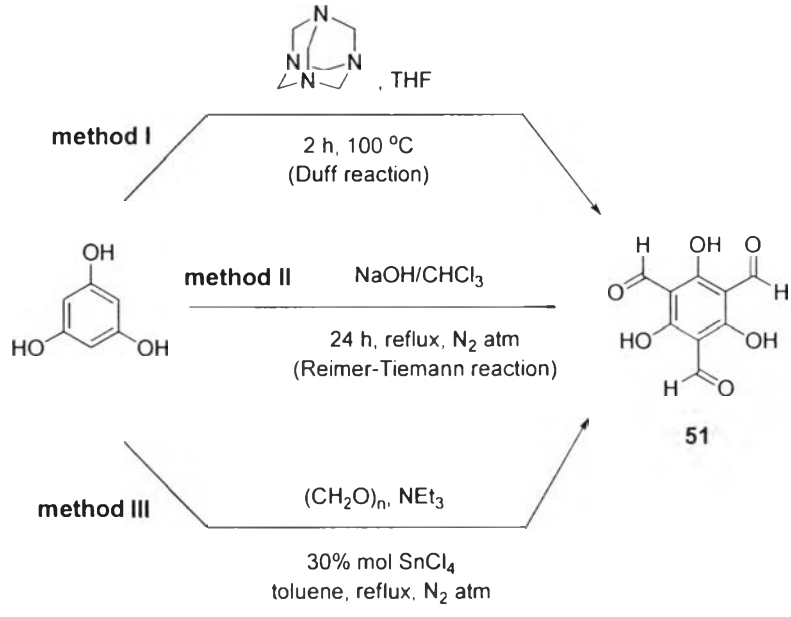


61 **65**

Scheme 3.6 Acetylation of compound **61**

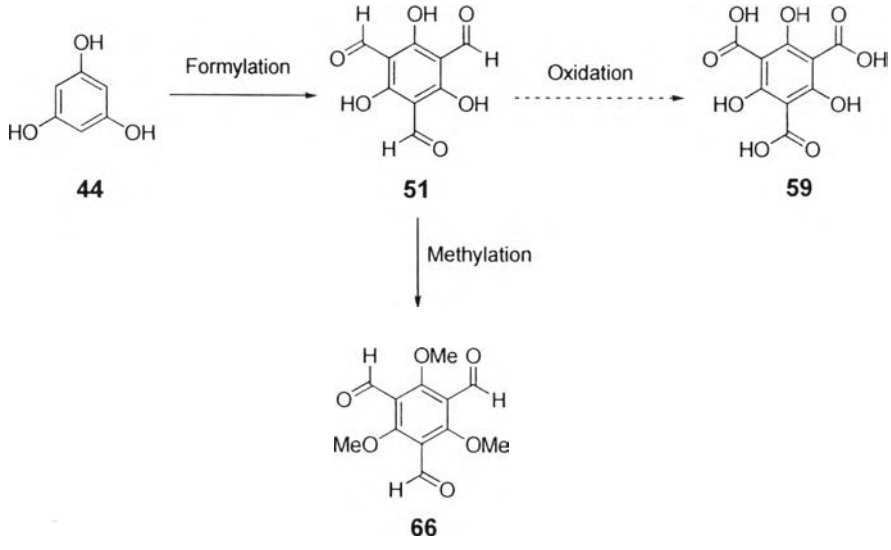
1,3,5-Triformyl-2,4,6-trihydroxybenzene **(51)** has been synthesized either by Duff reaction [79,82] or Reimer-Tiemann reaction [83] (**Scheme 3.7**). Duff reaction using hexamethylenetatramine (HMTA) as the formylating reagent afforded compound **51** in only 10% yield. While the Reimer-Tiemann reaction, through which phloroglucinol reacted with carbene, formed *in situ*, for 24 hours at reflux temperature, provided compound **51** in a better yield but lower quality. The mono-formylated product, 2,4,6-trihydroxybenzaldehyde, was instead obtained when the reaction time was shortened to just 8 hours. Paraformaldehyde [84] or dichloromethyl methyl ether [85] was tried as the formylating reagents in the presence of acid

catalyst. Treatment of phloroglucinol with paraformaldehyde in the presence of triethylamine and tin(IV) chloride gave product **51** in 29% yield. Finally, no reaction was observed with dichloromethyl methyl ether as the formylating agent.



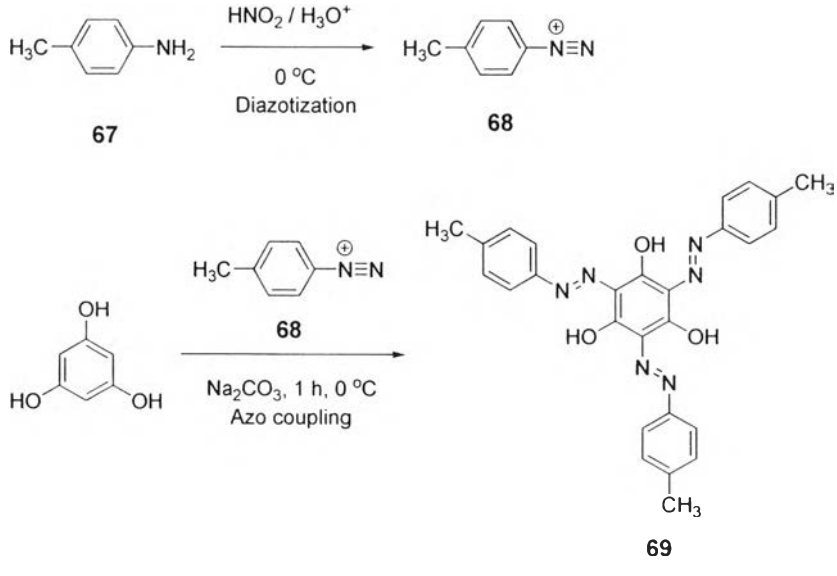
Scheme 3.7 Syntheses of 1,3,5-triformyl-2,4,6-trihydroxybenzene **(51)**

Compound **51** was found to be relatively unstable because it could not redissolved in the same solvent it had been separated from. Eventually, this compound was assumed to slowly turn into an unidentified solid that could be dissolved only in aqueous hydroxide. It was speculated that oxidation of **51** could have readily happened in the ambient atmosphere to become the corresponding tricarboxylic acid **59** (**Scheme 3.8**). Excessive methylations on the phenolic hydroxyl groups of compound **51** were immediately performed after its synthesis to prevent or slow down its decomposition. The methylated product **66** was obtained in 57% yield together with the presumably same unidentified solid. More other compounds were detected when stored compound **66** further for 2 days. Since compound **51** was not stable enough to be used in subsequent transformations and the oxidized byproduct could not be confirmed and made soluble, this potential core structure **51** was not further pursued.



