1999

Synthesis of o-isotoluenes, o-quinodimethanes, and benzoenynyl carbodiimides and their cyclizations to polycyclic and heterocyclic compounds

Quan Zhang
West Virginia University

Synthesis of *o*-Isotoluenes, *o*-Quinodimethanes, and Benzoenynyl Carbodiimides and Their Cyclizations to Polycyclic and Heterocyclic Compounds

Quan Zhang

A DISSERTATION

Submitted to the Eberly College of Arts and Sciences
at
West Virginia University
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Kung K. Wang, Ph.D., Chair
Kay M. Brummond, Ph.D.
Robert Griffith, Ph.D.
Katharine J. Covert, Ph.D.
Björn C. Söderberg, Ph.D.

Department of Chemistry
Morgantown, West Virginia
1999

Dedicated to

my wife, Annie (Shangshi), my daughter, Lana

and my parents

ACKNOWLEDGMENTS

I would like to express my sincere appreciation to my research advisor and committee chairperson Dr. Kung K. Wang, for his patience, encouragement, guidance, and support. I was very fortunate to have the opportunity to work for him and greatly benefitted by his great interest and deep knowledge of chemistry.

I would also like to express my gratitude to my research committee members, Dr. Kay M. Brummond, Dr. Katharine J. Covert, Dr. Robert Griffith, and Dr. Björn C. Söderberg for their precious time and assistance. My special thanks go to Dr. Kay M. Brummond for her constant encouragement and help.

I would also like to thank many people for their friendship and assistance during the years here while it is hard to name every individual.

My very special appreciation goes to my wife Annie (Shangshi) for her love, constant support, and encouragement during all these years and our daughter Lana for her love, cooporation and understanding. I would like to thank my parents for their patience, and my parents-in-law for taking care of Lana for several years.

The financial support of Department of Chemistry at West Virginia University, the U.S. Department of Energy and the National Science Foundation are gratefully acknowledged.

CONTENTS

Part I

SYNTHESIS OF 5-METHYLENE-1,3-CYCLOHEXADIENES (*o*-ISOTOLUENES) VIA ELECTROCYCLIZATION OF (4*Z*)-1,2,4,6-HEPTATETRAENES

PART II

GENERATION OF *o*-QUINODIMETHANES VIA THE ELECTROCYCLIC REACTION OF (4*Z*)-1,2,4,6,7-OCTAPENTAENES DERIVED FROM THE ORGANOBORATE COMPLEXES AND THEIR SUBSEQUENT REACTIONS

PART III

BIRADICALS FROM THERMOLYSIS OF *N*-[2-(1-ALKYNYL)PHENYL] -*N*′-PHENYL CARBODIIMIDES AND THEIR SUBSEQUENT TRANSFORMATIONS TO 6*H*-INDOLO[2,3-*b*]QUINOLINES

PART IV

AN EFFICIENT SYNTHESIS OF 5-AZA ANALOGUES OF ELLIPTICINE

PART V

EXPERIMENTAL SECTION

LIST OF TABLES

LIST OF FIGURE

ABSTRACT

Treatment of alkenyldicyclohexylboranes with 1-lithio-5-butyl-3,4-nonadien-1-yne, derived from 5-butyl-3,4-nonadien-1-yne, followed by trimethyltin chloride and acetic acid furnished the corresponding *o*-isotoluenes in a single operation. The reaction proceeded through an initial formation of (*Z*)-diene-allenes, which underwent facile eletrocyclizations to produce *o*-isotoluenes.

Treatment of allenyldicyclohexylborane with 1-lithio-5,5-pentamethylene-3,4-pentadien-1-yne produced the organoborate complex, which on further treatment with trimethyltin chloride furnished a (*Z*)-1,2,4,6,7-octapentaene (enediallene) derivative in situ. The subsequent electrocyclic reaction then generated the corresponding *o*-quinodimethane attached with a dicyclohexylboryl group and a trimethyltin group. The resulting *o*-quinodimethane then underwent a [1,5]-sigmatropic hydrogen shift, and on subsequent oxidative workup and protonation gave the 4-(1-cyclohexenyl)-3-methylphenol (51%). The presence of a boron group and a tin group in the benzene ring of a reaction intermediate also provides handles to allow their transformations to an allyl substituent and an iodo substituent to produce a tetrasubstituted benzene ring (30%) in a single operation. Attempts to capture the *o*-quinodimethane intermediate with a carbon–carbon double bond intramolecularly afforded a tricyclic phenol in low yield (6%). A number of other *o*-quinodimethanes were also generated by using different combinations of organoboranes and 1-lithio-1-alkynes.

6*H*-Indolo[2,3-*b*]quinolines were synthesized from *N*-[2-(1-alkynyl)phenyl]-*N*′-phenylcarbodiimides via a thermally-induced biradical-forming reaction. The Pd-catalyzed cross-coupling reaction between methyl 2-iodobenzoate and 1-alkynes furnished methyl 2-(1-

alkynyl)benzoates, which were hydrolyzed to afford the corresponding benzoic acids. Treatment of the benzoic acids with diphenyl phosphorazidate produced the 2-(1-alkynyl)phenyl isocyanates. The subsequent aza-Wittig reactions with the iminophosphorane, derived from aniline and $Ph_3P{\bullet}Br_2$ then gave the benzoenynyl carbodiimides. Thermolysis of the benzoenynyl carbodiimides in refluxing *p*-xylene at 138 °C produced the corresponding 6*H*-indolo[2,3-*b*]quinolines. Similarly, thermolysis of the carbodiimides having two benzoenynyl carbodiimide moieties produced compounds having two indoloquinoline units connected at the 11 and the 11′ positions with either a three-carbon or a five-carbon tether. By using 1,4-phenylene diisocyanate for the aza-Wittig reaction with two equiv of the iminophosphorane followed by thermolysis furnished a compound (66%) having two indoloquinoline units incorporated in the seven fused rings.

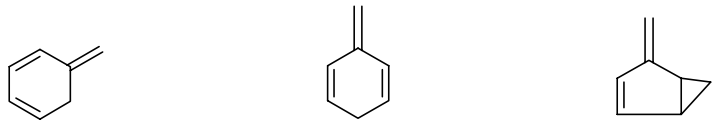
The synthetic pathway to the 6*H*-indolo[2,3-*b*]quinolines was successfully adopted for preparation of the 5-aza anologues of ellipticine, a naturally occuring alkaloid having potent anti-cancer properties. This approach, which constructs the B and the C rings in one step, is an efficient route in producing the aza analogues of the ellipticine family of antitumor alkaloids.

PART I

SYNTHESIS OF 5-METHYLENE-1,3-CYCLOHEXADIENES (*o*-ISOTOLUENES) VIA ELECTROCYCLIZATION OF (4*Z*)-1,2,4,6-HEPTATETRAENES

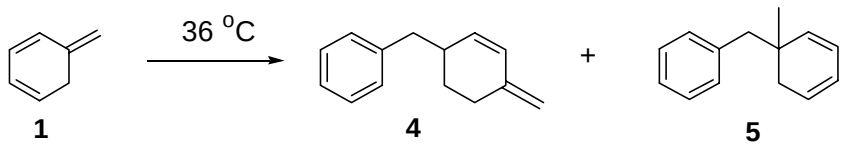
1. Introduction

o-Isotoluene, 5-methylene-1,3-cyclohexadiene (**1)** is one of the three alicyclic isomers of toluene which can be written by shifting the hydrogen from the methyl group to the *ortho*-, *para*- and *meta*- carbon atoms as shown in **1**, **2** and **3**, respectively.[1] Compared to toluene, the *o*-



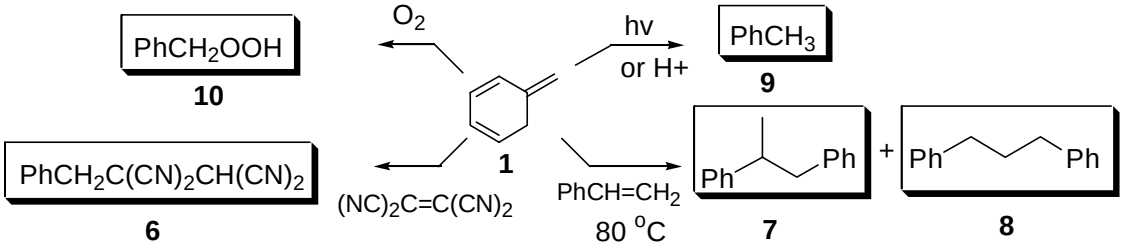
1 **2** **3**

isotoluene **1** possesses an additional 24 kcal/mol in energy,[2] which is mainly responsible for its unusual chemical reactivity. The *o*-isotoluene **1** is easily dimerized under mild thermal conditions via the concerted ene reactions to the corresponding dimers **4** and **5** (75% yield,



1 **4** **5**

4:**5** = 2:1).[3] Because of the formation of an aromatic system during dimerization of **1**, the rate of the ene reaction was greatly increased.[4] Treatment of **1** with tetracyanoethylene (TCNE) produced the corresponding ene adduct **6**.[5] Similarly, reaction of **1** with styrene at 80 °C gave 1,2-diphenylpropane (**7**) and 1,3-diphenypropane (**8**) in 90% total yield with a 3:1 ratio (Scheme 1).[6b] The *o*-isotoluene **1** is also sensitive to acid and oxygen, being rapidly converted to toluene (**9**)[6b] and benzyl hydroperoxide (**10**),[6] respectively.



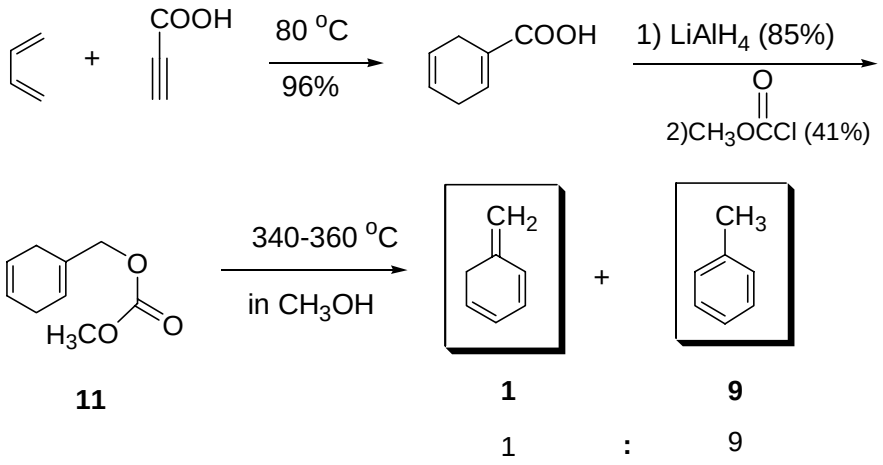
Scheme 1

The high reactivities of **1** and its derivatives put severe constraints on possible synthetic methods for these fascinating compounds. However, there were only a few synthetic methods in the literature that provided solutions to accomplish this difficult task.

1.1. Synthesis of *o*-Isotoluene by Thermolysis

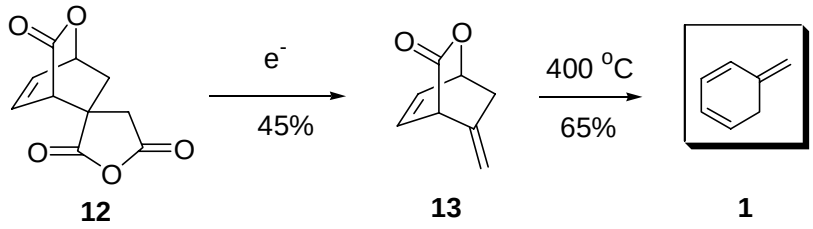
o-Isotoluene could be prepared by thermolysis of its suitable precursors. Bailey reported the first synthesis of *o*-isotoluene by pyrolysis of the ester **11** in 1962 (Scheme 2).[7a] The 5-methylene-1,3-cyclohexadiene (**1**) was separated by a preparative gas-phase chromatographic column in low yield. The compound was quite stable at dry ice temperature, in contrast the pure

liquid isomerized to toluene rapidly at room temperature.



Scheme 2

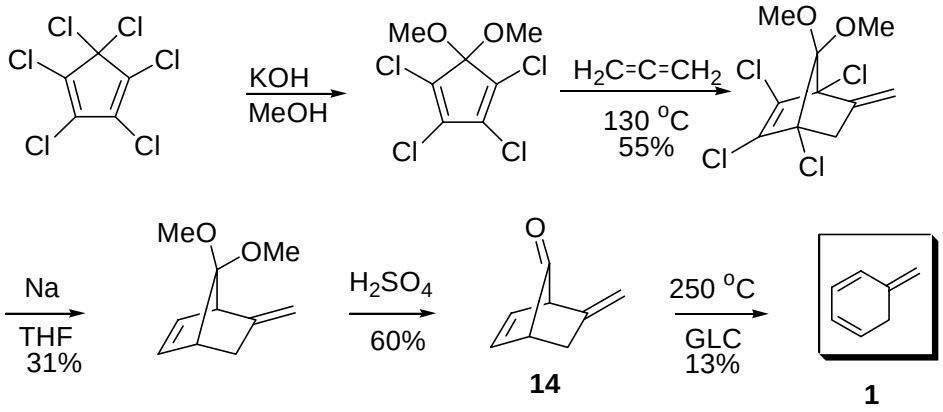
Kopecky [5b] reported a similar thermolysis of **13.** In his approach, **13** was generated by electrolysis of **12** (Scheme 3).



Scheme 3

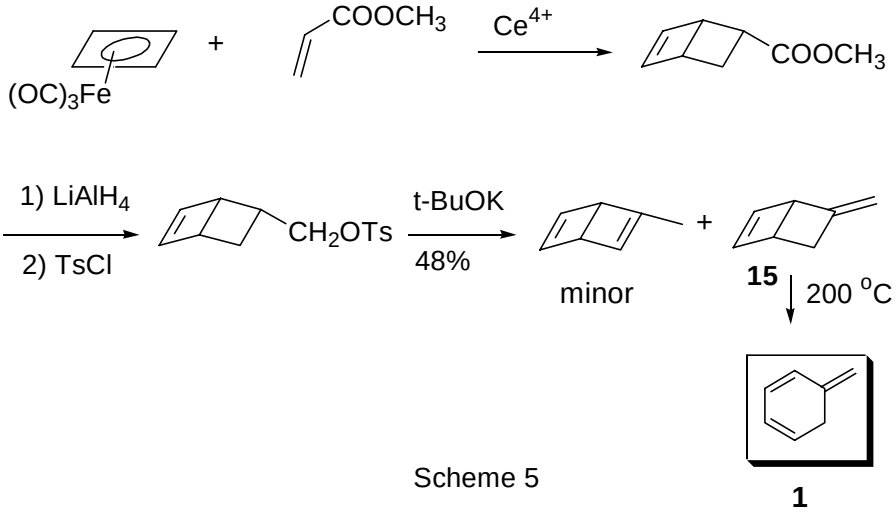
In 1979, Pryor et al. developed an alternative route to *o*-isotoluene (Scheme 4).[7b] The pyrolysis of the neat ketone **14** followed by GLC purification gave **1.** This methodology gave a fivefold increase in yield compared to the Bailey's route and it avoided the electrolysis step of

Kopecky's approach.



Scheme 4

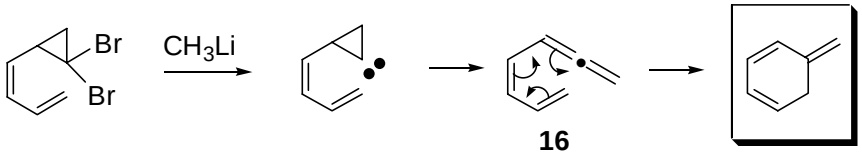
The *o*-isotoluene also can be obtained from thermolysis of its isomers. Hasselmann reported that thermolysis of 5-methylenebicyclo[2.2.0]hex-2-ene (**15**), a bicyclic isomer of toluene, afforded the *o*-isotoluene **1** (Scheme 5).[5a]



Scheme 5

1.2. Synthesis of *o*-Isotoluenes by Electrocyclization of Diene-Allenes

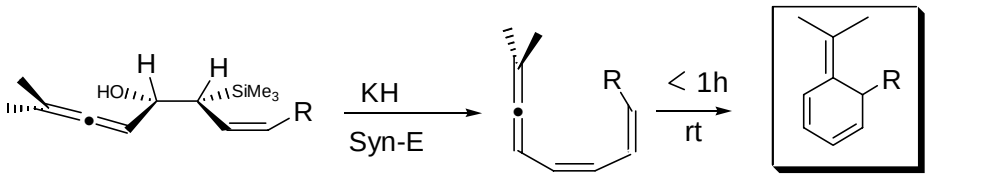
Alternatively, a facile electrocyclization of the transient (*Z*)-1,2,4,6-heptatetraene (diene-allene) has also been shown to produce *o*-isotoluene **1**.[8] Brinker and coworkers used a carbene rearrangement reaction to furnish the diene-allene **16**. The (*Z*)-diene-allene **16** then underwent cyclization to produce **1**. However, many by-products also were formed and it was difficult to separate **1** from the mixture (Scheme 6).



16 **1**

Scheme 6

Our group recently reported a simple and versatile route to (*Z*)-diene-allenes.[8b] This approach offers a practical synthesis of *o*-isotoluenes. Therefore, condensation of 4-methyl-2,3-pentadienal with γ-(trimethylsilyl)allylboranes afforded the hydroxyallylsilanes **17.** Treatment of **17** with KH gave the corresponding *o*-isotoluenes **19** (Scheme 7). Apparently, the initially formed diene-allene **18** underwent a facile electrocyclic reaction (<1 h, 25 °C), as observed



17 **18** **19 a** R=H; 82%
b R=Me; 81%

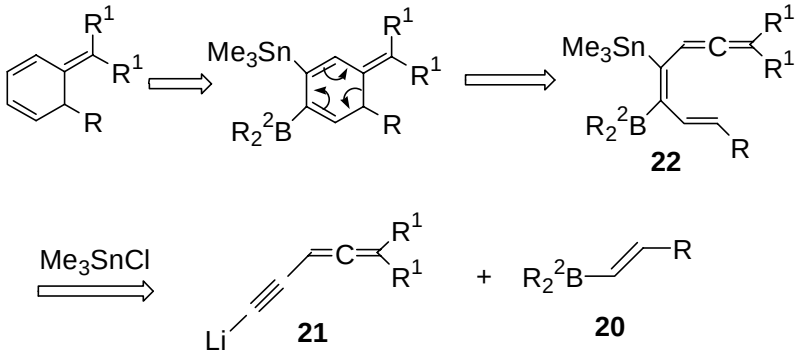
Scheme 7

previously for compounds with similar chemical structures,[8a,9] to afford **19**. It was noteworthy

that the central double bond of **18** must have the *Z* geometry in order to allow the following six-electron disrotatory electrocyclization reaction to occur. Surprisingly, *o*-isotoluenes **19** survived in the presence of KH and $KOSiMe_3$, without tautomerization (< 2 %) to the corresponding much more stable benzene derivatives. These *o*-isotoluenes are thermally stable and could be purified by distillation under reduced pressure at 35 °C.

2. Research Objective

The objective of this research project is to develop a practical synthetic route to (*Z*)-diene-allenes **22** for cyclizations to *o*-isotoluenes. The synthetic strategy involves treatment of alkenyldicyclohexylborane **20** with 1-lithio-3,4-pentadiene-1-ynes **21** to form the corresponding organoborate complexes followed by exposure to tributyltin chloride to promote a selective migration of the alkenyl group from the boron atom to the adjacent acetylenic carbon atom to furnish the (*Z*)-diene-allenes **22** (Scheme 8).

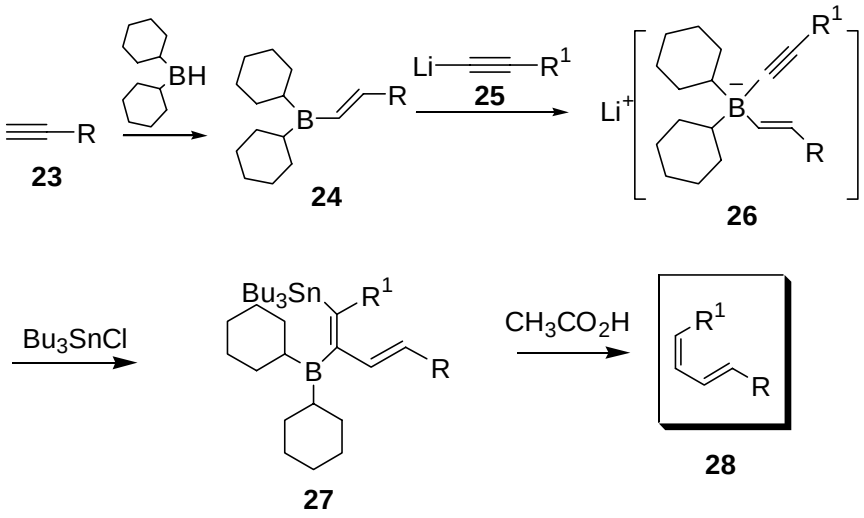


Scheme 8

3. Results and Discussion

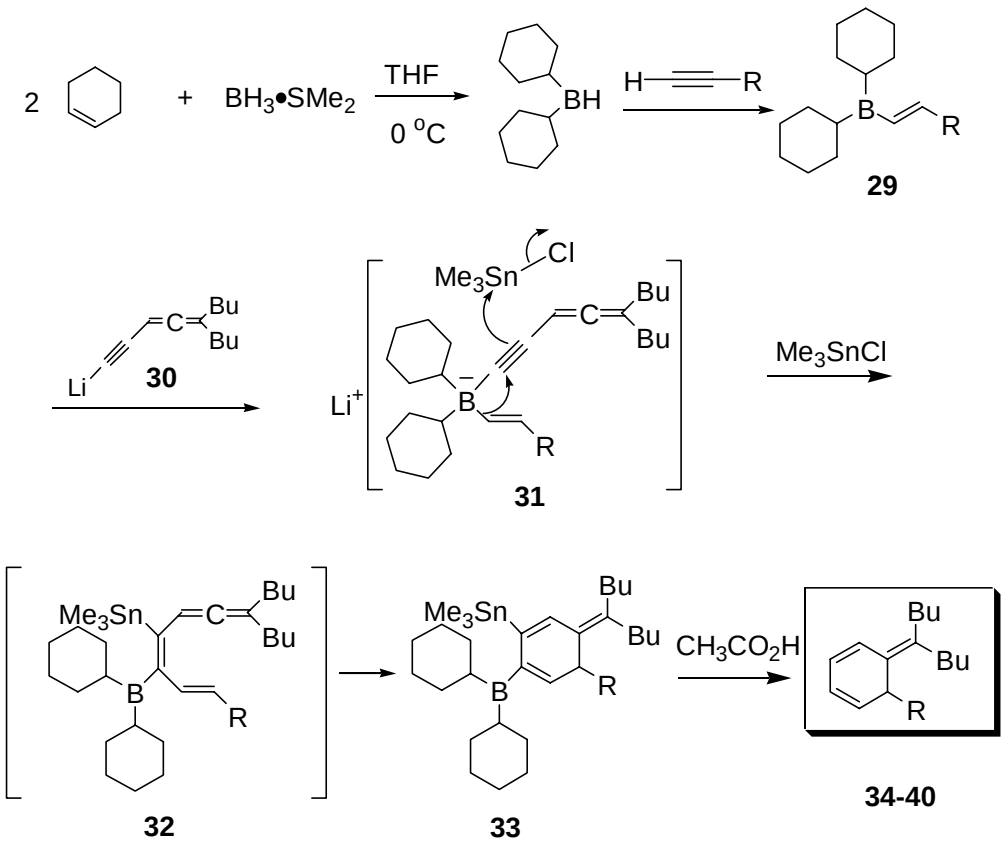
It was previously reported by Zweifel et al.[9] that treatment of alkenyldicyclohexylboranes

24, readily prepared from terminal alkynes **23** and dicyclohexylborane, with 1-lithio-1-alkynes **25** provided 1-alkynylalkenyldicyclohexylborates **26** (Scheme 9). Exposure of **26** to tributyltin chloride promoted a selective migration of the alkenyl group from the boron atom to the adjacent acetylenic carbon atom to furnish **27**, which on treatment with acetic acid was converted to the dienes **28** with high geometric purity.



Scheme 9

We envisioned that the reaction sequence outlined in Scheme 10 could be easily adopted for the synthesis of (*Z*)-diene-allenes **32** as transient intermediates toward *o*-isotoluenes (Scheme 10) by using the readily available 3,4-pentadien-1-yne[10] to produce 1-lithio-3,4-pentadien-1-yne (**30**) for the subsequent formation of the organoborate complexes.

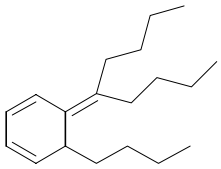
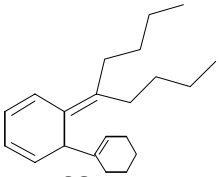
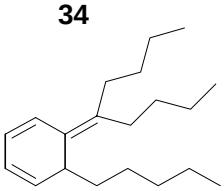
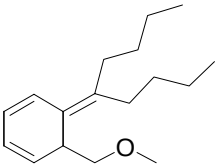
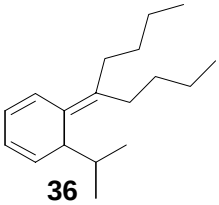
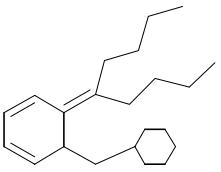
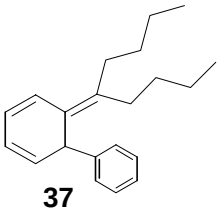


Scheme 10

Indeed, this synthetic route was found to be successful for the preparation of a variety of *o*-isotoluenes. Treatment of borane-dimethylsulfide with 2 equiv. of cyclohexene produced dicyclohexylborane as a white slurry.[11] Hydroboration of a terminal alkyne with dicyclohexylborane then furnished the alkenyldicyclohexylboranes **29**. Subsequent treatment of **29** with the lithium acetylide **30** gave the organoborate complexes **31**. Trimethyltin chloride then induced the migration of the alkenyl group to the adjacent acetylenic carbon, giving rise to the diene-allenes **32**. The electrocyclization of the diene-allenes **32** to **33** were generally very

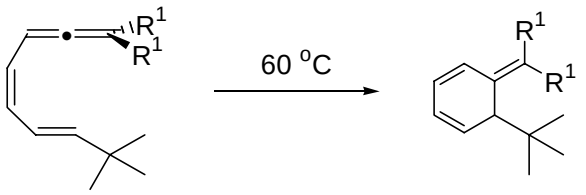
facile,[12] giving rise to the *o*-isotoluenes **34-40** after the treatment of **33** with acetic acid. Unlike the parent compound **1** without an R group on the six-membered ring, the *o*-isotoluenes **34** to **40** (Table 1) having an R group on the ring were stable to oxygen and could be isolated and purified by column chromatography as observed previously.[8b]

Table 1. Synthesis of *o*-Isotoluenes

***o*-Isotoluenes**	**Isolated Yield**	**o-Isotoluenes**	**Isolated Yield**
 **34**	**60%**	 **38**	**17%**
 **35**	**54%**	 **39**	**20%**
 **36**	**38%**	 **40**	**30%**
 **37**	**16%**		

However, in the presence of a sterically demanding *tert*-butyl group as the R group, the rate of electrocyclization was significantly reduced, allowing isolation of the diene-allene **41a**

(41%) and **41b**[13] (35%) after treatment with acetic acid. On heating in $CDCl_3$ at 60 °C for 96 h (t ½ = *ca*. 12 h), **41b** was smoothly converted to the *o*-isotoluene **42b** in 91% isolated yield (eq 1).[13]

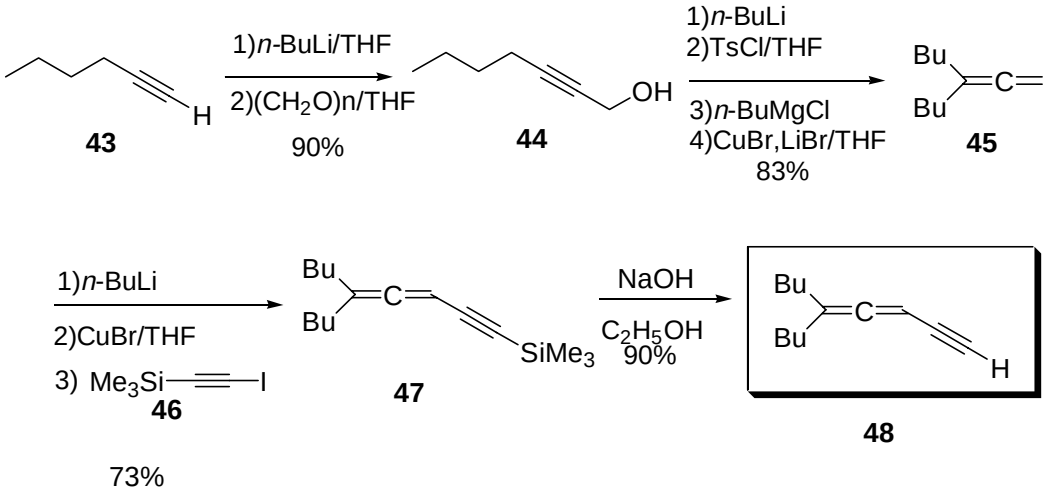


(1)

41 a: R^1 = Bu, 41%
41 b: R^1,R^1= -$(CH_2)_5$-, 35%

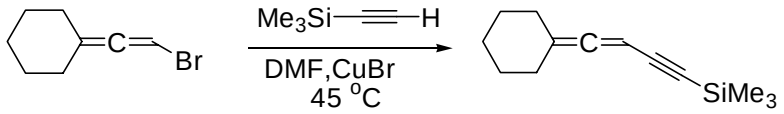
42 b: R^1, R^1 = -$(CH_2)_5$-, 91%

The conjugated allenyne **48** was synthesized according to the reported procedure.[10] Thus treatment of 1-hexyne with *n*-BuLi in THF followed by the addition of paraformaldehyde in THF produced 2-heptyn-1-ol (**44**) in 90% yield (Scheme 11). Sequential treatment of **44** with *n*-BuLi, *p*-toluenesulfonyl chloride in THF followed by a solution of *n*-butylmagnesium chloride and CuBr•LiBr afforded the disubstituted allene **45** in 83% yield.[14] The subsequent coupling with 1-iodo-2-(trimethylsilyl)acetylene (**46**)[15] followed by desilylation then produced the allenyne **48** in 90% yield.



Scheme 11

Alternatively, allenynes were also prepared by coupling the bromoallenes with trimethylsilyacetylene in the presence of copper (I) bromide (eq 2). This route was also used in our group for the synthesis of allenynes.



(2)

4. Conclusion

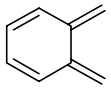
We have successfully developed a novel synthetic route to the *o*-isotoluene derivatives under mild conditions. The use of a suitable organoborates to allow a one-step conversion to the (*Z*)-diene-allenes followed by a facile electrocyclization to the *o*-isotoluenes is an especially attractive feature. This synthetic route is also very versatile, allowing easy access to *o*-isotoluenes with diverse structures.

PART II

GENERATION OF *o*-QUINODIMETHANES VIA THE ELECTROCYCLIC REACTION OF (4*Z*)-1,2,4,6,7-OCTAPENTAENES DERIVED FROM THE ORGANOBORATE COMPLEXES AND THEIR SUBSEQUENT REACTIONS

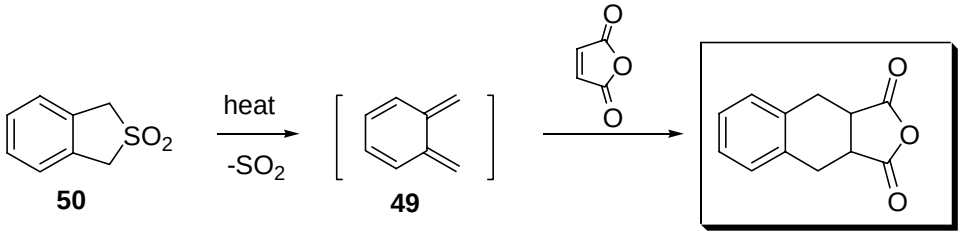
1. Introduction

o-Quinodimethane **49,** also known as *o*-xylylene, has been used extensively as a reactive intermediate in the synthesis of alkaloids, steroids and terpenes.[16] It was first recognized by



49

Cava and Napier in 1957 as a useful synthetic intermediate. Later, Cava et al. generated the parent *o*-quinodimethane by thermal elimination of sulfur dioxide from the sulfone **50**, it was trapped with maleic anhydride to form the Diels-Alder adduct.[17] Since then, many synthetic routes to *o*-quinodimethanes have been developed.

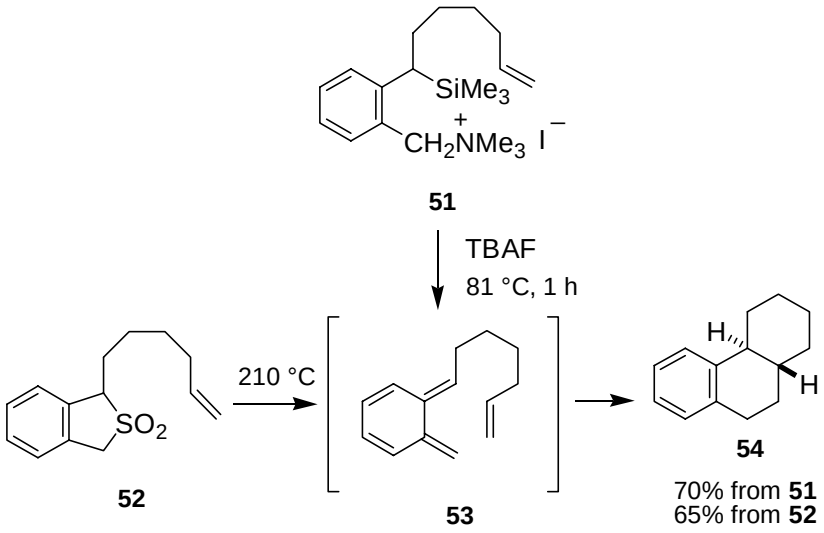


50 **49**

2. Synthetic Methods for *o*-Quinodimethanes

2.1. 1,4-Elinination of α,α'-Disubstituted *o*-Xylenes

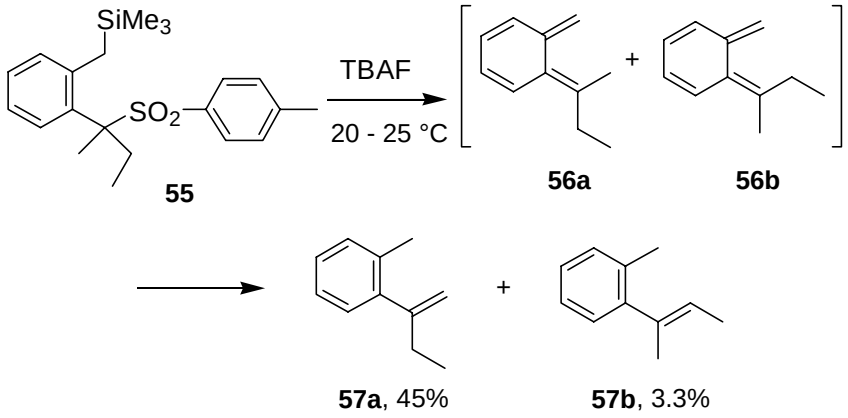
Many synthetic routes to *o*-quinodimethanes have been developed. Among them, the 1,4-elimination reactions of the α,α'-disubstituted *o*-xylenes as shown in Schemes 12 and 13, are the most versatile methods because of the readily availability of the starting materials. For example, treatment of **51** with tetrabutylammonium fluoride (TBAF) in refluxing acetonitrile induced a 1,4-elimination to form the *o*-quinodimethane **53** having the *E* geometry, which then underwent an intramolecular Diels-Alder reaction to furnish **54** having the *trans* ring junction (Scheme 12).[18] This synthetic route provides an efficient pathway to many polycyclic systems.



