

**Intramolecular Carbenoid Insertion:
Reactions of α -Diazoketones Derived
from Benzothienyl, Pyrrolyl and
Indolyl Alkanoic Acids
With Rhodium (II) Acetate.**

By

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ABSTRACT

Recent studies have shown that the rhodium (II) acetate decomposition chemistry observed for α -diazoketones tethered to thienyl, furanyl, and benzofuranyl moieties is dependent not only on the nature of the heteroatom but also on the length of the aliphatic tether linking the diazoketone moiety with the aromatic fragment. The present thesis expands on these results and focuses on α -diazoketones tethered to benzothiophenes, pyrroles and indoles by a methylene linker.

In the case of benzothiophenes, it was shown that the rhodium catalyst decomposition of 1-diazo-4-(3-benzothienyl)-2-butanone (**146**) and 1-diazo-4-(3-benzothienyl)-2-butanone (**152**) allow for the isolation of 1,2,3a,3b-tetrahydro-3*H*-benzo[*b*]cyclopenta[1,3]cyclopropa- [1,2-*d*]thiophen-3-one (**147**) and 1,2,3a,3b-tetrahydro-3*H*-benzo[*b*]cyclopenta[1,3]cyclopropa[1,2-*d*]thiophen-3-one (**153**). However treatment of 1-diazo-3-(3-Benzothienyl)-2-Propanone (**165**) with Rh(II) acetate results in the formation of 2,3-Dihydro-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-2-one (**159**), while 1-diazo-3-(2-Benzothienyl)-2-Propanone with the same condition gives 5,5-bis(1-benzothiophen-2-ylmethyl)-2(5*H*)-furanone (**166**) along with the tricycle **159**.

The chemistry of the pyrrolyl and the indolyl moieties linked to terminal α -diazoketone systems was also investigated. The decomposition of 1-diazo-(2-pyrrolyl)-2-propanone (**173**) results in the formation of two products; the N-H insertion product 1*H*-pyrrolizin-2(3*H*)-one (**176**) and the alkylation product 4,6-dihydrocyclopenta[*b*]pyrrol-5(1*H*)-one (**180**). When 1-Diazo-3-(3-indolyl)-3-propanone (**194**) is treated with catalytic amount of Rh (II) 3,4-dihydrocyclopenta[*b*]indol-2(1*H*)-one (**193**) is isolated quantitatively. The later reaction when monitored using ^1H NMR the intermediate **200**

can be seen whose structure was confirmed by the comparison to series of model compounds.

The mechanisms underlying these reactions as well as their synthetic utility is discussed.

ACKNOWLEDGMENTS

This thesis has been part of a personal journey, but not a solitary one. Many people had accompanied me with courage, and enabled me to finish my work successfully. Although it is not possible to mention each and everyone, I would like to express my gratitude here to those most vital to this work.

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INTRODUCTION

1.1.0 Carbenes and Carbenoids

Carbenes¹ are neutral molecules containing a divalent carbon covalently bonded to two other groups. The two non-bonding electrons can exist in one of two spins states: either a *triplet* or a *singlet* species. With the spin multiplicity given by the equation $2S + 1$, two electrons spin-paired ($S=0$) describe a singlet carbene while two electrons with parallel spins ($S=1$) describe a triplet carbene. The two possibilities are represented graphically in Figure 1. Both experimental and theoretical studies have shown that the triplet carbene is about 8 kcal/mol lower in energy than the singlet.

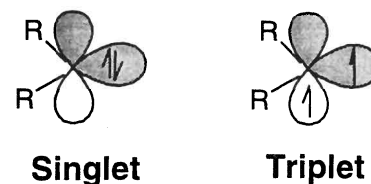
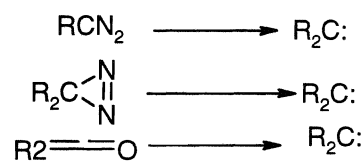


Figure 1

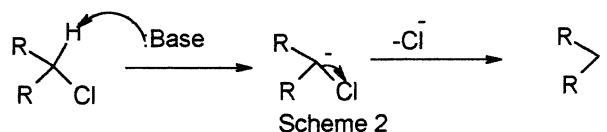
Carbenes can be generated from a number of reactions; the most common being the α -elimination of halogenated compounds (which don't contain β -hydrogens) and *via* the decomposition of compounds containing certain types of double bonds such as ketenes, diazo compounds, diazirines, salts of sulfonylhydrazones, epoxides, and α -halomercury compounds. The latter



Scheme 1

method generally involves homolytic cleavage of double bonds under various conditions such as photolysis, thermolysis, or metal-ion catalysis (Scheme 1). In the α -elimination reaction process (see Scheme 2),² a strong base is used to abstract a proton and generate an anion which subsequently loses a halide ion to give a carbene.

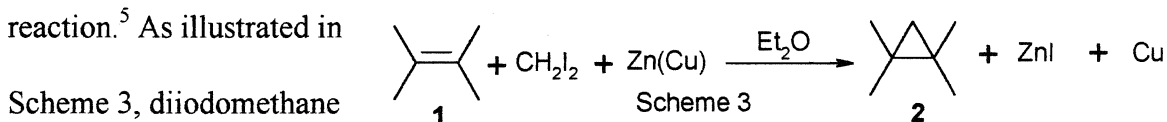
Carbenes are very reactive species, but can be trapped in inert matrices at low temperatures (< 77



K).³ Depending on the substitution of the carbene, a few can be generated and observed at room temperature.⁴ Carbenes generally have life times of less than a second.

The term carbenoid is used to refer to molecules that behave chemically like free carbenes with the carbenoid carbon atom generally bonded to a transition metal. Carbenoids are of greater synthetic utility than their free carbene counterparts since they are usually less reactive, require simpler reaction procedures for their preparation, can be used in reactions at room temperature, and provide high degrees of chemoselectivity and stereoselectivity.

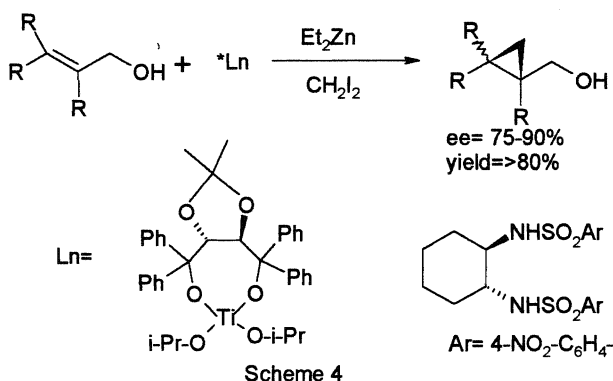
One of the classic protocols used to generate carbenoids is the Simmon-Smith reaction.⁵ As illustrated in



Scheme 3, diiodomethane and copper-zinc couple are

used to generate a carbenoid which adds to an alkene **1** to give a cyclopropane product **2**

in high yield. More recently,

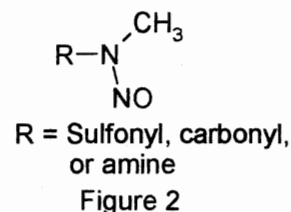


asymmetric variants of the Simmon-Smith reaction have appeared. These reactions give enantiomerically pure compounds by using a chiral ligand which directs the addition of the

carbenoid preferentially towards one face of the olefin (see Scheme 4).⁶

1.2.0 Diazoalkanes

The most used method for the generation of diazoalkanes is the base-catalyzed decomposition of N-alkane-N-nitroso amines of general structure illustrated in Figure 2, (where R represent a sulfonyl, carbonyl, or similar electron-withdrawing substituting). Figure 3

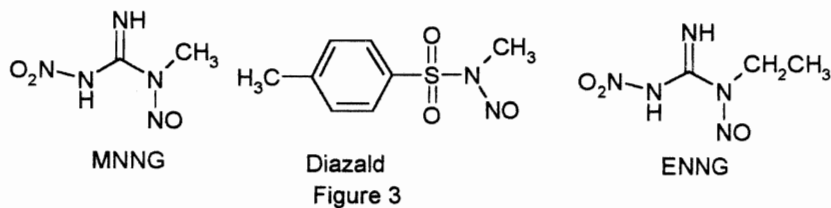


illustrates some of the commercially available precursors for making diazoalkanes; *N*-methl-*N*-nitro-*N*-nitrosoguanidine (MNNG) and *N*-methl-*N*-nitroso-*p*-toluensulfonamide (Diazald) to make diazomethane; and 1-ethyl-3-nitro-1-nitrosoguanidine (ENNG) to make diazoethane.

It is worthwhile mentioning at this point that diazoalkanes such as diazomethane are quite safe when

used as a dilute solution in an inert solvent such

as ether, however it



does presents several safety hazards. Diazomethane and some of its precursors are carcinogenic, very toxic and irritating. Explosions involving diazomethane have been reported. Rough surfaces, ground-glass joints, and any glassware that have not been fire polished have been proven to be initiators of detonation. Contact with alkali metals or drying agents such as calcium sulfate can also result in explosion and solutions of diazomethane are generally dried over potassium hydroxide pellets.⁷

1.3.0 Diazocarbonyl Compounds

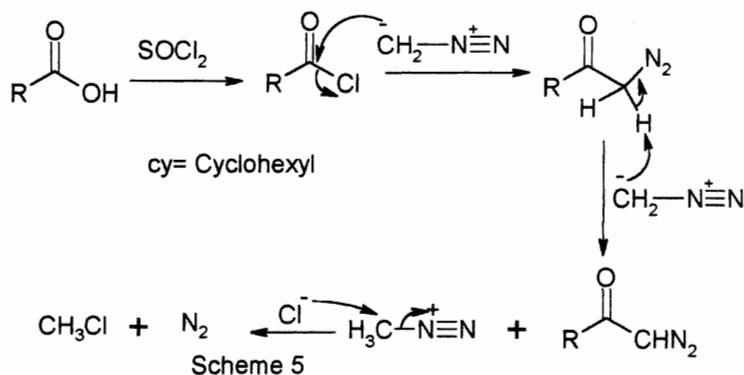
Diazocarbonyl compounds⁸ have been shown to be useful precursors to carbenoid compounds. Ketocarbenoid intermediates are readily generated by the decomposition of diazo compounds using transition metal such as Rh⁹, Pd¹⁰, Cu¹¹, and others. The driving force for making such reaction is the loss of N₂. These reactions have proved very popular for the formation of carbon-carbon bonds *via* intra- or intermolecular reactions with high degree of regioselectivity and stereoselectivity. Their synthetic utility is based on a number of factors: they are easy to prepare from readily available starting materials; they can be purified using column chromatography; and they are relatively stable under mild conditions.

1.3.1. Preparation of α -Diazoketones:

1.3.1.1. Acylation of Diazoalkanes:

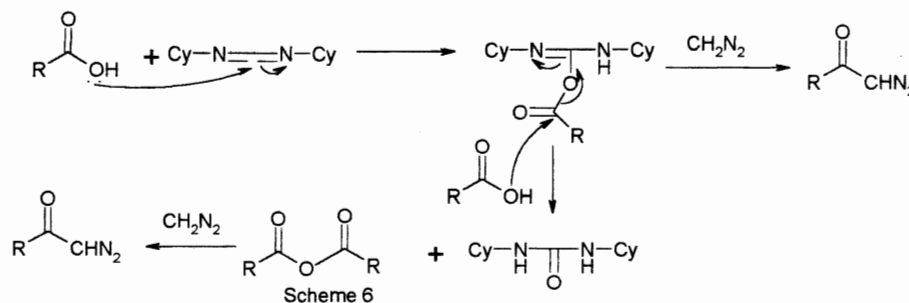
The first synthesis of a diazocarbonyl compound was reported in 1883 by Curtius¹² who described the synthesis of ethyl diazoacetate from glycine. Later, in 1920s, diazoketones were exploited by Arndt and Eistert¹³ and by Bradley and Robinson¹⁴ who generated these compounds *via* the acylation of an appropriate acyl chloride with an ethereal solution of diazomethane. Other syntheses of diazoketones have been developed and are described below.

Reaction between a diazoalkane and an acyl chloride is a common protocol for the preparation of α -diazoketones. This route begins with the



conversion of a carboxylic acid **3** to an acyl chloride **4** using chlorinating agent such as thionyl chloride or oxalyl chloride. After removing the excess chlorinating agent, a solution of this acyl

chloride is slowly added, without purification, to an excess of diazoalkane (2-3 equiv.) such as

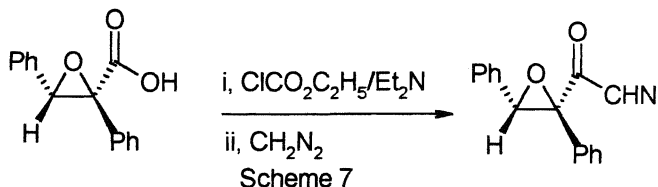


diazomethane or

diazoethane. As illustrated in Scheme 5, diazomethane adds to the carbonyl carbon to form a tetrahedral intermediate which collapses and loses a chloride ion. Abstraction of the hydrogen on the diazo carbon by a basic species gives the desired diazoketone **5**.

Note that if the base is the diazomethane, it will form a cation **6** which will react with the chloride ion to generate methyl chloride **7** and nitrogen gas. When the acyl chloride is not enolizable,¹⁵ the use of the excessive diazomethane can be avoided by including one equivalent of triethylamine in the diazomethane solution.¹⁶

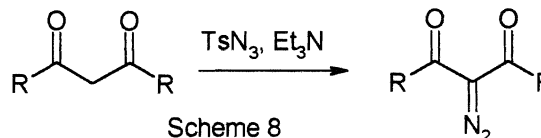
When the formation of the acyl chloride from the carboxylic acid is not efficient, other methods can be used to activate the carbonyl group.¹⁷ For example, an anhydride can be generated then attacked by the diazoalkane. Naturally,



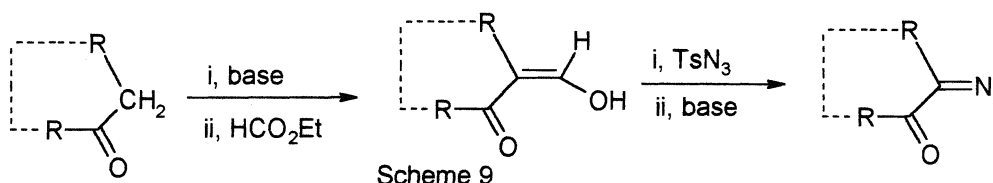
a symmetrical anhydride suffers from the disadvantage that only half of the starting acid is converted into diazoketone and hence unsymmetrical anhydrides are often used.¹⁸ Alternatively, mixing a carboxylic acid with a suitable carbodiimide (for example, dicyclohexylcarbodiimide) (Scheme 6) or chloroformate¹⁹ (such as methyl chloroformate, ethyl chloroformate, and isobutyl chloroformate) (Scheme 7) activates the carbonyl and facilitates the addition of the diazoalkane.²⁰

1.3.1.2 Diazo Transfer Reactions:

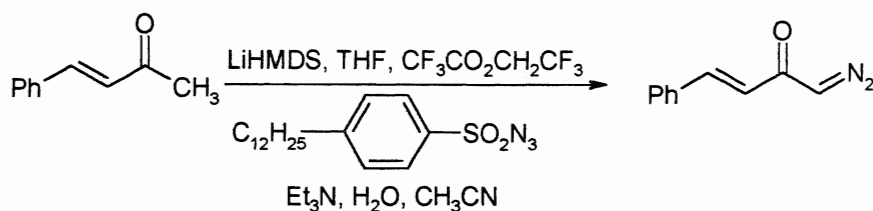
Acylation of diazoalkane are not applicable for the preparation of certain diazoketones (for example, non-terminal α -diazoketones or cyclic diazoketones). In these cases, one generally uses a diazo transfer reaction.²¹ In systems where an enolizable proton is present, treatment



with base to generate an enolate is followed by reaction with a sulfonyl azide (Scheme



8). Alternatively, one can employ a Regitz deformylating diazo transfer which involves a Claisen condensation of a ketone with ethyl formate to introduce the formyl group and



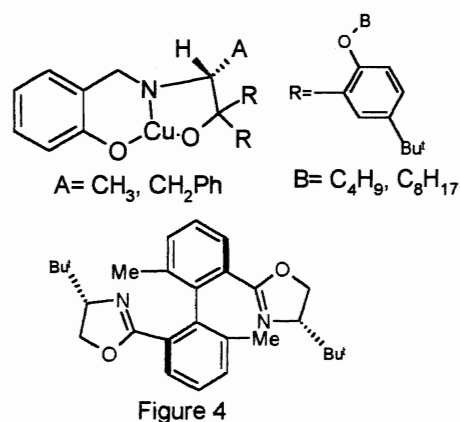
Scheme 10

subsequent treatment with a sulfonyl azide (Scheme 9). A modification of the Regitz procedure was developed by Doyle²², in which an enolate is treated with 2,2,2-trifluoroethyl trifluoroacetate (TFEA) to give the activated trifluoroacetyl group prior to treatment with a diazo donor. Danheiser and co-workers²³ used the Doyle procedure to good effect for the generation of a large number of functionalized substrates that were sensitive to Regitz conditions (Scheme 10).

1.3.2 Decomposition of α -Diazoketones:

A survey of the current carbenoid literature reveals that although a number of transition metal complexes (based on palladium,²⁴ iron,²⁵ cobalt,²⁶ molybdenum,²⁷ osmium²⁸ or ruthenium²⁹) can be used to generate α -carbonyl carbenoids from α -diazoketones, the most popular catalysts are based on either copper or rhodium. Traditionally, insoluble catalysts such as copper powder, copper bronze, cupric oxide *etc.* have been used to effect carbenoid generation.

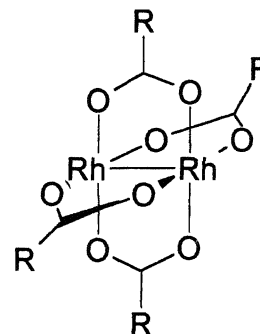
With the advent of homogeneous copper catalysts, however, the use of these catalysts has decreased significantly. Most recently, a number of chiral copper (II) complexes (see Figure 4) have been investigated extensively for



their use in asymmetric cyclopropanation.³⁰

Systematic screening of common transition metal complexes has revealed rhodium (II) species to be the mildest and most efficient catalysts for cyclopropanation.³¹ Among them, rhodium (II) carboxylates (see Figure 5) are the catalysts of choice.

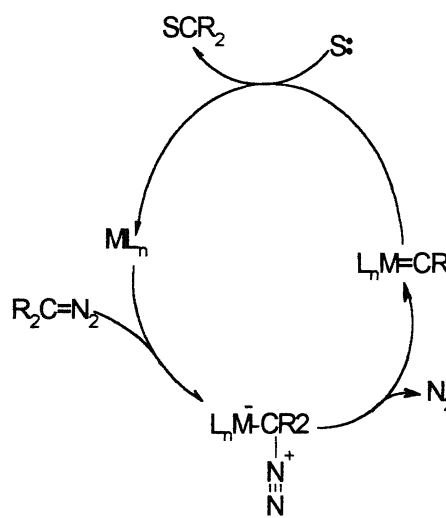
Rhodium (II) carboxylates are binuclear compounds with four bridging carboxylate ligands, possessing one vacant axial coordination site per metal atom. Studies have shown



rhodium complexes to effectively catalyze cyclopropanation of a wide variety of double bonds (substituted, terminal, *etc.*) with generally good yields.³² Furthermore, rhodium (II) carboxylates are thermally and air stable, resistant to carboxylate exchange, not susceptible to redox reactions with diazo compounds, and they generally do not coordinate with the olefin (unlike palladium and some copper catalysts)³².

1.4.0. Mechanism of Carbenoid Addition:

The catalytic cycle whereby a metal complex (L_nM) catalyzes the decomposition of a diazo compound (CR_2N_2) is illustrated in (Scheme 11).³³ The sequence begins with electrophilic attack of the catalyst at the diazo carbon with subsequent loss of nitrogen and the formation of a metal stabilized carbene ($L_nM=CR_2$). Transfer of the carbene entity to an



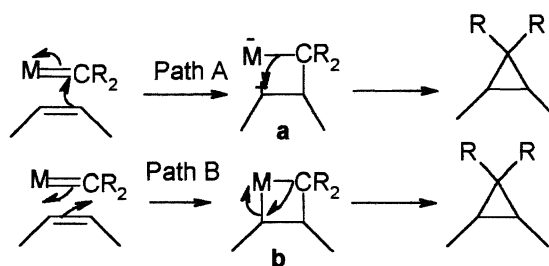
Scheme 11

electron-rich species (S:) completes the cycle. Carbenoids can perform a variety of chemical reactions including OH³⁴, NH³⁵ and CH³⁶ insertions, Wolff rearrangements³⁷ and cyclopropanations of double bonds³⁸, to name but a few. For the purposes of this thesis, we will focus on cyclopropane formation.

1.4.1 Mechanism of Cyclopropanation:

There are two mechanism that have been reported in the chemical literature for cyclopropanation of alkenes using

diazocarbonyls (Scheme 12). In the first mechanism (*Path A*) electrophilic attack of the alkene onto the carbenoid gives a polar intermediate (**a**), which



Scheme 12

loses the metal ligand through 1,2-bond

formation to give the cyclopropane. In the other mechanism (*Path B*) a reaction between the metal complex and the alkene forms a metalocycle intermediate through a concerted [2+2] cycloaddition or a stepwise mechanism. Reductive elimination of the metalocycle intermediate (**b**) gives cyclopropane.

1.5. Reactions of Carbenoids with Aromatic and Heteroaromatic Compounds:

Diazocarbonyl compounds react with a variety of aromatic compounds to give products that have found useful application in synthesis.

1.5.1 Carbene and Carbenoid insertion into Benzene and its Derivatives:

After Curtius synthesized

ethyl diazoacetate (EDA)

(**8**) in 1883, Büchner³⁹

commenced an

investigation of the

thermal decomposition

of ethyl diazoacetate in

the presence of different

unsaturated hydrocarbons. He reported that reaction between carbomethoxycarbene **9** and

benzene (Scheme 13) furnished a single product **10** which rearranged to several isomers

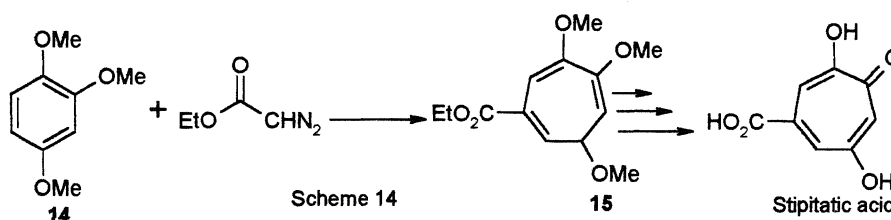
(**11-13**). This reaction is known as Büchner reaction and allows for access to derivatives

of cycloheptatrienyl esters. This reaction has been used in a number of synthetic

application. Johnson and co-workers⁴⁰ used the Büchner reaction to synthesis stipitatic

acid. The synthesis involved the decomposition of ethyl diazoacetate **8** in the presence of

1,2,4-trimethoxy-benzene **14** to yield the ester **15** in the key step (Scheme 14). Fused

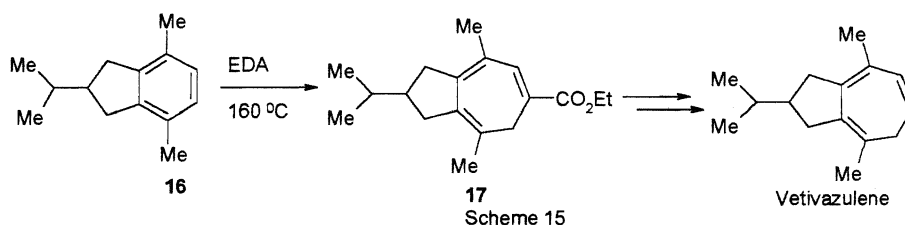


tricyclic cycloheptatrienyl systems are also accessible using this approach. In the synthesis

of vetivazulene⁴¹, a reaction between ethyl diazoacetate (EDA) with the bicyclic **16** gives

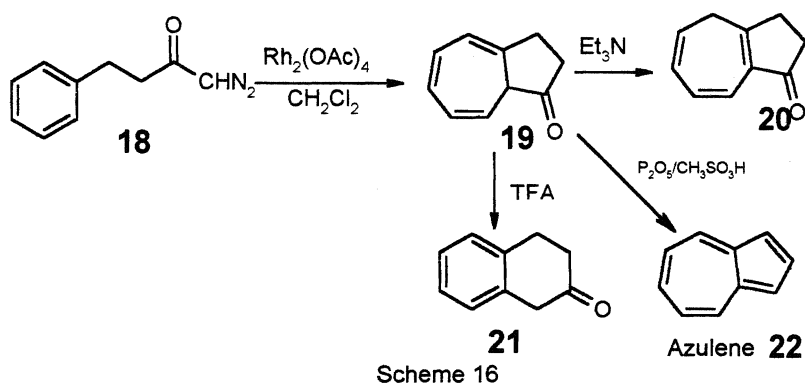
tricyclic cycloheptatriene **17**. A decarboxylation-dehydrogenation sequence lead to vetivazulene as shown in Scheme 15.

The low yields and separation problems associated with the classic Büchner reaction were solved in 1980 when a Belgian group⁴² used rhodium(II) catalysis. The improvement of the selectivity and efficiency could be easily quantified by comparing the thermal reaction of ethyl diazoacetate with anisole (7 products, 35% yield) with its rhodium(II) trifluoroacetate-catalyzed counterpart (2 products, 73%).



Intramolecular versions of the Büchner reaction were known for some time, but became of synthetic utility after Scott⁴³ used rhodium(II) acetate as decomposition agent.

Treating 1-diazo-4-(phenyl)-2-butanone **18** with catalytic amount of rhodium(II) acetate afforded 95% of trienone **19** (Scheme 16) which



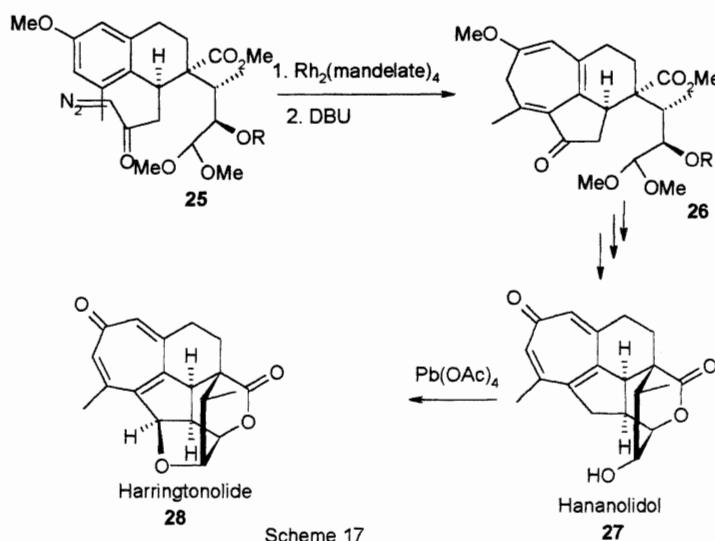
rearranged to a number of isomers depending on the conditions used. For example, chromatographic purification on alumina or treatment with triethylamine gives the isomer **20** while treatment of trienone with trifluoroacetic acid allows for isolation of the

bicyclic **21** in quantitative yield. Dehydration of the isomer **20** using phosphorous pentoxide and methanesulfonic acid produced azulene **22**.

Mander and co-workers⁴⁴ have employed intramolecular Büchner reaction in the synthesis of a number of naturally occurring products.

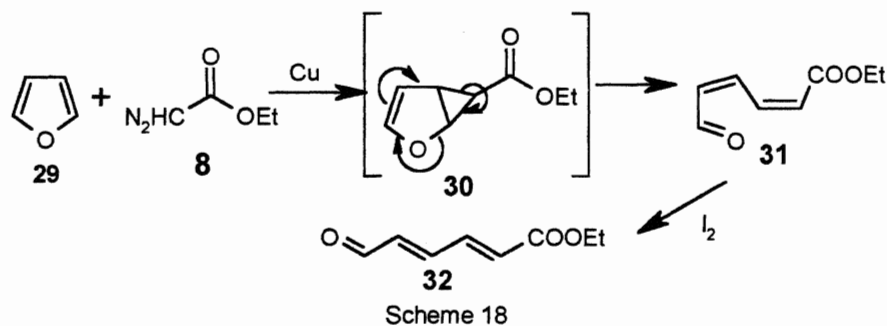
Scheme 17 illustrates the synthesis of hainanolidol **27** and

harringtonolide **28** using this methodology. Treatment of the precursor **25** with rhodium mandelate furnished an unstable adduct, which was immediately treated with 1,8-diazabicyclo[5.4.0]undec-7 (DBU) to give cycloheptatriene **26**. Further manipulations affords hainanolidol **27** which was transformed to harringtonolide **28** by means of lead tetraacetate.



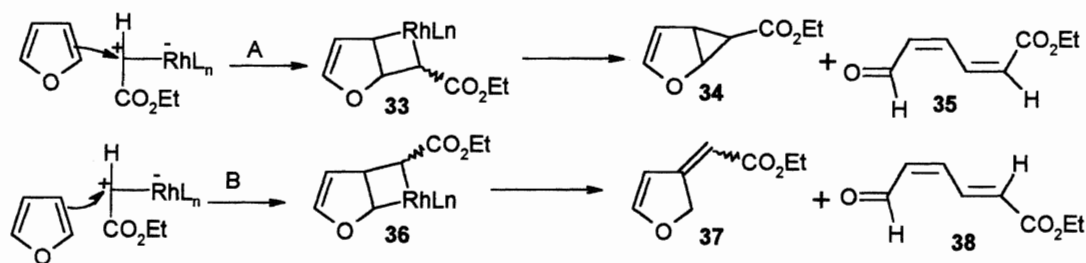
furnished an unstable adduct, which was immediately treated with 1,8-diazabicyclo[5.4.0]undec-7 (DBU) to give cycloheptatriene **26**. Further manipulations affords hainanolidol **27** which was transformed to harringtonolide **28** by means of lead tetraacetate.

1.5.2 Carbene and Carbenoid Insertion into Furan and its Derivatives:



In an early study, Novac and Sorm⁴⁵ observed that cyclopropanation of furan **29** by ethyl diazoacetate **8** under copper catalyzed conditions resulted in an unstable intermediate **30** that upon ring opening yielded the *Z,E*-diene **31** (see Scheme 18). Unraveling of the intermediate cyclopropane is thought to proceed *via* a [4+2]-cycloreversion to yield the conjugated ester-aldehyde **31**. The *Z,E*-diene can be isomerized to the *E,E*-diene **32** by the addition of a catalytic amount of iodine, making this reaction even more synthetically useful.⁴⁶ As will be seen later, this retro-cycloaddition is common in cyclopropanated furan systems.

Since this first cyclopropanation Novác and Šorm, a large number of publications have appeared in the literature expanding on this work. Wenkert and co-workers⁴⁷ performed a thorough study of the carbenoid insertion reactions involving furan and its derivatives with diazoesters and diazoketones. When Wenkert treated furan with ethyl diazoacetate (EDA) in the presence of rhodium(II) acetate, four products were isolated (*c.f.* the one product reported by Novác and Šorm) attesting to the mildness of the rhodium(II). As shown below in Scheme 19, the four products isolated are the cyclopropane adduct **34**, two isomers of the “ring-opened” dienes **35** and **38**, and a single isomer of a methylene dihydrofuran **37** in ratio of 17:10:5:1 respectively and in 66% overall yield.



Scheme 19

Wenkert explained the product distribution by invoking a metallocyclobutane intermediate. Addition of the double bond of the furan to the carbenoid complex to gives two intermediates **33** and **36**. Unravelling of these intermediates allow for access to the products formed.

These carbenoid insertions into furans have been employed to good synthetic effect in the total synthesis of ostopan acid (a plant cytotoxin),⁴⁸ corticocin⁴⁸ and a series of hydroxy-6,8,11,14-eicosatetraenoic (HETEs, mono-hydroxylated metabolites of arachidonic acid).⁴⁹

Employment of vinyl carbenoids

allows for a tandem

cyclopropanation-Cope

rearrangement and results in

[3+4]-cycloaddition products.

