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Construction of the Benzindenoazepine Skeleton via Cyclopentannulation of Fischer Aminocarbene Complexes: Total Synthesis of Bulgaramine

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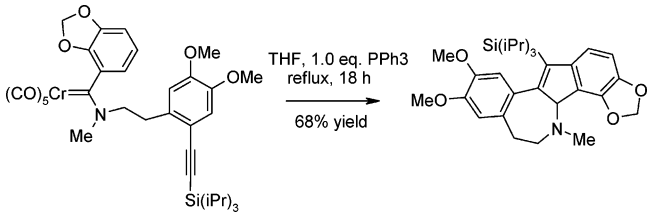
Received March 31, 2005



A total synthesis of bulgaramine has been accomplished with a longest linear sequence of eight steps and an overall yield of 23% from commercially available 3,4-dimethoxyphenethyl alcohol. An intramolecular cyclopentannulation reaction of a Fischer aminocarbene complex provided the key step and occurred under significantly milder conditions and in higher yields than those of other reported examples of this reaction type. The reaction solvent was a critical factor in the cyclopentannulation reaction, with measurable amounts of the desired product observed only when THF was utilized. The product yield could be further enhanced by the addition of two-electron donor ligands, demonstrating the first example of this effect on the thermal reaction of aminocarbene complexes with alkynes.

Introduction

Plants of the genus *Fumaria* have long been utilized in several Asian and eastern European countries as folk medicines for their antipyretic, analgesic, and diuretic properties.[1] A wealth of chemical constituents that may be responsible for these properties have been extracted from these plants, including a series of compounds based on the benzindenoazepine ring system.[2] Among the known benzindenoazepines, bulgaramine (Figure 1) has received attention because of its apparent central position in the biogenic pathway of *Fumaria*-derived alkaloids.[3]

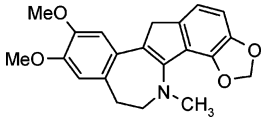


FIGURE 1. Bulgaramine.

It has been suggested that spirobenzylisoquinolines are the biological precursors to bulgaramine, which in turn is converted to other benzindenoazepines and/or related alkaloids of a higher oxidation state. Evidence for this hypothesis has been provided by semisynthetic transformations patterned after these proposed biological pathways.[4] In addition to these biogenic studies, the valuable medicinal properties and interesting architectural features of the benzindenoazepines have motivated the development of new synthetic methodology geared toward their synthesis.[5]

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(1) (a) Blasko, G. In *The Alkaloids*; Brossi, A., Ed.; Academic Press Inc.: New York, 1990; pp 157−224. (b) Lee, T. B. *Illustrated Flora of Korea*; Hanygmoonsa: Seoul, 1989; p 385.

(2) (a) Blasko, G.; Hussain, S. F.; Freyer, A. J.; Shamma, M. *Tetrahedron Lett*. **1981**, *22*, 3127. (b) Murugesan, N.; Blasko, G.; Minard, R. D.; Shamma, M. *Tetrahedron Lett*. **1981**, *22*, 3131. (c) Blasko, G.; Murugesan, N.; Hussain, S. F.; Minard, R. D.; Shamma, M.; Sener, B.; Tanker, M. *Tetrahedron Lett*. **1981**, *22*, 3135. (d) Blasko, G.; Murugesan, N.; Freyer, A. J.; Gula, D. J.; Sener, B.; Shamma, M. *Tetrahedron Lett*. **1981**, *22*, 3139. (e) Blasko, G.; Murugesan, N.; Freyer, A. J.; Minard, R. D.; Shamma, M. *Tetrahedron Lett*. **1981**, *22*, 3143.

(3) Yakimov, G. I.; Mollov, N. M.; Leet, J. E.; Guinaudeau, H.; Freyer, A. J.; Shamma, M. *J. Nat. Prod*. **1984**, *47*, 1048.

(4) For recent examples, see: (a) Kim, I. J.; Park, Y. J.; Kim, J. I.; Lee, K. T.; Kim, S. K. *Arch. Pharm. Res*. **1997**, *20*, 476. (b) Iwasa, K.; Kamigauchi, M.; Takao, N. *J. Nat. Prod*. **1988**, *51*, 1232. (c) Hanaoka, M.; Inoue, M.; Kobayashi, N.; Yasuda, S. *Chem. Pharm. Bull*. **1987**, *35*, 980.

10.1021/jo050631h CCC: $30.25 © 2005 American Chemical Society
Published on Web 07/01/2005

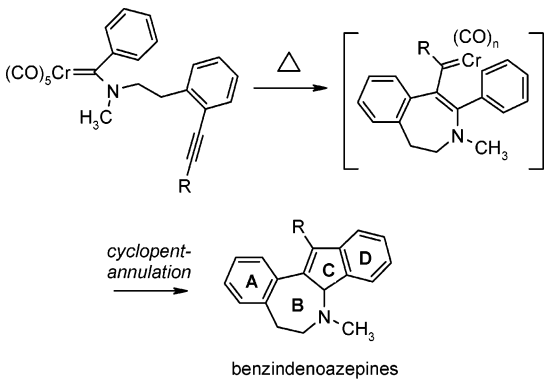


FIGURE 2. Proposed route to benzindenoazepine alkaloids.

Research in our laboratories has focused on thermal reactions of Fischer chromium carbene complexes with silyl-substituted alkynes in an inter- or intramolecular fashion. Under certain experimental conditions, we have observed novel and synthetically valuable annulation reactions that can be achieved with high efficiency.[6] During the course of our studies, we became interested in the benzindenoazepine ring system, noting that a Fischer aminocarbene complex could, in theory, provide a useful precursor for its assembly. Specifically, successful thermal intramolecular cyclopentannulation of a Fischer aminocarbene complex possessing an appropriately functionalized nitrogen-tethered alkyne would allow the benzindenoazepine B and C rings to be constructed in a single step (Figure 2).

Thermal reactions of aryl- and alkenyl-substituted Fischer carbene complexes with alkynes have been vigorously studied for several decades, and the number of different types of products that derive from these reactions is exceedingly large.[7] Trends in reactivity have emerged, however, and are based largely on the substitution pattern of the Fischer carbene complex. The most carefully studied examples entail thermal reactions of alkoxy-substituted carbene complexes with alkynes, which undergo benzannulation and/or pentannulation transformations as the major product-forming pathways. The benzannulation process, in which fragments from the carbene complex, alkyne, and a carbon monoxide ligand join together to form a new phenolic product, is commonly referred to as the Dötz reaction. The pentannulation process, in which a carbon monoxide is not incorporated into the products, is often a competitive reaction pathway to the Dötz reaction and, in fact, is hypothesized to derive from a common intermediate. Nonetheless, researchers have established a number of experimental parameters, including solvent, temperature, and ligand additives, by which either the benzannulation or pentannulation pathway can be favored.[8]

In contrast to the wealth of available information regarding Fischer alkoxycarbene complexes, thermal reactions of the corresponding amino-substituted carbene complexes with alkynes have been explored to a much lesser degree. Yamashita originally established that the pentannulation reaction pathway predominates with aryl-substituted aminocarbene complexes, such that essentially no products are observed in which a carbon monoxide ligand has been incorporated.[9] Subsequent investigations have verified this motif, although exceptions have been reported.[8a,10] The electronic difference between alkoxy- and amino-substituted carbene complexes is thought to provide the key reason for their divergence in reactivity. The greater electron-donating capacity of an amino vs an alkoxy substituent results in increased electron density at the metal center and, consequently, an increase in the strength of the bonds to the carbon monoxide ligands. This serves to disfavor carbon monoxide insertions during annulation processes, thereby resulting in the observed prevalence of pentannulation-derived products.

