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**Allene Cyclization Chemistry: Application to the Syntheses of Helical Polycyclic Aromatic
Hydrocarbons and the ABCD Ring Core of the Camptothecin Family of Alkaloids**

Weixiang Dai

**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
In
Organic Chemistry**

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Morgantown, West Virginia

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Keywords: Enyne-Allene, enallene-isonitrile, allene-nitrile, camptothecin

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ABSTRACT

Allene Cyclization Chemistry: Application to the Syntheses of Helical Polycyclic Aromatic Hydrocarbons and the ABCD Ring Core of the Camptothecin Family of Alkaloids

Weixiang Dai

Thermolysis of the benzannulated enyne-allenes provides an efficient pathway to a variety of novel helical polycyclic aromatic hydrocarbons, which are represented by a remarkably beautiful diindenophenanthrene with four congested phenyl substituents. For example, its X-ray structure shows that the four phenyl substituents are essentially parallel to one another but are virtually perpendicular to the helical axis of the diindenophenanthrene ring system. Viewing from the direction perpendicular to the helical axis, the structure resembles that of a segment of a spiral staircase having four parallel steps.

The Wagner-Meerwein rearrangement was successfully applied to 11*H*-benzo[*b*]fluorene-11-methanols and related fluorene derivatives leading to highly conjugated aromatic systems, which are prone to protonation for subsequent intramolecular electrophilic aromatic substitution reactions, leading to polycyclic aromatic hydrocarbons with novel architectures not easily attainable by other synthetic methods. Resolution of fluorenylmethanols derived from 15, 16-diaryl-diindeno[2,1-*b*:1',2'-*h*]phenanthrenes was successfully achieved by using Mosher's reagent, providing a good opportunity to obtain the pure enantiomers of the corresponding helical polycyclic aromatic hydrocarbons.

Thermolysis of the benzannulated enyne-allenes bearing a heteroaromatic substituent at the allenic terminus produced a variety of indeno-fused heteroaromatic ring systems, which are of interest as potential candidates for pharmacological applications. The simplicity of this synthetic method encouraged us to explore the corresponding enallene-isonitrile cyclizations.

Thermolysis of the pyridodiyne provides an excellent synthetic pathway to the analogs of the ABCD ring core of the camptothecin family of alkaloids. The facile thermal cyclization of the pyridodiyne compared with the corresponding benzodiyne encouraged us to explore the corresponding pyridoannulated nitrile-allene cyclizations.

Thermolysis of the pyridoannulated nitrile-allenes provides a very efficient synthetic pathway to the parent and substituted ABCD ring cores of the camptothecin family of alkaloids. This metal-free, base-catalyzed cyclization method may provide insight for new cyclization pathways and could be suitable for large scale synthesis and it represents the first successful allenic nitrile cyclization.

DEDICATED TO

My wife, Chunrong Cheng, and my parents

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CHAPTER 1

Prelude

I-1. Introduction

Allenes, two carbon-carbon double bonds connected directly, were once thought as reactive intermediates and not good materials for organic synthesis. The development of allene chemistry benefited greatly from the development of IR and Raman spectroscopy.¹ Recently, allenes have been widely used in various types of reactions including stereoselective reactions taking advantage of their substituents and axial chirality.² With the continued interest in allene chemistry, it is believed that many more new allene reactions will be discovered.

I-2. Enyne-allene cyclizations

In this dissertation, only a small branch of the allene chemistry, the enyne-allene type cyclizations, will be discussed. Enyne-allenes can undergo either Myers-Saito cyclizations³ (C^2-C^7) or Schmittel cyclizations⁴ (C^2-C^6). In a simple system such as **I-1**, the cyclization pathway depends on the alkynyl terminus substituent R (Scheme I-1). When R is a proton group or a 1° alkyl group, such as the methyl group or the ethyl group, the enyne-allene favors the Myers-Saito cyclization pathway to produce the $\alpha,3$ -didehydrotoluene/naphthalene biradical **I-2**; when R is an aryl group or a sterically demanding group, such as the *tert*-butyl group or the trimethylsilyl group, the enyne-allene favors the Schmittel cyclization pathway to produce the fulvene/benzofulvene biradical **I-3**.

Scheme I-1.

I-2.1. Earlier studies of Myers-Saito cyclizations

Our group reported Myers-Saito cyclizations of (Z)-1,2,4-heptatrien-6-ynes **I-4** (Scheme I-2).⁵ When compared to the parent (Z)-1,2,4-heptatrien-6-yne, the rate of cycloaromatization of **I-4a** is increased because of the formation of a more stable tertiary benzylic radical center in **I-5a**; but the rate of cycloaromatization of **I-4b** is not significantly affected because the formation of a more stable tertiary benzylic radical center in **I-5b** partially compensates for the increased steric interactions.

Scheme I-2.

I-2.2. Earlier studies of Schmittel cyclizations

Our group reported the Schmittel cyclizations of **I-7** with a benzene tether connecting the alkyne and the allene moiety to produce the benzofulvene biradicals **I-8** (Scheme I-3).⁶ The aryl groups at the allenic terminus of the enyne-allene system could further

participate in an intramolecular radical-radical coupling to form the formal Diels-Alder adducts **I-9**, after tautomerization, the tetracyclic hydrocarbons **I-10**.

Scheme I-3.

I-3. Application of enyne-allene Schmitt cyclization in the synthesis of helical polycyclic aromatic hydrocarbons

Our group reported a novel synthetic pathway to the 4,5-diaryldiindenophenanthrenes **I-19** having a helical twist in their structures (Scheme I-4).⁷ The synthetic sequence involves condensation of the *p*-dipivaloylbenzene with 2 equiv of the lithium acetylide derived from the diacetylenes **I-11** followed by protonation to produce the propargylic alcohols **I-12**. Reduction of **I-12** with triethylsilane in the presence of trifluoroacetic acid furnished the tetraacetylenic hydrocarbons **I-13** in nearly quantitative yields. Treatment of **I-13** with potassium *tert*-butoxide under refluxing toluene at 110 °C for up to 10 h then furnished the 4,5-diaryldiindenophenanthrenes **I-19**. Apparently, the transformation from **I-13** to **I-19** involves initial prototropic isomerizations to form the benzannulated enyne-allenes **I-14**. Two subsequent formal intramolecular Diels-Alder reactions via the biradicals **I-15** and **I-17** derived from the

C²-C⁶ cyclizations then led to **I-18**, which in turn underwent tautomerizations to give **I-19**.

Scheme I-4.

I-4. Application of enyne-heteroallene (enyne-carbodiimide) Schmitt cyclization in the synthesis of heterocycles structurally related to naturally occurring alkaloids

Ellipticine **I-20**, a naturally occurring alkaloid isolated from the leaves of *Ochrosia elliptica* Labill (family Apocynaceae),⁸ and many of its derivatives were found to exhibit potent antitumor activities.⁹ The 9-azaellipticines **I-21** and **I-22** are active on topoisomerase II and initiate the cleavage of DNA,^{9b,k,l} and **I-22** has undergone

clinical trials.^{9b,c}

Our group successfully synthesized 5-azaellipticines and 5,9-diazaellipticines **I-28** by thermolysis of benzannulated and pyridannulated enyne-carbodiimides (Scheme I-5).¹⁰ It is interesting to note that the cyclizations of the enyne-carbodiimides favor the C²-C⁶ pathway (Schmitt cyclization) even when R are methyl and propyl groups.

Scheme I-5.

I-5. The goal of this dissertation

Thermolysis of the enyne-allenes (including hetero enyne-allenes) provides efficient synthetic pathways to a variety of polycyclic aromatic hydrocarbons and heterocycles.

The simplicity of preparing diverse enyne-allene (including hetero enyne-allene)

intermediates, the efficient subsequent cycloaromatization, the novel structures of the hydrocarbons and the potential pharmacological applications of the heterocycles make this method especially attractive. The research efforts of this dissertation are aimed at further application of this very interesting method to the syntheses of novel helical polycyclic aromatic hydrocarbons and naturally occurring, biologically important heterocycles.

CHAPTER 2

Synthesis of helical polycyclic aromatic hydrocarbons

II-1. Synthesis and structural characterization of a helical diindenophenanthrene compound that exhibits a structure resembling a molecular spiral staircase.

II-1.1. Introduction

The distorted structure of 4,5-disubstituted phenanthrenes^{7,11} and related compounds¹² has long been a subject of interest. The nonbonded steric interactions between the two substituents at the C4 and C5 positions cause them to bend away from the mean plane of the aromatic system and exert a torsional force that produces a helical twist of the aromatic framework. The X-ray crystallographic structure of 4,5-dimethylphenanthrene (**II-1**) shows a 28° twist between the mean planes of the two outer aromatic rings (planes 1–2–3–4–4a–10a and 4b–5–6–7–8–8a).^{11b} The twist of the corresponding aromatic rings of **I-19a** (rings B and C), a diindeno-fused 4,5-diphenylphenanthrene, was more pronounced at 46°. ⁷ In addition, the two phenyl substituents are oriented essentially parallel to each other (within 1.3°), but are at a 53.1° angle from the diindenophenanthrene system as indicated by X-ray structure analysis. The presence of a helical twist in **I-19a** could also be discerned from its ¹H NMR spectrum with a set of AB quartet signals ($J = 21.0$ Hz) from the diastereotopic methylene hydrogens on the five-membered rings.

II-1

I-19a

II-1.2. Results and discussion

Our continued interest in nonplanar polycyclic aromatic compounds led us to apply

the synthetic sequence developed for **I-19a** to the construction of **II-8** having two additional phenyl substituents at the two outermost aromatic rings (Scheme II-1). Conversion of **II-2**,¹³ prepared from 1,1'-biphenyl-2-ol, to triflate **II-3** followed by coupling with phenylacetylene produced **II-4**, which was then treated with dimethyl (1-diazo-2-oxopropyl)phosphonate and K_2CO_3 ¹⁴ to afford diyne **II-5**. The transformations from **II-5** to **II-8** are similar to what were reported previously for **I-19a**. Condensation between 2 equiv of **II-5** and *p*-dipivaloylbenzene produced **II-6**, which was then reduced to furnish **II-7**. Treatment of **II-7** with potassium *t*-butoxide under refluxing *p*-xylene then produced **II-8** in a single operation. The transformation from **II-7** to **II-8** presumably involved two prototropic acetylene to allene rearrangements of the two internal acetylenic moieties followed by two formal intramolecular Diels–Alder reactions and subsequent prototropic rearrangements of the resulting Diels–Alder adduct as described previously for **I-19a**.

The X-ray structure of **II-8** (Figure II-1) shows that the four phenyl substituents are essentially parallel to one another but are virtually perpendicular to the helical axis of the diindenophenanthrene system. Because the perpendicular distances of ca. 3.1 Å between the neighboring phenyl substituents are shorter than the optimum π -system van der Waals contact distance of ca. 3.4 Å,¹⁵ the phenyl substituents are not directly on top of one another but are in a skew conformation. Sighting along the line joining C1 and C16, the dihedral angle between the bonds attaching the two phenyl substituents to C1 and C16 is 53.6°, whereas viewing along the C15–C16 line the dihedral angle between the bonds connecting the two inner phenyl groups to C15 and C16 is even more pronounced at 63.5°. As a result, the two outer phenyl substituents are pointed essentially in opposite directions. Viewing along the C1–C14 line and following the direction of rotation of the helical twist, the bond connecting a phenyl

substituent to C14 is rotated 184.3° from the bond connecting a phenyl substituent to C1. The diindenophenanthrene system is also severely distorted with a 29° twist angle between the mean planes of rings A and B and a more pronounced 59° twist angle between the mean planes of rings B and C, which is substantially larger than that of **I-19a** at 46° . Viewing from the direction perpendicular to the helical axis of the diindenophenanthrene ring system, the structure of **II-8** resembles that of a segment of a spiral staircase having four parallel steps or that of a portion of a single strand DNA containing four bases.¹⁶

Scheme II-1.

Figure II-1. Molecular structure of **II-8**. Its solid structure is constrained by a crystallographic two-fold rotation axis.

Due to additional buttressing effect, the rate of racemization of **II-8** could be expected to be even slower than that of **I-19a**, which is most likely to be conformationally stable at 25 °C.^{1c} The ¹H NMR spectrum (600 MHz) of **II-8** in CDCl₃ also exhibited a set of AB quartet at δ 4.34 and 4.39 (J = 21.0 Hz) from the diastereotopic methylene hydrogens, manifesting the presence of a helical twist.

The two most upfield signals (doublet) of the aromatic hydrogens at δ 5.34 and 5.68 are attributable to the *ortho* hydrogens of the two inner phenyl substituents connected to C15 and C16. The fact that two distinct signals were observed for these *ortho* hydrogens suggests that the rate of rotation of the two inner phenyl groups is relatively slow on the NMR time scale at 25 °C. Two distinct signals attributable to the *meta* hydrogens were also observed at δ 6.03 and 6.24. This is in sharp contrast to the ¹H NMR spectrum (600 MHz) of **I-19a** at 25 °C, which showed only one signal

(doublet) at δ 6.52 for the *ortho* hydrogens and one signal (triplet) at δ 7.00 for the *meta* hydrogens. However, temperature-dependent NMR study of **I-19a** showed that at -40 °C two doublets at δ 6.46 and 6.51 for the *ortho* hydrogens and two triplets at δ 6.93 and 7.05 for the *meta* hydrogens appeared, and the coalescence temperatures were determined to be -22 and -10 °C, respectively, corresponding to rotational barriers of 12.5 and 12.6 kcal/mol at these two temperatures.

Interestingly, signals from the *ortho* and *meta* hydrogens of the two outer phenyl substituents connected to C1 and C14 of **II-8** were conspicuously missing. Instead, broad humps could be discerned on the baseline due to restricted rotation of the phenyl groups. On lowering the temperature from 25 to -20 °C, additional peaks started to appear, and at -20 °C two doublets at δ 6.21 and 6.36 attributable to the *ortho* hydrogens and two triplets at δ 6.46 and 6.73 attributable to the *meta* hydrogens could be identified. The coalescence temperatures for the *ortho* and *meta* hydrogens are 25 °C and 30 °C, respectively, corresponding to rotational barriers of 14.3 and 14.2 kcal/mol at these two temperatures. At 55 °C on a 270 MHz NMR spectrometer, a single doublet at δ 6.29 for the *ortho* hydrogens and a single triplet at δ 6.58 for the *meta* hydrogens could be clearly discerned.

Compared to the synthesis of **I-19a**, the use of diyne **II-5** bearing a phenyl substituent on the central benzene ring resulted in a lower yield for **II-8**. A model study with **II-10** revealed that the expected benzo[*b*]fluorene **II-14** was produced via a sequence of reactions involving a prototropic rearrangement to form the benzannulated enyne–allene **II-11** followed by a Schmitt cyclization reaction⁴ to form biradical **II-12**, which in turn underwent an intramolecular radical–radical coupling and a prototropic rearrangement (Scheme II-2). However, two additional adducts, **II-15** and **II-16**, were also produced. A competing intramolecular [2 + 2] cycloaddition reaction

of **II-11** could account for **II-15**. The generation of biradical **II-13** from the Myers–Saito cyclization reaction³ of **II-11** followed by trapping the aryl radical center with the phenyl substituent and a prototropic rearrangement could furnish **II-16**. Presumably, the emergence of nonbonded steric interactions between the two phenyl substituents along the pathway toward **II-14** could be responsible for an increase of its activation energy, allowing a minor portion of **II-11** to undergo the Myers–Saito cyclization reaction.¹⁷ On the other hand, the use of the diyne without a phenyl substituent on the central benzene ring produced the corresponding benzo[*b*]fluorene exclusively in 90% yield.¹⁸

Scheme II-2.

II-1.3. Conclusion

A synthetic pathway to 6,9-bis(1,1-dimethylethyl)-5,10-dihydro-1,14,15,16-tetraphenyldiindeno[2,1-*b*:1',2'-*h*]phenanthrene **II-8**, a 4,5-diphenylphenanthrene derivative, using two consecutive Schmitt cyclization reactions of a precursor bearing two benzannulated enyne-allene moieties was developed. The four phenyl substituents are in close proximity to one another and suffer from severe nonbonded steric interactions, which exert a torsional force causing a helical twist of the

diindenophenanthrene framework. The X-ray structure shows that the four phenyl substituents are essentially parallel to one another but are virtually perpendicular to the helical axis of the diindenophenanthrene system. Viewing from the direction perpendicular to the helical axis, the structure resembles that of a segment of a spiral staircase having four parallel steps or that of a portion of one strand of DNA containing four bases.

II-2 Synthesis and structural characterization of a helical 9-ring system that also exhibits a very interesting twist X-ray structure.^{7,19}

II-2.1. Introduction

We have successfully synthesized novel structures of substituted diindenophenanthrenes by using two consecutive Schmitt cyclization reactions of precursors bearing two benzannulated enyne-allene moieties. Because of the nonbonded steric interactions, the aromatic diindenophenanthrene framework exhibits a helical twist. The X-ray crystallographic structure of **I-19a**, a diindeno-fused 4,5-diphenylphenanthrene, shows a 46° twist angle between the mean planes of the rings B and C and the two phenyl substituents are oriented essentially parallel to each other (within 1.3°), but are at a 53.1° angle from the diindenophenanthrene system. The X-ray crystallographic structure of **II-8**, a 1,14,15,16-tetraphenyldiindenophenanthrene, shows a more pronounced 59° twist angle between the mean planes of the rings B and C and a 29° twist angle between the mean planes of the rings A and B and the four phenyl substituents are oriented essentially parallel to one another but are virtually perpendicular to the helical axis of the diindenophenanthrene system. The structure of **II-8** resembles that of a segment of a spiral staircase having four parallel steps or that of a portion of a single strand DNA containing four bases.

II-2.2. Results and discussion

By placing two additional phenyl substituents at the two outermost aromatic rings, the diindenophenanthrene framework of **II-8** shows a more pronounced twist than that of **I-19a**. Our continued interest in nonplanar polycyclic aromatic compounds led us to apply the synthetic sequence developed for **I-19a** and **II-8** to the construction of **II-22** having two additional phenyl rings connecting to the two outermost aromatic rings of diindenophenanthrene framework (Scheme II-3). The benzannulated enediyne **II-19** was readily prepared by the Sonogashira reaction between phenylacetylene and **II-17** to form **II-18** followed by treatment of **II-18** with dimethyl(1-diazo-2-oxopropyl)-phosphonate. The transformations from **II-19** to **II-22** are similar to what were reported previously for **I-19a** and **II-8**. Condensation between 2 equiv of **II-19** and *p*-dipivaloylbenzene produced **II-20**, which was then reduced to furnish **II-21**. Treatment of **II-21** with potassium *t*-butoxide under refluxing toluene then produced **II-22** in a single operation. The transformation from **II-21** to **II-22** presumably involved two prototropic acetylene to allene rearrangements of the two internal acetylenic moieties followed by two formal intramolecular Diels–Alder reactions and subsequent prototropic rearrangements of the resulting Diels–Alder adduct as described previously for **I-19a** and **II-8**.

The structure of **II-22** was unequivocally established by the X-ray structure analysis. It is interesting to note that the crystal structure of **II-22** does not contain a crystallographic 2-fold rotation axis. As a result, the twist angles between mean planes of rings A and B and rings C and D are slightly different, at 22° and 23° respectively, which are substantially larger than that of **I-19a** at 14° and smaller than that of **II-8** at 29°. The twist angle between B and C at 56° is also significantly larger

than that of **I-19a** at 46° and smaller than that of **II-8** at 59° . The two phenyl substituents are bent away from each other with the dihedral angle between bonds attaching phenyl substituents to the polycyclic ring system at 67.2° , which is substantially smaller than that of **I-19a** at 84.0° and larger than that of **II-8** at 63.5° . The two phenyl substituents are oriented essentially parallel to each other and the perpendicular distance between the planes of them is ca. $2.9 \text{ \AA}$ much shorter than the optimum π -system van der Waals contact distance of ca. $3.4 \text{ \AA}$ and same as that of **I-19a** and shorter than that of **II-8** at $3.1 \text{ \AA}$.

Scheme II-3.

Figure II-2. ORTEP drawing of the crystal structure of **II-22**

Due to additional buttressing effect, the rate of racemization of **II-22** could be expected to be even slower than that of **I-19a**, which is most likely to be conformationally stable at 25 °C. The ^1H NMR spectrum (270 MHz) of **II-22** in CDCl_3 also exhibited a set of AB quartet at δ 4.38 and 4.57 ($J = 21.6$ Hz) from the diastereotopic methylene hydrogens, manifesting the presence of a helical twist.

Signals from the *ortho* and *meta* hydrogens of the two phenyl substituents in **II-22** were conspicuously missing. Instead, four broad humps at δ 5.8, 6.2, 6.6 and 6.9 could be discerned on the baseline due to restricted rotation of the phenyl groups. The rotation of the two phenyl groups in **I-19a** is relatively quick because only two peaks at δ 6.52 and 7.00 are contributed to the *ortho* and *meta* hydrogens of the two phenyl substituents respectively.

Compared to the synthesis of **I-19a** and **II-8**, the use of diyne **II-19** produced a yield for **II-22** similar to the yield for **I-19a** and higher than the yield for **II-8**. Similarly, the benzannulated enediynyl propargylic alcohol **II-23** was synthesized by condensation between 2,2-dimethylpropiophenone and the benzannulated enediyne **II-19**. Reduction of **II-23** followed by treatment of the resulting **II-24** with potassium *tert*-butoxide in refluxing toluene then afforded 8-(1,1-dimethylethyl)-13-phenyl-7*H*-dibenzo[*b,g*]fluorene (**II-28**) in 80% yield along with two minor adducts **II-29** and **II-30**. Presumably, a 1,3-prototropic rearrangement of **II-24** gave the benzannulated enyne–allene **II-25**, which could undergo either a Schmitt cyclization reaction to give biradical **II-26** leading to **II-28** or a Myers–Saito cyclization reaction to form biradical **II-27** leading to **II-29** and **II-30**. On the other hand, the use of the diyne **I-11a** without a phenyl substituent on the central benzene ring and diyne **II-5** with a phenyl substituent on the central benzene ring produced the corresponding

Scheme II-4.

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II-3 Synthesis and structural characterization of novel binaphthol derivatives.

II-3.1. Introduction

We recently developed an efficient transformation of the acetylenes **I-11**, **II-5** and **II-19** to the helical polycyclic aromatic hydrocarbons.^{7, 19} The synthetic route includes only three simple steps. **1**: Condensation between 2 equiv of the acetylenes **I-11**, **II-5** and **II-19** and *p*-dipivaloylbenzene to the corresponding diols **I-12**, **II-6** and **II-20**; **2**: Reduction of diols **I-12**, **II-6** and **II-20** to the corresponding tetraacetylenic hydrocarbons **I-13**, **II-7** and **II-21**; **3**: Treatment of tetraacetylenic hydrocarbons **I-13**, **II-7** and **II-21** with potassium *t*-butoxide under refluxing toluene or *p*-xylene to the helical polycyclic aromatic hydrocarbons **I-19**, **II-8** and **II-22** in a single operation. The transformation from the tetraacetylenic hydrocarbons **I-13**, **II-7** and **II-21** to the helical polycyclic aromatic hydrocarbons **I-19**, **II-8** and **II-22** presumably involved two prototropic acetylene to allene rearrangements of the two internal acetylenic moieties followed by two formal intramolecular Diels–Alder reactions and subsequent prototropic rearrangements of the resulting Diels–Alder adducts. Our interest in enantiopure helical compounds let us replace *p*-dipivaloylbenzene with a binaphthol derivative, the diketone **II-33** taking advantage of easy availability of enantiopure binaphthol derivatives and easy resolution of binaphthol derivatives.²⁰ It is also worth noting that binaphthol itself is a very useful asymmetric catalyst,²¹ the resulting binaphthol derivatives could also be good asymmetric catalysts.

II-3.2. Results and discussion

The synthetic sequence outlined in Scheme II-5 provides an efficient route to benzannulated enediyne **II-35**. Compound **II-31** was prepared according to the reported procedure.²² Alkylation of **II-31** with 2 equiv ethyl bromide in boiling

acetone and potassium carbonate as a base produced **II-32** in excellent yield.²³ Treatment of **II-32** with 4.4 equiv butyllithium followed by dry-ice then afforded a diacid,²³ which was transformed to **II-33** directly by treated with thionyl chloride followed by *t*-butyllithium.²⁴ Condensation between **II-33** and 2 equiv of **I-11a** produced **II-34**, which was then reduced to furnish **II-35**. Treatment of **II-35** with potassium *t*-butoxide under refluxing toluene then produced **II-36** and **II-37**. Compound **II-36** contains three pairs of diastereomers because it has two chiral carbons, a binaphthol axial chirality and a potential C2 symmetry; Compound **II-37** includes two pairs of diastereomers because it only has one chiral carbon and a binaphthol axial chirality. The structures of one diastereomer of **II-36** and both diastereomers of **II-37** were established by X-ray structure analysis.