Scheme 3.8 Further reactions of compound **51**

Phloroglucinol has been coupled with excess aromatic diazonium salts to create multidiazo hexasubstituted products. As an example, *p*-toluidine **(67)** was diazotized with nitrous acid to form the diazonium salt **68**, which readily coupled with phloroglucinol in basic condition (pH 9-10) to give the deep red tris-diazo compound **69** [86] (**Scheme 3.9**). Yield of this reaction was found to be slightly over 100% even after purification by column chromatography. Compound **69** was soluble in a wide range of solvent such as dichloromethane, ethyl acetate, acetone, acetonitrile, alcohols, *N,N*-dimethylformamide, dimethylsulfoxide and aqueous hydroxide.



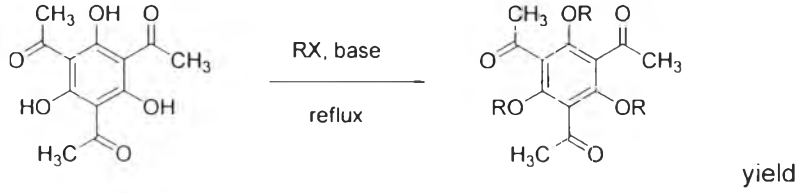
Scheme 3.9 Synthesis of tris-diazo **69**

3.2 Functionalization of 1,3,5-triacetyl-2,4,6-trihydroxybenzene (53)

From the successful synthesis of 1,3,5-triacetyl-2,4,6-trihydroxybenzene **(53)**, this flat platform was modified into *ababab* geometry by functionalization to various derivatives. The modifications had been done at three positions: (i) phenolic hydroxy groups, (ii) α-carbon atoms of acetyl groups and (iii) carbonyl ketone groups.

3.2.1 Alkylations of the phenolic hydroxy groups

1,3,5-Triacetyl-2,4,6-trihydroxybenzene **(53)** was functionalized on the phenolic hydroxy groups by alkylations in order to obtain the *ababab* geometry of the hexasubstituted benzene. Syntheses of three derivatives **70-72** were accomplished using dimethyl sulfate, benzyl bromide or 1,5-dibromopentane as the alkylating agents (RX) in basic condition, respectively (**Scheme 3.10**).



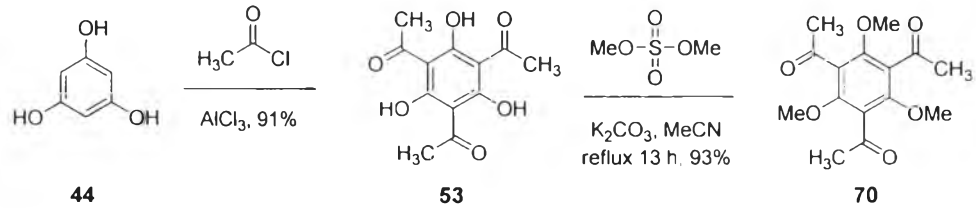
53

	yield
70 : R = Me	93%
71 : R = Bn	72%
72 : R = $(CH_2)_5Br$	77%

Scheme 3.10 Alkylations of 1,3,5-triacetyl-2,4,6-trihydroxybenzene **(53)**

Compound **53** was successfully methylated using dimethyl sulfate as alkylating agent to provide 1,3,5-triacetyl-2,4,6-trimethoxybenzene **(70)** in excellent yield (93%) (**Scheme 3.11**). The ^{1}H and ^{13}C-NMR characterizations (**Figure A.25 and A.26**) confirmed a symmetric structure of the methylated product. The proton signals showed two singlet peaks representing methyl protons (-C(O)C$\underline{H}_3$) and methoxy protons (-OC$\underline{H}_3$) while the carbon NMR spectrum showed the corresponding five different types of carbon atoms. Another methylating agent, methyl iodide, was used to synthesize compound **70** by similar condition. The result, however, gave the desired product in only 24% yield. The synthesis of compound **70** was attempted from direct acetylation of 1,3,5-trimethoxybenzene **(61)**. In this case, compound **70** was not

obtained because of the partial lost of methyl groups in acetylation condition as has been found earlier. (see **Section 3.1**)



44 **53** **70**

Scheme 3.11 Synthesis of 1,3,5-triacetyl-2,4,6-trimethoxybenzene **(70)**

Compounds **71** and **72** could be synthesized under the same condition using benzyl bromide and 1,5-dibromopentane as the alkylating agents giving the desired products in 72 % and 77% yield, respectively. The synthesis of compound **72** took very long time until completion (about 5 days). The reaction condition was later optimized to use more dilute concentration and added twelve equivalents of 1,5-dibromopentane and refluxed for 2 days. A more polar byproduct was found in small amount when rendering the reaction to a larger scale. The high similarity of both compounds as observed by ^{1}H and ^{13}C-NMR (**Figure 3.5**) and mass analysis suggested that this byproduct could simply be a conformer of compound **72** in which their interconversion was slow enough to be reported from each other.