Although this observed preference for pentannulation reactions would appear to provide the inviting opportunity for the construction of five-membered rings, a problematic corollary is that the increased stability of aminocarbene complexes relative to their alkoxy-substituted counterparts typically necessitates forcing conditions for reactions with alkynes to proceed.[9,11] This often leads to lower product yields and the formation of additional byproducts. In efforts to increase the productivity of annulation reactions with aminocarbene complexes, several researchers have attempted to tabulate additional factors that can affect product yield and distribution, including solvent, concentration, and the presence of ligand additives.[8b,c,12] It is clear, however, that the behavior of Fischer aminocarbene complexes remains less well understood than their alkoxy-substituted counterparts.

The differences in reactivity between alkoxy- and aminocarbenes have also resulted in a disparity in their utilization in synthetic endeavors. On one hand, the efficient and predictable nature of the Dötz benzannulation, coupled with the comparatively mild reaction conditions required, has motivated numerous natural product syntheses that use this transformation in either inter- or intramolecular fashion as a key step.[13] In contrast, the recalcitrant behavior of aminocarbene complexes in annulation reactions appears to have impeded their application in the total synthesis arena.[14] We, therefore, became highly motivated to pursue a total

(5) Fidalgo, J.; Castedo, L.; Dominguez, D. *Tetrahedron Lett*. **1993**, *34*, 7317.

(6) Moser, W. H.; Sun, L.; Huffman, J. *Org. Lett*. **2001**, *3*, 3389.

(7) For recent reviews on synthetic applications of Fischer carbene complexes, see: (a) de Meijere, A.; Duetsch, M.; Schirmer, H. *Angew. Chem., Int. Ed. Engl*. **2000**, *39*, 3964. (b) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev*. **1999**, *28*, 187. (c) Harvey, D. F.; Sigano, D. M. *Chem. Rev*. **1996**, *96*, 271. (d) Wulff, W. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 12, p 469. (e) Herndon, J. W. *Coord. Chem. Rev*. **2000**, *206*, 237.

(8) (a) Barluenga, J.; Lopez, L. A.; Martinez, S.; Tomas, M. *Tetrahedron* **2000**, *56*, 4967. (b) Wulff, W. D.; Bax, B. M.; Brandvold, T. A.; Chan, K. S.; Gilbert, A. M.; Hsung, R. P.; Mitchell, J.; Clardy, J. *Organometallics* **1994**, *13*, 102. (c) Wulff, W. D.; Gilbert, A. M.; Hsung, R. P.; Rahm, A. *J. Org. Chem*. **1995**, *60*, 4566.

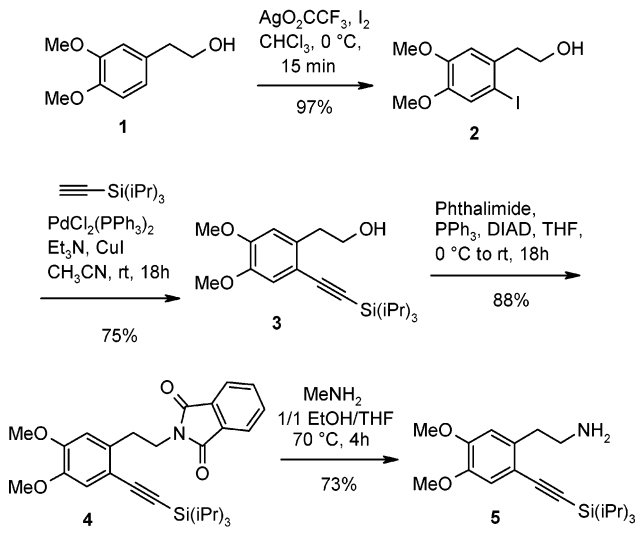
(9) Yamashita, A. *Tetrahedron Lett*. **1986**, *27*, 5915.

(10) (a) Leese, T.; Dötz, K. H. *Chem. Ber*. **1996**, *129*, 623. (b) Rahm, A.; Wulff, W. D. *Tetrahedron Lett*. **1995**, *36*, 8753. (c) Chelain, E.; Parlier, A.; Audouin, M.; Rudler, H.; Daran, J.-C.; Vaissermann, J. *J. Am. Chem. Soc*. **1993**, *115*, 10568.

(11) (a) Yamashita, A.; Toy, A.; Watt, W.; Muchmore, C. R. *Tetrahedron Lett*. **1988**, *29*, 3403. (b) Grotjahn, D. B.; Dötz, K. H. *Synlett* **1991**, 381.

(12) (a) Chan, K. S.; Peterson, G. A.; Brandvold, T. A.; Faron, K. L.; Challener, C. A.; Hyldahl, C.; Wulff, W. D. *J. Organometallic Chem*. **1987**, *334*, 9. (b) Bos, M. E.; Wulff, W. D.; Miller, R. A.; Chamberlin, S.; Brandvold, T. A. *J. Am. Chem. Soc*. **1991**, *113*, 9293.

SCHEME 1. Synthesis of Amine 5



synthesis of the alkaloid bulgaramine in which an intramolecular cyclopentannulation reaction of a Fischer aminocarbene complex provided the key assembly of the benzindenoazepine ring system. Success in this venture would not only provide valuable information regarding the cyclopentannulation reaction itself, but would also represent the first natural product synthesis derived from Fischer aminocarbene complexes.

Results and Discussion

The synthesis of appropriately substituted Fischer aminocarbene complexes began with the preparation of requisite amine **5**, as summarized in Scheme 1. Regioselective ortho iodination of 3,5-dimethoxyphenethyl alcohol (**1**) was achieved with AgO_2CCF_3/I_2 to produce aryl iodide **2**,[15] which was subsequently utilized in a Sonogashira coupling with (triisoproylsilyl)acetylene to provide aryl alkyne **3** in good overall yield. The alcohol functionality was then converted to an amino group. Specifically, phthalimide derivative **4** was prepared from alcohol **3** under Mitsunobu conditions and then treated with excess methylamine to afford the desired amine **5**.[16]