Cyclopropane forms this reaction

between the carbenoid and the π -

bond of furan and subsequent

rearrangement gives the resultant

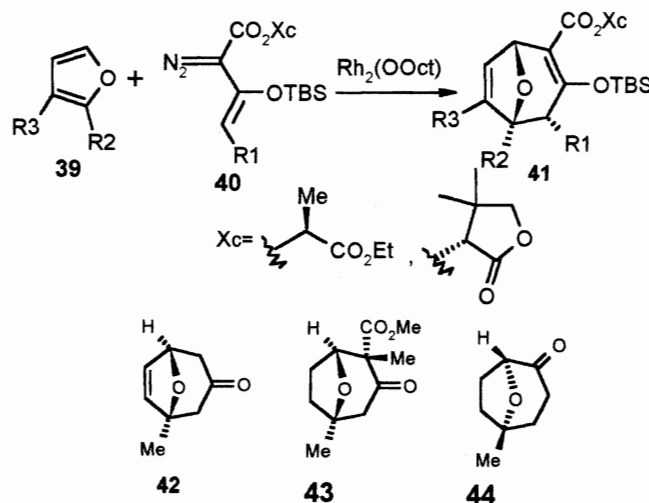
product. Davies⁵⁰ and his co-workers have shown that the reaction of furan with a vinyl diazocarbonyl is an efficient method for asymmetric synthesis of 8-

oxabicyclic[3.2.1]octan-3-ones. As shown in Scheme 20, treatment of enantiopure vinyl

diazocarbonyls **40** with $\text{Rh}_2(\text{OAc})_4$ in the presence of derivatized furans **39** give the

bicyclic ether **41** in good yield and diastereoselectivity (75-95% de). The use of the chiral

auxiliary (Xc) is the reason for the high asymmetric induction. The usefulness of this

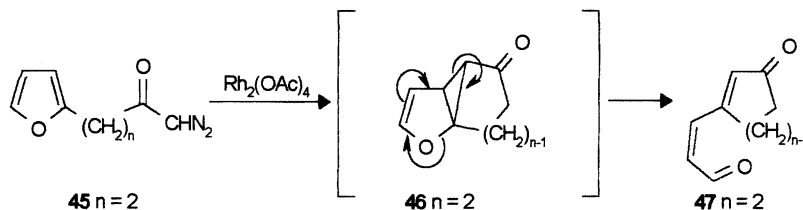


Scheme 20

methodology has been proven by the synthesis of the intermediates **42-44**, which had been used in racemic form as crucial building blocks in diastereoselective synthesis.

Intramolecular carbenoid insertions have also been studied. In his seminal paper published in 1989, Padwa⁵¹ investigated the chemistry carried out by a series of α -diazoketones tethered to furanyl, thienyl and benzofuranyl systems. Padwa⁵¹ showed that when 1-diazo-4-(2-

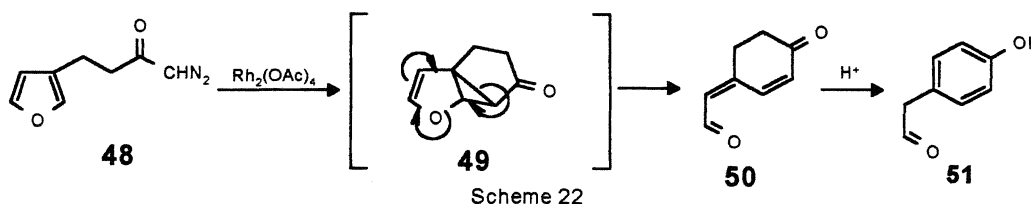
furanyl)-2-butanone **45** was exposed to rhodium (II) acetate, the *cis*-keto-aldehyde **47** was isolated



Scheme 21

in 86% yield. This is in

contrast to the work by Nwaji and Onyiriuka who cyclized the same substrate using copper (II) sulfate as the catalyst in refluxing cyclohexane. In this case, the more thermodynamically stable *trans*-cyclopentenone was isolated in 60% yield.⁵² In both cases the reaction proceeds *via* addition of the keto-carbene to the furanyl π -bond followed by a retro-[4+2] ring opening of the intermediate cyclopropane **46** to give the

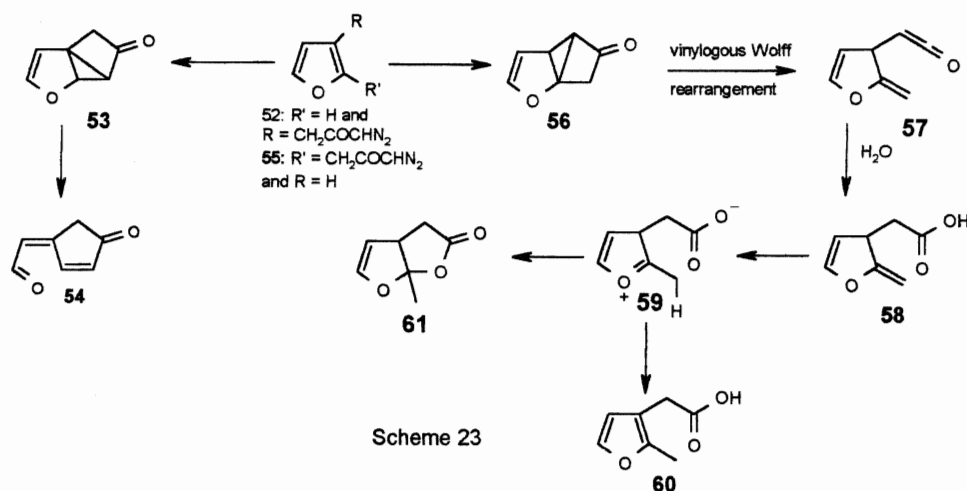


Scheme 22

keto-aldehyde **47**. Padwa's higher yield and ability to isolate the initially formed cisoid product demonstrates the superiority of the rhodium catalyst (Scheme 21).

Similar chemistry was exhibited by the isomeric 3-substituted furan, 1-diazo-4-(3-furanyl)-2-butanone **48** (see Scheme 22). Formation of the phenolic product isolated **51** could be rationalized as arising from intramolecular cyclopropanation to form the intermediate **49** followed by [4+2] cycloreversion to give the keto-aldehyde **51**, which then undergoes acid catalyzed rearomatization to form **51**.

The Capretta group became interested in the intramolecular carbenoid insertion chemistry of systems wherein the furanyl fragment is tethered to the α -diazoketone by a

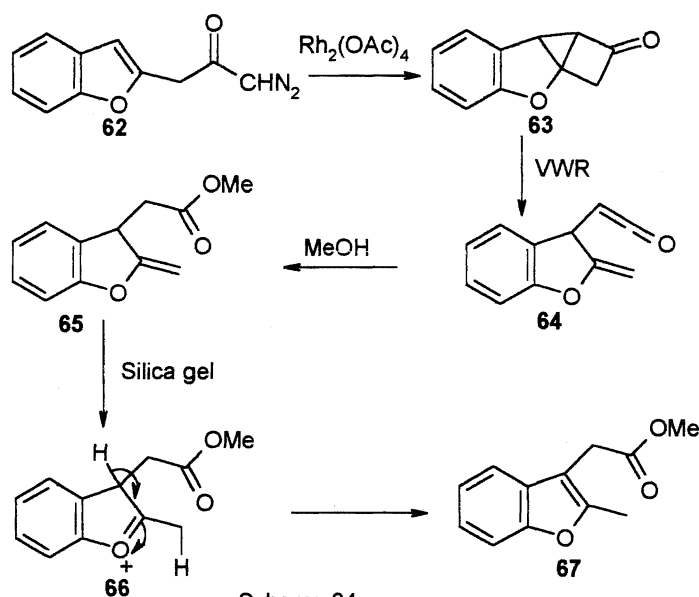


single methylene tether. The decomposition chemistry of the analogous 1-diazo-3-(3-furanyl)-2-propanone **52** was examined. As with homologous members of this series, treatment of **52** (Scheme 23) with Rh₂(OAc)₄ allows for the addition of the keto carbenoid generated to the furanyl π -bond to give cyclopropane **53**. [4+2]-Cycloreversion of this intermediate then affords the 2-(4-oxo-2-cyclopentenyliden)acetaldehyde **54** in quantitative yield (as determined by ¹H-NMR spectroscopy). Attempts to purify the keto-aldehyde **54** by column chromatography on silica gel resulted in decomposition.

While the isomeric 1-diazo-3-(2-furanyl)-2-propanone **55** has previously been studied by Padwa⁵¹, the compound was shown to carry out only an intermolecular Büchner reaction with the solvent benzene. Given the experience with **86** and that of Durst⁵³ working with comparable diazo compounds, system **55** was revisited by the Capretta group⁵⁴ and its intramolecular carbenoid insertion chemistry re-examined. Initial experiments with α -diazoketone **55** and rhodium (II) acetate in dry dichloromethane under an argon atmosphere at room temperature gave "the mixture" of products reported by Padwa.⁵¹ When water was introduced, however, the reaction proceeded smoothly so as to allow for the production of only two products: 2-methyl-3-furan acetic acid **60**⁵⁵ and the bicyclic lactone **61**. It would appear that the intermediate cyclopropane produced **56** does not unravel by the usual [4+2]-cycloreversion but, rather, opens *via* a vinylogous Wolff rearrangement (VWR). Although such rearrangement on a furanyl system has not been previously observed, Smith has demonstrated the operation of VWR mechanism in the reactions of a number of β,γ -unsaturated- α -diazoketones⁵⁶. Rearrangement of **56** *via* the VWR gave the vinyl ketene intermediate **57** which in the presence of water was trapped to yield acid **58**. Protonation of the exocyclic double bond gives the oxonium ion **59** which can either lose a proton to rearomatize to **60** in 60% yield or cyclize to **61** in 15% yield.

Padwa⁵¹ has also reported an extension of this intramolecular carbenoid insertion work involving benzofuran as the aromatic fragment. In contrast to the analogous furanyl systems, carbenoid insertion allows for an isolable cyclopropane intermediate (see discussion section).

Work in the Capretta group demonstrated that a single methylene tether linking the benzofuran and the α -diazoketone also allows for atypical chemistry. Exploratory experiments involving the treatment of 1-diazo-3-(2-benzofuran)-2-propanone **62** (Scheme 24) with rhodium(II) acetate in dichloromethane resulted in a complex mixture



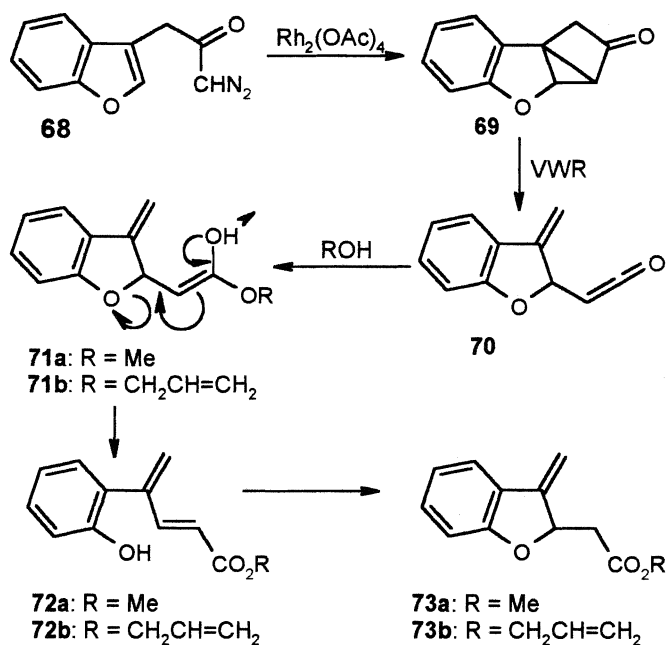
Scheme 24

and an inability to isolate any carbenoid insertion product. This led us to believe that, unlike the other homologous members of the benzofuranyl series, **62** behaved very much like 1-diazo-3-(2-furanyl)-2-propanone **55** in that the

intermediate cyclopropane participated in a vinylogous Wolff rearrangement. This was confirmed when the rhodium acetate decomposition of **62** was repeated in the presence of methanol. The reaction was monitored *via* ^1H -NMR and clearly showed the formation of one major product which we assigned as **65**. Clearly the VWR is the lower energy pathway given that [4+2]-cycloreversion of **63** would not only lead to disruption of aromaticity in the benzene moiety but would also produce a highly-strained cyclobutenone system. When a preparative scale reaction was carried out and the product purified by silica gel chromatography, ^1H -NMR revealed that the product **65** had

isomerized to methyl-(2-methyl-3-benzofuranyl) acetate **67** presumably *via* protonation of the exo-cyclic double bond to yield oxonium ion **66** followed by rearomatization.

Reactions involving the treatment of 1-diazo-3-(3-benzofuranyl)-2-propanone (**68**, Scheme 25) with rhodium acetate quickly revealed that the vinylogous Wolff rearrangement was again at work. Catalytic decomposition of **68** takes place to give



Scheme 25

cyclopropane **69** which undergoes a VWR to **70**. The trapping of the intermediate ketene by methanol, however, lead ultimately to the isolation of the polyunsaturated phenolic ester **72a** whose structure has been confirmed by MS, ^1H - and ^{13}C -NMR and the 2D-COSY. Rather than tautomerize to **73a** as would

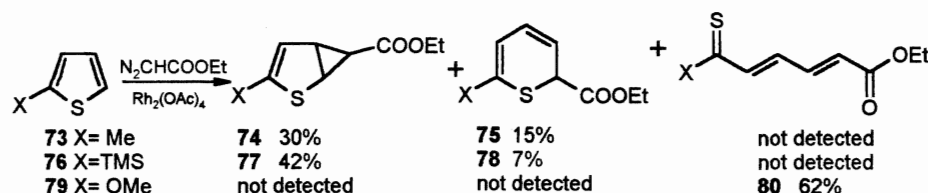
be expected, enol **71a** collapses to give the ring opened product **72a**. The additional conjugation possessed by **72a** explains, in part, the preference for its formation over **73a**. While the production of **72a** could also be the result of a retro-Michael addition of **73a**, this is unlikely since there was no evidence of **73a** detected in the reaction mixture. Further evidence for the mechanism shown in Scheme 24 was provided when the reaction of **68** was repeated in the presence of allyl alcohol to yield only compound **72b** and no **73b**. We are currently studying **72b** to determine whether the compound can be induced to carry out an intramolecular Diels- Alder reaction. It should also be noted that

a sample of **73b** (prepared by refluxing a sample of the unsaturated ester **72b** in toluene for 24 hours) was stable and did not undergo a retro-Michael addition at room temperature.

1.5.3 Carbene and carbenoid insertion into thiophene and its derivatives:

Intermolecular reactions between thiophenes and diazocarbonyls have also been known for several years⁵⁷, but unlike furanyl systems, thiophene reacts to give stable cyclopropanated products⁵⁸ or crystalline sulphur ylides⁶⁰.

Work by Capretta and Tranmer⁵⁹ has shown that appropriate substitution of the thiophene can allow for chemistry seen in the furanyl systems. They argued that the propensity for cyclopropanated furans to undergo a net [4+2]-cycloreversion (*c.f.* cyclopropanated thiophenes) is likely a result of the greater bond strength of the aldehyde C=O bond generated compared to the thioaldehyde C=S bond. The introduction of



Scheme 26

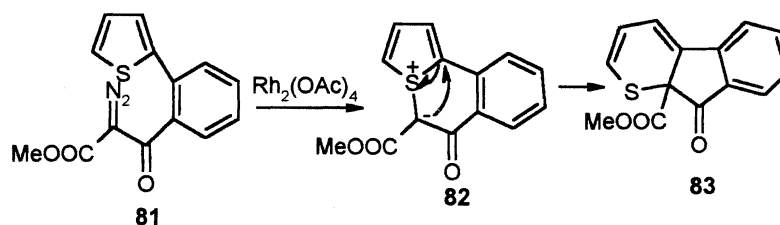
groups that can stabilize the thioacyl moiety (*i.e.* π - or σ -donors) should, therefore, help promote the [4+2]-cycloreversion in the thienyl series. With this in mind, they looked at the reactions of various 2-substituted thiophenes with ethyl diazoacetate in the presence of rhodium(II) acetate.

In the cases of 2-methylthiophene **73** and 2-(trimethylsilyl)thiophene **76**, cyclopropane **74** and **77** and thiopyran **75** and **78** products predominated while thiophene-2-thiol gave rise

to ethyl 2-(2-thienylsulfanyl)acetate and 2-(methylthio)thiophene gave rise to thiopyrans and ethyl 2-(2-thienylsulfanyl)acetate. No reaction was apparent when 2-pyrrolidinothiophene was used. 2-Alkoxythiophenes, however, allowed for the production of a series of ethyl 6-alkoxy-6-thioxo-2,4-hexadienoates. For example 2-methoxy thiophene **79** reacts with ethyl diazoacetate in the presence of rhodium(II) acetate and gave exclusively ethyl 6-methoxy-6-thioxo-2,4-hexadienoate **80**. These results were explained by a mechanism which involved a sulphur ylide as the key intermediate rather than a cyclopropane.

The intramolecular insertion of a carbenoid into thiophene has been known for some time and generally also results in cyclopropanation or sulfur ylide formation. An example of ylide

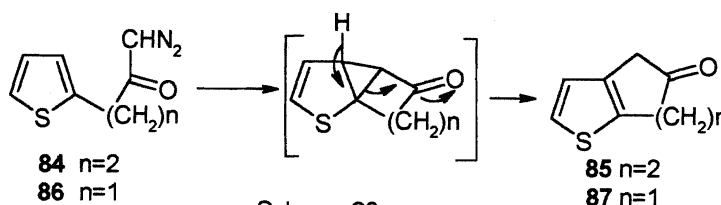
formation is the reaction carried by Skramstad⁶⁰ to



Scheme 27

establish ring contraction/enlargement reactions. Electrophilic attack of the carbenoid generated from diazoketone **81** of the sulfur to result in the formation of ylide **82** which in turn undergoes Stevens rearrangement⁶¹ to the tricycle product **83** (see scheme 27).

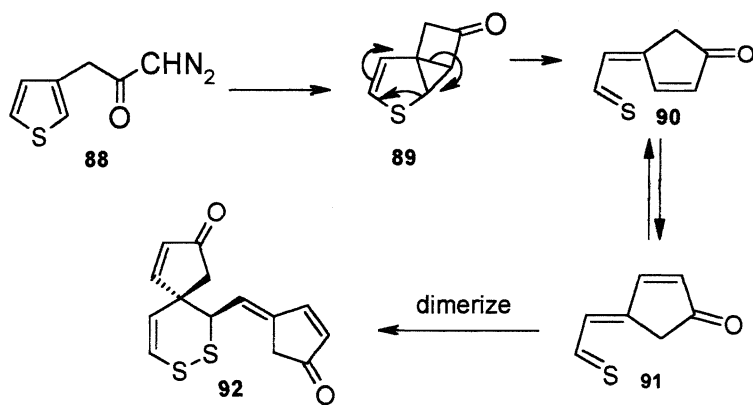
Padwa⁵¹ has demonstrated that 1-diazo-4-(2-thienyl)-2-butanone **84**



Scheme 28

can be converted to 4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-one **85** in the presence of rhodium (II) acetate. The reaction proceeds *via* cyclopropanation followed by acid-catalyzed ring opening to yield an enol which tautomerizes to the ketone shown in Scheme 28. The isomeric 1-diazo-4-(3-thienyl)-2-butanone was shown to undergo similar chemistry to give a mixture of 4,5,6,7-tetrahydrobenzo[*b*]thiophen-6-one and to 4,5,6,7-tetrahydrobenzo[*c*]thiophen-5-one.

Capretta *et al.* have recently demonstrated⁶² that treatment of 1-diazo-3-(2-thienyl)-2-propanone **86** with catalytic rhodium (II) acetate yields 5,6-dihydro-4*H*-



Scheme 29

cyclopenta[*b*]thiophen-5-one **87**, while under the same conditions, the isomeric 1-diazo-3-(3-thienyl)-2-propanone **88** gives the spiro-disulphide

92. In light of the

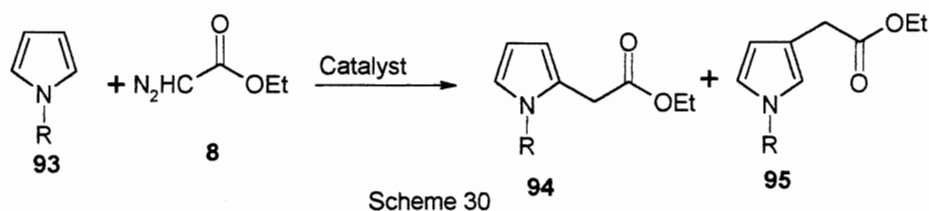
chemistry generally displayed by α -diazoketones tethered to thienyl systems, these results are significant since the former compound **86** behaves like the other homologous members of the thienyl series while the latter diazoketone **88** undergoes chemistry seen previously only in the furanyl series⁵¹. The unusual chemistry displayed by **88** can be attributed, in part, to the strain imparted by the short methylene tether to the intermediate cyclopropane **89** generated. Which undergoes apparent [4+2]-cycloreversion thioaldehyde **90**. Isomerization to **91** is then followed by a Diels-Alder dimerization to afford **92**

There have not been any studies involving the intramolecular carbenoid insertions into benzothienyl systems until the present thesis (*vide infra*).

1.5.4 Carbene and Carbenoid Insertions into Pyrroles:

A natural extension of the work being carried out in the Capretta laboratories involves the investigation of carbenoid insertions into pyrrole and indole. While studies involving these heterocyclic systems exist, the nature of the diazocarbonyl as well as the catalyst used varies and, as such, is not comparable to the systems studied above.

The first examples of intermolecular reaction between carbenoids and *N*-substituted pyrroles using copper were reported several years ago⁶³ and offers a ready synthesis of pyrrole acetic acids. The study, carried out by Maryanoff⁶⁴, involves the

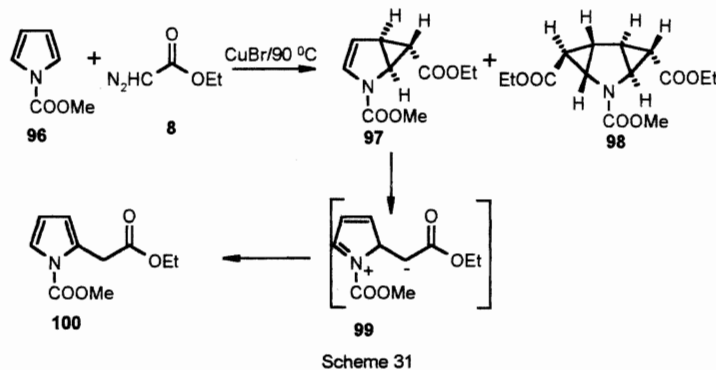


reaction of metal-stabilized carbenoids with pyrroles and substituted pyrroles in the presence of a wide number of decomposition agents. For example, treatment of pyrrole 93 with ethyl diazoacetate 8 and various catalysts allows for the formation of both the C(2) 94 and C(3) 95 isomers the ethyl ester of pyrrole acetic acid. Different catalysts give varying distribution ratios and total yield. Changing the substitution on the nitrogen also effects the ratio of the two products. Maryanoff found that pyrrole ($\text{R}=\text{H}$) gives mainly substitution at 2 position, while the 3-alkylation product can be obtained when $\text{R}=\textit{t}$ -butyl. Maryanoff rationalized this shift in isomer ratio by pointing to the steric

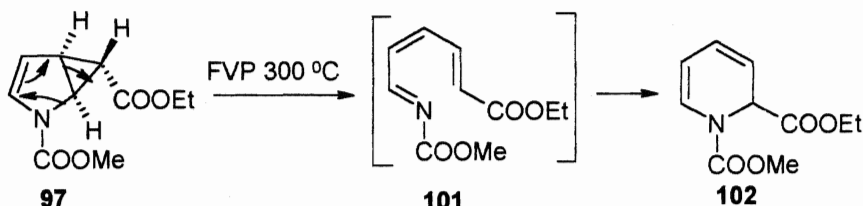
hindrance provided by the *t*-butyl group and believed that a net C-H insertion could only take place at C3.

The outcome of the reaction is changed again when an N-acyl group is introduced. Fowler⁶⁵ reported that when *N*-acyl pyrrole **96** was treated with ethyl diazoacetate and a catalytic amount of copper(I) bromide, cyclopropanation was the major product (see Scheme 31). Although the cyclopropane **97** is stable to purification by distillation, heating the mixture with copper(I) bromide at 150 °C results in the formation of ester **100**. Maryanoff proposes that the cyclopropane opens *via* a zwitterionic intermediate **99**. The fact that the copper catalyst was used to generate the carbenoid and was also capable of acting as a catalyst for isomerization of pyrrolocyclopropanes further complicates the analysis of the mechanistic pathways involved in the formation of alkylation products.⁶⁶

A different rearrangement was observed by Fowler and his co-workers when the cyclopropane **97** is subjected to flash vacuum



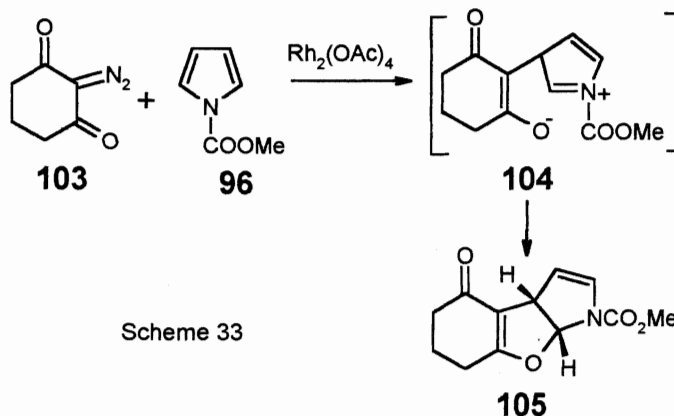
thermolysis at 300 °C in the absence of copper(I) bromide. Under these conditions, the dihydropyrridine **102** derivative is isolated in quantitative yield. The pathway for the formation of this product was studied using deuterium-labeling studies and its consistent with [4+2]-cycloreversion mechanism (as seen in the furanyl system) followed by electrocyclic ring closure of **101** to give the product **102**.



Scheme 32

Recently Pirrung and co-workers⁶⁷ also studied the reaction between carbenoids and *N*-acylated pyrroles. Reaction of 2-diazo-1,3-cyclohexanedione **103** with *N*-methoxycarbonyl pyrrole

96 in the presence of $\text{Rh}_2(\text{OAc})_4$ results in the formation of the tricyclic product **105**. Once again, the product is believed to arise via a zwitterionic



Scheme 33

intermediate **104**.

Normally the preferred site for electrophilic attack on pyrrole is the 2-position. In the present case, the authors postulate that **104** is the product of the unraveling an initially formed pyrrolecyclopropane. This analysis, however, isn't consistent with the regiochemical results observed by Maryanoff.

Davies⁶⁸ and his group have employed pyrrole derivatives **106** in the reaction with vinyl diazocarbonyls **107**. These systems allow cyclopropanation followed by Cope rearrangement and provide a very direct method for the synthesis of tropane system. This reaction is used to good effect in the synthesis of (\pm)-anhydroecgonine methyl ester **110** ($\text{R} = \text{OMe}$) and (\pm)-ferruginine **110** ($\text{R} = \text{Me}$).

A survey of the chemical literature reveals that most of the intramolecular carbenoid reactions involving pyrrole are restricted to those wherein the diazoketone

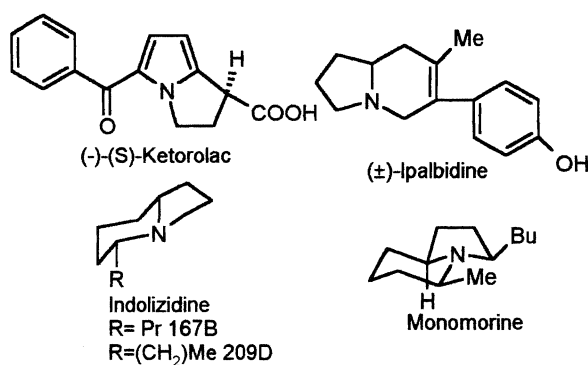
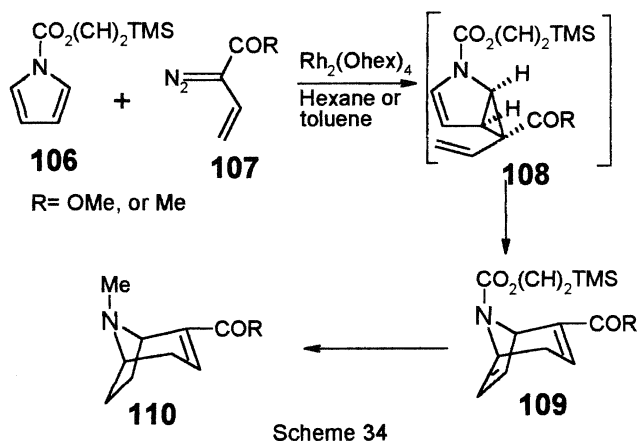


Figure 6



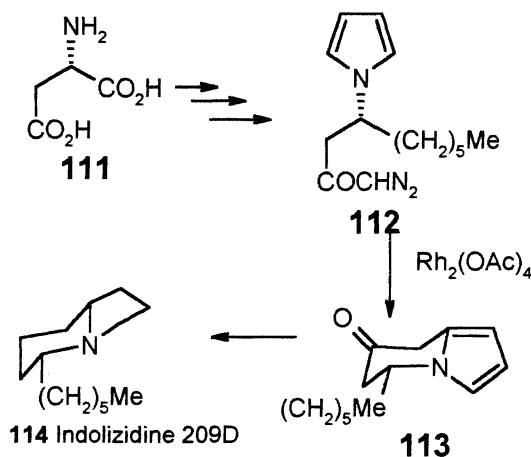
moieties are linked through the nitrogen. One of the first examples of an intramolecular carbenoid insertion involving a pyrrole was reported in 1983⁶⁹. Generally the product of the intramolecular carbenoid insertion is the

alkylation at 2-position. This methodology has been applied by Jefford and his co-workers⁷⁰ towards the synthesis of natural products such as indolizidine 167B and 209D, (+)-monomorine, (±)-ipalbidine, and by Müller⁷¹ and his co-worker for the synthesis of ketorolac (see Figure 7). Scheme 35 illustrates the key step for the synthesis of indolizidine 209D **114**. Using the readily available enantiopure amino acid **111** to make the diazoketone **112**, treatment of the diazoketone with rhodium acetate in dichloromethane furnishes the bicycle **113** in a very good yield, this follows by reduction gives the natural product **114** in 56% overall yield.

1.5.5 Mechanistic Considerations:

Two mechanisms have been postulated to account for the products seen in the reactions of cabenoids with pyrrole: a zwitterionic pathway and a pathway involving a cyclopropane intermediate.

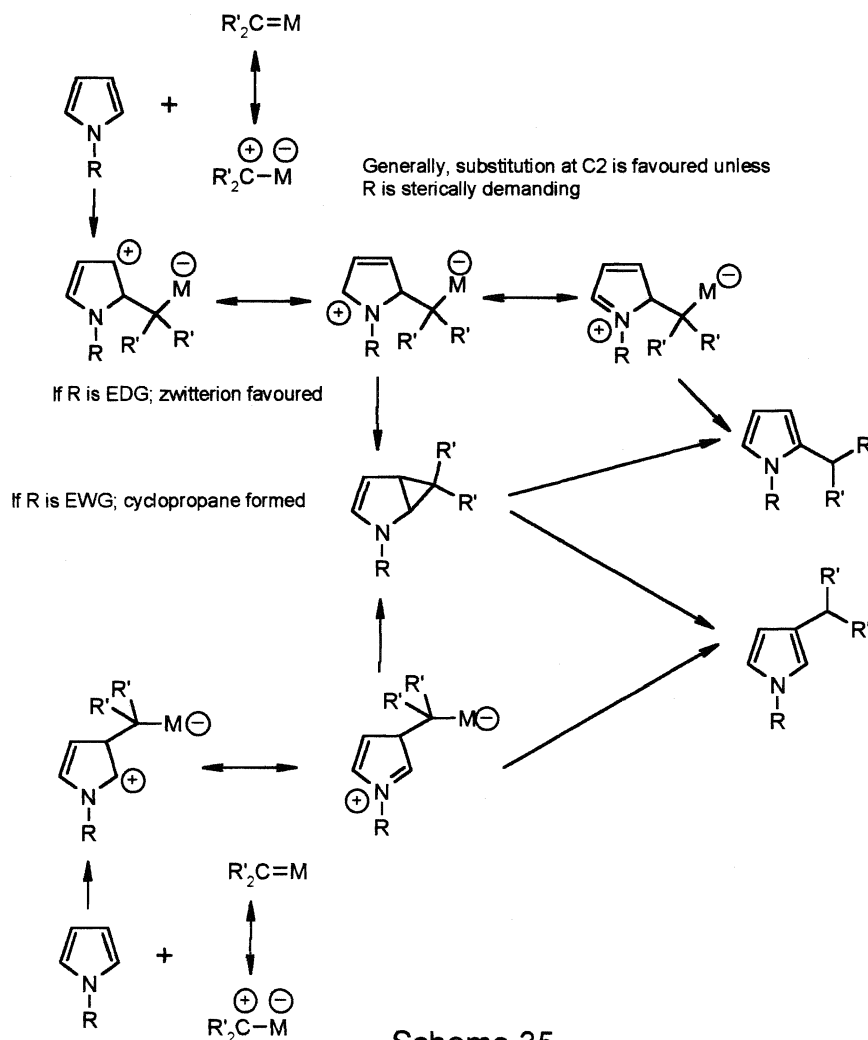
The zwitterionic mechanism envisions the reaction to proceed essentially as an electrophile aromatic substitution reaction. The electrophilic carbenoid attacks the pyrrole to give the dipolar



Scheme 35

intermediate shown which can rearomatize and shift a proton to give the alkylation products. The second mechanism involves the addition of the carbenoid across a π -bond of the pyrrole to give a cyclopropane intermediate which then unravels and rearomatizes to give the alkylation products.

