This is to certify that the
dissertation entitled

Synthesis of Carbazoquinocin-C,
Naphthopyrans and Conocurvone Analogs
With Carbene Complexes

presented by

Manish Rawat

has been accepted towards fulfillment
of the requirements for the

Doctoral degree in Chemistry

Major Professor's Signature

September 27, 2004

Date

SYNTHESIS OF CARBAZOQUINOCIN-C, NAPHTHOPYRANS AND CONOCURVONE ANALOGS WITH CARBENE COMPLEXES

By

Manish Rawat

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

2004

ABSTRACT

SYNTHESIS OF CARBAZOQUINOCIN-C, NAPHTHOPYRANS AND CONOCURVONE ANALOGS WITH CARBENE COMPLEXES

By

Manish Rawat

A successful syntheses of Fischer indole carbene complexes has been achieved and their utility in the synthesis of carbazoquinocin-C via the photochemical *ortho*-benzannulation with carbon monoxide and also via the thermal *ortho*-benzannulation with isonitriles has been demonstrated. An improved method for the oxidation of the hydroquinone of the natural product carbazoquinocin-C has also been developed.

Benzannulation reactions of chromene carbene complexes with simple alkynes have been investigated. High yields of naphthopyran phenols have been realized from these reactions and require *in-situ* protection of the phenolic functionality using protecting groups such as TMSCl, TBSCl, MOMCl, Ac_2O to be most effective. The corresponding quinones of these naphthopyran phenols are stable which is in contrast to the corresponding unprotected naphthopyran phenols.

Conocurvone, a remarkable anti-HIV active natural product, possesses a tris-naphthoquinone pyran core structure. In an effort towards the total synthesis of conocurvone the reaction of various aryl carbene complexes with bis-TIPS-1,3,5-hexatriyne and *ortho*-aryl diynes have been investigated. The reaction of the phenyl carbene complex with bis-TIPS 1,3,5-hexatriyne, intriguingly, forms a furan instead of a phenol by reacting at the central triple bond of the triyne. Furan

products have been observed before in the reaction of chromium Fischer carbene complex with alkynes but only as a minor product. Surprisingly, the reaction of the chromene carbene complex and the bis-TIPS 1,3,5-hexatriyne gave neither a furan nor a phenol. Instead, the reaction gave an unexpected product that results from an addition to the central alkyne of the triyne and then an addition to the double bond present in chromene carbene complex. The intriguing outcome of the phenyl carbene complex and chromenyl carbene complex with bis-TIPS 1,3,5-hexatriyne has been explained by PM3(TM) and DFT calculations.

ACKNOWLEDGMENTS

I would like to express my deep gratitude to Professor William D. Wulff for his patience, encouragement, suggestions and stimulating ideas over the last five years. It has been an enriching experience and a great honor to learn from Professor Wulff. Professor Wulff's sense of humor and genuine interest in all aspects of chemistry has been inspirational and educational.

I am indebted to Professor Robert E. Maleczka, Milton R. Smith and Professor David P. Weliky for being in my Ph.D. committee, their support, suggestions and writing letters of recommendation.

Thanks to Victor for helping me with the Computational studies, Dr. Jiang for conocurvone studies, Remy for the TIPS triyne synthesis and Dr. Rui Huang for elemental analysis/X-ray.

I, specially, thank Dr. Reddy, Vijay, Dr. Billy Mitchell, Glenn, Kostas and Victor for their valuable friendship and useful discussions on a wide range of topics including chemistry. It was a great pleasure for me to work with a number of past and present labmates who have made the five years here far more enjoyable including Yonghong, Yu, Yiqian, Ding, Gang, Cory, Kostas, Jie, Zhenjie, Chunrui and Alex.

I would like to thank Abhi/Manasi, Rg, Mahesh/Vasudha, Vivek, Shilu, Bhushan, Nag, Bala, Bani and Somnath for their friendship and moral support during these five years.

I dedicate this thesis to my parents whose unending love, support, and encouragement have helped me in achieving this milestone. I can never thank them enough for what they have given to me and many sacrifices they have made for me. I thank my brothers Mikku and Rinku for their cheerful nature and support.

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LIST OF ABBREVIATIONS

Ac	Acetyl
Bh	Benzhydryl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Bu	Butyl
t-BuNC	*tert*-Butyl isocyanide
CAN	Cerium Ammonium Nitrate
DBN	1,5-Diazabicyclo [4.3.0]non-5-ene
DBU	1,8-diazabicyclo[4.3.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-Benzoquinone
DFT	Density Functional Theory
DIPEA	N,N-Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethyl formamide
DMSO	Dimethylsulfoxide
DMP	2,6-Dimethylpyridine
DTBMP	2,6-di-*tert*-butyl-4-methyl pyridine
Et_2O	Diethyl ether

LF	Ligand Field
Me	Methyl
MLCT	Metal-to-ligand charge-transfer
MOM	Methoxymethyl Ether
NBS	N-Bromosuccinimide
NMI	N-methylimidazole
Ph	Phenyl
PMB	*para*-methoxy benzyl
PMP	1,2,2,6,6-pentamethylpiperidine
PPTS	Pyridinium *p*-toluene sulfonate
i-Pr	isopropyl
TBAF	Tetrabutylammonium Fluoride
TMEDA	N,N,N',N'-Tetramethylethylenediamine
Ts	*p*-Toluenesulfonyl
Tf_2O	Trifloromethanesulfonic anhydride
TFA	Trifloroacetic Acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
UV	Ultra-violet
VANOL	Vaulted Binaphthol
VAPOL	Vaulted Biphenanthrol

CHAPTER ONE

Dötz -Wulff Benzannulation Reaction

And

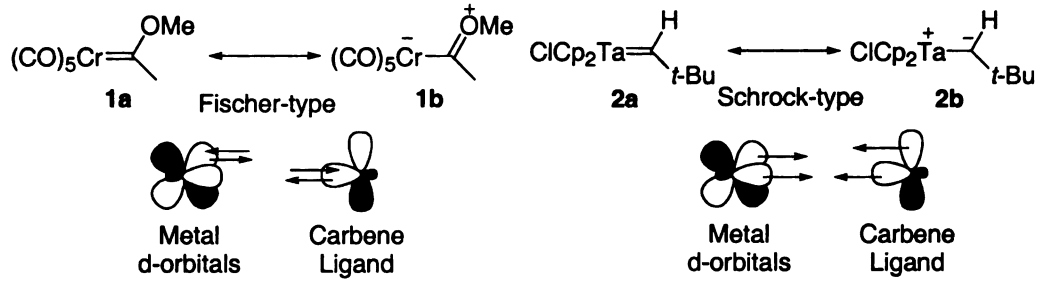
Ortho-Benzannulation of Dienyl Fischer Carbene Complexes

1.1 Introduction to Fischer carbene complexes

Compounds containing formal metal-to-carbon double bonds are known as carbene complexes. In 1964, Fischer and Maasböl reported the first example of a carbene complex which was prepared from the reaction of hexacarbonyltungsten with methyl or phenyl lithium followed by protonation and then reaction with diazomethane.[1] Fischer carbene complexes, represented by **1a** are characterized by having the metal in a low oxidation state, by π-accepting auxiliary ligands and by heteroatom substituents on the carbene carbon atom capable of donating π-electron density. They possess singlet carbene ligands as shown in Figure 1.1 since the carbon donates the pair of electrons present in the sp^2 orbital to the empty orbitals of the metal to form the σ-bond. This is accompanied by concurrent back-donation of the d-electrons from the metal to the empty p orbital of the carbene carbon. The heteroatom competes with the attached metal fragment for π-back donation into the empty p orbital of the

carbene carbon thereby stabilizing the carbene complex by reducing the carbon atom's electronic deficiency. This significantly increases the contribution from resonance structure **1b**, which is evident by the increased hindered rotation about the heteroatom-carbene complex bonds in going from the alkoxy to amino stabilized complexes (C-N: 25 kcalmol^{-1}, C-O: 14 kcalmol^{-1}).

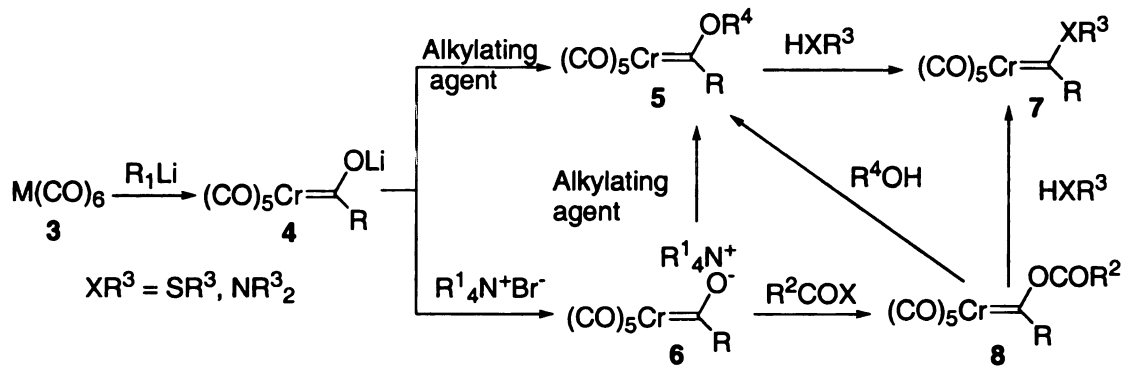
Figure 1.1 Electronic description of carbene complexes.



Ten years after the discovery of Fischer's electrophillic carbene complexes, Schrock discovered another class of carbene complexes, which are nucleophilic at the carbene carbon.[2] Schrock type carbene complexes **2a** are characterized by early transition metals in high oxidation states, by non-π-accepting auxiliary ligands, and by non-π-donating substituents on carbon. They can be viewed as derived from triplet carbene ligands as shown in Figure 1.1 in which the σ-bond is constructed from with one electron of its sp^2 orbital of the carbon and one electron of the d orbital of the metal. The π-bond is formed by one electron in the p orbital of the carbene ligand and one electron from the d orbital of Group 5 metal. In Schrock carbene complexes, larger contributions from the resonance structure **2b** are observed because of the absence of heteroatom stabilization of the complex.

The most widely used method for the generation of Fischer carbene complexes involves the reaction of an organolithium and a metal carbonyl, the same method that was originally reported by Fischer and Mossaböl in 1964.[1] The lithium acylate **4** so obtained can be converted to alkoxy, amino and thio carbene complexes via different pathways as shown in Scheme 1.1. Alkoxy carbene complex **5** can be obtained by alkylation of the lithium acylate using alkylating agents like trialkyloxonium salts or alkyl trifluoromethane sulfonates. Alternatively, the ammonium acylate **6** can be acylated to form acyloxycomplexes **8** which are not particularly stable but can readily be converted to a wide variety of carbene complexes **7** by substitution reactions with alcohols, amines and thiols.

Scheme 1.1 Schemetic diagram showing the synthesis of carbene complex.

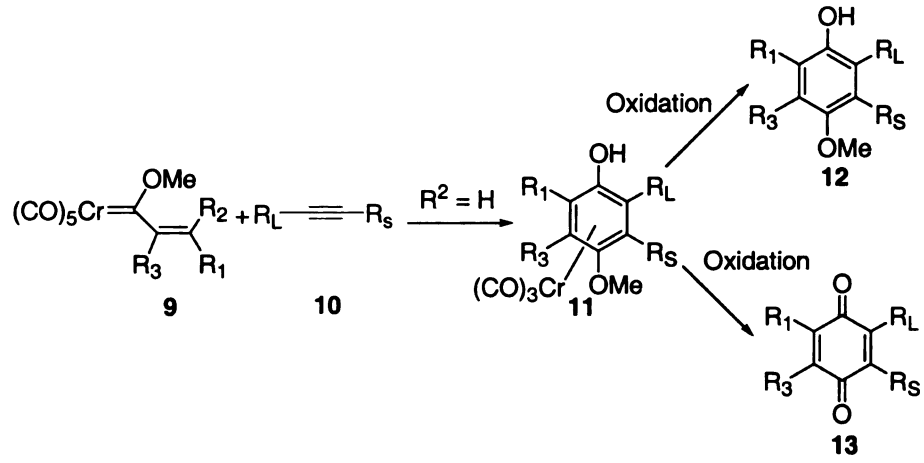


1.2 Benzannulation reaction of Fischer carbene complexes

In 1975, Dötz reported the first examples of the reaction of α,β-unsaturated Fischer carbene complexes **9** with alkynes **10** (Scheme 1.2).[3] This reaction furnishes chromium tricarbonyl complexed *para*-alkoxy phenols **11** which upon

oxidation provide phenols **12** or *para*-quinones **13**. This is an [3+2+1] annulation reaction in which the resulting benzene ring is comprised of three carbons from the α,β-unsaturated carbene complex, two carbons from the alkyne and one carbon from the carbon monoxide ligand. This reaction is quite general with yields as high has 99 % in certain cases.

Scheme 1.2 Benzannulation using Fischer carbene complex and alkyne

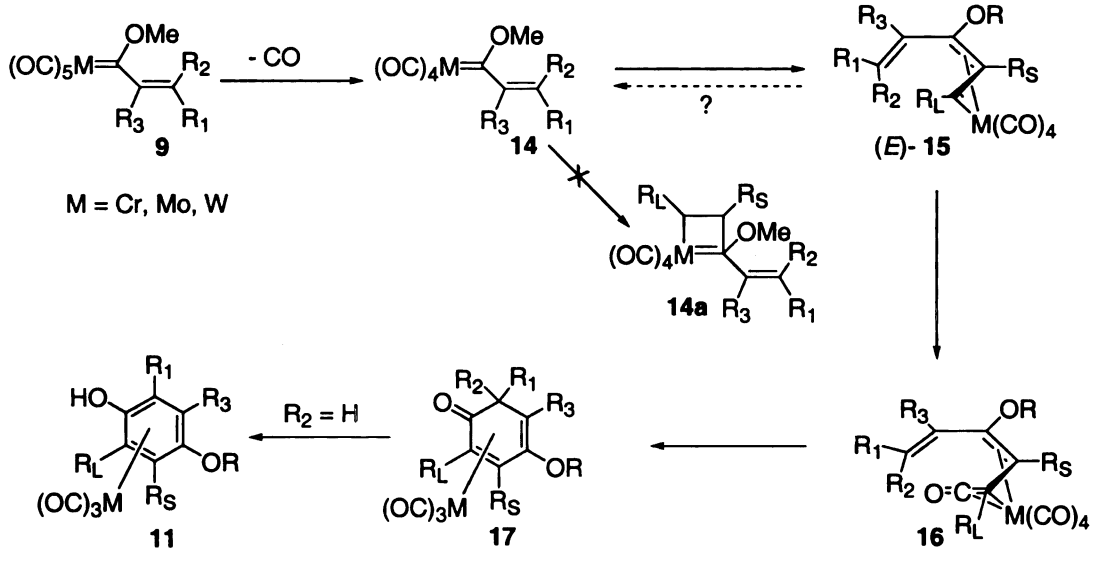


The metal-free phenol **12** can be derived from complex **11** by ligand displacement (CO, PPh_3)[4a,4b] or by oxidative workup (air, $FeCl_3$-DMF complex, [4c] pyridine N-oxide[4d]) (Scheme 1.2). Strong oxidizing agents like CAN,[4c] lead oxide, [4e] nitric acid,[4a] silver oxide[4f] and iodine[4g] generally forms quinone **13**.

The mechanism[5] of the benzannulation reaction of α,β-unsaturated Fischer carbene complex **9** with alkyne **10** is shown in Scheme 1.3. The reaction initiates with a CO loss giving 16-electron unsaturated species **14**. Kinetic studies designate this step as rate limiting.[5b] This is followed by alkyne coordination and insertion to form η^1-η^3 vinyl complex **15**. Extended Huckel calculations by Hoffmann in 1991, rule out a metallacyclobutene **14a** that would be expected

from a [2+2] addition of the carbene complex and the alkyne as an intermediate or a transition state in this step.[5c,5d] Carbon monoxide insertion in (*E*)-**15** then leads to η^4-vinyl ketene complex **16**, which upon six-electron cyclization and tautomerization furnishes the phenol-metal tricarbonyl complex **11** (Scheme 1.3). For alkenyl carbene complexes, carbon monoxide insertion and electrocyclic ring closure takes place in the same step, as there is no local minimum for the η^4-vinyl ketene complex **16**.[5e] This is, however, a two-step process for the aryl carbene complexes as revealed by the DFT calculations.[5e,5f,5g]

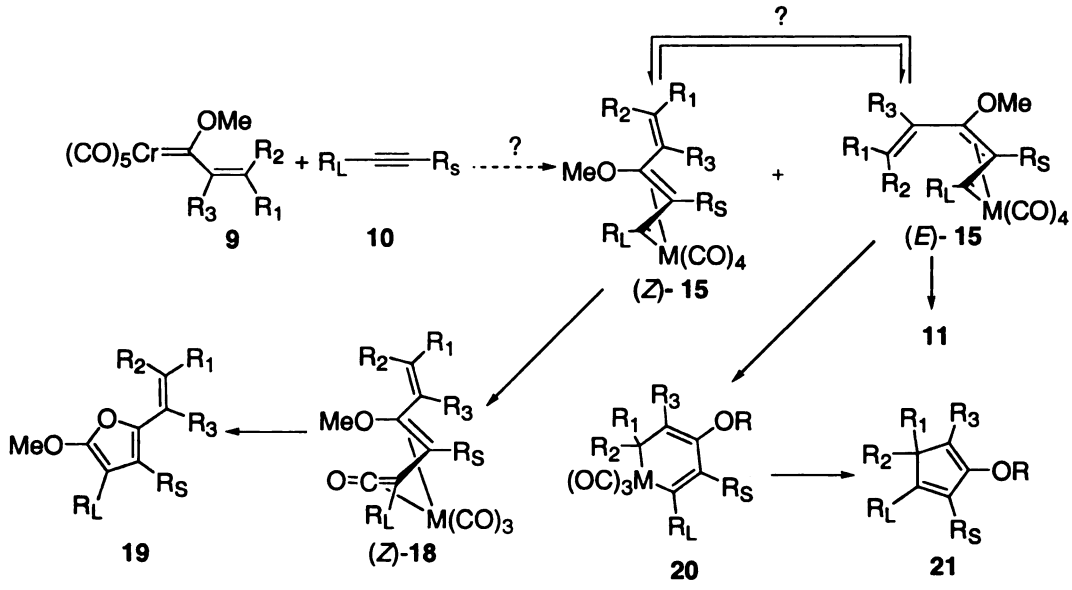
Scheme 1.3 Mechanism of the benzannulation reaction



The E configuration of the vinylidinecarbene complex (*E*)-**15** is a must for the formation of the phenol complex **11** (Scheme 1.3). However, the reaction of carbene complex **9** with alkyne **10** can give either the *Z* or *E* isomer of **15** (Scheme 1.4). Furthermore, it is possible that the *E*-vinylidine carbene complex (*E*)-**15** can undergo isomerization either via alkyne deinsertion or some other

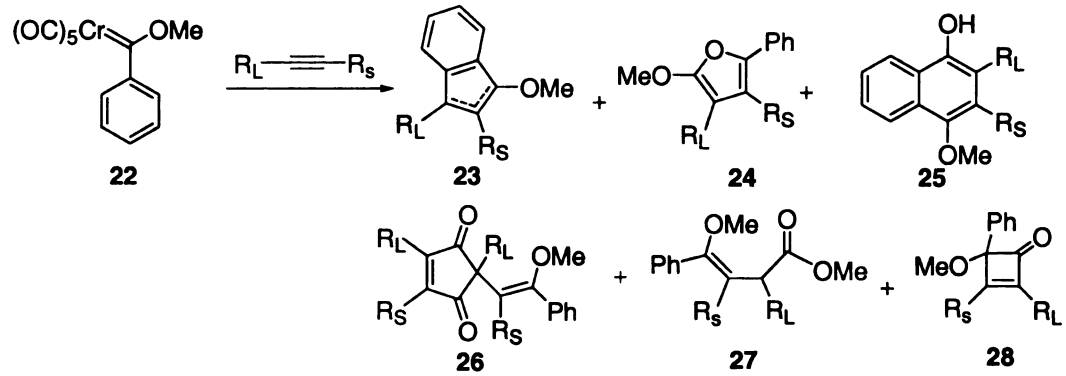
mechanism to give the *Z*-vinylidene complex (*Z*)-**15** (Scheme 1.4). The *Z*-vinylidene complex **15** has been implicated in the formation of furan products.[6] If the CO insertion is slow, as it is for tungsten and molybdenum complexes, then increased amount of cyclopentadienes or indenes **21** are obtained via metallacyclohexadiene **20** (Scheme 1.4).[7]

Scheme 1.4 Mechanism of cyclopentadiene and furan product formation



Scheme 1.5 shows some of the other products that can be obtained in addition to the phenol **25** from the reaction of an aryl Fischer carbene complex with an alkyne. Exhaustive studies have been done on a wide range of tungsten, chromium and molybdenum carbene complexes with several sterically and electronically perturbed alkynes.[5a] Based on these empirical results, the following generalizations can be made for factors that favor the formation of phenol products.

Scheme 1.5 Different reaction products in a benzannulation reaction



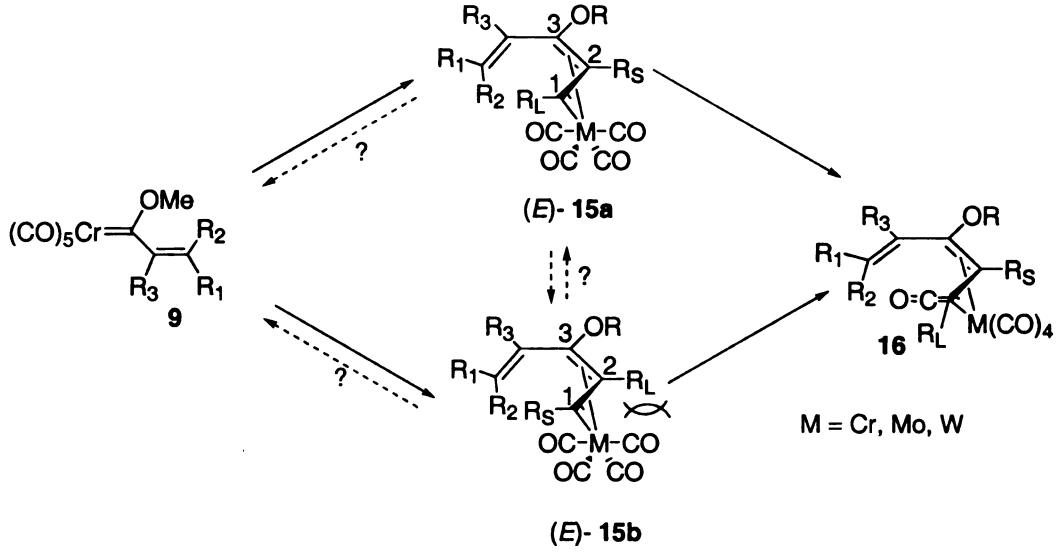
1. Metal Effect: The order of selectivity for the CO-inserted phenol product is chromium > tungsten > molybdenum. Tungsten and molybdenum carbene complexes, unlike chromium carbene complexes predominantly give non-CO inserted products like indenes and cyclopentadienes.

2. Carbene Ligand Effect: Fischer carbene complexes with alkenyl carbene ligands are less susceptible to reaction conditions (solvent, temperature and concentration) than are aryl carbene ligands. Furan products of the type **24** are more common for aryl carbene complex than for alkenyl complexes

3. Regioselectivity: The largest substituent on the alkyne is generally incorporated *ortho* to the phenol functionality in the product **25**. In the case of terminal alkynes, a single isomer is usually formed and regioisomeric ratios greater than 250:1 have been measured in certain cases.[8] The regioselectivity of internal alkynes depends on the difference in the steric bulk between the two substituents. The preferred regioselectivity in terminal alkynes has been explained on the basis of interactions of substitutents R_L and R_S from the alkyne

with the CO ligands in the vinyl carbene complexed intermediate **15b**. Hoffman's extended Huckel calculations shows that the substituent at 2-position of the vinyl carbene complexed intermediate is at least one angstrom closer to its nearest CO ligand than the substituent in the 1-position (Scheme 1.6).[5c,5d] However, it is not known for sure whether the alkyne insertion intermediates **15a** and **15b** are in equilibrium in favor of **15a**, or whether the regiodifferentiation takes place kinetically at the alkyne insertion step. For alkynes with a tributyl stannane substituents[9a] or for alkynes with electron withdrawing groups,[9b] opposite regioselectivity is observed. However, the predominance of electronic factors over steric factors is rare.

Scheme 1.6 Regioselectivity of Benzannulation Reaction



4. Chemoselectivity: Sterically hindered alkynes are less reactive than alkynes with smaller substituents. Terminal alkynes are more reactive than internal alkynes.

5. Solvents effects: Non-polar and non-coordinating polar solvents give higher yield of phenol products in most instances. The amount of side products increases in DMF and CH_3CN.

6. Concentration Effects: Higher alkyne concentrations favor phenol formation. This is known as the allochemical effect.[10] In the vinyl carbene complexed intermediate **15** (Scheme 1.3) either solvent or alkyne can displace the weakly coordinated double bond. Alkynes can act both as 2- and 4-electron donors so that the metal center would remain electronically saturated after the CO insertion if it occurs with a switch of the alkyne from 2 to 4 electron donor. This pathway is expected to be faster than the uninduced CO insertion (*E*)-**15** since maintaining an 18-electron metal species should lower the energy barrier

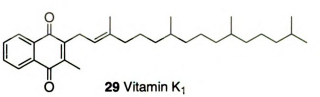
7. Temperature Effects: High temperature adversely affects the regioselectivity of the benzannulation reaction and favors the formation of non-CO inserted products.

8. Stereoselectivity: Chirality on the alkyne and on the carbene ligand has been used for introducing planar, axial and central chirality in the product. Central chirality can be induced using β,β-disubstituted α,β-unsaturated carbene complexes.

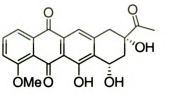
The reaction of carbene complexes with alkynes has been utilized for the synthesis of a plethora of biologically active natural products and drugs possessing *para*-oxygenated benzene products or *para*-quinone moieties. Some of the compounds that belong to this category, are vitamins K_1 **29**,[11] anthracyclones (daunomycinone **30**),[12] furanochromone (khellin **31** and sphondin

32),[13a,13b] and fredericamycin A **33**, (Figure 1.2).[14] The benzannulation reaction has also been used in the synthesis of the chiral vaulted biaryl ligands VAPOL **34** and VANOL **35**.[15a] These ligands have been used to generate superior catalysts for Diels-Alder reaction,[15b] aziridination reaction[15c] and iminoaldol reaction.[15d]

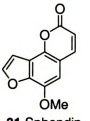
Figure 1.2 Natural products and asymmetric ligands



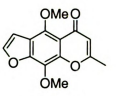
29 Vitamin K_1



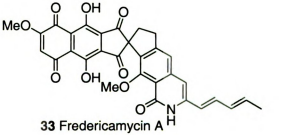
30 Daunomycinone



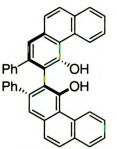
31 Sphondin



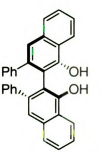
32 Khellin



33 Fredericamycin A



34 (*S*)-VAPOL

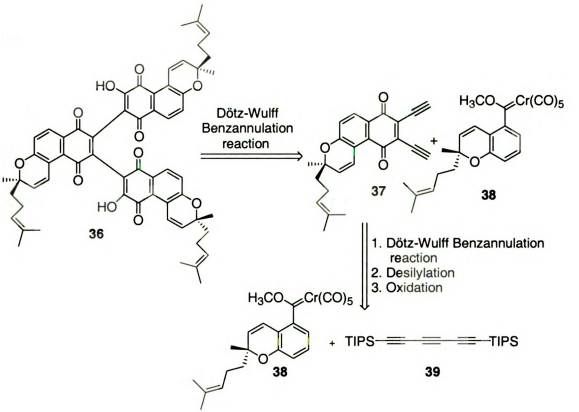


35 (*S*)-VANOL

One of the goals of this thesis is to develop an approach to conocurvone **36** based on the reaction of three equivalents of complex **38** with triyne **39**. Conocurvone **36** shows remarkable anti-HIV activity.[16] It possess three quinone units which prompted us to explore the reaction of the carbene complexes with conjugated triynes to acquire the three quinone rings in one step. The three

repeating units are derived from the natural product teretifolion-B, which constitutes of 3H-naphtho-7,10-dione[2,1-b]pyran unit. The reaction of chromene carbene complex **38** with triyne **39** could provide a direct route for the synthesis of the 3H-naphtho[2,1-b] pyran framework (Scheme 1.7). The synthetic efforts toward the total synthesis of conocurvone **36** and the utilization of Fischer carbene complexes in the synthesis of a library of 3H-naphtho-7,10-dione[2,1-b]pyrans will be discussed in Chapters four and three respectively.

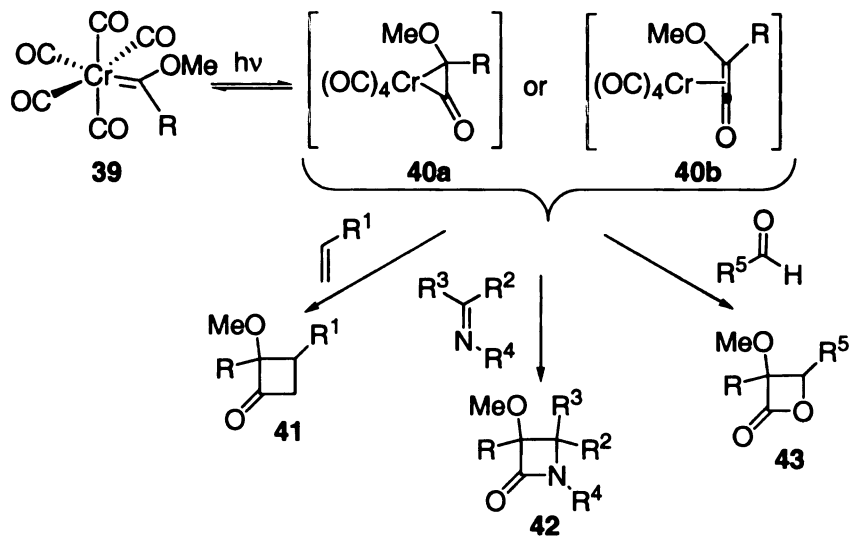
Scheme 1.7 Reterosynthetic analysis of conocurvone



1.3 *Ortho*-benzannulation of Fischer carbene complexes

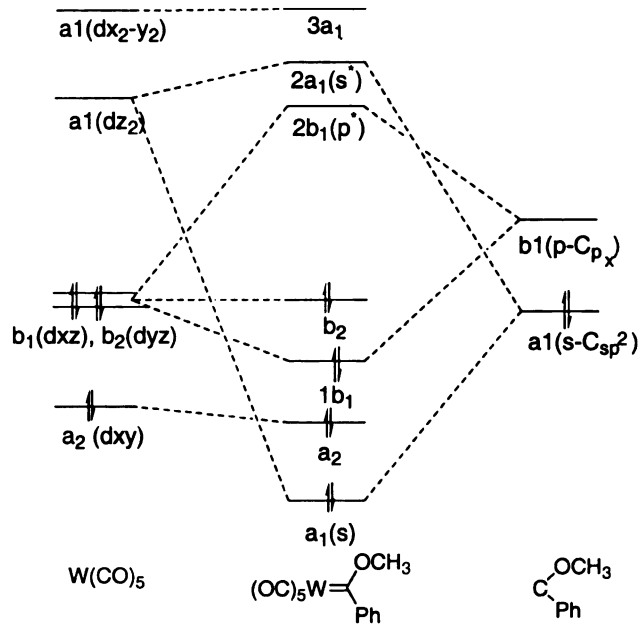
Heteroatom stabilized carbene complexes of the Group 6 metals are normally thermally stable to CO insertion to give ketene complexes. However, Hegedus and McGuire (1982) reported that metal coordinated vinyl ketenes **40a** or **40b** could be generated by photolysis of Fischer carbene complexes (Scheme 1.8).[17] They showed that CO insertion could be induced in chromium and molybdenum Fischer carbene complexes by irradiation into the Metal Ligand Charge Transfer (MLCT) band. This results in the generation of a transient species, either the short-lived metallacyclopropanone **40a** or metal bound ketene **40b**, which was found to have ketene like reactivity. Hegedus has exploited these metal ketene intermediates for various cycloadditions reactions to generate a variety of compounds such as cyclobutanones **41**, β-lactams **42** and β-lactones **43**.[18]

Scheme 1.8 Photoexcitation of Fischer carbene complexes



A number of photochemical studies of the Fischer carbene complexes have been carried out.[18] The electronic absorption spectrum of metal carbene complexes shows three low-lying bands at 500nm, 350-450nm and 300-350nm. These are respectively assigned to a spin-forbidden metal-to-ligand charge-transfer (MLCT) transition, a spin allowed MLCT transition, and ligand field (LF) transition. A simplified one-electron energy level diagram for the tungsten methoxy phenyl carbene complex is shown in Figure 1.3. The filled sp^2 orbital overlaps with the empty metal d_z^2 orbital to give bonding {a1(σ)} and antibonding {$2a_1(\sigma^*)$} combinations. A similar overlap of the empty carbene p_x orbital with a filled $d\pi$ orbital gives rise to bonding {$b_1(\pi)$} and antibonding {$2b_1(\pi^*)$} molecular orbitals. The molecular orbital calculation on [$Cr(CO)_5${C(OMe)Me} places $2b_1(\pi^*)$ below $2a_1(\sigma^*)$ in the energy level diagram. The LF bands are observed due to the promotions of the electron to the metal centered dx^2-y^2 orbital (or σ^*) orbital. The MLCT band results from the excitation of electron from a non-bonding metal-centered orbital to a carbene-carbon p orbital centered π^* orbital.

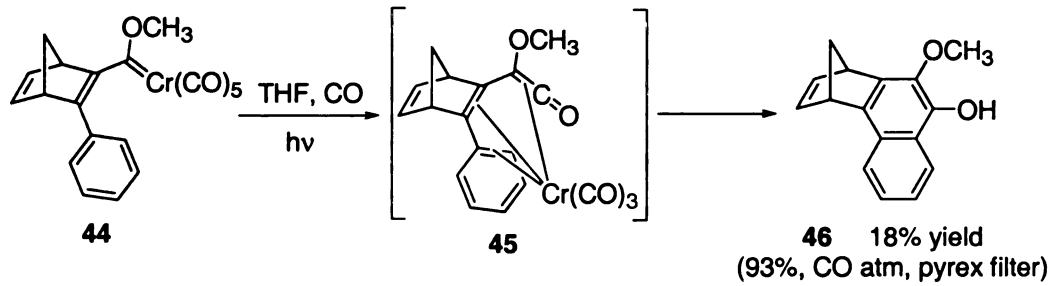
Figure 1.3 One-electron energy level diagram for tungsten complex [W(CO)$_5${C(OMe)Ph}]



Irradiation of Fischer carbene complexes into the LF bands results in the photodissociation of the CO ligand. Raman flash-photolysis study of $(OC)_5W{=}C(OMe)Me$ and matrix photolysis study of the corresponding chromium carbene complex gives two contrasting results. According to Raman flash-photoloysis, a transient species is formed due to the photoejection of CO in which the vacant site generated in the metal is blocked.[19] Whereas, matrix photolysis suggests that photolysis of tungsten carbene complex results in the reversible syn to anti-isomerization of the methoxy group.[19] Based on Hegedus results the transient species obtained on photolysis into MLCT band of tungsten complex is the metal bound vinyl ketene.

On the basis of these results, it was envisioned that photo-induced CO insertion in doubly unsaturated carbene complex would undergo 6-electron cyclization to generate 2-methoxy phenols. Wulff and Yang reported the first example of this photo-induced *ortho* benzannulation reaction in 1989 (Scheme 1.9).[20] Photolysis of complex **44** in THF furnished 2-methoxy naphthols **46** in 18% yield. Merlic improved the yield for this reaction by using pyrex filtered UV light under CO atmosphere.[21] It is presumed that pentacarbonyl chromium complex **44** on photolysis, results not only in CO insertion intermediate **45** but also CO ejection to form tetracarbonyl chromium complex (complex **44** with one CO less), which does not undergo CO insertion due to the enhanced π-backbonding. The tetracarbonyl chromium complex, which otherwise would result in decomposition or formation of side products, is converted back to complex **44** under CO atmosphere.

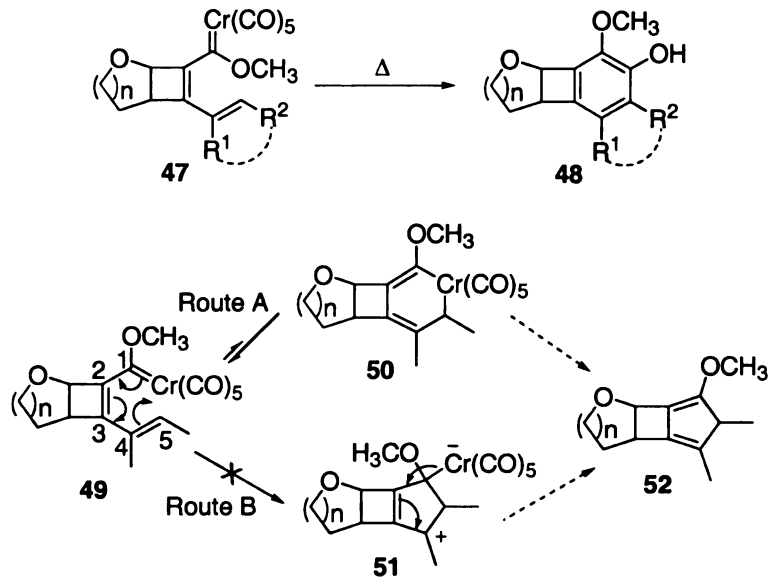
Scheme 1.9 Photoinduced *ortho*-benzannulation reaction



44 **45** **46** 18% yield (93%, CO atm, pyrex filter)

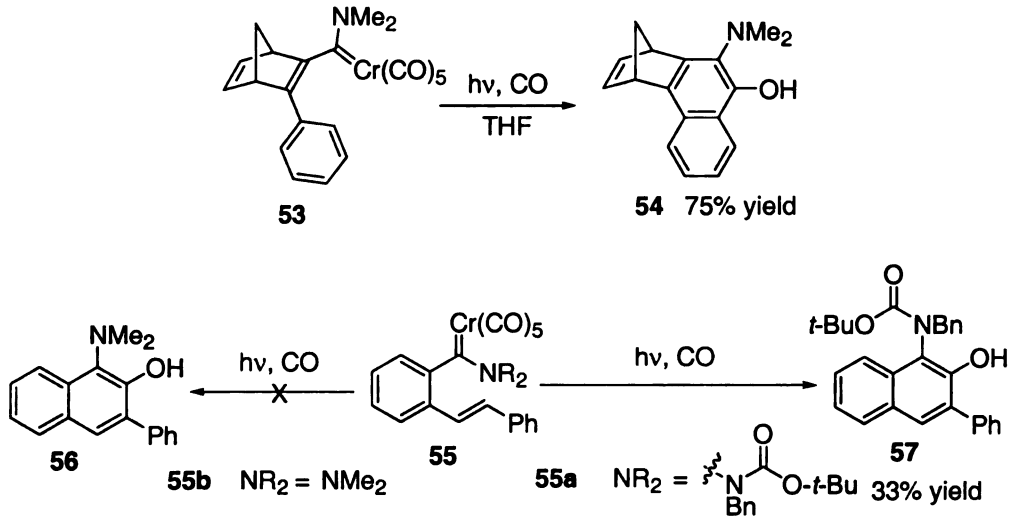
This reaction is quite effective for substrates with aryl substituents in the α,β-position and/or γ,δ-position. There are no examples in the literature, where the photoinduced *ortho*-benzannulation of substrates with alkenyl substituents in both the α,β-position and the γ,δ-position gives rise to *ortho*-alkoxy phenols. However the thermal reactions of these substrates are well developed and generally yield five membered rings. An exception is the carbene complex **47**, which has a strained cyclobutenyl ring in the α,β-position.[22] These substrates on heating yield *ortho*-alkoxy phenols **48** in moderate to good yields. The source of the unusual behavior of these substrates of furnishing six-membered rings instead of five-membered rings has been attributed to their geometries. Five-membered rings can be obtained via two pathways from substrate **49**: The first pathway (Route A) includes the electrocyclization followed by the reductive elimination, and the second pathway (Route B) would involve a nucleophilic attack of the terminal double bond on the carbene carbon atom to afford intermediate **51** (Scheme 1.10). It can be argued that in **49** the C1 and C 5 atoms are separated apart for the nucleophilic addition to take place and that in the intermediate **50** the reductive elimination is disfavored due to the large angles existing between the substituents of the cylobutene moiety. Thus the formation of five-membered ring formation over six-memebered ring is disfavored for **49**.

Scheme 1.10 Thermally controlled *ortho*-benzannulation



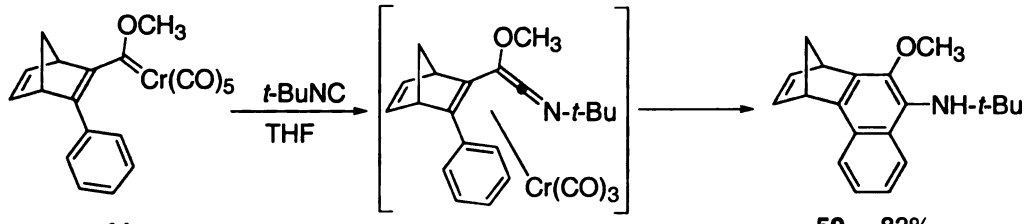
The photoinduced benzannulation has further been extended to amino carbene complex **53** which gave the *ortho*-amino phenol **54** (Scheme 1.11).[23] This reaction is not general for dialkylaminocabene complexes. However, carbene complexes with an electron withdrawing substitutent on the nitrogen atom are more useful as indicated by the conversion of **55a** to **57** (Scheme 1.11).[23] Dimethylamino complex **53** is the only example of a dialkylamino complex that undergoes the *ortho*-benzannulation reaction.

Scheme 1.11 Photo-Induced *ortho*-benzannulation of amino carbene complexes



Merlic has used isonitriles as a surrogate for CO to obtain *ortho*-methoxy aniline **59** (Scheme 1.12).[24] It is proposed that the reaction of the isonitriles with the carbene complex **44** results in the formation of the dienyliminoketene complex **58** analogues to the ketene **45**. This dienyl iminoketene complex then undergoes 6-electron cyclization to form *ortho*-methoxy anilines **59**.

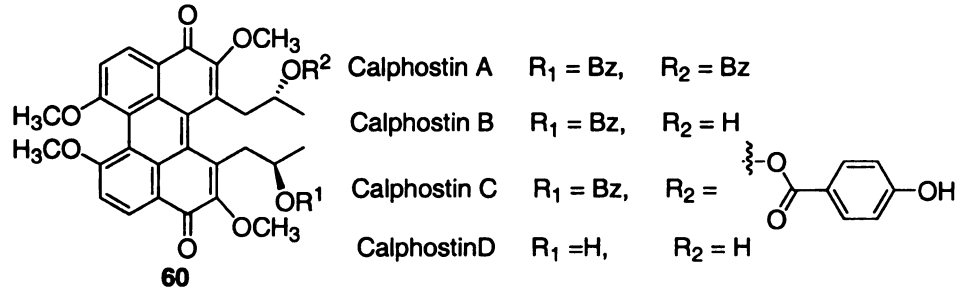
Scheme 1.12 Thermally controlled *ortho*-benzannulation of alkoxy carbene complexes using *t*-BuNC



44 **58** **59** 83%

This methodology provides an efficient route for the synthesis of *ortho*-alkoxy phenols and *ortho*-alkoxy anilines. Intriguingly, this methodology has found only limited use in the synthesis of natural products. In one of the few examples, Merlic has elegantly used this methodology in the total synthesis of the Calphostins **60** (Figure 1.4) which are known to be potent and specific inhibitors of protein kinase C and exhibit strong cytotoxic activity.[25]

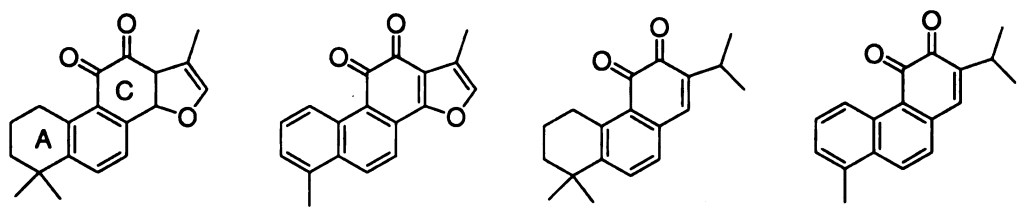
Figure 1.4 Structure of calphostins



60

Carbazole-3,4-quinone alkaloids[26] (Figure 1.6) and tanshinones[27] (Figure 1.5) are two of the important class of natural products with built-in *ortho*-quinone moieties. Tanshinones are a group of red pigments present in danshen, a dried root of the Chinese red-root sage *Salvia militiorrhiza Bunge* and is clinically useful for treatment of coronary heart and cerebrovascular disease. Chemically, tanshinones, such as cryptotanshinone **61**, tanshinone I **62**, rosemaryquinone **63** and miltrione **64** are 20-norditerpenes with an abietane-type skeleton containing a *ortho*-quinone moiety in the C-ring (Figure 1.5).

Figure 1.5 Structure of tanshinones

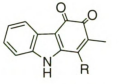


61 Cryptotanshinone **62** Tanshinone I **63** Rosmariquinone **64** Miltrione I

A major goal of this thesis is to develop a route to the synthesis of carbazoquinocin-C via the *ortho*-benzannulation of Fischer carbene complexes. Carbazoquinocin-C is a member of the carbazole-3,4-quinone alkaloid family which has largely been discovered upon screening several microorganisms for compounds possessing activity against lipid peroxidation and for those possessing neuronal cell protecting activity.[26] These molecules include carbazoquinocins A-F **65**, carbquinostatins A and B **66** and lavanduquinocin **67**.[26] Chapter 6 will discuss the application of *ortho*-benzannulation reaction in the synthesis of carbazoquinon-3,4-diones, in particular, carbazoquinocin-C **65C**.

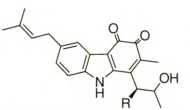
Both thermal and photoinduced *ortho*-benzannulation reactions are investigated and found to provide a general route for the synthesis of carbazole-3,4-quinone alkaloids.

Figure 1.6 Structure of carbazole-3,4-quinone alkaloids

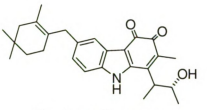


65 Carbazoquinocin A-F

A: $R=(CH_2)_2CHMeCH_2Me$
B: $R=(CH_2)_4CHMe_2$
C: $R=(CH_2)_6Me$
D: $R=(CH_2)_4CHMeCH_2Me$
E: $R=(CH_2)_5CHMe_2$
F: $R=(CH_2)_6CHMe_2$



66 Carquinostatin A **A:** R = H **B:** R =OH



67 Lavandoquinocin

CHAPTER TWO

SYNTHESIS AND PROPERTIES

OF

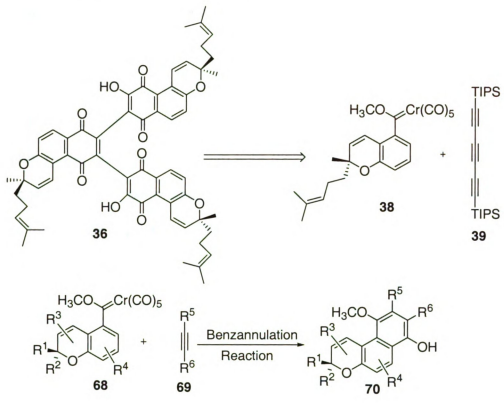
3H-NAPHTHO[2,1-b]PYRANS:

A HISTORICAL PERSPECTIVE

2.1 Introduction

The 3H-naphtho[2,1-b]pyran unit belongs to an important class of compounds. Naphthopyran units constitute the framework of a wide range of natural products[16,28,29] and have found wide application in optics due to their photochromic properties.[30] Conocurvone **36**, which shows remarkable anti-HIV activities, possess three naphthopyran-7,8-dione units (Scheme 2.1).[16] The presence of the *para*-quinone moiety has prompted us to explore the benzannulation reaction of chromene Fischer carbene complex **38** with triyne **39** to synthesize concorvone **36** and its analogues. This will be discussed in detail in Chapter 4. In addition, the benzannulation reaction of chromene carbene complexes of the type **68** with alkynes **69** would open a new synthetic avenue to access a library of 3H-naphtho[2,1-b]pyran compounds **70**. A detailed discussion on this will be given in Chapter 3. This Chapter gives a historical perspective on the synthesis and properties of naphthopyran compounds.

Scheme 2.1 Applications of chromene carbene complex in conocurvone and napthopyrans synthesis

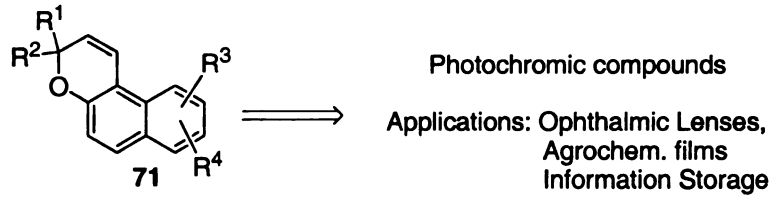


2.2 Introduction to photochromic properties of 3H-naphtho[2,1-b]pyrans

As mentioned in the previous section, naphthopyrans of the type **71** are important photochromic compounds (Scheme 2.2).[30] These photochromic compounds undergo reversible color change under the influence of a poly- or mono-chromatic light (UV for example) and return to their original color when the luminous irradiation ceases, or under the influence of temperature, or upon irradiation of a poly- or mono-chromatic light different from the first. Photochromic compounds have found wide applications in which a sunlight-induced reversible

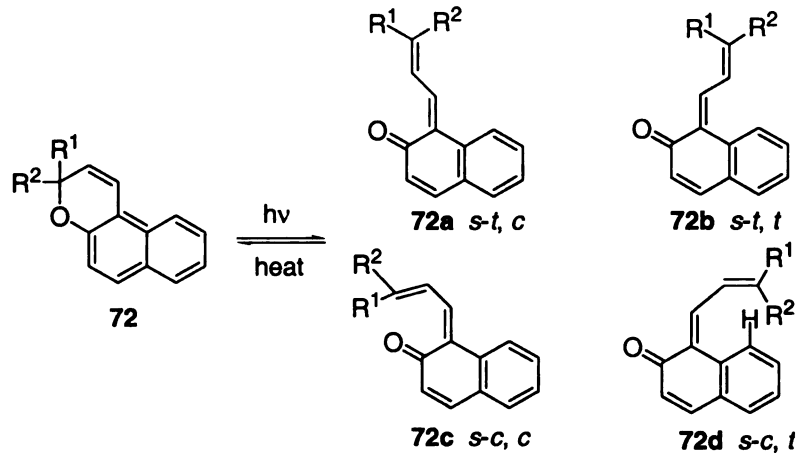
color change or darkening is desired e.g. for the manufacture of ophthalmic lenses, contact lenses, solar protection glasses, filters, camera optics, transmission devices, agrochem films, glazing, decorative objects or for information storage by optical inscription (coding). The photochromic compounds for the above stated applications are required to have the following characteristics: an absence or low coloration in the initial state, high colorability in the visible range after excitation with light (colorability is defined as the intensity of the color obtained on exposure to light), a high speed of coloration, a fast thermal fading rate (which is related to stability of the colored state) at room temperature and a high resistance to photodegradation ("fatigue resistance").[30]

Scheme 2.2 3H-naphto[2,1-b]pyrans shows photochromic properties



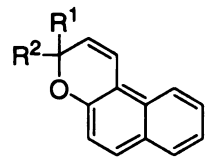
Photochromism of the naphthopyrans **71** is due to reversible heterolytic cleavage of the C-O bond of the pyran ring upon exposure to UV light or sunlight (Scheme 2.3). This is followed by extremely fast (i.e. 10^{-9} to 10^{-12} s) bond rearrangements resulting in the formation of the chromophoric species or photomerocyanines (MCs) that are responsible for the photogenerated colors (Scheme 2.3). Four different types of isomeric quinone methides are possible upon excitation, namely the *s-t,c* (*s-trans, cis*) **72a**, *s-t,t* (s-*trans,trans*) **72b**, *s-c,c* (*s-cis,cis*) **72c** and *s-c,t* (*s-cis,trans*) **72d** isomers.

Scheme 2.3 Behaviour of naphthopyrans on exposure to irradiation

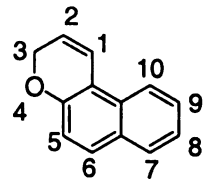


Substitutions at various positions in napthopyrans **71** (R^1, R^2, R^3, R^4) play a crucial rule in defining their photochromic characteristics. Replacement of methyl groups at C-3 carbon atom (R_1, R_2 = CH_3) by phenyl groups (R^1, R^2 = phenyl) notably enhances the photochromic properties of the naphthopyrans in favor of their usage in optics. This is illustrated from the data presented in Scheme 2.4. A notable bathochromic shift is observed as the methyl group is replaced by one (entry 2) and two phenyl groups (entry 3). The extended π-conjugation due to the additional phenyl rings leads to notable bathochromic shift (λ_1), enhanced absorption intensities or colorabilities (A_1) and increased open form stabilization i.e., low thermal bleaching rates (k_Δ) as is evident from entry 1, 2, 3. Another positive aspect of the aromatic substituents at C-3 position is increased fatigue resistance compared to the compounds obtained from the corresponding aliphatic substituents. All these absorption characteristics make the 3,3-diphenyl-substituted naphthopyrans suitable for use in photochromic lenses and other related applications.

Scheme 2.4 Substituent effect on photochromic properties of naphthopyran 72



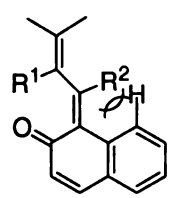
72



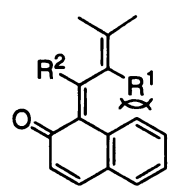
Entry	R^1	R^2	λ_1 (nm)	A_1	k_Δ (S^{-1})
1.	CH_3	CH_3	376	0.45	13, 0.15
2.	Ph	CH_3	399	0.48	2.3, 0.2
3.	Ph	Ph	432	0.84	0.009

Substitution at other carbon atoms also plays a crucial role in defining the photochromic properties of naphthopyrans. It has been generally observed that substitutions at the C-1 and C-2 positions (**73** and **74**) have negative effects on the photochromism. This is presumably because of the steric interaction of these substitutents with the naphthyl ring which expedites the thermal reversion of the ring-opened forms to the closed pyran form (Scheme 2.5).

Scheme 2.5 Steric effects from the substituents at C-1 and C-2 position



73

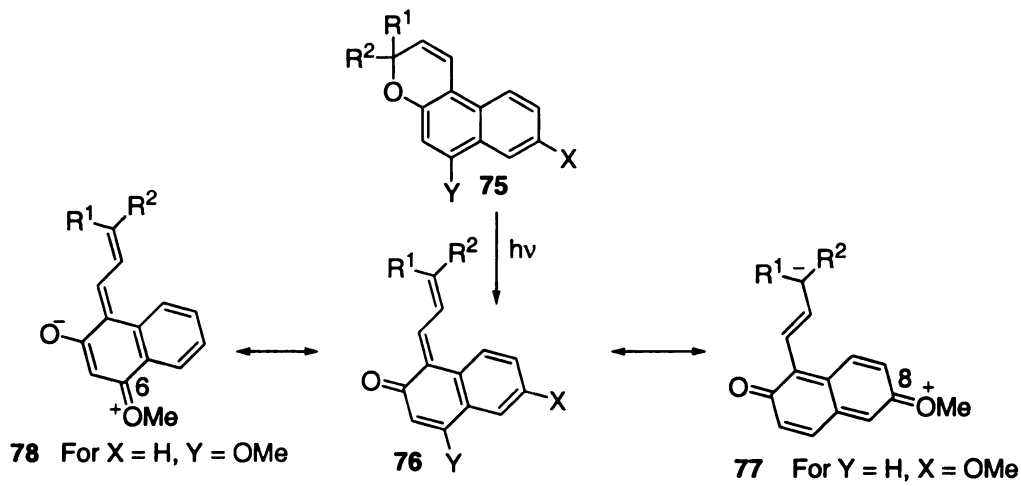


74

Heteroatom substituents at C-6 **78** and C-8 **77** positions have notable effect on the photochromic response of the naphthopyrans, which is not the case with substitution at C-7 and C-9 positions. This is because of the ability of the

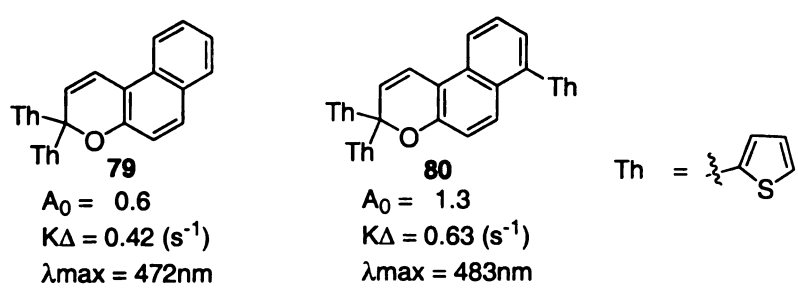
heteroatom lone pair to take part in resonance delocalization to the carbonyl in **76**, which makes them better photochromic compounds (Scheme 2.6).

Scheme 2.6 Photochemical response of 6- and 8- position substituted naphthopyran



Aromatic substituents at C-7 and C-8 also show enhanced bathochromic shift and colorability. Scheme 2.7 illustrates that the presence of aromatic substituent at C-7 position, such as **80**, enhances the colorability (A_0) and leads to a bathochromic shift that is good for their usage in optics.

Scheme 2.7 Thiophene substituted naphthopyrans



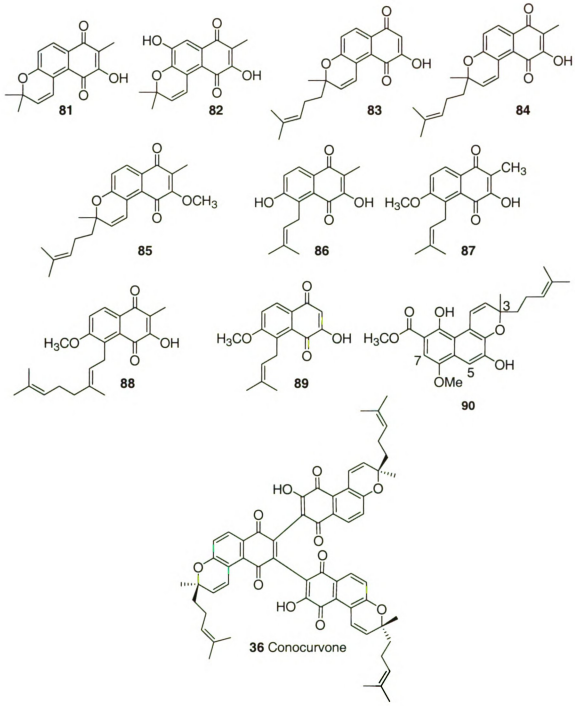
In brief, substitutions at the C-5 to C-10 positions have a significant impact on the absorption properties of these compounds. Although a number of patents

and publications on various naphthopyran derivatives have appeared in last two decades, a detailed study with aromatic and heteroatom substituents has not been done. This is likely due, at least in part, to the limited methods to generate these compounds.