Construction of the desired Fischer aminocarbene complexes, depicted in Scheme 2, began with aryl bromide **6**, which was prepared according to literature methods.[17] Metal−halogen exchange of **6** was followed by the addition of the resultant aryllithium to chromium hexacarbonyl and methylation with trimethyloxonium tetrafluoroborate to provide alkoxycarbene complex **7** in moderate to good yields. Subsequent treatment of **7** with amine **5** generated aminocarbene complex **8**, which was readily methylated under sodium hydride/iodomethane conditions to afford aminocarbene complex **9**. Notably, aryl(amino)carbene complexes **8** and **9a** were obtained as approximately 4:1 mixtures of rotamers because of hindered rotation about the nitrogen−carbene carbon bond. Partial separation of the rotamers via flash chromatography could be achieved to characterize the individual isomers. However, attempts at complete separation were not successful, and the originally obtained mixture was thus utilized in subsequent steps including cyclopentannulation reactions. This was not anticipated to pose a problem, as Wulff had previously demonstrated that the independent thermolysis of rotational isomers of alkenyl(amino)carbene complexes with nitrogen-tethered alkynes resulted in identical product distributions and yields.[10b]

We also planned to study the effect of the alkyne substituent on the course of the reaction and thus modified the carbene complex **9a** at this juncture. Aminocarbene complex **9a** was subjected to desilylation with tetrabutylammonium fluoride (TBAF) to yield aminocarbene complex **9b** possessing a terminal alkyne functionality. Aminocarbene complex **9b** was then silylated to afford aminocarbene complexes **9c** and **9d** bearing trimethylsilane (TMS) and triethylsilane (TES) groups, respectively. Aminocarbene complexes **9b**−**d** were also isolated as 4:1 mixtures of rotamers, and these mixtures were also directly utilized in subsequent steps.

A variety of factors including temperature, solvent, concentration, and additives are known to affect the course of thermal reactions between Fischer carbene complexes and alkynes.[7,8,12] With aminocarbene complexes **9a**−**d** in hand, the task was to determine optimal reaction conditions for a cyclopentannulation reaction that would lead to the indenobenzazepine skeleton.

The first parameter explored was the solvent (Table 1, entries 1−11). In annulation reactions involving alkoxycarbene complexes and alkynes, the effect of solvent on product distribution has been thoroughly studied. Previous observations are that polar and/or coordinating solvents such as DMF and acetonitrile favor cyclopentannulations, whereas less polar solvents such as benzene or toluene lead to benzannulation as the predominant pathway. Although one would assume that polar solvents would have a similar beneficial effect on pentannulation reactions of aminocarbene complexes, data to verify this hypothesis are scarce. The most commonly utilized solvent for pentannulation reactions with aminocarbene complexes is DMF. As alluded to previously, this is often a necessity because a solvent with higher refluxing temperature is typically required to induce decarbonylation of the robust aminocarbene complexes, which serves as the initial step of the pentannulation reaction.[9,11] We were, therefore, surprised to find that the desired pentannulation transformation of aminocarbene complex **9a** proceeded in refluxing THF at a reaction temperature that would be anticipated to be too low for the decarbonylation step. In contrast, thermolysis of **9a** in DMF at 120 °C resulted in no reaction and raising the temperature to 152 °C caused decomposition with no observable product formation. Similarly, ther-

(13) (a) Dötz, K. H.; Popall, M. *Angew. Chem., Int. Ed. Engl*. **1987**, *26*, 1158. (b) Boger, D. L.; Huter, O.; Mbiya, K.; Zhang, M. *J. Am. Chem. Soc*. **1995**, *117*, 11839. (c) Bao, J.; Wulff, W. D.; Dragisich, V.; Wenglowsky, S.; Ball, R. G. *J. Am. Chem. Soc*. **1994**, *116*, 7616. (d) Dötz, K. H.; Pruskil, I.; Muhlemeier, J. *Chem. Ber*. **1982**, *115*, 1278. (e) Semmelhack, M. F.; Bozell, J. J.; Keller, T.; Sato, T.; Spiess, E.; Wulff, W. D.; Zask, A. *Tetrahedron* **1985**, *41*, 5803. (f) Wulff, W. D.; Xu, Y.-C. *J. Am. Chem. Soc*. **1988**, *110*, 2312. (g) Parker, K. A.; Coburn, C. A. *J. Org. Chem*. **1991**, *56*, 1666. (h) King, J.; Quayle, P.; Malone, J. F. *Tetrahedron Lett*. **1990**, *31*, 5221. (i) White, J. D.; Smits, H. *Org. Lett*. **2005**, *7*, 235. (j) Pulley, S. R.; Czako, B. *Tetrahedron Lett*. **2004**, *45*, 5511.

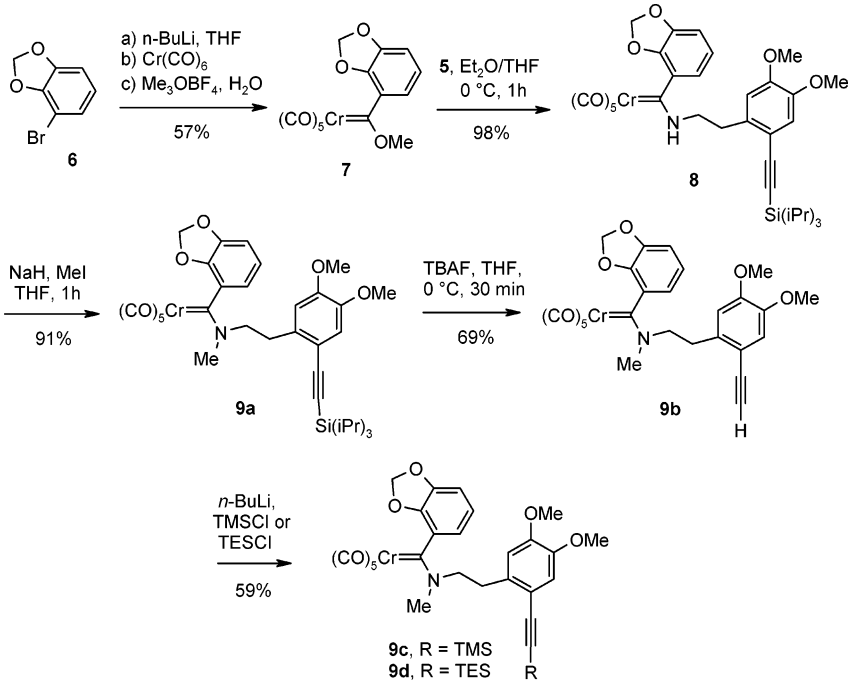
(14) For studies towards substituted lycoranes, see: Bouaucheau, C.; Parlier, A.; Rudler, H. *J. Org. Chem*. **1997**, *62*, 7247.

(15) Mulholland, G. K.; Zheng, Q. *Synth. Commun*. **2001**, *31*, 3059.

(16) Sen, S. E.; Roach, S. L. *Synthesis* **1995**, 756.

(17) Klix, R. C.; Cain, M. H.; Bhatia, A. V. *Tetrahedron Lett*. **1995**, *36*, 6413.

SCHEME 2. Synthesis of Aminocarbene Complexes



molysis in other polar coordinating solvents (acetonitrile or pyridine), polar noncoordinating solvents (chloroform), or nonpolar solvents (benzene or toluene) at their reflux temperatures resulted in decomposition of the starting aminocarbene complex with formation of little or none of the desired pentannulation product. When considering the successful pentannulation reaction, it is possible that the alkyne or oxygen substituents on the carbene complex may serve as intramolecular two-electron donors to the metal center, thereby decreasing the activation barrier to initial decarbonylation. However, this hypothesis still does not appear to explain the failure of the reaction with solvents other than THF.

