# ADVANCES IN NITROGEN HETEROCYCLES

*Editor:* CHRISTOPHER J. MOODY

*Volume 3* • 1998

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# PREFACE

Heterocyclic molecules account for over half of all known organic compounds. A large proportion of these heterocyclic compounds contain nitrogen; indeed many classes of important natural products, as well as a majority of synthetic drugs, dyes, etc. are based on nitrogen heterocycles. *Advances in Nitrogen Heterocycles* reflects the importance of this area, by providing up-to-date accounts of key research.

Volume 3 of the Series contains articles on a range of topics in heterocyclic chemistry. Harman and Hodges describe their work on the activation and manipulation of pyrroles by the formation of osmium(II) complexes. Edstrom addresses the synthesis of annelated pyrroles using acylation reactions, and Black discusses his work on the applications of iminium ion chemistry in the functionalization of activated indoles. Padwa and Beall discuss their work on nitrogen ylide cyclizations in the synthesis of a range of heterocycles, and finally Wood and Fryer describe work on the synthesis of kainoids, a family of highly biologically active nitrogen heterocycles.

We hope that these accounts from acknowledged experts will provide the reader with an interesting and informative look at an important area of organic chemistry.

Christopher J. Moody
*Series Editor*

# THE ACTIVATION AND MANIPULATION OF PYRROLES BY PENTAAMMINEOSMIUM(II)

L. Mark Hodges and W. Dean Harman



**Advances in Nitrogen Heterocycles**
**Volume 3, pages 1–44.**

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## ABSTRACT

In contrast to $\eta^1$- and $\eta^5$-pyrrole complexes, which generally react either at the nitrogen or at the α-positions, $\eta^2$-coordination of pyrrole by osmium(II)pentaammine activates the pyrrole ring toward regioselective protonation and electrophilic addition at the β-position. Depending on the reaction conditions, the resulting products are either 1*H*-pyrrole or 3*H*-pyrrolium complexes, the latter of which are several orders of magnitude less acidic than their uncomplexed counterparts and resist rearomatization. $\eta^2$-Pyrrole complexes also undergo a dipolarcycloaddition reaction with certain electrophiles to generate a wide variety of 7-azanorbornene complexes. In most cases, the metal can be removed from the products by oxidation or heating to generate functionalized pyrroles, azanorbornanes, or pyrrolizinines.

A series of β-vinylpyrrole complexes can be synthesized via initial electrophilic addition to the pyrrole ring. These vinylpyrrole complexes readily undergo a Diels–Alder cycloaddition reaction with electron-deficient olefins to give functionalized 5,6,7,7a-tetrahydroindole complexes. These complexes, which are stable to isomerization, can be decomplexed and oxidized with DDQ to generate highly substituted indoles in moderate to good yields.

## I. INTRODUCTION

The pyrrole nucleus is an integral part of many natural products, being found in chlorophylls, bile pigments, porphyrins, antibiotics, and polymer systems. Given that all of the carbons in the pyrrole ring are unsaturated, pyrroles represent valuable synthetic precursors to other aromatic heterocycles, cyclic alkaloids, and other biologically active compounds. Unfortunately, the synthetic utility of pyrroles is severely limited by its aromaticity. For example, pyrroles tend to undergo addition and substitution at the α-positions instead of the more biologically relevant β-positions, as well as polymerization in the presence of electrophiles.[1] Indeed, most pyrroles are synthesized from ring closure of appropriately substituted acyclic precursors. Common examples include the Knorr and Paal–Knorr pyrrole syntheses.[1,2] Three primary methods are available to synthesize β-substituted pyrroles from a pyrrolic precursor:[3] (a) placement of a removable electron-withdrawing group at the α-position, which directs electrophilic addition to the β-position on the

opposite side of the ring; (b) isomerization of an α-substituted pyrrole to the corresponding β-substituted isomer; and (c) placement of a bulky substituent on the nitrogen to direct electrophilic addition away from the α-position.

Pyrrole has also been utilized to some extent as a diene in Diels–Alder reactions to give functionalized 7-azabicylo[2.2.1]heptenes and 7-azabicyclo[2.2.1]heptadienes.[4] While the synthetic utility of this reaction is limited by the aromatic stability of the pyrrole ring, the use of Lewis acids, electron-withdrawing groups on the pyrrole, alkyne dienophiles, and high pressures have allowed pyrroles to be employed in the synthesis of several azanorbornane targets.[4]

Activation of the pyrrole ring toward regioselective and chemoselective functionalization can be achieved by coordination of the heterocycle to a transition metal. Depending on such factors as the electronic nature of the metal center and the type of binding, the reactivity of pyrroles can be drastically altered. While $\eta^5$-pyrrole complexes are generally unstable, $\eta^5$-pyrrolyl complexes are more robust, especially when electron-donating or alkyl groups are present.[5] These complexes typically undergo *N*-protonation or alkylation as a result of the high electron density present on the nitrogen. When the metal center is electron deficient, however, nucleophilic attack can be achieved at the α-position of the pyrrole ring. As reported by Zakrzewski, iodination of the $Re^{III}(PPh_3)_2(H)_2(\eta^5$-pyrrolyl) complex **1** followed by addition of an alkyllithium results in alkylation of the pyrrole at C-2 to give **3** (Figure 1).[5] Recently, DuBois and co-workers have reported complexes of the formula $Ru^{II}(PPh_3)_2(X)(\eta^5$-pyrrolyl) (**4**), which undergo nucleophilic attack at C-2 with a wider selection of nucleophiles including alkyllithiums, amides, certain Grignard reagents, and the lithium salt of propionitrile (Figure 1).[6] Alkylation or protonation of these adducts (**5**) results in the formation of $\eta^5$-pyrrole complexes, which are easily decomplexed to produce the free pyrroles. In a separate report, nucleophilic attack of an osmium(II) $\eta^5$-pentamethylpyrrole complex with either hydride or methoxide ion gives a dearomatized $\eta^4$-complex.[7]

Gladysz has reported a protonation study of the chiral *N*-bound rhenium $(Cp)(NO)(PPh_3)(\eta^1$-pyrrolyl) complex **6** (Figure 2).[8] Protonation of **6** with either triflic acid or $HBF_4 \bullet Et_2O$ initially gives the metal-stabilized *N*-bound 2*H*-pyrrolium complex **9**, which isomerizes to give the carbon-bound 2*H*-pyrrolium complex **10**. Electrophilic addition on the pyrrole ring of **6** can be achieved, but with varying regioselectivity. Acylation with trifluoroacetic anhydride occurs exclusively at C-3 to

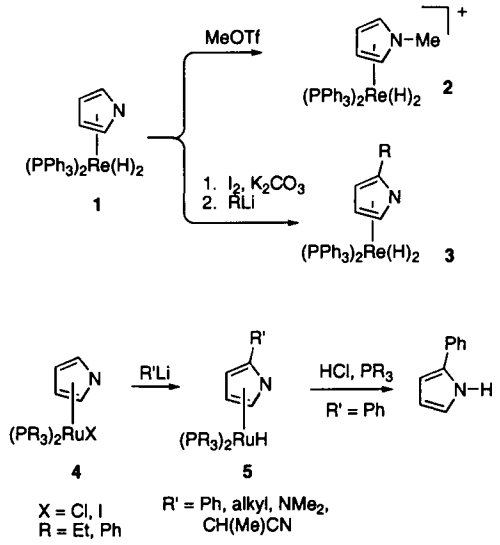



***Figure 1.*** Reactivity of $\eta^5$-pyrrolyl complexes.

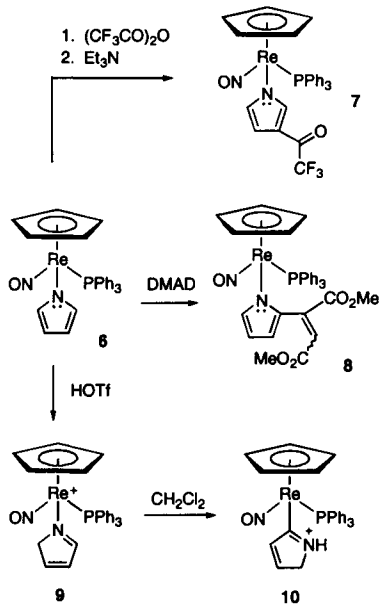



***Figure 2.*** Reactivity of $\eta^1$-pyrrolyl complexes.

give **7**, while Michael addition with DMAD occurs at C-2 to produce complex **8** (Figure 2).

When the pyrrolyl ligand is coordinated by a sterically bulky metal center, electrophilic addition can be directed to the β-position. Highly regioselective acylation, bromination, and cyanation occur on the pyrrole ring of the $\eta^1$-pyrrolyl-tungsten imido complex **11** to give the β-substituted pyrrolyl complexes **12–14** (Figure 3).[9] In the case of cyanation, β-selectivity exceeds that observed for the analogous reaction with TIPS-pyrrole, where the α-substituted isomer is heavily favored.[3] The pyrrole ligands are released from the metal via reduction with lithium aluminum hydride. Because this often results in concomitant reduction of the functional groups on the pyrrole, the overall synthetic applicability of this system is limited.

Although the reactivity of transition metal $\eta^5$- and $\eta^1$-pyrrole and pyrrolyl complexes is altered from that observed for the uncomplexed pyrrole (i.e., nucleophilic attack to **1**), it is generally limited to either the nitrogen or α-positions, and at present is demonstrated only for a few elementary transformations. A more synthetically versatile binding mode of a pyrrole is $\eta^2$-coordination. This interaction serves to *dearomatize* the ring, thus significantly altering the reactivity of the heterocycle (Figure 4).[10–14] Coordination of the metal across the C-4–C-5 double bond (**15**) renders the uncoordinated portion of the pyrrole ring an enamine, allowing it to undergo regioselective protonation or electrophilic addition at the β-position, C-3. Once formed, the 3*H*-pyrrolium

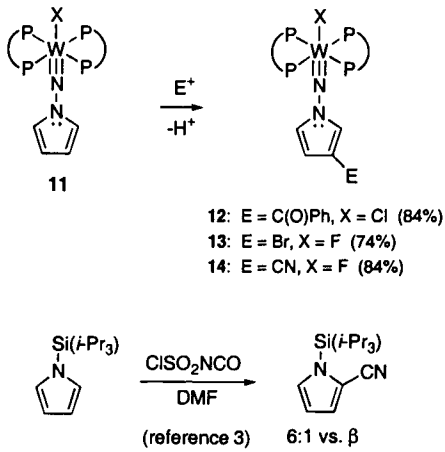



***Figure 3.*** Electrophilic additions to an $\eta^1$-pyrrolyl imido complex.

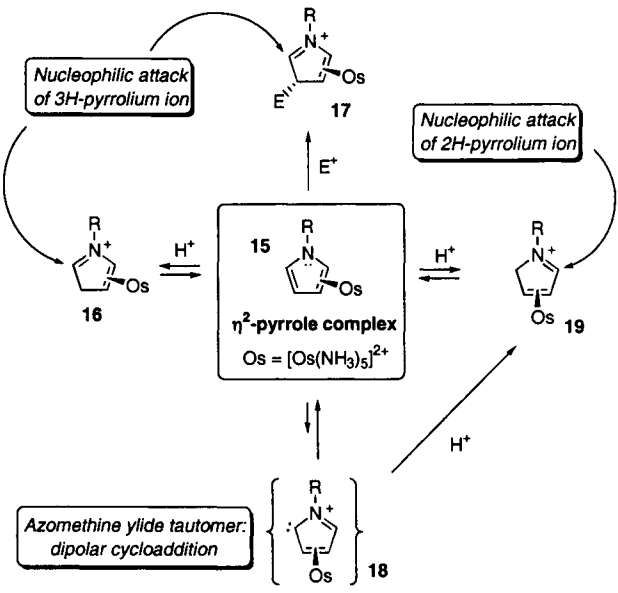


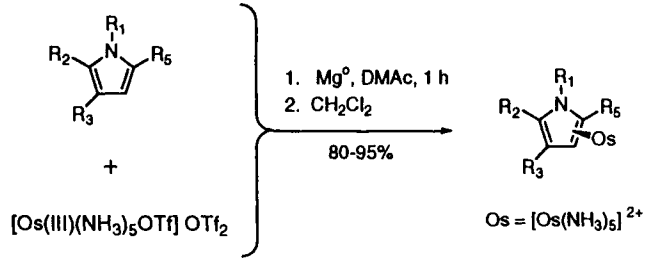

***Figure 4.*** Reactivity modes of $\eta^2$-pyrrole complexes.

species (**16**, **17**) are resistant toward rearomatization because of metal coordination. Isomerization of the metal to the opposite double bond involves formation of an intermediate azomethine ylide complex (**18**, Figure 4), which is susceptible to either a 1,3-dipolarcycloaddition reaction or protonation to give a 2*H*-pyrrolium complex (**19**). Not only does the metal serve to dearomatize the pyrrole ring, it also stabilizes the resulting pyrrolium cations, allowing further transformations to be carried out.

Coordination of pyrrole in this fashion was first observed by Cordone, Harman, and Taube in 1989 using pentaammineosmium(II), which to date remains the only metal center known to exhibit this type of binding with pyrrole.[10,15] Since this initial discovery, a thorough study of the synthesis and reactivity of $\eta^2$-coordinated pyrroles has been carried out, addressing all of the reactivity modes just described. This effort has led directly to the discovery of several classes of functionalized pyrrole and pyrrolium complexes, many of which have been elaborated into more complex and biologically relevant molecules, including the pyrrolizinone, indole, and azanorbornane ring systems. This review summarizes the results of these studies.

## II. SYNTHESIS AND REACTIVITY OF $\eta^2$-PYRROLE COMPLEXES

Complexes of the form $[Os(NH_3)_5(4,5\text{-}\eta^2\text{-pyrrole})](OTf)_2$[16] (**20–26**) are synthesized from various pyrroles in ≥ 80% yield by reducing the air-stable precursor $[Os(NH_3)_5(OTf)](OTf)_2$ in the presence of ~10 equiv of the pyrrole ligand either in DMAc solution or in a cosolvent mixture of DMAc and DME (Figure 5).[10–12,14] These complexes, which are isolated as light yellow or tan powders, are characterized by $^1H$ and $^{13}C$ NMR data as well as by cyclic voltammetry. While stable in DMAc/DME solvent mixtures, the pyrrole complexes will slowly undergo irreversible substitution with solvents such as acetonitrile or acetone at room temperature ($t_{1/2}$ = hours), but rapidly at 50 °C ($t_{1/2}$ = minutes, Table 1). Crystallographic data for the 2,5-dimethylpyrrole complex **22** shows lengthening of the C-3–C-4 double bond and shortening of the C-2–C-3 double bond relative to the free ligand, indicative of dearomatization of the pyrrole ring (Figure 5).[11]




| Ligand | Pdt | Ref |
|---|---|---|
| pyrrole | **20** | 10 |
| 1-methylpyrrole | **21** | 11 |
| 2,5-dimethylpyrrole | **22** | 11 |
| 1,2,5-trimethylpyrrole | **23** | 11 |
| 2-ethylpyrrole | **24** | 11 |
| 3-methylpyrrole | **25a** | 12 |
| 1-(trimethylsilyl)pyrrole | **26** | 14 |

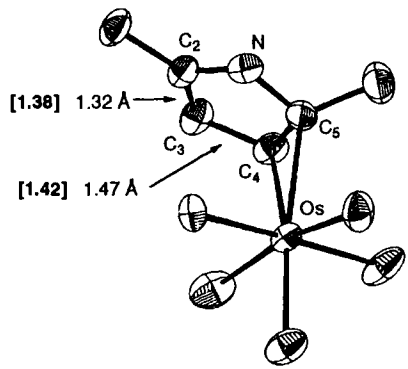
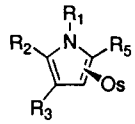



***Figure 5.*** Synthesis of $\eta^2$-pyrrole complexes and ORTEP drawing of $[Os(NH_3)_5(4,5\text{-}\eta^2\text{-2,5-dimethylpyrrole})](OTf)_2$ (**22**).

***Table 1.*** Yields and Substitution Half-Lives for $\eta^2$-Pyrrole Complexes **20–26**

| | *Complex* | $R_1$ | $R_2$ | $R_3$ | $R_5$ | *Yield* | $t_{1/2}$ *(min)*[a] |
|---|---|---|---|---|---|---|---|
|  | **20** | H | H | H | H | 85 | 227 |
| | **21** | Me | H | H | H | 95 | 153 |
| | **22** | H | Me | H | Me | 95 | 14 |
| | **23** | Me | Me | H | Me | 94 | 3 |
| | **24** | H | Et | H | H | 83 | [b] |
| | **25a** | H | H | Me | H | 92 | 220 |
| | **26** | TMS | H | H | H | 80 | 300 |

*Notes*: [a]Measured in $CD_3CN$ solution at 50 °C.

[b]Compound **24** gradually decomposes to an intractable mixture with no formation of the acetonitrile complex.

For all of the pyrrole complexes studied, the metal is bound predominately across C-4–C-5.[16] Isomerization of the metal to the 2,3-position occurs rapidly at room temperature for symmetric pyrrole complexes, and involves the formation of an intermediate azomethine ylide isomer in which the metal is bound across C-3–C-4. The rate of this isomerization depends strongly on the substituents on the pyrrole ring. For example, for the 1-methylpyrrole complex **21**, the specific rate of isomerization is approximately 100 $s^{-1}$ at 20 °C (see Table 5).[14] In the case of the 2,5-dimethylpyrrole complex **22**, the steric interaction between the methyl substituents and the metal destabilizes the 4,5- and 2,3-isomers, and the isomerization rate is increased ($k > 300$ $s^{-1}$).

## A. Protonation and Isomerization

### *Unsubstituted and α-Substituted Pyrrole Complexes*

Coordination of pentaammineosmium(II) across C-4 and C-5 of the pyrrole ring renders the remaining portion of the ring chemically similar to an enamine, now susceptible to regioselective and stereoselective protonation or other electrophilic addition at the β-carbon, C-3.[11–13] When treated with one equivalent of triflic acid (HOTf), the $\eta^2$-pyrrole complexes **20–24** undergo regioselective protonation at the β-position (C-3) on the ring face opposite the metal to give the corresponding 3*H*-pyrrolium isomers **27–31** (Figure 6).[11] These 3*H*-pyrrolium complexes are at least 10 orders of magnitude *less* acidic than their uncomplexed counterparts, making them stable enough to be isolated and stored

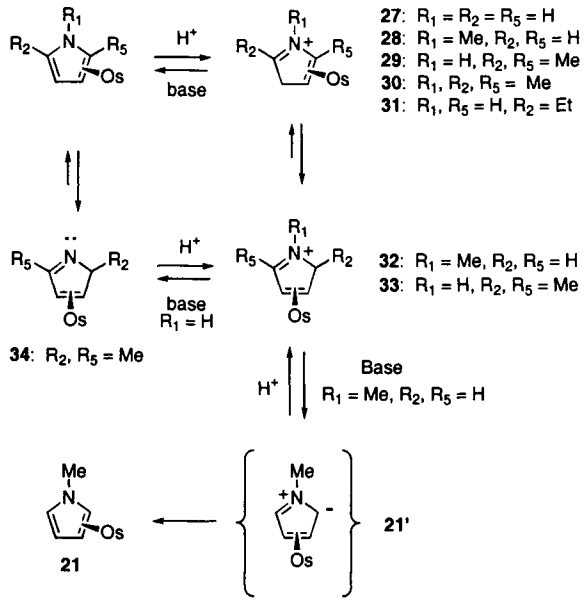



***Figure 6.*** Protonation and isomerization of $\eta^2$-pyrrole complexes.

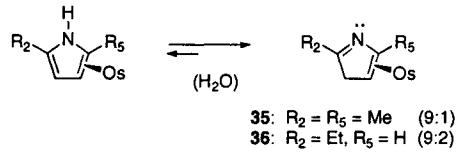
as solids for extended periods of time (Table 2). When the 1-methyl- and 2,5-dimethyl-3*H*-pyrrolium complexes (**28**, **29**) are treated with aniline in methanol solution, isomerization to the thermodynamically preferred 2*H*-pyrrolium complexes occurs (**32**, **33**; Figure 6).[11] When treated with

***Table 2.*** pKa Values for Selected $\eta^2$-Pyrrole Complexes and Pyrrolium Ions[11]

| *Cpd* | *Ligand* | *pKa* |
|---|---|---|
| **27** | 3*H*-pyrrolium | 4.2 |
| **28** | 1-methyl-3*H*-pyrrolium | 5.6 |
| **29** | 2,5-dimethyl-3*H*-pyrrolium | 7.5[a] (6.6) |
| **32** | 1-methyl-2*H*-pyrrolium | >8.8[b] (7.8) |
| **33** | 2,5-dimethyl-2*H*-pyrrolium | 7.9 |
| 2*H*-pyrrolium ion | | –3.8 |
| 3*H*-pyrrolium ion | | –5.9 |
| 1*H*-pyrrolium ion | | –10 |
| 1-methyl-2*H*-pyrrolium ion | | –2.9 |
| 2,5-dimethyl-2*H*-pyrrolium ion | | –0.71 |

*Notes*: [a]Value adjusted for coupled isomerization in water.

[b]Value adjusted for coupled linkage isomerization. The pK of equilibrium product is shown in parentheses.




**35**: $R_2 = R_5 = Me$ (9:1)
**36**: $R_2 = Et$, $R_5 = H$ (9:2)

***Figure 7.*** Isomerization of 1*H*-$\eta^2$-pyrrole complexes to the corresponding 3*H*-isomers in water.

stronger bases such as Proton Sponge™ or *i*-$Pr_2EtN$, the 2,5-dimethyl derivative **33** deprotonates at nitrogen, giving the 2*H*-pyrrole complex **34**. Deprotonation of the 1-methyl derivative **32** cannot occur at nitrogen. As a result, deprotonation occurs at the α-carbon to give azomethine ylide intermediate **21′**, which quickly rearranges to the 1*H*-isomer **21**.

While the neutral 1*H*-isomer predominates in aprotic solvents for all complexes synthesized, the possibility for formation of the 2*H*- or 3*H*-pyrrole isomer exists when the nitrogen is unsubstituted. When the 2,5-dimethylpyrrole complex **22** is dissolved in water, the 3*H*-pyrrole isomer **35** is observed in a 9:1 ratio with the 1*H*-isomer (Figure 7). Similarly, the 2-ethylpyrrole complex **36** exists in a 9:2 ratio favoring the 3*H*-isomer in aqueous solution.

### *β-Substituted Pyrrole Complexes*

Pyrrole complexes that possess a single substituent at the β-position exist with the metal coordinated to the double bond on the opposite side of the ring. Thus, protonation at the substituted β-carbon (C-3) on the ring face opposite the metal forces any substituent at C-3 to be on the same ring face as the metal. As a result, this isomer is destabilized relative to the unsubstituted analogue. When protonation (HOTf) of the 3-methylpyrrole complex **25a** is carried out in $CD_3CN$ solution, four different pyrrolium isomers (**25b–d** and **25f**) are initially present (Figure 8).[12b] Isomer **25c** is the sterically congested *syn*-alkylated 3*H*-pyrrolium isomer where protonation has occurred on the ring face opposite the metal, thus forcing the C-3-methyl substituent to be on the same face of the pyrrole ring as metal coordination. Also formed is the transitory *N*-protonated isomer **25b**. Both products are unstable relative to other isomers, and isomerize to complexes **25d** and **25f**. Isomer **25d** is characterized as the 3-methyl-*2,3*-$\eta^2$-4*H*-pyrrolium complex, which arises from isomerism of the metal to the more hindered double bond followed by protonation at the nonsubstituted β-carbon. Complex **25f** is the more

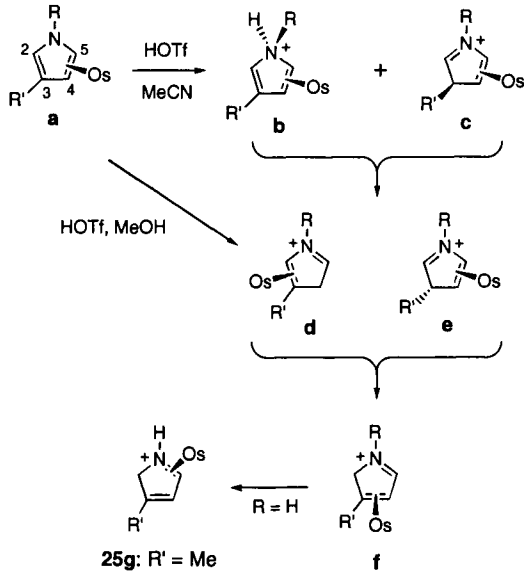



***Figure 8.*** Protonation and isomerization of β-substituted $\eta^2$-pyrrole complexes.

stable 2*H*-pyrrolium isomer, which is generated from isomerization of the metal to the 3,4-position followed by protonation of the resulting azomethine ylide. The C-3-epimer of **25c**, the *anti*-alkylated isomer **25e**, is formed only to a small extent, and its concentration does not change significantly over time. After longer time (30 h), a fifth isomer (**25g**) is formed. This material, produced directly from **25f**, is the product of a linkage isomerization in which the osmium shifts from *3,4*-$\eta^2$ to *1,5*-$\eta^2$ (Figure 8). This isomer is only observed for **25a**, when the nitrogen is unsubstituted. Protonation of the 1,3-dimethylpyrrole complex **37a** (*vide infra*) gives results similar to those for **25a** except that no 3,4- to 1,5-isomerization is observed.

Protonation of the 1-methyl-3-(3-oxobutyl)pyrrole complex **53a** (*vide infra*) initially gives the *syn*-alkylated adduct **53c** in high yield (Figure 9). In acidic acetonitrile solution, this product isomerizes over several hours to the more stable *anti* isomer **53e** with formation of a small amount of the corresponding 2*H*-isomer **53f**. Interestingly, when freshly prepared **53c** is isolated, then dissolved in neutral acetonitrile, the product rearranges to give the tetrahydrocyclopenta[*c*]pyrrolium adduct **53d** as a 5:2 ratio of diastereomers (Figure 9). Presumably, this product is

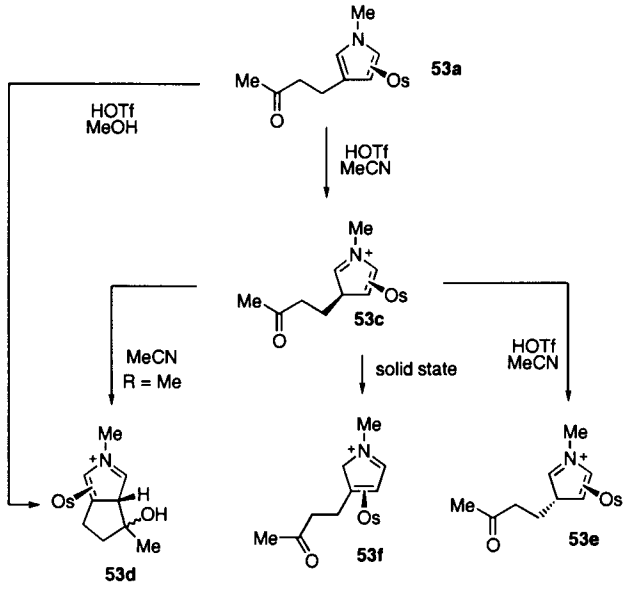



***Figure 9.*** Protonation and intramolecular aldol reaction of complex **53a**.

formed by initial deprotonation of **53c** at C-3 (pKa ~ 6) followed by isomerization of the metal. The proton then subsequently promotes an intramolecular aldol reaction to form **53d**. This compound can be formed directly by addition of a methanolic triflic acid solution to a methanol solution of **53a**.

## B. Electrophilic Additions

### *Acylation and Imination*

The 1-methylpyrrole complex **21** undergoes clean acylation at the β-position in the presence of $Ac_2O$/DMAP to give the 3-acetyl-1-methylpyrrole complex, **38** (Figure 10).[12b] Propionic anhydride reacts with **21** in a similar manner to form **39**. Under these reaction conditions, the parent pyrrole complex (**20**) undergoes exclusive *N*-acylation to give **40**, and the 2,5-dimethylpyrrole complex (**22**) gives a 7:3 ratio of *N*- to β-acylation.

Treatment of either the pyrrole (**20**) or 1-methylpyrrole (**21**) complex with methylacetonitrilium triflate gives the iminium-substituted 1*H*-pyrrole complexes **41** and **42**, respectively (Figure 10).[11b,12b] These complexes are surprisingly resistant to deprotonation with Proton Sponge™

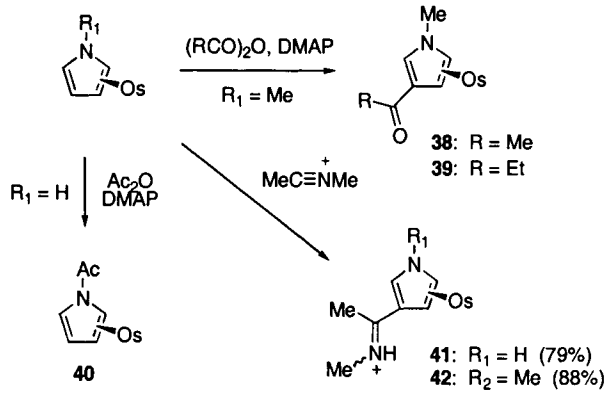



***Figure 10.*** Acylation of $\eta^2$-pyrrole complexes.

(pKa = 12.4), and to hydrolysis under either acidic or basic conditions. Reaction of the 2,5-dimethylpyrrole complex **22** under the same reaction conditions or at reduced temperature (−50 °C) gives a complex mixture of products. In contrast to the reactivity observed with acetic anhydride, electrophilic addition at the nitrogen does not occur to a significant degree with pyrrole complex **20**.

## *Aldol Reactions*

Aldol reactions at C-3, promoted by either Lewis or Brönsted acids, lead to several different $\eta^2$-pyrrole derivatives.[12b,13] Mukaiyama-type aldol reactions can be carried out with ketones and certain aldehydes using TBSOTf (Figure 11). Reaction of the pyrrole (**20**), 1-methylpyrrole (**21**), or 2,5-dimethylpyrrole (**22**) complex with excess acetone in the presence of TBSOTf produces the silylated 3*H*-pyrrolium aldol adducts **43–45** (Figure 11). Deprotonation of **45** with DBU occurs at nitrogen, producing the 3*H*-pyrrole complex **46**. However, addition of DBU to **44** results in elimination of TBSOH and the subsequent deprotonation of a methyl substituent to give the β-vinylpyrrole complex **47**. This transformation represents a general synthesis of β-vinylpyrrole complexes, which will be described later in this review. Reactions at the nitrogen can occur if the β-position away from metal coordination is substituted. Protonation of the 3-methylpyrrole complex **25a** in the presence of acetone results in formation of the 5-azafulvenium complex **48** (Figure 11).

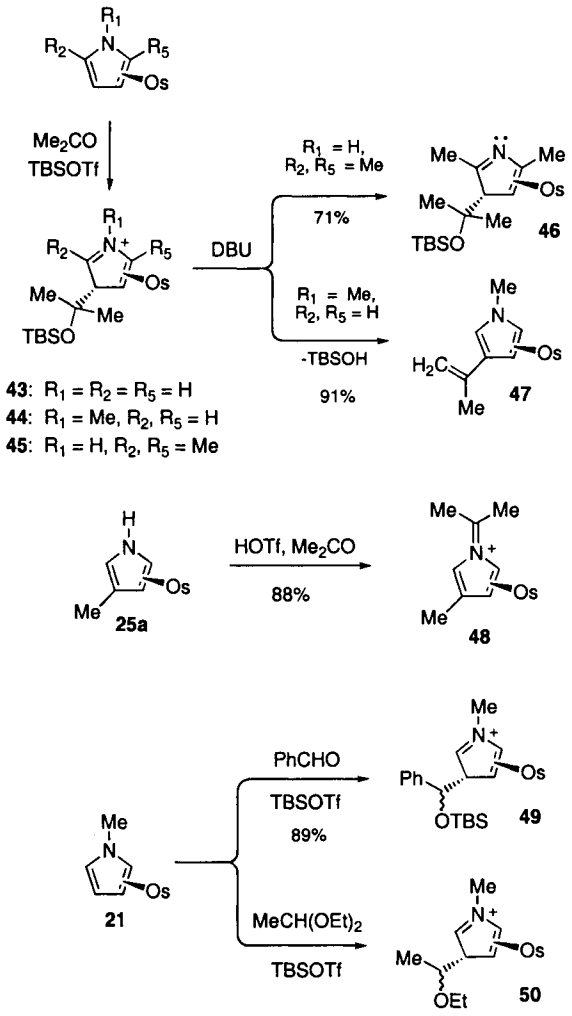



***Figure 11.*** Lewis Acid promoted aldol reactions of $\eta^2$-pyrrole complexes.

While aliphatic aldehydes fail to react cleanly, the reaction of **21** with benzaldehyde in the presence of 1 equiv of TBSOTf gives the TBS-substituted aldol adduct **49** as a 1:1 ratio of diastereomers. In addition to aldehydes and ketones, electrophilic additions can also be achieved with acetals (Figure 11). The reaction of **21** with acetaldehyde diethyl acetal promoted by TBSOTf gives 3*H*-pyrrolium complex **50** as a 1:1 ratio of diastereomers, a reaction that circumvents the poor results obtained with aliphatic aldehydes.

## *β-Alkylations and Michael Additions*

The alkylation of the 1-methylpyrrole complex **21** using methyl triflate in DME followed by base gives a 4:1 ratio of the 1,3-dimethylpyrrole (**37a**) and 1,1-dimethyl-1*H*-pyrrolium (**51**) complexes (Figure 12), which can be separated using ion-exchange chromatography.[11b] The analogous reaction with either the pyrrole (**20**) or 2,5-dimethylpyrrole (**22**) complex gives alkylation at the nitrogen rather than at the β-position to produce the 1-methyl-3*H*-pyrrolium (**28**) or 1,2,5-trimethyl-3*H*-pyrrolium (**30**) complexes, respectively.

Alkylation at the β-position can also be achieved through conjugate addition to Michael acceptors (Figure 12). Reaction of the 1-methylpyrrole complex **21** with 1 equiv of MVK in methanol gives the β-alkylated 1*H*-pyrrole species **53a** in 90% yield (Figure 12).[12] Similar results are obtained with acrolein to give **52**. Reaction of either the pyrrole (**20**) or ethylpyrrole (**24**) complex with 2 equiv of MVK gives the corresponding 1,3-dialkylated 1*H*-pyrrole complexes **54** and **55**. When only 1 equiv of MVK is used with **20**, a 1:1 ratio of **54** to starting material is isolated.

Electrophilic additions with activated alkynes also occur readily with $\eta^2$-pyrrole complexes.[12b,13b] In methanol solution, the pyrrole (**20**) and 1-methylpyrrole (**21**) complexes undergo conjugate addition cleanly at C-3 with 3-butyn-2-one to give the β-enone-substituted pyrrole complexes **56** and **58** in high yield (Figure 13). In contrast to what is observed

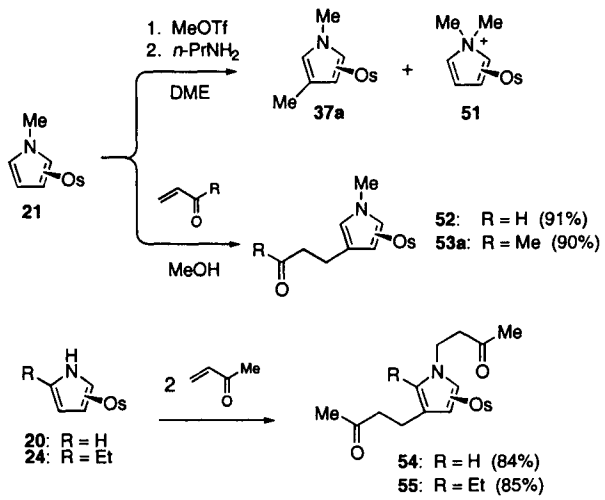



***Figure 12.*** Alkylation and Michael addition of $\eta^2$-pyrrole complexes.

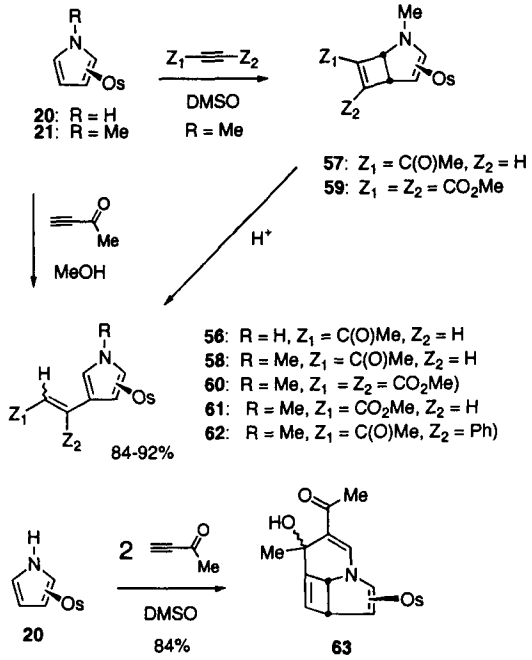
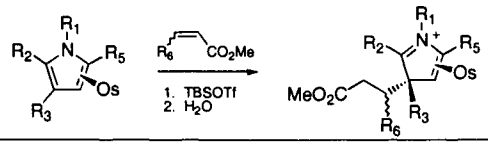



***Figure 13.*** Electrophilic addition of $\eta^2$-pyrrole complexes with activated alkynes.

with MVK, pyrrole complex **20** only undergoes monoaddition with 3-butyn-2-one, even in the presence of excess electrophile. Similarly, the reaction of **21** with methyl propiolate or 4-phenyl-3-butyn-2-one gives complexes **61** and **62**, respectively. In DMSO solution, 3-butyn-2-one reacts with **21** to generate the [3.2.0]azabicycloheptadiene **57**, resulting from a stepwise Michael–Mannich reaction sequence. Although **57** is stable in DMSO solution, addition of water results in a fast retro-Mannich reaction, generating **58** quantitatively. The reaction of the doubly activated DMAD with **21** in DMSO also generates the corresponding cyclobutene derivative **59**. While **59** is less sensitive to the retro-Mannich reaction than the acetyl derivative **57**, ring opening can be achieved in methanol ($t_{1/2} < 0.5$ h, 25 °C) to give **60** as one isomer (de > 95%). In contrast to what is observed in methanol, pyrrole complex **20** reacts with 3-butyn-2-one in DMSO with 1:2 stoichiometry to give the tricyclic indolizidine **63** shown in Figure 13.

In contrast to MVK or 3-butyn-2-one, the reaction of methyl acrylate with all of the pyrrole complexes studied requires activation of the

***Table 3.*** Lewis Acid Promoted Michael Reaction of $\eta^2$-Pyrrole Complexes




| *Starting Material* | $R_1$ | $R_2$ | $R_3$ | $R_5$ | $R_6$ | *Pdt* | *Yield* [a] |
|---|---|---|---|---|---|---|---|
| **20** | H | H | H | H | H | **64** | 45 |
| **21** | Me | H | H | H | H | **65** | 94 |
| **22** | H | Me | H | Me | H | **66** | 88 |
| **24** | H | Et | H | H | H | **67** | 66 |
| **25a** | H | H | Me | H | H | **68** | 60 |
| **21** | Me | H | H | H | Me | **69** | 71 |

*Note*: [a]Overall yield from the uncoordinated pyrrole.

electrophile with a suitable Lewis acid. Reaction of the pyrrole (**20**), 1-methylpyrrole (**21**), or 2,5-dimethylpyrrole (**22**) complex with methyl acrylate in the presence of TBSOTf gives the β-alkylated, 3*H*-pyrrolium adducts **64–66**, respectively, after hydrolysis (Table 3).[12] The presence of a substituent at C-2 or C-3 of the pyrrole ring or on the double bond of the electrophile appears to have little effect on this reaction. Reaction of the 2-ethylpyrrole (**24**) or 3-methylpyrrole (**25a**) complex gives a single product with alkylation occurring on the more hindered side of the ring to give the 2,3-disubstituted 3*H*-pyrrolium adducts **67** and **68**. The reaction of **21** with methyl crotonate gives the expected conjugate addition product **69** as a 4:1 ratio of diastereomers.[12]

## C. Nucleophilic Addition to Pyrrolium Complexes

### *Hydride Addition*

Both 2*H*- and 3*H*-pyrrolium isomers are moderately susceptible to nucleophilic addition at the iminium carbon. Their reactivity, however, is greatly reduced by π-backbonding effects of the metal to the point that they resist hydrolysis, even in aqueous solution. Dihapto-coordinated 2- and 3-pyrroline complexes can be synthesized in good yields by reduction of 3*H*- and 2*H*-pyrrolium complexes, respectively (Figure 14).[12b] Hydride reduction of the 3*H*-pyrrolium isomers of 1-methylpyrrole (**28**),

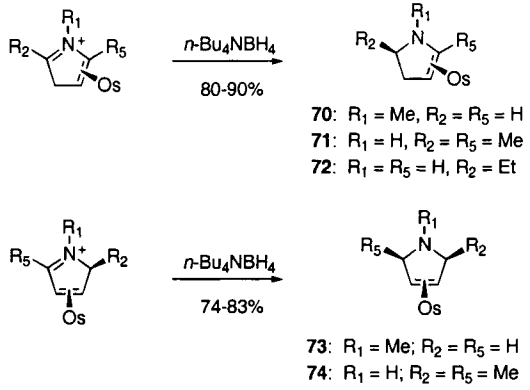



***Figure 14.*** Hydride reduction of 3*H*- and 2*H*-pyrrolium complexes.

2,5-dimethylpyrrole (**29**), or 2-ethylpyrrole (**31**) can be accomplished with $n$-$Bu_4NBH_4$ to give the corresponding 2-pyrroline complexes **70–72** (Figure 14). The reaction of the 2*H*-pyrrolium complexes **31** and **32** gives the corresponding 3-pyrroline complexes **73** and **74**. In all cases, both protonation and hydride addition occur on the ring face opposite metal coordination.

## *Carbon Nucleophiles*

Intermolecular addition of carbon nucleophiles to the $\eta^2$-pyrrolium complexes has shown limited success because of the decreased reactivity of the iminium moiety coupled with the acidity (pKa ~ 18–20) of the ammine ligands on the osmium, the latter of which prohibits the use of robust nucleophiles. Addition of cyanide ion to the 1-methyl-2*H*-pyrrolium complex **32** occurs to give the 2-cyano-substituted 3-pyrroline complex **75** as one diastereomer (Figure 15). In contrast, the 1-methyl-3*H*-pyrrolium species **28**, which possesses an acidic C-3-proton in an *anti* orientation, results in a significant (~30%) amount of deprotonation in addition to the 2-pyrroline complex **78** under the same reaction conditions. Uncharacteristically, **78** is isolated as a 3:2 ratio of isomers, presumably via epimerization at C-2.[17] Other potential nucleophiles such as the conjugate base of malononitrile, potassium acetoacetate, and the silyl ketene acetal 2-methoxy-1-methyl-2-(trimethylsiloxy)-1-propene either do not react or result in deprotonation under ambient conditions.

Nucleophilic addition has been achieved with azafulvenium complexes, which, like **32**, are kinetically slower to deprotonate. When the

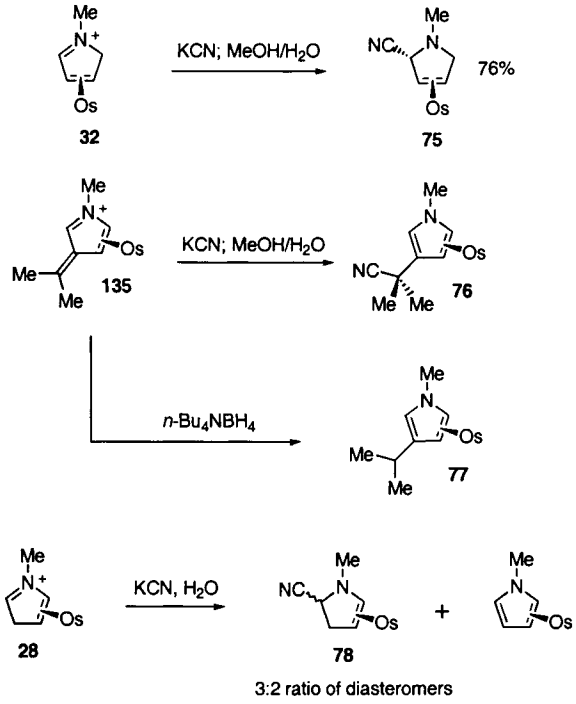



***Figure 15.*** Nucleophilic addition to pyrrolium and azafulvenium complexes.

2-azafulvenium complex **135** (*vide infra*) is allowed to react with KCN in methanol/water solution, a clean 1,4 addition ensues to give a 3-substituted 1*H*-pyrrole complex **76** (Figure 15). Borohydride reduction of **135** gives the 3-isopropyl-1-methylpyrrole complex **77** as the major product.[18]

The preceding sections describe *regioselective* electrophilic addition of pyrrole complexes at the *3-position* with various electrophiles to give β-substituted 1*H*-pyrrole or 3*H*-pyrrolium isomers. The latter compounds, in contrast to their noncomplexed counterparts, are only moderately acidic (pKa ~ 6) and therefore resist rearomatization and multiple alkylations. For example, when uncomplexed 2,5-dimethylpyrrole is treated with 1 equiv of methyl acrylate and TBSOTf, a statistical 1:2:1 ratio of starting material, monoalkylated **105** (*vide infra*), and 3,4-bis-alkylated product is found.[12] Treatment of 1-methylpyrrole under the same conditions results in at least four alkylated products along with starting material. In contrast, coordination by osmium results in smooth

monoalkylation with essentially all electrophiles studied. Only when the nitrogen is unsubstituted are double alkylations occasionally observed (e.g., **54**), and then only in the case in which the initial electrophilic addition produces a product more electron rich than the starting material.

Nucleophilic addition of the metal-stabilized pyrrolium complexes is readily achieved with borohydride and cyanide ion. The scope of this reactivity is bracketed by the diminished electrophilicity of the iminium carbons and the acidity of the ammine ligands, which prevents the use of strongly basic nucleophiles. Competing deprotonation of the acidic pyrrolium ring protons is observed primarily only with 3*H*-pyrrolium complexes or when bulky nucleophiles are used.

In addition to the high regiochemistry observed, the bulky osmium pentaammine metal center also effectively blocks one face of the pyrrole ring from attack. This directs each transformation carried out on the complex to occur on the same face of the pyrrole ring. For example, in the synthesis of 3-pyrroline complex **74**, both protonation and hydride addition occur from the same face of the pyrrole ring, producing **74** exclusively as the *cis*-isomer. This feature is also illustrated in the synthesis of pyrrolizinone **109** (*vide infra*), where a stereoselective hydride reduction allows the preparation of **109** as only one diastereomer.

## D. 1,3-Dipolar Cycloadditions

### *Synthesis*

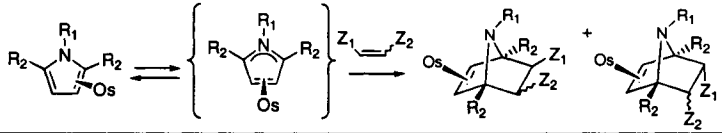
As previously mentioned, the *4,5*-$\eta^2$-pyrrole complexes are in rapid equilibration with the 2,3-isomer through a fluxional process that generates an azomethine ylide intermediate (Figure 1).[10,14] While the relative concentration of the azomethine ylide is very small compared with the 1*H*-isomer, it is sufficiently reactive to undergo 1,3-dipolar cycloaddition reactions with certain electrophiles. When pyrrole complex **20** is combined with maleic anhydride under ambient conditions, the 7-azabicyclo[2.2.1]nonene complex **79** is generated as a 4:1 ratio of *exo* to *endo* isomers (Table 4).[10] In sharp contrast to the organic ligand, which undergoes a facile cycloreversion at ambient temperatures, the complexed azanorbornene is indefinitely stable at room temperature.

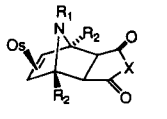
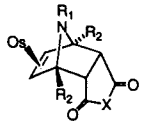
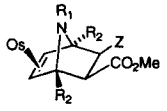
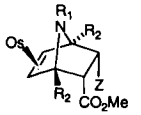
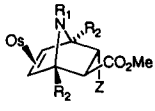
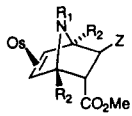
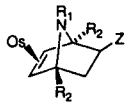
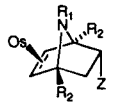
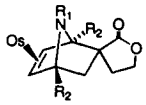
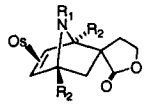
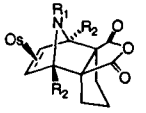
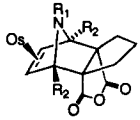
The dipolar cycloaddition reaction is general, and a structurally diverse series of azanorbornene complexes (**79–95**) have been synthesized. The yields and *exo*/*endo* ratios of these reactions are summarized in Table 4. The stereochemistry of the cycloadducts is assigned based primarily on $^1$H NMR (coupling constants, NOE) data. For 7-azanorbornene

complexes **80**, **85**, and **94**, the stereochemistry was confirmed by X-ray crystallography.[14]

The pentaammineosmium moiety occupies an *exo* orientation on all cycloadducts, indicating that cycloaddition takes place *anti* to the face of the pyrrole ring coordinated by the metal. The stereochemistry of the cycloaddition appears to be governed by the steric environment about the

***Table 4.*** Yields and *exo/endo* Ratios for Cycloadducts **79–95**



| *a (exo)* | *b (endo)* | *Cpd* | *X* | *R*1 | *R*2 | *Z* | *a/b*[a] | *Yield*[b] |
|---|---|---|---|---|---|---|---|---|
| | | **79** | O | H | H | | 4:1 | |
|  |  | **80** | NPh | H | H | | 6:1 | 85 |
| | | **81** | NPh | Me | H | | 1:6 | 85 |
| | | **82** | NPh | H | Me | | 5:1 | 89 |
| | | **83** | NPh | Me | Me | | 1:1 | 77 |
| | | **84** | NPh | TMS | H | | <1:20 | 89 |
|  |  | **85** | | H | Me | $CO_2Me$ | 2:1 | 82 |
| | | **86** | | H | Me | 3-Pyridyl | 9:1 | 83 |
|  |  | **87** | | H | H | $CO_2Me$ | — | 78 |
| | | **88** | | H | Me | $CO_2Me$ | — | 86 |
| | | **89** | | H | Me | 3-Pyridyl | 16:1 | 93 |
|  |  | **90** | | H | Me | $CO_2Me$ | 12:1 | 97 |
| | | **91** | | H | Me | CN | 5:1 | 83 |
| | | **92** | | Me | H | $CO_2Me$ | 1:1 | 84 |
| | | **93** | | Me | H | CN | 1:1 | 98 |
|  |  | **94** | | H | Me | | >20:1 | 96 |
|  |  | **95** | | H | Me | | >10:1 | 84 |

*Notes*: [a]The ratios of isomers were determined by $^1H$ NMR.

[b]Yields are reported for the crude mixtures of diastereomers.

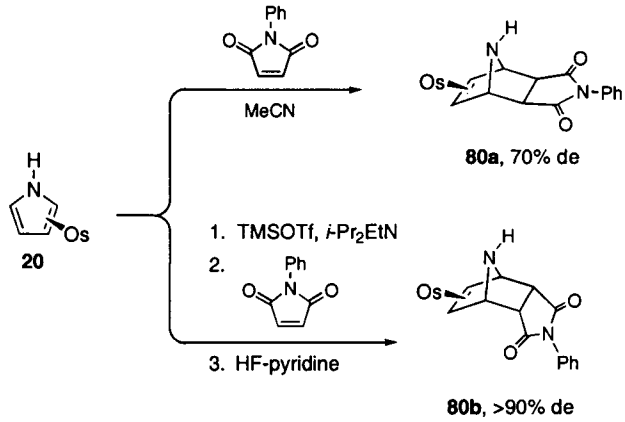



***Figure 16.*** Stereoselective dipolarcycloaddition between $\eta^2$-pyrrole complex **20** and *N*-phenylmaleimide.

pyrrole nitrogen. For cases where the nitrogen is not substituted, the major product has the electron-withdrawing group in an *exo* configuration, resulting from an *endo* transition state.[19] When the nitrogen is substituted, a marked decrease in the *exo/endo* ratio is observed, presumably reflecting an unfavorable steric interaction with the dipolarophile substituent. This effect is illustrated in the reactions of *N*-phenylmaleimide, for which the *exo/endo* ratio decreases when the steric profile of the nitrogen substituent increases (Table 4). As the stereochemistry of the cycloaddition is sensitive to steric bulk on the nitrogen, a bulky protecting group may be used in the selective synthesis of *endo* cycloadducts. For example, **80b** has been prepared in >90% de by the reaction of the TMS-substituted pyrrole complex **26** generated *in situ* and *N*-phenylmaleimide followed by deprotection (Figure 16).

The stereospecificity of this cycloaddition process can be utilized in setting the stereochemistry of substituents on the 7-azanorbornane nucleus. For example, reactions of **22** with the methyl esters of *Z*- and *E*-3-(3′-pyridyl) acrylates afford the corresponding *exo* and *endo* pyridyl complexes **86a** and **89a**, respectively (Figure 17).

### *Effect of Pyrrole Ring Substitution*

As previously described, the pyrrole ring substitution has a significant effect on the rate of isomerization of $\eta^2$-pyrrole complexes. This rate of isomerization is directly proportional to the rate of cycloaddition. As

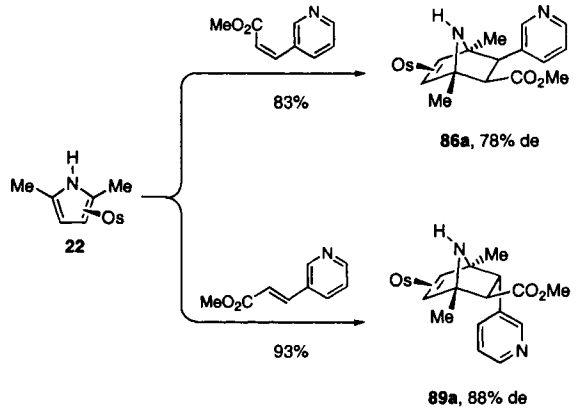
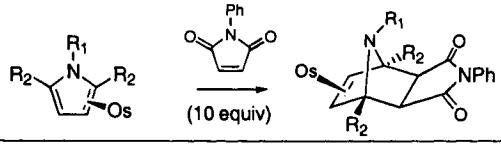



***Figure 17.*** Stereospecific dipolarcycloaddition of $\eta^2$-2,5-dimethylpyrrole complex **22** and *E*- and *Z*-pyridyl acrylates.

such, the 2,5-dimethyl- (**22**) and 1,2,5-trimethylpyrrole (**23**) complexes show the highest reactivity toward dipolarophiles followed by the *N*-methylpyrrole (**21**), pyrrole (**20**), and 1-trimethylsilylpyrrole (**26**) complexes (Table 5). Pyrrole complexes with substitution at the β-position (e.g., **25a** and **37a**) are completely inert toward typical dipolarophiles. While *N*-phenylmaleimide reacts quickly (< 1 h) at relatively low concentrations (~0.1 M, acetonitrile) with most pyrrole complexes, less reactive dipolarophiles such as those having only one electron-withdrawing group must be used in higher concentrations and/or in more polar solvents (e.g., DMAc) in order for cycloaddition to compete with solvent

***Table 5.*** Fluxionality and Reactivity Rate Constants for $\eta^2$-Pyrrole Complexes



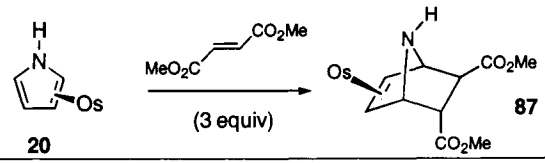

| *Pyrrole Complex* | $R_1$ | $R_2$ | *Pdt* | $k\,(s^{-1}M^{-1}) \times 10^{-3}$ | *Fluxionality Rate Constant* $k'(s^{-1})$ |
|---|---|---|---|---|---|
| **26** | TMS | H | **84** | 2.2 | $k' < 250$ |
| **20** | H | H | **80** | 110 | $k' < 70$ |
| **21** | Me | H | **81** | 1200 | $k' \sim 100$ |
| **22** | H | Me | **82** | > 2000 | $300 < k'$ |

substitution, especially with less reactive pyrrole complexes such as **20** and **21**.

### *Effect of Solvent*

There is a significant solvent effect on the rate of cycloaddition (Table 6). While the rate of the cycloaddition reaction in acetonitrile is high enough to give satisfactory results with the majority of dipolarophiles studied, a significant rate acceleration is observed in more polar aprotic solvents with high donor numbers[20] such as DMSO or DMAc. This effect has been successfully utilized in cases where the cycloaddition reaction is inherently slow. For example, compound **93** has been successfully synthesized from the 1-methylpyrrole complex **21** in the presence of neat acrylonitrile (15–20 equiv) containing 10 wt% DMAc (to solubilize the complex) in 2–3 h. The reaction between the 2,5-dimethylpyrrole complex **22** (1 M in DMAc) and methyl *Z*-3-(3′-pyridyl)acrylate (3 equiv), one of the least reactive dipolarophiles studied, is complete in ~18 h affording compound **86**. The cycloadditions are also catalyzed by lithium triflate, which affords a practical maximum rate enhancement of one order of magnitude. However, the use of stronger Lewis acids such as $BF_3$-$Et_2O$ results in other reactions such as β-electrophilic addition

***Table 6.*** Reaction Half-Lives as a Function of Solvent in the Synthesis of **87** from **20** and Dimethylfumarate




**20** **87**

| *Entry* | *Solvent* | $t_{1/2}$ *(min)* | *DN (kcal mol$^{-1}$)*[19] |
|---|---|---|---|
| 1 | MeCN | 185 | 14.1 |
| 2 | $Me_2CO$ | 111 | 17.0 |
| 3 | 2 M LiOTf (DME) | 25 | |
| 4 | MeOH | 22 | 19.0 |
| 5 | DMF | 15 | 26.6 |
| 6 | DMAc | 9 | 27.8 |
| 7 | NMF | 6 | |
| 8 | DMSO | 5 | 29.8 |
| 9 | DMPU | 5 | |
| 10 | 5 M LiOTf (DME) | 5 | |

and/or ring opening (*vide infra*).[12,14] An exception to this is the reaction of **26** with *N*-phenylmaleimide. This cycloaddition is moderately accelerated and affords a cleaner product when carried out in the presence of TMSOTf (see Figure 16).

