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CHEMICAL STUDIES ON SEROTONIN ANALOGS

by

Laxmikant Atmaram Gharat

A dissertation submitted to the Faculty of the

DEPARTMENT OF PHARMACEUTICAL SCIENCES

In Partial Fulfillment of the Requirements
For the Degree of

DOCTOR OF PHILOSOPHY

In the Graduate College

THE UNIVERSITY OF ARIZONA

1996

THE UNIVERSITY OF ARIZONA ®
GRADUATE COLLEGE

As members of the Final Examination Committee, we certify that we have read the dissertation prepared by LAXMIKANT A. GHARAT

entitled CHEMICAL STUDIES ON SEROTONIN ANALOGS

and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of DOCTOR OF PHILOSOPHY

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Dr. Karl H. Schram	Karl H. Schram	16 Nov 95 Date
Dr. Richard S. Glass	R S Glass	11/16/95 Date
Dr. Eugene A. Mash Jr.	Eugene A. Mash Jr.	11-16-95 Date

Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copy of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

Arnold Martin
Dissertation Director

22 Nov '95
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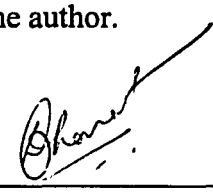
SIGNED: 

DEDICATION

To my parents **Mr. Atmaram M. Gharat** and **Mrs. Hansavati A. Gharat** without whose love, help and encouragement all this would not have been possible and my late grandfather **Mr. Atmaram M. Patil** who believed in the power of knowledge and education.

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At this point I would like to extend my thanks to Dr. Bhashyam Iyengar, Dr. Salah Sami, Nirav Merchant and all my friends in Tucson for their friendship and continuos moral support.

Most of all, I am grateful to my grandmother, my parents, my sister Ketki, my brother Prashant and my Mama's and Mamee's for their love and support throughout my career.

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ABSTRACT

The major focus of our research has been the design, synthesis and pharmacological evaluation of serotonin or 5-hydroxytryptamine (5-HT; **1**) analogs. These include the conformationally restricted, rigid and semirigid analogs and those with a variety of different substituents, both electron donating and electron withdrawing, on the critically important indole 5-position. Two most interesting analogs in the tryptamine series are 5-carboxamidotryptamine (5-CT; **3a**), a potent agonist at 5-HT_1 receptor and N,N-dipropyl-5-carboxamido tryptamine (5-DPCT; **3b**), a potent and selective agonist at the 5-HT_{1A} receptor. We have found that this potency also extends to the semirigid analogs, 5-carboxamido-3-tetrahydropyridyl indoles (**2a**, **2b**) (Agarwal et al., 1993; Dahlgren et al., 1995). In my research we decided to replace the 5-carboxyamido group by a group called the α-fluoroethenyl or the α-fluorovinyl group which was first proposed as an amide bond isostere in peptides (Allmendinger et al., 1990). We synthesized 5-(α-fluorovinyl)-3-tetrahydropyridyl indoles (**I**, **II**) and 5-(α-fluorovinyl) tryptamines (**III**, **IV**) which could be potential bioisosteres of **2a**, **2b**, **3a** and **3b**. The α-fluorovinyl group was introduced on the indole 5-position using an "atypical" Heck reaction to prepare 5-(α-fluorovinyl) indole (**5**), the starting material for all the target compounds. We also performed some experiments to confirm the mechanism of the base-catalyzed direct condensation of N-methyl-3- and -4-piperidones with indoles, a method employed for the synthesis of 3-tetrahydropyridylindoles **I** and **II**.

CHAPTER 1

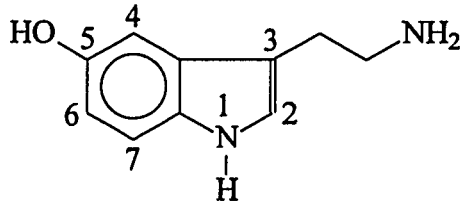
1. 1. 0 INTRODUCTION

As part of our continuing efforts to investigate structure activity relationship at the serotonin receptors, we have synthesized some 5-hydroxytryptamine (5-HT) analogs. These analogs posses an α-fluorovinyl or α-fluoroethenyl group, a carboxyamide isostere, at the indole 5-position. This group was introduced using an "atypical" Heck reaction. In the process of preparing these analogs, we also studied the mechanism of base-catalyzed condensation of indoles with N-alkyl-3- and -4-piperidones.

1. 1. 1 HISTORICAL BACKGROUND OF THE NEUROTRANSMITTER SEROTONIN

Stevens and Lee (1884) and Brodie (1900) were the first to discover the presence of an endogenous vasoconstictor substance in blood. Later in 1933, Espramer and colleagues in Italy identified a substance they called "enteramine" in the intestine (Espramer and Vialli; 1933), although the relationship of this compound to the serum factor was not yet known. Rapport and colleagues were able to purify the serum factor which they called "serotonin" to indicate its serum tonic abilities (Rapport et al., 1947). Two years later the structure of serotonin was identified as 5-hydroxytryptamine (5-HT, **1**; Rapport 1949). It was soon determined that the serum factor, enteramine and serotonin were the same substance.

Figure 1. The structure of Serotonin (**5-HT**)



1

Synthesis of 5-HT in 1951 (Hamlin and Fisher, 1951) led to an extensive research into its physiological properties. 5-HT was shown to be present not only in the blood serum and the intestine but also in the brain (Twarog and Page, 1953). Since then, scientific interest in this compound has increased dramatically. The growth in number of published papers and articles has been phenomenal. The number of papers published on serotonin jumped from 500 in the 1970's to nearly 3000 in 1994.

Serotonin has been known to be involved in many physiological activities such as blood platelet aggregation, temperature and blood pressure regulation, emotion, sexual responses, appetite etc. (Fozard, 1991; Peroutka, 1991; Zifa, 1992; Tollefson, 1991). The ability of serotonin to invoke diverse physiological responses is believed to arise from its differential interaction at the multiple 5-HT receptors and receptor subtypes.

1. 1. 2 CLASSIFICATION OF 5-HT RECEPTORS

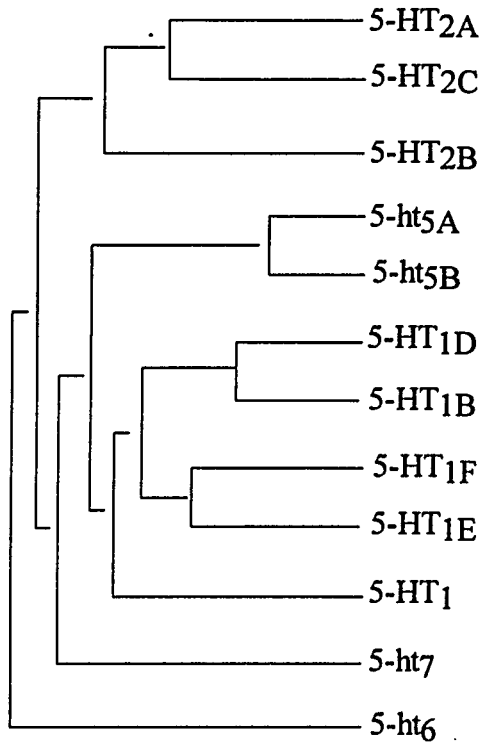
Early skepticism about the almost "unbelievable" number of 5-HT receptor types is no longer tenable, as more and more 5-HT receptor genes are cloned, the amino acid and corresponding receptor proteins deduced, and chromosome location of their genes

identified (Figure 2). Although 5-HT potently activates each the 5-HT receptor types and subtypes, the differences in the protein structure and consequent affinities for different synthetic chemicals, provide a basis for identifying selective ligands, either agonist or antagonist for each receptor. This provides an opportunity for the drug discovery by medicinal chemists (Humphery, 1992).

The three main criteria used to characterize a given receptor are : i) operational, i.e., drug related characteristics like selective agonist or antagonist and their ligand-binding affinities; ii) structural, gene and receptor structural sequences for their nucleotide and aminoacid components respectively; and iii) transductional, receptor-effect coupling events like ligand gated ion channel or G-protein linked (Humphery et al., 1993).

5-HT receptors have been classified into at least three and recently up to seven classes or groups (Bradley et al., 1986a; Zifa and Fillion, 1992; Peroutka, 1993). These include the 5-HT_1, 5-HT_2 and 5-HT_3 classes, the "uncloned" 5-HT_4 receptor and the 5-ht_5, 5-ht_6, 5-ht_7 receptors whose genes have been cloned recently (Table 1). The classification of 5-ht_5, 5-ht_6, and 5-ht_7 receptors remains tentative because of limited information on their operational and transductional characteristics. For this reason and in keeping with IUPHAR recommendations (Kenakin et al., 1992), the lower case appellation is currently used to define these gene products.

Figure 2



The dendrogram shows how 5-HT receptors cluster into subgroups according to aminoacid sequence similarity. The length of the horizontal bars is inversely proportional to sequence or group similarity. Dendrogram provided by Dr J. G.Sutcliffe, Dr. T.W. Lovenberg and Dr. M. G. Erlander, The Scripps Research Institute, La Jolla, CA.

Table 1. (Hoyer et, al., 1994)

Operational characteristics of 5-HT receptors.

Receptor	Location	Response	Agonist	Antagonist	Comment
5-HT_{1A}	Neuronal, mainly CNS	Neuronal hyper-polarization, hypotension	8-OH-DPAT, buspirone, 5-CT	WAY 100135 [methiotepin (nonselective)]	Well characterized but potent, silent, and selective antagonists only recently available.
5-HT_{1B}	CNS and some peri-pheral nerves	Inhibition of neurotransmitter release.	CP 93, 129, 5-CT	SDZ 21009 [methiotepin (Nonselective)]	Appears to be the rodent equivalent of $5\text{-HT}_{1D\beta}$ receptor subtype.

5-HT_{1D}	Mainly CNS	Inhibition of neurotransmitter release.	Sumatriptan, L694247, 5-CT	GR 127935 [metergoline, methiotepin (nonselective)	Two 5-HT_{1D} gene types cloned (5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$).
5-HT_{1E}	Only CNS	Inhibition of adenylyl cyclase.	5-HT	None [methiotepin weak]	Functions mediated in intact tissues not known.
5-HT_{1F}	Mainly CNS	Inhibition of adenylyl cyclase.	5-HT	None [methiotepin weak]	Functions mediated in intact tissue not known.
5-HT_{2A}	Vascular smooth muscle, platelets, lung, CNS, GI tract.	Vasoconstriction, platelet aggregation. bronchoconstriction.	α-methyl-5-HT DOI	Ketanserine, cinanserine, pirenperone	The classical 5-HT_2 receptor that increases phosphoinositol metabolism.
5-HT_{2B}	Mainly peripheral ?	Rat stomach fundic muscle contraction.	α-methyl-5-HT, DOI	SB200646 (also 5-HT_{2C} antagonist)	Like 5-HT_{2A} receptors linked to increased phosphoinositide metabolism.
5-HT_{2C}	CNS (high density in choroid plexus	Increased phosphoinositide turnover.	α-methyl-5-HT DOI	Mesulergine (also 5-HT_{2A} antagonist)	Like 5-HT_{2A} receptors linked to increased phosphoinositide metabolism.
5-HT_3	Peripheral and central neurons	Depolarization	2-methyl-5-HT, m-chlorophenyl-biguanide	Ondansetron, tropisetron	Mediates many of the neuronal reflex effects of 5-HT in the periphery.
5-HT_4	Gastrointestinal tract, CNS, Heart, urinary bladder	Activation of acetyl choline release in gut, tachycardia,↑ cAMP in CNS	Metoclopramide, renazapride(usually partial agonists) relative to 5-HT	GR113808, SB 204070, tropisetron (weak)	Pharmacologically distinct, but like certain other 5-HT receptors orphan in smooth muscle, 5-ht_6, 5-ht_7), the 5-HT_4 receptor is positively linked to adenylyl cyclase.
5-ht_{5a} and 5-ht_{5b}	CNS	Not known	5-HT	Methiotepin	Functions mediated in intact tissue not known (5-ht_{5A} and 5-ht_{5B} subtypes apparent). Transductional characteristics unknown.
5-ht_6	CNS	activation of adenylyl cyclase (HEK 293 cells)	5-HT	Methiotepin	Functions mediated in intact tissue not known. Positively coupled to adenylyl cyclase.
5-ht_7	CNS	activation of adenylyl cyclase (HeLa cells and COS cells)	5-HT	Methiotepin	Functions mediated in intact tissue not known. Positively coupled to adenylyl cyclase.

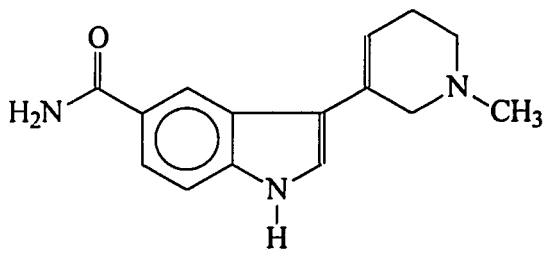
Besides these a number of functional receptors have been described that do not truly fulfill the criteria for admission into any of the receptor types described above and in this context are "orphans" of the present classification scheme.

1. 1. 3 GLOSSARY OF DRUG NAMES

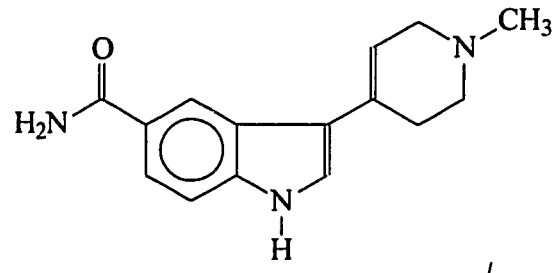
5-CT	5-Carboxamidotryptamine
8-OH-DPAT	8-Hydroxy-2-(di-N-propylamino)tetralin
CP 93, 129	3-(1,2,5,6-Tetrahydropyrid-4-yl)pyrrolo[3,2-b]pyrid-5-one
DOI	1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane
GR113808	[1-[2-(Methylsulfonyl)amino]ethyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate
GR127935	N-[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3yl)[1,1-biphenyl]-4-carboxamide
L694247	2-[5-[3-(4-Methylsulfonylamino)benzyl-1,2,4-oxadiazol-5-yl]-1H-indole-3-yl]ethylamine
SB200646	N-(1-Methyl-5-indolyl)-N-(3-pyridyl) urea
SB204070	(1-Butyl-4-piperidinylmethyl)-8-amino-7-chloro-1,4-benzodioxan-5-carboxylate
SDZ21009	4(3-Tertbutylamino-2-hydroxypropoxy)indol-2-carbonic acidisopropylester
WAY100135	N-tert-butyl-3-(4-[2-methoxyphenyl]piperazin-1-yl)-2-phenylpropanamide

1. 1. 4 THE DESIGN OF TARGET COMPOUNDS FOR PHARMACOLOGICAL EVALUATION

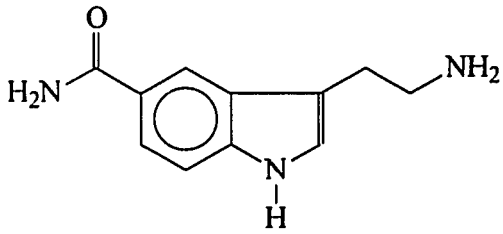
5-Carboxamidotryptamine (5-CT; **3a**) and its N,N-dipropyl derivative (**3b**) are potent agonists at the receptors for the neurotransmitter serotonin or 5-hydroxytryptamine (5-HT; **1**). 5-CT has a high affinity for both 5-HT_{1A} and 5-HT_{1D} subtypes, while **3b** is selective for the 5-HT_{1A} receptor (Hoyer, 1989). We have discovered that the high potency and selectivity for 5-HT_1 receptors extends to the 5-carboxamido-3-tetrahydropyridyl indoles (**2a, 2b**) which are conformationally restricted analogs of 5-CT..



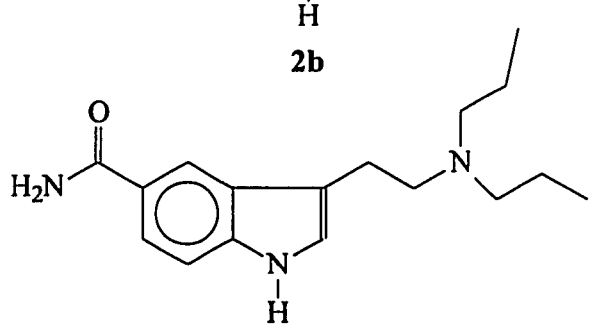
2a



2b



3a



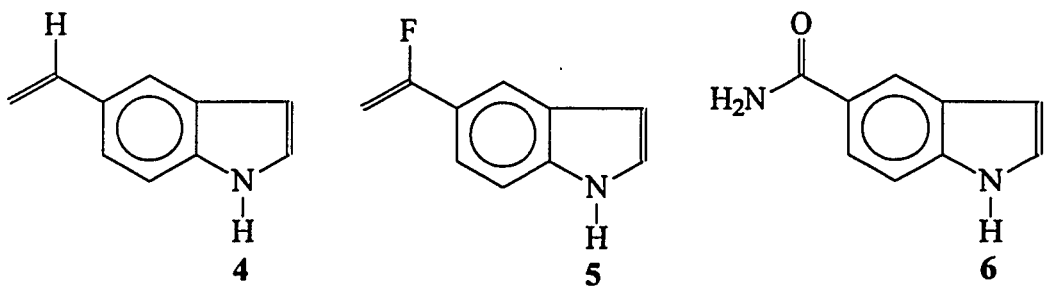
3b

Allmendinger and his colleagues proposed that α-fluoroethenyl or α-fluorovinyl group is an excellent bioisostere of carboxyamido group and they successfully employed it as a amide bond isostere in small peptide analogs of substance P (Allmendinger et al.,

1990). In peptides, it is incorporated for its resistance to hydrolysis and rapid degradation by peptidases, unlike a natural peptide bond. Comparison of electrostatic potential similarity (Allmendinger et al., 1990) and dipole moment (Abraham et al., 1986) calculations performed on N-methyl acetamide, trans-2-butene and 2-fluoro-2(Z)-butene as simple models of a peptide bond suggested that the fluoroethenyl group mimics both the steric and the electronic features of a peptide bond.

Based on the above result we proposed to make target compounds **I, II, III** and **IV** wherein the 5-carboxamido group of **2a, 2b, 3a** and **3b** is replaced by a α-fluoroethenyl or a α-fluorovinyl group (Figure 3).

We have also performed electrostatic potential similarity calculations using Biosyms INSIGHT II program, on 5-ethenylindole (**4**), 5-α-fluorovinylindole (**5**) and 5-carboxamidoindole (**6**) as simple models of our target compounds which indicated the very close similarity of **5** to **6** (Table 2). Figure 4 and Figure 5 are the ball and stick and space filled representation of **4, 5,** and **6**. Figure 6 shows overlap of **4, 5,** and **6** based on their electrostatic potential similarity.



4 **5** **6**

Figure 3. Proposed Target Compounds.