Scheme 12

Alternatively, thermolysis of the sulfone **52** at 210 °C promotes the extrusion of sulfur dioxide which leads to **53** and consequently **54** (*trans:cis* = 5:1) in 65% yield.[19]

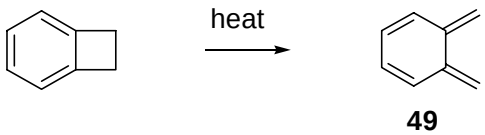
For the α-substituted *o*-quinodimethanes having a (*Z*)-allylic hydrogen, the [1,5] sigmatropic hydrogen shift is a facile process.[20] Shechter et al. recently reported that treatment of the sulfone **55** with TBAF produced both **57a** (45%) and **57b** (3.3%) (Scheme 13).[20a] Presumably, the reaction proceeded through an initial 1,4-elimination to form the *o*-quinodimethanes **56a** as the major isomer and **56b** as the minor isomer followed by a [1,5] sigmatropic hydrogen shift. In many cases, the 1,4-elimination reactions are conducted at ambient temperature. In contrast, elevated temperature is needed to induce SO_2-extrusion as indicated in **54** as well as from related compounds.



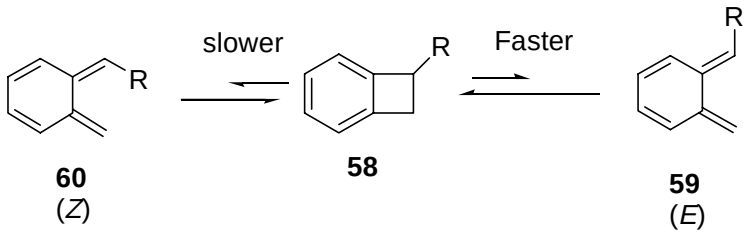
Scheme 13

2.2 Thermolysis of Benzocyclobutenes

The ready accessibility of benzocyclobutens together with their chemical inertness make them a reliable and convenient source of *o*-quinodimethanes. The transformation proceeds via



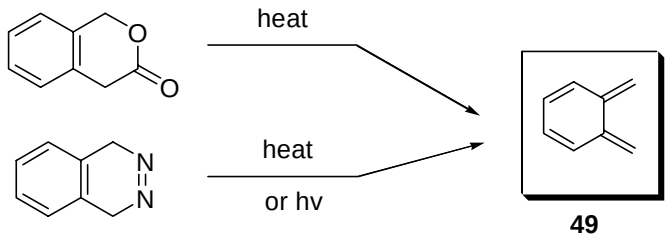
a thermally-allowed conrotatory electrocyclic ring opening. Benzocyclobutenes having a substituent on the 4-membered ring open outward to produce the sterically less hindered (*E*)-*o*-quinodimethanes **59** in preference to the (*Z*)-isomer **60.** The substituted benzocyclobutenes also undergo electrocyclic ring opening at a lower temperature than does the unsubstituted benzocyclobutenes (Scheme 14).[16a]



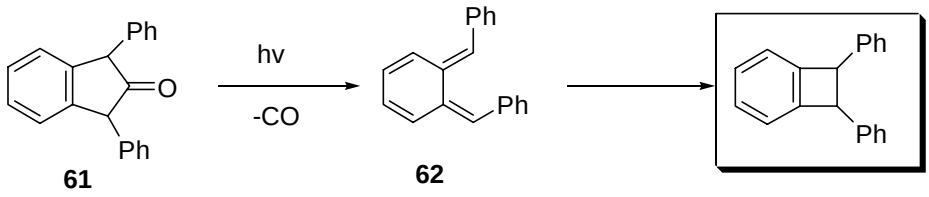
Scheme 14

2.3. Retro-Diels-Alder Reactions of Benzofused Heterocyclic Compounds

o-Quinodimethanes have also been generated from benzofused heterocyclic compounds by retro-Diels-Alder reactions in which a small molecule of nitrogen, carbon dioxide, or sulfur dioxide is lost by thermal or photochemical process.[16i]

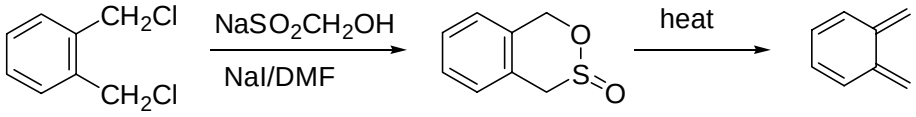


It is also interesting to note that **62** has been reported to be in thermal equilibrium with the cyclized benzocyclobutene.[16d]



61 **62**

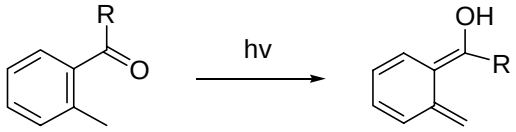
Dittmer et al. reported a one-step synthesis of sultine **63** in good yield by treatment of α,α'-dichloro-*o*-xylene with sodium hydroxymethane-sulfinate and sodium iodide in DMF. This new method for the generation of sultine **63** appears to be more convenient than the multistep processes reported earlier.[21]



63 **1**

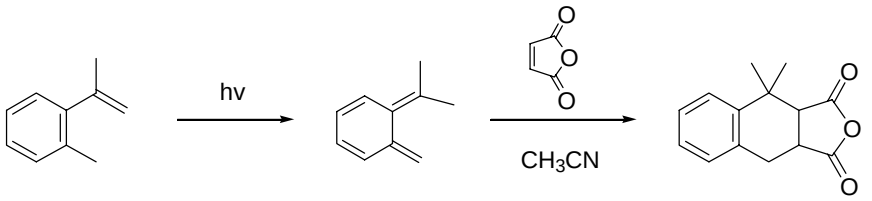
2.4. Photoenolization and Photorearrangement

The photochemical behavior of a series of *o*-alkyl substituted aromatic aldehydes and ketones were investigated. On irradiation they undergo photoenolization by a 1,5-hydrogen shift



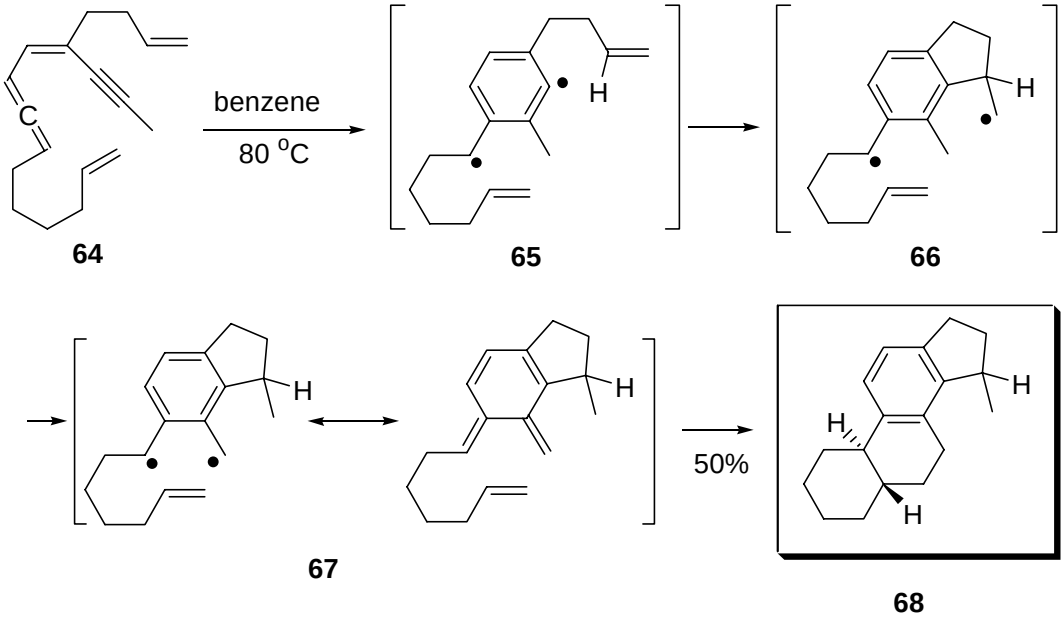
to form *o*-quinodimethanes.[22,23] It is thought that the *Z* isomer returns rapidly to the starting carbonyl compound by a [1,5] sigmatropic hydrogen shift, while the *E* isomer is relatively longer lived.

The photolysis of *o*-alkylstyrenes has also been reported to produce *o*-quinodimethanes via a [1,5] sigmatropic rearrangement.[24]



2.5. Thermolysis of (*Z*)-1,2,4-Heptatrien-6-ynes

Recently, our group reported the thermolysis of (*Z*)-1,2,4-heptatrien-6-ynes to generate α,3-didehydrotoluene biradicals for subsequent decay to *o*-quinodimethanes (Scheme 15).[20b,25] The thermally-induced cascade radical cyclization of the acyclic enyne-allene **64** to the fused steroidal ring system was carried out in refluxing benzene for 2.5 h to furnish **68** having predominantly the trans ring junction (*trans:cis* = 92:8). Thermolysis of **64** promoted the Myers cyclization to form the biradical **65**. Ring closure to form **66** is most likely the first event that occurs following the Myers cycloaromatization reaction. A subsequent 1,5-hydrogen shift then



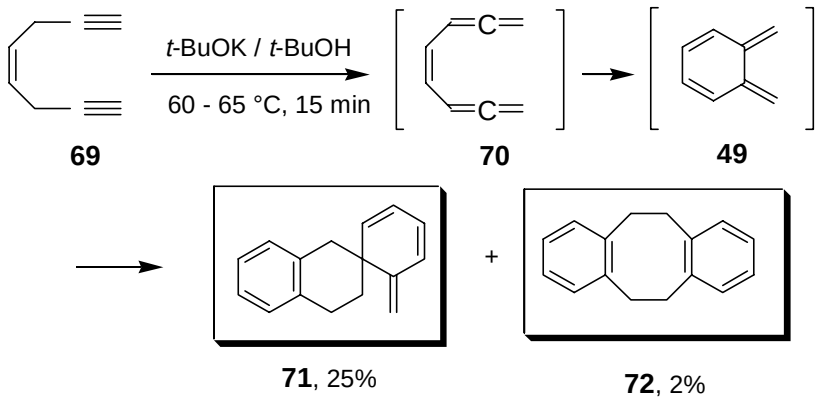
64 **65** **66** **67** **68**

Scheme 15

produced the *o*-quinodimethane **67**, which was in turn captured in an intramolecular Diels-Alder reaction to give **68**.

2.6. Electrocyclic Reaction of Enediallenes

An interesting but less studied route to *o*-quinodimethanes involves the electrocyclic reaction of (4*Z*)-1,2,4,6,7-octapentaenes (enediallenes). The parent (*Z*)-1,2,4,6,7-octapentaene (**70**) was generated in situ by treatment of (*Z*)-4-octene-1,7-diyne (**69**) with potassium *tert*-butoxide (Scheme 16).[26] The subsequent electrocyclic reaction gave the parent



Scheme 16

o-quinodimethane **49**, which then produced the spiro dimer **71** and the linear dimer **72**. Isomerization from **70** to **49** must be a very facile process. The corresponding benzofused[27,28] and naphthofused[27] analogues with a fused central carbon–carbon double bond isomerize rapidly to 2,3-naphthoquinodimethane and 2,3-anthraquinodimethane, respectively, at ambient or sub-ambient temperatures. In addition, the electrocyclic reaction of (4*Z*)-1,2,4,6-heptatetraenes to 5-methylene-1,3-cyclohexadienes (*o*-isotoluenes) is known to be vary facile.[29] However, with the exception of the benzofused and the naphthofused analogues, other *o*-quinodimethanes have

not been prepared via the electrocyclic reaction of enediallenes.

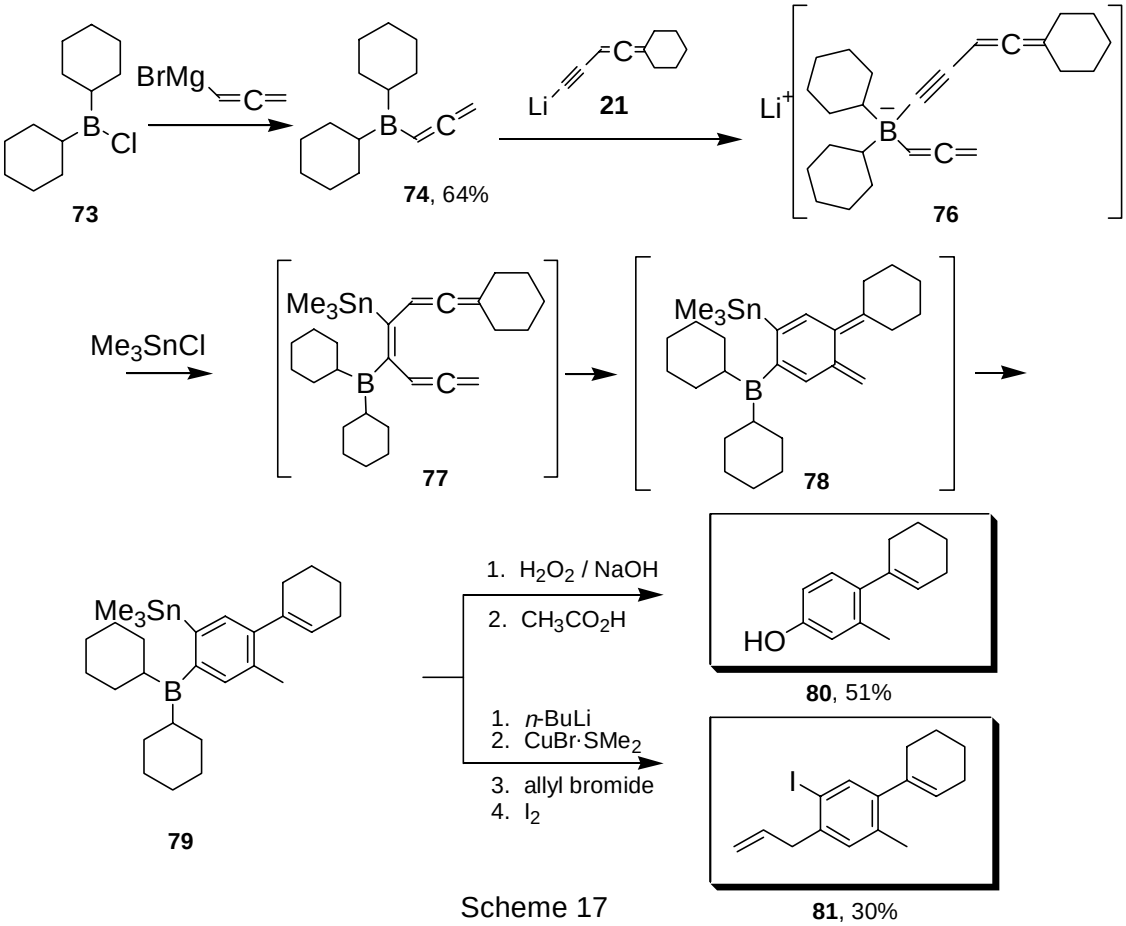
In the previous chapter, a facile synthesis of *o*-isotoluenes via the electrocyclic reaction of (4*Z*)-1,2,4,6-heptatetraenes was described (Scheme 10).[29d] Treatment of alkenyldicyclohexylboranes **29** with 1-lithio-3,4-pentadien-1-ynes, derived from lithiation of the corresponding 3,4-pentadien-1-ynes with *n*-butyllithium, followed by trimethyltin chloride and acetic acid furnished the *o*-isotoluenes **34-40**. Presumably, the reaction proceeds through the formation of the organoborate complexes **31** followed by the trimethyltin chloride-induced transformation to form **32** with the dicyclohexylboryl group and the trimethyltin group cis to each other.[30] The electrocyclic reaction of **32** then produces **33**, after protonation with acetic acid, the *o*-isotoluenes **34-40**. We envisioned that the reaction sequence outlined in Scheme 10 could be adopted for the synthesis of enediallenes for subsequent conversion to *o*-quinodimethanes by substitution of the alkenyldicyclohexylboranes **29** with allenyldicyclohexylboranes.

3. Research Objective

Recently we reported a novel electrocyclization of diene-allenes to *o*-isotoluenes. The diene-allenes were synthesized via selective migration of the alkenyl group from the boron atom to the adjacent acetylenic carbon atom of an organoborate complex.[29d] We envisioned that an allenyl group could also migrate from the borane atom to the adjacent acetylenic carbon atom of an organoborate complex to afford enediallenes. The subsequent electrocyclic reaction of enediallenes could generate the *o*-quinodimethanes for further synthetic elaborations.

4. Results and discussion

Allenyldicyclohexylborane (**74**) was readily prepared by treatment of chlorodicyclohexylborane (**73**) with allenylmagnesium bromide (Scheme 17). Sequential treatment of **74** with 1-lithio-3,4-pentadien-1-yne **75**, Me_3SnCl, an alkaline H_2O_2 solution, and acetic acid produced the phenol **80** in a single operation. Apparently, trimethyltin chloride also promoted a stereoselective migration of the allenyl group in **76** to the adjacent acetylenic carbon

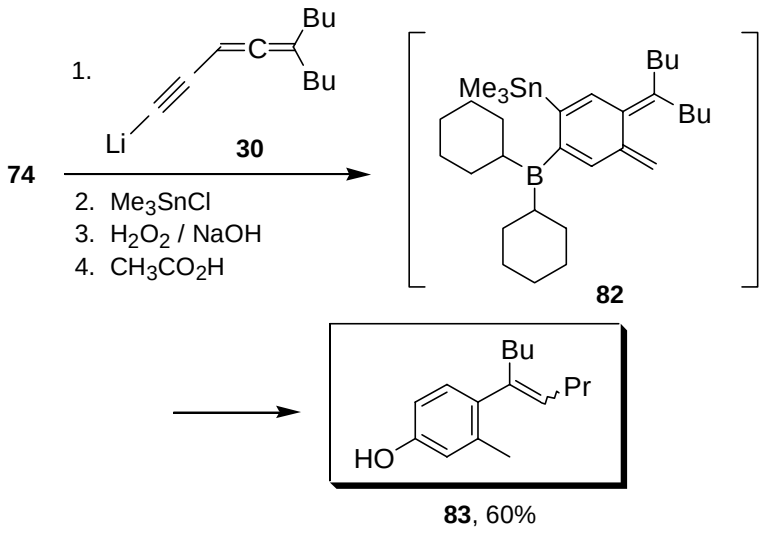


Scheme 17

atom to afford the enediallene **77**. The electrocyclic reaction of **77** then generated the *o*-quinodimethane **78**, giving rise to **79** through a [1,5]-sigmatropic hydrogen shift. Oxidative workup followed by protonation with acetic acid then gave **80** in 51% yield.

The presence of a dicyclohexylboryl group and a trimethyltin group in **79** also affords opportunities for other chemical transformations. Treatment of **79** with *n*-butyllithium followed by $CuBr \cdot SMe_2$ and allyl bromide transformed the dicyclohexylboryl substituent to the allyl group, presumably via an organocopper intermediate.[30e-h] Further treatment of the resulting adduct with I_2 replaced the trimethyltin group with an iodo substituent[30e-h] to furnish **27** having a tetrasubstituted benzene ring.

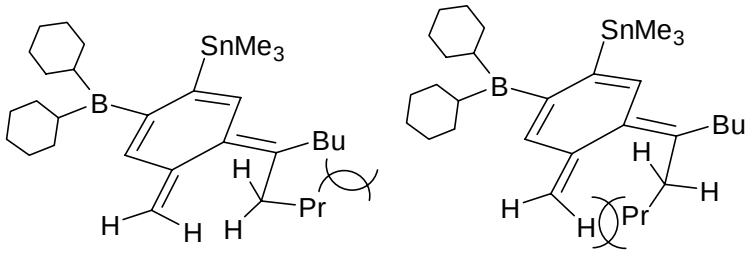
By using **30** to form the organoborate complex with **74**, the *o*-quinodimethane **82** was generated in situ (Scheme 6). The subsequent [1,5]-sigmatropic hydrogen shift then furnished **83**



Scheme 18

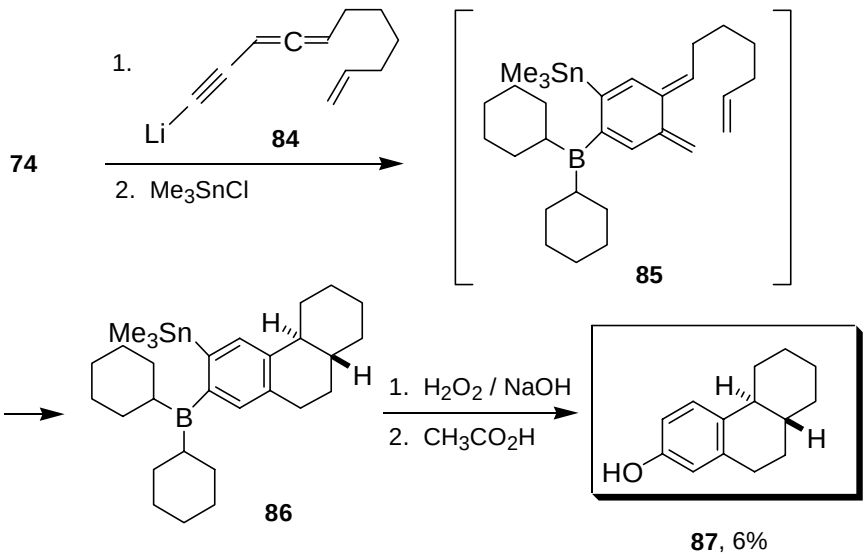
as a mixture of the *E* and the *Z* isomers (isomer ratio = 84:16) in 60% yield. Whether the *E* isomer or the *Z* isomer was produced as the predominant product has not been determined definitively. However, it is worth noting that the ^{1}H NMR chemical shift of the alkenyl hydrogen of the major product at δ 5.18 is 0.24 ppm upfield from that of the minor product at δ 5.42. It was reported previously that the ^{1}H NMR chemical shift of the alkenyl hydrogen of the *Z* isomer

of 1-(1-ethyl-1-propenyl)-2-methylbenzene at δ 5.35 is 0.24 ppm upfield from that of the *E* isomer at δ 5.59.[20a] The chemical shift correlation appears to suggest that the *Z* isomer of **83** is the predominant product. In any event, the *E* isomer is produced from the conformer **82a**, while the *Z* isomer is derived from the conformer **82b**. The relative severity of the A(1,2) allylic strain in **82a** versus the A(1,3) allylic strain[31] in **82b** determines the ratio of the resulting *E* and *Z* isomers. The preferential formation of the *E* isomer was reported previously in the system leading to the formation of 1-(1-ethyl-1-propenyl)-2-methylbenzene.[20a]



82a **82b**

It was possible to capture the *o*-quinodimethane in **85**, derived from **74** and **84**, with the carbon–carbon double bond for the intramolecular Diels-Alder reaction to afford **86**, which on oxidative workup and protonation gave the tricyclic phenol **87** having predominantly the trans ring junction (trans:cis > 10:1) (Scheme 19). Unfortunately, the overall isolated yield of **87** is only 6%. A small amount of 4-[(1*E*)-1,6-heptadienyl]-3-methylphenol (ca. 1%), presumably derived from a [1,5]-sigmatropic hydrogen shift of the *Z* isomer of **85**, was also produced. The effect of the boron and the tin substituents on the reactivity of the *o*-quinodimethane in **85** for the intramolecular Diels-Alder reaction remains to be determined.

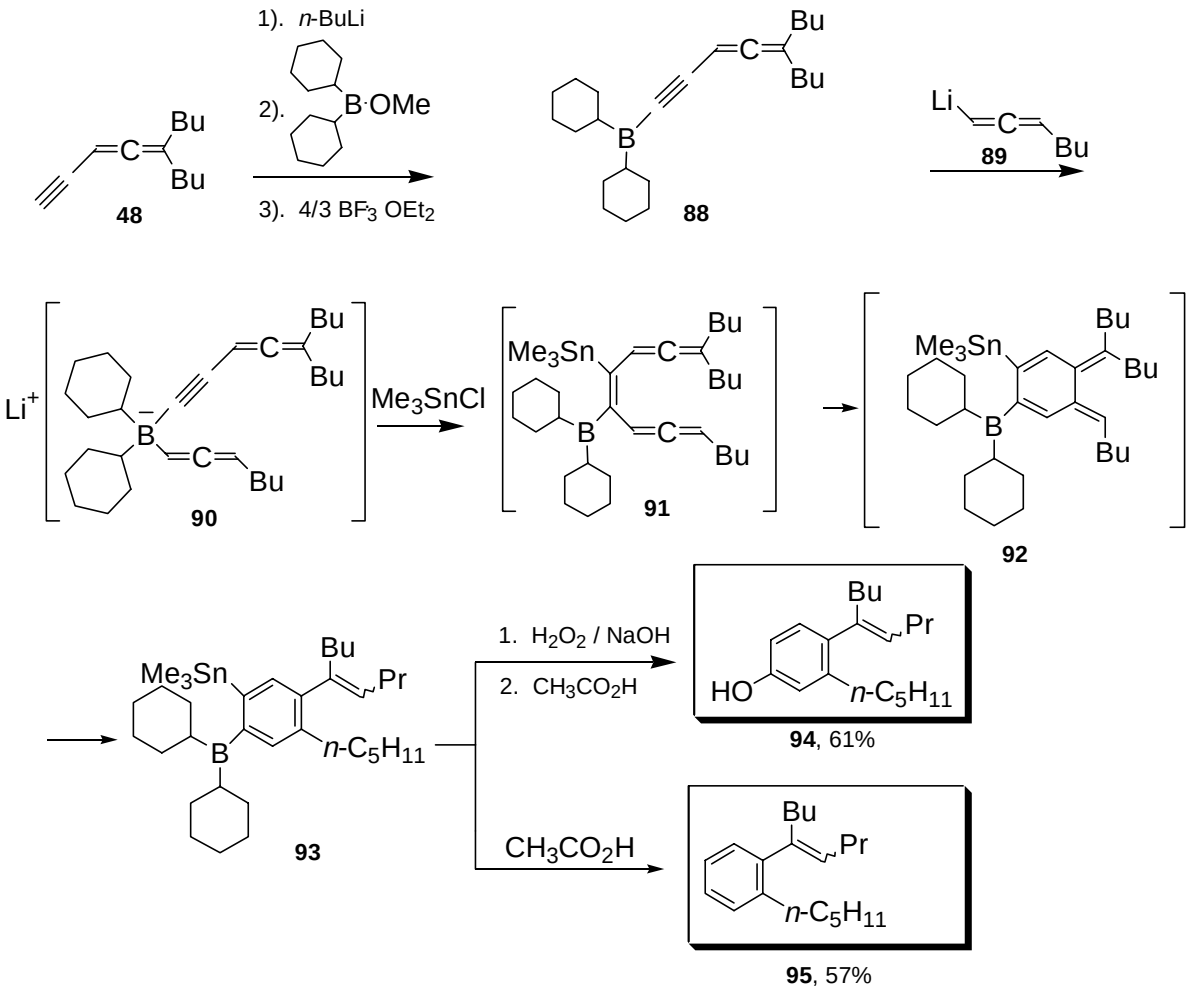


Scheme 19

An alternative pathway to the organoborate complexes for the subsequent formation of *o*-quinodimethanes has also been developed. Sequential treatment of 5-butyl-3,4-nonadien-1-yne (**48**) with *n*-butyllithium, *B*-methoxydicyclohexylborane, and 4/3 $BF_3 \cdot OEt_2$[32] generated **88** in situ (Scheme 20). Further treatment of **88** with 1-lithio-1,2-heptadiene (**89**) gave the requisite organoborate complex **90** for transformation to the *o*-quinodimethane **92**, leading to **93** and subsequently, after oxidative workup and protonation, the phenol **94** (61% yield, isomer ratio = 87:13). Direct protonation of **93** with acetic acid furnished **95** in 57% yield.

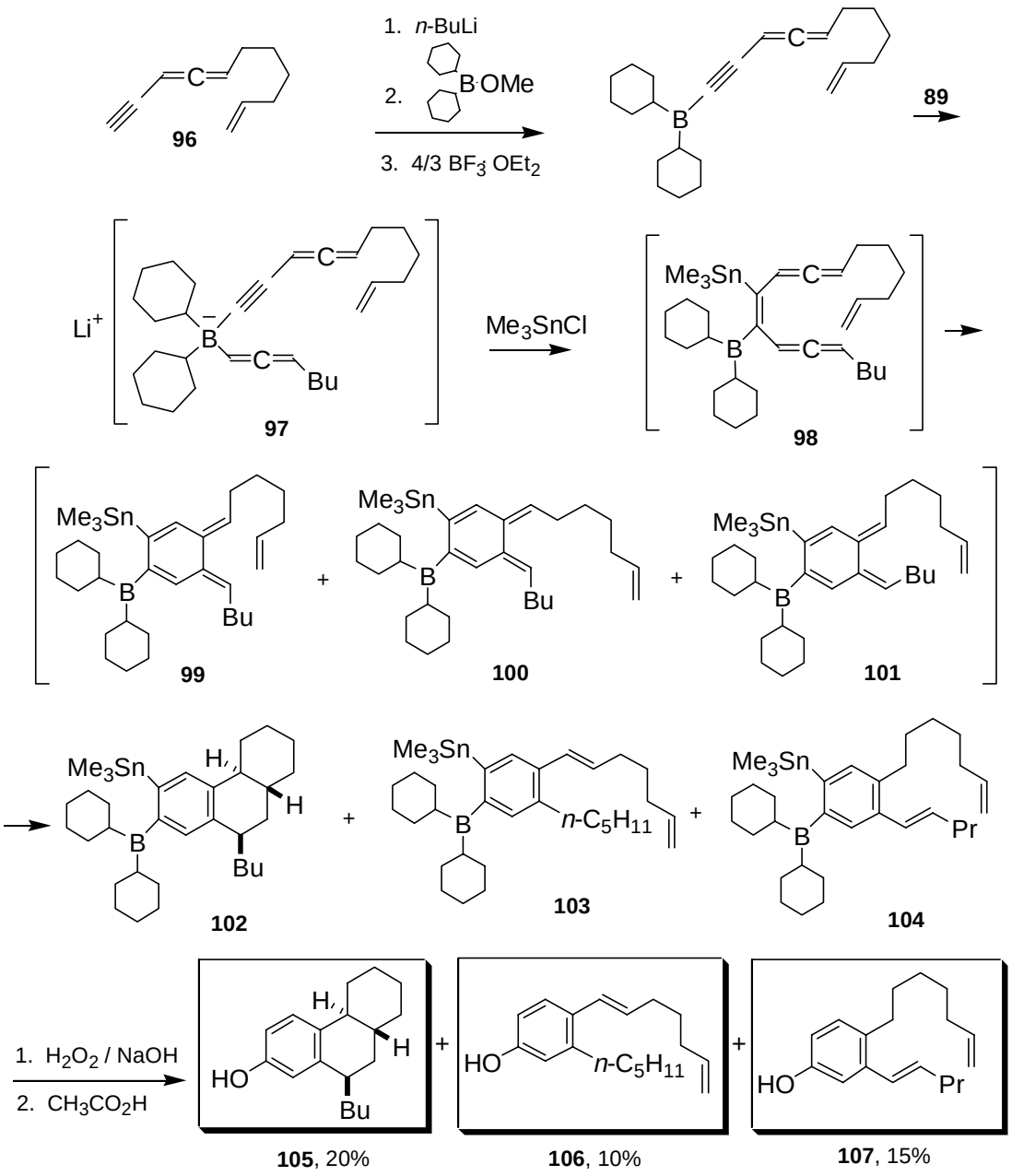
By using the combination of 3,4,10-undecatrien-1-yne (**96**) and **89** to form the organoborate complex **97**, the phenols **105** (20%), **106** (10%), and **107** (15%) were obtained (Scheme 21). Apparently, **105** was produced via the intramolecular Diels-Alder reaction of **99** to form **102**, whereas **106** and **107** were produced via the [1,5]-sigmatropic hydrogen shift of **100** and **101** to form **103** and **104**, respectively.

It is worth noting that the enediallene **98** is most likely a 1:1 mixture of the two



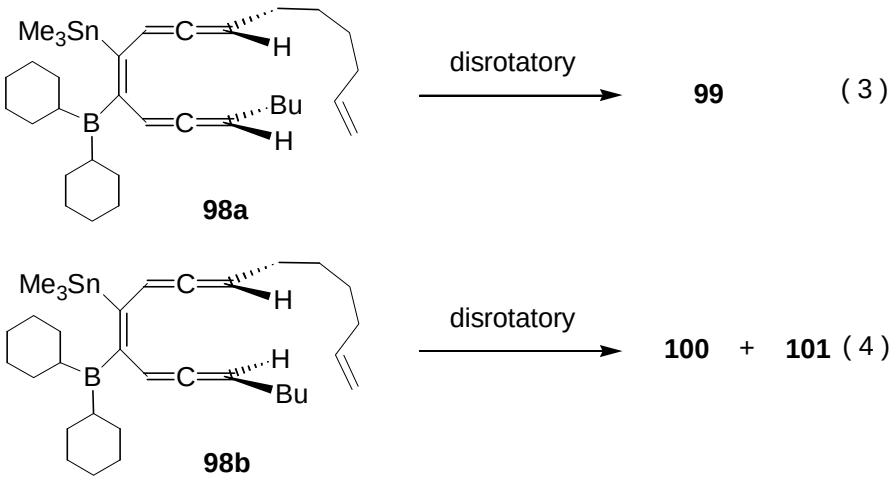
Scheme 20

diastereomers **98a** and **98b**. If the disrotatory motion of the six π-electron system is also required for the thermally-induced electrocyclic reactions of **98a** and **98b**, then **98a** will be the precursor of **99** (eq 3) whereas **98b** will be the precursor of both **100** and **101** (eq 4).[32] The fact that substantial amounts of **106** and **107** (combined yield = 25%) were produced appears to suggest that the stereoelectronic requirement for the electrocyclic reaction dictates the transformation of **98b** to the sterically less favorable **100** and **101** with one of the exocyclic double bonds having the *Z* geometry. Otherwise, one would expect a preferential formation of

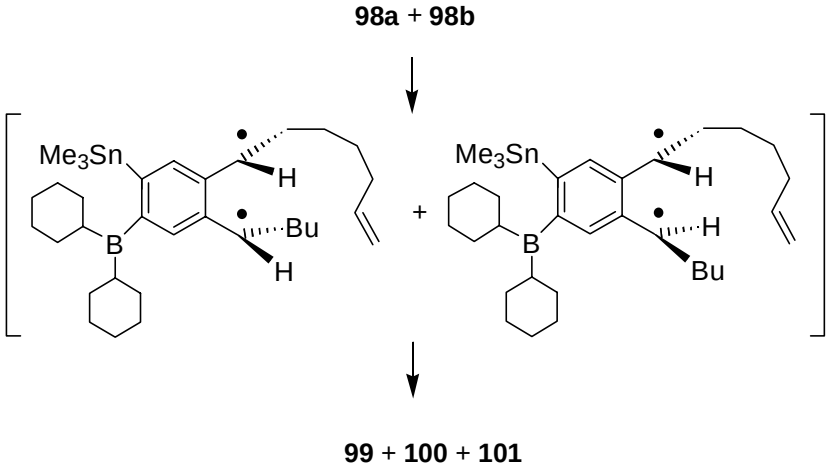


Scheme 21

99 with both of the exocyclic double bonds having the *E* geometry. However, the possibility of producing **99**–**101** from **98** via a biradical pathway without the requirement of an initial



disrotatory motion (Scheme 22) could not be ruled out. A one-step intramolecular ene reaction of **98** could also produce **103** and **104** directly.[34]



Scheme 22

5. Conclusions

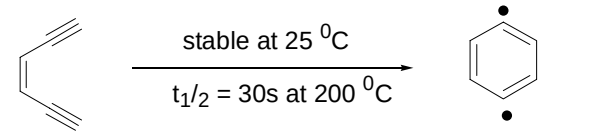
A new synthetic pathway to (4*Z*)-1,2,4,6,7-octapentaenes as precursors of *o*-quinodimethanes has been developed. The ability to generate enediallenes with high geometric purity via the corresponding organoborate complexes in a single operation is an especially attractive feature. The process is very flexible, allowing easy assembly of various readily available fragments to produce the requisite organoborate complexes. The presence of the boron and the tin substituents in the cyclized adducts also affords opportunities to introduce other functional groups onto the benzene ring.