Scheme II-5.

Figure II-3. ORTEP drawing of the crystal structures of diastereomer 1 (top) and diastereomer 2 (bottom) of **II-37**

Figure II-4. ORTEP drawing of the crystal structure of diastereomer 1 of **II-36**

Supposedly, the transformation from **II-35** to **II-36** and **II-37** involved initial prototropic isomerizations of **II-35** to form the benzannulated enyne-allene **II-38** (Scheme II-6). Two subsequent C^2-C^6 cyclization reactions generated the biradical **II-39**, which in turn underwent an intramolecular radical-radical coupling to give **II-40** and **II-41**. Intermediate **II-40** underwent either a direct radical-radical coupling to give **II-36**, which could also be considered resulting from [2+2] cyclizations of both enyne-allene moieties in **II-38** or an intramolecular radical-radical coupling involving a double bond of the naphthol ring, after tautomerization, to give **II-37**,

which could also be considered resulting from [4+2] cyclization of one enyne-allene moieties and [2+2] cyclization of the other enyne-allene moieties in **II-38**. Intermediate **II-41** underwent the direct radical-radical coupling to give **II-37**.

Scheme II-6.

II-3.3. Conclusion

In summary, a binaphthol derivative, the diketone **II-33** has been used to replace *p*-dipivaloylbenzene to involve in the efficient pathway to the helical polycyclic aromatic hydrocarbons. Because of steric hindrance, thermolysis of **II-35** led to **II-36**, [2+2] cyclizations of both enyne-allene moieties in **II-38**, and **II-37**, [2+2] cyclization of one enyne-allene moiety and [4+2] cyclization of the other enyne-allene moiety in **II-38**. [4+2] cyclizations of both enyne-allene moieties in **II-38** either did not occur or occurred in very small amount because the corresponding product was not observed.

II-4 Ring expansion of polycyclic hydrocarbons by Wagner-Meerwein rearrangement.

II-4.1. Introduction

The Wagner–Meerwein rearrangement of 9-fluorenylmethanols and related fluorene derivatives provides an efficient pathway for ring expansion to form phenanthrenes.²⁵ Specifically, the phosphorous pentoxide-induced rearrangement of the parent 9-fluorenylmethanol occurs in refluxing xylene to produce phenanthrene in excellent yield (eq II-1).^{25b} We recently reported the synthesis of a variety of 11*H*-benzo[*b*]-fluorenes and related derivatives via the benzannulated enediynyl propargylic alcohols.^{6,7,18,19,26} We now report the use of these benzofluorenyl derivatives to prepare 11*H*-benzo[*b*]fluorene-11-methanols for the subsequent Wagner–Meerwein rearrangement leading to phenanthrenes having extended conjugation and bearing one or two aryl substituents at the sterically most hindered positions. The presence of these aryl substituents also allows intramolecular electrophilic aromatic substitution reactions to occur, producing polycyclic aromatic hydrocarbons with novel architectures.

II-4.2. Results and discussion

Treatment of **II-28** with LDA followed by paraformaldehyde then produced **II-42** for the subsequent Wagner–Meerwein rearrangement to furnish 14-phenylnaphth[1,2-*a*]-anthracene (**II-43**) with the phenyl substituent at one of the most sterically hindered positions in 74% yield. Because of steric hindrance, the rotation of the carbon-carbon bond attaching the phenyl substituent to the naphth[1,2-*a*]anthracene system is restricted. As a result, the ¹H NMR signals (600 MHz) of the *ortho* and *meta*

hydrogens of the phenyl substituent appeared as broad humps at δ 8.2, 7.5, 6.7, and 6.1 at 25 °C. However, at -20 °C two doublets at δ 8.24/6.14 for the *ortho* hydrogens and two triplets at δ 7.49/6.67 for the *meta* hydrogens could be clearly discerned. The coalescence temperatures were determined to be at 50 °C for the *ortho* hydrogens and at 40 °C for the *meta* hydrogens on a 270 MHz spectrometer, corresponding to rotational barriers of 14.4 kcal/mol and 14.5 kcal/mol at these two temperatures, which are slightly higher than those of 1-phenylbenzo[*a*]phenanthrenes ($\Delta G^\ddagger_{\text{rot}}$ = ca. 13 kcal/mol) reported earlier.²⁷

Scheme II-7.

The benzo[*b*]fluorene derivative **II-14**¹⁹ was also successfully employed to produce **II-44** (Scheme II-8). However, attempts to promote the Wagner–Meerwein rearrangement to give **II-45** resulted in the formation of **II-46** even under mild reaction conditions (P₂O₅, 25 °C, 5 min). The structure of **II-46** was established by X-ray structure analysis. Apparently, protonation of the initially formed **II-45** and the subsequent intramolecular electrophilic aromatic substitution reaction are very facile under the reaction condition, preventing **II-45** from being isolated. The reaction sequence of protonation followed by an intramolecular electrophilic aromatic substitution reaction is reminiscent of what was reported previously in the

transformation of 1-phenylbenzo[*a*]anthracene to dibenzo[*a,l*]pyrene (Scheme II-9).²⁸

However, the resulting **II-46** is resistant to further transformation to **II-47** on heating in refluxing *p*-xylene at 138 °C for 12 h. Apparently, it is difficult to protonate the naphthalene moiety of **II-46** for the subsequent intramolecular electrophilic aromatic substitution reaction.

Scheme II-8.

Scheme II-9.

II-4.3. Conclusion

The Wagner–Meerwein rearrangement was successfully applied to 11H-benzo[*b*]fluorene-11-methanols **II-42** and **II-44** leading to highly conjugated aromatic systems bearing one or two phenyl substituents at the most sterically hindered positions. These sterically congested aromatic systems are prone to

protonation for subsequent intramolecular electrophilic aromatic substitution reactions, leading to polycyclic aromatic hydrocarbons with novel architectures not easily attainable by other synthetic methods. The synthetic sequence is simple and straightforward, making it easily adoptable for the synthesis of other polycyclic aromatic compounds.

II-5 Resolution of polycyclic hydrocarbons.

II-5.1. Introduction

Our group successfully expanded the two five-membered rings of **I-19a** to benzene rings by the Wagner–Meerwein rearrangement (Scheme II-10).²⁹ Treatment of **I-19a** with two equiv of LDA followed by paraformaldehyde produced **II-48a-c** as a mixture of three diastereomers in a 63 (**II-48a** or **II-48b**) : 34 (**II-48c**) : 3 (**II-48a** or **II-48b**) ratio in 76% combined yield. The use of a mixture of **II-48a-c** containing all three diastereomers for two consecutive Wagner–Meerwein rearrangements, promoted by P₂O₅ in *p*-xylene at 110 °C for 15 min, was also successful, giving rise to 17,18-diphenyldibenzo[*a,o*]pentaphene (**II-49**) with the two phenyl substituents at the most sterically congested C17 and C18 positions.

Scheme II-10.

The novel helical structures of **I-19a**, **II-8**, **II-22** and **II-49** might possess unique properties associated with their inherent chirality.³⁰ In order to exploit the potential properties of these novel compounds, resolution of them is first needed. Resolution of hydrocarbons without any functional group is not easy. Since two hydroxyl groups have been introduced during the ring expansion processes, the resolution of the corresponding diols could be much easier.

II-5.2. Results and discussion

Separation of the mixture of **II-48a-c** afforded two pure diastereomers, **II-48a** or **II-48b** having C_2 symmetry and **II-48c** without C_2 symmetry. The strategy to resolve the enantiomers of **II-48a** or **II-48b** and **II-48c** is to make diastereomers from them. Treatment of **II-48a** or **II-48b** and **II-48c** with Mosher's reagent afforded the corresponding Mosher's diesters **II-50a** or **II-50b** and **II-50c** in excellent yield (Scheme II-11). These Mosher's diesters could be separated by recrystallization using the mixed solvents of ethanol and methylene chloride. In each case, we could get one pure diastereomer which was crystallized first from the solvent mixture. The two diastereomers crystallized out first happened to have different type of helices which were indicated by the opposite optical rotations. Efforts trying to do ring expansion of the Mosher's diesters were not successful. Deprotection of Mosher's diesters was achieved by using excess amount lithium aluminum hydride. The use of DME as the solvent was critical; the deprotection reaction did not work when either ethyl ether or THF was used as the solvent

Scheme II-11.

Figure II-5. ORTEP drawing of the crystal structure of **II-49**

The X-ray structure of **II-49** shows that the two phenyl groups are oriented essentially parallel to each other with the dihedral angle between bonds attaching phenyl groups to the polycyclic ring system at 68.6° . The perpendicular distance between the planes of the two nearly parallel phenyl groups is ca. $2.6 \text{ \AA}$ much shorter than the optimum π -system van der Waals contact distance of ca. $3.4 \text{ \AA}$. It is interesting to note that the crystal structure of **II-49** does not contain a crystallographic 2-fold rotation axis. The full aromatic 7-ring system is also severely distorted with a 31° twist angle between the mean planes of rings A and B and a 27° twist angle between the mean planes of rings C and D and a more pronounced 43° twist angle between the mean planes of rings B and C.

II-5.3. Conclusion

Resolution of the diols from **I-19a** using the enantiopure Mosher's reagent provides an efficient chemical method to get pure enantiomers of these novel structures.

Table II-1. Comparison of X-ray structures of **II-1**, **I-19a**, **II-8**, **II-22** and **II-49**

	twist angle between the mean planes of rings B and C	twist angle between the mean planes of rings A and B (C and D if different)	dihedral angle between bonds attaching phenyl groups to the polycyclic ring system	perpendicular distances between neighboring phenyl groups
<p>II-1</p>	28°	N/A	N/A	N/A
<p>I-19a</p>	46°	14°	84.0°	2.9 Å
<p>II-8</p>	59°	29°	53.6°, to C1 and C16 63.5°, to C15 and C16	3.1 Å
<p>II-22</p>	56°	22°, for A and B 23°, for C and D	67.2°	2.9 Å
<p>II-49</p>	43°	31°, for A and B 27°, for C and D	68.6°	2.6 Å

CHAPTER 3

Synthesis of ABCD ring core of the camptothecin family of alkaloids

III-1. Retrosynthetic analysis

III-1.1. Introduction

The potent antitumor and antibiotic activities of the camptothecin family of alkaloids have stimulated intense interest in developing synthetic methods for the parent (20S)-camptothecin (**III-1a**) and related analogues.³¹ Diverse approaches to the assembly of the pentacyclic ring structure have been reported.^{31e} The efforts have borne fruits with the approval of topotecan (**III-1b**) by the FDA for the treatment of ovarian cancer and small-lung cancer³² and irinotecan (**III-1c**) for refractory colorectal cancer.³³ Several other camptothecin analogues are also in various stages of clinical trials.

While the lactone E ring of camptothecins is essential in targeting DNA topoisomerase I,³⁴ the ABCD ring core can be modified with substituents to promote DNA binding.^{34,35} Alkaloids structurally related to camptothecin but without the E

ring such as mappicine (**III-2a**) and mappicine ketone (**III-2b**) are also biologically important compounds.³⁶

III-2a: Mappicine

III-2b: Mappicine ketone

III-1.2. Representative strategies for construction of the ABCD ring core

The major synthetic strategies for the construction of the ABCD ring core include (i) the C-ring construction approach;³⁷ (ii) the cascade radical cyclization approach;³⁸ (iii) the Friedlander condensation approach;³⁹ (iv) the Michael addition approach⁴⁰ and (v) the Diels-Alder reaction approach.⁴¹

(i) the C-ring construction approach:

Connection of the AB- and D/E fragments via an *N*-alkylation followed by a sp^2 - sp^2 carbon-carbon bond formation is straightforward. This approach is represented by the Comin's asymmetric synthesis of **III-1a** (scheme III-1).^{37d}

The AB ring fragment **III-3** was synthesized from the commercially available 2-chloro-3-formyl quinoline by treatment of TMSI and triethylsilane. Lithiation of 2-methoxy pyridine followed by trapping with a formamide gave an intermediate, which was subsequently quenched with I_2 , after reduction by $NaBH_4$, to produce the pyridine **III-4**. Deprotection of the methyl ether in **III-4** and subsequent protection of the two hydroxyl groups were conducted in one pot under TMSI/paraformaldehyde conditions to give **III-5**. Lithiation of **III-5**, addition to a keto ester, subsequent

deprotection and simultaneous lactonization were achieved in one pot to give the lactone **III-6**. Alkylation of **III-6** with **III-3** afforded **III-7**, which then underwent a Heck coupling reaction to give **III-1a**.

Scheme III-1.

(ii) the cascade radical cyclization approach:

The A and D/E fragments involved in a cascade free-radical cyclization leading to the formation of the B and C rings. This approach is represented by Curran's elegant synthesis of **III-1a** (scheme III-2).^{38e}

Treatment of 2,6-dibromopyridine with sodium methoxide, BuLi/TMSCl produced **III-8**, which was sequentially subjected to *t*-BuLi, a formamide, BuLi, and I₂ to give pyridine **III-9**. Reductive etherification of **III-9** under Et₃SiH/TFA produced ether **III-10**, which then underwent a Heck reaction to give vinyl ether **III-11**. Sharpless asymmetric dihydroxylation followed by oxidation under CaCO₃/ I₂ of **III-11**

produced lactone **III-12**, which was then treated with ICl to give **III-13**. Deprotection of the methyl ether of **III-13**, followed by a selective *N*-alkylation and a radical annulation with phenyl isonitrile then produced **III-1a**.

Scheme III-2.

(iii) the Friedlander condensation approach:

Condensation of the A and the CD/E ring fragments offered a reliable approach to prepare camptothecin analogs. This approach is represented by the following asymmetric total synthesis of **III-1a** (scheme III-3).^{39e}

Reduction of lactone **III-16** with DIBAL-H followed by mesylation and elimination produced vinyl ether **III-18**, which was then subjected to a sharpless asymmetric dihydroxylation, a subsequent oxidation and an acidic condition for the removal of the acetal protective group to give lactone **III-20**. Friedlander condensation of **III-20**

with an acetal protected amino aldehyde then produced **III-1a**.

Scheme III-3.

(iv) the Michael addition approach:

Michael addition reactions have been applied to the construction of the pyridone D ring of camptothecin. This approach is represented by Ciufolini's asymmetric total synthesis of **III-1a** (scheme III-4).^{40a}

Enzymatic resolution of **III-21**, followed by diethyl amidization and reduction with DIBAL-H then afforded the aldehyde **III-23**. Treatment of **III-24** with a lithium phosphate produced **III-25**, which was condensed with **III-23** to give enone **III-26**. Intermolecular Michael addition of the potassium enolate of 2-cyanoacetamide to **III-26** produced **III-27**, which was then treated with SeO_2 and *t*-BuOOH to form the pyridone ring and subsequently with acid to give the pyridine lactone **III-28**. Reduction of the lactone of **III-28** followed by treatment with acid then gave **III-1a**.

Scheme III-4.

(v) the Diels-Alder reaction approach

Diels-Alder reactions have been applied to the construction of the pyridine B ring and pyridone D ring of camptothecin. This approach is represented by Fortunak's asymmetric total synthesis of **III-1b** (scheme III-5).^{41b}

Michael addition between **III-30** and **III-31** followed by hydrogenolysis gave acid **III-33**. An intramolecular Diels-Alder reaction of **III-34** afforded **III-35**, which was deprotected with HBr to give amine **III-36**. Coupling of amine **III-36** with acid **III-33** produced **III-37**, which was then treated with TFA followed by DDQ to give **III-38**. Reduction of the ester and subsequent lactonization afforded **III-39**, which underwent deprotection of the methyl ether and a Mannich reaction to give **III-1b**.

Scheme III-5.

III-1.3. Potential routes employing our allene cyclization chemistry

We have applied the $\text{C}^2\text{-C}^6$ allene (heteroallene) cyclization chemistry in synthesizing a variety of 6-5-6-6 tetracyclic aromatics including those structurally related to ellipticine.^{10,42} Our continued interest in allene cyclization chemistry prompted us to

apply it to the construction of the skeleton of the potent antitumor and antibiotic camptothecin family of alkaloids.

There are two potential routes to synthesize the ABCD ring core **III-40** employing our allene cyclization chemistry.

(i) the retrosynthetic enallene-isonitrile approach:

The ABCD ring core **III-40** could be generated from the enallene-isonitrile intermediate **III-41**, which is envisioned to be made from the formanilide **III-42**.

(ii) the retrosynthetic allene-nitrile approach:

The allene-nitrile intermediate **III-43** might have a chance to undergo [4+2] cycloaddition leading to the ABCD ring core **III-40**.

III-1.4. Challenges for enallene-isonitrile approach

We envision that the enallene-isonitrile intermediate **III-41** will be prepared from the 2-alkynylformanilide **III-42**. The challenges are that we need to generate the two active functionalities, the allene and the isonitrile, at the same time. Otherwise:

(i) if the isonitrile is generated first:

Benzannulated enyne-isonitriles could undergo nucleophile-induced cyclization under mild conditions to give the 2,3-disubstituted quinolines,⁴³ which will be very difficult to avoid.

(ii) if the allene is generated first:

Compounds **III-49** will be easy to undergo intramolecular cyclization to form compounds **III-50** under mild conditions,⁴⁴ which also will be difficult to avoid.

III-1.5. Challenges for allene-nitrile approach

Enediynes, enyne-allenes (including heteroallenes) and enyne-isonitriles have found success in organic synthesis, but the use of the isoelectronic nitrile group as a substitute for the alkynyl group was less successful. (Z)-2,4,5-Hexatrienenitriles **III-51** showed remarkable thermal stability at 150 to 260 °C⁵ and the related compound **III-52** polymerized at 150 °C.⁴⁵

III-51, R = Me or *t*-Bu

III-52

III-2. Preparation for enallene-isonitrile approach: Synthesis of indeno-fused derivatives of quinolizinium salts, imidazo[1,2-a]pyridine, pyrido[1,2-a]indole, and 4H-quinolizin-4-one via benzannulated enyne-allenes

III-2.1. Introduction

Benzannulated enyne-allenes bearing an aryl substituent at the alkynyl terminus have been shown to undergo the Schmittel cyclization reaction to produce the corresponding benzofulvene biradicals under mild thermal conditions.⁴ One such example involves a potassium *t*-butoxide-promoted 1,3-prototropic rearrangement of the benzannulated enediyne **III-53** to produce in situ enyne-allene **III-54** for the subsequent Schmittel cyclization reaction to generate biradical **III-55** (Scheme III-6).¹⁸ The presence of a second phenyl substituent at the allenic terminus of **III-54** permits an intramolecular radical-radical coupling to furnish the formal Diels-Alder adduct **III-56**, which in turn undergoes a prototropic rearrangement to afford **III-57** as a benzo[*b*]fluorene derivative. Several other synthetic methods have also been reported to furnish enyne-allenes for similar cascade transformations to a variety of benzo[*b*]fluorenes and related polycyclic aromatic compounds.⁴⁶

Scheme III-6.

By placing a heteroaromatic substituent at the allenic terminus of the enyne–allene system, the cascade reaction sequence has been reported to lead to the derivatives of 10*H*-indeno[1,2-*g*]quinoline, 9*H*-fluoreno[2,3-*b*]furan, 9*H*-fluoreno[2,3-*b*]thiophene, and 5*H*- and 6*H*-indeno[2,1-*f*]indolizines.^{4b,47} A similar strategy also finds success in the enyne–carbodiimide^{10,42d} and enallene–isonitrile systems,⁴⁸ producing a variety of novel heteroaromatic compounds. We have further applied this synthetic strategy to the preparation of the indeno-fused derivatives of quinolizinium salts, imidazo[1,2-*a*]pyridine, pyrido[1,2-*a*]indole, and 4*H*-quinolizin-4-one, taking advantage of the facile 1,3-prototropic rearrangements of the corresponding benzannulated enediynes to furnish the requisite enyne–allenes for subsequent cascade transformations to heteroaromatic ring systems.

III-2.2. Results and Discussion

The synthetic sequence outlined in Scheme III-7 provides an efficient route to benzannulated enediynes **III-63a–c**. The palladium-catalyzed Sonogashira reaction between 1-bromo-2-iodobenzene and phenylacetylene produced **III-58** as reported previously.⁷ Treatment of **III-58** with butyllithium followed by iodine then afforded

III-59, which was used for a second palladium-catalyzed coupling with propargyl alcohol to give **III-60** and subsequently, after treatment with methanesulfonyl chloride and triethylamine, mesylate **III-61**. Upon exposure of **III-61** to 4-aminopyridine, 4-(dimethylamino)pyridine, and 4-methoxypyridine, the benzannulated enediynes **III-63a–c** were obtained in essentially quantitative yield.⁴⁹ Efficient transformations of **III-63a–c** to the indeno-fused quinolizinium methanesulfonates **III-67a–c** were achieved also in essentially quantitative yield with triethylamine in ethanol. The products **III-67a–c** appeared to be free of other byproducts as judged by ¹H NMR spectra without the need for purification by column chromatography. The structures of **III-67a–c** were established by X-ray structure analyses. Presumably, a 1,3-prototropic rearrangement of **III-63** occurred to give the corresponding benzannulated enyne–allenes **III-64**, which then underwent either a concerted Diels–Alder reaction or a two-step process involving a Schmitt cyclization reaction to form biradical **III-65** followed by an intramolecular radical–radical coupling to afford **III-66**. A subsequent prototropic rearrangement then produced the indeno-fused quinolizinium methanesulfonates **III-67**. It is worth noting that several 2-amino-substituted quinolizinium salts and related compounds were reported to exhibit interesting biological activities and pronounced DNA-binding properties.⁵⁰

Scheme III-7.

It was reported earlier that placing a sterically demanding substituent, such as *t*-butyl or trimethylsilyl, at the alkynyl terminus of the enyne–allene system also directed the biradical-forming reaction toward the Schmitt cyclization pathway.^{4d} We have thus synthesized the benzannulated enediynes **III-71a** and **III-71b** bearing a *t*-butyl group and a trimethylsilyl group at the alkynyl terminus, respectively, as outlined in Scheme III-8. The starting iodide **III-68** was prepared by the palladium-catalyzed Sonogashira reaction between 1,2-diiodobenzene and propargyl alcohol as described previously.⁵¹ Unlike **III-63b**, which underwent cyclization on exposure to triethylamine at room temperature to form **III-67b**, it was necessary to heat the reaction mixtures of **III-71a** and **III-71b** under refluxing ethanol to produce **III-72a** and **III-72b**. It was also necessary to purify the resulting products by column chromatography because significant amounts of unidentified byproducts were present

as indicated by ^1H NMR spectra. Purification by column chromatography on neutral alumina resulted in an exchange of the mesylate anion by chloride to produce quinolizinium chlorides **III-73a** and **III-73b** in relatively low yields. The structure of **III-73a** was established by X-ray structure analysis.

Scheme III-8.

An attempt to alkylate imidazole with **III-61** in a mixture containing sodium hydroxide and tetrabutylammonium iodide to produce **III-74** resulted in the formation of the indeno-fused imidazo[1,2-*a*]pyridine **III-76** directly albeit in relatively low yield (Scheme III-9). Presumably **III-74** was formed initially, which then underwent a sodium hydroxide-promoted 1,3-prototropic rearrangement to the corresponding benzannulated enyne-allene **III-75** for the subsequent cascade reaction sequence to yield **III-76**. Alternatively, the palladium-catalyzed Sonogashira reaction between **III-59** and 1-(2-propynyl)-1*H*-imidazole (**III-77**)⁵² was employed to produce **III-74**. Under the reaction condition, a mixture of the benzannulated enediyne **III-74** and the cyclized adduct **III-76** (**III-74**:**III-76** = 1:4) was produced in 94% combined yield (Scheme III-10). Upon treatment of the mixture with potassium *t*-butoxide, **III-74**

was converted to **III-76** in essentially quantitative yield. The structure of **III-76** was established by X-ray structure analysis. A variety of imidazo[1,2-*a*]pyridine derivatives were also reported to exhibit useful pharmacological activities.⁵³

Scheme III-9.