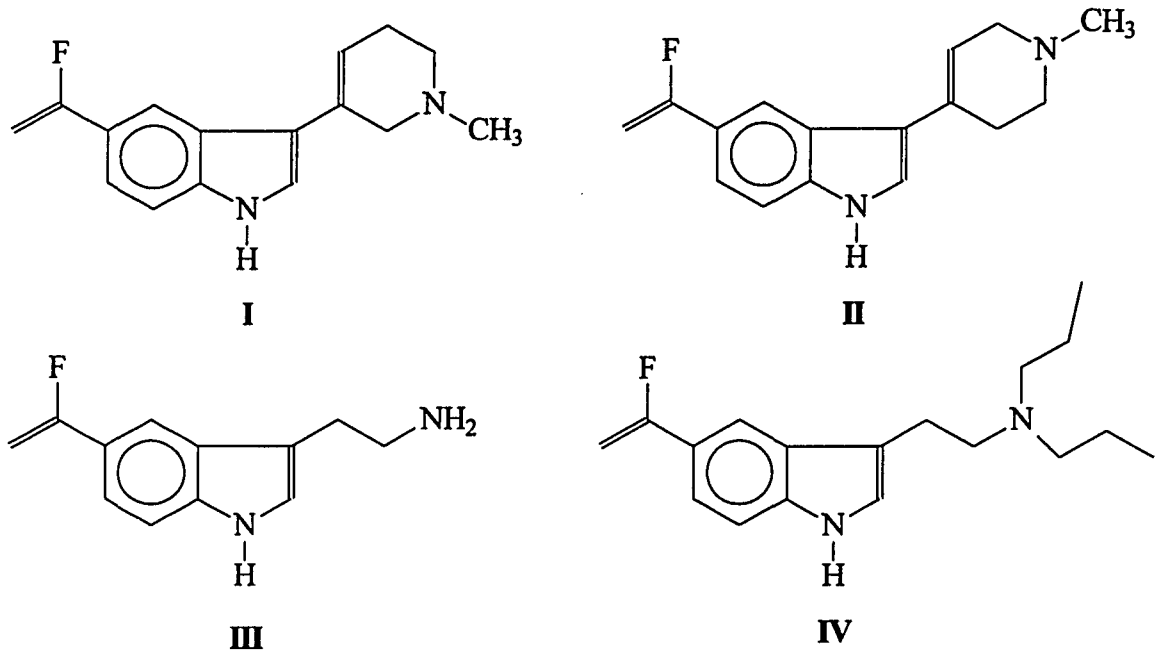


Table 2[#]. Electrostatic Potential similarity between compounds **4, 5** and **6**.

	4	**5**	**6**
4	1.0	0.804	0.630
5	0.804	1.0	0.950
6	0.630	0.950	1.0

Closer the value to 1.0, higher is the similarity.

Figure 4.

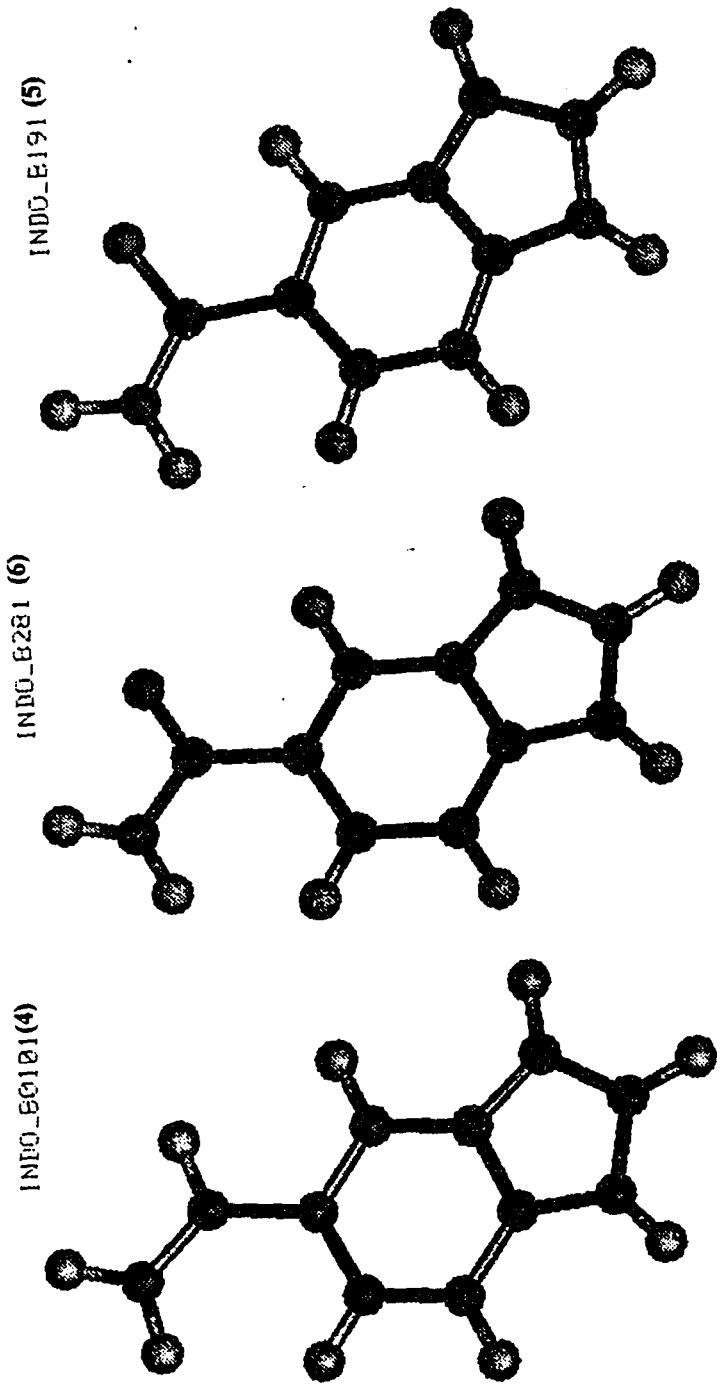


Figure 5.

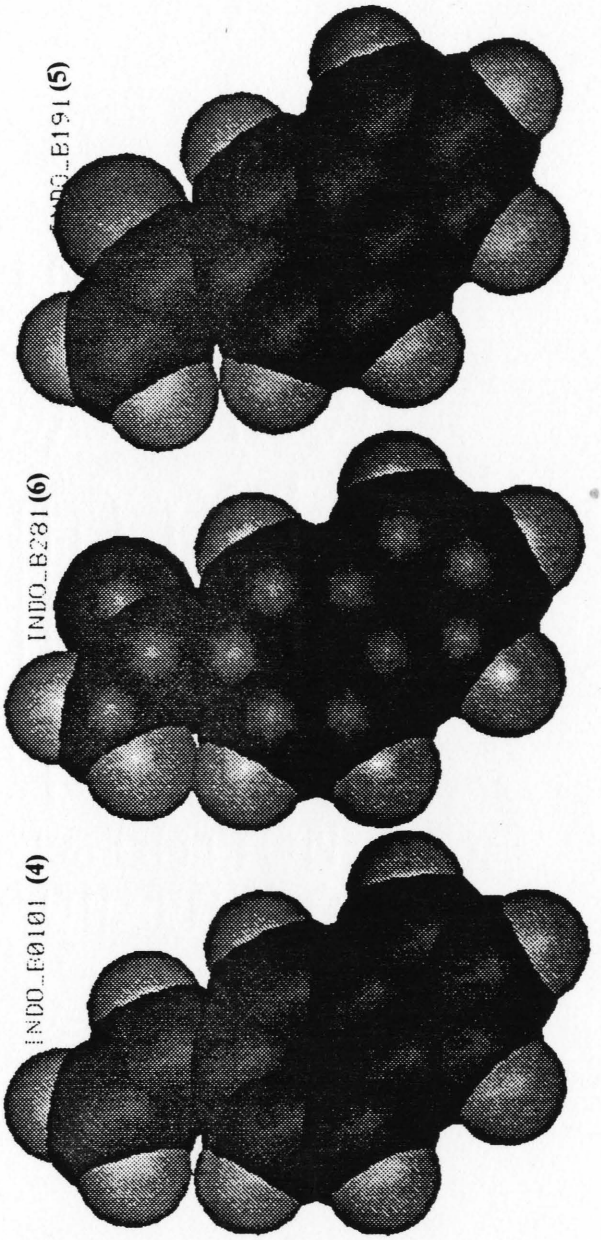
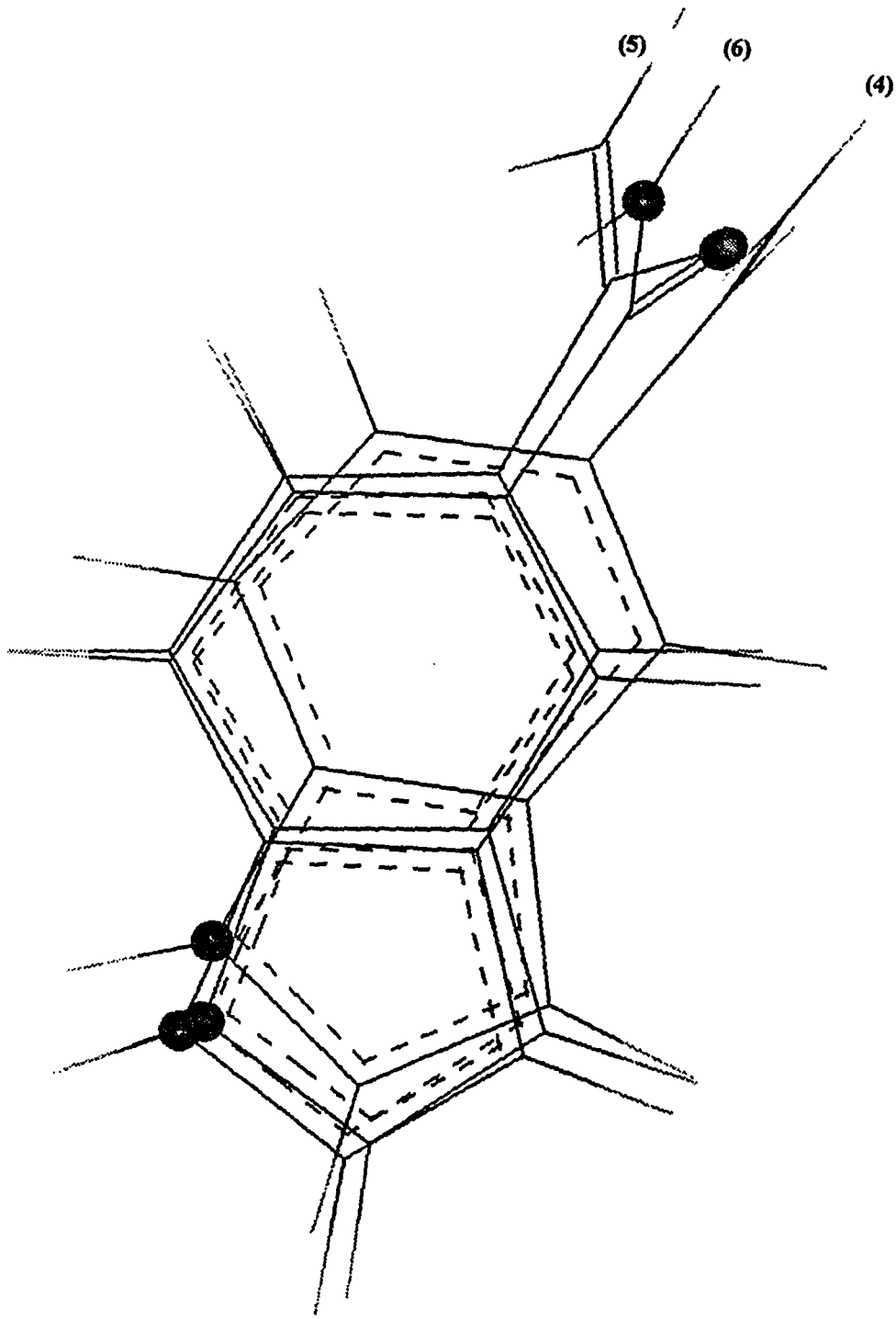


Figure 6.



CHAPTER 2

2. 1. 0 OVERVIEW OF HECK REACTION

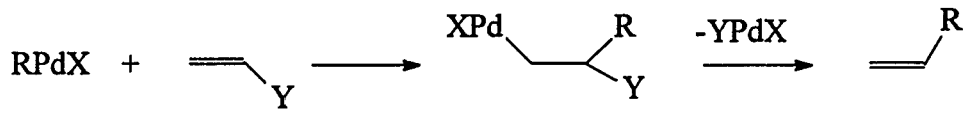
In 1968, Heck introduced a palladium mediated reaction for arylation of vinyl and other olefinic compounds (Heck, 1968). Closely related reactions in which arenes were coupled with olefins were discovered by Moritani and Fujiwara (1967). Since these discoveries there has been a explosion of activity resulting in a large number of successful palladium-mediated olefin substitution reactions (Heck, 1985).

The remarkable ease of addition of organopalladium compounds to olefins has led to the development of a series of useful synthetic reactions in which one of the vinylic hydrogens or a heteroatom (if attached to the olefinic carbon) in the olefins is replaced by the organic group of the organopalladium species. These reactions include cross coupling of the organopalladium reagents with olefins, enol ethers, enamides, vinyl silanes, vinyl phosphonates and vinyl halides. The very reactive organopalladium compounds are prepared in the presence of olefin that is to be coupled. The reaction yields products in which the organic group has added exclusively to the least substituted carbon of the double bond (Scheme 1) (Heck, 1968) or in which a new carbon-carbon bond is formed via 1,2-addition of the organopalladium reagent to a strongly polarized carbon-carbon double bond of a heteroatom substituted olefin (Scheme 2) (Daves and Hallberg, 1989).

Scheme 1.

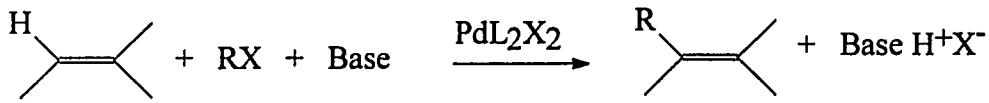
$$[R\ PdOAc] + R'CH{=}CH_2 \longrightarrow R'CH{=}CHR + [HPdOAc]$$

Scheme 2.



The palladium catalyzed vinylation of organic halides provides a very convenient method for forming carbon-carbon bond at the unsubstituted vinylic positions. Generally the reaction does not require anhydrous or anaerobic conditions although it is advisable to limit the access of oxygen when aryl phosphines are used as ligands of the palladium catalyst. This transformation is valuable because it can be carried out in a single step. The general reaction is as follows (Scheme 3).

Scheme 3.



R = Aryl, heterocyclic, benzyl or vinylic

X = Bromide, iodide or (rarely chloride)

L = a ligand

The organic halide employed is limited to aryl, heterocyclic, benzyl or vinyl types, with bromides and iodides used most often. Halides with an easily eliminated beta-hydrogen (i. e., alkyl halides) cannot be used since they form only olefins by the

elimination of the beta- hydrogen under normal reaction conditions. The base needed may be secondary or a tertiary amine, sodium or potassium acetate, or bicarbonate. The catalyst is commonly palladium acetate, although palladium chloride or preformed triarylphosphine palladium complexes can also be employed. A reactant, product or solvent may serve as the ligand for palladium in the reaction involving organic iodides, but generally a triarylphosphine or a secondary amine is required when organic bromides are used. The reaction temperatures range between 50°C to 160°C. Solvents such as acetonitrile, dimethylformamide, hexamethylphosphoramide, N-methyl pyrrolidinone or methanol can be used. The procedure is applicable to a wide range of reactants and the yields are generally good to excellent.

2. 1. 1 MECHANISM OF A TYPICAL HECK REACTION

The basic mechanism for olefinic substitution that Heck proposed has gained significant experimental support. It proceeds through four discrete organometallic reactions (Heck, 1969) (Scheme 4).

(1) An organopalladium reagent is formed *in situ* by oxidative addition of Pd(0) to the organic halide (Yamamoto, 1986). When organic bromides are used, the addition of a phosphine ligand is normally necessary (Dieck and Heck, 1974; Spencer, 1983). If a palladium (II) salt is used a reduction to Pd(0) must take place before the oxidative addition. The reduction is probably promoted by the olefin (Mizoraki et al., 1971) or the amine base (Collman et al., 1987) if present.

(2) A π-complex between the organo-palladium reagent and the olefin is formed.

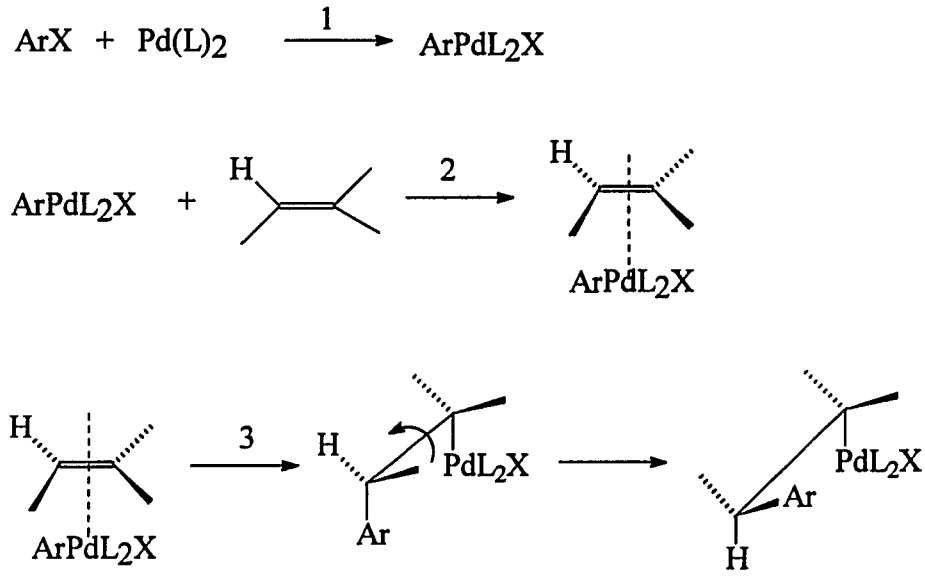
(3) The π-complex collapses by 1,2-addition of the organo-palladium reagent to the olefinic carbons to generate an unstable σ-organopalladium adduct (Yamamoto, 1986);

(4) The resulting σ-adduct decomposes with the elimination of hydridopalladium halide. The reaction is catalyzed by palladium in the presence of a base because the hydridopalladium halide dissociates reversibly and the base shifts the equilibrium to the palladium (0) species which restarts the process.

The direction of addition of the organo-palladium species to an unsymetrically substituted olefin appears to be largely sterically controlled. The organic group behaves as the larger part of the palladium complex and it attacks the less substituted carbon atom of the double bond (Dieck and Heck, 1974). If an electron withdrawing group is attached to one of the carbon atom of the double bond, however, addition of the organic group generally takes place predominantly on the other carbon atom. The presence of an electron donating substituent often causes mixtures of products to be formed with the sterically favored isomer to be predominant. For example, bromo or iodo benzene reacts with a variety of olefins giving products with the percentages of phenyl addition to the olefinic carbons as shown in Table 3 (Heck, 1979). A complication in this reaction may appear if there is more than one sp^3-bonded hydrogen atom beta to the palladium group in the olefin adduct. A mixture of geometric isomers may result or the double bond might be moved from its original position.

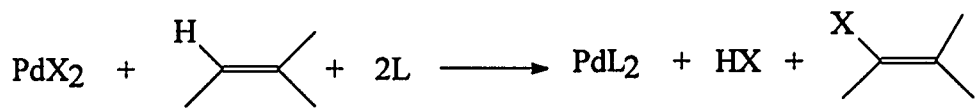
Scheme 4.

