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Palladium -catalyzed synthesis of carbazole derivatives and formal total syntheses of several naturally occurring carbazole alkaloids

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Palladium-Catalyzed Synthesis of Carbazole Derivatives and Formal Total Syntheses of Several Naturally Occurring Carbazole Alkaloids

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ABSTRACT

Palladium-Catalyzed Synthesis of Carbazole Derivatives and the Formal Total Syntheses of Several Naturally Occurring Carbazole Alkaloids

Tricia L. Scott

A mild and efficient route to substituted carbazolones has been developed. This novel procedure consists of two consecutive palladium-catalyzed reactions, an intermolecular Stille coupling followed by an intramolecular reductive *N*-heteroannulation. For example, 1,2-dihydro-4(3*H*)-carbazolone was prepared in good isolated yield (74%) by the reductive cyclization of 2-(2-nitrophenyl)-2-cyclohexen-1-one using $Pd(dba)_2$ (6 mol%), 1,3-bis(diphenylphosphino)propane (6 mol%), 1,10-phenanthroline monohydrate (12 mol%), and carbon monoxide (90 psi) in DMF at 80 ^{o}C. 2-(2-Nitrophenyl)-2-cyclohexen-1-one was prepared *via* a Stille coupling of 2-iodo-2-cyclohexen-1-one and 2-(tri-n-butylstannyl)-1-nitrobenzene. Many functional groups and ring sizes were tolerated in these reactions.

This novel approach to carbazolones was successfully applied to the formal total syntheses of several naturally occurring carbazole alkaloids including murrayaquinone A, murrayafoline A, koenigine-quinone A, murrayanine, dimeric *O*-demethylmurrayafoline A, and (+)-aspidospermidine. These new syntheses are generally more efficient and higher yielding compared to the previously reported syntheses of these natural products.

In addition, reductive cyclizations of 2-(2-nitrophenyl)-2-cycloalkenones using 10% Pd/C and 1 atm of hydrogen gas in methanol at ambient temperature yielded carbazole derivatives in excellent yields. For example, reduction of 2-(2-nitrophenyl)-2-cyclohexen-1-one gave 1,2,3,4-tetrahydrocarbazole in 95% yield. Methyl-substitution on the cyclohexenone ring regioselectively produced methyl-substituted tetrahydrocarbazoles, however substitution on the benzene ring led to mixtures of carbazole products.

Acknowledgments

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Part I

Synthesis of Carbazolones *via* Palladium-Catalyzed *N*-Heteroannulations

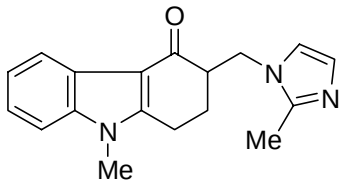
1. Introduction

Carbazole alkaloids have received considerable attention since their discovery in the 1960's and the realization of their pharmacological potential.[1] They exhibit a wide range of biological properties ranging from antibiotic to antitumor activity. Developing new synthetic methods toward the core carbazole structure in these alkaloids is of great interest to researchers.

1.1. Carbazolones

Carbazolones are carbazole derivatives that are interesting synthetic targets. Many carbazolones are biologically active. The synthetic drug ondansetron[2] shown in Figure 1 is a carbazolone that is a potent 5-HT_3 receptor antagonist used to prevent severe nausea often caused by chemotherapy and radiation treatments in cancer patients.

Figure 1

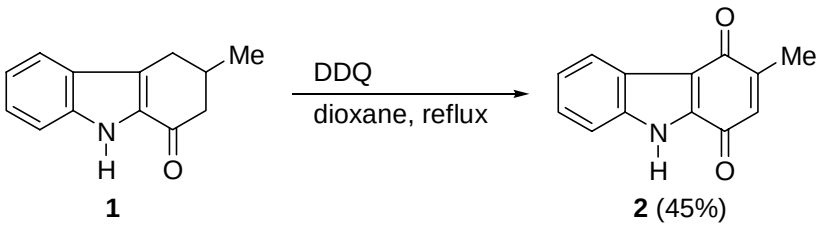


Ondansetron

Carbazolones are also of interest as synthetic precursors to naturally occurring carbazoles. A common method for preparing carbazolequinones involves the oxidation of

carbazolones. For example, carbazolone **1** was oxidized to the carbazole alkaloid murrayaquinone-A using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (Scheme 1).[3]

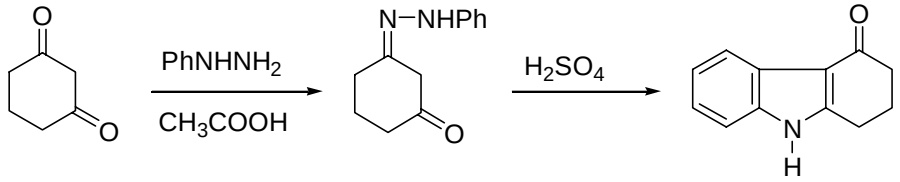
Scheme 1



1 **2** (45%)

A variety of methods have been utilized to obtain carbazolones. One of the most common methods used is the Fischer indole synthesis. 1,2-Dihydrocarbazol-4(3*H*)-one (**5**) was synthesized by the Fischer reaction of phenylhydrazine and 1,3-cyclohexanedione (Scheme 2).[4]

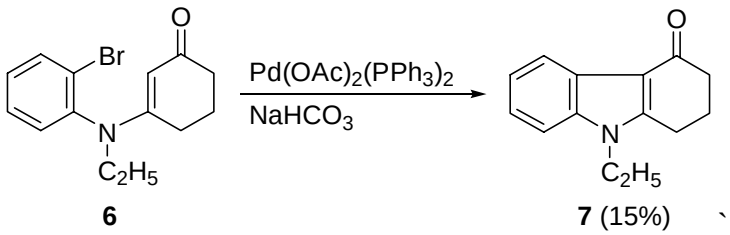
Scheme 2



3 **4** **5** (51%)

Palladium-catalyzed Heck-type reactions have also been used to produce carbazolones. The intramolecular catalytic cyclization of bromo enaminones such as **6** produced carbazolones in variable yields (Scheme 3).[5]

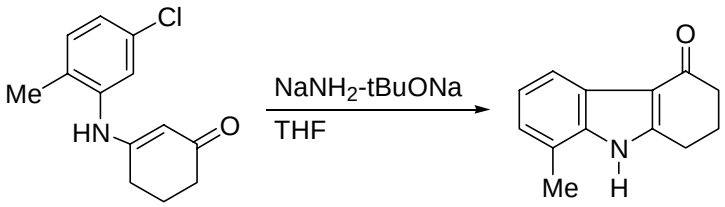
Scheme 3



6 **7** (15%)

Carbazolones have also been synthesized by the arynic condensation of enaminones in the presence of $NaNH_2$-tBuONa according to Scheme 4.[6]

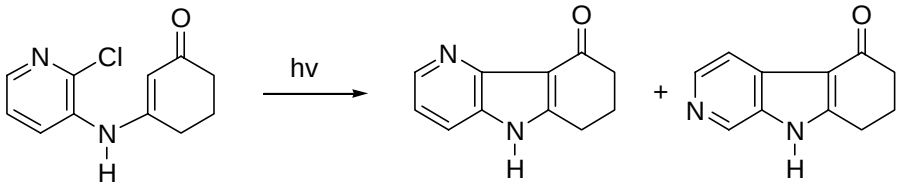
Scheme 4



8 **9**

In the search for new analogs of carbazole alkaloids with modified pharmacological activity azacarbazoles have been studied. One approach to azacarbazoles involves the photocyclization of *N*-(chloropyridinyl)enaminones (Scheme 5).[7]

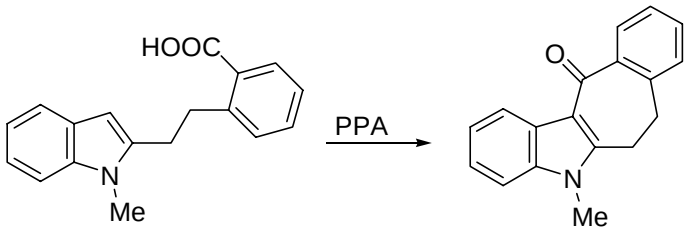
Scheme 5



10 **11** (33%) **12** (6%)

Benzo[5,6]cyclohepta[*b*]indol-6-one derivatives have been prepared by the intramolecular cyclization of acids such as **13** using a large excess of polyphosphoric acid (Scheme 6).[8] Derivatives of **14** are being studied for their antitumor potential.

Scheme 6

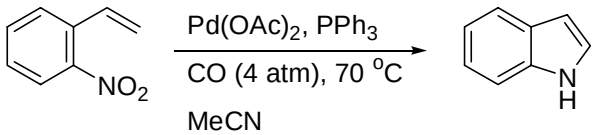


13 **14** (62%)

1.2. Reductive *N*-Heteroannulation Reactions

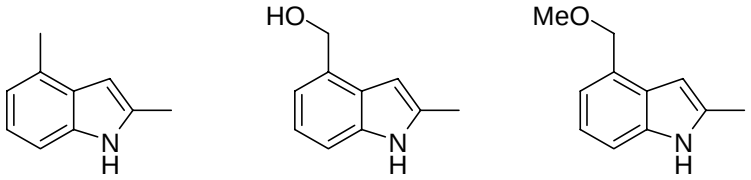
Recently, a new procedure for the synthesis of indoles was developed in our group.[9] This new procedure involves the palladium-catalyzed reductive *N*-heteroannulation reaction of 2-nitrostyrenes (Scheme 7). Three reagents were found to be crucial in this reaction: a palladium catalyst, a phosphine, and carbon monoxide. This reaction has proved to be useful for the synthesis of a number of indole products including several mushroom metabolites (Figure 2).[10]

Scheme 7



15 **16** (87%)

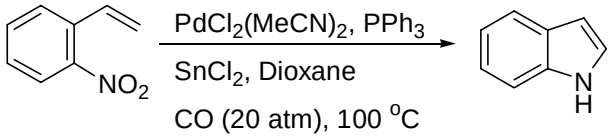
Figure 2



Mushroom Metabolites

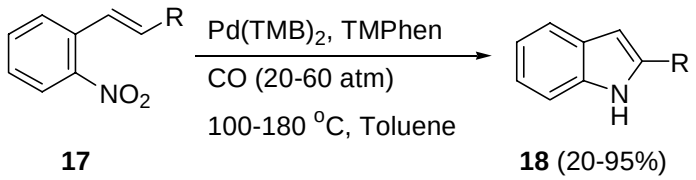
This type of reaction is not unknown in the literature. There are other reports of reductive carbonylations of nitroarenes with unsaturated groups in the ortho position leading to indoles. Watanabe *et al*[11] published a related procedure using a catalytic amount of $PdCl_2(MeCN)_2$ in the presence of triphenylphosphine, excess tin dichloride, and 20 atm of carbon monoxide (Scheme 8). Another very similar reaction was reported by Cenini *et al*[12] using $Pd(TMB)_2$/TMPhen (TMBH = 2,4,6-trimethylbenzoic acid; TMPhen = 3,4,7,8-tetramethyl-1,10-phenanthroline) as the catalytic system (Scheme 9). Many other kinds of heterocyclic compounds can be obtained from this type of reaction including amides, amines, oximes, ureas, carbamates, and isocyanates.[13]

Scheme 8



15 **16** (60%)

Scheme 9



17 **18** (20-95%)

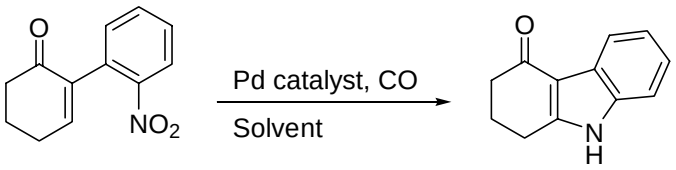
All these metal-catalyzed reductive cyclization reactions generally produce good yields of indoles. However, compared to the method developed in our group most of these methods employ rather harsh conditions. The reaction conditions developed in our group are much milder. Our reactions proceed at a much lower pressure of carbon monoxide, lower temperature, and do not require the addition of a Lewis acid such as tin dichloride.

Due to the inherent similarity between indoles and carbazoles, we decided to apply this new method to the synthesis of carbazole derivatives. The synthesis of several substituted carbazolones using this palladium-catalyzed reductive cyclization reaction is presented.

2. Results and Discussion

We envisioned that carbazolones could be prepared *via* the reductive cyclization of 2-(2-nitrophenyl)-2-cyclohexenones as shown in Scheme 10. First, we needed to develop a method to synthesize a variety of substituted 2-(2-nitrophenyl)-2-cycloalkenones in order to test the scope and limitations of our reductive cyclization.

Scheme 10



We decided to make our cyclization precursors *via* a Stille coupling reaction between cycloalkenones and nitrobenzenes. Johnson *et al*[14] have reported the Stille couplings of 2-iodocycloalkenones with aryl stannanes using 5 mol% $PdCl_2(PhCN)_2$, 10 mol% Ph_3As, and 10 mol% CuI in NMP (*N*-methylpyrrolidinone) to produce 2-phenyl-2-cyclohexenones in good yields. We adapted these conditions to our Stille reactions with good results (Scheme 11).

Table 1 shows the results of our Stille couplings to produce a variety of substituted 2-(2-nitrophenyl)-2-cycloalkenones. Some modifications of the reaction conditions were required for the synthesis of compounds **37** and **40**. Best yields of **37** were obtained when Ph_3As was replaced with dppf (1,1'-bis(diphenylphosphino)ferrocene). The yield of **40** was improved slighty by degassing the reaction mixture. Compound **38** was prepared *via* an alternative procedure using $PdCl_2(PPh_3)_2$ in DMF.

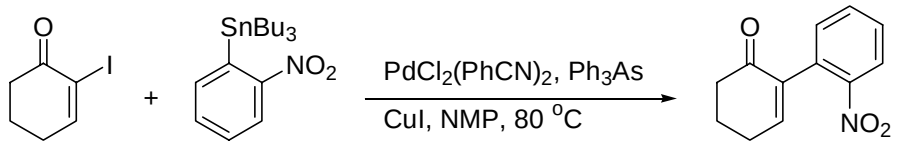
Most of the Stille couplings proceeded in good yields. Slightly lower yields were obtained from aryl bromides as compared to aryl iodides. The lower yields of **38** and **40** are probably due to steric factors. In comparing entries 1 and 6 we see very little difference in yield resulting from reversing the polarity of substrates in the reaction. The use of an aryl stannane and vinyl iodide or a vinyl stannane and an aryl iodide both give the Stille product in good yield.

Products of the Stille reactions were easily discernable from starting materials by ^1H NMR. For example, the C-H proton in iodocyclohexenone **19** shows up as a triplet at 7.76 ppm, while the same proton in coupling product **32** is located upfield at 6.98 ppm.

Some side-products complicating the purification of the desired compounds were identified in the Stille reactions (Figure 3). In some cases the homocoupling product **42** or **43** was present in significant amounts. Butyl group transfer also occurred in the reaction of **30** producing methyl 2-butyl-3-nitrobenzoate (**44**). Homocoupling of stannanes is a common side

reaction in Stille couplings.[15] Although the transfer of alkyl groups from the stannane is generally much slower than the transfer of aryl or vinyl groups, the transfer of alkyl groups is also sometimes observed.[16]

Scheme 11



76%

Table 1[a]

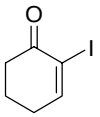
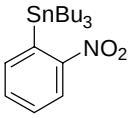
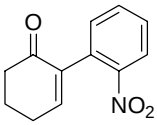
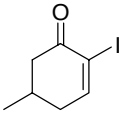
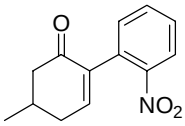
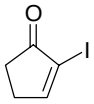
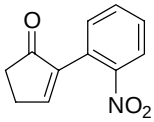
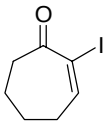
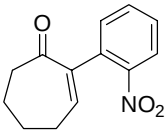
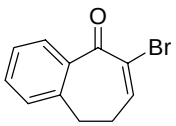
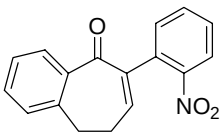
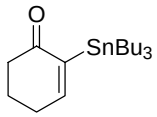
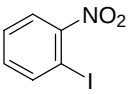
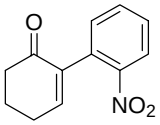
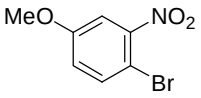
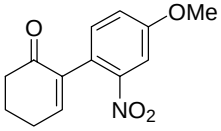
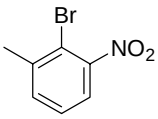
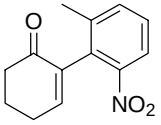
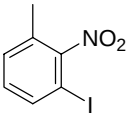
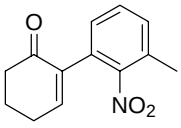
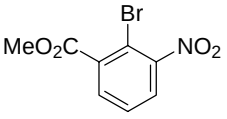
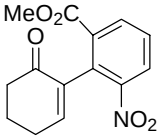
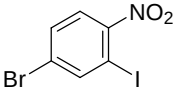
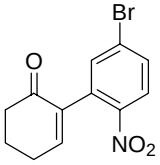
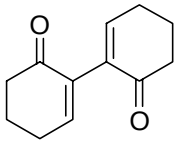
Entry	Cycloalkenone	Nitrobenzene	Stille Product
1	 **19**	 **25**	 **32** (76%)
2	 **20**	"	 **33** (74%)
3	 **21**	"	 **34** (65%)
4	 **22**	"	 **35** (68%)
5	 **23**	"	 **36** (46%)

Table 1 continued

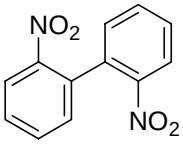
Entry	Cycloalkenone	Nitrobenzene	Stille Product
6	 **24**	 **26**	 **32** (71%)
7	"	 **27**	 **37** (67%)[b]
8	"	 **28**	 **38** (31%)[c]
9	"	 **29**	 **39** (62%)
10	"	 **30**	 **40** (44%)[d]
11	"	 **31**	 **41** (56%)

a) General conditions: 1.2 eq. Sn reagent, 5 mol% $PdCl_2(PhCN)_2$, 10 mol% Ph_3As, 10 mol% CuI, NMP, 80 ^oC. For more exact details see: Experimental Section. b) Ph_3As was replaced with dppf. c) Conditions used: $PdCl_2(PPh_3)_2$, DMF, 110 ^oC. d) Reaction mixture was degassed.

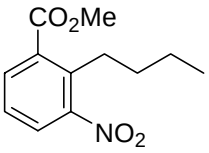
Figure 3



42



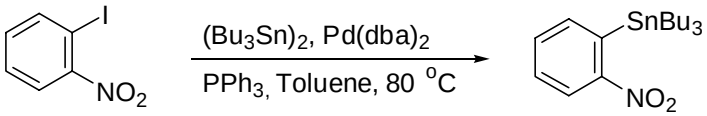
43



44

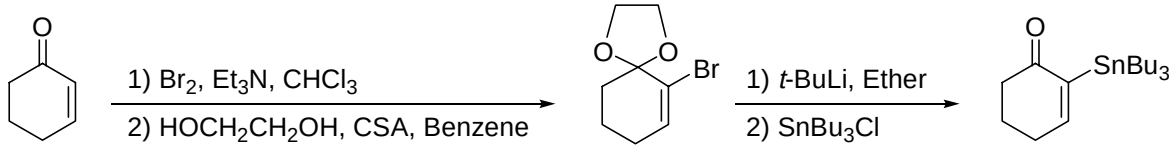
Two different organostannanes were prepared for the Stille reactions. Aryl stannane **25** was prepared from 1-iodo-2-nitrobenzene (**26**) according to Kosugi's procedure[17] (Scheme 12) using hexabutylditin, *in situ* formed $Pd(PPh_3)_4$, and toluene. Vinyl stannane **24** was prepared according to Scheme 13. The metal-halogen exchange reaction of **46** with *t*-BuLi, followed by addition of tributyltinchloride and deprotection of the ketone with acid produced the stannane **24** in 83% yield.

Scheme 12



26 **25** (80%)

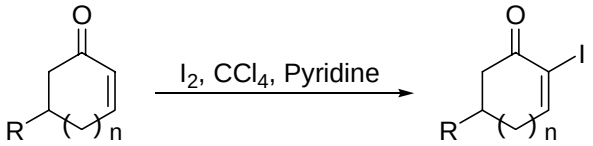
Scheme 13



45 **46** (89%) **24** (83%)

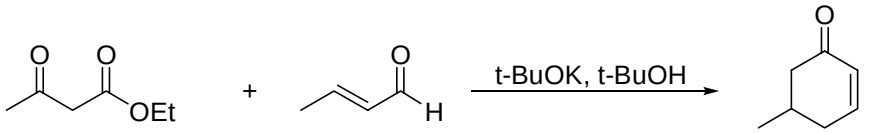
The literature procedure was followed for preparing 2-iodocycloalkenones **19** and **21**, and this method was utilized for the preparation of the previously unknown compounds **20** and **22** (Scheme 14).[18] Most of the cycloalkenone starting materials were commercially available. 5-Methyl-2-cyclohexen-1-one (**47**) was prepared according to literature procedure[19] (Scheme 15), although in our hands this reaction failed to produce the reported yield of 78% for this compound.