2.3 Natural products with the 3-H-naphtho[2,1-b]pyran skeleton

3-H-Naphtho[2,1-b]pyrans or their opened forms (opened pyran rings) have been found in several natural products as shown in Scheme 2.8. Cannon and coworker, isolated nine quinones (**81-89**) related to this family, from the roots of *conospermum teretifolium* in 1975 (Scheme 2.8).[28] Kimpe has recently isolated a naphthopyran related natural product with the chemical name methyl-5,10-dihydroxy-7-methoxy-3-methyl-3-[4-methyl-3-penten-yl]-3H-benzo[f]- chormene-9-carboxylate **90** from the roots of *Pentas bussei*, a plant found in Kenya (Scheme 2.8).[29] The decoction of the roots is used as a remedy for gonorrhea, syphilis and dysentery. The stereochemistry at C-3 carbon was not determined since the multiple hydroxyl functionalities interfered with the Mosher derivatization of the natural product. Decosterd and co-workers at the NCI discovered that *in-vitro* anti-HIV activity is exhibited by conocurvone **36**, a trimeric naphthoquinone (Scheme 2.8).[16] The synthetic studies toward conocurvone will be discussed in Chapter 4.

Scheme 2.8 Natural products with 3-H-naphtho[2,1-b]pyran skeleton

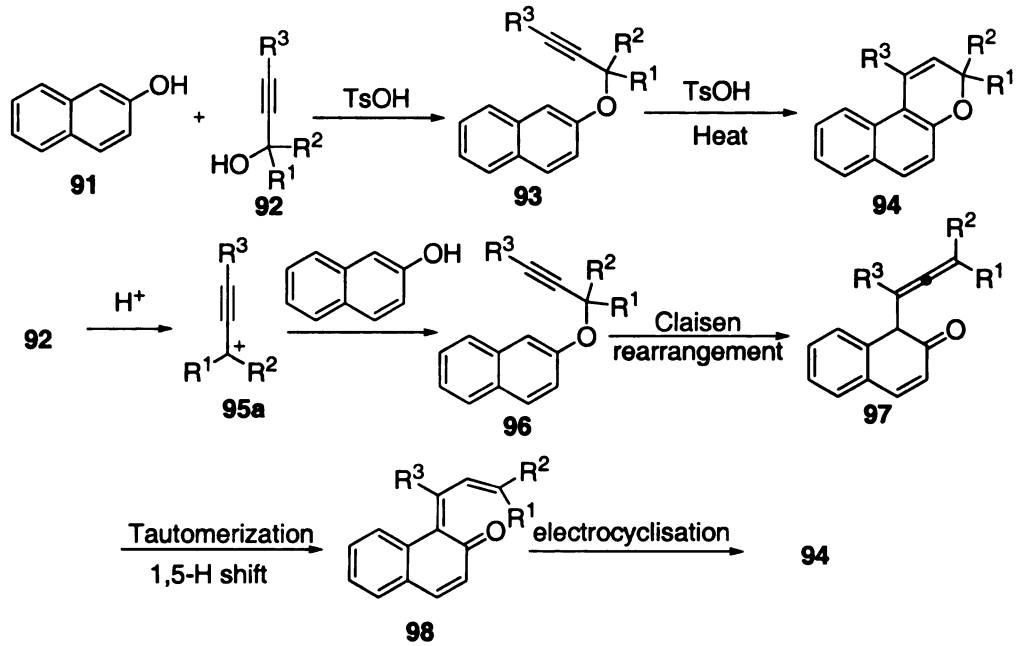


2.4 Conventional methods of synthesizing 3H-naptho[2,1-b]pyrans

Several methods have been reported for the synthesis of substituted naphthopyrans with alkyl or aryl substitutions at the C-3 positions. A few of the more commonly used methods are described below:

a) Acid and base catalyzed synthesis of naphthopyrans: The thermal cyclization of propargyl aryl ethers, first reported by Iwai and Ide gives 3H-naphthopyrans.[31] This reaction can be performed in one pot by heating 2-naphthol with propargyl or vinyl halides in the presence of base.[32] Alternatively, one pot condensation and cyclization of propargyl alcohol such as **92** with naphthols such as **91** can be invoked by using various acids (*para*-toluene sulfonic acid,[33] PPTS/$(CH_3O)_3CH$,[33] acidic alumina,[34] silica,[35] zeolite HSZ-360[36] to give 3H-naphtho[2,1-b]pyran derivatives **94** (Scheme 2.9). This is the most widely used method for accessing napthopyrans. A general mechanism for this reaction is shown below (Scheme 2.9). The first step in this reaction involves the generation of the propargyl aryl ether **93** by the acid catalyzed dehydration of the alcohol. This is followed by the thermal induced Claisen rearrangement, keto-enol tautomerisam, [1,5] hydride shift and 6-electron cyclization to furnish the naphthopyrans **94**.

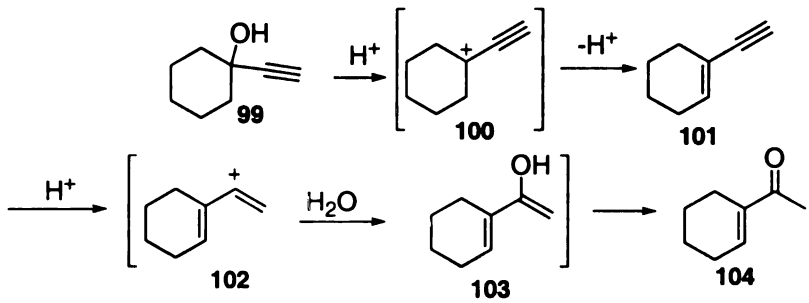
Scheme 2.9 Acid catalyzed cyclization of aryl-propargyl ethers



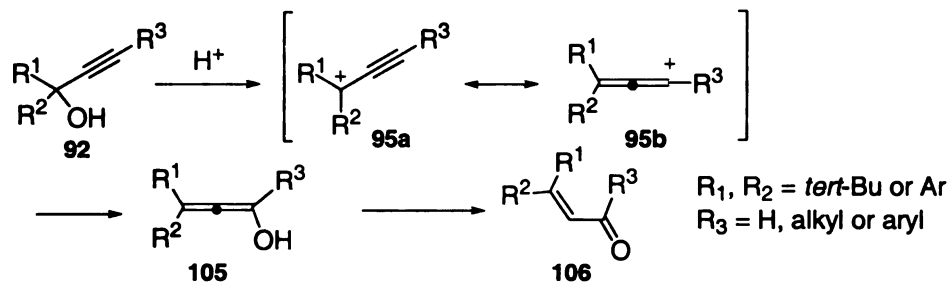
This approach is marred by low yields due to competitive Meyer-Schuster and Rupe rearrangements (Scheme 2.10).[37] The Rupe rearrangement deals with the acid-catalyzed isomerization of tertiary α-acetylenic alcohol **99** to predominantly form α,β-unsaturated ketone **104** rather than the α,β-unsaturated aldehydes formed in Schuster-Meyer rearrangement. This rearrangement is believed to proceed via a dehydration-hydration sequence with enynes as intermediates. The first step involves the acid catalyzed dehydration of alcohol to form the tertiary propargyl carbocation **100** followed by proton elimination to form enyne **101**. Further electrophillic attack of proton on enyne **101** gives secondary carbonium ion **102**, which upon quenching with water furnishes α,β-unsaturated ketone **104**. The Meyer-Schuster rearrangement is the isomerization of

secondary and tertiary α-acetylenic alcohols **92** to α,β-unsaturated carbonyl compounds **106**. The requirement for this rearrangement is the absence of hydrogen atom in the homopropargylic position. Thus the secondary or tertiary carbocation **95a** obtained upon acid catalyzed dehydration of the propargylic alcohol can not undergo proton elimination to form enynes. Instead, the propargylic carbocation **95a** reacts via the allenyl cation resonance structure **95b** which is trapped by water to furnish the α,β-unsaturated carbonyl product **106**. Effectively, the rearrangement involves a 1,3 shift of the hydroxyl group.

Scheme 2.10 Rupe rearrangement



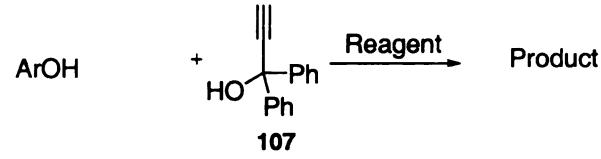
Schuster-Meyer Rearrangement



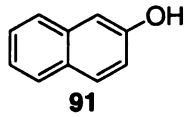
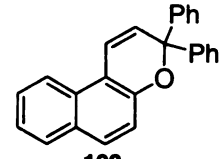
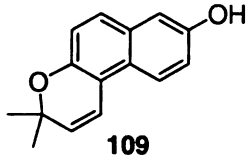
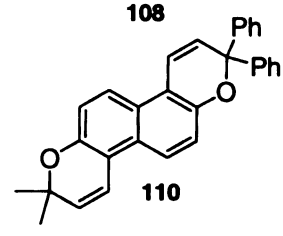
Carriera has dramatically improved the yields of these reactions by using $(MeO)_3CH$ as dehydrating agent in the presence of the PPTS (Scheme 2.11).[33] The reaction of diphenylpropargyl alcohols **107** and 2-naphthol **91** using the PPTS (pyridinium *p*-toluene sulfonate) and $(CH_3O)_3CH$ combination gives a 92%

yield of the napthopyran **108**, which is significantly higher than with *p*-TsOH (toluene solvent, 62% yield), *p*-TsOH with silica support (56%) or with PPTS alone (2% yield).[33]

Scheme 2.11 Carriera's protocol for synthesizing 3H-naphtho[2,1-b]pyran



107

ArOH	Reagent	Yield	Product
 **91**	PPTS, $(MeO)_3CH$	92%	 **108**
	p-TsOH/Silica	56%	
	p-TsOH	62%	
	PPTS	2%	
 **109**	PPTS, $(MeO)_3CH$	80%	 **110**
	Silica/*p*-TsOH	17%	
	p-TsOH	12%	

Tanaka has reported a solvent-free solid-state version of this reaction. In this protocol a mixture of diaryl propargyl alcohol, *p*-TsOH, 2-naphthol and a small amount of silica gel was thoroughly ground and left at room temperature for 1 hour to give the napthopyran (12-57% yield).[35]

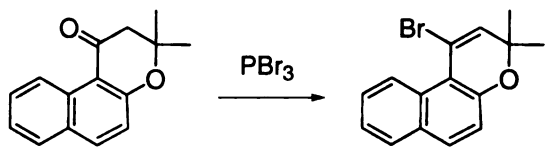
Sartori has utilized HSM-360 zeolite for the reaction of alkyl-aryl propargyl alcohol with 2-naphthol for synthesizing naphthopyrans. Zeolite HSM-360 and p-TsOH give comparable yields.[36]

In brief, Bronsted acids like *p*-TsOH provide a general approach for the synthesis of C-3 alkyl-alkyl, aryl-aryl and alkyl-aryl substituted naphthopyrans. In Carriera and Tanaka's reports, there are no examples of alkyl-alkyl substituted

naphthopyrans. Satori's method is general for obtaining C-3 alkyl-aryl or alkyl-alkyl substituted naphthopyrans.

b) Kabbe's synthesis: This synthesis commences with naphthopyran **111** and requires the reduction of ketone followed by dehydration (Scheme 2.12). Alternatively, naphthopyran **111** can be treated with PBr_3 to obtain bromo-derivatives of naphthopyrans **112**. This approach requires a multistep sequences and it is not as widely used.[38]

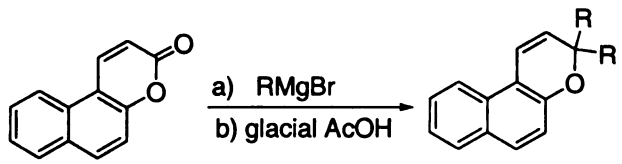
Scheme 2.12 Benzochromanone to 3,3-dialkyl naphthopyran



111 **112** 28% yield

c) Benzocoumarin approach: The reaction of benzocoumarin **113** with Grignard reagents and subsequent dehydration gives substituted naphthopyrans (Scheme 2.13). This method is low yielding for 3,3-diaryl naphthopyrans **108**.[39]

Scheme 2.13 Benzocoumarins to 3,3-dialkyl naphthopyran

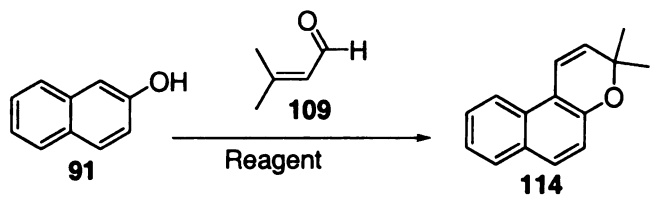


113

R		Yield
CH_3	**(114)**	75%
Ph	**(108)**	20%

d) Acid/Base catalyzed condensation of aldehydes and phenols: Condensation of 2-naphthol with α,β-unsaturated aldehydes can be effected by heating in 4-picoline,[40a] glacial acetic acid / $PhB(OH)_2$[40b] and the Lewis acid titaniumtetroethoxide[40c] to furnish naphthopyran **114** (Scheme 2.14).

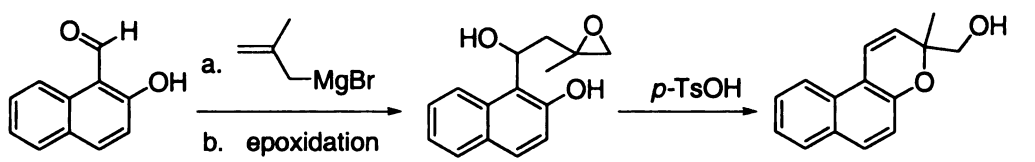
Scheme 2.14 Condensation of 2-naphthol and α,β-unsaturated aldehydes



Reagents (% Yield): 4-methylpyridine/heat (80%), glacial acetic acid/$PhB(OH)_2$ (95%) titanium tetraethoxide (39%)

e) Zammattio's Approach: Zammattio has utilized the acid catalyzed ring opening of epoxide **116** followed by dehydration as a method for synthesizing functionalized naphthopyran **117**. Epoxide **116** can be obtained in two steps by reaction of the commercially available 2-hydroxy-1-naphthaldehyde **115** with allyl Grignard reagents (Scheme 2.15).[41]

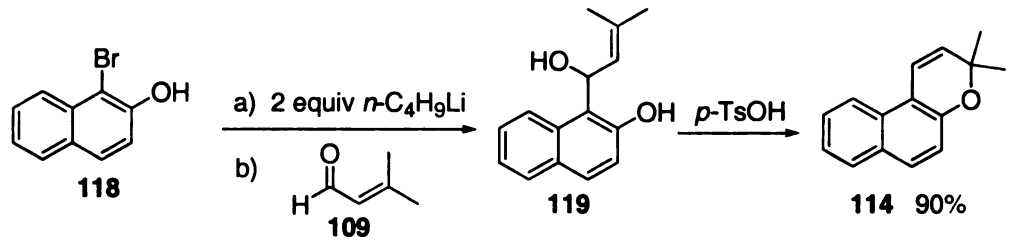
Scheme 2.15 Transformation of 116 to 3,3-dialkyl naphthopyran 117



115 **116** **117** 17% yield over 3 steps

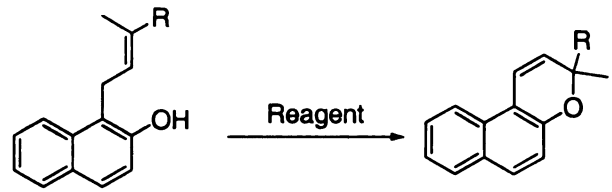
f) Talley's Approach: Lithium-halogen exchange of 1-bromo-2-naphthol **118** with *n*-butyllithium followed by reaction with **109** produces allylic alcohol **119**, which upon acid catalyzed cyclization yields 3,3-dimethyl naphthopyran **114** (Scheme 2.16).[42]

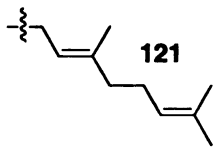
Scheme 2.16 Transformation of 118 to 3,3-dialkyl naphthopyran 114



g) Oxidation of *ortho*-allylic phenols: Cyclodehydrogenation of *ortho*-(3,3-dimethylallyl)naphthols (**120** and **121**) using 2,3-dichloro-5,6-dicyanobenzoquinone[43a] or trityltetrafluoroborate[43b] is another way of synthesizing naphthopyrans (**114** and **122**, Scheme 2.17).

Scheme 2.17 Oxidative cyclization of *ortho*-(3,3-dimethylallyl)naphthols



R		Reagent	% Yield (product)
CH_3	**120**	Trityltetrofluoroborate	85 (**114**)
	**121**	DDQ	46 (**122**)

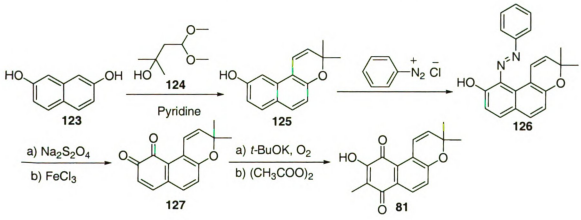
In summary, acid catalyzed condensation of the phenols and the propargyl alcohol is the best and the most widely used method to synthesize a diverse range of 3H-naphtho[2,1-b]pyrans. Other methods are also efficient but they only work well for specific substrates.

2.5 Total Synthesis of natural products 81 to 89

Cannon and coworkers have achieved the unambiguous characterization of naphthopyrans **81** to **89** by their total synthesis (Scheme 2.8).[28a,44] To confirm the structures of the nine quinones, compounds **81**, **83** and **89** were synthesized and subsequently derivatized to the quinones (**84**, **85**, **86**, **87**, **88**). The structure of compound **85** has been confirmed both by synthesis and X-ray analysis.[28a,b]

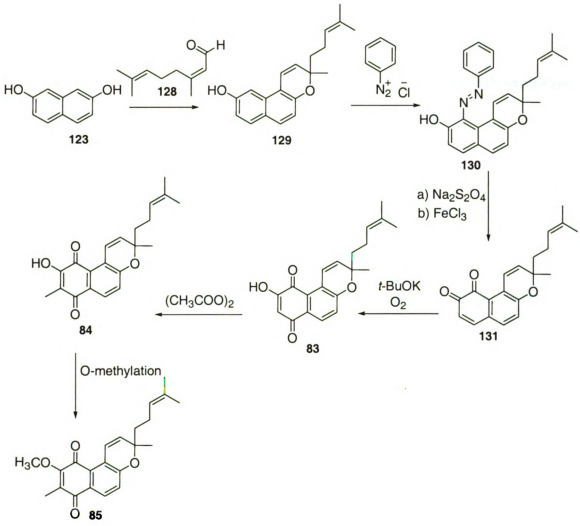
The synthesis of **81** is shown in Scheme 2.18. Reaction of naphthalene-2,7-diol **123** with 1,1-dimethoxy-3-methylbutan-3-ol **124** in pyridine solvent gave **125**, which upon reaction with phenyl diazonium chloride formed azo dye **126** (Scheme 2.18). Reduction of **126** with $Na_2S_2O_4$ and then oxidation of the product with $FeCl_3$ yielded *ortho*-quinone **127**. Compound **127** upon oxidation, using Baillie and Thomson's protocol[28c] and C-methylation furnished compound **81**.

Scheme 2.18 Synthesis of naphthoquinone pyran 81 synthesis from 123



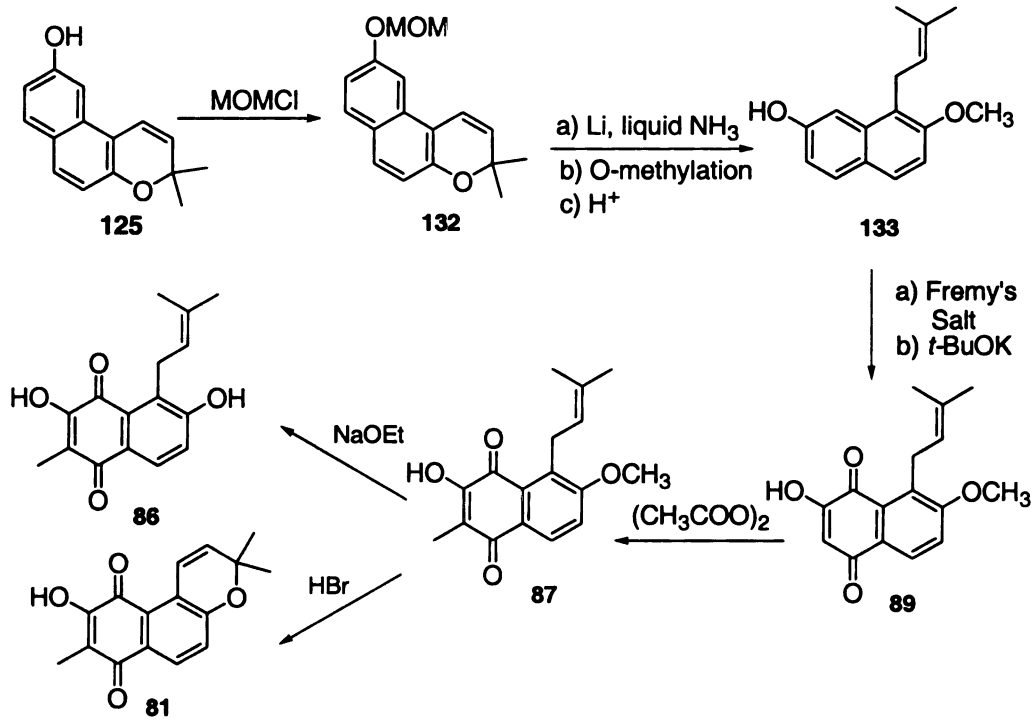
A similar sequence of reactions was used to prepare compound **83** from naphthalene-2,7-diol **123** (Scheme 2.19). Condensation of **123** with citral **128** in pyridine solvent gave compound **129**, subsequent diazotization with phenyl diazonium chloride, reduction with $Na_2S_2O_4$ and oxidation with $FeCl_3$ yielded *ortho*-quinone **131**. Compound **83** was obtained by oxidation of *ortho*-quinone **131**. C-methylation of **83** gave **84** and then O-methylation afforded compound **85**.

Scheme 2.19 Synthesis of naphthoquinone pyrans 83, 84 and 85 from 123



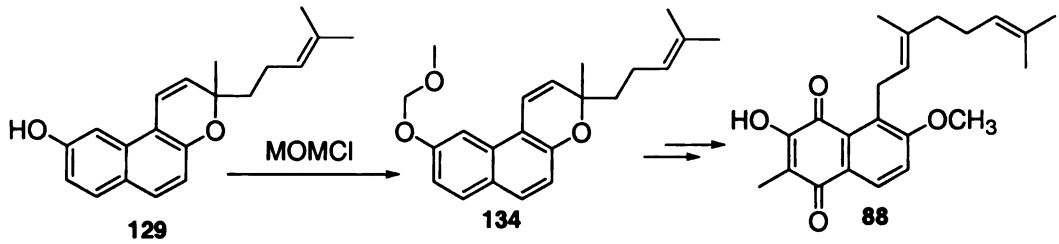
The synthesis of the naphthoquinone **86** with an open pyran ring was then achieved from **125**. The free alcohol in **125** was protected using MOMCl to afford **132** (Scheme 2.20). The protected naphthopyran **132** was reduced using Li in liquid NH_3 followed by immediate O-methylation and acid hydrolysis to give compound **133** (Scheme 2.20). Compound **133** was then oxidized to the *para*-quinone **89** with Fremy's salt. C-methylation of **89** yielded *para*-quinone **87**. Demethylation of compound **87** with sodium ethoxide afforded *para*-quinone **86**. Treatment of **87** with HBr resulted in demethylation followed by acid-catalyzed cyclization to furnish compound **81**.

Scheme 2.20 Synthesis of naphthoquinone pyran 81 and naphthoquinones 86 and 87



A reaction sequence similar to that used for the conversion of **125** to **86** (Scheme 2.20), was used to transform compound **129** to **88** (Scheme 2.21).

Scheme 2.21 Transformation of naphthopyran 129 to naphthoquinone 88



In summary, 3H-naphtho[2,1-b]pyrans are important structures in natural product chemistry and important photochromic compounds. However, there are limited numbers of method for synthesizing these naphthopyrans and naphthoquinone pyrans. One of the most widely used methods is the acid catalyzed cyclization of propargyl alcohols and naphthol derivatives. This method is, however, marred by low yields. Carriera has drastically improved the yield of this reaction by using trimethyl ortho formate with PPTS. This method is good for making napthopyrans with aryl substituents (alkyl substituents are not reported) at C-3 carbon atom. All other methods generally require multi-steps for the synthesis of naphthopyrans. Thus there is an essential need to develop new methodologies to access these compounds. Chapter 3 explores the benzannulation reaction of Fischer carbene complexes with alkynes as an unique new approach.

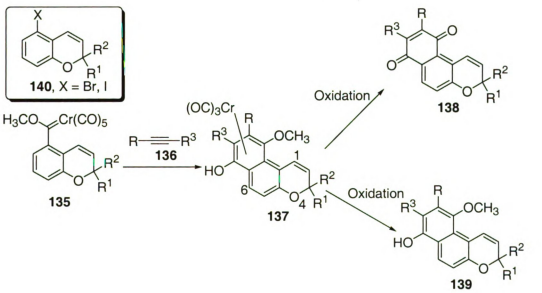
CHAPTER THREE

SYNTHESIS AND BENZANNULATION EXPLORATIONS OF CHROMEN-5-YL CARBENE COMPLEX

3.1 Introduction

Chapter two documents the importance of 3H-naphtho[2,1-b]pyrans. In this Chapter the synthesis of chromene carbene complex **135** and its reactions with various alkynes to access naphthoquinonepyrans of the type **138** and naphthopyrans of the type **139**, will be discussed. The study begins with targeted synthesis and reactions of carbene complex **135** where R_1, R_2 = CH_3 (Scheme 3.1).

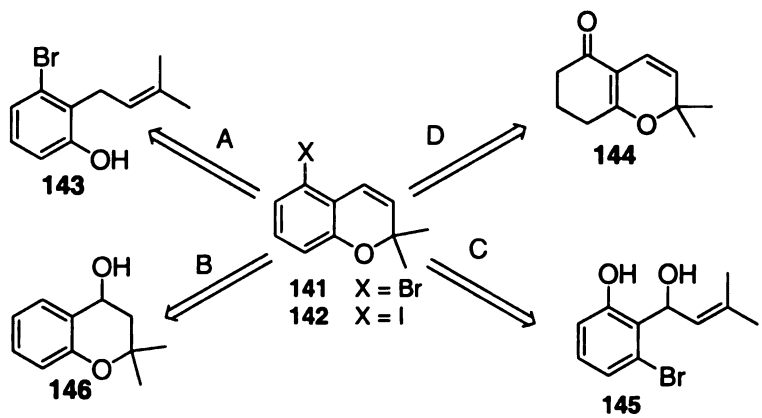
Scheme 3.1 Benzannulation of chromene carbene complex 135



3.2 Synthesis of chromium chromen-5-yl carbene complex 135

Fischer carbene complexes with aryl substituents are typically made from the corresponding aryl halides. In the case of carbene complex **135**, this would require the aryl halide of the type **140**. Four different strategies were considered for the synthesis of 5-halochromene (**141** or **142**) viz. Hepworth,[45] Nicolaou,[46] allylic alcohol cyclization[42,47,48] and chromenone[49,50] approaches (Scheme 3.2). The three out of four approaches i.e., Nicolaou's, allylic alcohol cyclization and chromenone approaches have been examined in the present work. Hepworth's approach has not yet been tried.

Scheme 3.2 Four approaches for synthesizing halochromene 141



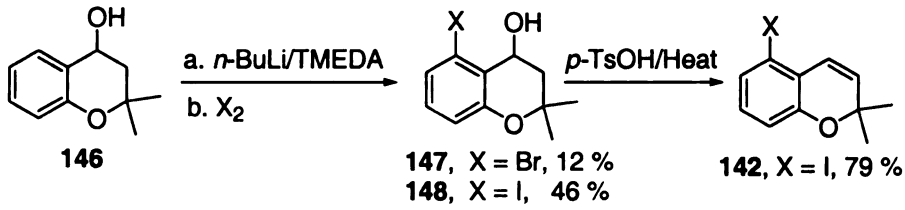
a) Nicolaou's Approach; b) Hepworth's Approach; c) Allylic Alcohol cyclization
d) Chromenone approach

3.2.1 Hepworth's Method

Hepworth has synthesized 5-iodochromene **142** starting from **146**, which was obtained from phenol in two steps (Scheme 3.3).[45] This utilizes the ability of benzylic alcohol to direct *ortho*-lithiation. The reaction of 2,2-dimethylchroman-4-

ol **146** with *n*-BuLi/TMEDA gave a dilithiated compound, which upon reaction with I_2 afforded iodide **148** in 46 % yield. This sequence gave a lower yield of 5-bromochromanol (12 %) **147**. The acid catalyzed dehydration of **148** furnished 5-iodo chromene **142** in 79 % yield.

Scheme 3.3 Hepworth protocol for synthesis of 5-Iodo-2H-chromene 142



146

147, X = Br, 12 %
148, X = I, 46 %

142, X = I, 79 %

3.2.2 Nicolaou's Method

Nicolaou's protocol uses the reaction of polystyrene based selenium-bromide resin and *ortho*-allylic phenols for synthesizing libraries of 2H-benzopyran units.[46] He has demonstrated that *ortho*-allylic phenol obtained by the reaction of phenol derivatives with allyl bromide, upon sequential treatment with phenyl selenyl bromide resin and hydrogen peroxide yields 2H-chromenes. The desired bromochromene **141** was isolated in 90 % purity using this method starting from commercially available 3-bromo-phenol **149** (Scheme 3.4).

However, the selective C-alkylation of 3-bromophenol **149** could not be achieved using the reported protocol. The reaction of sodium phenolate, generated from NaH and 3-bromophenol **149**, gave an inseparable mixture of products when reacted with 4-bromo-2-methyl-2-butene which was comprised of mono- and di-allylated products as indicated by GC-MS.

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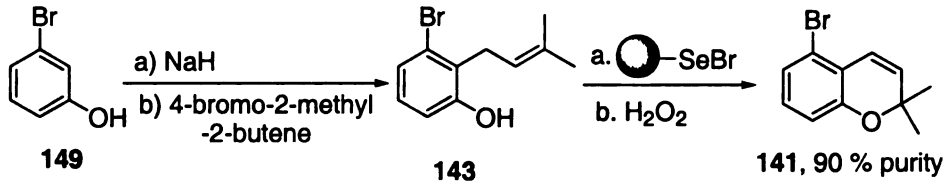
Scheme 3.4 Nicoloaou's protocol for synthesis of 5-bromochromene 141



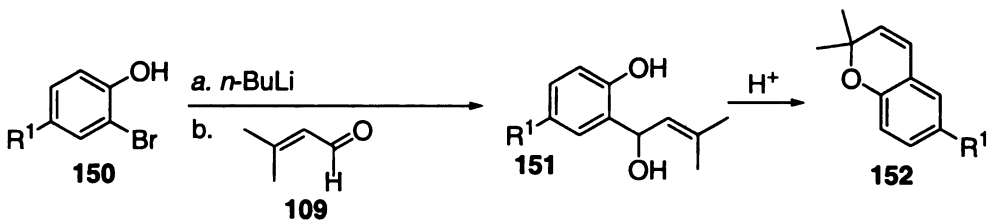
149 **143** **141, 90 % purity**

3.2.3 Allylic alcohol cyclization approach

Talley[42], Cruz-Almanza[47a] and Snieckus,[47b] have employed the reaction of *ortho*-lithiated aromatic alcohol with aldehyde to produce allyl-benzyl alcohols of the type **151** which upon cyclization yields the 2H-chromenes (Scheme 3.5).

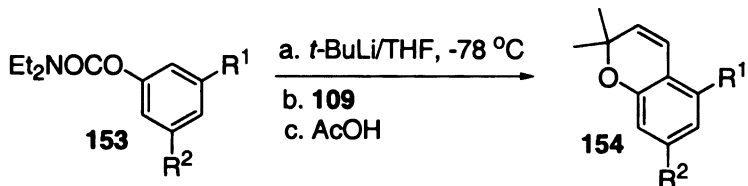
Scheme 3.5 Snieckus and Talley *ortho*-lithiation strategy

Talley, 1983



150 **109** **151** **152**

Snieckus, 2001



153 **154**

R^1 = $OCONEt_2$, OMe, F, OMOM;
R^2 = CH_3, OMe

This approach can not be utilized for the synthesis of 8-bromochromene. The generation of **145** would require selective metal-halogen exchange of 2,3-dibromophenol **155** (Scheme 3.6). The metal-halogen exchange could potentially

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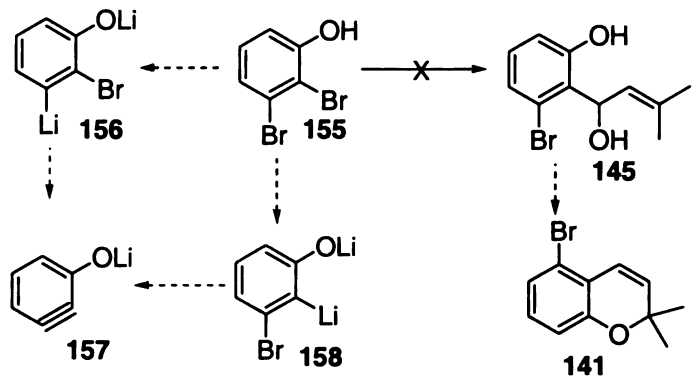
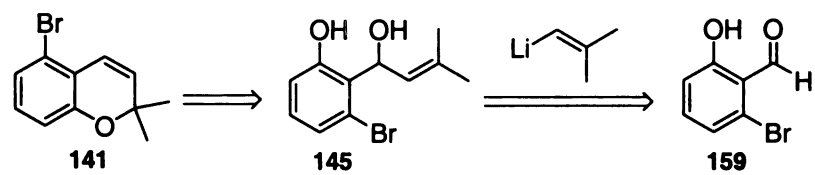
lead to the formation of two anions **156** and **158**. Further, these anions would be expected to be susceptible to bromide elimination to form benzyne **157**.

Scheme 3.6 O*rtho*-lithiation approach towards 141



An alternative approach to obtain benzylic-allylic alcohol **145**, for preparing 5-bromo-2H-chromene **141**, is by the reaction of 5-bromosalicaldehyde **159** with 2-methylpropenyllithium (Scheme 3.7). The requisite aldehyde **159** for this synthesis has been previously prepared by Couture for other purposes.[48]

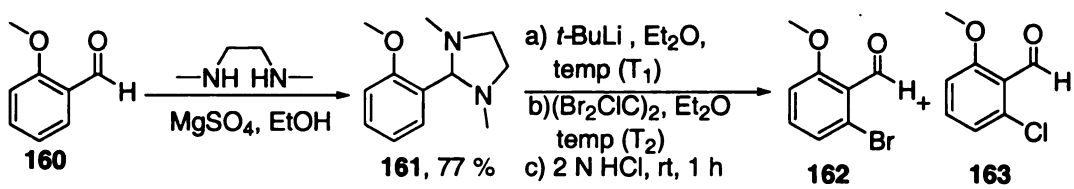
Scheme 3.7 Allylic-alcohol cyclization approach



Couture's synthesis of **159** started with installation of an *ortho*-directing imidazolidine group by reacting aldehyde **160** with bis-1,2-(methylamino)ethane to give **161**. Imidazolidine **161** was then *ortho*-lithiated (3 equiv of *t*-BuLi) and brominated using dibromotetrachloroethane (3 equiv) which, upon acidic workup provided 2-bromoanisaldehyde **162**. The *ortho*-lithiation and bromination step were reported at room temperature by Couture to give **162** in 78 % yield. When

this reaction was repeated under the same conditions, a 2:1 mixture of bromoanisaldehyde **162** and chloroanisaldehyde **163** was obtained in 35 % yield (entry 1, Scheme 3.8). It was found that the ratio of **162** : **163** showed a noticeable dependence on the temperature of the reaction (Scheme 3.8). Optimal conditions required *ortho*-lithiation at -40 °C and the addition of the brominating agent at -78 °C which gave a 69 % yield of **162** (entry 8) and only a trace amount of **163** (**162** : **163** = 50 : 1).

Scheme 3.8 Synthesis of bromoanisaldehyde 162



160 **161**, 77 % **162** **163**

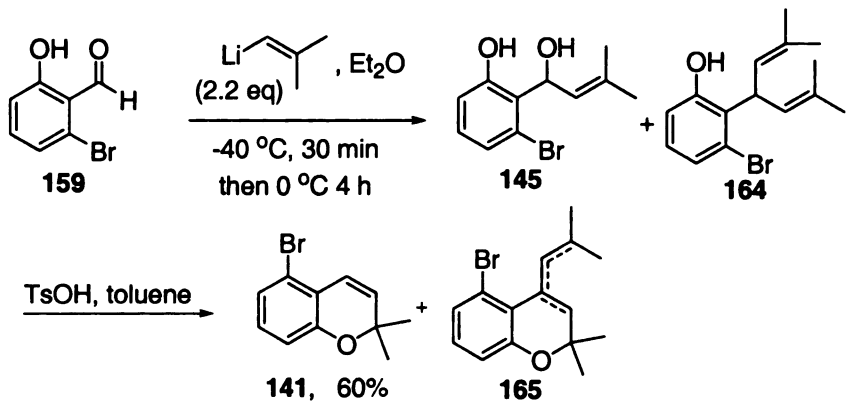
Entry	*t*-BuLi (Equivalent)	Temp T_1 (°C)	Temp T_2 (°C)	Ratio **162** : **163**	Yield **162** + **163** (%)
1	3.0	25	25	1 : 0.5	35
2	2.0	25	25	1 : 0.3	48
3	1.2	25	25	1 : 0.3	41
4	1.2	25	25	-	No product[a]
5	2.0	14	14 to 25	1 : 0.3	43
6	3.0	0	0 to 25	1 : 0.18	52
7	3.0	-20	-20 to 25	1 : 0.18	72
8	3.0	-40	-78 to 25	50 : 1	69

All reaction were carried out in Et_2O (0.1 M) solvent with 3 equiv of $(Br_2ClC)_2$ as the brominating agent. a) NBS (3 equiv) and Br_2 (3 equiv) were used as the brominating agent.

Demethylation of **162** using BBr_3 afforded 2-bromosalicaldehyde **159** in excellent yield (94 % yield). Aldehyde **159** was then reacted with 2-methyl propenyl lithium to obtain crude benzylic-allylic alcohol **145** (Scheme 3.9). The

crude reaction mixture was subjected to acid catalyzed cyclization which afforded a mixture of **141** and **165** after column chromatography (**141** : **165** = 10 : 1). Further purification using Kugelhrohr distillation afforded **141** : **165** in a 40:1 ratio and in 60 % yield from **159**. The structure for the compound **165** was assigned on the basis of its molecular weight. This route provided 5-bromo chromene **141** in 30 % overall yield from commercially available anisaldehyde **160**.

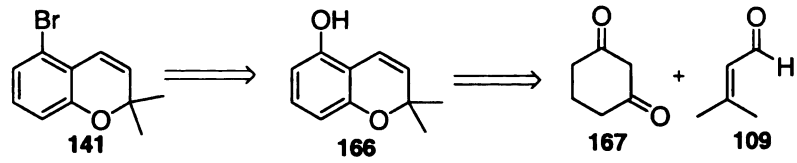
Scheme 3.9 Allylic alcohol cyclization approach continued



3.2.4 Chromenone approach

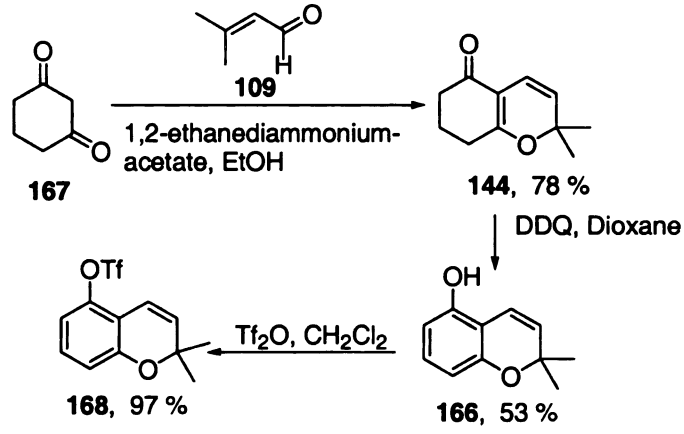
In order to improve the overall yield of **141** another route for its synthesis was explored. This pathway used 5-hydroxychromene **166**, which can be obtained in two steps from commercially available cyclohexadienone **167** and 3-methyl-2-butenal **109** (Scheme 3.10).[49] The proposed conversion of phenol **166** to bromochromene **141** is based on the methodology that has been developed for related compounds utilizing triflation, Pd catalyzed triflate-Sn exchange and NBS mediated Sn-Br transfer.[50a,b]

Scheme 3.10 Chromenone approach



According to the literature procedure, 1,2-ethanediammonium acetate catalyzed condensation of 1,3-cyclohexanedione **167** and 3-methyl-but-2-enal **109** in methanol afforded chromenone **144** in 78 % yield (Scheme 3.11).[49a] Groot and Jansen have reported a yield of 82 % for the same reaction when instead of using 1,2-ethanediammonium acetate the reaction was refluxed in pyridine.[49b] Sequential DDQ oxidation[50] and triflation of compound **144** gave chromene **168** in two steps and in 51 % yield.

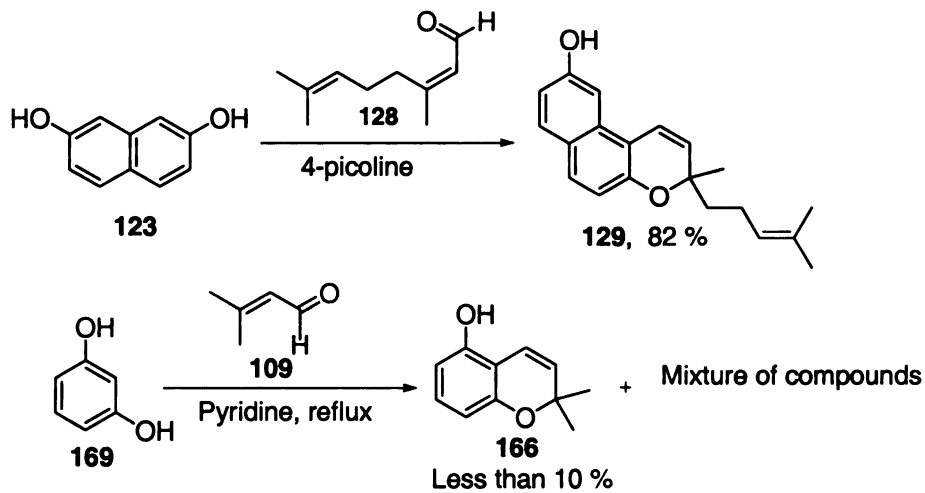
Scheme 3.11 Synthesis of chromene triflate 168



The DDQ oxidation of **144** to **166** was less than optimal (53 % yield). Thus, a high yielding method for chromenol **166** synthesis was desired. Jacobsen has reported that refluxing of naphthalen-2,7-diol **123** with citral **128** in 4-picoline gives 82 % yield of naphthopyran **129**.[44] This prompted us to examine the base assisted condensation of resorcinol **169** with **109** to synthesize **166**

even though Crombie and Whiting have reported low yields in a related reaction with resorcinol.[51] Refluxing a mixture of resorcinol **169** and **109** in pyridine or picoline solvent yielded a complex mixture of compounds, with the desired chromenol **166** being formed in less than 10 % yield in each case (Scheme 3.12).

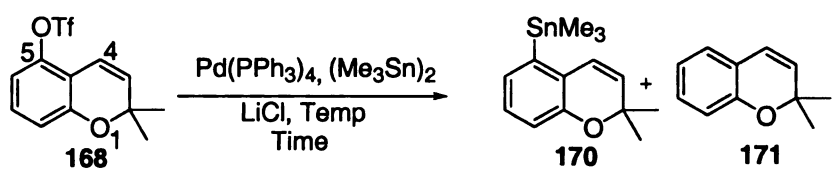
Scheme 3.12 Reaction of resorcinol 169 with 3-methyl-but-2-enal 109



The next step was to carry out palladium catalyzed triflate-tin exchange on triflate **168**. Heating **168** with hexamethylditin and $Pd(PPh_3)_4$ in THF solvent led to the recovery of most of the starting material after 48 h (Scheme 3.13, entry 1).[52a] Further optimization of the reaction conditions revealed that high reaction temperatures and long reaction times are requisite for the reaction to go to completion. GC analysis of the reaction mixture, after heating of reaction mixture at 110 °C for 96 h, showed the presence of the desired (2,2-dimethyl-2H-chromen-5-yl)-trimethyl-stannane **170** (84 %) along with chromene **171** (7 %) and another unidentified compound (9 %) (entry 4). The attempt at purification of **170** using silica gel column chromatography was of no avail, as it yielded a

mixture of **170**, **171** and triphenylphosphine. Attempts to reduce the reaction time by switching to high boiling solvents like DMF and dibutyl ether proved futile. Dibutyl ether resulted in the precipitation of the Pd black at 120 °C and the starting material remained intact after 8h (entry 5). A significant amount of the side product **171** was observed in DMF solvent, although the reaction was very fast with 100 % conversion in 20 minutes at 160 °C (entry 6). Reduction of the temperature from 160 to 120 °C didn't show any improvement in the ratio of **170** : **171** (entry 7).

Scheme 3.13 Palladium catalyzed triflate-Sn exchange



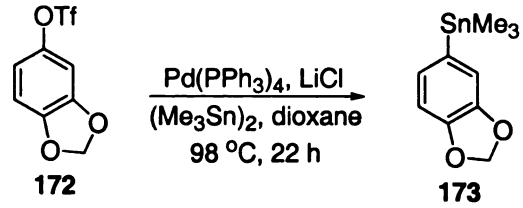
Entry	Solvent (0.1M)	Temp (°C)	Time (h)	Conversion (%)	GC Ratio **170** (%)	**171** (%)
1.	THF	60	48	3	3[a]	-
2.	Dioxane	105	8	10	10	-
3.	Dioxane	105	48	77	25	28
4.	Dioxane	110	96	100	84	7
5.	Dibutyl ether	120	8	2	-	-
6.	DMF	160	0.2	100	19	54
7.	DMF	110	100	100	29	69

Unless otherwise stated all reactions were carried using 0.1 M solution of solvent using **168**:$(Me_3Sn)_2$:$Pd(PPh_3)_4$:dppf:LiCl in the ratio of 1:0.9:0.02:0.45:6.0. a) no dppf used.

Steric hindrance from the hydrogen at C-4 in chromene trilflate **168** may be source of the low reactivity. It is known from previous studies that palladium catalyzed triflate-Sn exchange of phenyl triflate **172** using hexamethylditin

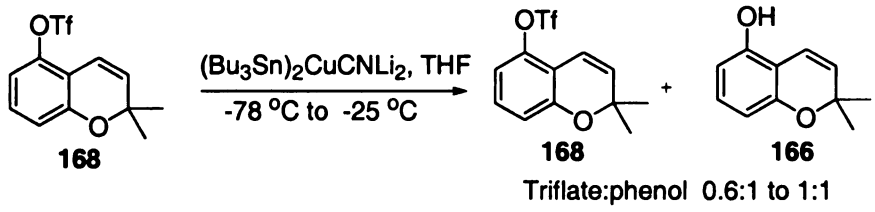
requires 22 h to go to completion at 98 °C in dioxane solvent (Scheme 3.14),[52b] whereas only 77 % conversion of chromenyl triflate **168** to stannane **170** was obtained in dioxane solvent at 105 °C after 48 h (entry 3, Scheme 3.13).

Scheme 3.14 Palladium catalyzed triflate-Sn exchange



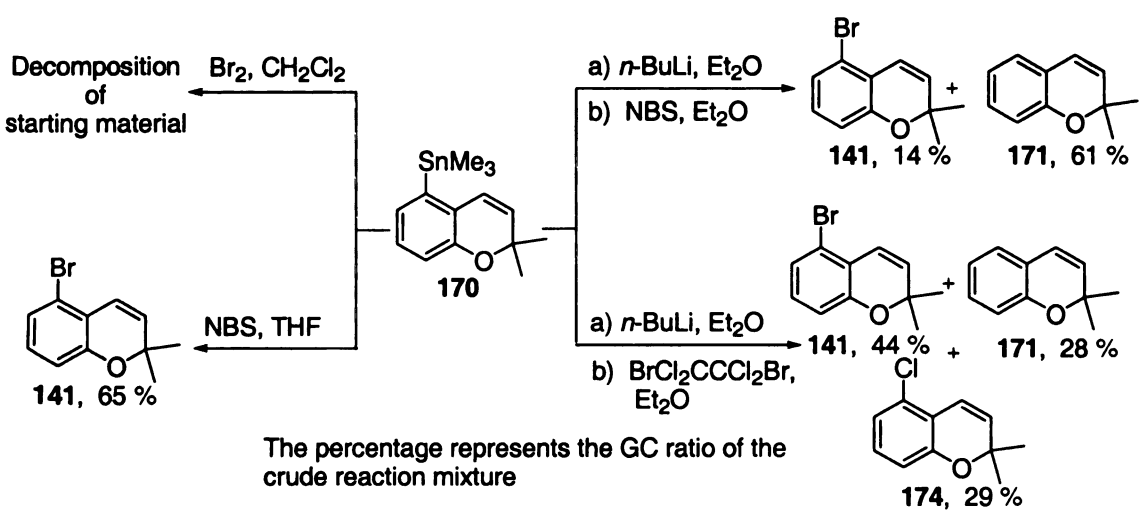
An alternative method to convert triflate **168** to stannane **170** is to use stannyl cuprates which can be synthesized in-situ using tributyltinhydride, *n*-BuLi and CuCN.[53] This method is attractive because all of the reagents are cheap. The coupling approach shown in Scheme 3.13, requires $Pd(PPh_3)_4$, dppf and hexamethylditin, all of which are expensive. The reaction of **168** with the tributylstannyl higher order cuprate was examined at different temperatures ranging from -78 °C to -25 °C, but in all cases a mixture of starting material **168** and phenol **166** was obtained in ratios ranging from 0.6 : 1 to 1 : 1 depending on the reaction temperature (Scheme 3.15). Thus the only way to access stannane **170** is via the coupling route.

Scheme 3.15 Stannyl cuprate addition to chromene triflate 168



The impure chromene stannane **170** obtained after silica gel purification was then converted to the corresponding bromochromene **141**. The reaction of stannane **170** with bromine resulted in decomposition of starting material (Scheme 3.16). Tin-lithium exchange of chromene stannane **170** with *n*-BuLi and then Li-Br exchange using NBS resulted in a mixture of bromochromene **141** and chromene **166** in the ratio of 14 : 61 by GC. A mixture of bromochromene **141**, chromene **171** and chlorochromene **174** was observed in the ratio of 44 : 28 : 29 by GC when NBS was replaced by dibromotetrachloroethane. The structure of compound **174** was assigned based on the molecular weight obtained using GC-MS. Eventually, treatment of **170** with the mild brominating agent NBS provided the desired Sn-Br exchange to give chromene **141** in 65 % yield from chromene triflate **168**. Furthermore, the overall yield of **141** from **168** can be increased to 75 % in two steps by quenching the crude reaction mixture containing chromene stannane **170** with NBS.

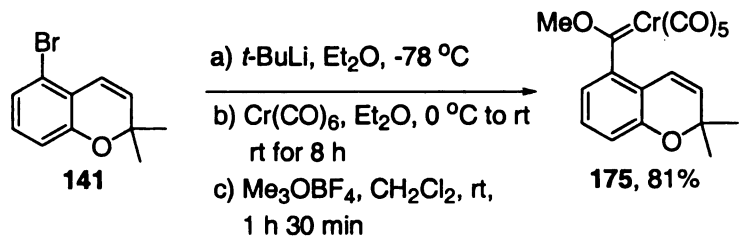
Scheme 3.16 Bromination of chromene stannane 170



The chromenone approach provides 5-bromochromene **141** in 30 % overall yield starting from cyclohexane-1,3-dione **167** and 3-methyl-but-2-enal **109**. The bromochromene **141** produced from this method can be obtained in pure form and does not require tedious workup or purification procedures. However this approach is marred by the use of expensive reagents as stated earlier. The initial approach involving the allylic alcohol cyclization provides overall comparable yield (30 %) but does not require use of expensive reagent. However in this approach, the bromochromene **141** was isolated in the ratio of 40 : 1 (**141** : **165**) after column chromatography and lengthy Kugelhrohr distillation. In addition, a disadvantage is that both bromides **141** and **165** are converted to carbene complexes and they can only be separated by careful chromatography. These shortcomings give the chromenone approach an edge over the allylic alcohol cyclization method.

Finally, the synthesis of chromene carbene complex **175** was achieved by the standard Fischer procedure as indicated in Scheme 3.17. Treatment of **141** with 2equiv of *t*-BuLi, subsequent reaction with $Cr(CO)_6$ and final alkylation with Me_3OBF_4 gave **175** in 81 % yield as red crystalline solid. This carbene complex is much more stable than other aryl carbene complex. It can be stored at room temperature for 6 - 7 days under Ar atmosphere without significant decomposition. Furthermore, it shows essentially no decomposition after 2 days in the presence of air and light.

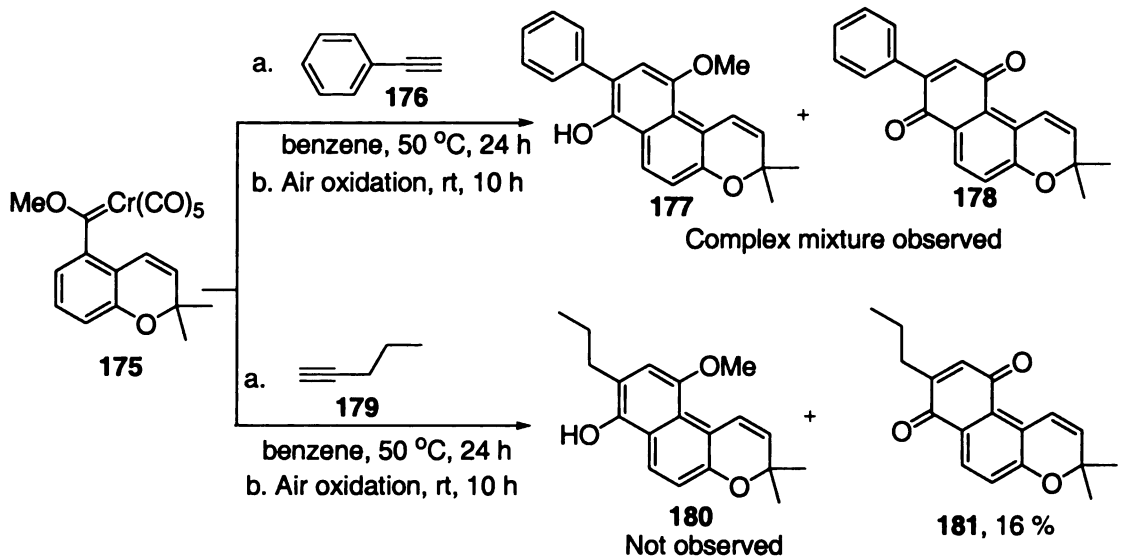
Scheme 3.17 Chromene carbene complex 175 synthesis



3.3 Chromium chromen-5-yl carbene complex 175: Study of Dötz-Wulff Benzannulation Reaction

With the synthesis of carbene complex **175**, the stage is set for exploring the benzannulation reaction of chromene carbene complex **175** and a new method for the synthesis of 3H-naphtho[2,1-b]pyrans. Four alkynes were selected for this study: phenyl acetylene, 3-hexyne, 1-pentyne and trimethylsilyl acetylene. The study was initiated with phenyl acetylene and as a consequence most of the optimization of temperature and solvent effect was performed on this alkyne. The first reaction of phenyl acetylene with carbene complex **175** gave disappointing results. Heating carbene complex **175** with phenyl acetylene for 24 h at 60 °C followed by air oxidation, to remove any chromium tricarbonyl group, yielded a mixture of compounds containing trace amounts of the desired naphtholpyran **177** and the corresponding quinone **178** (Scheme 3.18). On subjecting 1-pentyne to similar reaction conditions, naphtholpyran **180** was not obtained. Instead quinone **181** was isolated in 16 % yield. Similarly, 3-hexyne did not give a clean reaction with complex **175**.

Scheme 3.18 Benzannulation of complex 175 with phenyl acetylene

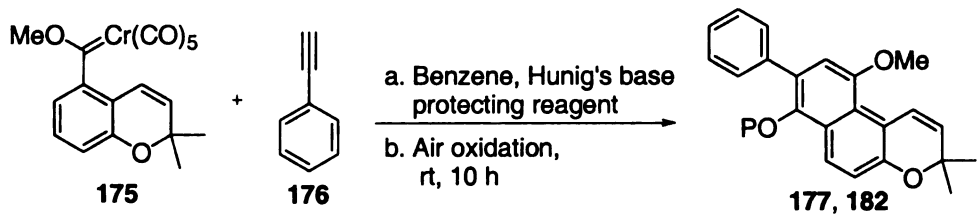


One possible explanation for these observations is that the phenols **177** and **180** (or their chromiumtricarbonyl complexes) are not stable to these reaction conditions. Specifically, these two phenols could be either decomposing during the course of the benzannulation reaction or could be sensitive to conditions of the air oxidation. To render phenols **177** and **180** more robust and thus increase the yields of these reactions, it was decided to trap the phenol products during the benzannulation reaction by adding protecting reagents at the beginning of the reaction.[54] This type of process has been previously reported for a number of different electrophiles.[54]

Upon heating complex **175** and phenyl acetylene in the presence of TBSCl and Hunig's base in benzene for 24 h at 50 °C, the product naphtholpyran **182** was isolated in 27 % yield (entry 2, Scheme 3.19). When the reaction was run at room temperature for 6 days, compound **182** was obtained in 45 % yield

(entry 3). The more reactive TBSOTf gave a slightly higher yield 57 % at 60 °C temperature (entry 4).