Catalytic Cycle:



$$HPdL_2X + Base \longrightarrow PdL_2 + BaseH^+X^-$$

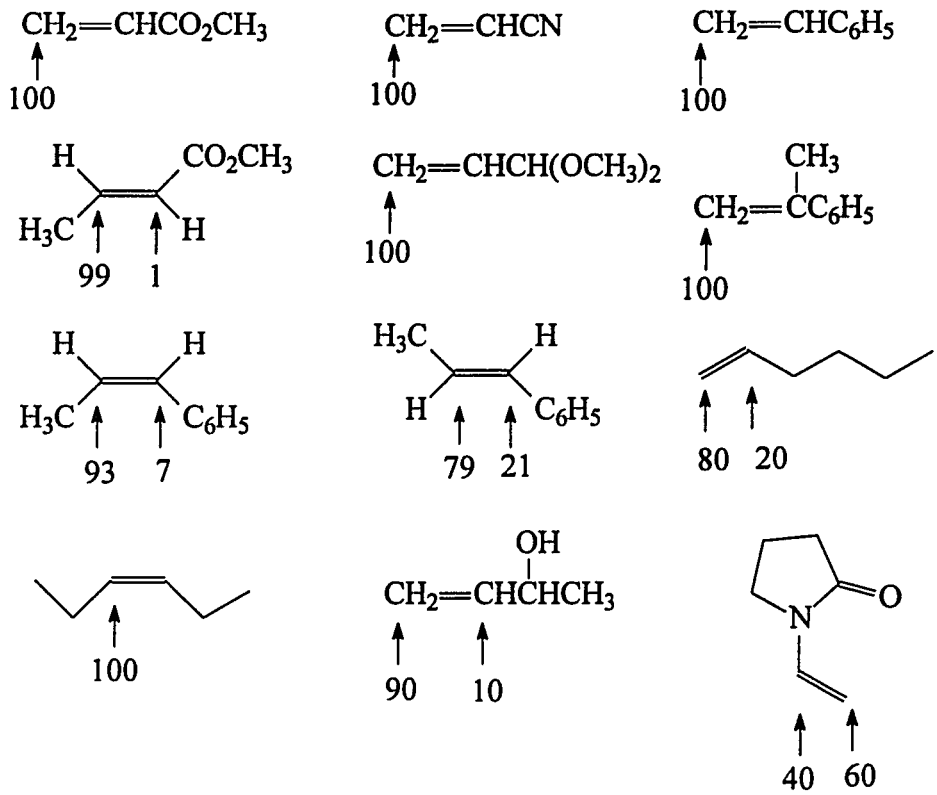
Catalyst formation:



L = Ligand

Table 3.

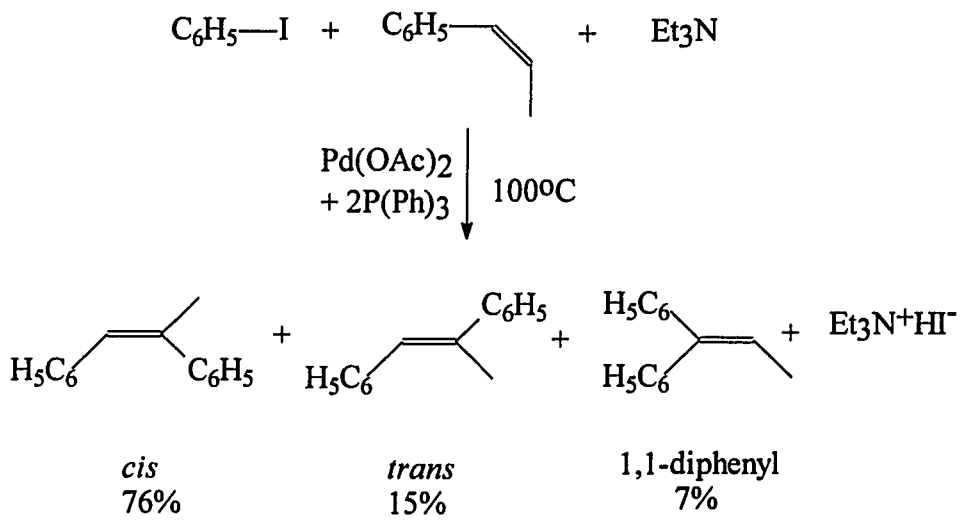
Orientation of Addition of Bromo- or Iodobenzene to Various Olefins



The addition of the organopalladium halide occurs in a *syn* manner and the elimination of the hydridopalladium halide is also *syn*. The stereospecificity of the reaction depends on the reaction conditions. The lower the temperature, the higher are the stereo and the regiospecificity (Dieck and Heck, 1974). Most important is the influence of triarylphosphines. Iodobenzenes and *cis*-1-phenyl-1-propene with triethylamine and palladium acetate as the catalyst at 100°C produce 13.5% *cis*-1,2-diphenyl-1-propene, the stereospecific product, and 57% of the *trans*-isomer. The same reaction with two

equivalents of triphenylphosphine added per palladium acetate gives 76% of the *cis*-isomer and only 15% of the *trans*-isomer. The presence of the phosphine does not affect the direction of addition of the phenylpalladium halide since about the same amount of the 1,1-diphenyl-1-propene is obtained in both reactions (Scheme 5).

Scheme 5.



The triphenylphosphine is believed to decrease the rate of readdition of the hydridopalladium group in an olefin π-complex intermediate to the double bond, relative to its rate of dissociation from the complex. The phosphine improves the selectivity for *cis*-products by reducing the reverse readdition and reelimination of metal hydride from the intermediate (Dieck and Heck, 1974).

2. 2. 0 SCOPE AND LIMITATIONS

2. 2. 1 THE ORGANIC HALIDE

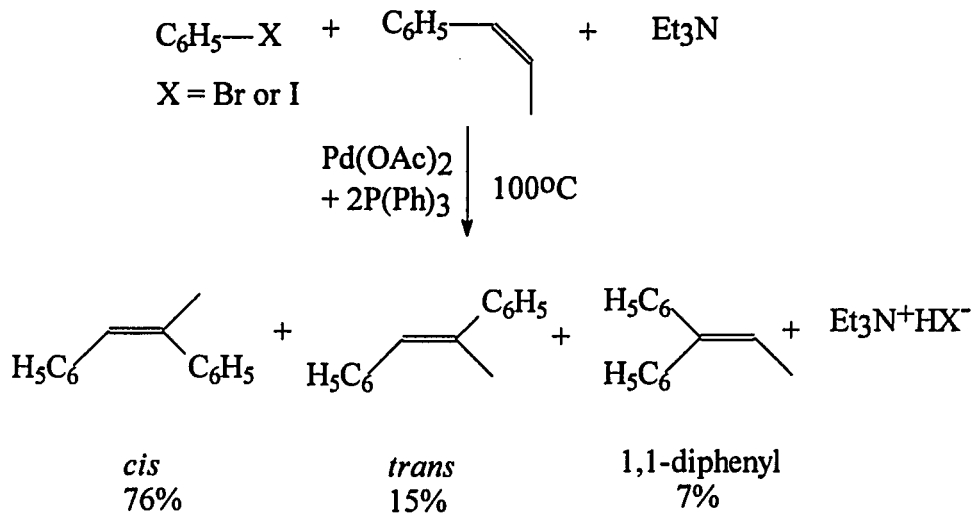
An organic halide with sp3-bonded hydrogen atoms beta to the halide group is a major limitation. The palladium alkyls formed from these halides undergo palladium hydride elimination more rapidly than addition to the olefins and only elimination products are produced. Aryl, many heterocyclic, benzyl and vinyl halides react normally. Some halides like methyl halides, haloacetate esters, phenacylbromide and neopentyl bromide do not yield the expected products under usual conditions.

A second limitation is the halogen atom present on the organic halide. Iodide is the best halogen for these type of coupling reactions. Bromide is also effective, but an iodide is found to be more reactive than a bromide. A typical example is the reaction between bromo or iodobenzene and cis-1-phenyl-1-propene at 100°C in presence of palladium acetate-triphenylphosphine catalyst (Scheme 6). The reaction products were essentially the same but the iodide reacted twice as fast as the bromide (Dieck and Heck, 1974). Chlorides generally do not undergo this reaction with some exceptions like benzyl chloride (Heck and Nolley, 1972). Organic fluorides have not been tried.

A wide range of substituents on the organic halide is permitted but an *ortho*-carboxyl group is found to impede the reaction although *ortho*-methyl ester reacts normally (Patel et al., 1977). The presence of strong electron-donating substituents on organic bromides give low yields. This is due to the quaternization of the phosphine

catalyst and/or the reduction of the halide to hydrocarbon. The quaternization of the phosphine can be avoided by using hindered phosphines like tri-o-tolyl phosphine.

Scheme 6.



2. 2. 2 THE OLEFIN

The size of the olefin and the number of substituents on the double bond of the olefin is the primary factor in determining the reactivity of the olefin. Rates of reaction and yields of product generally decrease with increasing size and the number of substituents around the double bond. Ethylene is the most reactive olefin (Plevyak and Heck, 1978). Most monosubstituted ethylenes react well. Disubstituted ethylenes react reasonably well but slowly. Poor yields are obtained with trisubstituted ethylenes (Melpolder and Heck, 1976). Dimerization of the organic halide is frequently observed as a side reaction when the olefin used has low reactivity. The presence of electron-withdrawing substituents on the double-bond carbon atom generally directs the incoming organic group selectively to

the other carbon atom of the double bond. However, electron-donating substituents generally cause addition to both carbon atoms. The amount of addition to each carbon atom in these reactions is strongly influenced by the steric effects in both the halide and the olefin. The organic group of the organo-palladium complex preferentially attacks the less substituted carbon atom of the double bond.

2. 3. 0 THE "ATYPICAL" HECK REACTION

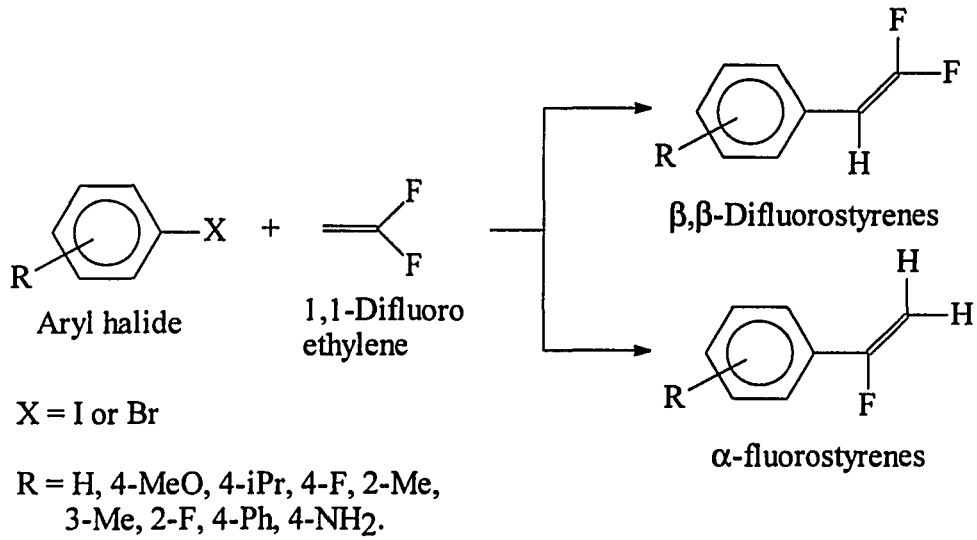
The Heck reaction, as described earlier in Chapter 3, is an extremely convenient method for arylation of olefinic compounds. Typically, the reaction proceeds by substitution of a vinylic hydrogen atom by the organic group of an organic halide. High regioselectivity was found when unsymetrically substituted olefins were used, resulting in arylation of the less substituted carbon from the carbon-carbon double bond of the olefin. This phenomenon is mainly explained by the steric factors involved. One of the key steps in this reaction is the β-hydride elimination.

Recently, two German scientists, Walter Heitz and Arno Knebelkamp (1990) tried to synthesize β, β-difluorostyrenes from a reaction between aryl halides with 1,1-difluoroethylene. Unexpectedly, the products obtained were α-fluorostyrenes due to the substitution of vinylic fluoride instead of a hydride from 1,1-difluoroethylene (Scheme 7). Even if β-hydride elimination is possible, the β-fluorine elimination is the preferred type of elimination as observed in the reaction of iodobenzene with vinyl fluoride to give styrene (Heitz and Knebelkamp, 1990) (Scheme 8).

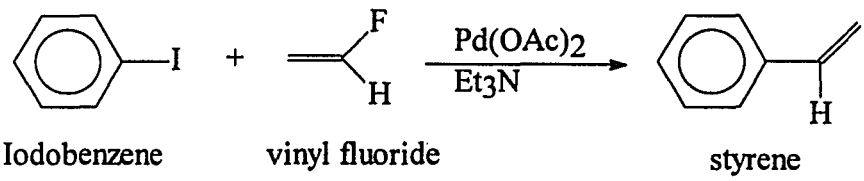
This was the first time that the α-fluorostyrenes were obtained in a one step reaction, catalyzed by palladium (II) acetate in yields ranging from 30% - 70%. Aryl iodides were found to be more appropriate substrates or starting materials than aryl bromides, since they show total conversion due to their high reactivity. Byproducts

formed in this reaction include acetophenones (1%) (Matsuda et al., 1962), β, β-difluorostyrenes (2%), biphenyls as coupling products of the organic halide with itself (10%), dehalogenated products (5%), 1,1-diphenylethylenes (3%) and the isomeric E/Z-monofluoro stilbene (5%).

Scheme 7.



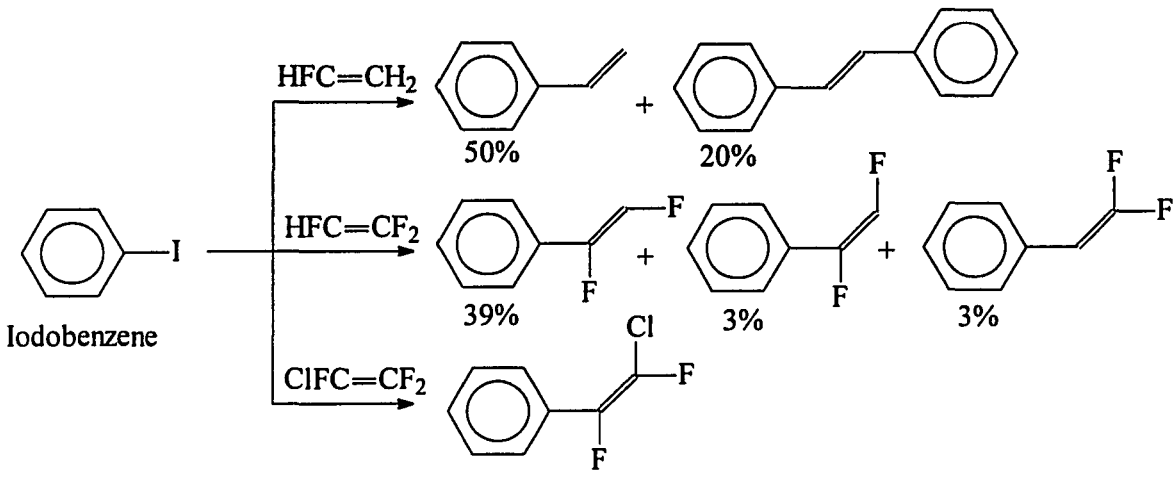
Scheme 8.



Heitz and Knebelkamp also tried reactions of iodobenzene with other fluoroolefins like vinyl fluoride, trifluoroethylene and chlorotrifluoroethylene. In all the cases, substitution of a vinyl fluoride was observed to be the common phenomenon for product formation

(Scheme 9). These results were also the first examples of electronic control in the Heck reaction which was significant in the presence of fluoroolefins.

Scheme 9.



2. 3. 1 MECHANISM OF "ATYPICAL" HECK REACTION

As in the normal Heck reaction, the mechanism of "atypical" Heck reaction is again divided into four discrete steps (Scheme 10).

(1) Oxidative addition of the palladium (0) complex, generated *in situ* (Heck, 1982; Collman et al., 1987), to aryl halide to form the organo-palladium species;

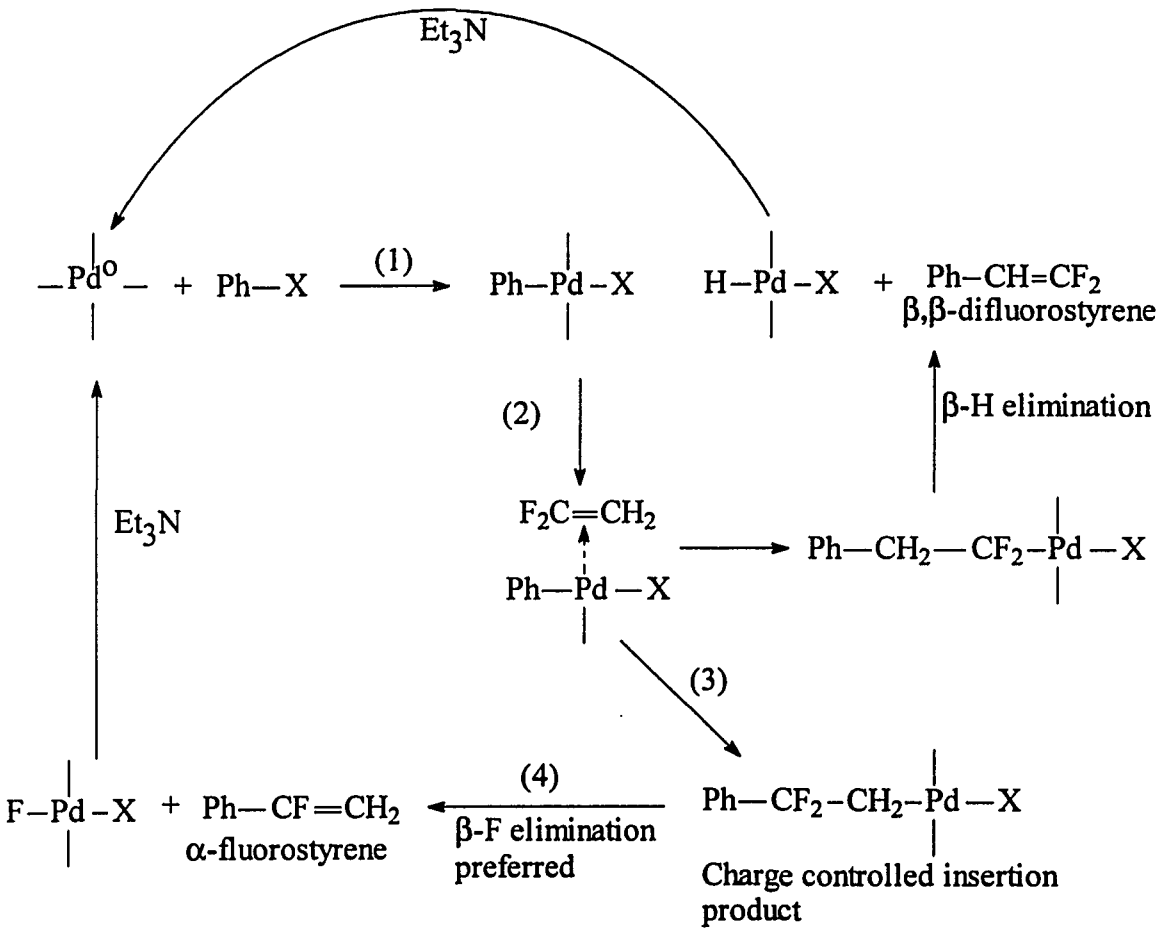
(2) The co-ordination of organo-palladium species to the olefinic double bond;

(3) Next, the insertion of the arene to the CF_2-group of 1,1-difluoroethylene. If steric aspects were relevant then the arene would probably add to the CH_2-group of 1,1-difluoroethylene, resulting in the formation of β, β-difluorostyrenes as the final product but only trace amounts of this product was detected. This is explained by the charge

control, emphasized by MNDO-calculations (Table 4). The charges on C1 and C2 differ considerably, so the addition of the arene occurs exclusively on the CF_2-group resulting in the selective formation of α-fluorostyrenes.