PART III

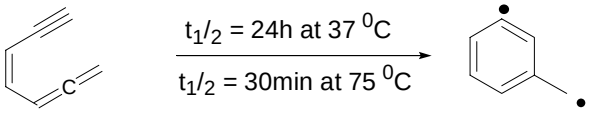
BIRADICALS FROM THERMOLYSIS OF *N*-[2-(1-ALKYNYL)PHENYL]-*N′*-PHENYLCARBODIIMIDES AND THEIR SUBSEQUENT TRANSFORMATIONS TO 6*H*-INDOLO[2,3-*b*]QUINOLINES

1.Introduction

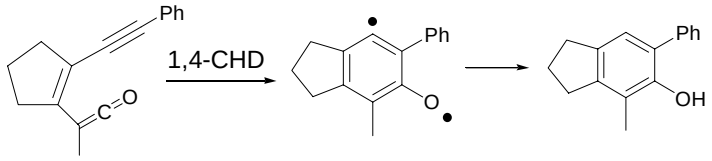
Since the discovery of the enediyne antitumor antibiotics,[41] the chemistry of biradicals have received great attention. The Bergman cyclization of (*Z*)-3-hexene-1,5-diynes (enediynes) to 1,4-didehydrobenzene biradicals (eq 5),[42] the Myers cyclization of (*Z*)-1,2,4-heptatrien-6-ynes (enyne–allenes) to α,3-didehydrotoluene biradicals (eq 6),[43] and the Moore cyclization of



(5)



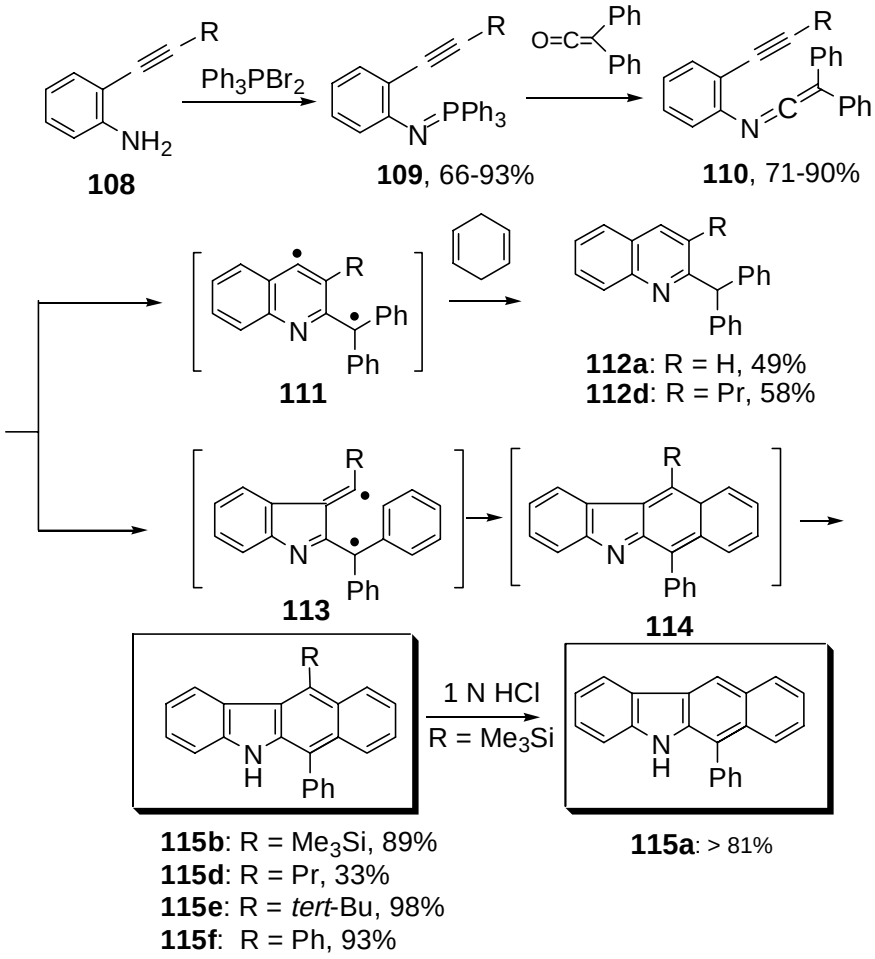
(6)



(7)

enyne–ketenes (eq 7)[44] to a phenoxy biradical species have been extensively studied. However,

the biradical-forming reactions involving other heteroatoms in the conjugated systems are rare.[45] Our group recently reported the use of iminophosphoranes **109**, readily prepared from treatment of 2-(1-alkynyl)anilines **108** with dibromotriphenylphosphorane ($Ph_3P•Br_2$), for the aza-Wittig reaction with diphenylketene to produce *N*-[2-(1-alkynyl)phenyl]ketenimines **110** (Scheme 23).[46] The ketenimines **110** then were converted to the quinolines **112** and/or the



Scheme 23

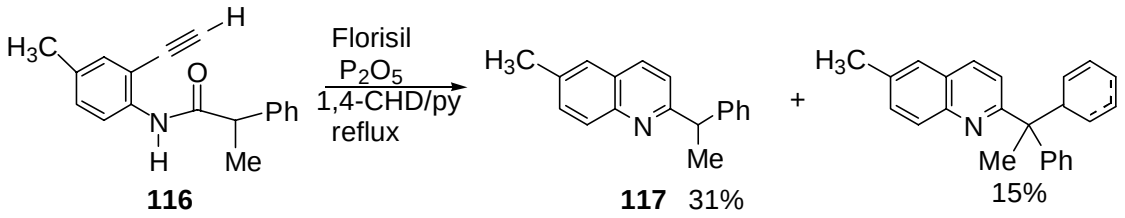
5*H*-benzo[*b*]carbazoles **115** depending on the nature of the substituent at the acetylenic terminus

under mild thermal conditions.

In the presence of an excess of 1,4-cyclohexadiene (1,4-CHD) as a hydrogen-atom donor, **110a** (R = H) was converted to the quinoline **112a** ($t_{1/2}$ = 0.37 h at 22 °C) in 49% yield. Apparently, the reaction proceeds through an initial cycloaromatization reaction to form the biradical **111a** followed by hydrogen-atom abstraction from 1,4-CHD. The transformation from **110a** to **111a** represents a new example of a growing list of the thermally-induced biradical-forming cycloaromatization reactions. The ability to produce **111a** from **110a** demonstrates the feasibility of placing a nitrogen atom in the conjugated system for the generation of biradicals under mild thermal conditions and provides a new avenue for the design of novel DNA-cleaving agents.[47]

Interestingly, when **110b** (R = $SiMe_3$) was heated under refluxing benzene, the benzocarbazole **115b** was produced exclusively ($t_{1/2}$ = 0.89 h at 72 °C). Presumably, the reaction proceeded through a different cascade sequence involving an initial formation of a five-membered ring to produce biradical **113b** followed by an intramolecular radical-radical combination to form **114b** and a subsequent tautomerization to furnish **115b**. While a one-step intramolecular Diels-Alder reaction of **110b** could also produce **114b** as reported previously in several analogous systems,[48] the presence of a sterically demanding trimethylsilyl group at the acetylenic terminus makes the concerted process unlikely to occur under mild thermal conditions. The reaction was directed toward **115b** presumably because of the emergence of a severe non-bonded steric interaction in **111b** (R = $SiMe_3$)[49] and the ability of the trimethylsilyl group in stabilizing an adjacent radical site in **113b**.[50] Such a change of the reaction pathway was also observed in a similar study[51] and in several analogous cases of ring closures of enyne–allenes[49,52]

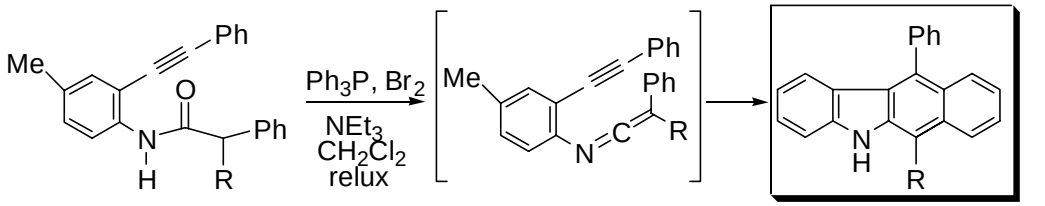
and enyne–ketenes.[53] Treatment of **115b** with 1 N HCl at 40 °C for one hour produced the desilylated adduct **115a** (>81% yield). It is worth noting that **115a** could not be obtained from **110a** directly. With the ketenimine **110d** (R = Pr), both the quinoline **112d** (58%) and the benzocarbazole **115d** (33%) were produced. In the cases of **110e** (R = *tert*-Bu) and **110f** (R = Ph), the benzocarbazoles **115e** and **115f** were produced exclusively. The presence of a sterically demanding *tert*-butyl group at the acetylenic terminus of **110e** makes the formation of **114e** via the concerted intramolecular Diels-Alder reaction unlikely.



116 **117** 31% 15%

Scheme 24

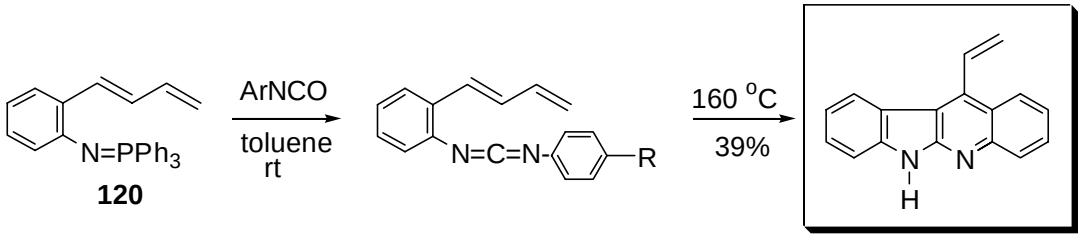
A similar study was also reported by Schmittel, Engels, and coworkers recently (Schemes 24 and 25).[51] They converted the amides **116** and **118** to the enyne-ketenimines, leading to quinolines **117** and benzocarbazoles **119**.



118 **119** R=Me (19%) R=Ph (69%)

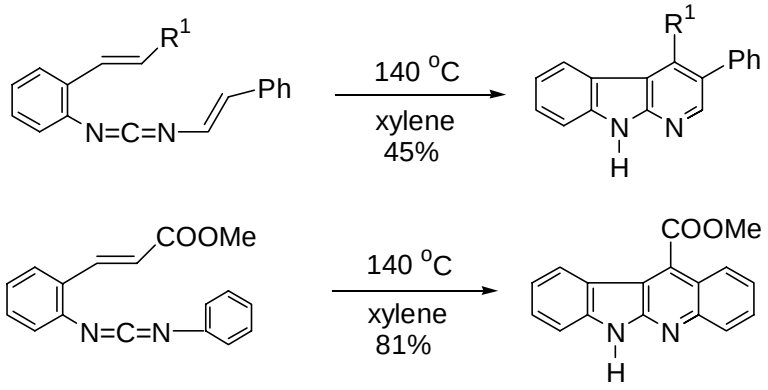
Scheme 25

Recently, there has been a surge of interest in developing new synthetic pathways to 6*H*-indolo[2,3-*b*]quinolines[48b,54] because several members of this group of compounds have been found to possess interesting biological activities.[55] Molina et al. reported an intramolecular [4+2] cycloaddition of C=C-conjugated carbodiimdes, prepared by the treatment of the iminophosphorane **120** with phenyl isocyanate (Scheme 26) to afford the indolo[2,3-*b*]quinoline **121**.[48b,54a]



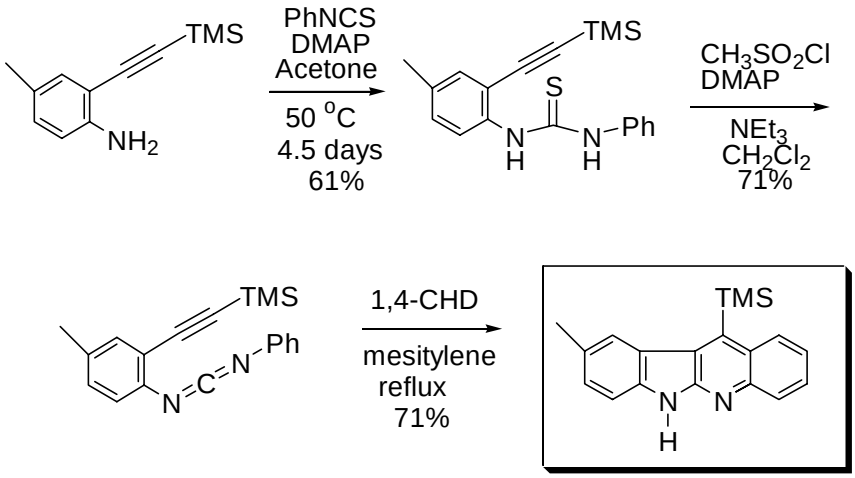
Scheme 26

Saito's group also reported a similar approach toward the synthesis of pyrido[2,3-*b*]indole and indolo[2,3-*b*]quinolines via intramolecular Diels-Alder reactions of conjugated carbodiimides (Scheme 27).[54b-c]



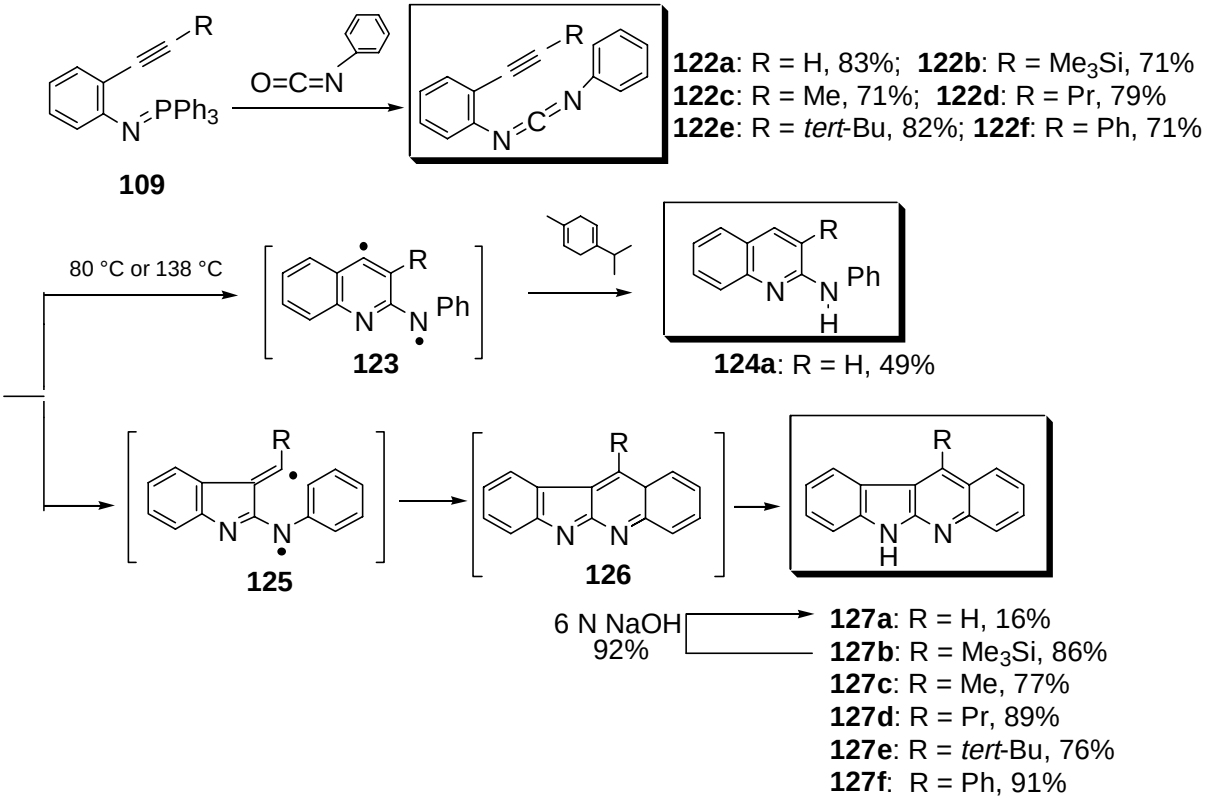
Scheme 27

Very recently, Schmittel et al. reported a synthetic strategy (Scheme 28)[56] similar to our work. His group prepared 6*H*-indolo[2,3-*b*]quinolines via thermally-induced biradical cyclizations of enyne-carbodiimides generated from thioureas.



Scheme 28

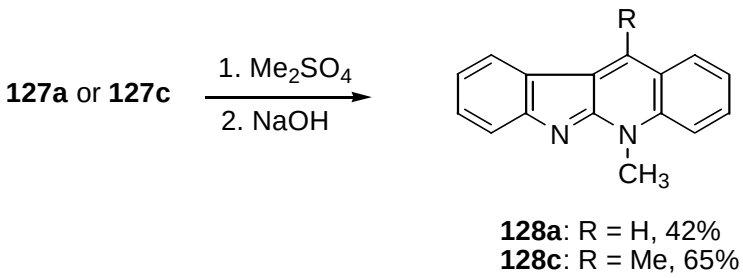
A logical extension of our recent work involves replacing the ketenimine moiety in **110** with other heterocumulenes. Carbodiimide appears to be an excellent candidate for such a substitution. Our group recently reported[57] the use of *N*-[2-(1-alkynyl)phenyl]-*N*′-phenylcarbodiimides **122** to produce biradicals and their subsequent transformations to 2-(phenylamino)quinoline (**124a**) and 6*H*-indolo[2,3-*b*]quinolines **127** (Scheme 29).[58] It was interesting to learn that carbodiimide **122a** had already been prepared previously by treatment of iminophosphorane **109a** (R = H) with phenyl isocyanate.[59] Thermolysis of **122a** in toluene at 160 °C in a sealed tube furnished 2-(phenylamino)quinoline (**124a**, 40%) and the parent 6*H*-indolo[2,3-*b*]quinoline (**127a**, 19%).[59] Our group was able to reproduce similar results by



Scheme 29

heating **122a**, isolated in 83% yield from treatment of **109a** with phenyl isocyanate, in γ-terpinene at 138 °C to afford **124a** (49%) and **127a** (16%). Apparently, **124a** was produced via the biradical **123a** followed by hydrogen-atom abstraction from γ-terpinene. A two-step biradical pathway through **125a** or a one-step intramolecular Diels-Alder reaction could furnish **126a**, which then underwent tautomerization to give **127a**. Several analogues examples in which a carbon-carbon double bond replaces the triple bond in **122** for the intramolecular Diels-Alder reaction have been reported.[48b,54] The indoloquinoline **127a** was used as an immediate precursor for the synthesis of a naturally occurring alkaloid, 5-methyl-5*H*-indolo[2,3-*b*]quinoline (**128a**)

(eq 8),[55,59] which was isolated from the roots of the West African plant *Cryptolepis sanguinolenta*[60] and was found to possess interesting biological activities.[55]



(8)

128a: R = H, 42%
128c: R = Me, 65%

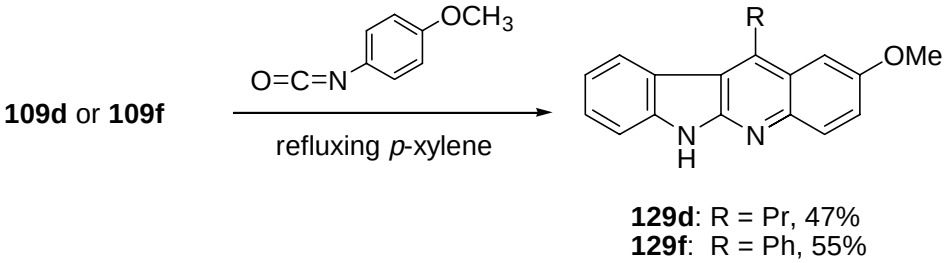
The reaction sequence outlined in Scheme 29 could provide an efficient route to the indoloquinoline **127a** if the competing pathway toward the quinoline **124a** could be suppressed. The result with **110b** suggests that a trimethylsilyl group at the acetylenic terminus could serve as a surrogate for the hydrogen atom in directing the reaction toward the indoloquinoline **127b**. A subsequent protodesilylation reaction could lead to **127a**. Indeed, thermolysis of **122b**, obtained in 71% from **109b** and phenyl isocyanate, in refluxing *p*-xylene at 138 °C produced **127b** in 86% yield. Similarly, heating the reaction mixture of **109b** and phenyl isocyanate in refluxing *p*-xylene without isolation of **122b** also gave **127b** (61%) in a single operation. Treatment of **127b** with 6 N NaOH in refluxing ethanol for 12 h then furnished **127a** in 92% yield.

When **122c** was subjected to thermolysis in *p*-xylene at 138 °C for 4 h, the indoloquinoline **127c** (77%) was produced exclusively, indicating a preferential formation of **126c** for subsequent tautomerization to **127c**. The corresponding quinoline **124c** (R = Me) was not detected. Direct thermolysis of the reaction mixture of **109c** and phenyl isocyanate in refluxing *p*-xylene without isolation of **122c** also afforded **127c** (59%) in a single operation. It

was reported that **127c** could serve as the immediate precursor of 5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (**128c**) (eq 8), which was found to display a strong antibacterial, antimycotic, and cytotoxic activity *in vitro*, as well as significant antitumor properties *in vivo*.[55]

Similarly, when **122d** was heated either in refluxing *p*-xylene or in γ-terpinene at 138 °C, the indoloquinoline **127d** (89%) was produced exclusively, in sharp contrast to the ketenimine **110d** (R = Pr) which furnished the quinoline **112d** preferentially. In addition, the carbodiimide **122d** is thermally less labile than the ketenimine **110d**, and a higher temperature is needed to promote the reaction. Treatment of **109d** with phenyl isocyanate in refluxing *p*-xylene without isolation of **122d** also afforded **109d** directly in a one-step operation in 72% yield. With **122e** having a sterically very demanding *tert*-butyl group, thermolysis in refluxing *p*-xylene for 14 h produced the indoloquinoline **127e** (76%). Again, the presence of a *tert*-butyl group at the acetylenic terminus of **122e** makes the formation of **126e** via the concerted intramolecular Diels-Alder reaction unlikely. With a phenyl substituent at the acetylenic terminus of **122f**, thermolysis under refluxing benzene (80 °C) for 4 h was sufficient to induce the transformation to **127f**[18] in 91% yield. Direct thermolysis of the reaction mixture of **109f** and phenyl isocyanate in refluxing benzene without isolation of **122f** also afforded **127f** in 67% yield.

4-Methoxyphenyl isocyanate was also used for the aza-Wittig reaction with **109d** and **109f**. Thermolysis of the reaction mixtures furnished the indoloquinolines **129d** and **129f**[48b] having a methoxy substituent at the C-2 position (eq 9).

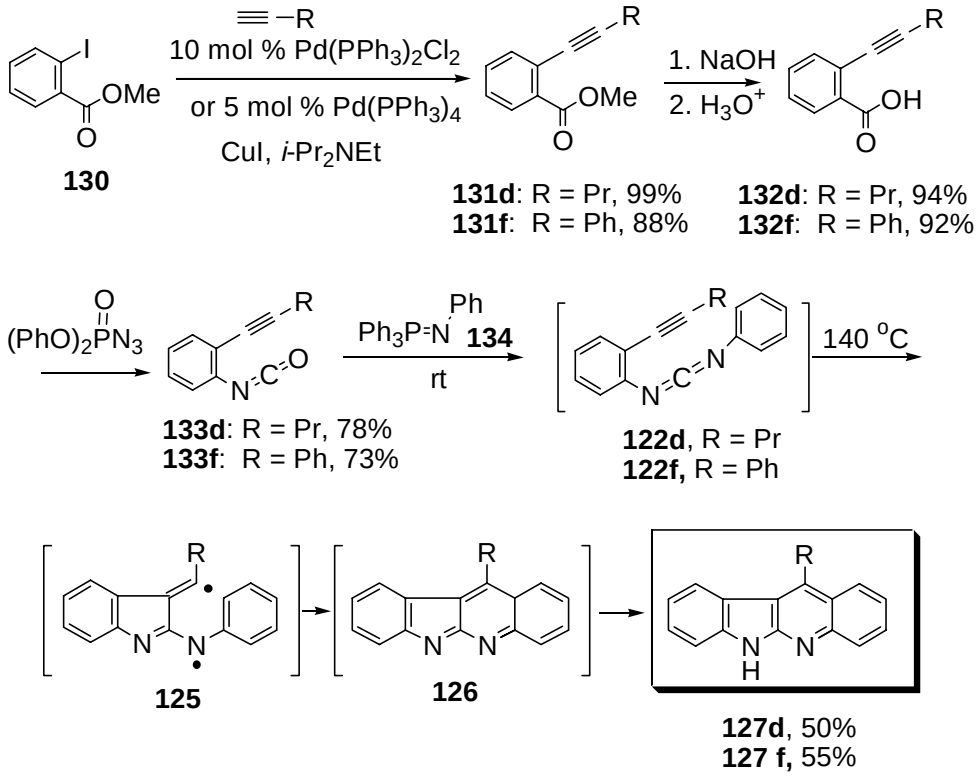


(9)

129d: R = Pr, 47%
129f: R = Ph, 55%

2. Results and Discussion

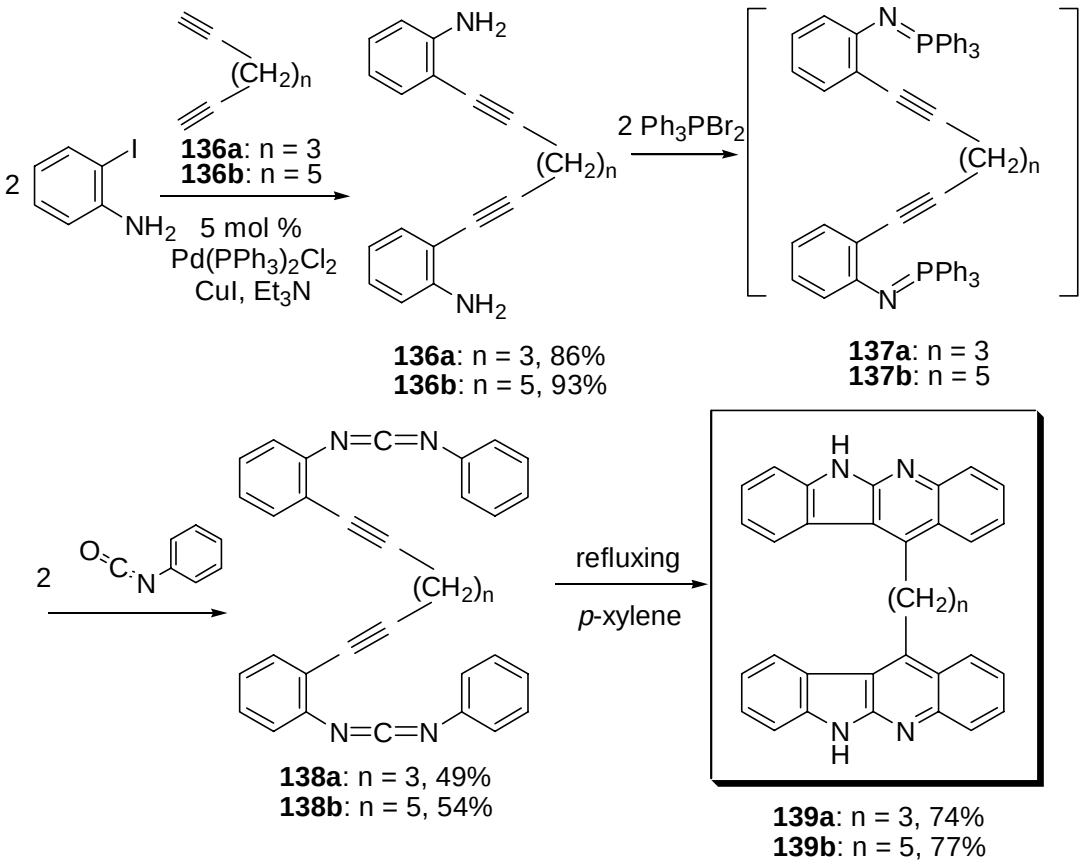
In order to further extend the synthetic applications of Scheme 29, an alternative pathway to the carbodiimides **122** was also developed (Scheme 30). The Pd-catalyzed cross-coupling



Scheme 30

reaction between **130** and 1-alkynes furnished methyl 2-(1-alkynyl)benzoates **131**, which were hydrolyzed to afford **132**. Treatment of **132** with diphenyl phosphorazidate (DPPA)[61] produced 2-(1-alkynyl)phenyl isocyanates **133**. The subsequent aza-Wittig reactions with the iminophosphorane **134**[62] then gave **122d** and **122f**. Thermolysis of the reaction mixtures of **133d** and **133f** with **134** in refluxing *p*-xylene also produced the indoloquinolines **127d** (50%) and **127f** (55%), respectively.

It is straightforward to adopt the synthetic sequence outlined in Scheme 29 for the preparation of **139a** and **139b** (Scheme 31) as potential bifunctional DNA intercalating agents.[63]

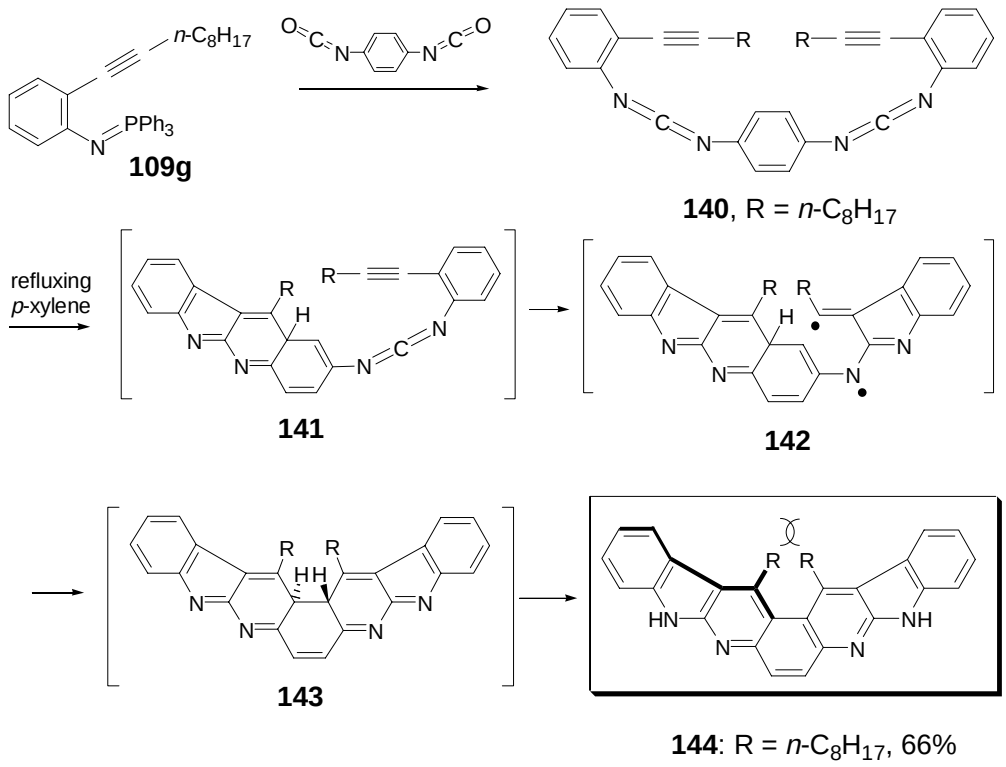


Scheme 31

The use of the diacetylenes **135a** and **135b** for cross coupling with two equiv. of 2-iodoaniline eventually allowed the connection of the two indoloquinoline units in **139a** and **139b** with either a three-carbon or a five-carbon tether at the 11 and the 11′ positions. The iminophosphoranes **137a** and **137b** were generated in situ from treatment of **136a** and **136b** with two equiv. of Ph_3PBr_2 for the subsequent aza-Wittig reaction with two equiv. of phenyl isocyanate, producing the carbodiimides **138a** and **138b** in 49% and 54% overall yield, respectively. It was possible to isolate the iminophosphoranes **137a** (20%) and **137b** (29%) by column chromatography (silica gel) albeit significant decomposition occured on the column. Treatment of the isolated **137a** with two equiv of phenyl isocyanate produced **138a** in 72% yield. Thermolysis of **138a** and **138b** in refluxing *p*-xylene then furnished **139a** (74%) and **139b** (77%), respectively.

Treatment of 1,4-phenylene diisocyanate with two equiv of **109g** for the aza-Wittig reaction produced **140** in situ, which on thermolysis in refluxing *p*-xylene furnished **144** (66%) having two indoloquinoline units incorporated in the seven fused rings (Scheme 32). It was also possible to isolate **140** by column chromatography (silica gel) in 44% yield. The presence of the two *n*-octyl groups in **144** greatly enhances its solubility in organic solvents.

The structure assignment of **144** is based on high-resolution mass spectra, the ^{1}H and ^{13}C NMR spectra, and the NOE studies. The molecular ion was detected on a high-resolution mass spectrometer (*m/z* = 582.3698). The ^{1}H and ^{13}C NMR spectra showed the right number of signals and pattern of multiplicity consistent with the structure of **144**. Interestingly, the ^{1}H NMR spectrum (Figure 1) exhibited two sets of signals with equal intensity at δ 4.00 (2 H, ddd, *J* = 12.9, 8.7, and 4.2 Hz) and 3.74 (2 H, dt, *J* = 13.4 and 8.0 Hz), indicating that the benzylic hydrogens are diastereotopic. The benzylic hydrogens are diastereotopic because the fused ring



Scheme 32

structure in **144** is helical due to nonbonded steric interactions of the two *n*-octyl groups. This is reminiscent of the structures of the 4,5-dimethylphenanthrenes, which have been shown to possess a helical twist.[64] The signals of the benzylic hydrogens in DMSO-d_6 remained well separated and exhibited no line broadening even at 110 °C, indicating that the rate of the helix inversion is relatively slow on the NMR time scale even at 110 °C. A significant nuclear Overhauser effect was observed between the doublet aromatic signal at δ 8.28 and the benzylic signal at δ 4.00. However, the nuclear Overhauser effect was negligible with the benzylic signal at δ 3.74. In addition, no NOE interaction between the singlet aromatic signal at δ 8.23 and the two benzylic signals was observed.