Scheme 3.19 Benzannulation of complex 175 with phenyl acetylene



175 176 177, 182

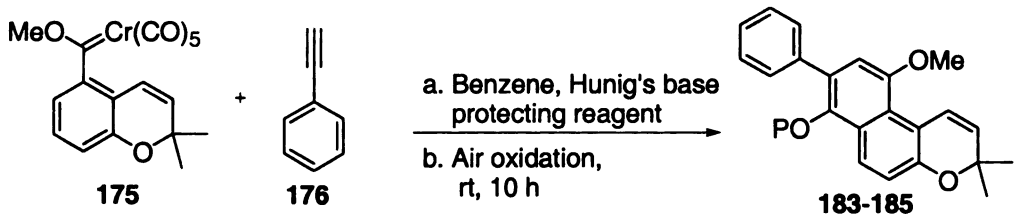
Entry	Protecting reagent	P	Compound (% Yield)
1	-	H	Complex mixture observed[a]
2	TBSCl	TBS	**182** (27)
3	TBSCl	TBS	**182** (45)[b]
4	TBSOTf	TBS	**182** (57)[c]

Unless otherwise specified, the benzannulation reactions were carried out in benzene (0.05 M) with protecting reagent (3 equiv), Hunig's base (5 equiv) and 1:2 mixture of complex **175** to phenyl acetylene for 24 h under Ar at 50 °C. a) No Hunig's base is used. b) Reaction was carried out at 25 °C for 6 days. c) Reaction was carried out at 60 °C, compound **182** (P=TBS) was isolated after column chromatography as mixture of compounds, the yield of compound **182** was determined using toluene as internal standard.

The size of the protecting group plays a role in this reaction. When the bulkier TBS group was replaced by smaller TMS protecting group, the yield of the reaction increased notably from 27 % to 65 % (entry 1, Scheme 3.20). Surprisingly, when the more reactive TMSOTf was employed the yield decreased markedly (entry 4). Encouraged by the success with the smaller trimethylsilyl protecting group, other protecting groups were examined. Reaction of complex **175** with phenyl acetylene in the presence of Ac_2O yielded compound **184** in a 57 % yield (entry 5). The structure of compound **184** has been confirmed by X-ray

crystallography. DMAP is known to greatly accelerate the acetylation of alcohols.[55] However, DMAP did not have any effect on the yield of the compound **184** (entry 6). Another smaller but less reactive protecting group, MOMCl, provided a yield of **185** (60 % yield) comparable to that of compound **183** from TMSCl (entry 7). Triflic anhydride as a protecting group was also investigated since it would provide a facile route for the introduction of carbon substitutents via metal-catalyzed coupling reactions. This reaction was tried via two different procedures: concurrent protection and stepwise protection (entry 8).[10] In the first approach, complex **175**, phenyl acetylene, Tf_2O and Hunig's base were dissolved in benzene and heated to 50 °C for 24 h. In the second approach, complex **175** and phenyl acetylene were first heated in benzene for 24 h at 50 °C. Then the reaction mixture was cooled and Tf_2O and Hunig's base were added and the reaction mixture was stirred for another 24 h at 25 °C under Ar atmosphere. Both pathways proved unsuccessful in yielding the desired compound. The stepwise approach was tested for phenylacetylene with a TMSCl additive which proved to be detrimental to the yield of the reaction. The yield decreased from 65 % (concurrent approach, entry 1) to 25 % (stepwise approach, entry 2). Compound **183** was isolated in a yield of 62 % when the reaction mixture was degassed, using freeze-pump-thaw, after addition of the additives TMSCl and Hunig's base (entry 3). This indicates that the low yield in stepwise approach was due to the trace amount of air which possibly entered the reaction flask during the addition of the additives.

Scheme 3.20 Benzannulation of complex 175 with phenyl acetylene using different protecting group.

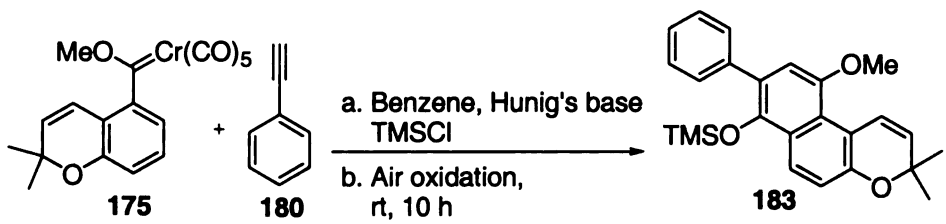


Entry	Protecting reagent	P	Compound (% yield)
1	TMSCl	TMS	**183** (65)
2	TMSCl	TMS	**183** (25)[a]
3	TMSCl	TMS	**183** (62)[b]
4	TMSOTf	TMS	**183** (25)
5	Ac_2O	Ac	**184** (57)
6	Ac_2O	Ac	**184** (57)[c]
7	MOMCl	MOM	**185** (60)
8	Tf_2O	Tf	Complex mixture observed[d]

Unless otherwise specified the benzannulation reactions were carried out in benzene (0.05 M) solvent with protecting reagent (3 equiv), Hunig's base (5 equiv) and 1 : 2 mixture of complex **175** to phenyl acetylene for 24 h under Ar at 50 °C. a) Stepwise method: After 24 h, TMSCl and Hunig's base was added and the reaction mixture was stirred for another 24 h at room temperature (No free-pump-thaw degassing done). b) Stepwise method: After 24 h, TMSCl and Hunig's base was added and reaction mixture was degassed using freeze-pump-thaw which was followed with stirring continued for another 24 h at room temperature under Ar. c) DMAP (5 mol %) used. d) Attempted with two procedures (see text).

The benzannulation of complex **175** with phenyl acetylene did not show any dependence on the temperature. Upon increasing the temperature from 50 to 125 °C there was only a small change in the yield of compound **183** (entry 1-4, Scheme 3.21). However, this reaction is dependent on the solvent used. There was a slight decrease in the yield of the reaction with an increase in the coordination ability of the solvent (entry 5 and 6).

Scheme 3.21 Benzannulation of complex 175 with phenyl acetylene using TMSCl protecting group in different solvents



Entry	Temperature (°C)	Solvent	% yield
1	50	Benzene	65
2	75	Benzene	67
3	100	Benzene	68
4	125	Benzene	68
5	50	THF	60
6	50	CH_3CN	55

Unless otherwise specified the benzannulation reactions were carried out in benzene (0.05 M) solvent with TMSCl (3 equiv), Hunig's base (5 equiv) and 1:2 mixture of complex **175** to phenyl acetylene for 24 h under Ar.

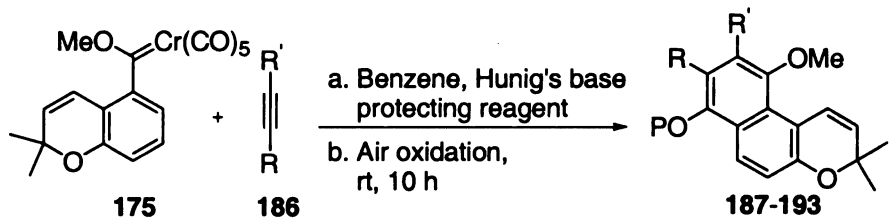
After documenting that TMS is the best protective group for the benzannulation product from the reaction of carbene complex **175** with phenyl acetylene, the investigation was then turned to examine the generality of this protecting group for other alkynes. The reaction of carbene complex **175** with 1-pentyne in the presence of TMSCl and Hunig's base furnished excellent yields (97 % of **187**) for the benzannulation product (entry 1, Scheme 3.22). The yield of **187** dropped from 97 % in concurrent approach (entry 1) to 50 % in stepwise approach (entry 2). Compound **187** could be isolated in a yield of 87 % when the stepwise approach involved the degassing of the reaction mixture using the freeze-pump-thaw method after addition of the additives (TMSCl, Hunig's base)

(entry 3). This incremental increase in yield upon degassing the solvent is consistent with the results of stepwise reaction of complex **175** with phenyl acetylene (Scheme 3.20 entry 1 and 2). This indicates that for a stepwise approach it is essential to freeze-thaw the reaction mixture after the addition of additives to obtain higher yields of benzannulated products. The relatively bulkier reagent TBSCl afforded a 78 % yield of the TBS protected napthopyranol **188** and 10 % of the corresponding quinone **181** (entry 4).

The TMSCl protecting group was further examined for 3-hexyne. The benzannulation reaction of complex **175** with 3-hexyne in the presence of TMSCl and Hunig's base gave a nearly quantitative yield of the product **189** (entry 5). Whereas the TMS group in **187** is stable to silica gel, the TMS group in **189** is not, but luckily essentially pure compound was obtained after filtration of the reaction mixture through Celite with pentane. As with 1-pentyne, the protection of the product from 3-hexyne with TBSCl gave a high yield (entry 6).

Benzannulation of trimethylsilyl acetylene with complex **175** did not give a clean reaction when the sterically bulky TBSCl was used as the protecting reagent for the phenol functionality (entry 8). The relatively smaller TMS protecting group again proved fruitful here and yielded the benzannulated product **191** in 89 % yield (entry 7). The less reactive but relatively small protecting group MOMCl also afforded excellent yield of **193** with trimethylsilylacetylene (entry 9). This benzannulation reaction was also done at room temperature in the presence of MOMCl, and after 5 days a 70 % yield of compound **193** was obtained (entry 10).

Scheme 3.22 Benzannulation of complex 175 with 1-pentyne, 3-hexyne and trimethylsilyl acetylene

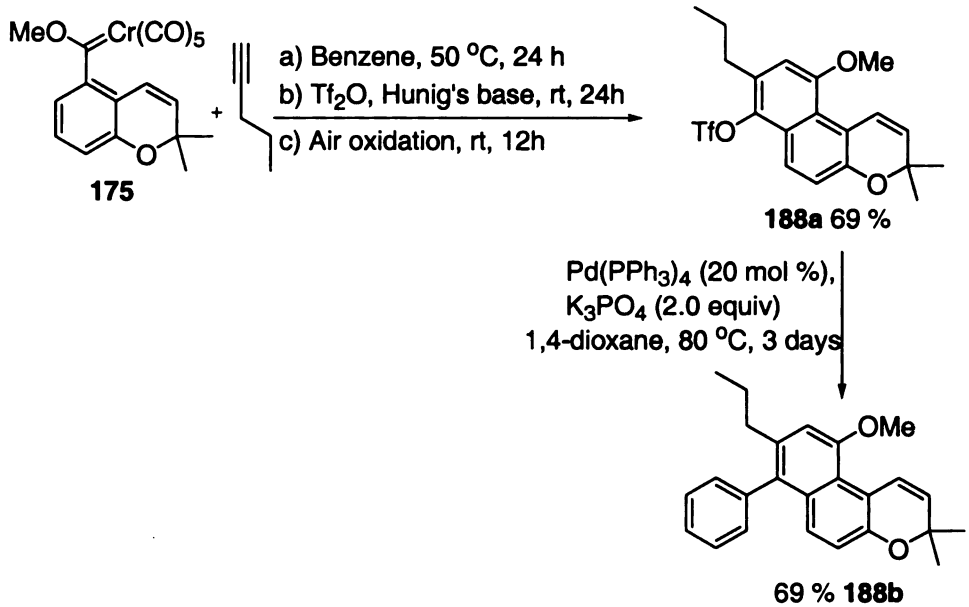


175 **186** **187-193**

Entry	Protecting Reagent	P	R	R'	Compound	Compound (% yield)[a]
1	TMSCl	TMS	Propyl	H	**187**	97
2	TMSCl	TMS	Propyl	H	**187**	50[b]
3	TMSCl	TMS	Propyl	H	**187**	89[c]
4	TBSCl	TBS	Propyl	H	**188**	78[d]
5	TMSCl	TMS	Ethyl	Ethyl	**189**	95[e]
6	TBSCl	TBS	Ethyl	Ethyl	**190**	85
7	TMSCl	TMS	TMS	H	**191**	89
8	TBSCl	TBS	TMS	H	**192**[e]	-
9	MOMCl	MOM	TMS	H	**193**	85
10	MOMCl	MOM	TMS	H	**193**	70[f]

Unless otherwise specified the benzannulation reactions were carried out in benzene (0.1 M) solvent with 1:2:3:5 ratio of complex **175**:alkyne:protecting reagent:Hunig's base for 24 h at 50 °C under Ar. a) Isolated by chromatography using silica gel. b) Stepwise method: After 24 h, TMSCl and Hunig's base was added and the reaction mixture was stirred for another 24 h at room temperature (No free-pump-thaw degassing done). c) Stepwise method: After 24 h, TMSCl and Hunig's base was added and reaction mixture was degassed using freeze-pump-thaw which was followed with stirring continued for another 24 h at room temperature under Ar. d) Slightly impure quinone **181** was isolated in 10 % yield. e) The product was isolated by filtration of crude reaction mixture through Celite using pentane. f) A complex mixture was observed which was not analyzed. f) The reaction was carried out at room temperature for 5 days.

Scheme 3.22 continued



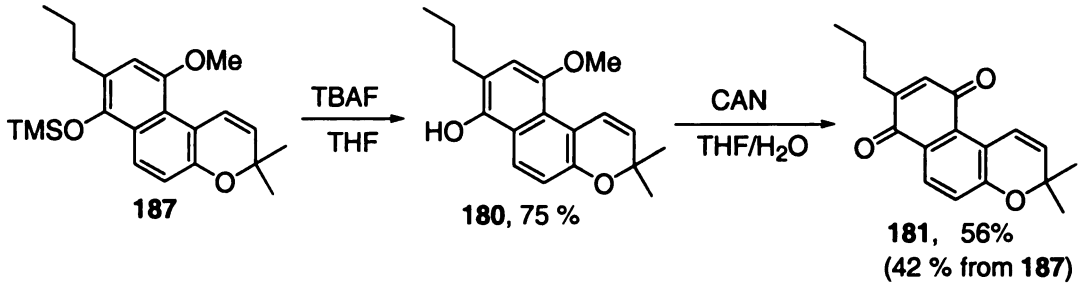
Naphthol pyran triflate **118a** could be obtained by the reaction of carbene complex **175** with 1-pentyne via stepwise method in which reaction mixture was degassed using freeze-pump-thaw after addition of TMSCl and Hunig's base, which was followed with continued stirring for another 24 h at room temperature under Ar. The Suzuki coupling of naphthol pyran triflate **118a** with phenyl boronic acid in the presence of Pd catalyst provided **188b** in 69 % yield.

After establishing the optimal conditions for the synthesis of protected naphtholpyrans of the type **139** (Scheme 3.1), attention was focused on their deprotection to form unprotected naphtholpyrans **139** and on their oxidation to naphthoquinonepyrans **138**. Compound **187**, which was isolated in quantitive yield from the benzannulation reaction of complex **175** with 1-pentyne, was chosen for these studies.

The desilylation of compound **187** using TBAF afforded naphtholpyran **180** in 75 % yield (Scheme 3.23). This alcohol is not particularly stable and was

contaminated with a small amount of unidentified impurity after purification. Ceric ammonium nitrate (CAN) oxidation of alcohol **180** furnished quinone **181** in 56 % yield. Quinone **181** is robust in air/light and does not decompose readily. Thus it was decided to optimize the conditions for the relatively stable quinone **181**.

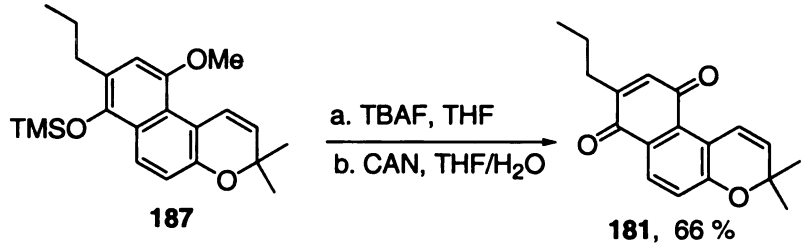
Scheme 3.23 Synthesis of quinone 181



187 **180**, 75 % **181**, 56% (42 % from **187**)

Considering the instability of the alcohol **180** it was decided not to isolate it after desilylation. The naphthopyran **187** was treated with TBAF in THF solvent for 10 min at 0 °C (Scheme 3.24). The reaction was then quenched with water and extracted with ethylacetate. Removal of organic solvent gave crude alcohol **180**, which, without any purification, was oxidized using CAN to afford quinone **181** in 66 % yield in two steps.

Scheme 3.24 Synthesis of quinone 181

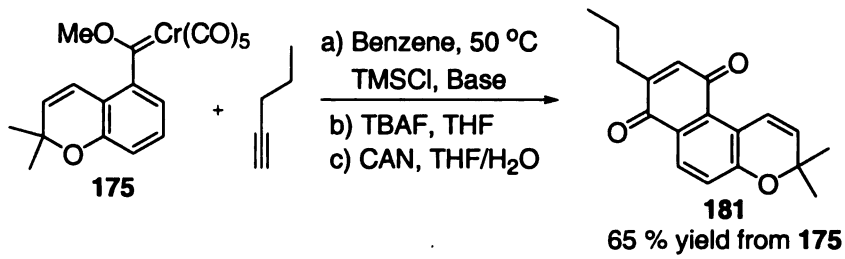


187 **181**, 66 %

Next, the efficiency of the conversion of carbene complex **175** to quinone **181** was examined when the protected phenol **187** was not purified. The crude

reaction mixture after benzannulation was first treated with TBAF and then, after workup, it was oxidized using CAN (Scheme 3.25). This resulted a 65 % yield of quinone **181**. Notice that this is essentially the same overall yield of **181** that is obtained when **187** is purified by silica gel chromatography (97 X 66 = 64 %).

Scheme 3.25 Synthesis of quinone 181

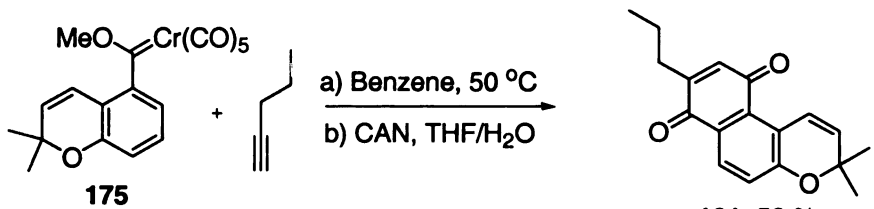


175 **181**

65 % yield from **175**

The direct conversion of carbene complex **175** to quinone **181** was investigated without *in-situ* protection of the phenol. After heating complex **175** and 1-pentyne in benzene solvent at 50 °C for 24 h, the crude reaction mixture was subjected to oxidation conditions using CAN. This reaction afforded naphthoquinone **181** in 58 % yield (Scheme 3.26). The proctection of the phenol during the course of the reaction thus has only a minimal effect on the outcome.

Scheme 3.26 Synthesis of quinone 181

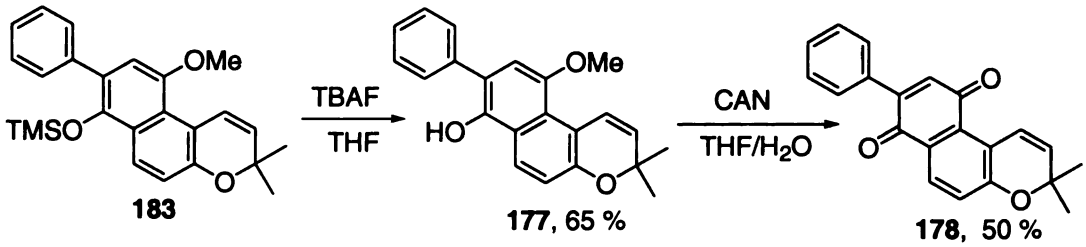


175 **181** 58 %

Now that the efficiency of the reaction of carbene complex **175** and 1-pentyne in the synthesis of naphthoquinone pyran **181** is well understood, the same reaction with phenyl acetylene was examined for the synthesis of quinone

178. First compound **183** was desilylated to obtain phenol **177** in 65 % yield which like phenol **180** was relatively unstable. CAN oxidation of **177** provided **178** in 50 % yield (Scheme 3.27). The overall yield of naphthoquinone **178** was 32 % starting from **183**. Naphthoquionone pyran **178** is stable to air and light as is quinone **181**.

Scheme 3.27 Synthesis of quinone 178



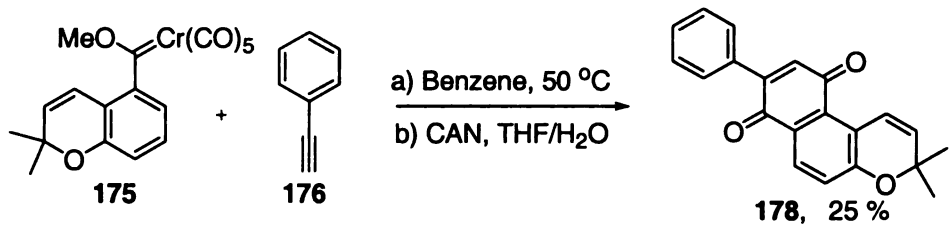
183

177, 65 %

178, 50 %
(32 % from **183**)

Next, the direct conversion of **175** to quinone **178** is investigated without the *in-situ* protection of the phenol. Reaction of **175** with phenyl acetylene in the absence of any additive followed by CAN oxidation provided a 25 % yield of the corresponding quinone **178** (Scheme 3.28). Notice that this is the essentially same overall yield that is obtained when protected phenol **183** is isolated (65 X 32 = 21 %). This suggests that the phenol and/or quinone from phenyl acetylene are more sensitive to the oxidation conditions (CAN) than they are from 1-pentyne. This suggests that in future work, the yields of these quinones might be optimized by screening other oxidizing agents.

Scheme 3.28 Synthesis of quinone 178



In summary, the naphthoquinone pyrans **178** and **181** were obtained in moderate yields from the benzannulation reaction of carbene complex **175** with 1-pentyne and phenyl acetylene. These quinones are highly stable and are not very sensitive to air and light. On the contrary, the unprotected naphtholpyrans **177** and **180** are unstable compounds and are relatively difficult to isolate in pure form. High yields for the benzannulation reaction of complex **175** with different alkynes can be obtained by the concurrent protection using protecting groups such as TMSCl, TBSCl, MOMCl, Ac_2O etc, which form naptholpyran derivatives of the type **139** with protected phenolic functionality. The success of these benzannulation reactions of chromene carbene complex **175** shows a dependence on the bulkiness of the protecting group and on the nature of the alkyne.

CHAPTER FOUR

Synthetic Studies toward Conocurvone

4.1 Introduction to conocurvone 36

Conospermum (Proteaceae) is a genus of about 50 species, all of which occur only in Australia. Most of these species inhabit the south of Western Australia with the exception of few which can be found in eastern states (Figure 4.1). They are generally called "smokebushes" because, with some species, the appearance of the flowering plant from a distance resembles puffs of smoke. *Conspermum incurvum* is one of the western species, which forms a spreading shrub up to 1.5 metres high. The leaves are linear and rounded in cross-section to about 25 mm long. The small, greyish-white flowers occur in late spring in clusters about 250 mm long at the ends of the branches.

Figure 4.1 Australia map and conospermum incurvum

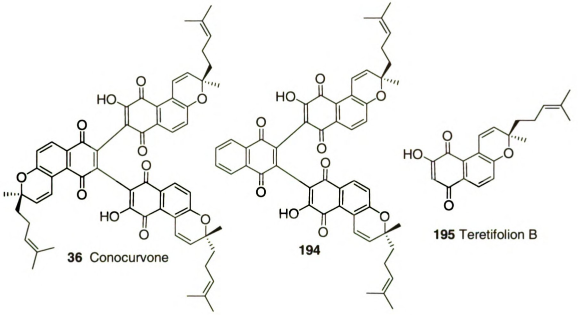
Conospermum species is found in the region colored in red.

Conospermum incurvum

Conospermum has traditionally been used by indigenous peoples for a variety of therapeutic purposes and especially for "old age" diseases such as rheumatism and lumbago. In the 1960s, smokebush was collected and screened for scientific purposes by the US National Cancer Institute (NCI), under license from the West Australian Government. This shrub was unsuccessfully tested for cancer resistant properties by NCI in early 1980s and was stored for several years. In the late 1980s testing was resumed, but this time for anti-HIV activity.

In 1993, Boyd and co-workers at NCI discovered that remarkable *in-vitro* anti-HIV activity is exhibited by the organic extract obtained from the shrub *conospermum-incurvum.*[16,56] Bioassay-guided fractionation and purification led to the isolation of conocurvone **36** as the active agent (Figure 4.2). Biological tests showed that conocurvone **36** completely averted the death of HIV 1 – infected human lymphoblastoid cells (CEM – SS) at a concentration of EC $\leq$ 0.02 μM. Conocurvone has an unusually high therapeutic index of 2500.

Figure 4.2 Conocurvone 36, its analogue 194 and teretifolione B 195

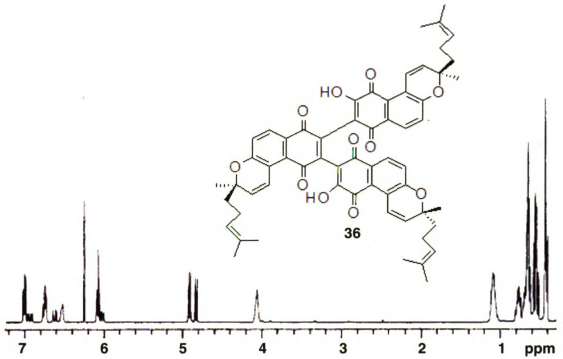


Conocurvone **36** is a novel trimeric naphthoquinone and a deoxy-trimer of teretifolion B **195**, a previously known compound that was first isolated from *conospermum teretifolium.* Conocurvone consists of two teretifolion B subunits joined at their C - 3 positions to the C - 2 and the C - 3 position of a 2-deoxyteretifolione B subunit. Conocurvone **36** was obtained in a yield of 22 mg per kg plant material.

The proton NMR of conocurvone **36** is very complex as it possesses some satellite peaks which show integrations of less than one proton (Figure 4.3). It was first speculated to be the impurities eluted along with conocurvone during the isolation from the organic extract of *conospermum incurvum.* However, the variation of the ratio of satellite peaks in proton NMR under different temperatures and solvents indicated that rotamers and tautomers of

conocurvone **36** were in equilibrium with each other on the NMR time scale and were responsible for these satellite peaks. The unambiguous characterization of conocurvone **36** was achieved by its synthesis from teretifolion B (Section 4.2), which showed a proton NMR spectrum identical to the natural product isolated from *conospermum incurvum*.

Figure 4.3 Proton NMR of conocurvone 36



Structure-activity relationship studies have revealed that conocurvone **36** and its derivative **194** show identical anti-HIV activity. However, the monomer teretifolione B **195** and its dimer does not show any HIV resistance. The mechanism of its action is not known, and it is surmised that its inhibitory action occurs in the late phase of the viral replication cycle, since a time course study showed that conocurvone **36**, if added 48 h post infection, could still protect T-cells from the cytopathogenic effect of HIV-1. The possibility has been

recognized that conocurvone **36** can assume a helical conformation that winds into the groove of the DNA strand. Additional interactions may be expected between the quinonoid hydroxyl groups and peptides, like those that play a role in coloring hair and skin with henna. It will be interesting to see if any of these hypotheses is confirmed. Furthermore, it will not only be interesting but very important to answer the following questions: will conocurvone **36** be the prototype of new class of anti-HIV active compounds and what role does the trimeric quinone carbon framework plays in the biological activity?

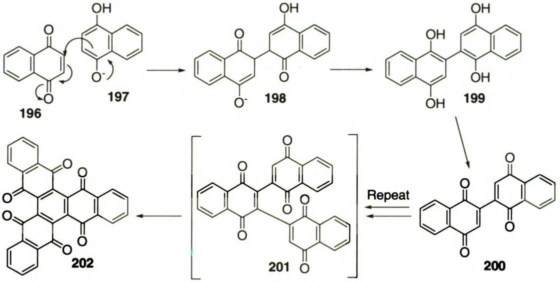
4.2 Oxidative oligomerization of monomeric quinone to synthesize cyclic tris-quinones similar to conocurvone 36

Oxidative oligomerization of quinones is a well-known phenomenon.[56] Direct oxidative dimerization of monomeric quinones like **196** requires harsh reaction conditions and needs a hydroxyl or amino group on the quinonoid double bond. However, it is also known that monomeric 1,4-quinones can be oligomerized much more easily under acidic or basic conditions.[57] Naphthoquinone, 1,4-anthraquinone, and numerous derivatives can be smoothly converted into dimers and cyclo-trimers (which are an important structural class of natural products) by heating in pyridine/ethanol, or by warming in acetic acid.[58]

It has been speculated that this process is autocatalytic in which traces of hydroquinone **197**, which are always present, does a Michael addition to the excess of quinone **196** to form a biaryltetrol **199** (Scheme 4.1).[59] Dehydrogenation of this intermediate by the monomeric quinone **196** yields the

biaryldiquinone **200** and further reaction with hydroquinone **197** occurs until all the monomeric quinone was transformed. The dimer **200** could then react further to yield trimer **201**. It was not possible to isolate the trimer **201** since it was easily converted into the trimeric cyclic quionone **202**. So the stability of conocurvone **36** is apparently due to the presence of hydroxyl groups at position 2 of the two terminal quinones which prevent cyclization.

Scheme 4.1 Autocatalytic oligomerization of quinones



4.3 Previous semisynthesis and synthetic approaches toward conocurvone 36

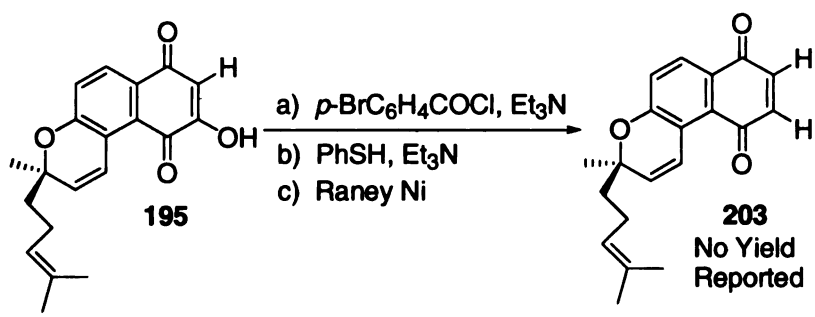
Boyd and co-workers at NCI unambiguously assigned the structure of conocurvone **36** by its semisynthesis.[16] In addition to this work two other groups, Liebeskind's group[60] from Emory University and Stagliano's group[61] from the University of Illinois at Chicago have developed two different approaches for

synthesizing the trimeric core of conocurvone **36**. However, no successful total synthesis of conocurvone **36** has been reported yet. All the three of these synthetic efforts are mentioned briefly in this section.

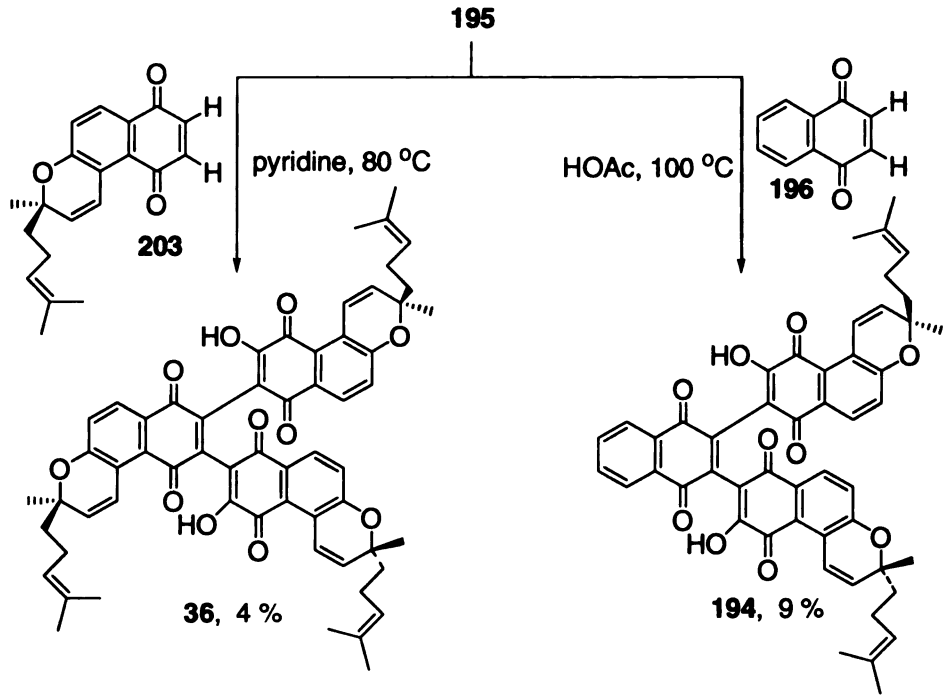
4.3.1 Boyd and co-workers

Boyd and co-workers have used the autocatalytic oxidation of quinones approach to synthesize conocurvone **36** from teretifolione B **195**.[16] The naturally occurring teretifolione B **195** was first deoxygenated to give **203** (Scheme 4.2). Compound **203** was then warmed with two equivalents of **195** in pyridine to afford conocurvone **36** in 4 % yield. Similarly, the analogue **194** was obtained in 9 % yield upon warming teretifoline B **195** with naphthoquinone **196** in glacial acetic acid.

Scheme 4.2 Boyd's semisynthesis of conocurvone 36



Scheme 4.2 Boyd's semisynthesis of conocurvone 36 continued



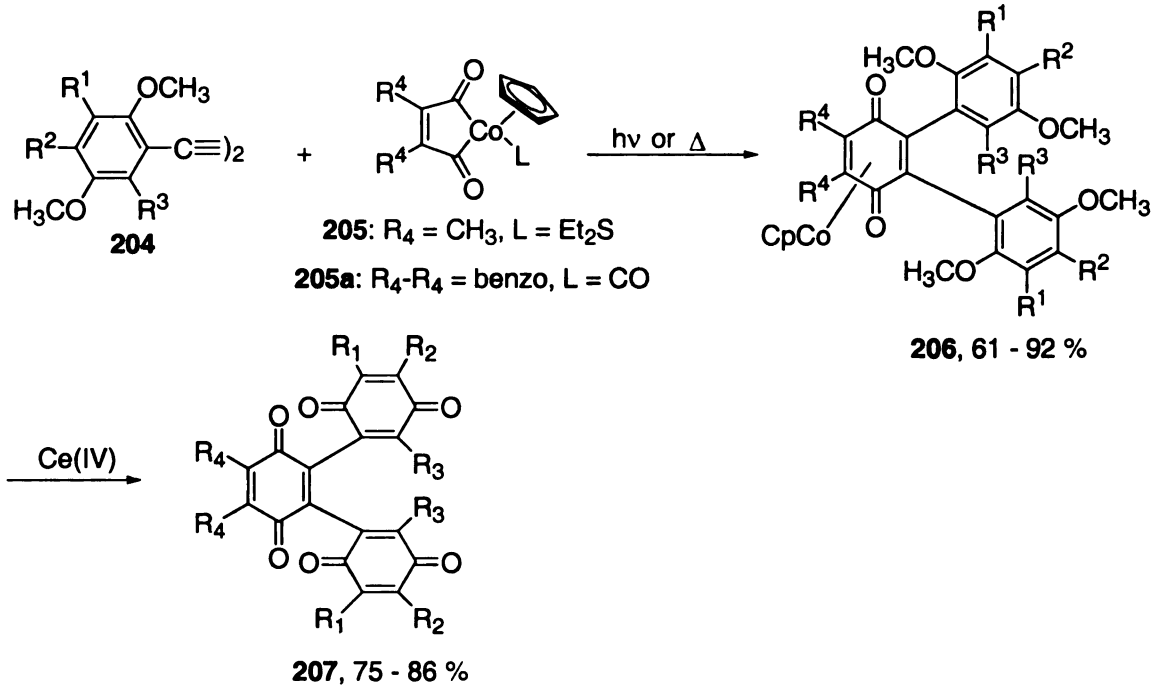
4.3.2 Liebeskind approach

Liebeskind's group has utilized thermal and photochemical induced reactions of cobalt complexes **205** and **205a** with biaryl acetylenes of the type **204** to obtain the quinone complex **206**, which could be converted to the corresponding tris-benzoquinones **207** upon CAN oxidation (Scheme 4.3).[60] The isolated tris-benzoquinones are yellow solids and are soluble in organic solvents such as CH_2Cl_2, THF and EtOAc. The tris-benzoquinones **207** are not as unstable as the corresponding tris-naphthoquinone described by Brockmann.[59] Upon exposure to air and light the solids quickly darken but without substantial decomposition. Two of the limitations of this approach are: a) the sterically hindered biaryl acetylenes of the type **204** are difficult to obtain using the Stille coupling reaction of bis(tri-*n*-butylstannyl)acetylene and the sterically hindered

iodoarenes the Stille cross-coupling reaction is known to be sensitive to sterics.[62]

b) The reaction of the cobalt complexes with diarylacetylenes fail to give any product with the alkynes of the type **204** where $R^3 \neq H$.

Scheme 4.3 Liebeskind's approach to conocurvone 36

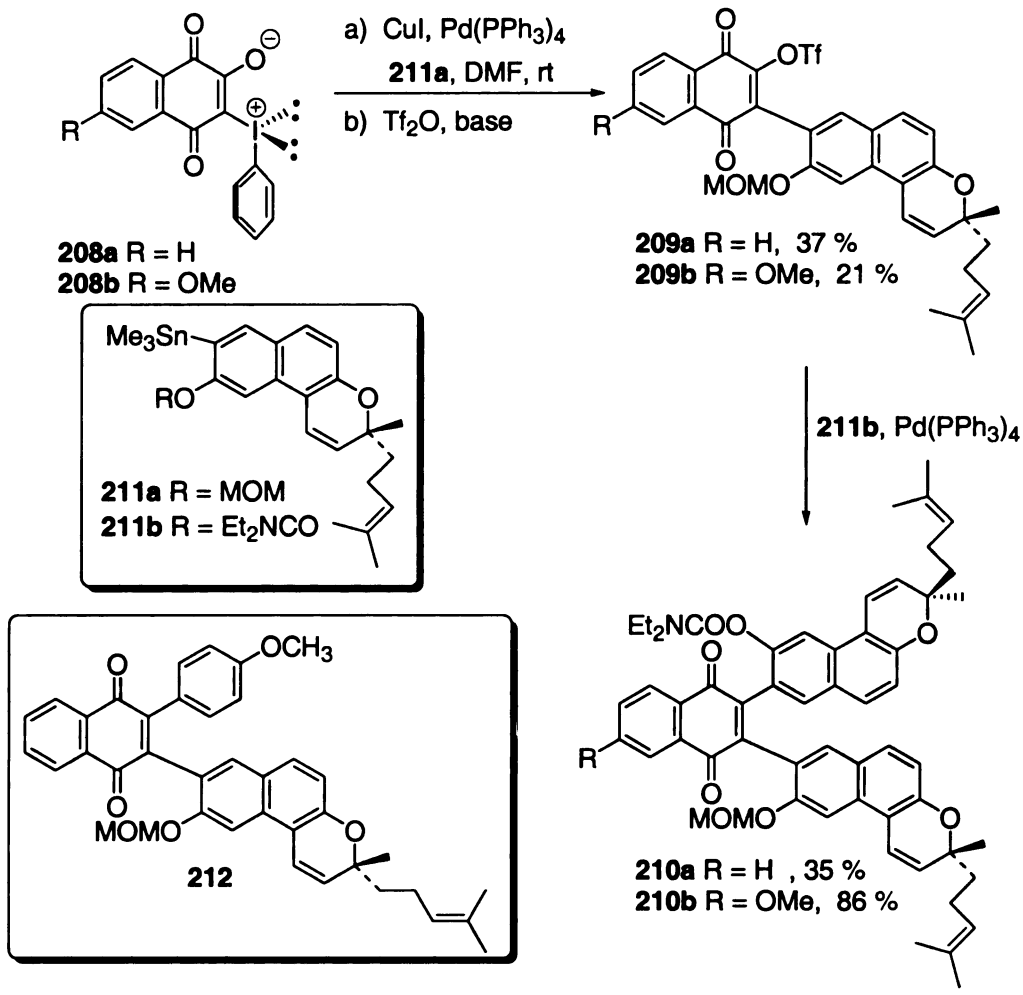


4.3.3 Stagliano's approach

The Stagliano group has used two different approaches to synthesize the trimeric framework of the conocurvone **36**.[61] The first approach involves the use of the doubly activated zwitterionic quinones **208**[63] for the regiocontrolled synthesis of the conocurvone core.[61a,b] The double activation of the quinone results from the presence of the reactive hypervalent iodide and unreactive masked triflate in the form of an alkoxide.

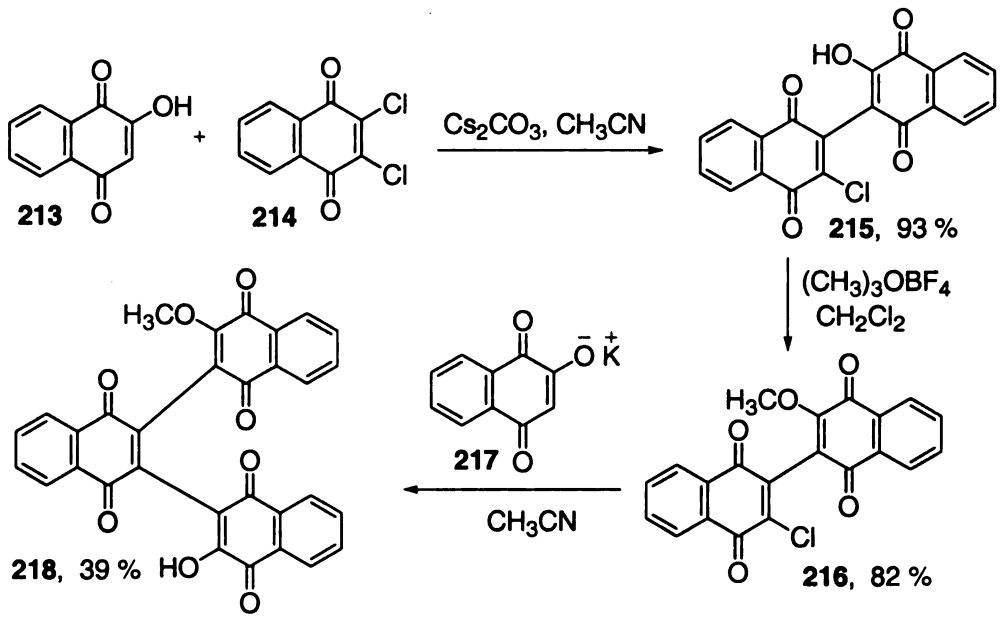
The palladium catalyzed coupling of quinone **208a** and **208b** with naphthopyranyl stannane **211a** and activation of the resulting phenol as a triflate provided the biaryl compounds **209a** and **209b** in moderate yields (Scheme 4.4).[61a,b] Triflate **209a** underwent palladium catalyzed coupling with **211b** to afford only a 35 % yield of the tris-aromatic compound **210a** along with other side products. Extensive studies, performed to increase the yield of **210a**, concluded that the sterically hindered *ortho*- substituted stannane **211** plays a role in the formation of the side products. An unhindered p-anisylstannane underwent coupling with **209a** to give a higher yield of the tris-arene **212** (53 %). On the other hand, the dimer **209b** gave excellent yields of **210b** (86 %) upon coupling with **211b**.

Scheme 4.4 Stagliano's use of doubly activated zwitterionic quinones



In Stagliano's second approach, 2,3-dihaloquinones of the type **214** were subjected to stepwise halogen exchange by hydroxyquinone **213** and **217** to furnish tris-benzoquinones having the conocurvone framework (Scheme 4.5).[61c] One of the examples of tris-benzoquinone synthesis using this approach is described here. The reaction of lawsone **213** with the commercially available 2,3-dichloronaphthoquionone **214** and Cs_2CO_3 in acetonitrile yielded **215** in 93 % yield. The free hydroxyl group in **215** was methylated to form dimer **216**. Dimer **216** was then reacted with potassium salt **217** to provide the brilliant red colored trimeric quinone monomethyl ether **218** in 39 % yield.

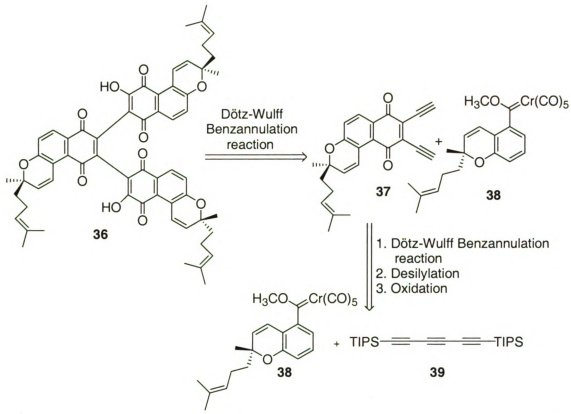
Scheme 4.5 Stagliano's synthesis of trimeric quinones using 2,3-dihaloquinones



4.3.4 Previous synthetic efforts in the Wulff laboratory

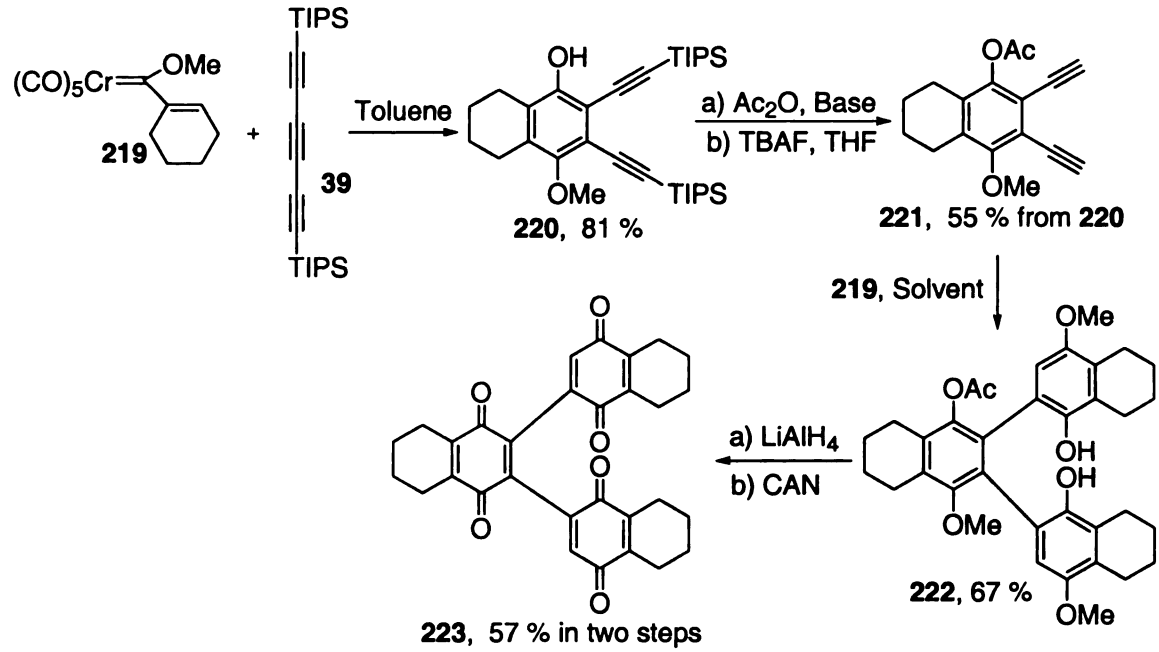
The retrosynthetic analysis developed by the Wulff group for the synthesis of conocurvone **36** is outlined in Scheme 4.6. The key step of this strategy involves the reaction of a chromium carbene complex **38** with conjugated triyne **39**. The reaction of one equivalent of chromene carbene complex **38** with hexatriyne **39** followed by oxidation and desilylation is anticipated to give diyne **37**. Further reaction of **37** with two equivalent of chromene carbene complex **38** is expected to furnish the conocurvone core. This project was initiated by graduate student Xiao-Wu Jiang and the results of her studies can be found in her thesis and is summarized below.[64]

Scheme 4.6 Retrosynthetic analysis of conocurvone 36



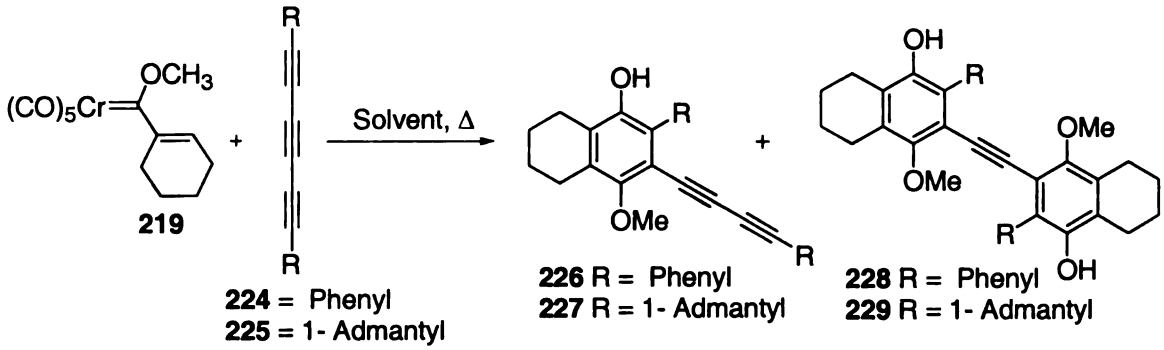
Jiang was able to successfully implement this strategy in the synthesis of tris-quinone **223** which utilizes cyclohexenyl chromium complex **219** and the silyl substituted hexatriyne **39** (Scheme 4.7). The reaction of complex **219** and TIPS triyne **39** gave the mono-benzannulated product **220** in 81 % yield. After acetylation of **220** and desilylation, the *ortho*-aryl diyne **221** so obtained was reacted with two more equivalent of carbene complex **219** to give **222**. Finally, compound **222** was converted to tris-quinone **223** (57 % from **222**) by reductive cleavage of acetyl groups using $LiAlH_4$ and exhaustive oxidation using CAN.[64]

Scheme 4.7 Benzannulation approach to tris-quinone 223



Jiang also explored the benzannulation reaction of the aryl- and alkyl-substituted triynes **224** and **225** with complex **219** (Scheme 4.8). The reaction of the cyclohexenyl complex **219** with 1,6-diphenylhexatriyne **224** gave a mixture of the products **226** and **228** (entry 1), both of which resulted from the reaction of the carbene complex at the end alkyne of the triyne. The reaction could be driven to give only the double-benzannulation product **228** with 5 equiv of carbene complex (entry 2). The selective formation of **226** could be accomplished if 5 equiv of triyne was used (entry 3). The use of the larger adamantyl groups on the triyne **225** did not result in the formation of any detectable amount at the product resulting from reaction of the central alkyne unit (entry 4).[64]

Scheme 4.8 Benzannulation reactions of cyclohexenyl carbene complex 219 with conjugated triynes 224 and 225



Entry	219 : Triyne	Triyne	Compound (% Yield)	Compound (% Yield)
1.	1:1	**224**	**226** (32)	**228** (6)
2.[a]	5:1	**224**	-	**228** (69)
3.[a]	1:5	**224**	**226** (43)	-
4.	1:1	**225**	**227** (41)	**229** (23)

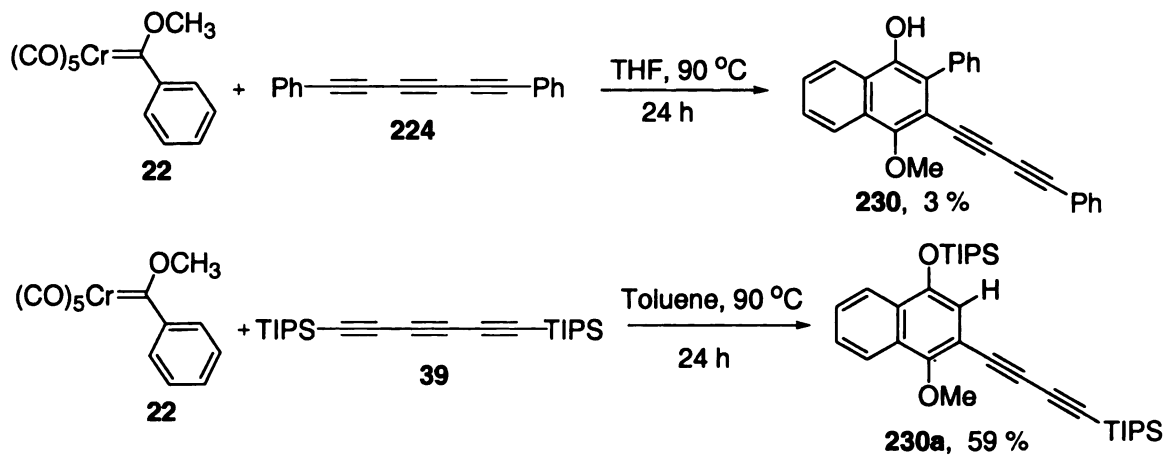
All reactions were carried out in THF (0.05 M) at 55 °C under Ar. a) The concentration of the solution was 0.2 M.

4.4 New studies toward the synthesis of conocurvone from the reaction of carbene complexes with triynes

Attempts to extend these reactions of conjugated triynes to aryl carbene complexes were also carried out by Jiang and the key results from her thesis are shown below. The reaction of complex **22** with the triyne **224** in THF at 90 °C for 24 h gave a complicated mixture of small amounts of products which was difficult to separate and characterize. One of the components was tentatively assigned as the naphthol **230** based on the ^{1}H NMR spectrum of partially purified material (Scheme 4.9). The reaction of the phenyl carbene complex **22** with bis-silyl triyne **39** was also investigated by Jiang. She reported that the reaction gave a 59 %

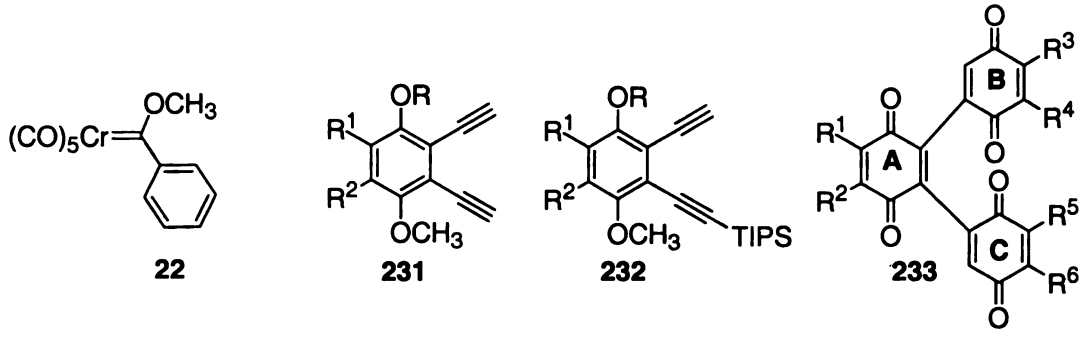
yield of a compound that was tentatively assigned as the naphthalene **230a** (Scheme 4.9). The rest of this chapter describes the extension of the methodology developed by Jiang for the synthesis of tris-quinones that is summarized above.

Scheme 4.9 Reaction of aryl carbene complex 219 with triynes 39 and 224



The aims of the present work are threefold: 1) to more completely define the outcome of the reaction of aryl carbene complexes with triynes **39** and **224**, 2) to examine the reaction of aryl carbene complexes with diynes of the type **231**, and 3) to investigate the reactions of both alkenyl and aryl carbene complexes with the mono-silylated diynes of the type **232** in an attempt to accomplish the regiocontrolled synthesis of tris-quinone framework of conocurvone with three different A, B and C rings **233** (Figure 4.4).

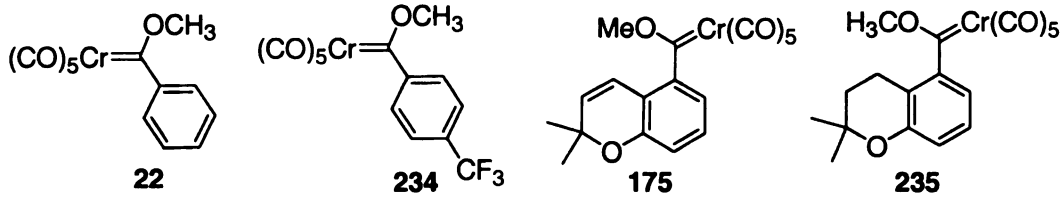
Figure 4.4 Diynes 231, 232 and tris-quinone derivative 233



4.4.1 Reaction of aryl carbene complexes with bis-TIPS triyne 39

This section will describe the reaction of the four aryl carbene complex shown in Figure 4.5 with triynes **39** and **224**.

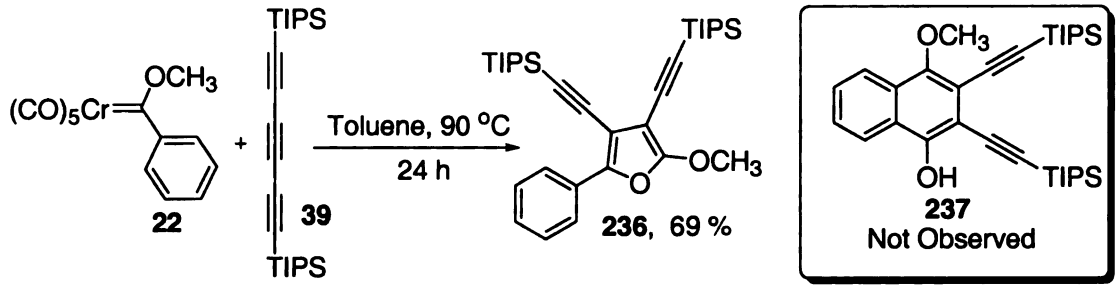
Figure 4.5 Aryl carbene complexes 22, 175, 234 and 235



4.4.1.1 Reaction of the phenyl carbene complex 22 with the bis-TIPS triyne 39

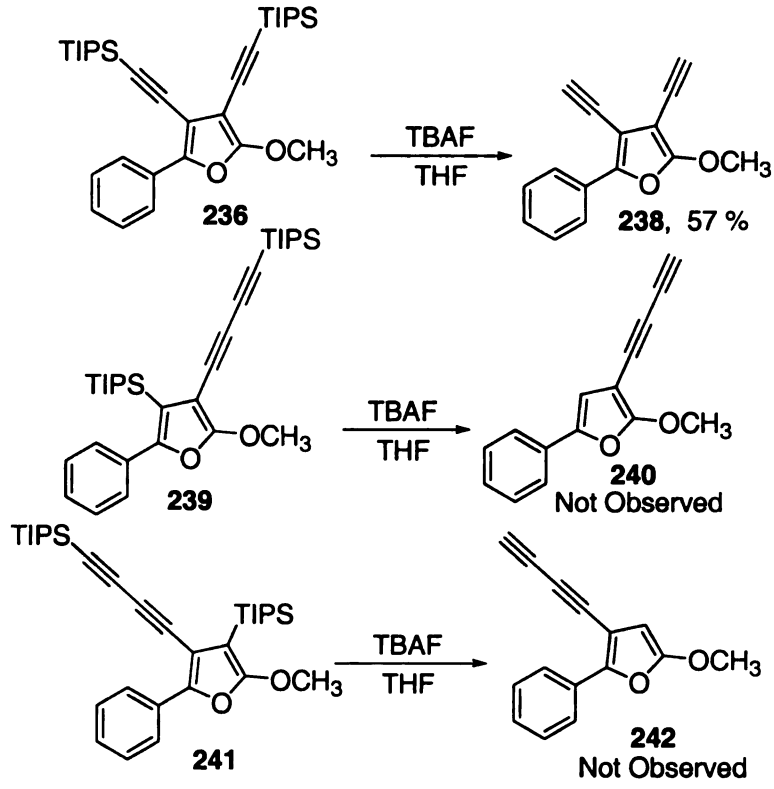
The reaction of the phenyl carbene complex **22** and triyne **39** that was originally carried out by Jiang was repeated since the ^{1}H NMR spectrum did not give a splitting pattern for the aromatic region that would be expected for the proposed naphthalene product **230a** (Scheme 4.9). When the reaction was repeated and all the spectral data collected and carefully analyzed it was concluded that the product from this reaction was the furan **236** (Scheme 4.10).