Scheme 14



19 (81%), R = H, n = 1
20 (85%), R = CH_3, n = 1
21 (42%), R = H, n = 0
22 (69%), R = H, n = 2

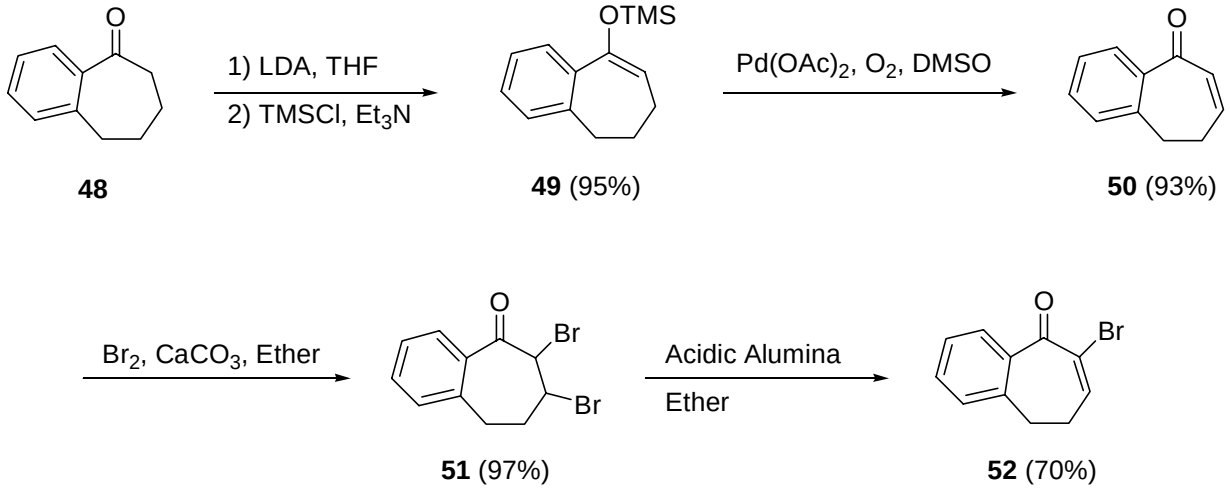
Scheme 15



47 (20%)

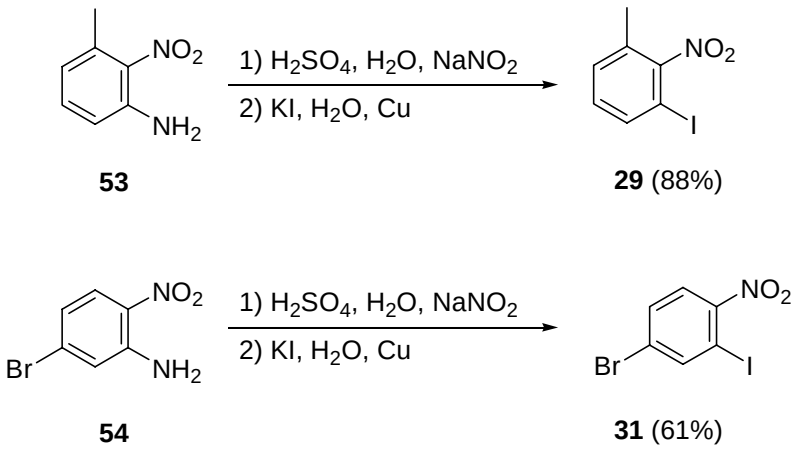
Bromobenzocycloheptenone **52** was prepared from 1-benzosuberone (**48**) according to Scheme 16. The silyl enol ether **49** was converted to benzocycloheptenone **50** by a palladium-catalyzed dehydrosilylation reaction.[20] Compound **52** was then prepared *via* a literature procedure consisting of a two step bromination-dehydrobromination sequence.[21]

Scheme 16



Nitrobenzenes **26** and **28** were commercially available. Compounds **27** and **30** were previously synthesized in our laboratory according to literature procedures.[9, 10] Compounds **29** and **31** were prepared by the Sandmeyer type reactions of their corresponding anilines (Scheme 17).

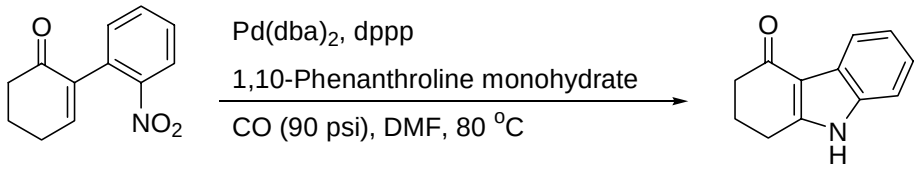
Scheme 17



With the preparation of several substituted 2-(2-nitrophenyl)-2-cycloalkenones we now had sufficient substrates ready to test the scope of the reductive cyclization reaction. Our first attempted *N*-heteroannulation of **32** using palladium diacetate (6 mol%), triphenylphosphine (24 mol%), and carbon monoxide (4 atm) in acetonitrile at 70 ^{o}C surprisingly gave only starting material. Since it is known that palladium phenanthroline complexes are particularly active catalysts for the reductive carbonylation of nitrobenzenes forming isocyanates,[22] we chose to modify our cyclization conditions to those shown in Scheme 18. The expected 1,2-dihydro-4(3*H*)-carbazolone (**5**) was obtained in good isolated yield using $Pd(dba)_2$ (6 mol%), dppp (1,3-bis(diphenylphosphino)propane) (6 mol%), 1,10-phenanthroline monohydrate (12 mol%), and carbon monoxide (90 psi) in DMF at 80 ^{o}C.

Next we tested these promising reaction conditions on the substrates shown in Table 1. Results of these reductive cyclizations are summarized in Table 2. All reactions proceeded smoothly affording excellent yields of products. Five-membered to seven-membered cycloalkenones all gave good results. Substitution on the cycloalkenone ring was also well tolerated in the reaction. The presence of electron donating or withdrawing groups at various positions on the aryl ring also presented no problems with the *N*-heteroannulation.

Scheme 18



32 **5** (74%)

Most of the reductive cyclizations were complete in 1-3 days. However, substrate **41** required an extended period of 8 days to go to completion. The yield of the bromocarbazolone **63** also was slightly lower than the other cyclizations. 4-Bromo substitution has previously been problematic in this type of reaction. The attempted cyclization of the related substrate, bromonitrostyrene **64,** performed previously in our laboratory yielded only starting material (Scheme 19).[9]

Table 2[a]

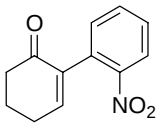
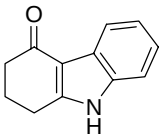
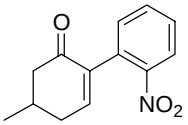
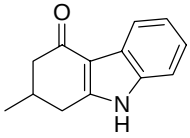
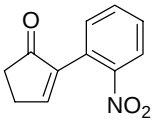
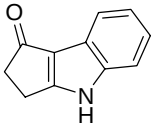
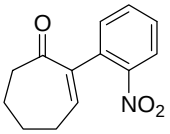
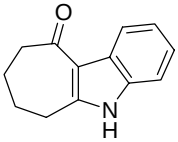
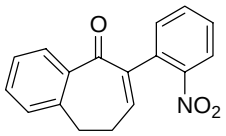
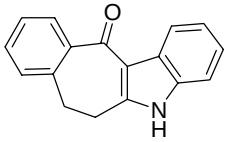
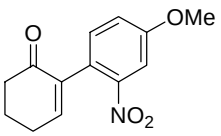
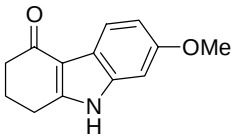
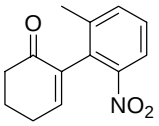
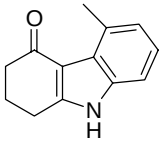
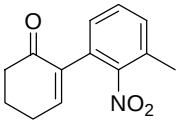
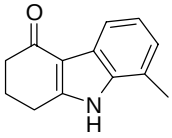
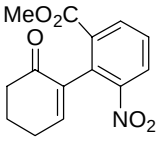
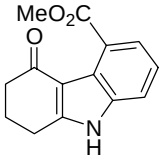
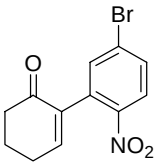
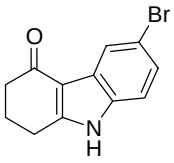
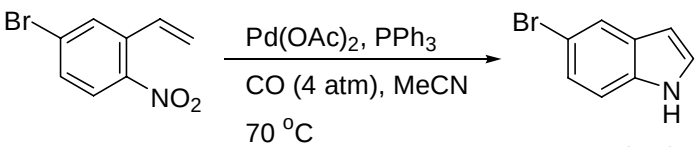
Stille Product	Carbazolone
 **32**	 **5** (74%)
 **33**	 **55** (89%)
 **34**	 **56** (86%)
 **35**	 **57** (66%)
 **36**	 **58** (86%)

Table 2 continued

Stille Product	Carbazolone
 **37**	 **59** (89%)
 **38**	 **60** (79%)
 **39**	 **61** (75%)
 **40**	 **62** (75%)
 **41**	 **63** (52%)

a) General conditions: $Pd(dba)_2$ (6 mol%), dppp (6 mol%), 1,10-Phenanthroline monohydrate (12 mol%), CO (90 psi), DMF, 80 ^{o}C. For more exact details see: Experimental Section.

Scheme 19



64 **65** (0%)

The formation of **58** is of substantial synthetic interest. Benzocycloheptaindole derivatives are being studied for their antitumor potential.[8] This reaction could be useful for the preparation of such compounds.

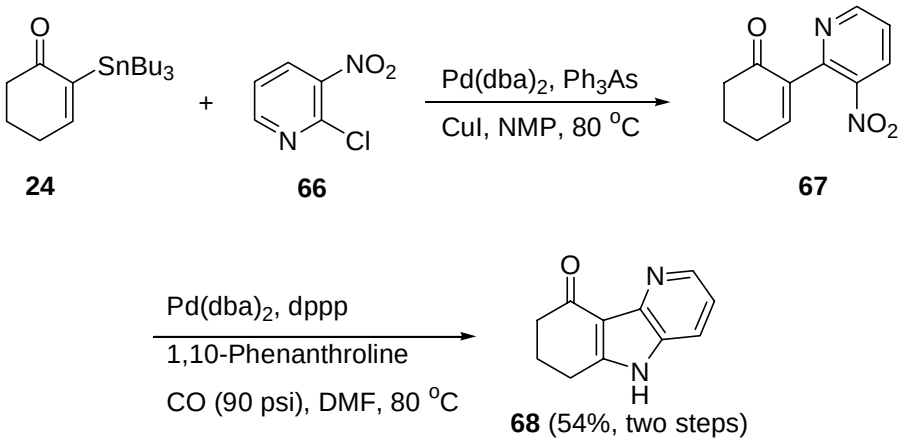
The cyclization reactions are typically monitored by thin layer chromatography. Progress of the reactions can also be determined by ^{1}H NMR. Cyclization products are distinguishable from starting materials by certain NMR characteristics including the presence of a broad N-H peak between 8 and 11 ppm and the disappearance of the triplet C-H signal of the starting material. For example, carbazolone **5** has a distinct N-H signal at 8.55 ppm and the C-H triplet at 6.98 of the starting material **32** has disappeared.

New synthetic analogs of carbazoles are currently being investigated for their modified biological activity. For this reason we decided to apply our reductive cyclization reaction toward the synthesis of an azacarbazole (Scheme 20). We constructed the cyclization precursor **67** *via* a Stille coupling reaction of 2-chloro-3-nitropyridine (**66)** and stannane **24**. The Stille product **67** could not be isolated in any significant amount, although the crude NMR indicated that the reaction was working well. We were convinced that the isolation problem was due to extensive decomposition upon purification by silica gel chromatography. We were unable to isolated the product in any yield greater that 33% after column chromatography. Therefore, we opted to carry on the crude Stille product to the cyclization reaction. This proved to be a good decision providing the azacarbazole **68** in 54% yield over two steps.

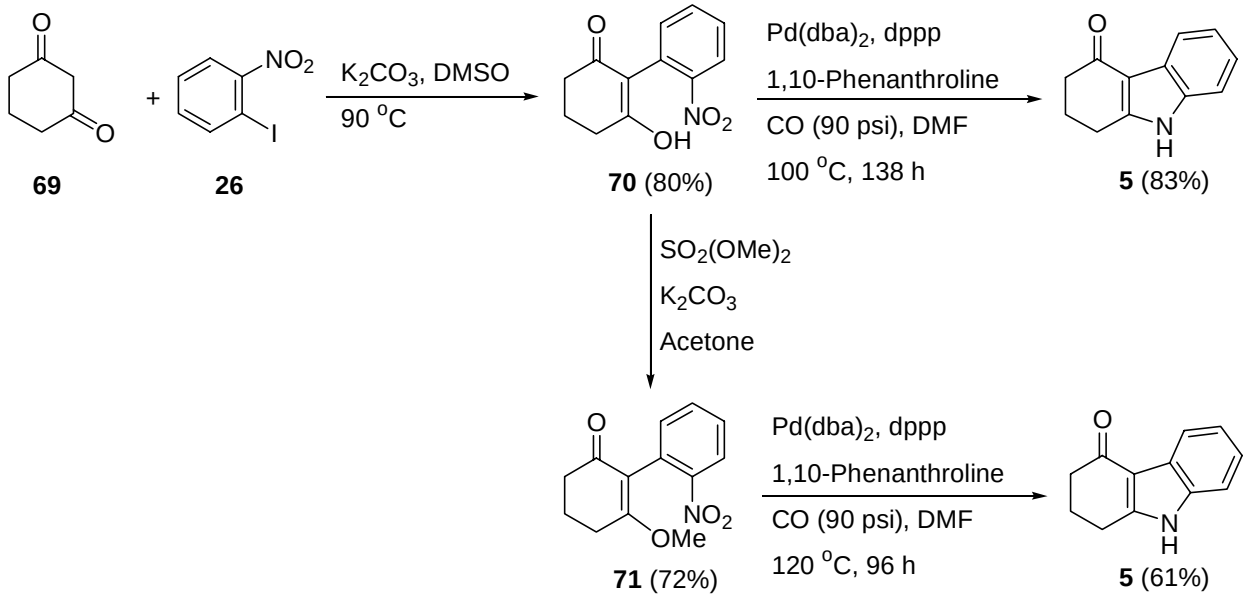
In a search for alternative substrates for the cyclization reaction we discovered an additional route to 1,2-dihydro-4(3*H*)-carbazolone (**5**). 2-(2-Nitrophenyl)-1,3-cyclohexanedione (**70**) and 3-methoxy-2-(2-nitrophenyl)-2-cyclohexenone (**71**), derived from 1,3-cyclohexanedione[23] (**69**), both gave the carbazolone product **5** in good yields, although reaction

times were much longer compared to the reductive cyclization of **32** even at elevated temperatures (Scheme 21).

Scheme 20



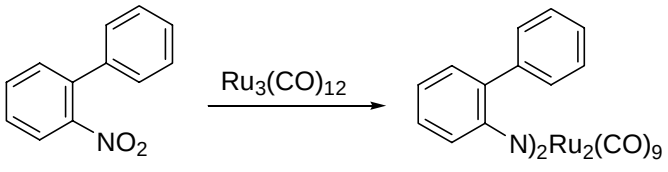
Scheme 21



At this time the mechanism for the reductive cyclization reaction remains unknown. It is very unlikely that the reaction proceeds by initial reduction of the nitro group to an amine followed by an amino-palladation β-hydride elimination sequence as in the Hegedus indole synthesis.[24] This type of reaction requires a palladium (II) catalyst which has to be regenerated by an added oxidant. No oxidant is present in these cyclization reactions. There are also mechanistic studies indicating that the formation of aniline is insignificant in the formation of indoles.[25] Additional evidence against the role of aniline in the carbazolone reactions is that the direct reduction of the nitro group in 2-(2-nitrophenyl)-2-cyclohexenones by palladium-catalyzed hydrogenation does not produce carbazolones. The results of this study are presented in part III.

Watanabe *et al* have proposed through some mechanistic studies that the reaction proceeds through the formation of an active transition metal nitrene intermediate followed by an insertion reaction.[26, 11] Although no metal-bound nitrene intermediates have been isolated in the indole syntheses, the reaction of 2-nitrobiphenyl (**72**) using $Ru_3(CO)_{13}$ produced the ruthenium-bound nitrene **73** (Scheme 22).[27] The structure of **73** was determined by X-ray crystallography. When treated with carbon monoxide **73** gives carbazole as well as 2-aminobiphenyl. This evidence supports the theory that a nitrene intermediate is involved in the synthesis of indoles.

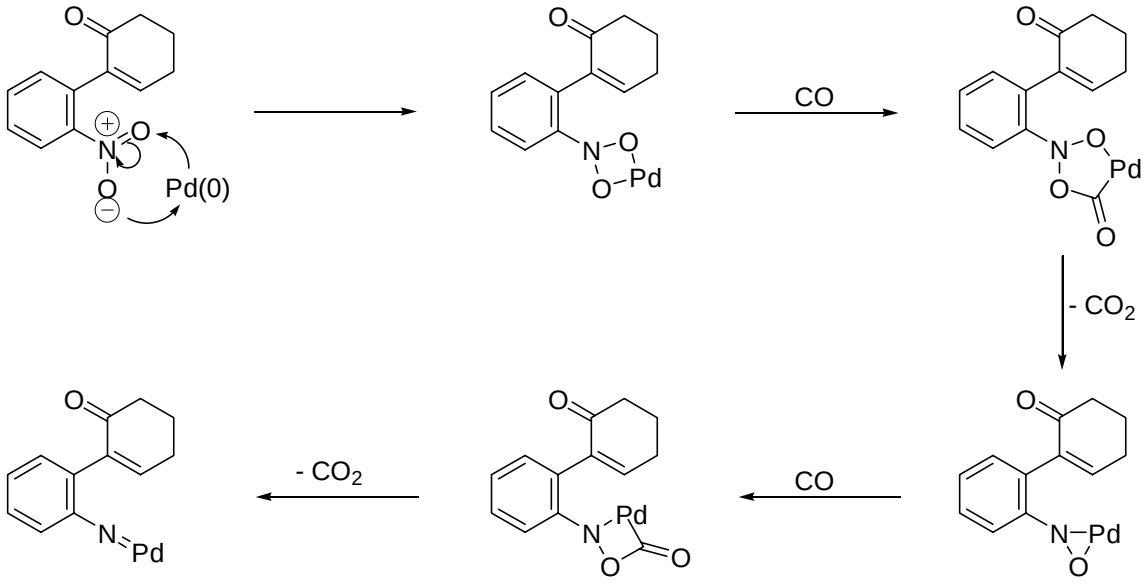
Scheme 22



72 **73**

One possible mechanism to a nitrenoid intermediate by a deoxygenative sequence is presented in Scheme 23. Palladium addition to the nitro group followed by carbon monoxide insertion and elimination of carbon dioxide could give a palladium-nitroso intermediate. Another insertion by carbon monoxide and subsequent elimination of carbon dioxide gives the palladium-bound nitrene. Insertion into the C-H bond of the cyclohexenone by the nitrene can follow to give the carbazolone product.

Scheme 23



3. Conclusions

We have successfully developed a mild and efficient method of preparing functionalized carbazolones. This novel route consists of two sequential palladium-catalyzed reactions, an intermolecular Stille coupling followed by a reductive *N*-heterocyclization. Many functional

groups and ring sizes are well tolerated in these reactions. This novel procedure has been applied to the synthesis of naturally occurring carbazole alkaloids presented in the next section.

Part II

Formal Total Syntheses of Carbazole Alkaloids

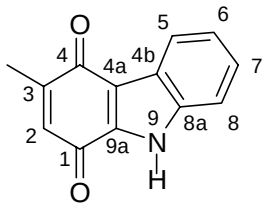
1. Introduction

Carbazole alkaloids are of great interest due to their numerous biological activities. For example, these natural products show antitumor, antibiotic, and antifungal properties, as well as having an inhibitory effect on mitosis and activity against malaria.[28] Many carbazole alkaloids have been isolated from plants belonging to the Rutaceae family. Most of these compounds have a one-carbon substituent in the 3-position and an oxygen functionality in the 1- or 2- position. Dimeric and quinoid structures are also known in this group. We have been interested in a number of these natural products, many of which are from plants of the genus *Murraya*. These plants consist of small trees and shrubs endemic to Southern Asia that have been used for years in folk medicine for analgesics and treatment of ailments such as eczema and rheumatism.[29]

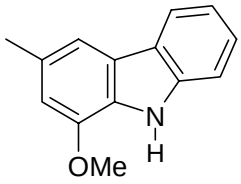
Figure 4 shows a few of the carbazole alkaloids that have been of synthetic interest to us. Murrayaquinone A, [30] murrayafoline A,[30] and dimeric *O*-demethylmurrayafoline A[31] are examples of alkaloids isolated from *Murraya euchrestifolia* Hayata. Murrayaquinone A is known to induce myocardial contraction. Dimeric *O*-demethylmurrayafoline A exhibits antiplasmodial activity against *P. falciparum in vitro*. Murrayanine[32] and koenigine-quinone A[33] were both isolated from *Murraya koenigii* Spreng (Figure 5).[34] *Murraya koenigii* Spreng is commonly known as the Indian curry tree. The leaves which have a distinct odor of anise are widely used as a flavoring in Indian curries. (+)-Aspidospermidine[35] has been found in plants of the *Aspidosperma* genus. While aspidospermidine in itself doesn't possess any significant

biological properties, alkaloids with similar ring structures are known to have antitumor activity. Therefore, it can be considered a model for the design of new synthetic approaches toward these more functionalized compounds.