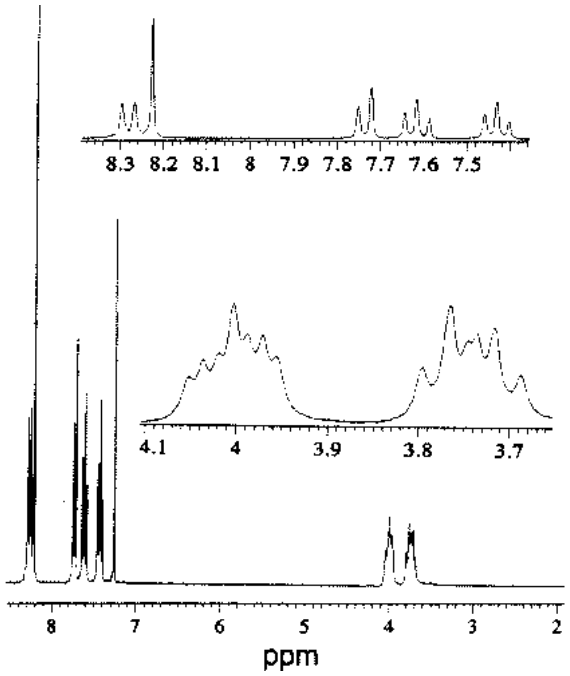
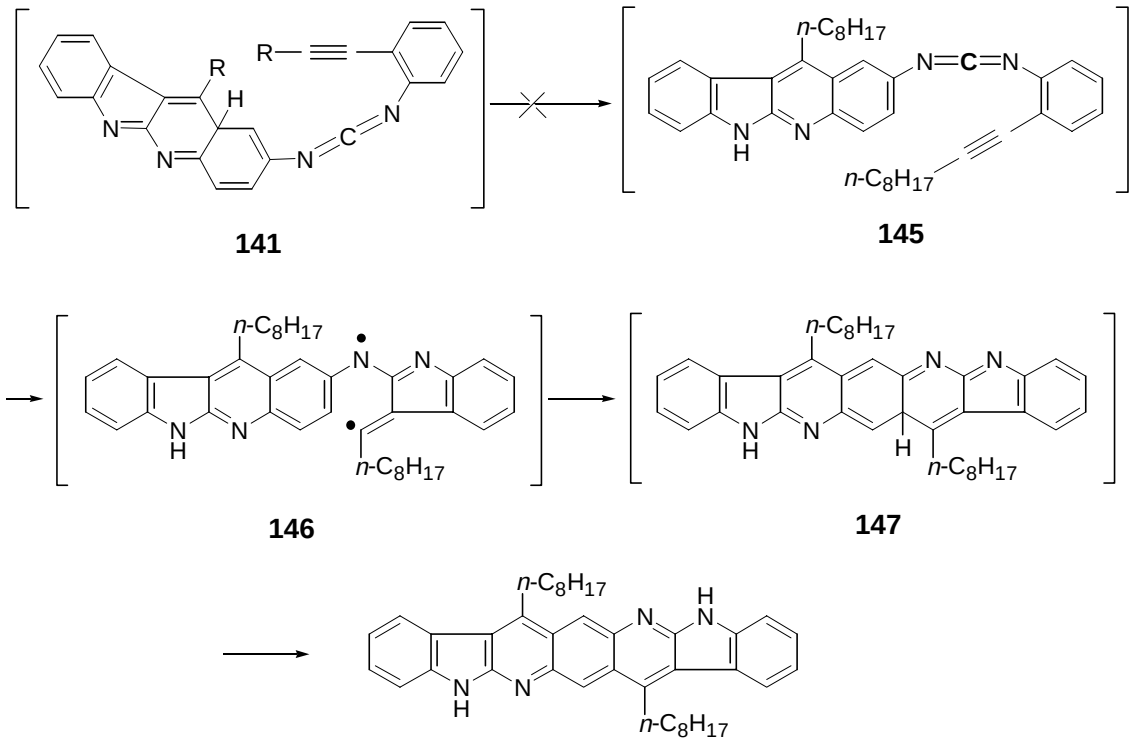


Figure 1. Partial ^{1}H NMR Spectrum of the Indoloquinoline **144** in $CDCl_3$.

The observation of two sets of benzylic signals and the lack of the NOE interaction with the singlet aromatic signal at δ 8.23 preclude the cycloaromatized isomer **148** depicted in Scheme 33 as the reaction product. Because **148** has essentially a planar ring structure, one would expect the ^{1}H NMR signal of the benzylic hydrogens of **148** to be a simple triplet as in the case of **127d**. Furthermore, one would also expect a strong NOE interaction between the benzylic hydrogens and the singlet aromatic hydrogens.

The preferential formation of **144** is presumably because the rate of transformation from **141** to **143** (Scheme 32) is faster than that of tautomerization of **141** to **145** (Scheme 33).



141 **145**

146 **147**

148

Scheme 33

Without a prior tautomerization, the biradical **142** has no choice but to cyclize to form **143**, producing **144** after two subsequent tautomerization reactions. Had the intermediate **141** underwent a tautomerization reaction to form **145** prior to the second indoloquinoline formation, one could have expected a preferential ring closure leading to **148** without nonbonded steric interactions between the two *n*-octyl groups. It is worth noting that the indoloquinoline **144** having an extended aromatic ring structure is potentially capable of intercalating DNA.[65]

3. Conclusions

Thermolysis of the carbodiimides **122** represents a new way of generating biradicals from unsaturated molecules having two nitrogen atoms in the conjugated system. The cascade sequence outlined in Schemes 29 and 30 also provide an efficient pathways to 6*H*-indolo[2,3-*b*]quinolines. The possibility of placing a wide variety of substituents at various positions of the 6*H*-indolo[2,3-*b*]quinoline structure by selecting suitable fragments for assembly is an especially attractive feature of this synthetic route.

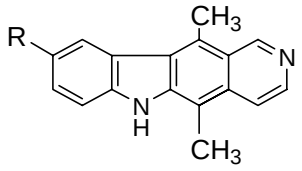
PART IV

AN EFFICIENT SYNTHESIS OF 5-AZA ANALOGUES OF ELLIPTICINE

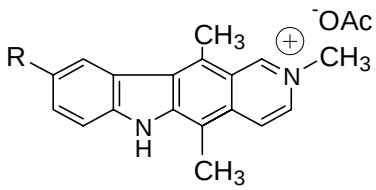
1. Introduction

1. 1. Ellipticine and Its Analogues

Several alkaloids containing the indolo structure as part of their polycyclic frameworks have been found to show potent biological activities. Over the past twenty years, members of the 6*H*-pyrido[4,3-*b*]carbazole class of alkaloids, particularly ellipticine (**149**, R = H) and 9-methoxyellipticine (**150**, R = OCH_3) and their derivatives, have been the subject of intense synthetic, biological and pharmacological studies.[67] The natural plant alkaloid ellipticine was first isolated in 1959 from the leaves of *Ochrosia elliptica Labill* (Apocynacae family), a plant harvested in Florida.[68] In 1967, the antitumor properties of ellipticine were revealed.[69] It was also found that 9-hydroxyellipticine is forty times more active than ellipticine on Leukaeuia L-1210.[70] Interests in ellipticine and ellipticine analogues as potential cancer chemotherapeutic agents have promoted considerable efforts in search for new analogues with superior autitumor activities.[70] 9-Hydroxy-2-methyl ellipticinium acetate **151** (9-HE) is one of several ellipticine analogues shown to possess significant antitumor activities and, during phase II clinical use in France, has been shown to elicit modest responses in patients with advanced breast cancers.[71] Recently, 9-methoxy-2-methyl-ellipticine acetate **152** has been shown to exhibit selective cytotoxicity against a subpanel of human central nervous system (CNS) tumors when compared



149: R = H
150: R = OCH_3

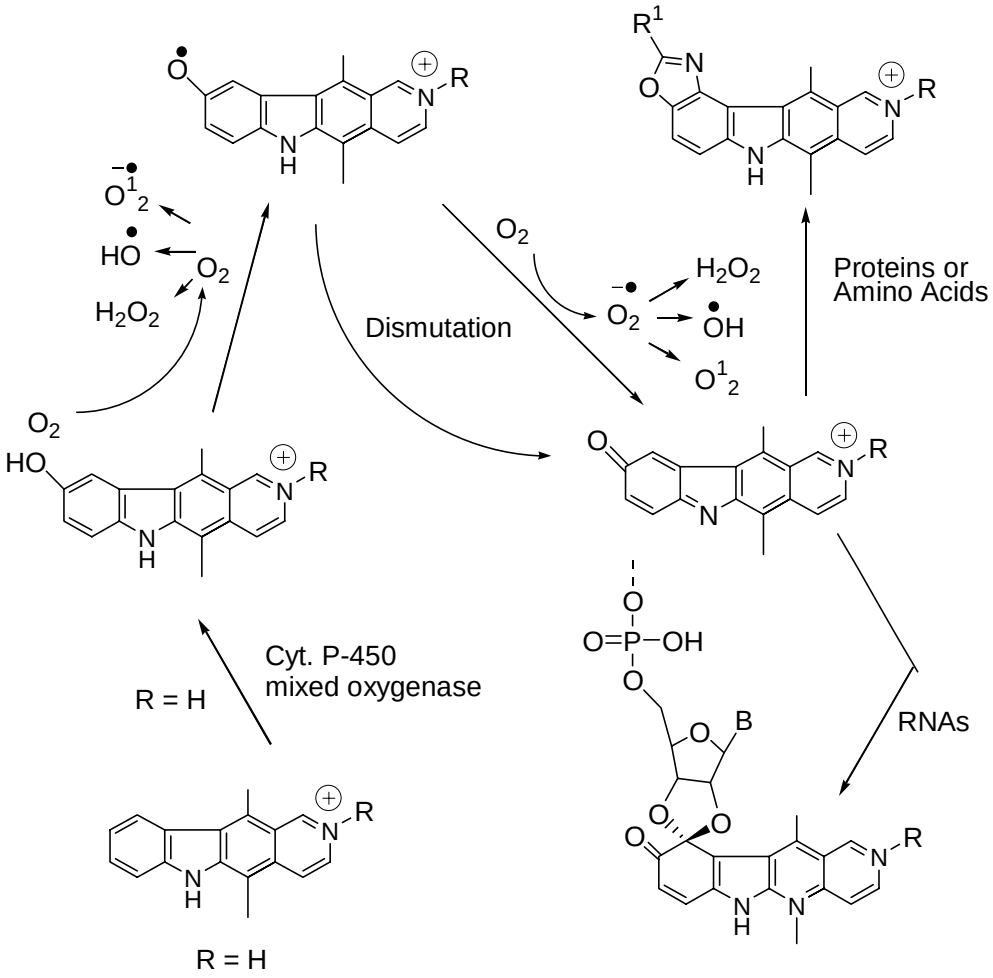


151: R = OH
152: R = OCH_3

with a broader panel of human tumor cells (*in vitro*).[72] Anderson et al. reported that 9-methoxy-2-methyl ellipticinium acetate **152** exerts anticancer effect without being transformed to 9-hydroxy-2 methylellipticinium acetate.[73]

Recently, the National Cancer Institute (NCI) has screened and analyzed the anticancer activity patterns of 112 ellipticine analogues using a hierachical clustering algorithm.[74] These compounds act by a combination of different mechanisms including DNA intercalation, inhibition of topoisomerase II, alkylation of macrobiomolecules, and redox generation of cytotoxic free radicals.[75] The high affinity of ellipticine and its derivatives to DNA and its intercalation between DNA base pair have long been considered the two main factors responsible for their antitumour activities. The strong cytotoxic activity of 9-HE, a biometabolite of ellipticine, suggests that ellipticine is biometabolised to 9-HE prior to interacting with DNAs. The antitumoral activity of ellipticine or general pyridocarbazoles could be explained on the basis of hypotheses which are related to DNA, RNAs and protein molecules as possible targets for 9-HE. These hypothesis are illustrated in Scheme 34.[67c]

The significant anti-cancer activities of ellipticine and its analogues have promoted considerable synthetic efforts in this area, and many synthetic approaches to the pyrido[4,3-*b*]carbazole ring system have been described.[67]



Scheme 34

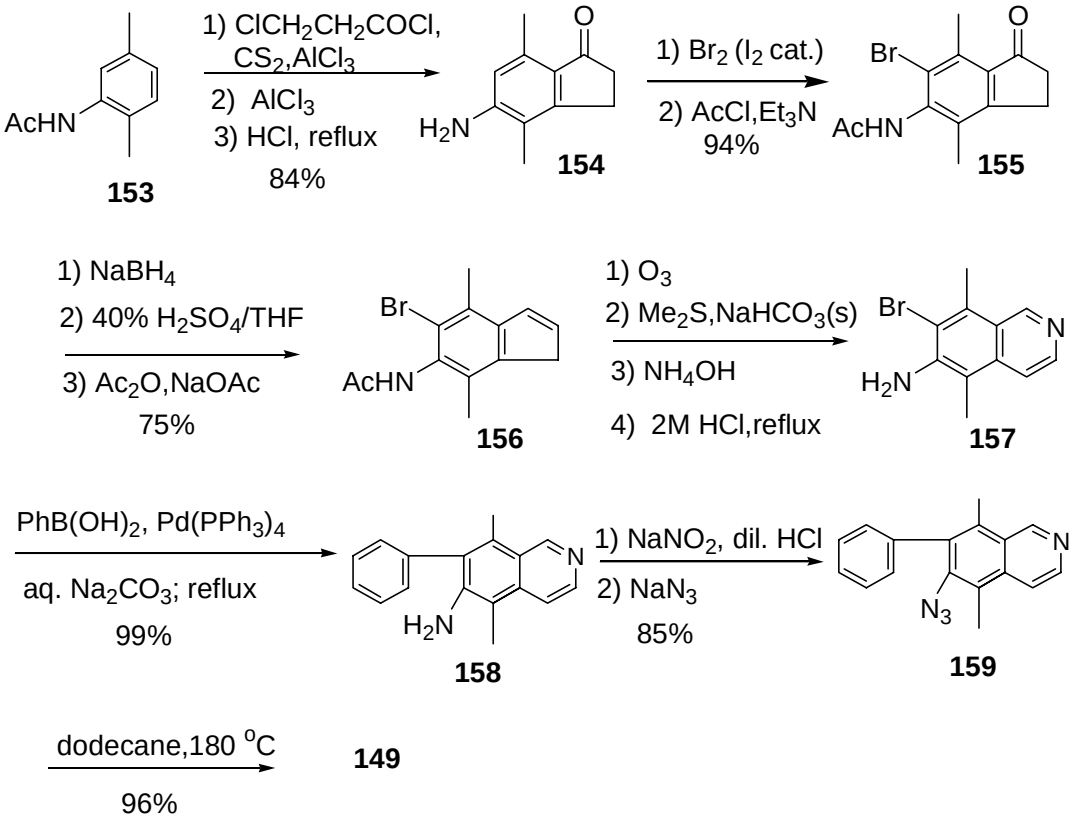
Intercalates Between DNA Base Pairs

1. 2. Synthetic Routes Toward Ellipticine and Its Analogues

Since the first total synthesis of ellipticine by Woodward et al. in 1959,[76] no less than 30 different routes to pyrido[4,3-*b*]carbazoles have been reported. All the known synthetic approaches are classified into four classes: the B-, C-, D- and (B+C)- type syntheses based on which rings are generated.

1. 2. 1. The B-Type Synthesis.

Miller[77] and his colleagues described a general and regiospecific synthesis of pyridocarbazole alkaloid. This methodology keeps the isoquinoline (ring C and D) and benzene (ring A) portions of the molecule separate until the latter stages of the synthesis and forms the pyrole ring (B) in the last step by a nitrene insertion reaction (Scheme 35). Acylation-alkylation

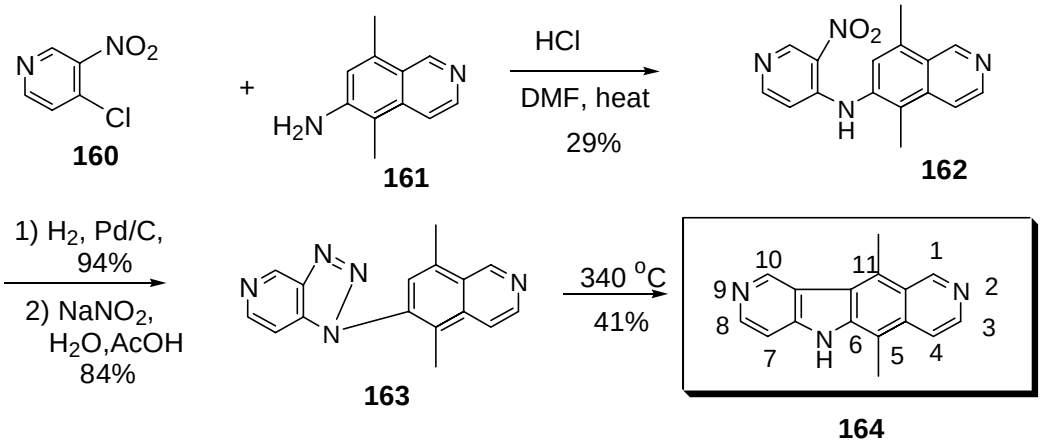


Scheme 35

of 2,5-dimethylacetanilide (**153**), prepared by acetylation of 2,5-dimethylaniline with 3-chloropropionyl chloride, gave an aminoindanone, which was hydrolyzed to give 5-amino-4,7-dimethylindan-1-one (**154**). Bromination of **154** followed by protection of the amino group gave **155,** which was reduced and eliminated to form the indene **156**. Hydrolysis of the acetamido

group in **156** afforded 6-amino-7-bromo-5,8-dimethylisoquinoline (**157**) in 50% overall yield from **153**. The Suzuki coupling of the aminobromoisoquinoline **157** with phenylboronic acid yielded **158** in 99% yield. The amine **158** was converted to 6-azido-5,8-dimethyl-7-phenylisoquinoline (**159**) by diazotization followed by treatment with sodium azide. The azidophenylisoquinesline **159** through thermolysis in dodecane at 180 °C afforded ellipticine as a yellow solid in 96% yield.

Another B-type syntheses of potent anticancer 9-azaellipticine derivatives was reported by Bisagni and co-worker (Scheme 36).[78,55a] Treatment of 4-chloro-3-nitropyridine (**160**) with 6-amino-5,8-dimethylisoquinoline (**161**) and HCl gave **162** in 29% yield. Catalytic hydrogenation of **162** (94%) followed by diazotization of the resulting amine furnished the triazole **163** (84%). The 9-azaellipticine **164** was obtained when **163** was heated at 320-340 °C in paraffin oil (41%).

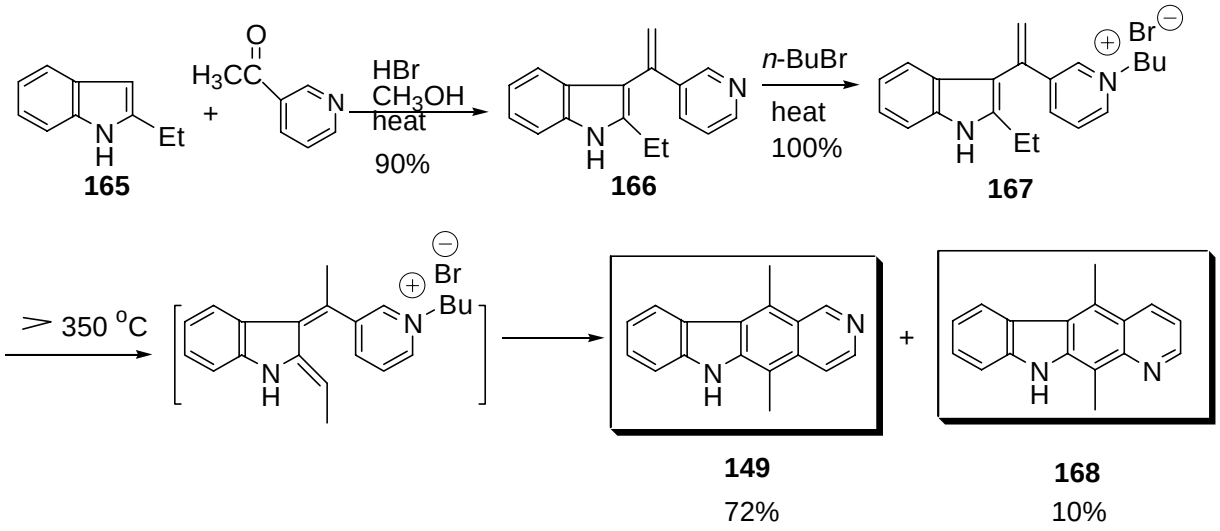


Scheme 36

1. 2. 2. The C-Type Synthesis

There are a large number of elegant synthetic efforts reported in the literature describing the C-type synthesis of the ellipticine and its analogues. In 1977, Bergman and Carlson[79]

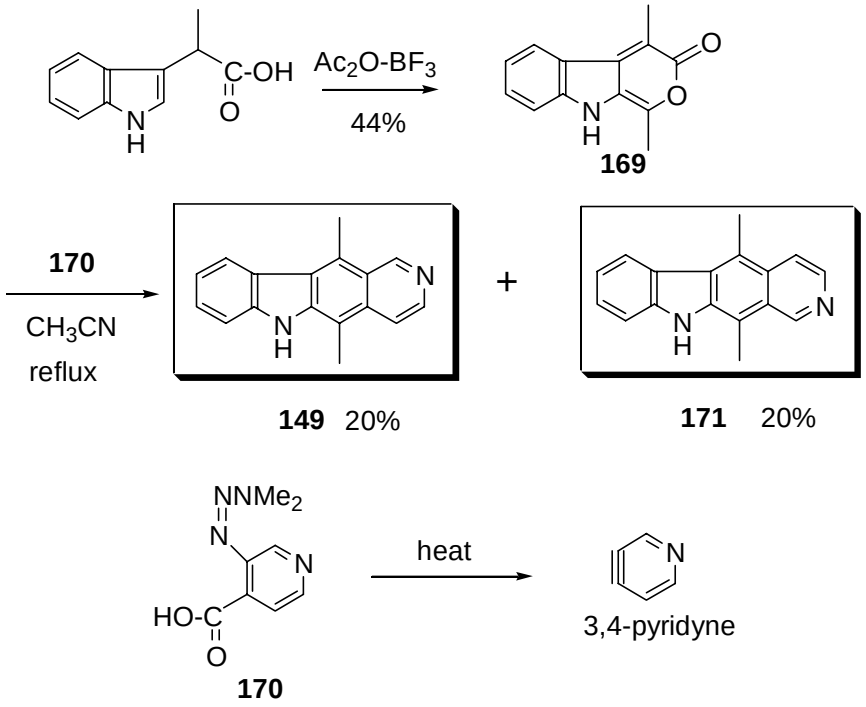
developed a very efficient synthesis of ellipticine (**149**) (Scheme 37). Acid-promoted condensation of 2-ethylindole (**165**) with 3-acetylpyridine gave **166** (90%). Alkylation of the pyridine nitrogen with *n*-butyl bromide (100%) and rapid pyrolysis (>350 °C, 5 min) of the resulting pyridinium salt **167** gave ellipticine **149** in 72% yield, along with about 10% of the pyrido[2,3-*b*]carbazole regioisomer **168**.



Scheme 37

Moody[80] et al. developed a new concise synthesis of ellipticine via a Diels-Alder reaction between a pyranoindolone and 3,4-pyridyne, generated *in situ* from thermolysis of **170**. Treatment of triazene acid with Ac_2O in the presence of $BF_3 \cdot Et_2O$ gave 1,4-dimethylpyrano[3,4-*b*]indole-3-one (**169**). A Diels-Alder reaction of **169** with 3,4-pyridyne (**170**) gave ellipticine **149** (20%) together with an equal amount of the isoellipticine **171** (Scheme 38).

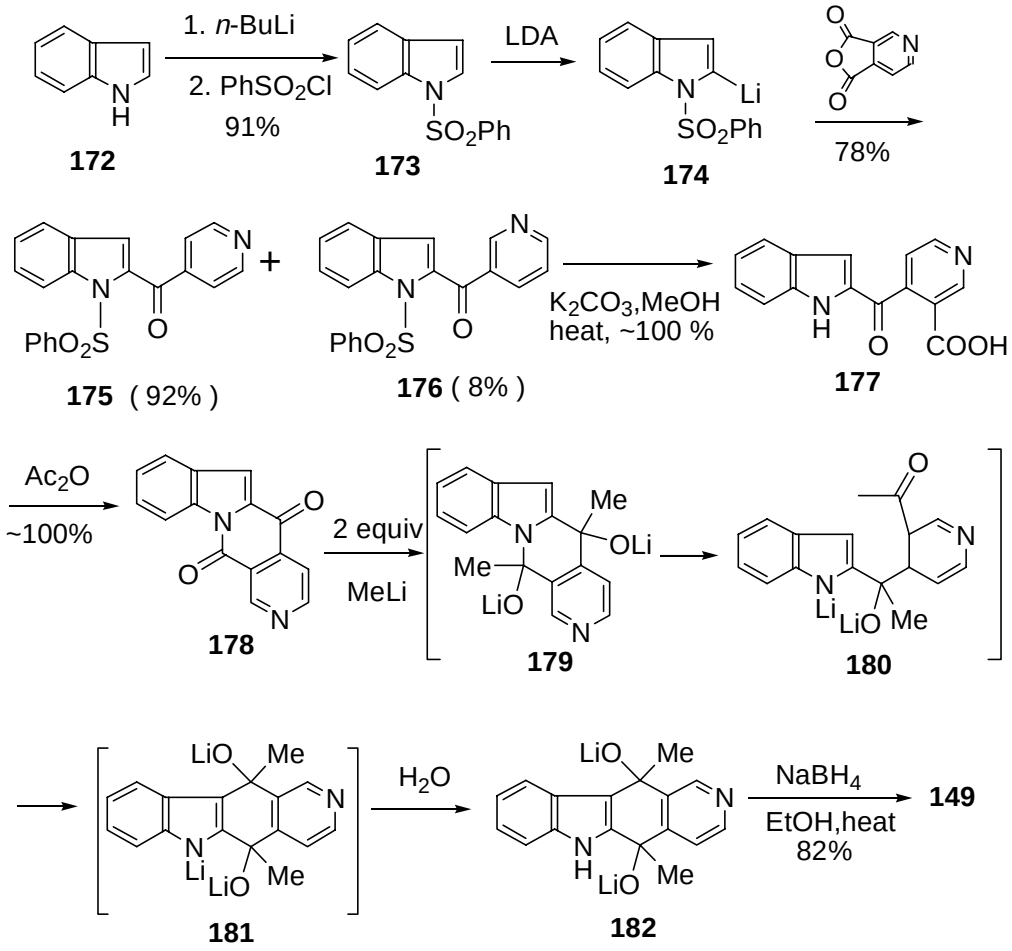
Recently, Gribble and coworkers[81] developed a Diels-Alder approach to ellipticin (Scheme 39). Indole **172** was converted to 1-(phenylsulfonyl)indole (**173**) in 91% yield. Regiospecific lithiation of **173** at the C-2 position was achieved by treatment of LDA and the



Scheme 38

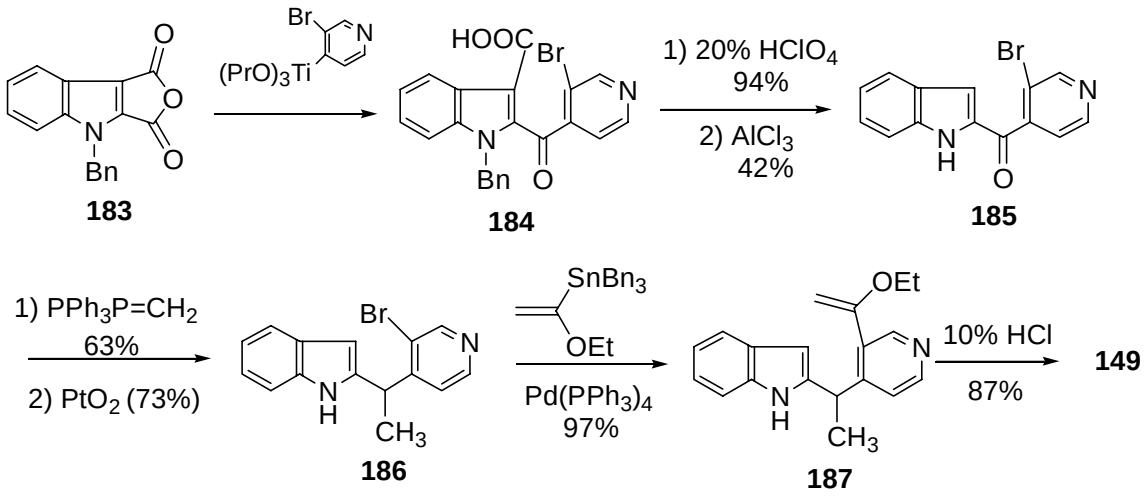
resulting **174** was rapidly treated with pyridine anhydride. This process produced a mixture of **175** and **176** in 78% yield and in a 92:8 ratio. The major isomer **175**, on hydrolysis with K_2CO_3 in MeOH followed by treatment with hot Ac_2O, furnished the keto lactam **178**. This keto lactam, on treatment with methyllithium (2 equiv), yielded a mixture of diols which on treatment with $NaBH_4$ gave the ellipticine **149** in 82% yield from **178** and 54% overall yield from indole (six steps), representing one of the most efficient synthesis of **149**.

Very recently, Miki[82] reported a simple and high yield synthesis of ellipticine. Treatment of *N*-benzylindole-2,3-dicarboxylic anhydride (**183**) with 3-bromo-4-pyridiyltitanium, a derivative prepared from 3-bromo-4-lithiopyridine and $ClTi(OPr^i)_3$ in THF, afforded the 2-acylindole-3-carboxylic acid **184** in 86% yield. Decarboxylation and debenzylation of **184**



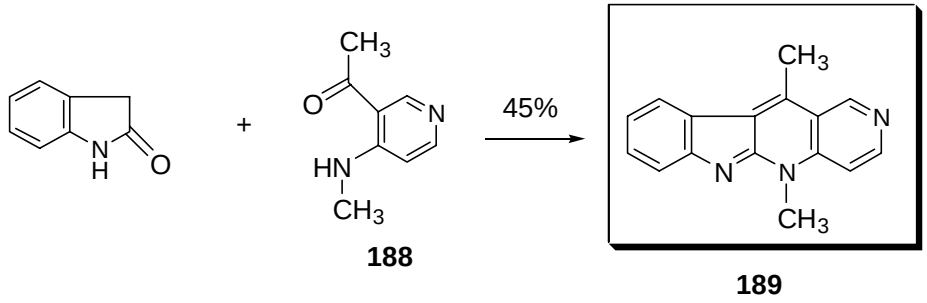
Scheme 39

furnished **185**. Treatment of **185** with methylenetriphenylphosphorane for the Wittig reaction followed by catalytic hydrogenation afforded **186**. Treatment of **186** with 1-ethoxyethenyltributyltin in the presence of a palladium catalyst gave the corresponding ethoxyvinyl derivative **187**, which was converted to ellipticine in 87% yield by treatment with 10% hydrochloric acid in THF (Scheme 40).



Scheme 40

Finally, Kononova and Semenov[83] reported the first synthesis of 5-azaellipticine by cyclocondensation of the acetylpyridine **188** with oxindole in the presence of piperdine at 200 °C (Scheme 41). The acetylpyridine **188** was prepared from 3-acetylpyridine in 7 steps in 3% overall yield.

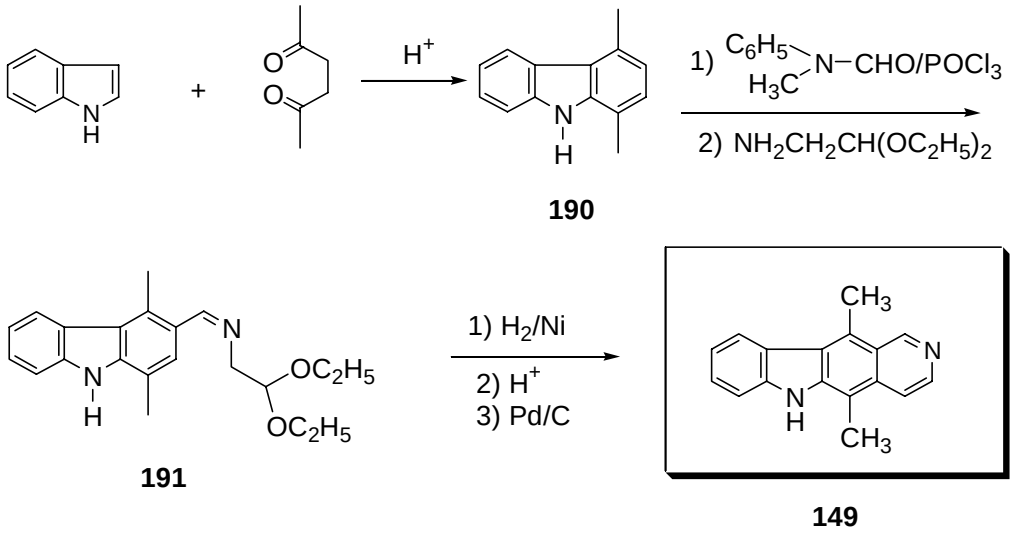


Scheme 41

1. 2. 3. The D-Type Synthesis

One of the most versatile routes to 6*H*-pyrido[4,3-*b*]carbazoles was first employed by Cranwell and Saxton (Scheme 42).[84] It is this approach that was employed in the commercial

manufacture of 2-methyl-9-hydroxyellipticinium acetate (**151**) for the treatment of myleoblastic leukemia, advanced breast cancer, and other solid tumors (Institute Pasteur brochure). A large number of procedures based on this general approach have been reported, including the Okay's synthesis[85] of 5-demethylellipticine, the Schannon's synthesis[86] of hydroxyellipticines and the Anderson's approach[73] of 9-substituted ellipticines and 2-methylellipticinium analogues. In the original procedure, ellipticine was synthesized from indole via 1,4-dimethylcarbazole (**190**). The Vilsmeier formylation generally gives the 3-carboxaldehyde as the major product. Condensation with aminoacetaldehyde acetal gives the imine acetal **191**, which, using various methods, can be cyclized to the ellipticine ring system (overall yield from indole ~1.5%).



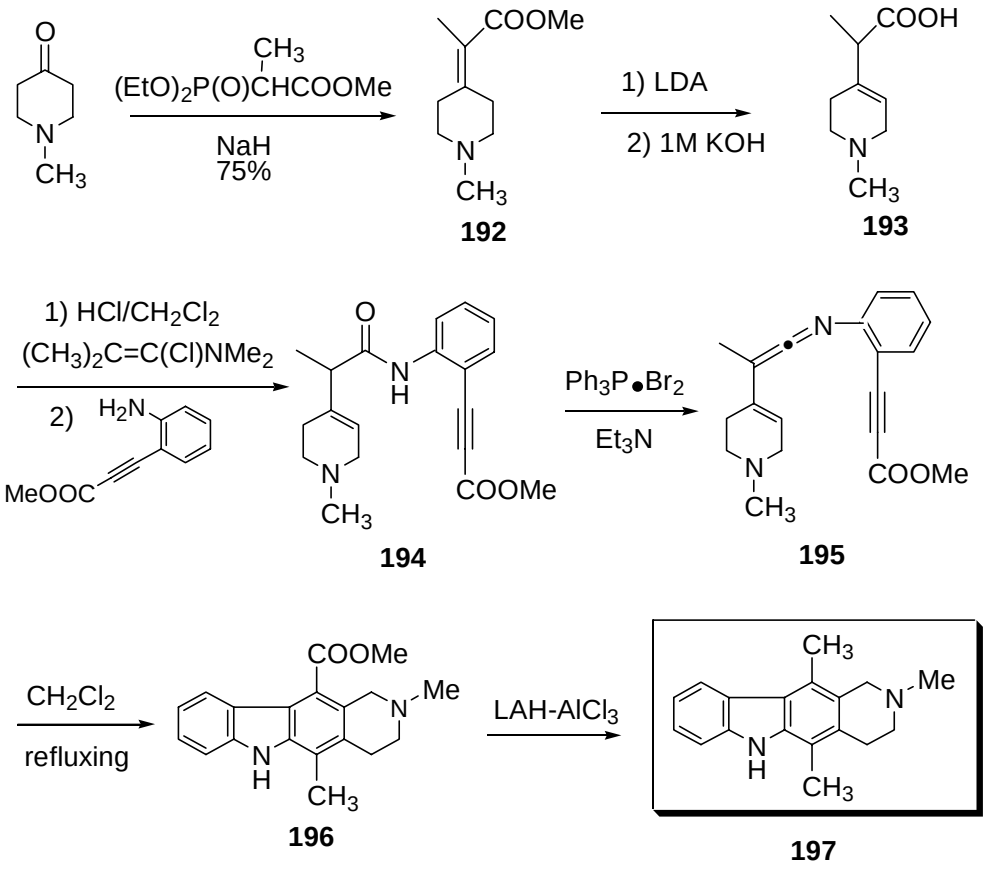
190 **191** **149**

Scheme 42

1. 2. 4. The (B+C)-Type Synthesis

An elegant synthetic approach to ellipticine was reported by Differding and Ghosez,[48a] employing an intramolecular Diels-Alder cycloaddition reaction of an acetylenic vinylketenimine as a key step to construct the B and C rings of the ellipticine simultaneously (Scheme 43).