Scheme 4.10 Reaction of complex 22 with silyl substituted triyne 39



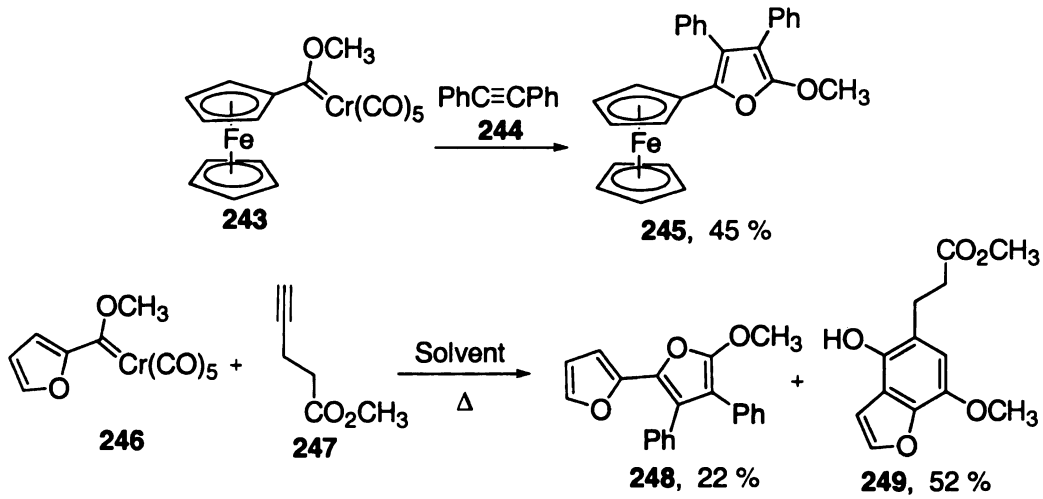
The chemoselectivity of the furan product **236** was unambiguously determined by the desilylation of furan **236** which yielded compound **238** showing two acetylenic protons in ^{1}H NMR (Scheme 4.11). This demonstrates that the reaction occurred on the central alkyne of **39**. Cleavage of the silyl groups in the other two possible isomers **239** and **241** resulting from the reaction of an end alkyne in **39**, would give products **240** and **242** with only one acetylene hydrogen.

Scheme 4.11 Desilylation of phenyl furan 236



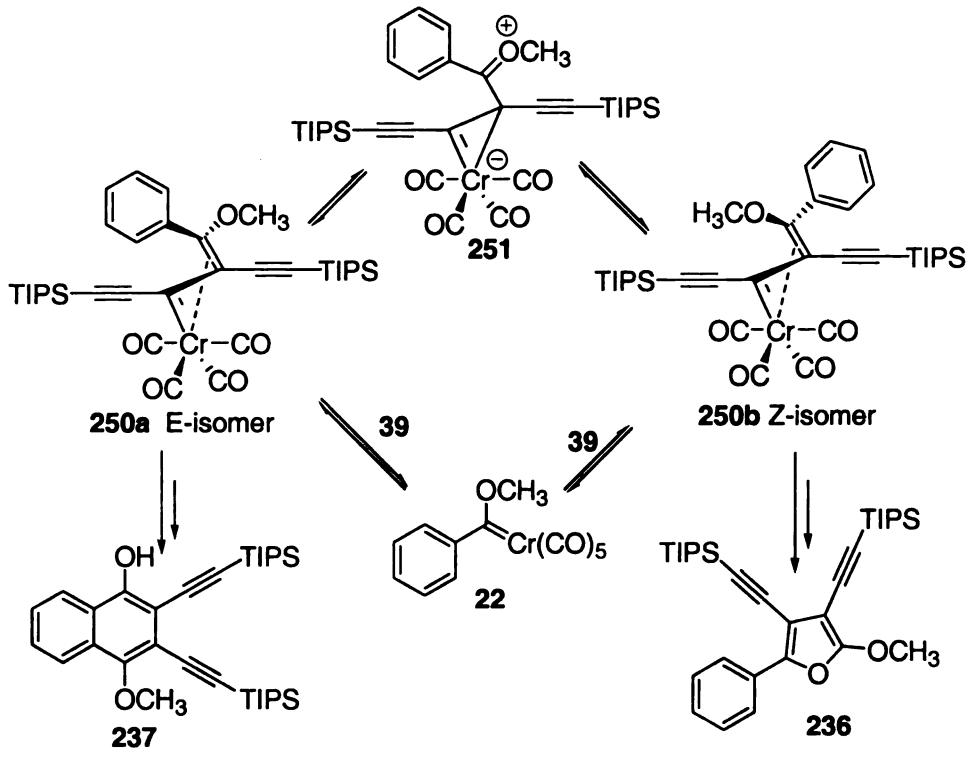
Furan products of this type have been observed before in the reaction of chromium Fischer carbene complex with alkynes, but usually only as a minor products.[6,65] An example where this is not the case is the reaction of the ferrocenyl Fischer carbene complex **243** with di-phenyl acetylene **244**, which exclusively gives the ferrocenyl furan complex **245** (Scheme 4.12).[65a] In another example, the reaction of furanyl complex **246** with methyl-4-pentynoate **247** gives a mixture of furanyl furan **248** and benzofuran **249** (Scheme 4.12).[65b]

Scheme 4.12 Aryl furan formation.



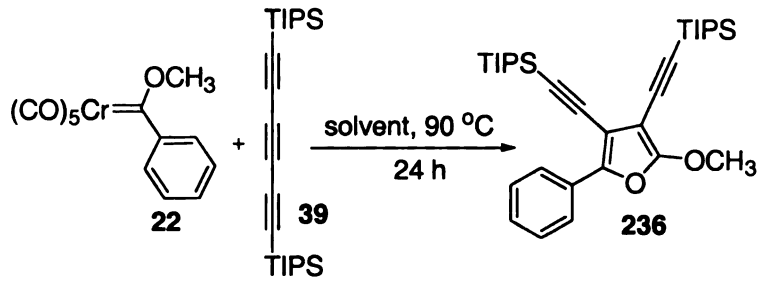
In effort to shift the outcome of the reaction of the phenyl carbene complex **22** and triyne **39** from the furan product **236** to the phenol product **237**, this reaction was examined in various solvents. It can be anticipated that solvents could influence the outcome of the reaction. The reaction of carbene complex **22** with triyne **39** could produce either the Z-vinyl carbene complexed intermediate **250b** or the E-vinyl carbene complexed intermediate **250a** or a mixture of both (Scheme 4.13). The phenol product **237** can only come from the E-isomer **250a** and previous studies indicate that the furan product **236** is formed from the Z-isomer **248b**.[65]

Scheme 4.13 Proposed pathway for the formation of 236 and 237



It can be anticipated that E and Z-vinyl carbene complexes **250a** and **250b** could be isomerized via the zwitterion **251**. Thus if the formation of **250b** is kinetically favored in toluene as solvent, then the switch to a more polar solvent may lead to the isomerization of **250b** to **250a** and an increase in the amount of **237** formed from the reaction. However, the data in Scheme 4.14 reveals that the yields of **236** are similar in a non-coordinating, non-polar solvent like toluene (69 %) and in a non-coordinating polar solvent such as dichloromethane (65 %) (Scheme 4.14). For the coordinating polar solvent THF, the yield decreased to 51 % and a complex mixture was observed for the highly coordinating acetonitrile solvent.

Scheme 4.14 Solvent study of reaction of complex 22 with triyne 39

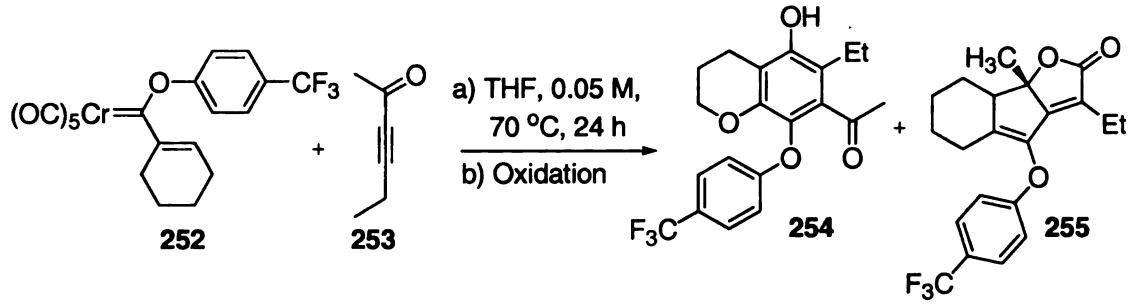


Entry	Solvent	**236**, Yield (%)
1	Toluene	69
2	Benzene	67
3	CH_2Cl_2	65
4	THF	51
5	CH_3CN	Mixture of compounds

Unless otherwise specified the reactions were carried out in 0.05 M solvent using 1 : 1 equivalent of complex **22** and triyne **39**

These results are consistent with the studies done by Waters and Wulff on the reaction of phenoxydihydropyranyl chromium carbene complex **252** with 3-hexyn-2-one **253** (Scheme 4.15).[66] Two different products **254** and **255** are obtained in this reaction via the intermediates (*E*)-**259a** and (*Z*)-**259b**, respectively (Scheme 4.17). The ratio of these two products did not show any significant dependence on the solvent used for the reaction.

Scheme 4.15 Waters and Wulff study on reaction of complex 252 with 3-hexyn-2-one 253

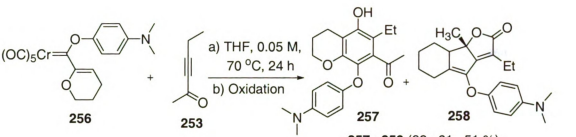


252 253 254 255

Entry	Solvent	**254 / 255**	Yield (%)
1	C_6H_6	74/26	67
2	CH_2Cl_2	72/28	51
3	THF	71/29	56
4	CH_3CN	68/32	37

However, the ratio of phenol **254** to lactone **255** could be controlled by changing the electron-deficient aryl group in complex **252** with an electron-rich substituent. Complex **256**, containing an electron-rich aryl group, upon reaction with 3-hexyn-2-one **253** in THF solvent gave 51 % yield of products **257** and **258** in a ratio of 39 : 61 (Scheme 4.16).

Scheme 4.16 Waters and Wulff study on reaction of complex 256 with 3-hexyn-2-one 253

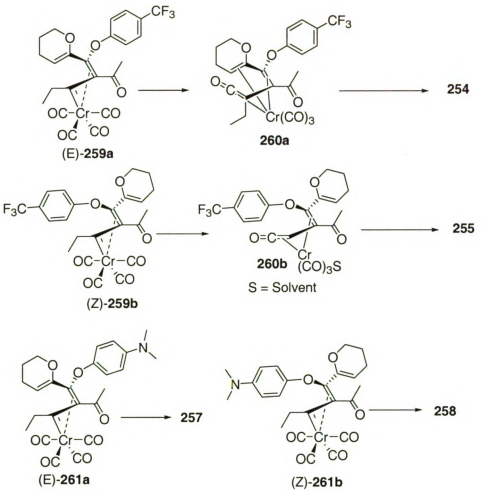


256 **253** **257** **258**

257 : **258** (39 : 61, 51 %)

The differences in the product distribution between the electron-poor complex **252** and the electron-rich complex **256** have been explained by Waters and Wulff according to the reaction intermediates shown in Scheme 4.17. First it is clear that in these reactions the phenol product **254** (or **257**) must come from the E-vinyl carbene complexed intermediate **259a** (or **261a**) and that the lactone product **255** (or **258**) must come from the Z-vinyl carbene complexed intermediate **259b** (or **261b**). The working hypothesis is that an increase in the electron-donating ability of the oxygen substituent leads to an increased preference for the Z-vinyl carbene complex intermediate which has the oxygen substituent trans to the ketone. Hence, in accord with observation, the amino substituted complex **256** would be expected to give a greater proportion of the lactone product than the CF_3 substituted **252**.

Scheme 4.17 Proposed intermediates for phenol and lactone formation

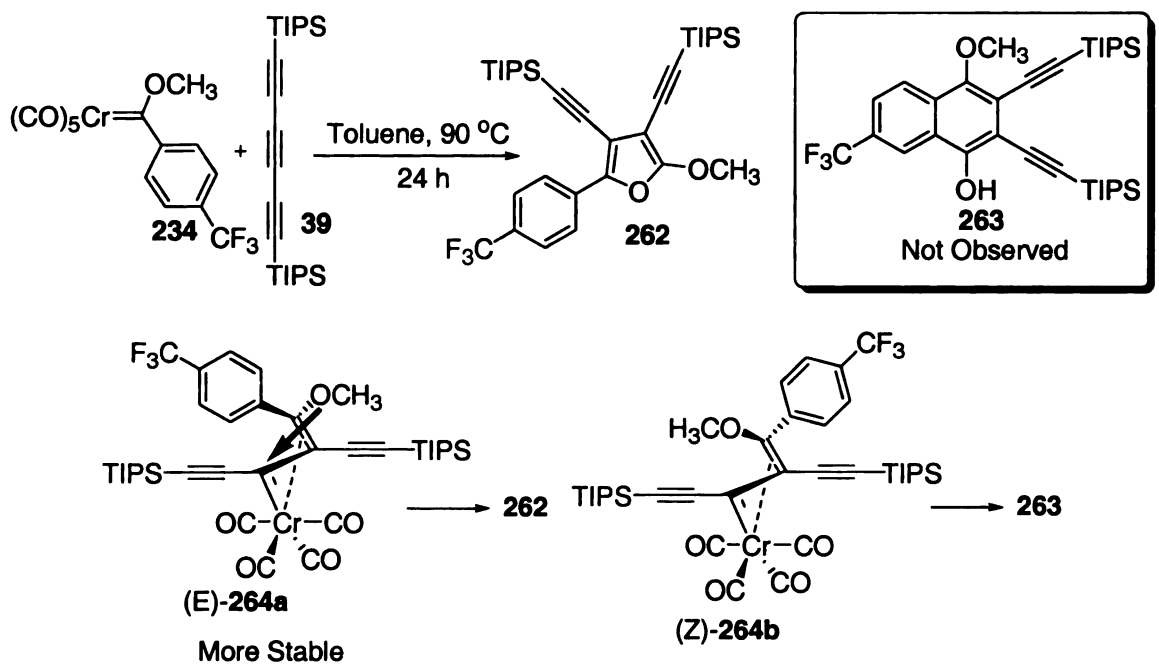


Waters and Wulff also concluded from their studies that in the absence of ketone group on the vinyl carbene compelxed intermediate (**259** or **261**, Scheme 4.17), there is then a tendency for an increased electron-donating ability of a substituent to have an increased preference for that substituent to be anti to the carbene carbon (C-1) of the vinyl carbene complexed intermediate.

Given unexpected and undesired formation of the furan **236** from the reaction of the phenyl carbene complex **22** with triyne **39**, it was thus considered

possible that this reaction could be shifted in favor of the desired phenol product **237** by proper control of the electronics (Scheme 4.10). For example, since the reaction of the phenyl carbene complex **22** with triyne **39** preferentially proceeds only through the Z-vinyl carbene complex **250b** (Scheme 4.13), it might be expected that the reaction of the para-CF_3 substituted phenyl carbene complex **234** (Scheme 4.18) might be shifted towards the E-vinyl carbene complex **264a** and lead to at least the formation of some phenol product **263**. However, as the experiment in Scheme 4.18 shows, this reaction only gave the furan product **262** in 65 % yield.

Scheme 4.18 Reaction of electron deficient complex 234 with triyne 39

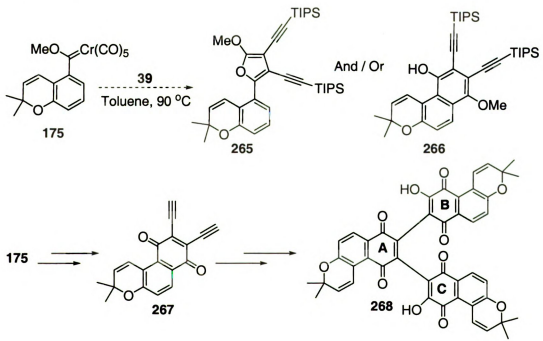


Thus the reaction with triynes must be subject to subtle differences not present in the reactions of simple alkynes.

4.4.1.2 Reaction of chromene carbene complex 175 and chromane complex 235 with bis-TIPS triyne 39

As a continuation of the effort to develop methodology for the synthesis of conocurvone and its analogs, the reaction of chromene carbene complex **175** with triyne **39** was investigated. Based on the reactivity of phenyl carbene complex **22** with this triyne (Scheme 4.10), it was anticipated the reaction of chromene carbene complex **175** with triyne **39** would preferably give furan **265** rather than 3H-naphtho[f]pyran **266** (Scheme 4.19). Nonetheless, the possibility that this complex could provide a direct access to an intermediate **267**, the key to a synthesis of conocurvone, was enough to stimulate the examination of the reaction.

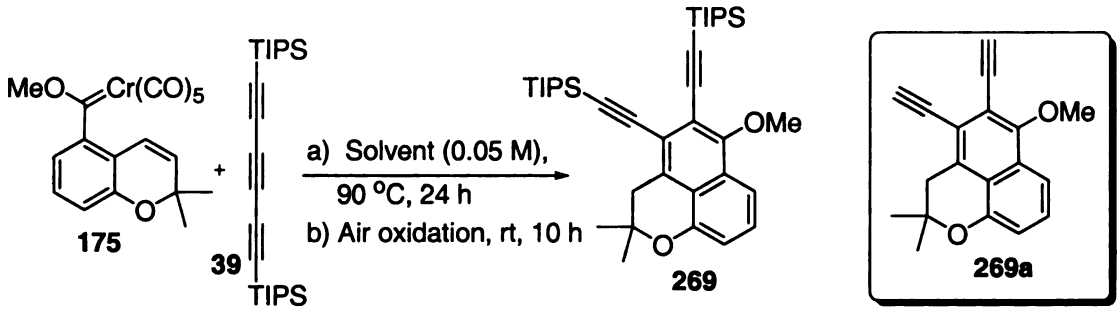
Scheme 4.19 Possible products on reaction of complex 175 with triyne 39



Surprisingly, the reaction of chromene carbene complex **175** and triyne **39** gave neither the furan **265** nor the phenol **266**. Instead, the reaction gave the unexpected product **269** that results from alkyne addition and thus an addition to the double bond present in carbene complex **175**. Given the instability of naphthopyran phenols **266** (Chapter 3) the benzannulation reaction of chromene carbene complex **175** with triyne **39** was initially done in the presence of additives TMSCl and DIPEA.[54] Upon heating a mixture of chromene carbene complex **175** and triyne **39** for 24 h at 50 °C in benzene, the TLC showed only starting material with a very faint spot corresponding to a product. The same reaction upon heating at 90 °C for 24 h yielded a non-TMS containing product (entry 1, Scheme 4.20). Similarly, when the TMSCl additive was replaced by MOMCl, the same product was isolated with no evidence of MOM incorporation (entry 2). Since these protecting groups were not incorporated the reaction was performed between chromene carbene complex **175** and triyne **39** in the absence of any additive which as expected afforded the same product in 80 % yield. The structure of this product has been assigned as **269** on the basis of its spectral data (Scheme 4.20). The chemoselectivity of the olefin-addition product **269** was unambiguously determined by the desilylation of **269** which yielded compound **269a** showing two acetylenic protons in ^{1}H NMR (Scheme 4.20). There is no precedent for this type of benzannulation reaction in the literature. The mechanistic details proposed for the formation of this product are given in section 4.8.2 along with calculations to support this mechanism.

Solvent studies reveal that the polar non-coordinating solvent dichloromethane gives the best yield for the reaction and that polar solvents with strong coordination abilities such as DMF and CH_3CN generally lead to only trace amount of **269** (Scheme 4.20).

Scheme 4.20 Benzannulation of complex 175 with triyne 39



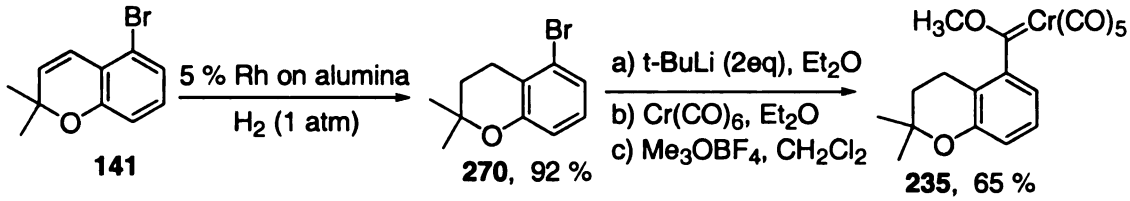
Entry	Solvent	**269** Yield (%)
1	Benzene[a]	74
2	Benzene[b]	71
3	Benzene	80
4	CH_2Cl_2	88
5	THF	75
6	CH_3CN[c]	-
7	DMF[c]	-

Unless otherwise specified the reactions were carried out in 0.05 M solvent using 1 : 1 equivalent of complex **175** and triyne **39** a) additive TMSCl and Hunig's base used, b) additive MOMCl and Hunig's base used. c) a complex mixture was observed which showed traces of **269** by TLC.

The intriguing involvement of the double bond in C1-C2 position of chromene carbene complex **175** in the reaction with the triyne **39** raises the question: what would be the product from the reaction of triyne **39** and chromane complex **235** where this double-bond has been removed? Bromochromane **270** was obtained by the hydrogenation of chromene **141** using 5 % Rh on alumina.[67]

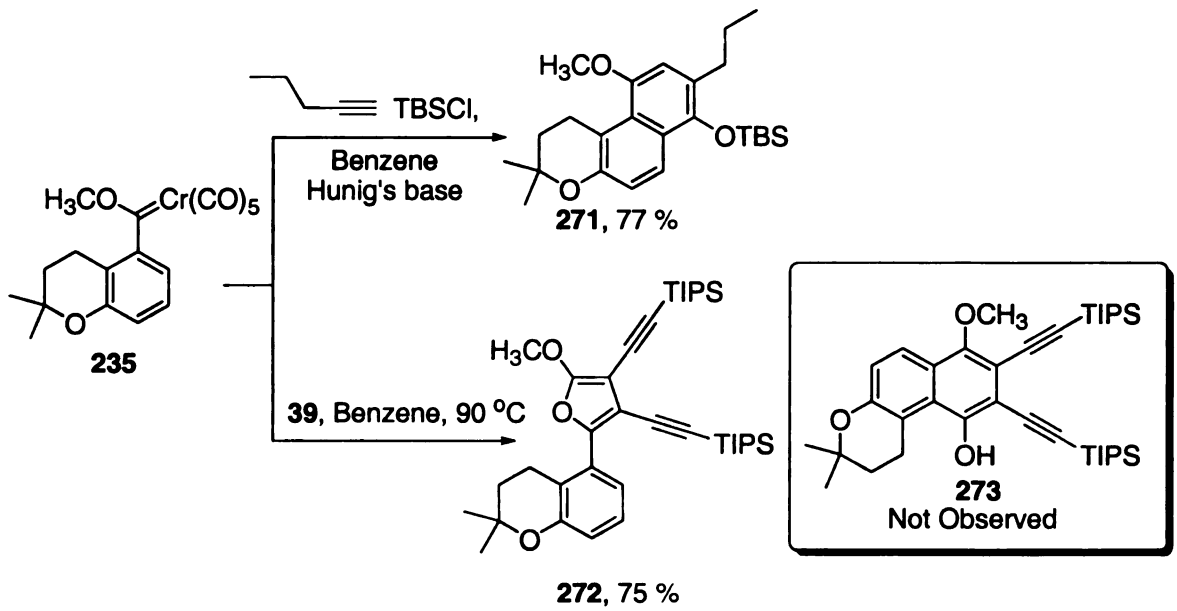
This Rh catalyst is known to selectively perform hydrogenation of double bonds in the presence of aryl halides.[67] Using the standard Fischer protocol, **270** was converted to chromane complex **235** in 65 % yield (Scheme 4.21).

Scheme 4.21 Chromane complex 235 synthesis



As expected, chromane complex **235**, reacted with 1-pentyne in the presence of TBSCl and Hunig's base to give the benzannulation product **271** (Scheme 4.22).[54] The reaction of the chromane complex **235** with the TIPS triyne **39** gave the furan product **272** in 75 % isolated yield.[6,65] Thus, chromane complex **235** displayed the same reactivity towards triyne **39** as the phenyl carbene complex **22** (Scheme 4.10).

Scheme 4.22 Benzannulation of complex 235 with 1-pentyne and triyne 39



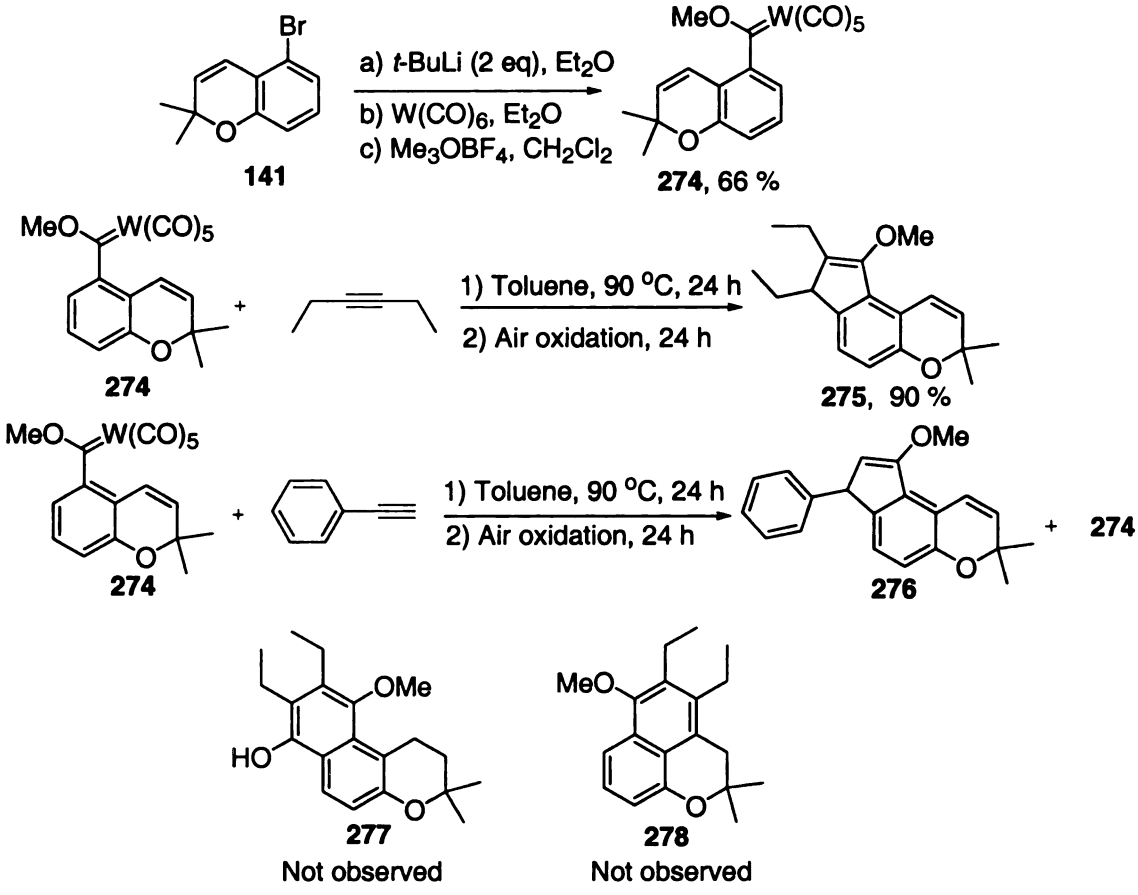
4.4.1.3 Tungsten carbene complex 274: synthesis and reactivity

Intrigued by the high yields of the non-CO inserted olefin-addition product **269** obtained from the reaction of chromene carbene complex **175** with triyne **39**, it was decided to explore the possibility of making this reaction general for simple aliphatic- and aromatic alkynes (Scheme 4.23). In contrast to the reaction of carbene complex **175** with triyne **39** (Scheme 4.20), the reaction of **175** with simple alkynes occur with CO-insertion and cyclization to give the normal benzannulated product (Chapter 3) and no observable amount of the product corresponding to **269** (Scheme 4.20) where the double-bond is involved. However, it may be possible that tungsten complexes would form products of the type **269** with simple alkynes. Tungsten carbene complexes are known to form non-CO inserted 5 membered ring products upon reaction with alkynes.[7] The CO insertion process is slower for tungsten than for chromium, and thus for the tungsten complex **274** reaction with the double-bond does not have to compete with CO insertion. The only question is can the reaction with the double-bond compete with the 5-membered ring formation.

The tungsten carbene complex **274** was made using the standard Fischer protocol from bromochromene **141** as shown in Scheme 4.23. The reaction of the complex **274** with 3-hexyne at 90 °C in toluene solvent gave cyclopentenone **275** in 90 % yield with no trace of the benzannulated product **277** or of product **278** resulting from cyclization to the double bond. A similar result was observed upon heating **274** with phenyl acetylene except that the reaction was slower. After 48 h at 90 °C the reaction mixture showed a mixture of compounds which consisted of

a significant amount of carbene complex **274** and very small amount of cyclized product **276**.

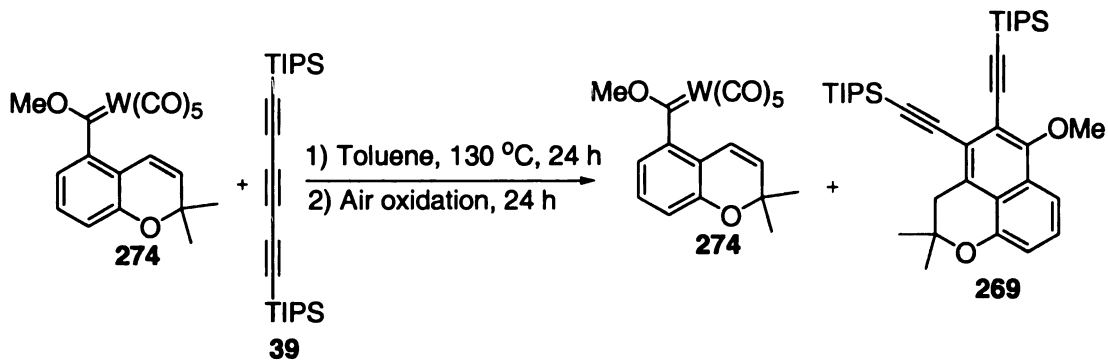
Scheme 4.23 Tungsten carbene complex 274: synthesis and reactivity



The reaction was further performed at 130 °C in which complex **274** (89 mg, 0.169 mmol) was heated with 1 equiv of triyne **39**. The reaction mixture was stirred for 24 h at 130 °C and for 12 h in air at room temperature. The reaction mixture was then filtered through celite, concentrated in vacuuo and the residue was chromatographed using 2 % ethyl acetate in hexane which afforded 85 mg of a mixture of compounds. The column was then flushed using a gradient of 5 % ethyl acetate in hexane to neat ethyl acetate to give 9 mg of a complex mixture which did not showed any aromatic protons in the ^{1}H NMR spectrum nor any

distinct spot in the TLC plate. The 85 mg of complex mixture was again purified using 2.5 % benzene in hexane which afforded three fractions: first fraction and the third fraction which weighed 30 mg and 18 mg, respectively showed very faint peaks at the aromatic region in ^{1}H NMR spectrum. The second fraction (30 mg) consisted of two compounds complex **274** and olefin-addition product **269** in the ratio of 10 : 1. The triyne **39** was consumed during the course of the reaction as revealed by the TLC. The recovery of approximately 30 % of the complex **274** and the total consumption of the triyne **269** indicates the possibility of oligomerization of triyne **269** initiated by the complex **269**. As tungsten complexes are known to induce polymerization of alkynes.[68] Surprisingly, no reaction was observed between triyne **39** and tungsten complex **274** at 90 °C. Upon heating to 160 °C both triyne and complex were consumed but no predominant product was observed on TLC and ^{1}H NMR analysis of the crude reaction mixture (Scheme 4.24).

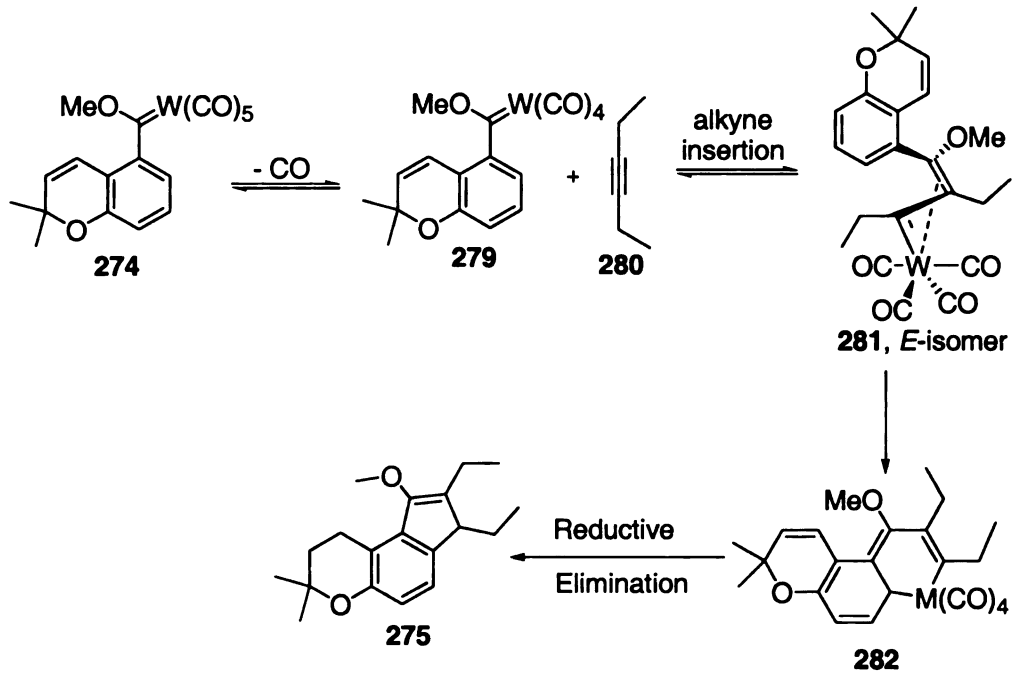
Scheme 4.24 Reaction of complex 274 with triyne 39



The mechanism for the formation of cyclopentenone **275** is shown in Scheme 4.25 and is based on a mechanism that has been proposed for related tungsten complexes.[7] The reaction is initiated by a CO loss from complex **274** to

form tetracarbonyl tungsten complex **279** which is followed by hexyne coordination and insertion to form the vinyl carbene complexed intermediate **281**. This complex **281** then forms cyclopentanone **275** via metallacyclohexadiene **282**.

Scheme 4.25 Mechanism for the formation of cyclopentenone 275.

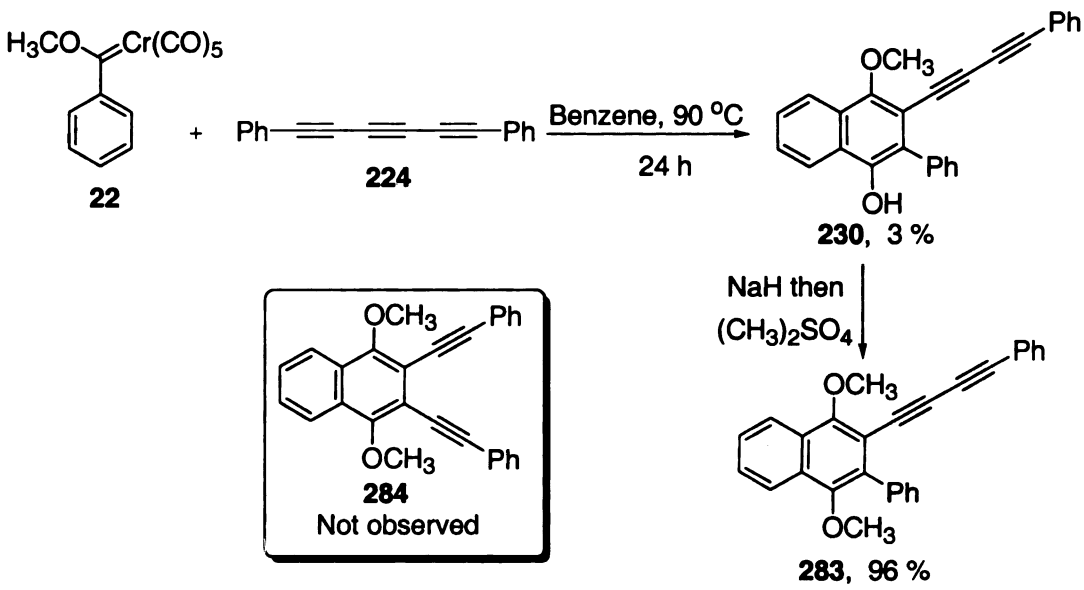


4.4.1.4 Reaction of bis-phenyl triyne 224 with aryl carbene complex 22 and 175

Reaction of cyclohexenyl complex **219** with bis-phenyl-1,3,5-hexatriyne **224** takes place at a terminal alkyne unit to give the product **226** (Scheme 4.8).[64] Thus it was expected that the reaction of phenyl carbene complex **22** with triyne **224** would give mono-benzannulated product. This product was tentatively identified from this reaction by Jiang as **230**, but its structure was not confirmed. This reaction was repeated and found to give several products but none were formed in more than a few percent yield. One of the major products was isolated

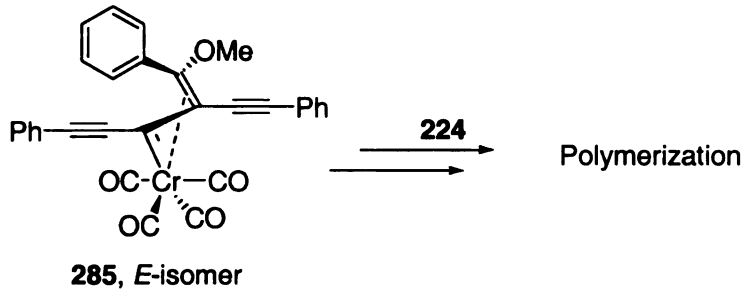
in 3 % yield and identified by its ^{1}H NMR spectrum as the naphthol **230** (Scheme 4.26). The regioselectivity of the reaction was probed by methylation of the hydroquinone **230** which gave an unsymmetrical diyne **283** (Scheme 4.26). A lack of symmetry in the proton NMR spectrum ruled out the regioisomer **284**. Due to the low yields, none of the products from this reaction were completely characterized.

Scheme 4.26 Reaction of complex 22 with triyne 224



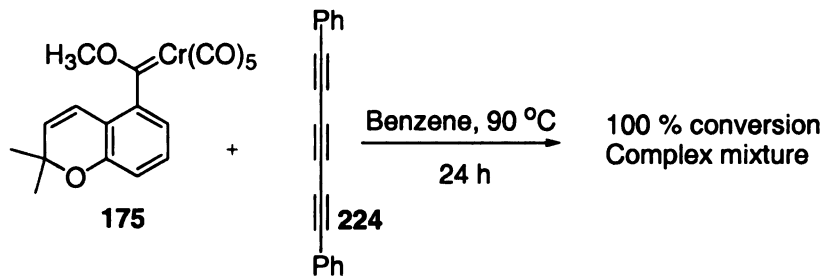
The low yield in this case could be due to multiple alkyne insertion in the vinyl carbene complex **285** by reaction with triyne **224** (Scheme 4.27).

Scheme 4.27 Possible polymerization pathway of complex 285.



A similar outcome was observed for the reaction of chromene carbene complex **175** with triyne **224**. This resulted in a complex mixture of compounds all of which were formed in small amounts. No benzannulation product could be detected in this reaction (Scheme 4.28).

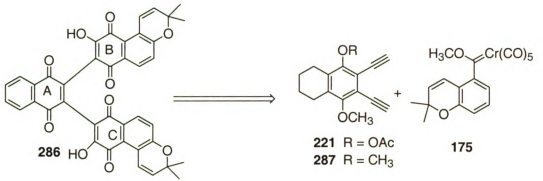
Scheme 4.28 Reaction of complex 175 with 224



4.4.2 Reaction of alkenyl and aryl carbene complexes with diyne

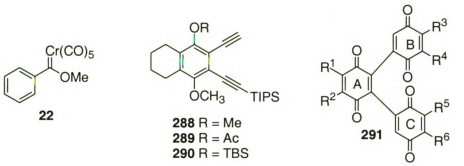
The results of the studies of aryl complexes with triyne **39** reveal that it will not be possible to introduce the A-ring of conocurvone **36** directly as a naphthoquinone. Attention was next focused on whether the B and C fused-rings of the conocurvone analogue **286** could be introduced directly as naphthoquinones by reaction of ortho-aryl diyne **221** with aryl complexes. As shown by Jiang, these complexes can be prepared directly by the reaction of the cyclohexenyl complex **219** with triyne **39** (Scheme 4.7). The reaction of chromene carbene complex **175** with *ortho*-aryl diyne **221** or **287**, after some chemical transformations, should give conocurvone analogue **286** (Scheme 4.29). This would be an important accomplishment based on the fact that anti-HIV activity of conocurvone **36** and its analogue **194** (Figure 4.2) is found to be identical by Boyd and co-workers at NCI.[16]

Scheme 4.29 Retrosynthesis for conocurvone analogue 286



This study will include the reactions of *ortho*-aryl diynes **221** and **287** with the chromene carbene complex **175** and the phenyl carbene complex **22**. In addition, *ortho*-aryl diynes **288**, **289, 290** will also be studied (Figure 4.6). These diynes would provide a facile tool for the synthesis of conocurvone derivatives of the type **291** with three different ring systems A, B and C.

Figure 4.6 Diynes 288, 289, 290 and tris-aryl derivative 291

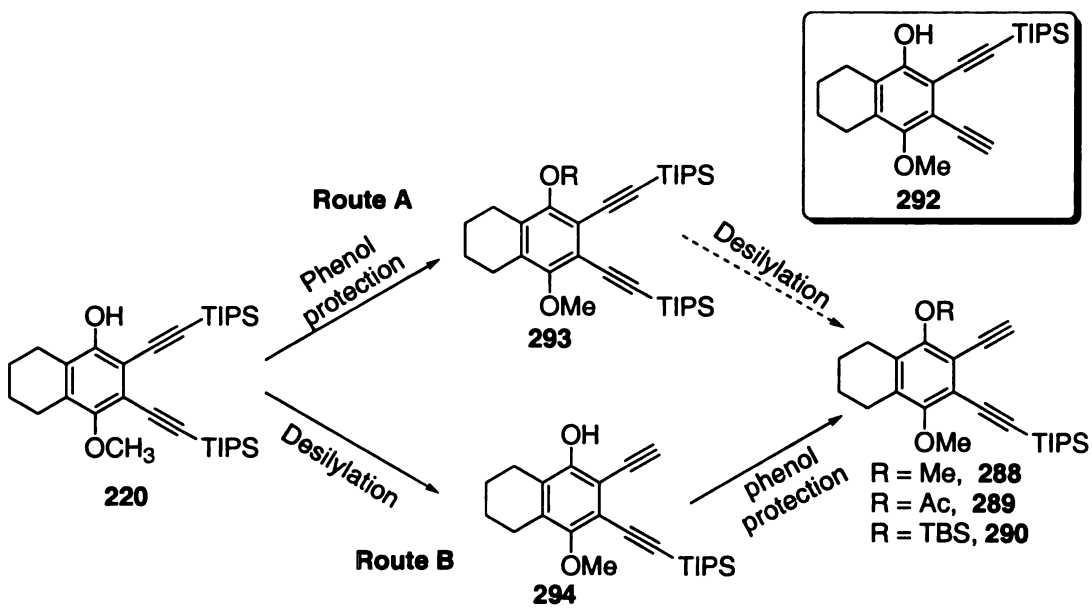


The preparation of *ortho*-aryl diynes **288**, **289**, **290** is discussed in section 4.4.2.1. The reactivity of all five diynes with the phenyl carbene complex **22** and the chromene carbene complex **175** is described in section 4.4.2.2. Finally, section 4.4.2.3 will explore the reaction of *ortho*-aryl diyne **289** with alkenyl complexes.

4.4.2.1 Synthesis of mono-silylated *ortho*-aryl diynes 288, 289, 290

Theoretically, two routes are possible for synthesizing the monosilylated *ortho*-aryl diynes **288**, **289** and **290** (Scheme 4.30). Route A involves phenol **220** protection followed by controlled desilylation of diyne **293**. In the second route, selective desilylation and then the protection of phenol **294** is required. The route that was examined in detail was Route B. After considerable experimentation, it was found that the desilylation of **220** could be made chemoselective.

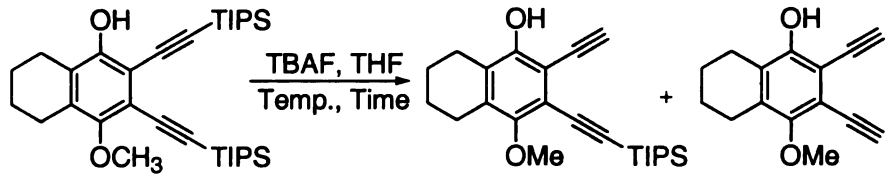
Scheme 4.30 Two possible routes for forming 288-290



Jiang has observed the chemoselective desilylation of **220** but the conditions were not optimized. Further, the structure of the desilylated product was wrongly assigned as **292** (Scheme 4.30), which has now been assigned as **294** based on an X-ray analysis of a derivative (vide infra). The selective desilylation of **220** under different reaction conditions is shown in Scheme 4.31. Reaction of phenol **220** with TBAF in THF solvent at room temperature for 1 h

affords a 21 % yield of monosilylated **294** and 41 % of nonsilylated **295**. Lowering the temperature to 0-10 °C yielded **294** : **295** in the ratio of 53 : 32. Exclusive formation of **294** was observed when the reaction was done either for 10 min at 0 °C or for 1 h at -20 °C in 86 % and 76 % yields, respectively. The chemoselectivity of mono-desilylation of **220** was confirmed by an X-ray structure of **299** (Scheme 4.35) which was derived from **289**.

Scheme 4.31 Chemoselective desilylation of phenol 220



220 **294** **295**

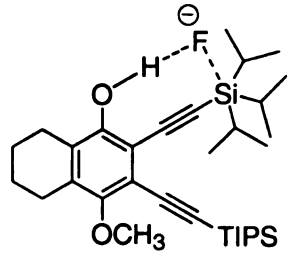
				Yield (%)	
Entry	Temp. (°C)	Conc. (M)	Time (h)	**294**	**295**
1	25	0.03	1	21	41
2	0-10	0.03	1	53	32
3	0-10	0.06	1	55	32
4	0	0.03	10 min	86[a]	-
5	-20	0.03	1	77	-

Unless otherwise specified the reactions were carried out in THF solvent using **220** (1 equiv) and TBAF (3 equiv) at the stated temperature and time.
a) Product was contaminated with small amount of impurities.

One possible explanation for the selective desilylation of the TIPS group in the position ortho to the free hydroxyl group in **220** could be the hydrogen bonding between hydrogen atom of the OH functional group and the fluoride ion as shown in Figure 4.7. The most favorable angle for the formation of hydrogen bonding (i.e., O-H···F angle for transition state **296**) is 180 degrees. Thus, the hydrogen bonding would place fluoride ion in proximity to the TIPS group in ortho

position to the hydroxyl group and hence favor its removal over the TIPS group ortho to the OMe functional group in **289**.

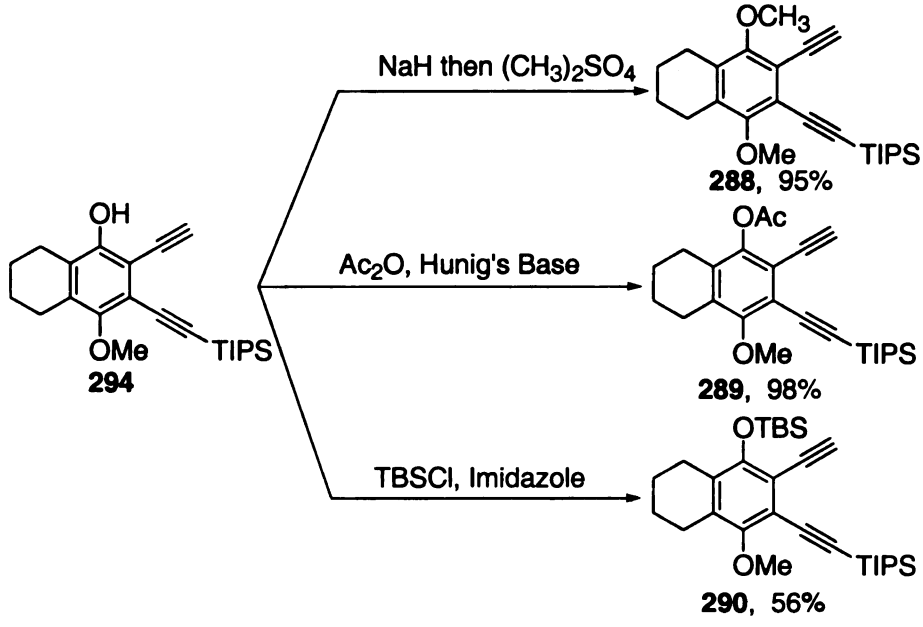
Figure 4.7 Transition state for chemoselective desilylation of 220



296

After selective desilylation, *ortho*-aryl diynes **288**, **289** and **290** could be prepared from **294** by using appropriate silylating, methylating and acetylating agents, respectively, as outlined in Scheme 4.32.

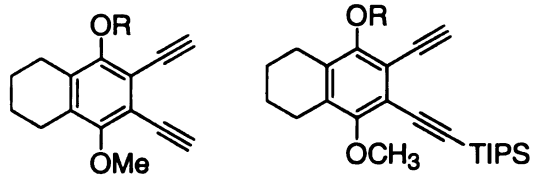
Scheme 4.32 Protection of phenol 294



4.4.2.2 Reaction of aryl carbene complex 22 with *ortho*-aryl diynes 221, 287, 288, 289, 290

The reactions of the phenyl carbene complex **22** with the five *ortho*-aryl diynes **221**, **287**, **288**, **289**, **290** were studied (Figure 4.8). The reactions were examined in toluene, CH_2Cl_2 and acetonitrile to study the effect of non-polar, polar non-coordinating and polar-coordinating solvents.

Figure 4.8 Diynes 221, 287, 288, 289 and 290

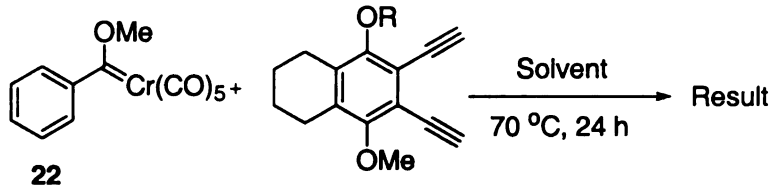


221 R = Ac
287 R = Me

288 R = Me
289 R = Ac
290 R = TBS

The reaction of the phenyl carbene complex **22** with ortho-aryl diynes **221** and **287** resulted in a mixture of compounds which were not easy to purify and identify. Attempts at purification by silica gel chromatography generally lead to the isolation of a mixture of products, which did not show any major products by TLC, GC-MS and ^1H NMR. The phenyl carbene complex **22** was either consumed during the reaction or remained in trace amounts as indicated by a faint spot by TLC. The *ortho*-aryl diynes **221** and **287** could be recovered in 10 % to 15 % yield after chromatography on silica gel (Scheme 4.33).

Scheme 4.33 Reaction of complex 22 with *ortho*-aryl diynes 221 and 287



22

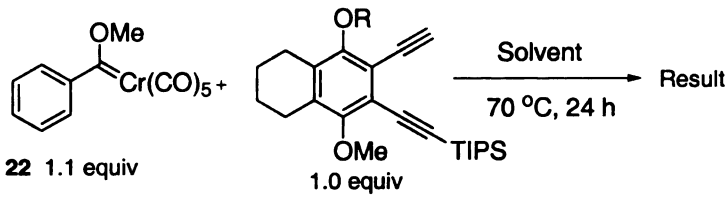
221 R = Ac
287 R = Me

Entry	R	Diyne	Solvent	Diyne recovered (%)
1.	Ac	**221**	Toluene	15
2.	Ac	**221**	CH_3CN	10
3.	Me	**287**	Toluene	12
4.	Me	**287**	CH_3CN	14

Unless otherwise specified reaction was done using diyne (1.0 equiv) and complex **22** (1.0 equiv) in indicated solvent (0.05 M). a) Generally, the TLC plate shows a mixture of very close compounds which were not possible to separate using column chromatography.

A summary of the results obtained from the reactions of the mono-silylated *ortho*-aryl diynes **288**, **289**, **290** and phenyl carbene complex **22** are shown in Scheme 4.34. These reactions resulted in the recovery of significant amount of diynes after silica gel chromatography, up to 64 % yield (entry 4). The corresponding carbene complex was either totally consumed or was only present in trace amounts as indicated by a very faint spot on the TLC plate. The reactions of *ortho*-aryl diynes **288**, **289**, **290** were also carried out with complex **22** in the presence of TMSCl and Hunig's base (entry 2, 7, 12). This should result in the formation of a bis-phenol with both phenol groups protected with TMS which

Scheme 4.34 Reaction of complex 22 with *ortho*-aryl diynes 288, 289, 290



Entry	R	Diyne	Additive	Solvent	Diyne recovery (% Yield)
1	OMe	**288**	-	Toluene	36
2	OMe	**288**	Hunig's base, TMSCl	Toluene	36
3	OMe	**288**	-	CH_2Cl_2	36
4	OMe	**288**	-	CH_3CN	64
5	OMe	**288**	-	Silica	24
6	OAc	**289**	-	Toluene	36
7	OAc	**289**	Hunig's base, TMSCl	Toluene	32
8	OAc	**289**	-	CH_2Cl_2	32
9	OAc	**289**	-	CH_3CN	40
10	OAc	**289**	-	Silica	48
11	OTBS	**290**	-	Toluene	30
12	OTBS	**290**	Hunig's base, TMSCl	Toluene	26
13	OTBS	**290**	-	CH_2Cl_2	26
14	OTBS	**290**	-	CH_3CN	20
15	OTBS	**290**	-	Silica	42

Unless otherwise specified reaction was done using diyne (1.0 equiv) and complex **22** (1.0 equiv) in indicated solvent (0.05 M).

might be more stable to the reaction conditions. However, the proton NMR of crude reaction mixture only showed 3-4 peaks near 0 ppm which were relatively

very small. This further documents that the reactions of phenyl carbene complex **22** with *ortho*-aryl diynes **288**, **289**, **290** are undergoing side reactions faster than the formation of phenol product (Scheme 4.34). Silica supported benzannulation of phenyl carbene complex **22** with the three diynes did not produce different results (entry 5, 10 and 15).[69] Finally, the reaction of the chromene carbene complex **175** with *ortho*-aryl diyne **221** was investigated. At 50 °C, no reaction took place and at 90 °C consumption of both of the starting materials was observed with the clear formation of no predominant silica gel mobile product.

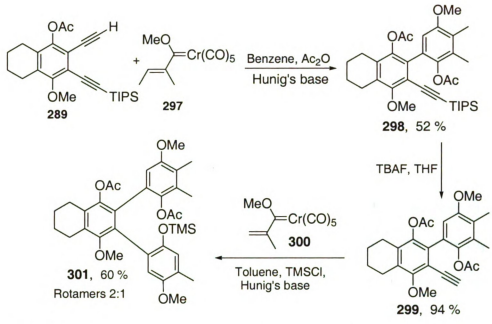
4.4.2.3 Reaction of *ortho*-aryl diyne 289 with alkenyl complexes

The *ortho*-aryl diyne **289** possesses two potential alkyne units where benzannulation can take place. However, sterically encumbered alkynes are known to undergo benzannulation reaction much slower than the sterically unhindered alkynes.[70] Thus, it was anticipated that the non-silylated alkyne in **289** would undergo benzannulation faster than the silylated alkyne in *ortho*-aryl diynes **288** - **290**.

The acetyl protected *ortho*-aryl diyne **289** was chosen to illustrate the ability of this route to provide a synthesis of conocurvone derivatives of the type **291** (Figure 4.6). Heating a mixture of *ortho*-aryl diyne **289**, carbene complex **297**, Ac_2O and Hunig's base in toluene gave compound **298** in 52 % yield after purification by column chromatography (Scheme 4.35). This biaryl compound **298** upon desilylation afforded compound **299** in a 94 % yield. The structure of compound **299** was confirmed by X-ray analysis, which also confirms the chemoselectivity of the mono-desilylation of phenol **220** (Scheme 4.31).

Compound **299** was reacted with 2-propenyl carbene complex **300** in the presence of TMSCl and Hunig's base and afforded two rotamers of compound **301** in a ratio of 2 : 1 in 60 % total yield.

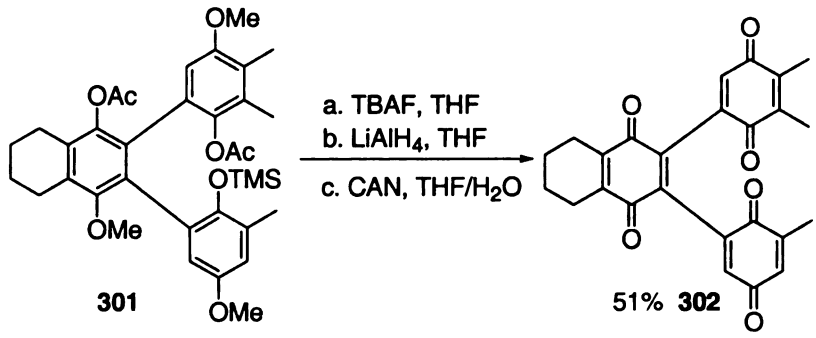
Scheme 4.35 Regiocontrolled synthesis trimer 301



The conversion of tris-phenol **301** to tris-quinone **302** is shown in Scheme 4.36. Desilylation of **301** using TBAF could be achieved by stirring at 0 °C for 20 min. The TLC of the desilylated reaction mixture showed the presence of two compounds corresponding to the two rotamers at R_f = 0.25 and R_f = 0.32 (Hexane : ethylacetate 9 : 2). The crude product so obtained after the workup of the reaction mixture was then reduced using $LiAlH_4$ by stirring at 0 °C for 1 h 30 min. After 1 h 30 min the reaction mixture was quenched with H_2O and extracted with ethyl acetate. The ethyl acetate was evaporated to obtain an oily residue. This residue was then dissolved in THF and was treated with 8 equivalents of CAN which at 0 °C for 10 min. The workup of the reaction mixture and the

purification of the residue obtained after the workup yielded the unsymmetrical tris-quinone in 51 % yield.