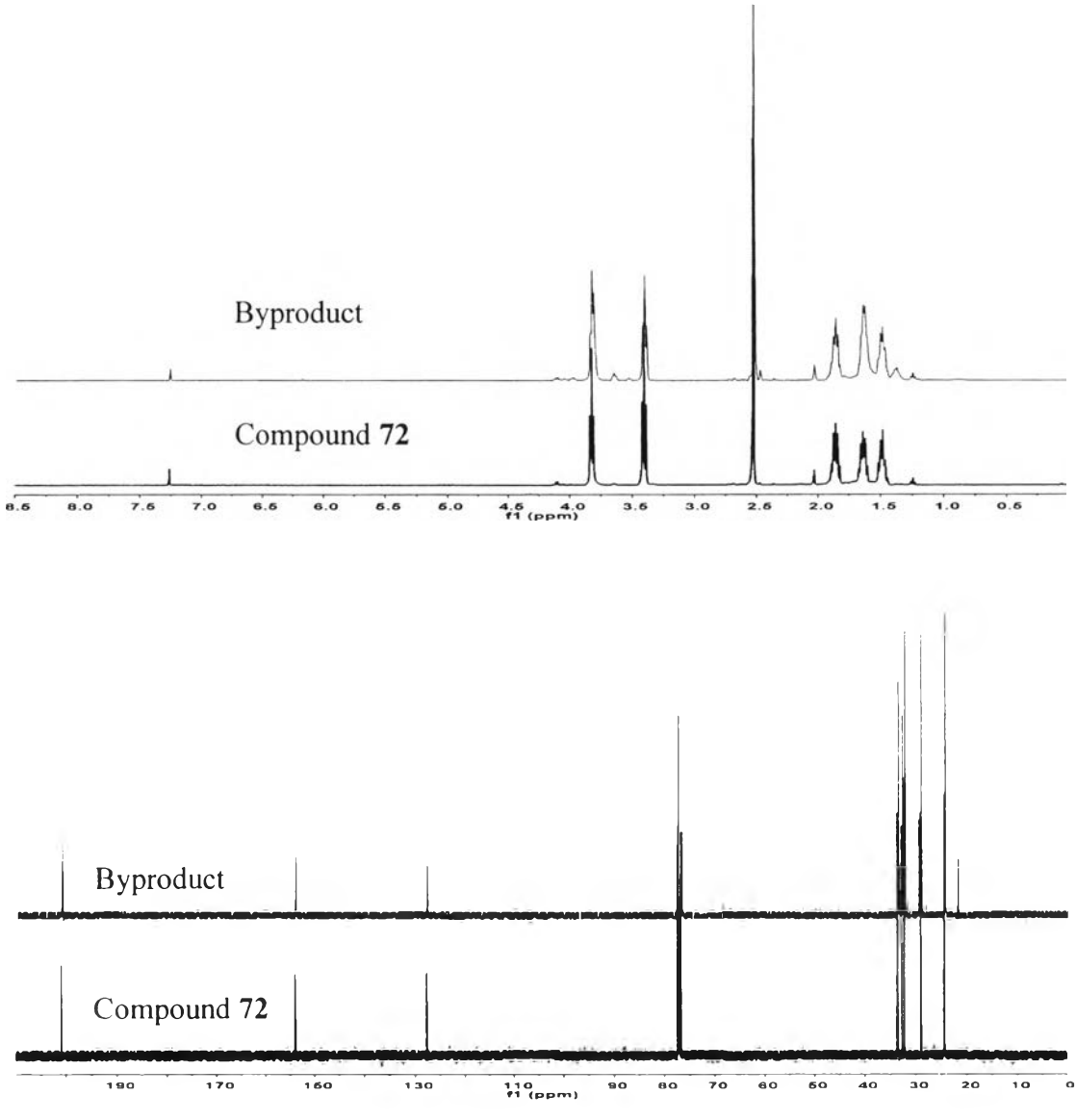


Figure 3.5 Comparisons of ^{1}H and ^{13}C-NMR signals between compound **72** and its byproduct

Many other haloalkanes have been surveyed for the alkylations including 1,2-dibromoethane, 2-bromoethanol, 2-chloroiodoethane, *N*-(2-bromoethyl) phthalimide, α-bromoacetaldehyde diethylacetal, bromoacetic acid, 1,3-dibromo propane and 3-chloropropylamine hydrochloride (**Figure 3.6**). These syntheses have been attempted using similar conditions from the synthesis of compounds **70-72**. Unfortunately, they were not successful. In most cases, only starting material was recovered, even with various conditions including: use of different bases such as potassium *tert*-butoxide,

sodium hydride, triethylamine and pyridine; solvents such as acetone, tetrahydrofuran and *N,N*-dimethylformamide.

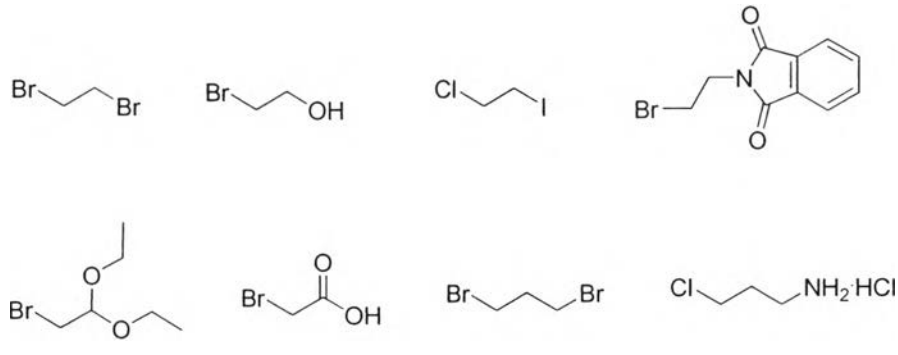
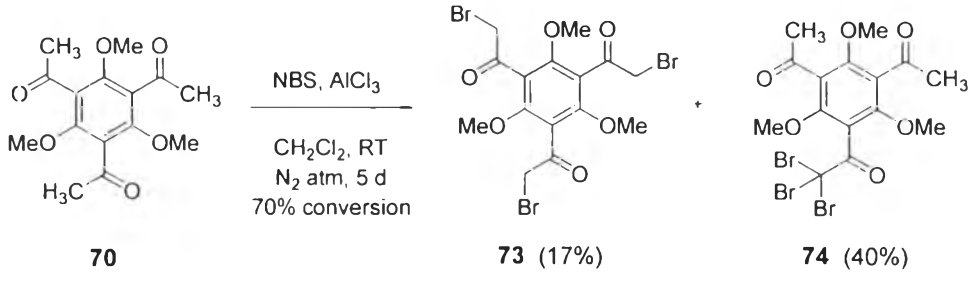


Figure 3.6 Structures of the alkylating agents surveyed

3.2.2 Modification of the α-carbon atoms of acetyl groups

The brominations of compounds **53, 70** and **71** were investigated using bromine (Br_2) or *N*-bromosuccinimide (NBS) [87]. Various conditions were tried including varying solvents and acid catalysts. The 1,3,5-tris(α-bromoacetyl)-2,4,6-trimethoxybenzene **(73)** was obtained in 17% yield with 30% recovered starting material. However, the major product of the reaction was the one that was brominated repeatedly at the same α-carbon atom compound **74** obtained in 40% yield (**Scheme 3.12**).

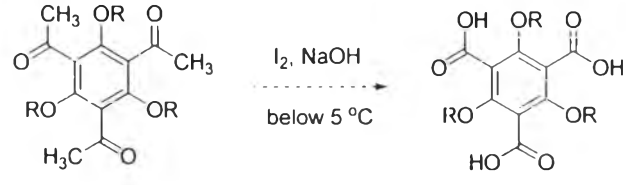


70 **73** (17%) **74** (40%)

Scheme 3.12 α-Brominations of compound **70**

The methyl ketone groups of compounds **53, 70** and **71** were subjected to be transformed to carboxylic acid derivatives by haloform reaction. The yellow precipitate of iodoform (CHI_3) was observed in the reactions of compounds **53** and **70**

(**Scheme 3.13**). A very high polar product was isolated from the acidified aqueous solution of the reaction but could not be characterized due to its insolubility in organic solvent. Tris-carboxylic acid **59** was expected to form and dissolve in aqueous hydroxide during the reaction. As for the reaction of compound **71**, iodoform formation was not observed and all of starting material was recovered.