Scheme III-10.

Unlike biradicals **III-65**, a direct intramolecular radical–radical coupling involving a π bond of the imidazole substituent of biradical **III-78** could not be achieved (Scheme III-11). Instead, a 6-*exo-trig* radical cyclization reaction involving the carbon–nitrogen double bond to form biradical **III-79** occurred and, after a prototropic rearrangement, produced **III-76**. This is reminiscent of what had been observed previously in a benzannulated enyne–allene system bearing a 1-pyrrolyl substituent at the allenic terminus.⁴⁷ It is also worth noting that because **III-81** was not observed the radical cyclization reaction did not appear to occur with the carbon–carbon double bond of the imidazole ring to give biradical **III-80**.

Scheme III-11.

The palladium-catalyzed Sonogashira reaction between **III-59** and 1-(2-propynyl)-1*H*-indole (**III-82**)⁵⁴ was successful in producing **III-83** in excellent yield (Scheme III-12). Treatment of **III-83** with potassium *t*-butoxide at room temperature for 48 hours produced the indeno-fused pyrido[1,2-*a*]indole **III-84** in 98% yield. It was reported that some pyrido[1,2-*a*]indole derivatives were unstable on exposure to air and decomposed to tarry materials in chloroform and methylene chloride solutions.⁵⁵ The ¹H NMR spectrum of **III-84** in CDCl₃, taken immediately after the solution was prepared, was found to be relatively clean. However, the solution gradually turned dark on standing at room temperature. Attempts to purify **III-84** by silica gel column chromatography also appeared to cause some decomposition.

Scheme III-12.

Similarly, **III-86** was produced from coupling between **III-59** and 1-(2-propynyl)-2(1*H*)-pyridinone (**III-85**)⁵² (Scheme III-13). Treatment of **III-86** with potassium *t*-butoxide under refluxing toluene for twelve hours produced the indeno-fused 4*H*-quinolizin-4-one **III-87** in 58% yield. The structure of **III-87** was established by X-ray structure analysis. Development of new synthetic pathways to 4*H*-quinolizin-4-ones is an area of interest because these heteroaromatic compounds could serve as precursors to naturally occurring alkaloids possessing interesting biological activities.⁵⁶

Scheme III-13.

III-2.3. Conclusions

Benzannulated enyne-allenes bearing a heteroaromatic substituent at the allenic terminus are excellent precursors of a variety of indeno-fused heteroaromatic ring systems. The use of the 1,3-prototropic rearrangement of the corresponding benzannulated enediynes to furnish enyne-allenes is especially attractive because of

simplicity of the procedure and ready availability of enediynes with diverse structural features. The resulting heteroaromatic compounds are of interest as potential candidates for pharmacological applications.

III-3. Enallene-isonitrile approach.

III-3.1. Introduction

Compounds **III-63** and **III-86** have successfully been the precursors to the tetracyclic **III-67** and **III-87**.⁵⁷ The transformations from **III-63** and **III-86** to **III-67** and **III-87** presumably involved the benzannulated enyne-allenes. Although the feasibility of generating biradicals by thermolysis of enyne-isonitriles did not appear to have been explored, the isonitrile group has been recognized as a synthon of geminal radical precursor and acceptor in radical chemistry.⁵⁸ We envisioned that replacing the enyne moieties with the reactive isonitrile, the resulting benzannulated enallene-isonitrile system might have excellent opportunities to generate biradicals under mild conditions, leading to the core heteroaromatic ring system of the camptothecin family of alkaloids.

III-3.2. Results and Discussion

Dr. Xiaoling Lu synthesized compound **III-88**, which upon exposure to POCl₃ for dehydration afforded **III-91** having the core heteroaromatic ring system of the camptothecin family of alkaloids (Scheme III-14).⁴⁸ Presumably, dehydration followed by the 1,3-prototropic rearrangement of the propargylic pyridinium salt as observed previously produced in situ **III-89**, which then underwent a sequence of reactions, including cycloaromatization, intramolecular radical-radical coupling, to **III-91**.

Dr. Xiaoling Lu also synthesized compound **III-92**, which upon exposure to POCl₃

afforded the 2-substituted indole **III-95** in essentially quantitative yield (Scheme III-15).⁴⁸ One of the pathways that could be used to account for the formation of **III-95** involves a rapid 1,3-prototropic rearrangement to produce the putative intermediate **III-93** before dehydration to form the isonitrile could occur. A subsequent intramolecular attack of the central carbon of the allenic moiety by the nitrogen of the formanilide or of the corresponding formimino phosphate could give **III-94** or a related phosphate derivative leading to **III-95**.

Scheme III-14.

Scheme III-15.

Compound **III-42** was prepared by the palladium-catalyzed cross-coupling between 2-iodoformanilide and **III-85** (Scheme III-16). Efforts to transfer **III-42** into **III-40**

were not successful. Presumably, the intermediate **III-41** was not formed, which might have chance to lead to **III-40** as the allene intermediates in synthesizing **III-67**, **III-87** and **III-91** did.^{48,57}

Scheme III-16.

Exposure of the mixture of the palladium-catalyzed cross-coupling solution between 2-iodoformanilide and **III-85** to air for a long time afforded **III-98** in essentially quantitative yield (Scheme III-17). Presumably, a rapid 1,3-prototropic rearrangement produced **III-96**, which then underwent an intramolecular cyclization leading to **III-97** as **III-93** leading to **III-95** or an intramolecular cyclization involving palladium catalyst produced **III-97** directly. **III-97** could then be oxidized to **III-98**.

Scheme III-17.

III-3.3. Conclusions

A new synthetic pathway involving the benzannulated enyne-isonitriles to

11*H*-indolizino[1,2-*b*]quinoline and related compounds was established. The successful cyclization of **III-88** to **III-91** via the benzannulated enallene-isonitrile intermediate **III-89** demonstrated that the isonitrile group could serve as a synthon of geminal radical in the biradical cyclizations. The failure of cyclizations of **III-42** and **III-92** to the corresponding tetracyclic heterocycles was probably because the corresponding benzannulated enallene-isonitriles were not formed.

III-4. Preparation for allene-nitrile approach.

III-4.1. Introduction

In the model reaction of synthesizing the ABCD ring core of camptothecin family of alkaloids, compound **III-86** only gave moderate yield of **III-87** (Scheme III-18).⁵⁷ Presumably, the transformations involved the formation of benzannulated enyne-allene intermediate **III-99**, which then underwent the C²-C⁶ cycloaddition, after tautomerization, to produce **III-87**. The pyridone ring substituent at the allenic terminus of benzannulated enyne-allene intermediate **III-99** could be responsible for the medium yield because the vinyl radical at **III-100** could then attack either carbon atom which is neighboring to the nitrogen atom on the pyridone ring.

Scheme III-18.

In order to avoid the possible loss of yield because the pyridone ring substituent is at the allenic terminus, a new system with the pyridone ring tether connecting the enyne and the possible allene moieties is needed to synthesize the polycyclic

heteroaromatics with a pyridone ring subunit.

III-4.2. Results and Discussion

Compound **III-102** was prepared by the palladium-catalyzed Sonogashira reaction between 2-bromo-6-methoxypyridine and phenylacetylene (Scheme III-19). Deprotection of the methyl ether in **III-102**,^{38k} followed by an *N*-alkylation with the propargyl bromide afforded the pyridodiyne **III-104**,⁵² which then underwent another palladium-catalyzed Sonogashira reaction with iodobenzene to produce pyridodiyne **III-105**. Thermolysis of **III-105** without any base under refluxing ethyl ethanol produced a mixture of **III-106** and **III-107**. It was worth noting that **III-105** in chloroform underwent slow cyclization reaction even at room temperature. It seemed that the cyclization reaction of **III-105** did not require the initial formation of the allene intermediate.

Scheme III-19.

Compound **III-108** was prepared by the palladium-catalyzed Sonogashira reaction between **III-104** and 2-bromopyridine (Scheme III-20). Thermolysis of **III-108** produced a mixture of **III-109** and **III-110**. It was interesting to note that the cycloaddition of **III-108** did not involve the carbon-nitrogen bond on the pyridyl ring.

If the corresponding allene intermediate was formed first, the cyclization would prefer to involve the carbon-nitrogen bond on the pyridyl ring.^{42d}

Scheme III-20.

It was interesting that thermolysis of **III-104** under refluxing *p*-xylene produced a mixture of **III-112** and **III-116** (Scheme III-21). Presumably, a direct [4+2] cycloaddition produced the cyclic allene intermediate **III-111**.⁵⁹ In the solvent of *p*-xylene, the aromatizing isomerization of **III-111** to **III-112** was slow so that a portion of **III-111** could undergo a six-electron electrocyclic opening to produce **III-113**, which was isomerized to **III-114**. [1,6]-electrocyclization of **III-114** produced the new cyclic allene intermediate **III-115**, which then underwent aromatizing isomerization to **III-116**.

Scheme III-21.

It was very encouraging to find that the thermal cyclization of the pyridodiyne **III-104** and **III-105** was easier compared with that of the corresponding benzodiyne **III-117**, **III-120**, **III-123** and **III-125** (Table III-1).^{59a} Thermal cyclization of **III-105** happened under refluxing ethyl ethanol (78 °C), but **III-117** and **III-120** required 100 °C and 170 °C respectively; thermal cyclization of **III-104** happened under refluxing *p*-xylene (138 °C), but thermal cyclization of **III-123** required 150 °C and **III-125** did not undergo cyclization even under 170 °C.

III-4.3. Conclusions

Pyridodiyne could undergo thermal cyclizations without requiring the initial formation of the corresponding allene intermediates. It provides an excellent new synthetic pathway to the analogs of the ABCD ring core of the camptothecin family of alkaloids.

Table III-1. Comparison of Thermal Cyclization of Benzodiyne and Pyridodiyne

III-5. Allene-nitrile approach.

III-5.1. Introduction

The use of nitrile group as a substitute of alkynyl group in the thermolysis of enediynes, enyne-allenes was less successful. Diels-Alder reactions involving unactivated nitriles proceed only under harsh conditions to produce pyridine exclusively.⁶⁰ But, compounds **III-104** and **III-105** are much easier to undergo the [4+2] cycloaddition compared with the corresponding benzene ring tether analogs. We envision that compound **III-43** with a pyridone ring tether connecting the nitrile and the allene moieties and with a phenyl group at the allenic terminus might have a chance to undergo either a C²-C⁶ biradical cyclization or a formal [4+2] Diels-Alder reaction. The reasons are the potential ability of the pyridone ring to activate the nitrile and the regain of the aromaticity after the cyclization reaction.

III-43

III-5.2. Results and Discussion

The synthetic sequence outlined in Scheme III-22 involved the *N*-alkylation of **III-126** with 3-bromo-1-phenylpropyne to produce **III-44** in 86% yield using Curran's protocol.⁶¹ Treatment of **III-44** with DBU produced **III-40** in essentially quantitative yield. Without DBU, **III-44** was recovered. Presumably, the transformation from **III-44** to **III-40** involved an initial 1,3-prototropic rearrangement to form the

corresponding allenic intermediate **III-43**, which underwent either a one step Diels–Alder reaction to the tetracyclic intermediate **III-128** or a C²-C⁶ cyclization to the biradical intermediate **III-127** and a subsequent intramolecular radical-radical coupling to **III-128** followed by a second prototropic rearrangement to regain aromaticity to give **III-40**.

Scheme III-22.

We next demonstrated the feasibility to incorporate substituents on the A ring. All *N*-alkylations with the methoxyl group at different positions gave excellent yields (table 1). Cyclization of **III-129** produced the only possible product **III-133** in essentially quantitative yield. Cyclization of **III-130** did not occur at the carbon connect to the methoxyl group, giving the only product **III-134** in essentially quantitative yield. Cyclization of **III-131** afforded a mixture of **III-135** and **III-136** (3 : 4) in essentially quantitative yield. The product **III-135** with the methoxyl group on the 10-position of the ABCD ring core is especially interesting.^{32,33} Compound **III-132** with methoxyl group on both ortho and meta positions produced the only

product **III-137** having a methoxyl group on the 10-position of the ABCD ring core in essentially quantitative yield.

Table III-2. *N*-alkylation and Cyclization with substituted A ring

2 equiv. propargyl bromide 2 equiv. LiBr; 1.05 equiv. NaH DME : DMF (4 : 1) 65 °C, 15 h;	1 equiv. DBU, 120 °C, immediately quantitative yield
<p>III-129, 92% X-ray</p>	<p>III-133</p>
<p>III-130, 86%</p>	<p>III-134 OMe</p>
<p>III-131, 84%</p>	<p>III-135 OMe</p>
	<p>III-136 X-ray</p>
	<p>III-135 : III-136 (3 : 4)</p>
<p>III-132, 76%</p>	<p>III-137 OMe</p>

Nitrile group has been employed for the construction of the ABCD ring core **III-40** by Bowman and Coworkers (Scheme III-23).^{38k} Treatment of **III-138** with hexamethylditin produced **III-40** via one pot cascade radical reactions in 73% yield. One of the proposed mechanism was that the vinyl radical **III-139** was initiated by the trimethyltin radical first, followed by a 5-exo cyclization onto the nitrile group to the iminyl radical intermediate **III-140**, then a 6-endo cyclization onto the carbon-carbon

double bond of the benzene ring to the tetracyclic π -radical intermediate **III-141**, after losing a hydrogen, to the ABCD ring core **III-40**. Our approach to the ABCD ring cores is in a way similar to this. If the allenic nitrile intermediates could generate the biradical intermediates, the iminyl radical of which should be more prone to attack the carbon-carbon double bond of the benzene ring and the resulting tetracyclic intermediates should also be easier to regain the aromaticity to the ABCD ring cores. But the use of the isoelectronic nitrile group as a substitute for the alkynyl group of enyne-allene systems was less successful and there is no reported C²-C⁶ allenic nitrile cyclization so far.

Scheme III-23.

Heating compound **III-138** without hexamethylditin also produced the ABCD ring core **III-40** albeit in trace amount (eq III-1), which might indicate the mechanism involving a Diels-Alder cycloaddition to the tetracyclic intermediate **III-142** followed by 1,4-conjugate elimination of HI. This could be appropriate to account for the mechanism of our approach to the ABCD ring cores. The Diels-Alder cycloaddition of unactivated nitrile group is still a challenge in organic synthesis, but the pyridone ring could activate the nitrile group. The ease to regain the aromaticity of the Diels-Alder adducts could be the driving force for the cyclization.

The bromide **III-143** was prepared by treatment of 3-(2-methoxyphenyl)-2-propyn-1-ol⁶² with methanesulfonyl chloride and triethylamine, then lithium bromide. The palladium-catalyzed Sonogashira reaction between 1-iodo-2,3-dimethoxybenzene and propargyl alcohol produced **III-144**, which was then treated with methanesulfonyl chloride and triethylamine, followed by lithium bromide to produce the bromide **III-145** (Scheme III-24).

Scheme III-24.

III-5.3. Conclusions

In conclusion, a new synthetic pathway to the parent and substituted ABCD ring cores of the camptothecin family of alkaloids has been developed. This metal-free, base-catalyzed cyclization method may provide insight for new cyclization pathways and could be suitable for large scale synthesis and it represents the first successful allenic nitrile cyclization.

Chapter 4

Experimental Section

General Experimental Methods

All reactions were conducted in oven-dried (120 °C) glassware under a nitrogen atmosphere. Diethyl ether and tetrahydrofuran (THF) were distilled from benzophenone ketyl and triethylamine was distilled over CaH₂ prior to use. Melting points were uncorrected. ¹H (270 MHz) and ¹³C (67.9 MHz) NMR spectra were recorded in CDCl₃ using CHCl₃ (¹H δ 7.26) and CDCl₃ (¹³C δ 77.00) as internal standards unless otherwise indicated.

Experimental Section of Chapter 2.1

4-(Dimethylamino)pyridine, trifluoromethanesulfonic anhydride, phenylacetylene, Pd(PPh₃)₂Cl₂, copper(I) iodide, dimethyl (2-oxopropyl)phosphonate, triethylsilane, trifluoroacetic acid, 2.5 M solution of butyllithium in hexanes, 1.0 M solution of potassium *t*-butoxide in THF, *p*-xylene (anhydrous), toluene (anhydrous), and 2,2-dimethylpropiophenone were purchased from chemical suppliers and were used as received. 2-Hydroxy-[1,1'-biphenyl]-3-carboxaldehyde (**II-2**) was prepared from 1,1'-biphenyl-2-ol according to the reported procedure.¹³ Dimethyl-(1-diazo-2-oxopropyl)phosphonate¹⁴ was prepared from dimethyl-(2-oxopropyl)phosphonate and *p*-dipivaloylbenzene⁷ was prepared from terephthaloyl chloride as reported previously.

Triflate II-3. To a mixture of **II-2** (560 mg, 2.83 mmol), 4-(dimethylamino)pyridine (17 mg, 0.14 mmol, 5 mol %) in 7 mL of methylene chloride and 7 mL of pyridine

under a nitrogen atmosphere at 0 °C was added dropwise 0.95 mL of trifluoromethanesulfonic anhydride (5.65 mmol). After 1.5 h of stirring at 0 °C, 20 mL of water was added. The resulting mixture was then extracted with diethyl ether (3 × 30 ml), and the combined organic layers were washed with 1 M HCl and brine, dried over sodium sulfate, and concentrated. Purification by flash column chromatography (silica gel/hexanes) gave **II-3** (880 mg, 95% yield) as a colorless liquid: IR 1712, 1698, 1213, 1138, 882, 766, 700 cm⁻¹; ¹H δ 10.32 (1 H, s), 8.00 (1 H, dd, *J* = 7.6, 1.8 Hz), 7.75 (1 H, dd, *J* = 7.6, 1.8 Hz), 7.61 (1 H, t, *J* = 7.6 Hz), 7.48 (5 H, s); ¹³C δ 186.9, 146.6, 137.7, 137.2, 134.7, 129.9, 129.7, 129.5, 128.9, 128.7, 118.0 (quartet, *J* = 320.4 Hz); MS *m/z* 330 (M⁺), 169.

Aldehyde II-4. To a mixture of **II-3** (375 mg, 1.14 mmol), Pd(PPh₃)₂Cl₂ (24 mg, 0.034 mmol) and copper(I) iodide (11 mg, 0.057 mmol) in 10 mL of triethylamine was added 140 mg of phenylacetylene (1.37 mmol). After 12 h of stirring at 85 °C, 10 mL of a saturated aqueous ammonium chloride solution and 20 mL of diethyl ether were added. The organic layer was separated, and the aqueous layer was back extracted with diethyl ether. The combined organic layers were washed with brine and water, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (silica gel/hexanes) afforded 276 mg of **II-4** (0.98 mmol, 86% yield) as a pale yellow solid: mp 105–106 °C; IR 2211, 1694, 1239, 756, 690 cm⁻¹; ¹H δ 10.80 (1 H, s), 7.98 (1 H, dd, *J* = 7.6, 1.3 Hz), 7.70–7.62 (3 H, m), 7.56–7.42 (4 H, m), 7.32 (5 H, s); ¹³C δ 192.3, 145.5, 139.4, 136.1, 134.8, 131.4, 129.4, 128.9, 128.4, 128.3, 128.00, 127.95, 126.0, 125.2, 122.4, 99.7, 84.4; MS *m/z*

282 (M^+), 281, 253, 252.

Benzannulated Eneidyne II-5. To a mixture of 458 mg (1.62 mmol) of **II-4** and 450 mg (3.24 mmol) of potassium carbonate in 20 mL of anhydrous methanol was added 373 mg (1.94 mmol) of dimethyl (1-diazo-2-oxopropyl)phosphonate at room temperature. After 12 h of stirring, 40 mL of diethyl ether was added, and the reaction mixture was washed with a 5% aqueous sodium bicarbonate solution, dried over magnesium sulfate, and concentrated. Purification of the residue by flash column chromatography (silica gel/ hexanes) afforded 367 mg of **II-5** (1.32 mmol, 81% yield) as a pale yellow solid: mp 76–77 °C; IR 3290, 2214, 1490, 1456, 758, 689 cm^{-1} ; ^1H δ 7.72–7.64 (2 H, m), 7.58 (1 H, dd, $J = 7.6, 1.6$ Hz), 7.54–7.27 (10 H, m), 3.43 (1 H, s); ^{13}C δ 144.3, 140.1, 131.5, 131.4, 129.8, 129.3, 128.3, 128.2, 127.9, 127.8, 127.7, 125.5, 124.6, 123.3, 96.7, 87.7, 82.6, 81.0; MS m/z 278 (M^+); HRMS calcd for $\text{C}_{22}\text{H}_{14}$ 278.1096, found 278.1085.

Propargylic Diol II-6. To a solution of 489 mg of **II-5** (1.76 mmol) in 20 mL of THF under a nitrogen atmosphere at 0 °C was added 0.70 mL of a 2.5 M solution of butyllithium (1.76 mmol) in hexanes. After 30 min of stirring, a solution of 195 mg (0.79 mmol) of *p*-dipivaloylbenzene in 20 mL of THF was introduced via cannula, and the reaction mixture was allowed to warm to room temperature. After an additional 2 h, 30 mL of water was introduced, and the reaction mixture was extracted with diethyl ether. The combined organic extracts were dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (silica gel/20% diethyl ether in hexanes) to provide 590 mg (0.74 mmol, 94% yield, 1:1

mixture of diastereomers) of **II-6** as a white solid. Some fractions were found to contain only one of the two diastereomers. Diastereomer 1 ($R_f = 0.1$): mp 218–220 °C; IR 3563, 3454, 2211 cm^{-1} ; ^1H δ 7.70–7.60 (8 H, m), 7.53–7.31 (12 H, m), 7.22 (10 H, m), 2.41 (2 H, s), 1.09 (18 H, s); ^{13}C δ 144.8, 141.0, 140.3, 131.4, 131.2, 129.3, 128.21, 128.17, 127.9, 127.6, 126.5, 125.8, 123.9, 123.2, 96.5, 96.1, 88.2, 85.0, 79.5, 39.8, 25.6; MS m/z 825 (MNa^+), 728, 666; HRMS calcd for $\text{C}_{60}\text{H}_{50}\text{O}_2\text{Na}$ (MNa^+) 825.3703, found 825.3740. Diastereomer 2 ($R_f = 0.2$): mp 90–92 °C; IR 3567, 3462, 2212 cm^{-1} ; ^1H δ 7.67–7.62 (8 H, m), 7.55–7.31 (12 H, m), 7.17 (10 H, s), 2.29 (2 H, s), 1.09 (18 H, s); ^{13}C δ 144.8, 141.1, 140.3, 131.4, 131.0, 129.4, 128.2, 127.9, 127.6, 126.6, 125.9, 124.1, 123.2, 96.5, 96.2, 88.2, 85.0, 79.5, 39.7, 25.6.

Benzannulated Eneidyne II-7. To a mixture of **II-6** (590 mg, 0.74 mmol) and triethylsilane (262 mg, 2.21 mmol) in 20 mL of methylene chloride was added 0.45 mL of trifluoroacetic acid (673 mg, 5.91 mmol). After 5 min of stirring at room temperature, 315 mg of sodium carbonate (2.96 mmol) was added followed by 10 mL of water and 50 mL of diethyl ether. The organic layer was separated, dried over sodium sulfate, and concentrated. Purification by flash column chromatography (silica gel/5% diethyl ether in hexanes) provided 536 mg (0.70 mmol, 94% yield, 1:1 mixture of diastereomers) of **II-7** as a white solid: mp 105–107 °C; IR 2228, 757, 690 cm^{-1} ; ^1H (1:1 mixture) δ 7.69–7.60 (4 H, m), 7.52–7.38 (8 H, m), 7.37–7.28 (8 H, m), 7.22 (10 H, s), 3.71 and 3.69 (2 H, two singlets, 1:1 ratio), 1.06 (18 H, s); ^{13}C (1:1 mixture) δ 144.6, 140.5, 137.45, 137.41, 131.4, 131.2, 131.1, 129.4, 129.0, 128.6, 128.1, 128.0, 127.8, 127.7, 127.5, 127.1, 127.0, 123.9, 123.8, 123.4, 123.3, 96.2, 96.1,

95.72, 95.66, 88.6, 88.5, 82.82, 82.79, 50.3, 35.6, 35.5, 27.8.

