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Synthesis of Novel Heteromacrocyclic Compounds

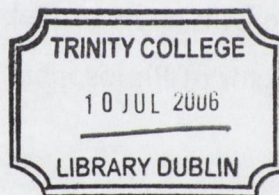
by

David Bradley

A thesis submitted to the University of Dublin for the degree of
Doctor of Philosophy

Trinity College Dublin

May 2005



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Abstract.

Macromolecular systems containing pyridine subunits have been the focus of much attention. The availability of the lone-pair electrons of the pyridine nitrogen atom makes these moieties particularly attractive as chelating units in supramolecular assemblies, novel catalysts, artificial enzymes, and transition metal ligands. In substituted pyridines, the availability of the lone-pair electrons is strongly influenced by the nature of the substituents on the pyridine ring. 4-Dimethylaminopyridine (DMAP) constitutes an electron-rich pyridine ring and has been widely used as an acylation catalyst. Macrocyclic systems containing pyridine or DMAP moieties may therefore be expected to display interesting catalytic and/or ion-binding properties.

A number of symmetrical 2,6-disubstituted DMAP derivatives containing halogen substituents were synthesised. These compounds were used to prepare acetylenic DMAP derivatives as potential precursors for the construction of macrocycles containing DMAP residues. However, attempts to prepare macrocycles from these acetylenes *via* palladium- or copper-catalysed acetylenic coupling reactions proved unsuccessful.

Several pyridyl ethers were also prepared and the one-step synthesis of a macrocyclic pyridyl ether was achieved.

A novel macrocycle containing a pyridine ring and an acetylene group was synthesised by a molybdenum- catalysed alkyne metathesis reaction.

Abbreviations.

BuLi	Butyllithium
dba	Dibenzylideneacetone
DMAP	4-Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethyl sulphoxide
IR	Infrared
LDA	Lithium diisopropylamide
LiDMAE	Lithium dimethylaminoethoxide
LiTMP	Lithium tetramethylpiperidide
m.p.	Melting point
NMP	<i>N</i> -methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
PPY	4-Pyrrolidinopyridine
r.t.	Room temperature
TBAF	Tetra- <i>n</i> -butylammonium fluoride
THF	Tetrahydrofuran
TIPSA	Triisopropylsilylacetylene
TMEDA	Tetramethylethylene diamine
TMSCl	Trimethylsilyl chloride

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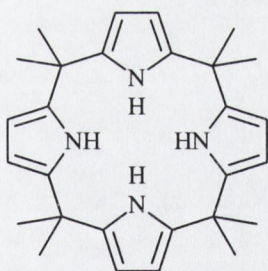
Chapter 1
Introduction

1.1. Introduction.

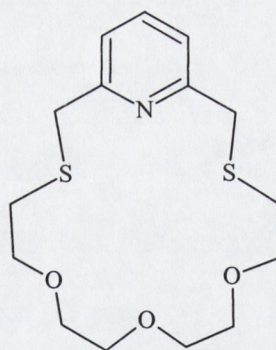
The following introduction is intended to give an overview of macrocyclic systems as they pertain to the present investigation and to briefly outline some of the methods used in the synthesis of these compounds. It does not attempt to present an exhaustive study of the various classes of macrocyclic compounds as such a study would require more space than is available here. Relevant classes of macrocyclic compounds will be elaborated upon in the subsequent chapters.

1.1.1. Heteromacrocycles.

Synthetic macrocycles constitute a venerable class of compounds dating back to 1886 and Baeyer's¹ synthesis of macrocycle **1.1**. The work of Pedersen,² Lehn,³ Gutsche,⁴ and others has generated much interest in macrocyclic structures. Many of these compounds have the ability to accept guest ions or molecules within the molecular cavity and their binding properties can often be modified by minor alterations to ring size and/or functionality. For example, macrocycle **1.2** renders sodium permanganate soluble in chloroform while potassium permanganate remains undissolved. However, when **1.2** is converted to its *N*-oxide both sodium and potassium permanganate are solubilised.⁵



1.1



1.2

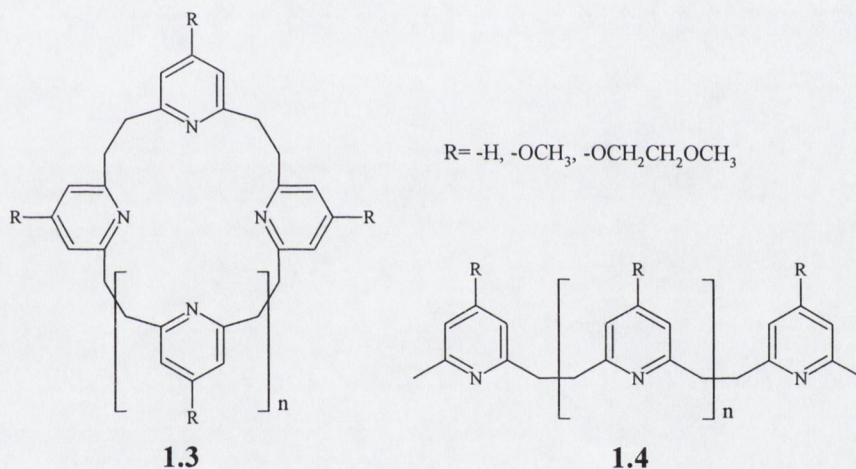
The ability of macrocycles to bind ions or molecules is of considerable importance and many of these compounds have found applications in phase transfer catalysis,⁶ molecular recognition,⁷ and template synthesis.⁸ The growth of supramolecular chemistry has prompted the design and synthesis of macrocycles of increasing complexity and structural diversity and many compounds containing two or more

different heteroatoms have been synthesised.^{9,10} In particular, emphasis has been placed on compounds containing nitrogen and oxygen donor atoms.¹¹

1.1.2. Pyridine macrocycles.

The literature is abounding in examples of macrocycles containing pyridine or bipyridine subunits.¹² Pyridine is particularly attractive as a complexing unit in macrocyclic systems owing to the ability of the nitrogen atom to coordinate metal ions. Furthermore, the basicity of the pyridine nitrogen, and hence its binding ability, can be modified by changing the substituents on the pyridine ring.^{13,14}

The superiority of cyclic systems to straight-chain ligands in binding metal ions was demonstrated by Vögtle *et al.*¹⁴ using a series of calixpyridines **1.3** and their open-chain analogues **1.4**.



In studies on the extraction of various transition metal ions (Ag^+ , Hg^{2+} , Pd^{2+} , Au^{3+}) the macrocycles proved to be more efficient than the open-chain oligomers and exhibited greater selectivity.

1.1.3. Synthesis of macrocyclic systems.

Two major factors oppose the formation of macrocyclic systems: (i) the low tendency of reacting systems to form large- or medium-sized rings and (ii) the formation of oligomeric or polymeric chains.

The growing importance of macrocyclic entities in the field of supramolecular chemistry has prompted the search for efficient methods for the synthesis of these compounds.¹⁵ The influences of factors such as reactant concentration,¹⁶ reaction solvent,¹⁷ template effects,¹⁸ and substrate structure¹⁹ have been extensively studied in order to develop high-yielding syntheses of these compounds.

Use of high dilution.

A major impediment to the formation of macrocyclic compounds is the tendency of systems to form oligomeric or polymeric chains. Figure 1.1 presents a schematic representation of the reaction pathways open to a linear substrate incorporating functional groups X and Y where X and Y are groups that react with each other to form a new group Z. Such a system may undergo intramolecular reaction to give cyclic products (Figure 1.1, path A) or intermolecular reaction leading to linear products (Figure 1.1, path B). This system may also form cyclic products by intermolecular reaction of the substrate and/or one of the linear products formed during the course of the reaction (Figure 1.1, path C) or by intramolecular reaction of one of the linear oligomers (Figure 1.1, path D).

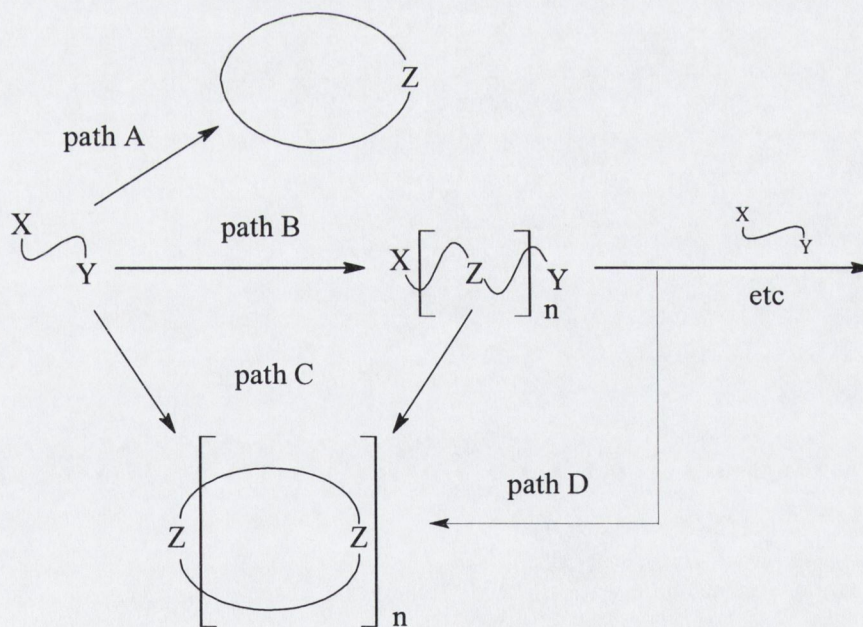


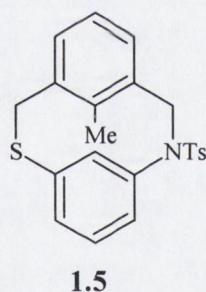
Figure 1.1

For the formation of five- and six-membered rings, the intramolecular ring-closing reaction (Figure 1.1, path A) is faster than the intermolecular reaction towards open-chain products (Figure 1.1, path B). For higher-membered rings, this relationship is reversed and the formation of open-chain products is favoured. The use of high dilution helps to overcome the tendency towards open-chain products and promote the formation of cyclic systems. At very low concentrations, the probability of the chain terminals coming close enough to each other for reaction to occur is greatly increased.

Solvent effects.

The use of dipolar aprotic solvents may help to raise the yield of cyclic products. In nonpolar solvents like hexane or benzene, hydrocarbon chains are tightly solvated and adopt linear conformations. As the polarity of the solvent increases, the solvation of alkyl residues decreases leading to greater freedom of movement.

In the synthesis of metacyclophane **1.5**, acetonitrile was found to be a superior solvent to a mixture of benzene and ethanol.¹⁷

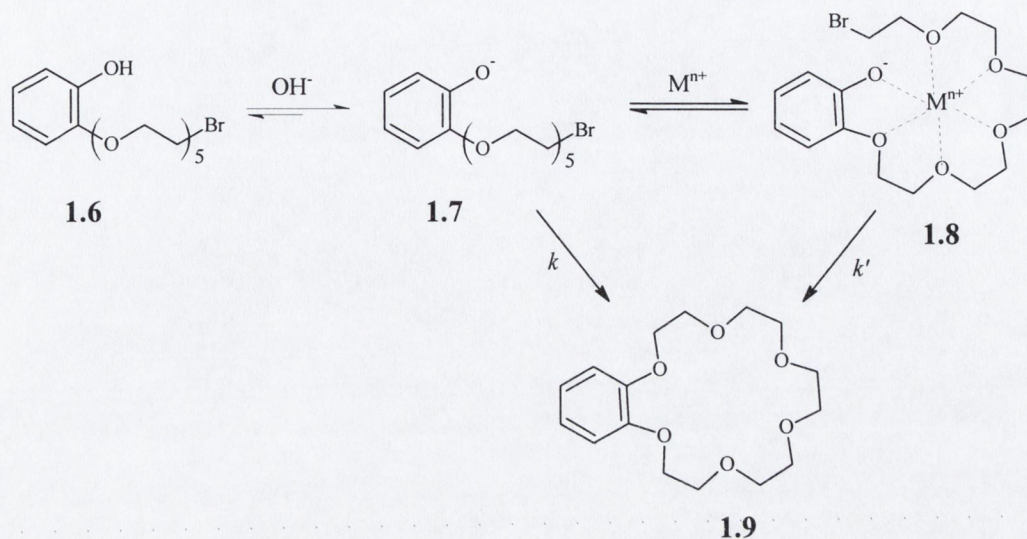


In benzene/ethanol, **1.5** was obtained in 9% yield. The use of acetonitrile as solvent raised the yield of **1.5** to 27%.

Template effects.

Metal ions or organic guest molecules may act as templates in cyclisation reactions.¹⁵ These templates operate by forming complexes with the open-chain precursors prior to the ring-forming reaction thus bringing reactive centres close enough to each other for reaction to occur.

Mandolini and Masci studied the effect of various metal ions (Na^+ , K^+ , Ba^{2+} , Sr^{2+}) on the formation of benzo-18-crown-6 (**1.9**, Scheme 1.1) from the linear polyether **1.6** in aqueous solution.²⁰



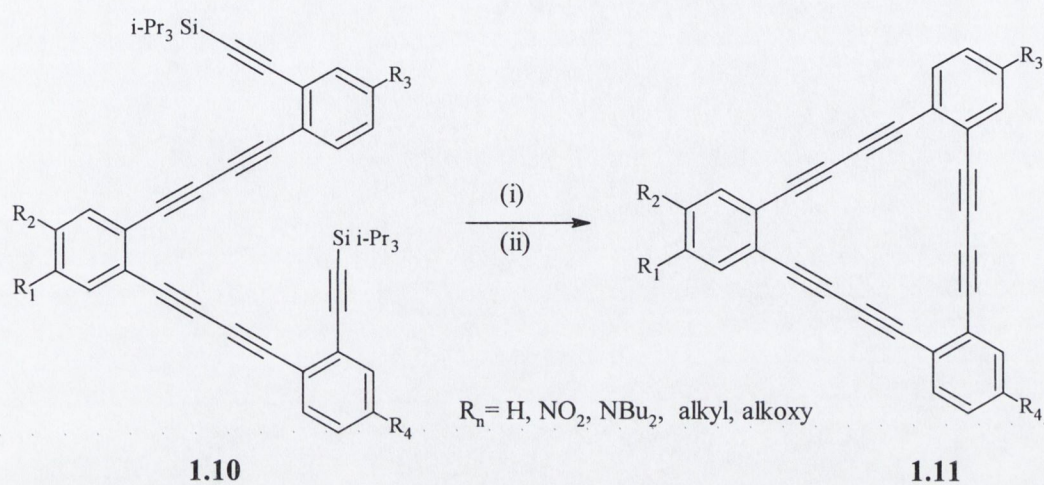
Scheme 1.1

In the presence of metal ions, a marked increase in reaction rate was observed compared to the reaction in the absence of the metal. As a control, tetraethylammonium hydroxide was used as the base for these studies. Since the Et_4N^+ cation is too large to fit into the cavity of **1.9**, the increase in reaction rate was attributed to binding of the metal ion by the oxygen atoms of **1.7** to give the templated species **1.8**. The formation of this complex serves to bring the phenoxide and bromide moieties into close proximity with each other and thus facilitates the ring-closing reaction.

Pre-organisation of the substrate. Rigid groups.

In general, the speed of ring formation decreases as the chain length of the starting material increases. Increasing the chain length of the starting material increases the number of degrees of freedom available to the system. Molecules with longer chains can adopt a greater number of conformations and the probability of the system adopting a conformation leading to ring-closure is reduced.

The introduction of rigid groups into a molecule reduces the number of degrees of freedom and can help to raise the yield of cyclic products. Haley *et al.* successfully applied this principle to the synthesis of a number of dehydrobenzo[18]annulenes **1.11**²¹ (Scheme 1.2).



Reagents and conditions: (i) TBAF (2.5 equiv.), THF/MeOH (10:1 v/v). (ii) $\text{Cu}(\text{OAc})_2$ (25 equiv.), CuCl (20 equiv.), pyridine.

Scheme 1.2

The open-chain precursors **1.10** were prepared in a stepwise manner using palladium-catalysed procedures.²² The geometry of these linear precursors in combination with their rigid nature limits the number of possible conformations these systems can adopt leading to high yields of cyclic products.

1.1.4. Objectives.

The aim of the present work is to synthesise a number of novel macrocycles containing pyridine and/or 4-dimethylaminopyridine (DMAP) residues within the macrocyclic framework. DMAP has been widely used as an acylation catalyst²³ and as a ligand for transition metals.²⁴ Macrocycles containing DMAP moieties may therefore be expected to exhibit interesting catalytic and/or ion-binding behaviour. The proposed macrocycles will also contain other functional groups that may be further derivatised in order to provide a series of highly adaptable compounds.

Of particular interest are the tetraketone macrocycles shown in Figure 1.2 together with their *ortho*-substituted analogues (not shown).

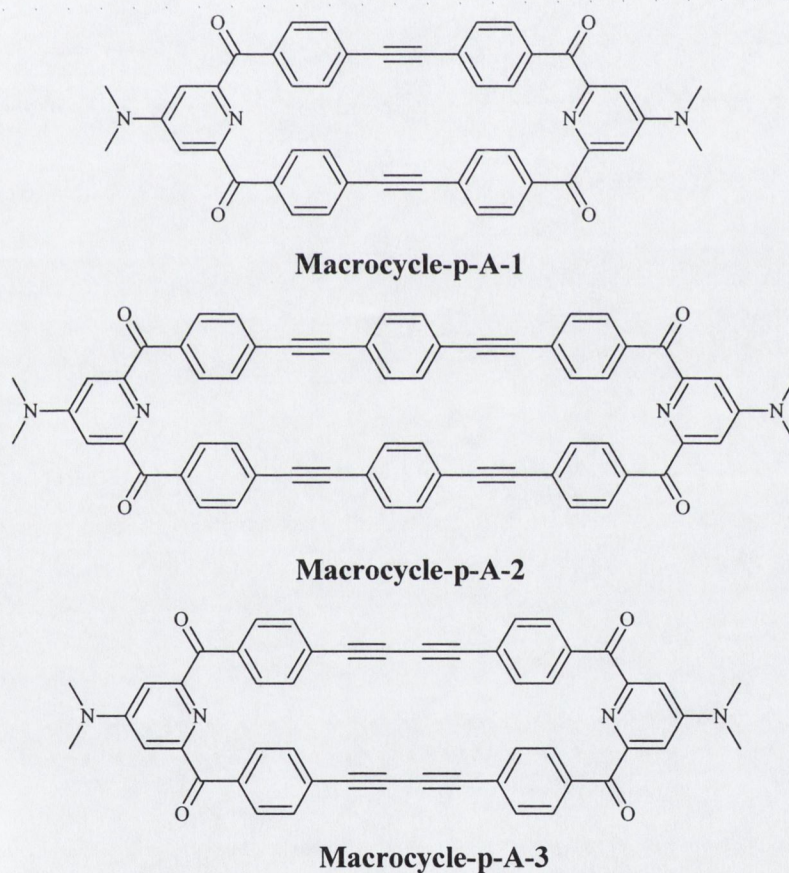
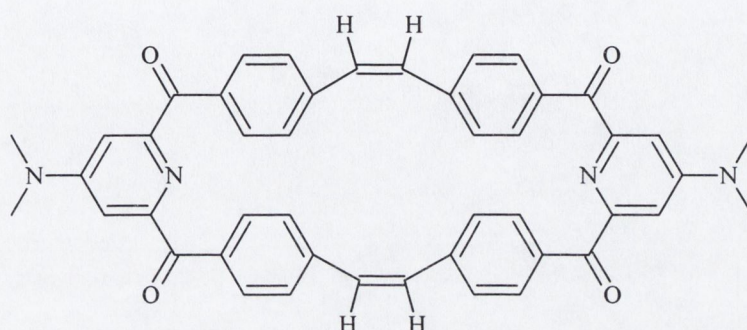
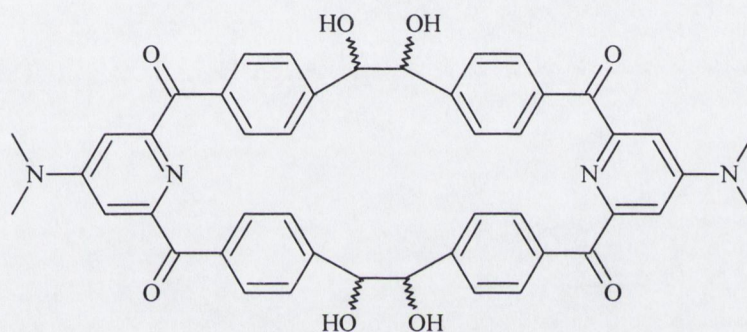


Figure 1.2

The above compounds offer interesting possibilities for further functionalisation *via* synthetic manipulation of the carbonyl and acetylene groups. For example, partial hydrogenation of the acetylene moieties of Macrocycle-p-A-1 may afford the *cis/cis* diene **1.12**. Subsequent hydroxylation of the alkene groups of **1.12** should give the tetrahydroxy macrocycle **1.13**.



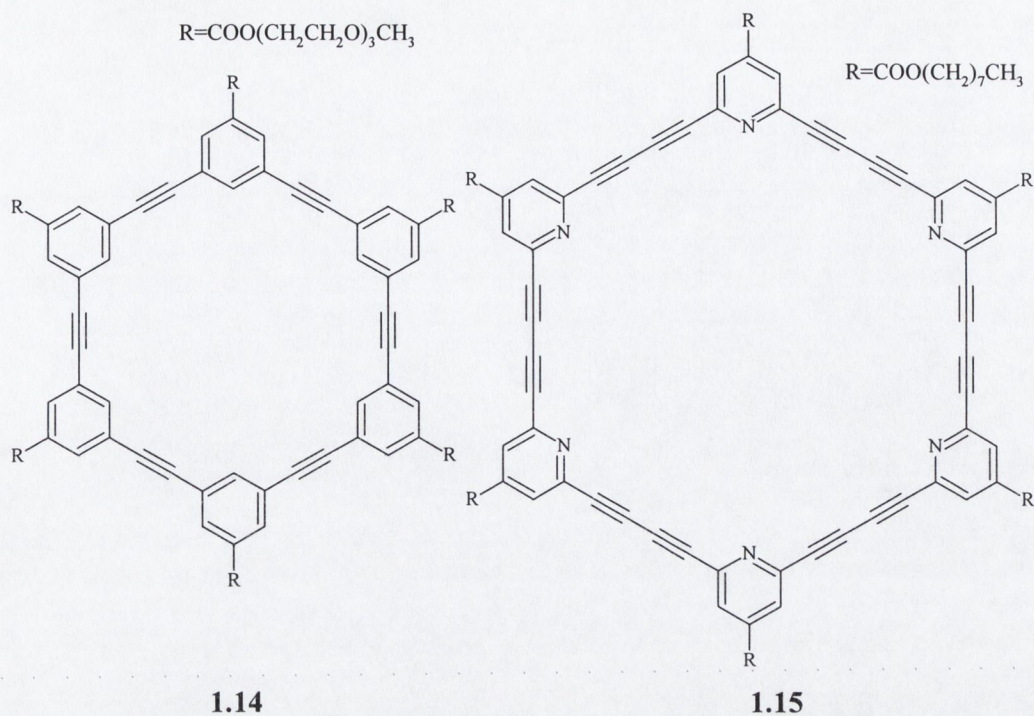
1.12



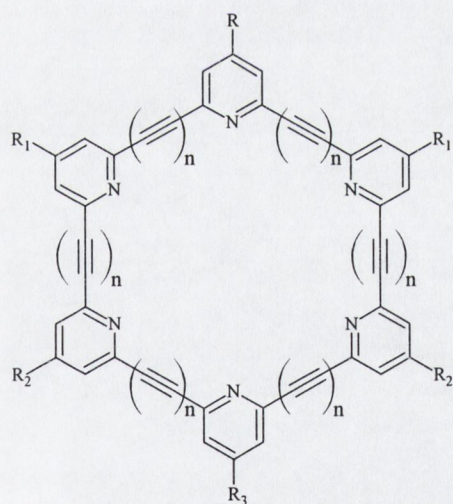
1.13

In addition to their potential for further elaboration and their inherent aesthetic appeal, the compounds shown in Figure 1.2 present an interesting synthetic challenge and the development of methodology for the synthesis of these structures would be of some value.

Moore has described the synthesis of phenylene ethynylene macrocycles (*e.g.* **1.14**) *via* palladium-mediated reactions.²⁵ In similar work, Tobe *et al.* have prepared pyridinophane **1.15** and demonstrated its ability to bind organic cations.²⁶



It is intended to use this methodology for the synthesis of a number of novel pyridinophanes containing DMAP moieties (Figure 1.3).



Macrocycle B-1: $R = R_1 = R_2 = R_3 = \text{NMe}_2$
 $n = 1$

Macrocycle B-2: $R = R_1 = R_2 = R_3 = \text{NMe}_2$
 $n = 2$

Macrocycle B-3: $R = R_3 = \text{NMe}_2/$
 $R_1 = R_2 = \text{H}$
 $n = 1$

Macrocycle B-4: $R = R_3 = \text{NMe}_2/$
 $R_1 = R_2 = \text{H}$
 $n = 2$

Macrocycle B-5: $R = R_2 = \text{NMe}_2/$
 $R_1 = R_3 = \text{H}$
 $n = 1$

Macrocycle B-6: $R = R_2 = \text{NMe}_2/$
 $R_1 = R_3 = \text{H}$
 $n = 2$

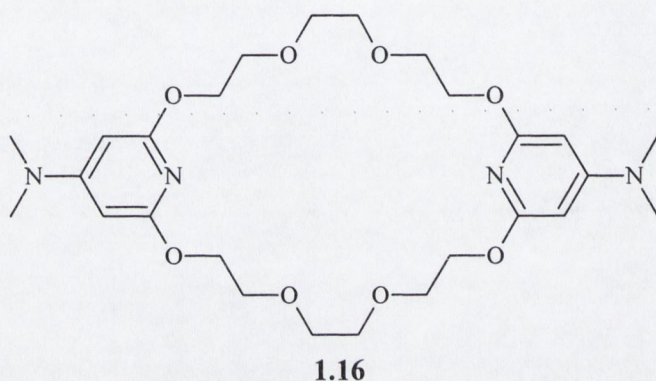
Macrocycle B-7: $R = R_1 = \text{NMe}_2/$
 $R_2 = R_3 = \text{H}$
 $n = 1$

Macrocycle B-8: $R = R_1 = \text{NMe}_2/$
 $R_2 = R_3 = \text{H}$
 $n = 2$

Figure 1.3

In the light of Tobe's²⁶ findings for pyridinophane **1.15**, the projected DMAP pyridinophanes shown in Figure 1.3 may be expected to exhibit interesting ion-binding properties and it may be possible to tune these binding properties by varying the number and position of the DMAP moieties and/or the number of acetylene units linking the pyridine groups. In addition, the introduction of the *N*-oxide function into one or more sites on the macrocycle may further modify these binding properties.

In addition to the rigid systems described above, it is intended to undertake the synthesis of more flexible systems containing DMAP residues (*e.g.* **1.16**).



Many other possibilities exist including macrocycles incorporating both rigid and flexible moieties. The methods employed towards the synthesis of a number of macrocyclic compounds containing pyridine and/or DMAP residues will be described in the subsequent chapters.

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- ²³ E. Scriven, *Chem. Soc. Rev.*, 1983, **12**, 129.
- ²⁴ M. Otsuka, A. Hamasaki, H. Karosaki and M. Goto, *J. Organomet. Chem.*, 2000, **611**, 577.
- ²⁵ J. Moore, S. Lahiri and J. Thompson, *J. Am. Chem. Soc.*, 2000, **122**, 11315.

²⁶ Y. Tobe, A. Nagano, K. Kawabata, M. Sonoda and K. Naemura, *Org. Lett.*, 2000, **2**, 3265.

Chapter 2
Synthesis of 2,6-disubstituted 4-dimethylaminopyridine
derivatives

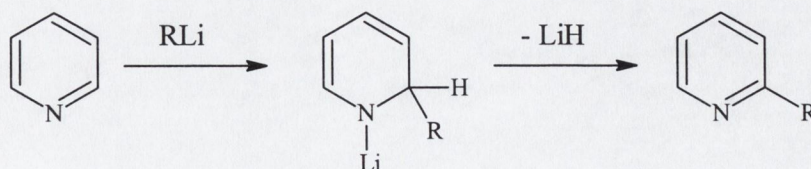
2.1. Introduction.

Symmetrical 2,6-disubstituted 4-dialkylaminopyridines would constitute useful starting materials for the construction of macrocyclic and/or oligomeric frameworks incorporating electron-rich pyridine moieties. It was therefore of interest to develop efficient syntheses for these extremely useful compounds.

Although the literature contains numerous examples of the synthesis of symmetrical 2,6-disubstituted 4-dialkylaminopyridines, many of these compounds have been prepared by introduction of the dialkylamino group into the 4 position of a 2,6-disubstituted pyridine ring.¹⁻⁴ These procedures generally involve several synthetic steps and overall yields are low. Relatively few instances of the synthesis of symmetrical 2,6-disubstituted 4-dialkylaminopyridines directly from the parent 4-dialkylaminopyridines are reported and, in several cases, these compounds have been obtained as side-products from the synthesis of the corresponding monosubstituted derivatives.^{5,6}

2.1.1. Synthesis of α -substituted pyridine derivatives.

The demand for functionalised pyridines for use in the synthesis of supramolecular assemblies,⁴ novel catalysts,⁷ artificial enzymes,⁸ and transition metal ligands,⁹ has prompted the design of efficient and selective methods for the introduction of functional groups onto the pyridine ring.^{5,10} The use of lithiated pyridines has been the focus of much attention and has resulted in the synthesis of numerous new derivatives.¹¹ Although lithium – halogen exchange is an efficient process,¹² lithium – hydrogen exchange represents a more direct route to substituted derivatives. Unfortunately, due to the π -deficiency of pyridines, treatment with alkyllithiums usually results in nucleophilic attack on the azomethine bond and the formation of the alkylated pyridine¹³ (Scheme 2.1).

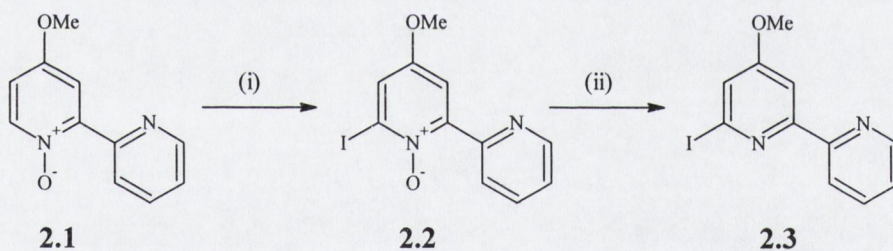


Scheme 2.1

Although this addition reaction can often be suppressed by the use of hindered, non-nucleophilic lithium dialkylamides such as lithium diisopropylamide¹⁴(LDA) or lithium tetramethylpiperidide¹⁵ (LiTMP), the use of these bases has, in some instances, resulted in the exclusive formation of the 2,2'-bipyridyl.^{5,16}

Pyridine *N*-oxides.

The difficulties inherent in the metallation of pyridines with alkyllithiums may often be overcome by converting the pyridine to its *N*-oxide prior to lithiation. In contrast to pyridines, pyridine *N*-oxides are metallated by simple alkyllithiums and lithium dialkylamides.¹⁷ In pyridine *N*-oxides, electron withdrawal by the *N*-oxide function enhances the acidity of the α -protons and facilitates the deprotonation reaction.¹⁸ The *N*-oxide group can be reduced in a subsequent synthetic step to afford the free pyridine. Quéguiner *et al.* successfully exploited this strategy in the synthesis of antibiotic agents.¹⁹ Lithiation of 4-methoxy-2,2'-bipyridine *N*-oxide (**2.1**) followed by reaction with iodine gave 6-iodo-4-methoxy-2,2'-bipyridine *N*-oxide (**2.2**). Reduction of **2.2** with phosphorus tribromide gave 6-iodo-4-methoxy-2,2'-bipyridine (**2.3**), a key intermediate in the synthesis of caerulomycin A (Scheme 2.2).



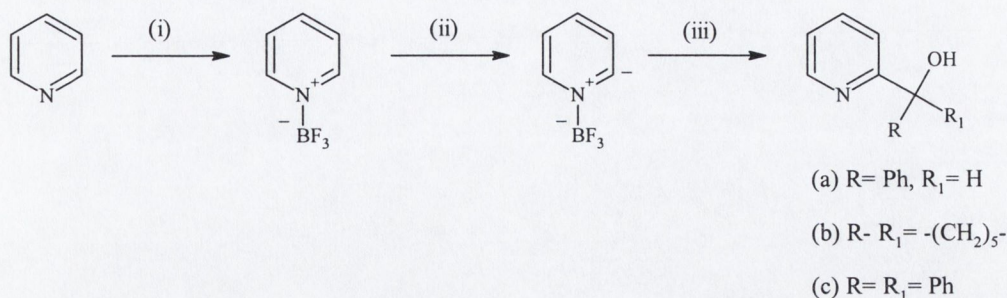
Reagents and conditions: (i) LiTMP (1 equiv.), THF, -70 °C, 1 hr, I₂ (2 equiv.), -70 °C, 1 hr.
 (ii) PBr₃ (3 equiv.), CHCl₃, reflux 45 min.

Scheme 2.2

Pyridine-boron trifluoride complexes.

In 1991, Kessar *et al.* reported the efficient synthesis of certain α -pyridyl alcohols *via* the boron trifluoride complex of pyridine⁵ (Scheme 2.3). Complexation to boron trifluoride rendered the α -protons sufficiently acidic to allow their removal by a base. Subsequent reaction of the lithiated pyridine with carbonyl compounds

gave the α -pyridyl alcohols in high yields. This procedure has since been widely used for the preparation of α -substituted pyridines.²⁰⁻²⁵



Reagents and conditions: (i) BF₃.OEt₂ (1.05 equiv.), 0 °C, 15 min. (ii) LiTMP (1.1 equiv.), -78 °C, 15 min. (iii) RC(=O)R₁ (1.1 equiv.), -78 °C, 1 hr.

Scheme 2.3

Lithium aminoalkoxide reagents.

Fort *et al.* have developed a series of lithiating reagents based on aggregates of *n*-butyllithium with lithium aminoalkoxides (*n*-BuLi/ROLi reagents, Figure 2.1) and assessed their efficiency as metallating agents.¹⁰

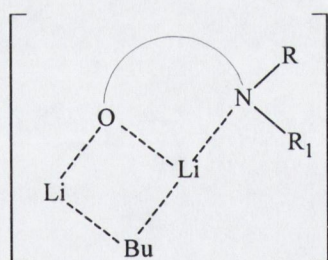
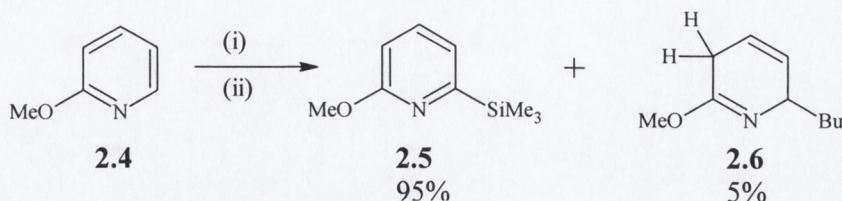


Figure 2.1

The *n*-BuLi/ROLi reagents were prepared by mixing 1 equivalent of the aminoalcohol with 2 equivalents of *n*-butyllithium in hexane at 0 °C. Of the various aminoalkoxides examined, lithium dimethylaminoethoxide (LiDMAE) proved to be the most efficient. Metallation of 2-methoxypyridine (**2.4**) with LiDMAE and subsequent reaction with trimethylsilyl chloride (TMSCl) gave a 95% yield of 2-methoxy-6-trimethylsilylpyridine (**2.5**) with only 5% of the addition product **2.6**

being formed (Scheme 2.4). With the other aminoalkoxides examined, substantial amounts of **2.6** were obtained.¹⁰

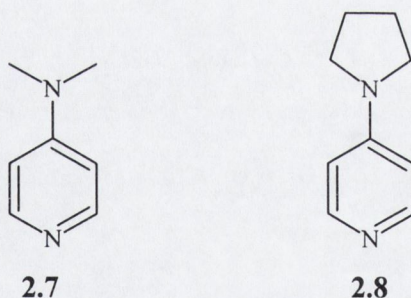


Reagents and conditions: (i) *n*-BuLi/LiDMAE (4 equiv.), hexane, 0 °C, 1 hr. (ii) TMSCl, 0 °C, 1.5 hr.

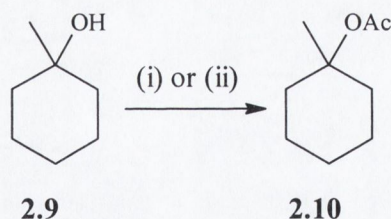
Scheme 2.4

2.1.2. 4-Dialkylaminopyridines as acylation catalysts.

The reaction of acetic anhydride or acetyl chloride with alcohols or amines in the presence of pyridine has been used as a general method for the acylation of these compounds since the procedure was first developed by Verley and Bölsing in 1901.²⁶ However, this method often proves unsatisfactory for the acylation of sterically hindered substrates. In 1969, Steglich and Höfle reported the extremely strong catalytic activity of 4-dimethylaminopyridine (DMAP, **2.7**) and 4-pyrrolidinopyridine (PPY, **2.8**) in the acylation of certain sterically hindered alcohols.²⁷



Treatment of 1-methylcyclohexanol (**2.9**) with acetic anhydride in pyridine gave less than 5% of the acetate **2.10**. In the presence of a catalytic amount (4 mol %) of DMAP and one equivalent of triethylamine **2.10** was obtained in 86% yield²⁷ (Scheme 2.5).



Reagents and conditions:

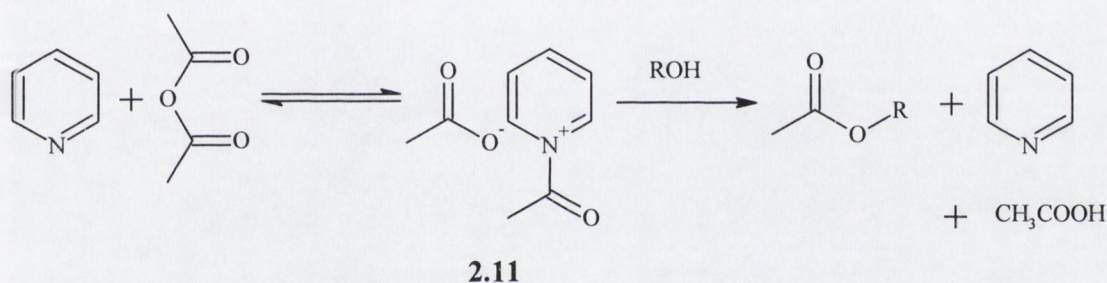
(i). Ac_2O , pyridine, 14h, r.t. (< 5% yield)

(ii). Ac_2O , DMAP (4 mol %), 14h, r.t. (86% yield)

Scheme 2.5

The role of the base in acyl – transfer reactions is threefold:

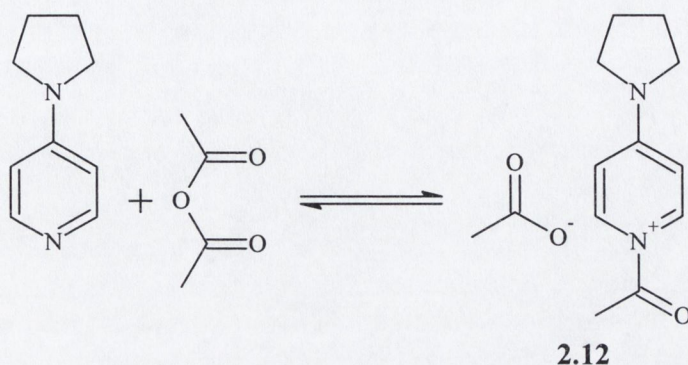
1. **Nucleophilic catalysis.** Acetic anhydride reacts with pyridine to form small amounts of *N*-acetylpyridinium acetate (**2.11**) which, because of its charge, is more capable of transferring an acyl residue to a nucleophile than the anhydride itself²⁸ (Scheme 2.6).



Scheme 2.6

The extent of this nucleophilic catalysis depends on the concentration of **2.11** which in turn is dependant on the position of the equilibrium in Scheme 2.6. In a given reaction solvent, the position of this equilibrium is dictated by the relative affinities of the pyridine and the acetate anion for the acyl group.²⁹ The use of polar solvents that can efficiently solvate the acetylpyridinium salt **2.11** will serve to shift the equilibrium in favour of **2.11**. Although the presence of **2.11** in aqueous solution was detected by UV spectroscopy, its existence in aprotic solvents could not be demonstrated.³⁰ However, in mixtures of acetic anhydride with DMAP or PPY, significant quantities of *N*-acetyl-4-dialkylpyridinium acetate were detected

by NMR spectroscopy in $\text{CDCl}_3/\text{CD}_2\text{Cl}_2$ at low temperatures.³¹ At $-115\text{ }^\circ\text{C}$ in $\text{CDCl}_3/\text{CD}_2\text{Cl}_2$ PPY was completely converted into **2.12** with 1.5 equivalents of acetic anhydride and it has been estimated that some 5–10% of **2.12** is present in solution at room temperature³¹ (Scheme 2.7).



Scheme 2.7

This shift in equilibrium (relative to pyridine) is due to the increased mesomeric stabilisation of the *N*-acetyl-4-dialkylaminopyridinium ion (Figure 2.2). The existence of mesomeric form **2.13c** has been demonstrated by NMR spectroscopy.³¹ At low temperatures, two sets of signals are observed for the α - and β - protons of the pyridine nucleus which arise from restricted rotation around the acetyl – nitrogen bond.

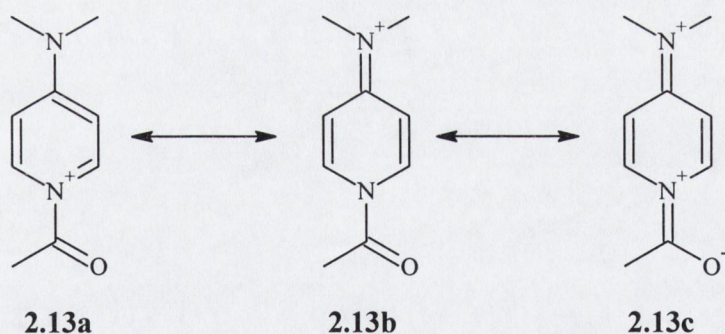
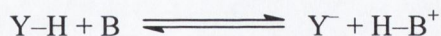


Figure 2.2

2. **General base catalysis.** The base may also function as a Brønsted base B by abstracting a proton from the substrate to produce an anion Y^- (Equation 2. 1).



Equation 2.1

This anion is a better nucleophile than $Y-H$ and reacts more rapidly with the acylating reagent. The extent of this general base catalysis is dependant upon the position of the acid – base equilibrium in Equation 2.1.