(4) Finally, β-fluorine elimination results in the formation of product and a palladium (II) salt which is converted back to palladium (0) by triethylamine to restart the catalytic cycle.

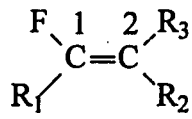
Scheme 10[a].



a. Co-ordination of palladium is completed by triphenylphosphine or the solvent used in the reaction like dimethylformamide , acetonitrile or N-methylcaprolactam , depending on the reaction conditions.

This mechanism is supported by the charge calculations done on C1 and C2 of some vinyl fluorides (Table 4) (Dewar and Thiel, 1979).

Table 4: Vinyl Fluorides : Calculated charges on C1 and C2 by MNDO methods.



Olefin	Net atomic charges C1	C2
$R_1 = R_2 = R_3 = H$	+ 0.11	- 0.11
$R_1 = F, R_2 = R_3 = H$	+ 0.31	- 0.12
$R_1 = R_2 = F, R_3 = H$	+ 0.28	+ 0.09
$R_1 = R_2 = F, R_3 = Cl$	+ 0.33	+ 0.12

2. 4. 0 DIFFERENT SYNTHETIC APPROACHES TO α-FLUOROSTYRENES

A few methods for the synthesis of α-fluorostyrenes have been reported in literature.

The first successful approach towards α-fluorostyrenes was recorded in the early 60's by a group of scientists at the American Cyanamid Company (Matsuda et al., 1962). A number synthetic routes were attempted before they finally succeeded in developing this two step route, the first step of which was synthesis of α,α-difluoroethyl benzene by one of the methods shown in Equations 1 - 4 (Scheme 11).

Scheme 11.

$$C_6H_5{-}C{\equiv}CH + 2\,HF \xrightarrow{\text{Ether, } 0^oC} C_6H_5{-}CF_2{-}CH_3 \qquad (1)$$

$$C_6H_5{-}C{\equiv}CH + 2\,HF \xrightarrow[\text{on act. charcoal}]{\text{13 - 14\% HgO}} C_6H_5{-}CF_2{-}CH_3 \qquad (2)$$
$$150^oC$$

$$C_6H_5{-}\overset{\displaystyle Cl}{\overset{|}{C}}{=}CH_2 + 2\,HF \xrightarrow[\text{- HCl}]{\text{Ether, } 0^oC} C_6H_5{-}CF_2{-}CH_3 \qquad (3)$$

$$C_6H_5{-}\overset{\displaystyle Cl}{\overset{|}{C}}{=}CH_2 + 2\,HF \xrightarrow[\text{on act. charcoal}]{\text{13 - 14\% HgO}} C_6H_5{-}CF_2{-}CH_3 \qquad (4)$$
$$150^oC, \text{ - HCl}$$

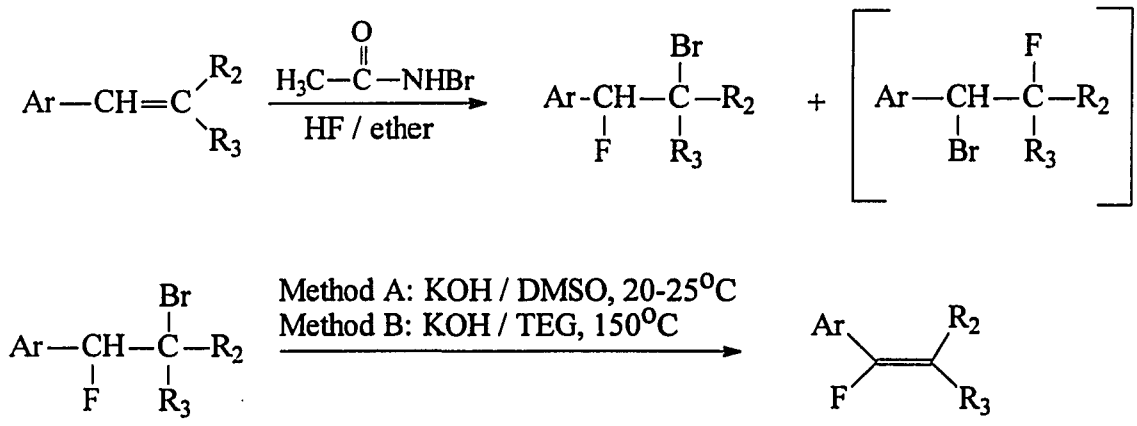
The α,α-difluoroethyl benzene was then pyrolyzed to give the desired α-fluorostyrene and hydrogen fluoride (Equation 5).

$$C_6H_5—CF_2-CH_3 \xrightarrow{350 - 450^oC} \underset{\alpha\text{-fluorostyrene}}{C_6H_5—CF{=}CH_2} + HF \qquad (5)$$

The best method to make α,α-difluoroethyl benzene was the one in equation 2. This method gave yields of 40 - 45% at phenylacetylene conversion levels of almost 100%.

Another approach to the synthesis of α-fluorostyrenes was published in 1978 by Eckes and Hanack (Eckes and Hanack, 1978). This was a three step process which required the corresponding styrene to be used as the starting material to make the respective α-fluorostyrene (Scheme 12). The overall yield of the α-fluorostyrenes is shown in Table 5.

Scheme 12.



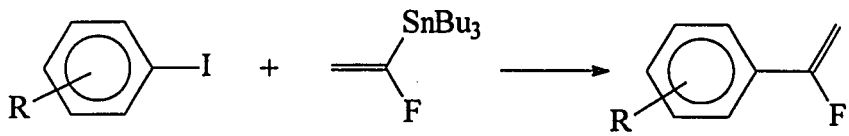
KOH = Potassium hydroxide
DMSO = Dimethyl sulfoxide
TEG = Triethylene glycol

Table 5: Overall yields from Scheme 12

R_1	R_2	R_3	Overall Yield (%)
C_6H_5	H	H	63
$H_3C—C_6H_4$	H	H	72
$H_3CO—C_6H_4$	H	H	40
$H_3C—C_6H_4$	CH_3	H	39
$H_3CO—C_6H_4$	CH_3	CH_3	55

A third approach to α-fluorostyrenes is a much more recent approach, which involves a coupling reaction between α-fluorovinyl tributyltin , a synthetic equivalent of α-fluoroethene anion and iodoarenes (Scheme 13) (Matthews et al., 1994). α-fluorovinyl tributyltin can also be coupled with substrates other than iodoarenes as shown in Table 6.

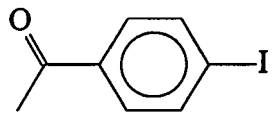
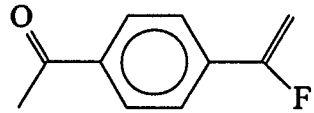
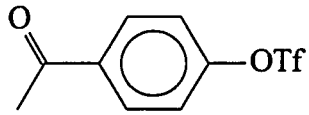
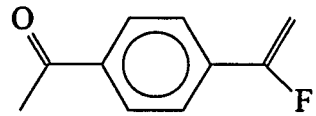
Scheme 13.



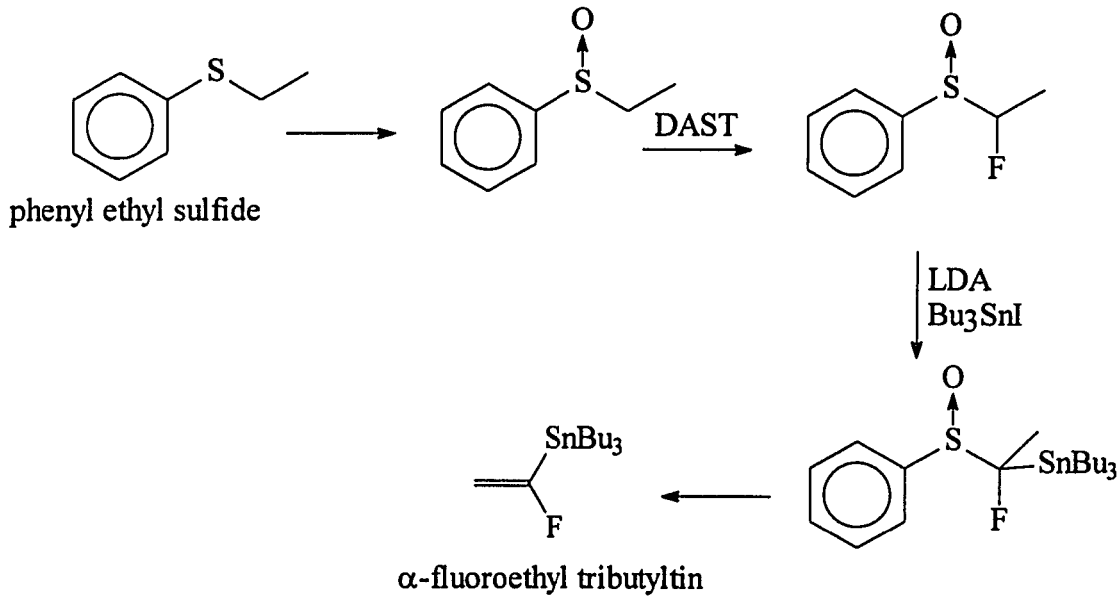
Iodoarenes α-fluorovinyl tributyltin α-fluorostyrenes

However, this method requires the synthesis of α-fluorovinyl tributyltin, which involves a five step procedure starting from phenyl ethyl sulfide as outlined in Scheme 14.

Table 6: Yields from Scheme 13.

Substrate	Conditions	Product	Yield
	$Pd(PPh_3)_4$ THF, 65°C		66 %
	$Pd(PPh_3)_4$,LiCl THF, 65°C (1h)		65 %

Scheme 14.



α-fluoroethyl tributyltin

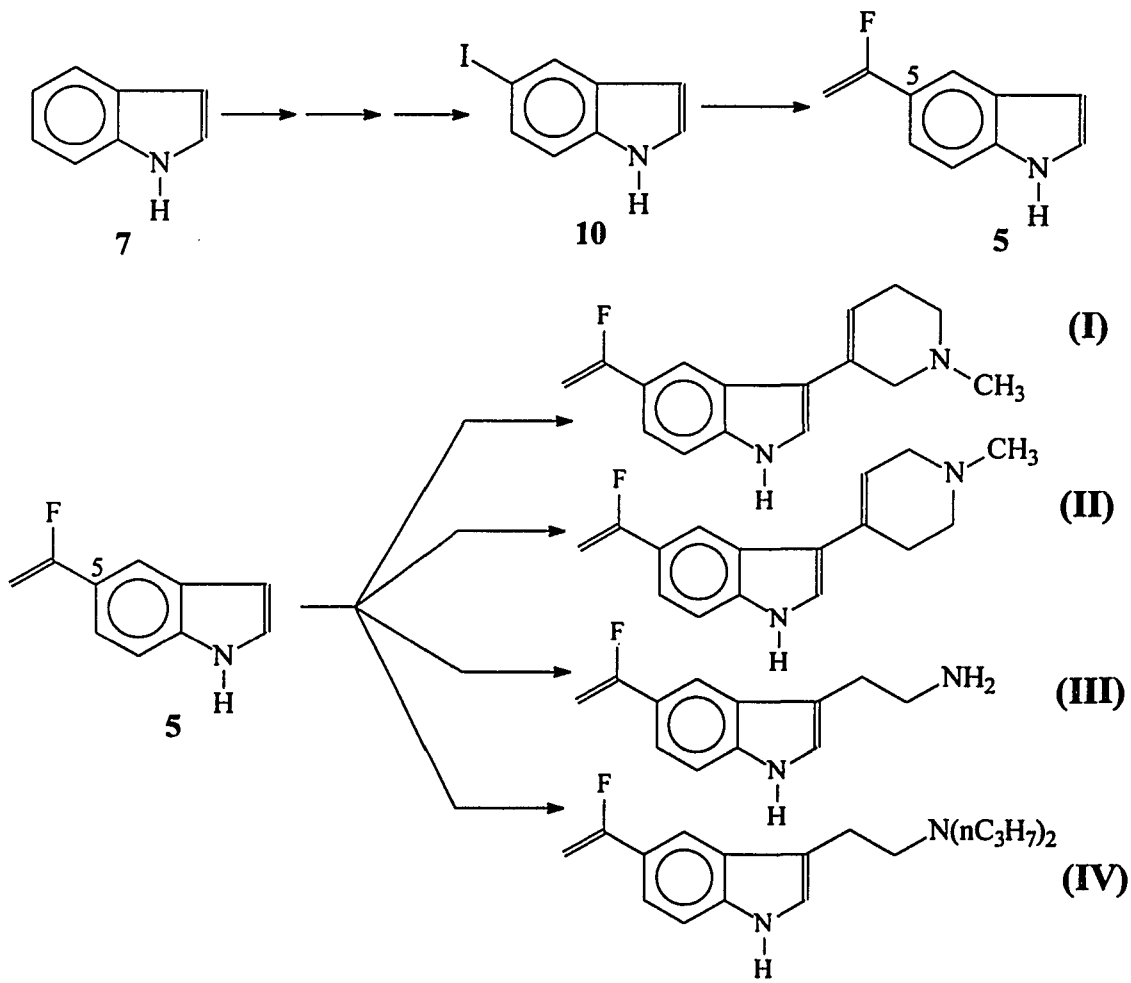
DAST = Diethylaminosulfurtrifluoride
LDA = Lithium diisopropylamine

CHAPTER 3: CHEMISTRY AND DISCUSSION

3. 1. 0 THE SYNTHESIS OF 5-(α-FLUOROVINYL) INDOLE

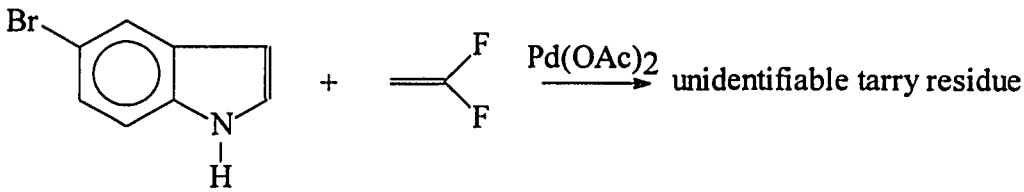
5-(α-fluorovinyl)indole (5-FVI; **5**) is the starting material used for the synthesis of all the proposed target compounds (**I, II, III, IV**). Therefore the first step in the synthetic approach (Scheme 15) towards these target compounds was to prepare 5-FVI.

Scheme 15. Summarized Synthetic approach



There are a few methods reported in the literature to introduce an α-fluorovinyl group into aromatic systems (Matsuda et al., 1962; Eckes and Hanack, 1978; Matthews et al., 1994). Because of potential shortcomings anticipated with these methods, like severe reaction conditions, number of steps involved and the availability of the starting materials, we decided to investigate the "atypical" Heck reaction discovered by Heitz and Knelbelkamp (Heitz and Knebelkamp, 1991). The reaction conditions here are much simpler, the starting materials are readily available and it is a single step reaction from 5-iodoindole (**10**). Commercially available 5-bromoindole was initially employed as the aryl halide to react with 1,1-difluoroethylene gas in presence of palladium acetate as the coupling catalyst at 1000 psi and 120°C. All that was recovered was unidentifiable, sticky, tarry, complex residue (Scheme 16).

Scheme 16.

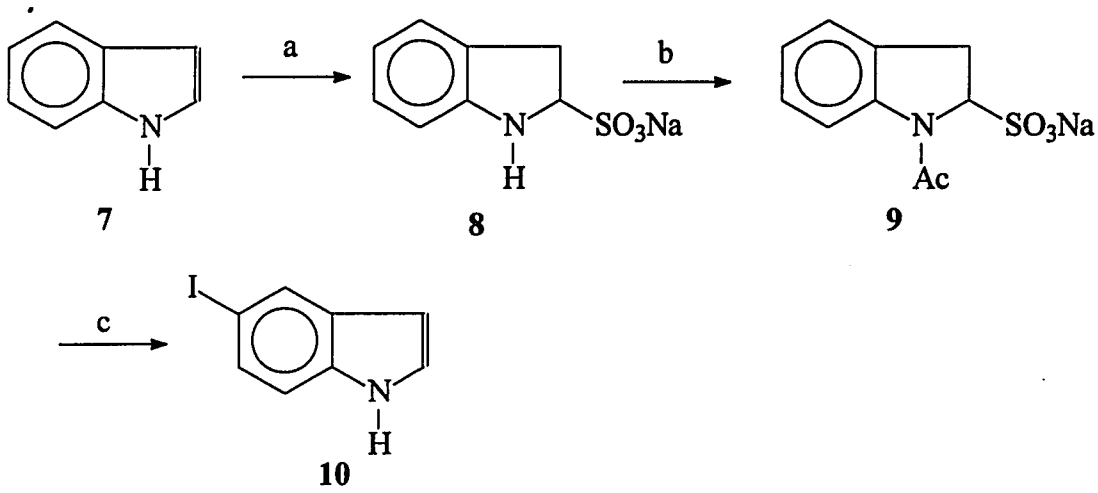


5-bromoindole 1,1-difluoroethylene

Protection of the indole nitrogen with p-toluenesulfonyl group (Illi, 1979) avoided this apparent polymerization but the reaction was too slugish. GCMS analysis of the reaction mixture after 96 hr. still showed 35% of the aryl halide unreacted and only 20% product formation. This prompted us to examine the use of 5-iodoindole (**10**) as the aryl halide since aryl iodides are known to be more reactive in the Heck reaction

(Heitz and Knebelkamp, 1991). **10** was prepared by the literature method (Russell et al., 1985) (Scheme 17) and its nitrogen was protected by the p-toluenesulfonyl group.

Scheme 17.

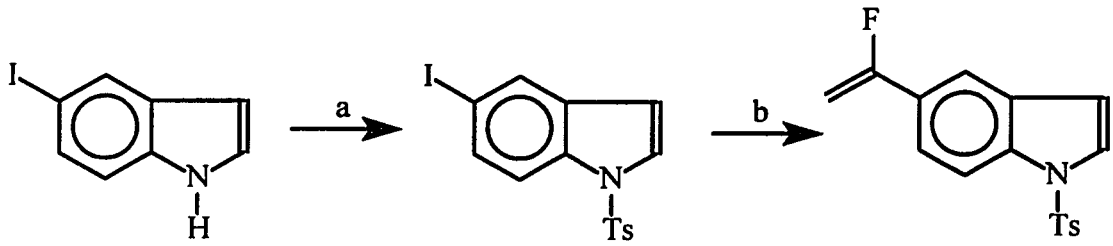


Conditions: a. $NaHSO_3$, EtOH
b. Acetic anhydride
c. i) Iodine monochloride, KI
ii) NaOH, H_2O

The reaction of 5-iodo-N-tosyl indole (**11**) with 1,1-difluoroethylene under similar reaction conditions (except much lower pressure, about 250 psi) was much faster, with complete consumption of **10** in 24 hr. (Scheme 18). The yield was only 35-37% on our first few attempts but was finally improved to 50% by increasing the pressure of the 1,1-difluoroethylene gas in the reaction vessel to 800 psi at 120°C. The product, 5-α-fluorovinyl-N-tosyl indole (**12**) was obtained in white crystalline form after work up and purification. The N-tosyl group can be removed in nearly quantitative yield using sodium methoxide/methanol whenever required to obtain the desired 5-α-fluorovinyl indole (**5**). The unprotected 5-α-fluorovinyl indole was found to be unstable to atmospheric conditions, possibly explaining the failure to isolate

characteristic products either when 5-bromo- or 5-iodoindole were employed as aryl halide.