6,9-Bis(1,1-dimethylethyl)-5,10-dihydro-1,14,15,16-tetraphenyldiindeno[2,1-*b*:1',2'-*h*]phenanthrene (II-8). To a solution of 150 mg of **II-7** (0.195 mmol) in 10 mL of anhydrous *p*-xylene under a nitrogen atmosphere was added 0.40 mL of a 1.0 M solution of potassium *t*-butoxide in THF (0.40 mmol) and 0.4 mL of *t*-butyl alcohol. The reaction mixture was heated under reflux for 12 h. After the reaction mixture was allowed to cool to room temperature, 10 mL of water and 40 mL of methylene chloride were introduced, and the organic layer was separated, dried over sodium sulfate, and concentrated. Recrystallization of the residue from methylene chloride/ethanol afforded 30 mg of **II-8** (0.039 mmol, 20% yield) as a yellow solid: Compound turns black without melting at 280 °C; IR 1464, 755, 694 cm⁻¹; ¹H (600 MHz) δ 7.76 (2 H, s), 7.34 (2 H, d, J = 7.2 Hz), 7.09 (2 H, t, J = 7.2 Hz), 6.71 (2 H, t, J = 7.2 Hz), 6.7 and 6.5 (4 H, very broad), 6.68 (2 H, d, J = 7.2 Hz), 6.40 (2 H, t, J = 7.2 Hz), 6.3 (4 H, very broad), 6.24 (2 H, t, J = 7.2 Hz), 6.03 (2 H, t, J = 7.2 Hz), 5.68 (2 H, d, J = 7.2 Hz), 5.34 (2 H, d, J = 7.2 Hz), 4.39 (2 H, d, J = 21.0 Hz), 4.34 (2 H, d, J = 21.0 Hz), 1.84 (18 H, s). The decoupling experiments showed that the doublet at δ 5.34 is coupled to the triplet at δ 6.03, whereas the doublet at δ 5.68 is coupled to the triplet at δ 6.24. The triplets at δ 6.40 and 6.71 are assigned to the *para* hydrogens of the two inner phenyl substituents and the *para* hydrogens of the two outer phenyl substituents, respectively. The signals at δ 7.34, 7.09, and 6.68 are assigned to the hydrogens on C4/C11, C3/C12, and C2/C13, respectively.; ¹³C (150 MHz) δ 144.8, 142.1, 138.53, 138.50, 137.98, 137.95, 136.9, 136.0, 134.2, 132.1, 131.6, 130.7, 129.9,

129.4, 128.3, 127.7 (broad) 126.9, 125.8, 125.0, 124.6, 121.8, 121.6, 40.3, 37.9, 33.8; MS m/z 772, 771, 770 (M^+), 747, 746, 745, 731; HRMS calcd for $C_{60}H_{50}$ 770.3907, found 770.3905. The structure of **II-8** was established by X-ray structure analysis.

Calculation of rotational barriers of the *ortho* and *meta* hydrogens of the two outer phenyl substituents connected to C1 and C14 of **II-8**:

Calculated with the formula: $K_e = \pi(\delta\Delta)/2^{0.5}$ (1)

$$\Delta G^* = 4.57 T_c (10.32 + \log T_c / K_e) \quad (2)$$

K_e : exchange rate; $\delta\Delta$: difference of chemical shift (Hz); T_c : coalescence temperature.

For the *ortho* hydrogens:

$$\delta\Delta = (6.36 - 6.21) \times 600 = 90 \text{ Hz}; T_c = 298.15 \text{ K}; \Delta G^* = 14.3 \text{ kcal/mol}$$

For the *meta* hydrogens:

$$\delta\Delta = (6.73 - 6.46) \times 600 = 162 \text{ Hz}; T_c = 303.15 \text{ K}; \Delta G^* = 14.2 \text{ kcal/mol}$$

Propargylic Alcohol II-9. To a solution of 367 mg of **II-5** (1.32 mmol) in 15 mL of THF under a nitrogen atmosphere at 0 °C was added 0.53 mL of a 2.5 M solution of butyllithium (1.32 mmol) in hexanes. After 30 min of stirring, 193 mg (1.19 mmol) of 2,2-dimethylpropiophenone in 10 mL of THF was introduced via cannula, and the reaction mixture was allowed to warm to room temperature. After an additional 2 h, 30 mL of water was introduced, and the reaction mixture was extracted with diethyl ether. The combined organic extracts were dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (silica gel/hexanes:diethyl ether = 1:1) to provide 449 mg (1.02 mmol, 86% yield) of **II-9** as a viscous liquid: IR 3564, 2212, 756, 701 cm^{-1} ; ^1H δ 7.88–7.78 (2 H, m), 7.72–7.63 (2 H, m), 7.60–7.16

(14 H, m), 2.54 (1 H, br s), 1.16 (9 H, s); ^{13}C δ 144.7, 142.1, 140.3, 131.4, 131.1, 129.3, 128.2, 128.1, 127.9, 127.8, 127.6, 127.3, 127.1, 125.8, 124.0, 123.1, 96.5, 96.2, 88.2, 84.9, 79.6, 39.7, 25.6; MS m/z 463 (MNa^+), 423, 383; HRMS calcd for $\text{C}_{33}\text{H}_{28}\text{ONa}$ (MNa^+) 463.2038, found 463.2054.

Benzannulated Eneidyne II-10. To a mixture of **II-9** (367 mg, 0.835 mmol) and triethylsilane (146 mg, 1.25 mmol) in 10 mL of methylene chloride was added 0.26 mL of trifluoroacetic acid (388 mg, 3.39 mmol). After 5 min of stirring at room temperature, 359 mg of sodium carbonate (3.39 mmol) was added followed by 10 mL of water and 40 mL of diethyl ether. The organic layer was separated, dried over sodium sulfate, and concentrated. Purification by flash column chromatography (silica gel/1% diethyl ether in hexanes) provided 307 mg (0.724 mmol, 88% yield) of **II-10** as a yellow liquid: IR 2225, 758, 700 cm^{-1} ; ^1H δ 7.74–7.66 (2 H, m), 7.61–7.42 (6 H, m), 7.40–7.16 (10 H, m), 3.81 (1 H, s), 1.16 (9 H, s); ^{13}C δ 144.6, 140.5, 139.2, 131.4, 131.1, 129.8, 129.4, 128.7, 128.0, 127.8, 127.6, 127.5, 127.0, 126.6, 123.8, 123.4, 96.1, 95.6, 88.5, 82.8, 50.7, 35.5, 27.8.

Compounds II-14, II-15, and II-16. To a solution of 204 mg of **II-10** (0.481 mmol) in 10 mL of anhydrous toluene under a nitrogen atmosphere was added 0.50 mL of a 1.0 M solution of potassium *t*-butoxide in THF (0.50 mmol) and 0.5 mL of *t*-butyl alcohol. The reaction mixture was heated under reflux for 12 h. After the reaction mixture was allowed to cool to room temperature, 10 mL of water and 40 mL of diethyl ether were introduced, and the organic layer was separated, dried over sodium sulfate, and concentrated. Purification by flash column chromatography (silica

gel/hexanes) provided 116 mg (0.273 mmol, 57% yield) of **II-14** as a pale yellow solid, **II-15** (17% yield based on the ^1H NMR integration of the crude product before purification) as a pale yellow solid, and **II-16** (6% yield based on the ^1H NMR integration of the crude product before purification) as a colorless solid. Small portions of relatively pure samples of **II-15** and **II-16** were isolated for structural elucidation. **II-14**: mp 103–106 °C; IR 914, 753, 699 cm^{-1} ; ^1H δ 8.60 (1 H, d, J = 8.7 Hz), 7.71 (1 H, dd, J = 8.7, 1.6 Hz), 7.49–7.32 (2 H, m), 7.31–7.11 (2 H, m), 7.10–6.85 (7 H, m), 6.66–6.78 (4 H, m), 4.62 (2 H, s), 1.93 (9 H, s); ^{13}C δ 145.3, 143.1, 140.1, 139.4, 139.0, 138.9, 138.0, 137.4, 133.7, 131.6, 131.2, 130.1, 129.1, 129.0, 128.3, 127.8, 127.7, 127.5, 127.0, 126.9, 125.7, 125.6, 41.1, 38.9, 34.3; MS m/z 424 (M^+), 367, 289. **II-15**: ^1H δ 7.38–7.33 (4 H, m), 7.24–7.09 (8 H, m), 7.03–6.95 (4 H, m), 6.88 (2 H, t, J = 7.6 Hz), 6.45 (1 H, s), 1.19 (9 H, s). The ^1H NMR signal at δ 6.45 is attributable to the alkenyl hydrogen on the five-membered ring as observed previously in a related system.^{1c} **II-16**: mp 212–215 °C; IR 752, 701 cm^{-1} ; ^1H δ 8.43 (1 H, s), 7.96–7.90 (2 H, m), 7.84 (1 H, d, J = 7.4 Hz), 7.72–6.88 (13 H, m), 6.33 (1 H, d, J = 7.6 Hz), 4.05 (1 H, s), 1.05 (9 H, s); ^{13}C δ 142.9, 142.0, 139.7, 139.5, 136.4, 134.5, 130.6, 129.9, 129.5, 128.8, 128.4, 128.3, 127.7, 127.6, 127.5, 127.2, 126.9, 126.4, 125.8, 125.7, 123.4, 121.1, 119.5, 57.5, 35.8, 29.7. The structure of **II-16** was established by X-ray structure analysis.

Experimental Section of Chapter 2.2

1-bromo-2-naphthalenecarboxaldehyde (**II-17**) was purchased from chemical supplier and was used as received.

1-(Phenylethynyl)-2-naphthaldehyde (**II-18**). To a mixture of **II-17** (1.00 g, 4.26 mmol), Pd(PPh₃)₂Cl₂ (0.091 g, 0.13 mmol), and copper(I) iodide (0.025 g, 0.13 mmol) in 20 mL of triethylamine was added 0.478 g of phenylacetylene (4.69 mmol). After 12 h of stirring at room temperature, 20 mL of a saturated aqueous ammonium chloride solution and 40 mL of diethyl ether were added. The organic layer was separated, and the aqueous layer was back extracted with diethyl ether. The combined organic layers were washed with brine and water, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (silica gel/2% diethyl ether in hexanes) afforded 1.08 g of **II-18** (4.22 mmol, 99%) as a pale yellow solid: mp 122–123 °C; IR 1675, 758 cm⁻¹; ¹H δ 10.90 (1 H, s), 8.67–8.58 (1 H, s), 8.00 (1 H, d, *J* = 8.5 Hz), 7.95–7.86 (2 H, m), 7.75–7.64 (4 H, m), 7.49–7.42 (3 H, m); ¹³C δ 192.2, 135.8, 134.2, 133.1, 131.8, 129.4, 128.9, 128.7, 128.5, 127.7, 127.5, 127.2, 122.3, 122.1, 102.3, 82.9.

2-Ethynyl-1-(phenylethynyl)naphthalene (**II-19**). To a mixture of 0.540 g (2.11 mmol) of **II-18** and 0.582 g (4.22 mmol) of potassium carbonate in 20 mL of anhydrous methanol was added 0.486 g (2.53 mmol) of dimethyl (1-diazo-2-oxopropyl)phosphonate⁷ at room temperature. After 4 h of stirring, 40 mL of diethyl ether was added, and the reaction mixture was washed with a 5% aqueous sodium bicarbonate solution, dried over magnesium sulfate, and concentrated. Purification of the residue by flash column chromatography (silica gel/hexanes) afforded 0.398 g of **II-19** (1.58 mmol, 75%) as a pale yellow liquid: IR 3286, 819, 753 cm⁻¹; ¹H δ 8.45 (1 H, d, *J* = 8.4 Hz), 7.84 (1 H, d, *J* = 7.6 Hz), 7.77 (1 H, d, *J* =

8.4 Hz), 7.73–7.67 (2 H, m), 7.66–7.51 (3 H, m), 7.46–7.36 (3 H, m), 3.49 (1 H, s); ^{13}C δ 132.9, 132.7, 131.8, 128.7, 128.5, 128.4, 128.16, 128.13, 127.4, 127.2, 126.6, 124.7, 123.3, 123.0, 99.1, 86.2, 83.1, 81.9.

Propargylic Diol II-20. To a solution of 206 mg of **II-19** (0.82 mmol) in 10 mL of THF under a nitrogen atmosphere at 0 °C was added 0.33 mL of a 2.5 M solution of butyllithium (0.82 mmol) in hexanes. After 30 min of stirring, a solution of 91 mg (0.37 mmol) of *p*-dipivaloylbenzene in 5 mL of THF was introduced via cannula, and the reaction mixture was allowed to warm to room temperature. After an additional 2 h, 10 mL of water was introduced, and the reaction mixture was extracted with diethyl ether. The combined organic extracts were dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (silica gel/20% diethyl ether in hexanes) to provide 218 mg (0.29 mmol, 78% yield, 1:1 mixture of diastereomers) of **II-20** as a white solid. Some fractions were found to contain only one of the two diastereomers. The more polar diastereomer 1: ^1H δ 8.43 (2 H, d, J = 8.2 Hz), 7.83 (2 H, d, J = 7.4 Hz), 7.76 (2 H, d, J = 8.7 Hz), 7.65 (4 H, s), 7.64–7.49 (12 H, m), 7.35–7.28 (4 H, m), 2.42 (2 H, s), 1.09 (18 H, s); The structure of the more polar diastereomer of **II-20** was established by X-ray structure analysis. The less polar diastereomer 2: ^1H δ 8.45 (2 H, d, J = 8.2 Hz), 7.83 (2 H, d, J = 7.9 Hz), 7.76 (2 H, d, J = 8.7 Hz), 7.69 (4 H, s), 7.66–7.49 (10 H, m), 7.36–7.17 (6 H, m), 2.41 (2 H, s), 1.11 (18 H, s); ^{13}C δ 141.1, 133.2, 132.5, 131.7, 128.5, 128.3, 128.2, 127.4, 127.0, 126.6, 126.4, 123.8, 123.6, 123.1, 98.8, 97.2, 86.6, 85.6, 79.5, 39.8, 25.6.

Benzannulated Eneidyne II-21. To a mixture of **II-20** (48 mg, 0.064 mmol) and

triethylsilane (23 mg, 0.19 mmol) in 5 mL of methylene chloride was added 58 mg of trifluoroacetic acid (0.51 mmol). After 5 min of stirring at room temperature, 28 mg of sodium carbonate (0.26 mmol) was added followed by 2 mL of water and 5 mL of diethyl ether. The organic layer was separated, dried over sodium sulfate, and concentrated. Purification by flash column chromatography (silica gel/5% diethyl ether in hexanes) provided 32 mg (0.045 mmol, 69% yield, 1:1 mixture of diastereomers) of **II-21** as a white solid; ^1H (1:1 mixture) δ 8.43 (2 H, dd, $J = 7.6, 2.4$ Hz), 7.82 (2 H, dd, $J = 7.6, 4.7$ Hz), 7.74 (2 H, t, $J = 8.2$ Hz), 7.66–7.46 (10 H, m), 7.38–7.28 (10 H, m), 3.72 and 3.70 (2 H, two singlets, 1:1 ratio), 1.06 (18 H, s); ^{13}C (1:1 mixture) δ 137.5, 137.4, 133.3, 132.2, 131.7, 129.0, 128.81, 128.77, 128.4, 128.3, 128.1, 128.0, 127.22, 127.20, 126.6, 126.4, 124.9, 123.4, 123.35, 123.29, 123.21, 98.39, 98.35, 96.91, 96.86, 86.91, 86.85, 83.47, 83.44, 50.4, 35.61, 35.57, 27.9.

Compound II-22. To a solution of 50 mg of **II-21** (0.07 mmol) in 5 mL of anhydrous toluene under a nitrogen atmosphere was added 0.07 mL of a 1.0 M solution of potassium *t*-butoxide in THF (0.07 mmol) and 0.1 mL of *t*-butyl alcohol. The reaction mixture was heated under reflux for 12 h. After the reaction mixture was allowed to cool to room temperature, 2 mL of water and 10 mL of methylene chloride were introduced, and the organic layer was separated, dried over sodium sulfate, and concentrated. Purification by flash column chromatography (silica gel/10% methylene chloride in hexanes) provided 20 mg of **II-22** (0.028 mmol, 40% yield) as a pale yellow solid; ^1H δ 7.89 (2 H, s), 7.64 (2 H, d, $J = 8.2$ Hz), 7.57 (2 H, d, $J = 8.2$ Hz), 7.03–6.93 (2H, m), 6.9 (2 H, very broad), 6.69 (2 H, t, $J = 7.4$ Hz), 6.6 (2 H, very

broad), 6.44-6.35 (4 H, m), 6.2 and 5.8 (4 H, very broad), 4.57 (2 H, d, $J = 21.6$ Hz), 4.38 (2 H, d, $J = 21.6$ Hz), 1.91 (18 H, s). The structure of **II-22** was established by X-ray structure analysis.

Propargylic Alcohol II-23. To a solution of 0.289 g of **II-19** (1.15 mmol) in 15 mL of THF under a nitrogen atmosphere at 0 °C was added 0.46 mL of a 2.5 M solution of *n*-butyllithium (1.15 mmol) in hexanes. After 30 min of stirring, 0.187 g (1.15 mmol) of 2,2-dimethylpropiophenone in 10 mL of THF was introduced via cannula, and the reaction mixture was allowed to warm to room temperature. After an additional 2 h, 30 mL of water was introduced, and the reaction mixture was extracted with diethyl ether. The combined organic extracts were dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (silica gel/hexanes:diethyl ether = 9:1) to provide 0.436 g (1.05 mmol, 92%) of **II-23** as a viscous liquid: IR 3457, 753, 689 cm^{-1} ; ^1H δ 8.44 (1 H, d, $J = 8.2$ Hz), 7.86–7.73 (4 H, m), 7.64–7.49 (5 H, m), 7.41–7.31 (3 H, m), 7.30–7.20 (3 H, m), 2.47 (1 H, OH), 1.13 (9 H, s); ^{13}C δ 142.1, 133.2, 132.5, 131.8, 128.6, 128.43, 128.36, 128.2, 127.8, 127.4, 127.3, 127.1, 127.0, 126.4, 123.8, 123.5, 123.2, 98.8, 97.2, 86.6, 85.5, 79.7, 39.8, 25.6.

Benzannulated Eneidyne II-24. To a mixture of **II-23** (0.391 g, 0.944 mmol) and triethylsilane (0.165 g, 1.41 mmol) in 10 mL of methylene chloride was added 0.29 mL of trifluoroacetic acid (0.438 g, 3.83 mmol). After 5 min of stirring at room temperature, 0.406 g of sodium carbonate (3.83 mmol) was added followed by 10 mL of water and 40 mL of diethyl ether. The organic layer was separated, dried over sodium sulfate, and concentrated. The residue was purified by flash column

chromatography (silica gel/hexanes) to provide 0.298 g (0.749 mmol, 79%) of **II-24** as a colorless liquid: IR 817, 752, 702, 689 cm^{-1} ; ^1H δ 8.43 (1 H, d, $J = 8.5$ Hz), 7.82 (1 H, d, $J = 7.4$ Hz), 7.74 (1 H, d, $J = 8.7$ Hz), 7.64–7.44 (7 H, m), 7.41–7.32 (3 H, m), 7.29–7.20 (3 H, m), 3.77 (1 H, s), 1.09 (9 H, s); ^{13}C δ 139.2, 133.2, 132.2, 131.8, 129.8, 128.7, 128.35, 128.28, 128.1, 128.0, 127.6, 127.2, 126.65, 126.62, 126.3, 124.8, 123.4, 123.2, 98.3, 96.7, 86.9, 83.4, 50.8, 35.6, 27.8.

8-(1,1-Dimethylethyl)-13-phenyl-7H-dibenzo[*b,g*]fluorine II-28 and Compounds

II-29 and II-30. To a solution of 0.242 g of **II-24** (0.608 mmol) in 10 mL of anhydrous toluene under a nitrogen atmosphere was added 0.61 mL of a 1.0 M solution of potassium *tert*-butoxide in THF (0.61 mmol) and 0.61 mL of *tert*-butyl alcohol. The reaction mixture was heated under reflux for 12 h. After the reaction mixture was allowed to cool to room temperature, 10 mL of water and 40 mL of diethyl ether were introduced, and the organic layer was separated, dried over sodium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/hexanes) to provide 0.194 g (0.487 mmol, 80%) of **II-28** as a pale green solid, **II-29** (5% yield based on the ^1H NMR integration of the crude product before purification) as a pale yellow solid, and **II-30** (5% yield based on the ^1H NMR integration of the crude product before purification) as a pale yellow solid. Small portions of relatively pure samples of **II-29** and **II-30** were isolated for structural elucidation. **II-28**: mp 233–235 $^{\circ}\text{C}$; IR 803, 765, 701 cm^{-1} ; ^1H δ 8.65 (1 H, d, $J = 8.4$ Hz), 8.03 (1 H, d, $J = 8.5$ Hz), 7.78 (1 H, d, $J = 7.9$ Hz), 7.73 (1 H, d, $J = 7.9$ Hz), 7.60 (1 H, d, $J = 8.2$ Hz), 7.52–7.31 (7 H, m), 7.26–7.14 (2 H, m), 6.75 (1 H, t, $J =$

7.8 Hz), 4.62 (2 H, s), 1.96 (9 H, s); ^{13}C δ 143.6, 141.3, 140.6, 140.3, 138.3, 135.6, 134.1, 133.3, 132.6, 132.2, 131.1, 129.4, 128.5, 127.86, 127.80, 127.76, 127.3, 125.8, 124.1, 123.8, 123.4, 122.0, 41.4, 39.0, 34.4. Recrystallization of **II-28** from a mixture of CH_2Cl_2 /hexanes produced a single crystal suitable for X-ray structure analysis. **II-29**: ^1H δ 8.62–8.53 (1 H, m), 8.44 (2 H, d, $J = 4.0$ Hz), 7.93–7.81 (2 H, m), 7.76 (1 H, d, $J = 9.0$ Hz), 7.62–7.53 (2 H, m), 7.45 (3 H, broad), 7.39–7.00 (7 H, m), 4.11 (1 H, s), 0.97 (9 H, s); ^{13}C δ 142.93, 142.85, 142.3, 140.2, 132.0, 131.0, 130.4, 130.0, 128.5, 128.0, 127.9, 127.7, 127.0, 126.8, 126.5, 126.4, 125.9, 124.2, 122.6, 57.4, 36.0, 29.4; MS m/z 400 (M^+), 343, 265; HRMS calcd for $\text{C}_{31}\text{H}_{28}$ 400.2191, found 400.2185. **II-30**: ^1H δ 8.62–8.53 (1 H, m), 8.42 (2 H, d, $J = 10.5$ Hz), 7.91–7.86 (1 H, m), 7.83 (1 H, d, $J = 9.0$ Hz), 7.75 (1 H, d, $J = 8.7$ Hz), 7.63–7.53 (2 H, m), 7.43 (4 H, broad), 7.32–7.23 (4 H, m), 7.22–7.14 (4 H, m), 7.07 (2 H, d, $J = 8.2$ Hz), 4.08 (1 H, s), 3.94 (2 H, s), 0.95 (9 H, s); ^{13}C δ 142.9, 141.2, 140.3, 140.1, 138.5, 132.0, 131.0, 130.4, 130.0, 129.0, 128.5, 128.36, 128.28, 128.0, 127.9, 127.0, 126.9, 126.8, 126.5, 126.4, 126.0, 124.2, 122.5, 56.9, 41.4, 36.0, 29.4; MS m/z 490 (M^+), 433, 265; HRMS calcd for $\text{C}_{38}\text{H}_{34}$ 490.2661, found 490.2663.

Experimental Section of Chapter 2.3

Ethyl bromide, thionyl chloride, *tert*-butyllithium (1.7 M) in pentane, $\text{CuBr} \cdot \text{SMe}_2$ and 1.0 M solution of potassium *t*-butoxide in *t*-butyl alcohol were purchased from chemical suppliers and were used as received. 1,2-Bis[(2-ethynylphenyl)ethynyl]-benzene⁷ and 7,7'-dibromo-1,1'-binaphthalene-2,2'-diol (**II-31**)²² were prepared as reported previously.