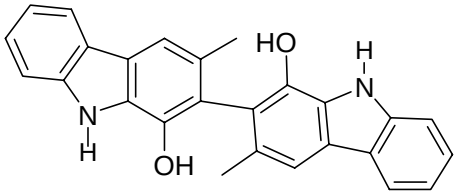
Figure 4



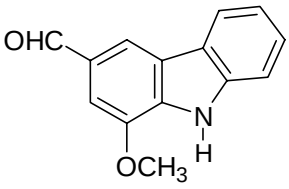
Murrayaquinone A



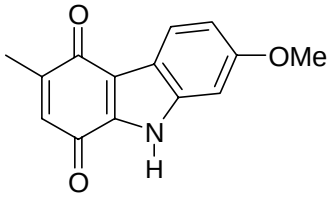
Murrayafoline A



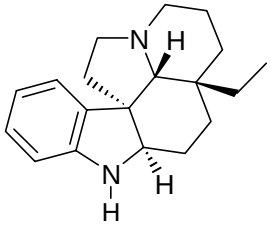
Dimeric *O*-demethylmurrayafoline A



Murrayanine



Koenigine-quinone A



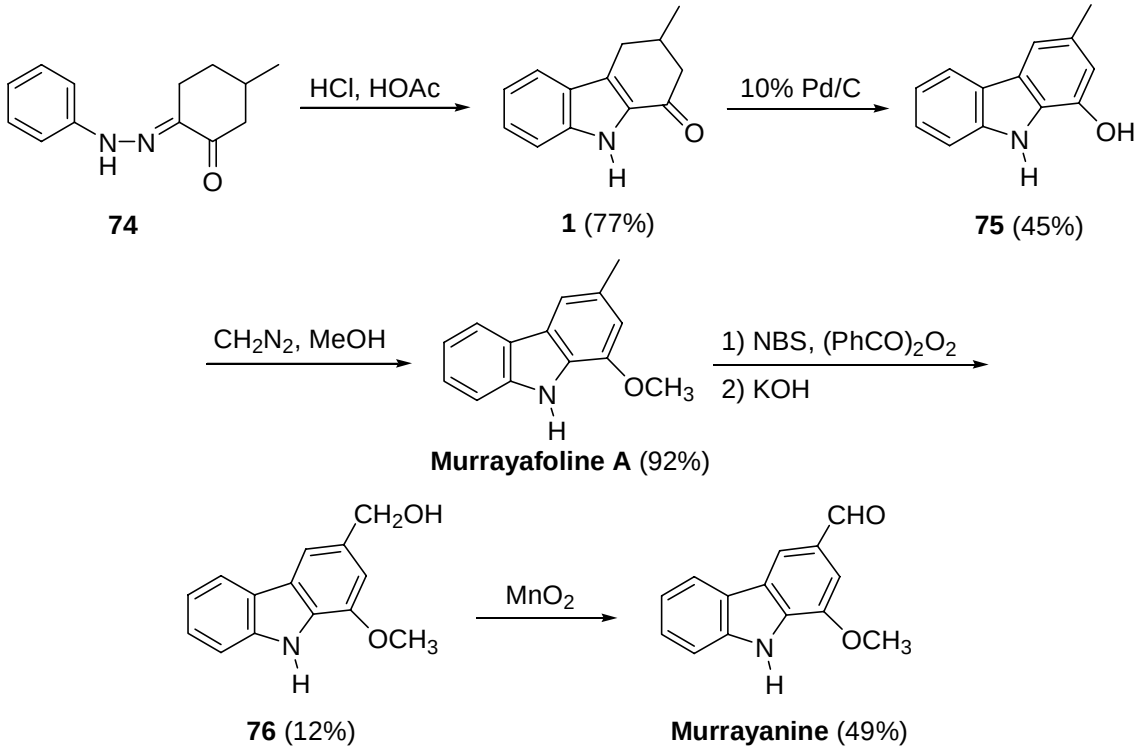
(+) - Aspidospermidine

Figure 5

***Murraya koenigii* Spreng**

There have been several syntheses of these carbazole alkaloids presented in the literature. One common approach to carbazoles is *via* the Fischer method. Murrayanine and murrayafoline A were prepared in this manner (Scheme 24).[32] The Fischer indole synthesis was used to prepare carbazolone **1** which was converted to carbazole **75** via dehydrogenation. Methylation produced murrayafoline A, followed by bromination and then hydrolysis with KOH to compound **76**. Manganese dioxide oxidation of **76** produced the product, murrayanine.

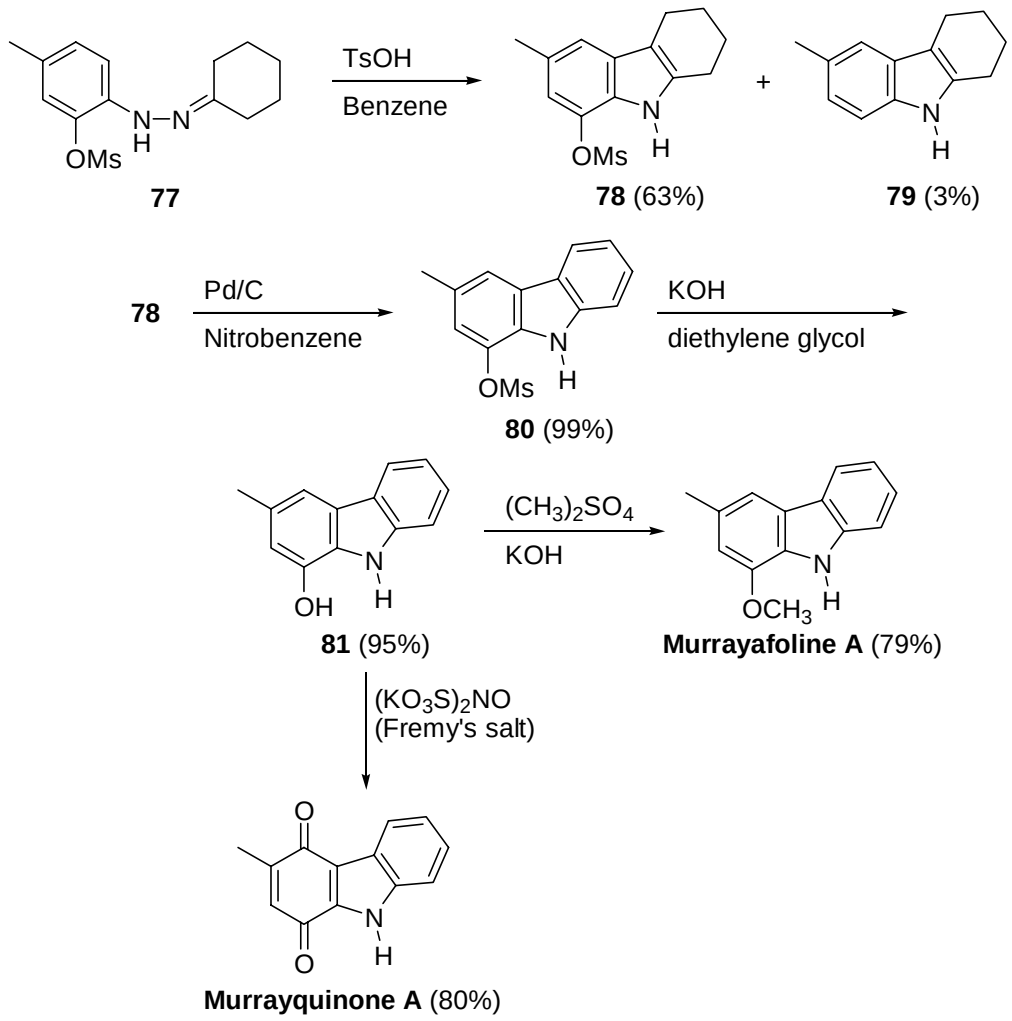
Scheme 24



Murrayafoline A and murrayaquinone A have also been synthesized by a similar approach (Scheme 25).[36] The key carbazole intermediate **78** along with a small amount of **79** was also produced by the Fischer method. Dehydrogenation of tetrahydrocarbazole **78** to the

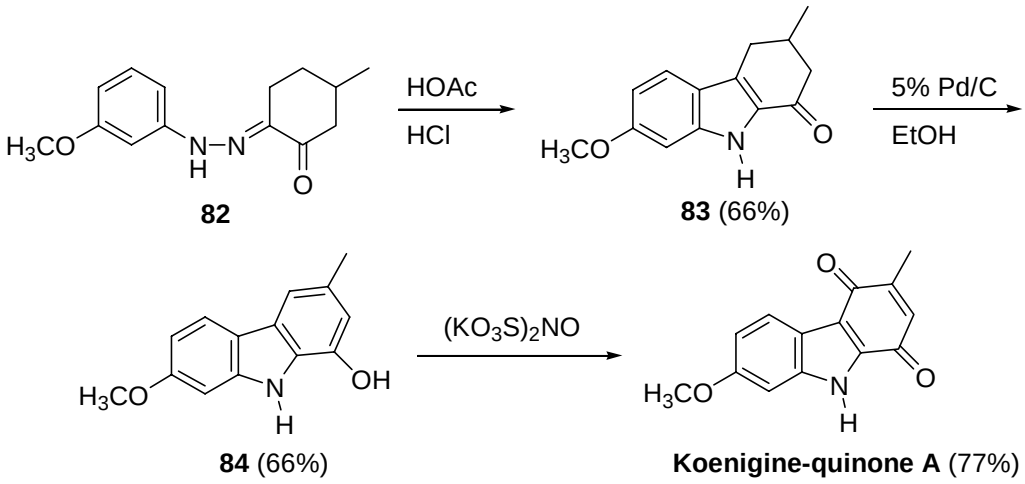
carbazole **80**, followed by hydrolysis of the mesyl group gave **81**. Compound **81** could then be converted either to murrayafoline A by methylation, or to murrayaquinone A by oxidation.

Scheme 25

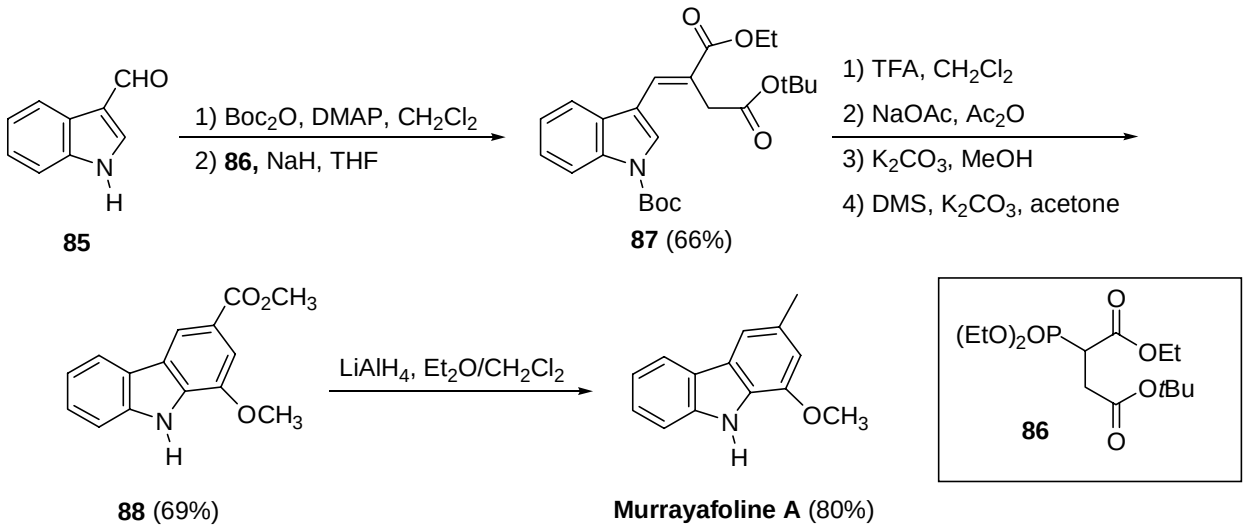


Koenigine-quinone A also was synthesized via a Fischer indole synthesis-dehydrogenation-oxidation sequence (Scheme 26).[33]

Scheme 26



Scheme 27

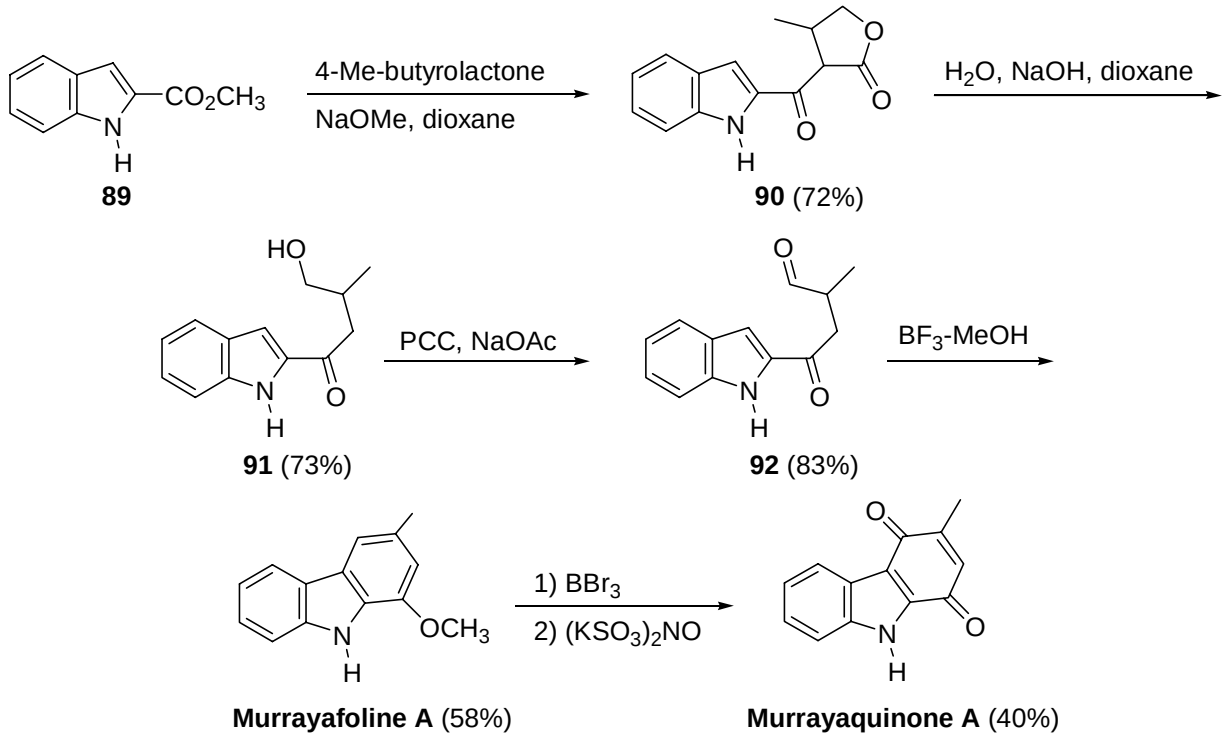


Another synthetic method to the carbazole, murrayafoline-A, is outlined in Scheme 27.[28] Bringmann *et al* constructed the carbazole skeleton starting with the indole **85**. Boc-protection of the indole nitrogen and olefination with phosphonate **86** using the Horner-Emmons method gave **87**. Cyclization with sodium acetate in acetic anhydride followed by methanolysis and then

O-methylation gave **88**. Carbazole **88** was converted to murrayafoline A by lithium aluminum hydride reduction.

Moody *et al* have developed a method toward 1-oxygenated carbazoles starting from indole-2-carboxylates (Scheme 28).[37] Murrayafoline A was formed from indole-2-carboxylate **89** by condensation with 4-methylbutyrolactone to give lactone **90**, followed by hydrolysis and decarboxylation to alcohol **91**, and then oxidation to aldehyde **92**. Aldehyde **92** cyclized to murrayafoline A upon treatment with boron trifluoride-methanol. Murrayafoline A was converted to murrayaquinone A *via* a two step demethylation-oxidation sequence.

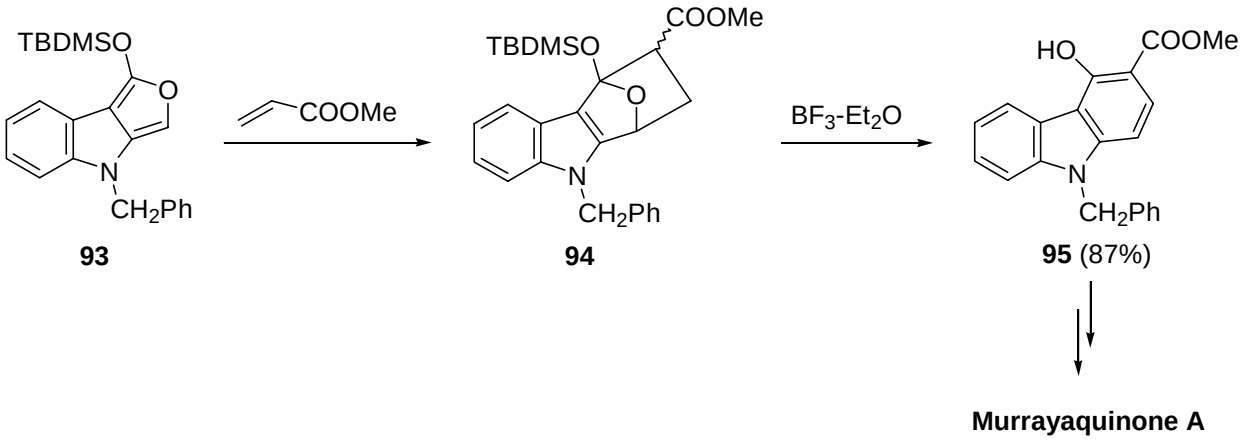
Scheme 28



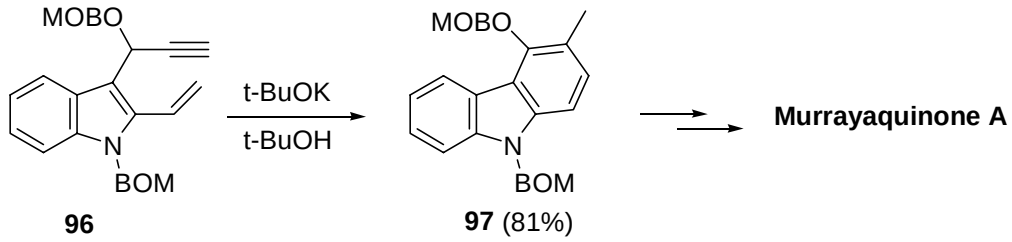
Some other synthetic methods to key intermediates of murrayaquinone A include the novel Diels-Alder approach by Miki *et al*[38] (Scheme 29), the thermal electrocyclization reactions

by Hibino and coworkers[39] (Scheme 30), and the annulations of bromo-1,4-benzoquinones and enaminones presented by Murphy *et al*[40] (Scheme 31).

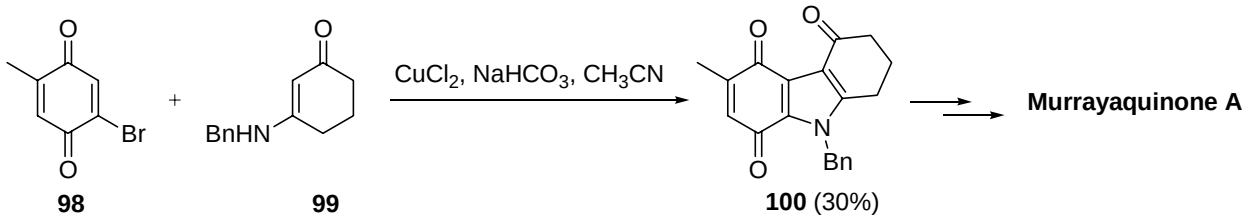
Scheme 29



Scheme 30

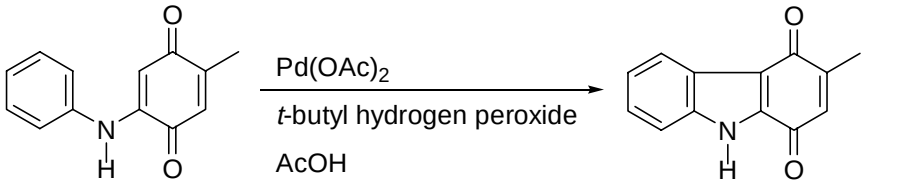


Scheme 31



Åkermark and coworkers[41] have also reported the palladium-catalyzed oxidative cyclization of 2-arylamino-1,4-quinones to yield several carbazole alkaloids including murrayaquinone A (Scheme 32).

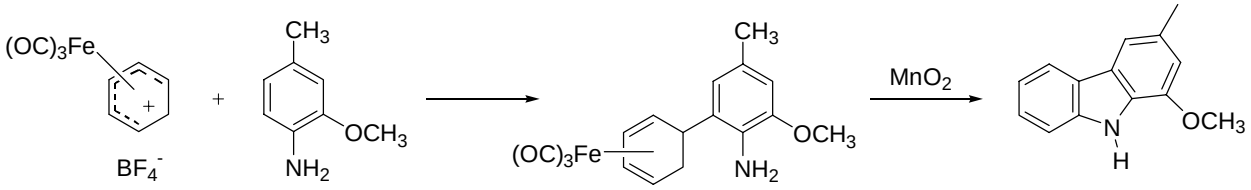
Scheme 32



101 **Murrayaquinone A** (65%)

Another metal-mediated reaction toward the synthesis of carbazoles was developed by Knölker and coworkers[42] (Scheme 33). They use an electrophilic aromatic substitution such as that of aniline **103** with a cyclohexadienyltricarbonyliron cation as the key step in the synthesis of several carbazoles.