53: R = H
70: R = Me

R = H

Scheme 3.13 Iodoform reactions of compounds **53** and **70**

3.2.3 Modification of the ketone carbonyls

Functionalizations on the carbonyl groups of compounds **53** and **70** with variety of amines to form C=N derivatives had been explored. These starting amine precursors included various alkyl amines, aromatic amines, hydroxylamine hydrochloride, hydrazine hydrochloride, semicarbazide hydrochloride and amino acids (**Figure 3.7**).

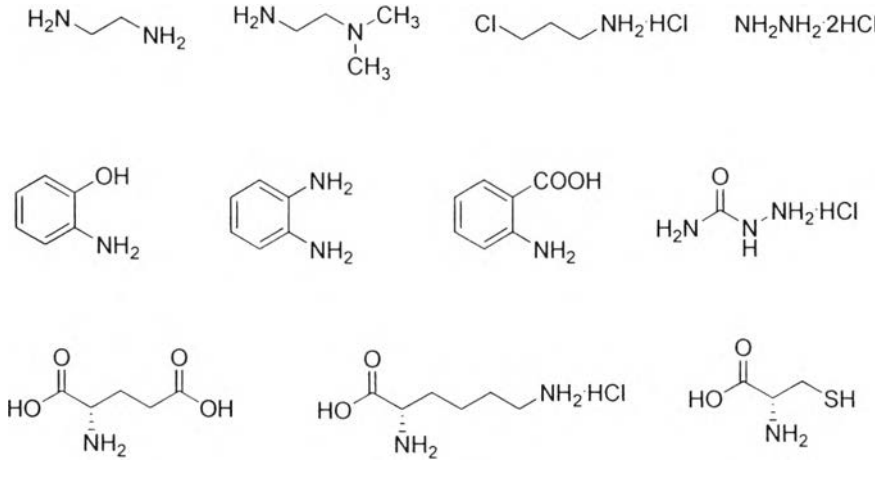
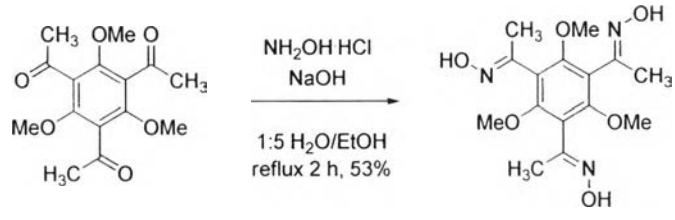


Figure 3.7 Structures of amine precursors

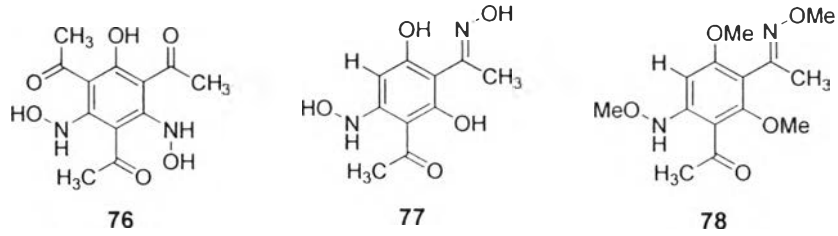
Various types of bases and solvents, amounts of reagents and temperature had also been surveyed. The only achievement in this category was the reaction of the ketone groups of compound **70** and hydroxylamine hydrochloride in the presence of hydroxide base to obtain tris-oxime **75** in 53% yields [88] (**Scheme 3.14**).



70 **75**

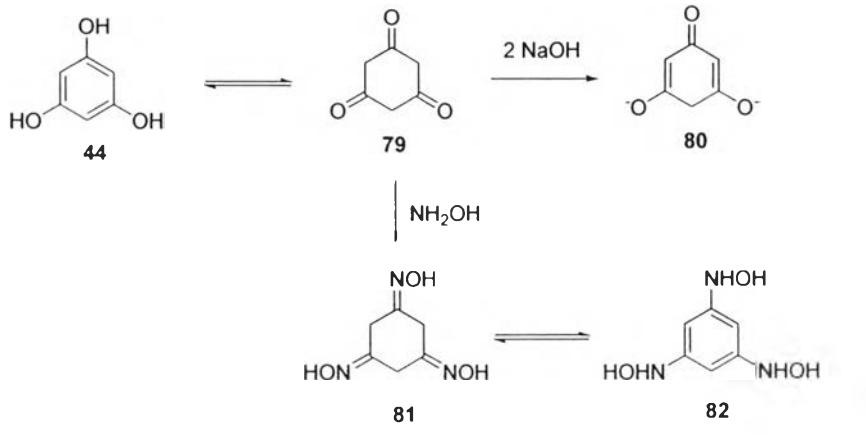
Scheme 3.14 Synthesis of tris-oxime **75**

The reaction of compound **53** with hydroxylamine hydrochloride provided several products. Only two of them could be isolated in appreciable amount and characterized. Nevertheless, spectroscopic data could not help identify or confirm any possible structures of the products. Some possibility such as compounds **76** and 77 were showed in **Figure 3.8** based on the previous reports that phloroglucinol **(44)** could be converted to the keto form **79** by keto-enol tautomerization [89] or dianion **80** upon dissolving in aqueous strong base [90] (**Scheme 3.15**). Compounds **81** and **82** could be generated by treating such keto form of phloroglucinol with hydroxylamine. In ^{1}H-NMR spectrum (**Figure A.50**), compound 77 showed a singlet peak of an aromatic proton upfield at 6.46 ppm and two different signals of methyl groups. To confirm the aromatic proton, compound 77 was treated with exhaustive methylations to the methylated compound **78**. Aromatic proton still remained in ^{1}H-NMR (**Figure A.53**) with two methoxy groups observed. No significant change in chemical shift of the carbon signals except one aromatic carbon showed downfield shift from 104.3 to 121.6 ppm (**Figure A.54**).



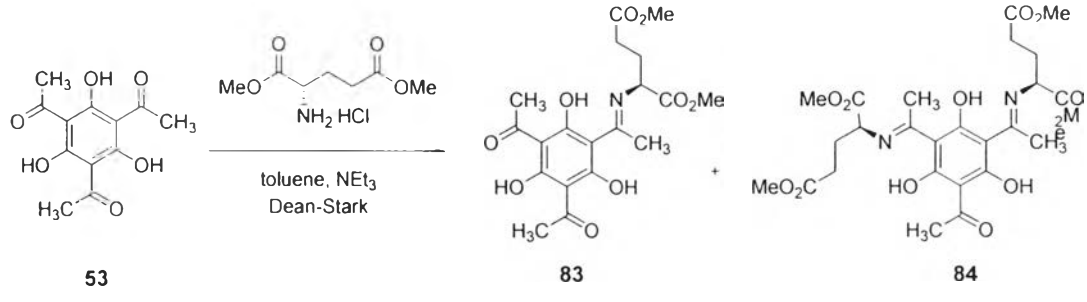
76 **77** **78**

Figure 3.8 Possible products **76** and 77 and the methylated compound **78**



Scheme 3.15 Keto-enol tautomerization of phloroglucinol and phloroglucinol trioxime

In the case of L-glutamate dimethyl ester, imine **83** and bis-imine **84** were generated in 24% and 19% yields, respectively (**Scheme 3.16**). They were relatively unstable and slowly decomposed back to compound **53** during the purification processes.