Scheme 4.36 Transformation of 301 to 302



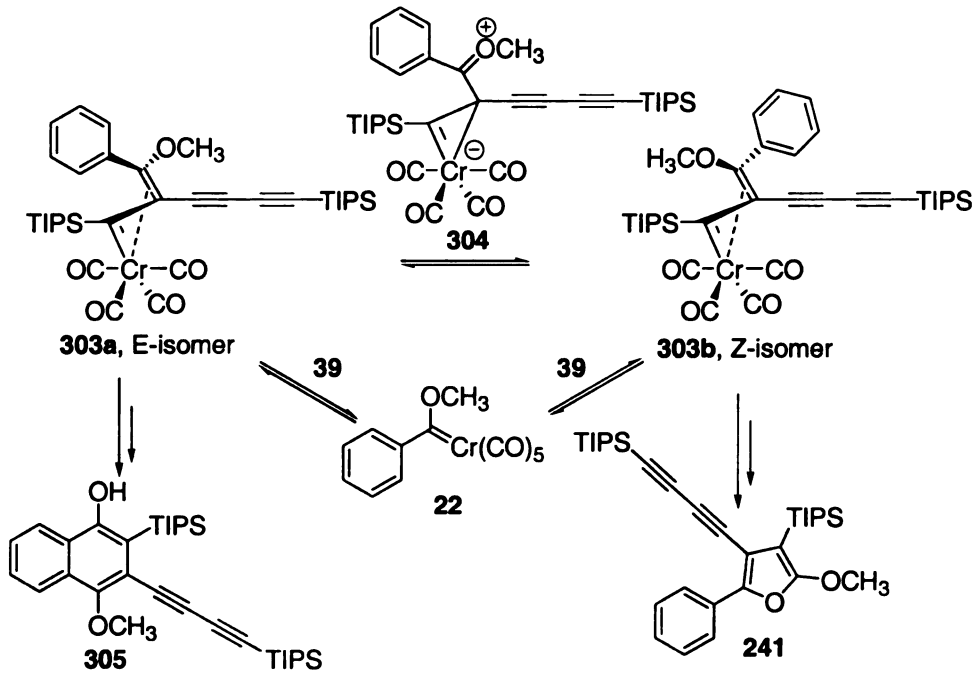
4.5 Mechanistic Considerations

This section considers possible mechanisms for the reaction of phenyl carbene complex **22** and the chromene carbene complex **175** with triyne **39**. These considerations are taken from what is known about the mechanism of the reaction of Fischer carbene complexes with simple alkynes[5] and also from calculations done here at MSU with help from Victor Prutyanov.

4.5.1 The Mechanism of reaction of complex 22 with triyne 39

Six different products are possible from the reaction of phenyl carbene complex **22** with the triyne **39**. Two of the possible products **236** and **237** arise from the reaction at the internal position of the triyne and these are shown in Scheme 4.39. Two other possibilities (phenol **305** and furan **241**) arise from the vinyl carbene complexed intermediates from (*E*)- **303a** and (*Z*)-**303b** and these, in turn, arise from the reaction of phenyl carbene complex **22** at the terminal position of triyne **39** (Scheme 4.37).

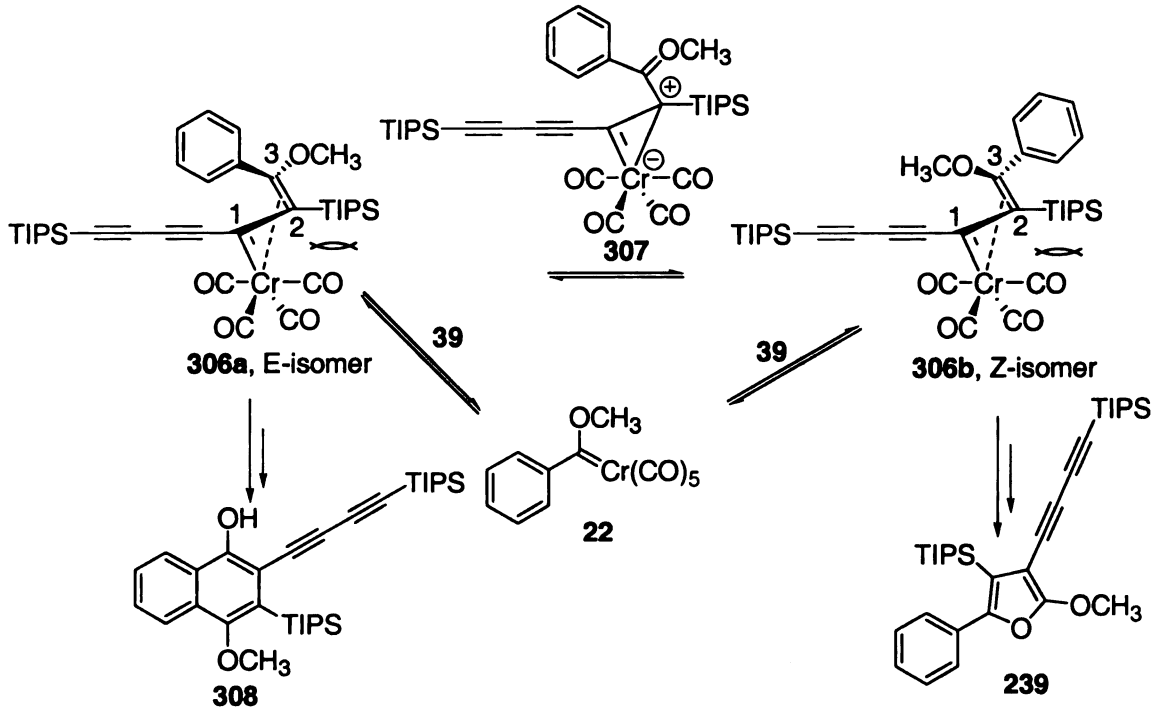
Scheme 4.37 Possible intermediates from the reaction of phenyl carbene complex 22 at the terminal position of triyne 39



The remaining two possible products **308** and **239** arises from vinyl carbene complexed intermediates **306a** and **306b** and are regioisomers of **305** and **241**, respectively (Scheme 4.38). In **306a** and **306b** the bulky TIPS substituent on carbon C-2 is 1Å closer to a CO ligand than it would be if it were on carbon C-1 such as they are in intermediates **303a** and **303b**.[5c,5d] The steric interaction between the TIPS substituent on carbon C-2 and the CO ligand on chromium render the formation of intermediates **306a** and **306b** energetically unfavorable in comparison to the intermediates **303a** and **303b**. This same steric argument has been used to explain the regioselectivity of simple internal

alkynes.[7] Thus the probability of formation of products **308** and **239** is considered to be unlikely.

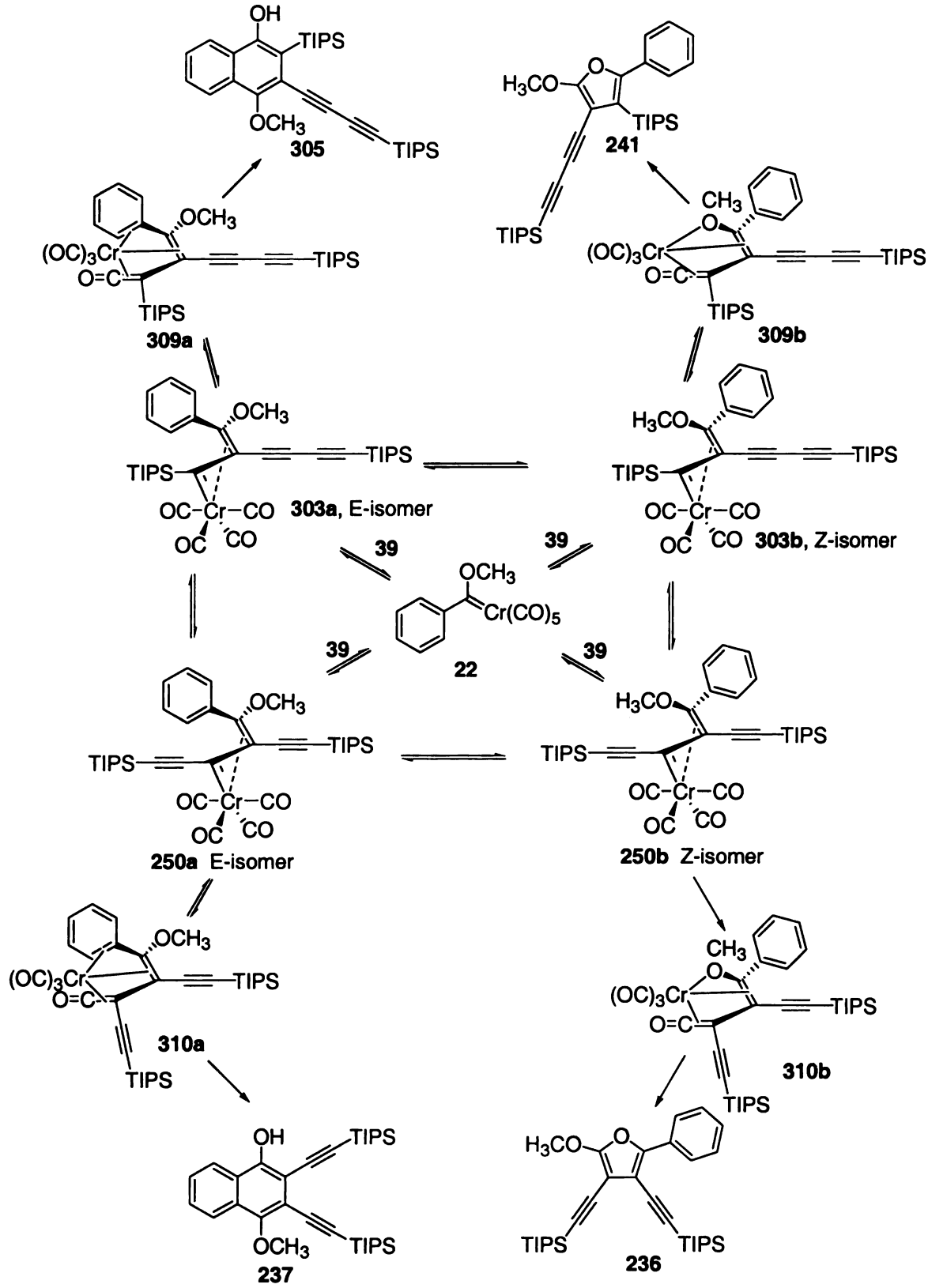
Scheme 4.38 Possible intermediates and products from the reaction of complex 22 at the terminal position of triyne 39



The mechanism shown in Scheme 4.39 can be used to account for the exclusive formation of furan **236** out of all of the four remaining possible products. Complex **22** would be expected to undergo a rate determining loss of a CO ligand[5b] followed by either insertion of the central alkyne in **39** to give the η^1,η^3-vinyl carbene complexed intermediates (*E*)-**250a** and (Z)-**250b** or insertion at the end-alkyne in **39** to give the η^1,η^3-vinyl carbene complexed intermediates (E)-**303a** and (Z)-**303b**. Here it is assumed that these intermediates are in rapid equilibrium with each other with respect to CO insertion which gives the vinyl ketene intermediates **309a**, **309b**, **310a** and **310b**. DFT calculations by Hess[5e]

and experimental results for reactions with simple alkynes from our lab[6b] have established that, for reactions with simple alkynes, cyclization and aromatization of the vinyl ketene intermediate is faster than deinsertion of the carbon monoxide which regenerates the η^1,η^3-vinyl carbene complexed intermediate. However, these studies did not include any examples of triynes or even diynes nor any examples of mono-ynes that have a silicon substituent. It is thus assumed here that the cylizations of vinyl ketene intermediate **309a** is slow relative to CO deinsertion. Support for the slow electrocyclization of **309a** comes from the known ability of silicon to greatly increase the stability of metal-free ketenes[71a] and from observations that stable metal-free silyl-substituted vinyl ketenes can be isolated from the reaction of Fischer carbene complexes and silyl-substituted alkynes.[71b,c,d] In addition, electrocyclization in **309a** and **310a** would be accompanied with the disruption of aromaticity of the phenyl ring. This will help to slow down electrocyclization of both **309a** and **310a**.

Scheme 4.39 Mechanism for the formation of furan 236

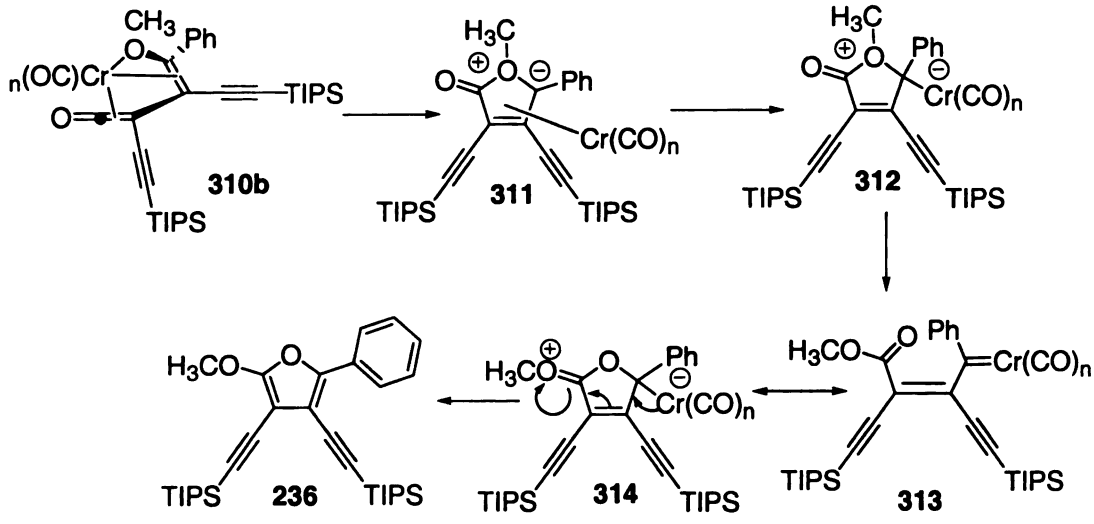


The Z-isomers **250b** and **303b** are proposed to be in equilibrium with each other and with the E-isomers of **250a** and **303a** (Scheme 4.39). The Z-isomers, **250b** and **303b** can be in equilibrium with the corresponding CO insertion products i.e., **310b** and **309b**. It would be expected that of the two ketenes **310b** and **309b**, the silicon stabilized ketene **309b** should be less reactive towards nucleophillic attack by the methoxy oxygen. Based on this expectation, the observation that the silyl-substituted triyne produces furan **236** as a result of reaction at the central alkyne can then be accounted for by reversible CO insertion in (*E*)-**303a**, (*Z*)-**303b** and (*E*)-**250a** and a non-reversible CO insertion in **250b** which can then lead to a depletion of an equilibrium between (*E*)-**303a**, (*Z*)-**303b** and (*E*)-**250a** via intramolecular nucleophilic attack of the methoxy group at the ketene carbon and the formation of **236**. The reason for these reversible CO insertions in ketenes **309a** and **309b** is the stabilization of the ketene by the silicon substituent,[71] and in **310a** it is the disruption of aromaticity of the phenyl ring which would accompany the electrocyclization step. It is not possible to rule out another scenario that involves a non-reversible CO insertion for all of the vinyl ketene intermediates and a product determination that is the result of equilibrium between (*E*)-**303a**, (*Z*)-**303b**, (*E*)-**250a**, (Z)-**250b**, where the formation of (*Z*)-**250b** is favored, and thus the furan **236**.

The most likely mechanism for the conversion of the ketene complex **310b** to furan **236** is shown in Scheme 4.40. Nucleophilic attack of methoxy oxygen on the ketene carbon would give zwitterion **311**, which upon rearrangement furnishes furan **236** via the intermediacy of the carbene complex **313** which

provides the furan ring upon nucleophilic addition of the carbonyl oxygen to the carbene carbon (Scheme 4.40). This proposal is based on the mechanism for the formation of furans from carbene complexes with mono-alkynes that bas been worked out by the research groups of Wulff[65b] and Rudler.[65g]

Scheme 4.40 Furan 236 formation from (*Z*)-ketene complex 310b



Preliminary calculation studies were performed with Victor Prutyanov to rationalize the formation of furan **236** and are discussed below. In these calculations the central issue will be the relative energies of intermediates on the paths to furan **236** vs phenol **237**. Thus, the energies of the products **305** and **241** and the intermediates involved **303a**, **303b**, **309a** and **309b**, arising from the reaction of phenyl carbene complex **22** to the terminal alkyne of triyne **39** are not considered. To help render the calculations simpler, the TIPS substituent in all the intermediates and products has been replaced by the TMS group. The PM3(TM) method was used to optimize the silylated intermediates (**250a**, **250b**, **310a**, **310b**) and the products (**236**, **237**). The single point energy of these PM3(TM) optimized structures (Figure 4.10) were then calculated using the DFT

(BP86/DN*) method. The energy of intermediates **250a**, **250b**, **310a**, **310b** and the products **236** and **237** from the reaction are shown in Table 4.1.

In evaluating the relative energies of the intermediates and products for this reaction an immediate problem was encountered. While, the intermediates **250a**, **250b**, **310a** and **310b** are metal complexes, the products that are actually isolated from these reactions, furan **236** and phenol **237** are not metal complexes. This will lead to large energy differences between the intermediates and products. As a solution to this problem the energy of furan **236** and of phenol **237** was determined by adding the energy of a tricarbonyl chromium fragment using the equations shown in Scheme 4.41.

The energy of furan **236** was determined to be E(DFT)**236** = -1545.68194 which is extremely low in comparison to the intermediates **250a**, **250b**, **310a**, **310b**. This is because of the absence of chromium and the CO ligands in **236**. Thus the energy of **236** was calculated using the equation shown in Scheme 4.41. It is assumed that the reaction of complex **22** with **39** in benzene would form complex **315** along with the furan product **236**. The chromium tricarbonyl complex of furan **236** is identified as **236*** but it is not clear how the chromium tricarbonyl group would be complexed to **236**. The energy of **236*** was calculated by subtracting the energy of benzene (E(DFT) = -232.31431 h/p) from the summation of the energy of furan **236** (E(DFT) = -1545.68194 h/p) and the energy of **315** (E(DFT) = -1617.24843 h/p).

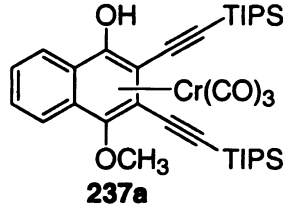
The problem of naphthol **237** not having a metal was handled in two different ways. In the first case the calculation were performed on chromium

tricarbonyl complex of **237** (i.e., of complex **237a**) and E(DFT)**237a** = -2930.60909 h/p (Table 4.1, entry 2) was obtained. Complex **237a** was chosen because its formation would be consistent with the experimental observation that the product of the reaction of carbene complex with alkynes is a chromium tricarbonyl complex where the chromium is η^6-coordinated to the newly formed benzene ring.[3] In the second method, the energy of the metal complex of naphthol **237** was determined in the same way as was the metal complex of furan **236**. Thus, **237*** was calculated by adding the energy of naphthol **237** (E(DFT)**237** = -1545.6842 h/p) and energy of complex **315** (E(DFT)**315** = -1617.24843 h/p) and deducting the energy of benzene (E(DFT)benzene = -232.31431 h/p). This energy was found to be E(DFT) **237*** = -2930.61832 h/p. Although the energies for the two methods of accounting for the metal complex of **237** vary by 5.8kcal / mole, this is not large enough difference to affect the overall conclusion from the calculations.

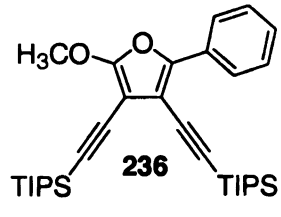
Scheme 4.41 Energy of furan 236

E(DFT) **236*** (Table 1, entry 5) = E(DFT) **236** + E(DFT) **315** - E(DFT) Benzene

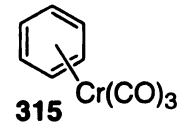
E(DFT) **237*** (Table 1, entry 7) = E(DFT) **237** + E(DFT) **315** - E(DFT) Benzene



237a



236



315

Table 4.1 Energetic of the products 236 and 237 and intermediates involved in their formation

Entry	Intermediates and Products[a]	PM3(TM) Heat of Formation[b] (kcal/mol)	Single point energy[c] (h/p)[d]	Energy difference[e] (E_{n1} –2930.61606) X 627.5 (kcal/mol)
1.	**236***	87.106	-2930.61606	0
2.	**237a**	-75.935	-2930.60909	4.37367
3.	**237***	-75.935	-2930.61832	-1.41815
4.	**250a**	-88.535	-2930.55835	36.21303
5.	**250b**	-90.054	-2930.47528	87.93785
6.	**310a**	-60.91	-2930.44371	108.14960
7.	**310b**	-104.64	-2930.55683	37.16682

a) The energy calculated is that of the intermediates and the products when TIPS group in the acetylenic position is replaced by TMS. b) Intermediates shown in column 1 were optimized and their heat of formation were calculated using PM3(TM) method. c) Single point energy of PM3(TM) optimized structure was calculated using DFT(BP86)/DN* method. d) h/p = hartree/particle. e) E_{n1}= energy of the intermediate in column 1.

The following assumption has been made to interpret the results of the calculations: the energy of the intermediates correlate with the energy of their transition states. The profile of the reaction of phenyl carbene complex **22** with triyne **39** is shown in Figure 4.9. The calculations show that (E)-**310b** is more stable than (Z)-**310a** by 71 kcal/mol. One of the possible explanations for such a big difference in energy is that, in (E)-**310a**, the 18 electron chromium complex formation requires the coordination of the double bond of the benzene ring which would lead to the disruption of aromaticity. This is, however, not the case in **310b**, in which a lone pair of electrons from the oxygen can coordinate with chromium to make it an 18 electron chromium complex. Another important point

to note from reaction profile in Figure 4.9 is that, (*E*)-**250a** is more stable than (*Z*)-**250b**. The stability of (E)-**250a** can be explained in terms of the trans-effect. The "trans-effect" favors an electron-donating substituent (i.e., OMe in (E)-**250a**) at the C-3 position of vinyl carbene complex intermediate (E)-**250a** to be trans to the carbene carbon (C-1) of the vinyl carbene complexed intermediate (E)-**250a** (For details see section 4.4.1.1).[66] The calculations further reveal that the furan precursors vinyl carbene complex (*Z*)-**250b** and (*Z*)-vinyl ketene **310b** are both lower in energy than the (*E*)-ketene **310a** that is responsible for phenol product formation. Thus an equilibrium between (*E*)-**250a**, (Z)-**250b**, (*E*)-**310a** and (*Z*)-**310b** would favor the relatively low energy intermediate (*Z*)-ketene **310b** which would then undergo irreversible nucleophilic addition and rearrangement to form furan **236**.

Figure 4.9 Energy of the intermediates and the products where TIPS group is replaced by TMS group

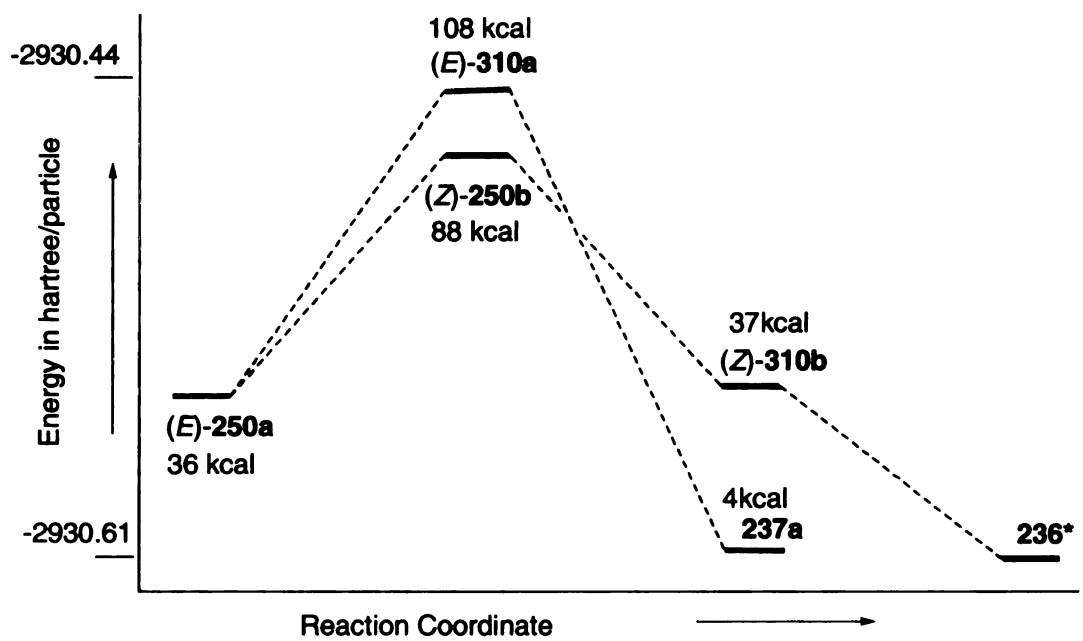
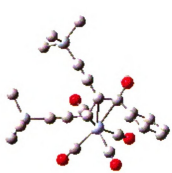
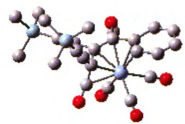


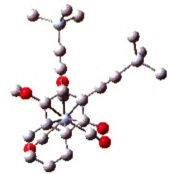
Figure 4.10 PM3(TM) optimized structure of the intermediates and the products where TIPS group is replaced by TMS group



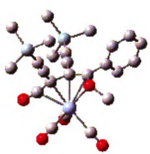
(E)-**250a**



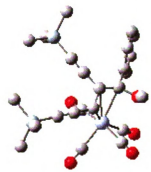
(E)-**310a**



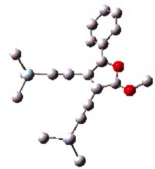
237a



(Z)-**310b**



(Z)-**250b**



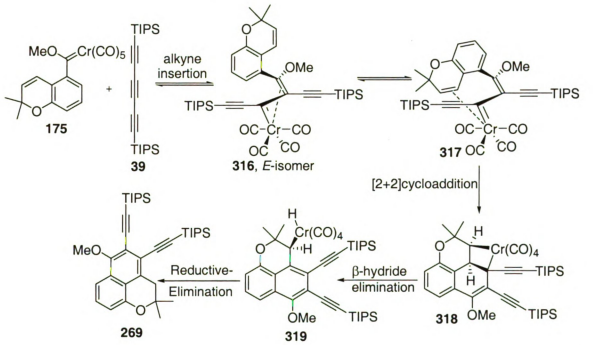
236

4.5.2 The formation of the olefin-addition product 269 from the reaction of chromene carbene complex 175 with triyne 39

A possible mechanism for the formation of unprecedented product **269** formed in the reaction of chromene carbene complex **175** and triyne **39** is as shown in Scheme 4.42. As in the reaction of the phenyl carbene complex **22** with **39** the first step most likely involves the rate limiting loss of CO from chromene carbene complex **175** to give a 16-electron complex which undergoes alkyne

coordination and insertion to form vinyl carbene complex (*E*)-**316** (Scheme 4.42). It is then proposed that vinyl carbene complex (*E*)-**316** undergoes a rearrangement to form another vinyl carbene complexed intermediate **317**. The [2 + 2] cycloaddition of olefins and Fischer carbene complexes are well established[72,73] and in this case intermediate **317** would undergo [2+2] cycloaddition to form chromacyclobutane **318**. Finally, chromacyclobutane **318** could undergo β-hydride elimination and reductive elimination to give compound **269**.

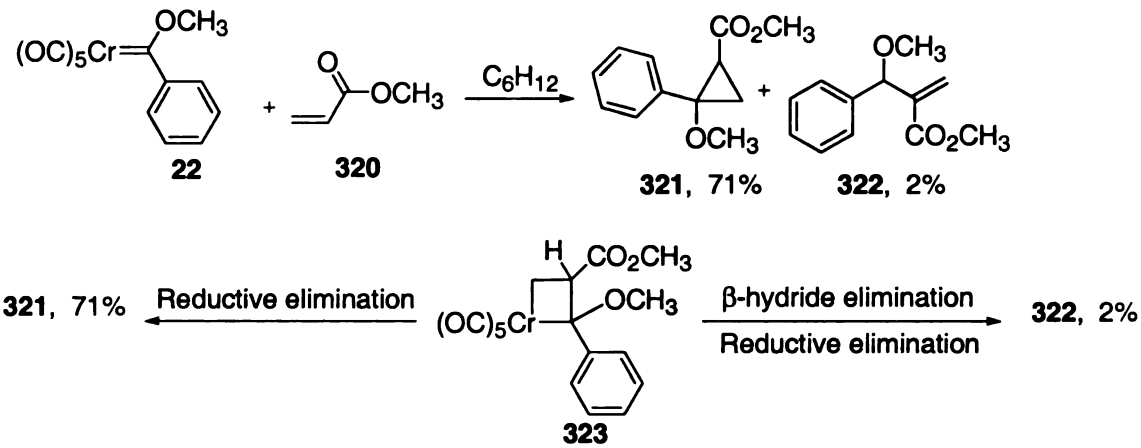
Scheme 4.42 Proposed mechanism for the formation of 269



Chromacyclobutanes are known to be intermediates involved in the cyclopropanation reaction of α,β-unsaturated ester such as **320** with complexes such as **22** (Scheme 4.43).[72] The cyclopropanation reaction in a few case has

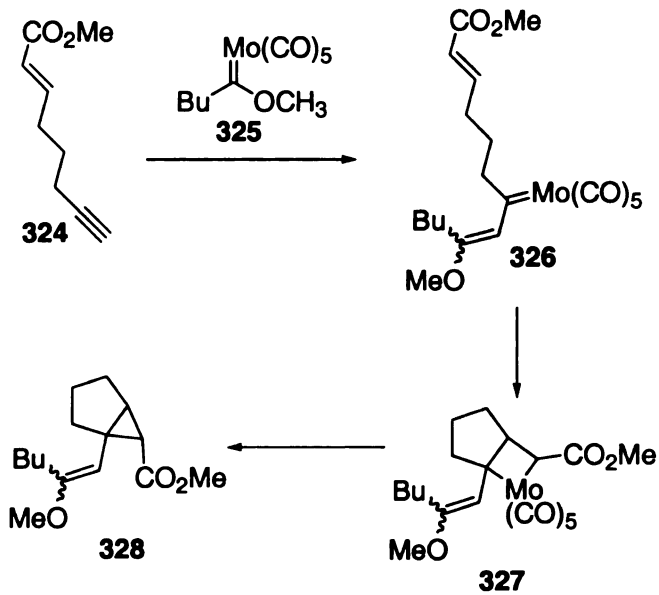
been observed to give a side product of the type **322** which results from β-hydride elimination in the chromacyclobutane **323**.[72c]

Scheme 4.43 Chromacyclobutane intermediate in cyclopropanation reaction



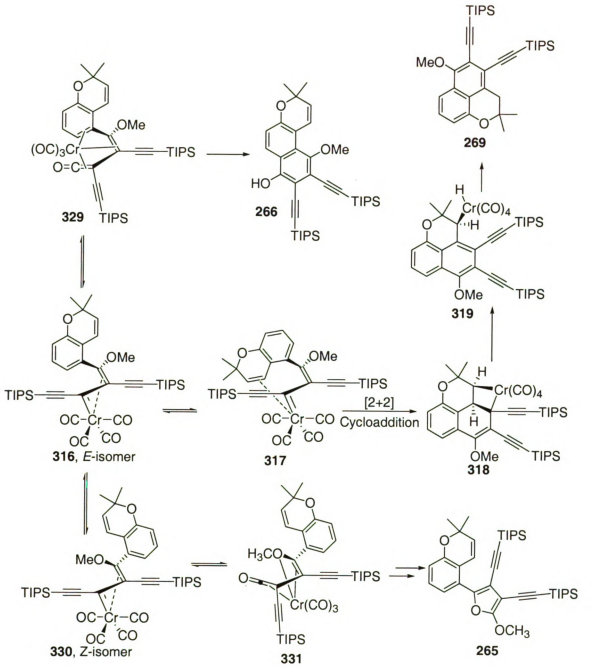
Harvey has reported the tandem alkyne insertion and cyclopropanation reaction of the reaction of Fischer carbene complex **325** with enyne **324** (Scheme 4.44).[73] This reaction is very similar to the reaction of chromene carbene complex **175** with triyne **39** since it also involves the insertion of an alkyne into the carbene ligand and then an intermolecular [2 + 2] cycloaddition of the in-situ generated carbene complex **326** with an alkene. The difference here is two fold: one, that the metallocyclobutane intermediate **327** undergoes reductive elimination rather than β-hydride elimination and, two, the olefin is part of the acetylene and not part of the carbene complex.

Scheme 4.44 Tandem alkyne insertion and cyclopropanation reaction



In addition to the olefin-addition product **269**, two other possible products from this reaction are the furan **265** and the naphthol **266** (Scheme 4.45). Carbon monoxide insertion in (*E*)-**316** would form vinyl ketene complex (*E*)-**329** which upon electrocyclic ring closure should give **266**. Alternatively, (*E*)-**316** may undergo isomerization to form Z-vinyl carbene complex **330** which upon CO insertion and cyclization will afford chromenyl furan **265** (Scheme 4.45).[6,65]

Scheme 4.45 Proposed mechanism for the formation of 265, 266 and 269



It is proposed that intermediate (*E*)-**316** is in equilibrium with the intermediates **317**, (*Z*)-**330**, (*Z*)-**331** and **329**. The electrocyclization of intermediate **329** is expected to be a slow process as it would be accompanied by the disruption of aromaticity of chromene ring. It is further proposed that irreversible [2+2] cycloaddition of intermediate **317** is faster than the nucleophilic attack of methoxy oxygen on the ketene carbon in **331**. The exclusive formation of olefin-addition product **269** can then be explained by the irreversible [2 + 2] cycloaddition in **317** which would deplete the equilibrium between (*E*)-**316**, **317**, (*E*)-**329** and (*Z*)-330 in favor of **317** and hence to preferential formation of **269**.

Another possibility could be that CO insertion is not reversible and that a product determination results from an equilibrium between (*E*)-**316**, **317** and (*Z*)-**330** and which is more favorable for **317**.

Preliminary calculations performed with Victor Prutyanov to rationalize the formation of olefin-addition product **269** are discussed below. To simplify the calculations, the TIPS substituent in all the intermediates and products has been replaced by a TMS group. The PM3(TM) method was used to optimize the silylated intermediates ((*E*)-**316**, **317**, **318**, **319**, (*E*)-**329**, (*Z*)-**330**, (*Z*)-**331**) and products (**265**, **266**, **269**). The single point energy of these PM3(TM) optimized structures (Figure 4.12) were then calculated using the DFT (BP86/DN*) method. The energy of all the intermediates and possible products from the reaction are shown in Table 4.2.

Table 4.2 Energetics of the products 265, 266, 269 and the intermediates involved in their formation

Entry	Intermediates and Products[a]	PM3(tm) Heat of Formation[b] (kcal/mol)	Single point energy[c] (h/p)[d]	Energy difference[e] (E_{n1} –2930.61606) X 627.5 (kcal/mol)
1.	**265***	-68.316	-3200.05654	0
2.	**266a**	-103.165	-3200.00234	33.9854
3.	**266***	-130.032	-3200.0636	-4.45525
4.	**269***	-85.999	-3200.00852	30.10243
5.	**316**	-114.897	-3200.00162	34.43720
6.	**317**	-128.571	-3199.93228	77.54645
7.	**318**	-114.352	-3199.98966	41.94210
8.	**319**	-124.397	-3199.28895	79.64858
9.	**329**	-87.148	-3199.89670	100.2745
10.	**330**	-114.939	-3199.28811	84.9133
11.	**331**	-82.106	-3199.90603	94.41993

a) The energy calculated is that of the intermediates and the products when TIPS group in the acetylenic position is replaced by TMS. b) Intermediates and products shown in column 1 were optimized and their heat of formation were calculated using PM3(TM) method. c) The single point energy of the PM3(TM) optimized structure was calculated using DFT(BP86)/DN* method. d) h/p = hartree/particle. e) E_{n1} = energy of the intermediate in column 1.

The problem of the lack of a chromium and its CO ligands in the products **269**, **265** and **266** was handled in a manner similar to that for the reaction of complex **22** with triyne **39** (Scheme 4.39). The chromium tricarbonyl complexes **of 269** and **265** are indicated by **269*** and **265***, respectively. The energies of **265*** and **269*** was calculated according to the equation shown in Scheme 4.46. The energy of the metal complex **265*** (Table 4.2, entry 1) was calculated by

subtracting the energy of benzene (E(DFT)benzene = -232.31431 h/p) from the summation of the energy of furan **265** (E(DFT)**265** = -1815.12242 h/p) and energy of complex **315** (E(DFT)**315** = -1617.24843 h/p).

The energy of olefin-addition product **269*** (Table 4.2, entry 4) was calculated by subtracting the energy of benzene (E(DFT)benzene = -232.31431 h/p) from the summation of the energy of **269** (E(DFT)**269** = -1701.78933 h/p), energy of CO (E(DFT)CO = -113.36183 h/p) and the energy of **315** (E(DFT)**315** = -1617.24843 h/p) as shown in Scheme 4.46 . Notice that for calculating the energy of olefin-addition product **269**, the energy of CO has also been included since **269** is a non-CO inserted olefin-addition product.

The energy of metal complex of naphtholpyran **266** was calculated in two different ways. In the first case, the calculation was performed on the tricarbonyl complex of **266a** and an energy of E(DFT)**266a** = -3199.95101 h/p was obtained (Table 4.2, entry 2). As was the case for **237**, the kinetic product of the reaction is expected to be the arene complex **266a** with the $Cr(CO)_3$ group coordinated to the newly formed benzene as has been clearly established in the reaction of Fischer carbene complexes with mono-ynes.[3] In the second case and without prejudice for where the $Cr(CO)_3$ group is, the energy of the naphtholpyran **266***, (Table 4.2, entry 3) was calculated by adding the energy of naphtholpyran **266** (E(DFT)**266** = -1815.12952) and energy of complex **315** (E(DFT)**315** = -1617.24843 h/p) and deducting the energy of benzene (E(DFT)benzene = -232.31431 h/p) from their summation, as shown in Scheme 4.46. The energy difference between E(DFT)**266a** and E(DFT)**266*** is approximately 38 kcal/mol.

This difference is much larger than it was for **237** but does not effect the conclusions from the calculations.

Scheme 4.46 Energy of furan 265 and olefin-addition product 269

E(DFT) **265*** (Table 2, entry 1) = E(DFT) **265** + E(DFT) **315** - E(DFT) Benzene

E(DFT) **266a** (Table 2, entry 2) = E(DFT) **266** + E(DFT) **315** - E(DFT) Benzene

E(DFT) **269*** (Table2, entry 4) = {E(DFT) **269** + E(DFT) **315** + E(DFT) CO - E(DFT) Benzene}

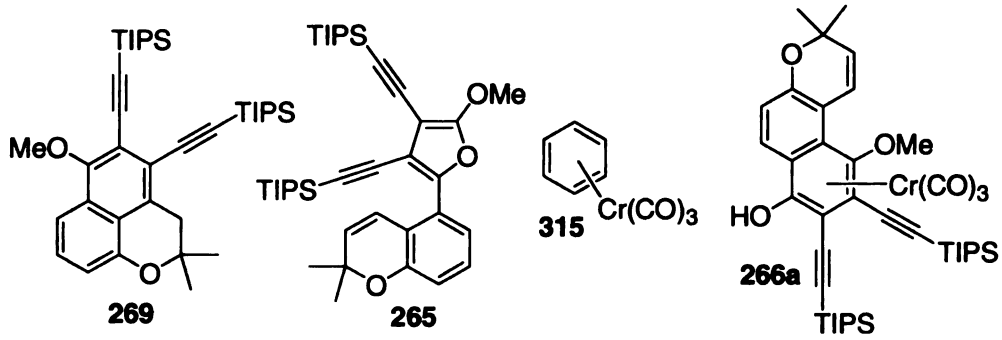
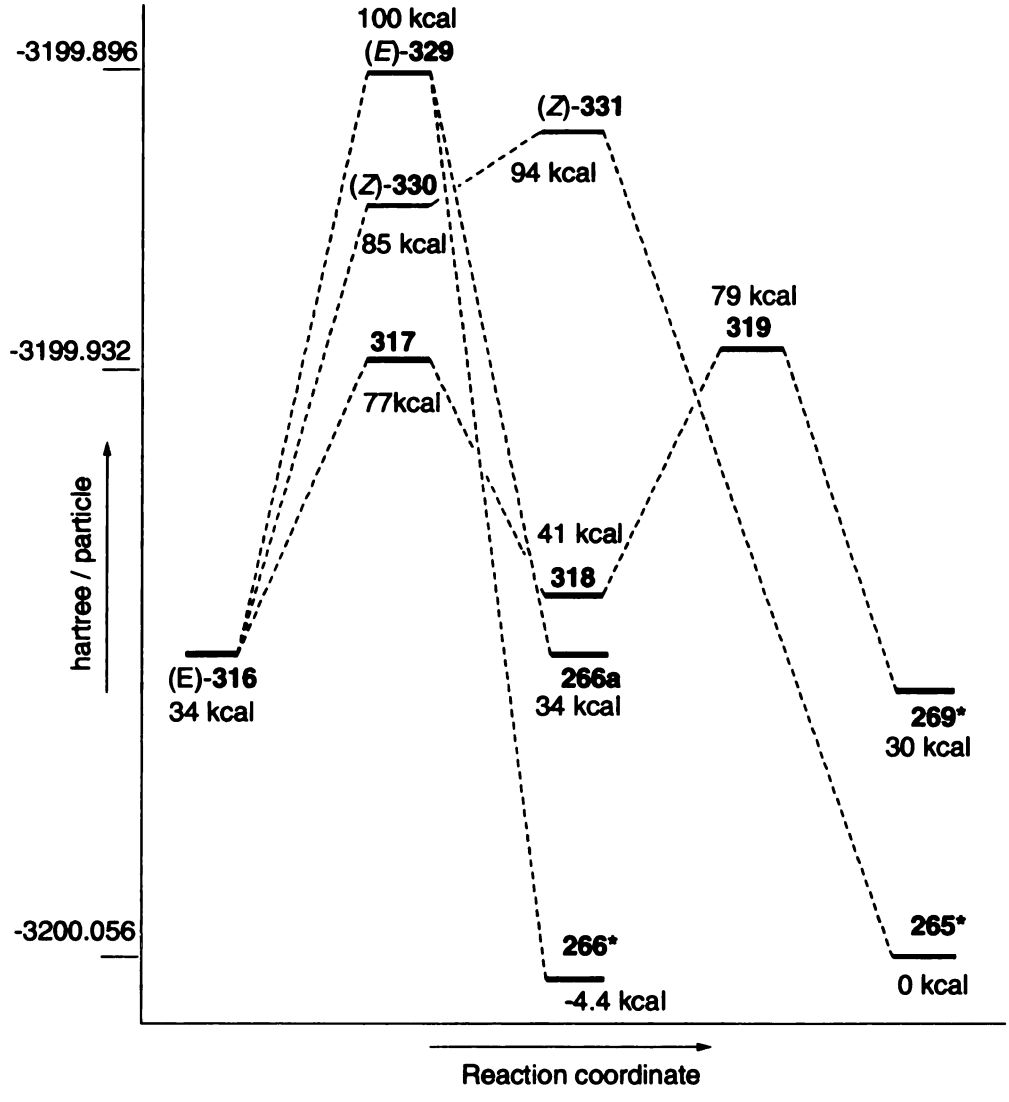


Figure 4.11 shows the energy profile of the formation of olefin-addition product **269**. To interpret the results of the calculation the following assumption is made: the energy of the intermediates correlates with the energy of their transition states. It is further assumed that [2+2] cycloaddition is an irreversible step.

Figure 4.11 Energy of the intermediates and the products where TIPS group is replaced by TMS group

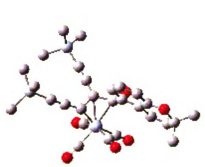


The calculations show that (*Z*)-**331** is more stable than (*E*)-**329** by 6 kcal/mol and (*E*)-**316** is more stable than (*Z*)-**330** by 51 kcal/mol. The explanation for increased stability of intermediates (*Z*)-**331** and (*E*)-**316** is same as that of the

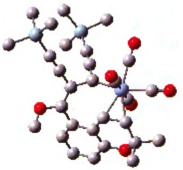
stability of (*E*)-**250a** and (*Z*)-**310b** over (*Z*)-**250b** and (*E*)-**310a** as discussed in section 4.5.1. However, the energy difference between (*E*)-**329** and (*Z*)-**331** is only 6 kcal/mol which is much smaller than the energy difference between (E)-**310a** and (Z)-**310b** (71kcal/mol) in which the chromenyl ring is replaced by phenyl ring (Scheme 4.39). The reason for such a big discrepancy in energy is not well understood.

It is evident from the reaction profile that the formation of the olefin-addition product **269** involves two high-energy steps: rearrangement of the (E)-vinyl carbene complex (*E*)-**316** to form the carbene olefin complex **317** and then β-hydride elimination in complex **318** to give **319** which leads to product upon reductive elimination. However the energies of the intermediates **317** and **319** on this pathway are significantly lower than the energy of (*E*)-**329** and (*Z*)-**330** which are on the pathway for the formation of products **266** and **265**, respectively. Thus, an equilibrium between (*E*)-**316**, **317**, (*E*)-**329**, (*Z*)-**330** and (*Z*)-**331** would be in favor of (*E*)-**316** which upon [2+2] cycloaddition, β-hydride elimination, and reductive elimination would furnish olefin-addition product **269**.

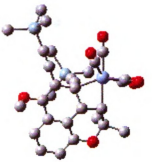
Figure 4.12 PM3(TM) optimized structure of the intermediates and the products where TIPS group is replaced by TMS group



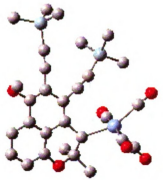
(E)-316



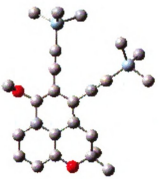
317



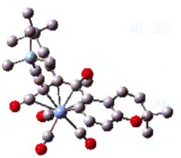
318



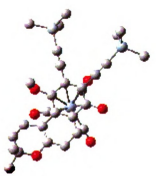
319



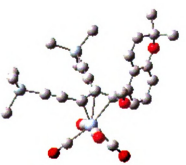
269



329



266a



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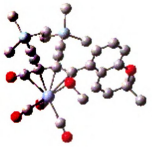
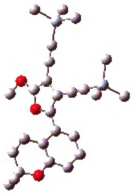


331



265

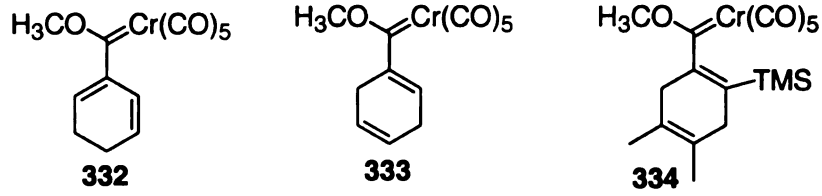
4.6 Summary

In summary, it has been established that aromatic carbene complexes **22**, **234**, **235** (Figure 4.5) will react with bis-TIPS-triyne **39** give aryl furans **236**, **262**, **272**. The formation of aryl furans is neither perturbed by reaction temperature nor by the electronics of the carbene complex. The reactions of aryl carbene complexes **22** and **175** with bisphenyl-1,3,5-triyne **224** give either very low yields of the benzannulation product or decomposition of the starting materials. Furthermore, reactions of the phenyl carbene complex **22** with *ortho*-aryl diynes **221**, **287**, **288**, **289**, **290** result in the consumption of the starting carbene complex but in no discreet product formation. The reaction of chromene carbene complex **175** with bis-TIPS triyne gives an undesired but unprecedented olefin-addition product **269**. The formation of this new product, if generalized for simple internal and terminal alkynes, would provide an excellent pathway to access a new class of naphthopyrans.

4.7 Future Work

The reactions of the cyclohexenyl carbene complex **219** and bis-TIPS-triyne **39** or *ortho*-aryl diynes **221** and **289** work extremely well for synthesizing tris-quinones the type **223** (Scheme 4.7). This is, however, not the case for aromatic carbene complexes. An alternative approach to access aromatic tris-quinone of the type **286** (Scheme 4.29) is to use α,β-unsaturated carbene complexes of the type **332**, **333** and **334** (Figure 4.13). Complexes **332** and **333** are not known in the literature. However, the synthesis of their corresponding vinyl bromides is known.[74,75]

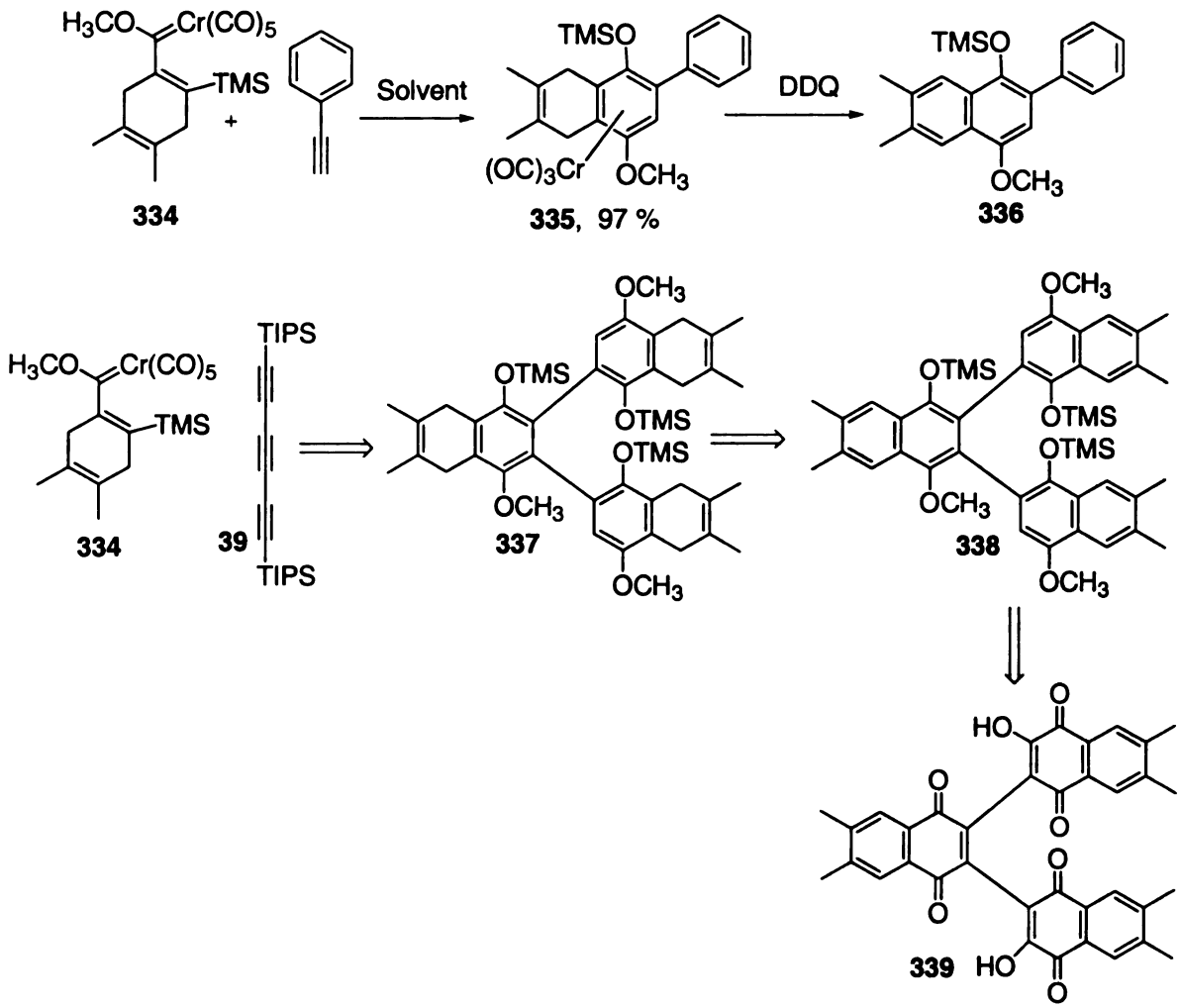
Figure 4.13 Alkenyl carbene complexes 332, 333 and 334



332 **333** **334**

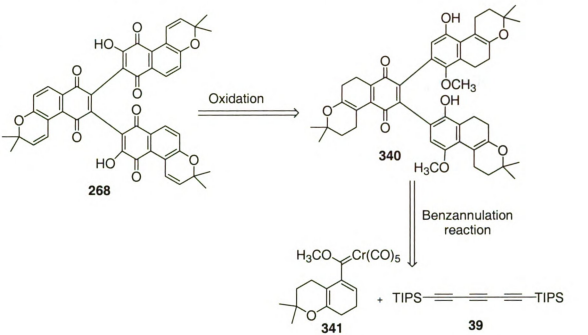
Yang and Wulff have reported the synthesis of complex **334**.[76] It has been shown that the reaction of complex **334** with phenyl acetylene affords dihydronaphthalene **335** which was converted to naphthalene **336** upon DDQ oxidation (Scheme 4.47). Thus, the reaction of carbene complex **334** with triyne **39** could give rest of the tris-aromatic phenols **338** or tris-aromatic quinones **339** (Scheme 4.47).

Scheme 4.47 Reaction of complex 334: Surrogate for an aryl complex



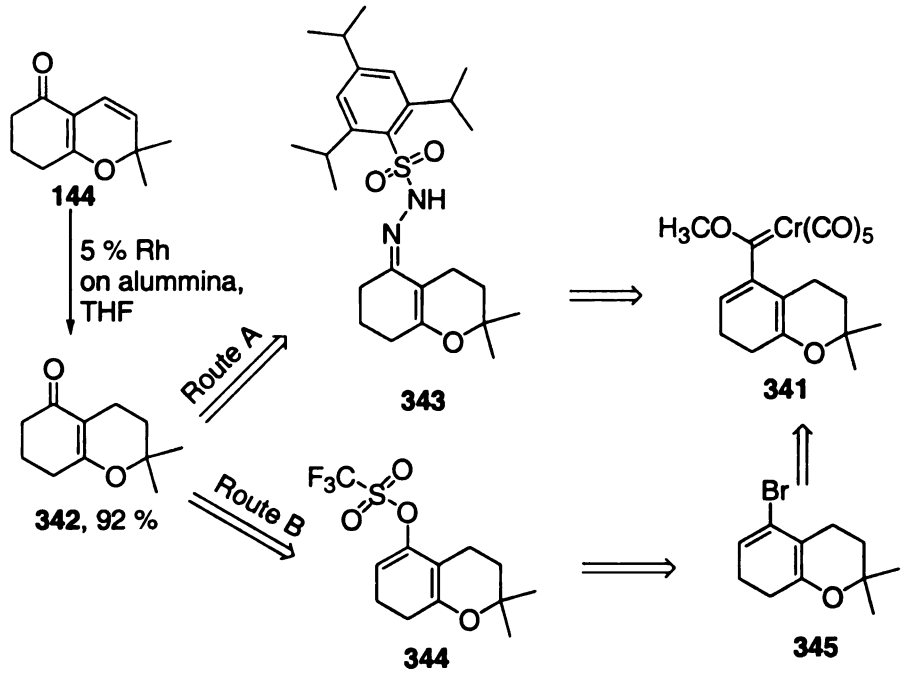
With this same strategy, tris-quinones of the type **268** would require the reaction of bis-TIPS triyne **39** and chromane complex **341** (Scheme 4.48).

Scheme 4.48 Retrosynthesis of formation of conocurvone analogue 340



The chromane complex **341** can be obtained via two different routes (Scheme 4.49). Route A involves the transformation of chromenone **342** to hydrazone **343**,[77] which is expected to give complex **341**, upon its sequential treatment with *t*-BuLi, $Cr(CO)_6$ and a methylating agent (Scheme 4.49). Shapiro reaction has been previously used for the formation of carbene complexes.[12b] In Route B, the chromanone **342** can be converted to vinyltriflate **344** which on palladium catalyzed triflate-tin exchange followed by quenching with a brominating agent would afford bromochromane **345** (Scheme 4.49). Standard Fischer protocol would transform **345** to **341**. Chromanone **342** can be isolated in 92 % from the reductive hydrogenation of **144** using 5 % Rh on alumina. However this reaction does not go to completion when Wilkinson's catalyst is used instead of 5 % Rh on alumina.

Scheme 4.49 Retrosynthesis of formation of complex 341



In summary, synthesis of tris aromatic quinones of the type **339** and **268** would require the α,β-unsaturated Fischer carbene complexes of the type **334**, **341**, respectively.

CHAPTER FIVE

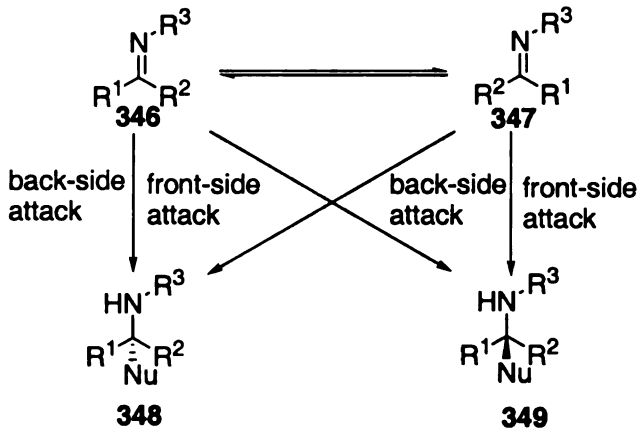
Asymmetric Allylation of Imines

5.1 Introduction

Nature possesses a plethora of chiral nitrogen containing molecules which are of significant biological importance. There is an utmost need of creating facile synthetic pathways for the synthesis of enatiomerically pure nitrogen-containing compounds using readily available and environmentally benign starting materials. Nucleophilic addition to imines for the construction of C-H bonds by reductive amination and C-C bonds by allylation, aza Diels-Alder reactions, imino-aldol additions, imino-cyanation and imino-ene reactions are but a few of the methods used to access chiral amines.[78]

Although catalytic enantioselective additions to aldehydes and ketones have been well investigated, there are only a limited numbers of reports on additions to the asymmetric additions to imines. The two main reasons which make the reaction of imines less favorable are: a) the turnover of the catalyst is limited by normally greater basicity of the product amine versus the imine starting material, and b) the ability of the imines to exist in E and Z-ismers and therefore can give rise to diastereomers upon binding with the catalyst which decreases the selectivity of the nucleophile and result in lower asymmetric induction (Scheme 5.1).

Scheme 5.1 *E-Z* isomerization of C-N bond and selectivity of the reaction



Catalytic asymmetric allylation is one of the reactions of imines which has not been studied in detail. This chapter discusses an attempt to access chiral homoallylic amines by reaction of aldimines with allyltributyl stannane.

5.2 Asymmetric allylation: Background information

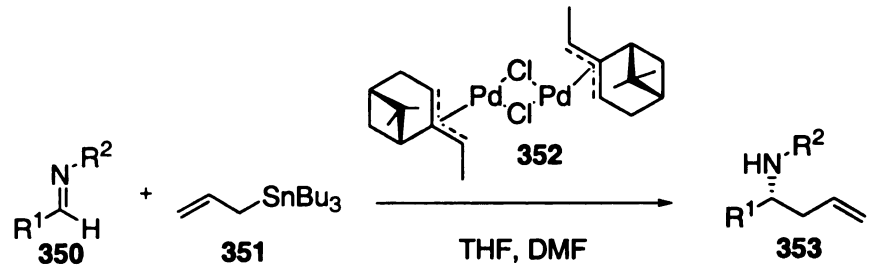
There are only four reports on the catalytic version of the enantioselective allylation reaction of imines and these are discussed below.