In *N*-acetylpyridinium salts, the importance of the structure of the ion pair in general base catalysis has been demonstrated by Steglich and Höfle.³¹ Increased mesomeric stabilisation leads to a greater expansion of the ion pair which facilitates attack by a nucleophile. In addition, the acetate ion can serve to increase the reaction rate by abstracting a proton from the nucleophile (Figure 2.3).

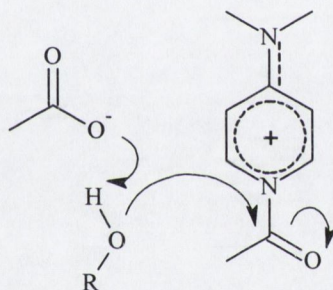


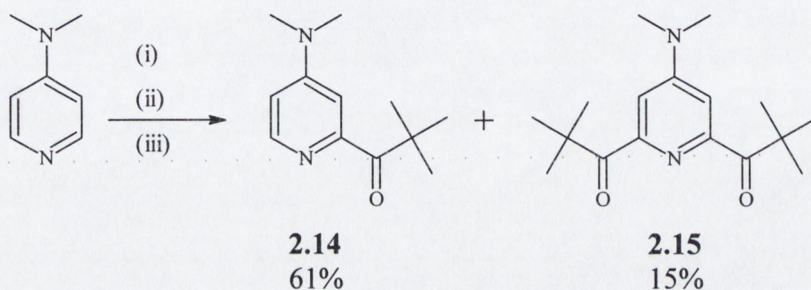
Figure 2.3

3. The third role of the base is to neutralise the acid generated in the reaction and at least one equivalent of base must be present for this purpose in order to maintain catalytic activity. Thus acylations catalysed by DMAP or PPY are generally performed in the presence of another base such as triethylamine or pyridine.²⁷

2.1.3. 2,6-Disubstituted 4-dialkylaminopyridines.

Although the literature contains examples of the synthesis of symmetrical 2,6-disubstituted 4-dialkylaminopyridines directly from 4-dialkylaminopyridines, these compounds have been often obtained as side-products from the synthesis of the corresponding monosubstituted derivatives.

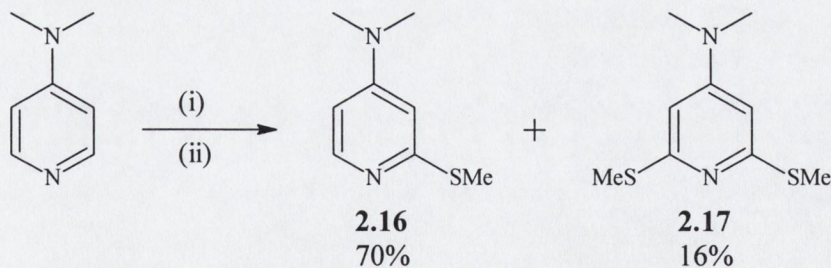
Vedejs *et al.* used Kessar's⁵ methodology for the synthesis of 2-pivaloyl-DMAP **2.14** and obtained a 15% yield of 2,6-dipivaloyl-DMAP **2.15** in addition to the desired monosubstituted compound²⁰ (Scheme 2.8).



Reagents and conditions: (i) $\text{BF}_3 \cdot \text{OEt}_2$ (1.1 equiv.), THF, 0 °C, 0.5 hr. (ii) LiTMP (1.1 equiv.), -78 °C, 0.5 hr. (iii) *t*-BuCOCl (2 equiv.), -78 °C, 4.5 hrs.

Scheme 2.8

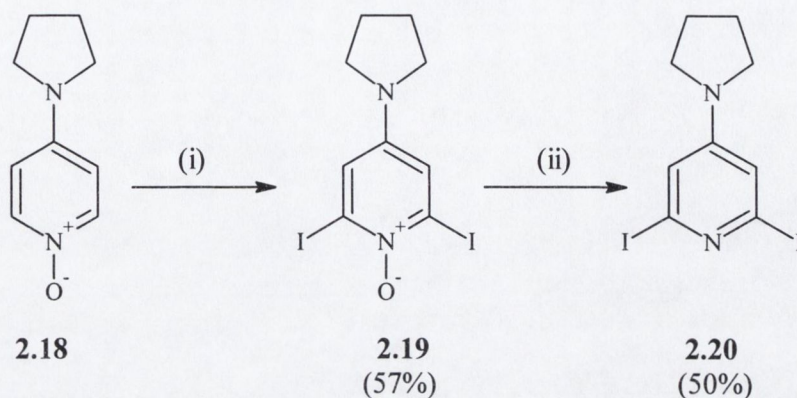
In a study of lithium dimethylaminoethoxide (LiDMAE) as a reagent for the direct α -lithiation of DMAP, Fort *et al.* prepared 2-methylthio-DMAP **2.16** and obtained a 16% yield of the 2,6-disubstituted derivative **2.17** as a side-product of the reaction⁶ (Scheme 2.9).



Reagents and conditions: (i) *n*-BuLi/LiDMAE (2 equiv.), hexane, 0 °C, 1 hr. (ii) MeSSMe (2.5 equiv.), 0 °C, 1.5 hr.

Scheme 2.9

Sammakia and Hurley prepared 2,6-diiodo-4-pyrrolidinopyridine *N*-oxide (**2.19**) *via* metallation of the *N*-oxide **2.18** and reaction of the metallated pyridine with iodine. Subsequent reduction of the *N*-oxide function using phosphorus tribromide gave the free pyridine **2.20**²² (Scheme 2.10).



Reagents and conditions: (i) LDA (4 equiv.), THF, -78 °C, 1 hr., I₂ (4 equiv.), -78 °C – r.t. (ii) PBr₃ (3 equiv.), CHCl₃, reflux 3 hrs.

Scheme 2.10

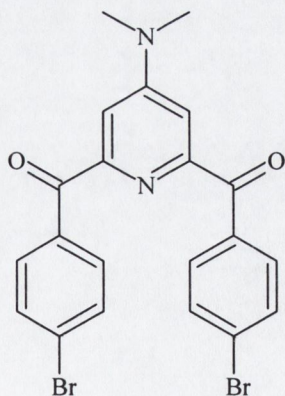
The above methodology was applied to the synthesis of a number of symmetrical 2,6-disubstituted 4-dimethylaminopyridine derivatives directly from 4-dimethylaminopyridine (**2.7**). These compounds were required as precursors for the synthesis of macrocyclic compounds containing the 4-dimethylaminopyridine moiety. The syntheses of these symmetrical DMAP derivatives are described in the following sections.

2.2. Results and discussion.

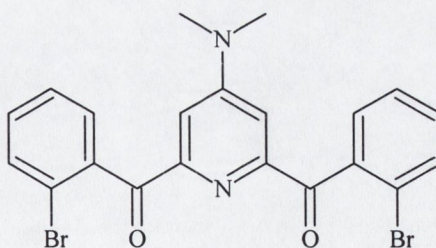
A number of 2,6-disubstituted 4-dimethylaminopyridines were synthesised as precursors for the construction of macrocycles containing the DMAP moiety. Substituents were chosen with a view to further functionalisation or for their ability to act as good leaving groups. The synthesis of these compounds using existing methodology met with limited success. Yields were generally low (less than 20%) and products were often difficult to purify. Reactions performed using DMAP *N*-oxide often gave amounts of tarry material that proved difficult to separate from the desired products. In the case of compounds prepared using Kessar's method,⁵ the products isolated by column chromatography were often found to be contaminated by unreacted 4-dimethylaminopyridine-boron trifluoride complex (DMAP-BF₃). In many experiments, the reaction mixtures proved inseparable by standard techniques.

2.2.1. Synthesis of 2,6-di-(4'-bromobenzoyl)-4-dimethylaminopyridine and 2,6-di-(2'-bromobenzoyl)-4-dimethylaminopyridine.

The diketones 2,6-di-(4'-bromobenzoyl)-4-dimethylaminopyridine (**2.21**) and 2,6-di-(2'-bromobenzoyl)-4-dimethylaminopyridine (**2.22**) have been previously synthesised in this laboratory.²³ These compounds were particularly attractive as macrocycle precursors since they offered interesting possibilities for further functionalisation *via* synthetic manipulation of the bromine and/or carbonyl groups. Derivatives of **2.21** or **2.22** would therefore provide a series of highly adaptable compounds for the synthesis of macrocycles incorporating DMAP residues.



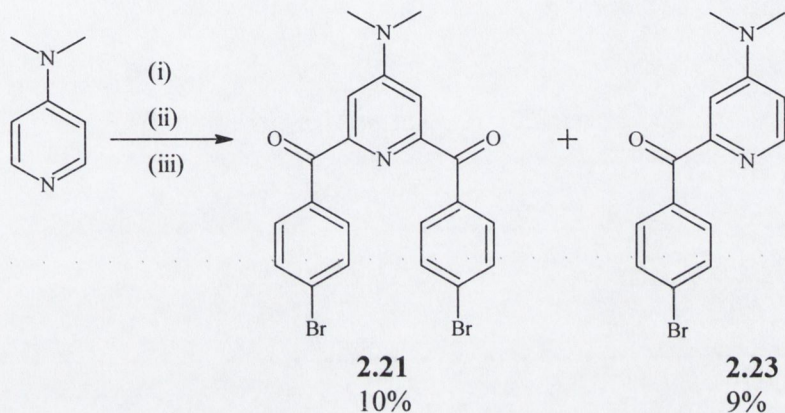
2.21



2.22

2,6-Di-(4'-bromobenzoyl)-4-dimethylaminopyridine.

2,6-Di-(4'-bromobenzoyl)-4-dimethylaminopyridine (**2.21**) was prepared using the method described by Vedejs²⁰ for the synthesis of 2-pivaloyl-4-dimethylaminopyridine (**2.14**). Analogous to Kessar's results with pyridine,⁵ DMAP was activated by conversion to its boron trifluoride complex (DMAP-BF₃). Treatment of this complex with lithium tetramethylpiperidide (LiTMP) and subsequent reaction with two equivalents of 4-bromobenzoyl chloride gave **2.21** in 10% yield together with a 9% yield of the monosubstituted derivative **2.23** (Scheme 2.11).



Reagents and conditions: (i) BF₃·OEt₂ (1.1 equiv.), THF, 0 °C, 0.5 hr. (ii) LiTMP (2.2 equiv.), -78 °C, 0.5 hr. (iii) *p*-BrC₆H₄COCl (2.2 equiv.), -78 °C, 4.5 hrs. (iv) MeOH/ H₂O.

Scheme 2.11

Since it was anticipated that multigram quantities of the diketones **2.21** and **2.22** would be required for the preparation of the projected macrocycles it was decided to attempt to improve the yields of these intermediates.

Attempts were made to improve the yield of **2.21** by varying the reaction conditions but no significant improvement in yield was observed. The conditions employed for these experiments are summarised in Table 2.1.

Table 2.1. Reaction conditions for the synthesis of **2.21**^[a]

Run.	Preparation DMAP-BF ₃ .		Lithiation reaction. ^[b]		Reaction with aroyl halide.		% Yield ^[c] 2.21
	Time. (hrs)	Temp. (°C)	Time. (hrs)	Temp. (°C)	Time. (hrs)	Temp. (°C)	
1.	0.5	0	0.5	-78	4.5	-78	11
2.	1.0	0	0.5	-78	4.5	-78	9
3.	0.25	0	0.5	-78	4.5	-78	9
4.	0.5	0	1.0	-78	4.5	-78	11
5.	0.5	0	1.5	-78	4.5	-78	10
6.	0.5	0	1.0	-78	9.0	-78	10
7.	0.5	0	1.0	-50	4.5	-78	9
8.	0.5	0	1.0	-78	4.5	-50	9
9.	0.5	0	1.0	-78	4.5	-100	10
10.	0.5	0	0.25	-78	4.5	-78	9
11.	0.5	0	1.0	-78	1.5	-78	5

^[a]All reactions performed using 2 mmol DMAP. ^[b]LiTMP used as base. ^[c]Isolated yield.

Extending the time for the lithiation reaction (runs 4 and 5) or the reaction with the aroyl halide (run 6) failed to improve the yield of **2.21**. Although shortening the reaction time for the metallation reaction had no effect (run 10), reducing the time for the condensation reaction lowered the yield to 5% (run 11). Changing the reaction temperature (runs 7, 8 and 9) had little effect on the yield.

Use of excess LiTMP (4 equivalents) gave no improvement in yield. Reversing the order of addition by adding the aroyl halide to the lithiated pyridine resulted in the formation of large amounts of insoluble tarry material and only traces (< 1% yield) of impure **2.21** were isolated from the reaction mixture.

Changing the solvent from tetrahydrofuran to diethyl ether or hexane failed to give the reaction, probably as a result of the relative insolubility of DMAP in these solvents.

Using lithium diisopropylamide (LDA) as base gave similar results to those obtained using LiTMP. When *n*-butyllithium was used considerable amounts of tar were formed. Analysis of this reaction mixture by thin-layer chromatography showed no trace of **2.21**.

In contrast to Kessar's findings,³² *tert*-butyllithium gave better results than LiTMP. The use of *t*-BuLi as base gave an increased yield (15 – 18%) and a product of improved purity. The ¹H NMR spectrum of the product after aqueous workup showed that the mixture consisted of **2.21** and methyl 4-bromobenzoate (from reaction of 4-bromobenzoyl chloride with methanol during workup) with only trace amounts of impurities. However, attempts to increase the yield by varying the reaction conditions as outlined in Table 2.1. failed to improve on the 18% yield.

The recovery from the reaction was examined in order to discount the possibility that the low yield of **2.21** was due to the formation of some side-product which was removed from the reaction mixture during workup. The reaction mixture was quenched with methanol and heated under reflux for 30 minutes to ensure complete de-complexation of unreacted DMAP. After removal of the solvents, column chromatography was performed without prior aqueous workup. Methyl 4-bromobenzoate and **2.21** were isolated by elution with dichloromethane. Unreacted DMAP was isolated using dichloromethane/methanol (95:5) as eluent. The results of this analysis are presented in Table 2.2.

Table 2.2. Product recovery from the synthesis of 2.21.

Compound	Weight used (g)	Weight recovered (g)	Recovery (%)
DMAP	0.53	0.35	78.3 ^[a]
<i>p</i> -BrC ₆ H ₄ COCl	2.10	—	—
2.21	—	0.35	16.4 ^[b]
<i>p</i> -BrC ₆ H ₄ COOMe	—	1.48	84.3 ^[a]

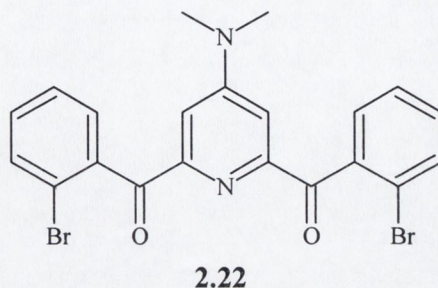
^[a] % of starting materials recovered based on yield of **2.21**. ^[b] % yield.

Based on the yield of **2.21** (0.35 g, 16.4%), the weight of methyl 4-bromobenzoate obtained (1.48 g) was 84.3% of the calculated yield of this ester from reaction of unreacted 4-bromobenzoyl chloride with methanol. The weight of DMAP recovered (0.35 g) was 78.3% of the expected recovery. Increasing the methanol content of the eluent to 20% gave a small amount (38 mg) of unidentified tarry material but no further fractions were obtained even when the methanol content of the eluent was increased to 40%. The calculated overall weight deficit was some 13.1% of the expected weight. Unfortunately, the signals in the aromatic region of the ^1H NMR spectrum of the crude product from this reaction appeared as a broad band showing considerable baseline distortion so it was not possible to correlate the spectra of the isolated products with the spectrum of the crude material. However, in view of the low weight deficit and the high recovery of starting materials, it is unlikely that the poor yield of **2.21** was due to the formation of any significant amount of a side-product which was not eluted during chromatography. The shortfall in weight was probably due to mechanical losses incurred during solution transfers and chromatography.

The existence of 2,6-dilithio-4-dimethylaminopyridine in solution was confirmed by quenching a solution of the metallated pyridine with D_2O . The ^1H NMR spectrum of the product showed only a trace of the signal at δ 8.23 from the protons at the 2 and 6 positions of the pyridine ring. Thus it would appear that DMAP-BF_3 is almost completely converted into the dilithio species by 2 equivalents of *tert*-butyllithium. The low yield of **2.21** could not therefore be due to incomplete metallation of DMAP.

2,6-Di-(2'-bromobenzoyl)-4-dimethylaminopyridine.

Treatment of DMAP-BF₃ with *t*-BuLi and subsequent reaction with 2-bromobenzoyl chloride gave 2,6-di-(2'-bromobenzoyl)-4-dimethylaminopyridine (**2.22**) in 16% yield.



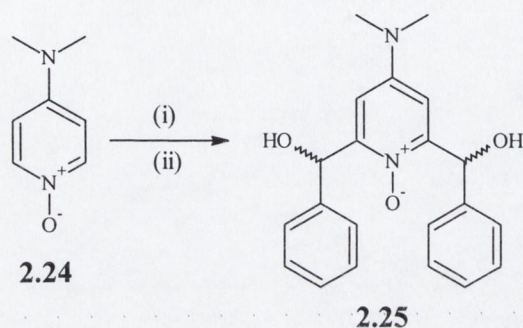
Attempts to improve the yield of **2.22** using the conditions outlined in Table 2.1 proved unsuccessful.

In the ¹H NMR spectrum of the '*para*' compound **2.21**, the protons at the 3 and 5 positions of the pyridine ring appear as a singlet at δ 7.47. The protons on the phenyl rings come into resonance downfield from the pyridine protons as a pair of doublets. The protons *ortho* to the carbonyl group resonate at δ 8.04 while those *ortho* to bromine appear at δ 7.56. In contrast, the phenyl protons of the *ortho*-substituted analogue **2.22** resonate *upfield* from the pyridine protons. The pyridine protons appear at δ 7.58 and the signals from the phenyl protons occur as multiplets at δ 7.39, δ 7.27, and δ 7.16. Only three signals appear for these protons due to overlap of the signals for the protons at the 4 and 5 positions of the phenyl rings.

2.2.2. Attempted alternative syntheses of 2,6-di-(4'-bromobenzoyl)-4-dimethylaminopyridine.

Alternative routes to diketone **2.21** were also explored in an effort to improve the yield of this compound.

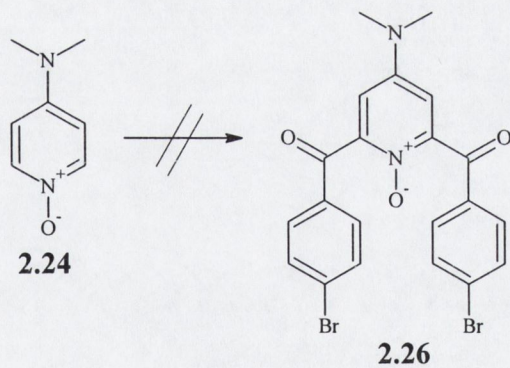
Aubert, working in this laboratory, prepared diol **2.25** by reaction of DMAP *N*-oxide **2.24** with benzaldehyde in the presence of *n*-BuLi³³ (Scheme 2.12).



Reagents and conditions: (i) *n*-BuLi (2.2 equiv.), THF, -78 °C, 0.5 hr. (ii) C_6H_5CHO (1.1 equiv.), 3 hrs.

Scheme 2.12

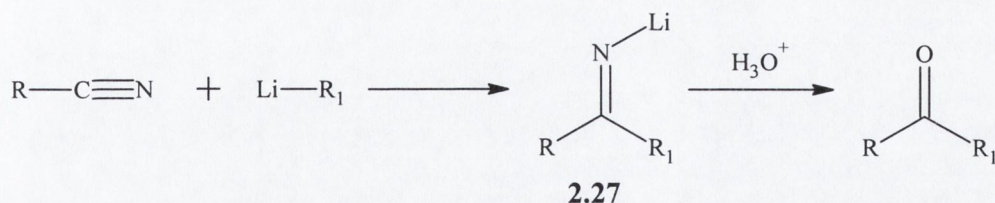
This reaction suggested an alternative means of obtaining **2.21** *via* lithiation of DMAP *N*-oxide and reaction with 4-bromobenzoyl chloride followed by reduction of the resulting substituted *N*-oxide. Attempts to obtain *N*-oxide **2.26** by this method gave only recovered **2.24** and methyl 4-bromobenzoate (Scheme 2.13).



Reagents and conditions: (i) *t*-BuLi (2.2 equiv.), THF, -78 °C, 1 hr. (ii) $p\text{-BrC}_6\text{H}_4\text{COCl}$ (2.2 equiv.), -78 °C, 4.5 hrs.

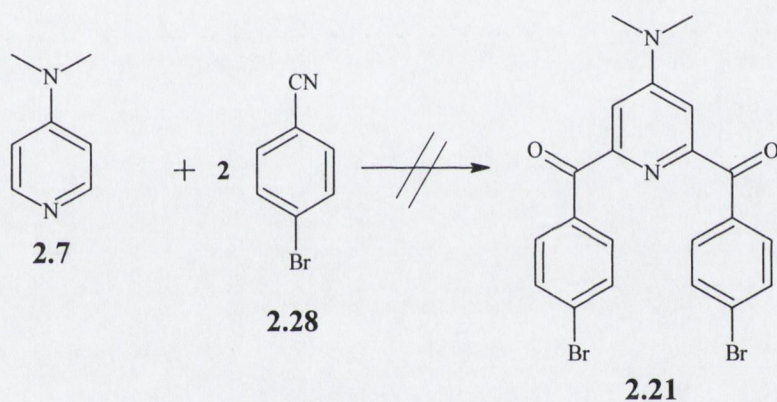
Scheme 2.13

Nitriles react with organolithium reagents to give lithio-iminium species (**2.27**) which can be hydrolysed to ketones³⁴ (Scheme 2.14).



Scheme 2.14

This reaction therefore appeared to be a viable alternative route to **2.21**. However, treatment of 4-bromobenzonitrile (**2.28**) with the lithiated DMAP- BF_3 complex gave no reaction and only starting materials were isolated from the reaction mixture (Scheme 2.15).



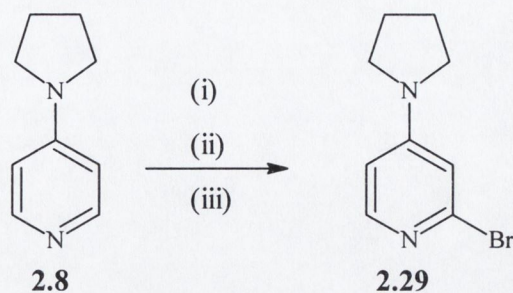
Reagents and conditions: (i) $\text{BF}_3 \cdot \text{OEt}_2$ (1.1 equiv.), THF, 0 °C, 0.5 hr. (ii) *t*-BuLi (2.2 equiv.), -78 °C, 1 hr. (iii) *p*-BrC₆H₄CN (2.2 equiv.) -78 °C, 4.5 hrs. (iv) $\text{H}^+/\text{H}_2\text{O}$.

Scheme 2.15

Attempts to obtain the substituted *N*-oxide **2.26** *via* reaction of metallated DMAP *N*-oxide with this nitrile also proved unsuccessful.

2.2.3. Synthesis of 2,6-dibromo-4-dimethylaminopyridine.

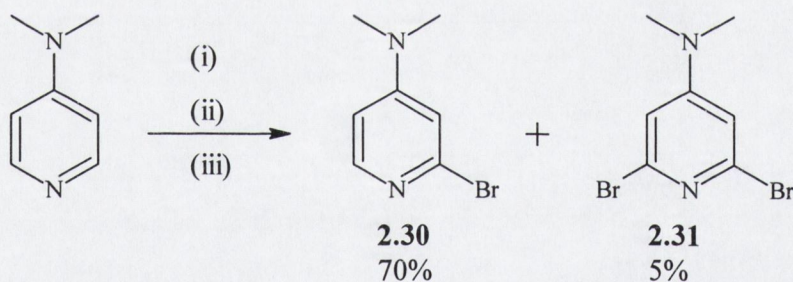
In 1999, Sammakia *et al.* described the synthesis of 2-bromo-4-(1'-pyrrolidinyl)pyridine (**2.29**) from 4-(1'-pyrrolidinyl)pyridine (**2.8**) using Kessar's⁵ methodology²² (Scheme 2.16).



Reagents and conditions: (i) $\text{BF}_3 \cdot \text{OEt}_2$ (1.1 equiv.), THF, 0 °C, 0.5 hr. (ii) BuLi (1.6 equiv.), -78 °C, 0.5 hr. (iii) Br_2 (1.6 equiv.), -78 °C, 1 hr.

Scheme 2.16

Lee, working in this laboratory, repeated this experiment using DMAP and obtained a 70% yield of 2-bromo-4-dimethylaminopyridine (**2.30**) together with a small amount (5%) of 2,6-dibromo-4-dimethylaminopyridine (**2.31**) as a side-product of the reaction²⁴ (Scheme 2.17).



Reagents and conditions: (i) $\text{BF}_3 \cdot \text{OEt}_2$ (1.1 equiv.), THF, 0 °C, 0.5 hr. (ii) BuLi, -78 °C, 0.5 hr. (iii) Br_2 , -78 °C, 1 hr.

Scheme 2.17

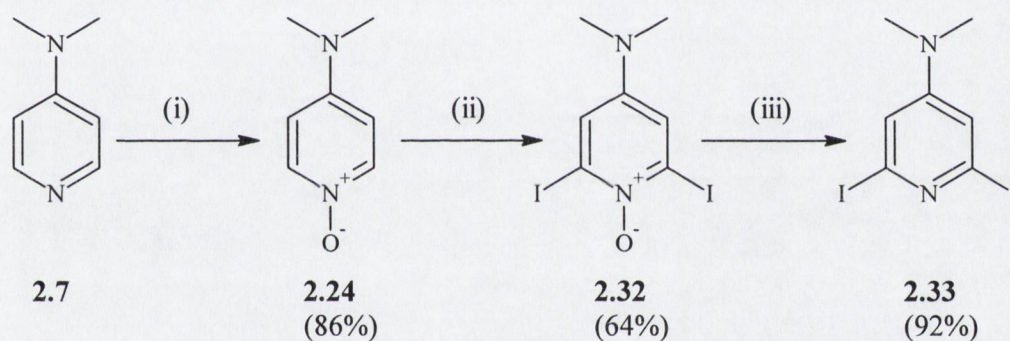
Attempts to make **2.31** the major product of the reaction by using 2 equivalents of *n*-BuLi proved unsuccessful. Using *tert*-butyllithium as base and extending the reaction time to 4 hours gave **2.31** in 17% yield together with a 52% yield of the monobromo compound. Further extension of the reaction time (6 hours) failed to

increase the yield of **2.31**. Sammakia *et al.* subsequently reported a 23% yield of this compound using LDA as base.²⁵

2.2.4. Synthesis of 2,6-diiodo-4-dimethylaminopyridine *N*-oxide and 2,6-diiodo-4-dimethylaminopyridine.

The synthesis of 2,6-diiodo-4-dimethylaminopyridine (**2.33**) was initially attempted *via* lithiation of DMAP- BF_3 and reaction of the metallated pyridine with iodine. However, this method gave only a 5% yield of **2.33**. A more efficient synthesis of this compound was realised using a variation of the method described by Sammakia for the synthesis of the 4-pyrrolidinopyridine analogue.²²

DMAP was converted to its *N*-oxide **2.24** by treatment with Oxone®.³⁵ Metallation of **2.24** with *t*-BuLi and subsequent reaction with iodine gave 2,6-diiodo-4-dimethylaminopyridine *N*-oxide (**2.32**). Reduction of the *N*-oxide function using phosphorus tribromide gave **2.33** in 51% overall yield (Scheme 2.18).



Reagents and conditions: (i) Oxone® (2 equiv.), aq. KOH, r.t. 18 hrs. (ii) *t*-BuLi (2.2 equiv.), THF, -78 °C, 1 hr., I_2 (4 equiv.), -78 °C, 2 hrs. (iii) PBr_3 (3 equiv.), CHCl_3 , reflux 3 hrs.

Scheme 2.18

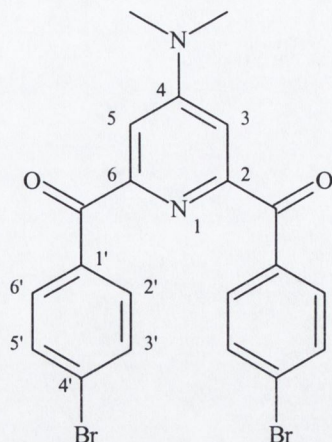
The compounds described above were prepared in order to provide suitable precursors for the construction of macrocycles containing DMAP moieties. In the following chapters, the further elaboration of these compounds and the attempts to use these compounds in the synthesis of DMAP macrocycles are described.

2.3. Experimental.

General experimental conditions.

^1H NMR spectra (400.1 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded for solutions in CDCl_3 using a Bruker Avance DPX 400 MHz spectrometer. Chemical shifts are measured in ppm. J values are given in Hz. IR spectra were recorded as nujol mulls or as thin films between sodium chloride plates using a Mattson Genesis II FTIR spectrometer. Mass spectra were recorded using a VG Alto Spec (HRMS) or a Kratos (FAB) instrument. Melting points were measured in unsealed capillary tubes using an Electrothermal 9000 melting point apparatus and are uncorrected. Thin layer chromatography was carried out using Merck Kieselgel 60 F₂₅₄ 0.2 mm silica gel plates. Column chromatography was performed using Merck Kieselgel 60 (70 – 230 mesh) silica gel. THF was distilled from sodium wire and benzophenone before use. Triethylamine, pyridine, and toluene were distilled from calcium hydride. All other solvents and reagents were used as received.

2,6-Di-(4'-bromobenzoyl)-4-dimethylaminopyridine (2.21).²³



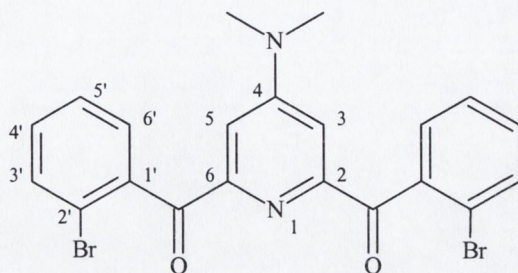
To a solution of 4-dimethylaminopyridine (0.550 g, 4.5 mmol) in dry THF (15 mL) at 0 °C under a nitrogen atmosphere was added boron trifluoride diethyl etherate (0.6 mL, 0.678 g, 4.8 mmol). The resulting suspension was stirred at 0 °C for 30 minutes and then cooled to -78 °C. A 1.7 M solution of *tert*-butyllithium (5.8 mL, 9.9 mmol) in pentane was added dropwise and the solution was stirred at -78 °C for 1 hour. The resulting yellow solution was added dropwise to a solution of 4-bromobenzoyl chloride (2.102 g, 9.6 mmol) in dry THF (10 mL) at -78 °C. After stirring at -78 °C for 4.5 hours, the mixture was allowed to rise to room temperature. Methanol (3 mL) and water (10 mL) were added and the solution was stirred overnight. The organic solvents were evaporated and the aqueous residue was extracted with chloroform (3×15 mL). The combined chloroform extracts were washed with dilute HCl (2×10 mL) and water (10 mL), dried over MgSO₄, and evaporated to dryness. Column chromatography on silica gel using dichloromethane as eluent gave 2,6-di-(4'-bromobenzoyl)-4-dimethylaminopyridine (0.408 g, 18 %) as a pale yellow solid, m.p. 137 – 139 °C (lit.²³ 136 – 138 °C).

δ_{H} : 3.19 (6H, s, N(CH₃)₂), 7.47 (2H, s, H3 and H5), 7.56 (4H, d, *J* 8.5, H3' and H5'), 8.04 (4H, d, *J* 8.5, H2' and H6') ppm.

δ_{C} : 39.0 (N(CH₃)₂), 108.6 (C3 and C5), 127.5 (C4'), 130.7 (C3' and C5'), 132.2 (C2' and C6'), 134.8 (C1'), 153.6 (C2 and C6), 155.4 (C4), 192.1 (C=O) ppm.

$\nu_{\max}$ (nujol): 2923, 2853, 1672 (C=O), 1601, 1581, 1462, 1377, 1293, 1258, 1178, 1075, 1013, 980, 922, 860, 803, and 764 cm^{-1}

2,6-Di-(2'-bromobenzoyl)-4-dimethylaminopyridine (2.22).²³



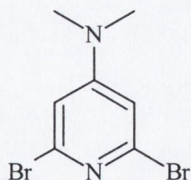
2,6-Di-(2'-bromobenzoyl)-4-dimethylaminopyridine was prepared by the method described above using 4-dimethylaminopyridine (0.601 g, 4.9 mmol), boron trifluoride diethyl etherate (0.7 mL, 0.791 g, 5.6 mmol), *tert*-butyllithium (6.4 mL of 1.7 M, 10.8 mmol) and 2-bromobenzoyl chloride (2.311 g, 10.5 mmol). Purification by column chromatography using dichloromethane as eluent gave 2,6-di-(2'-bromobenzoyl)-4-dimethylaminopyridine (0.390 g, 16%) as a yellow solid, m.p. 136 – 139 °C (lit.²³ 136 – 140 °C).

δ_{H} : 3.20 (6H, s, $\text{N}(\text{CH}_3)_2$), 7.16 (4H, m, J 6.0, H4' and H5'), 7.28 (2H, m, J 6.0, H3'), 7.39 (2H, m, J 6.0, H6'), 7.57 (2H, s, H3 and H5) ppm.

δ_{C} : 39.2 ($\text{N}(\underline{\text{C}}\text{H}_3)_2$), 107.9 (C3 and C5), 119.3 (C2'), 125.7 (C3'), 129.1 (C4'), 129.9 (C5'), 131.7 (C6'), 139.9 (C1'), 152.1 (C2 and C6), 155.4 (C4), 195.4 (C=O) ppm.

$\nu_{\max}$ (nujol): 2927, 1770 (C=O), 1680, 1590, 1462, 1378, 1295, 1230, 1131, 1092, 1056, 1025, 1001, 975, 953, 921, 858, 804, 741 and 723 cm^{-1}

2,6-Dibromo-4-dimethylaminopyridine (2.31).²⁵



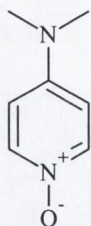
To a solution of 4-dimethylaminopyridine (0.552 g, 4.5 mmol) in dry THF (15 mL) at 0 °C under a nitrogen atmosphere was added boron trifluoride diethyl etherate (0.6 mL, 0.678 g, 4.9 mmol). The resulting suspension was stirred at 0 °C for 30 minutes and then cooled to -78 °C. A 1.7 M solution of *tert*-butyllithium (6 mL, 10.2 mmol) was added dropwise and the resulting solution was stirred at -78 °C for 30 minutes. Bromine (1.2 mL, 3.732 g, 13.5 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 4 hours. The reaction mixture was allowed to rise to room temperature and saturated sodium thiosulphate solution (20 mL) was added. The layers were separated and the aqueous layer was extracted with chloroform (3×20 mL). The combined organic extracts were washed with brine (2×20 mL) and water (20 mL) and dried over MgSO₄. The solvents were removed under reduced pressure and the residue was purified by column chromatography on silica gel using hexane/ ethyl acetate (3:2) as eluent to afford 2,6-dibromo-4-dimethylaminopyridine (0.211 g, 17%) as a yellow solid, m.p. 146 – 147 °C (lit.²⁵ 148 °C).

δ_{H} : 3.02 (6H, s, N(CH₃)₂), 6.84 (2H, s, H3 and H5) ppm.

δ_{C} : 30.1 (N(CH₃)₂), 108.5 (C3 and C5), 140.3 (C2 and C6), 156.2 (C4) ppm.

ν_{max} (nujol): 2922, 2854, 1573, 1459, 1376, 1262, 1282, 1224, 1149, 1076, 960, 819, and 721 cm⁻¹

4-Dimethylaminopyridine *N*-oxide (2.24).³⁵



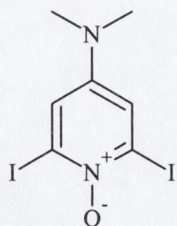
4-Dimethylaminopyridine (5.024 g, 40 mmol) was dissolved in potassium hydroxide solution (0.5 M, 400 mL) and Oxone® (24.401 g, 80 mmol) was added in small portions over a 30 minute period. The solution was stirred overnight and then neutralised with concentrated phosphoric acid. The solvent was evaporated and the resulting salt cake was extracted with boiling chloroform (3×100 mL). The combined chloroform extracts were dried over MgSO₄ and evaporated to dryness. Recrystallisation from chloroform gave 4-dimethylaminopyridine *N*-oxide (4.913 g, 86%) as a brown solid, m.p. 216 – 218 °C (lit.³⁵ 216 – 218 °C).

δ_{H} : 3.0 (6H, s, N(CH₃)₂), 6.48 (2H, d, *J* 8.2, H3 and H5), 7.93 (2H, d, *J* 8.2, H2 and H6) ppm.

δ_{C} : 38.7 (N(CH₃)₂), 107.6 (C3 and C5), 138.9 (C2 and C6), 149.8 (C4) ppm.

ν_{max} (nujol): 2923, 2726, 2372, 1735, 1629, 1461, 1377 (N–O), 1214, 1153, 1070, 1024, 947, and 720 cm⁻¹

2,6-Diiodo-4-dimethylaminopyridine *N*-oxide (2.32).²⁴



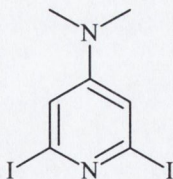
A 1.7 M solution of *tert*-butyllithium (4.8 mL, 8 mmol) in pentane was added dropwise to a suspension of 4-dimethylaminopyridine *N*-oxide (0.512 g, 3.6 mmol) in dry THF (50 mL) under a nitrogen atmosphere at -78°C and the resulting solution was stirred for 1 hour. A solution of iodine (3.721 g, 14 mmol) in dry THF (10 mL) was added dropwise over a 20 minute period. The reaction mixture was maintained at -78°C for 2 hours and then allowed to rise to room temperature. Saturated sodium thiosulphate solution was added with constant stirring until the dark colour of the iodine was discharged. The THF was evaporated and the aqueous residue was extracted with dichloromethane (3×50 mL). The combined organic extracts were dried over MgSO_4 and evaporated to dryness. Recrystallisation from chloroform gave 2,6-diiodo-4-dimethylaminopyridine *N*-oxide (0.900 g, 64%) as a yellow solid, m.p. $191 - 192^{\circ}\text{C}$. (lit.²⁴ $191.7 - 192.7^{\circ}\text{C}$).

δ_{H} : 2.99 (6H, s, $\text{N}(\text{CH}_3)_2$), 7.12 (2H, s, H3 and H5) ppm.

δ_{C} : 39.6 ($\text{N}(\text{CH}_3)_2$), 107.3 (C2 and C6), 118.9 (C3 and C5), 146.6 (C4) ppm.

ν_{max} (nujol): 3299, 2925, 2725, 2669, 1595, 1459, 1377 (N–O), 1147, 1059, 966, 820, and 725 cm^{-1}

2,6-Diiodo-4-dimethylaminopyridine (2.33).



Phosphorus tribromide (0.6 mL, 1.728 g, 6.4 mmol) was slowly added to a solution of 2,6-diiodo-4-dimethylaminopyridine *N*-oxide (0.812 g, 2.1 mmol) in chloroform (20 mL) at 0 °C and the resultant slurry was brought to reflux for 3 hours. The solution was cooled to room temperature and poured into a saturated sodium bicarbonate solution (60 mL) at 0 °C. Ethyl acetate (40 mL) was added and the layers were separated. The aqueous phase was extracted with ethyl acetate (3×40 mL). The combined organic extracts were washed with brine (2×30 mL) and water (30 mL), dried over MgSO₄, and evaporated to dryness to afford 2,6-diiodo-4-dimethylaminopyridine (0.711 g, 92%) as a yellow solid, m.p. 148 – 152 °C. Recrystallisation from ethyl acetate/ hexane gave m.p. 154 – 156 °C.

δ_{H} : 2.97 (6H, s, N(CH₃)₂), 6.89 (2H, s, H3 and H5) ppm.

δ_{C} : 38.8 (N(CH₃)₂), 115.5 (C3 and C5), 116.2 (C2 and C6), 154.6 (C4) ppm.

ν_{max} (CCl₄ smear): 3401, 3104, 2922, 2853, 2365, 1637, 1575, 1492, 1425, 1388, 1281, 1225, 1151, 1076, 960, 819, and 721 cm⁻¹

MS (ES): Calculated for [C₇H₈I₂N₂] m/z 373.8776. Found m/z 374.8844 [M+H]⁺

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Chapter 3

Palladium and copper-catalysed coupling of 4-dimethylaminopyridine derivatives

3.1. Introduction.

In Chapter 2, the syntheses of a number of symmetrical 2,6-disubstituted 4-dimethylaminopyridine derivatives were described (Figure 3.1).

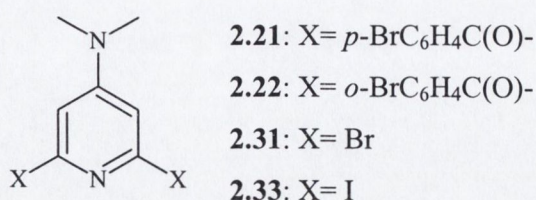
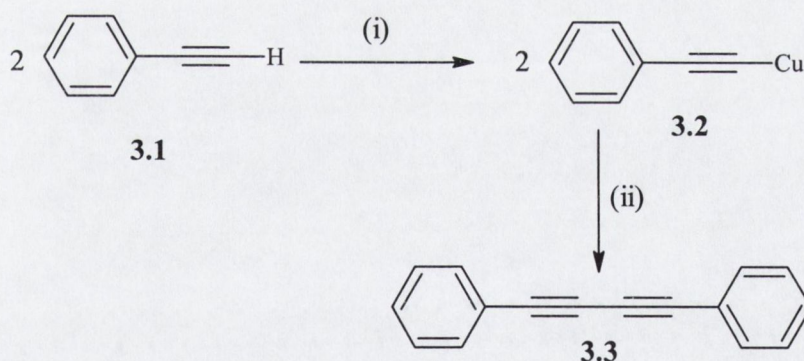


Figure 3.1

The present chapter describes the conversion of the above compounds to terminal acetylene derivatives and details the attempts made to use these derivatives in the construction of macrocyclic compounds. The methodology employed for the synthesis of these acetylene derivatives is outlined below.

3.1.1. Oxidative coupling of acetylenes. The Glaser reaction.

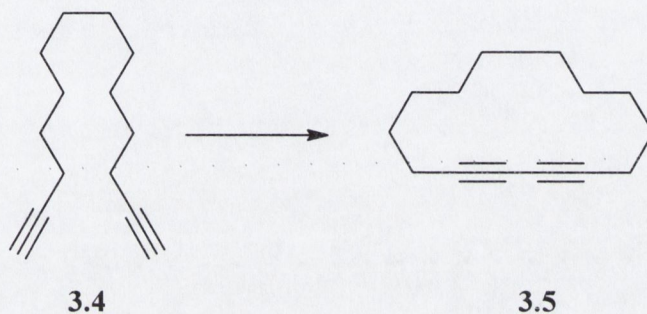
In 1869, Glaser reported the dimerisation of copper(I) phenylacetylide (3.2) to 1,4-diphenyl-1,3-butadiyne (3.3) in the presence of air¹ (Scheme 3.1).