Scheme 18.



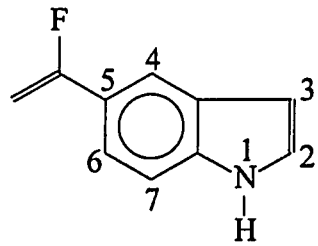
10 **11** **12**

Reagents: a. p-TsCl, $(n\text{-}Bu)_4NHSO_4$, 15% NaOH, toluene, r.t, 3 hrs.
b. 1,1-difluoroethylene, $Pd(OAc)_2$, Et_3N, DMF, 24 hrs.

p-TsCl = p-toluenesulfonyl chloride

3. 2. 0 SYNTHESIS OF THE PROPOSED TARGET COMPOUNDS

5-(α-fluorovinyl) indole (5-FVI) (**5**) was used as the starting material for all the target compounds (**I, II, III** and **IV**). It was prepared from 5- iodoindole (**10**) as discussed chapter 6.



5

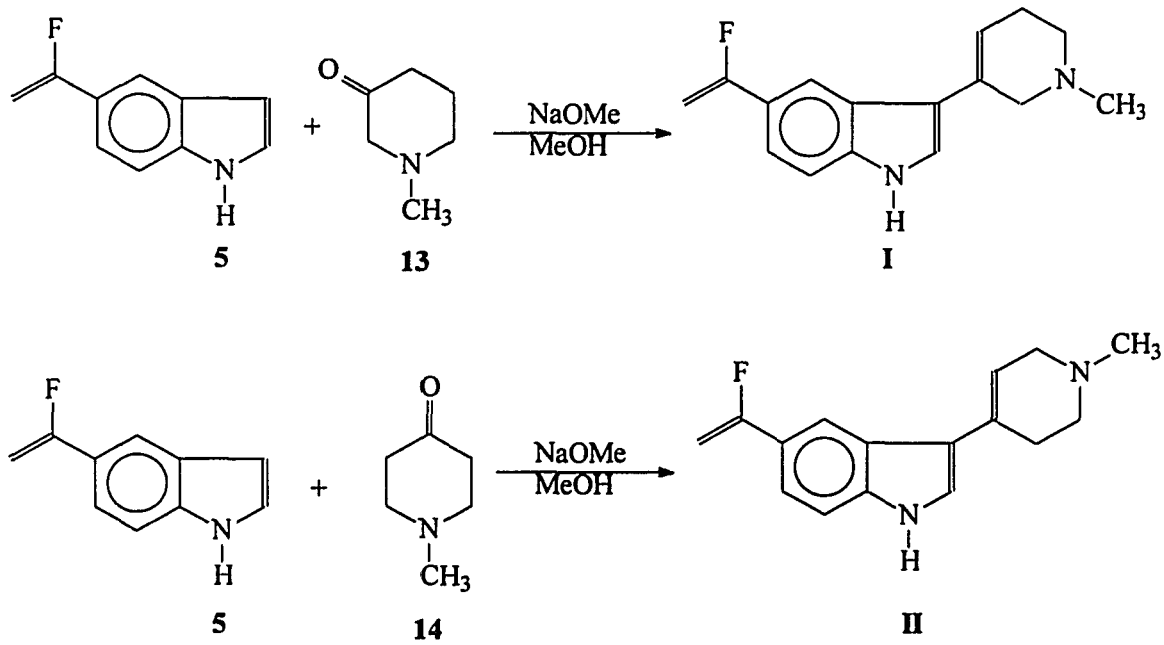
3. 2. 1 SYNTHESIS OF 5-(α-FLUOROVINYL)-3-(1',2',5',6'-TETRAHYDRO PYRIDIN-3'- AND -4'-YL) INDOLES (**I** AND **II**)

5-(α-fluorovinyl)-3-tetrahydropyridyl indoles **I** and **II** were prepared by base catalyzed direct condensation of 5-FVI with N-methyl-3- and -4-piperidones respectively (Agarwal et al., 1993) (Scheme 19). Condensation of 5-FVI with N-methyl-4-piperidone (**14**) was much more efficient and higher yielding than that with N-methyl-3-piperidone (**13**). Therefore an alternative approach for the preparation of 5-substituted-N-methyl-(1,2,5,6-tetrahydropyridyl)-3-yl indoles developed by our group (Zheng et al., 1994) was attempted for the synthesis of **I**. This involved the palladium catalyzed cross-coupling of N-tosyl-3-indolyl boronic acids (**17**) with N-methyl-3-hydroxy-1,2,5,6-tetrahydropyridine

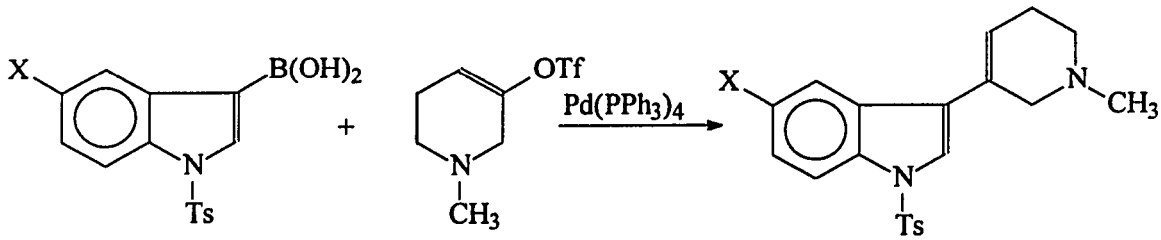
triflate (**18**) (Scheme 20). Indolyl-3-boronic acids (**17**) were prepared from N-tosyl indole (**15**) via 3-acetoxymercurio-N-tosyl indoles (**16**) (Scheme 21). This approach did not take us to our target but yielded an interesting result. The α-fluorovinyl group on 5-(α-fluorovinyl)-N-tosylindole (**12**) was converted to an acetyl group during its acetoxymercuration to give **20** (Scheme 22). The proposed mechanism is shown in Scheme 23. The base catalyzed direct condensation method gave us **I** and **II** in 25% and 55% yields respectively.

In both cases the N-tosyl-5-FVI (**12**) can be used directly without detosylation since the tosyl group on the nitrogen of indole is removed under sodium methoxide-methanol conditions and does not interfere in the condensation.

Scheme 19.

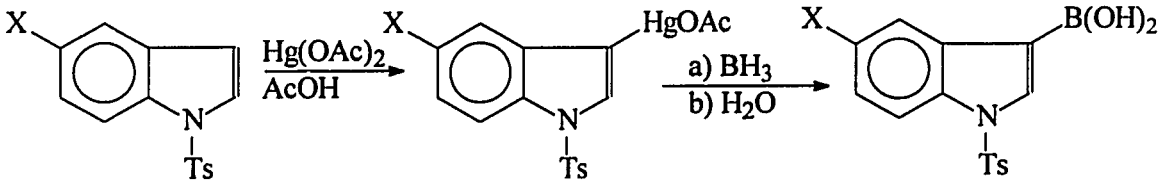


Scheme 20.



17 18 19

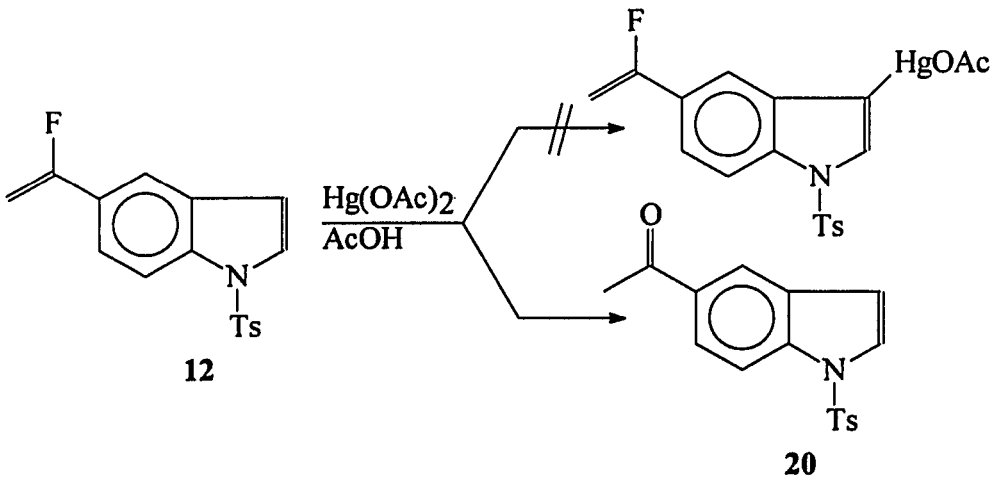
Scheme 21



15 16 17

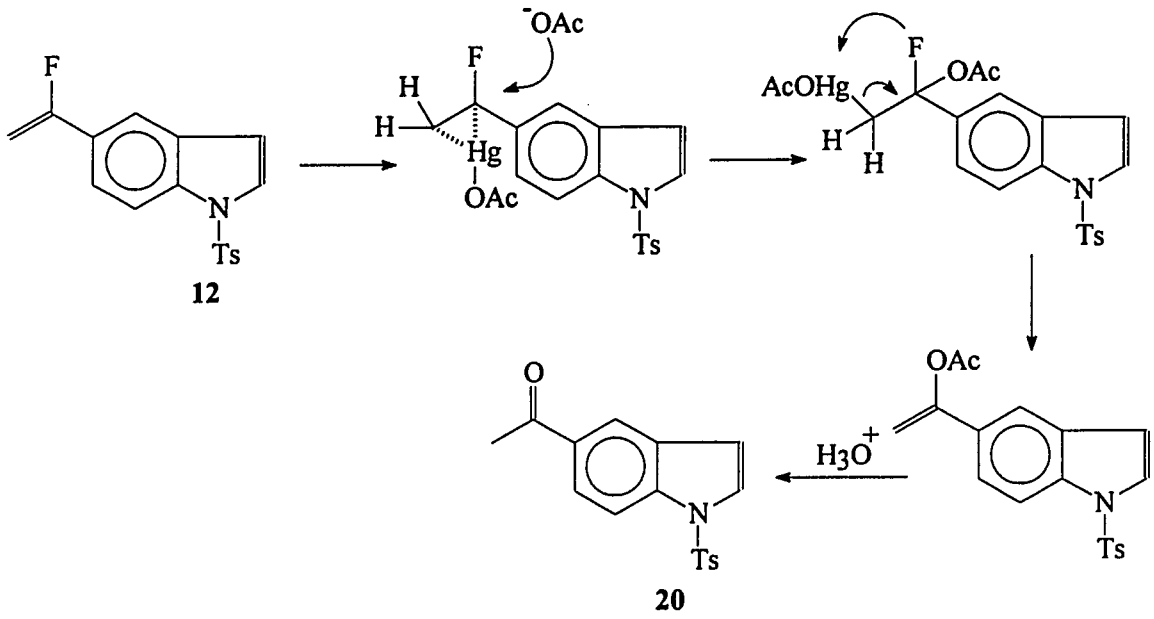
X = H, CH_3O
Ts = p-toluenesulfonyl

Scheme 22.



12 20

Scheme 23.



One of the reason for low yields in direct condensation of indoles with N-methyl-3-piperidone (**13**) is the tendency of this piperidone to self condense and form dimers and trimers of itself under the reaction conditions employed. The best yields of 25 - 30% were obtained only after several modifications in the method of addition of the piperidone to the reaction mixture. We found that dropwise addition of a very dilute solution of the piperidone to a concentrated solution of 5-FVI in sodium methoxide-methanol under refluxing conditions gave us the best yields of the condensed product **I**.

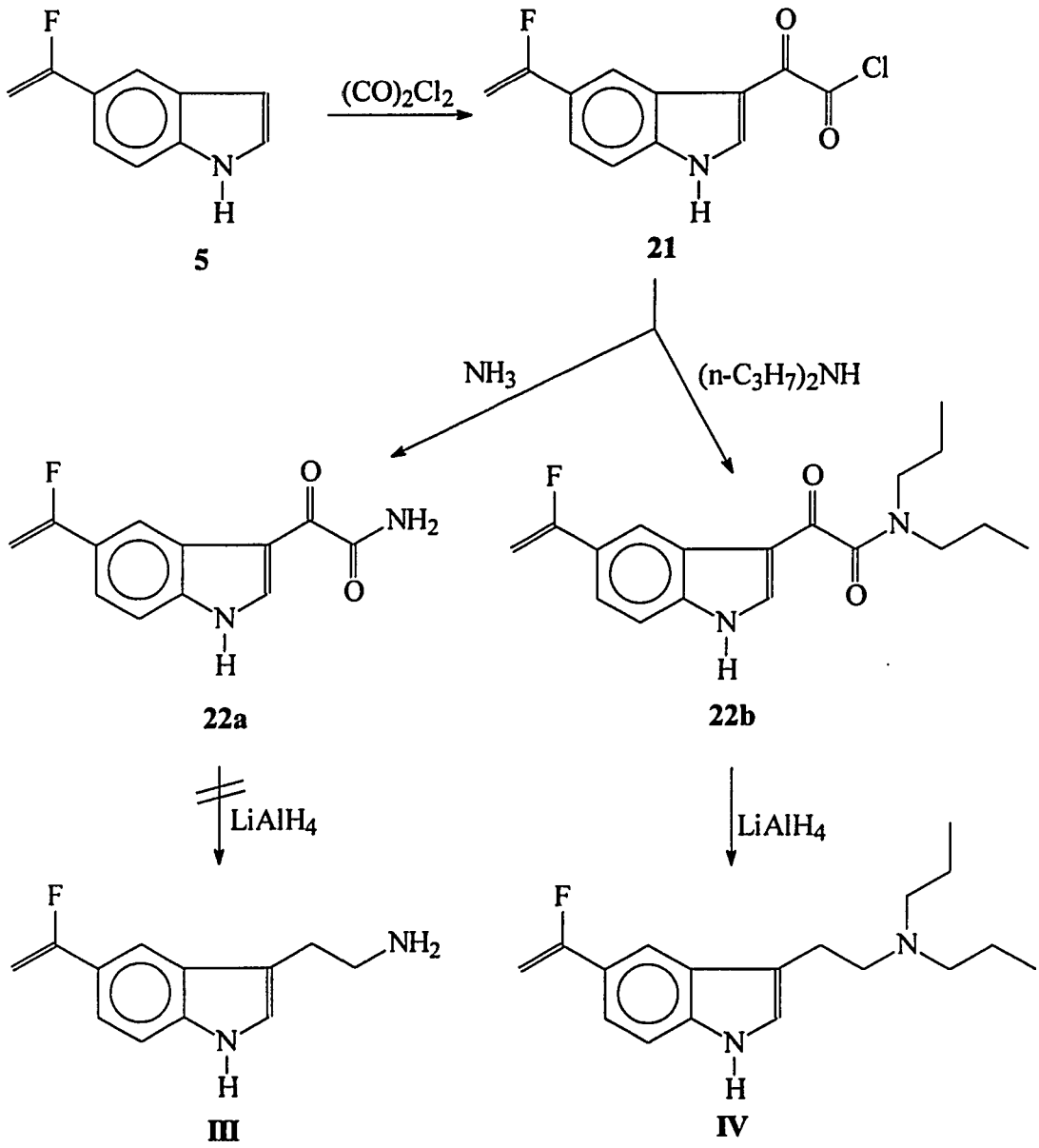
The direct condensation of 5-FVI with N-methyl-4-piperidone (**14**) was straightforward and simple. The product **II** was isolated as nice yellow shiny flakes

directly by allowing the reaction mixture to cool slowly down to room temperature and then cooling it further down to ice bath temperatures.

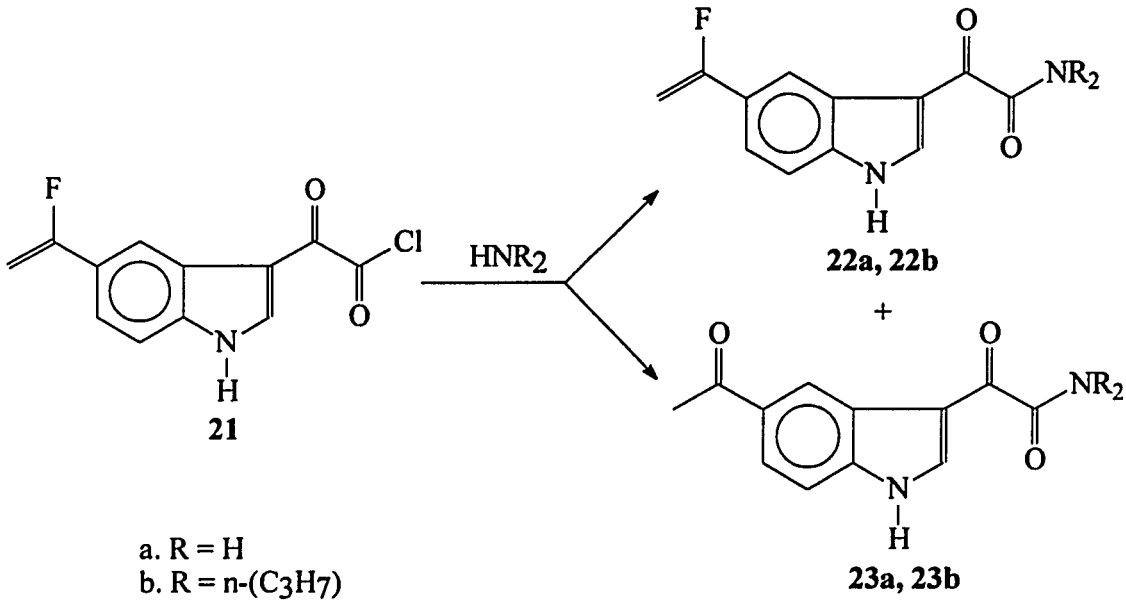
3. 2. 2 5-(α-FLUOROVINYL) TRYPTAMINES (III AND IV) :

The initial strategy for the synthesis of these compounds was the preparation of glyoxyl chloride (**21**) by reacting 5-FVI with oxalyl chloride, subsequent reaction of **21** with appropriate amine components to give the respective glyoxylamides (**22a**, **22b**) (Speeter, 1958) and the reduction of these glyoxylamides with lithium aluminum hydride (Kametani et al., 1972) (Scheme 24). The glyoxyl chloride **21** was obtained in about 80% yield but an unexpected result was obtained in the subsequent reaction of **21** with the amine components. In addition to the desired product **22a** or **22b**, a second product, 5-acetyl-3-glyoxylamide (**23a** or **23b**), formed via acid-catalyzed hydrolysis was obtained (Scheme 25). The proposed mechanism is shown in Scheme 26 (Matsuda et al., 1962). The unexpected products were analyzed by GCMS, ^{1}H-NMR, ^{13}C-NMR, and ^{19}F-NMR. The glyoxylamide **22b** was separated from **23b** by chromatography and further reduced by lithium aluminum hydride to the desired target compound **IV**. The glyoxylamide **22a** could not be separated easily from **23a** and furthermore, it was insoluble in ether, THF, and dioxane, the solvents used in the subsequent $LiAlH_4$ reduction. This prompted us to search for new methods to synthesize 5-α-fluorovinyl tryptamine **III**.