N-Methylpiperidone was transformed to the ester **192** by a Wittig-Horner reaction (75%). Treatment of **192** with LDA followed by quenching with NH_4Cl yielded the β,γ-unsaturated ester (~100% crude yield), which was directly saponified (2 equiv of 1 N KOH, 2 h, 60 °C) to the acid **193** (75%). Conversion of **193** to the acid chloride followed by addition of *o*-carbomethoxyacetylenic aniline gave the anilide **194** in 42% overall yield. Treatment of **194** with $Ph_3P \bullet Br_2$ and Et_3N generated the vinylketenimine **195,** which underwent an intramolecular cycloaddition reaction to furnish **196** (50%). Reduction of **196** by LAH-$AlCl_3$ readily furnished *N*-2-methyltetrahydroellipticine **197** (71%).

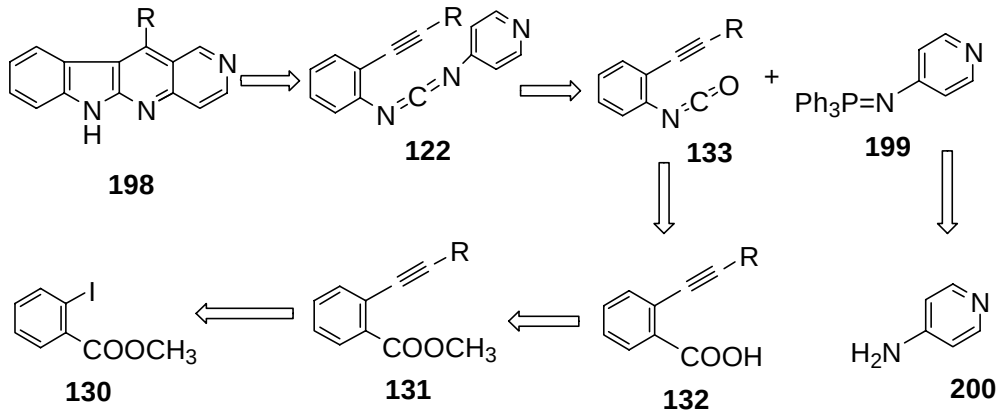


Scheme 43

2. Result and Discussion

One of the problems encountered in using the naturally occurring antitumor alkaloid ellipticine for clinical applications is its low solubility in water. To overcome the limited water solubility of ellipticine, several ellipticine analogues incorporated with polar groups on the N-2 nitrogen, such as 9-methoxy-2-methylellipticinium acetate **152**, were prepared. We envision that one way to increase the solubility is to replace the C-5 carbon with a nitrogen atom to produce aza-ellipticine. Only one precedent of such aza-ellipticine was reported previously (Scheme 41).[83] Our method for the synthesis of the indoloquinoline derivatives was readily adopted for the preparation of these aza-ellipticine analogues.[57]

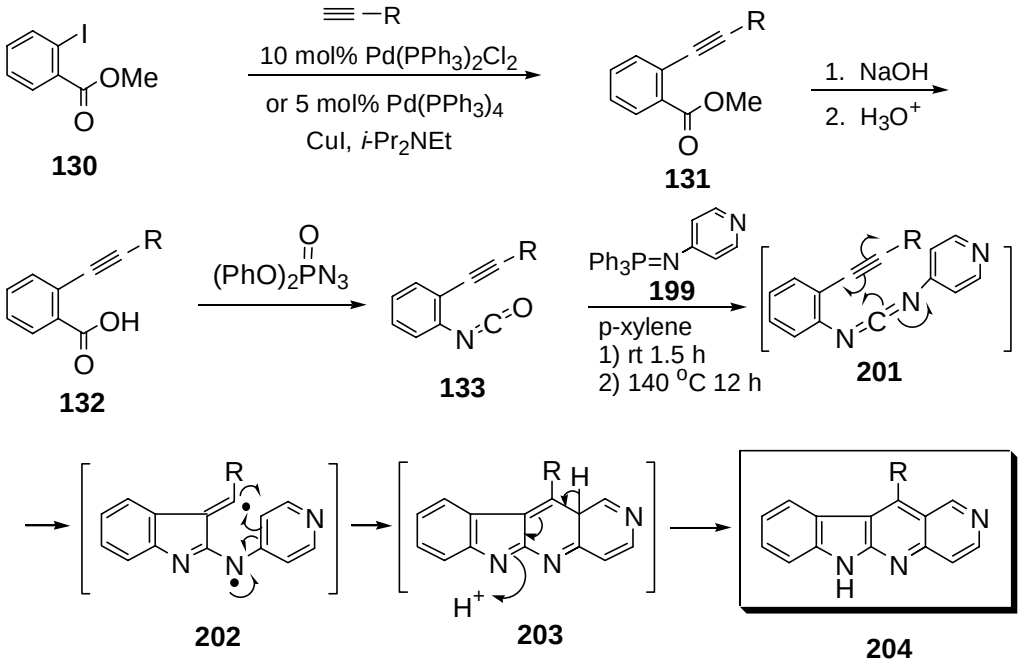
The general features of the synthesis of 5-azallipticine analogues are outlined in a retrosynthetically in Scheme 44. The key step for the synthesis of 5-aza-ellipticine skeleton was achieved by using the biradical cyclization reaction of the carbodimides **122** that had been



Scheme 44

developed in our group. The carbodiimids **122** were prepared by the aza-Wittig reaction of the isocyanates and the iminophosphorane **199**. The requisite alkynylphenyl isocyanates **133** were obtained either from the corresponding benzoic acids employing the Curtius-type rearrangement or from the corresponding anilines by treatment with triphosgene.[87] The benzoic acids were obtained by hydrolysis of the corresponding esters which in turn was prepared by a Pd-catalyzed cross-couping reaction with terminal alkynes. The ylide **199** was obtained by treatment of 4-aminopyridine (**200**) with $Ph_3P{\bullet}Br_2$.

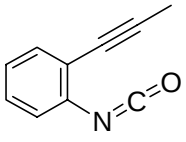
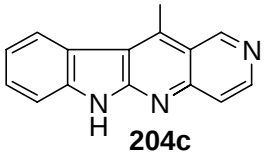
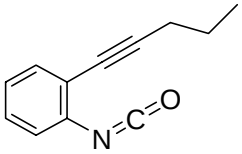
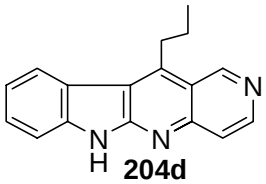
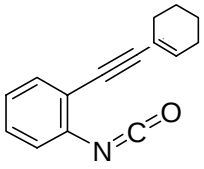
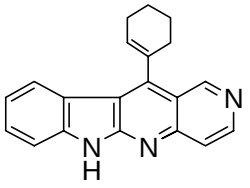
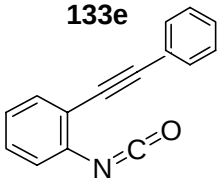
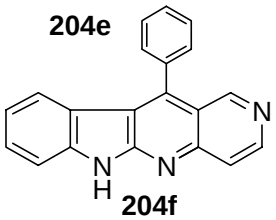
A complete outline of our synthetic pathway to the 5-aza-ellipticine and its analogues is illustrated in Scheme 45. Treatment of methyl 2-iodobenzoate (**130**) with a degassed solution



Scheme 45

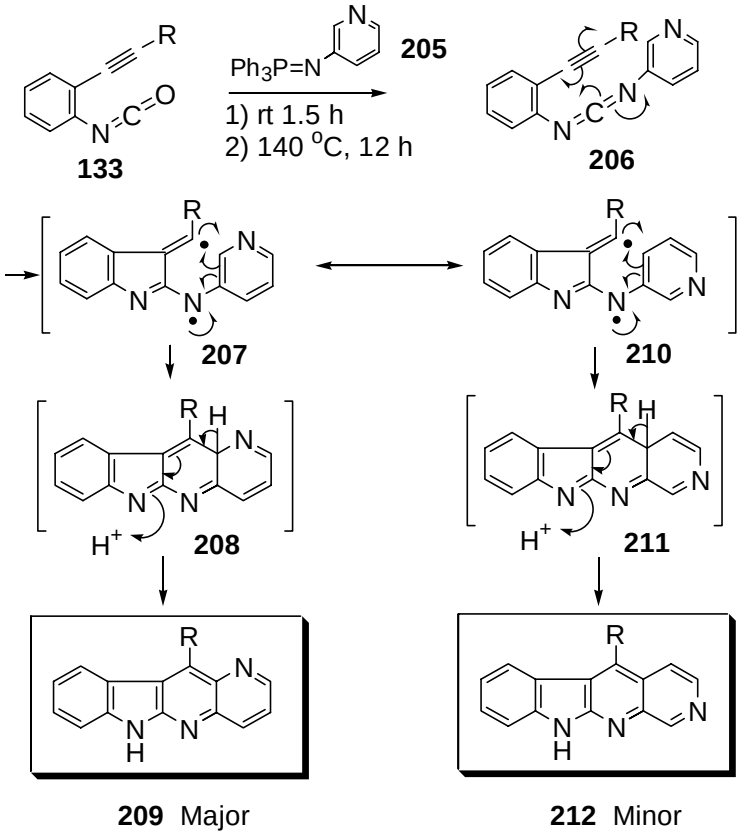
containing 1-alkynes, dichlorobis(triphenylphosphine)palladium, copper (I) iodide, and *N*,*N*-diisopropylethylamine in DMF at room temperature for 24 h gave the cross-coupling product methyl 2-(1-alkynyl)benzoates **131** in excellent yields. The benzoates **131** were further saponified (1 M NaOH, 12 h, 60 °C) to afford the benzoic acids **132**. The hydrolysis reaction went smoothly and gave excellent yields. Treatment of the benzoic acids **132** with diphenyl phosphorazidate (DPPA)[61] via a modified Curtius rearrangement produced the

Table 2. Synthesis of 5-Azaellipticine Analogues From 4-Iminophosphorane

Isocyanates	Products	Isolated Yield
 **133c**	 **204c**	**49 %**
 **133d**	 **204d**	**51 %**
 **133e**	 **204e**	**83 %**
 **133f**	 **204f**	**58 %**

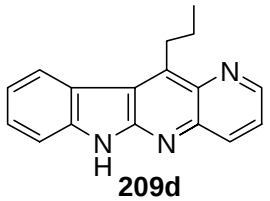
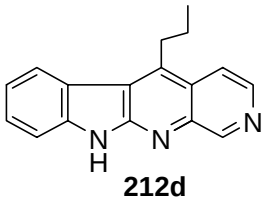
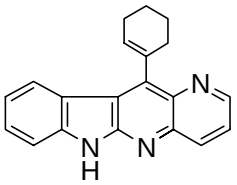
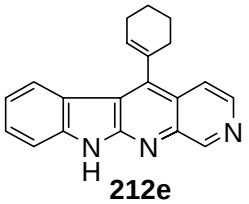
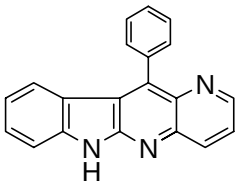
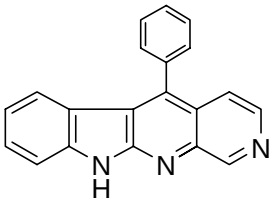
2-(1-alkynyl)phenyl isocyanates **133**. The subsequent aza-Wittig reaction with the iminophosphorane **199** then gave the carbodiimides **201**, which were used directly. Thermolysis of **201** then furnished the 5-aza-ellipticine and its analogues **204** (Table 2). The transformation from **201** to **204** can proceed either through a two-step biradical mechanism or a one-step intramolecular Diels-Alder reaction to furnish **203**, which then undergoes tautomerization to give **204**.

The iminophosphorane **205** was also allowed to react with the isocyanates **133**, producing **209** as the major isomer and **212** as the minor isomer (Scheme 46). The results are summerized in Table 3.

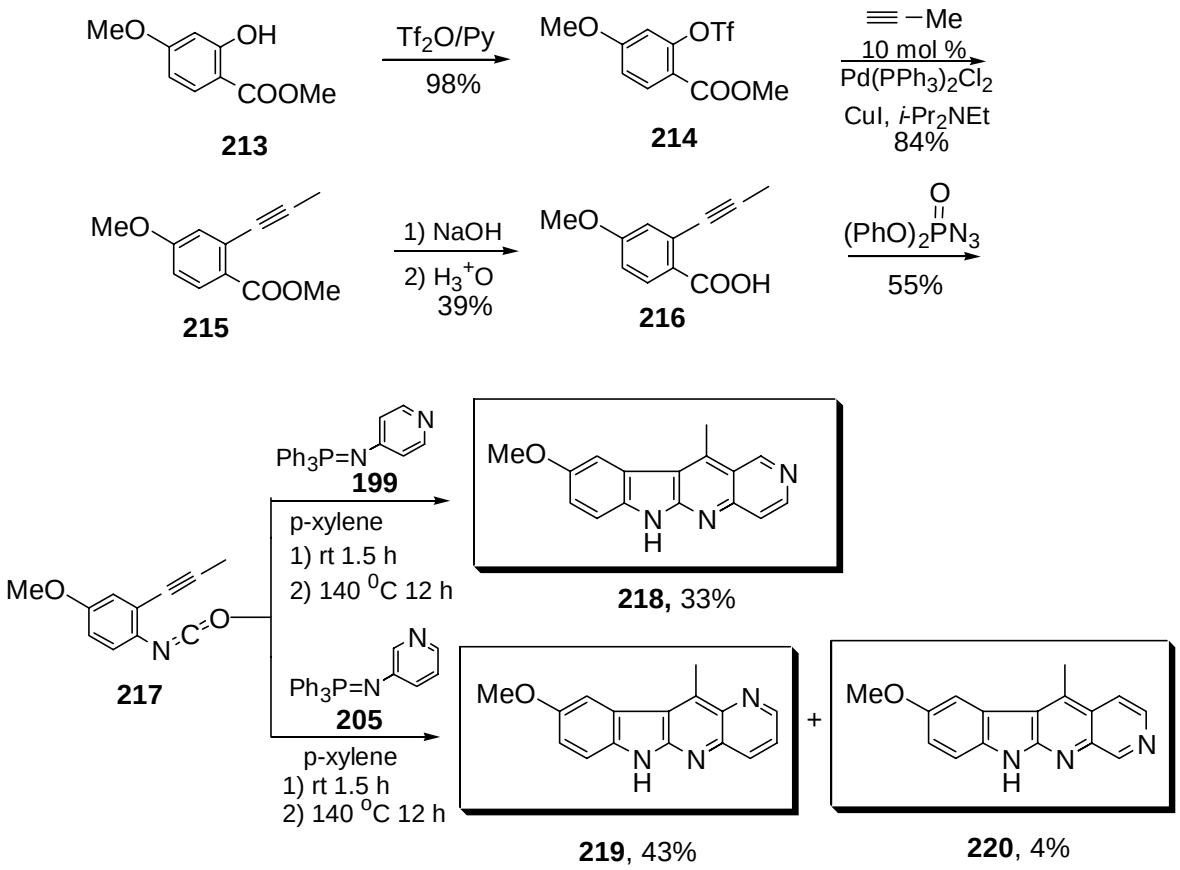


Scheme 46

Table 3. Synthesis of 5-Azaellipticine Analogues From 3-Iminophosphorane

Compounds	Isolated Yield	Compounds	Isolated Yield
 **209d**	**67 %**	 **212d**	**5 %**
 **209e**	**78 %**	 **212e**	**9 %**
 **209f**	**75 %**	 **212f**	**17 %**

The synthetic sequences outlined in Schemes 45 and 46 can also be adopted for the synthesis of 9-methoxy-5-azaellipticine **218** and its analogues **219** and **220** (Scheme 47). The 9-methoxy-2-methylellipticinium acetate has been found to exhibit remarkable selectivities *in vitro* against the NCI human CNS cancer subpanel[71b] and also has much improved water solubility than ellipticine. The commercially available methyl 4-methoxysalicylate (**213**) was first converted to the triflate **214** by treatment with triflic anhydride in 98% yield. The remaining sequence resembles the procedure described in Scheme 45 and 46.



Scheme 47

3. Conclusions

We have successfully extended the synthetic sequence for 6*H*-indolo[2,3-*b*]quinolines to the synthesis of 5-aza ellipticine and its analogues. This approach, which constructs the B and the C ring in one step, provides an efficient route in producing the aza analogues of the ellipticine family of antitumor alkaloids.

PART V

EXPERIMENTAL SECTION

All reactions were conducted in oven-dried (120 °C) glassware under a nitrogen atmosphere. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from benzophenone ketyl prior to use. Chlorodicyclohexylborane (**73**, 1.0 M solution in hexanes), trimethyltin chloride (1.0 M solution in THF), *n*-butyllithium (2.5 M solution in hexanes), $CuBr{\cdot}SMe_2$, $BF_3{\cdot}OEt_2$, propargyl bromide (80 weight % solution in toluene), dibromotriphenylphosphorane (Ph_3PBr_2), phenyl isocyanate, 1,4-phenylene diisocyanate, diphenylphosphorazidate (DPPA), $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, *p*-xylene (anhydrous), *N*,*N*-dimethylformamide (DMF), and *N*,*N*-diisopropylethylamine were purchased from Aldrich Chemical Co., and were used as received. 2-Iodoaniline was purchased from Oakwood Products, Inc. and was used as received. 1-Alkynes were obtained from Farchan Laboratories, Inc. and were used without further purification. Iminophosphoranes **137** were prepared according to the reported procedure.[46,54a] Methyl 2-iodobenzoate was purchased from Lancaster. Allenylmagnesium bromide was prepared according to the reported procedure.[35] *B*-methoxydicyclohexylborane was prepared by treatment of dicyclohexylborane with methanol.[36] 5,5-(Pentamethylene)-3,4-pentadien-1-yne and 5-butyl-3,4-nonadien-1-yne (**48**) were prepared as reported previously.[29d] Similarly, 3,4,10-undecatrien-1-yne (**96**) was synthesized in 52% overall yield from cross–coupling of 1,2,8-nonatriene[37] with 1-iodo-2-(trimethylsilyl)ethyne (69%) followed by desilylation (75%). 1,2-Heptadiene was prepared as reported previously.[38] Triethylamine was distilled from CaH_2. The anilines **136**

(86–93% yield) were prepared from 2-iodoaniline according to the reported procedures.[46,66] Melting points are uncorrected. ^{1}H (270 MHz) and ^{13}C (67.9 MHz) NMR spectra were recorded in $CDCl_3$ using $CHCl_3$ (^{1}H δ 7.26) or $CDCl_3$ (^{13}C δ 77.00) as internal standard unless otherwise indicated.

6-Butyl-5-dibutylmethylene-1,3-cyclohexadiene (34). The following procedure for the synthesis of *o*-isotoluene **34** is representative. To 1.5 mL of a 2.0 M solution of BH_3•SMe_2 (3.0 mmol) in 8.0 mL of THF under a nitrogen atmosphere was added 0.61 mL (0.492 g, 6.0 mmol) of cyclohexene at 0 °C. After 30 min, a white slurry of dicyclohexylborane appeared.[11] The mixture was kept at 0 °C for an additional 30 min before cooling to -15 °C. A solution of 0.246 g of 1-hexyne (3.0 mmol) in 3.0 mL of THF was then introduced. After 2 h at 0 to 5 °C, the reaction mixture became homogeneous and was used immediately to form the organoborate complex. To a second flask containing 0.528 g of **48** (3.0 mmol) in 3.0 mL of THF at -25 °C was added 1.2 mL of a 2.5 M solution of *n*-butyllithium (3.0 mmol) in hexanes. After 15 min at –25 °C, the resulting 1-lithio-5-butyl-3,4-nonadien-1-yne was introduced via cannula to the flask containing (*E*)-1-hexenyldicyclohexylborane at -25 °C. The reaction mixture was stirred at rt for 1 h before cooling to 0 °C. A solution of trimethyltin chloride (3.0 mL, 1.0 M, 3.0 mmol) in THF was then introduced with a syringe. After an additional 1 h at rt, 2.0 mL of glacial acetic acid was added, and the mixture was heated to 50 °C for 1 h before cooling to rt. Methanol (5.0 mL), 6.3 mL of a 6 N NaOH solution, and 1.74 mL of 30% H_2O_2 were then introduced sequentially, and the reaction mixture was heated to 50 °C for 1 h. The mixture was then extracted with pentane (3 x 10 mL), and the combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography

(silica gel/hexanes) to furnish 0.465 g (60%) of **34** as a light yellow liquid: IR (neat) 1636, 1466,1378, 735 cm^{-1}, ^{1}H δ 6.34 (1 H, d, *J* = 9.9 Hz), 5.94 (1 H, dd, J = 3.0 and 1.0 Hz), 5.93 (1 H, dd, *J* = 3.0 and 1.0 Hz), 5.72 (1 H, dt, *J* = 9.9 and 3.0 Hz), 3.23 (1 H, m), 2,2 (2 H, m), 2.07 (1 H, m), 1.95 (1 H, m), 1,5 (1 H, m), 1.3 (13 H, m), 0.92 (9 H, m); ^{13}C δ 141.05, 132.82, 131.71, 124.76, 122.51, 121.09, 37.81, 37.46, 31.82, 31.66, 31.40, 30.90, 28.14, 23.22, 23.04, 23.02, 14.12, 14.09, 14.07; MS (*m/z*) 260 (M^{+}), 203, 161, 147, 133, 119, 105, 91.

5-Dibutylmethylene-6-pentyl-1,3-cyclohexadiene (35). The same procedure was repeated as described for **34** except that 1-heptyne (0.350 g, 3.64 mmol) and 5-butyl-3,4-nonadien-1-yne (0.64 g, 3.64 mmol) were used to afford 0.533 g (54%) of **35** as a light yellow liquid: IR (neat) 2934, 2858, 1466, 1377, 980, 734 cm^{-1}; ^{1}H δ 6.36 (1 H, d, *J* = 9.9 Hz), 5.95 (1 H, dd, *J* = 3.0 and 1.0 Hz), 5.73 (1 H, dt, *J* = 9.9 and 3.0 Hz), 3.25 (1 H, m), 2.30 (2 H, m), 2.08 (1 H, m), 1.95 (1 H, m), 1.56 (1 H, m), 1.31 (15 H, m), 0.92 (9 H, m); ^{13}C δ 140.91, 132.76, 131.76, 124.70, 122.50, 121.10, 38.01, 37.48, 32.17, 31.81, 31.65, 31.38, 30.87, 25.53, 23.20, 22.99, 22.63, 14.04, 13.99, 13.91; MS (*m/z*) 274 (M^{+}), 231, 203, 175, 147, 133, 91, 55.

5-Dibutylmethylene-6-isopropyl-1,3-cyclohexadiene (36). The same procedure was repeated as described for **34** except that 3-methyl-1-butyne (0.1362 g, 2.0 mmol) and 5-butyl-3.4-nonadien-1-yne (0.1362 g, 2.0 mmol) were used to obtain **36** (0.187 g, 38%) as a colorless liquid: IR (neat) 2956, 1465, 1378, 986, 755 cm^{-1}; ^{1}H δ 6.35 (1 H, d, *J* = 9.7 Hz), 6.01 (1 H, dd, *J* = 9.5 and 5.2 Hz), 5.84 (1 H, dd, *J* = 9.5 and 5.6 Hz), 5.66 (1 H, dd, *J* = 9.8 and 5.2 Hz), 3.18 (1 H, t, *J* = 5.4 Hz), 2.27 (2 H, m), 2.02 (1 H, m), 1.89 (1 H, m), 1.64 (1 H, m), 1.35 (8 H, m), 0.904 (3 H, d, *J* = 6.9 Hz), 0.901 (3 H, t, *J* = 6.7 Hz), 0.85 (3 H, d, *J* = 6.7 Hz); ^{13}C δ 142.02, 131.36, 129.75, 125.80, 124.27, 121.19, 43.51, 36.63, 31.93, 31.79, 31.23, 30.77, 23.21, 23.06, 20.25, 17.35,

14.10; MS (*m/z*) 246 (M^+), 244, 229, 203, 187, 160, 147, 117, 91, 77, 55.

5-Dibutylmethylene-6-phenyl-1,3-cyclohexadiene (37). The same procedure was repeated for **34** except that phenylacetylene (0.33 mL, 3.0 mmol) and 5-butyl-3,4-nonadien-1-yne (0.528 g, 3.0 mmol) were used to obtain **37** (0.135 g, 16%) as a light yellow liquid: IR (neat) 2956, 1599, 1451, 1378, 787, 762, 698 cm^{-1}; ^1H δ 7.25 (5 H, m), 6.53 (1 H, d, *J* = 9.7 Hz), 5.87 (2 H, m), 5.78 (1 H, dt, *J* = 9.7 and 4.4 Hz), 4.33 (1 H, d, *J* = 3.7 Hz), 2.19 (2 H, m), 1.99 (1 H, m), 1.80 (1 H, m), 1.34 (4 H, m), 1.18 (4 H, m), 0.91 (3 H, t, *J* = 7.1 Hz), 0.77 (3 H, t, *J* = 7.1 Hz); ^{13}C δ 146.34, 143.88, 132.41, 129.77, 128.59, 127.04, 126.18, 125.07, 120.92, 120.65, 44.59, 32.65, 31.68, 31.38, 30.22, 23.14, 23.06, 14.04, 13.96; MS (*m/z*) 280 (M^+), 251, 223, 195, 167, 165, 128, 115, 91, 55.

6-(1-Cyclohexenyl)-5-dibutylmethylene-1,3-cyclohexadiene (38). The same procedure was repeated as described for **34** except that 1-ethynylcyclohexene (0.212 g, 2.0 mmol) and 5-butyl-3,4-nonadien-1-yne (0.352 g, 2.0 mmol) were used to furnish **38** (0.233 g, 41%) as a light yellow liquid: IR (neat) 2929, 1682, 1462, 1377, 1260, 993, 755 cm^{-1}; ^1H δ 6.38 (1 H, d, *J* = 10.1 Hz), 5.91 (1 H, m) 5.67 (1 H, m), 5.49 (1 H, br s), 3.84 (1 H, d, *J* = 5.4 Hz), 2.3 - 2.1 (4 H, m), 2.0 (4 H, m), 1.6 - 1.2 (12 H, m), 0.9 (6 H. m); ^{13}C δ 143.28, 140.80, 131.39, 128.61, 125.31,121.85, 120.94, 120.53, 47.37, 32.43, 31.75, 31.61, 31.47, 30.83, 25.53, 24.44, 23.31, 23.08, 22.52, 14.13, 14.04; MS (*m/z*) 284 (M^+), 242, 227, 199, 171, 159, 129, 117, 91, 55.

5-Dibutylmethlene-6-(methoxymethyl)-1,3-cyclohexadiene (39). The same procedure was repeated as described for **34** except that methyl propargyl ether (0.140 g, 2.0 mmol) and 5-butyl-3,4-nonadien-1-yne (0.352 g, 2.0 mmol) were used and the product was purified by column chromatography (silica gel/5% diethyl ether in hexanes) to afford **39** (0.095 g, 20%) as a

colorless liquid: IR (neat) 2957, 1458, 1378, 1190, 1113, 734, 672 cm^{-1}; ^{1}H δ 6.33 (1 H, d, *J* = 9.9 Hz), 6.00 (2 H, m), 5.73 (1 H, dt, *J* = 9.6 and 3.3 Hz), 3.58 (1 H, dt, *J* = 9.6 and 4.5 Hz), 3.40 (1 H, t, *J* = 9.3 Hz), 3.32 (3 H, s), 3.13 (1 H, dd, *J* = 8.9 and 5.2 Hz), 2.21 (2 H, m), 2.08 (1 H, m), 1.95 (1 H, m), 1.45 - 1.25 (8 H, m), 0.92 (3 H, t), 0.91 (3 H, t); ^{13}C δ 143.06, 130.74, 127.38, 124.74, 123.40, 121.17, 78.05, 58.94, 38.30, 31.76, 31.36, 31.03, 23.18, 22.97, 14.10, 14.05; MS (*m/z*) 248 (M^{+}), 216, 203, 185, 147, 133, 117, 91, 77, 45.

6-(Cyclohexylmethyl)-5-dibutylmethylene-1,3-cyclohexadiene (40). The same procedure was repeated as described for **34** except that 3-cyclohexyl-1-propyne (0.244 g, 2.0 mmol), and 5-butyl-3,4-nonadien-1-yne (0.352 g, 2.0 mmol) were used to obtain **40** (0.175 g, 30%) as a light yellow liquid. IR (neat) 2923, 1448, 1377, 989,786, 762, 734 cm^{-1}; ^{1}H δ 6.33 (1 H, d, *J* = 9.7 Hz), 5.94 (2 H, m), 5.73 (1 H, m), 3.29 (1 H, td, *J* = 5.7 and 4.6 Hz), 2.19-0.9 (31 H, m); ^{13}C δ 140.67, 132.98, 132.32, 124.52, 122.45, 121.01, 46.06, 35.06, 34.41, 34.18, 32.40, 31.85, 31.66, 31.57, 31.01, 26.77, 26.51, 26.42, 23.30, 23.05; MS (*m/z*) 300 (M^{+}), 241, 203, 185, 147, 133, 91, 55.

9-Butyl-2,2-dimethyl-3,5,7,8-tridecatetraene (41a). The same procedure was repeated as described for **34** except that 3,3-dimethyl-1-butyne (0.25 mL, 2.0 mmol) and 5-butyl-3,4-nonadien-1-yne (0.352 g, 2.0 mmol) were used to obtain **41a** (0.213 g, 41%) as a colorless liquid: IR (neat) 2957, 1950, 1465, 1366, 978 cm^{-1}; ^{1}H δ 6.38 (1 H, dd, *J* = 15.3 and 11.0 Hz), 6.22 (1 H, dd of quintet, *J* = 11.1, 2.8, and 1 Hz), 5.87 (1 H, t, *J* = 10.8 Hz), 5,73 (1 H, d, *J* = 15.2 Hz), 5.68 (1 H, t, *J* = 10.9 Hz), 1.97 (4 H, dt, *J* = 2.8 and 8.1 Hz), 1.45 - 1.25 (8 H, m), 1.05 (9 H, s), 0.89 (3 H, t); ^{13}C δ 205.42, 146.47, 127.95, 124.79, 120.20, 105.50, 90.93, 33.46, 32.39, 29.81, 29.56, 22.40, 13.99.

2-Heptyn-1-ol (44). To a 500 mL flask were introduced 150 mL of dry THF, 24.65 g (300

mmol) of 1-hexyne under N_2, and the mixture was cooled to -20 °C. A solution of 120 mL of *n*-BuLi (2.5 M in hexanes, 300 mmol) was added and the reaction temperature was kept at 0 °C. The resulting yellow solution was stirred for another 15 min. A suspension of 18 g of paraformaldehyde in 100 mL of THF was introduced rapidly and the cooling bath was removed. After 2 h of stirring, the reaction mixture was quenched with a saturated ammonium chloride solution and the mixture was stirred for 10 min. The mixture was then extracted with pentane (3 x 20 mL). The combined pentane layers were washed with a sodium chloride solution and dried over magnesium sulfate. Solvent was removed and the residue was distilled (bp 81 °C/6.0 mmHg) under reduced pressure to afford **44** (30.24 g, 90%) as a colorless liquid: IR (neat) 3346, 2931, 2225, 1466, 1137, 1012 cm^{-1}; ^1H δ 4.20 (2 H, s), 2.19 (2 H, tt, *J* = 6.9 and 1.9 Hz), 1.42 (4 H, m), 0.86 (3 H, t, *J* = 6.9 Hz); ^{13}C δ 85.74, 78.39, 50.63, 30.65, 21.86, 18.32, 13.43; MS (*m/z*) 112 (M^+), 97, 93, 83, 79, 70, 65, 55, 52.

3-Butyl-1,2-heptadiene (45). To a 500-mL flask were charged with **44** (22.4 g, 200 mmol) and 200 mL of THF. A 2.5 M solution of *n*-BuLi (80 mL, 200 mmol) was added below 10 °C and the solution was stirred at 0 °C for another 30 min before cooling to -78 °C with a dry ice-acetone bath. A solution of *p*-toluenesulfonyl chloride (38.13 g, 200 mmol) in 100 mL of THF was added. After 30 min at -50 °C the cooling bath was removed and the pale yellow reaction mixture was allowed to warm to room temperature, and it was stirred for 2 h. To a 1 L-flask equipped with a mechanical stirrer was introduced anhydrous lithium bromide (19.63 g, 226 mmol) and anhydrous cuprous bromide (32.42 g, 226 mmol), which were dried under 0.06 Torr at 120 °C for 5 h before use. The reaction flask was evacuated and the contents were briefly heated. After 30 min, dry nitrogen was introduced to restore pressure. Then 150 mL of THF was

added at room temperature with vigorous stirring, and the mixture was cooled to -40 °C. A 2.0 M solution of *n*-butylmagnesium chloride in THF (100 mL, 200 mmol) was added rapidly via cannula. After 30 min of vigorous stirring for at -40 °C, the reaction mixture was cooled to -70 °C. The reaction mixture in the 500-mL flask was transferred via cannula over 45 min to the cuperate mixture kept at -70 °C with a dry ice-acetone bath. After 30 min, the bath was removed and the reaction mixture was stirred at room temperature for 2 h. The mixture was then poured into a saturated NH_4Cl solution (200 mL), pentane (100 mL) was added and the mixture was filtered. The organic layer was separated, and the aqueous layer was extracted with pentane (3 x 50 mL). The combined organic layers were washed with water (10 x 50 mL), dried over $MgSO_4$, and concentrated. The residue was distilled (bp 79 °C/4.0-6.0 mmHg) under reduced pressure to afford **45** (25.22 g, 83 %) as a colorless liquid: IR (neat) 2959, 2872, 1962, 1466, 1363, 1177, 1070, 912, 692 cm^{-1}; ^1H δ 4.62 (2 H, quintet, *J* = 3.2 Hz), 1.93 (4 H, m), 1.38 (8 H, m), 0.90 (6 H, t, *J* = 6.9 Hz); ^{13}C δ 205.78, 103.29, 75.15, 31.91, 29.82, 22.51, 13.99; MS (*m/z*) 152 (M^+), 137, 123, 110, 107, 95, 81, 68, 55, 41.

1-Iodo-2-(trimethylsilyl)acetylene (46). To a 500-mL flask containing trimethylsilylacetylene (15.72 g, 160 mmol) and 160 mL of THF solution was introduced *n*-BuLi (64 mL, 2.5 M, 160 mmol) by cannula at -30 °C. After 30 min, a solution of I_2 (42.64 g, 168 mmol) in 100 mL THF was introduced. During the early stage of the addition, the I_2 brown color disappeared quickly until the reaction almost reach the end point and a brown solution was formed. The solution was then poured to a flask containing 160 mL H_2O at 0 °C and stirred for 10 min. Then a solution of sodium thiosulfate was added to remove the unreacted I_2. After separation of the two layers, the aqueous layer was extracted with pentane (3 x 40 mL) and the combined organic layers were

washed with water (10 x 50 mL) to remove THF solvent. The organic layer was then dried over magnesium sulfate and concentrated. The crude product was distilled (bp 45 °C, 6.0 mmHg) to afford **46** (29.77 g, 83%) as a colorless liquid: IR (neat) 2959, 2899, 2100, 1409, 1251, 869, 746, 701 cm^{-1}; ^{1}H δ 0.17 (9 H, s); ^{13}C δ 104.10, 20.77, -0.087; MS (*m/z*) 224 (M^{+}), 209, 179, 170, 155, 127, 104, 97, 67, 53.

1-(Trimethylsilyl)-5-butyl-3,4-nonadien-1-yne (47). To 3-butyl-1,2-heptadiene **45**[15] (7.362 g, 48.2 mmol) in 150 mL of THF at -60 °C under an N_2 atmosphere was added 19.3 mL of a 2.5 M solution of *n*-butyllithium in hexanes. After 1 h at -60 °C, 7.61 g (53.0 mmol) of anhydrous CuBr in 60 mL of THF was introduced via cannula, and the mixture was allowed to warm to -20 °C. The mixture was then cooled to -40 °C and 11.88 g (53 mmol) of 1-iodo-2-(trimethylsilyl)acetylene[15] was added dropwise over 1 h. After an additional 1 h at -40 °C, the mixture was allowed to warm to 0 °C and then was poured into a saturated NH_4Cl solution. Pentane (30 mL) was added and the mixture was filtered. The organic layer was separated, and the aqueous layer was extracted with pentane (3 x 40 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. The residue was distilled (bp 75 °C, 0.2 Torr) to afford 1-(trimethylsilyl)-5-butyl-3,4-nonadien-1-yne (**47**) (8.658 g, 73%) as a colorless liquid[10a]: ^{1}H δ 5.32 (1 H, quintet, *J* = 2.9 Hz), 1.98 (4 H, m), 1.38 (8 H, m), 0.88 (6 H, t, *J* = 7.1 Hz), 0.15 (9 H, s); ^{13}C δ 210.33, 106.76, 99.59, 93.33, 76.26, 32.02, 29.52, 22.35, 13.94, 0.05; MS (*m/z*) 233 (M^{+}-CH_3), 219, 191, 177, 164, 149, 131, 107, 97, 73, 59.