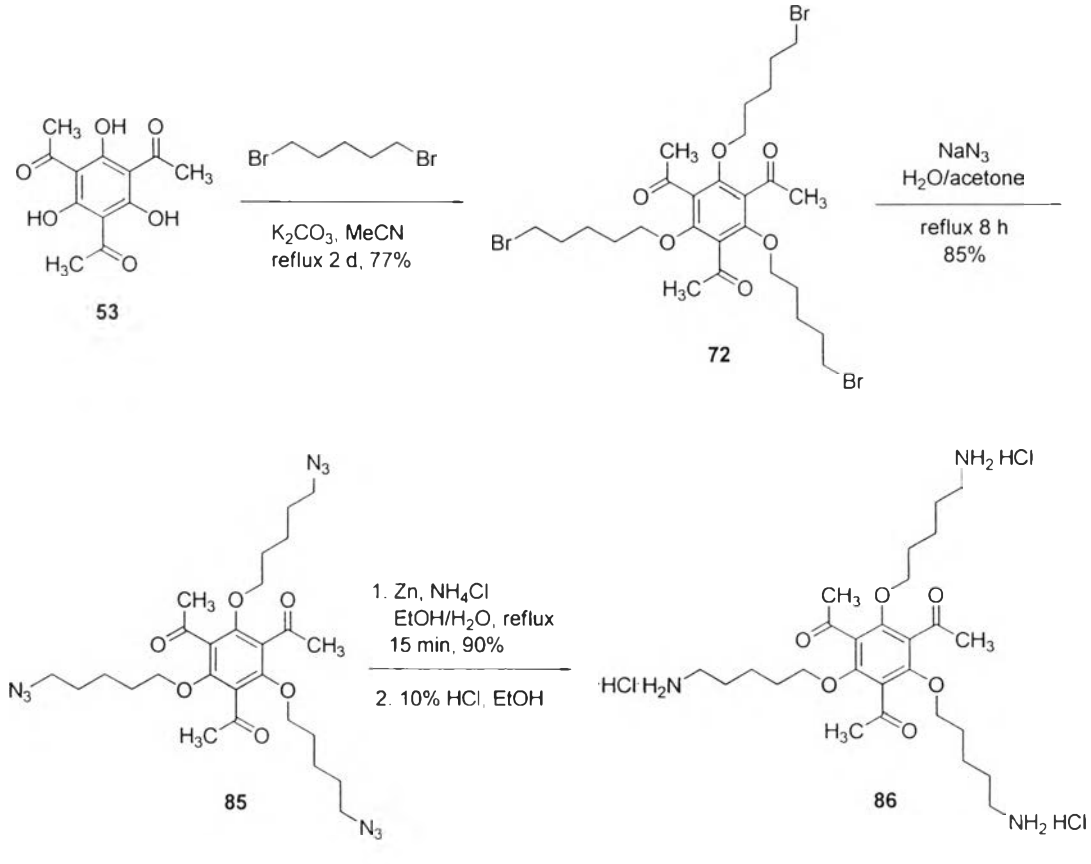
Scheme 3.16 Imine formations between compound **53** and L-glutamate dimethyl ester

Unfortunately, most of other attempts on the carbonyl functionalizations of compounds **53** and **70** into imines were not successful. The highly steric crowded among the substituents may be the reason that made these carbonyls to be relatively inactive towards nucleophiles and the condensed products seemed to be easily converted back to the starting ketones. In most cases, mixture of various unidentifiable products and unreacted starting material were often encountered.

3.3 Synthesis of tripodal ligands

3.3.1 Modification of 1,3,5-triacetyl-2,4,6-tris(5'-bromopentyloxy)benzene (72)

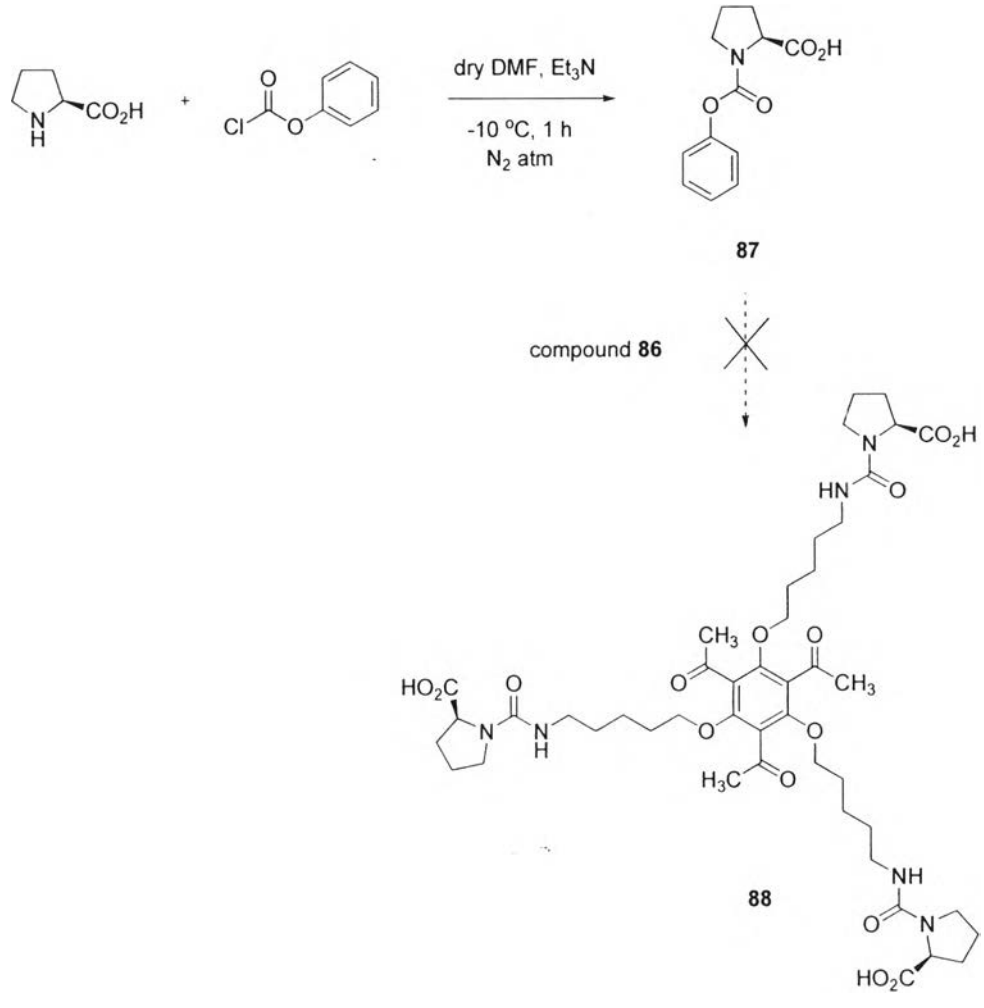
The tris-amine ligand **86** was synthesized from platform **53** through triple *O*-alkylation by 1,5-dibromopentane generating the symmetric intermediate **72** in 77% yield (**Scheme 3.17**). The subsequent substitutions with sodium azide gave tris-azide **85** in 85% yield. The following reduction with Zn/NH_4Cl obtained the corresponding tris-amine in 90% yield [91]. The tris-amine was stored in the more stable hydrochloride salt form **86**. The overall yield of compound **86** was 59% starting from compound **53**. Compound **86** was characterized by NMR spectroscopy in the more stable *N*-acetylated derivatives. During the earlier survey for the reduction step, the Staudinger reaction [55] had been attempted to convert the tris-azide to tris-amine using triphenylphosphene (PPh_3) or tributylphosphene (PBu_3) as reducing agents (see **Section 1.3.2.3**). In these cases, the reduction of compound **85** to compound **86** was not observed. Only the starting material remained.