Reagents and conditions: (i) CuCl, NH₄OH, EtOH. (ii) NH₄OH, EtOH, air.

Scheme 3.1

Glaser's original method failed to see widespread application since it involved isolation of the potentially explosive copper acetylide prior to the coupling reaction, a procedure which often proved difficult due to the poor crystallisation properties of the copper salts. Several modifications of Glaser's original procedure which do not require isolation of the copper acetylide have been introduced.² In 1959, Eglinton and Galbraith reported the synthesis of a number of macrocyclic diynes using copper(II) acetate in methanolic pyridine³ (Scheme 3.2). Although the reaction could be performed using a catalytic amount of the copper salt if oxygen was bubbled through the solution, the use of excess catalyst was found to be more convenient under the high-dilution conditions employed.



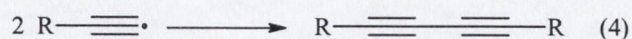
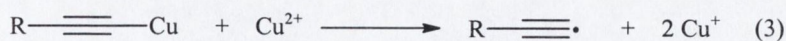
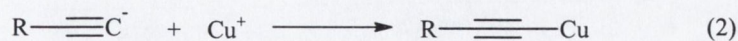
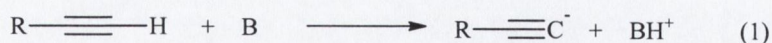
Reagents and conditions: $\text{Cu}(\text{OAc})_2$ (4 equiv.), pyridine/ Et_2O /MeOH, O_2 , reflux 72 hrs.

Scheme 3.2

Another important modification was introduced by Hay, who performed the coupling reaction in acetone using a catalytic amount of copper(I) complexed with *N,N,N,N*-tetramethylethylenediamine (TMEDA) in the presence of oxygen.⁴ The greater activity of this catalyst system allowed the use of lower temperatures and shorter reaction times.

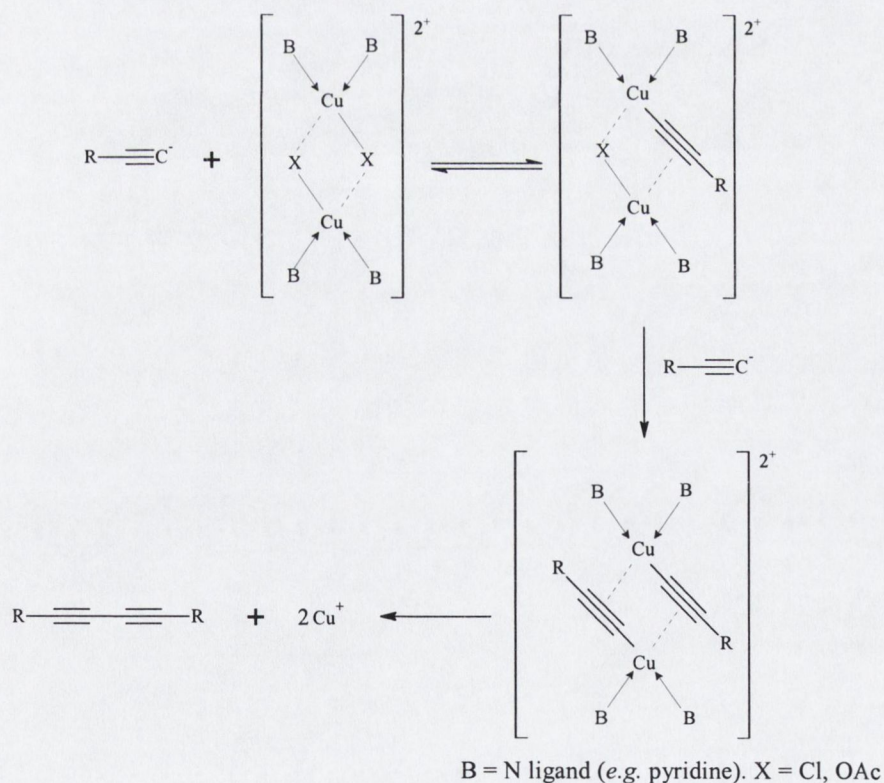
Early mechanistic proposals for the copper-mediated coupling of acetylenes postulated the formation of acetylenic free radicals which then combined to give the diacetylenes.² Clifford and Waters studied the reaction using copper(II) acetate in pyridine in the absence of oxygen and found that the addition of copper(I) ions was necessary in order for the reaction to proceed.⁵ They proposed a mechanism in which a copper(I) acetylide was oxidised by transfer of a single electron to

copper(II) through an acetate ligand bridge to generate a copper (II) acetylide which rapidly decomposed to give the free radicals (equation 3, Scheme 3.3).



Scheme 3.3

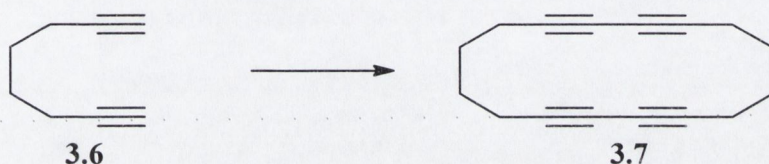
Bohlmann *et al.* questioned the free-radical mechanism on the basis that mixtures of different alkynes gave predominantly self-coupled products whereas no such selectivity could be expected of free radicals.⁶ Given the highly reactive nature of free radicals, a mixture of different alkynes would be expected to give both self-coupled and cross-coupled products. They proposed the formation of a dinuclear copper(II) acetylide complex which collapsed directly to the coupled products (Scheme 3.4).



Scheme 3.4

Acetylenic coupling reactions have been widely used for the construction of macrocyclic systems.² Indeed, these reactions have proved to be the methods of choice for the synthesis of cyclophane⁷ and annulene⁸ derivatives. The simplicity of the experimental procedures, the mild reaction conditions, and the ability to tolerate a wide variety of functional groups have made these reactions particularly attractive as a means of carbon-carbon bond formation.

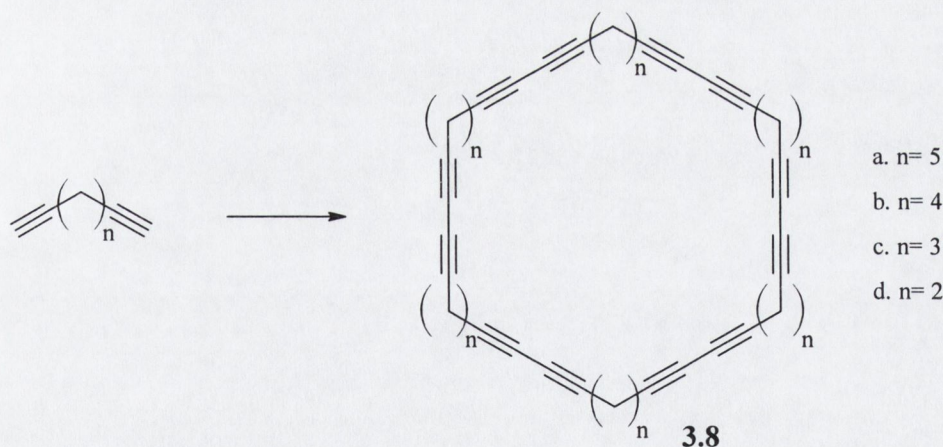
In the course of studies on the oxidative coupling of terminal diacetylenes, Sondheimer *et al.* obtained cyclic tetrayne **3.7** by dimerisation of octa-1,7-diyne (**3.6**) in the presence of copper(I) chloride and ammonium chloride⁹ (Scheme 3.5).



Reagents and conditions: CuCl , NH_4Cl , H_2O .

Scheme 3.5

This group later reported the synthesis of a number of polyacetylene macrocycles **3.8** using copper(II) acetate in pyridine.¹⁰ The corresponding trimers, tetramers, and pentamers were also obtained in these reactions (Scheme 3.6).



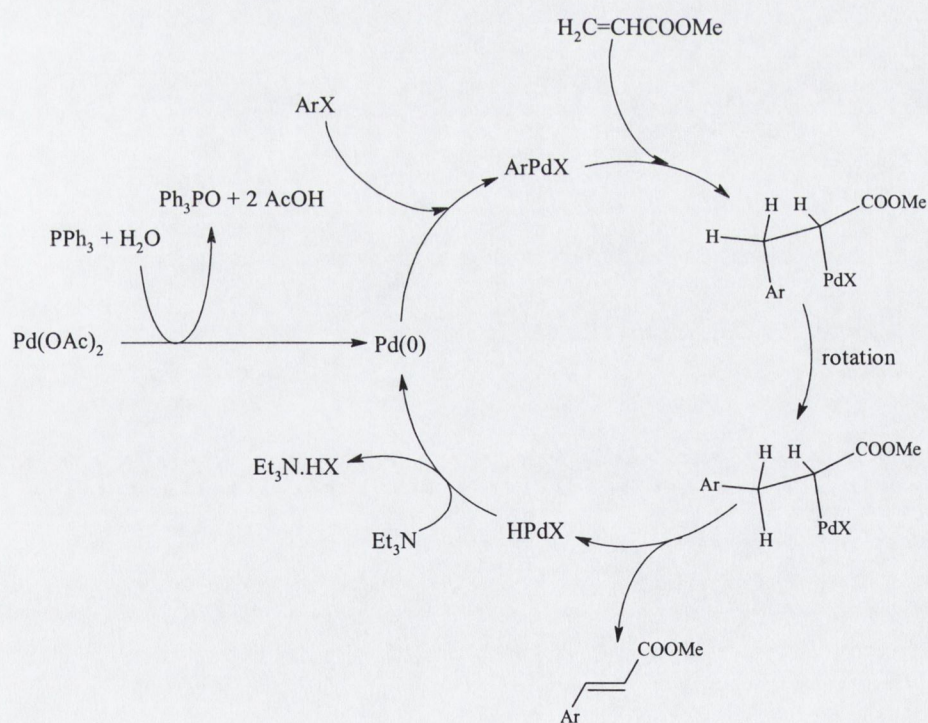
Reagents and conditions: $\text{Cu}(\text{OAc})_2$ (15 equiv.), pyridine, 55°C , 3 hrs.

Scheme 3.6

Early examples of acetylenic macrocycles were prepared *via* the copper-mediated coupling of terminal acetylenes.^{3,10} Later, the application of palladium-catalysed reactions to the coupling of alkynes led to the use of these procedures in macrocycle synthesis.^{7,8} Frequently, both copper- and palladium-mediated reactions have been used in the course of a synthetic sequence.^{11,12}

3.1.2. The Heck reaction.

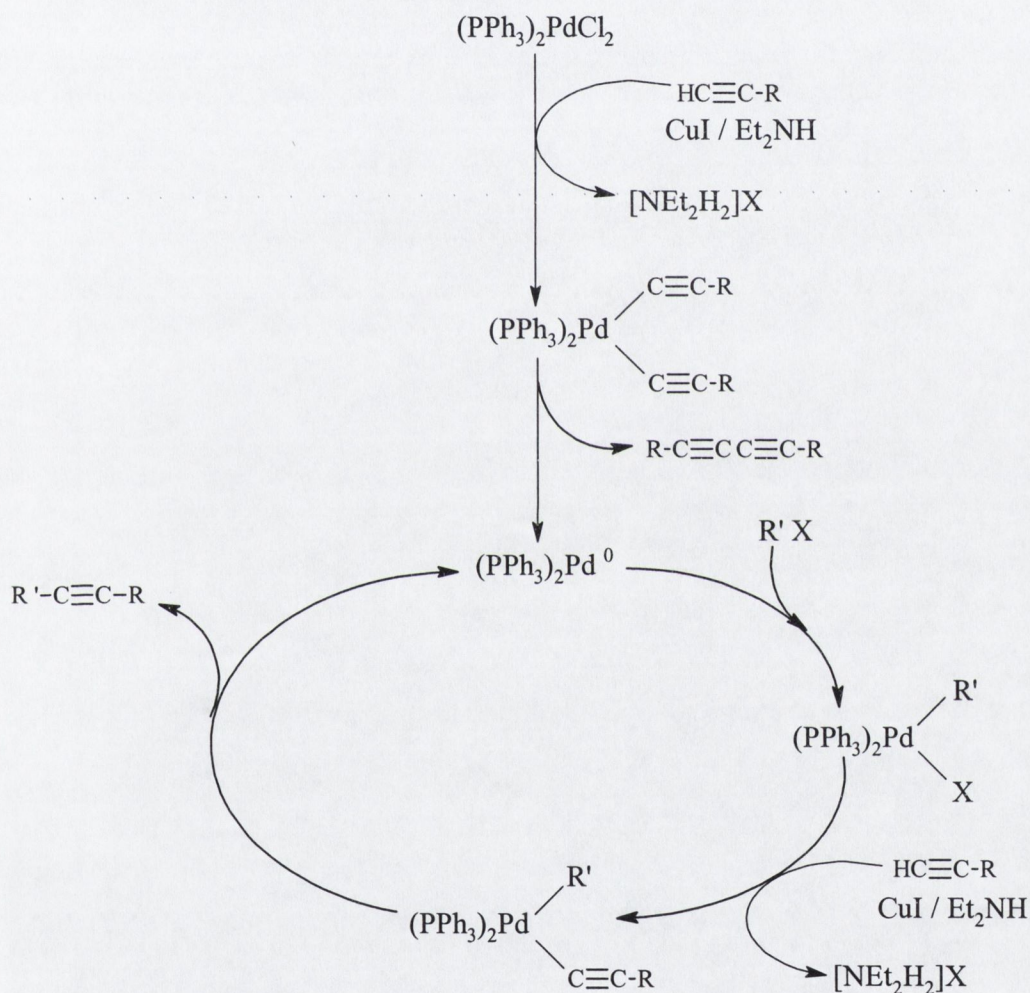
As originally formulated, the Heck reaction involves the reaction of an aryl halide with an alkene in the presence of a catalytic amount of palladium(0) to give the aryl-substituted alkene.¹³ The most commonly employed catalyst system is a mixture of palladium(II) acetate and triphenylphosphine. Under the reaction conditions, palladium(II) is reduced to palladium(0) in a preliminary initiating step. The reaction sequence involves (i) oxidative addition of the aryl halide to palladium(0) followed by (ii) 1,2-addition to the alkene and (iii) β -hydride elimination to give the substituted olefin and a palladium hydride species. The reaction is usually performed in the presence of a base such as triethylamine which serves to facilitate the reductive elimination of a hydrogen halide from the palladium hydride species to regenerate Pd(0) (Scheme 3.7).



Scheme 3.7

3.1.3. Palladium-catalysed coupling of acetylenes with aryl halides.

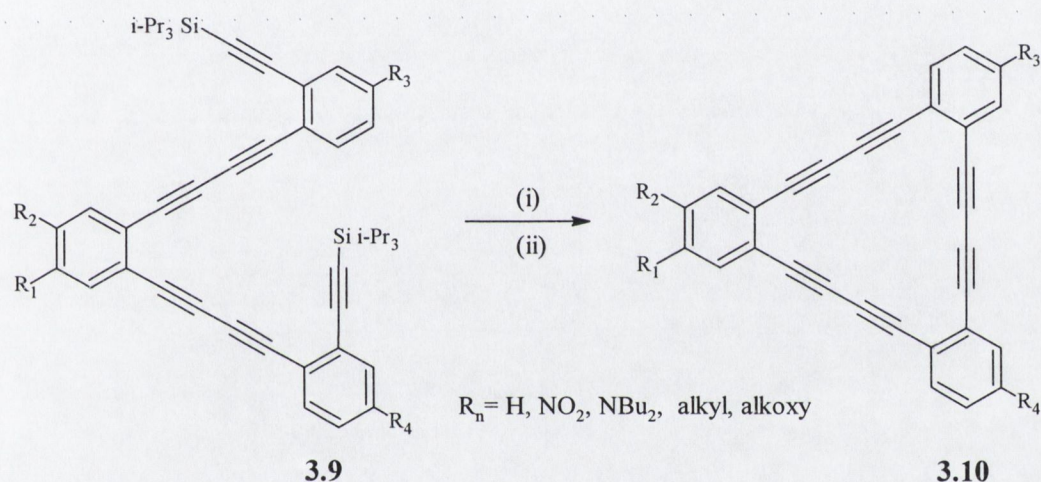
In 1975, three groups independently reported the palladium-catalysed coupling of aryl bromides and iodides with terminal acetylenes.¹⁴⁻¹⁶ Sonogashira *et al.* found that the reaction occurred under mild conditions using a mixture of copper(I) iodide and bis(triphenylphosphine)palladium(II) chloride as the catalyst and proposed a mechanism in which the catalytic palladium(0) species was generated by reductive elimination of a 1,4-butadiyne from an initially-formed bis(triphenylphosphine)dialkynylpalladium(II) complex¹⁶ (Scheme 3.8).



Scheme 3.8

Sabourin and Onopchenko examined the Sonogashira reaction of *m*-bromonitrobenzene with 2-methyl-3-butyn-2-ol and found that the rate of reaction was greatly enhanced by the addition of triphenylphosphine to the catalyst system.¹⁷ In the absence of added triphenylphosphine, the reaction often could not be taken to complete conversion.

Haley *et al.*¹⁸ have used these acetylenic coupling reactions for the synthesis of a series of functionalised dehydrobenzo[18]annulenes **3.10**. The intermediates **3.9** were prepared in a stepwise manner *via* Sonogashira reaction of terminal acetylene derivatives with substituted iodoarenes.¹⁹ After removal of the protecting groups, the cyclisation reaction was performed using Cu(OAc)₂/CuCl in pyridine under high-dilution conditions (Scheme 3.9).

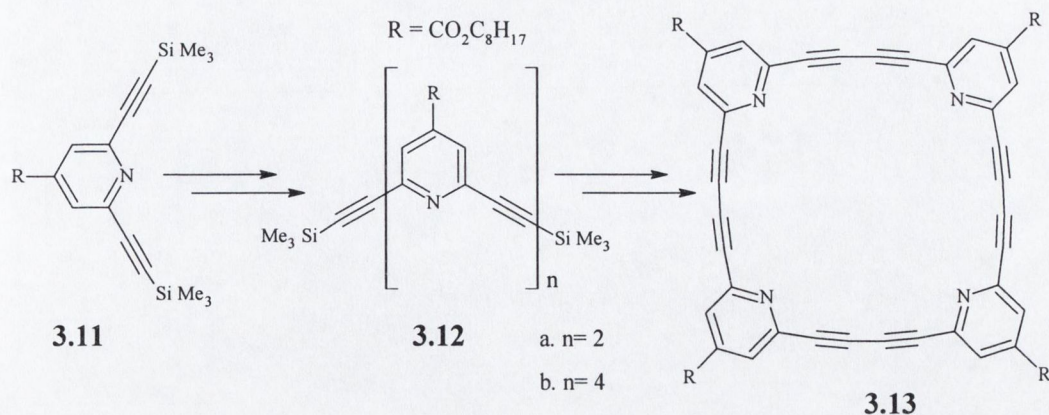


Reagents and conditions: (i) TBAF (2.5 equiv.), THF/MeOH (10:1 v/v), (ii) Cu(OAc)₂ (25 equiv.), CuCl (20 equiv.), pyridine.

Scheme 3.9

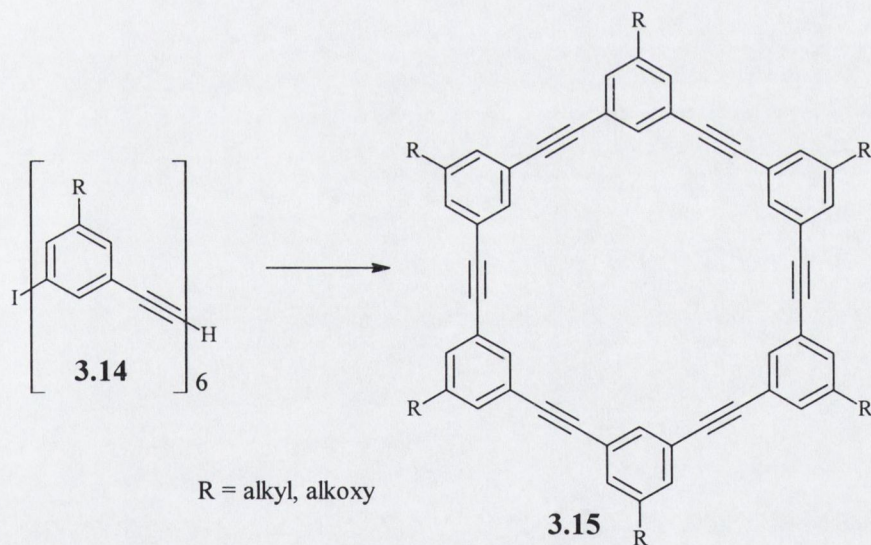
Tobe *et al.*¹¹ used a similar synthetic strategy for the synthesis of pyridinophane **3.13**. The monomer **3.11** was prepared *via* Sonogashira coupling of trimethylsilylacetylene with the 2,6-dichloropyridine derivative. Partial deprotection of **3.11** and subsequent self-coupling using CuCl/TMEDA (Hay reaction) gave dimer **3.12a**. Repetition of this sequence gave tetramer **3.12b**.

Removal of the protecting groups and intramolecular coupling of the terminal acetylene moieties gave pyridinophane **3.13** (Scheme 3.10).



Scheme 3.10

Moore *et al.* used the Sonogashira reaction to synthesise a number of phenylene ethynylene macrocycles **3.15** (Scheme 3.11). The linear precursors **3.14** were prepared using an iterative couple – deprotect – couple sequence.²⁰

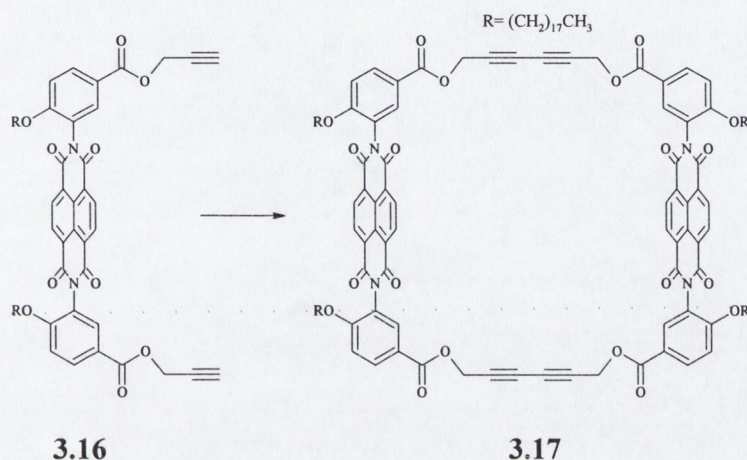


Reagents and conditions: $\text{Pd}(\text{dba})_2$ (45 mol %), CuI (64 mol %), PPh_3 (27 mol %), $\text{Et}_3\text{N}/\text{CH}_3\text{CN}$, 68 °C, 20 hrs.

Scheme 3.11

In addition to the planar systems described above, acetylenic coupling reactions have been used to effect ring-closure in more complex systems.

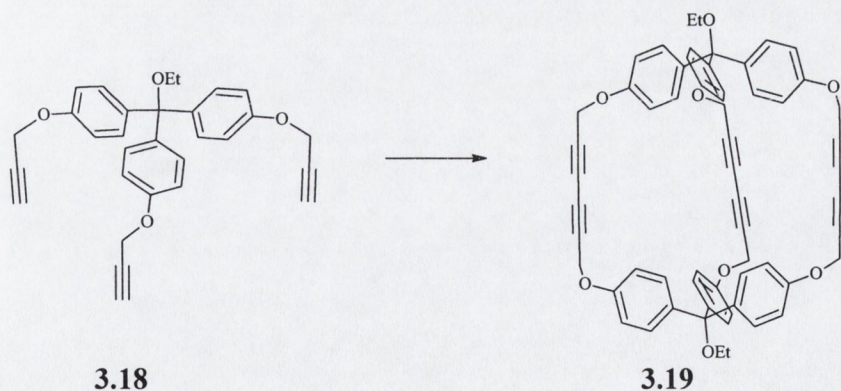
Shimizu and Chong²¹ obtained macrocycle **3.17** by copper-mediated dimerisation of **3.16**. The macrocycle was obtained as a mixture of conformational isomers in which the carboxylate moieties adopted conformations *syn*- or *anti*- to each other. Scheme 3.12 shows the *syn*-/*syn*- isomer.



Reagents and conditions: CuCl (29 equiv.), Cu(OAc)₂·H₂O (48 equiv.), pyridine/DMF, r.t., 7 days.

Scheme 3.12

Vögtle and Berscheid used copper(II) acetate in acetonitrile for the coupling of **3.18** and obtained a 32% yield of the triply-bridged species **3.19**²² (Scheme 3.13).



Reagents and conditions: Cu(OAc)₂·H₂O (9 equiv.), CH₃CN, 60 °C, 1 hr.

Scheme 3.13

The high yield of **3.19** was attributed to a template effect with acetonitrile acting as the template. When the reaction was performed in pyridine the yield was only 18%.

3.2. Results and discussion.

The halogen groups of the DMAP derivatives described in Chapter 2 (Figure 3.2) were converted to terminal acetylenes by palladium-catalysed coupling reactions with masked acetylene derivatives and subsequent removal of the protecting group.

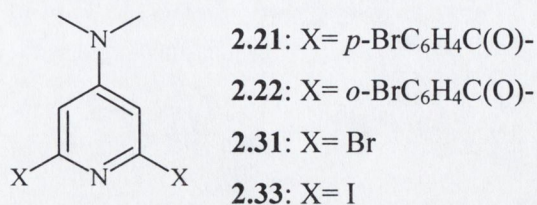
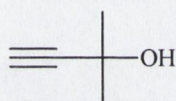
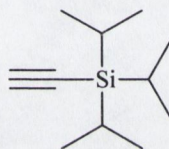


Figure 3.2

Two masked acetylenes were used for these reactions: 2-methyl-3-butyn-2-ol (**3.20**) and triisopropylsilylacetylene (TIPSA, **3.21**).



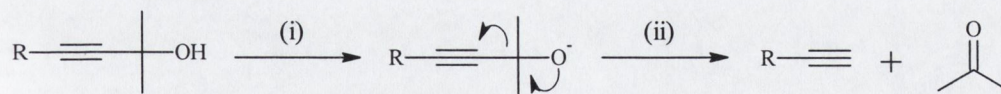
3.20



3.21

After the coupling reaction, derivatives of **3.20** and **3.21** may be unmasked to provide the terminal alkyne.

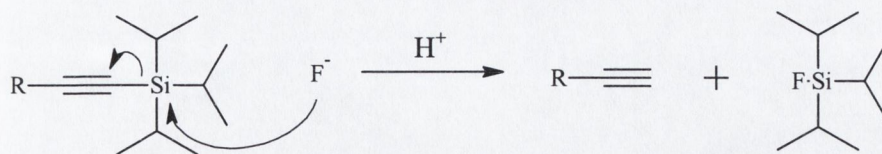
Derivatives of alkynol **3.20** may be converted to terminal acetylenes by heating with sodium or potassium hydroxide¹⁷ or sodium hydride²³ followed by hydrolysis of the resulting acetylide (Scheme 3.14).



Reagents and conditions: (i) Base, reflux. (ii) H⁺

Scheme 3.14

Treatment of derivatives of **3.21** with fluoride ion in the presence of a proton source gives the terminal acetylene. Typically, the reaction is performed using tetrabutylammonium fluoride (TBAF) in a mixture of tetrahydrofuran and methanol (Scheme 3.15).



Reagents and conditions: TBAF, THF/MeOH.

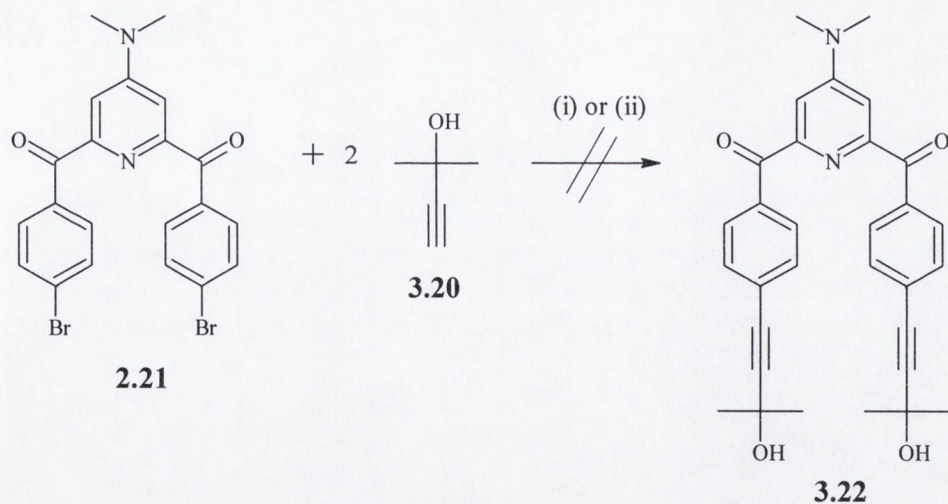
Scheme 3.15

The catalyst systems employed for these reactions were $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2/\text{CuI}/\text{PPh}_3$ (Sonogashira's catalyst) or $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ (Heck's catalyst).

In the following sections, the preparation of acetylenic DMAP derivatives and the attempts to prepare macrocycles from these compounds are described.

3.2.1. Synthesis of 2,6-di-(4'-ethynylbenzoyl)-4-dimethylaminopyridine and 2,6-di-(2'-ethynylbenzoyl)-4-dimethylaminopyridine.

Although the palladium-catalysed reaction of aryl halides with acetylene gas is an efficient route to diarylacetylenes,¹⁶ the synthesis of terminal alkynes usually requires the use of protected acetylene derivatives that are subsequently deprotected to give the terminal alkyne.¹⁹ Sabourin and Onopchenko¹⁷ have reported the synthesis of 4-ethynylphthalic anhydride using the relatively cheap reagent 2-methyl-3-butyne-2-ol (**3.20**). Havens and Hergenrother have also used this compound for the synthesis of several arylacetylenes.²³ However, treatment of 2,6-di-(4-bromobenzoyl)-4-dimethylaminopyridine (**2.21**, prepared as described in Chapter 2) with **3.20** in triethylamine using either $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2/\text{CuI}/\text{PPh}_3$ (Sonogashira conditions) or $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ (Heck conditions) as catalyst failed to provide the desired acetylene intermediate **3.22** (Scheme 3.16).

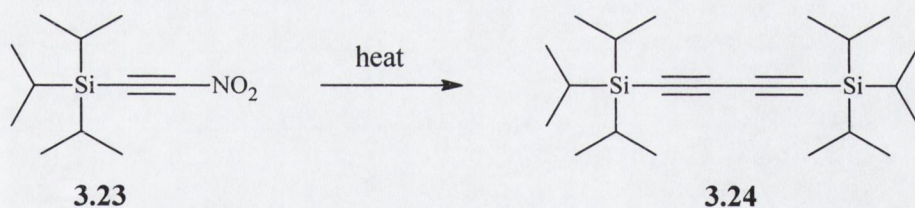


Reagents and conditions: (i) $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.1 mol %)/ CuI (0.3 mol %)/ PPh_3 (0.4 mol %), Et_3N , reflux 4 hrs.

(ii) $\text{Pd}(\text{OAc})_2$ (8 mol %)/ PPh_3 (20 mol %), Et_3N , reflux 4 hrs.

Scheme 3.16

Treatment of **2.21** with triisopropylsilylacetylene (TIPSA, **3.21**) under Sonogashira conditions gave only recovered **2.21** and a compound giving ^1H NMR and IR spectra consistent with those reported for 1,4-bis(triisopropylsilyl)buta-1,3-diyne (**3.24**) by Bottaro *et al.* who obtained this compound upon heating 1-nitro-2-triisopropylsilylacetylene (**3.23**) to *ca.* 200 °C in the presence of air²⁴ (Scheme 3.17).

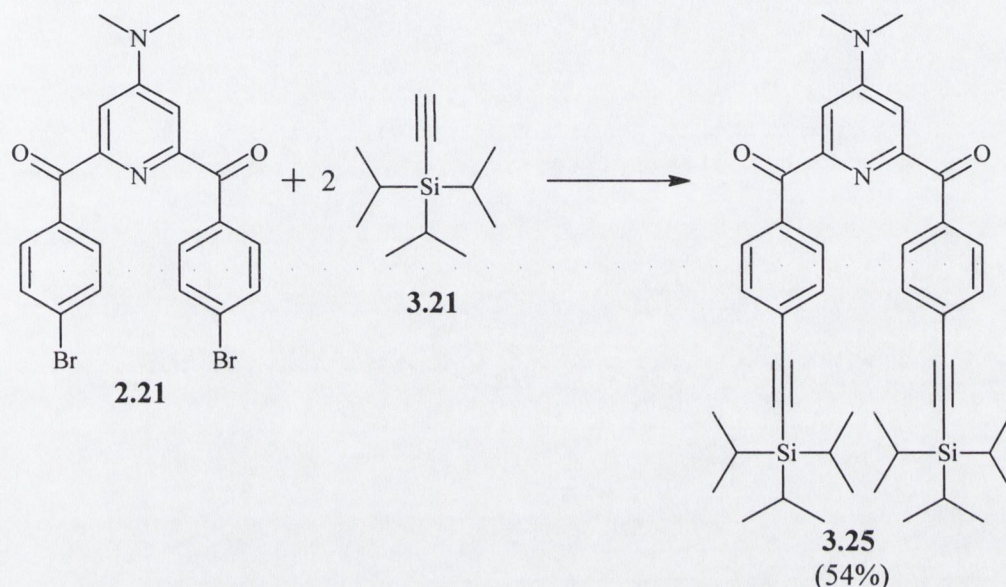


Scheme 3.17

Several groups have reported such homocoupling of terminal acetylenes in the course of Sonogashira reactions.²⁵⁻³² Ho *et al.* have attributed the formation of this side-product to the presence of oxygen in the reaction mixture.³¹ In the mechanism of the Sonogashira reaction (see Scheme 3.8), the catalytic palladium(0) species is generated by elimination of an acetylenic dimer from a dialkynylpalladium(II)

complex. Oxygen present in the reaction mixture can re-oxidise this palladium(0) species back to palladium(II) which in turn gives rise to more of the dimeric acetylene. Although the reaction is usually performed in an inert atmosphere, the system is never completely free from oxygen.

When the catalyst system was changed to $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ the protected acetylene derivative 2,6-di-(4'-{2''-triisopropylsilyl}ethynyl}benzoyl)-4-dimethylaminopyridine (**3.25**) was obtained in 54% yield (Scheme 3.18).



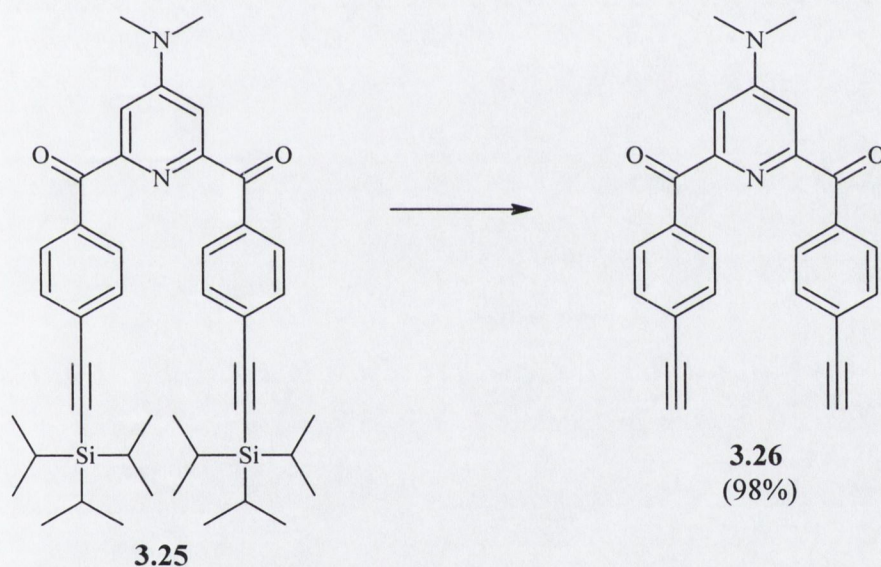
Reagents and conditions: $\text{Pd}(\text{OAc})_2$ (8 mol %)/ PPh_3 (20 mol %), Et_3N , reflux 4 hrs.

Scheme 3.18

The ^1H NMR spectrum of the dibromo compound **2.21** shows four signals. The protons at the 3 and 5 positions of the pyridine ring appear as a singlet at δ 7.47. The protons on the phenyl rings come into resonance downfield from the pyridine protons and appear as a pair of doublets. The protons *ortho* to the carbonyl group resonate at δ 8.04 and those *ortho* to bromine appear at δ 7.56. The protons of the dimethylamino group appear as a singlet at δ 3.19. The ^1H NMR spectrum of the protected acetylene derivative **3.25** shows these four signals together with an additional signal at δ 1.16 from the protons of the isopropyl groups.

The ^{13}C NMR spectrum of **2.21** shows nine carbon environments. The carbonyl carbons appear at δ 192.1. The pyridine C4 carbon appears at δ 155.4 and the C2 and C6 carbons appear at δ 153.6. The signals from the carbons of the phenyl rings appear at δ 134.8, δ 132.2, δ 130.7, and δ 127.5. The signal from the pyridine C3 and C5 carbons is at δ 108.6 and the carbons of the dimethylamino groups appear at δ 39.0. These signals are present in the ^{13}C NMR spectrum of the protected acetylene derivative **3.25** which shows a further four signals from the carbons of the acetylene and isopropyl moieties. The acetylene carbons appear at δ 106.0 and δ 94.1. The methyl carbons of the isopropyl groups appear at δ 18.2 and the methine carbons are at δ 10.8.

Removal of the triisopropylsilyl groups from **3.25** by treatment with tetra-*n*-butylammonium fluoride¹⁸ (TBAF) gave the terminal acetylene 2,6-di-(4'-ethynylbenzoyl)-4-dimethylaminopyridine (**3.26**) in 98% yield (Scheme 3.19).



Reagents and conditions: TBAF (2.5 equiv.), THF/MeOH (10:1 v/v), r.t.

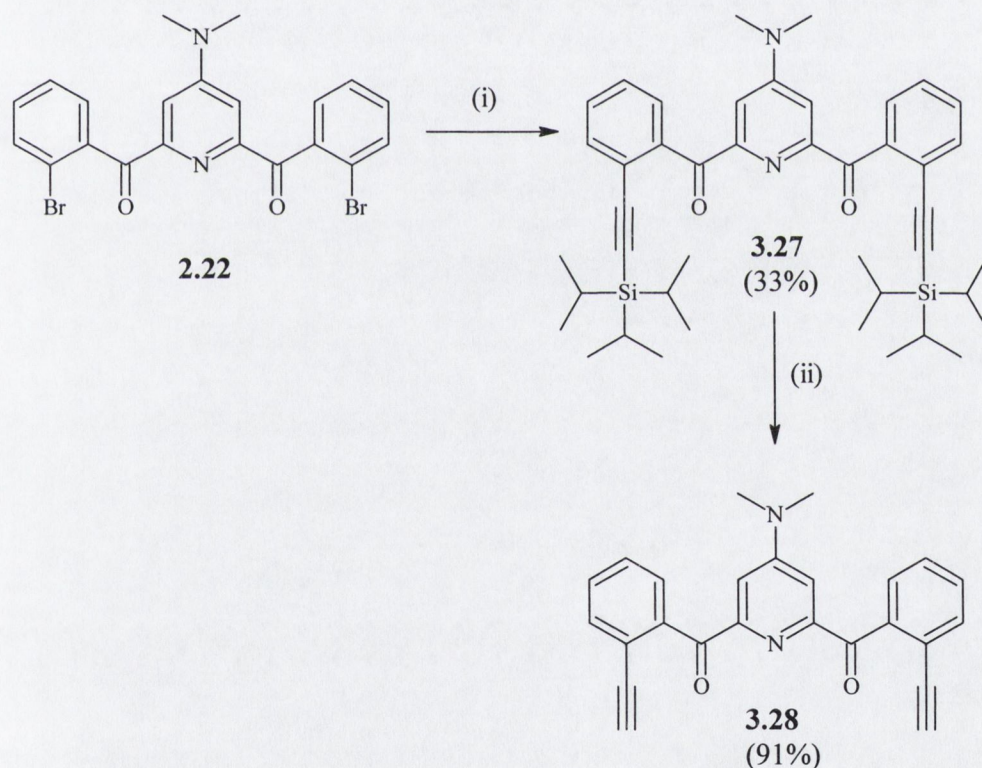
Scheme 3.19

In the ^1H NMR spectrum of the protected acetylene **3.25** the protons of the isopropyl groups appear as a large singlet at δ 1.16. As expected, this signal is

absent from the spectrum of the deprotected species **3.26** which shows a new signal at δ 3.26 from the terminal acetylenic protons.

The removal of the triisopropylsilyl groups is also confirmed by comparison of the ^{13}C NMR spectra of **3.25** and **3.26**. In the spectrum of the protected species **3.25** the carbons of the isopropyl groups appear at δ 18.2 and δ 10.8. These signals are absent in the spectrum of the deprotected compound **3.26**. The removal of the protecting groups also caused an upfield shift in the signals from carbon atoms of the acetylene groups. In the ^{13}C NMR spectrum of the protected compound **3.25** the acetylenic carbons resonate at δ 106.0 and δ 94.1 while in the spectrum of the deprotected species **3.26** these carbons appear at δ 82.6 and δ 79.6.

The *ortho*-substituted derivatives 2,6-di-(2'-{2''-triisopropylsilyl}ethynyl}benzoyl)-4-dimethylaminopyridine (**3.27**) and 2,6-di-(2'-ethynylbenzoyl)-4-dimethylaminopyridine (**3.28**) were prepared using the method outlined above (Scheme 3.20).



Reagents and conditions: (i) $\text{Pd}(\text{OAc})_2$ (8 mol %)/ PPh_3 (20 mol %), TIPSAs, Et_3N , reflux 4 hrs.

(ii) TBAF (2.5 equiv.), THF/MeOH (10:1), r.t.

Scheme 3.20

Although replacement of the bromine atoms by acetylene moieties had little effect on the chemical shifts of the protons on the phenyl rings in the ^1H NMR spectra of the 'para' series of compounds, the effects of this substitution on the chemical shifts of the phenyl protons in the spectra of the 'ortho' analogues were quite pronounced. Figure 3.3 shows the aromatic regions of the ^1H NMR spectra of **2.22** and **3.28**.