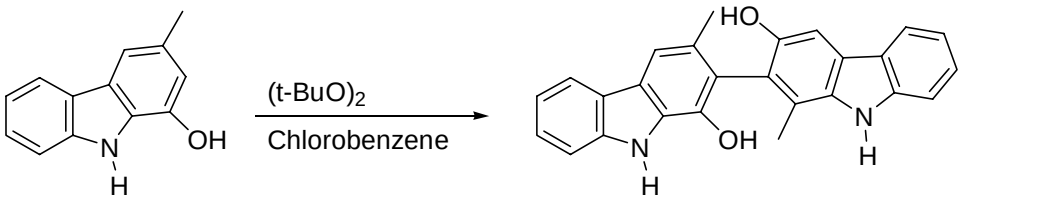
Scheme 33



102 **103** **104** **Murrayafoline A**

Dimeric alkaloids such as dimeric *O*-demethylmurrayafoline A have been produced *via* the oxidative couplings of carbazole monomers (Scheme 34).[43]

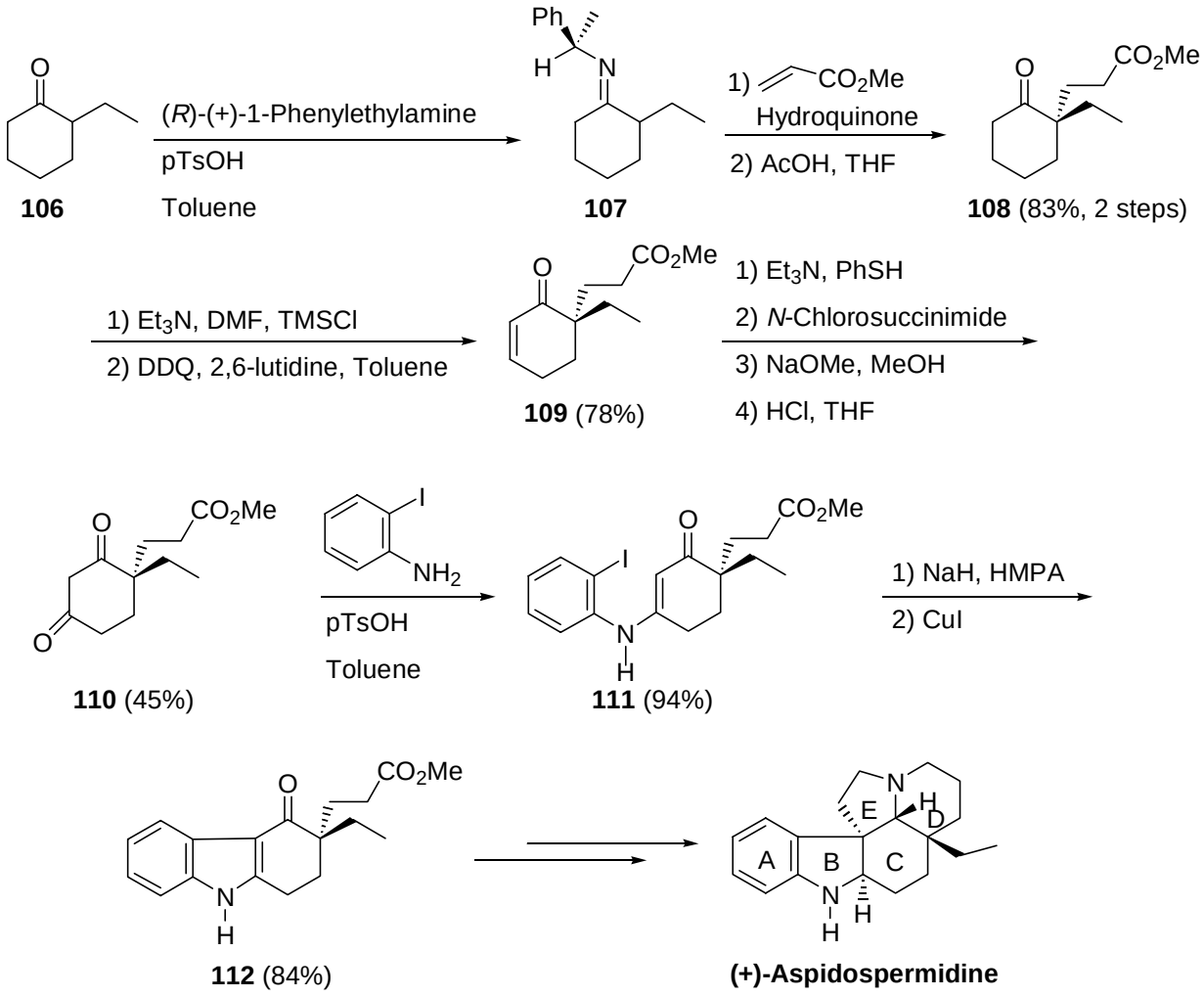
Scheme 34



105

Dimeric *O*-demethylmurrayafoline A (87%)

Scheme 35



106

107

108 (83%, 2 steps)

109 (78%)

110 (45%)

111 (94%)

112 (84%)

(+)-Aspidospermidine

The [ABC]-type subunit in (+)-aspidospermidine has been constructed using a copper(I)iodide-promoted arylation originally reported by Suzuki[44] in the synthesis by Desmaele and d'Angelo (Scheme 35).[35] The critical stereochemistry at the CD ring junction was set by the asymmetric Michael addition of chiral imine **107** to methyl acrylate. The *ee* obtained in this reaction was only 86%, but the optical purity of **108** could be efficiently upgraded through semicarbazone derivatization and crystallization. The synthesis of dione **110** was carried out in several steps from **108**. The preparation of intermediate **112** was achieved by condensation of **110** with 2-iodoaniline, followed by cyclization of the enaminone **111**. This synthesis of (+)-aspidospermidine was completed in a linear sequence of 22 steps from 2-ethylcyclohexanone with a 2.7% overall yield.

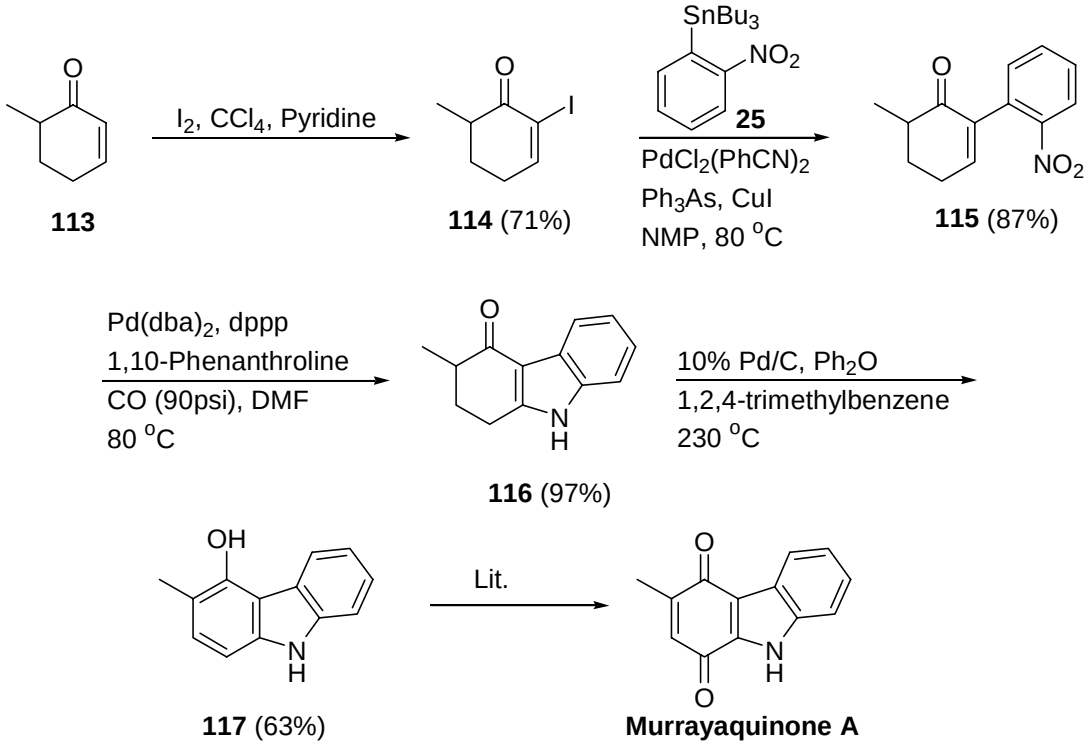
While there are many methods for preparing carbazoles, these methods are not without limitations. Some of the traditional methods lack regioselectivity, and the conditions employed are too harsh for some sensitive functional groups. Another limitation is the availability of starting materials for these transformations. Upon developing our method for the synthesis of carbazolones presented in the previous section we decided to apply our approach to the synthesis of natural products. Regioselectivity is not a problem in our method, and a number of functional groups are tolerated in these reactions. The availability of starting materials has also not been a difficulty. The formal total syntheses of several naturally occurring carbazole alkaloids is presented.

2. Results and Discussion

2.1. Formal Total Synthesis of Murrayaquinone A

Carbazolequinones have been efficiently synthesized *via* the oxidation of hydroxycarbazole precursors as previously described. It is known in the literature[38,45] that 3-methyl-4-hydroxycarbazole can be oxidized to murrayaquinone A using Fremy's salt ($(KO_3S)_2NO$) in excellent yield (83%). Therefore, we decided that a potentially useful route to the alkaloid would be through carbazolone **116** (Scheme 36). Dehydrogenation of **116** would lead to hydroxycarbazole **117**, thus completing the formal total synthesis of murrayaquinone A.

Scheme 36



Carbazolone **116** was prepared according to our method previously described, a Stille coupling followed by a *N*-heteroannulation reaction. 2-Iodo-6-methyl-cyclohexen-1-one (**114**)

was prepared from cyclohexenone **113** in 71% yield by the iodination method previously described in Scheme 14. The Stille reaction of **114** and stannane **25** in the presence of $PdCl_2(PhCN)_2$, Ph_3As, and CuI in NMP at 80 ^oC gave **115** in an excellent yield of 87%. The reductive cyclization of **115** also proceeded in an excellent yield (97%) of carbazolone **116**. The dehydrogenation reaction of carbazolone **116** using 10% Pd/C in a mixture of diphenyl ether and 1,2,4-trimethylbenzene at 230 ^oC gave hydroxycarbazole **117**. It was discovered that the addition of a small amount of 1,2,4-trimethylbenzene was critical for the dehydrogenation to occur.[31]

Our synthesis of the murrayaquinone A precursor **116** is much more efficient and higher yielding than the synthesis by Miki *et al*.[38] Their synthesis took nine steps from dimethyl indole-2,3-dicarboxylate with an overall yield less than 16%. Our synthesis was completed in only four steps from 6-methyl-2-cyclohexen-1-one with an overall yield of 38%.

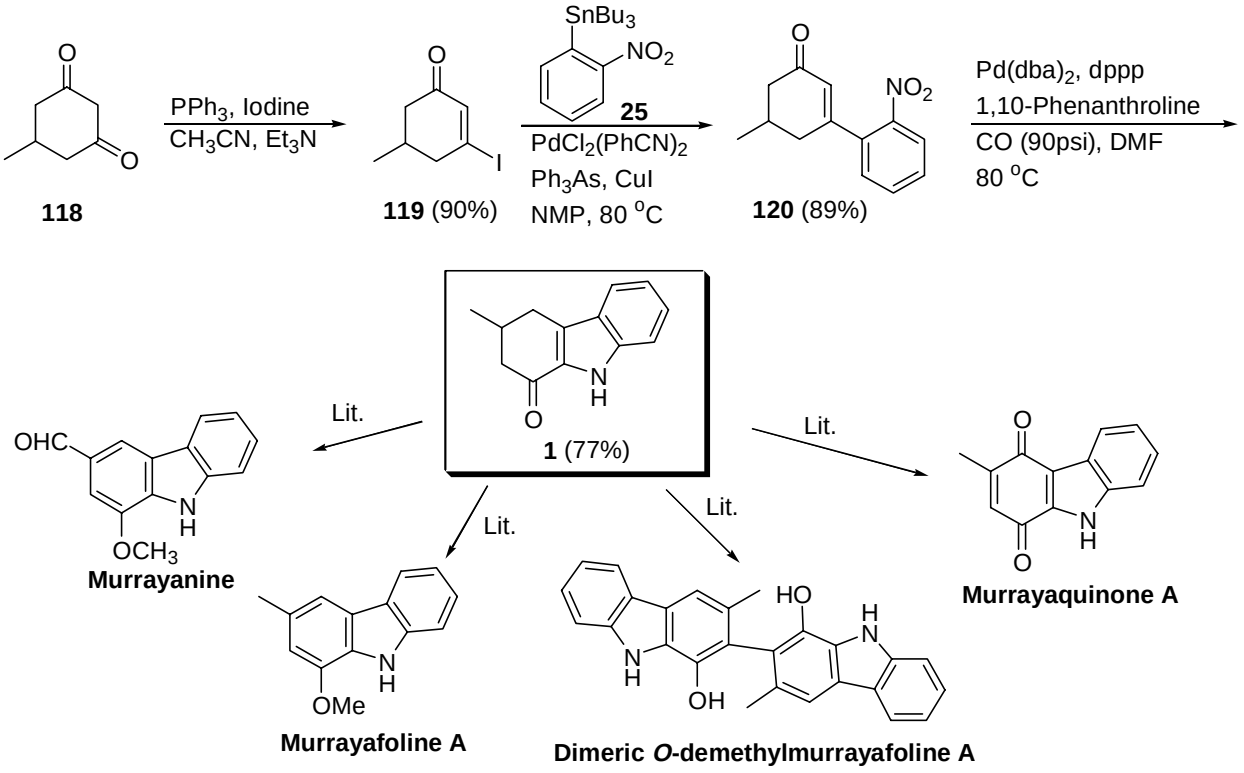
2.2. Formal Synthesis of Four Carbazole Alkaloids

While working on our first synthesis of murrayaquinone A, we were also investigating an alternative route to this compound *via* carbazolone **1** (Scheme 37). We applied the conditions to prepare β-iodo-α, β-unsaturated ketones originally developed by Piers and Nagakura[46] to prepare 3-iodo-5-methyl-2-cyclohexen-1-one (**119**). The Stille coupling of the cyclohexenone **119** and stannane **25** produced **120** in excellent yield (89%). The reductive cyclization of **120** gave carbazolone **1** also in good yield (77%).

Carbazolone **1** is an advanced intermediate in reported syntheses of four different carbazole alkaloids. Not only has this intermediate been used in the synthesis of murrayaquinone A, but also in the preparation of murrayafoline A, murrayanine, and dimeric *O*-

demethylmurrayafoline A. Carbazolone **1** can be converted to murrayaquinone A through DDQ oxidation in 45% yield.[47] In the same synthetic sequence murrayafoline A was prepared *via* the dehydrogenation of **1** followed by methylation (see Scheme 24), and then murrayanine was produced in two steps from murrayafoline A.[32] Dimeric *O*-demethylmurrayafoline A can also be prepared from this intermediate. 1-Hydroxy-3-methylcarbazole,[32] the dehydrogenation product of carbazolone **1**, under oxidative coupling conditions gives the dimeric alkaloid in 87% yield.[31,48]

Scheme 37

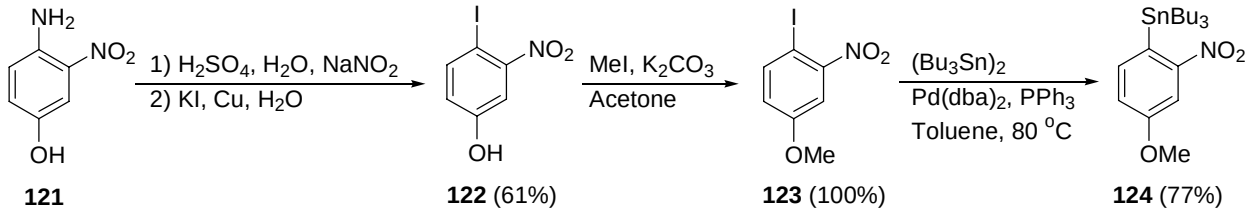


2.3. Formal Synthesis of Koenigine-quinone A

The formal synthesis of koenigine-quinone A was carried out in much the same manner as the other syntheses described above. Stannane **124** was first prepared starting from

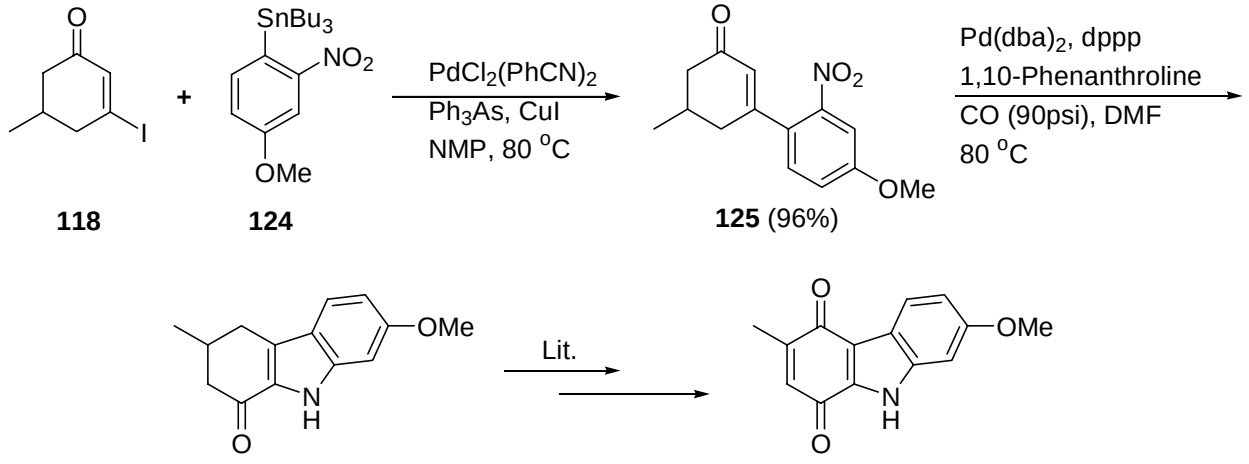
aminophenol **121** (Scheme 38). Sandmeyer type reaction of aminophenol **121** produced iodophenol **122** which was methylated to **123**. Stannane **124** was prepared from **123** using Kosugi's procedure.[17] Stille reaction of **118** and **124** under our usual conditions produced **125** in excellent yield (96%) (Scheme 39). The reductive cyclization also proceeded smoothly giving the key intermediate carbazolone **83** in 79%. Koenigine-quinone A can be synthesized by the dehydrogenation reaction of carbazolone **83** followed by oxidation with Fremy's salt as in the synthesis by Saha and Chowdhury.[33] Their synthesis gives an overall yield for **83** of 50% in two steps from 2-hydroxymethylene-5-methylhexanone and 3-methoxyphenyldiazonium chloride while our synthesis produced this intermediate in 76% yield in two steps.

Scheme 38



121 **122** (61%) **123** (100%) **124** (77%)

Scheme 39



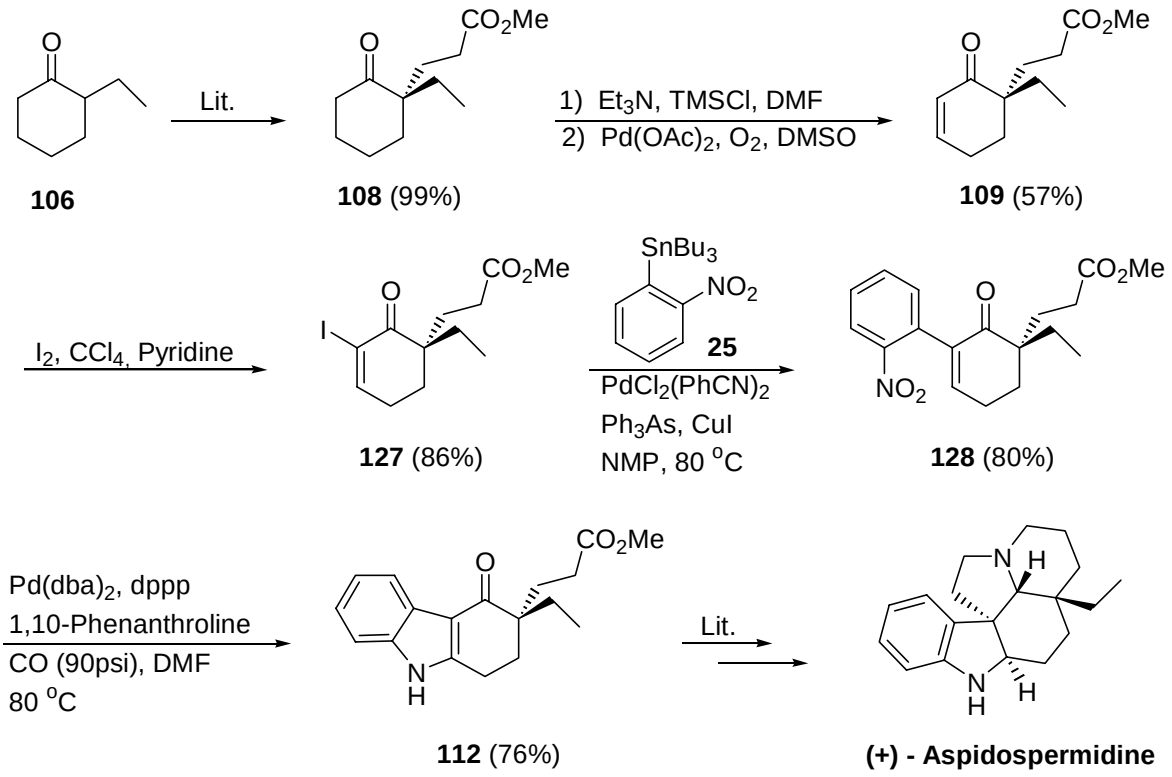
118 **124** **125** (96%)

83 (79%) **Koenigine-quinone A**

2.4. Formal Synthesis of (+)-Aspidospermidine

Desmaele and d'Angelo's synthesis of (+)-aspidospermidine involves the synthesis of the key carbazolone intermediate **112** (Scheme 35).[35] The synthesis of this intermediate required nine steps from 2-ethylcyclohexanone in 23% yield. With our new method for making carbazolones we thought we could improve upon the synthesis of this intermediate.

Scheme 40



We prepared cyclohexenone **109** according to the literature procedure from 2-ethylcyclohexenone except that we replaced the DDQ oxidation with the palladium-catalyzed

dehydrosilylation (Scheme 40). In our hands, the DDQ method failed to produce **109**. Iodide **127** was prepared using iodine and pyridine in carbon tetrachloride in 86% yield. The Stille reaction of **127** and **25** with the usual palladium-catalyzed conditions produced **128** in good yield (80%). Cyclization of **128** proceeded smoothly to carbazolone **112** in 76% yield.

The synthesis of carbazolone **112** is slightly improved by our method. In only six steps from 2-ethylcyclohexanone we produced this intermediate with an overall yield of 30%.

3. Conclusions

We have successfully applied our novel method of preparing carbazolones to the synthesis of several carbazole alkaloids. The formal total syntheses of murrayaquinone A, murrayafoline A, murrayanine, dimeric *O*-demethylmurrayafoline A, koenigine-quinone A, and (+)-aspidospermidine have been achieved using a Stille reaction followed by a palladium-catalyzed reductive *N*-heteroannulation as the key steps. These new syntheses are generally more efficient and higher yielding than the previous syntheses of these alkaloids.

Part III

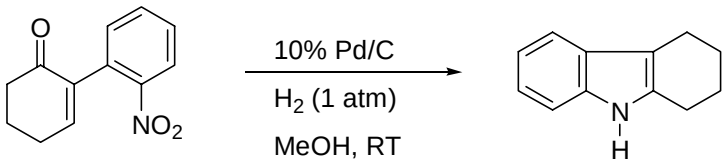
Synthesis of Carbazole Derivatives *via* Palladium-Catalyzed Hydrogenation Reactions

1. Introduction

We described a novel route to substituted carbazolones in the previous sections. Although the mechanistic details of this reaction are unclear it is doubtful that the reaction proceeds through an aniline-type intermediate resulting from reduction of the nitro group. We were curious as to what products might result from the direct reduction of the nitro group in 2-(2-nitrophenyl)-2-cyclohexen-1-one (**32**).

We chose to effect the reduction by a palladium-catalyzed hydrogenation reaction (Scheme 41). Compound **32** in the presence of 10% Pd/C and 1 atm of hydrogen gas in methanol at ambient temperature produced 1,2,3,4-tetrahydrocarbazole (**129**) in 95% yield. No additional products were produced in the reaction.