II-32 A mixture of 1.72 g of **II-31** (3.87 mmol), 2.70 g of bromoethane (24.8 mol), 2.3 g of dry potassium carbonate, and a catalytic amount of NaI (0.2 g) in 10 mL of dry acetone was stirred and refluxed under anhydrous conditions (CaCl₂ tube) for three days. After cooling to room temperature, the reaction mixture was poured into water and extracted with methylene chloride. The combined organic layers were dried over magnesium sulfate, and the solvent was removed in vacuo after filtration. The residue was purified by flash column chromatography (silica gel/50% CH₂Cl₂ in hexanes) to provide 1.90 g (3.79 mmol, 98%) of **II-32** as a white solid: mp 204–205 °C; ¹H δ 7.91 (2 H, d, *J* = 9.2 Hz), 7.72 (2 H, d, *J* = 8.7 Hz), 7.41 (2 H, d, *J* = 9.0 Hz), 7.39 (2 H, dd, *J* = 8.7, 2.3 Hz), 7.26 (2 H, s), 4.07 (4 H, q, *J* = 6.9 Hz), 1.06 (6 H, t, *J* = 6.9 Hz).

II-33 A solution of 1.61 g of **II-32** (3.22 mmol) in 40 mL of dry THF was cooled to –78 °C and 5.67 mL of *n*-BuLi in *n*-hexane (2.5 M) (14.2 mmol) was added at such a rate in order not to allow the temperature to exceed –70 °C. After 5 h of stirring at this temperature, 937 g dry ice (21.3 mmol) was added so that the temperature remained below –50 °C. After stirring for 1 h at this temperature, 1 N HCl was added to the reaction solution until it is acidic as indicated by the pH paper. The solution was filtrated and the solid was washed by water and ethyl ether and dried. mp > 350 °C; The diacid was transferred into 10 mL of thionyl chloride and was heated under ca 80 °C for 6 h. The thionyl chloride was then removed in vacuo and the diacetyl chloride was dissolved in 10 mL of THF. To a suspension of 1.59 g of CuBr·SMe₂ (7.73 mmol) in 40 mL of THF was added 4.5 mL of a 1.7 M solution of tert-butyllithium (7.73

mmol) in pentane at $-50\text{ }^{\circ}\text{C}$. After 30 min of stirring, the solution of the diacetyl chloride in 10 mL of THF was introduced dropwise via cannula. After an additional 4 h at $-50\text{ }^{\circ}\text{C}$, the reaction mixture was allowed to warm to room temperature and treated with 20 mL of a saturated aqueous ammonium chloride solution. The organic layer was separated, and the aqueous layer was back extracted with diethyl ether. The combined organic layers were washed with brine and water, dried over sodium sulfate, and concentrated. Purification by flash column chromatography (silica gel/30% methylene chloride in hexanes) afforded 1.04 g of **II-33** (2.03 mmol, 63%) as a white solid: mp $190\text{--}191\text{ }^{\circ}\text{C}$; IR 2979, 1670, 1238, 1174, 1122, 838 cm^{-1} ; ^1H δ 7.96 (2 H, d, $J = 9.0\text{ Hz}$), 7.87 (2 H, d, $J = 8.4\text{ Hz}$), 7.61 (2 H, dd, $J = 8.4, 1.8\text{ Hz}$), 7.54 (2 H, s), 7.50 (2 H, d, $J = 9.0\text{ Hz}$), 4.16-3.98 (4 H, m), 1.07 (6 H, t, $J = 6.8\text{ Hz}$), 1.04 (18 H, s).

II-34 To a solution of 636 mg of **I-11a** (3.15 mmol) in 20 mL of THF under a nitrogen atmosphere at $0\text{ }^{\circ}\text{C}$ was added 1.26 mL of a 2.5 M solution of butyllithium (3.15 mmol) in hexanes. After 30 min of stirring, a solution of 320 mg (0.63 mmol) of **II-33** in 20 mL of THF was introduced via cannula, and the reaction mixture was allowed to warm to room temperature. After an additional 2 h, 30 mL of water was introduced, and the reaction mixture was extracted with diethyl ether. The combined organic extracts were dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (silica gel/40% diethyl ether in hexanes) to provide 539 mg (0.59 mmol, 94% yield) of **II-34** as a pale yellow solid.

II-35 To a mixture of **II-34** (539 mg, 0.59 mmol) and triethylsilane (209 mg, 1.76 mmol) in 20 mL of methylene chloride was added 0.36 mL of trifluoroacetic acid

(536 mg, 4.71 mmol). After 5 min of stirring at room temperature, 251 mg of sodium carbonate (2.36 mmol) was added followed by 10 mL of water and 50 mL of diethyl ether. The organic layer was separated, dried over sodium sulfate, and concentrated. Purification by flash column chromatography (silica gel/20% methylene chloride in hexanes) provided 406 mg (0.46 mmol, 78% yield) of **II-35** as a pale yellow solid; ^1H (mixture of diastereomers) δ 7.92–6.83 (28 H, m), 4.10–3.78 (4 H, m), 3.56–3.35 (2 H, m), 1.10–0.75 (24 H, m); ^{13}C (mixture of diastereomers) δ 154.53, 154.47, 154.3, 154.2, 137.1, 137.0, 136.8, 133.9, 133.7, 133.6, 132.1, 132.0, 131.9, 131.7, 131.6, 128.67, 128.62, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.15, 127.06, 126.8, 126.4, 126.23, 126.17, 126.0, 125.4, 125.30, 125.26, 123.2, 120.6, 120.5, 120.3, 115.6, 115.3, 115.1, 95.84, 95.76, 95.6, 95.5, 92.71, 92.67, 92.6, 88.6, 88.5, 82.4, 82.3, 65.2, 65.0, 64.9, 35.5, 35.4, 15.00, 14.96.

II-36 and II-37 To a solution of 135 mg of **II-35** (0.153 mmol) in 10 mL of anhydrous toluene under a nitrogen atmosphere was added 0.67 mL of a 1.0 M solution of potassium *t*-butoxide in *t*-butyl alcohol (0.67 mmol). The reaction mixture was heated under reflux for 12 h. After the reaction mixture was allowed to cool to room temperature, 10 mL of water and 40 mL of methylene chloride were introduced, and the organic layer was separated, dried over sodium sulfate, and concentrated. Purification by flash column chromatography (silica gel/30% methylene chloride in hexanes) provided 10.8 mg (0.012 mmol, 8% yield) of **II-36** as an orange solid and 30.0 mg (0.034 mmol, 22% yield) of **II-37** as a pale yellow solid. Small amounts of the pure diastereomer 1 of **II-36** and the mixture of diastereomer 2 and 3 of **II-36** and

the pure diastereomer 1 and 2 of **II-37** were separated for structure analyses.

Diastereomer 1 of **II-36**: mp 274-275 °C; IR 1622, 1504, 1231, 755, 690 cm⁻¹; ¹H (270 MHz) δ 7.82 (2 H, d, J = 16.3 Hz), 7.79 (2 H, d, J = 16.1 Hz), 7.51-7.57 (6 H, m), 7.47 (1 H, d, J = 1.6 Hz), 7.44 (1 H, d, J = 1.6 Hz), 7.28-7.32 (2 H, m), 7.16-7.23 (12 H, m), 7.11 (4 H, d, J = 9.0 Hz), 6.97-7.04 (2 H, m), 5.82 (2 H, s), 3.65-3.77 (2 H, m), 3.42-3.54 (2 H, m), 0.75 (18 H, s), 0.72 (6 H, t, J = 7.1 Hz); ¹³C (67.9 MHz) δ 154.35, 154.32, 154.24, 154.17, 152.3, 150.9, 147.7, 140.4, 135.0, 134.7, 133.7, 129.1, 128.9, 128.8, 128.7, 128.6, 128.2, 127.8, 126.2, 125.3, 125.2, 123.7, 123.3, 121.6, 121.1, 116.3, 111.2, 75.7, 65.3, 36.6, 28.3, 14.8. The structure of diastereomer 1 of **II-36** was established by X-ray structure analysis. Diastereomer 2 and 3 (1:1) of **II-36**: mp 153-155 °C; IR 1623, 1504, 1231, 755, 690 cm⁻¹; ¹H (270 MHz) δ 7.79-7.86 (6 H, m), 7.50-7.59 (8 H, m), 7.42-7.47 (4 H, m), 7.27-7.36 (12 H, m), 6.94-7.25 (26 H, m), 6.17 (2 H, s), 6.10 (2 H, s), 3.83-4.05 (2 H, m), 3.49-3.61 (2 H, m), 3.17-3.30 (2 H, m), 0.98 (18 H, s), 0.94 (6 H, t, J = 7.1 Hz), 0.63 (18 H, s), 0.57 (6 H, t, J = 7.1 Hz); ¹³C (67.9 MHz) δ 154.5, 154.4, 154.3, 154.2, 152.25, 152.20, 151.02, 150.96, 147.5, 147.4, 140.5, 140.2, 134.7, 134.4, 133.7, 133.4, 129.2, 129.0, 128.74, 128.70, 128.66, 128.58, 128.54, 128.46, 128.37, 128.26, 127.7, 127.6, 126.4, 126.3, 125.6, 125.3, 124.9, 124.6, 123.9, 123.6, 123.315, 123.307, 121.4, 121.1, 120.9, 116.6, 115.4, 111.15, 111.09, 75.7, 65.33, 65.31, 36.9, 36.6, 28.5, 28.2, 15.0, 14.7. Diastereomer 1 of **II-37**: ¹H (600 MHz) δ 8.09 (2 H, d, J = 8.4 Hz), 7.85 (1 H, d, J = 8.4 Hz), 7.84 (1 H, d, J = 9.0 Hz), 7.72 (1 H, d, J = 7.8 Hz), 7.59 (2 H, t, J = 7.8 Hz), 7.56 (1 H, d, J = 9.6 Hz), 7.45-7.50 (1 H, m), 7.35-7.42 (3 H, m), 7.31-7.33 (1 H, m), 7.27-7.30 (1 H,

m), 7.21-7.25 (5 H, m), 7.18 (1 H, t, $J = 7.8$ Hz), 7.05 (2 H, t, $J = 7.8$ Hz), 6.90 (1 H, d, $J = 8.4$ Hz), 6.89 (1 H, t, $J = 7.8$ Hz), 6.45 (1 H, t, $J = 7.8$ Hz), 5.97 (1 H, t, $J = 7.8$ Hz), 5.90 (1 H, s), 5.01 (1 H, d, $J = 8.4$ Hz), 4.24 (1 H, d, $J = 21.0$ Hz), 4.11 (1 H, d, $J = 20.4$ Hz), 3.58-3.64 (1 H, m), 3.33-3.40 (1 H, m), 3.18-3.26 (2 H, m), 1.77 (9 H, s), 1.18 (9 H, s), 0.67 (3 H, t, $J = 6.6$ Hz), 0.48 (3 H, t, $J = 6.6$ Hz). The structure of diastereomer 1 of **II-37** was established by X-ray structure analysis. Diastereomer 2 of **II-37**: ^1H (600 MHz) δ 7.95 (2 H, d, $J = 8.4$ Hz), 7.91 (1 H, d, $J = 8.4$ Hz), 7.84 (1 H, d, $J = 9.6$ Hz), 7.81 (1 H, d, $J = 7.8$ Hz), 7.59 (1 H, d, $J = 9.0$ Hz), 7.49 (1 H, d, $J = 7.8$ Hz), 7.41 (2 H, t, $J = 7.8$ Hz), 7.36 (4 H, d, $J = 9.0$ Hz), 7.31 (2 H, d, $J = 7.8$ Hz), 7.28 (2 H, d, $J = 7.8$ Hz), 7.25 (1 H, t, $J = 9.0$ Hz), 7.22 (1 H, t, $J = 8.4$ Hz), 7.13 (1 H, t, $J = 7.8$ Hz), 6.90 (1 H, d, $J = 9.6$ Hz), 6.87 (1 H, t, $J = 7.8$ Hz), 6.41 (1 H, t, $J = 7.8$ Hz), 6.40 (1 H, s), 5.73 (1 H, bump), 5.63 (1 H, t, $J = 7.8$ Hz), 4.86 (1 H, d, $J = 7.8$ Hz), 4.22 (1 H, d, $J = 21.6$ Hz), 4.08 (1 H, d, $J = 21.0$ Hz), 3.58-3.64 (1 H, m), 3.32-3.38 (1 H, m), 3.20-3.27 (2 H, m), 1.76 (9 H, s), 1.14 (9 H, s), 0.64 (3 H, t, $J = 7.8$ Hz), 0.50 (3 H, t, $J = 7.8$ Hz). The structure of diastereomer 2 of **II-37** was established by X-ray structure analysis.

Experimental Section of Chapter 2.4

Lithium diisopropylamide (LDA, 2.0 M) in heptane/THF/ethylbenzene and phosphorus pentoxide were purchased from chemical suppliers and were used as received.

8-(1,1-Dimethylethyl)-13-phenyl-7*H*-dibenzo[*b,g*]fluorene-7-methanol (**II-42**).

To a solution of 0.066 g (0.16 mmol) of **II-28** in 5 mL of THF under a nitrogen

atmosphere at 0 °C was added 0.10 mL of a 2.0 M solution of LDA (0.20 mmol) in heptane/tetrahydrofuran/ethylbenzene. After 10 min at 0 °C, 0.006 g (0.2 mmol) of paraformaldehyde was introduced via a 120° angle glass tubing fitted with ground joints at both ends. The reaction mixture was then allowed to warm to room temperature. After an additional 15 min, 2 mL of a saturated sodium bicarbonate solution was introduced, and the reaction mixture was extracted with diethyl ether. The combined organic extracts were washed with brine and water, dried over magnesium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/20% diethyl ether in hexanes) to afford 0.057 g of **II-42** (0.13 mmol, 80%) as a white solid: mp 180–182 °C; IR 3413, 756, 703 cm⁻¹; ¹H δ 8.64 (1 H, d, *J* = 8.7 Hz), 8.01 (1 H, d, *J* = 8.4 Hz), 7.83 (1 H, d, *J* = 8.2 Hz), 7.76 (1 H, d, *J* = 8.2 Hz), 7.74 (1 H, d, *J* = 8.2 Hz), 7.68 (1 H, very broad), 7.50 (1 H, t, *J* = 7.1 Hz), 7.42–7.30 (2 H, m), 7.24–7.15 (2 H, m), 7.04 (3 H, very broad), 6.78 (1 H, t, *J* = 7.1 Hz), 5.20 (1 H, dd, *J* = 7.1, 4.2 Hz), 4.30 (1 H, m), 3.61 (1 H, m), 1.95 (9 H, s), 1.48 (1 H, OH); ¹³C δ 144.2, 141.03, 140.98, 139.4, 136.4, 134.5, 133.7, 133.0, 132.2, 131.9, 129.8, 128.8 (br), 128.3, 128.0, 127.8, 127.4, 125.8, 124.3, 124.2, 123.9, 121.9, 68.3, 52.6, 38.7, 34.3.

14-Phenylnaphth[1,2-*a*]anthracene (II-43). To a flask containing 0.040 g (0.093 mmol) of **II-42** were added 0.20 g (1.4 mmol) of phosphorus pentoxide and 10 mL of benzene. After 5 min at room temperature, 10 mL of a saturated sodium bicarbonate solution was introduced, and the organic layer was separated. The aqueous layer was back extracted with diethyl ether. The combined organic extracts were washed with

water, dried over magnesium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/10% methylene chloride in hexanes) to provide 0.027 g of a pale yellow solid containing ca. 90% of **II-43** (0.068 mmol, 74% yield) and ca. 10% of adducts retaining a *tert*-butyl group most likely at C5 to C9 positions. **II-43**: ^1H δ (600 MHz at $-20\text{ }^\circ\text{C}$) 8.53 (1 H, s), 8.34 (1 H, d, $J = 9.0$ Hz), 8.24 (1 H, d, $J = 7.2$ Hz), 8.17 (1 H, d, $J = 7.8$ Hz), 7.92 (1 H, d, $J = 8.4$ Hz), 7.89 (1 H, d, $J = 8.4$ Hz), 7.85 (1 H, d, $J = 8.4$ Hz), 7.76 (1 H, d, $J = 8.4$ Hz), 7.67 (1 H, d, $J = 5.4$ Hz), 7.66 (1 H, d, $J = 8.4$ Hz), 7.61 (1 H, t, $J = 7.2$ Hz), 7.52 (1 H, t, $J = 7.8$ Hz), 7.49 (1 H, t, $J = 7.2$ Hz), 7.20 (1 H, t, $J = 7.2$ Hz), 7.02–6.98 (2 H, m), 6.67 (1 H, t, $J = 7.2$ Hz), 6.14 (1 H, d, $J = 7.8$ Hz); ^{13}C δ 140.6, 138.3, 132.3, 132.07, 132.03, 131.4, 130.4, 130.0, 129.7, 128.4, 128.0, 127.6, 127.5, 127.31, 127.27, 126.5, 126.4, 126.2, 126.0, 125.5, 125.3, 124.60, 124.58.

10-(1,1-Dimethylethyl)-4,5-diphenyl-11H-benzo[*b*]fluorene-11-methanol (II-44).

To a solution of 0.065 g (0.15 mmol) of **II-14** in 5 mL of THF under a nitrogen atmosphere at $0\text{ }^\circ\text{C}$ was added 0.10 mL of a 2.0 M solution of LDA (0.20 mmol) in heptane/tetrahydrofuran/ethylbenzene. After 10 min at $0\text{ }^\circ\text{C}$, 0.006 g (0.2 mmol) of paraformaldehyde was introduced via a 120° angle glass tubing fitted with ground joints at both ends. The reaction mixture was then allowed to warm to room temperature. After an additional 15 min, 2 mL of a saturated sodium bicarbonate solution was introduced, and the reaction mixture was extracted with diethyl ether. The combined organic extracts were washed with brine and water, dried over magnesium sulfate, and concentrated. The residue was purified by flash column

chromatography (silica gel/30% diethyl ether in hexanes) to afford 0.041 g of **II-44** (0.090 mmol, 59%) as a white solid: mp 214–215 °C; IR 3384 (br), 1048 cm⁻¹; ¹H δ 8.60 (1 H, d, *J* = 9.0 Hz), 7.66 (1 H, dd, *J* = 8.4, 1.3 Hz), 7.58 (1 H, d, *J* = 7.4 Hz), 7.42 (1 H, ddd, *J* = 8.2, 6.6, 1.3 Hz), 7.32 (1 H, d, *J* = 7.6 Hz), 7.27 (1 H, d, *J* = 7.6 Hz), 7.22 (1 H, ddd, *J* = 8.2, 6.6, 1.1 Hz), 7.12–6.72 (8 H, m), 6.58 (2 H, d, *J* = 6.6 Hz), 5.20 (1 H, dd, *J* = 7.4, 4.2 Hz), 4.19 (1 H, broad), 3.45 (1 H, t, *J* = 7.9 Hz), 1.94 (9 H, s), 1.56 (1 H, OH); ¹³C δ 145.7, 142.7, 140.9, 140.4, 139.5, 138.8, 138.0, 137.8, 134.1, 132.22, 132.15, 130.9, 130.3, 129.4, 128.4, 127.84, 127.77, 127.4, 127.3, 127.2, 126.7, 125.8, 125.7, 124.2, 123.7, 122.3, 68.4, 52.9, 38.6, 34.2. Recrystallization of **II-44** from a mixture of CH₂Cl₂/hexanes produced a single crystal suitable for X-ray structure analysis.

Hydrocarbon II-46. To a flask containing 0.030 g (0.066 mmol) of **II-44** were added 0.20 g (1.4 mmol) of phosphorus pentoxide and 10 mL of benzene. After 5 min at room temperature, 10 mL of a saturated sodium bicarbonate solution was introduced, and the organic layer was separated. The aqueous layer was back extracted with diethyl ether. The combined organic extracts were washed with water, dried over magnesium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/5% methylene chloride in hexanes) to provide 0.020 g of **II-46** (0.053 mmol, 80%) as a colorless solid: mp 211–216 °C; ¹H δ 8.27 (1 H, dd, *J* = 7.8, 1.4 Hz), 8.17 (1 H, d, *J* = 7.1 Hz), 7.81 (1 H, d, *J* = 8.2 Hz), 7.70 (1 H, d, *J* = 8.2 Hz), 7.65–7.57 (1 H, m), 7.52 (1 H, t, *J* = 7.8 Hz), 7.48–7.39 (3 H, m), 7.38–7.17 (4 H, m), 7.16–6.82 (4 H, m), 6.66 (1 H, broad), 3.75 (1 H, d, *J* = 16.9 Hz), 3.47 (1 H, d,

$J = 16.9$ Hz); ^{13}C δ 148.5, 144.4, 139.1, 138.4, 137.9, 137.1, 134.3, 132.0, 130.9, 128.7, 128.1, 127.9, 127.25, 127.20, 126.8, 126.7, 126.2, 125.8, 125.7, 125.39, 125.35, 123.3, 119.2, 54.5, 38.8. Recrystallization of **II-46** from a mixture of CH_2Cl_2 /hexanes produced a single crystal suitable for X-ray structure analysis.

Experimental Section of Chapter 2.5

(+)-Mosher's reagent, DCC, lithium aluminum hydride and DME were purchased from chemical suppliers and were used as received.

Diols II-48a-c. To a solution of 0.344 g (0.557 mmol) of **I-19a** in 60 mL of benzene and 50 mL of THF under a nitrogen atmosphere at 0 °C was added 1.80 mL of a 2.0 M solution of LDA (3.60 mmol) in heptane/tetrahydrofuran/ethylbenzene. After 20 min at 0 °C, 0.220 g (7.33 mmol) of paraformaldehyde was transferred into the reaction mixture via a 120° angle glass tubing fitted with ground joints at both ends. The reaction mixture was allowed to warm to room temperature. After an additional 30 min, 10 mL of a saturated sodium bicarbonate solution was introduced, and the reaction mixture was extracted with diethyl ether. The combined organic extracts were washed with brine and water, dried over magnesium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/50% diethyl ether in hexanes) to afford 0.287 g of **II-48a-c** (0.423 mmol, 76%, a mixture of three isomers, isomer ratio = 63:34:3) as a pale yellow solid. The ^1H NMR spectrum suggests that all three diastereomers, **II-48a** and **II-48b** having a C_2 symmetry (63% and 3% not necessarily respectively) and **II-48c** without a C_2 symmetry (34%), were produced. The major isomer (**II-48a** or **II-48b**) and **II-48c** were further separated by

column chromatography on a silica gel column. **II-48a-c**: mp 221–225 °C; IR 3412 (br), 1052, 704 cm⁻¹; ¹H (**II-48a** or **II-48b**) δ 7.81 (2 H, s), 7.49 (2 H, d, J = 7.5 Hz), 7.13 (2 H, tm, J = 7.5, 1 Hz), 7.10 (2 H, tm, J = 7.5, 1 Hz), 6.99 (4 H, t, J = 7.5 Hz), 6.78 (2 H, t, J = 7.2 Hz), 6.46 (4 H, d, J = 6.9 Hz), 6.22 (2 H, d, J = 7.9 Hz), 4.70 (2 H, dd, J = 5.9, 3.0 Hz), 4.47 (2 H, m), 3.82 (2 H, m), 1.82 (18 H, s), 1.13 (2 H, OH); ¹³C (**II-48a** or **II-48b**) δ 146.6, 140.7, 140.6, 138.7, 137.4, 135.1, 134.9, 132.1, 131.2, 128.2, 126.56, 126.51, 126.0, 123.8, 122.9, 121.9, 67.0, 50.7, 37.7, 34.3; ¹H (**II-48c**) δ 7.97 (1 H, d, J = 9.7 Hz), 7.88 (1 H, d, J = 9.3 Hz), 7.50 (1 H, d, J = 7.5 Hz), 7.45 (1 H, d, J = 7.1 Hz), 7.19-6.91 (8 H, m), 6.83-6.74 (2 H, m), 6.47 (4 H, t, J = 8.1 Hz), 6.32 (2 H, t, J = 6.9 Hz), 4.85 (1 H, dd, J = 7.7, 3.8 Hz), 4.73 (1 H, dd, J = 6.1, 3.2 Hz), 4.47 (1 H, m), 4.36 (1 H, m), 3.74 (1 H, m), 3.47 (1 H, t, J = 8 Hz), 1.86 (9 H, s), 1.85 (9 H, s), 1.64 (1 H, OH), 1.17 (1 H, OH); ¹³C (**II-48c**) δ 146.7, 146.6, 140.8, 140.5, 140.4, 139.0, 138.9, 138.5, 138.4, 137.3, 135.9, 134.9, 134.6, 133.3, 133.0, 132.5, 132.2, 127.7, 126.9, 126.6, 126.1, 123.8, 123.5, 123.3, 123.0, 122.8, 122.1, 69.6, 67.2, 52.2, 50.7, 38.3, 37.8, 34.5, 34.2; The ¹H NMR signals attributable to the minor isomer having a C₂ symmetry (**II-48a** or **II-48b**) were observed at δ 8.05 (2 H, s) and 1.90 (18 H, s); MS m/z 678 (M⁺), 664, 647, 605; HRMS calcd for C₅₀H₄₆O₂ 678.3492, found 678.3496.