### *Competing β-Michael Additions*

Under certain circumstances, the conjugate addition and cycloaddition reaction pathways overlap for α,β-unsaturated electrophiles. For example, when the 2,5-dimethylpyrrole complex **22** is combined with 1 equiv of MVK in acetonitrile, a 1:1 ratio of the β-alkylated 3*H*-pyrrole complex **96** and the α-alkylated 2*H*-pyrrole complex **98** is isolated (Figure 18). When the reaction is monitored by $^1$H NMR in $CD_3CN$, an intermediate 7-azabicyclo[2.2.1]heptene complex (**97**) is observed at early reaction times, and eventually converts ($t_{1/2}$ ~1 h) to compound **98** via a retro-Mannich reaction followed by proton transfer.

The conjugate addition/cycloaddition manifold is highly influenced by a number of factors, including the pyrrole complex, electrophile, solvent, temperature, and, in some cases, concentration. The key for predicting the course of the reaction between the olefin and an $\eta^2$-pyrrole complex is the coordination site of the metal at the time of electrophilic attack (Figure 19). Although the intermediate azomethine ylide, where

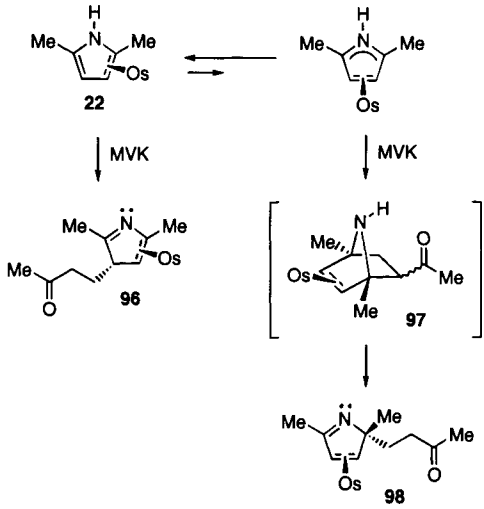



***Figure 18.*** Cycloaddition and Michael addition reactions of $\eta^2$-dimethylpyrrole complex **22** and MVK.

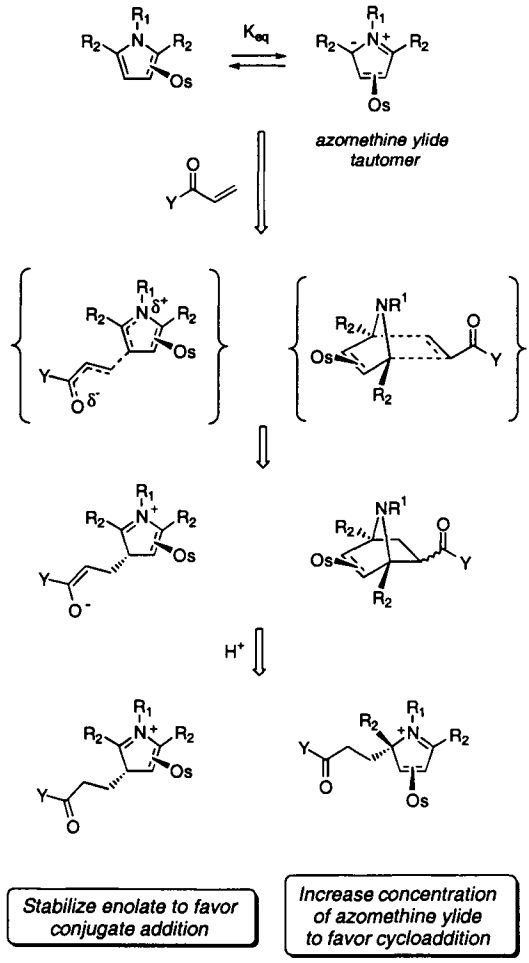



***Figure 19.*** Michael addition versus cycloaddition/ring opening reaction manifold for $\eta^2$-pyrrole complexes.

the osmium is coordinated *3,4*-$\eta^2$, is significantly less stable than the *4,5*-$\eta^2$ analogue, it is clearly the more reactive isomer toward electrophiles such as maleimides as well as fumarate and maleate esters. For β-substituted pyrrole complexes, *3,4*-$\eta^2$ coordination is further destabilized relative to *4,5*-$\eta^2$ binding, and the rate of cycloaddition is insignificant. In contrast, for the 2,5-dimethylpyrrole complex (**22**), the methyl substituents decrease the stability of the *2,3*-$\eta^2$ and *4,5*-$\eta^2$ isomers. As a result, the population of the *3,4*-$\eta^2$ form is increased relative

to that for the unsubstituted pyrrole complex (**20**) to the point that cycloaddition becomes the dominant pathway, even for dipolarophiles as mild as methyl acrylate or acrylonitrile.[12,14]

To the extent that the enolate resulting from conjugate addition at the β-carbon can be stabilized, the rate of this reaction pathway is enhanced. For example, β-Michael additions are observed for MVK, acrolein, and acetylenic electrophiles even without the presence of a Lewis acid. Furthermore, MVK reacts with the 2,5-dimethylpyrrole complex (**22**) to form a considerable amount of β-alkylation product, whereas only cycloaddition is observed for methyl acrylate. The use of a Lewis acid or protic solvent further enhances the reactivity at the β-position relative to cycloaddition. While methyl acrylate forms a cycloadduct with the 2,5-dimethylpyrrole complex (**22**) in the absence of external Lewis acids, the addition of TBSOTf to the reaction mixture results in exclusive conjugate addition (Tables 3 and 4).

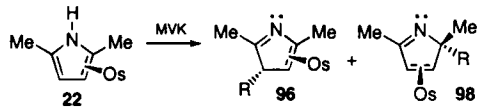
The choice of solvent and temperature also plays a significant role in the selectivity between the formation of **96** and **98** in the reaction between the 2,5-dimethylpyrrole complex **22** and MVK (Table 7). For polar aprotic solvents such as acetonitrile or DMF, an approximate 1:1 ratio of the two products is obtained, while in protic solvents such as methanol or water, the formation of conjugate addition products is favored.

In methanol, a strong preference for conjugate addition is observed at reduced temperatures, where a 50:1 ratio of **96** to **98** was obtained at –50 °C. In either methanol or acetonitrile, running the reaction at temperatures above room temperature has no effect on reaction selectivity. In DMSO, the selectivity of the reaction has a pronounced dependence on concentration of the osmium complex. Running the reaction under dilute (0.035 M) conditions results in an 8:1 ratio of cycloaddition to conjugate addition products. Increasing the concentration of the reaction steadily erodes the selectivity to where it almost becomes 1:1 at 0.59 M (Table 7, entries 9–13). In water, this concentration dependence was barely discernible. This effect is presumably related to the $[Os(NH_3)_5]^{2+}$ moiety itself acting as a mild Brønsted acid through its acidic ammine ligands.

### *Ring Opening Reactions*

The spontaneous ring opening observed in acetonitrile in the transformation of **97** to **98** also occurs for other cycloadducts, although at considerably slower rates (Figure 20). This reactivity seems to be partly governed by stability of the resulting enolate anion. In contrast to the

***Table 7.*** Effect of Experimental Parameters on the Reaction between **22** and MVK




**22** **96** **98**

R = $(CH_2)_2C(O)Me$

| *Entry* | *Solvent* | *[22], M* | *MVK equiv* | *Temp °C* | *Product Ratio* **96 : 98** |
|---|---|---|---|---|---|
| 1 | MeCN | 0.33 | 1.1 | 25 | 1 : 1 |
| 2 | MeCN | 0.32 | 2.0 | −10 | 4 : 1 |
| 3 | MeOH | 0.23 | 1.3 | 25 | 3 : 1 |
| 4 | MeOH | 0.32 | 2.0 | −10 | 9 : 1 |
| 5 | MeOH | 0.32 | 1.7 | −50 | 49 : 1 |
| 6 | $H_2O$ | 0.020 | 1.2 | 25 | 9 : 1 |
| 7 | $H_2O$ | 0.30 | 1.0 | 25 | 9 : 1 |
| 8 | DMF | 0.26 | 1.0 | 25 | 1 : 1 |
| 9 | DMSO | 0.59 | 1.2 | 25 | 4 : 5 |
| 10 | DMSO | 0.40 | 1.1 | 25 | 2 : 3 |
| 11 | DMSO | 0.25 | 2.2 | 25 | 1 : 2 |
| 12 | DMSO | 0.057 | 1.2 | 25 | 1 : 4 |
| 13 | DMSO | 0.035 | 1.4 | 25 | 1 : 9 |

MVK adduct **97**, the methyl acrylate-derived analogue **90** and its conjugate acid are both resistant to ring opening. Although cycloadducts other than **97** are relatively stable in polar aprotic solvents such as acetonitrile or DMAc, some undergo facile ring opening to 2*H*-pyrrole complexes in water. On attempted purification by ion-exchange chromatography, compounds **84**, **92**, and the *exo*-pyridyl cycloadduct **86a** convert to the 2*H*-pyrrole complexes **99**, **100**, and **101**, respectively. In contrast, both isomers of the acrylonitrile adduct **91** and the *endo*-pyridyl isomer **89a** are stable under these conditions and can be stored as tetraphenylborate monohydrate salts. When necessary, ring opening can be initiated by treatment with an appropriate Lewis acid to give the corresponding 2*H*-pyrrolium isomer. For example, cycloadducts **90** and **92** are easily converted to the α-substituted 2*H*-pyrrolium complexes **100**•HOTf and **102** with TBSOTf. Interestingly, the maleate cycloadduct **85a** undergoes a quantitative isomerization to the fumarate complex **88** that is complete in <5 min in water and in several days in methanol. This *exo*-to-*endo* epimerization, which is observed *only* for **85a**, presumably occurs

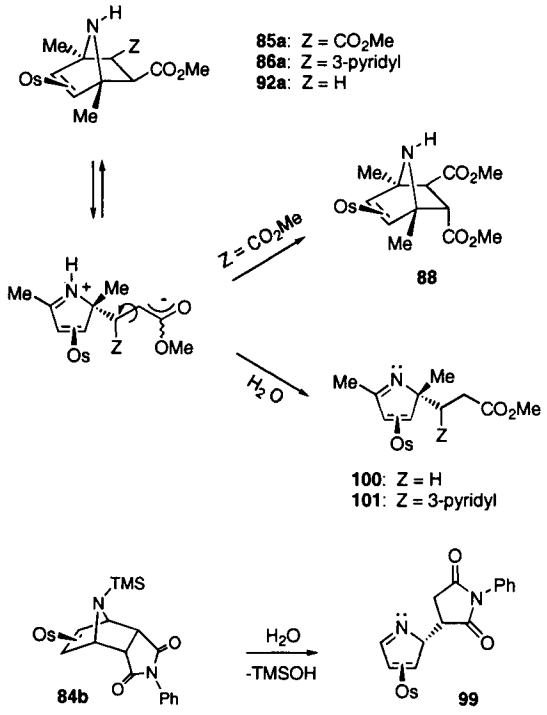



***Figure 20.*** Ring opening of $\eta^2$-azanorbornene complexes.

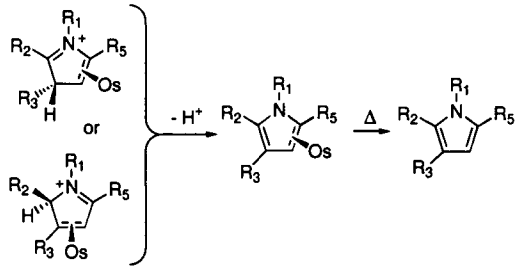
through a retro-Mannich/Mannich reaction sequence as shown in Figure 20.

## III. LIGAND DECOMPLEXATION

### A. Aromatic 1*H*-Pyrroles

1*H*-Pyrrole and pyrrolium complexes capable of rearomatization can be decomplexed simply by moderate heating (Table 8).[12] For example, pyrroles **103** and **104** can be generated cleanly from the corresponding $\eta^2$-1*H*-pyrrole complexes by heating in acetonitrile under anaerobic conditions. In the case of the 2,5-dimethyl-3*H*-pyrrolium adduct **66**, prior deprotonation is not necessary as heating (80 °C, $CH_3CN$) gives **105** directly in 95% isolated yield. In the case of the analogous 1-methyl-3*H*-pyrrolium complex **65**, deprotonation is required prior to the decomplexation step. The α-substituted pyrrole **107** can be synthesized (47%

***Table 8.*** Synthesis of 1*H*-Pyrroles from $\eta^2$-Pyrrole and Pyrrolium Complexes



| *Starting Material* | $R_1$ | $R_2$ | $R_3$ | $R_5$ | *Pdt* | *Yield*[a] |
|---|---|---|---|---|---|---|
| **38** | Me | H | Ac | H | **103** | 73 |
| **53a** | Me | H | $(CH_2)_2C(O)Me$ | H | **104** | 95 [75] |
| **66** | H | Me | $(CH_2)_2CO_2Me$ | Me | **105** | [90] |
| **65**[b] | Me | H | $(CH_2)_2CO_2Me$ | H | **106** | 74 |
| **102**[b] | Me | $(CH_2)_2CO_2Me$ | H | H | **107** | [47] |

*Notes*: [a]Percentages given are NMR yields from the uncomplexed pyrrole; numbers in brackets are isolated yields.

[b]Deprotonation to give the 1*H*-pyrrole complex carried out prior to heating.

overall yield from **21**) by deprotonation of the 2*H*-pyrrolium adduct **102** followed by heating in acetonitrile.

## B. 3-Pyrroline and Cycloadduct Complexes

Liberation of the organic ligand in 3-pyrroline complexes can be accomplished in good yield either by oxidation ($Ce^{IV}$ or DDQ), or by heating under anaerobic conditions.[12,14] Synthesis of the pyrrolizinone **109** is accomplished by first reducing the ring-opened 2*H*-pyrrolium

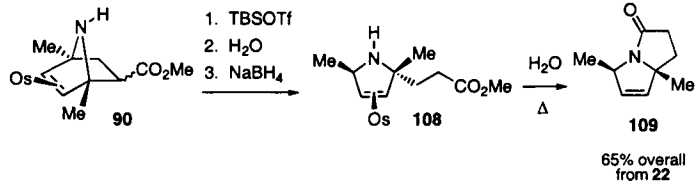



***Figure 21.*** Decomplexation of an $\eta^2$-azanorbornene complex to give a substituted pyrrolizinone.

complex (**100**·HOTf) to give the 3-pyrroline complex **108**. Heating gives the free pyrroline, which ring closes during aqueous workup to give **108** in 65% overall yield from **22** (de > 90%) (Figure 21).[12]

In general, decomplexation of 7-azanorbornene complexes can be accomplished by oxidation with either $Ce^{IV}(NH_4)_2(NO_3)_6$ (CAN, 1 equiv) or DDQ (0.5 equiv) in the presence of excess (~3 equiv) triflic acid in acetonitrile to give azanorbornene salts such as **110a** (Figure 22).[14] Performing the reaction in the absence of acid results in a fast retrocycloaddition to give the pyrrole and dipolarophile. Although the 7-azanorbornene salts are unstable and difficult to isolate, they are readily hydrogenated to stable 7-azanorbornanes (e.g., **111a**) while preserving the stereochemistry at C-2 and C-3. The reaction sequence of protonation, oxidation, and hydrogenation has been applied to the synthesis of a series of 7-azanorbornanes (**111–116**, Table 9). No significant change in the ratio of diastereomers is observed in the transformation of the cycloadduct complexes to the organic products.

Alternatively, chemical modification of the electron-withdrawing substituents on the ring allows isolation of 7-azanorbornenes. For example, when the carboxylate group on **90** is reduced to the primary alcohol, the reduced complex can be decomplexed with 1 equiv of CAN in an excess of HOTf (~5 equiv) to give the intact organic ligand **117**. Again, failure to treat the complex with acid prior to oxidation results in a greatly reduced yield.

In contrast to the conventional Diels–Alder reaction with free pyrroles, which requires specialized functionalization on both the pyrrole and dienophile, the [2+3] dipolar cycloadditions described herein allow the use of simple alkenes (i.e., bearing at least one electron-withdrawing group) and pyrroles containing no electron-withdrawing groups. Use of

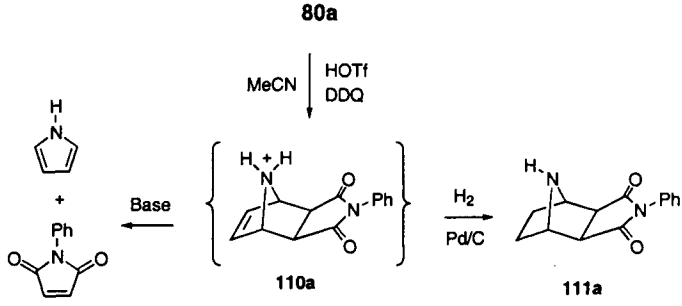
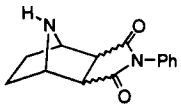
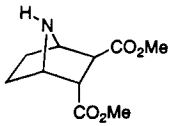
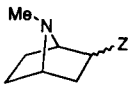
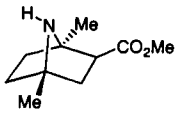
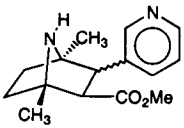



***Figure 22.*** Oxidative decomplexation of $\eta^2$-azanorbornene complexes.

***Table 9.*** Yields of 7-Azanorbornanes from Cycloadduct Complexes

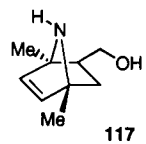
| *7-Azanorbornane*[a] | Z | *Cpd* | *De (%)*[b] | *Yield (%)*[c] |
|---|---|---|---|---|
|  | *(exo)* | **111a** | 66 | 39 |
| | *(endo)* | **111b** | >90 | 41 |
|  | | **112** | — | 42 |
|  | $CO_2Me$ | **113** | 0 | 65 |
| | CN | **114** | 0 | 67 |
|  | | **115** | 84 | 60 |
|  | *(exo)* | **116a** | 78 | 46 |
| | *(endo)* | **116b** | 88 | 69 |

*Notes:* [a]Prepared from crude reaction mixtures.

[b]Diastereoselectivity based on $^1H$ NMR data prior to chromatographic separation.

[c]This represents the isolated yield of *both* isomers, either as a mixture or separated, following chromatography.

an alkene allows the construction of one or more stereocenters in the ring-forming step, and this method proves useful in the stereospecific synthesis of substituted 7-azanorbornanes. In addition, the steps of complex formation, cycloaddition, decomplexation, and hydrogenation may be combined into two integrated transformations starting with commercially available pyrroles. Although most of the work described in this review was performed in a glovebox out of convenience (the starting pyrrole complexes **20–26** are air sensitive), the synthesis of



**117**

compound **114** [from $Os(NH_3)_5OTf_3$ and 1-methyl pyrrole] has been routinely performed on the benchtop on a 10-mmol scale using standard glassware. The ester **113** and nitrile **114** are obtained in 55–65% *overall* yield from *N*-methylpyrrole using this procedure.[14]

## C. 2-Pyrroline Complexes

While 3-pyrrolines are readily decomplexed, 2-pyrrolines present a problem because of their inherent nucleophilicity and/or tendency to polymerize. Attempts to isolate characterizable organic products from the oxidation of 2-pyrroline complex **70** fail under a variety of conditions. However, when the nitrogen is first quaternized using $CH_3OTf$ (**118**), oxidation with 1.0 equiv of either Ce(IV) (70%) or DDQ (55%) in $HOTf/CD_3CN$ solution cleanly gives the vinyl ammonium product (**119**) shown in Figure 23.[12b] An alternative method to remove an organic fragment from 2-pyrroline complexes can be used when the nitrogen is unsubstituted. Acylation of the 2,5-dimethyl-2-pyrroline complex **71** with $Ac_2O$/pyridine gives the *N*-acetyl derivative **120**. Oxidation of the carbonyl-protonated species followed by hydrolysis and ring opening eventually gives amide **121** in 44% yield (Figure 23).

In summary, the metal can be readily removed from both 1*H*-pyrrole and 3-pyrroline (including azanorbornene) complexes to give a wide variety of highly functionalized molecules not readily obtained from the aromatic precursors without the use of osmium. The inherent instability of 2-pyrrolines prevents clean decomplexation unless quaternization or acylation of the nitrogen is carried out prior to oxidation of the metal.

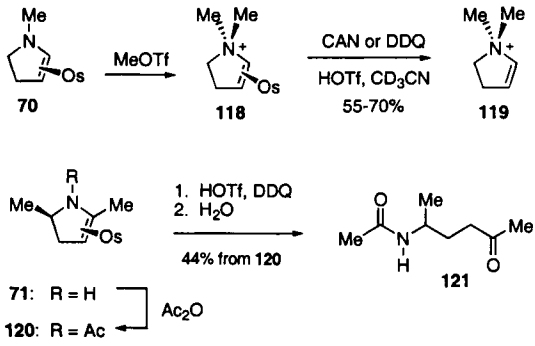



***Figure 23.*** Decomplexation of $\eta^2$-2-pyrroline complexes.

## IV. SYNTHESIS AND UTILITY OF β-VINYLPYRROLE AND TETRAHYDROINDOLE COMPLEXES

As previously shown in Figure 11, β-vinylpyrrole complex **47** is easily synthesized via a Lewis acid promoted aldol reaction of the 1-methylpyrrole complex **21** with acetone. Vinylpyrrole complex **47** undergoes a facile Diels–Alder cycloaddition with *N*-phenylmaleimide under ambient temperatures to generate a complexed 5,6,7,7a-tetrahydroindole (**122**) in 80% yield.[13] The cycloadduct precipitates from solution as a single stereoisomer and is resistant to isomerization. Decomplexation and oxidation by DDQ provides the corresponding indole (**123**) in ~60% overall yield *from 1-methylpyrrole* (Figure 24). As most indole syntheses classically rely on ring closure of the heterocyclic ring from arene precursors, this result represents a complementary method for the synthesis of functionalized indoles.[21,22] The last section of this review summarizes the findings of an investigation into the synthesis and reactivity of β-vinylpyrrole complexes and their potential for the synthesis of functionalized indoles.[13]

### A. Synthesis of β-Vinylpyrrole Complexes

#### *Aldol Condensations*

The Lewis acid promoted Mukaiyama-type aldol reaction between pyrrole complexes and ketones is general and gives the corresponding 3*H*-pyrrolium adducts **43–45** and **124–128** in near quantitative yield (Figures 11 and 25). In most cases, these adducts are not isolated, but are converted directly to the corresponding 3-vinylpyrrole complexes in a two-step integrated procedure. Addition of DBU results in elimination of TBSOH and deprotonation of an α-hydrogen from one of the remaining substituents to give the corresponding β-vinylpyrrole complexes **47** and **129–134** in 35–91% overall yields (Figure 25). This transformation

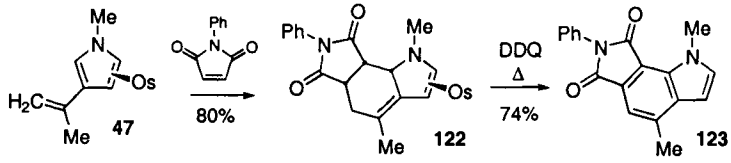



***Figure 24.*** Diels–Alder reaction of β-vinylpyrrole complex **47** and elaboration to indole **123**.

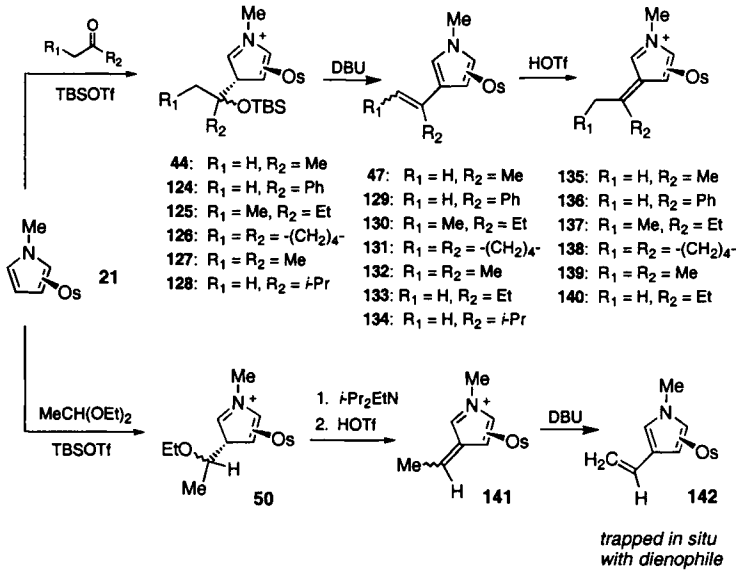



***Figure 25.*** Synthesis of β-vinylpyrrole and 2-azafulvenium complexes via aldol reactions.

presumably goes through an intermediate 2-azafulvenium complex, and protonation of the isolated vinylpyrrole complexes gives the highly stable 2-azafulvenium complexes **135–140** in good yield. When the ketone used in the aldol reaction is not symmetric, both structural vinylpyrrole isomers (e.g., **132** and **133**) are often isolated. In the case of the vinylpyrrole complex **130**, derived from **21** and 3-pentanone, a single isomer is formed with the methyl and ethyl substituents having a relative *cis*-stereochemistry.

## *Acetal Additions*

As previously described, the 3*H*-pyrrolium adduct **50** is obtained from the TBSOTf-promoted aldol reaction between the 1-methylpyrrole complex **21** and acetaldehyde diethylacetal (Figure 11). Deprotonation of **50** occurs at C-3 with *i*-$Pr_2EtN$ to give the corresponding β-substituted 1*H*-pyrrole complex. Addition of triflic acid results in the elimination of ethanol to give the azafulvenium complex **141** as a 3:2 mixture of diastereomers (Figure 25). Deprotonation of **141** results in formation of the unstable unsubstituted β-vinylpyrrole complex **142**, which can be trapped *in situ* with *N*-phenyl maleimide (*vide infra*).

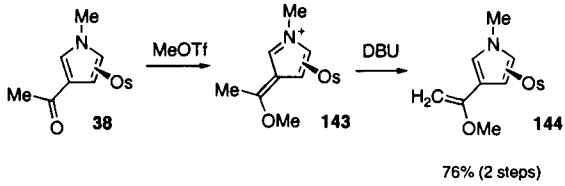



***Figure 26.*** Synthesis of a methoxy-substituted β-vinylpyrrole complex from the 3-acetyl-1-methylpyrrole complex **38**.

### *Acylation and Alkylation*

A third route to 3-vinylpyrrole complexes originates from 3-acylpyrrole complexes and readily provides access to alkoxy-substituted β-vinylpyrrole complexes. The carbonyl oxygen on these complexes is nucleophilic, and treatment of the 3-acetylpyrrole complex **38** with methyl triflate gives the methoxy-2-azafulvenium complex **143**. Addition of DBU to **143** at low temperature results in deprotonation of the pendant methyl group on C-6 to give the methoxy-substituted β-vinylpyrrole complex **144** (Figure 26).

### *Michael Additions*

β-Vinylpyrrole complexes with pendant electron-withdrawing groups (**56**, **58**, **60–62**) are easily synthesized by the Michael addition of activated alkynes to $\eta^2$-pyrrole complexes as described earlier in this review (see Figure 13).

## B. Linkage Isomerization of β-Vinylpyrrole Complexes

At room temperature, β-vinylpyrrole complexes slowly undergo a pyrrole-to-vinyl linkage isomerization in acetonitrile solution to give complexes **145–147** (Figure 27). The half-life of the ring-bound isomer is dependent on the electronics of the β-vinyl substituent and ranges from 22 h for the methoxy-substituted complex **144** to 92 h for the β-(acetylvinyl)pyrrole complex **58**. The stability of **58** is attributed to the donor–acceptor nature of the conjugated system and the fact that this conjugation must be momentarily broken for the metal to migrate out of the ring.

Protonation of **146** occurs at C-2 of the pyrrole ring to give the vinyl-bound 2*H*-pyrrolium complex **148**. Complex **148** has a pKa of approximately −1.5 in acetonitrile, demonstrating that the metal exhibits

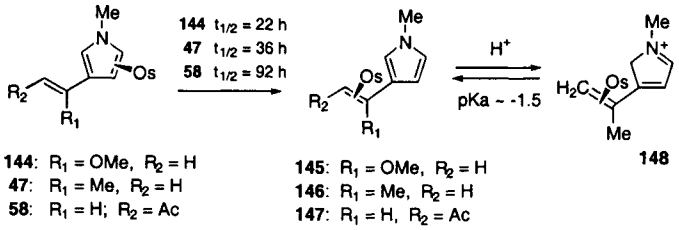



***Figure 27.*** Linkage isomerization of β-vinylpyrrole complexes.

a stabilizing influence even when not bound directly to the pyrrolium ring.[18]

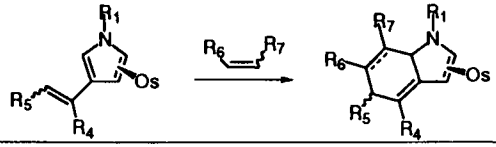
## C. Diels–Alder Reactions and the Synthesis of Indoles

### *Synthesis of Tetrahydroindole Complexes*

The uncoordinated portion of the β-vinylpyrrole complexes described above resembles an electron-rich diene, and undergoes a Diels–Alder reaction under mild conditions with electron-deficient alkenes and alkynes to give functionalized 5,6,7,7a-tetrahydroindole complexes **122** and **149–164** in moderate to excellent yields (Table 10). In most cases, only one stereoisomer is observed even though up to four new stereocenters are formed. For tetrahydroindole complexes **122** and **150**, relative stereochemistry has been assigned and is consistent with cycloaddition occurring through an *endo*-transition state as well as dienophile attack occurring *anti* to metal coordination. Furthermore, no isomerization occurs to the 4,5,6,7-tetrahydroindole system, which predominates for uncoordinated tetrahydroindoles.[23]

This reaction is general for all of the vinylpyrrole complexes described, and has been carried out with a broad array of dienophiles including 4-cyclopentene-1,3-dione, *N*-phenyl maleimide, DMAD, dimethyl fumarate, and methyl acrylate. As expected, the rate of this reaction is sensitive to the electronic and steric nature of both reactants. For example, dienophiles with only one electron-withdrawing group such as methyl acrylate give satisfactory results only when run in excess dienophile or in a polar solvent such as DMAc. When the vinylpyrrole complex contains an electron-withdrawing group (e.g., **58**), the vinylpyrrole is deactivated and only highly electron-deficient dienophiles such as maleimides react at a sufficient rate that linkage isomerization does not become the dominant pathway.

***Table 10.*** Yields for Diels–Alder Reaction of $\eta^2$-β-Vinylpyrrole Complexes



| *Precursor* | $R_1$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | *Alkene*[a] | *Pdt* | *Yld*[b] |
|---|---|---|---|---|---|---|---|---|
| **47** | Me | Me | H | -C(O)N(Ph)C(O)- | | NPM | **122** | 77 |
| **129** | Me | Ph | H | -C(O)N(Ph)C(O)- | | NPM | **149** | 82 |
| **47** | Me | Me | H | $CO_2Me$ | $CO_2Me$ | DMFum | **150** | 79 |
| **129** | Me | Ph | H | $CO_2Me$ | $CO_2Me$ | DMFum | **151** | 84 |
| **129** | Me | Ph | H | H | $CO_2Me$ | MeAcr[c] | **152** | 79 |
| **142**[d] | Me | H | H | -C(O)N(Ph)C(O)- | | NPM | **153** | 78 |
| **47** | Me | Me | H | $CO_2Me$ | $CO_2Me$ | DMAD[e] | **154** | 81 |
| **144** | Me | OMe | H | -C(O)N(Ph)C(O)- | | NPM | **155** | 77 |
| **144** | Me | OMe | H | H | $CO_2Me$ | MeAcr[c] | **156** | 76 |
| **58** | Me | H | Ac | -C(O)N(Ph)C(O)- | | NPM | **157** | 84 |
| **61** | Me | H | $CO_2Me$ | -C(O)N(Ph)C(O)- | | NPM | **158** | 82 |
| **60** | Me | $CO_2Me$ | $CO_2Me$ | -C(O)N(Ph)C(O)- | | NPM | **159** | 75 |
| **62** | Me | Ph | Ac | -C(O)N(Ph)C(O)- | | NPM | **160** | 82 |
| **56** | H | H | Ac | -C(O)N(Ph)C(O)- | | NPM | **161** | 78 |
| **47** | Me | Me | H | $-C(O)CH_2C(O)-$ | | CPD | **162** | 44 |
| **130** | Me | Et | Me | $-C(O)CH_2C(O)-$ | | CPD | **163** | 65 |
| **131** | Me | $-(CH_2)_4-$ | | -C(O)N(Ph)C(O)- | | NPM | **164** | 84 |

*Notes*: [a]Abbreviations for dienophiles: NPM = *N*-phenylmaleimide; DMFum = dimethylfumarate; MeAcr = methyl acrylate; DMAD = dimethylacetylenedicarboxylate; CPD = 4-cyclopentene-1,3-dione.

[b]Yield calculated from the uncomplexed pyrrole.

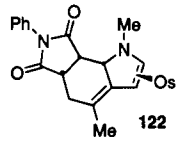
[c]DMAc used as solvent.

[d]Trapped *in situ*.

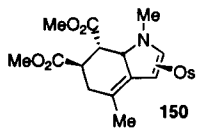
[e]Reaction carried out at –50 °C in 2:1 MeCN/EtCN.

## *Synthesis of Indoles*

The conversion of tetrahydroindole complexes to indoles is achieved in moderate to good yields by heating in the presence of 2 equiv of DDQ in either acetonitrile or DMAc solution, the latter of which gives slightly higher yields (Table 11). In this reaction, the oxidant serves both to

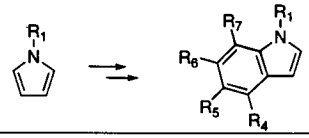


**122**



**150**

***Table 11.*** Synthesis of Indoles from $\eta^2$-Pyrrole Complexes



| *Precursor* | $R_1$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | *Indole* | *Yield*[a] |
|---|---|---|---|---|---|---|---|
| **122** | Me | Me | H | -C(O)N(Ph)C(O)- | | **123** | 58 (74) |
| **149** | Me | Ph | H | -C(O)N(Ph)C(O)- | | **165** | 48 (60) |
| **150** | Me | Me | H | $CO_2Me$ | $CO_2Me$ | **166** | 35 (42) |
| **151** | Me | Ph | H | $CO_2Me$ | $CO_2Me$ | **167** | 48 (55) |
| **152** | Me | Ph | H | H | $CO_2Me$ | **168** | 39 (49) |
| **153** | Me | H | H | -C(O)N(Ph)C(O)- | | **169** | 7 (12) |
| **155** | Me | OMe | H | -C(O)N(Ph)C(O)- | | **170** | 29 (37) |
| **156** | Me | OMe | H | H | $CO_2Me$ | **171** | 12 (17) |
| **157** | Me | H | Ac | -C(O)N(Ph)C(O)- | | **172** | 46 (52) |
| **158** | Me | H | $CO_2Me$ | -C(O)N(Ph)C(O)- | | **173** | 14 (17) |
| **159** | Me | $CO_2Me$ | $CO_2Me$ | -C(O)N(Ph)C(O)- | | **174** | 49 (66) |
| **160** | Me | Ph | Ac | -C(O)N(Ph)C(O)- | | **175** | 22 (27) |
| **161** | H | H | Ac | -C(O)N(Ph)C(O)- | | **176** | 4 (5) |
| **163** | Me | Et | Me | -C(O)$CH_2$C(O)- | | **177** | 9 (14) |
| **164** | Me | -$(CH_2)_4$- | | -C(O)N(Ph)C(O) | | **178** | 38 (45) |
| **178** | Me | -(CH=CH)$_2$- | | -C(O)N(Ph)C(O) | | **179**[b] | 16 (40) |
| **28** | Me | Ph | H | -C(O)N(Ph)C(O) | | **165**[c] | 37 |
| **28** | Me | Me | H | $CO_2Me$ | $CO_2Me$ | **166**[c] | 40 |

*Notes*: [a]Yields listed are from the uncomplexed pyrrole; numbers in parentheses represent yields from the precursor.

[b]Note that this is the fully oxidized benzindole.

[c]Reaction performed on bench starting from 1-methyl-3*H*-pyrrolium complex **28**.

liberate the ligand from the metal and to oxidize the tetrahydroindole ligand to the indole. The yield of the decomplexation/oxidation process varies considerably (5–74%) depending on the substituents present on the tetrahydroindole complex. Interestingly, use of 3 equiv of DDQ, which would allow stoichiometric oxidation of the osmium and of the tetrahydroindole ring, gives *lower* overall yields of indole, leading to speculation that the metal is coordinated during dehydrogenation of the indole ring system.[13b]

Because of the air sensitivity of some of the intermediate pyrrole complexes, most of the work described above was carried out under an inert atmosphere in a drybox for convenience. Some of the indoles, however, can be synthesized on the bench using this methodology with

the only precaution being keeping the reaction mixtures under an inert atmosphere. The air-stable 1-methyl-3*H*-pyrrolium complex **28** can be synthesized by reduction (Zn/Hg) of the air-stable complex $Os^{III}(NH_3)_5(OTf)_3$ in the presence of 1-methylpyrrole followed by protonation. This complex can then be deprotonated *in situ* and reacted to give indoles in a one-pot reaction sequence. Indoles **165** and **166** were prepared using this methodology in 37–40% overall yield from 1-methylpyrrole (Table 11, Figure 28).

The last section of this review summarizes the preparation of a variety of functionalized indoles from transition-metal-activated β-vinylpyrroles. Although transition metals such as palladium have been heavily employed in the synthesis and functionalization of indoles,[24] the majority of cases involve either ring closure of the heterocyclic ring or further manipulation of an intact indole ring. While the synthesis of indoles has also been achieved from uncomplexed vinylpyrroles,[23] success has been limited by several factors, including the relative difficulty in synthesizing 3-vinylpyrroles versus 2-vinylpyrroles as well as competing side reactions such as Michael addition.[25] Furthermore, *uncomplexed* 3a,4,5,6-tetrahydroindoles, which result from the reaction of 2-vinylpyrroles with alkene dienophiles, quickly isomerize to the aromatic 4,5,6,7-tetrahydroindole isomers, which resist further dehydrogenation.[23c]

The osmium methodology provides a great deal of flexibility for the functionalization of carbons 4–7 in the indole ring. For example, substitution on carbons 4 and 5 originates from the choice of ketones in the initial aldol reaction, or from substitution installed on the β-vinylpyrrole complex during the acylation or Michael addition steps. Functionalization on carbons 6 and 7 depends on the choice of dienophile. This overall

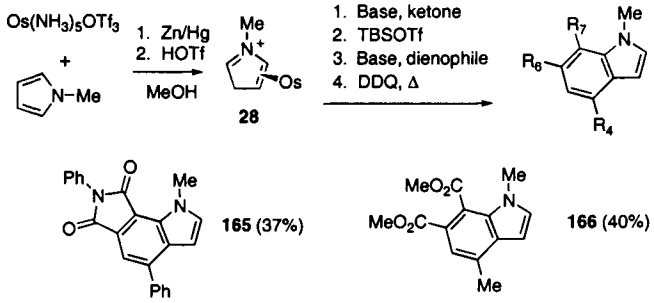
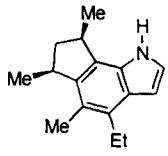
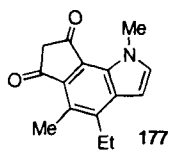


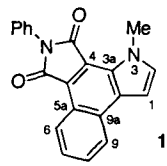

***Figure 28.*** Bench synthesis protocol for the direct synthesis of indoles from 1-methylpyrrole and $[Os(NH_3)_5(OTf)](OTf)_2$.




Herbindole B




177




179

3*H*-Benz[e]indole

flexibility is illustrated by the synthesis of indole **177**, which contains the carbon framework of the herbindoles and trikentrins,[26] as well as the synthesis of the benzindole ring system (**179**).

A limitation of this chemistry is the inability to prepare indoles possessing an unsubstituted nitrogen. In an attempt to solve this problem, several *N*-protecting groups were installed on the pyrrole ring prior to complexation. Unfortunately, only *N*-benzyl derivatives permitted the synthesis to reach the indole stage, and repeated attempts to remove this protecting group failed to give a clean deprotected product.[13b]

In conclusion, osmium(II)-$\eta^2$-pyrrole complexes show a remarkable scope of reactivity that vastly differs from that of their uncomplexed counterparts. Not only do they undergo clean, regioselective and chemoselective electrophilic addition at the β-position, but the resulting metal-stabilized pyrrolium complexes can be isolated and elaborated into more complex molecules. Under certain circumstances, $\eta^2$-pyrroles undergo clean and facile dipolar cycloaddition reactions with dipolarophiles to allow a viable entry into the azanorbornane ring system. Finally, the synthesis of several classes of functionalized β-vinylpyrrole complexes allows a fast entry into the synthesis of indoles, where a high degree of functional flexibility is obtainable on the six-membered ring. While regioselective nucleophilic addition and a few examples of electrophilic substitutions with $\eta^1$- and $\eta^5$-pyrrolyl complexes have been reported, $\eta^2$-binding represents a novel, highly versatile binding mode allowing controlled, synthetically useful transformations to be achieved with this aromatic heterocycle.

## ACKNOWLEDGMENTS

The authors gratefully acknowledge those researchers who are directly responsible for the work covered in this review. In particular, special thanks go to Dr. William H. "Moongun" Myers, Dr. Javier Gonzalez, Dr. Michal Sabat, Dr. Michael L. Spera, Jason I. Koontz, Kent Nilsson, Marcus W. Moody, and Linda K. Neely.

## LIST OF ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DDQ | 2,3-dichloro-5,6-dicyanobenzoquinone |
| DMAc | *N*,*N*-dimethylacetamide |
| DMAD | dimethylacetylenedicarboxylate |
| DMAP | 4-dimethylaminopyridine |
| DME | 1,2-dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| MVK | methyl vinyl ketone |
| NMF | *N*-methylformamide |
| Os | $[Os(NH_3)_5]^{2+}$ $(OTf)_2$ |
| $OTf^-$ | $CF_3SO_3^-$ (triflate) |
| Ph | phenyl |
| Proton Sponge™ | 1,8-bis-(dimethylamino)naphthalene |
| TBS | *tert*-butyldimethylsilyl |
| TBSOTf | *tert*-butyldimethylsilyl triflate |
| TIPS | triisopropylsilyl |

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# SYNTHESIS OF [*b*]-ANNELATED PYRROLES VIA AN ACYLATION APPROACH

Eric D. Edstrom



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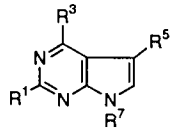
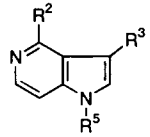
# I. INTRODUCTION

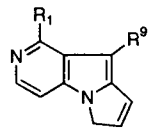
The efficient and regioselective synthesis of substituted pyrrole rings continues to be an important goal in organic synthesis. Much of the motivation derives from the diverse array of naturally occurring compounds that contain either pyrrole rings or pyrrole rings embedded within their structural frameworks. Examples that are of particular relevance to this chapter include pyrrolo[2,3-*d*]pyrimidines, pyrrolo[1,2-*c*]pyridines, pyrido[3,4-*b*]pyrrolozidines, 3,4-disubstituted indoles, indole-4,7-quinones, and pyrrolo[1,2-*a*]indoles, as revealed below. These nitrogenous heterocyclic systems constitute an important group that are present in numerous alkaloid families. Recently, pyrrole-annulated structures have also found new, less conventional, roles in the design and synthesis of conducting polymers[1] and "molecular yardsticks" for determining enzyme binding site dimensions.[2]



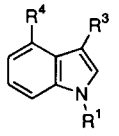

Pyrrolo[3,2-d]pyrimidines



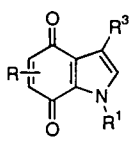

Pyrrolo[1,2-*c*]pyridines



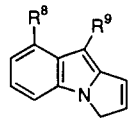

Pyrido[3,4-*b*]pyrrolizidines




3,4-Disubstituted indoles




Indole-4,7-quinones

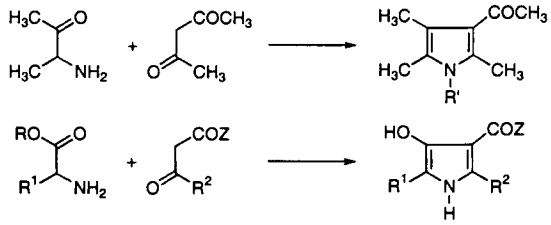



Pyrrolo[1,2-*a*]indoles

# II. HISTORICAL BACKGROUND

## A. Knorr Method and Variants

The time-proven approaches for the synthesis of pyrroles and more elaborate systems have been thoroughly reviewed in the literature. Our focus is drawn to the Knorr synthesis of pyrroles as the [3 + 2] component condensation-type approach which serves as the foundation for the methodology discussed in this chapter.[3] The classic reaction entails the reaction of an α-aminoketone with a β-dicarbonyl compound (Eq. 1). The likely intermediate is a β-aminoenone, which undergoes an acid-catalyzed internal cyclization reaction leading to the pyrrole ring. A variation of this process involves the condensation of α-aminoesters and

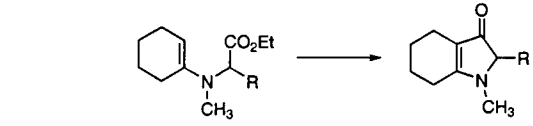


(1)

(2)

β-dicarbonyl compounds and leads to the synthesis of 3-hydroxypyrrole derivatives (Eq. 2).

The acylation of enamines is an important method for the formation of carbon–carbon bonds.[4] The intramolecular version of this reaction has demonstrated utility for the construction of new ring structures. For example, acid-catalyzed internal acylation of an *N*-(carboxymethyl)amino-substituted enamine affords a pyrrol-3-one (Eq. 3). In a variation of this simple cyclodehydrative reaction, Franck and co-workers reported that the condensation of amino acid salts with cyclic 1,3-diketones generates β-aminoenones, which, on further heating in acetic anhydride, results in 3-acetyloxytetrahydroindole-4-ones (Eq. 4).[5a] In a related study, Hickmott and Woodward[6] have extended this approach for the synthesis of pyrrolo[1,2-*a*]indoles, pyrrolizines, and pyrido[3,4-*b*]pyrrolizidin-1-ones. Other scattered reports involving the acylative cyclization of *N*-phenylglycines to 3-acetoxyindoles have appeared.[7] The further utility and extension of this acylative method for pyrrole synthesis had not been developed at the time our efforts commenced.[8]



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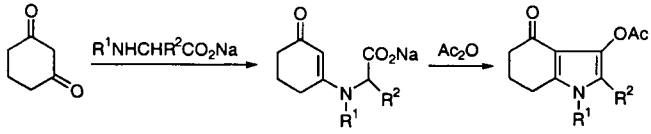


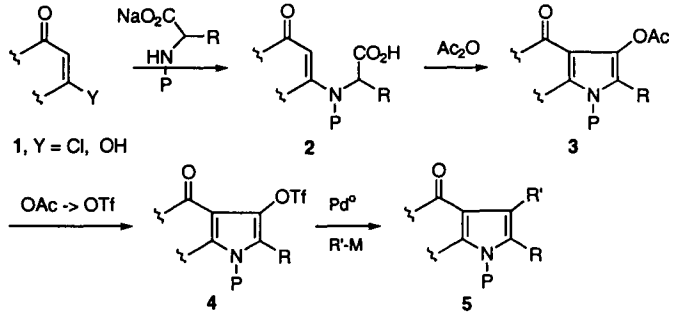
(4)

## B. General Scheme for Acylative Pyrrole Annulation

In 1990 we initially became interested in the possibility of utilizing the acylative version of the Knorr pyrrole synthesis for the construction of pyrrolo[2,3-*d*]pyrimidines. Over the past 7 years this notion has been

expanded into a useful strategy for the construction of several pyrrole-annulated heterocyclic systems including pyrrolo[2,3-*d*]pyrimidines,[8a,g] pyrrolo[1,2-*c*]pyridines,[8c] imidazo[1,2-*c*]pyrimidin-3-ones,[8b] 3,4-disubstituted indoles,[8f] indole-4,7-quinones, and pyrrolo[1,2-*a*]indoles. The generalized approach involves the annulation of pyrroles onto a preexisting six-membered ring utilizing the acylative variant of the Knorr reaction developed by Franck and co-workers[5a] (Scheme 1). Thus, combination of amino acid salts with either β-chloroenones, or 1,3-dicarbonyl compounds, **1**, affords substitution products **2**. These materials can be internally cyclized to 3-acetyloxy pyrrole derivatives **3** on exposure to acetic anhydride. Further conversion of **3** into the trifluoromethanesulfonyloxy derivatives **4** generates versatile substrates for palladium-catalyzed carbon–carbon bond-forming reactions.[9] This aspect became an attractive consideration in view of the rapidly expanding literature base involving the use of aromatic, and heteroaromatic triflates in synthesis. Incorporating such a process, the resulting 3-substituted pyrrole adducts **5** can serve as versatile intermediates in the synthesis of more complex structures. Thus, we saw the opportunity to revitalize a largely overlooked variant of the classic Knorr pyrrole synthesis within the context of more recently proven utility of palladium-catalyzed methodologies involving heteroaromatic triflates.[10]

There are two important features of this overall approach. One is the convenient use of readily available, inexpensive starting materials, i.e., cyclic 1,3-dicarbonyl derivatives and amino acids. The other is the opportunity to introduce oxygen functionality into the β-position on a pyrrole ring without having to resort to direct oxidation methods.[10c] By a simple conversion of the 3-acetoxy pyrrole functionality into pyrrole-3-triflate derivatives the door is opened for a wide variety of palladium-



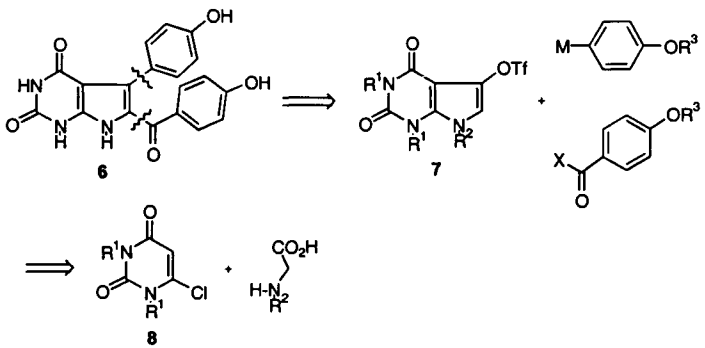

***Scheme 1.***

catalyzed bond-forming processes. In the text that follows we provide a summary of our major findings in this context.

## III. AREAS OF APPLICATION

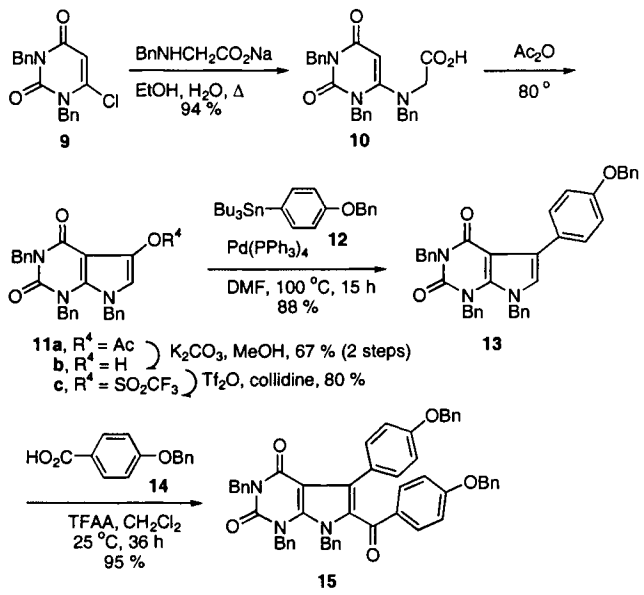
### A. Pyrrolo[2,3-*d*]pyrimidines

Our initial effort in this area was stimulated by the report of a novel pyrrolo[2,3-*d*]pyrimidine alkaloid, rigidin (**6**), isolated from the Okinawan marine tunicate *Eudistoma* cf. *rigida*.[11] Of some significance was that this compound was found to inhibit calmodulin-activated brain phosphodiesterase with an $I_{50}$ value of $5 \times 10^{-5}$ M. However, it is not clear how rigidin functions biologically. The discovery of new pharmacological agents that inhibit specific calmodulin-sensitive enzymes could serve as valuable research tools.[12] Because of the limited availability of rigidin (0.0015% wet weight) from localized tunicate species a total synthesis effort was justified and served as a means of demonstrating the acylative pyrrole annulation approach. The key retrosynthetic recognition was the C-3 aryl and C-2 acyl bond disconnections leading to the C-3 triflate intermediate **7**. This material can be seen to arise from the uracil precursor **8** and the appropriate glycine derivative via a substitution/cyclodehydration reaction sequence (Eq. 5).



(5)

At first we focused on the preparation of pentabenzyl rigidin, **15**, which led to the development of a viable reaction path to the carbon skeleton of **6** (Scheme 2). The choice of benzyl protecting groups was largely a consequence of providing stable and easily identifiable intermediates. Thus, combination of 6-chloro-1,3-dibenzyluracil (**9**) with the sodium salt of *N*-benzylglycine afforded the substitution adduct **10** in




***Scheme 2.***

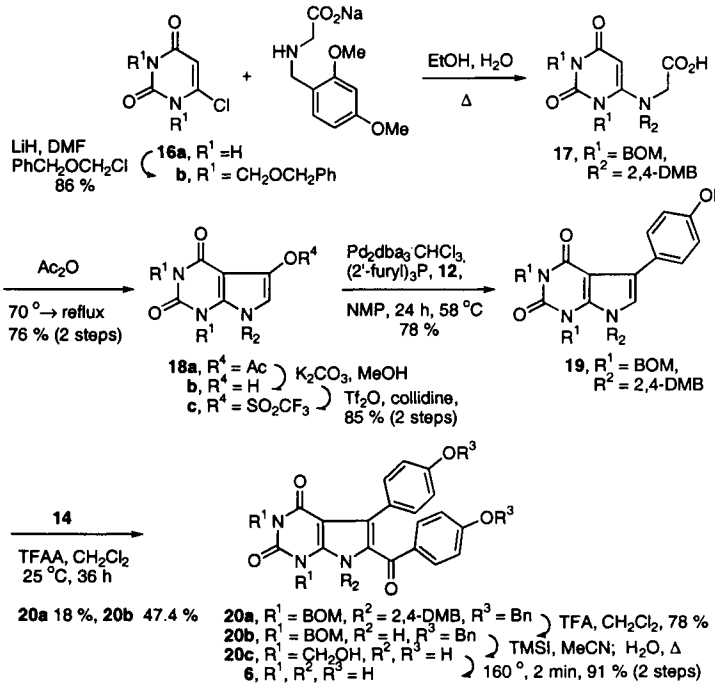
high yield following an acidic workup. Ring closure of **10**, via an internal acylation reaction, was conveniently promoted by heating in acetic anhydride at 80 °C for 4 h. The resulting 3-acetoxy pyrrole was hydrolyzed to the 5-hydroxy derivative **11a** in 65% yield for the two steps. Conversion of **11b** into the triflate **11c** occurred without incident.[13] The palladium-catalyzed cross coupling with the electron-rich aryl stannane **12** using typical Stille conditions[4] afforded cross coupled adduct **13** in high yield. Acylation of **10** was carried out most effectively using a preformed mixed anhydride reagent[14] derived from 4-benzyloxybenzoic acid (**14**) and TFAA. The reaction of this reagent with the activated pyrrole ring in **13** was found to proceed more readily on the addition of 6.0 equiv of TFA to the reaction mixture and stirring at room temperature for 16 h. The pentabenzyl-rigidin precursor **15** was then isolated in 95% yield. Because attempts to remove the benzyl groups from **15** proved futile,[15] design of a new protection strategy was necessary if a viable route to rigidin was to be realized.

In view of some of the difficulties in removing heterocyclic nitrogen-protecting groups,[16] it was felt that acid-labile groups such as benzyloxymethyl (BOM)[17a] for the uracil-type nitrogens and an electron-rich benzyl group[17b] at the pyrrole nitrogen would provide the most flexible

and efficient deprotection scheme. The appropriate choice of either protic or Lewis acidic reagents for the final deprotection step could be determined and thereby avoid alteration of the C-14 carbonyl functionality.[15]

Starting with 6-chlorouracil (**16a**), alkylation with BOMCl using lithium hydride as a base afforded 86% of 6-chloro-1,3-dibenzyloxymethyluracil (**16b**). The readily obtained *N*-2,4-dimethoxybenzyl derivative of sodium glycinate[18] was condensed with **16b** in refluxing ethanol to provide the substitution product **17**. Subsequent warming in acetic anhydride, followed by a brief reflux, provided the 3-acetoxypyrrolo[2,3-*d*]pyrimidine **18a** in 76% yield over two steps. Subsequent acetate hydrolysis and then immediate processing of the hydroxypyrrole led to the crystalline triflate derivative **18c** (85%, two steps). Cross coupling of this material using stannane **12** and under typical Stille conditions proceeded poorly (23% of **19**) in contrast to the benzyl derivative **11c**. Fortunately, the procedure developed by Farina et al.[19] using the air-stable Pd° source of $Pd_2(dba)_3$ and trifurylphosphine as the ligand provided a satisfactory 76% yield of the C-5 aryl adduct **19**. The acylation at the C-6 position of **19** proved to be one of the more challenging steps to optimize. Prior mixing of carboxylic acid **14** with TFAA followed by stirring with **19** for 36 h at 25 °C afforded an 18% yield of the fully protected rigidin precursor **20a** and 47% of **20b**, which resulted from further cleavage of the dimethoxybenzyl group under the acidic reaction conditions. The latter material was found to be most efficiently converted into the natural product using the following protocol: cleavage of the remaining benzyloxy and benzyl groups using excess TMSI in refluxing acetonitrile followed by heating of the crude 1,3-bis(iodomethyl) intermediate in water to provide the readily isolated bis(hydroxymethyl) compound **20c**.[13a] Simple heating of **20c** at 160 °C for 2 min afforded a pure sample of rigidin[20] in 91% overall yield for the complete deprotection procedure. The pyrrole-protected acylation product **20a** could be conveniently converted into **20b** by treatment with TFA in $CH_2Cl_2$. Attempts to convert **20a** directly into **6** using the above protocol proceeded in somewhat lower yields and was complicated by the appearance of minor by-products.