Scheme 24.

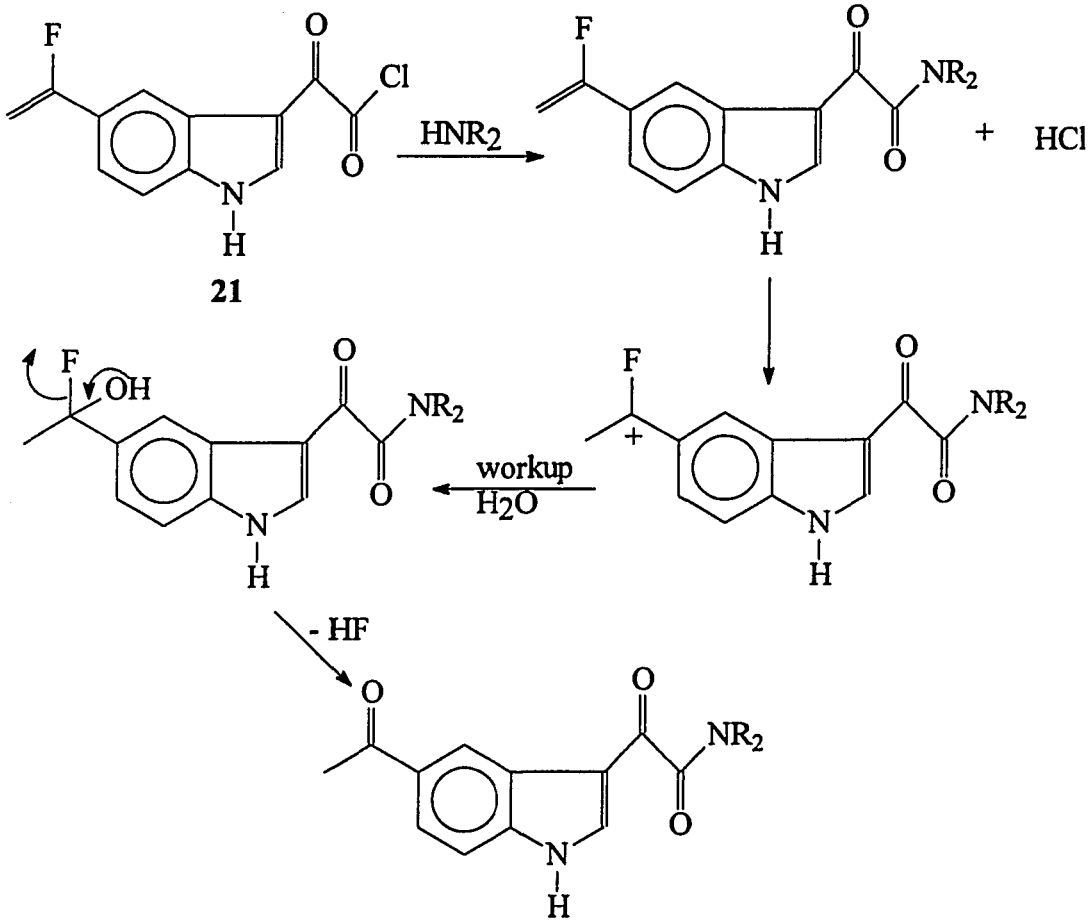


Scheme 25.



Attempted reaction of 5-FVI indole Grignard reagent **24** with aziridine (Bocourt et al., 1960), and its reaction with chloroacetonitrile and subsequent $LiAlH_4$ reduction (Speeter, 1956) failed due to the apparent instability of 5-FVI Grignard reagent (Scheme 27). Another approach involving the preparation of 3-nitrovinyl indole and its subsequent $LiAlH_4$ reduction to tryptamine (Buchi and Mak, 1977) was also attempted but was unsuccessful due instability of 5-FVI towards trifluoroacetic acid, the solvent used in this case (Scheme 28).

Scheme 26.

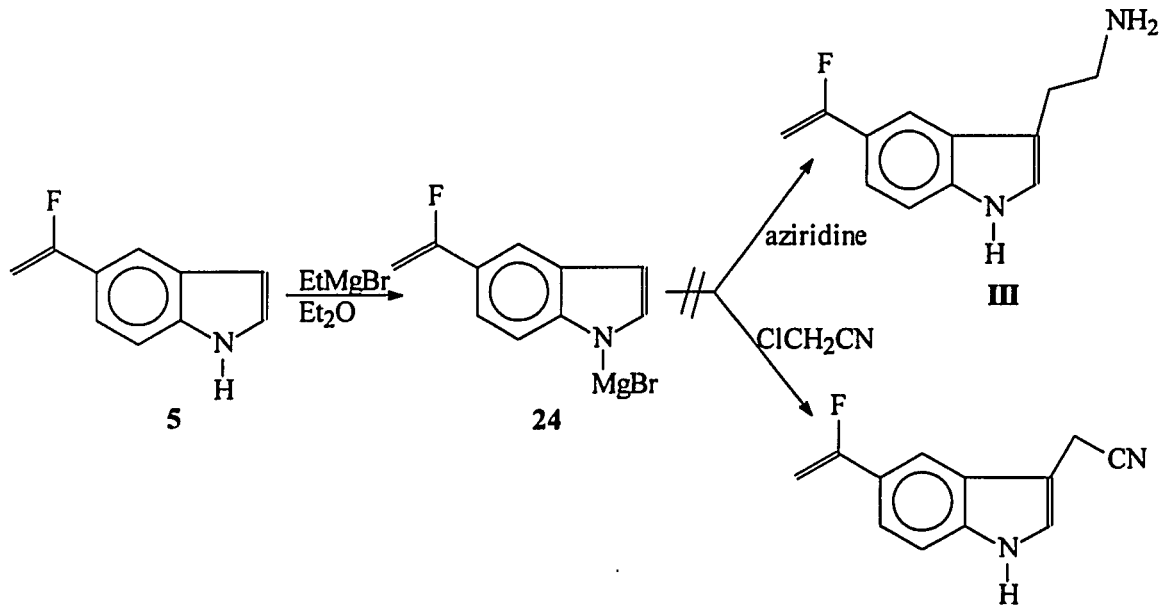


23a, 23b

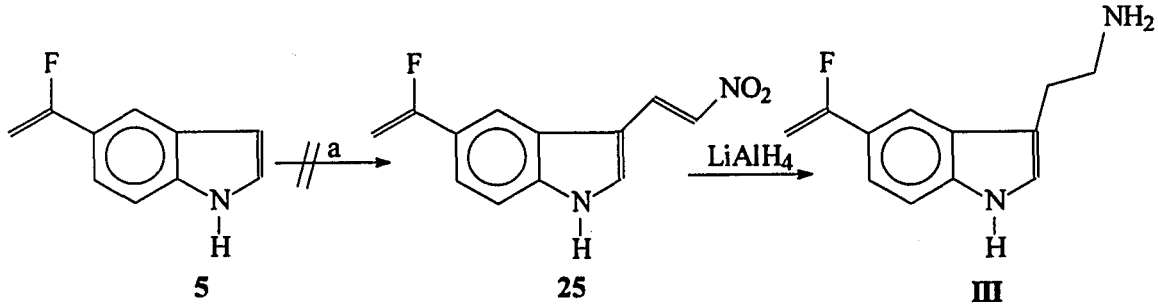
We finally succeeded in getting to the primary 5-(α-fluorovinyl) tryptamine (**III**) through the gramine route. The key here was to avoid strongly acidic conditions. Very weak acidic conditions are essential for the reaction to be faster and efficient. If the reaction is carried out in absence of acid then the reaction takes very long time since it goes through the formation of N-gramine and its subsequent isomerisation to the desired 3-gramine. Some 1,3-digramine is also formed in the process. Reaction temperature is

also important here. This reaction is normally performed at room temperature but here, the reaction had to be carried out at reflux temperatures of the solvent used, in this case, ethanol, to achieve full conversion of 5-FVI. Thus, 5-(α-fluorovinyl) gramine (**26**) was prepared in 75% yield from 5-FVI, paraformaldehyde, and 40% aqueous solution of dimethylamine and 1 equivalent of glacial acetic acid (Swaminathan and Ranganathan, 1957; Monti and Johnson, 1970). The gramine (**26**) was easily converted to 5-(α-fluorovinyl)-3-acetonitrile (**27**) in 95% yield and subsequently reduced with $LiAlH_4$ to obtain the target compound **III** (Scheme 29).

Scheme 27.

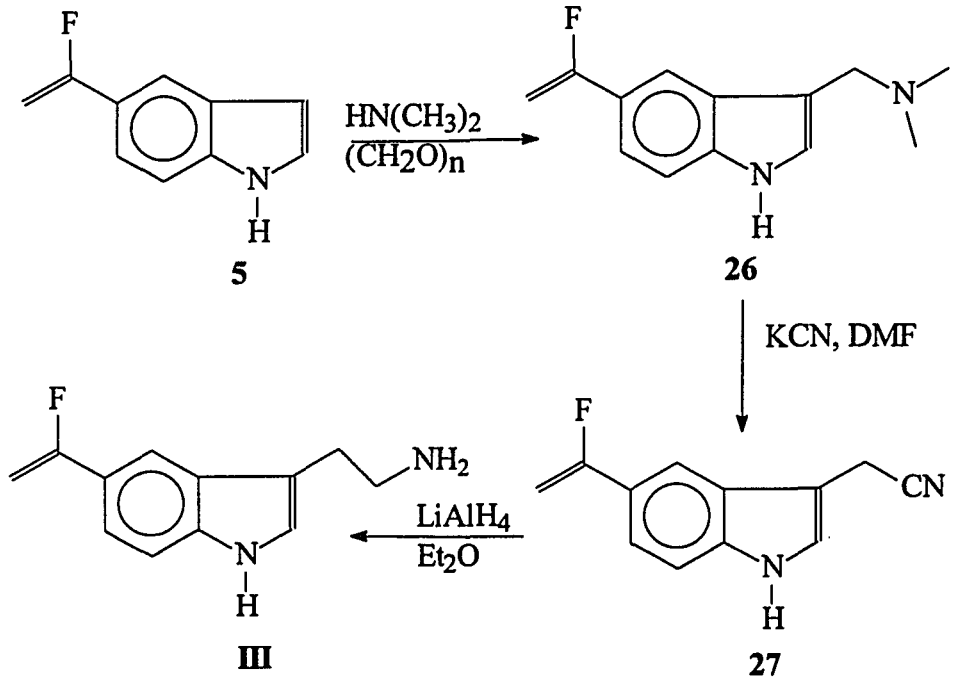


Scheme 28.



a: N,N-Dimethyl-2-nitrovinylamine, TFA

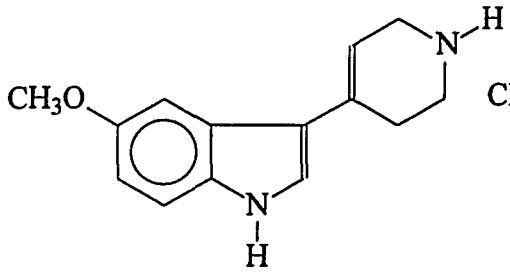
Scheme 29



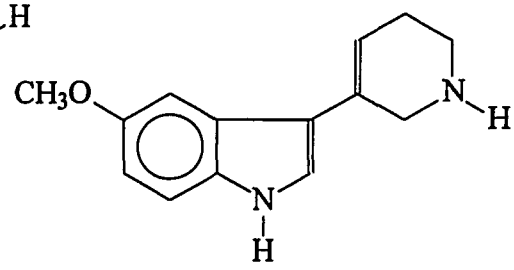
CHAPTER 4

4. 1. 0 BASE CATALYZED CONDENSATION OF INDOLES WITH N-ALKYL-3-PIPERIDONES: FACILE REGIOSELECTIVE DEHYDRATION OF THE INTERMEDIATE TERTIARY ALCOHOL

RU24969 (**28**) and its isomer RU28253 (**29**) represent conformationally constrained analogs of serotonin or 5-hydroxytryptamine (5-HT; **1**). These compounds are of great interest because of their high potency and potential selectivity for 5-HT receptor subtypes (Euvrard et al., 1980; Hunt et al., 1981; Dumuis et al., 1988).



RU24969 (**28**)

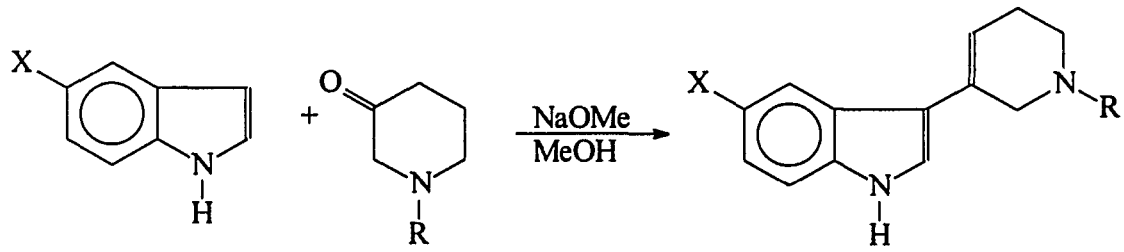


RU28253 (**29**)

Our group (Agarwal et al., 1993) and others (Guillaume et al., 1987; Macor et al., 1990) have synthesized several derivatives of RU24969 and tested them for their binding affinity towards 5-HT receptor subtypes (Taylor et al., 1988). The reaction conditions employed above proved to be unsuitable for the synthesis of RU28253 analogs. We found, however, that N-alkyl-3-piperidone (**30**) could be successfully condensed with indoles in anhydrous methanol with sodium methoxide to give the desired 3-(1',2',5',6'-

tetrahydropyridin-3'-yl) indoles (**31**) (Scheme 30). We had previously concluded (based on the gc/ms analysis of the product) that a mixture of the desired allylamine (**31**) and the undesired enamine product (**32**), derived from the tertiary alcohol (**33**) as a common intermediate, resulted from these condensations (Figure 7). The allylamine proton has a characteristic resonance at 6.1 - 6.2 ppm in the ^{1}H-nmr (Zheng et al., 1994). Furthermore, conversion of the allylamine isomer to the thermodynamically more stable enamine isomer occurs under gas chromatographic conditions, clearly demonstrating that gc/ms is an inappropriate analytical method in this case. Molecular mechanics calculations (MM2) confirm that enamine is ~ 2.5 Kcal/mole more stable than the allyamine. We have proposed a mechanistic explanation for the exclusive formation of allylamine as opposed to enamine product (scheme 31). Some simple experiments were performed to prove this interesting result.

Scheme 30.



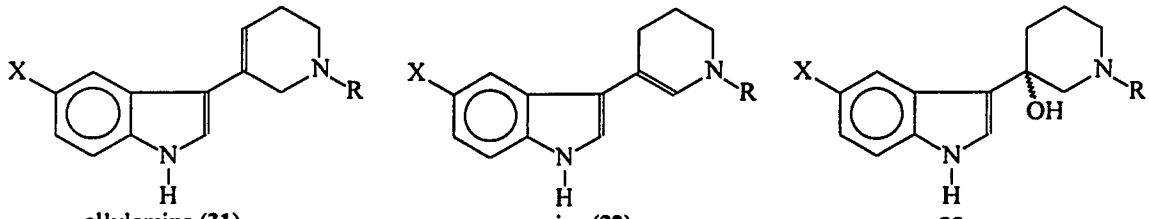
30

R = CH_3, C_2H_5 or n-C_3H_7

31

RU28253 derivatives

Figure 7.



allylamine (31) enamine (32) 33

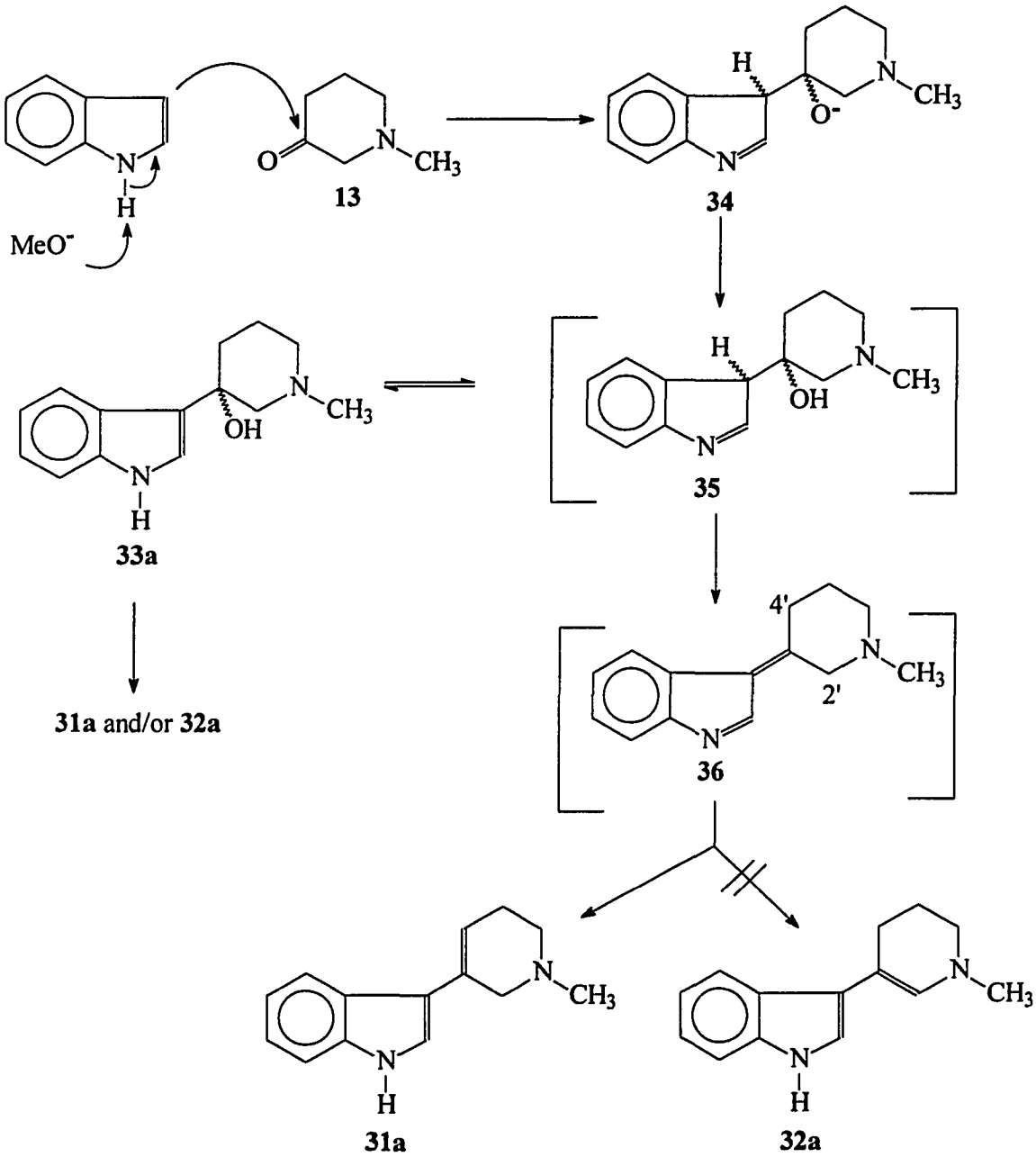
4. 1. 1 PROPOSED MECHANISM

The proposed mechanism is shown in Scheme 31. N-methyl-3-piperidone (**13**) is used as an example of the piperidone to be condensed. The first step involves abstraction of the proton from indole nitrogen by sodium methoxide, followed by the attack of the indolyl anion on the carbonyl carbon of N-methyl-3-piperidone (**13**) to form **34**. This intermediate takes up a proton from the solvent, methanol, to give **35** which then undergoes dehydration to form **36**. Regioselective tautomerisation of **36** with loss of the more acidic 4' proton followed by reprotonation by the solvent provides the allylamine **31a**. Tautomerisation of **36** with loss of the 2' proton to form the enamine **32a**, apparently does not occur due to the unfavorable electrostatic interaction between the lone pair of electrons on the piperidinyl nitrogen and the 2'-piperidinyl anion that would be generated by the abstraction of the 2' proton.