5-Butyl-3,4-nonadien-1-yne (48). The conjugated allenyne **48** was synthesized according to the reported procedures.[10] To 3.754 g (15.14 mmol) of 1-(trimethylsilyl)-5-butyl-3,4-nonadien-1-yne in 140 mL of ethanol under a nitrogen atmosphere was added 36.0 mL of a 0.1 N aqueous NaOH

solution. After 24 h at rt, the mixture was poured into ice/water and was extracted with pentane. The organic layer was washed with a saturated NH_4Cl solution, dried over $MgSO_4$, and concentrated. The residue was distilled (bp 38 °C, 0.09 Torr) to furnish 2.383 g (90%) of **48** as a colorless liquid: IR (neat) 3314, 2105, 1955, 1466, 1379 cm^{-1}; ^1H δ 5.30 (1 H, sextet, *J* = 2.8 Hz), 2.75 (1 H, d, *J* = 2.4 Hz), 1.99 (4 H, m), 1.37 (8 H, m), 0.90 (6 H, t); ^{13}C δ 210.47, 107.34, 78.32, 76.20, 74.98, 31.89, 29.44, 22.32, 13.85; MS *m/z* 161 (M^+-CH_3), 147, 134, 119, 105, 91, 77.

Allenyldicyclohexylborane (74). The procedure for the synthesis of *B*-allenyl-9-borabicyclo[3.3.1]nonane[39] was adopted for the preparation of **74**. Allenylmagnesium bromide was prepared as described previously.[35] To 0.48 g (20.0 mmol) of magnesium turnings under a nitrogen atmosphere were added 20 mL of anhydrous diethyl ether and 2 drops of 1,2-dibromoethane. After 10 min, 0.010 g of mercury(II) chloride was added followed by dropwise addition of 1.34 mL of a 80% (weight) solution of propargyl bromide (12.0 mmol) in toluene over 20 min. The reaction flask was immersed in a cold water bath when the Grignard reaction became too vigorous. The reaction mixture was stirred at rt for 1 h. The resulting mixture was then transferred via cannula to a flask containing 10.0 mL of a 1.0 M solution of chlorodicyclohexylborane (10.0 mmol) in hexanes and 20 mL of diethyl ether maintained at −78 °C. After 30 min, the mixture was allowed to warm to rt. After 1 h, stirring was discontinued to allow magnesium salt to settle. The solution was transferred via cannula to centrifuge tubes for centrifugation. The clear supernatant liquid was transferred via cannula to a flask and was concentrated *in vacuo*. The residue was distilled *in vacuo* (bp 98 °C, 0.02 Torr) to give 1.372 g (6.35 mmol, 64%) of **74** as a colorless liquid: ^1H δ 5.56 (1 H, t, *J* = 6.5 Hz), 4.56 (2 H, d, *J* = 6.7 Hz), 1.76–1.62 (6 H, m), 1.53–1.43 (4 H, m), 1.28–1.14 (12 H, m); ^{13}C δ 220.15, 87.5 (br),

68.54, 34.5 (br), 27.49, 27.43, 27.01.

4-(1-Cyclohexenyl)-3-methylphenol (80). The following procedure for the preparation of **80** is representative. To 0.264 g (2.00 mmol) of 5,5-(pentamethylene)-3,4-pentadien-1-yne in 20 mL of THF at −78 °C was added 1.25 mL (2.00 mmol) of a 1.6 M solution of *n*-butyllithium in hexanes. After 30 min at −78 °C, 0.475 g (2.20 mmol) of **74** in 10.0 mL of THF was introduced via cannula. After 30 min, the mixture was allowed to warm to rt. After an additional 2 h, the mixture was cooled to 0 °C, and 2.0 mL of a 1.0 M solution of trimethyltin chloride (2.0 mmol) in THF was added with a syringe. After 15 h stirring at rt, the mixture was transferred via cannula to a flask containing a mixture of 2.0 mL of a 30% H_2O_2 solution and 2 mL a 6 N NaOH solution in 15 mL of methanol at 0 °C. The reaction mixture was heated at 50 °C for 1 h before it was allowed to cool to rt. Glacial acetic acid (2.0 mL) was added, and the mixture was heated at 50 °C for 2 h. The organic layer was separated, and the aqueous layer was extracted with pentane (3 × 20 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel/20% Et_2O in hexanes) to furnish 0.192 g (1.02 mmol, 51%) of **80** as a light yellow liquid: IR (neat) 3331, 1605, 1581, 1226, 857, 812 cm^{-1}; ^1H δ 6.96 (1 H, d, *J* = 8.1 Hz), 6.68 (1 H, d, *J* = 2.6 Hz), 6.65 (1 H, dd, *J* = 8.1 and 2.6 Hz), 5.60 (1 H, s), 5.54 (1 H, tt, *J* = 3.6 and 1.8 Hz), 2.25 (3 H, s), 2.21–2.14 (4 H, m), 1.82–1.65 (4 H, m); ^{13}C δ 153.60, 138.17, 137.47, 136.66, 129.37, 125.76, 116.61, 112.23, 30.32, 25.38, 23.09, 22.15, 19.84; MS (*m/z*) 188 (M^+), 173, 160, 159, 145.

1-(1-Cyclohexenyl)-5-iodo-2-methyl-4-(2-propenyl)benzene (81). The same procedure was repeated as described for **80** except that after 15 h of stirring following the introduction of trimethyltin chloride, the mixture was cooled to −78 °C. A solution of a 1.6 M *n*-butyllithium in

hexanes (1.25 mL, 2.0 mmol) was added with a syringe. After 15 min, the reaction mixture was transferred via cannula to a flask containing 0.452 g (2.20 mmol) of $CuBr{\cdot}SMe_2$ and 15 mL of THF maintained at −78 °C. After 1 h at −78 °C, 0.726 g (6.00 mmol) of allyl bromide was introduced dropwise, and the reaction mixture was stirred at −78 °C for 1 h before it was allowed to warm to rt. A solution of 1.02 g of iodine (4.00 mmol) in 10 mL of diethyl ether was added via cannula. The resulting mixture was stirred at rt for 1 h followed by the addition of a saturated $Na_2S_2O_3$ solution to destroy excess I_2. An additional 30 mL of water and 40 mL of Et_2O were added, and the organic layer was then separated, washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel/hexanes) to afford 0.203 g (0.60 mmol, 30%) of **81** as a yellow oil: IR (neat) 991, 914 cm^{-1}; ^1H δ 7.54 (1 H, s), 7.00 (1 H, s), 5.96 (1 H, ddt, *J* = 16.6, 10.3, and 6.6 Hz), 5.55 (1 H, tt, *J* = 5.5 and 2.8 Hz), 5.14 (1 H, dq, *J* = 10 and 1.6 Hz), 5.12 (1 H, dq, *J* = 17 and 1.8 Hz), 3.44 (2 H, dt, *J* = 6.5 and 1.5 Hz), 2.20 (3 H, s), 2.19–2.11 (4 H, m), 1.79–1.62 (4 H, m); ^{13}C δ 144.70, 140.34, 138.73, 137.31, 136.01, 135.51, 131.04, 126.48, 116.44, 96.75, 44.42, 29.89, 25.33, 22.96, 22.06, 19.36; MS (*m/z*) 338 (M^+), 297, 211, 170, 169. Anal. Calcd for $C_{16}H_{19}I$: C, 56.82; H, 5.66. Found: C, 57.04; H, 5.68.

4-(1-Butyl-1-pentenyl)-3-methylphenol (83). The same procedure was repeated as described for **80** except that 0.352 g (2.00 mmol) of 5-butyl-3,4-nonadien-1-yne (**48**) was treated with 0.80 mL (2.00 mmol) of a 2.5 M solution of *n*-butyllithium in hexanes to produce **30** followed by 0.561 g (2.6 mmol) of **74**. The phenol **83** (0.279 g, 1.20 mmol, 60%) was isolated as a light yellow liquid: IR (neat) 3353, 1607, 1581, 1235, 860, 816 cm^{-1}; ^1H δ 6.89 (1 H, d, *J* = 8.1 Hz), 6.63 (1 H, dd, *J* = 2.6 Hz), 6.58 (1 H, dd, *J* = 8.1 and 2.6 Hz), 5.18 (1 H, t, *J* = 7.3 Hz), 4.65 (1 H,

br s, OH), 2.28 (2 H, t, *J* = 7.4 Hz), 2.20 (3 H, s), 2.12 (2 H, q, *J* = 7.3 Hz), 1.43 (2 H, sextet, *J* = 7.3 Hz), 1.34–1.20 (4 H, m), 0.94 (3 H, t, *J* = 7.3 Hz), 0.87 (3 H, t, *J* = 6.8 Hz); ^{13}C δ 153.68, 140.09, 137.39, 136.93, 130.09, 129.69, 116.48, 111.91, 31.71, 30.36, 30.11, 23.02, 22.83, 20.04, 14.01, 13.90; MS (*m/z*) 232 (M^+), 217, 203, 190, 175, 161, 148, 147. A minor set of the ^{1}H NMR signals attributable to the presence of the other geometric isomer (isomer ratio = 84:16) at δ (partial) 6.80 (1 H, d, *J* = 8.1 Hz), 6.66 (1 H, d, *J* = 2.6 Hz), and 5.42 (1 H, tt, *J* = 7.3 and 1.1 Hz) was also observed.

***trans*-(±)-4b,5,6,7,8,8a,9,10-Octahydro-2-phenanthrenol (87).** The same procedure was repeated as described for **80** except that 0.292 g (2.00 mmol) of 3,4,10-undecatrien-1-yne (**96**) was used to prepare **84**. To facilitate purification of **87**, the products isolated after column chromatography were treated with an excess of a 2.0 M solution of $BH_3{\cdot}SMe_2$ in THF followed by oxidation with an alkaline 30% H_2O_2 solution. This treatment allowed conversion of undesired side products containing a terminal carbon–carbon double bond to more polar adducts having a hydroxyl group. Further purification by column chromatography afforded 0.023 g (0.11 mmol, 6 %) of **87**[40] as a white solid: IR 3302, 1610, 1247, 802 cm^{-1}; ^{1}H δ 7.14 (1 H, d, *J* = 8.3 Hz), 6.61 (1 H, dd, *J* = 8.4 and 2.9 Hz), 6.54 (1 H, d, *J* = 2.8 Hz), 4.51(1 H, br s, OH), 2.84 (1 H, ddd, *J* = 17.0, 11.5, and 5.9 Hz), 2.73 (1 H, ddd, *J* = 16.8, 6.0, and 2.4 Hz), 2.39 (1 H, dm, *J* = 12.9 and 3.4 Hz), 2.18 (1 H, td, *J* = 10.7 and 2 Hz), 1.93–1.84 (1 H, m), 1.8–1.7 (3 H, m), 1.5–1.1 (6 H, m); ^{13}C δ 153.09, 138.68, 133.10, 126.61, 115.16, 112.62, 43.24, 40.80, 34.24, 31.19, 30.64, 30.01, 26.89, 26.31; MS (*m/z*) 202 (M^+), 174, 159, 145. The assignment of the trans geometry to **87** is based on the coupling constant of ca. 10.7 Hz for the two anti hydrogen atoms with the benzylic methine hydrogen at 2.18 ppm. The ^{1}H NMR chemical shift of the

benzylic methine hydrogen and the ^{13}C NMR chemical shifts of the aliphatic carbons are also consistent with the assignment of the trans geometry to **34** when compared with those of *trans*-1,2,3,4,4a,9,10,10a-octahydrophenanthrene reported previously.[3a] A minor set of the ^{1}H NMR signals (partial) attributable to 4-[(1*E*)-1,6-heptadienyl]-3-methylphenol (ca. 1%) at δ 7.28 (1 H, d, *J* = 9 Hz), 6.48 (1 H, dt, *J* = 15.8 and 1.5 Hz), 5.94 (1 H, dt, *J* = 15.6 and 6.9 Hz) was also observed.

4-(1-Butyl-1-pentenyl)-3-pentylphenol (94). The following procedure for the preparation of **94** is representative. To 0.352 g (2.00 mmol) of 5-butyl-3,4-nonadien-1-yne (**48**) in 20 mL of THF at −78 °C under a nitrogen atmosphere was added 0.80 mL (2.0 mmol) of a 2.5 M solution of *n*-butyllithium in hexanes. After 30 min at −78 °C, 0.416 g (2.00 mmol) of *B*-methoxydicyclohexylborane in 10.0 mL THF was introduced via cannula. After 1.5 h of stirring at −78 °C, 0.33 mL (2.67 mmol) of $BF_3 \cdot OEt_2$ was added with a syringe, and the mixture was allowed to warm to rt. Solvent was removed *in vacuo*, and the remaining yellow viscous residue was dissolved in 30 mL of pentane. The solution was transferred to centrifuge tubes via cannula for centrifugation. The supernatant liquid was then transferred via cannula to a flask. Pentane was removed *in vacuo* to furnish **88** as a colorless viscous liquid. Anhydrous THF (35 mL) was added, and the solution was cooled to −78 °C. To a second flask containing 0.202 g (2.1 mmol) of 1,2-heptadiene in 15 mL of THF −78 °C was added 0.80 mL (2.0 mmol) of a 2.5 M solution of *n*-butyllithium in hexanes. After 30 min of stirring at −78 °C, 1-lithio-1,2-heptadiene (**89**) was added via cannula to the flask containing **88**. After 1 h of stirring at −78 °C, the mixture was allowed to warm to rt and stirred for an additional 3 h. The mixture was then cooled to 0 °C, and 2.0 mL of a 1.0 M solution of trimethyltin chloride in THF was introduced with a syringe.

After 14 h of stirring at rt, the mixture was transferred via cannula to a flask containing 2 mL of 30% H_2O_2, 2.0 mL of a 6 N NaOH solution, and 15 mL of methanol at 0 °C. The reaction mixture was heated at 50 °C for 1 h. Glacial acetic acid (2 mL) was added, and the mixture was heated at 50°C for an additional 2 h before it was allowed to cool to rt. The organic layer was separated, and the aqueous layer was extracted with pentane (3 × 20 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel/20% Et_2O in hexanes) to furnish 0.351 g (1.22 mmol, 61%) of **94** as a light yellow liquid: IR (neat) 3341, 1606, 1581, 1230, 817 cm^{-1}; ^1H δ 6.91 (1 H, d, *J* = 8.3 Hz), 6.70 (1 H, d, *J* = 2.6 Hz), 6.61 (1 H, dd, *J* = 8.1 and 2.8 Hz), 5.21 (1 H, t, *J* = 7.3 Hz), 5.17 (1 H, br s, OH), 2.52 (2 H, t, *J* = 8.0 Hz), 2.29 (2 H, t, *J* = 7.3 Hz), 2.15 (2 H, q, *J* = 7.3 Hz), 1.6–1.5 (2 H, m), 1.45 (2 H, sextet, *J* = 7.3 Hz), 1.37–1.23 (8 H, m), 0.97 (3 H, t, *J* = 7.3 Hz), 0.90 (3 H, t, *J* = 6.7 Hz), 0.87 (3 H, t, *J* = 6.9 Hz); ^{13}C δ 153.73, 141.96, 140.03, 137.12, 130.41, 129.80, 115.30, 111.93, 32.94, 32.27, 31.98, 31.28, 30.41, 30.14, 23.03, 22.86, 22.54, 14.02, 13.99, 13.90; MS (*m/z*) 288 (M^+), 259, 231, 217, 189, 175, 161; HRMS calcd for $C_{20}H_{32}O$ 288.2453, found 288.2442. Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.15; H, 11.19. A minor set of the ^1H NMR signals (partial) at δ 6.81 (1 H, d, *J* = 8.3 Hz), 6.74 (1 H, d, *J* = 2.6 Hz), 6.64 (1 H, dd, *J* = 8 and 2.6 Hz), and 5.45 (1 H, tt, *J* = 7.1 and 1.2 Hz) attributable to the presence of the other geometric isomer (isomer ratio = 87:13) was also observed.

1-(1-Butyl-1-pentenyl)-2-pentylbenzene (95). The same procedure was repeated as described for **94** except that the reaction mixture was treated with acetic acid directly. Purification by column chromatography (silica gel/hexanes) furnish 0.310 g (1.14 mmol, 57%) of **95** as a yellow oil: IR (neat) 1457, 758 cm^{-1}; ^1H δ 7.24–7.20 (2 H, m), 7.19–7.11 (1 H, m), 7.07 (1 H, dm, *J* =

6.9 and 1.3 Hz), 5.28 (1 H, t, *J* = 7.3 Hz), 2.61 (2 H, t, *J* = 8.0 Hz), 2.38 (2 H, t, *J* = 7.3 Hz), 2.21 (2 H, q, *J* = 7.3 Hz), 1.63 (2 H, m), 1.50 (2 H, sextet, *J* = 7.3 Hz), 1.42–1.28 (8 H, m), 1.02 (3 H, t, *J* = 7.3 Hz), 0.94 (3 H, t, *J* = 6.7 Hz), 0.91 (3 H, t, *J* = 6.7 Hz); ^{13}C δ 144.31, 140.63, 140.20, 129.60, 129.34, 128.75, 126.30, 124.97, 32.98, 32.19, 32.10, 31.55, 30.49, 30.14, 23.06, 22.91, 22.59, 14.05, 13.99, 13.92; MS (*m/z*) 272 (M^+), 215, 201, 173, 159, 145, 117; HRMS Calcd for $C_{20}H_{32}$ 272.2504, found 272.2481. A minor ^{1}H NMR signal of the alkenyl hydrogen of the other geometric isomer at δ 5.50 (tt, *J* = 7.1 and 1 Hz) was also observed.

(±)-10β-Butyl-4bα,5,6,7,8,8aβ,9,10-octahydro-2-phenanthrenol (105), 4-[(1*E*)-1,6-Heptadienyl]-3-pentylphenol (106), and 4-(6-Heptenyl)-3-[(*E*)-1-pentenyl]phenol (107). The same procedure was repeated as described for **94** except that 0.292 g (2.0 mmol) of **96** was used. Purification by column chromatography (silica gel/10% diethyl ether in hexanes) furnished 0.232 g (0.90 mmol, 45%) of a mixture of **105** (20%), **106** (10%) and **107** (15%) as a colorless liquid. The amounts of **105**, **106**, and **107** in the mixture were determined by integration of the ^{1}H NMR spectrum. It was possible to separate **105** and **107** from the mixture by HPLC. A fraction containing predominantly **106** was also obtained. **105**: IR (neat) 3342, 1609, 1582, 1244, 733 cm^{-1}; ^{1}H δ 7.13 (1 H, d, *J* = 8.8 Hz), 6.63 (1 H, d, *J* = 8 Hz), 6.60 (1 H, s), 4.77 (1 H, br s, OH), 2.66 (1 H, m), 2.39 (1 H, dm, *J* = 12 and 3 Hz), 2.12 (1 H, tm, *J* = 11 and 3 Hz), 1.94–1.1 (16 H, m), 0.92 (3 H, t, *J* = 7.1 Hz); ^{13}C δ 153.13, 143.85, 132.76, 126.21, 115.38, 112.71, 43.74, 38.21, 37.84, 35.61, 34.34, 33.92, 30.96, 30.38, 26.92, 26.43, 22.84, 14.13; MS (*m/z*) 258 (M^+), 201, 174, 159, 145, 133. **106**: ^{1}H (partial) δ 7.29 (1 H, d, *J* = 8.2 Hz), 6.60 (2 H, m), 6.51 (1 H, dt, *J* = 15.4 and 1.6 Hz), 5.94 (1 H, dt, *J* = 15.4 and 6.9 Hz); ^{13}C δ 154.36, 141.50, 138.76, 130.22, 129.43, 127.11 (2 carbons), 115.86, 114.55, 112.97, 33.32, 33.20, 32.65, 31.72, 30.46, 28.73,

22.53, 14.03. **107**: IR (neat) 3354, 1640, 1607, 1578, 1245, 993, 964, 909, 867, 821 cm^{-1}; ^1H δ 6.96 (1 H, d, *J* = 8.2 Hz), 6.90 (1 H, d, *J* = 2.6 Hz), 6.62 (1 H, dd, *J* = 8.3 and 2.7 Hz), 6.54 (1 H, dt, *J* = 15.7 and 1.1 Hz), 6.05 (1 H, tt, *J* = 15.6 and 6.9 Hz), 5.80 (1 H, ddt, *J* = 17.0, 10.2, and 6.6 Hz), 4.98 (1 H, dm, *J* = 17 and 2 Hz), 4.93 (1 H, dm, *J* = 10 and 1 Hz), 4.73 (1 H, br s, OH), 2.56 (2 H, t, *J* = 7.7 Hz), 2.19 (2 H, qd, *J* = 7.3 and 1.7 Hz), 2.04 (2 H, qm, *J* = 6.6 and 1 Hz), 1.6–1.3 (8 H, m), 0.95 (3 H, t, *J* = 7.3 Hz); ^{13}C δ 153.57, 139.08, 137.74, 132.58, 132.22, 130.51, 127.27, 114.20, 113.77, 112.24, 35.31, 33.71, 32.49, 31.06, 28.94, 28.75, 22.55, 13.68; MS (*m/z*) 258 (M^+), 229, 215, 201, 187, 175, 145, 133. The assignment of the trans ring junction to **105** is based on the ^1H NMR chemical shift of the benzylic methine hydrogen at 2.12 ppm as observed in the case of **87**. The structures of **106** and **107** were assigned on the basis of the ^1H NMR chemical shifts of the aromatic hydrogens at the *meta* position. The chemical shift of the *meta* aromatic hydrogen of **106** at 7.29 ppm is essentially identical to that of 4-[(1*E*)-1,6-heptadienyl]-3-methylphenol at 7.28 ppm.

2-(1-Decynyl)-*N*-(triphenylphosphoranylidene)benzenamine (109g).[46] To 3.68 g (8.72 mmol) of Ph_3PBr_2 were added 1.815 g (7.93 mmol) of 2-(1-decynyl)aniline (**108g**), 2.1 mL of anhydrous triethylamine, and 60 mL of anhydrous benzene under a nitrogen atmosphere. The reaction mixture was heated under reflux for 5 h. The white triethylammonium bromide precipitate was removed by filtration, and the filtrate was concentrated. Purification by column chromatography (silica gel/20% diethyl ether in hexanes) afforded 2.876 g (5.88 mmol, 74%) of **109g** as a yellow liquid: IR (neat) 3053, 1584, 749, 716, 694 cm^{-1}; ^1H δ 7.87–7.78 (6 H, m), 7.55–7.4 (9 H, m), 7.30 (1 H, dt, *J* = 7.7 and 2.0 Hz), 6.81 (1 H, td, *J* = 7.7 and 1.7 Hz), 6.58 (1 H, t, *J* = 7.3 Hz), 6.49 (1 H, d, *J* = 7.9 Hz), 2.49 (2 H, t, *J* = 7.3 Hz), 1.66 (2 H, quintet, *J* = 7.3 Hz), 1.45 (2 H,

quintet, *J* = 6.9 Hz), 1,24 (8 H, br), 0.86 (3 H, t, *J* = 6.7 Hz); ^{13}C δ 152.26, 132.87, 132.68 (d, *J* = 9.8 Hz), 131.49 (d, *J* = 2.6 Hz), 131.36 (d, *J* = 99.9 Hz), 128.38 (d, *J* = 11.9 Hz), 127.58, 121.51 (d, *J* = 9.3 Hz), 119.44 (d, *J* = 21.7 Hz), 117.10, 92.41, 81.36, 31.81, 29.27, 29.24, 29.18, 22.61, 20.10, 14.07.

***N*-[2-(1-Pentynyl)phenyl]-*N′*-phenylcarbodiimide (122d).** To 0.247 g of the iminophosphorane **134**[20] (0.700 mmol) in 10 mL of anhydrous benzene was introduced via cannula a solution of 0.13 g of 2-(1-pentynyl)phenyl isocyanate **133d** (0.70 mmol) in 10 mL of dry benzene under a nitrogen atmosphere at rt. After 1 h, the reaction mixture was concentrated *in vacuo,* and the residue was purified by flash column chromatography (silica gel/7% benzene in hexanes) to afford 0.093 g (0.358 mmol, 51%) of **122d** as a yellow oil: IR (neat) 2247, 2143, 2107, 1592, 756, 689 cm^{-1}; ^{1}H δ 7.44 (1H, dd, *J* = 7.9 and 1.5 Hz), 7.4–7.08 (8 H, m), 2.10 (2 H, t, *J* = 7.2 Hz), 1.46 (2 H, sextet, *J* = 7.3 Hz), 0.93 (3 H, t, *J* = 7.3 Hz); ^{13}C δ 139.16, 138.72, 133.65, 133.01, 129.25, 128.39, 125.12, 125.05, 124.25, 124.19, 120.78, 98.70, 76.87, 21.69, 21.53, 13.40; MS *m/z* 260 (M^+), 245, 231, 218; HRMS calcd for $C_{18}H_{16}N_2$ 260.1314, found 260.1312.

***N*-[2-(2-Phenylethynyl)phenyl]-*N′*-phenylcarbodiimide (122f).** The same procedure was repeated as described for **122d** by using the method outlined in Scheme 3. Treatment of 0.541 g of **134**[20] (1.530 mmol) with 0.336 g 2-(2-phenylethynyl)phenyl isocyanate **133f** (1.53 mmol) in 15 mL of anhydrous benzene afforded 0.353 g (1.20 mmol, 78%) of **122f** as a pale yellow oil: IR (neat) 2138, 1590, 754, 689 cm^{-1}; ^{1}H δ 7.53 (1 H, dm, *J* = 7.7 and 1.5 Hz), 7.37–7.06 (13 H, m); ^{13}C δ 138.75, 138.68, 133.25, 132.88, 131.54, 129.31, 129.27, 128.36, 128.05, 125.27, 125.19, 124.60, 124.31, 122.69, 119.99, 96.22, 85.56; MS *m/z* 294 (M^+), 264, 216, 190, 176, 147, 77;

HRMS calcd for $C_{21}H_{14}N_2$ 294.1157, found 294.1171.

11-Propyl-6*H*-indolo[2,3-*b*]quinoline (127d). To 0.247 g of the iminophosphorane **134**[20] (0.700 mmol) in 10 mL of *p*-xylene was introduced via cannula a solution of 0.13 g of 2-(1-pentynyl)phenyl isocyanate (**133d**, 0.70 mmol) in 10 mL of *p*-xylene under a nitrogen atmosphere. After 2 h at rt, the reaction mixture was heated under reflux for 12 h. The reaction mixture was then concentrated, and the residue was purified by flash chromatography (silica gel/30% diethyl ether in hexanes) to afford 0.091 g (0.35 mmol, 50%) of **127d** as yellow solid: IR (KBr) 3455, 1611, 739 cm^{-1}; ^1H δ 12.23 (1 H, br s, NH), 8.30 (1 H, d, *J* = 8.4 Hz), 8.22 (1 H, d, *J* = 8.2 Hz), 8.17 (1 H, d, *J* = 7.9 Hz), 7.77 (1 H, d, *J* = 7.6 Hz), 7.6–7.48 (3 H, m), 7.31 (1 H, t, *J* = 7.6 Hz), 3.65 (2 H, t, *J* = 8.0 Hz), 1.98 (2 H, sextet, *J* = 7.6 Hz), 1.24 (3 H, t, *J* = 7.4 Hz); ^{13}C δ 153.44, 146.26, 144.31, 141.38, 128.71, 127.45, 127.04, 124.17, 123.41, 122.67, 121.39, 119.99, 116.63, 110.93, 30.93, 22.92, 14.70; MS *m/z* 260 (M^+), 231.

The indoloquinoline **127d** (50% yield) was also synthesized in a one-pot operation from **134** and phenyl isocyanate **133d** without isolation of **122d**.

11-Phenyl-6*H*-indolo[2,3-*b*]quinoline (127f).[18] To 0.225 g of the iminophosphorane **134**[20] (0.637 mmol) in 10 mL of anhydrous benzene was introduced via cannula a solution of 0.140 g of 2-(2-phenylethynyl)phenyl isocyanate (**133f**, 0.639 mmol) in 10 mL of dry benzene under a nitrogen atmosphere at rt. After 1 h, the reaction mixture was heated under reflux for 5 h. The reaction mixture was then concentrated, and the residue was purified by flash chromatography (silica gel/5% diethyl ether in hexanes) to afford 0.103 g (0.350 mmol, 55%) of **127f** as pale yellow solid: IR (KBr) 1593, 743 cm^{-1}; ^1H δ 12.46 (1 H, br s, NH), 8.28 (1 H, d, *J* = 8.4 Hz), 7.81–7.73 (3 H, m), 7.7–7.65 (3 H, m), 7.57–7.52 (3 H, m), 7.44–7.37 (2 H, m), 7.08 (1 H, d, *J* =

7.4 Hz), 6.98 (1 H, td, *J* = 7.5 and 1.1 Hz); ^{13}C δ 153.36, 146.18, 142.80, 141.55, 136.37, 129.35, 128.95, 128.55, 127.87, 126.59, 126.40, 123.69, 123.06, 122.85, 121.04, 119.70, 116.75, 110.79; MS *m/z* 294 (M^+), 293, 264, 146. Anal. Calcd for $C_{21}H_{14}N_2$: C, 85.69; H, 4.79; N, 9.52. Found: C, 85.74; H, 4.84; N, 9.50.

The indoloquinoline **127f** (55% yield) was also synthesized in a one-pot operation from **134** and 2-(2-phenylethynyl)phenyl isocyanate **133f** without isolation of **122f**.

Methyl 2-(1-Propynyl)benzoate (131c). The following procedure for the preparation of **131c** is representative. To a degassed solution containing 1.53 g of $Pd(PPh_3)_2Cl_2$ (2.18 mmol), 0.414 g of CuI (2.18 mmol), 6.685 g of methyl 2-iodobenzoate (**130**, 25.0 mmol), and 13.75 mL of *N*,*N*-diisopropylethylamine (79.0 mmol) in 80.0 mL of DMF was treated with 1000 mL of gaseous propyne intraduced with a gaslight syringe (45.0 mmol). After 24 h at rt, the reaction mixture was poured into a flask containing 100 mL of a saturated NH_4Cl solution and 100 mL of pentane. After filtration, the organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel/5% diethyl ether in hexanes) to afford **131c** (4.26 g, 24.5 mmol, 98%) as a light yellow liquid: IR (neat) 1731, 1250, 757, 502 cm^{-1}; ^{1}H δ 7.89 (1 H, dd, *J* = 7.9 and 1.4 Hz), 7.52 (1 H, dd, *J* = 7.7 and 1.3 Hz), 7.42 (1 H, td, J = 7.6 and 1.4 Hz), 7.31 (1 H, td, *J* = 7.3 and 1.4 Hz), 3.92 (3 H, s), 2.13 (3 H, s); ^{13}C δ 166.85, 134.26, 131.75, 131.55, 130.12, 127.14, 124.57, 91.47, 78.30, 52.12, 4.77; MS *m/z* 174 (M^+), 159, 143, 115, 77, 51; HRMS calcd for $C_{11}H_{10}O_2$ 174.0681, found 174.0686.

Methyl 2-(1-Pentynyl)benzoate (131d). To a degassed solution containing 1.755 g of $Pd(PPh_3)_2Cl_2$ (2.50 mmol), 0.488 g of CuI (2.56 mmol), 6.55 g of methyl 2-iodobenzoate (**130**, 25.0 mmol), and 14.0 mL of *N*,*N*-diisopropylethylamine (80.4 mmol) in 80 mL of DMF was

added via cannula a degassed solution of 3.4 g (4.9 mL) of 1-pentyne (50 mmol) in 25 mL DMF. After 24 h at rt, the reaction mixture was poured into a flask containing 200 mL of a saturated NH_4Cl solution and 200 mL of pentane. After filtration, the organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated. The residue was distilled *in vacuo* to afford 5.00 g (24.8 mmol, 99%) of **131d** as a light yellow oil: IR (neat) 2234, 1731, 757, 702 cm^{-1}; ^1H δ 7.84 (1 H, dd, *J* = 7.9 and 1.5 Hz), 7.47 (1 H, dd, *J* = 7.8 and 1.4 Hz), 7.36 (1 H, td, *J* = 7.7 and 1.5 Hz), 7.25 (1 H, td, *J* = 7.4 and 1.5 Hz), 3.86 (3 H, s), 2.41 (2 H, t, *J* = 7.1 Hz), 1.62 (2 H, sextet, *J* = 7.2 Hz), 1.03 (3 H, t, *J* = 7.4 Hz); ^{13}C δ 166.74, 133.99, 131.74, 131.26, 129.92, 126.92, 124.28, 95.61, 79.21, 51.80, 21.97, 21.57, 13.36; MS *m/z* 202 (M^+), 174, 159, 143.

Methyl 2-[2-(1-Cyclohexenyl)ethynyl]benzoate (131e). The same procedure was repeated as described for **131c** except that 1.053 g of $Pd(PPh_3)_2Cl_2$ (1.50 mmol), 0.285 g of CuI (1.50 mmol), 3.931 g of methyl 2- iodobenzoate **130** (15.0 mmol), and 7.84 mL of *N*,*N*-diisopropylethylamine (45.0 mmol) in 30.0 mL of DMF was added via cannula a degassed solution of 2.46 g of 1-ethynylcyclohexene (22.94 mmol) in 10.0 mL of DMF to afford **131e** (3.27 g, 13.63 mmol, 91%) as a light yellow liquid: IR (neat) 2201, 1731, 1594, 756, 700 cm^{-1}; ^1H δ 7.91 (1 H, dd, *J* = 7.8 and 1.4 Hz), 7.52 (1 H, dd, *J* = 7.7 and 1.5 Hz), 7.42 (1 H, td, *J* = 7.5 and 1.5 Hz), 7.30 (1 H, td, *J* = 7.5 and 1.5 Hz), 6.27 (1 H, m), 2.26 (2 H, m), 2.14 (2 H, m), 1.66 (4 H, m); ^{13}C δ 166.85, 135.98, 133.81, 133.81, 131.53, 130.33, 127.30, 124.19, 120.92, 96.38, 85.67, 52.05, 29.03, 25.83, 22.29, 21.49; MS *m/z* 240 (M^+), 225, 210, 197, 179, 165, 79; HRMS calcd for $C_{16}H_{16}O_2$ 240.1150, found 240.1148.

Methyl 2-(Phenylethynyl)benzoate (131f). The same procedure was repeated as described for **131d** except that a solution of 4.692 g of phenylacetylene (46.00 mmol) in 20 mL of DMF was

introduced via cannula to a degassed solution containing 1.734 g of $Pd(PPh_3)_4$ (1.50 mmol), 0.58 g of CuI (3.0 mol), 8.022 g of **130** (30.61 mmol), and 11.64 g of *N*,*N*-diisopropylethylamine (90.06 mmol) in 40 mL of DMF. Purification by flash chromatography (silica gel/5% diethyl ether in hexanes) afforded 6.36 g of **131f** (27.0 mmol, 88%) as a yellow liquid: IR (neat) 2217, 1730, 756, 691 cm^{-1}; ^1H δ 7.98 (1 H, dd, *J* = 7.8 and 1.1 Hz), 7.65 (1 H, dd, *J* = 7.7 and 1.0 Hz), 7.61–7.57 (2 H, m), 7.49 (1 H, td, *J* = 7.5 and 1.6 Hz), 7.41–7.33 (4 H, m), 3.97 (3 H, s); ^{13}C δ 166.63, 133.91, 131.75, 131.66, 130.41, 128.46, 128.29, 127.83, 123.61, 123.22, 94.26, 88.15, 52.14; MS *m/z* 236 (M^+), 221, 205, 193, 176, 165, 151, 150.