At the conclusion, the total synthesis of rigidin (**6**) proceeded in nine steps and nearly 26% overall yield starting from 6-chlorouracil and ethyl 2,4-dimethoxybenzylglycinate. The utility of the acylative pyrrole annulation approach to a highly substituted pyrrolo[2,3-*d*]pyrimidine system was thus revealed. Next we chose to focus our attention on representative

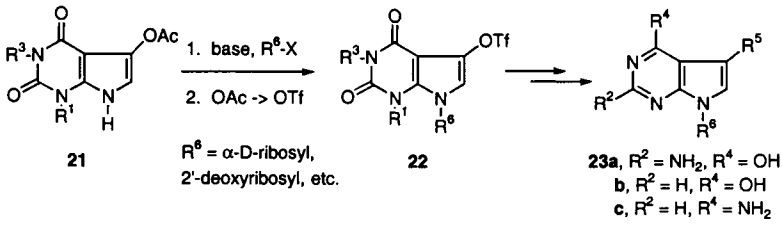



***Scheme 3.***

pyrrolo[2,3-*d*]pyrimidine-based nucleotide analogues because of their widespread interest in the areas of medicine and molecular biology.

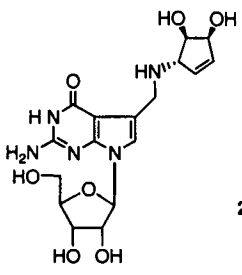
In our next adventure an approach to pyrrolo[2,3-*d*]pyrimidine-derived nucleotide analogues based on an acylative pyrrole annulation methodology was pursued (Scheme 4). This strategy is pivoted on the common synthetic intermediate **22**, which incorporates a differentially protected pyrimidine-2,4-dione ring portion and a C-5 triflate functional handle. Besides the variety of C-5 substituents that can be introduced via palladium-catalyzed procedures, a number of cyclic and acyclic carbohydrate portions can be attached by alkylation of the free pyrrole precursor **21**, which, in turn, is obtained via a cyclodehydrative pyrrole annulation reaction. By using a differentially protected pyrimidine-2,4-dione ring portion in the form of a 7-deazaxanthine, conversion into 2-amino-4-oxo-, 4-oxo-, and 4-aminopyrrolo[2,3-*d*]pyrimidine nucleoside analogues **23a–c** (7-deazaguanosines, 7-deazainosines, and 7-deazaadenosines, respectively) can, in principle, be realized.

In the past three decades, pyrrolo[2,3-*d*]pyrimidine (7-deazapurine) nucleoside analogues, both of natural and of nonnatural[21] origin, have

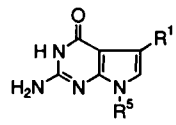



***Scheme 4.***

revealed significant biological profiles, including broad-spectrum antitumor, antiviral, and antibacterial activities. The intense interest in this class of compounds was initiated by the discovery of the antibacterial and antitumor agents tubercidin, toyocamycin, and sangivamycin.[22] A major subset of pyrrolo[2,3-*d*]pyrimidine nucleosides has the common structural feature of a C-5 substituent which can be derived from a carboxylate residue and a 7-deazaguanine-type base portion. A prominent example is the hypermodified nucleoside Q (queuosine) **24**, which is located at the first position of the anticodon of various tRNAs.[23] The related nucleoside component, cadeguomycin **25a**, was isolated from a strain of the actinomycete culture filtrate *Streptomyces hygroscopicus* IM7912T and has exhibited antitumor activity against transplantable animal tumors.[24] More recently, the structurally intriguing nucleoside, archaeosine **25b**, was identified as a phylogenetically distinct residue in tRNA of the Archaea domain and represents one of the most conserved sites throughout numerous tRNA sequences known from archaeal kingdoms.[25] The echiguanines A, **25c**, and B, **25d**, were isolated from the culture broth of *Streptomyces* strain M1698-50F1, lack a carbohydrate portion connected to the pyrrole nitrogen, and have amide substituents at the C-5 position.[26] These simplified pyrrolo[2,3-*d*]pyrimidines were found to be potent inhibitors of phosphatidylinositol kinase.



**24**



**25a**, $R^1 = CO_2H$, $R^5$ = α-D-ribosyl
**b**, $R^1 = C{=}NHNH_2$, $R^5$ = α-D-ribosyl
**c**, $R^1 = CONH(CH_2)_2C{=}NHNH_2$, $R^5 = H$
**d**, $R^1 = CONH(CH_2)_3NH_2$, $R^5 = H$

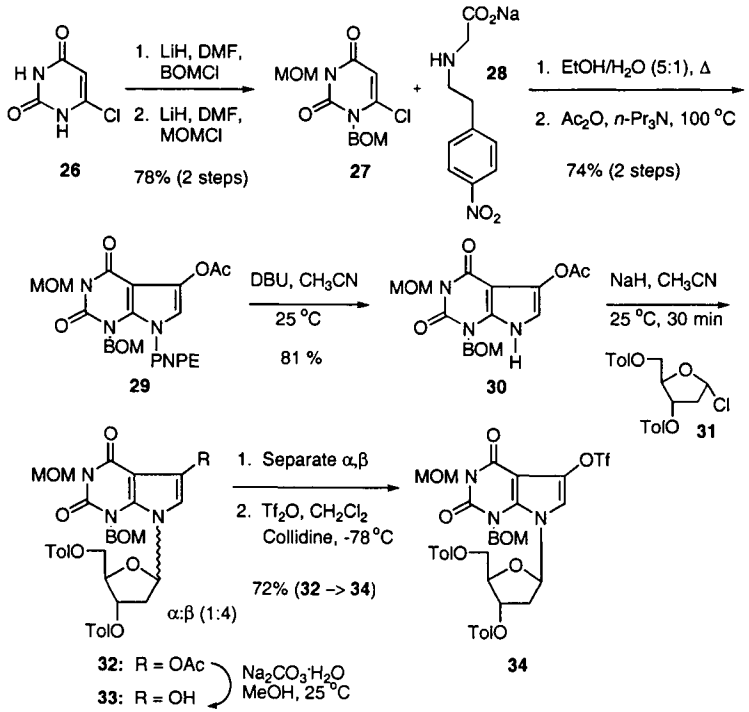
Over this period, considerable effort has been directed toward the synthesis of the variously substituted pyrrolo[2,3-*d*]pyrimidine base subunits[27] and their nucleoside derivatives resulting in many notable efforts.[28] In most cases, the synthetic source of the pyrrolo[2,3-*d*]pyrimidine portion comes from the pioneering work of Davoll[29a] or Noell and Robins.[29b] The more recent development of the sodium salt glycosidation method[28a] has greatly improved the access to key pyrrolo[2,3-*d*]pyrimidine nucleoside analogues. However, some difficulties still remain regarding the limited solubility and manipulation of key intermediates. As well, the desired substitution pattern on the base portion can require many steps to introduce different types of functional groups. A number of new methods for the synthesis of pyrrolo[2,3-*d*]pyrimidines have appeared in recent years that are applicable to specific ring substitution patterns.[30]

Our initial goal was to prepare 2′-deoxyribosyl-substituted pyrrolo[2,3-*d*]pyrimidine nucleosides that would serve as the basis for the elaboration of other analogues having variously modified carbohydrate portions. Focusing on the base portion, a number of key issues needed to be addressed, such as the choice of the appropriate protecting groups for the N-1, N-3, and N-7 nitrogens, at which stage to introduce the C-5 substituent, and when to modify the pyrimidine-2,4-dione ring portion. In considering protecting groups, the following requirements had to be met: differential protection at N-1 and N-3 which allowed for selective deprotection at either position later on, an alkyl protecting group for the pyrrole nitrogen which was compatible with the pyrrole annulation step, and the need for removal of these groups under mild reaction conditions. Another issue is the stage when the carbohydrate portion is introduced. We chose the sodium salt glycosidation method of Revankar and Robins,[28a] which involves alkylation of a pyrrolo[2,3-*d*]pyrimidine-based anion with a protected 2′-deoxyribosyl chloride. The stereochemical outcome of this step is dependent on the reactivity of the pyrrole anion which, in turn, was expected to be influenced by the electronic effect of the C-5 substituent. It was also anticipated that the steric size of the N-1 protecting group would have an influence on the glycosidation stereochemistry and further dictate when the pyrimidine-2,4-dione ring portion was modified.

A methoxymethyl (MOM) protecting group at N-3 was chosen based on its successful use in the total synthesis of nucleoside Q.[31] Our previous experience with the total synthesis of rigidin (*vide supra*) suggested BOM protection for the N-1 position and a 2,4-dimethoxybenzyl (DMB)

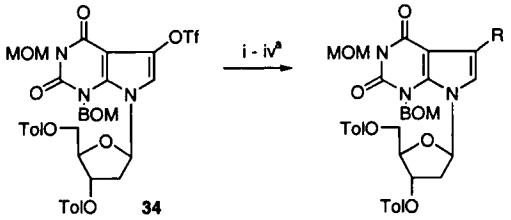
group for the pyrrole nitrogen because of their ease of removal using TMSI and/or TFA for the latter. However, the DMB group proved unworkable in the current scheme[32] and was abandoned. In its place we elected to try a new protecting group that could be cleaved under mild base conditions in analogy with previous work involving the protection of the O-6 position in guanosine nucleosides.[33] The choice became the *p*-nitrophenethyl (PNPE) group because of its ease of incorporation into our synthetic scheme.

Our primary target became the key C-5 triflate intermediate **34** having the standard bistoluoyl ester protected 2′-deoxyribosyl portion and the other protecting groups mentioned above, attached as shown below (Scheme 5). Starting with 6-chlorouracil (**26**), sequential alkylation at N-1[34] and then N-3 using LiH in DMF with the appropriate alkyl chloride provided the differentially protected uracil derivative **27** in 78% yield. Treatment of **27** with the sodium salt derived from ethyl *N*-*p*-nitrophenethylglycinate (**28**) afforded a substitution adduct that was isolated as its crude acid. Subsequent exposure of this material to acetic




***Scheme 5.***

anhydride and amine base, with heating, afforded the 5-acetyloxy-pyrrolo[2,3-*d*]pyrimidine-2,4-dione **29** in 74% isolated yield for the two steps. It proved advantageous at this stage to remove the PNPE blocking group using mild base conditions to afford the free pyrrole **30**. In the next step, sodium-salt glycosidation[28a] of **30** involving 1-chloro-2-deoxy-3,5-ditoluoyl-α-D-*erythro*-pentofuranose (**31**) could be effected with a preference for the β isomer (α:β, 1:4).[35] This result contrasts with the glycosidation stereochemistry observed for a system having an electron-withdrawing group at the C-5 position, as discussed below. The resulting adduct **32** from above was treated with mild base to effect hydrolysis of the 5-acetyloxy group and provide the 5-ketopyrrole **33**. The resulting mixture of α and β isomers revealed the unique advantage of being readily separable by simple column chromatography over silica gel. Attempted separation of the α and β isomers at later stages proved much more tedious (*vide infra*). With the pure β isomer of **33** in hand, conversion to the 5-trifluoromethanesulfonylpyrrolo[2,3-*d*]pyrimidine-2,4-dione **34** was effected in high yield.




(6)

i $Pd(OAc)_2$, $Ph_3P$[b], CO, $Et_3N$, DMF, MeOH, 68 °C, 2 h

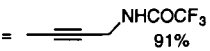
ii $Pd(PPh_3)_4$, CuI[c], $Et_3N$, DMF, $HCCCH_2NHCOCF_3$, 30 °C, 1 h

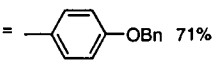
iii $Pd(PPh_3)_2Cl_2$, $Et_3N$, DMF, $H_2C{=}CHCO_2Et$, 90 °C, 17 h

iv $Pd_2dba_3$, $(furyl)_3P$[d], $ArSn(n\text{-}Bu)_3$, NMP, 55 °C, 16 h

**35**: R = $CO_2Me$, 83%

**36**: = $CH{=}CHCO_2Et$, 82%

**37**: =  91%

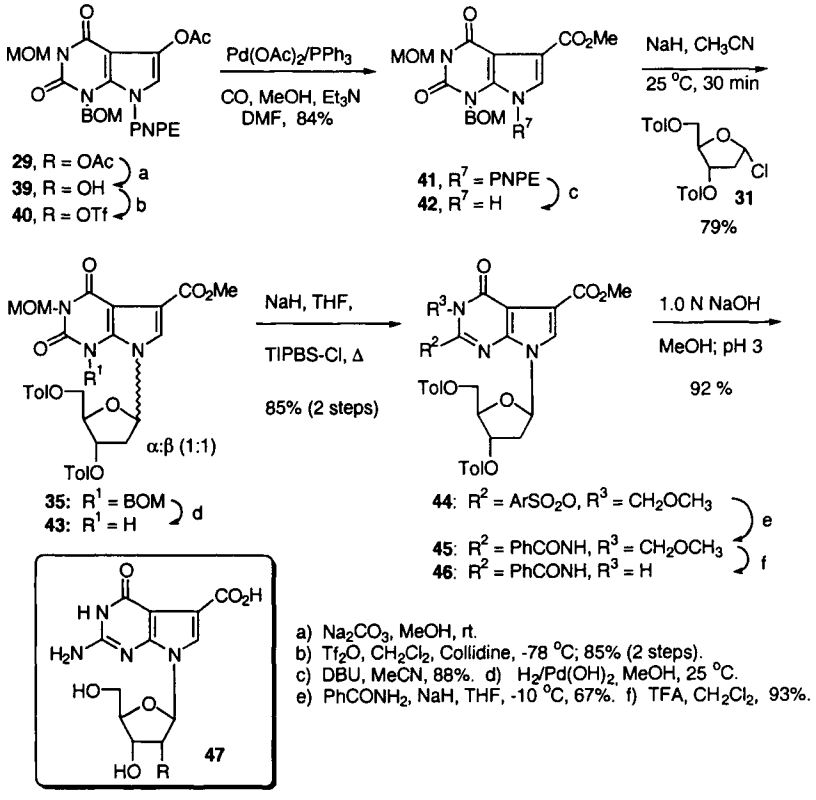
**38**: =  71%

[a]All reactions used 10 mol % palladium catalyst. [b]Metal to ligand ratio (1:3). [c]20 mol % CuI used. [d]Metal to ligand ratio (1:2).

Representative reactions of pyrrolo[2,3-*d*]pyrimidine triflate **34**[36] using four major types of palladium-catalyzed carbon–carbon bond-forming reactions are illustrated in Eq. 6. Thus, methoxycarbonylation of **34** was performed using the standard protocol of Ortar and co-workers[37a] and afforded ester **35** in good yield. The Heck reaction with an electron-deficient alkene, represented by ethyl acrylate, provided **36** in respectable yield.[37b] The copper (I)-promoted coupling with *N*-trifluoro-

acetylpropargylamine, leading to **37**, proceeded in high yield using reaction conditions that proved effective in related 5-iodopyrrolo[2,3-*d*]pyrimidine derivatives.[36] The Stille-type coupling with a more demanding electron-rich aryl stannane was carried out using the modified reaction conditions developed by Farina and co-workers.[37c] The C-5 aryl-substituted compound **38** was isolated in a reasonable 71% yield. Based on this reactivity study, it can be expected that **34** will reveal general reactivity toward other coupling partners in these types of palladium-catalyzed reactions.

At this stage we focused on the conversion of the pyrrolo[2,3-*d*]pyrimidine-2,4-dione ring portion into a 2-amino-4-oxopyrrolo[2,3-*d*]pyrimidine characteristic of 7-deazaguanosines (Scheme 6). As an end target of this venture we elected to synthesize 2′-deoxycadeguomycin **47**,[38] a known analogue of cadeguomycin (**25a**). Starting with the 5-




***Scheme 6.***

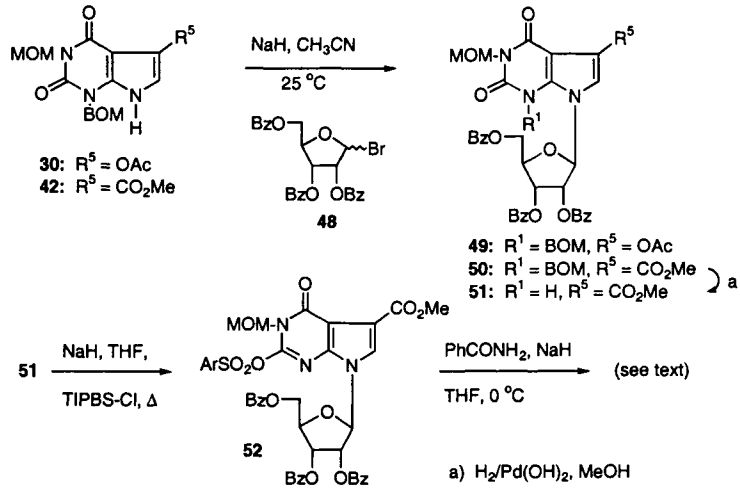
acetyloxy-pyrrolo[2,3-*d*]pyrimidine-2,4-dione 29, hydrolysis under mild basic conditions afforded the trione **39** which was directly processed to the C-5 triflate derivative **40** in 85% yield for the two steps. Palladium-catalyzed methoxycarbonylation, as described above, provided an 84% yield of ester **41**. The PNPE group was cleanly removed from the pyrrole nitrogen using DBU in acetonitrile at room temperature. The reaction of the pyrrole anion derived from **42** with ribosyl chloride **31** provided adduct **35** as a 1:1 mixture of α and β isomers. This contrasts with the C-5 acetoxy-substituted system from above and other pyrrolo[2,3-*d*]pyrimidine anions[28a,b] which show moderate to exclusive preferences for the β isomer. Thus, the electron-withdrawing ester group in **42**, by stabilizing the corresponding negative charge on its pyrrole nitrogen, diminishes its reactivity allowing time for the ribosyl chloride to isomerize under the reaction conditions. Another factor that would inhibit the reactivity of the pyrrole anion derived from **42** would be the steric bias provided by the adjacent N-1 BOM protecting group.

The next key transformation involved introduction of the 2-amino substituent on the pyrrolo[2,3-*d*]pyrimidine ring. Differential protection of the N-1 and N-3 positions allowed us to selectively remove the N-1 BOM group from **35** using Pearlman's catalyst.[39] The resulting free amide **43** was converted into its 2-*O*-sulfonyl derivative **44** (α:β, 1:1) by treatment with sodium hydride and triisopropylbenzenesulfonyl chloride (TIPBS-Cl). The pure β isomer of **44** was obtained somewhat tediously by sequential recrystallizations from ethyl acetate/hexanes. Attempted separations at later stages proved impossible because of the similar $R_f$ values of the two isomers. The amination at C-2 in compound **44** presented difficulties as a result of competing side reactions. For example, the reaction with various nitrogen nucleophiles ($NH_3$, $CH_3CONHNa$) afforded significant amounts of precursor **43** resulting from cleavage of the sulfonyl ester bond.[40] This problem was circumvented by using a sterically larger nucleophile derived from benzamide. As a result, the desired amination product **45** was afforded in 67% yield with the 2-amino group conveniently introduced as its protected benzamide derivative. At this stage, the methoxymethyl group at N-3 was removed by treatment with TFA to afford **46** in high yield. The final step involved simple base hydrolysis of the toluoyl esters from the 3′ and 5′ hydroxyl groups, the benzamide group at the 2-amino position, and the methyl ester at C-5. The final product, 2′-deoxycadeguomycin (**47**), was conveniently isolated by precipitation from the reaction solution following acidification to pH 3. The identity of our sample of 2′-deoxycadeguomy-

cin with the literature[38] was confirmed by comparison of $^1$H NMR, UV, and m.p. data.

An improved synthetic route to 2′-deoxycadeguomycin (**47**) was now in place by utilizing the chemistry developed in Scheme 5. The advantage of introducing the C-5 ester group after the glycosidation step becomes obvious. Since the glycosidation stereochemistry obtained from alkylation of the 5-acetyloxypyrrolo[2,3-*d*]pyrimidine **30** gave a preference for the β isomer, and the ready separation of the minor α isomer was easily accomplished by simple silica gel chromatography of the subsequently derived pyrrolo[2,3-*d*]pyrimidine-2,4,5-trione **33**, an overall higher chemical throughput to the pure β ester **35** was provided. This compound was then processed into **47** using the same route shown in Scheme 6.

In efforts to extend aspects of this approach to the synthesis of ribose-containing 7-deazapurine nucleosides, glycosidation studies of the differentially protected pyrrolo[2,3-*d*]pyrimidine-2,4-dione derivatives **30** and **42** were initiated (Scheme 7). By utilizing the sodium-salt glycosidation method of Robins,[28a] and the known tribenzoylribosyl bromide **48**, reasonable yields of the glycosidated products **49** and **50** were obtained. In both cases exclusive formation of the β isomer was observed as is typically seen using this ribose derivative. Further transformation of the ester adduct **50** by removal of the BOM protecting group afforded **51**, which, on sulfonation, gave the 2-*O*-sulfonyl derivative **52**. Attempts to aminate this compound using the protocol developed above




***Scheme 7.***

(Scheme 6) resulted in a mixture of highly polar compounds. Indirect chemical evidence suggested that competing cleavage of the benzoyl protecting groups on the ribose portion had occurred. Because of solubility problems at the temperature required to achieve the desired amination, further efforts along this route were abandoned.

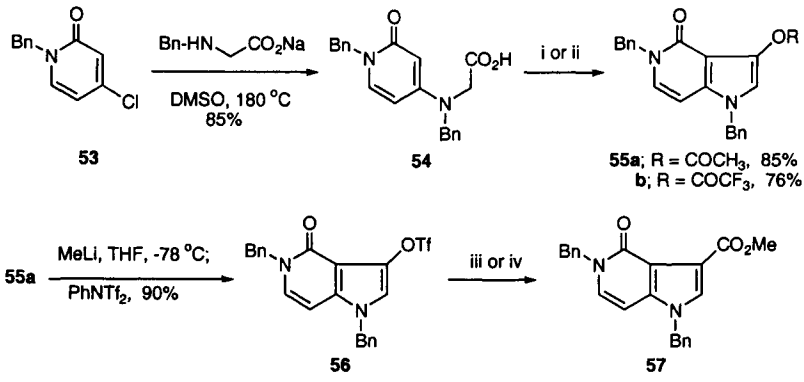
At this stage a new approach for the synthesis of 7-deazapurine nucleosides has been demonstrated leading to the synthesis of 2-deoxycadeguomycin. A key feature is the conversion of differentially protected 2′-deoxyribosylpyrrolo[2,3-*d*]pyrimidine-2,4-dione into a protected 2-aminopyrrolo[2,3-*d*]pyrimidine-4-one. Efforts toward the ribo-series of intermediates has revealed some promise although issues regarding the choice of ribose protecting groups need to be sorted out.

Future studies may be directed toward the conversion of key intermediates related to compounds **35–38** into 4-amino- and 4-oxopyrrolo[2,3-*d*]pyrimidine nucleoside analogues (7-deazaadenosines and 7-deazainosines, respectively).

## B. Pyrrolo[3,2-*c*]pyridin-2-ones and Pyrido[3,4-*b*]pyrrolizidin-1-ones

Our interest in expanding the acylative pyrrole annulation approach to additional heterocyclic systems has led to an efficient synthesis of pyrrolo[3,2-*c*]pyridin-2-ones and pyrido[3,4-*b*]pyrrolizidin-1-ones starting from 4-chloro-*N*-benzyl-2(1*H*)-pyridinone and amino acid salts.[8c] Over the years pyrrolo[3,2-*c*]pyridines (5-azaindoles)[41] have been of interest for applications as elements in new drug design, nucleotide analogues,[42] and biochemical tools. However, available synthetic routes to multifunctionalized members from this class of heterocyclic structures are limited.[41–43]

The synthetic plan is outlined below (Scheme 8). The requisite cyclization precursor was obtained by heating *N*-benzyl-4-chloro-2(1*H*)-pyridinone (**53**)[44] with sodium *N*-benzylglycinate in DMSO for 45 min followed by an acidic workup. Exposure of the isolated free acid **54** to acetic anhydride with added base catalyst, and then heating for 4 h, afforded the 3-acetoxy pyrrole derivative **55a**[6] in high yield. This acylative cyclodehydration reaction could also be effected using TFAA and added base with lower reaction temperatures being required. Notably, even in the presence of excess acetic anhydride or TFAA, further acylation at the electron-rich C-2 position of the pyrrole ring was not observed.

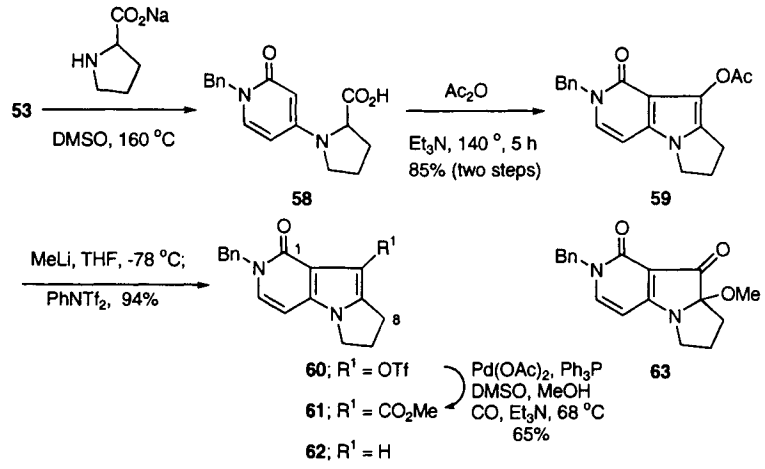



i $Ac_2O$, $Et_3N$, 130 °C. ii TFAA, $Et_3N$, $CH_2Cl_2$, 35 °C. iii $Pd(OAc)_2$:dppp (1:1), DMSO, CO, MeOH, $Et_3N$, 65%. iv $Pd(OAc)_2$:$Ph_3P$ (1:4.5), DMF, CO, MeOH, $Et_3N$, 80%.

***Scheme 8.***

Conversion of the 3-acetoxy pyrrole **55a** into its triflate derivative **56** proved more difficult than expected. Reaction conditions that had proven successful in the case of pyrrolo[2,3-*d*]pyrimidin-2,4-diones ($Na_2CO_3$, MeOH, Δ, 5 min; $Tf_2O$, collidine, –78 °C)[8a] afforded none of the desired triflate **56**. During the base hydrolysis step, rapid and drastic color changes were noted.[45] $^1H$ NMR analysis of the crude reaction mixture indicated that the formation of the intermediate pyrrolo[3,2-*c*]pyridin-2,3-dione was accompanied by extensive formation of uncharacterized by-products.[46] Fortunately, this problem was surmounted by reaction of **55a** with 2 equiv of methyl lithium at –78 °C, which presumably led to the formation of an enolate intermediate. This species could then be efficiently trapped with *N*-phenyl triflimide at low temperature[47] before it had an opportunity to self-condense. In this way, high yields of the desired triflate **56** were routinely obtained. To demonstrate a representative palladium-catalyzed reaction, the triflate intermediate **56** was subject to methoxycarbonylation utilizing the procedure of Dolle and co-workers to afford the ester **57** in 65% yield.[48a] By using $Ph_3P$ as the ligand and DMF as the solvent, the carbonylation yield increased to 80%.[48b]

So as to expand the methodology by incorporating a cyclic amino acid, compound **53** was treated with sodium prolinate in hot DMSO to afford the crude substitution adduct **58** (Scheme 9). Subsequent cyclodehydration using acetic anhydride provided the pyrido[3,4-*b*]pyrrolizidin-1-one **59**[49] in high overall yield for the two steps. Following the protocol




*Scheme 9.*

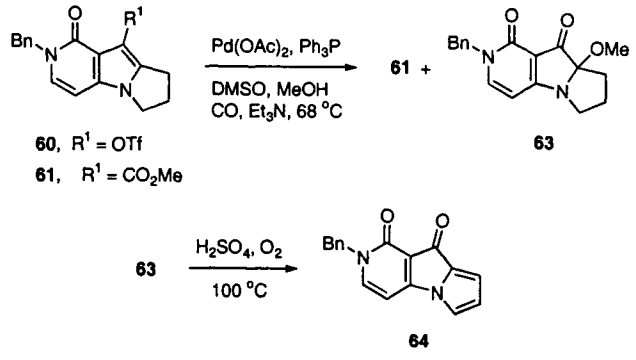
described above, this compound was converted into the triflate intermediate **60** in high yield. The methoxycarbonylation of this compound, leading to the ester **61**, proved somewhat difficult and was attributed to steric hindrance at C-9 arising from peri-interactions at the adjacent C-1 and C-8 positions. For example, using dppp as the ligand[48a] and $Pd(OAc)_2$ as the catalyst source, the reduction product, **62**, was coproduced along with the desired product and a new compound, **63**. Procedures[48b] using $Ph_3P$ as the ligand with 5–10% palladium catalyst afforded varied mixtures of ester **61** and compound **63** which were dependent on the time required to consume the starting material.[50] It was found that the desired carbonylation reaction could be best reproduced in 60–65% yield using 30% catalyst and $Ph_3P$ as the ligand (ligand-to-palladium ratio of 4.5:1). These conditions greatly accelerated the consumption of the triflate and minimized formation of the by-product **63**. Further details regarding the unusual oxidative hydrolysis process leading to **63** will be discussed in the next section.

A new approach for the synthesis of pyrrolo[3,2-*c*]pyridin-2-ones and pyrido[3,4-*b*]pyrrolizidin-1-ones starting from a simple 4-chloro-2-pyridinone intermediate and amino acid salts has been demonstrated. Synthetically versatile triflate intermediates **56** and **60** are provided which can serve as precursors for a variety of novel structures. The further development of this methodology for the synthesis of aza-mitosene[51] and 5-azaindole nucleoside analogues is now possible.

## C. Ionization of Pyrrole-3-triflates

In recent years the advent of heteroaromatic triflates[10] as building blocks for the synthesis of more elaborate heterocyclic structures using palladium-catalyzed carbon–carbon bond-forming reactions has become well recognized. The background for this effort was preceded somewhat by major developments involving the utility of aryl and vinyl triflates in synthesis.[9] Although these latter two classes of compounds have been known for years, their fundamental chemistry remained largely unknown until the early 1970s.[52] Notably, Stang and co-workers pioneered the use of vinyl triflates as precursors for the generation of unsaturated cations and carbenes.[53] In the 1990s, the subfield of organotriflate chemistry involving unsaturated systems is dominated by applications as partners in palladium-catalyzed bond-forming reactions.

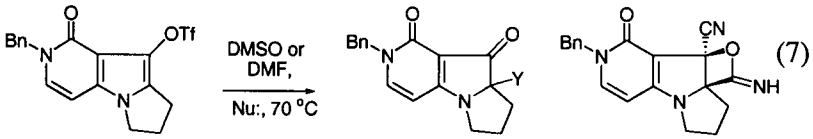
At the time we were exploring aspects of pyrrole-3-triflate systems, the fundamental chemistry of unsaturated triflates appeared well understood. As mentioned in the preceding section, our expectation for running what appeared to be a straightforward methoxycarbonylation reaction with a new type of pyrrole-3-triflate system resulted in an unexpected discovery. Thus, when the palladium-catalyzed methoxy-carbonylation of pyrido[3,4-*b*]pyrrolizidine triflate **60** into the desired ester **61** was attempted, a minor side product arose, which was determined to be the 8*a*-methoxy-pyrido[3,4-*b*]pyrrolizidin-1,9-dione, **63** (Scheme 10). Compound **63** revealed the following spectral characteristics. The $^1$H NMR showed sets of diastereomeric proton signals for each of the ring and the benzyl methylene protons. The IR spectrum revealed the presence of two carbonyl groups at 1713 and 1646 cm$^{-1}$, which was consistent




***Scheme 10.***

with two signals in the $^{13}C$ NMR at 194.0 and 172.7 ppm. To further support the structure assigned to **63**,[54] exposure of this material to hot sulfuric acid in the presence of air resulted in elimination of methanol and *in situ* oxidation of the pyrroline intermediate to afford the aromatic compound **64** in 90% yield.[55]

To determine the necessary elements needed for this transformation, each of the key reaction components was systematically left out. It was noted that an absence of base led to a greatly increased yield of compound **63**. In fact, the only required components are a polar aprotic solvent (DMSO or DMF), methanol, and gentle heating. In this way a high yield of **63** could be obtained (Eq. 7). The palladium (II) salt in solution was



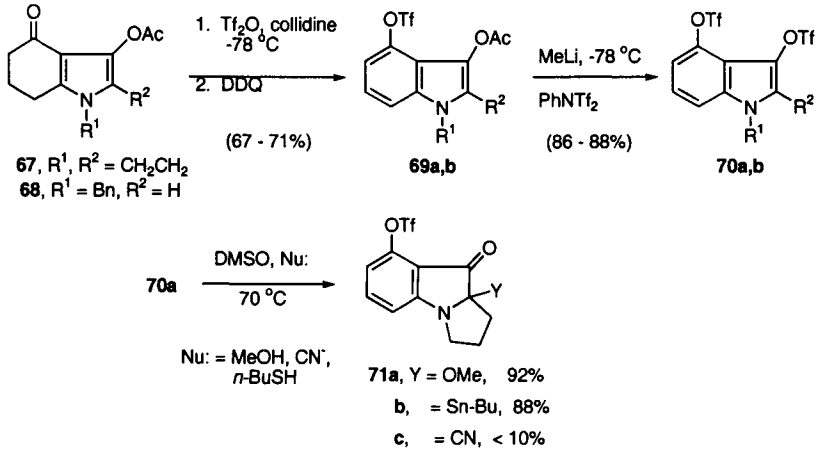

**60** Nu: = MeOH, $CN^-$, *n*-BuSH

**63** Y = OMe, 82%
**64** = CN, 72%
**65** = S(*n*-Bu), 82%

**66** (7)

not found to be necessary for the reaction to proceed. Methanol can be seen to serve as a nucleophile in this process. To test this proposal, the reaction was run in the presence of other nucleophiles. Gentle heating of a solution of compound **60** and a slight excess of KCN in DMF or butanethiol in DMSO resulted in the isolation of adducts **64** and **65** in good yield. Interestingly, treatment of **60** with an excess of NaCN in DMSO afforded a new compound **66**[56] in 55% yield which incorporated 2 mol of cyanide.[57] A likely mechanistic rational accounting for the formation of this compound would have the second equivalent of cyanide adding to the C-9 carbonyl group of **64** forming a cyanohydrin intermediate. It can be imagined that the newly formed hydroxy group then adds across the adjacent *cis*-oriented nitrile group at C-8a leading to the formation of the cyclic imidate ring.[58]

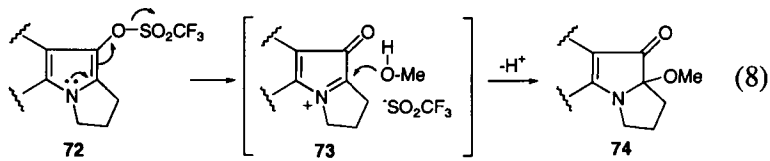
To test the generality of this reaction, the indole systems **70a,b** were prepared from hexahydro-8-oxopyrrolo[1,2-*a*]indole **67** and tetrahydro-4-oxindole **68** (Scheme 11). These compounds in turn were readily obtained from cyclohexane-1,3-one and the appropriate amino acid salt according to Franck's pyrrole acylation protocol.[5a] Attempts to directly oxidize **67** or **68** to the hydroxyindole oxidation state using DDQ met with failure despite numerous attempts involving variation in solvent and reaction temperature. To circumvent this limitation, it was reasoned that




***Scheme 11.***

dehydrogenation from a preformed enol derivative would be more facile and should lead to a phenolic derivative in a two-step process. Attempts to form enolsilane or enol acetate derivatives from **68** resulted in no reaction. Fortunately, the more reactive combination of $Tf_2O$ and collidine afforded an unstable enol derivative which was directly oxidized with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to afford the triflate derivatives **69a,b**. Utilizing our one-step protocol revealed earlier (Scheme 8), **68a,b** were converted into the bistriflate derivatives **70a,b**. These two compounds were subject to the same solvolytic reaction conditions discussed above. The pyrrolo[1,2-*a*]indole **70a** was found to react cleanly and afford adducts **71a,b** in good yield. In contrast, the 2-unsubstituted indole system **70b** did not react under these conditions. This can be attributed to the need to stabilize the developing positive charge on the α-carbon atom (*vide infra*).

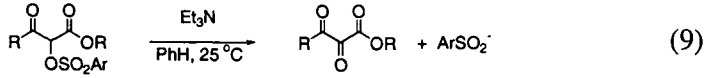
A mechanistic rational for the ionization of pyrrole-3-triflates **72** was proposed as shown below (Eq. 8). Heterolytic cleavage of the sulfonate ester bond, assisted by donation of the nitrogen lone pair, results in loss of the triflinate ion[59] and gives rise to the C-acyl iminium ion intermediate **73**. This process is further facilitated by the stabilizing effect of a




(8)

polar aprotic solvent. An external nucleophile, such as a solvent molecule of methanol, then attacks at the α-carbon of **73** and results in the observed product **74**, following proton loss. The overall process can be seen as a solvolysis reaction with a concomitant internal redox process, i.e., reduction of the S–O bond and oxidation at the pyrrole α-carbon. This form of reactivity for aromatic triflates was unprecedented.

Typically, vinyl triflates form vinyl carbocation intermediates through loss of the triflate ion.[53] On the other hand, attempts to form aryl cations by ionization of aryl triflates have not been successful confirming the high energy of these species. What is interesting about the process proposed is the relative ease with which the aromatic ring is disrupted leading to intermediate **73**. Likely, the weakness of the sulfate ester bond is a consequence of relieving lone pair repulsion between the pyrrole nitrogen and the sulfenate ester oxygen atom. Similar reasoning can be used to explain why many 3-hydroxypyrroles exist in their 3-keto tautomeric forms.[60] On examination of the literature, examples of reaction processes that involve the loss of triflinate (triflone) ion from a heteroatom are few. The reductive cleavage of 2-(*p*-nitrobenzenesulfonyl)oxy-1,3-dicarbonyl compounds to 1,2,3-tricarbonyl derivatives involves the loss of nitrobenzenesulfinite from an oxygen atom (Eq. 9).[61] The conversion of alcohols into triflates by reaction with triflic anhydride in the presence of certain amine bases can give rise to minor amounts of sulfinites (triflinates).[62] The source of these by-products was proposed to arise from the breakdown of a preformed ammonium salt into a triflinate salt which reacts further to form a mixed anhydride, as shown below (Eq. 10).

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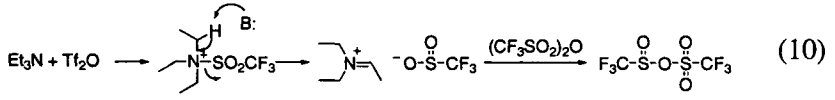
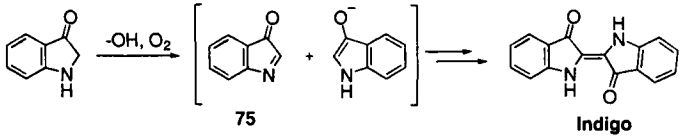



(10)

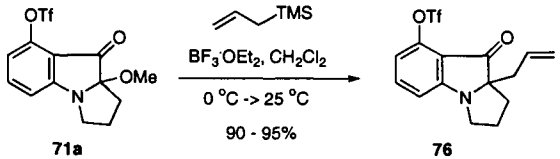
The viability of the "azacyclopentanadienone" ion **73**,[63] as proposed in our mechanism, fits in with other literature precedents. Recently, based on mechanistic evidence, the oxidative dimerization of indoles to bisindol-3-ones has been suggested to proceed via α-ketoiminium ion analogous to **73**.[64] The neutral relative to such a species, 3*H*-indol-3-one (**75**), has been suggested as a possible intermediate in the base-catalyzed




(11)

oxidative dimerization of 3-indoxyl leading to the formation of indigo (Eq. 11).[63] In fact, **75** has recently been isolated and characterized as a pigment in pink mushrooms.[65] The *N*-protonated C-3 methylene analogue of **75** has long been proposed as a stabilized cationic intermediate in reactions of indole-3-methanol under acidic conditions.[66]

To provide further evidence for the intermediacy of cyclic C-acyl iminium ions of the type mentioned above, a preliminary experiment was conducted (Eq. 12). It seemed reasonable that the mixed aminal linkage



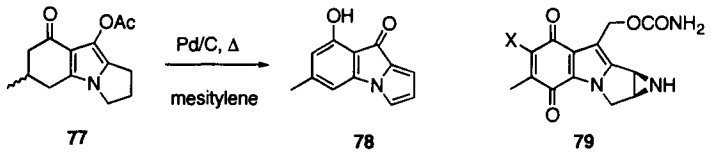

(12)

in **71a**, on exposure to Lewis acid, would generate a reactive electrophilic species that could be trapped with a soft carbon nucleophile such as an allylsilane. In practice it was found that both $BF_3$ etherate or tin(IV) chloride worked equally well to afford the allylated product **76** in high yield. As a result, a basis for introducing carbon functionality at the C-9a position of the pyrrolo[1,2-*a*]indole skeleton has been established.

By good fortune we have uncovered an unknown form of reactivity for heteroaromatic-based organotriflates. In particular, pyrrole-3-triflates bearing an alkyl group in the α-position are seen to undergo an overall oxidative hydrolysis process in polar aprotic solvents, which leads to the synthesis of α-substituted 3-ketopyrroles. Synthetically useful functional groups can be introduced to the α-position including methoxy, cyano, and alkylmercapto. Further use of α-methoxy-3-ketopyrroles for the synthesis of geminally substituted 3-ketopyrrole subunits has been established in one case and can serve as the basis for further methodological developments. Application of this methodology for the synthesis of novel azamitosene[67] and mitomycin precursors[68] can be considered.

## D. Pyrrolo[1,2-*a*]indoles

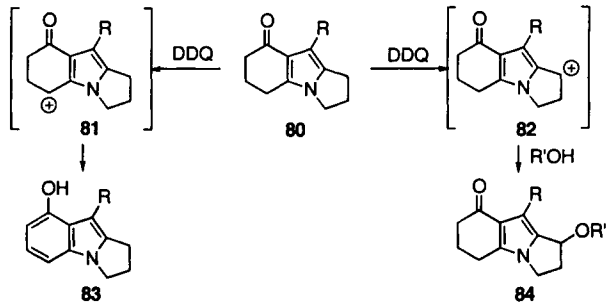
The origin of Franck's approach to the mitosenes was the 2,3,5,6,7,8-hexahydro-8-oxo-1*H*-pyrrolo[1,2-*a*]indole **77**, easily prepared in two




77 78 79

steps from 5-methylcyclohexane-1,3-dione and sodium prolinate via a pyrrole acylation approach.[5a] In seeking a more fully functionalized mitosene precursor, dehydrogenation of **77** over palladium on carbon afforded the completely aromatized compound **78** in variable yields. Further efforts along these lines were not pursued. The remaining challenges toward this objective would entail elevation of the A-ring to an aminoquinone, installation of a carbon appendage at C-9, and incorporation of the aziridine ring as depicted in the generalized aziridinomitosene **79**. We felt that the possibility for regio- and chemoselective oxidative functionalization of hexahydro-8-oxo-1*H*-pyrrolo[1,2-*a*]indoles still presented opportunities for accessing highly functionalized mitosene analogues. The availability of compounds such as **77** in quantity made such an effort attractive from an economic standpoint.

In the initial phases of this effort a means for introducing appropriate functionality in the C-1/C-2 positions from an unsubstituted precursor such as **80** that would eventually lead to an aziridine ring in the final target compound(s) was needed. When considering the oxidation of simple hexahydro-8-oxo-1*H*-pyrrolo[1,2-*a*]indoles using DDQ, two mechanistic pathways are possible leading to either of the carbocationic intermediates **81** or **82** via hydride abstraction at C-5 or C-1, respectively (Scheme 12).[69] Proton loss from **81** would ultimately lead to the phenolic product **83** whereas nucleophilic trapping of intermediate **82** by alcohols would afford the C-1-substituted ethers **84**. Oxidative transformations at

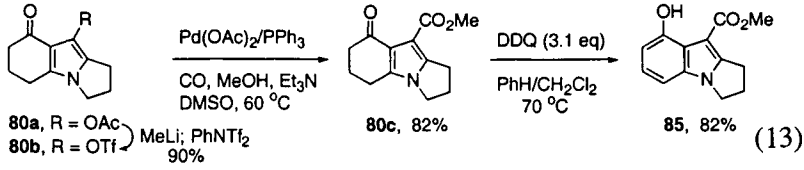



81 80 82 83 84

*Scheme 12.*

the benzylic position induced by DDQ are well-known methods in organic synthesis.[70] On the other hand, examples of oxidative transformations of methylene groups adjacent to heteroaromatic rings are less common. In the case of triisopropylsilyl-protected furan rings, regioselective functionalization occurs at only the methylene group in the α-position.[71] For certain 2,3-dialkyl-substituted indoles, only the C-3 position is functionalized.[72] In the context of the present study, it was felt that the electronic effect of the C-9 substituent on the pyrrolo[1,2-*a*]indole ring in **80** would play an important role in dictating the eventual regiochemical course of the reaction.[73]

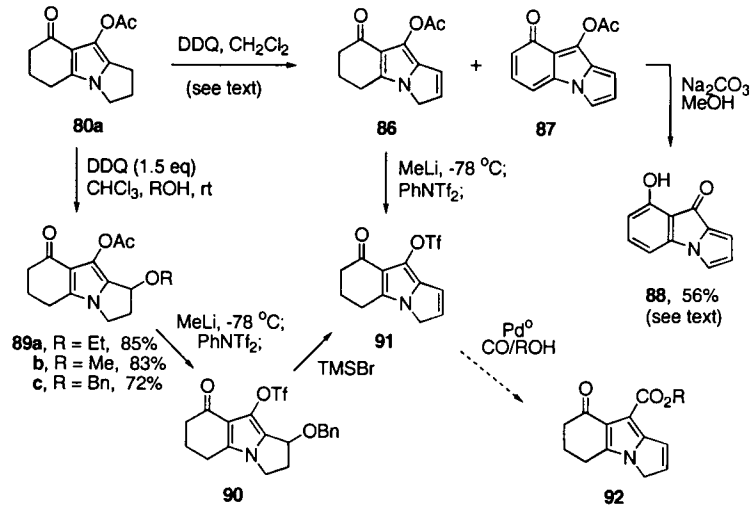
The C-9-substituted 8-oxopyrrolo[1,2-*a*]indole systems **80a–c** were prepared using methodology developed previously in our route to pyrrolo[3,2-*c*]pyridin-4-ones and indolequinones.[8c,f] Thus, treatment of C-9 acetoxy compound **80a** with MeLi (2.0 equiv) at −78 °C followed by *N*-phenyltriflimide afforded the triflate **80b** in high yield. Exposure of **80b** to modified[74] palladium-catalyzed methoxy-carbonylation conditions provided ester **80c** in 82% yield (Eq. 13). Exposure of this com-



(13)

pound to 3.0 equiv of DDQ afforded a good yield of the 8-hydroxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole **85** in accord with our previous observations involving 4-oxotetrahydroindoles.[8f] Limiting amounts of DDQ afforded only **85** and recovered starting material with no evidence of intermediate compounds.

On the other hand, compounds **80a,b**, when treated with varying amounts of DDQ using different solvents and reaction temperatures, presented some interesting results (Scheme 13). The C-9 triflate **80b** proved unreactive, even under reflux in benzene or $CHCl_3$ for extended periods of time. In contrast, the C-9 acetoxy compound **80a** afforded the unexpected oxidation product **87** when treated with 3.0 equiv of reagent in benzene at 80 °C for 30 min. The structure of **87** was confirmed by its subsequent conversion to the 9-oxopyrrolo[1,2-*a*]indole **88** on mild basic hydrolysis. However, when **80a** was exposed to a limiting amount of oxidant (1.0 equiv) at room temperature in $CH_2Cl_2$ for 1.5 h, the tetrahy-




*Scheme 13.*

dro-3*H*-pyrrolo[1,2-*a*]indole **86** was produced admixed with starting material and 10% of compound **87**. The nearly inseparable mixture of **86** and **80a** was obtained in a ratio of 2:1 which accounted for 70% of the overall mass. With some effort, pure **86** could be isolated from the crude reaction mixture in 38% yield by careful recrystallization from ethyl acetate/hexanes. Although this result showed initial promise, difficulties isolating quantities of **86** rendered this approach impractical.

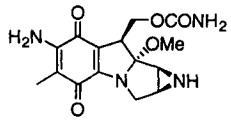
Attempts to optimize the conversion of **80a** to **86** by variation of solvent and reaction temperature fortuitously led to the isolation of the C-1-substituted ether **89a** as a minor by-product. This was attributed to traces of ethanol present in the chloroform. By adding in several equivalents of various alcohols, good yields of the C-1 functionalized ethers **89a–c** could be realized. At this stage further conversion into the C-1 triflate derivative **91** was needed. Either of two approaches proved workable. From alkene **86**, exposure to MeLi at –78 °C followed by $PhNTf_2$, according to the protocol reported earlier (Section III.B),[8c] afforded a modest yield of **91**. An alternative path to this compound was realized by first treating C-1 benzyl ether **89c** with the same reaction conditions to give a new triflate **90**. Hoping to cleave the benzyl ether and generate a C-1 alcohol, treatment of **90** with TMSBr led instead to the unsaturated triflate **91** via direct elimination of benzyl alcohol. As a result, a more convenient route to this compound was uncovered. Unfor-

tunately, attempts to effect the palladium-catalyzed alkoxy- or hydroxycarbonylation of **91** leading to **92**, using a variety of established procedures,[48] met with failure. Basically, no reaction was observed and attempts to force the reaction by heating or CO pressurization led to the precipitation of palladium black. At this stage the only remaining way to salvage our approach would have to rely on a reordering of steps, i.e., carbonylation of C-1 substituted triflate **90** and then liberation of the C-1/C-2 alkene after the carboxy group was in place. Realizing our position and desiring to move into the actual system that would ultimately lead to authentic mitosene structures, we turned our attention to the C-5 methyl-substituted system **98** (*vide infra*).

The results from this preliminary study demonstrated the reality of effecting the regioselective oxidative functionalization of simple 8-oxo-1*H*-pyrrolo[1,2-*a*]indoles as a function of the electronics of the C-9 ring substituent. Access to the C-1-substituted ethers **89a–c** and tetrahydro-3*H*-pyrrolo[1,2-*a*]indole **86** allows for an entry into the mitosenes that was not previously possible.[68]

## E. 7-Aminoaziridinomitosenes

Synthetic efforts directed toward the pyrrolo[1,2-*a*]indole ring system are a major area of interest[75] because of the presence of this structural subunit in the mitomycin and mitosene class of anticancer alkaloids. Notably, mitomycin C (**93**) is an important clinical drug that has been used extensively in cancer chemotherapy treatments although its utility is plagued with many toxic side effects. The 7-aminoleucoaziridinomitosene (**94**) is believed to be the key bioactive factor[76] which is derived from **1** via reductive activation. The oxidized relative of **94**, 7-aminoaziridinomitosene (**95**, X = $NH_2$), can be chemically derived[76] from mitomycin C, although it does not reveal significant anticancer activity unlike other 7-substituted aziridinomitosenes.[77] Considerable effort has been directed toward understanding the mode of action for mitomycin C and related agents and continues unabated.[78] In addition to the formidable challenges presented in the total synthesis of these targets, there remains an interest in the synthesis and biological evaluation of structural ana-



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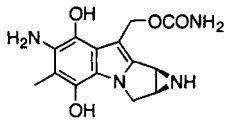

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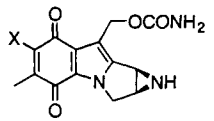

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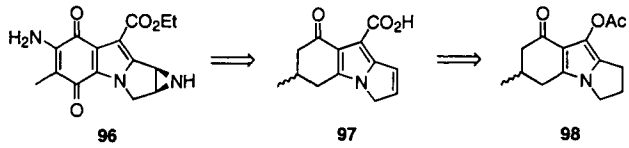
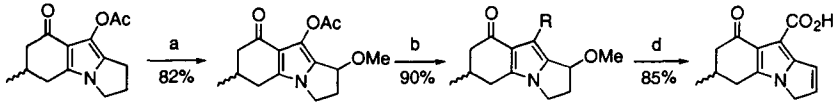


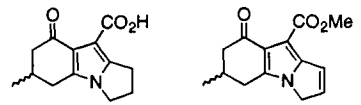

logues[79] that maintain high activity toward cancer cells and reveal lower associated toxicity toward healthy cells.

As outlined retrosynthetically below, we realized the good fortune of developing an efficient 12-step route to a fully functionalized aziridinomitosene analogue **96** commencing from the easily obtained 2,3,5,6,7,8-hexahydro-8-oxo-1*H*-pyrrolo[1,2-*a*]indole **98** and proceeding via the known unsaturated acid **97**.[80] As already mentioned, Franck and coworkers[5a] have reported a highly efficient two-step route to compound **98** starting with commercially available 5-methyl-cyclohexane-1,3-dione and sodium prolinate.

On the basis of the findings in our preliminary model studies (Scheme 13), an improved route to the known unsaturated acid **97** from Franck's compound **98** was deemed a worthy venture (Scheme 14). Thus, reaction of **98** with DDQ in the presence of methanol predictably afforded the C-1 methyl ether **99** in good yield. Subsequent conversion into the triflate **100** proceeded without incident. The palladium-catalyzed methoxycarbonylation of this compound proved troublesome at first. Under typical reaction conditions reported in the literature ($Ph_3P$:Pd°, 4.5:1),[48b] palladium black precipitated within minutes after warming the reaction mixture, and the yield of desired ester **101** was low (< 20%). Using the bidentate ligand, dppp,[48a] afforded similar results. Fortunately, it was found that to preserve catalyst life a high ratio of phosphine ligand to




[a]Reagents: (a) DDQ (1.3 eq), $CH_2Cl_2$, MeOH, rt, 1 h; (b) MeLi (2.0 eq), THF, -78 °C; $PhNTf_2$; (c) $Pd(OAc)_2$/CO, MeOH, DMSO, $Et_3N$, 70 °C; (d) TMSCl, LiBr, MeCN, 55 °C

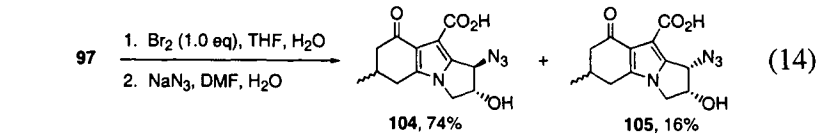



***Scheme 14.***

palladium (7.2:1) was necessary. In this way, reasonable yields of **101** could be realized. In the next transformation, it was hoped that simultaneous cleavage of the methyl ester and elimination of methanol would occur and lead to the unsaturated acid **97**. Initial attempts using *in situ*-generated TMSI proved troublesome. Exposure of **101** to 2.1 equiv of this reagent in acetonitrile at 50 °C for 4 h resulted in the formation of two new spots by TLC analysis. An $^1$H NMR analysis of the crude reaction mixture indicated that the minor product of this reaction was the desired alkene **97**. The major product was later determined to be the reduction product **102**. Shortening the reaction time improved the yield of **97** toward 50%, although considerable quantities of the intermediate **103** remained. Since the reduction of the desired product appeared to be the consequence of excess iodide ion in solution, it was reasoned that use of trimethylsilyl bromide (TMSBr)[81] would avoid this undesired reaction. In practice, exposure of **101** to excess TMSBr provided the desired unsaturated acid **97** in good yield following aqueous workup. This compound proved identical in all respects with the material originally reported by Rebek.[80] The original route to this compound proceeded in eight steps and 17% overall yield from *trans*-4-hydroxyproline and 3-methylglutaric anhydride. By way of comparison, the route below proceeds in six steps and 26% overall yield from sodium prolinate and 5-methylcyclohexane-1,3-dione.

In Rebek's work, compound **97** was used for the preparation of various C-1/C-2 disubstituted mitosene derivatives, however, attempts to make aziridinomitosene systems from this intermediate were not pursued.[80] Our interest then became whether this compound could be relayed into a fully functionalized 7-aminoaziridinomitosene. The only demonstrated fully synthetic route to these types of mitosene derivatives was reported from Rapoport's group.[75c] Here, the final target obtained was a 7-methoxyaziridinomitosene bearing a C-9 ester group and a benzyl group on the aziridine nitrogen. More commonly, mitosene derivatives are derived semisynthetically from naturally occurring mitomycins.[1,2] In pursuit of developing a fully synthetic route to aziridinomitosenes, we were fortunate to be able to incorporate two key transformations developed by Rebek,[80] i.e., installations of the aminoquinone portion and the azidomesylate functionality at C-1 and C-2.

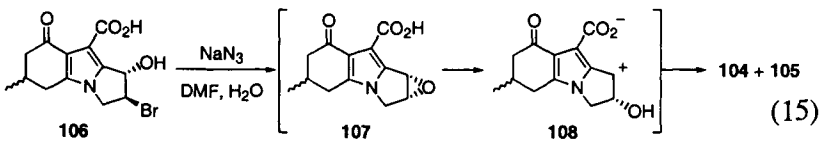
In our hands **97** was treated with aqueous bromine to afford a high yield of bromohydrin, which was directly treated with sodium azide in aqueous DMF to afford an easily separable mixture of the *trans*- and *cis*-azido alcohols, **104** and **105**, respectively (Eq. 14). Notably, Rebek




(14)

only reported isolation of the *trans*-isomer in his study. The assignment of the minor isomer having *cis*-stereochemistry and relative regiochemistry, as shown for **105**, is based on the following $^1$H NMR analysis. Two overlapping doublets for H-1 appeared in the range 5.36–5.38 ppm with a coupling to the adjacent H-2 proton of $J_{1,2} = 5.8$ Hz. The signal for H-2 appeared as a broad multiplet centered at 4.87 ppm. In a subsequent deuterium exchange experiment the signal for H-2 simplified to a broadened five-line pattern, from which the two coupling constants were measured, $J_{1,2} = 5.7$ Hz and $J_{2,3} = 7.2$ Hz. The two overlapping peaks for H-1 remained unchanged. This confirmed the position of the OH group at C-2. The possibility for the *trans*-2-azido-1-hydroxy isomer being assigned to **105** was ruled out based on comparison of $^1$H spectral data with authentic compounds prepared first by Remers et al.[82] and later by Rebek.[80] Furthermore, the $^1$H NMR data for the *trans*-isomer **104**, and similar compounds, reveal a coupling constant for $J_{1,2}$ near zero in all cases. Thus, the *cis*-configuration for **105** was assigned based on the constant for $J_{1,2}$ of 5.8 Hz.