Evidence favours the mechanism involving the zwitterionic intermediates since the regiochemical preference is for alkylation at C2 as opposed to C3. Further more, increasing the steric bulk on the nitrogen favours substitution at C3 as one would expect if the zwitterionic pathway were operating. Bulky groups on the nitrogen should have no effect if a cyclopropane were generated in a concerted manner. One may, however, envision cyclopropanes to be formed in a stepwise fashion and, if so, the cyclopropane pathway is an extension of the zwitterionic mechanism.



Scheme 35

With pyrroles and N -alkylpyrroles, alkylation products are invariably formed, but with N -acylpyrroles a variety of products derived from pyrrolocyclopropanes are formed. This would seem to indicate that pyrrolocyclopropanes are only generated when the nitrogen is substituted with electron withdrawing groups (EWG) and generally not seen when the nitrogen is substituted with electron donating groups (EDG). When substituted with EDG, the zwitterionic species is stabilized (since the positive charge delocalized on the pyrrole ring is stabilized) and sufficiently long-lived as to continue to do the chemistry. When substituted with EWG, the zwitterionic species is less stable and closure

to the cyclopropane becomes energetically favorable. The cyclopropane can then revert to the zwitterion and continue the chemistry or fall apart via the "enol" mechanism.

1.5.6 Carbene and Carbenoid Insertion into Indoles:

Ethyl diazoacetate reacts with indole **115** under heat or via copper catalysis and gives the β -alkylation

product⁷² **116**. The

intermediate cyclopropane

was not seen in these

reactions. Attempts to test the

fate of the reaction and trap

the cyclopropane intermediate were done by Wenkert⁷³. Copper-catalyzed decomposition

of ethyl diazoacetate in 1,3-dimethylindole **117** afford ethyl 1,3 dimethylindole-2-acetate

118 in low yield (7%). 1,2 Dimethylindole **119** gives ethyl 1,2 dimethylindole-3-acetate

120 in good yield (53%). Decreasing the

electron availability on the indole nitrogen

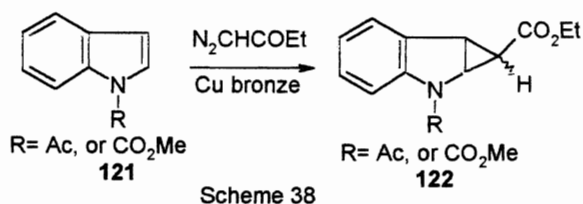
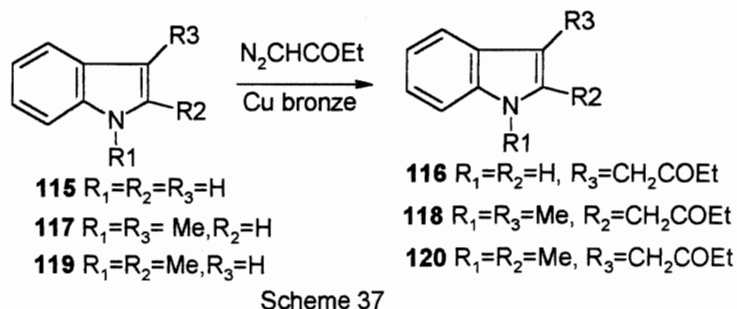
stabilizes the cyclopropane intermediate.

Reaction of ethyl diazoacetate with indoles

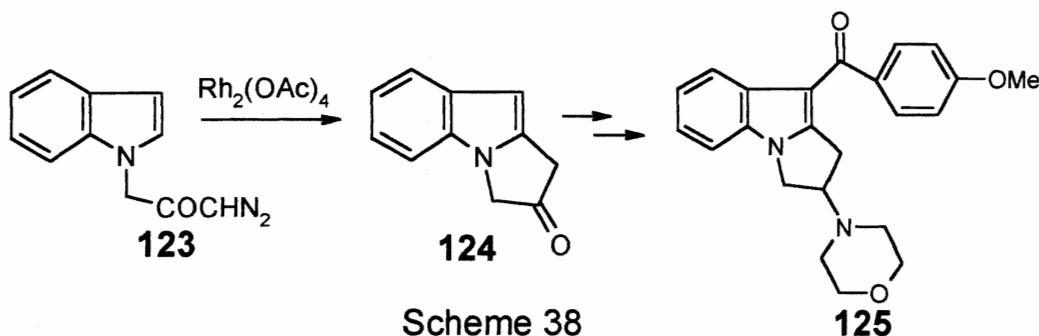
of the type shown in Scheme 38 (**121**) having electron withdrawing groups at the nitrogen

such as acetyl, and carbomethoxy result in the formation of the cyclopropane **122** in

moderate yields.



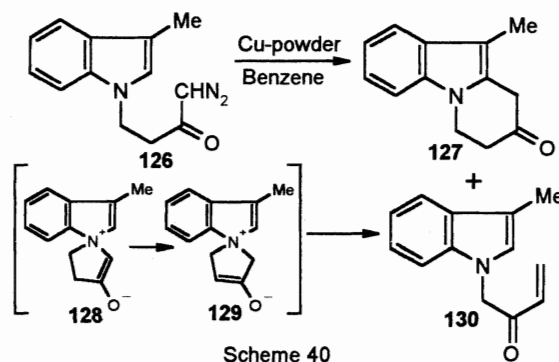
D'Ambra and his co-workers⁷⁴ used the intramolecular carbenoid insertion into indole for the synthesis conformationally-restricted, nonacidic analogues of non-steroidal



anti-inflammatory pravadoline. Intramolecular carbenoid reaction of diazocarbonyl **123** resulted in the formation of the pyrroloindole **124** in very good yield.

Decomposition of 3-methylindole with longer chain linked to the nitrogen in the presence of copper gave two products **127** in 7% yield and **130** in 24% yield. The former resulted from alkylation at 2-

position. The formation of the later product **130** has been rationalized as resulting from the reaction of the carbenoid at the indole nitrogen to generate the



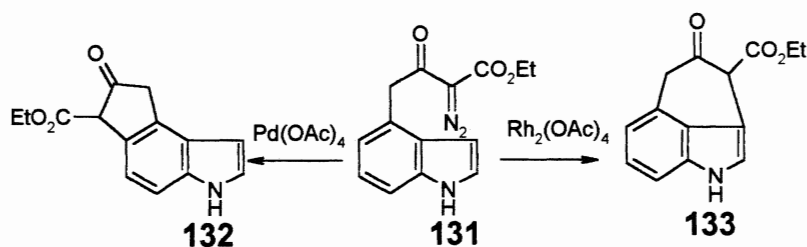
zwitterion **128**. Equilibration of **128** to the isomeric **129** followed by an elimination reaction results in the formation of the unsaturated ketone **130**.

Another example of intramolecular carbenoid insertion was reported by Matsumoto *et al.*⁷⁵ The regiochemical competition between alkylation at the 3- and 6-position of indole occurred when the diazoketone treated with different decomposition

agents. Treatment of diazoketone **131** with rhodium(II) acetate resulted in the formation of **132** (a result of the attack of the carbenoid at the benzene ring), however palladium(II) acetate gave the tricycle **133** (resulting from the nucleophilic addition at the pyrrole ring).

1.6 Aims and Objectives:

As seen above, many of the reaction involving carbenoid insertions into pyrrole and indole have been



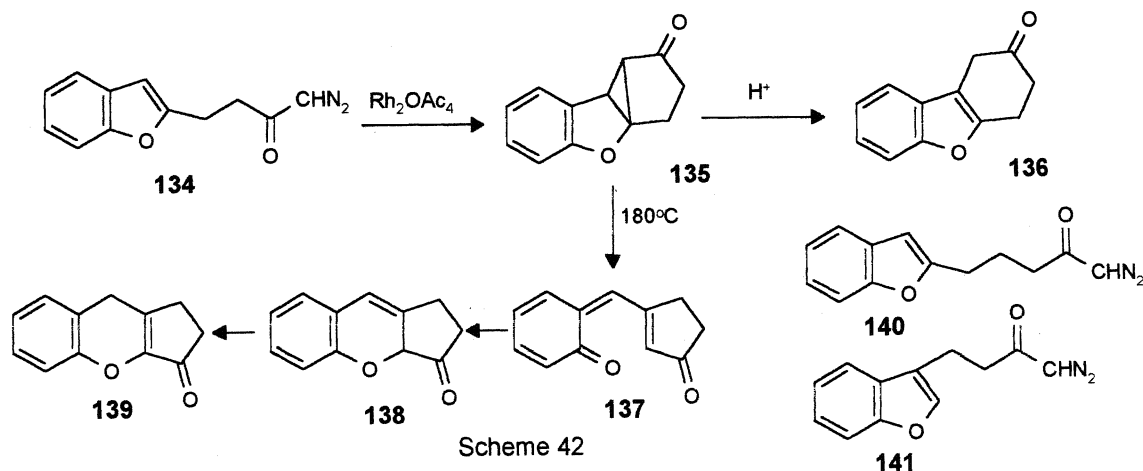
Scheme 41

carried out on substrates wherein the terminal diazoketone is linked to the aromatic system through the nitrogen. In an effort to expand on the work developed in the Capretta labs (see analogous compounds **52**, **55**, **62**, **68**, **86** and **88**), we will look at systems wherein the diazoketones are linked through a methylene tethers at positions α and β to the nitrogen. The employment of a single methylene tether seems to allow for atypical chemistry in the furan and thiophene systems and it would be interesting to see if the novel chemistry continues into the pyrrole series. The decomposition catalyst will be rhodium(II) acetate, exclusively. In addition, the chemistry of benzothiophenes linked to diazoketones will also be examined.

Results and Discussion

2.1. Intramolecular Insertions Of Carbenoids Into Benzothiophene

2.1.1 Rhodium(II) Acetate Catalyzed Decomposition of 1-Diazo-4-(2-benzothieryl)-2-butanone (**146**) and 1-Diazo-4-(3-benzothieryl)-2-butanone (**152**):

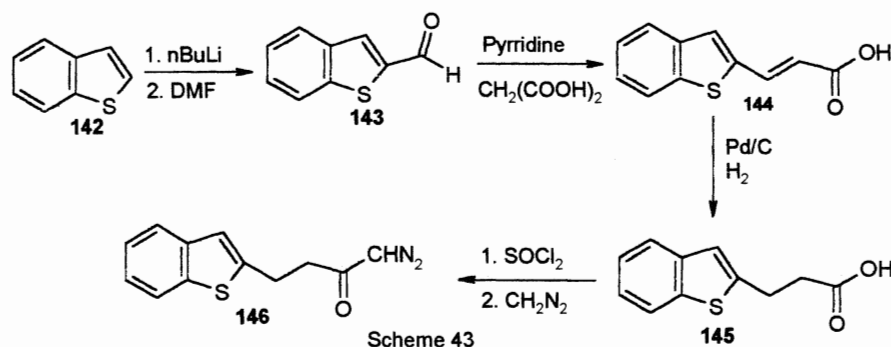


Work involving the intramolecular insertions of carbenoids into benzothiophene systems has not been previously described in the chemical literature. Our interest in these systems stems from Padwa's demonstration⁵¹ that the chemistry exhibited by α -diazoketones containing benzofuranyl moieties is different to that shown by the analogous furanyl substrates. For example, when 1-diazo-4-(2-benzofuran)-2-butanone (**134**, Scheme 42) was exposed to a solution containing rhodium acetate, the cyclopropane **135** was isolated. Treatment with 1% sulfuric acid solution converted the cyclopropane to compound **136** via the enol pathway discussed previously. [4+2]-Cycloreversion can be induced at 180°C to give the ortho-quinoidal system **137**. The forcing conditions are required since the cycloreversion effectively destroys the aromaticity of the system. **137** Rapidly undergoes electrocyclic ring closure to **138**

which, in turn, isomerizes to the more conjugated **139**. Benzofuranyl systems with longer tethers (for example, 1-diazo-5-(2-benzofuran)-2-pentanone, **140**) or with 3-substituted tethers (for example, 1-diazo-4-(3-benzofuran)-2-butanone, **141**) exhibit the same type of chemistry.

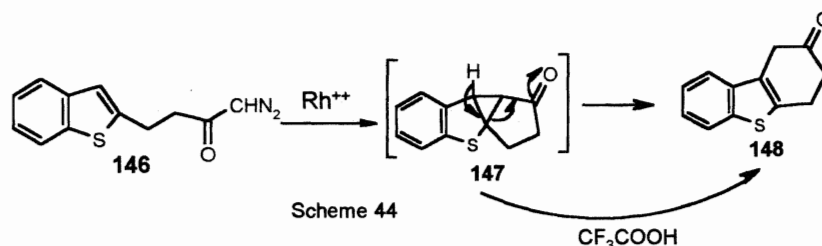
In order to examine the effect of a fused benzene on the reactions carried out by thienyl-based α -diazoketones, an investigation of α -diazoketones systems containing benzothienyl fragments was undertaken. Systems containing two methylenes tethering the aromatic system and the diazo moiety will be described initially.

Preparation of 1-diazo-4-(2-benzothienyl)-2-butanone **146** by the standard procedure of acylation of diazomethane first required the synthesis of the precursor



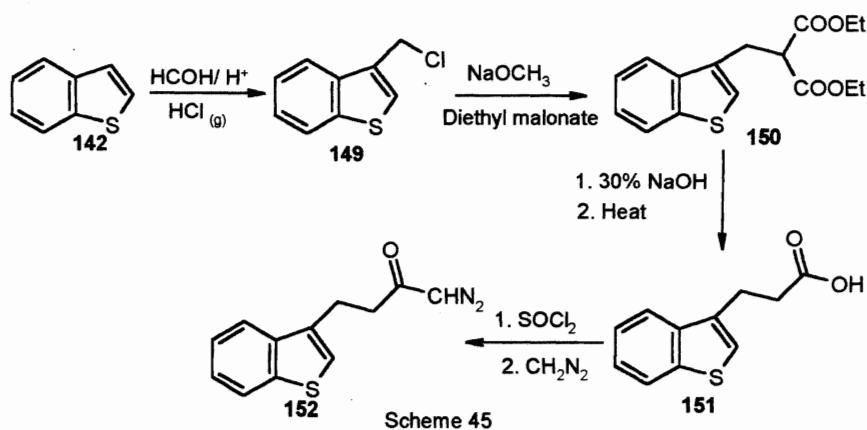
carboxylic acid **145**. Modification of literature procedures allowed for the development of the synthetic route shown in Scheme 43. Following the procedure described by Ried and Bender⁷⁶, 2-benzothiophene-2-propionic acid **145** was derived from 2-benzothiophene aldehyde **143**. Lithiation of benzothiophene **142** at -70°C leads exclusively to the formation of thiophenyl-2-lithium which when added to a solution of dimethylformamide resulted in the formation of the 2-benzothiophene aldehyde **143**. Reaction between malonic acid and benzothiophene aldehyde **143** in the presence of a strong base results in the formation of the benzothiophene acrylic acid **144**.

Hydrogenation of the α,β -unsaturated acid using Pd/C and hydrogen gas furnished the desired benzothiophene 2-proponic acid **145**. Treatment of the carboxylic acid with thionyl chloride in the presence of catalytic amount of dimethylformamide generates the acyl chloride which is added to an excess of ethereal solution of diazomethane (without purification) to afford the 1-diazo-4-(2-benzothiophenyl)-2-butanone **146**.



Exposure of 1-diazo-4-(2-benzothiophenyl)-2-butanone **146** to rhodium(II) acetate in dichloromethane at room temperature for two hours afforded two products 1,2,3a,3b-tetrahydr-3*H*-benzo[*b*]cyclopenta[2,3]cyclopropa[1,2-*d*]thiophen-3-one **147** in 70% yield and 1,2,3,4-tetrahydrodibenzo[*b,d*]thiophen-2-one **148** in 13% yield. Treatment of a solution of **147** with a drop of trifluoroacetic acid leads to quantitative conversion to **148**. This result is consistent with the other analogous diazoketones **134** and **141**, which form cyclopropanes as well.

The effect of the position of substitution was then examined by carrying out the rhodium(II) acetate catalyzed



decomposition chemistry of 1-diazo-4-(3-benzothieryl)-2-butanone **152**. Once again, the desired diazoketone had to be derived from the corresponding carboxylic acid precursor **151**. 3-Benzothiophene propionic acid **151** was prepared by the method described by Campaigne and Knapp⁷⁷ as shown in Scheme 45. Treatment of benzothiophene **142** with acidic formaldehyde and hydrochloric acid gas results exclusively in the formation of the 3-chloromethyl benzothiophene **149**. Deprotonation of diethyl malonate with sodium methoxide generates the enolate which was alkylated by **149** to afford the diester **150**. Hydrolysis followed by decarboxylation provided the carboxylic acid **151**. Once again the general procedure for making diazoketone was applied and 3-benzothiophene propionic acid **151** was treated with thionyl chloride and a catalytic amount of dimethylformamide to give the acyl chloride which was added to a diazomethane solution to produce the diazoketone **152**.

The chemistry of 1-diazo-4-(3-benzothieryl)-2-butanone **152** was shown to be the same as the isomeric compound **146**. Decomposition of diazoketone **152** in the presence of rhodium(II) acetate gave the metal carbene complex which added across the π bond to give the cyclopropane 1,2,3a,3b-tetrahydro-3*H*-benzo[*b*]cyclopenta[1,3]cyclopropa[1,2-*d*]thiophen-3-one **153** in very good yield. The cyclopropane **153** was confirmed by NMR and mass spectroscopy. Treatment of **153** with a drop of trifluoroacetic acid allowed for an acid catalyzed ring opening to yield the tricycle 1,2,3,4-tetrahydrodibenzo[*b,d*]thiophen-3-one **154**.

Attempts to investigate the chemistry of the cyclopropane were also undertaken.

It is generally accepted that opening of the cyclopropane will occur at the bond which has a maximum

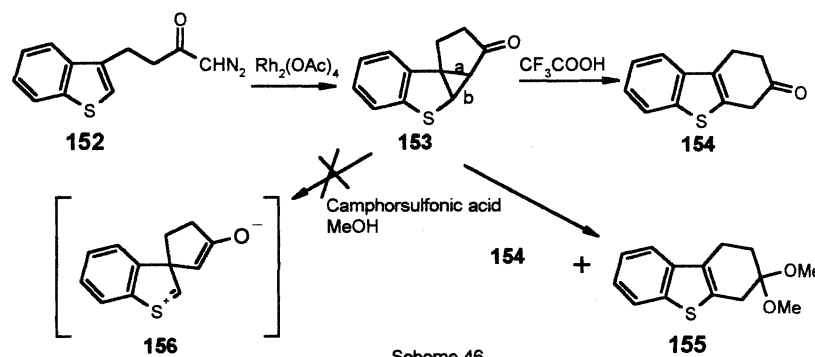
overlap with the π

orbital of the

carbonyl group.

Examination of

molecular models

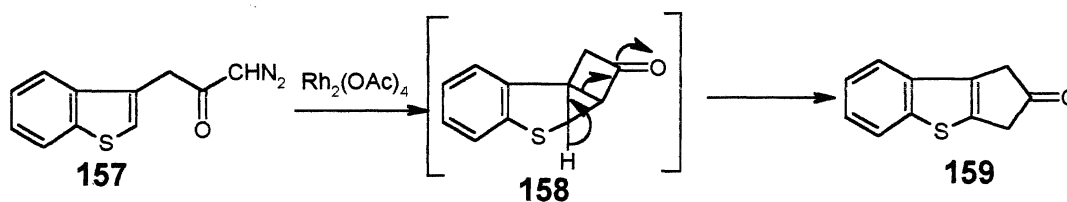


indicates the exterior bond (bond b) in compound **153** is more likely to cleave first since this bond is aligned almost orthogonally to the π -system of the carbonyl group. Rupture of the interior bond (bond a) would violate the stereoelectronic principle formulated by Norin and Dauben⁷⁸. In an effort to trap the intermediate spiro cation **156** which would result from such a rupture, the cyclopropane **153** was treated with camphorsulfonic acid in methanol. This resulted in the isolation of two products: the tricycle **154**; and 3,3-dimethoxy-1,2,3,4-tetrahydrodibenzo[b,d]thiophene (**155**, the ketal of **154**). When the cyclopropane **153** was heated in toluene to 150 °C, starting material was recovered as well as the tricycle **154**. It seems unlikely, therefore, that rearrangement of **153** to **154** proceeds by cleavage of bond b unless 1,2 migration of the proposed spiro cation **156** is faster than trapping by methanol. An alternative mechanism for the cyclopropane opening involves acid-catalyzed ring opening which aromatizes first to yield an enol then tautomerizes to the ketone. This mechanism is consistent with the results of the MeOH/CSA trapping experiment.

2.1.2 Rhodium(II) Acetate Catalyzed Decomposition of 1-diazo-3-(3-benzothieryl)-2-propanone (**157**) and 1-diazo-3-(2-benzothieryl)-2-propanone (**165**):

The strain imparted to intermediate cyclopropanes by the short methylene tethers has allowed for some unusual chemistry (see Scheme 24 and 25). We extended our study to include 1-diazo-3-(3-benzothieryl)-2-propanone **157** and 1-diazo-3-(2-benzothieryl)-2-propanone **165** in order to examine the effect of single methylene tethers on the chemistry shown above.

Kelvin Yong of the Capretta group showed that treatment of 1-diazo-3-(3-benzothieryl)-2-propanone **157** with $\text{Rh}_2(\text{OAc})_4$ produced 2,3-dihydro-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-2-one **159** (77% yield) without isolation of the intermediate cyclopropane **158**. Unlike the intermediate cyclopropane generated in the conversion of **88** \rightarrow **92** (Scheme 29), the [4+2]-cycloreversion of **158** is avoided since a



Scheme 47

similar unraveling would lead to the disruption of aromaticity.

Yong also examined the catalytic decomposition of 1-diazo-3-(2-benzothieryl)-2-propanone **165**. The later diazoketone was also derived from the corresponded carboxylic acid **164** which was obtained from 2-thionaphthaldehyde **13** seen before according to the procedure described by Degenhardt⁷⁹. The one carbon chain extension of aldehyde **143** was obtained using the modified Wittig reagent dimethyl aminomethylene diphosphonate **162**. Thus treatment of the compound **162** with sodium hydride followed by addition of the aldehyde afforded the phosphonate **163**, which was hydrolyzed using hydrochloric acid to give benzothiophene-2-acetic acid **164**. The modified Wittig reagent **162** was obtained from the reaction of dimethylchloroformiminium chloride **160** (from

dimethylformamide and oxalyl chloride⁸⁰) and

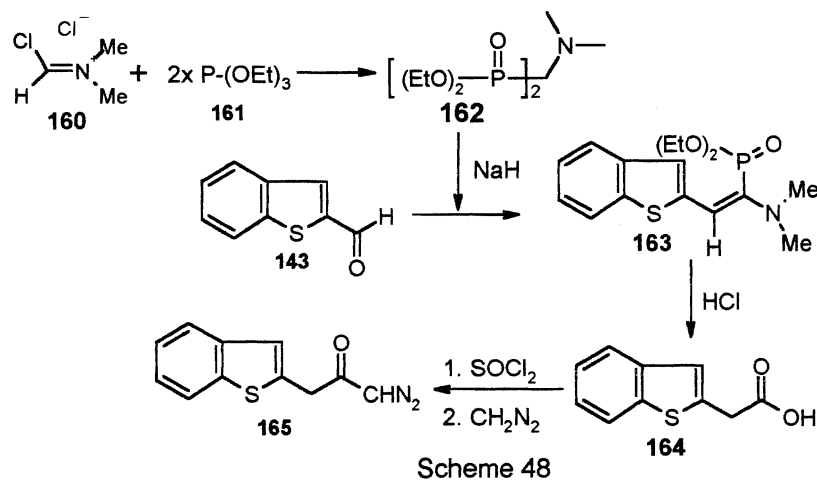
triethyl phosphite **161**

using the procedure

described by Gross and

Costisella.⁸¹ The

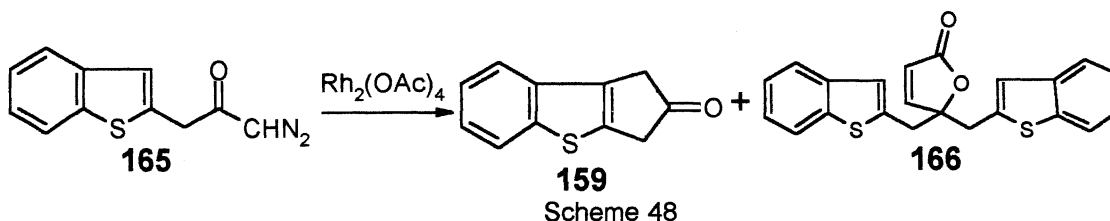
desired diazoketone



165 was prepared using the standard procedure, used before for diazoketone **146**, from its corresponded carboxylic acid **164**.

The results were confusing in that the reaction allowed for the production not only of the expected 2,3-dihydro-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-2-one **159** (in 21% yield) but also a white crystalline product in 58% yield. Mass spectroscopy showed that the latter product was a dimer and had a molecular ion at $m/z = 192$. Confusion arose when the NMR and the x-ray crystallography gave conflicting results. ¹H NMR clearly

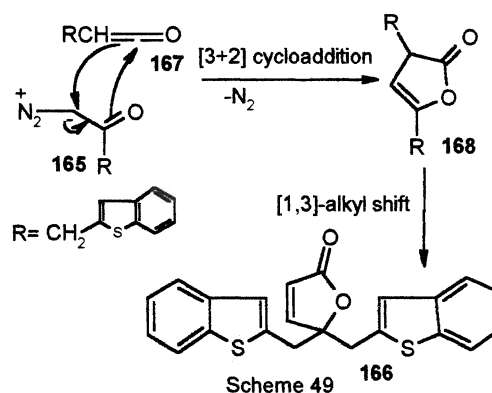
showed two different benzothienyl moieties. Crystals grown from ethyl acetate were sent for x-ray crystallography and the structure solved by Dr. Christopher S. Frampton, Roche Products, U.K. The resultant structure failed to refine to an acceptable level but did



indicates the presence of two equivalent benzothienyl moieties.

The system was revisited and a more thorough investigation was initiated. Once again the decomposition of 1-diazo-3-(2-benzothiophenyl)-2-propanone **165** resulted in the formation of 2,3-dihydro-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-2-one **159** and the dimer. It was shown however that the dimer rearranged slowly over a period of days. Once the complete rearrangement had taken place, the NMR and x-ray information were re-examined and shown to be consistent. As a result the dimer was assigned the spirocyclic structure **166** shown in Scheme 48.

The spiro compound **166** is likely the result of a [3+2] cycloaddition involving the α -diazoketone **165** and the ketene **167** generated by a Wolff rearrangement of **165**⁸². The initial lactone formed **168** then undergoes a [1,3]-alkyl shift to the more thermodynamically favored α,β -unsaturated lactone **166**. A similar



transformation has been reported⁸³ in the thermolysis of α -diazoacetophenone. It is not

clear why **165** is the only member of this benzothieryl series which participates in this type of chemistry. The initial confusion between the x-ray structure and the NMR was likely due to the fact that the NMR was of structure **168** while the x-ray was of the rearranged **166**.

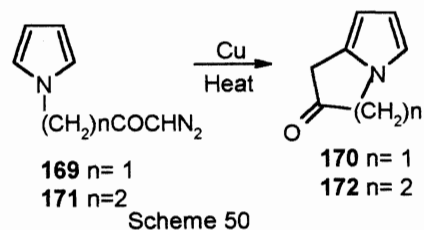
Overall, the carbenoid insertions in benzothiophene above reveals that the chemistry is, for the most part, predictable and a rather straightforward method for the preparation of cycloalkanone systems fused to benzothiophenes.

2.2. Intramolecular Insertions Of Carbenoids Into Pyrrole

2.2.1 Rhodium(II) acetate Catalyzed Decomposition of 1-Diazo(2-pyrrolyl)-2-propanone (173):

To date, the only attempts at the intramolecular insertion of a carbenoid into pyrrole have been reported by Galeazzi⁶⁹ and by Jefford⁸⁴.

In these cases, the tethered diazoketone is bonded to



the pyrrole through the nitrogen and the catalyst

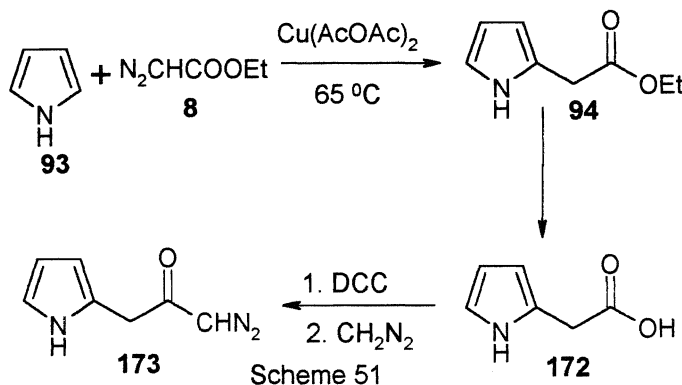
used is copper-based. For example, treatment of 1-diazo-3-(1-pyrrolyl)-2-propanone **169** and 1-diazo-3-(1-pyrrolyl)-2-butanone **171** with copper under reflux in benzene afforded 1*H*-pyrrolizin-2-(3*H*)-one **170** and 5,6-dihydroindolizin-7 (8*H*)-one **172** respectively (scheme 50). These products were rationalized as having been generated by a C-H insertion.

In an effort to compare heterocycles, we chose to prepare systems analogous to the ones investigated above. As a result, pyrroles tethered at either the 2- or 3-position by

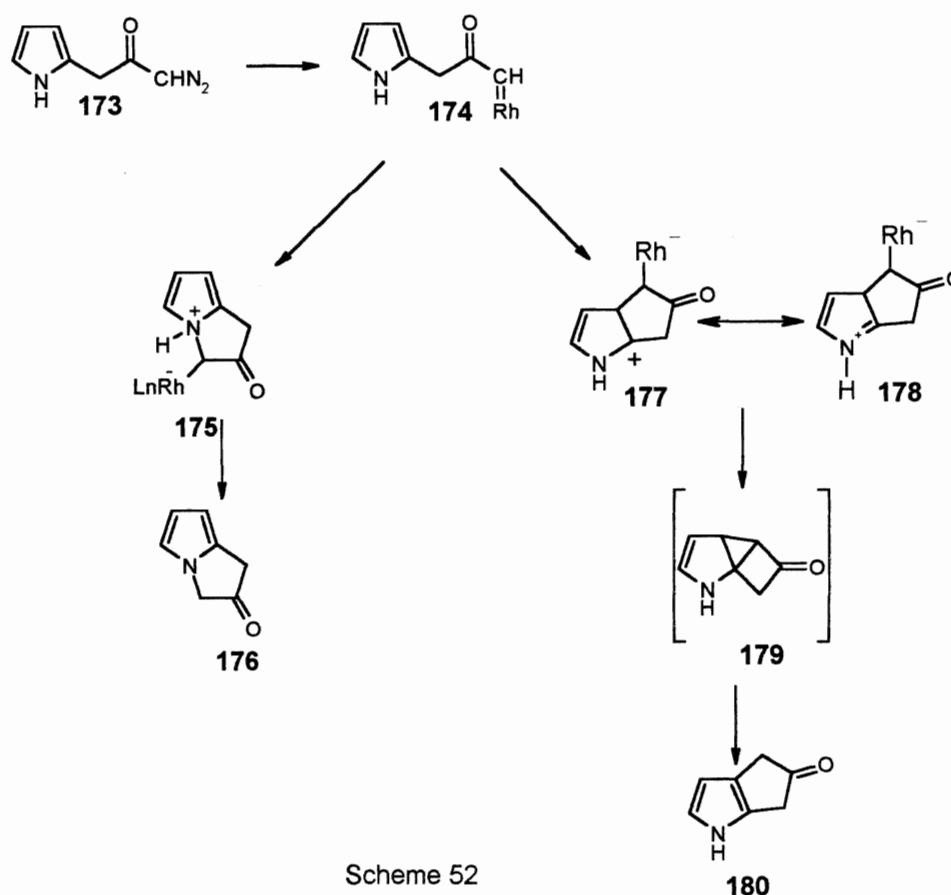
a single methylene to a terminal α -diazoketone were prepared and their $\text{Rh}_2(\text{OAc})_4$ decomposition chemistry studied.