Although the desired cyclopentannulation product was the major component observed in thermal reactions with THF, the conversion was relatively poor and multiple byproducts were also being formed.[18] In studies with alkoxycarbene complexes, it has previously been demonstrated that reducing the concentration of the alkyne substrate can favor cyclopentannulation pathways relative to benzannulations because of a decrease of the allochemical effect.[19] More specifically, it has been proposed that the presence of alkynes as available ligands can facilitate CO insertions by serving as 4π-electron donors to the metal center, thereby avoiding higher energy electron-deficient organometallic intermediates that would normally ensue from the CO insertion step. Assuming that one or more of the desired byproducts could derive from pathways involving CO insertions, the thermolysis of **9a** in THF was repeated at a more dilute concentration (0.008 M vs 0.022 M). This alteration did result in a modest increase in the yield of **10** (Table 1, entry 12). However, in the absence of further experimentation, we can only surmise that this increase may be due to a reduction of the allochemical effect or a minimization of intermolecular cyclizations.

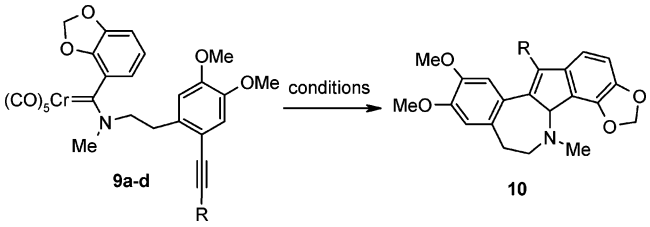
To further probe the effect of electron donors on the efficiency of the reaction, a series of experiments were attempted in which ligating reagents were added to the reaction solution. It has been reported by both De-Meijere[19] and Wulff[8c] that the presence of ligating reagents increases the selectivity for cyclopentannulation pathways in reactions with Fischer alkoxycarbene complexes. Indeed, we were pleased to find that the addition of 1 equiv of either tri-*n*-butylphosphine, triphenylphosphine, or pyridine resulted in a significant increase in the yield of **10**, along with an essentially complete suppression of byproduct formation (Table 1, entries 13−17). This result is consistent with the ability of a two-electron donor to stabilize reaction intermediates leading to chromacycle formation and reductive elimination, which are the hypothesized key steps leading to the cyclopentannulation product. Although conversion was much slower in the presence of added pyridine, the desired product appeared to be completely stable to the reaction conditions. The reaction time of all subsequent experiments was therefore extended to ensure complete conversion. Because the yield of **10** was essentially the same in the presence of all ligands that were attempted, tri-*n*-butylphosphine was employed in all future experiments due to the ease of workup.

The final parameter explored was the alkyne substituent. Subjecting aminocarbene complex **9b**, containing a terminal alkyne, to the optimal conditions observed for **9a** resulted in a rapid disappearance of the carbene complex. After 6 h, ^{1}H NMR analysis of the crude reaction mixture indicated that bulgaramine was being formed

(18) Isolation of reaction products was extremely difficult because of oxidative degradation during flash chromatography on silica gel. Initially, the product yields and/or ratios were estimated by ^{1}H NMR analysis of the crude reaction mixtures. Fortuitously, it was discovered that treatment of THF solutions of the crude reaction mixtures with methanolic HCl allowed the desired product **10** to be cleanly isolated as its HCl salt.

(19) Flynn, B. L.; Schirmer, H.; Duetsch, M.; de Meijere, A. *J. Org. Chem*. **2001**, *66*, 1747.

TABLE 1. Cyclopentannulation of Aminocarbene Complexes 9a–d



entry	R	solvent	temp (°C)	time (h)	M	additive	yield of **10**
1	TIPS	benzene	80	24	0.022	none	no reaction
2	TIPS	benzene	80	72	0.022	none	decomp[a]
3	TIPS	toluene	111	48	0.022	none	trace[a]
4	TIPS	DMF	120	20	0.022	none	trace
5	TIPS	DMF	152	24	0.022	none	decomp
6	TIPS	ACN	82	4	0.022	none	decomp
7	TIPS	$CDCl_3$	62	4	0.022	none	no reaction
8	TIPS	$CDCl_3$	62	24	0.022	none	decomp
9	TIPS	pyridine	66	8	0.022	none	no reaction
10	TIPS	pyridine	80	18	0.022	none	decomp
11	TIPS	THF	66	8	0.022	none	24%
12	TIPS	THF	66	8	0.008	none	32%
13	TIPS	THF	66	8	0.022	PBu_3 (1.0 equiv)	62%
14	TIPS	THF	66	8	0.022	PPh_3 (1.0 equiv)	63%
15	TIPS	THF	66	20	0.022	pyridine (1.0 equiv)	62%
16	TIPS	THF	66	20	0.008	PBu_3 (1.0 equiv)	67%[b]
17	TIPS	THF	66	20	0.008	PBu_3 (3.0 equiv)	0%[c]
18	H	THF	66	6	0.008	PBu_3 (1.0 equiv)	38% (enamine)[d]
19	TMS	THF	66	20	0.008	PBu_3 (1.0 equiv)	56% (1:1 mix)[e]
20	TES	THF	66	20	0.008	PBu_3 (1.0 equiv)	37%[e]

[a] Minor amounts of starting carbene obtained. [b] Average of 6 trials. [c] No starting carbene or cyclopentannulation product identified by crude NMR. [d] Bulgaramine was obtained directly as the only product. [e] Contained inseparable impurities.

directly as the only identifiable product. Isolation of this product from the crude reaction mixture, however, proved to be difficult because of the propensity for oxidation under chromatographic conditions. Fortunately, we observed that the use of argon pressure rather than air during flash chromatographic purification minimized oxidative degradation, affording a 38% isolated yield of bulgaramine (Table 1, entry 18). The fact that bulgaramine, which contains an enamine moiety, was generated rather than the allylamine functionality present in product **10** attests to the ability of the silyl group to localize the double bond following cyclopentannulation. The diminished yield obtained with **9b** also mirrors previous literature reports in which intramolecular reactions of alkoxycarbene complexes containing terminal alkynes have met with disappointing results.[13e,20]

Aminocarbene complexes **9c** and **9d** were also subjected to the identical reaction conditions, and crude ^{1}H NMR analysis of the reaction mixtures indicated formation of the desired cyclopentannulation products along with varying amounts of byproducts (Table 1, entries 19 and 20). Isolating the products again proved to be difficult, and analytically pure samples could not be isolated. Although these experiments indicate that carbene complex **9a**, in which the pendant alkyne bears a TIPS group, provides the most effective precursor in the context of the bulgaramine synthesis, they do little to shed light on the effect of the steric bulk of the silyl group on the annulation process. That is, although the diminished yields observed with the TMS- or TES-substituted alkynes suggest a reduced efficiency for the annulation process, it is possible that the greater fragility of these groups relative to the TIPS group leads to decomposition following the annulation step.