The stereochemical outcome of this transformation deserves special comment. Based on established mechanistic grounds, the likely intermediate in this process is the transient 1,2-epoxide, **107** (Eq. 15). Reaction with nucleophiles occurs exclusively at C-1 as a result of powerful electronic effects, as evidenced by the exclusive formation of 1-azidoadducts **104** and **105**. However, the resulting stereochemistry of the 1-substituted-2-hydroxy adducts depends greatly on the reaction conditions. For example, Rebek reported that a *cis*-1-methoxy-2-hydroxy adduct was isolated as the major product when bromohydrin **106** was exposed to basic reaction conditions (NaOMe/MeOH).[80] In this case the product *cis/trans* ratio was found to be inversely proportional to the base concentration, a fact suggesting that the minor *trans*-adduct arose directly via $S_N2$ attack on the epoxide **107**. To explain the formation of the *cis*-adduct,

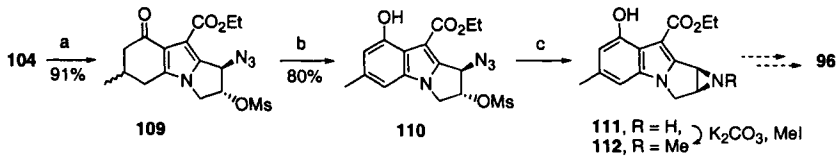



(15)

intervention of a short-lived zwitterionic intermediate, **108**, evolving from a solvolysis reaction component, was proposed. Here the incipient alkoxide ion is protonated by a solvent molecule, i.e., MeOH, which then attacks the carbocation from the same side.

On the other hand, reaction of **106** with azide as the nucleophile presents a more difficult case to rationalize. Notably, we were able to isolate a minor amount of the *cis*-adduct **105** under the same conditions reported by Rebek. A likely explanation for their result is that the more polar *cis*-isomer was in fact formed, but was not eluted from the silica gel column during purification (hexanes/ethyl acetate as the eluant). In our hands column chromatography required elution of **105** using EtOAc/MeOH (9:1) compared with the more mobile *trans*-isomer which was eluted quickly using $CHCl_3$/EtOAc (1:1). To explain the reaction outcome, direct $S_N2$ attack of azide on the epoxide **107** would logically lead to the *trans*-adduct **104**. It would seem necessary, however, to invoke the intermediacy of the zwitterion **108** to explain the formation of the *cis*-isomer. What is troubling is how such a species would form via a solvolysis process, in this case aqueous DMF, and not see the formation of secondary products, i.e., 1,2-diols. This suggests that intermediate **108** is sufficiently long-lived to allow effective competition by azide for the $C^1$ carbocation. This brings up another plausible explanation that the entire reaction manifold proceeds via **108** and the subsequent stereochemical outcome is dictated by steric preferences alone. In this case the azide ion preferentially attacks C-1 opposite the hydroxy group leading to *trans*-stereochemistry. These salient mechanistic details merit further investigation, especially in regard to solvent effects and the nature of the nucleophile. Similar peculiarities involving the stereochemistry for ring opening reactions of mitomycins and aziridinomitosenes are well-known.[75b,80]

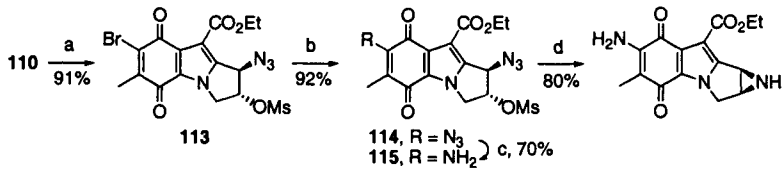
Proceeding from the *trans*-azidoalcohol **104**, an improved, one-step method for the conversion into the C-9 ester-mesylate **109** was developed. Previously, Rebek converted the C-2 alcohol into its mesylate derivative, then esterified the C-9 carboxyl group using a time-intensive alkylation reaction. Conveniently, we found that exposure of **104** to excess mesyl chloride presumably generated a transient acyl mesylate along with mesylation of the C-2 hydroxyl which, on quenching the crude reaction mixture with ethanol, led directly to the ethyl ester **109** in high yield. As expected, DDQ mediated dehydrogenation of this compound afforded the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole **110**. At this stage we were eager to establish the aziridine ring and were pleased to demonstrate




(a) MsCl, $Et_3N$, THF; EtOH; (b) DDQ, EtOAc; (c) $Ph_3P$, $Et_3N$, THF, $H_2O$.

this task, via the agency of an iminophosphorane intermediate,[83] to afford compound **111**. However, further attempts to convert this material, or its *N*-methyl derivative **112**, into mitosenes, e.g., **96**, met with failure. Apparently the aziridine ring would not tolerate reaction conditions[84] required to elevate the oxidation state of the A-ring phenol into a quinone, and complex reaction mixtures were typically observed.

To realize the final end target, an aminoaziridinomitosene, it became apparent that the sensitive aziridine ring would have to be installed in the last step. Thus, solvolytic bromination of **110** according to Rebek's procedure[80] gave an instantaneous reaction resulting in the high-yield conversion into the bromoquinone **113**. The next challenge became the installation of the 7-amino group. Initially, Rebek's method was tried, i.e., exposure of **113** to excess sodium azide in hot DMF, but only 25–40% yield of the desired aminoquinone **115** was afforded. Attempts to carry out direct amination of **113** by exposure to aminodiphenylmethane gave no reaction in acetonitrile, whereas in DMF, the reaction produced a deep-colored polar material that could not be readily characterized. On the other hand, reaction of **113** with a slight excess of sodium azide in acetonitrile afforded a high yield of the 7-azidoquinone **114**. Attempts to selectively reduce the azido group in this compound by treatment with triphenylphosphine in the presence of water, gave numerous products as evidenced by TLC analysis. Fortunately, recourse to the long-known path of thermal disproportionation of azidohydroquinones provided a satisfactory outcome.[85] In anticipation, exposure of **114** to sodium dithionite afforded a sensitive azidohydroquinone intermediate




(a) $Br_2$, THF, $H_2O$, AcOH, NaOAc; (b) $NaN_3$, $CH_3CN$, $H_2O$; (c) $Na_2S_2O_4$, EtOH; $CHCl_3$, Δ; $PhCH_3$, Δ; (d) $Ph_3P$, $Et_3N$, THF, $H_2O$.

that was used directly without isolation in the subsequent thermal reaction. After considerable experimentation, it was found that the desired 7-aminoquinone **115** could be obtained by refluxing the azidohydroquinone in chloroform for 8 h, removal of solvent, introduction of toluene, and refluxing for 4 h. In this way **115** could be isolated in 70% yield from **114**. Interestingly, if the azidohydroquinone was heated directly in toluene, an unknown by-product appeared; this material was minimized with the chloroform preheating step. What appears to be happening is a stepwise disproportionation process that is facilitated in the desired direction by a two-stage heating process. Finally, the aziridine was readily introduced in the last step utilizing the method mentioned earlier to afford the 7-aminoaziridinomitosene **96** in 80% yield as a purple solid.[86]

An efficient and economical new approach toward the synthesis of 7-aminoaziridinomitosenes, as represented by compound **96**, has been developed in less than 15 total operations from commercially available chemicals. Overall our scheme represents the second total synthesis of a fully functionalized aziridinomitosene. At one stage, new insights into the mechanistic details involving the reaction of 1,2-epoxypyrrolo[1,2-*a*]indoles with nucleophiles are provided. Notably, the route presented has the advantage of accessing both the aziridine and 7-amino substituents in deprotected form. Further application of this synthetic approach to additional C-9-substituted mitosenes can be anticipated.

## ACKNOWLEDGMENTS

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55. The spectral data for compound **66** revealed a straightforward set of five heteroaromatic protons at δ 7.62 (*d*, $J$ = 7.0 Hz), 6.92 (*dd*, $J$ = 2.8, 0.8 Hz), 6.74 (*dd*, $J$ = 3.5, 0.8 Hz), 6.32 (*dd*, $J$ = 3.5, 2.8 Hz), and 6.21 (*d*, $J$ = 7.0 Hz).
56. Key spectral features of **66** that suggested the assigned structure are IR (KBr) 3449, 1781, 1653 $cm^{-1}$; $^1H$ NMR (DMSO) δ 9.95 (s, 1 H, $D_2O$ disappear); $^{13}C$ NMR (DMSO) δ 160.3, 155.0, 115.2.

57. We attribute this change in product distribution to the greater concentration of cyanide in solution. TLC analysis of this reaction after short periods of time revealed the presence of **64** which disappeared with time. In an independent experiment, treatment of **64** with NaCN in DMSO resulted in its clean conversion into **66**.
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# APPLICATIONS OF IMINIUM CATION CHEMISTRY TO ACTIVATED INDOLES

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## ABSTRACT

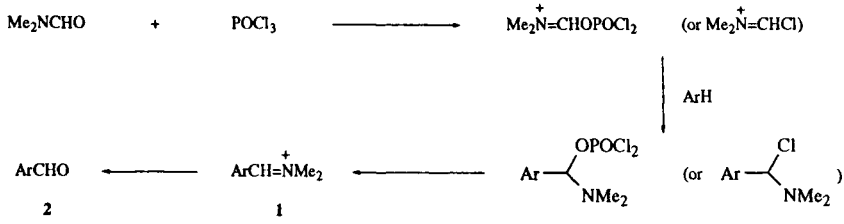
The combination of tertiary amides, such as dimethylformamide, and phosphoryl chloride generates reactive electrophiles capable of being attacked by electron-rich nucleophiles and is widely used as the Vilsmeier formylation process. The Vilsmeier process has become more general, with the use of more varied amides, and has been particularly successful for the functionalization of pyrroles and indoles. Greater flexibility has been achieved with the replacement of phosphoryl chloride by trifluoromethanesulfonic anhydride.

Our applications of the Vilsmeier synthetic strategy have concentrated on the combination of new electron-rich 4,6-dimethoxyindoles with secondary lactams, resulting in the direct linkage of such indoles with a wide range of nitrogen-containing heterocyclic rings. For example, the use of pyrrolidin-2-ones generates pyrrolines and pyrroles, piperidin-2- ones give tetrahydropyridines, oxazolidin-2-ones give oxazolines, and indolin-2-ones give indoles.

This synthetic strategy offers an excellent route to a wide variety of biindolyls, which are increasingly appearing as structural moieties in biologically active natural products, and are therefore desirable synthetic targets.

## I. INTRODUCTION

The Vilsmeier–Haack reaction (herein, "Vilsmeier reaction") provides an effective method for the formylation of aromatic systems. The combination of phosphoryl chloride with *N*-methylaniline or dimethylformamide generates an iminium phosphorus derivative or chloro-iminium cation that is the active electrophile in an electrophilic substitution reaction. The resulting substitution product is an iminium salt **1**, which is hydrolyzed on workup with alkali to give the carbaldehyde product **2** (Scheme 1).[1,2] The method is particularly useful with activated arenes or electron-rich heterocycles, such as pyrroles, furans, thiophenes, and indoles. We had a special interest in the preparation of indole-7-carbaldehydes, namely, their properties as isosteres of salicylaldehyde. Thus, we became involved in a wide-ranging investigation of 4,6-dimethoxy-




***Scheme 1.***

indoles, which were designed to activate C-7 to electrophilic substitution. These indoles show increased general reactivity toward electrophiles, and regiochemistry therefore becomes a significant issue. Furthermore, the Vilsmeier reaction can be extended beyond the synthesis of carbaldehydes, and the combination of phosphoryl chloride with secondary amides leads to imine products that can survive the alkaline workup without undergoing hydrolysis. In this chapter we survey our results in this area.

## II. FORMYLATION

### A. Reaction of 2,3-Disubstituted-4,6-dimethoxyindoles

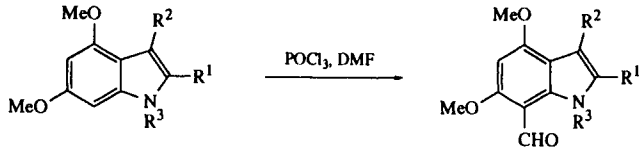
In order to probe the reactivity of the C-7 position, without the possible complication of the formation of regioisomers, 4,6-dimethoxy-2,3-diphenylindole **3a** was prepared by the Bischler reaction from 3,5-dimethoxyaniline and benzoin.[3] Vilsmeier formylation occurred smoothly to give the 7-carbaldehyde **4a** in 82% yield. In a related manner, the other 2,3-disubstituted-4,6-dimethoxyindoles **3b–d**[3] were converted in yields of 62–70% to the corresponding 7-carbaldehydes **4b–d**[4,5] (Scheme 2). More recently, the tetrahydrocarbazole **3e**[6,7] was also formylated at the equivalent 8-position in 82% yield.[7]


| | R1 | R2 |
|---|---|---|
| a | Ph | Ph |
| b | Me | Me |
| c | $CO_2Me$ | $CO_2Me$ |
| d | 2-Py | 2-Py |
| e | $-(CH_2)_4-$ | |

***Scheme 2.***

Formylation also occurs readily at C-7 in a range of 1,2,3-trisubstituted-4,6-dimethoxyindoles **5a–h**, or at the equivalent C-8 in the related tetrahydrocarbazole **5i**. The *N*-substituents have been allyl, substituted allyl, including 2-cyclohexenyl, or propargyl and yields ranged from 58 to 97%[7] (Scheme 3). In general, the yields are at least as good as for the equivalent NH indoles, so that any detrimental steric effect is outweighed by increased activity. It is significant that *N*-allylation of the partially deactivated indole-7-carbaldehydes **4** cannot be achieved.[7] Some more complex 2,3-disubstituted-4,6-dimethoxyindoles, which incorporate a 2-indolyl substituent at C-2, also undergo formylation at C-7. In the synthesis of 2,2′-biindolyls, two routes have been employed and each involves Vilsmeier formylation in the sequence of steps. The 2,2′-indolylindoline **8**, obtained through the acid-catalyzed dimerization of 4,6-dimethoxyskatole **7**,[8,9] undergoes formylation at both the indole C-7 and indoline *N*-1 to give the formyl-formamide **9**. A sequence of oxidation, amide hydrolysis, and further formylation effectively gave the 2,2′-biindolyl-7,7′-dicarbaldehyde **10**.[10,11] This last compound **10** can also be obtained in 80% yield by direct formylation of the 2,2′-biindolyl **11**[10,11] (Scheme 4).

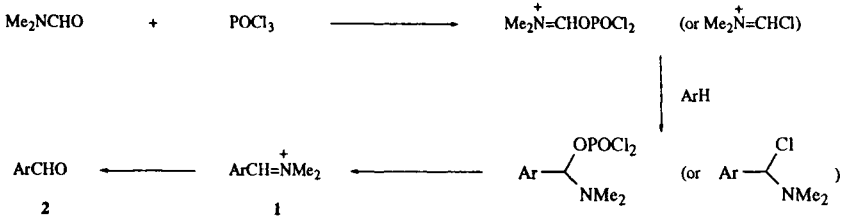
Diindolylmethanes can also be formylated at the indole C-7. For example, the 2,2′-diindolylmethane **12** can be smoothly formylated to give the dicarbaldehyde **13** in 72% yield.[12] Also the 2,7′-diindolylmethane **14** undergoes selective formylation at C-7 to give the mono-




5 6

| | R¹ | R² | R³ |
|---|---|---|---|
| a | Ph | Ph | allyl P |
| b | Ph | Ph | 2-methylallyl |
| c | Ph | Ph | 3-methylallyl |
| d | Ph | Ph | 3,3-dimethylallyl |
| e | Ph | Ph | 3-phenylallyl |
| f | Ph | Ph | 2-cyclohexenyl |
| g | Ph | Ph | propargyl |
| h | $CO_2Me$ | $CO_2Me$ | allyl |
| i | | $-(CH_2)_4-$ | allyl |

***Scheme 3.***




***Scheme 1.***

indoles, which were designed to activate C-7 to electrophilic substitution. These indoles show increased general reactivity toward electrophiles, and regiochemistry therefore becomes a significant issue. Furthermore, the Vilsmeier reaction can be extended beyond the synthesis of carbaldehydes, and the combination of phosphoryl chloride with secondary amides leads to imine products that can survive the alkaline workup without undergoing hydrolysis. In this chapter we survey our results in this area.

## II. FORMYLATION

### A. Reaction of 2,3-Disubstituted-4,6-dimethoxyindoles

In order to probe the reactivity of the C-7 position, without the possible complication of the formation of regioisomers, 4,6-dimethoxy-2,3-diphenylindole **3a** was prepared by the Bischler reaction from 3,5-dimethoxyaniline and benzoin.[3] Vilsmeier formylation occurred smoothly to give the 7-carbaldehyde **4a** in 82% yield. In a related manner, the other 2,3-disubstituted-4,6-dimethoxyindoles **3b–d**[3] were converted in yields of 62–70% to the corresponding 7-carbaldehydes **4b–d**[4,5] (Scheme 2). More recently, the tetrahydrocarbazole **3e**[6,7] was also formylated at the equivalent 8-position in 82% yield.[7]


| | $R^1$ | $R^2$ |
|---|---|---|
| a | Ph | Ph |
| b | Me | Me |
| c | $CO_2Me$ | $CO_2Me$ |
| d | 2-Py | 2-Py |
| e | $-(CH_2)_4-$ | |

***Scheme 2.***

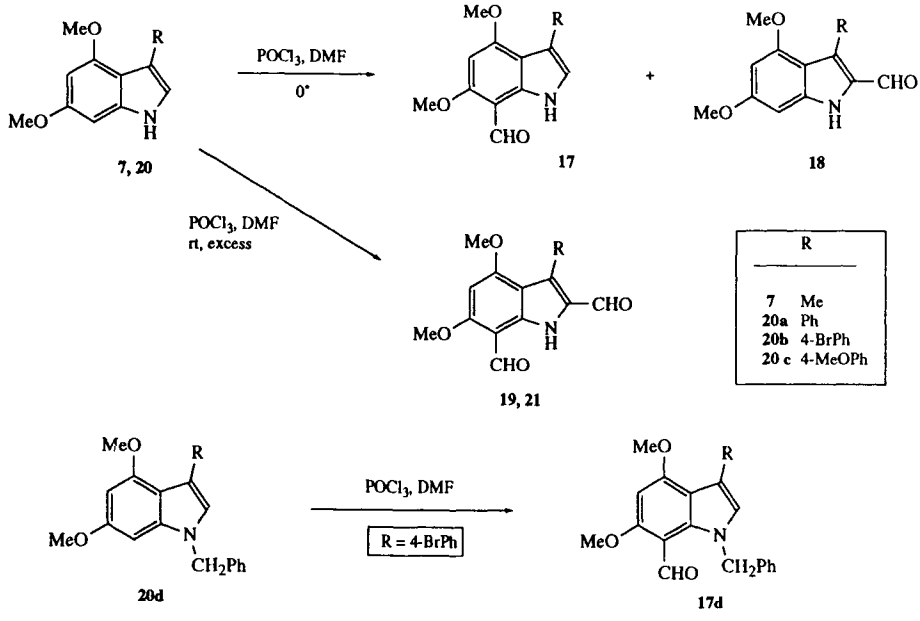
aldehyde **15**,[13] but can also be diformylated to the 2,7-dicarbaldehyde **16**[14] (Scheme 5).

## B. Reaction of 3-Substituted-4,6-dimethoxyindoles

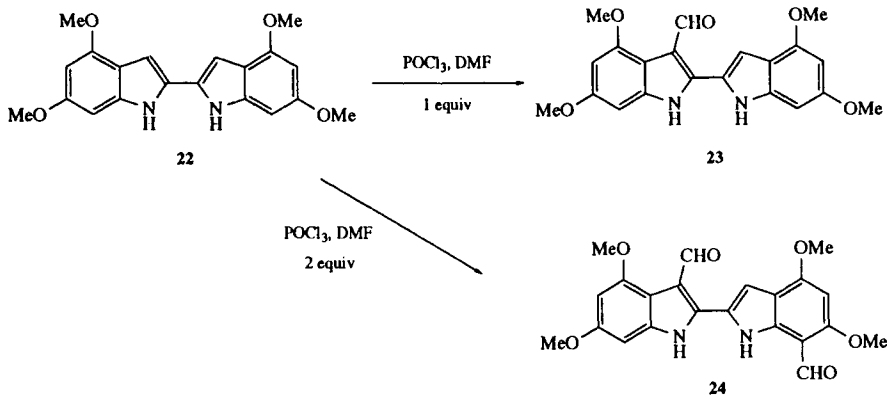
The question of regiochemistry arises in the formylation of 3-substituted-4,6-dimethoxyindoles, as both C-2 and C-7 are activated. 4,6-Dimethoxyskatole **7** gives a mixture of 2- and 7-carbaldehydes **17** and **18**, and can be cleanly diformylated with excess reagent to give the 2,7-dicarbaldehyde **19** in 84% yield.[8,9] However, the situation changes for 3-aryl-4,6-dimethoxyindoles **20a–c**,[15] and 7-formylation is heavily favored. Once again, the 2,7-dicarbaldehydes **21a–c** can be obtained readily in excellent yield[14] (Scheme 6). The *N*-benzyl-3-(4-bromophenyl)-4,6-dimethoxyindole **20d** gives the 7-formyl product **17d** exclusively[12] (Scheme 6).

## C. Reaction of 2-Substituted-4,6-dimethoxyindoles

A systematic study of the formylation of 2-substituted-4,6-dimethoxyindoles has not been carried out, but several examples confirm



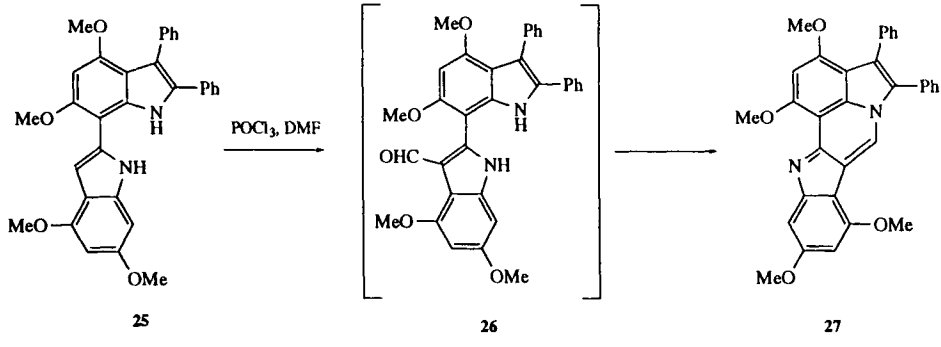

*Scheme 6.*



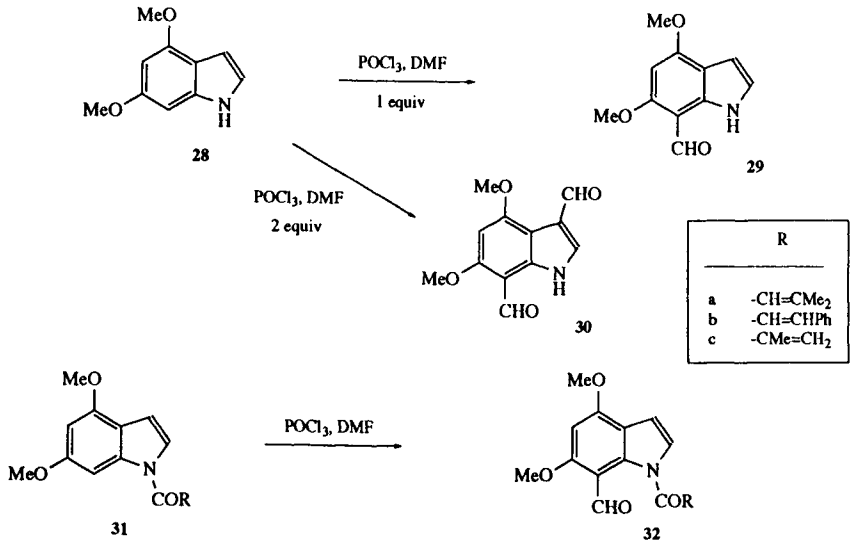

***Scheme 7.***

the reactivity of both C-3 and C-7. Vilsmeier formylation of the tetramethoxy-2,2′-biindolyl **22** with 1 equiv of phosphoryl chloride gave the monoformyl compound **23** and with 2 equiv gave the diformyl compound **24**.[10] Significantly, the first formylation occurs at C-3, but the second at C-7, quite dramatically influenced by the less electron rich substituent at C-2 of the reacting indole (Scheme 7). Clearly the relative reactivity of C-3 and C-7 is finely balanced.

Formylation of the 2,7′-biindolyl **25** did not yield an aldehyde, but the 3-carbaldehyde **26** is clearly implicated as an intermediate in the formation of the indolopyrroloquinoline product **27**[16] (Scheme 8).




***Scheme 8.***




*Scheme 9.*

### D. Reaction of Unsubstituted-4,6-dimethoxyindoles

The otherwise unsubstituted 4,6-dimethoxyindole **28**[17] was shown to undergo reaction at 10 °C, with formylation at C-7 in preference to C-3, to give aldehyde **29** in 56% yield. The 3,7-dialdehyde **30** could be formed readily under conditions involving 2 equiv of phosphoryl chloride, in reaction at 35 °C.[17] In contrast, it is interesting to note that 4,5,6-trimethoxyindole can be formylated only at C-3, presumably because of the buttressing hindrance conveyed to the C-7 position. If the indole nitrogen atom of 4,6-dimethoxyindole **28** is acylated, formylation proceeds exclusively at C-7, as the result of the deactivation at C-3 by the conjugated acyl group. Thus, the acylindoles **31** on Vilsmeier formylation yield the aldehydes **32** in the relatively modest yields of 41–57%[7] (Scheme 9).

## III. ACYLATION

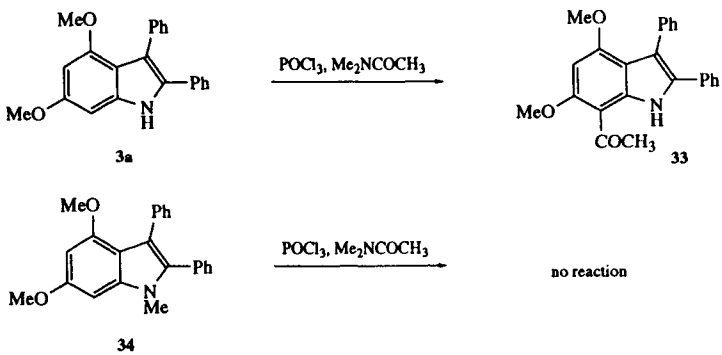
### A. Reaction of 2,3-Disubstituted-4,6-dimethoxyindoles

Dimethylacetamide has been used in place of dimethylformamide in combination with phosphoryl chloride to effect acetylation rather than

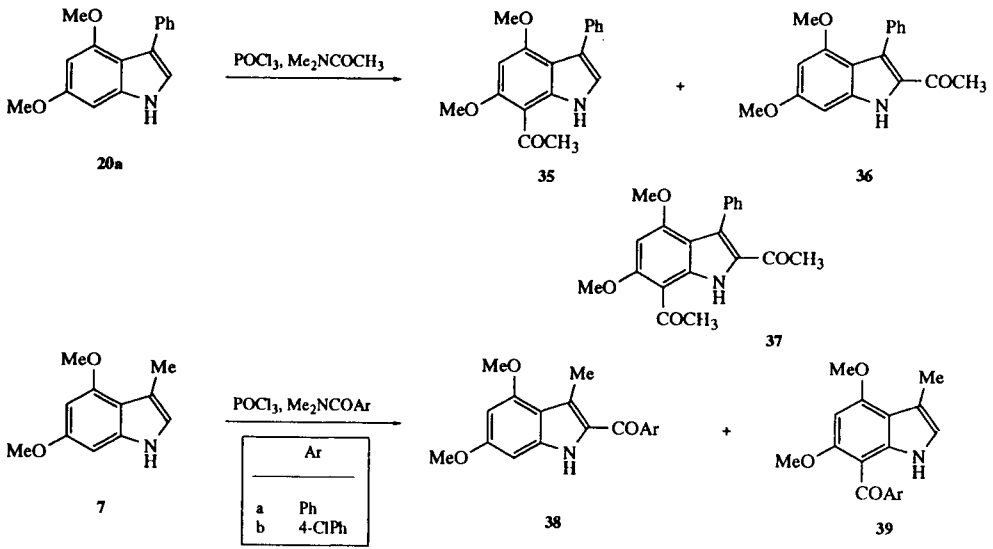
formylation.[18] Thus, Vilsmeier acetylation has been applied to the dimethoxyindole **3a** to yield the 7-acetyl product **33** in 88%[19] (Scheme 10). The reaction is much slower than formylation and requires reflux at 40–60 °C for 48 h. Nevertheless, the Vilsmeier conditions are superior to those Friedel–Crafts conditions investigated, the best of which combined acetyl chloride and stannic chloride and gave a 53% yield of the product **33**. Attempts to acetylate the *N*-methylindole **34** were unsuccessful using both Vilsmeier and Friedel–Crafts conditions. This contrasts with the ease of formylation of the *N*-substituted indoles **6**.[7] Various other acetylation reactions have been carried out at the 7-position of the indole **3a**.[18,20] However, the use of acid chlorides or anhydrides is necessary and the combination of tertiary amides and phosphoryl chloride is ineffective.

## B. Reaction of 3-Substituted-4,6-dimethoxyindoles

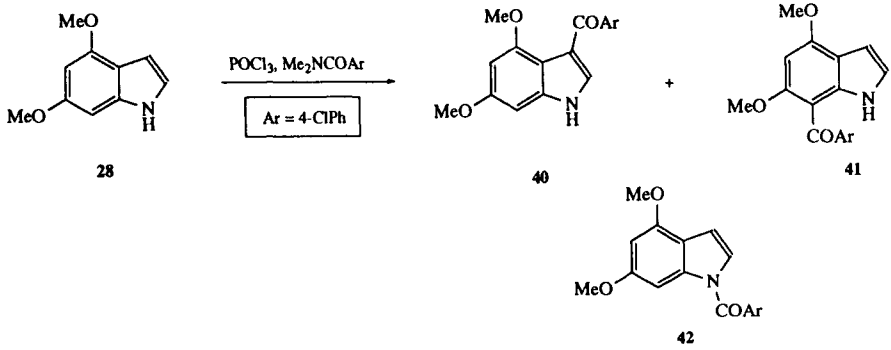
Reaction of an excess of dimethylacetamide and phosphoryl chloride with the 3-phenylindole **20a** gave the 7-acetyl compound **35** as the major product in 65% yield, together with 20% of the 2-acetyl compound **36** and 8% of the 2,7-diacetyl compound **37**[21] (Scheme 11). Vilsmeier aroylation has been applied successfully to the more reactive 3-methylindole **7** and leads to a more even distribution of 2- and 7-isomers, but usually with a slight preference for 2-substitution.[22,23] Thus, the use of *N,N*-dimethylbenzamide and 4-chloro-*N,N*-dimethylbenzamide gave the 2- and 7-acylindoles **38a,b** and **39a,b**, respectively, in good yields (Scheme 11).




***Scheme 10.***


MeO
Ph
MeO
N
H
20a
POCl3, Me2NCOCH3
COCH3
35
+
36
37
Me
7
POCl3, Me2NCOAr
Ar
a Ph
b 4-ClPh
COAr
38
39

*Scheme 11.*




***Scheme 12.***

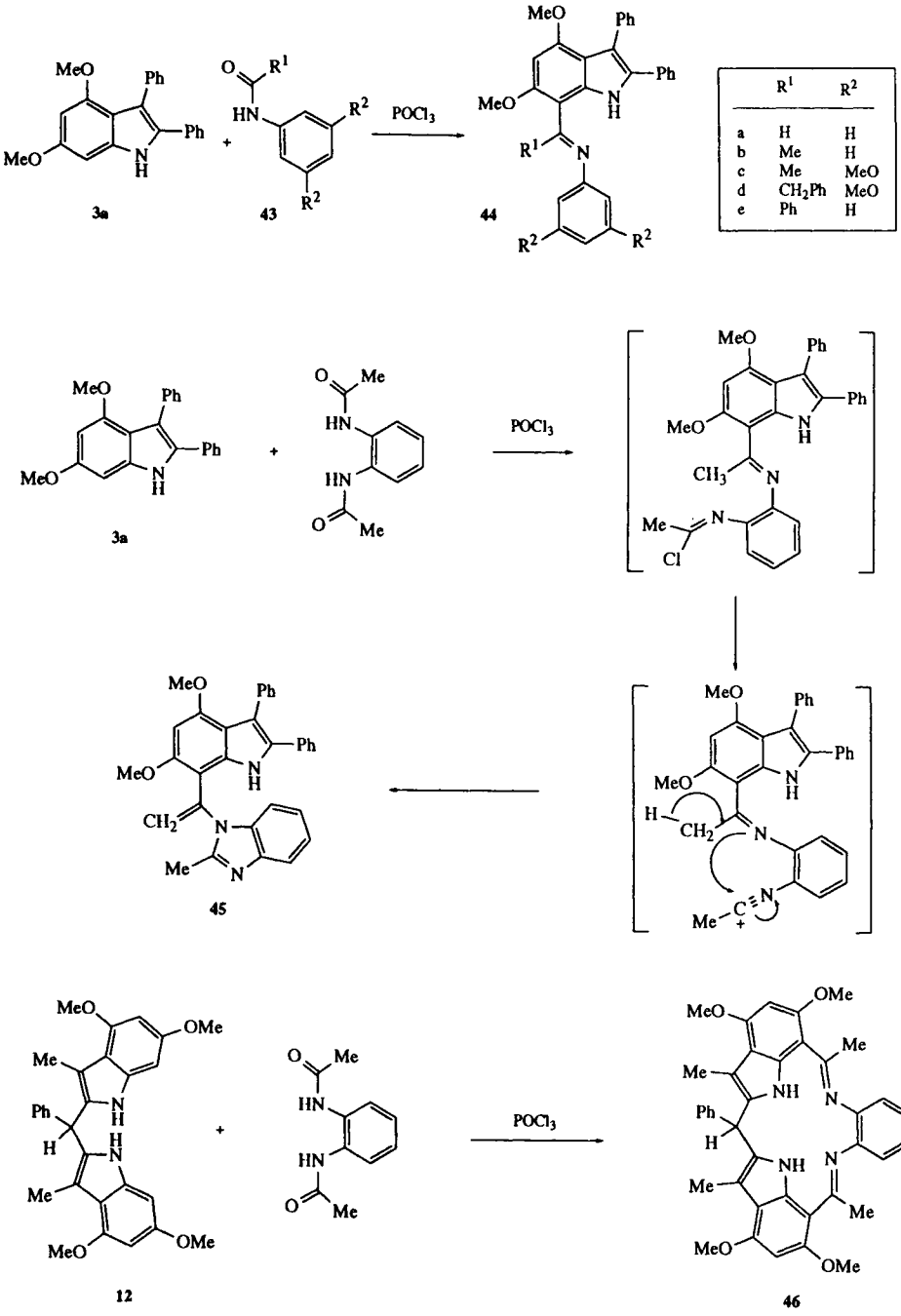
### C. Reaction of Unsubstituted-4,6-dimethoxyindoles

The 2,3-unsubstituted indole **28** undergoes reaction with 4-chloro-*N,N*-dimethylbenzamide and phosphoryl chloride at 80 °C to give a mixture of the 3-aroyl derivative **40** (50%), 7-aroyl derivative **41** (20%), and *N*-aroyl derivative **42** (30%)[12] (Scheme 12).

## IV. FORMATION OF IMINES

### A. Reaction of 2,3-Disubstituted-4,6-dimethoxyindoles

The replacement of tertiary amides such as dimethylformamide by secondary amides in the Vilsmeier reaction leads to the formation of imines, which are sufficiently stable to be isolated from the reaction mixture. In this situation it is suggested that the reactions proceed via imidoyl chlorides.[24,25] The imines **44a–e** were formed in yields of 63–92% by the reaction of 4,6-dimethoxy-2,3-diphenylindole **3a** with the anilides **43a–e**[25,26] (Scheme 13). Both *E*- and *Z*-imine isomers were observed only in the case of compound **44e**. The reactions are carried out with freshly distilled phosphoryl chloride in refluxing chloroform and worked up using aqueous bicarbonate solution. The reaction has some value because of the relative difficulty of preparing ketimines by direct condensation of ketones and primary amines. For instance, compound **44b** could not be obtained from the 7-acetylindole **33** and aniline. Reaction of indole **3a** with *N,N'*-diacetyl-1,2-diaminobenzene and phosphoryl chloride was carried out in an attempt to generate the related bisketimine, but the indole enamine **45** was isolated in 70% yield[26]


MeO
Ph
Ph
MeO
N
H
3a
O
R1
HN
R2
43
POCl3
44
R1
R2
a H H
b Me H
c Me MeO
d CH2Ph MeO
e Ph H
CH3
Me
Cl
CH2
45
H
Me
12
46
OMe
NH

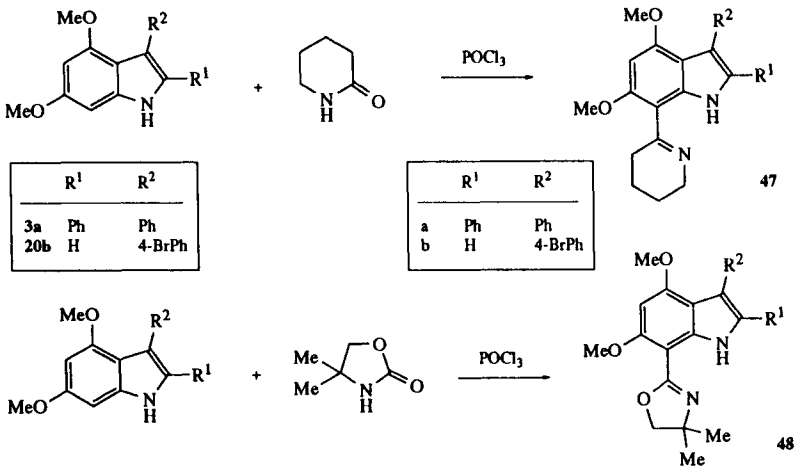
*Scheme 13.*

(Scheme 13). A possible mechanistic pathway involves imidoyl chloride and nitrilium cation intermediates. A similar reaction of *N,N'*-diacetyl-1,2-diaminobenzene and phosphoryl chloride with the 2,2'-diindolylmethane **12** did form the macrocycle **46**, but only in a very low yield[12] (Scheme 13).

Cyclic imines can be formed by the use of lactams in combination with phosphoryl chloride. Examples involving pyrrolidinones and indolinones will be dealt with in the following sections on the formation of indolopyrroles and biindolyls, respectively. Other examples making use of piperidinone and an oxazolidinone are considered here. The diphenylindole **3a** combines with phosphoryl chloride and piperidin-2-one to give the 7-indolyl-tetrahydropyridine **47a** in 86% yield[27] (Scheme 14). The product serves as a precursor to the related 7-(2-pyridyl)indole. Of more general interest is the use of 4,4-dimethyl-2-oxazolidinone[28] in combination with phosphoryl chloride to give the 2-(7-indolyl)oxazoline **48a** in 52% yield[27] (Scheme 14). This route offers a convenient alternative to the usual approach of reacting a carboxylic acid derivative with an amino-alcohol. Indeed, the standard route in this case gave the oxazoline **48a** in a poor yield of only 15%.

## B. Reaction of 3-Substituted-4,6-dimethoxyindoles

Similar reactions with piperidin-2-one and 4,4-dimethyl-2-oxazolidinone have been carried out using 3-(4-bromophenyl)-3,6-dimethoxyin-



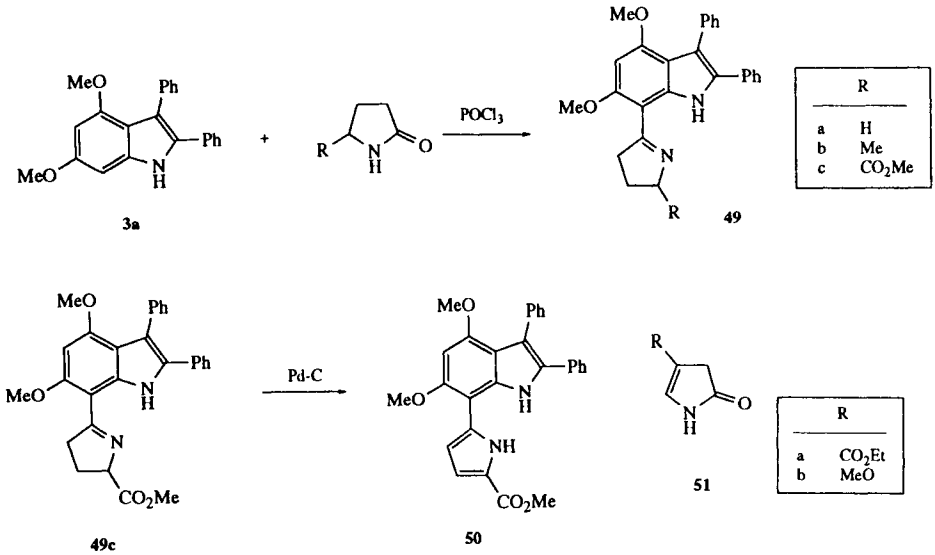

***Scheme 14.***

dole **20b**[15] and the related products **47b** and **48b**, respectively, in 65 and 50% yield (Scheme 14). Only traces of the related 2-substituted products were observed, so these reactions are even more regioselective than the similar formylations, presumably because of the greater size of the electrophiles.

## V. FORMATION OF INDOLOPYRROLES

### A. Reaction of 2,3-Disubstituted-4,6-dimethoxyindoles

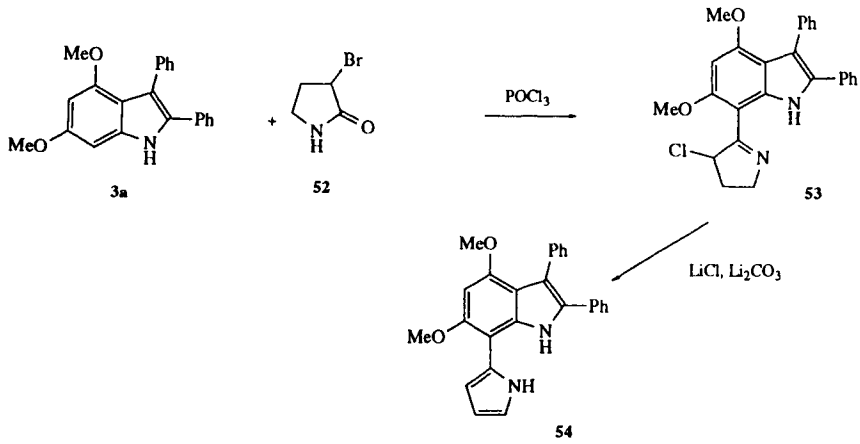
The use of pyrrolidinones in modified Vilsmeier reactions with pyrroles has been described for the synthesis of bipyrroles and terpyrroles.[29–31] The diphenylindole **3a** can be converted into the 7-indolylpyrrolines **49a,b** in approximately 80% yield by reaction with pyrrolidin-2-one and 5-methylpyrrolidin-2-one, respectively[11,27,32] (Scheme 15). As it was desired to produce 2-(7-indolyl)pyrroles, attempts were made to dehydrogenate the pyrroline **49a**, but these were unsuccessful. However, methyl pyroglutamate, with its electron-withdrawing group, has been shown to generate pyrrolines more amenable to dehydrogenation.[31] Consequently, methyl pyroglutamate with phosphoryl chloride reacted with the diphenyl indole **3a** to give a 60% yield of the 7-indolylpyrroline



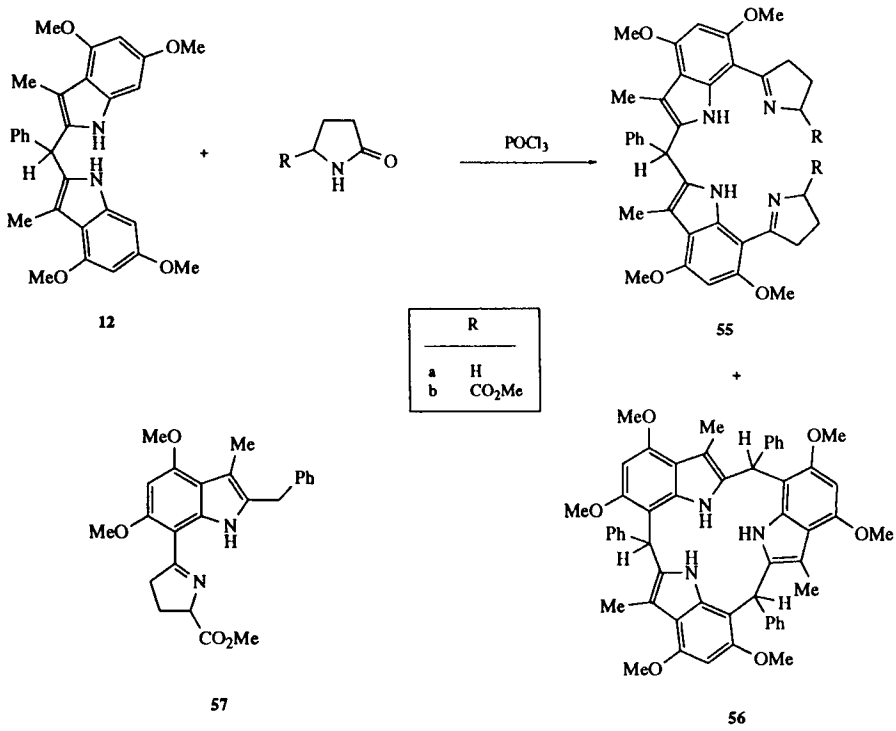

*Scheme 15.*

**49c**, which could then be dehydrogenated to the 7-indolylpyrrole **50**, also in 60% yield[33] (Scheme 15). Dehydrogenation is not an ideal process for the generation of a pyrrole ring, so alternatives were investigated. Direct pyrrole formation was sought by the use of the pyrrolinones **51a,b**, but contrary to their formation of bipyrroles from pyrroles, no pyrrolic products of the indole **3a** could be detected. Attention was therefore directed toward the use of 3-bromopyrrolidin-2-one **52**, readily obtainable from the bromination of 2-methoxypyrroline followed by treatment with hydrogen bromide.[34] The presence of the bromine atom in the pyrrolidinone **52** actually results in a dramatic increase in reactivity in the modified Vilsmeier reaction. Treatment of the indole **3a** with lactam **52** and phosphoryl chloride gave a 65% yield of the 2-(7-indolyl)pyrroline **53** after only 3 h of moderate conditions. In this reaction the bromo atom is exchanged for chloro from interaction with phosphoryl chloride. The dehydrochlorination of the chloropyrroline **53** was achieved most efficiently by reaction with a mixture of lithium bromide and lithium carbonate in dimethylformamide,[35] and the 7-indolylpyrrole **54** was isolated in 77% yield[33] (Scheme 16).

The 2,2′-diindolylmethane **12** also undergoes reaction with pyrrolidin-2-one and phosphoryl chloride to give the 7,7′-di-(1-pyrrolin-2-yl) derivative **55a** in 36% yield.[11,36] A significant by-product in this reaction is the calix[3]indole **56**, which arises from the direct reaction of compound **12** with phosphoryl chloride[22,23] (Scheme 17). A similar reaction with methyl pyroglutamate was less successful and gave only a




***Scheme 16.***

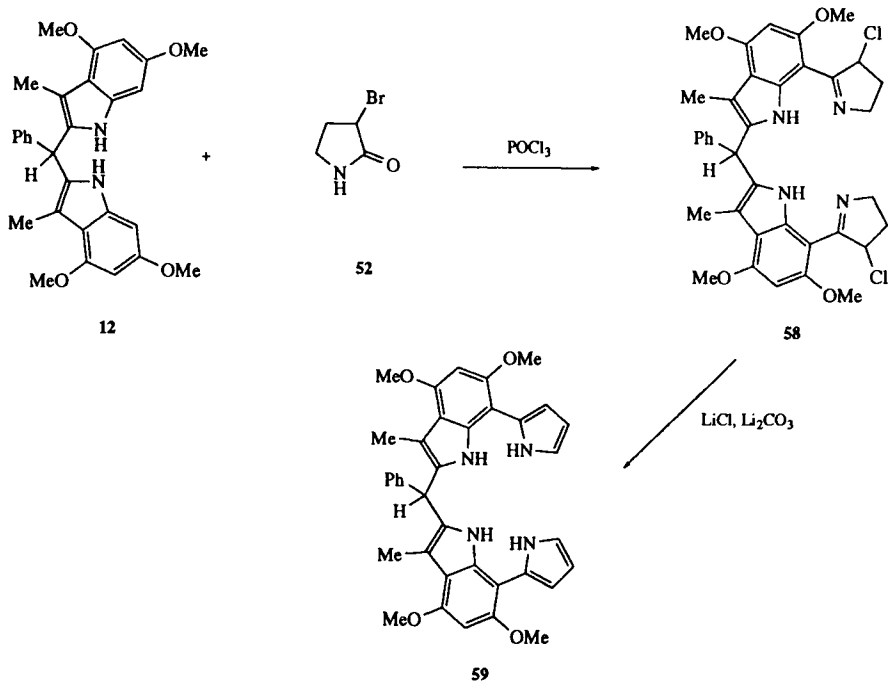



*Scheme 17.*

15% yield of the derivative **55b**, together with several by-products. The only identifiable by-product was the 2-benzylindole **57**, formed by a fragmentation process of some kind. Once again, reaction with 3-bromopyrrolidin-2-one **52** was quite clean and gave the pyrrolinyl derivative **58** in 45% yield. Dehydrochlorination smoothly generated the pyrrole **59** in 92% yield[36] (Scheme 18).

## B. Reaction of 3-Substituted-4,6-dimethoxyindoles

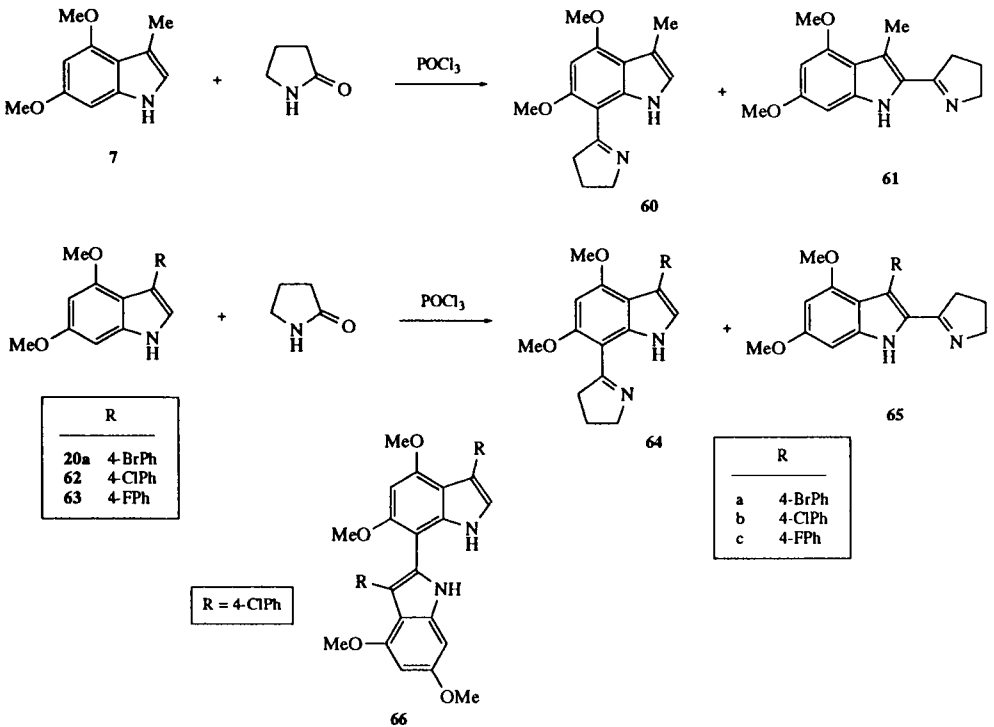
The Vilsmeier methodology for pyrrole attachment to 3-substituted indoles was investigated with particular reference to regiochemistry. Dimethoxyskatole **7** showed modest selectivity in its reaction with 2-pyrrolidinone and phosphoryl chloride and gave the 7- and 2-pyrrolinyl compounds **60** and **61**, respectively, in 36 and 12% yields[33] (Scheme 19). Regioselectivity could not be improved by lowering the reaction temperature. However, replacement of the electron-donating 3-methyl group



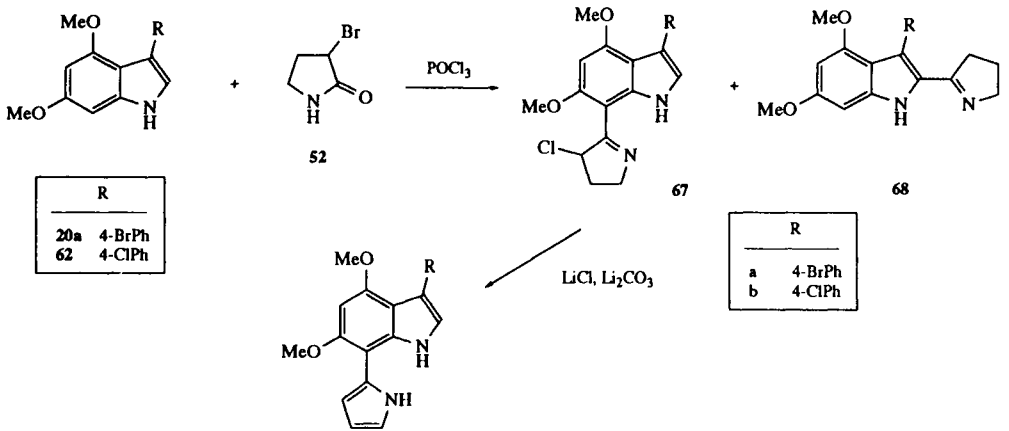

***Scheme 18.***

of indole **7** with several electron-withdrawing 4-halophenyl groups gave greatly improved selectivity. Thus, similar reactions of the indoles **20b, 62**, and **63** gave mixtures of the 7- and 2-indolylpyrrolines with at least a 6:1 predominance of the 7-isomers **64a–c** over the 2-isomers **65a–c**[33] (Scheme 19). In the reaction of indole **62**, a trace of the 2,7′-biindolyl **66** was isolated, presumably arising from chlorination of indole **62** at C-3 and followed by attack at C-2 of the resulting chloro-indole by another molecule of indole **62** and a final step of dehydrochlorination. 2,3′-Biindolyls have been prepared by a related process.[37,38] The *N*-benzyl-3-(4-bromophenyl)-4,6-dimethoxyindole **20d** failed to give any reaction with pyrrolidinones and phosphoryl chloride.

Almost complete regioselectivity for reaction at C-7 was found when the indoles **20a** and **62** were combined with 3-bromo-2-pyrrolidinone **52** and phosphoryl chloride. While traces of the 2-isomers **68a,b** were observed, only the latter could be isolated in 3% yield. In contrast, the 7-pyrrolinyl compounds **67a,b** were isolated in 65% yield[33] (Scheme 20).


MeO
Me
MeO
N
H
7
POCl3
60
61
R
20a 4-BrPh
62 4-ClPh
63 4-FPh
64
65
a 4-BrPh
b 4-ClPh
c 4-FPh
R = 4-ClPh
NH
OMe
66

*Scheme 19.*


MeO
R
MeO
N
H
20a 4-BrPh
62 4-ClPh
Br
O
52
POCl3
Cl
67
68
a 4-BrPh
b 4-ClPh
LiCl, Li2CO3
69
NH

*Scheme 20.*

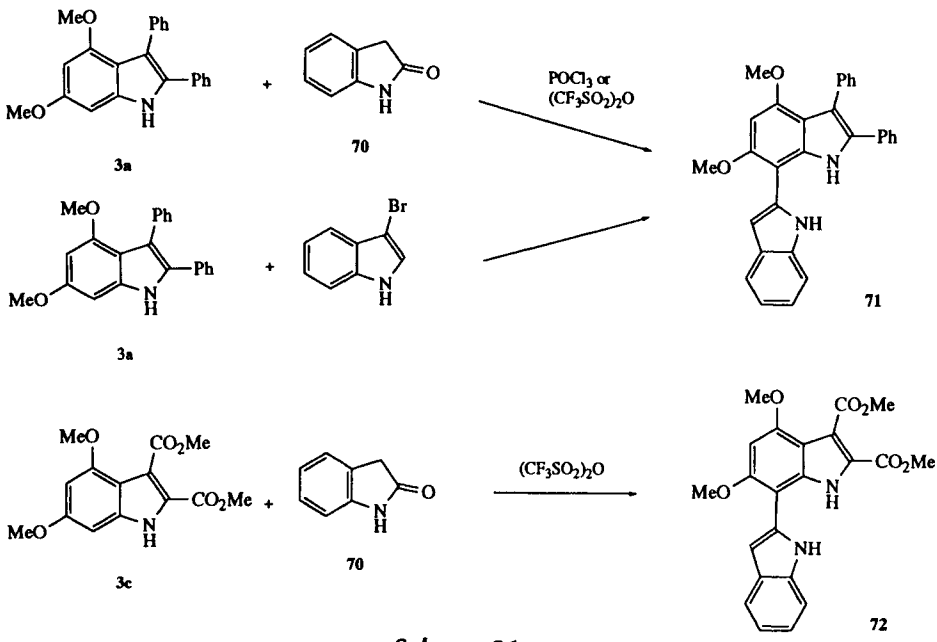
Again, dehydrochlorination of compounds **67** gave the 7-indolylpyrroles **69** in 85% yield (Scheme 20).