Since the alcohol **33a** was not observed in this reaction, we think that the rate of tautomerisation of **35** to **33a** is much slower than the rate of dehydration of **35** to **36**. We

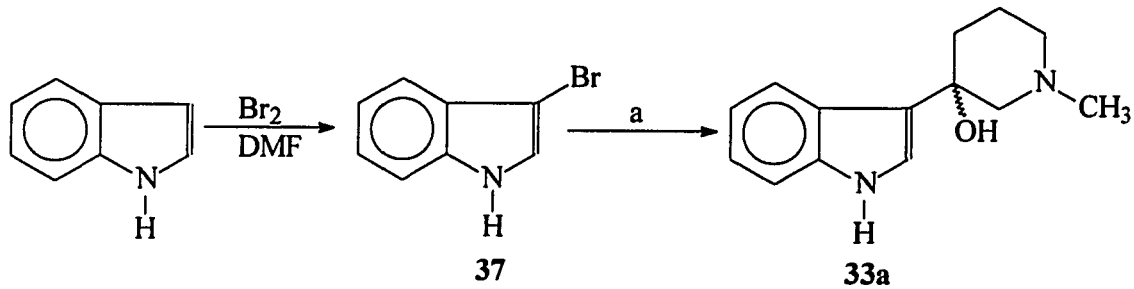
also believe that if the alcohol **33a** was formed in the reaction, we should have been able to isolate it as a product because of its observed stability.

Scheme 31.



Alcohol **33a** was synthesized separately (Scheme 32) (Yang et al., 1992) via 3-bromoindole (**37**) (Bocchi et al., 1982) and subjected to refluxing sodium methoxide-methanol. A minimum of 24 hours was required for the alcohol to be completely consumed and form the corresponding allylamine **31a**. However, in this reaction about a 15 % yield of indole was also formed as indicated by hplc studies on the reaction mixture, suggesting that a reverse reaction is taking place (Scheme 33).

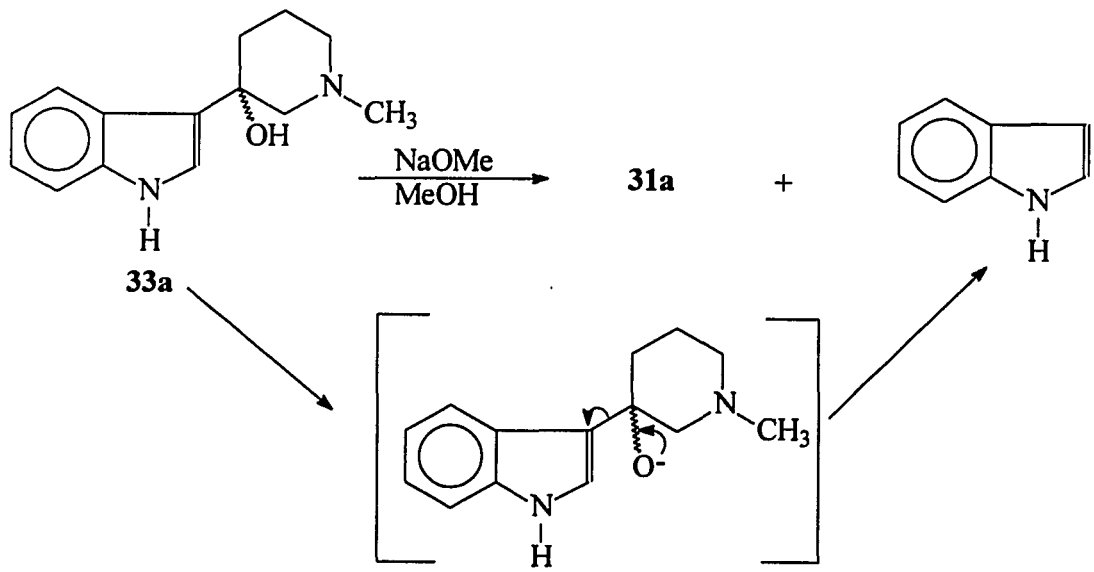
Scheme 32.



37 **33a**

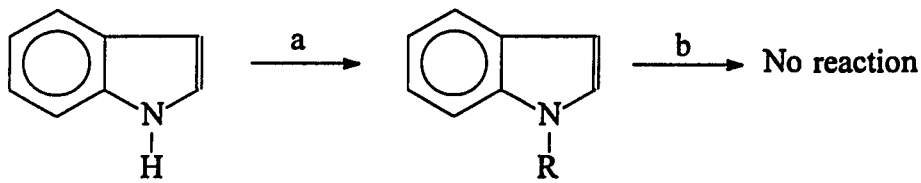
Conditions: a. i) KH, t-BuLi, THF, ii) N-methyl-3-piperidone, THF.

Scheme 33.



An additional observation that supports the proposed mechanism was that the hydrogen on the indole nitrogen is essential for the condensation reaction to occur, since neither N-methyl (**38a**) or N-benzylindole (**38b**) (Santaniello et. Al., 1979) reacted with the N-alkyl-3- or -4-piperidones (scheme 34). Furthermore, alcohol 40 (Curphey et. Al., 1968), prepared via 3-bromo-N-benzylindole (**39**), was recovered unchanged after being subjected to sodium methoxide in refluxing methanol for 72h (scheme 35).

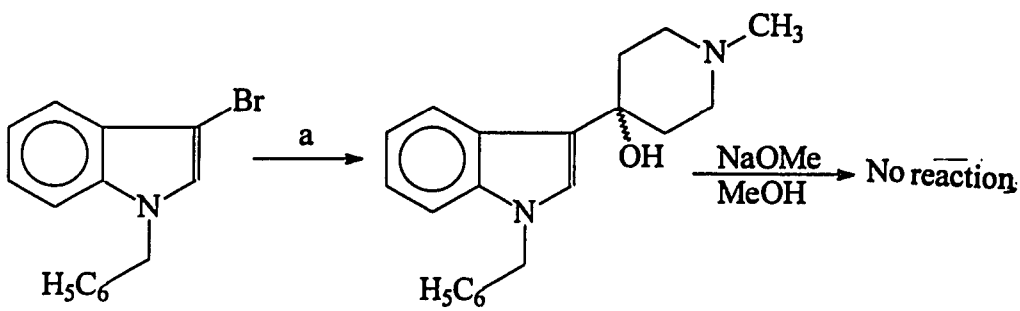
Scheme 34.



R = CH_3 (**38a**) or $CH_2C_6H_5$ (**38b**)

Conditions: a. CH_3I or C_6H_5Cl, KOH, toluene, reflux.
b. N-methyl-3- or -4-piperidone, NaOMe, methanol.

Scheme 35.



Conditions: a. t-BuLi, N-methyl-4-piperidone, THF

CHAPTER 5

EXPERIMENTAL

General Methods:

Melting points were determined with an Electrothermal capillary melting point apparatus and are uncorrected.

Proton magnetic resonance spectra were obtained for all compounds using Bruker AM-250 (250 MHz) or Varian Gemini 200 (200 MHz) spectrometers.

Gas chromatography mass spectra were obtained on Hewlett Packard 5970 MSD and Fison MD-800 spectrometers.

Elemental analyses were performed by Desert Analytics, Tucson, AZ.

Purified products were shown to be homogenous by thin-layer chromatography on silica gel plates (1 x 3 in) with visualization by iodine vapors.

Column chromatography was performed using low pressure or flash liquid chromatography with glass columns packed with silica gel (60 ^{o}A) unless indicated otherwise.

All the chemical reactions requiring inert atmosphere were carried out under nitrogen in oven-dried glassware using septum techniques.

Tetrahydrofuran (THF), diethyl ether (ether), benzene and toluene were dried and distilled from sodium prior to use. Triethylamine (TEA) was distilled from potassium

hydroxide. Chloroform and dichloromethane (DCM) were distilled from phosphorus pentoxide. N, N-Dimethylformamide (DMF) was dried over 3 ^{o}A molecular sieves and distilled under reduced pressure.

AR-grade methanol, N-methyl-4-piperidone, N-ethyl-3-piperidone hydrochloride and 1,1-difluoroethylene were obtained from Aldrich Chemical Company.

The pressure reaction vessel used was a 600 mL Parr Pressure Reaction Apparatus, model no. 4563M.

Sodium Indoline-2-sufonate Monohydrate (8)

To a solution of 23.4 g of sodium bisulfite (59 % as SO_2) in 80 mL of water was poured slowly, with mechanical stirring, a solution of 11.7 g (0.1 mol) of indole in 25 mL of ethanol. The resulting yellowish mixture was stirred at room temperature for 20 h. The final thick, slightly green slurry was filtered by suction and the solid was washed with 25 mL of methanol, two 50 mL portions of ether and air-dried to yield 22.4 g (96 %) of white amorphous solid*.

Sodium 1-Acetylindoline-2-sulfonate Hemihydrate (9)

A slurry of 23.9 g (0.1 mol) of the salt **8** in 150 mL of acetic anhydride was heated to 70 ^{o}C and was maintained at this temperature for 2 h with mechanical stirring. The temperature was then raised to 90 ^{o}C for 0.5 h during which time the very thick slurry thinned and turned a pale tan color. The reaction mixture was cooled in a ice bath and the

solid was collected by suction. The white solid was then washed with three 40 mL portions of ether and air-dried overnight to give 25.2 g (91 %) of white powder*.

5-Iodoindole (10)

To a solution of 14.1 g (0.052 mol) of **9** and 10 g (0.06 mol) of potassium iodide in 60 mL of water, cooled to 0-5 ^{o}C, was added dropwise over a 1 h period iodine monochloride (24.4 g, 7.6 mL, 0.15 mol). The temperature was maintained below 5 ^{o}C. The deep maroon slurry was allowed to warm to room temperature over 30 min, poured into 200 mL of water with stirring, the flask rinsed with 50 mL of water and about 16 g of sodium bisulfite added to destroy the excess iodine. The faint yellow solution was neutralized with 70-80 mL of 20 % sodium hydroxide, 6 g of solid sodium hydroxide added and the mixture refluxed overnight (20 h). The reaction mixture was cooled in an ice bath obtain a dark tanned precipitate which was filtered, washed thoroughly with ice water and air dried to give 8.5 g (67 %) of dark tan solid. Recrystallization from cyclohexane gave about 7 g of white shiny needles of 5-iodoindole. mp 96-98 ^{o}C*.

*Russell et al., 1985.

5-Iodo-*N*-tosylindole (11)

5-Iodoindole (8.33 g, 35 mmol), *p*-toluenesulfonyl chloride (9.98 g, 52.5 mmol) and tetrabutylammonium bisulfate (1.76 g, 5.18 mmol) were dissolved in 102 mL of toluene in 1 liter flask. The clear solution was cooled in an ice bath. To this was added

102 mL of 15 % aqueous NaOH. The two phase mixture was stirred vigorously at room temperature for 3 h. The organic phase was separated and washed with 56 mL of 1N HCl followed by saturated $NaHCO_3$ and water. After drying the organic phase with anhydrous Na_2SO_4, it was evaporated under reduced pressure to obtain 11.8 g (86 %) of light tan crystalline solid. mp 136-138 ^oC. Mass spectrum: m/z (relative intensities) 397 (81), 242 (37), 155 (86), 115 (73), 91 (100), 65 (56). ^1H-Nmr (200 MHz,$CDCl_3$): δ 2.35 (3H, s, tosyl-CH_3), 6.59 (1H, dd, indole 3-H, J = 0.7 and 3.8 Hz), 7.22 (2H, d, tosyl H adjacent to methyl, J = 8.7 Hz), 7.39 (1H, dd, indole 6-H, J = 2.2 and 9.4 Hz), 7.56 (1H, d, indole 2-H, J = 3.8 Hz), 7.65 (1H, d, indole 4-H, J = 2.2 Hz), 7.73 (2H, d, tosyl H adjacent to sulfonyl, J = 8.7 Hz), 7.87 (1H, d, indole 7-H, J = 9.4 Hz). *Anal.* Calcd. for $C_{15}H_{12}NO_2IS$: C, 45.35; H, 3.04; I, 31.94; N, 3.52; S, 8.07. Found: C, 45.05; H, 3.02; I, 31.90; N, 3.48; S, 8.04.

5-(α-Fluorovinyl)-*N*-tosylindole (12)

5-Iodo-*N*-tosylindole (**11**) (11.76 g, 30 mmol), Et_3N (7.57 g, 75 mmol), and palladium acetate (0.2 g, 0.9 mmol) were placed in a pressure reaction vessel along with 70 mL of dimethylformamide (DMF). The reaction vessel was degassed twice, cooled in a dry ice-ether bath to about -60 ^oC and at this point was introduced 1,1-difluoroethylene gas till the pressure gauge reached up to 100 psi. The temperature at this point rose to -35 ^oC. Then the reaction mixture was allowed to attain room temperature. The pressure read 350 psi. The reaction mixture was heated up to 120 ^oC and allowed to stir vigorously at

this temperature for 24 h. Then it was cooled to room temperature and poured into 200 mL of ice water to give a dark yellow sticky precipitate. This was extracted in ether (100 mL x 3). The ether extract was concentrated to give a dark brown viscous residue which was chromatographed on silica gel (Hexane : EtOAc = 9 : 1) to obtain 4.5 g (48 %) of light yellow oil which solidified on refrigeration. Rf = 0.4 (10 % EtOAc/Hexane). mp 84-86 ^{o}C. Ms: m/z (relative intensities) 315 (100), 155 (78), 163 (15), 133 (21), 91 (99), 65 (22). ^{1}H-Nmr (200 MHz, $CDCl_3$) : δ 2.32 (3H, s, tosyl CH_3), 6.65 (1H, d, indole 3-H), 7.21 (2H, d, tosyl H adjacent to methyl, J = 8.2 Hz), 7.5 (1H, dd, indole 6-H, J = 2.08 and 8.4 Hz), 7.58 (1H, d, indole 2-H, J = 3.7 Hz), 7.71 (1H, d, indole 4-H, J = 2.1 Hz), 7.76 (2H, d, tosyl H adjacent to sulfonyl, J = 8.2 Hz), 7.96 (1H, d, indole 7-H, J = 8.4 Hz). *Anal.* Calcd. for $C_{17}H_{14}NO_2FS$: C, 64.74; H, 4.47; N, 4.44; F, 6.02; S, 10.16. Found: C, 64.91; H, 4.43; N, 4.47; F, 6.15; S, 10.18.

5-α-Fluorovinylindole (5)

To a solution of NaOMe in AR-grade methanol, prepared by reacting 46 mg (2 mmol) of sodium metal in 1 mL AR-grade methanol, was added 315 mg (1 mmol) of **12**. The reaction mixture was refluxed for 5-7 h, cooled to room temperature and the solvent evaporated under reduced pressure to obtain a pale yellow viscous residue which was purified by column chromatography on silica gel (Hexane : EtOAc = 9 : 1) to give 140

mg (87.5 %) of pale yellow viscous liquid (to be stored under nitrogen in the refrigerator). Ms: m/z 161 ($M^{+\cdot}$).

1-Methyl-3-piperidone (13)

Sodium (17.9 g, 777 mmol) was placed in a 1 liter flask and 150 mL methanol was added with cooling. The mixture was refluxed until a clear solution was obtained (about 1 h). Into this solution was dropped a solution of 3-hydroxypyridine (64 g, 673 mmol) in 150 mL of methanol at 0 ^{o}C. The mixture was heated under reflux for 40 min. The reddish solution was cooled to 0 ^{o}C and treated with iodomethane (206 g, 1.45 mol). After the addition the mixture was heated under reflux for 7 h. The solvent removed under reduced pressure and water (800 mL) was added to dissolve the residue. After cooling in an ice bath, the solution in a liter beaker was treated with sodium borohydride (52 g, 1.37 mol; added in small portions) over 1 h. After addition was completed, the solution was basified with 100 g of potassium carbonate to pH 12. The solution was extracted with ether (100 mL x 10) and the ether layers were combined and dried over anhydrous sodium carbonate. The ether solution was concentrated, and the residual oil was distilled under reduced pressure to give 45.75 g of product. b.p 56-58 ^{o}C/11 mm Hg (Lit. Lyle, 1959; 60-63 ^{o}C/ 11 mm Hg). Yield: 53 %, Ms: m/e 127 ($M^{+}\cdot$).

To a 100 mL flask containing the above 1-methyl-1,2,5,6-tetrahydro-3-pyridyl methyl ether (9.2 g, 72 mmol) cooled to 0 ^{o}C was added 48 % HBr solution (30 mL, 177 mmol). After refluxing for 6 h, the solution was basified with 2N NaOH under cooling to

pH 11 and extracted with ether (50 mL x 10). The combined ether extracts were concentrated and the residual oil distilled at 150 ^{o}C *in vacuo*. The fraction distilling at 63-67 ^{o}C/13 mm Hg (lit. Lyle, 1959; 63-64 ^{o}C/13 mm Hg) was collected to give 4.87 g of colorless product (60 %).

The product is unstable to atmospheric conditions and should be stored under nitrogen in a refrigerator.

5-(α-Fluorovinyl)-3-(1'-methyl-1'2'5'6'-tetrahydropyridin-3'-yl) indole (I).

To a solution of NaOMe in AR-grade methanol, prepared by reacting 46 mg (2 mmol) of sodium in 1 mL AR-grade methanol, was added 160 mg (1 mmol) of 5-(α-fluorovinyl) indole. The solution was refluxed for about 30 min. and then a solution of N-methyl-3-piperidone (226 mg, 2 mmol) in 5mL of AR-grade methanol was added dropwise to the above refluxing solution over a period of 15 min. The reaction mixture was refluxed for 72 h. and then cooled and concentrated *in vacuo* (aspirator). Cold water was added to the reddish brown residue which was extracted with ether. The ether layer was separated, washed with water and brine, dried over $MgSO_4$, concentrated to a very small volume and cooled in an ice bath to obtain 65 mg (25%) of pale yellow crystalline solid. mp 190-192 ^{o}C; ^{1}H-Nmr (DMSO-d_6): δ 2.25 (s, 3H), 2.48 (m, 2H), 3.2 (s, 2H), 3.4 (m, 2H), 4.8 (dd, 1H, J = 3.8 and 19.2 Hz), 5.24 (dd, 1H, J = 3.8 and 52.3 Hz), 6.15 (m, 1H, vinyl-H), 7.35-7.48 (m, 3H), 7.95 (s, 1H), 11.35 (bs, 1H, indole N-H); Ms: m/z

(relative intensities) 256 (78), 227 (19), 213 (100), 198 (32), 174 (55). *Anal.* Calcd. for $C_{16}H_{17}FN_2$: C, 74.97; H, 6.68; N, 10.93. Found: C, 74.74; H, 6.56; N, 10.74.