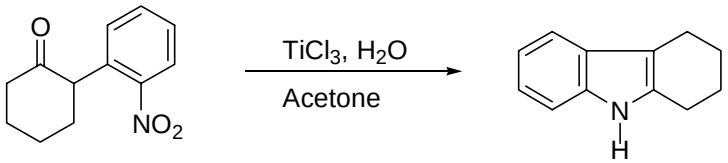
Scheme 41



32 **129** (95%)

Reduction of compounds related to **32** with $TiCl_3$ have been reported to give 1,2,3,4-tetrahydrocarbazoles.[49] The reduction of **130** with aqueous $TiCl_3$ in acetone gave 1,2,3,4-tetrahydrocarbazole in 88% yield (Scheme 42). This latter reaction is inherently regioselective.

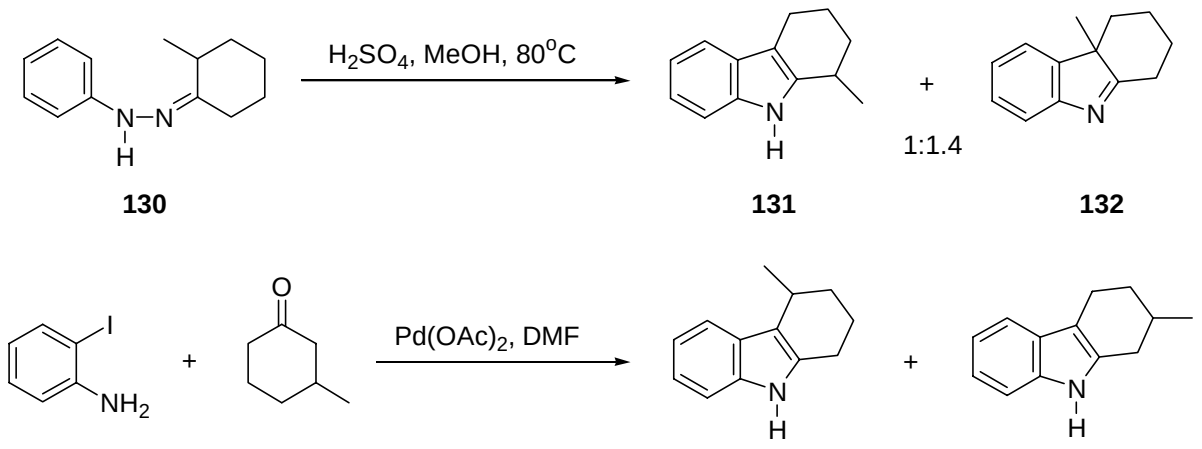
Scheme 42



130 **129** (88%)

Other common methods to form carbazoles such as the Fischer indole synthesis[50] and palladium-catalyzed annulations between iodoanilines and ketones[51] often suffer from the lack of regioselectivity and produce isomers (Scheme 43).

Scheme 43

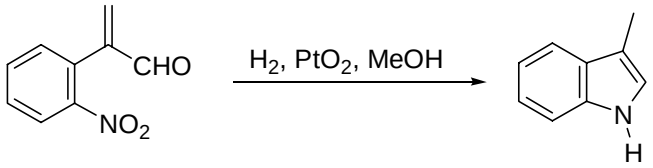


130 **131** **132**

132 **133** **134** (8%) **135** (65%)

To the best of our knowledge there is only one example in the literature of a reductive cyclization involving a nitrobenzene and an α, β-unsaturated ketone moiety. The reduction of 2-(2-nitrophenyl)propenal using PtO_2 and hydrogen (1 atm) in methanol was reported to produce 3-methylindole in 40% yield (Scheme 44).[52]

Scheme 44



136 **137** (40%)

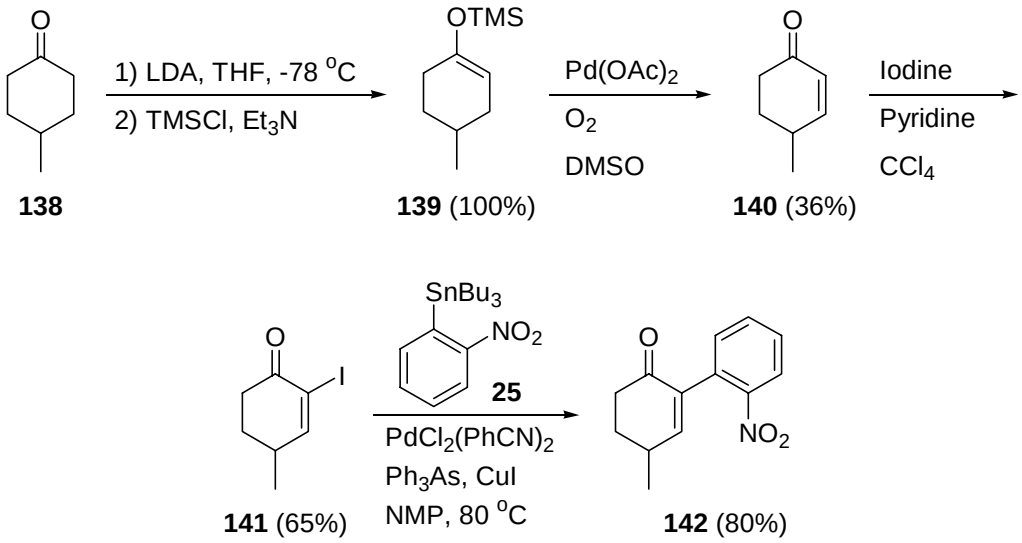
We envisioned the reductive cyclization of compounds such as **32** using simple hydrogenation procedures to be potentially promising for the synthesis of carbazole derivatives. We have investigated the scope and limitations of this reaction using several examples.

2. Results and Discussion

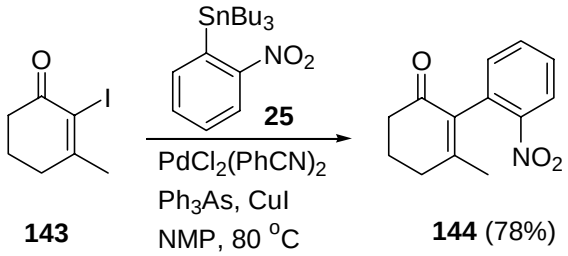
We had previously prepared a number of substituted 2-(2-nitrophenyl)-2-cycloalkenones for the synthesis of carbazolones as described in Part I and II. Additional substrates were made according to similar procedures. Compound **142** was synthesized starting from 4-methylcyclohexanone (**138**) (Scheme 45). The silyl enol ether **139** was prepared, followed by palladium-catalyzed dehydrosilylation[20] to give 4-methyl-2-cyclohexen-1-one (**140**). The low yield of the dehydrosilylation reaction may be contributed to the volatility of the product. Iodide **141** was prepared according to Johnson's procedure[18] using iodine and pyridine in carbon tetrachloride in 65% yield. The Stille reaction of **141** and stannane **25** using $PdCl_2(PhCN)_2$,

Ph_3As, and CuI in NMP gave **142** in good yield (80%). Compound **144** was prepared similarly from the Stille coupling of 2-iodo-3-methylcyclohexenone[18] (**143**) and **25** in 78% yield (Scheme 46).

Scheme 45



Scheme 46



The results of the reductive cyclizations are summarized in Table 3. The reductions were carried out using 10% Pd/C (~20 mol% Pd) and hydrogen gas (1 atm, balloon) in methanol at room temperature. Most of the reactions were complete in 20 minutes to 2 hours as monitored by thin layer chromatography. Some of the compounds appeared to be acid-sensitive, so for

these compounds additional handling precautions were taken such as using base-washed glassware, filtering NMR solvents through potassium carbonate prior to use, and using a small amount of triethylamine in the chromatography solvents.

Excellent yields of methyl-substituted carbazoles were obtained from the reductions of substrates **115**, **33**, **142**, and **144**. These reactions were very regioselective producing only one product per substrate without the formation of other isomers.

Investigation of ring-size in the reductive cyclization reaction gave a different result. Cycloheptenone **35** gave the expected product 5,6,7,8,9,10-hexahydrocyclohepta[*d*]indole (**147**). However, cyclopentenone **34** produced the unexpected product **146**.

Substitution on the benzene ring greatly affected the types of products produced. Not only were tetrahydrocarbazole products produced but tetrahydrocarbazolones and hexahydrocarbazoles as well. There appears to be no correlation between the electron donating or withdrawing nature of substituents and the type of products produced. Two products were isolated for the reaction of each substrate **37**, **39**, and **40**.

Substrate **70** also gave a surprising result. The reductive cyclization of this compound not only produced the expected carbazolone **5**, but 1,2,3,4-tetrahydrocarbazole (**129**) as well. In order to determine what was happening in this reaction, carbazolone **5** was subjected to the hydrogenation conditions (Scheme 47). Carbazolone **5** did yield some tetrahydrocarbazole **129**, but 39% of the starting material was still present even after 3 days.

Table 3

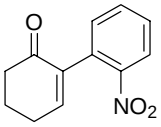
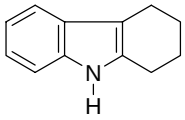
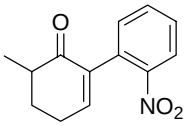
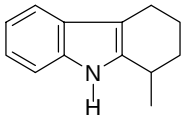
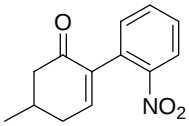
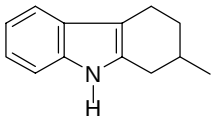
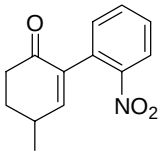
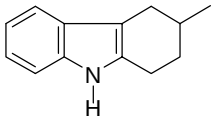
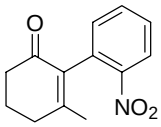
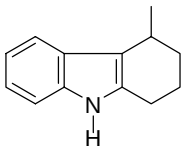
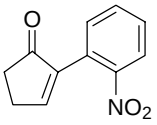
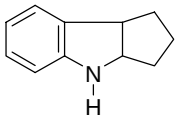
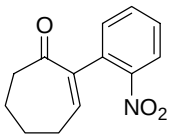
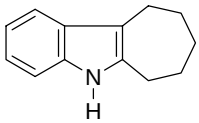
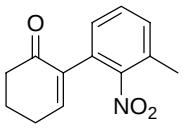
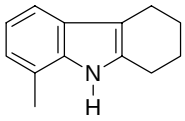
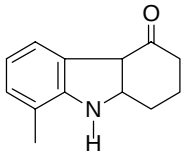
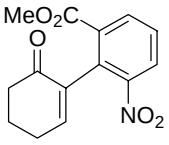
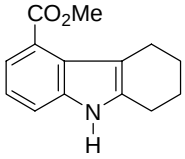
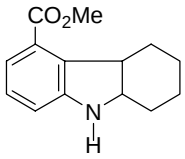
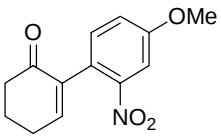
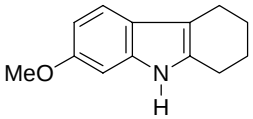
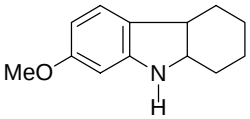
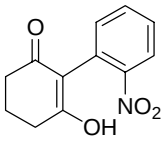
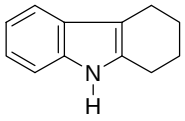
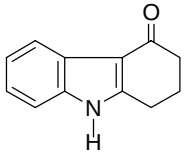
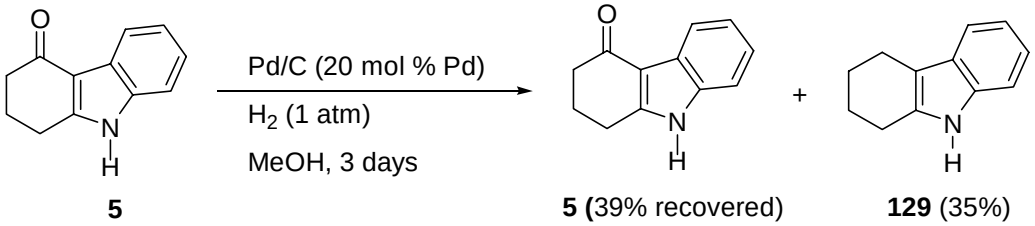
Stille Product	Carbazole(s)
 **32**	 **129** (95%)
 **115**	 **131** (91%)
 **33**	 **135** (92%)
 **142**	 **145** (89%)
 **144**	 **134** (78%)
 **34**	 **146** (83%)
 **35**	 **147** (72%)

Table 3 continued

Stille Product	Carbazole(s)	
 **39**	 **148** (17%)	 **149** (40%)
 **40**	 **150** (25%)	 **151** (39%)
 **37**	 **152** (62%)	 **153** (9%)
 **70**	 **129** (22%)	 **5** (45%)

General conditions: 10% Pd/C (~20 mol% Pd), hydrogen gas (1 atm, balloon), MeOH, RT. For more exact details see: Experimental Section.

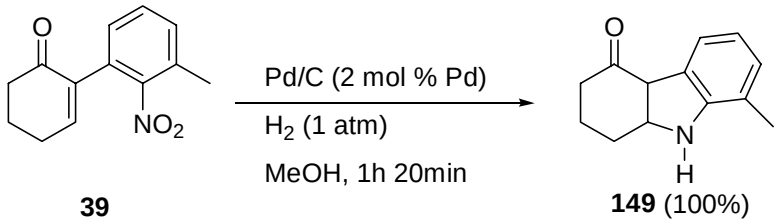
Scheme 47



5 **5 (**39% recovered) **129** (35%)

We also investigated the effect of the amount of palladium in this reaction (Scheme 48). Substrate **39** gave only **149** in quantitative yield when the amount of palladium was decreased to 2 mol%. This result leads us to believe that the product distribution in other reactions can be controlled by adjusting the amount of palladium used. The reductive cyclizations of other substrates have yet to be performed with reduced amounts of catalyst.

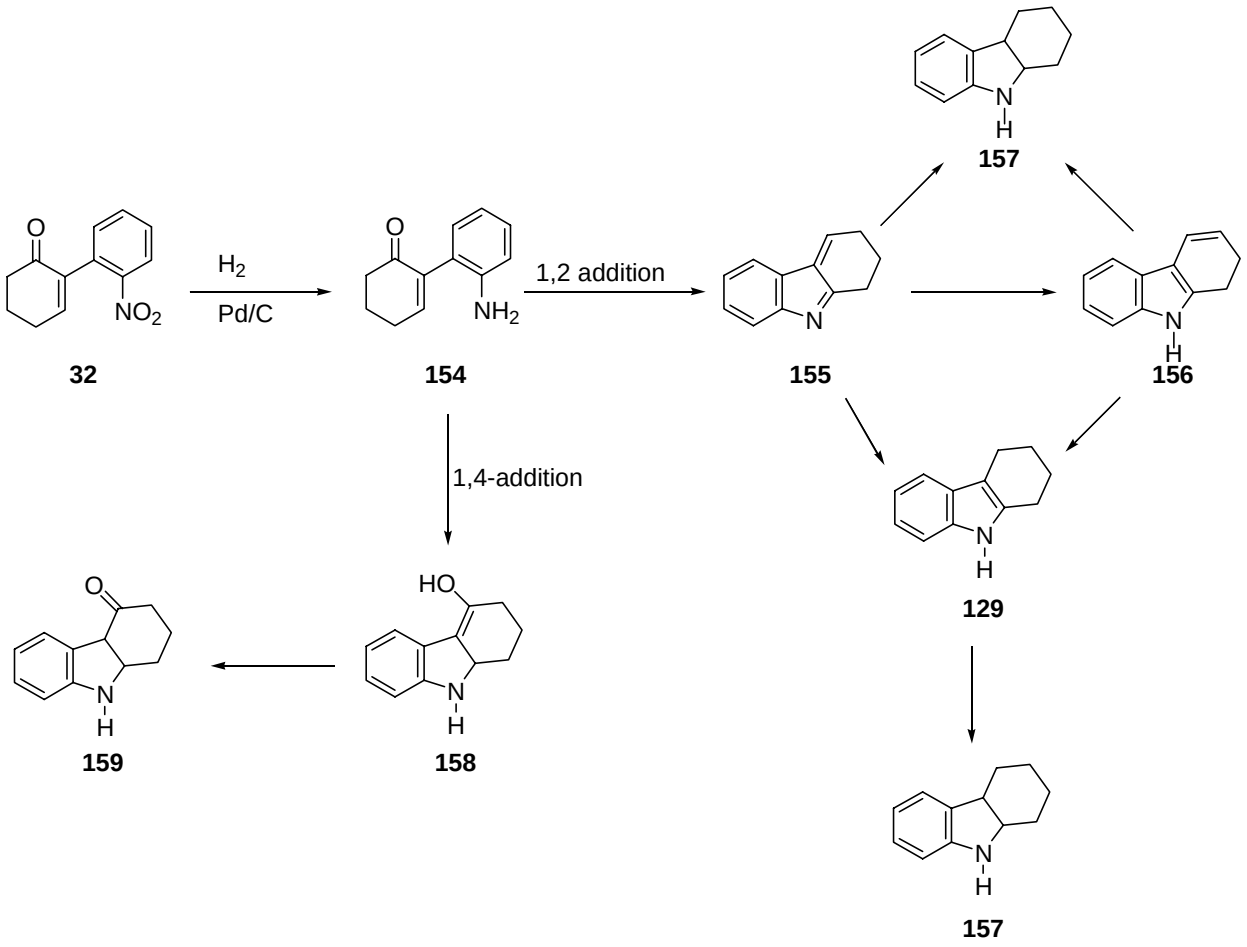
Scheme 48



39 **149** (100%)

Scheme 49 shows the possible intermediates in this reaction. Reduction of the nitro group produces an amine intermediate **154** which can react in either a 1,2- or a 1,4-addition fashion with the enone. The 1,2-addition pathway can give compound **155** which leads to tetrahydrocarbazole **129** by direct reduction and isomerization or through intermediate **156** with subsequent reduction. A hexahydrocarbazole product can be formed from many different intermediates. Reduction of intermediates **155** and **156**, as well as the tetrahydrocarbazole product **129**, could all yield a hexahydrocarbazole. Although the latter pathway is the least likely due to the aromaticity of the the tetrahydrocarbazole **129**. Tetrahydrocarbazolone **159** can be produced through a 1,4-addition of amine **154** to the enone, followed by tautomerization of enol **158**.

Scheme 49



32 **154** **155** **156** **129** **157** **158** **159** **157**

3. Conclusions

We have developed a mild and efficient route to carbazole derivatives through two consecutive palladium-catalyzed reactions, a Stille coupling followed by a reductive cyclization reaction. Unsubstituted 2-cyclohexenone and methyl-substituted cyclohexenone starting materials give the corresponding 1,2,3,4-tetrahydrocarbazole products exclusively in excellent yields. Substitution on the benzene ring leads to mixtures of 1,2,3,4-tetrahydrocarbazoles, 1,2,4a,9a-tetrahydro-4(3*H*)carbazolones, and 1,2,3,4,4a,9a-hexahydrocarbazoles. The cycloheptenone **35** underwent the reductive cyclization to give the expected 5,6,7,8,9,10-

hexahydrocyclohepta[*d*]indole, whereas the cyclopentenone **34** resulted in 1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole. As of now, there are no explanations for the types and mixtures of products in some of these reactions. However, the method does seem to be excellent for selectively producing methyl-substituted carbazoles which can be difficult by other means. Further studies of the regiochemistry and mechanism of the reductive cyclization are currently underway.

Part IV

Experimental Section

1. General Procedures

All NMR spectra were determined in $CDCl_3$ at 270 MHz (^1H NMR) and 67.5 MHz (^{13}C NMR). The chemical shifts are expressed in δ values relative to Me_4Si (0.00, ^1H and ^{13}C) or $CDCl_3$ (7.26, ^1H and 77.00, ^{13}C) internal standards. ^1H-^1H coupling constants are reported as calculated from spectra; thus, a slight difference between $J_{a,b}$ and $J_{b,a}$ is usually obtained. Results of APT (attached proton test) ^{13}C NMR experiments are shown in parentheses, where relative to $CDCl_3$, (-) denotes CH_3 or CH and (+) denotes CH_2 or C.

Tetrahydrofuran (THF), toluene, and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Pyridine, triethylamine, hexanes, acetonitrile, diisopropylamine, and ethyl acetate were distilled from calcium hydride. Chemicals prepared according to literature procedures have been footnoted the first time they are used; all other reagents were obtained from commercial sources and used as received. Silica gel (200-400 mesh) was used for flash chromatography. All reactions were performed in oven-dried glassware under an argon atmosphere unless otherwise noted. Solvents were removed on a rotary evaporator at water aspirator pressure unless otherwise stated. IR spectra were recorded on neat compounds using NaCl plates unless otherwise noted. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. High Resolution Mass Spectra (HRMS) were performed at University of California Riverside Mass Spectrometry Center.

2. Experimental Details

2-Iodo-5-methyl-2-cyclohexen-1-one (20).

To a solution of 5-methyl-2-cyclohexen-1-one[19] (**47**) (502 mg, 4.55 mmol) in 20 mL of 1:1 CCl_4/pyridine cooled to 0 ^oC was added dropwise a solution of iodine (2.30 g, 9.04 mmol) dissolved in 20 mL of 1:1 CCl_4/pyridine with stirring. The reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was diluted with ether (100 mL) and washed successively with water (40 mL), HCl (5%, aq, 2 x 40 mL), water (40 mL), and $Na_2S_2O_3$ (20%, aq, 40 mL). The organic phase was dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by flash chromatography (hexanes/EtOAc, 9:1) to give **20** (911 mg, 3.86 mmol, 85%) as a light yellow solid: mp 39-40 ^oC; IR 2955, 1682, 1590 cm^{-1}; ^1H NMR δ 1.08 (d, *J* = 5.9 Hz, 3H), 2.11-2.53 (m, 4H), 2.69-2.83 (m, 1H), 7.72 (dd, *J* = 5.9 and 2.9 Hz, 1H); ^{13}C NMR δ 20.6 (-), 30.4 (-), 37.9 (+), 45.0 (+), 103.5 (+), 158.6 (-), 192.5 (+); HRMS (EI) calcd for C_7H_9IO (M^+) 235.9698, found 235.9703.

2-Iodo-2-cyclohepten-1-one[53] (22).

To a solution of 2-cyclohepten-1-one (535 mg, 4.86 mmol) in 20 mL of 1:1 CCl_4/pyridine cooled to 0 ^oC was added dropwise a solution of iodine (2.71 g, 10.7 mmol) dissolved in 20 mL of 1:1 CCl_4/pyridine with stirring. The reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was diluted with ether (100 mL) and washed successively with water (40 mL), HCl (5%, aq, 2 x 40 mL), water (40 mL), and $Na_2S_2O_3$ (20%, aq, 40 mL). The organic phase was dried ($MgSO_4$) and concentrated under vacuum. The crude

product was purified by flash chromatography (hexanes/EtOAc, 9:1) to give **22** (786 mg, 3.33 mmol, 69%) as a light yellow solid.