## VI. FORMATION OF BIINDOLYLS

### A. Reaction of 2,3-Disubstituted-4,6-dimethoxyindoles

The extension of the use of lactams to include indolin-2-ones provides a Vilsmeier-type methodology for the construction of biindolyl systems, which are of considerable current interest.[37,39–43] In this situation, the initially formed imines are indolenines, which readily isomerize to the related 2-indolyl derivatives.[43] In view of our general interest in activated indoles, as well as a specific interest in continuing to synthesize structures containing indoles directly linked to each other, we investigated not only reactions with indolinone itself but also with substituted derivatives. These were variously methoxy-substituted at C-4 and C-6, and in some cases substituted also at C-3 with methyl, phenyl, or dithiolan groups.

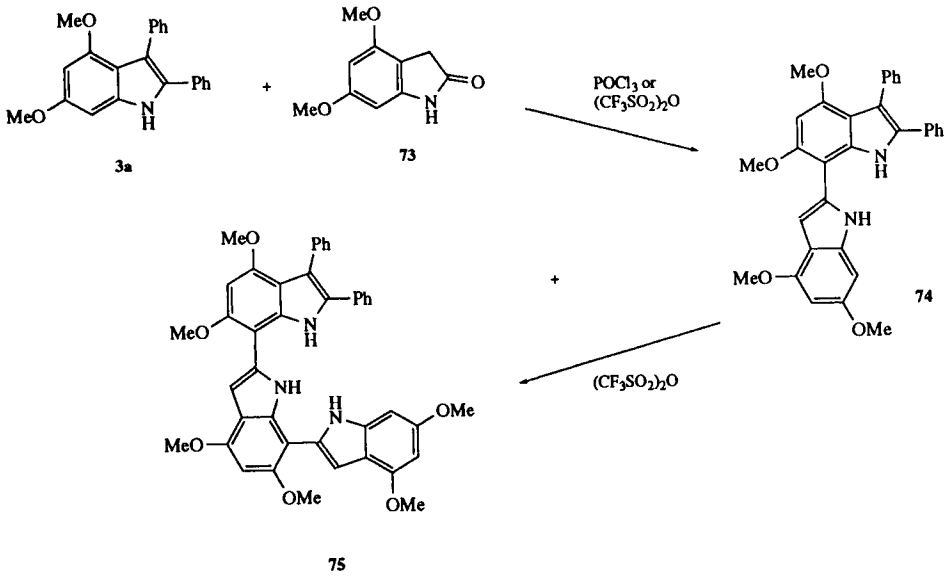
The combination of indolin-2-one **70** and phosphoryl chloride reacted smoothly with 4,6-dimethoxy-2,3-diphenylindole **3a** to give the 2,7′-biindolyl **71** in 75% yield[43,44] (Scheme 21). Attempts to react the indole-2,3-dicarboxylic ester **3c** and the tetrahydrocarbazole **3e** with indolinone **70** and phosphoryl chloride under the same conditions were unsuccessful and either no reaction or indiscriminate decomposition occurred. Application of the method of Bocchi and Palla[37] allowed reaction of 3-bromoindole with the diphenylindole **3a** and gave an 80% yield of the 2,7′-biindolyl **71**. However, there was still no reaction with the other indoles **3c** and **3e**. Trifluoromethanesulfonic anhydride (triflic anhydride) has been used instead of phosphoryl chloride in Vilsmeier-type reactions with dimethylformamide and results in formation of a more highly reactive iminium salt.[45] As a consequence, formylation of less activated aromatic systems has been accomplished, and milder conditions than usual can be used for the formylation of activated systems. Such conditions using indolinone **70** converted the diphenylindole **3a** quantitatively into the 2,7′-biindolyl **71**. Furthermore, under these conditions the indole diester **3c** gave the 2,7′-biindolyl diester **72** in 70% yield (Scheme 21). Not only does the use of triflic anhydride offer a highly reactive reagent, but the iminium triflate salt precipitates out and can be isolated and purified prior to basification to obtain the indole product.




***Scheme 21.***

4,6-Dimethoxyindolin-2-one **73** can be formed either by Wolff–Kishner reduction of the related isatin hydrazone[43] or zinc reduction of the product of the combination of dimethoxyaniline and diethyl mesoxalate.[17] The indolinone **73** undergoes reaction with indole **3a** and phosphoryl chloride to give the 2,7′-biindolyl **74** in 55% yield, together with the terindolyl **75** in 30% yield[44] (Scheme 22). Replacement of phosphoryl chloride by triflic anhydride allowed formation of a quantitative yield of the biindolyl **74**, without the need for chromatography. Reaction of indole **3a** with excess phosphoryl chloride and indolinone **73** gave the terindolyl **75** in 75% yield. However, even with a large excess of triflic anhydride and indolinone **73** in this reaction, no terindolyl **75** was observed. On the other hand, the terindolyl **75** could be produced in 50% yield when the biindolyl **74** was reacted with the indolinone **73** and triflic anhydride (Scheme 22). Despite the fact that the terindolyl **75** contains one reactive C-7 and two reactive C-3 positions, further substitution could not be effected.

Reaction of 3-methylindolin-2-one **76** with diphenylindole **3a** and phosphoryl chloride gave the 2,7′-biindolyl **77** in 71% yield together with a trace of 2-chloro-3-methylindole **78**[16] (Scheme 23). Clearly the pres-

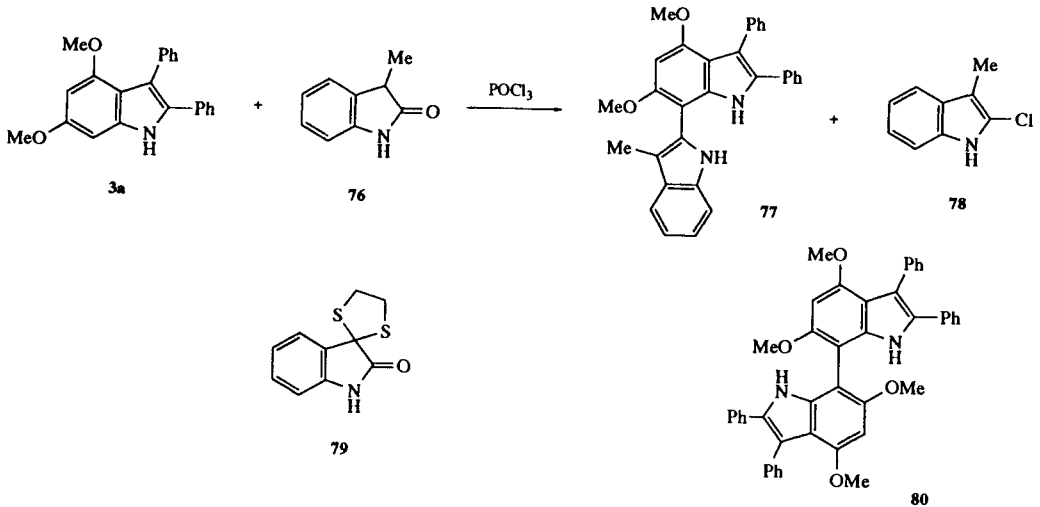



***Scheme 22.***

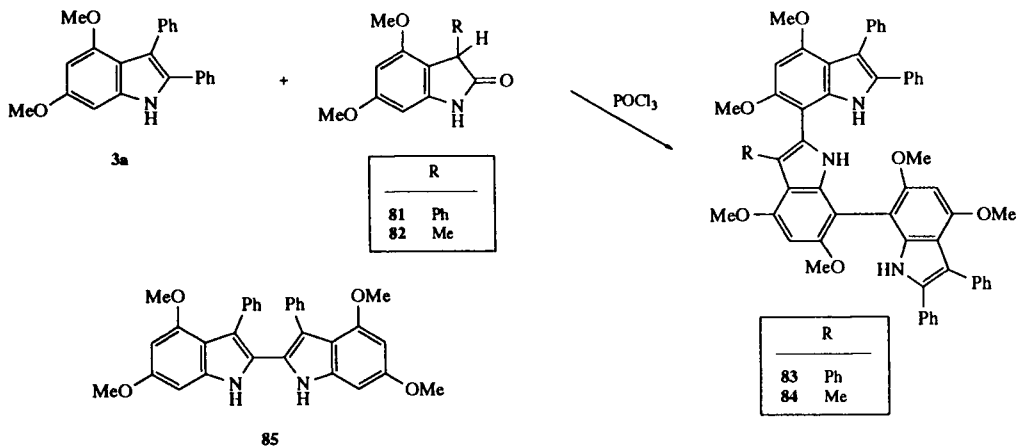
ence of the 3-methyl group lowers the reactivity of the crucial reagent, allowing indole **78** to be detected. The more hindered spiro-indolin-2-one **79** is quite unreactive under a wide range of conditions, and the only observed product was the 7,7′-biindolyl **80**, formed by oxidative dimerization[20,46] of indole **3a**.

The 3-phenyl- and 3-methyl-4,6-dimethoxyindoles **81** and **82** reacted with diphenylindole **3a** and phosphoryl chloride to give predominantly the 7,7′- and 2,7′-terindolyl compounds **83** and **84** in 45 and 38% yields, respectively (Scheme 24). It would appear that the desired 2,7′-biindolyl is formed, but unable to avoid further combination with a second equivalent of the indole **3a**, giving rise to formation of the 7,7′-linkage. Once again, traces of the 7,7′-biindolyl **80** were formed in each reaction, together with a 5% yield of the 2,2′-biindolyl **85** generated in the reaction involving indolinone **81**. Presumably the biindolyl **85** is formed by the oxidative coupling of the intermediate 2-chloroindole. The replacement of phosphoryl chloride with triflic anhydride led to cleaner reactions and higher yields (60 and 50%, respectively) of the terindolyls **83** and **84**. Again, traces of the 7,7′-dimer **80** were observed (Scheme 24).

The electron-rich spiro-indolinone **86**, in contrast to compound **79**, did combine with phosphoryl chloride and the diphenylindole **3a** to yield


MeO
Ph
Ph
MeO
N
H
3a
+
Me
O
N
H
76
POCl3
MeO
Ph
Ph
MeO
N
H
Me
NH
77
+
Me
Cl
N
H
78
S
S
O
N
H
79
MeO
Ph
Ph
MeO
N
H
H
N
OMe
Ph
Ph
OMe
80

*Scheme 23.*


MeO
Ph
Ph
MeO
N
H
3a
+
MeO
R
H
O
MeO
N
H
R
81 Ph
82 Me
POCl3
MeO
Ph
Ph
MeO
N
H
R
NH
OMe
MeO
OMe
MeO
HN
Ph
Ph
R
83 Ph
84 Me
MeO
Ph
Ph
OMe
MeO
N
H
N
H
OMe
85

*Scheme 24.*

a product. However, this product was not the anticipated 2,7′-biindolyl, but a 7,7′-biindolyl, which was shown to have the unusual structure **87**, arising from rearrangement of the dithiolan ring[16] (Scheme 25). The sulfur ring expansion could lead to a carbocation, which could then undergo nucleophilic attack from the indole **3a** to give the product **87**.

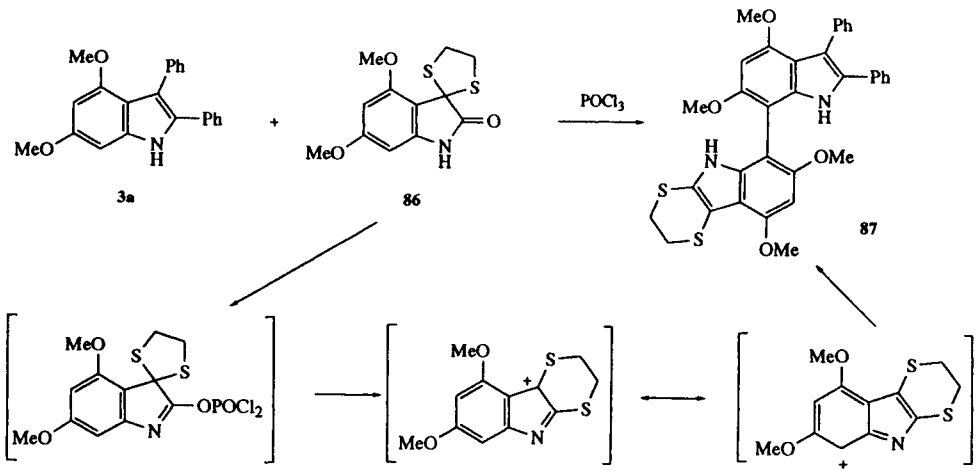
### B. Reaction of 3-Substituted-4,6-dimethoxyindoles

Reaction of the 3-methyl-4,6-dimethoxyindole **7** with indolin-2-one **70** and phosphoryl chloride gives a mixture of the 2,2′-biindolyl **88** and 2,7′-biindolyl **89** in 33 and 27% yields, respectively[44] (Scheme 26). Similar reaction with the more activated dimethoxyindolinone **73** gave a complex mixture of products. The 3-arylindole **20b**, which is less reactive than the 3-methylindole **7**, failed to undergo reaction with the indolinone **70** and phosphoryl chloride under the usual conditions: forcing conditions resulted in extensive decomposition. The only isolable product was the 2,7′-biindolyl **90** in 5% yield. However, employment of triflic anhydride in this combination made a spectacular difference and gave the 2,7′-biindolyl **90** in 100% yield (Scheme 26). Similarly, the dimethoxy analogue **91** was produced quantitatively when dimethoxyindolinone **73** was used. Both the 2,7′-biindolyls **90** and **91** were unable to be converted into terindolyls by further reaction, though there was some inconclusive spectroscopic evidence for the formation of a terindolyl from biindolyl **90**. Reaction of the 3-(4-methoxyphenyl)indole **20c** with excess indolinone **70** and triflic anhydride gave the terindolyl **92** in 50% yield (Scheme 26). This result shows again the directing ability of the 3-(4-methoxyphenyl) group to C-2 as well as C-7.

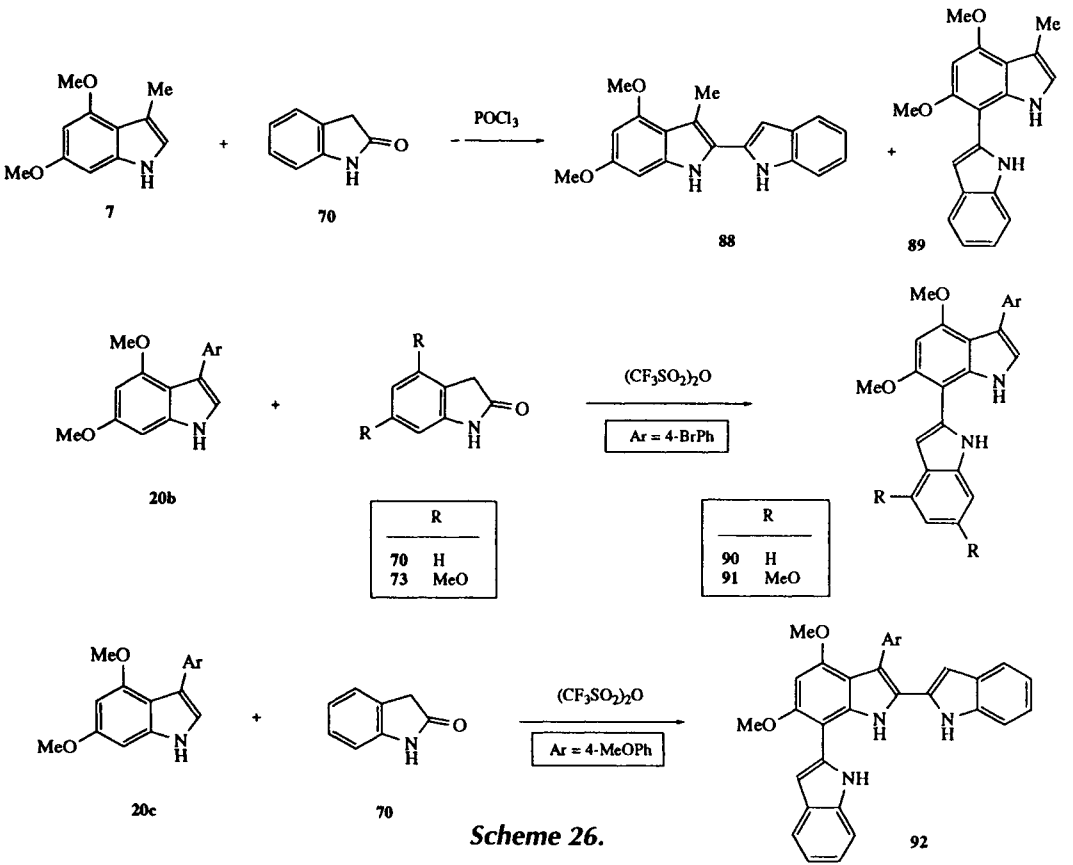
### C. Reaction of 2-Substituted-4,6-dimethoxyindoles

4,6-Dimethoxy-2-phenylindole **93**[47] undergoes reaction with indolin-2-one **70** and phosphoryl chloride at both C-3 and C-7 to give the 2,3′-biindolyl **94** and the 2,7′-biindolyl **95** in 56 and 25% yield, respectively[44] (Scheme 27). Furthermore, the similar reaction with the activated indolinone **73** gave the 2,3′-biindolyl **96** in 30% yield and only a trace of the 2,7′-biindolyl **97** (Scheme 27).

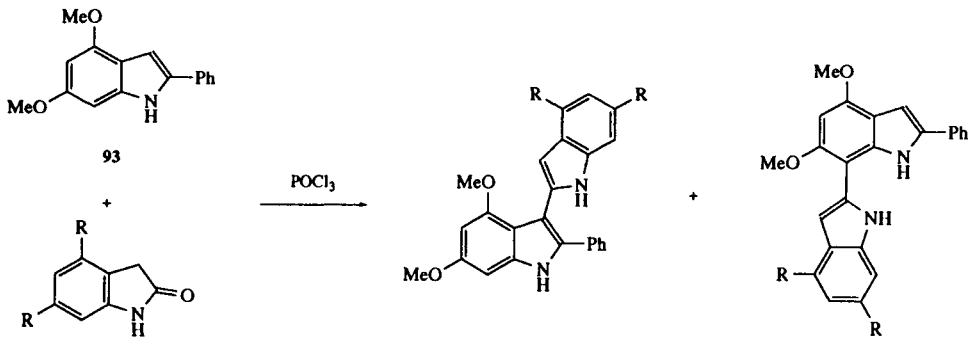
Reaction of the simple, unactivated 2-phenylindole **98** was investigated for comparison. In combination with the indolin-2-one **70** and phosphoryl chloride, it gave the 2,3′-biindolyl **99** in 60% yield and the terindolyl **100** in 19% yield[44] (Scheme 28). As the terindolyl **100** is clearly the result of further reaction at the active C-3 position of one of


MeO
Ph
Ph
MeO
N
H
3a
+
MeO
S
S
O
MeO
N
H
86
POCl3
MeO
Ph
Ph
MeO
N
H
H
N
OMe
S
S
OMe
87
MeO
S
S
OPOCl2
MeO
N
MeO
S
+
S
MeO
N
MeO
S
S
MeO
N
+

*Scheme 25.*


MeO
Me
MeO
7
70
POCl3
88
89
20b
(CF3SO2)2O
Ar = 4-BrPh
R
70 H
73 MeO
90 H
91 MeO
20c
Ar = 4-MeOPh
92

*Scheme 26.*

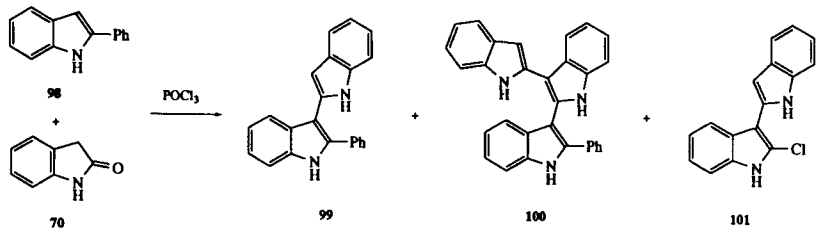



| R | |
|---|---|
| 70 | H |
| 73 | MeO |

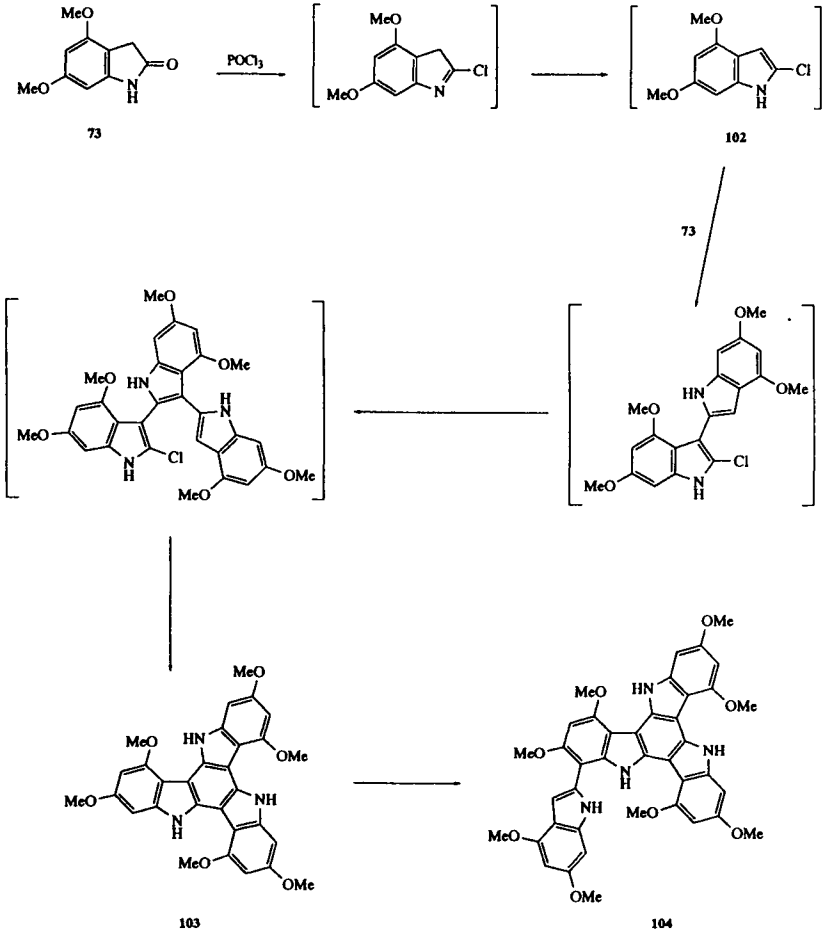
| R | |
|---|---|
| 94 | H |
| 96 | MeO |

| R | |
|---|---|
| 95 | H |
| 97 | MeO |

*Scheme 27.*




***Scheme 28.***




***Scheme 29.***

the indole rings, use of excess reagent raises its yield to 60%, and under these conditions a trace of the chlorobiindolyl **101** is also formed.

### D. Reaction of 4,6-Dimethoxyindolin-2-one with Phosphoryl Chloride

In the various reactions involving 4,6-dimethoxyindolin-2- one **73** and phosphoryl chloride, there is the possibility that the likely intermediate, 2-chloro-4,6-dimethoxyindole **102**, could react with itself, as it is both electrophilic at C-2 and nucleophilic at C-3 and C-7. Even though no products of such a self-condensation process were observed in any of the reactions with indoles, an investigation of this combination of reactants was carried out. The reaction was indeed quite slow, but eventually very small yields (2 and 1%) of the rather interesting heterocyclic system **103** and its further substituted product **104** were isolated[44] (Scheme 29). A possible mechanism is indicated in Scheme 29. A similar 1-methylindole trimer has been synthesized from 2-iodo-1-methylindole by both direct and stepwise routes.[39,40] So far attempts to generalize the phosphoryl chloride reaction and improve the product yields have not met with success.

## VII. CONCLUSION

Applications of the Vilsmeier-type reaction to the synthesis of a variety of imine-substituted indoles have been reported. The scope appears to be very wide and further examples will undoubtedly be forthcoming. Perhaps the most important development is the use of triflic anhydride in combination with amides to generate highly reactive imino-triflate reagents *in situ*, and this general area of reagent modification is also likely to develop.

## ACKNOWLEDGMENTS

It is a privilege to acknowledge the work of skillful and dedicated collaborators, whose names appear in the various references. The financial support of the Australian Research Council is also gratefully acknowledged.

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# APPLICATION OF NITROGEN YLIDE CYCLIZATIONS FOR ORGANIC SYNTHESIS

L. Scott Beall and Albert Padwa



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## I. INTRODUCTION

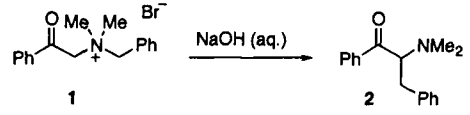
Base-initiated structural isomerizations involving quaternary ammonium ylides have been known for some time.[1] The [1,2]-migration first observed by Stevens and co-workers[2] was subsequently generalized and subjected to further study by that group.[3] The *ortho*-shift in benzylic systems was initially reported by Sommelet[4] but was not examined in any detail until subsequent investigations by Hauser's research group.[5] Consequently, this [2,3]-sigmatropic reaction is often referred to in the literature as the Sommelet–Hauser rearrangement. Our understanding of the scope and mechanism of these reactions has matured over the past few decades. These rearrangement reactions proceed with high regio-, stereo-, and enantioselectivities and have become a powerful tool for the synthetic organic chemist. Numerous examples of the utility of nitrogen ylide rearrangements have been recorded in the chemical literature and this number continues to grow. Details of the earlier work in this area have been summarized elsewhere[6] and some excellent reviews on ylide chemistry nicely illustrate the synthetic uses of these rearrangements.[7]

Another method for preparing ammonium ylides exploits the interaction of carbenes or carbenoids with the unshared electron pair of a nitrogen atom.[8] Compounds such as imines and nitriles that contain an electron pair in the $sp^2$ or $sp$ state of hybridization also interact with carbenes to form unsaturated nitrogen ylides. A widespread upsurge of activity in the application of azomethine ylides and nitrile ylides to new synthetic transformations has occurred.[9] A rather diverse range of chemistry has surfaced in recent years. It is the intent of this chapter to define the boundaries of our present knowledge in this area of heterocyclic chemistry. Emphasis will be placed on recent applications of all three classes of nitrogen ylides for the synthesis of nitrogen heterocycles.

## II. AMMONIUM YLIDES

### A. Base-Promoted [1,2]-Sigmatropic Rearrangements

The first example of an ammonium ylide rearrangement was encountered in 1928 by Stevens and co-workers who observed that a novel [1,2]-benzyl shift occurred when ammonium salt **1** was heated in dilute



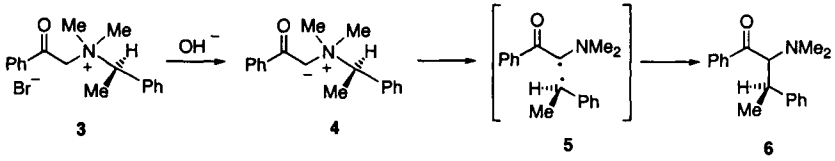

1 2

aqueous sodium hydroxide.[2] They speculated that the formation of the rearranged amino ketone **2** proceeded by way of a benzyl radical shift. Much later, mechanistic studies by Ollis and co-workers revealed that treatment of an ammonium salt, such as **3**, with base produced the nitrogen ylide **4** which underwent homolysis to afford the radical pair **5**.[10] This was followed by a recombination of the radicals to give the tertiary amine product **6**. The radical pair mechanism of the [1,2]-rearrangement accounts for the retention of configuration at the migrating center.

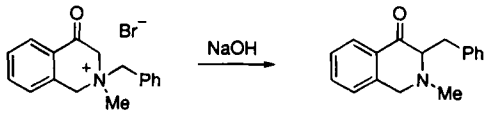
In recent years, the Stevens rearrangement applied to cyclic systems has resulted in the formation of a variety of novel heterocycles. For example, benzylammonium salt **7** was found to undergo a facile [1,2]-benzyl shift in aqueous sodium hydroxide at 5 °C to form the tetrahydroisoquinoline derivative **8**.[11]

If the migrating carbon is part of a ring system, the Stevens rearrangement products arise by means of a ring expansion. For example, treatment of pyrrolinium salt **9** with base led to the isolation of a crystalline pyrrolinium ylide that gave the rearranged derivative **10** on further heating.[12] Similarly, ylide **11** was smoothly transformed into amino ketone **12**.[13]

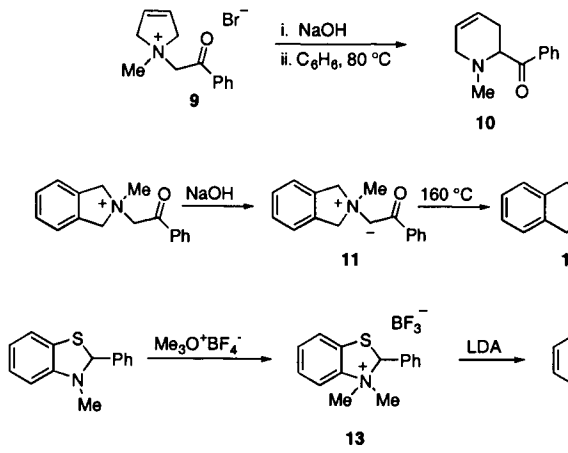
Benzyl substituents are not the only groups capable of undergoing migration as was discovered by Inamoto and co-workers.[14] The reaction of benzothiazolinium salt **13** with LDA provided amine **14**, which corresponds to the product of a methyl group migration.




3 4 5 6



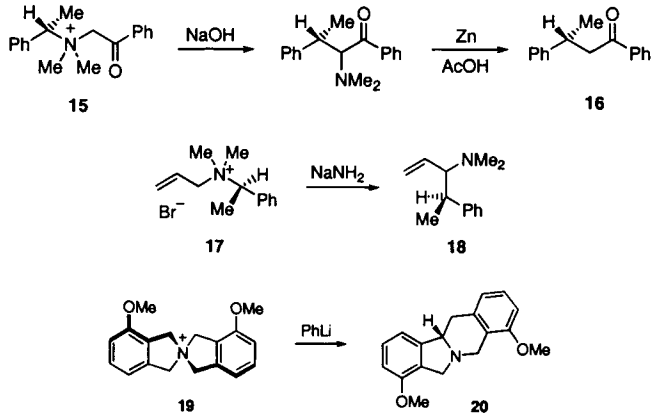

7 8



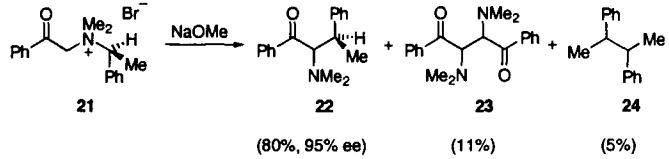

9 10 11 12 13 14

As previously mentioned, the radical ion pair mechanism nicely accounts for the retained configuration of the migrating group in the Stevens rearrangement. A typical example illustrating this point involves rearrangement of the optically active ammonium salt **15** which afforded ketone **16**, after reductive removal of the amino group, in >98% ee.[15] Similarly, the allylic ammonium ylide **17** gave amine **18** with >90% retention at the migrating phenethyl group.[16] The spiro-quaternary ammonium salt (*R*)-**19** was also examined and found to rearrange to alkaloid (*S*)-**20**.[17]

Finally, the ammonium ylide derived from **21** gave rise to amine **22** in 95% ee. This example also illustrates the radical pair nature of the Stevens rearrangement in that diamine **23** and alkane **24** were isolated as




15 16 17 18 19 20



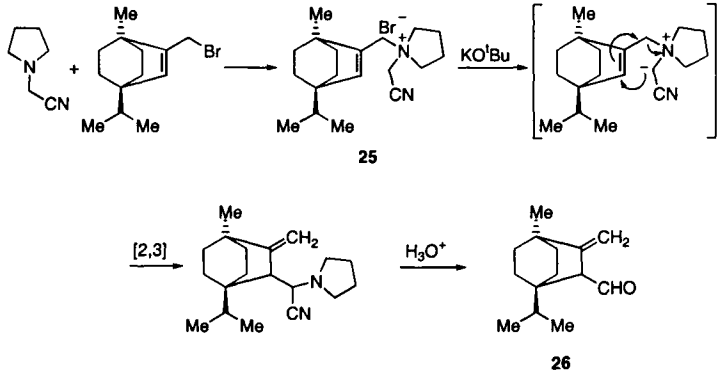

by-products. This was attributed to radicals that wandered outside the solvent cage.[10,18]

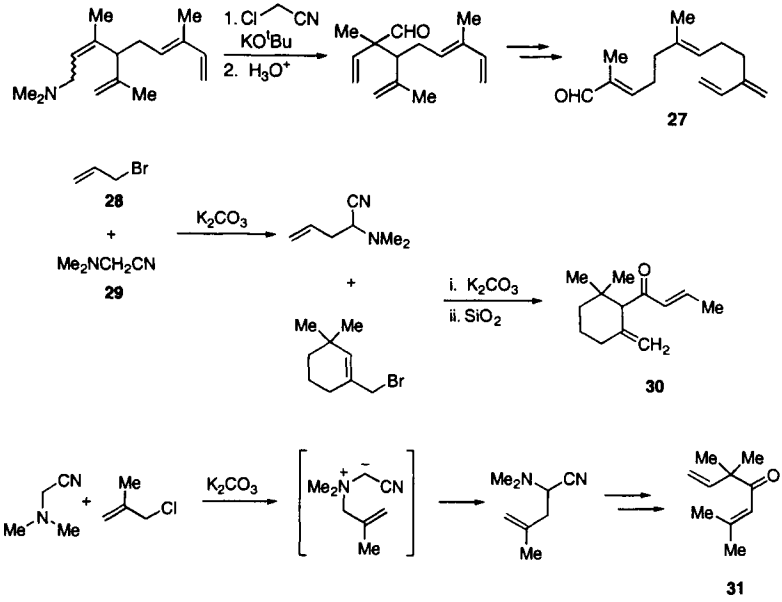
## B. Base-Promoted [2,3]-Sigmatropic Rearrangements

The [2,3]-sigmatropic rearrangement of allylic ammonium ylides is a concerted symmetry-allowed process that shows high regio-, diastereo-, and enantioselectivites. Unlike the base-promoted Stevens rearrangement, this reaction has been widely used in organic synthesis. An early example was carried out by Büchi and co-workers who showed that β,γ-unsaturated carbonyl compounds are accessible via this [2,3]-rearrangement. Thus, treatment of ammonium salt **25** with base initiated the [2,3]-rearrangement which produced the β,γ-unsaturated compound **26** after hydrolysis.[19] Starting from the allylic bromide precursor, the isolated yield of the resulting aldehyde was consistently between 90 and 95%.

Using this method, Büchi and Wüest were able to synthesize α-sinensal (**27**) from *trans*-3-methyl-2,4-pentadien-1-ol in an overall yield of 27%.[20]

Amrollah-Madjdabadi and Stella used a similar approach for the rapid and concise synthesis of γ-damascone (**30**) in three steps starting from allyl bromide (**28**) and dimethylaminoacetonitrile (**29**).[21] These investi-



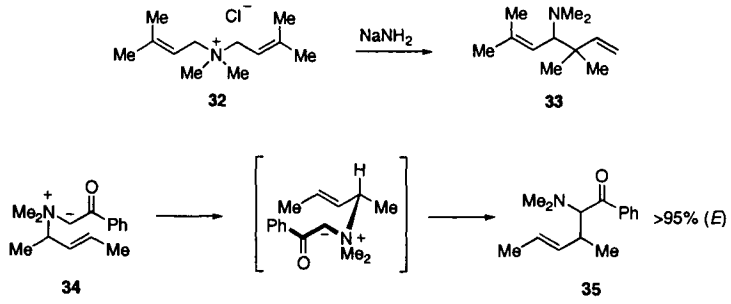


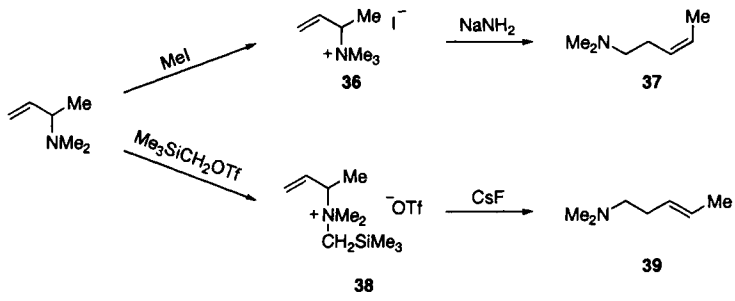

gators also reported a four-step synthesis of artemesia ketone (**31**) which proceeded with an overall yield of 77%.[22]

Ylides lacking electron-withdrawing groups attached to the nitrogen atom also undergo this rearrangement. Rautenstrauch and co-workers demonstrated this point by transforming the symmetrical allylic ammonium salt **32** into amine **33**. The overall yield for this process was 87%.[23]

The [2,3]-sigmatropic reaction was found to proceed with high regioselectivity for the formation of the rearranged product. Thus, ammonium ylide **34** gave amine **35** with >95% trans-selectivity.[24] This is undoubtedly a consequence of the concerted nature of the reaction.

In another example, the base-promoted reaction of ammonium salt **36** led to *cis*-alkene **37** in 72% yield. Interestingly, desilylation of the related

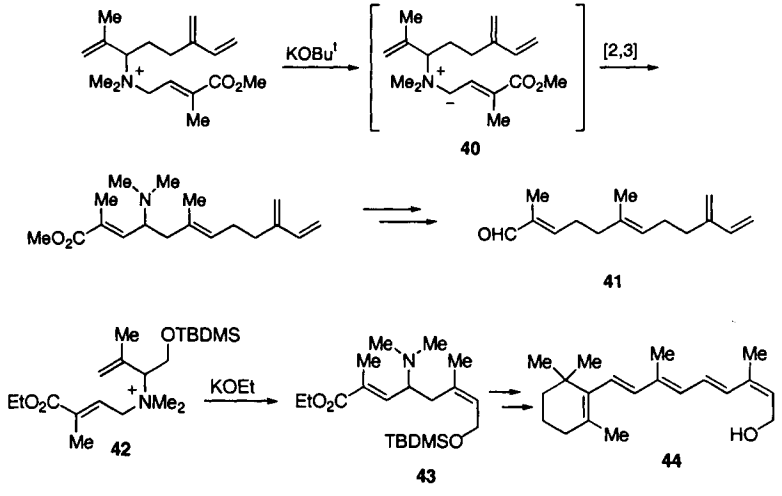


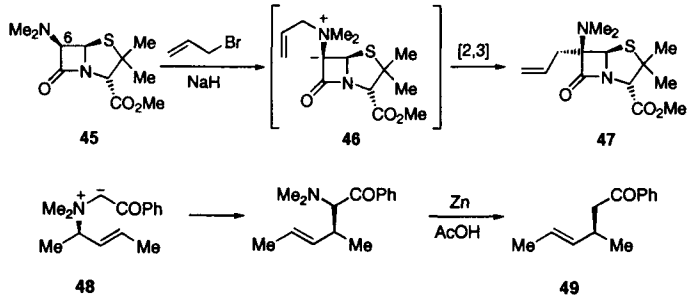



silyl triflate salt **38** with CsF resulted in the exclusive formation of the *trans*-alkene **39** in 68% yield.[25] Utilizing this methodology, Honda and co-workers prepared β-sinensal (**41**) by a [2,3]-sigmatropic rearrangement of ammonium ylide **40**.[26] The *cis*-stereoisomer was the only product formed. Also, the side chain of the monoterpenoid 13-*cis*-retinol (**44**) was constructed from the (*E,Z*)-synthon **43** which was obtained by the rearrangement of ammonium salt **42**.[27]

A valuable part of the [2,3]-sigmatropic rearrangement of ammonium ylides is the fact that stereochemical information can be transferred. For example, Kaiser and co-workers stereoselectively alkylated the C-6 position of penicillin using the nitrogen ylide **46** derived from lactam **45**.[28] Quaternization of **45** with allyl bromide followed by ylide generation using sodium hydride effected the [2,3]-rearrangement. This resulted in the exclusive formation of β-lactam **47** in 75% yield.

Using simple allylic ammonium salts, Hill and co-workers showed that the rearrangement of *trans*-(*R*)-ammonium ylide **48** followed by

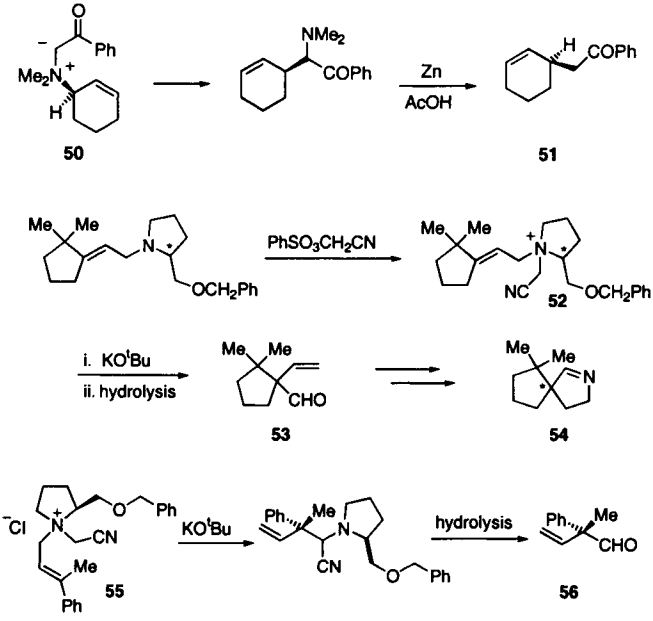


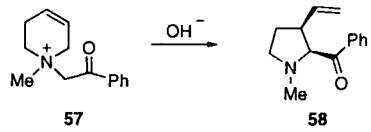



reductive cleavage of the amino group gave *trans*-(*R*)-**49** in 88% ee. Similarly, nitrogen ylide (*R*)-(+)-**50** provided ketone (*R*)-(−)-**51** with an overall inversion of configuration.[24]

Ammonium ylides derived from chiral amines are ideal candidates for effecting asymmetric induction using the [2,3]-sigmatropic rearrangement. By employing (L)-benzyloxyprolinol as the chiral auxiliary, the rearrangement of ammonium salt **52** gave the chiral aldehyde **53** in 68% yield. This compound was used as an important precursor to (+)-polyzonimine (**54**).[29] Similarly, the prolinol-derived salt *trans*-**55** gave aldehyde (*R*)-(+)-**56** in 65% ee.[30]

In an interesting transformation, Ollis and co-workers demonstrated that the six-membered cyclic ammonium salt **57** underwent [2,3]-sigma-



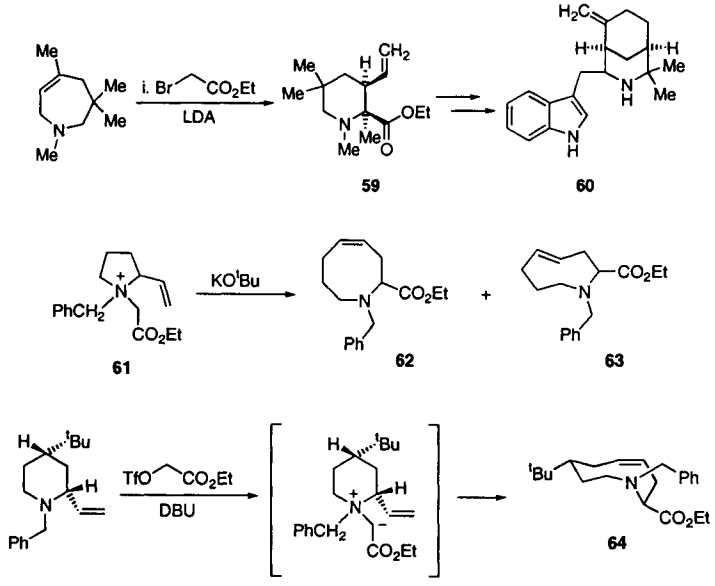


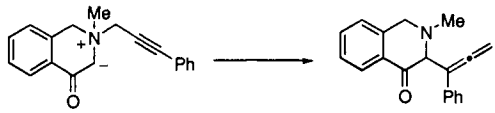

tropic rearrangement in the presence of base to give pyrrolidine **58** exclusively as the *syn*-isomer.[12,31] This protocol was subsequently utilized by Neeson and Stevenson to synthesize *syn*-piperidine **59** in an approach to (+)-makomakine (**60**).[32]

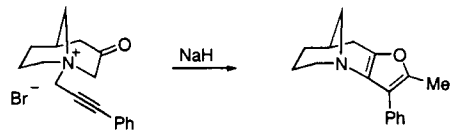
The [2,3]-sigmatropic rearrangement can also produce eight- and nine-membered ring heterocycles through expansion of pyrrolidine and piperidine rings. An example of this sequence was carried out by Vedejs and co-workers who effected ring expansion of the piperidinium salt **61** to produce a 3:2 mixture of azacyclooctenes **62** and **63**.[33]

Introduction of a 4-*t*-butyl group on the piperidine ring resulted in a dramatic regiochemical influence by forcing the six-membered ring into a boat conformation so as to place the *t*-butyl group in the equatorial position. The presence of the carbanionic portion of the ylide in the axial position resulted in the exclusive formation of *cis*-olefin **64**.[34]

Propargylic groups are also known to participate in [2,3]-sigmatropic rearrangements and lead to the isolation of allenes as the major products. For example, the nitrogen ylide **65** was formed by treating the corresponding ammonium salt with NaH in DMSO afforded allene **66** in 86%

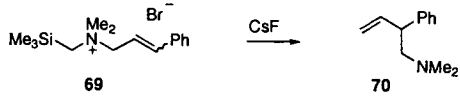





yield.[35] Similarly, reaction of the propargylic ammonium salt **67** furnished furan **68** in 99% yield via a subsequent reaction of the initially formed allene with the ketone carbonyl group.[36]

There is considerable synthetic interest in effecting the [2,3]-sigmatropic rearrangement in the absence of a strong base since this sequence would be amenable to synthesis of complex structures containing base-sensitive functional groups. In one such method involving a desilylation reaction, the fluoride-ion-induced desilylation of ammonium salt **69** was carried out to give **70** in 77% yield.[37]

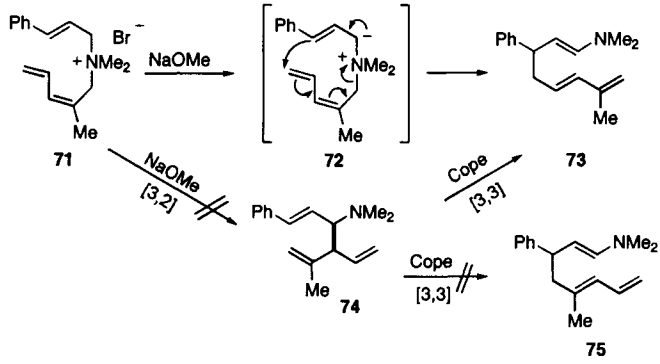



## C. Base-Promoted [5,4]-Sigmatropic Rearrangements

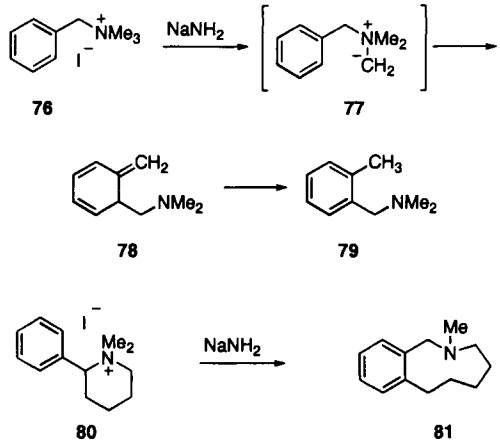
The base-promoted rearrangement of the allyl(pentadienyl)ammonium cation **71** proceeded at room temperature via ammonium ylide **72** and produced the *trans,trans*-enamine **73** via a [5,4]-sigmatropic rearrangement. The alternative pathway involving a [2,3]-sigmatropic rearrangement to produce amine **74** followed by a [3,3]-Cope rearrangement was eliminated. This was done because the above reaction was carried out at room temperature whereas a Cope rearrangement would require elevated temperatures. In addition, product **75** derived from rotation about the highlighted bond followed by a [3,3]-Cope rearrangement was not detected in the crude reaction mixture.[38]

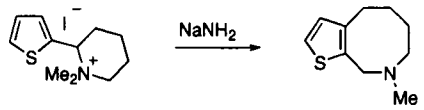
## D. Sommelet–Hauser Rearrangements

The Sommelet–Hauser rearrangement formally involves the conversion of a benzyl ammonium salt such as **76** into a benzyl amine (e.g., **79**).




The reaction proceeds via a concerted, symmetry-allowed [2,3]-sigmatropic shift. Kantor and Hauser proposed a mechanism that involves deprotonation at the benzylic position to generate an ammonium ylide which isomerizes to give nitrogen ylide **77**. This transient species undergoes a [2,3]-sigmatropic rearrangement to furnish triene **78** which rearomatizes under the basic reaction conditions to form benzyl amine **79**.[39] In a subsequent paper, Lednicer and Hauser showed that this sequence of reactions is amenable to ring expansion.[40] Treatment of ammonium salt **80** with $NaNH_2$ resulted in rearrangement to give the nine-membered nitrogen-containing heterocycle **81** in 83% yield. The aromatic ring involved in the Sommelet–Hauser reaction does not need to be a benzenoid π-system. For example, treatment of thienylpyrrolidinium or thienylpiperidinium salts (e.g., **82**) with $NaNH_2$ resulted in the formation of the thiophene-appended nitrogen heterocycle **83**.[41]

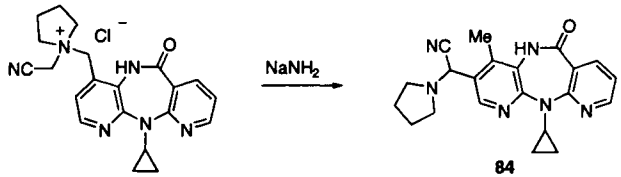


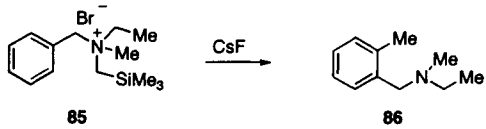


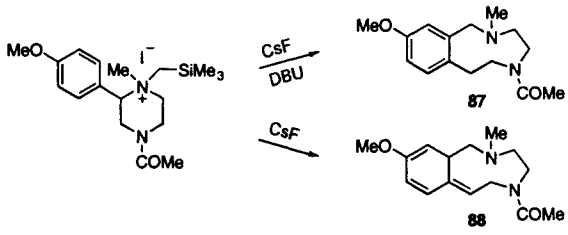

82 83

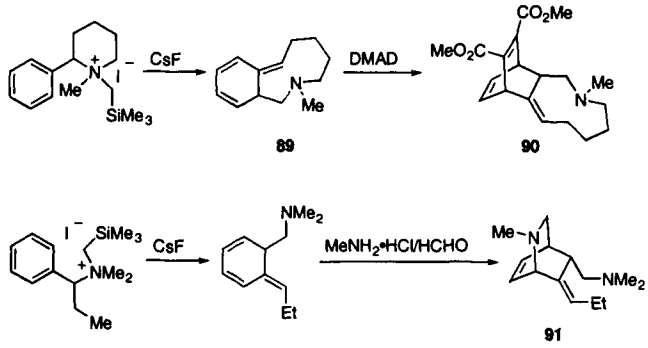
Klunder nicely exploited the Sommelet–Hauser reaction to synthesize dipyridodiazepine derivatives, such as **84**, whose structural analogues show potent inhibition of HIV-1 reverse transcriptase.[42] The key step here involves a [2,3]-sigmatropic rearrangement across the pyridine ring.

Under strongly basic reaction conditions, the Sommelet–Hauser and Stevens rearrangements sometimes become competitive. If a β-hydrogen is present, elimination becomes a possible side reaction. To limit this alternative reaction pathway, Sato and co-workers have taken advantage of the nonbasic ylide-forming desilylation method to promote the Sommelet–Hauser rearrangement. For example, treatment of ammonium salt **85** with CsF cleanly gave amine **86** in 93% yield.[43] As a consequence of these mild nonbasic reaction conditions, triene intermediates such as **78** or **88** can be trapped or even isolated and allowed to react in such a way as to form multicyclic ring systems. On the other hand, simple treatment of these transient species with DBU generally affords the standard Sommelet–Hauser product (i.e., **87**).[44] When the conversion of **80** to **81** is carried out using the desilylation protocol, triene **89** can be trapped



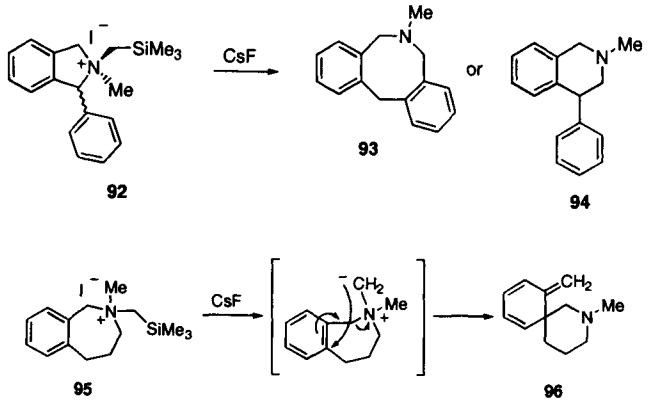






with DMAD to produce the Diels–Alder adduct **90** in 63% yield.[45] These transient dienes have also been trapped with heterodienophiles such as *N*-methylene-methylamine to produce bicyclo compounds (i.e., azabicyclo[2.2.2]octaene **91**).[46]

Recently, Sato and co-workers have shown that the *cis*-ammonium salt **92** gives predominantly the Sommelet–Hauser rearrangement product **93**.[47] Interestingly, the *trans*-diastereomer affords only the Stevens rearrangement product **94**. Sato attributed this difference in behavior to the proximity of the phenyl substituents to the nitrogen ylide anionic center. When the phenyl substituents are in close proximity to the ylide carbanion, a [2,3]-sigmatropic process occurs to produce **93**. On the other hand, when the ylide carbanion is located far from the phenyl groups, the reaction proceeds through a diradical pathway which favors the Stevens rearrangement product **94**.

Spiro-cyclic compounds are also accessible through a CsF-induced rearrangement of ammonium salt **95** which gave the novel amine **96**.[48]

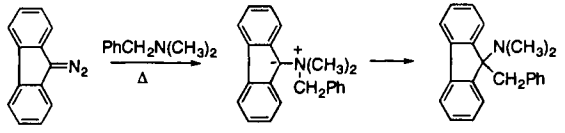


## E. Carbene-Promoted [1,2]-Sigmatropic Rearrangements

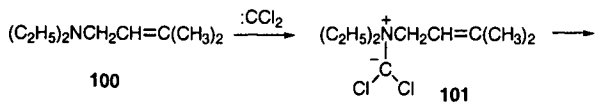
Carbenoid generation of nitrogen ylides represents a useful alternative to the widely employed base-promoted methodology.[49] The reaction of aliphatic diazo compounds with tertiary amines was first investigated by Bamford and Stevens in 1952.[50] The formation of α-benzyl-α-dimethylaminofluorene (**99**) from the reaction of diazofluorene (**97**) with benzyldimethylamine is consistent with a mechanism involving the generation of ammonium ylide **98** which then undergoes a [1,2]-benzyl shift.

The reaction of dichlorocarbene with *N,N*-diethyl-3-methyl-2-butenamine (**100**) produced *N,N*-diethyl-4-methyl-2-pentenamide (**103**) as the major product.[51] The formation of this material was attributed to the generation of ammonium ylide **101** followed by a [1,2]-allylic shift to give intermediate **102** which then hydrolyzed during workup to produce amide **103**. No product resulting from a [2,3]-sigmatropic rearrangement of ylide **101** was detected in the crude reaction mixture.