The first system to be studied was the 1-diazo-(2-pyrrolyl)-2-propanone **173**.

Once again, its preparation required the synthesis of the precursor pyrrole-2-acetic acid **172**. A convenient route to the ethyl ester of this compound involves alkylation of pyrrole using



ethyl diazoacetate. As outlined by Marynoff⁸⁵, addition of ethyl diazoacetate to a warm solution of pyrrole and copper acetoacetate affords the ethyl pyrrole-2-acetate **94**. Access to the desired acid is achieved via basic hydrolysis of the ester **94**. Attempts to make the diazoketone from corresponding carboxylic acid, however, using our general procedure described before for the synthesis of diazoketone **146** resulted only in decomposition of the starting material. Treatment of pyrrole acetic acid with oxalyl chloride or thionyl chloride resulted in an intractable black tar with no formation of the acyl chloride. At this stage our attention focused on the use of the coupling reagent dicyclohexylcarbodiimide (DCC) to activate the carbonyl group. The carboxylic acid treated with (DCC) in dichloromethane, then the mixture was added to a solution of diazomethane to allow for clean production of the desired α -diazoketone **173**.



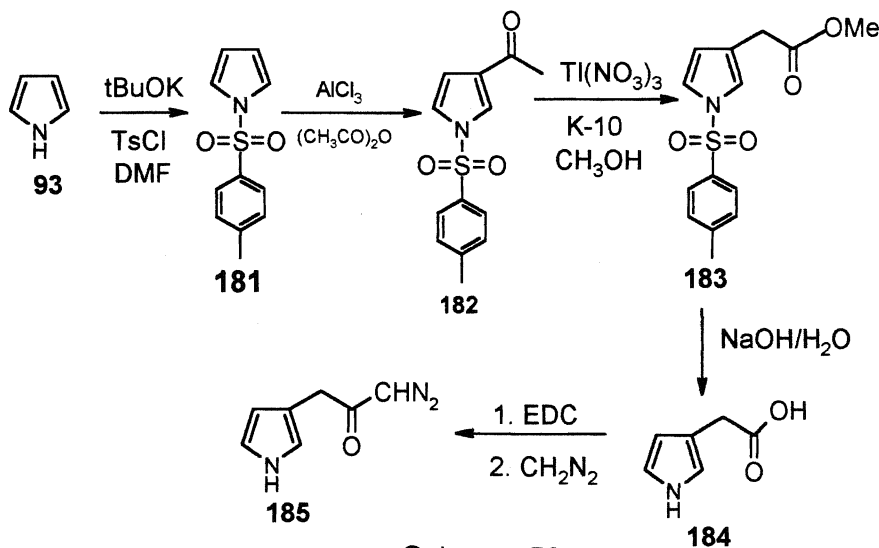
Decomposition of 1-diazo(2-pyrrolyl)-2-propanone **173** using rhodium(II) acetate results in the formation of two products 1H-pyrrolizin-2(3H)-one **176** and 4,6-dihydrocyclopenta[b]pyrrol-5(1H)-one **180**. There are a number of mechanistic pathways that can account for the formation of the two products. Product **176** appears to be the result of an NH insertion and, after a search of the chemical literature, is the only example of such an insertion into a pyrrole NH. We can rationalize this product as arising from a concerted N-H bond insertion of the carbenoid **174** or *via* an intermediate nitrogen ylid **175** followed by an H^+ migration. The bicyclic **180** can be derived from a zwitterionic intermediate (shown as the resonance structures **177** and **178**) or *via* a cyclopropane intermediate **179**. If one extends the arguments used in the intermolecular

insertion of carbenoids into pyrroles (see Introduction), the substitution product is formed (**180**) because the electron-donating ability of the nitrogen stabilizes the zwitterionic intermediate and, consequently, cyclopropanation does not occur.

2.2.2 Rhodium(II) acetate Catalyzed Decomposition of 1-Diazo(3-pyrrolyl)-2-propanone (**185**):

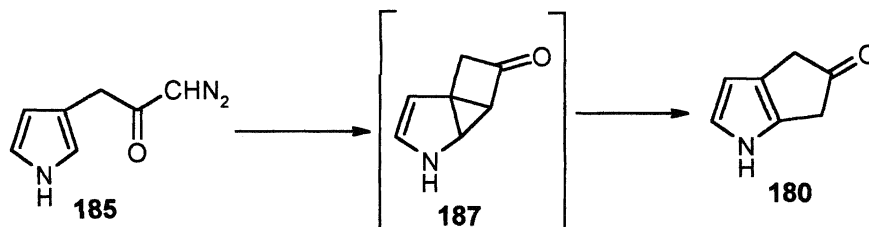
In both the furanyl **52** and thienyl **88** systems, α -diazoketones tethered to a 5-membered heterocycle by a single methylene at the 3-position have undergone net [4+2]-cycloreversions to give polyene products **53** and **90**, respectively (see Introduction). In order to examine the chemistry in the pyrrolyl series, 1-diazo(3-pyrrolyl)-2-propanone **185** was prepared from the corresponding carboxylic acid **185** as illustrated in Scheme 53.

Pyrrole usually undergoes Friedel-Crafts reactions at 2-position. The 3-substituted isomer can be obtained by either increasing the steric bulk on the nitrogen or by introducing electron withdrawing groups at the nitrogen. Lemaire and his group⁸⁶ take advantage of



these factors in their synthesis of **184**. Reaction between 1-pyrrole potassium, generated from pyrrole **93** and potassium tert-butoxide, and tosylchloride results in the formation of 1-tosyl pyrrole **181** in very good yield. Friedel-Crafts acylation of **181** using AlCl_3 and acetic anhydride in dichloromethane afforded 1-tosyl-3-acetylpyrrole **182** in 95% yield and no 2-substitution was seen. Conversion of **182** to **183** is carried out by using thallium(III) nitrate supported on K-10 clay in a modified Willgerodt-Kindler reaction. The product was then hydrolyzed under basic conditions to give the desired carboxylic acid **184**. With the pyrrole-3-acetic acid **184** in hand, attempts to synthesis the diazoketone by making the acyl chloride resulted in decomposition of the starting material similar to 2-substituted analogue. The use of DCC did result in the formation of the diazoketone, but purification difficulties necessitated a switch to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimidehydro-chloride **186** (EDC, a water soluble diimide coupling agent). Treatment of pyrrole-3-acetic acid **184** with EDC in dichloromethane followed by addition to a solution of diazomethane resulted in the formation the diazoketone **185** which was purified by chromatography on silica gel.

Decomposition of 1-diazo(3-pyrrolyl)-2-propanone **185** using rhodium(II) acetate resulted in the formation of one product which we assigned as the bicyclic **180**. Once



Scheme 54

again, production of **180** can be rationalized *via* the zwitterionic or cyclopropane mechanism. Not surprisingly, no product corresponding to a C-H insertion at position 4 was seen.

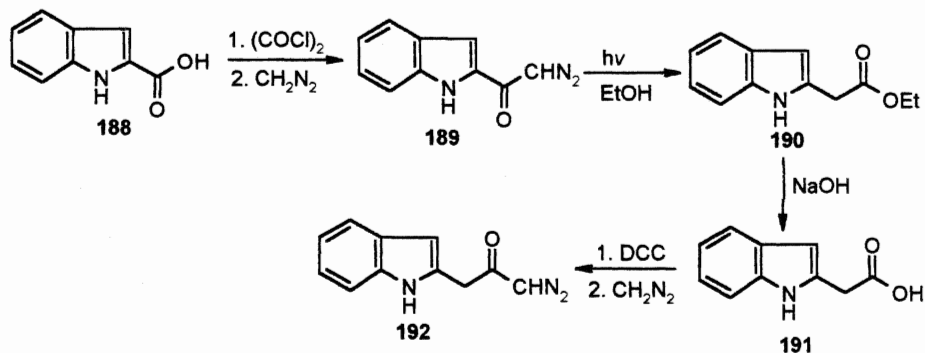
It is interesting to note that unlike the analogous furanyl (**53**) and thienyl (**89**) cyclopropanes, **187** does not undergo a [4+2]-cycloreversion. This would seem to support the zwitterionic mechanism and therefore, it is unlikely that **187** is an intermediate in the conversion of **185** to **180** (see above).

2.3. Intramolecular Insertions Of Carbenoids Into Indoles

2.3.1 Rhodium(II) acetate Catalyzed Decomposition of 1-diazo-3-(2-indolyl)-2-propanone (**192**):

In order to determine the effect of a fused benzene on the pyrrole-based carbenoid chemistry, the investigation was expanded to include α -diazoketones containing indole moieties. Pellicciari and his group⁸⁷ have described the synthesis of a novel conformationally restricted analog of tryptophan **196**. The key step is the Lewis-acid catalyzed intramolecular cyclization of 1-diazo-3-(3-indolyl)-2-propanone **194**. Direct

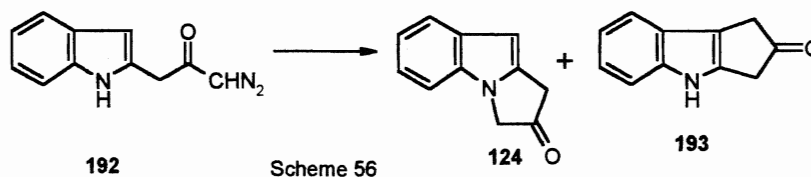
comparison of this system to those presented above is difficult since it is well known



that the overall chemistry exhibited by α -diazoketones is, in part, a function of the decomposition agent used. As a result, the 1-diazo-3-(3-indolyl)-2-propanone **194** system was revisited as were homologous systems containing longer tether chains. The chemistry of the isomeric 1-diazo-3-(2-indolyl)-2-propanone **192** will be described initially.

The prerequisite carboxylic acid indole-2-acetic acid **191** was prepared *via* a Arndt-Eistert homologation of indole-2-carboxylic acid **188** (as shown in Scheme 55).⁸⁸ Indole 2-carboxylic acid **188** was treated with oxalyl chloride and catalytic amount of dimethylformamide, then subsequently treated with a solution of diazomethane to yield **189**. Irradiation of the diazoketone **189** using medium pressure mercury lamp in H₂O/THF resulted in the formation of the acid although in very low yields. Photolysis of the indole-2-diazoketone **189** using ethanol as the solvent, however, results in complete conversion to ethyl indole-2-acetate **190**. Hydrolysis of the ester **190** using aqueous sodium hydroxide results in the formation of the acid **191** in low yield (likely a result of decarboxylation during work-up an aqueous solution is acidified to give 2-methyl indole as evidenced by TLC). The inability to generate the acyl chloride of **57** with either oxalyl chloride or thionyl chloride prompted the use of 1,3-dicyclohexylcarbodiimide (DCC). Treatment with diazomethane results in the formation of 1-diazo-3(2-indolyl)-2-propanone **192**.

Catalytic
decomposition
of 1-diazo-3(2-

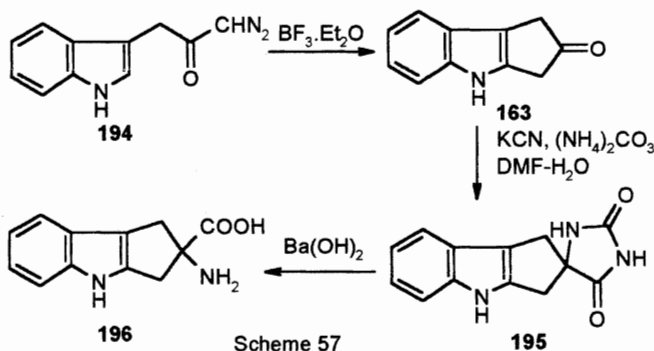


indolyl)-2-propanone **192** with rhodium(II) acetate resulted in the formation of two

products, **124** and **193**. The chemistry of this system is much like the corresponding 1-diazo-(2-pyrrolyl)-2-propanone **173** with the formation of an apparent C-H insertion product 1H-pyrrolo[1,2-a]indol-2(3H)-one **124** (unprecedented in the chemical literature) and the tricycle **59**.

2.3.2 Rhodium(II) acetate Catalyzed Decomposition of 1-diazo-3-(3-indolyl)-2-propanone (**194**):

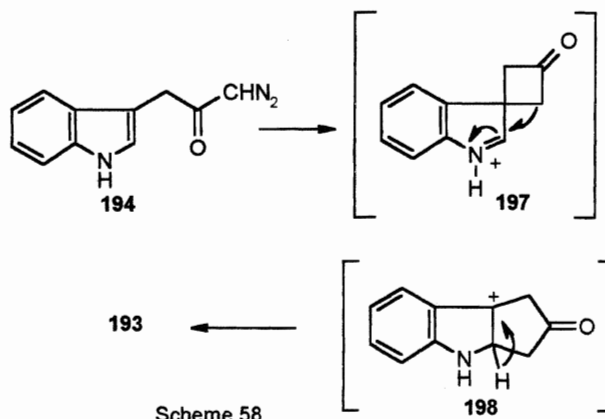
As mention above,
Pellicciari and his group⁸⁷ have
used the Lewis-acid catalyzed
intramolecular cyclization of
diazoketone **194** as the key step
in the synthesis of a novel



conformationally restricted analog of tryptophan (**196**, Scheme 57).

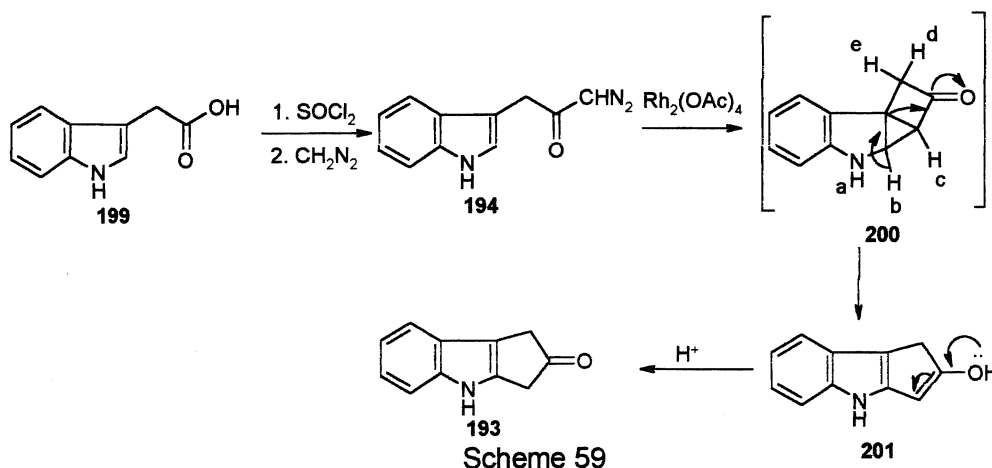
When tricycle **193** was treated with potassium cyanide and ammonium carbonate in aqueous dimethylformamide, spirocyclic compound **195** was isolated in 68% yield. The tryptophan analog **196** was

obtained by heating compound **195** in an aqueous solution of barium hydroxide. The authors describe a mechanism for the conversion of diazoketone **194** to **193** (illustrated in scheme 58).



First Lewis acid is complexed with the diazoketone, this is followed by nucleophilic attack by π -bond leading to the formation of a spiroindolenine **197** which is rapidly unraveled to the cyclopentanone **193**. Given the unusual claim for the intermediacy of **197**, we revisited the 1-diazo-3-(3-indolyl)-2-propanone **194** system and examined its rhodium(II) acetate decomposition chemistry.

The requisite diazoketone could be prepared from the commercially available indole-3-acetic acid **199** using the standard procedure described before for the synthesis of diazoketone **146**. Treatment of diazoketone **194** with catalytic amount of rhodium(II) acetate at room temperature results in the formation of tricycle **193** in 95% yield. When this reaction was carried out in an NMR tube and the reaction was monitored by ^1H NMR (a spectrum taken every 10 minutes) the intermediate **200** (illustrated in Scheme 59) can be seen. The intermediate **200** showed ^1H NMR: (CDCl_3 , 300 MHz): δ 2.55 (1H, dd, $J=16, 5$ Hz) for one of the methylene protons, 2.85 (1H, dd, $J=16, 5$ Hz) for the other methylene proton, 4.41 (1H, br t) for the Hb and 5.23 (1H) for the Hc proton. The assignments were further confirmed by a COSY spectrum as well as by comparison to model compounds (see below). The ABX system generated by the methylene α to the carbonyl (He and Hd) and Hb is rather unusual considering that the effect is seen over 4-

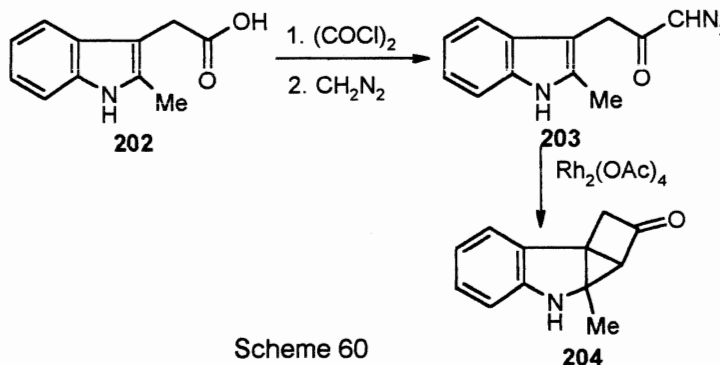


bonds. However the caged nature of cyclopropane **200** is likely the explanation. There are a number of examples⁸⁹ wherein substantial coupling is seen between remote H's in compounds containing small, fused rings.

The intermediate (**200**) then undergoes acid catalyzed ring opening to give the enol **201** which undergoes proton shift to give the product **193**. To our knowledge, this is first evidence for a cyclopropane intermediate in the single methylene series. The existence of **200** rules out a C-H insertion in the conversion of **194** to **193**.

2.3.3 Rhodium(II) acetate Catalyzed Decomposition of 1-Diazo-(3[2-methyl indolyl)-2-one (**203**):

In order to assure proper assignment of the NMR signals for **200**, a series of model compounds were prepared and studied. In each one of these model compounds, one of the cyclopropane protons was substituted with a methyl group. The first model compound studied was 1-diazo-3-(2-methyl indolyl)-2-propanone **203** which was obtained from the corresponding commercially available carboxylic acid **202**.



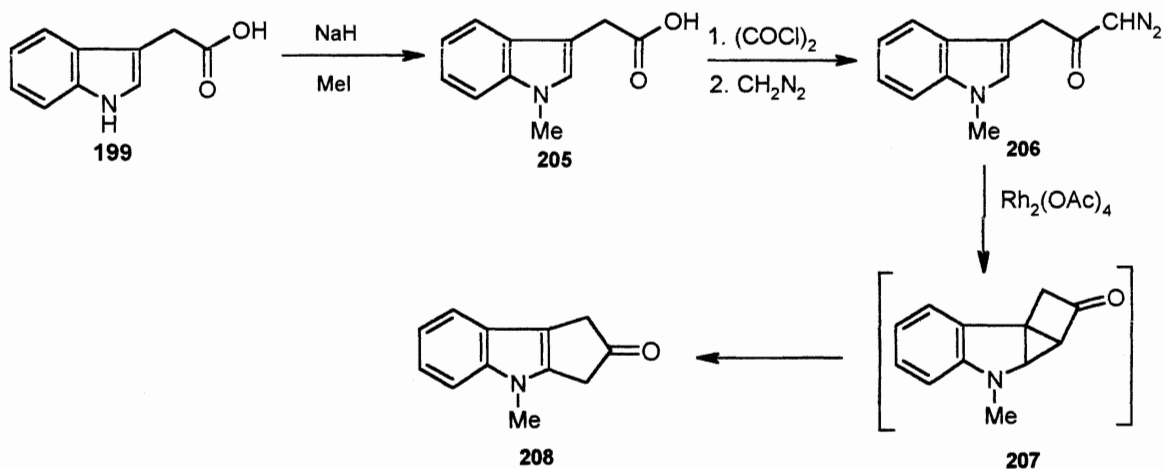
Applying the general

procedure described above for the synthesis of diazoketone **146** resulted in the formation of **203** in 75% yield. When the diazoketone **203** was treated with catalytic amount of rhodium(II) acetate at room temperature a mixture of products were formed. The major

product cyclopropane **204** was isolated as yellow oil in 65% yield. The structure was established by ^1H , ^{13}C NMR, MS, HRMS, and 2D COSY and HETCORR experiments (see Experimental). The cyclopropane is stable at room temperature and can be chromatographed on silica gel. This stability can be explained by the absence of the proton H_b in **200** which is responsible for the re-aromatization. Attempts to crystallize this cyclopropane for the purposes of obtaining an X-ray structure were unsuccessful. Making derivatives of this cyclopropane such as the hydrazone or the oxime resulted in the decomposition of the cyclopropane **204**.

2.3.4 Rhodium(II) acetate Catalyzed Decomposition of 1-Diazo-3-(3-[1-methyl indolyl])-2-propanone (**206**):

1-Methyl indole-3-acetic acid **205**, the precursor for diazoketone **206**, was obtained following the procedure described by Ward and his co-workers⁹⁰. Treatment of indole-3-acetic acid with sodium hydride at 0 °C allows for deprotonation of the N-H



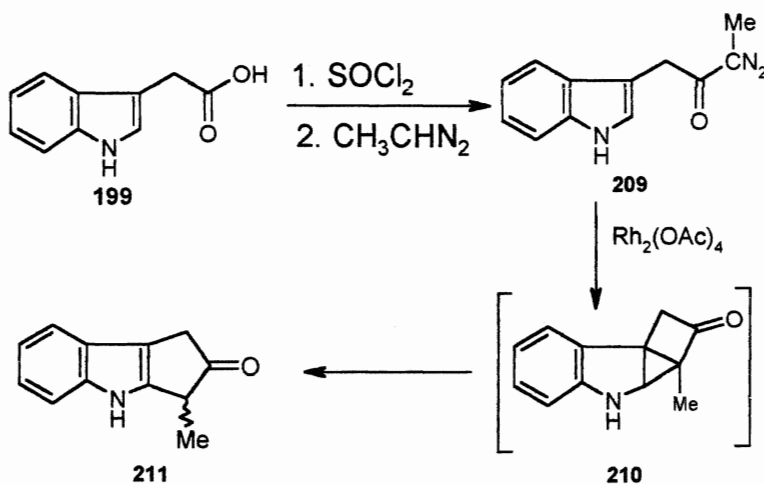
proton to generate the anion which in the presence of methyl iodide gives N-methyl indole-3-acetic acid **205** in 95% yield. Again standard procedure with oxalyl chloride

and diazomethane resulted in the formation of diazoketone **206**. Rhodium(II) acetate catalyzed decomposition of diazoketone **206** at room temperature afforded the tricycle ketone **208** in 95% yield. Similarly when the reaction was repeated in NMR tube and the reaction was monitored by ^1H NMR (a spectrum taken every 10 minutes), intermediate **207** was clearly evident. The intermediate showed: (CDCl_3 , 300 MHz): δ 2.64 (1H, dd, $J=16, 5$ Hz) for one of the methylene protons, 2.99 (1H, dd, $J=16, 5$ Hz) for the other methylene proton, 4.41 (1H, br t) for the Hb. This results confirms that the broad peak in the NMR spectrum of **200** (at 4.41 ppm) corresponds to the proton (**Hb**) at C-2 carbon

2.3.5 Rhodium(II) acetate Catalyzed Decomposition of 2-Diazo-4-(3-indolyl)-3-butanone (**209**):

There are a number of different ways to synthesize α -alkyl α -diazocarbonyl compounds (see Introduction). Diazo transfer to the appropriate ketone is one method. In an effort to prepare 2-diazo-4-(3-indolyl)-3-butanone **209**, however, we chose a route involving the acylation of

diazooethane. Basic hydrolysis of 1-ethyl-3-nitro-1-nitrosoguanidine (ENNG) at 50°C gave an ethereal solution of diazoethane. Treatment of an ethereal solution of



diazooethane with the acyl chloride generated from the reaction between indole-3-acetic

acid **199** and thionyl chloride in the presence of catalytic amount of dimethylformamide gave the diazoketone **209**. Decomposition of 2-diazo-4-(3-indolyl)-3-butanone **209** using rhodium(II) acetate resulted in the formation of 3-methyl-3,4-dihydrocyclopenta[*b*]indol-2-(1H)-one **211** in 90% yield. When the reaction was monitored by ^1H NMR (a spectrum taken every 10 minutes) an intermediate can be seen again which has been assigned as cyclopropane **210**. This intermediate showed ^1H NMR (CDCl_3 , 300 MHz): δ 2.59 (1H, dd, $J = 16, 5$ Hz) for one of the methylene protons, 3.00 (1H, dd, $J = 16, 5$ Hz) for the other methylene proton.

With compounds **204**, **207** and **210** in hand, the NMR assignment for **200** were secured (see NMR Spectra).

3.6 Mechanistic Considerations: "Zwitterion vs Cyclopropane" Revisited:

In his 1979 work on carbenoid insertions, Marynoff states: "Cyclopropane derivatives have never been observed or implicated in carbenic reactions of pyrroles and indoles lacking nitrogen substitution that depletes their (hetero) aromaticity." Clearly, the present

work has shown that this is not the case. The

existence of a

cyclopropane

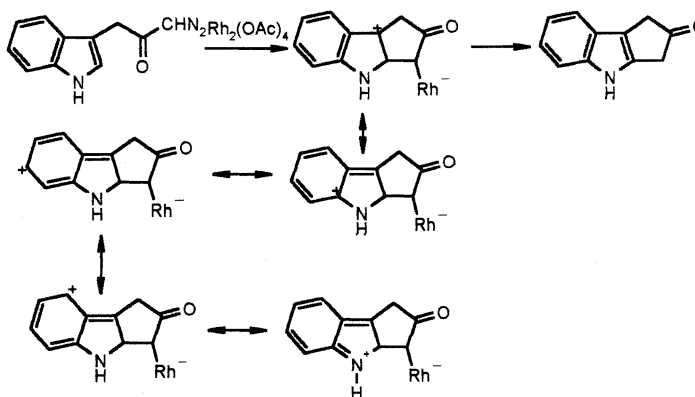
intermediate in the

indole series came,

initially, as very much

of a surprise. If the current mechanistic interpretation was correct, an intermediate

zwitterion should be stabilized to a greater extent over that of the analogous pyrrole



system due to delocalization of charge through the fused benzo moiety. However, such resonance delocalization would come at the cost of disruption of the aromatic system. It would appear that retention of an intact benzene fragment offsets the stability gained by delocalizing charge onto the heteroatom. As a result, the localized charge allows for access to the cyclopropane system. In other words, it is energetically favorable to localize the charge and retain aromaticity rather than stabilize the zwitterion and lose the aromaticity. Hence the preference for the cyclopropane.

2.3.7 Rhodium(II) acetate Catalyzed Decomposition of 1-Diazo-4-(3-indole)-2-butanone (141):

We have previously described the decomposition of 1-diazo-4-(3-benzothienyl)-2-butanone **152** which gave the cyclopropane **153** as the sole product. Treatment with acid allows for the formation of **154**. Interestingly, the analogous benzofuranyl system can be induced to

undergo different chemistry.

Padwa⁵¹ and his

group showed

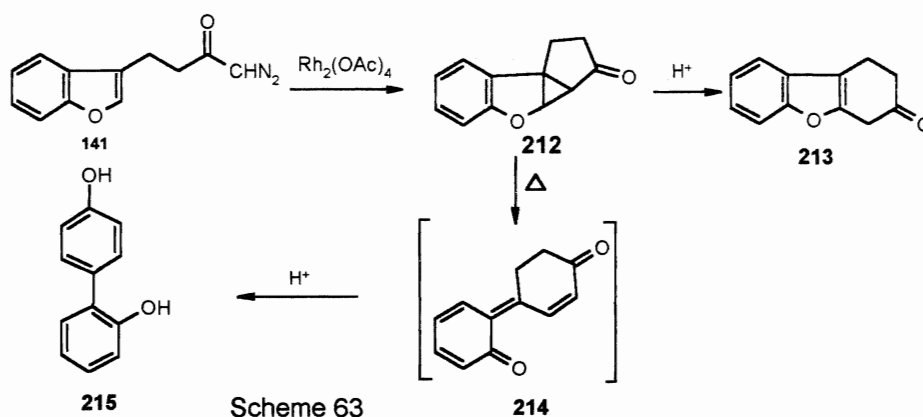
that rhodium(II)

acetate catalyzed

decomposition of 1-diazo-4-(3-benzofuryl)-2-butanone **141** gave the cyclopropane **212**.

Acid catalyzed ring opening of the cyclopropane **212** gave the tricyclic ketone **213**.

However, when the cyclopropane **212** was heated to 180 °C, the biphenyldiol **215** was



isolated in 82%. The formation of **215** is likely involves the intermediate **214** which is the result of apparent [4+2]-cycloreversion, then **214** undergoes a number of chemical shifts to give the more stable fully aromatized system **215**. Our work with compound **153** (the analogous benzothienyl cyclopropane) showed that heating does not allow for similar chemistry. It would be very interesting to examine the chemical outcome of the 1-diazo-

4-(3-indole)-2-butanone **217**, and from mechanistic point view, determine what effect changing the heteroatom would make on the reaction course.

Reaction of the commercially available indole-3-propionic acid **216** with thionyl chloride followed by addition to a ethereal solution of diazomethane resulted in the formation of 1-diazo-4-(3-

indole)-2-butanone **217** in 70% yield. When this diazoketone

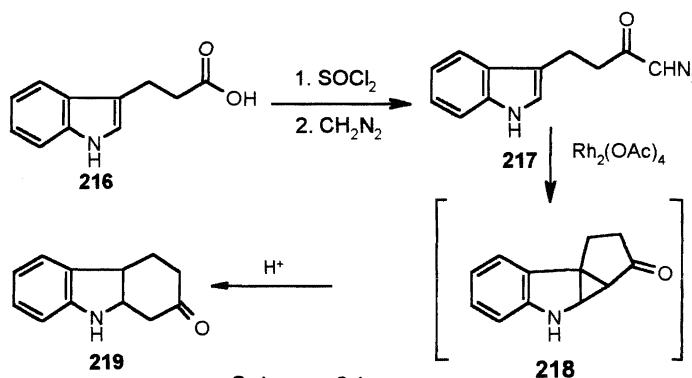
was treated with rhodium(II) acetate, one product was

isolated, the tricycle ketone **219**,

in 75% yield. No ^1H NMR

evidence for the cyclopropane **218** can be seen when the reaction was done in a NMR tube and monitored. There is no obvious explanation for the unstability of this

intermediate (**218**), it could be that it is easier to break the internal bond in the case of this five-three-five tricycle.



