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A Biomimetic Approach to the Pyoverdinin Chromophore

by

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A Doctoral Thesis Submitted in partial fulfilment of the
requirements

For award of Doctor of Philosophy of Loughborough
University

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Abstract

Pyoverdins are siderophores which chelate with ferric ions forming a ligand complex. Pyoverdins are excreted from bacteria such as *Pseudomonas*, for example, *Pseudomonas fluorescens*, when grown in iron-deficient conditions, to scavenge for iron. Although, different species of *Pseudomonas* produce different pyoverdins with various constituents in their amino acid chains, they all share a common chromophore structure within the various natural siderophores. The possible biosynthesis of the pyoverdins chromophore is discussed.

Herein, a biomimetic synthesis of a model of the chromophore unit based on an oxidative cyclisation pathway was carried. Hypervalent iodine oxidation of a phenol-substituted tetrahydropyrimidine, and subsequent dehydrogenation, led to the pyrimidoquinoline ring system of the pyoverdin chromophore. Synthesis of the 7-membered diazepinoquinoline analogue was also accomplished, and oxidative cyclisation of the 5-membered cyclic amidine was achieved. With the success of the biomimetic synthesis of these models, cyclic amidines were constructed as oxidative cyclisation substrates having the catechol system, the C-terminus and the N-terminus of the pyoverdin chromophore.

Acknowledgements

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Abbreviations

Acetonitrile	MeCN
Acetyl	Ac
Allyloxycarbonyl	Aloc
Benzyl Bromide	BnBr
Benzyl group	Bn
Benzyloxycarbonyl	Cbz
<i>tert</i> -Butyl	tBu
<i>tert</i> -Butyloxycarbonyl	Boc
<i>Bis</i> -(trifluoroacetoxy)iodobenzene	BTIB
Diacetoxy iodobenzene	DAIB
1,8-Diazabicyclo[5.4.0]undec-7-ene	DBU
2,3-Dichloro-5,6-dicyanobenzoquinone	DDQ
Dichloromethane	DCM
<i>N,N</i> -Dicyclohexylcarbodiimide	DCC
Dihydroxyphenylalanine	DOPA
Diisopropylethylamine (Hünig's base)	DIPEA
Dimethylformamide	DMF
Dimethylsulfoxide	DMSO
Ethanol	EtOH
Ethyl Acetate	EtOAc
Iodobenzene	PhI
Methanol	MeOH
Methyl trifluoromethanesulfonate	Methyl triflate, TfOMe
<i>N</i> -Bromosuccinimide	NBS
<i>N</i> -Chlorosuccinimide	NCS
<i>N</i> -Hydroxysuccinimide	HOSu
Oxidative Cyclisation	O.C
Phthalyl	Phth
Polyphenol Oxidase	PPO
Pyrrolyl	Pyr
Tetrahydrofuran	THF
Triethylamine	TEA

Toluenesulfonyl

(Trichloroethoxy)carbonyl

Trifluoroacetic acid

Trifluoromethanesulfonylazide

Trifluoromethanesulfonic acid

Ts

Troc

TFA

Triflyl azide, TfN₃

Triflic acid, TFSA

1.0 Introduction – Pseudodipeptides With Cyclic Amidines

Replacement of the amide bonds in biologically active peptides is recognized as a valid strategy for either the inhibition of proteolytic enzymes or the development of agonists and antagonists at peptide receptors.¹ Examples of amide bond replacement in many peptides, such as ACE (angiotensin converting enzyme) substrates, enkephalins, CCK-4- (cholecystokinin) and insect neurokinins, have been reported.² Since the relationship between the amide and amidine functional groups was identified,³ work on the pseudopeptide cyclic amidines, e.g. 2-imidazolines (4,5-dihydroimidazoles) or related derivatives, has been reported (Figure 1) from the Jones group. This peptide bond replacement seems likely to prevent proteolytic degradation when a typical amide peptide bond is substituted with a basic heterocyclic structure.⁴

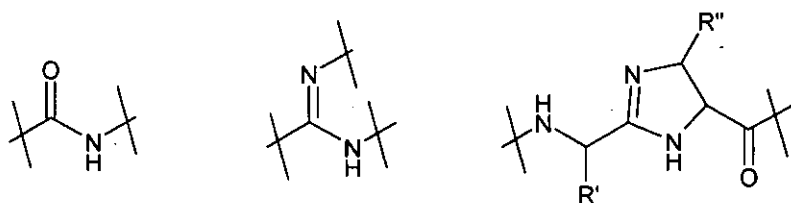


Figure 1.

The pseudopeptide 2-imidazoline is the first member of a possible series of cyclic pseudopeptide amidines. Extension of the work with 5-membered ring imidazolines to the 6-membered cyclic ring system tetrahydropyrimidine was also of interest. Attention on the tetrahydropyrimidine homologue as a peptide bond isostere was enhanced by the discovery of a group of natural compounds which contain a cyclic amidine structure. It had been found that a group of bacterial siderophores, pyoverdins,⁵ e.g. Pf CCM 2798 (**1**), excreted from microorganisms often contain a tetrahydropyrimidine amino acid component and also contain a modified cyclic amidine derivative as a chromophore (Figure 2).

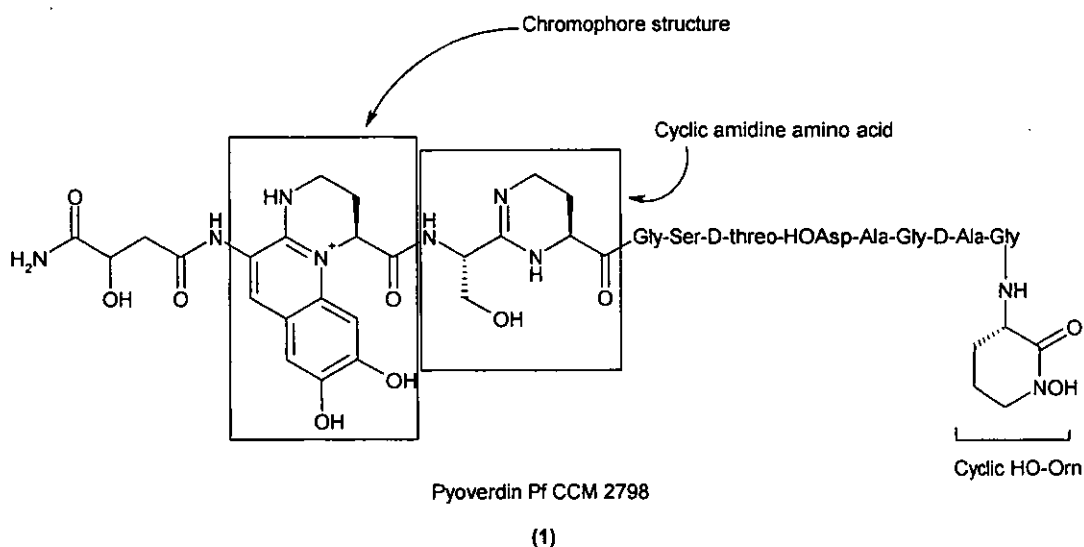


Figure 2.

1.1 What Are Pyoverdins?

To maintain a sufficient supply of iron, bacteria in soil need to excrete as scavengers low molecular weight compounds with a high complexation constant for iron(III), Fe^{3+} . Due to the low solubility of its various oxide hydrates, the concentration of free Fe^{3+} in the soil is at best about 10^{-17} mol/L at pH values around 7. Complexing ligands play an important role for the redox processes in many biological systems, and in the case of iron above, the redox potential between two oxidation states, Fe^{2+} and Fe^{3+} , can be strongly influenced by the presence of complexing ligands. The complexing ligands associated with the ferric ions are known as “siderophores”. These siderophores are usually excreted by microorganisms, such as the fluorescent bacterium *Pseudomonas fluorescens* if grown under the iron deficient conditions.⁵ All the *Pseudomonas* species produce pseudobactins commonly called pyoverdins. According to *Bergey's Manual of Systematic Bacteriology*, the *Pseudomonas* species producing pyoverdins include *P. aeruginosa*, *P. chlororaphis*, *P. fluorescens*, *P. putida* and *P. syringae*⁶ and these bacteria can be found in the rhizosphere of some plants and are also called plant growth promoting rhizobacteria (PGPR). Many more siderophores from *Pseudomonas* strains have been discovered,

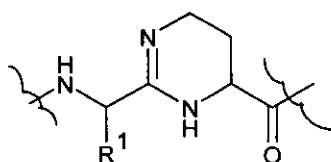
structurally identified through mass spectrometry⁷ and nuclear magnetic resonance spectroscopy⁸ and their specific physicochemical functionality also investigated throughout the past decade.⁹

Pyoverdins have a common structural feature which is a dihydroxyquinoline nucleus responsible for the yellowish-green fluorescence. It is one of the three bidentate binding sites for Fe³⁺; the other two necessary to form an octahedral complex are contained in a peptide chain attached to the quinoline chromophore. Pyoverdins contain up to 12 amino acid chains linked together (both D and L). The other binding sites are either two hydroxamate units derived from ornithine (Orn), or one hydroxamate and one α -hydroxycarboxylate. The various fluorescent *Pseudomonas spp.* produce pyoverdins differing in their peptide chains, which are responsible for recognition at the cell surface. Siderophores usually scavenge extracellular iron(III), solubilize it and transport it inside cells through the cell membrane.

As a fluorescent pigment, pyoverdin represents a ready marker for bacterial differences and, as a siderophore, it performs an important physiological function in satisfying the absolute iron requirement of these strictly aerobic bacteria. Although there are over 40 different pyoverdins, each is characterized with their own particular peptide part. Each pyoverdin is produced from a very specific strain of *Pseudomonas* and usually acts as an iron transporter for its own strain of bacterium with high specificity and efficiency. The strong chelating properties of siderophores exert an antagonist action against plant parasites which are no longer able to acquire essential supplies of iron. In some instances, cross-reactivity occurs, for example, the strains *Pseudomonas aeruginosa* ATCC15692 and *Pseudomonas fluorescens* ATCC 13525 give different pyoverdins but either pyoverdin can be recognised with high efficiency due to their structurally closely related peptide chains.¹⁰ Some of the siderophore-mediated iron transport systems in *Pseudomonas* could also potentially function as antibiotics.

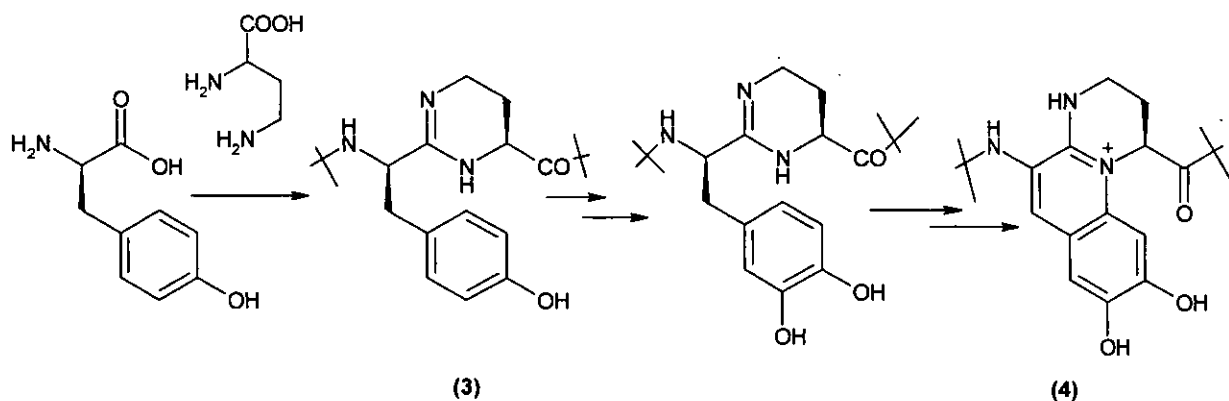
1.1.1 Example Of Siderophores – *Pseudomonas fluorescens*

One of the typical siderophores is pyoverdinin Pf CCM 2798 (1),⁵ produced from the strain of *Pseudomonas fluorescens* CCM 2798. It is a Gram-negative bacterium which belongs to the fluorescent *Pseudomonas* biotype B.¹¹ This pyoverdinin is the siderophore of the microorganism and shown to be an antagonist of the growth of *Pseudomonas aeruginosa* ATCC 15692. Pf CCM 298 comprises a fluorescent chromophore, a cyclic amidine tetrahydropyrimidine amino acid (THP) (2) and some other peptide residues as a long chain including 3 glycines, 2 alanines, 1 serine, 1 cyclic N^{δ} -hydroxyornithine and 1 β -threo-hydroxyaspartic acid.^{5b} Furthermore, the fluorescent chromophore (4) in the pyoverdinin could be derived biosynthetically (Scheme 1) from an oxidative cyclisation of cyclic amidine ferribactin unit (3), based on a tyrosine-derived residue. The detail of this possible biogenesis is discussed in the next chapter.



Tetrahydropyrimidine (THP)

(2)

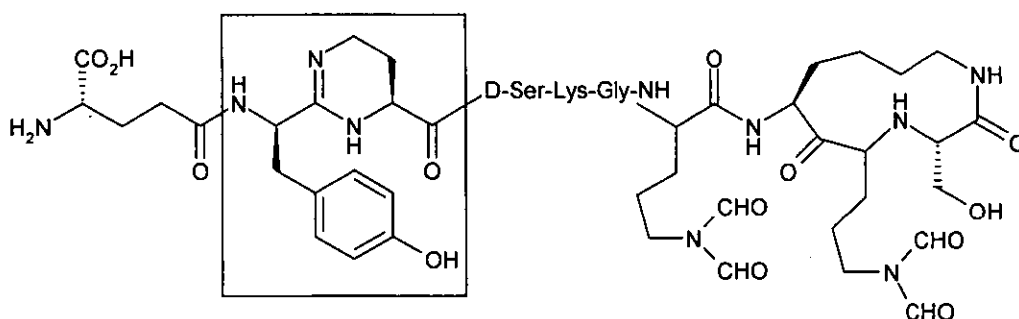


(3)

(4)

Scheme 1.

Another group of products of *Pseudomonas fluorescens* with related characteristics are the ferribactins, e.g. ferribactin ATCC 13525 (5), which are co-occurring compounds with pyoverdins that are produced from the bacterium *Pseudomonas fluorescens* ATCC 13525 (Figure 3). The ferribactins also contain the tetrahydropyrimidine unit, presumably derived from 2,4-diaminobutyric acid and tyrosine, but lack the chromophore structure, and are plausible biogenetic precursors to the pyoverdinin chromophore.^{12, 13} Although the ferribactins do not contain the chromophore, they do also chelate iron(III). Gould's studies¹² have shown by incorporation that tyrosine acted as a precursor to pseudobactin, another siderophore produced. Study of the siderophores is of potential therapeutic significance since they are essential growth factors for their parent organisms, and several strains of *Pseudomonas* are severe human pathogens.



Ferribactin ATCC 13525

(5)

Figure 3.

1.2 The Aeruginosins

In addition to the fluorescent chromophore structure of pyoverdins, probably derived from oxidative cyclisation of a cyclic amidine, novel bicyclic octahydroindole amino acids as part of the aeruginosins have been isolated from natural sources. Aeruginosins 98-A (6) (Figure 4) form a group of peptidic thrombin / trypsin inhibitors isolated from blue-green algae,^{12, 14} which consist of linear peptides that contain the novel

octahydroindole amino acid which may also be derived biosynthetically from an oxidative cyclisation of a tyrosine residue related to the oxidative cyclisation that produces the pyoverdine chromophore.

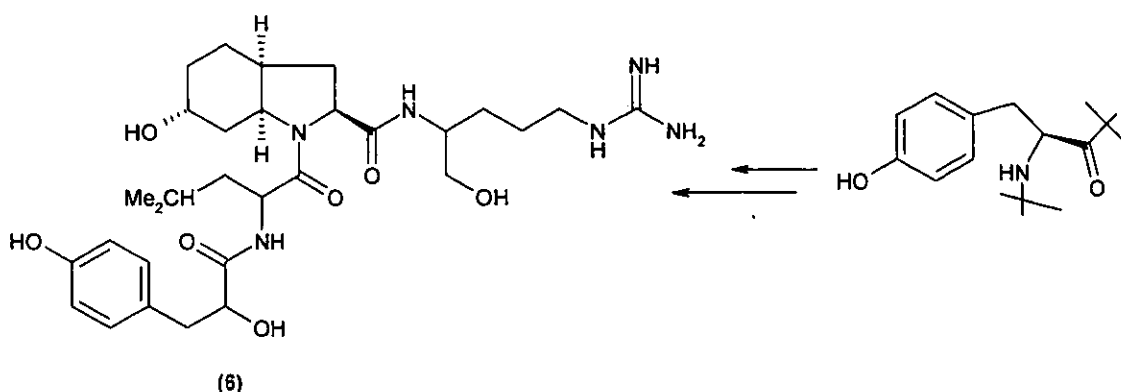


Figure 4.

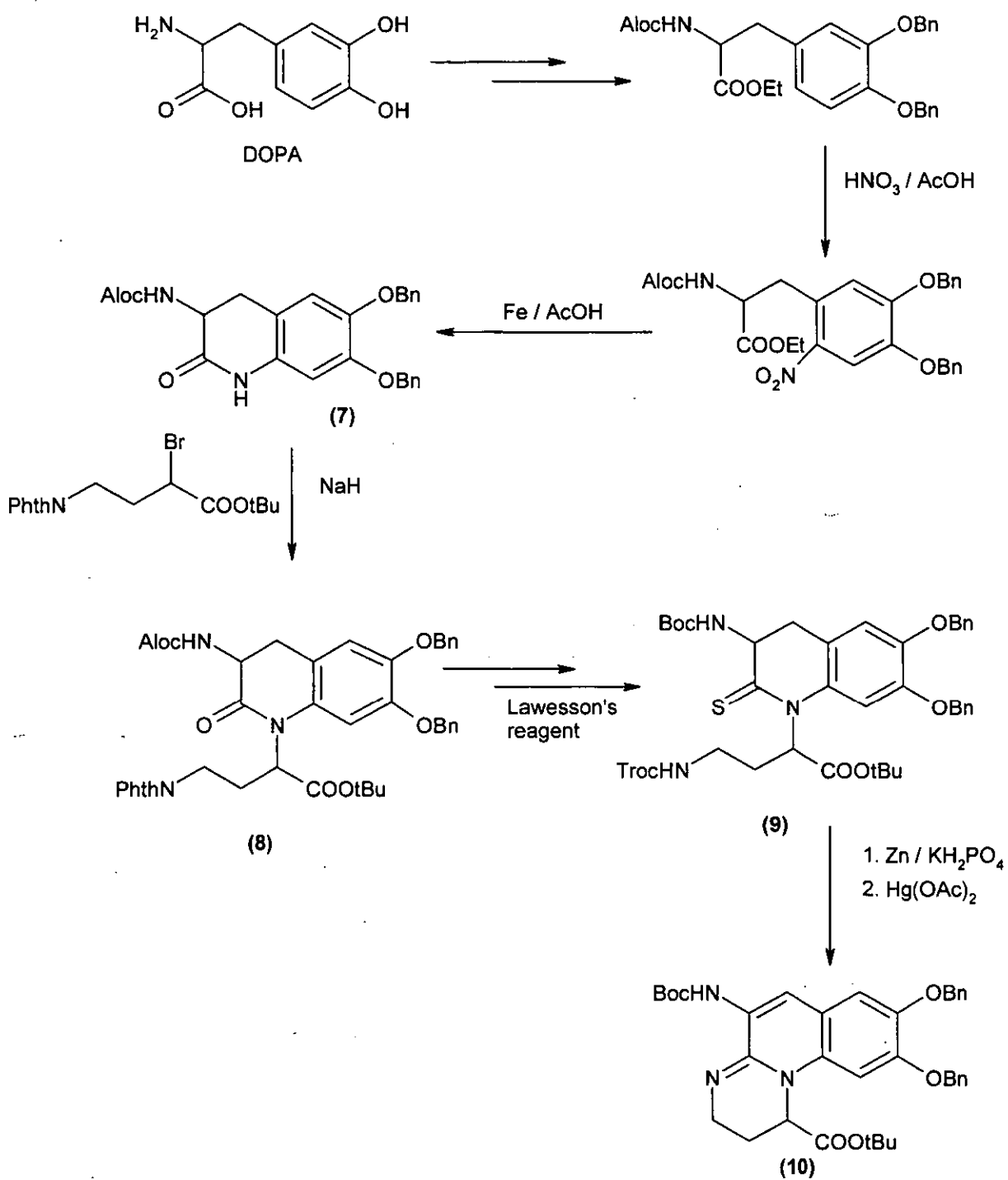
Aeruginosins 98-A and B are linear peptides isolated from the cultured freshwater blue-green alga *Microcystis aeruginosa* (NIES-98) which have the function of trypsin inhibitors.^{12, 15} Aeruginosin 98-A inhibited trypsin with an IC_{50} of 0.6 $\mu\text{g/ml}$ and plasmin and thrombin with IC_{50} of 6.0 $\mu\text{g/ml}$ and 7.0 $\mu\text{g/ml}$, respectively. Aeruginosin 98-B also inhibited trypsin, plasmin and thrombin with IC_{50} of 0.6, 7.0 and 10.0 $\mu\text{g/ml}$, respectively.

2.0 Formation Of Pyoverdins

Since the structures of various pyoverdins were identified with their common chromophore structure, several publications have appeared on the synthesis of the tricyclic chromophore unit of pyoverdins by three different approaches: chemically, biologically, as well as by biomimetic synthesis.

2.1 Chemical Synthesis

One of the earliest synthetic approaches towards the formation of the fluorescent chromophore was reported by Miller and Kolasa.¹⁶ A physiologically important amino acid, D,L-dihydroxyphenylalanine (DOPA), was selected to be the direct precursor of the fluorescent fragment of the pyoverdins as it contains a catechol unit. The synthesis starts with amination of the DOPA aromatic ring *via* nitration and reduction (Scheme 2), followed by cyclisation to give dihydroquinolin-2-one (**7**) and alkylation with a protected α -halo- γ -aminobutyric acid derivative in the presence of sodium hydride in THF to form (**8**). Further conversion to thioamide (**9**) with Lawesson's reagent promoted quantitative cyclisation to give the fluorescent chromophore (**10**).



Scheme 2.

2.2 Biogenesis

Based on many isolation studies of the pyoverdins in the last two decades, several compounds biogenetically related to pyoverdins were identified and recognized as possible precursors towards the formation of the pyoverdin chromophore.¹⁷ Such precursors include the ferribactins and dihydropyoverdins (Figure 5). Dihydroisopyoverdin and isopyoverdin are related natural products that have been isolated.

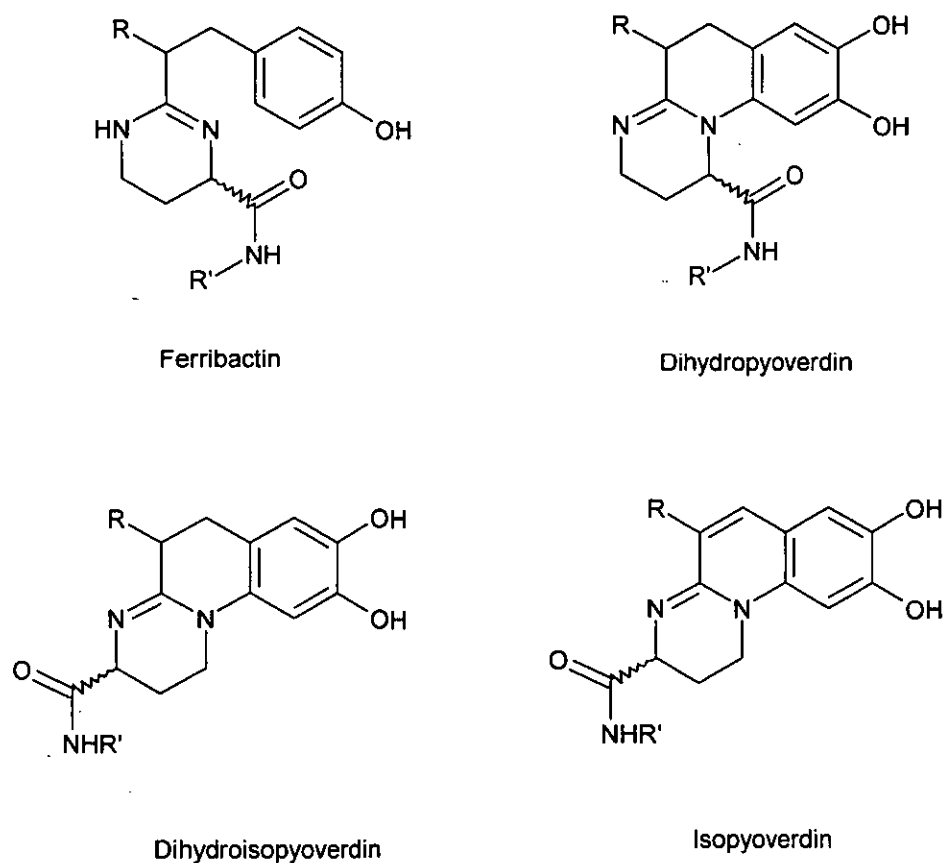
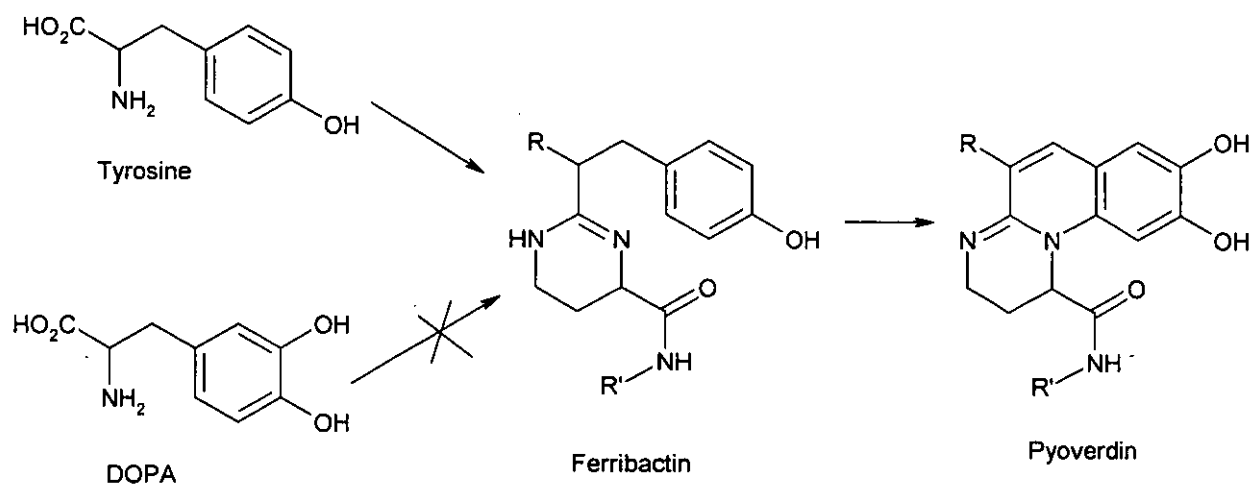


Figure 5.

Among the discoveries, the ferribactins are the most likely intermediates from condensation of tyrosine and L-2,4-diaminobutyric acid (Dab). They would subsequently

give the tricyclic chromophore *via* a dihydropyoverdin formed from oxidative cyclisation.¹⁷

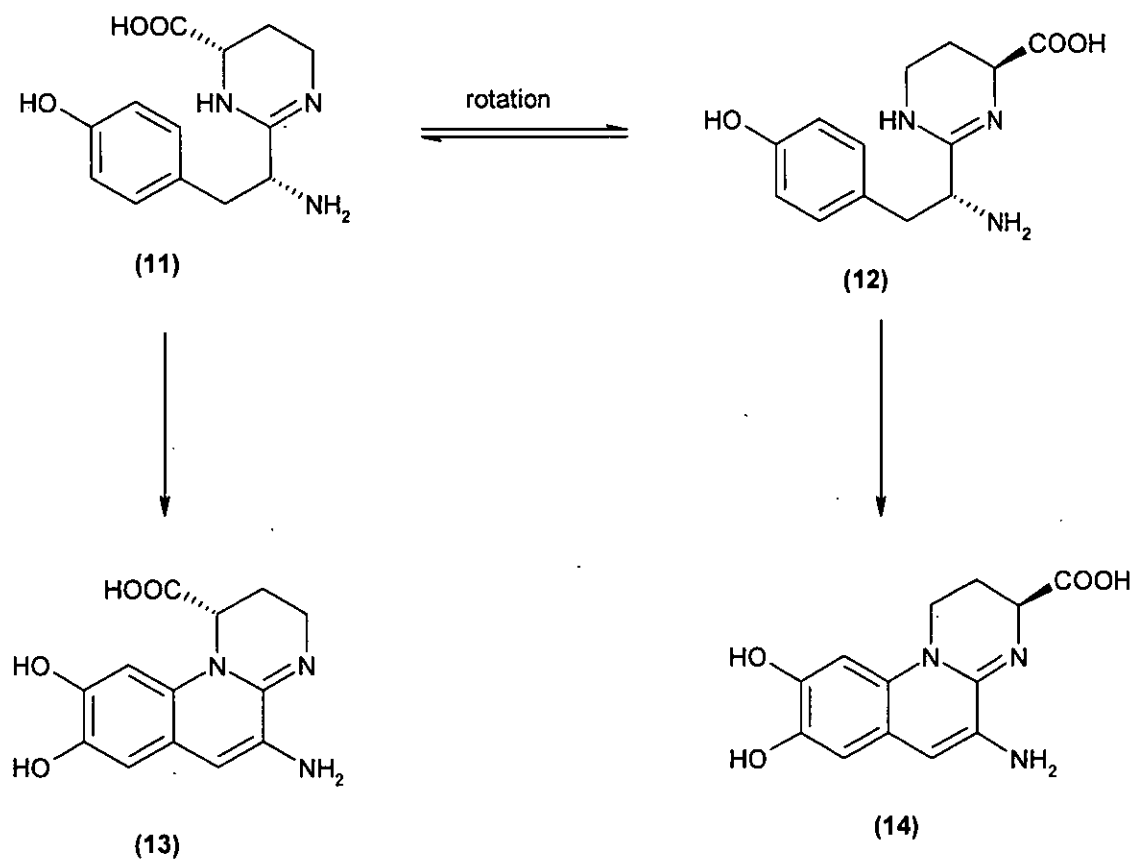
A biosynthetic study found that feeding of tyrosine to cultures of *Pseudomonas fluorescens* was successful, while DOPA was not incorporated into the chromophore.¹² This implicated tyrosine as the appropriate preliminary precursor in the biosynthesis of the pyoverdin chromophore. In other experiments, it was suggested that the catechol ring is formed by oxidation after the combination of D,L-tyrosine and diaminobutyric acid (Scheme 3),^{12, 13} again suggesting that DOPA was unlikely to be the initial precursor. Isolation of ferribactins in *Pseudomonas* provided further evidence against the possibility of DOPA being involved in the biosynthesis.



Scheme 3.

Budzikiewicz also demonstrated that a labelled [¹⁵N]-pyoverdin chromophore can be identified by mass spectrometry and NMR spectroscopic techniques after *Pseudomonas aeruginosa* was grown in the presence of labelled 2,4-[4-¹⁵N]-diaminobutyric acid in a culture medium and proposed that the formation of the chromophore unit is the result of condensation of L-diaminobutyric acid and D-Phe or D-Tyr amino acids.

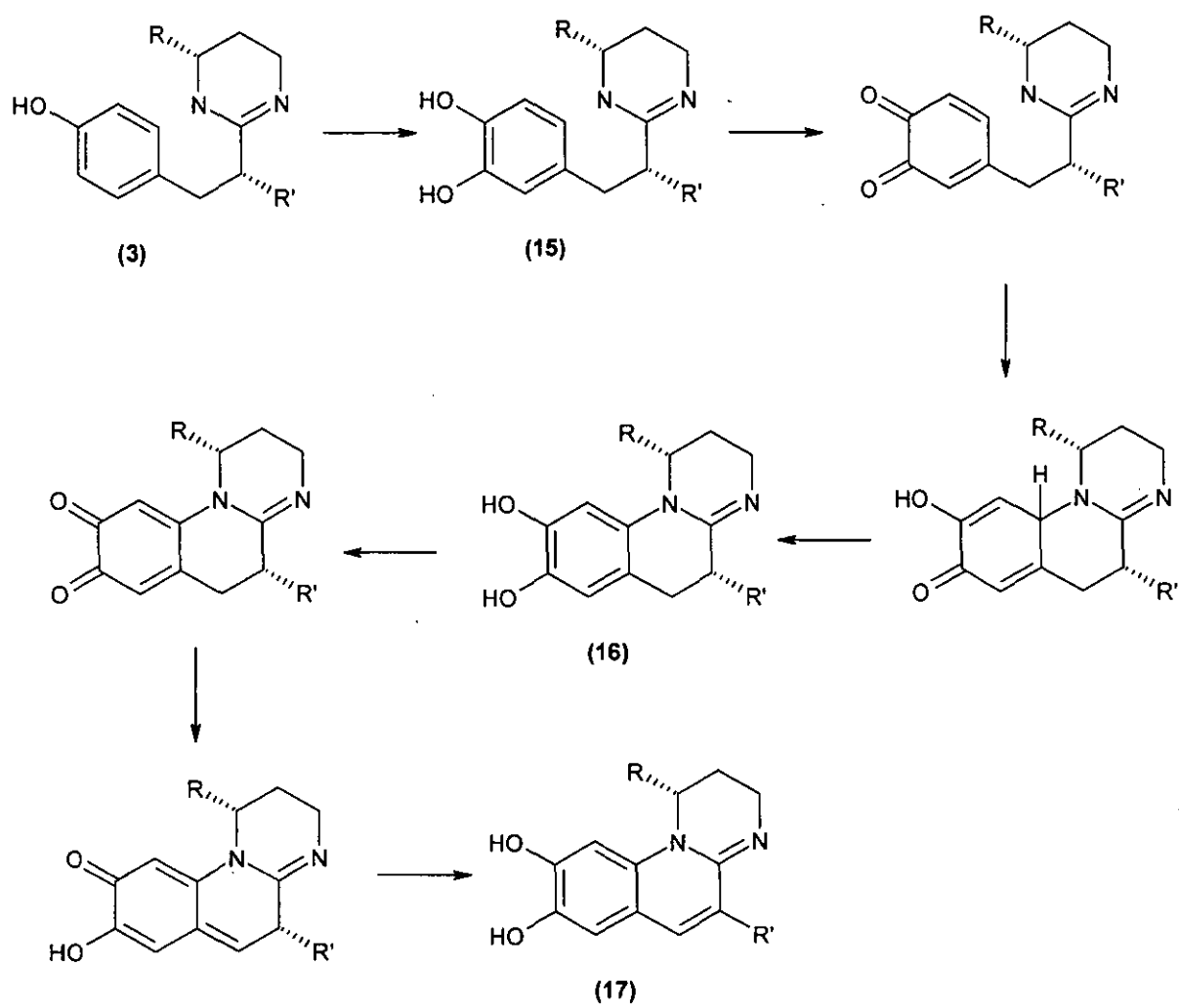
To further strengthen the biosynthetic hypothesis, 5,6-dihydroisopyoverdin (from the culture medium of *Azomonas macrocytogenes* ATCC 12334) and isopyoverdin (from the culture medium of *Pseudomonas putida* BTP 1) were also isolated by Budzikiewicz.¹⁷ Due to the possible rotation of the tetrahydropyrimidine ring in ferribactins (**11**, **12**), either of the nitrogen atoms could participate in the oxidative cyclisation, to afford (via the dihydro derivatives) pyoverdin or isopyoverdin. The C-3 chiral centres of pyoverdin (**13**) or isopyoverdin (**14**) had identical S-configurations (Scheme 4) as expected since they were both biosynthesized from condensation of D-tyrosine and L-diaminobutyric acid.



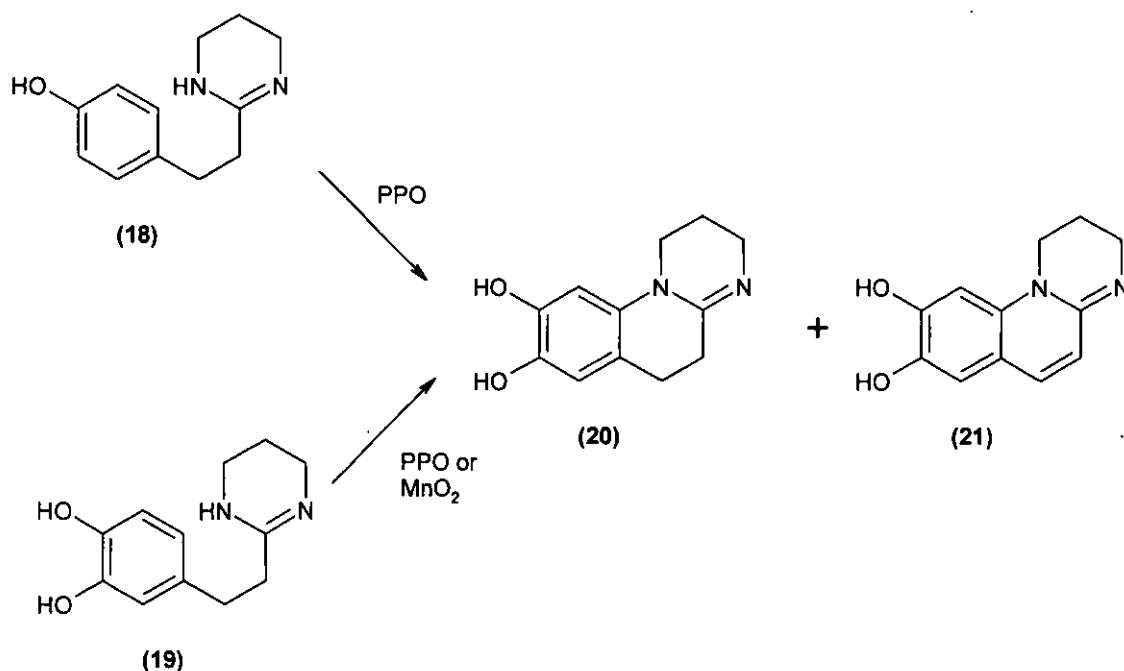
Scheme 4.

2.3 Biomimetic Synthesis

During the time of our research, formation of a chromophore model of pyoverdinin was reported by an enzymic "oxidative cascade" that involves the use of polyphenol oxidase (PPO).¹⁸ The results of this work strongly supported the assumption of catechol formation only occurring after the forming of ferribactin. The biosynthetic mechanistic proposal (Scheme 5) involves a series of oxidations based on the isolation of biogenetically related pyoverdinin compounds, such as ferribactin (**3**), catechol (**15**), and dihydropyoverdinin (**16**). They are described as the intermediates during the oxidative cascade, but from the enzymic synthesis of the chromophore model, only the dihydropyoverdinin (**20**) and the pyoverdinin chromophore (**21**) were isolated from enzymic oxidation of the hydroxyphenyltetrahydropyrimidine (**18**) and the dihydroxy analogue (**19**) (Scheme 6), and the chemical yield was relatively insignificant. This demonstrated that the second hydroxyl in the phenolic structure could be introduced by enzymic oxidation. The pyoverdinin chromophore model was also formed by treating both ferribactinin model (**18**) and catechol (**19**) with a cell free extract from *P. aeruginosa*, grown under iron-limiting condition to induce the pyoverdinin biosynthetic genes. Only the catechol (**19**) could be oxidized chemically with manganese dioxide to either the dihydropyoverdinin or pyoverdinin model, again in very low yield. Further oxidation of the dihydropyoverdinin (**20**) with polyphenol oxidase also demonstrated the formation of pyoverdinin (**21**) but neither the yield nor details of the method were given.



Scheme 5.



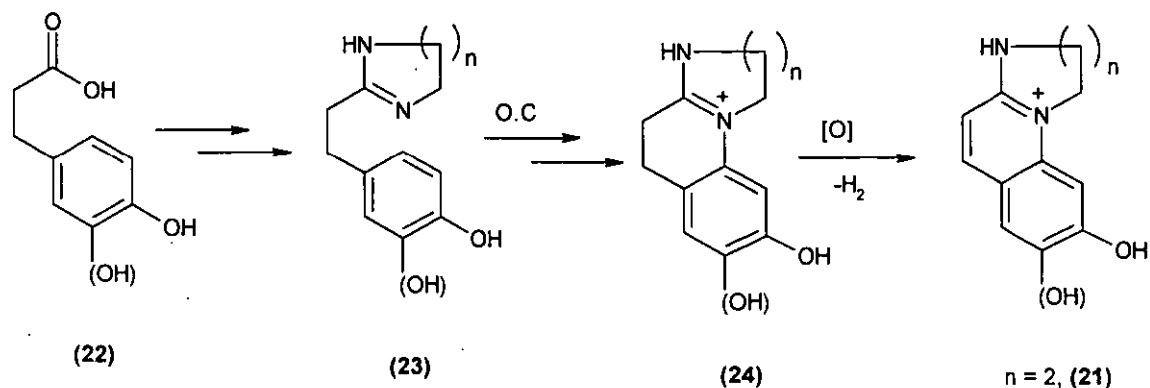
Scheme 6.

2.4 Aim Of The Project

The initial aim of the work in this thesis is to complete a biomimetic synthesis of the pyoverdinin chromophore model (21) (mono- or dihydroxy; Scheme 7), by oxidative cyclization of the corresponding cyclic amidine (23) or of related peptide or peptide-derived segments, and hence to enable synthesis of the siderophores and relevant analogues. In addition, the octahydroindole amino acid in the aeruginosins might be formed based on the similar methodology. Moreover, extension of the synthesis of the 6-membered ring cyclic amidines may also lead to 5- and 7-membered ring structures, and hence to homologues of the pyoverdinin chromophore model.

The first objective is thus to achieve the quinoline chromophore model of pyoverdinin (21) *via* oxidative cyclisation of a cyclic amidine (Scheme 7), based on the simplified

tyrosine-related residue which can be obtained from 4-hydroxy or 3,4-dihydroxy-phenylpropionic acid (**22**).



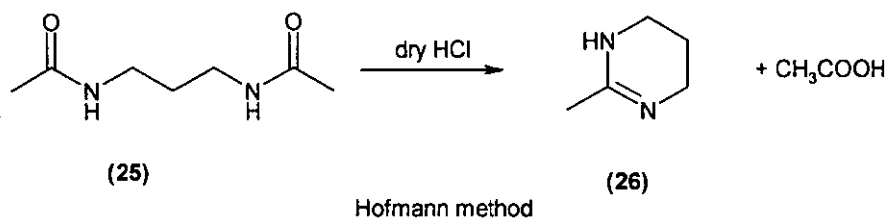
Scheme 7.

The methods developed above will then be used to synthesize the actual tetrahydropyrimidine amino acid units found in pyoverdins in order to attempt their oxidative cyclisation. Hopefully this will enable the total synthesis of a simple pyoverdinin-type siderophore.

To achieve the chromophore model, the initial targets are the cyclic amidines (**23**), including 2-[2-(4-hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidine, 2-[2-(4-hydroxyphenyl)ethyl]-4,5-dihydroimidazole as well as a 2-[2-(4-hydroxyphenyl)ethyl]-4,5,6,7-tetrahydro-1*H*-[1,3]diazepine. By oxidizing these phenolic cyclic amidines with a hypervalent iodine reagent, as a mimic of the biomimetic oxidative cyclization, pyrimidoquinolinones, imidazoquinolinones and diazepinoquinolinones (**24**) should be formed as models of the dihydropyoverdins in nature. These compounds (**24**) could be further converted into the tricyclic chromophore model by a biomimetic oxidation, such as dehydrogenation. Methods for the synthesis of cyclic amidines, followed by a discussion of hypervalent iodine reagents and dehydrogenation systems is therefore presented herein.

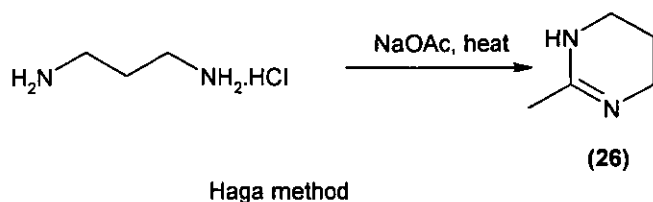
3.0 History Of Cyclic Amidine Synthesis

In general the synthetic procedures start from reaction of a diaminoalkane with carboxylic acid derivatives such as esters, acids, nitriles or iminoethers (various imidate salts) that are obtained from amides or nitriles. The first claim of preparation of 2-methyl-3,4,5,6-tetrahydropyrimidine (**26**) was by Hofmann ^{19a} in the late 19th century. He reported that the cyclic amidine was prepared by heating diacetyltrimethylenediamine (**25**) in a stream of dry hydrogen chloride (Scheme 8), but neither yields nor physical constants of the base or any derivatives were properly recorded. But later, Branch and Titherley ^{19b} reported no success in attempting the synthesis of 2-phenyl-3,4,5,6-tetrahydropyrimidine based on Hofmann's method.



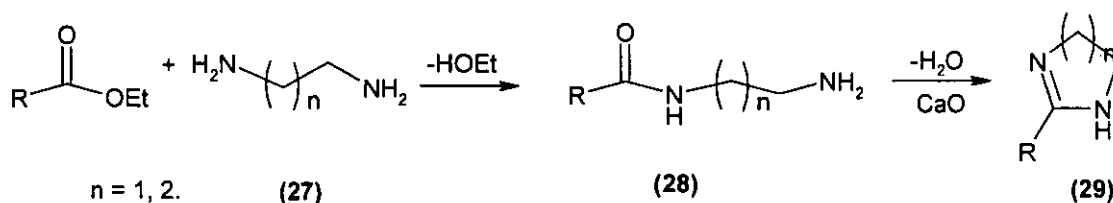
Scheme 8.

During the same period, Harries and Haga ²⁰ obtained 2,4,6-trimethyl-3,4,5,6-tetrahydropyrimidine in a relatively pure state by fusing the hydrochloride of 2,4-diaminopentane in the presence of sodium acetate. A similar method was adopted by Haga and Majima ²¹ to prepare 2-methyl-3,4,5,6-tetrahydropyrimidine (**26**) (Scheme 9). However, use of this type of method for the preparation of 5-membered ring analogues, such as 2-methyl-4,5-dihydroimidazole only produced very poor results.



Scheme 9.

In 1939, Aspinnall *et al.*²² developed a different method to produce 2-alkyl (or aryl)-4,5-dihydroimidazoles (29) efficiently by dehydration of monoacylethylenediamines (28) which he obtained from reaction of the corresponding ester and 1,2-ethylenediamine (27) after elimination of ethanol (Scheme 10). This method was also found to be reliable for the synthesis of 2-alkyl (or aryl)-3,4,5,6-tetrahydropyrimidine analogues from monoacyltrimethylenediamines. Other substituted 1,4,5,6-tetrahydropyrimidine derivatives and substituted imidazolines were obtained with promising results based on the Aspinnall method by Skinner and Wunz and by Brown and Evans.²³

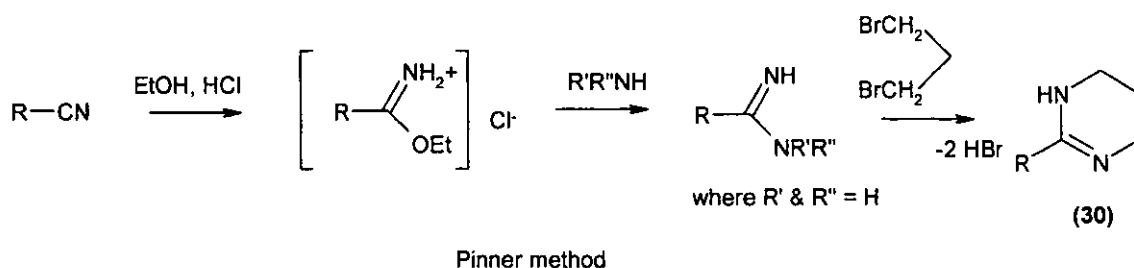


Aspinnall method - formation of dihydroimidazole & tetrahydropyrimidine

Scheme 10.

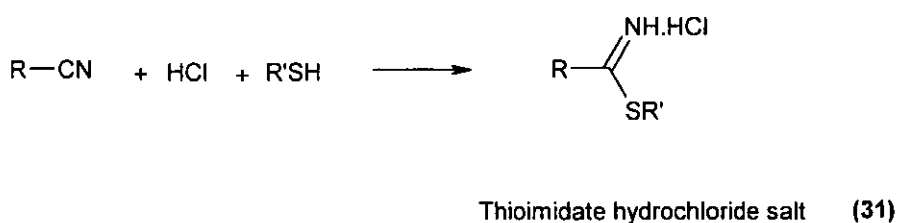
In fact, the most widely used general method for the synthesis of amidines was not any of the above, but was introduced by Pinner²⁴ in 1893. He reported the use of imidate salts (iminoether salts), formed from reaction of nitrile and anhydrous alcohol in the presence of the acid catalyst hydrogen chloride, on treatment with ammonia or amines in absolute

ethanol to produce many amidines in excellent yield. Further reaction of the amidine with trimethylene dibromide can afford a small amount of cyclic amidine (**30**), e.g. 2-phenyl-3,4,5,6-tetrahydropyrimidine, when the reaction is left for several weeks (Scheme 11).



Scheme 11.

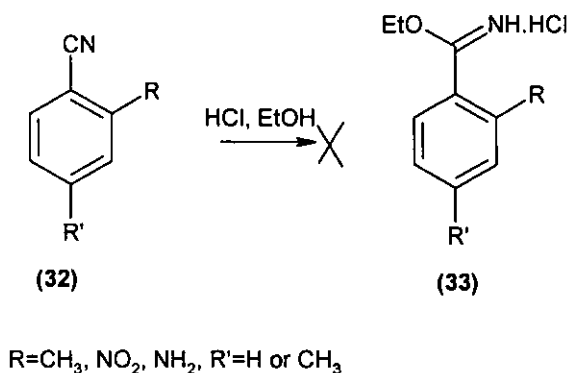
As well as using nitriles to form imidate salts prior to cyclic amidine formation, another type of imidate salt, the hydrogen chloride salt of a thioimidate was also formed from nitriles by Pinner. This type of route was used later for the formation of cyclic amidines by Jones.^{2, 4} Reaction was carried out by treating nitriles with an anhydrous thiol instead of alcohol in the presence of acid catalyst, which resulted in the thioimidate hydrohalide salts (**31**) (Scheme 12).^{24, 25}



Scheme 12.

Although Pinner's synthetic method for general formation of amidines was successful at that time, several limitations were discovered and mostly were in the formation of the imidate salts.²⁶ One limitation was the availability of the starting nitriles.²⁷ In addition,

Pinner was not able to obtain the imidate salt (33) when he reacted hydrogen chloride and ethanol with *ortho*-substituted benzonitrile (32) (Scheme 13).



Scheme 13.

The failure was due to steric hindrance from an *ortho*-substituted alkyl group adjacent to a cyano group in an aromatic system, since other isomers readily yielded the imidate salts. In addition, *N,N*-disubstituted amidines cannot be synthesized by this general method. Although a cyano group cannot condense with alcohol and hydrogen halide when a bulky *ortho*-substituted group is situated next to it, several imidate salts have been successfully isolated by *O*-alkylation of the corresponding *o*-substituted amides in the presence of silver oxide.^{27, 28}

Nevertheless, the Pinner approach *via* imidate salt formation has become the most common route for the synthesis of cyclic amidines. Since Pinner's work, many amidines can be formed successfully based on the Pinner method through imidate salts but from various starting materials other than just from the nitrile. A survey of the various methods for the formation of imidate salts that lead to the formation of cyclic amidines is presented below.

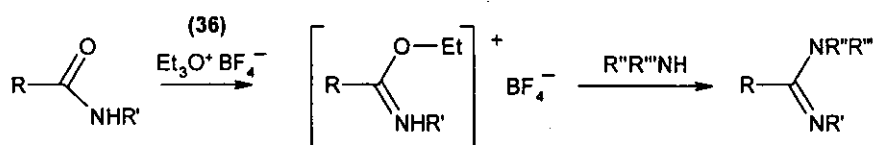
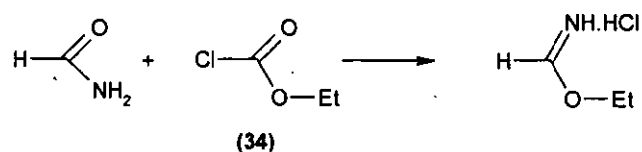
3.1 Formation Of Imidates

Because of the usefulness of imidates for forming cyclic amidines and as a result of the limitations on the use of nitriles for the formation of imidate salts, a number of investigations on the formation of imidates (and hence of amidines) that have improved from the Pinner method have been reported and summarised.^{27, 29}

3.1.1 Imidates From Amides

Using amides as the starting materials for the synthesis of amidines *via* imidates has been depicted as more convenient and versatile than the traditional use of nitriles.²⁹ Both *N*-substituted and *N,N*-disubstituted amidines may be prepared from amides through the intermediate imino chloride obtained by reacting secondary and tertiary amides with PCl_5 , POCl_3 , SOCl_2 or COCl_2 . However, these reagents usually dehydrate primary amides, making the procedure of little value for unsubstituted amidines.²⁶

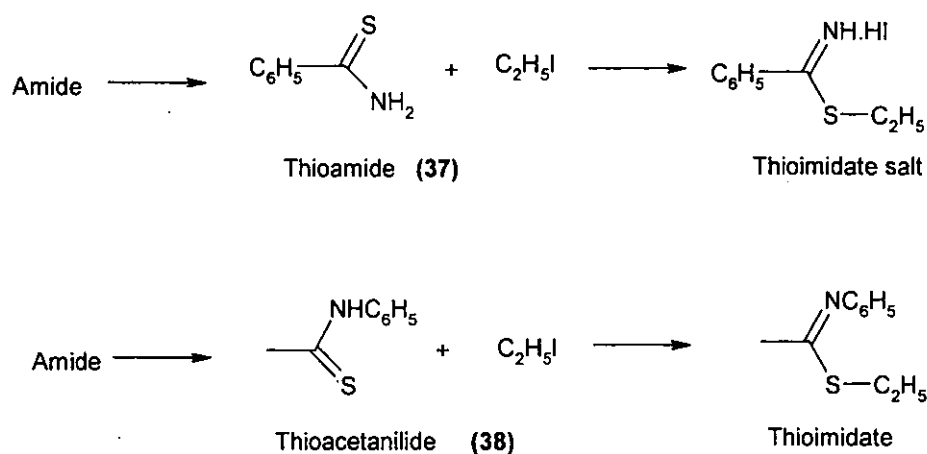
On the other hand, imidate salts can be produced by direct *O*-alkylation of primary or secondary amides with ethyl chloroformate (**34**) in benzene at room temperature.³⁰ Amides and thioamides may also be alkylated directly with dimethyl sulfate (**35**) at temperature below 100 °C to yield the methyl hydrogen sulfate salts of imidates or thioimidates.³¹ Among many alkylating reagents, triethyloxonium tetrafluoroborate (Meerwein reagent) (**36**) is apparently superior for the *O*-alkylation of amides, reaction is said to occur simply at room temperature when mixing triethyloxonium tetrafluoroborate and amide with CH_2Cl_2 as the solvent (Scheme 14). Amidines have also been formed *via* imidate tetrafluoroborate salts.^{29, 32}



Scheme 14.

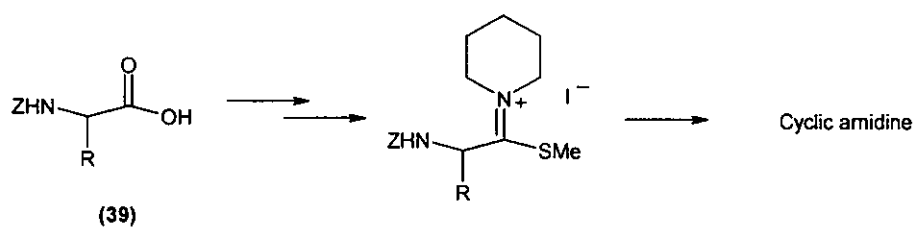
3.1.2 Thioimidates From Amides Or Carboxylic Acids

Thioimidates were first reported by Pinner as mentioned above, prepared in a similar way to the imidate formation from nitrile. They can also be prepared from direct *S*-alkylation of thioamide (37) or thioacetanilide (38), which were obtained from amides, with an alkyl iodide to yield a thiobenzimidate salt (Scheme 15), or in the presence of sodium ethoxide to yield *N*-phenylthioacetimidate.^{27,33}



Scheme 15.

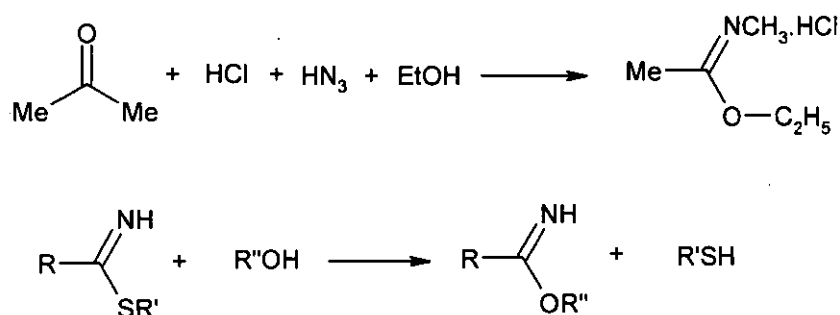
Carboxylic acids are another source for the preparation of thioimidate salts *via* piperidine thioamides (Scheme 16), an approach which was employed by Lawesson³⁴ and Jones.² The reactions were carried out by use of *C*-terminal amino acids (39) *via* their piperidine amides, treatment with Lawesson reagent to make the thioamide followed by methyl iodide for *S*-methylation. It has been found that thioimidate salts are equally reactive to *O*-imidates towards the formation of amidines.



Scheme 16.

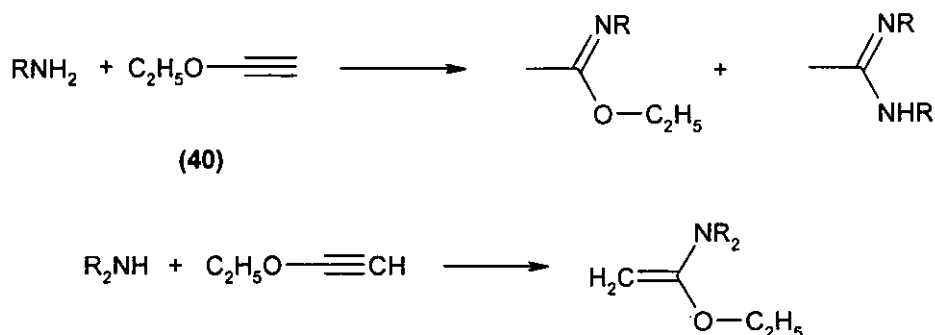
3.1.3 Imidates *Via* Other Methods

Some other substrates containing electrophilic carbon may also lead to imidates. In the presence of alcohol, hydrochloric acid, hydrazoic acid and ketone, imidate hydrochloride salts can be produced by a methyl group rearrangement (Scheme 17).²⁷ Transesterification can be carried out to yield *O*-imidates from thioimidates.³⁵



Scheme 17.

Imidates may be derived from alkynyl ethers. Addition of primary amines to ethoxyacetylene (40) at reflux in ethanol gives rise to imidates, but amidines are likely to form as by-products because further interaction occurs between the imidates and the primary amines (Scheme 18).³⁶ This further reaction cannot occur when secondary amine is used, as the intermediate is incapable of undergoing the tautomeric shift.

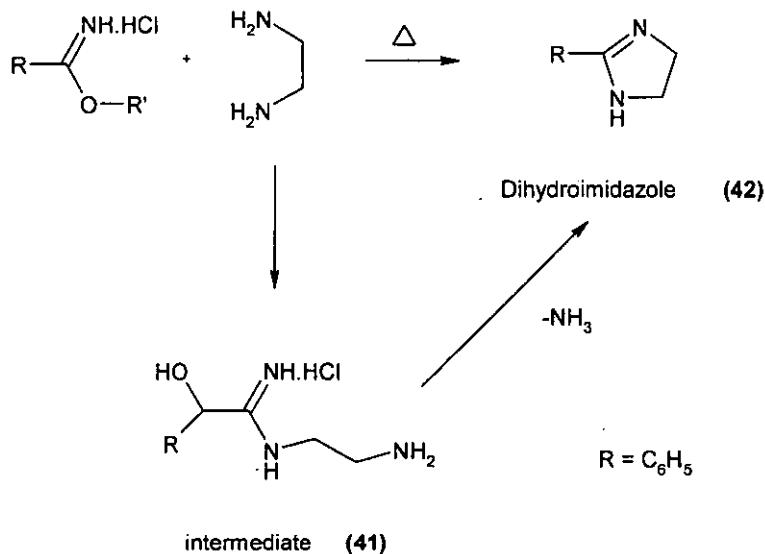


Scheme 18.

3.2 Use Of Imidates To Prepare Cyclic Amidines

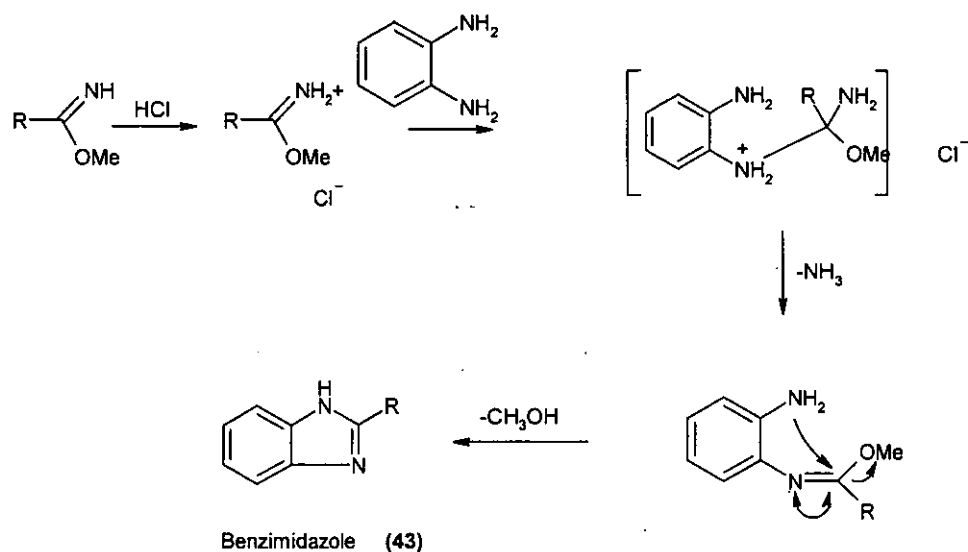
Amidines could be derived from imidates and amines due to the success of the many imidate salt formations based on the general Pinner method. Cyclic amidines, such as tetrahydropyrimidine or dihydroimidazole, may thus be formed like ordinary amidines but with use of diamines as the *bis*-nucleophilic reagent to construct the carbon backbone of the ring in good yield.

2-Substituted-4,5-dihydroimidazoles (**42**) have been extensively reported from heating diaminoalkanes with imidates or their salts.²⁷ These 2-position substituents in imidates include phenyl, tolyl, phenylacetyl, α -aminoalkyl or other amide groups. The mechanism of the heterocycle formation was indicated, for example, by isolation of an intermediate *N*-(2-aminoethyl)mandelamidinium hydrochloride (**41**) whose cyclisation was completed by losing ammonia slowly at room temperature (Scheme 19), or more readily in hot alcohol to give the corresponding dihydroimidazole.³⁷



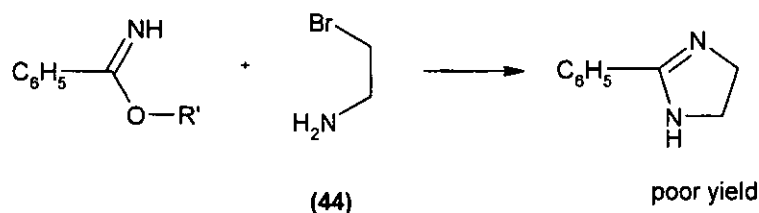
Scheme 19.

Another suggestion for the mechanism of reaction of imidates with *o*-phenylenediamine was investigated by King and Acheson.³⁸ Benzimidazole (43) was formed in the presence of one or at most two equivalents of acid, where the initial tetrahedral intermediate formed from amine attack at the imidate carbon eliminated ammonia to afford an intermediate *N*-substituted imidate. Elimination of alcohol took place as cyclisation was completed by a second nucleophilic attack from the second amine in an intramolecular condensation (Scheme 20) to give the corresponding benzimidazole (43).



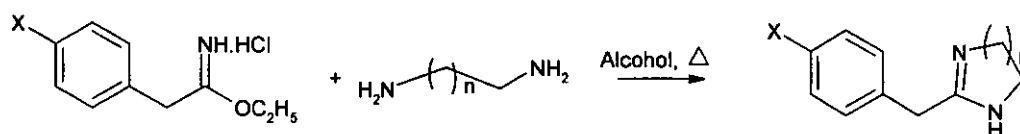
Scheme 20.

Similar reaction to form dihydroimidazoles by using 2-bromoethylamine (44) instead of diamine gave only disappointing yields of imidazoline product (Scheme 21).³⁹



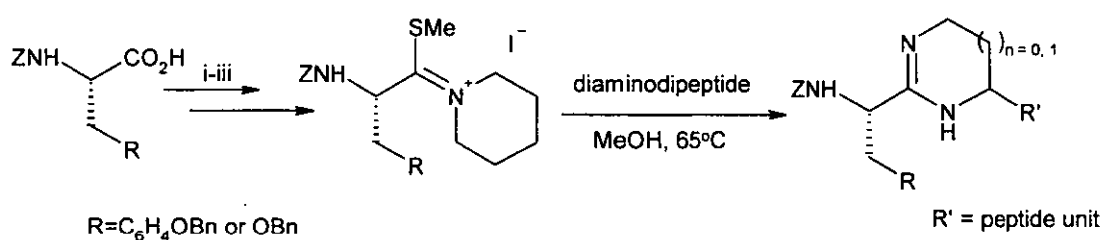
Scheme 21.

Extension of the cyclic amidine formation from reaction of imidates with 1,2-diaminoethane to 1,3-diaminopropane produces tetrahydropyrimidines. Both 2-substituted 3,4,5,6-tetrahydropyrimidines and 4,5-dihydroimidazoles were obtained effectively under the same conditions when ethyl 4-substituted-phenylacetimidate salts were reacted with 1,2-diaminoethane or 1,3-diaminopropane under reflux with ethanol for 10 hours (Scheme 22).⁴⁰



Scheme 22.

5- and 6-Membered ring amidine units could also be assembled from thioimidates made from carboxylic acids *via* piperidine thioamides and *S*-alkylation. Jones's group was able to synthesise a number of pseudopeptide units, such as imidazolines⁴ and tetrahydropyrimidine² amino acid units when some other imidate salts seemed to be unstable towards the conditions of cyclic amidine formation. He reported the successful synthesis of 5- and 6-membered ring amidines by coupling of *S*-methyl thioimidate salts with the appropriate corresponding diaminoester or diaminodipeptide (Scheme 23).



i, DCC, pentafluorophenol; then piperidine; ii, Lawesson's reagent, toluene, 80°C; iii, MeI, 40°C.

Scheme 23.

4.0 Hypervalent Iodine

The term hypervalency is used to refer to bonding in elements of Group V-VIII of the periodic table where those elements contain a valency higher than normal, with 10 or 12 electrons in their outer shell.

Iodanes ArIL_2 with decet structure are known as aryl- λ^3 -iodanes and are the most common iodanes. They have pseudotrigonal bipyramid geometry with an aryl group and lone pairs of electron in equatorial positions and two heteroatom ligands (L) in axial positions. These molecules contain a hypervalent linear three-centre four-electron (3c-4e) bond system with 2 electrons from a doubly occupied 5p orbital on iodine and one electron from each of the ligands.

The partial negative charges on the apical heteroatom ligands and partial positive charge on the central iodine atom are due to the filled non-bonding molecular orbital which has a node at the central iodine (Figure 6). The resulting highly polarized 3c-4e bond makes the aryl- λ^3 -iodine an electrophilic agent. Most of the electron density is placed at the ends of the linear L-I-L triad, explaining why electronegative ligands stabilize iodanes.

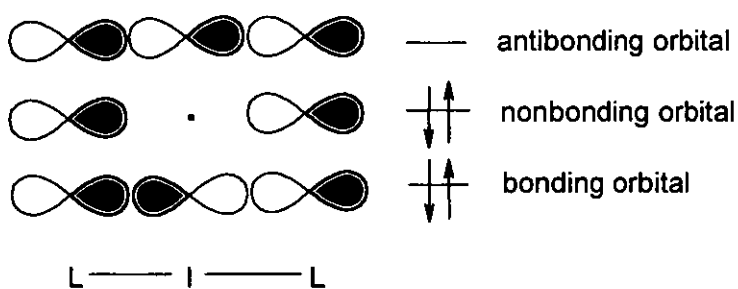


Figure 6.

The hypervalent bonds between the iodine and ligands (L-I-L) can be regarded as ionic bonds, where the aryl carbon-iodine bond is covalent and made up of two electrons with $5sp^2$ hybridization at iodine to form a $C_{Ar}-I$ σ -bond.

Organo- λ^3 -iodanes are the most common hypervalent iodine reagents used in organic synthesis, due to the strong soft electrophilic iodine centre that can be attacked by virtually any nucleophile and the superleaving group ability of the phenyliodonio group. Various numbers of carbon or heteroatom ligands attached to the iodine atom can affect their reactivity. RIL_2 and R_2IL are the most common types classified. The presence of two heteroatom ligands in RIL_2 , at the apical positions relative to their iodine atom is particularly useful in functional group oxidations, where one is used for a ligand exchange step and the other used for a reductive elimination reaction, where both of the ligands act as leaving groups. The weak hypervalent bond means that the intermediates in reactions are readily broken down resulting in reductive elimination of iodobenzene and formation of the end-product. The second class of λ^3 -iodanes, R_2IL , are not good oxidizing agents, but can transfer one carbon ligand to a variety of nucleophiles.

In general, the majority of organo- λ^3 -iodanes utilise two modes of ligand exchange reactions: (i) introduction of a nucleophile, occurring at iodine(III) with no change in the oxidation state and (ii) the reduction of hypervalent iodine to iodide, called reductive elimination. Heteroatom ligands of iodanes can be readily substituted by introducing another nucleophile. Two mechanistic alternatives, associative and dissociative are suggested where one adds a nucleophile prior to loss of the ligand, and the other eliminates its ligand first, respectively (Figure 7), but the earlier mechanism is preferred since it requires minimum energy in the intermediate species. The highly energetic dicoordinated iodonium species involved in the dissociated pathway is unlikely.⁴¹

Associative pathway



Dissociative pathway

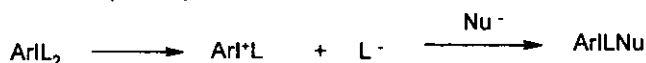


Figure 7.

Nucleophiles react with partially positively charged iodine at the C-I σ^* orbital and result in intermediate formation of a *trans*-tetracoordinate iodate with a square-planar arrangement (Figure 8). Isomerisation to *cis* iodate followed by elimination of a heteroatom ligand L produces a new aryl- λ^3 -iodane ArI(Nu)L. The whole process is called heteroatom ligand exchange with a nucleophile *via* addition-elimination. Further ligand exchange with another nucleophile may also occur with a similar sequence to produce ArINu₂ or even ArINuNu'.

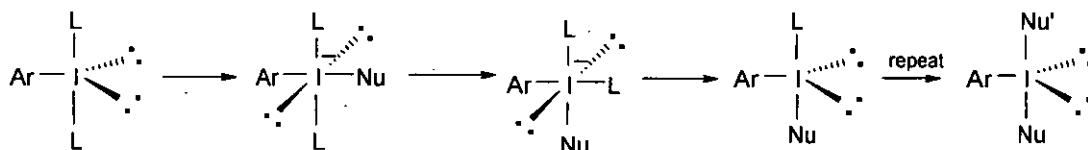


Figure 8.

Ligand exchange can occur with a range of nucleophiles including oxygen nucleophiles, nitrogen nucleophiles, heteroatom nucleophiles or carbon nucleophiles.

One of the important transformations of the hypervalent λ^3 -iodanes is the reductive elimination to afford a univalent iodide. It has been described as a facile and energetically favourable process and often proceeds without the assistance of added reagents. Elimination of an iodide from organo- λ^3 -iodane reagents often results in the formation of

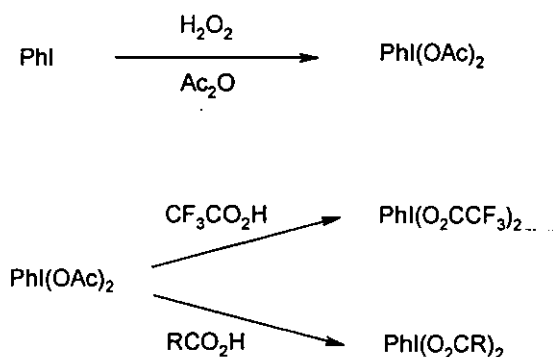
a cationic, electron-deficient intermediate so the ability of aryl- λ^3 -iodanyl groups to undergo elimination increases with increase in the electron-withdrawing nature of the ring substituents and the leaving aryl- λ^3 -iodanyl group is termed a hypernucleofuge.

4.1 Preparation Of Hypervalent Iodine Reagents

In order to modify the reactivity and ligand exchange character at hypervalent iodine, many varieties of hypervalent iodine reagents can be prepared, developed and substituted conveniently by introducing a new heteroatom group, from a fundamental iodobenzene.

4.1.1 *Bis(acyloxy)iodoarenes*

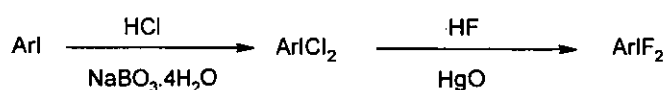
Diacetoxy-iodobenzene (DAIB) is regarded as one of the basic hypervalent iodine reagents and can be prepared from iodobenzene, hydrogen peroxide and acetic anhydride (Scheme 24).⁴² Other *bis(acyloxy)iodoarenes* can be made by further substitution of the DAIB, for example, *bis(trifluoroacetoxy)iodobenzene* (BTIB) is obtained from reaction of boiling trifluoroacetic acid with DAIB or more generally, *bis(acyloxy)iodobenzenes* are produced by reacting the diacetoxy-iodobenzene with any acid (Scheme 24).⁴³ The BTIB reagent is far more reactive in oxidations than the original DAIB reagent.



Scheme 24.

4.1.2 Dihaloiodoarenes

Reaction of iodobenzene with hydrochloric acid in the presence of sodium perborate tetrahydrate and acetonitrile yields dichloriodobenzene. Further reaction of this dichloriodobenzene with hydrofluoric acid and yellow mercuric oxide gave difluoriodobenzene (Scheme 25). Many difluoriodoarenes are stable at ambient temperature and prepared *in situ*. They can melt without decomposition if they are pure and should be kept in PTFE or polyethylene containers rather than glass containers to avoid slow attack on the glass.⁴⁴

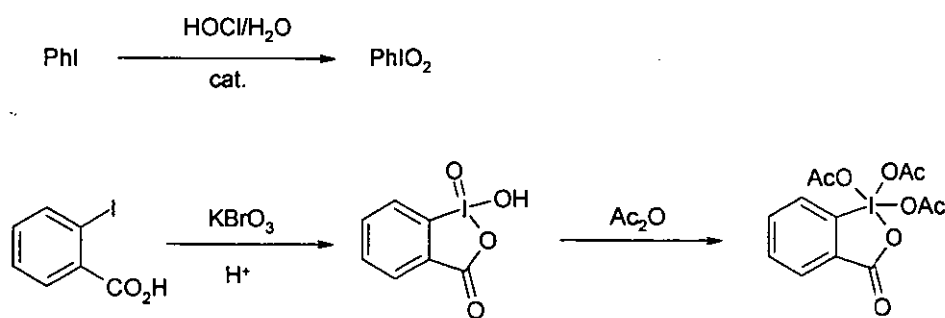


Scheme 25.