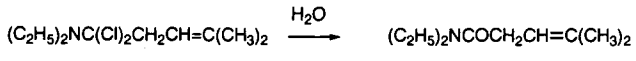
The chemistry of ammonium ylides formed from the reaction of cyclic amines with carbenes was found to be dependent on the ring size of the amine.[52] For example, treatment of 1-benzylazetidine (**104**) with ethyl diazoacetate in the presence of a copper (II) catalyst afforded pyrrolidine **106** in 96% yield. This result is consistent with ammonium ylide formation followed by ring expansion. In contrast, treatment of 1-phenethylaziridine (**107**) under identical conditions gave the fragmentation product **109** in quantitative yield. Similar results were observed for the reaction of aziridine **107** with dichlorocarbene.[53] On the other hand, reaction of 1-phenethylpyrrolidine with ethyl diazoacetate in the presence of a



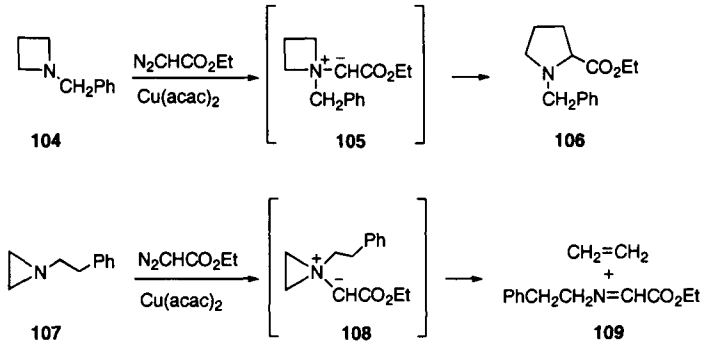

**97** **98** **99**




**100** **101**



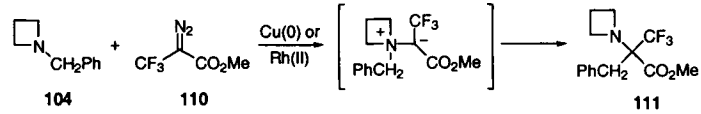

**102** **103**

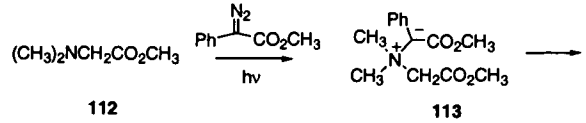



copper(II) catalyst afforded only recovered starting material. It would seem that an important factor determining the course of these reactions is the amount of ring strain energy released. It should be noted that the related reaction of 1-benzylazetidine (**104**) with 3,3,3-trifluoro-2-diazopropionate (**110**) gave the α-$CF_3$-incorporated α-amino acid **111** which is formed via a benzyl migration.[54]

It has generally been recognized that the insertion of carbenes into C–H bonds of compounds containing heteroatoms proceeds with a distinct preference for insertion into the α-CH bond to the heteroatom. For example, methoxycarbonylphenylcarbene is known to undergo a C–H insertion reaction with triethylamine. Other amines bearing electron-withdrawing β-substituents (i.e., **112**), when treated with methoxycarbonylphenylcarbene, afford compounds corresponding to the least favored C–H insertion products.[55] Preference for insertion of an electrophilic carbene should be into the most electron rich C–H bond. These results can be accommodated by a mechanism involving carbene addition to the nitrogen atom to generate ammonium ylide **113**. A [1,3]-proton transfer produces zwitterion **114** which then undergoes a [1,2]-shift to give amine **115**. Support for the above mechanism was obtained by treating ammonium bromide **116** with sodium methoxide and finding that amine **115** is formed in almost quantitative yield. Similarly, the reaction of *N,N*-dimethylbenzylamine (**117**) and diethyl diazomalonate (**118**) gave α-amino ester **119** in 97% yield.[56]

Ammonium ylides possessing a β-hydrogen often undergo an elimination reaction to provide the corresponding amine and alkene.[55,57–60] For





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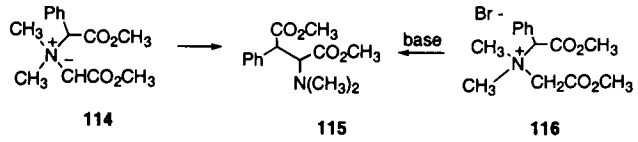

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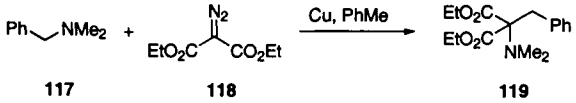
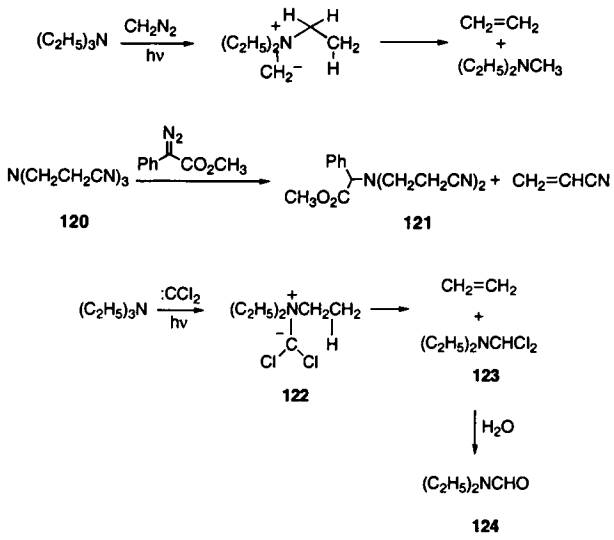


117 118 119

example, the irradiation of diazomethane in the presence of triethylamine gave diethylmethylamine and ethylene.[58,59] In a similar manner, treatment of methoxycarbonylphenylcarbene with cyanoethylamine **120** produced acrylonitrile and amine **121**.[55] These two transformations occur via β-hydride elimination from a transient ammonium ylide.

The reaction of triethylamine with dichlorocarbene produced diethylformamide (**124**) as the major product.[59] This result is also consistent with β-elimination from an initially formed nitrogen ylide **122** which

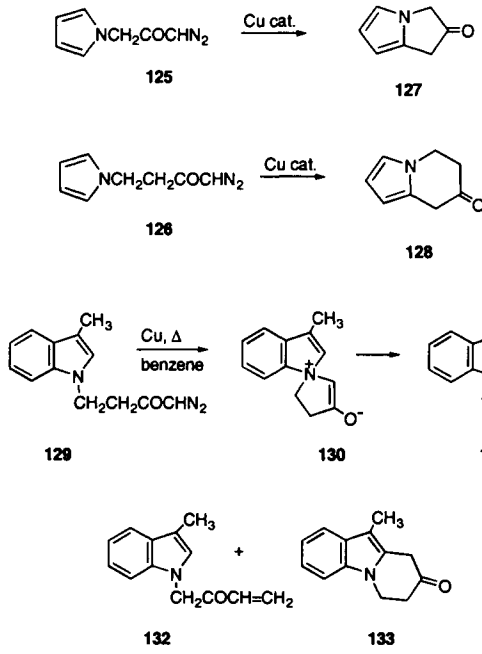


120 121

122 123 124

gives diethyldichloromethylamine (**123**) and ethylene. Hydrolysis of dichloride **123** affords formamide **124**.

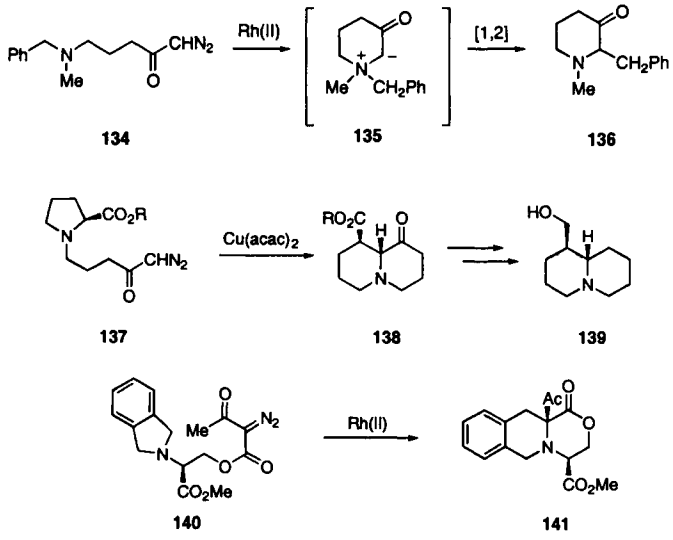
Although suitable for ylide production, carbenes generated photochemically and thermally, in the presence of organic compounds containing heteroatoms, are relatively indiscriminate. The potentially more general catalytic approach to carbenoid generation began to evolve with the use of copper catalysts.[60,61] The carbenoid species formed from the copper-catalyzed reaction of 1-diazo-3-(pyrrol-1-yl)-2-propanone (**125**) and 1-diazo-4-(pyrrol-1-yl)-2-butanone (**126**) gave the annulated pyrroles **127** and **128** in excellent yields.[62] The use of the copper catalyst ensures that a Wolff rearrangement is suppressed. The same catalyzed reaction involving indole diazoketone **129**, however, afforded the annulated indole **133** in low yield. The major product produced here corresponds to enone **132**. A plausible mechanism for the formation of enone **132** involves addition of the electrophilic carbenoid onto the indole nitrogen to produce the azaspirocyclic zwitterion **130** which then isomerizes to form zwitterion **131**. β-Elimination of intermediate **131** gives rise to enone **132**. The difference in reactivity of the pyrrole and indole systems was attributed to the decreased nucleophilicity at the α-carbon of the indole nucleus.

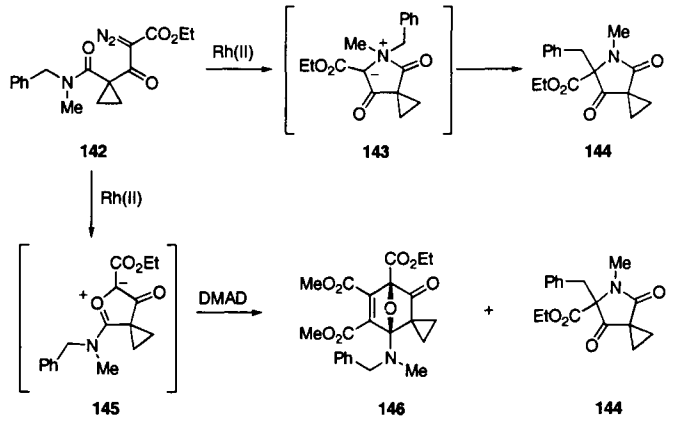


Both rhodium and copper catalysts have been used to generate ammonium ylides which may undergo Stevens or [2,3]-sigmatropic rearrangement. The Rh(II) generation of ammonium ylide **135** from diazo compound **134**, which bears a dialkylamino substituent six centers away, has been studied.[63] The resulting nitrogen heterocycle **136** is the consequence of a [1,2]-benzyl shift of **135**. Although C–H insertion into the carbon backbone represents a competing pathway, preferred reaction of the electron-deficient carbenoid is with the amine lone pair to give ylide **135** which undergoes a Stevens rearrangement.

By taking advantage of the fact that the Stevens rearrangement proceeds with retention of stereochemistry at the migrating center, West and Naidu were able to use the chiral (L)-proline benzyl ester **137** to synthesize amine **138** in 84% yield and in 75% ee.[64] Bicyclic amine **138** was converted to (–)-epilupinine (**139**) in three steps. Zaragoza used a similar protocol to synthesize a single diastereomer of the tetrahydroisoquinoline derivative **141** starting from diazoester **140** using Rh(II) catalysis.[65]

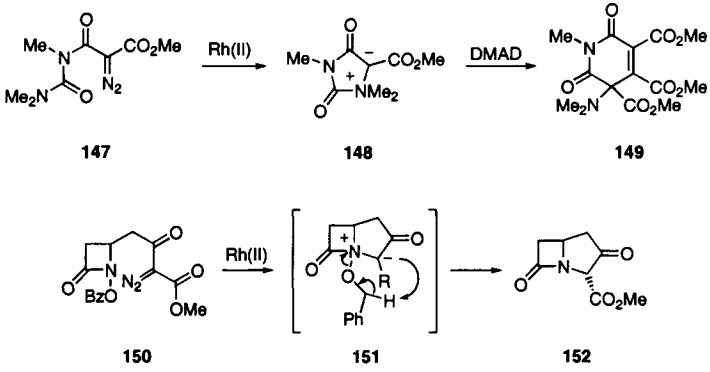
Recently, Padwa's group has encountered an interesting Stevens rearrangement sequence which occurred when α-diazo ketoamide **142** was subjected to Rh(II)-catalyzed conditions.[66] In the presence of DMAD, the expected product **146** derived from the trapping of dipole **145** was isolated (57%) together with the unexpected lactam **144** (23%). In the absence of DMAD, lactam **144** was the only product obtained in 62% yield. The formation of **144** was attributed to the initial generation of ammonium ylide **143** followed by a [1,2]-benzyl shift.






In a related study, Kappe also investigated this phenomenon and found that when diazoamide **147** was treated with $Rh_2(OAc)_4$ in the absence of a dipolarophile, ammonium ylide **148** could be isolated as a crystalline solid in 70% yield.[67] The structure of the ylide was confirmed by X-ray crystallography. In the presence of DMAD, ylide **148** was converted to cycloadduct **149**.

Another interesting use of nitrogen ylides in synthesis was reported by Williams and Miller who employed this intermediate in the preparation of a bicyclo β-lactam. β-Lactam **152** was formed in a single step from the diazo precursor **150**.[68] The proposed mechanism involves a Rh(II)-catalyzed generation of ammonium ylide **151** which abstracts a proton from the benzylic position and then undergoes N–O bond heterolysis to generate the cyclized product and benzaldehyde.

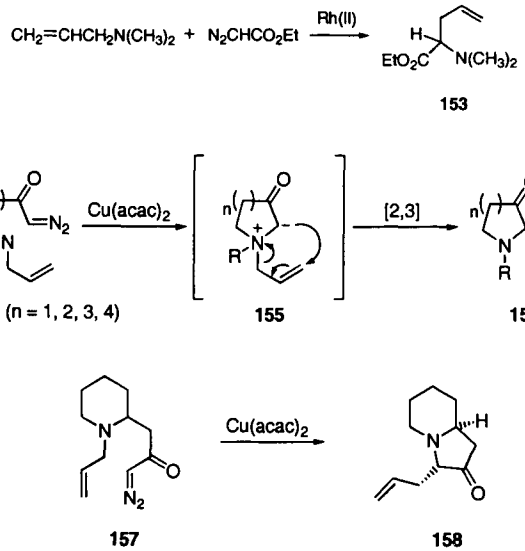


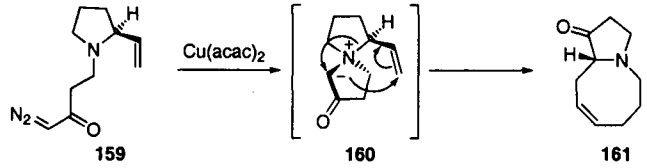
## F. Carbene-Promoted [2,3]-Sigmatropic Rearrangements

Doyle and co-workers were among the first to study the reaction of tertiary allyl amines with various rhodium(II) carboxylates.[69] Stable metal carbenes characteristically undergo nucleophilic addition at the carbene carbon and, in certain cases, stable addition products have been obtained from the reaction of amines with carbene complexes.[70] With these systems the rhodium catalysts were found to be superior to copper catalysts for generating nitrogen ylides. Thus, treatment of dimethylallylamine with ethyl diazoacetate in the presence of rhodium(II) acetate or hexadecacarbonylhexarhodium produced an ammonium ylide which underwent a [2,3]-sigmatropic rearrangement to give amine **153** in good yield. No products resulting from cyclopropanation or C–H insertion were observed in the crude reaction mixture.

Clark and Hodgson have recently studied the [2,3]-sigmatropic rearrangement of ammonium ylides using copper carbenoids.[71] A typical example consists of treating diazo ketone **154** with $Cu(acac)_2$ in refluxing benzene which afforded the cyclic amino ketone **156** via a [2,3]-rearrangement of the corresponding ammonium ylide **155**. A particularly interesting case involves the formation of indolizidine **158** from piperidine **157** using this one-step procedure.

Starting from the optically active (*S*)-proline derivative **159**, Clark and Hodgson were able to synthesize azabicyclo[6.3.0]undecane **161** with

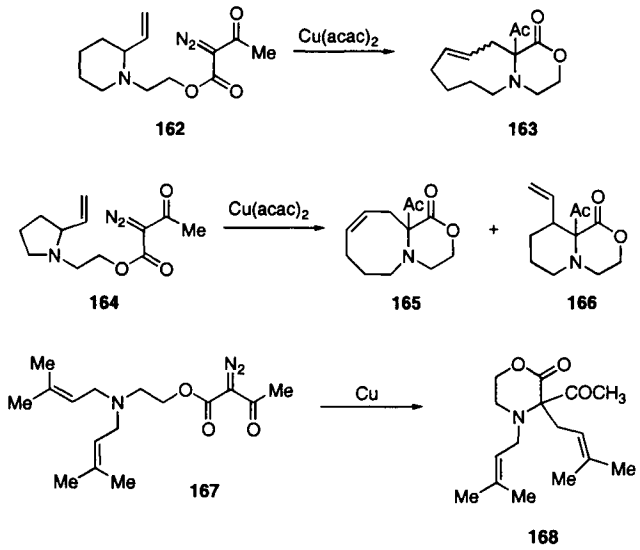





high enantioselectivity. This compound contains the CE ring system found in the manzamine family of alkaloids. The reaction proceeds via a rearrangement of ylide **160** to **161** (56% yield) with >98% ee.[72]

Through a similar series of reactions, McMills and co-workers prepared the azacyclooctene **165** and azacyclononene **163** ring systems starting from (L)-proline **164** or the piperidine derivative **162**, respectively.[73] The proline derivative **164** gave azacyclooctene **165** in 95% ee together with a by-product resulting from a competing Stevens rearrangement (i.e., **166**).

West and Naidu showed that the [2,3]-rearrangement can be fully suppressed when there is significant steric crowding about the terminal alkene.[74] For example, the copper-catalyzed decomposition of diazo compound **167** resulted only in the product of a Stevens rearrangement (i.e., **168**) in 72% isolated yield.

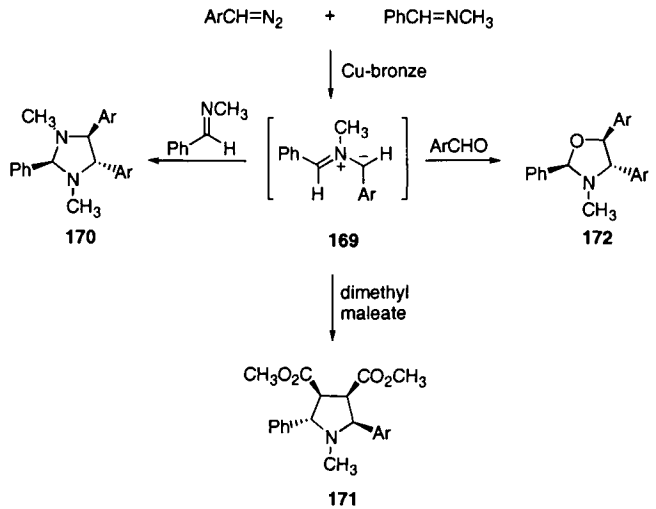


# III. AZOMETHINE YLIDES

## A. Formation of Azomethine Ylides Derived from Imines

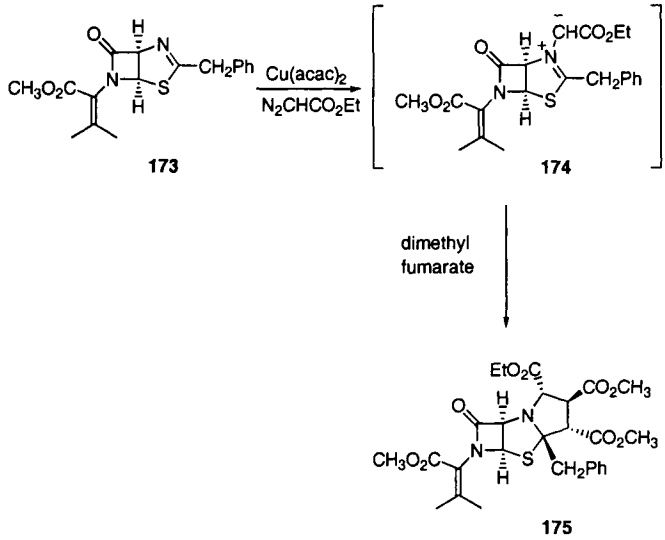
The interaction of a metallo carbene with an imine nitrogen atom to give a transient azomethine ylide has attracted attention over the past decade.[75] Some of the standard methods for generating azomethine ylides involve the thermal or photolytic ring opening of aziridines,[76] desilylation[77] or dehydrohalogenation[78] of iminium salts, and proton abstraction from imine derivatives of α-amino acids.[79] Azomethine ylides are of interest because these dipoles undergo facile 1,3-dipolar cycloaddition with π-bonds to give pyrrolidines which, in turn, have been used to prepare a variety of alkaloids.[80]

The tandem reaction of carbenoids with simple imines to form azomethine ylides which then undergo 1,3-dipolar cycloaddition with various dipolarophiles was first reported in 1972.[81] Treatment of phenyldiazomethane with copper bronze in the presence of excess *N*-benzylidenemethylamine resulted in the isolation of imidazoline **170**. Formation of this product was rationalized by carbenoid addition onto the imine nitrogen to give azomethine ylide **169** which then underwent a 1,3-dipolar cycloaddition with another molecule of imine to produce the observed product. Bartnik and Mloston subsequently extended this observation by using other dipolarophiles.[82] For example, catalytic decomposition of phenyldiazomethane and *N*-benzylidenemethylamine in the presence of dimethyl maleate or benzaldehyde gave pyrrolidine **171**



and oxazolidine **172**, respectively. In both cases, no product resulting from the trapping of the ylide with a molecule of imine could be observed. Catalytic decomposition of phenyldiazomethane with other Schiff bases was found to proceed via formation of a *trans*-1,3-dipole. Depending on the size and quantity of the substituent groups, the ylide either undergoes cyclization in a conrotatory sense to a *cis*-aziridine or [3+2]-cycloaddition to an available π-bond. The reactivity of double bonds toward the ylide was found to decrease in the order C=C > C=O > C=N.

Since they were first isolated from penicillins, thiazoloazetidinones such as **173** have become versatile intermediates in the synthesis of various β-lactam antibiotics. Preferred attack by soft electrophiles is at the sulfur atom whereas hard electrophiles react with the thiazoline nitrogen. Thomas and co-workers have investigated the reaction of thiazoloazetidinone **173** with metal carbenoids.[83] Treatment of **173** with a large excess of ethyl diazoacetate in the presence of copper(II) acetoacetonate and dimethyl fumarate gave the *bis*methoxycarbonyl adduct **175**. The formation of this material involves an initial addition of the ethoxycarbonyl carbenoid onto the thiazoline nitrogen to produce azomethine ylide **174**. This reactive dipole undergoes a subsequent 1,3-dipolar cycloaddition with the added dipolarophile to give the observed product. The reaction was found to be both regio- and stereoselective. No products derived from the reaction of the carbenoid at the sulfur atom or at the C=C bond were observed. The stereochemistry of

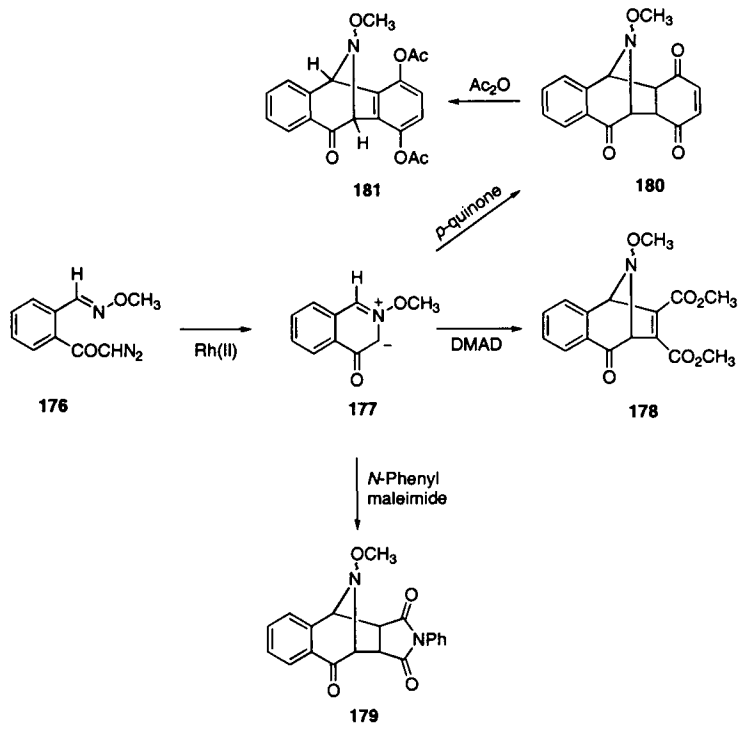



**173** **174** **175**

the cycloadduct is consistent with approach of the fumarate ester from the less hindered side of the ylide.

### B. Formation of Azomethine Ylides Derived from Oximes

The formation and intramolecular dipolar cycloaddition of azomethine ylides formed by carbenoid reaction with C=N bonds has recently been studied by the authors' group.[84] Treatment of 2-(diazoacetyl)benzaldehyde *O*-methyl oxime (**176**) with rhodium(II) octanoate in the presence of dimethyl acetylenedicarboxylate or *N*-phenylmaleimide produced cycloadducts **178** and **179**, respectively. The cycloaddition was also carried out using *p*-quinone as the dipolarophile. The major product isolated corresponded to cycloadduct **180**. The subsequent reaction of this material with excess acetic anhydride in pyridine afforded diacetate **181** in 67% overall yield from **176**. The latter compound incorporates the basic dibenzo[*a,d*]-cycloheptene-5,10-imine skeleton found in MK-801,[85] which is a selective ligand for brain cyclidine (PCP) receptors that has attracted considerable attention as a potent anticonvulsive and neuroprotective agent.[86,87]



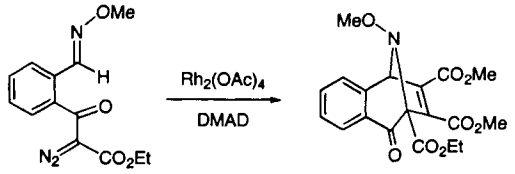
The oxime nitrogen lone pair of electrons must be properly oriented so as to interact with the rhodium carbenoid.[84] Thus, subjection of the *E*-oximino isomer **182** to a catalytic quantity of $Rh_2(OAc)_4$ in $CH_2Cl_2$ (40 °C) with a slight excess of DMAD afforded the bimolecular cycloadduct **184** in 93% yield. In sharp contrast, when the isomeric *Z*-oximino diazo derivative **183** was exposed to the same reaction conditions, only indanone-oxime **185** (80%) was obtained. The formation of this product is most likely the result of an intramolecular C–H insertion reaction.

The success achieved with the Rh(II)-catalyzed transformations of *E*-oximino diazo carbonyl compounds prompted our group to study some additional systems where the C–N π-bond was configurationally locked so that azomethine ylide formation would readily occur. Toward this end, we investigated the Rh(II)-catalyzed behavior of isoxazoline **186** in the presence of DMAD. This reaction afforded the azomethine-derived cycloadduct **187** as a 4:1 mixture of diastereomers in 65% yield. A similar transformation occurred using the α-diazoacetophenone derivative **188** which produced isoxazolo[3,2-*a*]isoquinoline **189** as a 2:1 mixture of diastereomers in 82% yield.[84]

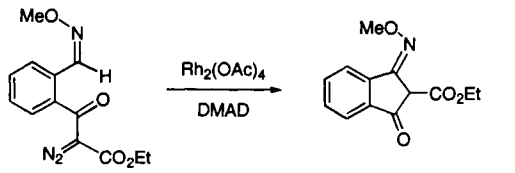
## C. Pyridinium Ylides

### *Bimolecular Reactions*

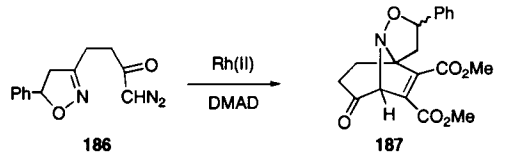
Since their introduction in 1960,[88] pyridine ylides have become increasingly popular probes into the dynamics of carbenes which lack chromophores.[89–94] The combination of high reactivity, favorable spec-




**E-182** **184**




**Z-183** **185**

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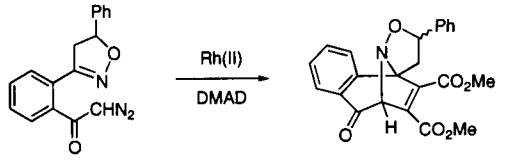
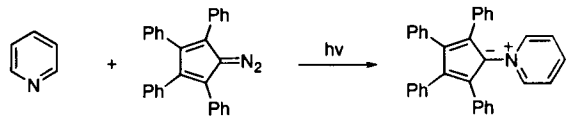


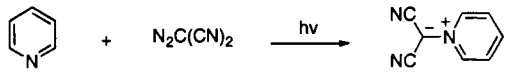

188 189

troscopic properties, and long ylide lifetime has allowed the study of the dynamics of a variety of "invisible" carbenes.[95] The technique has found use in the study of aryl, arylhalo, alkyl, alkylalkoxy, alkylhalo, arylsiloxy, and dialkyl carbenes.[96–99] A number of examples dealing with the preparation of stable pyridinium ylides have also been reported in the literature.[100–103] Pyridinium tetraphenylcyclopentadienylide (**191**) was synthesized by irradiating 2,3,4,5-tetraphenyldiazocyclopentadiene (**190**) in pyridine. Addition of water precipitated the purple ylide **191** in almost quantitative yield.[100–102] This process appears to be general for a number of substituted pyridines (i.e., 2-picoline, 3-picoline, and 2,6-lutidine). In an analogous fashion, *N*-dicyanomethylide **192** was prepared from the photolysis of diazomethanedicarbonitrile in pyridine.[103]

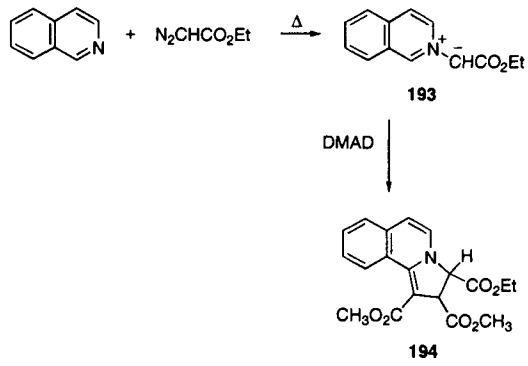
Although the transition-metal-catalyzed reaction of α-diazocarbonyl compounds with aromatic molecules has received much attention in recent years,[104] the metal-catalyzed behavior of these compounds with N-containing heteroaromatics has not been extensively studied. An early example involved the preparation of isoquinoline-carboethoxymethylide




190 191

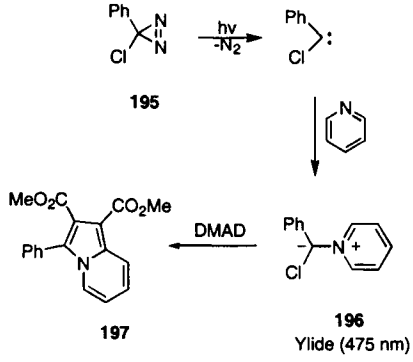


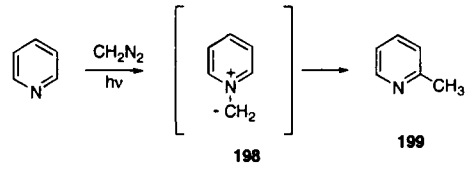

192




**193** by the thermal decomposition of ethyl diazoacetate in the presence of isoquinoline.[105] The same ylide could also be obtained from *N*-carboethoxymethylene isoquinolinium bromide by the elimination of hydrogen bromide. Ylide **193** is a red crystalline solid that is stable in the absence of moisture. The dipolar character of **193** was established by its reaction with dimethyl acetylene-dicarboxylate which led to the formation of cycloadduct **194**. Platz and co-workers reported that the photolysis of phenylchlorodiazirine **195** in the presence of both pyridine and DMAD produced cycloadduct **197** in 30% yield by dipolar cycloaddition of DMAD to the ylide followed by loss of HCl.[106]

These same pyridinium ylides have been generated photochemically. The irradiation of diazomethane in pyridine gave 2-picoline (**199**) in 83% yield.[107] The high yield and specificity of attack at the 2-position of the ring seem to be at variance with electrophilic carbene insertion into a C–H bond as the preferred site of this reaction is at the 3-position. This result is consistent, however, with initial electrophilic attack of the



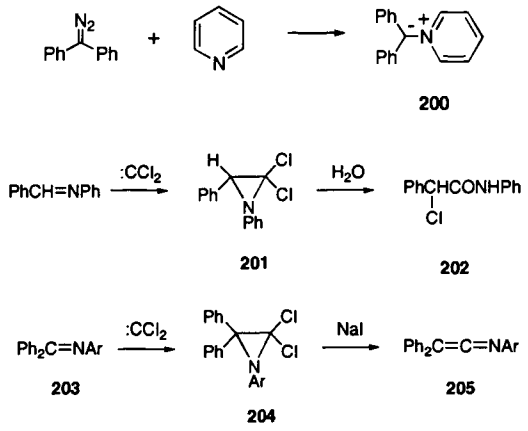


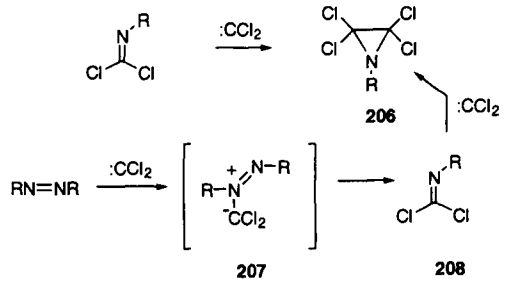

198 199

carbene at the nitrogen atom of pyridine to form dipole **198** which then undergoes an intramolecular reorganization reaction.

The kinetics of the reaction of triplet diphenylcarbene with pyridine has been studied.[108] Laser flash photolysis of diphenyldiazomethane in the presence of pyridine results in the formation of pyridinium ylide **200**. This reactive species shows an absorption band at 500 nm. Based on the low activation energy of the reaction, it was concluded that the data were inconsistent with a simple preequilibrium model. Instead, it was suggested that the intersystem crossing step occurs at a point other than at the minimum of singlet diphenylcarbene.[108]

The addition of dihalocarbenes to C=N bonds to produce dihaloaziridines was first uncovered by Fields and Sandri in 1959.[109] For example, dichlorocarbene undergoes addition to *N*-benzylideneaniline to give 1,3-diphenyl-2,2-dichloroethylenimine (**201**) in 55% yield. This reaction is thought to proceed via an azomethine ylide intermediate which cyclizes to produce the observed product. Treatment of aziridine **201** with water converts it to α-chloro-α-phenylacetanilide (**202**). A similar process was observed on treating diphenylmethylenearylamine **203** with dichlorocarbene.[110] Reaction of the resulting dichloroaziridine **204** with sodium iodide gave ketenimine **205** in excellent yield.

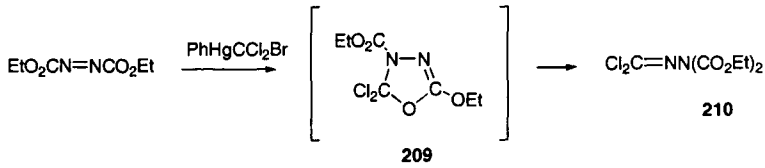


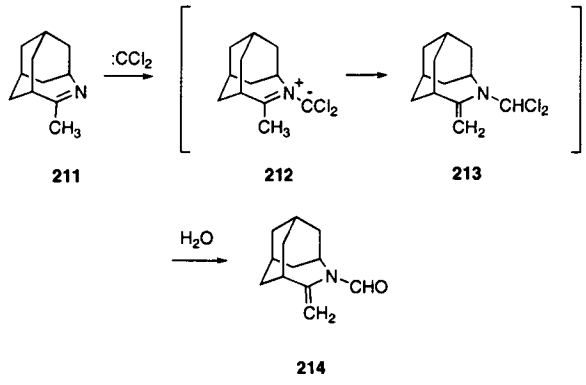



Phenyl(bromodichloromethyl)mercury has been found to transfer $CCl_2$ to alkyl and arylcarbonimidoyl dichlorides producing 1-alkyl or (1-aryl)-2,2,3,3 tetrachloroaziridine (**206**) in good yield.[111] Interestingly, treatment of azobenzene under the same reaction conditions also gave tetrachloroaziridine **206**. This result has been rationalized in terms of the initial generation of ylide **207** which then fragments to produce phenylcarbonimidoyl dichloride **208** and phenyl nitrene. The latter species reacts with dichlorocarbene or phenyl(bromodichloromethyl)mercury to give more phenylcarbonimidoyl dichloride **208**. Dichlorocarbene then adds to the dichloride to produce tetrachloroaziridine **206**.

The decomposition of phenyl(bromodichloromethyl)mercury in the presence of azodicarboxylate ester yields a compound that was identified as structure **210**.[112] The formation of this material seemingly involves azomethine ylide generation followed by cyclization producing intermediate **209** which subsequently rearranges to dichloride **210**. The appearance and disappearance of intermediate **209** could be observed by monitoring the reaction by NMR and IR spectroscopy. The disappearance of the spectroscopic signals corresponding to **209** was concurrent with the appearance of signals related to product **210**.

4-Azahomoadamantane derivatives are known as potential biologically active compounds and several synthetic routes to this skeleton have been reported.[113] The reaction of 5-methyl-4-azahomoadamant-4-ene (**211**) with dichlorocarbene resulted in the formation of 4-formyl-5-methylene-4-azahomoadamantane (**214**) in 66% yield.[114] The isolation of this material is consistent with a mechanism involving carbene addi-





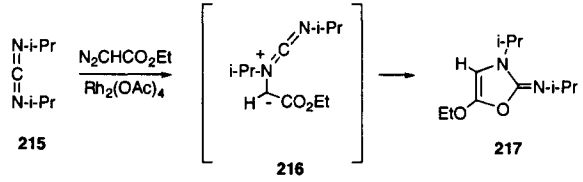

211 212 213 214

tion onto the imine nitrogen to generate an azomethine ylide (**212**). Loss of a proton or hydrogen migration gave **213** and this was followed by hydrolysis of the dichloromethyl group to furnish the observed product.

Hubert and co-workers have reported that alkyl diazoacetates react with *N,N'*-diisopropylcarbodiimide in the presence of transition metal salts to give 2-isopropylimino-3-isopropyl-5-alkoxy-4-oxazolines.[115] For example, treatment of ethyl diazoacetate with rhodium(II) acetate in the presence of *N,N'*-diisopropylcarbodiimide (**215**) produced 2-isopropylimino-3-isopropyl-5-ethoxy-4-oxazoline (**217**) in good yield. The formation of oxazoline **217** was interpreted in terms of an addition of ethoxycarbonylcarbene onto one of the nitrogen atoms of the carbodiimide to give the transient ylide **216** which then cyclized to produce the observed heterocycle.

## *Intramolecular Processes*

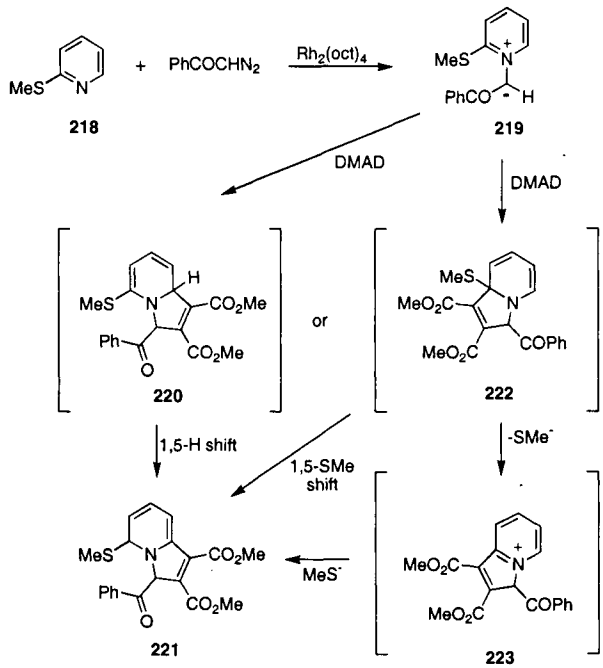
As part of our group's continuing involvement with the chemistry of azomethine ylides, we became interested in examining the cyclization of α-diazo substituted N-containing heteroaromatic systems as a method for ylide generation. Aside from the above examples using pyridines[96] and isoquinolines,[105] little was known about the diazo cyclization process with N-heteroaromatic systems when we initiated our work in this

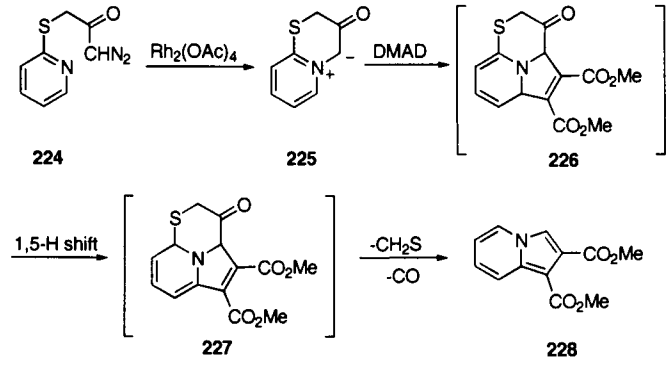



215 216 217

area.[116] The Rh(II)-catalyzed reaction of α-diazoacetophenone in the presence of 2-methylthiopyridine (**218**) and dimethyl acetylenedicarboxylate gave 3-benzoyl-1,2-dicarbomethoxy-3,5-dihydro-5-methylthioindolizine (**221**). The formation of **221** proceeds via a pyridinium ylide formed by attack of the nitrogen lone pair on the electrophilic keto carbenoid. Subsequent dipolar cycloaddition of ylide **219** with DMAD occurs at the less substituted carbon atom to give cycloadduct **220**. This transient species is converted to **221** by means of a 1,5-sigmatropic hydrogen shift. The results are also consistent with the formation of the regio-isomeric cycloadduct **222** which undergoes a 1,5-thiomethyl shift perhaps via the tight ion pair **223**.

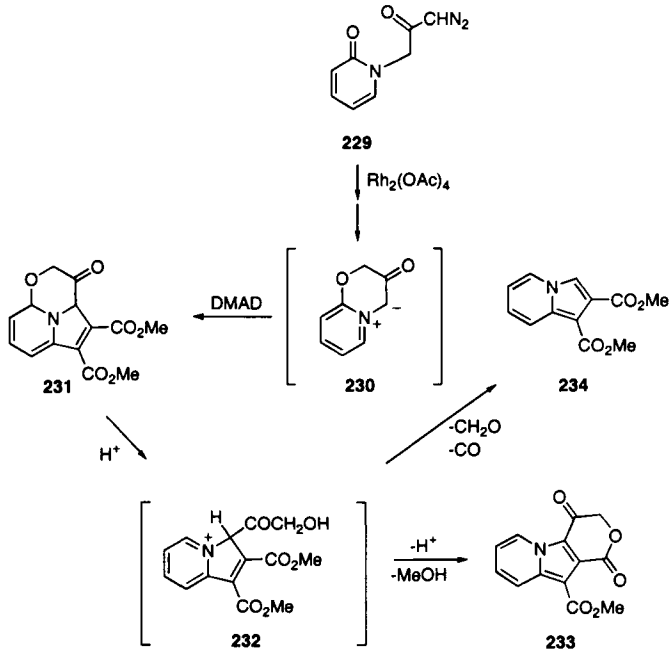
A related cyclization occurred using 1-diazo-3-[(2-(pyridyl)thio]-2-propanone (**224**). The initial reaction involves generation of the expected pyridinium ion **225** by intramolecular cyclization of the keto carbenoid onto the nitrogen atom of the pyridine ring. Dipolar cycloaddition of **225** with DMAD affords cycloadduct **226** which undergoes a subsequent [1,5]-hydrogen shift to give **227** followed by fragmentation of CO and $CH_2S$ to produce indolizine **228**.



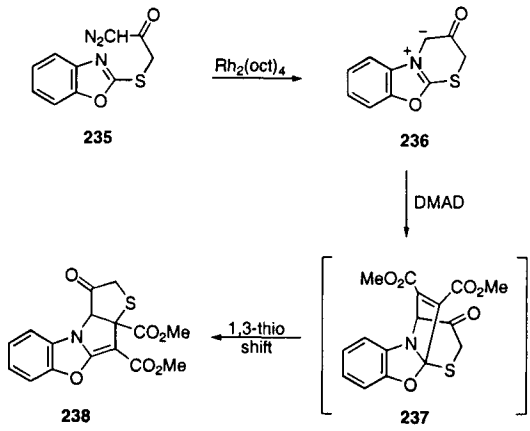



224 225 226 227 228

Interestingly, the Rh(II)-catalyzed reaction of 1-(3′-diazo)-acetonyl-2-pyridone (**229**) with DMAD was found to give cycloadducts derived from an azomethine ylide. The initial reaction involves generation of the expected carbonyl ylide dipole by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group. A subsequent proton exchange generates the thermodynamically more stable azomethine ylide **230** which is trapped by DMAD eventually producing cycloadduct **231**. The formation of products **233** and **234** from cycloadduct **231** proceeds by an acid-catalyzed C–O bond cleavage giving pyridinium ion

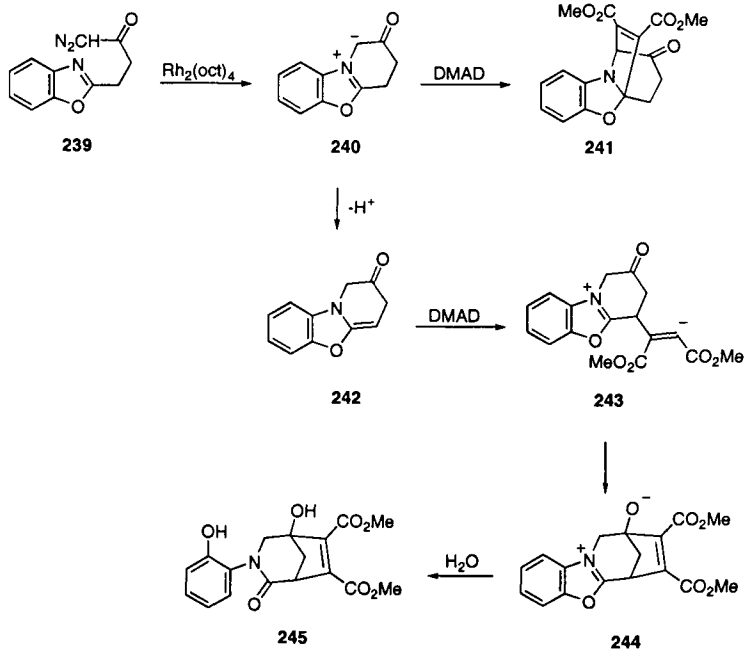



229 231 230 234 232 233




**232**. This transient species can lose a proton and lactonize to **233** or else undergo fragmentation to afford formaldehyde, carbon monoxide, and indolizine **234**.

Azomethine ylide cycloadducts derived from keto carbenoid cyclization onto a thiobenzoxazole have also been encountered in our studies. When 1-diazo-3-[2-(benzoxazolyl)thio]-2-propanone (**235**) was used, the initially formed cycloadduct **237** undergoes a subsequent [1,3]-



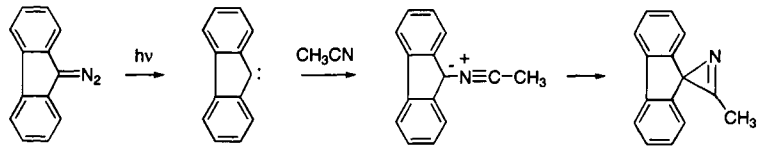
sigmatropic thio shift to give the thermodynamically more stable product **238**. Good analogy exists in the literature for the suggested 1,3-sigmatropic shift.[117]

An entirely different reaction occurred when 2-(4-diazo-3-oxobutyl)-benzoxazole (**239**) was treated with Rh(II) octanoate. In addition to undergoing dipolar cycloaddition to produce cycloadduct **241** (20%), the highly stabilized dipole (i.e., **240**) formed from the benzoxazole loses a proton to produce the cyclic ketene *N,O*-acetal **242**. This compound reacts further with the activated $\pi$-bond of DMAD to give zwitterion **243**. The anionic portion of **243** then adds to the adjacent carbonyl group, producing a new zwitterionic intermediate **244**. In the presence of water, this species is converted to the observed phenolic lactam **245**.

## IV. NITRILE YLIDES DERIVED FROM DIAZOCARBONYLS AND NITRILES

The reaction of a carbene or carbenoid with a nitrile to produce an intermediate nitrile ylide has recently emerged as a useful method for generating these dipoles. Some of the more traditional methods used to prepare nitrile ylides include the thermal elimination of hydrogen chloride from imidoyl chlorides,[118] cycloelimination of carbon dioxide from oxazolin-5-ones,[119] extrusion of alkyl esters of phosphoric acid from 2,3-dihydro-1,4,2$\lambda^5$-oxazaphospholes,[120] and the photolytic ring opening of 2*H*-azirines.[121] Nitrile ylides are versatile intermediates that readily undergo 1,3-dipolar cycloaddition to give complex heterocycles.[80] These same species are also known to undergo [1+2]-, [1+3]-, and [3+6]-cycloadditions.[80]

The potential of laser flash photolysis in the study of carbene reactions with heteroatoms has come to be recognized in recent years. A number of kinetic studies using this technique have been carried out with carbene precursors in nitrile solvents.[122–127] An absorption band at 470 nm was observed in the laser flash photolysis of diazofluorene (**246**) in inert solvents. This band was assigned to triplet fluorenylidene (**247**). In acetonitrile, however, a second band was also detected at 400 nm and whose buildup is concurrent with the decay at 470 nm.[122] Laser flash experiments in other nitrile solvents (i.e., benzonitrile and pivalonitrile) also produced a transient absorption band which is very similar to that observed in acetonitrile. The band at 400 nm was assigned to an intermediate nitrile ylide (**248**). This absorption could be quenched on addition of an electron-deficient olefin providing good support for its

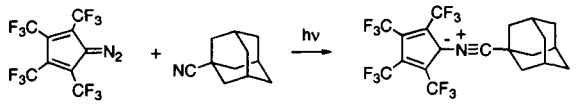



**246** **247** **248** **249**

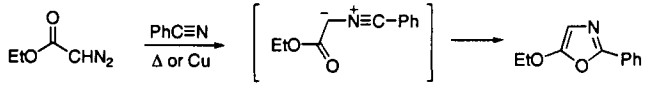
assignment. In the absence of a dipolarophile, nitrile ylide **248** cyclized to form azirine **249**. Other diazo aromatic compounds were also used to study the interaction of carbenes with nitriles and afforded similar results.[125–127]

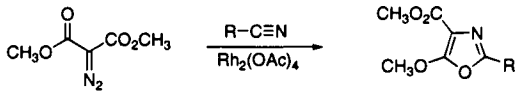
The first example of a stable nitrile ylide formed via carbene addition to a nitrile was reported by Arduengo and co-workers in 1984.[128] Irradiation of diazotetrakis(trifluoromethyl)cyclopentadiene (**250**) in the presence of 1-adamantyl nitrile (**251**) afforded the stable nitrile ylide **252** as a crystalline solid. This structure was unequivocally established using single crystal X-ray analysis. The central ylidic system is very close to linear with only 4° bends at the nitrilium carbon and nitrogen centers. The nitrogen-to-cyclopentadienyl bond is fairly short at 138.9 pm while the central nitrilium CN bond is only 113.1 pm. These bond lengths and angles more closely resemble a nitrile oxide than previously studied theoretical models. The stability of this ylide is partially related to the steric bulk of the adamantane moiety which renders cycloaddition with a second 1-adamantyl nitrile molecule very difficult. Charge delocalization into the cyclopentadienyl ring system also helps to stabilize the dipole.

1,3-Oxazoles of various substitution patterns are well known heterocycles for which a number of methods of synthesis have been reported.[129] Acyl carbenes or functionally equivalent species have been found to undergo cyclization with nitriles to give oxazoles in high yield via nitrile ylide intermediates.[130,131] This reaction can be induced to occur under thermal, photolytic, or catalytic conditions.[129,132,133] Huisgen and coworkers were the first to study this process in some detail.[132] Thermolysis (or copper catalysis) of a mixture of ethyl diazoacetate and benzonitrile resulted in the formation of oxazole **254**. The isolation of this product is




**250** **251** **252**



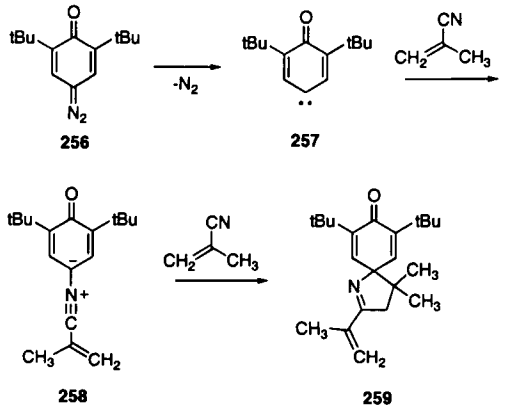



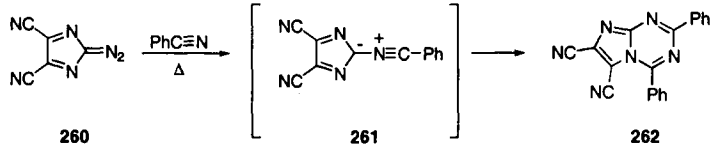

most consistent with a mechanism involving metallo carbene addition onto the nitrile nitrogen atom to generate dipole **253** which then cyclizes to produce oxazole **254**.

Dimethyl diazomalonate undergoes reaction with nitriles in the presence of rhodium(II) acetate to give 2-substituted-4-carbomethoxy-1,3-oxazoles (**255**). The reaction proceeds with a wide range of nitriles,[133–139] although cyclopropanation is a competing process in the case of unsaturated nitriles.[129]

Kende and co-workers have reported the formation of a nitrile ylide intermediate from carbenes and methyl acrylonitrile. Thermolysis of *p*-diazooxide **256** in methyl acrylonitrile as solvent gave spirocyclic product **259** in 48% yield.[140] The formation of **259** was interpreted in terms of the generation of nitrile ylide **258** followed by 1,3-dipolar cycloaddition across the C=C bond of a second molecule of methylacrylonitrile. The regiochemistry of the cycloaddition is consistent with FMO theory.

In a somewhat similar manner, diazodicyanoimidazole (**260**) was found to give the fused heterocycle **262** when heated in benzonitrile.[141] This reaction presumably involves the intermediacy of nitrile ylide **261**.






**260** **261** **262**

## V. CONCLUSION

The chemistry of nitrogen ylides continues to be of great interest both mechanistically and synthetically. Effective ylide formation in transition-metal-catalyzed reactions of α-diazo compounds depends on the catalyst, the α-diazo species, the nature of the substrate, and competition with other processes. The many structurally diverse and highly successful examples cited in this chapter clearly indicate that the rearrangement chemistry of nitrogen ylides has evolved as an important strategy for the synthesis of polyaza heterocycles. It is reasonable to expect that future years will see a continued usage of these reactive intermediates in organic synthesis.

## ACKNOWLEDGMENTS

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# SYNTHESIS OF KAINOIDS AND KAINOID ANALOGUES

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## ABSTRACT

This chapter covers recent developments in the synthesis of kainoids and kainoid analogues, particularly concentrating on the highly neuroexcitatory acromelic acids. The synthetic work involves the development of a short and versatile route to such derivatives starting from relatively cheap and readily available *trans*-4-hydroxy-L-proline. Syntheses of naturally occurring kainoids and synthetic analogues are covered.

# I. INTRODUCTION

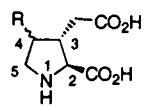
## A. The Kainoids

The kainoids are a well-known group of naturally occurring, nonproteinogenic amino acids of general structure **1** (Figure 1). They vary only in the nature of the C-4 substituent (which is always attached to the pyrrolidine ring via an $sp^2$ center) and the absolute configuration at this position. All of the isolated derivatives exhibit *S* absolute stereochemistry at C-2 and a *trans* relative disposition of the C-2 and C-3 substituents.

Accomplishments in kainoid chemistry up to 1996 have been thoroughly reviewed by Parsons.[1]

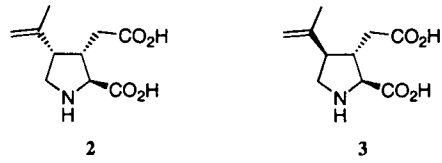
### *(–)-α-Kainic Acid and (+)-α-Allokainic Acid*

(–)-α-Kainic acid **2** was the first kainoid to be isolated[2] (from the Japanese marine alga *Digenea simplex* in 1953) and it is thus classified as the parent of this amino acid family. (+)-α-Allokainic acid **3** was similarly isolated from the same source and is the only example so far of




**1**

***Figure 1.***




2 3

***Figure 2.***

a naturally occurring kainoid that exhibits a *trans* relative disposition of the C-3 and C-4 substituents (Figure 2). Final confirmation of the structure of (–)-α-kainic acid **2** was accomplished by Oppolzer in 1982.[3] (–)-α-Kainic acid **2** has subsequently been isolated from a number of other natural sources.

## *(–)-Domoic Acid*

(–)-Domoic acid **4** (Figure 3) was isolated in 1958 from another Japanese marine alga, *Chondria armata*.[4] Determination of the stereochemistry at C-5′ proved problematic until it was confirmed as *R* by Ohfune in a total synthesis achieved in 1982.[5] Structurally related derivatives, isodomoic acids A–F and domoilactones A and B have subsequently been isolated from *Chondria armata*.

## *Acromelic Acids*

A number of kainoids have been isolated from the poisonous Japanese mushroom, *Clitocybe acromelalga*. Acromelic acid A **5** and acromelic acid B **6** were isolated from this source by Shirahama and co-workers[6] in 1983, their structures being confirmed from total syntheses by Takano et al.[7,8] and semisynthetic approaches by Shirahama.[9–11] More recently, an additional three acromelates have been isolated: acromelic acids C (**7**),[12] D (**8**), and E (**9**) (Figure 4).[13]

This review covers mainly advances in the synthesis of naturally occurring acromelic acids and unnatural analogues, centering around

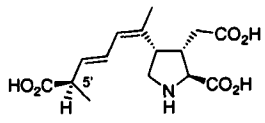



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***Figure 3.***

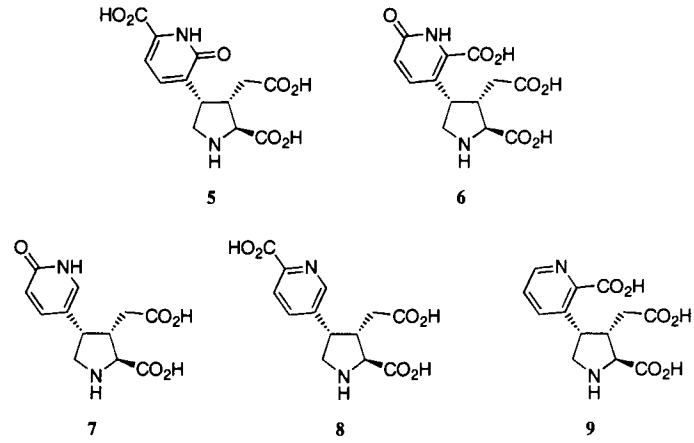



***Figure 4.***

recent studies carried out in the laboratories of Professor Sir Jack E. Baldwin in Oxford, United Kingdom.