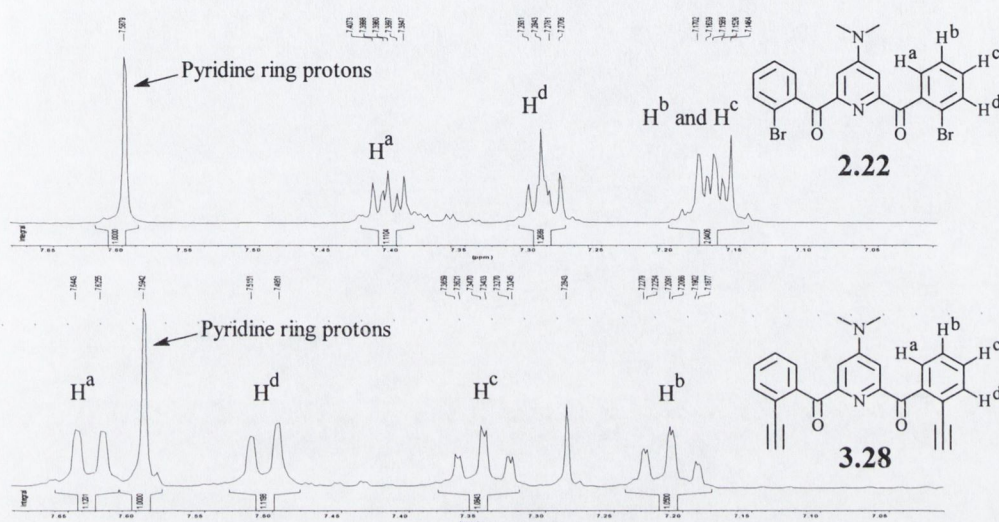


Figure 3.3. Aromatic regions of ^1H NMR spectra of **2.22** and **3.28**

In the ^1H NMR spectrum of the dibromo compound **2.22**, the protons at the 3 and 5 positions of the pyridine ring appear as a singlet at δ 7.58. The protons on the phenyl rings resonate upfield from the pyridine protons and appear as multiplets at δ 7.39, δ 7.27, and δ 7.16. Only three signals appear for these protons due to overlap of the signals from the protons H^b and H^c . In contrast, the spectrum of the acetylene derivative **3.28** shows four well-resolved peaks for the phenyl protons. The replacement of the bromine atoms by the acetylene groups resulted in a downfield shift of these protons. The pyridine protons occur as a singlet at δ 7.59. The H^a protons now resonate *downfield* from the pyridine protons as a doublet at δ 7.64 while protons H^b and H^c appear as two well-separated double doublets at δ 7.34 and δ 7.20 respectively.

The compounds described above were synthesised as precursors for the construction of tetraketone macrocycles containing DMAP moieties. It was anticipated that these compounds would undergo copper- or palladium-mediated coupling reactions to provide macrocyclic derivatives.

3.2.2. Attempted synthesis of tetraketone macrocycles.

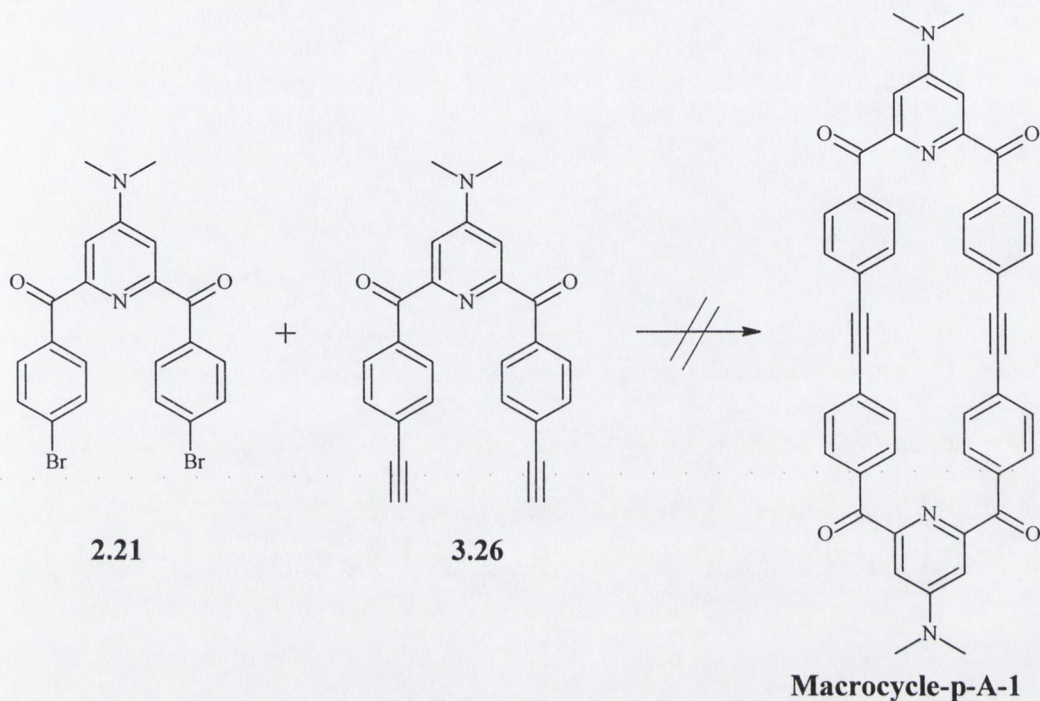
Several attempts were made to prepare macrocycles from the DMAP derivatives described in the preceding section. These reactions were performed under high-dilution conditions using either copper- or palladium-mediated coupling procedures. Isolation of the products from these reactions proved difficult. Most reactions gave complex mixtures which proved inseparable by column chromatography. In many experiments, only unreacted starting materials were recovered from the reaction mixtures.

Palladium-catalysed coupling of DMAP derivatives.

Initial efforts to prepare DMAP macrocycles concentrated on the palladium-catalysed coupling of the dibromo derivatives **2.21** and **2.22** with their respective acetylene derivatives **3.26** and **3.28**. The syntheses of these compounds were attempted under a variety of conditions but all of these reactions gave only quantitative or near-quantitative recovery of unreacted starting materials.

Attempted synthesis of Macrocycle-p-A-1.

The first macrocyclisation reaction attempted was the palladium-catalysed coupling of 2,6-di-(4'-bromobenzoyl)-4-dimethylaminopyridine (**2.21**) with 2,6-di-(4'-ethynylbenzoyl)-4-dimethylaminopyridine (**3.26**) (Scheme 3.21).



Reagents and conditions: $\text{Pd}(\text{OAc})_2$ (8 mol %)/ PPh_3 (20 mol %), Et_3N , reflux 4 hrs.

Scheme 3.21

Treatment of a mixture **2.21** and **3.26** with $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ in triethylamine under high dilution conditions failed to provide Macrocycle-p-A-1. Analysis of the reaction mixture by thin-layer chromatography showed only the presence of the starting materials and the triphenylphosphine from the catalyst system. Subsequent column chromatography gave only recovered **2.21** (91% of initial loading) and **3.26** (94% of initial loading).

The reaction was repeated using higher catalyst loadings, higher concentrations and an extended reaction time. These reactions gave similar results to those obtained in the first experiment. The conditions employed for these experiments are summarised in Table 3.1.

Table 3.1 Reaction conditions for attempted synthesis of Macrocycle-p-A-1.

Run	Catalyst system	Catalyst loading (mol %)	Solvent	Concentration ^[c] (mol dm ⁻³)	Time (hrs)
1	Pd(OAc) ₂ /PPh ₃ ^[a]	4	Et ₃ N	4×10 ⁻³	4
2	Pd(OAc) ₂ /PPh ₃ ^[a]	8	Et ₃ N	4×10 ⁻³	8
3	Pd(OAc) ₂ /PPh ₃ ^[a]	8	Et ₃ N/pyridine ^[d]	0.05	6
4	Pd(PPh ₃) ₂ Cl ₂ /CuI/PPh ₃ ^[b]	5	Et ₃ N/pyridine ^[d]	8×10 ⁻³	6

^[a]Pd(OAc)₂/PPh₃ mol ratio=1:2.5. ^[b]Pd(PPh₃)₂Cl₂/CuI/PPh₃ mol ratio=1:3:4. ^[c]All reactions performed using 0.4 mmol of **2.21** and 0.4 mmol **3.26**. ^[d]Et₃N/pyridine vol/vol ratio=1:1.

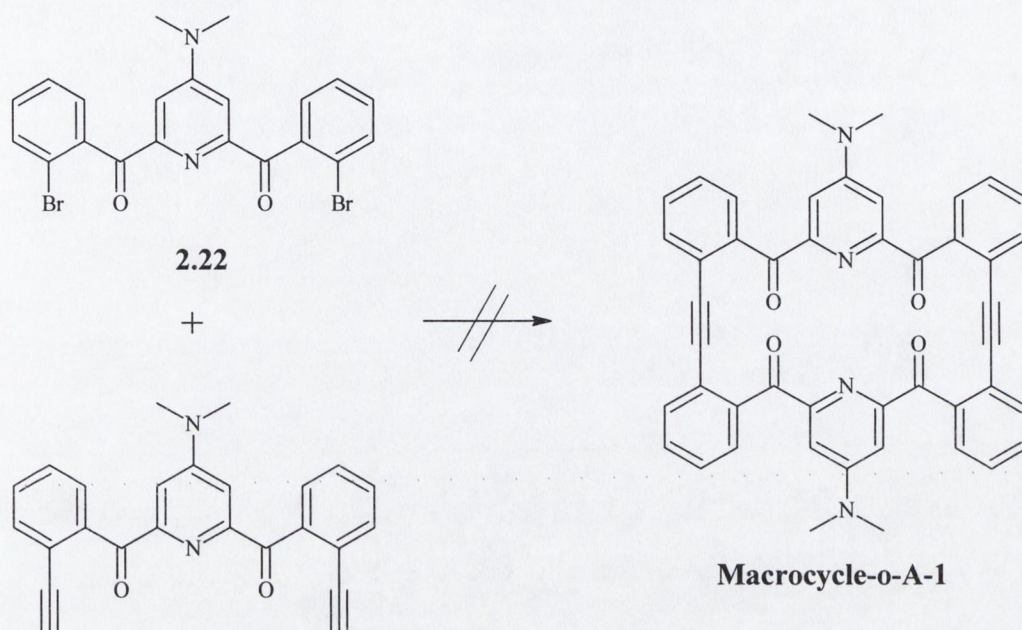
Repetition of the experiment using a higher catalyst loading and an extended reaction time (run 2) gave only recovered starting materials and a small amount of a brown/black precipitate. When these palladium-catalysed reactions are performed in triethylamine, the hydrogen halide salt of triethylamine is formed as a by-product. This salt is insoluble in triethylamine and precipitates out of solution. In a typical workup procedure, this material is filtered off at the end of the reaction. The precipitate from the above reaction was examined in order to ensure that the desired product had not precipitated out of solution. However, extraction of the precipitate with chloroform and evaporation of the chloroform extracts gave only a small amount (< 1 mg) of oily aliphatic material. Thorand and Krause have reported the formation of a similar black precipitate from decomposition of the catalyst when reaction mixtures were subjected to prolonged heating.²⁹

The experiment was repeated at higher concentration (run 3) and with the same high catalyst loading. Both **2.21** and **3.26** are poorly soluble in triethylamine so pyridine was added as a co-solvent for this reaction. This experiment also gave only unreacted starting materials.

Since no reaction was observed in the presence of Pd(OAc)₂/PPh₃, it was decided to attempt the reaction using Pd(PPh₃)₂Cl₂/CuI/PPh₃ as catalyst. However, the use of this catalyst system (run 4) also failed to give the reaction.

Attempted synthesis of Macrocycle-o-A-1.

The synthesis of the *ortho* linked isomer Macrocycle-o-A-1 was attempted using the methods described above (Scheme 3.22).

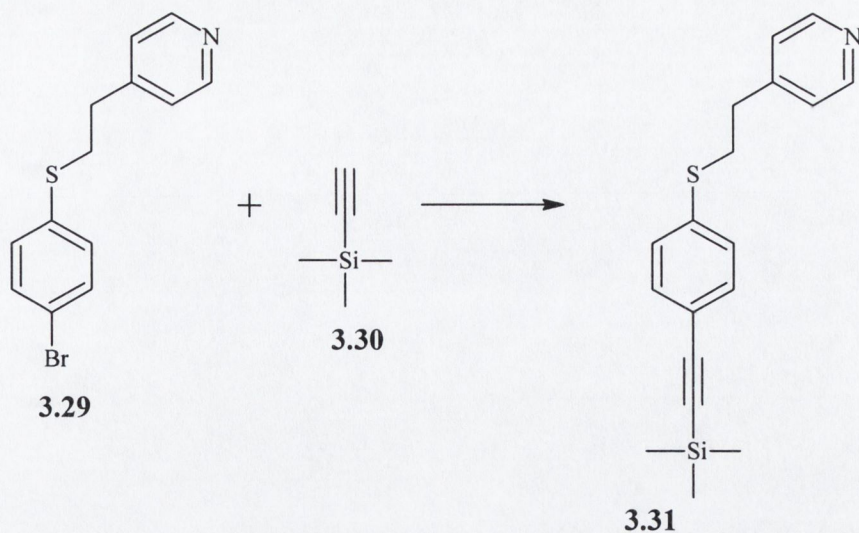


Reagents and conditions: Pd(OAc)₂ (8 mol %)/PPh₃ (20 mol %), Et₃N, reflux 4 hrs.

Scheme 3.22

These experiments also failed to provide the desired macrocycle and only unreacted starting materials were recovered from the reaction mixtures.

A possible explanation for the failure of the above reactions is that the catalyst systems employed were unsuitable for the coupling of these substrates. The correct choice of catalyst is often crucial in palladium-catalysed reactions.³³ In attempts to prepare acetylene derivative **3.31**, Yu *et al.* found that a number of palladium catalysts were ineffective for the coupling of **3.29** with trimethylsilylacetylene (**3.30**) (Scheme 3.23).

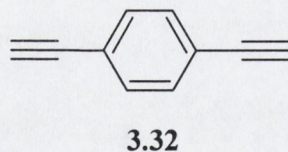


Reagents and conditions: Pd(dba)₂ (10 mol %)/CuI (15 mol %)/PPh₃ (75 mol %), *i*-Pr₂NH/DMF, 60 °C, 16 hrs.

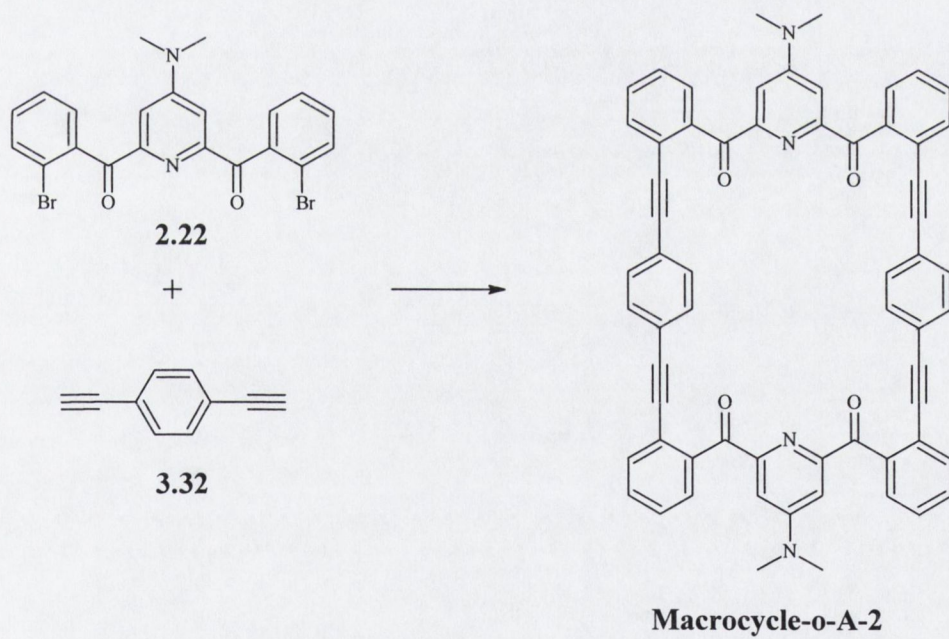
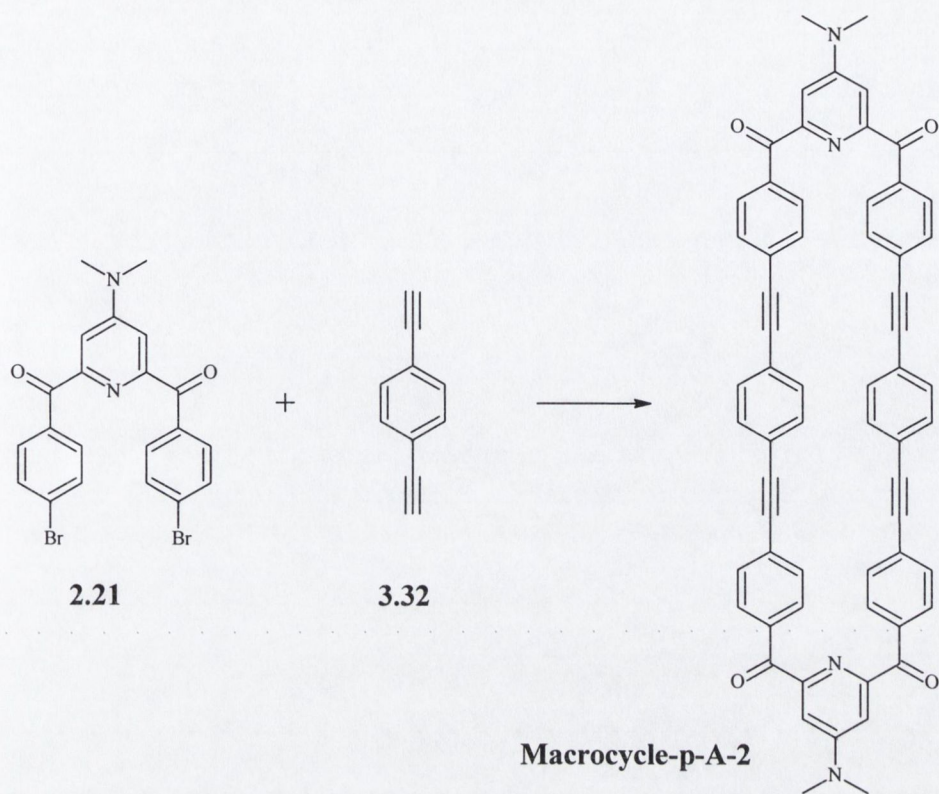
Scheme 3.23

Ultimately, it was found that a high concentration (> 10 mol%) of bis(dibenzylideneacetone)palladium(0) and a reaction time of 16 hours were required to effect the coupling reaction.²⁷

Since attempts to couple dibromo compounds **2.21** and **2.22** with their respective acetylene derivatives **3.26** and **3.28** had proved unsuccessful it was decided to attempt the coupling of **2.21** and **2.22** with other acetylene derivatives. The diacetylene 1,4-diethynylbenzene (**3.32**) was chosen for this purpose.



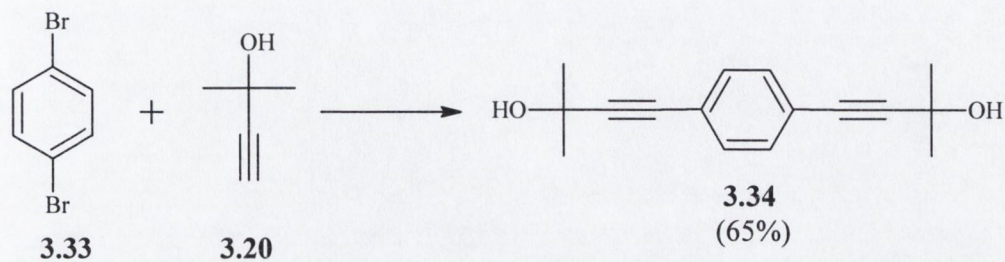
It was expected that the palladium-catalysed coupling of **3.32** with **2.21** would afford Macrocycle-p-A-2 and that a similar reaction with **2.22** would afford Macrocycle-o-A-2 (Scheme 3.24).



Scheme 3.24

1,4-diethynylbenzene (**3.32**) was prepared from 1,4-dibromobenzene (**3.33**) in two steps.

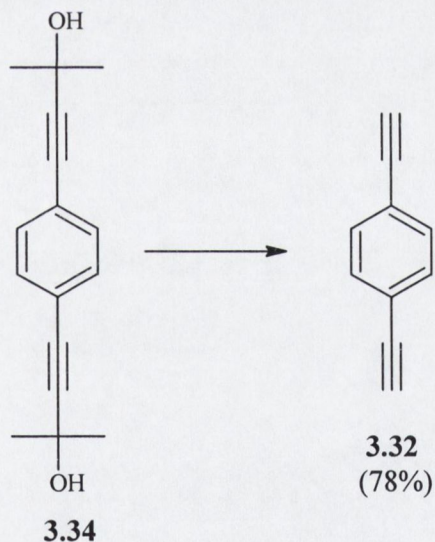
Sonogashira reaction of **3.33** with 2-methyl-3-butyn-2-ol (**3.20**) gave the masked acetylene derivative **3.34** (Scheme 3.25).



Reagents and conditions: $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.1 mol %)/ CuI (0.3 mol %)/ PPh_3 (0.4 mol %), Et_3N , reflux 4 hrs.

Scheme 3.25

Removal of the 2-hydroxypropyl groups of **3.34** using sodium hydride in refluxing toluene gave 1,4-diethynylbenzene (**3.32**) (Scheme 3.26).

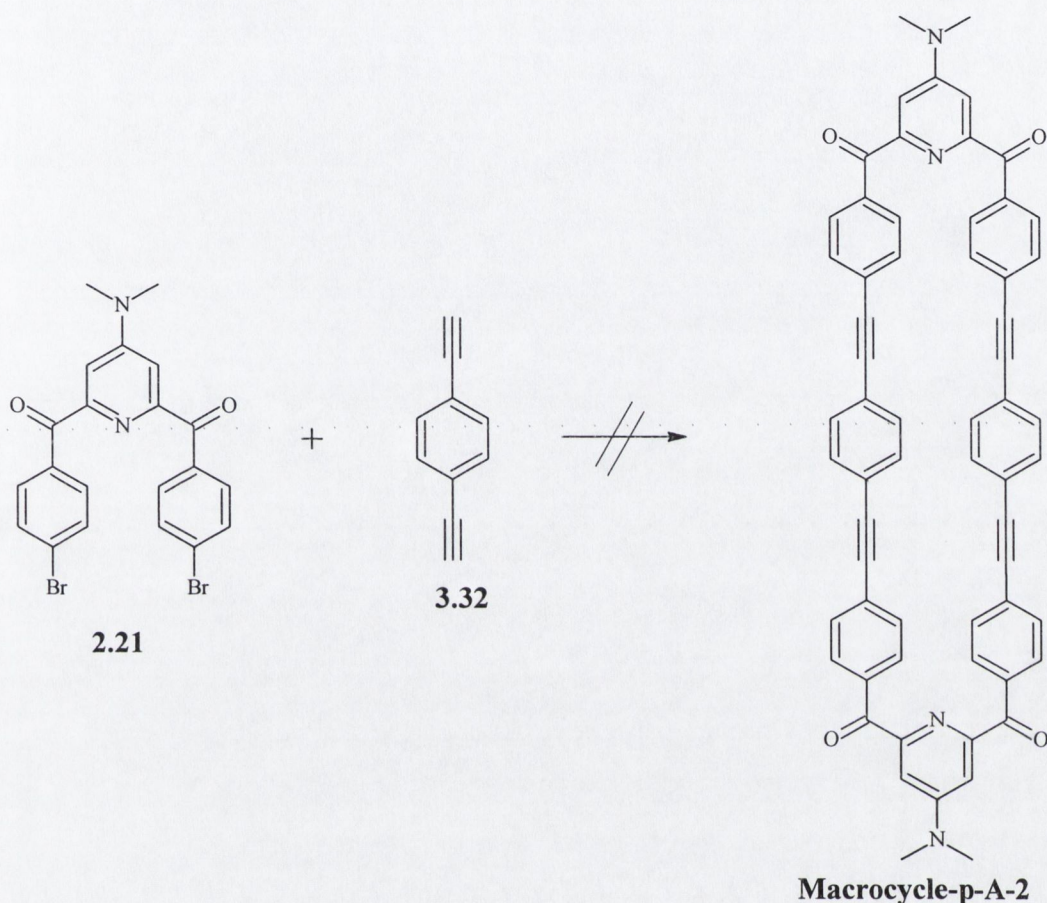


Reagents and conditions: NaH (1.1 equiv.), toluene, reflux 2 hrs.

Scheme 3.26

Attempted synthesis of Macrocycle-p-A-2.

1,4-diethynylbenzene (**3.32**) was reacted with **2.21** in triethylamine using $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ as catalyst in an attempt to obtain Macrocycle-p-A-2 (Scheme 3.27).



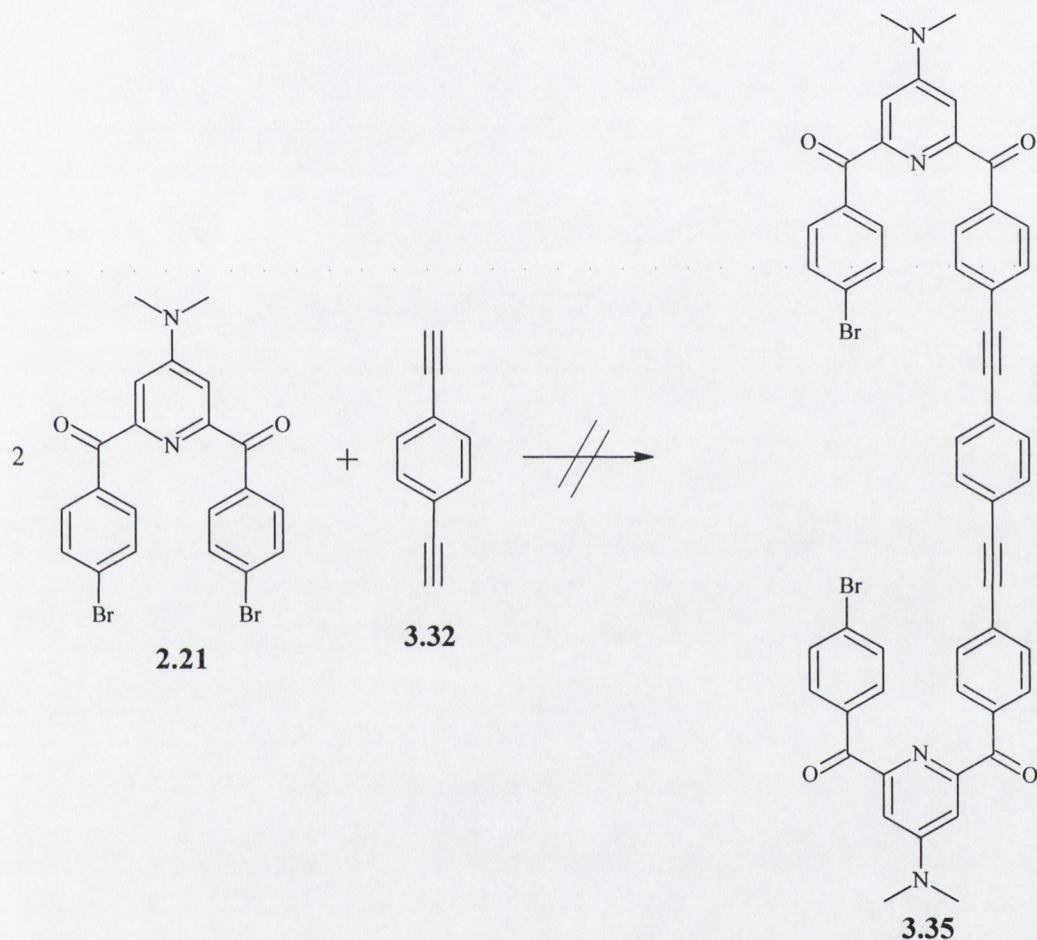
Reagents and conditions: $\text{Pd}(\text{OAc})_2$ (8 mol %)/ PPh_3 (20 mol %), Et_3N , reflux 4 hrs.

Scheme 3.27

This reaction resulted in the formation of large amounts of intractable tarry material. The reaction mixture was analysed by thin-layer chromatography using a variety of solvent systems but none of the systems tried gave clean separation of the reaction products. In all cases, considerable streaking on the chromatographic plates was observed. Chow *et al.* have reported similar difficulties in chromatographic separation of products from Sonogashira reactions.³⁰

Column chromatography of this reaction mixture using dichloromethane/methanol (95:5) as eluent gave only unreacted **2.21** (25% of initial loading) which was contaminated by triphenylphosphine from the catalyst system. The methanol content of the mobile phase was gradually increased to 40% and the column was flushed repeatedly with this solvent mixture but no further material was eluted.

The reaction was repeated using two equivalents of **2.21** and one equivalent of **3.32** in an attempt to obtain the linear species **3.35** (Scheme 3.28).

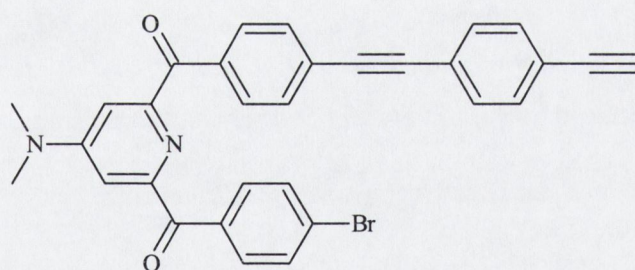


Reagents and conditions: $\text{Pd}(\text{OAc})_2$ (9.5 mol %)/ PPh_3 (20 mol %), Et_3N , reflux 4 hrs.

Scheme 3.28

Attempts to separate the products of this reaction by thin-layer chromatography also proved unsuccessful. Separation by column chromatography was attempted by careful division of the reaction mixture into 200 fractions using the best solvent system found (hexane/ethyl acetate). These fractions were analysed by thin-layer chromatography. This analysis also showed streaking on the chromatographic plates but three poorly-separated components appeared to be present. After removal of the solvent, these three fractions were analysed by ^1H NMR spectroscopy.

The first of the three fractions consisted of triphenylphosphine from the catalyst system and a small amount of the dibromo compound **2.21**. The second fraction consisted of unreacted **2.21**. The ^1H NMR spectrum of the third fraction showed a large number of peaks in both the aromatic and aliphatic regions. The ^1H NMR spectrum of **2.21** shows a signal at δ 8.04 from the phenyl protons *ortho* to the carbonyl group. The protons of the dimethylamino group of **2.21** appear at δ 3.18. Both of these signals were present in the spectrum of the third fraction. Analysis of this material by mass spectrometry showed a large number of peaks between m/z 200 and m/z 1400 but the spectrum showed no peaks consistent with the mass of **3.35** (m/z 940.675). However, the spectrum did show a peak at m/z 556.277 which is consistent with the $[\text{M}+\text{Na}]^+$ ion for the mono-substituted derivative **3.36**.



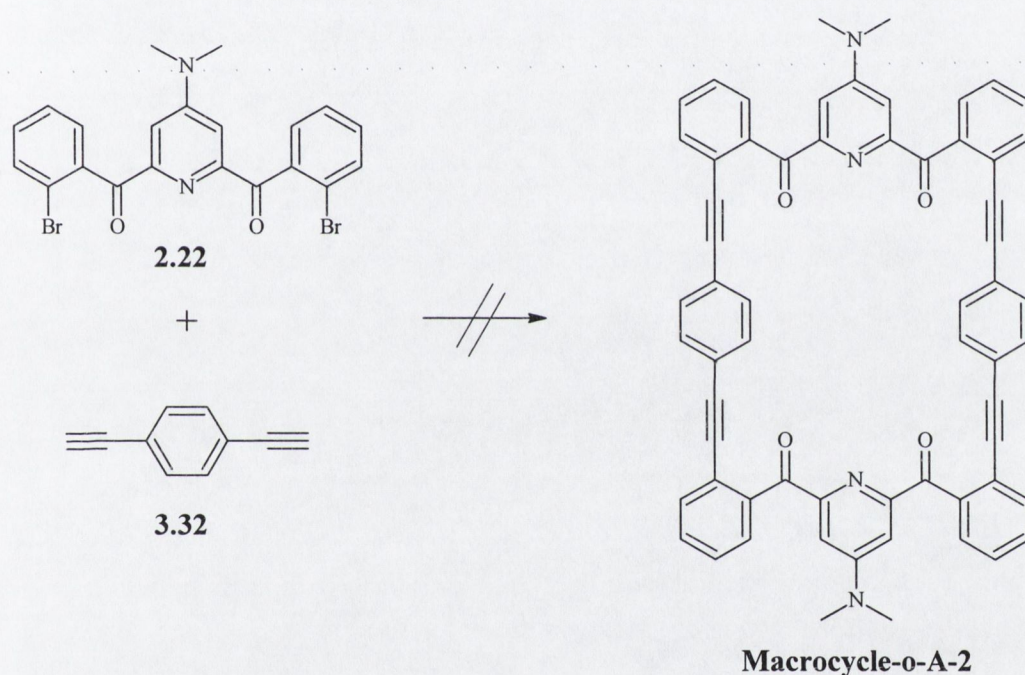
3.36

The evidence from ^1H NMR spectroscopy, mass spectrometry, and thin-layer chromatography suggested that this fraction was a mixture of compounds. This material was therefore re-analysed by thin-layer chromatography using a variety of solvent systems but none of the systems tried gave clean separation of the mixture.

Extraction of the precipitate from this reaction with chloroform gave a small amount (ca. 5 mg) of sticky brown tar which gave a ^1H NMR spectrum showing a broad band of unresolved signals between δ 8.5 and δ 7.0. Analysis of this material by thin-layer chromatography also showed streaking on the chromatographic plates and attempts to find a suitable eluent system to separate this material proved unsuccessful.

Attempted synthesis of Macrocycle-o-A-2.

A mixture of diacetylene **3.32** and dibromo derivative **2.22** in triethylamine was treated with $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ in an attempt to obtain Macrocycle-o-A-2 (Scheme 3.29).



Reagents and conditions: $\text{Pd}(\text{OAc})_2$ (8 mol %)/ PPh_3 (20 mol %), Et_3N , reflux 4 hrs.

Scheme 3.29

Analysis of this reaction mixture by thin-layer chromatography showed only the presence of the reactants and subsequent column chromatography gave quantitative recovery of starting materials. The failure of this reaction may have been due to steric hindrance by the carbonyl groups of **2.22** since Sonogashira reactions

involving aryl halides substituted in one or both of the *ortho* positions are often difficult.^{29,33}

The reaction time was extended to 18 hours but this prolonged heating resulted in decomposition of the catalyst and, as in the earlier experiment, only starting materials were recovered.

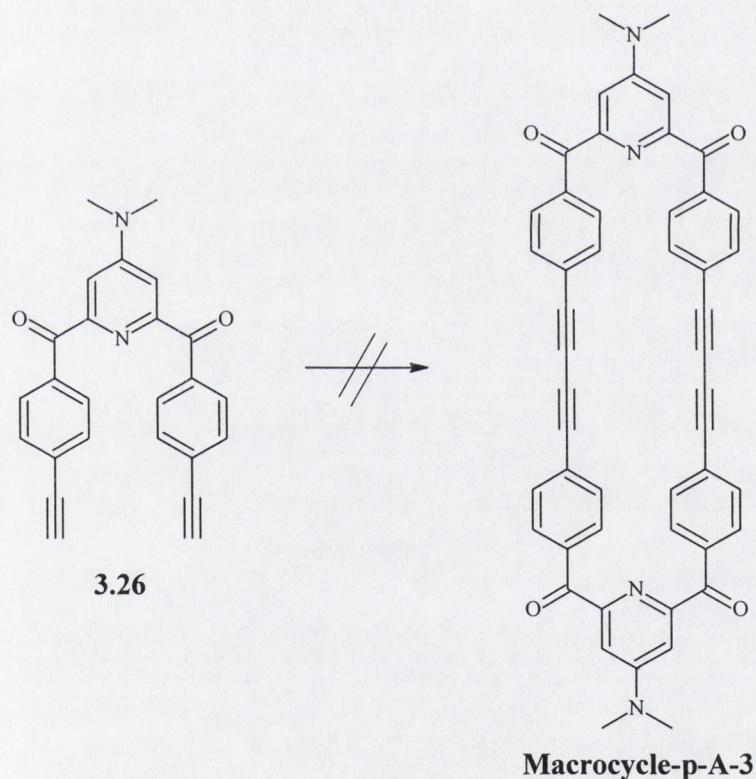
Copper-catalysed homocoupling of acetylenes.

Since the palladium-catalysed reactions described above had failed to provide the desired macrocycles it was decided to attempt the copper-catalysed homocoupling of the acetylene derivatives **3.26** and **3.28**.

In contrast to the palladium-catalysed reactions described above, these copper-mediated procedures generally resulted in complete conversion of the starting materials. However, the products from these reactions proved to be almost completely insoluble in organic solvents. In most experiments, material recovery was low despite repeated extractions of the crude product.

Attempted synthesis of Macrocycle-p-A-3.

The synthesis of Macrocycle-p-A-3 was attempted by treatment of diacetylene **3.26** with copper(I) chloride in pyridine in the presence of oxygen under high-dilution conditions (Scheme 3.30).



Reagents and conditions: CuCl (1.4 equiv.), O₂, pyridine, r.t. 5 days.

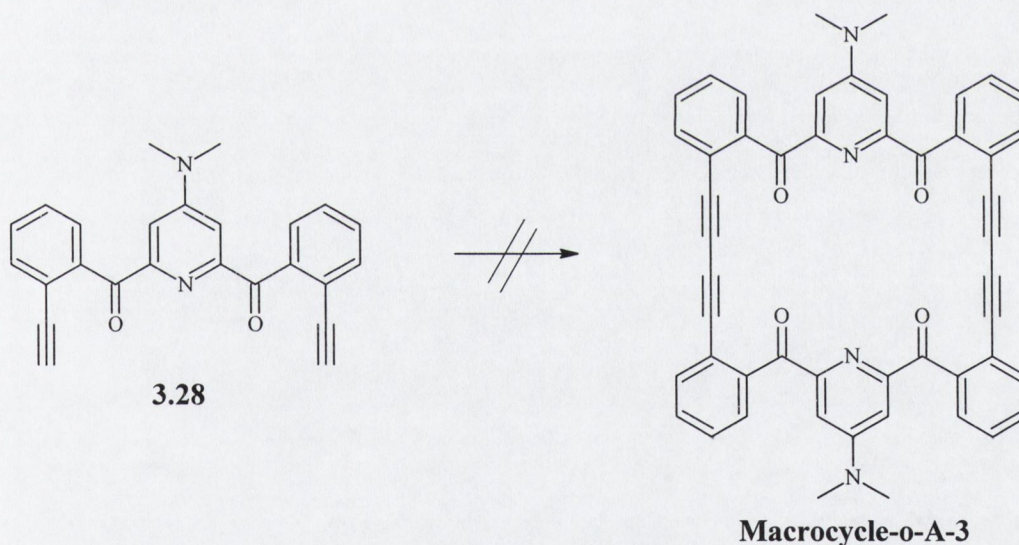
Scheme 3.30

Evaporation of the solvent gave a sticky brown residue which was extracted with chloroform to afford 20 mg of a yellow solid. The weight of this recovered solid amounted to only 10% of the initial loading of diacetylene **3.26**. However, further extractions with chloroform failed to provide any additional material.

The aromatic region of the ^1H NMR spectrum of the product from this reaction showed two broad bands of poorly-resolved signals centred at δ 8.0 and δ 7.5 respectively. Analysis of this material by thin-layer chromatography indicated the presence of several compounds. Attempts were made to separate these compounds using a variety of solvent systems but none of the systems tried gave clean separation. Column chromatography was attempted by careful elution of the crude product into 150 fractions but this method failed to separate the reaction products.

Attempted synthesis of Macrocycle-o-A-3.

The synthesis of Macrocycle-o-A-3 was attempted using the method described above (Scheme 3.31).



Reagents and conditions: CuCl (1.4 equiv.), O₂, pyridine, r.t. 5 days.

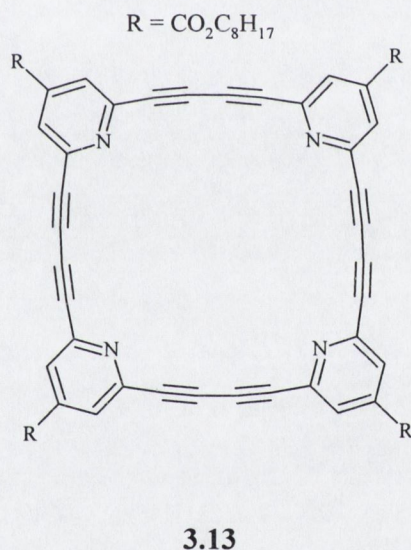
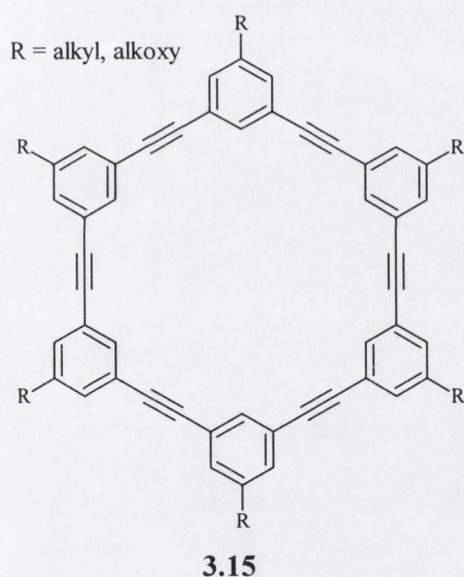
Scheme 3.31

The product from this reaction proved insoluble in organic solvents. Repeated extractions with chloroform gave only a small amount (< 2 mg) of unidentifiable tarry material. The aromatic region of the ^1H NMR spectrum of this material appeared as a broad band in which individual signals were unresolved.

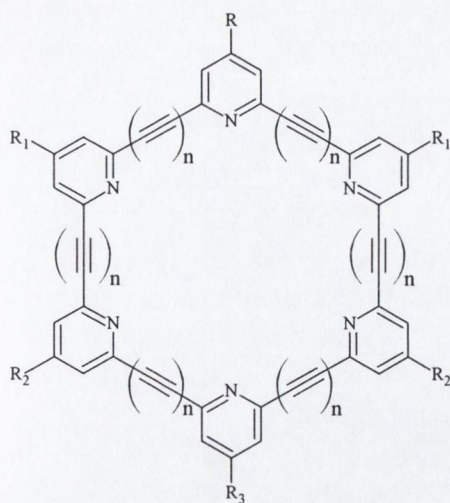
In addition to the synthesis of the tetraketone macrocycles described above, acetylenic coupling reactions were applied to the synthesis of pyridinophane derivatives containing 4-dimethylaminopyridine moieties. The following sections describe the attempts to synthesise these novel pyridinophanes.

3.2.3. DMAP pyridinophanes.

Moore *et al.*²⁰ have successfully used acetylenic coupling reactions for the synthesis of phenylacetylene macrocycles **3.15**. In related work, Tobe and co-workers¹¹ have used these procedures to prepare pyridinophane **3.13**.