4.1.3 Reagents Of Iodine(V)

Common iodine(V) oxidizing reagents can be prepared from oxidation of iodobenzene. For example, iodylbenzene was obtained directly by oxidizing iodobenzene using aqueous hypochlorite solution (Scheme 26) at pH 8.2 and a phase transfer catalyst, tetrabutylammonium hydrogen sulfate, at room temperature for less than an hour.⁴⁵

The famous Dess-Martin reagent is also one of the best known iodine(V) reagents used for oxidation. It is prepared in two steps from *o*-iodobenzoic acid. Initial reaction with potassium bromate and acid, and then further treatment with acetic anhydride and *p*-toluenesulfonic acid hydrate (Scheme 26) yields the Dess-Martin reagent, 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(*1H*)-one.⁴⁶



Scheme 26.

4.2 Use Of Hypervalent Iodine Compounds

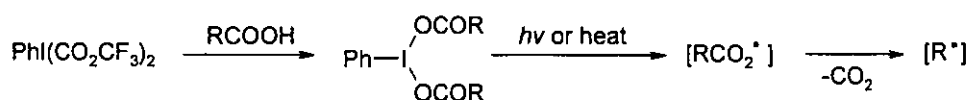
In recent years, a number of uses of hypervalent iodine reagents in organic synthesis have been reported and many of them involve carbon-carbon or carbon-hetero bond formation through two general pathways. First, reaction may involve hypervalent iodine precursors that generate carbon-centered reactive intermediates, such as free radicals, carbocations or cation-radicals and then trapping with organic substrate. In general, this reaction is an oxidation of organic substrate with *bis*(acyloxy)iodoarenes. The second type of reaction proceeds *via* coupling of carbon ligands in the tricoordinate iodine intermediate that can be generated by addition of a carbon nucleophile to an iodonium salt. Hypervalent iodine(V) reagents are well known for oxidation of alcohols to form ketones or aldehydes, whilst iodine(III) reagents provide more variety of oxidation, such as spirocyclic oxidation, aromatic nucleophilic addition or heterocyclic alkylation.

4.2.1 Radical Decarboxylative Alkylation With *Bis*(trifluoroacetoxy)-iodobenzene

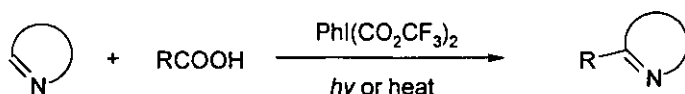
Heterocyclic compounds are alkylated by mixing of carboxylic acid with *bis*(trifluoroacetoxy)iodobenzene where the iodobenzene reagent can serve as an alkyl

radical generator in the presence of carboxylic acid *via* decarboxylative radical decomposition (Scheme 27).⁴¹ The heterocycle can be regarded as the appropriate organic substrate to trap the alkyl radical being generated, and this results in the formation of alkylated heterocycle compound.

Generate radical



Overall



Scheme 27.

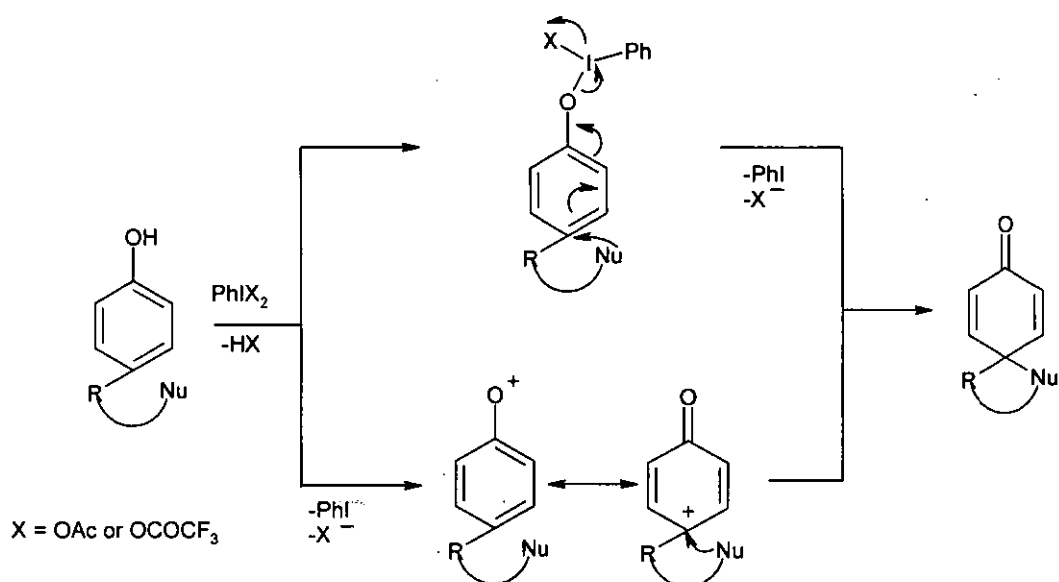
Hypervalent iodine(III) reagents can also be used for the radical alkylation of electron-deficient alkenes to give a reductive addition product.

4.2.2 Phenol Oxidation – Spirocyclic Intramolecular Reaction

The use of hypervalent iodine reagents in the oxidative cyclisation of phenols or phenol ethers has been reported increasingly in the past decade and it has become a key synthetic tool for natural product synthesis because of its effectiveness in intramolecular oxidative spirocyclization. A brief review of the reaction is presented here and further detail of this reaction will be discussed in a later section since this oxidative cyclization is also a key step in our plans for the biomimetic synthesis of the pyoverdinin chromophore.

Reagents like *bis*(acyloxy)iodoarenes are useful for the formation of spirodienones by oxidation of an appropriate *p*-substituted phenol in the presence of a suitable external or

internal nucleophilic source. The construction of the spirodienone molecule proceeds either *via* concerted addition-and-elimination of iodine reagent or *via* formation of phenoxenium ions (Scheme 28). The hypervalent iodine oxidation of *para*- and *ortho*-substituted phenols with nucleophilic side chains could afford a variety of spirocyclohexadienone derivatives effectively. Many natural product syntheses employ hypervalent iodine reagents as part of the sequence. Reaction with a phenolic substrate is followed by nucleophilic attack of alcohol, water, alkene, amide, carboxylic acid, oxime, fluoride ion or electron-rich aromatic ring to give a cross-conjugated cyclohexadienone either by an inter- or intramolecular reaction pathway.⁴⁷



Scheme 28.

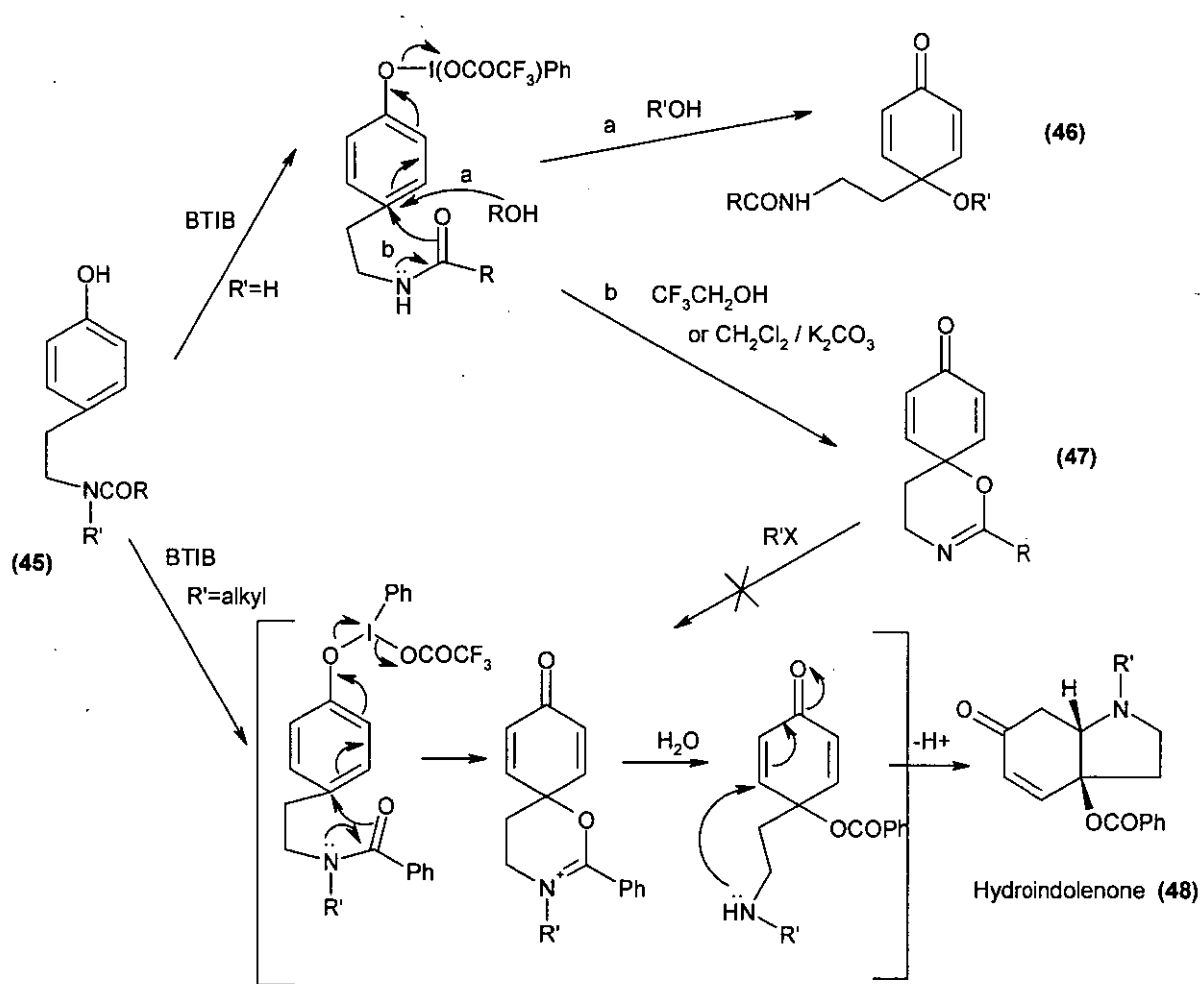
Kita and co-workers in 1987 used reactive BTIB to give quinone monoacetals or spiro lactones from *ortho* or *para*-substituted phenols in the presence of external alcohols.⁴⁸ When water is employed instead of alcohol, a quinone is formed.⁴⁹ This method is useful for formation of various 1,4-naphthoquinones and aza-analogues.⁵⁰

4.3 Oxidative Cyclization - Formation Of Cyclic Systems

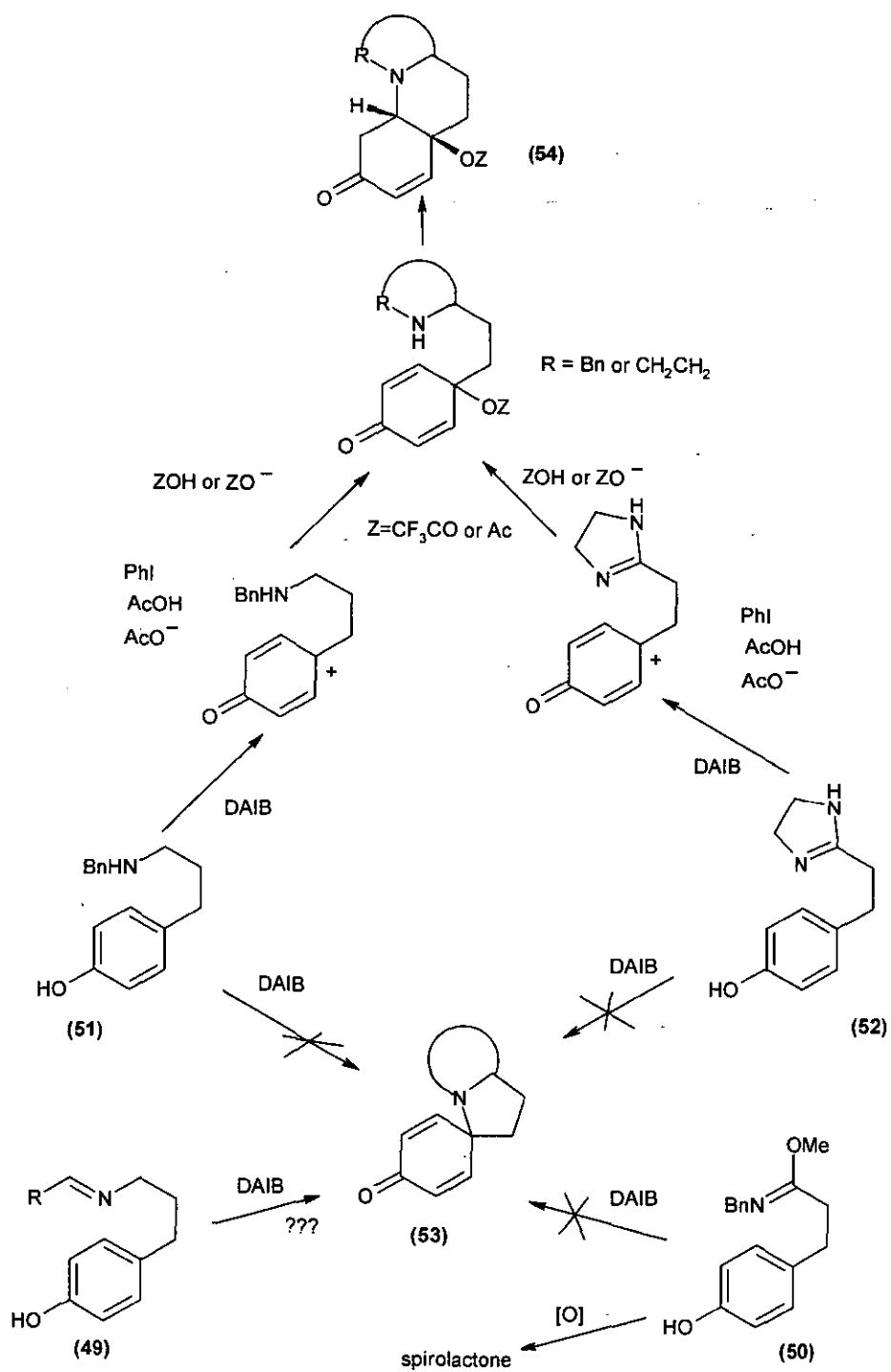
Reports indicate that a possible biosynthesis of the pyoverdinin chromophore is from an oxidative cyclization of a tyrosine derived tetrahydropyrimidine.^{12, 18} Efforts to model this have led to a focus on hypervalent iodine(III) reagents which are able to oxidize phenols as described in previous sections. Other than just for oxidation of phenol or phenol ether, several papers also report the synthesis of spiroheterocyclic products by oxidative cyclization of phenolic amines or amides with diacetoxyiodobenzene (DAIB) or *bis*(trifluoroacetoxy)iodobenzene (BTIB), but some unexpected cyclised quinolines or indoles were also observed when various phenolic *N*-substituents were used.^{51, 52} This unusual phenomenon was first explained by Kita (Scheme 29) when he oxidized *N*-alkyl-*N*-benzoyltyramines (**45**) with DAIB to give bicyclic hexahydroindol-6-ones (**48**) in fair yield (Scheme 29).⁵¹ He proposed that the formation of reduced indolones (**48**) was due to an intramolecular Michael-type addition of the amino group (formed by hydrolysis of an intermediate) to the double bond of the dienone intermediate where as secondary amides would give either the spirocyclic hexadienones (**47**) or the corresponding quinol ethers (**46**) depending on the solvent used. In all cases, if the amide has acted as a nucleophile, it is through the oxygen rather than the nitrogen atom. Cyclisation through nitrogen is needed for the pyoverdinin series.

After Kita's discovery, Ciufolini *et al.* also reported similar formation of spirocyclic lactams and lactones as well as reduced quinolone derivatives (Scheme 30).⁵² He attempted to investigate the formation of spiro lactams (**53**), i.e. an internal *N*-nucleophile, from *N*-substituted phenolic imines (**49**), *N*-substituted imino ethers (**50**), secondary phenolic amines (**51**) and phenolic imidazolines (**52**) but none led to the formation of spiro lactam (**53**) (Scheme 30). Instead the quinolones (**54**) were said to be isolated from secondary phenolic amines (**51**) and phenolic imidazolines (**52**) (although no experimental details were given) and a spiro lactone was obtained from the *N*-substituted imino ether (**50**). He suggested that the reason for bicyclic rather than the usual

spirocyclic formation was due to the suppression of the nucleophilicity of nitrogen in the amine or amidine under the acidic conditions of DAIB so they would not compete effectively with the solvent or acetate ion, hence bicyclic amine formed. However the presence of basic or acid scavengers did not alter the outcome. Ciufolini proposed a mechanism for the oxidative cyclisation as a unimolecular reaction, i.e. forming a dienone cation by loss of iodobenzene etc., followed by nucleophilic attack (Scheme 28), whereas Kita suggested a bimolecular reaction which a nucleophilic attack is concerted with the iodine reagent leaving the associated oxy group (Scheme 29).

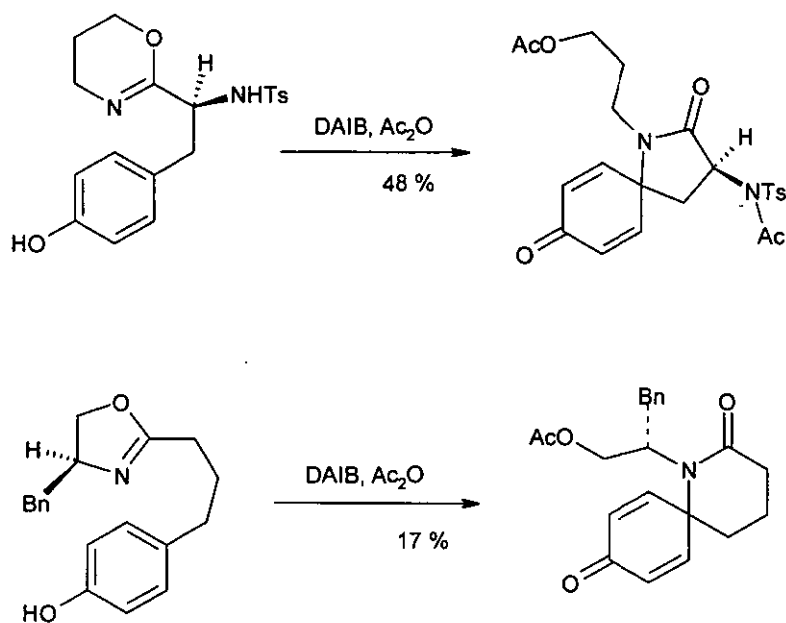


Scheme 29.



Scheme 30.

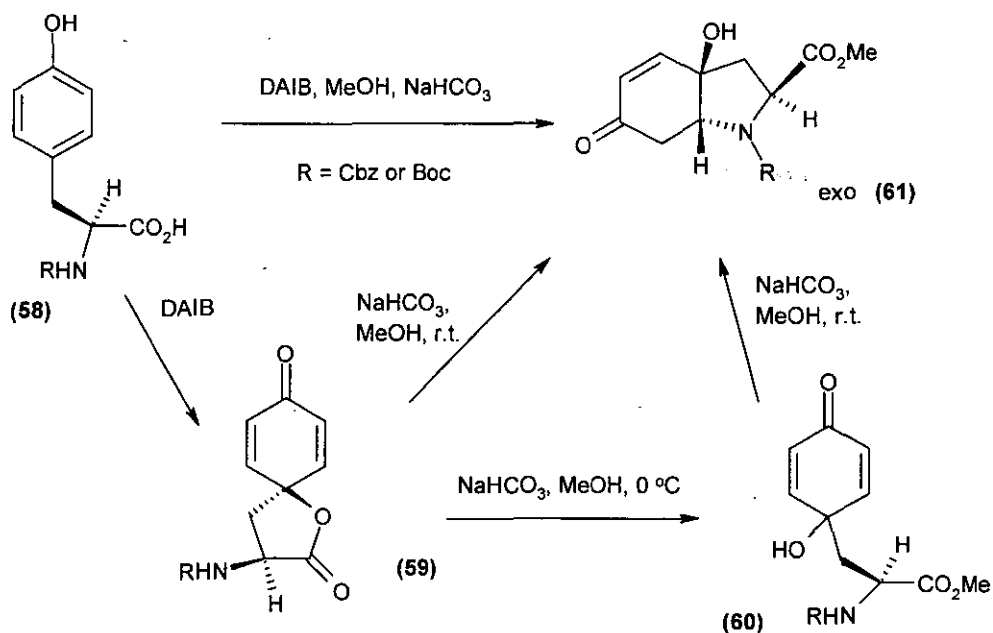
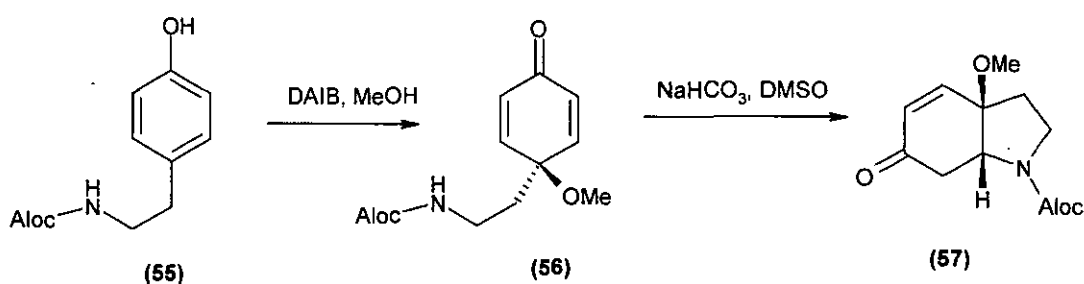
Ciufolini also attempted oxidative cyclisation of oxazoline and oxazine derivatives under the same hypervalent iodine conditions, resulting in the formation of spiro lactams (Scheme 31) by *N*-nucleophile attack while both the oxazine and oxazoline ring were opened by subsequent hydrolysis without any sign of quinolone formation.



Scheme 31.

Nevertheless, Kita's work on hypervalent iodine chemistry has broadened the synthesis of spirocyclic lactones or lactams by hypervalent iodine oxidation to bicyclic hydroindolenones and hydroquinolenones. Wipf⁵³ has adopted Kita's method to synthesize some *Stemona* alkaloid natural products 'useful alkaloids of pharmaceutical interest' *via* a formation of azabicyclic hydroindolenone derivatives (**57**) in highly stereoselective fashion, by oxidation of tyramine or tyrosine derivatives with a small excess of BTIB or DAIB, respectively, in the presence of an alcohol. In reaction with protected tyramine (**55**), methanol as nucleophilic source and also as co-solvent attacks the electrophilic aromatic ring created by the hypervalent iodine reagent, forming the spiroaddition of methoxy dienone (**56**) (Scheme 32). On basification, attack by the

nitrogen lone pair from the carbamate led to stereoselective *cis*-azabicyclic enone formation (**57**). Similar reaction with tyrosines (**58**) also yielded another *cis*-azabicyclic enone (exo) derivative (**61**) (Scheme 32) either through separate steps, *via* spirocyclic (**59**) and then ring opening to hydroxydienone (**60**) followed by ring closure, or in one pot, but the mechanistic approach is quite different from the tyramine case due to the carboxyl group that is present. One possible explanation of *exo*-isomer formation is the presence of an intramolecular H-bond between the tertiary alcohol and the ester functionality that is responsible for the extra stability in the *exo*-isomer.



Scheme 32.

5.0 Dehydrogenation

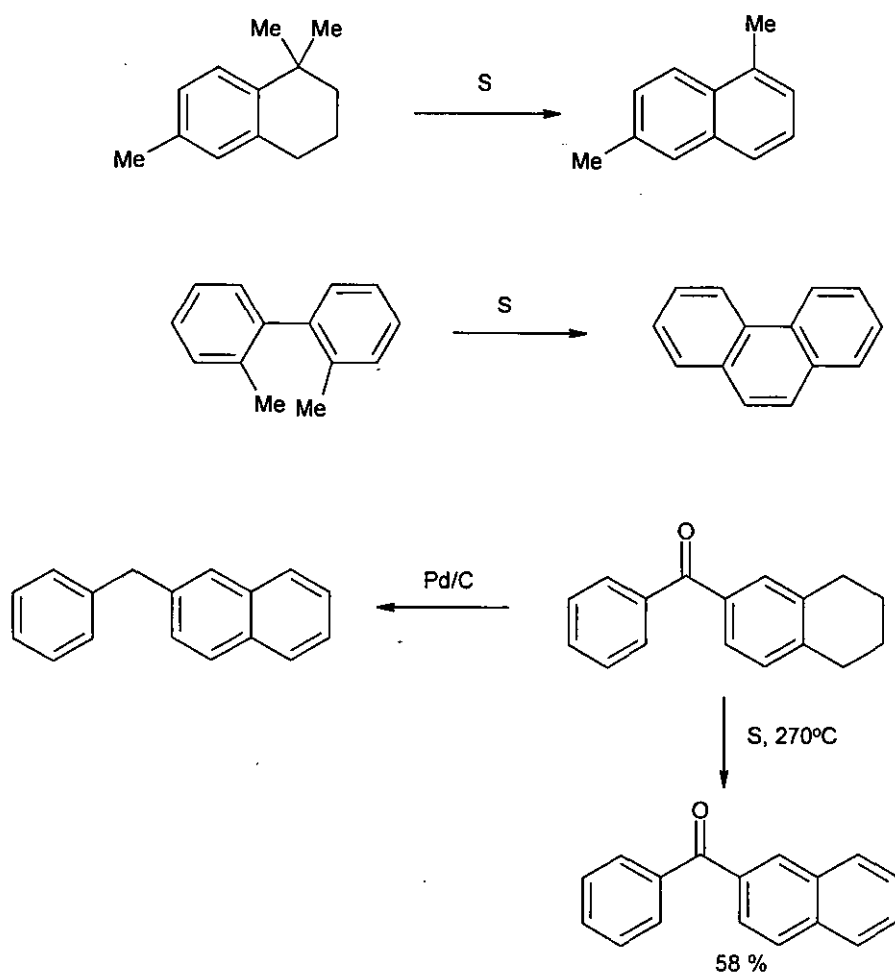
Dehydrogenation reactions are becoming of broad synthetic utility. A typical reaction is when a pair of hydrogen atoms are removed in a reaction substrate to give unsaturated bonds in the product. Dehydrogenation is often used during the last step of a synthesis for forming polycyclic aromatic compounds or their derivatives or formation of steroid derivatives.⁵⁴ More recently, it was also used for coupling of secondary silanes⁵⁵ or for inversion of a β -chiral carbon centre of a steroid-based substrate.⁵⁶

Traditional methods of dehydrogenation often involved sulfur or selenium. They are still useful for the synthesis of unsubstituted polycyclic aromatic ring systems even though they are unpleasant to handle. Apart from the sulfur-type dehydrogenation, metal catalysed dehydrogenation is also common, such as palladium or platinum supported on activated charcoal. Oxidising reagents like manganese dioxide, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or *o*-iodoxybenzoic acid (IBX) have been reported as used for dehydrogenation. Newer catalytic transition metal complexes reported by Crabtree⁵⁷ and Jensen⁵⁸ have been of interest over the last two decades. Crabtree used an iridium complex to dehydrogenate cyclopentanes to cyclopentadienyls using a hydrogen acceptor. This iridium complex, now known as a “pincer-ligated iridium” complex, has been used for selective dehydrogenation of alkanes and alkyl groups.⁵⁹

5.1 Dehydrogenation With Sulfur And Selenium

Sulfur and selenium are the classical reagents for dehydrogenation. Sulfur exists in several molecular forms including a stable eight-membered ring crown conformation or as linear chains of widely variable length.⁶⁰ Selenium also exists in various forms, such as a cyclic Se₈ structure.

The reason sulfur and selenium act as dehydrogenation reagents is due to their tendency to complete their outer electronic configurations of 3s²3p⁴ or 4s²4p⁴. This can be achieved by acquisition of two electrons with formation of the gases, H₂S and H₂Se, that are however toxic with distinctive odours. The exact mechanism of dehydrogenation by using selenium and sulfur is not well established hence it will not be discussed here. Evidence suggests a radical mechanism is involved, with abstraction of hydrogen atoms from allylic or benzylic positions, while other possible mechanisms are not conclusively ruled out.⁶⁰ Some typical examples of dehydrogenation of hydroaromatic compounds are shown below (Scheme 33). It is interesting to compare the dehydrogenation of the phenyl ketone using sulfur and palladium-carbon; the carbonyl group survived well under the sulfur conditions whereas reaction over palladium-carbon gave the reduced but aromatic hydrocarbon 2-benzyl-naphthalene as product.⁶¹

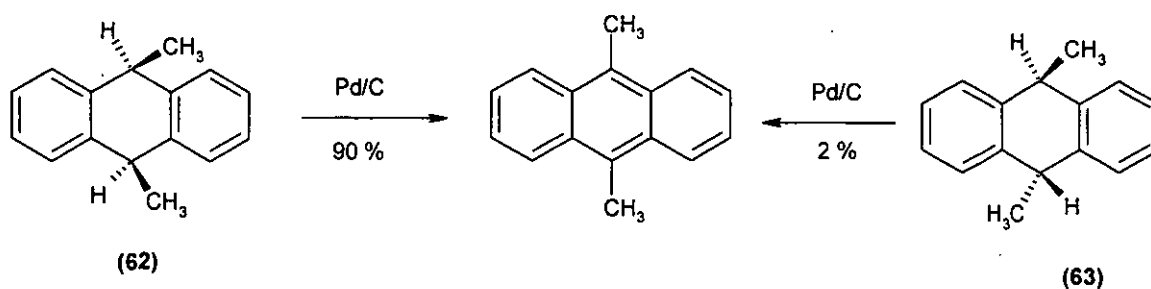


Scheme 33.

5.2 Catalytic Dehydrogenation

In general, dehydrogenation on a metal catalyst proceeds more readily and in better yield when the starting material structure is closer to aromatic. Bulky substituents tend to reduce the rate of reaction, but alkyl substitution has little influence on the overall reaction rate or the temperature required, except where the substituent interferes with adsorption on the catalyst surface. Therefore, methyl groups may cause inhibition to a dehydrogenation reaction since steric blockage may hinder association with the catalyst.⁶² The rate of dehydrogenation of *cis*-9,10-dimethyl-9,10-dihydroanthracene (**62**) to 9,10-

dimethylanthracene over 10 % Pd/C in refluxing diglyme greatly exceeded that of the corresponding *trans* stereoisomer (63) as measured by the percentage conversion (90 % and 2 % respectively) in a 12 hour reaction (Scheme 34).⁶³ Similar results were obtained using monoethyl and diethyl homologues of (62).



Scheme 34.

Catalytic dehydrogenation may or may not necessarily employ a solvent. In the absence of solvent, reactions are usually carried out at higher temperature, 300 °C and above. Reactions in solution are generally conducted in high boiling solvents at reflux, such as cumene, nitrobenzene, quinoline and polyglycol ethers.⁶³

Catalytic dehydrogenation is a reverse of catalytic hydrogenation, the two processes involving the same mechanisms but proceeding from the opposite direction. Unlike hydrogenation, little study of dehydrogenation has been conducted. Experimental evidence supports the generalization that hydrogenation involves *cis* addition of two hydrogen atoms from the less hindered side of the double bond or polycyclic ring system. Hence, dehydrogenation involves predominantly *cis* hydrogen abstraction. Competing secondary processes, including olefin isomerisation, hydrogen exchange and epimerisation, may occur simultaneously on the catalyst surface, complicating attempts to study the mechanism of the hydrogenation-dehydrogenation process. In spite of these difficulties, it is now reasonably well established that hydrogenation occurs by stepwise

transfer of hydrogen atoms to the adsorbed molecule, rather than by concerted *cis* addition. The simplest explanation of the mechanism of dehydrogenation was proposed by Horiuti and Polanyi.⁶⁴

5.3 Quinone Reagents

Quinone reagents have become more popular in recent years for dehydrogenation. They have been used for a wide range of compounds including natural products and carcinogenic hydrocarbon metabolites,⁶⁵ such as steroid or chromone derivatives. One reason for their popularity is due to mild reaction conditions, usually around 100 °C or below. Among many quinone reagents, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), *p*-chloranil and *o*-chloranil are the most widely used (Figure 9). For dehydrogenation of steroids, traditional reagents such as 9,10-phenanthraquinone and its nitro derivatives are frequently used⁶² but DDQ is increasingly employed for the same purpose.

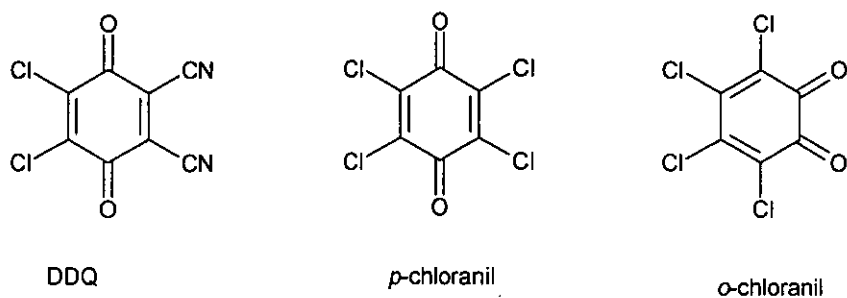


Figure 9.

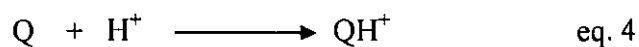
A first versatile use of DDQ for dehydrogenation was reported by Linstead, Braude, Jackman and co-workers^{54,66} with an ionic mechanism suggested for the process.⁶⁷

The reaction is a bimolecular process, where the initial rate determining step is based on slow hydride ion transfer from the substrate to the quinone (eq. 1). The resulting product conjugate acid transfers its remaining proton much more rapidly to the hydroquinone anion, leading to the dehydrogenation product and the hydroquinone (eq. 2).



Other than initial hydride ion transfer, it is worth mentioning that a charge transfer complex may intervene in the initial step of the overall reaction sequence (eq. 3),⁵⁴ since the effective quinones are also known to favour forming such complexes.

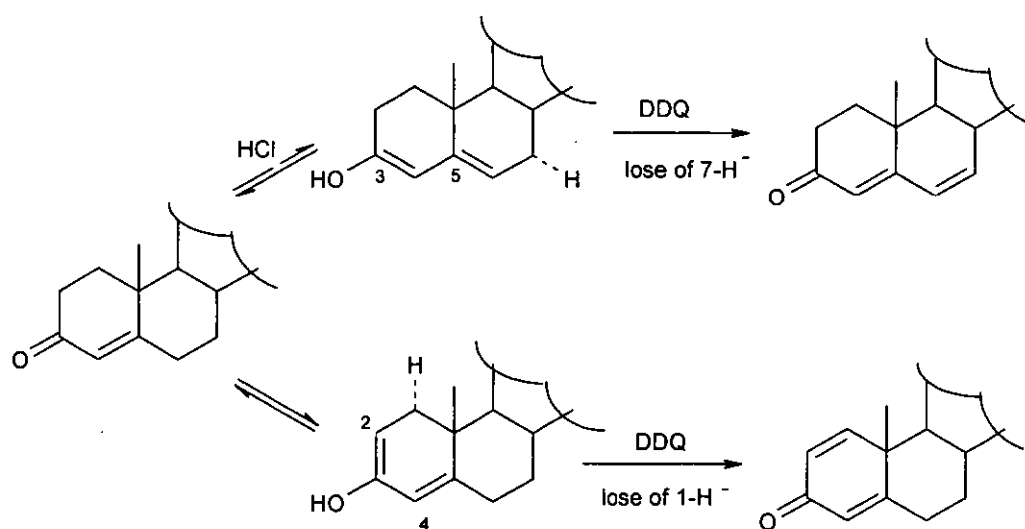
Acid catalysed conditions promoting the protonated quinone cation, QH^+ , could also increase the efficiency of quinones as hydride acceptors (eq. 4 – 6). Others have however suggested that the reaction might proceed simultaneously rather than by stepwise hydrogen transfer.



The solvent polarity is known to affect the stereoselectivity of elimination. When benzene is used with DDQ in dehydrogenation it gives the *cis* elimination product, but when the solvent polarity increases, the *cis* elimination ability decreases.⁵⁴ Most proton eliminations give the alkene product, but in some cases, Wagner-Meerwein-type

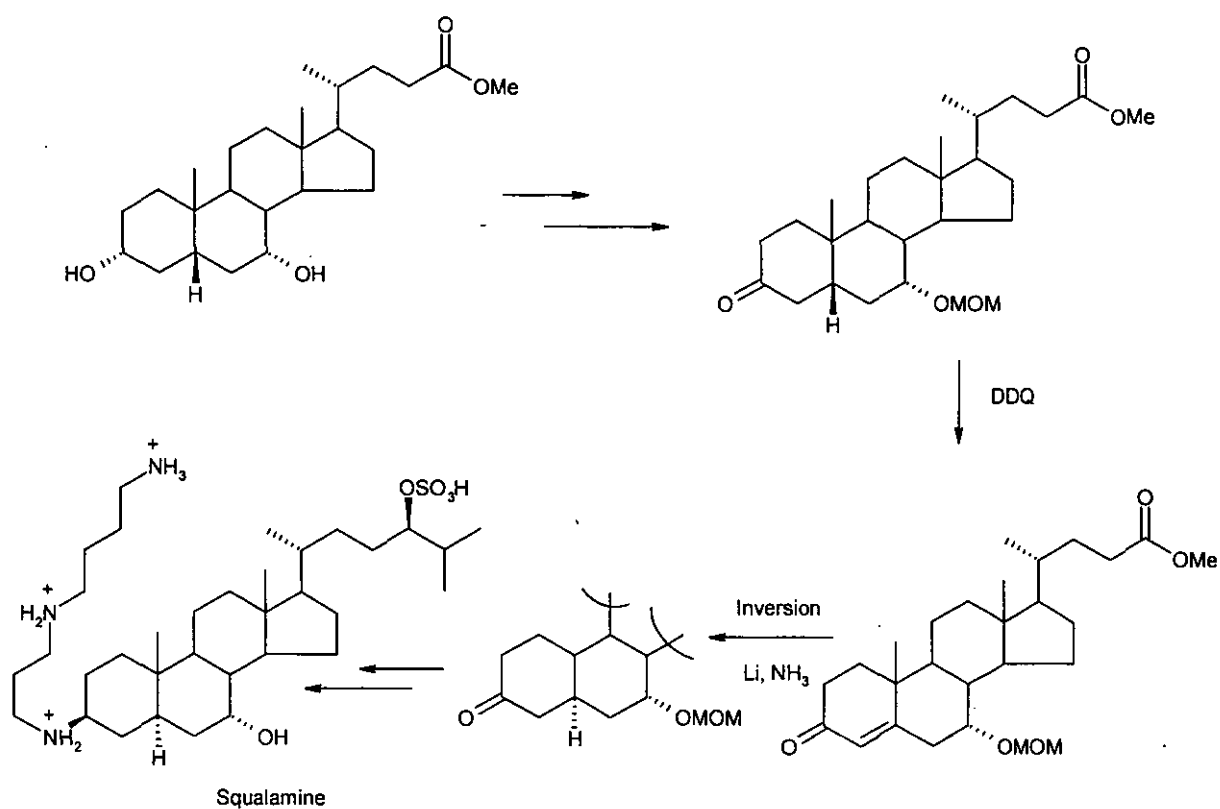
rearrangements occur prior to loss of proton, therefore attention must be paid to predict which intermediates may undergo Wagner-Meerwein-type rearrangements.⁵⁴

One of the most common uses of dehydrogenation is for steroid synthesis, where a hydride ion is removed from an allylic position. Selection of the quinone reagent used can lead to regioisomeric products. Δ^4 -3-Keto steroids react with DDQ alone to give $\Delta^{1,4}$ -3-keto steroids while reaction with chloranil leads to $\Delta^{4,6}$ -3-keto steroids. In the presence of anhydrous hydrogen chloride as a catalyst, DDQ reaction also gives the $\Delta^{4,6}$ -3-keto steroids (Scheme 35). The outcomes can be explained based on preferred enols under different conditions.



Scheme 35.

DDQ has also been used within the synthesis of a squalamine from methyl chenodeoxylcholanate⁵⁶ (Scheme 36) where the α,β -unsaturated ketone is formed *via* a dehydrogenation process which is followed by reduction with lithium in ammonia which resulted in inversion at the β -chiral carbon centre.



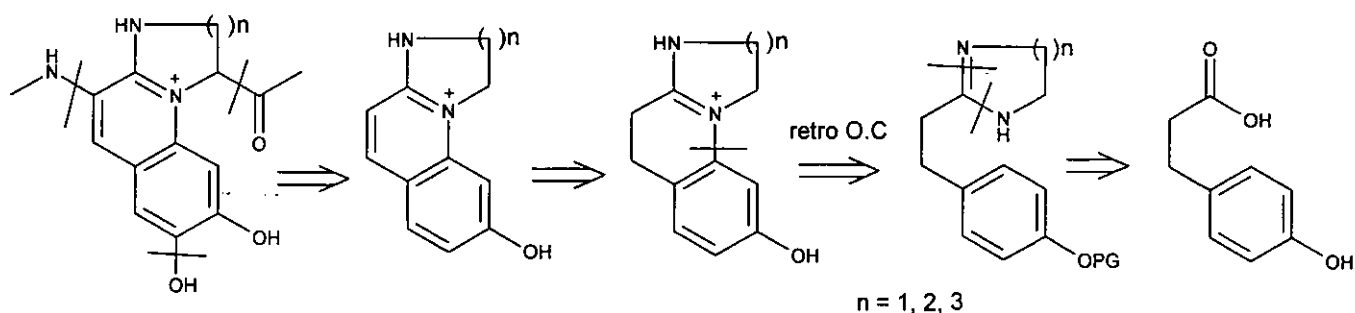
Scheme 36.

In summary, dehydrogenation *via* quinone reagents proceeds as a bimolecular reaction, with the reaction being faster in polar solvents than in non-polar solvents. The rate is unaffected by radical initiators, but influenced by the oxidation potential of the quinone and catalysed by proton donors. Consideration of which reagent to use and the mechanism leading to any intermediates can be useful if a particular regioisomer is required.

6.0 Result And Discussion

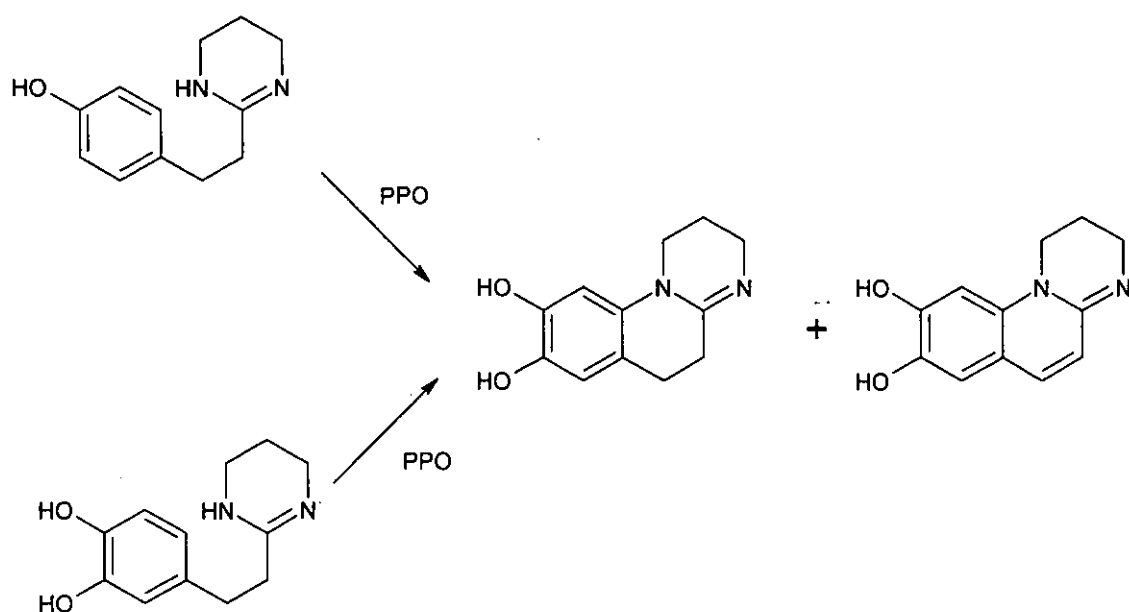
6.1 Basic Chromophore Unit

As outlined in the introduction, it was proposed initially to prepare models of the pyoverdin chromophore lacking the *N* and *C* termini of the pseudopeptide moiety (Scheme 37). We also planned to investigate formation of the lower (5-membered) and higher (7-membered) homologues in the cyclic amidine ring. The biomimetic synthesis proposed would mean that the tricyclic unit could be obtained from oxidative cyclisation (O.C.) of a cyclic amidine carrying a phenolic substituent, in the presence of a hypervalent iodine reagent. Further oxidation of the cyclised tricyclic unit would produce the aromatic tricyclic quinoline as the chromophore model unit.



Scheme 37.

The synthesis began with formation of the cyclic amidines required as precursors for the oxidative cyclisation. The 6-membered ring cyclic amidine, a tetrahydropyrimidine, can be considered as a model for the key unit of ferribactins, where the ferribactin is oxidized during biogenesis of the pyoverdin chromophore in the presence of enzymes. Begley also obtained models of dihydropyoverdin and the pyoverdin chromophore from cyclic amidines through oxidation using enzymes such as *PolyPhenol Oxidase* (PPO) (Scheme 38).¹⁸

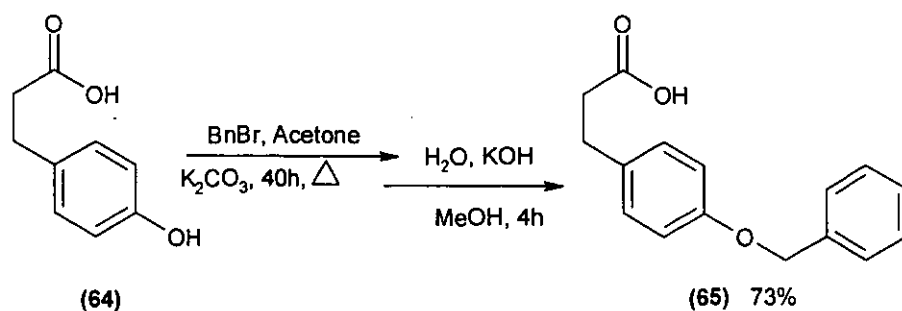


Scheme 38.

Cyclic amidines can be formed from an imidate salt corresponding to the C-2 carbon. To generate the cyclic amidine ring, a diaminoalkane is introduced and both of the amine groups act as nucleophiles while the imidate carbon serves as the electrophile.

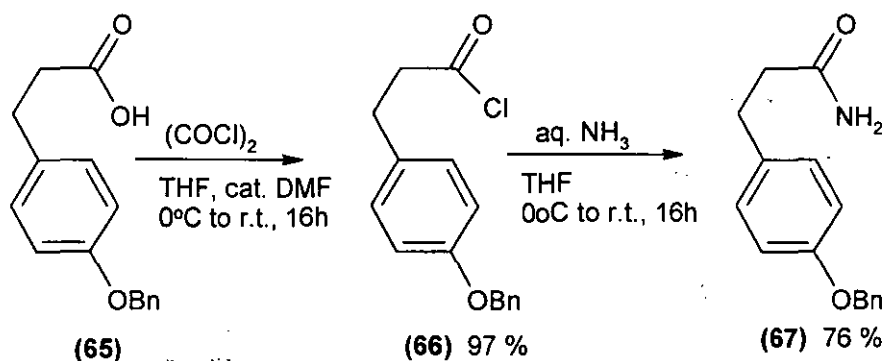
6.1.1 Formation Of Cyclic Amidine – A Ferribactin Model

Our synthesis commenced with a simple, commercially available, carboxylic acid, 3-(4-hydroxyphenyl)propionic acid (**64**) which was first reacted with 2 mole equivalent of benzyl bromide in acetone at reflux in the presence of potassium carbonate to protect the phenolic group. The carboxylic acid was also converted into the benzyl ester, so that the carboxylic acid group was liberated by hydrolysis with aqueous potassium hydroxide under reflux to afford phenol protected 3-(4-benzyloxyphenyl)propionic acid (**65**) in 73% overall yield (Scheme 39).



Scheme 39.

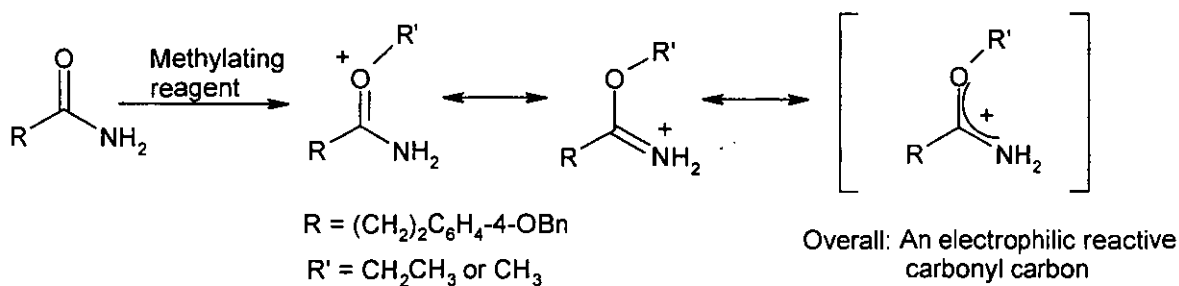
Theoretically, amides can be formed directly by reaction of a carboxylic acid with aqueous ammonia, but due to the low electrophilic reactivity of the carboxylate ion the rate of nucleophilic substitution is very slow and requires forcing conditions. Hence the carboxylic acid was activated by conversion with oxalyl chloride into the acyl chloride (**66**) before reaction with concentrated ammonia solution to give 3-(4-benzyloxyphenyl)propanamide (**67**) in 73% yield over the 2 steps (Scheme 40).



Scheme 40.

The cyclic amidines can be constructed through an intermediate imidate formed by *O*-alkylation of the amide, as described in the introduction. In order to activate the amide as an imidate, two good alkylating reagents were chosen for this *O*-alkylation,

triethyloxonium tetrafluoroborate (Meerwein's reagent) and methyl trifluoromethanesulfonate (methyl triflate). Weintraub *et al.*¹⁹ have shown that Meerwein's reagent is superior to dimethyl sulfate for *O*-alkylation of amides. Preparation of cyclic amidines *via O*-imidates is an alternative to the *S*-methyl thioimide route used by some previous workers in our group (see earlier) that usually takes more steps; the unpleasant smell of sulfur compounds (or Lawesson's reagent) can also be avoided. With insertion of the alkyl group onto the carbonyl oxygen, *via* lone pair donation from the amide nitrogen atom into the carbonyl to promote oxygen alkylation, electrophilicity of the carbonyl carbon should be increased and hence provide the reactivity required for amidine formation. Imidate salts can be written in two octet resonance forms (Scheme 41) with an electrophilic carbon atom. They are isolable, although sensitive to moisture.

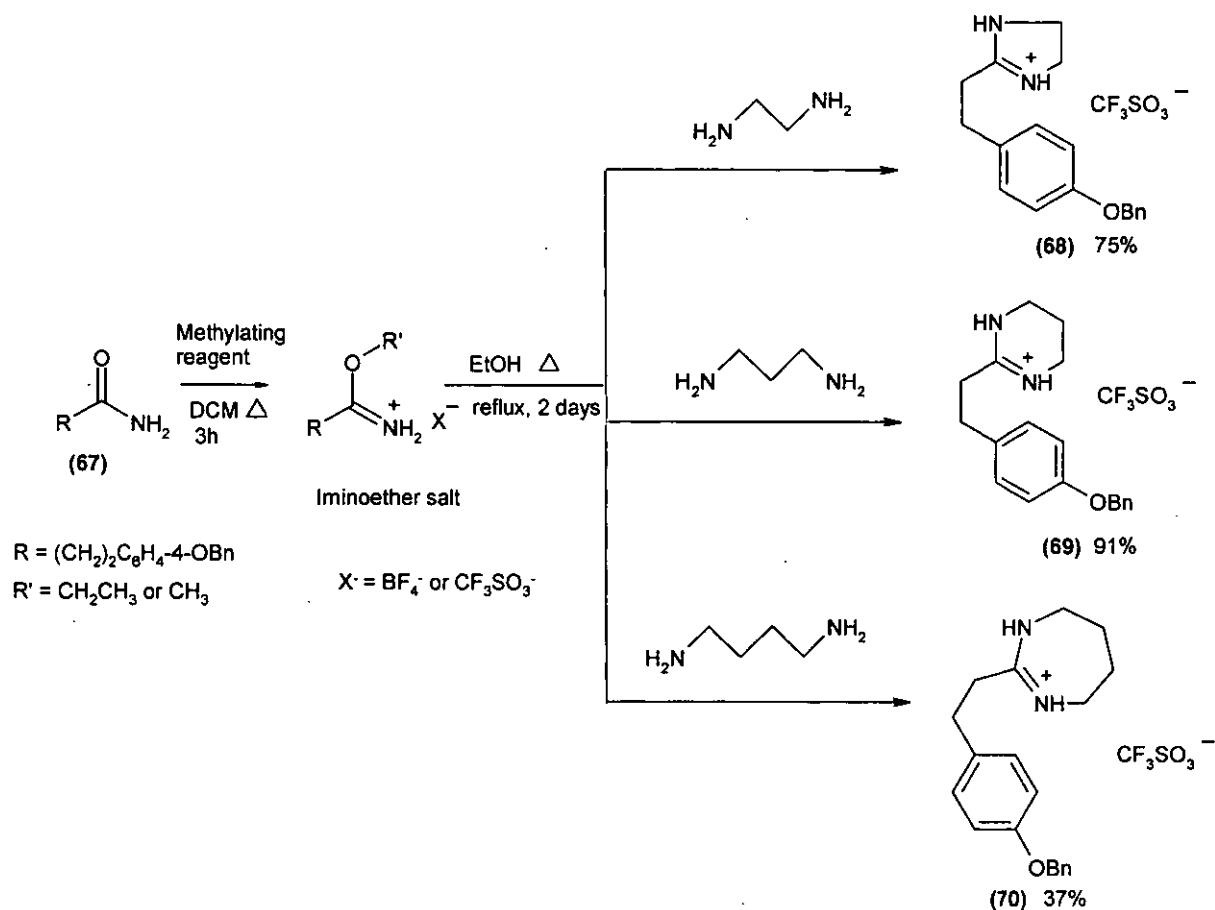


Scheme 41.

The yield of imidate salt formation is highly affected by three factors: hydrolysis, temperature and alcoholysis. Hydrolysis resulting in ester formation, usually from adventitious moisture, is most serious among the factors. This reaction is accelerated by protons and the use of anhydrous diluents and reactants is necessitated. The hydrolysis is fast and effective in the case of the lower aliphatic members, which tend to be hygroscopic in nature,¹⁵ but less problematic with aromatic imidates. For this reason our reactions were performed under anhydrous conditions. The reactions were performed by reacting the 3-(4-benzyloxyphenyl)propanamide with the alkylating reagent in dry DCM as solvent during *O*-alkylation to form the imidate salts, after which the solvent was

removed and then dry diamine (1,2-diaminoethane, 1,3-diaminopropane or 1,4-diaminobutane) was added in the presence of dry ethanol for the cyclic amidine formation *in situ*. According to many reports, formation of imidates *via* *O*-alkylation of amides with Meerwein's reagent, and then formation of cyclic amidine should be straightforward even through the intermediate imidate is moisture sensitive. But during our work, it was found that when triethyloxonium tetrafluoroborate was used according to the standard method, barely 10% of the corresponding cyclic amidines (**68** and **69**; **tetrafluoroborate salts**) was obtained with another 40% starting amide compound recovered without any of the imidates isolated. Little improvement was seen even if the starting material, reagents and solvent were freshly dried for the reaction.

On the other hand, when methyl trifluoromethanesulfonate was used as alkylating agent, the yields could be increased substantially for both 5- and 6-membered cyclic amidines (Scheme 42), based on the cyclic amidinium salt produced without basic work up. The trifluoromethanesulfonate salt of methyl 3-(4-benzyloxyphenyl)propaniminoether derived from the propanamide was reacted with 1,2-diaminoethane and with 1,3-diaminopropane to yield 75% of 2-[2-(4-benzyloxyphenyl)ethyl]-4,5-dihydroimidazole (**68**) and 91% of 2-[2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidine (**69**) respectively (Table 1.). For the 7-membered ring amidine synthesis, 2-[2-(4-benzyloxyphenyl)ethyl]-4,5,6,7-tetrahydro-1*H*-[1,3]diazepinium (**70**) was formed in 37% yield by activating the amide with methyl triflate and then treating with 1,4-diaminobutane *in situ*. The seven-membered ring amidine thus gave much lower yield than its 5- or 6- cyclic amidine homologues. This is presumably due to less favourable geometry for ring closure and a less stable product.



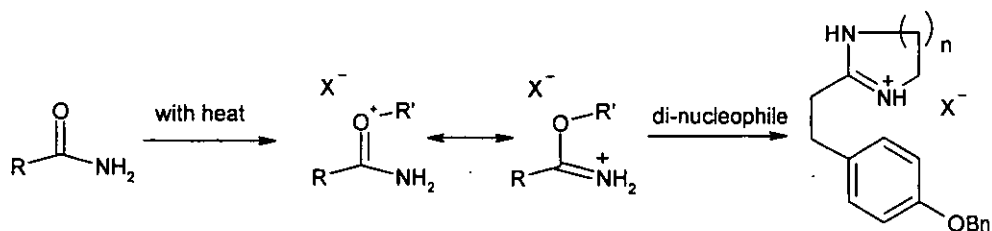
Scheme 42.

The reaction was monitored throughout by TLC, and it was found that the alkylation step was incomplete at room temperature, i.e. incomplete formation of iminoether salt, whichever of the alkylating reagents was used. As a result only around 50% cyclic amidine was produced initially from the triflate reagent when the reaction proceeded at ambient temperature. However, if the methylation was carried out at higher the temperature of reflux with DCM for 3 hours (Scheme 43), the yield of amidine was enhanced to as much as 90% for the 6-membered ring amidine despite reducing the duration of the heating with diaminoalkane to 1 to 2 days (Table 1), less than half of the original timing. Prolonging the heating beyond 3 hours during the alkylation gave no further improvement in the yield for either 5- or 6-membered cyclic amidine. This implied the cyclisation reaction was critically dependent on the methylation step where

the alkyl group attached onto the amide oxygen. If the amide could not be fully alkylated, lower quantities of iminoether would be present for the formation of cyclic amidine. Treating the imidate salt with diamine in the presence of alcohol also showed no sign of any reaction of the imidate salt with alcohol to produce the ester, which is presumably due to the more reactive nucleophilic diamine being present. Our results are summarized below in Table 1.

Table 1. A summary of formation of cyclic amidines *via* *O*-alkylation.

Alkylating reagent / conditions	Diaminoalkane / conditions	Product – the yield is based on the assumption of salt!
Triethyloxonium tetrafluoroborate, ambient temp. in DCM 1 day	1,3-diaminopropane in EtOH, reflux 4 days	10 % + 40 % s.m.
Triethyloxonium tetrafluoroborate, ambient temp. in DCM 1 days	1,2-diaminoethane in MeOH, reflux 4 days	10 % + 32 % s.m.
Methyl triflate, r.t in DCM 3 days	1,3-diaminopropane in EtOH, reflux 3 days	35-46 % + 30 % s.m.
Methyl triflate, r.t in DCM 3 days	1,2-diaminoethane in EtOH, reflux 3 days	37-46 % + 39 % s.m.
Methyl triflate, reflux 30mins in DCM, r.t 1 days	1,3-diaminopropane in EtOH, reflux 2 days	31 %
Methyl triflate, reflux 2 h in DCM	1,3-diaminopropane in EtOH, reflux 2 days	45 % + 23 % s.m.
Methyl triflate, reflux 3 h in DCM, r.t 2 days	1,3-diaminopropane in EtOH, reflux 2 days	91 % + 4 % s.m.
Methyl triflate, reflux 3 h in DCM	1,2-diaminoethane in EtOH, reflux 2 days	75 % + ~15 % s.m.
No significant improvement over 2 or 3 h reflux with the methyl triflate		



Scheme 43.

Our original procedure proposed a basification with aqueous hydroxide during work up in order to obtain salt-free cyclic amidine. Unfortunately, only partial salt removal was achieved, and the aqueous basic extraction led to lowering the yield of 2-[2-(4-benzyloxyphenyl)ethyl]-4,5,6,7-tetrahydro-1*H*-[1,3]diazepinium (**70**) by at least 10%. We decided to maintain the presence of counter ion without basification. To confirm its presence and identify the counter ion, it was necessary to crystallise an amidine for X-ray crystallography analysis.

The structure of the 6-membered ring product, 2-[2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate (**69**), was confirmed by X-ray crystallography (Figure 9) with a triflate anion coordinated with a nitrogen atom of the amidinium cation in a repeating chain (Figure 10). The structure also showed that the cyclic amidine exists as a planar amidinium portion with the centre of the three carbon unit, labeled as C2A or C2B below found to be pointing away from the rest of the plane, in what is known as “an open envelope” conformation similar to that found in cyclopentanes (for detail of X-ray results see Appendix I).

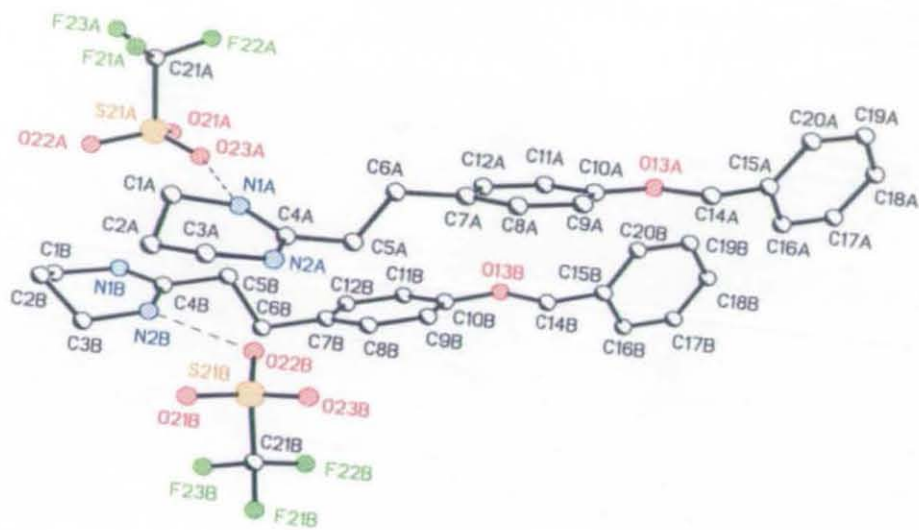


Figure 9.

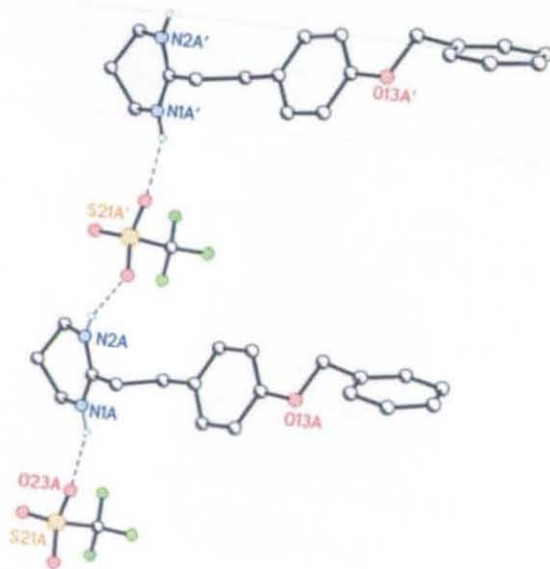
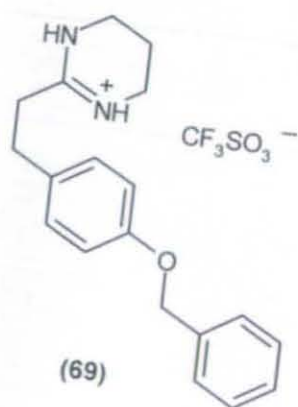
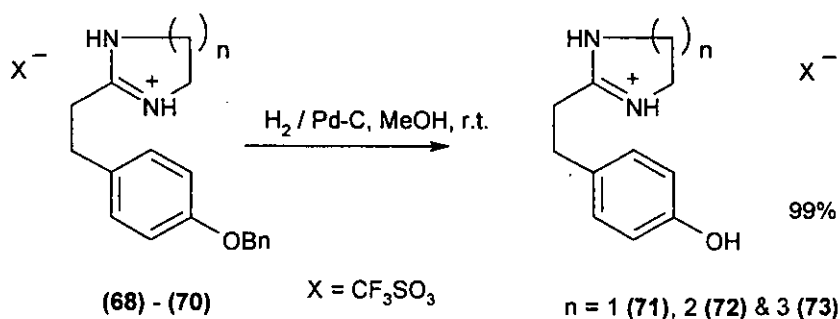


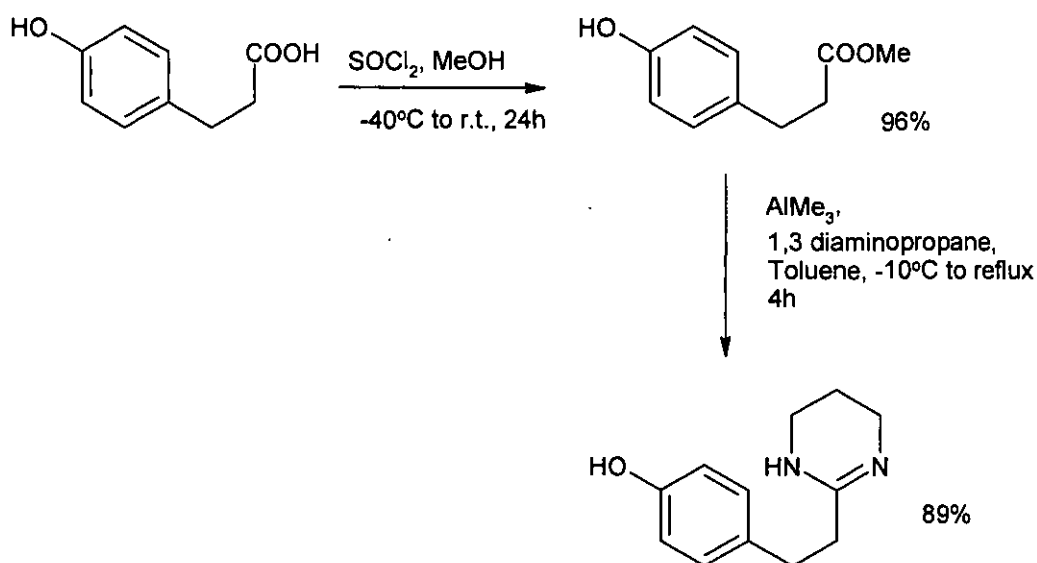
Figure 10.

Removal of the protecting benzyl group can be achieved simply by hydrogenolysis with 10% palladium on carbon and under an atmosphere of hydrogen to afford separately the triflate salts of 2-[2-(4-benzyloxyphenyl)ethyl]4,5-dihydroimidazolium (71), 2-[2-(4-hydroxyphenyl)ethyl]3,4,5,6-tetrahydropyrimidinium (72) and 2-[2-(4-hydroxyphenyl)ethyl]-4,5,6,7-tetrahydro-1*H*-[1,3]diazepinium (73) in up to 99% yield (Scheme 44). Since the polarity of the amidinium phenols increases significantly over the benzyl ethers, in order to obtain the pure phenols, the amidinium salts of the benzyl compounds must be purified by silica chromatography prior to the hydrogenolysis. The triflate salts survived chromatography intact. The unprotected phenolic imidazolium salt was found to be less stable than the 6- & 7-membered ring cyclic amidinium salts.



Scheme 44.

After our synthesis was complete, an alternative route to the tetrahydropyrimidine (72) was reported in supplementary information (Scheme 44a) by Begley *et al.* although only in very small scale.¹⁸ Our attempts to repeat their approach in the 3,4-dihydroxy series were unsuccessful in the ring formation step (see later).



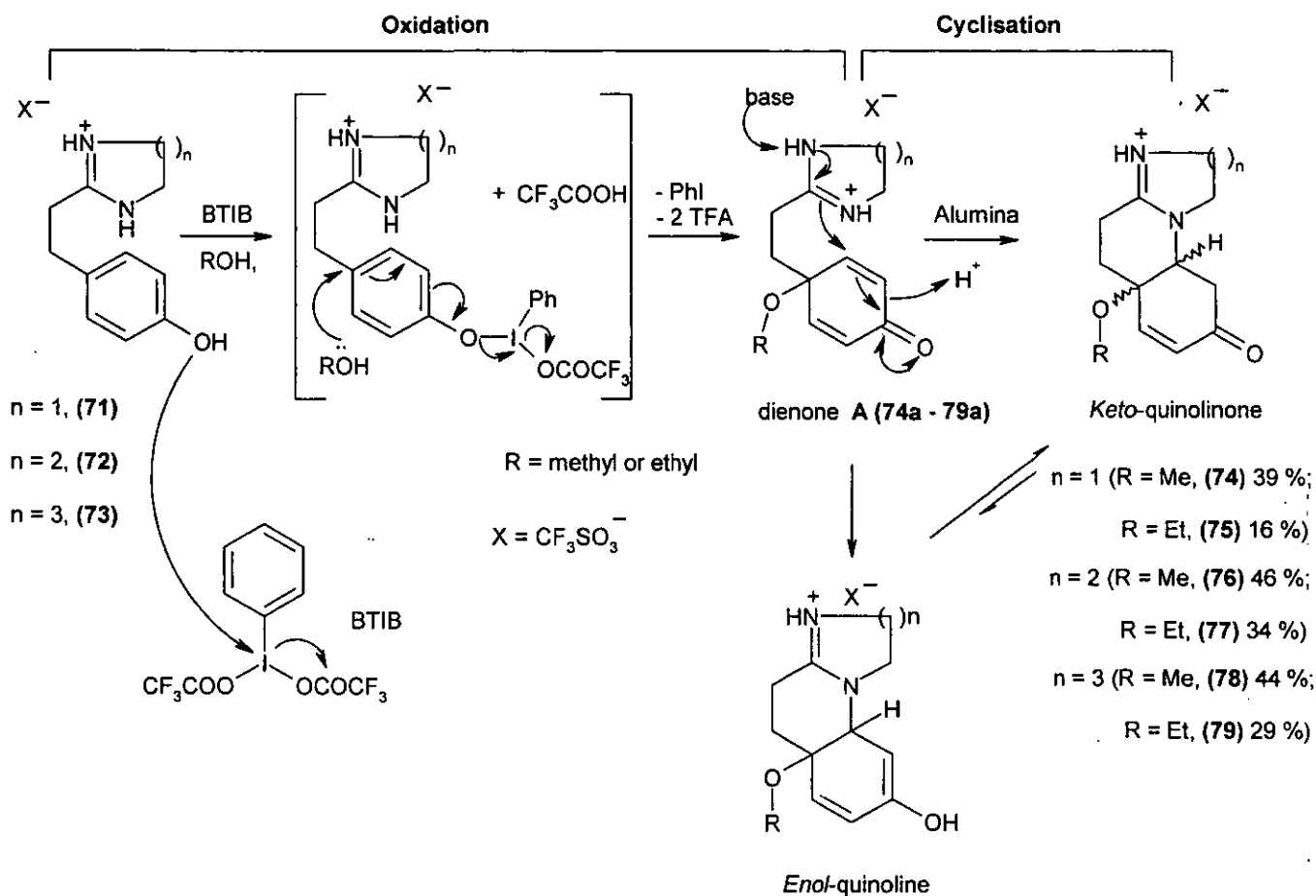
Scheme 44a

6.1.2 Formation Of Quinolinone

In order to synthesize the chromophore model based on the pyoverdine siderophore, oxidative cyclisation of the phenolic cyclic amidinium salts was carried out with the mild selective hypervalent iodine(III) compound *bis*(trifluoroacetoxy)iodobenzene (BTIB) as an oxidising reagent. The method was based on the reports by Kita and Ciufolini.^{51,52} The iodine(III) oxidizing reagents behave characteristically for hypervalent iodine, where the phenolic group was oxidized to alkoxy cyclohexadienones (**A**) (R = Me, Et; n = 1, 2, 3) in the presence of alcohol **I** (Scheme 45), where the alkoxy groups (OR) are alcohol dependent. Ethanol and methanol were used herein as the solvent and as well as the source of nucleophile leading to the formation of the cyclohexadienone. The hypervalent iodine reagent acted as electrophile which was attacked by the mild nucleophilic phenol oxygen and the oxidation took place by nucleophilic alcohol attack at the *para* position to the phenolic group hence furnishing the alkoxy 4,4-disubstituted cyclohexa-2,5-dienone with loss of iodobenzene (Scheme 45). The alkoxy dienones are susceptible to

nucleophile, here the cyclic amidine nitrogen, which would promote a subsequent intramolecular 1,4-Michael cyclisation.

The cyclohexadienones (A) were hard to isolate in pure form due to their instability and their high polarity, although NMR spectroscopic evidence indicated their formation. Attempts to isolate the products were unsuccessful by silica chromatography or neutral Florisil, but these cyclohexadienones could be spontaneously cyclised and separated in the presence of basic alumina *via* intramolecular Michael-type 1,4-addition by the lone pair of electrons from the amidinium nitrogen atom onto the α,β -unsaturated cyclohexadienone β -carbon. This resulted in 39 - 46% of various *keto*-methoxyquinolinones (74, 76 & 78) from BTIB oxidations in methanol, which were separated on a basic alumina column; no *enol*-methoxyquinolinones were obtained. The moderate yields in these oxidative cyclisations were not unusual as many hypervalent iodobenzene transformations of complex phenolic substrates reportedly proceed in only around 50% yield, which may suggest an innate limitation of oxidation with hypervalent iodine reagents. The cyclisation can either be carried out *in situ* with a mixture of BTIB and basic alumina in the reaction, or it can take place during alumina chromatography of the cyclohexadienone. This kind of intramolecular cyclisation also takes place in the basic environment of sodium or potassium carbonate with polar solvent, as reported by Kita and Wipf,^{51, 53} due to neutralization of the amidine salt under basic conditions. The corresponding ethoxyquinolinones (75, 77 & 79) were isolated from basic alumina chromatography after BTIB oxidations in ethanol.



Scheme 45.

A milder hypervalent iodine reagent, diacetoxyiodobenzene (DAIB) was also used in the oxidative cyclisation to give relatively similar yields of the quinolinone product as obtained using BTIB but the rate of reaction was slower since the electronegativity of the two acetoxy ligands is far less than the *bis*-trifluoroacetoxy, hence the electrophilicity of the iodine atom is reduced and therefore the overall reactivity is lower. Reaction with DAIB took at least several hours to reach the yield that could be obtained with BTIB in less than 30 minute at ambient temperature and no advantage was observed.