General procedure for Mosher's diester: A mixture of one equivalent of the diol, 2.2 equivalent of Mosher's reagent, 4 equivalent of DCC and catalytic amount of DMAP in methylene chloride was stirred at room temperature for 12 h. The solvent was removed and the residue was purified by flash column chromatography (silica

gel/20% ethyl ether in hexanes) to give the corresponding Mosher's diester.

Crystallization for Mosher's diester: The corresponding Mosher's diester from one diol was dissolved in small amount of methylene chloride and ethyl alcohol was added until precipitate appeared. Methylene chloride was added again to dissolve the precipitate. Slowly evaporating the solvent, the first precipitate contained most of one diastereomer of the Mosher's diester (depending on the evaporation speed). Crystallization again using the first precipitate might be needed.

Deprotection of the Mosher's diester: the Mosher's diester was dissolved in DME solvent, excess amount of LAH was added. After stirring at room temperature for 12 h, saturated sodium bicarbonate solution was introduced, and the reaction mixture was extracted with diethyl ether then following the separation procedure for diols II-48a-c.

Pure enantiomer of II-50a or II-50b $[\alpha]_D^{25} = -948^\circ$ ^1H (600 MHz) δ 7.78 (2 H, s), 7.28-7.23 (4 H, m), 7.18 (2 H, d, $J = 7.2$ Hz), 7.16-7.07 (8 H, m), 6.97 (4 H, t, $J = 7.2$ Hz), 6.94 (2 H, t, $J = 7.2$ Hz), 6.72 (2 H, t, $J = 7.8$ Hz), 6.40 (4 H, d, $J = 7.8$ Hz), 6.10 (2 H, d, $J = 8.4$ Hz), 5.15 (2 H, dd, $J = 10.8, 1.8$ Hz), 4.83 (2 H, d, $J = 4.8$ Hz), 4.43 (2 H, dd, $J = 10.8, 6.6$ Hz), 3.22 (6 H, s), 1.81 (18 H, s); ^{13}C (150 MHz) δ 166.3, 145.6, 140.7, 140.4, 138.7, 138.0, 137.3, 135.2, 135.1, 131.7, 131.3, 129.2, 128.19, 128.16, 127.1, 126.60, 126.56, 126.1, 123.5, 123.2, 121.8, 70.3, 55.1, 47.0, 37.6, 34.2.

Pure enantiomer of II-50c $[\alpha]_D^{25} = +992^\circ$ ^1H (600 MHz) δ 7.98 (1 H, d, $J = 9.6$ Hz), 7.89 (1 H, d, $J = 9.0$ Hz), 7.60 (2 H, d, $J = 6.6$ Hz), 7.50-7.42 (4 H, m), 7.34-7.26 (1 H, m), 7.24-7.16 (6 H, m), 7.11 (1 H, t, $J = 6.6$ Hz), 7.06-6.92 (5 H, m), 6.82 (1 H, dt, $J = 7.2, 2.4$ Hz), 6.76-6.68 (2 H, m), 6.48 (2 H, d, $J = 6.6$ Hz), 6.39 (2 H, d, $J = 6.6$ Hz),

6.23 (1 H, d, $J = 7.8$ Hz), 6.20 (1 H, d, $J = 8.4$ Hz), 5.26 (1 H, d, $J = 10.8$ Hz), 5.07 (1 H, d, $J = 10.2$ Hz), 4.91 (1 H, d, $J = 10.2$ Hz), 4.82 (1 H, d, $J = 7.2$ Hz), 4.17 (1 H, t, $J = 8.4$ Hz), 3.88 (1 H, t, $J = 10.2$ Hz), 3.63 (3 H, s), 3.20 (3 H, s), 1.88 (9 H, s), 1.85 (9 H, s); ^{13}C (150 MHz) δ 166.3, 145.6, 140.7, 140.4, 138.7, 138.0, 137.3, 135.2, 135.1, 131.7, 131.3, 129.2, 128.19, 128.16, 127.1, 126.60, 126.56, 126.1, 123.5, 123.2, 121.8, 70.3, 55.1, 47.0, 37.6, 34.2.

Experimental Section of Chapter 3.2

Compounds **III-58**,⁷ **III-68**,⁵¹ **III-69b**,⁵¹ **III-77**,⁵² **III-82**,⁵² and **III-85**⁵² were prepared according to the reported procedures. 4-Aminopyridine, 4-(dimethylamino)-pyridine, 4-methoxypyridine, propargyl alcohol, methanesulfonyl chloride, 3,3-dimethyl-1-butyne, (trimethylsilyl)ethyne, imidazole, tetrabutylammonium iodide were purchased from chemical suppliers and were used as received.

Propargylic Alcohol III-60. To a solution of **III-58** (480 mg, 1.87 mmol) in 20 mL of anhydrous diethyl ether at $-78\text{ }^{\circ}\text{C}$ was added dropwise 0.9 mL of a 2.5 M solution of *n*-butyllithium (2.25 mmol) in hexanes. After one hour of stirring at $-78\text{ }^{\circ}\text{C}$, a solution of 640 mg of iodine (2.52 mmol) in 30 mL of anhydrous diethyl ether was added dropwise via cannula. The reaction mixture was allowed to warm to room temperature before 15 mL of a 5% sodium thiosulfate solution was introduced. The organic layer was separated, washed with water, dried over sodium sulfate, and concentrated to give 477 mg of **III-59**. To a mixture of 477 mg of the crude iodide **III-59**, 55 mg (0.078 mmol) of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, and 29 mg (0.15 mmol) of copper(I) iodide in 25 mL of

triethylamine under a nitrogen atmosphere was added dropwise via cannula a solution of 240 mg of propargyl alcohol (4.29 mmol) in 5 mL of triethylamine. The reaction mixture was stirred vigorously at 75 °C for 12 h before it was allowed to cool to room temperature. Then 50 mL of a saturated NH₄Cl solution and 50 mL of diethyl ether were introduced. The organic layer was separated, and the aqueous layer was back extracted with diethyl ether. The combined organic layers were washed with water, dried over MgSO₄, and concentrated. The residue was purified by column chromatography (silica gel/diethyl ether:hexanes = 3:7) to give 286 mg (1.23 mmol, 66% overall yield) of **III-60** as a colorless liquid: IR 3334, 2217, 755, 690 cm⁻¹; ¹H δ 7.45-7.60 (4 H, m), 7.23-7.40 (5 H, m), 4.57 (2 H, d, *J* = 5.9 Hz), 1.75 (1 H, t, *J* = 6.2 Hz); ¹³C δ 131.9, 131.7, 128.5, 128.4, 128.2, 127.9, 125.8, 125.0, 123.1, 93.5, 91.3, 88.0, 84.5, 51.8; MS *m/z* 232 (M⁺), 231, 202, 101.

Propargyl Methanesulfonate III-61. To a solution of **III-60** (322 mg, 1.39 mmol) and triethylamine (211 mg, 2.01 mmol) in 10 mL of methylene chloride at -50 °C under a nitrogen atmosphere was added dropwise methanesulfonyl chloride (207 mg, 1.81 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 h before 5 mL of water was introduced. The organic layer was separated, and the aqueous layer was back extracted with methylene chloride. The combined organic layers were washed with water, dried over MgSO₄, and concentrated. The residue was purified by column chromatography (silica gel/diethyl ether:hexanes = 3:7) to give 353 mg (1.14 mmol, 82%) of **III-61** as a colorless liquid: IR 2217, 1360 cm⁻¹; ¹H δ 7.48-7.61 (4 H, m), 7.28-7.42 (5 H, m), 5.18 (2 H, s), 3.12 (3 H, s); ¹³C δ

132.3, 132.0, 131.7, 129.2, 128.8, 128.5, 128.1, 126.2, 123.5, 122.7, 93.9, 88.1, 87.5, 84.6, 58.5, 39.2.

Pyridinium Methanesulfonate III-63a. To a solution of **III-61** (186 mg, 0.600 mmol) in 5 mL of methylene chloride was added dropwise a solution of 4-aminopyridine (56 mg, 0.60 mmol) in 5 mL of methylene chloride. The reaction mixture was stirred at room temperature for 24 h and concentrated. The residue was washed with diethyl ether to give 242 mg (0.599 mmol, 100%) of **III-63a** as a colorless solid: mp 189-190 °C; IR 3330, 3120, 1197 cm^{-1} ; ^1H δ 8.11 (2 H, s), 7.97 (2 H, d, $J = 6.9$ Hz), 7.22-7.52 (9 H, m), 6.96 (2 H, d, $J = 6.9$ Hz), 5.23 (2 H, s), 2.79 (3 H, s); ^{13}C δ 159.7, 140.9, 132.2, 132.0, 131.5, 129.2, 129.0, 128.6, 128.2, 126.0, 123.3, 122.4, 93.7, 88.0, 87.4, 83.6, 47.6, 39.7.

Pyridinium Methanesulfonate III-63b. To a solution of **III-61** (186 mg, 0.600 mmol) in 5 mL of methylene chloride was added dropwise a solution of 4-(dimethylamino)pyridine (73 mg, 0.60 mmol) in 5 mL of methylene chloride. The reaction mixture was stirred at room temperature for 24 h and concentrated. The residue was washed with diethyl ether to give 259 mg (0.600 mmol, 100%) of **III-63b** as a viscous liquid: IR 1651, 1192, 765 cm^{-1} ; ^1H δ 8.64 (2 H, d, $J = 7.9$ Hz), 7.46-7.57 (4 H, m), 7.29-7.42 (5 H, m), 6.51 (2 H, d, $J = 7.9$ Hz), 5.53 (2 H, s), 3.07 (6 H, s), 2.81 (3 H, s); ^{13}C δ 156.2, 141.6, 131.8, 131.7, 129.0, 128.7, 128.5, 128.3, 125.5, 123.5, 122.6, 107.7, 93.0, 88.4, 87.9, 83.7, 47.5, 40.1, 39.5.

Pyridinium Methanesulfonate III-63c. To a solution of **III-61** (30 mg, 0.097 mmol) in 5 mL of methylene chloride was added dropwise a solution of 4-methoxypyridine

(11 mg, 0.101 mmol) in 5 mL of methylene chloride. The reaction mixture was stirred at room temperature for 24 h and concentrated. The residue was washed with diethyl ether to give 41 mg (0.097 mmol, 100%) of **III-63c** as a colorless solid: mp 133–134 °C; IR 2216, 1192, 762 cm^{-1} ; ^1H δ 9.19 (2 H, d, $J = 6.9$ Hz), 7.31–7.55 (9 H, m), 6.99 (2 H, d, $J = 6.9$ Hz), 5.86 (2 H, s), 3.96 (3 H, s), 2.78 (3 H, s); ^{13}C δ 171.1, 145.7, 131.9, 131.7, 129.3, 128.9, 128.7, 128.5, 128.4, 125.7, 123.2, 122.6, 113.2, 93.0, 89.8, 87.9, 82.7, 57.8, 49.9, 39.5.

2-Amino-12-phenyl-7H-indeno[1,2-*b*]quinolizin-5-ium Methanesulfonate

(III-67a). A solution of **III-63a** (45 mg, 0.11 mmol) and triethylamine (11 mg, 0.11 mmol) in 10 mL of ethanol was heated under reflux for 12 h. The solvent was removed and the residue was washed with diethyl ether to give 45 mg (0.11 mmol, 100%) of **III-67a** as a yellow solid: compound becomes black at 270 °C without melting; IR 3361, 1652, 1194 cm^{-1} ; ^1H δ 8.67 (1 H, d, $J = 7.4$ Hz), 8.63 (1 H, s), 7.60–7.62 (3 H, m), 7.52 (1 H, d, $J = 7.6$ Hz), 7.28–7.39 (4 H, m), 7.05 (1 H, t, $J = 7.6$ Hz), 6.33–6.43 (2 H, m), 4.13 (2 H, s), 2.99 (2 H, s), 2.75 (3 H, s); ^{13}C (10% CD_3OD in CDCl_3) δ 153.9, 145.5, 145.1, 144.4, 136.9, 136.6, 133.4, 131.9, 131.0, 130.0, 129.4, 129.1, 128.5, 127.5, 126.7, 125.4, 125.2, 112.9, 101.6, 38.9, 33.8. Recrystallization of **III-67a** from a mixture of chloroform and methanol produced a crystal suitable for X-ray structure analysis.

2-(Dimethylamino)-12-phenyl-7H-indeno[1,2-*b*]quinolizin-5-ium

Methanesulfonate (III-67b). A solution of **III-63b** (51 mg, 0.12 mmol) and triethylamine (12 mg, 0.12 mmol) in 10 mL of ethanol was stirred at room

temperature for 72 h. The solvent was removed and the residue was washed with diethyl ether to give 51 mg (0.12 mmol, 100%) of **III-67b** as a yellow solid: compound becomes black at 228 °C without melting; IR 1647, 1195 cm^{-1} ; ^1H δ 9.62 (1 H, d, J = 7.6 Hz), 9.39 (1 H, s), 7.61–7.71 (3 H, m), 7.55 (1 H, d, J = 7.7 Hz), 7.26–7.41 (4 H, m), 7.07 (1 H, t, J = 7.9 Hz), 6.43 (1 H, d, J = 8.2 Hz), 6.27 (1 H, d, J = 2.9 Hz), 4.22 (2 H, s), 3.04 (6 H, s), 2.87 (3 H, s); ^{13}C δ 152.0, 146.3, 145.7, 143.8, 138.8, 136.8, 133.9, 132.4, 131.0, 130.3, 130.1, 129.7, 129.2, 127.4, 126.6, 125.6, 125.3, 109.8, 99.6, 39.7, 39.6, 34.3. Recrystallization of **III-67b** from a mixture of dichloromethane and hexanes produced a crystal suitable for X-ray structure analysis.

2-Methoxy-12-phenyl-7H-indeno[1,2-*b*]quinolizin-5-ium Methanesulfonate

(III-67c). A solution of **III-63c** (150 mg, 0.358 mmol) and triethylamine (36 mg, 0.36 mmol) in 40 mL of ethanol was stirred at room temperature for 15 h. The solvent was removed and the residue was washed with diethyl ether to give 150 mg (0.358 mmol, 100%) of **III-67c** as a yellow solid: compound becomes black at 228 °C without melting; IR 1644, 1193 cm^{-1} ; ^1H δ 10.09 (1 H, s), 9.99 (1 H, d, J = 7.7 Hz), 7.69–7.78 (3 H, m), 7.64 (1 H, d, J = 7.9 Hz), 7.37–7.52 (4 H, m), 7.14 (1 H, t, J = 7.8 Hz), 6.87 (1 H, d, J = 3.0 Hz), 6.52 (1 H, d, J = 8.2 Hz), 4.39 (2 H, s), 3.86 (3 H, s), 2.92 (3 H, s); ^{13}C δ 163.8, 148.0, 146.9, 144.5, 140.3, 136.4, 136.2, 133.1, 132.3, 131.9, 130.5, 130.1, 129.2, 127.9, 127.7, 125.8, 125.6, 114.4, 103.2, 56.6, 39.6, 34.8. Recrystallization of **III-67c** from a mixture of dichloromethane and hexanes produced a crystal suitable for X-ray structure analysis.

Propargylic Alcohol III-69a. To a mixture of 269 mg (1.04 mmol) of **III-68**, 22 mg

(0.030 mmol) of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, and 11 mg (0.060 mmol) of copper(I) iodide in 20 mL of triethylamine under a nitrogen atmosphere was added dropwise via cannula a solution of 103 mg of 3,3-dimethyl-1-butyne (1.25 mmol) in 5 mL of triethylamine. The reaction mixture was stirred at room temperature for 12 h before 20 mL of a saturated NH_4Cl solution and 50 mL of diethyl ether were introduced. The organic layer was separated, and the aqueous layer was back extracted with diethyl ether. The combined organic layers were washed with water, dried over MgSO_4 , and concentrated. The residue was purified by column chromatography (silica gel/diethyl ether:hexanes = 1:2) to give 203 mg (0.96 mmol, 92%) of **III-69a** as a colorless liquid: IR 3331, 1025, 755 cm^{-1} ; ^1H δ 7.33-7.42 (2 H, m), 7.14-7.25 (2 H, m), 4.52 (2 H, s), 1.97 (1 H, br), 1.33 (9 H, s); ^{13}C δ 131.6, 131.5, 128.1, 127.1, 126.6, 124.9, 103.0, 90.6, 84.6, 77.7, 51.6, 30.9, 28.1; MS m/z 212 (M^+), 197, 178, 165.

Propargyl Methanesulfonate III-70a. To a solution of **III-69a** (68 mg, 0.32 mmol) and triethylamine (49 mg, 0.48 mmol) in 10 mL of methylene chloride at $-50\text{ }^\circ\text{C}$ under a nitrogen atmosphere was added dropwise methanesulfonyl chloride (48 mg, 0.42 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 h before 5 mL of water was introduced. The organic layer was separated, and the aqueous layer was back extracted with methylene chloride. The combined organic layers were washed with water, dried over MgSO_4 , and concentrated. The residue was purified by column chromatography (silica gel/ethyl acetate:hexanes = 1:2) to give 76 mg (0.26 mmol, 81%) of **III-70a** as a colorless liquid: IR 2239, 1362, 1179 cm^{-1} ; ^1H δ 7.35-7.44 (2 H, m), 7.28 (1 H, td, $J = 7.6, 1.6\text{ Hz}$), 7.21 (1 H, td, $J = 7.4, 1.6\text{ Hz}$), 5.11

(2 H, s), 3.16 (3 H, s), 1.34 (9 H, s); ^{13}C δ 132.0, 131.8, 129.0, 127.2, 127.1, 103.6, 88.3, 83.8, 77.3, 58.4, 39.2, 30.9, 28.1.

Propargyl Methanesulfonate III-70b. To a solution of **III-69b** (164 mg, 0.72 mmol) and triethylamine (109 mg, 1.08 mmol) in 10 mL of methylene chloride at $-50\text{ }^{\circ}\text{C}$ under a nitrogen atmosphere was added dropwise methanesulfonyl chloride (108 mg, 0.94 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 h before 5 mL of water was introduced. The organic layer was separated, and the aqueous layer was back extracted with methylene chloride. The combined organic layers were washed with water, dried over MgSO_4 , and concentrated. The residue was purified by column chromatography (silica gel/ethyl acetate:hexanes = 1:4) to give 196 mg (0.64 mmol, 89%) of **III-70b** as a colorless liquid: IR 2232, 2159, 1367, 1177 cm^{-1} ; ^1H δ 7.41–7.50 (2 H, m), 7.25–7.35 (2 H, m), 5.12 (2 H, s), 3.17 (3 H, s), 0.27 (9 H, s); ^{13}C δ 132.4, 132.2, 129.1, 128.3, 126.1, 124.0, 102.7, 99.4, 87.9, 84.4, 58.4, 39.3, -0.1 .

Pyridinium Methanesulfonate III-71a. To a solution of **III-70a** (26 mg, 0.090 mmol) in 5 mL of methylene chloride was added dropwise a solution of 4-(dimethylamino)pyridine (11 mg, 0.090 mmol) in 5 mL of methylene chloride. The reaction mixture was stirred at room temperature for 24 h and concentrated. The residue was washed with diethyl ether to give 36 mg (0.087 mmol, 97%) of **III-71a** as a colorless solid: mp $127\text{--}128\text{ }^{\circ}\text{C}$; IR 2238, 1652, 1192 cm^{-1} ; ^1H δ 8.56 (2 H, d, $J = 7.4$ Hz), 7.35–7.41 (2 H, m), 7.16–7.28 (2 H, m), 6.96 (2 H, d, $J = 7.6$ Hz), 5.44 (2 H, s), 3.22 (6 H, s), 2.75 (3 H, s), 1.25 (9 H, s); ^{13}C δ 156.5, 141.9, 132.3, 131.9, 129.0,

127.3, 126.8, 123.1, 108.1, 103.2, 88.6, 82.7, 47.7, 40.3, 39.5, 30.9, 28.1.

Pyridinium Methanesulfonate III-71b. To a solution of **III-70b** (26 mg, 0.085 mmol) in 5 mL of methylene chloride was added dropwise a solution of 4-(dimethylamino)pyridine (10.4 mg, 0.085 mmol) in 5 mL of methylene chloride. The reaction mixture was stirred at room temperature for 24 h and concentrated. The residue was washed with diethyl ether to give 36 mg (0.084 mmol, 99%) of **III-71b** as a colorless solid: compound becomes black at 162 °C without melting; IR 2158, 1652, 1194 cm^{-1} ; ^1H δ 8.61 (2 H, d, $J = 7.4$ Hz), 7.43–7.49 (2 H, m), 7.28–7.34 (2 H, m), 6.97 (2 H, d, $J = 7.7$ Hz), 5.48 (2 H, s), 3.25 (6 H, s), 2.79 (3 H, s), 0.21 (9 H, s); ^{13}C δ 156.6, 141.9, 132.5, 132.4, 129.1, 128.4, 125.7, 123.5, 108.1, 103.0, 98.9, 88.3, 83.2, 47.8, 40.3, 39.5, 0.0.

2-(Dimethylamino)-12-(1,1-dimethylethyl)-7H-indeno[1,2-*b*]quinolizin-5-ium

Chloride (III-73a). A solution of **III-71a** (26 mg, 0.063 mmol) and triethylamine (6 mg, 0.06 mmol) in 10 mL of ethanol was heated under reflux for 48 h. The solvent was removed in vacuo, and the residue was purified by column chromatography (neutral alumina/ethanol:methylene chloride = 1:10) to give 7 mg (0.020 mmol, 32%) of **III-73a** as a yellow solid: mp > 360 °C; IR 1646, 1236, cm^{-1} ; ^1H δ 10.14 (1 H, d, $J = 7.6$ Hz), 9.52 (1 H, s), 8.03 (1 H, dd, $J = 6.9, 2.1$ Hz), 7.60 (1 H, d, $J = 6.6$ Hz), 7.41–7.51 (2 H, m), 7.24 (1 H, dd, $J = 7.6, 2.9$ Hz), 7.11 (1 H, d, $J = 2.6$ Hz), 4.17 (2 H, s), 3.27 (6 H, s), 1.77 (9 H, s); ^{13}C δ 150.4, 148.1, 146.3, 143.5, 139.1, 138.6, 136.2, 133.7, 130.4, 129.7, 127.1, 126.7, 125.7, 109.1, 101.8, 40.1, 37.1, 34.7, 31.8. Recrystallization of **III-73a** from a mixture of dichloromethane and hexanes produced

a crystal suitable for X-ray structure analysis.

2-(Dimethylamino)-12-(trimethylsilyl)-7*H*-indeno[1,2-*b*]quinolizin-5-ium

Chloride (III-73b). A solution of **III-71b** (30 mg, 0.070 mmol) and triethylamine (7 mg, 0.07 mmol) in 10 mL of ethanol was heated under reflux for 48 h. The solvent was removed in vacuo, and the residue was purified by column chromatography (neutral alumina/ethanol:methylene chloride = 1:10) to give 11 mg (0.030 mmol, 43%) of **III-73b** as a yellow solid: mp > 360 °C; IR 1646, 1235 cm⁻¹; ¹H δ 10.16 (1 H, d, *J* = 7.6 Hz), 9.70 (1 H, s), 7.93 (1 H, d, *J* = 7.6 Hz), 7.62 (1 H, d, *J* = 7.6 Hz), 7.40–7.56 (3 H, m), 7.21 (1 H, dd, *J* = 7.6, 2.9 Hz), 6.98 (1 H, d, *J* = 2.6 Hz), 4.15 (2 H, s), 3.26 (6 H, s), 0.62 (9 H, s); ¹³C δ 157.1, 151.4, 147.0, 146.6, 139.2, 138.2, 132.6, 131.2, 130.5, 127.7, 126.7, 125.9, 125.3, 109.2, 103.2, 40.1, 34.5, 2.6.

11-Phenyl-6*H*-indeno[1,2-*d*]imidazo[1,2-*a*]pyridine (III-76). To a stirred mixture of imidazole (10 mg, 0.15 mmol), tetrabutylammonium iodide (27 mg, 0.073 mmol) and sodium hydroxide (50% aqueous solution, 0.52 mL) in toluene (0.41 mL) was added **III-61** (47 mg, 0.15 mmol). After 15 min at room temperature, toluene (0.5 mL) and water (0.5 mL) were added. The organic layer was separated, washed with water, dried over MgSO₄, and concentrated. The residue was purified by column chromatography (silica gel/diethyl ether:methanol = 100:3) to give 11 mg (0.039 mmol, 26%) of **III-76** as a pale yellow solid.