5-(α-Fluorovinyl)-3-(1'-methyl-1'2'5'6'-tetrahydropyridin-4'-yl) indole (II)

To a solution of NaOMe in AR-grade methanol, prepared by reacting 46 mg (2 mmol) of sodium in 1mL AR-grade methanol, was added 160 mg (1 mmol) of 5-(α-fluorovinyl) indole (**5**). The solution was refluxed for about 30 min and then a solution of N-methyl-4-piperidone (226 mg, 2 mmol) in 5mL of AR-grade methanol was added dropwise to the above refluxing solution over a period of 15 min. The reaction mixture was refluxed for 48 h and then cooled in ice bath to obtain pale yellow shiny flakes which were filtered and washed with cold methanol. The mother liquor was further concentrated, and the residue recrystallised from methanol. Total yield 130 mg (58 %). mp 220-222 ^{o}C; ^{1}H-Nmr (DMSO-d_6): δ 2.28 (s, 3H), 2.5-2.58 (m, 4H), 3.06 (b d, 2H), 4.8 (dd, 1H, J = 3.8 and 19.4 Hz), 5.26 (dd, 1H, J = 3.8 and 51.8 Hz), 6.12 (m, 1H, vinyl-H), 7.4-7.5 (m, 3H), 7.95 (s, 1H), 11.28 (bs, 1H, indole N-H). Ms: m/z (relative intensities) 256 (100), 227 (24), 212 (16), 174 (23), 94 (15), 42 (23). *Anal.* Calcd. for $C_{16}H_{17}FN_2$: C, 74.97; H, 6.68; N, 10.93. Found: C, 74.76; H, 6.51; N, 11.07.

5-Acetyl-N-tosyl indole (20)

Mercuric acetate (80 mg, 0.25 mmol) was dissolved in 0.35 ml of glacial acetic acid and stirred for 1 h. The residual particles were filtered of and 5-α-fluorovinyl-N-tosylindole (63 mg, 0.2 mmol) was added to the clear solution. The reaction mixture was stirred for 24 h and then the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel (Hexane : EtOAc = 9 : 1) to obtain 40 mg (65 %) of white amorphous product. ^{1}H-Nmr ($CDCl_3$): δ 2.34 (s, 3H), 2.63 (s, 3H), 6.75 (d, 1H), 7.25 (d, 2H, J = 7.05 Hz), 7.64 (d, 1H), 7.78 (d, 2H, J = 7.05 Hz), 7.94 (d, 1H, J = 7.76 Hz), 8.05 (d, 1H, J = 7.76 Hz), 8.18 (d, 1H, J = 2.1Hz). Ms: m/z (relative intensities) 313 (37), 298 (51), 155 (30), 143 (27), 115 (17), 91 (100), 65 (26), 43 (12).

5-(α-Fluorovinyl)indol-3-yl glyoxylamide (22a) and 5-(acetyl)indol-3-yl glyoxylamide (23a)

To an ice cold solution of 5-(α-fluorovinyl)indole (**5**) (160 mg, 1 mmol) in 2mL of anhydrous ether was added oxalyl chloride (0.1 mL, 1.1 mmol), dropwise. A pale yellow clear solution resulted. Within 5 min a nice bright yellow precipitate formed. The reaction was allowed to stir for 6-8 h at room temperature. The yellow precipitate (**21**) was filtered, washed with cold ether, air dried and resuspended in dry benzene (2 mL). Ammonia was bubbled into this suspension for 10 min. The resulting dull yellow precipitate was filtered, washed with cold water and air dried. Yield 168 mg (92 %). This

precipitate was a mixture of the desired product (**22a**) and the rearranged product (**23a**). They were separated by preparative TLC to obtain 92 mg (40 %) of **22a** and 65 mg (28 %) of **23a.**

22a. ^{1}H-Nmr (DMSO-d_6): δ 4.9 (dd, 1H, J = 3.78 and 18.9 Hz), 5.28 (dd, 1H, J = 3.78 and 52.2 Hz), 7.58 (s, 2H), 7.77 (bs, 1H, amide N-H), 8.10 (bs, 1H, amide N-H), 8.43 (s, 1H), 8.73 (s, 1H), 12.39 (bs, 1H, indole N-H). Ms: m/z (relative intensities) 232 (24), 188 (100), 160 (10), 133 (13), 44 (9), 28 (9). Anal. Calcd. for $C_{12}H_9FN_2O_2$: C, 62.06; H, 3.9; N, 12.06; F, 8.18. Found: C, 61.89; H, 3.58; N, 11.90; F, 8.07.

23a. Ms: m/z (relative intensities) 230 (12), 186 (100), 143 (14), 115 (5), 44 (11), 28 (16).

5-(α-Fluorovinyl)-indol-3-yl-N,N-dipropyl glyoxylamide (22b) and 5-(acetyl)-indol-3-yl-N,N-dipropyl glyoxylamide (23b)

To a solution of 5-(α-fluorovinyl) indole (**5**) (160 mg, 1 mmol) in 2 mL of anhydrous ether was added oxalyl chloride (0.1 mL, 1.1 mmol), dropwise a under ice bath cooling. A pale yellow clear solution resulted. Within 5 min a nice bright yellow precipitate formed. The reaction was allowed to stir for 6-8 h at room temperature. The yellow precipitate (**21**) was filtered, washed with cold ether, air dried, and dissolved in 5mL of dry THF. To this was added dropwise, a solution of N,N-dipropyl amine (0.34 mL, 2.5 mmol) in 2.5 mL of dry THF at room temperature. The reaction mixture was stirred for 1 h at room temperature and then the solvent was evaporated under reduced

pressure. The resulting viscous residue was partitioned between water/EtOAc. The organic layer was separated, washed with saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuo (aspirator) to give a pale yellow viscous oil which was chromatographed on silica gel (EtOAc : Hexane : MeOH = 1 : 1 : 0.1) to obtain 128 mg (40 %) of **22b** and 82 mg (26 %) of **23b.**

22b. Rf = 0.5; mp 142-144 °C; ^{1}H-Nmr ($CDCl_3$): δ 0.77 (t, 3H), 0.96 (t, 3H), 1.48-1.77 (m, 4H), 3.21 (t, 2H), 3.39 (t, 2H), 4.8 (dd, 1H, J = 3.7 and 18.2 Hz), 5.02 (dd, 1H, J = 3.7 and 50.2 Hz), 7.22 (d, 1H, J = 8.3 Hz), 7.38 (d, 1H, J = 8.3 Hz), 7.56 (d, 1H, 1.8 Hz), 8.47 (s, 1H, indole 2-H), 10.42 (bs, 1H, indole N-H). ^{19}F-Nmr shows a doublet of doublet with J = 18.31 and 50 Hz (without reference). Ms: m/z (relative intensities) 316 (3), 188 (100), 160 (8), 133 (13), 100 (15), 86 (5). *Anal.* Calcd. for $C_{18}H_{21}FN_2O_2$: C, 68.34; H, 6.69; N, 8.85; F, 6.00. Found: C, 68.28; H, 6.49; N, 8.52; F, 5.58.

23b. Rf = 0.43; mp 146-148°C; ^{1}H-Nmr($CDCl_3$): δ 0.8 (t, 3H), 0.96 (t, 3H), 1.5-1.8 (m, 4H), 2.67 (s, 3H, acetyl-CH_3), 3.27 (t, 2H), 3.44 (t, 2H), 7.32 (d, 1H, J = 8.32 Hz), 7.74 (s, 1H), 7.88 (d, 1H, J = 8.32 Hz), 8.85 (s, 1H, indole 2-H), 10.45 (bs, 1H, indole N-H). ^{13}C-Nmr was consistent with the structure. ^{19}F-Nmr showed no peaks. Ms: m/z (relative intensities) 314 (3), 186 (100), 143 (18), 128 (8), 115 (5), 100 (15), 86(8). *Anal.* Calcd. for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: 68.59; H, 7.10; N, 8.77.

5-(α-Fluorovinyl)-N,N-dipropyl tryptamine (IV)

To a suspension of $LiAlH_4$ (38 mg, 1.0 mmol) in 4mL of dry THF was added dropwise, a solution of **22b** (63 mg, 0.2 mmol) in 2ml of dry THF. The suspension was refluxed for 90 min then cooled and neutralized with 0.038 mL of water followed by 0.038 mL of 15 % NaOH and 0.114 mL of water again. A nice white granular precipitate resulted, which was filtered and washed thoroughly with THF. The combined filtrate was concentrated *in vacuo* (aspirator) to obtain 40 mg of pale yellow viscous oil which was purified by preparative TLC on silica gel (Hexane : EtOAc = 3 : 1) to give 35 mg (61 %) of pure **IV**. Rf = 0.5; ^{1}H-Nmr ($CDCl_3$): δ 0.88 (t, 6H), 1.4-1.6 (m, 4H), 2.44-2.52 (m, 4H), 2.72-2.96 (m, 4H), 4.75 (dd, 1H, J = 3.8 and 18.3 Hz), 4.94 (dd, 1H, J = 3.8 and 51.6 Hz), 7.02 (d, 1H, J = 2.0 Hz), 7.29 (d, 1H, J= 8.33 Hz), 7.38 (dd, 1H, J = 2.0 and 8.33 Hz), 7.8 (s, 1H), 8.16 (bs, 1H, indole N-H). Ms: m/z (relative intensities) 288 (1), 188 (18), 174 (27), 154 (12), 114 (100), 86 (39), 72 (35). *Anal.* Calcd. for $C_{18}H_{25}FN_2$. HCl: C, 66.5; H, 8.07; N, 8.62; F, 5.85. Found: C, 66.20; H, 7.95; N, 8.58; F, 5.79.

5-(α-Fluorovinyl) gramine (26)

To a suspension of paraformaldehyde (30 mg, 1.0 mmol) in 3mL of ethanol was added glacial acetic acid (60 mg, 1.0 mmol) and 0.12 mL of 40 % aqueous dimethylamine (equivalent to 1 mmol of dimethylamine). The suspension was warmed until clear and then cooled to room temperature. A solution of 5-(α-fluorovinyl) indole (**5**) (140 mg, 0.875 mmol) in 3 mL ethanol was then added to the above clear solution.

The reaction mixture was refluxed for 24-28 h and then the solvent was evaporated under reduced pressure. The resulting pale yellow viscous residue was chromatographed on neutral alumina (Hexane : EtOAc : MeOH = 1.2 : 0.8 : 0.1) to obtain 140mg (74%) of pure white crystalline solid of **26**. Rf = 0.3; mp 142-144°C; ^{1}H-Nmr ($CDCl_3$): δ 2.3 (s, 6H), 3.55 (s, 2H), 4.77 (dd, 1H, J = 3.78 and 18 Hz), 4.99 (dd, 1H, J = 3.78 and 50.2 Hz), 7.15 (s, 2H), 7.23-7.49 (m, 2H), 7.93 (s, 1H), 8.42 (bs, 1H, indole N-H). Ms: m/z (relative intensities) 218 (20), 174 (100), 154 (18), 127 (9), 101 (5), 77 (5), 58 (5). *Anal.* Calcd. for $C_{13}H_{15}FN_2$: C, 71.53; H, 6.92; N, 12.83. Found: C, 71,67; H, 6.80; N, 12.56.

5-(α-Fluorovinyl) indol-3-yl acetonitrile (27)

To a solution of potassium cyanide (0.42 g, 6.5 mmol) in 5mL of water was added a solution of **26** (0.140 g, 0.65 mmol) in 5 mL DMF. The reaction mixture was refluxed for 1 h and then cooled to room temperature. 10 mL ice cold water was added to it. White turbidity resulted. The mixture was extracted with benzene (10 mL x 3). The combined extract was washed with water and brine and after drying over anhydrous Na_2SO_4, it was evaporated under reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2) to obtain 120 mg (93 %) of pale yellow viscous oil which solidified after sometime. Rf = 0.55; ^{1}H-Nmr ($CDCl_3$): δ 3.9 (s, 2H), 4.82 (dd, 1H, J = 3.7 and 19.2 Hz), 5.2 (dd, 1H, J = 3.7 and 49.8 Hz), 7.3 (s, 1H), 7.4-7.6 (m, 2H), 7.8 (s, 1H), 8.3 (bs, 1H, indole N-H). Ms: m/z (relative intensities) 200 (100), 199 (97), 174 (46), 154 (22), 125 (22), 100 (10).

5-(α-Fluorovinyl) tryptamine (III)

To a suspension of $LiAlH_4$ (0.126 g, 3.6 mmol) in dry ether was added dropwise, a solution of **27** (120 mg, 0.6 mmol) in 5mL of dry ether over a period of 5 min. at room temperature. The suspension was refluxed for 5 h and then cooled and neutralized with 0.13 mL of water followed by 0.13 mL of 15 % NaOH and 0.39 mL of water. A white sticky residue formed. The ether layer was decanted and the residue washed thoroughly with more ether. The combined ether layer was then evaporated and the residue was chromatographed on silica gel ($CHCl_3$: CH_2Cl_2 : MeOH : NH_4OH = 10 : 8 : 2 : 0.4) to obtain 80 mg (65 %) of pure **I** as yellowish oil. Rf = 0.2; ^{1}H-Nmr ($CDCl_3$+MeOD): δ 2.98 (m, 4H), 3.35 (s, 2H, NH_2 protons), 4.72 (dd, 1H, J = 3.62 and 18.5 Hz), 4.98 (dd, 1H, J = 3.62 and 50.5 Hz), 7.1 (s, 1H), 7.39 (s, 2H), 7.59 (s, 1H). Ms: m/z (relative intensities) 204 (17), 174 (100), 154 (22), 127 (11), 30 (69). *Anal.* Calcd. for $C_{12}H_{13}FN_2$: C, 70.56; H, 6.42; N, 13.71. Found: C, 70.23; H, 6.32; N, 13.50.

3-Bromoindole (37)

A solution of bromine (0.816 g, 5.1 mmol) in 20 mL of dimethylformamide was dropped within a few minutes to a clear solution of indole (0.583 g, 5 mmol) in 20 mL of dimethylformamide at room temperature under stirring. The reaction mixture was then poured in 200 mL of ice water containing ammonia (0.5 %) and sodium metabisulfite (0.1 %). The white precipitate that formed, was filtered, washed with cold water and dried

under vaccum to give 0.9 g (92 %) of product. mp 64 - 66 °C (lit. 65 °C, Bocchi and Palla, 1982).

3-(1'-methyl-4'-hydroxypiperidin-4-yl)indole (33a)

A 0.4 g quantity of 35 % potassium hydride suspension in mineral oil (preshaken), equivalent to 3.5 mmol of potassium hydride, was placed in 50 mL round bottom flask. Eight mL of dry THF was added to it under nitrogen and the suspension was cooled to 0 °C. A solution of 3-bromoindole (0.686 g, 3,5 mmol) in 8 mL of dry THF was added dropwise through a dropping funnel to the above suspension. The pale yellow reaction mixture was cooled to -90 °C and 4.2 mL (7 mmol) of 1.7M t-butyl lithium solution in pentane was added dropwise via a cannula to the reaction mixture. The yellow reaction mixture was stirred for 15 min and then a solution of N-methyl-3-piperidone (0.78 g, 7 mmol) in 8 mL dry THF (precooled to -90 °C) was added dropwise to the above reaction mixture. The reaction was maintained at -90 °C for 2 h and the allowed to warm to room temperature overnight. The reaction mixture was then poured into 24 mL of 1M phosphoric acid under stirring. The aqueous layer was separated, basified to pH 10 with potassium carbonate and extracted with ether (40 mL x 3). The ether extracts were combined, concentrated in vacuo and the residue was chromatographed on neutral alumina (hexane : EtOAc : MeOH = 1 : 1 : 0.1) to give about 100 mg (15 %) of white crystalline product. Rf = 0.3; mp 180-182 °C; ^{1}H-Nmr ($CDCl_3$) δ 8.1 (br s, 1 H), 7.9 (d, 1 H), 7.38 (d, 1 H), 7.1 -7.2 (m, 4 H), 3.7 (br s, 1 H), 2.8-3.0 (2 H), 2.3-2.5 (4 H), 1.9-2.1 (4

H), 1.7 (1 H). Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.87; N, 12.16. Found: C, 72.82; H, 8.04; N, 11.85.

N-Benzylindole (38b)

A mixture of indole (10 g, 0.085 mol), powdered potassium hydroxide (7.2 g, 0.128 mol) and 18-crown-6 (0.17 g, 0.0028 mol) in 100 mL toluene was refluxed for 2 h with vigorous stirring. A solution of benzyl chloride (11.34 g, 0.09 mol) in 15 mL toluene was added to the above reaction mixture and refluxed for another 4-5 h. The reaction was monitored by TLC. At the end , the solvent was removed under reduced pressure on a rotary evaporator and the reddish brown residue was distilled to give 14.2 g of clear viscous liquid product. (b.p 145-150 ^{o}C/0.5 mm Hg, lit. 140^{o}C/16 mm Hg, Santaniello et al., 1979).

3-Bromo-N-benzylindole (39)

A solution of bromine (0.408 g, 2.55 mmol) in 10 mL of dimethylformamide was dropped within a few minutes to a clear solution of N-benzylindole (0.517 g, 2.5 mmol) in 100 mL of dimethylformamide at room temperature under stirring. The reaction mixture was then poured in 100 mL of ice water containing ammonia (0.5 %) and sodium metabisulfite (0.1 %). The white precipitate that formed was filtered, washed with cold water and dried under vacuum to give 0.65 g (95 %) of product. mp 63-66^{o}C; ^{1}H-Nmr ($CDCl_3$); δ 5.3 (s, 2H), 7.1-7.4 (complex multiplet, 9H), 7.6 (d, 1H).

1-Benzyl-3-(1'-methyl-4'-hydroxypiperidin-4-yl)indole (40)

A solution of 3-bromo-N-benzylindole (0.5 g, 1.7 mmol) in 10 mL of dry THF was cooled to -78 °C. To this solution was added dropwise 3.5 mL (3.5 mmol) of 1M t-butyl lithium solution via a cannula. The reaction mixture was stirred for 15 min at -78 °C and then a solution of N-methyl-3-piperidone (0.4 g, 3.5 mmol) in 5 mL of dry THF was added dropwise to the reaction mixture via a cannula. The reaction mixture was stirred at -78 °C for about 5 h and then quenched by pouring into 12 mL of 1M ice cold phosphoric acid. The aqueous layer was then basified to pH 10 with potassium carbonate and extracted with ether. The combined ether extracts were washed with ice water followed by brine, concentrated to a very small volume and kept in an ice bath to obtain white crystalls which were filtered and washed with ice cold ether to give 240 mg (35 %) of white crystalline product. mp 182-186 °C; ^{1}H-Nmr ($CDCl_3$); δ 7.95 (d, 1 H), 7.0-7.4 (m, 4 H), 5.3 (s, 1 H), 2.8 (2 H), 2.5 (2 H), 2.2-2.4 (5 H), 2.1 (2 H), 1.7 (br s, 1 H). Anal. Calcd. For $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 77.82; H, 7.57; N, 8.57.

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