In these systems, the rigid nature of the linear precursors limits the number of possible conformations they can adopt and facilitates the ring-closure reaction. This methodology therefore appeared to be an attractive means of obtaining pyridinophane derivatives containing 4-dimethylaminopyridine groups (Figure 3.4).



Macrocycle B-1: $R=R_1=R_2=R_3=NMe_2$
 $n=1$

Macrocycle B-2: $R=R_1=R_2=R_3=NMe_2$
 $n=2$

Macrocycle B-3: $R=R_3=NMe_2/ R_1=R_2=H$
 $n=1$

Macrocycle B-4: $R=R_3=NMe_2/ R_1=R_2=H$
 $n=2$

Macrocycle B-5: $R=R_2=NMe_2/ R_1=R_3=H$
 $n=1$

Macrocycle B-6: $R=R_2=NMe_2/ R_1=R_3=H$
 $n=2$

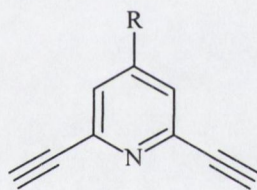
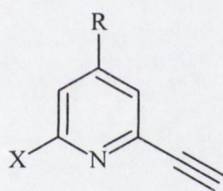
Macrocycle B-7: $R=R_1=NMe_2/ R_2=R_3=H$
 $n=1$

Macrocycle B-8: $R=R_1=NMe_2/ R_2=R_3=H$
 $n=2$

Figure 3.4

Synthesis of the pyridinophane precursors.

A number of acetylenic pyridine derivatives were required for the construction of the projected DMAP pyridinophanes (Figure 3.5).

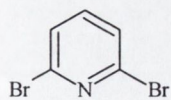


$R = NMe_2, H$

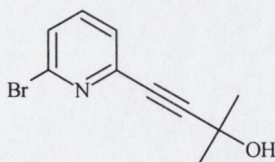
$X = Br, I$

Figure 3.5

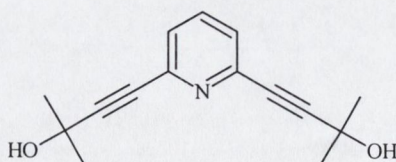
As a first step, it was decided to perform the synthesis of acetylenic pyridines **3.38** and **3.39** using the commercially-available 2,6-dibromopyridine (**3.37**).



3.37

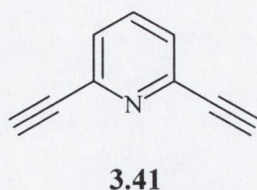
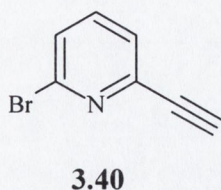


3.38



3.39

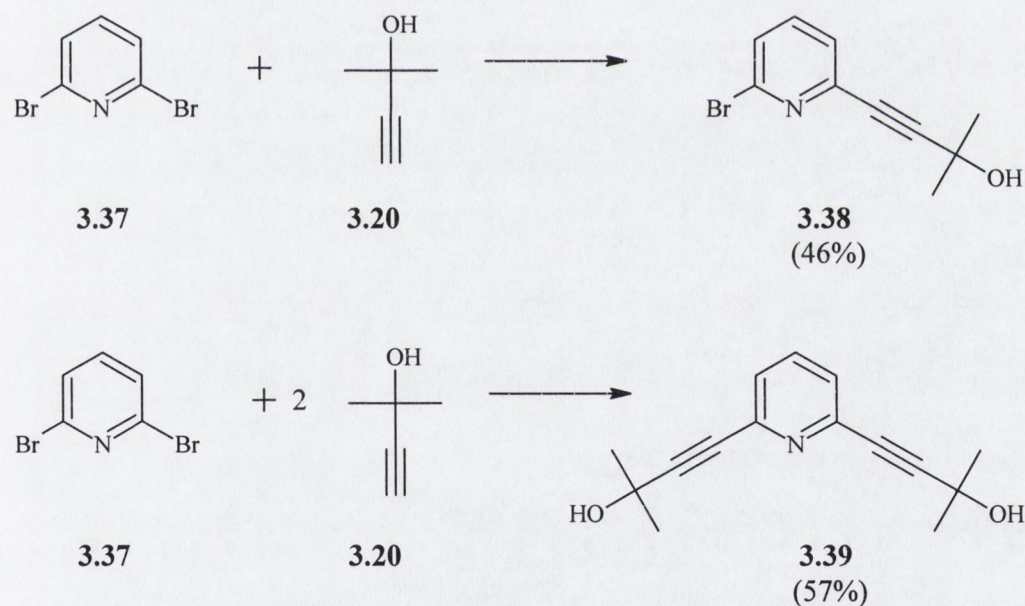
Removal of the 2-hydroxypropyl groups from **3.38** and **3.39** would then afford the terminal acetylenes **3.40** and **3.41**.



These reactions would provide a model for the synthesis of the required acetylenic DMAP derivatives and the products would also prove useful for the construction of a number of the desired pyridinophanes.

Synthesis of 2-bromo-6-ethynylpyridine and 2,6-diethynylpyridine.

The protected acetylene derivatives **3.38** and **3.39** were prepared *via* Sonogashira reaction of dibromopyridine **3.37** with 2-methyl-3-butyn-2-ol (**3.20**) (Scheme 3.32).

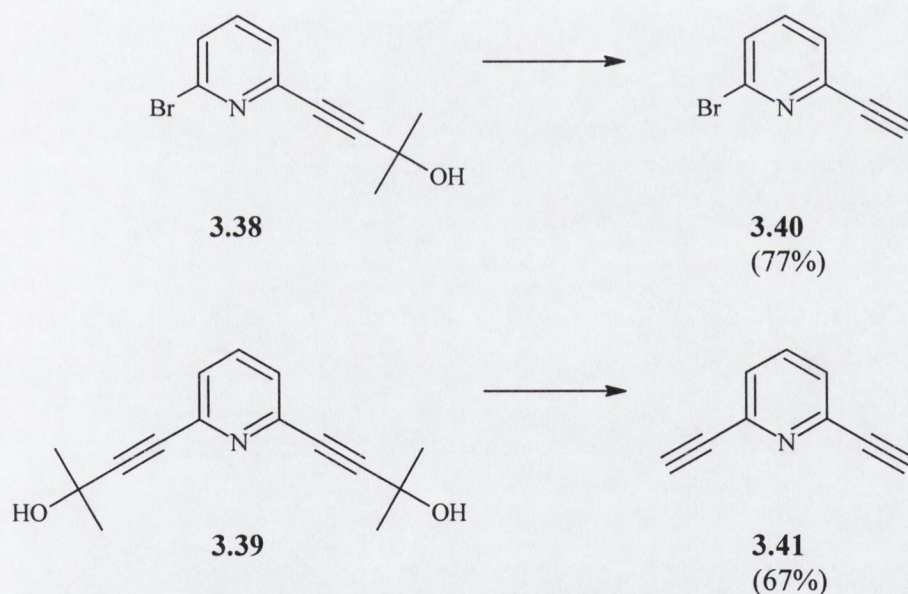


Reagents and conditions: $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.1 mol %)/ CuI (0.3 mol %)/ PPh_3 (0.4 mol %), Et_3N , reflux 4 hrs.

Scheme 3.32

Removal of the 2-hydroxypropyl groups from **3.38** and **3.39** was initially performed by treatment with excess potassium hydroxide in refluxing isopropanol.³⁴ However, this method proved somewhat erratic. In several experiments, the reaction failed to go to completion. Increasing the reaction time resulted in the formation of sticky gums (presumably decomposition products) and purification of the acetylene proved difficult.

Havens and Hergenrother have described the cleavage of 4-aryl-2-methyl-3-butyne-2-ols using a catalytic amount (10 – 15 mol %) of sodium hydride in toluene.²³ The use of this method for the cleavage of **3.38** and **3.39** gave better results than those obtained using potassium hydroxide but problems with conversion were still encountered and it often proved necessary to add further amounts of hydride to the reaction mixture and extend the reaction time. Ultimately, the use of a stoichiometric amount of sodium hydride proved to be the most convenient means of ensuring complete conversion (Scheme 3.33).



Reagents and conditions: NaH (1.1 equiv.), toluene, reflux 2 hrs.

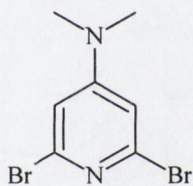
Scheme 3.33

The IR spectra of the protected species **3.38** and **3.39** both show a strong peak from the alcoholic O–H stretch. In the spectrum of the mono-substituted compound **3.38**

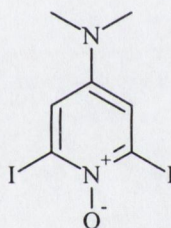
the O–H stretch appears at 3244 cm^{-1} ; in the spectrum of the diol **3.39** the O–H stretch is at 3338 cm^{-1} . The removal of the 2-hydroxypropyl groups was confirmed by the absence of these peaks in the IR spectra of the deprotected species **3.40** and **3.41**. In the ^1H NMR spectra of the protected species **3.38** and **3.39** the methyl groups of the 2-hydroxypropyl moieties appear at δ 1.6. This signal is absent in the spectra of the deprotected compounds **3.40** and **3.41** which show a new signal at δ 3.2 from the acetylenic protons. In the ^{13}C NMR spectra of the protected species **3.38** and **3.39** the methyl carbons of the 2-hydroxypropyl group appear at δ 30.6 and the quaternary carbons of this group are at δ 64.9. Both of these signals are absent in the spectra of the deprotected compounds.

Synthesis of 2,6-diethynyl-4-dimethylaminopyridine.

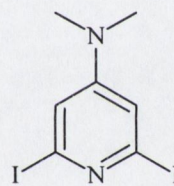
The next step was to apply the above methodology to the synthesis of acetylenic DMAP derivatives. In Chapter 2, the syntheses of 2,6-dibromo-4-dimethylaminopyridine (**2.31**), 2,6-diiodo-4-dimethylaminopyridine *N*-oxide (**2.32**) and 2,6-diiodo-4-dimethylaminopyridine (**2.33**) were described.



2.31



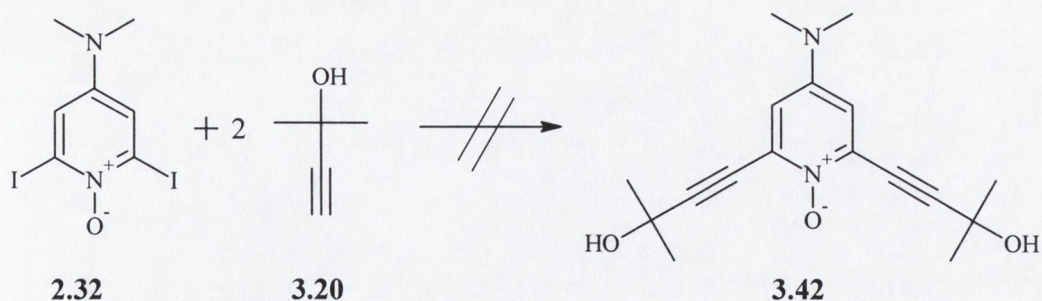
2.32



2.33

These compounds provided suitable starting materials for the synthesis of acetylenic DMAP derivatives. Since *N*-oxide **2.32** was available in relatively large amounts, it was decided to attempt the synthesis using this compound first.

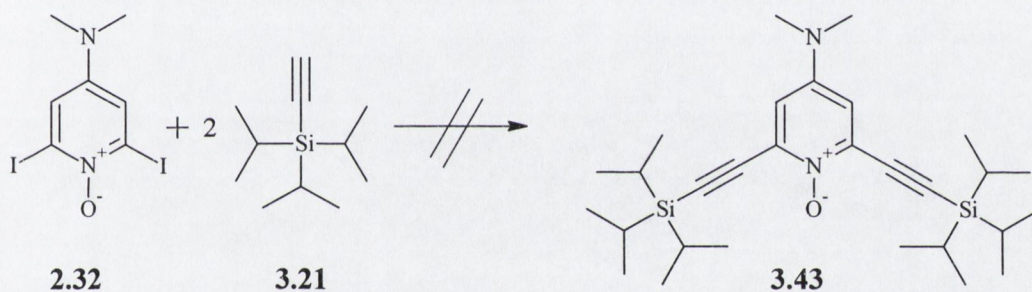
Attempts to prepare acetylene derivatives from *N*-oxide **2.32** proved unsuccessful. When a mixture of **2.32** and 2-methyl-3-butyn-2-ol (**3.20**) in triethylamine was treated with $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2/\text{CuI}/\text{PPh}_3$ (Sonogashira's catalyst) and the reaction was monitored by thin-layer chromatography no reaction was observed after 4 hours at reflux. Extending the reaction time resulted in decomposition of the catalyst and subsequent column chromatography gave only recovered **2.32** (Scheme 3.34).



Reagents and conditions: $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.1 mol %)/ CuI (0.3 mol %)/ PPh_3 (0.4 mol %), Et_3N , reflux 4 hrs.

Scheme 3.34

Treatment of **2.32** with triisopropylsilylacetylene (TIPSA, **3.21**) using $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ as catalyst also failed to provide the desired acetylene derivative (Scheme 3.35).



Reagents and conditions: $\text{Pd}(\text{OAc})_2$ (8 mol %)/ PPh_3 (20 mol %), Et_3N , reflux 4 hrs.

Scheme 3.35

The failure of *N*-oxide **2.32** to undergo the coupling reaction may have been due to the presence of the *N*-oxide function. A feature of the chemistry of pyridine *N*-oxides is their ability to undergo both electrophilic and nucleophilic substitution.³⁵ On the one hand, the positively-charged nitrogen can facilitate nucleophilic attack and, on the other, the negatively-charged oxygen can donate electrons into the ring to encourage electrophilic addition.

Aryl halides containing electron-donating groups are poor electrophiles and do not readily undergo palladium-catalysed alkynylation reactions.³³ A possible explanation for the failure of 2,6-diiodo-4-dimethylaminopyridine *N*-oxide (**2.32**) to undergo the reaction is provided by an examination of some of the canonical forms for this compound. Both the dimethylamino group and the *N*-oxide oxygen of **2.32** can donate electrons into the aromatic ring (Figure 3.6).

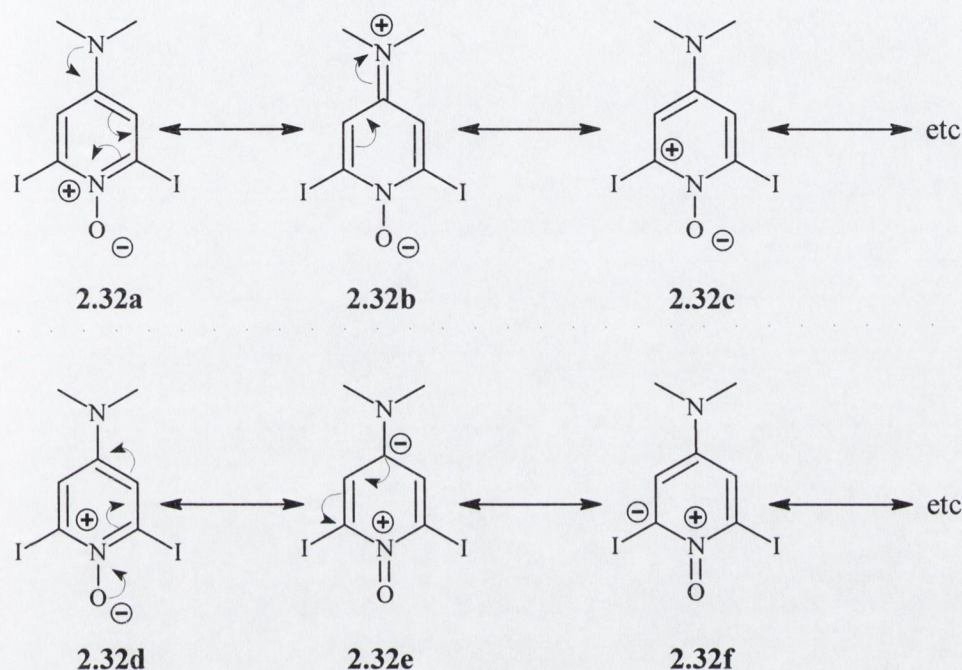
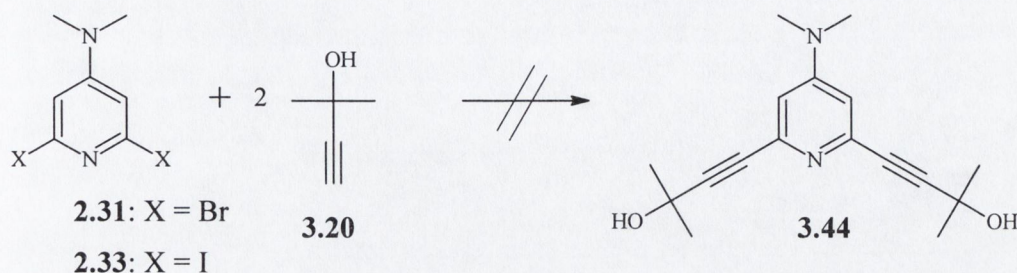


Figure 3.6

Although canonical form **2.32c** may be expected to facilitate nucleophilic attack at the α -carbon, this form requires that the formal positive charge reside on a carbon atom which is bonded to two electron-withdrawing groups (iodine and nitrogen). Canonical form **2.32c** is therefore likely to contribute little to the resonance hybrids of 2,6-diiodo-4-dimethylaminopyridine *N*-oxide. On the other hand, in canonical form **2.32f** the α -carbon bears a formal negative charge which is stabilised by electron-withdrawal by the iodine atom and by the adjacent positive charge on the ring nitrogen. This form is therefore likely to make a greater contribution to the resonance hybrids than form **2.32c**. Thus, nucleophilic substitution at the α -carbons of 2,6-diiodo-4-dimethylaminopyridine *N*-oxide is disfavoured.

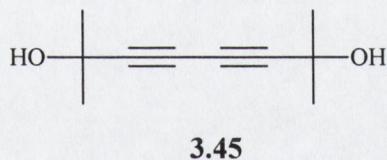
Since the *N*-oxide **2.32** failed to provide the desired acetylene derivative, the reaction was performed using the free pyridines 2,6-dibromo-4-dimethylaminopyridine (**2.31**) and 2,6-diiodo-4-dimethylaminopyridine (**2.33**) in attempts to obtain diacetylene **3.44** (Scheme 3.36).



Reagents and conditions: $\text{Pd(PPh}_3)_2\text{Cl}_2$ (3 mol %)/ CuI (9 mol %)/ PPh_3 (12 mol %), Et_3N , reflux 4 hrs.

Scheme 3.36

Treatment of **2.31** with 2-methyl-3-butyn-2-ol (**3.20**) in triethylamine using $\text{Pd(PPh}_3)_2\text{Cl}_2/\text{CuI}/\text{PPh}_3$ as catalyst gave a very dirty reaction which resulted in the formation of considerable amounts of intractable tarry material. Careful chromatography of the reaction mixture gave only recovered **2.31** and a compound which was identified by ^1H NMR, IR and melting point³¹ as 2,7-dimethylocta-3,5-diyne-2,7-diol (**3.45**).

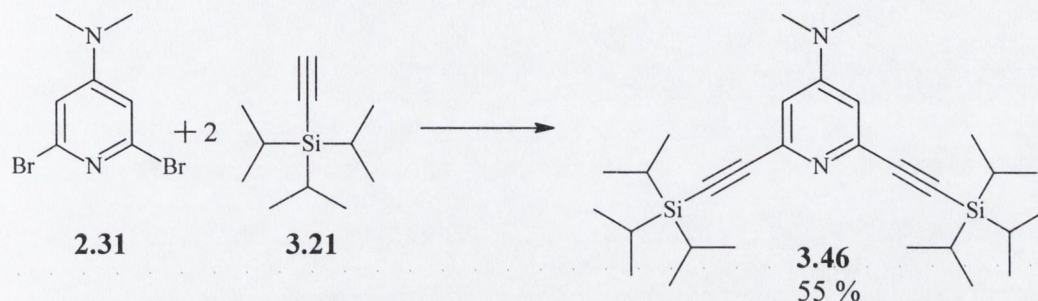


Gallagher and Maleczka³² have also reported obtaining this compound as a by-product of Sonogashira reactions involving **3.20**.

The reaction was repeated using the more reactive 2,6-diiodo-4-dimethylaminopyridine (**2.33**) but this compound also failed to react under these conditions. The failure of these reactions may have been due to the electron-rich nature of **2.31** and **2.33** since aryl halides containing electron-donating groups often prove unreactive in the Sonogashira reaction.³⁰⁻³³ Presumably, under the

above conditions the homocoupling reaction of **3.20** to give the diyne diol **3.45** is faster than the reaction with the halogenated DMAP derivatives.

The synthesis of an acetylenic DMAP derivative was eventually accomplished by treatment of 2,6-dibromo-4-dimethylaminopyridine (**2.31**) with triisopropylsilylacetylene (TIPSA, **3.21**) using $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ as catalyst and a reaction time of 14 hours (Scheme 3.37).

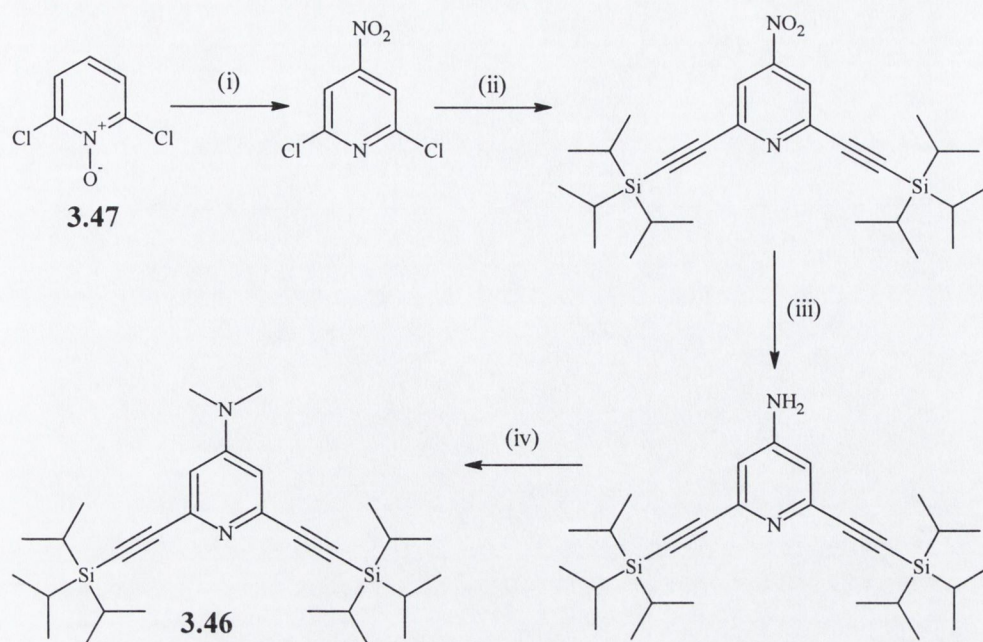


Reagents and conditions: $\text{Pd}(\text{OAc})_2$ (10 mol %)/ PPh_3 (31 mol %), Et_3N , reflux 14 hrs.

Scheme 3.37

Repetition of the reaction using the more reactive 2,6-diiodo-4-dimethylaminopyridine (**2.33**) and extending the reaction time to 18 hours improved the yield of the acetylene derivative **3.46** to 95%.

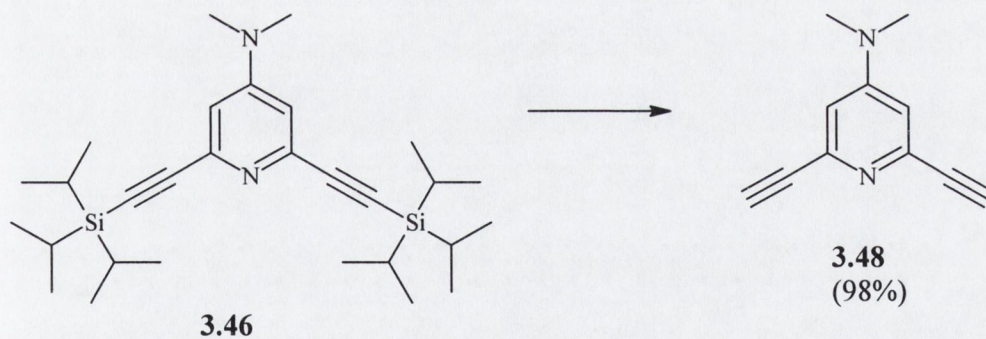
Moore and Heemstra³⁶ have recently described the synthesis of the acetylene derivative **3.46** from 2,6-dichloropyridine *N*-oxide (**3.47**) *via* the route outlined in Scheme 3.38.



Reagents and conditions: (i) H_2SO_4 , HNO_3 , 120°C , 25%. (ii) TIPSA, $\text{Pd}(\text{dba})_2$, CuI , PPh_3 , Et_3N , 42%. (iii) Fe , AcOH , 70°C , 78%. (iv) CH_2O , NaBH_3CN , AcOH , 78%.

Scheme 3.38

Deprotection of **3.46** was accomplished by treatment with tetra-*n*-butylammonium fluoride (TBAF) to afford the terminal acetylene, 2,6-diethynyl-4-dimethylaminopyridine (**3.48**) (Scheme 3.39).



Reagents and conditions: TBAF (2.5 equiv.), THF/MeOH (10:1 v/v), r.t.

Scheme 3.39

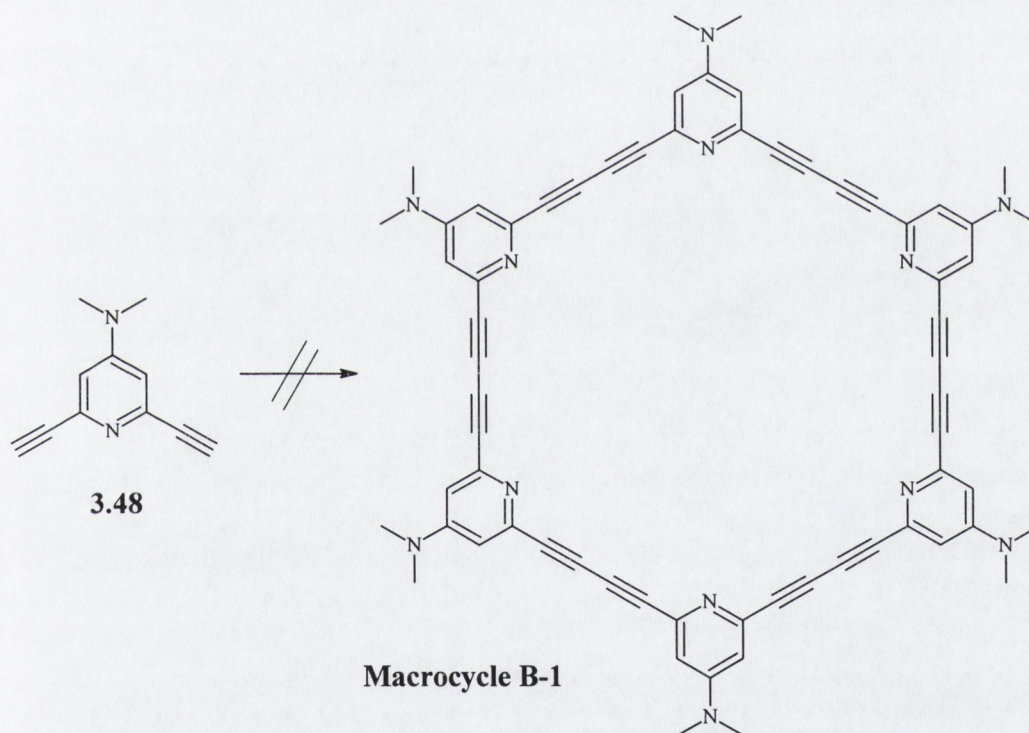
The removal of the triisopropylsilyl groups was confirmed by comparison of the NMR spectra of **3.46** and **3.48**. In the ^1H NMR spectrum of the protected acetylene **3.46** the protons at the 3 and 5 positions of the pyridine ring appear at δ 6.65. The protons of the dimethylamino group are at δ 3.03 and the protons of the isopropyl groups appear as a large singlet at δ 1.14. In the spectrum of the deprotected compound **3.48** the signal at δ 1.14 is absent and a new signal appears at δ 3.03 from the protons of the terminal acetylene moieties.

Attempted synthesis of pyridinophanes.

Attempts to prepare pyridinophane derivatives *via* copper- or palladium-catalysed coupling of the acetylenic pyridines described above proved unsuccessful. These reactions generally resulted in the formation of polymeric tars which proved to be almost completely insoluble in organic solvents. In most cases, material recovery was practically negligible despite numerous extractions of the crude product with a variety of organic solvents.

Attempted synthesis of Macrocycle B-2.

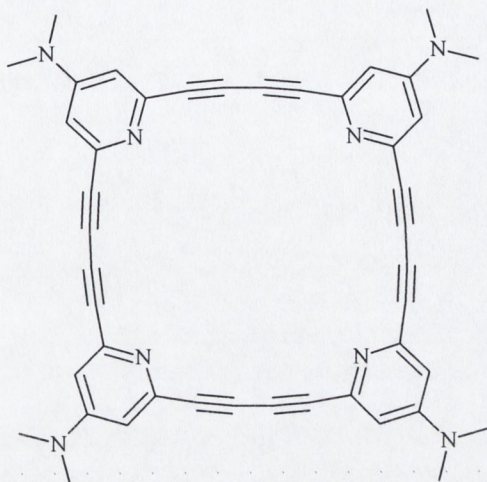
The first reaction attempted was the synthesis of Macrocycle B-2 by the copper-mediated homocoupling of 2,6-diethynyl-4-dimethylaminopyridine (**3.48**). It was hoped that this reaction might provide a simple 'one-pot' procedure for the synthesis of this macrocycle (Scheme 3.40).



Reagents and conditions: CuCl (20 equiv.), Cu(OAc)₂·H₂O (25 equiv.), pyridine, r.t., 7 days.

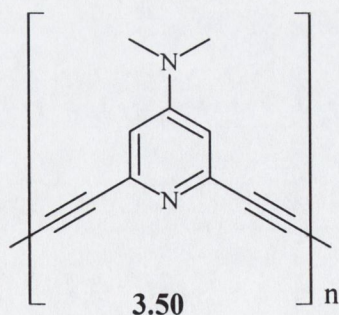
Scheme 3.40

Although this reaction could also result in formation of other cyclic products (*e.g.* **3.49**), the geometry of the starting material **3.48** suggested that the cyclic hexamer Macrocycle B-2 would be favoured over other cyclic products since this compound would show less ring strain than other cyclic oligomers.

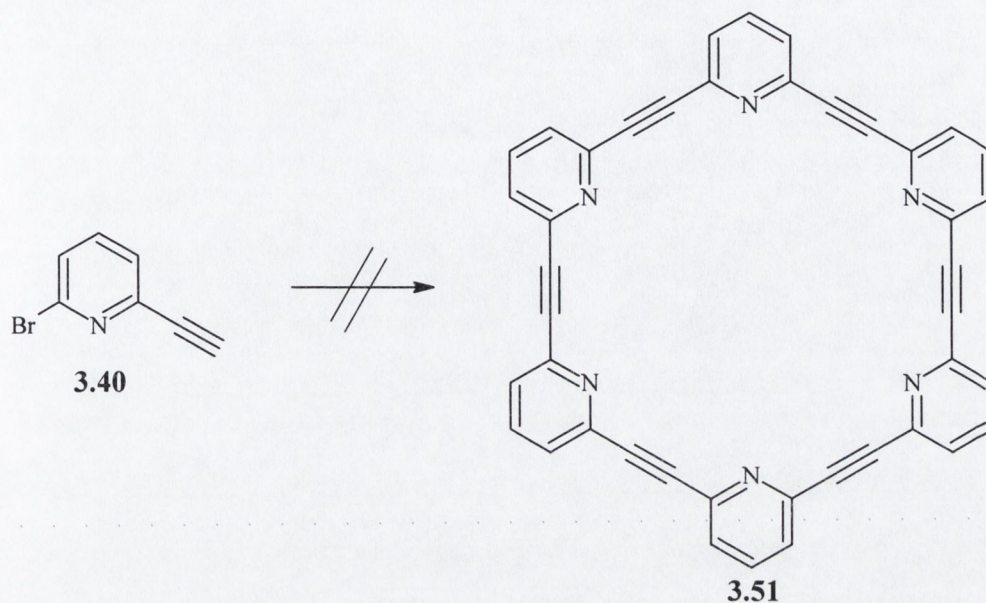


3.49

The coupling of 2,6-diethynyl-4-dimethylaminopyridine (**3.48**) was performed using a mixture of copper(I) chloride and copper (II) acetate in pyridine (the Eglinton reaction³). The crude product from this reaction proved to be almost completely insoluble in organic solvents. After removal of the solvent the resulting salt cake was extracted repeatedly with chloroform but only a small amount (< 1 mg) of tarry material was obtained. Further extractions using a variety of organic solvents (toluene, hexane, ethyl acetate, diethyl ether) failed to provide any additional material. Presumably, this reaction resulted in the formation of insoluble polymers of type **3.50**.



In a related procedure, the palladium-catalysed homocoupling of 2-bromo-6-ethynylpyridine (**3.40**) was performed in an attempt to obtain pyridinophane **3.51** (Scheme 3.41).



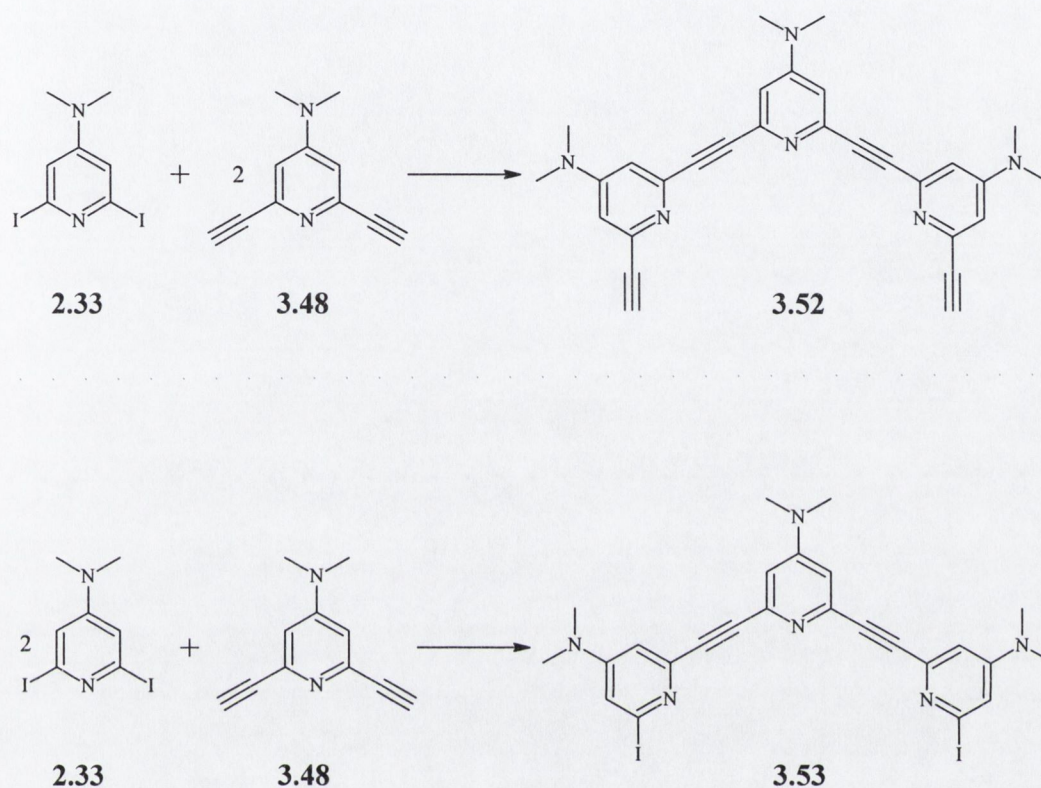
Reagents and conditions: $\text{Pd}(\text{OAc})_2$ (8 mol %)/ PPh_3 (20 mol %), Et_3N , reflux 4 hrs.

Scheme 3.41

This reaction also resulted in the formation of insoluble products and low material recovery. Repeated extractions using a variety of organic solvents (chloroform, toluene, hexane, ethyl acetate, diethyl ether) gave less than 5% of the expected weight recovery. The ^1H NMR spectrum of this material bore a superficial resemblance to the spectrum of the starting material **3.40** but accurate peak assignments were difficult due to the presence of triphenylphosphine from the catalyst system. Analysis this crude product by thin-layer chromatography failed to provide a solvent system capable of separating this material.

Since the above simple 'one-pot' procedures had failed to provide the projected macrocycles, it was decided to attempt a stepwise approach to the synthesis of DMAP pyridinophanes.

It was expected that the palladium-catalysed coupling of 2,6-diiodo-4-dimethylaminopyridine (**2.33**) with two equivalents of 2,6-diethynyl-4-dimethylaminopyridine (**3.48**) would afford the linear species **3.52**. Similarly, reaction of two equivalents of **2.33** with one equivalent of **3.48** should afford **3.53** (Scheme 3.42).



Reagents and conditions: $\text{Pd}(\text{OAc})_2$ (8 mol %)/ PPh_3 (20 mol %), Et_3N , reflux 12 hrs.

Scheme 3.42

The above compounds would provide useful synthons for the construction of macrocyclic DMAP derivatives. For example, it was expected that the palladium-catalysed coupling of **3.52** with **3.53** would afford Macrocycle B-1 (Scheme 3.43).

Experimental.

General procedures for palladium-catalysed coupling of acetylenes with aryl halides.

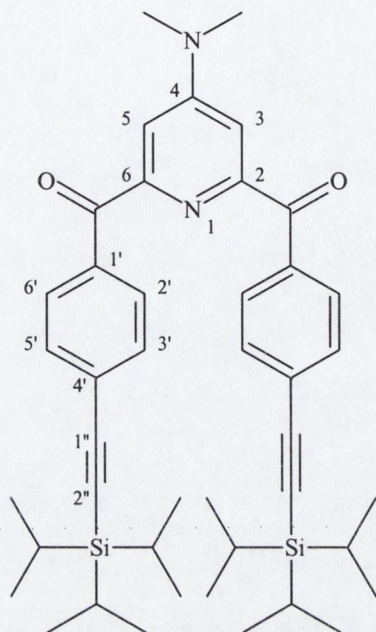
Procedure A.

A rapidly-stirred mixture of the aryl halide (1 equiv.), palladium acetate (0.08 equiv.) and triphenylphosphine (0.2 equiv.) in dry triethylamine was heated to 50°C under a nitrogen atmosphere. A solution of the acetylene (2 equiv.) in dry triethylamine was added *via* syringe and the mixture was brought to reflux for 4 hours. The solution was allowed to cool to room temperature and the precipitated triethylamine hydrohalide was filtered off. The precipitate was washed with ether until the washings were clear. The combined filtrates were evaporated *in vacuo* and the residue was dissolved in dichloromethane. The dichloromethane solution was washed twice with brine and once with water and dried over magnesium sulphate. The solvent was removed *in vacuo* and the product was purified by column chromatography.

Procedure B.

A mixture of the aryl halide (1 equiv.), bis(triphenylphosphine)palladium(II) chloride (0.001 equiv.) and triphenylphosphine (0.004 equiv.) in dry triethylamine was stirred for 5 minutes under a nitrogen atmosphere. Copper(I) iodide (0.003 equiv.) was added and the mixture was stirred for a further 5 minutes. A solution of the acetylene (2 equiv.) in dry triethylamine was added *via* syringe and the mixture was heated at reflux for 4 hours. The mixture was cooled to room temperature and the precipitated triethylamine hydrohalide was filtered off. The precipitate was washed with ether until the washings were clear. The solvents were removed *in vacuo* and the residue was dissolved in dichloromethane. The solution was washed twice with brine and once with water and dried over magnesium sulphate. The solvent was evaporated *in vacuo* and the product was purified by column chromatography.

2,6-di-(4'-{2''-triisopropylsilylethynyl}benzoyl)-4-dimethylaminopyridine (3.25).



Prepared by general acetylene coupling procedure A using 2,6-di-(4'-bromobenzoyl)-4-dimethylaminopyridine (**2.21**) (380 mg, 0.8 mmol), palladium acetate (15 mg, 0.07 mmol), triphenylphosphine (50 mg, 0.19 mmol) and triisopropylsilylacetylene (570 mg, 3.1 mmol) in dry triethylamine (15 mL). Column chromatography on silica gel using dichloromethane as eluent gave 2,6-di-(4'-{2''-triisopropylsilylethynyl}benzoyl)-4-dimethylaminopyridine (290 mg, 54%) as a pale yellow solid, m.p. 77 – 80 °C.

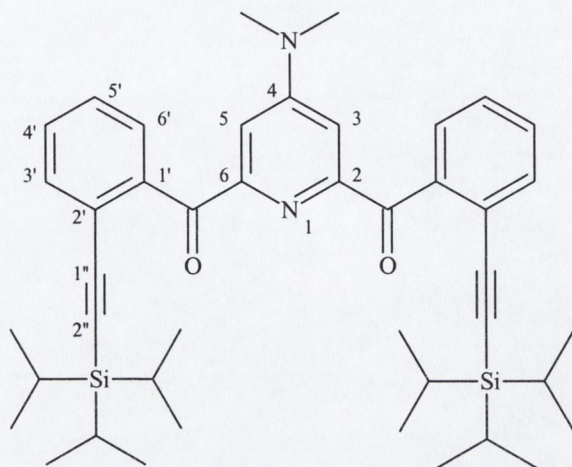
δ_{H} : 1.16 (42H, s, *i*-Pr groups), 3.18 (6H, s, N(CH₃)₂), 7.42 (2H, s, H3 and H5), 7.52 (4H, d, *J* 8.5, H3' and H5'), 8.16 (4H, d, *J* 8.5, H2' and H6') ppm.

δ_{C} : 10.8 (SiCH(CH₃)₂), 18.2 (SiCH(CH₃)₂), 39.0 (N(CH₃)₂), 94.2 (C2''), 106.0 (C1''), 108.6 (C3 and C5), 127.6 (C4'), 130.6 (C3' and C5'), 131.0 (C2' and C6'), 135.2 (C1'), 154.1 (C2 and C6), 155.3 (C4), 192.4 (C=O) ppm.

ν_{max} (thin film): 2943, 2866, 2154 (C≡C), 1662 (C=O), 1597, 1502, 1462, 1381, 1294, 1257, 1176, 1072, 1003, 926, 883, 837, 775, and 677 cm⁻¹

MS (ES): Calculated for [C₄₃H₅₈N₂O₂Si₂] *m/z* 690.4037. Found *m/z* 691.4137 [M+H]⁺

2,6-di-(2'-{2''-triisopropylsilylethynyl}benzoyl)-4-dimethylaminopyridine (3.27).