2-(tri-*n*-Butylstannyl)-2-cyclohexen-1-one[54] (24).

tert-Butyllithium (34.5 mL of a 1.7 M solution in hexanes, 58.7 mmol) was added dropwise to a solution of 6-bromo-1,4-dioxaspiro[4,5]dec-6-ene[55] (**46**) (6.00 g, 27.4 mmol) in diethyl ether (480 mL) cooled to –78 ^{o}C. After 30 min, tributyltinchloride (8.2 mL, 30.2 mmol) was added slowly, and the reaction mixture stirred another 30 min at –78 ^{o}C. The reaction mixture was allowed to warm to room temperature, and HCl (10%, aq, 200mL) was added slowly. The reaction mixture was stirred for 3 h. After dilution with diethyl ether (500 mL), the reaction mixture was washed successively with water (500 mL), NH_4OH (10%, aq, 500 mL), and water (500 mL). The organic phase was dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 95:5) to give **24** (8.38 g, 21.8 mmol, 79%) as a clear, colorless oil.

3-Iodo-2-nitrotoluene[56] (29).

To a mixture of 3-methyl-2-nitroaniline (502 mg, 3.30 mmol), ice, water (4mL), and H_2SO_4 (conc., 0.2 mL) cooled in an ice bath was added a solution of $NaNO_2$ (251 mg, 3.64 mmol) in water (1 mL) very slowly (~1 drop/min). After the addition, the reaction mixture was stirred 20 min and additional H_2SO_4 (conc., ~0.07 mL) was added. The reaction mixture was poured slowly into an ice-cold solution of KI (656 mg, 3.95 mL) in water (1 mL). After a few minutes Cu powder (4 mg, 0.06 mmol) was added, and the reaction mixture was warmed slowly to 80 ^{o}C for about 30 min. The reaction mixture was allowed to cool, was extracted with CH_2Cl_2

(3 x 50 mL), washed with $Na_2S_2O_3$ (20%, aq, 50 mL), dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash chromatography (hexanes/EtOAc, 8:2) to give **29** (764 mg, 2.90 mmol, 88%) as a yellow-orange solid.

4-Bromo-2-iodo-1-nitrobenzene (31).

To a mixture of 5-bromo-2-nitroaniline[57] (**54**) (198 mg, 0.910 mmol), ice, water (5 mL), and H_2SO_4 (conc., 0.2 mL) cooled to 0 ^oC was added a solution of $NaNO_2$ (70.2 mg, 1.02 mL) very slowly (~1 drop/min). The reaction mixture was stirred for 1.5 h at room temperature, and then was added very slowly to an ice-cold solution of KI (190 mg, 1.14 mmol) in water (1 mL). After a few min Cu powder (2 mg, 0.03 mmol) was added, and the reaction mixture was heated slowly to 80 ^oC for 20 min. The reaction mixture was allowed to cool, was extracted with CH_2Cl_2 (3 x 50 mL), washed with $Na_2S_2O_3$ (10%, aq, 50 mL), dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash chromatography (hexanes/EtOAc, 9:1) to give **31** (182 mg, 0.55 mmol, 61%) as a yellow solid: mp 77-79 ^oC; IR 1563, 1518, 1335 cm^{-1}; ^1H NMR δ (dd, *J* = 8.5 and 2.0 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 8.22 (d, J = 2.0 Hz, 1H); ^{13}C NMR δ 87.4 (+), 126.4(-), 127.7 (+), 132.2 (-), 144.1 (-), 151.7 (+).

2-(2-Nitrophenyl)-2-cyclohexen-1-one[23] (32).

To a solution of 2-iodo-2-cyclohexen-1-one (**19**)[18] (808 mg, 3.64 mmol) and 2-(tri-*n*-butylstannyl)-1-nitrobenzene (**25**)[17] (1.80 g, 4.34 mmol) in *N*-methylpyrrolidinone (NMP) (4 mL) was added $PdCl_2(PhCN)_2$ (77.5 mg, 0.20 mmol), Ph_3As (117 mg, 0.40 mmol), and CuI (77.2 mg, 0.40 mmol). The reaction mixture was heated at 80 ^oC for 20 h. The reaction mixture was diluted with EtOAc (100 mL) and washed successively with NH_4OH (10%, aq, 3 X 30 mL)

and H_2O (2 X 30 mL). The aqueous portions were extracted with EtOAc (50 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 9:1) to give **32** (603 mg, 2.77 mmol, 76%) as a light yellow solid.

Alternate procedure: Compound **32** was also prepared repeating the above procedure except using 2-(tri-*n*-butylstannyl)-2-cyclohexenone (**24**) (931 mg, 2.42 mmol), 1-iodo-2-nitrobenzene (**26**) (502 mg, 2.01 mmol), $PdCl_2(PhCN)_2$ (38.5 mg, 0.10 mmol), Ph_3As (70.1 mg, 0.22 mmol), CuI (41.9 mg, 0.22 mmol), and NMP (4 mL) to give **32** (309 mg, 1.42 mmol, 71%).

5-Methyl-2-(2-nitrophenyl)-2-cyclohexen-1-one (33).

The same procedure as described for **32** was repeated except that a mixture of 2-iodo-5-methyl-2-cyclohexen-1-one (**20**) (241 mg, 1.02 mmol), 1-(tri-*n*-butylstannyl)-2-nitrobenzene (**25**) (455 mg, 1.10 mmol), $PdCl_2(PhCN)_2$ (20.6 mg, 0.05 mmol), Ph_3As (31.6 mg, 0.10 mmol), CuI (19.1 mg, 0.10 mmol), and NMP (1 mL) gave **33** (175 mg, 0.75 mmol, 74%) as a pale yellow solid: mp 107-109 ^oC; IR 1672, 1517, 1340 cm^{-1}; ^1H NMR δ 1.03 (d, *J* = 8.1 Hz, 3H), 2.10-2.35 (m, 3H), 2.44-2.59 (m, 2H), 6.90 (dd, *J* = 5.5 and 2.8 Hz, 1H), 7.16 (dd, *J* = 7.5 and 1.6 Hz, 1H), 7.35 (td, *J* = 6.4 and 1.6 Hz, 1H), 7.49 (td, *J* = 7.3 and 1.2 Hz, 1H), 7.88 (dd, *J* = 8.1 and 1.2, 1H); ^{13}C NMR δ 20.9 (-), 29.9 (-), 34.3 (+), 46.1 (+), 123.9 (-), 128.6 (-), 131.5 (-), 131.7 (+), 133.2 (-), 138.8 (+), 146.0 (-), 148.4 (+), 196.5 (+); HRMS (DEI) calcd for $C_{13}H_{13}NO_3$ (MH^+) 232.0974, found 232.0965.

2-(2-Nitrophenyl)-2-cyclopenten-1-one (34).

The same procedure as described for **32** was repeated except that a mixture of 2-iodo-2-cyclopenten-1-one (**21**)[18] (290 mg, 1.40 mmol), 1-(tri-*n*-butylstannyl)-2-nitrobenzene (**25**) (643 mg, 1.56 mmol), $PdCl_2(PhCN)_2$ (26.7 mg, 0.07 mmol), Ph_3As (43.7 mg, 0.14 mmol), CuI (29.2 mg, 0.15 mmol), and NMP (2.8 mL) gave **34** (183 mg, 0.90 mmol, 65%) as a pale yellow solid: mp 94.5-96.5 ^oC; IR 1697, 1518, 1349 cm^{-1}; ^1H NMR δ 2.56-2.60 (m, 2H), 2.78-2.83 (m, 2H), 7.32 (dd, *J* = 7.5 and 1.6 Hz, 1H), 7.49 (td, *J* = 7.5 and 1.4 Hz, 1H), 7.61 (td, *J* = 7.5 and 1.4 Hz, 1H), 7.69 (t, *J* = 2.8 Hz, 1H), 8.02 (dd, *J* = 8.1 and 2.6 Hz, 1H); ^{13}C NMR δ 27.0 (+), 34.5 (+), 124.3 (-), 127.1 (+), 129.1 (-), 131.2 (-), 133.0 (-), 143.7 (+), 148.2 (+), 159.0 (-), 205.3 (+); Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46. Found: C, 65.15; H, 4.46.

2-(2-Nitrophenyl)-2-cyclohepten-1-one (35).

The procedure as described for **32** was repeated except that a mixture of 2-iodo-2-cyclohepten-1-one (**22**) (389 mg, 1.65 mmol), 1-(tri-*n*-butylstannyl)-2-nitrobenzene (**25**) (820 mg, 1.99 mmol), $PdCl_2(PhCN)_2$ (31.9 mg, 0.08 mmol), Ph_3As (51.7 mg, 0.16 mmol), CuI (31.2 mg, 0.16 mmol), and NMP (1.6 mL) gave after purification by flash chromatography (benzene/CH_2Cl_2, 95:5) **35** (259 mg, 1.12 mmol, 68%) as a pale yellow sold: mp 83-85 ^oC; IR 1665, 1517, 1340 cm^{-1}; ^1H NMR δ 1.81-1.99 (m, 4H), 2.53-2.61 (m, 2H), 2.74-2.80 (m, 2H), 6.74 (t, *J* = 6.5 Hz, 1H), 7.28 (dd, *J* = 7.5 and 1.6 Hz, 1H), 7.43 (td, *J* = 8.1 and 1.6 Hz, 1H), 7.58 (td, *J* = 7.5 and 1.6 Hz, 1H) 8.00 (dd, *J* =8.1 and 1.2 Hz, 1H); ^{13}C NMR δ 21.0 (+), 25.0 (+), 27.8 (+), 42.4 (+), 124.2 (-), 128.5 (-), 132.6 (-), 133.5 (-), 135.1 (+), 142.9 (+), 143.1 (-), 147.2 (+), 202.5 (+); HRMS (EI) calcd for $C_{13}H_{13}NO_3$ (M^+) 231.0895, found 231.0895.

8,9-Dihydro-5*H*-6-(2-nitrophenyl)-benzocyclohepten-5-one (36).

The same procedure as described for **32** was repeated except that a mixture of 6-bromo-8,9-dihydro-5H-benzocyclohepten-5-one (**23**)[21] (250 mg, 1.06 mmol), 1-(tri-*n*-butylstannyl)-2-nitrobenzene (**25**) (496 mg, 1.20 mmol), $PdCl_2(PhCN)_2$ (21.5 mg, 0.06 mmol), Ph_3As (34.1 mg, 0.11 mmol), CuI (21.0 mg, 0.11 mmol), and NMP (1 mL) after 40 h gave **36** (183 mg, 0.90 mmol, 65%) as an orange oil: IR 3408, 2941, 1665, 1517, 1340 cm^{-1}; ^1H NMR δ 2.78 (q, *J* = 5.1 Hz, 2H), 3.14 (t, *J* = 5.1 Hz, 2H), 6.81 (t, *J* = 5.1 Hz, 1H), 7.19-7.70 (m, 7H), 8.07 (dd, *J* = 8.1 and 2.9 Hz, 1H); ^{13}C NMR δ 30.6 (+), 33.7 (+), 124.3 (-), 127.0 (-), 128.2 (-), 128.6 (-), 129.9 (-), 132.1 (-), 132.5 (-), 133.4 (-), 136.2 (+), 139.1 (+), 140.9 (+), 141.5 (+), 144.2 (-), 148.1 (+), 194.2 (+); HRMS (DEI) calcd for $C_{14}H_{15}NO_4$ (MH^+) 280.0974, found 280.0964.

Impurity: 1-nitro-2-(2-nitrophenyl)benzene (43). Partial ^1H NMR δ 8.23 (d, *J* = 8.1 Hz). Partial ^{13}C NMR δ 124.8, 129.2, 130.9, 133.5.

2-(4-Methoxy-2-nitrophenyl)-2-cyclohexen-1-one (37).

The same procedure as described for **32** was repeated except that a mixture of 2-(tri-*n*-butylstannyl)-2-cyclohexen-1-one (**24**) (183 mg, 0.48 mmol), 1-bromo-2-nitro-4-methoxybenzene (**27**)[58] (103 mg, 0.44 mmol), $PdCl_2(PhCN)_2$ (8.2 mg, 0.02 mmol), dppf (24.1 mg, 0.04 mmol), CuI (8.9 mg, 0.04 mmol), and NMP (1 mL) after 3 days gave **37** (73.4 mg, 0.30 mmol, 67%) as a yellow-orange solid: mp 63-65 ^oC; IR 1682, 1531, 1357, 1234 cm^{-1}; ^1H NMR δ 2.14 (pentet, *J* = 5.9 Hz, 2H), 2.52-2.60 (m, 4H), 3.85 (s, 3H), 6.96 (t, *J* = 4.1, 1H), 7.13-7.16 (m, 2H), 7.55 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR δ 22.6 (+), 26.2 (+), 38.3 (+), 55.8 (-), 109.1 (-), 119.5 (-), 124.1 (+), 132.4 (-), 139.0 (+), 146.2 (-), 149.0 (+), 159.5 (+), 196.8 (+); HRMS (EI) calcd for $C_{13}H_{13}NO_3$ (M^+) 247.0845, found 247.0849.

2-(6-Methyl-2-nitrophenyl)-2-cyclohexen-1-one (38).

The same procedure as described for **32** was repeated except that a mixture of 2-(tri-*n*-butylstannyl)-2-cyclohexen-1-one (**24**) (351 mg, 0.91 mmol), 2-bromo-3-nitrotoluene (**28**) (177 mg, 0.82 mmol), $PdCl_2(PPh_3)_2$ (27.7 mg, 0.04 mmol), and DMF (5 mL) heated at 110 ^oC for 26 h gave **38** (58.2 mg, 0.25 mmol, 31%) as a pale yellow solid: mp 79-80 ^oC; IR 1671, 1520, 1356 cm^{-1}; ^1H NMR δ 2.09-2.20 (m, 2H), 2.22 (s, 3H), 2.51 (q, *J* = 5.7, 2H), 2.57-2.74 (m, 2H), 6.72 (t, *J* = 4.2 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR δ 20.0 (-), 22.5 (+), 26.0 (+), 38.2 (+), 121.6 (-), 127.9 (-), 131.4 (+), 134.4 (-), 137.2 (+), 138.3 (+), 146.8 (-), 149.4 (+), 196.8 (+); HRMS (EI) calcd for $C_{13}H_{13}NO_3$ (M^+) 231.0895, found 231.0902.

2-(3-Methyl-2-nitrophenyl)-2-cyclohexen-1-one (39).

The same procedure as described for 32 was repeated except that a mixture of 2-(tri-*n*-butylstannyl)-2-cyclohexen-1-one (**24**) (385 mg, 1.00 mmol), 3-iodo-2-nitrotoluene (**29**) (215 mg, 0.82 mmol), $PdCl_2(PhCN)_2$ (15.7 mg, 0.04 mmol), Ph_3As (25.3 mg, 0.08 mmol), CuI (16.1 mg, 0.08 mmol), and NMP (2.5 mL) after 2 days gave **39** (117 mg, 0.51 mmol, 62%) as a pale yellow solid: mp 129-131 ^oC; IR 1677, 1523, 1362 cm^{-1}; ^1H NMR δ 2.10 (pentet, *J* = 6.2 Hz, 2H), 2.39 (s, 3H), 2.48-2.58 (m, 4H), 6.99 (t, *J* = 4.3 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR δ 18.5 (-), 22.5 (+), 26.3 (+), 38.3 (+), 128.9 (-), 130.4 (-), 130.6 (+), 130.7 (+), 131.2 (-), 137.8 (+), 148.6 (-), 150.3 (+), 196.5 (+); HRMS (EI) calcd for $C_{13}H_{13}NO_3$ (M^+) 231.0895, found 231.0898.

2-(6-Carbomethoxy-2-nitrophenyl)-2-cyclohexen-1-one (40).

The same procedure as described for **32** was repeated except that a mixture of 2-(tri-*n*-butylstannyl)-2-cyclohexen-1-one (**24**) (887 mg, 2.30 mmol), 1-carbomethoxy-2-bromo-3-nitrobenzene (**30**)[10] (501 mg, 1.92 mmol), $PdCl_2(PhCN)_2$ (38.2 mg, 0.10 mmol), Ph_3As (59.8 mg, 0.20 mmol), CuI (39.7 mg, 0.20 mmol), and NMP (4 mL) was degassed by four freeze-pump-thaw cycles (-78 ^oC to rt) and was heated at 80 ^oC for 96 h to give **40** (233 mg, 0.84 mmol, 44%) as a yellow-orange solid: mp 86.5-88.5 ^oC; IR 1730, 1681, 1531, 1357, 1294, 1273 cm^{-1}; ^1H NMR δ 2.15 (pentet, *J* = 6.3 Hz, 2H), 2.47 (q, *J* = 5.3 Hz, 2H), 2.63 (t, *J* = 6.3 Hz, 2H), 6.66 (t, *J* = 4.1 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H) 7.99 (d, *J* = 8.1, 1H), 8.12 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR δ 22.2 (+), 26.0 (+), 38.0 (+), 52.3 (-), 126.9 (-), 128.5 (-), 132.5 (+), 132.7 (+), 133.8 (-), 136.9 (+), 144.6 (-), 150.3 (+), 165.4 (+), 196.3 (+); HRMS (EI) calcd for $C_{14}H_{15}NO_4$ (M^+) 275.0794, found 275.0804.

Impurity: Methyl 2-butyl-3-nitrobenzoate (44). ^1H NMR δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.25-1.42 (m, 4H), 1.64 (pentet, *J* = 6.9, 2H), 3.63 (s, 3H), 7.68 (t, *J* = 7.9 Hz, 1H), 8.28-8.33 (m, 2H). Partial ^{13}C NMR δ 13.4 (-), 17.4 (+), 26.6 (+), 27.6 (+), 52.4 (-), 127.7 (-), 128.8 (-), 134.7 (-).

2-(5-Bromo-2-nitrophenyl)-2-cyclohexen-1-one (41).

The same procedure as described for **32** was repeated except that a mixture of 2-(tri-*n*-butylstannyl)-2-cyclohexen-1-one (**24**) (459 mg, 1.19 mmol), 4-bromo-2-iodo-1-nitrobenzene (**31**) (318 mg, 0.97 mmol), $PdCl_2(PhCN)_2$ (18.9 mg, 0.05 mmol), Ph_3As (30.5 mg, 0.10 mmol), CuI (18.2 mg, 0.10 mmol), and NMP (3 mL) after 2 days gave **41** (160 mg, 0.54 mmol, 56%) as a yellow-orange solid: mp 168-169 ^oC; IR 2948, 1668, 1520, 1557, 1520, 1348 cm^{-1}; ^1H NMR δ

2.14 (p, *J* = 5.8 Hz, 2H), 2.52-2.61 (m, 4H), 7.02 (t, *J* = 3.2 Hz, 1H), 7.41 (d, *J* = 3.5, 1H), 7.59 (dd, *J* = 8.9 and 3.4 Hz, 1H), 7.90 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR δ 22.4 (+), 26.2 (+), 38.1 (+), 125.7 (-), 127.9 (+), 131.7 (-), 133.9 (+), 134.4 (-), 134.5 (+), 138.4 (+), 147.3 (-), 196.1 (+); HRMS (DEI) calcd for $C_{12}H_{10}BrNO_3$ (M^+) 295.9923, found 295.9915.

[(6,7-Dihydro-5*H*-benzocyclohepten-9-yl)oxy]trimethylsilane[59] (49).

Butyllithium (10.7 mL of a 1.6 M solution in hexanes, 17.1 mmol) was added dropwise to a solution of diisopropylamine (2.85 mL, 20.3 mmol) in THF (42 mL) cooled to –78 ^{o}C. The reaction mixture was stirred 5 min, and a solution of 1-benzosuberone (2.49 g, 15.6 mmol) in THF (13 mL) was added slowly to the reaction mixture. The reaction mixture was stirred for 45 min, and then TMSCl (2.4 mL, 18.9 mmol) and Et_3N (4.35 mL, 31.2 mmol) were added slowly. The reaction mixture was allowed to warm to ambient temperature over 1 h. The reaction mixture was diluted with diethyl ether (200 mL), washed with water (3 x 50 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (hexanes/Et_2O, 9:1) to give **49** (3.43 g, 14.8 mmol, 95%) as a clear, colorless oil.

8,9-Dihydro-5*H*-benzocyclohepten-5-one[60] (50).

To a solution of **49** (3.04 g, 13.1 mmol) in DMSO (100 mL) was added $Pd(OAc)_2$ (293 mg, 1.30 mmol). The reaction flask was flushed with O_2 for 5 min. The reaction mixture was stirred at 40 ^{o}C under O_2 (1 atm, balloon) for 27 h. The reaction mixture was allowed to cool, and then was diluted with 400 mL of EtOAc and washed with water (3 x 100 mL). The organic phase was dried ($MgSO_4$) and concentrated. The crude product was purified by flash

chromatography (hexanes:EtOAc, 9:1) to give **50** (1.92 g, 12.2 mmol, 93%) as a clear, colorless oil.

1,2-Dihydrocarbazol-4(3*H*)-one[4] (5).

2-(2-Nitrophenyl)-2-cyclohexen-1-one (**32**) (285 mg, 1.31 mmol), $Pd(dba)_2$ (45.3 mg, 0.08 mmol), dppp (32.5 mg, 0.08 mmol), 1,10-phenanthroline monohydrate (31.2 mg, 0.16 mmol), and DMF (5 mL) were placed into a pressure tube fitted with a pressure head. The tube was flushed 3 times with CO, and the reaction was heated and stirred at 80 ^{o}C under CO (90 psi) for 24 h. The reaction mixture was filtered through Celite and was concentrated under high vacuum. The product was purified via flash chromatography (hexanes/EtOAc, 7:3) to give **5** (180 mg, 0.97 mmol, 74%) as a white powder.

Alternate procedure A for compound 5. Compound **5** was also prepared using the above procedure except that a mixture of 2-(2-nitrophenyl)-1,3-cyclohexanedione[23] (**70**) (202 mg, 0.87 mmol), $Pd(dba)_2$ (29.7 mg, 0.05 mmol), dppp (22.5 mg, 0.05 mmol), 1,10-phenanthroline monohydrate (23.5 mg, 0.12 mmol), and DMF (5 mL) heated at 100 ^{o}C for 90 h gave **5** (133 mg, 0.72 mmol, 83%).