53 → 72 → 85 → 86

Scheme 3.17 Synthesis of 1,3,5-triacetyl-2,4,6-tris(5'-aminopentyloxy)benzene **(86)**

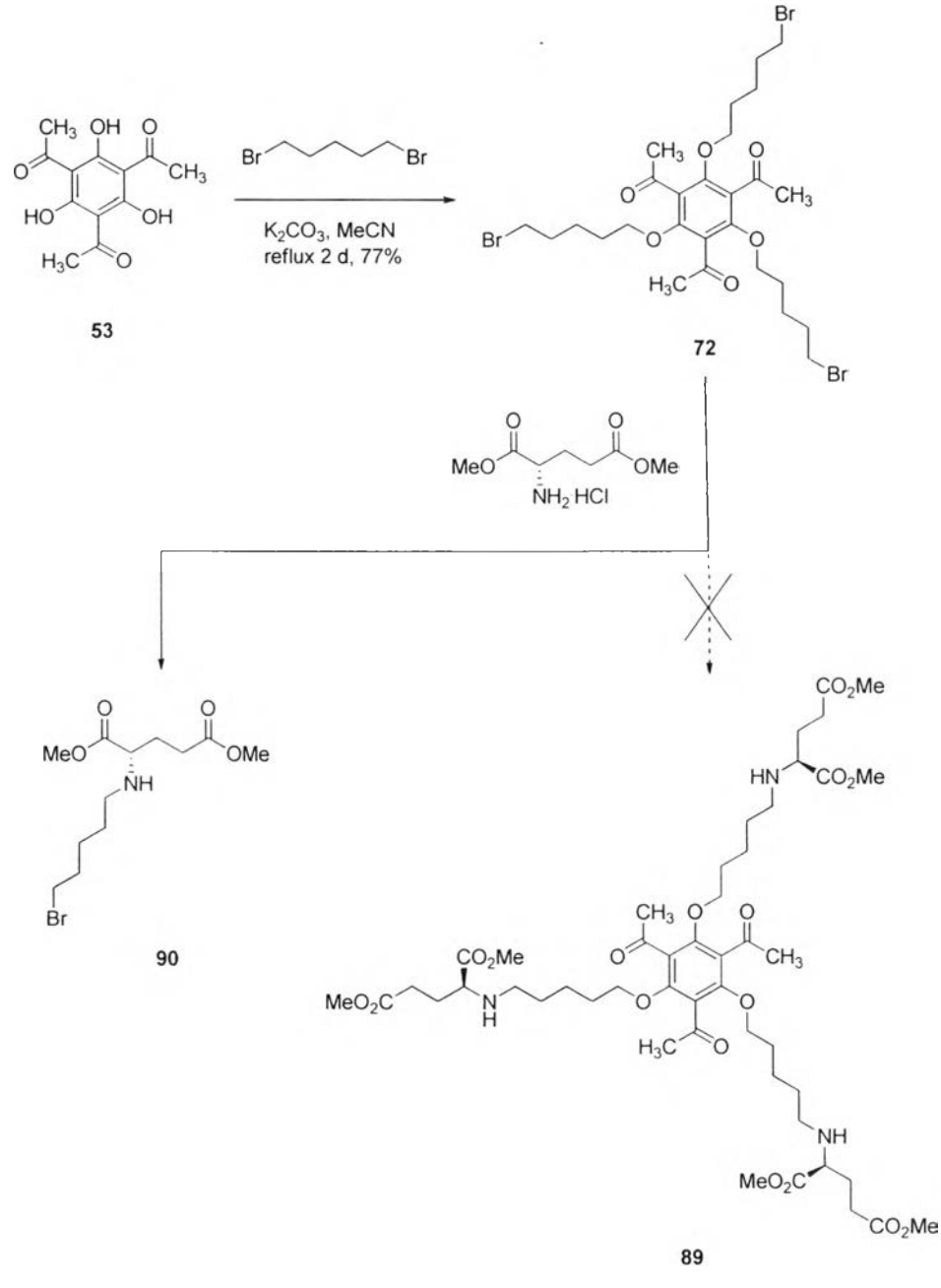
Compound **86** was treated with L-proline carbamate derivative **87** aiming to produce chiral tripodal ligand **88**. Compound **87** was prepared from L-proline and phenyl chloroformate in the presence of triethylamine in 57% yield [92]. However, subsequent reaction of tris-amine **86** and compound **87** did not yield the expected ligand **88** (**Scheme 3.18**). Compound **87** seemed to be much less reactive toward substitution and large amount of recovered tris-amine **86** was found.