5.2.1 Yamamoto and co-workers

The first asymmetric catalytic allylation of imines was reported by Yamamoto and co-workers (1998) using chiral π-allyl palladium catalyst **352** and allyltributyl stannane as nucleophile (Scheme 5.2).[79a,b,c] It has been proposed that allyltributyl stannane **351** reacts with the Pd(II) catalyst to form a chiral nucleophillic bis-π-palladium species which selectively reacts with imines to form the enatiomerically enriched homoallylic amines **353**. The reaction tolerated

aromatic, aliphatic and α,β-unsaturated imines and gave good yields (30 % - 80 %) and enantioselectivities (40 % - 91 %).

Scheme 5.2 Palladium catalyst for asymmetric allylation

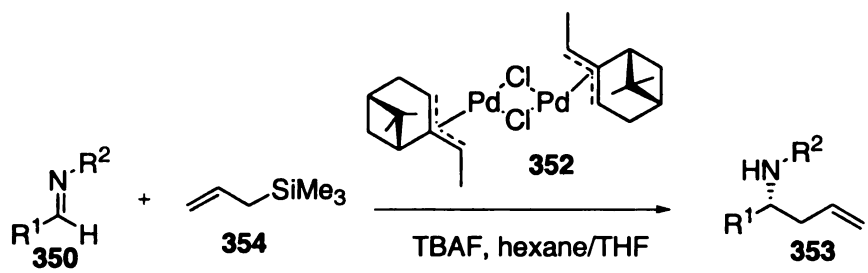


R_1 = Phenyl, p-$MeOC_6H_4$, 2-naphthyl, Ph-CH=CH, cyclohexyl
R_2 = Bn, p-$MeOC_6H_4CH_2$, phenyl, propyl

Yield 30 - 83 %
ee 40 - 82 %

Yamamoto has further extended the scope of the reaction, by replacing the toxic allyltributyl stannane **351** with the environmentally benign allyltrimethylsilanes **354** and obtained the homoallylic amines **353** in yields as high as 95 % with moderate to high enantioselectivities (52 % - 90 %) (Scheme 5.3).[79d,e] The reactions of imines with allylsilanes are generally very slow and sluggish. This problem was overcome by using a palladium-TBAF cocatalyst system.

Scheme 5.3 Allyl-palladium catalyst for asymmetric allylation



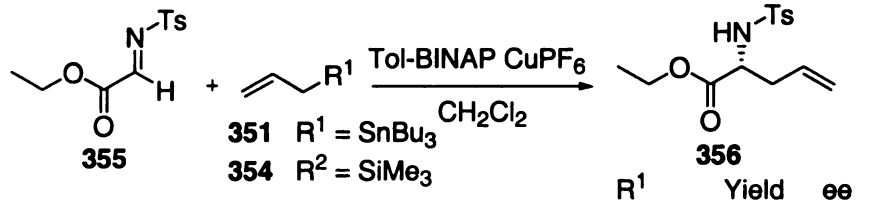
R_1 = Phenyl, *p*-$MeOC_6H_4$, 2-naphthyl, Ph-CH=CH, cyclohexyl
R_2 = Bn, *p*-$MeOC_6H_4CH_2$, propyl

Yield 34 - 96 %
ee 64 - 80 %

5.2.2 Jørgensen and co-workers

In 1999, Jørgensen and co-workers reported the catalytic asymmetric allylation of N-tosyl α-imino ester **355** using allyl stannane **351** and silane **354** (Scheme 5.4).[80] The allyl silane gave low yields (58 % - 64 %) and moderate enantioselectivities (34 % - 47 %). However, allyltributyl stannane afforded high yields (up to 90 %) and moderate to high enantioselectivities (23 % - 83 %).

Scheme 5.4 Copper catalyst for asymmetric allylation

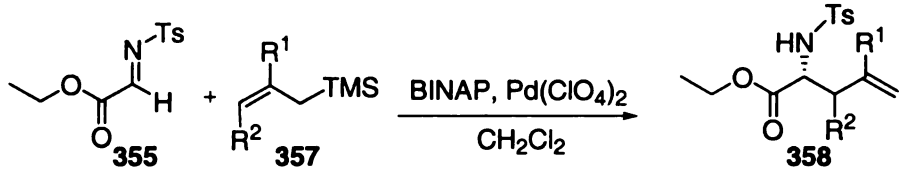


R^1	Yield	ee
$SnBu_3$	87 %	80 %
$SiMe_3$	34 %	58 %

5.2.3 Lectka and co-workers

Lectka (2002) has demonstrated the successful asymmetric reaction of N-tosyl α-imino esters and allylsilanes using a palladium BINAP catalyst.[81] Excellent yields of homoallylic amines **358** have been observed in all the reported cases. However, the enantioselectivity varied from 64 % - 92 % (Scheme 5.5).

Scheme 5.5 Palladium chlorate catalyst for asymmetric allylation



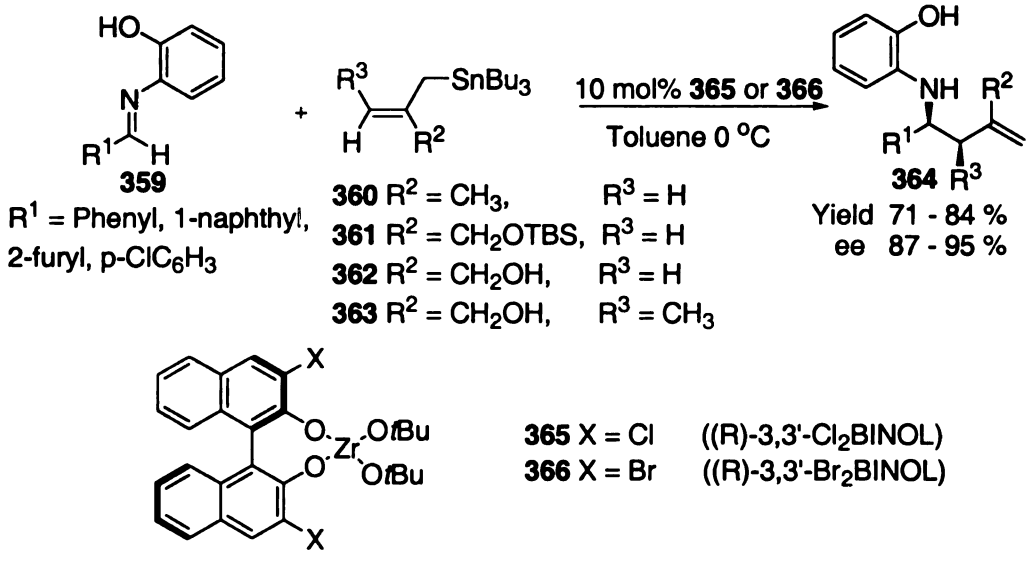
R^1 = H, Ph, Me
R^2 = H, Me

Yield 85 - 91%
ee 64 - 92 %

5.2.4 Kobayashi and co-workers

Kobayashi has used the bidendate imines of the type **359**, allyl tributyl stannanes (**360**, **361**, **362**, **363**) and the zirconium-based catalyst **365** and **366** for asymmetric allylation reactions.[82] The acceleration in rate and incremental increase in enantioselectivity was observed when the free alcohol functionality was present in the allylating agent such as in **362** and **363**. He proposed that the free alcohol functionality in **362** and **363** binds to the Zr catalyst along with the bidendate imine which is followed by intramolecular attack of allyl stannne to the imine **359**. This reaction provided 71 % - 85 % yield and 87 % - 99 % ee. However, this approach has two limitations. First, it is applicable to only aryl imines with the exception of imine derived from cyclohexanecarboxaldehyde. Second, the allylating agent (allyltributyl stannane) must have a CH_2OH substitutent (**362** and **363**) at the C-3 position for faster reaction rate and high asymmetric induction.

Scheme 5.6 Zirconium catalyst for asymmetric allylation

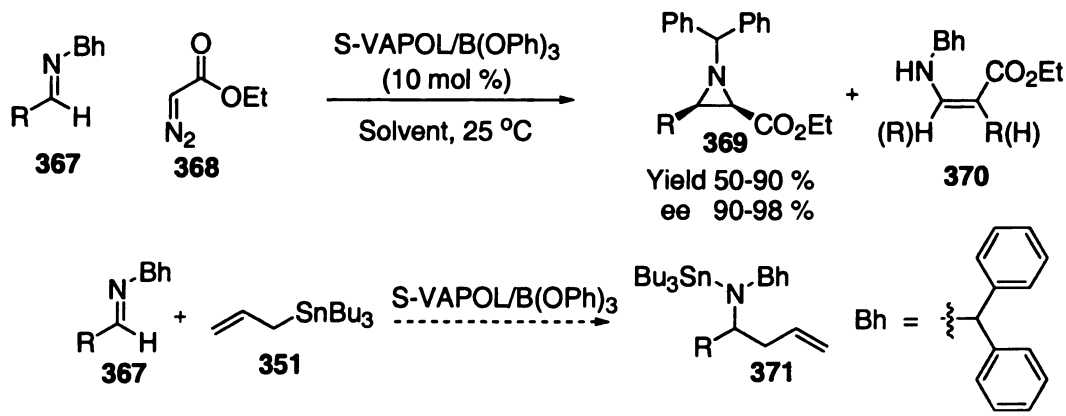


In summary, Yamamoto's palladium catalyst **352** is general for the asymmetric allylation of a wide variety of aliphatic and aromatic imines. Jørgensen's and Lectka's catalysts are limited to only N-tosyl-α-imino esters for the allylation reaction. The Zr catalyst used by Kobayashi is useful for allylation reaction of aromatic imines with allyl stannanes possessing a methylene alcohol functionality in the C-3 position. Therefore, thus far there is no general Lewis acid catalyzed asymmetric allylation reaction of imines derived from both alkyl and aryl aldehydes.

5.3 Attempted allylation of benzhydrylimines of the type 367

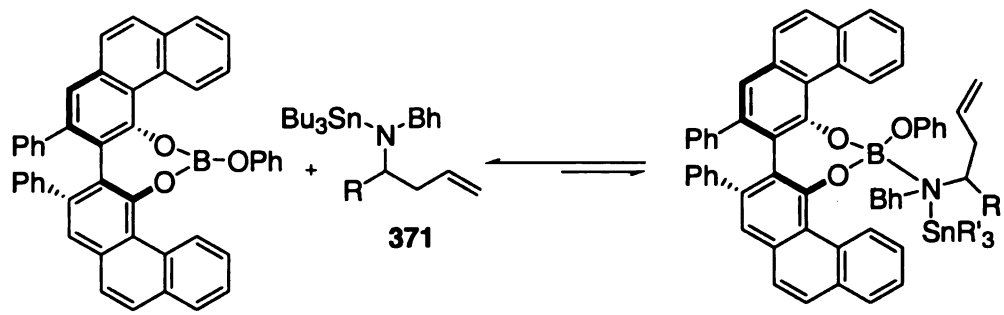
Antilla and Wulff have reported an asymmetric aziridination of imines (obtained from benzhydryl amine and aldehydes) using ethyldiazoacetate and a triphenylborate-(S)-VANOL catalyst.[83] The high asymmetric induction in the aziridination reaction of imines using this $B(OPh)_3$ - (S)-VANOL catalyst inspired the present investigation of this catalyst for asymmetric allylation reaction (Scheme 5.7).

Scheme 5.7 $B(OPh)_3$/(S)-VAPOL catalyst for aziridination reaction



The first and foremost problem that was anticipated for VAPOL - Boron catalyst in asymmetric allylation reaction, was the issue of turnover. However, it could be imagined that the complex between the homoallylic amine **371** and the catalyst **372** would be weak because of steric reasons (Scheme 5.8). If the steric interactions in the catalyst – homoallylic amine complex **373** were great enough they could shift the equilibrium towards the free catalyst **372** which would result in its high turnover.

Scheme 5.8 Boron catalyst for asymmetric allylation



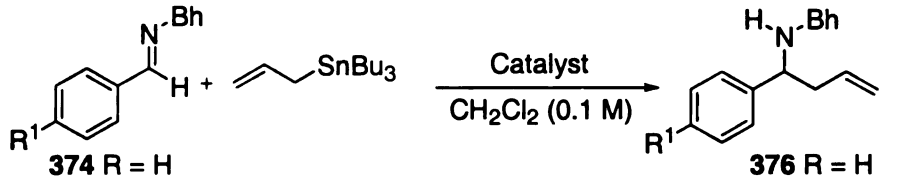
372 **373**

Allylation studies were initiated with the imines **374** and **375** derived from the reaction of benzhydryl amines and benzaldehyde and the more reactive *para*-nitrobenzaldehyde respectively (Scheme 5.9). The allylating agent employed for allylation was allyltributyl stannane. A variety of catalysts were screened which were obtained from the reaction of VAPOL with Lewis acids such as triphenylborate, titanium tetra-isopropoxide, zirconium tetraisopropoxde, bromoborane, diethylaluminum chloride and dichloro-diisopropoxy titanium (IV).

Scheme 5.9 summarizes the catalyst preparation and shows the results of the allylation reactions performed using these catalysts. Both the imines **374** (entry 1, 3, 4, 5, 9, 10, 11, 12, 13) and **375** (entry 2, 6, 7, 8, 9)

showed low conversions and poor enantioselectivities. In order to address the low conversion problem different additives like *i*-PrSMR'$_n$ (MR'$_n$) = $SiMe_3$, BEt_2, $AlEt_2$ were considered. Yu and Coworkers have used additives of the type *i*-PrSMR'$_n$ as synergetic reagents to construct an effective catalytic cycle in the allylation reaction of aldehydes with allyl stannanes catalyzed by BINOL-Ti catalyst.[84] They proposed that the synergetic effect arises from the Sn-S and M-O bond-forming steps which reinforces regeneration of the BINOL-Ti catalyst by producing strong Sn-S and M-O bonds rather than weaker M-S bond. However, the addition of *i*-PrSBEt_2 did not have any effect on the yield or on the enantioselectivity of the allylation reaction with imines (entries **3** and **7**).

Scheme 5.9 Catalyst investigated for asymmetric allylation



374 R = H
375 R = NO_2

376 R = H
377 R = NO_2

Entry	Catalyst Preparation	Reaction Temperature/ Reaction Time	Imine	Conversion (%)	ee (%)
1.	0.2 equiv $B(OPh)_3$ + 0.2 equiv (R)-VANOL	25 °C, 24 h	**374**	No reaction	-
2.	0.2 equiv $B(OPh)_3$ + 0.2 equiv (S)-VANOL	-78 °C, 2 h; 0 °C, 18 h	**375**	16	22.0
3.	0.2 equiv $B(OPh)_3$ + 0.2 equiv (S)-VANOL + 1.1 equiv *i*-PrSBEt$_2$	25 °C, 24 h	**374**	14	2.3
4.	0.2 equiv $H_2BBr.SMe_2$ + 0.2 equiv (S)-VANOL	25 °C, 24 h	**374**	5	-
5.	0.2 equiv Et_2AlCl + 0.2 equiv (S)-VANOL	-78 °C, 2 h; 0 °C, 18 h	**374**	5	-
6.	0.2 equiv Et_2AlCl + 0.2 equiv (S)-VANOL + 0.2 equiv PhOH	25 °C, 24 h	**375**	13	18.7
7.	0.2 equiv Et_2AlCl + 0.2 equiv (S)-VANOL + 0.2 equiv PhOH + 1.1 equiv *i*-PrSBEt$_2$	-78 °C to rt 3 h, rt for 24 h	**375**	4	-
8.	0.2 equiv Et_2AlCl + 0.2 equiv (S)-VANOL + 0.2 equiv AgOTf	-78 °C, 2 h; 0 °C, 18 h	**375**	14	10.9
9.	0.2 equiv Ti(O*i*-Pr)$_4$ + 0.2 equiv (S)-VANOL	-78 °C, 2 h; 25 °C, 18 h	**374/375**	No reaction	-
10.	0.2 equiv $Ti(O$*i*$-Pr)_2Cl_2$ + 0.2 equiv (S)-VANOL + 4 A M. S.	25 °C, 24 h	**374**	No reaction	-
11.	0.2 equiv $Ti(O$*i*$-Pr)_2Cl_2$ + 0.2 equiv (S)-VANOL + 4 A M.S. +0.4 equiv AgOTf	25 °C, 24 h	**374**	50	0
12.	0.2 equiv Zr(O*i*-Pr)$_4$.*i*-PrOH + 0.2 equiv (S)-VANOL	25 °C, 24 h	**374**	No reaction	-
13.	0.2 equiv Zr(O*i*-Pr)$_4$.*i*-PrOH + 0.2 equiv (S)-VANOL + NMI	25 °C, 24 h	**374**	No reaction	-

Unless otherwise specified the reaction was carried out in CH_2Cl_2 (0.1M). Chiralcel OD column was used to determine the enantiomeric excess of amines **376** and **377**.

5.4 Attempted allylation of benzaldimines 378

Attention was then focused on benzaldimines of the type **378** for the allylation reaction (Scheme 5.10). Kobayashi has used this type of imine for allylation reactions but with only specific types of allyl stannanes as mentioned in Section 5.2. The bidendate imine **378** coordinates with the catalyst through the N and O atoms. This restricts the conformation of the imine in the catalyst-imine complex and increases the probability of selectivity control in the reaction.

The preliminary investigations of the allylation of imine **378** with allyltributyl stannane employed chiral Lewis acids derived from $Yb(OTf)_3$, a chiral ligand ((S)-VAPOL, (S)-VANOL, (R)-BINOL), and various amine additives. This class of chiral Lewis acid catalyst system has been developed and implemented by Kobayashi in Diels-Alder reactions,[85] aza Diels-Alder reactions[86] and 1,3-dipolar cycloaddition[87] reactions but not for the allylation reactions.

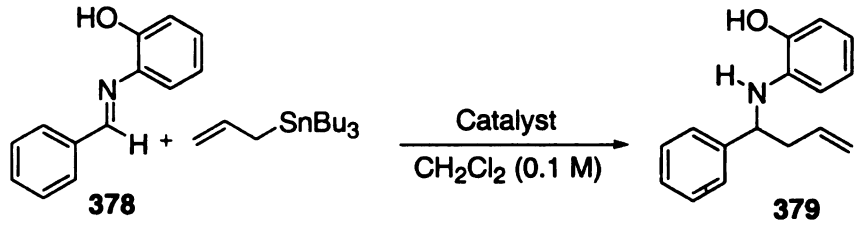
The chiral catalyst for the allylation reaction was prepared using 0.21 equiv of $Yb(OTf)_3$, 0.21 equiv of the bis-phenol ((R)-BINOL, (S)-VANOL and (S)-VAPOL) and 0.42 equiv of DBU (1,8-diazabicyclo[4.3.0]undec-7-ene). In addition to aldimine **378**, allyltributyl stannane **351**, and the chiral catalyst derived from $Yb(OTf)_3$ and DBU, another amine additive DTBMP (2, 6-di-*tert*-butyl-4-methyl pyridine) was used. The yields for the allylation reaction varied from 16 % - 92 % and enantioselectivity of up to 67 % could be obtained as shown in Scheme 5.10.

A comparison of entry 1, entry 14 and entry 15 shows a dependence of the yield and enantioselectivity on the steric bulk of the catalyst. For the catalyst derived from bulky VAPOL ligand, both the yield and enantioselectivity were low

(entry 14). For relatively less sterically hindered BINOL ligand the yield (92 %) was excellent which contrasts with an extremely poor enantioselectivity. The VANOL ligand which falls between VANOL and BINOL in terms of steric bulkiness, afforded both moderate yield and moderate enantioselectivity (entries 1 - 8).

Two factors were varied in an effort to improve the yield and asymmetric induction in the reaction: temperature of the reaction and the different amine additive. Temperature studies revealed that -20 °C is the optimum temperature for the reaction with the VANOL catalyst (entries 5 and 6). At very low temperature (-40 °C) no reaction was observed (entries 7 and 8) and the reaction at room temperature compromised the enantioselectivity of the product (entry 1). Several different amine additives were tested to improve the enantioselectivity of the homoallylic amine and they are DTBMP (2,6-di-tert-butyl-4-methyl pyridine, DBU (1,8-diazabicyclo[4.3.0]undec-7-ene), DBN (1,5-diazabicyclo [4.3.0]non-5-ene), DMP (2,6-dimethylpyridine), NMI (N-methylimidazole) and 2,4,6-collidine. Surprisingly, all these additives failed to give any reaction (entries 9 - 13) with the exception of 2,4,6 collidine (entry 8) which afforded very low yield but moderate enantioselectivity for the reaction.

Scheme 5.10 Ytterbium triflate catalyst for asymmetric allylation



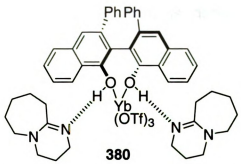
378 **379**

Entry	Catalyst	Amine Additive	Temp (°C) / Time(h)	Yield (%)	ee (%)
1.	$Yb(OTf)_3$ + (S)-VANOL + DBU[a] + 4Å MS, 0 °C, 45 min	DTBMP[b]	25 °C, 8h	56	49.3
2.		DTBMP	0 °C, 3 h 10 °C, 15 h	77	52.0
3.		DTBMP	0 °C, 19 h	46	61.3
4.		DTBMP	0 °C, 40 h	62	62.0
5.		DTBMP	-20 °C, 20 h	46	67.0
6.		DTBMP	-20 °C, 42 h	23	66.0
7.		DTBMP	-40 °C, 21 h	No reaction	-
8.		2,4,6-Collidine	-40 °C to 10 °C, 3 h; 10 °C, 15 h	16	53.0
9.		DBU	"	No reaction	-
10.		PMP[c]	"	"	-
11.		DBN[d]	"	"	-
12.		NMI[e]	"	"	-
13.		DMP[f]	"	"	-
14.	$Yb(OTf)_3$ + (S)-VAPOL + DBU + 4Å M.S., 0 °C, 45 min	DTBMP	25 °C, 8 h	28	5.2
15.	$Yb(OTf)_3$ + (R)-BINOL + DBU + 4Å M.S., 0 °C, 45 min	DTBMP	25 °C, 8 h	92	3.0

In all reactions allyltributyltin **351** : Imine **375** : amine additive were used in the ratio of 2 : 1 : 1. All reactions were performed in dichloromethane (0.1 M). Chiralcel OD column was used to determine the enantiomeric excess of amine **379**. a) DBU = 1,8-diazabicyclo[4.3.0]undec-7-ene, b) DTBMP = 2, 6-di-*tert*-butyl-4-methyl pyridine c) PMP = 1,2,2,6,6-pentamethylpiperidine, d) DBN =1,5-diazabicyclo[4.3.0]non-5-ene, e) NMI =N-methyl imidazole , f) DMP = 2, 6-dimethylpyridine.

The proposed structure **380** of the chiral Yb catalyst shown in Scheme 5.11 is based on a similar structure proposed by Kobayashi for the Diels-Alder reaction with BINOL.[85,87] In the chiral catalyst, (S)-VANOL coordinates with $Yb(OTf)_3$ and two molecule of DBU forms hydrogen bonds with the two phenolic hydrogens of the ligand (S)-VANOL. Thus in this catalyst the axial chirality of (S)-VANOL is transferred via the hydrogen bonds to the amine (DBU).

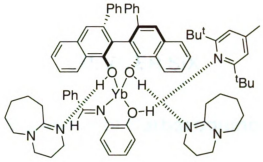
Scheme 5.11 Proposed structure of Yb-VANOL catalyst



380

The proposed structure for the transition state of the catalyst-imine complex **381** is based on a similar structure proposed by Kobayashi for the aza Diels-Alder reaction is shown in Scheme 5.12.[86] The imine **378** acts as a bindendate ligand and its N and O atoms coordinate with the Yb of the catalyst **380**. The amine (DTBMP) additive is believed to form hydrogen bonds with the phenolic hydrogen of the coordinated imine **378**. This restricts the conformation of the imine **378** and results in moderate selectivity. According to the proposed structure, the top face of the imine is shielded by the DBU and the allyltributyl stannane then approach from the bottom face to afford enantiomerically enriched homoallylic amine.

Scheme 5.12 Proposed transition state of the catalyst 380-imine complex



381

In summary, it has been shown that moderate yields and enantioselectivities can be obtained for the allylation reaction of aldimine **378** with allyltributyl stannane using catalyst systems derived from (S)-VANOL, $Yb(OTf)_3$, DBU and DTBMP.

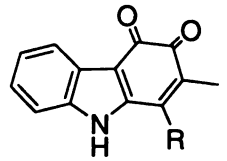
CHAPTER SIX

Total Synthesis of Carbazoquinocin-C: Application of the *ortho*-Benzannulation of Fischer Carbene Complexes to Carbazole 3,4-quinone Alkaloids

6.1 Introduction

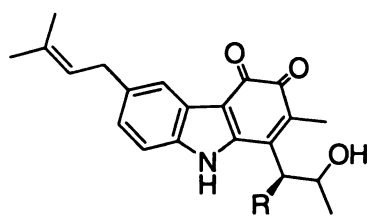
The carbazole-3,4-quinone unit has been found in a number of molecules which have been discovered largely upon screening several microorganims for compounds possessing activity against lipid peroxidation and for those possessing neuronal cell protecting activity.[26] These molecules include carbazoquinocins A-F **65**, carquinostatins A and B **66** and lavanduquinocin **67** (Figure 6.1). The potency of these molecules together with the unique carbazole-3,4-quinone substructure in these molecules have prompted the development of a number of synthetic strategies to this family of natural products.[88] The syntheses reported to date include carbazoquinocins A,[88h] B,[88e] C,[88a-g] D,[88e,h] E-F,[88e] carquinostatin A,[88b,i,j] and lavanduquinocin.[88k,l]

Figure 6.1 Carbazole-3,4-quinone alkaloids

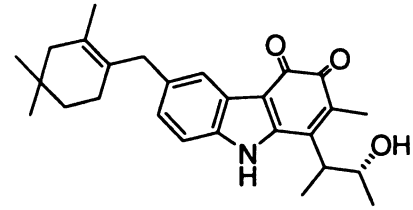


65 Carbazoquinocin A-F

A: $R=(CH_2)_2CHMeCH_2Me$
B: $R=(CH_2)_4CHMe_2$
C: $R=(CH_2)_6Me$
D: $R=(CH_2)_4CHMeCH_2Me$
E: $R=(CH_2)_5CHMe_2$
F: $R=(CH_2)_6CHMe_2$



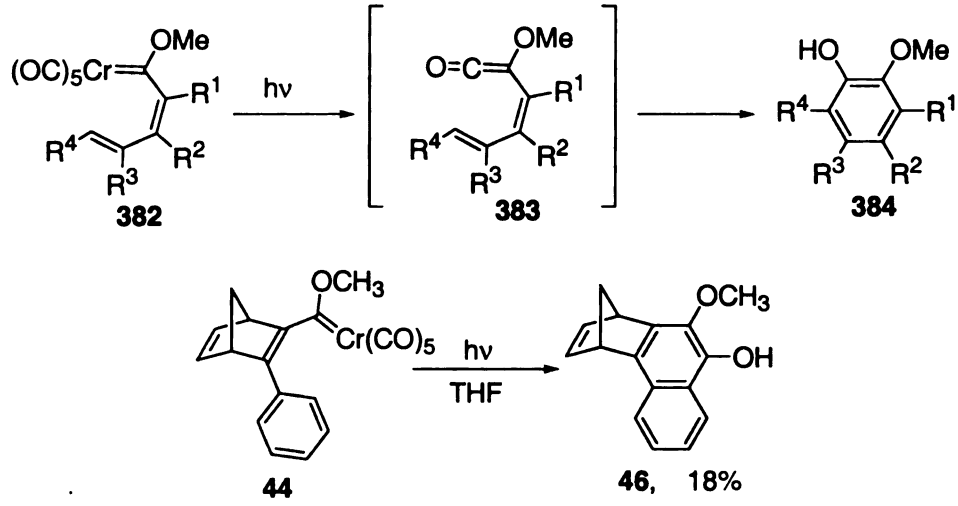
66 Carquinostatin A **A:** R = H **B:** R =OH



67 Lavandoquinocin

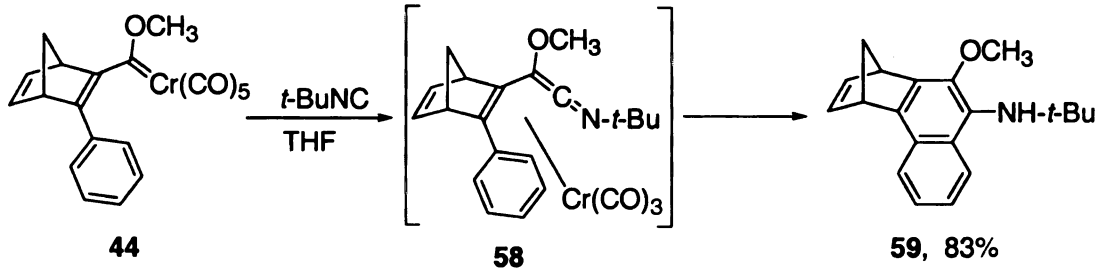
This chapter discusses a unique approach to the synthesis of the carbazole-3,4-quinone alkaloids in which the *ortho*-quinone unit is constructed via an *ortho*-benzannulation reaction of a doubly unsaturated Fischer carbene complex. Inspired by the pioneering work of Hegedus,[17] Wulff and Yang envisioned the possibility of such a reaction that involves the photoinduced coupling of a carbon monoxide ligand and a carbene ligand to give a doubly unsaturated ketene of the type **383** which undergoes electrocyclic ring closure to give an *ortho*-methoxyphenol of type **384** (Scheme 6.1). In 1989, Yang and Wulff reported the first example of *ortho*-benzannulation of carbene complex **44**, which yielded the *ortho*-alkoxyphenol **46** in 18% yield (Scheme 6.1).[20]

Scheme 6.1 Photoinduced *ortho*-benzannulation reaction of 382 via 383



Merlic and coworkers later improved the yield (from 18% to 93%) of this reaction by performing it under a CO atmosphere.[21] Merlic further extended the scope of the reaction by using isoelectronic isocyanides as a surrogate for CO. Thus reaction of complex **44** with *tert*-BuNC yielded *ortho*-alkoxy aniline **59** via dienylketimine complex **58** (Scheme-6.2).[24]

Scheme 6.2 Thermal ortho-benzannulation of 44 via 58



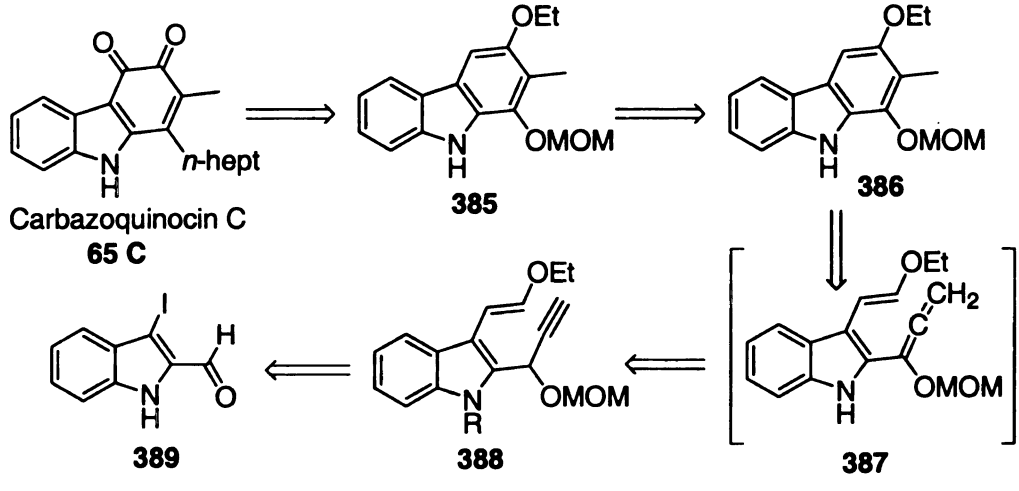
Carbazoquinocin-C **65C** has been targeted to document the application of *ortho*-benzannulation methodology towards carbazole-3,4-quinone alkaloids

(Figure 6.1). The generality of this reaction makes this approach amenable for the synthesis of other members of this family.

6.2 Conventional routes to synthesize carbazoquinocin-C:

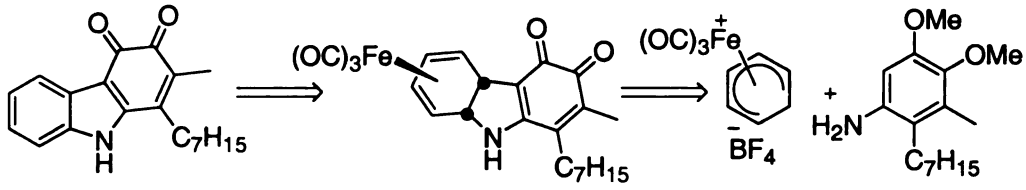
Hibino reported the first total synthesis of carbazoquinocin-C in 1997.[88e] Hibino utilized the electrocyclic ring closure of an *in-situ* generated diene-allene **387** to synthesize the carbazole framework **386** of carbazoquinocin-C (Scheme 6.3). The 3-alkenyl-2-propargyl indole **388** obtained from 3-iodoindole carboxaldehyde **389** was heated in *tert*-BuOH in the presence of potassium *tert*-butoxide to generate allene **387**, which immediately underwent electrocyclization to form carbazole **386**. Carbazole **386** was then converted to carbazoquinocin-C **65C** in seven steps.

Scheme 6.3 Hibino's approach to cabazoquinocin C



Knölker has reported three syntheses of carbazoquinocin-C using the Fe mediated and Pd mediated/catalyzed coupling reactions.[88] In his first approach, carbazole framework **390** was derived from coupling of the η^5-iron complex **391** with the highly functionalized aniline **392** (Scheme 6.4).[88c]

Scheme 6.4 Knölker's approach to cabazoquinocin-C



Carbazaquinocin C
65 C

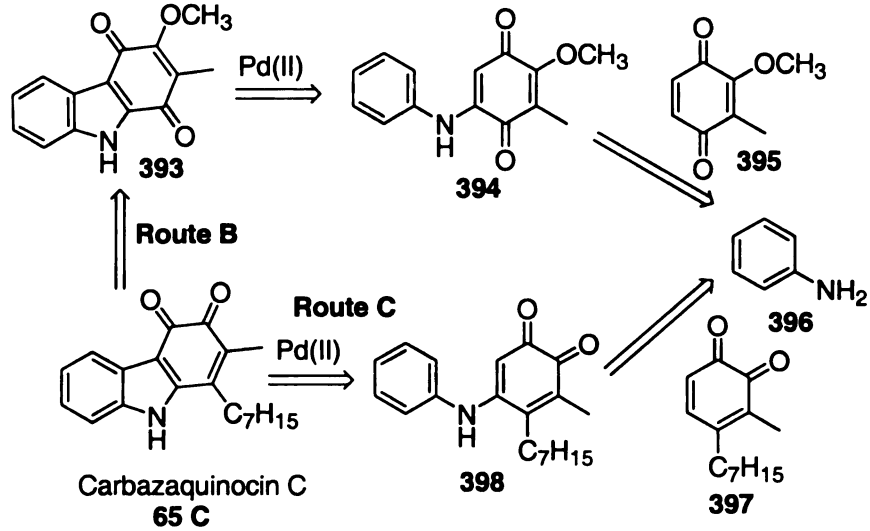
390

391

392

The key step in his second route (Route B) is the palladium-catalyzed oxidative cyclization of N, N-diarylamines **394** derived from aniline **396** and *para*-quinone **395** (Scheme 6.5).[88d] His third route utilizes the palladium-mediated oxidative cyclization of N, N diaryl amine **398** obtained from aniline **396** and *ortho*-quinone **397** (Scheme 6.5).[88b]

Scheme 6.5 Knölker's approach to cabazoquinocin C

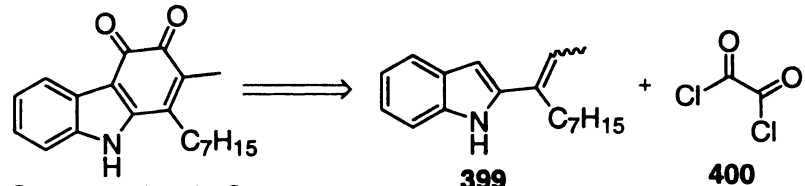


Carbazaquinocin C
65 C

Pindur has synthesized carbazoquinocin-C via $AlCl_3$ mediated cyclization of 2-vinyl indole **399** and oxalyl chloride **400** (Scheme 6.6).[88f,g] Vinyl indole **399** was prepared from the commercially available starting material 1-

(phenylsulfonyl)indole in two steps. This is the most efficient approach for the synthesis of carbazoquinocin-C in comparison to all the approaches described above. The *ortho*-benzannulation approach for the synthesis of carbazoquinocin-C, described in this chapter requires at least five more steps from the vinyl indole of the type **25**. Thus, the *ortho*-benzannulation approach is less effective than Pindur's synthesis of carbazoquinocin-C. Nonetheless, the synthesis described in this chapter documents a useful application of *ortho*-benzannulation approach in the synthesis of carbazole-3,4-quinone alkaloids.

Scheme 6.6 Pindur's approach to cabazoquinocin C

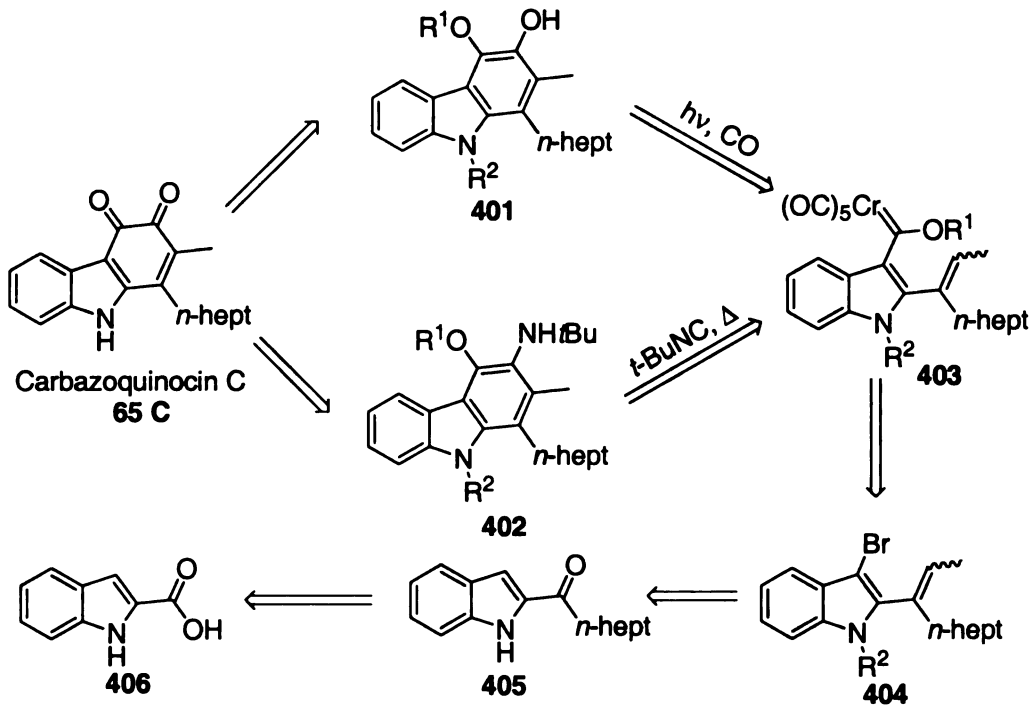


6.3 Synthesis of carbazoquinocin-C

The retrosynthetic synthetic analysis of carbazoquinocin-C that is employed in the present work is outlined in Scheme 6.7. This strategy for the synthesis of carbazoquinocin-C involves the intermediacy of the 3-hydroxy-4-methoxycarbazole **401**, or as an alternative, the 3-amino-4-methoxycarbazole **402** from either of which the natural product can be generated by oxidation of the phenol ring. The key steps in the synthesis are thus to be the photoinduced CO insertion/cyclization and/or the thermally induced *tert*-BuNC insertion/cyclization of the $\alpha,\beta,\gamma,\delta$ -unsaturated carbene complex **403**. It was envisioned that this

3-bromo(2-vinyl)indolylcarbene complex **403** could be prepared from the commercially available indole-2-caboxylic acid **406**. The different N-protecting groups evaluated are TBS, benzyl and the relatively labile PMB group.

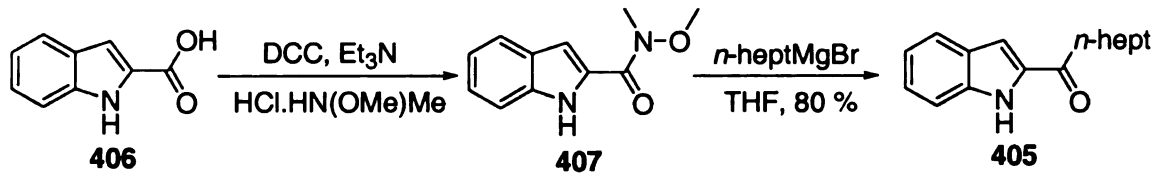
Scheme 6.7 Retrosynthetic analysis of cabazaquinocin C



6.3.1 Synthesis of carbene complexes of the type 403

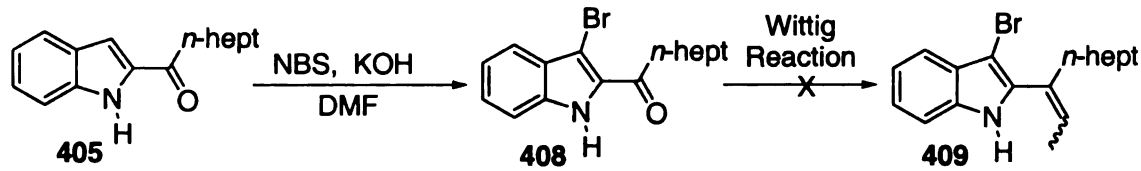
The commercially available indole-2-carboxylic acid **406** was converted to the Weinreb's amide **407** using a reported procedure (Scheme-6.8).[89] Amide **407** upon treatment with heptyl magnesium bromide afforded 1-(1H-indol-2-yl)-octan-1-one **405** in 80 % yield.

Scheme 6.8 Indolyl heptyl ketone 405 from indole-2-carboxylic acid 406



The conversion of **405** to protected indole of the type **404** (Scheme 6.7) requires N-protection, olefination, and bromination and considerable time was spent investigating the optimal order of these steps. Bromination of indole **405** was successful to give 3-bromoindole **408** but all attempts to carryout a Wittig reaction on this substrate failed (Scheme 6.9).

Scheme 6.9 Vinyl indole 409 from indole heptyl ketone 405

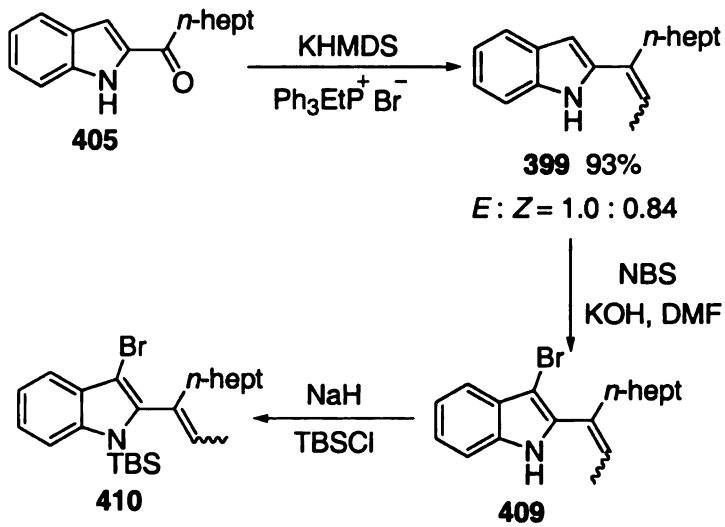


Entry	Equiv	Reagent	Time (h)	Temperature (°C)	Result
1	2.4	Et_3PPh_3Br, *n*-BuLi, THF	4	25	Starting material observed
2.	"	"	4	80	Low conversion
3.	1.2	Et_3PPh_3Br, KHMDS, THF	24	25	Starting material observed
4.	2.4	"	24	25	Starting material observed
5.	5	"	24	25	Low conversion

Unless otherwise specified all reactions were carried out in THF solvent (0.1M) at 25 °C.

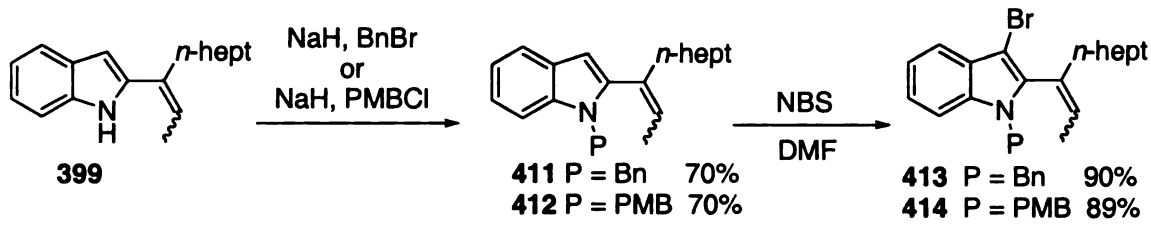
In contrast, the olefination of ketone **405** proceeded smoothly to give the 2-vinyl indole **399** in 93% yield as a 1.0 : 0.84 mixture of E/Z isomers (Scheme 6.10). The bromination of **399** was successful; however, the resulting 3-bromoindole **409** is not particularly stable. Immediate treatment with NaH and TBSCl gave the stable N-silylated indole **410** in 45 % yield for two steps.

Scheme 6.10 Synthesis of carbene complex precursor 410



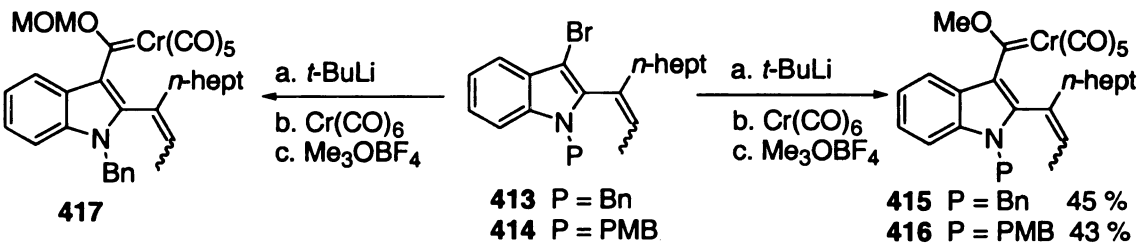
Given the instability of bromoindole **409**, the reverse of the bromination/protection sequence was investigated and found to be far more practical. The 2-vinylindole **399** was first protected either as the N-benzyl- or N-*para*-methoxybenzyl derivatives **411** and **412** in 70 % and 72 % yield, respectively (Scheme 6.11). Bromination gave the carbene precursors **413** and **414** in excellent yields.

Scheme 6.11 Synthesis of carbene complex precursors 413 and 414



Carbene complexes **415** – **417** were prepared by the standard Fischer procedure in moderate yields. These complexes were usually obtained with a small amount (5 - 10 %) of a side product resulting from the reduction of the bromide in the precursors **413** and **414** (Scheme 6.12). These reduced products were not easily separated from the carbene complexes and thus were carried to the next step in those cases where they could be removed. The yields for the carbene complexes **415** - **416** have the amount of the reduced products factored out. The TBS-protected indole **410** could not be converted to the corresponding carbene complex. The only observable product was the 3-unsubstituted indole resulting from reduction of the bromide in **410**.

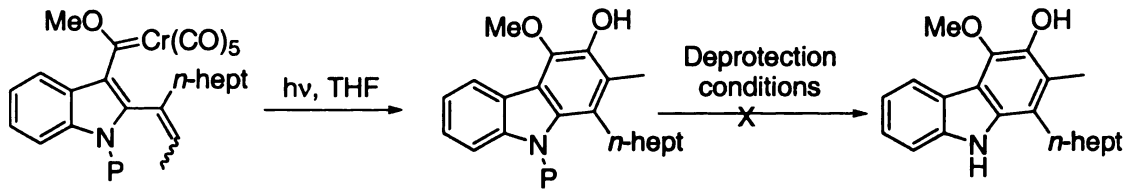
Scheme 6.12 Synthesis of carbene complexes 415, 416 and 417



6.3.2 Photoinduced route to cabazoquinocin C

Although the *ortho*-benzannulation of certain electron-rich complexes has been reported to fail,[23] the photolysis of 3-indolyl carbene complexes **415** and **416** under an atmosphere of carbon monoxide gave the carbazoles **418** and **419** in 65 % and 62 % yields respectively (Scheme 6.13).[90] All that remains to complete the synthesis of carbazoquinocin-C is the adjustment of the oxidation state and deprotection of the indole nitrogen. Deprotection of the N-benzylindole **418** was resistant to initial efforts. Hydrogenation with palladium on carbon led to over-reduced products. Deprotection with $AlCl_3$[91] or with sodium thioethoxide[92] lead to the destruction of the starting material. In an attempt to remove the relatively labile protecting group carbazole **419**, it was heated with TFA and DMB which resulted in no reaction and only the recovery of starting material was observed (entry 11).[93] DDQ oxidation of carbazole **419** in toluene showed a mixture of starting material and the corresponding quinone and no PMB deprotection was observed (entry 12 and 13).[93]

Scheme 6.13 Photoinduced *ortho*-benzannulation of 41 and 42



415 P = Bn
416 P = PMB

418 P = Bn 65%
419 P = PMB 62%

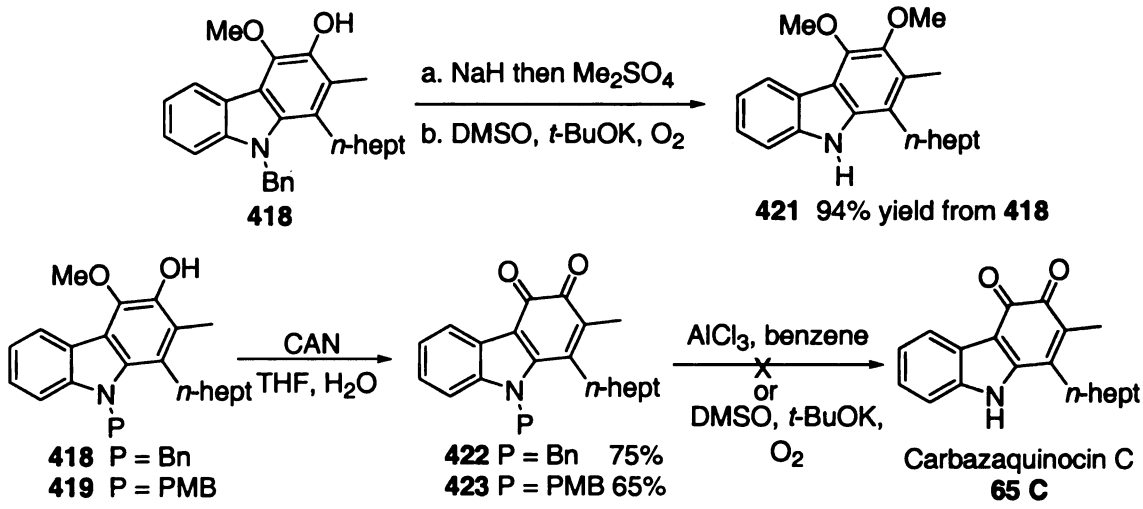
420

Entry	P	Deprotection Conditions	Temp. (°C)	Time (h)	Result
1.	Bn	H_2, Pd/activated C, MeOH	25	12	Starting material Recovered
2.	Bn	"	80	5	"
3.	Bn	H_2, Pd/activated C, MeOH and AcOH	35	12	"
4.	Bn	H_2, Pd on charcoal, AcOH, $HClO_4$	25	15	Over reduction[a]
5.	Bn	"	25	3	"
6.	Bn	H_2, Pd on charcoal, AcOH	25	3	"
7.	Bn	$AlCl_3$, Benzene	25	0.5	Decomposition observed
8.	Bn	$AlCl_3$, Benzene	0	0.5	"
9.	Bn	NaSEt, DMF	120	12	"
10.	Bn	DMSO, *t*-BuOK, O_2	25	0.5	"
11.	PMB	TFA, H_2O DMB,CH_2Cl_2	45	0.5	Starting material recovered
12.	PMB	DDQ (2.5 eq.), Toluene	50	0.5	Starting material and **423** observed
13.	PMB	DDQ (2.5 eq.), Toluene	80	0.5	"

a. Along with the deprotection the reduction of the benzene ring was also observed.

Deprotection of 418 was only achieved when the phenol function was derivatized as its methyl ether. Benzyl cleavage could then be achieved with potassium *tert*-butoxide in DMSO in the presence of oxygen to give the dimethyl ether 421 in 94 % yield for two steps (Scheme 6.14).[94] The reverse of this sequence did not prove to be viable. The oxidation of 418 and 419 with CAN gave the corresponding *ortho*-quinones 422 and 423 in good yields. Attempts to remove the benzyl group in 422 using $AlCl_3$ and DMSO/*t*-BuOK met with failure presumably due to the sensitivity of the carbazaquionocin C natural product (Scheme 6.14).

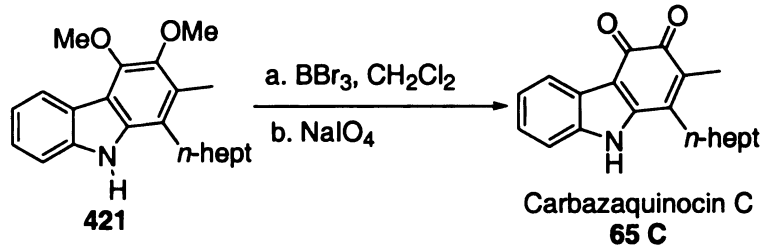
Scheme 6.14 Debenzylation of 418 and 419



Finally, the conversion of the 3,4-dimethoxycarbazole **421** to carbazoquinocin-C was achieved in a two-step process. The direct oxidation of **421** to the natural product with CAN did not give a clean conversion. Following the protocol introduced by Knölker,[88c] this transformation was achieved in two

steps beginning with the cleavage of the methyl ethers with borontribromide. Knölker reported that the resulting hydroquinone would readily undergo oxidation in air to give carbazoquinocin-C. Our finding is that this air oxidation is not clean and gives other products in addition to the natural product. Silver oxide gives a mixture of products that is very similar to that observed upon air oxidation. Carbazoquinocin-C binds tightly to silica gel, and attempts to purify the natural product by silica gel chromatography result in substantial loss of material. Thus, we decided to look for oxidizing agents that would give clean conversion of the hydroquinone and such a condition was found with sodium *meta*-periodate. Simple filtration of the crude reaction mixture through Celite and removal of solvent gave carbazoquinocin-C that was pure by ^{1}H and ^{13}C NMR and had a melting point identical to that reported for the natural product (Scheme 6.15).

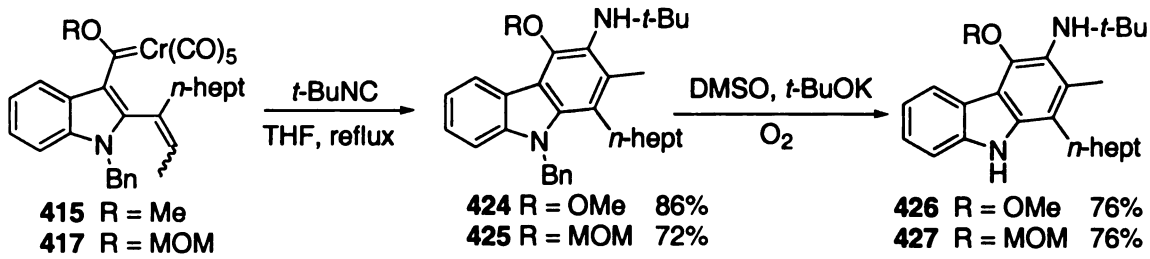
Scheme 6.15 Demethylation and oxidation of 421 to carbazoquinocin-C



6.3.3 Thermal *ortho*-benzannulation route to carbazoquinocin-C

The reaction of carbene complex **415** with *tert*-butylisonitrile in refluxing THF gave the 3-aminocarbazole **424** in 86% yield (Scheme 6.16).[24] This could be readily debenzylated with *tert*-butoxide in DMSO to give **426** in good yield.

Scheme 6.16 Thermal *ortho*-benzannulation of 415 and 417



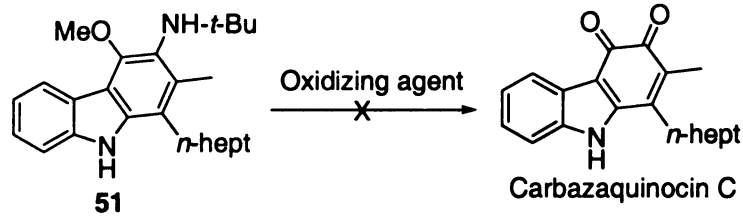
415 R = Me
417 R = MOM

424 R = OMe 86%
425 R = MOM 72%

426 R = OMe 76%
427 R = MOM 76%

Considerable effort was extended to directly oxidize **426** to carbazoquinocin-C but all was to no avail. Compound **426** was resistant to reaction with sodium *meta*-periodate and other oxidizing agents including DDQ, CAN, $KMnO_4$, $Pb(OAc)_4$, Ag_2O, and $FeCl_3$ led to complex mixtures of products (Scheme 6.17).

Scheme 6.17 Oxidation of 426 to carbazoquinocin-C



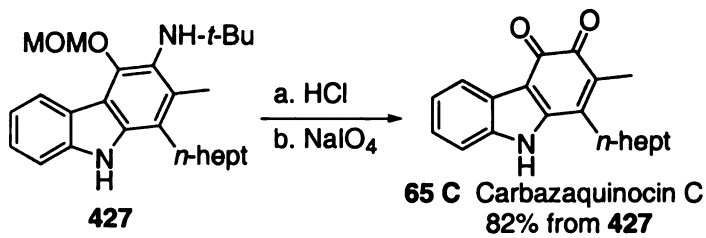
51 Carbazaquinocin C

Entry	Reaction conditions	Result
1.	$NaIO_4$, CH_2Cl_2, H_2O	Starting material recovered
2.	DDQ (2.5eq), CH_2Cl_2, rt	Decomposition of starting material
3.	CAN (2.5eq), THF/H_2O, rt	Decompositon of starting material
4.	$KMnO_4$, $CaSO_4.2H_2O$, H_2O *t*-BuOH, rt	Decomposition of starting material
5.	$KMnO_4$, CH_2Cl_2, Adogen 464, AcOH, rt	Decomposition of starting material
6.	$Pb(OAc)_4$, MeOH, AcOH, rt	Decomposition of starting material
7.	Ag_2O, MeOH, AcOH, rt	Decomposition of starting material
8.	$FeCl_3$, CH_2Cl_2, rt	Decomposition of starting material
9.	48 % HBr, CH_3CO_2H, 115 °C	Complex mixture observed
10.	CF_3COOH, CH_2Cl_2, reflux	Starting material recovered
11.	BBr_3, CH_2Cl_2, -75 °C to 25 °C	Starting material + side products observed

Given the success in oxidation of the hydroquinone derived from **421** with sodium *meta*-periodate (Scheme 6.15), attempt was made to remove the methyl ether in **426** by treatment with BBr_3 but this led to the formation of unidentified

products. Final success began with the preparation of the MOM-protected carbene complex **417**. This complex reacted with *tert*-butylisonitrile to give the carbazole **425** in 72 % yield, this compound could be debenzylated to give **427** in 76 % yield (Scheme 6.16). The MOM group could be cleaved in intermediate **427** with HCl, and the resulting *ortho*-aminophenol could be oxidized with sodium *meta*-periodate to give carbazoquinocin-C in 82 % yield for the last two steps (Scheme 6.18).