Alternate procedure B for compound 5. Compound **5** was also prepared using the above procedure except that a mixture of 3-methoxy-2-(2-nitrophenyl)-2-cyclohexen-1-one[23] (**71**) (141 mg, 0.57 mmol), $Pd(dba)_2$ (20.6 mg, 0.04 mmol), dppp (16.3 mg, 0.04 mmol), 1,10-phenanthroline monohydrate (15.4 mg, 0.08 mmol), and DMF (5 mL) heated at 120 ^{o}C for 96 h gave **5** (64.5 mg, 0.35 mmol, 61%).

2-Methyl-1,2-dihydrocarbazol-4(3*H*)-one (55).

The same procedure as described for **5** was repeated except that a mixture of 5-methyl-2-(2-nitrophenyl)-2-cyclohexenone (**33**) (98.3 mg, 0.42 mmol), $Pd(dba)_2$ (14.7 mg, 0.03 mmol), dppp (10.5 mg, 0.03 mmol), 1,10-phenanthroline monohydrate (10.2 mg, 0.05 mmol), and DMF (5 mL) after 36 h gave **55** (75.1 mg, 0.38 mmol, 89%) as a white powder: mp 260-261 ^{o}C; IR (Nujol) 2925, 1630, 1583, 1458, 1376 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 1.19 (d, J = 6.2 Hz, 3H), 2.22-2.71 (m, 4H), 2.98-3.11 (m, 1H), 7.11-7.21 (m, 2H), 7.32-7.40 (m, 1H), 8.04-8.12 (m, 1H), 11.25 (s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 20.3 (-), 30.4 (+), 30.7 (-), 45.6 (+), 110.5 (-), 111.1 (+), 119.7 (-), 120.7 (-), 121.6 (-), 123.7 (+), 135.4 (+), 150.8 (+), 192.4 (-).

3,4-Dihydrocyclopent[*b*]indol-1(2*H*)-one[61] (56).

The same procedure as described for **5** was repeated except that a mixture of 2-(2-nitrophenyl)-2-cyclopenten-1-one (**34**) (125 mg, 0.61 mmol), $Pd(dba)_2$ (21.2 mg, 0.04 mmol), dppp (15.7 mg, 0.04 mmol), 1,10-phenanthroline monohydrate (14.8 mg, 0.07 mmol), and DMF (5 mL) after 3 days gave **56** (90.4 mg, 0.53 mmol, 86%) as a white powder.

6,7,8,9-Tetrahydrocyclohept[*b*]indol-10(5*H*)-one[5] (57).

The same procedure as described for **5** was repeated except that a mixture of 2-(2-nitrophenyl)-2-cycloheptenone (**35**) (136 mg, 0.59 mmol), $Pd(dba)_2$ (20.4 mg, 0.04 mmol), dppp (14.5 mg, 0.04 mmol), 1,10-phenanthroline monohydrate (14.7 mg, 0.07 mmol), and DMF (5 mL) after 48 h gave **57** (77.9 mg, 0.39 mmol, 66%) as a white powder.

6,7-Dihydrobenzo[4,5]cyclohept-[1,2-*b*]indol-12(5*H*)-one[8] (58).

The same procedure as described for **5** was repeated except that a mixture of **36** (31.5 mg, 0.11 mmol), $Pd(dba)_2$ (5.1 mg, 0.009 mmol), dppp (3.5 mg, 0.009 mmol), 1,10-phenanthroline monohydrate (3.4 mg, 0.017 mmol), and DMF (3 mL) after 30 h gave **58** (24.1 mg, 0.098 mmol, 86%) as a white powder.

7-Methoxy-1,2-dihydrocarbazol-4(3*H*)-one[5] (59).

The same procedure as described for **5** was repeated except that a mixture of 2-(4-methoxy-2-nitrophenyl)-2-cyclohexen-1-one (**37**) (43.5 mg, 0.18 mmol), $Pd(dba)_2$ (6.3 mg, 0.01 mmol), dppp (4.6 mg, 0.01 mmol), 1,10-phenanthroline monohydrate (4.5 mg, 0.02 mmol), and DMF (5 mL) after 22 h gave **59** (33.8 mg, 0.16 mmol, 89%) as a white powder.

5-Methyl-1,2-dihydrocarbazol-4(3*H*)-one (60).

The same procedure as described for **5** was repeated except that a mixture of 2-(6-methyl-2-nitrophenyl)-2-cyclohexen-1-one (**38**) (117 mg, 0.51 mmol), $Pd(dba)_2$ (17.5 mg, 0.03 mmol), dppp (12.7 mg, 0.03 mmol), 1,10-phenanthroline monohydrate (12.4 mg, 0.06 mmol), and DMF (5 mL) after 36 h gave **60** (79.5 mg, 0.40 mmol, 79%) as a white powder: mp 234-235 ^{o}C; IR (Nujol) 1711, 1620, 1575 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 2.16 (pentet, J = 5.9 Hz, 2H), 2.50 (t, J = 5.9 Hz, 2H), 2.86 (s, 3H), 2.97 (t, J = 5.9 Hz, 2H), 6.88 (d, J = 7.2, 1H), 7.03 (t, J = 7.4 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 11.47 (s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 23.3 (-), 23.6 (+), 23.9 (+), 38.9 (+), 109.4 (-), 113.5 (+), 123.2 (-), 123.7 (-), 124.6 (+), 131.7 (+), 137.0 (+), 153.0 (+), 192.1 (+); HRMS (EI) calcd for $C_{13}H_{13}NO$ (M^+) 199.0997, found 199.0997.

8-Methyl-1,2-dihydrocarbazol-4(3*H*)-one[6] (61).

The same procedure as described for **5** was repeated except that a mixture of 2-(3-methyl-2-nitrophenyl)-2-cyclohexen-1-one (**39**) (108 mg, 0.47 mmol), $Pd(dba)_2$ (16.5 mg, 0.03 mmol), dppp (11.9 mg, 0.03 mmol), 1,10-phenanthroline monohydrate (11.4 mg, 0.06 mmol), and DMF (5 mL) after 144 h gave **61** (69.8 mg, 0.35 mmol, 75%) as a white powder.

Methyl 1,2-dihydrocarbazol-4(3*H*)-one-5-carboxylate[62] (62).

The same procedure as described for **5** was repeated except that a mixture of 2-(6-carbomethoxy-2-nitrophenyl)-2-cyclohexen-1-one (**40**) (158 mg, 0.57 mmol), $Pd(dba)_2$ (19.7 mg, 0.03 mmol), dppp (14.2 mg, 0.03 mmol), 1,10-phenanthroline monohydrate (13.6 mg, 0.07 mmol), and DMF (5 mL) after 96 h gave **62** (105 mg, 0.43 mmol, 75%) as a white powder.

6-Bromo-1,2,3,9-tetrahydro-4*H*-carbazol-4-one[63] (63).

The same procedure as described for **5** was repeated except that a mixture of 2-(5-bromo-2-nitrophenyl)-2-cyclohexen-1-one (**41**) (123 mg, 0.42 mmol), $Pd(dba)_2$ (14.3 mg, 0.025 mmol), dppp (10.4 mg, 0.025 mmol), 1,10-phenanthroline monohydrate (9.9 mg, 0.050 mmol), and DMF (5 mL) after 8 days gave **63** (56.9 mg, 0.22 mmol, 79%) as a white powder.

6,7,8,9-Tetrahydro-5*H*-pyrido[3,2-*b*]indol-9-one[7] (68).

A mixture of 2-(tri-*n*-butylstannyl)-2-cyclohexen-1-one (**24**) (621 mg, 1.61 mmol), 2-chloro-3-nitropyridine (**66**) (201 mg, 1.26 mmol), $Pd(dba)_2$ (22.1 mg, 0.038 mmol), Ph_3As (47.1 mg, 0.15 mmol), and toluene (5 mL)were heated at reflux for 20 h. The reaction was diluted with benzene (100 mL) and washed with NH_4OH (10%, aq, 3 X 50 mL) and H_2O (2 X 50 mL).

The organic phase was dried ($MgSO_4$) and concentrated. The crude product (**67**) was used in the next procedure without purification. The same procedure as described for **5** was repeated except that the mixture of crude **67**, $Pd(dba)_2$ (43.6 mg, 0.075 mmol), dppp (31.2 mg, 0.076 mmol), 1,10-phenanthroline monohydrate (30.1 mg, 0.152 mmol), and DMF (5 mL) after purification by flash chromatography ($CHCl_3$ to $CHCl_3$/MeOH, 9:1) gave **68** (128 mg, 0.685 mmol, 54%) as a tan solid.

2-Iodo-6-methyl-2-cyclohexen-1-one (114).

To a solution of 6-methyl-2-cyclohexen-1-one[19] (**113**) (441 mg, 4.00 mmol) in 20 mL of 1:1 CCl_4/pyridine cooled to 0 ^oC was added dropwise a solution of iodine (2.09 g, 8.23 mmol) dissolved in 20 mL of 1:1 CCl_4/pyridine with stirring. The reaction was allowed to warm to ambient temperature overnight. The reaction mixture was diluted with ether (100 mL) and washed successively with water (40 mL), HCl (5%, aq, 2 x 40 mL), water (40 mL), and $Na_2S_2O_3$ (20%, aq, 40 mL). The organic phase was dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by flash chromatography (hexanes/EtOAc, 9:1) to give **114** (675 mg, 2.86 mmol, 71%) as a light yellow oil: IR 2929, 1682, 1594, 1454 cm^{-1}; ^1H NMR δ 1.21 (d, *J* = 6.7 Hz, 3H), 1.75-1.91 (m, 1 H), 2.06-2.18 (m, 1H), 2.35- 2.68 (m, 3H), 7.68-7.73 (m, 1H); ^{13}C NMR δ 15.2 (-), 29.0 (+), 29.9 (+), 40.7 (-), 102.8 (+), 158.3 (-), 193.9 (+); HRMS (EI) calcd for C_7H_9IO (M^+) 235.9698, found 235.9688.

2-(2-Nitrophenyl)-6-methyl-2-cyclohexen-1-one (115).

The same procedure as described for **32** was repeated except that a mixture of 2-iodo-6-methyl-2-cyclohexen-1-one (**114**) (606 mg, 2.57 mmol), 1-(tri-*n*-butylstannyl)-2-nitrobenzene

(**25**) (1.26 g, 3.07 mmol), $PdCl_2(PhCN)_2$ (48.9 mg, 0.13 mmol), Ph_3As (78.5 mg, 0.26 mmol), CuI (48.7 mg, 0.26 mmol), and NMP (5 mL) after 1.5 days gave **115** (491 mg, 2.12 mmol, 83%) as a pale yellow oil: IR 2931, 1679, 1524, 1349 cm^{-1}; ^1H NMR δ 1.19 (d, *J* = 6.7 Hz, 3H), 1.82-1.98 (m, 1H), 2.12-2.23 (m, 1H), 2.50-2.67 (m, 3H), 6.96 (td, *J* = 3.6 and 2.0 Hz, 1 H), 7.26 (dd, *J* = 8.3 and 1.6 Hz, 1H), 7.47 (td, *J* = 7.5 and 1.6 Hz, 1H), 7.59 (td, *J* = 7.7 and 1.6 Hz, 1H), 8.02 (dd, *J* = 8.1 and 1.4 Hz, 1H); ^{13}C NMR δ 14.7 (-), 25.5 (+), 30.3 (+), 41.5 (-), 123.9 (-), 128.5 (-), 131.6 (-), 132.1 (+), 133.2 (-), 138.6 (+), 146.0 (-), 148.3 (+), 198.9 (+); HRMS (DEI) calcd for $C_{13}H_{13}NO_3$ (MH^+) 232.0974, found 232.0968.

Impurity: 1-nitro-2-(2-nitrophenyl)benzene (43). ^1H NMR δ 7.30 (dd, *J* = 8.1 and 1.6 Hz), 7.70 (td, *J* = 7.5 and 1.6 Hz), 8.23 (dd, *J* = 8.1 and 1.6 Hz). Partial ^{13}C NMR δ 124.4, 128.9, 130.8, 134.0.

1,2,3,9-Tetrahydro-3-methyl-4*H*-carbazol-4-one[35] (116).

The same procedure as described for **5** was repeated except that a mixture of 6-methyl-2-(2-nitrophenyl)-2-cyclohexenone (**115**) (187 mg, 0.80 mmol), Pd(dba)2 (31.0 mg, 0.05 mmol), dppp (22.2 mg, 0.05 mmol), 1,10-phenanthroline monohydrate (21.4 mg, 0.10 mmol), and DMF (5 mL) after 48 h gave **116** (156 mg, 0.78 mmol, 97%) as a white powder.

3-Methyl-9*H*-carbazol-4-ol[64] (117).

A mixture of 3-methyl-1,2-dihydrocarbazol-4(3H)-one (**116**) (159 mg, 0.80 mmol), 10% Pd/C (108 mg), diphenyl ether (6 mL), and 1,2,4-trimethylbenzene (0.75 mL) was degassed by bubbling argon through the mixture for 10 min. The reaction mixture was heated at 230 °C for 20 h. The reaction was filtered through a short column of silica gel using petroleum ether

followed by CH_2Cl_2/formic acid (99.9:0.1) to give **117** (98.9 mg, 0.50 mmol, 63%) as a white solid.

3-Iodo-5-methyl-2-cyclohexen-1-one (119).

To a solution of triphenylphosphine (4.75 g, 18.1 mmol) in acetonitrile (80 mL) was added iodine (4.53 g, 17.8 mmol). The reaction mixture was stirred for 2 h. Triethylamine (2.6 mL, 18.7 mmol) was added slowly, followed by 5-methyl-1,3-cyclohexanedione (2.04 g, 16.2 mmol). The reaction mixture was stirred for 14 days at ambient temperature. The solvent was evaporated, and the crude product was purified by flash chromatography (hexanes/EtOAc, 95:5) to give **119** (3.44 g, 14.6 mmol, 90%) as a light yellow oil: IR 2956, 1676, 1592 cm^{-1}; ^1H NMR δ 1.07 (dd, *J* = 6.5 and 1.8 Hz, 3H), 2.10 (ddd, *J* = 12.1, 11.7, and 3.6 Hz, 1H), 2.24-2.40 (m, 1H), 2.46-2.65 (m, 2H), 2.95-3.06 (m, 1H), 6.77-6.82 (m, 1H); ^{13}C NMR δ 19.9 (-), 30.9 (+), 44.0 (-), 47.6 (-), 125.7 (+), 139.4 (-), 194.3 (+); HRMS (EI) calcd for C_7H_9IO (M^+) 235.9698, found 235.9696.

3-(2-Nitrophenyl)-5-methyl-2-cyclohexen-1-one (120).

The same procedure as described for **32** was repeated except that a mixture of 3-iodo-5-methyl-2-cyclohexen-1-one (**119**) (1.00 g, 4.24 mmol), 1-(tri-*n*-butylstannyl)-2-nitrobenzene (**25**) (2.10 g, 5.08 mmol), $PdCl_2(PhCN)_2$ (81.3 mg, 0.21 mmol), Ph_3As (130 mg, 0.42 mmol), CuI (80.8 mg, 0.42 mmol), and NMP (8.4 mL) gave after 48 h **120** (873 mg, 3.78 mmol, 89%) as a pale yellow solid: mp 62-64.5 ^oC; IR 2956, 1669, 1525, 1346 cm^{-1}; ^1H NMR δ 1.14 (d, *J* = 5.5 Hz, 3H), 2.13-2.63 (m, 5H), 5.99 (s, 1H), 7.32 (d, *J*= 7.5 Hz, 1H), 7.56 (td, *J* = 7.5 and 2.4 Hz, 1H), 7.69 (td, *J* = 7.7 and 2.4 Hz, 1H), 8.11 (d, *J*= 8.1 Hz, 1H);^{13}C NMR δ 20.9 (-), 30.7 (-), 38.8

(+), 45.4 (+), 124.8 (-), 127.1 (-), 129.4 (-), 129.6 (-), 133.8 (-), 136.4 (+), 146.5 (+), 159.8 (+), 199.0 (+); HRMS (DEI) calcd for $C_{13}H_{13}NO_3$ (MH^+) 232.0974, found 232.0974.

2,3,4,9-Tetrahydro-3-methyl-1*H*-carbazol-1-one[31] (1).

The same procedure as described for **5** was repeated except that a mixture of 5-methyl-3-(2-nitrophenyl)-2-cyclohexenone (**120**) (133 mg, 0.58 mmol), $Pd(dba)_2$ (19.9 mg, 0.03 mmol), dppp (14.3 mg, 0.03 mmol), 1,10-phenanthroline monohydrate (13.7 mg, 0.07 mmol), and DMF (6 mL) after 72 h gave **1** (88.5 mg, 0.44 mmol, 77%) as a white powder.

4-Iodo-3-nitrophenol[65] (122).

The same procedure as described for **29** was repeated except that 4-amino-3-nitrophenol (1.01 g, 6.55 mmol), water (8mL), concentrated H_2SO_4 (1mL), $NaNO_2$ (506 mg, 7.33 mmol), KI (1.30 g, 7.8 mmol), and Cu powder (8.00 mg, 0.13 mmol) gave **122** (1.06 g, 4.00 mmol, 61%) as a yellow solid.

1-Iodo-2-nitro-4-methoxybenzene[66] (123).

4-iodo-3-nitrophenol (**122**) (1.00 g, 3.78 mmol), MeI (2.35 mL, 37.7 mmol), K_2CO_3 (2.63 g, 19.0 mmol), and acetone (16 mL) were combined and heated at reflux for 20 h. The reaction mixture was allowed to cool and was filtered. The filtrate was concentrated to yield **122** (1.05 g, 3.78 mmol, 100%) as a yellow solid.

1-(tri-*n*-Butylstannyl)-2-nitro-4-methoxybenzene (124).

To a solution of **123** (923 mg, 3.32 mmol) in toluene (6 mL) was added hexabutylditin (2.50 mL, 4.95 mmol), $PdCl_2(PPh_3)_2$ (23.6 mg, 0.03 mmol), and PPh_3 (17.6 mg, 0.06 mmol). The reaction was heated at 80 ^oC for 4 days. The reaction was diluted with benzene (100 mL) and washed with NH_4OH (10%, aq, 3 X 30 mL) and H_2O (2 X 30 mL). The organic phase was dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography (hexanes) to give **124** (1.13 g, 2.55 mmol, 77%) as a yellow oil: IR 2956, 1528, 1344 cm^{-1}; ^1H NMR δ 0.87 (t, *J* = 7.3 Hz, 3H), 1.10 (t, *J* = 7.7Hz, 2H), 1.30 (sextet, *J* = 4.0 Hz, 2H), 1.42-1.54 (m, 2H), 3.89 (s, 3H), 7.19 (dd, *J* = 8.1 and 2.6 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.85 (d, *J* = 4.3 Hz, 1H); ^{13}C NMR δ 10.8 (+), 13.6 (-), 27.3 (+), 29.0 (+), 55.5 (-), 108.8 (-), 120.6 (-), 130.0 (+), 138.0 (-), 154.5 (+), 160.5 (+): HRMS (FAB) calcd for $C_{19}H_{33}NO_3Sn$ (M^-) 443.1482, found 443.1491.

3-(4-Methoxy-2-nitrophenyl)-5-methyl-2-cyclohexen-1-one (125).

The same procedure as described for **32** was repeated except that a mixture of 3-iodo-5-methyl-2-cyclohexen-1-one (**119**) (208 mg, 0.88 mmol), 1-(tri-*n*-butylstannyl)-4-methoxy-2-nitrobenzene (**124**) (445 mg, 1.00 mmol), $PdCl_2(PhCN)_2$ (17.2 mg, 0.04 mmol), Ph_3As (27.1 mg, 0.08 mmol), CuI (17.8 mg, 0.09 mmol), and NMP (2 mL) after 2 days gave **125** (222 mg, 0.84 mmol, 96%) as a yellow solid: mp 45-47 ^oC; IR 2953, 1666, 1531, 1350 cm^{-1}; ^1H NMR δ 1.11 (d, *J* = 6.1, 3H), 2.11-2.61 (m, 5H), 3.9 (s, 3H), 5.96 (s, 1H), 7.18-7.21 (m, 2H), 7.58 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR δ 21.0 (-), 30.7 (-), 38.9 (+), 45.4 (+), 56.0 (-), 109.81 (-), 119.9 (-), 127.3 (-), 128.7 (+), 130.7 (-), 147.5 (+), 159.9 (+), 160.03 (+), 199.34 (-); HRMS (DEI) calcd for $C_{14}H_{15}NO_4$ (MH^+) 262.1080, found 262.1078.

2,3,4,9-Tetrahydro-7-methoxy-3-methyl-1*H*-carbazol-1-one[33] (83).

The same procedure as described for **5** was repeated except that a mixture of 5-methyl-3-(4-methoxy-2-nitrophenyl)-2-cyclohexenone (**125**) (73.6 mg, 0.28 mmol), $Pd(dba)_2$ (9.7 mg, 0.02 mmol), dppp (6.9 mg, 0.02 mmol), 1,10-phenanthroline monohydrate (6.7 mg, 0.04 mmol), and DMF (5 mL) gave **83** (57.7 mg, 0.25 mmol, 89%) as a white powder.

Methyl (+)-(*S*)-1-ethyl-2-oxo-3-cyclohexene-1-propanoate[35] (109).

To a solution of methyl (+)-(*S*)-1-ethyl-2-oxocyclohexane-1-propanoate[35] (**108**) (3.25 g, 15.3 mmol) in DMF (23 mL) was added triethylamine (11.3 mL, 81.1 mmol). Trimethylsilyl chloride (5.93 mL, 46.7 mmol) was added slowly to the reaction mixture. The reaction mixture was heated at 100 ^{o}C for 3 days. The reaction mixture was allowed to cool to RT, and then was diluted with hexanes (50 mL) and poured into cold water (50 mL). The layers were separated, and the aqueous portion was extracted with hexanes (3 X 50 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated. To a portion of the crude silyl enol ether[35] (1.94 g, 6.82 mmol) in DMSO (50 mL) was added $Pd(OAc)_2$ (159 mg, 0.71 mmol). The flask containing the reaction mixture was flushed with oxygen, and was kept under oxygen (1 atm, balloon) while being heated at 40 ^{o}C for 72 hrs. Additional $Pd(OAc)_2$ (95.6 mg, 0.43 mmol) was added to the reaction mixture, and the reaction was heated at 60 ^{o}C for 24 hrs. The reaction mixture was cooled and diluted with ethyl acetate (200 mL). The reaction mixture was washed with water (3 X 50 mL), dried ($MgSO_4$), and concentrated. The product was purified by flash chromatography (hexanes/EtOAc, 7:3) to give **109** (820 mg, 3.90 mmol, 57%) as a colorless oil.