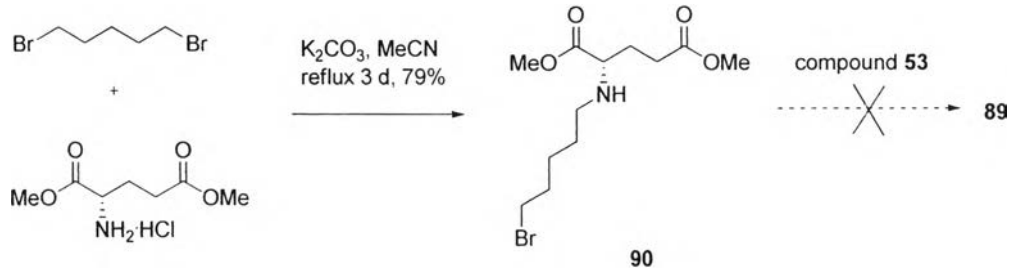
Scheme 3.18 Attempted synthesis of tripodal ligand **88**

In another strategy, compound **72** was allowed to react with various nucleophiles to synthesize chiral tripodal ligands. Four chiral nucleophiles were chosen: L-glutamate dimethyl ester, (*R*)-(+)-1-phenylethylamine, (-)-shikimate ketal derivative and *N*-Boc-L-phenylalaninol. Substitutions were investigated in the presence of weak bases to avoid epimerization or elimination process on the chiral reagents. Direct aminations of compound **72** with L-glutamate dimethyl ester

hydrochloride were performed at reflux temperature expecting compound **89**. Unfortunately, the reaction provided only compound **90** as the major product (**Scheme 3.19**). By switching the *O*-alkylation and amination steps, compound **90** was first generated in 79% yield by refluxing 1,5-dibromopentane and L-glutamate dimethyl ester with K_2CO_3 in acetonitrile (**Scheme 3.20**). When put together, compounds **53** and **90** did not react even with various conditions attempted such as types of weak bases (triethylamine and pyridine), solvents (acetone and DMF) and amounts of reagents.

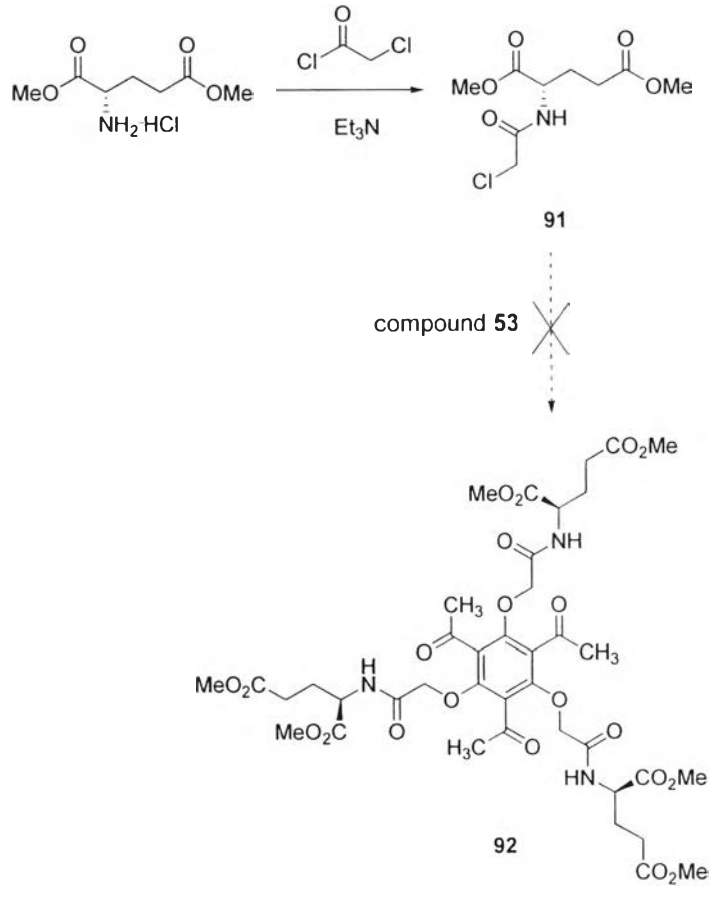


Scheme 3.19 Attempted linear synthesis of compound **89**



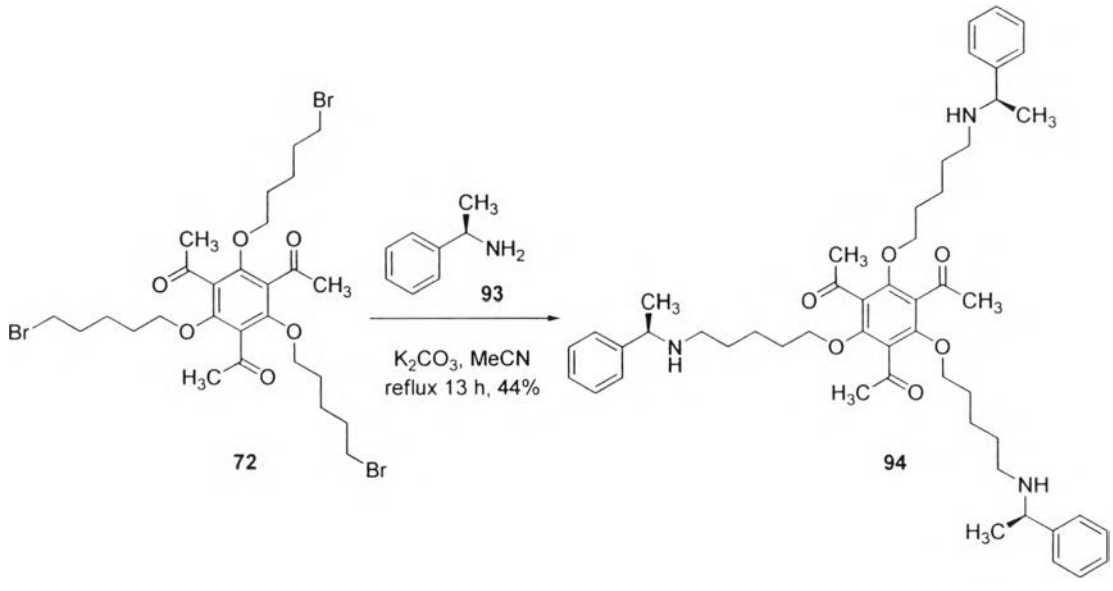
Scheme 3.20 Attempted convergent synthesis of tripodal ligand **89**

In another experiment, L-glutamate dimethyl ester was treated with chloroacetyl chloride to synthesize *N*-chloroacetamide derivative **91**, which was subsequentially used to produce ligand **92** by *O*-alkylations with the starting platform **53** (**Scheme 3.21**). The reaction was yet unsuccessful, with mostly unreacted starting materials recovered.