It has been known that the oxidation of phenol with hypervalent iodine (III) reagent would promote nucleophilic addition to the *ortho* / *para* positions but this has been little

applied for nucleophilic nitrogen. Both oxygen and fluoride nucleophile,⁶⁸ for example from alcohol and pyridinium polyhydrogen fluoride, have been used for *para*-oxidation of phenol. One example of the spirocyclic addition by a nitrogen nucleophile with oxazine and oxazoline was reported by Ciufolini *et al.*, and this will be discussed later. Ciufolini and his co-workers carried out a series of experiments related to our alkoxy addition with hypervalent iodine(III) reagent which included endeavoring to work on spirocyclic addition of imidazolines but only generated quinolinones through oxygen spiro addition and nitrogen 1,4-Michael cyclisation (Scheme 30), similar to the oxidative cyclisations that we report herein. However, no experimental details were presented.⁵²

Of the by-products of the oxidation reaction, the iodine(III) reagent produced iodobenzene from the reductive elimination, that was removed by extraction between petroleum ether and acetonitrile, and the TFA by-product was partially removed by reduced pressure rotary evaporation, or remained on the basic alumina during chromatography. Formation of the bridgehead methoxy-octahydroazepinoquinolinone (78), methoxy-hexahydropyrimidoquinolinone (76) and methoxy-hexahydroimidazoquinolinone (74) from methanol gave at least 10 to 20 percent better yield than the ethoxy quinolinone counterparts (79, 77 and 75) deriving from ethanol as solvent, and perhaps this was due to the slightly less steric hindrance to insertion of the nitrogen in the Michael addition.

Generation of the 5-membered ring methoxy- and ethoxy-hexahydroimidazoquinolinones (74, 75) afforded lower overall yields than other quinolinones (76 - 79). Perhaps the substrates were less reactive or the products were more difficult to purify using chromatography. Similar derivatives obtained by Ciufolini were also reported in around 30 % yield. The geometry of the 5-membered ring dihydroimidazole possibly restricted the approach trajectory required for the 1,4-Michael cyclisation onto the α,β -unsaturated cyclohexadienone. It must also be noticed that the *keto*-quinoline could exist with diastereomeric configurations at the ring junction.

Crystallisation of the triflate salt of ethoxy-hexahydropyrimidoquinolinone (**77**) from chloroform provided crucial information after carrying out the X-ray crystallography. The data confirmed the *cis* ring junction configuration with the cyclisation having taken place from the opposite face to the ethoxy group (Figure 11 & Appendix II). Once again the triflate counter ion was seen to coordinate with a protonated nitrogen atom. No sign of *trans* diastereoisomer was observed or identified either from the NMR spectrum or the X-ray structure.

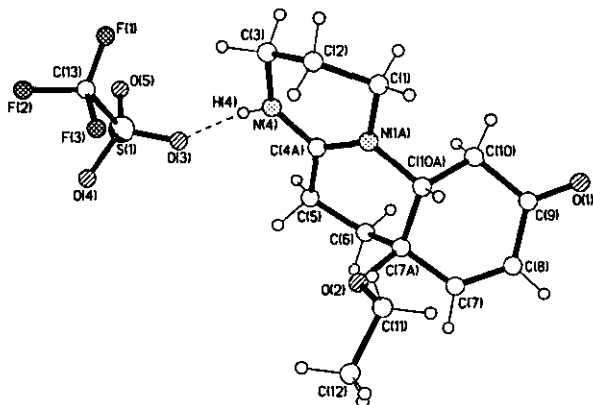
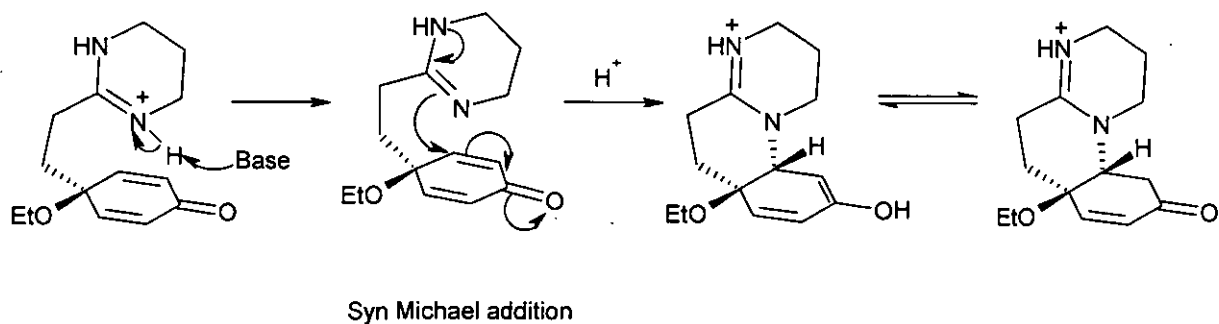
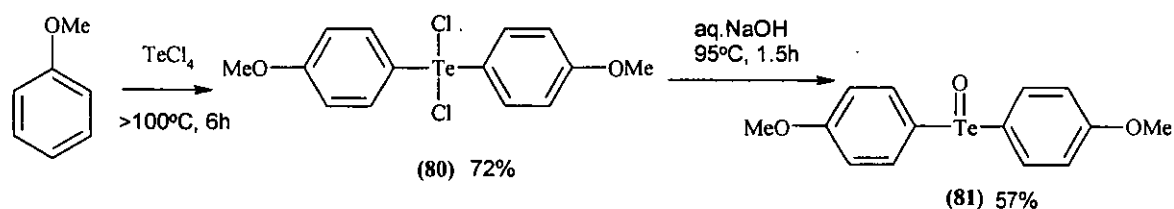


Figure 11.

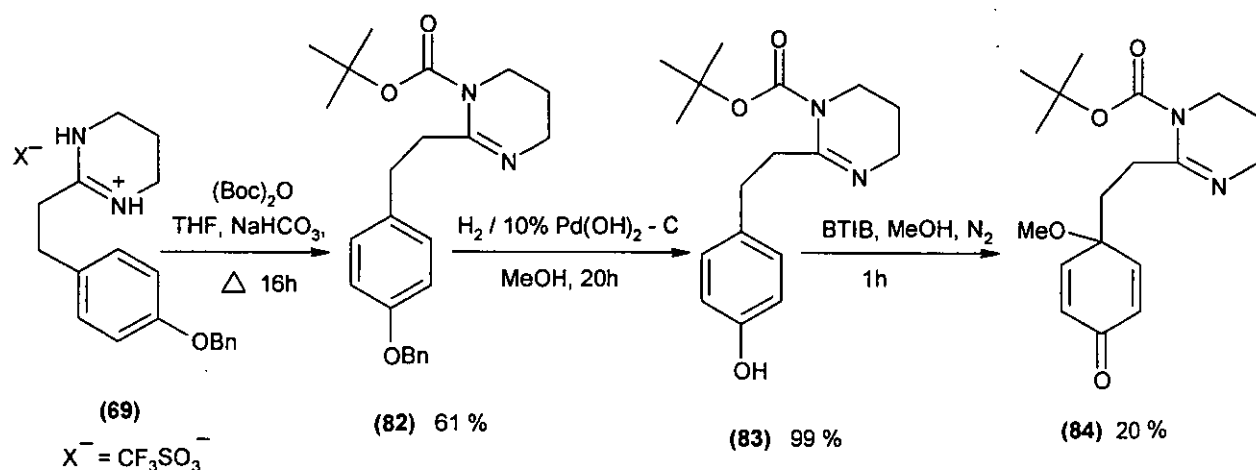
An effort to oxidatively cyclise the phenolic amidine (**72**) with *N*-chlorosuccinimide failed to afford the cyclised product after alumina column. It is suggested a chlorinated phenol may have been formed by using NCS.⁶⁹ Another mild oxidizing reagent, *bis*(4-methoxyphenyl)tellurium oxide (**81**) was made from base hydrolysis of *bis*(4-methoxyphenyl)tellurium dichloride (**80**),⁷⁰ derived from dry anisole and tellurium tetrachloride (Scheme 46),⁷¹ to attempt the oxidation and cyclisation of the 2-[2-(4-hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium (**72**) but again this failed to afford any substantial product.



Scheme 46.

Due to the instability and polarity of the intermediate cyclohexadienone, it was impossible to separate any of the cyclohexadienone. Thus, it was not clear whether the moderate yield was due to the oxidation step or the intramolecular cyclisation step. A strategy was adopted to attempt to reduce the polarity of the dienone by protecting the amidine with a *tert*-butyloxycarbonyl (Boc) group in the hope that the dienone compounds might be able to isolate and purify. 2-[2-(4-Benzyloxyphenyl)ethyl]-1(3)-*tert*-butyloxycarbonyl-3,4,5,6-tetrahydropyrimidine (**82**) was produced from di-*tert*-butyl dicarbonate and the corresponding pyrimidinium triflate (**69**) and this was subsequently hydrogenated to remove its benzyl protecting group as before and produce phenol (**83**) (Scheme 47), which was then treated with BTIB in methanol to oxidize without cyclisation, to yield dienone (**84**) in only 20 % yield. The compound was isolated after silica chromatography but appeared to be unstable, decomposing by the next day at room temperature which may be due to the sensitive dienone group. Although we do not have

definitive evidence to explain why the oxidative cyclisation was overall moderate-yielding, it is likely to be due to the instability of the dienone formed.



Scheme 47.

6.1.3 Formation Of Tetrahydropyrimidoquinolinium Salt – A Dihydropyoverdin Model

According to the hypotheses for the biosynthesis of the pyoverdins,^{17, 18} dihydropyoverdins were recognised as one of the key intermediates in the process of pyoverdin chromophore formation, that occur after oxidative cyclisation of ferribactin but before oxidation to the final pyoverdin chromophore. Following this pathway, preparation of our pyoverdin chromophore model through a biomimetic strategy requires that the alkoxy quinolinone undergoes an elimination of the alkoxy group in order to regain the benzene aromaticity such that the model is then equivalent to the dihydropyoverdin in a biomimetic sense.

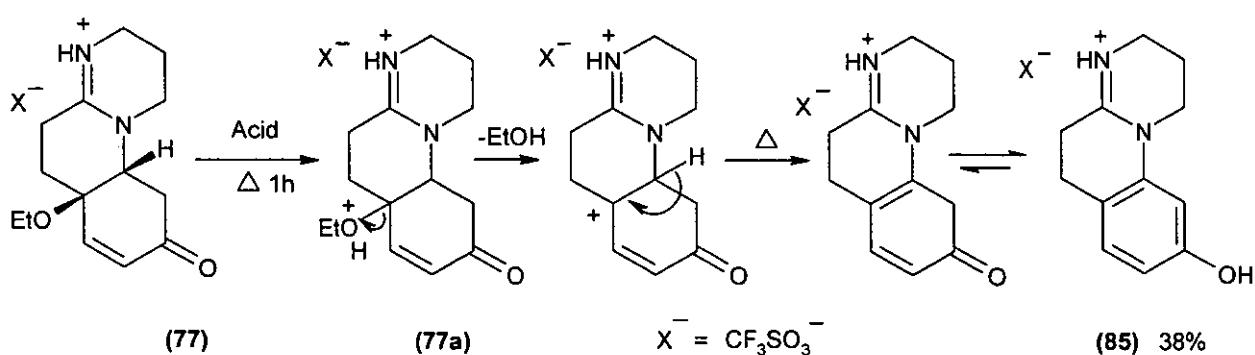
Both the methoxy and ethoxy bridgehead substituents of the *keto*-quinolinones (**74** - **79**) need to be removed to achieve the aromatic ring. Elimination of alcohol could be carried

out by acidification, where the alkoxy functionality is protonated prior to elimination. Various acidic protocols were attempted using (77) with the results summarised in Table 2 below. Neither neat trifluoroacetic acid nor hydrochloric acid at ambient temperature or at reflux gave any sign of the desired hydroxyquinoline product. Passing the compound through acidic or basic Amberlyst resin also did not afford any product. Elimination using DBU as base also failed to yield product. Use of neat trifluoromethanesulfonic acid (TFSA) at room temperature and then distillation in a Kugelrohr apparatus did however give the expected hydroxyquinoline from the ethoxyquinolinone. Later it was found that the reaction would not occur if heating was not used, despite TFSA being one of the most powerful monoprotic acids. Heating the reaction with TFSA is thus crucial.

Table 2. Conditions used in attempting to remove the ethoxy group from (77).

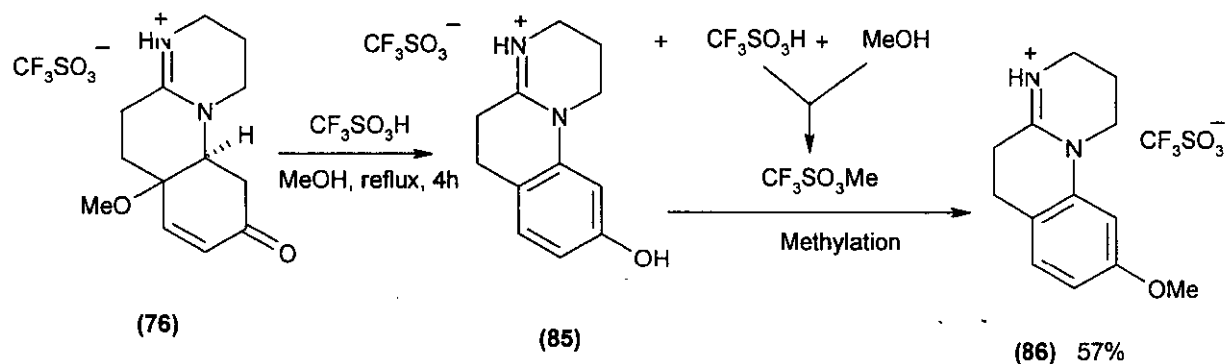
Conditions	Work up	Results
In trifluoroacetic acid at ambient temperature	Acid removed by high vacuum rotary evaporation	No change
In TFA with reflux for an hour	As above	No change
Acidic Amberlyst resin in methanol at room temperature	Filtration then remove solvent	No change
Acidic Amberlyst resin in DCM with reflux	As above	No change
Stirring at room temperature with HCl	Remove acid	No change
Basic Amberlyst resin in ethanol at room temperature	As above	No change
Basic Amberlyst resin in ethanol with reflux	As above	No change
DBU in DCM reflux	No	No change
Trifluoromethanesulfonic acid (TFSA) at room temperature	Acid removed by Kugelrohr then neutralised	ethoxy group removed, gave 38%
TFSA at room temperature	Neutralised to pH 8	No change

Although both the bridgehead ethoxy and methoxy groups in the tetrahydropyrimidinoquinolines were removed successfully using TFSA, different quinoline derivatives were obtained. Elimination of ethanol from 6a-ethoxy-2,3,6,6a,10,10a-hexahydro-1*H*,5*H*-pyrimido[1,2-*a*]quinolin-9-one (**77**) in the presence of neat TFSA took place firstly by protonation of the ethoxy group followed by ethanol elimination on heating and tautomerisation to the 2,3,5,6-tetrahydro-1*H*-pyrimido[1,2-*a*]quinolin-9-ol salt (**85**) in 38% yield.



Scheme 48.

Elimination of the methoxy group from (**76**) surprisingly gave a different quinoline, and this was identified by the observation of an unexpected singlet peak at $\delta 3.8$ in the proton NMR spectrum which corresponded to a methoxy group. This can be explained by the elimination of methanol which further reacted with the excess triflic acid to form methyl triflate (Scheme 49). This methyl triflate acted as an alkylating reagent with the initial elimination product 2,3,5,6-tetrahydro-1*H*-pyrimido[1,2-*a*]quinolin-9-ol resulting in the formation of 9-methoxy-2,3,5,6-tetrahydro-1*H*-pyrimido-[1,2-*a*]quinolinium salt (**86**) as well as a small quantity of the 2,3,5,6-tetrahydro-1*H*-pyrimido[1,2-*a*]quinolin-9-ol salt (**85**). The conversion was improved by using a combination of trifluoromethanesulfonic acid and excess of methanol at reflux for 2 - 3 hours to give 32% of the methoxyquinolinol (**86**) exclusively. When heating was prolonged for a further one to two hours, a maximum 57% of product was obtained.



Scheme 49.

Analogous to the methoxyquinolinol formation, elimination of the ethoxy group from the ethoxyquinolinone (**77**), as ethanol, should generate some ethyl triflate that might act as an ethylating agent on the phenolic group. In fact, this did not happen here, implying that the ethyl triflate is less effective toward the alkylation and perhaps elimination leading to formation of ethane also intervened.

The formation of 9-methoxy-2,3,5,6-tetrahydro-1*H*-pyrimido[1,2-*a*]quinoline salt (**86**) was confirmed by X-ray crystallographic examination (Appendix II). The X-ray structure confirmed the presence of the methoxy group at the C-9 position which supported the theory of re-methylation, and showed the triflate anion coordinated with the protonated N4 nitrogen where the protonated imine nitrogen is associated with two of the sulfonate oxygen atoms (Figure 12 & Appendix III) (Crystallographic atom numbering illustrated).

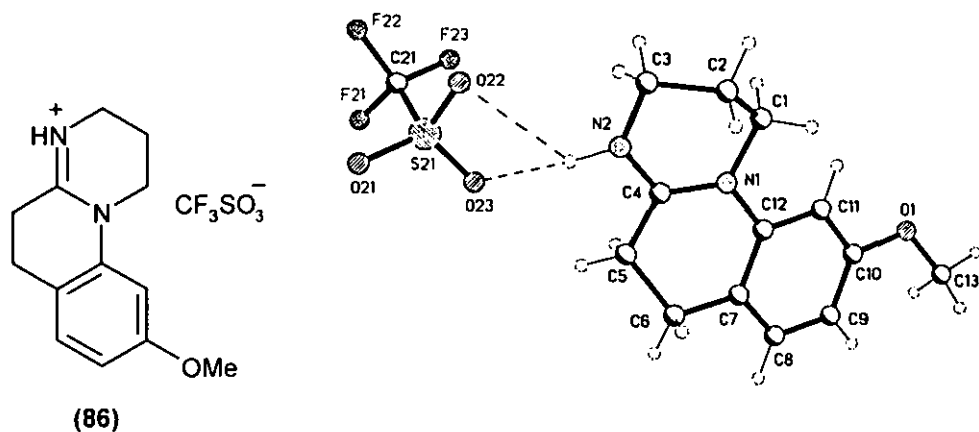


Figure 12.

The counter anion was difficult to remove by basic washing and the source of anion was inherited either from the earlier tetrahydropyrimidine formation or from the triflic acid used during the alcohol elimination. A single crystal X-ray crystallography structural examination of the benzyloxytetrahydropyrimidine (see Figure 9 earlier) suggested that the triflate anion is probably retained throughout the synthesis.

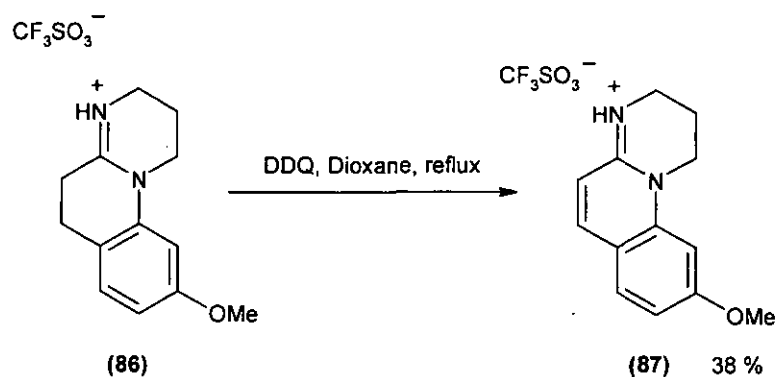
Although aromatisation of the benzene ring of the quinoline could be accomplished, the process of protonation and elimination was harder to complete than was anticipated. This was probably due to the cyclic amidine nitrogen being protonated, which meant that in order to protonate the alkoxy group, the molecule must exist as a di-cationic species (77a) (Scheme 48).

6.1.4 Formation Of Dihydropyrimidoquinolinium Salt – A Pyoverdin Model

In order to complete the biomimetic synthesis of the key pyoverdin chromophore model, the 9-methoxy-2,3,5,6-tetrahydro-1*H*-pyrimido[1,2-*a*]quinolinium salt (**86**) must be converted through removal of the hydrogens at C-5 and C-6 by oxidative dehydrogenation. Utilizing oxidizing reagents such as manganese dioxide, the dehydrogenation catalyst palladium-on-carbon, or through NBS bromination followed by dehydrobromination failed to promote formation of the desired product (Table 3). When the reaction was carried out with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) at reflux in dioxane it yielded up to 38% dehydrogenated product. Another high boiling point solvent, nitromethane, was used initially to give a similar effectiveness of dehydrogenation, but due to safety concerns of heating nitromethane, dioxane remained the preferred choice (Scheme 50). It is important to emphasize that the purification of the resulting dehydrogenated product was problematic. Neither silica nor florisil flash chromatography were able to deliver the pure product, it either eluted with the starting material or associated with the DDQ reagent or its by-product. Running liquid chromatography-mass spectrometry indicated that the starting material and dehydrogenated product were co-eluting. Fortunately, pure 9-methoxy-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinolinium salt (**87**), could be obtained by column chromatography of the crude products over basic alumina with a gradual increase in eluent polarity of methanol in dichloromethane from 3 – 6%.

Table 3. Conditions used for dehydrogenation of 9-methoxy-2,3,5,6-tetrahydro-1*H*-pyrimido[1,2-*a*]quinolinium salt (86).

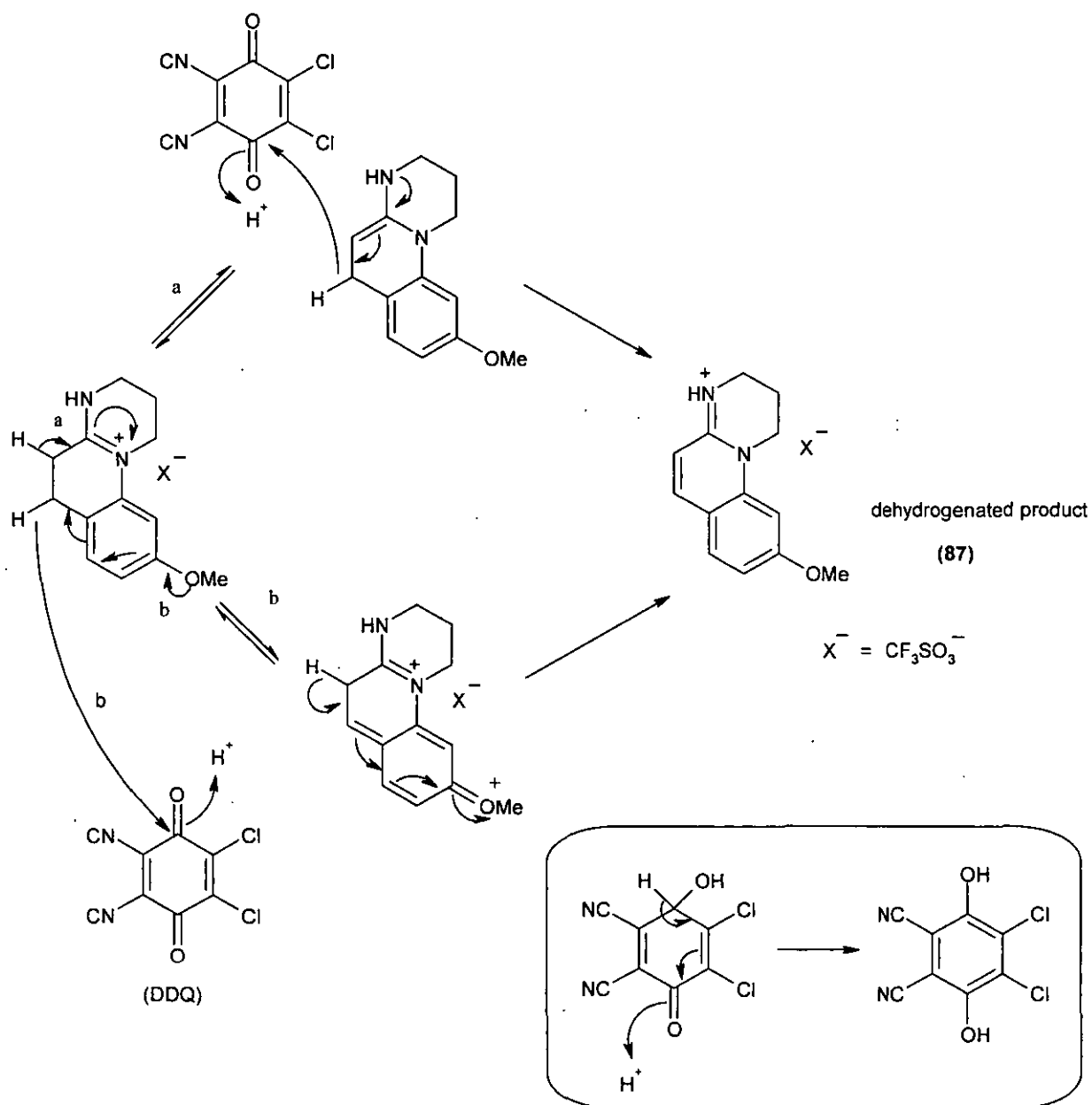
Reagent	Conditions	Column	Product
Pd-C	Reflux 3 day, CH ₃ NO ₂	None	No reaction
MnO ₂	Reflux 3 day, MeCN	None	No reaction
NBS	UV	None	No bromination
DDQ	Reflux 2 day, CH ₃ NO ₂	Silica	Impure, < 20 %
DDQ	Reflux 2 day, MeCN	Silica	Impure, < 20 %
DDQ	Reflux 2 day, CH ₃ NO ₂ +CCl ₄	Silica	Impure, < 20 %
DDQ	Reflux 2 day, dioxane	Silica	Impure, < 20 %
DDQ	Reflux 2 day, diglyme	Silica	No isolation
DDQ	On silica, microwave	Silica	Impure, 30 %
DDQ	Reflux 2 day, dioxane	Florisil	Impure, 21 %
DDQ	Reflux 2 day, dioxane	Basic alumina	Pure, 38 %



Scheme 50.

It is not exactly known what is the mechanism of the DDQ dehydrogenation. Two possible proposals are shown below (Scheme 51) in terms of H⁺ loss to form a dienamine followed by loss of H⁻ (path a) with DDQ reducing from quinone to quinol, or vice versa by losing a hydride anion, picked up by DDQ, and then elimination of proton (path b). The final oxidized methoxyquinolinium product (87) was recrystallized in ether and

chloroform to produce a sample suitable for X-ray crystallography. From the X-ray structure result (Figure 13 & Appendix IV), it was found that the triflate counter ion had stayed firmly with the pyrimidino system and the aromatic quinoline now existed as a planar structure once the pair of hydrogen atoms were removed.



Scheme 51.

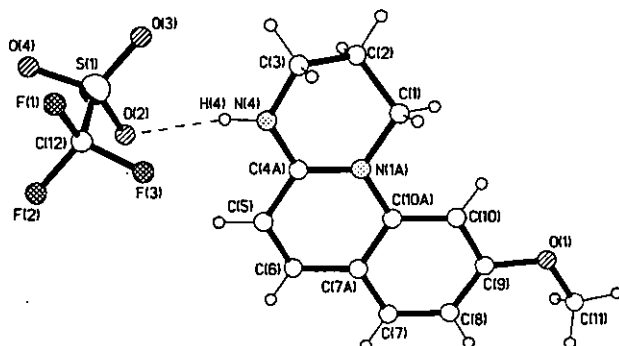
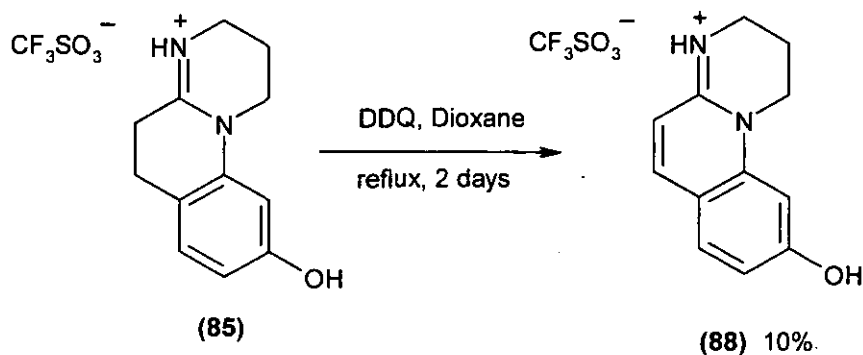


Figure 13.

Prior to the formation of the methoxyquinolinium (**87**), we also prepared the much more polar hydroxyquinolinium (**88**) compound (Scheme 52) after the DDQ dehydrogenation of the 2,3,5,6-tetrahydro-1*H*-pyrimido[1,2-*a*]quinolin-9-ol salt (**85**). A proton NMR spectrum proved the success of the dehydrogenation but no further spectroscopic data was obtained as only a small quantity of product was identified and this proved much more difficult to handle than the less polar methoxy derivative (**87**). Compound (**88**) is potentially a zwitterionic species, due to the basic amidine functional group and the acidic phenolic group.

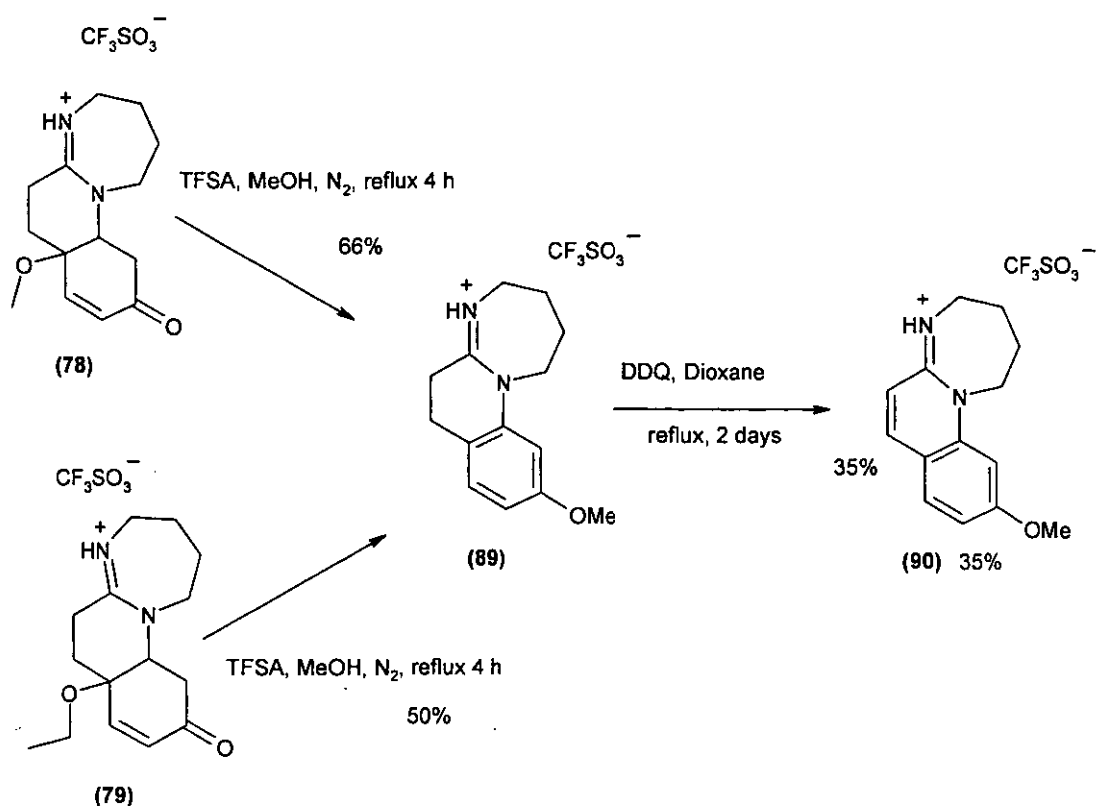


Scheme 52.

6.1.5 Formation Of Methoxytetrahydrodiazepinoquinolinium Salt – A Diazepine Analogue

The methoxy bridgehead substituent of the homologous octahydrodiazepinoquinolinone (**78**) was also removed by elimination, again using trifluoromethanesulfonic acid and excess methanol, to give only a methoxy hexahydrodiazepinoquinolinium salt (**89**) in 66% yield (Scheme 53). It was believed that the use of excess methanol (10 times) would lead exclusively to the exclusive methoxy product *via in situ* formation of methyl triflate as a methylating agent as proposed earlier. The original work on the removal of the ethoxy bridgehead of the tetrahydropyrimidoquinolinone (**77**) in neat triflic acid without any methanol gave a mixture of both the methoxy and hydroxy tetrahydropyrimidoquinolinium salts in lower yield. Elimination of the ethoxy bridgehead of the octahydrodiazepinoquinolinone (**79**) in the presence of a methanol and triflic acid led exclusively to the methoxyhexahydrodiazepinoquinolinium salt (**89**) in 50 % yield. This demonstrated that the presence of methanol was key to pure methoxyquinoline formation.

Dehydrogenation of the 10-methoxy-1,2,3,4,6,7,-hexahydro[1,3]diazepino[1,2-*a*]quinolinium salt (**89**) with DDQ and dioxane at reflux for 2 days gave the desired 10-methoxy-1,2,3,4-tetrahydro[1,3]diazepino[1,2-*a*]quinolinium (**90**) in 35 % yield, once again after column chromatography on basic alumina. Thus the 6- and 7-membered fused amidiniums pyrimidoquinolinone and diazepinoquinolinone were transformed to the final model chromophore structure and its homologue, except that the methoxytetrahydropyrimidoquinolinium was found to be difficult to isolate pure after the alkoxy elimination, until basic alumina was used for the separation.



Scheme 53.

6.1.6 Fluorescence Of The Quinolinium Salts

To assess whether the 9-methoxy-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinolinium salt (87) and 10-methoxy-1,2,3,4-tetrahydro-[1,3]diazepino[1,2-*a*]quinolinium salt (90) possess fluorescent characteristic similar to the natural pyoverdins, both quinolinium salts were tested for their UV absorption and hence their fluorescence. Measurement of the UV absorption was set to between 200 nm and 550 nm wavelength. At a concentration of 1.098×10^{-5} M, i.e. 1 mg 6-membered ring quinolinium in 250 ml 1 : 1 ratio of water and methanol, the UV absorption was measured respectively at pH 6.5 (original) and pH 9.0. It was found that by changing the pH from 6.5 to 9 or even milder acid condition gave no major changes in the maximum wavelength of absorption or the extinction coefficient for

both the 6- and 7-membered ring quinoliniums (Diagram 1). At pH 6.5, the wavelength maxima were at 219 nm, 338 nm and 353 nm with the extinction coefficients, $\epsilon = 63 \times 10^3$, 23×10^3 and 20×10^3 . Based on this measurement, the fluorescence of the methoxydihydropyrimidoquinolinium was excited at the wavelength of 219 nm, 338 nm and 353 nm (Diagram 2) which resulted in maximum emission at 382 nm from excitation at 353 nm, and 372 nm from excitation at 338 nm with fluorescence of 4.8×10^6 and 5.09×10^6 respectively at pH 6.5. Fluorescence measured at 219 nm excitation produced only a negligible value, the maximum emission being 1200 times less than the measurement at 353 nm. Very little change was observed when the measurement was carried out at pH 9.0. This indicated that pH adjustment has little effect in the 6-membered ring methoxy compound on either the UV absorption or the fluorescence character. Although the 7-membered ring methoxydiazepinoquinolinium produced similar UV spectra, the fluorescence tests only afforded a quarter of the fluorescence values compared to the 6-membered ring series (See Diagram 3).

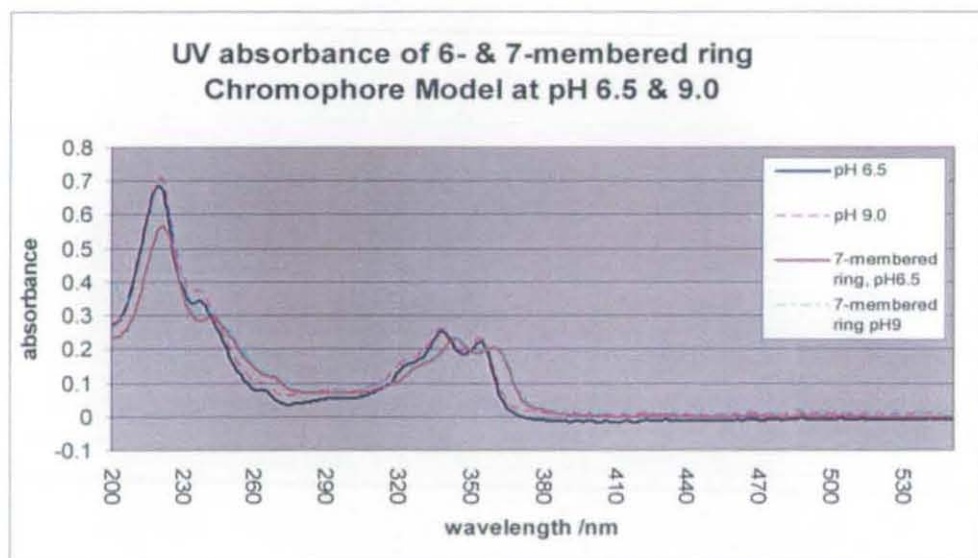


Diagram 1.

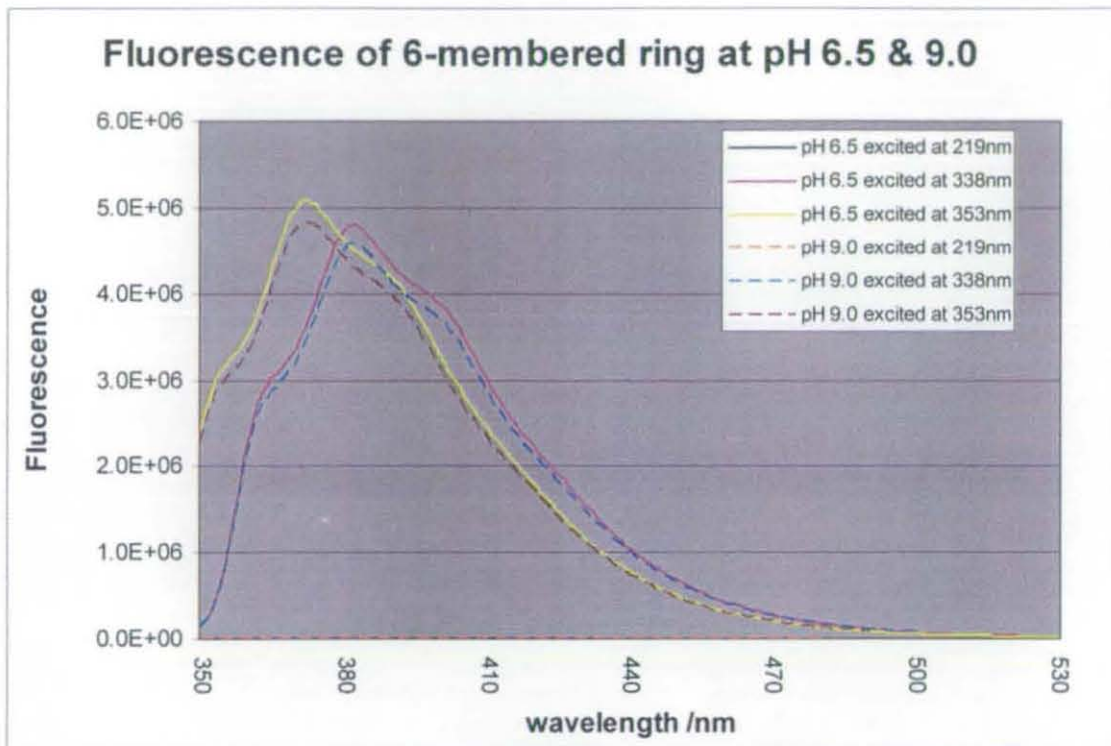


Diagram 2.

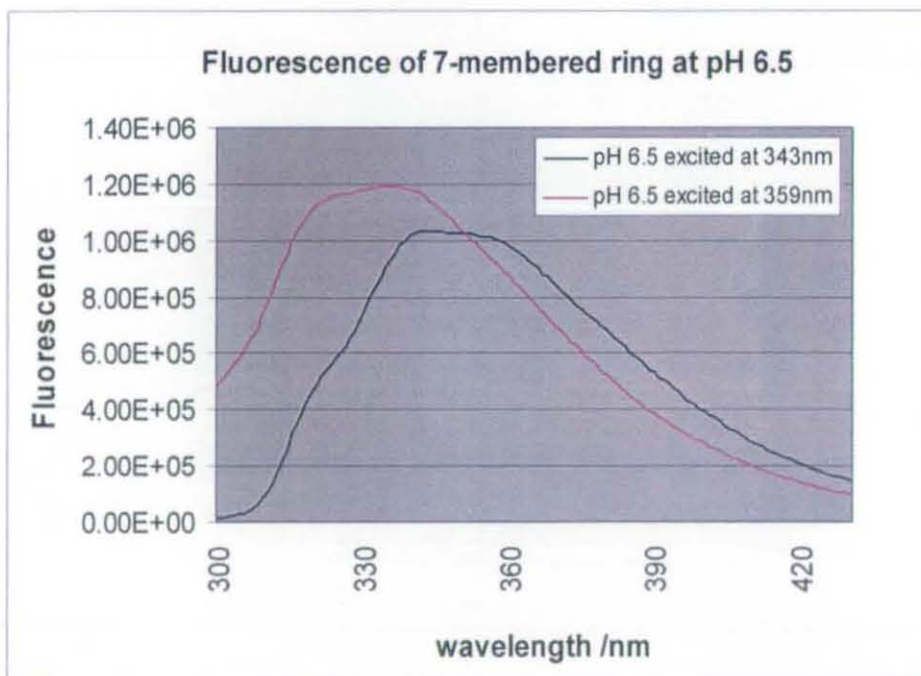


Diagram 3.

The UV and fluorescence data as reported from Begley's synthesized chromophore model pyoverdins (**21**) were different to ours.¹⁸ He reported UV spectra at pH 7.5 (391nm, 265 nm & 233 nm), at pH 3.5 (359nm, 308nm, 248nm & 220nm) and pH 9.5 (406nm, ϵ 100,000), as well as the fluorescence from excitation at 390nm, pH 7.5, giving emission at 445nm. This can be explained by structural variation since Begley's compound contained a dihydroxyphenyl group that is susceptible to basic conditions, as well as the amidine group that can be protonated in an acidic environment (Figure 14). Nevertheless, the methoxypyrimidoquinolinium proved to be remarkably fluorescent whilst the methoxydiazepinoquinolinium also possessed this character but to a much lesser extent.

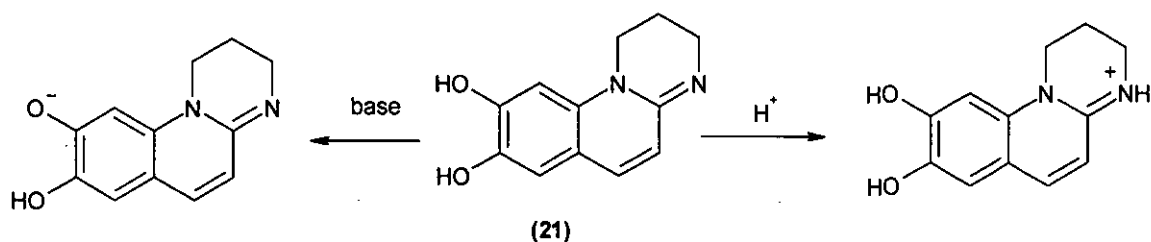


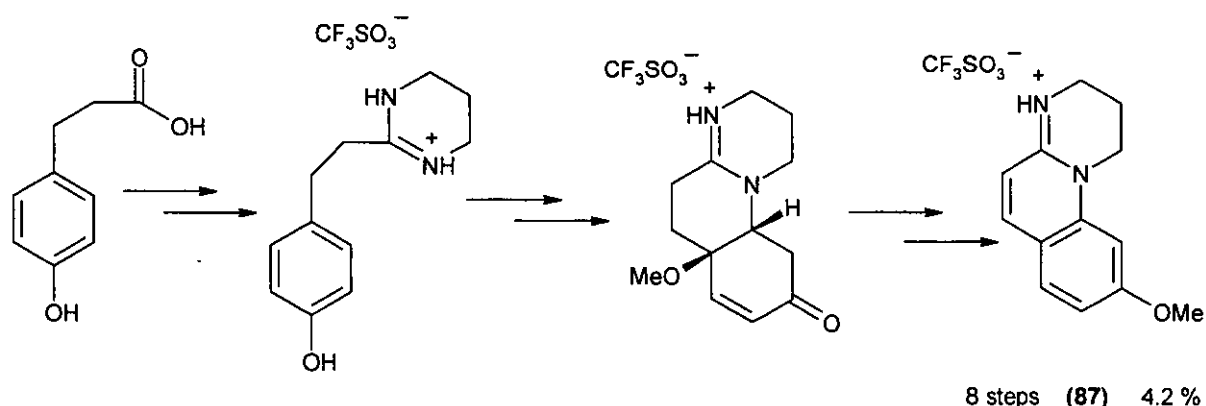
Figure 14.

6.1.7 Conclusion

In order to mimic the biosynthetic proposal for the formation of pyoverdinin chromophore, a key precursor model, the tetrahydropyrimidinium unit, was prepared. Oxidative cyclisation of this intermediate *via* alkoxydienone and intramolecular conjugate addition, was the crucial step to form the important tricyclic ring quinolinone and this was followed by elimination to yield the quinolinium salt.

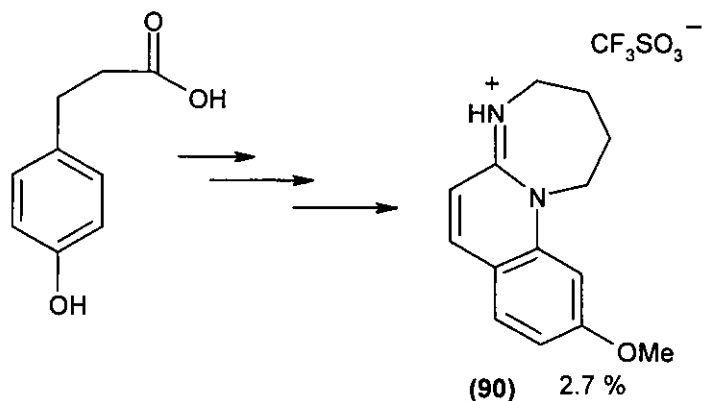
Synthesis of the fluorescent chromophore model of the pyoverdinin structure, 9-(methoxy)-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoline (**87**) was successful after dehydrogenation. The

total biomimetic procedure gave an overall 4.2% yield (Scheme 54) from the propionic acid through an amidine to the dehydrogenated product in 8 steps, i.e. regarding some two stage reactions as one step when the intermediates were not isolated.



Scheme 54.

The seven-membered ring diazepine analogue was also synthesized, oxidatively cyclised and further reacted to give 10-methoxy-1,2,3,4-tetrahydro[1,3]diazepino[1,2-*a*]quinoline (90) as final product in overall 2.7% yield (Scheme 55).



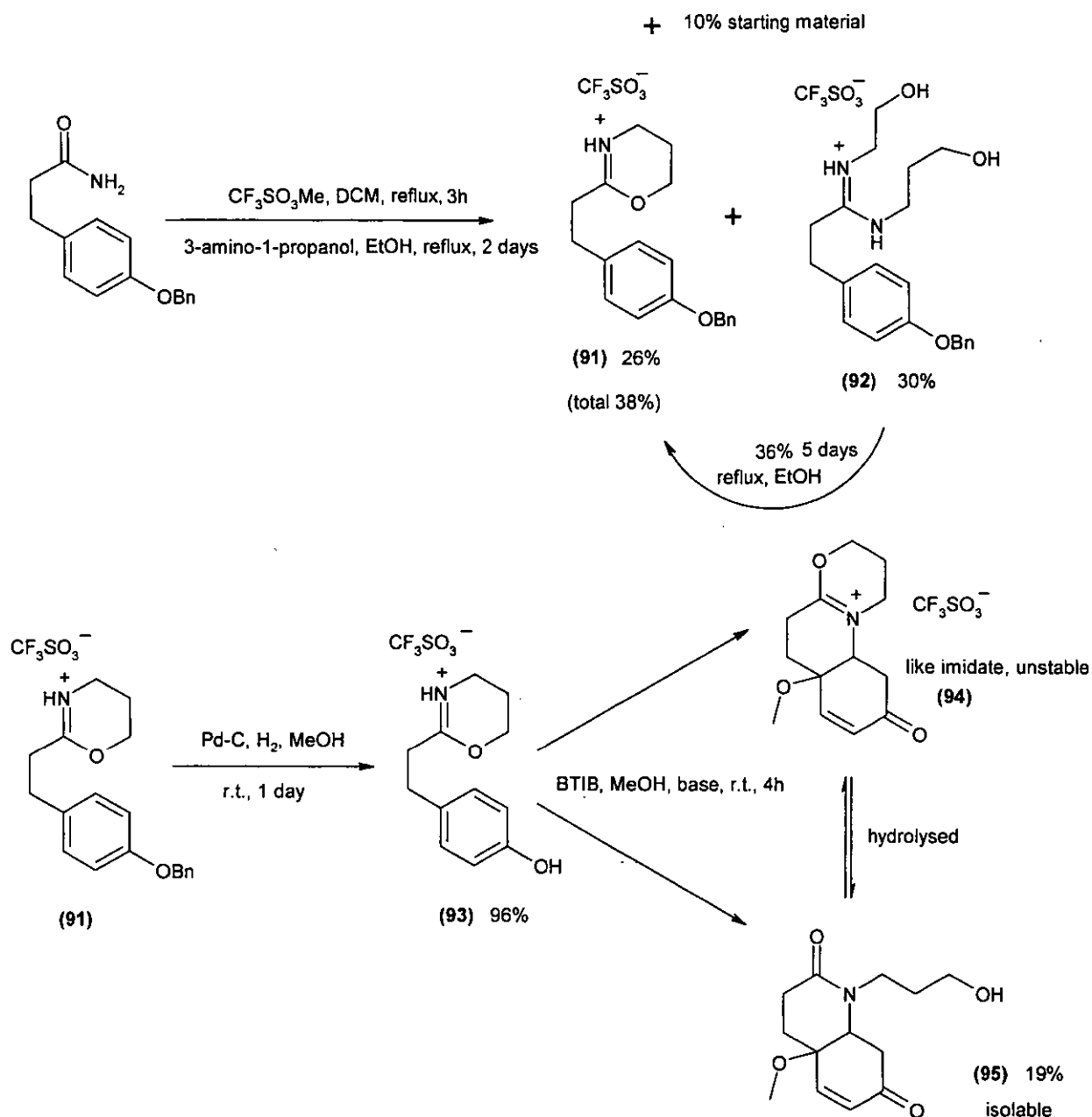
Scheme 55.

The X-ray crystal structures provided detailed confirmation of the progress of this biomimetic synthesis of the chromophore model. From the cyclic amidine to the

oxidatively cyclised alkoxyquinolinone, the eliminated alkoxyquinoline and the final fluorescent quinoline chromophore, four intermediates were characterized by X-ray crystallography studies.

6.2 Formation Of Oxazine Analogues

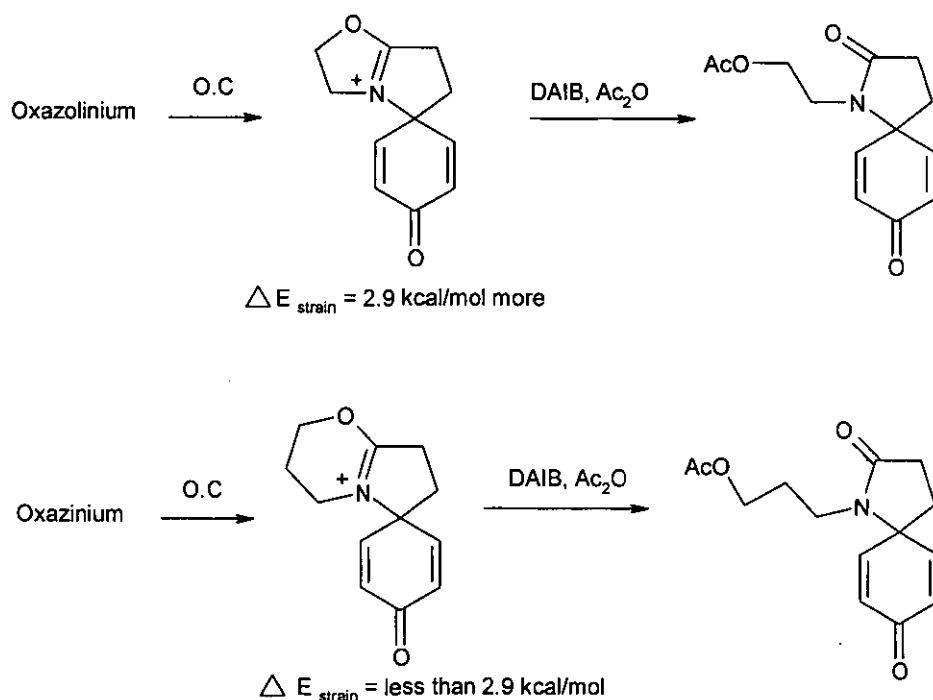
Following the successful oxidative cyclisation of cyclic amidines, 5-, 6- and 7-membered, we decided to investigate the cyclic imidate analogues. Thus the oxazine derivative, 2-[2-(4-benzyloxyphenyl)ethyl]-5,6-dihydro-4*H*-[1,3]oxazinium salt (**91**), which may be regarded as analogous to the tetrahydropyrimidine series, was also synthesized by reacting 3-(4-benzyloxyphenyl)propanamide with methyl triflate (Scheme 56) and then with 1.5 equivalent of 3-aminopropan-1-ol. This cyclic imidate derivative was formed in a relatively low yield of 26% with the propanamide starting material being recovered in 10% yield, as well as *N,N'*-bis(3-hydroxypropyl)-3-(4-benzyloxyphenyl)propanamidinium salt (**92**) in 30%. The isolation of the *bis*(hydroxypropyl)amidinium salt might indicate that the reactions of the first formed imidate salt with the amine were far more favourable than with the alcohol nucleophile, suggesting quantitative formation of the *bis*(hydroxypropyl)amidinium as the initial product. This was supported by the finding that further extensive heating at reflux of the *bis*(hydroxypropyl)amidinium salt (**92**) for 5 days produced extra quantities of the dihydro-oxazinium product (**91**) in up to a total 38 % yield. Attempting to increase the yield by reducing the ratio of the 3-aminopropan-1-ol and propanamide to 1 : 1 did not improve the formation of the oxazinium salt or lower the proportion of the *bis*(hydroxypropyl)amidinium salt significantly.



Scheme 56.

Once the benzyl protecting group of (91) was removed by hydrogenolysis in the usual way, the 2-[2-(4-hydroxyphenyl)ethyl]-5,6-dihydro-4*H*-[1,3]oxazinium salt (93) this formed was oxidized with *bis*(trifluoroacetoxy)iodobenzene (BTIB) in methanol in the presence of solid sodium bicarbonate to form the ring-opened structure 1-(3-

hydroxypropyl)-4a-methoxy-4,4a,8,8a-tetrahydro-1*H*,3*H*-quinoline-2,7-dione (**95**) in only 19% yield after column chromatography (Scheme 56). The expected octahydro-oxazaphenanthren-6-one salt (**94**) was not obtained. A similar ring-opening phenomenon was reported by Ciufolini and Braun *et al.*⁵² who noted that the ring-opening could occur for both oxazinium and oxazolinium salts after employing diacetoxyiodobenzene (DAIB) during an oxidation process in non-nucleophilic solvents, to give ring opened spirocyclic lactams. They found that the 5-membered ring oxazolinium salt leading to the spiro lactam gave a lower yield presumably because more strain energy is involved in the oxidation reaction intermediate than in the 6-membered ring oxazinium analogue during the spirocyclisation (Scheme 57).



Scheme 57.

The reaction that we attempted was not planned to undergo a spirocyclic lactamisation, due to the nucleophilic solvent present. We presume that the expected 4-methoxydienone underwent spontaneous 1,4-Michael type cyclisation followed by hydrolysis of the imino ether-type reactive imidate (Scheme 56).

Theoretically, it would be possible to access the oxidative cyclised octahydro-oxazaphenanthren-6-one salt by *O*-methylating the ring opened lactam (**95**) and provoking cyclisation to the oxazine under strictly anhydrous conditions, but the sensitive azaphenanthrenone may not be particularly stable, so our studies on the imidates were concluded at this point.

6.2.1 Conclusion

Attempts to synthesize an oxazine substrate for oxidative cyclisation afforded a maximum 38% yield of the desired product. Oxidative cyclisation did proceed and led to a ring-opened lactam of a type analogous to those which had been reported by others.

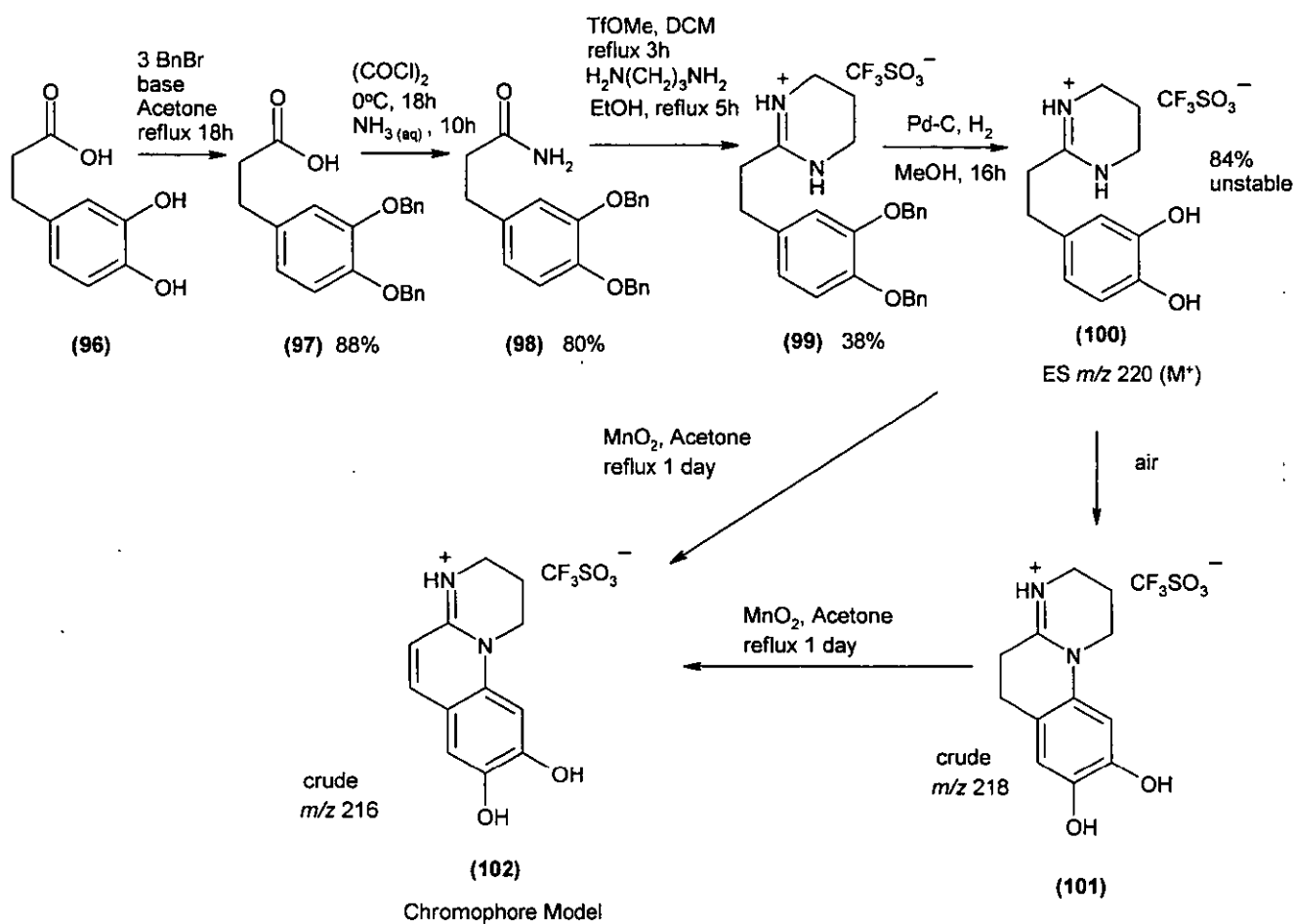
6.3 Dihydroxyphenyl Chromophore Model

After the success of the oxidative cyclisation methodology to produce a monohydroxyphenyl chromophore model, the work was further expanded into the dihydroxyphenyl unit. 3-(3,4-Dihydroxyphenyl)propionic acid (**96**) was selected as the appropriate starting compound for this dihydroxy species. In the biosynthesis, the second hydroxyl group is believed to be inserted after ferribactin formation during an oxidation with an oxidase enzyme.

The catechol group of the 3-(3,4-dihydroxyphenyl)propionic acid was protected by reaction with 4 mol. equiv of benzyl bromide and base, followed by hydroxide hydrolysis to afford a dibenzyloxy protected phenylpropionic acid (**97**) in 88% yield (Scheme 58). Following the methodology established in the monohydroxyphenyl series described above, the dibenzyl protected propionic acid was then converted to the corresponding

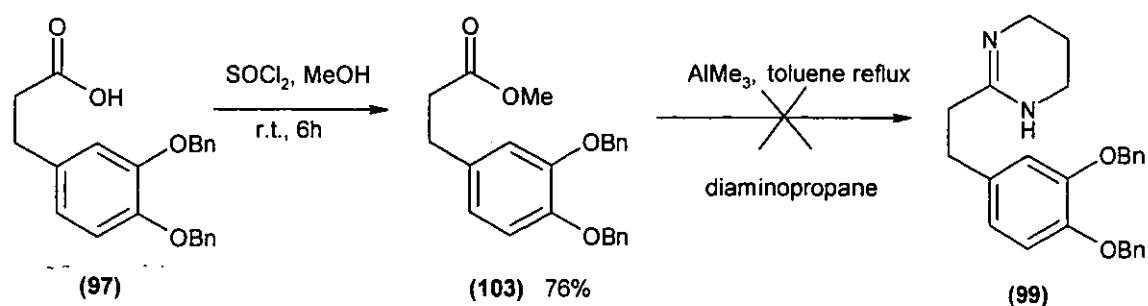
propanamide (**98**) through an acyl chloride intermediate in 80% yield over 2 steps. The 3-(3,4-dibenzyloxyphenyl)propanoyl chloride was much less stable compared with the monobenzyloxy counterpart. By methylating the propanamide with methyl trifluoromethanesulfonate in DCM at reflux, evaporation of the solvent and replacement with ethanol, and subsequent introduction of 1,3-diaminopropane to the solution at reflux, the 2-[2-(3,4-dibenzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium salt (**99**) was produced in 69% yield.

When the two benzyl protecting groups were removed by hydrogenolysis with palladium-on-carbon, a very unstable dihydroxyphenyl tetrahydropyrimidinium salt (**100**) was obtained which was found to be sensitive to oxidation in air at room temperature. On some occasions, this dihydroxyphenyltetrahydropyrimidinium salt was partially oxidized directly in air to give some of the oxidative cyclisation product 2,3,5,6-tetrahydro-1*H*-pyrimido[1,2-*a*]quinolinium-8,9-diol salt (**101**). Evidence that the cyclised compounds were formed was provided by ¹H NMR spectroscopy of the partially oxidized amide material, and confirmed by reverse phase liquid chromatography-mass spectrometry (LC-MS). A mixed chromatograph showing masses of *m/z* 220 (M^+) for free base and *m/z* 218 (M^+) was observed where the mass *m/z* 218 detected was due to the loss of 2 protons during oxidative cyclisation (Scheme 58). Unfortunately, both compounds were highly polar and similar in character on silica or alumina, thus it proved impossible to separate them. Either the pure dihydroxyphenyltetrahydropyrimidinium salt (**100**) or the mixture with the dihydroxypyrimidoquinolinium diol salt (**101**) could be oxidized further using manganese dioxide to lead to the same conjugated compound, presumably the 2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinolinium-8,9-diol salt (**102**). Since the polarity of the oxidized compound remained high, the product was only distinguished by reverse phase LC-MS once again, with a single product of mass *m/z* 216 (M^+) identified. Only one final oxidized compound was identified from the manganese dioxide oxidation, this implied that the dihydroxyphenyltetrahydropyrimidinium salt (**100**) was highly susceptible to the full oxidation sequence, especially in the presence of MnO₂, while a mild oxidation in air gave the unconjugated quinoline diol (**101**).



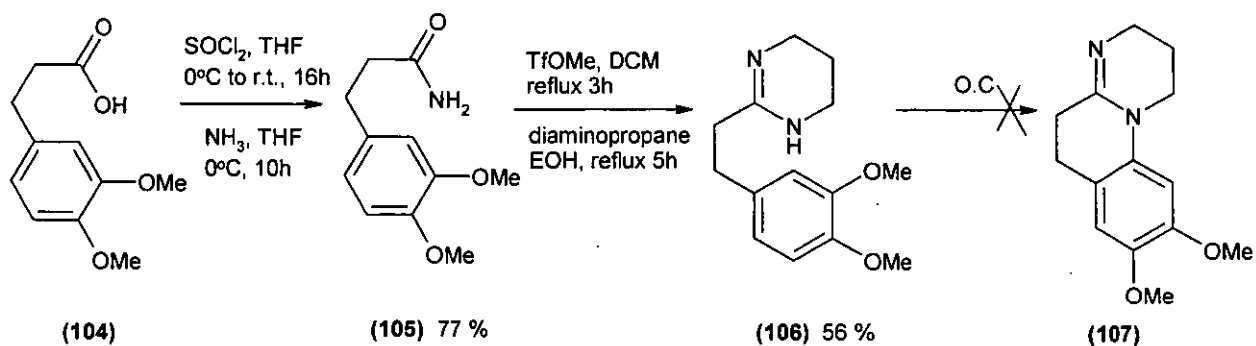
Scheme 58.

Efforts to synthesise the same dibenzyloxyphenyltetrahydropyrimidine (99) from the corresponding propionic acid methyl ester (103) (prepared from the acid (97) with thionyl chloride in methanol at reflux) with trimethylaluminium and 1,3-diaminopropane according to the report by Begley *et al.* (Scheme 59)¹⁸ failed to produce the tetrahydropyrimidine after several attempts.

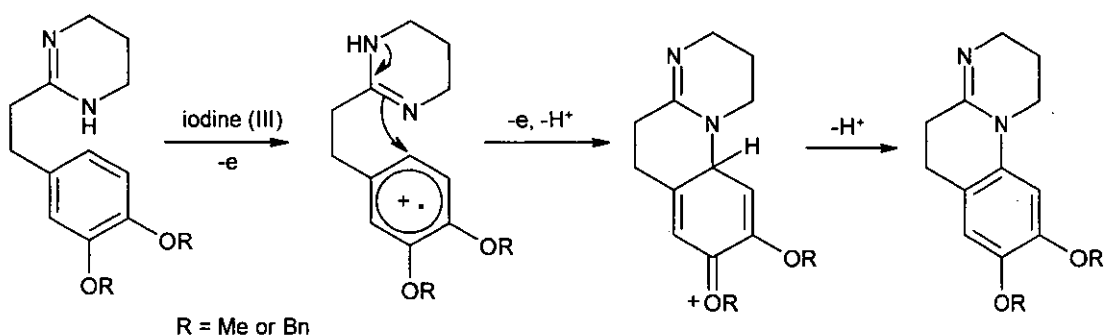


Scheme 59.

As an alternative for the 3,4-dioxygenated series, the dimethoxyphenylpropionic acid (**104**) was also converted to the tetrahydropyrimidine (**106**) using the usual methodology and in higher yield than the dibenzoyloxytetrahydropyrimidine derivative (**99**) (Scheme 60). The proposal was to use the dimethoxyphenyltetrahydropyrimidine for the promotion of a possible radical cation hypervalent iodine reaction (Scheme 60) due to the strong electron donating effect from the dimethoxy group. Several dimethoxyaryl compounds have been reported to undergo successful biaryl coupling reactions through the use of hypervalent iodine. However, it was not possible to isolate the desired product in our case, using BTIB as oxidant.



Possible radical mechanism



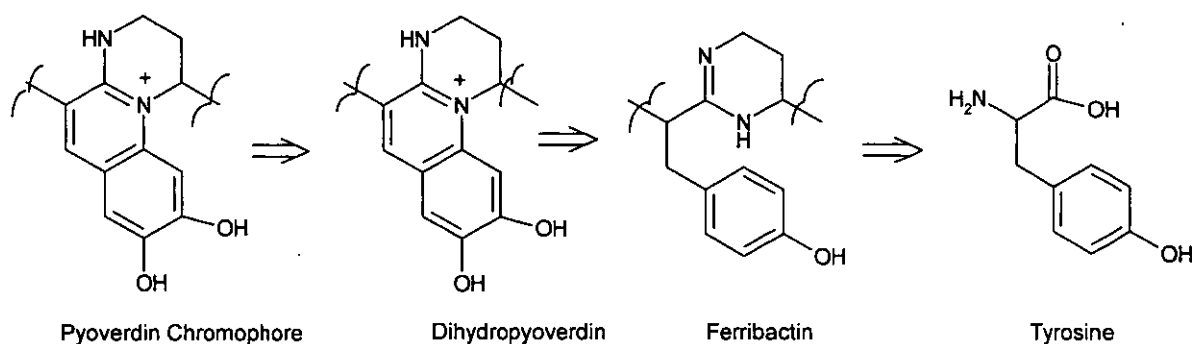
Scheme 60.

6.3.1 Conclusion

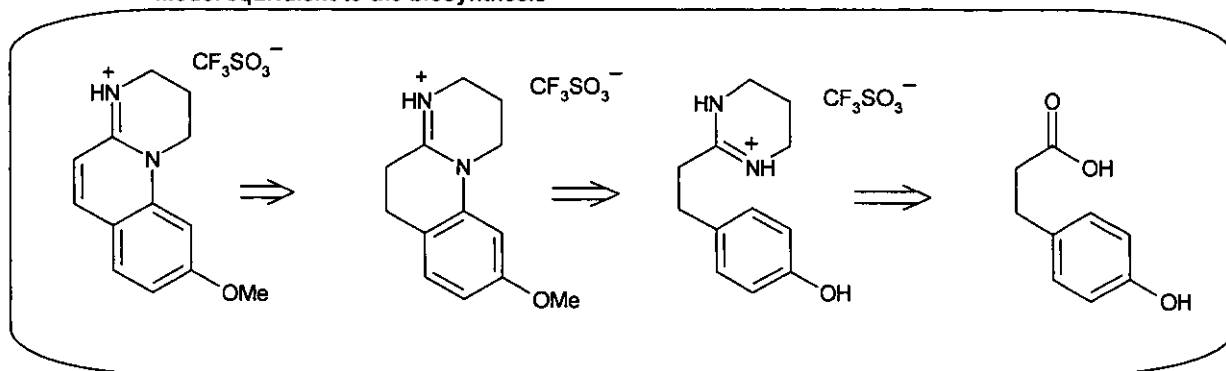
The dihydrophenyl synthesis gave 69% of the corresponding cyclic amidine with benzyl protection (99) and up to 56% from methyl protection (106). Deprotection in the former case produced the free dihydroxytetrahydropyrimidine which was found to be easily oxidized and led directly to the formation of quinolines although the products were very difficult to purify *via* traditional column chromatography. It may be possible to achieve the purification using preparative scale reverse phase HPLC.

6.4 Biomimetic Synthesis With Amino Acid Units

The successful biomimetic approaches to dihydropyrimidoquinolines and hexahydrodiazepinoquinolines described above, as models equivalent to the pyoverdin chromophore were based on the stepwise biosynthetic hypothesis for pyoverdin compounds (Scheme 61), where the tetrahydropyrimidine and tetrahydrodiazepine before oxidative cyclisation can be regarded as ferribactin models and the tetrahydropyrimidoquinoline and hexahydrodiazepinoquinoline as dihydropyoverdin models. We next wished to extend this biomimetic approach from the tricyclic chromophore model unit to the complete peptidic unit where the *N*- and *C*-termini would be involved in the synthesis. Both of the termini should be present prior to the ferribactin unit formation in order to follow the biosynthetic findings. To mimic the bioprocess, the *N*-terminus can be derived from a tyrosine amino acid starting material instead of a phenylpropanoic acid, since the same amino acid is a precursor in the biosynthesis of pyoverdins. The *C*-terminus can be obtained directly from a L-2,4-diaminobutyric acid instead of the 1,3-diaminopropane, for the construction of the cyclic amidine peptidic unit. Single enantiomers of diaminobutyric acid or the racemic mixture, and single enantiomers of tyrosine, are readily available commercially.

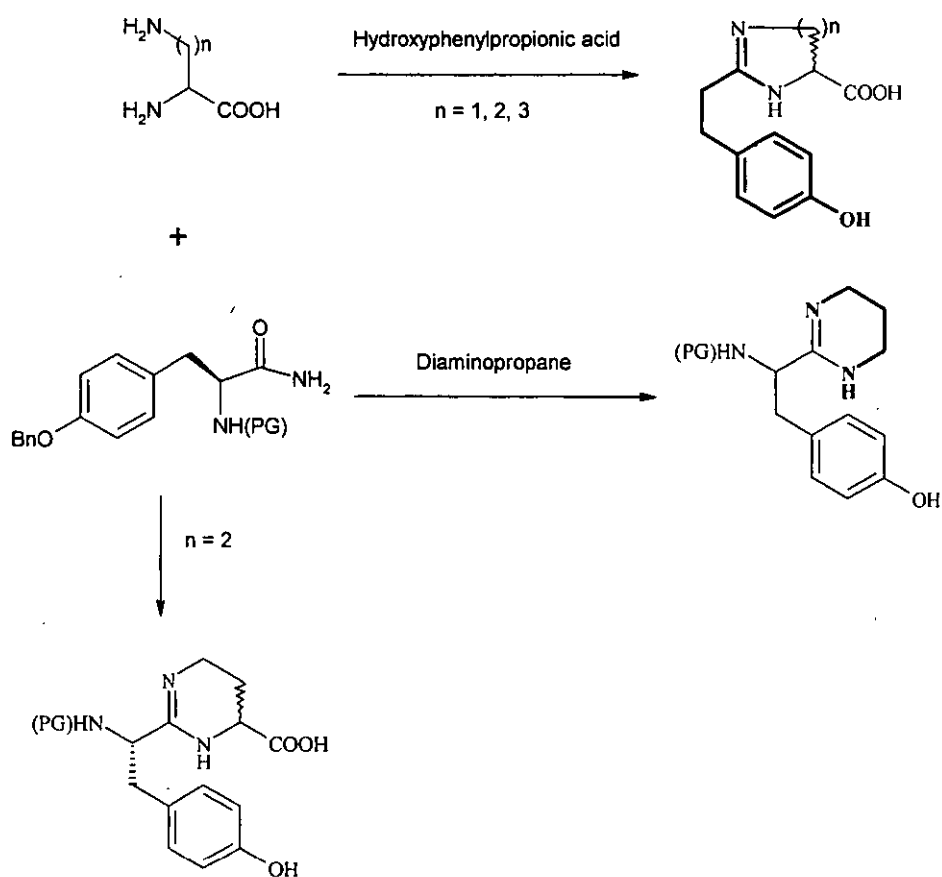


Model equivalent to the biosynthesis



Scheme 61.