Taken together, these results are consistent with the following mechanism, as discussed by others in the context of related results (Figure 3). Reversible decarbonylation of **A** to yield tetracarbonyl complex **B** occurs at an uncharacteristically low temperature for aminocarbene complexes and appears to be aided by the presence of THF as a donor solvent. Intramolecular chelation by oxygen atoms has been postulated in related examples to facilitate decarbonylation and may also have the same effect in this case.[21] However, the unreactivity of carbene complexes **9a–d** in solvents other than THF suggests that the solvent must play the key role. Intramolecular displacement of the solvent by the alkyne provides intermediate **C**, which would then insert the alkyne to yield the 18-electron allylidene chelate complex **D**. Coordination of the two-electron donor phosphine ligand dechelates the alkyene moiety in intermediate **D** to give the 18-electron vinyl carbene complex **E** and induces chromacycle formation and reductive elimination to afford cyclopentadiene **G**. At this point, rearomatization could occur to yield two possible isomers, allylamine **H** or enamine **I**. Although Dötz has reported a similar cyclopentannulation where tautomerization occurs via a suprafacial [1,5]-H shift to afford an enamine intermediate,[21] only the allylamine is observed on thermolysis of **9a**, **9c**, or **9d**. This appears to be a consequence of stabilization by the silyl group because thermolysis of carbene complex **9b**, containing a terminal alkyne, proceeds directly to bulgaramine, which contains the enamine moiety.

With the optimal conditions for the cyclopentannulation reaction now established, our attention was turned toward the conversion of the benzindenoazepine skeleton **10a** to bulgaramine via desilylation and double bond migration (Scheme 3). The resiliency of the TIPS group, which allowed precipitation of **10a** as the HCl salt without desilylation,[18] rendered this transformation difficult. A variety of common desilylating reagents were attempted, including TBAF, aqueous acids and bases, and anhydrous organic acids such as methanesulfonic acid and TFA, all with no success. Desilylation was finally accomplished by the addition of 10% HBr/HOAc in dry dichloromethane, which afforded two products as indicated by ^{1}H NMR analysis of the crude reaction mixture. These two products were presumed to be alkene regioisomers because interconversion of similar regioisomers has previously been reported.[22] Indeed, treatment of this mixture for 5 min in a 10% solution of KOH

(20) (a) Wulff, W. D.; McCallum, J. S.; Kunng, F.-A. *J. Am. Chem. Soc.* **1988**, *110*, 7419. (b) Gross, M. F.; Finn, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10921.

(21) Dötz, K. H.; Schafer, T.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 176.

(22) Irie, H.; Tani, S.; Yamane, H. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2986.

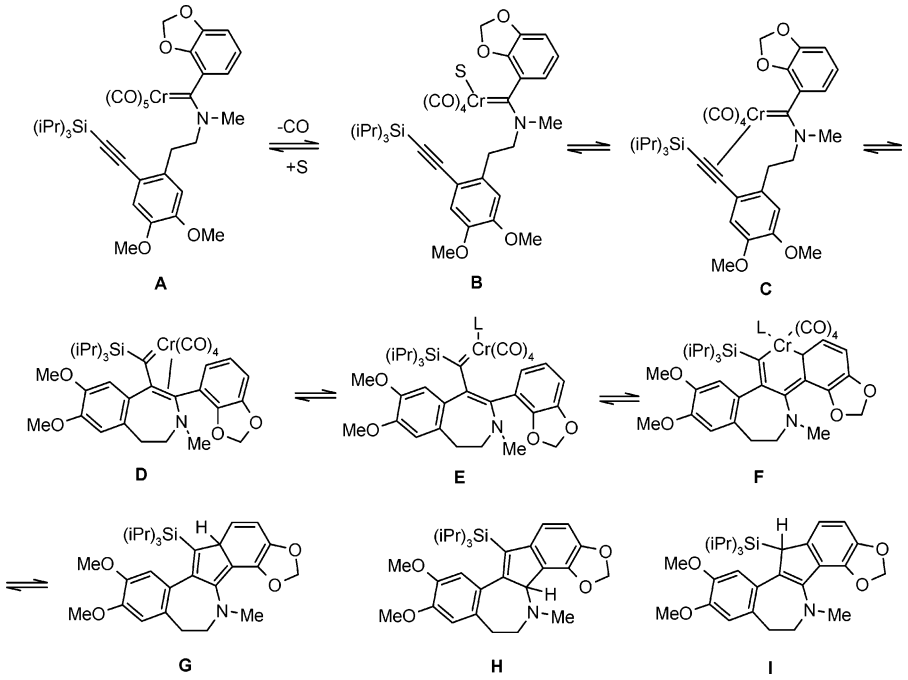
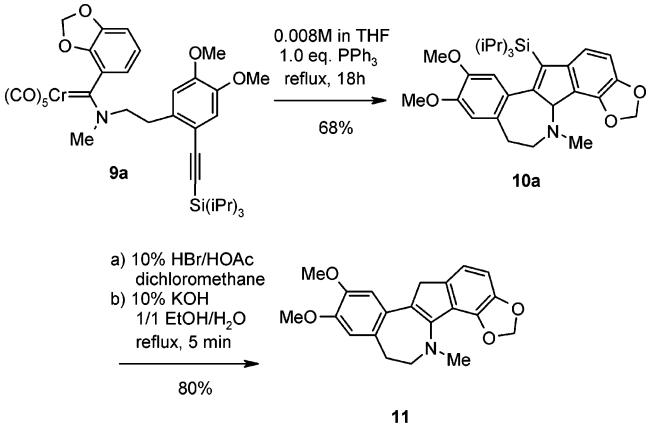


FIGURE 3. Proposed mechanism for the optimized cyclopentannulation reaction.

SCHEME 3. Completion of Bulgaramine via Cyclopentannulation Reaction



in a 1:1 H_2O/EtOH mixture afforded analytically pure bulgaramine in 80% yield as the sole product. The spectroscopic properties of this synthetic material were identical with those reported for the naturally occurring compound.[3]

Conclusions

In conclusion, a rapid and efficient synthesis of bulgaramine has been accomplished with a longest linear sequence of eight steps and an overall yield of 23% from commercially available 3,4-dimethoxyphenethyl alcohol. An intramolecular cyclopentannulation reaction of a Fischer aminocarbene complex provided the key step and occurred under significantly milder conditions and in higher yields than other reported examples of this reaction type. The reaction solvent was a critical factor in the cyclopentannulation reaction, with measurable amounts of the desired product observed only when THF was utilized. The product yield could be further enhanced by the addition of two-electron donor ligands, demonstrating the first example of this effect on the thermal reaction of aminocarbene complexes with alkynes. We anticipate that the methodology reported here will prove useful in the synthesis of additional indenobenzazepine alkaloids.