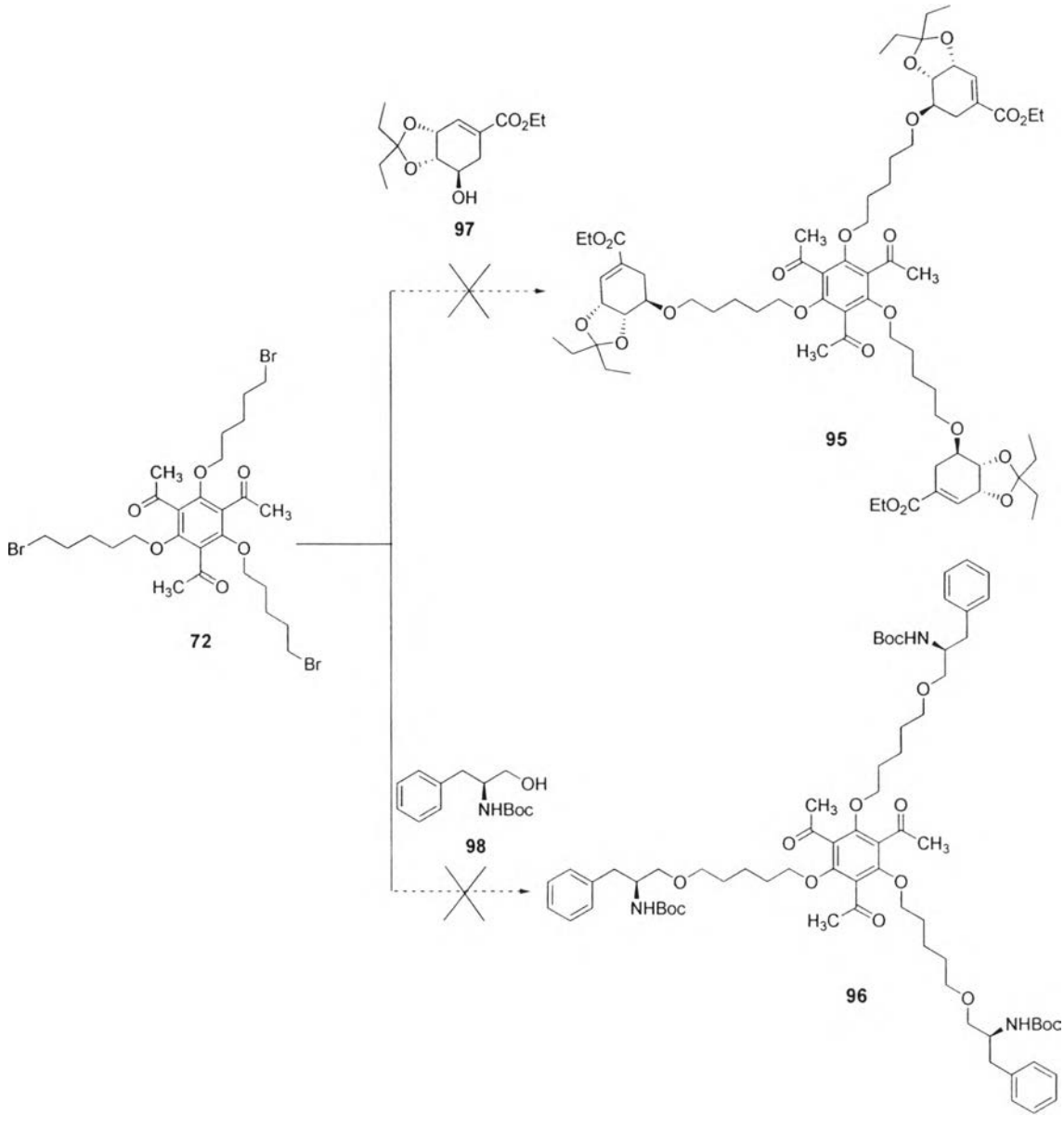
Scheme 3.21 Attempted convergent synthesis of tripodal ligand **92**

Aminations of compound **72** with (*R*)-(+)-1-phenylethylamine **(93)** was performed by refluxing the starting pair in acetonitrile using K_2CO_3 as base, obtaining yellow oil of ligand **94** in 44% yield (**Scheme 3.22**). Structure of compound **94** was confirmed by NMR data and showed to be a symmetric molecule. This compound was later tested as a receptor for chiral recognitions.



Scheme 3.22 Synthesis of tripodal ligand **94**

The syntheses of ligands **95** and **96** were investigated by treating compound **72** with either (-)-shikimate ketal derivative **97** or *N*-Boc- L-phenylalaninol **(98)** through *O*-alkylations in weak base conditions, respectively (**Scheme 3.23**). The syntheses in both cases were nevertheless unsuccessful. Either a lot of undesirable byproducts or no conversion of the starting material was observed.

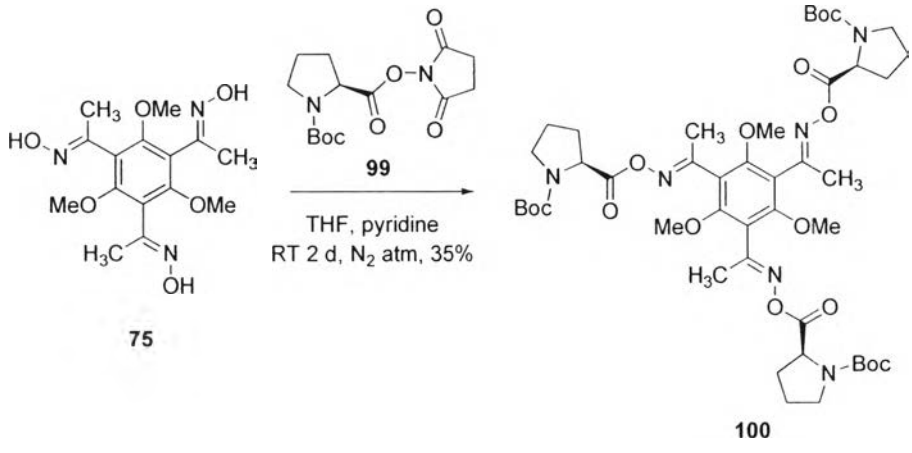


Scheme 3.23 Attempted synthesis of tripodal ligands **95** and **96**

3.3.2 Modification of 1,3,5-tris((*N*-hydroxyimino)ethyl)-2,4,6-trimethoxybenzene (75)

The alkylation of compound **75** with Boc-L-proline *N*-hydroxysuccinimide ester or Boc-Pro-OSu **(99)** has been performed. The reaction gave the desired ligand **100** as the product in 35% yield (**Scheme 3.24**). Ligand **100** was found not to be a symmetric molecule because, in ^{1}H-NMR spectrum (**Figure A.72**), the splittings of some types of protons into two groups such as methyl and methoxy protons were

clearly observed. The ^{13}C-NMR data (**Figure A.73**) confirmed the unsymmetric molecule with each carbon signal also splitted into two. The two possible unsymmetric structures could be considered: (i) the core structure did not remain in the *ababab* conformer or (ii) the product contained the mixture of various geometric isomers of *cis*- and *trans*-oximes.



Scheme 3.24 Synthesis of tripodal ligand **100**