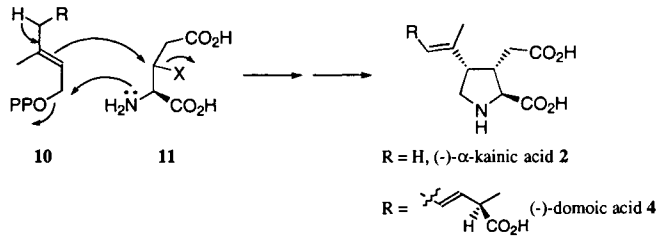
## B. Biosynthesis of the Kainoids

### *Biosynthesis of (–)-α-Kainic Acid and (–)-Domoic Acid*

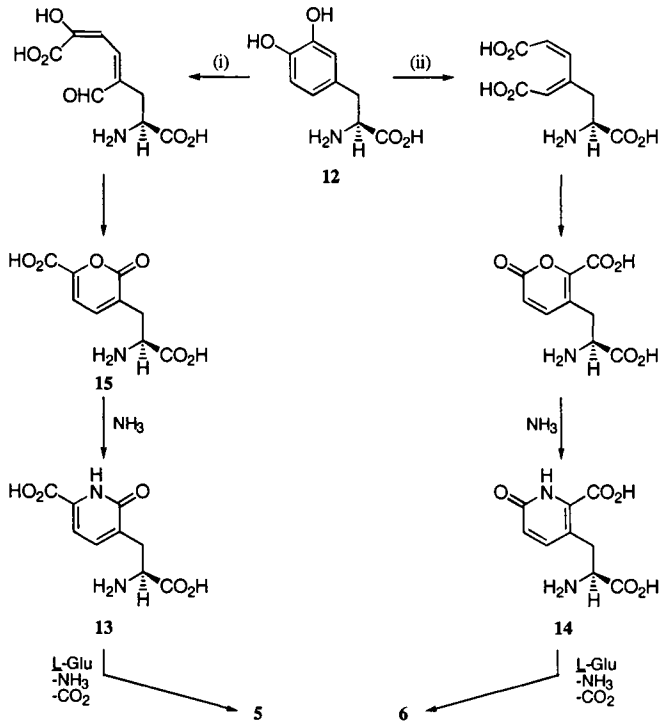
The biogenetic pathway to (–)-α-kainic acid **2** and (–)-domoic acid **4** has been proposed to involve a condensation between an isoprenoid unit **10** and a β-activated *S*-glutamate unit **11** (Scheme 1).[14]

### *Biosynthesis of Acromelic Acids*

A similar cyclization sequence, incorporating a functionalized pyridine-containing unit rather than an isoprenoid derivative, is thought to give rise to the acromelic acids. It has been suggested that the various




***Scheme 1.***




***Scheme 2.***

pyridine-based rings of the acromelates are derived from L-dihydroxyphenylalanine (L-dopa) **12** via extra- (i) and intra-diol (ii) cleavage pathways with subsequent recyclization and ammonia incorporation to give pyridone carboxylic acids **13** and **14**. Derivatives **13** and **14** then undergo condensation with glutamic acid followed by deamination and decarboxylation to give acromelic acids A **5** and B **6**[11] (Scheme 2).

This hypothesis is strongly supported by the presence of stizolobinic acid **15** (Scheme 2 and Figure 5) in plant extracts.[15] An isomer of

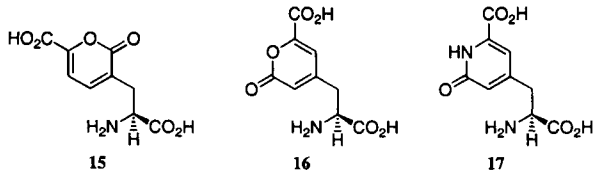
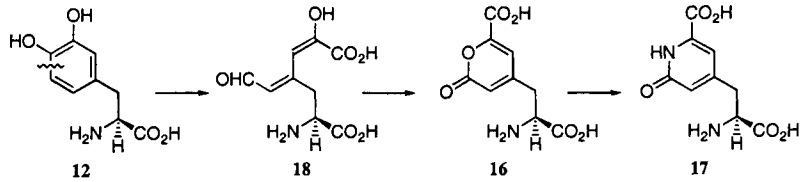



***Figure 5.***




***Scheme 3.***

stizolobinic acid is also a naturally occurring amino acid, known as stizolobic acid **16** (Figure 5), as is the corresponding pyridone carboxylate, 3-(6-carboxy-2-oxo-4-pyridyl)alanine **17** (Figure 5).[16–19]

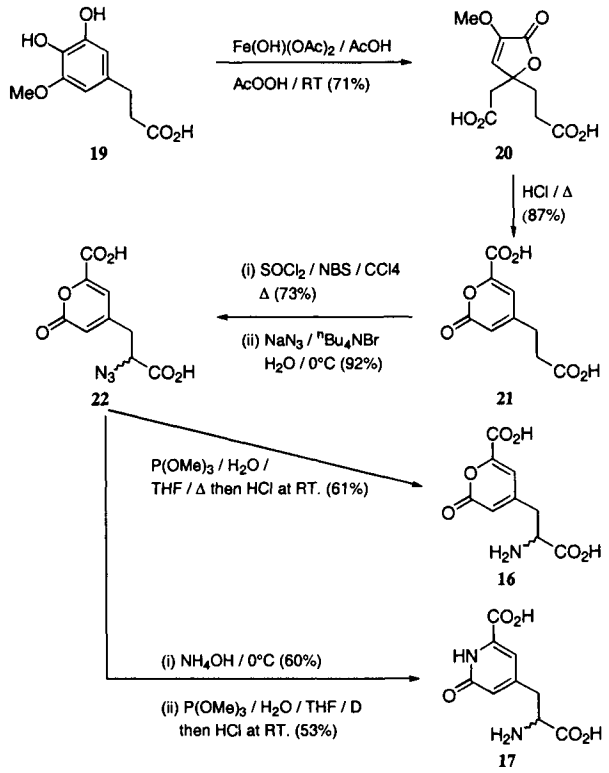
Stizolobinic acid **15** has been formally proposed as a biosynthetic precursor to acromelic acid A **5**[20] and, importantly, radiolabeling studies have shown that it is derived biosynthetically from L-dopa.[21]

The chemical viability of the L-dopa diol cleavage process involved in the generation of the acromelic acid C-4 substituents has been examined in a "biomimetic" sense by Baldwin's group in syntheses of stizolobic acid **16**,[22] 3-(6-carboxy-2-oxo-4-pyridyl)alanine **17**,[22] and stizolobinic acid **15**[23] (Figure 5).

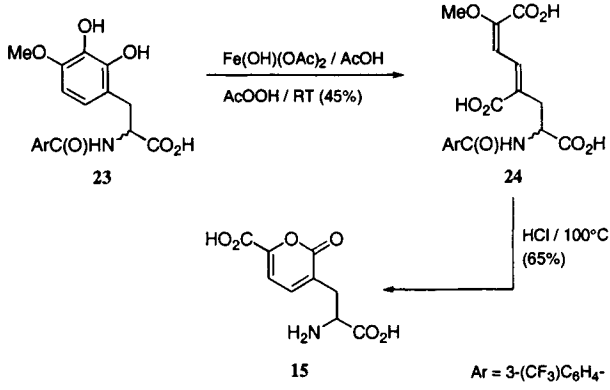
The distal extradiol cleavage of L-dopa **12**, catalyzed by an iron-dependent dioxygenase, gives an alanyl muconic semialdehyde derivative **18** which, on cyclization and lactol oxidation, yields stizolobic acid **16**. The pyrone ring is then ammonolyzed[24] to give 3-(6-carboxy-2-oxo-4-pyridyl)alanine **17** (Scheme 3).

A biomimetic catechol cleavage reaction was carried out on dihydrocaffeic acid derivative **19**[22] using the iron(III)-catalyzed peracetic acid cleavage process of Pandell.[25] This produced the cyclized muconic acid derivative **20** which could be transformed into pyrone **21** by treatment with hydrochloric acid. Bromination followed by azide displacement gave key intermediate **22** which could either be reduced directly to (±)-stizolobic acid **16** or ammonolyzed and then reduced to give (±)-3-(6-carboxy-2-oxo-4-pyridyl)alanine **17** (Scheme 4).

An analogous biomimetic route to stizolobinic acid **15**, the biosynthetic side chain precursor to acromelic acid A **5**, was also carried out.[23] Iron(III)-catalyzed peracetic acid cleavage of the catechol portion of **23** gave alanyl muconic acid **24** which was cyclized and concomitantly deprotected to (±)-stizolobinic acid **15** (Scheme 5). Use of Schöllkopf bislactim ether methodology[26] also allowed the formation of enantiomerically pure **15** by an analogous route.




***Scheme 4.***




***Scheme 5.***

These results lend strong support to the L-dopa diol cleavage proposal for the biosynthesis of acromelic acid C-4 pyridone moieties.

## C. Biological Activity of the Kainoids

Interest in the kainoids centers around their remarkable, diverse biological properties.

### *Insecticidal Activity*

The Japanese have used extracts from *Chondria armata* as an insecticide, the active component being (–)-domoic acid **4**.[27] Insecticidal activity is found to depend on the nature of the kainoid C-4 substituent.

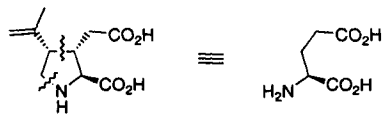
### *Anthelmintic Activity*

The ability of the alga *Digenea simplex* to combat intestinal worms has been exploited for many years in Japan.[28] The active component has been shown to be (–)-α-kainic acid **2** [NB: not (+)-α-allokainic acid **3**] and similar properties have been reported for (–)-domoic acid **4**.[4b] Insecticidal and/or anthelmintic properties of the acromelic acids have not been reported to date.

### *Neuroexcitatory Activity*

The intense neuroexcitatory properties of the kainoids have been well documented and this class of molecule is now inextricably linked with neurochemical research.[29] They appear to act as conformationally "locked" analogues of L-glutamic acid **25** (Figure 6), causing neuronal death in glutaminergic systems found in the brain.

The neuronal degradation caused by the kainoids closely resembles that seen in patients suffering from neurodegenerative disorders such as Huntington's chorea, Alzheimer's disease, and epilepsy. The neuronal death observed closely mimics the cell loss seen in cases of senile dementia (see Ref. 1 for comprehensive referencing of this research




2 25

***Figure 6.***

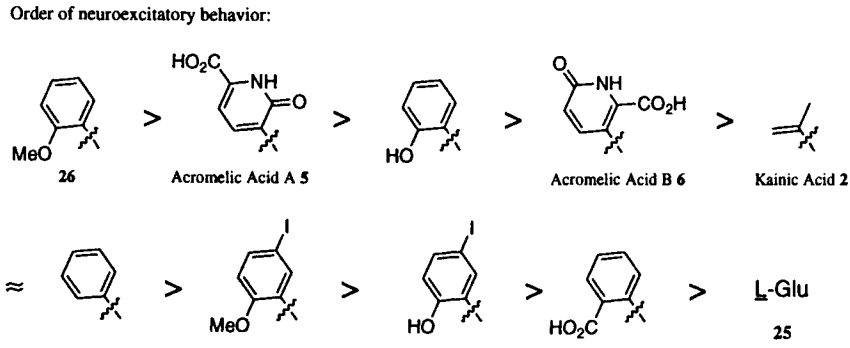



***Figure 7.***

field). This is consistent with the discovery that the receptor for L-glutamic acid **25** is involved in the acquisition of memory and learning.[30]

Of the naturally occurring kainoids, the most potent neuroexcitatory activity has been observed for the acromelic acids, and hence, much synthetic activity has been undertaken in this area. Synthetic studies have been reported, not only on the naturally occurring derivatives **5–9**, but also on modified derivatives containing a number of differing aromatic substituents in the C-4 position.

Of particular interest is a structure–activity study carried out by Shirahama and co-workers which has revealed an order of depolarizing activity as assayed in the newborn rat spinal motoneuron for the naturally occurring kainoids and synthetic analogues shown in Figure 7.[31] (Note: Figure 7 refers to the kainoid **1** having a *cis* relative disposition of the C-3 and C-4 substituents.)

The high potency of the *o*-anisyl derivative **26** had been noted earlier,[32,33] and so far, no natural or unnatural kainoid with higher neuroexcitatory behavior has been reported. This review covers recent progress made toward a general synthesis of this important class of kainoid, which will be referred to as "acromelic acid analogues."

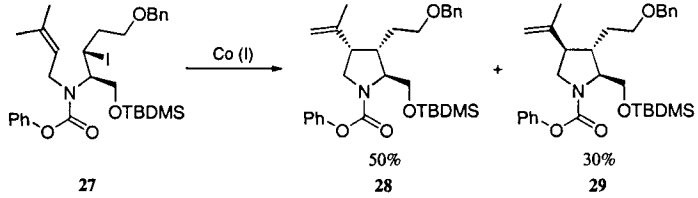
## II. PREVIOUS ACROMELIC ACID/ANALOGUE SYNTHESES

For a full review of previous acromelic acid and other kainoid syntheses, the reader is directed to Ref. 1. Only syntheses important in the context of our work will be covered here. For convenience, the syntheses can be divided into two categories:

1. Pyrrolidine ring synthesis from an acyclic precursor
2. Modification of an existing pyrrolidine ring

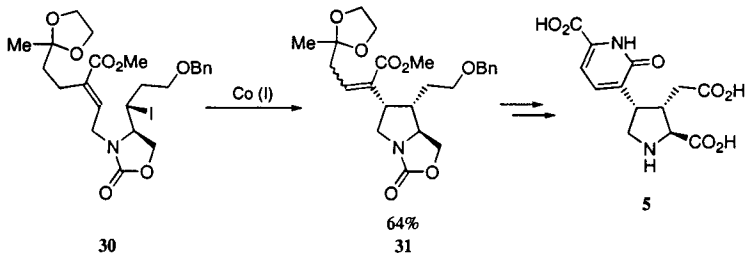
## A. Pyrrolidine Ring Synthesis from an Acyclic Precursor

Previous work in Baldwin's group based around cobalt(I)-mediated cyclization had led to syntheses of (–)-α-kainic acid **2**, (+)-allokainic acid **3**,[34] and acromelic acid A **5**.[35] A cobaloxime-mediated cyclization of **27** gave the separable pyrrolidines **28** and **29**, suitable for conversion to (–)-α-kainic acid **2** and (+)-allokainic acid **3**, respectively.[34] In this instance, the required stereoisomer **28** for the preparation of (–)-α-kainic acid **2** predominated in a ratio of **28** : **29**, 1.7 : 1 (Scheme 6). Both **28** and **29** were carried through to the respective kainoids **2** and **3**. In this case, asymmetry was introduced at a very early stage in the synthesis via a Sharpless asymmetric epoxidation.

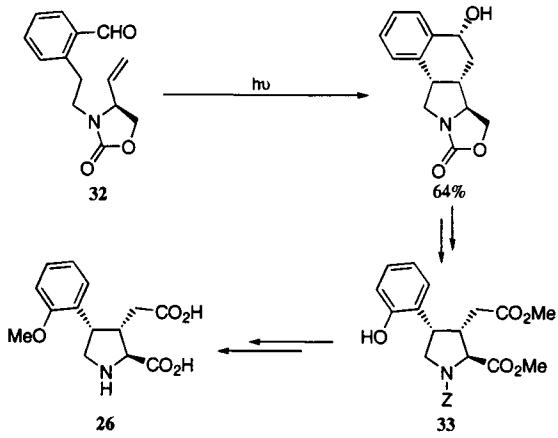



*Scheme 6.*

For the analogous synthesis of acromelic acid A **5**, a more complex precursor **30** was prepared for cobaloxime-mediated cyclization.[35] This yielded pyrrolidine derivative **31** in a 64% yield as a 1 : 1 mixture of the two side-chain double bond diastereoisomers (Scheme 7). The C-4 epimer was obtained in an 11% yield (i.e., a 6 : 1 ratio of C-4 epimers),




*Scheme 7.*




*Scheme 8.*

a significant improvement in stereocontrol over the previous cyclization.[34]

Other radical cyclization methodologies have been used to generate the kainoid substituted pyrrolidine skeleton.[1]

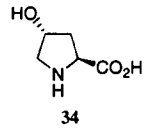
In preparing the highly neuroexcitatory *o*-anisyl derivative **26**, Shirahama and co-workers utilized a photoinduced intramolecular Diels–Alder reaction of precursor **32**, itself derived from optically active vinyl glycinol (Scheme 8).[32] Although an attractive and relatively short synthetic route, the possibilities for modification of the C-4 aryl substituent were felt too limited for our purposes.

Further manipulation of key C-4 hydroxyphenyl intermediate **33** facilitated the synthesis of other kainoid derivatives illustrated in Figure 7.[31]

## B. Modification of an Existing Pyrrolidine Ring

Although there is no doubting the elegance of some of the ring syntheses for specific kainoids, in view of the number of requests from neuropharmacologists and workers in the agrochemicals industry for a variety of natural and unnatural kainoids, it was felt that a highly versatile and short synthesis was required which could yield relatively large quantities of the target amino acids.

There are many abundant naturally occurring compounds containing a pyrrolidine ring system. Remarkably, however, syntheses of kainoids from such materials have received relatively little attention. An important



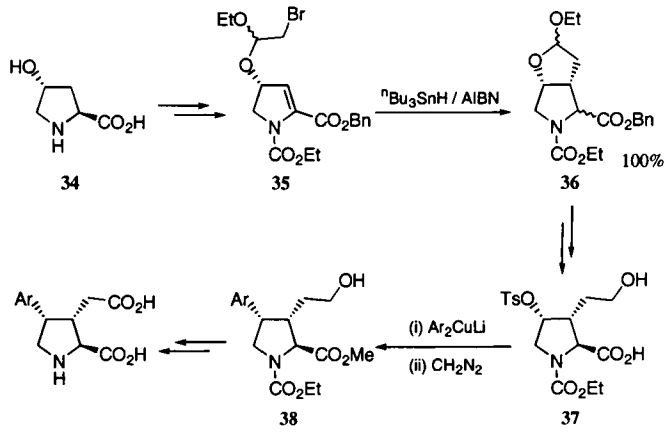

34

***Figure 8.***

exception is a route to C-4 aryl-substituted kainoids reported by Shirahama and co-workers, starting from *trans*-4-hydroxy-L-proline **34** (Figure 8).[33]

*trans*-4-Hydroxy-L-proline **34** is available relatively cheaply in large quantities from the hydrolysate of collagen and thus represents an attractive starting material for the asymmetric synthesis of kainoids and other pyrrolidine derivatives.

Key steps in Shirahama's synthesis include an intramolecular *5-exo trig* radical cyclization with the primary alkyl radical derived from bromo-acetal **35** which establishes the required C-2/C-3 *trans* relative stereochemistry in intermediate **36** and a displacement of a tosylate **37** (derived from the C-4 hydroxyl group) by various lithium diaryl cuprates with retention of configuration. This step gave the required (2*S*, 3*S*, 4*S*) stereochemistry in the final products **38** which were subsequently manipulated into the corresponding acromelic acid analogues (Scheme 9). Using this methodology, four different acromelic analogues were prepared.




Ar = Ph, *o*-anisyl, *p*-anisyl, *o,p*-dimethoxyphenyl

***Scheme 9.***

Although offering greater versatility than many of the routes to kainoids from acyclic precursors, again, it was felt that the number of steps (ca. 23) in this methodology would limit its applicability in the synthesis of substantial quantities of acromelic acid analogues and other kainoids. The appeal of using *trans*-4-hydroxy-L-proline **34** as a starting material nonetheless remained and hence the investigation of new routes began. Although acromelic acid derivatives were intended as the main targets, consideration would also be given to adaptation of any new route to other natural and unnatural kainoids.

## III. NEW APPROACHES TO ACROMELIC ACID/ANALOGUE SYNTHESIS

The problems associated with the synthesis of kainoids are well documented.[1] In addition to establishing trisubstitution from C-2 to C-4 of a pyrrolidine ring, possibly the greatest challenge to the synthetic chemist is in ensuring a *cis* relationship between the C-3 and C-4 substituents. This may help to explain why (+)-α-allokainic acid **3** is such a popular synthetic target, despite its lack of biological activity! An efficient kainoid synthesis must address this problem, in particular, aiming for stereospecificity rather than just selectivity.

### A. *trans*-4-Hydroxy-L-proline as a Starting Material

*trans*-4-Hydroxy-L-proline **34** (Figure 8) has proved to be a relatively cheap and highly versatile starting material for the synthesis of proline and pyrrolidine derivatives as well as many other species.[36] The presence of functional groups at chiral centers C-2 and C-4 makes stereoselective functionalization at all positions of the ring possible. In this respect, Shirahama utilized the C-4 hydroxyl group stereochemistry to good effect in establishing the correct C-3/C-4 relative stereochemistry in his acromelic acid analogue syntheses.[33] *trans*-4-Hydroxy-L-proline **34** was chosen as the starting material for the following synthetic work for these reasons.

### B. Manipulation of 4-Keto-L-proline

#### *Previous Studies*

In building up the required substitution pattern around the pyrrolidine ring, a different approach was chosen to that used by Shirahama.[33] The

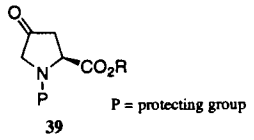
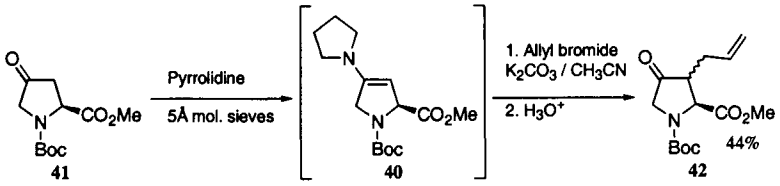



*Figure 9.*

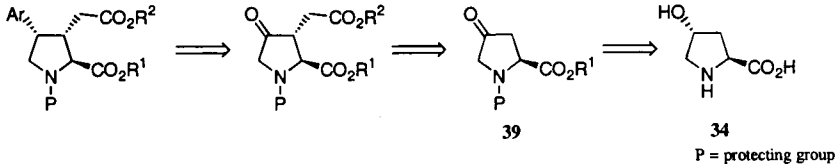



*Scheme 10.*

intention was to use the C-2 stereochemistry of **34** to establish the *trans* relative disposition of the C-2 and C-3 substituents and to oxidize the C-4 hydroxyl group to a ketone for further modification at this position. Attention was therefore turned to reactions of protected derivatives of 4-keto-L-proline **39** (Figure 9).

Of the several studies made of enolates derived from such α-aminoketones,[37] the most interesting one from the point of view of this work came from Holladay and co-workers who studied alkylation reactions of pyrrolidine enamine **40** derived from protected 4-keto-L-proline **41** with allyl bromide (Scheme 10).[38] A 44% yield of two diastereoisomers of allylated material **42** was obtained with a quoted isomer ratio of *trans* : *cis* of 2 : 1.

It was felt that a similar alkylation reaction would allow the facile introduction of the kainoid C-3 side chain if a bromoacetate ester was used in place of allyl bromide as the alkylating agent. The aim was to attempt to increase stereoselectivity by using the bulky ester *tert*-butyl bromoacetate. Appropriately protected 4-keto-L-proline **39** derivatives




*Scheme 11.*

were therefore required which were to be prepared from the corresponding protected *trans*-4-hydroxy-L-proline.

A basic retrosynthetic analysis for our planned approaches is illustrated in Scheme 11.

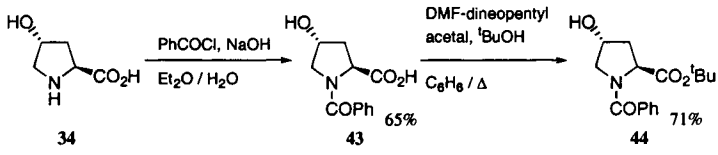
## *Protected trans-4-Hydroxy-L-proline*

For subsequent transformations, it was necessary to protect the amino and C-2 carboxyl groups of *trans*-4-hydroxy-L-proline **34**. Throughout all of the synthetic work to be described, *N*-benzoyl amide protection was chosen as it was felt likely that such a functional group would be resistant to most reaction conditions. Initially, a C-2 *tert*-butyl ester was chosen in an attempt to maximize the stereoselectivity in the planned enamine alkylation reaction; however, later experiments revealed that the more straightforward to introduce C-2 methyl ester was equally effective. The preparations for all of the derivatives used are described here.

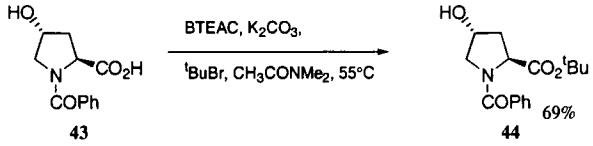
Schotten–Baumann type *N*-benzoylation was carried out on *trans*-4-hydroxy-L-proline **34**,[39] giving amide **43** in a satisfactory yield of 65%. The disappointing yield here could be attributed to difficulties experienced in recrystallization of the product **43**. The amide **43** was esterified to give *tert*-butyl ester **44** using a modification of a procedure described by Widmer[40] with dimethylformamide-dineopentyl acetal and *tert*-butanol as reagents. This provided crystalline **44** in 71% yield from **43** with no evidence of *tert*-butyl ether formation at the C-4 hydroxyl group (Scheme 12).

An alternative approach to the esterification reaction via a more recently reported procedure using *tert*-butyl bromide, benzyltriethylammonium chloride, and potassium carbonate[41] gave a comparable yield of 69% of **44** from **43** (Scheme 13). It was felt, however, that this alternative procedure was not viable because of the large excess of *tert*-butyl bromide which was required (48 equiv).

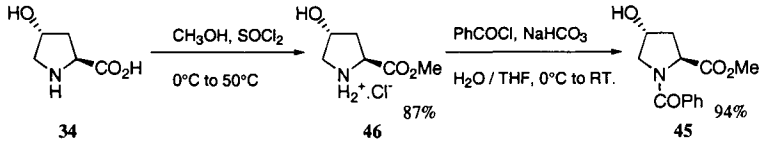
The order of transformations was reversed to obtain the corresponding methyl ester **45**. *trans*-4-Hydroxy-L-proline methyl ester was prepared




***Scheme 12.***




***Scheme 13.***




***Scheme 14.***

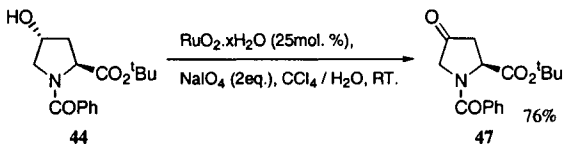
in high yield (87%) as its hydrochloride salt **46** using the straightforward esterification procedure reported by Kemp and co-workers.[42] This product was subsequently *N*-benzoylated to give the required, highly crystalline, protected carbinol **45** in excellent yield (94%, Scheme 14).

Methods were then investigated for oxidation of carbinols **44** and **45** to the corresponding 4-keto-L-proline derivatives.

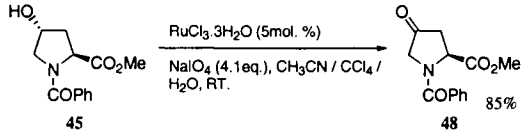
## *Oxidation of Protected trans-4-Hydroxy-L-prolines*

A procedure using ruthenium(IV) oxide and sodium metaperiodate[43] was chosen initially for **44**. Protected 4-keto-L-proline derivative **47** was obtained in 76% yield, a reaction that could be satisfactorily repeated on several occasions using the same batch of ruthenium(IV) oxide (Scheme 15). Attempts to repeat the procedure using different batches of ruthenium(IV) oxide, however, gave variable results, the exact reasons for this not being clear.

The optimized ruthenium tetraoxide oxidation conditions reported by Sharpless and co-workers[44] gave a significantly higher and consistent




***Scheme 15.***




*Scheme 16.*

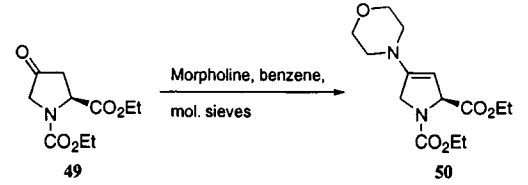
yield (85%, Scheme 16) for the conversion of **45** into the corresponding 4-keto-L-proline derivative **48**. These conditions were therefore used for future experiments, particularly attractive being the considerably lower quantities of ruthenium required (5 mol% of $RuCl_3$[44] as opposed to 25 mol% of $RuO_2 \cdot xH_2O$[43]).

## *Pyrrolidine Enamines from 4-Keto-L-proline*

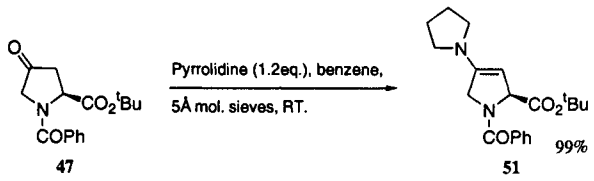
Conventionally, enamines are formed using azeotropic distillation methods to remove the by-product water from a mixture of the ketone and appropriate secondary amine. Benzene and toluene are therefore generally the solvents of choice. Taguchi and Westheimer demonstrated that molecular sieves can have a beneficial effect on this reaction, acting not only as a dehydrating agent but also as a catalyst.[45]

Prior to the work of Holladay and co-workers,[38] there was good literature precedent for 4-keto-L-proline derivatives **39** giving the required 3,4-dehydro isomer of the enamine rather than the 4,5-dehydro isomer in a report by Friary and co-workers.[46] It was found that the protected 4-keto-L-proline derivative **49** gave enamine **50** on treatment with morpholine in the presence of molecular sieves (Scheme 17).

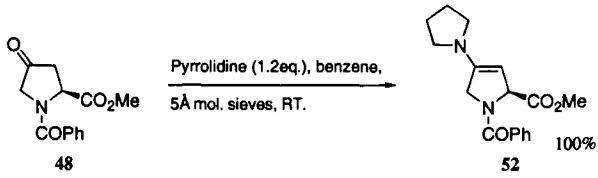
Repeating the enamine formation conditions of Holladay and co-workers[38] using 4-keto-L-proline derivative **47** and pyrrolidine (1.2 equiv) in the presence of activated 5-Å molecular sieves at room temperature gave essentially quantitative conversion to required enamine **51** after a reaction time of 16 h (Scheme 18). Analytical data were consistent




*Scheme 17.*




*Scheme 18.*




*Scheme 19.*

with the required enamine structure **51** although the NMR spectra ($^{1}H$ and $^{13}C$) of the product were severely complicated, most likely by the presence of rotameric species. Unfortunately, this could not be confirmed by coalescence experiments as the enamine appeared to be unstable at the temperatures required by the NMR experiments.

Although this method proved successful for 4-keto-L-proline methyl ester **48**, it was decided to investigate the conventional azeotropic dehydration method. Derivative **48** and pyrrolidine (1.2 equiv) were heated under reflux in benzene, collecting the water produced using a Dean and Stark apparatus. A quantitative yield of the corresponding enamine **52** was obtained after only 30 min (Scheme 19). Again, full assignment of NMR spectra was complicated by the apparent presence of rotameric structures.

The simplification of the enamine formation procedure was felt to be advantageous, and with both enamines **51** and **52** in hand, alkylation reactions were investigated.

## *Pyrrolidine Enamine Alkylation Reactions*

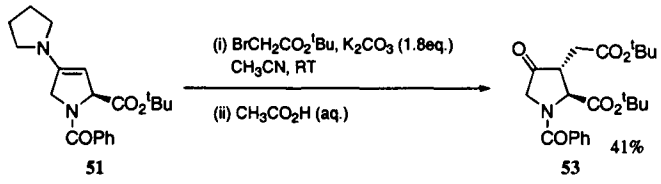
Initiated by Stork and co-workers,[47] the scope and stereochemistry of enamine alkylations have been well explored. In general, good stereoselectivities can be obtained using bulky directing groups, polar aprotic solvents, and low temperatures.

It was hoped that in the case of enamine **51**, the bulky C-2 *tert*-butyl ester would direct any subsequent alkylation reactions predominantly

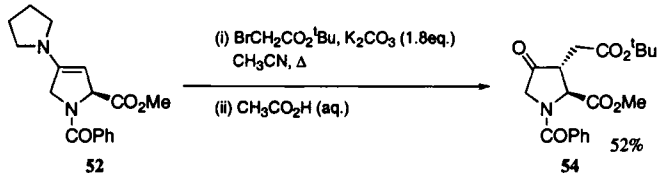
*trans* to the C-2 substituent and also help to avoid the dialkylation problems reported by Holladay and co-workers.[38] The use of *tert*-butyl bromoacetate as the alkylating agent was also expected to enhance this selectivity.

A heterogeneous mixture of enamine **51**, potassium carbonate (1.8 equiv), and *tert*-butyl bromoacetate (1 equiv) in anhydrous acetonitrile was stirred at room temperature for 5 days and the product enamine was hydrolyzed under aqueous acidic conditions. Extensive chromatography gave the alkylated derivative **53** in satisfactory yield (41%) and up to 20% of the starting ketone **47** could also be recovered (Scheme 20). No evidence could be found for any stereoisomeric or dialkylated material and no C-5 alkylated products were obtained, adding support to the structure of enamine **51**. This procedure gave consistent results on repetition although chromatographic purification could prove problematic.

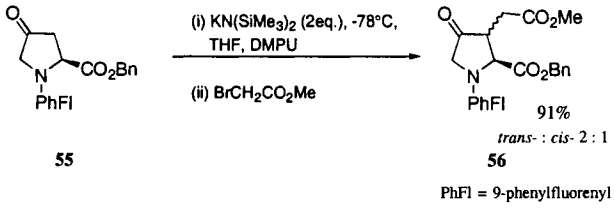
Initial attempts to repeat the same procedure using enamine **52** gave disappointing results with alkylated derivative **54** being obtained in low yield (25%). It was found that carrying out the enamine alkylation at higher temperature (under reflux in acetonitrile) resulted in not only substantially increased yields of **54** (generally ca. 52%) but also significantly reduced reaction times (18 h for the alkylation reaction) (Scheme 21). Most importantly, however, the product obtained was much easier to purify than in previous attempts, **54** being highly crystalline. Pleasingly, it was apparent that changing the C-2 ester from *tert*-butyl to methyl had no influence on the stereoselectivity of the enamine alkylation.




***Scheme 20.***



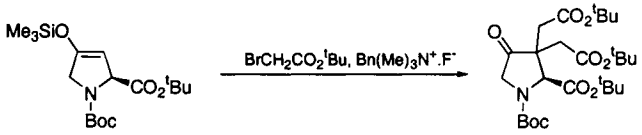

***Scheme 21.***




55 56

PhFl = 9-phenylfluorenyl

***Scheme 22.***




57 58

***Scheme 23.***

Using this procedure, large quantities (up to 20 g[48]) of alkylated ketone **54** were regularly prepared.

Confirmation that the relative stereochemistry between the C-2 and C-3 substituents was *trans* was obtained by measurement of the coupling constant between the C-2 and C-3 protons. It has been reported that the values expected for *trans* disubstituted pyrrolidines are significantly smaller (2–6 Hz) than for the corresponding *trans* isomers (8–9 Hz).[49] $^1$H NMR confirmed the stereochemical assignments.

Gill and Lubell have also reported a complementary 4-keto-L-proline alkylation procedure using the potassium enolate of ketone **55**.[50] In this instance, regiospecific alkylation using methyl bromoacetate gave a 91% yield of a 2:1 *trans* : *cis* ratio of diastereoisomers of ketone **56** (Scheme 22).

Attempts to use a silyl enol ether (**57**) alkylation in this system have been made by Young and co-workers.[51] Unfortunately, only dialkylated material **58** was obtained (Scheme 23).

With alkylated ketones **53** and **54** in hand, attention was turned toward methods for stereospecific incorporation of the required C-4 substituents.

## C. Introduction of the C-4 Substituent

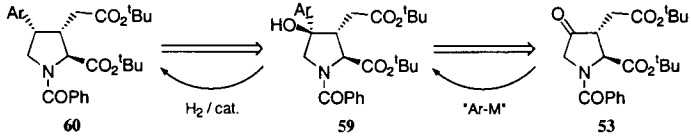
At this stage in the synthetic work, a method was required that would allow a variety of substituents (particularly aryl) to be introduced at C-4 by manipulation of the ketone functionality. Any approaches used must

address the problem of stereoselectivity. Two methods for carbon–carbon bond formation were investigated.

### *Addition of Organometallic Reagents/Carbinol Reduction*

A report that aryl Grignard reagents add to *N*-protected 4-keto-L-proline derivatives to give the corresponding *cis*-carbinols[52] led to an examination of such reactions with 4-keto-L-prolines **39** and **53**.

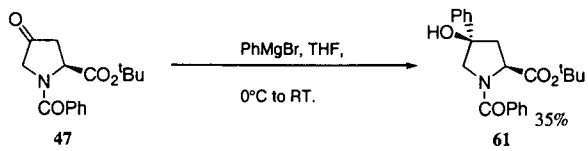
It was hoped that the resulting benzylic carbinols **59** could be stereoselectively reduced by catalytic hydrogenation to the required protected kainoid derivatives **60** (Scheme 24). The reduction of benzylic alcohols varies in stereospecificity depending on the catalyst employed.[53] Hydrogenation over Raney nickel generally proceeds via retention of configuration, whereas hydrogenation over palladium on charcoal leads to inversion at the benzylic carbon.



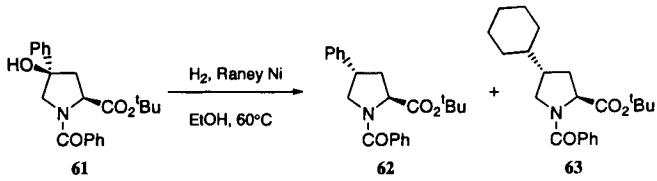

***Scheme 24.***

Using 4-keto-L-proline derivative **47** as a model for the C-3-alkylated derivatives, phenylmagnesium bromide was found to add in disappointing (35%) yield to give tertiary carbinol **61** (Scheme 25).[54]

The C-4 stereochemistry was assumed to be as required[52] and catalytic hydrogenolysis of **61** was attempted using a Raney nickel catalyst in ethanol at elevated temperature. The reaction proceeded extremely slowly and appeared to give two products, one of which appeared to contain a cyclohexyl group. It was believed that the two products were the desired 4-phenyl proline derivative **62** and C-4 cyclohexyl derivative **63** although conclusive proof was not obtained (Scheme 26).




***Scheme 25.***



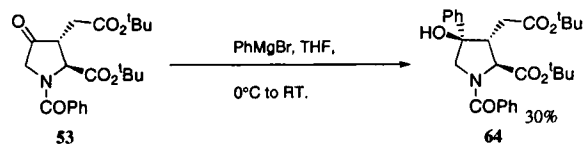

*Scheme 26.*

Despite this disappointing result, aryl Grignard additions were attempted on C-3-alkylated 4-keto-L-proline derivative **53**. Using THF as solvent, a disappointing 30% yield of the corresponding tertiary carbinol **64** was obtained on treatment with 4 equiv of phenylmagnesium bromide (Scheme 27).

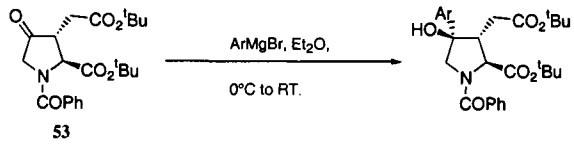
It was believed that this low yield could be related to the ketone functionality being hindered toward attack of the organometallic reagent and that ketone enolization could be a competitive process with the Grignard reagent acting as a base. In an attempt to minimize the amount of enolization, the solvent used for the Grignard addition reactions was changed to diethyl ether. This gave a significant improvement in yield of tertiary carbinol **64** (50%) and other aryl Grignard reagents were found to add with approximately equal efficiency (Scheme 28 and Table 1). Unfortunately, 2-methoxyphenylmagnesium bromide gave none of the corresponding tertiary carbinol **65** under these conditions, this compound being required to access the highly neuroexcitatory 2-methoxyphenyl-substituted kainoid **26**.

Attempts to use less basic organocerium reagents[55] also gave disappointing results with mixtures of C-4 epimeric tertiary carbinols being obtained. This did, however, lead to the isolation of very small quantities of the 2-methoxyphenyl derivative **65**.

Catalytic hydrogenolysis of tertiary carbinol **64** over Raney nickel unfortunately gave rise mainly to decomposition of the starting material. Slow reduction could be effected using 10% palladium on activated



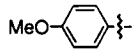
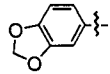

*Scheme 27.*



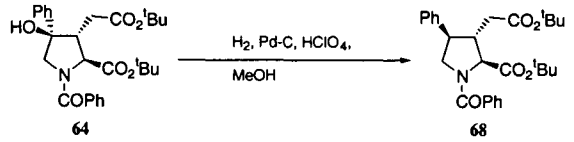

53

***Scheme 28.***

***Table 1.***

| *Ar* | *Product* | *Yield* |
|---|---|---|
|  | **64** | 50% |
|  | **65** | 0% |
|  | **66** | 46% |
|  | **67** | 41% |

charcoal as catalyst in the presence of perchloric acid but this, as expected, produced the C-4 epimer **68** in 41% yield. The C-4 stereochemistry was confirmed by NOE difference experiments (Scheme 29).



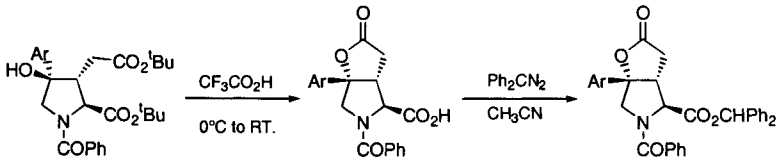

64 68

***Scheme 29.***

Of obviously limited scope and efficiency, the Grignard addition method nevertheless provided a usable method for the formation of some of the required tertiary carbinols. An improved method for their stereoselective reduction was therefore sought.

### *Lactonization/Benzylic Lactone Reduction*

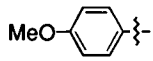
It was felt that the reactivity of the benzylic hydroxyl group needed to be increased under the reduction conditions. Benzylic hydrogenolysis using a variety of transition metal catalysts has revealed this to be a




64, 66 69, 70 71, 72

***Scheme 30.***

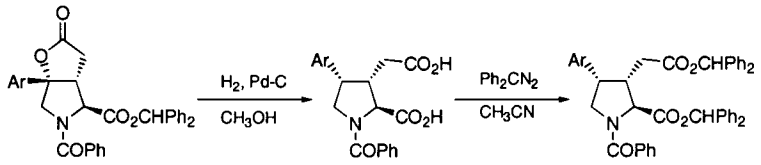
***Table 2.***

| *Substrate* | *Product* | *Ar* | *Yield* |
|---|---|---|---|
| **64** | **69** |  | 100% |
| **66** | **70** |  | 100% |

stereoselective process,[53] and importantly, the reaction conducted over palladium catalysts has been observed to proceed with mainly inversion of configuration at the original benzylic carbon.[56] This therefore led to an examination of possible methods for preparing a fused bicyclic lactone system from carbinols **64–67** using the C-4 hydroxyl group and the C-3 side-chain carboxyl functionality.

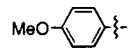
Tertiary carbinols **64** and **66** were found to quantitatively form lactones **69** and **70**, respectively, on treatment with trifluoroacetic acid. Inversion of configuration occurred as expected at C-4 and the presence of a five-ring lactone was indicated by a strong carbonyl stretch at (typically) 1788 $cm^{-1}$ in the IR spectrum of the crude product. Free acids **69** and **70** were converted to their corresponding benzhydryl esters, **71** and **72**, respectively (by treatment with diphenyldiazomethane), for full characterization (Scheme 30 and Table 2). No formation of bridged lactones with the C-2 carboxyl group was observed, possibly because of the higher ring strain in the resulting bicyclic system.

Catalytic hydrogenation of benzylic lactones **71** and **72** over 10% palladium on activated charcoal gave diacids **73** and **74** which were isolated as their corresponding dibenzhydryl esters **75** and **76** after treatment of the crude hydrogenolysis product with diphenyldia-




*Scheme 31.*

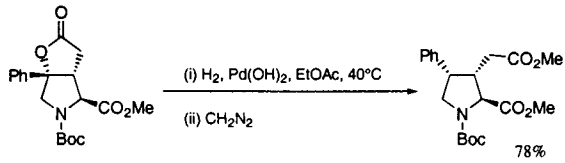
*Table 3.*

| *Substrate* | *Product* | *Ar* | *Yield* |
|---|---|---|---|
| **71** | **75** |  | 64% |
| **72** | **76** |  | 16% |

zomethane. Only the products derived from inversion of configuration at the benzylic C-4 center could be isolated (Scheme 31 and Table 3).

The disappointing results from the Grignard and organocerium addition reactions led to a search for a more general and efficient method for C-4 substituent introduction.

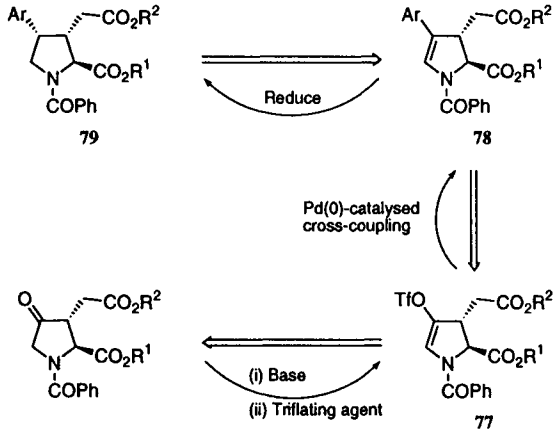
A more detailed examination of the lactone hydrogenolysis method will be described later although it is worth mentioning at this stage that Shirahama has subsequently adopted this method in a related kainoid synthesis (Scheme 32).[57]




*Scheme 32.*

## *Palladium(0)-Catalyzed Cross-Coupling Reactions*

Palladium(0)-catalyzed cross-coupling reactions between organic electrophiles (usually vinyl or aryl halides or triflates) and a variety of organometallic reagents and boronic acids have become a popular




*Scheme 33.*

method of carbon–carbon bond formation in recent years.[58] Of particular interest in the context of this work was the availability of methods for the regiospecific generation of vinyl triflates from ketones.[59]

Regiospecific generation of vinyl triflate **77** from ketones such as **53** and **54** was planned for the introduction of C-4 substituents via palladium(0)-catalyzed cross-coupling reactions to give dehydropyrrolidine enamide derivatives **78** which could be reduced stereospecifically to protected kainoid derivatives **79** (Scheme 33).

Target vinyl triflates were therefore **80** and **81** (Figure 10), prepared from ketones **53** and **54**, respectively.

Removal of the sterically more accessible protons at C-5 was required and hence it was reasoned that "kinetic" deprotonation conditions were required, namely, strong, nonnucleophilic base and low temperature. Model reactions were carried out initially on 4-keto-L-proline ester **47**, in the hope of optimizing the triflation conditions before moving to C-3-alkylated derivatives **53** and **54**.

A solution of the ketone in tetrahydrofuran was added slowly to a cold (–78 °C) solution of the appropriate base [lithium hexamethyldisily-

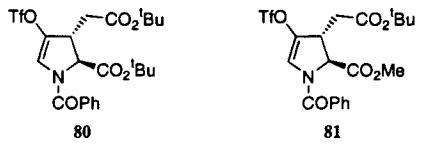
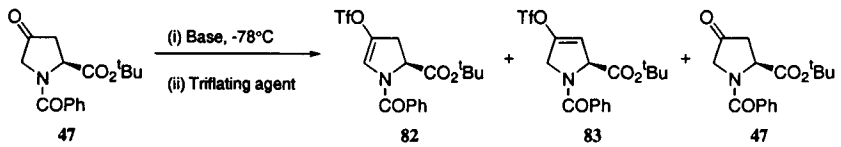



*Figure 10.*

lamide (LHMDS) or lithium diisopropylamide (LDA)] in the same solvent. In all cases, the resulting mixture was stirred for 45 min at –78 °C before addition of the triflating agent. Although the required vinyl triflate **82** could be obtained, it was always accompanied by significant amounts of the regioisomer **83** and unreacted ketone **47**. Variation of base and triflating agent failed to alleviate this problem. Attempts to reduce the amount of unreacted starting material **47** by warming the base/ketone mixture to –20 °C and cooling again to –78 °C before addition of the triflating agent and by using considerable excesses of base (up to 2 equiv), were not successful. *N*-Phenyltriflimide was finally chosen as the triflating agent[61] instead of triflic anhydride because of its relative ease of handling (particularly in its stability toward long-term storage) and also because its use led to the formation of a lower number of side products. A change of solvent to diethyl ether also failed to give any improvement in yield. Important results are summarized in Scheme 34 and Table 4.

It was decided at this point that deprotonation at C-5 may be preferred if the C-3 side chain was in place, and hence, attention was turned away from these model studies for an investigation of ketones **53** and **54**, with initial investigations concentrating on **53**. Again, both LHMDS and LDA were employed as strong bases but the effect of the addition of a cosolvent was also investigated. The use of a cosolvent was thought appropriate,




***Scheme 34.***

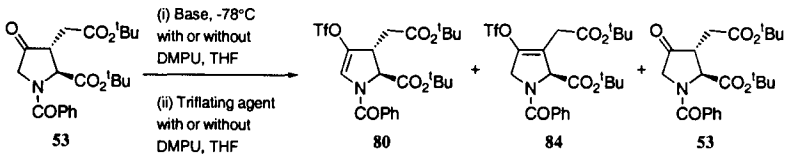
***Table 4.***

| *Base* | *Solvent* | *Triflating Agent* | *Yield of* **82** |
|---|---|---|---|
| LHMDS | THF | $PhN(SO_2CF_3)_2$ | 29% |
| LHMDS | THF | $Tf_2O$ | Negligible |
| LHMDS | $Et_2O$ | $Tf_2O$ | 15% |
| LDA | THF | $PhN(SO_2CF_3)_2$ | 23% |
| LDA | THF | $Tf_2O$ | Negligible |

given the quantities of unreacted ketone **47** recovered in the model studies. *N,N'*-Dimethyl-*N,N'*-propylene urea (DMPU)[62,63] was chosen in preference to hexamethylphosphoramide (HMPA) given the known toxicity of the latter.

Although both LDA and LHMDS were examined as bases, it was found that the most consistent results were obtained with commercial solutions of LHMDS, and hence, most experiments were conducted with this base. Importantly, it was found that the addition of DMPU as cosolvent resulted in complete consumption of ketone **53**. The optimum yield of 53% of triflate **80** was obtained when the DMPU was added with the *N*-phenyltriflimide solution to the preformed enolate. The results of these studies are summarized in Scheme 35 and Table 5. It is worth noting that recovered ketone **53** from the earlier attempts at this reaction showed no sign of C-3 epimerization, suggesting that deprotonation had only occurred at C-5.

Under the optimized conditions found for ketone **53**, **54** was found to give an excellent (93%) yield of the corresponding vinyl triflate **81**. This proved to be readily repeatable on a gram scale with vinyl triflate **81** demonstrated to be stable toward silica gel chromatography (Scheme 36).

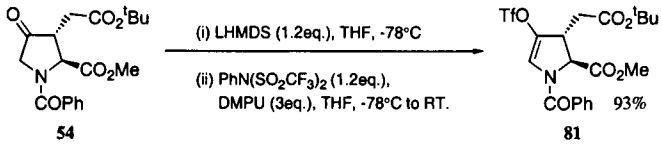



***Scheme 35.***

***Table 5.***

| *Base* | *DMPU (equiv)* | *Yield of* **80** | *Yield of* **84** | *Yield of* **53** |
|---|---|---|---|---|
| LHMDS | 0 | 16% | 16% | 40% |
| LDA | 0 | 14% | 14% | 34% |
| LHMDS | 23[a] | 29% | 35% | 0% |
| LHMDS | 4[a] | 40% | 0% | 0% |
| LHMDS | 3[b] | 53% | 0% | 0% |

*Notes:* [a]DMPU added to generated enolate before *N*-phenyltriflimide solution.
[b]DMPU added with *N*-phenyltriflimide solution.

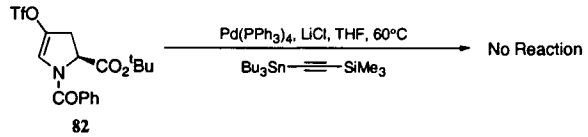



***Scheme 36.***

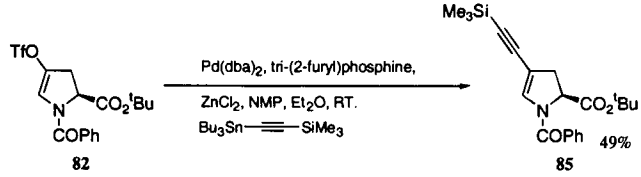
To test the palladium(0)-catalyzed cross-coupling methodology, model experiments were initiated with vinyl triflate **82**. Stille methodology was initially employed using transmetallation from organostannanes.[64] Of the various alternatives, alkynyl stannanes have been reported to transfer most rapidly to palladium(II) during the rate-limiting transmetallation step, and hence, initial experiments were carried out using trimethylsilylethynyltributyltin. Coupling could not be effected under standard Stille conditions[65] (Scheme 37), but the improved coupling conditions of Farina and co-workers[66] did give a moderate yield of coupled product **85** (Scheme 38).

Transfer of these reaction conditions to C-3-alkylated vinyl triflate **80** proved successful using both trimethylsilylethynyltributyltin and vinyltributyltin, giving coupled products **86** and **87** in 44 and 58% yields, respectively. It was found advantageous to raise the reaction temperature to 60 °C for these coupling reactions (Scheme 39).

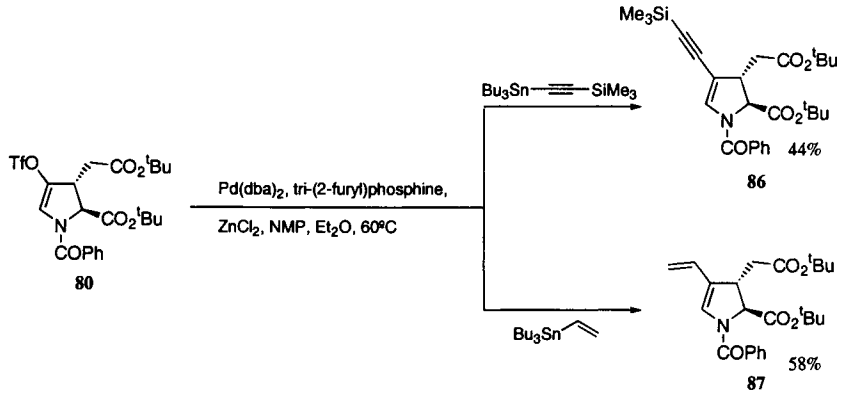
Initially, disappointing results were obtained on attempting to cross-couple to aryl stannanes. Phenyltributyltin, tetraphenyltin, (2-methoxyphenyl)tributyltin, and (4-methoxyphenyl)tributyltin gave no coupling under Farina's conditions with vinyl triflate **80**. Pleasingly,




***Scheme 37.***



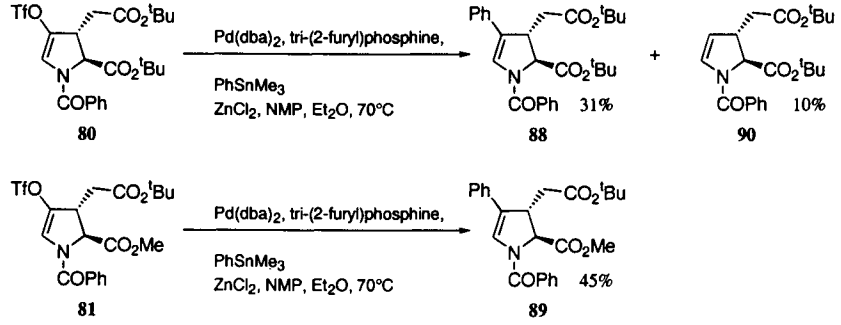

***Scheme 38.***



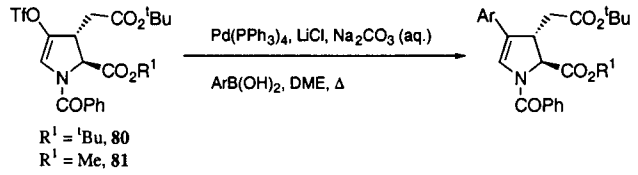

***Scheme 39.***

phenyltrimethyltin did couple to both vinyl triflates **80** and **81** to give the required products **88** and **89**, respectively (Scheme 40). Reduction of vinyl triflate **80** was also observed under these conditions, resulting in the formation of enamide **90**. Vinyl iodides have also been observed to undergo similar reduction reactions during such coupling reactions.[67]

Given the relatively low yields from the Stille cross-coupling reactions and particularly the hazards associated with the synthesis and handling of highly toxic trimethyltin derivatives, Suzuki methodology was applied to vinyl triflates **80** and **81**. Transmetallation was attempted from phenylboronic acid and the three anisylboronic acids (prepared using standard methodology[68]) using the conditions of Wustrow and Wise.[69] This met with a higher degree of success, the reactions being higher yielding and much easier to work-up and purify. This method was therefore employed




***Scheme 40.***




$R^1$ = $^t$Bu, **80**
$R^1$ = Me, **81**

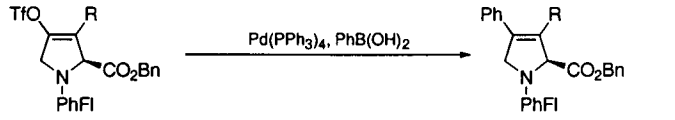
***Scheme 41.***

***Table 6.***

| *Substrate* | *Product* | $R^1$ | *Ar* | *Yield* |
|---|---|---|---|---|
| **80** | **88** | $^t$Bu | Ph- | 78% |
| **81** | **89** | Me | Ph- | 73% |
| **80** | **91** | $^t$Bu | 2-MeOPh- | 52% |
| **81** | **92** | Me | 2-MeOPh- | 89% |
| **80** | **93** | $^t$Bu | 3-MeOPh- | 53% |
| **81** | **94** | Me | 3-MeOPh- | 68% |
| **80** | **95** | $^t$Bu | 4-MeOPh- | 62% |
| **81** | **96** | Me | 4-MeOPh- | 72% |

for all subsequent introductions of aryl C-4 substituents. The results obtained are summarized in Scheme 41 and Table 6.

A similar Suzuki cross-coupling reaction has also been employed by Gill and Lubell in a synthesis of an unsaturated kainoid analogue.[50] Vinyl triflates **97** and **98** were cross-coupled with phenylboronic acid using tetrakis(triphenylphosphine)palladium(0) to give the corresponding coupled products **99** and **100** with high efficiencies (Scheme 42).