Experimental Section

2-(2-Iodo-4,5-dimethoxyphenyl)ethanol (2). To a solution of 3,4-dimethoxy phenethyl alcohol (5.02 g, 27.6 mmmol) and AgO_2CCF_3 (7.00 g, 31.7 mmol) in $CHCl_3$ at 0 °C was added I_2 (8.04 g, 31.7 mmol) in 150 mL of $CHCl_3$ via cannula. After the addition, stirring was continued for 15 min. The mixture was then filtered through Celite, and the filtrate was washed sequentially with saturated aqueous $Na_2S_2O_5$, water, and brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated. Purification of the residue via flash chromatography (60 g of SiO_2, ramp eluent from 2:1 to 1:2 hexane/ethyl acetate) afforded **2** as a white solid after trituration with Et_2O (8.25 g, 97%): IR (neat) 3499 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.21 (s, 1H), 6.77 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.82 (m, 2H), 2.93 (t, J = 6.6 Hz, 2H), 1.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 149.5, 148.4, 133.6, 122.0, 113.2, 88.3, 62.5, 56.2, 56.0, 43.3; HRMS (ESI) $[M + Na]^+$ *m/z* calcd for $C_{10}H_{13}NaO_3I$ 330.9807, found 330.9807.

2-{4,5-Dimethoxy-2-[(triisopropylsilanyl)ethynyl]-phenyl}ethanol (3). A solution of aryl iodide **2** (7.93 g, 25.7 mmol), triisopropylsilyl acetylene (6.35 mL, 28.3 mmol), and freshly distilled triethylamine (10.76 mL, 77.2 mmol) in 100 mL of acetonitrile was freeze−thaw degassed three times. To this solution was added CuI (980 mg, 5.20 mmol) and $PdCl_2(PPh_3)_2$ (1.81 g, 2.60 mmol), and the red mixture was stirred at room temperature overnight. The resulting black solution was filtered through Celite, and the filtrate was washed sequentially with saturated aqueous NH_4Cl, water, and brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated to an orange solid. The orange solid was recrystallized from boiling hexane and purified via flash chromatography (70 g of SiO_2, ramp eluent from 3:2 to 2:3 hexane/ethyl acetate) to afford **3** as a pale yellow solid (7.04 g, 75%): IR (neat) 3503, 2143 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.93 (s, 1H),

6.72 (s, 1H), 3.87 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.01 (t, J = 6.6 Hz, 2H), 1.45 (s, 1H), 1.11 (s, 21H); ^{13}C NMR ($CDCl_3$) δ 149.6, 147.4, 134.5, 115.5, 115.2, 112.9, 105.6, 92.8, 63.1, 56.1, 56.0, 37.9, 18.7, 11.4; HRMS (ESI) $[M + Na]^+$ m/z calcd for $C_{21}H_{34}NaO_3Si$ 385.2175, found 385.2171.

1-(2-{4,5-Dimethoxy-2-[(triisopropylsilanyl)ethynyl]-phenyl}ethyl)-3-propenyl-4-vinylpyrrole-2,5-dione (4). To a solution of alcohol **3** (6.90 g, 19.0 mmol), phthalimide (2.94 g, 19.9 mmol), and PPh_3 (5.24 g, 19.9 mmol) in 75 mL of THF at 0 °C was added diisopropyl azodicarboxylate (3.91 mL, 19.9 mmol) dropwise via syringe. The resulting mixture was allowed to warm to room temperature overnight with stirring. The mixture was then partitioned between saturated aqueous $NaHCO_3$ and EtOAc, and the aqueous layer was extracted with additional portions of EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a tan solid. Recrystallization from methanol provided **4** as a white crystalline solid (8.19 g, 88%): IR (neat) 2145, 1712, 1767 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.76 (m, 2H), 7.66 (m, 2H), 6.90 (s, 1H), 6.51 (s, 1H), 3.99 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.60 (s, 3H), 3.16 (t, J = 6.6 Hz, 2H), 1.13 (s, 21H); ^{13}C NMR ($CDCl_3$) δ 168.0, 149.3, 147.3, 133.9, 133.8, 132.1, 123.1, 115.4, 115.3, 112.1, 105.2, 93.0, 55.9, 55.7, 38.2, 32.7, 18.7, 11.4; HRMS (ESI) $[M]^+$ m/z calcd for $C_{29}H_{37}NO_4Si$ 491.2492, found 491.2502.

2-{4,5-Dimethoxy-2-[(triisopropylsilanyl)ethynyl]-phenyl}ethylamine (5). Phthalimide derivative **4** (8.19 g, 16.7 mmol) was dissolved in 330 mL of a 2:1 mixture of EtOH/THF, and 83 mL of 40% aqueous methylamine was added. The solution was warmed to 70 °C for 4 h and then diluted with ethyl acetate and washed sequentially with saturated aqueous NH_4Cl and water. The organic layer was dried over $MgSO_4$, filtered, and concentrated to a white solid. Purification via flash chromatography (60 g of Al_2O_3; ramp eluent from EtOAc to 3:1 EtOAc/MeOH to MeOH with 10% NH_3/MeOH) provided **5** as a white solid (4.41 g, 73%): IR (neat) 3368, 2143 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.91 (s, 1H), 6.69 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.95 (m, 2H), 2.89 (m, 2H), 1.62 (br s, 2H), 1.11 (s, 21H); ^{13}C NMR ($CDCl_3$) δ 149.6, 147.2, 135.7, 115.5, 115.4, 112.6, 105.8, 92.5, 56.1, 56.0, 43.0, 38.7, 18.7, 11.4; HRMS (ESI) $[M + H]^+$ m/z calcd for $C_{21}H_{36}NO_2Si$ 362.2515, found 362.2516.

Alkoxycarbene Complex 7. To a solution of aryl bromide **6** (5.43 g, 27.0 mmol) in 50 mL of THF at −78 °C was added n-BuLi (1.6 M in hexane, 17.7 mL, 28.4 mmol) dropwise via syringe, and the mixture was stirred at −78 °C for 1.5 h. In a separate flask, $Cr(CO)_6$ (6.24 g, 28.4 mmol) was suspended in 50 mL of THF, cooled to −78 °C, and the aryllithium was transferred to this slurry via cannula. The resulting mixture was warmed to room temperature and allowed to stir for 3 h. The volume of the solvent was reduced, and the resulting solids were removed by filtration through Celite. The filtrate was then concentrated to a thick yellow oil. This residue was taken up in 30 mL of H_2O, Me_3OBF_4 (4.79 g, 32.4 mmol) was added, and the mixture was stirred for 15 min to afford a thick red solution. This solution was extracted with EtOAc (5 × 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to a red oil. Purification by flash chromatography (100 g of SiO_2, 9:1 hexane/ethyl acetate) and recrystallization from hexane provided **7** as a red crystalline solid (5.46 g, 57%): IR (neat) 2064, 1929 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.85 (m, 2H), 6.61 (d, 1H, J = 8.1 Hz), 5.97 (s, 2H), 4.48 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 312.0, 224.5, 215.8, 147.8, 138.0, 135.1, 121.8, 116.2, 109.4, 101.4, 66.3; HRMS (EI) $[M]^+$ m/z calcd for $C_{14}H_8O_8Cr$ 355.9624, found 355.9634.