It was decided that the synthetic work on the amino acid units would be built up sequentially with incorporation of a single precursor amino acid first, either the tyrosine or the diaminobutyric acid to introduce either the *N*- or *C*-terminus, with another non-amino acid unit as the partner (Scheme 62) before investigating construction of the full ferribactin unit with both amino acid units combining together.

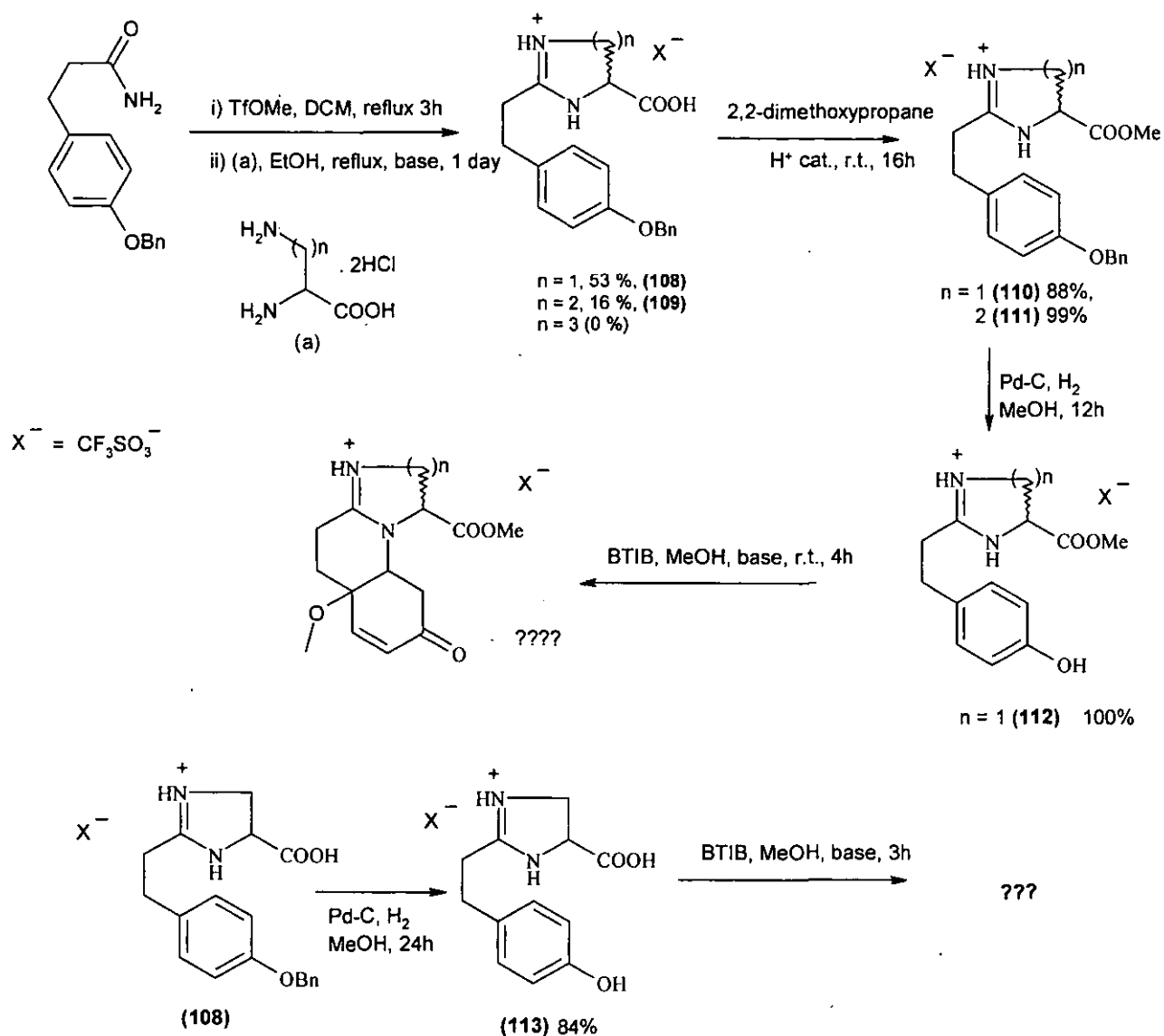


Scheme 62.

6.4.1 Cyclic Amidines With a C-Terminus

To synthesize the carboxylic acid substituted cyclic amidines, different diaminocarboxylic acids, such as D,L-2,3-diaminopropionic acid monohydrochloride, L-2,4-diaminobutyric acid dihydrochloride and D,L-2,5-diaminopentanoic acid monohydrochloride were used. Each of the diaminocarboxylic acids was reacted with 3-(4-benzyloxyphenyl)propanamide *via* the reactive imidate formed by *O*-alkylation with methyl triflate as discussed earlier (Scheme 63). As the carbon chain length increases, solubility of the carboxylic acid in ethanol decreases proportionally, hence the reactivity reduced along with the carbon chain increase. The use of the free acids in the ring formation was based on published precedence.⁷² Formation of 2-[2-(4-

benzyloxyphenyl)ethyl]-4,5-dihydroimidazole-4-carboxylic acid (**108**) provided 53% of the desired product, whereas the 2-[2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidine-4-carboxylic acid (**109**) was formed in only 16% yield at maximum after several attempts. 2-[2-(4-Benzyloxyphenyl)ethyl]-4,5,6,7-tetrahydro-3*H*-[1,3]diazine-4-carboxylic acid failed to form from the reaction of D,L-2,5-diaminopentanoic acid and the activated benzyloxyphenylpropanamide, presumably since the diaminopentanoic acid was almost insoluble in ethanol during reflux. To remove the problem of polarity, both the 5- and 6-membered ring cyclic amidine carboxylic acids were esterified with 2,3-dimethoxypropane using a small quantity of acid as catalyst to furnish methyl 2-[2-(4-benzyloxyphenyl)ethyl]-4,5-dihydro-3*H*-imidazole-4-carboxylate (**110**) and methyl 2-[2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidine-4-carboxylate (**111**) in over 95% yield. The diamino acids were not esterified before reaction with the imidate, since intramolecular lactam formation is known to occur. Removal of the benzyl protecting group from (**110**) by hydrogenolysis afforded quantitatively the hydroxyphenyl compound (**112**) that was ready for the oxidative cyclisation, but no evidence of cyclisation, methoxy insertion from methanol or even of the methyl ester group was detected by proton NMR spectroscopy in the reaction mixture from treatment of this phenolic amidino-ester with *bis*(trifluoroacetoxy)iodobenzene in methanol. An attempt at oxidative cyclisation of 2-[2-(4-hydroxyphenyl)ethyl]-4,5-dihydroimidazole-4-carboxylic acid (**113**) after hydrogenolysis of acid (**108**) gave no sign of cyclisation.



Scheme 63.

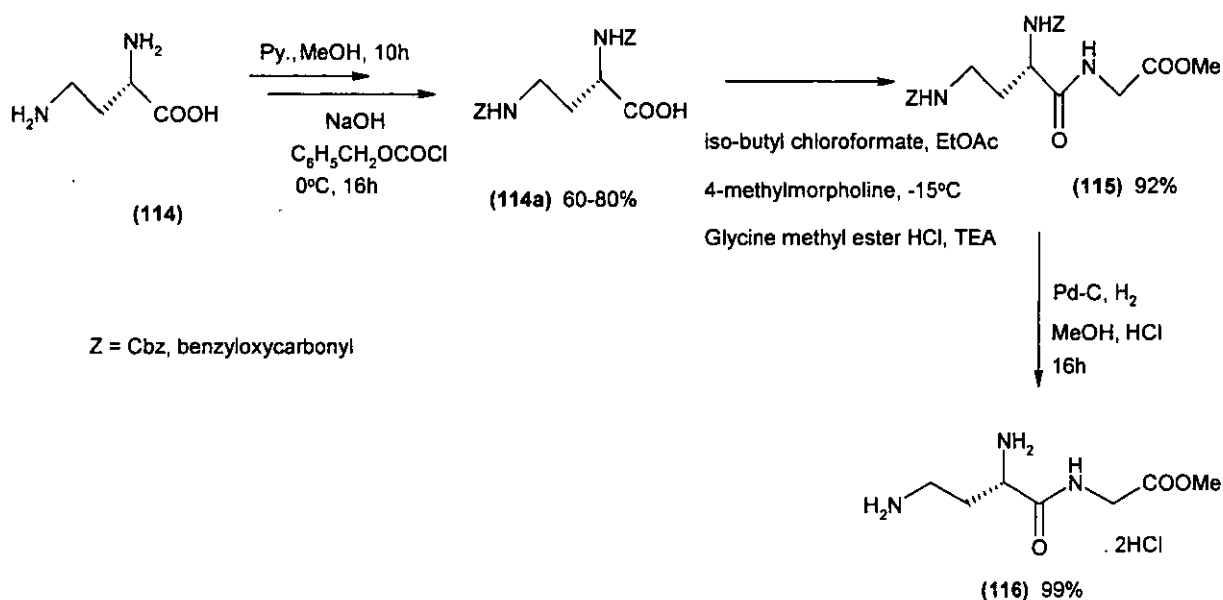
It was unknown whether the methyl ester group adjacent to the amidine would affect the oxidative cyclisation. To prevent such possible interference, the carboxylic acid was converted into another less reactive functional group, such as an amide derived from another amino acid, which it was believed might inhibit any influence of the ester group during the crucial oxidative cyclisation with the hypervalent iodine(III) reagent. In

addition, in ferribactin the corresponding carboxylic acid is found as an amide as part of a short peptide.

The carboxylic acid group of L-2,4-diaminobutyric acid (**114**) was therefore coupled with glycine methyl ester, the simplest amino acid being selected as the amide partner, in order to minimize any possible steric effects on the synthesis. Before introducing the second amino acid by any standard peptide coupling method, the two amino groups must be protected. This also prevents lactamisation upon C-activation. The benzyloxycarbonyl protecting group was chosen to mask the diamino unit as this would form stable carbamates and the cleavage process can be achieved simply and effectively when required.

One common problem in peptide coupling is racemisation during the base-catalysed coupling reaction of an *N*-protected carboxyl activated amino acid, where an intermediate oxazolone can be formed in which the α -proton is significantly acidic. *N*-Carbamate formation from the amino acid can minimize this kind of occurrence and is thus preferable to other *N*-protecting groups, such as *N*-acyl protection.

2 Mol. equiv. of benzyl chloroformate was thus reacted with the L-2,4-diaminobutyric acid (**114**) under basic conditions to yield up to 80% of doubly *N*-protected acid (**114a**). The peptide coupling was performed by a mixed anhydride protocol, using *iso*-butyl chloroformate and 4-methylmorpholine followed by the addition of glycine methyl ester hydrochloride at $-10\text{ }^{\circ}\text{C}$ for 2 hours (Scheme 64). To reveal the amino functional groups, the *N,N*-diprotected diaminobutyric acid amide (**115**) was subject to hydrogenolysis over Pd on charcoal in methanol in the presence of concentrated hydrochloric acid. It is essential to carry out the benzyloxycarbonyl group removal under acidic conditions since the dipeptide product, L-2,4-diaminobutyrylaminoacetic acid methyl ester (**116**), is then formed as a stable dihydrochloride salt rather than as the sensitive free diaminoester, likely to polymerize by itself.

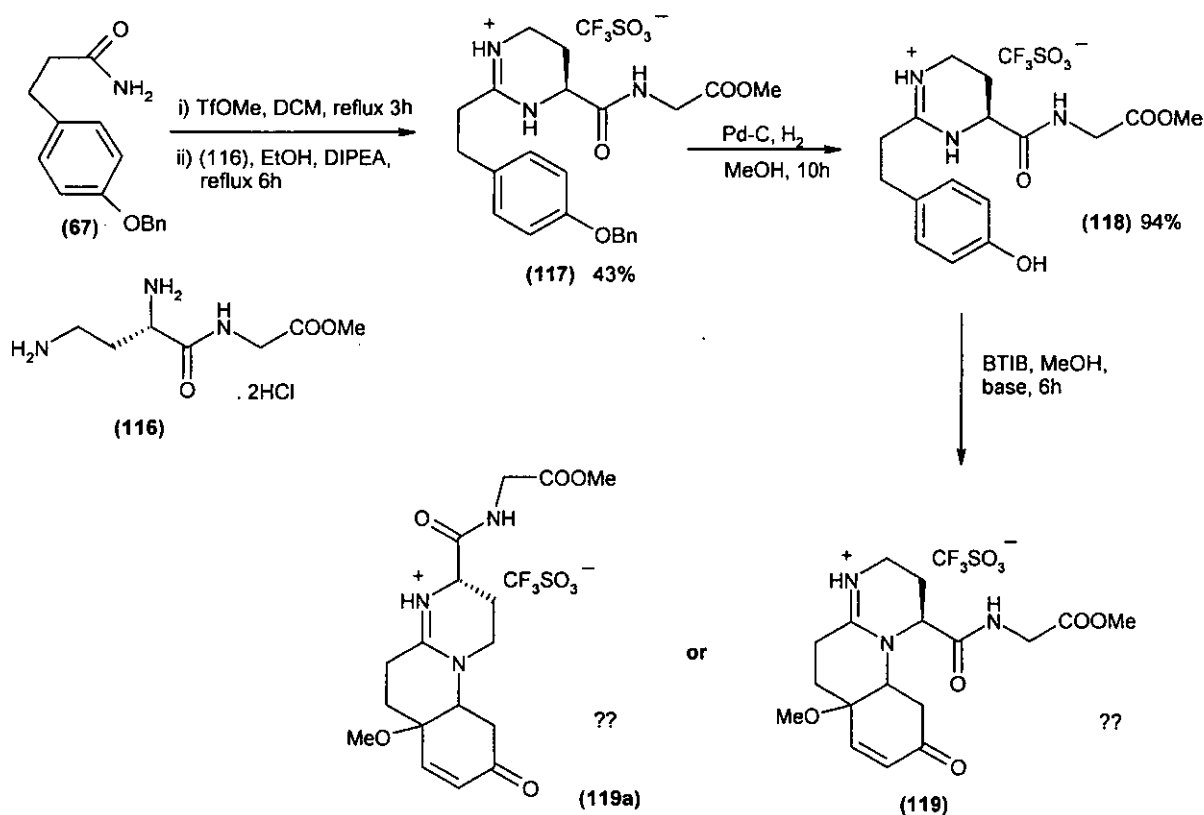


Scheme 64.

The target L-2-[2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidine-4(S)-carboxylaminoacetic acid methyl ester (**117**), was obtained in 43% by our standard cyclic amidine formation. Thus 2-(4-benzyloxyphenyl)propanamide (**67**) was methylated with methyl triflate and the reactive imidate treated with excess L-2,4-diaminobutyrylaminoacetic acid methyl ester dihydrochloride salt (**116**) in the presence of Hünigs base. The increase in yield of cyclic amidine from 16% to 43% when compared to the use of L-2,4-diaminobutyric acid (Scheme 65) proved that masking the carbonyl unit did improve the reaction yield substantially. The phenolic function of the carbonyl substituted tetrahydropyrimidine was revealed by hydrogenolysis to provide (**118**) as a substrate for oxidative cyclisation.

Oxidative cyclisation of the hydroxyphenyl pyrimidine (**118**) with *bis*(trifluoroacetoxy)iodobenzene in methanol in the presence of solid potassium bicarbonate initially afforded a small quantity of the corresponding cyclised quinoline, L-

[(6a-methoxy-9-oxo-2,3,,5,6,6a,9,10a-octahydro-1*H*-pyrimido[1,2-*a*]quinoline-1-carbonyl)amino]acetic acid methyl ester (**119**), from the proton NMR spectrum of the crude products. Reverse phase LC-MS detected the desired product with mass m/z 350 (M^+) being present. Isolation and purification of the desired product was however problematic. Alumina, silica or reverse phase silica chromatography only purified slightly the reaction mixture while the proton NMR spectroscopy still showed the compound to be impure. Although the 1H NMR spectra indicated the presence of impurity, nevertheless the chemical shift of the two alkene protons in the cyclised enone (**119**) were observed as doublets at 6.12 ppm and 6.96 ppm while the two symmetric signals of total 4 protons from the 4-hydroxyphenyl residue of the starting material would be further downfield at 6.61 ppm and 6.96 ppm, indicating the oxidative cyclisation reaction did occur. It is also possible that the oxidative cyclisation reaction might lead to formation of a regioisomer (**119a**), depending on which *N* atom underwent cyclisation. This is seen in pyoverdins biosynthesis, where isopyoverdins have also been isolated.



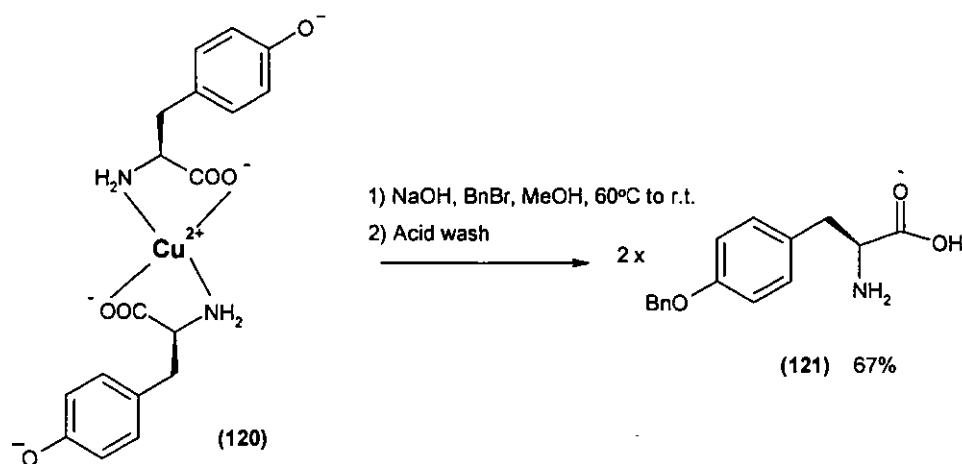
Scheme 65.

6.4.1.1 Conclusion

Construction of the carbonyl-substituted 5- and 6-membered cyclic amidine was quite straightforward, except the yields of tetrahydropyrimidine were disappointing due to the poor solubility of the diaminobutyric acid in the reaction medium, but once the carbonyl unit was masked by another amino acid the yield was improved significantly. Oxidative cyclisation of acid and ester derivatives in the dihydroimidazole and tetrahydropyrimidine series was unsuccessful. Preliminary work on the oxidative cyclisation of the aminocarboxyltetrahydropyrimidine, having a glycine C-terminus carboxylic acid, proved the oxidation to be feasible but separation of the pure products remains as a challenge.

6.4.2 Cyclic Amidines With an *N*-Terminus

To investigate the influence of an *N*-terminus substituent on the biomimetic synthesis of chromophore models, L-tyrosine was employed as the *N*-terminal starting material. The tyrosine amino acid is one of the key compounds involved in the biosynthesis of the pyoverdinin chromophore. To allow the L-tyrosine to react specifically at its carbonyl group in cyclic amidine formation both the phenolic side-chain and the amino group need to be protected. In the presence of copper sulfate and sodium hydroxide solution, a copper tetrahedral complex (**120**) was formed by coordinating the Cu²⁺ ion with two molecules of tyrosine through their α -amino acid functions (Scheme 66). While the amino and carboxyl group complexed with the copper ion, the phenolic side chain was free for protection to take place. Under basic conditions, benzyl bromide was reacted with the tyrosine copper complex, resulting in 67% of *O*-benzyl-L-tyrosine (**121**) after acidic washing to remove the copper ion. Attempting to protect the hydroxyphenyl side-chain directly with benzyl bromide without forming the copper complex did not prove to be efficient; both the amino and carboxy groups could be competitive for the benzylation leading to alternative benzylated tyrosines.



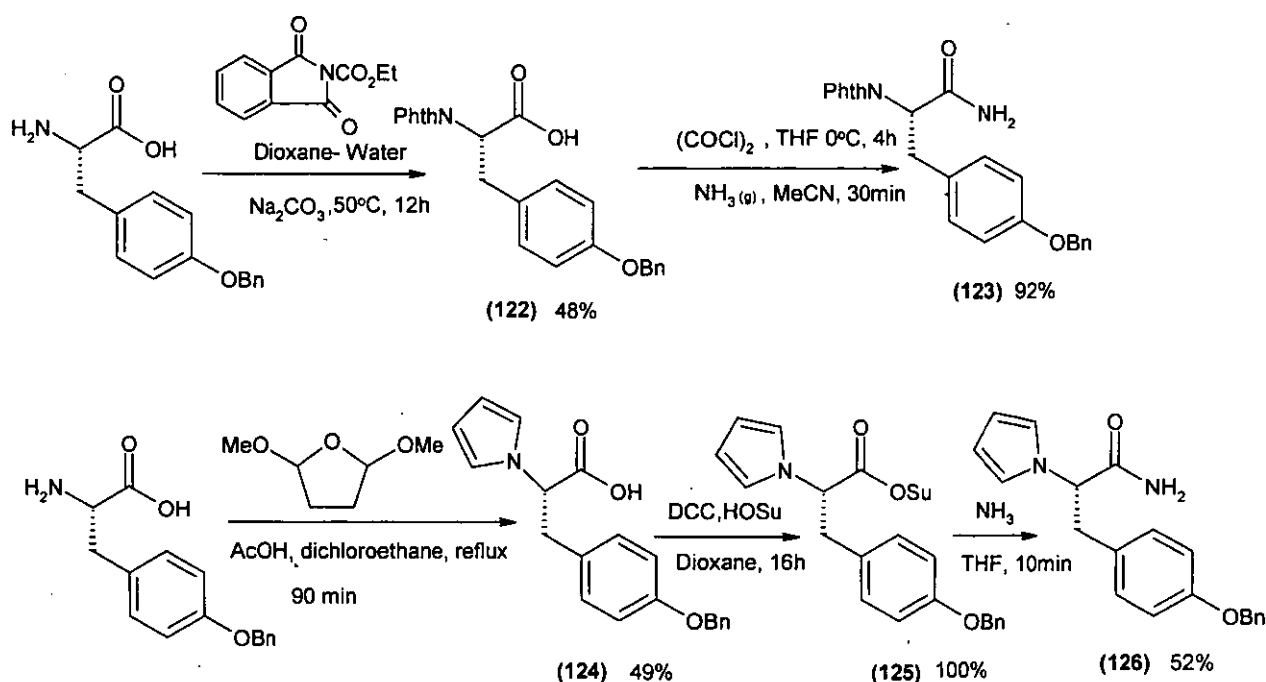
Scheme 66.

Choosing the appropriate amino protecting group for the synthesis is essential to maintain compatibility during the cyclic amidine formation sequence. The previously established methodology for the mono-hydroxyphenyl chromophore formation does highlight the likely hazards involved throughout the synthesis. The *N*-protecting group must be robust under basic conditions for reaction with the diamino nucleophile to form the cyclic amidine. It must also be stable towards hydrogenolysis, and also stable under certain acidic conditions since the key step oxidative cyclisation would produce acidic by-product. Amongst the many possible amine protecting groups, neither the popular 9-fluorenylmethoxycarbonyl (Fmoc), benzyloxycarbonyl (Cbz) carbamate protecting groups nor the benzyl (Bn) group were suitable for the purpose as they are susceptible to the conditions used during the series of reactions. The Fmoc group is easily cleaved in the presence of the diamine base in amidine formation,⁷³ whereas the Cbz or Bn group would not survive under the hydrogenation conditions which are an essential part of our synthesis for revealing the tyrosine phenolic group.

To decide on the most suitable protection, a range of protecting groups, phthalyl (Phth), pyrrolyl (Pyr), *tert*-butyloxycarbonyl (Boc), toluenesulfonyl (Ts) and azide (N₃) were selected for the optimization of the *N*-terminus protection.

The first attempt was to protect the amino nitrogen with a cyclic derivative such as an *N*-phthalyl or *N*-pyrrolyl group. *N*-(Ethoxycarbonyl)phthalimide was used for the *N*-terminal protection of *O*-benzyltyrosine under base conditions to yield *N*-phthalyl-*O*-benzyl-L-tyrosine (**122**) in 48% yield.⁷⁴ Alternatively, the *O*-benzyl-L-tyrosine was also protected by employing a pyrrole protective strategy by reaction with tetrahydro-2,5-dimethoxyfuran under mild acidic conditions⁷⁵ to give the corresponding *N*-pyrrolyl-*O*-benzyl-L-tyrosine (**124**) in 49 % yield (Scheme 67). The reaction mechanism of pyrrole formation is suggested to be similar to the Paal-Knorr pyrrole synthesis where a diketone is involved. It was reported that the enantiomeric configuration of the pyrrole protected amino acids can be fully maintained under these conditions, with acetic acid and water : 1,2-dichloroethane solvent mixtures.

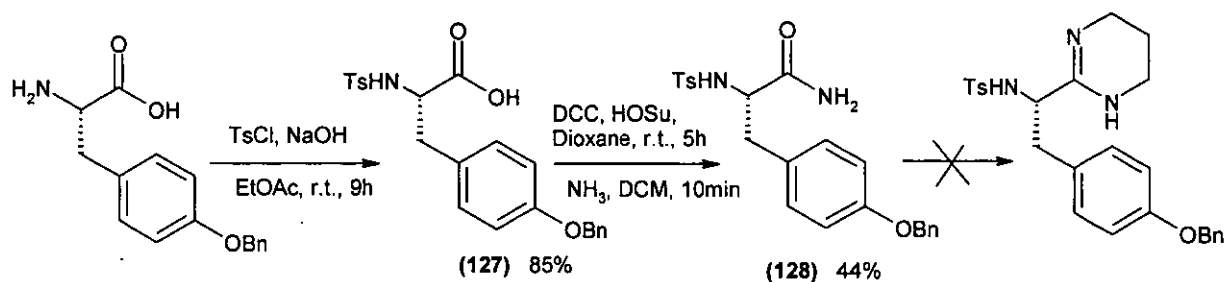
The *N*-phthalyl-*O*-benzyl-L-tyrosine (**122**) was converted to its amide (**123**) in 92% yield *via* acyl chloride formation and then treatment by passing ammonia gas through a THF solution of the chloride instead of the aqueous ammonia conditions we had used earlier, since the *N*-phthalyl group was sensitive when exposed to the aqueous conditions for a long time. The yield was doubled by changing from concentrated aqueous ammonia to ammonia gas (Scheme 67). However, it did not prove possible to form the 2-[1-*N*-(phthalyl)amino-2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidine on methyl triflate activation of the amide and 1,3-diaminopropane treatment. A literature report indicates that the *N*-phthalyl group could be sensitive in certain amine containing environments when heated for a period of time at reflux.⁷⁶ Alternatively, the phthalyl imide may be attacked by the methyl triflate. For the *N*-pyrrolyl-*O*-benzyl-L-tyrosine (**124**),⁷⁷ it was reacted to furnish the amide (**126**) in 52% yield by treatment with DCC, HOSu to form pyrrolyltyrosine succinimide (**125**) and then passing ammonia gas through a DCM solution of the active ester. Unfortunately, this proved unsuccessful for the *N*-pyrrolyltyrosine amide, and we speculate that this is due to pyrrole cleavage by the diaminopropane.



Scheme 67.

N-Sulfonylamides can be prepared by reaction between amines and sulfonyl chlorides in the presence of base and constitute one of the most stable types of nitrogen protective groups, since they are stable to basic hydrolysis and some catalytic reduction conditions. A method reported for conversion of serine into *N*-tosylserine was used for the synthesis of *N*-tosyl-*O*-benzyl-L-tyrosine.⁷⁸ The *O*-benzyl-L-tyrosine was dissolved in water before mixing with toluenesulfonyl chloride in organic solution with slow addition of sodium hydroxide solution to produce the *N*-tosyl-*O*-benzyl-L-tyrosine (**127**) in up to 85% (Scheme 68). Yields were not consistent on repetition of this two phase protocol, which may be due to the solubility of the tyrosine derivative formed after the reaction and work up. *N*-Tosyl-*O*-benzyl-L-tyrosinamide was obtained from the corresponding *N*-tosyl-*O*-benzyl-L-tyrosine on reaction under the peptide coupling method used above (DCC, HOSu followed by ammonia gas). This resulted in only 44% of the desired *N*-toluenesulfonyl-*O*-benzyl-L-tyrosinamide (**128**) after chromatography, which had not been necessary for the other tyrosinamide derivatives. Degradation during the reaction seemed to be the major reason for the poor yield. In any case, reaction of the

tyrosinamide with methyl triflate and 1,3-diaminopropane did not afford the *N*-tosylamino-tetrahydropyrimidine after several attempts and further significant degradation was observed from the reacted crude product. Analysing the crude mixture with LC-MS did indicate traces of product presence but purification through silica chromatography did not yield the desired product.



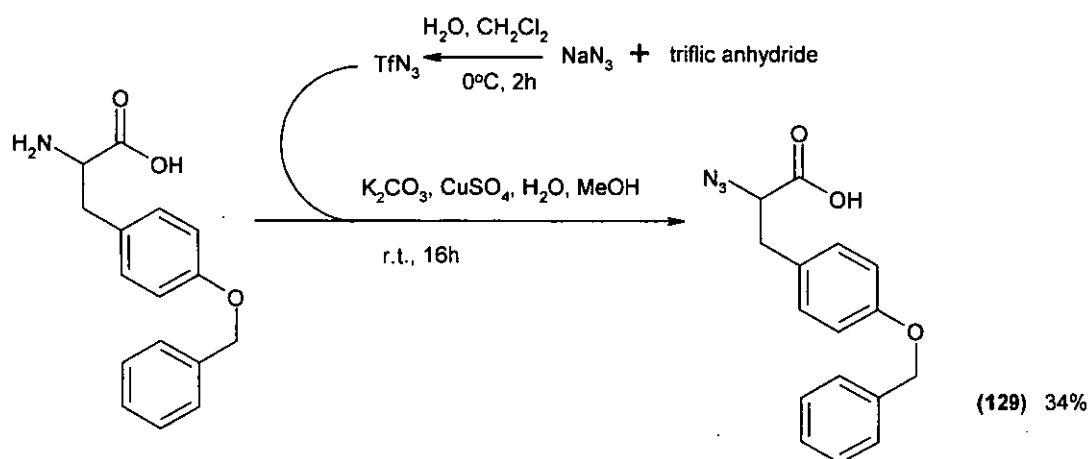
Scheme 68.

Azides have been reported as masked amine groups⁷⁹ and amino sugars⁸⁰ have been prepared from the analogous azides. This methodology provided a useful method for hindered systems and has been described to be reproducible, reliable and can be executed effectively in the presence of other reactive groups and reactive solvents using commercially available reagents.

It has been reported that the azide masking group could be derived from triflyl azide, TfN_3 , via metal catalysed diazo transfer where the TfN_3 is prepared from triflic anhydride and sodium azide. The diazo transfer is subject to divalent copper ions as catalyst, for example CuSO_4 , and homogenous reaction mixture, such as DCM, H_2O and MeOH , and the addition of approximately 1mol % concentrations of CuSO_4 is enough to cause the reaction to go completion within several minutes in the case of mono amine substrates.⁸⁰

The exact mechanism of the metal-catalyzed diazo transfer is not known and little work on this has been carried out. Neat triflic azide is potentially explosive without solvent,

hence it should always be used in solution. The *S*-2-azido-3-(4-benzyloxyphenyl)propionic acid (**129**) was prepared in 34% from *O*-benzyltyrosine and triflic azide solution in the presence of solid potassium carbonate, 1% CuSO₄ and mixed solvent of water and methanol (Scheme 69). Unfortunately, conversion of the azide protected tyrosine to its amide failed to yield the expected product. Therefore, the work with this azide protective group was abandoned.



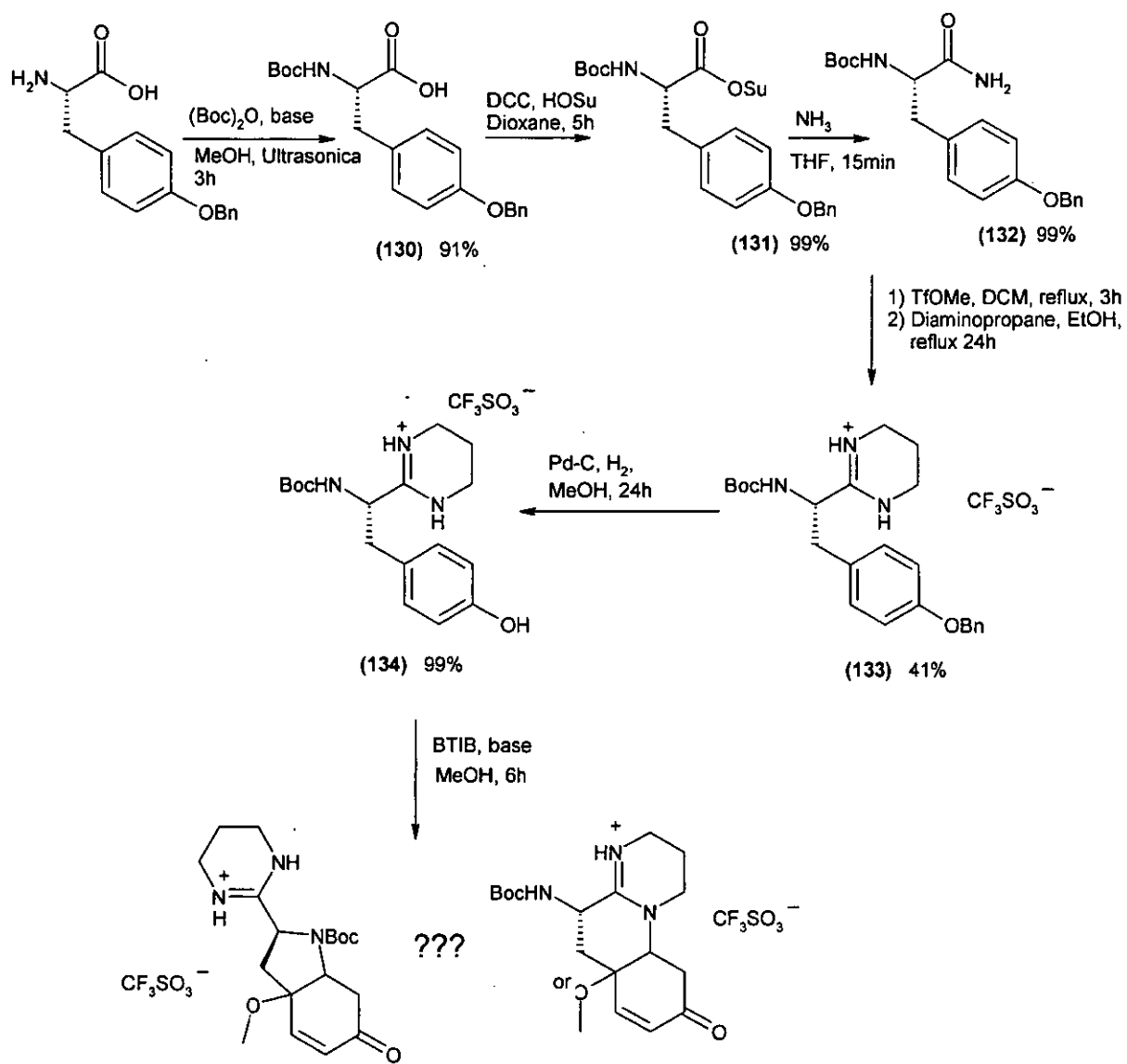
Scheme 69.

One of the commonest protecting groups for amine is the Boc group, *tert*-butyloxycarbonyl, but a major drawback of this functional group is the potential instability under the acidic conditions which would be encountered during the oxidative cyclisation from the trifluoroacetic acid by-product. Fortunately, the oxidative cyclisation reaction could be carried out in the presence of sodium bicarbonate to promote the cyclisation and scavenge the acid by-product in the reaction. Hopefully, this would not make any significant impact on the Boc group present in the compound. Based on this hypothesis, the Boc carbamate protecting group was introduced to the *O*-benzyl-L-tyrosine by sonication for 3-4 hours with (Boc)₂O to give 90% yield of (**130**) under basic conditions (Scheme 70).⁸¹ Boc-protected tyrosine (**130**) was also formed by heating the reaction at reflux in DCM overnight to furnish a similar yield from this more standard method for the protection of an amine substituent with a Boc group. The carboxylic acid

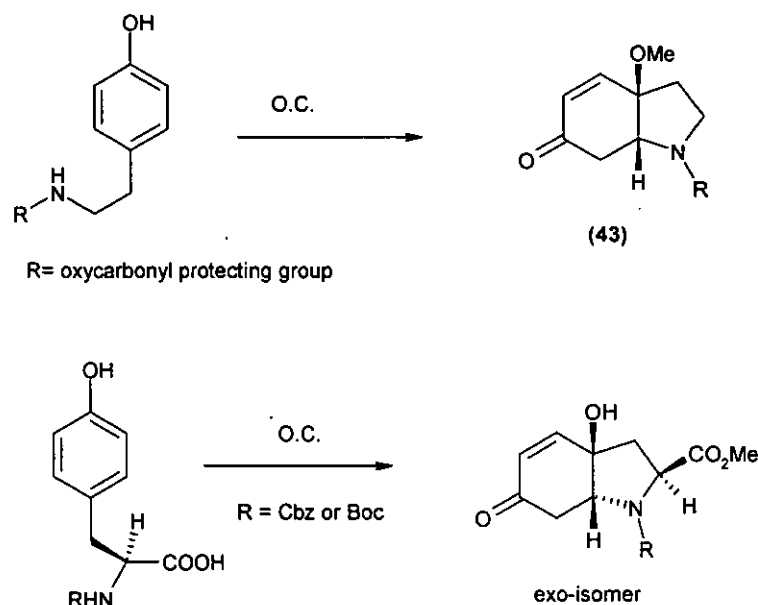
was next transformed into the amide (**133**) via a peptide bond formation protocol, i.e. activation with dicyclohexycarbodiimide (DCC) then *N*-hydroxysuccinimide (HOSu) as (**132**), followed by passing ammonia gas through the mixture. One advantage of the DCC, HOSu coupling over the acyl chloride strategy was the relatively stable activated intermediate formed (**132**) without the acid present when SOCl₂ is used. The Boc group is known to be sensitive to acid cleavage.

S-2-[1-*N*-(Boc-Amino)-2-(4-hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium salt (**134**) was synthesized successfully from the amide (**132**) in 41% yield over our standard 3 steps, namely *O*-methylation with methyl triflate and cyclisation with 1,3-diaminopropane to give *S*-2-[1-*N*-(Boc-Amino)-2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium salt (**133**), and then benzyl ether cleavage by hydrogenolysis.

The attempted oxidative cyclisation of the *S*-2-[1-*N*-(Boc-amino)-2-(4-hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium salt (**134**) with BTIB in methanol did not give any identifiable oxidized and cyclised product due to problems with purification (Scheme 70). More effort and investigation is needed to characterize the possible cyclised compounds. Whether any cyclisation proceeds through the desired amidine nitrogen atom or the protected amino nitrogen atom remains to be investigated once the products are purified. There are some reports of oxidative cyclisation. (Ciufolini⁵² and Wipf⁵³) using amine carbamates that show no significant cleavage using either Cbz, Boc, or Alloc carbamates or tosyl protecting groups when the reaction is carried out using hypervalent iodine reagent, but in these cases, the protected nitrogen atom of the tyrosine was involved as the nucleophile in the cyclisation (Scheme 71).



Scheme 70.



Scheme 71.

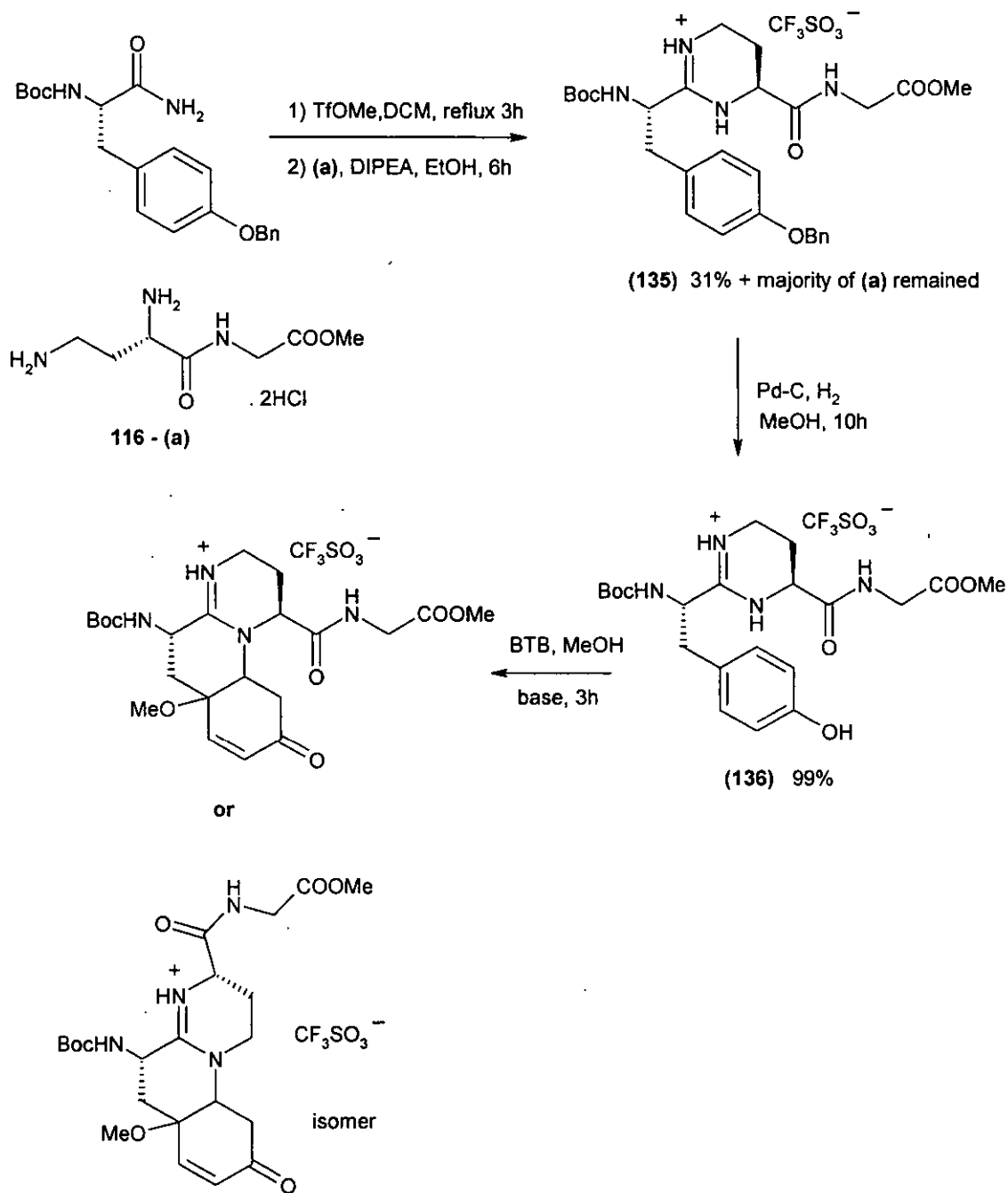
6.4.2.1 Conclusion

Amongst the amino protecting groups introduced to the tyrosine, only the Boc protection showed promise, affording the *N*-protected amino-substituted cyclic amidine in 41% yield. Oxidative cyclisation has so far produced inconclusive results.

6.5 Peptidic Cyclic Amidines – A Ferribactin Formation

In parallel with the reactions described above between the *N*-protected-tyrosine and the diaminoalkane, the *N*-Boc-*O*-benzyltyrosinamide was also reacted with L-2,4-diaminobutyrylaminoacetic acid methyl ester (**116**). Incorporation of both the *N*-terminal amino acid and the *C*-terminal amino acid would produce an analogue of the ferribactin sub unit, a biosynthetic precursor towards the dihydropyoverdins and pyoverdins.

2-[1-(*N*-Boc-Amino)-2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium-4(S)-carbonylaminoacetic acid methyl ester (**135**) was synthesized in only 31% yield from the *N*-Boc-*O*-benzyltyrosinamide (via methyl triflate activation) and L-2,4-diaminobutyrylaminoacetic acid methyl ester dihydrochloride (**116**) (Scheme 72). Similar to the problems experienced earlier, the solubility of the diamino compound in the reaction mixture limited the yield of the reaction. Column chromatography also recovered at least 50% of the diaminobutyric amide starting material. Removal of the benzyl protecting group by hydrogenolysis afforded the 2-[1-(*N*-Boc-amino)-2-(4-hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium-4(S)-carbonylaminoacetic acid methyl ester (**136**) as an analogue of the ferribactin unit relevant to the biosynthesis of pyoverdins. The hydroxyphenyl compound was subject to one attempt at oxidative cyclisation using BTIB. The initial result did not provide conclusive confirmation as to whether the cyclisation had taken place or whether a regioisomer, iso-dihydropyoverdin-type compound might have been formed.



Scheme 72.

6.5.1 Conclusion

The ferribactin analogue unit (**136**), an *N*-Boc-*C*-aminocarbonyltetrahydropyrimidine, was formed in 31% yield with the majority of diamino starting material being recovered due to poor solubility in the reaction solvent. Oxidative cyclisation of this ferribactin analogue remains a challenge and needs further work. A regioisomeric cyclisation is also possible.

7.0 Final Conclusion And Future Work

An initial approach to the biomimetic synthesis of pyoverdine chromophore model was successful. A six-membered ring methoxyquinoline unit was synthesized successfully in a total yield of just below 5%, as well as a seven-membered ring analogue formation with a yield of below 3%. It is the first time this chromophore model unit was chemically synthesized directly through a sequence analogous to the biosynthetic pathway, i.e. *via* cyclic amidine as the ferribactin, tetrahydropyrimidoquinoline as the dihydropyoverdine and dihydropyrimidoquinoline as the pyoverdine. Analysis of the fluorescent properties of the compounds proved that the six-membered ring quinoline is highly fluorescent and the seven-membered ring quinoline is much less significant. A dihydroxyphenyl analogue unit of the chromophore model could be easily oxidized and the products identified by LC-MS, but to date no further attempts to purify this compound have proved successful. An attempt to build a pseudopeptide analogue of the chromophore with either a protected tyrosine or a diaminobutyric acid, or both, led to the peptidic ferribactin formation. Oxidative cyclisation of this ferribactin remains to be investigated.

The problem of the high polarity of both the dihydroxyphenyl and pseudodipeptidic chromophore units remain challenging, ion exchange chromatography could be the solution for this purification since either of the compounds may contain a counter ion or exist as zwitterion. This separation technique can also be incorporated within other steps of the methodology. As an alternative strategy, protecting the hydroxyphenyl oxygen

directly after oxidation *in situ* might reduce the polarity greatly and hence make it possible to identify the product more easily. The regioisomeric pyoverdinin chromophore may form during the oxidative cyclised peptidic unit and this will need to be determined. Although DOPA was suggested not to be involved in the actual bioprocess (see introduction), its dihydroxyphenyl functional group may enhance the oxidative cyclisation and result in direct formation of the peptidic chromophore unit.

8.0 Experimental - General

Infrared spectra were recorded in the range between 4000 – 500 cm^{-1} on a Perkin Elmer Paragon 1000 FT-IR spectrometer as liquid films, nujol mulls, chloroform solution, neat (from evaporation of an acetonitrile or dichloromethane solution) or in KBr discs as stated.

NMR spectra were recorded in solution on either a Bruker 250 MHz (^1H at 250MHz) or 400 MHz (^1H at 400 MHz; ^{13}C at 100 MHz) FTNMR spectrometer using CDCl_3 , d_6 -acetone, d_4 -methanol or d_6 -DMSO as the solvent as stated. Chemical shifts are quoted in a unit of parts per million (ppm) with the following abbreviations; s - singlet, d - doublet, t - triplet, q - quartet, dd - double doublet, dt - double triplet, m - multiplet and brs - broad singlet. Coupling constant (J) values are given in Hertz (Hz).

Liquid Chromatography - Mass Spectrometry (LC-MS) were measured on a Waters 600 controller instrument with a column of Waters Symmetry C8 3.5 μm , 4.6 x 50 nm column and a Waters 996 photodiode array detector attached to a Micromass Platform mass spectrometer using electrospray (ES) as the ionisation technique. High resolution mass spectra were recorded on a Jeol JMS SX-102 mass spectrometer using electron impact (EI) or fast atom bombardment (FAB) as the ionisation technique as indicated.

Flash column chromatography was performed on silica gel 60 (40-63 μ , 230-400 mesh, 60 A) or on Fluka aluminium oxide (basic type pH 9.5 ± 0.5 , 50-150 μ). TLC analyses were performed on Merck UV active aluminium plates coated with 0.2 mm silica 60 F₂₅₄ or on alumina plastic plates.

Melting point measurements were performed on a Gallenkamp hot stage or a Stuart Scientific (SMP3) melting point apparatus and are uncorrected.

Optical rotations were obtained from a PolAAR 2001 optical activity polarimeter at 20 °C with methanol as the solvent and a 30mm cell was used and $[\alpha]_D^{20}$ values were given in $10^{-1} \text{deg cm}^2 \text{g}^{-1}$.

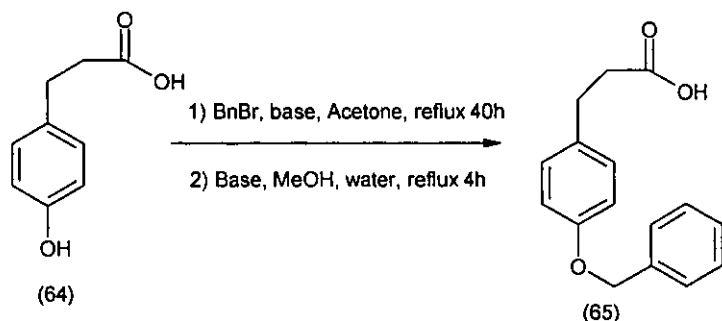
Combustion microanalysis was recorded on Perkin Elmer Analyser 2400 CHN and results are given in percentage.

Commercial reagents were normally used without further purification, unless stated. Dry tetrahydrofuran (THF) was prepared from pre-dried THF, in the presence of potassium carbonate, and distilled over sodium and benzophenone under an atmosphere of nitrogen. Ethyl acetate was distilled over calcium chloride, and petroleum ether (b.p. 40-60°C) was distilled in the presence of anti-bumping granules, according to standard methods⁸² for general use. Dry ethanol (100 %) and methanol used in reactions was purified from magnesium under an atmosphere of nitrogen from standard purification procedures. Dry dichloromethane was distilled in the presence of anhydrous calcium hydride. Both 1,2-diaminoethane and 1,3-diaminopropane were distilled and stored in the presence of potassium carbonate prior to use in reactions.

UV and Fluorescence were measured on a Hewlett-Packard 8453 photodiode array UV/Visible spectrophotometer and a Spex FluoroMAX spectrofluorimeter respectively.

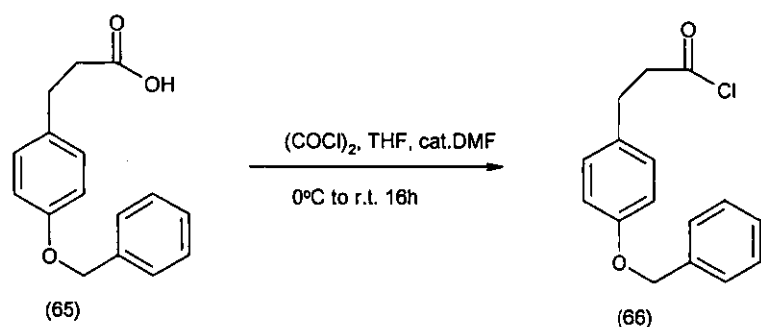
8.1 Experimental

3-(4-Benzyloxyphenyl)propionic acid (65)



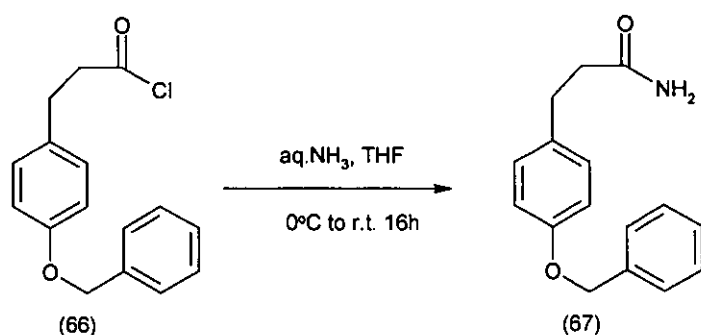
Potassium carbonate (18.28 g, 132.45 mmol), benzyl bromide (15.75 ml, 132.45 mmol) and 3-(4-hydroxyphenyl)propionic acid (64) (10.00 g, 60.24 mmol) in acetone (150 ml) were heated at reflux for 40 h. The solution was evaporated to dryness under reduced pressure and the residue extracted into ethyl acetate (100 ml) and washed with deionised water (100 ml). The organic layer was concentrated under reduced pressure, and the residue dissolved in methanol (100 ml) and heated at reflux with potassium hydroxide (6.75 g, 120.53 mmol) in deionised water (40 ml) for 4 h. The reaction mixture was diluted with deionised water (200 ml), washed with diethyl ether (3 x 100 ml) and the aqueous layer was carefully acidified to pH 1 with concentrated hydrochloric acid. The white precipitated product was collected by vacuum filtration and dried under vacuum over P₂O₅ to give 3-(4-benzyloxyphenyl)propionic acid (65) (15.13 g, 98 %) as a colourless crude solid. M.p: (benzene/hexane) 119-121 °C (lit.,⁸³ 122-123 °C); ν_{\max} (KBr)/cm⁻¹ 3031 (OH), 2923, 1694 (C=O), 1515, 1452, 1309, 1240 (COC), 1014 (COC), 950, 827 and 734; δ_{H} (250 MHz; CDCl₃) 2.66 (2 H, t, *J* 7.5, CH₂Ph), 2.91 (2 H, t, *J* 7.5, CH₂COOH), 5.04 (2 H, s, OCH₂Ph), 6.92 (2 H, d, *J* 8.3, 2 x Ph-H), 7.13 (2 H, d, *J* 8.3, 2 x Ph-H) and 7.33 – 7.45 (5 H, m, 5 x Ph-H); δ_{C} (100 MHz, CDCl₃) 30.15 (CH₂), 36.20 (CH₂), 70.46 (OCH₂Ph), 115.34 (2 x CH, 2 x ArCH), 127.85 (2 x CH, 2 x ArCH), 128.32 (CH, ArCH), 128.96 (2 x CH, 2 x ArCH), 129.65 (2 x CH, 2 x ArCH), 132.92 (C, ArC), 137.50 (C, ArC), 157.79 (CO, ArCO) and 179.25 (CO₂H); *m/z* (EI⁺) 256.1096 (M⁺ - C₁₆H₁₆O₃ requires 256.1100); *m/z* (EI⁺) 256 (M⁺, 13%), 91 (100) and 65 (8).

3-(4-Benzyloxyphenyl)propanoyl chloride (66)



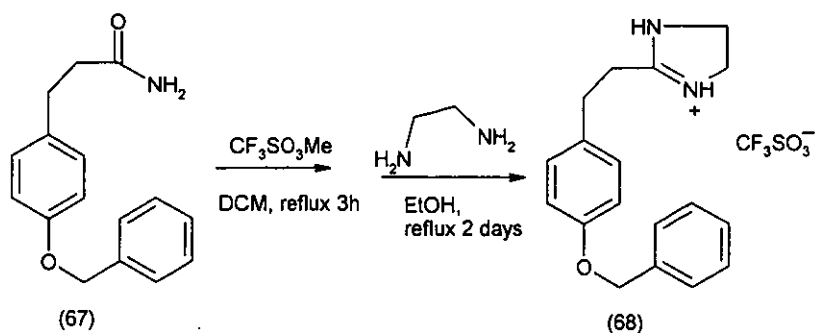
To 3-(4-benzyloxyphenyl)propionic acid (**65**) (11.32 g, 44.20 mmol) and oxalyl chloride (5.83 ml, 66.14 mmol) in dry THF (100 ml) under an atmosphere of nitrogen at 0 °C was added a catalytic amount of *N,N*-dimethylformamide (0.10 ml). The mixture was allowed to reach room temperature and stirred for 16 h, and then the solvent was removed under reduced pressure to yield 3-(4-benzyloxyphenyl)propanoyl chloride (**66**) (12.40 g, 97 %) as a white solid that was used without further purification. M.p: 56-58 °C (lit.,⁸⁴ 75-78 °C); ν_{\max} (KBr)/cm⁻¹ 3032 (Ph-H), 2935, 2858, 1792 (COCl), 1610, 1511, 1452, 1401, 1386, 1240 (COC), 1177, 1039 (COC), 1027, 955, 827, 797 and 737; δ_{H} (250 MHz CDCl₃) 2.96 (2 H, t, *J* 7.4, CH₂Ph), 3.18 (2 H, t, *J* 7.4, CH₂CO), 5.05 (2 H, s, OCH₂Ph), 6.93 (2 H, d, *J* 8.4, 2 x Ph-H), 7.12 (2 H, d, *J* 8.4, 2 x Ph-H) and 7.33 – 7.46 (5 H, m, 5 x Ph-H); δ_{C} (100 MHz CDCl₃) 30.14 (CH₂), 36.24 (CH₂), 70.43 (OCH₂Ph), 115.30 (2 x CH, 2 x ArCH), 127.88 (2 x CH, 2 x ArCH), 128.35 (CH, ArCH), 128.99 (2 x CH, 2 x ArCH), 129.67 (2 x CH, 2 x ArCH), 132.90 (C, ArC), 137.47 (C, ArC), 157.76 (CO, ArCO) and 179.39 (C=O).

3-(4-Benzyloxyphenyl)propanamide (67)



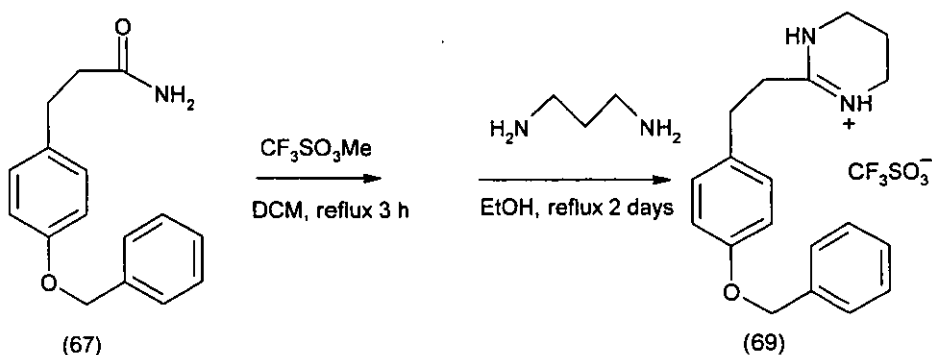
Aqueous ammonia (S.G.0.880, 50 ml) was added to 3-(4-benzyloxyphenyl)propanoyl chloride (**66**) (11.00 g, 40.07 mmol) in THF (100 ml) at 0 °C and the reaction mixture stirred at room temperature for 16 h. After dilution with water (100 ml) the mixture was extracted with ethyl acetate (3 x 80 ml), and the combined organic layer was dried with anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The crude 3-(4-benzyloxyphenyl)propanamide (**67**) (7.72 g, 76 %) was obtained as a white solid, which was recrystallised from methanol and dried under vacuum over P₂O₅ to give white crystals (7.11 g, 70 %). M.p: 157-158 °C; Found: C, 75.11; H, 6.53; N, 5.48. C₁₆H₁₇NO₂ requires C, 75.27; H, 6.71; N, 5.49%; ν_{\max} (KBr)/cm⁻¹ 3391 (NH₂), 3100 (NH₂), 1638 (C=O), 1612 (C=O), 1518, 1425, 1260, 1232 (COC), 1039 (COC), 824 and 733; δ_{H} (250 MHz, CDCl₃) 2.50 (2 H, t, *J* 7.3, CH₂Ph), 2.92 (2 H, t, *J* 7.3, CH₂CONH₂), 5.04 (2 H, s, OCH₂Ph), 5.32 (2 H, brs, NH₂), 6.91 (2 H, d, *J* 8.1, 2 x Ph-H), 7.13 (2 H, d, *J* 8.1, 2 x Ph-H) and 7.35 – 7.42 (5 H, m, 5 x Ph-H); δ_{C} (100 MHz CDCl₃) 30.94 (CH₂), 38.17 (CH₂CO), 70.42 (OCH₂Ph), 115.32 (2 x CH, 2 x ArCH), 127.87 (2 x CH, 2 x ArCH), 128.34 (CH, ArCH), 128.89 (2 x CH, 2 x ArCH), 129.70 (2 x CH, 2 x ArCH), 133.36 (C, ArC), 137.45 (C, ArC), 157.72 (CO, ArCO) and 174.83 (C=O); *m/z* (EI+) 255.1258 (M⁺ - C₁₆H₁₇NO₂ requires 255.1259); *m/z* (EI+) 255 (M⁺, 18%), 91 (100) and 65 (7).

2-[2-(4-Benzoyloxyphenyl)ethyl]-4,5-dihydroimidazolium triflate salt (68)



To 3-(4-benzyloxyphenyl)propanamide (**67**) (1.375 g, 5.38 mmol) in dry dichloromethane (50 ml) under an atmosphere of nitrogen was added dropwise methyl trifluoromethanesulfonate (0.91 ml, 8.07 mmol, 1.5 mol. equiv.) and the reaction mixture stirred at reflux for 3 h and then at room temperature for 2 days. The solvent was removed under reduced pressure to leave a pale yellow-white moisture sensitive salt. This salt in dry ethanol (40 ml) was heated under reflux with dry 1,2-diaminoethane (0.54 ml, 8.07 mmol) under an atmosphere of nitrogen for 2 days. The solvent was removed under reduced pressure and the crude product purified by flash column chromatography using methanol : dichloromethane (5 : 95 v/v) to yield the recovered amide (**67**) (207 mg, 15 %) and 2-[2-(4-benzyloxyphenyl)ethyl]-4,5-dihydroimidazolium triflate salt (**68**) (1.73 g , 75 %). M.p: 170-171 °C; Found: C, 53.31; H, 4.78; N, 6.48. $C_{10}H_{21}N_2O_4F_3S$ requires C, 53.02; H, 4.92; N, 6.50%; ν_{\max} (CHCl₃)/cm⁻¹ 3396, 3237, 3176, 1600 (C=N), 1515(C=N), 1457, 1414, 1287, 1249 (COC), 1154 (C-N), 1038 (COC), 839 and 742; δ_H (250 MHz, DMSO) 2.74 (2 H, t, *J* 7.2, CH₂C=N), 2.86 (2 H, t, *J* 7.2, CH₂Ph), 3.79 (4 H, s, NCH₂CH₂N), 5.08 (2 H, s, OCH₂Ph), 6.97 (2 H, d, *J* 8.3, 2 x Ph-H), 7.16 (2 H, d, *J* 8.3, 2 x Ph-H) and 7.36 – 7.42 (5 H, m, 5 x Ph-H); δ_C (100 MHz, DMSO) 28.24 (CH₂), 30.31 (CH₂), 44.43 (2 x NCH₂), 69.53 (OCH₂Ph), 115.26 (2 x CH, 2 x ArCH), 127.97 (2 x CH, 2 x ArCH), 128.15 (CH, ArCH), 128.77 (2 x CH, 2 x ArCH), 129.54 (2 x CH, 2 x ArCH), 131.49 (C, ArC), 137.47 (C, ArC), 157.43 (CO, ArC-O) and 170.71 (N-C=N); *m/z* (EI+) 280.1580 (M⁺ - C₁₈H₂₀N₂O requires 280.1576); *m/z* (EI+) 280 (M⁺, 10%), 239 (13), 189 (51), 120 (20), 91 (100) and 57 (37).

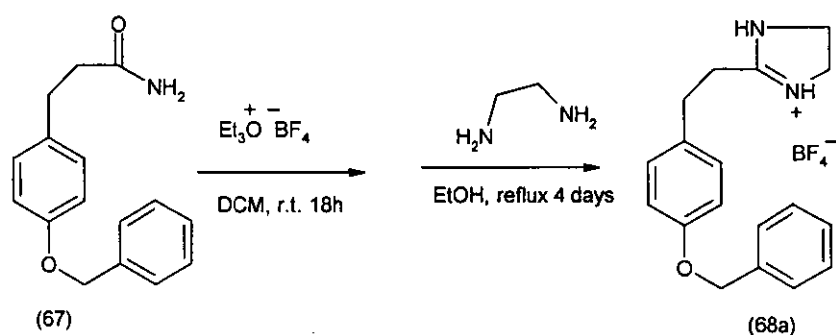
2-[2-(4-Benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (69)



To 3-(4-benzyloxyphenyl)propanamide (**67**) (1.00 g, 3.92 mmol) in dry dichloromethane (50 ml) under an atmosphere of nitrogen was added methyl trifluoromethanesulfonate (0.66 ml, 5.88 mmol, 1.5 mol. equiv.) at room temperature, the solution was stirred at reflux for 3 h and cooled to room temperature with further stirring for 2 days. The solvent was removed to dryness under reduced pressure to give a very pale yellow solid which was dissolved in dry ethanol (50 ml) and dry 1,3 diaminopropane (0.65 ml, 7.78 mmol, 1.98 mol. equiv.) was added under a nitrogen atmosphere at room temperature. The reaction mixture was heat under reflux for 2 days and then the solvent was removed under reduced pressure to leave a residue which was purified by flash chromatography, *via* solid packed loading, using methanol : dichloromethane (5 : 95 v/v) to yield the recovered amide (**67**) (40 mg, 4%) and a very pale yellow solid, 2-[2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (**69**) (1.44 g, 83 %). M.p: 97-99 °C; Found: C, 54.49; H, 5.16; N, 6.22. C₂₀H₂₃N₂O₄F₃S requires C, 54.05; H, 5.22; N, 6.30; ν_{\max} (KBr)/cm⁻¹ 3294, 3065, 1657 (C=N), 1617(C=N), 1514, 1457, 1387, 1240 (COC), 1150 (C-N), 1035 (COC), 835 and 745; δ_{H} (250 MHz CDCl₃) 1.75 (2 H, s, CH₂CH₂CH₂), 2.68 (2 H, t, *J* 7.6, CH₂Ph), 2.90 (2 H, t, *J* 7.6, CH₂C=N), 3.27 (4 H, s, 2 x NCH₂), 4.96 (2 H, s, OCH₂Ph), 6.85 (2 H, d, *J* 8.3, 2 x Ph-H), 7.15 (2 H, d, *J* 8.3, 2 x Ph-H), 7.27 – 7.38 (5 H, m, 5 x Ph-H) and 8.47 (2 H, s, 2 x NH, disappeared after D₂O exchange); δ_{C} (60 MHz, CDCl₃) 18.13 (CH₂CH₂CH₂), 32.04 (CH₂), 34.92 (CH₂), 39.09 (2 x NCH₂), 70.21 (OCH₂Ph), 115.30 (2 x CH, 2 x ArCH), 127.79 (2 x CH, 2 x ArCH), 128.25 (CH, ArCH), 128.84 (2 x CH, 2 x ArCH), 129.89 (2 x CH, 2 x ArCH), 130.74 (C, ArC), 137.22 (C, ArC), 157.92 (CO, ArC-O) and 164.06 (N-C=N); *m/z* (EI⁺) 294.1739

(M^+ - $C_{19}H_{22}N_2O$ requires 294.1732); m/z (EI+) 294 (M^+ , 6%), 203 (100), 111 3), 91 (47), and 57 (7).

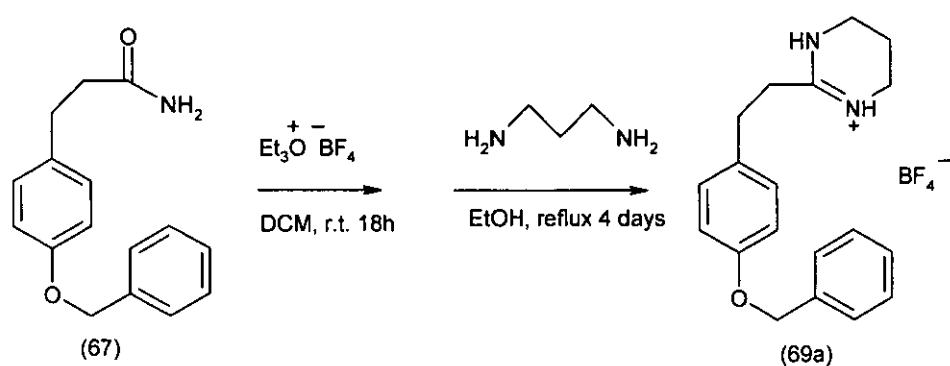
2-[2-(4-Benzyloxyphenyl)ethyl]-4,5-dihydroimidazolium tetrafluoroborate (68a)



To 3-(4-benzyloxyphenyl)propanamide (**67**) (1.00 g, 3.92 mmol) in dry dichloromethane (20 ml) under an atmosphere of nitrogen, was added dropwise a 1M solution of triethylxonium tetrafluoroborate in dichloromethane (4.70 ml, 4.70 mmol) at room temperature and the reaction was stirred for 18 h. The solvent was removed under reduced pressure, and to the white residue in dry ethanol (50 ml) was added dry 1,2-diaminoethane (0.30 ml, 4.49 mmol) and the mixture heated at reflux for 4 days. The solvent was removed under reduced pressure and the residue purified by flash column chromatography with dichloromethane : methanol (95 : 5 v/v) to give a white solid of recovered amide (**67**) (320 mg, 32 %) and 2-[2-(4-benzyloxyphenyl)ethyl]-4,5-dihydroimidazolium tetrafluoroborate (**68a**) (170 mg, 10 %). M.p: 139-144 °C; ν_{max} ($CHCl_3$)/ cm^{-1} 3395,1651 (C=N), 1514, 1454, 1417, 1252 (COC), 1174 (C-N), 1108, 1013 (COC), 814 and 739; δ_H (400 MHz DMSO) 2.10 (2 H, d, J 7.2, CH_2Ar), 2.29 (2 H, t, J 7.7, $CH_2C=N$), 2.50 (2 H, d, J 8.0, NCH_2), 2.73 (2 H, t, J 7.7, NCH_2), 5.06 (2 H, s, OCH_2Ph), 6.75 (1 H, brs, NH), 6.91 (2 H, d, J 8.4, 2 x Ph-H), 7.12 (2 H, d, J 8.4, 2 x PhH), 7.24 (1 H, br, NH) and 7.31 – 7.45 (5 H, m, 5 x Ph-H); δ_C (100 MHz, DMSO) 25.20 (CH_2), 29.94 (CH_2), 30.38 (NCH_2), 37.34 (NCH_2), 69.45 (OCH_2Ph), 114.91 (2 x CH, 2 x ArCH), 127.96 (2 x CH, 2 x ArCH), 128.09 (CH, ArCH), 128.75 (2 x CH, 2 x

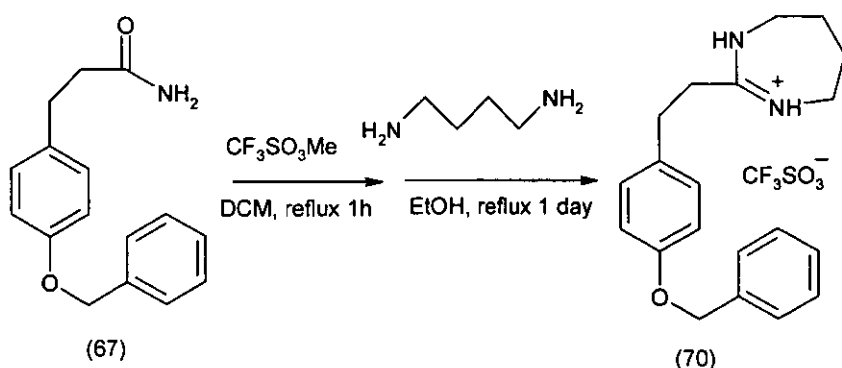
ArCH), 129.49 (2 x CH, 2 x ArCH), 133.96 (C, ArC), 137.61 (C, ArC), 156.89 (CO, ArC-O) and 173.83 (N-C=N).

2-[2-(4-Benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium tetrafluoroborate (69a)



Tetrafluoroborate compound (**69a**) was prepared by the same procedure as described above for the formation of 2-[2-(4-benzyloxyphenyl)ethyl]-3,4-dihydroimidazolium salt (**47b**), but using dry 1,3-diaminopropane (0.37 ml, 4.49 mmol) instead of 1,2-diaminoethane. This reaction yielded a white solid of recovered amide (**67**) (40 mg, 40%) and 2-[2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium tetrafluoroborate (**69a**) (79 mg, 10 %) after flash column chromatography using methanol : dichloromethane (5 : 95 v/v). δ_{H} (250 MHz, CDCl_3), 1.77 (2 H, t, J 5.6, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.68 (2 H, t, J 7.6, CH_2Ar), 2.89 (2 H, t, J 7.6, $\text{CH}_2\text{C}=\text{N}$), 3.30 (4 H, s, 2 x NCH_2), 4.98 (2 H, s, OCH_2Ph), 6.86 (2 H, d, J 8.5, 2 x Ph-H), 7.14 (2 H, d, J 8.5, 2 x Ph-H), 7.30 – 7.38 (5 H, m, Ph-H) and 7.73 (2 H, s, 2 x NH). LC-MS m/z (ES+) 295 ($\text{MH}^+ - \text{C}_{19}\text{H}_{22}\text{N}_2\text{O} + \text{H}$ requires 295).