Methyl (*S*)-1-ethyl-2-oxo-3-iodo-3-cyclohexenone-1-propanoate (127).

The same procedure was repeated as described for **22** except that a solution of iodine (1.26 g, 4.96 mmol) in CCl_4 (5 mL) and pyridine (5 mL) was added to a solution of **109** (508 mg, 2.42 mmol) in CCl_4 (5 mL) and pyridine (5 mL). The product was purified via flash chromatography (hexanes/EtOAc, 8:2) to give **127** (698 mg, 2.08 mmol, 86%) as a light yellow oil: IR 3450, 2944, 1732, 1679 cm^{-1}; ^1H NMR δ 0.83 (t, *J* = 7.5 Hz, 3H), 1.49-1.71 (m, 2H), 1.80-2.01 (m, 4H), 2.11-2.36 (m, 2H), 2.43-2.50 (m, 2H), 7.64 (t, *J* = 4.1 Hz, 1H); ^{13}C NMR δ 7.9 (-), 26.8 (+), 28.5 (+), 28.5 (+), 30.0 (+), 47.7 (+), 51.4 (-), 103.4 (+), 157.3 (-), 173.5 (+), 195.3 (+); HRMS (DEI) calcd for $C_{12}H_{17}IO_3$ (MH^+) 336.0222, found 336.0210.

Methyl (*S*)-1-ethyl-2-oxo-3-(2-nitrophenyl)-3-cyclohexenone-1-propanoate (128).

The same procedure as described for **32** was repeated except that a mixture of **127** (250 mg, 0.74 mmol), 1-(tri-n-butylstannyl)-2-nitrobenzene (**25**) (369 mg, 0.89 mmol), $PdCl_2(PhCN)_2$ (14.9 mg, 0.04 mmol), Ph_3As (23.1 mg, 0.08 mmol), CuI (14.5 mg, 0.08 mmol), and NMP (1.4 mL) after 40 h gave **128** (196 mg, 0.59 mmol, 80%) as a yellow oil: IR 3446, 2939, 1736, 1669, 1526, 1353 cm^{-1}; ^1H NMR δ 0.87 (t, *J* = 7.5 Hz, 3H), 1.52-2.05 (m, 6H), 2.28 (t, *J* = 7.7 Hz, 2H), 2.58 (q, *J* = 4.6 Hz, 2H), 6.94 (t, *J* = 4.2 Hz, 1H), 7.24 (dd, *J* = 7.5 and 1.4 Hz, 1H), 7.44 (td, *J* = 7.6 and 1.4 Hz, 1H), 7.57 (td, *J* = 7.5 and 1.4 Hz, 1H), 7.96 (dd, *J* = 8.1 and 1.2 Hz, 1H); ^{13}C NMR δ 7.8 (-), 22.6 (+), 26.2 (+), 28.4 (+), 28.5 (+), 30.0 (+), 46.8 (+), 51.4 (-), 123.7 (-), 128.5 (-), 131.8 (-), 132.1 (+), 132.9 (-), 138.0 (+), 145.4 (-), 148.7 (+), 174.0 (+), 199.3 (+); HRMS (DEI) calcd for $C_{12}H_{17}IO_3$ (MH^+) 332.1498, found 332.1512.

Methyl (-)-(*S*)-[3-ethyl-4-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl]propanoate[35] (112).

The same procedure as described for **5** was repeated except that a mixture of **128** (184 mg, 0.56 mmol), $Pd(dba)_2$ (19.5 mg, 0.03 mmol), dppp (14.0 mg, 0.03 mmol), 1,10-phenanthroline monohydrate (13.5 mg, 0.06 mmol), and DMF (5 mL) after chromatography and recrystallization (hexanes/EtOAc, 2:1) gave **112** (126 mg, 0.42 mmol, 76%) as a white crystalline solid.

1,2,3,4-Tetrahydrocarbazole[49a] (129).

Hydrogen gas was bubbled through a mixture of 2-(2-nitrophenyl)-2-cyclohexen-1-one (**32**) (54.3 mg, 0.25 mmol) and 10% Pd/C (50.7 mg) in MeOH (10 mL) for 5 min. The reaction mixture was stirred under H_2 (1 atm, balloon) for 2 h. The reaction mixture was filtered through Celite and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 8:2) to yield **129** (41.1 mg, 0.24 mmol, 95%) as a white solid.

Alternate procedure A for 129 and 5. The same procedure as described above was repeated except that a mixture of **70** (52.9 mg, 0.23 mmol) and 10% Pd/C (51.6 mg) in MeOH (10 mL) gave **129** (8.5 mg, 0.049 mmol, 22%) and **5** (18.9 mg, 0.10 mmol, 45%).

Alternate procedure B for 129. The same procedure as described above was repeated except that a mixture of **5** (18.5 mg, 0.10 mmol) and 10% Pd/C (19.0 mg) in MeOH (5 mL) gave **129** (6.0 mg, 0.035 mmol, 35%) and recovered **5** (7.3 mg, 0.039 mmol, 39%) after 3 days.

[(4-Methyl-1-cyclohexen-1-yl)oxy]trimethylsilane[49a] (139).

Butyllithium (20.0 mL of a 2.5 M solution in hexanes, 50.0 mmol) was added dropwise to a solution of diisopropylamine (8.15 mL, 58.2 mmol) in THF (160 mL) cooled to –78 ^{o}C

under an argon atmosphere. The reaction mixture was stirred 10 min and a solution of 4-methylcyclohexanone (5.01 g, 44.6 mmol) in THF (40 mL) was added slowly to the reaction mixture. The reaction mixture was stirred for 30 min, and then TMSCl (6.80 mL, 53.6 mmol) and Et_3N (12.5 mL, 89.7 mmol) were added slowly. The reaction mixture was allowed to warm to room temperature over 1 h. The reaction mixture was diluted with diethyl ether (400 mL), washed with water (3 x 100 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 9:1) to give **139** (8.23 g, 44.6 mmol, 100%) as a clear, colorless oil.

4-Methyl-2-cyclohexen-1-one[19] (140).

To a solution of **139** (3.14, 17.0mmol) in DMSO (100 mL) was added $Pd(OAc)_2$ (366 mg, 1.63 mmol). The reaction flask was flushed with O_2 for 5 min. The reaction mixture was stirred at 40 ^oC under O_2 (1 atm, balloon) for 24 h. The reaction mixture was allowed to cool, and then was diluted with 400 mL of EtOAc and washed with water (3 x 100 mL). The organic phase was dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (hexanes:EtOAc, 9:1) to give **140** (676 g, 6.14 mmol, 36%) as a clear, colorless oil.

2-Iodo-4-methyl-2-cyclohexen-1-one (141).

The same procedure was repeated as described for **22** except that a solution of iodine (2.97 g, 11.7 mmol) in CCl_4 (10 mL) and pyridine (10 mL) was added dropwise to a solution of **140** (628 mg, 5.70 mmol) in CCl_4 (10 mL) and pyridine (10 mL) to yield **141** (873 mg, 3.70 mmol, 65%) as a yellow oil: IR 2958, 2870, 1686, 1585, 1454 cm^{-1}; ^1H NMR δ 1.19 (d, J = 7.2

Hz, 3H), 1.68-1.83 (m, 1H), 2.11-2.23 (m, 1H), 2.48-2.82 (m, 3H), 7.61 (d, *J* = 2.9 Hz, 1H); ^{13}C NMR δ 19.7 (-), 30.6 (+), 35.6 (+), 35.7 (-), 103.0 (+), 164.7 (-), 192.0 (+).

4-Methyl-2-(2-nitrophenyl)-2-cyclohexen-1-one (142).

The same procedure as described for **32** was repeated except that a mixture of 2-iodo-4-methyl-2-cyclohexen-1-one (**141**) (405 g, 1.72 mmol), 1-(tri-*n*-butylstannyl)-2-nitrobenzene (**25**) (854 mg, 2.07 mmol), $PdCl_2(PhCN)_2$ (32.9 mg, 0.09 mmol), Ph_3As (52.6 mg, 0.17 mmol), CuI (32.7 mg, 0.17 mmol), and NMP (4 mL) after 2 days gave **142** (318 mg, 1.38 mmol, 80%) as a light yellow oil: IR 2960, 2871, 1682, 1525, 1352 cm^{-1}; ^{1}H NMR δ 1.26 (d, *J* = 7.1 Hz, 3H), 1.74-1.91 (m, 1H), 2.14 (m, 1H), 2.46-2.84 (m, 3H), 6.81 (m, 1H), 7.25 (d, *J* = 5.9 Hz, 1H), 7.47 (t, *J* = 6.3 Hz, 1H), 7.60 (t, *J* = 7.9 Hz, 1 H), 8.02 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR δ 20.2 (-), 30.5 (+), 31.6 (-), 37.0 (+),124.1 (-), 128.7 (-), 131.6 (-), 131.9 (+), 133.2 (-), 138.1 (+), 148.5 (+), 152.1 (-), 196.4 (+).

Impurity: 1-Nitro-2-(2-nitrophenyl)benzene (43). Partial ^{1}H NMR δ 7.79 (t, *J* = 7.9 Hz), 8.22 (d, *J* = 8.1 Hz). Partial ^{13}C NMR δ 124.6 (-), 129.0 (-), 130.8 (-), 133.4 (-), 134.0.

3-Methyl-2-(2-nitrophenyl)-2-cyclohexen-1-one (144).

The same procedure as described for **32** was repeated except that a mixture of 2-iodo-3-methyl-2-cyclohexen-1-one[18] (**143**) (404 mg, 1.71 mmol), 1-(tri-*n*-butylstannyl)-2-nitrobenzene (**25**) (850 mg, 2.06 mmol), $PdCl_2(PhCN)_2$ (32.9 mg, 0.09 mmol), Ph_3As (52.4 mg, 0.17 mmol), CuI (32.8 mg, 0.17 mmol), and NMP (4 mL) gave **144** (309 mg, 1.33 mmol, 78%) as a light yellow solid: mp 75-77 ^{o}C; IR 2943, 2873, 1663, 1622, 1522, 1356 cm^{-1}; ^{1}H NMR δ 1.78 (s, 3H), 1.99-2.22 (m, 2H), 2.42-2.64 (m, 4H), 7.16 (dd, *J* = 7.5 and 1.6 Hz, 1H), 7.47 (td, *J* = 7.7

and 1.6 Hz, 1H), 7.60 (td, *J* = 7.5 and 1.4 Hz, 1H), 8.08 (dd, *J* = 8.1 and 1.4Hz, 1H); ^{13}C NMR δ 21.8 (+), 22.4 (-), 32.3 (+), 37.5 (+), 124.4 (-), 128.4 (-), 131.7 (+), 132.5 (-), 133.0 (-), 135.1 (+), 148.8 (+), 156.5 (+), 196.6 (+).

1-Methyl-1,2,3,4-tetrahydrocarbazole[67] (131).

The same procedure as described for **129** was repeated except that a mixture of 6-methyl-2-(2-nitrophenyl)-2-cyclohexen-1-one (**115**) (37.0 mg, 0.16 mmol), 10% Pd/C (37.4 mg), and MeOH (10 mL) after 2 h and chromatography (hexanes/EtOAc, 95:5) gave **131** (27.2 mg, 0.15 mmol, 91%) as a white solid.

4-Methyl-1,2,3,4-tetrahydrocarbazole[68] (134).

The same procedure as described for **129** was repeated except that a mixture of 3-methyl-2-(2-nitrophenyl)-2-cyclohexen-1-one (**144**) (155 mg, 0.67 mmol), 10% Pd/C (151 mg), and MeOH (10 mL) after 30 min and chromatography (hexanes/EtOAc/Et_3N, 98:2:1 mL per 500 mL of solvent) gave **134** (97.6 mg, 0.52 mmol, 78%) as a white solid.

2-Methyl-1,2,3,4-tetrahydrocarbazole[51] (135).

The same procedure as described for **129** was repeated except that a mixture of 5-methyl-2-(2-nitrophenyl)-2-cyclohexen-1-one (**33**) (100 mg, 0.43 mmol), 10% Pd/C (100 mg), and MeOH (10 mL) after 2 h and chromatography (hexanes/EtOAc/Et_3N, 98:2:1 mL/500 mL of solvent) gave **135** (73.6 mg, 0.40 mmol, 92%) as a white solid.

3-Methyl-1,2,3,4-tetrahydrocarbazole[50a] (145).

The same procedure as described for **129** was repeated except that a mixture of 4-methyl-2-(2-nitrophenyl)-2-cyclohexen-1-one (**142**) (150 mg, 0.65 mmol), 10% Pd/C (175 mg), and MeOH (10 mL) after 30 min and chromatography (hexanes/EtOAc/Et_3N, 98:2:1 mL/500 mL of solvent) gave **145** (107 mg, 0.58 mmol, 89%) as a white solid.

1,2,3,3a,4,8b-Hexahydrocyclopent[*b*]indole[69] (146).

The same procedure as described for **129** was repeated except that a mixture of 2-(2-nitrophenyl)-2-cyclopenten-1-one (**34**) (117 mg, 0.58 mmol), 10% Pd/C (115 mg), and MeOH (10 mL) after 20 min without purification gave **146** (76.1 mg, 0.48 mmol, 83%) as a white solid.

5,6,7,8,9,10-Hexahydrocyclohept[*b*]indole[68] (147).

The same procedure as described for **129** was repeated except that a mixture of 2-(2-nitrophenyl)-2-cyclohepten-1-one (**35**) (65.8 mg, 0.28 mmol), 10% Pd/C (66.0 mg), and MeOH (10 mL) after 2.5 h and chromatography (hexanes/EtOAc, 95:5) gave **147** (37.8 mg, 0.20 mmol, 72%) as a white solid.

8-Methyl-1,2,3,4-tetrahydrocarbazole[70] (148) and 8-Methyl-1,2,3,4,4a,9a-hexahydrocarbazol-1-one (149).

The same procedure as described for **129** was repeated except that a mixture of 2-(3-methyl-2-nitrophenyl)-2-cyclohexen-1-one (**39**) (90.7 mg, 0.39 mmol), 10% Pd/C (90.5 mg), and MeOH (10 mL) after 20 min and chromatography (hexanes/EtOAc/Et_3N, 98:2:1 mL per 500 mL of solvent) gave a mixture of **148** (12.7 mg, 0.07 mmol, 17%) as a white solid and **149** (31.9 mg,

0.16 mmol, 40%) as a white solid: mp 102-104 ^{o}C; IR 2934, 1707, 1516, 1370 cm^{-1};^{1}H NMR δ 1.73-2.58 (m, 7H, 2.33 (s, 3H), 3.64 (dd, *J* = 12.4 and 5.3 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR δ 17.7 (-), 25.4 (+), 27.5 (+), 35.1 (+), 42.1 (+), 52.4 (-), 127.4 (-), 129.5 (+), 129.9 (-), 130.0 (-), 130.8 (+), 151.4 (-), 207.7 (+).

Alternate procedure for compound 149. 8-Methyl-1,2,3,4,4a,9a-hexahydrocarbazol-1-one (**149**) was also prepared exclusively in the same manner as described above using a mixture of **39** (141 mg, 0.61 mmol), 10% Pd/C (13.4 mg), and MeOH (10 mL) after 1 h 20 min to give **149** (136 mg, 0.67 mmol, 100%).

5-Carbomethoxy-1,2,3,4-tetrahydrocarbazole (150) and 5-Carbomethoxy-1,2,3,4,4a,9a-hexahydrocarbazol-1-one (151).

The same procedure as described for **129** was repeated except that a mixture of 2-(6-carbomethoxy-2-nitrophenyl)-2-cyclohexen-1-one (**40**) (50.8 mg, 0.18 mmol), 10% Pd/C (54.9 mg), and MeOH (10 mL) after 2 h and chromatography (hexanes/EtOAc, 95:5) gave a mixture of **150** (10.7 mg, 0.05 mmol, 25%) and **151** (16.8 mg, 0.07 mmol, 37%) as white solids: **150** ^{1}H NMR δ 1.77-1.97 (m, 4H), 2.73-2.82 (m, 2H), 2.85-2.93 (m, 2H), 3.94 (s, 3H), 7.11 (td, *J* = 7.7 and 1.7 Hz, 1H), 7.43 (dt, *J* = 8.1 and 1.7 Hz, 1H), 7.64 (dt, *J* = 7.4 and 1.7 Hz, 1H), 7.93 (s, 1H); **151** ^{1}H NMR δ 1.58-1.77 (m, 4H), 1.89-2.06(m, 2H), 3.51 (p, *J* = 6.2 Hz, 1H), 3.80-3.87 (m, 2H), 3.88 (s, 3H), 6.84 (d, *J* = 7.9 Hz, 1 H), 7.07 (t, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H).

7-Methoxy-1,2,3,4-tetrahydrocarbazole[71] (152) and 7-Methoxy-1,2,3,4,4a,9a-hexahydrocarbazol-1-one[72] (153)

The same procedure as described for **129** was repeated except that a mixture of 2-(4-methoxy-2-nitrophenyl)-2-cyclohexenone (**37**) (105 mg, 0.42 mmol), 10% Pd/C (104 mg), and MeOH (10 mL) after 20 min and chromatography (hexanes/EtOAc/Et_3N, 95:5:1 mL per 500 mL of solvent) gave an inseparable mixture of **152** (52.5 mg, 0.26 mmol, 62%) and **153** (7.9 mg, 0.04 mmol, 9%). Yields were estimated from the ^1H NMR spectrum.

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B.S., Summa Cum Laude, Chemistry, Fairmont State College, Fairmont, West Virginia, 1996.

Research Experience

West Virginia University, 1998-2001

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The preparation of carbazole derivatives *via* two palladium-catalyzed reactions, a Stille coupling followed by a reductive *N*-heteroannulation was investigated. This method was applied to the syntheses of several naturally occurring carbazole alkaloids. The reduction of 2-(2-nitrophenyl)-2-cyclohexenones, followed by cyclization, leading to 1,2,3,4-tetrahydrocarbazoles is currently being investigated.

West Virginia University, 1997-1998

Research Director: Professor Debra L. Mohler

The development of cyclopentadienyl metal complexes as new agents for the modification of oligonucleotides was investigated. The mechanism of DNA modification, the attachment of DNA recognition elements to the complexes, and the use of chemiluminescent detection methods in DNA affinity cleavage and sequencing experiments were also studied.

Fairmont State College, Spring 1994

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An enzyme-linked immunochemical assay to measure the titer of antibodies directed at specific antigens was developed and characterized.

Teaching Experience

West Virginia University

Teaching Assistant for undergraduate General Chemistry and Organic Chemistry, Fall 1996, Summer 1998, Fall 1998.

Designed a project appropriate for undergraduate research and supervised the research activities of undergraduate students, Summer 1997, Spring 1998, Spring 2001.

Fairmont State College

Teaching Assistant for undergraduate General Chemistry, Fall 1995 and Spring 1996.

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Departmental Safety Committee member, West Virginia University, January 1998 – June 2001.

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Honors and Awards

West Virginia University Safety Committee Achievement Award, 1999, 2000, and 2001.
American Chemical Society Women Chemists Committee Travel Award, 2000.
Winifred Knutti Outstanding Female Graduate Student, 1998.
Phi Lambda Upsilon Chemistry Honorary Society Member, 1997-present.
Trotter Fellowship, 1996-2001.
Hodge Fellowship, 1996-2001.
Eberly College of Arts and Sciences Endowed Fellowship, 1996-2000.

William C. Ruoff Memorial Fund Award, 1996.
Outstanding Senior Chemistry Award, 1996.
Eleanor M. Ford Outstanding Senior in Science and Mathematics Award, 1996.
Fairmont State College ACS Outstanding Junior in Chemistry Award, 1995.
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Publications

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Mohler, D. L.; Dain, D. R.; Kerekes, A. D.; Nadler, W. R.; Scott, T. L. "*Organometallic Photonucleases: A Novel Class of DNA-Cleaving Agents*," *Bioorganic and Medicinal Chemistry Letters* **1998**, *8*, 871.

Söderberg, B. C. G.; Scott, T. L. "*Novel Palladium-Catalyzed Synthesis of Carbazolones*," manuscript under preparation.

Söderberg, B. C. G.; Scott, T. L. "*Palladium-Catalyzed Synthesis of Carbazolones and the Formal Total Syntheses of Several Carbazole Alkaloids*," manuscript under preparation.

Presentations

Söderberg, B. C.; Scott, T. L. "*Synthesis of Tetrahydrocarbazoles*," presented at the 221st ACS National Meeting, San Diego, California, April 2001; ORGN-381.

Söderberg, B. C.; Scott, T. L. "*Novel Palladium-Catalyzed Synthesis of Carbazolones and the Formal Total Syntheses of Several Naturally Occurring Carbazole Alkaloids*," presented at the 220th ACS National Meeting, Washington, D. C., August 2000; ORGN-459.

Söderberg, B. C.; Turner, M. R.; Scott, T. L. "*Novel Synthesis of 3-Substituted Indoles and Carbazoles*," presented at the 218th ACS National Meeting, New Orleans, August 22-26, 1999; ORGN-301.

Söderberg, B. C.; Turner, M. R.; Scott, T. L.; Arrington, A. K.; O'Neil, S. N.; Shriver, J.A.; Rector, S. R.; Criser, A. L.; Chisnell, A. C. "*Palladium-Catalyzed Synthesis of Indoles and Carbazoles*," presented at the 17th International Congress of Heterocyclic Chemistry, Vienna, Austria, August 1-6, 1999; Abstract 572.

Mohler, D. L.; Scott, T. L.; Flood, M. R. "*Cyclopentadienyl Metal Complexes As Photonucleases: A Novel Class of DNA Cleaving Agents*," presented at the West Virginia University ACS Meeting-In-Miniature, Morgantown, WV, April 18, 1998; paper O4.

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Scott, T. L.; Wolfe, K. L.; Magro, A. "*Development of A Rapid and Sensitive Assay for Antigen Specific Immunoglobulins*," presented at the West Virginia Academy of Science, Fairmont, WV, April 1994.

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