Scheme 64

Figure 7: Progress of Reaction **199** \rightarrow **193** Monitored by ^1H -NMR

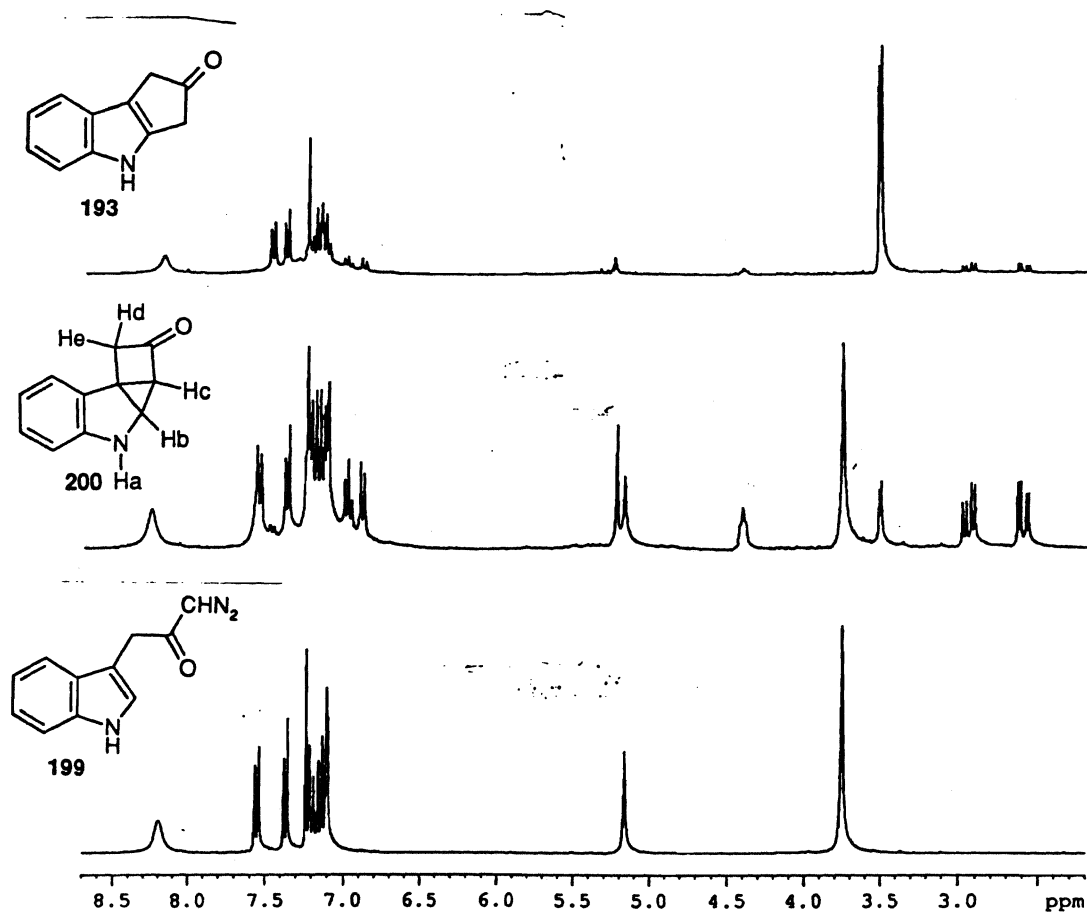


Figure 8: ^1H -NMR of 204

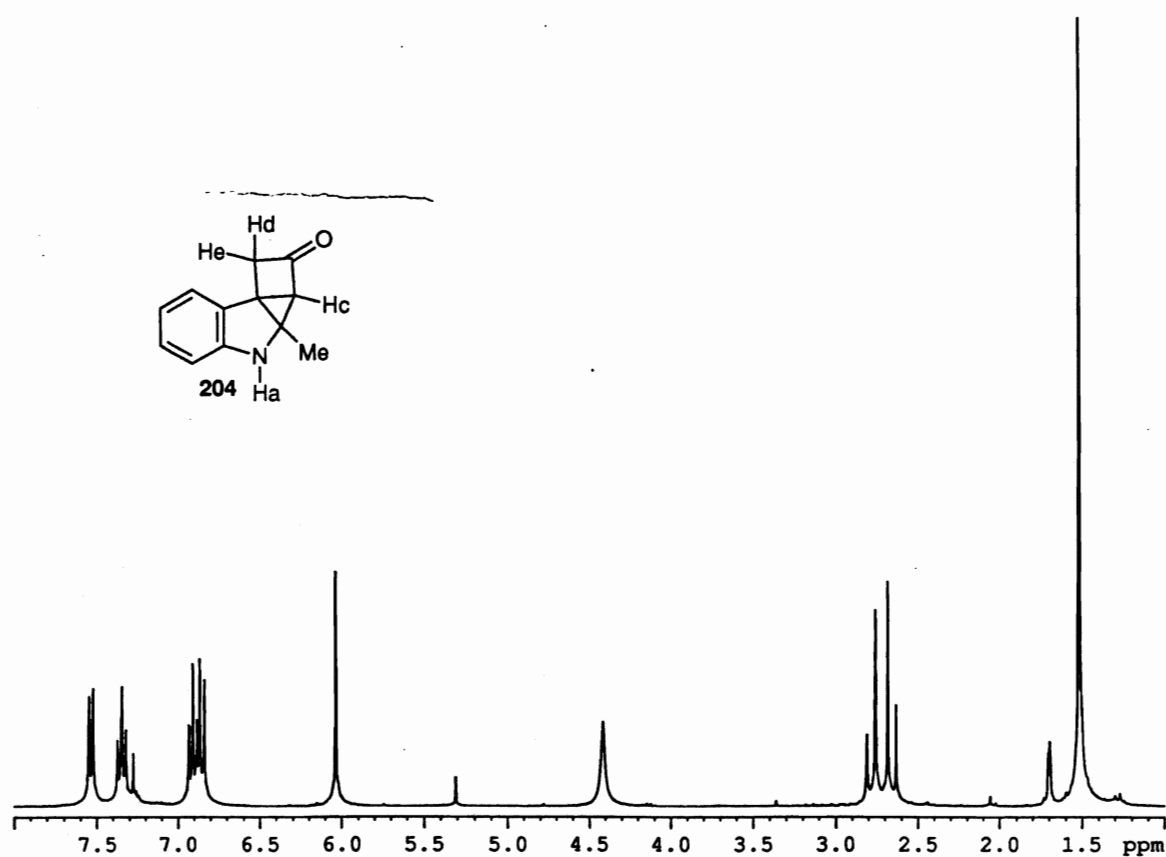
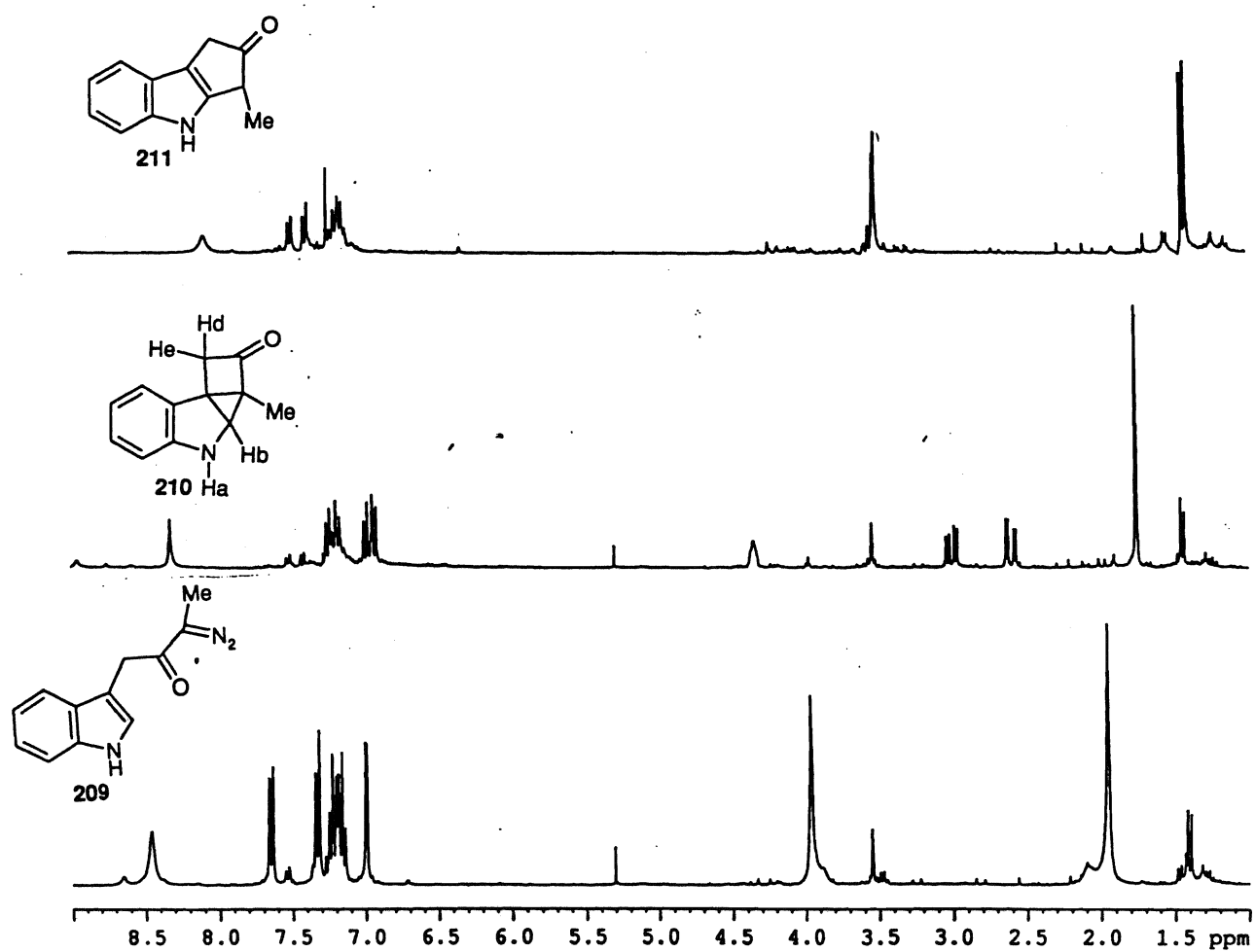
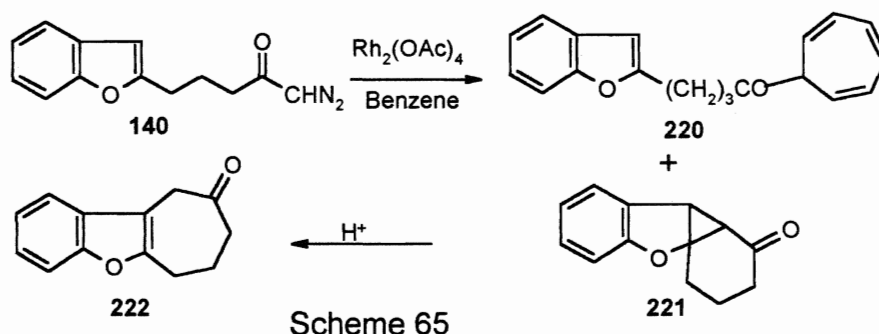


Figure 9: Progress of Reaction **209** \rightarrow **211** Monitored by ^1H -NMR



3.7 Rhodium(II) acetate Catalyzed Decomposition of 1-Diazo-5-(3-indole)-2-pentanone(225)
Padwa⁵¹ and

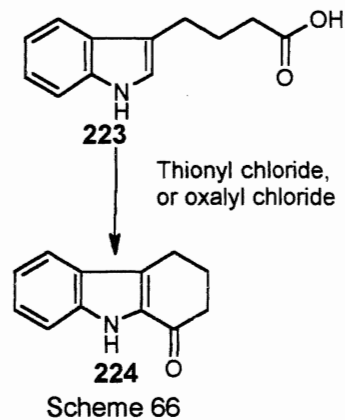
his group tested the
effect of the tether
length on the
intramolecular
carbenoid insertions



involving benzofurans. Treatment of diazoketone **140** with a catalytic amount of rhodium acetate in benzene resulted in the formation of two products the cycloheptatriene **220** in 56% yield and the cyclopropane **221** in 38% yield. The major product cycloheptatriene derived from the bimolecular addition of the rhodium carbenoid to benzene followed by tautomerization (a Buchner reaction) see scheme 65. This result indicates that the additional methylene group in **140** sufficiently retarded the rate of intramolecular addition so as to allow for the bimolecular reaction to occur. Acid-induced conversion of **221** to cycloheptabenzofuranone **222** was also carried out.

When the reaction was done in dichloromethane the cyclopropane **221** was only product isolated in 79% yield.

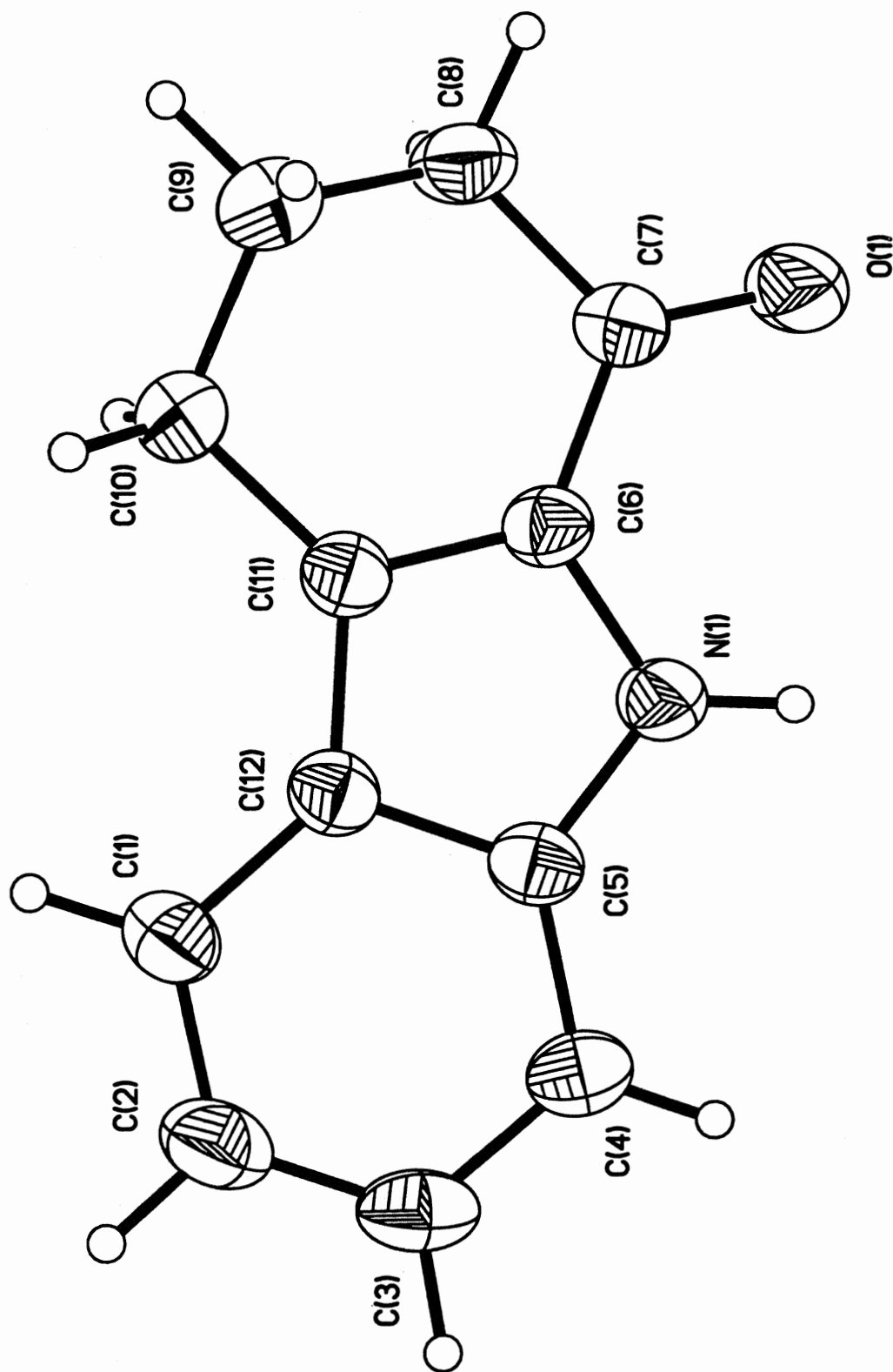
Extension of this work to the indole series was also carried out. The desired diazoketone **225** was derived from the corresponding commercially available indole-3-butyric acid **223**. The standard procedure was applied and the carboxylic acid **223** was treated with



thionyl chloride and catalytic amount of dimethylformamide. When the reaction mixture

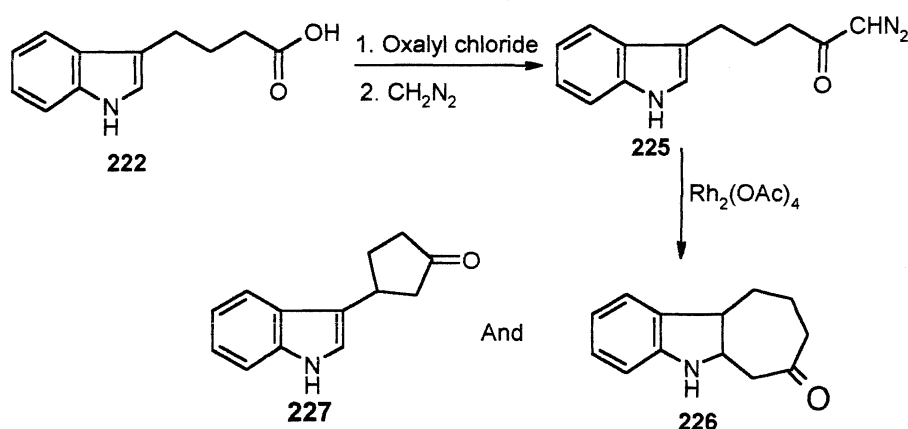
was concentrated to remove the excess of the thionyl chloride then treated with an ethereal solution of diazomethane, the only product was isolated 2,3,4,9-tetrahydrocarbazol-1-one **224** in 95% yield. The structure of **224** is supported by ^1H , ^{13}C , NMR, MS, HRMS, and x-ray structure. This transformation can be explained by formation of the acyl chloride which undergoes electrophilic substitution at 2-position to give the Friedel-Crafts product.

Figure 10: ORTEP of 2,3,4,9-Tetrahydrocarbazol-1-one 224



The desired diazocarbonyl was obtained by treatment of the carboxylic acid with oxalyl chloride at 0 °C for one hour, then the solution was transferred (with concentration) to an ethereal solution of diazomethane. Purification using column chromatography on silica gel gave 1-diazo-5(-3-indole)-2-pentanone **225** in 65% yield in pure form along with the methyl ester of the acid **223** and the tricycle **224**.

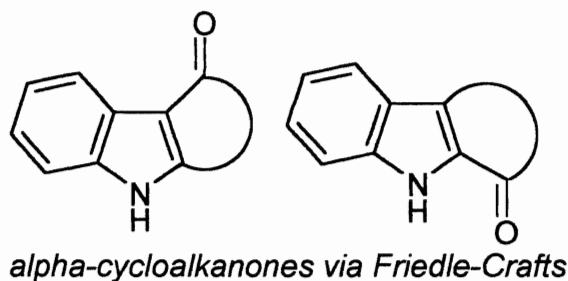
Exposure of diazoketone **225** to the rhodium catalyst in dichloromethane resulted in the formation of one product based on TLC. After the silica gel chromatography, the ^1H and ^{13}C NMR indicates the presence of two isomers, the NMR spectroscopy for the



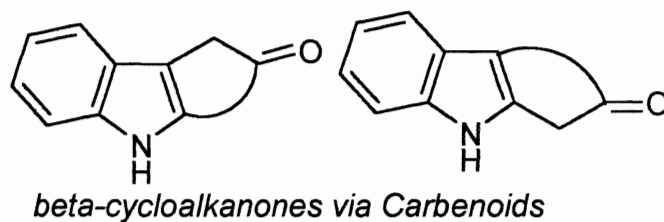
Scheme 67

proton showed two peaks for nonequivalent N-H and the presence of a peak at 6.99 ppm correspond to the proton at 2-indole, ^{13}C showed two different peaks at the region of carbonyl group. Mass spectroscopy showed this product to be a monomer with a molecular ion at $m/z = 199$. From these observation we think that the reaction gave two products the cycloheptanone (**226**) and the cyclopentanone (**227**).

It is worth pointing out that the chemistry described above has not only provided an increased understanding of the mechanism involved in the intramolecular carbenoid insertion in indole but has also allowed for a facile synthetic route to an interesting class of heterocycle.



Cycloalkanones fused to indoles can be arrived at using a Friedel Crafts



acylation approach. This places the carbonyl alpha to the indole moiety. The carbenoid methodology provides a complementary approach allowing for access to the systems wherein the carbonyl is beta to the indole fragment.

Conclusion

The results from our study (this study, and the one done by Kelvin Yong) of intramolecular carbenoid insertion into 5-membered heteroaromatic systems shows that the resultant chemistry is dependent on the nature of the heteroatom, position of substitution, the length of the aliphatic tether and the substitution on the aromatic moiety.

While the rhodium(II) acetate catalyzed decomposition of some of α -diazoketones linked to furan and thiophene resulted in cyclopropane intermediates which unravel via one of three different pathways: the [4+2]-cycloreversion, the “enol” mechanism or the vinylogous Wolff rearrangement, benzothiophene, pyrrole, and indole gave only the “enol” mechanism products.

All the inter and intramolecular carbenoid insertion into pyrrole and indole have rationalized in the literature as C-H insertion, we have shown that α -diazoketone linked to indole with one methylene chain results in the formation of a cyclopropane intermediate which can be seen only using ^1H NMR spectra.

FUTURE WORK

The resultant dimer obtained from the rhodium (II) catalyzed decomposition of α -diazoketone linked to benzothiophene with one methylene chain was very interesting, that this is the first example of α -diazoketone tethered to heterocyclic compound gives [3+2]-cycloaddition type product. More investigation is required for a better understanding why this system behave so differently.

A number of examples in the literature⁶⁵⁻⁶⁸ have shown that metal catalyzed decomposition of α -diazocarbonyl in the presence *N*-acyl pyrrole results in the formation

of a cyclopropane. In some cases heating the cyclopropane results induced the cyclopropane to unreveal through [4+2]-cycloreversion. It would be very interesting to study the intramolecular carbenoid insertion into *N*-substituted pyrrole with electron withdrawing group.

EXPERIMENTAL

APPARATUS AND MATERIALS

Proton magnetic resonance (^1H -NMR) spectra were recorded on either a Bruker AC-200 FT spectrometer (at 200.13 MHz) or a Bruker Avance DPX-300 Digital FT spectrometer (at 300.13 MHz) with chloroform- d as the solvent unless otherwise noted. Unless specified, the usual internal references were tetramethylsilane (TMS) or chloroform. The abbreviations (s)=singlet, (d)=doublet, (t)=triplet, (q)=quartet, (m)=multiplet and (br)=broad are used in the description of the spin-spin splitting pattern present in the spectra.

The natural abundance carbon-13 magnetic resonances (^{13}C -NMR) were recorded on a Bruker Avance DPX-300 Digital FT spectrometer (at 75.03 MHz) using chloroform- d as the solvent and internal reference unless otherwise noted. All ^{13}C spectra were broad band decoupled.

Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were obtained on Carlo Erba/Kratos HRGS/MS Concept 1S double focusing mass spectrometer interfaced to a Kratos DART acquisition system and a SUN SPARC workstation. Samples were introduced through a direct inlet system. Ions were generated using electron impact (EI).

Crystallographic structure determinations were carried out on a Rigaku AFC7R diffractometer with graphite-monochromated Mo- $K\alpha$ radiation ($\lambda = 0.71069 \text{ \AA}$). The crystals were cooled with an Oxford Cryosystem Cooler.⁹¹ The structures were solved

with direct methods, SHELXS-90⁹² and refined with full-matrix least-squares refinement

on F^2 with SHELXL-93.⁹³ R -values; $R1 = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}$ and $wR2 = \sqrt{\frac{\sum w(F_o^2 - F_c^2)^2}{\sum w(F_c^2)^2}}$

Further details of the crystal structure investigation can be obtained from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Cambridge CB2 1EW, U.K.

Melting points were recorded on a Kofler Hot Stage melting point apparatus and are uncorrected.

Starting materials were purchased from Aldrich Chemical Co. and used without further purification.

Tetrahydrofuran (THF) was dried by refluxing and distilling from sodium and benzophenone under dry nitrogen. THF was collected from the distillation apparatus as required. *N,N*-Dimethylformamide (DMF) was refluxed and subsequently distilled from BaO. All other solvents employed were reagent grade, purchased from Caledon Laboratory Ltd.

NMR solvents chloroform- d , methylene chloride- d_2 , dimethylsulfoxide- d_6 and benzene- d_6 were purchased from Isotec Inc. and stored over molecular sieves (4Å) prior to use.

Column chromatography was performed by the "flash" method of Still, Kahn, and Mitra.⁹⁴ The silica gel used for column chromatography (5.0% of 100 mesh up; 47.6% of 100-200 mesh and 47.4% of 200 mesh down) was purchased from Aldrich Chemical Co.. Silica gel 60 F₂₅₄ (E. Merck Co.) plates of 0.2 mm thickness were used for analytical thin layer chromatography (TLC). Visualization was achieved using a UV lamp at 254

nm or *via* treatment of the TLC with either a molybdic acid spray (20 g of molybdic acid and 15 g of ceric sulphate dissolved in 1 litre of 10% sulphuric acid); a vanillin spray (5 g of vanillin dissolved in 200 ml of 95% ethanol followed by addition of 5 ml of sulfuric acid slowly); a potassium permanganate dip (12.5 g of potassium permanganate and 62.5 g of sodium carbonate added to 1.25 litre of water) or a ninhydrin spray (0.2% ninhydrin in ethanol) followed by heating.

SYNTHETIC PROTOCOLS

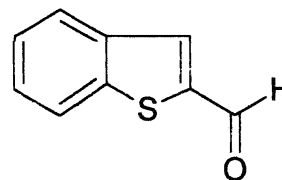
Preparation of alcohol free diazomethane solution⁹⁵

An ethereal solution of diazomethane free from ethanol is essential for the preparation of diazoketones. The following procedure was carried out in glassware with clear glass joints.

Potassium hydroxide (6g) was dissolved in 10 ml of water and 35 ml of carbitol (di(ethyleneglycol) ethyl ether) in a 250 ml round bottom flask. The basic solution was stirred and heated to 70°C in an oil bath, with distillation apparatus connected to a 500 ml round bottom flask in an ice-salt bath. An ethereal solution (125 ml) of Diazald (*N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide) was added slowly, over 20 minutes. Rinse the dropping with 2 x 20 ml portion of ether and added to the reaction flask. Ether was added to the reaction flask until the distillate was colourless. The bright yellow diazomethane solution is stored under potassium hydroxide pellets for one day to remove water. The anhydrous solution is decanted and stored in the freezer.

Synthesis of 2-Thianaphthaldehyde (143)⁷⁹

A solution of benzothiophene (**142**) (4.84 g, 36.3 mmol) in dry tetrahydrofuran (35 ml) was stirred and cooled to -78 °C under an atmosphere of argon. To this solution was added n-buthyl lithium in hexane (16.0 ml, 2.5 M, 40 mmol) and the mixture warmed to 0 °C. The reaction mixture and transferred into a solution of *N,N*-dimethylformamide (2.9 ml, 2.75 g, 37.5 mmol) in dry tetrahydrofuran (40 ml) under argon using a cannula. The mixture was left to stir overnight at room temperature. The reaction mixture was poured into 3M hydrochloric acid (15 ml) and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3 x 30 ml) and the combined organic layers were washed with 1M hydrochloride acid (3 x 25 ml) followed by saturated sodium bicarbonate (30 ml). The collected organic fractions were dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The product was purified by dissolving the crude product in ethanol (10 ml) and treating with saturated sodium bisulfite solution (40 ml). The resulting mixture was stirred for 10 minutes and left to stand for 1 hour. The precipitate was filtered and washed with ether until the solid became white in color. The solid was dried under vacuum. The aldehyde was regenerated by dissolving the solid in a small amount of hot water (heat is necessary for dissolution) and treating with a saturated sodium carbonate solution (25 ml). The aldehyde precipitated at 0 °C. The product was collected using suction filtration, washed with water and dried under high vacuum. The product **143** was isolated in (4.2 g, 25.9 mmol, 71% yield) and showed.



TLC: R_f = 0.63 (ethyl acetate : hexane, 1:4)

^1H NMR: (CDCl_3 , 300 MHz): δ 7.39-7.51 (2H, m, Ar-H), 7.88 (1H, d, J = 8 Hz, Ar-H), 7.92 (1H, d, J = 8 Hz, Ar-H), 8.00 (1H, s, Ar-H), 10.09 (1H, s, CHO).

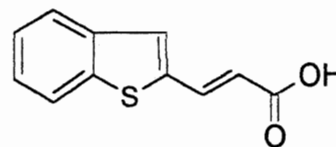
^{13}C NMR: (CDCl_3 , 75 MHz): δ 123.27, 125.22, 126.24, 128.13, 134.43, 138.51, 142.64, 143.32, 184.63 (CO).

MS $[\text{EI}]^+$: m/z (RI%): 162 $[\text{M}]^+$ (100), 133 $[\text{M}-\text{CHO}]^+$ (18.3), 89 $[\text{M}-\text{SCCHO}]^+$ (32).

HRMS: for $\text{C}_9\text{H}_6\text{OS}$: calculated 162.0139, observed 162.0146.

Synthesis of 3-(2-Benzothieryl)acrylic acid (**144**)⁷⁶

A solution of 2-thiophene aldehyde (**143**) (4.0 g, 24.7 mmol) and dry malonic acid (2.7 g, 25.9 mmol) in dry pyridine (8 ml) was heated at 60 $^\circ\text{C}$ for 8 hours. The



mixture was transferred to a 500 ml round bottomed flask and a solution of saturated sodium carbonate (10 ml) was added. The pyridine was removed by steam distillation and the starting material was removed by Kugelrohr distillation. To the residue, 3M hydrochloric acid was added, the acid precipitated, the resulting mixture was filtered using vacuum filtration. The precipitate was washed with water until the washing reached neutrality. The product **144** (3.5 g, 17.3 mmol, 70% yield) was then dried and showed:

^1H NMR: ($\text{C}_6\text{H}_6\text{SO}$, 300 MHz): δ 6.25 (1H, d, J = 15 Hz, CH), 7.40 (2H, m, ArH), 7.78-7.87 (3H, m, ArH), 7.97 (1H, d, J = 15 Hz, CH).

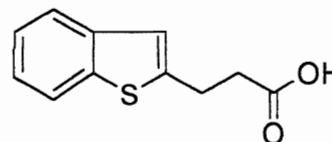
^{13}C NMR: ($\text{C}_6\text{H}_6\text{SO}$, 75 MHz): δ 122.54, 123.51, 125.33, 125.87, 127.07, 129.59, 137.10, 140.12, 140.26, 168.09.

MS [EI] $^+$: m/z (RI%): 204 [M] $^+$ (100), 187 [M-OH] $^+$ (23), 158 [M-COOH] $^+$ (20), 147 [M-COOH] $^+$ (14), 134 [M-CCHCOOH] $^+$ (11).

HRMS: For $\text{C}_{11}\text{H}_8\text{O}_2\text{S}$ calculated 204.02450, observed 204.0256

Synthesis of 3-(2-Benzothieryl)propionic acid (**145**)⁷⁶

A mixture of benzothiophene 2-acrylic acid (**144**) (2.0 g, 9.8 mmol) and a catalytic amount of Pd/C (10%) (0.2 g) in dry tetrahydrofuran (40



ml) was stirred under an atmosphere of hydrogen gas using a balloon. When no further change was observed in the size of the balloon (about 45 min), the mixture was filtered through celite and the solvent was evaporated under reduced pressure to give benzothiophene 2-propionic acid (1.9 g, 9.3 mmol, 95% yield).

^1H NMR: (CDCl_3 , 300 MHz): δ 2.85 (2H, t, J = 7 Hz, CH_2), 3.27 (2H, t, J = 7 Hz, CH_2), 7.08 (1H, s, SC=CH), 7.31 (2H, m, ArH), 7.70 (1H, d, J = 7 Hz, ArH), 7.79 (1H, d, J = 7 Hz, ArH).

^{13}C NMR: (CDCl_3 , 75 MHz): δ 26.06 (CH_2), 35.58 (CH_2), 121.67, 122.56, 123.37, 124.21, 124.65, 139.77, 140.38, 144.00, 178.70 (CO).

MS [EI] $^+$: m/z (RI%): 206 [M] $^+$ (53.3), 161 [M-COOH] $^+$ (17.4), 147 [$\text{M-CH}_2\text{COOH}$] $^+$ (100).

HRMS: for $\text{C}_{12}\text{H}_{10}\text{O}_2\text{S}$: calculated 206.04015, observed 206.0411.

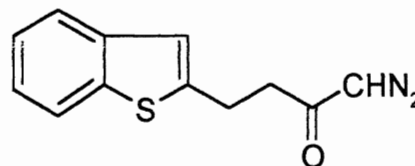
Synthesis of 1-Diazo-4-(3-benzothiienyl)-2-butanone (146):

The 3-(2-benzothiienyl)propionic acid (145)

(0.38 g, 1.85 mmol) was dissolved in dry

tetrahydrofurane (35 ml) and treated with 4 drops

of dimethylformamide (4 drops). The mixture was



stirred under argon and cooled using an ice bath. Thionyl chloride (0.24 g, 2.02 mmol)

was added slowly and the reaction mixture was left to stir for another 2 hours. The

solvent and the excess thionyl chloride were removed under reduced pressure and the

residue was redissolved in dry tetrahydrofuran. This solution was added slowly to an

ethereal solution of diazomethane (40 ml) at 0 °C. The reaction mixture was stirred for 3

hours and was filtered. The solvent was removed under a reduced pressure and the

residue purified by silica gel column chromatography using ethyl acetate-hexane (1:4) as

the eluent, to give 1-diazo-4-(2-benzothiienyl)-2-butanone (0.27 g, 1.2 mmol, 65% yield).