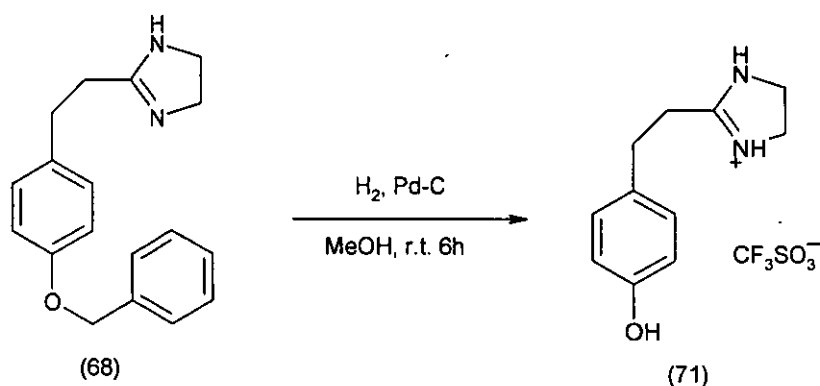
2-[2-(4-Benzyloxyphenyl)ethyl]-4,5,6,7-tetrahydro-1*H*-[1,3]diazepinium triflate salt (70)



To 3-(4-benzyloxyphenyl)propanamide (**67**) (1.00 g, 3.92 mmol) in a dry flask with dry dichloromethane (40 ml) was added methyl trifluoromethanesulfonate (0.66 ml, 5.88 mmol, 1.5 mol. equiv.) under a nitrogen atmosphere, and the mixture was stirred at reflux for 1 h and then for a further 1 day at ambient temperature. The solvent was removed to dryness under reduced pressure to give a very pale yellow solid which was re-dissolved in dry ethanol (50 ml) and 1,4-diaminobutane (0.79 ml, 7.84 mmol, 2 mol. equiv.) was added under a nitrogen atmosphere at room temperature. The reaction was brought to reflux for 1 day and the solvent was then removed under reduced pressure to afford a residue that was purified by flash column chromatography using methanol : dichloromethane (5 : 95 v/v) *via* solid packed loading to yield the very pale yellow solid, 2-[2-(4-benzyloxyphenyl)ethyl]-4,5,6,7-tetrahydro-1*H*-[1,3]diazepinium triflate salt (**70**) (0.426 g, 24 %). M.p: 98-100 °C; ν_{\max} (CHCl₃)/cm⁻¹ 3448, 3306 (OH), 3080, 2936, 1654 (C=N), 1512, 1455, 1381, 1331, 1243 (C-N), 1165, 1029 (COC) and 825; δ_{H} (250 MHz CDCl₃) 1.81 (4 H, s, 2 x NCH₂CH₂CH₂CH₂N), 2.67 (2 H, t, *J* 7.6, CH₂), 2.91 (2 H, t, *J* 7.6, CH₂), 3.43 (4 H, s, 2 x NCH₂), 4.96 (2 H, s, OCH₂Ph), 6.86 (2 H, d, *J* 8.8, Ph-H), 7.18 (2 H, d, *J* 8.8, Ph-H), 7.28 – 7.40 (5 H, m, Ph-H) and 8.40 (2 H, s, NH); δ_{C} (100 MHz, CDCl₃) 26.24 (CH₂CH₂CH₂CH₂), 32.58 (CH₂CH₂), 36.84 (CH₂CH₂), 43.95 (2 x NCH₂), 70.29 (OCH₂Ph), 115.40 (2 x CH, 2 x ArCH), 127.89 (2 x CH, 2 x ArCH), 128.33 (CH, ArCH), 128.93 (2 x CH, 2 x ArCH), 130.11 (2 x CH, 2 x ArCH), 130.77 (C, ArC), 137.33 (C, ArC), 158.01 (CO, ArCO) and 169.28 (C=NH); *m/z* (EI⁺) 308.1897

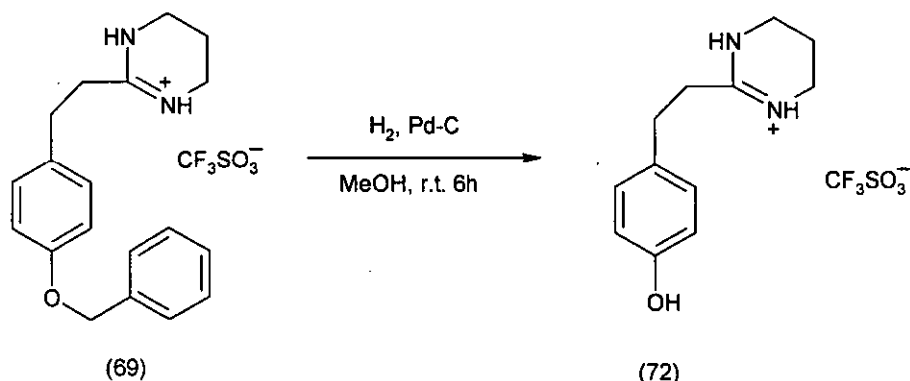
(M^+ - $C_{20}H_{24}N_2O$ requires 308.1894); m/z (FAB) 308 (M^+ , 7%), 255 (27), 235 (34) 217 (100), 115v (25), 91 (29) and 65 (38).

2-[2-(4-Hydroxyphenyl)ethyl]-4,5-dihydroimidazolium triflate salt (71)



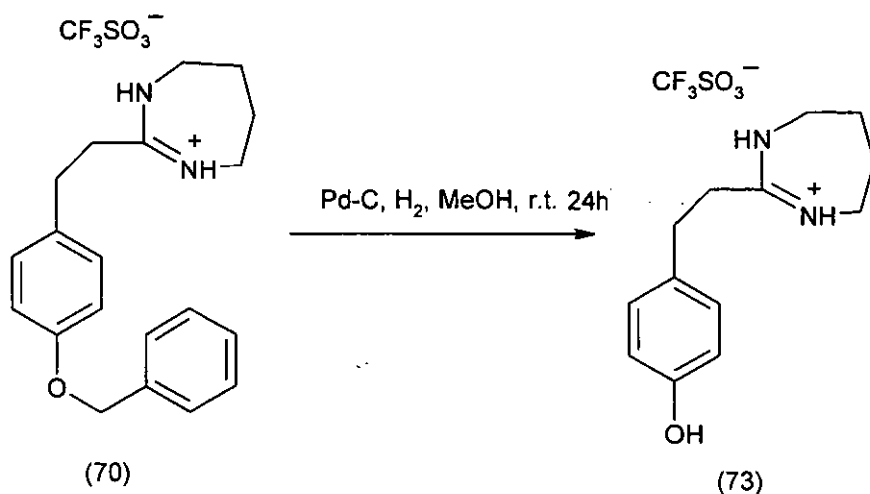
To 2-[2-(4-benzyloxyphenyl)ethyl]-4,5-dihydroimidazolium triflate salt (**68**) (384 mg, 1.37 mmol) was added palladium-carbon (10 %) (60 mg, 15 %w/w) followed by methanol (20 ml). After degassing three times and filling the flask with hydrogen gas, reaction was carried out by stirring under 1 atmosphere of hydrogen at room temperature for 6 h. The palladium-carbon catalyst was removed by filtration through celite and washed with methanol (20 ml). The solvent was removed to dryness to leave a yellow liquor of 2-[2-(4-hydroxyphenyl)ethyl]-4,5-dihydroimidazolium triflate salt (**71**) (260 mg, 100 %). ν_{max} (Nujol)/ cm^{-1} 3292 (NH), 3100, 2676, 1643 (C=N), 1609 (C=N), 1558, 1514, 1497, 1256 (C-N), 1169, 1030 and 828; δ_H (250 MHz, DMSO) 2.31 (2 H, t, J 8.0, CH_2Ph), 2.72 (2 H, t, J 8.0, t, $CH_2C=N$), 3.38 (4 H, s, 2 x NCH_2), 6.67 (2 H, d, J 8.1, 2 x Ph-H) and 7.01 (2 H, d, J 8.1, 2 x Ph-H); δ_C (100 MHz, DMSO) 31.15 (CH_2), 31.57 (CH_2), 49.23 (2 x NCH_2), 115.39 (2 x CH, 2 x ArCH), 129.34 (2 x CH, 2 x ArCH), 131.81 (C, ArC), 155.72 (COH, ArCOH) and 167.35 (N=C-N); m/z (FAB) 191.1185 (MH^+ - $C_{11}H_{14}N_2O + H$ requires 191.1184).

2-[2-(4-Hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (72)



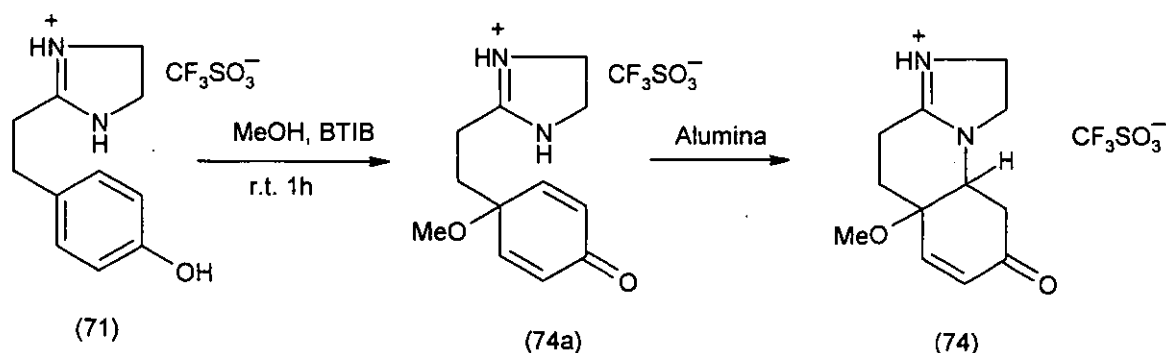
To 2-[2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (**69**) (683 mg, 2.32 mmol) and palladium-carbon (10%) catalyst (104 mg, 15 % w/w), was added methanol (60 ml). After degassing the solution, the mixture was hydrogenated under 1 atmosphere of hydrogen at room temperature for 6 h. After filtering off the palladium-carbon catalyst over celite and washing with methanol (30 ml), the methanol was removed under reduced pressure to yield a yellow liquor, 2-[2-(4-hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (**72**) (471 mg, 99 %). ν_{\max} (Nujol)/ cm^{-1} 3302 (NH), 3162, 1660 (C=N), 1627 (C=N), 1514, 1322, 1255(C-N), 1165, 1029 834, 763 and 723; δ_{H} (250 MHz, DMSO) 1.79 (2 H, t, J 5.5, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.58 (2 H, t, J 7.3, CH_2Ph), 2.81 (2 H, t, J 7.3, $\text{CH}_2\text{C}=\text{N}$), 3.29 (4 H, t, J 5.1, 2 x NCH_2), 6.72 (2 H, d, J 8.1, 2 x Ph-H) and 7.03 (2 H, d, J 8.1, 2 x Ph-H); δ_{C} (100 MHz, DMSO) 15.97 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 29.62 (CH_2), 32.42 (CH_2), 36.36 (2 x NCH_2), 113.52 (2 x CH, 2 x ArCH), 127.45 (2 x CH, 2 x ArCH), 154.23 (C, ArC), 160.73 (COH, ArCOH) and 170.06 (N=C-N); m/z (FAB) 205 (MH^+ , 100%), 107 (8), 98 (13) and 57 (10); m/z (FAB) 205.1340 ($\text{MH}^+ - \text{C}_{12}\text{H}_{16}\text{N}_2\text{O} + \text{H}$ requires 205.1341).

2-[2-(4-Hydroxyphenyl)ethyl]-4,5,6,7-tetrahydro-1*H*-[1,3]diazepinium triflate salt
(73)



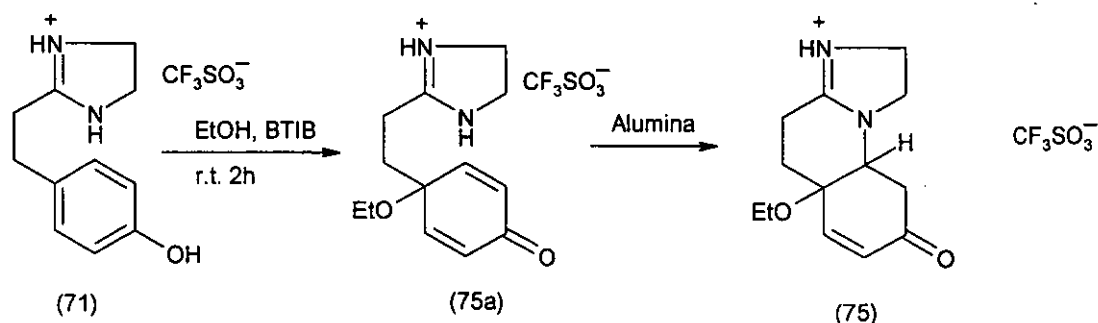
To 2-[2-(4-benzyloxyphenyl)ethyl]-4,5,6,7-tetrahydro-1*H*-[1,3]diazepinium triflate salt (70) (668 mg, 1.46 mmol) was added palladium-carbon (10%) (100 mg, 15 %w/w) and methanol (50 ml). The reaction mixture was degassed first by attaching the reaction flask under vacuum before proceeding with hydrogenation under a hydrogen balloon (1 atm) for 24 h. The palladium-carbon was removed by filtration over celite and this washed with methanol (40 ml). The filtrate was evaporated to dryness to give amidinium salt (73) as a pale yellow oily product (522 mg, 97 %). ν_{max} (acetone)/ cm^{-1} 3294 (OH), 3072, 2939, 1648 (C=N), 1614, 1515, 1453, 1361, 1332, 1242 (C-N), 1167, 1029 (COC) and 830; δ_{H} (250 MHz CD_3CN) 1.84 – 1.88 (4 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 2.57 (2 H, t, J 7.5, CH_2Ph), 2.83 (2 H, t, J 7.5, $\text{CH}_2\text{C}=\text{N}$), 3.41 – 3.47 (4 H, m, 2 x NCH_2), 5.74 (1 H, brs, NH), 6.75 (2 H, d, J 8.3, 2 x Ph-H) and 7.03 (2 H, d, J 8.3, 2 x Ph-H); δ_{C} (100 MHz, CD_3CN) 26.60 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 31.84 (CH_2), 37.61 (CH_2), 44.15 (2 x NCH_2), 116.58 (2 x CH, 2 x ArCH), 130.00 (C, ArC), 130.50 (2 x CH, 2 x ArCH), 157.63 (COH, ArCOH) and 169.59 (N-C=N); m/z (EI+) 218 (M^+ , 74%), 165 (24), 120 (30), 107 (100), 98 (45), 77 (25) and 70 (23); m/z (EI+) 218.1420 (M^+ - $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$ requires 218.1419).

5a-Methoxy-1,2,5,5a,9,9a-hexahydro-4*H*-imidazo[1,2-*a*]quinolin-8-one triflate salt (74) via 4-[2-(4,5-dihydro-1*H*-imidazol-2-yl)ethyl]-4-methoxy-cyclohexa-2,5-dienone triflate salt (74a)



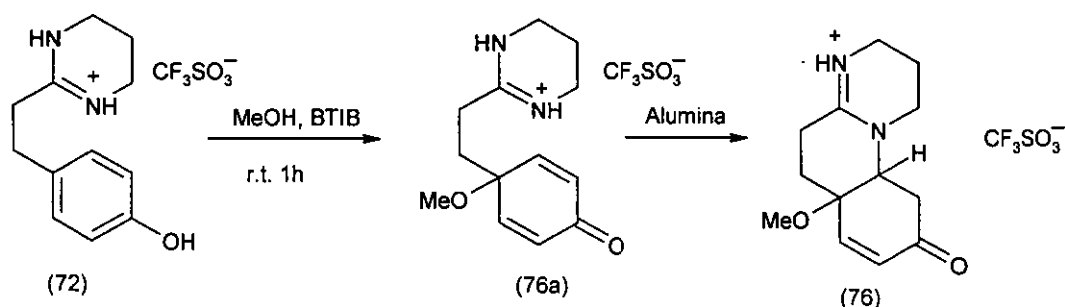
2-[2-(4-Hydroxyphenyl)ethyl]-4,5-dihydroimidazolium triflate salt (**71**) (390 mg, 2.05 mmol) was mixed with *bis*(trifluoroacetoxy)iodobenzene (BTIB) (1.05 g, 2.46 mmol, 1.2 mol. equiv.) in dry methanol (8 ml). The yellow mixture was swirled at room temperature under an atmosphere of nitrogen for 1 h and then the solvent was removed to give a brown residue. The residue was partitioned between petroleum ether (3 x 30 ml) and acetonitrile (30 ml) to remove the iodobenzene into the petroleum ether layer. The acetonitrile layer was evaporated to dryness under reduced pressure for basic alumina column chromatography of the residue using methanol and dichloromethane (3 : 97 v/v) to give quinolinone triflate salt (**74**) as a brown oil (178 mg, 39 %). ν_{\max} (CHCl₃)/cm⁻¹ 3360, 2936, 1693 (C=O), 1682 (C=N), 1614, 1455, 1417, 1271 (C-N), 1217, 1099 and 1013 (COC); δ_{H} (250 MHz, CDCl₃) 1.87 – 1.93 (1 H, m, NCH(H)), 2.06 – 2.11 (1 H, m, NCH(H)), 2.34 – 2.44 (2 H, m, NCH₂CH₂N), 2.59 – 2.68 (2 H, m, CH₂C), 2.99 – 3.08 (2 H, m, CH₂C=N), 3.33 (3 H, s, OCH₃), 3.50 – 3.78 (3 H, m, CHCH₂C=O & NCH), 6.16 (1 H, d, *J* 10.3, CH=CHCO) and 6.75 (1 H, d, *J* 10.3, CH=CHCO); δ_{C} (100 MHz, CDCl₃) 20.68 (CH₂), 27.24 (CH₂), 38.96 (CH₂C=O), 47.99 (NCH₂), 49.84 (OCH₃), 51.14 (NCH₂), 57.39 (NCHCH₂C=O), 71.63 (C-OCH₃), 131.16 (CH=CHCO), 148.01 (CH=CHCO), 161.03 (N-C=N) and 195.66 (C=O); *m/z* (FAB) 221.1293 (MH⁺ - C₁₂H₁₆N₂O₂ + H requires 221.1290); *m/z* (FAB) 221 (MH⁺, 100%), 149 (24), 136 (26), 91 (25), 69 (28), 55 (42) and 41 (37).

5a-Ethoxy-1,2,5,5a,9,9a-hexahydro-4H-imidazo[1,2-a]quinolin-8-one triflate salt (75) via 4-[2-(4,5-dihydro-1H-imidazol-2-yl)ethyl]-4-ethoxy-cyclohexa-2,5-dienone triflate salt (75a)



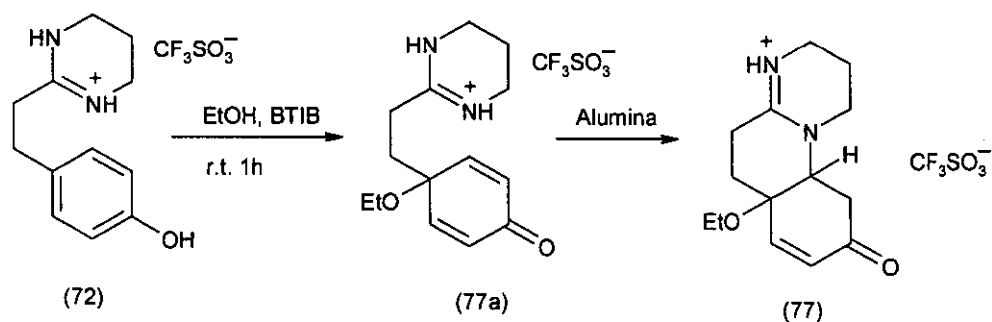
To the 2-[2-(4-hydroxyphenyl)ethyl]-4,5-dihydroimidazolium triflate salt (**71**) (365 mg, 1.92 mmol) in ethanol (5 ml), was added *bis*(trifluoroacetoxy)iodobenzene (BTIB) (989 mg, 3.20 mmol 1.2 mol. equiv.) in ethanol (5 ml) under an atmosphere of nitrogen. The yellow mixture was swirled at room temperature for 2 h and then the solvent was removed to dryness under reduced pressure. The residue was partitioned between petroleum ether (3 x 30 ml) and acetonitrile (30 ml) to remove the iodobenzene into the petroleum ether layer. The acetonitrile layer was evaporated to dryness under reduced pressure for basic alumina column chromatography of the residue using methanol and dichloromethane (3 : 97 v/v) to give quinolinone triflate salt (**75**) as a brown liquor (70 mg, 16 %). ν_{max} (CHCl_3)/ cm^{-1} 3017, 2976, 2937, 2872, 1684 (C=O), 1623 (C=N), 1419, 1270, 1215 (C-N), 1111, 1082 (COC) and 755; δ_{H} (250 MHz, CDCl_3) 1.17 (3 H, t, J 6.9, CH_2CH_3), 1.84 – 1.92 (1 H, m, 1 H, $\text{NCH}(\text{H})$), 2.05 – 2.15 (1 H, m, $\text{NCH}(\text{H})$), 2.21 – 2.43 (2 H, m, NCH_2), 2.60 – 2.69 (1 H, m, $\text{CH}(\text{H})$), 2.99 – 3.08 (1 H, m, $\text{CH}(\text{H})$), 3.03 (2 H, m, CH_2), 3.51 (4 H, m, OCH_2CH_3 & CHCH_2CO), 3.66 – 3.79 (1 H, m, NCH), 6.12 (1 H, d, J 10.4, $\text{CH}=\text{CHCO}$) and 6.74 (1 H, d, J 10.4, $\text{CH}=\text{CHCO}$); δ_{C} (100 MHz, CDCl_3) 16.34 (CH_2CH_3), 22.17 (CH_2), 29.23 (CH_2), 40.34 ($\text{CH}_2\text{C}=\text{O}$), 49.47 (NCH_2), 52.66 (NCH_2), 58.98 (OCH_2CH_3), 59.46 ($\text{CHCH}_2\text{C}=\text{O}$), 72.11 (C-O), 132.24 ($\text{CH}=\text{CHCO}$), 149.96 ($\text{CH}=\text{CHCO}$), 162.55 (N=C-N) and 197.21 (C=O); m/z LC-MS (ES+) 235 (MH^+ , 100%), 191 (44), 189 (56), 161 (20), 146 and 84 (20); m/z (FAB) 235.1450 (MH^+ - $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_2 + \text{H}$ requires 235.1447).

6a-Methoxy-2,3,6,6a,10,10a-hexahydro-1*H*,5*H*-pyrimido[1,2-*a*]quinolin-9-one triflate salt (76) via 4-methoxy-4-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)ethyl]cyclohexa-2,5-dienone triflate salt (76a)



2-[2-(4-Hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (72) (885 mg, 4.33 mmol) and the *bis*(trifluoroacetoxy)iodobenzene (BTIB) (2.23 g, 5.19 mmol, 1.2 mol. equiv.) in dry methanol (10 ml) under an atmosphere of nitrogen was swirled for 1 h at ambient temperature before removal of the solvent to yield a pale brown residue. The by-product iodobenzene was removed by partitioning of the residue between petroleum ether (3 x 30 ml) and acetonitrile (40 ml). The acetonitrile layer was collected and evaporated to dryness under reduced pressure for flash column chromatography of the residue with basic alumina pH 9.5 using methanol and dichloromethane (3 : 97 v/v). The brown liquor obtained from the chromatography was the quinolinone triflate salt (76) (464 mg, 46 %). ν_{\max} (CHCl₃)/cm⁻¹ 3511, 3284, 3152, 2957, 1691 (C=O), 1644 (C=N), 1597, 1324, 1254 (C-N), 1159, 1030 (COC) and 757; δ_{H} (250 MHz, acetone) 2.11 – 2.21 (3 H, m, CH₂ & CH(H)), 2.79 – 2.91 (4 H, m, 2 x CH₂), 3.04 (1 H, dd, *J* 16.7 & 5.2, CH(H)), 3.38 (3 H, s, OCH₃), 3.44 – 3.51 (2 H, m, CH₂), 3.62 – 3.67 (1 H, m, CH(H)), 3.77 – 3.86 (1 H, m, CH(H)), 4.45 (1 H, dd, *J* 12.3 & 5.2, NCH), 6.13 (1 H, d, *J* 10.4, CH=CHCO), 7.05 (1 H, d, *J* 10.4, CH=CHCO). δ_{C} (100 MHz, acetone) 19.90 (CH₂CH₂CH₂), 25.10 (CH₂), 25.39 (CH₂), 40.05 (CH₂C=O), 41.29 (NCH₂), 47.11 (NCH₂), 51.77 (OCH₃), 59.57 (CH), 74.34 (C-OCH₃), 132.30 (CH=CHCO), 152.05 (CH=CHCO), 161.76 (N-C=N) and 195.25 (C=O); *m/z* (EI⁺) 234.1373 (M⁺ - C₁₃H₁₈N₂O₂ requires 234.1368).

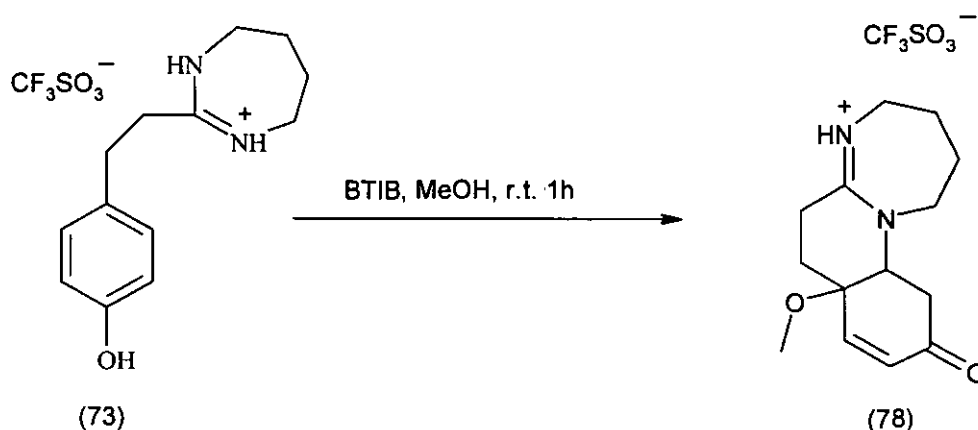
6a-Ethoxy-2,3,6,6a,10,10a-hexahydro-1*H*,5*H*-pyrimido[1,2-*a*]quinolin-9-one triflate salt (77) via 4-ethoxy-4-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)ethyl]cyclohexa-2,5-dienone triflate salt (77a)



To 2-[2-(4-hydroxyphenyl)ethyl]-3,4,5-tetrahydropyrimidinium triflate salt (72) (490 mg, 2.40 mmol) in ethanol (8 ml) was added *bis*(trifluoroacetoxy)iodobenzene (BTIB) (1.24 g, 2.88 mmol, 1.2 mol. equiv) in ethanol (8 ml) under an atmosphere of nitrogen. The yellow mixture was swirled under an atmosphere of nitrogen at ambient temperature for 1 h before removing the solvent to yield a pale brown residue. Extraction of the residue was carried out to remove the by-product iodobenzene by using petroleum ether (3 x 30 ml) and acetonitrile (30 ml). The acidic polar organic layer, acetonitrile at pH 1, was collected and evaporated to dryness under reduced pressure then purified by flash column chromatography with basic alumina pH 9.5 using methanol and dichloromethane (3 : 97 v/v). A pale yellow solid was collected after solvent removal as the corresponding cyclised quinolinone triflate salt (77) (204 mg, 34 %). M.p: (ethyl acetate) 154-155 °C; Found: C, 44.91; H, 5.07; N, 6.89. C₁₅H₂₁N₂O₅F₄S requires C, 45.22; H, 5.31; N, 7.03%; ν_{\max} (CHCl₃)/cm⁻¹ 3018, 1688 (C=O), 1645 (C=N), 1214 (C-N), 1028 (COC) and 757; δ_{H} (250 MHz, CDCl₃) 1.19 (3 H, t, *J* 6.9, CH₂CH₃), 2.03 – 2.09 (4 H, m, CH₂CH₂), 2.66 (1 H, dd, *J* 12.4 & 16.4, CH(H)), 2.89 – 2.94 (2 H, m, CH₂), 3.01 – 3.10 (1 H, m, CH(H)), 3.29 – 3.26 (1 H, m, CH(H)), 3.43 – 3.51 (4 H, m, OCH₂CH₃ & CH₂), 3.58 – 3.68 (1 H, m, CH(H)), 3.98 (1 H, dd, *J* 5.0 & 12.4, NCH), 6.11 (1 H, d, *J* 10.4, CH=CHCO) and 6.84 (1 H, d, *J* 10.4, CH=CHCO); δ_{C} (100 MHz, CDCl₃) 14.88 (CH₃), 17.80 (CH₂CH₂CH₂), 22.95 (CH₂), 23.73 (CH₂), 37.81 (CH₂C=O), 39.55 (NCH₂), 45.15

(NCH₂), 58.17 (OCH₂CH₃), 58.46 (CH), 71.71 (C-O), 130.05 (CH=CHCO), 150.29 (CH=CHCO), 159.30 (N-C=N), 193.31 (C=O); *m/z* (EI+) 248.1525 (M⁺ - C₁₄H₂₀N₂O₂ requires 248.1525); *m/z* (EI+) 248 (M⁺, 100%), 219 (94), 203 (96), 191 (27), 176 (88), 165 (27), 122 (28), 109 (42), 98 (24), 91 (25), 77 (34), 54 (67) and 41 (40).

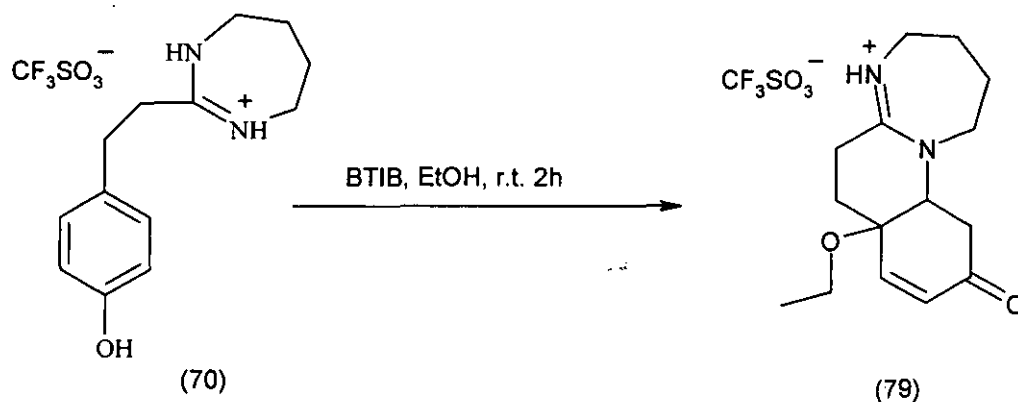
4a-Methoxy-1,5,6,8,9,10,11,12a-octahydro-4aH-azepino[1,2-a]quinolin-2-one triflate salt (78)



To 2-[2-(4-hydroxyphenyl)ethyl]-4,5,6,7-tetrahydro-1*H*-[1,3]diazepinium triflate salt (**73**) (427 mg, 1.95 mmol) in dry methanol (20 ml) was added *bis*(trifluoroacetoxy)iodobenzene (1.01 g, 2.35 mmol, 1.2 mol. equiv.) in dry methanol (20 ml). After stirring for 1 h at ambient temperature, the solvent was removed under pressure. The iodobenzene by-product was removed by partitioning the residue between acetonitrile (30 ml) and petroleum ether (3 x 30 ml). The acetonitrile layer was collected and the solvent was removed under reduced pressure for flash column chromatography of the residue over basic alumina with methanol : dichloromethane (5 : 95 v/v) to yield a brown oily product (**78**) (204 mg, 44%). ν_{\max} (CHCl₃)/cm⁻¹ 3279, 3131, 2939, 1691 (C=O), 1631 (C=N), 1455, 1367, 1328, 1272, 1246 (C-N), 1157 and 1029 (COC); δ_{H} (250 MHz CDCl₃) 2.11 (4 H, bs, CH₂CH₂CH₂CH₂), 2.70 (1 H, dd, *J* 11.9 & 16.8, NCH(H)), 2.95 (2 H, t, *J* 6.6, CH₂CH₂), 3.06 (1 H, dd, *J* 5.1 & 16.4, NCH(H)), 3.33 (3 H,

s, OCH₃), 3.35 – 3.47 (1 H, m, CH(H)C=O), 3.62 – 3.79 (4 H, m, CH₂CH₂ & NCH₂), 3.86 – 3.95 (1 H, m, CH(H)C=O), 4.00 (1 H, dd, *J* 4.8 & 11.9, NCH), 6.15 (1 H, d, *J* 10.3, CH=CHCO) and 6.87 (1 H, d, *J* 10.3, CH=CHCO); δ_C (100 MHz, CDCl₃) 25.01 (CH₂CH₂CH₂CH₂), 25.95 (2 x CH₂), 41.23 (NCH₂), 43.64 (NCH₂), 51.33 (CH₂C=O), 51.38 (OCH₃), 60.94 (CHCH₂), 73.24 (C), 131.79 (CH=CHCO), 150.59 (CH=CHCO), 166.33 (N-C=N) and 194.60 (C=O); *m/z* (FAB) 249.1603 (MH⁺ - C₁₄H₂₀N₂O₂ + H requires 249.1603); *m/z* (FAB) 249 (MH⁺, 100%), 187 (18), 141 (43), 97 (31) and 83 (47).

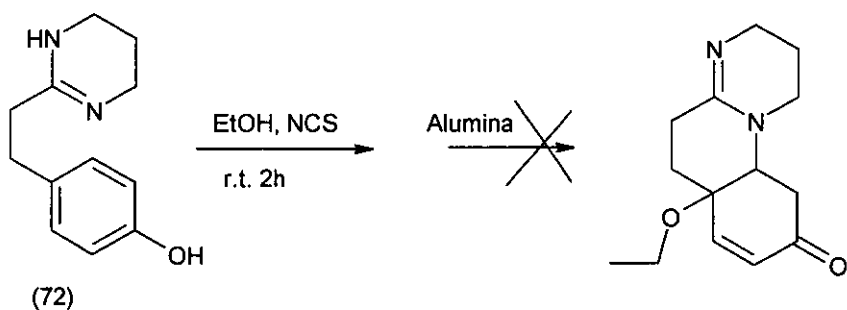
7a-Ethoxy-1,2,3,4,7,7a,11,11a-octahydro-6H-[1,3]diazepino[1,2-a]quinolin-10-one triflate salt (79)



To 2-[2-(4-hydroxyphenyl)ethyl]-4,5,6,7-tetrahydro-1H-[1,3]diazepinium triflate (70) (748 mg, 2.03 mmol) in dry ethanol (30 ml) was added *bis*(trifluoroacetoxy)iodobenzene (1.31 g, 3.05 mmol, 1.5 mol. equiv.) and basic alumina (2.0 g). The reaction mixture was swirled under a nitrogen atmosphere at ambient conditions for 2 h, the alumina was filtered off and washed with ethanol (10 ml). The filtrate was concentrated under reduced pressure and the residue purified by flash column chromatography over basic alumina with methanol and dichloromethane (6 % MeOH). The pale yellow solid obtained was identified as 7a-ethoxy-1,2,3,4,7,7a,11,11a-octahydro-6H-[1,3]diazepino[1,2-a]quinolin-10-one triflate salt (79) (233 mg, 29 %). M.p: 165-166 °C; ν_{max} (Acetonitrile)/cm⁻¹ 3282,

3133, 2972, 1684, 1635, 1475, 1249, 1259, and 1029; δ_{H} (400 MHz Acetone) 1.2.1 (3 H, t, J 7.0, OCH_2CH_3), 1.29 (1 H, m, $\text{NCH}_2\text{CH}(\text{H})$), 2.15 – 2.26 (4 H, m, NCH_2 & CH_2), 2.86 – 2.94 (3 H, m, CH_2 & $\text{NCH}(\text{H})$), 3.08 (1 H, dd, J 5.2 & 16.9, $\text{CHCH}(\text{H})\text{C}=\text{O}$), 3.58 – 3.78 (5 H, m, CH_2 , NCH_2 & $\text{CHCH}(\text{H})\text{C}=\text{O}$), 3.90 – 4.18 (2 H, m, OCH_2), 4.47 (1 H, dd, J 5.2 & 12.4, $\text{NCHCH}_2\text{C}=\text{O}$), 6.10 (1 H, d, J 10.4, $\text{CH}=\text{CHCO}$), 7.09 (1 H, d, J 10.4, $\text{CH}=\text{CHCO}$) and 8.68 (1 H, brs, NH^+); δ_{C} (100 MHz, Acetone) 16.23 (OCH_2CH_3), 25.49 (CH_2), 25.71 (CH_2), 25.85 (CH_2), 26.58 (CH_2), 41.57 (NCH_2), 43.96 (NCH_2), 51.63 ($\text{CH}_2\text{C}=\text{O}$), 59.64 (OCH_2CH_3), 61.90 (CH_2CH), 73.89 ($\text{C}-\text{OCH}_2\text{CH}_3$), 131.58, ($\text{CH}=\text{CHCO}$), 152.00 ($\text{CH}=\text{CHCO}$), 161.20 ($\text{N}=\text{C}-\text{N}$) and 194.72 ($\text{C}=\text{O}$); m/z (FAB) 263.1756 ($\text{MH}^+ - \text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_2 + \text{H}$ requires 263.1756); m/z (FAB) 263 (MH^+ , 38%), 154 (22), 136 (32), 107 (34), 89 (72), 77 (100), 63 (55) and 51 (63).

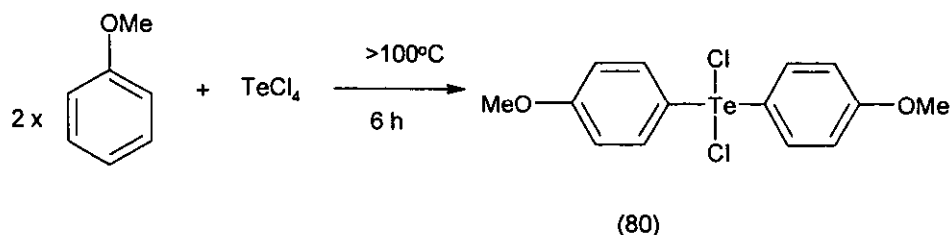
Treatment of 2-[2-(4-hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt with NCS.



To the 2-[2-(4-hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (72) (250 mg, 1.22 mmol) dissolved in ethanol (5 ml) was added an excess of *N*-chlorosuccinimide (543 mg, 1.26 mmol, 1.1 mol. equiv.) in ethanol (5 ml) under a nitrogen atmosphere. The solution gradually became yellow while swirling at room temperature for 2 h. The solvent was removed under reduced pressure for flash column chromatography of the residue with basic alumina but yielded none of the desired quinolinone product and the amidine recovered.

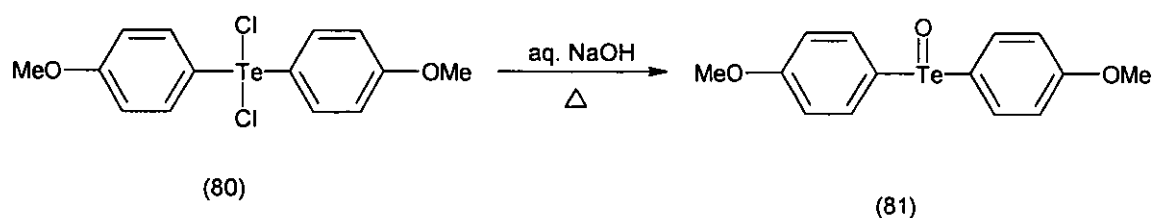
Di-(4-methoxyphenyl)tellurium dichloride (**80**)⁸⁵

In a dry 500 ml 3-neck round bottom flask equipped with a thermometer and a reflux



condenser fitted with a calcium chloride drying tube, were placed tellurium tetrachloride (18.0 g, 66 mmol) and dry anisole (43.2 g, 0.40 mol). The mixture was heated at reflux for 6 h, as the yellow solid dissolved over 100 °C, and then cooled to room temperature before the solvent was removed by evaporation under high vacuum. The yellow residue of crude solid was dissolved in boiling acetonitrile (200 ml) and the solution was filtered hot and then cooled down to -25 °C immediately to give (**80**) as a very pale pink solid (18.82 g, 72 %). M.p: 169-171 °C (lit.,⁸⁵ 182-183 °C); ν_{\max} (Nujol)/cm⁻¹ 2921, 2850, 2725, 2669, 1582, 1454, 1376, 1296, 1258, 1173, 1019, 814, 803, 787 and 722; δ_{H} (400 MHz DMSO) 3.82 (6 H, s, 2 x OCH₃), 7.11 (4 H, d, *J* 9.0, 4 x Ph-H) and 7.88 (4 H, d, *J* 9.0, 4 x Ph-H); δ_{C} (100 MHz, DMSO) 55.81 (2 x OCH₃), 115.11 (4 x CH, 4 x ArCH), 128.64 (2 x C, 2 x ArC), 136.46 (4 x CH, 4 x ArCH) and 161.39 (2 x C, 2 x ArC).

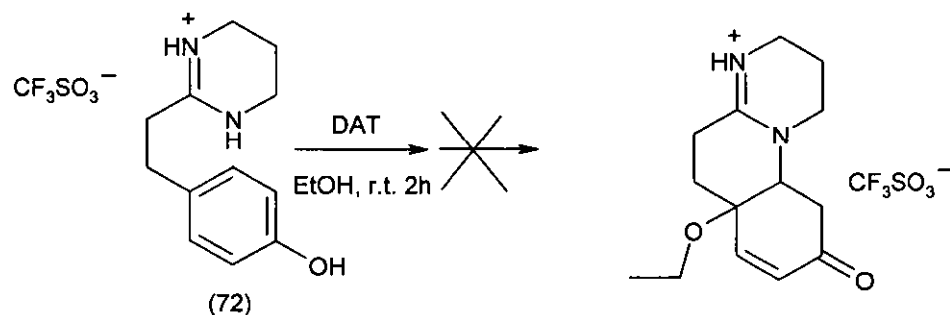
Di-(4-methoxyphenyl)tellurium oxide (DAT) (**81**)⁸⁶



In aqueous sodium hydroxide (100 ml, 5 %) was added *di*-(4-methoxyphenyl)tellurium dichloride (**80**) (5.00 g, 12.60 mmol). The undissolved mixture was heated to 95 °C for

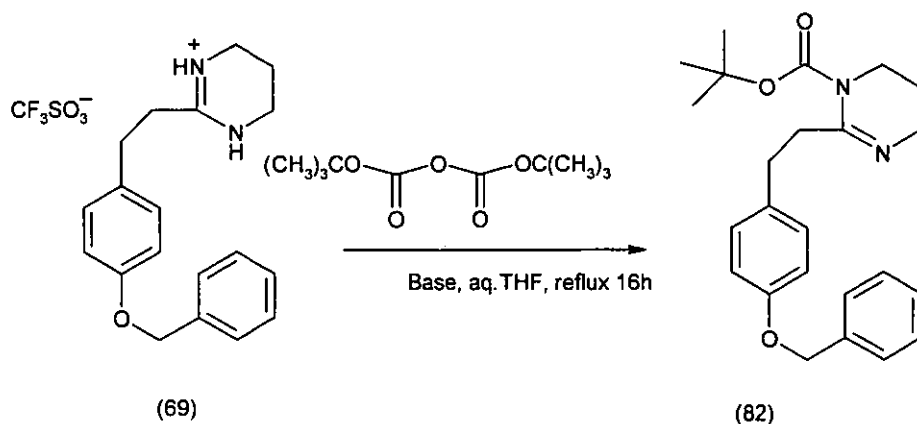
1.5 h to form a white solid precipitate. The precipitate was filtered off and washed with deionised water (3 x 10 ml) then dried over P₂O₅ to give DAT (**81**) as a pale yellow solid (2.58 g, 57 %). M.p: 182-183 °C (lit., ⁸⁶ 187-189 °C); ν_{\max} (Nujol)/cm⁻¹ 2922, 2852, 1581, 1487, 1469, 1376, 1290, 1245, 1177, 1025, 822, 810, 787 and 722; δ_{H} (250 MHz DMSO) 3.74 (6 H, s, 2 x OCH₃), 7.01 (4 H, d, *J* 8.2, 4 x Ph-H) and 7.70 (4 H, d, *J* 8.2, 4 x Ph-H); δ_{C} (100 MHz, DMSO) 56.16 (2 x OCH₃), 115.62 (4 x CH, 4 x ArCH), 130.89 (2 x C, 2 x ArC), 132.87 (4 x CH, 4 x ArCH) and 162.00 (2 x C, 2 x ArC).

Oxidation of 2-[2-(4-hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt with hypervalent tellurium oxidising reagent



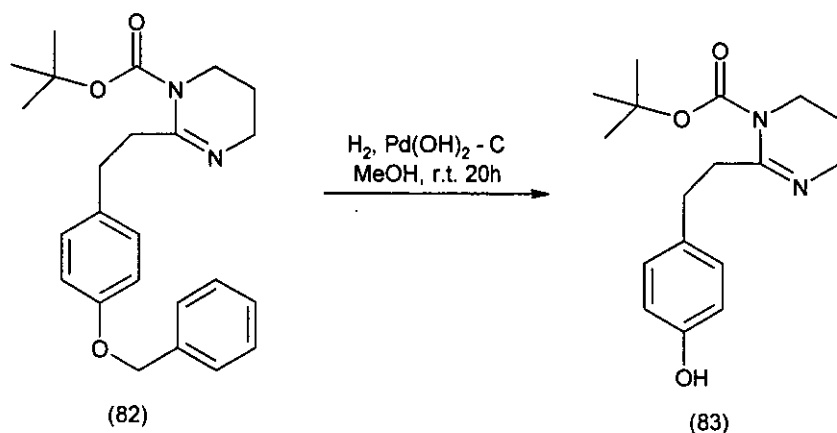
To 2-[2-(4-hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (**72**) (506 mg, 2.47 mmol) was added *di*-(4-methoxyphenyl)tellurium oxide (DAT) (**81**) (1.38 g, 3.705 mmol, 1.5 mol. equiv.) in dry ethanol (20 ml). The yellow reaction mixture was swirled at ambient temperature under an atmosphere of nitrogen for 2 h. The ethanol was removed to reduced pressure and flash column chromatography of the residue with basic alumina using methanol: dichloromethane (3 : 97 v/v) gave some white solid that could not be characterised.

2-[2-(4-Benzyloxyphenyl)ethyl]-1(3)-*tert*-butyloxycarbonyl-3,4,5,6-tetrahydro-
pyrimidine(82)⁸⁷



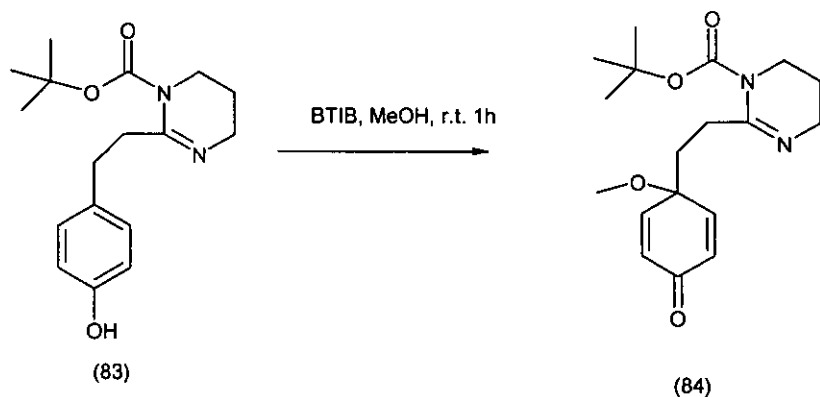
2-[2-(4-Benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (**69**) (1.00 g, 3.40 mmol) and sodium bicarbonate (0.58 g, 6.90 mmol) in aqueous THF (1 : 1 %v/v, 60 ml) was treated with di-*tert*-butyl dicarbonate (1.42 g, 6.78 mmol) in THF (10 ml). The reaction mixture was heated under reflux for 16 h and then concentrated by evaporation under reduced pressure. The residue was partitioned between chloroform (100 ml) and saturated aqueous sodium bicarbonate (60 ml) and the organic layer was washed with deionised water and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography using methanol : dichloromethane (5 : 95 v/v) to yield the desired product (**82**) as a white solid (817 mg, 61 %). M.p: 108-109 °C (lit.,⁸⁷ 111-112 °C); ν_{\max} (CHCl₃)/cm⁻¹ 3360, 3314, 2975, 2939, 1688 (NCOO), 1639 (C=N), 1534, 1512, 1453, 1365, 1279, 1249 (C-N), 1174, 1015 (COC) and 740; δ_{H} (250 MHz, CDCl₃) 1.42 (9 H, s, 3 x CH₃), 1.50 (2 H, bs, NCH₂CH₂CH₂N), 2.44 (2 H, t, *J* 7.5, CH₂CH₂), 2.89 (2 H, t, *J* 7.5, CH₂CH₂), 2.99 – 3.02 (2 H, m, NCH₂), 3.20 – 3.23 (2 H, m, NCH₂), 5.00 (2 H, s, OCH₂Ph), 6.87 (2 H, d, *J* 8.6, 2 x Ph-H) 7.10 (2 H, d, *J* 8.6, 2 x Ph-H) and 7.33 – 7.39 (5 H, m, 5 x Ph-H); δ_{C} (100 MHz, CDCl₃) 28.79 (3 x CH₃), 30.57 (CH₂), 31.27 (CH₂), 37.30 (CH₂), 37.70 (CH₂), 39.11 (CH₂), 70.42 (OCH₂Ph), 79.69 (OC(CH₃)₃), 115.20 (CH, ArCH), 127.83 (CH, ArCH), 128.29 (CH, ArCH), 128.94 (CH, ArCH), 129.68 (CH, ArCH), 133.62 (C, ArC), 137.52 (C, ArC), 157.02 (C-O, ArCO), 157.56 (C=O) and 172.89 (N-C=N).

2-[2-(4-Hydroxyphenyl)ethyl]-1(3)-*tert*-butyloxycarbonyl-3,4,5,6-tetrahydro-pyrimidine(83)⁸⁷



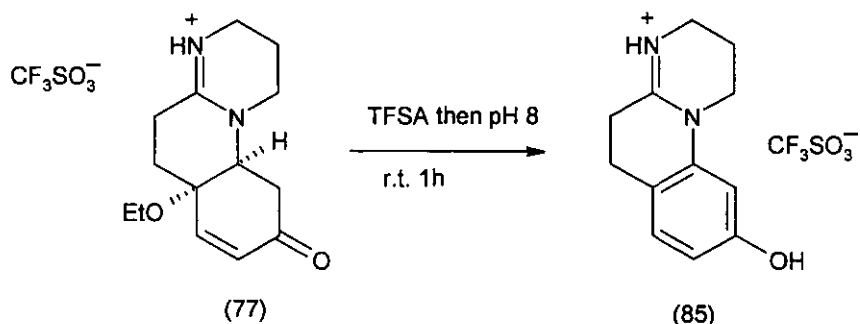
To 2-[2-(4-benzyloxyphenyl)ethyl]-1(3)-*tert*-butyloxycarbonyl-3,4,5,6-tetrahydro-pyrimidine(82) (344 mg, 0.87 mmol) in a dry 50 ml flask was added palladium hydroxide-carbon (10%) (35 mg, 10 %w/w) followed by methanol (10 ml). Under an atmosphere of hydrogen, the reaction was degassed through evacuation and refilled three times with a 3-way tap before swirling under 1 atmosphere of hydrogen for 20 h. The resulting suspension was filtered through celite to remove the catalyst, the solids were washed with methanol (20 ml) and the filtrate was evaporated under reduced pressure to give the title compound (83) as a yellow oil (263 mg, 99 %). ν_{\max} (CHCl₃)/cm⁻¹ 3325, 2977, 2931, 1689 (NCOO), 1519, 1450, 1365, 1249 (C-N), 1164, 833 and 756; δ_{H} (250 MHz, CDCl₃) 1.42 (9 H, s, 3 x CH₃), 1.46 – 1.52 (2 H, m, CH₂CH₂CH₂), 2.42 (2 H, t, *J* 7.3, CH₂), 2.84 (2 H, t, *J* 7.3, CH₂), 2.99 (2 H, d, *J* 5.8, NCH₂), 3.16 – 3.21 (2 H, m, NCH₂), 6.75 (2 H, d, *J* 8.3, 2 x Ph-H) and 6.98 (2 H, d, *J* 8.3, 2 x Ph-H); δ_{C} (100 MHz, CDCl₃) 28.79 (3 x CH₃), 30.23 (CH₂CH₂CH₂), 31.31 (CH₂), 36.36 (CH₂), 37.47 (NCH₂), 39.05 (NCH₂), 79.96 (C(CH₃)₃), 115.95 (2 x CH, 2 x ArCH) 129.69 (2 x CH, 2 x ArCH), 131.99 (C, ArC), 153.40 (COH, ArCOH), 157.27 (C=O) and 173.81 (N-C=N).

4-Methoxy-4-[2-(1-*tert*-butyloxycarbonyl-3,4,5,6-tetrahydropyrimid-2-yl)ethyl]-cyclohexa-2,5-dienone (84)⁸⁷



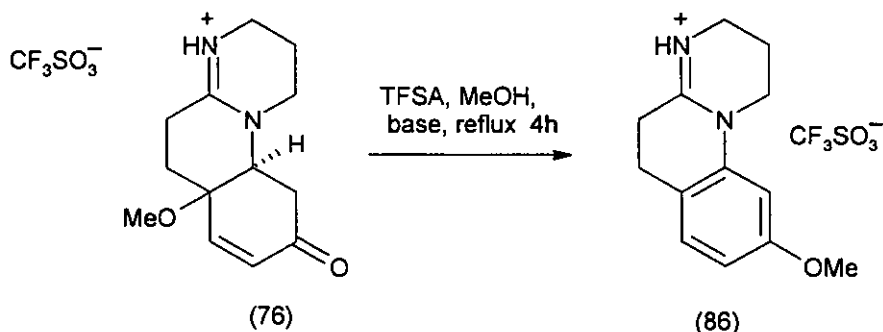
To 2-[2-(4-hydroxyphenyl)ethyl]-1(3-*tert*-butyloxycarbonyl-3,4,5,6-tetrahydropyrimidin-2-yl)ethanone triflate salt (**83**) (290 mg, 0.953 mmol) was added *bis*(trifluoroacetoxy)iodobenzene (BTIB) (603 mg, 1.14 mmol) and dry methanol (8 ml). Under an atmosphere of nitrogen, the mixture was swirled for 1 h at room temperature and the methanol was removed under reduced pressure to give a brown liquor. The iodobenzene by-product formed from the reaction was removed from the brown liquor by partitioning between petroleum ether (3 x 30 ml) and acetonitrile (30 ml). The acetonitrile layer was collected and the solvent removed under pressure. The crude residue was purified by flash column chromatography using ethyl acetate to yield the title compound as a colourless oil (**84**) (60 mg, 20 %) that turned to a brown oil after 24 hour. ν_{\max} (CHCl₃)/cm⁻¹ 3325, 2974, 2933, 1685 (NCOO), 1669 (C=N), 1531, 1451, 1390, 1366, 1275, 1252 (C-N), 1170, 1094, 1074 (COC) and 862; δ_{H} (250 MHz, CDCl₃) 1.42 (9 H, s, 3 x CH₃), 1.54 – 1.59 (2 H, m, CH₂CH₂CH₂), 2.09 – 2.17 (4 H, m, 2 x CH₂), 3.13 (2 H, q, *J* 6.0, NCH₂), 3.20 (3 H, s, OCH₃), 3.22 – 3.27 (2 H, m, NCH₂), 6.35 (2 H, d, *J* 10.4, 2 x CH=CHCO) and 6.74 (2 H, d, *J* 10.4, 2 x CH=CHCO); δ_{C} (100 MHz, CDCl₃) 28.76 (3 x CH₃), 30.51 (CH₂CH₂CH₂), 30.97 (CH₂), 34.88 (CH₂), 36.28 (NCH₂), 37.40 (NCH₂), 53.52 (OCH₃), 75.54 (C(CH₃)₃), 79.87 (C-O), 132.12 (2 x CH=CHCO), 150.93 (2 x CH=CHCO), 157.16 (C=O), 185.62 (N-C=N) and 198.88 (C=O).

2,3,5,6-Tetrahydro-1*H*-pyrimido[1,2-*a*]quinolin-9-ol triflate salt (85)



To 6a-ethoxy-2,3,6,6a,10,10a-hexahydro-1*H*,5*H*-pyrimido[1,2-*a*]quinolin-9-one triflate salt (**77**) (78 mg, 0.31 mmol) was added trifluoromethanesulfonic acid (0.5 ml). The reaction was swirled at room temperature for 1 h before the remaining acid and by-product were removed by kugelrohr distillation at 110 °C (3 mbar). The brown residue obtained was dissolved in dichloromethane (30 ml) and then neutralised to pH 8 with saturated sodium carbonate solution (10 ml). The organic layer was collected, dried with anhydrous magnesium sulfate and evaporated to dryness under reduced pressure to give a yellow oil, which was purified by flash column chromatography using methanol : dichloromethane (7 : 93 to 10 : 90 v/v) to yield a pale yellow oil (**85**) (24 mg, 38 %). m/z (EI+) 202.1109 (M^+ - $C_{12}H_{14}N_2O$ requires 202.1106); ν_{\max} ($CHCl_3$)/ cm^{-1} 3267 (OH), 3116, 2958, 1647 (C=N), 1604, 1496, 1442, 1326, 1276, 1249 (C-N), 1222, 1203, 1157 and 1029; δ_H (250 MHz, acetone) 2.35 (2 H, t, J 5.5, $NCH_2CH_2CH_2N$), 3.00 (4 H, s, CH_2CH_2), 3.64 (2 H, t, J 5.5, NCH_2), 4.04 (3 H, t, J 5.5, NCH_2), 5.42 (1 H, brs, OH), 6.86 (1 H, dd, J 2.0 & 8.2, Ph-H), 7.12 (1 H, d, J 2.0, Ph-H) and 7.34 (1 H, d, J 8.2, Ph-H); δ_C (100 MHz, acetone) 18.21 ($CH_2CH_2CH_2$), 21.23 (CH_2), 21.32 (CH_2), 38.12 (NCH_2), 43.65 (NCH_2), 107.02 (CH, ArCH), 114.76 (CH, ArCH), 121.82 (C-N), 128.88 (CH, ArCH), 138.59 (C, ArC), 156.20 (CO, ArCO) and 16.87 (N-C=N); m/z (EI+) 202 (M^+ , 100%), 174, 146 (40) and 117.

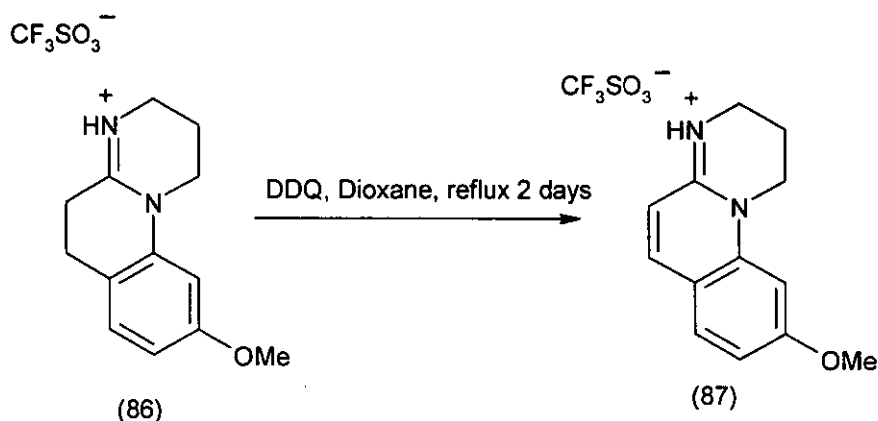
9-Methoxy-2,3,5,6-tetrahydro-1*H*-pyrimido-[1,2-*a*]quinolinium triflate salt (86)



To 6a-methoxy-2,3,6,6a,10,10a-hexahydro-1*H*,5*H*-pyrimido[1,2-*a*]quinolin-9-one triflate salt (76) (94 mg, 0.40 mmol) was added trifluoromethanesulfonic acid (0.5 ml) and dry methanol (3 ml) and this was heated at reflux for 4 h. The solvent was removed from the brown reaction mixture and the residue was neutralized with saturated sodium carbonate solution (10 ml) to pH 8 and extracted with ethyl acetate (4 x 10 ml). The organic layers were combined and dried with anhydrous magnesium sulfate. After solvent removal under reduced pressure, the residue was purified by flash column chromatography using methanol : dichloromethane (10 : 90 v/v) to give a brown solid, identified as the title compound (86) (49 mg, 57 %). Recrystallisation from dichloromethane and a few drops of ethyl acetate gave colourless crystals which proved to be the trifluoromethanesulfonate salt of the quinoline from X-ray crystallography. M.p: 120-121 °C; Found: C, 45.83; H, 4.47; N, 7.57. $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_4\text{F}_3\text{S}$ requires C, 45.90; H, 4.67; N, 7.64; ν_{max} (CHCl_3)/ cm^{-1} 3479, 3301, 2958, 1660 (C=N), 1619, 1510, 1326, 1281, 1253 (C-N), 1224, 1162 and 1030 (COC); δ_{H} (250 MHz CDCl_3) 2.29 (2 H, q, J 5.8, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.80 – 2.86 (2 H, m, CH_2), 2.93 – 2.98 (2 H, m, CH_2), 3.62 (2 H, t, J 5.8, NCH_2), 3.82 (3 H, s, OCH_3), 3.92 (2 H, t, J 5.8, NCH_2), 6.69 – 6.73 (2 H, m, 2 x Ph-H) and 7.13 (1 H, d, J 8.8, Ph-H); δ_{C} (100 MHz, CDCl_3) 18.99 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 22.11 (CH_2CH_2), 28.42 (CH_2CH_2), 38.62 (NCH_2), 44.19 (NCH_2), 55.82 (OCH_3), 103.45 (CH, ArCH), 110.43 (CH, ArCH), 118.38 (C, ArC), 129.26 (CH, ArCH), 137.89 (C, ArC), 159.78 (CO, ArCO) and 161.53 (N-

C=N); m/z (EI+) 216.1259 (M^+ - $C_{13}H_{16}N_2O$ requires 216.1262); LC-MS m/z (ES+) 217 (MH^+ , 100%), 202 (23), 115 (33), 106 (30) and 74 (22).

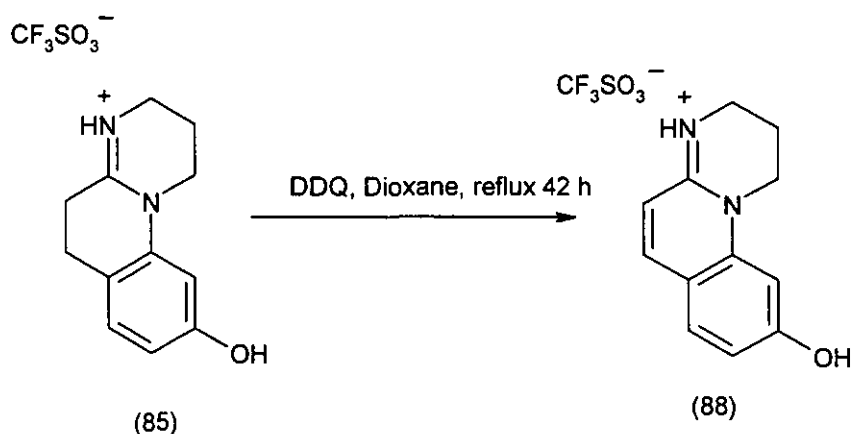
9-(Methoxy)-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinolinium triflate salt (87)



To 9-methoxy-2,3,5,6-tetrahydro-1*H*-pyrimido-[1,2-*a*]quinolinium triflate salt (**86**) (64 mg, 0.30 mmol) was added 1,4-dioxane (5 ml) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (104 mg, 0.45 mmol, 1.5 mol. equiv.) and the mixture heated at reflux under a nitrogen atmosphere for 2 days. A pale brown precipitate was filtered off and the filtrate was concentrated under reduced pressure to give a brown residue that was purified by flash column chromatography over basic alumina with methanol and dichloromethane (3 – 6 % MeOH) to yield a yellow oil (24 mg, 38 %) which was crystallized with ether and dichloromethane to give yellow crystals of the quinolinium triflate salt (**87**). M.p: 159 °C; ν_{max} (Acetonitrile)/ cm^{-1} 3253, 2922, 1642 (C=N), 1623, 1586, 1523, 1274, 1237 (C-N), 1156, 1028 (COC) and 839; δ_H (250 MHz CD_3OD) 2.32 (2 H, q, J 5.9, $CH_2CH_2CH_2$), 3.58 (2 H, t, J 5.9, NCH_2), 3.99 (3 H, s, OCH_3), 4.40 (2 H, t, J 6.0, NCH_2), 6.77 (1 H, d, J 9.2, Qu-H), 7.15 (1 H, dd, J 2.3 & 8.9, Qu-H), 7.25 (1 H, d, J 2.3, Qu-H), 7.77 (1 H, d, J 8.9, Qu-H) and 8.01 (1 H, d, J 9.2, Qu-H); δ_C (100 MHz, CD_3OD) 19.82 ($CH_2CH_2CH_2$), 39.05 (NCH_2), 45.84 (NCH_2), 56.62 (OCH_3), 99.94 (CH, QuCH), 112.48 (CH, QuCH), 115.07 (CH, QuCH), 117.79 (C, QuC), 132.51 (CH, QuCH), 140.93 (C, QuC), 141.73 (CH, QuCH), 153.96 (CO, QuCO)

and 165.09 (N=C-N); m/z (EI+) 214.1185 (M^+ - $C_{13}H_{15}N_2O$ requires 214.1184); m/z (EI+) 214 (M^+ , 100%), 199 (30), 159 (73), 69 (28) and 57 (33).

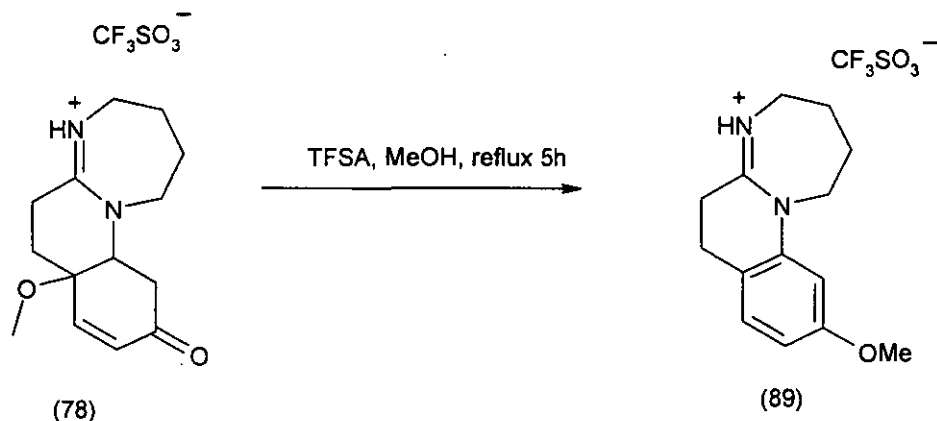
2,3-Dihydro-1*H*-pyrimido[1,2-*a*]quinolin-9-ol triflate salt (**88**)



To 2,3,5,6-tetrahydro-1*H*-pyrimido[1,2-*a*]quinolin-9-ol triflate salt (**85**) (72 mg, 3.56×10^{-4} mol) in dry acetonitrile (20 ml) was added 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (97 mg, 4.27×10^{-4} mol) and the mixture was heated at reflux under a nitrogen atmosphere for 42 h. After removal of the solvent under reduced pressure, the orange residue was purified twice by flash column chromatography with silica using MeOH : DCM (15 : 85 v/v) to yield a small quantity of product (**88**) (8 mg, 10 %). δ_H (250 MHz Acetone) 2.45 (2 H, brs, $NCH_2CH_2CH_2N$), 3.72 (2 H, brs, NCH_2), 4.56 (2 H, t, J 5.7, NCH_2), 6.97 (1 H, d, J 9.2, Qu-H), 7.13 (1 H, d, J 8.6, Qu-H), 7.35 (1 H, s, Qu-H), 7.81 (1 H, d, J 8.6, Qu-H) and 8.14 (2 H, d, J 9.2, Qu-H).

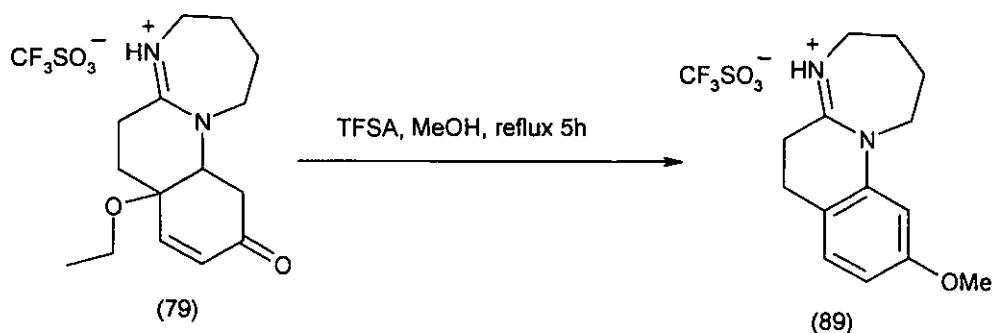
10-Methoxy-1,2,3,4,6,7,-hexahydro-[1,3]diazepino[1,2-a]quinolinium triflate salt

(89)



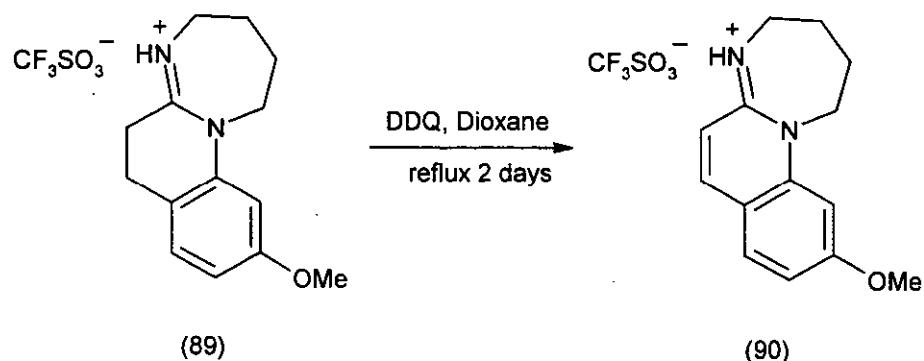
To 4a-methoxy-1,5,6,8,9,10,11,12a-octahydro-4a*H*-azepino[1,2-*a*]quinolin-2-one triflate salt (78) (60 mg, 0.15 mmol) was added methanol (5 ml) and trifluoromethanesulfonic acid (1 ml) and the solution was brought to reflux for 5 h. The solvent was removed under reduced pressure and the residue was diluted with ethyl acetate (10 ml) and neutralized to pH 8 - 9 with saturated sodium carbonate solution (15 ml). The organic layer was collected and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure for flash column chromatography of the residue with methanol and dichloromethane (2 - 6 % MeOH) to yield the desired product (89) as an oil (38 mg, 66 %). ν_{\max} (CHCl₃)/cm⁻¹ 3269, 3107, 2954, 1613 (C=N), 1512, 1453, 1244 (C-N), 1160 and 1029 (COC); δ_{H} (250 MHz CDCl₃) 2.21 - 2.30 (4 H, m, CH₂CH₂CH₂CH₂), 2.77 (2 H, t, *J* 7.0, CH₂), 3.00 (2 H, t, *J* 7.0, CH₂), 3.83 (3 H, s, OCH₃), 3.84 - 3.89 (2 H, m, NCH₂), 4.28 (2 H, t, *J* 5.8, NCH₂), 6.70 (1 H, d, *J* 2.4, Ph-H), 6.74 (1 H, dd, *J* 2.4 & 8.2, Ph-H) and 7.13 (1 H, d, *J* 8.2, Ph-H); δ_{C} (100 MHz, Acetone) 23.05 (CH₂CH₂CH₂CH₂), 25.09 (CH₂CH₂CH₂CH₂), 25.47 (CH₂CH₂), 31.92 (CH₂CH₂), 44.94 (NCH₂), 51.96 (NCH₂), 56.04 (OCH₃), 105.13 (CH, ArCH), 111.77 (CH, ArCH), 121.03 (C, ArC), 129.44 (CH, ArCH), 141.66.48 (CH, ArCH), 160.64 (CO, ArCO) and 168.71 (N-C=N); *m/z* (EI⁺) 230.1419 (M⁺ - C₁₄H₁₈N₂O requires 230.1419); *m/z* (EI⁺) 230 (M⁺, 100%), 201 (65), 176 (36), 91 (29), 69 (30) and 57 (48).

**10-Methoxy-1,2,3,4,6,7,-hexahydro-[1,3]diazepino[1,2-a]quinolinium triflate salt
(89)**



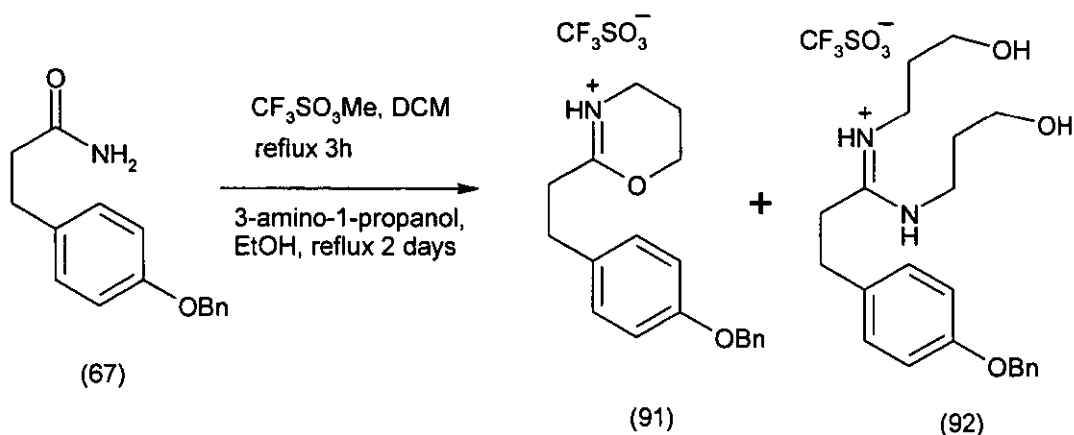
To the dissolved 7a-ethoxy-1,2,3,4,7,7a,11,11a-octahydro-6H-[1,3]diazepino[1,2-a]quinolin-10-one triflate salt (79) (153 mg, 0.37 mmol) in dry methanol (20 ml) was added trifluoromethanesulfonic acid (1 ml). The mixture was heated at reflux under a nitrogen atmosphere for 5 h and the solvent was removed under pressure. The brown residue was diluted with ethyl acetate (10 ml) and basified with saturated sodium carbonate solution (15 ml). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 15 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was removed for flash column chromatography of the residue with methanol and dichloromethane (3 – 6 % MeOH). The resulting product (70 mg, 50 %) was identified as 10-methoxy-1,2,3,4,6,7,-hexahydro-[1,3]diazepino[1,2-a]quinolinium triflate salt (89), having identical spectral data to those reported above for the material prepared from the methoxydiazepinoquinolinone triflate salt (78).

10-Methoxy-1,2,3,4-tetrahydro-[1,3]diazepino[1,2-a]quinolinium triflate salt (90)



To 10-methoxy-1,2,3,4,6,7,-hexahydro-[1,3]diazepino[1,2-*a*]quinolinium triflate salt (**89**) (68 mg, 0.18 mmol) in 1,4-dioxane (5 ml) was added 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (154 mg, 0.358 mmol, 2 mol. equiv.). The mixture was heated at reflux under an atmosphere of nitrogen for 2 days after which time the solvent was removed under reduced pressure and the residue purified by column chromatography over basic alumina with methanol (3-6 %) in dichloromethane to yield a yellow orange oil (24 mg, 35 %) of the quinolinium triflate salt (**90**). ν_{\max} (CHCl₃)/cm⁻¹ 3284, 2921, 1633 (C=N), 1574, 1455, 1361, 1246 (C-N), 1156, 1029 (COC) and 846; δ_{H} (250 MHz CDCl₃) 2.13 – 2.17 (2 H, m, CH₂CH₂CH₂CH₂), 2.29 – 2.33 (2 H, m, CH₂CH₂CH₂CH₂), 3.88 – 3.92 (2 H, m, NCH₂), 3.98 (3 H, s, OCH₃), 4.60 (2 H, t, *J* 6.1, NCH₂), 7.01 (1 H, d, *J* 2.2, Qu-H), 7.09 (1 H, dd, *J* 2.2 & 8.7, Qu-H), 7.34 (1 H, d, *J* 9.3, Qu-H), 7.67 (1 H, d, *J* 8.7, Qu-H) and 7.84 (1 H, d, *J* 9.3, Qu-H); δ_{C} (100 MHz CDCl₃) 23.17 (CH₂CH₂CH₂CH₂), 23.75 (CH₂CH₂CH₂CH₂), 44.62 (NCH₂), 50.27 (NCH₂), 56.12 (OCH₃), 99.15 (CH, QuCH), 113.69 (CH, QuCH), 114.34 (CH, QuCH), 117.36 (C, QuC), 131.15 (CH, QuCH), 139.93 (C, QuC), 140.46 (CH, QuCH), 158.21 (CO, QuCO) and 163.52 (N=C-N); *m/z* (EI+) 229.1336 (MH⁺ - C₁₄H₁₆N₂O + H requires 229.1341); *m/z* (EI+) 229 (M⁺, 89%), 215 (16), 201 (65), 176 (36), 91 (29), 69 (30), 57 (48) and 41 (30).