2-(1-Propynyl)benzoic Acid (132c). The following procedure for the preparation of **132c** is representative. A solution of 3.934 g (22.61 mmol) of **131c** in 100.0 mL of THF and 99.0 mL of 1 N NaOH was heated at 50 °C for 12 h. The reaction mixture was cooled in an ice-water bath and was acidified with dilute HCl. The organic layer was separated, washed with water, dried over $MgSO_4$ and concentrated. The residue was purified by recrystallization from 50% of diethyl ether in hexanes to afford **132c (**2.20 g, 13.75 mmol, 61%) as light yellow solid: IR 2915, 1675, 1284, 754 cm^{-1}; ^1H δ 11.82 (1 H, br s), 8.05 (1 H, dd, *J* = 8.0 and 1.3 Hz), 7.54 (1 H, dd, *J* = 7.9 and 1.4 Hz), 7.48 (1 H, td, *J* = 7.7 and 1.5 Hz), 7.35 (1 H, td, *J* = 7.7 and 1.5 Hz), 2.4 (3 H, s); ^{13}C δ 171.54, 134.36, 132.36, 131.04, 130.60, 127.29, 124.85, 92.73, 78.13, 4.78; MS *m/z* 160 (M^+), 145, 118, 89, 77, 43; HRMS calcd for $C_{10}H_8O_2$ 160.0524, found 160.0523.

2-(1-Pentynyl)benzoic Acid (132d). A solution of 5.000 g (24.75 mmol) of **131d** in 30 mL of THF and 140 mL of 1 N NaOH was heated at 50 °C for 12 h. The reaction mixture was cooled in an ice–water bath and was acidified with dilute HCl. The organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by recrystallization

from 50% of diethyl ether in hexanes to afford 4.354 g (23.16 mmol, 94%) of **132d** as pale yellow needles: IR 2962, 2234, 1692, 757 cm^{-1}; ^{1}H δ 11.4 (1 H, br), 8.06 (1 H, dd, *J* = 7.9 and 1.1 Hz), 7.55 (1 H, dd, *J* = 7.7 and 1.2 Hz), 7.48 (1 H, td, *J* = 7.4 and 1.5 Hz), 7.35 (1 H, td, *J* = 7.4 and 1.5 Hz), 2.47 (2 H, t, *J* = 7.0 Hz), 1.68 (2 H, sextet, *J* = 7.4 Hz), 1.09 (3 H, t, *J* = 7.4 Hz); ^{13}C δ 171.53, 134.31, 132.34, 131.06, 130.64, 127.27, 124.91, 97.24, 79.00, 21.95, 21.77, 13.50; MS *m/z* 188 (M^+), 160, 159, 131, 118; HRMS calcd for $C_{12}H_{12}O_2$ 188.0837, found 188.0829.

2-[2-(1-Cyclohexenyl)ethynyl]benzoic Acid (132e). The same procedure was repeated as described for **132c** except that 2.98 g (12.41 mmol) of **131e** in 100.0 mL of THF was treated with 46.0 mL of 1 N NaOH to afford **132e (**2.42 g, 10.71 mmol, 86%) as pale yellow needles: IR 2929, 2201, 1694, 752 cm^{-1}; ^{1}H δ 8.08 (1 H, dd, J = 7.7 and 1.0 Hz), 7.56 (1 H, dd, J = 7.6 and 1.4 Hz), 7.49 (1 H, td, *J* = 7.3 and 1.4 Hz), 7.36 (1 H, td, *J* = 7.6 and 1.7 Hz), 6.30 (1 H, m), 2.28 (2 H, m), 2.17 (2 H, m), 1.67 (4 H, m); ^{13}C δ 171.04, 136.51, 133.94, 132,39, 131.25, 130.32, 127.46, 124.61, 120.79, 97.67, 85.40, 28.78, 25.86, 22.26, 21.45; MS *m/z* 226 (M^+), 197, 181, 165, 141, 105, 67; HRMS calcd for $C_{15}H_{14}O_2$ 226.0994, found 226.0992.

2-(Phenylethynyl)benzoic Acid (132f). The same procedure was repeated as described for **132c** except that 3.114 g of **18f** (13.2 mmol) was used to afford 2.69 g (12.11 mmol, 92%) of **132f** as pale yellow needles: IR 3061, 2210, 1695, 754, 690 cm^{-1}; ^{1}H δ 8.15 (1 H, dd, *J* = 7.8 and 1.2 Hz), 7.7 (1 H, dd, *J* = 7.6 and 1.1 Hz), 7.6–7.54 (3 H, m), 7.44 (1 H, td, *J* = 7.6 and 1.3 Hz), 7.35–7.29 (3 H, m); ^{13}C δ 171.12, 134.18, 132.60, 131.75, 131.39, 130.46, 128.64, 128.38, 128.00, 124.30, 123.05, 95.39, 87.96; MS *m/z* 222 (M^+), 194, 165.

2-(1-Propynyl)phenyl Isocyanate (133c). The following procedure for the preparation of **133c** is representative. To a solution of 2.163 g (15.32 mmol) of **132c** in 30 mL of anhydrous benzene

were added 1.9 mL of triethylamine and 3.0 mL (13.52 mmol) of DPPA. After 3 h at rt, the reaction mixture was heated at reflux for 2 h until the nitrogen gas evolution had ceased. The reaction mixture was then washed with a saturated NH_4Cl solution, water, dried over $MgSO_4$, and concentrated. The reside was purified by flash chromatography (silica gel/5% diethyl ether in hexanes) to afford **133c** (1.65 g, 10.51 mmol, 78%) as a light yellow liquid: IR (neat) 2288, 2240, 1723, 1520, 755 cm^{-1}; ^1H δ 7.37 (1 H, dd, *J* = 7.6 and 1.7 Hz), 7.21 (1 H, td, *J* = 7.7 and 1.62 Hz), 7.10 (1 H, td, *J* = 7.6 and 1.4 Hz), 7.00 (1 H, dd, *J* = 7.9 and 1.1 Hz), 2.13 (3 H, s); ^{13}C δ 135.41, 131.76, 128.51, 125.21, 123.26, 121.45, 95.35, 75.67, 4.41; MS *m/z* 157 (M^+), 129, 102, 76, 63, 51; HRMS calcd for $C_{10}H_7NO$ 157.0528, found 157.0525.

2-(1-Pentynyl)phenyl Isocyanate (133d). To a solution of 3.22 g (17.1 mmol) of **132d** in 30 mL of anhydrous benzene were added 2.4 mL of triethylamine and 3.83 mL (17.8 mmol) of DPPA. After 3 h at rt, the reaction mixture was heated at reflux for 2 h until the nitrogen gas evolution had ceased. The reaction mixture was then washed with a saturated NH_4Cl solution, water, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel/3% diethyl ether in hexanes) to afford 2.48 g (13.41 mmol, 78%) of **133d** as a colorless oil: IR (neat) 2244, 1599, 1506, 755 cm^{-1}; ^1H δ 7.40 (1 H, dd, *J* = 7.7 and 1.7 Hz), 7.20 (1 H, td, *J* = 7.2 and 1.7 Hz), 7.10 (1 H, td, *J* = 7.5 and 1.5 Hz), 7.00 (1 H, dd, *J* = 7.9 and 1.2 Hz), 2.50 (2 H, t, *J* = 7.1 Hz), 1.72 (2 H, sextet, *J* = 7.2 Hz), 1.10 (3 H, t, *J* = 7.4 Hz); ^{13}C δ 135.10, 131.95, 128.38, 127.38, 125.10, 123.19, 121.52, 99.38, 76.36, 21.62, 21.49, 13.46; MS *m/z* 185 (M^+), 170, 156, 130, 128; HRMS calcd for $C_{12}H_{11}NO$ 185.0841, found 185.0849.

2-[2-(1-Cyclohexenyl)ethynyl]phenyl Isocyanate (133e). The same procedure was repeated as described for **133c** except that 2.14 g (9.46 mmol) of **132e** was treated with 1.32 mL of

triethylamine and 2.03 mL (9.46 mmol) of DPPA to afford **133e** (1.614 g, 7.24 mmol, 77%) as a light yellow liquid: IR (neat) 2926, 2256, 1593, 1505, 753 cm^{-1}; ^{1}H δ 7.41 (1 H, dd, *J* = 7.7 and 1.7 Hz), 7.21 (1 H, td, *J* = 7.7 and 1.7 Hz), 7.12 (1 H, td, *J* = 7.5 and 1.4 Hz), 7.01 (1 H, dd, *J* = 7.9 and 1.2 Hz), 6.34 (1 H, septet?, *J* = 1.9 Hz), 2.27 (2 H, m), 2.17 (2 H, m), 1,67 (4 H, m); ^{13}C δ 136.53, 134.50, 132.07, 128.66, 127.16, 125.28, 123.39, 121.46, 120.26, 99.44, 82.15, 28.55, 25.81, 22.19, 21.40; MS *m/z* 223 (M^+), 194, 180, 167, 117, 80; HRMS calcd for $C_{15}H_{13}NO$ 223.0997, found 223.0988.

2-(Phenylethynyl)phenyl Isocyanate (133f). The same procedure was repeated as described for **133d** except that 0.542 g of **132f** (2.441 mmol) in 15 mL of anhydrous benzene, 0.34 mL of triethylamine, and 0.54 mL (2.5 mmol) of DPPA were used to afford 0.391 g (1.785 mmol, 73%) of **133f** as a colorless oil: IR (neat) 2235, 755, 684 cm^{-1}; ^{1}H δ 7.66–7.62 (2 H, m), 7.54 (1 H, dd, *J* = 7.8 and 1.6 Hz), 7.41–7.36 (3 H, m), 7.29 (1 H, td, *J* = 7.7 and 1.7 Hz), 7.18 (1 H, td, *J* = 7.6 and 1.5 Hz), 7.08 (1 H, dd, *J* = 7.9 and 1.2 Hz); ^{13}C δ 134.72, 132.21, 131.42, 129.22, 128.81, 128.34, 127.01, 125.37, 123.51, 122.33, 120.92, 97.40, 84.75; MS *m/z* 219 (M^+), 190, 163.

Aniline 136a. To a degassed solution containing 0.702 g of $Pd(PPh_3)_2Cl_2$ (1.00 mmol), 0.19 g of CuI (1.00 mmol), 4.60 g of 2-iodoaniline (21.0 mmol), and 80 mL of Et_3N was added 1.17 mL of 1,6-heptadiyne (**135a**, 10.2 mmol). After 16 h at rt, the reaction mixture was heated at 45 °C for 8 h. Then the reaction mixture was poured into a flask containing 200 mL of a saturated NH_4Cl solution and 100 mL of Et_2O. After filtration, the organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (silica gel/50% diethyl ether in hexanes) to furnish 2.415 g (8.814 mmol, 86%) of **136a** as a yellow oil: IR (neat) 3467, 3371, 1612, 748 cm^{-1}; ^{1}H δ 7.30 (2 H, dd, *J* = 8.0 and 1.4

Hz), 7.13 (2 H, td, *J* = 8.5 and 1.5 Hz), 6.74–6.69 (4 H, m), 4.21 (4 H, br s, NH), 2.69 (4 H, t, *J* = 6.9 Hz), 1.94 (2 H, quintet, *J* = 7.0 Hz), ^{13}C δ 147.61, 131.92, 128.88, 117.66, 114.06, 108.37, 94.22, 77.77, 27.82, 18.70; MS *m/z* 274 (M^+), 207, 191, 144, 131.

Aniline 136b. The same procedure was repeated as described for **136a** except that a solution of 1.404 g of $Pd(PPh_3)_2Cl_2$ (2.00 mmol), 0.38 g of CuI (2.00 mmol), 9.20 g of 2-iodoaniline (42.0 mmol), and 2.404 g (20.0 mmol) of 1,8-nonadiyne (**135b**) in 160 mL of Et_3N was used. Purification by column chromatography afforded 5.61 g of **136b** (18.6 mmol, 93%) as a yellow liquid: IR (neat) 3468, 3373, 1613, 748 cm^{-1}; ^{1}H δ 7.30 (2 H, dd, *J* = 7.4 and 1.2 Hz), 7.12 (2 H, td, *J* = 7.7 and 1.5 Hz), 6.72–6.66 (4 H, m), 4.18 (4 H, br s, NH), 2.54 (4 H, t, *J* = 6.2 Hz), 1.70 (6 H, m); ^{13}C δ 147.51, 131.80, 128.67, 117.57, 113.96, 108.54, 95.22, 77.13, 28.23, 27.97, 19.38.

Iminophosphorane 137a. The reaction mixture of 0.965 g (3.52 mmol) of **136a**, 3.12 g (7.39 mmol) of Ph_3PBr_2, 2.0 mL of anhydrous triethylamine, and 30 mL of anhydrous benzene was heated under reflux for 5 h. Triethylammonium bromide was removed by filtration, and the filtrate was concentrated. The residue was purified through a short column (silica gel/40% diethyl ether and 5% ethanol in hexanes) to afford 0.565 g (0.711 mmol, 20%) of **137a** as colorless crystals: IR 1583, 1477, 1435, 694 cm^{-1}; ^{1}H δ 7.81 (12 H, m), 7.44 (18 H, m), 7.32 (2 H, dt, *J* = 7.7 and 2.1 Hz), 6.84 (2 H, td, *J* = 7.7 and 1.6 Hz), 6.59 (2 H, t, *J* = 7.2 Hz), 6.52 (2 H, d, *J* = 7.9 Hz), 2.72 (4 H, t, *J* = 7.2 Hz), 2.07 (2 H, quintet, *J* = 7.2 Hz); ^{13}C δ 152.27, 133.94, 132.64 (d, *J* = 9.8 Hz), 131.56 (d, *J* = 2.6 Hz), 131.15 (d, *J* = 99.9 Hz), 128.44 (d, *J* = 11.9 Hz), 127.68, 121.63 (d, *J* = 9.3 Hz), 119.39 (d, *J* = 22.3 Hz), 117.13, 91.67, 81.97, 29.05, 19.68.

Iminophosphorane 137b. The same procedure was repeated as described for **137a** except that a

solution of 1.10 g (3.64 mmol)of **136b** and 3.224 g (7.64 mmol) of Ph_3PBr_2 in 2.04 mL of anhydrous triethylamine and 40 mL of anhydrous benzene was heated under reflux for 4 h. Purification by column chromatography afforded 0.882 g (1.07 mmol, 29%) of **137b** as a white solid: IR 1583, 1477, 1436, 717, 694 cm^{-1}; ^1H δ 7.85–7.77 (12 H, m), 7.51–7.38 (18 H, m), 7.30 (2 H, dt, *J* = 7.7 and 2.1 Hz), 6.80 (2 H, td, *J* = 7.9 and 1.9 Hz), 6.56 (2 H, t, *J* = 7.42 Hz), 6.47 (2 H, d, *J* = 7.9 Hz), 2.47 (4 H, t, *J* = 6.2 Hz), 1.74–1.64 (6 H, m); ^{13}C δ 152.34, 132.94, 132.70 (d, *J* = 9.8 Hz), 131.57 (d, *J* = 2.6 Hz), 131.36 (d, *J* = 99.9 Hz), 128.44 (d, *J* = 11.9 Hz), 127.64, 121.58 (d, *J* = 9.3 Hz), 119.43 (d, *J* = 22.3 Hz), 117.14, 92.25, 81.50, 28.95, 28.70, 20.05.

Carbodiimide 138a. A mixture of 1.096 g (4.00 mmol) of **136a**, 3.518 g (8.33 mmol) of Ph_3PBr_2, 2.2 mL of anhydrous triethylamine, and 40 mL of anhydrous benzene was heated under reflux for 5 h. Triethylammonium bromide was removed by filtration, and the filtrate was concentrated. The crude **137a** was used directly without further purification. To the crude **137a** in 20 mL of anhydrous benzene was introduced via cannula a solution of 0.953 g (8.01 mmol) of phenyl isocyanate in 60 mL of anhydrous benzene under a nitrogen atmosphere at rt. After 4 h, the reaction mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (silica gel/5% diethyl ether in hexanes) to afford 0.941 g (1.98 mmol, 49% overall yield from **136a**) of **138a** as a yellow oil: IR (neat) 2136, 2102, 1590, 1482, 754 cm^{-1}; ^1H δ 7.37 (2 H, dd, *J* = 7.7 and 1.7 Hz), 7.3–7.18 (10 H, m), 7.13–7.06 (6 H, m), 2.11 (4 H, t, *J* = 7.2 Hz), 1.48 (2 H, quintet, *J* = 7.2 Hz); ^{13}C δ 139.05, 138.78, 133.69, 133.11, 129.34, 128.64, 125.20, 124.33, 124.22, 120.54, 97.51, 77.35, 26.94, 18.93; MS *m/z* 476 (M^+), 359, 277, 194; HRMS calcd for $C_{33}H_{24}N_4$ 476.2001, found 476.2012.

The carbodiimide **138a** was also obtained by treatment of the purified **137a** with phenyl

isocyanate. To 0.156 g of **137a** (0.196 mmol) in 10 mL of anhydrous benzene was introduced via cannula a solution of 0.047 g of phenyl isocyanate (0.39 mmol) in 5 mL of anhydrous benzene under a nitrogen atmosphere at rt. After 4 h, the reaction mixture was concentrated *in vacuo*, and the residue was purified by flash chromatography (silica gel/2% diethyl ether in hexanes) to afford 0.067 g (0.141 mmol, 72%) of **138a**.

Carbodiimide 138b. The same procedure was repeated as described for **138a** except that a mixture of 0.305 g (1.01 mmol) of **136b**, 0.895 g (2.12 mmol) of Ph_3PBr_2, 0.57 mL of anhydrous triethylamine, and 30 mL of anhydrous benzene was heated under reflux for 5 h. To the crude **137b** in 10 mL of anhydrous benzene was introduced via cannula a solution of 0.240 g (2.02 mmol) of phenyl isocyanate in 30 mL of anhydrous benzene under a nitrogen atmosphere at rt. After 4 h, the reaction mixture was concentrated, and the residue was purified by column chromatography (silica gel/2–5% diethyl ether in hexanes) to afford 0.276 g (0.55 mmol, 54% overall yield from **136b**) of **138b** as a colorless liquid: IR (neat) 2135, 1591, 1482 cm^{-1}; ^1H δ 7.38 (2 H, dd, *J* = 7.7 and 1.7 Hz), 7.33–7.19 (10 H, m), 7.16–7.03 (6 H, m), 2.02 (4 H, t, *J* = 6.4 Hz), 1.29 (6 H, m); ^{13}C δ 139.19, 138.73, 133.75, 133.05, 129.34, 128.50, 125.21, 125.14, 124.33, 124.25, 120.76, 98.66, 76.91, 28.03, 27.68, 19.51; MS *m/z* 504 (M^+), 310, 281, 245, 231, 194; HRMS calcd for $C_{35}H_{28}N_4$ 504.2314, found 504.2334.

Indoloquinoline 139a. A solution of 0.246 g (0.52 mmol) of **138a** in 80 mL of *p*-xylene was heated under reflux for 5 h. After the reaction mixture was cooled to rt, the yellow precipitate was separated by centrifugation. After two cycles of heating the precipitate in 20 mL of *p*-xylene at 60 °C followed by centrifugation and decanting the supernatant liquid, the remaining solid was pumped to dryness *in vacuo* to afford 0.183 g (0.384 mmol, 74 %) of **139a** as a yellow solid:

IR 1699, 870, 755 cm^{-1}; ^{1}H (DMSO-d_6) δ 11.69 (2 H, br s, NH), 8.56 (2 H, d, *J* = 8.3 Hz), 7.99 (2 H, d, *J* = 8.4 Hz), 7.75–7.68 (4 H, m), 7.51 (2 H, t, *J* = 7.6 Hz), 7.40 (4 H, d, *J* = 3.9 Hz), 6.95 (2 H, m, *J* = 4.2 Hz), 3.96 (4 H, t, *J* = 7.3 Hz), 2.33 (2 H, m); ^{13}C (DMSO-d_6) δ 153.02, 147.01, 143.06, 141.86, 129.11, 128.23, 128.03, 124.90, 123.72, 123.45, 123.26, 120.70, 119.95, 116.00, 111.28, 30.16, 28.28; MS *m/z* 476 (M^+), 401, 375, 277, 245, 232; HRMS calcd for $C_{33}H_{24}N_4$ 476.2001, found 476.2025.

Indoloquinoline 139b. The same procedure was repeated as described for **139a** except that 0.216 g (0.428 mmol) of **138b** in 15 mL of *p*-xylene was used to afford 0.167 g (0.33 mmol, 77%) of **139b** as a yellow solid: IR (KBr) 3442, 1613, 742 cm^{-1}; ^{1}H (DMSO-d_6) δ 11.69 (2 H, s), 8.31 (2 H, d, *J* = 8.6 Hz), 8.21(2 H, d, *J* = 7.7 Hz), 7.96 (2 H, d, *J* = 8.3 Hz), 7.70 (2 H, t, *J* = 7.6 Hz), 7.56–7.43 (6 H, m), 7.27 (2 H, td, *J* = 7.7 and 1.8 Hz), 3.69 (4 H, br), 1.93 (6 H, br); ^{13}C (DMSO-d_6) δ 153.06, 146.95, 143.67, 141.93, 128.97, 128.15, 128.07, 124.70, 123.84, 123.26, 123.13, 120.97, 120.34, 115.89, 111.39, 30.30, 29.99, 28.74; MS *m/z* 504 (M^+), 245, 231; HRMS calcd for $C_{35}H_{28}N_4$ 504.2314, found 504.2292.

Carbodiimide 140. To 2.876 g (5.88 mmol) of **109g** in 10 mL of anhydrous benzene was introduced via cannula a solution of 0.471 g (2.94 mmol) of 1,4-phenylene diisocyanate in 60 mL of anhydrous benzene under a nitrogen atmosphere at rt. After 2 h, the reaction mixture was concentrated *in vacuo,* and the residue was purified by column chromatography (silica gel/2% diethyl ether in hexanes) to afford 0.75 g (1.29 mmol, 44%) of **140** as a colorless liquid: IR 2103, 836, 755 cm^{-1}; ^{1}H δ 7.39 (2 H, dm, *J* = 7.7 and 2 Hz), 7.22 (2 H, td, *J* = 6.9 and 1.7 Hz), 7.17 (4 H, s), 7.10 (4 H, t, *J* = 7.2 Hz), 2.13 (4 H, t, *J* = 6.9 Hz), 1.43 (4 H, quintet, *J* = 7.2 Hz), 1.24 (20 H, br), 0.87 (6 H, t, *J* = 6.6 Hz); ^{13}C δ 138.56, 136.28, 133.70, 133.10, 128.48, 125.33, 125.12,

124.36, 120.91, 99.10, 76.79, 31.83, 29.19, 29.12, 28.99, 28.36, 22.66, 19.80, 14.11.

Indoloquinoline 144. To a solution of 0.14 g (0.286 mmol) of **109g** in 10 mL of anhydrous *p*-xylene was added via cannula a solution of 0.023 g (0.144 mmol) of 1,4-phenylene diisocyanate in 50 mL of anhydrous *p*-xylene under a nitrogen atmosphere at rt. After 1 h, the reaction mixture was heated under reflux for 6 h. The reaction mixture was then concentrated, and the residue was purified by column chromatography (silica gel/20% diethyl ether and 5% ethanol in hexanes) to afford 0.055 g (0.094 mmol, 66%) of **144** as a yellow solid: IR 1600, 818, 735 cm^{-1}; ^{1}H δ 11.08 (2 H, s), 8.28 (2 H, d, *J* = 7.9 Hz), 8.23 (2 H, s), 7.74 (2 H, d, *J* = 8.1 Hz), 7.62 (2 H, t, *J* = 7.4 Hz), 7.43 (2 H, t, *J* = 7.3 Hz), 4.00 (2 H, ddd, *J* = 12.9, 8.7, and 4.2 Hz), 3.74 (2 H, dt, *J* = 13.4 and 8.0 Hz), 1.79 (2 H, br), 1.62 (2 H, br), 1.15–0.82 (20 H, m), 0.67 (6 H, t, *J* = 7.0 Hz); ^{1}H (DMSO-d_6) δ 11.96 (2 H, s), 8.23 (2 H, d, *J* = 8.1 Hz), 7.90 (2 H, s), 7.58 (2 H, d, *J* = 7.3 Hz), 7.53 (2 H, t, *J* = 8.1 Hz), 7.32 (2 H, t, *J* = 6.9 Hz), 3.96 (2 H, m), 3.59 (2 H, m), 1.48 (2 H, br), 1.22 (2 H, br), 1.05–0.56 (26 H, m); ^{13}C δ 152.01, 145.65, 140.35, 130.17, 126.97, 123.39, 121.49, 120.40, 119.74, 115.05, 111.28, 33.89, 31.58, 29.90, 29.18, 28.87, 22.41, 13.94; ^{13}C (DMSO-d_6) δ 151.98, 146.07, 144.40, 140.96, 130.85, 127.20, 123.61, 120.94, 120.37, 119.43, 113.94, 111.59, 32.70, 31.47, 29.48, 28.66, 28.38, 28.24, 22.33, 14.31; MS *m/z* 582 (M^+), 469, 384, 371, 272; HRMS calcd for $C_{40}H_{46}N_4$ 582.3722, found 582.3698.

Iminophosphorane 199. The reaction mixture of 0.753 g (8.0 mmol) of 4-aminopyridine, 3.72 g (8.8 mmol) of Ph_3PBr_2, 2.46 mL of anhydrous triethylamine, and 60 mL of anhydrous benzene was heated under reflux for 5 h. Triethylammonium bromide was removed by filtration, and the filtrate was concentrated. The residue was purified through a short column (silica gel/20% ethanol in diethyl ether) to furnish **199** (2.096 g, 5.921 mmol, 74%) as a light brown solid: IR

1585, 1495, 1360, 1109, 719, 694 cm^{-1}; ^{1}H δ 8.04 (2 H, d, *J* = 5.0 Hz), 7.58 (1 H, m), 6.59 (2 H, d, *J* = 5.7 Hz); ^{13}C δ 158.74, 149.41, 132.46, 132.13, 130.28, 129.54, 128.80, 118.71; MS *m/z* 355 (MH^+), 279, 257, 201, 183, 120; HRMS calcd for $C_{23}H_{20}N_2P$ (M+1) 355.1364, found 355.1386.

Aza-Ellipticine Analogue 204c. The following procedure for the preparation of **204c** is representative. To 0.354 g (1.0 mmol) of the iminophosphorane **199** in 40 mLof anhydrous *p*-xylene was introduced via cannula a solution of 0.157 g (1.0 mmol) of 2-(1-propynyl)phenyl isocyanate **133c** in 10.0 mL of anhydrous *p*-xylene under a nitrogen atmosphere at rt. After 1.5 h, the reaction mixture was heated under reflux for 15 h. The reaction mixture was then concentrated. After three cycles of washing the precipitate in 40.0 mL of diethyl ether followed by centrifugation and decanting the supernatant liquid, the remaining solid was pumped to dryness *in vacuo* to afford **204c** (0.114 g, 0.49 mmol, 49%) as a brown solid: IR 1604, 1569, 1462, 1393, 1237, 1032, 825, 740, 718 cm^{-1}; ^{1}H δ 9.68 (1 H, s), 8.73 (1 H, d, *J* = 5.9 Hz), 8.29 (1 H, d, *J* = 7.9 Hz), 7.85 (1 H, d, *J* = 5.9 Hz), 7.55 (2 H, m), 7.38 (1 H, td, *J* = 8.1 and 1.5 Hz), 3.31 (3 H, s); ^{13}C δ (DMSO-d_6) 154.96, 150.21, 149.35, 145.79, 141.82, 140.89, 129.33, 128.65, 124.56, 121.52, 120.98, 120.82, 117.73, 111.71, 14.84; MS *m/z* 233 (M^+), 205, 179, 152, 133, 116, 98, 77, 55; HRMS calcd for $C_{15}H_{11}N_3$ 233.0953, found 233.0963.

Aza-Ellipticine Analogue 204d. The same procedure was repeated as described for **204c** except that to 0.354 g (1.0 mmol) of the iminophosphorane **199** in 40 mL of anhydrous *p*-xylene was treated with a solution of 0.185 g (1.0 mmol) of 2-(1-pentynyl)phenyl isocyanate **133d** in 10.0 mL of anhydrous *p*-xylene. Purification by flash column chromatography (silica gel/5% ethanol and 20% diethyl ether in hexanes) afforded **204d** (0.133 g, 0.51 mmol, 51%) as a brown solid: IR

2870, 1602, 1462, 817, 734 cm^{-1}; ^{1}H δ 12.09 (1 H, br s, NH), 9.59 (1 H, s), 8.60 (1 H, d, *J* = 5.9 Hz), 8.06 (1 H, d, *J* = 7.9 Hz), 7.77 (1 H, d, *J* = 5.6 Hz), 7.42 (2 H, s), 7.31 (1 H, m), 3.62 (2 H, t, *J* = 7.3 Hz); ^{13}C δ (DMSO-d_6) 155.14, 155.00, 150.08, 149.48, 145.81, 145.15, 141.89, 141.74, 128.68, 124.18, 121.14, 120.91, 119.42, 117.20, 111.81, 29.71, 23.68, 14.67; MS *m/z* 261 (M^+), 232, 205, 179, 127, 77; HRMS calcd for $C_{17}H_{15}N_3$ 261.1266, found 261.1260; Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.01; H, 5.78; N, 16.04.

Aza-Ellipticine Analogue 204e. The same procedure was repeated as described for **204c** except that 0.361 g (1.02 mmol) of **199** was treated with 0.227 g (1.02 mmol) of **204e**. Purification by flash column chromatography (silica gel/10% ethanol and 20% diethyl ether in hexanes) afforded **204e** (0.253 g, 0.846 mmol, 83%) as yellow crystals: IR 3072, 2922, 1596, 1404, 1233, 822, 726 cm^{-1}; ^{1}H δ 11.12 (1 H, br s, NH), 9.50 (1 H, s), 8.73 (1 H, d, *J* = 5.9 Hz), 8.14 (1 H, d, *J* = 7.9 Hz), 7.91 (1 H, d, *J* = 5.9 Hz), 7.54 (2 H, d, *J* = 3.9 Hz), 7.32 (1 H, sextet, *J* = 3.9 Hz), 6.06 (1 H, s), 2.46 (4 H, m), 2.04 (4 H, m); ^{13}C δ 155.36, 151.28, 149.24, 146.35, 145.90, 140.88, 132.23, 129.56, 128.40, 123.52, 121.03, 119.84, 119.16, 116.54, 111.05, 29.33, 25.44, 22.97, 22.07; MS *m/z* 299 (M^+), 270, 256, 244, 219, 149, 128; HRMS calcd for $C_{20}H_{17}N_3$ 299.1422, found 299.1417.

Aza-Ellipticine Analogue 204f. The same procedure was repeated as described for **204c** except that 0.522 g of **199** (1.474 mmol) was treated with 0.323 g of phenyl isocyanate **133f** (1.474 mmol). Purification by flash column chromatography (silica gel/10% ethanol and 20% diethyl ether in hexanes) afford **204f** (0.253 g, 0.86 mmol, 58%) as a light yellow solid: IR 3063, 1610, 1594, 1387, 1242, 731, 613 cm^{-1}; ^{1}H δ 13.62 (1 H, br s, NH), 8.94 (1 H, s), 8.56 (1 H, d, *J* = 5.9 Hz), 7.81 (1 H, d, *J* = 5.9 Hz), 7.68 (3 H, m), 7.41 (2 H, dd, *J* = 6.5 Hz and 1.2 Hz), 7.18(1 H, d,

J = 7.7 Hz), 7.08 (2 H, dd, *J* = 15.6 Hz and 7.3 Hz), 6.91 (1 H, t, *J* = 7.6 Hz); ^{13}C δ 154.71, 151.26, 148.78, 145.53, 143.32, 141.20, 134.08, 129.39, 129.20, 128.96, 128.34, 122.90, 120.32, 120.27, 119.17, 118.91, 117.48, 110.98; MS *m/z* 295 (M^+),191, 84, 43; HRMS calcd for $C_{20}H_{13}N_3$ 295.1111, found 295.1124.

Iminophosphorane 205. The same procedure was repeated as described for **199** except that a mixture of 1.412 g (15.0 mmol) of 3-aminopyridine, 7.281 g (17.2 mmol) of Ph_3PBr_2, 4.61 mL of anhydrous triethylamine, and 80 mL of anhydrous benzene was heated under reflux for 5 h. The reaction mixture was purified by flash chromatography (silica gel/10% ethanol in hexanes) to furnish **205** (4.04 g, 11.41 mmol, 76%) as a brown solid: IR 3054, 2205, 1567, 1346, 1106, 910, 713, 694, 571 cm^{-1}; ^{1}H δ 8.11 (1 H, d, *J* = 2.7 Hz), 7.87 (1 H, dd, *J* = 5.6 and 1.4 Hz), 7.73 (6 H, m), 7.48 (9 H, m), 7.04 (1 H, d, J = 8.2 Hz), 6.91 (1 H, dd, J = 8.2 and 4.6 Hz); ^{13}C δ 147.56, 145.07, 138.33, 132.44, 131.91, 130.29, 129.36, 128.72, 123.28; MS *m/z* 355 (MH^+), 279, 201, 183; HRMS calcd for $C_{23}H_{20}N_2P$ (M+1) 355.1364, found 355.1368.

Aza-Ellipticine Analogue 209d and Aza-Ellipticine Analogue 212d. The following procedure for the preparation of **209d** and **212d** is representative. To 0.354 g (1.0 mmol) of the iminophosphorane **205** in 40.0 mL of anhydrous *p*-xylene was introduced via cannula a solution of 0.185 g (1.0 mmol) of 2-(1-pentynyl)phenyl isocyanate **133d** in 10.0 mL of anhydrous *p*-xylene under a nitrogen atmosphere at rt. After 1.5 h, the reaction mixture was heated under reflux for 15 h. The reaction mixture was then concentrated, and the residue was purified by column chromatography (silica gel/10% ethanol and 20% diethyl ether in hexanes) to afford **209d** (0.174 g, 0.667 mmol, 67%) and **212d** (0.013 g, 0.0498 mmol, 5%) as brown solids. **209d**: IR 1613, 1457, 817, 764, 720 cm^{-1}; ^{1}H δ 11.32 (1 H, br s, NH), 8.91 (1 H, dd, *J* = 4.2 and 3.1

Hz), 8.27 (1 H, dd, *J* = 8.4 and 1.4 Hz), 8.12 (1 H, d, *J* = 7.9 Hz), 7.50 (3 H, m), 7.30 (1 H, m), 3.28 (2 H, t, *J* = 8.0 Hz), 1.91 (2 H, sextet, *J* = 7.7 Hz), 1.20 (3 H, t, *J* = 7.4 Hz); ^{13}C δ 152.66, 146.54, 146.35, 141.38, 141.17, 139.48, 134.58, 128.08, 124.06, 123.42, 121.47, 120.71, 119.09, 110.86, 29.55, 22.76, 14.72; MS *m/z* 261 (M^+), 246, 233, 219, 130; HRMS calcd for $C_{17}H_{15}N_3$ 261.1266, found 261.1265; Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.27; H, 5.79; N, 16.05. **212d**: IR 2922, 1614, 1472, 1263, 797, 726 cm^{-1}; ^{1}H δ 9.71 (1 H, br s, NH), 9.56 (1 H, s), 8.60 (1 H, d, *J* = 5.9 Hz), 8.22 (1 H, d, *J* = 7.6 Hz), 8.06 (1 H, d, *J* = 5.9 Hz), 7.59 (2 H, m), 7.38 (1 H, m), 3.64 (2 H, t, *J* = 3.9 Hz), 1.96 (2 H, sextet, *J* = 7.7 Hz); ^{13}C δ (DMSO-d_6) 153.55, 152.30, 142.68, 140.13, 129.33, 126.32, 124.70, 120.89, 120.28, 117.46, 111.74, 30.01, 23.14, 14.68; MS *m/z* 261 (M^+), 232, 205, 151; HRMS calcd for $C_{17}H_{15}N_3$ 261.1266, found 261.1261.