Prepared by general acetylene coupling procedure A using 2,6-di-(2'-bromobenzoyl)-4-dimethylaminopyridine (**2.22**) (170 mg, 0.35 mmol), palladium acetate (10 mg, 0.04 mmol), triphenylphosphine (30 mg, 0.11 mmol) and triisopropylsilylacetylene (254 mg, 1.39 mmol) in dry triethylamine (8 mL). Column chromatography on silica gel using dichloromethane as eluent gave 2,6-di-(2'-{2''-triisopropylsilylethynyl}benzoyl)-4-dimethylaminopyridine (80 mg, 33%) as a pale yellow solid, m.p. 80 – 83 °C.

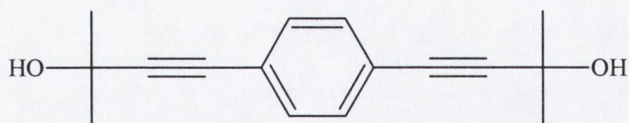
δ_{H} : 0.99 (42H, s, *i*-Pr groups), 3.16 (6H, s, N(CH₃)₂), 7.18 (2H, dd, *J* 7.5, H5'), 7.30 (2H, dd, *J* 7.5, H4'), 7.44 (2H, d, *J* 7.5, H3'), 7.55 (2H, s, H3 and H5), 7.62 (2H, d, *J* 7.5, H6') ppm.

δ_{C} : 10.8 (SiCH(CH₃)₂), 18.1 (SiCH(CH₃)₂), 39.0 (N(CH₃)₂), 94.8 (C2''), 104.8 (C1''), 108.0 (C3 and C5), 121.8 (C2'), 126.8 (C5'), 128.8 (C4'), 128.9 (C3'), 132.6 (C6'), 140.9 (C1'), 153.2 (C2 and C6), 155.3 (C4), 195.4 (C=O) ppm.

ν_{max} (nujol): 2941, 2864, 2155 (C≡C), 1760 (C=O), 1674, 1592, 1462, 1378, 1298, 998, 926, 882, 757, and 670 cm⁻¹

MS (ES): Calculated for [C₄₃H₅₈N₂O₂Si₂] *m/z* 690.4037 Found *m/z* 713.3901 [M+Na]⁺

4-[4-(3-hydroxy-3-methylbut-1-ynyl)phenyl]-2-methylbut-3-yn-2-ol (3.34).³⁷



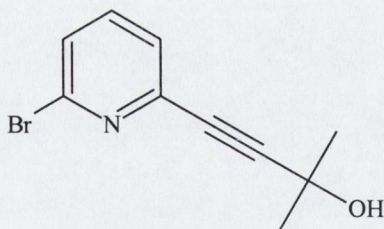
Prepared by general acetylene coupling Procedure B using 1,4-dibromobenzene (2.405 g, 10.2 mmol), copper iodide (5 mg, 0.03 mmol), bis(triphenylphosphine)-palladium(II) chloride (5 mg, 0.01 mmol), triphenylphosphine (10 mg, 0.04 mmol) and 2-methylbut-3-yn-2-ol (3.412 g, 40.5 mmol) in triethylamine (20 mL). Purification by column chromatography on silica gel using hexane/ethyl acetate (4:1) as eluent gave 4-[4-(3-hydroxy-3-methylbut-1-ynyl)phenyl]-2-methylbut-3-yn-2-ol (1.606 g, 65%) as a brown solid, m.p. 161 – 162 °C (lit.³⁷ 163 °C).

δ_{H} : 1.63 (12H, s, CH₃), 7.36 (4H, s, phenyl H₂, H₃, H₅, and H₆) ppm.

δ_{C} : 31.0 ($-\underline{\text{C}}\text{H}_3$), 65.1 ($-\underline{\text{C}}\text{OH}$), 81.3 ($\text{PhC}\equiv\underline{\text{C}}$), 95.0 ($\text{Ph}\underline{\text{C}}\equiv\text{C}$), 122.2 (phenyl C₁ and C₄), 131.0 (phenyl C₂, C₃, C₅ and C₆) ppm.

ν_{max} (nujol): 3382 (O–H), 2980, 2931, 2235 (C $\equiv$ C), 1637, 1507, 1486, 1363, 1271, 1161, 1070, 1010, 961, 905, 824, and 789 cm⁻¹

4-(6-bromopyridin-2-yl)-2-methylbut-3-yn-2-ol (3.38).



Prepared by general acetylene coupling Procedure B using 2,6-dibromopyridine (2.101 g, 8.9 mmol), copper iodide (5 mg, 0.03 mmol), bis(triphenylphosphine)-palladium(II) chloride (5 mg, 0.01 mmol), triphenylphosphine (10 mg, 0.04 mmol) and 2-methylbut-3-yn-2-ol (820 mg, 9.7 mmol) in triethylamine (20 mL). Purification by column chromatography on silica gel using hexane/ethyl acetate

(4:1) as eluent gave 4-(6-bromopyridin-2-yl)-2-methylbut-3-yn-2-ol (980 mg, 46%) as a brown solid, m.p. 63 – 64 °C.

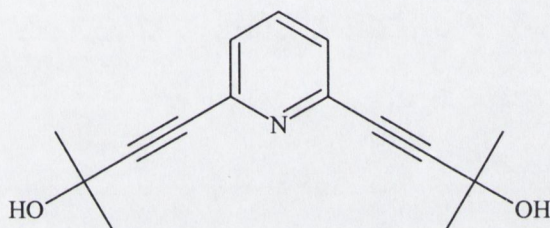
δ_H : 1.63 (6H, s, CH₃), 7.38 (1H, d, *J* 7.5, H3), 7.44 (1H, d, *J* 7.5, H5), 7.51 (1H, dd, *J* 7.5, H4) ppm.

δ_C : 30.6 (-CH₃), 65.0 (-C(OH)), 80.0 (-C≡C-(CH₃)₂OH), 94.9 (-C≡C-(CH₃)₂OH), 125.5 (C3), 127.1 (C5), 137.8 (C4), 141.2 (C2), 143.0 (C6) ppm.

ν_{max} (nujol): 3244 (O-H), 2954, 2853, 2234 (C≡C), 2015, 1567, 1544, 1460, 1377, 1283, 1199, 1161, 1120, 967, 921, 834, 797, and 724 cm⁻¹

MS (ES): Calculated for [C₁₀H₁₀BrNO] *m/z* 238.9946. Found *m/z* 261.9841 [M+Na]⁺

4-[6-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl]-2-methylbut-3-yn-2-ol (3.39).



Prepared by general acetylene coupling Procedure B using 2,6-dibromopyridine (2.410 g, 10.1 mmol), copper iodide (5 mg, 0.03 mmol), bis(triphenylphosphine)-palladium(II) chloride (5 mg, 0.01 mmol), triphenylphosphine (10 mg, 0.04 mmol) and 2-methylbut-3-yn-2-ol (3.402 g, 40.5 mmol) in triethylamine (20 mL). Purification by column chromatography on silica gel using hexane/ethyl acetate (4:1) as eluent gave 4-[6-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl]-2-methylbut-3-yn-2-ol (1.4 g, 57%) as a brown solid, m.p. 105 – 107 °C.

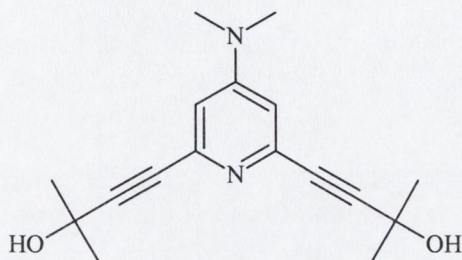
δ_H : 1.64 (12H, s, CH₃), 7.35 (2H, d, *J* 7.5, H3 and H5), 7.60 (1H, dd, *J* 7.5, H4) ppm.

δ_C : 30.7 (-CH₃), 64.8 (-C(OH)), 80.6 (-C≡C-(CH₃)₂OH), 94.2 (-C≡C-(CH₃)₂OH), 125.8 (C3 and C5), 136.0 (C4), 142.8 (C2 and C6) ppm.

ν_{max} (nujol): 3338 (O–H), 2981, 2933, 2260 (C≡C), 1579, 1560, 1444, 1377, 1311, 1259, 1207, 1164, 962, 887, and 810 cm^{-1} .

MS (ES): Calculated for $[\text{C}_{15}\text{H}_{17}\text{BrNO}_2]$ m/z 243.1259. Found m/z 266.1150 $[\text{M}+\text{Na}]^+$

Attempted synthesis of 4-[4-(dimethylamino)-6-(3-hydroxy-3-methylbut-1-ynyl)-pyridin-2-yl]-2-methylbut-3-yn-2-ol (3.44).



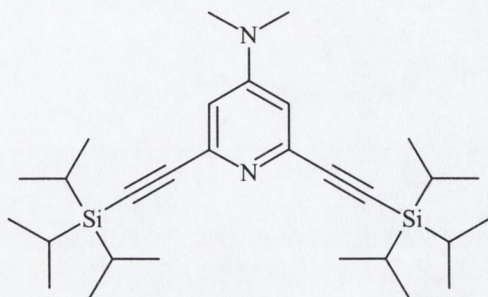
The synthesis of **3.44** was attempted by general acetylene coupling procedure B using 2,6-dibromo-4-dimethylaminopyridine (40 mg, 0.144 mmol), copper iodide (2 mg, 0.013 mmol), bis(triphenylphosphine)palladium(II) chloride (3 mg, 0.004 mmol), triphenylphosphine (4 mg, 0.017 mmol) and 2-methylbut-3-yn-2-ol (30 mg, 0.357 mmol) in triethylamine (3mL). Column chromatography on silica gel using hexane/ethyl acetate (4:1) as eluent gave only recovered 2,6-dibromo-4-dimethylaminopyridine (33 mg, 83% of initial loading) and 2,7-dimethylocta-3,5-diyne-2,7-diol **3.45** (8 mg, 27%) as a white solid, m.p. 128 – 131 °C (lit.³¹ 130 °C).

Spectroscopic data for diol **3.45**:

δ_{H} : 1.64 (s, CH_3 groups) ppm.

ν_{max} (nujol): 3283 (O–H) 2926, 2851, 2144 (C≡C), 1529, 1526, 1466, 1400, 1364, 1211, 1171, 965, 889, 834 and 734 cm^{-1}

2,6-di-(2'-triisopropylsilylethynyl)-4-dimethylaminopyridine (3.46).³⁶



Prepared by general acetylene coupling procedure A using 2,6-diiodo-4-dimethylaminopyridine (700 mg, 1.9 mmol), triisopropylsilylacetylene (1.360 g, 7.5 mmol), palladium acetate (50 mg, 0.2 mmol), and triphenylphosphine (150 mg, 0.6 mmol) in dry triethylamine (30 mL). Column chromatography using dichloromethane as eluent gave 2,6-di-(2'-triisopropylsilylethynyl)-4-dimethylaminopyridine (860 mg, 95%) as a pale yellow solid, m.p. 191 – 192 °C (lit.³⁶ 187 – 189 °C).

δ_{H} : 1.13 (42H, s, *i*-Pr groups), 3.02 (6H, s, N(CH₃)₂), 6.64 (2H, s, H3 and H5) ppm.

δ_{C} : 10.8 (SiCH(CH₃)₂), 18.2 (SiCH(CH₃)₂), 38.7 (N(CH₃)₂), 89.0 (C≡C-Si-), 106.3 (C≡C-Si-), 110.0 (C3 and C5), 143.0 (C2 and C6), 153.7 (C4) ppm.

ν_{max} (nujol): 2923, 2853, 2157 (C≡C), 1586, 1526, 1459, 1377, 1229, 1190, 1156, 1120, 1070, 1017, 997, 882, 834, and 721 cm⁻¹

General procedures for the deprotection of acetylene derivatives.

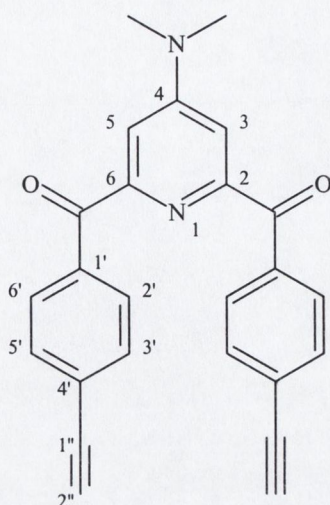
Deprotection Procedure A: Removal of the 2-hydroxypropyl group.

To a stirred solution of the protected acetylene (1 equiv.) in dry toluene was added sodium hydride (1.1 equiv. as a 60% dispersion in mineral oil). The mixture was heated at reflux for 2 hours and then distilled until the temperature of the distillate reached 110°C. The solution was cooled to room temperature and methanol was added. The solution was washed twice with brine and once with water, dried over MgSO₄, and evaporated to dryness. The crude product was then purified by column chromatography.

Deprotection Procedure B: Removal of the triisopropylsilyl group.

The protected acetylene derivative (1 equiv.) was dissolved in a mixture of tetrahydrofuran and methanol (10:1 v/v). A 1M solution of tetra-*n*-butylammonium fluoride (TBAF, 2.5 equiv.) in tetrahydrofuran was added and the mixture was stirred at room temperature until thin-layer chromatography showed complete consumption of the starting material. The solvent was removed *in vacuo* and the residue was filtered through a short column of silica gel to afford the free acetylene.

2,6-Di-(4'-ethynylbenzoyl)-4-dimethylaminopyridine (3.26).



Prepared by Deprotection Procedure B using 2,6-di-(4'-{2''-triisopropylsilylethynyl}benzoyl)-4-dimethylaminopyridine (**3.25**) (280 mg, 0.41 mmol) and TBAF (2.1 mL of a 1M solution in THF, 2.1 mmol) in THF/MeOH (10:1 v/v, 30 mL). The mixture was stirred overnight, evaporated to dryness and filtered through a short column of silica gel using hexane/ethyl acetate (4:1) as eluent to afford 2,6-di-(4'-ethynylbenzoyl)-4-dimethylaminopyridine (150 mg, 98%) as a pale yellow solid, m.p. 108 – 110 °C.

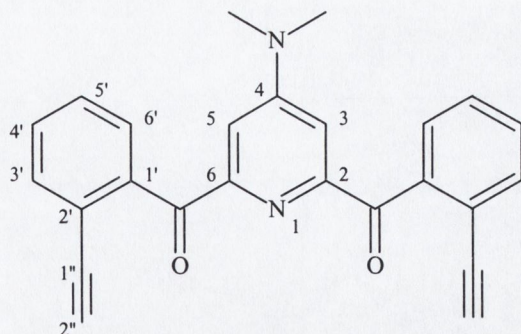
δ_{H} : 3.18 (6H, s, $\text{N}(\text{CH}_3)_2$), 3.26 (2H, s, $\text{C}\equiv\text{CH}$), 7.46 (2H, s, H3 and H5), 7.53 (4H, d, J 8.5, H3' and H5'), 8.13 (4H, d, J 8.5, H2' and H6') ppm.

δ_{C} : 39.0 ($\text{N}(\underline{\text{C}}\text{H}_3)_2$), 94.2 ($\text{C}2''$), 106.0 ($\text{C}1''$), 108.6 ($\text{C}3$ and $\text{C}5$), 127.6 ($\text{C}4'$), 130.6 ($\text{C}3'$ and $\text{C}5'$), 131.0 ($\text{C}2'$ and $\text{C}6'$), 135.3 ($\text{C}1'$), 154.1 ($\text{C}2$ and $\text{C}6$), 155.3 ($\text{C}4$), 192.4 ($\underline{\text{C}}=\text{O}$) ppm.

ν_{max} (nujol): 3243 ($\text{C}\equiv\text{C}-\text{H}$), 2942, 2103 ($\text{C}\equiv\text{C}$), 1656 ($\text{C}=\text{O}$), 1597, 1377, 1261, 1071, 1019, 928, 846, 803, 778, and 668 cm^{-1}

MS (ES): Calculated for $[\text{C}_{25}\text{H}_{18}\text{N}_2\text{O}_2]$ m/z 378.1368. Found m/z 401.1284 $[\text{M}+\text{Na}]^+$

2,6-Di-(2'-ethynylbenzoyl)-4-dimethylaminopyridine (3.28).



Prepared by Deprotection Procedure B using 2,6-di-(2'-{2''-triisopropylsilyl-ethynyl}benzoyl)-4-dimethylaminopyridine (**3.27**) (130 mg, 0.19 mmol), TBAF (1 mL of a 1M solution in THF, 1 mmol) in THF/methanol (10:1 v/v, 25 mL). Filtration through a short column of silica gel using hexane/ethyl acetate (7:3) as eluent gave 2,6-di-(2'-ethynylbenzoyl)-4-dimethylaminopyridine (65 mg, 91%) as a pale yellow solid, m.p. 88 – 92 °C.

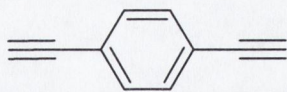
δ_{H} : 3.06 (2H, s, C $\equiv$ CH) 3.18 (6H, s, N(CH₃)₂), 7.20 (2H, dd, $J_{4'5'}$ 7.6, $J_{5'6'}$ 7.5, H5'), 7.34 (2H, dd, $J_{3'4'}$ 8.0, $J_{4'5'}$ 7.6, H4'), 7.49 (2H, d, J 8.0, H3'), 7.58 (2H, s, H3 and H5), 7.63 (2H, d, J 7.5, H6') ppm.

δ_{C} : 39.0 (N(CH₃)₂), 80.6 (C2''), 81.5 (C1''), 108.2 (C3 and C5), 120.6 (C2'), 127.1 (C5'), 129.3 (C4'), 129.5 (C3'), 132.8 (C6'), 140.7 (C1'), 153.1 (C2 and C6), 155.2 (C4), 194.9 (C=O) ppm.

ν_{max} (nujol): 3189 (C $\equiv$ C-H), 2942, 2864, 2167 (C $\equiv$ C), 1766 (C=O), 1653, 1596, 1462, 1380, 1301, 998, 946, 882, 724, and 675 cm⁻¹

MS (ES): Calculated for [C₂₅H₁₈N₂O₂] m/z 378.1368. Found m/z 401.1256 [M+Na]⁺

1,4-Diethynylbenzene (3.32).³⁷



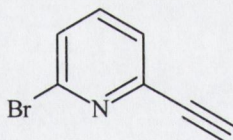
Prepared by Deprotection Procedure A using 4-[4-(3-hydroxy-3-methylbut-1-ynyl)phenyl]-2-methylbut-3-yn-2-ol (**3.34**) (500 mg, 2 mmol), sodium hydride (182 mg) in dry toluene (10 mL). Filtration through a short column of silica using hexane/ethyl acetate (3:2) as eluent gave 1,4-diethynylbenzene (203 mg, 78%) as a brown solid, m.p. 95 – 97 °C (lit.³⁷ 96 – 97 °C).

δ_{H} : 3.19 (2H, s, C $\equiv$ CH), 7.46 (4H, s, phenyl H2, H3, H5, and H6) ppm.

δ_{C} : ppm. 78.6 (PhC $\equiv$ C), 82.6 (PhC $\equiv$ C), 122.1 (phenyl C1 and C4), 131.5 (phenyl C2, C3, C5 and C6) ppm.

ν_{max} (thin film): 3306, 3275 (C $\equiv$ C–H), 2103 (C $\equiv$ C), 1918, 1672, 1462, 1377, 1261, 1104, 1014, 836, and 787 cm⁻¹

2-Bromo-6-ethynylpyridine (3.40).



Prepared by Deprotection Procedure A using 4-(6-bromopyridin-2-yl)-2-methylbut-3-yn-2-ol (**3.38**) (1.203 g, 5 mmol) and sodium hydride (130 mg, 5.5 mmol) in dry toluene (15 mL). Filtration through a short column of silica gel using hexane/ethyl acetate (4:1) as eluent gave 2-bromo-6-ethynylpyridine (700 mg, 77%) as a white solid, m.p. 68 – 70 °C.

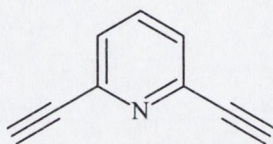
δ_{H} : 3.22 (1H, s, C $\equiv$ CH), 7.43 (1H, d, *J* 7.5, H3), 7.49 (1H, d, *J* 7.5, H5), 7.54 (1H, dd, *J* 7.5, H4) ppm.

δ_{C} : 78.3 ($-\text{C}\equiv\text{CH}$), 81.0 ($-\text{C}\equiv\text{CH}$), 125.9 (C3), 127.8 (C5), 137.9 (C4), 141.3 (C2), 142.3 (C6) ppm.

ν_{max} (nujol): 3282 ($\text{C}\equiv\text{C}-\text{H}$), 2923, 2853, 2096 ($\text{C}\equiv\text{C}$), 1578, 1459, 1377, 1283, 1141, 1091, 989, 906, 812, and 729 cm^{-1}

MS (ES): Calculated for $[\text{C}_7\text{H}_4\text{BrN}]$ m/z 180.9627. Found m/z 203.9630 $[\text{M}+\text{Na}]^+$

2,6-Diethynylpyridine (3.41).³⁸



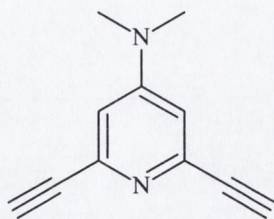
Prepared by Deprotection Procedure A using 4-[6-(3-hydroxy-3-methylbut-1-ynyl)pyridin-2-yl]-2-methylbut-3-yn-2-ol (3.39) (1.102 g, 4.5 mmol), sodium hydride (0.240 g, 9.9 mmol) in toluene (10 mL). Filtration through a short column of silica gel using hexane/ethyl acetate (4:1) as eluent gave 2,6-diethynylpyridine (507 mg, 67%) as a yellow solid, m.p. 68 – 69 °C (lit.³⁸ 70 °C).

δ_{H} : 3.17 (2H, s, $\text{C}\equiv\text{CH}$), 7.47 (2H, d, J 8.0, H3 and H5), 7.66 (1H, dd, J 8.0, H4) ppm.

δ_{C} : 81.6 ($-\text{C}\equiv\text{CH}$), 95.7 ($-\text{C}\equiv\text{CH}$), 126.6 (C3 and C5), 136.0 (C4), 142.3 (C2 and C6) ppm.

ν_{max} (nujol): 3274 ($\text{C}\equiv\text{C}-\text{H}$), 2923, 2097 ($\text{C}\equiv\text{C}$), 1576, 1457, 1377, 1249, 1141, 1080, 989, 908, 810, and 730 cm^{-1}

2,6-Diethynyl-4-dimethylaminopyridine (3.48).³⁹



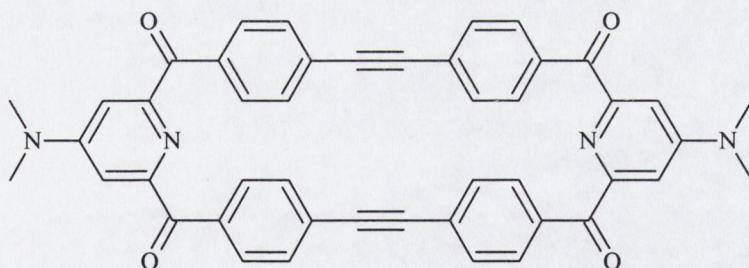
Prepared by Deprotection Procedure B using 2,6-di-(2'-triisopropylsilylethynyl)-4-dimethylaminopyridine (**3.46**) (800 mg, 1.16 mmol), TBAF (6 mL of a 1M solution in THF, 6 mmol) in THF/methanol (10:1 v/v, 25 mL). Filtration through a short column of silica gel using hexane/ethyl acetate (3:2) as eluent gave 2,6-diethynyl-4-dimethylaminopyridine (280 mg, 98%) as a pale yellow solid, m.p. 142 – 144 °C (lit.³⁹ 144 – 145 °C).

δ_{H} : 3.02 (6H, s, $\text{N}(\text{CH}_3)_2$), 3.03 (2H, s, $\text{C}\equiv\text{CH}$), 6.70 (2H, s, H3 and H5) ppm.

δ_{C} : 38.7 ($\text{N}(\text{CH}_3)_2$) 75.5 ($-\text{C}\equiv\text{CH}$), 82.8 ($-\text{C}\equiv\text{CH}$), 109.6 (C3 and C5), 141.9 (C2 and C6), 153.8 (C4) ppm.

ν_{max} (nujol): 3299, 3122 ($\text{C}\equiv\text{C}-\text{H}$), 2923, 2489, 2094 ($\text{C}\equiv\text{C}$), 1594, 1523, 1459, 1375, 1201, 1153, 1066, 1016, 970, 827, 763, 657, and 624 cm^{-1}

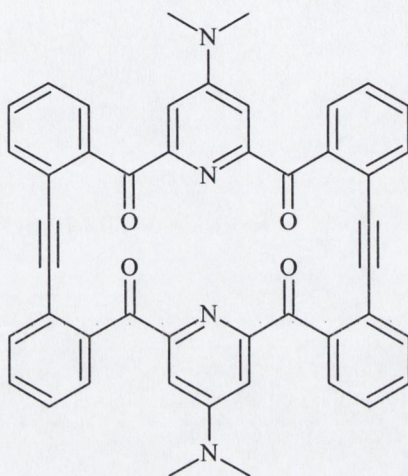
Attempted synthesis of Macrocycle-p-A-1.



A mixture of 2,6-di-(4'-bromobenzoyl)-4-dimethylaminopyridine (**2.21**) (200 mg, 0.4 mmol), 2,6-di-(4'-ethynylbenzoyl)-4-dimethylaminopyridine (**3.26**) (160 mg, 0.4 mmol), palladium acetate (7 mg, 0.03 mmol), and triphenylphosphine (21 mg, 0.08 mmol) in dry triethylamine (102 mL) was heated at reflux for 4 hours under a

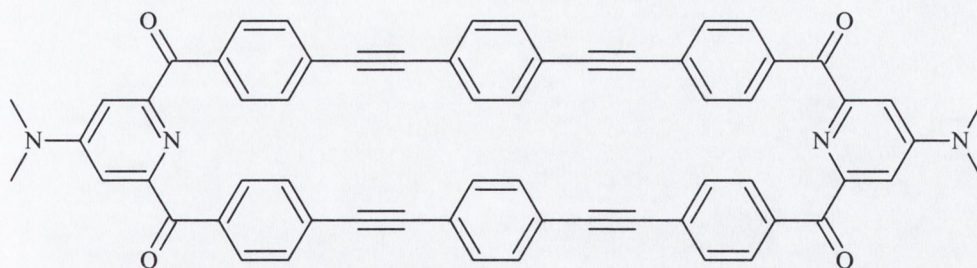
nitrogen atmosphere. The reaction mixture was filtered and the filtrate was evaporated to afford a brown residue. Column chromatography using dichloromethane as eluent gave only recovered **2.21** (182 mg, 91%) and **3.26** (150 mg, 94%).

Attempted synthesis of Macrocycle-o-A-1.



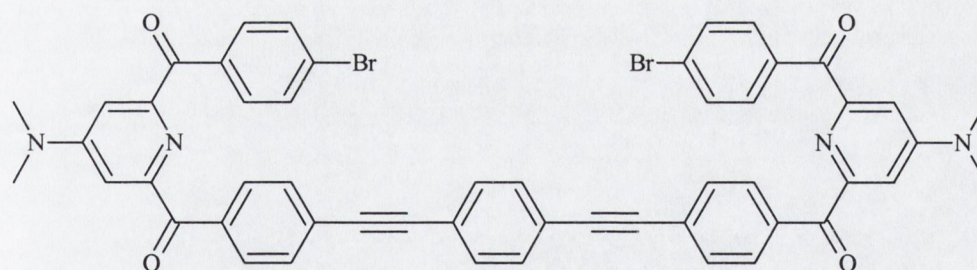
The same method was employed for the attempted synthesis of Macrocycle-o-A-1 using 2,6-di-(2'-bromobenzoyl)-4-dimethylaminopyridine (**2.22**) (202 mg, 0.4 mmol), 2,6-di-(2'-ethynylbenzoyl)-4-dimethylaminopyridine (**3.28**) (163 mg, 0.4 mmol), palladium acetate (7 mg, 0.03 mmol), and triphenylphosphine (21 mg, 0.08 mmol) in dry triethylamine (100 mL). Column chromatography using dichloromethane as eluent gave only recovered **2.22** (190 mg, 95%) and **3.28** (147 mg, 92%).

Attempted synthesis of Macrocycle-p-A-2.



A mixture of 2,6-di-(4'-bromobenzoyl)-4-dimethylaminopyridine (**2.21**) (103 mg, 0.21 mmol), 1,4-diethynylbenzene (26 mg, 0.21 mmol), palladium acetate (4 mg, 0.02 mmol), and triphenylphosphine (12 mg, 0.04 mmol) in dry triethylamine (25 mL) was heated at reflux for 6 hours under a nitrogen atmosphere. The reaction mixture was filtered and the filtrate was evaporated to afford a brown residue. Column chromatography using dichloromethane/methanol (95:5) gave only unreacted **2.21** (25 mg, 25%) which was contaminated by triphenylphosphine. The methanol content of the eluent was gradually increased to 40% and the column was flushed repeatedly but no further material was eluted.

Attempted synthesis of [4-(4-{4-[6-(4-Bromobenzoyl)-4-dimethylamino-pyridine-2-carbonyl]-phenylethynyl}-phenylethynyl)-phenyl]-[6-(4-bromobenzoyl)-4-dimethylamino-pyridin-2-yl]-methanone (**3.35**).

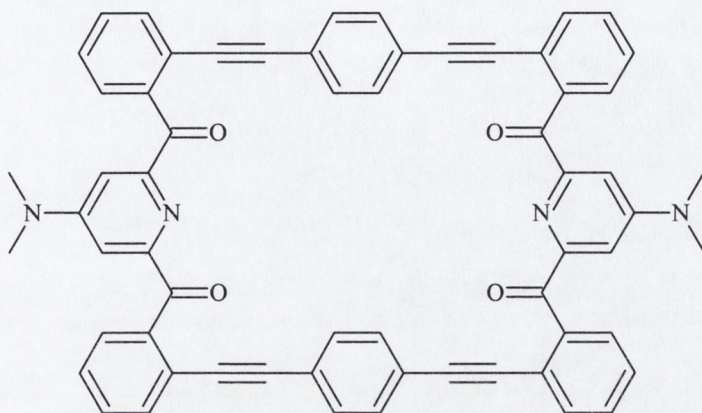


3.35

The synthesis of compound **3.35** was attempted using 2,6-di-(4'-bromobenzoyl)-4-dimethylaminopyridine (**2.21**) (200 mg, 0.21 mmol), 1,4-diethynylbenzene (27 mg, 0.21 mmol), palladium acetate (4 mg, 0.02 mmol), and triphenylphosphine (12 mg,

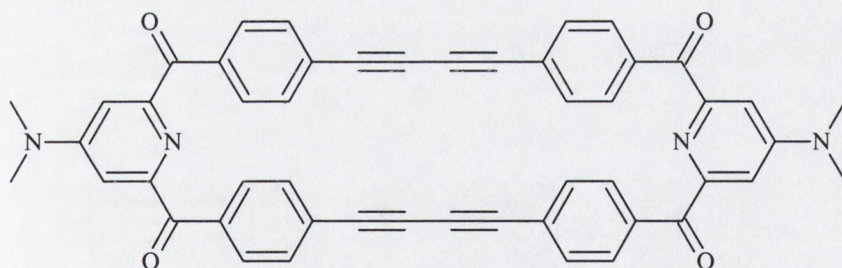
0.04 mmol) in dry triethylamine (25 mL). Attempts to separate the products from this reaction by column chromatography proved unsuccessful.

Attempted synthesis of Macrocycle-o-A-2.



The same method was employed for the attempted synthesis of Macrocycle-o-A-2 using 2,6-di-(2'-bromobenzoyl)-4-dimethylaminopyridine (**2.22**) (207 mg, 0.4 mmol), 1,4-diethynylbenzene (52 mg, 0.4 mmol), palladium acetate (7 mg, 0.03 mmol), and triphenylphosphine (21 mg, 0.08 mmol). Column chromatography using hexane/ethyl acetate (3:2) as eluent gave only recovered **2.22** (203 mg, 98%) and 1,4-diethynylbenzene (50 mg, 96%).

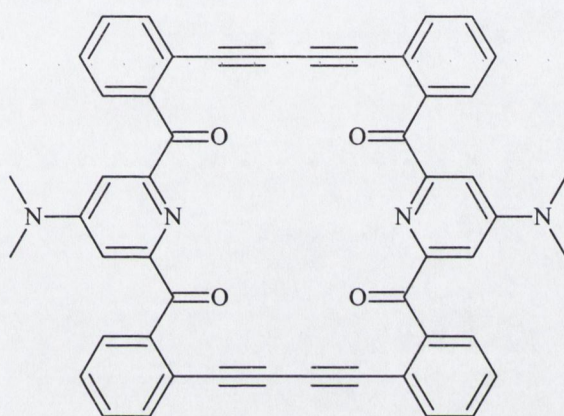
Attempted synthesis of Macrocycle-p-A-3 by the method of Baxter.⁴⁰



A solution of copper(I) chloride (70 mg, 0.71 mmol) in pyridine (5 mL) was added to a solution of 2,6-di-(4'-ethynylbenzoyl)-4-dimethylaminopyridine (**3.26**) (202 mg, 0.53 mmol) in pyridine (250 mL). The resulting olive green solution was

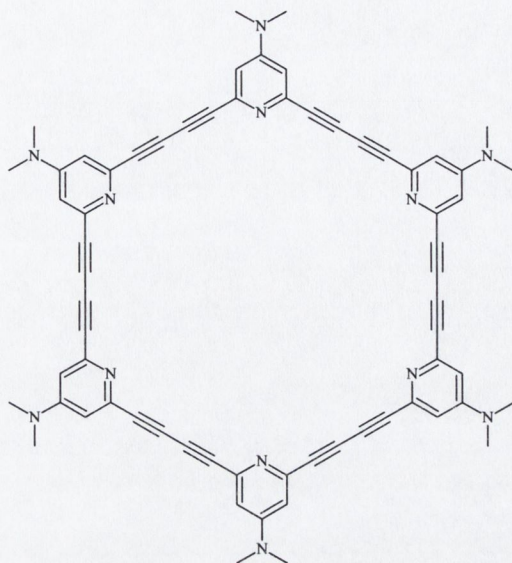
stirred vigorously and bubbled with oxygen for 5 days. The mixture was filtered and the filtrate was evaporated until approximately 4 – 5 mL of solution remained. Saturated potassium cyanide solution (20 mL) was added and the mixture was stirred for 24 h at room temperature. The mixture was filtered and the solvent was evaporated to afford a brown residue. The residue was heated at reflux with chloroform (150 mL) for 30 minutes, allowed to stand overnight, and filtered. Evaporation of the filtrate gave an orange solid (20 mg). Column chromatography on silica gel using hexane/ethyl acetate (4:1) as eluent failed to separate the reaction products.

Attempted synthesis of Macrocycle-o-A-3.



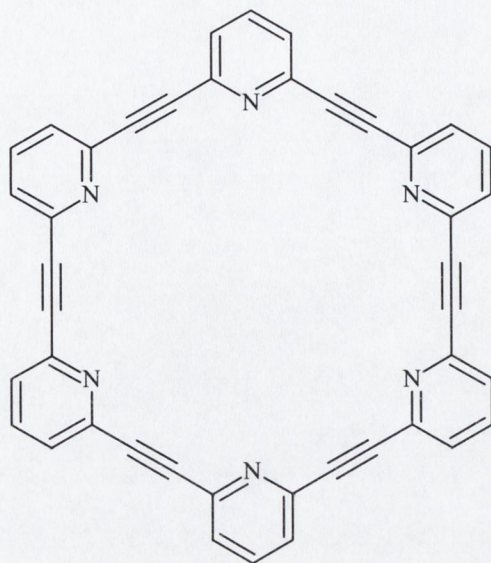
The same method was employed for the attempted synthesis of Macrocycle-o-A-3 using 2,6-di-(2'-ethynylbenzoyl)-4-dimethylaminopyridine (**3.28**) (198 mg, 0.52 mmol) and copper(I) chloride (72 mg, 0.71 mmol) in pyridine (250 mL). Removal of the solvent gave an insoluble brown residue. Extraction of the residue with chloroform (6×50 mL) gave a brown tar (2 mg). Attempts to purify this material by column chromatography using hexane/ethyl acetate (4:1) proved unsuccessful.

Attempted synthesis of Macrocycle B-2.



To a stirred solution of 2,6-diethynyl-4-dimethylaminopyridine (104 mg, 0.6 mmol) in pyridine (150 mL) was added copper(I) chloride (1.21 g, 11.8 mmol,) and copper (II) acetate monohydrate (2.92 g, 14.7 mmol) and the mixture was stirred at room temperature for 7 days. The solvent was removed *in vacuo* and the resulting salt cake was extracted with chloroform (6×50 mL). The combined chloroform extracts were washed with brine (2×100 mL) and water (2×100 mL), dried over MgSO₄, and evaporated to afford < 1 mg of brown tarry material. Further extractions of the salt cake with toluene (2×50 mL), hexane (2×50 mL), ethyl acetate (2×50 mL) and diethyl ether (2×50 mL) failed to provide any additional material.

Attempted synthesis of pyridinophane 3.51.



To a solution of 2-bromo-6-ethynylpyridine (250 mg, 1.4 mmol) in dry triethylamine (70 mL) was added palladium(II) acetate (12 mg, 0.05 mmol) and triphenylphosphine (36 mg, 0.14 mmol). The mixture was heated at reflux under a nitrogen atmosphere for 18 hrs and cooled to room temperature. The solvent was removed *in vacuo* and the resulting residue was extracted with chloroform (4×50 mL). The combined chloroform extracts were washed with brine (2×50 mL) and water (2×50 mL), dried over MgSO₄, and evaporated to afford a sticky brown residue (6 mg). Attempts to separate this material by thin-layer chromatography proved unsuccessful.

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Chapter 4

Pyridyl ethers

4.1. Introduction.

The failure of the extremely rigid systems described in Chapter 3 to provide the projected macrocycles prompted an investigation of more flexible systems. It was expected that systems containing alkyl or polyether residues would exhibit greater solubility in organic solvents and thus facilitate isolation of the reaction products. Indeed, several investigators have used alkyl and/or polyether moieties as solubilising groups in macrocycle synthesis.¹⁻³ Macrocyclic polyethers have been widely used as metal chelates⁴ and as phase-transfer catalysts.⁵ Polyether macrocycles incorporating pyridine and/or DMAP moieties may therefore be expected to exhibit interesting binding and/or catalytic behaviour.

4.1.1. Crown ethers.

In 1967, Pedersen⁶ reported the synthesis of a number of cyclic polyethers (crown ethers) and demonstrated their ability to form stable complexes with a variety of metal ions (Figure 4.1).

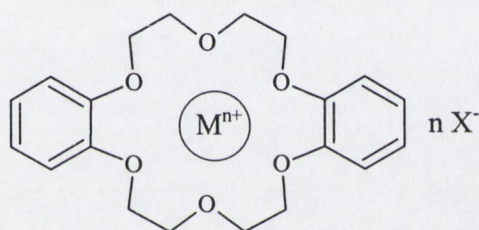
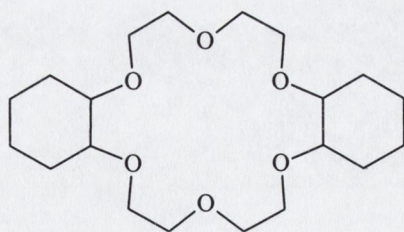


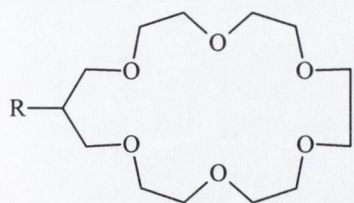
Figure 4.1

One of the most interesting features of crown ethers is their ability to exhibit selectivity in the binding of metal ions. For example, dicyclohexyl-18-crown-6 (4.1) shows a high affinity for Hg^{2+} but no affinity for Cd^{2+} or Zn^{2+} . This compound also selectively binds potassium in the presence of other alkali metals.⁷



4.1

Rastetter and Phillion⁸ used a crown ether as a template to effect ring-closure of macrocyclic lactones. The crown ether template consisted of a 19-crown-6 centre functionalised with a thiol group (**4.2a**).

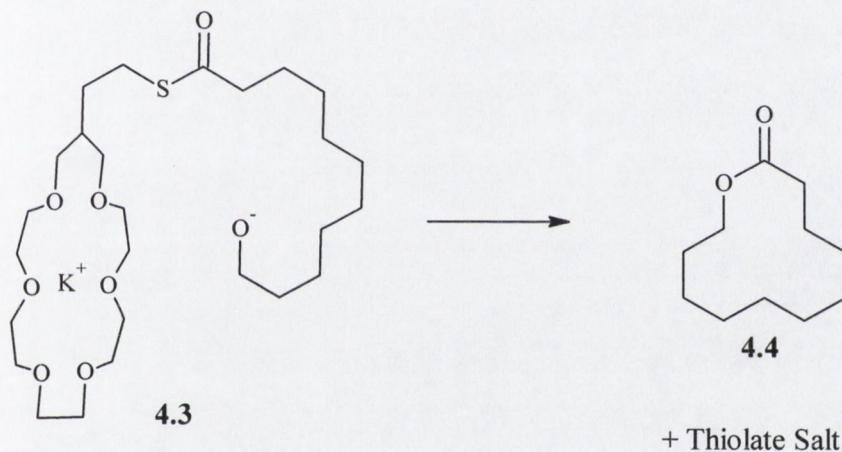


4.2

a. $R = \text{CH}_2\text{CH}_2\text{SH}$

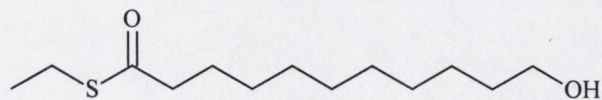
b. $R = \text{CH}_2\text{CH}_2\text{SCO}(\text{CH}_2)_{10}\text{OH}$

Treatment of the hydroxy thioester crown **4.2b** with potassium *tert*-butoxide gave the macrocyclic lactone **4.4** via the templated alkoxide **4.3** (Scheme 4.1).



Scheme 4.1

The templated precursor **4.3** gave a 44% yield of the lactone **4.4**. When the cyclisation reaction was performed using the ethyl thioester **4.5** only 1% of the lactone was obtained.