2-[2-(4-Benzyloxyphenyl)ethyl]-5,6-dihydro-4*H*-[1,3]oxazinium triflate salt (91) & *N,N'*-bis-(3-hydroxypropyl)-3-(4-Benzyloxyphenyl)propionamidinium triflate salt (92)



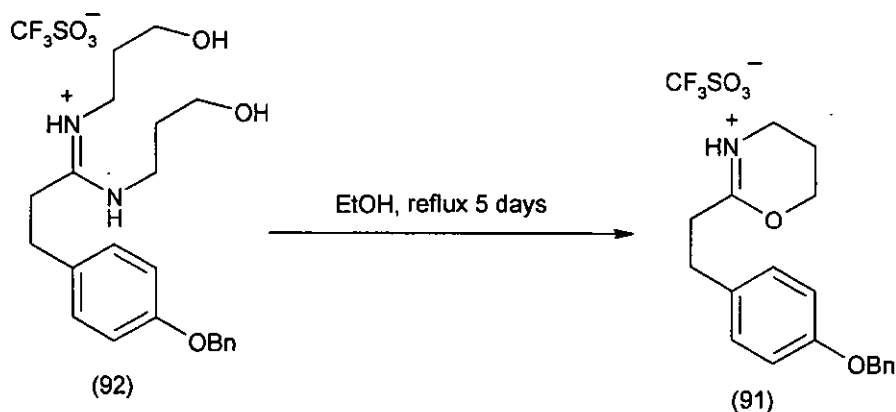
To 3-(4-benzyloxyphenyl)propanamide (67) (500 mg, 1.98 mmol) in dry dichloromethane (20 ml) was added methyl trifluoromethanesulfonate (0.33 ml, 2.94 mmol, 1.5 mol. equiv.) under an atmosphere of nitrogen. The reaction was heated under reflux for 3 h and then stirred for a further 2 days at ambient temperature. The solvent was removed under reduced pressure which gave a white solid that was re-dissolved in ethanol (20 ml) to which was added 3-aminopropan-1-ol (221 mg, 0.23 ml, 2.94 mmol) and the mixture heated at reflux under an atmosphere of nitrogen for 2 days. The organic solvent was removed under pressure and the residue was purified by solid loading flash column chromatography with MeOH : DCM (5-10 % MeOH) to yield, first eluting recovered amide (67) (50 mg, 10 %), then white crystals of oxazinium salt (91) (238 mg, 26 %) and lastly the oily dihydroxypropylamidinium triflate salt (92) (309 mg, 30 %).

For the 2-[2-(4-benzyloxyphenyl)ethyl]-5,6-dihydro-4*H*-[1,3]oxazinium triflate salt (91): M.p: 130-131 °C; ν_{max} (CHCl_3)/ cm^{-1} 3297, 2905, 2864, 1638 (C=N), 1555, 1512, 1453, 1250 (COC), 1013 (COC), 916, 817 and 740; δ_{H} (250 MHz CDCl_3) 1.58 (2 H, q, J 6.11, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.46 (2 H, t, J 7.5, CH_2), 2.91 (2 H, t, J 7.5, CH_2), 3.33 – 3.40 (2 H, m, NCH_2), 3.50 (2 H, t, J 5.6, OCH_2CH_2), 5.04 (2 H, s, OCH_2Ph), 5.72 (1 H, brs, NH salt), 6.90 (2 H, d, J 8.7, 2 x Ph-H), 7.12 (2 H, d, J 8.7, 2 x Ph-H) and 7.32 - 7.44 (5 H, m, 5 x

Ph-H); δ_c (100 MHz CDCl₃) 30.88 (CH₂CH₂CH₂), 32.22 (CH₂CH₂), 36.25 (CH₂CH₂), 38.67 (NCH₂), 59.24 (N=C-OCH₂), 70.08 (OCH₂Ph), 114.99 (2 x CH, 2 X ArCH), 127.42 (2 x CH, 2 x ArCH), 127.92 (CH, ArCH), 128.56 (2 x CH, 2 x ArCH), 129.35 (2 x CH, 2 x ArCH), 133.05 (C, ArC), 137.12 (C, ArC), 157.36 (CO, ArCO) and 173.37 (O-C=N); m/z (EI+) 313.1594 (MH₂O⁺ - C₁₉H₂₁NO₂ + H₂O requires 313.1600); m/z (EI+) 313 (MH⁺, 13%), 121 (10), 91 (100), 69 (15), 57 (11) and 55 (11).

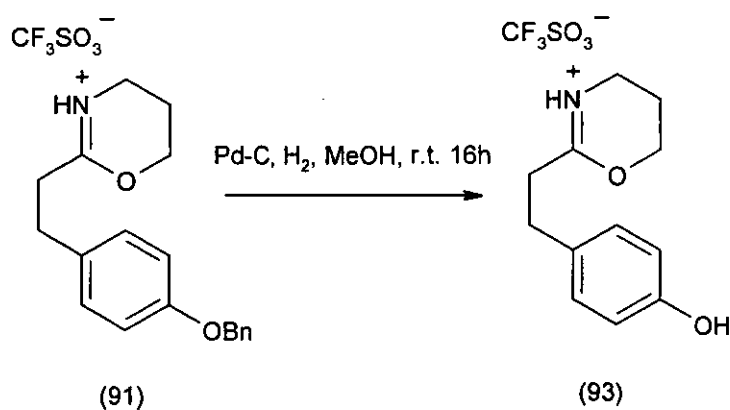
For the *N,N'*-bis-(3-hydroxypropyl)-3-(4-benzyloxyphenyl)propionamidinium triflate salt (**92**): ν_{\max} (CHCl₃)/cm⁻¹ 3416 (OH), 2929 (OH), 1655 (C=N), 1511, 1453, 1246 (C-N), 1167, 1029 (COC), 913, and 742; δ_H (400 MHz CDCl₃) 1.73 – 1.80 (4 H, m, 2 x NCH₂CH₂CH₂), 2.72 (2 H, t, *J* 7.6, CH₂), 2.86 (2 H, t, *J* 7.6, CH₂), 3.29 – 3.34 (4 H, m, 2 x NCH₂), 3.60 (2 H, t, *J* 5.6, CH₂CH₂OH), 3.70 (2 H, t, *J* 5.6, CH₂CH₂OH), 4.99 (2 H, s, OCH₂Ph), 6.89 (2 H, d, *J* 8.8, 2 x Ph-H), 7.10 (2 H, d, *J* 8.8, 2 x Ph-H), 7.29 – 7.39 (5 H, m, 5 x Ph-H), 8.20 (1 H, brs, OH) and 8.32 (1 H, brs, OH); δ_c (100 MHz CDCl₃) 29.65 (CH₂CH₂CH₂), 30.81 (CH₂CH₂CH₂), 31.59 (CH₂CH₂), 32.04 (CH₂CH₂), 39.53 (NCH₂), 42.74 (NCH₂), 59.29 (CH₂OH), 60.36 (CH₂OH), 70.04 (OCH₂Ph), 115.32 (2 x CH, 2 X ArCH), 127.46 (2 x CH, 2 x ArCH), 127.97 (CH, ArCH), 128.56 (2 x CH, 2 x ArCH), 129.50 (2 x CH, 2 x ArCH), 130.29 (C, ArC), 136.90 (C, ArC), 157.89 (CO, ArCO) and 165.70 (N=C-N); m/z (FAB) 371.2327 (MH⁺ - C₂₂H₃₀N₂O₃ + H requires 371.2334); m/z (FAB) 371 (MH⁺, 19%), 338 (7), 219 (24), 163 (9), 109 (11), 91 (34), 69 (49), 57 (100) and 43 (47).

2-[2-(4-Benzyloxyphenyl)ethyl]-5,6-dihydro-4*H*-[1,3]oxazinium triflate salt (91)



Further reflux of *N,N'*-bis-(3-hydroxypropyl)-3-(4-benzyloxyphenyl)-propionamidinium triflate salt (92) (309 mg, 0.59 mmol) in ethanol (30 ml) for 5 days under a nitrogen atmosphere followed by solvent removal for flash column chromatography of the residue with methanol and dichloromethane (3 – 6 % MeOH) furnished 2-[2-(4-benzyloxyphenyl)ethyl]-5,6-dihydro-4*H*-[1,3]-oxazinium triflate salt (91) (98 mg, 36 %) with spectroscopic identical to the earlier sample.

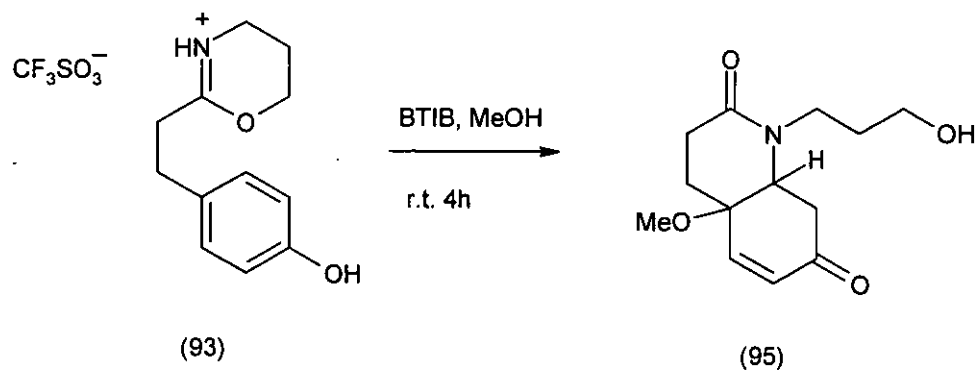
2-[2-(4-Hydroxyphenyl)ethyl]-5,6-dihydro-4*H*-[1,3]oxazinium triflate salt (93)



To 2-[2-(4-benzyloxyphenyl)ethyl]-5,6-dihydro-4*H*-[1,3]oxazinium triflate salt (91) (107 mg, 0.240 mmol) and palladium-carbon (10 %) catalyst (16 mg) was added methanol (20

ml). The reaction proceeded with stirring under 1 atmosphere of hydrogen overnight and the catalyst was filtered off over celite and the solids washed with methanol (20 ml). The filtrate was collected and concentrated under reduced pressure to give 2-[2-(4-hydroxyphenyl)ethyl]-5,6-dihydro-4*H*-[1,3]oxazinium triflate salt (**93**) as an oil (82 mg, 96 %). ν_{\max} (CHCl₃)/cm⁻¹ 3304 (OH), 2943, 1659, 1642, 1631 (C=N), 1553, 1515, 1452, 1370, 1237, 1070 and 830; δ_{H} (400 MHz CD₃OD) 1.49 – 1.57 (2 H, m, NCH₂CH₂CH₂), 2.30 (2 H, t, *J* 7.6, CH₂CH₂), 2.69 (2 H, t, *J* 7.6, CH₂CH₂), 3.11 (2 H, t, *J* 6.9, NCH₂CH₂), 3.39 (2 H, t, *J* 6.3, OCH₂CH₂CH₂N), 6.57 (2 H, d, *J* 8.4, 2 x Ph-H) and 6.89 (2 H, d, *J* 8.4, 2 x Ph-H); δ_{C} (100 MHz CD₃OD) 32.24 (NCH₂CH₂), 33.19 (CH₂CH₂), 37.28 (CH₂CH₂), 39.47 (NCH₂CH₂), 60.32 (OCH₂CH₂), 116.62 (2 x CH, 2 x ArCH), 130.30 (2 x CH, 2 x ArCH), 132.28 (C, ArC), 157.80 (CO, ArCO) and 175.69 (O-C=N); *m/z* (FAB) 205.1105 (MH⁺ - C₁₂H₁₅NO₂ + H requires 205.1103); *m/z* (FAB) 205 (MH⁺, 6%), 120 (87), 107 (100), 91 (18) and 76 (30).

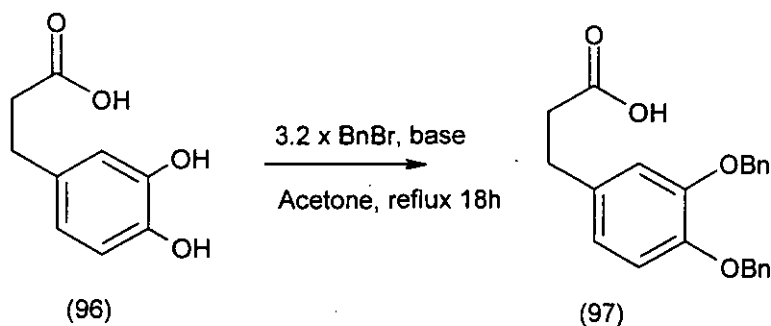
1-(3-Hydroxypropyl)-4a-methoxy-4,4a,8,8a-tetrahydro-1*H*,3*H*-quinoline-2,7-dione
(**95**)



To 2-[2-(4-hydroxyphenyl)ethyl]-5,6-dihydro-4*H*-[1,3]oxazinium salt (**93**) (82 mg, 0.231 mmol) in a 50 ml round bottom flask, was added excess *bis*(trifluoroacetoxy)iodobenzene (119 mg, 0.227 mmol, 1.2 mol. equiv.), dry methanol (20 ml) and sodium bicarbonate (30 mg). The reaction mixture was left to stir for 4 hour at ambient temperature before evaporating off the solvent under reduced pressure. The crude residue was purified by

flash column chromatography on silica with MeOH : DCM (3 – 9 % MeOH) to yield a colourless oil (**95**) (11 mg, 19 %). No other compounds were obtained from the eluent. ν_{max} (neat)/ cm^{-1} 3395 (NH), 2936, 1681 (C=O), 1614 (NH), 1484, 1454, 1416, 1371, 1324, 1253, 1225, 1082 (COC), 921, and 788; δ_{H} (250 MHz CD_3OD) 1.77 – 1.86 (2 H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 2.06 – 2.21 (2 H, m, CH_2CH_2), 2.40 – 2.69 (2 H, m, CH_2CH_2), 2.98 – 3.09 (2 H, m, NCH_2), 3.36 (3 H, s, OCH_3), 3.54 – 3.59 (3 H, m, CH_2OH & $\text{CH}(\text{H})$), 3.80 – 3.85 (1 H, m, $\text{CH}(\text{H})$), 4.20 – 4.27 (1 H, m, NCH), 6.10 (1 H, d, J 10.3, $\text{CH}=\text{CHCO}$) and 7.05 (1 H, d, J 10.3, $\text{CH}=\text{CHCO}$); δ_{C} (100 MHz, CD_3OD) 27.47 (CH_2CH_2), 28.41 ($\text{NCH}_2\text{CH}_2\text{CH}_2$), 31.58 (CH_2CH_2), 42.88 ($\text{CHCH}_2\text{C}=\text{O}$), 43.62 (NCH_2CH_2), 51.21 (OCH_3), 56.88 (CHCH_2), 60.07 (CH_2OH), 75.09 (CH_3OC), 131.60 ($\text{CH}=\text{CHCO}$), 153.95 ($\text{CH}=\text{CHCO}$), 172.13 ($\text{NC}=\text{O}$) and 197.72 ($\text{C}=\text{O}$); m/z (EI+) 253.1309 (M^+ - $\text{C}_{13}\text{H}_{19}\text{NO}_4$ requires 253.1314); m/z (EI+) 253 (M^+ , 34%), 235 (41), 221 (46), 209 (39), 152 (59), 124 (100), 91 (48) and 55 (36).

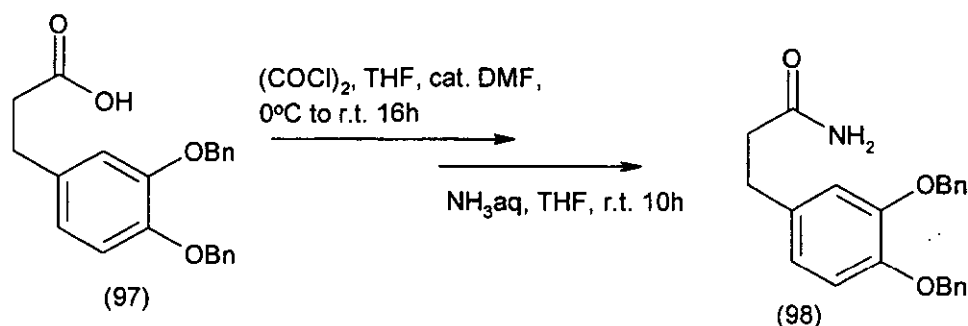
3-(3,4-Dibenzyloxyphenyl)propionic acid (**97**)



3-(3,4-Dihydroxyphenyl)propionic acid (**96**) (5.00 g, 27.45 mmol), benzyl bromide (15.01 g, 10.44 ml, 87.76 mmol, 3.2 mol. equiv.) and potassium carbonate (12.13 g, 87.76 mmol, 3.2 mol. equiv.) in dry acetone (150 ml) were heated at reflux for 18 h. The solvent was evaporated under reduced pressure to leave a residue which was extracted with ethyl acetate (150 ml) and washed with water (3 x 50 ml). The organic layer was concentrated under reduced pressure and the residue was re-dissolved in methanol (100

ml) to which was added potassium hydroxide (3.08 g, 54.90 mmol, 2 mol. equiv.) in water (30 ml) and the mixture heated at reflux for 4 h. The reaction mixture was cooled, diluted with water (150 ml) and washed with diethyl ether (3 x 70 ml). The aqueous layer was collected and acidified to pH 1 with concentrated hydrochloric acid to form a pale brown precipitate which was collected by filtration and dried over P₂O₅ in a drying pistol to yield the 3-(3,4-dibenzyloxyphenyl)propionic acid (**97**) (8.70 g, 88 %). M.p: 104-107 °C (lit.,⁸⁸ 116-117 °C - MeOH); ν_{\max} (neat)/cm⁻¹ 3031 (OH), 2912, 1702 (C=O), 1516, 1452, 1428, 1301, 1261 (C-O), 1138, 1016, 734 and 695; δ_{H} (400 MHz CD₃Cl) 2.65 (2 H, t, *J* 7.8, CH₂), 2.87 (2 H, t, *J* 7.8, CH₂), 5.16 (2 H, s, OCH₂Ph), 5.17 (2 H, s, OCH₂Ph), 6.76 (1 H, dd, *J* 2.4 & 8.2, Ph-H), 6.84 (1 H, d, *J* 2.4, Ph-H), 6.91 (1 H, d, *J* 8.2, Ph-H) 7.34 - 7.40 (6 H, m, 6 x Ph-H) and 7.45-7.47 (4 H, m, 4 x Ph-H); δ_{C} (100 MHz, CD₃Cl) 30.13 (CH₂), 35.64 (CH₂), 71.45 (OCH₂Ph), 71.53 (OCH₂Ph), 115.46 (CH, ArCH), 115.62 (CH, ArCH), 121.12 (CH, ArCH), 127.33 (2 x CH, 2 x ArCH), 127.41 (2 x CH, 2 x ArCH), 127.76 (CH, ArCH), 127.80 (CH, ArCH), 128.46 (2 x CH, 2 x ArCH), 128.47 (2 x CH, 2 x ArCH), 133.66 (C, ArC), 137.33 (C, ArC), 137.45 (C, ArC), 147.65 (CO, ArCO), 149.01 (CO, ArCO) and 178.56 (C=O).

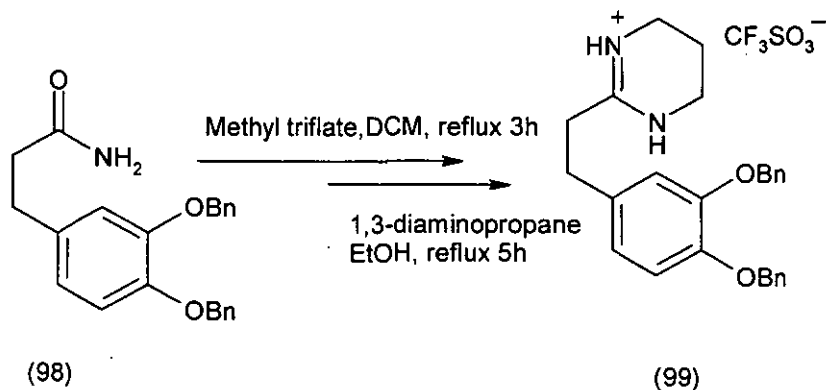
3-(3,4-Dibenzyloxyphenyl)propanamide (**98**)



To 3-(3,4-dibenzyloxyphenyl)propionic acid (**97**) (1 g, 2.76 mmol) and oxalyl chloride (0.54 g, 0.37 ml, 4.14 mmol, 1.5 mol. equiv.) in dry THF (40 ml) under an atmosphere of

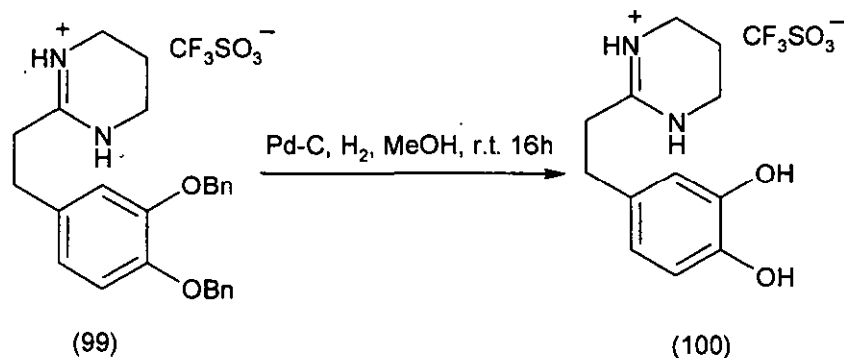
nitrogen at 0 °C was added *N,N*-dimethylformamide catalyst (0.01 ml). The reaction mixture was left at room temperature for 16 h before removing the solvent under reduced pressure to give an unstable green liquor. The liquor was dissolved in THF (30 ml), concentrated ammonia solution (20 ml) was added and the mixture was left to stir for 10 h. Water (50 ml) was added to the reaction and extracted with ethyl acetate (3 x 30 ml). The combined organic layers were dried over anhydrous sodium sulfate, and solvent removal under reduced pressure afforded a pale white solid (0.80 g, 80 %) which was identified as 3-(3,4-dibenzyloxyphenyl)propanamide (**98**). M.p: 108-110 °C (lit., ⁸⁸ 126 °C -MeOH); ν_{\max} (neat)/cm⁻¹ 3387 (NH), 3200, 2927, 1650 (C=O), 1515, 1453, 1425, 1382, 1262, 1137 and 1008; δ_{H} (400 MHz CD₃Cl) 2.42 (2 H, t, *J* 7.6, CH₂), 2.85 (2 H, d, *J* 7.6, CH₂), 5.13 (2 H, s, OCH₂Ph), 5.15 (2 H, s, OCH₂Ph), 5.20 (1 H, brs, NH), 5.39 (1 H, brs, NH), 6.71 (1 H, dd, *J* 2.1 & 8.4, Ph-H), 6.80 (1 H, d, *J* 2.1, Ph-H), 6.85 (1 H, d, *J* 8.4, Ph-H), 7.28 – 7.38 (6 H, m, 6 x Ph-H) and 7.43 – 7.45 (4 H, m, 4 x Ph-H); δ_{C} (100 MHz, CD₃Cl) 20.94 (CH₂), 37.67 (CH₂), 71.22 (OCH₂Ph), 71.45 (OCH₂Ph), 115.34 (CH, ArCH), 115.48 (CH, ArCH), 121.14(CH, ArCH), 127.33 (2 x CH, 2 x ArCH), 127.39 (2 x CH, 2 x ArCH), 127.78 (2 x CH, 2 x ArCH), 128.48 (2 x CH, 2 x ArCH), 128.49 (2 x CH, 2 x ArCH), 134.05 (C, ArC), 137.36 (C, ArC), 137.41 (C, ArC), 147.52 (CO, ArCO), 148.84 (CO, ArCO) and 169.59 (NH₂C=O); *m/z* (EI+) 361.1675 (M⁺ - C₂₃H₂₃NO₃ requires 361.1678); *m/z* (EI+) 361 (M⁺, 6%), 270 (2), 181 (7), 91 (100) and 65 (6).

2-[2-(3,4-Dibenzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (**99**)



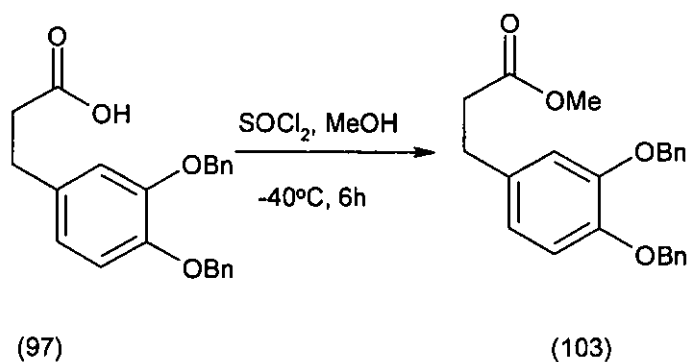
To 3-(3,4-dibenzyloxyphenyl)propanamide (**98**) (500 mg, 1.38 mmol) dissolved in DCM (50 ml) was added 1.5 equivalent of methyl triflate (0.34 g, 0.23 ml, 2.08 mmol) and the mixture left at reflux for 3 h under an atmosphere of nitrogen before further stirring at ambient temperature overnight. The solvent was removed under reduced pressure to give a residue which was re-dissolved in ethanol (40 ml) and 2 equivalent of 1,3-diaminopropane (0.23 ml, 2.76 mmol) was introduced before heating at reflux for 5 h under an atmosphere of nitrogen. The reaction solvent was evaporated under reduced pressure to give a solid for flash column chromatography with MeOH : DCM (6 : 94 v/v) which yielded as a pale yellow oil the 2-[2-(3,4-dibenzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (**99**) (500 mg, 69 %). ν_{\max} (neat)/ cm^{-1} 3293, 3246, 3065, 2928, 1660 (C=N), 1625, 1513, 1454, 1427, 1378, 1321, 1246 (C-N), 1224, 1162, 1136 and 1028 (COC); δ_{H} (400 MHz CD_3Cl) 1.55 – 1.61 (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.57 (2 H, t, J 8.0, CH_2), 2.83 (2 H, t, J 8.0, CH_2), 3.46 (4 H, brs, 2 x NCH_2), 5.03 (2 H, s, OCH_2Ph), 5.12 (2 H, s, OCH_2Ph), 5.16 (2 H, s, OCH_2Ph), 6.68 (1 H, dd, J 2.0 & 8.2, Ph-H), 6.78 (1 H, d, J 8.2, Ph-H), 6.95 (2 H, d, J 2.0, Ph-H), 7.26 – 7.33 (6 H, m, 6 x Ph-H) and 7.38 – 7.45 (4 H, m, 4 x Ph-H); δ_{C} (100 MHz, CD_3Cl) 17.69 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 32.25 (CH_2), 34.60 (CH_2), 38.65 (NCH_2), 70.92 (OCH_2Ph), 71.32 (OCH_2Ph), 115.11 (CH, ArCH), 115.16 (CH, ArCH), 121.13 (CH, ArCH), 127.48 (2 x CH, 2 x ArCH), 127.61 (2 x CH, 2 x ArCH), 127.84 (CH, ArCH), 127.87 (CH, ArCH), 128.45 (2 x CH, 2 x ArCH), 128.47 (2 x CH, 2 x ArCH), 131.84 (C, ArC), 137.18 (C, ArC), 137.27 (C, ArC), 147.52 (CO, ArCO), 148.94 (CO, ArCO) and 163.53 (N-C=N); m/z (FAB) 401.2233 (MH^+ - $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_2$ + H requires 401.2229); m/z (FAB) 401 (MH^+ , 100%), 309 (22), 219 (20), 191 (21), 91 (92), 69 (66), 55 (94) and 43 (50).

2-[2-(3,4-Dihydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (100)



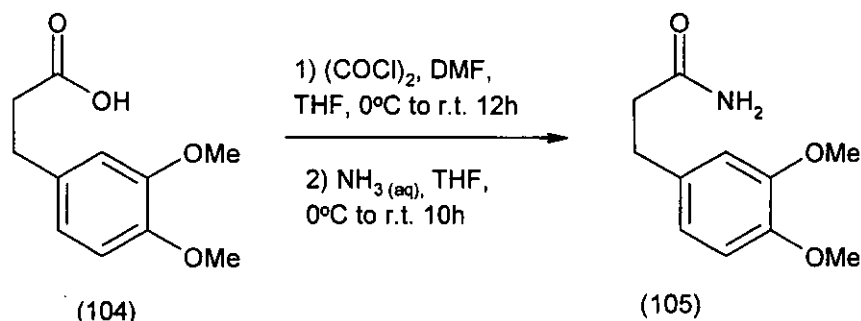
To 2-[2-(3,4-dibenzoyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (99) (231 mg, 0.42 mmol) was added palladium-carbon (10 %) (46 mg, 20 %w/w) followed by methanol (40 ml). After degassing the solution, the mixture was stirred under 1 atmosphere of hydrogen for 16 h. The dark solution was filtered through celite under a nitrogen blanket and the solids were washed with methanol (20 ml). The filtrate was evaporated under reduced pressure to furnish a dark green oil (100) (130 mg 84 %). It is important to keep the reaction and product under an inert atmosphere because of the instability of the compounds. ν_{max} (Acetonitrile)/ cm^{-1} 3615, 3538, 3318 (OH), 3162, 3000 (OH), 2942, 1660 (C=N), 1625, 1519, 1444, 1374, 1271 (C-N), 1159, 1032, 917 and 749; δ_{H} (400 MHz CD_3OD) 1.91 (2 H, brs, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.62 (2 H, brs, CH_2), 2.82 (2 H, brs, CH_2), 3.35 (4 H, brs, 2 x NCH_2), 6.55 (1 H, d, J 7.2, Ph-H), 6.67 (1 H, s, Ph-H) and 6.73 (1 H, d, J 7.2, Ph-H); δ_{C} (100 MHz, CD_3OD) 19.02 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 33.17 (CH_2), 36.04 (CH_2), 39.82 (2 x NCH_2), 116.57 (2 x CH, 2 x ArCH), 120.79 (CH, ArCH), 131.41 (C, ArC), 145.26 (CO, ArCO), 146.49 (CO, ArCO) and 164.77 (N-C=N); m/z (FAB) 221.1292 ($\text{MH}^+ - \text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2 + \text{H}$ requires 221.1290); m/z (FAB) 221 (MH^+ , 100%) 98 (25) and 55 (22).

3-(3,4-Dibenzyloxyphenyl)propionic acid methyl ester (103)



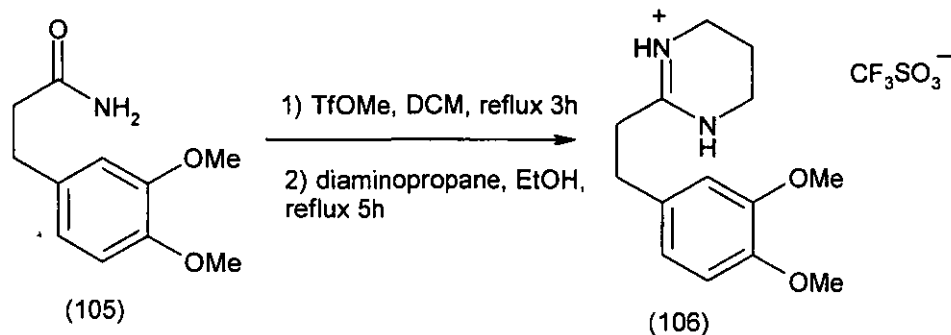
To 3-(3,4-dibenzyloxyphenyl)propionic acid (**97**) (5.00 g, 13.80 mmol) in methanol (150 ml) and cooled to -40 °C in acetonitrile-dry ice bath, was added thionyl chloride (3.28 g, 2.00 ml, 27.60 mmol, 2 mol. equiv.) dropwise with stirring and the reaction mixture was left to stir for 6h to give a brown solution. After removing the solvent under reduced pressure, the brown residue was partitioned between DCM (3 x 50 ml) and water (80 ml) and the DCM layers were collected, dried with anhydrous magnesium sulfate and evaporated under reduced pressure to give a brown oil (3.94 g, 76 %), 3-(3,4-dibenzyloxyphenyl)propionic acid methyl ester (**103**). ν_{\max} (neat)/cm⁻¹ 3029, 2947, 2864, 1731 (C=O), 1588, 1512, 1453, 1433, 1379, 1260 (C-O), 1222, 1135, 1024, 851, 807, 736 and 696; δ_{H} (400 MHz CD₃Cl) 2.58 (2 H, t, *J* 7.8, CH₂), 2.86 (2 H, t, *J* 7.8, CH₂), 3.66 (3 H, s, OCH₃), 5.14 (2 H, s, OCH₂Ph), 5.15 (2 H, s, OCH₂Ph), 6.72 (1 H, dd, *J* 2.1 & 8.2, Ph-H), 6.83 (1 H, d, *J* 2.1, Ph-H), 6.87 (1 H, d, *J* 8.2, Ph-H), 7.20 – 7.29 (6 H, m, 6 x Ph-H) and 7.34 - 7.37 (4 H, m, 4 x Ph-H); δ_{C} (100 MHz, CD₃Cl) 30.50 (CH₂), 35.85 (CH₂), 51.60 (OCH₃), 71.42 (OCH₂Ph), 71.53 (OCH₂Ph), 115.47 (CH, ArCH), 115.60 (CH, ArCH), 121.13 (CH, ArCH), 127.33 (2 x CH, 2 x ArCH), 127.39 (2 x CH, 2 x ArCH), 127.75 (CH, ArCH), 127.79 (CH, ArCH), 128.47 (4 x CH, 4 x ArCH), 134.06 (C, ArC), 137.37 (C, ArC), 137.50 (C, ArC), 147.58 (CO, ArCO), 149.01 (CO, ArCO) and 173.36 (C=O); *m/z* (EI+) 376.1680 (M⁺ - C₂₄H₂₄O₄ requires 376.1675); *m/z* (EI+) 376 (M⁺, 19%), 285 (8), 181 (19), 91 (100) and 65 (18).

3-(3,4-Dimethoxyphenyl)propanamide (105)



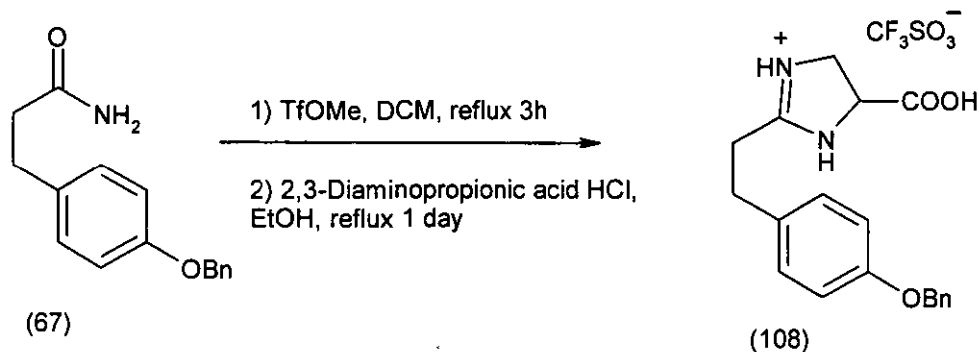
To 3-(3,4-dimethoxyphenyl)propanoic acid (**104**) (2.00 g, 9.51 mmol) was added THF (20 ml) and oxalyl chloride (1.81 g, 1.27 ml, 14.27 mmol, 1.5 mol. equiv.) at 0 °C in an ice bath while under an atmosphere of nitrogen. To the mixture in the ice bath, a catalytic amount of *N,N*-dimethylformamide (0.01 ml) was slowly added which led to gas evolution. After 30 min stirring at 0 °C, the reaction was stirred at room temperature for 12 h before removing the THF under reduced pressure to give a yellow liquor. To the yellow liquor re-dissolved in THF (30 ml) was added concentrated ammonia solution (S.G 0.888, 10 ml) under ice bath cooling and the mixture further stirred for 10 h at ambient temperature. After dilution with water (30 ml), the mixture was extracted with ethyl acetate (3 x 50 ml) and the combined organic layer was dried with anhydrous magnesium sulfate and the solvent evaporated under reduced pressure to yield a white solid (1.54 g, 77 %) as 3-(3,4-dimethoxyphenyl)propanamide (**105**). M.p: 113-114 °C (lit.,⁸⁹ 120-121 °C); Found: C, 63.00; H, 7.02; N, 6.61. C₁₁H₁₅NO₃ requires C, 63.14; H, 7.22; N, 6.69%; ν_{\max} (neat)/cm⁻¹ 3415 (NH), 3307 (NH), 3215, 2954, 1657 (C=O), 1618, 1513, 1463, 1403, 1227, 1137, 1026 and 805; δ_{H} (250 MHz CD₃Cl) 2.52 (2 H, t, *J* 7.6, CH₂), 2.92 (2 H, t, *J* 7.6, CH₂), 3.86 (3 H, s, OCH₃), 3.87 (3 H, s, OCH₃), 5.40 (2 H, brs, NH₂) and 6.72 – 6.76 (3 H, m, 3 x Ph-H); δ_{C} (100 MHz, CD₃Cl) 31.06 (CH₂), 37.85 (CH₂), 55.84 (OCH₃), 55.91 (OCH₃), 111.29 (CH, ArCH), 111.65 (CH, ArCH), 120.11 (CH, ArCH), 133.28 (C, ArC), 147.49 (CO, ArCO), 148.91 (CO, ArCO) and 174.61 (NH₂C=O); *m/z* (EI+) 209.1050 (M⁺ - C₁₁H₁₅NO₃ requires 209.1052); *m/z* (EI+) 209 (M⁺, 55%) 164 (20), 91 (14) and 77 (12).

2-[2-(3,4-Dimethoxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (106)



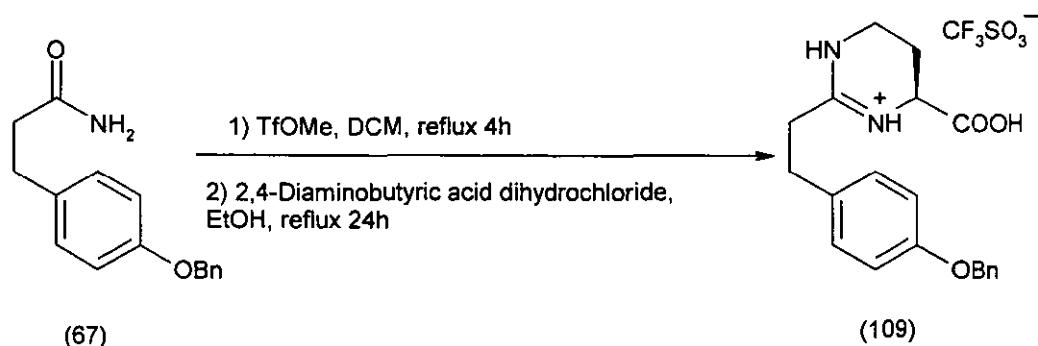
To 3-(3,4-dimethoxyphenyl)propanamide (**105**) (1.00 g, 4.78 mmol) in dry DCM (30 ml) was added methyl triflate (1.17 g, 0.79 ml, 7.17 mmol, 1.5 mol. equiv.) and the mixture heated at reflux for 3 h and then stirred at room temperature for 6 h. After solvent removal under reduced pressure, the residue was re-dissolved in ethanol (30 ml), 1,3-diaminopropane (710 mg, 0.80 ml, 9.56 mmol, 2 mol. equiv.) was added and the mixture heated at reflux for 5 h. The solvent was removed under reduced pressure, and the solid was purified by flash column chromatography with MeOH : DCM (6 % MeOH) to afford a pale yellow solid, 2-[2-(3,4-dimethoxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (**106**) (1.10 g, 56 %). M.p: 126-127 °C; Found: C, 45.04; H, 5.18; N, 6.99. $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_5\text{F}_3\text{S}$ requires C, 45.22; H, 5.31; N, 7.03; ν_{max} (neat)/ cm^{-1} 3298, 3245, 3069, 2942, 1660 (C=N), 1625, 1515, 1446, 1245 (C-N), 1157 and 1028; δ_{H} (400 MHz CD_3Cl) 1.82 – 1.88 (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.66 (2 H, dd, J 5.6 & 7.2, CH_2), 2.89 (2 H, dd, J 5.6 & 7.2, CH_2), 3.33 (4 H, t, J 4.4, 2 x NCH_2), 3.81 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 6.71 (1 H, d, J 8.2, Ph-H), 6.74 (1 H, dd, J 8.2 & 1.8, Ph-H) 6.85 (1 H, d, J 1.8, Ph-H) and 8.53 (2 H, brs, 2 x NH); δ_{C} (100 MHz, CD_3Cl) 17.90 ($\text{CH}_2\text{-CH}_2\text{CH}_2$), 32.42 (CH_2), 34.68 (CH_2), 38.84 (2 x NCH_2), 55.84 (2 x OCH_3), 111.18 (CH, ArCH), 111.82 (CH, ArCH), 120.43 (CH, ArCH), 130.84 (C, ArC), 147.77 (CO, ArCO), 149.00 (CO, ArCO) and 163.88 (N-C=N); m/z (FAB) 249.1603 ($\text{MH}^+ - \text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_2 + \text{H}$ requires 249.1603); m/z (FAB) 249 (MH^+ , 100%), 233 (5), 154 (9), 136 (8) and 98 (8).

2-[2-(4-Benzyloxyphenyl)ethyl]-4,5-dihydroimidazolium-4-carboxylic acid triflate salt (108)



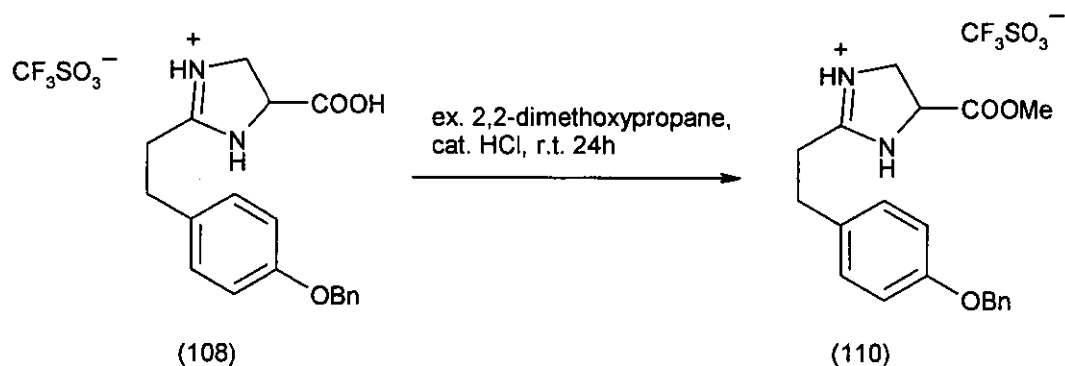
To 3-(4-benzyloxyphenyl)propanamide (67) (1.00g, 3.92 mmol) in dry dichloromethane (40 ml) was added methyl trifluoromethanesulfonate (0.66 ml, 5.88 mmol, 1.5 mol. equiv.) and the mixture heated at reflux for 3 h and then stirred at room temperature for a further 1 day. A white residue was obtained after removing the solvent and this was re-dissolved in ethanol (40 ml) to which was added 2,3-D,L-diaminopropionic acid dihydrochloride (826 mg, 5.88 mmol) and diisopropylethylamine (1.02 ml, 760 mg, 5.88 mmol). The reaction mixture was heated at reflux for 1 day under an atmosphere of nitrogen. The white precipitate formed from the reaction was filtered off, washed with ethanol (5 ml) and the solid recrystallised from acetone / dichloromethane to give a solid (108) (987 mg, 53 %) as the white triflate salt. M.p: 150 °C; ν_{\max} (Acetonitrile)/ cm^{-1} 3192 (OH), 1749, 1614 (C=N), 1513, 1242 (C-N), 1177, 1028 and 636; δ_{H} (400 MHz Acetone) 2.90 – 3.01 (4 H, m, CH_2CH_2), 4.19 (2 H, d, J 10.0, NCH_2), 4.89 (1 H, t, J 10.0, CH_2CHCOOH), 5.05 (2 H, s, OCH_2Ph), 6.94 (2 H, d, J 8.6, 2 x Ph-H), 7.22 (2 H, d, J 8.6, 2 x Ph-H), 7.29 – 7.46 (5 H, m, 5 x Ph-H) and 9.33 (1 H, s, NH); δ_{C} (100 MHz Acetone) 29.90 (CH_2), 32.00 (CH_2), 49.47 (CHCH_2), 60.47 (CHCH_2), 70.83 (OCH_2Ph), 116.25 (2 x CH, 2 x ArCH), 128.80 (2 x CH, 2 x ArCH), 129.01 (CH, ArCH), 129.68 (2 x CH, 2 x ArCH), 130.79 (2 x CH, 2 x ArCH), 132.53 (C, ArC), 138.80 (C, ArC), 159.04 (CO, ArCO), 171.83 (N-C=N) and 175.66 (C=O); m/z (FAB) 325.1556 (MH^+ - $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3$ + H requires 325.1552); m/z (FAB) 325 (MH^+ , 100%), 279 (62), 154 (40), 136 (39) and 107 (26).

2-[2-(4-Benzyloxyphenyl)ethyl]-1,4,5,6-tetrahydropyrimidinium-4(S)-carboxylic acid triflate salt (109)



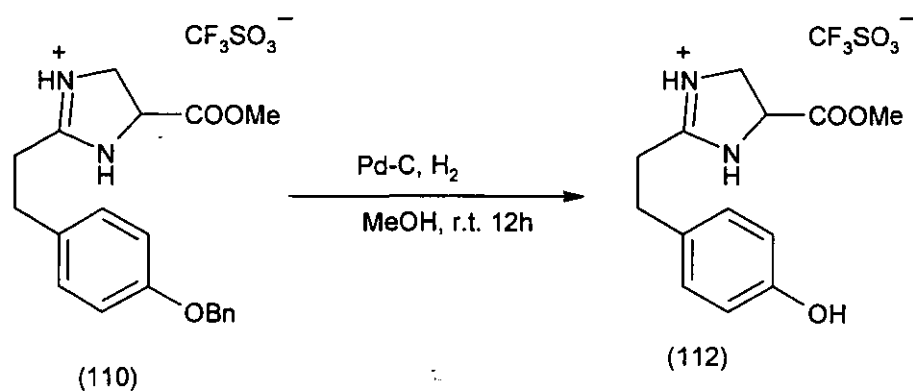
To 3-(4-benzyloxyphenyl)propanamide (**67**) (1.00 g, 3.92 mmol) in dichloromethane (40 ml) was added methyl trifluoromethanesulfonate (0.66 ml, 5.88 mol, 1.5 mol. equiv.) and the mixture was heated at reflux for 4 hours followed by further stirring at room temperature for 1 day. The solvent was removed under reduced pressure, the white solid residue was re-dissolved in ethanol (30 ml) and L-2,4-diaminobutyric acid dihydrochloride (757 mg, 3.96 mmol) and diisopropylethylamine (DIPEA, 2 ml) were added. The mixture was heated at reflux for 24 h and the white precipitate filtered off, this was identified as unchanged diaminobutyric acid. The filtrate was acidified with hydrochloric acid to pH 2 and the solvent was removed for flash column chromatography of the residue with polar eluent, methanol : dichloromethane (15 : 85 v/v) to recover further diaminobutyric acid and the desired product as an oil (**109**) (310 mg, 16 %). $[\alpha]_D^{20}$ 51.0 ($c = 10.0$ in MeOH); δ_H (250 MHz CD₃OD) 2.04 – 2.06 (2 H, m, NCH₂CH₂CH), 2.72 (2 H, t, J 7.2, CH₂CH₂), 2.95 (2 H, t, J 7.2, CH₂CH₂), 3.20 – 3.45 (2 H, m, NCH₂CH₂), 4.01 – 4.04 (1 H, m, CH₂CHCOOCH₃), 5.05 (2 H, s, OCH₂Ph), 6.94 (2 H, d, J 8.4, 2 x Ph-H), 7.18 (2 H, d, J 8.4, 2 x Ph-H) and 7.30 – 7.39 (5 H, m, 5 x Ph-H); δ_C (100 MHz CD₃OD) 22.69 (NCH₂CH₂CH), 33.03 (CH₂CH₂), 35.85 (CH₂CH₂), 38.52 (NCH₂CH₂), 55.87 (CH₂CHCOOCH₃), 71.00 (OCH₂Ph), 116.28 (2 x CH, 2 x ArCH), 128.57 (2 x CH, 2 x ArCH), 128.88 (CH, ArCH), 129.52 (2 x CH, 2 x ArCH), 130.53 (2 x CH, 2 x ArCH), 132.36 (C, ArC), 138.79 (C, ArC), 159.14 (CO, ArCO), 164.20 (COOCH₃) and 171.27 (N-C=N); m/z (FAB) 339.1709 (MH⁺ - C₂₀H₂₂N₂O₃ + H requires 339.1709); m/z (FAB) 339 (MH⁺, 100%), 294 (6), 247 (8), 154 (18, 136 (20), 107 (13), 91 (58), 77 (18) and 56 (13).

2-[2-(4-Benzyloxyphenyl)ethyl]-4,5-dihydroimidazolium-4-carboxylic acid methyl ester triflate salt (110)



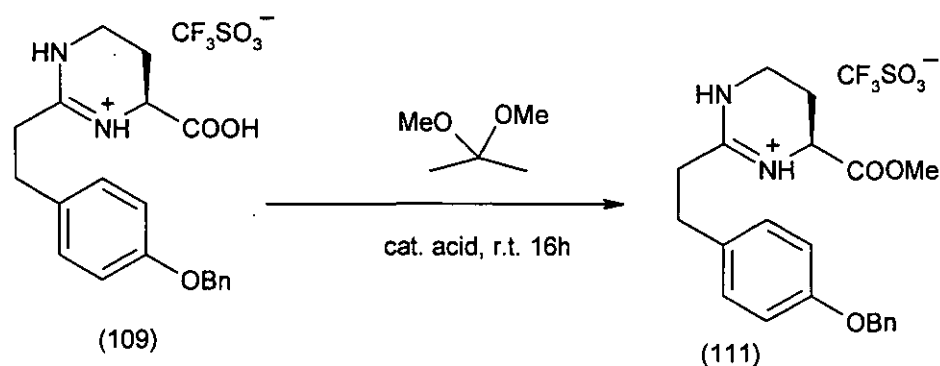
2-[2-(4-Benzyloxyphenyl)ethyl]-4,5-dihydroimidazolium-4-carboxylic acid triflate salt (**108**) (310 mg, 0.81 mmol) was mixed with 2,2-dimethoxypropane (20 ml) and hydrochloric acid catalyst (1 ml) at room temperature for 24 h. The white precipitate was filtered and dried under reduced pressure to give the expected product (**110**) (284 mg, 88 %). M.p: 147-148 °C; ν_{max} (Acetonitrile)/ cm^{-1} 3228, 2960, 1748 (C=O), 1609, 1512, 1457, 1244 (C-N), 1163, 1027, 838, 815, 743 and 696; δ_{H} (250 MHz CD_3OD) 2.80 – 2.99 (4 H, m, CH_2CH_2), 3.81 (3 H, s, COOCH_3), 4.09 (2 H, dd, J 3.0 & 11.4, NCH_2), 4.89 – 4.96 (1 H, m, $\text{CH}_2\text{CHCOOMe}$), 5.1 (2 H, s, OCH_2Ph), 6.96 (2 H, dd, J 2.2 & 6.7, 2 x Ph-H), 7.16 (2 H, dd, J 2.2 & 6.7, 2 x Ph-H) and 7.30 – 7.37 (5 H, m, 5 x Ph-H); δ_{C} (100 MHz CD_3OD) 29.71 ($\underline{\text{C}}\text{H}_2\text{CH}_2$), 31.96 ($\text{CH}_2\underline{\text{C}}\text{H}_2$), 48.67 ($\text{N}\underline{\text{C}}\text{H}_2\text{CH}$), 53.67 ($\text{COO}\underline{\text{C}}\text{H}_3$), 59.00 ($\text{CH}_2\underline{\text{C}}\text{HCOOMe}$), 70.95 (OCH_2Ph), 116.29 (2 x CH, 2 x ArCH), 128.53 (2 x CH, 2 x ArCH), 128.88 (CH, ArCH), 129.51 (2 x CH, 2 x ArCH), 130.44 (2 x CH, 2 x ArCH), 131.88 (C, ArC), 138.70 (C, ArC), 159.25 (CO, ArCO), 170.60 (N-C=N) and 172.42 ($\underline{\text{C}}\text{OOCH}_3$); m/z (EI+) 338.1632 (M^+ - $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3$ requires 338.1630); m/z (EI+) 338 (M^+ , 25%), 279 (8), 247 (100), 187 (10) and 91 (91).

2-[2-(4-Hydroxyphenyl)ethyl]-4,5-dihydroimidazolium-4-carboxylic acid methyl ester triflate salt (112)



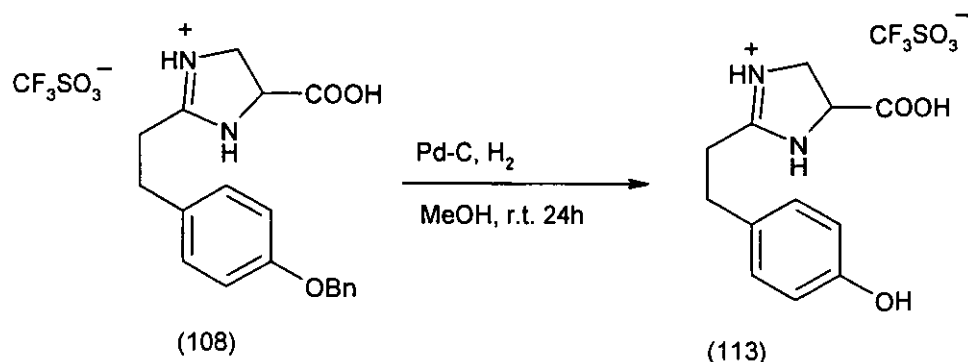
To 2-[2-(4-benzyloxyphenyl)ethyl]-4,5-dihydroimidazolium-4-carboxylic acid methyl ester triflate salt (**110**) (363 mg, 0.91 mmol) and palladium-carbon (10 %) (55 mg, 15 %w/w) was added methanol (30 ml). After degassing, the hydrogenation proceeded under 1 atmosphere of hydrogen for 12 h. The palladium-carbon catalyst was filtered off over celite and the solids washed with methanol (20 ml). The filtrate was collected and the solvent removed under reduced pressure to give a pale yellow oil (**112**) (280 mg, 100 %). ν_{max} (Acetonitrile)/ cm^{-1} 3245 (OH), 2996, 1744 (COOCH_3), 1611, 1517, 1442, 1257 (C-N), 1172, 1029, 832 and 761; δ_{H} (250 MHz CD_3OD) 2.74 - 2.93 (4 H, m, CH_2CH_2), 3.80 (3 H, s, COOCH_3), 4.03 - 4.13 (2 H, m, NCH_2CH), 4.83 - 4.94 (1 H, m, $\text{CH}_2\text{CHCOOCH}_3$), 6.71 - 6.74 (2 H, d, J 8.2, 2 x Ph-H) and 7.03 - 7.06 (2 H, d, J 8.2, 2 x Ph-H); δ_{C} (100 MHz CD_3OD) 28.98 ($\underline{\text{C}}\text{H}_2\text{CH}_2$), 31.09 ($\text{CH}_2\underline{\text{C}}\text{H}_2$), 47.84 ($\text{N}\underline{\text{C}}\text{H}_2\text{CH}$), 49.02 ($\text{COO}\underline{\text{C}}\text{H}_3$), 58.23 ($\text{CH}_2\underline{\text{C}}\text{HCOOCH}_3$), 115.62 (2 x CH, 2 x ArCH), 129.55 (2 x CH, 2 x ArCH), 129.62 (C, ArC), 156.42 (CO, ArCO), 169.89 (N=C-N) and 171.45 ($\underline{\text{C}}\text{OOCH}_3$); m/z (EI+) 248.1165 (M^+ - $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_3$ requires 248.1161); m/z (EI+) 234 (M^+ , 9%), 189 (21), 164 (13), 147 (20), 120 (8), 107 (100), 91 (11) and 77 (15).

2-[2-(4-Benzyloxyphenyl)ethyl]-1,4,5,6-tetrahydropyrimidinium-4(S)-carboxylic acid methyl ester triflate salt (111)



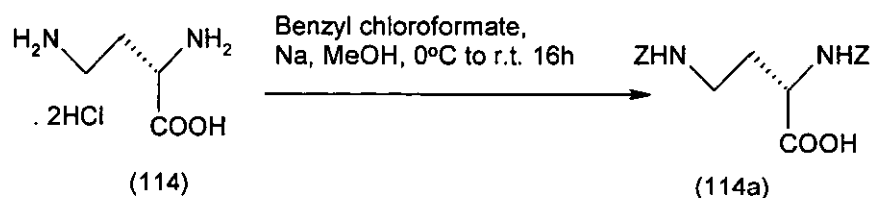
To 2-[2-(4-benzyloxyphenyl)ethyl]-1,4,5,6-tetrahydropyrimidinium-4(S)-carboxylic acid triflate salt (**109**) (178 mg, 0.364 mmol) in 2,2-dimethoxypropane (10 ml) was added concentrated hydrochloric acid (2 ml) as catalyst and the mixture stirred at room temperature for 16 h. The solvent was removed to give a yellow oil as the desired product (**111**) (180 mg, 99 %). $[\alpha]_D^{20}$ 42.1 ($c = 11$ in MeOH); ν_{\max} (neat)/ cm^{-1} 3149, 2950, 3787, 1745 (COOCH₃), 1650 (C=N), 1613, 1513, 1453, 1237 (C-N), 1177, 1024, 825, 742 and 697; δ_{H} (250 MHz CD₃OD) 2.10 – 2.15 (2 H, m, NCH₂CH₂CH), 2.71 – 2.78 (2 H, m, CH₂CH₂), 2.93 – 2.96 (2 H, m, CH₂CH₂), 3.39 – 3.45 (2 H, m, NCH₂CH₂), 3.79 (3H, s, COOCH₃), 4.36 – 4.38 (1 H, m, CH₂CHCOOCH₃), 5.06 (2 H, s, OCH₂Ph), 6.93 – 6.96 (2 H, d, J 8.4, 2 x Ph-H), 7.17 – 7.20 (2 H, d, J 8.4, 2 x Ph-H) and 7.29 – 7.38 (5 H, m, 5 x Ph-H); δ_{C} (100 MHz CD₃OD) 21.75 (NCH₂CH₂), 33.14 (CH₂CH₂), 35.79 (CH₂CH₂), 37.85 (NCH₂CH₂), 52.00 (COOCH₃), 53.72 (CH₂CHCOOCH₃), 71.03 (OCH₂Ph), 116.32 (2 x CH, 2 x ArCH), 128.60 (2 x CH, 2 x ArCH), 128.91 (CH, ArCH), 129.56 (2 x CH, 2 x ArCH), 130.78 (2 x CH, 2 x ArCH), 132.13 (C, ArC), 138.80 (C, ArC), 159.17 (CO, ArCO), 164.99 (C=O) and 171.27 (N-C=N); m/z (FAB) 353.1866 (MH⁺ - C₂₁H₂₄N₂O₃ + H requires 353.1865); m/z (FAB) 353 (MH⁺, 100%), 339 (23), 156 (21), 119 (28), 105 (24), 91 (73) and 55 (41).

2-[2-(4-Hydroxyphenyl)ethyl]-4,5-dihydroimidazolium-4-carboxylic acid triflate salt (113)



2-[2-(4-Benzyloxyphenyl)ethyl]-4,5-dihydroimidazolium-4-carboxylic acid triflate salt **(108)** (224 mg, 0.51 mmol) with palladium-carbon (15 %) (33 mg, 15% w/w) and methanol (30 ml), was hydrogenated under 1 atmosphere of hydrogen for 24 h. The reaction was filtered through celite to remove the palladium-carbon and the solids were washed with methanol (15 ml). The filtrate was collected and the solvent removed under reduced pressure to yield the oily product **(113)** (165 mg, 84 %). ν_{max} (Acetonitrile)/ cm^{-1} 3270 (OH), 3014, 1621 (C=N), 1558, 1434, 1251 (C-N), 1176, 1031 and 638; δ_{H} (250 MHz CD_3OD) 2.76 (2 H, brs, CH_2CH_2), 2.89 (2 H, brs, CH_2CH_2), 3.95 – 4.10 (2 H, m, CHCH_2), 4.60 (1 H, brs, CHCH_2), 6.73 (2 H, d, J 7.0, 2 x Ph-H) and 7.07 (2 H, d, J 7.0, 2 x Ph-H); δ_{C} (100 MHz CD_3OD) 30.35 (CH_2), 32.41 (CH_2), 50.07 (CHCH_2), 61.49 (CHCH_2), 116.96 (2 x CH, 2 x ArCH), 130.85 (2 x CH, 2 x ArCH), 131.26 (C, ArC), 157.70 (CO, ArC), 171.81 (N-C=N) and 177.16 (COOH); m/z (EI+) 234.1006 (M^+ - $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3$ requires 234.1004); m/z (EI+) 234 (M^+ , 9%), 189 (21), 164 (13), 147 (20), 107 (100) and 77 (15).

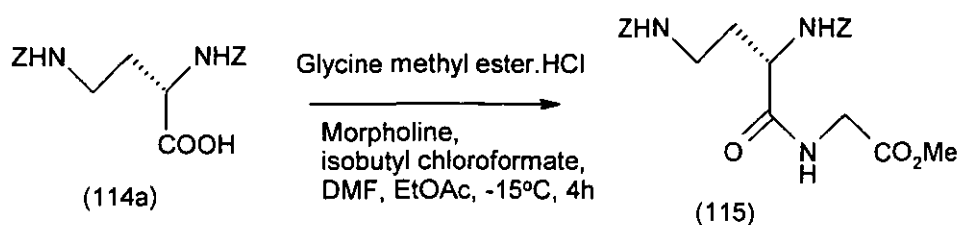
L-2,4-Bis-(benzyloxycarbonylamino)butyric acid (114) ⁷³



To finely ground L-2,4-diaminobutyric acid dihydrochloride (**114**) (2.50 g, 13.20 mmol) in methanol (50 ml) was added pyridine (5 ml) and the mixture stirred at room temperature for 10 h. The white precipitate formed was collected through filtration and the solids were dried under vacuum to give the corresponding monohydrochloride product (2.0 g). To this L-2,4-diaminobutyric acid monohydrochloride (2.0 g, 13 mmol) in aqueous sodium hydroxide (2 M, 20.00 ml, 39 mmol, 3 mol. equiv.) were added simultaneously with vigorous stirring, benzyl chloroformate (4.50 ml, 31 mmol, 2.4 mol. equiv.) and aqueous sodium hydroxide (2 M, 15.50 ml, 31 mmol, 2.4 mol. equiv.) at 0 °C. The reaction mixture was left to stir vigorously overnight at ambient temperature and the resulting solution was then washed with diethyl ether before acidifying to pH 1 with concentrated hydrochloric acid and extracting with chloroform (3 x 50 ml). The organic layers were combined and dried with Na₂SO₄. The desired product was obtained after evaporating the solvent under reduced pressure to give a yellow solid, L-2,4-bis-(benzyloxycarbonylamino)butyric acid (**114a**) (2.79 g, 56 %). (pure compound might only be obtained after column chromatography of the yellow liquor at this stage). M.p: 100-103 °C (lit., ⁹⁰ 91-92 °C); $[\alpha]_D^{20}$ -10.0 ($c = 10.0$ in MeOH); ν_{\max} (neat)/cm⁻¹ 3332 (OH), 3064, 2953, 1728 (C=O), 1665, 1532 (NH), 1476, 1334 (C-N), 1255 (C-O), 1045 and 741; δ_H (400 MHz CD₃OD) 1.84 – 1.87 (1 H, m, CH(H)), 2.08 – 2.12 (1 H, m, CH(H)), 3.18 – 3.33 (2 H, m, NHCH₂), 4.25 (1 H, dd, J 4.4 & 9.6, CH), 5.08 (2 H, s, OCH₂), 5.11 (2 H, s, OCH₂) and 7.29 – 7.36 (10 H, m, 10 x Ph-H); δ_C (100 MHz, CD₃OD) 32.82 (CH₂), 38.59 (NCH₂CH₂), 53.09 (CH₂CHCOOCH₃), 67.51 (OCH₂), 67.73 (OCH₂), 128.82 (2 x CH, 2 x ArCH), 128.98 (2 x CH, 2 x ArCH), 129.02 (2 x CH, 2 x ArCH), 129.50 (2 x CH, 2 x ArCH), 129.60 (2 x CH, 2 x ArCH), 138.19 (C, ArC),

138.36 (C, ArC), 158.76 (OC=O), 158.90 (OC=O) and 175.66 (COOH); m/z (EI-) 385.1392 (MH^+ - $C_{20}H_{22}N_2O_6$ requires 385.1400).

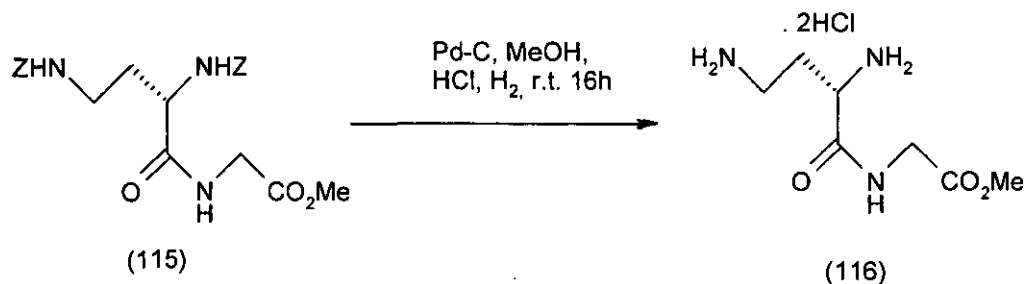
L-2,4-Bis-(benzyloxycarbonylamino)butyrylaminoacetic acid methyl ester (115) ⁷³



To L-2,4-*bis*-(benzyloxycarbonylamino)butyric acid (**114a**) (2.79 g, 7.22 mmol) in ethyl acetate (100 ml) was added *iso*-butyl chloroformate (0.94 ml, 7.22 mmol) dropwise at -15 °C under nitrogen followed by 4-methylmorpholine (0.79 ml, 7.22 mmol) after 10 min of stirring. The mixture was allowed to stir for a further 20 min at -15 °C before adding dropwise a suspension of glycine methyl ester hydrochloride and triethylamine (1.0 ml, 7.22 mmol) in a mixture of dimethylformamide and ethyl acetate (1:1 v/v, 100 ml). The mixture was further stirred for 4 h at -15 °C before being allowed warm to room temperature for another 4 h. Precipitates from the reaction as hydrochlorides were filtered off and washed thoroughly with ethyl acetate, and the filtrate was evaporated under reduced pressure to give a yellow oil. The oil was poured into water in an ice bath to form a white solid that was dried over P_2O_5 under vacuum in a drying pistol to give the expected product, L-2,4-*bis*-(benzyloxycarbonylamino)butyrylaminoacetic acid methyl ester (**115**) (3.13 g, 92 %). M.p: 126-127 °C (lit. ⁷³, 116-117 °C); $[\alpha]_D^{20}$ -11.7 ($c = 10.0$ in MeOH); ν_{max} (neat)/ cm^{-1} 3317 (NH), 3064, 2951, 1702 ($COOCH_3$), 1531, 1454, 1249 (C-N), 1215, and 1027; δ_H (400 MHz CD_3Cl) 1.82 – 1.92 (1 H, m, $CH(H)$), 1.91 – 1.99 (2 H, m, CH_2), 3.08 – 3.13 (2 H, m, $NHCH_2$), 3.51 – 3.56 (1 H, m, CH), 3.72 (3 H, s, OCH_3), 3.90 (1 H, dd, J 5.0 & 17.9, $CH(H)$), 4.08 (1 H, dd, J 5.0 & 17.9, $CH(H)$), 4.32 – 4.38 (1 H, m, CH), 5.08 (4 H, s, 2 x OCH_2), 5.50 (1 H, brs, NH), 5.85 (1 H, brs, NH), 7.29 – 7.36 (10 H, m, 10 x Ph-H) and 7.52 (1 H, brs, OH); δ_C (100 MHz, CD_3Cl) 34.16

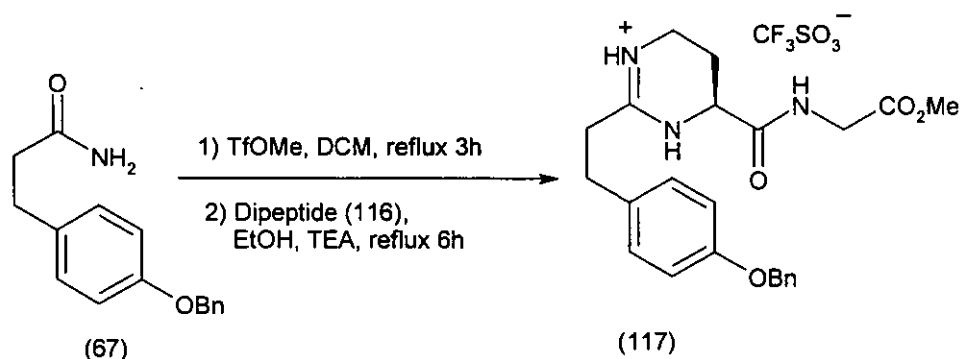
(CH₂), 37.21 (NHCH₂CH₂), 41.14 (NHCH₂COOCH₃), 51.96 (OCH₃), 52.35 (CH₂CHC=O), 66.90 (OCH₂), 67.08 (OCH₂), 127.90 (2 x CH, 2 x ArCH), 128.04 (2 x CH, 2 x ArCH), 128.13 (2 x CH, 2 x ArCH), 128.20 (2 x CH, 2 x ArCH), 128.53 (CH, ArCH), 128.74 (CH, ArCH), 136.18 (C, ArC), 136.40 (C, ArC), 156.26 (NHC=O), 157.32 (NHC=O), 170.13 (C=O) and 171.82 (NHC=O); *m/z* (EI+) 457.1843 (M⁺ - C₂₃H₂₇N₃O₇ requires 457.1849); *m/z* (EI+) 457 (M⁺, 5%), 368 (8), 353 (9), 341 (44), 280 (19), 242 (25), 146 (35), 108 (60), 91 (100) and 79 (38).

L-2,4-Diaminobutyrylaminoacetic acid methyl ester dihydrochloride (116)⁷³



To L-2,4-*bis*-(benzyloxycarbonylamino)butyrylaminoacetic acid methyl ester (**115**) (1.75 g, 4.05 mmol), palladium-carbon (10 %) (351 mg, 20 %w/w), methanol (60 ml) and hydrochloric acid (0.84 ml, 8.10 mmol) were added in that order. After degassing, the mixture was stirred under a hydrogen atmosphere for 16 h. The reaction was filtered through celite, the solids washed with methanol and the filtrate evaporated under reduced pressure to furnish a pale yellow sticky solid (**116**) (1.05 g, 99 %) as the L-2,4-diaminobutyrylaminoacetic acid methyl ester dihydrochloride. $[\alpha]_{\text{D}}^{20}$ 4.7 (*c* = 10.0 in MeOH); ν_{max} (neat)/cm⁻¹ 3618, 3538, 3162, 3001, 2942, 1443, 1374, 1038, 917 and 749; δ_{H} (400 MHz CD₃OD) 2.28 – 3.32 (2 H, m, NH₂CH₂CH₂CH), 3.19 – 3.26 (2 H, m, NH₂CH₂), 3.75 (3 H, s, OCH₃), 3.94 (1 H, d, *J* 17.6, CH) and 4.15 – 4.17 (2 H, m, NHCH₂COOCH₃); δ_{C} (100 MHz, CD₃OD) 30.29 (NH₂CH₂CH₂), 36.52 (NH₂CH₂), 41.81 (NHCH₂COOCH₃), 51.91 (OCH₃), 52.89 (CH), 169.56 (C=O) and 171.53 (NHC=O).

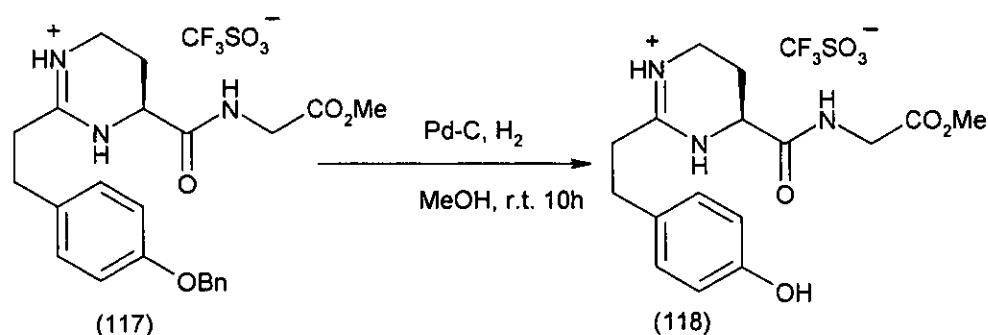
L-2-[2-(4-Benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium-4(S)-carbonyl-aminoacetic acid methyl ester triflate salt (117)



To 3-(4-benzyloxyphenyl)propanamide (**67**) (250 mg, 0.98 mmol) in DCM (30 ml) was added methyl triflate (0.16 ml, 1.47 mmol, 1.5 mol. equiv.) and the mixture was heated at reflux for 3 h under an atmosphere of nitrogen and then left to stand at room temperature overnight. The solvent was removed under reduced pressure to give a white solid that was re-dissolved in ethanol (70 ml) and L-2,4-diaminobutyrylaminoacetic acid methyl ester dihydrochloride (388 mg, 1.47 mmol) and triethylamine (0.45 ml, 3.58 mmol) were added. The mixture was heated at reflux under an atmosphere of nitrogen for 6 h. The reaction solvent was removed under reduced pressure and the residue was purified by flash column chromatography twice with MeOH : DCM (5 – 10 % MeOH) to yield recovered propanamide (18 mg, 15 %) and a pure white solid (**117**) (234 mg, 43 %). M.p: 85-86 °C. ν_{max} (neat)/ cm^{-1} 3317 (NH), 2951, 1702 (COOCH_3), 1531, 1454, 1249 (C-O), 1215, 1027, 751 and 697; δ_{H} (400 MHz CD_3Cl) 2.00 – 2.04 (1 H, m, $\text{NCH}_2\text{CH}(\text{H})\text{CH}$), 2.14 – 2.18 (1 H, m, $\text{NCH}_2\text{CH}(\text{H})\text{CH}$), 2.74 (2 H, t, J 7.6, CH_2), 2.95 (2 H, t, J 7.6, CH_2), 3.33 – 3.40 (2 H, m, NCH_2CH_2), 3.72 (3 H, s, COOCH_3), 3.97 – 4.00 (2 H, m, $\text{NHCH}_2\text{C}=\text{O}$), 4.27 (1 H, t, J 4.2, CH), 5.07 (2 H, s, OCH_2Ph), 6.96 (1 H, d, J 8.6, Ph-H), 7.18 (1 H, d, J 8.6, Ph-H) and 7.30 – 7.43 (5 H, m, 5 x Ph-H); δ_{C} (100 MHz, CD_3Cl) 22.64 ($\text{NCH}_2\text{CH}_2\text{CH}$), 32.95 (CH_2), 36.03 (CH_2), 37.55 (NCH_2), 41.96 ($\text{NHCH}_2\text{COOCH}_3$), 49.28 (CH_2CH), 52.73 (COOCH_3), 70.98 (OCH_2Ph), 116.31 (2 x CH, 2 x ArCH), 128.53 (2 x CH, 2 x ArCH), 128.86 (CH, ArCH), 129.49 (2 x CH, 2 x ArCH), 130.61 (2 x CH, 2 x ArCH), 132.10 (C, ArC), 138.37 (C, ArC), 159.19 (CO, ArCO), 165.35 (N-C=N), 171.42 (C=O) and 172.10 ($\text{NHC}=\text{O}$); m/z (FAB) 410.2080

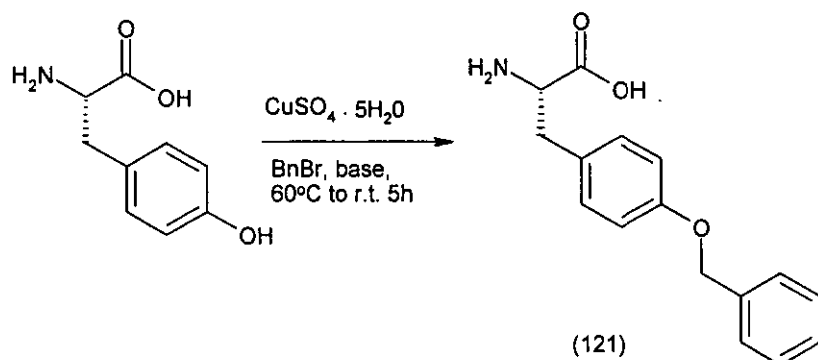
($MH^+ - C_{23}H_{27}N_3O_4 + H$ requires 410.2080); m/z (FAB) 410 (MH^+ , 10%), 130 (61), 109 (21), 91 (43), 69 (75), 55 (100) and 41 (88).