Alternatively, **III-76** was synthesized by treatment of a mixture of 15 mg (0.021 mmol) of Pd(PPh₃)₂Cl₂, 7.5 mg (0.039 mmol) of copper(I) iodide, and 200 mg (0.658 mmol) of **III-59** under a nitrogen atmosphere with 5 mL of DMF, 2 mL of

triethylamine, and a solution of 85 mg (0.80 mmol) of **III-77** in 5 mL of DMF. The reaction mixture was heated at 100 °C for 48 h before it was allowed to cool to room temperature. The reaction mixture was then poured into a flask containing 40 mL of ethyl acetate and 5 mL of a saturated NH₄Cl solution. The organic layer was separated, washed with water, dried over MgSO₄, and concentrated. The residue was purified by column chromatography (silica gel/diethyl ether:methanol = 100:3) to give 181 mg (0.642 mmol, 98%) of a mixture of **III-74** and **III-76** (1:4) as a pale yellow solid. The ¹H NMR spectrum of the mixture exhibited a singlet at δ 5.02, attributable to the methylene hydrogens of **III-74**.

To a solution of 181 mg (0.642 mmol) of a mixture of **III-74** and **III-76** (1:4) in 5 mL of *t*-butyl alcohol under a nitrogen atmosphere was added 0.64 mL of a 1.0 M solution of potassium *t*-butoxide in *t*-butyl alcohol. The reaction mixture was stirred at room temperature for 12 h before 5 mL of water and 20 mL of ethyl acetate were introduced. The organic layer was separated, washed with water, dried over MgSO₄, and concentrated. The residue was purified by column chromatography (silica gel/diethyl ether:methanol = 100:3) to give 181 mg (0.642 mmol, 100%) of **III-76** as a pale yellow solid: mp 217-218 °C; IR 1301, 1234, 727, 699 cm⁻¹; ¹H δ 8.34 (1 H, s), 7.68 (1 H, d, *J* = 1.2 Hz), 7.47-7.64 (7 H, m), 7.29 (1 H, td, *J* = 7.4, 1.0 Hz), 7.08 (1 H, t, *J* = 7.9 Hz), 6.87 (1 H, d, *J* = 7.9 Hz) 4.07 (2 H, s); ¹³C δ 145.7, 144.0, 139.3, 137.2, 134.9, 133.8, 129.6, 129.1, 128.6, 128.4, 128.1, 126.9, 125.1, 123.9, 120.0, 112.3, 33.6. Recrystallization of **III-76** from a mixture of dichloromethane and hexanes produced a crystal suitable for X-ray structure analysis.

Indole III-83. To a mixture of 7 mg (0.010 mmol) of Pd(PPh₃)₂Cl₂, 4 mg (0.020 mmol) of copper(I) iodide, and 104 mg (0.34 mmol) of **III-59** under a nitrogen atmosphere was added in sequence 5 mL of DMF, 2 mL of triethylamine, and a solution of 58 mg (0.38 mmol) of **III-82** in 5 mL of DMF. After 4 h of stirring at room temperature, the reaction mixture was poured into a flask containing 40 mL of ethyl acetate and 5 mL of a saturated NH₄Cl solution. The organic layer was separated, washed with water, dried over MgSO₄, and concentrated. The residue was purified by column chromatography (silica gel/hexanes:methylene chloride = 95:5) to give 111 mg (0.335 mmol, 99%) of **III-83** as a white solid: mp 123-124 °C; IR 2216, 1494, 755, 742, 690 cm⁻¹; ¹H δ 7.67-7.71 (1 H, m), 7.48-7.58 (3 H, m), 7.39-7.46 (3 H, m), 7.28-7.38 (5 H, m), 7.14-7.26 (2 H, m), 6.52 (1 H, dd, *J* = 3.2, 0.8 Hz), 5.19 (2 H, s); ¹³C δ 135.8, 132.1, 131.9, 131.7, 128.8, 128.4, 128.33, 128.28, 127.9, 127.3, 125.9, 124.7, 122.9, 121.8, 121.0, 119.7, 109.4, 101.8, 93.4, 87.9, 86.9, 84.0, 36.7.

12-Phenyl-7*H*-indeno[1',2':4,5]pyrido[1,2-*a*]indole (III-84). To a solution of 41 mg (0.12 mmol) of **III-83** in 5 mL of anhydrous toluene under a nitrogen atmosphere was added 0.1 mL of a 1.0 M solution of potassium *t*-butoxide in *t*-butyl alcohol. After 48 h of stirring at room temperature, 5 mL of water and 20 mL of ethyl acetate were introduced. The organic layer was separated, washed with water, dried over MgSO₄, and concentrated. The residue was purified by column chromatography (silica gel/hexanes:methylene chloride = 95:5) to give 40 mg (0.12 mmol, 98%) of **III-84** as a pale yellow solid: mp 170-173 °C; IR 1459, 1323, 762, 724, 700 cm⁻¹; ¹H δ 8.44 (1 H, s), 7.90 (1 H, d, *J* = 7.6 Hz), 7.70 (1 H, d, *J* = 7.6 Hz), 7.50-7.65 (5 H, m), 7.48 (1

H, d, $J = 7.6$ Hz), 7.22-7.35 (3 H, m), 7.05 (1 H, t, $J = 7.5$ Hz), 6.79 (1 H, d, $J = 7.9$ Hz), 6.31 (1 H, s), 4.09 (2 H, s); ^{13}C δ 144.4, 139.5, 138.5, 137.0, 134.5, 129.5, 129.1, 128.2, 127.8, 126.7, 125.2, 123.9, 123.7, 122.4, 120.3, 119.4, 118.1, 110.0, 91.9, 33.6.

2(1*H*)-Pyridinone III-86. To a mixture of 12 mg (0.017 mmol) of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, 6.5 mg (0.034 mmol) of copper(I) iodide, and 171 mg (0.56 mmol) of **III-59** under a nitrogen atmosphere was added in sequence 5 mL of DMF, 2 mL of triethylamine, and a solution of 82 mg (0.62 mmol) of **III-85** in 5 mL of DMF. After 1 h of stirring at room temperature, the reaction mixture was poured into a flask containing 40 mL of ethyl acetate and 10 mL of a saturated NH_4Cl solution. The organic layer was separated, washed with water, dried over MgSO_4 , and concentrated. The residue was purified by column chromatography (silica gel/hexanes:ethyl acetate = 1:1) to give 171 mg (0.553 mmol, 99%) of **III-86** as a colorless solid: mp 76-78 °C; IR 1660, 1588, 1538, 757 cm^{-1} ; ^1H δ 7.91 (1 H, dt, $J = 6.9, 0.9$ Hz), 7.45-7.57 (4 H, m), 7.24-7.39 (6 H, m), 6.58 (1 H, dd, $J = 9.2, 0.5$ Hz), 5.93 (1 H, dt, $J = 6.7, 0.8$ Hz), 5.07 (2 H, s); ^{13}C δ 162.1, 139.7, 135.7, 132.0, 131.9, 131.7, 128.6, 128.4, 128.1, 125.9, 124.3, 122.8, 120.2, 106.4, 93.4, 87.8, 86.6, 85.6, 38.5.

4,7-Dihydro-12-phenylindeno[2,1-*g*]quinolizin-4-one (III-87). To a solution of 155 mg (0.502 mmol) of **III-86** in 30 mL of anhydrous toluene under nitrogen atmosphere was added 0.5 mL of a 1.0 M solution of potassium *t*-butoxide in *t*-butyl alcohol. The reaction mixture was heated under reflux for 12 h. After the reaction mixture was allowed to cool to room temperature, 20 mL of water and 50 mL of ethyl acetate were

introduced. The organic layer was separated, washed with water, dried over MgSO_4 , and concentrated. The residue was purified by column chromatography (silica gel/methanol:methylene chloride = 1:100) to give 87 mg (0.28 mmol, 56%) of **III-87** as a pale yellow solid: mp 205-207 °C; IR 1659, 1482 cm^{-1} ; ^1H δ 9.44 (1 H, s), 7.59-7.72 (3 H, m), 7.50-7.59 (2 H, m), 7.32-7.43 (3 H, m), 7.08 (1 H, t, J = 7.9 Hz), 6.69 (1 H, d, J = 8.6 Hz), 6.46 (1 H, d, J = 7.9 Hz), 6.36 (1 H, d, J = 7.9 Hz), 4.18 (2 H, s); ^{13}C δ 145.5, 143.4, 141.9, 138.1, 137.0, 135.6, 130.5, 129.8, 129.7, 129.5, 129.0, 128.9, 127.3, 125.4, 124.8, 121.7, 107.4, 103.3, 34.4. Recrystallization of **III-87** from a mixture of dichloromethane and hexanes under a nitrogen atmosphere produced a crystal suitable for X-ray structure analysis.

Experimental Section of Chapter 3.3

Compound III-42 To a mixture of 161 mg (0.23 mmol) of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, 43.8 mg (0.23 mmol) of copper(I) iodide, and 1906 mg (7.72 mmol) of 2-iodoformanilide under a nitrogen atmosphere was added in sequence 10 mL of DMF, 5 mL of triethylamine, and a solution of 1232 mg (9.26 mmol) of **III-85** in 10 mL of DMF. After 12 h of stirring at room temperature, the reaction mixture was poured into a flask containing 100 mL of ethyl acetate and 20 mL of a saturated NH_4Cl solution. The organic layer was separated, washed with water, dried over MgSO_4 , and concentrated. The residue was purified by column chromatography (silica gel/ethyl acetate:methanol = 50:1) to give 1653 mg (6.56 mmol, 85%) of **III-42** as a colorless solid: mp 106-107 °C.

Compound III-98 To a mixture of 32 mg (0.046 mmol) of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, 8.8 mg

(0.046 mmol) of copper(I) iodide, and 379 mg (1.53 mmol) of 2-iodoformanilide under a nitrogen atmosphere was added in sequence 5 mL of DMF, 2 mL of triethylamine, and a solution of 245 mg (1.84 mmol) of **III-85** in 10 mL of DMF. After 12 h of stirring at room temperature, the mixture was exposed to air for 3 months. The residue was dissolved in the mixture of 40 mL of ethyl acetate and 10 mL of a saturated NH_4Cl solution. The organic layer was separated, washed with water, dried over MgSO_4 , and concentrated. The residue was purified by column chromatography (silica gel/ethyl acetate:methanol = 50:1) to give 435 mg (1.53 mmol, 100%) of **III-98** as a colorless solid: 164-165 °C. The structure of **III-98** was established by X-ray structure analysis.

Experimental Section of Chapter 3.4

2-bromo-6-methoxyl-pyridine, TMSCl , propargyl bromide, iodobenzene and 2-bromopyridine were purchased from chemical suppliers and were used as received.

Compound III-102 To a mixture of 2-bromo-6-methoxyl-pyridine (1.88 g, 10 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.21 g, 0.3 mmol) and copper(I) iodide (0.057 g, 0.3 mmol) in 20 mL of triethylamine was added 1.22 g of phenylacetylene (12 mmol). After 12 h of stirring at room temperature, 20 mL of a saturated aqueous ammonium chloride solution and 40 mL of diethyl ether were added. The organic layer was separated, and the aqueous layer was back extracted with diethyl ether. The combined organic layers were washed with brine and water, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (silica gel/hexanes:ethyl ether = 10:1) afforded 2.0 g of **II-102** (9.6 mmol, 96% yield); ^1H δ 7.65-7.49 (3 H, m),

7.40-7.32 (3 H, m), 7.14 (1 H, dd, $J = 7.3, 0.6$ Hz), 6.72 (1 H, dd, $J = 8.3, 0.6$ Hz), 3.99 (3 H, s); ^{13}C δ 163.8, 140.2, 138.4, 131.9, 128.8, 128.3, 122.4, 120.7, 111.0, 88.8, 88.5, 53.5.

Compound III-104 Chlorotrimethylsilane (2.0 mL, 15.4 mmol) was added slowly to a mixture of **III-102** (1.05 g, 5.02 mmol) and sodium iodide (2.31 g, 15.4 mmol) in acetonitrile (8 mL) and stirred at 80 °C for 6 h. The resultant solution was cooled to room temperature, poured into 5% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and brine and extracted with ethyl acetate. The combined organic layers were dried and concentrated. The residue was purified by column chromatography (silica gel/methylene chloride:ethyl acetate = 1:1) to give 0.83 g of **III-103** (Containing small amount impurities). To a mixture of 0.83 g of **III-103** and potassium carbonate (1.38 g, 10 mmol) in dry DME (10 mL) was added a solution of propargyl bromide (80% in toluene, 1.1 g, 7.5 mmol). The resulting mixture was stirred at 60 °C for 16 h. The mixture was then filtered, the filtrate evaporated in vacuo and the residue dissolved in methylene chloride (50 mL) and washed with water. The organic layer was separated, dried (MgSO_4), and concentrated. The residue was purified by column chromatography (silical gel, methylene chloride:ethyl acetate = 4:1) to give 515 mg (2.21 mmol, 44%) of **III-104** as a colorless solid: mp 110-114 °C; ^1H (600 MHz) δ 7.59-7.56 (2 H, m), 7.45-7.37 (3 H, m), 7.31-7.25 (1 H, m), 6.63 (1 H, dd, $J = 9.6, 0.6$ Hz), 6.54 (1 H, dd, $J = 6.6, 0.6$ Hz), 5.06 (2 H, d, $J = 2.4$ Hz), 2.28 (1 H, t, $J = 2.4$ Hz); ^{13}C (150 MHz) δ 161.7, 138.6, 131.8, 131.1, 129.8, 128.6, 121.7, 112.3, 97.6, 81.8, 78.1, 71.8, 35.4.

Compound III-105 To a mixture of iodobenzene (108 mg, 0.53 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$

(19 mg, 0.027 mmol) and copper(I) iodide (5 mg, 0.027 mmol) in 5 mL of triethylamine was added 123 mg of **III-104** (0.53 mmol) in 2 mL of THF. After 1 h of stirring at room temperature, 5 mL of a saturated aqueous ammonium chloride solution and 20 mL of methylene chloride were added. The organic layer was separated, and the aqueous layer was back extracted with methylene chloride. The combined organic layers were washed with brine and water, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (silica gel/ methylene chloride:ethyl acetate = 4:1) afforded 127 mg of **III-105** (0.41 mmol, 77% yield) as a pale yellow solid: ^1H (600 MHz) δ 7.61-7.58 (2 H, m), 7.43-7.36 (5 H, m), 7.32-7.22 (4 H, m), 6.66 (1 H, dd, J = 9.0, 0.6 Hz), 6.57 (1 H, dd, J = 7.2, 0.6 Hz), 5.30 (2 H, s); ^{13}C (150 MHz) δ 161.8, 138.6, 132.0, 131.9, 129.8, 129.3, 129.1, 128.9, 128.6, 128.4, 128.2, 121.7, 112.3, 97.7, 83.7, 83.5, 82.2, 36.2.

Compound III-106 and III-107 A solution of **III-105** (50 mg, 0.16 mmol) in 5 mL of ethanol was heated under reflux for 12 h. The solvent was removed in vacuo and the residue was purified by flash column chromatography (silica gel/ methylene chloride:ethyl acetate = 1:2) to give 26.5 mg of **III-106** and then (silica gel/ethyl acetate) to give 15 mg of **III-107**. **III-106**: mp submit > 260 °C ^1H (600 MHz) δ 8.27 (1 H, s), 8.01 (1 H, d, J = 8.4 Hz), 7.74 (1 H, d, J = 8.4 Hz), 7.62-7.47 (6 H, m), 7.40-7.37 (2 H, m), 6.93 (1 H, d, J = 6.6 Hz), 6.58 (1 H, d, J = 9.6 Hz), 5.05 (2 H, s); ^{13}C (150 MHz) δ 161.8, 148.0, 140.1, 136.9, 135.6, 133.6, 133.13, 133.08, 131.4, 129.3, 129.0, 128.8, 128.3, 127.4, 126.5, 126.1, 120.3, 118.0, 99.0, 52.3. The structure of **III-106** was established by X-ray structure analysis. **III-107**: mp 243-244 °C ^1H

(600 MHz) δ 8.07 (1 H, s), 7.96 (1 H, d, J = 8.4 Hz), 7.64-7.55 (5 H, m), 7.44 (1 H, td, J = 7.2, 1.8 Hz), 7.39-7.35 (2 H, m), 7.23 (1 H, td, J = 7.2, 1.8 Hz), 6.49 (1 H, d, J = 9.0 Hz), 5.46 (1 H, d, J = 7.2 Hz), 5.31 (2 H, s); ^{13}C (150 MHz) δ 161.8, 147.6, 140.0, 136.7, 136.4, 134.1, 134.0, 132.8, 129.6, 129.2, 128.5, 128.0, 127.3, 126.9, 126.5, 121.8, 117.6, 102.6, 51.7. The structure of **III-107** was established by X-ray structure analysis.

Compound III-108 To a mixture of 2-bromopyridine (79 mg, 0.50 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (12 mg, 0.017 mmol) and copper(I) iodide (3 mg, 0.017 mmol) in 5 mL of triethylamine was added 78 mg of **III-104** (0.33 mmol) in 2 mL of THF. After 12 h of stirring at room temperature, 5 mL of a saturated aqueous ammonium chloride solution and 20 mL of methylene chloride were added. The organic layer was separated, and the aqueous layer was back extracted with methylene chloride. The combined organic layers were washed with brine and water, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (silica gel/ methylene chloride:ethyl acetate = 1:1) afforded 32 mg of **III-108** (0.10 mmol, 77% yield) as a pale yellow solid.

Compound III-109 and III-110 A solution of **III-108** (25 mg, 0.08 mmol) in 5 mL of ethanol was heated under reflux for 36 h. The solvent was removed in vacuo and the residue was purified by flash column chromatography (silica gel/ethyl acetate:methanol = 20:1) to give 19.5 mg of **III-109** and 2.0 mg of **III-110**. The structures of both **III-109** and **III-110** were established by X-ray structure analysis.

Compound III-112 and III-116 A solution of **III-104** (68 mg, 0.29 mmol) in 5 mL of

p-xylene was heated under reflux for 20 h. The mixture was purified by flash column chromatography (silica gel/ methylene chloride:ethyl acetate = 3:2) to give a mixture of 61 mg of **III-112** and **III-116** (ratio = 2:1 as indicated by the proton NMR). The structure of **III-112** was established by X-ray structure analysis.

Experimental Section of Chapter 3.5

Sodium hydride, DMF, DBU and 1-iodo-2,3-dimethoxybenzene were purchased from chemical suppliers and were used as received.

Compound III-44 To a solution of 6-oxo-1,6-dihydropyridine-2-carbonitrile (120 mg, 1 mmol) in DME (2.0 mL) and DMF (0.5 mL) under nitrogen was added 60% NaH (42 mg, 1.05 mmol) at 0 °C. LiBr was added (174 mg, 2 mmol) 10 min later. The mixture was stirred 15 min at room temperature, the phenyl propargyl bromide⁶³ (390 mg, 2 mmol) was added, and the reaction was heated at 65 °C for 15 h. After cooled to room temperature, the mixture was poured into brine (50 mL), extracted with AcOEt (2 x 50 mL), and dried over sodium sulfate and concentrated. The residue was purified by column chromatography (silical gel, AcOEt) to give 201 mg (0.86 mmol, 86%) of **III-44** as a colorless solid: mp 104-105 °C; IR 2222, 1655, 1586, 1148, 815, 758, 686 cm⁻¹; ¹H δ 7.48-7.38 (2 H, m), 7.36-7.21 (4 H, m), 6.84 (1 H, dd, *J* = 9.4, 1.2 Hz), 6.77 (1 H, dd, *J* = 6.9, 1.5 Hz), 5.14 (2 H, s); ¹³C δ 160.1, 137.6, 132.0, 128.8, 128.2, 127.4, 121.8, 120.7, 116.2, 112.3, 85.3, 81.7, 36.7.

Compound III-40 The mixture of **III-44** (50 mg, 0.21 mmol), DBU (32 mg, 0.21 mmol) in 4 mL 1,2-dichlorobenzene was heated to 120 °C under nitrogen. After cooled to room temperature, the mixture was purified by column chromatography

(silical gel, AcOEt:MeOH = 6:1) to give 50 mg (0.21 mmol, 100%) of **III-40** as a pale orange solid: mp 252-253 °C; IR 1666, 1599, 803, 784, 757, 730 cm^{-1} ; ^1H δ 8.31 (1 H, s), 8.18 (1 H, d, J = 8.6 Hz), 7.87 (1 H, d, J = 8.2 Hz), 7.78 (1 H, td, J = 6.9, 1.5 Hz), 7.71-7.56 (2 H, m), 7.28 (1 H, d, J = 6.9 Hz), 6.71 (1 H, dd, J = 8.9, 0.5 Hz), 5.22 (2 H, d, J = 0.5 Hz); ^{13}C δ 161.5, 152.8, 148.7, 146.0, 140.3, 130.9, 130.3, 129.5, 128.5, 128.02, 127.97, 127.6, 120.5, 100.9, 49.9. The structure of **III-40** was established by X-ray structure analysis.

Compound III-129 To a solution of 6-oxo-1,6-dihydropyridine-2-carbonitrile (120 mg, 1 mmol) in DME (2.0 mL) and DMF (0.5 mL) under nitrogen was added 60% NaH (42 mg, 1.05 mmol) at 0 °C. LiBr was added (174 mg, 2 mmol) 10 min later. The mixture was stirred 15 min at room temperature, the 4-methoxyphenyl propargyl bromide (450 mg, 2 mmol) was added, and the reaction was heated at 65 °C for 15 h. After cooled to room temperature, the mixture was poured into brine (50 mL), extracted with AcOEt (2 x 50 mL), and dried over sodium sulfate and concentrated. The residue was purified by column chromatography (silical gel, AcOEt) to give 243 mg (0.92 mmol, 92%) of **III-129** as a colorless solid: mp 130-131 °C; IR 2221, 1656, 1583, 1510, 1245, 1144, 1032, 836, 800, 725, 663 cm^{-1} ; ^1H δ 7.42-7.25 (3 H, m), 6.89-6.73 (4 H, m), 5.13 (2 H, s), 3.77 (3 H, s); ^{13}C δ 160.1, 160.0, 137.6, 133.5, 127.4, 120.6, 116.2, 113.8, 112.3, 85.2, 80.3, 55.2, 36.8. The structure of **III-129** was established by X-ray structure analysis.

Compound III-130 To a solution of 6-oxo-1,6-dihydropyridine-2-carbonitrile (120 mg, 1 mmol) in DME (2.0 mL) and DMF (0.5 mL) under nitrogen was added 60% NaH

(42 mg, 1.05 mmol) at 0 °C. LiBr was added (174 mg, 2 mmol) 10 min later. The mixture was stirred 15 min at room temperature, the 2-methoxyphenyl propargyl bromide⁶⁴ (450 mg, 2 mmol) was added, and the reaction was heated at 65 °C for 15 h. After cooled to room temperature, the mixture was poured into brine (50 mL), extracted with AcOEt (2 x 50 mL), and dried over sodium sulfate and concentrated. The residue was purified by column chromatography (silical gel, AcOEt) to give 227 mg (0.86 mmol, 86%) of **III-130** as a pale yellow solid: mp 136-137 °C; IR 2234, 1660, 1581, 1266, 1024, 822, 756 cm⁻¹; ¹H δ 7.41 (1 H, dd, *J* = 7.4, 1.7 Hz), 7.38-7.24 (2 H, m), 6.92-6.81 (3 H, m), 6.78 (1 H, dd, *J* = 6.7, 1.2 Hz), 5.21 (2 H, s), 3.85 (3 H, s); ¹³C δ 160.4, 160.1, 137.6, 134.0, 130.3, 127.4, 120.8, 120.3, 116.2, 112.3, 111.0, 110.6, 85.6, 81.9, 55.7, 36.9.