Aza-Ellipticine Analogue 209e and Aza-Ellipticine Analogue 212e. The same procedure was repeated as described for **209d** and **212d** except that 0.233 g **133e** (1.0 mmol) was treated with 0.354 g (1.0 mmol) of the iminophosphorane **205**. Purification by flash column chromatography (silica gel/10% ethanol and 20% diethyl ether in hexanes) afford **209e** (0.233 g, 0.78 mmol, 78%) and **212e** (0.0258 g, 0.0862 mmol, 9%) both as yellow needle. **209e**: IR 3065, 2923, 1606, 1398, 905, 729, 603 cm^{-1}; ^{1}H δ 10.73 (1 H, br s, NH), 8.97 (1 H, dd, *J* = 3.1 and 1.7 Hz), 8.39 (1 H, dd, *J* = 7.6 and 1.7 Hz), 8.33 (1 H, d, *J* = 7.9 Hz), 7.62 (1 H, dd, *J* = 8.7 and 4.2 Hz), 7.50 (2 H, m), 7.27 (1 H, m), 6.08 (1 H, m), 2.39 (1 H, d, *J* = 16.2 Hz), 2.38 (3 H, m), 2.01 (4 H, m); ^{13}C δ 153.28, 146.61, 146.54, 141.85, 141.20, 138.91, 134.35, 133.82, 128.06, 127.65, 123.78, 122.93, 121.17, 120.07, 118.51, 110.78, 29.16, 25.44, 22.98, 22.09; MS *m/z* 299 (M^+), 270, 244, 226, 197, 165, 115, 77, 57; HRMS calcd for $C_{20}H_{17}N_3$ 299.1422, found 299.1425; Anal. Calcd for

$C_{20}H_{17}N_3$: C, 80.24; H, 5.72; N, 14.04. Found: C, 80.11; H, 5.71; N, 13.91. **212e**: IR 2930, 1607, 1452, 1406, 1375, 1242, 1211, 733 cm^{-1}; ^1H δ 9.51 (1 H, s), 9.34 (1 H, br s, NH), 8.56 (1 H, d, *J* = 5.9 Hz), 8.18 (1 H, d, *J* = 7.9 Hz), 7.92 (1 H, d, *J* = 5.9 Hz), 7.56 (2 H, m), 7.31 (1 H, td, *J* = 7.9 and 1.5 Hz), 6.02 (1 H, m), 2.46 (4 H, m), 2.01 (4 H, m); ^{13}C δ 153.90, 151.00, 143.97, 141.85, 141.15, 140.03, 132.61, 129.25, 129.14, 126.38, 123.98, 120.71, 120.46, 118.93, 118.35, 111.18, 28.79, 25.42, 22.99, 22.10; MS *m/z* 299 (M^+), 270, 257, 244, 190, 155, 133, 119, 85, 71, 57; HRMS calcd for $C_{20}H_{17}N_3$ 299.1422, found 299.1418.

Aza-Ellipticine Analogue 209f and Aza-Ellipticine Analogue 212f. The same procedure was repeated as described for **209d** and **212d** except that 0.219 g (1.00 mmol) of **133f** was treated with 0.354 g (1.0 mmol) of iminophosphorane **205.** Purification by flash column chromatography (silica gel/10% ethanol and 20% diethyl ether in hexanes) afforded **209f** (0.220 g, 0.75 mmol, 75%) and **212f** (0.050 g, 0.17 mmol, 17%) both as a yellow solid. **209f**: IR 3061, 1611, 1402, 730, 699, 619 cm^{-1}; ^1H δ 9.55 (1 H, br s, NH), 8.93 (1 H, dd, *J* = 4.8 and 1.7 Hz), 8.43 (1 H, dd, *J* = 7.6 and 1.7 Hz), 7.65 (6 H, m), 7.48 (2 H, d, *J* = 3.6 Hz), 7.24 (1 H, d, *J* = 8.1 Hz), 7.04 (1 H, sextet, *J* = 4.1 Hz); ^{13}C δ 152.67, 147.60, 143.60, 141.61, 141.55, 139.24, 135.54, 134.29, 129.69, 128.70, 128.64, 123.86, 123.31, 121.04, 120.39, 119.53, 110.80; MS *m/z* 294 $(M-1)^+$, 281, 207, 73, 44; HRMS calcd for $C_{20}H_{12}N_3$ 294.1031, found 294.1034. Anal. Calcd for $C_{20}H_{13}N_3$: C, 81.34; H, 4.44; N, 14.23. Found: C, 80.58; H, 4.39; N, 14.14. **212f**: IR 3056, 1611, 1377, 728, 701 cm^{-1}; ^1H δ 10.05 (1 H, br s, NH), 9.62 (1 H, s), 8.50 (1 H, d, *J* = 5.9 Hz), 7.69 (3 H, m), 7.57 (5 H, m), 7.20 (1 H, d, *J* = 8.1 Hz), 7.05 (1 H, td *J* = 7.6 and 1.5 Hz); ^{13}C δ 153.58, 151.08, 141.96, 141.28, 141.06, 141.06, 140.45, 134.81, 129.37, 129.29, 129.22, 129.13, 126.82, 123.86, 120.48, 120.31, 119.91, 118.60, 111.07; MS *m/z* 295 (M^+), 268, 242, 207, 44; HRMS

calcd for $C_{20}H_{13}N_3$ 295.1109, found 295.1107.

Triflate 214. A solution of 0.547 g (3.0 mmol) of methyl 4-methoxysalicylate and 1.53 mL of pyridine (1.89 mmol) at 0 °C was treated dropwise with 0.555 mL (3.34 mmol) of trifluoromethanesulfonic anhydride (triflic anhydride). After 5 min of stirring at 0 °C followed by an additional 2 h of stirring at rt, the reaction mixture was heated at 40 °C for 24 h. The reaction mixture was then poured into a flask containing 20 mL of H_2O and 20 mL of Et_2O. The organic layer was separated, washed with water, 10% aq HCl, H_2O and saturated NaCl, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (silica gel/20% diethyl ether in hexanes) to furnish **214** (0.923 g, 2.94 mmol, 98%) as a pale yellow liquid: IR (neat) 1727, 1618, 1427, 1277, 1210, 1142, 832 cm^{-1}; ^1H δ 8.04 (1 H, d, *J* = 9.0 Hz), 6.96 (1 H, dd, *J* = 8.8 and 2.4 Hz), 6.76 (1 H, d, *J* = 2.2 Hz), 3.92 (3 H, s), 3.88 (3 H, s); ^{13}C δ 163.94, 163.90, 149.56, 134.06, 121.03, 116.31, 116.22, 113.35, 108.84, 55.95, 52.26; MS *m/z* 314 (M^+),283, 219, 153, 125, 107, 79, 69, 51; HRMS calcd for $C_{10}H_9F_3O_6S$ 314.0072, found 314.0086.

Methyl 4-methoxyl-2-(1-propynyl)benzoate (215). The same procedure was repeated as described for **131c** except that 2.10 g of Pd $(PPh_3)_4Cl_2$ (3.0 mmol), 0.57 g of CuI (3.0 mmol), 9.08 g of triflic salicylate **214** (29 mmol), and 16.5 mL of *N*,*N*-diisopropylethylamine (95 mmol) in 120 mL of DMF were treated with 1300 mL of gaseous propyne (58 mmol) to afford **215** (4.983 g, 24.4 mmol, 84%) as a light yellow liquid: IR (neat) 2949, 2235, 1727, 1598, 1261, 858, 779, 614 cm^{-1}; ^1H δ 7.88 (1 H, d, *J* = 8.7 Hz), 6.99 (1 H, d, *J* = 2.5 Hz), 6.82 (1 H, dd, *J* = 8.8 and 2.7 Hz), 3.87 (3 H, s), 3.82 (3 H, s), 2.13 (3 H, s); ^{13}C δ 166.00, 161.75, 132.13, 126.48, 123.60, 118.54, 113.41, 91.27, 78.35, 55.17, 51.57, 4.54; MS *m/z* 204 (M^+), 189, 173, 161, 145, 102, 76;

HRMS calcd for $C_{12}H_{12}O_3$ 204.0787, found 204.0796.

4-Methoxyl-2-(1-propynyl)benzoic Acid (216). The same procedure was repeated as described for **132c** except that **215** (0.726 g, 3.56 mmol) in 10 mL of THF was treated with 20.4 mL of 1 N NaOH to afford **216** (0.261 g, 1.374 mmol, 39%) as a white solid: IR (neat) 1671, 1594, 1210, 849, 778, 646 cm^{-1}; ^1H δ 8.05 (1 H, d, *J* = 9.0 Hz), 7.02 (1 H, d, *J* = 2.5 Hz), 6.88 (1 H, dd, 8.8 and 2.7 Hz), 3.86 (3 H, s), 2.15 (3 H, s); ^{13}C δ 169.57, 162.62, 133.55, 126.49, 122.80, 118.78, 114.04, 93.19, 78.25, 55.53, 4.84; MS *m/z* 190 (M^+), 173, 147, 135, 119, 91, 83, 63; HRMS calcd for $C_{11}H_{10}O_3$ 190.0630, found 190.0625.

4-Methoxyl-2-(1-propynyl)phenyl Isocyanate (217). The same procedure was repeated as described for **133c** except that 0.158 g (0.832 mmol) of **216** was treated with 0.12 mL of triethylamine and 0.185 mL (0.832 mmol) of DPPA to afford **217** (0.086 g, 0.46 mmol, 55%) as a light yellow liquid: IR (neat) 2262, 1513, 1204, 1032, 812, 716 cm^{-1}; ^1H δ 6.92 (1 H, d, *J* = 9.0 Hz), 6.90 (1 H, d, *J* = 3.9 Hz), 6.75 (1 H, dd, *J* = 8.7 and 3.1 Hz), 3.77 (3 H, s), 2.12 (3 H, s); ^{13}C δ 156.75, 128.23, 127.30, 124.16, 122.10, 116.34, 114.91, 95.13, 75.73, 55.53, 4.47; MS *m/z* 187 (M^+), 172, 144, 116, 89, 63, 52; HRMS calcd for $C_{11}H_9NO_2$ 187.0633, found 187.0640.

Aza-Ellipticine Analogue 218. The same procedure was repeated as described for **204c** except that 0.157 g (0.445 mmol) of **199** was treated with 0.076 g (0.404 mmol) of **217**. After three cycles of washing with diethyl ether, the solid was refluxed in 40 mL of benzene for 1 h. Then the mixture was cooled to rt followed by centrifugation and decanting the supernatant liquid. The remaining solid was pumped to dryness *in vacuo* to afford **218** (0.035 g, 0.133 mmol, 33%) as a brown solid: IR 3077, 1603, 1578, 1481, 1298, 1212, 1151, 811 cm^{-1}; ^1H δ (DMSO-d_6) 11.92 (1 H br s, NH), 9.72 (1 H, s), 8.62 (1 H, d, *J* = 6.2 Hz), 7.86 (1 H, d, *J* = 2.2 Hz), 7.80 (1 H, d, *J*

= 5.9 Hz), 7.47 (1 H, d, *J* = 8.7 Hz), 7.24 (1 H, dd, *J* = 8.7 and 2.5 Hz), 3.91 (3 H, s), 3.29 (3 H, s); ^{13}C δ (DMSO-d_6) 155.76, 154.77, 150.19, 148.58, 142.12, 142.03, 136.13, 129.83, 121.79, 121.65, 118.51, 116.84, 112.57, 108.88, 56.40, 14.99; MS *m/z* 263 (M^+), 248, 220, 192, 146, 111, 75, 57; HRMS calcd for $C_{16}H_{13}N_3O$ 263.1059, found 263.1051.

Aza-Ellipticine Analogue 219 and Aza-Ellipticine Analogue 220. The same procedure was repeated as described for **204d** except that 0.056 g (0.299 mmol) of **217** was treated with 0.117 g (0.329 mmol) of the iminophosphorane **205.** Purification by washing three times of the crude with 30 mL of Et_2O afforded **219** (0.034 g, 0.128 mmol, 43%) as a yellow solid. The mother liquid was pumped to dryness *in vacuo* and was further purified by flash column chromatography (silica gel/10% ethanol and 20% diethyl ether in hexanes) to afford **220** (0.0031 g, 0.012 mmol, 4%) as a yellow solid. **219**: IR 3075, 2989, 1582, 1490, 1463, 1209, 831, 788, 696 cm^{-1}; ^{1}H δ 8.95 (1 H, d, *J* = 3.1 Hz), 8.34 (1 H, d, *J* = 8.1 Hz), 7.78 (1 H, d, *J* = 2.0 Hz), 7.63 (1 H, dd, *J* = 4.1 and 4.5 Hz), 7.44 (1 H, d, *J* = 8.7 Hz), 7.18 (1 H, dd, *J* = 2.2 and 6.5 Hz), 3.96 (3 H, s), 3.35 (3 H, s); ^{1}H δ (DMSO-d_6) 11.78 (1 H, s), 8.91 (1 H, dd, *J* = 1.5 and 2.5 Hz), 8.34 (1 H, dd, *J* = 1.3 and 7.3 Hz), 7.80 (1 H, d, *J* = 2.5 Hz), 7.74 (1 H, dd, *J* = 3.9 and 8.4 Hz), 7.46 (1 H, d, *J* = 8.7 Hz), 7.22 (1 H, *J* = 2.4 and 7.6 Hz), 3.91 (3 H, s), 3.28 (3 H, s); ^{13}C δ (DMSO-*d6*) 154.31, 152.56, 146.50, 141.28, 141.04, 138.77, 136.63, 135.40, 124.19, 121.84, 119.54, 116.82, 112.26, 108.50, 56.33, 14.01; MS *m/z* 263 (M^+), 248, 220, 192, 166, 131, 110, 96, 78, 51; HRMS calcd for $C_{16}H_{13}N_3O$ 263.1059, found 263.1052. **220**: ^{1}H δ (DMSO-*d6*) 12.23 (1 H, s), 9.69 (1 H, s), 8.69 (2 H, s), 7.96 (1 H, d, *J* = 2.2 Hz), 7.56 (1 H, d, 8.7 Hz), 7.36 (1 H, dd, *J* = 2.2 and 6.5 Hz), 3.94 (3 H, s), 3.28 (3 H, s); MS *m/z* (M^+) 263, 248, 221, 220; HRMS calcd for $C_{16}H_{13}N_3O$ 263.1059, found 263.1057.

References

1. Horning, E. C. *Chem. Rev.* **1943**, *33*, 89.
2. Bartmess, J. E.; Griffith, S. S. *J. Am. Chem. Soc*. **1990**, *112*, 2931-2936.
3. (a) Gajewski, J. J.; Gortva, A. M. *J. Am. Chem. Soc*. **1982**, *104*, 334-335. (b) Gajewski, J. J.; Gortva, A. M. *J. Org. Chem*. **1989**, *54*, 373-378.
4. Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl*. **1969**, *8*, 556-557.
5. (a) Hasselmann, D.; Loosen, K. *Angew. Chem., Int. Ed. Engl*. **1978**, *17*, 606-608. (b) Kopecky, K. R.; Lau, M.-P. *J. Org. Chem*. **1978**, *43*, 525-526.
6. Pryor, W. A.; Graham, W. D. *J. Org. Chem*. **1978**, *43*, 770-772.
7. (a) Bailey, W. J.; Baylouny, R. A. *J. Org. Chem*. **1962**, *27*, 3476-3478. (b) Graham, W. D.; Green, J. G.; Pryor, W. A. *J. Org. Chem*. **1974**, *44*, 907-914.
8. (a) Brinker, U. H.; Fleischhauer, I. *Angew. Chem., Int. Ed. Engl*. **1979**, *18*, 396-397. (b) Andemichael, Y. W.; Wang, K. K. *J. Org. Chem*. **1992**, *57*, 796-798.
9. Zweifel, G.; Backlund, S. J. *J. Organomet. Chem*. **1978**, *156*, 159-170.
10. (a) Ruitenberg, K.; Meijer, J.; Vermeer, P. *J. Organomet. Chem*. **1981**, *217*, 267-271. (b) Baker, C. S. L.; Landor, P. D.; Landor, S. R. *J. Chem. Soc* **1965**, 4659-4664.
11. Brown, H. C.; Mandal, A. K.; Kulkarni, S. U. *J. Org. Chem*. **1977**, *42*, 1392-1398.
12. Okamura, W. H.; Peter, R.; Reischl, W. *J. Am. Chem. Soc*. **1985**, *107*, 1034-1041.
13. This work was finished by Junkai Liao in our group.
14. Vermeer, P.; Meijer, J.; Brandsma, L. *Rec Trav. Chim. Pays-Bas* **1975**, *94*, 112-114.
15. Jeffery, T. *J. Chem. Soc., Chem. Commun*. **1988**, 909-910.
16. (a) Oppolzer, W. *Synthesis* **1978**, 793. (b) Oppolzer, W. *Heterocycles* **1980,** *14*, 1615.

(c) Funk, R. L. ; Vollhardt, K. P. C. *Chem. Soc. Rev*. **1980**, *9*, 41. (d) McCullough, J. J. *Acc. Chem*. *Res*. **1980**, *13*, 270. (e) Magnus, P.; Gallagher, T; Brown, P.; Pappalardo, P. *Acc. Chem. Res*. **1984**, *17*, 35. (f) Fallis, A.G.; *Can. J. Chem*. **1984**, *62*, 183. (g) Charlton, J. L.; Alauddin, M. M. *Tetrahedron* **1987**, *43*, 2873. (h) Pindur, U; Erfanian-Abdoust, H. *Chem. Rev*. **1989**, *89*, 1681. (i)Martin, N.; Seoane, C.; Hanack, M. *Org. Prep. Proc. Intl*. **1991**, *23*, 237. (j) Oppolzer, W. in: Trost, B. M.; Fleming, I. (Eds), *Comprehensive Organic Synthesis*, Pergamon Press, New York, **1991**, *Vol.5* p. 385. (k) Chou, T.-s. *Rev. Heteroatom*. *Chem*. **1993**, *8*, 65.

17. Cava, M. P.; Deana, A. A. *J. Am. Chem. Soc*. **1959**, *81*, 4266

18. Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc*. **1980**, *102*, 863.

19. (a) Nicolaou, K. C.; Barnette, W. E.; Ma, P. *J. Org. Chem*. **1980**, *45*, 1463. (b) Oppolzer, W. Roberts, D. A.; Bird, T.G.C. *Helv. Chem. Acta*. **1979**, *62*, 2017.

20. (a) Lenihan, B. D.; Shechter, H. *J. Org. Chem*. **1998**, *63*, 2072. (b) Andemichael, Y.W.; Gu, Y. G.; Wang, K. K. *J. Org. Chem*. **1992**, *57*, 794. (c) de Fonseka, K. K.; McCullough, J. J.; Yarwood, A. J. *J. Am. Chem. Soc*. **1979**, *101*, 3277.

21. Jarvis, W. F.; Hoey, M. D.; Finocchio, A. L.; Dittmer, D. C. *J. Org. Chem*. **1988**, *53*, 5750

22. Sammes, P. G. J. *Tetrahedron* **1976**, *32*, 405.

23. Quinkert, G.; Stark, H. *Angew. Chem., Int. Ed. Engl*. **1983**, *22*, 637.

24. Hornback, J. M.; Barrows, R. D. *J. Org. Chem*. **1982**, *47*, 4285.

25. (a) Wang, K. K. *Chem. Rev*. **1996**, *96*, 207. (b) Wang, K. K.; Wang, Z.; Tarli, A. Gannett, P. *J. Am. Chem. Soc*. **1996**, *118*, 10783. (c) Andemichael, Y. W.; Huang, Y.; Wang, K. K.; *J. Org*. *Chem*. **1993**, *58*, 1651.

26. Ben-Efraim, D. A.; Sondheimer, F. *Tetrahedron Lett*. **1963**, 313.

27. Bowes, C. M.; Montecalvo, D. F.; Sondheimer, F. *Tetrahedron Lett*. **1973**, 3181.

28. Braverman, S.; Duar, Y. *Tetrahedron Lett*. **1978**, 1493.

29. (a) Brinker, U. H.; Fleischhauer, I. *Angew. Chem., Int. Ed. Engl*. **1979**, *18*, 396. (b) Okamura, W. H.; Peter, R.; Reischl, W. *J. Am. Chem. Soc*. **1985**, *107*, 1034. (c) Andemichael, Y. W.; Wang, K. K. *J. Org. Chem*. **1992**, *57*, 796. (d) Wang, K. K.; Zhang, Q.; Liao, J. *Tetrahedron Lett*. **1996**, *37*, 4087.

30. (a) Hooz, J.; Mortimer, R. *Tetrahedron Lett*. **1976**, 805. (b) Zweifel, G.; Backlund, S. J. *J. Organomet. Chem*. **1978**, *156*, 159. (c) Wrackmeyer, B.; Bihlmayer, C.; Schilling, M. *Chem. Ber*. **1983**, *116*, 3182. (d) Wang, K. K.; Chu, K. -H. *J. Org. Chem*. **1984**, *49*, 5175. (e) Chu, K. -H.; Wang, K. K. *J. Org. Chem*. **1986**, *51*, 767. (f) Wang, K. K.; Chu, K. -H.; Lin, Y.; Chen, J.-H *Tetrahedron* **1989**, *45*, 1105. (g) Wang, Z.; Wang, K. K. *J. Org. Chem*. **1994**, *59*, 4738. (h) Tarli, A.; Wang, K. K. *J. Org. Chem*. **1997**, *62*, 8841. For reviews of chemistry of organoborates, see: (i) Vaultier, M.; Carboni, B. in: Abel, E. W.; Stone, F.G.A.; Wilkinson, G. (Eds). *Comprehensive Organometallic Chemistry II*. a Review of the Literature **1982–1994**, *vol. 11*, pp 227-229, Pergamon Press, Oxford, **1995**. (j) Negishi, E.-i. *J. Organomet. Chem*. **1976**, *108*, 281.

31. (a) Johnson, F. *Chem. Rev*. **1968**, *68*, 375. (b) Hoffmann, R. W. *Chem. Rev*. **1989**, *89*, 1841.

32. Brown, H. C.; Sinclair, J. A. *J. Organomet. Chem*. **1977**, *131*, 163.

33. (a) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc*. **1965**, *87*, 395. (b) Okamura, W. H.; De Lera, A. R. in: Trost, B. M.; Fleming, I. (Eds). *Comprehensive Organic Synthesis*, Pergamon Press, New York, **1991**, *vol.5*, p. 699.

34. (a) Braverman, S.; Duar, Y.; Segev, D. *Tetrahedron Lett*. **1976**, 3181. (b) Braverman, S.; Segev, D. *J. Am. Chem. Soc*. **1974**, *96*, 1245.

35. Hopf, H.; Bohm, I.; Kleinschroth, J. *Org. Syn*. **1981**, *60*, 41.

36. Kramer, G.W.; Brown, H. C.; *J. Organomet. Chem*. **1974**, *73*, 1.

37. Skattebol, L. *J. Org. Chem*. **1966**, *31*, 2789.

38. Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes, Elsevier*, Amsterdam, **1981**, p. 157.

39. (a) Brown, H. C.; Khire, U. R.; Racherla, U. S. *Tetrahedron Lett*. **1993**, *34*, 15. (b) Brown, H. C.; Khire, U. R.; Narla, G.; Racherla, U. S. *J. Org. Chem*. **1995**, *60*, 544.

40. Alcaide, B.; Luengo, J. I.; Fernandez, F. *An. Quim., Ser. C* **1981**, *77*, 200.

41. For full reviews see: (a) Nicoloau, K. C.; Dai, W-M. *Angew Chem., Int. Ed. Engl*. **1991**, *30*, 1387-1416. (b) Maier, M. E. *Synlett*. **1995**, 13-26.

42. (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660–661. (b) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082–4090. (c) Bharucha, K. N.; Marsh, R. M.; Minto, R. E.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 3120–3121. For recent reviews, see: (d) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207–222. (e) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang. D. *Tetrahedron* **1996**, *52*, 6453–6518.

43. (a) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057–8059. (b) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 9130–9132. (c) Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I. *Tetrahedron Lett.* **1989**, *30*, 4995–4998. (d) Nagata, R.; Yamanaka, H.; Murahashi, E.; Saito, I. *Tetrahedron Lett.* **1990**, *31*, 2907–2910. (e) Wang, K. K.; Wang, Z.; Tarli, A.; Gannett, P. *J. Am. Chem. Soc.* **1996**, *118*, 10783–10791 and

references cited therein. (f) Grissom, J. W.; Klingberg, D.; Huang, D.; Slattery, B. J. *J. Org. Chem.* **1997**, *62*, 603–626 and references cited therein.

44. (a) Moore, H. W.; Yerxa, B. R. *Chemtracts* **1992**, 273–313. (b) Tarli, A.; Wang, K. K. *J. Org. Chem.* **1997**, *62*, 8841–8847.

45. (a) David, W. M.; Kerwin, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 1464–1465. (b) Hoffner, J.; Schottelius, M. J.; Feichtinger, D.; Chen, P. *J. Am. Chem. Soc.* **1998**, *120*, 376–385. (c) Braverman, S.; Duar, Y.; Freund, M. *Isr. J. Chem.* **1985**, *26*, 108–114.

46. Shi, C.; Wang, K. K. *J. Org. Chem.* **1998**, *63*, 3517–3520.

47. (a) Maier, M. E. *Synlett* **1995**, 13–26. (b) Nicolaou, K. C.; Dai, W.-H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387–1416.

48 (a) Differding, E.; Ghosez, L. *Tetrahedron Lett.* **1985**, *26*, 1647–1650. (b) Molina, P.; Alajarín, M.; Vidal, A.; Sánchez-Andrada, P. *J. Org. Chem.* **1992**, *57*, 929–939.

49. Gillmann, T.; Hulsen, T.; Massa, W.; Wocadlo, S. *Synlett* **1995**, 1257–1259.

50. Wilt, J. W.; Aznavoorian, P. M. *J. Org. Chem.* **1978**, *43*, 1285–1286.

51. Schmittel, M.; Steffen, J.-P.; Angel, M. A. W.; Engels, B.; Lennartz, C.; Hanrath, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1562–1564.

52. (a) Schmittel, M.; Steffen, J.-P.; Auer, D.; Maywald, M. *Tetrahedron Lett.* **1997**, *38*, 6177–6180. (b) Schmittel, M.; Strittmatter, M.; Kiau, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1843–1845. (c) Schmittel, M.; Kiau, S.; Siebert, T.; Strittmatter, M. *Tetrahedron Lett.* **1996**, *37*, 7691–7694. (d) Schmittel, M.; Strittmatter, M.; Vollmann, K.; Kiau, S. *Tetrahedron Lett.* **1996**, *37*, 999–1002. (e) Schmittel, M.; Maywald, M.; Strittmatter, M. *Synlett* **1997**, 165–166. (f) Schmittel, M.; Strittmatter, M.; Kiau, S. *Tetrahedron Lett.* **1995**,

36, 4975–4978. (g) Garcia, J. G.; Ramos, B.; Pratt, L. M.; Rodriguez, A. *Tetrahedron Lett.* **1995**, *36*, 7391–7394.

53. Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975–989.

54. (a) Molina, P.; Alajarín, M.; Vidal, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1277–1279. (b) Saito, T.; Ohmori, H.; Furuno, E.; Motoki, S. *J. Chem. Soc., Chem. Commun.* **1992**, 22–24. (c) Saito, T.; Ohmori, H.; Ohkubo, T.; Motoki, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1802–1803.

55. (a) Peczyńska-Czoch, W.; Pognan, F.; Kaczmarek, L.; Boratyński, J. *J. Med. Chem.* **1994**, *37*, 3503–3510. (b) Kaczmarek, L.; Balicki, R.; Nantka-Namirski, P.; Peczyńska-Czoch, W.; Mordarski, M. *Arch. Pharm.* (*Weinheim*) **1988**, *321*, 463–467.

56. After the original manuscript had been submitted for publication, a similar study was reported: Schmittel, M.; Steffen, J.–P.; Engels, B.; Lennartz, C.; Hanrath, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2371–2373.

57. Shi, C.; Zhang, Q.; Wang, K. K. *J. Org. Chem*. **1999**, *64*, 925.

58. This work was finished by Chongsheng Shi in our group.

59. Alajarín, M.; Molina, P.; Vidal, A. *J. Nat. Prod.* **1997**, *60*, 747–748.

60. (a) Sharaf, M. H. M.; Schiff, P. L., Jr.; Tackie, A. N.; Phoebe, C. H., Jr.; Martin, G. E. *J. Heterocycl. Chem.* **1996**, *33*, 239–243. (b) Cimanga, K.; De Bruyne, T.; Pieters, L.; Claeys, M.; Vlietinck, A. *Tetrahedron Lett.* **1996**, *37*, 1703–1706.

61. (a) Shioiri, T.; Ninomiya, K.; Yamada, S.-i. *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205. (b) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151–2157. (c) Rigby, J. H.;

Balasubramanian, N. *J. Org. Chem.* **1989**, *54*, 224–228.

62. Horner, L.; Oediger, H. *Justus Liebigs Ann. Chem.* **1959**, *627*, 142–162.

63. Gribble, G. W.; Saulnier, M. G. *J. Chem. Soc., Chem. Commun.* **1984**, 168–169.

64. (a) Armstrong, R. N.; Ammon, H. L.; Darnow, J. N. *J. Am. Chem. Soc.* **1987**, *109*, 2077–2082. (b) Newman, M. S.; Hussey, A. S. *J. Am. Chem. Soc.* **1947**, *69*, 3023–3027.

65. (a) Pindur, U.; Erfanian-Abdoust, H. *Liebigs Ann. Chem.* **1988**, 803–805. (b) Pindur, U.; Erfanian-Abdoust, H. *Chem. Rev.* **1989**, *89*, 1681–1689.

66. (a) Villemin, D.; Goussu, D. *Heterocycles*, **1989**, *29*, 1255–1261. (b) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581–2584. (c) Iritani, K.; Matsubara, S.; Utimoto. K. *Tetrahedron Lett.* **1988**, *29*, 1799–1802.

67. For reviews of the synthesis and biological activity of pyridocarbazoles and related compounds, see: (a) Gribble, G. W. *The alkaloids*; Brossi, A., Ed.; Academic: New York, **1990**; *Vol. 39*, p1. (b) Bergman, J.; Pelcman, B. *Tetrahedron* **1988**, *44*, 5215. (c) Kansal, V. K.; Potier, P. *Tetrahedron* **1986**, *42*, 2389. (d) Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1985**, *23*, 1277. (e) Sainsbury, M. *Synthesis* **1977**, 437.

68. Goodin, S.; Smith, A. F.; Horning, E. C. *J. Am. Chem. Soc*. **1959**, *81*, 1903.

69. Daton, L. K.; Demerac, S.; Elmes, B. C.; Loder, J. W.; Swan, J. M; Tertei, T. *Aust. J. Chem.* **1967**, *20*, 2715.

70. Kansal, V. K.; Potier, P. *Tetrahddron*, **1986**, *40*, 2389

71. (a) Rouesse, J.; Spielmann, M.; Turpin, F.; Lechevalier, T.; Azab, M.; Mondesir, J. M. Phase II study of Ellipticine Acetate Salvage Treatment of Advanced Breast Cancer. *Eur. J. Cancer*. **1993**, *29*, 856. (b) Jurayj, J.; Haugwitz, R. D.; Varma, R. K.; Paull, K. D. ; Barrett, J. B.;

Cushman, M. *J. Med. Chem*. **1994**, *37*, 2190.

72. Acton, E.M.; Narayanan, V. L.; Cushman, M.; Haugwitz, R. D.; Risbood, P.; Monks, A.; Scudiero, D.; Shoemaker, R. H.; Boyd, M. R. Anticancer Specificity of Some Ellipticinium Salt against Human Brain Tumors *in virto*. In *Proceedings of the Eighty-Third Annual Meeting of the American Association for Cancer Research*: San Diego, California, **1992**; pp 488, Abstract Number 2917.
73. Aderson, W. K.; Gopalsamy, A.; Redely, P. S.; *J. Med. Chem.* **1994**, *37*, 1955.
74. Shi, L. M.; Fan, Y.; Myers, T. G.; O'Connor, P. M.; Paull, K. D. ; Friend, S. H. ; Weinstein, J. N. *J. Chem. Inf. Comput. Sci*. **1998**, *38*, 189.
75. Davraj, R.; Barret, J. F.; Fernadez, J. A.; Katzenellenbogen, J. A.; Cushman, M. *J. Med. Chem*. **1996**, *39*, 3367
76. Woodword, R. B.; Lacobucii, G. A.; Hochstein, F. A. *J. Am. Chem. Soc*. **1960**, *82*, 1142
77. Miller, R. B.; Dugar, B. *Tetrahedron Lett*. **1989**, *30*, 297
78. (a) Rivalle, C.; Ducrocq, C.; Bisagni, E. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 138. (b) Ducrosq, C.; Bisagni, E.; Lhoste, J. M. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 142. (c) Rivalle, C.; Ducocq, C.; Bisagni, E. *J. Org. Chem*. **1980**, *45*, 2176
79. Bergman, J.; Carlson, R. *Tetrahedron Lett*. **1977**, 4663.
80. May, C.; Moody, C. J. *J. Chem. Soc., Chem. Commun*. **1984**, 926.
81. Gribble, G.W.; Saulnier, M.G.; Obaza-Nutaitis, J. A.; Ketcha, D. M. *J. Org. Chem*, **1992**, *57*, 5891.
82. Niki, y.; Tada, Y.; Yanase, N.; Hachiken, H.; Matsushita, K. *Tetrahedron Lett*. **1996**, *37*, 7753.

83. Komonova, V. V.; Semenov, A. A. *Khim. Geterotsikl. Soedin*. **1982**, 1211

84. Granwell, P. A.; Saxton, J. E. *J. Chem. Soc*. **1962**, 3842.

85. Ergun, Y.; Patir, S.; Okay, G. *J. Heterocyclic. Chem.* **1998**. *35*, 1445.

86. Dharmasena, P. M.; Shannon, P. V. R.; *Tetrahedron Lett*. **1994**, *35*, 7119.

87. Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl*. **1987**, *26*, 894.

APPENDIX

Publications Related to This Dissertation

1. "A Novel and Efficient Synthesis of 5-Aza Analogues of Ellipticine" Quan Zhang, Chongshen Shi and Kung K. Wang (manuscript in preparation for *Journal of Organic Chemistry*. **1999**, as a full paper).

2. "Biradicals from Thermolysis of *N*-[2-(1-Alkynyl)phenyl]-*N'*-phenylcarbodiimides and Their Subsequent Transformations to 6*H*-Indolo[2,3-*b*]quinolines" Chongshen Shi, Quan Zhang and Kung K. Wang. *Journal of Organic Chemistry*. **1999**, *64*, 925.

3. "Generation of *o*-Quinodimethanes via the Electrocyclic Reaction of (4*Z*)-1,2,4,6,7-Octapentaenes Derived from the Organoborate Complexes and their Subsequent Reactions" Quan Zhang and Kung K. Wang. A special issue of the *Journal of Organometallic Chemistry* with the theme *Boron Chemistry at the Millennium* (in press, **1999**, as a full paper).

4. "Synthesis of 5-Methylene-1,3-cyclohexadienes (*o*-Isotoluenes) via Electrocyclization of (4*Z*)-1,2,4,6-Heptatetraenes" Kung K. Wang, Quan Zhang and Junkai Liao. *Tetrahedron Lett*. **1996**, *37*, 4087.

5. "Biradicals from Thermolysis of *N*-[2-(1-Alkynyl)-*N'*-phenylcarbodiimides and Subsequent Transformations to 2-(Phenylamino)quinolines and 6*H*-Indolo[2,3-*b*]quinolines" Chongshen Shi, **Quan Zhang** and Kung K. Wang. Presented at the 216th National Meeting of the American Chemical Society, ORGN584, Boston, MA, **1998**.

6. "Preparation and Reactions of *o*-Quinodimethanes via Electrocyclization of (*Z*)-1,2,4,6,7-Octapentaenes Derived from Organoborate" Kung K. Wang and **Quan Zhang**. Presented at the 215th National Meeting of the American Chemical Society, ORGN306, Dallas, TX, **1998**.