Aminocarbene Complex 8. To a solution of alkoxycarbene complex **7** (3.95 g, 11.1 mmol) in 75 mL of Et_2O at 0 °C was added a solution of amine **5** (4.41 g, 12.2 mmol) in 60 mL of THF via cannula. The resulting pale orange solution was stirred at 0 °C for 1 h and then concentrated to a yellow oil. Purification of the yellow oil via flash chromatography (120 g of SiO_2, 3:1 hexane/ethyl acetate) provided **8** (inseparable 4:1 mixture of rotamers) as a fluffy yellow solid (7.48 g, 98%). For characterization purposes, partial separation of the rotamers could be achieved via flash chromatography utilizing a solvent system of 4:1 hexane/ether. Minor rotamer: IR (neat) 3229, 2141, 2054, 1979, 1917 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.80 (br s, 1H), 6.91 (s, 1H), 6.75 (m, 3H), 6.35 (d, J = 8.8 Hz, 1H), 5.84 (s, 2H), 4.39 (m, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.30 (m, 2H), 1.05 (s, 21H); ^{13}C NMR ($CDCl_3$) δ 275.0, 223.5, 217.1, 150.1, 147.9, 147.5, 138.0, 136.0, 132.4, 121.9, 115.7, 115.3, 115.2, 112.1, 108.0, 105.1, 100.9, 94.1, 56.1, 55.9, 53.7, 33.5, 18.7, 11.3, 10.5; HRMS (EI) $[M]^+$ m/z calcd for $C_{34}H_{39}NO_9CrSi$ 685.1799, found 685.1811. Major rotamer: IR (neat) 3347, 3291, 2141, 2054, 1979, 1917 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.98 (br s, 1H), 6.93 (s, 1H), 6.81 (t, J = 7.4 Hz, 3H), 6.67 (d, J = 8.8 Hz, 1H), 6.11 (d, J = 7.4 Hz, 1H), 5.96 (s, 1H), 5.84 (s, 1H), 3.87 (s, 6H), 3.60 (m, 2H), 2.99 (m, 2H), 1.08 (s, 21H); ^{13}C NMR ($CDCl_3$) δ 277.8, 224.6, 218.6, 151.6, 149.7, 149.0, 138.0, 133.6, 132.4, 123.8, 117.5, 116.7, 115.7, 114.0, 108.9, 106.3, 102.7, 95.6, 57.8, 57.5, 52.7, 36.0, 20.3, 12.9; HRMS (EI) $[M]^+$ m/z calcd for $C_{34}H_{39}NO_9CrSi$ 685.1799, found 685.1832.

Aminocarbene Complex 9a. A solution of aminocarbene complex **8** (7.48 g, 10.9 mmol) in 110 mL of THF was cooled to −78 °C, and NaH (60% dispersion in mineral oil, 622 mg, 15.5 mmol) and iodomethane (968 μL, 15.5 mmol) were added. The resultant mixture was allowed to warm to room temperature and then quenched with saturated aqueous NH_4Cl. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to a yellow oil. Purification via flash chromatography (120 g of SiO_2, 3:1 hexane/ethyl acetate eluent) provided **9a** (inseparable 4:1 mixture of rotamers) as a fluffy yellow solid (6.96 g, 91%). For characterization purposes, partial separation of the rotamers could be achieved via flash chromatography using 4:1 hexane/ether eluent. Minor rotamer: IR (neat) 2142, 2054, 1973, 1917 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.90 (m, 3H), 6.66 (d, J = 6.6 Hz, 1H), 6.28 (d, J = 6.6 Hz, 1H), 5.99 (s, 1H), 5.84 (s, 1H), 4.50 (t, J = 8.1 Hz, 2H), 3.874 (s, 3H), 3.871 (s, 3H), 3.36 (m, 2H), 3.07 (s, 3H), 1.11 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 269.9, 223.4, 217.2, 150.1, 147.8, 147.7, 135.1, 135.0, 132.3, 122.6, 115.9, 114.9, 113.3, 112.6, 106.6, 105.6, 101.0, 93.5, 63.7, 56.1, 55.9, 43.7, 33.5, 18.7, 11.4; HRMS (EI) $[M - 5CO]^+$ m/z calcd for $C_{30}H_{41}NO_4CrSi$ 559.2210, found 559.2184 (because of low volatility and thermal instability this was the only peak observed). Major rotamer: IR (neat) 2144, 2054, 1973, 1917 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.83 (m, 3H), 6.65 (d, J = 7.4 Hz, 1H), 6.18 (s, 1H), 6.01 (s, 1H), 5.81 (s, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.74 (s, 3H), 3.63 (m, 2H), 2.99 (m, 2H), 1.11 (s, 21H); ^{13}C NMR ($CDCl_3$) δ 271.8, 223.6, 217.0, 149.9, 147.8, 147.6, 135.4, 134.1, 132.1, 122.1, 115.4, 114.9, 113.9, 111.6, 106.4, 104.8, 100.9, 93.1, 59.0, 56.1, 55.7, 49.2, 33.3, 18.7, 11.4; HRMS (EI) $[M - 5CO]^+$ m/z calcd for $C_{30}H_{41}NO_4CrSi$ 559.2210, found 559.2195 (because of low volatility and thermal instability this was the only peak observed).

Aminocarbene Complex 9b. A solution of aminocarbene complex **9a** (3.50 g, 5.00 mmol) in 100 mL of THF was cooled to 0 °C, and TBAF (1.0 M in THF, 6.11 mL, 6.11 mmol) was added dropwise via syringe. The solution was allowed to stir at 0 °C for 30 min and then was diluted with Et_2O and quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a yellow oil. Purification via flash chromatography (100 g SiO_2, 3:1 hexane/ethyl acetate eluent) provided **9b** (inseparable 4:1 mixture of rotamers) as a fluffy yellow solid (1.90 g, 69%). Because of the limited success of this substrate in cyclopentannulation experiments, no further attempts were made to separate the rotamers and the mixture of rotamers was characterized by ^{1}H NMR only. The chemical signals for the major and minor rotamers were assigned on the basis of the integral values. Chemical signals for the minor rotamer are reported as normalized (×4) values. Minor rotamer: ^{1}H NMR ($CDCl_3$) δ

6.87 (m, 3H), 6.65 (m, 1H), 6.28 (d, J = 8.1 Hz, 1H), 5.96 (s, 1H), 5.83 (s, 1H), 4.47 (m, 2H), 3.86 (s, 6H), 3.31 (m, 2H), 3.25 (s, 1H), 3.14 (s, 3H). Major rotamer: ^{1}H NMR ($CDCl_3$) δ 6.89 (m, 2H), 6.65 (m, 1H), 6.22 (s, 1H), 6.17 (d, J = 8.1 Hz, 1H), 6.01 (s, 1H), 5.81 (s, 1H), 3.96 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H), 3.64 (m, 2H), 3.16 (s, 1H), 2.97 (m, 2H).