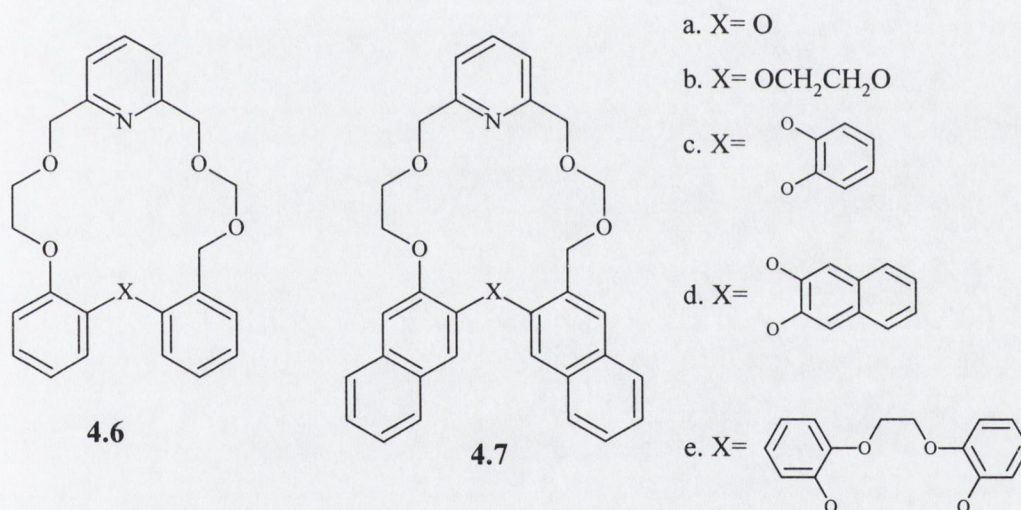
4.5

The cyclisation of ethyl thioester **4.5** in the presence of unfunctionalised 19-crown-6 also proved ineffective.⁸

4.1.2. Pyridino-crown ethers.

The literature is rich in examples of macrocycles containing pyridine subunits.⁹ The use of pyridine as a complexing unit in macrocyclic systems offers interesting coordination possibilities towards metal ions owing to the orientation of the nitrogen electron lone pair. In addition to their ability to bind metal ions, macrocycles containing pyridine units have been found to form host-guest inclusion compounds with a variety of neutral organic molecules and the selectivities of these macrocyclic hosts can often be varied by altering the molecular cavity.^{10,11}

Weber *et al.*¹¹ prepared a series of pyridino-crown ether macrocycles and examined their ability to bind a variety of organic substrates (Scheme 4.2).

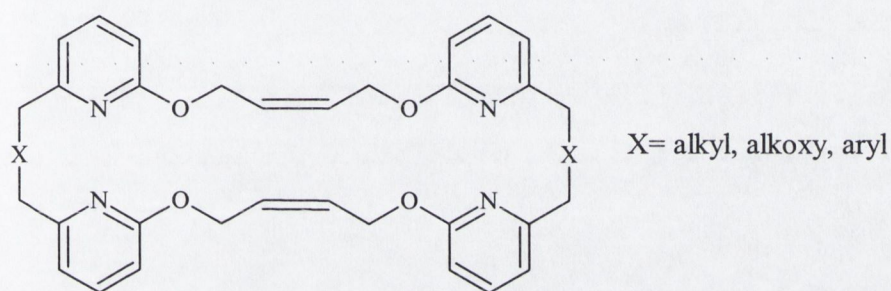


Scheme 4.2

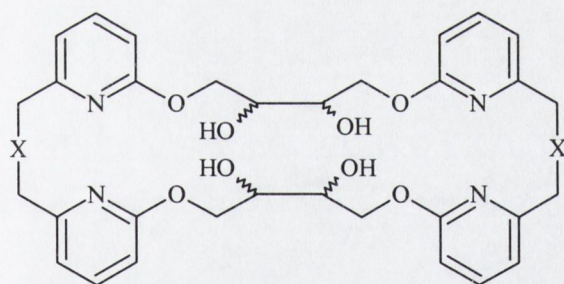
The above macrocycles were found to bind a number of organic solvents (DMF, DMSO, dichloromethane, benzene, toluene) with varying degrees of efficiency. While macrocycle **4.6d** formed a number of solid-state complexes with organic solvents, macrocycles **4.6b** and **4.6c** allowed only a few. Macrocycle **4.6c** was

found to form complexes with polar solvents (nitromethane, acetonitrile) but failed to bind aromatic substrates. On the other hand, macrocycle **4.7b** was found to favour aromatic solvents (nitrobenzene, benzonitrile).

Polyether macrocycles containing pyridine and/or DMAP residues may be expected to exhibit interesting host-guest behaviour. It was therefore decided to undertake the synthesis of macrocyclic ethers containing these moieties. It was also decided to attempt to retain adaptable functional groups within the macrocyclic framework. For example, macrocycles of type **4.8** containing alkene moieties could be hydroxylated to afford the new macrocyclic species **4.9** which may be further derivatised *via* synthetic manipulation of the resulting hydroxyl groups.



4.8

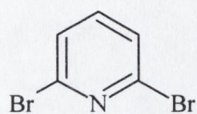


4.9

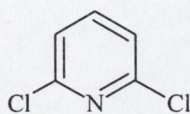
In addition, the presence of other functional groups within the linking group X would enable the synthesis of a number of different macrocyclic entities.

4.2. Results and discussion.

A number of linear pyridyl ethers were synthesised as precursors for the construction of pyridino polyether macrocycles. As a first step, it was decided to perform the syntheses of these pyridyl ethers using the commercially-available 2,6-dibromopyridine (**3.37**) and 2,6-dichloropyridine (**4.10**) and to subsequently apply this methodology to the synthesis of the corresponding DMAP derivatives.

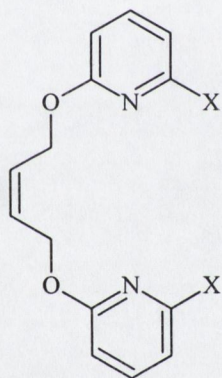


3.37



4.10

Of particular interest were the pyridyl ethers 2-chloro-6-({4-[(6-chloropyridin-2-yl)oxy]but-2-enyl}oxy)pyridine (**4.11**) and 2-bromo-6-({4-[(6-bromopyridin-2-yl)oxy]but-2-enyl}oxy)pyridine (**4.12**).



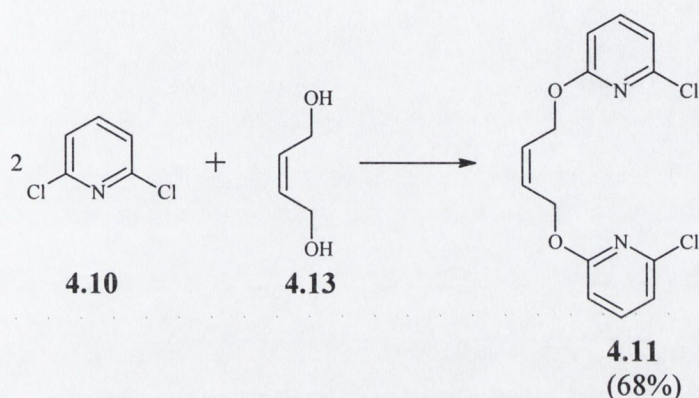
4.11: X = Cl

4.12: X = Br

These compounds were considered to be useful synthons for the construction of macrocycles since the terminal halogens would provide good leaving groups for nucleophilic substitution reactions and the alkene moieties would provide sites for further synthetic manipulation of the derived macrocycles.

4.2.1. Synthesis of 2-chloro-6-({4-[(6-chloropyridin-2-yl)oxy]but-2-enyl}oxy)-pyridine (**4.11**).

The first pyridyl ether prepared was the dichloro derivative **4.11**. This compound was prepared *via* reaction of 2 equivalents of 2,6-dichloropyridine (**4.10**) with one equivalent of *cis*-2-butene-1,4-diol (**4.13**) in the presence of sodium hydride in *N*-methylpyrrolidinone (Scheme 4.3).



Reagents and conditions: NaH (2.2 equiv.), NMP, 80 °C, 2 hrs.

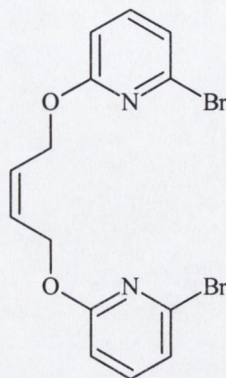
Scheme 4.3

In the ^1H NMR spectrum of **4.11** the protons at the 4 positions of the pyridine rings appear as a double doublet at δ 7.51. The pyridine protons at the 5 positions (adjacent to the alkoxy substituent) appear as a doublet at δ 6.92 while the protons at the 3 positions (adjacent to the chloro substituent) appear as another doublet at δ 6.69. The alkene protons resonate as a triplet at δ 5.94 and the methylene protons appear as a doublet at δ 5.03.

In the ^{13}C NMR spectrum of **4.11** the pyridine carbons bearing the oxygen substituents appear at δ 162.5. The carbons bearing the chloro substituents are at δ 147.9. The pyridine C4 carbons appear at δ 140.1 and the C3 and C5 carbons are at δ 116.0 and δ 108.8 respectively. The signal from the alkene carbons is at δ 128.0 and the methylene carbons appear at δ 61.9.

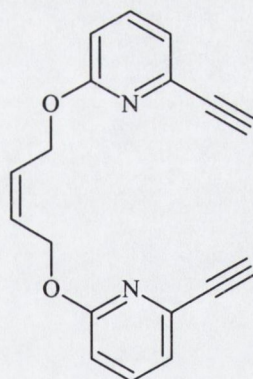
4.2.2. Synthesis of 2-bromo-6-({4-[(6-bromopyridin-2-yl)oxy]but-2-enyl}oxy)-pyridine (4.12).

The corresponding bromo pyridyl ether **4.12** was prepared using the same method employed for the synthesis of the chloro derivative **4.11**.



4.12

It was expected that the bromo groups of **4.12** would undergo the palladium-catalysed reactions described in the previous chapter and provide a source of novel acetylene derivatives (*e.g.* **4.14**) for the construction of acetylenic macrocycles.



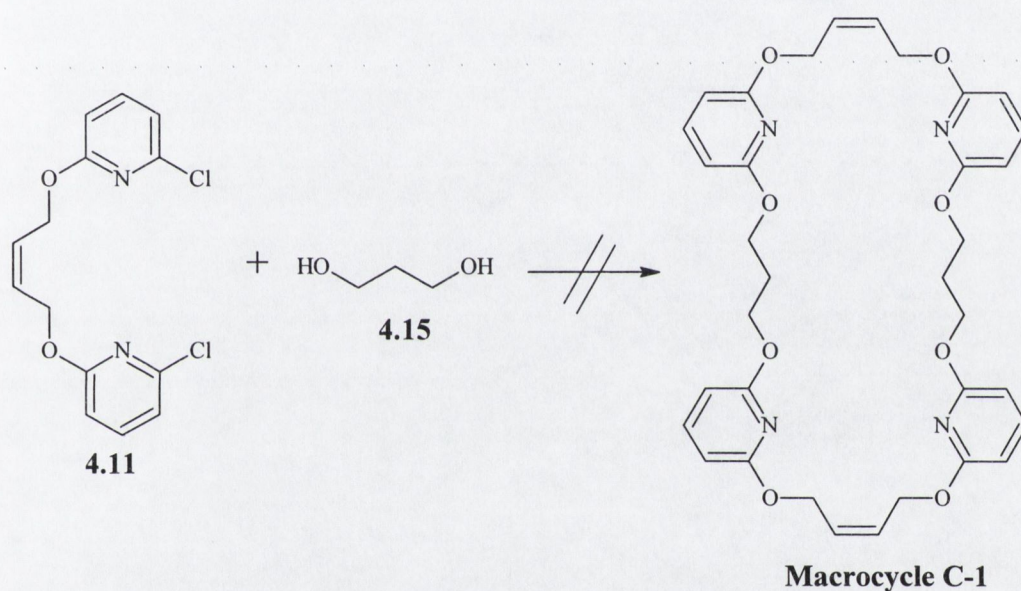
4.14

4.2.3. Attempted synthesis of macrocyclic pyridyl ethers.

Attempts to prepare macrocyclic derivatives of **4.11** and **4.12** proved unsuccessful. In several reactions, only starting materials were recovered from the reaction mixtures. As in the case of the reactions described in the previous chapter, isolation of reaction products was frequently hampered by the poor solubility of the crude material in organic solvents.

Attempted synthesis of Macrocycle C-1.

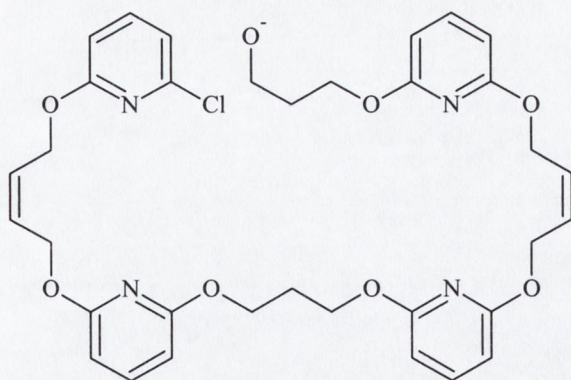
It was decided to first attempt the synthesis of macrocyclic derivatives of pyridyl ether **4.11** by displacement of the terminal chlorine atoms of **4.11** with alkoxides derived from simple diols (Scheme 4.4).



Reagents and conditions: NaH (2.2 equiv.), NMP, 80 °C, 2 hrs.

Scheme 4.4

Propane-1,3-diol (**4.15**) was selected as a suitable alcohol for these experiments. It was expected that the short chain length of this diol would limit the degrees of freedom available to open-chain species such as **4.16** and facilitate the ring-closing reaction.



4.16

The synthesis of the macrocyclic ether Macrocycle C-1 was initially attempted under high dilution conditions using the same reaction time and temperature employed for the synthesis of the pyridyl ether starting material **4.11**. The pyridyl ether **4.11** was added to a solution of the alkoxide of propane-1,3-diol (**4.15**) in *N*-methylpyrrolidinone (NMP) and the mixture was heated at 80 °C for 2 hours. However, although this method had proved successful for the synthesis of the pyridyl ether **4.11**, it was found to be ineffective for the reaction of **4.11** with diol **4.15** and the reaction gave only quantitative recovery of the pyridyl ether **4.11**.

The pyridyl ether **4.11** was prepared by displacement of one of the chlorine atoms from 2,6-dichloropyridine (**4.10**) by reaction with the alkoxide of *cis*-2-butene-1,4-diol (**4.13**). After the initial substitution reaction, electron donation into the pyridine ring by the alkoxy substituent makes displacement of the second chlorine atom more difficult.

The use of the more reactive bromo substituted pyridyl ether **4.12** in place of the chloro derivative **4.11** also failed to give the reaction under the above conditions.

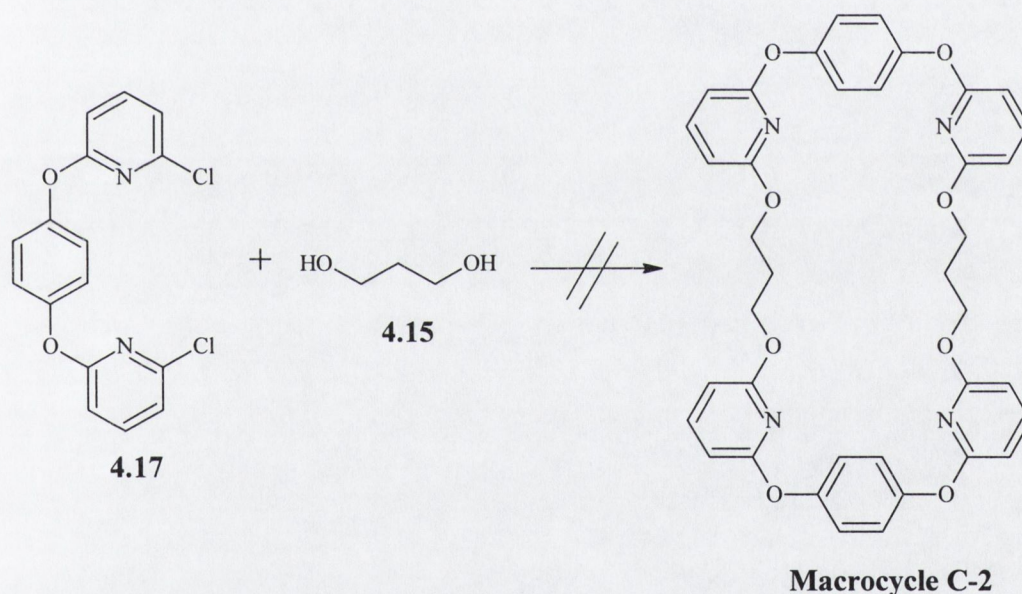
The reaction of the chloro pyridyl ether **4.11** with propane-1,3-diol (**4.15**) was repeated using an increased reaction time of 18 hours and a temperature of 120 °C. This experiment resulted in the formation of considerable amounts of intractable tarry material. Attempts to purify this material by thin-layer chromatography using a variety of solvent systems proved unsuccessful. Separation by column chromatography was attempted by careful division of the crude material into 150

chromatographic fractions using hexane/ethyl acetate (4:1) as eluent. These fractions were analyzed by thin-layer chromatography. This analysis showed only the presence of the starting material **4.11**. This was confirmed by analysis of these fractions by ^1H NMR spectroscopy which showed that they consisted of pyridyl ether **4.11** contaminated by small amounts of aliphatic material.

Reaction of the bromo pyridyl ether **4.12** with propane-1,3-diol (**4.15**) under these conditions also gave large amounts of tarry material which proved to be almost completely insoluble in organic solvents.

Attempted synthesis of Macrocycle C-2.

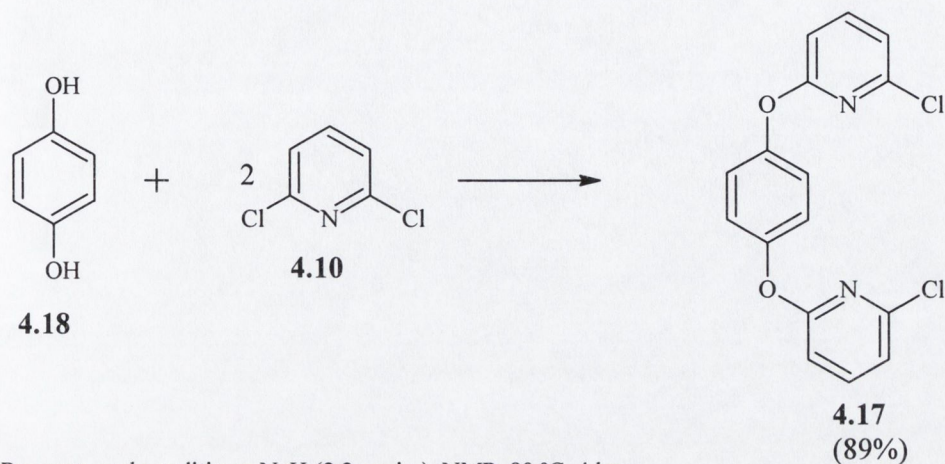
In a related experiment, the synthesis of Macrocycle C-2 was attempted *via* reaction of 2-chloro-6-{4-[(6-chloropyridin-2-yl)oxy]phenoxy}pyridine (**4.17**) with propane-1,3-diol (**4.15**) (Scheme 4.5).



Reagents and conditions: NaH (2.2 equiv.), NMP, 80 °C, 18 hrs.

Scheme 4.5

The intermediate 2-chloro-6-{4-[(6-chloropyridin-2-yl)oxy]phenoxy}pyridine (**4.17**) was prepared by reaction of 2 equivalents of 2,6-dichloropyridine (**4.10**) with one equivalent of hydroquinone (**4.18**) in the presence of sodium hydride in *N*-methylpyrrolidinone (Scheme 4.6).

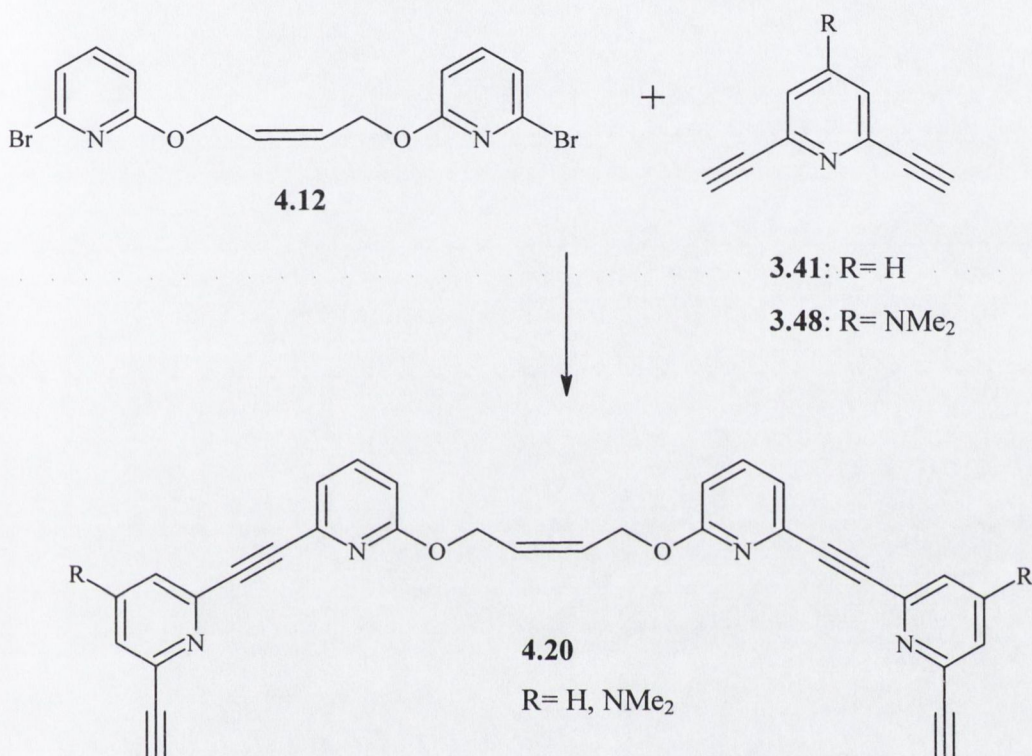


Scheme 4.6

Attempts to obtain Macrocycle C-2 by reaction of **4.17** with propane-1,3-diol (**4.15**) proved unsuccessful. As in the case of the reactions with the alkenyl pyridyl ethers **4.11** and **4.12** described above, the products from this reaction proved inseparable by thin-layer chromatography.

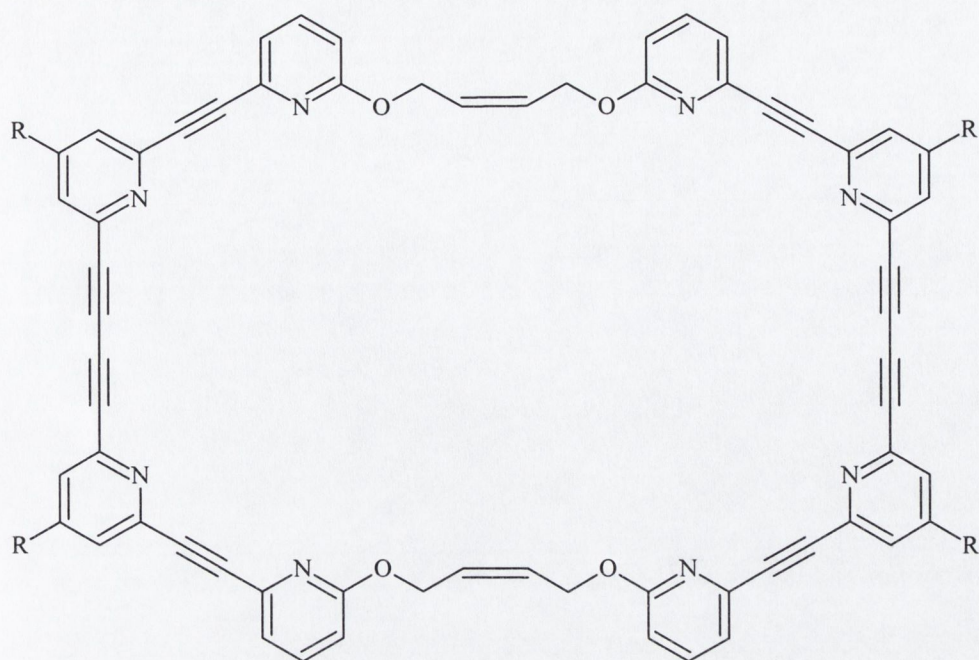
4.2.4. Attempted synthesis of acetylenic pyridyl ethers.

Although the reaction of the bromo pyridyl ether **4.12** with alkoxides had proved unsuccessful this compound was still considered to be a useful synthon for the construction of macrocycles *via* the palladium-catalysed coupling of this bromo ether with acetylene derivatives. Thus, it was expected that the palladium-catalysed coupling of bromo ether **4.12** with 2,6-diethynylpyridine (**3.41**) or 2,6-diethynyl-4-dimethylaminopyridine (**3.48**) would afford the linear species **4.20** (Scheme 4.7).



Scheme 4.7

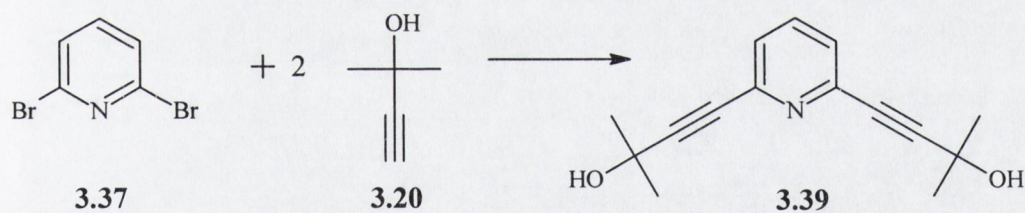
Subsequent copper-catalysed homocoupling of the linear species **4.20** should afford macrocycle **4.21**.



4.21

R = H, NMe₂

In Chapter 3, the successful palladium-catalysed coupling of 2,6-dibromopyridine (**3.37**) with 2-methyl-3-butyn-2-ol (**3.20**) was described (Scheme 4.8).

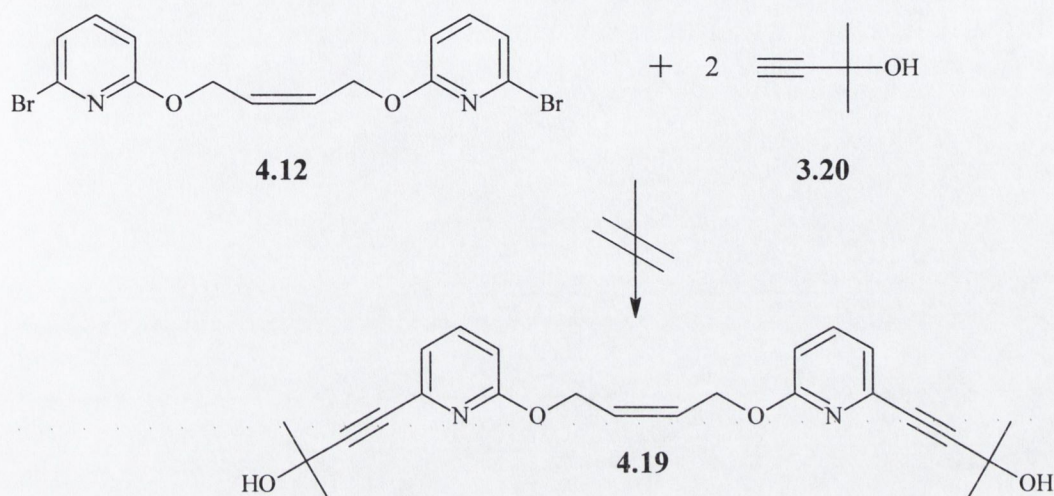


Reagents and conditions: Pd(PPh₃)₂Cl₂ (0.1 mol %)/CuI (0.3 mol %)/PPh₃ (0.4 mol %), Et₃N, reflux 4hrs.

Scheme 4.8

It was expected that the bromo pyridyl ether **4.12** would also undergo the above reaction. It was therefore decided to attempt the synthesis of an acetylenic derivative of bromo pyridyl ether **4.12**.

The possibility of obtaining acetylenic derivatives of bromo pyridyl ether **4.12** was explored by attempting the synthesis of acetylene derivative **4.19** *via* reaction of bromo pyridyl ether **4.12** with 2-methyl-3-butyn-2-ol (**3.20**) in the presence of $\text{Pd(PPh}_3)_2\text{Cl}_2/\text{CuI/PPh}_3$ (Scheme 4.9).



Reagents and conditions: $\text{Pd(PPh}_3)_2\text{Cl}_2$ (1 mol %)/ CuI (3 mol %)/ PPh_3 (4 mol %), Et_3N , reflux 4 hrs.

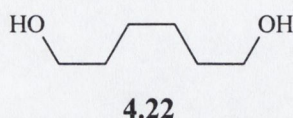
Scheme 4.9

Analysis of the reaction mixture by thin-layer chromatography after a reaction time of 4 hours showed only the presence of the starting material. Extension of the reaction time to 6 hours resulted in decomposition of the catalyst. Subsequent column chromatography gave almost quantitative recovery of the bromo pyridyl ether **4.12**.

The failure of the above reaction is presumably due to the presence of the electron-donating alkoxy substituents on the pyridine rings since aryl bromides containing electron-donating groups are often unreactive in these palladium-catalysed coupling reactions.¹²

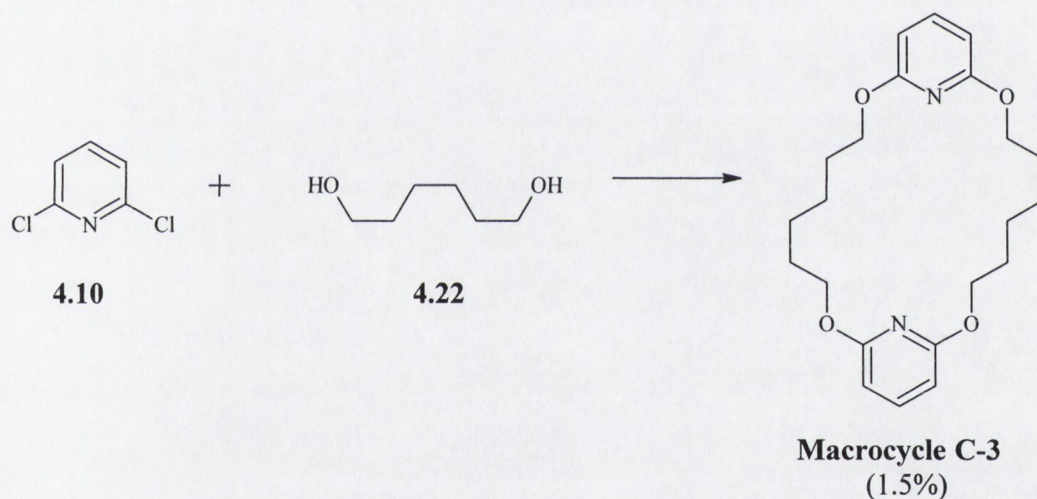
4.2.5 Synthesis of 2,9,15,22-Tetraoxa-27,28-diaza-tricyclo[21.3.1.1*10,14*]-octacos-1(26),10,12,14 (28),23(27),24-hexaene (Macrocycle C-3).

In the light of the failure of the above reactions it was decided to discontinue the above investigation and attempt the synthesis of a macrocyclic pyridyl ether by reaction of a 2,6-dihalopyridine with the alkoxide of a simple long-chain diol. The diol hexane-1,6-diol (**4.22**) was selected for this purpose.



Synthesis of Macrocycle C-3.

Reaction of 2,6-dichloropyridine (**4.10**) with hexane-1,6-diol (**4.22**) in *N*-methylpyrrolidinone (NMP) in the presence of sodium hydride under high-dilution conditions gave the cyclic pyridyl ether Macrocycle C-3 in 1.5% yield (Scheme 4.10).



Reagents and conditions: NaH (2.2 equiv.), NMP, 80 °C, 18 hrs.

Scheme 4.10

The symmetry of Macrocycle C-3 is evident from the NMR spectra of this compound. In the ^1H NMR spectrum of Macrocycle C-3 the protons at the 4 positions of the pyridine rings appear as a double doublet at δ 7.46. The protons at the 3 and 5 positions appear as a doublet at δ 6.27. Three signals appear for the

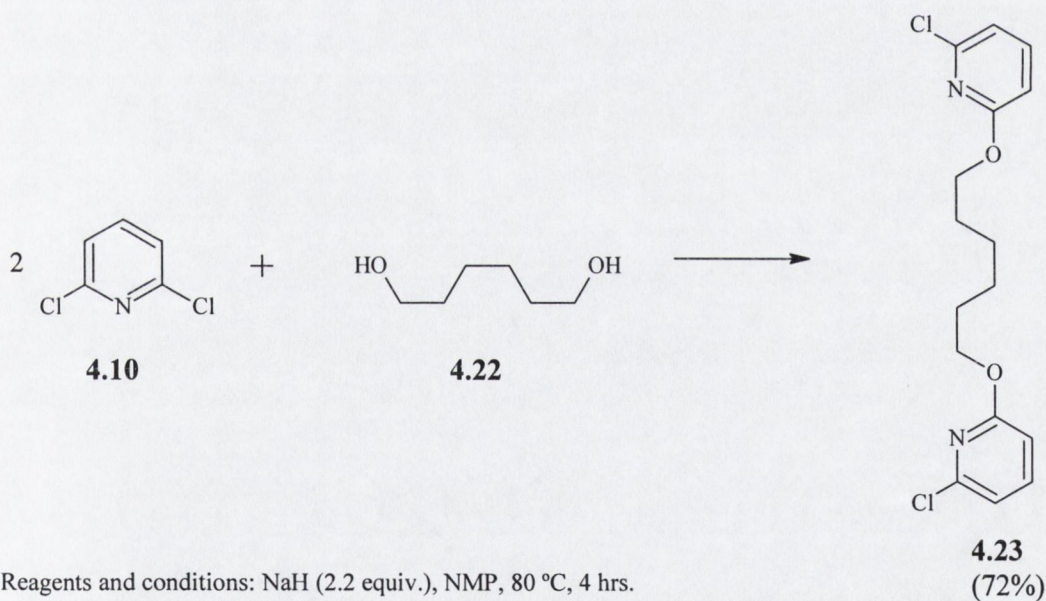
protons of the methylene groups which resonate progressively upfield as distance from the oxygen atoms increases. These protons appear at δ 4.34, δ 1.83, and δ 1.48 respectively.

The ^{13}C NMR spectrum of Macrocycle C-3 shows six carbon environments. The carbons at the 2 and 6 positions of the pyridine ring appear at δ 161.9. The carbons at the pyridine 4 positions resonate at δ 140.5 and the carbons at the 3 and 5 positions are at δ 100.8. The methylene carbons appear at δ 64.7, δ 28.5 and δ 24.9.

The macrocycle was identified as the bipyridine species from its mass spectrum which shows peaks at m/z 387.2230 ($[\text{M}+\text{H}]^+$) and m/z 409.2109 ($[\text{M}+\text{Na}]^+$).

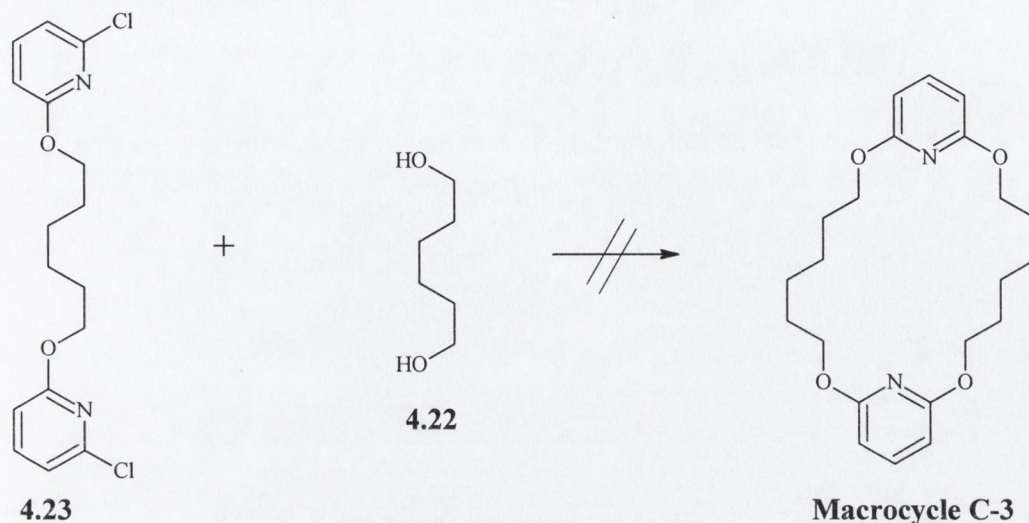
An attempt was made to improve the yield of Macrocycle C-3 by performing the synthesis in a stepwise manner.

Reaction of two equivalents of 2,6-dichloropyridine (**4.10**) with one equivalent of hexane-1,6-diol (**4.22**) gave the linear pyridyl ether 2-chloro-6-({6-[(6-chloropyridin-2-yl)oxy]hexyl}oxy)pyridine (**4.23**) (Scheme 4.11).



Scheme 4.11

The linear species **4.23** was then reacted with one equivalent of hexane-1,6-diol (**4.22**) (Scheme 4.12).



Reagents and conditions: NaH (2.2 equiv.), NMP, 80 °C, 18 hrs.

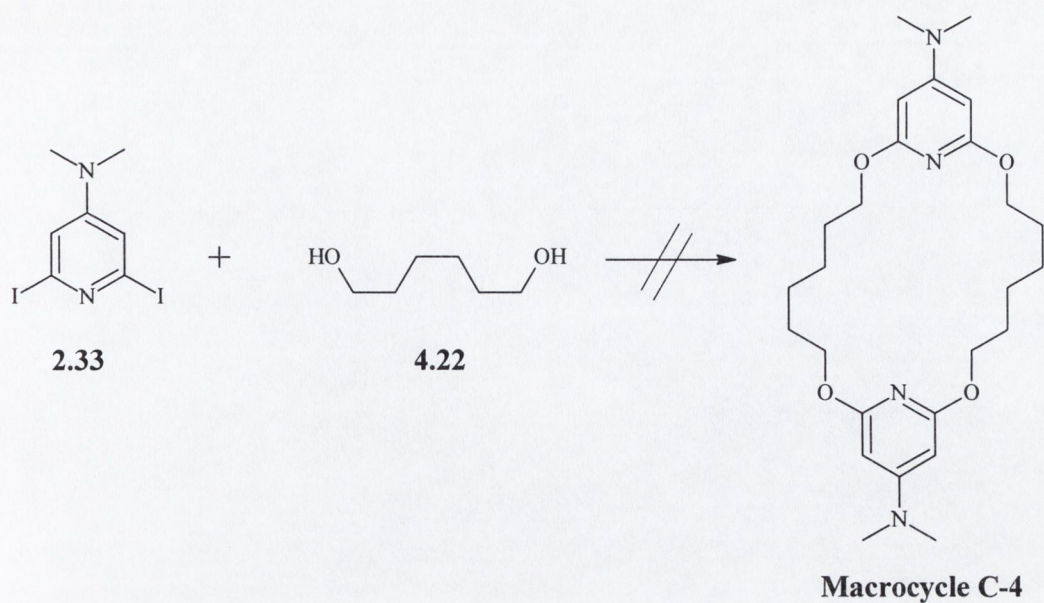
Scheme 4.12

However, this method failed to provide Macrocycle C-3. Analysis of the reaction mixture by thin-layer chromatography showed considerable streaking on the chromatographic plates and attempts to find a solvent system to purify this material proved unsuccessful.

Attempted synthesis of Macrocycle C-4.

Since the direct synthesis of Macrocycle C-3 from 2,6-dichloropyridine **4.10** and hexane-1,6-diol **4.22** had proved successful, this method was applied to the synthesis of the DMAP analogue Macrocycle C-4.

The synthesis of Macrocycle C-4 was attempted by reaction of 2,6-diiodo-4-dimethylaminopyridine **2.33** with hexane-1,6-diol **4.22** in *N*-methylpyrrolidinone (NMP) in the presence of sodium hydride under high-dilution conditions (Scheme 4.13).



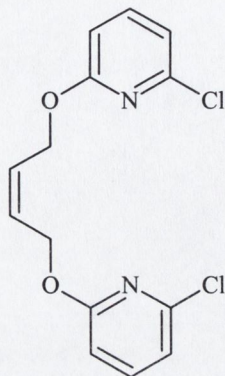
Reagents and conditions: NaH (2.2 equiv.), NMP, 80 °C, 18 hrs.

Scheme 4.13

The crude product from this reaction proved to be largely insoluble in organic solvents. Repeated extractions with chloroform gave only a small amount (5 mg) of tarry material which gave a very complex ^1H NMR spectrum showing a large number of overlapping peaks between δ 4.0 and δ 1.0. The aromatic region of this spectrum showed only trace peaks between δ 8.0 and δ 6.0. Attempts to purify this material by thin-layer chromatography proved unsuccessful.

4.3. Experimental.

2-Chloro-6-(4-[(6-chloropyridin-2-yl)oxy]but-2-enyl)pyridine (4.11).



To a rapidly-stirred suspension of sodium hydride (270 mg, 11 mmol) in *N*-methylpyrrolidinone (20 mL) was added *cis*-but-2-ene-1,4-diol (450 mg, 5 mmol) and the mixture was stirred at room temperature for 20 minutes. 2,6-dichloropyridine (1.501 g, 10 mmol) was added in small portions over a 15 minute period and the mixture was heated to 80 °C for 2 hours. The mixture was cooled to room temperature and methanol (2 mL) was added. The solution was poured into ice-water and the precipitated product was collected by vacuum filtration. Recrystallisation from ethanol gave 2-chloro-6-(4-[(6-chloropyridin-2-yl)oxy]but-2-enyl)pyridine (1.070 g, 68%) as a white solid, m.p. 36 – 37 °C.

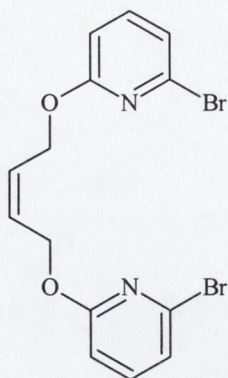
δ_{H} : 5.03 (4H, d, J 5.0, CH₂), 5.93 (2H, m, J 5.0, C=CH), 6.67 (2H, d, J 7.5, H3), 6.90 (2H, d, J 7.5, H5), 7.53 (2H, dd, J 7.5, H4) ppm.

δ_{C} : 61.9 (CH₂), 108.8 (pyridine C3), 116.0 (pyridine C5), 128.1 (C=C), 140.2 (pyridine C4), 147.8 (pyridine C2), 162.5 (pyridine C6) ppm.

ν_{max} (nujol): 2954, 1590 (C=C), 1562, 1459, 1376, 1294, 1261, 1160, 1072, 989, 902, 788, 725, and 676 cm⁻¹

MS (ES): Calculated for [C₁₄H₁₂Cl₂N₂O₂] m/z 310.0276 Found m/z 333.0165 [M+Na]⁺

2-Bromo-6-({4-[(6-bromopyridin-2-yl)oxy]but-2-enyl}oxy)pyridine (4.12).



Prepared by the method described above using *cis*-but-2-ene-1,4-diol (241 mg, 2.7 mmol) 2,6-dibromopyridine (1.302 g, 5.5 mmol) and sodium hydride (140 mg, 6 mmol) in *N*-methylpyrrolidinone (20 mL). Recrystallisation from ethanol gave 2-bromo-6-({4-[(6-bromopyridin-2-yl)oxy]but-2-enyl}oxy)pyridine (899 mg, 82%) as a white solid, m.p. 54 – 55 °C.