TLC: R_f = 0.19 (ethyl acetate : hexane, 1:4).

^1H NMR: (CDCl_3 , 300 MHz): δ 2.79 (2H, br t, CH_2), 3.27 (2H, t, J = 7 Hz, CH_2), 5.26

(1H, br s, CHN_2), 7.05 (1H, s, $\text{SC}=\text{CH}$), 7.30 (2H, m, ArH), 7.68 (1H, d, J = 7

Hz, ArH), 7.77 (1H, d, J = 7 Hz, ArH).

^{13}C NMR: (CDCl_3 , 75 MHz); δ 25.93 (CH_2), 41.77 (CH_2), 54.99 (CHN_2), 120.44, 121.44,

122.52, 124.31, 124.51, 139.43, 140.02, 144.25, 193.02 (CO).

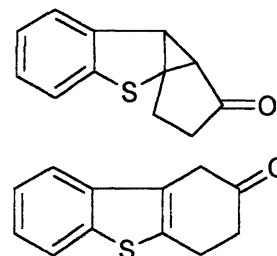
MS $[\text{EI}]^+$: m/z (RI%); 230 $[\text{M}]^+$ (11), 202 $[\text{M}^+ - \text{N}_2]^+$ (13), 161 $[\text{M} - \text{COCHN}_2]^+$ (28), 147

(80).

HRMS: For $C_{12}H_{10}N_2OS$: calculated 230.0514, observed 230.0516.

Synthesis of 1,2,3a,3b-Tetrahydro-3H-benzo[b]cyclopenta[1,3]cyclopropa- [1,2-d]thiophen-3-one (**147**) and 1,2,3,4-Tetrahydrodibenzo[b,d]thiophen-3-one (**148**):

1-Diazo-4-(2-benzothieryl)-2-butanone (**146**) (0.1 g, 4.35 mmol) was dissolved in dry dichloromethane (35 ml) and to this a catalytic amount of rhodium (II) acetate (10 mg) was added. The reaction mixture was stirred under argon at room temperature for 2 hours. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography using ethyl acetate-hexane (1:4) as the eluent and yielded 1,2,3a,3b-tetrahydr-3H-benzo[b]cyclopenta[2,3]cyclopropa[1,2-d]thiophen-3-one (**147**) in 70% yield and 1,2,3,4-tetrahydrodibenzo[b,d]thiophen-2-one (**148**) in 13% yield. The intermediate (**147**) isomerizes to the product **148** over time, instantaneously following the addition of a few drops of trifluoroacetic acid.



The product **147** showed:

TLC: $R_f = 0.30$ (ethyl acetate : hexane, 1:4).

1H NMR: ($CDCl_3$, 300 MHz): δ 1.45 (1H, br s, CH), 2.16-2.39 (3H, m, 3 of CH_2CH_2), 2.56 (1H, m, 1 of CH_2CH_2), 3.34 (1H, d, $J = 1$ Hz, CH), 7.07-7.22 (3H, m, ArH), 7.38 (1H, d, $J = 7$ Hz, ArH).

^{13}C NMR: ($CDCl_3$, 75 MHz): δ 26.41, 34.69, 37.00, 40.45, 48.81, 122.83, 125.18, 126.16, 128.28, 138.04, 141.89, 211.38 (CO).

MS [EI]⁺: m/z (RI%): 202 [M]⁺(37%), 174 [M-CO]⁺(100%), 160 [M-COCH₂] (51), 146 (41).

HRMS: For C₁₂H₁₀OS: calculated 202.0452, observed 202.0448.

The product **148** showed:

TLC: R_f = 0.41 (ethyl acetate : hexane, 1:4).

¹H NMR: (CDCl₃, 300 MHz): δ 2.87 (2H, t, *J* = 7 Hz, CH₂), 3.30 (2H, t, *J* = 7 Hz, CH₂), 3.67 (2H, s, CH₂), 7.39 (2H, m, ArH), 7.54 (1H, t, *J* = 7 Hz, ArH), 7.82 (1H, d, *J* = 7 Hz, ArH).

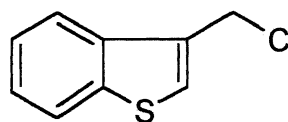
¹³C NMR: (CDCl₃, 75 MHz): δ 25.09 (CH₂), 39.07 (CH₂), 39.54 (CH₂), 120.79, 122.97, 124.82, 124.91, 127.29, 135.51, 138.96, 140.06, 210.04 (CO).

MS [EI]⁺: m/z (RI%): 202 [M]⁺(64), 173 (19), 160 [M-COCH₂] (100), 147 (11).

HRMS: For C₁₂H₁₀OS: calculated 202.0452, observed 202.0449.

Synthesis of 3-Chloromethyl Benzothiophene (**159**)⁷⁷

Benzothiophene (**142**) (5.0 g, 37.3 mmol) and 37% aqueous formaldehyde (3.4 ml, 41 mmol) were stirred in 12N hydrochloric acid (5 ml) until most of



the solid had dissolved, at which time a rapid stream of hydrogen chloride gas was then bubbled through the reaction mixture for six hours. The reaction mixture was diluted with 20 ml of ice water, and the aqueous layer was extracted with 3 x 50 ml portions of ether. The combined organic layers were then washed with water, saturated sodium bicarbonate, and water respectively. The organic layer was dried with magnesium sulfate, and the solvent was removed under reduced pressure. The desired product was purified

by vacuum distillation (90 °C @ 0.15mmHg) to give recovered starting material (0.7 g), and the desired 3-chloromethyl benzothiophene (**159**) (4.1 g, 22.5 mmol, 60% yield). The product showed :

TLC: R_f = 0.59 (ethyl acetate : hexane, 1:2).

^1H NMR: (CDCl_3 , 300 MHz): δ 4.90 (2H, s, CH_2), 7.49 (1 H, s, ArH), 7.51 - 7.60 (2H, m, 2 x ArH), 8.00 (2H, t, $J=9$ Hz, 2 x ArH).

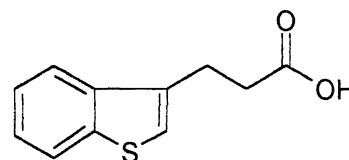
^{13}C NMR: (CDCl_3 , 300 MHz): δ 39.99 (CH_2), 122.34, 123.38, 124.86, 15.24, 126.70, 132.33, 136.66, 140.97 (8 x Ar).

MS [EI^+]: m/z (RI%); 182 [M^+] (26), 147 [$\text{M}-\text{Cl}^+$] (100).

HRMS: For $\text{C}_9\text{H}_7\text{ClS}$: calculated 181.9957, observed 181.9953

Synthesis of 3-(3-benzothieryl)propionic acid (**151**)⁷⁷

A solution of sodium methoxide (5.4 g, 0.1 mol), and diethylmalonate (16.0 g, 0.1 mol) in absolute ethanol (50 ml) was stirred under argon at



room temperature. To this solution was added 3-chloromethylbenzo-[b]thiophene (**159**) (15.47 g, 0.085 mol) in ethanol (7 ml) dropwise using a syringe pump over 2 hours at 0°C. The reaction was left to stir for another 3 hours at 0 °C. The reaction mixture was poured into water (150 ml) and the organic layer was separated. The aqueous layer was further extracted with 3 x 30 ml of chloroform and the combined organic layers were washed with water, dried over magnesium sulfate and treated with activated charcoal. Filtration to remove the charcoal was followed by evaporation of the solvent under reduced pressure to give an oily residue, to which a solution of NaOH in water (50 ml

0.5 N) was added. The mixture was then stirred and refluxed for 0.5 hours. Once the mixture had cooled, it was diluted with 25 ml of water and the solution was separated from insoluble gum. This solution treated with activated charcoal, filtered using gravity filtration and then was acidified with hydrochloric acid (120 ml, 6N). The solution was left at room temperature overnight allowing for crystallization of dicarboxylate product **150**. The solid was decarboxylated by heating on a hot plate gave the desired product (4.7 g, 23 mol, 45% yield).

^1H NMR: (CDCl_3 , 300 MHz): δ 2.81 (2H, t, $J = 7$ Hz, CH_2), 3.81 (2H, t, $J = 7$ Hz, CH_2), 7.14 (1H, s, SCH), 7.38 (2H, m, $J = 6$, 2 Hz, ArH), 7.73 (1H, dd, $J = 6$, 2 Hz, ArH), 7.83 (1H, dd, $J = 6$, 2 Hz, ArH), 10.27 (1H, br, COOH).

^{13}C NMR: (CDCl_3 , 300 MHz): δ 23.86 (CH_2), 33.61 (CH_2), 121.78, 122.22, 123.35, 124.44, 124.79, 134.89, 138.92, 140.86, 177.77 (CO).

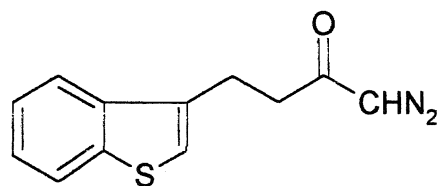
MS [EI^+]: m/z (RI%); 206 [M] $^+$ (54), 161 [$\text{M}-\text{CO}_2\text{H}$] $^+$ (14), 147 [$\text{M}-\text{CH}_2\text{CO}_2\text{H}$] $^+$ (100).

HRMS: For $\text{C}_{11}\text{H}_{10}\text{O}_2\text{S}$: calculated 206.04015, observed 206.0408.

Synthesis of 1-Diazo-4-(3-benzothiophenyl)-2-butanone (**152**):

3-Benzothiophene propionic (**151**)

acid (0.3 g, 1.45 mmol) was dissolved in a dry tetrahydrofuran (30 ml) and treated with dimethylformamide (4 drops). The



mixture was cooled in an ice bath and thionyl chloride (0.2 g, 1.74 mmol) was added slowly. The reaction mixture was left to stir for 2 hours at which time the solvent and excess of the thionyl chloride was removed under reduced pressure. The residue was

redissolved in dry tetrahydrofuran and added slowly a solution of ethereal diazomethane (40 ml) at 0 °C. The reaction mixture was stirred for 3 hours and then was filtered using gravity filtration. The solvent evaporated under reduced pressure and the residue was purified by silica gel column chromatography using dichloromethane as the eluent. The diazoketone product (0.23 g, 1.01 mmol, 70% yield) showed:

TLC: $R_f = 0.26$ (dichloromethane)

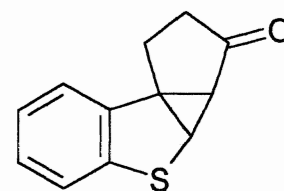
^1H NMR: (CDCl_3 , 300 MHz): δ 2.76 (2H, t, $J=7$ Hz, CH_2), 3.20 (2H, t, $J=7$ Hz, CH_2), 5.21 (1H, s, CHN_2), 7.13 (1H, s, S-CH), 7.38 (2H, m, ArH), 7.7 (1H, d, $J=7$ Hz, ArH), 7.86 (1H, d, $J=7$ Hz, ArH).

^{13}C NMR: (CDCl_3 , 75 MHz): δ 24.00 (CH_2), 40.44 (CH_2), 55.10 (CHN_2), 121.12, 122.28, 123.36, 124.45, 124.77, 135.38, 139.00, 140.88, 194.14 (CO).

MS $[\text{EI}]^+$: m/z (RI%); 202 $[\text{M}-\text{N}_2]^+$ (25), 174 $[\text{M}-\text{CO}-\text{N}_2]^+$ (80), 161 $[\text{M}-\text{COCHN}_2]^+$ (55).

Synthesis of 1,2,3a,3b-Tetrahydro-3H-benzo[b]cyclopenta[1,3]cyclopropa[1,2-d]thiophen-3-one (153):

1-Diazo-4-(3-benzothieryl)-2-butanone **152** (0.1 g, 0.43 mmol) was dissolved in dry dichloromethane (60 ml) and treated with a catalytic amount of rhodium (II) acetate (10% mol). The reaction was stirred overnight under argon at room temperature.



TLC revealed one major spot and 2D TLC showed no decomposition. The solvent was evaporated and the residue was purified by column chromatography using silica gel and

dichloromethane as an eluent to give 1,2,3a,3b-tetrahydro-3*H*-

benzo[*b*]cyclopenta[1,3]cyclopropa[1,2-*d*]thiophen-3-one (0.08 g, 0.4 mmol, 91% yield).

TLC: $R_f = 0.32$ (dichloromethane).

^1H NMR: (CDCl_3 , 300 MHz): δ 1.50 (1H, d, $J = 1$ Hz, CH), 2.25 (1H, m, $J = 11, 10, 8$ Hz), 2.38 (1H, m, $J = 11, 10, 8$ Hz), 2.49 (1H, m, $J = 13, 8, 8$ Hz), 2.87 (1H, m, $J = 13, 10, 10$ Hz), 3.56 (1H, d, $J = 1$ Hz, CH), 7.14-7.27 (3H, m, ArH), 7.37 (1H, d, $J = 7$ Hz, ArH).

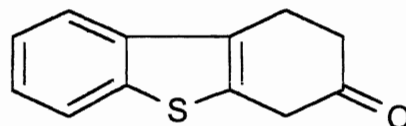
^{13}C NMR: (CDCl_3 , 75 MHz): δ 24.17, 34.69, 37.15, 37.90, 50.23, 122.86, 124.46, 124.94, 128.70, 138.10, 142.10, 211.88.

MS [EI] $^+$: m/z (RI%): 202[M] $^+$ (50), 200 (100), 174 [M-CO] $^+$ (37), 160 (70).

HRMS: For $\text{C}_{12}\text{H}_{10}\text{OS}$: calculated 202.0452, observed 202.0448.

Synthesis of 1,2,3,4-tetrahydrodibenzo[*b,d*]thiophen-3-one (**154**):

1,2,3a,3b-Tetrahydro-3*H*-benzo[*b*]cyclopenta[1,3]cyclopropa-[1,2-*d*]thiophen-3-one (**153**) (20 mg, 0.1 mmol) was dissolved in dry dichloromethane (10 ml) and treated with one drop of trifluoroacetic acid. The mixture was stirred for 10 minutes at which time the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography using dichloromethane as an eluent to give 1,2,3,4-tetrahydrodibenzo[*b,d*]thiophen-3-one (**154**) (19 mg, 0.95 mmol, 97% yield).



TLC: $R_f = 0.71$ (dichloromethane).

^1H NMR: (CDCl_3 , 300 MHz): δ 2.81 (2H, t, $J = 7$ Hz, CH_2), 3.16 (2H, t, $J = 7$ Hz, CH_2), 3.75 (2H, s, CH_2), 7.23 (1H, s, S-CH), 7.35 (2H, m, ArH), 7.60 (1H, d, $J = 7$ Hz, ArH), 7.78 (1H, d, $J = 7$ Hz, ArH).

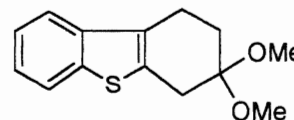
^{13}C NMR: (CDCl_3 , 75 MHz): δ 22.86 (CH_2), 38.67 (CH_2), 40.37 (CH_2), 121.32, 122.96, 124.81, 129.29, 132.83, 138.43, 139.60, 210.77 (CO).

MS $[\text{EI}]^+$: m/z (RI%): 202 $[\text{M}]^+$ (67), 173 $[\text{M}-\text{CO}]^+$ (16), 160 (100) $[\text{M}-\text{CH}_2\text{CO}]^+$.

HRMS: For $\text{C}_{12}\text{H}_{10}\text{OS}$: calculated 202.0452, observed 202.0450.

Synthesis of 3,3-dimethoxy-1,2,3,4-tetrahydrodibenzo[*b,d*]thiophene (**155**):

1,2,3a,3b-Tetrahydro-3*H*-benzo[*b*]cyclopenta[1,3]-cyclopropa[1,2-*d*]thiophen-3-one (**153**) (50 mg, 0.24 mmol) was dissolved in dry methanol (25 ml) and a catalytic amount of camphor sulphonic acid (5 mg) was added. The reaction mixture was stirred under argon at room temperature for 5 hours. The solvent was evaporated under reduced pressure and the residue was purified by preparative plate silica gel chromatography using dichloromethane-hexane (1:1) as an eluent. Two products were isolated; 1,2,3,4-tetrahydrodibenzo[*b,d*]thiophen-3-one (**154**) (25 mg, 0.12 mmol, 50% yield) and 3,3-dimethoxy-1,2,3,4-tetrahydrodibenzo[*b,d*]thiophene (**155**) (24 mg, 0.096 mmol, 40% yield).



TLC: $R_f = 0.73$ (dichloromethane).

^1H NMR: (CDCl_3 , 300 MHz): δ 2.17 (2H, t, $J = 7$ Hz, CH_2), 2.84 (2H, t, $J = 7$ Hz, CH_2), 3.13 (2H, s, CH_2), 3.33 (6H, s, CH_3), 7.32 (2H, m, ArH), 7.58 (1H, d, $J = 8$ Hz, ArH), 7.77 (1H, d, $J = 8$ Hz, ArH).

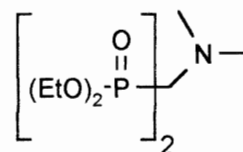
^{13}C NMR: (CDCl_3 , 75 MHz): δ 21.39 (CH_2), 28.72 (CH_2), 34.23 (CH_2), 48.23 (OCH_3), 100.58 (CC_4), 120.66, 122.32, 123.64, 123.92, 128.80, 133.47, 138.92, 139.01.

MS $[\text{EI}]^+$: m/z (RI%): 248 $[\text{M}]^+$ (27), 216 $[\text{M}-\text{OMe}]^+$ (25), 160 $[\text{M}-\text{CH}_2\text{CO}-2\text{xOMe}]^+$ (100).

HRMS: For $\text{C}_{14}\text{H}_{16}\text{O}_2\text{S}$: calculated 348.08710, observed 248.08786.

Synthesis of Tetraethyldimethylaminomethylenediphosphonate (**162**)⁸¹

A solution of dimethylformamide (3.8 ml, 3.58 g, 49 mmol) in 75 ml of anhydrous ether was stirred under argon atmosphere and cooled using an ice bath. Then oxalyl chloride (4.3 ml, 6.25 g, 50 mmol) in 20 ml of anhydrous ether was added, the reaction was stirred for addition 2 hours. To this mixture, triethyl phosphite (**161**) (17.5 ml, 18 g, 108 mmol) was then added dropwise and the reaction mixture was stirred for another one hour. The solvent was removed under reduced pressure then vacuum distillation (135°C @ 0.15 mmHg) afforded 85% yield (13.8 g, 41.6 mmol) of **162** as pale yellow oil. The product showed:



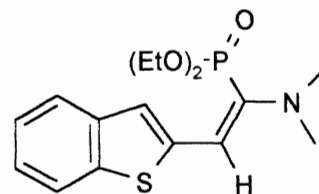
^1H NMR: (CDCl_3 , 300 MHz): δ 1.22 (12H, t, $J=6.9$, CH_2CH_3), 2.50 and 2.51 (each 3H, s, $\text{N}(\text{CH}_3)_2$), 3.21 (1H, broad t, $J\sim 24.9$ Hz, $\text{CH}-\text{P}$), 4.06 (8H, q, $J=6.8$ Hz, CH_2CH_3).

MS $[\text{EI}]^+$: m/z (RI%): 331 $[\text{M}]^+$ (5.2), 133 $[\text{M}-\text{PO}(\text{OEt})_2]^+$ (100).

HRMS: for $\text{C}_{11}\text{H}_{27}\text{NO}_6\text{P}_2$: calculated 331.1313, observed 331.1300.

Synthesis of the 2-Benzothiophene Phosphonate (**163**)⁷⁹

40% Sodium hydride dispersed in mineral oil (325 mg, 13.5 mmol) was washed three times with hexanes, the suspended in 10 ml of tetrahydrofuran (THF). A solution of tetraethyldimethylaminomethylenediphosphonate (**162**) (3.1 g, 9.4 mmol) in 75 ml of THF was then added slowly while stirring. The reaction mixture was stirred for another one hour and a solution of 2-thianphthaldehyde (**143**) (1.58 g, 9.8 mmol) in 10 ml of THF was added, and the resultant mixture was refluxed for one hour. The solvent was then removed under reduced pressure and the residue was partitioned between ether and water. The aqueous layer was extracted with 3 x 20 ml of ether. The combined extracts were dried over magnesium sulfate and evaporated to dryness at reduced pressure. The crude product was purified by colmun chromatography using silica gel with 20% ethyl acetate in hexanes as eluent to give 60% yield (2.0 g, 5.9 mmol) of the desired product **163**. The product showed:



TLC: R_f = 0.29 (1:1) ethyl acetate : hexanes.

¹H NMR: (CDCl₃, 300 MHz): δ 1.34 (6H, t, J =6.9 Hz, CH₂CH₃), 2.65 and 2.66 (each 3H, s, N(CH₃)₂), 4.12 (4H, q, J =6.6 Hz, CH₂CH₃), 7.24-7.36 (4H, m, ArH), 7.67-7.74 (2H, m, Ar-H).

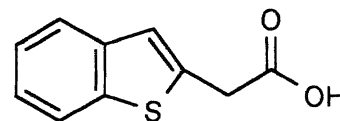
¹³C NMR: (CDCl₃, 75 MHz): δ 16.19, 43.91, 61.56, 121.98, 123.66, 125.14, 127.24, 131.49, 131.99, 137.35, 137.92, 142.38 (Ar).

MS[EI⁺]: m/z (RI%): 339 [M]⁺ (100), 295 [M-NMe₂]⁺ (20), 202 [M-PO(OEt)₂]⁺ (84), 187 [M-PO(OEt)₂-Me]⁺ (48), 172 [M-PO(OEt)₂-Me₂]⁺ (70).

HRMS: for $C_{16}H_{22}NO_3PS$: calculated 339.07744, observed 339.1044.

Synthesis of 2-Benzothiophene acetic acid (**164**)⁷⁹

A solution of the phosphonate **163** (1.0 g, 2.95 mmol) in 50 ml of 12N hydrochloric acid was refluxed for 30 minutes. The mixture was then cooled, poured into 300 ml of ice-water, and extracted 4 times with 100 ml of ether. The combined organic layer was then dried with magnesium sulfate and treated with activated charcoal to give a pale yellow solution of **164**. Evaporation of the ether gave 500 mg of **164** as yellowish crystalline solid (2.60 mmol, 88% yield). The compound showed :



M.P.: 140-142°C.

1H NMR: ($CDCl_3$, 300 MHz): δ 3.98(2H, s, CH_2), 7.18 (1H, s, C3H), 7.25-7.36 (2H, m, Ar-H), 7.73 (1H, d, $J=6.8$ Hz, ArH), 7.81 (1H, d, $J=7.5$ Hz, ArH), 9.40 (1H, broad, COOH).

MS[EI⁺]: m/z (RI%): 192[M]⁺(39), 147[M-COOH]⁺(100).

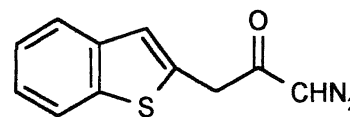
HRMS: for $C_{10}H_8O_2S$: calculated 192.0245, observed 192.0243.

Synthesis of 1-Diazo-3-(2-Benzothieryl)-2-Propanone (**165**):

The diazoketone was prepared in 76% yield following the procedure employed for the synthesis of diazoketone **146**.

The reaction mixture was purified by column chromatography

using silica gel with 33% hexanes in dichloromethane as eluent. The product showed:



TLC: R_f = 0.64 (1:1) ethyl acetate : hexanes.

^1H NMR: (CDCl_3 , 300 MHz): δ 3.85 (2H, s, CH_2), 5.31 (1H, s, CHN_2), 7.14 (1H, s, ArH), 7.26-7.35 (2H, m, Ar-H), 7.70 (1H, d, $J=6.8$ Hz, Ar-H), 7.77 (1H, d, $J=7.1$ Hz, Ar-H).

^{13}C NMR: (CDCl_3 , 75 Hz): δ 42.44 (CH_2), 54.97 (CHN_2), 122.15, 123.23, 123.87, 124.27, 124.43, 136.69, 139.74, 140.05, 190.71 (C=O)

MS[EI+]: m/z (RI%): 216 $[\text{M}]^+$ (13), 188 $[\text{M}-\text{N}_2]^+$ (69), 160 $[\text{M}-\text{CO}-\text{N}_2]^+$ (100), 147 $[\text{M}-\text{CO}-\text{N}_2-\text{CH}]^+$ (90), 115 (57).

HRMS: for $\text{C}_{11}\text{H}_8\text{N}_2\text{OS}$: calculated 216.0357, observed 216.0368.

Rhodium(II) Acetate Catalyzed Decomposition of 1-Diazo-3-(2-Benzothienyl)-2-Propanone (165):

To a stirred solution of diazoketone **165** (140 mg, 0.66 mmol) in 50 ml dichloromethane under an argon atmosphere, 1 mg of rhodium (II) acetate was added. The reaction was stirred for 1 hour at which time the solvent was evaporated under reduced pressure and the products separated by column chromatography on silica gel using 50% dichloromethane in hexanes as the eluent. Two major products were obtained. 2,3-Dihydro-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-2-one (**159**) (26.1 mg, 0.14 mmol, 21% yield) showed:

TLC: R_f = 0.20 (using 50% dichloromethane in hexanes as the eluent)

^1H NMR: (CDCl_3 , 300 MHz): δ 3.53 (2H, s, C5H), 3.64 (2H, s, C3H), 7.30-7.41 (2H, m, C9H and C10H), 7.60 (1H, d, $J=7.4$ Hz, C8H), 7.85 (1H, d, $J=7.8$ Hz, C11H).

^{13}C NMR: (CDCl_3 , 75 Hz): δ 40.78 (C5), 42.44(C3), 121.84, 123.25, 124.45, 124.72, 134.75, 135.19, 136.89, 141.95 (8 C_{Ar}), 213.16(CO).

MS [EI $^{+}$]: m/z (RI%): 188 [M] $^{+}$ (38), 160 [M-CO] $^{+}$ (100), 115 (29).

HRMS: for $\text{C}_{10}\text{H}_8\text{O}_2\text{S}$: calculated 188.0296, observed 188.0292.

Dimeric product **168** (71.0 mg, 0.19 mmol, 56% yield) showed:

TLC: R_f = 0.73 (using 50% ethyl acetate in hexanes as the eluent)

^1H NMR: (CDCl_3 , 300 MHz): δ 3.32, 3.41 (1H each, dd, J = 5.0, 15.1 Hz), 4.87, 4.93 (1H each, t, J = 2.0 Hz), 4.97 (1H, br), 5.25 (1H, t(br), J = 5.2 Hz), 6.85 (2H, m), 6.97, 7.04 (1H each, s), 7.12 (2H, d, J = 3.3 Hz), 7.30 (2H, m), 7.67, 7.74 (1H each, dd, J = 2.2, 6.8 Hz)

MS[EI $^{+}$]: m/z (RI%): 376 [M] $^{+}$ (18), 147 (100).

HRMS: for $\text{C}_{22}\text{H}_{16}\text{O}_2\text{S}_2$: calculated 376.0592, observed 376.0570.

The product **166** showed:

TLC: R_f = 0.7 (using 50% ethyl acetate in hexanes as the eluent)

^1H NMR: (CDCl_3 , 500 MHz): δ 3.44 (2H, d, J = 15 Hz), 3.49 (2H, d, J = 15 Hz), 5.88 (1H, d, J = 6 Hz, CH), 7.10 (2H, s, 2 x SCH), 7.27-7.32 (4H, m, ArH), 7.39 (1H, d, J = 6 Hz, CH), 7.68 (2H, d, J = 7 Hz, ArH), 7.75 (2H, d, J = 7 Hz, ArH).

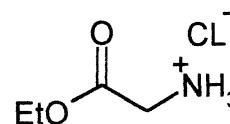
^{13}C NMR (CDCl_3 , 75 MHz): δ 38.62, 89.45, 122.54, 123.43, 123.69, 124.72, 124.82, 125.22, 136.84, 140.00, 140.38, 157.26, 168.05.

MS[EI $^{+}$]: m/z (RI%): 376 [M] $^{+}$ (18), 147 (100).

HRMS: for $\text{C}_{22}\text{H}_{16}\text{O}_2\text{S}_2$: calculated 376.0592, observed 376.0570.

Synthesis of glycine ethyl ester hydrochloride:

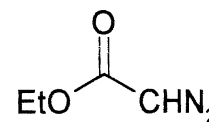
Thionyl chloride (30 ml) and dry ethanol (100 ml) were placed in a two-necked round bottom flask. To this solution was added glycine (25.6 g, 341 mol) slurried in absolute ethanol (~400 ml) in small portions.



Additional thionyl chloride (12 ml) was slowly added. The round bottom flask was fitted with a condensor and the reaction mixture refluxed. The solution became clear and gas was evolved. The reaction mixture refluxed for 18 hours at which time the solvent and excess thionyl chloride were removed by evaporation under a reduced pressure. The product was recrystallised from ethanol. Small white needles (40.2 g, 289 mmol, 85% yield) were collected by filtration and dried under high vacuum. m.p 148-150 °C.

Synthesis of Ethyl diazoacetate (8):

A solution of glycine ethyl ester hydrochloride (12 g, 86.0 mmol) in dichloromethane (50 ml) and water (30 ml) was cooled to -5 °C and treated with a solution of sodium nitrate (8 g) in cooled water (25 ml).

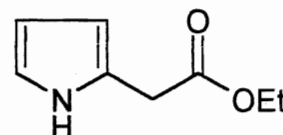


The reaction stirred under an argon atmosphere and the temperature lowered to -10 °C. 5% Sulfuric acid (12 ml) was added dropwise using the dropping funnel at such a rate that the temperature did not exceed -10 °C. Upon complete addition, the reaction mixture was stirred for a further 30 minutes. The mixture was transferred to a separatory funnel and the organic layer was added to 5% sodium carbonate (40 ml), the organic layer was separated again and the sodium carbonate solution was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate. The

solution was filtered using gravity filtration and the solvent was removed under reduced pressure to afford the desired product (7.8 g, 69.0 mmol) at 80% yield.

Synthesis of ethyl pyrrole-2- acetate (**94**)⁸⁵

A mixture of freshly distilled pyrrole (**93**) (2.5 g, 37.3 mmol), copper (II) acetylacetonate (0.49 g, 0.18 mmol) and dry dichloromethane (45 ml) was refluxed at 50-55 °C in two neck round bottom flask equipped with a condensor. A solution of ethyl diazoacetate (**8**) (1.6 g, 14.0 mmol) in dichloromethane (~ 7 ml) was slowly added to the reaction mixture using a syringe pump over two hours. The solvent was removed by evaporation under a reduced pressure and the product was purified by column chromatography using silica gel using ether : hexane (1:2) as the eluent to give ethyl pyrrole acetate (**94**) (1.3 g, 8.5 mmol, 61% yield). The product showed:



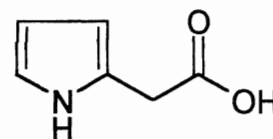
TLC: $R_f = 0.38$ (ether : hexane, 1:2).

¹H NMR: (CDCl₃, 300 MHz): 1.33 (3H, t, $J = 7.5$ Hz, CH₃), 3.71 (2H, s, CH₂), 4.24 (2H, q, $J = 7.5$ Hz, CH₂), 6.08 (1H, s, ArH), 6.20 (1H, m, ArH), 6.78 (1H, m, ArH), 8.28 (1H, br, N-H).

¹³C NMR: (CDCl₃, 75 MHz): δ 14.56 (CH₃), 33.71 (CH₂), 44.30 (OCH₂), 107.46, 108.66, 118.13, 134.05, 171.67 (CO).

Synthesis of Pyrrole-2- acetic acid (**172**):

Ethyl pyrrole acetate (**94**) (0.9 g, 5.9 mmol) and 30% sodium hydroxide (40 ml) were stirred for 18 hours at room temperature. The solution was



acidified using hydrochloric acid to pH 4, and extracted with ethyl acetate (3 x 40 ml).

The combined organic layers were washed with saturated sodium chloride and dried over sodium sulfate. The solvent was removed to give the pyrrole-3-acetic acid (**172**) as a white solid (0.59 g, 4.7 mmol, 80% yield). The product showed:

^1H NMR: (CDCl_3 , 300 MHz): 3.75 (2H, s, CH_2), 6.08 (1H, s, ArH), 6.17 (1H, m, ArH), 6.79 (1H, s, ArH), 8.57 (1H, br, N-H).