Scheme 6.18 Conversion of 427 to carbazoquinocin-C



In conclusion, this chapter describes the successful synthesis of Fischer indole carbene complexes **415** and **417** and their application to the synthesis of carbazoquinocin-C via the photochemical *ortho*-benzannulation with carbon monoxide and also by the thermal *ortho*-benzannulation with isonitriles. An improved method for the oxidation of the hydroquinone of the natural product carbazoquinocin-C has also been developed.

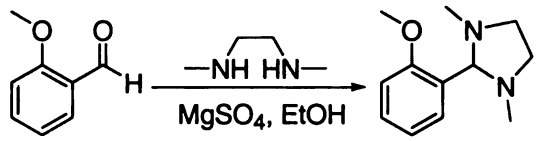
CHAPTER SEVEN

EXPERIMETAL SECTION

General Information

Unless and otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. Prior to use, tetrahydrofuran and diethyl ether were distilled from Na/benzophenone ketyl, toluene was distilled from Na and methylene chloride was prepared by distillation from calcium hydride. Routine NMR spectra were recorded on 300MHz, 500MHz INOVA and VXR instruments. Both low and high resolution massspectra were obtained from the Michigan State University Mass Spectrometry Facility. Elemental analyses were done by the Michigan State University Elemental Analysis Facility.

Synthesis of imidazolidine (161)



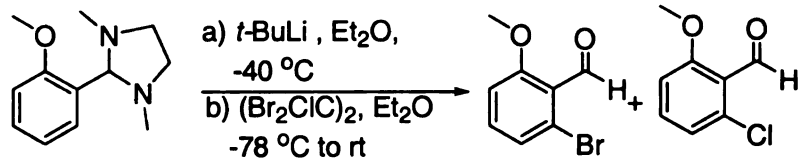
160 **161** 77% yield

To a stirred solution of *ortho*-anisaldehyde **160** (6.67 gm, 49.3 mmol) in EtOH (200 mL) was added N,N-dimethylethylenediamine (5.27 gm, 60 mmol) dropwise. The reaction mixture was stirred at room temperature for 24 h followed by filtration through a pad of $MgSO_4$ and washing by ether. The ether/ethanol

solution was concentrated in vacuo and the product was purified by crystallization from hexane to afford the 7.65 gm of imidazolidinone **161** as white crystalline solid.

Spectral data for **161**: Mp 40 - 42 °C (lit[48] 41 - 42 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 6 H), 2.54-2.60 (m, 4 H), 3.80 (s, 3 H), 4.01 (s, 1 H), 6.87 (dd, 1 H, J = 1.0, 8.4 Hz), 6.95 (dt, J=7.4, 0.9 Hz), 7.21 (m, 1 H), 7.65 (dd, 1 H, J = 1.9, 7.4 Hz).

Synthesis of anisaldehyde (162)

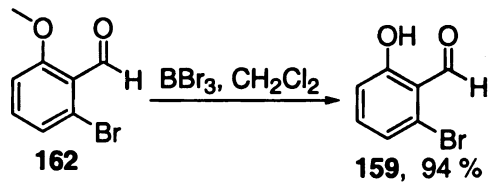


To a stirred solution of **161** (9.05 gm, 43.8 mmol) in 350 mL ether at -40 °C was added *tert*-BuLi (52 mL, 87.6 mmol, 1.7 M solution in pentane) over 1 h. The reaction mixture was warmed to -20 °C and stirred at this temperature for 7 h then the reaction mixture was cooled to -78 °C and transferred by Cannula to a solution of $(BrCl_2C)_2$ (29 mg, 87.6 mmol) in 150 mL Et_2O at 0 °C over 1h. The reaction mixture was warmed to room temperature over 2 h and then the mixture was stirred at this temperature for 12 h. The reaction was then quenched carefully with 2 N HCl (750 mL) and stirred at room temperature for 1 h. This was followed by extraction of the water layer with 4 x 200 mL CH_2Cl_2. The CH_2Cl_2 layer was washed with 200 mL of a saturated solution of ammonium chloride solution. The water layer was then back extracted with 3 x 100 mL dichloromethane. The combined organic layer was dried and concentrated in

vacuo. The product was purified by silica gel column chromatography using (20 % to 40 %) EtOAc : hexane to give 6.5 gm of a mixture of **162** and **163** in the ratio of 50 : 1 (**162** : **163**) as off-white solid. When the reaction was run at 25 °C a 2 : 1 mixture of **162** and **163** obtained. The structure of **162** was assigned by comparison of the reported ^{1}H NMR spectrum and M.P. The structure of **163** was tentatively assigned by the presence of peaks at δ = 10.36 in the crude ^{1}H NMR spectrum and by two a peak at m/z = 170 and 172 in a 3 : 1 ratio in the mass spectrum.

Spectral data for **162**: Mp = 56 - 58 °C (lit[48] 57 - 58 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H), 6.92 (d, 1 H, J = 8.2 Hz), 7.21 (d, 1 H, J = 8.5 Hz), 7.30 (t, 1 H, J = 8.3 Hz), 10.39 (s, 1 H).

Synthesis of salicaldehyde (159)

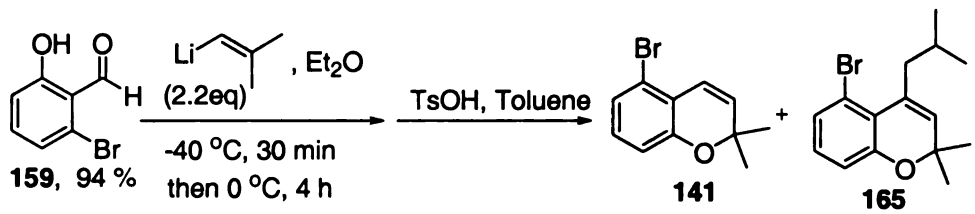


162 **159**, 94 %

To a stirred solution of **162** (6.5 gm, 30 mmol) in 50 mL CH_2Cl_2 was added 40 mL of BBr_3 (1.0 M solution in CH_2Cl_2) dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 30 min before quenching with 20 mL of water. The organic layer was separated and the aqueous layer was extracted with 2x50 mL of CH_2Cl_2. The organic layer was dried over $MgSO_4$, concentrated in vacuo and purified by silica gel column chromatography using ether / hexane (1 / 10) eluent to give bromosalicaldehyde **159** (94 % yield) as light green solid.

Spectral data for **159**: Mp = 50 - 52 °C (lit[95] 51 - 52 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (d, 1 H, J = 8.3 Hz), 7.13 (dd, 1 H, J = 1.0, 7.8 Hz), 7.30 (t, 1 H, J = 8.3 Hz) 10.30 (s, 1 H), 11.95 (s, 1 H).

Synthesis of bromochromene (141)



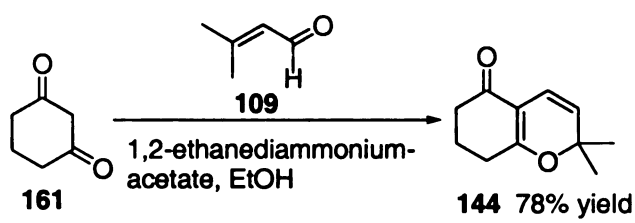
141 : **165** = 40 : 1, 60 % yield

To a stirred solution of 1-bromo-2-methyl-penten-1-ene (3.87 gm, 28.67 mmol) in 100 mL ether at -78 °C was added *tert*-BuLi (34 mL, 57.34 mmol) over 15 min. After stirring for 30 min, the reaction mixture was transferred by cannula to a solution of **159** (2.62 gm, 13.03 mmol) in 100 mL ether at -78 °C. The solution was stirred at -78 °C for 2 h and slowly warmed to room temperature. The stirring was continued at room temperature for another 16 h. After 16 h, the reaction was quenched by careful addition of 20 mL water and 20 mL saturated ammonium chloride solution. The water layer was extracted with 3 x 30 mL ether. The organic layer was then washed with 20 x 2 mL of brine, dried over $MgSO_4$ and concentrated in vacuo to give a light green oil. The crude compound so obtained was dissolved in toluene and TsOH (50 mg) was added. The reaction mixture was heated to 50 °C for 1 h. After 1 h, the reaction mixture was filtered through Celite, concentrated in vacuo and purified by silica gel column chromatography using (1 %) EtOAc : hexane solvent system. This gave a mixture of compounds **141** and **165** in the ratio of 5 : 1 (**141** : **165**) along with a

small amount of an unidentified impurity. Further purification was done using Kugelrohr distillation which afforded a 60 % yield of bromochromene **141** and **165** in the ratio (**141** : **165**) of 40 : 1 as colorless liquid (GC). The structure of **165** was tentatively assigned by two peaks at m/z = 294 and 296 in a 100 : 98 ratio in the mass spectrum.

Spectral data for **141**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 6 H), 5.68 (d, 1 H, J = 10.0 Hz), 6.62 (d, 1H, J = 6.62 Hz), 6.70 (d, 1 H, J = 9.0), 6.92 (t, 1 H, J = 8.1 Hz), 7.06 (dd, 1 H, J = 1.1, 8.0 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 127.72, 76.29, 115.80, 121.12, 121.14, 121.42, 124.711, 129.44, 132.18, 154.10; Mass spectrum (EI) *m/z* (% rel. int.) 240 (8, ^{81}Br), 238 (9, ^{79}Br), 226 (12, ^{81}Br), 224 (18, ^{79}Br), 225 (100, ^{81}Br), 223 (83, ^{79}Br), 144 (17, ^{81}Br), 115 (12, ^{79}Br).); IR (neat) 3056, 2976, 2926, 1558, 1444 cm^{-1}; Anal. calcd. for $C_{11}H_{11}BrO$: C, 55.25; H, 4.64. Found: C, 55.52; H, 4.72.

Synthesis of chromenone (144)

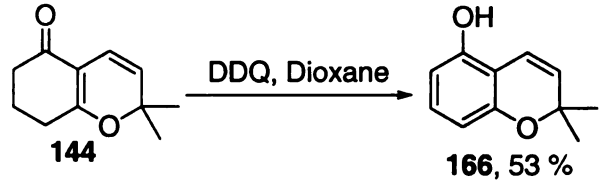


To a stirred solution of cyclohexane-1,3-dione **161** (24.1 gm, 215 mmol) and 1,2-ethanediammoniumacetate in methanol (300 mL) was added 3-methyl-but-2-enal (18.11 gm, 215 mmol) over a duration of 5 h. The reaction mixture was then stirred for 24 h at room temperature. After 24 h, the reaction mixture was diluted with 500 mL ether and washed with 50 mL water and 50 mL brine. The water layer was extracted with 2 X 50 mL ether. The combined organic layer was dried

over $MgSO_4$ and concentrated in vacuo. The product was purified by silica gel column chromatography using ether : hexanes (1 : 7) as eluent to give 30.5 gm of chromenone **144** (78 %) yield.

Spectral data for **144**: Mp = 40 - 42 °C (lit[49b] 40 - 41 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66 (s, 6 H), 1.85-1.95 (m, 2 H), 2.26-2.36 (m, 4 H), 5.17 (d, 1 H, J = 9.3 Hz), 6.34 (d, 1 H, J = 9.8 H).

Synthesis of chromenol (166)

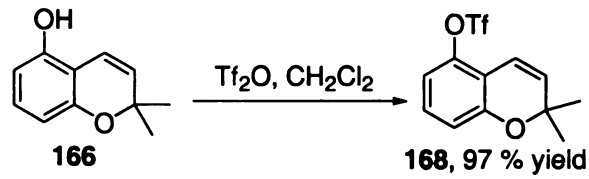


144 **166**, 53 %

To a stirred solution of chromenone **144** (3.36 gm, 18.8 mmol) in 230 mL dioxane was added a solution of DDQ (8.96 gm, 39.5 mmol) in 60 mL dioxane. The reaction mixture was stirred at room temperature for 3h and then heated to 110 °C for 42 h. After 42 h, the reaction mixture was cooled to room temperature and filtered through Celite, concentrated in vacuo and the residue was purified by silica gel column chromatography using a gradient of 1 % to 5 % of EtOAc in hexane eluent. The yellow solid so obtained was then recrystallized with ether to afford chromenol **166** as yellow crystalline solid in 53 % yield.

Spectral data for **166**: Mp = 113 - 115 °C; (lit[49c] 114 - 116 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 6 H), 4.83 (s, 1 H), 5.58 (d, 1 H, J = 9.7 Hz), 6.28 (d, 1 H, J = 8.3 Hz), 6.40 (d, 1 H, J = 8.8 Hz), 6.61 (d, 1 H, J = 10.2 Hz), 6.92 (t, 1 H, J = 7.8 Hz).

Synthesis of chromene triflate (168)

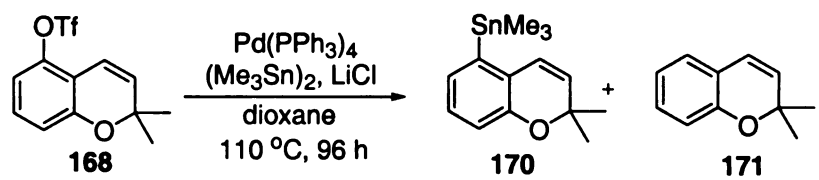


166 **168**, 97 % yield

To a stirred solution of **166** (200 mg, 1.13 mmol) in 10 mL CH_2Cl_2 at 0 °C was added diisopropylethyl amine (235 μL, 1.35 mmol) and Tf_2O (208 μL, 1.13 mmol). The reaction mixture was stirred at 0 °C for 2 h. After 2 h, the reaction mixture was concentrated in vacuo, purified by silica gel column chromatography using 5 % EtOAc : hexane solvent system to give compound **168** (324 mg, 93 % yield) as colorless oil.

Spectral data for **168**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 6 H), 5.76 (d, 1 H, J = 8.2 Hz), 6.51 (d, 1 H, J = 9.7 Hz), 6.78 (d, 2 H, J = 7.8 Hz), 7.11 (t, 1 H, J = 8.3 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 27.71, 76.72, 113.28, 115.01, 115.17, 116.48, 118.62 (q, J = 319 Hz), 129.04, 132.99, 145.17, 154.31. IR (neat) 2980, 2937, 1637, 1616, 1568 cm^{-1}; Mass spectrum (FAB) *m/z* (% rel. int.) 308 (M^+) (5), 293 (24), 256 (5), 161 (13), 160 (100), 159 (17), 132 (13); Anal. calcd. for $C_{12}H_{11}F_3O_4S$: C, 46.75; H, 3.60. Found: C, 46.52; H, 3.35.

Synthesis of chromene stannane (170)



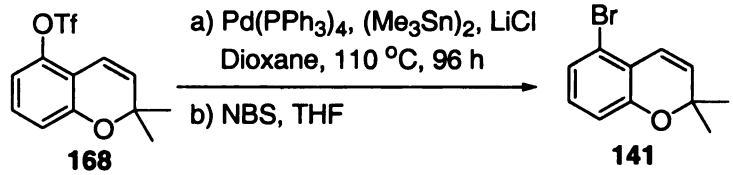
168 **170** **171**

To a mixture of hexamethylditin (675 mg, 2.17 mmol), $Pd(PPh_3)_4$ (50 mg, 0.04 mmol) dppf (54 mg, 0.10 mmol) and LiCl (552 mg, 13.02 mmol) was added a

solution of compound **168** (670 mg, 2.17 mmol) in 15 mL dioxane. The solution was deoxygenated using the freeze-thaw method (-196 to 25 °C, 3 cycles). The reaction mixture was then stirred at 110 °C for 3 days. After 3 days, the reaction mixture was filtered through Celite and washed using hexane. The solvent was then concentrated in vacuo to give a mixture of compounds which consisted of **170** and **171** (84 : 7) along with triphenyl phosphine and small amounts of other impurities. This mixture was loaded onto silica gel column and eluted with and hexane and EtOAc (20 : 1) to give a mixture of compounds but with the amounts of **170** and **171** enhanced and in the same ratio. The following ^{1}H NMR data for **170** was extracted from the ^{1}H NMR spectrum of the mixture

Spectral data for **170**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.30 (s, 9 H), 1.41 (s, 6 H), 5.61 (d, 1 H, J = 9.6 Hz), 6.28 (s, 1 H, J = 9.0 Hz), 6.74 (dd, 1 H, J = 0.5, 8.0 Hz), 6.94 (dd, 1 H, J = 0.6, 7.2 Hz), 7.06 (t, 1 H, J = 7.4 Hz).

Synthesis of bromochromene (141)



168 **141**

To a mixture of hexamethylditin (675 mg, 2.17 mmol), $Pd(PPh_3)_4$ (50 mg, 0.04 mmol), dppf (54 mg, 0.10 mmol) and LiCl (552 mg, 13.02 mmol) was added solution of compound **168** (670 mg, 2.17 mmol) in 15 mL dioxane. The solution was deoxygenated using freeze-thaw method (-196 to 25 °C, 3 cycles). The reaction mixture was then stirred at 110 °C for 3 days. After 3 days, the reaction mixture was filtered through Celite and washed using hexane. The solvent was

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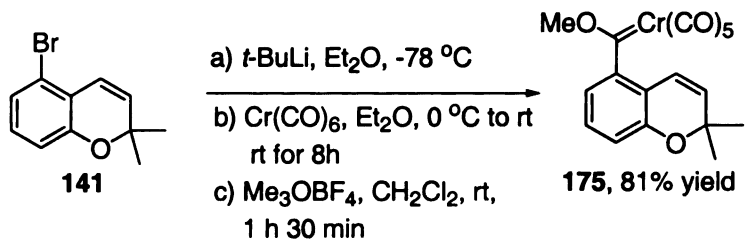
then evaporated using rotary evaporater to give an oily residue, which was again dissolved in THF and solid NBS (579 mg, 3.25 mmol) was added. After stirring for 1 h at room temperature, the reaction mixture was concentrated in vacuo and purified by flash silica gel column chromatography (5 %) ether : pentane to give 5-bromo chromene **141** as colorless oil in 75 % yield. The compound from this reaction had spectral data identical with that reported above.

Synthesis of chromene carbene complex (175)

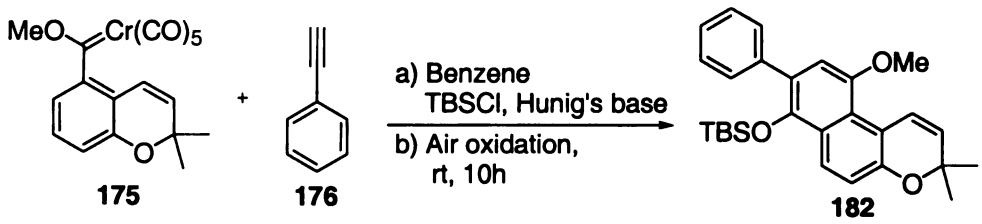


To a flame-dried 100 mL round-bottomed flask containing a solution of bromochromene **141** (1.310 gm, 5.5 mmol) in ether (25 mL) at -78 °C was added *ter* BuLi (6.5 mL, 11 mmol, 1.7 M solution in pentane). The reaction mixture was warmed to 0 °C, stirred at this temperature for 5 min and cooled to -78 °C before it was transferred by cannula to a suspension of $Cr(CO)_6$ (1.32 gm, 6.0 mmol) in 15 mL ether maintained at 0 °C. The reaction mixture turned dark red in 5 min. Stirring was continued for 6 h at room temperature which was followed by removal of ether under vacuum and addition of 10 mL dichloromethane. Me_3OBF_4 (1.63 gm, 11 mmol) was then added at room temperature and reaction was further stirred for 2 h. The reaction mixture was then filtered through Celite and concentrated in vacuo. The product was purified by silica gel column

chromatography using EtOAc : hexane (5 %) to give 1.75 gm (81 % yield) of carbene complex **175** as red crystalline solid.

Spectral data for **175**: Mp = 95 - 97 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 6 H), 4.18 (s, 3 H), 5.56 (d, 1 H, J = 10.2 Hz), 5.96 (d, 1 H, J = 10.0 Hz), 6.37 (d, 1 H, J = 7.70 Hz), 6.70 (dd, 1 H, 0.9, 8.3 Hz), 7.14 (t, 1 H, J = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.63, 65.66, 76.16, 110.98, 112.93, 116.38, 118.17, 129.06, 132.68, 152.88, 215.85, 224.60, 357.52, one sp^2 C not located; IR (neat) 2980, 2064, 1934, 1566, 1442 cm^{-1}; Mass spectrum (FAB) *m/z* (% rel. int.) 394 M^+, 366 (82), 310 (78), 282 (100), 254 (70), 203 (25); Anal. calcd. for $C_{18}H_{14}CrO_7$: C, 54.83; H, 3.58. Found: C, 54.53; H, 3.41.

Synthesis of naphthol pyran (182)



To a flame-dried 25 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added chromene carbene complex **175** (100 mg, 0.254 mmol), 5 mL benzene, phenyl acetylene **176** (56 μL, 0.508 mmol), TBSCl (115 mg, 0.762 mmol) and N,N-diisopropylethylamine (55 μL, 1.270 mmol). The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The reaction mixture was then stirred at 50 °C for 24 h and then at room temperature for another 24 h. The reaction mixture was opened to air and allowed to stir for

12 h. The reaction mixture was filtered through Celite, concentrated in vacuo and the product was purified by silica gel column chromatography using (5 %) EtOAc and hexanes to give naphthopyran **182** (31 mg) in 27 % yield as a colorless liquid.

Spectral data for **182**: ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.41 (s, 6 H), 0.97 (s, 9 H), 1.47 (s, 6 H), 3. 92 (s, 3 H), 5.58, (d, 1 H, J = 10.2 Hz), 6.83 (s, 1 H), 7.04 (d, 1 H, J = 9.1 Hz), 7.27-7.34 (m, 1 H), 7.40 (t, 2 H, J = 7.8Hz), 7.63 (dd, 2 H, J = 1.4, 7.2 Hz), 7.76 (d, 1 H, J = 10.2 Hz), 7.98 (d, 1 H, J = 9.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.36, 18.45, 26.08, 27.86, 55.85, 74.72, 109.75, 114.40, 118.14, 122.47, 123.32, 124.61, 125.19, 125.89, 126.66, 127.11, 128.11, 130.25, 140.16, 142.01, 151.57, 151.92; IR (neat) 2955, 2930, 2856, 1452, 1381 cm^{-1}; Mass spectrum (EI) *m/z* (% rel. int.) 447 M^+ + 1 (16), 446 M^+ (9), 422 (27), 432 (100), 417 (6), 390 (3); Anal. calcd. for $C_{28}H_{34}O_3Si$: C, 75.29; H, 7.67. Found: C, 74.99; H, 7.40.

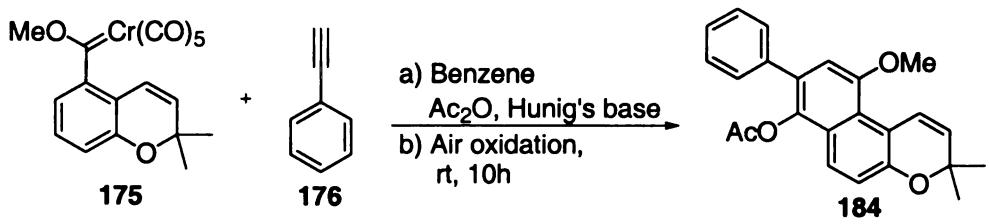
Synthesis of naphtholpyran (183)

175 **176** **183**

To a flame-dried 10 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added chromene carbene complex **175** (25 mg, 0.063 mmol), 1.2 mL benzene, phenyl acetylene (14 μL, 0.126 mmol), TMSCl (24 μL, 0.189 mmol) and N,N-diisopropylethylamine (55 μL, 0.315 mmol). The

system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The reaction mixture was then stirred at 50 °C for 24 h and then at room temperature for another 24 h. The reaction mixture was opened to air and allowed to stir for 12 h. The reaction mixture was filtered through Celite, concentrated in vacuo and the product was purified by silica gel column chromatography using (5 %) EtOAc : hexanes to give naphthopyran **183** (16.5 mg) in 65 % yield as colorless liquid. Spectral data for **183**: ^{1}H NMR (500 MHz, $CDCl_3$) δ - 0.16 (s, 9 H), 1.47 (s, 6 H), 3.91 (s, 3 H), 5.58 (d, 1 H, J = 10.1 Hz), 6.79 (s, 1 H), 7.04 (d, 1 H, J = 9.6 Hz), 7.26-7.34 (m, 1 H), 7.41 (t, 2 H, J = 7.5 Hz), 7.58 (dd, 2 H, J = 1.6, 6.9 Hz), 7.75 (d, 1 H, J = 10.2 Hz), 7.85 (d, 1 H, J = 9.34 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.32, 27.35, 55.87, 74.76, 109.53, 114.51, 118.50, 112.48, 123.29, 124.64, 124.87, 125.89, 126.75, 127.18, 128.20, 130.17, 140.09, 142.43, 151.59, 151.99; IR (neat) 2965, 2939, 2848, 1452, 1366 cm^{-1}; Mass spectrum (EI) *m/z* (% rel. int.) 405 M^+ + 1 (11), 404 M^+ (36), 391 (23), 390 (100), 376 (6), 375 (15), 374 (5), 302 (5); Anal. calcd. for $C_{25}H_{28}O_3Si$: C,74.22; H, 6.98. Found: C, 73.99; H, 7.39.

Synthesis of naphtholpyran (184)



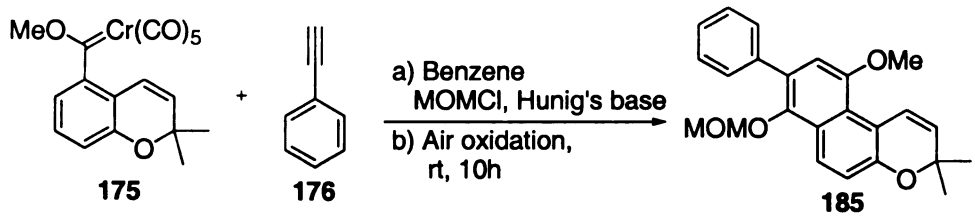
175 **176** **184**

To a flame-dried 25 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added chromene carbene complex **175** (100 mg,

0.254 mmol), benzene (5.0 mL), phenyl acetylene (56 μL, 0.508 mmol), acetic anhydride (72 μL, 0.762 mmol) and N,N-diisopropylethylamine (221 μL, 1.270 mmol). The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The reaction mixture was then stirred at 50 °C for 24 h and then at room temperature for another 24 h. The reaction mixture was opened to air and allowed to stir for 12 h. The reaction mixture was filtered through Celite, concentrated in vacuo and the product was purified by silica gel column chromatography using (15 %) EtOAc : hexane to give naphthopyran **184** (58 mg) in 58 % yield as white solid.

Spectral data for **184**: Mp = 164 - 166 °C ^{1}H NMR (500 MHz, $CDCl_3$) 1.45 (s, 6 H), 2.15 (s, 3 H), 3.95 (s, 3 H), 5.60 (d, 1 H, J = 10.2 Hz), 6.83 (s, 1 H), 7.09 (d, 1 H, J = 8.8 Hz), 7.31-7.37 (m, 1 H), 7.42 (t, 2 H, J = 7.60 Hz), 7.50 (dd, 2 H, J = 1.4, 7.6 Hz), 7.59 (d, 1 H, J = 8.8 Hz), 7.72 (d, 1 H, J = 10.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.71, 27.19, 55.71, 74.86, 108.10, 115.15, 120.01, 122.30, 122.71, 123.06, 124.45, 127.37, 127.74, 128.14, 128.38, 128.96, 137.22, 138.18, 152.16, 154.89, 169.65; IR (neat) 3059, 3014, 2970, 2926, 1759, 1622 cm^{-1}; Mass spectrum (EI) *m/z* (% rel. int.) 375 M^+ + 1 (23), 374 M^+ (77), 360 (11), 318 (100), 302 (26); Anal. calcd. for $C_{22}H_{30}O_3Si$: C,76.99; H, 5.92. Found: C, 77.09; H, 6.16.

Synthesis of naphthol pyran (185)



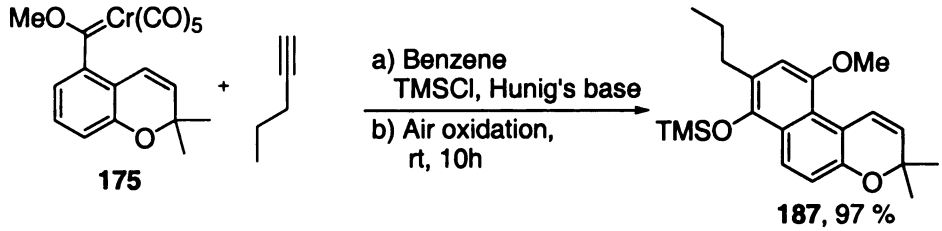
175 **176** **185**

To a flame-dried 25 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added chromene carbene complex **175** (100 mg, 0.254 mmol) in benzene (5.0 mL), phenyl acetylene **176** (56 μL, 0.508 mmol), acetic anhydride (58 μL, 0.762 mmol) and N,N-diisopropylethylamine (221 μL, 1.270 mmol) in benzene (5.0 mL). The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The reaction mixture was then stirred at 50 °C for 24 h and then at room temperature for another 24 h. The reaction mixture was opened to air and allowed to stir for 12 h. The reaction mixture was filtered through Celite, concentrated in vacuo and the product was purified by silica gel column chromatography using (5 %) EtOAc : hexane to give naphthopyran **185** (57 mg) in 60 % yield as colorless liquid.

Spectral data for **185**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 6 H), 3.17 (s, 3 H), 3.93 (s, 3 H), 4.7 (s, 2 H), 5.58 (d, 1 H, J = 10.2Hz), 6.80 (s, 1 H), 7.10 (d, 1 H, J = 9.3 Hz), 7.28-7.37 (m, 1 H), 7.43 (t, 2 H, J = 7.5 Hz), 7.62 (dd, 2 H, J = 1.4, 7.5 Hz), 7.73 (d, 1 H, 10.1 Hz), 8.06 (d, 1H, J = 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.25, 55.74, 57.55, 74.78, 99.71, 108.92, 114.79, 119.33, 122.47, 123.17,

124.15, 126.11, 126.96, 127.38, 127.60, 128.34, 129.63, 139.25, 143.87, 152.12, 153.43; IR (neat) 2974, 2934, 1613, 1591, 1371 cm^{-1}; Mass spectrum (EI) *m/z* (% rel. int.) 377 $M^+ + 1$ (29), 376 M^+ (100), 363 (12), 332 (40), 330 (17), 301 (11), 300 (14); Anal. calcd. for $C_{24}H_{24}O_4$: C,76.57; H, 6.43. Found: C, 76.75; H, 6.29.

Synthesis of naphthol pyran (187)



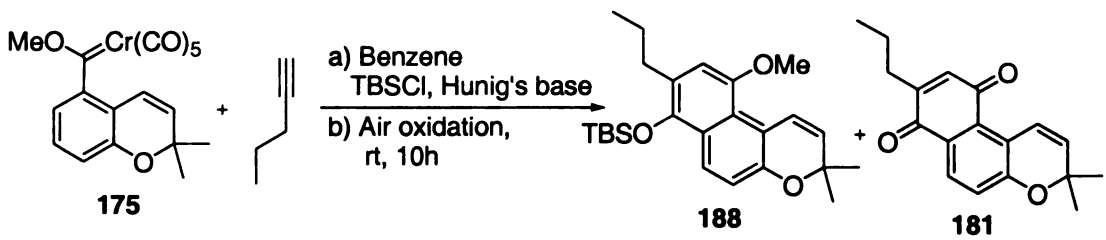
175 **187**, 97 %

To a flame-dried 10 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added chromene carbene complex **175** (25 mg, 0.063 mmol), benzene (1.2 mL), 1-pentyne (13 μL, 0.126 mmol), TMSCl (24 μL, 0.189 mmol) and N,N-diisopropylethylamine (55 μL, 0.315 mmol). The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The reaction mixture was then stirred at 50 °C for 24 h and room temperature for another 24 h. The reaction mixture was opened to air and allowed to stir for 12 h. The reaction mixture was filtered through Celite, concentrated in vacuo and the product was purified by silica gel column chromatography using (5 %) EtOAc : hexanes to give naphthopyran **187** (22.4 mg) in 98 % yield as colorless liquid.

Spectral data for **187**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.25 (s, 9 H), 0.97 (t, 3 H, J = 7.17 Hz), 1.44 (s, 6 H), 1.59-1.74 (m, 2 H), 2.68-2.78 (m, 2 H), 3.88 (s, 3 H), 5.55 (d, 1 H, J = 10.1 Hz), 6.63 (s, 1 H), 6.98 (dd, 1 H, J = 0.6, 9.1 Hz), 7.71 (dd, 1 H,

J = 0.6, 10.3 Hz), 7.80 (d, 1 H, J = 9.07 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.91, 14.20, 23.48, 27.33, 32.91, 55.85, 74.59, 109.45, 114.45, 118.09, 121.55, 123.39, 124.25, 124.38, 125.57, 127.04, 142.81, 151.22, 141.32; IR (neat) 2961, 2930, 2870, 1591, 1454, 1307 cm^{-1}; Mass spectrum (EI) *m/z* (% rel. int.) 371 M^+ + 1 (24), 370 M^+ (82), 358 (11), 356 (100), 355 (19); Anal. calcd. for $C_{22}H_{30}O_3Si$: C, 71.31; H, 8.16. Found: C, 71.75; H, 8.43.

Synthesis of naphthol pyran (188)



175 **188** **181**

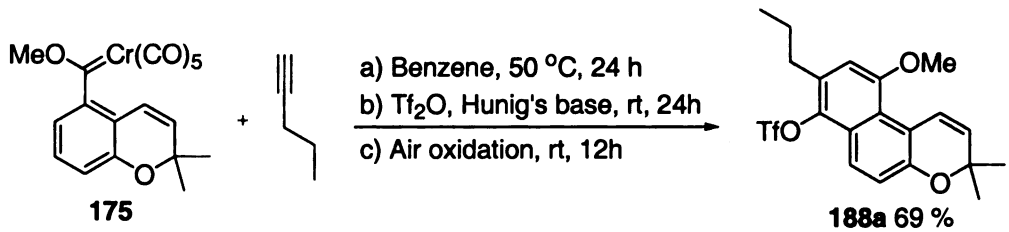
188 : **181** = 7 : 1, 89 % yield

To a flame-dried 25 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added chromene carbene complex **175** (100 mg, 0.254 mmol), benzene (5.0 mL), 1-pentyne (56 μL, 0.508 mmol), TBSCl (115 mg, 0.762 mmol) and N,N-diisopropylethylamine (55 μL, 1.270 mmol) were then added to the reaction mixture. The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The reaction mixture was then stirred at 50 °C for 24 h and then at room temperature for another 24 h. The reaction mixture was opened to air and allowed to stir for 12 h. The reaction mixture was filtered through Celite, concentrated in vacuo and the product was purified by silica gel column chromatography using (25 %) benzene : hexane to give **188** in 78 % yield along with 10 % yield of slightly impure quinone **181**.

Spectral data for **188**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 6 H), 0.93 (t, 3 H, J = 7.2 Hz), 1.07 (s, 9 H), 1.43 (s, 6 H), 1.52-1.70 (m, 2 H), 2.63 (t, 2 H, J = 7.7 Hz), 3.87 (s, 3 H), 5.53 (d, 1 H, J = 10.2 Hz), 6. 63 (s, 1 H), 6.95 (d, 1 H, J = 9,1 Hz), 7.70 (d, 1 H, J = 10.2 Hz), 7.83 (d, 1 H, J = 9.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ -3.29, 14.02, 18.64, 23.61, 26.12, 27.26, 32.61, 55.84, 74.53, 109.55, 114.27, 117.61, 121.56, 123.39, 124.49, 124.72, 125.39, 126.91, 142.32, 151.16, 151.24; IR (neat) 2959, 2930, 2858, 1591, 1454, 1337 cm^{-1}; Mass spectrum (EI) *m/z* (% rel. int.) 413 M^+ + 1 (95), 412 M^+ (15), 400 (22), 399 (79), 398 (100), 383 (6); Anal. calcd. for $C_{25}H_{36}O_3Si$: C, 72.77; H, 8.79; Found: C, 72.60; H, 8.40.

Spectral data for **181**: Refer to page 192.

Synthesis of naphthol pyran (188a)



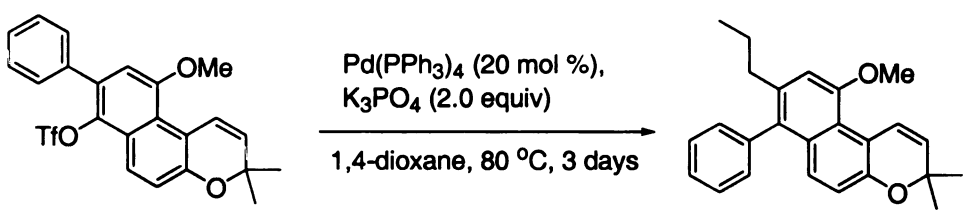
175 **188a** 69 %

To a flame-dried 25 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added chromene carbene complex **175** (75 mg, 0.189 mmol) in benzene (3.8 mL) and 1-pentyne (47 μL, 0.473 mmol). The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature, sealed and the mixture was then stirred at 55 °C for 24 h. The reaction mixture was cooled to 0 °C and was added trifloromethane sulfonic anhydride (48 μL, 0.283 mmol) and N,N-diisopropylethylamine (66 μL, 0.378 mmol). The system was deoxygenated

by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles) and back-filled with Ar at room temperature. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was opened to air and allowed to stir for 12 h. The reaction mixture was then filtered through Celite, concentrated in vacuo and the product was purified by silica gel column chromatography using (5 %) EtOAc : hexane to give naphthopyran **188a** (56 mg) in 69 % yield as off-white solid.

Spectral data of **188a**: Mp = 90-92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, 3 H, J = 7.3 Hz), 1.62-1.76 (m, 2 H), 2.74-2.82(m, 2 H), 3.94 (s, 3 H), 5.59 (d, 1 H, J = 10.3 Hz), 6.64 (s, 1 H), 7.14 (d, 1 H, J = 9.3 Hz), 7.64 (d, 1 H, J = 9.8 Hz), 7.80 (d, 1 H, J = 9.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.89, 23.32, 27.24, 32.52, 55.64, 74.90, 107.37, 115.02, 118.87 (q, J = 318 Hz), 120.46, 121.91, 122.33, 122.66, 124.36, 128.14, 130.12, 136.37, 152.07, 156.27. IR (neat) 2970, 2936, 2876m 1628m 1456 cm^{-1}; Mass spectrum (FAB) *m/z* (% rel. int.) 430 M^+ (98), 415 (20), 297 (100), 281 (15), 267 (15); HRMS (FAB) calcd for m/z $C_{20}H_{21}F_3O_5S$ 430.1062, measd 430.1064.

Synthesis of Suzuki Coupling Product (188b)



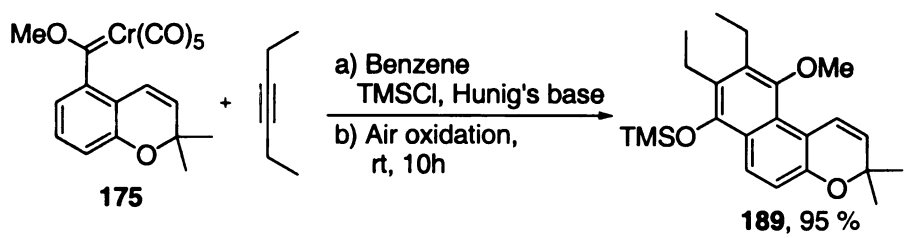
188a 69 % **188b**

To a flame-dried 25 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added $Pd(PPh_3)_4$ (20 mg, 0.017 mmol), phenyl boronic acid (17 mg, 0.14 mmol), K_3PO_4 (30 mg, 0.14 mmol) and naphthol pyran

triflate **188a** (31 mg, 0.07 mmol) in 1,4 dioxane (4 mL). The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature, sealed and the reaction mixture was stirred at 80 °C for 3 days. The reaction mixture was then filtered through Celite, concentrated in vacuo and the product was purified by silica gel column chromatography using (5 %) EtOAc : hexane to give coupling product **188b** (17.4 mg) in 69 % yield as off-white solid.

Spectral data of **188b**: Mp = 107-108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, 3 H, J = 7.3 Hz), 1.44 (s, 6 H), 1.46-1.58 (m, 2 H), 2.34-2.42 (m, 2 H), 3.98 (s, 3 H), 5.57 (d, 1 H, J = 10.2 Hz), 6.78 (s, 1 H), 6.86 (d, 1 H, J = 9.3 Hz), 7.10 (d, 1 H, J = 9.3 Hz), 7.10 (d, 1 H, J = 9.3 Hz), 7.18-7.22 (m, 2 H), 7.36-7.40(m, 1 H), 7.40-7.46 (m, 2 H), 7.76 (d, 1 H, J = 10.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.13, 24.64, 27.15, 35.87, 55.46, 74.46, 108.25, 114.41, 118.51, 120.52, 123.68, 126.73, 127.06, 128.10, 128.18, 130.83, 130.88, 131.46, 135.42, 140.08, 150.88, 156.05; IR (neat) 2959, 2928, 2870, 1630; Mass spectrum (FAB) *m/z* (% rel. int.) 359 M^+ +1 (60), 358 M^+ (100), 343 (60); HRMS (FAB) calcd for m/z $C_{25}H_{26}O_2$ 358.1933, measd 358.1935.

Synthesis of naphthol pyran (189)

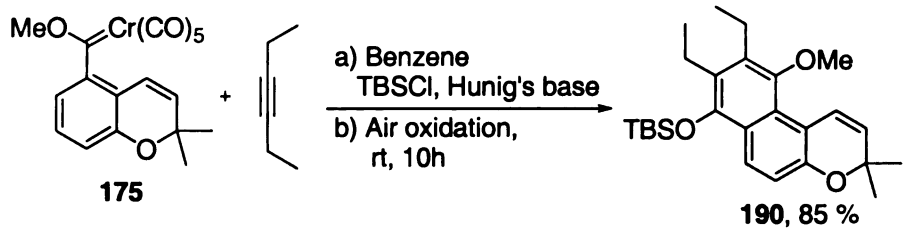


175 **189**, 95 %

To a flame-dried 10 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added chromene carbene complex **175** (18 mg, 0.045 mmol), benzene (1.9 mL), 3-hexyne (11 μL, 0.090 mmol), TMSCl (12 μL, 0.135 mmol) and N,N-diisopropylethylamine (39 μL, 0.742 mmol). The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The reaction mixture was then stirred at 50 °C for 24 h and then at room temperature for another 24 h. The reaction mixture was opened to air and allowed to stir for 12 h, filtered through Celite and concentrated in vacuo. The reaction mixture was diluted in 10 mL of pentane and kept at 0 °C for 5 h. After 5 h, the pentane solution was filtered through Celite and concentrated in vacuo to give 16.5 mg (95 %) of pure naphthopyran **189** as a light yellow oil.

Spectral data for **189**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.26 (s, 9 H), 1.14 (t, 3 H, J = 7.8 Hz), 1.22 (t, 3 H, J = 7.3 Hz), 1.46 (s, 6 H), 2.71 (q, 2 H, J = 7.6 Hz), 2.79 (q, 2 H, J = 7.5 Hz), 3.63 (s, 3 H), 5.59 (d, 1 H, J = 9.8 Hz), 6.93 (d, 1 H, J = 8.8 Hz), 7.59 (d, 1 H, J = 9.8 Hz), 7.80 (d, 1 H, J = 9.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.94, 14.64, 16.00, 20.23, 20.61, 27.09, 61.38, 74.64, 113.03, 117.01, 123.00, 123.43, 123.99, 124.68, 126.80, 126.96, 134.83, 145.80, 148.70, 151.40; IR (neat) 2970, 2936, 2882, 1639 cm^{-1}; Mass spectrum (FAB) *m/z* (% rel. int.); 385 M^+ + 1 (40), 384 M^+ (100), 369 (40), 283 (5); HRMS (FAB) calcd for m/z $C_{23}H_{32}O_3Si$ 384.2120, measd 384.2124.

Synthesis of naphthol pyran (190)



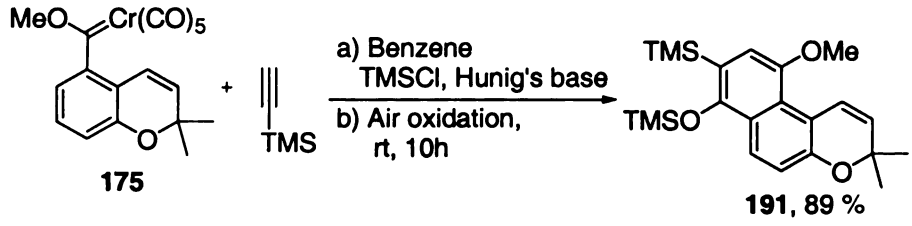
175 **190**, 85 %

To a flame-dried 25 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added chromene carbene complex **175** (100 mg, 0.254 mmol), benzene (5.0 mL), 3-hexyne (58 μL, 0.508 mmol), TBSCl (115 mg, 0.762 mmol) and N,N-diisopropylethylamine (55 μL, 1.270 mmol). The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The reaction mixture was then stirred at 50 °C for 24 h and then at room temperature for another 24 h. The reaction mixture was opened to air and stirred for 12 h. The reaction mixture was filtered through Celite, concentrated in vacuo and the product was purified by silica gel column chromatography using (25 %) benzene : hexane to give naphthopyran **190** (92 mg) in 85 % yield as a white solid.

Spectral data for **190**: Mp = 104 - 106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 6 H), 1.07 (s, 9 H), 1.09 (t, 3 H, J = 7.5 Hz), 1.22 (t, 3 H, 7.4 Hz), 1.46 (s, 6 H), 2.60-2.90 (m, 4 H), 3.63 (s, 3 H), 5.59 (d, 1 H, J = 10.0 Hz), 6.90 (d, 1 H, J = 9.1 Hz), 7.59 (d, 1 H, J = 10.0 Hz), 7.83 (d, 1 H, J = 9.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ -3.09, 14.91, 16.04, 18.70, 20.17, 20.33, 26.10, 27.06, 61.37, 74.63, 112.89, 116.58, 123.06, 123.50, 123.84, 125.24, 126.86, 127.04, 134.94, 145.27, 148.70, 151.41; IR (neat) 2969, 2982, 2869, 1449, 1377, 1257 cm^{-1}; Mass

spectrum (EI) *m/z* (% rel. int.) 427 M^+ + 1 (75), 426 M^+ (8), 413 (54), 412 (100), 411 (10); Anal. Calcd. for $C_{26}H_{38}O_3Si$: C,73.19; H, 8.98. Found: C, 73.45; H, 9.21.

Synthesis of naphthol pyran (191)



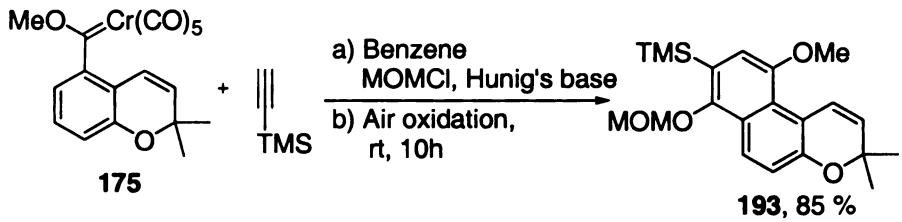
175 **191**, 89 %

To a flame-dried 10 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added chromene carbene complex **175** (25 mg, 0.063 mmol), benzene (1.2 mL), trimethylsilylacetylene (25 μL, 0.126 mmol), TMSCl (24 μL, 0.189 mmol) and N,N-diisopropylethylamine (55 μL, 0.315 mmol) were then added to the reaction mixture. The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The reaction mixture was stirred at 50 °C for 24 h and then at room temperature for another 24 h. The reaction mixture was opened to air and stirred for 12 h, filtered through Celite and concentrated in vacuo. The product was purified by silica gel column chromatography using (2 %) EtOAc : hexanes to give naphthopyran **191** (22.5 mg) in 89 % yield as white solid.

Spectral data for **191**: Mp = 79 - 81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.25 (s, 9 H), 0.34 (s, 9 H), 1.44 (s, 6 H), 3.88 (s, 3 H), 5.54 (d, 1 H, J = 10.1 Hz), 6.77 (s, 1 H), 6.96 (dd, 1 H, J = 0.9, 9.2 Hz), 7.71 (dd, 1 H, J = 0.7, 10.1 Hz), 7.85 (d, 1 H, J = 9.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.26, 1.62, 27.32, 55.92, 74.77, 112.41, 114.41, 117.63, 120.26, 123.30, 123.98, 124.96, 125.07, 126.89, 150.96, 151.58,

152.11; IR (neat) 2955, 2926, 2855, 1448, 1389 cm^{-1}; Mass spectrum (EI) *m/z* (% rel. int.) 400 M^+ (24), 387(12), 386 (100), 371 (6), 297 (5); Anal. calcd. for $C_{22}H_{32}O_3Si_2$: C, 65.95; H, 8.05. Found: C, 66.06; H, 8.40.

Synthesis of naphthol pyran (193)



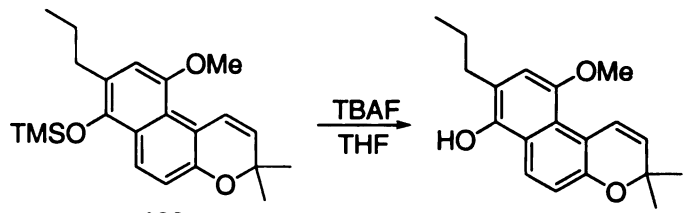
175 **193**, 85 %

To a flame-dried 10 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added chromene carbene complex **175** (100 mg, 0.254 mmol) and benzene (5 mL). The trimethylsilyl acetylene (72 μL, 0.508 mmol), MOMCl (58 μL, 0.762 mmol) and N,N-diisopropylethylamine (221 μL, 1.270 mmol) were then added to the reaction mixture. The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The reaction mixture was stirred at 50 °C for 24 h and then at room temperature for another 24 h. The reaction mixture was opened to air stirred for 12 h, filtered through Celite and concentrated in vacuo. The product was purified by silica gel column chromatography using (5 %) benzene : hexane to give naphthopyran **193** (81 mg) in 85 % yield as a white solid.

Spectral data for **193**: Mp = 86 - 88 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.35 (s, 9 H), 1.44 (s, 6 H), 3.63 (s, 3 H), 3.90 (s, 3 H), 5.02 (s, 2 H), 5.55 (d, 1 H, J = 9.8 Hz), 6.78 (s, 1 H), 7.05 (dd, 1 H, J = 1.0, 8.8 Hz), 7.70 (d, 1 H, J = 10.2 Hz), 8.0 (d, 1 H, J = 9.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.01, 27.25, 55.74, 57.71,

74.79, 101.00, 111.28, 114.28, 118.91, 123.20, 124.12, 124.31, 125.54, 125.40, 127.09, 152.32, 153.04, 153.31; IR (neat) 2953, 2895, 2840, 1603, 1450 cm^{-1}; Mass spectrum (EI) *m/z* (% rel. int.) 373 M^+ + 1 (100), 372 M^+ (80), 358 (66), 357 (18), 328 (16), 298 (23), 297 (22), 296 (23); Anal. calcd. for $C_{21}H_{28}O_4Si$: C, 67.71; H, 7.58. Found: C, 68.08; H, 7.96.

Synthesis of naphthol pyran (180)



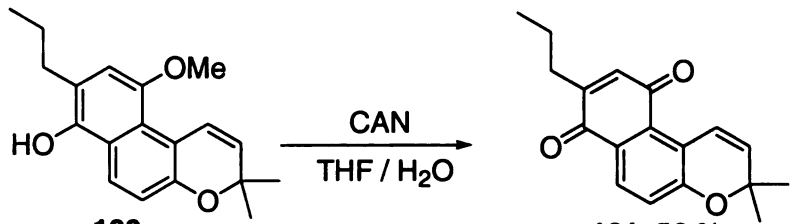
186 **180**, 75 %

To a stirred solution of **186** (31 mg, 0.083 mmol) in 5 mL THF at 0 °C was added TBAF (166 μL, 0.166 mmol, 1.0 M solution in THF) dropwise. The reaction mixture was stirred for 30 min and, quenched with 5 mL water and extracted with EtOAc (2 x 10 mL). The organic layer was concentrated in vacuo and the product was purified by silica gel column chromatography using 5 % EtOAc : hexane to give slightly impure compound **180** in 75 % yield (18.5 mg) as a colorless oil. This compound contained slight amounts of impurities and its purity could not be enhanced by additional chromatography. This compound was fully characterized upon conversion to quinone **181**.

Spectral data for **180**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (t, 3 H, J = 7.3 Hz), 1.44 (s, 6 H), 1.60-1.78 (m, 2 H), 2.63 (t, 2 H, J = 7.7 Hz), 3.87 (s, 3 H), 4.63 (s, 1 H), 5.56 (d, 1 H, J = 10.1 Hz), 6.60 (s, 1 H), 7.03 (dd, 1 H, J = 0.6, 9.1 Hz), 7.71 (dd, 1 H, J = 0.6, 10.5 Hz), 7.95 (d, 1H, J = 9.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ

14.03, 23.34, 27.20, 32.09, 56.15, 74.62, 109.75, 114.52, 118.39, 118.45, 121.58, 122.16, 122.83, 123.26, 127.28, 142.52, 150.84, 1 sp^2 C not located; IR (neat) 3455, 2961, 2930, 2870, 1626, 1454 cm^{-1}; Mass spectrum (EI) *m/z* (% rel. int.) 298 M^+ (29), 284 (21), 283 (100), 268 (21), 239 (10).

Synthesis of naphthoquinone pyran (181)



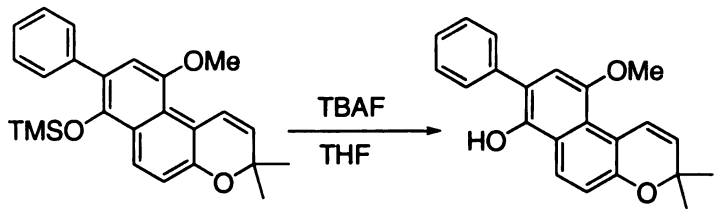
180 **181**, 56 %

To a stirred solution of **180** (9.0 mg, 0.030 mmol) in 2 mL THF at 0 °C was added CAN (41 mg, 0.075 mmol) in 0.2 mL water. The reaction mixture was stirred for 30 min at 0 °C and then quenched with water. The water layer was then extracted with 2 x 10 mL EtOAc. The combined organic layer was washed with 5 mL of water, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel column chromatography using 5 % EtOAc : hexane to give a 65 % yield of quinone **181** as a yellow oil.

Spectral data for **181**: ^1H NMR (500 MHz, $CDCl_3$) δ 0.97 (t, 3 H, J = 7.3 Hz), 1.45 (s, 6 H), 1.50-62 (m, 2 H), 2.42-2.52 (m, 2 H), 5.89 (d, 1 H, J = 10.2 Hz), 6.63 (t, 1 H, J = 1.3 Hz), 7.03 (dd, 1 H, J = 0.8, 8.5 Hz), 7.74 (dd, 1 H, J = 0.7, 10.4 Hz), 7.94 (d, 1 H, J = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.85, 21.17, 27.99, 31.05, 76.88, 119.88, 120.47, 121.08, 126.57, 126.81, 128.90, 134.69, 136.12, 150.11, 158.58, 184.50, 188.06; Mass spectrum (EI) *m/z* (% rel. int.) 282 M^+, 268 (21),

267 (100), 239 (4), 238 (4), 210 (4); IR (neat) 2964, 2930, 2874, 1657, 1298 cm^{-1} ; Anal. calcd. for $C_{18}H_{18}O_3$: C,76.57; H, 6.43. Found: C, 76.42; H, 6.01.

Synthesis of naphthol pyran (177)

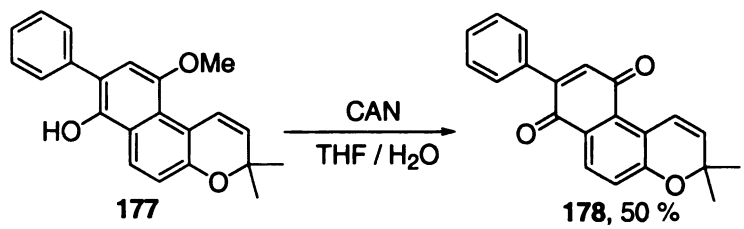


183 **177**, 65 %

To a stirred solution of **183** (20 mg, 0.049 mmol) in 5 mL THF at 0 °C was added TBAF (73 μL, 0.073 mmol, 1.0 M solution in THF) dropwise. The reaction mixture was stirred for 30 min and then quenched with 2 mL water. The reaction mixture was extracted with EtOAc (2 x 10 mL), dried over $MgSO_4$ and then the organic layer was concentrated in vacuo and purified by silica gel column chromatography using 5 % EtOAc : hexane to give compound **177** in 65 % yield as a colorless oil. The ^1H NMR spectrum revealed that the phenol **177** was not completely pure. The compound was not stable long enough to provide a good ^{13}C NMR spectrum. This compound was characterized by conversion to the quinone **178**.

Spectral data for **177**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 6 H), 3.89 (s, 3 H), 5.40 (s, 1 H), 5.59 (d, 1 H, J = 10.1 Hz), 6.73 (s, 1 H), 7.08 (d, 1 H, J = 8.8 Hz), 7.36-7.44 (m, 1 H) 7.48-7.54 (m, 4 H), 7.75 (d, 1 H, J = 10.0 Hz), 8.10 (d, 1 H, J = 9.1 Hz); Mass spectrum (EI) *m/z* (% rel. int.) 332 M^+ (39), 318 (26), 317 (15), 303 (27); IR (neat) 3555, 2970, 2926, 2851.1626, 1591, 1454 cm^{-1}.

Synthesis of naphthoquinone pyran (178)

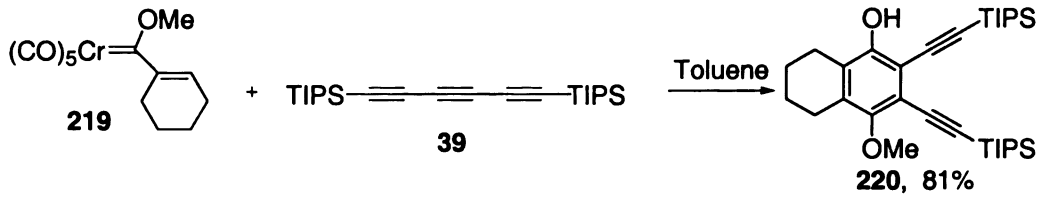


177 **178**, 50 %

To a stirred solution of **177** (10.5 mg, 0.031 mmol) in 2 mL THF at 0 °C was added CAN (43 mg, 0.077 mmol) in 0.5 mL water. The reaction mixture was stirred for 30 min at 0 °C and then quenched with water. The water layer was then extracted with 2 x 10 mL EtOAc. The combined organic layer was washed with 5 mL of water, dried over $MgSO_4$ and concentrated in vacuo. The product was purified by silica gel column chromatography using 5 % EtOAc : hexane to give a 65 % yield of quinone **178** as orange solid.