R = H, **97**
R = $CH_2CO_2Me$, **98**

R = H, **99**, 72%
R = $CH_2CO_2Me$, **100**, 92%

***Scheme 42.***

## D. Establishment of the Correct C-3/C-4 Relative Stereochemistry

Having introduced the C-2 substituent stereospecifically *trans* to the C-2 ester and also having developed a general method for carbon–carbon

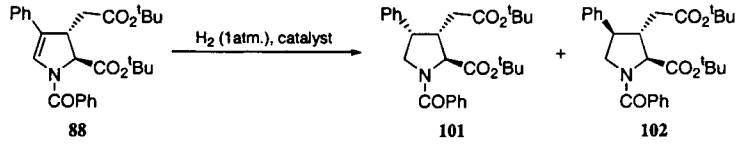
bond formation at C-4 via palladium(0)-catalyzed cross-coupling reactions, it remained to find an appropriate method for the stereospecific reduction of enamides **88**, **89**, and **91–96**. Four methods were examined which met with varying degrees of success.

## *Catalytic Hydrogenation of Enamides*

Heterogeneous catalytic hydrogenation was initiated using enamide substrate **88**. Various catalysts were employed and the effects of pressure and solvent variation were investigated (Scheme 43). The results obtained at atmospheric pressure are summarized in Table 7.

Unfortunately, it was found that the C-2 ester was in all cases directing the hydrogenation giving mainly the undesired C-4 epimer **102** of the protected kainoid analogue. The relative stereochemistry between the C-3 and C-4 substituents in **102** was confirmed by NOE experiments. A summary of the observed enhancements is shown in Figure 11.

An analogous result had previously been reported by Ito and co-workers in a racemic synthesis of α-allokainic acid.[70] Unsaturated derivative **103** was reduced under heterogeneous hydrogenation conditions to give a 1 : 19 ratio of epimers **104** : **105** in an overall 90% yield, the C-2 methyl ester influencing the stereoselectivity (Scheme 44).

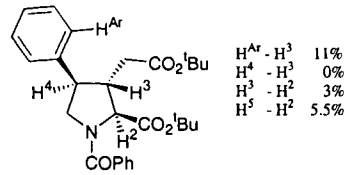



***Scheme 43.***

***Table 7.***

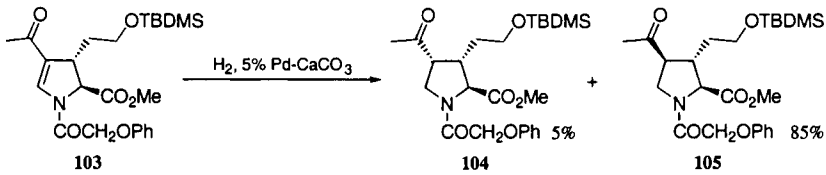
| *Catalyst* | *Solvent* | *Reaction Duration* | **101:102** |
|---|---|---|---|
| 10% Pd-C | EtOAc | 20 h | 1 : 12 |
| Pd black | EtOAc | 6 h | 0 : 1 |
| Raney Ni | EtOH | 6 h | a |
| $PtO_2$ | EtOH | 6 h | a |
| $PtO_2$ | EtOH | 1 h | 1 : 6 |
| $Pd(OH)_2$-C | EtOH | 6 h | 1 : 8 |
| Rh-C | EtOAc | 3 days | b |

*Notes:* [a]Reduction of phenyl groups observed.
[b]No reduction observed.




102

*Figure 11.*



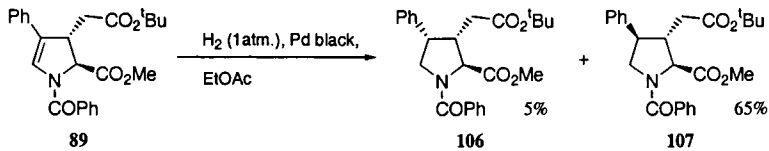

103 104 105

*Scheme 44.*

Palladium black gave the highest yield (81%) in the reduction of enamide **88** with complete stereoselectivity for C-4 epimer **102**. Proof that the selectivity observed was a steric effect associated with the bulk of the C-2 *tert*-butyl ester was obtained by repeating the reduction with methyl ester **89**. Using palladium black as a catalyst under identical conditions to those used in the reduction of **88**, a 70% overall yield of products **106** and **107** in a ratio of 1 : 13 (isolated yield/ratio after chromatographic purification) was obtained (Scheme 45).

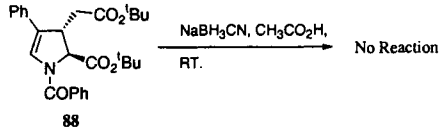
Enamide **88** proved to be unreactive under homogeneous hydrogenation conditions using either Wilkinson's or Crabtree's catalysts even at high temperature and pressure suggesting that the trisubstituted double bond was too hindered to participate in such a process.

Other methods were therefore investigated for enamide reduction.




89 106 107

*Scheme 45.*



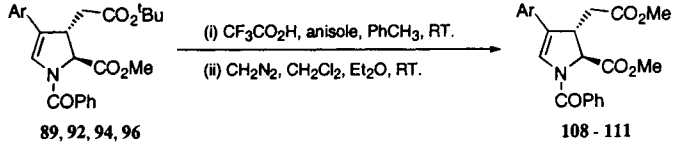

*Scheme 46.*

## *Enamide Reduction with Silanes*

Methods for "hydride-type" reductions of the enamide derivatives gave rise to more encouraging results. Initial experiments using sodium cyanoborohydride under acidic conditions[71] gave no reduction of **88** (Scheme 46), but the use of triethylsilane proved much more effective.

Enamides **89**, **92**, **94**, and **96** were first converted to the corresponding dimethyl esters **108** to **111** by removal of the C-3 *tert*-butyl esters with trifluoroacetic acid at room temperature followed by esterification with diazomethane (Scheme 47 and Table 8).

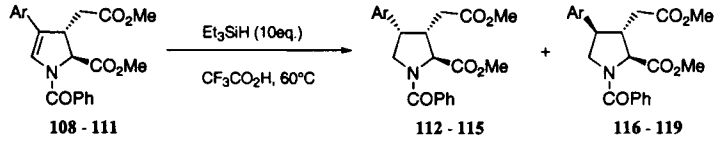
The dimethyl esters were reduced with an excess of triethylsilane in trifluoroacetic acid[72] giving essentially equimolar quantities of each of the required protected kainoid analogues **112** to **115** and their corresponding C-4 epimers **116** to **119** in reasonable overall yields after chromatographic separation (Scheme 48 and Table 9). It is interesting to note here that isomers **112** to **115** were all found to be less polar than their corresponding C-4 epimers **116** to **119**.




*Scheme 47.*

*Table 8.*

| *Substrate* | *Product* | *Ar* | *Yield (2 steps)* |
|---|---|---|---|
| **89** | **108** | Ph- | 90% |
| **92** | **109** | 2-MeOPh- | 96% |
| **94** | **110** | 3-MeOPh- | 96% |
| **96** | **111** | 4-MeOPh- | 68% |




108 - 111 112 - 115 116 - 119

***Scheme 48.***

***Table 9.***

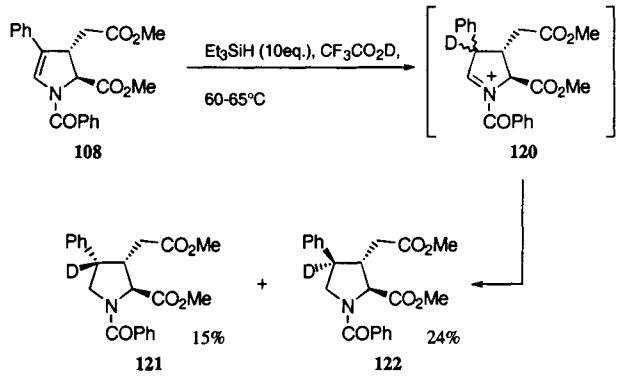
| *Substrate* | *Product* | *Ar* | *Yield* | *Overall Yield* |
|---|---|---|---|---|
| **108** | **112** | Ph- | 28% | 56% |
| **109** | **113** | 2-MeOPh- | 38% | 76% |
| **110** | **114** | 3-MeOPh- | 37% | 72% |
| **111** | **115** | 4-MeOPh- | 38% | 72% |
| **108** | **116** | Ph- | 28% | 56% |
| **109** | **117** | 2-MeOPh- | 38% | 76% |
| **110** | **118** | 3-MeOPH- | 35% | 72% |
| **111** | **119** | 4-MeOPh- | 34% | 72% |

Evidence that this reduction proceeds mainly via an *N*-acyl iminium ion intermediate **120** was obtained by carrying out the triethylsilane reduction of **108** in deuterated trifluoroacetic acid (Scheme 49). As before, two C-4 epimeric protected kainoid analogues **121** and **122** were obtained, $^{1}H$ NMR showing loss of the C-4 proton in both products accompanied by a simplification in the spin–spin coupling pattern of the C-5 protons.[73] A close examination of the $^{2}H$ NMR spectrum of each diastereoisomer did, however, reveal a trace of deuteration at C-5 indicating that a small percentage of the reduction also occurs via a benzylic carbocation intermediate **123** (Figure 12).

Although this route did allow access to reasonable quantities of the required protected kainoid analogues **112** to **115**, a more stereoselective route was thought to be more desirable, and hence, two further enamide reduction methods were explored.

### *Lactonization/Benzylic Lactone Hydrogenolysis*

The efficient stereocontrol observed in the benzylic lactone hydrogenolyses described in the section on Lactonization/Benzylic Lactone Reduction prompted an investigation into methods for preparing analogous fused bicyclic lactones from enamides **89**, **92**, **94**, and **96**. The possible intermediacy of benzylic carbocation **123** in the triethylsilane




*Scheme 49.*

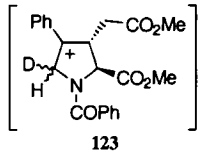
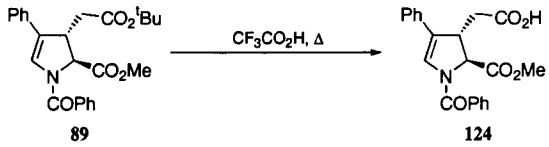



*Figure 12.*

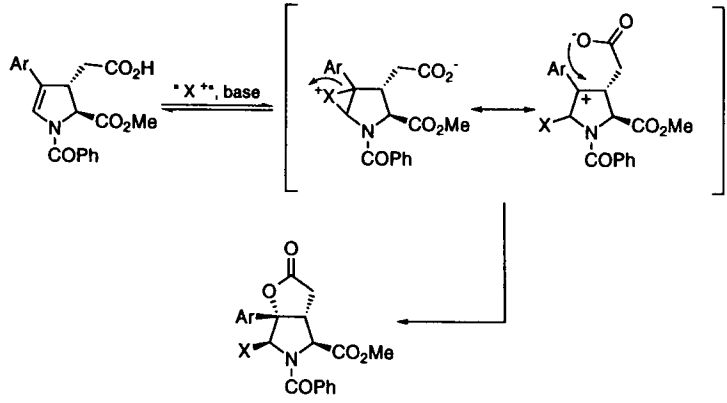
reduction suggested that prolonged treatment of enamides **89**, **92**, **94**, and **96** with strong acid may lead to the formation of the corresponding lactones via C-3 *tert*-butyl ester cleavage followed by C-5 protonation and carbocation trapping by the free carboxylic acid group. Unfortunately, this did not prove to be the case with only deprotection of the C-3 *tert*-butyl ester being observed to give free acid **124** when **89** was heated in trifluoroacetic acid under reflux for several days (Scheme 50).

The availability of free acids such as **124** led to attempts to "activate" the lactonization procedure, the general principle being shown in Scheme 51.

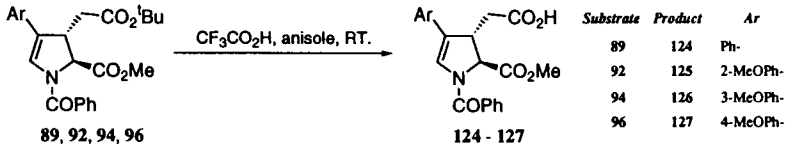
Enamides **89**, **92**, **94**, and **96** were initially deprotected to the corresponding C-3 free acids **124** to **127** by treatment with trifluoroacetic acid




*Scheme 50.*




***Scheme 51.***

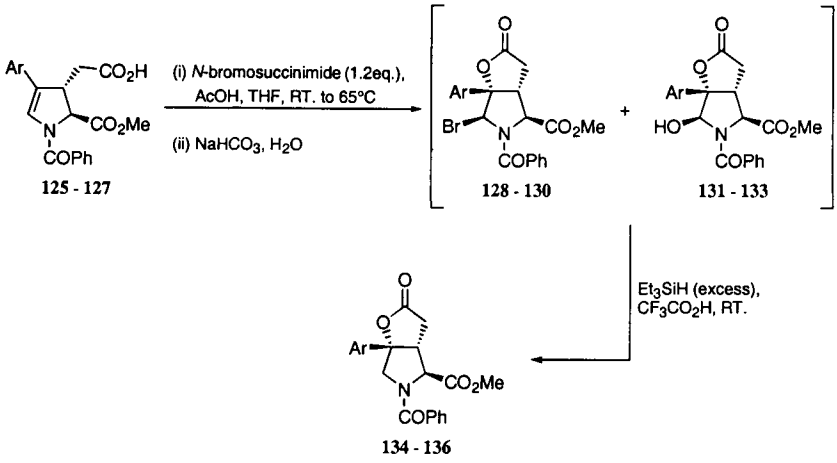



| *Substrate* | *Product* | *Ar* |
|---|---|---|
| 89 | 124 | Ph- |
| 92 | 125 | 2-MeOPh- |
| 94 | 126 | 3-MeOPh- |
| 96 | 127 | 4-MeOPh- |

***Scheme 52.***

in the presence of anisole as a cation scavenger. Yields of acids **124** to **127** were essentially quantitative (Scheme 52).

Conventional iodolactonization conditions[74] applied to acids **124** to **127** resulted in complex product mixtures which appeared to be relatively unstable. A degree of success was nonetheless achieved using bromolactonization. Although inconsistent results were obtained with molecular bromine as the electrophile (conditions used were identical to those employed for iodolactonization[74]), *N*-bromosuccinimide[75] proved to be the reagent of choice. The C-4 phenyl- and C-4 *m*-anisyl-substituted acids **124** and **126** appeared to react very slowly with *N*-bromosuccinimide in the presence of acetic acid but the other two derivatives **125** and **127** gave more promising results. Usable results were obtained for derivatives **125** to **127**, and in all three reactions, the crude product appeared to consist of two relatively labile major products. On the basis of $^1$H NMR, IR, and mass spectrometric data obtained on the crude bromolactonization products, these major components were tentatively assigned to the bromolactones **128** to **130** and hemiaminals **131** to **133**.




*Scheme 53.*

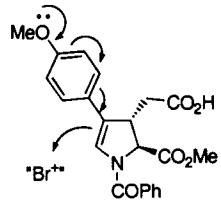
*Table 10.*

| *Substrate* | *Product* | *Ar* | *Yield* |
|---|---|---|---|
| **125** | **128 131 134** | 2-MeOPh- | 77% |
| **126** | **129 132 135** | 3-MeOPh- | 33% |
| **127** | **130 133 136** | 4-MeOPh- | 80% |

Due to the apparent lability of these products, the mixtures were reduced without further purification or characterization to the required bicyclic lactones **134** to **136**. Excess triethylsilane in trifluoroacetic acid gave smooth reduction (Scheme 53 and Table 10—yields are quoted for the two steps, i.e., bromolactonization followed by reduction).

The lack of reactivity of the C-4 phenyl-substituted acid **124** and the relatively low reactivity of the C-4 *m*-anisyl-substituted derivative **126** compared with the *o*-anisyl and *p*-anisyl analogues **125** and **127** was ascribed to the activation of the enamide double bond in the latter two cases by the methoxy substituents (e.g., Figure 13).

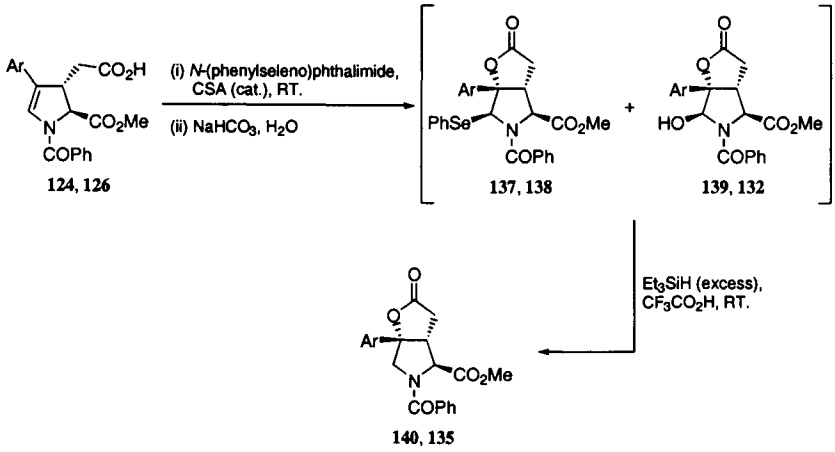
This lack of reactivity could be circumvented to some extent by the use of an analogous selenolactonization/reduction procedure.[76] *N*-(phenylseleno)phthalimide was used as the electrophilic selenium source in the presence of a catalytic quantity of camphorsulfonic acid. Analysis of the crude product mixture obtained using acids **124** and **126** suggested




127

*Figure 13.*

the presence of the required selenolactones **137** and **138** and the corresponding hemiaminals **139** and **132**. These crude reaction products were partially purified by silica gel chromatography and then subjected to the triethylsilane/trifluoroacetic acid reduction conditions.This gave an acceptable yield of the C-4 phenyl-substituted bicyclic lactone **140** (49%) and an improved yield of the C-4 *m*-anisyl derivative **135** (62%). These results are summarized in Scheme 54 and Table 11.

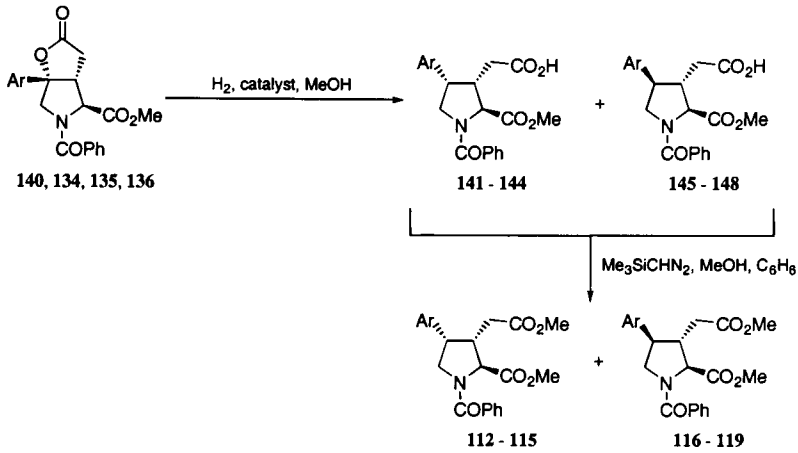



*Scheme 54.*

*Table 11.*

| *Substrate* | *Product* | *Ar* | *Yield* |
|---|---|---|---|
| **124** | **137 139 140** | Ph- | 49% |
| **126** | **138 132 153** | 3-MeOPh- | 62% |

With the desired lactones **140**, **134**, **135**, and **136** in hand, hydrogenolysis with a variety of heterogeneous catalysts was carried out following the general principles outlined in the section on Lactonization/Benzylic Lactone Reduction. The crude products containing acids **141** to **144** and their corresponding C-4 epimers **145** to **148** were

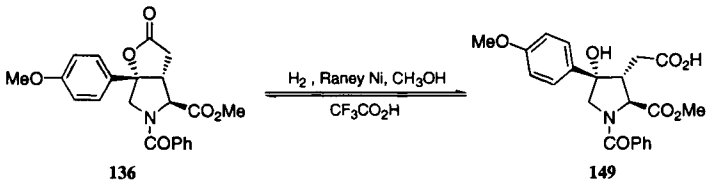



***Scheme 55.***

***Table 12.***

| *Substrate* | *Ar* | *Catalyst* | *Pressure (atm)* | *4S : 4R* |
|---|---|---|---|---|
| **140** | Ph- | 10% Pd-C | 1 | 10 : 1 |
| | | Pd black | 1 | 5 : 1 |
| **134** | 2-MeOPh- | 10% Pd-C | 1 | 3 : 2 |
| | | Pd black | 1 | 3 : 2 |
| | | $Pd(OH)_2$ | 2.25 | 1 : 1 |
| | | 10% Pd-C | 3.5 | 1 : 1 |
| | | 10% Pd-C, $HClO_4$ (cat.) | 1 | 2 : 3 |
| **135** | 3-MeOPh- | 10% Pd-C | 1 | 5 : 1 |
| | | Pd black | 1 | 13 : 1 |
| **136** | 4-MeOPh- | 10% Pd-C | 1 | 4 : 1 |
| | | Pd black | 1 | 12 : 1 |
| | | $Pd(OH)_2$ | 3.5 | 4 : 1 |
| | | Raney Ni | 1 | a |
| | | 10% Pd-C, $HClO_4$ (cat.) | 1 | 3 : 1 |

*Note*: [a]Only lactone hydrolysis occurred.




***Scheme 56.***

esterified using trimethylsilyldiazomethane[77] to give the protected kainoid analogues **112** to **115** and **116** to **119**, the product ratios being determined from integration of the $^1$H NMR spectra of the crude esterification products. In all cases, yields were essentially quantitative. The C-4 epimer ratios were found to vary with catalyst/reaction conditions but also, most importantly, with C-4 substituent which had not been suggested by the earlier results. In particular, the important C-4 *o*-anisyl derivative **134** gave a disappointing ratio of C-4 epimers, only marginally favoring the diastereoisomer with the natural kainoid stereochemistry **113** under all of the conditions used (Scheme 55 and Table 12).

The reasons for these variations are unclear although it is worth noting that the use of Raney nickel (which would have been expected to give retention of configuration at the benzylic center[56b]) gave only lactone hydrolysis (despite extensive washing of the catalyst) with the *p*-anisyl derivative **136**. This reaction proved to be readily reversible, the hydroxy acid **149** readily re-forming lactone **136** on treatment with trifluoroacetic acid (Scheme 56). Also of note is the fact that the addition of catalytic quantities of perchloric acid led to a worsening of the 4*S* : 4*R* ratio.

Overall, the most reliable catalyst for these hydrogenolyses proved to be palladium black which gave the most rapid reactions at atmospheric pressure and in all cases apart from the C-4 phenyl derivative **140**, gave the best 4*S* : 4*R* ratio.

Given the disappointing result obtained with the C-4 *o*-anisyl derivative **134**, it was evident that this method for setting up the C-3/C-4 *cis* stereochemistry would be very much dependent on the nature of the C-4 substituent in a manner that would not be readily predictable. A more general method for reduction of the enamides **89**, **92**, **94**, and **96** was therefore still required.

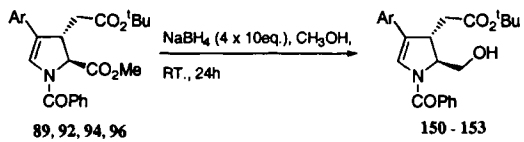
## *Hydroxyl-Group-Directed Enamide Reduction*

The directing effects of hydroxyl groups in homogeneous hydrogenation reactions are well established but the equivalent effect is also

observed under heterogeneous hydrogenation conditions.[78] Given that the enamide reduction required for C-4 aryl derivatives **89**, **92**, **94**, and **96** involved delivery of hydrogen to the carbon–carbon double bond from the same face of the dehydropyrrolidine ring as the C-2 ester, chemoselective reduction of this ester to a primary hydroxyl group was investigated.

The yields and chemoselectivities for all four derivatives **89**, **92**, **94**, and **96** were found to be high using a large excess (40 equiv) of sodium borohydride in methanol (Scheme 57 and Table 13). The reduction reaction occurred relatively slowly (4 × 10 equiv of sodium borohydride was added over a 24-h period at room temperature) and it was thought that destruction of the borohydride reagent by the solvent was competing with the reduction process. Attempts were made to improve the efficiency of this process by using ethanol or isopropanol as the solvent in the hope that this would slow the destruction of the borohydride but this was not successful with complex mixtures of products being obtained, some possibly reflecting ester exchange reactions.

Reduction of the resulting primary alcohols **150** to **153** over palladium black proved to be a relatively slow process at atmospheric pressure, the reactions requiring up to 2 days to reach completion, but most importantly, good yields were obtained accompanied by complete stereocontrol. Only the products **154** to **157** with the correct kainoid C-3/C-4 *cis* relative stereochemistry were obtained (Scheme 58 and Table 14). The C-2 primary alcohol functionality appeared to be responsible for this



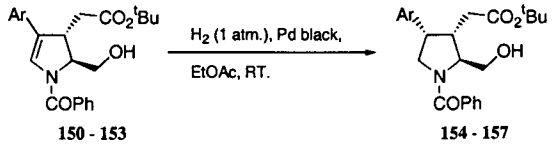

89, 92, 94, 96 150 - 153

***Scheme 57.***

***Table 13.***

| *Substrate* | *Product* | *Ar* | *Yield* |
|---|---|---|---|
| **89** | **150** | Ph- | 91% |
| **92** | **151** | 2-MeOPh- | 80% |
| **94** | **152** | 3-MeOPh- | 80%[a] |
| **96** | **153** | 4-MeOPh- | 71% |

*Note:* [a]94% based on recovered starting material.




150 - 153 154 - 157

***Scheme 58.***

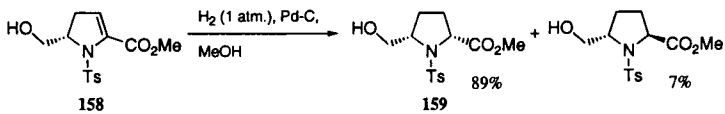
***Table 14.***

| *Substrate* | *Product* | *Ar* | *Yield* |
|---|---|---|---|
| **150** | **154** | Ph- | 91% |
| **151** | **155** | 2-MeOPh- | 89% |
| **152** | **156** | 3-MeOPh- | 89% |
| **153** | **157** | 4-MeOPh- | 85% |

stereocontrol, this conclusion being supported by the fact that hydrogenation experiments carried out on similar dehydropyrrolidine derivatives with a free carboxyl group at C-2 did not show the same stereocontrol.[48]

Speckamp and co-workers have published a related enamide hydrogenation that appears not to be directed by a primary alcohol group.[79] C-5 hydroxymethyl-substituted dehydroproline derivative **158** was reduced using palladium on activated charcoal as catalyst in methanol. This gave mainly the 2,5-*cis* reduced product **159** in contrast to the results obtained for dehydropyrrolidines **150** to **153** (Scheme 59). A possible explanation for this observation could lie with Speckamp's choice of solvent. Solvents with a low dielectric constant are known to enhance the binding affinity of the substrate to a heterogeneous catalyst[80] with methanol possibly competing for binding to the palladium with **158**. Such a competitive binding of solvent could ensure that the reduction process reverts to steric control.

Having found an efficient method for setting up the correct C-3/C-4 relative stereochemistry, all that remained prior to deprotection was to




158 159

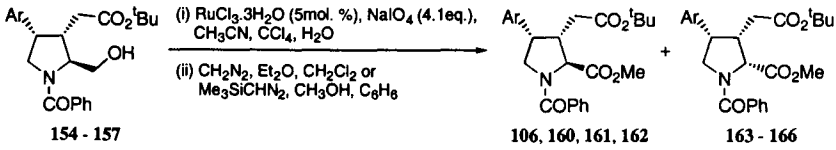
***Scheme 59.***

reoxidize the primary alcohols **154** to **157** to the corresponding carboxylic acids.

## E. Reoxidation of C-2 Primary Alcohols

Initially, the oxidation conditions chosen for **154** to **157** were the modified ruthenium tetraoxide conditions of Sharpless and co-workers.[44] The crude oxidation products were converted to methyl esters **106, 160, 161,** and **162** and their C-2 epimers **163** to **166** using either diazomethane or trimethylsilyldiazomethane.[77] The epimer ratios were determined from integration of the $^1$H NMR spectra of the crude esterification products to ensure that accurate ratios were obtained without "losing" minor isomers during chromatography. The results obtained are summarized in Scheme 60 and Table 15.

Epimerization during this oxidation procedure was thought to be related to the optical lability of the aldehyde intermediate formed during the two-step process. Monitoring the oxidation reaction by thin-layer chromatography revealed intermediates of lower polarity than both the alcohols **154** to **157** and the corresponding carboxylic acids, consistent with the intermediacy of such aldehydes. Although this epimerization was slightly disappointing, the ratios were felt to be acceptable and the C-2 epimers of the esters were readily separable by flash chromatography.




**154 - 157** **106, 160, 161, 162** **163 - 166**

***Scheme 60.***

***Table 15.***

| *Substrate* | *Products* | *Ar* | *2S : 2R* | *Yield of 2S isomer isolated* |
|---|---|---|---|---|
| **154** | **106 163** | Ph- | 14 : 1 | 47% |
| **155** | **160 164** | 2-MeOPh- | 7 : 1 | 53% |
| **156** | **161 165** | 3-MeOPh- | 8 : 1 | 62% |
| **157** | **162 166** | 4-MeOPh- | 8 : 1 | 71% |

*Table 16.*

| *Oxidizing Agent* | *Substrate* | *Products* | *Ar* | *2S : 2R* | *Overall Yield* |
|---|---|---|---|---|---|
| $RuCl_3 \cdot H_2O$ (40 mol%), $NaIO_4$ | **155** | **160** **164** | 2-MeOPh- | 9 : 1 | 57% |
| PDC (5 equiv), DMF, 40 °C | **154** | **106** **163** | Ph- | 1 : 0 | 41% |
| PDC (5 equiv), DMF, 40 °C | **155** | **160** **164** | 2-MeOPh- | 1 : 0 | 24% |
| $CrO_3$, c.$H_2SO_4$, $H_2O$, acetone[81] | **154** | **106** **163** | Ph- | 8 : 1 | 76% |
| $CrO_3$, c.$H_2SO_4$, $H_2O$, acetone[81] | **155** | **160** **164** | 2-MeOPh- | 15 : 1 | 83% |
| $O_2$ (1 atm), $PtO_2$[82] | **155** | **160** **164** | 2-MeOPh- | — | 0% |
| $O_2$ (2 atm), $PtO_2$[82] | **155** | **160** **164** | 2-MeOPh- | 8 : 1 | 32%[a] |

*Note*: [a]67% based on recovered **155**.

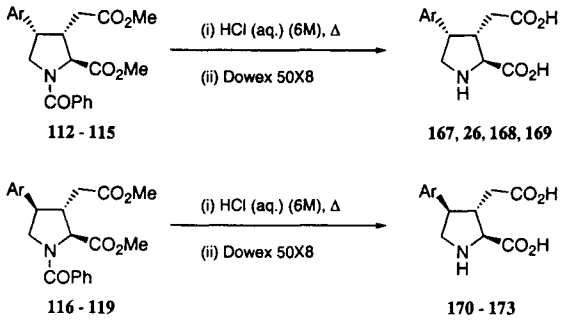
A variety of other oxidation conditions were investigated; overall, the ruthenium tetraoxide method gave the most consistent results and, importantly, required the least purification. The results obtained are summarized in Table 16.

Pyridinium dichromate (PDC) in dimethylformamide gave the best C-2 epimer ratio with **154** and **155**, only giving **106** and **160**, respectively. Unfortunately, the yields obtained here were poor and the reaction products required extensive chromatographic purification, and hence, ruthenium tetraoxide was deemed the most suitable reagent for carrying out the required transformation with the best overall efficiency.

With all four of the required protected acromelic acid analogues **106**, **160**, **161**, **162** and **112** to **115** available in reasonable quantities as single diastereoisomers along with the C-4 epimers **116** to **119**, it only remained to carry out global deprotection.

## F. Deprotection

The use of amide and *tert*-butyl/methyl esters as protecting groups throughout the later synthetic routes allowed the use of a single deprotection step. This was accomplished for all protected derivatives by heating overnight at reflux in 6 M aqueous hydrochloric acid. The crude products thus obtained were separated from the by-product benzoic acid by ion-exchange chromatography using Dowex 50X8. The results obtained for derivatives **112** to **115** and **116** to **119** are typical of those obtained for all protected derivatives and these are summarized in Scheme 61 and Table 17. The free amino acids were obtained as white, apparently amorphous powders after freeze-drying the solutions ob-




112 - 115 167, 26, 168, 169

116 - 119 170 - 173

*Scheme 61.*

*Table 17.*

| *Substrate* | *Product* | *Ar* | *Yield* |
|---|---|---|---|
| **112** | **167** | Ph- | 100% |
| **113** | **26** | 2-MeOPh- | 97% |
| **114** | **168** | 3-MeOPh- | 96% |
| **115** | **169** | 4-MeOPh- | 96% |
| **116** | **170** | Ph- | 71% |
| **117** | **171** | 2-MeOPh- | 82% |
| **118** | **172** | 3-MeOPh- | 82% |
| **119** | **173** | 4-MeOPh- | 96% |

tained from the ion-exchange chromatography. These solids could be crystallized from boiling water.

In agreement with results reported by Shirahama and co-workers, the *cis* C-3/C-4 stereochemistry in products **167**, **26**, **168** and **169** could be diagnosed by the proton at C-4 appearing at lower field than for the corresponding *trans* cases **170** to **173**.[33,83] Further structural confirmation was obtained by X-ray crystallography on *o*-anisyl derivative **26** (Figure 14).[84] This also confirmed the expected zwitterionic structure of the amino acid.

## G. Interim Summary

So far, the results suggested a versatile synthesis of C-4 aryl kainoid analogues (or acromelic acid analogues) had been developed. In summary form, the most efficient synthesis achieved involves 12 steps from *trans*-4-hydroxy-L-proline **34** (Scheme 62). This route allows access to these biologically important molecules on a relatively large scale.

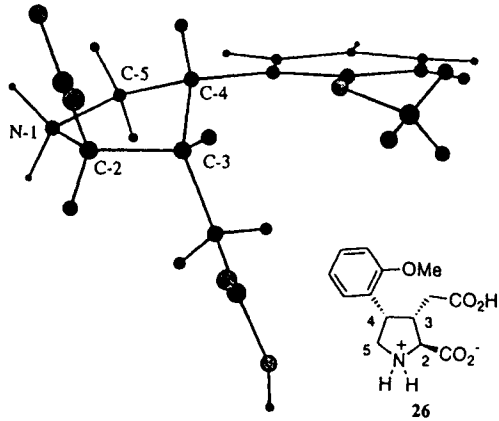
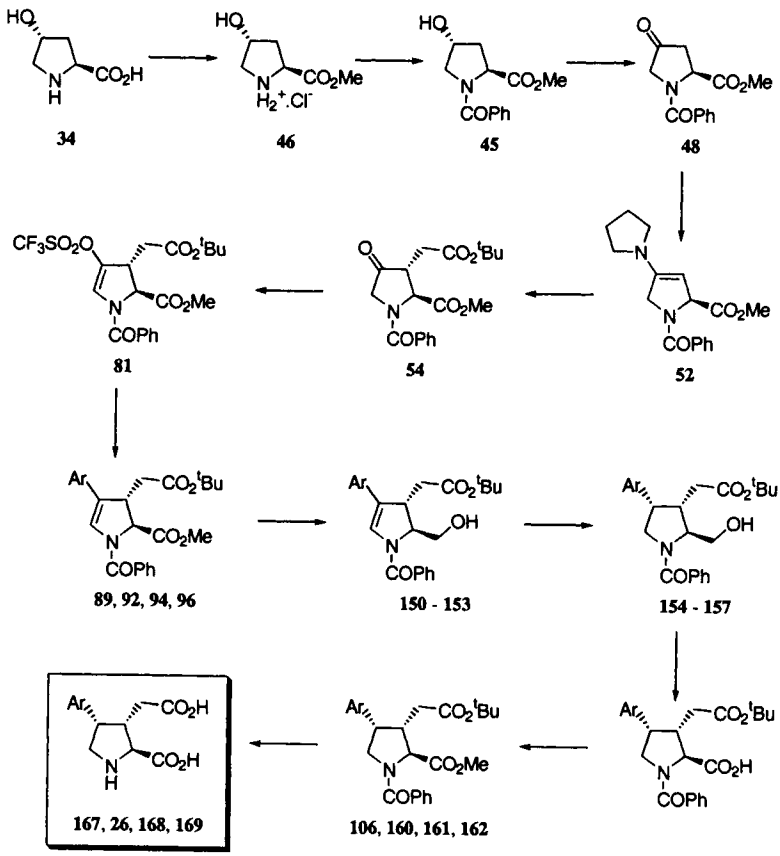
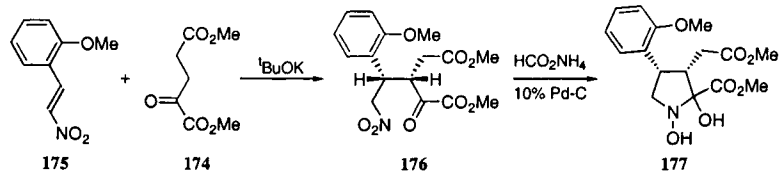



*Figure 14.*




*Scheme 62.*




*Scheme 63.*

Recently, Kraus and Maeda have reported an elegant synthesis of the important C-4 *o*-anisyl derivative **26** in racemic form.[85] This route involves pyrrolidine ring synthesis with key steps being Michael addition of the enolate of dimethyl α-ketoglutarate **174** to nitrostyrene derivative **175** followed by cyclization of the adduct **176** under reductive conditions to hemiaminal **177** (Scheme 63).

To test the versatility of our synthetic scheme, it only remained to apply it to naturally occurring acromelic acids.

## H. An Efficient Synthesis of Acromelic Acid A and an Approach to Acromelic Acid B

It was decided to make an attempt to combine the successful biomimetic pyridone syntheses described in the section on Biosynthesis of Acromelic Acids with the newly developed general kainoid synthesis in the preparation of acromelic acids A **5** and B **6**.

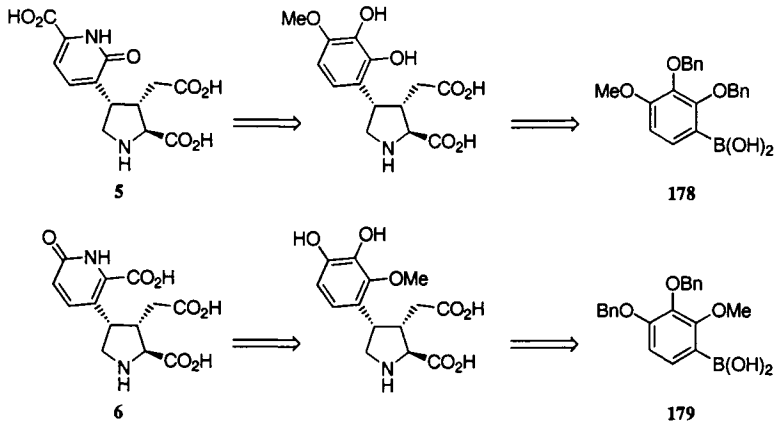
### *Retrosynthetic Analysis*

Assuming that the general methodology in Scheme 62 would be applicable, catechol precursors were required for the C-4 pyridone substituents of **5** and **6**. This led (using analogies to the catechol cleavages illustrated in Schemes 4 and 5) to a requirement for boronic acids **178** and **179** for use in the Suzuki cross-coupling step (Scheme 64).

The intention was to produce the pyridone moieties toward the end of the synthetic scheme, hence the catechol protecting groups chosen were benzyl with the intention of removing them during the hydroxyl-directed enamide reduction step.

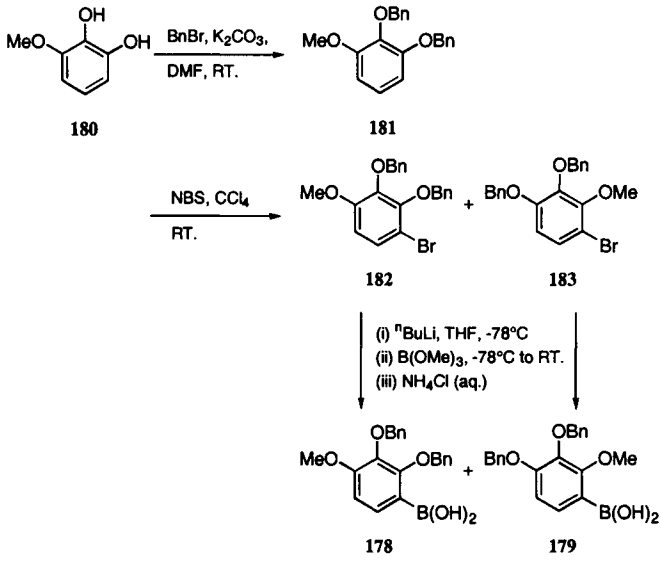
### *Boronic Acid Preparation/Suzuki Cross-Coupling*

3-Methoxycatechol **180** was dibenzylated to give fully protected derivative **181**. The latter was brominated using *N*-bromosuccinimide,

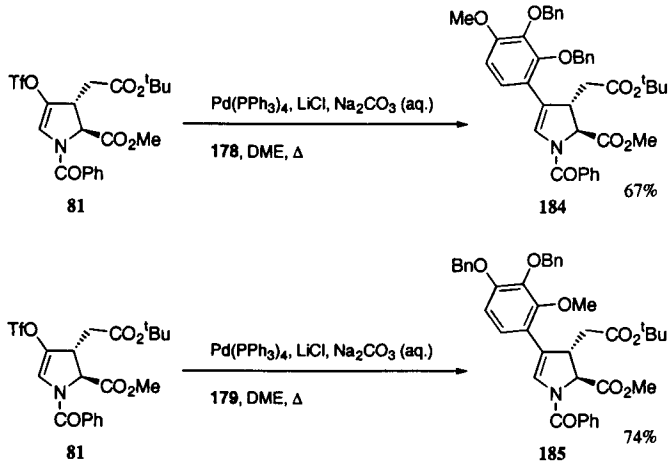



***Scheme 64.***

resulting in an equimolar mixture of the two isomeric bromides **182** and **183** which were successfully separated by a combination of flash chromatography on silica gel and fractional crystallization. The separated bromides **182** and **183** were treated sequentially with *n*-butyllithium followed by trimethyl borate, yielding the required boronic acids **178** and **179**, respectively, on mildly acidic workup (Scheme 65).




***Scheme 65.***

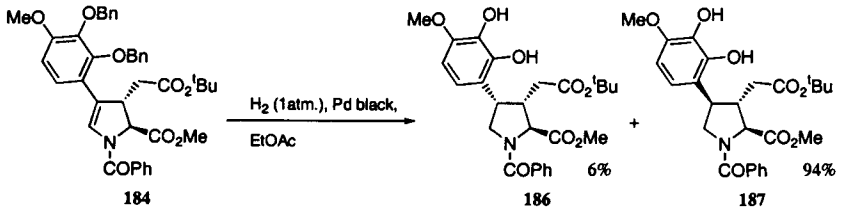



***Scheme 66.***

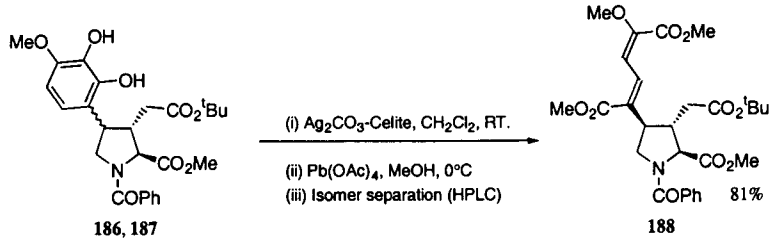
Both boronic acids were successfully cross-coupled to vinyl triflate **81** using the previously successful conditions, giving the required enamides **184** and **185** (Scheme 66).

## *"Allo-" Acromelic Acid A*

To check that the catechol cleavage methodology would be compatible with the remaining functionality, a synthesis of the C-4 epimer of acromelic acid A was first attempted. Instead of following the extra steps required in the hydroxyl directed enamide hydrogenation, fully protected enamide **184** was reduced over palladium black at atmospheric pressure. This gave not only reduction of the enamide to a 1 : 15 ratio of C-4 epimers but also facilitated the required cleavage of the benzyl ethers, resulting in a quantitative overall yield of **186** and **187**. As expected, the predominant C-4 epimer was the "unnatural" isomer, **187** (Scheme 67).



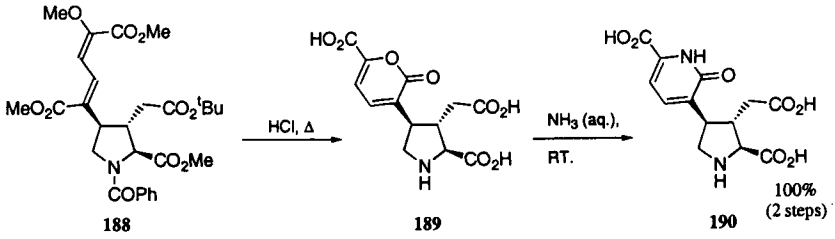

***Scheme 67.***




***Scheme 68.***

At this stage, a modification of the previously employed catechol cleavage procedure was adopted. The mixture of epimers **186** and **187** was oxidized to the intermediate *ortho*-quinones using Fétizon's reagent[86] in dichloromethane. *In situ* oxidative cleavage using lead tetraacetate in methanol[87] followed by epimer separation by preparative HPLC gave muconate **188** as a single diastereoisomer (Scheme 68).

Muconate **188** was cyclized under strongly acidic conditions with concomitant deprotection to the required pyrone **189** which was quantitatively ammonolyzed to give so-called "*allo*-" acromelic acid A **190** (Scheme 69). It is worth noting the excellent overall yield achieved for the construction of the C-4 pyridone moiety from the starting protected catechol.

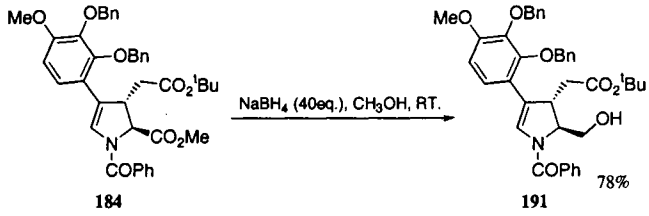



***Scheme 69.***

Given the success of this biomimetic synthesis, attention was turned to the natural isomer acromelic acid A **5**.

## *Acromelic Acid A*

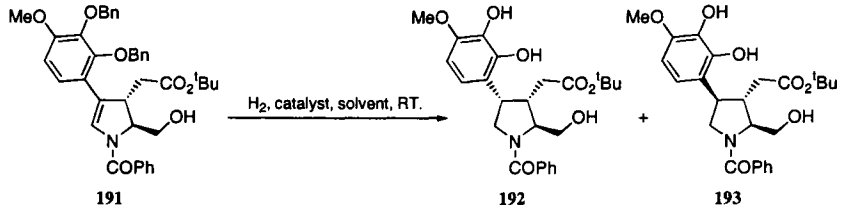
The first step required was the stereoselective reduction of enamide **184** to give the necessary C-3/C-4 *cis* stereochemistry. To enable the use of the hydroxyl group directed hydrogenation described in the section on Hydroxyl-Group-Directed Enamide Reduction, enamide **184** was




***Scheme 70.***

chemoselectively reduced using an excess of sodium borohydride in methanol to give primary alcohol **191** (Scheme 70).

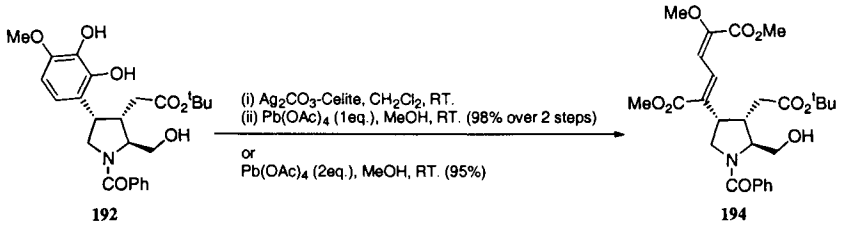
Various catalyst, pressure, and solvent systems were investigated in an attempt to maximize the stereoselectivity of the enamide hydrogenation. In contrast to the results obtained on the more straightforward derivatives **150** and **151**, a mixture of C-4 epimers was obtained under all of the conditions tried. The results obtained are summarized in Scheme 71 and Table 18 below. (Note: Solvents/solvent mixtures were chosen with as low a polarity as possible in an attempt to maximize coordination of the substrate to the heterogeneous catalyst.[80]) Overall yields in all cases where reduction occurred were essentially quantitative.




***Scheme 71.***

***Table 18.***

| *Catalyst* | *Solvent* | *Pressure (atm)* | **192 : 193** *(4S : 4R)* |
|---|---|---|---|
| Pd black | Ethyl acetate | 4 | 10 : 1 |
| Pd black | 10 : 1 v/v hexane : 1,4-dioxane | 4 | 11 : 1 |
| Pd black | 10 : 1 v/v hexane : 1,4-dioxane | 1.5 | 8 : 1 |
| Pd black | Benzene | 4.5 | 11 : 1 |
| 10% Pd-C | 10 : 1 v/v hexane : 1,4-dioxane | 1 | 3 : 1 |
| 10% Pd-C | Ethyl acetate | 1 | 3 : 1 |
| Raney Ni | Ethyl acetate | 3.5 | No reaction |




***Scheme 72.***

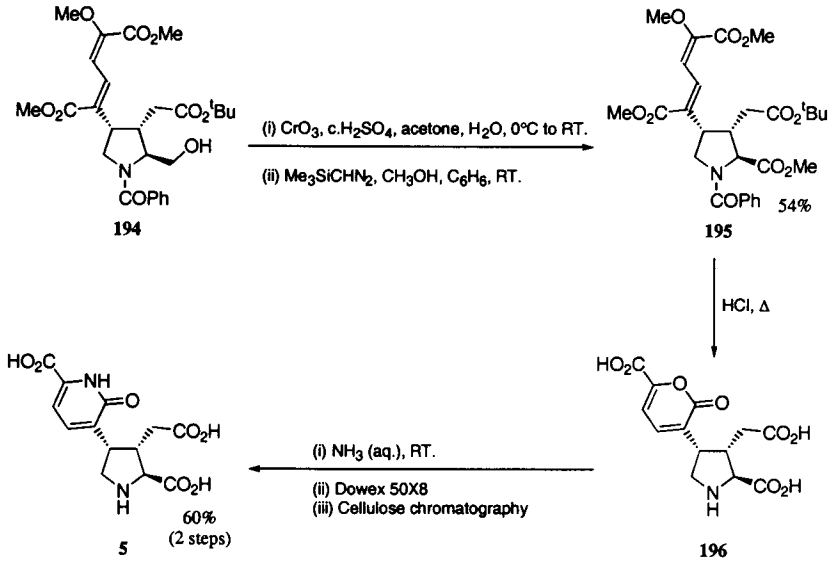
The best results were obtained using palladium black as the catalyst under 4 atm of hydrogen pressure, the solvent being 10 : 1 v/v hexane : 1,4-dioxane. Here the ratio of **192** : **193** was 11 : 1 with the expected cleavage of the benzyl ethers also occurring.

From here onwards, the 11 : 1 mixture of C-4 epimers was carried through all of the subsequent synthetic steps until the final purification. All of the following diagrams will show only the 4*S* isomers for clarity.

Oxidative cleavage of the catechol moiety of **192** could be achieved in two ways. First, the method described in the preceding section was employed with Fétizon's reagent oxidation to the *ortho*-quinone followed by lead tetraacetate in methanol to give an overall 98% yield of the corresponding muconates. Alternatively, oxidative cleavage could be achieved in a single step with high efficiency by the use of two molar equivalents of lead tetraacetate in methanol (Scheme 72—only one isomer of the muconate **194** shown).

The C-2 methyl ester functionality was reinstated by oxidation using Jones' reagent followed by esterification with trimethylsilyldiazomethane with no epimerization being observed at C-2 during this process which proceeded in 54% yield over the two steps. The muconate **195** was then cyclized under acidic conditions to the corresponding pyrone **196** which was ammonolysed to give acromelic acid A **5** which was separated from its C-4 epimer **190** by cellulose chromatography following ion-exchange. This gave a 60% yield of **5** over the pyrone formation/ammonolysis steps (Scheme 73).

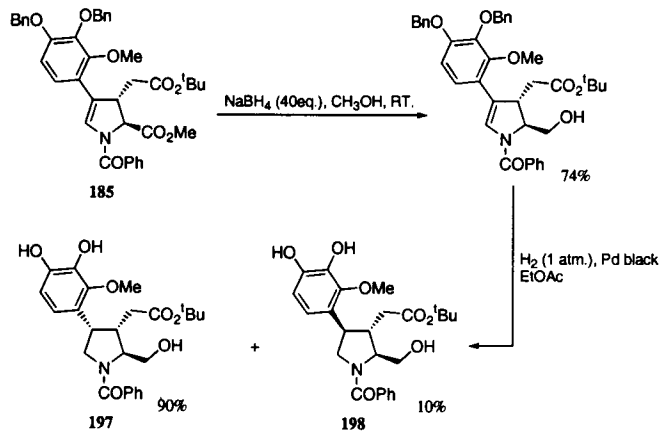
The acromelic acid A **5** obtained had physical properties (including specific rotation) identical to natural material, the overall yield from *trans*-4-hydroxy-L-proline **34** being 9%. Initial experiments led to the isolation of 60 mg of purified **5** although this synthetic route would be amenable to preparation on a significantly larger scale.



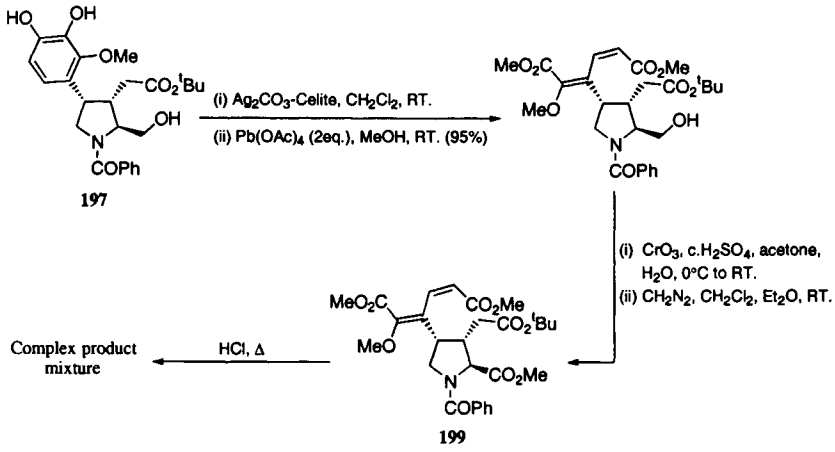

*Scheme 73.*

## *Acromelic Acid B*

An analogous synthesis of acromelic acid B **6** was also attempted using enamide **185**. C-2 methyl ester reduction and hydroxyl-directed enamide hydrogenation proceeded smoothly giving a 10 : 1 mixture of C-4 epimeric catechols, **197** and **198** (Scheme 74).




*Scheme 74.*




***Scheme 75.***

The mixture of catechols was subjected to the lead tetraacetate cleavage conditions, giving the corresponding muconates (**197** only shown) which were reoxidized and esterified to the corresponding C-2 methyl esters (**199** only shown), again with no C-2 epimerization observed. Unfortunately, the hydrolysis with concomitant pyrone formation gave rise to a complex mixture of products, ruling out this method for the synthesis of acromelic acid B **6** (Scheme 75—major isomers only shown).

## IV. SUMMARY

This chapter reviews recent developments in the synthesis of both naturally occurring and unnatural acromelic acids, important members of the kainoid class of neuroexcitatory nonproteinogenic amino acid.

It centers around synthetic methods recently developed in Baldwin's group in Oxford, which have been successful in producing a concise route to C-4 aryl kainoids, using *trans*-4-hydroxy-L-proline **34** as a relatively cheap starting material. A series of C-4 aryl-substituted kainoid analogues have been prepared, differing in the nature of the C-4 substituent and the absolute stereochemistry at this position, and the versatility of the methodology has been emphasized with a short and efficient synthesis of naturally occurring acromelic acid A **5**. Importantly, the methodology allows access to relatively large quantities of these compounds and should be readily applicable to other kainoids.

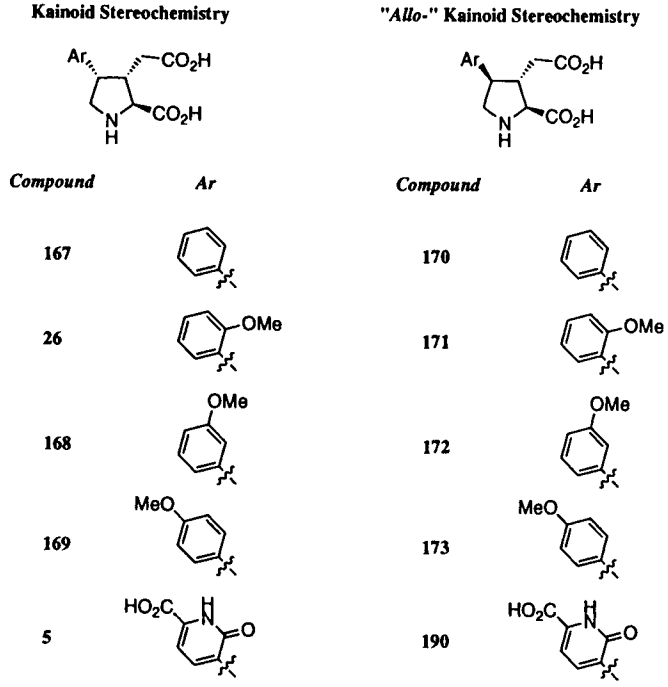



*Figure 15.*

The review concentrates and elaborates on the work described in four communications[88–91] and four full papers,[92–95] putting the results obtained into context and providing comparisons with recent reports from other workers in this field.

The kainoids prepared so far using this chemistry are illustrated in Figure 15.

## ACKNOWLEDGMENTS

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# INDEX

# Advances in Cycloaddition

Edited by **Michael Harmata**,
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