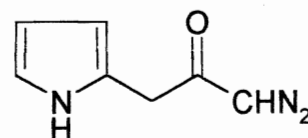
^{13}C NMR: (CDCl_3 , 75 MHz): δ 33.01 (CH_2), 107.92, 108.51, 118.06, 122.23, 176.57 (CO).

MS: m/z (RI%): 125 $[\text{M}]^+$ (37), 80 $[\text{M}-\text{COOH}]^+$ (100).

HRMS: For $\text{C}_6\text{H}_7\text{NO}_2$ calculated 125.04768, observed 125.04794.

Synthesis of 1-Diazo-(2-pyrrolyl)-2-propanone (**173**):

Pyrrole-3-acetic acid (**172**) (0.50 g, 4.0 mmol) and 1,3-dicyclohexylcarbodiimide (DCC) (0.89 g, 4.3 mmol) were dissolved



in dichloromethane (60 ml) and the reaction mixture was stirred under argon at room temperature for one hour. The solution was slowly added to stirred cooled (ice bath) solution of ethereal diazomethane (12 mmol) and allowed to react for three hours. The solvent was removed by evaporation under reduced pressure. The dicyclohexylurea (DCU) was removed from the residue by recrystallization several times from cooled ether. The remainder was purified by column chromatography using silica gel and ethyl acetate : hexane (1:2). The product was isolated as yellow crystals (0.48 g, 3.2 mmol, 80% yield) and showed:

TLC: R_f = 0.27 (ethyl acetate : hexane, 1:2).

^1H NMR: (CDCl_3 , 300 MHz): δ 3.59 (2H, s, CH_2), 5.25 (1H, s, CHN_2), 5.99 (1H, s, ArH), 6.12 (1H, m, ArH), 6.72 (1H, m, ArH), 8.71 (1H, br, N-H).

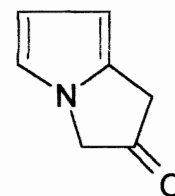
^{13}C NMR: (CDCl_3 , 75 MHz): δ 40.01 (CH_2), 55.19 (CHN_2), 108.13, 108.92, 118.61, 124.49, 193.07 (CO).

MS: m/z (RI%): 149 $[\text{M}]^+$ (40), 121 $[\text{M}-\text{N}_2]^+$ (12), 93 $[\text{M}-\text{N}_2-\text{CO}]^+$ (34), 80 $[\text{M}-\text{COCHN}_2]^+$ (100).

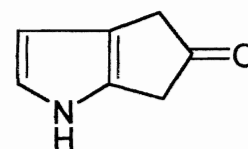
HRMS: For $\text{C}_7\text{H}_7\text{N}_3\text{O}$ calculated 149.05891, observed 149.05929.

$\text{Rh}_2(\text{OAc})_4$ Catalyzed Decomposition of 1-Diazo(2-pyrrolyl)-2-propanone (173):

To a stirred solution of 1-diazo(2-pyrrolyl)-2-propanone (**173**) (0.26 g, 1.7 mmol) in dry dichloromethane (40 ml), a catalytic amount of rhodium (II)acetate (28 mg) was added. The reaction was stirred under Ar at room temperature for 2 hours. The solvent was removed by evaporation under a reduced pressure and the products were purified by column chromatography using silica gel and ethyl acetate : hexane (1:4) as the eluent. Two products were collected: 1H-pyrrolizin-2(3H)-one (**176**) (NH insertion product (0.13 g, 1.1 mmol, 65 % yield) at 65%



yield 4,6-dihydrocyclopenta[b]pyrrol-5(1H)-one (**180**) (0.05 g, 0.41 mmol, 24% yield).



The products showed:

The compound **176**:

TLC: R_f = 0.57 (ethyl acetate : hexane, 1:4).

^1H NMR: (CDCl_3 , 300 MHz): δ 3.55 (2H, s, CH_2), 4.41 (2H, s, CH_2), 6.03 (1H, d, J = 3 Hz, ArH), 6.29 (1H, m, ArH), 6.78 (1H, d, J = 2 Hz, ArH).

^{13}C NMR: (CDCl_3 , 75 MHz): δ 37.87 (CH_2), 54.79 (CH_2), 102.23, 111.61, 115.86, 130.54, 210.09 (CO).

MS: m/z (RI%): 121 $[\text{M}]^+$ (50), 93 $[\text{M}-\text{CO}]^+$ (100).

HRMS: For $\text{C}_7\text{H}_7\text{NO}$ calculated 121.05276, observed 121.05337.

The compound **180**:

TLC: R_f = 0.26 (ethyl acetate : hexane, 1:4).

^1H NMR: (CDCl_3 , 300 MHz): δ 3.34 (2H, s, CH_2), 3.38 34 (2H, s, CH_2), 6.26 (1H, s, ArH), 6.77 (1H, s, ArH), 8.32 (1H, br, N-H).

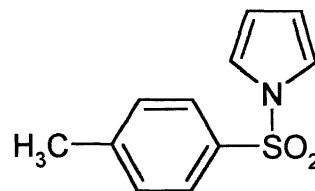
^{13}C NMR: (CDCl_3 , 75 MHz): δ 39.45 (CH_2), 40.72 (CH_2), 104.80, 119.65, 129.41, 216.51 (CO).

MS: m/z (RI%): 121 $[\text{M}]^+$ (50), 93 $[\text{M}-\text{CO}]^+$ (100).

HRMS: For $\text{C}_7\text{H}_7\text{NO}$ calculated 121.05276, observed 121.05332.

Synthesis of 1-Tosylpyrrole (**181**)⁸⁶

Freshly distilled pyrrole (**93**) (5.0 g, 74.6 mmol) was added slowly at 0°C to a solution of potassium t-butoxide (10.0 g, 89.5 mmol) in dry N,N-dimethylformamide (DMF) (50 ml). The reaction mixture was stirred for one hour at room temperature. The reaction mixture was cooled again to 0°C and a solution of tosylchloride (19.9 g, 104 mmol) in dry N,N-dimethylformamide (DMF) (70 ml) was added. The reaction mixture was stirred for 18 hours. The excess of potassium t-butoxide and tosylchloride were destroyed by adding the reaction mixture to water (100 ml). The resulting solution was extracted with ethyl acetate (4 x 150 ml) and the combined



organic layers were dried over magnesium sulfate, filtered and evaporated to dryness by evaporation under a reduced pressure. Recrystallisation from dichloromethane : hexane 1 : 8) afforded 1-tosylpyrrole (**181**) (13.2 g, 59.6 mmol, 80% yield). The product showed:

TLC: $R_f = 0.61$ (ethyl acetate : hexane, 1:2).

^1H NMR: (CDCl_3 , 300 MHz): δ 2.40 (3H, s, CH_3), 6.29 (2H, m, ArH), 7.16 (1H, m, ArH), 7.29 (2H, d, $J = 8$ Hz, ArH), 7.75 (2H, d, $J = 8$ Hz, ArH).

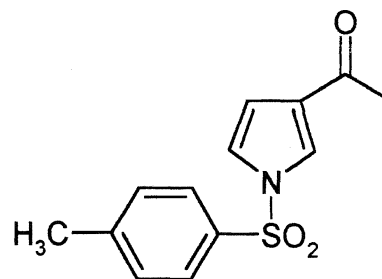
^{13}C NMR: (CDCl_3 , 75 MHz): δ 22.00 (CH_3), 113.93, 121.11, 127.22, 130.39, 136.50, 145.39.

MS: m/z (RI%): 221 $[\text{M}]^+$ (32), 155 $[\text{Ts}]^+$ (30), 91 $[\text{Ts-SO}_2]^+$ (100).

HRMS: For $\text{C}_{11}\text{H}_{11}\text{NO}_2\text{S}$ calculated 221.04323, observed 221.05149.

Synthesis of 1-Tosyl-3-acetylpyrrole (**182**)⁸⁶

Aluminum chloride (18.4 g, 133.34 mmol) was suspended in dry dichloromethane (80 ml) and the mixture cooled to 0°C (ice bath) under an argon atmosphere. Acetic anhydride (6.2 g, 102.0 mmol) was added to reaction flask and the mixture stirred for a half hour at room temperature.



The reaction mixture was cooled again to 0°C and a solution of 1-tosylpyrrole (5.7 g, 25.7 mmol) in dry dichloromethane (30 ml) was added. The reaction mixture was stirred for 18 hours at room temperature. The reaction was quenched by adding water slowly (a vigorous reaction occurs otherwise). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 75 ml). The combined organic layers were dried over sodium sulfate and the solvent removed under reduced pressure.

The product was purified by crystallization from dichloromethane and hexane (1 : 8) to afford the product **182** (6.4 g, 24.4 mmol, 95% yield). The product showed:

TLC: $R_f = 0.42$ (dichloromethane).

^1H NMR: (CDCl_3 , 300 MHz): δ 2.39 (3H, s, CH_3), 2.41 (3H, s, CH_3), 6.66 (1H, m, ArH), 7.13 (1H, m, ArH), 7.33 (2H, d, $J = 8$ Hz, ArH), 7.72 (1H, m, ArH), 7.80 (2H, d, $J = 8$ Hz, ArH).

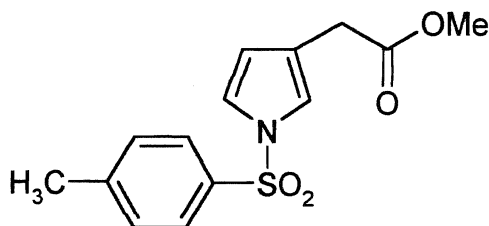
^{13}C NMR: (CDCl_3 , 75 MHz): δ 22.08 (CH_3), 27.68 (CH_3), 112.72, 122.00, 124.97, 127.18, 127.62, 129.70, 130.74, 135.46, 146.41, 193.27 (CO).

MS: m/z (RI%): 263 $[\text{M}]^+$ (31), 248 $[\text{M}-\text{CH}_3]^+$ (32), 155 $[\text{Ts}]^+$ (32), 91 $[\text{Ts}-\text{SO}_2]^+$ (100).

HRMS: For $\text{C}_{13}\text{H}_{13}\text{NO}_3\text{S}$ calculated 263.06162, observed 263.06178.

Synthesis of Methyl 2-(-1-tosyl-3-pyrrolyl)acetate (**183**)⁸⁶

Thallium(III) nitrate trihydrate (5.0 g, 11.2 mmol), trimethylorthoformate (12.5 ml) and methanol (20 ml) were placed in a round bottom flask and stirred for 15 minutes at which

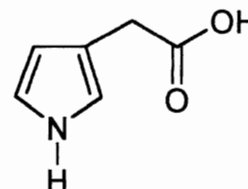


time K-10 montmorillonite (11.5 g) was added. After an additional thirty minutes, the solvent was removed by distillation and a solution of 1-tosyl-3-acetylpyrrole (2.5 g, 9.5 mmol) in methanol (60 ml) was added. The reaction was stirred for 18 hours at room temperature. The solution was filtered and the precipitate washed with water several times. The organic layer was separated, washed with water, and dried over magnesium

sulfate. The solvent was removed by evaporation under reduced a pressure to give methyl 2-(-1-tosyl-3-pyrrolyl)acetate (**183**) as oil (2.6 g, 9.0 mmol, 95% yield).

The Synthesis of 2-(3-Pyrrolyl)acetic acid (**184**)⁸⁶

Methyl 2-(-1-tosyl-3-pyrrolyl)acetate (**183**) (2.5 g, 8.5 mmol) was dissolved in methanol (25 ml) and 5N sodium hydroxide (25 ml) was slowly added to the stirred solution. The reaction mixture was stirred for 18 hours at which time the methanol was removed by evaporation under a reduced pressure. The remaining aqueous mixture was washed with diethylether (10 ml) and then acidified with 3M hydrochloric acid to the pH 3.5-4.0. Saturated sodium chloride was added 10 ml) and the mixture extracted with ethyl acetate (4 x 50 ml). The organic layer was dried over sodium sulfate and the solvent was evaporated under reduced pressure. A white solid (0.74 g, 6.0 mmol, 70% yield) was collected from the flask, which turned to black over time. The product showed:



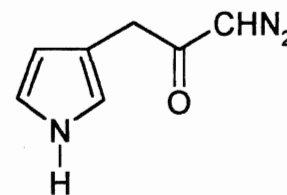
¹H NMR: (CDCl₃, 300 MHz): δ 3.59 (2H, s, CH₂), 6.21 (1H, d, *J*= 1.5 Hz, ArH), 6.78 (1H, m, ArH), 7.27 (1H, s, ArH), 8.17 (1H, br, N-H), 11.03 (1H, br, OH).

¹³C NMR: (CDCl₃, 75 MHz): δ 33.01 (CH₂), 109.73, 115.27, 117.21, 118.66, 178.17 (CO).

MS [EI]⁺: *m/z* (RI%): 125 [M]⁺ (45), 80 [M-COOH]⁺ (100).

Synthesis of 1-Diazo-(3-pyrrolyl)-2-propanone (185):

Pyrrole-3-acetic acid (**184**) (0.50 g, 4.0 mmol) was dissolved in dry dichloromethane (30 ml) and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.84 g, 4.4 mmol). Stirring under argon was continued for two hours at which time the reaction mixture was added to a cooled (ice bath) ethereal solution of diazomethane (14 mmol). The solution was stirred for two hours during which time a black precipitate was formed. The solution was filtered and the filtrate was concentrated under reduced pressure. The product was purified by column chromatography using silica gel and ethyl acetate : hexane (1:3) as an eluent to afford 1-diazo-(3-pyrrolyl)-2-propanone (0.27 g, 1.8 mmol, 45% yield). The product showed:



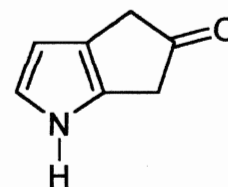
TLC: $R_f = 0.44$ (ethyl acetate : hexane, 1:1).

^1H NMR: (CDCl_3 , 300 MHz): δ 3.53 (2H, s, CH_2), 5.26 (1H, s, CHN_2), 6.14 (1H, m, $J = 1$ Hz, ArH), 6.71 (1H, s, ArH), 6.78 (1H, m, ArH), 8.20 (1H, br, N-H).

^{13}C NMR: (CDCl_3 , 75 MHz): δ 39.72 (CH_2), 54.06 (CHN_2), 109.05, 115.84, 116.90, 118.51, 195.13 (CO).

$\text{Rh}_2(\text{OAc})_4$ Catalyzed Decomposition of 1-diazo-(3-pyrrolyl)-2-propanone (185):

To a solution of 1-diazo-(3-pyrrolyl)-2-propanone (**185**) (0.10 g, 0.67 mmol) in dichloromethane (35 ml) was added a catalytic amount of rhodium(II) acetate (10%). The solution was stirred under argon at room temperature for four hours. The solvent was removed by evaporation under reduced pressure and the residue was purified



by column chromatography using silica gel and ethyl acetate : hexane (1:1). The product 4,6-dihydrocyclopenta[b]pyrrol-5(1H)-one (**180**) (0.068 g, 0.57 mmol, 85% yield) showed:

TLC: $R_f = 0.26$ (ethyl acetate : hexane, 1:4).

^1H NMR: (CDCl_3 , 300 MHz): δ 3.34 (2H, s, CH_2), 3.38 (2H, s, CH_2), 6.26 (1H, s, ArH), 6.77 (1H, s, ArH), 8.32 (1H, br, N-H).

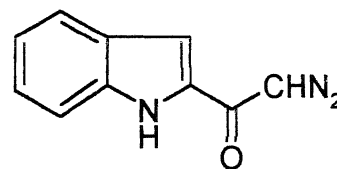
^{13}C NMR: (CDCl_3 , 75 MHz): δ 39.45 (CH_2), 40.72 (CH_2), 104.80, 119.65, 129.41, 216.51 (CO).

MS: m/z (RI%): 121 $[\text{M}]^+$ (50), 93 $[\text{M}-\text{CO}]^+$ (100).

HRMS: For $\text{C}_7\text{H}_7\text{NO}$ calculated 121.05276, observed 121.05332.

Synthesis of 1-Diazo-2-(2-indolyl)-2-one (**189**)

To a solution of 2-indole carboxylic acid (**188**) (0.70 g, 4.3 mmol) in dry tetrahydrofuran (100 ml) was added oxalyl chloride (0.60 g, 4.7 mmol) followed by a catalytic amount of dry



dimethylformamide (4 drops). The flask was equipped with a reflux condenser and the reaction mixture was heated to 50°C for 2 hours. The reaction mixture was allowed to cool to room temperature and an excess of cooled (ice bath) ethereal diazomethane (12.9 mmol, ~100 ml) was then slowly added. The reaction mixture was stirred for another 2 hours at which time the solvent was removed under reduced pressure to give a yellow residue. The product was purified by recrystallization from a minimum amount of dichloromethane to give 1-Diazo-2-(2-indolyl)-2-one (**189**) (0.55 g, 3.0 mmol). A second

crystallization of the mother liquor gave (0.12 g, 0.64 mmol) of product for a total 85% yield. The product showed:

TLC: R_f = 0.66 (ethyl acetate : hexane, 1: 1)

^1H NMR: (CDCl_3 , 300 MHz): δ 5.88 (1H, s, CHN_2), 6.90 (1H, s, ArH), (1H, t, J = 7.5 Hz, ArH), 7.30 (1H, t, J = 7.5 Hz, ArH), 7.43 (1H, d, J = 8.0, ArH), 7.65 (1H, d, J = 8.0, ArH), 9.43 (1H, br, N-H).

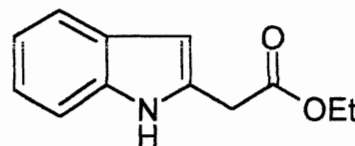
^{13}C NMR: (CDCl_3 , 75 MHz): δ 54.59 (CHN_2), 105.69, 112.48, 121.40, 122.96, 126.13, 128.00, 134.44, 137.49, 178.61 (CO).

MS $[\text{EI}]^+$: m/z (RI%): 185 $[\text{M}]^+$ (100), 157 $[\text{M}-\text{N}_2]^+$ (15), 144 $[\text{M}-\text{CHN}_2]^+$ (30), 129 $[\text{M}-\text{N}_2-\text{CO}]^+$ (85), 102 $[\text{M}-\text{COCHN}_2-\text{NH}]^+$ (47).

HRMS: For $\text{C}_{10}\text{H}_7\text{N}_3\text{O}$ calculated 185.05891, observed 185.05979.

Synthesis of Ethyl indole-2- acetate (**190**)⁸⁸

1-Diazo-2-(2-indolyl)-2-one (**189**) (0.5 g, 3.0 mmol) was dissolved in dry ethanol (150 ml) and photolyzed under



UV light for 6 hours. The reaction was monitored by TLC

and after the starting material had completely reacted, the solvent was removed under reduced pressure to give ethyl indole-2- acetate (**190**) quantitatively (0.60 mg, 2.95 mmol). The product showed:

TLC: R_f = 0.42 (dichloromethane)

^1H NMR: (CDCl_3 , 300 MHz): δ 1.35 (3H, t, J = 7 Hz, CH_3), 3.86 (2H, s, CH_2), 4.27 (2H, q, J = 7Hz, OCH_2), 6.43 (1H, s, ArH), 7.19 (2H, m, ArH), 7.38 (1H, d, J = 7.5, ArH), 7.64 (1H, d, J = 7.5, ArH), 8.86 (1H, br, N-H).

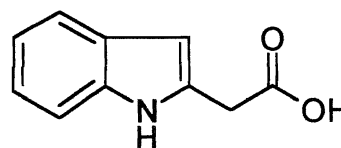
^{13}C NMR: (CDCl_3 , 75 MHz): δ 13.99 (CH_3), 33.86 (CH_2), 61.27 (CH_2), 101.62, 110.74, 119.60, 119.95, 121.51, 128.08, 130.53, 136.23, 170.63 (CO).

MS $[\text{EI}]^+$: m/z (RI%): 203 $[\text{M}]^+$ (45), 130 $[\text{M}-\text{COOCH}_2\text{CH}_3]^+$ (100).

HRMS: For $\text{C}_{12}\text{H}_{13}\text{NO}_2$ calculated 203.09463, observed 203.09562.

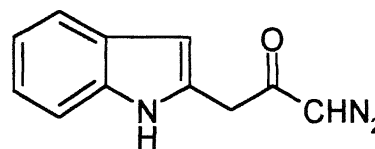
Synthesis of Indole-2-acetic acid (**191**):

To a solution of ethyl 2-indole acetate (**190**) (0.4 g, 2 mmol) dissolved in methanol (~2 ml), a solution of 25% sodium hydroxide (15 ml) was added. The reaction mixture was stirred for 18 hours after which time the methanol was evaporated under reduced pressure. The reaction mixture was then acidified to pH 3-4 using 3M hydrochloric acid and the clear solution was extracted with ethyl acetate (3 x 25 ml). The combined organic layers were dried over sodium sulfate, filtered and the solvent removed under reduced pressure to give indole-2-acetic acid (0.17 g, 1 mmol, 50% yield). The formation of the acid was confirmed by converting it to the corresponding methyl ester using ethereal solution of diazomethane.



Synthesis of 1-diazo-3-(2-indolyl)-2-propanone (**192**):

To a solution of indole-2-acetic (**191**) (0.1 g, 0.57 mmol) dissolved in dry dichloromethane (35 ml) was added dicyclohexylcarbodiimide (DCC) (0.13 g, 0.63 mmol). The reaction mixture was stirred under an argon atmosphere for one hour. The resulting solution was added slowly to a cooled (ice bath) solution of ethereal



diazomethane (20 ml). The reaction mixture was stirred for another hour and the solvent removed under a reduced pressure to give a solid residue. The dicyclohexylurea (DCU) was removed by crystallization from cooled ether, and the supernatant purified by column chromatography using silica gel and ethyl acetate:hexane (1:2) as eluent 1-diazo-3-(2-indolyl)-2-propanone (**192**) (0.056 g, 0.28 mmol, 50% yield) as well as with the methyl ester of the starting acid were isolated. The desired product showed:

TLC: R_f = 0.23 (ethyl acetate : hexane, 1:2).

^1H NMR: (CDCl_3 , 300 MHz): δ 3.37 (2H, s, CH_2), 5.28 (1H, br, CHN_2), 6.32 (1H, s, ArH), 7.11 (2H, m, ArH), 7.31 (1H, d, J = 8 Hz, ArH), 7.54 (1H, d, J = 8 Hz, ArH), 8.72 (1H, br, NH).

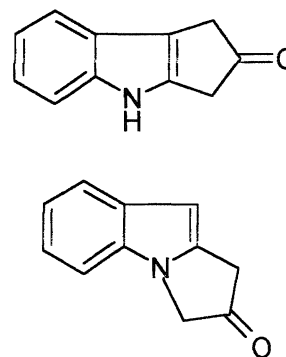
^{13}C NMR: (CDCl_3 , 75 MHz): δ 40.53 (CH_2), 55.64 (CHN_2), 102.45, 111.34, 120.34, 120.53, 122.33, 128.68, 131.76, 136.92, 192.05 (CO).

MS $[\text{EI}]^+$: m/z (RI%): 199 $[\text{M}]^+$ (7), 171 $[\text{M}-\text{N}_2]^+$ (31), 143 $[\text{M}-\text{N}_2-\text{CO}]^+$ (52), 130 $[\text{M}-\text{COCHN}_2]^+$ (27).

HRMS: For $\text{C}_{11}\text{H}_9\text{N}_3\text{O}$ calculated 199.07456, observed 199.07528.

*$\text{Rh}_2(\text{OAc})_4$ Catalyzed Decomposition of 1-diazo-3-(2-indolyl)-2-propanone (**192**):*

The reaction was carried out using the general procedure described above for the decomposition of diazoketone **173**. The solvent was evaporated, and the residue was purified by column chromatography using silica gel and ethyl acetate: hexane (1:2) as eluent to give 3,4-dihydrocyclopenta[*b*]indol-2(3*H*)-one (**193**), and



1H-pyrrolo[1,2-a]indol-2(3H)-one (**124**) (NH insertion product), in 25%, and 70% yield respectively.

The product **193** showed:

TLC: $R_f = 0.42$ (ethyl acetate : hexane, 1:2).

^1H NMR: (CDCl_3 , 300 MHz): δ 3.54 (2H, s, CH_2), 3.57 (2H, s, CH_2), 7.20 (2H, m, ArH), 7.42 (1H, d, $J = 8$ Hz, ArH), 7.51 (1H, d, $J = 7.5$ Hz, ArH), 8.12 (1H, br, N-H).

^{13}C NMR: (CDCl_3 , 75 MHz): δ 39.77 (CH_2), 39.84 (CH_2), 112.00, 114.21, 119.35, 120.76, 122.47, 124.84, 136.44, 138.79, 214.58 (CO).

MS $[\text{EI}]^+$: m/z (RI%): 171 $[\text{M}]^+$ (48), 143 $[\text{M}-\text{CO}]^+$ (100), 115 $[\text{M}-\text{C}_2\text{H}_4\text{CO}]^+$ (15).

HRMS: For $\text{C}_{11}\text{H}_9\text{NO}$ calculated 171.06841, observed 171.06947.

The product **124** showed:

TLC: $R_f = 0.68$ (ethyl acetate : hexane, 1:2).

^1H NMR: (CDCl_3 , 300 MHz): δ 3.75 (2H, s, CH_2), 4.51 (2H, s, NCH_2), 6.40 (1H, s, ArH), 7.20 (2H, m, ArH), 7.28 (1H, d, $J = 7$ Hz, ArH), 7.64 (1H, d, $J = 7$ Hz, ArH).

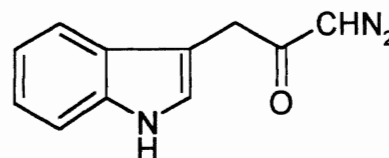
^{13}C NMR: (CDCl_3 , 75 MHz): δ 37.96 (CH_2), 52.70 (CH_2), 96.17, 110.08, 120.76, 121.27, 121.95, 130.92, 133.99, 136.90, 209.03 (CO).

MS $[\text{EI}]^+$: m/z (RI%): 171 $[\text{M}]^+$ (70), 143 $[\text{M}-\text{CO}]^+$ (100), 115 $[\text{M}-\text{C}_2\text{H}_4\text{CO}]^+$ (31).

HRMS: For $\text{C}_{11}\text{H}_9\text{NO}$ calculated 171.06841, observed 171.06890.

Synthesis of 1-Diazo-3-(3-indoly)-3-propanone (194):

A solution of indole-3-acetic acid (**199**) (0.4 g, 2.3 mmol) in a dry tetrahydrofuran (30 ml) was cooled to 0 °C



(ice bath) and stirred under argon. Two drops of a dry

dimethylformamide were added to the flask. Thionyl chloride (0.3 g, 2.5 mmol) was

slowly added. The reaction mixture was changed to a brown color and stirring was

continued for another two hours. The solvent was removed under reduced pressure, and

redissolved in dry dichloromethane. The solution was slowly added to cooled ethereal

solution of diazomethane and the reaction mixture was stirred for two hours. The product

was purified by chromatography on silica gel using ethyl acetate: hexane (1: 2) as an

eluent to give 1-diazo-3-(3-indolyl)-3-propanone (**194**) (0.4 g, 1.9 mmol, 80% yield).

TLC: R_f = 0.44 (ethyl acetate : hexane, 1:1).

^1H NMR: (CDCl_3 , 300 MHz): δ 3.79 (2H, s, CH_2), 5.21 (1H, s, CHN_2), 7.11 (1H, s, ArH), 7.22 (2H, m, ArH), 7.30 (1H, d, J = 8 Hz, ArH), 7.90 (1H, d, J = 8 Hz, ArH), 8.36 (1H, br, N-H).

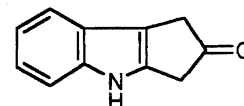
^{13}C NMR: (CDCl_3 , 75 MHz): δ 38.41 (CH_2), 54.70 (CHN_2), 109.38, 111.82, 119.11, 120.38, 122.90, 123.90, 127.52, 136.72, 194.74 (CO).

MS $[\text{EI}]^+$: m/z (RI%): 199 $[\text{M}]^+$ (14), 171 $[\text{M}-\text{N}_2]^+$ (83), 143 $[\text{M}-\text{N}_2-\text{CO}]^+$ (83), 130 $[\text{M}-\text{COCHN}_2]^+$ (100), 115 $[\text{M}-\text{CH}_2\text{COCHN}_2]^+$ (28).

HRMS: For $\text{C}_{11}\text{H}_9\text{N}_3\text{O}$ calculated 199.07456, observed 199.0754

Rh₂(OAc)₄ Catalyzed Decomposition of 1-Diazo-3-(3-indolyl)-3-propanone (194):

A solution of 1-diazo-3-(3-indolyl)-3-propanone (~5 mg) in CDCl₃ was placed in NMR tube and a catalytic amount of rhodium(II) acetate was added. The reaction was monitored by ¹H



NMR (a spectrum taken every 10 minutes). A preparative scale reaction was also undertaken (150 mg) and the product purified by column chromatography using silica gel and dichloromethane as an eluent. The product **193** (0.126 mg, 0.74 mmol, 95% yield) showed:

TLC: R_f = 0.42 (ethyl acetate : hexane, 1:2).

¹H NMR: (CDCl₃, 300 MHz): δ 3.54 (2H, s, CH₂), 3.57 (2H, s, CH₂), 7.20 (2H, m, ArH), 7.42 (1H, d, *J* = 8 Hz, ArH), 7.51 (1H, d, *J* = 7.5 Hz, ArH), 8.12 (1H, br, N-H).

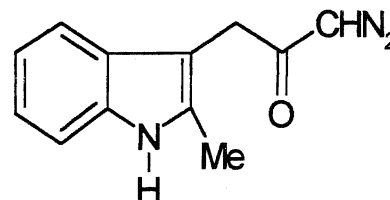
¹³C NMR: (CDCl₃, 75 MHz): δ 39.77 (CH₂), 39.84 (CH₂), 112.00, 114.21, 119.35, 120.76, 122.47, 124.84, 136.44, 138.79, 214.58 (CO).

MS [EI]⁺: *m/z* (RI%): 171 [M]⁺ (48), 143 [M-CO]⁺ (100), 115 [M-C₂H₄CO] (15).

HRMS: For C₁₁H₉NO calculated 171.06841, observed 171.06947.

Synthesis of 1-Diazo-3-(2-methyl indolyl)-2-propanone (203):

2-Methyl indole-3-acetic acid (**202**) (0.2 g, 1.0 mmol) was dissolved in dry tetrahydrofuran (25 ml), cooled to 0°C and stirred under an atmosphere of argon. Oxalyl chloride (0.15 g, 1.2 mmol) was added slowly followed by two drops of DMF. The reaction mixture was stirred at room



temperature for one hour. To remove excess of oxalyl chloride, the solvent was evaporated under a reduced pressure and dry benzene (10 ml) was added and subsequently evaporated under a reduced pressure. The residue was redissolved in dry tetrahydrofuran (15 ml) and was added dropwise to a cooled (ice bath) solution of diazomethane in ether (25 ml). The reaction mixture was stirred for another hour, filtered, and the solvent evaporated under a reduced pressure. The residue was purified by column chromatography using silica gel and ethyl acetate:hexane (1:2) as an eluent, to give **203** (0.16 g, 0.75 mmol, 75% yield).

TLC: R_f = 0.27 (ethyl acetate : hexane, 1:2).

^1H NMR: (CDCl_3 , 300 MHz): δ 2.36 (3H, s, CH_3), 3.73 (2H, s, CH_2), 5.13 (1H, s, CHN_2), 7.18 (2H, m, ArH), 7.28 (1H, d, $J=7$, ArH), 7.48 (1H, d, $J=7$, ArH), 8.51 (1H, s, NH).

^{13}C NMR: (CDCl_3 , 75 MHz): δ 12.08 (CH_3), 37.40 (CH_2), 54.33 (CHN_2), 105.32, 110.90, 118.15, 120.26, 121.99, 128.78, 133.47, 135.68, 194.87 (CO).

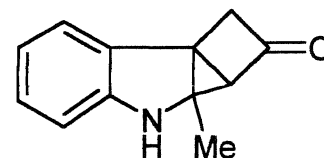
MS $[\text{EI}]^+$: m/z (RI%): 213 $[\text{M}]^+$ (20), 185 $[\text{M}-\text{N}_2]^+$ (59), 144 $[\text{M}-\text{COCHN}_2]^+$ (100).

HRMS: For $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}$ calculated 213.09021, observed 213.09090.