L-2-[2-(4-Hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidin-4(S)-carbonyl-aminoacetic acid methyl ester triflate salt (118)



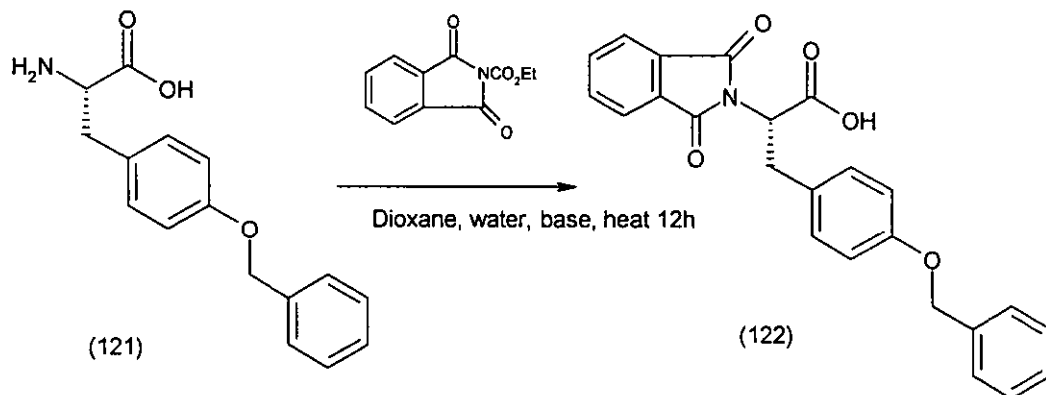
To L-2-[2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidine-4(S)-carbonylaminoacetic acid methyl ester triflate salt (**117**) (177 mg, 0.32 mmol) with palladium-carbon (10 %) (28 mg, 15 % w/w) was added methanol (50 ml) and the mixture degassed before stirring at room temperature under 1 atmosphere of hydrogen for 10 h. The palladium-carbon was removed by filtration through celite and the solids washed with methanol (10 ml), then the filtrate was evaporated under reduced pressure to afford a yellow liquor (**118**) (139 mg, 94 %). ν_{max} (neat)/ cm^{-1} 3304 (NH), 3064 (NH), 2924, 1740 (COOCH₃), 1654 (C=N), 1517, 1253 (C-O), 1170 and 1031; δ_H (400 MHz CD₃OD) 1.89 – 2.01 (2 H, m, NCH₂CH₂), 2.53 – 2.55 (2 H, brs, CH₂), 2.78 – 2.79 (2 H, brs, CH₂), 3.03 – 3.26 (2 H, m, NCH₂), 3.25 (3 H, m, COOCH₃), 3.86 (2 H, brs, NHCH₂C=O), 4.05 (1 H, brs, CH₂CH), 6.61 (2 H, d, J 7.7, 2 x Ph-H) and 6.96 (2 H, d, J 7.7, 2 x Ph-H); δ_C (100 MHz, CD₃OD) 23.02 (NCH₂CH₂), 33.15 (CH₂), 36.79 (CH₂), 37.81 (NCH₂), 42.00 (NHCH₂COOCH₃), 49.90 (CH₂CH), 53.62 (COOCH₃), 116.62 (2 x CH, 2 x ArCH), 130.60 (2 x CH, 2 x ArCH), 130.85 (C, ArC), 157.71 (CO, ArCO), 164.58 (N-C=N), 171.47 (C=O) and 171.62 (NHC=O); m/z (FAB) 320.1611 ($MH^+ - C_{16}H_{22}N_3O_4 + H$ requires 320.1610).

O-Benzyl-L-tyrosine (121)^{91a}



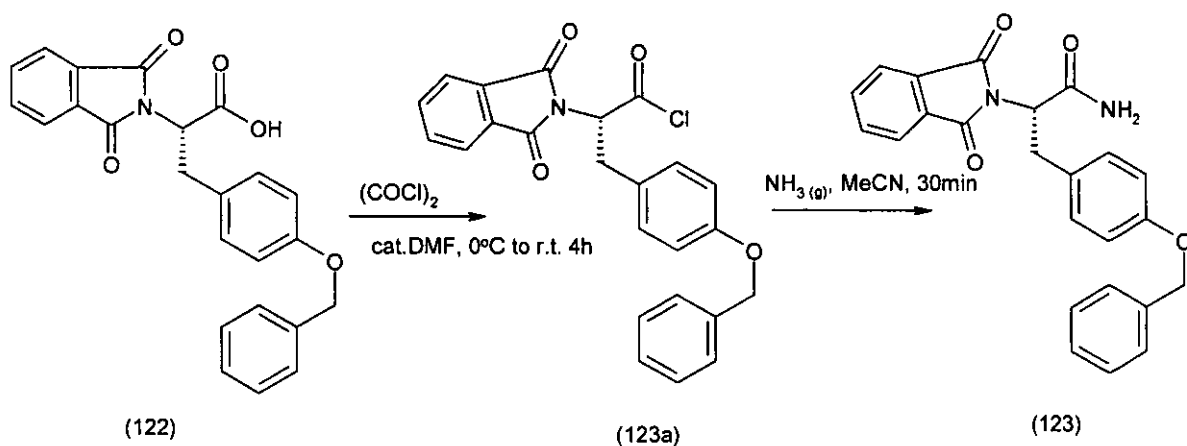
Copper(II) sulfate pentahydrate (14.06 g, 56.32 mmol) dissolved in deionised water (50 ml) was added to a stirred solution of L-tyrosine (20 g, 110.4 mmol) in 2M sodium hydroxide solution (112 ml, 2.03 mol. equiv.) which gave blue precipitation. The mixture was heated at 60 °C and then cooled down to room temperature again. Methanol (400 ml), 2M NaOH (16 ml) and benzyl bromide (22.66 g, 15.8 ml, 132.48 mmol, 1.2 mol. equiv.) were added and the mixture was stirred at room temperature for 5 h. The reaction mixture was filtered and the blue residue was washed with methanol (50 ml) and deionised water (150 ml & 50 ml). The blue residue was triturated in 2M hydrochloric acid (5 x 80 ml) to yield a white residue which was washed with water (3 x 150 ml) and 2M ammonium hydroxide solution (4 x 60 ml). After further washing with acetone (2 x 50 ml), water (2 x 50 ml) and ether (2 x 50 ml), the white product was dried in a drying pistol overnight to remove water and other solvents. *O*-Benzyl-L-tyrosine (121) was obtained (20.2 g, 67 %). Due to its low solubility, the proton NMR spectrum was run at high temperature (>50 °C). M.p: 227-229 °C (lit.,^{91a} 224-226 °C); $[\alpha]_{\text{D}}^{24}$ -9.5 ($c = 10.0$ in Acetic acid) (lit.,^{91b} $[\alpha]_{\text{D}}^{23}$ -10.2 in acetic acid); δ_{H} (250 MHz DMSO) 2.90 – 3.05 (1 H, m, CH), 3.16 – 3.21 (2 H, m, CH₂), 4.12 (2 H, brs, NH₂), 5.08 (2 H, s, CH₂), 6.94 (2 H, d, J 8.4, 2 x Ph-H), 7.18 (2 H, d, J 8.4, 2 x Ph-H) and 7.33 – 7.44 (5 H, m, 5 x Ph-H).

N-Phthalyl-*O*-benzyl-L-tyrosine (122)



To *O*-benzyl-L-tyrosine (121) (1.00 g, 3.68 mmol) in dioxane : deionised water (100 ml, 1 : 2), was added sodium carbonate (0.40 g, 3.68 mmol). The suspension was heated at 70 °C for 45 mins until all the solids dissolved. The mixture was cooled down to 45-50 °C, and then *N*-ethoxycarbonylphthalimide (1.21 g, 5.52 mmol, 1.5 mol. equiv.) was added with pH falling from 10 to 7. A precipitate formed soon after the addition and the mixture was left to stir for 12 h at 50 °C. The mixture was then cooled to room temperature and the precipitate filtered off, the filtrate was collected and acidified with 2M hydrochloric acid to give a white precipitate. The precipitate was filtered and washed with a little acetone and ether and then dried under reduced pressure to yield the *N*-protected tyrosine (122) (0.70 g, 48 %). M.p: 212-213 °C (lit., ⁷⁴212-214 °C); ν_{\max} (Acetonitrile)/cm⁻¹ 1768, 1741 (Phth), 1691 (COOH), 1611, 1512, 1392, 1344, 1254, 1113, 1042 (COC) and 736; δ_{H} (250 MHz DMSO) 3.38 – 3.45 (2 H, m, CHCH₂), 4.98 (2 H, s, OCH₂Ph), 5.09 (1 H, dd, *J* 11.4 & 5.0, CHCH₂), 6.83 (1 H, d, *J* 8.6, Ph-H), 7.08 (1 H, d, *J* 8.6, 1 H, Ph-H), 7.32 – 7.37 (5 H, m, 5 x Ph-H) and 7.86 (4 H, s, 4 x Ph-H); δ_{C} (100 MHz DMSO) 33.38 (CHCH₂), 53.48 (CHCH₂), 69.33 (OCH₂Ph), 114.91 (2 x CH, 2 x ArCH), 123.77 (2 x CH, 2 x ArCH), 128.05 (2 x CH, 2 x ArCH), 128.11 (CH, ArCH), 128.69 (2 x CH, 2 x ArCH), 129.69 (C, ArC), 130.08 (2 x CH, 2 x ArCH), 131.07 (2 x C, 2 x ArC), 135.31 (2 x CH, 2 x ArCH), 137.35 (C, ArC), 157.27 (CO, ArCO), 167.50 (2 x C=O) and 170.48 (COOH); *m/z* (EI+) 401.1256 (M⁺ - C₂₄H₁₉NO₅ requires 401.1263); *m/z* (EI+) 401 (M⁺, 4%), 254 (15), 197 (6), 174 (11), 115 (10), 91 (100) and 69 (10).

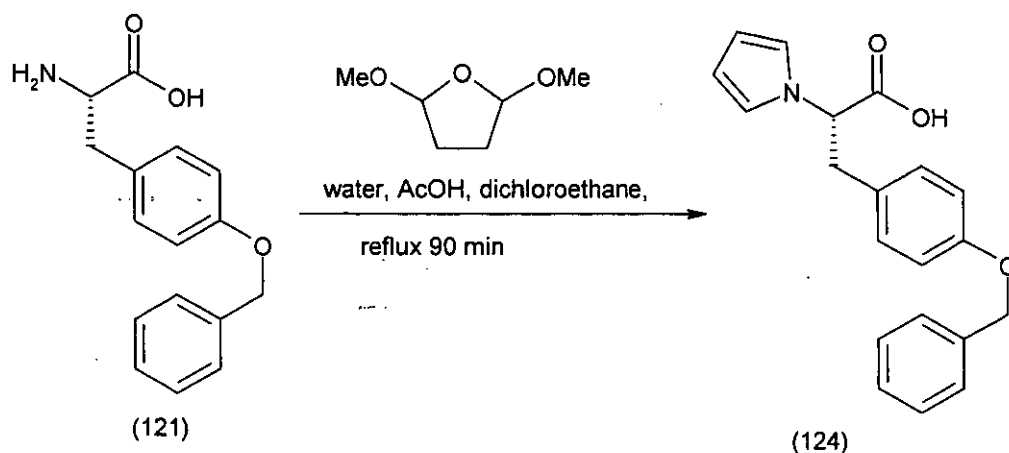
N-Phthalyl-*O*-benzyl-L-tyrosinamide (**123**)



To *N*-phthalyl-*O*-benzyl-L-tyrosine (**122**) (1500 mg, 3.75 mmol) in dried tetrahydrofuran (50 ml) was added oxalyl chloride (960 mg, 0.66 ml, 7.50 mmol) under an atmosphere of nitrogen at 0 °C and DMF (0.05 ml) was also added slowly as the reaction catalyst. After stirring for 4 h, the solvent was removed from the yellow solution under reduced pressure to give, as a yellow solid the corresponding acyl chloride (**123a**). Ammonia gas was slowly bubbled through this acyl chloride in acetonitrile (50 ml) for 30 min at ambient temperature while stirring. The reaction was monitored by TLC while a yellow precipitate formed. After removing the precipitate by filtration through celite and washing the solids with acetonitrile (15 ml), the filtrate was evaporated under reduced pressure to yield the desired product *N*-phthalyl-*O*-benzyl-L-tyrosinamide (**123**) (2.76 g, 92 %). M.p: 156-157 °C (lit.,⁹² 158 °C); $[\alpha]_{\text{D}}^{20}$ -109.3 ($c = 10.0$ in MeOH) (lit.,⁹² $[\alpha]_{\text{D}}^{22}$ -162.1 in MeOH); Found: C, 71.78; H, 4.74; N, 6.91. $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_4$ requires C, 71.99; H, 5.03; N, 6.99%; ν_{max} (Acetonitrile)/ cm^{-1} 1770, 1712 (Phth), 1510, 1384, 1347, 1241, 1116, 1084 (COC), 878 and 719; δ_{H} (250 MHz DMSO) 3.23 – 3.48 (2 H, m, CHCH_2), 4.88 (1 H, dd, J 11.7 & 4.3, CH_2CH), 4.95 (2 H, s, OCH_2Ph), 6.79 (2 H, d, J 8.1, 2 x Ph-H), 7.03 (2 H, d, J 8.1, 2 x Ph-H), 7.31 – 7.34 (6 H, m, 4 x Ph-H & NH_2), 7.69 (1 H, s, Ph-H) and 7.80 (4 H, s, 4 x Ph-H); δ_{C} (100 MHz DMSO) 32.80 (CHCH_2), 54.36 (CHCH_2), 68.89 (OCH_2Ph), 114.43 (2 x CH, 2 x ArCH), 122.96 (2 x CH, 2 x ArCH), 127.57 (2 x CH, 2 x ArCH), 127.64 (CH, ArCH), 128.23 (2 x CH, 2 x ArCH), 129.54 (2 x CH, 2 x ArCH), 129.74 (C, ArC), 131.20 (C, ArC), 134.37 (2 x CH, 2 x ArCH), 136.91

(C, ArC), 156.73 (CO, ArCO), 167.41 (C=O) and 169.62 (C=O); m/z (EI+) 400.1429 (M^+ - $C_{24}H_{20}N_2O_4$ requires 400.1423); m/z (EI+) 400 (M^+ , 4%), 253 (34), 197 (3), 130 (4), 104 (5) and 91 (100).

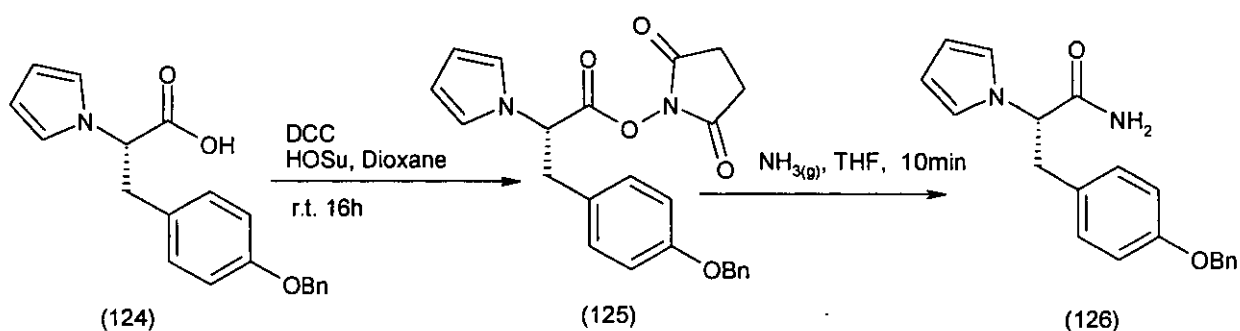
N-Pyrrolyl-*O*-benzyl-L-tyrosine (**124**)



O-Benzyl-L-tyrosine (**121**) (1.00 g, 3.68 mmol) and 2,5-dimethoxytetrahydrofuran (0.47 g, 0.48 ml, 3.68 mmol) were mixed together in deionised water (10 ml) with acetic acid (5 ml) and 1,2-dichloroethane (80 ml) and the mixture heated at reflux for 90 min with vigorous stirring. After cooling to room temperature, the reaction mixture was extracted with dichloromethane (3 x 25 ml). The combined organic layers were collected and dried with anhydrous magnesium sulfate. The organic layer was evaporated for flash column chromatography of the residue with diethyl ether to furnish a brown solid (**124**) (580 mg, 49 %). M.p: 100-103 °C; ν_{\max} ($CHCl_3$)/ cm^{-1} 3031 (Pyr-CH), 2928 (COOH), 1718 (COOH), 1610, 1511, 1275, 1242, 1177, 1092 (COC) and 727; δ_H (250 MHz $CDCl_3$) 3.24 (1 H, dd (ABX), J 9.2 & 14.1, CHCH(H)), 3.40 (1 H, dd (ABX), J 6.0 & 14.1, CHCH(H)), 4.75 (1 H, dd, J 6.0 & 9.2, CHCH₂), 5.04 (2 H, s, OCH₂Ph), 6.18 (1 H, t, J 2.1, Pyr-H), 6.71 (1 H, t, J 2.1, Pyr-H), 6.84 (2 H, d, J 8.5, Ph-H), 6.93 (2 H, d, J 8.5, 2 x Ph-H) and 7.32 - 7.40 (5 H, m, 5 x Ph-H); δ_c (100 MHz $CDCl_3$) 38.70 (CH₂), 64.07 (CH), 70.42 (OCH₂Ph), 109.35 (2 x CH, 2 x PyrCH), 115.41 (2 x CH, 2 x ArCH), 120.70 (2 x

CH, PyrCH), 127.96 (2 x CH, 2 x ArCH), 128.43 (CH, ArCH), 128.80 (C, ArC), 129.03 (2 x CH, 2 x ArCH), 130.35 (2 x CH, 2 x ArCH), 137.38 (C, ArC), 158.35 (CO, ArCO) and 176.55 (C=O); m/z (EI+) 321.1365 (M^+ - $C_{20}H_{19}NO_3$ requires 321.1366); m/z (EI+) 321 (M^+ , 9%), 225 (15), 197 (23), 183 (11), 107 (32) and 91 (100).

***N*-Pyrrolyl-*O*-benzyl-L-tyrosinamide (126) via *N*-pyrrolyl-*O*-benzyl-L-tyrosine-*O*-succinimide (125)**

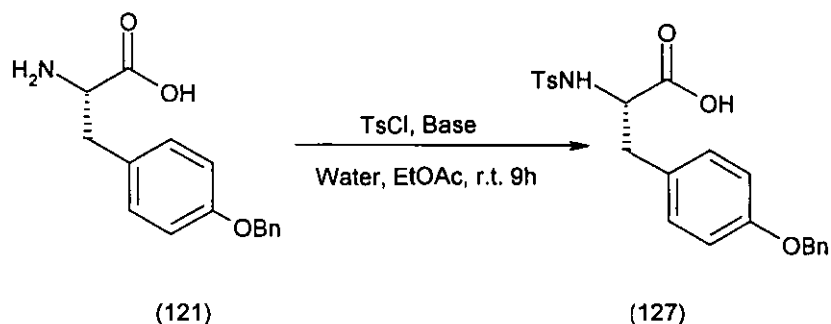


To *N*-pyrrolyl-*O*-benzyl-L-tyrosine (**124**) (361 mg, 1.12 mmol) in 1,4-dioxane (30 ml) was added dicyclohexylcarbodiimide (DCC, 232 mg, 1.12 mmol) and *N*-hydroxysuccinimide (129 mg, 1.12 mmol). After stirring the mixture overnight at room temperature, the white precipitate formed during the reaction was filtered off and the filtrate was evaporated under reduced pressure to leave a white solid intermediate, *N*-pyrrolyl-*O*-benzyl-L-tyrosine-*O*-succinimide (**125**) (466 mg, 100 %). M.p: 108-111 °C; ν_{max} ($CHCl_3$)/ cm^{-1} 2931 (COOH), 1814 (OCNCO), 1783, 1737 (OCNCO), 1610, 1512, 1241, 1203, 1072 (COC) and 732; δ_H (400 MHz $CDCl_3$) 2.65 (4 H, s, 2 x $CH_2C=O$), 3.35 (1 H, dd (ABX), J 9.8 & 14.2, CHCH(H)), 3.51 (1 H, dd (ABX), J 5.0 & 14.2, CHCH(H)), 5.00 (s, 2 H, OCH_2Ph), 5.04 (1 H, dd, J 5.0 & 9.8, CHCH₂), 6.17 (2 H, t, J 2.2, 2 x Pyr-H), 6.71 (2 H, t, J 2.2, 2 x Pyr-H), 6.84 (2 H, d, J 8.8, 2 x Ph-H), 6.92 (2 H, d, J 8.8, 2 x Ph-H) and 7.34 - 7.40 (5 H, m, 5 x Ph-H); δ_c (100 MHz $CDCl_3$) 25.90 (2 x $CH_2C=O$), 39.22 (CH_2), 61.84 (CH), 70.31 (OCH_2Ph), 109.73 (2 x CH, 2 x PyrCH), 115.32 (2 x CH, 2 x ArCH), 120.77 (2 x CH, 2 x ArCH), 127.92 (2 x CH, 2 x ArCH),

127.96 (C, ArC), 128.38 (CH, ArCH), 128.97 (2 x CH, 2 x ArCH), 130.40 (2 x CH, 2 x ArCH), 137.27 (C, ArC), 158.43 (CO, ArCO), 166.37 (C=O), 168.96 (C=O); m/z (EI+) 418.1530 (M^+ - $C_{24}H_{22}N_2O_5$ requires 418.1529); m/z (EI+) 418 (M^+ , 17%), 276 (8), 197 (60), 91 (100) and 43 (27).

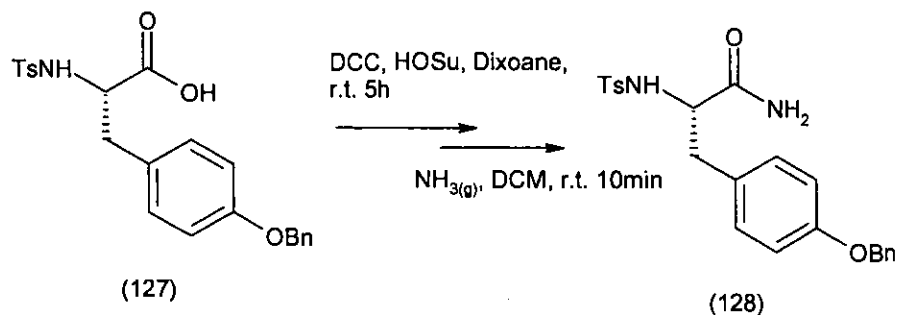
The white solid of *N*-pyrrolyl-*O*-benzyl-*L*-tyrosine-*O*-succinimide (**125**) (131 mg, 0.312 mmol) was dissolved in tetrahydrofuran (15 ml) and ammonia gas bubbled through the mixture for about 10 minutes whenupon white precipitate formed. The precipitate was filtered off and washed with a small amount of tetrahydrofuran (5 ml), and the filtrate was evaporated under reduced pressure to give a pale brown solid of *N*-pyrrolyl-*O*-benzyl-*L*-tyrosinamide (**126**) (81 mg, 81 %). M.p: 95-97 °C; $[\alpha]_D^{20}$ -290.0 ($c = 10.0$ in MeOH); ν_{max} (CHCl₃)/cm⁻¹ 3316 (NH), 1682 (C=O), 1510, 1240, 1024 (COC) and 730; δ_H (400 MHz CDCl₃) 3.19 (1 H, dd, J 10.8 & 14.4, CHCH(H)), 3.60 (1 H, dd, J 4.2 & 14.4, CHCH(H)), 4.64 (1 H, dd, J 4.2 & 10.8, CHCH₂), 4.99 (2 H, s, OCH₂Ph), 5.46 (1 H, brs, NH), 5.96 (1 H, brs, NH), 6.21 (2 H, t, J 2.0, 2 x Pyr-H), 6.68 (2 H, t, J 2.0, 2 x Pyr-H), 6.87 (4 H, m, 4 x Ph-H) and 7.32 – 7.42 (5 H, m, 5 x Ph-CH); δ_c (100 MHz CDCl₃) 35.96 (CHCH₂), 64.13 (CHCH₂), 68.92 (OCH₂Ph), 108.67 (2 x CH, 2 x PyrCH), 113.82 (2 x CH, 2 x ArCH), 119.23 (2 x CH, 2 x ArCH), 126.45 (2 x CH, 2 x ArCH), 126.91 (CH, ArCH), 127.53 (2 x CH, 2 x ArCH), 128.55 (C, ArC), 128.73 (2 x CH, 2 ArCH), 135.97 (C, ArC) 156.65 (C, ArC) and 172.21 (C, ArC); m/z (EI+) 320.1531 (M^+ - $C_{20}H_{20}N_2O_2$ requires 320.1525); m/z (EI+) 320 (M^+ , 3%), 279 (68), 224 (53), 167 (54), 149 (100), 143 (28), 99 (40), 91 (37), 70 (26), 56 (65) and 43 (22).

N-Tosyl-*O*-benzyl-L-tyrosine (127)



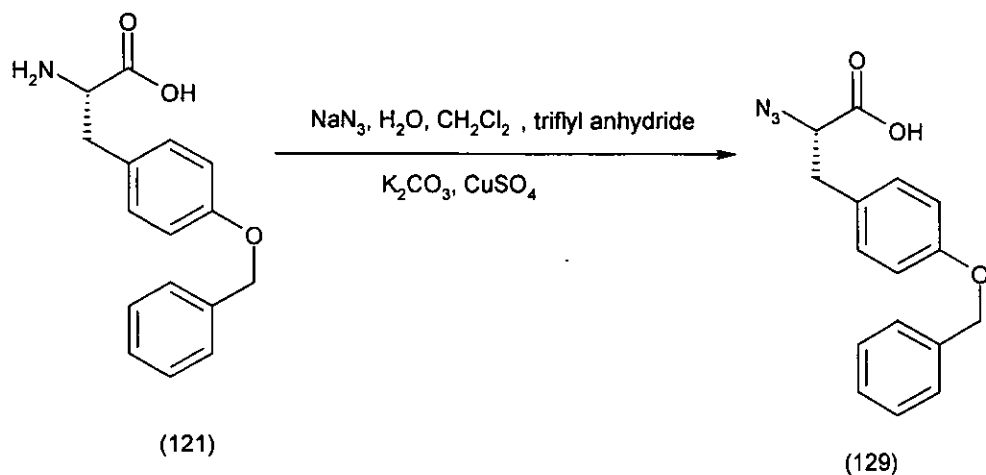
To *O*-benzyl-L-tyrosine (**121**) (250 mg, 0.92 mmol) partially dissolved in water (30 ml) was added *p*-toluenesulfonyl chloride (351 mg, 1.84 mmol, 2 mol. equiv.) in ethyl acetate (10 ml). To the mixture, saturated sodium hydroxide solution (10 ml) was slowly added over 5 min while the starting material gradually dissolved and a white precipitate appeared. After 9 h at room temperature, the ethyl acetate was evaporated, and the residue and the aqueous layer were acidified with concentrated hydrochloric acid to pH 2 and kept in an ice bath for 2 h. The pale yellow solid formed was filtered off and dried under vacuum in a drying pistol to give *N*-tosyl-*O*-benzyl-L-tyrosine (**127**) (332 mg, 85 %). M.p: 127-128 °C; $[\alpha]_{\text{D}}^{20}$ 8.3 ($c = 10.0$ in MeOH); ν_{max} (neat)/ cm^{-1} 3260, 3031, 1727, 1609, 1511, 1453, 1330, 1242, 1158, 1090 and 813; δ_{H} (250 MHz, CD_3OD) 2.38 (3 H, s, CH_3), 2.91 – 3.06 (2 H, m, CHCH_2), 4.10 – 4.16 (1 H, m, CH), 5.01 (2 H, s, OCH_2Ph), 6.83 (2 H, d, J 8.6, 2 x Ph-H), 6.99 (2 H, d, J 8.6, 2 x Ph-H), 7.20 (2 H, d, J 8.3, 2 x Tol-H) 7.33 – 7.43 (5 H, m, 5 x Ph-H) and 7.60 (2 H, d, J 8.3, 2 x Tol-H); δ_{C} (100 MHz, CDCl_3) 21.64 (CH_3), 38.02 (CHCH_2), 56.46 (CHCH_2), 66.83 (OCH_2Ph), 114.97 (2 x CH, 2 x ArCH), 126.96 (C, ArC), 127.12 (2 x CH, 2 x Tol-H), 127.48 (2 x CH, 2 x ArCH), 128.03 (CH, ArCH), 128.62 (2 x CH, 2 x ArCH), 129.66 (2 x CH, 2 x ArCH), 130.55 (2 x CH, 2 x ArCH), 136.50 (C, ArC), 136.89 (SO_2C , Tol-C), 143.76 (C, Tol-C), 158.13 (CO, ArCO) and 175.06 (COOH); m/z (EI+) 425.1294 (M^+ - $\text{C}_{23}\text{H}_{23}\text{NO}_5\text{S}$ requires 425.1297); m/z (EI+) 425 (M^+ , 3%), 269 (3), 225 (3), 197 (49), 178 (3), 155 (5), 134 (5), 107 (11), 91 (100) and 65 (12).

N-Tosyl-*O*-benzyl-L-tyrosinamide (128)



To *N*-tosyl-*O*-benzyl-L-tyrosine (127) (311 mg, 0.73 mmol) dissolved in 1,4-dioxane (60 ml) was added *N*-hydroxysuccinimide (84 mg, 0.73 mmol) and dicyclohexylcarbodiimide (150 mg, 0.78 mmol) at room temperature. After 5 h stirring, the white precipitate formed was filtered off and the dioxane was removed under reduced pressure to give a yellow solid intermediate. The yellow solid was re-dissolved in DCM (60 ml) and ammonia gas was bubbled through the solution, and the white precipitate formed was removed by filtration. The filtrate was evaporated to give a pale yellow solid that was purified by column chromatography with DCM to yield a white solid (128) (137 mg, 44 %). M.p: 150-151 °C; $[\alpha]_{\text{D}}^{20}$ -4.3 ($c = 10.0$ in MeOH); ν_{max} (neat)/ cm^{-1} 3322(NH), 2925, 2848, 1626(NH), 1569, 1436, 1309 (S=O), 1242, 1087 and 891; δ_{H} (400 MHz, CD_3OD) 2.33 (3 H, s, CH_3), 2.75 (1 H, dd, J 8.5 & 13.8, $\text{CHCH}(\text{H})$), 2.96 (1 H, dd, J 5.5 & 13.8, $\text{CHCH}(\text{H})$), 3.95 (1 H, dd, J 5.5 & 8.5, CH), 5.00 (2 H, s, OCH_2Ph), 6.77 (2 H, d, J 8.6, 2 x Ph-H), 6.99 (2 H, d, J 8.6, 2 x Ph-H), 7.17 (2 H, d, J 8.3, 2 x Tos-H), 7.28 – 7.42 (5 H, m, 5 x Ph-H) and 7.51 (2 H, d, J 8.3, 2 x Tos-H); δ_{C} (100 MHz, CD_3OD) 20.84 (CHCH_2), 21.58 (CH_3), 39.09 (CHCH_2), 70.96 (OCH_2Ph), 115.79 (2 x CH, 2 x ArCH), 128.03 (2 x CH, 2 x TosCH), 128.60 (2 x CH, 2 x ArCH), 128.91 (CH, ArCH), 129.56 (2 x CH, 2 x TosCH), 130.10 (C, ArC), 130.50 (2 x CH, 2 x ArCH), 131.50 (2 x CH, 2 x ArCH), 138.82 (C, ArC), 139.11 (SO_2C , TosC), 144.40 (C, TosC), 159.20 (CO, ArCH) and 175.31 (COOH); m/z (EI+) 424.1462 ($\text{M}^+ - \text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$ requires 424.1457).

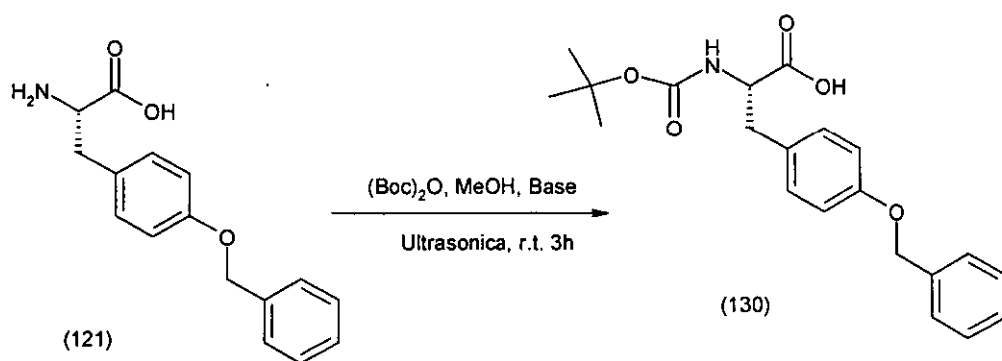
S-2-Azido-3-(4-benzyloxyphenyl)propionic acid (**129**)



Sodium azide (1.20 g, 18.4 mmol, 10 mol. equiv.) was dissolved in deionised H₂O (5ml), CH₂Cl₂ (10 ml) was added and the mixture cooled on an ice bath. Trifluoromethanesulfonic anhydride (1.04g, 0.62 ml, 3.68 mmol, 2 mol. equiv.) was added slowly over 5 min followed by stirring the mixture for another 2 h. The cloudy white mixture was placed in a separating funnel and the CH₂Cl₂ phase was removed. The aqueous phase was extracted with CH₂Cl₂ (2 x 5 ml) and the combined organic phases, containing the triflyl azide were collected and washed with saturated sodium carbonate solution (20 ml) and used without further purification. *O*-Benzyl-L-tyrosine (**121**) (500 mg, 1.84 mmol) was combined with potassium carbonate (500 mg, 3.63 mmol), copper sulfate pentahydrate (10 mg, 40 μmol), deionised water (10ml), methanol (20 ml) and the triflyl azide solution in dichloromethane (20 ml). The reaction mixture was stirred at ambient temperature overnight and then the organic solvent was removed under reduced pressure to give a pale blue aqueous slurry which was diluted with deionised water (50 ml). The aqueous solution was acidified to pH 6 with concentrated hydrochloric acid, diluted with phosphate buffer pH 7.0 (50 ml) and extracted with ethyl acetate (4 x 30 ml) to remove the sulfonamide byproduct. The aqueous phase was further acidified to pH 2 with concentrated hydrochloric acid and the product was obtained by extraction with ethyl acetate (3 x 30 ml), which was dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure to yield a pale solid (**129**) (191 mg, 34 %). M.p: 87-88 °C; ν_{\max} (CHCl₃)/cm⁻¹ 3031, 2924, 2112 (N₃), 1718 (COOH), 1610, 1512, 1453,

1382, 1241 (COOH), 1176, 1028, 809, 737 and 697; δ_{H} (250 MHz CDCl_3) 3.00 (1 H, dd (ABX), J 8.7 & 14.2, CHCH(H)), 3.20 (1 H, dd (ABX), J 5.0 & 14.2, CHCH(H)), 4.13 (1 H, dd, J 5.0 & 8.7, CHCH₂), 5.07 (2 H, s, OCH₂Ph), 6.97 (2 H, d, J 8.6, 2 x Ph-H), 7.20 (2 H, d, J 8.6, 2 x Ph-H), 7.34 - 7.46 (5 H, m, 5 x Ph-H) and 9.40 (1 H, brs, OH); δ_{C} (100 MHz CDCl_3) 36.75 (CHCH₂), 63.25 (CHCH₂), 70.08 (OCH₂Ph), 115.15 (2 x CH, 2 x ArCH), 127.54 (2 x CH, 2 x ArCH), 127.87 (C, ArC), 128.05 (CH, ArCH), 128.63 (2 x CH, 2 x ArCH), 130.37 (2 x CH, 2 x ArCH), 136.90 (CH, ArCH), 158.16 (CO, ArCO) and 175.36 (C=O); m/z (EI⁺) 297.1109 (M^+ - $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_3$ requires 297.1113); m/z (EI⁺) 297 (M^+ , 2%), 225 (17), 197 (14), 134 (26), 91 (100) and 65 (10).

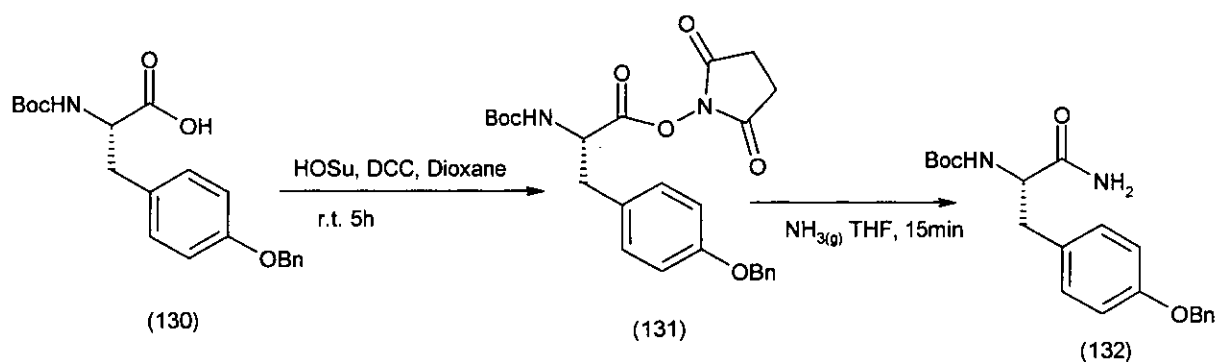
N-tert-Butoxycarbonyl-*O*-benzyl-L-tyrosine (130)



To *O*-benzyl-L-tyrosine (**121**) (500 mg, 1.84 mmol) mixed with sodium bicarbonate (500 mg) in methanol (20 ml) was added di-*tert*-butyl dicarbonate (403 mg, 1.84 mmol). The milky mixture was sonicated for 3 h until almost colourless. The solvent was evaporated, and after the addition of water (20 ml) to the residue the aqueous solution was acidified to pH 1-2 from pH 9 with conc. hydrochloric acid as a white precipitate appeared. The product was obtained by ethyl acetate extraction (3 x 40 ml), drying the organic layers over anhydrous sodium sulfate and then removing the solvent under reduced pressure to yield a white solid (**130**) (600 mg, 91 %). M.p: 99-100 °C (lit., ⁹³ 109-110 °C); $[\alpha]_{\text{D}}^{20}$ 9.7 ($c = 10.0$ in MeOH) (lit., ⁹³ $[\alpha]_{\text{D}}^{26}$ 16.35 in MeOH); ν_{max} (Acetonitrile)/ cm^{-1} 3318, 2976, 1698 (COOH), 1611 (NH), 1504, 1454, 1393, 1367, 1243 (CO), 1175, 1055, 1024 (COC), 829, 735 and 696; δ_{H} (400 MHz DMSO) 1.32 (9 H, s, 3 x CH₃), 2.75 (1 H, dd, J

10.2 & 13.8, CHCH(H)), 2.94 (1 H, dd, J 4.6 & 13.8, CHCH(H)), 3.38 (1 H, brs, OH), 3.99 – 4.05 (1 H, m, CHCH₂), 5.05 (2 H, s, OCH₂Ph), 6.91 (2 H, d, J 8.8, 2 x Ph-H), 7.16 (2 H, d, J 8.8, 2 x Ph-H), 7.31 – 7.44 (5 H, m, 5 x Ph-H) and 7.80 (1 H, brs, OH); δ_c (100 MHz DMSO) 29.02 (3 x CH₃), 36.42 (CHCH₂), 56.31 (CHCH₂), 69.95 (OCH₂Ph), 78.88 (C(CH₃)₃), 115.28 (2 x CH, 2 x ArCH), 128.51 (2 x CH, 2 x ArCH), 128.63 (CH, ArCH), 129.27 (2 x CH, 2 x ArCH), 130.98 (2 x CH, 2 x ArCH), 138.06 (2 x C, 2 x ArC), 156.34 (CO, ArCO), 157.81 (C=O) and 174.58 (C=O); m/z (EI⁺) 371.1734 (M^+ - C₂₁H₂₅NO₅ requires 371.1733); m/z (EI⁺) 371 (M^+ , 1%), 310 (1), 298 (2), 270 (1), 254 (2), 226 (2), 197 (28), 107 (5), 91 (100) and 57 (11).

***N*-tert-Butoxycarbonyl-*O*-benzyl-L-tyrosinamide (132) via *N*-tert-butoxycarbonyl-*O*-benzyl-L-tyrosine-*O*-succinimide (131)**

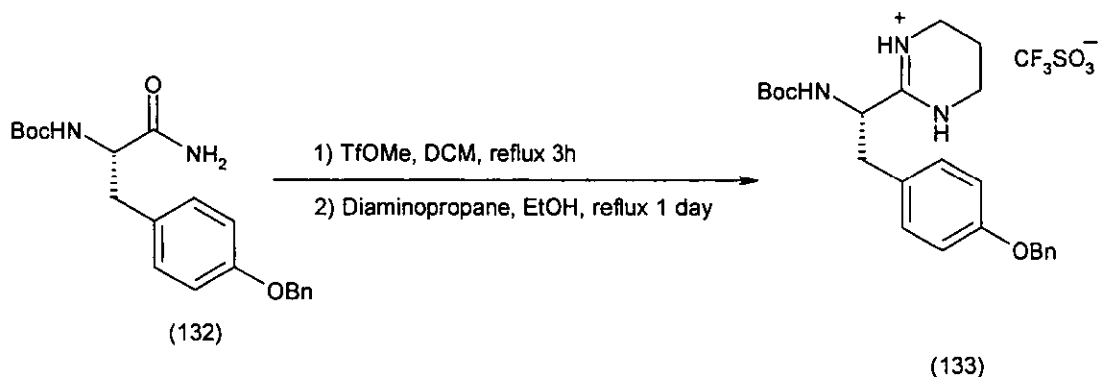


To *N*-tert-butoxycarbonyl-*O*-benzyl-L-tyrosine (**130**) (670 mg, 1.80 mmol) was added dicyclohexylcarbodiimide (DCC, 370 mg, 1.80 mmol), *N*-hydroxysuccinimide (HOSu, 207 mg, 1.80 mmol) and 1,4-dioxane (30 ml). After 5 h stirring at ambient temperature, the white precipitate was filtered off and the filtrate was evaporated to dryness under reduced pressure to give a white solid intermediate, *N*-tert-butoxycarbonyl-*O*-benzyl-L-tyrosine-*O*-succinimide (**131**) (810 mg, 99 %). M.p: 144-146 °C; ν_{\max} (CHCl₃)/cm⁻¹ 3349, 2976, 2931, 1814 (OCNCO), 1785, 1741, 1512, 1366, 1247, 1204, 1167, and 1064 (COC); δ_H (400 MHz Acetone) 1.31 (9 H, s, 3 x CH₃), 2.84 (4 H, s, 2 x CH₂C=O), 3.04 (1 H, dd (ABX), J 9.6 & 14.2, CHCH(H)), 3.26 (1 H, dd (ABX), J 4.8 & 14.2,

CHCH(H)), 4.68 – 4.74 (1 H, m, CHCH₂), 5.05 (2H, s, OCH₂Ph), 6.45 (1 H, d, NH), 6.93 (2 H, d, *J* 8.4, 2 x Ph-H), 7.27 – 7.37 (5 H, m, 5 x Ph-H) and 7.43 – 7.45 (2 H, m, 2 x Ph-H); δ_c (100 MHz Acetone) 26.74 (2 x CH₂C=O), 28.91 (3 x CH₃), 37.30 (CHCH₂), 54.92 (CHCH₂), 70.78 (OCH₂Ph), 80.28 (C(CH₃)₃), 115.99 (2 x CH, 2 x ArCH), 128.84 (2 x CH, 2 x ArCH), 129.03 (CH, ArCH), 129.71 (2 x CH, 2 x ArCH), 129.84 (C, ArC), 131.80 (2 x CH, 2 x ArCH), 138.85 (C, ArC), 156.43 (CO, ArCO), 159.27 (C=O), 169.51 (2 x C=O), and 170.71 (C=O); *m/z* (EI+) 468.1907 (M⁺ - C₂₅H₂₈N₂O₇ requires 468.1897); *m/z* (EI+) 468 (M⁺, 3%), 270 (5), 237 (6), 226 (5), 197 (69), 149 (14), 115 (22), 91 (100), 69 (10), 57 (31).

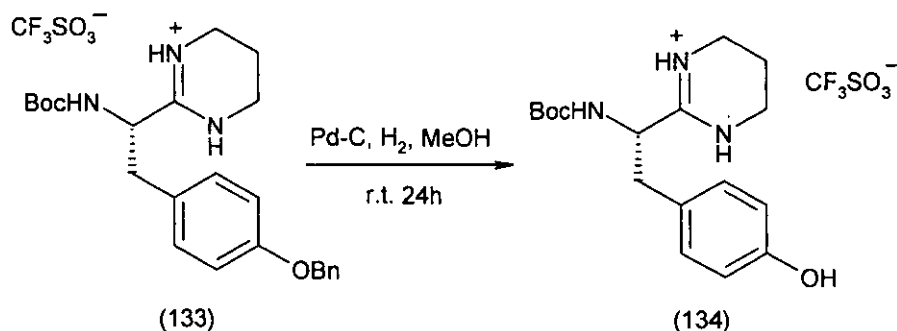
N-tert-Butoxycarbonyl-*O*-benzyl-L-tyrosine-*O*-succinimide solid (**131**) (781 mg, 1.73 mmol) was dissolved in tetrahydrofuran (20 ml) and ammonia gas was bubbled through the solution for 15 mins until a white precipitate fully emerged. The precipitate was filtered off and washed with a small amount of tetrahydrofuran (5 ml). The filtrate was evaporated under reduced pressure to give a white solid of *N-tert*-butoxycarbonyl-*O*-benzyl-L-tyrosinamide (**132**) (630 mg, 99 %). M.p: 170-171 °C (lit., ⁹⁴ 171-172 °C); $[\alpha]_D^{20}$ 8.6 (*c* = 10.0 in MeOH) (lit., ⁹⁴ $[\alpha]_D^{24}$ 4.6 in MeOH); ν_{\max} (Acetone)/cm⁻¹ 3348, 2981, 2928, 1680 (C=O), 1660 (C=O), 1513, 1245, 1167 and 1023; δ_H (400 MHz Acetone) 1.32 (9 H, s, 3 x CH₃), 2.83 (1 H, dd (ABX), *J* 8.4 & 14.0, CHCH(H)), 3.07 (1 H, dd (ABX), *J* 5.2 & 14.0, CHCH(H)), 4.26 – 4.29 (1 H, m, CHCH₂) 5.04 (2 H, s, CH₂), 5.94 (1 H, br d, NH), 6.51 (1 H, brs, NH), 6.89 (2 H, d, *J* 8.4, 2 x Ph-H), 6.97 (1 H, brs, NH), 7.16 (2 H, d, *J* 8.4, 2 x Ph-H), 7.29 – 7.43 (3 H, m, 3 x Ph-H) and 7.44 – 7.45 (2 H, m, 2 x Ph-H); δ_c (100 MHz Acetone) 28.53 (3 x CH₃), 38.11 (CHCH₂), 56.45 (CHCH₂), 70.35 (OCH₂Ph), 79.14 (C(CH₃)₃), 115.34 (2 x CH, 2 x ArCH), 128.36 (2 x CH, 2 x ArCH), 128.53 (CH, ArCH), 129.23 (2 x CH, 2 x ArCH), 130.96 (C, ArC), 131.22 (2 x CH, 2 x ArCH), 138.53 (C, ArC), 156.12 (CO, ArCO), 158.50 (C=O) and 174.30 (C=O).

S-2-[1-*N-tert*-Butoxycarbonyl-2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (133)



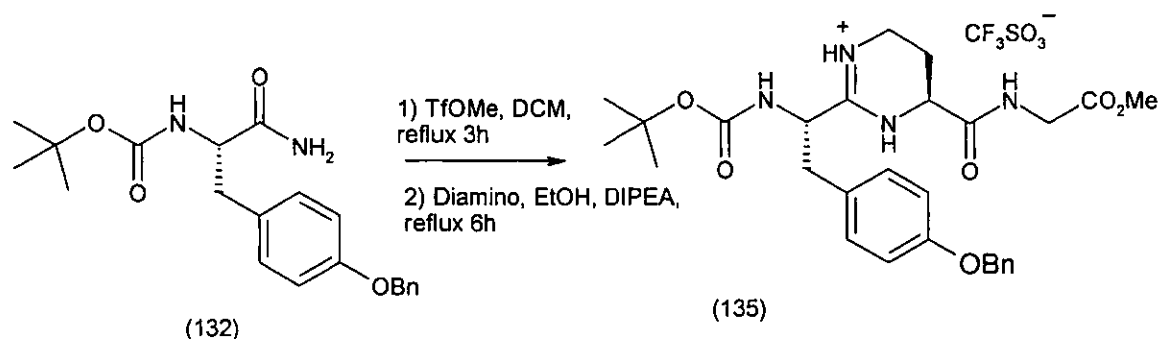
To *N-tert*-butoxycarbonyl-*O*-benzyl-*L*-tyrosinamide (**130**) (184 mg, 0.497 mmol) in dry dichloromethane (20 ml) was added methyl trifluoromethanesulfonate (98 mg, 0.067 ml, 0.596 mmol) and the mixture heated at reflux for 3 h before stirring at room temperature for a further 24 h. The solvent was evaporated under reduced pressure and the residue was re-dissolved in dry methanol (15 ml) with addition of 1,3-diaminopropane (44 mg, 0.050 ml, 0.596 mmol). The mixture was heated at reflux for 1 day before the solvent was completely removed under reduced pressure for flash column chromatography of the residue with methanol (3 – 6 %) in dichloromethane. The isolated colourless liquid was identified as the desired product (**133**) (129 mg, 47 %). In addition, the tetrahydropyrimidine with the *N-tert*-butoxycarbonyl group removed was also recovered. ν_{\max} (CHCl₃)/cm⁻¹ 3294, 3238, 3054, 2977, 1717, 1667 (C=N), 1615, 1514, 1456, 1368, 1280, 1242 (C-N), 1224, 1158, 1028 and 756; δ_{H} (250 MHz CDCl₃) 1.34 (9 H, s, 3 x CH₃), 1.83 (2 H, t, *J* 5.3, CH₂CH₂CH₂), 2.96 – 3.15 (2 H, m, CHCH₂), 3.28 – 3.42 (4 H, m, NCH₂), 4.44 – 4.51 (1 H, m, CHCH₂), 4.96 (2 H, s, OCH₂Ph), 6.03 (1 H, brs, NH), 6.86 (2 H, d, *J* 8.3, 2 x Ph-H), 7.20 (2 H, d, *J* 8.3, 2 x Ph-H), 7.31 – 7.37 (5 H, m, 5 x Ph-H) and 8.73 (1 H, brs, NH); δ_{C} (100 MHz CDCl₃) 18.32 (CH₂CH₂CH₂), 28.46 (3 x CH₃), 37.66 (CHCH₂), 39.22 (2 x NCH₂), 55.29 (CHCH₂), 70.26 (OCH₂Ph), 81.27 (C(CH₃)₃), 115.49 (2 x CH, 2 x ArCH), 127.66 (C, ArC), 127.89 (2 x CH, 2 x ArCH), 128.36 (CH, ArCH), 128.94 (2 x CH, 2 x ArCH), 130.83 (2 x CH, 2 x ArCH), 137.24 (C, ArC), 156.10 (CO, ArCO), 158.44 (C=O) and 165.33 (N-C=N); *m/z* (FAB) 410.2442 (MH⁺ - C₂₄H₃₁N₃O₃ + H requires 410.2444); *m/z* (FAB) 410 (MH⁺, 100%), 354 (43), 155 (43), 137 (39), 113 (36) and 92 (48).

S-2-[1-*N*-*tert*-butoxycarbonyl-2-(4-hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (134)



To S-2-[1-*N*-*tert*-butoxycarbonyl-2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (**133**) (170 mg, 0.304 mmol) was added palladium-carbon (10%) (30 mg, 18 %w/w) and methanol (30 ml). After degassing, hydrogenation proceeded under a balloon of hydrogen at 1 atmosphere for 24 hour. After filtering off the palladium-carbon through celite which was washed with methanol (15 ml), the filtrate was evaporated under reduced pressure to yield the desired oil (**134**) (123 mg, 87 %). $[\alpha]_{\text{D}}^{20}$ 2.5 ($c = 10.6$ in MeOH); ν_{max} (Acetonitrile)/ cm^{-1} 3301 (OH), 3248, 3054 (OH), 2979, 1712, 1667 (C=N), 1614, 1517, 1446, 1369, 1250 (C-N), 1165, 1029 and 638; δ_{H} (400 MHz Acetone) 1.30 (9 H, s, 3 x CH₃), 1.79 (2 H, brs, CH₂CH₂CH₂), 2.85 – 2.90 (2 H, m, CHCH₂), 3.20 – 3.26 (4 H, m, 2 x NCH₂), 4.21 (1 H, brs, CH), 6.66 (2 H, d, J 8.0, 2 x Ph-H) and 6.98 (2 H, d, J 8.0, 2 x Ph-H); δ_{C} (100 MHz Acetone) 18.07 (CH₂CH₂CH₂), 27.59 (3 x CH₃), 37.53 (CHCH₂), 38.84 (2 x NCH₂), 55.48 (CHCH₂), 80.66 (C(CH₃)₃), 115.63 (2 x CH, 2 x ArCH), 125.99 (C, ArC), 130.52 (2 x CH, 2 x ArCH), 156.39 (CO, ArCO), 157.09 (C=O) and 164.65(N-C=N); m/z (EI+) 319.1897 (M^+ - C₁₇H₂₅N₃O₃ requires 319.1896); m/z (EI+) 319 (M^+ , 11%), 245 (26), 203, (70), 156 (19), 139 (33), 112 (46), 107 (63), 56 (100) and 44 (86).

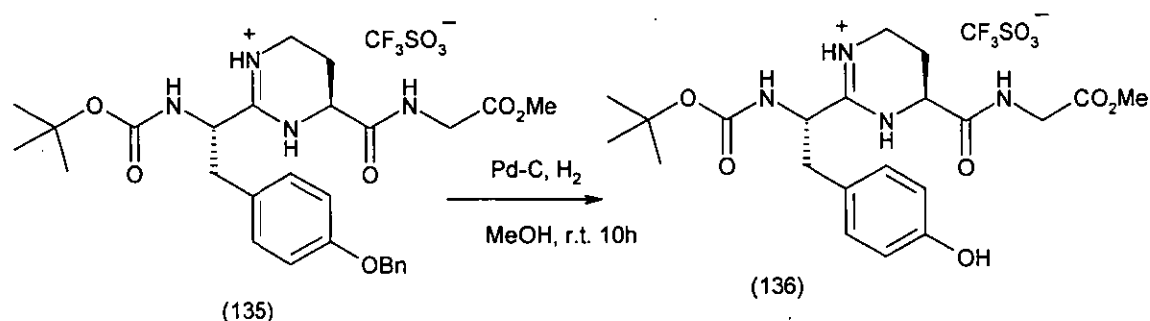
2-[1-(*N*-*tert*-Butoxycarbonylamino)-2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium-4-carbonylaminoacetic acid methyl ester triflate salt (135)



To *N*-*tert*-butoxycarbonyl-*O*-benzyl-L-tyrosinamide (**132**) (150 mg, 0.41 mmol) in DCM (30 ml) was added methyl triflate (101 mg, 0.07 ml, 0.62 mmol, 1.5 mol. equiv.) and the mixture heated at reflux under an atmosphere of nitrogen for 3 h and then stirred overnight at room temperature. The solvent was removed under reduced pressure to produce an imidate intermediate which was re-dissolved in ethanol (50 ml). To this solution, L-2,4-diaminobutyrylaminoacetic acid methyl ester dihydrochloride (**116**) (148 mg, 0.57 mmol, 1.4 mol. equiv.) and diisopropylethylamine (DIPEA) (117 mg, 0.14 ml, 0.82 mmol, 2 mol. equiv.) were added simultaneously and the solution heated for 6 h at reflux under an atmosphere of nitrogen. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography twice with MeOH : DCM (10 % MeOH) to produce a pure yellow oil (**135**) (86 mg, 31 %) followed by recovered starting diamine (74 mg, 50 %). ν_{\max} (neat)/ cm^{-1} 3299 (NH), 1748 (COOCH₃), 1666 (C=O), 1513, 1245 (C-O), 1163 and 1028; δ_{H} (250 MHz CD₃Cl) 1.34 (9 H, s, 3 x CH₃), 1.82 (2 H, brs, NCH₂CH₂), 3.12 (2 H, d, *J* 7.6, CHCH₂), 3.48 – 3.53 (3 H, m, CH₂CHC=O & NCH₂), 3.68 (3 H, s, COOCH₃), 3.88 – 4.21 (2 H, m, NHCH₂C=O), 4.42 (1 H, brs, CH₂CHNH), 4.98 (2 H, s, OCH₂Ph), 6.18 (1 H, brs, NH), 6.90 (2 H, d, *J* 8.5, 2 x Ph-H), 7.20 (2 H, d, *J* 8.5, 2 x Ph-H), 7.33 – 7.40 (5 H, m, 5 x Ph-H), 9.10 (1 H, brs, NH) and 9.15 (1 H, brs, NH); δ_{C} (100 MHz, CD₃Cl) 21.01 (NCH₂CH₂), 27.99 (3 x CH₃), 36.44 (CHCH₂), 36.63 (NCH₂), 41.27 (NHCH₂C=O), 51.78 (CH₂CHC=O), 52.29 (COOCH₃), 55.90 (NHCHCH₂), 69.94 (CH₂O), 81.56 (C(CH₃)₃), 115.32 (2 x CH, 2 x

ArCH), 126.60 (C, ArC), 127.49 (2 x CH, 2 x ArCH), 128.00 (CH, ArCH), 128.56 (2 x CH, 2 x ArCH), 130.41 (2 x CH, 2 x ArCH), 136.80 (C, ArC), 156.28 (C=O), 158.25 (CO, ArCO), 165.54 (N-C=N), 169.59 (C=O) and 169.67 (NHC=O); m/z (FAB) 525.2711 ($MH^+ - C_{28}H_{36}N_4O_6 + H$ requires 525.2713); m/z (FAB) 525 (MH^+ , 100%), 469 (39), 227 (16), 154 (29), 136 (27), 91 (77) and 57 (47).

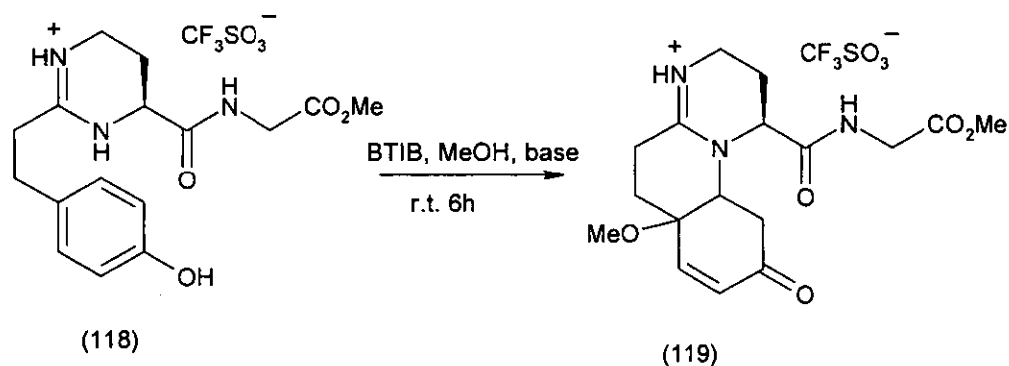
2-[1-(*N*-*tert*-Butoxycarbonylamino)-2-(4-hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium-4-carbonylaminoacetic acid methyl ester triflate salt (136)



To 2-[1-(*N*-*tert*-butoxycarbonylamino)-2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium-4-carbonylaminoacetic acid methyl ester triflate salt (**135**) (55 mg, 0.82 mmol) palladium-carbon (10 %) (11 mg, 20 % w/w) and methanol (30 ml) were added. After degassing the solution, the reaction was carried out by stirring under 1 atmosphere of hydrogen for 10 h. After removal of the solids by filtering through celite and washing with methanol (10 ml), the filtrate was collected and the solvent evaporated under reduced pressure to give as a yellow oil the hydroxyphenyl compound (**136**) (36 mg, 70 %). $[\alpha]_D^{20}$ 33.3 ($c = 10.0$ in MeOH); ν_{\max} (neat)/ cm^{-1} 3355 (NH), 1653 (C=O), 1253 (C-O) and 1030; δ_H (250 MHz CD_3OD) 1.39 (9 H, s, 3 x CH_3), 1.84 – 1.90 (1 H, m, $\text{NCH}_2\text{CH}(\text{H})$), 2.00 – 2.02 (1 H, m, $\text{NCH}_2\text{CH}(\text{H})$), 2.92 (2 H, d, J 7.3, CHCH_2), 3.29 – 3.35 (3 H, m, $\text{CH}_2\text{CHC}=\text{O}$ & NCH_2), 3.70 (3 H, s, COOCH_3), 3.92 – 4.02 (2 H, m, $\text{NHCH}_2\text{C}=\text{O}$), 4.16 – 4.22 (1 H, m, CH_2CHNH), 6.72 (2 H, d, J 8.4, 2 x Ph-H) and 7.08 (2 H, d, J 8.4, 2 x Ph-H); δ_C (100 MHz, CD_3OD) 23.44 (NCH_2CH_2), 28.63 (3 x CH_3),

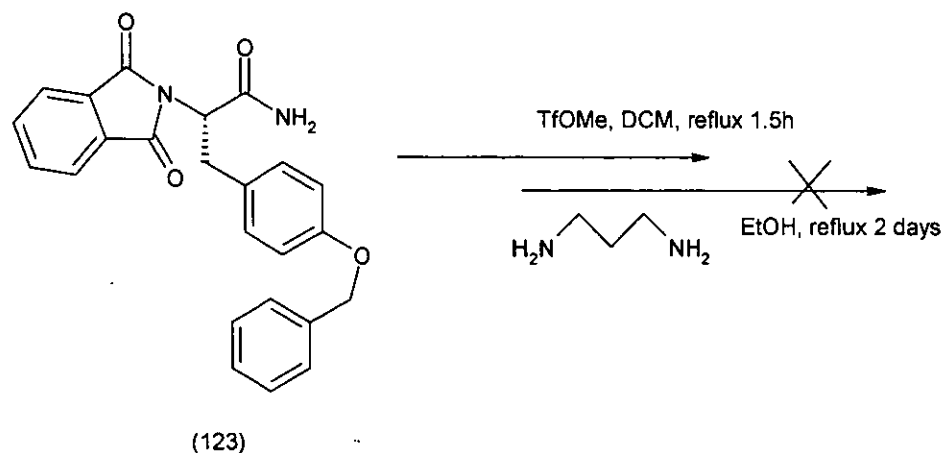
37.80 (CH₂CH₂), 38.56 (NCH₂), 41.91 (NHCH₂C=O), 49.89 (CH₂CHC=O), 55.01 (COOCH₃), 57.84 (CH₂CHNH), 81.30 (C(CH₃)₃), 116.42 (2 x CH, 2 x ArCH), 127.75 (C, ArC), 131.50 (2 x CH, 2 x ArCH), 157.85 (CO, ArCO), 163.66 (N-C=N), 171.39.59 (C=O) and 174.65 (NHC=O); *m/z* (FAB) 435.2239 (MH⁺ - C₂₁H₃₀N₄O₆ + H requires 435.2244); *m/z* (FAB) 435 (MH⁺, 100%), 379 (43), 227 (12), 195 (10), 176 (22), 154 (19), 136 (29), 107 (19) 83 (14), and 57 (32).

Attempted oxidative cyclisation of S-2-[2-(4-hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium-4-carboxylaminoacetic acid methyl ester triflate salt (118) with BTIB



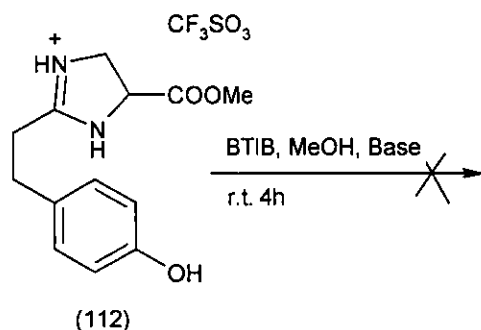
To S-2-[2-(4-hydroxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium-4-carboxylaminoacetic acid methyl ester triflate salt (118) (100 mg, 0.31 mmol) dissolved in methanol (50 ml) was added *bis*(trifluoroacetoxy)iodobenzene (159 mg, 0.37 mmol) and basic alumina (200 mg). After stirring at room temperature for 6 hour, the reaction was stopped by removing the solvent under reduced pressure and the residue was partitioned between petroleum ether and acetonitrile. The acetonitrile layer was collected but initial column chromatography on alumina (DCM : MeOH, 3 - 15 % MeOH) failed to produce any product or starting material. LC-MS of the crude residue after extraction indicated the presence of the oxidative cyclised compound (119). LC-MS *m/z* (ES⁺) 350.64 (MH⁺ - C₁₇H₂₅N₃O₅ + H requires 350.40)

Attempted synthesis of 2-[1-(phthalylamino)-2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt



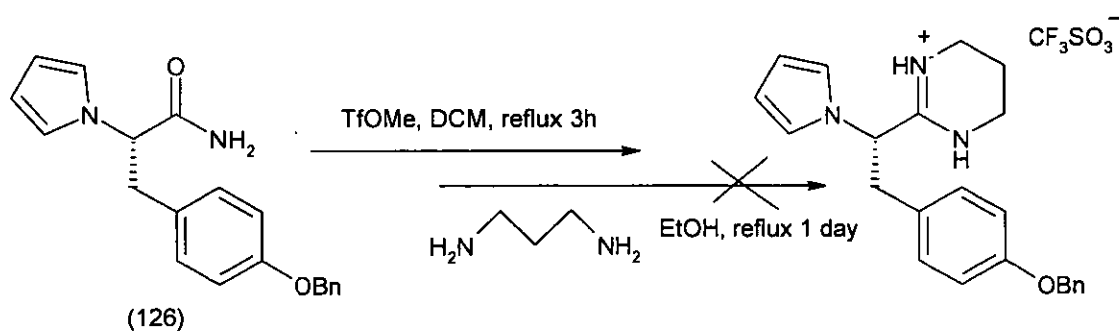
To *N*-phthalyl-*O*-benzyl-*L*-tyrosinamide (**123**) (200 mg, 0.50 mmol) in dry acetonitrile (15 ml) under an atmosphere of nitrogen was added dropwise methyl trifluoromethanesulfonate (0.065 ml, 0.57 mmol, 1.1 mol. equiv.) and the reaction mixture was stirred at reflux for 1.5 h and then for a further 1 day at room temperature. The solvent was removed under reduced pressure to leave a pale yellow white salt. This pale yellow white salt in dry methanol (20 ml) was heated under refluxed with 1,3-diaminopropane (37 mg, 0.042 ml, 0.50 mmol) and diisopropylethylamine (65, mg, 0.087 ml, 0.5 mmol) under an atmosphere of nitrogen for 2 days. The solvent was removed under reduced pressure, and attempts to isolate any product from the residue by flash column chromatography on silica using methanol : dichloromethane (5 : 95 v/v) failed, with no conclusive product being obtained.

Attempted oxidative cyclisation of 2-[2-(4-hydroxyphenyl)ethyl]-4,5-dihydroimidazolium-4-carboxylic acid methyl ester triflate salt (112)



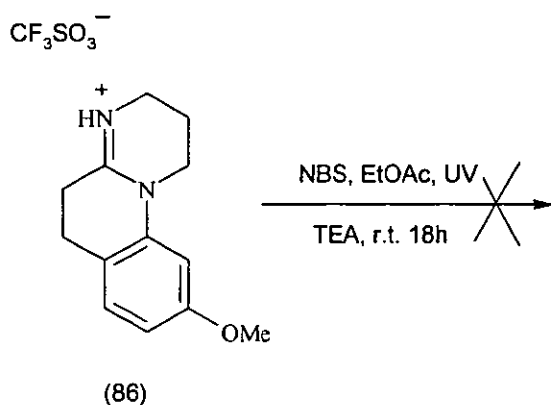
To 2-[2-(4-hydroxyphenyl)ethyl]-4,5-dihydroimidazolium-4-carboxylic acid methyl ester triflate salt (**112**) (157 mg, 0.394 mmol) dissolved in dry methanol (20 ml), was added BTIB reagent (203 mg, 0.473 mmol, 1.2 mol. equiv.) and basic alumina (1 g). The reaction was stirred at ambient temperature for 4 h and the solid alumina was filtered off, the filtrate was evaporated under reduced pressure to give a brown residue. ^1H NMR spectroscopy of the crude residue indicated no signal for the expected methoxy group. Further attempts to purify the crude product on silica or alumina TLC plates failed to give any conclusive identification of the expected product.

Attempted synthesis of S-2-[1-(1-pyrrole)-2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt



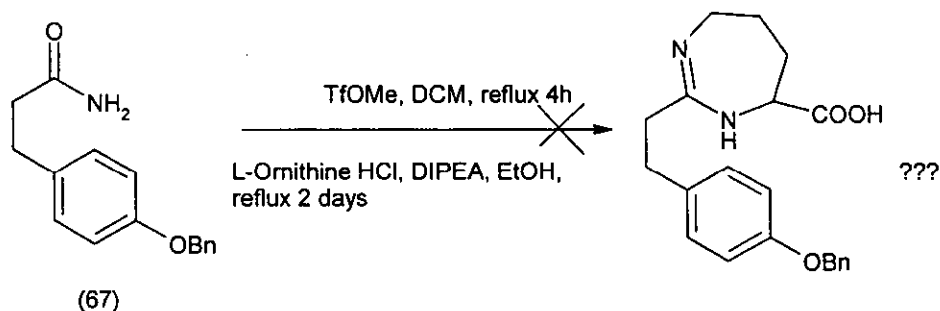
To *N*-pyrrolyl-*O*-benzyl-*L*-tyrosinamide (**126**) (166 mg, 0.518 mmol) in dichloromethane (10 ml) was added methyl trifluoromethanesulfonate (0.07 ml, 0.622 mmol) and the mixture heated at reflux for 3 h then left at room temperature for 1 day. The solvent was removed under reduced pressure and the residue was re-dissolved in ethanol (20 ml) and 1,3-diaminopropane (57mg, 0.065 ml, 0.77 mmol, 1.5 mol. equiv.) and the mixture was heated at reflux for 2 days. The solvent was removed under reduced pressure and the residue was subject to chromatography on silica with methanol : dichloromethane (3 : 97 v/v) but ¹H NMR spectroscopy of the eluent indicated the loss of the pyrrole protecting group.

Bromination of 9-methoxy-2,3,5,6-tetrahydro-1*H*-pyrimido[1,2-*a*]quinolinium triflate salt (**86**)



To 9-methoxy-2,3,5,6-tetrahydro-1*H*-pyrimido-[1,2-*a*]quinolinium triflate salt (**86**) (48 mg, 0.131 mmol) in ethyl acetate (20 ml) was added *N*-bromosuccinimide (NBS) (1.1 mg, 0.144 mmol, 1.1 mol. equiv.) and a few drops of triethylamine. The reaction was irradiated under an ultraviolet lamp for 18 h in a flask fitted with a reflux condenser. The precipitate formed was filtered off and washed with ethyl acetate (5 ml). Neither the precipitate nor the filtrate could be identified as the desired product. The starting material was identified by ¹H NMR spectroscopy of the filtrate after the solvent was removed under reduced pressure.

Attempted synthesis of 2-[2-(4-benzyloxyphenyl)ethyl]-,4,5,6,7-tetrahydrodiazepinium-4-carboxylic acid triflate salt



To 3-(4-benzyloxyphenyl)propanamide (67) (500 mg, 1.96 mmol) in dichloromethane (40 ml) was added methyl trifluoromethanesulfonate (0.33 ml, 2.94 mmol, 1.5 mol. equiv.) and the mixture heated to reflux for 4 hour and then stood at room temperature for 2 days. The solvent was removed and the residue was re-dissolved in ethanol (40 ml) and L-ornithine hydrochloride (661 mg, 3.92 mmol, 2 mol. equiv.) was added with diisopropylethylamine (507 mg, 0.68 ml, 3.92 mmol). The mixture was heated under reflux for 29 h with most of the L-ornithine remaining insoluble. The majority of the starting diamino acid was recovered through filtration. The filtrate was evaporated under reduced pressure for flash column chromatography of the residue using silica with MeOH : DCM (6 : 94 v/v), but there was very little sign of the desired product.