Aminocarbene Complex 9c. To a solution of aminocarbene complex **9b** (799 mg, 1.47 mmol) in 25 mL of THF at −78 °C was added *n*-BuLi (1.6 M in hexanes, 964 μL, 1.54 mmol) via syringe. After maintaining the solution at −78 °C for 1 h, we added TMSCl (559 μL, 4.41 mmol) via syringe. The resultant solution was allowed to warm to room temperature with stirring overnight. The mixture was then partitioned between saturated aqueous $NaHCO_3$ and Et_2O, and the aqueous layer was extracted with additional portions of Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a yellow oil. Purification via flash chromatography (40 g of SiO_2, 3:1 hexane/ether eluent) provided **9c** (inseparable 4:1 mixture of rotamers) as a fluffy yellow solid (538 mg, 59%). Because of the limited success of this substrate in cyclopentannulation experiments, no further attempts were made to separate the rotamers and the mixture of rotamers was characterized by ^{1}H NMR only. The chemical signals for the major and minor rotamers were assigned on the basis of the integral values. Chemical signals for the minor rotamer are reported as normalized (×4) values. Minor rotamer: ^{1}H NMR ($CDCl_3$) δ 6.92 (m, 4H), 6.66 (m, 1H), 6.26 (m, 1H), 6.12 (s, 1H), 5.83 (s, 1H), 4.44 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.29 (m, 2H), 3.17 (s, 3H), 0.21 (s, 9H). Major rotamer: ^{1}H NMR ($CDCl_3$) δ 6.86 (m, 2H), 6.66 (m, 1H), 6.17 (m, 1H), 6.14 (s, 1H), 6.01 (s, 1H), 5.80 (s, 1H), 3.95 (s, 3H), 3.82 (s, 3H), 3.72 (s, 3H), 3.61 (m, 2H), 2.96 (m, 2H), 0.25 (s, 9H).

Aminocarbene Complex 9d. To a solution of aminocarbene complex **9b** (799 mg, 1.47 mmol) in 25 mL of THF at −78 °C was added *n*-BuLi (1.6 M in hexanes, 964 μL, 1.54 mmol) via syringe. After maintaining the solution at −78 °C for 1 h, we added TESCl (271 mL, 1.62 mmol) via syringe. The resultant solution was allowed to warm to room temperature with stirring overnight. The mixture was then partitioned between saturated aqueous $NaHCO_3$ and Et_2O, and the aqueous layer was extracted with additional portions of Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a yellow oil. Purification via flash chromatography (40 g of SiO_2, 3:1 hexane/ether eluent) provided **9d** (inseparable 4:1 mixture of rotamers) as a fluffy yellow solid (541 mg, 59%). Because of the limited success of this substrate in cyclopentannulation experiments, no further attempts were made to separate the rotamers and the mixture of rotamers was characterized by ^{1}H NMR only. The chemical signals for the major and minor rotamers were assigned on the basis of the integral values. Chemical signals for the minor rotamer are reported as normalized (×4) values. Minor rotamer: ^{1}H NMR ($CDCl_3$) δ 6.88 (m, 3H), 6.67 (m, 1H), 6.28 (m, 1H), 6.01 (s, 1H), 5.83 (s, 1H), 4.45 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.32 (m, 2H), 3.12 (s, 3H), 0.65 (m, 15H). Major rotamer: ^{1}H NMR ($CDCl_3$) δ 6.85 (m, 2H), 6.65 (m, 1H), 6.16 (m, 1H), 6.15 (s, 1H), 6.01 (s, 1H), 5.81 (s, 1H), 3.92 (s, 3H), 3.82 (s, 3H), 3.73 (s, 3H), 3.62 (m, 2H), 2.97 (m, 2H), 0.99 (m, 15H).

Cyclopentadiene 10a. A solution of aminocarbene complex **9a** (1.00 g, 1.43 mmol) in 180 mL of THF was degassed by evacuation and backfilling with argon (4×). To this solution was added PBu_3 (360 μL, 1.43 mmol), and the mixture was heated to reflux for 18 h during which time the color changed from yellow to dark orange. The mixture was concentrated, redissolved in 30 mL of THF, and anhydrous HCl (1.0 M in Et_2O, 7.25 mL, 7.25 mmol) was added dropwise via syringe. The mixture was stirred for 15 min during which time a precipitate formed. The precipitate was collected by filtration, dissolved in $CHCl_3$, and neutralized with saturated aqueous $NaHCO_3$. The organic layaer was then washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a yellow solid after trituration with Et_2O. Recrystallization from boiling EtOH at 0 °C afforded cyclopentadiene **10a** as a yellow crystalline solid (479 mg, 68%): ^{1}H NMR (CD_2Cl_2) δ 6.96 (d, J = 8.1 Hz, 1H), 6.93 (s, 1H), 6.68 (d, J = 8.1 Hz, 1H), 6.66 (s, 1H), 5.98 (d, J = 4.4 Hz, 2H), 4.31 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.62 (m, 1H), 3.14 (m, 1H), 2.86 (m, 2H), 2.88 (s, 3H), 0.88 (m, 21H); ^{13}C NMR (CD_2Cl_2) δ 147.7, 147.1, 145.9, 141.7, 140.0, 139.2, 135.1, 129.4, 126.8, 126.6, 116.4, 114.8, 112.9, 104.7, 100.8, 57.1, 56.6, 56.2, 44.3, 40.7, 33.9, 19.4, 19.1, 12.4; HRMS (ESI) $[M + H]^+$ *m/z* calcd for $C_{30}H_{42}NO_4Si$ 508.2883, found 508.2887.

Bulgaramine 11. A solution of cyclopentadiene **10a** (789 mg, 1.55 mmol) in 75 mL of DCM was cooled to 0 °C and 7.5 mL of 30% HBr in HOAc was added via syringe. The ice bath was removed, and the solution was allowed to stir at room temperature for 6 h during which time the color changed from yellow to blue-green. The solution was diluted with $CHCl_3$ and neutralized with saturated aqueous K_2CO_3. The aqueous layer was extracted with additional portions of $CHCl_3$ (3 × 30 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give an orange solid. This solid was suspended in 70 mL of 10% KOH in a 1:1 mixture of H_2O/EtOH, stirred under reflux for 5 min, and sealed under argon and placed in a −10 °C freezer overnight. The solid which precipitated was collected by filtration and partitioned between H_2O and CH_2Cl_2. The aqueous layer was extracted with additional portions of CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give an orange solid. This residue was then suspended in 30 mL of Et_2O, heated to reflux for 5 min, and collected via filtration to afford **11** as a pale orange powder (436 mg, 80%): ^{1}H NMR ($CHCl_3$) δ 7.00 (s, 1H), 6.88 (d, J = 7.4 Hz, 1H), 6.69 (d, J = 7.4 Hz, 1H), 6.69 (s, 1H), 6.01 (s, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 3.81 (s, 2H), 3.21 (m, 2H), 2.97 (m, 2H), 2.91 (s, 3H); ^{13}C NMR ($CHCl_3$) δ 147.0, 146.8, 146.4, 144.1, 138.6, 136.1, 133.4, 127.8, 126.9, 121.0, 116.2, 113.0, 110.9, 105.4, 100.5, 56.1, 55.9, 53.6, 43.1, 39.7, 33.7; HRMS (ESI) $[M + H]^+$ *m/z* calcd for $C_{21}H_{22}NO_4$ 352.1549, found 352.1546.

Acknowledgment. Financial support provided by the American Chemical Society Petroleum Research Fund (38338-AC1), and the Indiana University-Purdue University Indianapolis School of Science is gratefully acknowledged.

Supporting Information Available: Copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050631H