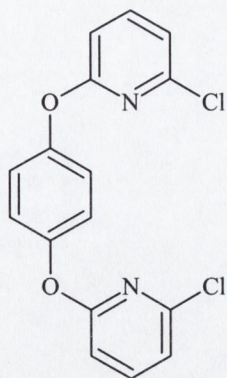
δ_{H} : 5.05 (4H, d, J 5.0, CH_2), 5.93 (2H, m, J 5.0, $\text{C}=\text{CH}$), 6.72 (2H, d, J 7.5, H3), 7.08 (2H, d, J 7.5, H5), 7.44 (2H, dd, J 7.5, H4) ppm.

δ_{C} : 62.1 (CH_2), 109.1 (pyridine C3), 119.9 (pyridine C5), 128.1 ($\text{C}=\text{C}$), 138.0 (pyridine C2), 139.9 (pyridine C4), 162.4 (pyridine C6) ppm.

ν_{max} (nujol): 3018 ($\text{C}=\text{C}-\text{H}$), 2939, 1594 ($\text{C}=\text{C}$), 1473, 1432, 1284, 1143, 989, 858, 779, and 736 cm^{-1}

MS (ES): Calculated for $[\text{C}_{14}\text{H}_{12}\text{Br}_2\text{N}_2\text{O}_2]$ m/z 397.9266. Found m/z 398.9414 $[\text{M}+\text{H}]^+$

2-Chloro-6-{4-[(6-chloropyridin-2-yl)oxy]phenoxy}pyridine (4.17).



Prepared by the method described above using hydroquinone (2.021 g, 18 mmol) 2,6-dichloropyridine (5.700 g, 38 mmol) and sodium hydride (1.104 g, 46 mmol) in *N*-methylpyrrolidinone (40 mL). Recrystallisation from hexane/ethyl acetate gave 2-chloro-6-{4-[(6-chloropyridin-2-yl)oxy]phenoxy}pyridine (6.322 g, 89%) as a white solid, m.p. 182–183 °C.

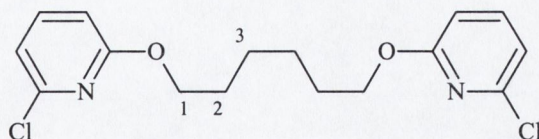
δ_{H} : 6.82 (2H, d, J 8.0, pyridine H3), 7.08 (2H, d, J 7.5, pyridine H5), 7.20 (4H, s, phenyl protons), 7.66 (1H, dd, $J_{3,4}$ 8.0, $J_{4,5}$ 7.5, pyridine H4) ppm.

δ_{C} : 108.8 (pyridine C3), 118.1 (pyridine C5), 121.7 (phenyl C2, C3, C5, and C6), 141.1 (pyridine C4), 148.6 (phenyl C1 and C4), 149.9 (pyridine C2) 162.6 (pyridine C6) ppm.

ν_{max} (nujol): 2926, 1735, 1587, 1508, 1459, 1421, 1376, 1263, 1254, 1191, 1157, 1104, 985, 923, 843, 789, 720, and 679 cm^{-1}

MS (ES): Calculated for $[\text{C}_{16}\text{H}_{10}\text{Cl}_2\text{N}_2\text{O}_2]$ m/z 333.0198. Found m/z 333.0207

2-Chloro-6-({6-[(6-chloropyridin-2-yl)oxy]hexyl}oxy)pyridine (4.23).



Prepared by the method described above using hexane-1,6-diol (2.303 g, 19.5 mmol) 2,6-dichloropyridine (6.062 g 41 mmol) and sodium hydride (1.210 g, 49 mmol) in *N*-methylpyrrolidinone (40 mL). Recrystallisation from ethyl acetate gave 2-chloro-6-({6-[(6-chloropyridin-2-yl)oxy]hexyl}oxy)pyridine (4.803 g, 72%) as a white solid, m.p. 104 – 105 °C.

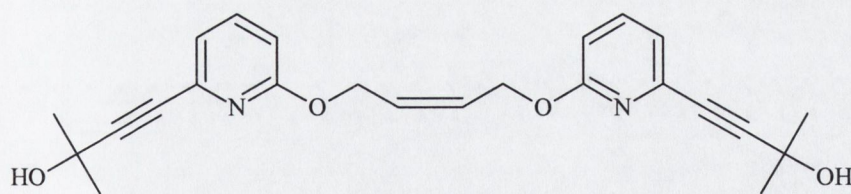
δ_{H} : 1.53 (4H, m, H3), 1.81 (4H, m, J 6.5, H2), 4.31 (4H, t, J 6.5, H1), 6.66 (2H, d, J 8.0, pyridine H3) 6.90 (2H, d, J 7.5, pyridine H5), 7.51 (2H, dd, $J_{3,4}$ 8.0, $J_{4,5}$ 7.5, pyridine H4) ppm.

δ_{C} : 25.3 (C3), 28.3 (C2), 66.1 (C1) 108.7 (pyridine C3), 115.6 (pyridine C5), 140.1 (pyridine C4), 147.9 (pyridine C2), 163.3 (pyridine C6) ppm.

ν_{max} (nujol): 2958, 2873, 1606, 1581, 1442, 1376, 1317, 1240, 1139, 1076, 1043, 968, 902, 862, 788 and 728 cm^{-1}

MS (ES): Calculated for $[\text{C}_{16}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_2]$ m/z 340.0745. Found m/z 341.0836 $[\text{M}+\text{H}]^+$

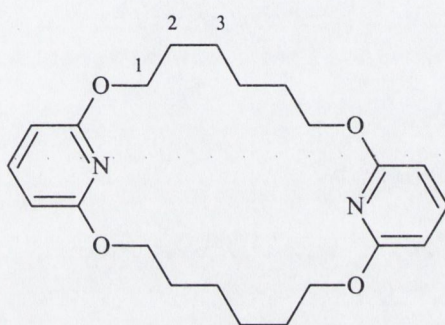
Attempted synthesis of 4-(6-({(Z)-4-[6-(3-Hydroxy-3-methyl-but-1-ynyl)-pyridin-2-yloxy]-but-2-enyloxy}-pyridin-2-yl)-2-methyl-but-3-yn-2-ol (4.19).



A mixture of 2-bromo-6-({4-[(6-bromopyridin-2-yl)oxy]but-2-enyl}oxy)pyridine (4.12) (200 mg, 0.5 mmol), copper iodide (3 mg, 0.015 mmol), bis(triphenylphosphine)palladium(II) chloride (4 mg, 0.005 mmol), triphenylphosphine (5 mg,

0.02 mmol) and 2-methylbut-3-yn-2-ol (168 mg, 2 mmol) in triethylamine (20 mL) was refluxed for 4 hours. The solvent was removed *in vacuo* and the crude product was dissolved in dichloromethane (20 mL). The dichloromethane solution was washed twice with brine (2×10 mL) and water (10 mL). The organic layer was dried over MgSO₄ and evaporated to dryness. Column chromatography on silica gel gave only recovered **4.12** (188 mg, 94%).

2,9,15,22-Tetraoxa-27,28-diaza-tricyclo[21.3.1.1*10,14*]octacosal-1(26),10,12,14 (28),23(27),24-hexaene (Macrocycle C-3).



To a rapidly-stirred suspension of sodium hydride (610 mg, 25 mmol) in *N*-methylpyrrolidinone (250 mL) was added hexane-1,6-diol (750 mg, 6.4 mmol) and the mixture was stirred at room temperature for 20 minutes. The mixture was heated to 80 °C and a solution of 2,6-dichloropyridine (942 mg, 6.4 mmol) in *N*-methylpyrrolidinone (100 mL) was added dropwise over 4 hours. The mixture was heated at 80 °C for 18 hours and then cooled to room temperature. Methanol (10 mL) was added and the solution was poured into ice-water (350 mL). The aqueous solution was extracted with dichloromethane (4×150 mL). The combined organic extracts were washed with brine (2×150 mL) and water (2×150 mL), dried over MgSO₄, and evaporated to afford a brown residue. Purification by column chromatography on silica gel using hexane/ethyl acetate (4:1) as eluent gave Macrocycle C-3 (37 mg, 1.5%) as a white solid, m.p. 142 – 144 °C.

δ_{H} : 1.48 (4H, m, H3), 1.83 (4H, m, *J* 7.5, H2), 4.34 (4H, t, *J* 7.5, H1), 6.27 (2H, d, *J* 8.0, pyridine H3 and H5), 7.51 (1H, dd, *J* 8.0, pyridine H4) ppm.

δ_C : 24.9 (C3), 28.5 (C2), 64.9 (C1) 100.8 (pyridine C3 and C5), 140.5 (pyridine C4), 162.0 (pyridine C2 and C6) ppm.

$\nu_{\max}$ (nujol): 2930, 1686, 1581, 1444, 1375, 1316, 1239, 1140, 1076, 1025, 901, 788 and 728 cm^{-1}

MS (ES): Calculated for $[\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_4]$ m/z 386.2206. Found m/z 387.2230 $[\text{M}+\text{H}]^+$ and m/z 409.2109 $[\text{M}+\text{Na}]^+$

References.

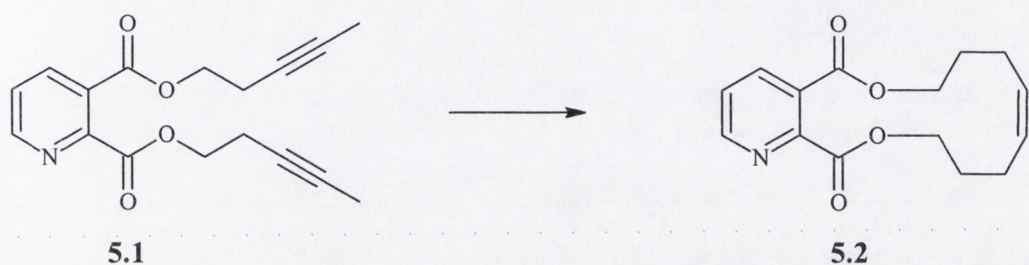
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Chapter 5

Synthesis of a novel pyridine macrocycle *via*
molybdenum-catalysed alkyne metathesis

5.1. Introduction.

Alkyne metathesis reactions catalysed by tungsten¹ or molybdenum² complexes have been shown to be a powerful means of effecting ring-closure to give macrocyclic products. Although the tungsten-catalysed reaction¹ was found to be ineffective for the metathesis of pyridine derivative **5.1**, this compound was successfully converted to the cyclic derivative **5.2** using a molybdenum catalyst² (Scheme 5.1).

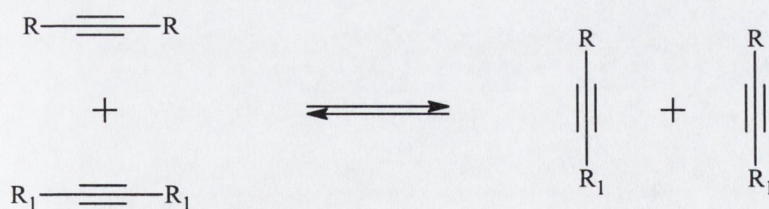


Scheme 5.1

It was therefore of interest to apply the molybdenum-catalysed metathesis reaction to the synthesis of a macrocyclic pyridine derivative. In the present chapter the synthesis of a macrocyclic pyridine *via* alkyne metathesis is described.

5.1.1. Alkyne metathesis reactions.

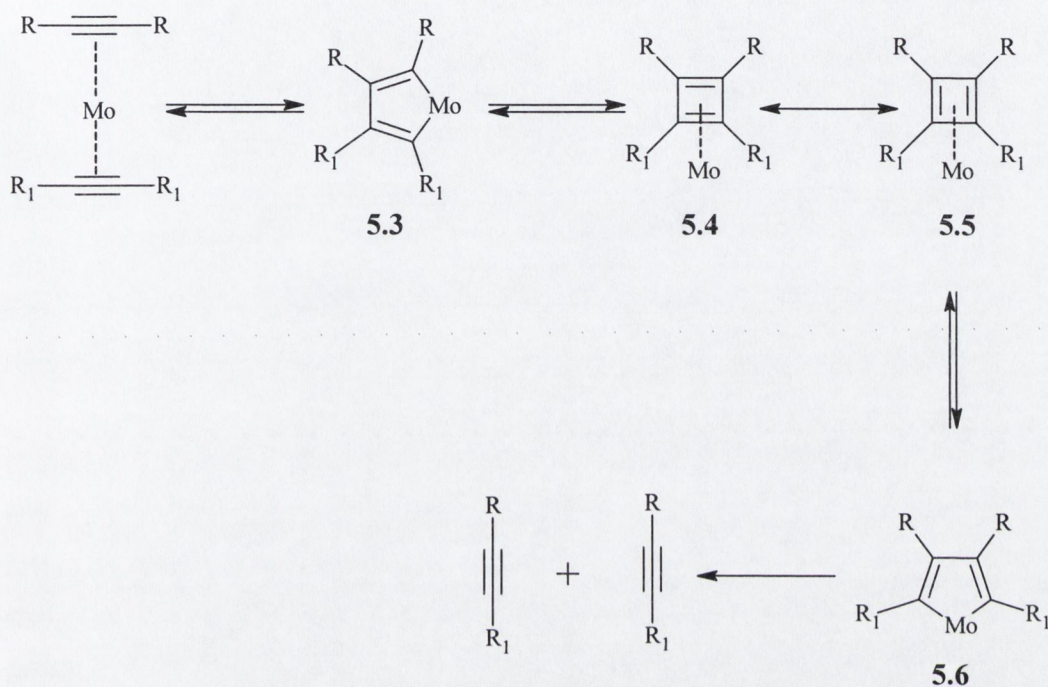
When internal alkynes are treated with molybdenum or tungsten catalysts they undergo a metathesis reaction to give new alkynes³ (Scheme 5.2).



Scheme 5.2

Although the metathesis reaction is successful for internal alkynes, terminal alkynes do not give the reaction.³

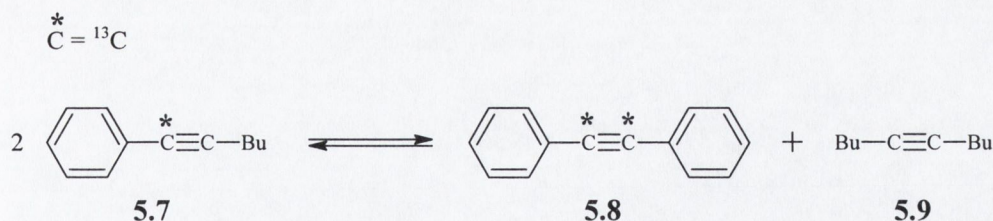
Kaneta *et al.*⁴ studied the molybdenum-catalysed metathesis reaction and proposed a mechanism in which the exchange reaction occurs *via* the formation of a molybdacyclopentadiene species **5.3** (Scheme 5.3).



Scheme 5.3

Elimination of molybdenum from the molybdacyclopentadiene species **5.3** gives the molybdenum cyclobutadiene complex **5.4** which isomerises to the cyclobutadiene complex **5.5**. Re-insertion of molybdenum into cyclobutadiene **5.5** gives the new molybdacyclopentadiene **5.6** which is a regioisomer of molybdacyclopentadiene **5.3**. Subsequent collapse of this new molybdacyclopentadiene complex **5.6** gives the metathesis products.

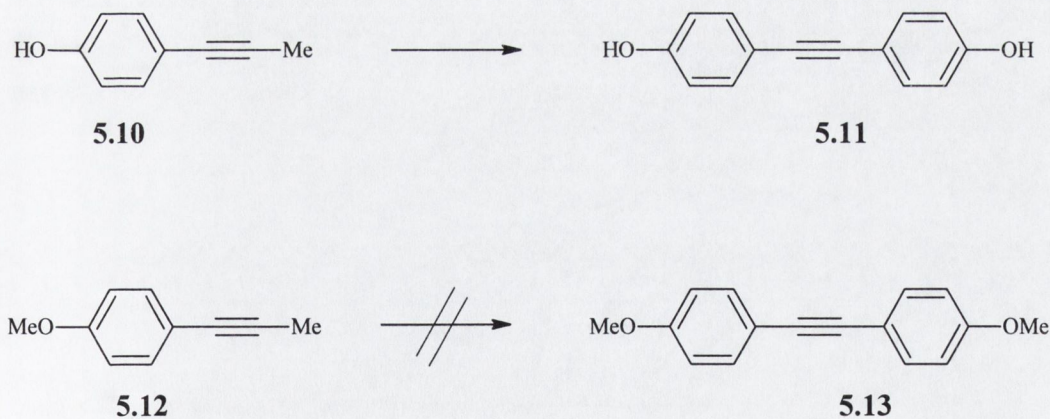
Mortreux and Petit⁵ demonstrated that the metathesis reaction occurs *via* cleavage of the triple bond rather than by a transalkylation process using hex-1-ynylbenzene (**5.7**) enriched with ^{13}C at the C1 carbon of the acetylene moiety (Scheme 5.4).



Scheme 5.4

The products of this reaction consisted of recovered hex-1-ynylbenzene (5.7) and equal amounts of diphenylacetylene (5.8) and 5-decyne (5.9). Analysis of the products by ${}^{13}\text{C}$ NMR spectroscopy showed that the ${}^{13}\text{C}$ labelled carbons were incorporated in the starting material 5.7 and diphenylacetylene (5.8). This result indicates that the reaction occurred *via* scission of the triple bond rather than by a transalkylation process since the latter process would have led to a statistical distribution of the ${}^{13}\text{C}$ label among the three acetylenic products.⁵

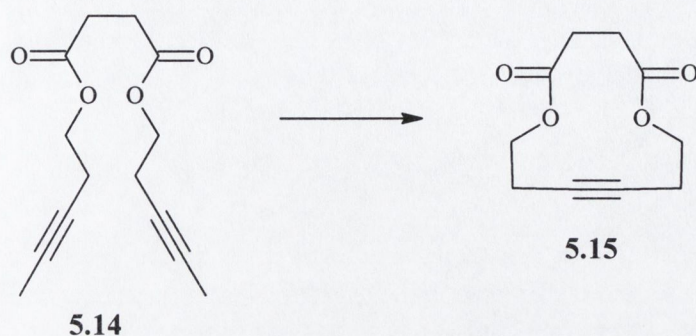
A mixture of molybdenum hexacarbonyl and a phenol have been found to be an effective catalyst for the metathesis reaction.⁴⁻⁶ Although its role is unclear, it has been shown that the phenol is necessary for the reaction to proceed.⁴ Kaneta *et al.* examined the role of the phenol using a series of alkynes bearing hydroxyphenyl groups.⁴ Treatment of *p*-hydroxyphenylpropyne (5.10) with $\text{Mo}(\text{CO})_6$ gave the metathesis product 5.11 but the reaction failed for *p*-methoxyphenylpropyne (5.12) in the absence of phenol (Scheme 5.5).



Scheme 5.5

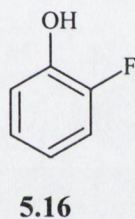
However, treatment of **5.12** with Mo(CO)_6 in the presence of phenol gave the expected metathesis product **5.13**.

Grela and Ignatowska⁶ evaluated a number of substituted phenols as additives in the molybdenum-catalysed metathesis of diacetylene **5.14** (Scheme 5.6).

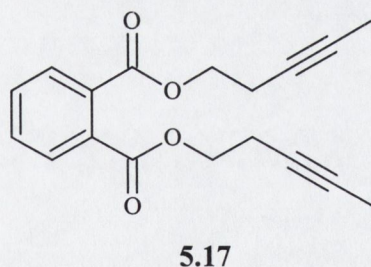


Scheme 5.6

Of the various phenol examined, 2-fluorophenol (**5.16**) was found to be the most active.



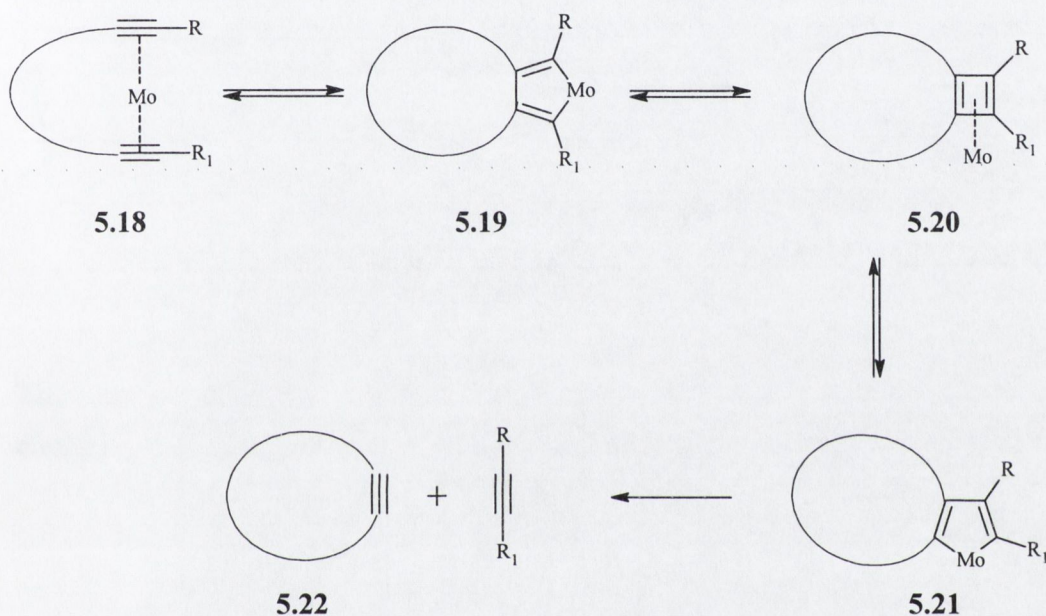
The use of **5.16** and Mo(CO)_6 as catalyst gave higher yields than the other phenols examined. In addition, this catalyst system was found to convert diynes (*e.g.* **5.17**) previously found to be incompatible with Mo(CO)_6 /phenol systems.⁶



5.1.2. Applications of alkyne metathesis to macrocycle synthesis.

Alkyne metathesis reactions have proved to be extremely efficient as a means of effecting ring-closure in the synthesis of macrocyclic compounds.⁷ Fürstner *et al.* have used these reactions to prepare a large number of macrocyclic compounds in high (70 – 90%) yields.^{1,7}

The high yield of macrocyclic products from these metathesis reactions is presumably due to the operation of a template effect with molybdenum acting as the template (Scheme 5.7).

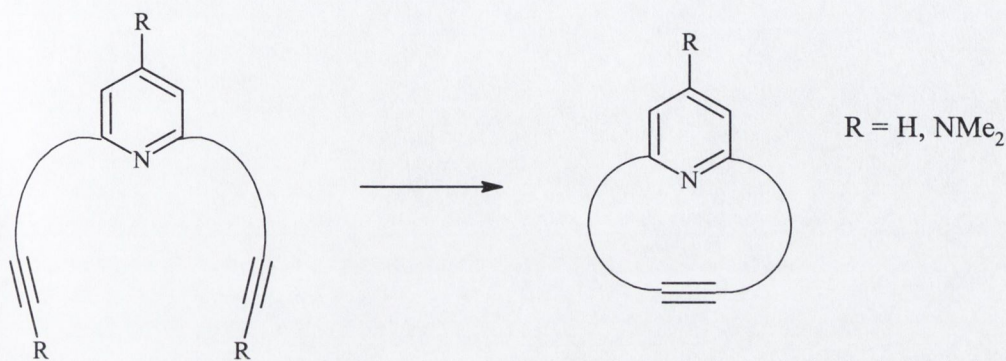


Scheme 5.7

After the formation of the molybdacyclopentadiene species **5.19**, the chain terminals are tethered in close proximity to each other throughout the reaction leading to high yields of the cyclic product **5.22**. The alkyne metathesis reaction therefore appeared to be an attractive means of obtaining a macrocyclic pyridine derivative. The following section describes the application of this methodology to the synthesis of a macrocyclic pyridine.

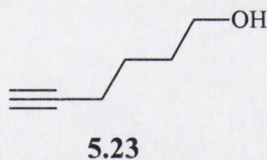
5.2. Results and discussion.

The high yields of macrocyclic products reported by Fürstner¹ and Grela⁶ for alkyne metathesis reactions prompted an investigation of the possibility of applying this methodology to the synthesis of macrocyclic pyridine derivatives (Scheme 5.8).



Scheme 5.8

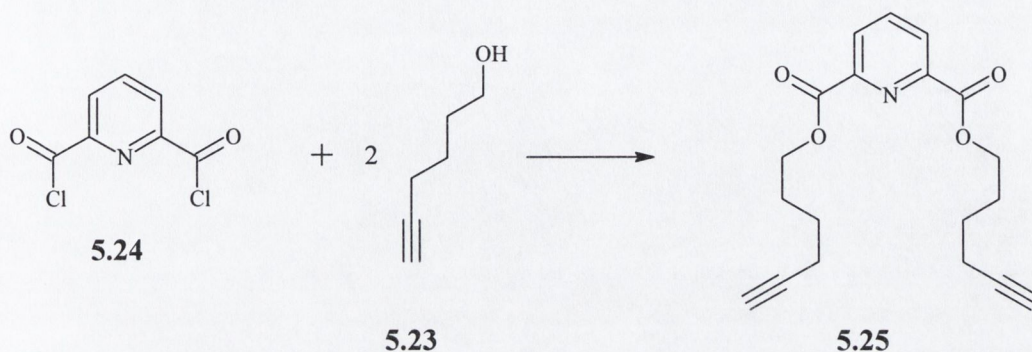
The commercially-available acetylenic alcohol hex-5-yn-1-ol (**5.23**) was considered to be a suitable starting material for these experiments.



In addition to providing a good nucleophile for reaction with electrophilic species, the hydroxyl group of alkynol **5.23** could be converted to a variety of other functional groups (e. g. halides, tosylates, carbonyl derivatives) and the terminal acetylene moiety could be alkylated⁸ or arylated⁹ to provide the required internal alkyne.

5.2.1. Synthesis of dihex-5-ynyl pyridine-2,6-dicarboxylate (5.25).

Dihex-5-ynyl pyridine-2,6-dicarboxylate (**5.25**) was prepared by treatment of pyridine 2,6-dicarbonyl dichloride (**5.24**) with two equivalents of hex-5-yn-1-ol (**5.23**) in pyridine solution (Scheme 5.2).



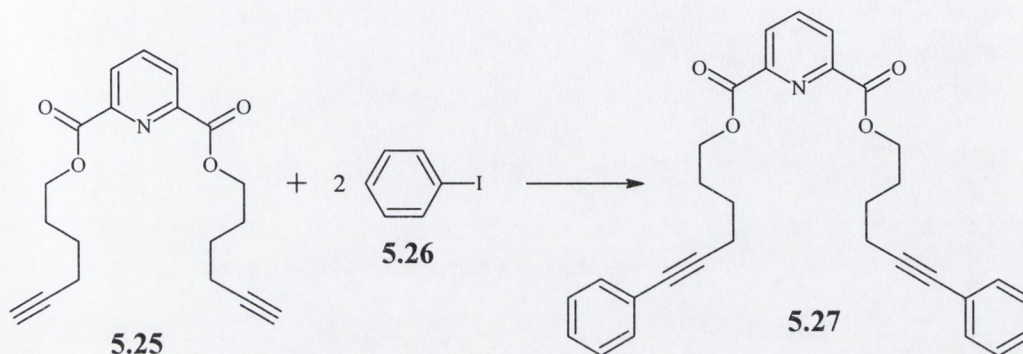
Reagents and conditions: pyridine, r.t., 2 hrs.

Scheme 5.9

In the ^1H NMR spectrum of the diester **5.25** the protons at the 3 and 5 positions of the pyridine ring appear as a doublet at δ 8.28. The proton at the 4 position appears as a double doublet at δ 8.01. The spectrum shows four signals for the protons of the alkyl chains. The signal from the protons of the oxygen-bearing methylene groups is at δ 4.45. The methylene protons adjacent to the acetylene moieties resonate as a triplet at δ 2.29. This signal shows further splitting from coupling of these protons with the terminal acetylene protons with a coupling constant $J = 2.7$ Hz. The signal from the acetylene protons appears at δ 1.98 and is subsumed beneath the signal from the methylene protons at the 2 positions of the alkyl chains. The protons at the 3 position of the alkyl chains appear as a quintet at δ 1.71.

5.2.2. Synthesis of pyridine-2,6-dicarboxylic acid bis-(6-phenyl-hex-5-ynyl) ester (**5.27**).

The terminal acetylene groups of diester **5.25** were converted to the internal alkyne required for the metathesis reaction by Sonogashira reaction⁹ of diester **5.25** with iodobenzene (**5.26**) (Scheme 5.10).



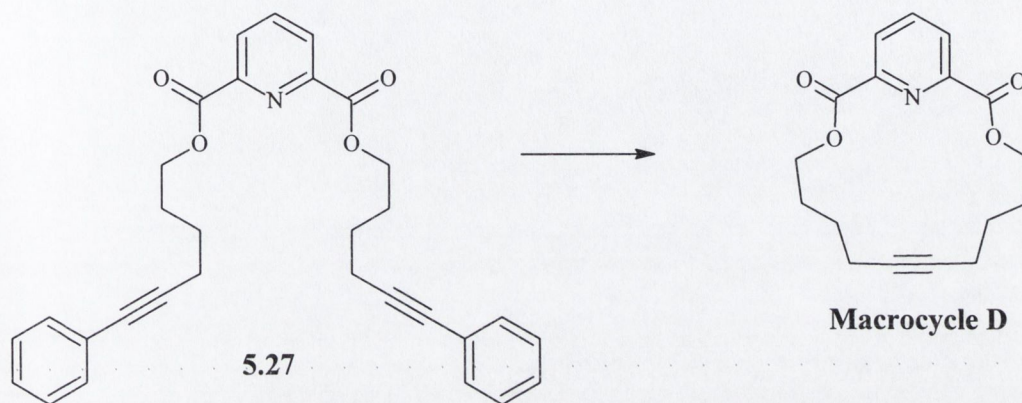
Reagents and conditions: Pd(PPh₃)₂Cl₂ (1 mol %)/CuI (8 mol %), Et₃N, reflux 4hrs.

Scheme 5.10

In the ¹H NMR spectrum of the substituted acetylene **5.27** the phenyl protons *ortho* to the acetylene groups appear as a multiplet at δ 7.41. The protons at the *meta* and *para* positions resonate as a multiplet at δ 7.29. In the spectrum of the starting material **5.25** the signal from the methylene groups at the 2 position of the alkyl chains appears as a distorted multiplet due to coincidence of the signal from the terminal acetylene protons. This combined signal integrates for six protons. In the spectrum of the product **5.27** these methylene protons appear as a symmetrical quintet at δ 2.04. In addition, the signal from the methylene groups adjacent to the acetylene moieties no longer shows the splitting from coupling to the acetylene protons.

5.2.3. Synthesis of 3,14-dioxa-20-azabicyclo[14.3.1]icosa-1(20),16,18-trien-8-yne-2,15-dione (Macrocycle D).

Treatment of diacetylene **5.27** with Mo(CO)_6 and 2-fluorophenol gave the novel pyridine macrocycle 3,14-dioxa-20-azabicyclo[14.3.1]icosa-1(20),16,18-trien-8-yne-2,15-dione (Macrocycle D) in 48% yield (Scheme 5.11).



Reagents and conditions: Mo(CO)_6 (10 mol %)/2-fluorophenol (1 equiv.), PhCl, reflux 4 hrs.

Scheme 5.11

In the ^1H NMR spectrum of Macrocycle D the protons at the 3 and 5 positions of the pyridine ring resonate as a doublet at δ 8.34. The proton at the 4 position appears as a double doublet at δ 8.02. The spectrum shows four signals for the alkyl ring protons. The protons of the oxygen-bearing methylene groups resonate as a triplet at δ 4.39. The signal from the methylene protons adjacent to the acetylene moiety is at δ 2.25. The central two methylene groups appear as multiplets at δ 2.03 and δ 1.84 with the methylene group closest to the oxygen at lowest field.

The ^{13}C NMR of Macrocycle D shows nine carbon environments. The carbonyl carbons appear at δ 164.7. The carbons at the 2 and 6 positions resonate at δ 147.8. The pyridine carbon at the 4 position is at δ 137.8 and the carbons at the 3 and 5 positions appear at δ 127.2. The signal from the acetylene carbons is at δ 80.4. The oxygen-bearing carbons appear at δ 65.4 and the carbons adjacent to the acetylene

group are at δ 27.0. The central two methylene carbons resonate at δ 26.5 and δ 18.0 with the methylene carbon closest to oxygen at lowest field.

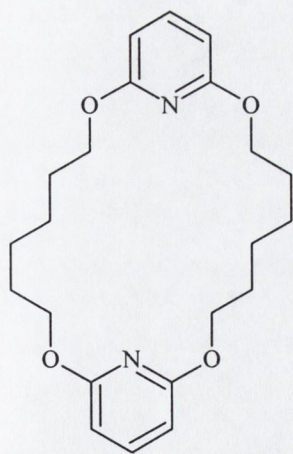
The macrocycle was identified as the monopyridine species from its mass spectrum which shows a peak at 324.1226 from the $[M+Na]^+$ ion.

Conclusions.

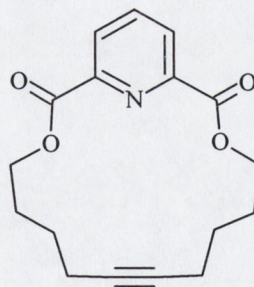
On the basis of the results obtained it would appear that the synthesis and (possibly more importantly) the purification of 2,6-disubstituted 4-dimethylaminopyridine derivatives is considerably more difficult than the preparation and isolation of the corresponding pyridines. Vedejs and Chen have also reported difficulties in the purification of 4-dimethylaminopyridine derivatives.¹⁰

The reluctance of DMAP derivatives to undergo the substitution reactions normally associated with pyridines¹¹ may be rationalised in terms of mesomeric donation of electrons by the dimethylamino group into the pyridine ring which renders the carbon atoms of the ring relatively inert to nucleophilic substitution. However, the behaviour of the dilithiated DMAP derivatives (which should themselves be nucleophilic) is less easily understood. While it is tempting to postulate a deactivation of the pyridine ring after the initial reaction of the dilithiated pyridine with the first equivalent of the electrophile, the results obtained from the reactions of dilithiated DMAP with benzoyl chlorides (see Chapter 2) suggest that this is not the case since these reactions routinely gave the disubstituted DMAP derivative.

Although attempts to prepare macrocyclic pyridine derivatives *via* palladium- or copper-mediated reactions proved unsuccessful, two novel pyridine macrocycles were synthesised *via* etherification and alkyne metathesis reactions (Figure 5.1).



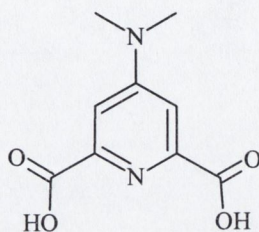
Macrocycle C-3



Macrocycle D

Figure 5.1

The synthesis of Macrocycle D *via* alkyne metathesis is particularly encouraging. The relatively facile synthesis of this macrocycle provides a model for the synthesis of more elaborate structures. For example, the synthesis of 4-dimethylaminopyridine-2,6-dicarboxylic acid (**5.28**) has been reported¹² and this compound would provide a suitable precursor for the construction of the DMAP analogue of Macrocycle D.

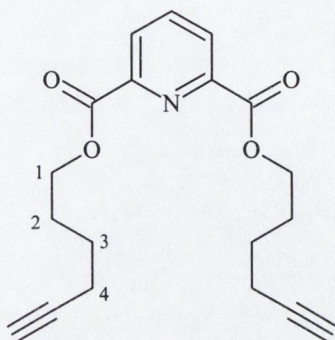


5.28

Alkyne metathesis would appear to be an extremely efficient means of preparing macrocyclic compounds. It may therefore be expected that the application of the alkyne metathesis reaction to compounds of greater structural diversity than those studied should provide access to a class of interesting macrocyclic structures.

5.3. Experimental.

Dihex-5-ynyl pyridine-2,6-dicarboxylate (5.25).



Pyridine-2,6-dicarbonyl dichloride (452 mg, 2.2 mmol) was added in small portions to a solution of hex-5-yn-1-ol (542 mg, 5.5 mmol) in dry pyridine (15 mL) at 0 °C. The solution was allowed to rise to room temperature and stirred for a further 2 hours. The mixture was poured into ice-water (50 mL) and the precipitated solid was isolated by vacuum filtration. The precipitate was dissolved in diethyl ether (20 mL) and the solution was washed with saturated sodium carbonate solution (2×15 mL) and water (15 mL). The organic layer was dried over MgSO₄ and evaporated to dryness. Recrystallisation from aqueous ethanol gave dihex-5-ynyl pyridine-2,6-dicarboxylate (411 mg, 57%) as a white solid, m. p. 55 – 57 °C.

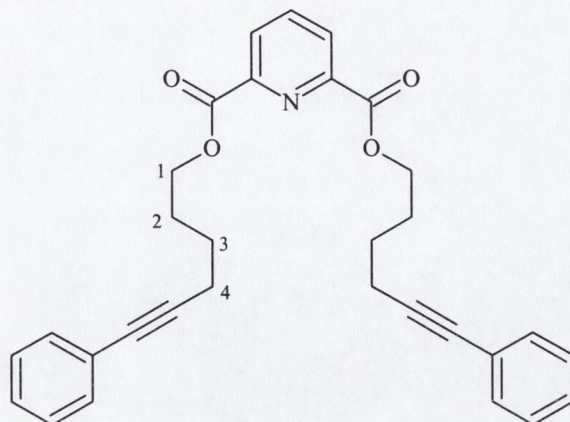
δ_{H} : 1.71 (4H, quin, J 6.8, H3), 1.97 (6H, m, J 6.8, H2 and C≡CH), 2.30 (4H, m, J 6.8, H4), 4.45 (4H, t, J 6.8, H1) 8.01 (1H, dd, J 8.2, pyridine C4), 8.28 (2H, d, J 8.2, pyridine C3 and C5) ppm.

δ_{C} : 17.7 (C3), 24.5 (C2), 27.1 (C4), 65.2 (C1) 68.4 (C≡CH) 83.3 (C≡CH) 127.4 (pyridine C3 and C5), 137.8 (pyridine C4), 148.0 (pyridine C2 and C6), 164.1 (C=O) ppm.

ν_{max} (nujol): 3262 (C≡C–H), 2921, 2123 (C≡C), 1729 (C=O), 1585, 1456, 1373, 1315, 1241, 1133, 1079, 952, 850, 752, 721, and 655 cm^{–1}

MS (ES): Calculated for [C₁₀H₂₁NO₄] m/z 327.1368. Found m/z 328.1516 [M+H]⁺ and m/z 350.1368 [M+Na]⁺

Pyridine-2,6-dicarboxylic acid bis-(6-phenyl-hex-5-ynyl) ester (5.27).



A mixture of dihex-5-ynyl pyridine-2,6-dicarboxylate (204 mg, 0.6 mmol), iodobenzene (511 mg, 2.4 mmol), bis(triphenylphosphine)palladium(II) chloride (5 mg, 0.007 mmol), and copper(I) iodide (10 mg, 0.05 mmol) in dry triethylamine (10 mL) was refluxed for 4 hours. The solution was cooled to room temperature and the precipitated triethylamine hydroiodide was filtered off. The filtrate was concentrated *in vacuo* and dissolved in dichloromethane (10 mL). The dichloromethane solution was washed with brine (2×10 mL) and water (10 mL), dried over MgSO_4 , and evaporated to afford a brown residue. Purification by column chromatography on silica gel using dichloromethane as eluent gave pyridine-2,6-dicarboxylic acid bis-(6-phenyl-hex-5-ynyl) ester (272 mg, 91%) as a white solid, m.p. 70 – 72 °C.

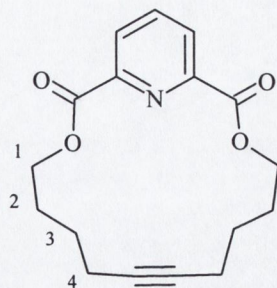
δ_{H} : 1.80 (4H, quin, J 6.8, H3), 2.04 (4H, quin, J 6.8, H2), 2.52 (4H, t, J 6.8, H4), 4.50 (4H, t, J 6.8, H1) 7.29 (phenyl H4, H3 and H5), 7.40 (phenyl H2 and H6) 8.00 (1H, dd, J 7.5, pyridine H4), 8.28 (2H, d, J 7.5, pyridine H3 and H5) ppm.

δ_{C} : 18.7 (C3), 24.8 (C2), 27.3 (C4), 65.4 (C1), 80.7 ($\text{C}\equiv\text{CPh}$), 83.3 ($\text{C}\equiv\text{CPh}$), 123.5 (phenyl C4), 127.2 (pyridine C3 and C5), 127.4 (phenyl C3 and C5), 127.8 (phenyl C2 and C6), 131.1 (phenyl C1), 148.7 (pyridine C2 and C6), 164.2 (C=O) ppm.

ν_{max} (nujol): 2925, 2214 ($\text{C}\equiv\text{C}$), 1730 (C=O), 1595, 1579, 1511, 1469, 1377, 1290, 1256, 1172, 1106, 1014, 803, 754, and 691 cm^{-1}

MS (ES): Calculated for $[\text{C}_{31}\text{H}_{29}\text{NO}_4]$ m/z 479.2096. Found m/z 502.3144 $[\text{M}+\text{Na}]^+$

**3,14-Dioxa-20-azabicyclo[14.3.1]icosa-1(20),16,18-trien-8-yne-2,15-dione
(Macrocycle D).**



A solution of pyridine-2,6-dicarboxylic acid bis-(6-phenyl-hex-5-ynyl) ester (204 mg, 0.4 mmol), Mo(CO)_6 (11 mg, 0.04 mmol), and 2-fluorophenol (48 mg, 0.4 mmol) in chlorobenzene (20 mL) was refluxed for 4 hours. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel using ether/hexane (4:1) as eluent to afford 3,14-dioxa-20-azabicyclo[14.3.1]icosa-1(20),16,18-trien-8-yne-2,15-dione (62 mg, 48%) as a white solid, m.p. 112 – 113 °C.

δ_{H} : 1.84 (4H, quin, $J_{2,3}$ 5.5, $J_{3,4}$ 6.0, H3), 2.03 (4H, m, J 5.5, H2), 2.25 (4H, m, J 6.0, H4), 4.39 (4H, t, J 5.5, H1) 8.01 (1H, dd, J 8.0, pyridine C4), 8.28 (2H, d, J 8.0, pyridine C3 and C5) ppm.

δ_{C} : 18.1 (C3), 26.5 (C2), 27.0 (C4), 65.4 (C1) 80.4 ($\text{C}\equiv\text{C}$) 127.2 (pyridine C3 and C5), 137.8 (pyridine C4), 147.8 (pyridine C2 and C6) 164.7 ($\text{C}=\text{O}$) ppm.

ν_{max} (CCl_4 smear): 2956, 2854, 1774, 1712 ($\text{C}=\text{O}$), 1587, 1380, 1324, 1245, 1153, 1074, 993, 844 and 748 cm^{-1}

MS (ES): Calculated for $[\text{C}_{17}\text{H}_{29}\text{NO}_4]$ m/z 301.1212. Found m/z 324.1226 $[\text{M}+\text{Na}]^+$

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