Compound III-131 To a solution of 6-oxo-1,6-dihydropyridine-2-carbonitrile (120 mg, 1 mmol) in DME (2.0 mL) and DMF (0.5 mL) under nitrogen was added 60% NaH (42 mg, 1.05 mmol) at 0 °C. LiBr was added (174 mg, 2 mmol) 10 min later. The mixture was stirred 15 min at room temperature, the 3-methoxyphenyl propargyl bromide (450 mg, 2 mmol) was added, and the reaction was heated at 65 °C for 15 h. After cooled to room temperature, the mixture was poured into brine (50 mL), extracted with AcOEt (2 x 50 mL), and dried over sodium sulfate and concentrated. The residue was purified by column chromatography (silical gel, AcOEt) to give 222 mg (0.84 mmol, 84%) of **III-131** as a colorless solid: mp 95-96 °C; IR 2224, 1668, 1593, 1149, 801, 774, 684 cm⁻¹; ¹H δ 7.32 (1 H, dd, *J* = 9.4, 6.7 Hz), 7.21-7.14 (1 H, m), 7.07-6.99 (1 H, m), 6.98-6.93 (1 H, m), 6.90-6.81 (2 H, m), 6.77 (1 H, dd, *J* = 6.7,

1.2 Hz), 5.14 (2 H, s), 3.75 (3 H, s); ^{13}C δ 160.0, 159.1, 137.7, 129.2, 127.4, 124.4, 122.6, 120.6, 116.5, 116.2, 115.5, 112.3, 85.1, 81.4, 55.2, 36.6.

Compound III-132 To a solution of 6-oxo-1,6-dihydropyridine-2-carbonitrile (48 mg, 0.4 mmol) in DME (1.0 mL) and DMF (0.25 mL) under nitrogen was added 60% NaH (17 mg, 0.42 mmol) at 0 °C. LiBr was added (70 mg, 0.8 mmol) 10 min later. The mixture was stirred 15 min at room temperature, the 2,3-dimethoxyphenyl propargyl bromide⁶⁵ (204 mg, 0.8 mmol) was added, and the reaction was heated at 65 °C for 15 h. After cooled to room temperature, the mixture was poured into brine (20 mL), extracted with AcOEt (2 x 20 mL), and dried over sodium sulfate and concentrated. The residue was purified by column chromatography (silical gel, AcOEt) to give 89 mg (0.3 mmol, 76%) of **III-132** as a colorless solid: mp 124-125 °C; IR 2230, 1663, 1475, 1100, 997, 806, 787, 753 cm^{-1} ; ^1H δ 7.33 (1 H, dd, J = 9.4, 6.7 Hz), 7.03-6.82 (4 H, m), 6.78 (1 H, dd, J = 6.7, 1.2 Hz), 5.19 (2 H, s), 3.89 (3 H, s), 3.82 (3 H, s); ^{13}C δ 160.1, 152.6, 150.8, 137.7, 127.4, 125.2, 123.7, 120.7, 116.4, 116.2, 113.4, 112.3, 85.6, 81.5, 61.1, 55.9, 36.9.

III-133 The mixture of **III-129** (50 mg, 0.19 mmol), DBU (29 mg, 0.19 mmol) in 4 mL 1,2-dichlorobenzene was heated to 120 °C under nitrogen. After cooled to room temperature, the mixture was purified by column chromatography (silical gel, AcOEt:MeOH = 6:1) to give 50 mg (0.19 mmol, 100%) of **III-133** as a pale yellow solid: mp 250-251 °C; IR 1666, 1618, 1597, 1224, 1130, 1023, 813, 767, 751, 725 cm^{-1} ; ^1H δ 8.27 (1 H, s), 7.77 (1 H, d, J = 9.2 Hz), 7.66 (1 H, dd, J = 8.9, 6.9 Hz), 7.51 (1 H, s), 7.34-7.24 (2 H, m), 6.71 (1 H, d, J = 9.2 Hz), 5.21 (2 H, s), 3.99 (3 H, s); ^{13}C

δ 161.5, 152.6, 150.3, 146.0, 140.3, 130.9, 128.9, 126.6, 123.5, 121.3, 120.3, 106.9, 100.9, 55.7, 49.9.

III-134 The mixture of **III-130** (50 mg, 0.19 mmol), DBU (29 mg, 0.19 mmol) in 4 mL 1,2-dichlorobenzene was heated to 120 °C under nitrogen. After cooled to room temperature, the mixture was purified by column chromatography (silical gel, AcOEt:MeOH = 6:1) to give 50 mg (0.19 mmol, 100%) of **III-134** as a pale yellow solid: mp 270-271 °C; IR 1657, 1589, 1570, 1366, 1261, 1187, 1150, 1113, 806 cm^{-1} ; ^1H δ 8.76 (1 H, s), 7.77 (1 H, d, J = 8.4 Hz), 7.73-7.62 (2 H, m), 7.28 (1 H, d, J = 6.5 Hz), 6.92 (1 H, d, J = 6.9 Hz), 6.72 (1 H, dd, J = 9.2, 1.0 Hz), 5.22 (1 H, d, J = 0.7 Hz), 4.04 (3 H, s); ^{13}C δ 161.5, 155.1, 152.9, 149.4, 146.1, 140.2, 130.3, 127.6, 125.8, 121.4, 120.5, 120.4, 105.1, 100.9, 55.8, 50.0.

III-135 and **III-136** The mixture of **III-131** (50 mg, 0.19 mmol), DBU (29 mg, 0.19 mmol) in 4 mL 1,2-dichlorobenzene was heated to 120 °C under nitrogen. After cooled to room temperature, the mixture was purified by column chromatography (silical gel, AcOEt:MeOH = 6:1) to give 50 mg (0.19 mmol, 100%) of a mixture of **III-135** and **III-136** (3 : 4) as a pale yellow solid: **III-135** ^1H δ 8.28 (1 H, s), 8.16 (1 H, d, J = 9.4 Hz), 7.68 (1 H, dd, J = 8.9, 6.9 Hz), 7.47 (1 H, dd, J = 9.2, 2.7 Hz), 7.33 (1 H, d, J = 6.9 Hz), 7.17 (1 H, d, J = 2.7 Hz), 6.72 (1 H, d, J = 8.9 Hz), 5.27 (2 H, s), 3.98 (3 H, s); **III-136** mp 281-283 °C; IR 1656, 1591, 1259, 1239, 1155, 758, 712 cm^{-1} ; ^1H δ 8.35 (1 H, s), 7.67 (1 H, dd, J = 8.9, 6.9 Hz), 7.61-7.45 (2 H, m), 7.40 (1 H, d, J = 6.9 Hz), 7.15 (1 H, dd, J = 7.7, 1.2 Hz), 6.72 (1 H, d, J = 8.9 Hz), 5.27 (2 H, s), 4.14 (3 H, s); ^{13}C δ 161.5, 155.5, 152.0, 146.0, 140.8, 140.3, 130.9, 129.23, 129.20,

128.0, 120.4, 120.0, 108.5, 101.5, 56.3, 49.9. The structure of **III-136** was established by X-ray structure analysis.

III-137 The mixture of **III-132** (50 mg, 0.17 mmol), DBU (26 mg, 0.17 mmol) in 4 mL 1,2-dichlorobenzene was heated to 120 °C under nitrogen. After cooled to room temperature, the mixture was purified by column chromatography (silical gel, AcOEt:MeOH = 6:1) to give 50 mg (0.17 mmol, 100%) of **III-137** as a pale yellow solid: mp 216-218 °C; IR 1659, 1595, 1443, 1262, 1112, 1092, 1048, 988, 799, 736 cm^{-1} ; ^1H δ 8.61 (1 H, d, J = 0.7 Hz), 7.95 (1 H, d, J = 9.4 Hz), 7.64 (1 H, dd, J = 8.9, 6.7 Hz), 7.57 (1 H, d, J = 9.4 Hz), 7.22 (1 H, d, J = 6.2 Hz), 6.69 (1 H, dd, J = 8.9, 0.7 Hz), 5.23 (2 H, d, J = 1.0 Hz), 4.04 (3 H, s); ^{13}C δ 161.5, 151.2, 149.3, 146.1, 144.2, 142.0, 140.3, 128.6, 125.6, 124.9, 123.9, 120.2, 118.7, 100.5, 61.4, 56.7, 50.0.

III-143 To a solution of 3-(2-methoxyphenyl)-2-Propyn-1-ol (648 mg, 4 mmol) and triethylamine (607 mg, 5.78 mmol) in 20 mL of methylene chloride at -50 °C under a nitrogen atmosphere was added dropwise methanesulfonyl chloride (596 mg, 5.21 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 h and LiBr (3.48g, 40 mmol) in 20 mL of THF was then added. The mixture was stirred for 12 h at room temperature before 10 mL of water was introduced. The organic layer was separated, and the aqueous layer was back extracted with methylene chloride. The combined organic layers were washed with water, dried over MgSO_4 , and concentrated. The residue was purified by column chromatography (silical gel, diethyl ether:hexane = 1:10) to give 801 mg (3.56 mmol, 89%) of **III-143** as a colorless liquid: IR 2217, 1491, 1270, 1022, 749 cm^{-1} ; ^1H δ 7.42 (1 H, dd, J = 7.7, 1.7

Hz), 7.31 (1 H, td, $J = 8.2, 1.7$ Hz), 6.96-6.82 (2 H, m), 4.23 (2 H, s), 3.87 (3 H, s); ^{13}C δ 160.1, 133.9, 130.3, 120.4, 111.1, 110.5, 88.1, 83.1, 55.7, 15.8.

III-144 To a mixture of 1-Iodo-2,3-dimethoxybenzene (528 mg, 2 mmol), 70 mg (0.1 mmol) of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, and 38 mg (0.2 mmol) of copper(I) iodide in 25 mL of triethylamine under a nitrogen atmosphere was added dropwise via cannula a solution of 224 mg of propargyl alcohol (4 mmol) in 5 mL of triethylamine. The reaction mixture was stirred vigorously at 90 °C for 12 h before it was allowed to cool to room temperature. Then 50 mL of a saturated NH_4Cl solution and 50 mL of diethyl ether were introduced. The organic layer was separated, and the aqueous layer was back extracted with diethyl ether. The combined organic layers were washed with water, dried over MgSO_4 , and concentrated. The residue was purified by column chromatography (silical gel, diethyl ether:hexanes = 1:1) to give 180 mg (0.94 mmol, 47%) of **III-144** as a pale yellow liquid: IR 3420, 2227, 1470, 1260, 1096, 1001, 784, 745 cm^{-1} ; ^1H δ 7.04-6.86 (3 H, m), 4.53 (2 H, s), 3.92 (3 H, s), 3.86 (3 H, s), 1.80 (1 H, s); ^{13}C δ 152.6, 150.4, 125.1, 123.9, 117.2, 113.1, 91.2, 81.7, 61.0, 55.9, 51.8.

III-145 To a solution of **III-144** (170 mg, 0.89 mmol) and triethylamine (135 mg, 1.29 mmol) in 10 mL of methylene chloride at -50 °C under a nitrogen atmosphere was added dropwise methanesulfonyl chloride (133 mg, 1.16 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 h and LiBr (783 mg, 9 mmol) in 10 mL of THF was then added. The mixture was stirred for 12 h at room temperature before 5 mL of water was introduced. The organic layer was separated, and the aqueous layer was back extracted with methylene chloride. The

combined organic layers were washed with water, dried over MgSO_4 , and concentrated. The residue was purified by column chromatography (silical gel, diethyl ether:hexane = 1:10) to give 181 mg (0.71 mmol, 80%) of **III-145** as a colorless liquid: IR 2229, 1470, 1262, 1102, 998, 783, 744 cm^{-1} ; ^1H δ 7.03-6.86 (3 H, m), 4.21 (2 H, s), 3.93 (3 H, s), 3.86 (3 H, s); ^{13}C δ 152.6, 150.7, 125.2, 123.8, 116.8, 113.4, 88.0, 82.9, 61.2, 55.9, 15.5.

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Figure 6. ORTEP drawing of the crystal structure of **II-8**

Figure 7. ORTEP drawing of the crystal structure of **II-16**

Figure 8. ORTEP drawing of the crystal structure of diastereomer 1 of **II-20**

Figure 9. ORTEP drawing of the crystal structure of **II-28**

Figure 10. ORTEP drawing of the crystal structures of two independent molecules of **II-44**

Figure 11. ORTEP drawing of the crystal structures of two independent molecules of **II-46**

Figure 12. ORTEP drawing of the crystal structure of **III-67a**

Figure 13. ORTEP drawing of the crystal structure of **III-67b**

Figure 14. ORTEP drawing of the crystal structure of **III-67c**

Figure 15. ORTEP drawing of the crystal structure of **III-73a**

Figure 16. ORTEP drawing of the crystal structure of **III-76**

Figure 17. ORTEP drawing of the crystal structure of **III-87**

Figure 18. ORTEP drawing of the crystal structure of **III-98**

Figure 19. ORTEP drawing of the crystal structure of **III-106**

Figure 20. ORTEP drawing of the crystal structure of **III-107**

Figure 21. ORTEP drawing of the crystal structure of **III-109**

Figure 22. ORTEP drawing of the crystal structure of **III-110**

Figure 23. ORTEP drawing of the crystal structure of **III-112**

Figure 24. ORTEP drawing of the crystal structure of **III-40**

Figure 25. ORTEP drawing of the crystal structure of **III-129**

Figure 26. ORTEP drawing of the crystal structure of **III-136**

Figure 27. ORTEP drawing of the crystal structure of a substituted ABCD ring core

Figure 28. ORTEP drawing of the crystal structure of a substituted ABCD ring core

Figure 29. ORTEP drawing of the crystal structure of a polycyclic hydrocarbon

dai2sidecyc12704

Pulse Sequence: s2pul

Solvent: CDCl3

Temp. 25.0 C / 298.1 K

INOVIA-600 "inovae600"

Pulse 44.2 degrees

Acq. time 1.892 sec

Width 8000.0 Hz

8 repetitions

OBSERVE H1, 599.6669979 MHz

DATA PROCESSING

FI size 32768

Total time 0 min, 15 sec

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
 Solvent: CDCl₃
 Temp: 25.0 °C / 298.1 K
 INOVA-500 "Inova500"
 Pulse 48.0 degrees
 Acq time 1.892 sec
 Width 8000.0 Hz
 8 repetitions
 OBSERVE H1, 599.666945 MHz
 DATA PROCESSING
 F1: 599.666945 MHz
 Total time 0 min, 13 sec

II-37, Diastereomer 1

The sample also contains minor amount of diastereomer 2

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp.: 25.0 C / 298.1 K
 File: 42and42m100
 INOVA-500 "nova000"
 Pulse 48.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 8 repetitions
 OBSERVE H1, 599.666945 MHz
 DATA PROCESSING
 File size 3384
 Total time 0 min, 15 sec

II-37, Diastereomer 2

STANDARD CARBON PARAMETERS
 Archive directory: /export/home/wang/vnmrSYS/data
 Sample directory:
 File: CARBON

Pulse Sequence: s2pu1
 Solvent: CDCl3
 Temp: 28.0 C / 301.1 K
 User: 1-14-87
 INOVA-600 "INOVAS600"

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.300 sec
 Width 17.000 Hz
 1000 repetitions
 OBSERVE C13, 150.7863842 MHz
 DECOUPLE H1, 599.6700024 MHz
 Power 40 dB
 continuously on
 VAPORPROOFED
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 131072
 Total time 38 min, 29 sec

da1no-c2_30Mar2005

Archive directory: /export/home/wang/vmarsys/data
Sample directory: da1no-c2_30Mar2005
File: PROT0N

Pulse Sequence: szpu1

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "Inova600"

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 0.25 sec

Width 7196.2 Hz

8 repetitions

OBSERVE H1, 599.6670039 MHz

DATA PROCESSING

File size 32768

Total time 0 min, 23 sec

STANDARD CARBON PARAMETERS

Archive directory: /export/home/wang/vnmrSYS/data
 Sample directory:
 File: CARBON

Pulse Sequence: szpul

Solvent: CDCl₃
 Temp. 28.0 C / 301.1 K
 User: 1-14-87
 INOVA-600 "Inova600"

Relax. delay 1.000 sec
 Acq. time 1.300 sec
 Width 31670.6 Hz

512 repetitions

OBSERVE C13, 150.7863851 MHz

DECOUPLE H1, 599.6700024 MHz

continuous on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 131072

Total time 19 min, 42 sec

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pu1
 Solvent: CDCl3
 Temp: 25.0°C / 298.1 K
 INOVA-600 "1HNOVA600"
 Pulse 48.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 8 repetitions
 OBSERVED F1: 599.669926 MHz
 DATA ACQ. DATE: 06/05/2007
 FT size 327680
 Total time 0 min, 15 sec

STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul

Solvent: CDCl₃

Temp: 25.0 °C / 298.1 K

USC: 14.5

INNOVA-600 "Innova600"

Pulse 37.7 degrees

Acq. time 1.300 sec

Width 25000.0 Hz

256 repetitions

OBSERVE C13, 150.7663891 MHz

DECOUPLE H1, 500.1360992 MHz

continuous on

VALT2-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 5 min, 35 sec

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
 Solvent: CDCl₃ 298.1 K
 INOVA-500 "INOVAS00"
 Pulse 48.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 8 repetitions
 OBSERVE H1, 599.6669931 MHz
 QNP1 PROCESSING
 FT size 32768
 Total time 0 min, 15 sec

The sample also contains minor amounts of III-106 & III-107

STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul

Solvent: CDCl₃

Temp: 25.0 °C / 298.1 K

Ufwd: 151.07

INNOVA-600 "Inova600"

Pulse 37.7 degrees

Acq. time 1.300 sec

Width 25000.0 Hz

256 repetitions

DECK: CH₃, 500.7863861 MHz

DECOUPLE H₂, 509.6700024 MHz

Power 40 dB,

continuously on

VALT2-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

File size 63556

Total time 5 min, 35 sec

III-105

The sample also contains minor amounts of III-106 & III-107

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp: 25.0 °C / 298.1 K
 INOVA-600 "Inova600"
 Pulse 48.0 degrees
 Acq. time 1.592 sec
 Width 8000.0 Hz
 8 repetitions
 OBSERVE H1, 599.666931 MHz
 DATA PROCESSING
 F1 size 32768
 Total time 0 min, 15 sec

STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul

Solvent: CDCl₃

Temp: 25.1°C / 298.1 K

User: 1-14-87

INOVA-600 "Inova600"

Pulse 37.7 degrees

Acq. time 1.300 sec

Width 25000.0 Hz

256 repetitions

Observed C-13, 766368 MHz

Observed CH, 539.6700024 MHz

Decouple CH, 539.6700024 MHz

Power 40 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Time processing 0.5 Hz

FT 128533

Total time 5 min, 35 sec

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
 Solvent: CDCl₃
 Temp: 300.2 K
 INOVA-600 "NOVA600"
 Pulse 48.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 8 repetitions
 OBSERVE H1, 599.668931 MHz
 DATA PROCESSING
 Processing time 1.00 sec
 Total time 0 min, 15 sec

STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul
 Solvent: CDCl₃
 Temp.: 25.4 °C / 298.1 K
 User: 1-14-87
 INOVA-600 "nova600"

Pulse 37.7 degrees
 Acq. time 1.300 sec
 Width 25000.0 Hz
 256 repetitions
 QSCN: CH₃, 50.7663853 MHz
 DECOUPLE CH₁, 159.6700024 MHz
 Power 40 dB
 continuously on

WALTZ-16 modulated
 DATA PROCESSING
 F₁ line broadening 0.5 Hz
 F₂ line broadening 0.5 Hz
 Total time 5 min, 35 sec

and ligand, with these components being dissociable from the parent complex in reverse order as the collision voltage was increased. — GJC

J. Am. Chem. Soc. 10.1021/ja0450307 (2004).

CHEMISTRY

Phenyls with a Twist

Planar arrays of fused aromatic rings are stabilized by electron delocalization in their extended π -network, which leads to the bright colors that make these molecules such useful dyes. However,

Spiral staircase configuration of the four phenyls.

chemists interested in the competing interplay of steric and electronic factors have long tried to coax such molecules out of planarity by appending bulky substituents. Dai *et al.* have managed to crowd four pendant phenyls along a 10-carbon stretch of a diindenophenanthrene frame-

work. The compound was formed in 20% yield from a precursor with four alkyne spacers, which were fused into the heptacyclic core through a series of intramolecular rearrangements. Crystallography revealed a severely twisted, nonplanar core geometry, particularly in the central phenanthrene ring. The dangling phenyl substituents

are stacked parallel to one another in a partial helix, with the outer phenyls oriented 184° apart, presumably the result of both steric and π -stacking interactions. Nuclear magnetic resonance spectroscopy revealed a rotational barrier of ~ 14 kcal/mol for the outer phenyls and a higher barrier for the two rings between them. — JSY

Org. Lett. 10.1021/ol0481434 (2004).

NEUROSCIENCE

Doing Without an Adaptor

Adaptor proteins (APs) are involved in the packaging of proteins into clathrin-coated vesicles during intracellular transport. The AP-3 subclass, in particular AP-3A, plays a role in membrane protein transport and in the biogenesis of lysosomes and lysosome-related organelles. The AP-3B adaptors are found only in neurons, and their precise role has been unclear. Nakatsu *et al.* describe the phenotype of mice engineered to lack AP-3B and suggest that this adaptor is important in the biogenesis of synaptic vesicles. Mutant mice were prone to spontaneous recurrent epileptic seizures, and their brains displayed synapses with morphological abnormalities. In hippocampal slices, the ability to release the inhibitory neurotransmitter GABA was diminished, probably because of reduced levels of the GABA transporter. Thus, AP-3B is important in the production of a subset of synaptic vesicles in inhibitory neuronal pathways, and this mouse model may be useful in future studies of epilepsy. — SMH

J. Cell Biol. 167, 293 (2004).

HIGHLIGHTED IN SCIENCE'S SIGNAL TRANSDUCTION KNOWLEDGE ENVIRONMENT

Tolerating ER Stress

Cells monitor how well the synthesis of proteins in the endoplasmic reticulum (ER) is going, and when stressful conditions cause the accumulation of unfolded proteins, the unfolded protein response (UPR) is initiated. Ito *et al.* used a microarray screen to detect genes whose products were expressed specifically in response to an agent causing ER stress. They identified *stanniocalcin 2* (*STC2*), which is related to a hormone originally described in fish that functions to prevent hypercalcemia. Expression of *STC2* was increased in cultured cells undergoing the UPR after exposure to thapsigargin, an inhibitor of the sarco(endo)plasmic reticulum Ca^{2+} -ATPase. Like other UPR genes, *STC2* was also expressed in rat brain tissue after transient cerebral ischemia. Expression of *STC2* appears to require signaling from the PERK serine-threonine kinase, a known mediator of the UPR, to the transcription factor ATF4, because mouse embryo fibroblasts lacking PERK or ATF4 failed to increase expression of *STC2*. Increased synthesis of *STC2*, which was secreted from cells undergoing ER stress, appears to contribute to signaling mechanisms that help protect cells under stressful conditions. — LBR

Mol. Cell Biol. 24, 9456 (2004).

Dedicated to
Dr. Jeffrey L. Petersen
for his help with X-ray
structure analyses

Publications

Ring expansion of 11H-benzo[*b*]fluorene-11-methanols and related compounds leading to 17,18-diphenyldibenzo[*a,o*]pentaphene and related polycyclic aromatic hydrocarbons with extended conjugation and novel architectures Yang, Y.; Dai, W.; Zhang, Y.; Petersen, J. L.; Wang, K. K. *Tetrahedron* in Press.

Synthesis of indeno-fused derivatives of quinolizinium salts, imidazo[1,2-*a*]pyridine, pyrido[1,2-*a*]indole, and 4*H*-quinolizin-4-one via benzannulated enyne-allenes Dai, W.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2005**, *70*, 6647-6652.

Synthesis and structure of a helical diindenophenanthrene with four congested phenyl substituents as a molecular spiral staircase Dai, W.; Petersen, J. L.; Wang, K. K. *Org. Lett.* **2004**, *6*, 4355-4357. The results of this study were also featured in the Editors' Choice section of the November 5, 2004 issue of *Science*.

Presentations

Synthesis of the parent and substituted tetracyclic ABCD ring cores of camptothecin via allenic nitriles Wang, K. K.; Dai, W.; Petersen, J. L. Presented at 231st ACS National Meeting, Atlanta, GA March 26-30, 2006. (Oral)

Synthesis and structure of a helical diindenophenanthrene with four congested phenyl substituents as a molecular spiral staircase Dai, W.; Petersen, J. L.; Wang, K. K. Presented at 228th ACS National Meeting, Philadelphia, PA August 26-30, 2004. (Poster including Sci-Mix)