9.0 References

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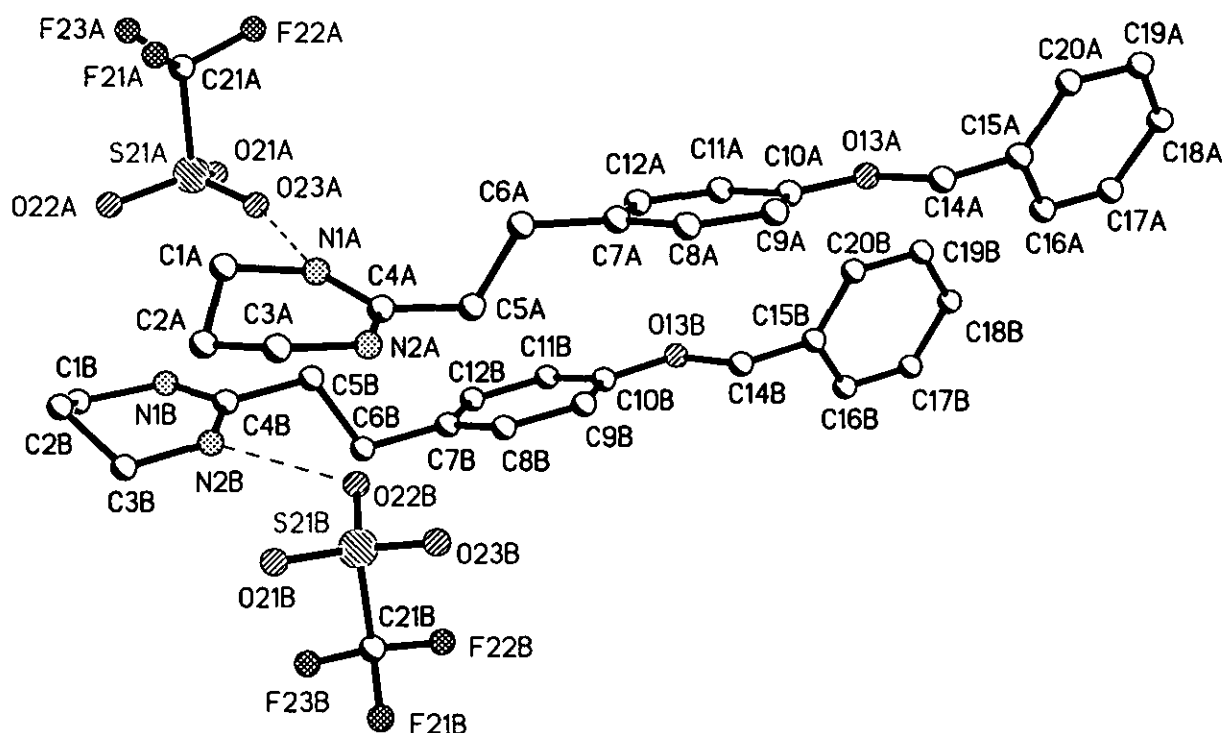
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Appendix I

X-Ray crystal structure of 2-[2-(4-benzyloxyphenyl)ethyl]-3,4,5,6-tetrahydropyrimidinium triflate salt (69)



Data were collected at 150(2) K on a Bruker SMART 1000 diffractometer. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using the SHELXTL suite of programs¹. All the non-hydrogen atoms were refined with anisotropic atomic displacement parameters; hydrogen atoms were inserted at calculated positions using a riding model except for those bonded to nitrogen, which were located from difference maps and not further refined. Details of the data collection and structure refinement are given in Table 1.

1. Sheldrick G.M. (2001). SHELXTL version 6.12, Bruker AXS, Madison, Wisconsin, USA.

The asymmetric unit contains two independent pairs of cations and anions. The triflate anions link the cations into 1D chains running parallel to *b*; there are two independent types of chain, those containing the atoms labeled “A” and those containing the atoms labeled “B”.

Table 1. Crystal data and structure refinement for compd 69.

Identification code	rcfj9	
Empirical formula	C ₂₀ H ₂₃ F ₃ N ₂ O ₄ S	
Formula weight	444.46	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.7172(12) Å	α = 85.946(2)°.
	b = 9.9309(12) Å	β = 88.961(2)°.
	c = 22.313(3) Å	γ = 75.522(2)°.
Volume	2079.6(4) Å ³	
Z	4	
Density (calculated)	1.420 Mg/m ³	
Absorption coefficient	0.212 mm ⁻¹	
F(000)	928	
Crystal size	0.40 x 0.19 x 0.14 mm ³	
Crystal description	Colourless block	
Theta range for data collection	1.83 to 25.00°.	
Index ranges	-11 ≤ h ≤ 11, -11 ≤ k ≤ 11, -26 ≤ l ≤ 26	
Reflections collected	14782	
Independent reflections	7290 [R(int) = 0.0358]	
Completeness to theta = 25.00°	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.869189	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	7290 / 0 / 541	
Goodness-of-fit on F ²	1.037	
Final R indices [I > 2σ(I)]	R1 = 0.0520, wR2 = 0.1348	
R indices (all data)	R1 = 0.0732, wR2 = 0.1492	
Largest diff. peak and hole	0.938 and -0.502 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compd 69. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
N(1A)	9881(2)	4079(2)	3597(1)	25(1)
C(1A)	9968(3)	4277(3)	4239(1)	29(1)
C(2A)	9163(3)	3371(3)	4596(1)	31(1)
C(3A)	9629(3)	1885(3)	4418(1)	31(1)
N(2A)	9568(2)	1878(2)	3763(1)	26(1)
C(4A)	9676(3)	2925(3)	3395(1)	23(1)
C(5A)	9685(3)	2753(3)	2737(1)	27(1)
C(6A)	11195(3)	2039(3)	2547(1)	35(1)
C(7A)	11358(3)	1628(3)	1909(1)	27(1)
C(8A)	11727(3)	237(3)	1784(1)	31(1)
C(9A)	12015(3)	-163(3)	1203(1)	30(1)
C(10A)	11934(3)	839(3)	736(1)	24(1)
C(11A)	11534(3)	2242(3)	850(1)	29(1)
C(12A)	11246(3)	2625(3)	1429(1)	30(1)
O(13A)	12245(2)	575(2)	146(1)	32(1)
C(14A)	12659(3)	-859(3)	14(1)	36(1)
C(15A)	13004(3)	-944(3)	-641(1)	28(1)
C(16A)	11935(3)	-456(3)	-1067(1)	35(1)
C(17A)	12231(3)	-575(3)	-1670(1)	39(1)
C(18A)	13590(4)	-1194(3)	-1857(1)	40(1)
C(19A)	14661(3)	-1680(3)	-1437(1)	38(1)
C(20A)	14369(3)	-1548(3)	-831(1)	32(1)
N(1B)	6263(2)	8824(2)	3690(1)	27(1)
C(1B)	5948(3)	9129(3)	4319(1)	31(1)
C(2B)	6453(3)	7812(3)	4718(1)	28(1)
C(3B)	5861(3)	6664(3)	4493(1)	29(1)
N(2B)	6195(2)	6549(2)	3854(1)	27(1)
C(4B)	6402(3)	7586(3)	3493(1)	24(1)
C(5B)	6785(3)	7337(3)	2852(1)	27(1)
C(6B)	5531(3)	7174(3)	2476(1)	27(1)
C(7B)	6023(3)	6717(3)	1860(1)	23(1)
C(8B)	6517(3)	5310(3)	1763(1)	26(1)
C(9B)	6986(3)	4866(3)	1203(1)	26(1)

C(10B)	6959(3)	5838(3)	726(1)	24(1)
C(11B)	6470(3)	7255(3)	816(1)	25(1)
C(12B)	6004(3)	7679(3)	1375(1)	26(1)
O(13B)	7404(2)	5539(2)	153(1)	31(1)
C(14B)	7792(3)	4097(3)	28(1)	32(1)
C(15B)	8145(3)	3988(3)	-626(1)	25(1)
C(16B)	7083(3)	4337(3)	-1059(1)	33(1)
C(17B)	7412(3)	4178(3)	-1659(1)	37(1)
C(18B)	8797(3)	3656(3)	-1836(1)	35(1)
C(19B)	9861(3)	3310(3)	-1412(1)	36(1)
C(20B)	9539(3)	3474(3)	-809(1)	30(1)
S(21B)	5967(1)	2835(1)	3627(1)	25(1)
O(21B)	5961(2)	2757(3)	4267(1)	49(1)
O(22B)	6435(2)	3992(2)	3339(1)	33(1)
O(23B)	6553(2)	1541(2)	3365(1)	38(1)
C(21B)	4101(3)	3227(3)	3428(2)	48(1)
F(21B)	3516(2)	2209(2)	3635(1)	57(1)
F(22B)	3952(2)	3372(3)	2837(1)	91(1)
F(23B)	3392(2)	4351(3)	3660(2)	118(1)
S(21A)	10049(1)	8205(1)	3572(1)	24(1)
O(21A)	9661(2)	9351(2)	3130(1)	35(1)
O(22A)	9496(2)	8506(3)	4158(1)	48(1)
O(23A)	9964(2)	6900(2)	3373(1)	46(1)
C(21A)	11939(3)	7990(3)	3675(1)	40(1)
F(21A)	12455(2)	6986(2)	4095(1)	58(1)
F(22A)	12652(2)	7669(3)	3179(1)	79(1)
F(23A)	12213(2)	9150(2)	3845(1)	81(1)

Table 3. Bond lengths [Å] and angles [°] for compd 69.

N(1A)-C(4A)	1.321(3)	C(5B)-C(6B)	1.539(4)
N(1A)-C(1A)	1.467(3)	C(6B)-C(7B)	1.511(3)
C(1A)-C(2A)	1.510(4)	C(7B)-C(12B)	1.388(4)
C(2A)-C(3A)	1.511(4)	C(7B)-C(8B)	1.390(4)
C(3A)-N(2A)	1.464(3)	C(8B)-C(9B)	1.386(3)
N(2A)-C(4A)	1.304(3)	C(9B)-C(10B)	1.382(4)
C(4A)-C(5A)	1.490(3)	C(10B)-O(13B)	1.371(3)
C(5A)-C(6A)	1.528(4)	C(10B)-C(11B)	1.396(4)
C(6A)-C(7A)	1.504(3)	C(11B)-C(12B)	1.379(3)
C(7A)-C(8A)	1.384(4)	O(13B)-C(14B)	1.433(3)
C(7A)-C(12A)	1.393(4)	C(14B)-C(15B)	1.497(3)
C(8A)-C(9A)	1.387(4)	C(15B)-C(20B)	1.388(4)
C(9A)-C(10A)	1.377(4)	C(15B)-C(16B)	1.388(4)
C(10A)-O(13A)	1.376(3)	C(16B)-C(17B)	1.381(4)
C(10A)-C(11A)	1.390(4)	C(17B)-C(18B)	1.377(4)
C(11A)-C(12A)	1.377(3)	C(18B)-C(19B)	1.377(4)
O(13A)-C(14A)	1.429(3)	C(19B)-C(20B)	1.387(4)
C(14A)-C(15A)	1.497(4)	S(21B)-O(21B)	1.424(2)
C(15A)-C(20A)	1.385(4)	S(21B)-O(23B)	1.4301(19)
C(15A)-C(16A)	1.391(4)	S(21B)-O(22B)	1.4439(19)
C(16A)-C(17A)	1.379(4)	S(21B)-C(21B)	1.813(3)
C(17A)-C(18A)	1.381(5)	C(21B)-F(23B)	1.293(4)
C(18A)-C(19A)	1.384(4)	C(21B)-F(22B)	1.324(4)
C(19A)-C(20A)	1.384(4)	C(21B)-F(21B)	1.330(4)
N(1B)-C(4B)	1.310(3)	S(21A)-O(23A)	1.421(2)
N(1B)-C(1B)	1.466(3)	S(21A)-O(22A)	1.427(2)
C(1B)-C(2B)	1.508(4)	S(21A)-O(21A)	1.4322(19)
C(2B)-C(3B)	1.518(4)	S(21A)-C(21A)	1.813(3)
C(3B)-N(2B)	1.461(3)	C(21A)-F(22A)	1.309(3)
N(2B)-C(4B)	1.315(3)	C(21A)-F(21A)	1.326(3)
C(4B)-C(5B)	1.493(3)	C(21A)-F(23A)	1.327(4)
C(4A)-N(1A)-C(1A)	122.8(2)	C(4A)-N(2A)-C(3A)	123.8(2)
N(1A)-C(1A)-C(2A)	109.5(2)	N(2A)-C(4A)-N(1A)	121.1(2)
C(1A)-C(2A)-C(3A)	110.5(2)	N(2A)-C(4A)-C(5A)	118.5(2)
N(2A)-C(3A)-C(2A)	109.1(2)	N(1A)-C(4A)-C(5A)	120.2(2)

C(4A)-C(5A)-C(6A)	108.8(2)	O(13B)-C(10B)-C(11B)	115.1(2)
C(7A)-C(6A)-C(5A)	115.6(2)	C(9B)-C(10B)-C(11B)	119.5(2)
C(8A)-C(7A)-C(12A)	118.0(2)	C(12B)-C(11B)-C(10B)	120.2(2)
C(8A)-C(7A)-C(6A)	120.6(2)	C(11B)-C(12B)-C(7B)	121.1(2)
C(12A)-C(7A)-C(6A)	121.2(2)	C(10B)-O(13B)-C(14B)	116.82(19)
C(7A)-C(8A)-C(9A)	121.4(2)	O(13B)-C(14B)-C(15B)	108.9(2)
C(10A)-C(9A)-C(8A)	119.7(3)	C(20B)-C(15B)-C(16B)	118.6(2)
O(13A)-C(10A)-C(9A)	125.1(2)	C(20B)-C(15B)-C(14B)	120.4(2)
O(13A)-C(10A)-C(11A)	115.0(2)	C(16B)-C(15B)-C(14B)	120.9(3)
C(9A)-C(10A)-C(11A)	119.8(2)	C(17B)-C(16B)-C(15B)	120.5(3)
C(12A)-C(11A)-C(10A)	119.9(2)	C(18B)-C(17B)-C(16B)	120.5(3)
C(11A)-C(12A)-C(7A)	121.1(3)	C(19B)-C(18B)-C(17B)	119.5(3)
C(10A)-O(13A)-C(14A)	116.41(19)	C(18B)-C(19B)-C(20B)	120.2(3)
O(13A)-C(14A)-C(15A)	108.9(2)	C(19B)-C(20B)-C(15B)	120.6(3)
C(20A)-C(15A)-C(16A)	119.1(3)	O(21B)-S(21B)-O(23B)	114.99(13)
C(20A)-C(15A)-C(14A)	120.9(3)	O(21B)-S(21B)-O(22B)	115.51(12)
C(16A)-C(15A)-C(14A)	119.9(3)	O(23B)-S(21B)-O(22B)	113.56(11)
C(17A)-C(16A)-C(15A)	120.4(3)	O(21B)-S(21B)-C(21B)	103.95(15)
C(16A)-C(17A)-C(18A)	120.3(3)	O(23B)-S(21B)-C(21B)	103.31(15)
C(17A)-C(18A)-C(19A)	119.7(3)	O(22B)-S(21B)-C(21B)	103.38(13)
C(18A)-C(19A)-C(20A)	120.1(3)	F(23B)-C(21B)-F(22B)	109.4(3)
C(19A)-C(20A)-C(15A)	120.4(3)	F(23B)-C(21B)-F(21B)	106.7(3)
C(4B)-N(1B)-C(1B)	123.2(2)	F(22B)-C(21B)-F(21B)	108.1(3)
N(1B)-C(1B)-C(2B)	109.5(2)	F(23B)-C(21B)-S(21B)	111.3(3)
C(1B)-C(2B)-C(3B)	109.6(2)	F(22B)-C(21B)-S(21B)	110.2(2)
N(2B)-C(3B)-C(2B)	108.8(2)	F(21B)-C(21B)-S(21B)	111.1(2)
C(4B)-N(2B)-C(3B)	123.7(2)	O(23A)-S(21A)-O(22A)	115.78(14)
N(1B)-C(4B)-N(2B)	120.6(2)	O(23A)-S(21A)-O(21A)	114.64(12)
N(1B)-C(4B)-C(5B)	120.2(2)	O(22A)-S(21A)-O(21A)	114.40(13)
N(2B)-C(4B)-C(5B)	119.1(2)	O(23A)-S(21A)-C(21A)	103.38(14)
C(4B)-C(5B)-C(6B)	113.2(2)	O(22A)-S(21A)-C(21A)	102.44(13)
C(7B)-C(6B)-C(5B)	111.0(2)	O(21A)-S(21A)-C(21A)	103.83(13)
C(12B)-C(7B)-C(8B)	118.0(2)	F(22A)-C(21A)-F(21A)	107.6(3)
C(12B)-C(7B)-C(6B)	121.4(2)	F(22A)-C(21A)-F(23A)	107.6(3)
C(8B)-C(7B)-C(6B)	120.6(2)	F(21A)-C(21A)-F(23A)	107.3(3)
C(9B)-C(8B)-C(7B)	121.6(2)	F(22A)-C(21A)-S(21A)	111.8(2)
C(10B)-C(9B)-C(8B)	119.6(2)	F(21A)-C(21A)-S(21A)	111.2(2)
O(13B)-C(10B)-C(9B)	125.4(2)	F(23A)-C(21A)-S(21A)	111.2

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compd 69. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1A)	36(1)	21(1)	21(1)	-4(1)	1(1)	-10(1)
C(1A)	39(2)	27(1)	23(1)	-6(1)	-2(1)	-12(1)
C(2A)	41(2)	30(2)	24(1)	-7(1)	1(1)	-10(1)
C(3A)	45(2)	25(1)	24(2)	0(1)	-2(1)	-11(1)
N(2A)	36(1)	19(1)	24(1)	-4(1)	-2(1)	-9(1)
C(4A)	21(1)	22(1)	25(1)	-4(1)	0(1)	-4(1)
C(5A)	34(2)	25(1)	23(1)	-4(1)	-2(1)	-7(1)
C(6A)	35(2)	52(2)	20(1)	-5(1)	1(1)	-14(1)
C(7A)	24(1)	38(2)	22(1)	-6(1)	2(1)	-13(1)
C(8A)	34(2)	34(2)	23(1)	5(1)	3(1)	-6(1)
C(9A)	36(2)	24(1)	27(2)	-2(1)	7(1)	-6(1)
C(10A)	28(1)	26(1)	22(1)	-3(1)	2(1)	-12(1)
C(11A)	40(2)	24(1)	24(1)	-1(1)	2(1)	-12(1)
C(12A)	39(2)	26(1)	27(2)	-9(1)	2(1)	-11(1)
O(13A)	53(1)	23(1)	20(1)	-5(1)	9(1)	-12(1)
C(14A)	55(2)	21(1)	32(2)	-5(1)	11(1)	-8(1)
C(15A)	43(2)	19(1)	25(1)	-5(1)	6(1)	-11(1)
C(16A)	34(2)	31(2)	42(2)	-5(1)	4(1)	-10(1)
C(17A)	52(2)	37(2)	32(2)	-3(1)	-10(1)	-19(2)
C(18A)	65(2)	35(2)	23(2)	-9(1)	8(1)	-18(2)
C(19A)	42(2)	36(2)	35(2)	-8(1)	14(1)	-7(1)
C(20A)	33(2)	30(2)	32(2)	-3(1)	2(1)	-7(1)
N(1B)	40(1)	21(1)	24(1)	-1(1)	0(1)	-12(1)
C(1B)	45(2)	24(1)	26(2)	-8(1)	3(1)	-11(1)
C(2B)	30(2)	33(2)	23(1)	-6(1)	3(1)	-11(1)
C(3B)	37(2)	26(1)	24(1)	1(1)	3(1)	-11(1)
N(2B)	38(1)	20(1)	26(1)	-7(1)	5(1)	-12(1)
C(4B)	23(1)	24(1)	24(1)	-2(1)	-1(1)	-7(1)
C(5B)	27(2)	33(2)	25(1)	-4(1)	2(1)	-12(1)
C(6B)	24(1)	33(2)	24(1)	-5(1)	3(1)	-6(1)
C(7B)	20(1)	31(1)	22(1)	-4(1)	1(1)	-10(1)

C(8B)	29(2)	29(1)	21(1)	2(1)	2(1)	-9(1)
C(9B)	31(2)	22(1)	25(1)	-4(1)	2(1)	-8(1)
C(10B)	26(1)	28(1)	22(1)	-5(1)	3(1)	-12(1)
C(11B)	32(2)	24(1)	23(1)	0(1)	1(1)	-12(1)
C(12B)	30(2)	25(1)	26(1)	-7(1)	1(1)	-8(1)
O(13B)	52(1)	23(1)	22(1)	-7(1)	10(1)	-16(1)
C(14B)	47(2)	21(1)	27(2)	-3(1)	7(1)	-8(1)
C(15B)	36(2)	18(1)	24(1)	-4(1)	4(1)	-12(1)
C(16B)	31(2)	32(2)	35(2)	3(1)	3(1)	-8(1)
C(17B)	45(2)	42(2)	30(2)	2(1)	-8(1)	-22(2)
C(18B)	54(2)	34(2)	22(2)	-7(1)	8(1)	-20(1)
C(19B)	37(2)	36(2)	34(2)	-5(1)	10(1)	-8(1)
C(20B)	33(2)	31(2)	27(2)	-2(1)	-1(1)	-9(1)
S(21B)	29(1)	23(1)	24(1)	-4(1)	1(1)	-10(1)
O(21B)	54(1)	83(2)	24(1)	-11(1)	5(1)	-40(1)
O(22B)	39(1)	21(1)	42(1)	-5(1)	5(1)	-13(1)
O(23B)	47(1)	19(1)	49(1)	-6(1)	7(1)	-9(1)
C(21B)	32(2)	45(2)	63(2)	13(2)	-8(2)	-11(2)
F(21B)	45(1)	81(2)	55(1)	18(1)	-13(1)	-40(1)
F(22B)	66(2)	142(2)	72(2)	62(2)	-44(1)	-59(2)
F(23B)	38(1)	62(2)	243(4)	-17(2)	27(2)	10(1)
S(21A)	25(1)	22(1)	25(1)	-1(1)	0(1)	-8(1)
O(21A)	45(1)	24(1)	36(1)	3(1)	-7(1)	-9(1)
O(22A)	30(1)	81(2)	28(1)	-4(1)	7(1)	-3(1)
O(23A)	59(2)	21(1)	61(2)	0(1)	-17(1)	-15(1)
C(21A)	30(2)	42(2)	45(2)	2(2)	4(1)	-7(1)
F(21A)	34(1)	67(1)	64(1)	12(1)	-11(1)	4(1)
F(22A)	39(1)	116(2)	70(2)	6(1)	30(1)	-1(1)
F(23A)	49(1)	63(1)	143(2)	-13(1)	-33(1)	-29(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$) for compd 69.

	x	y	z	U(eq)
H(1A1)	9556	5268	4314	34
H(1A2)	10975	4025	4368	34
H(2A1)	8131	3737	4522	37
H(2A2)	9337	3398	5030	37
H(3A1)	10611	1458	4560	37
H(3A2)	8998	1333	4607	37
H(5A1)	9367	3676	2515	33
H(5A2)	9026	2181	2644	33
H(6A1)	11814	2673	2606	42
H(6A2)	11543	1191	2817	42
H(8A)	11784	-459	2104	37
H(9A)	12267	-1123	1127	35
H(11A)	11461	2936	528	34
H(12A)	10967	3586	1502	36
H(14A)	11877	-1310	116	43
H(14B)	13502	-1351	257	43
H(16A)	10995	-38	-941	42
H(17A)	11497	-231	-1958	47
H(18A)	13790	-1284	-2273	48
H(19A)	15597	-2106	-1564	46
H(20A)	15110	-1873	-545	38
H(1B1)	4912	9503	4370	38
H(1B2)	6431	9841	4432	38
H(2B1)	6132	7984	5136	34
H(2B2)	7505	7523	4717	34
H(3B1)	6287	5769	4720	34
H(3B2)	4819	6886	4552	34
H(5B1)	7568	6483	2838	33
H(5B2)	7137	8127	2671	33
H(6B1)	5087	6476	2685	33
H(6B2)	4806	8075	2435	33

H(8B)	6534	4636	2089	31
H(9B)	7323	3900	1147	31
H(11B)	6459	7929	490	30
H(12B)	5664	8646	1431	31
H(14C)	6995	3667	130	38
H(14D)	8625	3596	274	38
H(16B)	6123	4687	-941	39
H(17B)	6677	4432	-1951	44
H(18B)	9016	3536	-2249	42
H(19B)	10819	2957	-1532	43
H(20B)	10279	3233	-519	36
H(1NA)	9951	4812	3332	40
H(2NA)	9400	1139	3601	40
H(1NB)	6441	9536	3463	40
H(2NB)	6315	5681	3720	40

Table 6. Torsion angles [°] for compd 69.

C(4A)-N(1A)-C(1A)-C(2A)	-25.6(3)
N(1A)-C(1A)-C(2A)-C(3A)	51.0(3)
C(1A)-C(2A)-C(3A)-N(2A)	-50.9(3)
C(2A)-C(3A)-N(2A)-C(4A)	25.7(4)
C(3A)-N(2A)-C(4A)-N(1A)	1.4(4)
C(3A)-N(2A)-C(4A)-C(5A)	176.3(2)
C(1A)-N(1A)-C(4A)-N(2A)	-1.4(4)
C(1A)-N(1A)-C(4A)-C(5A)	-176.3(2)
N(2A)-C(4A)-C(5A)-C(6A)	-83.4(3)
N(1A)-C(4A)-C(5A)-C(6A)	91.6(3)
C(4A)-C(5A)-C(6A)-C(7A)	172.9(2)
C(5A)-C(6A)-C(7A)-C(8A)	-112.7(3)
C(5A)-C(6A)-C(7A)-C(12A)	72.1(3)
C(12A)-C(7A)-C(8A)-C(9A)	1.6(4)
C(6A)-C(7A)-C(8A)-C(9A)	-173.7(3)
C(7A)-C(8A)-C(9A)-C(10A)	0.0(4)
C(8A)-C(9A)-C(10A)-O(13A)	177.4(2)
C(8A)-C(9A)-C(10A)-C(11A)	-1.4(4)
O(13A)-C(10A)-C(11A)-C(12A)	-177.8(2)
C(9A)-C(10A)-C(11A)-C(12A)	1.1(4)
C(10A)-C(11A)-C(12A)-C(7A)	0.5(4)
C(8A)-C(7A)-C(12A)-C(11A)	-1.9(4)
C(6A)-C(7A)-C(12A)-C(11A)	173.5(2)
C(9A)-C(10A)-O(13A)-C(14A)	1.2(4)
C(11A)-C(10A)-O(13A)-C(14A)	180.0(2)
C(10A)-O(13A)-C(14A)-C(15A)	-178.0(2)
O(13A)-C(14A)-C(15A)-C(20A)	115.6(3)
O(13A)-C(14A)-C(15A)-C(16A)	-66.6(3)
C(20A)-C(15A)-C(16A)-C(17A)	0.2(4)
C(14A)-C(15A)-C(16A)-C(17A)	-177.7(2)
C(15A)-C(16A)-C(17A)-C(18A)	0.6(4)
C(16A)-C(17A)-C(18A)-C(19A)	-0.7(4)
C(17A)-C(18A)-C(19A)-C(20A)	0.0(4)
C(18A)-C(19A)-C(20A)-C(15A)	0.8(4)

C(16A)-C(15A)-C(20A)-C(19A)	-0.9(4)
C(14A)-C(15A)-C(20A)-C(19A)	176.9(2)
C(4B)-N(1B)-C(1B)-C(2B)	25.3(4)
N(1B)-C(1B)-C(2B)-C(3B)	-52.1(3)
C(1B)-C(2B)-C(3B)-N(2B)	52.3(3)
C(2B)-C(3B)-N(2B)-C(4B)	-26.1(4)
C(1B)-N(1B)-C(4B)-N(2B)	3.2(4)
C(1B)-N(1B)-C(4B)-C(5B)	-177.4(2)
C(3B)-N(2B)-C(4B)-N(1B)	-2.6(4)
C(3B)-N(2B)-C(4B)-C(5B)	178.0(2)
N(1B)-C(4B)-C(5B)-C(6B)	-106.7(3)
N(2B)-C(4B)-C(5B)-C(6B)	72.8(3)
C(4B)-C(5B)-C(6B)-C(7B)	-171.7(2)
C(5B)-C(6B)-C(7B)-C(12B)	-92.3(3)
C(5B)-C(6B)-C(7B)-C(8B)	87.4(3)
C(12B)-C(7B)-C(8B)-C(9B)	0.3(4)
C(6B)-C(7B)-C(8B)-C(9B)	-179.4(2)
C(7B)-C(8B)-C(9B)-C(10B)	-0.3(4)
C(8B)-C(9B)-C(10B)-O(13B)	179.3(2)
C(8B)-C(9B)-C(10B)-C(11B)	0.5(4)
O(13B)-C(10B)-C(11B)-C(12B)	-179.6(2)
C(9B)-C(10B)-C(11B)-C(12B)	-0.7(4)
C(10B)-C(11B)-C(12B)-C(7B)	0.7(4)
C(8B)-C(7B)-C(12B)-C(11B)	-0.5(4)
C(6B)-C(7B)-C(12B)-C(11B)	179.2(2)
C(9B)-C(10B)-O(13B)-C(14B)	6.6(4)
C(11B)-C(10B)-O(13B)-C(14B)	-174.5(2)
C(10B)-O(13B)-C(14B)-C(15B)	176.0(2)
O(13B)-C(14B)-C(15B)-C(20B)	109.4(3)
O(13B)-C(14B)-C(15B)-C(16B)	-73.6(3)
C(20B)-C(15B)-C(16B)-C(17B)	-0.2(4)
C(14B)-C(15B)-C(16B)-C(17B)	-177.3(2)
C(15B)-C(16B)-C(17B)-C(18B)	0.8(4)
C(16B)-C(17B)-C(18B)-C(19B)	-1.0(4)
C(17B)-C(18B)-C(19B)-C(20B)	0.6(4)
C(18B)-C(19B)-C(20B)-C(15B)	0.0(4)

C(16B)-C(15B)-C(20B)-C(19B)	-0.2(4)
C(14B)-C(15B)-C(20B)-C(19B)	176.9(2)
O(21B)-S(21B)-C(21B)-F(23B)	56.5(3)
O(23B)-S(21B)-C(21B)-F(23B)	176.9(3)
O(22B)-S(21B)-C(21B)-F(23B)	-64.5(3)
O(21B)-S(21B)-C(21B)-F(22B)	178.0(2)
O(23B)-S(21B)-C(21B)-F(22B)	-61.6(3)
O(22B)-S(21B)-C(21B)-F(22B)	57.0(3)
O(21B)-S(21B)-C(21B)-F(21B)	-62.3(3)
O(23B)-S(21B)-C(21B)-F(21B)	58.1(3)
O(22B)-S(21B)-C(21B)-F(21B)	176.7(2)
O(23A)-S(21A)-C(21A)-F(22A)	57.8(3)
O(22A)-S(21A)-C(21A)-F(22A)	178.5(2)
O(21A)-S(21A)-C(21A)-F(22A)	-62.2(2)
O(23A)-S(21A)-C(21A)-F(21A)	-62.5(2)
O(22A)-S(21A)-C(21A)-F(21A)	58.2(3)
O(21A)-S(21A)-C(21A)-F(21A)	177.5(2)
O(23A)-S(21A)-C(21A)-F(23A)	178.0(2)
O(22A)-S(21A)-C(21A)-F(23A)	-61.3(3)
O(21A)-S(21A)-C(21A)-F(23A)	58.0(3)

Table 7. Hydrogen bonds for compd 69 [\AA and $^\circ$].

D-H...A	d(D-H)	d(H...A)	d(D...A)	\angle (DHA)
N(1A)-H(1NA)...O(23A)	0.92	2.09	2.831(3)	137.4
N(2A)-H(2NA)...O(21A)#1	0.89	2.09	2.947(3)	162.0
N(1B)-H(1NB)...O(23B)#2	0.89	2.02	2.825(3)	150.1
N(2B)-H(2NB)...O(22B)	0.91	1.91	2.816(3)	172.0

Symmetry transformations used to generate equivalent atoms:

#1 $x, y-1, z$ #2 $x, y+1, z$

Appendix II

X-ray crystal structure of 6a-Ethoxy-2,3,6,6a,10,10a-hexahydro-1*H*,5*H*-pyrimido[1,2-*a*]quinolin-9-one triflate salt (77) in *cis*-formation

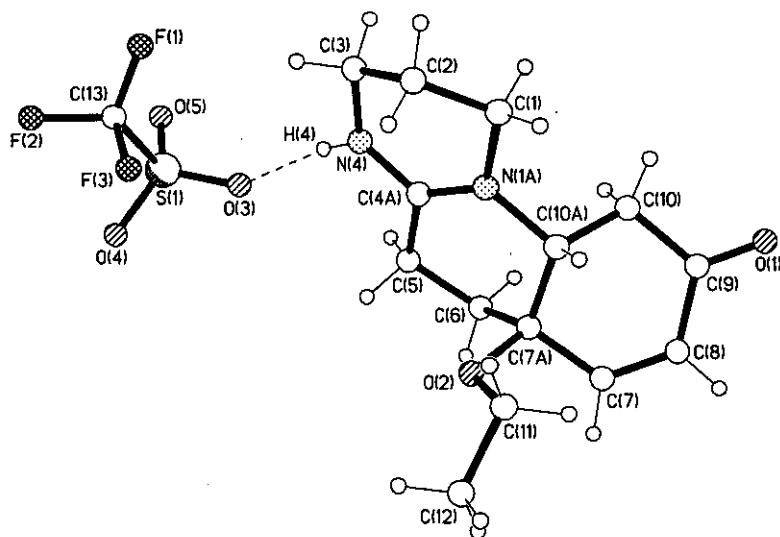


Table 1. Crystal data and structure refinement for compd 77.

Identification code	rcfj12	
Chemical formula	$C_{15}H_{21}F_3N_2O_5S$	
Formula weight	398.40	
Temperature	150(2) K	
Radiation, wavelength	MoK α , 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/c$	
Unit cell parameters	$a = 10.3397(8)$ Å	$\alpha = 90^\circ$
	$b = 17.5817(14)$ Å	$\beta = 114.243(2)^\circ$
	$c = 10.9510(9)$ Å	$\gamma = 90^\circ$
Cell volume	$1815.2(3)$ Å ³	
Z	4	

Calculated density	1.458 g/cm ³
Absorption coefficient μ	0.237 mm ⁻¹
F(000)	832
Crystal colour and size	colourless, 0.30 × 0.16 × 0.04 mm ³
Reflections for cell refinement	3181 (θ range 2.16 to 26.69°)
Data collection method	Bruker SMART 1000 CCD diffractometer ω rotation with narrow frames
θ range for data collection	2.16 to 25.00°
Index ranges	h -12 to 12, k -20 to 20, l -13 to 13
Completeness to $\theta = 25.00^\circ$	100.0 %
Intensity decay	0%
Reflections collected	13091
Independent reflections	3196 ($R_{\text{int}} = 0.0406$)
Reflections with $F^2 > 2\sigma$	2134
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.932 and 0.991
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0350, 3.7526
Data / restraints / parameters	3196 / 86 / 267
Final R indices [$F^2 > 2\sigma$]	R1 = 0.0540, wR2 = 0.1143
R indices (all data)	R1 = 0.0899, wR2 = 0.1386
Goodness-of-fit on F^2	1.048
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.505 and -0.419 e Å ⁻³

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (\AA^2) for compd 77. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1A)	0.2837(3)	0.36176(17)	0.2787(3)	0.0294(7)
C(1)	0.4172(4)	0.3310(2)	0.3797(3)	0.0394(10)
C(2)	0.5405(4)	0.3544(3)	0.3482(4)	0.0485(11)
C(3)	0.5148(4)	0.3320(3)	0.2070(4)	0.0453(11)
N(4)	0.3711(3)	0.35431(19)	0.1169(3)	0.0336(8)
C(4A)	0.2676(4)	0.36931(19)	0.1531(3)	0.0280(8)
C(5)	0.1314(4)	0.3963(2)	0.0454(3)	0.0315(8)
C(6)	0.0077(4)	0.3982(2)	0.0859(3)	0.0306(8)
C(7A)	0.0566(4)	0.4302(2)	0.2278(3)	0.0290(8)
C(7)	-0.0659(4)	0.4364(2)	0.2678(4)	0.0350(9)
C(8)	-0.0936(4)	0.3873(2)	0.3451(4)	0.0389(9)
C(9)	-0.0099(5)	0.3185(2)	0.3954(4)	0.0436(10)
O(1)	-0.0380(4)	0.27242(17)	0.4643(4)	0.0683(10)
C(10)	0.1109(4)	0.3047(2)	0.3538(4)	0.0353(9)
C(10A)	0.1711(4)	0.37874(19)	0.3251(3)	0.0284(8)
O(2)	0.1097(3)	0.50451(13)	0.2203(2)	0.0314(6)
C(11)	0.1597(4)	0.5488(2)	0.3418(3)	0.0363(9)
C(12)	0.1281(6)	0.6302(2)	0.3049(4)	0.0592(14)
C(13)	0.5297(6)	0.4099(3)	-0.1689(6)	0.0795(13)
F(1)	0.6128(19)	0.3588(9)	-0.0857(17)	0.117(5)
F(2)	0.5995(14)	0.4464(11)	-0.2334(16)	0.133(4)
F(3)	0.5271(18)	0.4682(7)	-0.0864(14)	0.137(4)
F(1X)	0.5803(13)	0.3497(5)	-0.0863(10)	0.071(2)
F(2X)	0.5891(9)	0.3983(10)	-0.2597(8)	0.117(3)
F(3X)	0.5769(11)	0.4724(4)	-0.1073(12)	0.113(3)
S(1)	0.34277(12)	0.39427(6)	-0.26301(9)	0.0398(3)
O(3)	0.2926(3)	0.3860(2)	-0.1606(3)	0.0673(10)
O(4)	0.2923(5)	0.4595(2)	-0.3465(4)	0.0841(12)
O(5)	0.3401(4)	0.3266(2)	-0.3337(3)	0.0804(12)

Table 3. Bond lengths [Å] and angles [°] for compd 77.

N(1A)–C(4A)	1.322(4)	N(1A)–C(1)	1.472(5)
N(1A)–C(10A)	1.480(4)	C(1)–C(2)	1.509(5)
C(2)–C(3)	1.509(5)	C(3)–N(4)	1.460(5)
N(4)–C(4A)	1.312(5)	C(4A)–C(5)	1.495(5)
C(5)–C(6)	1.517(5)	C(6)–C(7A)	1.530(5)
C(7A)–O(2)	1.432(4)	C(7A)–C(7)	1.504(5)
C(7A)–C(10A)	1.523(5)	C(7)–C(8)	1.320(5)
C(8)–C(9)	1.457(6)	C(9)–O(1)	1.221(5)
C(9)–C(10)	1.515(5)	C(10)–C(10A)	1.530(5)
O(2)–C(11)	1.442(4)	C(11)–C(12)	1.486(5)
C(13)–F(3X)	1.277(7)	C(13)–F(1)	1.316(8)
C(13)–F(1X)	1.350(7)	C(13)–F(2)	1.360(8)
C(13)–F(3)	1.374(8)	C(13)–F(2X)	1.381(8)
C(13)–S(1)	1.800(6)	S(1)–O(5)	1.413(3)
S(1)–O(3)	1.423(3)	S(1)–O(4)	1.425(3)
C(4A)–N(1A)–C(1)	119.8(3)	C(4A)–N(1A)–C(10A)	123.8(3)
C(1)–N(1A)–C(10A)	116.3(3)	N(1A)–C(1)–C(2)	110.3(3)
C(1)–C(2)–C(3)	110.7(3)	N(4)–C(3)–C(2)	109.0(3)
C(4A)–N(4)–C(3)	125.4(3)	N(4)–C(4A)–N(1A)	121.6(3)
N(4)–C(4A)–C(5)	116.5(3)	N(1A)–C(4A)–C(5)	121.9(3)
C(4A)–C(5)–C(6)	114.2(3)	C(5)–C(6)–C(7A)	109.8(3)
O(2)–C(7A)–C(7)	109.8(3)	O(2)–C(7A)–C(10A)	112.1(3)
C(7)–C(7A)–C(10A)	110.2(3)	O(2)–C(7A)–C(6)	104.6(3)
C(7)–C(7A)–C(6)	110.8(3)	C(10A)–C(7A)–C(6)	109.2(3)
C(8)–C(7)–C(7A)	124.8(4)	C(7)–C(8)–C(9)	122.2(4)
O(1)–C(9)–C(8)	122.0(4)	O(1)–C(9)–C(10)	120.9(4)
C(8)–C(9)–C(10)	117.1(3)	C(9)–C(10)–C(10A)	112.4(3)
N(1A)–C(10A)–C(7A)	112.0(3)	N(1A)–C(10A)–C(10)	110.0(3)
C(7A)–C(10A)–C(10)	112.6(3)	C(7A)–O(2)–C(11)	116.2(2)
O(2)–C(11)–C(12)	108.3(3)	F(3X)–C(13)–F(1)	102.8(13)
F(3X)–C(13)–F(1X)	111.2(8)	F(1)–C(13)–F(1X)	15.9(13)
F(3X)–C(13)–F(2)	72.5(7)	F(1)–C(13)–F(2)	110.3(9)
F(1X)–C(13)–F(2)	125.2(10)	F(3X)–C(13)–F(3)	28.0(5)
F(1)–C(13)–F(3)	103.7(10)	F(1X)–C(13)–F(3)	104.5(10)
F(2)–C(13)–F(3)	98.5(7)	F(3X)–C(13)–F(2X)	108.8(6)
F(1)–C(13)–F(2X)	92.4(11)	F(1X)–C(13)–F(2X)	101.7(7)
F(2)–C(13)–F(2X)	37.7(6)	F(3)–C(13)–F(2X)	135.9(6)
F(3X)–C(13)–S(1)	121.4(6)	F(1)–C(13)–S(1)	122.3(10)
F(1X)–C(13)–S(1)	107.1(6)	F(2)–C(13)–S(1)	116.7(8)
F(3)–C(13)–S(1)	100.6(7)	F(2X)–C(13)–S(1)	104.8(6)
O(5)–S(1)–O(3)	114.5(2)	O(5)–S(1)–O(4)	114.0(2)
O(3)–S(1)–O(4)	115.6(2)	O(5)–S(1)–C(13)	102.5(2)
O(3)–S(1)–C(13)	102.6(2)	O(4)–S(1)–C(13)	105.6(2)

Table 4. Hydrogen coordinates and isotropic displacement parameters (\AA^2) for compd 77.

	x	y	z	U
H(1A)	0.4116	0.2748	0.3810	0.047
H(1B)	0.4318	0.3502	0.4695	0.047
H(2A)	0.6282	0.3296	0.4120	0.058
H(2B)	0.5538	0.4101	0.3586	0.058
H(3A)	0.5845	0.3576	0.1804	0.054
H(3B)	0.5264	0.2764	0.2020	0.054
H(4)	0.356(4)	0.360(2)	0.039(4)	0.040
H(5A)	0.1066	0.3626	-0.0334	0.038
H(5B)	0.1460	0.4481	0.0179	0.038
H(6A)	-0.0301	0.3462	0.0827	0.037
H(6B)	-0.0691	0.4304	0.0225	0.037
H(7)	-0.1278	0.4786	0.2350	0.042
H(8)	-0.1707	0.3972	0.3688	0.047
H(10A)	0.0767	0.2725	0.2725	0.042
H(10B)	0.1875	0.2767	0.4260	0.042
H(10C)	0.2165	0.4069	0.4118	0.034
H(11A)	0.2632	0.5416	0.3924	0.044
H(11B)	0.1117	0.5323	0.3991	0.044
H(12A)	0.1728	0.6455	0.2453	0.089
H(12B)	0.1654	0.6615	0.3861	0.089
H(12C)	0.0252	0.6373	0.2591	0.089

Table 5. Torsion angles [°] for compd 77.

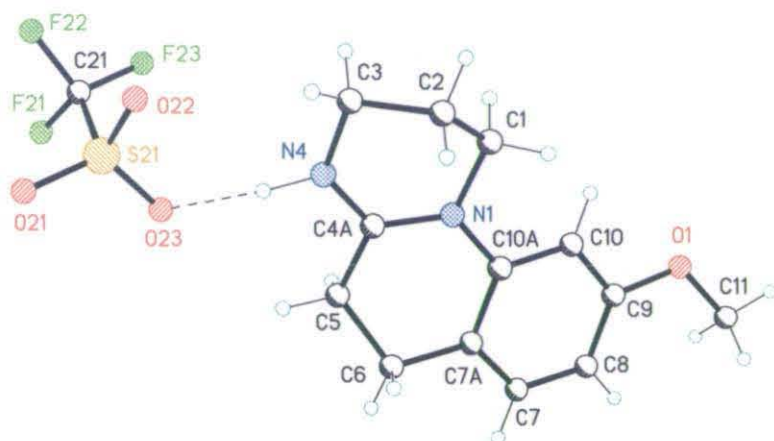
C(4A)–N(1A)–C(1)–C(2)	33.2(5)	C(10A)–N(1A)–C(1)–C(2)	–150.0(3)
N(1A)–C(1)–C(2)–C(3)	–54.2(5)	C(1)–C(2)–C(3)–N(4)	46.6(5)
C(2)–C(3)–N(4)–C(4A)	–19.1(6)	C(3)–N(4)–C(4A)–N(1A)	–3.3(6)
C(3)–N(4)–C(4A)–C(5)	175.9(4)	C(1)–N(1A)–C(4A)–N(4)	–4.2(5)
C(10A)–N(1A)–C(4A)–N(4)	179.3(3)	C(1)–N(1A)–C(4A)–C(5)	176.7(3)
C(10A)–N(1A)–C(4A)–C(5)	0.1(5)	N(4)–C(4A)–C(5)–C(6)	168.8(3)
N(1A)–C(4A)–C(5)–C(6)	–12.0(5)	C(4A)–C(5)–C(6)–C(7A)	42.3(4)
C(5)–C(6)–C(7A)–O(2)	58.9(4)	C(5)–C(6)–C(7A)–C(7)	177.2(3)
C(5)–C(6)–C(7A)–C(10A)	–61.3(4)	O(2)–C(7A)–C(7)–C(8)	–144.4(4)
C(10A)–C(7A)–C(7)–C(8)	–20.5(5)	C(6)–C(7A)–C(7)–C(8)	100.5(4)
C(7A)–C(7)–C(8)–C(9)	–3.1(6)	C(7)–C(8)–C(9)–O(1)	–178.2(4)
C(7)–C(8)–C(9)–C(10)	–0.7(6)	O(1)–C(9)–C(10)–C(10A)	–154.5(4)
C(8)–C(9)–C(10)–C(10A)	27.9(5)	C(4A)–N(1A)–C(10A)–C(7A)	–19.7(5)
C(1)–N(1A)–C(10A)–C(7A)	163.6(3)	C(4A)–N(1A)–C(10A)–C(10)	106.4(4)
C(1)–N(1A)–C(10A)–C(10)	–70.3(4)	O(2)–C(7A)–C(10A)–N(1A)	–65.9(4)
C(7)–C(7A)–C(10A)–N(1A)	171.5(3)	C(6)–C(7A)–C(10A)–N(1A)	49.6(4)
O(2)–C(7A)–C(10A)–C(10)	169.4(3)	C(7)–C(7A)–C(10A)–C(10)	46.8(4)
C(6)–C(7A)–C(10A)–C(10)	–75.1(4)	C(9)–C(10)–C(10A)–N(1A)	–177.3(3)
C(9)–C(10)–C(10A)–C(7A)	–51.5(4)	C(7)–C(7A)–O(2)–C(11)	59.3(4)
C(10A)–C(7A)–O(2)–C(11)	–63.5(4)	C(6)–C(7A)–O(2)–C(11)	178.3(3)
C(7A)–O(2)–C(11)–C(12)	–146.2(4)	F(3X)–C(13)–S(1)–O(5)	169.1(8)
F(1)–C(13)–S(1)–O(5)	–56.9(11)	F(1X)–C(13)–S(1)–O(5)	–61.8(7)
F(2)–C(13)–S(1)–O(5)	84.1(11)	F(3)–C(13)–S(1)–O(5)	–170.7(8)
F(2X)–C(13)–S(1)–O(5)	45.6(7)	F(3X)–C(13)–S(1)–O(3)	–72.0(9)
F(1)–C(13)–S(1)–O(3)	62.0(11)	F(1X)–C(13)–S(1)–O(3)	57.2(7)
F(2)–C(13)–S(1)–O(3)	–156.9(11)	F(3)–C(13)–S(1)–O(3)	–51.7(8)
F(2X)–C(13)–S(1)–O(3)	164.6(7)	F(3X)–C(13)–S(1)–O(4)	49.5(9)
F(1)–C(13)–S(1)–O(4)	–176.5(11)	F(1X)–C(13)–S(1)–O(4)	178.6(6)
F(2)–C(13)–S(1)–O(4)	–35.5(11)	F(3)–C(13)–S(1)–O(4)	69.7(8)
F(2X)–C(13)–S(1)–O(4)	–73.9(7)		

Table 6. Hydrogen bonds for compd 77 [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
N(4)–H(4)...O(3)	0.81(4)	2.06(4)	2.860(4)	171(4)

Appendix III

X-Ray crystal structure of 9-methoxy-2,3,5,6-tetrahydro-1*H*-pyrimido-[1,2-*a*]quinolinium triflate salt (85)



Usual data collection conditions – summarized in Table 1.

The structure was solved by direct methods and refined by full-matrix least-squares on F^2 . All non-hydrogen atoms were refined with anisotropic atomic displacement parameters and hydrogen atoms bonded to carbon were inserted at calculated positions, and that bonded to N2, was located from difference maps and not further refined.

The structure comprises zig-zag chains of alternating cations and anions, linked by hydrogen bonding. The chains interact with each other via π - π stacking.

Table 1. Crystal data and structure refinement for compd 85.

Identification code	rcfj6	
Empirical formula	C14 H17 F3 N2 O4 S	
Formula weight	366.36	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 7.7502(10) Å	$\alpha = 90^\circ$.
	b = 10.3944(14) Å	$\beta = 101.093(2)^\circ$.
	c = 19.814(3) Å	$\gamma = 90^\circ$.
Volume	1566.4(4) Å ³	
Z	4	
Density (calculated)	1.554 Mg/m ³	
Absorption coefficient	0.262 mm ⁻¹	
F(000)	760	
Crystal size	0.50 x 0.13 x 0.08 mm ³	
Theta range for data collection	2.09 to 24.99°.	
Index ranges	-9 ≤ h ≤ 9, -12 ≤ k ≤ 8, -23 ≤ l ≤ 23	
Reflections collected	8878	
Independent reflections	2715 [R(int) = 0.0334]	
Completeness to theta = 24.99°	98.2 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.00000 and 0.771695	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2715 / 0 / 217	
Goodness-of-fit on F ²	1.045	
Final R indices [I > 2σ(I)]	R1 = 0.0423, wR2 = 0.1049	
R indices (all data)	R1 = 0.0567, wR2 = 0.1154	
Largest diff. peak and hole	0.677 and -0.388 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compd 85. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
N(1)	7211(2)	-161(2)	1410(1)	24(1)
C(1)	5891(3)	-638(2)	1798(1)	28(1)
C(2)	6796(3)	-1139(2)	2489(1)	30(1)
C(3)	8136(3)	-2153(2)	2403(1)	32(1)
N(2)	9228(2)	-1660(2)	1934(1)	27(1)
C(4)	8792(3)	-712(2)	1500(1)	24(1)
C(5)	10100(3)	-257(2)	1088(1)	30(1)
C(6)	9963(3)	1192(2)	996(1)	30(1)
C(7)	8099(3)	1538(2)	701(1)	27(1)
C(8)	7629(3)	2501(3)	220(1)	34(1)
C(9)	5883(3)	2798(3)	-48(1)	33(1)
C(10)	4578(3)	2101(2)	168(1)	28(1)
C(11)	4995(3)	1113(2)	645(1)	26(1)
C(12)	6746(3)	841(2)	910(1)	24(1)
O(1)	2815(2)	2287(2)	-74(1)	35(1)
C(13)	2326(4)	3377(3)	-510(1)	39(1)
S(21)	12876(1)	-3925(1)	1979(1)	26(1)
O(21)	14707(2)	-3999(2)	2252(1)	43(1)
O(22)	11761(3)	-4059(2)	2473(1)	52(1)
O(23)	12350(2)	-2902(2)	1496(1)	40(1)
C(21)	12439(4)	-5370(3)	1463(1)	38(1)
F(21)	13564(3)	-5461(2)	1035(1)	85(1)
F(22)	12658(2)	-6424(2)	1841(1)	56(1)
F(23)	10817(3)	-5403(2)	1107(1)	83(1)

Table 3. Bond lengths [Å] and angles [°] for compd 85.

N(1)-C(4)	1.334(3)	C(9)-C(10)	1.377(3)
N(1)-C(12)	1.434(3)	C(10)-O(1)	1.371(3)
N(1)-C(1)	1.479(3)	C(10)-C(11)	1.391(3)
C(1)-C(2)	1.506(3)	C(11)-C(12)	1.387(3)
C(2)-C(3)	1.512(3)	O(1)-C(13)	1.431(3)
C(3)-N(2)	1.464(3)	S(21)-O(21)	1.4203(18)
N(2)-C(4)	1.307(3)	S(21)-O(22)	1.4309(19)
C(4)-C(5)	1.495(3)	S(21)-O(23)	1.4358(18)
C(5)-C(6)	1.519(4)	S(21)-C(21)	1.813(3)
C(6)-C(7)	1.495(3)	C(21)-F(23)	1.318(3)
C(7)-C(8)	1.381(4)	C(21)-F(22)	1.321(3)
C(7)-C(12)	1.402(3)	C(21)-F(21)	1.332(3)
C(8)-C(9)	1.389(3)		
C(4)-N(1)-C(12)	120.50(19)	C(9)-C(10)-C(11)	120.7(2)
C(4)-N(1)-C(1)	119.7(2)	C(12)-C(11)-C(10)	119.4(2)
C(12)-N(1)-C(1)	119.70(18)	C(11)-C(12)-C(7)	121.0(2)
N(1)-C(1)-C(2)	109.96(19)	C(11)-C(12)-N(1)	120.5(2)
C(1)-C(2)-C(3)	110.4(2)	C(7)-C(12)-N(1)	118.5(2)
N(2)-C(3)-C(2)	108.73(19)	C(10)-O(1)-C(13)	116.9(2)
C(4)-N(2)-C(3)	124.93(19)	O(21)-S(21)-O(22)	115.20(13)
N(2)-C(4)-N(1)	121.8(2)	O(21)-S(21)-O(23)	115.39(11)
N(2)-C(4)-C(5)	118.7(2)	O(22)-S(21)-O(23)	113.31(12)
N(1)-C(4)-C(5)	119.5(2)	O(21)-S(21)-C(21)	103.52(12)
C(4)-C(5)-C(6)	109.9(2)	O(22)-S(21)-C(21)	103.49(13)
C(7)-C(6)-C(5)	109.01(19)	O(23)-S(21)-C(21)	103.86(11)
C(8)-C(7)-C(12)	117.7(2)	F(23)-C(21)-F(22)	106.7(2)
C(8)-C(7)-C(6)	123.5(2)	F(23)-C(21)-F(21)	109.4(2)
C(12)-C(7)-C(6)	118.8(2)	F(22)-C(21)-F(21)	106.0(2)
C(7)-C(8)-C(9)	122.2(2)	F(23)-C(21)-S(21)	112.26(19)
C(10)-C(9)-C(8)	118.9(2)	F(22)-C(21)-S(21)	112.16(18)
O(1)-C(10)-C(9)	124.0(2)	F(21)-C(21)-S(21)	110.1(2)
O(1)-C(10)-C(11)	115.3(2)		

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compd 85. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	23(1)	24(1)	28(1)	0(1)	10(1)	-1(1)
C(1)	27(1)	25(1)	36(1)	3(1)	15(1)	-1(1)
C(2)	34(1)	28(1)	33(1)	2(1)	15(1)	-3(1)
C(3)	31(1)	27(1)	38(1)	6(1)	10(1)	-4(1)
N(2)	23(1)	24(1)	35(1)	0(1)	6(1)	-1(1)
C(4)	23(1)	24(1)	27(1)	-5(1)	6(1)	-3(1)
C(5)	24(1)	34(2)	35(1)	-1(1)	12(1)	0(1)
C(6)	26(1)	33(1)	33(1)	4(1)	8(1)	-7(1)
C(7)	28(1)	26(1)	27(1)	-2(1)	10(1)	-6(1)
C(8)	33(1)	37(2)	35(1)	5(1)	10(1)	-8(1)
C(9)	40(1)	32(2)	28(1)	7(1)	6(1)	-1(1)
C(10)	27(1)	30(1)	26(1)	-4(1)	5(1)	0(1)
C(11)	27(1)	26(1)	27(1)	-1(1)	9(1)	-2(1)
C(12)	28(1)	22(1)	23(1)	-4(1)	8(1)	-2(1)
O(1)	29(1)	36(1)	38(1)	6(1)	3(1)	4(1)
C(13)	41(1)	37(2)	35(1)	1(1)	-1(1)	6(1)
S(21)	25(1)	25(1)	29(1)	0(1)	8(1)	-1(1)
O(21)	30(1)	32(1)	63(1)	3(1)	0(1)	-3(1)
O(22)	58(1)	60(1)	48(1)	-8(1)	34(1)	-15(1)
O(23)	45(1)	25(1)	47(1)	6(1)	6(1)	6(1)
C(21)	50(2)	29(2)	34(1)	1(1)	3(1)	3(1)
F(21)	145(2)	57(1)	70(1)	-22(1)	62(1)	-2(1)
F(22)	64(1)	25(1)	68(1)	9(1)	-11(1)	-7(1)
F(23)	85(1)	43(1)	91(2)	-12(1)	-56(1)	4(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$) for compd 85.

	x	y	z	U(eq)
H(1A)	5189	-1334	1536	34
H(1B)	5082	69	1862	34
H(2A)	5914	-1514	2733	36
H(2B)	7389	-421	2770	36
H(3A)	8880	-2358	2854	38
H(3B)	7531	-2950	2212	38
H(5A)	9874	-682	633	36
H(5B)	11302	-489	1327	36
H(6A)	10343	1624	1445	36
H(6B)	10740	1481	683	36
H(8)	8528	2976	68	41
H(9)	5595	3472	-374	40
H(11)	4089	630	787	31
H(13A)	1043	3409	-649	58
H(13B)	2856	3303	-919	58
H(13C)	2745	4165	-259	58
H(1N)	10467	-1936	2017	40

Table 6. Torsion angles [°] for compd 85.

C(4)-N(1)-C(1)-C(2)	31.5(3)	C(11)-C(10)-O(1)-C(13)	173.7(2)
C(12)-N(1)-C(1)-C(2)	-152.0(2)	O(21)-S(21)-C(21)-F(23)	-173.4(2)
N(1)-C(1)-C(2)-C(3)	-55.2(3)	O(22)-S(21)-C(21)-F(23)	66.1(2)
C(1)-C(2)-C(3)-N(2)	48.8(3)	O(23)-S(21)-C(21)-F(23)	-52.5(2)
C(2)-C(3)-N(2)-C(4)	-19.8(3)	O(21)-S(21)-C(21)-F(22)	66.5(2)
C(3)-N(2)-C(4)-N(1)	-5.3(4)	O(22)-S(21)-C(21)-F(22)	-54.1(2)
C(3)-N(2)-C(4)-C(5)	175.9(2)	O(23)-S(21)-C(21)-F(22)	-172.63(19)
C(12)-N(1)-C(4)-N(2)	-177.4(2)	O(21)-S(21)-C(21)-F(21)	-51.3(2)
C(1)-N(1)-C(4)-N(2)	-1.0(3)	O(22)-S(21)-C(21)-F(21)	-171.8(2)
C(12)-N(1)-C(4)-C(5)	1.5(3)	O(23)-S(21)-C(21)-F(21)	69.6(2)
C(1)-N(1)-C(4)-C(5)	177.9(2)		
N(2)-C(4)-C(5)-C(6)	-143.8(2)		
N(1)-C(4)-C(5)-C(6)	37.3(3)		
C(4)-C(5)-C(6)-C(7)	-53.6(3)		
C(5)-C(6)-C(7)-C(8)	-142.4(2)		
C(5)-C(6)-C(7)-C(12)	36.4(3)		
C(12)-C(7)-C(8)-C(9)	0.8(4)		
C(6)-C(7)-C(8)-C(9)	179.7(2)		
C(7)-C(8)-C(9)-C(10)	-0.7(4)		
C(8)-C(9)-C(10)-O(1)	-178.3(2)		
C(8)-C(9)-C(10)-C(11)	-0.1(4)		
O(1)-C(10)-C(11)-C(12)	179.0(2)		
C(9)-C(10)-C(11)-C(12)	0.7(4)		
C(10)-C(11)-C(12)-C(7)	-0.5(3)		
C(10)-C(11)-C(12)-N(1)	179.1(2)		
C(8)-C(7)-C(12)-C(11)	-0.2(3)		
C(6)-C(7)-C(12)-C(11)	-179.1(2)		
C(8)-C(7)-C(12)-N(1)	-179.9(2)		
C(6)-C(7)-C(12)-N(1)	1.2(3)		
C(4)-N(1)-C(12)-C(11)	157.9(2)		
C(1)-N(1)-C(12)-C(11)	-18.5(3)		
C(4)-N(1)-C(12)-C(7)	-22.4(3)		
C(1)-N(1)-C(12)-C(7)	161.2(2)		
C(9)-C(10)-O(1)-C(13)	-8.1(3)		

Table 7. Hydrogen bonds for compd 85 [\AA and $^\circ$].

D-H...A	d(D-H)	d(H...A)	d(D...A)	$\angle(\text{DHA})$
N(2)-H(1N)...O(23)	0.99	2.19	3.013(3)	140.5
N(2)-H(1N)...F(22)#1	0.99	2.50	3.086(2)	117.9
N(2)-H(1N)...O(22)	0.99	2.52	3.225(3)	128.6

Symmetry transformations used to generate equivalent atoms: #1 $-x+5/2, y+1/2, -z+1/2$

Appendix IV

X-Ray crystal structure of 9-(Methoxy)-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinolinium triflate salt (87)

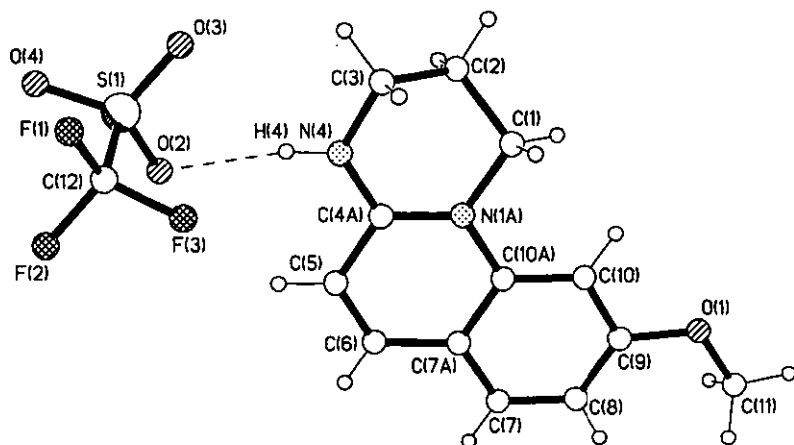


Table 1. Crystal data and structure refinement for compd 87.

Identification code	rcfj10	
Chemical formula	$C_{14}H_{15}F_3N_2O_4S$	
Formula weight	364.34	
Temperature	150(2) K	
Radiation, wavelength	MoK α , 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/c$	
Unit cell parameters	$a = 6.6746(12)$ Å	$\alpha = 90^\circ$
	$b = 22.837(4)$ Å	$\beta = 94.556(3)^\circ$
	$c = 10.1575(18)$ Å	$\gamma = 90^\circ$
Cell volume	$1543.4(5)$ Å ³	
Z	4	
Calculated density	1.568 g/cm ³	
Absorption coefficient μ	0.266 mm ⁻¹	
F(000)	752	
Crystal colour and size	pale yellow, $0.31 \times 0.16 \times 0.09$ mm ³	
Reflections for cell refinement	3452 (θ range 2.20 to 27.46°)	
Data collection method	Bruker SMART 1000 CCD diffractometer ω rotation with narrow frames	

θ range for data collection	1.78 to 24.99°
Index ranges	h -7 to 7, k -26 to 27, l -12 to 12
Completeness to $\theta = 24.99^\circ$	99.9 %
Intensity decay	0%
Reflections collected	10854
Independent reflections	2706 ($R_{\text{int}} = 0.0443$)
Reflections with $F^2 > 2\sigma$	2041
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.922 and 0.977
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0542, 13.5055
Data / restraints / parameters	2706 / 70 / 237
Final R indices [$F^2 > 2\sigma$]	R1 = 0.0970, wR2 = 0.2538
R indices (all data)	R1 = 0.1185, wR2 = 0.2635
Goodness-of-fit on F^2	1.187
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	1.007 and -0.378 e \AA^{-3}

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (\AA^2) for compd 87. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1A)	0.5495(8)	0.3501(2)	0.3455(5)	0.0292(13)
C(1)	0.5267(11)	0.2856(3)	0.3304(8)	0.0372(17)
C(2)	0.732(2)	0.2583(6)	0.3359(18)	0.040(4)
C(3)	0.846(3)	0.2736(12)	0.463(2)	0.038(5)
C(2X)	0.675(3)	0.2531(7)	0.428(2)	0.042(5)
C(3X)	0.887(4)	0.2753(13)	0.420(2)	0.034(5)
N(4)	0.8656(10)	0.3386(3)	0.4542(7)	0.0470(17)
C(4A)	0.7164(11)	0.3726(3)	0.4086(7)	0.0310(16)
C(5)	0.7396(11)	0.4350(3)	0.4224(7)	0.0347(17)
C(6)	0.5946(11)	0.4706(3)	0.3725(7)	0.0348(17)
C(7A)	0.4116(11)	0.4478(3)	0.3079(7)	0.0307(16)
C(7)	0.2584(12)	0.4839(3)	0.2544(7)	0.0381(18)
C(8)	0.0872(12)	0.4604(3)	0.1900(7)	0.0410(19)
C(9)	0.0673(11)	0.4004(3)	0.1771(7)	0.0359(17)
C(10)	0.2198(10)	0.3633(3)	0.2280(7)	0.0330(16)
C(10A)	0.3935(11)	0.3866(3)	0.2934(6)	0.0306(16)
O(1)	-0.0957(8)	0.3724(2)	0.1164(5)	0.0460(14)
C(11)	-0.2486(13)	0.4081(4)	0.0488(8)	0.055(2)
C(12)	1.2114(12)	0.3690(3)	0.8233(8)	0.0397(18)
F(1)	1.2796(8)	0.3308(2)	0.9163(4)	0.0573(14)
F(2)	1.2515(9)	0.4224(2)	0.8719(5)	0.0680(17)
F(3)	1.0108(8)	0.3641(3)	0.8111(6)	0.0755(18)
S(1)	1.3165(3)	0.35685(8)	0.66859(18)	0.0332(5)
O(2)	1.2116(8)	0.3990(2)	0.5823(5)	0.0432(14)
O(3)	1.2638(10)	0.2969(2)	0.6379(6)	0.0566(18)
O(4)	1.5265(8)	0.3681(3)	0.6960(6)	0.0523(16)

Table 3. Bond lengths [Å] and angles [°] for compd 87.

N(1A)–C(4A)	1.343(9)	N(1A)–C(10A)	1.403(9)
N(1A)–C(1)	1.488(8)	C(1)–C(2)	1.505(16)
C(1)–C(2X)	1.535(18)	C(2)–C(3)	1.49(3)
C(3)–N(4)	1.49(3)	C(2X)–C(3X)	1.52(3)
C(3X)–N(4)	1.50(3)	N(4)–C(4A)	1.317(9)
C(4A)–C(5)	1.438(10)	C(5)–C(6)	1.333(10)
C(6)–C(7A)	1.438(10)	C(7A)–C(7)	1.390(10)
C(7A)–C(10A)	1.410(10)	C(7)–C(8)	1.379(11)
C(8)–C(9)	1.381(11)	C(9)–O(1)	1.367(9)
C(9)–C(10)	1.392(10)	C(10)–C(10A)	1.394(10)
O(1)–C(11)	1.439(9)	C(12)–F(2)	1.335(9)
C(12)–F(1)	1.339(8)	C(12)–F(3)	1.340(9)
C(12)–S(1)	1.792(8)	S(1)–O(4)	1.431(6)
S(1)–O(3)	1.442(6)	S(1)–O(2)	1.444(5)
C(4A)–N(1A)–C(10A)	121.0(6)	C(4A)–N(1A)–C(1)	120.1(6)
C(10A)–N(1A)–C(1)	118.8(5)	N(1A)–C(1)–C(2)	108.7(8)
N(1A)–C(1)–C(2X)	110.9(8)	C(2)–C(1)–C(2X)	40.3(8)
C(3)–C(2)–C(1)	109.7(15)	C(2)–C(3)–N(4)	102.6(18)
C(3X)–C(2X)–C(1)	111.0(16)	N(4)–C(3X)–C(2X)	102(2)
C(4A)–N(4)–C(3)	122.8(11)	C(4A)–N(4)–C(3X)	124.9(12)
C(3)–N(4)–C(3X)	20.9(10)	N(4)–C(4A)–N(1A)	121.2(6)
N(4)–C(4A)–C(5)	118.5(6)	N(1A)–C(4A)–C(5)	120.3(7)
C(6)–C(5)–C(4A)	119.9(7)	C(5)–C(6)–C(7A)	121.1(7)
C(7)–C(7A)–C(10A)	119.5(7)	C(7)–C(7A)–C(6)	122.4(7)
C(10A)–C(7A)–C(6)	118.0(7)	C(8)–C(7)–C(7A)	120.7(7)
C(7)–C(8)–C(9)	120.0(7)	O(1)–C(9)–C(8)	125.1(7)
O(1)–C(9)–C(10)	114.5(7)	C(8)–C(9)–C(10)	120.4(7)
C(9)–C(10)–C(10A)	120.1(7)	C(10)–C(10A)–N(1A)	121.2(6)
C(10)–C(10A)–C(7A)	119.2(7)	N(1A)–C(10A)–C(7A)	119.6(6)
C(9)–O(1)–C(11)	117.3(6)	F(2)–C(12)–F(1)	106.7(6)
F(2)–C(12)–F(3)	106.3(6)	F(1)–C(12)–F(3)	106.9(7)
F(2)–C(12)–S(1)	112.6(6)	F(1)–C(12)–S(1)	112.5(5)
F(3)–C(12)–S(1)	111.3(6)	O(4)–S(1)–O(3)	115.6(4)
O(4)–S(1)–O(2)	114.7(3)	O(3)–S(1)–O(2)	113.8(3)
O(4)–S(1)–C(12)	104.3(4)	O(3)–S(1)–C(12)	103.4(4)
O(2)–S(1)–C(12)	103.0(3)		

Table 4. Hydrogen coordinates and isotropic displacement parameters (\AA^2) for compd 87.

	x	y	z	U
H(1A)	0.4517	0.2764	0.2449	0.045
H(1B)	0.4506	0.2697	0.4022	0.045
H(1C)	0.5504	0.2743	0.2388	0.045
H(1D)	0.3873	0.2744	0.3463	0.045
H(2A)	0.7199	0.2152	0.3279	0.048
H(2B)	0.8056	0.2728	0.2614	0.048
H(3A)	0.9799	0.2545	0.4715	0.046
H(3B)	0.7713	0.2622	0.5396	0.046
H(2X1)	0.6346	0.2587	0.5190	0.050
H(2X2)	0.6698	0.2106	0.4083	0.050
H(3X1)	0.9831	0.2551	0.4838	0.041
H(3X2)	0.9317	0.2705	0.3296	0.041
H(4)	0.9815	0.3548	0.4802	0.056
H(5)	0.8581	0.4507	0.4669	0.042
H(6)	0.6126	0.5118	0.3798	0.042
H(7)	0.2717	0.5252	0.2622	0.046
H(8)	-0.0171	0.4855	0.1545	0.049
H(10)	0.2056	0.3222	0.2181	0.040
H(11A)	-0.3037	0.4351	0.1118	0.082
H(11B)	-0.3563	0.3831	0.0092	0.082
H(11C)	-0.1899	0.4307	-0.0207	0.082

Table 5. Torsion angles [°] for compd 87.

C(4A)–N(1A)–C(1)–C(2)	–25.3(12)	C(10A)–N(1A)–C(1)–C(2)	155.1(9)
C(4A)–N(1A)–C(1)–C(2X)	17.6(13)	C(10A)–N(1A)–C(1)–C(2X)	–162.0(11)
N(1A)–C(1)–C(2)–C(3)	58.2(18)	C(2X)–C(1)–C(2)–C(3)	–42.4(16)
C(1)–C(2)–C(3)–N(4)	–63.9(18)	N(1A)–C(1)–C(2X)–C(3X)	–52(2)
C(2)–C(1)–C(2X)–C(3X)	43.0(17)	C(1)–C(2X)–C(3X)–N(4)	60(2)
C(2)–C(3)–N(4)–C(4A)	42.5(19)	C(2)–C(3)–N(4)–C(3X)	–60(5)
C(2X)–C(3X)–N(4)–C(4A)	–44(2)	C(2X)–C(3X)–N(4)–C(3)	48(5)
C(3)–N(4)–C(4A)–N(1A)	–12.4(15)	C(3X)–N(4)–C(4A)–N(1A)	12.7(16)
C(3)–N(4)–C(4A)–C(5)	170.6(12)	C(3X)–N(4)–C(4A)–C(5)	–164.3(13)
C(10A)–N(1A)–C(4A)–N(4)	–178.0(7)	C(1)–N(1A)–C(4A)–N(4)	2.4(10)
C(10A)–N(1A)–C(4A)–C(5)	–1.0(10)	C(1)–N(1A)–C(4A)–C(5)	179.5(6)
N(4)–C(4A)–C(5)–C(6)	177.3(7)	N(1A)–C(4A)–C(5)–C(6)	0.2(11)
C(4A)–C(5)–C(6)–C(7A)	1.7(11)	C(5)–C(6)–C(7A)–C(7)	–179.6(7)
C(5)–C(6)–C(7A)–C(10A)	–2.8(10)	C(10A)–C(7A)–C(7)–C(8)	1.5(10)
C(6)–C(7A)–C(7)–C(8)	178.2(7)	C(7A)–C(7)–C(8)–C(9)	–0.5(11)
C(7)–C(8)–C(9)–O(1)	179.5(7)	C(7)–C(8)–C(9)–C(10)	–0.5(11)
O(1)–C(9)–C(10)–C(10A)	–179.4(6)	C(8)–C(9)–C(10)–C(10A)	0.6(11)
C(9)–C(10)–C(10A)–N(1A)	–179.9(6)	C(9)–C(10)–C(10A)–C(7A)	0.4(10)
C(4A)–N(1A)–C(10A)–C(10)	–179.9(6)	C(1)–N(1A)–C(10A)–C(10)	–0.3(10)
C(4A)–N(1A)–C(10A)–C(7A)	–0.2(10)	C(1)–N(1A)–C(10A)–C(7A)	179.4(6)
C(7)–C(7A)–C(10A)–C(10)	–1.4(10)	C(6)–C(7A)–C(10A)–C(10)	–178.3(6)
C(7)–C(7A)–C(10A)–N(1A)	178.9(6)	C(6)–C(7A)–C(10A)–N(1A)	2.0(10)
C(8)–C(9)–O(1)–C(11)	6.9(11)	C(10)–C(9)–O(1)–C(11)	–173.2(7)
F(2)–C(12)–S(1)–O(4)	56.3(6)	F(1)–C(12)–S(1)–O(4)	–64.4(6)
F(3)–C(12)–S(1)–O(4)	175.6(5)	F(2)–C(12)–S(1)–O(3)	177.5(5)
F(1)–C(12)–S(1)–O(3)	56.8(6)	F(3)–C(12)–S(1)–O(3)	–63.2(6)
F(2)–C(12)–S(1)–O(2)	–63.8(6)	F(1)–C(12)–S(1)–O(2)	175.6(5)
F(3)–C(12)–S(1)–O(2)	55.5(6)		

Table 6. Hydrogen bonds for compd 87 [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
N(4)–H(4)...O(2)	0.88	2.05	2.908(8)	165.0