$\text{Rh}_2(\text{OAc})_4$ Catalyzed Decomposition of 1-Diazo-3(3-[2-methyl indolyl])-2-propanone

(203):

1-Diazo-3(3-[2-methyl indolyl])-2-propanone (0.12 g, 0.56 mmol) was dissolved in dry dichloromethane (40 ml) and treated with a catalytic amount of rhodium (II) acetate (10% mol). The



reaction was stirred for three hours under argon at room temperature. The solvent was

evaporated under a reduced pressure and the residue purified using silica gel column chromatography with ethyl acetate: hexane (1:3) as an eluent. The only identifiable fraction was the cyclopropane **204** (0.067 g, 0.36 mmol, 65% yield). The product showed:

TLC: R_f = 0.29 (ethyl acetate : hexane, 1:1).

^1H NMR: (CDCl_3 , 300 MHz): δ 1.52 (3H, s, CH_3), 2.65 (1H, d, J = 15 Hz, $1\times\text{CH}_2$), 2.78 (1H, d, J = 15 Hz, $1\times\text{CH}_2$), 4.38 (1H, br, N-H), 6.04 (1H, s, CH), 6.85 (1H, d, J = 8 Hz, ArH), 6.91 (1H, t, J = 7 Hz, ArH), 7.35 (1H, t, J = 8 Hz, ArH), 7.53 (1H, d, J = 7 Hz, ArH).

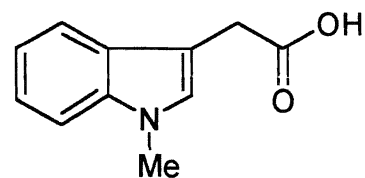
^{13}C NMR: (CDCl_3 , 75 MHz): δ 29.65 (CH_3), 52.44 (CH_2), 71.72 (CH), 112.74, 116.86, 120.21, 120.37, 125.77, 133.89, 154.86, 182.44, 206.72 (CO).

MS $[\text{EI}]^+$: m/z (RI%): 185 $[\text{M}]^+$ (79), 170 $[\text{M}-\text{CH}_3]^+$ (100), 157 $[\text{M}-\text{CO}]^+$ (31), 144 $[\text{M}-\text{CO}-\text{CH}]^+$ (10), 115 $[\text{M}-\text{CH}_3-\text{CH}_2\text{COCH}]^+$ (20).

HRMS: For $\text{C}_{12}\text{H}_{11}\text{NO}$ calculated 185.08406, observed 185.08408.

Synthesis of 1-Methyl indole-3-acetic acid (**205**)⁹⁰

A dispersion of sodium hydride in mineral oil (60 %, 0.68 g, 28.5 mmol) was washed with dry THF several times, suspended in dry THF (40 ml) and cooled to 0°C under an argon atmosphere. A solution of indole-3-acetic acid (**199**)



(2.00 g, 11.4 mmol) in dry THF (10 ml) was added dropwise over 20 minutes. After 30 minutes a solution of methyl iodide (5.40 g, 2.37 ml, 38 mmol) in dry THF (15 ml) was

added dropwise over 15 minutes at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred under argon overnight. The reaction was quenched with methanol and water (50 ml, in ratio of 1:1) to destroy the excess sodium hydride. The reaction mixture was then extracted with dichloromethane (3 x 100 ml). The combined organic layers were dried with sodium sulfate and concentrated to 30 ml. Petroleum ether was added and the mixture was left to stand for overnight during which time the desired product **205** crystallized (2.04 g, 10.83 mmol, 95% yield).

¹H NMR: (CDCl₃, 300 MHz): δ 3.78 (3H, s, CH₃), 3.82 (2H, s, CH₂), 7.06 (1H, s, NCH), 7.16 (1H, m, ArH), 7.27 (1H, m, ArH), 7.37 (1H, d, *J* = 5 Hz, ArH), 7.65 (1H, d, *J* = 6 Hz, ArH).

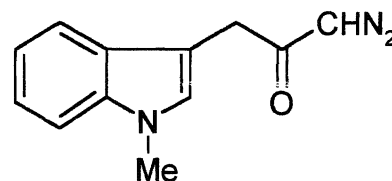
¹³C NMR: (CDCl₃, 75 MHz): δ 31.28 (CH₃), 33.09 (CH₂), 106.47, 109.71, 119.30, 119.70, 122.29, 127.96, 128.28, 137.31, 178.07 (CO).

MS [EI]⁺: *m/z* (RI%): 189 [M]⁺ (35.7%), 144 [M-CO₂H]⁺ (100%).

HRMS: For C₁₁H₁₁NO₂ calculated 189.07898, observed 189.07982

Synthesis of 1-Diazo-3-(3-[1-methyl indolyl])-2-propanone (**206**):

1-Methyl indole-3-acetic acid (**205**) (0.3 g, 1.6 mmol) was dissolved in dry dichloromethane (25 ml) and the solution was stirred under argon. Oxalyl chloride (0.24 g, 1.92 mmol) was added slowly followed by two drops of



DMF and the reaction mixture stirred at room temperature for one hour. To remove the excess of oxalyl chloride, the solvent was evaporated under a reduced pressure and dry benzene (10 ml) was added and subsequently evaporated under a reduced pressure. The

residue was redissolved in dry dichloromethane (15 ml) and added dropwise to an ethereal solution of diazomethane (35 ml) at 0 °C. The reaction mixture was stirred for another two hours at which time the solution was filtered and the solvent evaporated under a reduced pressure. The residue was purified by column chromatography using silica gel and ethylacetate:hexane (1:2) as the eluent to give the desired product (0.29 g, 1.36 mmol, 85% yield).

TLC: R_f = 0.48 (ethyl acetate : hexane, 1:1).

^1H NMR: (CDCl_3 , 300 MHz): δ 3.77 (2H, s, CH_2), 3.80 (3H, s, CH_3), (1H, s, CHN_2), 7.01 (1H, s, NCH), 7.20 (1H, t, $J=7, 8$, ArH), 7.27 (1H, d, $J=8$, ArH), 7.34 (1H, t, $J=7, 8$, ArH), 7.58 (1H, d, $J=7$, ArH).

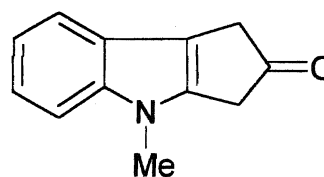
^{13}C NMR: (CDCl_3 , 75 MHz): δ 33.17 (CH_3), 38.33 (CH_2), 54.52 (CHN_2), 107.87, 109.88, 119.24, 119.91, 122.48, 128.00, 128.50, 137.50, 194.57 (CO).

MS $[\text{EI}]^+$: m/z (RI%): 213 $[\text{M}]^+$ (34%), 185 $[\text{M}-\text{N}_2]^+$ (25%), 157 $[\text{M}-\text{CON}_2]^+$ (22%), 144 $[\text{M}-\text{COCHN}_2]^+$ (100%).

HRMS: For $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}$ calculated 213.09021, observed 213.09113.

Synthesis of 3,4-dihydrocyclopenta[b]indol-2(1H)-one (208):

To a solution of rhodium (II) acetate (20 mg) in dichloromethane (40 ml) was added a solution of 1-diazo-3-(1-methyl-3-indole)-2-propanone (0.2 g, 0.94 mmol) in dichloromethane via a syringe pump. The



reaction was allowed to stir under an argon atmosphere at room temperature for an additional 30 minutes at which time the solvent was evaporated under a reduced pressure

and the residue was purified by filtration through a short pad of silica gel and dichloromethane as an eluent. The compound **208** (0.16 g, 0.89 mmol, 95% yield) showed:

TLC: R_f = 0.73 (ethyl acetate : hexane, 1:1).

^1H NMR: (CDCl_3 , 300 MHz): δ 3.51 (2H, s, CH_2), 3.56 (2H, s, CH_2), 3.73 (3H, s, CH_3), 7.18 (1H, t, $J=7$ Hz, ArH), 7.27 (1H, t, $J=7$, ArH), 7.34 (1H, d, $J=7$, ArH), 7.50 (1H, d, $J=7$, ArH).

^{13}C NMR: (CDCl_3 , 75 MHz): δ 31.66 (CH_2), 38.71 (CH_2), 40.35 (CH_3), 110.00, 111.86, 119.33, 120.20, 121.82, 124.81, 139.39, 139.54, 214.27 (CO).

MS $[\text{EI}]^+$: m/z (RI%): 185 $[\text{M}]^+$ (75%), 157 $[\text{M}-\text{CO}]^+$ (100%), 142 $[\text{M}-\text{COCH}_3]^+$ (13%), 128 $[\text{M}-\text{CH}_2\text{CO}-\text{CH}_3]^+$ (4%).

HRMS: For $\text{C}_{12}\text{H}_{11}\text{NO}$ calculated 185.08406, observed 185.08427.

Preparation of Diazoethane:

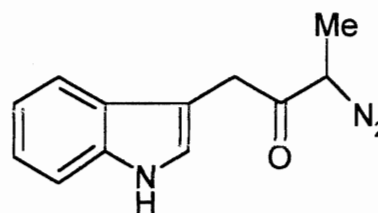
Safety Note: Diazoethane is explosive! Ground glass joints were avoided and additional precautions were taken while performing the experiment.

A suspension of 1-ethyl-3-nitro-1-nitrosoguanidine (5.0 g, 31 mmol) in 100 ml of ether was slowly added using dropping funnel to a vigorously stirred aqueous solution of potassium hydroxide (50 ml, 30%) at 50 $^{\circ}\text{C}$. The ethereal solution of the diazo compound was collected using the modified condenser (crushed dry ice as cooling source). The excess of the diazoketone which did not trapped by the condenser was destroyed in an ethereal solution of acetic acid. The diazoketone solution was dried by adding potassium hydroxide, and was stored in the fridge. Titration with benzoic acid and

back titration with standard aqueous sodium hydroxide to the phenolphthalein end point indicated that the yield was 75%

Synthesis of 2-Diazo-4-(3-indolyl)-3-butanone (209):

To a solution of indole-3-acetic acid (199) (0.3 g, 1.7 mmol) dissolved in dry tetrahydrofuran (35 ml) stirred under argon at 0°C, was added thionyl chloride (0.22 g, 1.8 mmol) and two drops of dry dimethylformamide. Twenty minutes



following the addition, the color of the reaction mixture changed to brown. Stirring was continued for another two hours. The solvent was removed by evaporation under a reduced pressure and the residue redissolved in a dry tetrahydrofuran (20 ml). The solution was added dropwise to a stirred solution of ethereal diazoethane (roughly three equivalents) at 0°C. The reaction mixture was stirred for another two hours at which time a few drops of acetic acid were added to destroy the excess of the diazoethane. The reaction mixture was filtered and evaporated to dryness under a reduced pressure. The product was purified by chromatography on silica gel using ethyl acetate: hexane 1:2 as an eluent. The product was isolated in 65% Yield.

The product showed:

TLC: R_f = 0.28 (ethyl acetate : hexane, 1:2).

^1H NMR: (CDCl_3 , 300 MHz): δ 1.9 (3H, s, CH_3CN_2), 3.91 (2H, s, CH_2), 6.99 (1H, s, ArH), 7.15 (2H, m, ArH), 7.31 (1H, d, J = 8 Hz, ArH), 7.61 (1H, d, J = 8 Hz, ArH), 8.28 (1H, br, N-H).

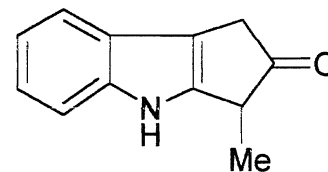
^{13}C NMR: (CDCl_3 , 75 MHz): δ 8.40 (CH_3), 35.55 (CH_2), 62.43 (CN_2), 108.32, 111.19, 118.44, 118.80, 119.69, 122.21, 123.21, 127.00, 136.05, 192.42 (CO).

MS: m/z (RI%): 213 $[\text{M}]^+$ (3), 185 $[\text{M}-\text{N}_2]^+$ (56), 170 $[\text{M}-\text{N}_2-\text{CH}_3]^+$ (6), 157 $[\text{M}-\text{CH}_2\text{CN}_2]^+$ (27), 130 $[\text{M}-\text{COCN}_2(\text{CH}_3)]^+$ (100).

HRMS: For $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}$ calculated 213.09021, observed 213.09031.

$\text{Rh}_2(\text{OAc})_4$ Catalyzed Decomposition of 2-Diazo-4-(3-indolyl)-3-butanone (209):

2-Diazo-4-(3-indolyl)-3-butanone (**209**) (10 mg, 0.47 mmol) was dissolved in CDCl_3 (1 ml) and this was placed in NMR tube. Following the recording of ^1H NMR spectrum of the starting material, a small amount of rhodium (II) acetate was added to the NMR tube. ^1H NMR spectra were taken every five minutes. The reaction was repeated in a normal flask in a bigger scale. The solvent was removed under reduced pressure, and the product was purified by flash chromatography on silica gel using dichloromethane as an eluent. The yield of the isolated product was 90%.



The product **211** showed:

TLC: R_f = 0.54 (dichloromethane).

^1H NMR: (CDCl_3 , 300 MHz): δ 1.46 (3H, d, J = 7 Hz, CH_3), 3.54-3.62 (3H, m, CH+ CH_2), 7.20 (2H, m, ArH), 7.42 (1H, d, J = 8 Hz, ArH), 7.53 (1H, d, J = 8 Hz, ArH), 8.14 (1H, br, N-H).

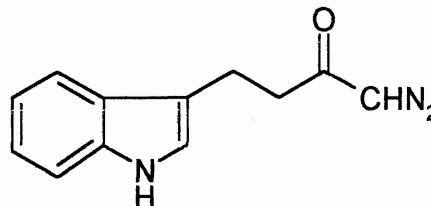
^{13}C NMR: (CDCl_3 , 75 MHz): δ 15.88 (CH_3), 38.86 (CH_2), 44.26 (CH_2), 112.07, 112.30, 119.51, 120.78, 122.46, 124.80, 138.75, 142.07, 217.58 (CO).

MS: m/z (RI%): 185 $[M]^+$ (56), 157 $\{M-CO\}^+$ (100), 130 $[M-C_3H_5O]^+$ (47), 115 $[M-C_4H_6O]^+$ (5).

HRMS: For $C_{12}H_{11}NO$ calculated 185.08406, observed 185.08499.

Synthesis of 1-Diazo-4(-3-indole)-2-butanone (217):

Indole-3-propionic acid (**216**) (0.3 g, 1.5 mmol) was dissolved in dry tetrahydrofuran (30 ml) and stirred under an argon atmosphere while cooling to 0 °C using an ice bath. Dimethylformamide (two drops) were added to the reaction flask followed by thionyl chloride (0.22 g, 1.9 mmol). The reaction was stirred for two hours at 0 °C at which time the solvent was removed by evaporation under a reduced pressure. The residue was redissolved in dry tetrahydrofuran and immediately added slowly to a stirred ethereal solution of diazomethane (50 ml, ~ 5 mmol) at 0 °C. The reaction mixture was stirred for two hours, then filtered using gravity filtration and the solvent was evaporated to dryness under a reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate : hexane 1:2 as an eluent to give 1-diazo-4(-3-indolyl)-2 butanone (0.23 g, 1.1 mmol, 70% yield).



The product showed:

TLC: R_f = 0.48 (ethyl acetate : hexane, 1:1)

1H NMR: ($CDCl_3$, 300 MHz): δ 2.69 (2H, t, J = 7 Hz, CH_2), 3.10 (2H, t, J = 7 Hz, CH_2), 5.12 (1H, s, CHN_2), 6.91 (1H, s, ArH), 7.17 (2H, m, ArH), 7.32 (1H, d, J = 8 Hz), 7.58 (1H, d, J = 8 Hz, ArH), 8.36 (1H, br, N-H).

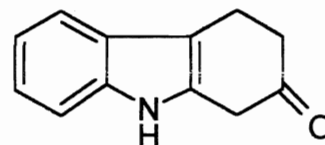
^{13}C NMR: (CDCl_3 , 75 MHz): δ 20.51(CH_2), 41.10 (CH_2), 54.53 (CHN_2), 111.18, 114.25, 118.36, 119.03, 121.66, 121.74, 126.89, 136.17, 195.06 (CO).

MS: m/z (RI%): 213 $[\text{M}]^+$ (5), 185 $[\text{M}-\text{N}_2]^+$ (37), 156 $[\text{M}-\text{N}_2-\text{CO}]^+$ (29), 143 $[\text{M}-\text{COCHN}_2]^+$ (27), 130 $[\text{M}-\text{CH}_2\text{COCHN}_2]^+$ (100), 115 $[\text{M}-\text{CH}_2\text{CH}_2\text{COCHN}_2]^+$ (9).

HRMS: For $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}$ calculated 213.09021, observed 213.08976

$\text{Rh}_2(\text{OAc})_4$ Catalyzed Decomposition of 1-Diazo-4(-3-indolyl)-2-butanone (217):

1-Diazo-4(-3-indolyl)-2-butanone (**217**) (0.1 g, 0.47 mmol) was dissolved in dry dichloromethane (30 ml) under an argon atmosphere and treated with rhodium



(II) acetate (~ 10 mg). The reaction was stirred at room temperature for three hours at which time the solvent was removed by evaporation under a reduced pressure. The product was purified by chromatography on silica gel using ethyl acetate : hexane 1 : 2 . 1,3,4,9-tetrahydro-2H-carbazol-2-one (**219**) was isolated in 75% yield (65.2 mg, 0.35mmol). The product showed:

TLC: R_f = 0.48 (ethyl acetate : hexane, 1:1)

^1H NMR: (CDCl_3 , 300 MHz): δ 2.76 (2H, t, J = 7 Hz, CH_2), 3.08 (2H, t, J = 7 Hz, CH_2), 3.61 (2H, s, CH_2), 7.15 (2H, m, ArH), 7.30 (1H, d, J = 8 Hz, ArH), 7.49 (1H, d, J = 8 Hz, ArH), 7.86 (1H, br, N-H).

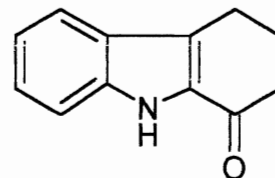
^{13}C NMR: (CDCl_3 , 75 MHz): δ 20.15 (CH_2), 38.81 (CH_2), 39.91 (CH_2), 109.92, 111.27, 118.51, 120.19, 122.36, 127.00, 130.46, 136.98, 208.79 (CO).

MS [EI]⁺: m/z (RI%): 185 [M]⁺ (93), 156 [M-CO]⁺ (38), 143 [M-CH₂CO]⁺ (100), 130 [M-C₂H₄CO]⁺ (14), 115 [M-C₃H₆CO]⁺ (11).

HRMS: For C₁₂H₁₁NO calculated 185.08406, observed 185.08418.

Synthesis of 2,3,4,9-tetrahydro-1H-carbazol-1-one (**224**):

Indol-3-butyric acid (**223**) (0.2 g, 0.98 mmol) was dissolved in dry tetrahydrofuran (20 ml) and the solution stirred under an argon atmosphere and cooled using an ice bath. Two drops of dry dimethylformamide were added followed by thionyl chloride (0.14 g, 1.18 mmol). The cooled reaction was stirred for one hour at which time the solvent was removed by evaporation under a reduced pressure. The product was recrystallized from dichloromethane/hexane to afford (0.17 g, 0.93 mmol, 95% yield) of **224**:



TLC: R_f = 0.48 (ethyl acetate : hexane, 1:2).

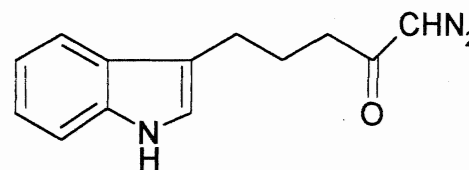
¹H NMR: (CDCl₃, 300 MHz): δ 2.24 (2H, m, CH₂), 2.68 (2H, t, *J* = 6 Hz, CH₂), 2.98 (2H, t, *J* = 6 Hz, CH₂), 7.13 (1H, m, ArH), 7.36 (1H, m, ArH), 7.49 (1H, d, *J* = 8 Hz, ArH), 7.64 (1H, d, *J* = 8 Hz, ArH), 9.96 (1H, br, N-H).

¹³C NMR: (CDCl₃, 75 MHz): δ 21.29, (CH₂), 24.89 (CH₂), 38.17 (CH₂), 112.75, 120.13, 121.15, 125.64, 126.86, 129.62, 131.12, 138.16, 191.70 (CO).

MS: m/z (RI%): 185 [M]⁺ (100), 156 [M-CO]⁺ (25), 143 [M-CH₂CO]⁺ (24), 129 [M-C₂H₄CO]⁺ (72), 115 [M-C₄H₆O]⁺ (5).

HRMS: For C₁₂H₁₁NO calculated 185.08406, observed 185.08385.

Synthesis of 1-Diazo-(3-indolyl)-2-pentanone (225):



A solution of indole-3-butyric acid (**222**) (0.4 g, 1.96 mmol) and two drops of dry dimethylformamide in dry tetrahydrofuran (50 ml) were cooled (ice bath) and stirred under an argon atmosphere. Thionyl chloride (0.28 g, 2.36 mmol) was added and the reaction mixture was stirred for one hour. The solution was slowly transferred to cooled ethereal solution of diazomethane (50 ml, 6 mmol) and allowed to react for two hours. The solvent was removed by evaporation under a reduced pressure and the resultant residue was purified by column chromatography on silica gel using ethyl acetate : hexane (1:2) as the eluent. The product (0.29 g, 1.3 mmol, 65% yield) was a yellow solid:

TLC: R_f = 0.51 (ethyl acetate : hexane, 1:1).

^1H NMR: (CDCl_3 , 300 MHz): δ 1.96 (2H, m, CH_2), 2.32 (2H, br t, CH_2), 2.73 (2H, t, J = 7 Hz, CH_2), 6.92 (1H, s, ArH), 7.08 (2H, m, ArH), 7.30 (1H, d, J = 8 Hz, ArH), 7.52 (1H, d, J = 8 Hz, ArH), 8.71 (1H, br, N-H).

^{13}C NMR: (CDCl_3 , 75 MHz): δ 24.88 (CH_2), 25.95 (CH_2), 40.88 (CH_2), 54.78 (CHN_2), 111.75, 115.46, 119.11, 119.33, 122.06, 122.28, 127.75, 136.78, 195.81 (CO).

MS: m/z (RI%): 227 [M] $^+$ (6), 199 [$\text{M}-\text{N}_2$] $^+$ (19), 170 [$\text{M}-\text{N}_2-\text{H}-\text{CO}$] $^+$ (25), 156 [$\text{M}-\text{COCH}_2\text{N}_2$] $^+$ (8), 143 [$\text{M}-\text{C}_3\text{H}_4\text{N}_2\text{O}$] $^+$ (100), 130 [$\text{M}-\text{C}_2\text{H}_4\text{COCHN}_2$] $^+$ (74), 115 [$\text{M}-\text{C}_3\text{H}_7\text{N}_2\text{O}$] $^+$ (13).

HRMS: For $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}$ calculated 227.10586, observed 227.10730.

APPENDIX I

Table 1. Crystal data and structure refinement for csf84s.

Identification code	csf84s	
Empirical formula	C ₁₂ H ₁₁ N ₁ O ₁	
Formula weight	185.22	
Temperature	200(1) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 10.247(3) Å	α = 90°.
	b = 5.8100(18) Å	β = 97.49(3)°.
	c = 15.877(3) Å	γ = 90°.
Volume	937.2(4) Å ³	
Z	4	
Density (calculated)	1.313 Mg/m ³	
Absorption coefficient	0.084 mm ⁻¹	
F(000)	392	
Crystal size	0.20 x 0.30 x 0.60 mm ³	
Theta range for data collection	2.24 to 26.37°.	
Index ranges	-12 ≤ h ≤ 12, -6 ≤ k ≤ 7, -19 ≤ l ≤ 19	
Reflections collected	8897	
Independent reflections	1919 [R(int) = 0.0303]	
Completeness to theta = 26.37°	99.8 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	1919 / 0 / 127	
Goodness-of-fit on F ²	1.050	
Final R indices [I > 2σ(I)]	R1 = 0.0546, wR2 = 0.1586	
R indices (all data)	R1 = 0.0641, wR2 = 0.1651	
Largest diff. peak and hole	0.783 and -0.433 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for csf84s. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	3524(1)	1481(3)	519(1)	51(1)
N(1)	4673(1)	2255(3)	-1048(1)	39(1)
C(1)	4400(2)	6777(4)	-2591(1)	45(1)
C(2)	5319(2)	6163(4)	-3106(1)	51(1)
C(3)	6060(2)	4141(4)	-2967(1)	46(1)
C(4)	5904(2)	2681(4)	-2304(1)	41(1)
C(5)	4985(2)	3318(3)	-1763(1)	34(1)
C(6)	3735(2)	3578(3)	-725(1)	33(1)
C(7)	3188(2)	3108(3)	52(1)	36(1)
C(8)	2190(2)	4863(4)	263(1)	46(1)
C(9)	1516(2)	6213(4)	-477(2)	56(1)
C(10)	2420(2)	7205(4)	-1058(1)	45(1)
C(11)	3420(2)	5464(3)	-1233(1)	34(1)
C(12)	4228(2)	5350(3)	-1898(1)	34(1)

Table 3. Bond lengths [Å] and angles [°] for csf84s.

O(1)-C(7)	1.224(2)
N(1)-C(5)	1.366(2)
N(1)-C(6)	1.381(2)
C(1)-C(2)	1.372(3)
C(1)-C(12)	1.406(3)
C(2)-C(3)	1.401(3)
C(3)-C(4)	1.378(3)
C(4)-C(5)	1.404(2)
C(5)-C(12)	1.413(3)
C(6)-C(11)	1.374(3)
C(6)-C(7)	1.445(2)
C(7)-C(8)	1.512(3)
C(8)-C(9)	1.503(3)
C(9)-C(10)	1.505(3)
1(0)-C(11)	1.492(3)
C(11)-C(12)	1.426(2)
N(1)-H(1A)	0.8800
C(1)-H(1B)	0.9500
C(2)-H(2A)	0.9500
C(3)-H(3A)	0.9500
C(4)-H(4A)	0.9500
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
CC10-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(5)-N(1)-C(6)	107.89(15)
C(2)-C(1)-C(12)	118.6(2)
C(1)-C(2)-C(3)	121.6(2)
C(4)-C(3)-C(2)	121.48(18)
C(3)-C(4)-C(5)	117.28(19)
N(1)-C(5)-C(4)	129.53(18)

N(1)-C(5)-C(12)	108.70(15)
C(4)-C(5)-C(12)	121.75(17)
C(11)-C(6)-N(1)	110.26(15)
C(11)-C(6)-C(7)	124.35(17)
N(1)-C(6)-C(7)	125.36(16)
O(1)-C(7)-C(6)	123.62(17)
O(1)-C(7)-C(8)	122.11(17)
C(6)-C(7)-C(8)	114.23(16)
C(9)-C(8)-C(7)	115.70(17)
C(10)-C(9)-C(8)	114.97(18)
C(11)-C(10)-C(9)	110.31(17)
C(6)-C(11)-C(12)	106.48(15)
C(6)-C(11)-C(10)	123.07(16)
C(12)-C(11)-C(10)	130.45(16)
C(1)-C(12)-C(5)	119.27(17)
C(1)-C(12)-C(11)	134.09(17)
C(5)-C(12)-C(11)	106.64(15)
C(5)-N(1)-H(1A)	126.1
C(6)-N(1)-H(1A)	126.1
C(2)-C(1)-H(1B)	120.7
C(12)-C(1)-H(1B)	120.7
C(1)-C(2)-H(2A)	119.2
C(3)-C(2)-H(2A)	119.2
C(4)-C(3)-H(3A)	119.3
C(2)-C(3)-H(3A)	119.3
C(3)-C(4)-H(4A)	121.4
C(5)-C(4)-H(4A)	121.4
C(9)-C(8)-H(8A)	108.4
C(7)-C(8)-H(8A)	108.4
C(9)-C(8)-H(8B)	108.4
C(7)-C(8)-H(8B)	108.4
H(8A)-C(8)-H(8B)	107.4
C(10)-C(9)-H(9A)	108.5
C(8)-C(9)-H(9A)	108.5
C(10)-C(9)-H(9B)	108.5
C(8)-C(9)-H(9B)	108.5

H(9A)-C(9)-H(9B)	107.5
C(11)-C(10)-H(10A)	109.6
C(9)-C(10)-H(10A)	109.6
C(11)-C(10)-H(10B)	109.6
C(9)-C(10)-H(10B)	109.6
H(10A)-C(10)-H(10B)	108.1

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for csf84s. 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}
O(1)	52(1)	62(1)	40(1)	17(1)	14(1)	14(1)
N(1)	34(1)	46(1)	38(1)	9(1)	10(1)	9(1)
C(1)	55(1)	42(1)	42(1)	6(1)	16(1)	-2(1)
C(2)	61(1)	51(1)	44(1)	2(1)	22(1)	-10(1)
C(3)	41(1)	56(1)	42(1)	-11(1)	17(1)	-13(1)
C(4)	32(1)	50(1)	43(1)	-5(1)	10(1)	-1(1)
C(5)	28(1)	42(1)	32(1)	-1(1)	5(1)	-4(1)
C(6)	28(1)	40(1)	32(1)	0(1)	4(1)	1(1)
C(7)	31(1)	46(1)	32(1)	2(1)	4(1)	-1(1)
C(8)	43(1)	59(1)	38(1)	2(1)	15(1)	8(1)
C(9)	54(1)	60(1)	59(1)	9(1)	24(1)	17(1)
C(10)	52(1)	41(1)	45(1)	3(1)	16(1)	9(1)
C(11)	33(1)	36(1)	33(1)	-1(1)	5(1)	-3(1)
C(12)	34(1)	35(1)	33(1)	-1(1)	6(1)	-4(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$) for csf84s.

	x	y	z	U(eq)
H(1A)	5011	958	-832	46
H(1B)	3891	8136	-2700	54
H(2A)	5455	7134	-3568	61
H(3A)	6683	3767	-3339	55
H(4A)	6399	1299	-2215	49
H(8A)	1509	4056	539	55
H(8B)	2639	5960	682	55
H(9A)	871	5196	-814	67
H(9B)	1019	7489	-255	67
H(10A)	1900	7686	-1599	54
H(10B)	2869	8582	-791	54

Table 6. Torsion angles [°] for csf84s.

C(12)-C(1)-C(2)-C(3)	1.4(3)
C(1)-C(2)-C(3)-C(4)	-0.4(3)
C(2)-C(3)-C(4)-C(5)	-0.9(3)
C(6)-N(1)-C(5)-C(4)	178.30(17)
C(6)-N(1)-C(5)-C(12)	-0.17(19)
C(3)-C(4)-C(5)-N(1)	-177.20(18)
C(3)-C(4)-C(5)-C(12)	1.1(3)
C(5)-N(1)-C(6)-C(11)	1.1(2)
C(5)-N(1)-C(6)-C(7)	-176.98(16)
C(11)-C(6)-C(7)-O(1)	-176.34(17)
N(1)-C(6)-C(7)-O(1)	1.4(3)
C(11)-C(6)-C(7)-C(8)	1.3(3)
N(1)-C(6)-C(7)-C(8)	179.11(17)
O(1)-C(7)-C(8)-C(9)	-158.7(2)
C(6)-C(7)-C(8)-C(9)	23.6(3)
C(7)-C(8)-C(9)-C(10)	-47.8(3)
C(8)-C(9)-C(10)-C(11)	44.0(3)
N(1)-C(6)-C(11)-C(12)	-1.52(19)
C(7)-C(6)-C(11)-C(12)	176.55(16)
N(1)-C(6)-C(11)-C(10)	179.05(17)
C(7)-C(6)-C(11)-C(10)	-2.9(3)
C(9)-C(10)-C(11)-C(6)	-19.9(3)
C(9)-C(10)-C(11)-C(12)	160.9(2)
C(2)-C(1)-C(12)-C(5)	-1.1(3)
C(2)-C(1)-C(12)-C(11)	177.9(2)
N(1)-C(5)-C(12)-C(1)	178.51(16)
C(4)-C(5)-C(12)-C(1)	-0.1(3)
N(1)-C(5)-C(12)-C(11)	-0.75(19)
C(4)-C(5)-C(12)-C(11)	-179.37(16)
C(6)-C(11)-C(12)-C(1)	-177.7(2)
C(10)-C(11)-C(12)-C(1)	1.6(3)
C(6)-C(11)-C(12)-C(5)	1.38(18)
C(10)-C(11)-C(12)-C(5)	-179.26(18)

Table 7. Hydrogen bonds for csf84s [\AA and $^\circ$].

D-H...A	d(D-H)	d(H...A)	d(D...A)	$\angle(\text{DHA})$
N(1)-H(1A)...O(1)#1	0.88	2.08	2.903(2)	155.9

Symmetry transformations used to generate equivalent atoms:

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

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