Spectral data for **178**: Mp = 156 - 158 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 6 H), 5.93 (d, 1 H, J = 10.2 Hz), 6.94 (s, 1 H), 7.09 (dd, 1 H, J = 1.0, 8.8 Hz), 7.68-7.90 (m, 3 H), 7.50-7.52 (m, 2 H), 7.78 (d, 1 H, 10.1 Hz), 8.03 (d, 1 H, 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.02, 77.03, 119.84, 120.43, 121.39, 126.93, 128.29, 129.38, 129.39, 129.82, 133.30, 134.95, 136.48, 146.64, 158.74, 183.60, 187.95, one sp^2 C not located; IR (neat) 3061, 2978, 2930,1655 cm^{-1}; Mass spectrum (EI) *m/z* (% rel. int.) 316 M^+ (2), 302 (26), 301 (100), 273 (2); HRMS (FAB) calcd for m/z $C_{21}H_{16}O_3$ 316.3499, measd 317.1177 (M^+ + 1).

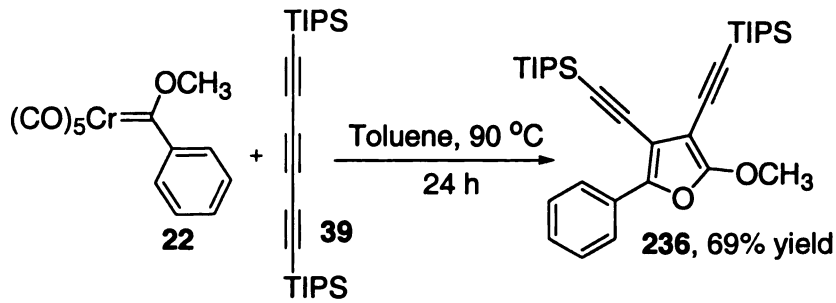
Synthesis of ortho-aryl diyne (220)



To a flame-dried 10 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added cyclohexenyl carbene complex **219** (0.885 mg, 2.8 mmol), bis-TIPS triyne **39** (1.1 gm, 2.8 mmol) and toluene (44 mL). The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The mixture was then stirred at 90 °C for 24 h. After 24h, the reaction mixture was opened to air and stirred for 12h, filtered through Celite and concentrated in vacuo. The product was purified by silica gel chromatography using hexane and ethyl acetate (10 : 1) as eluent to give an 81 % yield of **220** as an orange oil.

Spectral data for **220**: ^{1}H (300 MHz, $CDCl_3$) δ 1.08-1.13 (m, 42 H), 1.71-1.73 (m, 4 H), 2.65-2.69 (m, 4 H), 3.80 (s, 3 H), 6.01 (s, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 11.16, 11.34, 18.73, 21.95, 22.07, 23.54, 23.82, 60.38, 98.26, 100.23, 108.56, 101.42, 101.17, 114.66, 125.50, 133.77, 151.70, 153.38, one sp^3 C not located; IR (neat): 3502, 2941, 2868, 2132, 1468, 1452, 1408, 1311, 1043, 884 cm-1; Mass spectrum (EI) *m/z* (% rel. int.) 538 M^+ (25), 454 (18), 453 (55), 168 (18), 154 (19), 141 (16), 87 (33), 73 (59), 59 (100), HRMS (FAB) calcd for m/z $C_{33}H_{54}O_2Si_2$ 538.3662, measd 538.3664. Anal, Calcd. for $C_{33}H_{54}O_2Si_2$: C, 73.54; H, 10.10. Found: C, 72.84, H, 10.66.

Synthesis of furan (236)

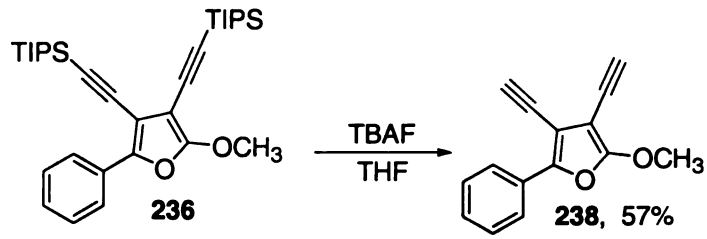


To a flame-dried 10 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added phenyl carbene complex **22** (80 mg, 0.254 mmol), bis-TIPS triyne **39** (100 mg, 0.254) and toluene (6.0 mL). The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The reaction mixture was then stirred at 90 °C for 24 h. After 24 h, the mixture was opened to air and allowed to stir for 4 h. The reaction mixture was filtered through Celite, concentrated in vacuo and the product was purified by silica gel column chromatography using benzene and hexane (3 : 10) to give phenyl furan **236** in 69 % yield as a yellow oil.

Spectral data for **236**: ^{1}H (300 MHz, $CDCl_3$) δ 1.14 (m, 21 H), 1.18 (m, 21 H), 4.24 (s, 3 H), 7.26-7.39 (m, 4 H), 8.04-8.07 (m, 1 H); ^{1}H (500 MHz, C_6D_6): 0.80-1.40 (m, 42 H), 3.59 (s, 3 H), 7.03 (t, 1H, J = 7.5 Hz), 7.20 (t, 2H, J = 7.8 Hz), 8.16 (dd, 2H, J = 1.0, 8.6 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 11.31, 11.34, 18.71, 18.72, 59.32, 85.92, 94.86, 95.98, 98.27, 98.81, 106.06, 124.29, 127.57, 128.33, 129.65, 145.63, 161.09; IR (neat): 2946, 2888, 2149, 1605, 1464, 1387, 1161,

1119, 1065, 995, 884, 793, 762, 677 cm-1; Mass spectrum (EI) *m/z* (% rel. int.) 534 M^+ (82), 434 (100), 391 (15), 168 (27), 154 (19), 105 (22), 73 (27), 59 (65), HRMS (FAB) calcd for m/z $C_{33}H_{50}O_2Si_2$ 534.3349, measd 534.3348.

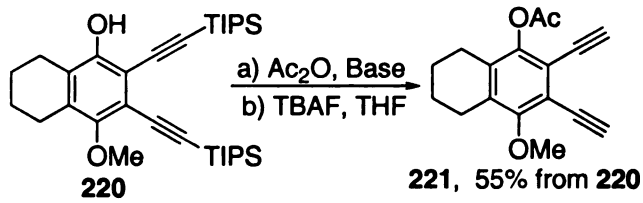
Synthesis of furan (238)



236 **238**, 57%

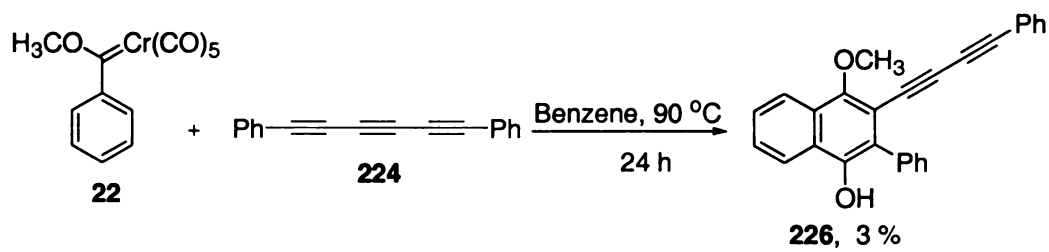
To a stirred solution of **236** (86 mg, 0.159 mmol) in 3 mL THF at 0 °C was added TBAF (500 μL, 0.447 mmol, 1.0 M solution in THF). The reaction mixture was warmed to room temperature and stirring continued at this temperature for 3 h. The reaction mixture was quenched with sat aq ammonium chloride (1 x 5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The product was purified by silica gel column chromatography (1 % EtOAc / Hexane) to give 20 mg (57 % yield) of a light brown oil that was identified as **238**. The presence of two alkynyl hydrogens is only consistent with structure **238**. Spectral data for **238**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.22 (s, 1 H), 3.49 (s, 1 H), 4.19 (s, 3 H), 7.27 (tt, 1 H, J = 7.5, 1.1 Hz), 7.35-7.40 (m, 2 H), 7.90-7.95 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 59.0, 73.2, 75.3, 81.4, 84.3, 84.6, 104.6, 124.1, 127.9, 128.5, 129.2, 145.9, 160.8; IR (neat): 3300, 2924, 2856, 2584, 2114, 1728, 1610 cm-1; Mass spectrum (FAB) *m/z* (% rel. int.) 222 M^+ (100), 207 (16); HRMS (FAB) calcd for m/z $C_{15}H_{10}O_2$ 222.0681, measd 222.0678.

***Synthesis of ortho-aryl diyne* (221)**



The following procedure is slightly modified from that originally reported by Jiang.[64] To a solution of compound **220** (0.62 gm, 1.16 mmol) in CH_2Cl_2 (20 mL) was added 0.14 mL Ac_2O, 0.14 mL pyridine and 14 mg DMAP in that order. The mixture was stirred at room temperature for 18 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The extract was washed with H_2O and brine and then dried over $MgSO_4$. After concentration, the residue was dissolved in 20 mL THF and TBAF (5 mmol, 5 mL of a 1.0 M solution in THF) was added at 0 °C. The mixture was stirred at 0 °C temperature for 15 min. The reaction was quenched by water and extracted with ether. The organic layer was washed with H_2O (1 X 10) and brine (1 X 10) and then dried with $MgSO_4$. The organic layer was concentrated in vacuo and the product was purified by silica gel column chromatography using hexanes and EtOAc (10 : 1) to give 0.180 g of compound **221** as a white solid. The yield was 58 %. The spectral data for **221** matched that previously reported by Jiang.[64]

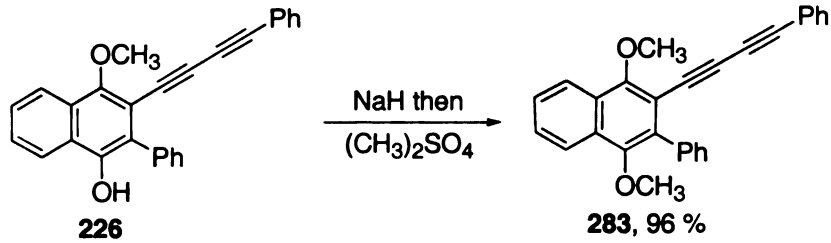
Synthesis of naphthol (226)



To a flame-dried 10 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added phenyl carbene complex **22** (80 mg, 0.254 mmol), bis-phenyl triyne **224** (57 mg, 0.254 mmol) and benzene (6.0 mL). The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The mixture was then stirred at 90 °C for 24 h. The reaction mixture was diluted with 10 mL CH_2Cl_2, allowed to stir opened to air for 12 h. The solution was filtered through a fritted funnel dry packed with Celite 545 and concentrated using a rotary evaporator. The crude reaction mixture appeared by TLC and ^{1}H NMR to be a complicated mixture of many compounds none of which was estimated (after column chromatography) to have been formed in more than 8 - 10 % yield. The crude mixture was loaded onto a silica gel column and elueted with a solvent gradient that ranged from pure hexanes to 5 % EtOAc in hexanes. Several fractions were collected but only one compound was obtained in pure form. This compound was tentatively identified as the phenol **226** which was judged to have been formed in 3 % yield based the amount isolated material (5 mg) and the weight of additional fractions that contained **226** along with other compounds.

Spectral data for **226**: ^{1}H NMR (500 MHz, CDCl3) δ 4.15 (s, 3 H), 5.41 (s, 1 H), 7.12- 7.18 (m, 2 H), 7.20-7.26 (m, 2 H), 7.46-7.60 (m, 8 H), 8.14-8.16 (m, 1 H), 8.20-8.25 (m, 1 H).

Synthesis of naphthol derivative (283)

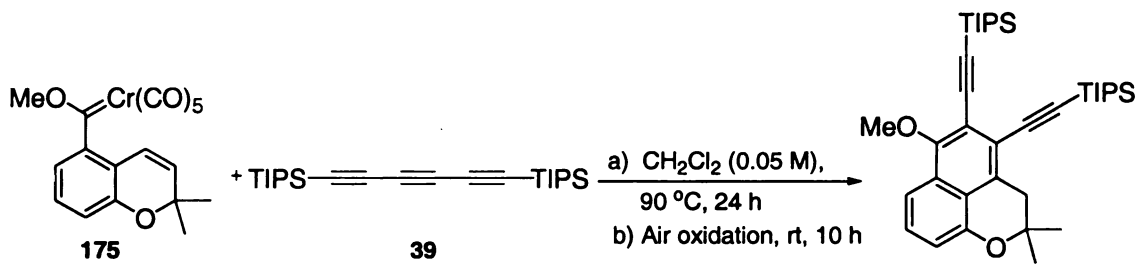


226 **283**, 96 %

A flame-dried round-bottomed flask (5 mL) filled with Argon was charged with a solution of **226** (5 mg, 0.013 mmol) in 1 mL THF. Solid NaH (10 mg, 60 % disperson in mineral oil) was then added to the reaction mixture at room temperature. After 5 minutes, dimethylsulfate (50 μL) was added and stirring was continued at room temperature for 6 h. The reaction mixture was loaded onto a silica gel column and eluted using (5 %) EtOAc in hexane to give a 96 % yield of a yellow solid.

Spectral data for **283**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.51 (s, 3 H), 4.18 (s, 3 H), 7.17-7.21 (m, 2 H), 7.22-7.26 (m, 3 H), 7.39-7.44 (m, 1 H), 7.45-7.51 (m, 2 H), 7.53-7.59 (m, 4 H), 8.12-8 .17 (m, 1 H), 8.17-8.21 (m, 1 H).

Synthesis of olefin-addition product (269)



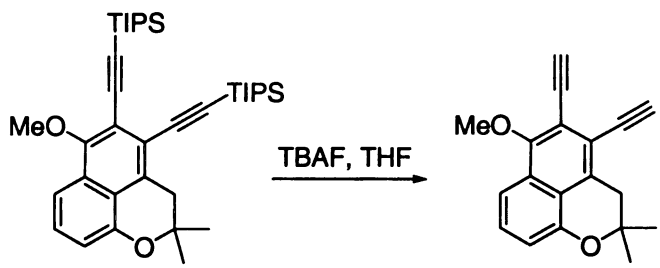
175 **39** **269**, 88 %

To a flame-dried 10 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added chromene carbene complex **175** (50 mg,

0.127 mmol), bis-TIPS triyne **39** (49 mg, 0.127) and dichloromethane (2.5 mL). The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The mixture was then stirred at 90 °C for 24 h. The reaction was opened to air and allowed to stir for 12 h. The reaction mixture was filtered through Celite and concentrated in vacuo. The product was purified by silica gel column chromatography using (2 : 98) EtOAc : hexane to give an olefin-addition product **269** (66 mg) in 88 % yield as a brown oil.

Spectral data for **269**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (s, 21 H), 1.15 (s, 21 H), 1.36 (s, 6 H), 3.22 (s, 2 H), 4.03 (s, 3 H), 6.91 (dd, 1 H, J = 0.8, 7.7 Hz), 7.39 (t, 1 H, J = 8.2 Hz), 7.60 (dd, 1 H, J = 1.1, 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.40, 11.48, 18.81, 18.82, 26.29, 39.65, 61.63, 75.39, 99.64, 100.03, 101.47, 103.21, 112.56, 114.20, 119.04, 121.08, 128.00, 128.33, 130.62, 151.82, 158.26, one sp^2 C not located; Mass spectrum (FAB) *m/z* (% rel. int.) 588 M^+ (100), 488 (60), 445 (20), 157 (19); IR (neat) 2943, 2888, 2145, 1464 cm^{-1}; Anal. calcd. for $C_{37}H_{56}O_2Si_2$: C,75.45; H, 9.58. Found: C, 75.59; H, 9.56.

Synthesis of olefin-addition product (269a)

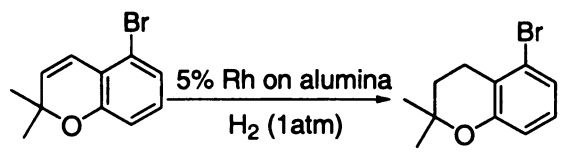


269 **269a**, 68 %

To a stirred solution of **269** (54 mg, 0.09 mmol) in 5 mL THF at room temperature was added TBAF (0.27 mmol, 270 μL, 1 M solution in THF). After 5 min at room temperature, the reaction mixture was quenched with 5 mL water and diluted with EtOAc (20 mL). The organic layer was washed with 5 mL water, dried over $MgSO_4$, concentrated in vacuo. The product was purified by silica gel column chromatography using hexane / EtOAc (20 / 1) as eluent to give 17 mg of compound **269a** (68 % yield) as a colorless oil.

Spectral data for **269a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 6 H), 3.20 (s, 2 H), 3.55 (s, 1 H), 3.61 (s, 1 H), 4.09 (s, 3 H), 6.95 (dd, 1 H, J = 1.0, 6.9 Hz), 7.43 (t, 1 H, J = 7.8 Hz), 7.64 (dd, 1 H, J = 1.0, 8.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.88, 39.10, 61.89, 75.52, 78.75, 79.96, 85.20, 85.69, 112.81, 113.09, 114.29, 117.80, 121.16, 128.10, 128.75, 130.36, 151.95, 158.11; IR (neat) 3289, 2974, 2928, 2851, 1578, 1489 cm^{-1}; Mass spectrum (EI) *m/z* (% rel. int.); 276 (M^+), 275 (47), 261 (42), 260 (48), 246 (30), 245 (23), 203 (65), 202 (67); Anal. calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84; Found: C, 82.39; H, 5.62.

Synthesis of bromochromane (270)



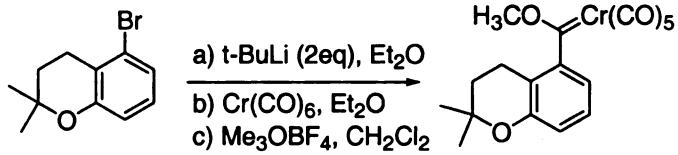
141 **270**, 92% yield

To a stirred solution of **141** (100 mg, 0.418 mmol) in 15 mL EtOH was added 50 mg of Rh on alumina (5 % Rh on alumina). The reaction mixture was stirred for 2 h at room temperature under H_2 atmosphere (1 atm). After 2 h, the reaction mixture was filtered through Celite and concentrated in vacuo. The product was

purified by silica gel column chromatography using hexane / EtOAc (20 / 1) as eluent to give bromochromane **270** in 92 % yield as a colorless oil.

Spectral data for **270**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 6 H), 1.81 (t, 2 H, J = 6.8 Hz), 2.74 (t, 2 H, J = 6.9 Hz), 6.74 (d, 1 H, J = 8.2 Hz), 6.95 (t, 1 H, J = 8.1 Hz), 7.09 (d, 1 H, J = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.85, 26.47, 32.75, 74.30, 116.50, 121.27, 123.44, 125.19, 127.93, 144.07; IR (neat) 2976.54, 2930, 1593, 1566 cm^{-1}; Mass spectrum (FAB) *m/z* (% rel. int.) 242 (96, ^{81}Br), 240 (100, ^{79}Br), 227 (12, ^{81}Br), 225 (13, ^{79}Br), 187 (14, ^{81}Br), 185 (17, ^{79}Br), 161 (91), 146 (28), 145 (29); Anal. calcd. for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43. Found: C, 54.66; H, 5.20.

Synthesis of chromane carbene complex (235)



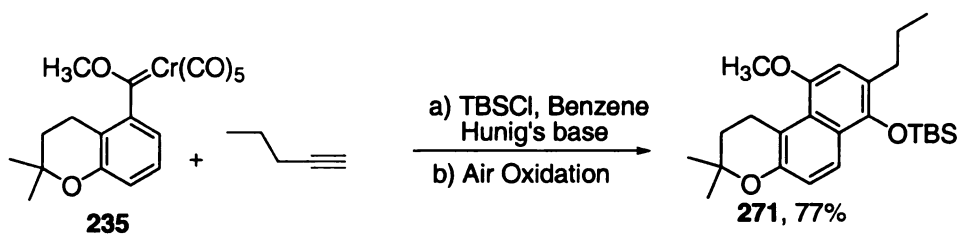
270 **235**, 65% yield

To a flame-dried 100 mL round-bottomed flask containing a solution of bromochromane **270** (310 mg, 1.45 mmol) in ether (10 mL) at -78 °C was added *tert*-BuLi (1.7 mL, 2.90 mmol, 1.7 M solution in pentane). The mixture was warmed to 0 °C, stirred at 0 °C temperature for 5 min and cooled to -78 °C before it was transferred by cannula to a suspension of $Cr(CO)_6$ (350 gm, 1.59 mmol) in 10 mL ether maintained at 0 °C. The reaction mixture turned dark red in 5 min. Stirring was continued for 6 h at room temperature which was followed by removal of ether under vacuum and addition of 10 mL dichloromethane. Me_3OBF_4 (1.63 gm, 11 mmol) was then added at room temperature and reaction

was further stirred for 2 h. The reaction mixture was then filtered through Celite and concentrated in vacuo. The product was purified by silica gel column chromatography (5 %) EtOAc : hexane to give 344 mg (65 % yield) of carbene complex **235** as an orange solid.

Spectral data for **235**: Decomposes above 108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 6 H), 1.78 (br, s, 2 H), 2.43 (br, s, 2 H), 4.25 (br, s, 3 H), 6.35 (d, 1 H, J = 6.84), 6.70 (d, 1 H, J = 7.81 Hz), 7.14 (d, 1 H, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.94, 26.82, 32.25, 65.47, 74.23, 110.11, 111.44, 117.12, 127.56, 154.05, 216.00, 224.22, 359.39, one sp^2 C not located; Mass spectrum (FAB) *m/z* (% rel. int.) 396 M^+ (38), 368 (80), 312 (82), 284 (100), 256 (90), 205 (38), 189 (40); IR (neat) 2978, 2064, 1930, 1576 cm^{-1}; Anal. calcd. for $C_{18}H_{16}CrO_7$: C, 54.55; H, 4.07. Found: C, 54.66; H, 3.96.

Synthesis of naphthol pyran (271)

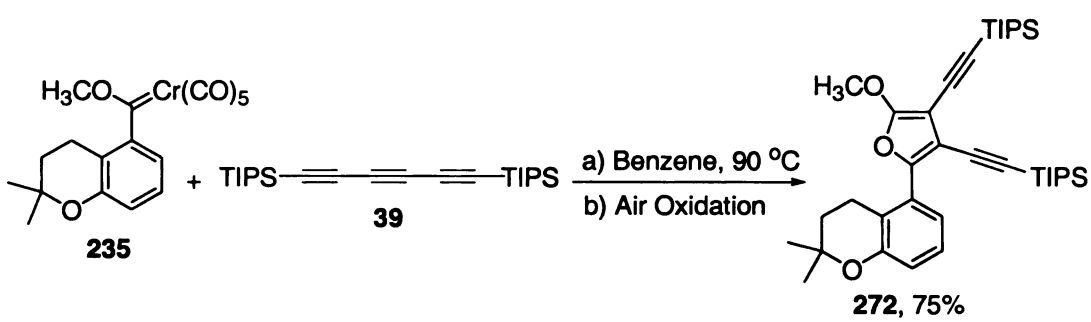


To a flame-dried 10 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added chromane carbene complex **235** (35 mg, 0.088 mmol), benzene (1.7 mL), 1-pentyne (18 μL, 0.090 mmol), TBSCl (40 mg, 0.264 mmol) and N,N-diisopropylethylamine (77 μL, 0.440 mmol). The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The mixture

was then stirred at 50 °C for 24 h and at 25 °C for another 24 h. The reaction was opened to air and allowed to stir for 12 h. The reaction mixture was filtered through Celite, concentrated in vacuo and the product was purified by silica gel column chromatography using hexane and EtOAc (20 : 1) to give a 77 % yield of naphthopyran **271** (28 mg) as a colorless oil.

Spectral data for **271**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11(s, 6 H), 0.93 (t, 3 H, J = 7.3 Hz), 1.08 (s, 9 H), 1.34 (s, 6 H), 1.55-1.65 (m, 2 H), 1.79 (t, 2 H, J = 6.6 Hz), 2.58-2.68 (m, 2 H), 3.41 (t, 2 H, J = 6.8 Hz), 3.84 (s, 3 H), 6.59 (s, 1 H), 6.90 (d, 1 H, J = 9.9 Hz), 7.77 (d, 1 H, J = 9.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ -3.30, 14.02, 18.64, 23.04, 23.67, 26.13, 26.52, 32.60, 33.57, 55.74, 72.98, 108.92, 113.69, 118.82, 122.68, 124.21, 125.00, 125.02, 142.20, 151.04, 151.83; IR (neat) 2957, 2930, 2858, 1603, 1460 cm^{-1}; Mass spectrum (FAB) *m/z* (% rel. int.) 415 M^+ + 1 (40), 414 (100), 413 (20), 400 (10), 399 (10), 357 (5); HRMS (FAB) calcd for m/z $C_{25}H_{38}O_3Si$ 414.2590, measd 414.2587.

Synthesis of furan (272)

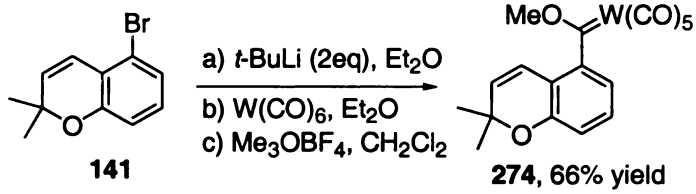


To a flame-dried 10 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added chromane carbene complex **235** (50 mg, 0.126 mmol), bis-TIPS triyne **39** (49 mg, 0.127) and benzene (2.6 mL). The

system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The mixture was then stirred at 90 °C for 24 h. The reaction was opened to air and allowed to stir for 2 h. The reaction mixture was filtered through Celite, concentrated in vacuo and the product was purified by silica gel column chromatography using (1 : 2) benzene : hexane to give chromanylfuran **272** (49 mg) in 63 % yield as brown oil. This compound decomposes quickly and as a result it was not possible to obtain a ^{13}C NMR spectrum.

Spectral data for **272**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 21 H), 1.153 (s, 21 H), 1.37 (s, 6 H), 1.80 (t, 2 H, J = 6.6 Hz), 2.88 (t, 2 H, J = 6.6 Hz), 4.24 (s, 3 H), 6.82 (dd, 1 H, J = 1.3, 8.2 Hz), 7.09 (t, 1 H, J = 8.0 Hz), 7.40 (dd, 1 H, J = 1.3, 7.6 Hz); Mass spectrum (FAB) *m/z* (% rel. int.) 619 M^+ + 1 (38), 618 M^+ (40), 591 (45), 578 (32); IR (neat) 2943, 2868, 2148, 1606, 1579 cm^{-1}; Anal. calcd. for $C_{38}H_{58}O_3Si_2$: C, 73.73; H, 9.44; Found: C, 73.55; H, 9.62.

Synthesis of tungsten carbene complex (274)



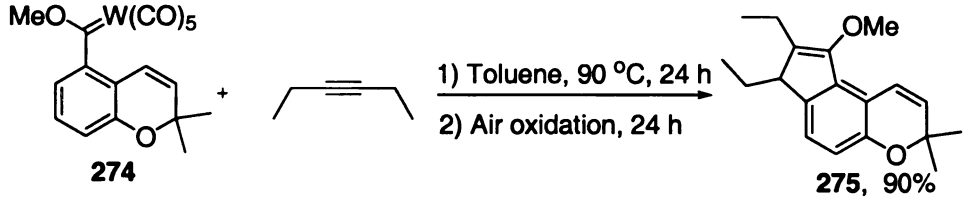
141 **274**, 66% yield

To a flame-dried 100 mL round-bottomed flask containing a solution of bromochromene **141** (536 mg, 2.24 mmol) in ether (20 mL) at -78 °C was added *tert*-BuLi (2.6 mL, 4.48 mmol, 1.7 M solution in pentane). The reaction mixture was warmed to 0 °C, stirred at this temperature for 5 min and cooled to -78 °C before it was transferred by cannula to a suspension of $W(CO)_6$ (867 mg, 2.46

mmol) in 10 mL ether maintained at 0 °C. Stirring was continued for 6 h at room temperature which was followed by removal of ether under vacuum and addition of 10 mL dichloromethane. Me_3OBF_4 (497 gm, 3.36 mmol) was then added at room temperature and reaction was further stirred for 2h. This was followed by filtration through Celite, concentration in vacuo and purification by silica gel column chromatography (5 %) EtOAc and hexane to give 773 mg (66 % yield) of carbene complex **274** as an orange solid.

Spectral data for **274**: Mp = 76 - 78 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 6 H), 4.54 (br, s, 3 H), 5.65 (d, 1 H, J = 9.8 Hz), 6.04 (d, 1 H, J = 9.9 Hz), 6.49 (d, 1 H, J = 6.9 Hz), 6.68 (dd, 1 H, J = 0.8, 8.1 Hz), 7.11 (t, 1 H, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.64, 76.00, 77.20, 114.44, 111.86, 116.58, 118.48, 128.29, 132.00, 152.58, 196.77, three Cs not located; Mass spectrum (FAB) *m/z* (% rel. int.) 526 M^+ (40), 498 (40), 469 (38),; 442 (50), 386 (25), 341 (20), 203(100); IR (neat) 2980, 2071, 1925, 1442 cm^{-1}; Anal. calcd. for $C_{18}H_{14}O_7W$: C, 41.09; H, 2.68;. Found: C, 41.49; H, 2.70.

Synthesis of cyclopentene (275)



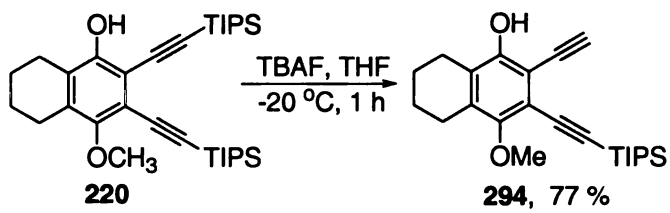
274 **275**, 90%

To a flame-dried 10 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added chromene carbene complex **274** (107 mg, 0.203 mmol), toluene (4 mL) and 3-hexyne (46 μL, 0.406 mmol). The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The

flask was back-filled with Ar at room temperature and sealed. The mixture was then stirred at 90 °C for 24 h. After 24 h, the reaction was opened to air and allowed to stir for 12 h. The reaction mixture was filtered through Celite, concentrated in vacuo and the product was purified by silica gel column chromatography using hexane and benzene (5 : 2) to give **275** (52 mg) in 91 % yield as a colorless oil.

Spectral data for **275**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.54 (t, 3 H, J = 7.3 Hz), 1.11 (t, 3 H, J = 7.6 Hz), 1.40 (s, 3 H), 1.43 (s, 3 H), 1.66-1.76 (m, 1 H), 1.88-1.99 (m, 1 H), 2.06-2.16 (m, 1 H), 2.60-2.72 (m, 1 H), 3.26 (t, 1 H, J = 4.8 Hz), 3.75 (s, 3 H), 5.61 (d, 1 H, J = 9.8 Hz), 6.57 (d, 1 H, J =7.8 Hz), 7.01 (d, 1 H, J = 10.3 Hz), 7.02 (d, 1 H, J = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.34, 14.19, 18.10, 22.40, 27.51, 27.97, 45.17, 60.37, 75.25, 112.35, 113.65, 119.26, 122.61, 130.14, 135.08, 135.89, 137.48, 151.70, 153.98; IR (neat) 2968, 2932, 2870, 1631, 1593 cm^{-1}; Mass spectrum (FAB) *m/z* (% rel. int.) 285 M^+ + 1 (90), 284 M^+ (100), 283 (70), 269 (80), 255 (30), 225 (30); HRMS (FAB) calcd for m/z $C_{19}H_{24}O_2$ 284.1776, found 284.1777 (M^+).

Synthesis of ortho-aryl diyne (294)



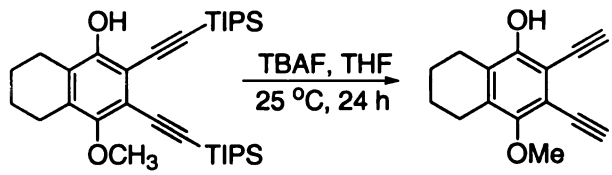
220 **294**, 77 %

To a stirred solution of **220** (1.1 gm, 2.04 mmol) in 20 mL THF at -20 °C was added TBAF (4 mL, 4.04 mmol, 1.0 M solution in THF). The reaction mixture was stirred at -20 °C for 1 h, quenched with 10 mL water and extracted with 2 X 20

mL EtOAc. The organic layer was dried over $MgSO_4$, concentrated in vacuo and the product was purified by silica gel column chromatography using a gradient of hexane and benzne (3 : 1 to 1 : 1) as eluent to give a 77 % yield of **294** (600 mg) as a light brown oil.

Spectral data for **294**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (s, 21 H), 1.65-1.80 (m, 4 H), 2.55-2.75 (m, 4 H), 3.56 (s, 1 H), 3.83 (s, 3 H), 5.73 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.35, 18.67, 21.88, 22.01, 23.50, 23.81, 60.44, 77.65, 86.75, 98.72, 101.11, 107.60, 115.60, 125.95, 134.10, 151.48, 153.07; IR (neat) 3518, 3308, 2939, 2864, 2155, 1450 cm^{-1}; Mass spectrum (EI) *m/z* (% rel. int.) 382 M^+ (80), 339 (100), 340 (29), 339 (100), 325 (66), 283 (24), 282 (23); Anal. Calcd. for $C_{24}H_{34}O_2Si$: C, 75.34; H, 8.96; Found: C, 75.04; H, 8.88.

Synthesis of ortho-aryl diyne (295)

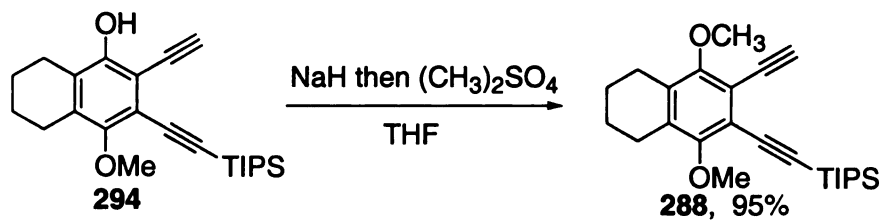


220 **295**

To a stirred solution of **220** (21 mg, 0.039 mmol) in 5 mL THF was added TBAF (120 µl, 0.117 mmol, 1.0 M solution in THF). The mixture was stirred at room temperature for 12 h and then quenched with 5 mL water. The reaction mixture was then extracted with 2 X 10 mL of EtOAc. The organic layer was dried over $MgSO_4$, concentrated in vacuo and the product was purified by silica gel column chromatography using hexane and EtOAc (10 : 1) to give diyne **295** in 70 % yield as a colorless oil.

Spectral data for **295**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60-1.70 (m, 4 H), 2.50-2.59 (m, 4 H), 3.46 (s, 1 H), 3.64 (s, 1 H), 3.83 (s, 3 H), 5.75 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.76, 21.87, 23.49, 23.77, 60.56, 77.20, 79.35, 84.15, 86.85, 107.39, 113.97, 126.65, 134.33, 151.58, 153.48; IR (neat) 3507, 3287, 2936, 2862, 2839, 2106, 1452; Mass spectrum (EI) *m/z* (% rel. int.) 227 M^+ + 1 (80), 227 (90), 225 (35), 165 (35), 152 (30); Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24; Found: C, 79.99; H, 6.35.

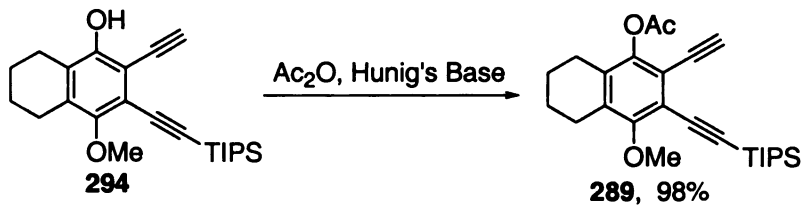
Synthesis of ortho-aryldiyne (288)



To a stirred solution of **294** (556 mg, 1.45 mmol) in 10 mL THF was added solid sodium hydride (76 mg, 1.90 mmol, 60 % dispersion in mineral oil). The reaction mixture was stirred for 15 min at room temperature and then $(CH_3)_2SO_4$ (275 μL, 2.90 mmol) was added. After stirring for 24 h at room temperature, the reaction mixture was quenched with 5 mL water and diluted with 20 mL EtOAc. The aqueous layer was washed with another 10 mL of EtOAc. The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The product was purified by silica gel column chromatography using hexane and benzene (1 : 1) to give the diyne **288** as an off-white solid in 95 % (432 mg) yield.

Spectral data for **288**: Mp = 48 - 50 °C; ^{1}H NMR (500 MHz, $CDCl_3$)) δ 1.05 (s, 21 H), 1.56-1.68 (m, 4 H), 2.52-2.64 (m, 4 H), 3.31 (s, 1 H), 3.74 (s, 3 H), 3.77 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.36, 18.66, 22.00, 22.01, 23.74, 60.19, 60.28, 78.75, 84.50, 99.06, 101.05, 116.36, 117.91, 133.10, 133.55, 155.70, 155.96, one sp^3 C not located; IR (neat) 3314, 2939, 2864, 2152, 2112, 1454 cm^{-1}; Mass spectrum (EI) *m/z* (% rel. int.) 396 M^+ (100), 354 (27), 339 (17), 324 (15), 311 (28), 281 (22); Anal. Calcd. for $C_{25}H_{36}O_2Si$: C, 75.70; H, 9.15; Found: C, 75.60; H, 8.85.

Synthesis of ortho-aryldiyne (289)

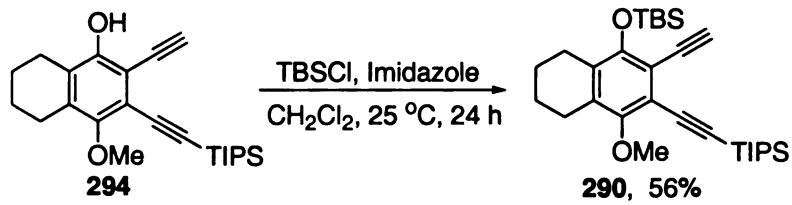


To a solution of **294** (26 mg, 0.068 mmol) in CH_2Cl_2 (5 mL) was added DMAP (1.7 mg, 0.014 mmol), Ac_2O (10 μL, 0.081 mmol) and Hunig's base (24 μL, 0.136 mmol). The reaction mixture was stirred at room temperature for 24 h, quenched with 5 mL water and extracted with EtOAc (2 X 20 mL). The organic layer was washed with 10 mL water, dried over $MgSO_4$ and concentrated in vacuo. The product was purified by silica gel column chromatography using hexane : EtOAc (20 : 1) to give 28 mg of **289** (98 % yield) as an off-white solid.

Spectral data for **289**: Mp = 96 - 98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (s, 21 H), 1.65-1.75 (m, 4 H), 2.30 (s, 3 H), 2.42-2.58 (m, 2 H), 2.62-2.78 (m, 2 H), 3.31 (s, 1 H), 3.88 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.35, 18.67, 20.58, 21.68, 21.79, 23.71, 23.78, 60.29, 77.17, 84.54, 99.84, 100.65, 117.11, 117.97, 132.14,

133.60, 146.55, 157.21, 168.63; IR (neat) 3314, 2939, 2884, 2154, 1768, 1452 cm^{-1}; Mass spectrum (EI) *m/z* (% rel. int.) 424 M^+ (10), 383 (91), 382 (100), 340 (20), 267 (7); Anal. Calcd. for $C_{26}H_{36}O_3Si$: C, 73.54; H, 8.54; Found: C, 73.77; H, 9.03.

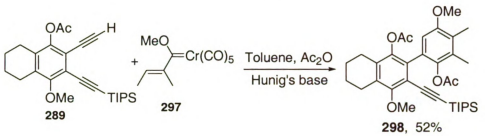
Synthesis of ortho-aryl diyne (290)



To a stirred solution of **294** (200 mg, 0.523 mmol) in 10 mL CH_2Cl_2 was added TBSCl (157 mg, 1.046 mmol) and imidazole (107 mg, 1.569). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then concentrated in vacuo and the product was purified by silica gel column chromatography using hexane and benzene (3 : 1) to give a 56 % yield of **290** (145.5 mg) as an off white solid.

Spectral data for **290**: 62 - 64 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 0.25 (s, 6 H), 1.02 (s, 9 H), 1.14 (s, 21 H), 1.63-1.74 (m, 4 H), 2.58 (t, 2 H, J = 5.9 Hz), 2.69 (t, 2 H, J = 6.2 Hz), 3.27 (s, 1 H), 3.85 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -2.39, 11.42, 18.71, 22.04, 22.21, 23.82, 25.29, 26.20, 60.25, 80.76, 84.79, 98.59, 101.62, 114.35, 117.85, 131.38, 133.24, 151.09, 154.06, one sp^3 C not located; IR (neat) 3314, 2937, 2862, 2152, 1462 cm^{-1}; Mass spectrum (EI) *m/z* (% rel. int.) 496 M^+ (16), 440 (42), 425 (100), 383 (15), 341 (19); Anal. Calcd. for $C_{30}H_{48}O_2Si_2$: C, 72.52; H, 9.74; Found: C, 72.53; H, 9.64.

Synthesis of bis-aryl phenol derivative (298)

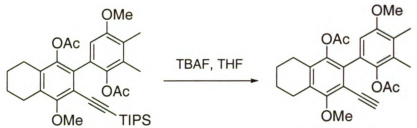


To a flame-dried 10 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added 2-butenyl carbene complex **297** (108.24 mg, 0.373 mmol), toluene (7.0 mL), bis-alkyne **289** (144 mg, 0.339 mmol), Ac_2O (106 μL, 1.119 mmol) and N,N-diisopropylethylamine (325 μL, 1.865 mmol). The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The reaction mixture was then stirred at 80 °C for 48 h. After 48 h, the reaction mixture was opened to air and allowed to stir for 12 h. The reaction mixture was filtered through Celite, concentrated in vacuo and the product was purified by silica gel column chromatography using hexane and EtOAc (10 :1) to give a 57 % yield (125 mg) of biaryl **298** as a brownish oil.

Spectral data for **298**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (s, 21 H), 1.60-1.85 (m, 4 H), 1.95 (s, 3 H), 1.97 (s, 3 H), 2.01 (s, 3 H), 2.12 (s, 3 H), 2.28-2.68 (m, 2 H), 2.68-2.82 (m, 2 H), 3.70 (s, 3 H), 3.90 (s, 3 H), 6.54 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.14, 12.00, 13.47, 18.32, 20.42, 20.45, 21.91, 21.98, 23.60, 23.95, 55.63, 60.20, 98.11, 101.12, 110.04, 115.82, 125.84, 126.33, 130.00, 131.48, 131.96, 132.16, 140.77, 142.76, 154.60, 157.21, 168.78, 169.62; IR (neat) 2941, 2864, 2154, 1765 cm^{-1}; Mass spectrum (FAB) *m/z* (% rel. int.) 593 M^+ + 1 (40),

551 (45), 550 (100), 549 (90), 508 (40), 507 (70), 465 (35); Anal. calcd. for $C_{35}H_{48}O_6Si$: C, 70.91; H, 8.16; Found: C, 71.27; H, 8.19.

Synthesis of bis-aryl phenol derivative (299)



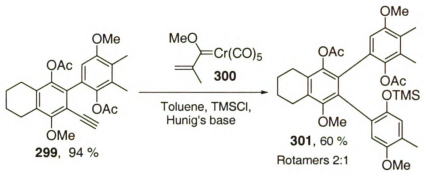
298 **299**, 94 %

To a stirred solution of **298** (35 mg, 0.059 mmol) in 1 mL THF at 0 °C was added TBAF (118 μL, 0.118 mmol, 1.0 M solution in THF). After stirring for 1 h at 0 °C, the reaction mixture was diluted with 10 mL EtOAc and quenched with 5 mL water. The organic layer was separated and the aqueous layer was washed with 2 X 10 mL EtOAc. The organic layer was washed with 5 mL of water, dried over $MgSO_4$, conc. in vacuo and purified by silica gel column chromatography using hexane : EtOAc (3 : 1) as eluent to give **299** (24 mg, 94 % yield) as a white crystalline solid. The compound was characterized by X-ray diffraction. The data is in the appendix.

Spectral data for **299**: Mp = 149 - 151 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64-1.84 (m, 4 H), 1.95 (s, 3 H), 1.98 (s, 3 H), 2.07 (s, 3 H), 2.17 (s, 3 H), 2.30-2.60 (m, 2 H), 2.70-2.82 (m, 2 H), 3.10 (s, 1 H), 3.73 (s, 3 H), 3.88 (s, 3 H), 6.59 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.23, 13.59, 20.38, 20.47, 21.86, 21.90, 23.61, 24.04, 55.76, 60.34, 78.14, 84.33, 110.49, 114.28, 125.87, 126.12, 130.01, 131.73, 132.07, 132.61, 140.57, 142.80, 154.56, 157.86, 168.74, 169.25; IR (neat) 3283, 2937, 2862, 1761 cm^{-1}; Mass spectrum (EI) *m/z* (% rel. int.) 437 M^+ + 1, 395 (31),

394 (100), 380 (22), 353 (55), 338 (50); Anal. calcd. for $C_{26}H_{28}O_6$: C, 71.54; H, 6.47. Found: C, 71.47; H, 6.41.

Synthesis of tris-aryl phenol derivative (301)



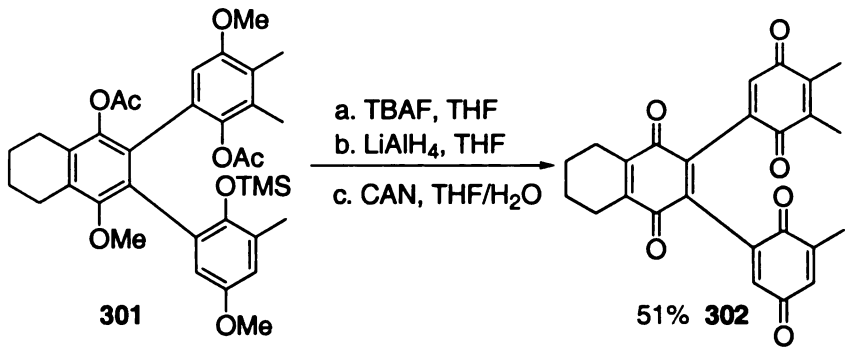
To a flame-dried 10 mL flask with the 14/20 joint replaced by a high-vacuum threaded Teflon stopcock was added the 2-propenyl carbene complex **300** (33 mg, 0.120 mmol), toluene (1.6 mL), biaryl alkyne **299** (35 mg, 0.080 mmol), TMSCl (30 μL, 0.240 mmol) and N,N-diisopropylethylamine (70 μL, 0.400 mmol). The system was deoxygenated by the freeze-pump-thaw method (-196 to 25 °C, 3 cycles). The flask was back-filled with Ar at room temperature and sealed. The mixture was then stirred at 50 °C for 24 h. After 24 h, the reaction was opened to air and allowed to stir for 12 h. The reaction mixture was filtered through Celite, concentrated in vacuo and the product was purified by silica gel column chromatography using hexane and EtOAc (4 : 1) as eluent to give 33 mg of major rotamer (R_f = 0.42, 20 % of ethyl acetate in hexanes) as a colorless oil and 16.6 mg of minor rotamer (R_f = 0.38, 20 % of ethyl acetate in hexanes) as a colorless oil, a mixture of two rotamers of triaryl phenol derivative **301** (49.6 mg, 60 % yield).

Spectral data for **301** (Minor Rotamer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 9 H), 1.68-1.90 (m, 4 H), 1.85 (s, 3 H), 1.99 (s, 6 H), 2.05 (s, 3 H), 2.07 (s, 3 H), 2.32-2.50 (m, 1 H), 2.58-2.72 (m, 1 H), 2.76 (s, 2 H), 3.26 (s, 3 H), 3.41 (s, 3 H), 3.57 (s, 3 H), 6.32 (s, 1 H), 6.38 (s, 1 H), 6.45 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.36, 12.03, 13.66, 16.07, 20.57, 20.62, 22.19, 22.32, 23.83, 23.99, 55.67, 55.72, 59.48, 111.02, 114.59, 120.33, 124.96, 125.63, 126.48, 128.99, 129.60, 129.70, 130.42, 130.94, 140.71, 142.85, 146.98, 150.55, 153.76, 153.93, 3 sp^2 Cs not located;

Spectral data for **301** (Major Rotamer) : ^{1}H NMR (500 MHz, $CDCl_3$) δ; 0.11 (s, 9 H), 1.60-2.00 (m, 4 H), 1.96 (s, 3 H), 2.04 (s, 6 H), 2.08 (s, 6 H), 2.30-2.90 (m, 4 H), 3.29 (s, 3 H), 3.24 (s, 3 H), 3.42 (s, 3 H), 6.27 (s, 1 H), 6.42 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.42, 12.06, 13.26, 14.03, 16.10, 20.64, 22.28, 22.31, 22.36, 23.99, 55.28, 55.79, 59.84, 111.79, 114.47, 120.27, 124.71, 125.68, 126.89, 128.74, 130.56, 141.02, 142.78, 146.97, 151.21, 154.21. 168.88, 1 carbonyl C and 5 sp^2 Cs not located.

Spectral data for **301** (Mixture of rotamers): IR (neat) 2936, 2860, 1759, 1510 cm^{-1}; Mass spectrum (FAB) *m/z* (% rel. int.) 621 M^+ + 1 (60 %), 620 M^+ (100), 579 (50), 578 (70), 536 (40), 506 (20); Anal. calcd. for $C_{35}H_{44}O_8Si$: C, 67.71; H, 7.14; Found: C, 67.66; H, 7.13.

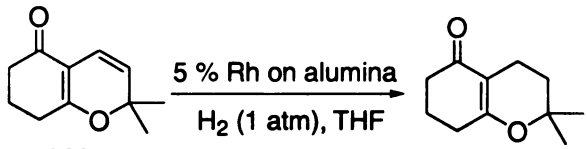
Synthesis of tris-quinone (302)



To a stirred solution of **301** (35 mg, 0.056 mmol) in 5 mL THF at 0 °C added TBAF (112 μL, 0.112 mmol, 1.0 M solution in THF). After 20 min, the reaction mixture was quenched with water (5 mL) and diluted with ethyl acetate (10 mL). The organic layer was separated and the water layer was extracted with (2 x 10 mL) ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated in vacuuo. The residue was redissolved in 5 mL THF and cooled at 0 °C. $LiAlH_4$ (224 μL, 0.224 mmol) was added to this reaction mixture. After stirring for 1 h at 0 °C, the reaction mixture was carefully quenched with 5 mL water. The water layer was extracted with ethyl acetate (5 x 10 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuuo. The residue was dissolved in 8 mL THF and maintained at 0 °C. A solution of CAN (245 mg, 0.448 mmol) in 2 mL water was then added to the reaction mixture. After 10 min, the reaction was quenched by 5 mL H_2O. The water layer was extracted with ethyl acetate (3 x 10 mL). The organic layer was dried over $MgSO_4$, concentrated in vacuuo and purified using silica gel column chromatography to furnish tris-quinone **302** as a yellow solid (12.2 mg, 52 % yield).

Spectral Data: Mp 188-190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68-1.74 (m, 4 H), 1.99 (d, 3 H, J = 1.1 Hz), 2.01 (d, 3 H, J = 1.1 Hz), 2.03 (d, 3 H, J = 1.6 Hz), 2.40-2.48 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.64, 185.98, 185.04, 184.18, 146.42, 143.18, 143.15, 141.62, 141.33, 139.54, 134.41, 133.36, 22.72, 22.70, 20.79, 15.73, 12.52, 12.27 (7 carbons not located); IR (CH_2Cl_2) 3277, 2928, 2856, 1651 cm^{-1}; Mass spectrum (FAB) *m/z* (% rel. int.) 417 M^+ + 1 (25), 252 (82). HRMS (FAB$^+$) calcd for $C_{25}H_{20}O_6$ m/z 416.1260, measd 417.1341 M^+ + 1.

Synthesis of chromanone 342

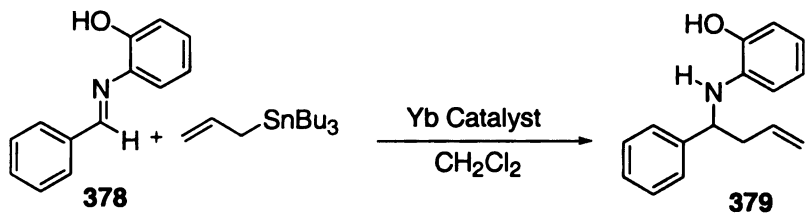


144 **342**, 92 %

To a solution of **144** (2.00 gm, 11.22 mmol) in 60 ml THF added 5 % on alumina (200 mg). The reaction mixture was flushed with H_2 and was stirred at room temperature under 1 atm of H_2 for 1 h 30 min. The reaction mixture was filtered through Celite and purified using silica gel column chromatography (2 : 1, hexane : EtOAc) to give chromenone **342** in 92 % yield as an oil which solidified at 0 °C.

Spectral Data: Mp 28 - 30°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 6 H), 1.58 (t, 2 H, J = 6.6 Hz), 1.80-1.94 (m, 2 H), 2.16 (tt, 2 H, J = 1.7, 6.6 Hz), 2.22-2.33 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.57, 20.90, 26.46, 29.06, 32.15, 36.64, 76.87, 109.90, 170.39, 198.05; IR (CH_2Cl_2) 2976, 2941, 2870, 1653, 1620 cm^{-1}; mass spectrum (EI) m/z (% rel intensity) 181 M^+ + 1(100), 180 M^+ (4), 137 (7), 109 (4)

Typical procedure for the allylation of imine 378

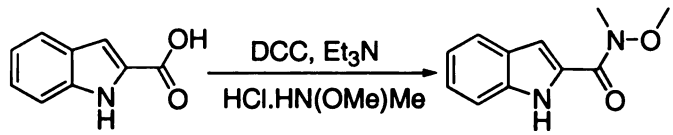


378 **379**

To a mixture of $Yb(OTf)_3$ (22 mg, 0.036 mmol), (S)-VANOL (17.6 mg, 0.040 mmol) and 4Å MS (100 mg) was added DBU (12 μL, 0.080 mmol) in dichloromethane (1.3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. A solution of imine **378** (36 mg, 0.182 mmol) in 0.050 mL dichloromethane, a solution of DTBMP (38 mg, 0.182 mmol) in 0.05 mL dichloromethane and allyltributyl stannane (113 μL, 0.364 mmol) was added at 0 °C and stirred for 40 h. The reaction mixture was diluted with dichloromethane (20 mL) and quenched with water (5 mL). The organic layer was dried over $MgSO_4$, concentrated in vacuuo and the product was purified by silica gel column chromatography (10 : 1, hexane : EtOAc) to give **379** (62 %) as colorless liquid.

Spectral Data: ^1H NMR (300 MHz, $CDCl_3$) δ 2.42-2.70 (m, 2 H), 4.41 (s, 1 H), 4.89 (brs, 1 H), 5.19 (d, 1 H, J = 14 Hz), 5.25 (d, 1 H, J = 18 Hz), 5.72-5.92 (m, 1 H), 6.44 (d, 1 H, J = 8.0 Hz), 6.54-6.62 (m, 1 H), 6.62-6.82 (m, 2 H), 7.24-7.30 (m, 1 H), 7.34 (t, 2 H, J = 7.2 Hz), 7.40 (d, 2 H, J = 7.9 Hz), one exchangeable proton not located; ^{13}C NMR (300 MHz, $CDCl_3$) δ 43.06, 57.67, 113.63, 114.18, 117.63, 118.21, 121.45, 126.35, 126.95, 128.49, 134.56, 135.97, 143.40, 143.51; IR (CH_2Cl_2) 3422, 3061, 3028, 2924, 1610, 1512 cm^{-1}; mass spectrum (EI) m/z (% rel intensity) 240 M^+ + 1 (18), 239 M^+ (6), 238 (13), 199 (17), 198 (100), 120 (20).

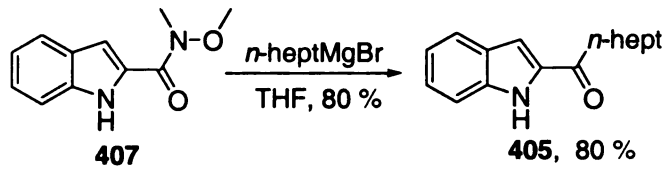
Synthesis of N-methoxy-N-methyl-1H-indole-2-carboxamide (407).[89]



406 **407**

To a flame-dried round-bottomed flask under a N_2 atmosphere was added indole-2-carboxylic acid (500 mg, 3.1 mmol), N,O-dimethylhydroxylamine hydrochloride (300 mg, 3.1 mmol), triethylamine (0.44 mL, 3.1 mmol) and anhydrous methylene chloride (20 mL). After stirring at room temperature for 5 min, the reaction mixture was cooled to 0 °C and solid dicyclohexylcarbodiimide (640 mg, 3.1 mmol) was added. The reaction mixture was allowed to warm to room temperature over 15 min and then stirring was continued at room temperature for 3 h. The solvent was removed under vaccum and the crude product was purified by silica gel chromatography (30 % acetone/hexanes) to give 475 mg (75 %) of the desired amide **407** as a bright yellow solid.[89] Spectral data for **407**: Mp 147-149 °C (acetone/hexanes) (lit: mp 147-149 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.44 (s, 3 H), 3.84 (s, 3 H), 7.12 (ddd, 1 H, J = 8.1, 7.1, 1.1 Hz), 7.23 (dd, 1 H, J = 2.0, 0.9 Hz), 7.29 (ddd, 1 H, J = 8.1, 7.1, 1.1 Hz), 7.42 (dd, 1 H, J = 8.2, 0.9 Hz), 7.69 (dd, 1 H, J = 8.2, 0.9 Hz), 9.56 (br, s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.2, 61.3, 108.0, 111.7, 120.4, 122.5, 124.8.0, 128.0, 128.2, 135.8, 161.7; mass spectrum (EI) m/z (% rel. intensity) 204 M^+ (57), 144 (100), 116 (91), 889 (100); IR (CH_2Cl_2, cm^{-1}) 3276, 1605. Anal calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found C, 64.98; H, 5.79; N, 13.69.

Synthesis of 1-(1H-indol-2-yl)octan-1-one (405)

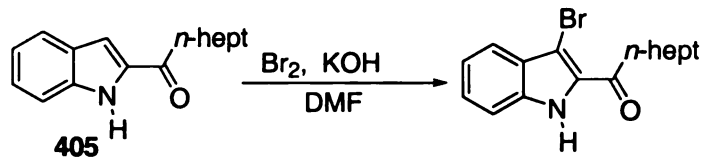


407 **405**, 80 %

To a stirred suspension of Mg (4.8 g, 196 mmol) in 20 mL THF under N_2 atmosphere was added 1-chloroheptane (7.5 mL, 49 mmol) and a pinch of I_2 to give a brown colored solution. The mixture was refluxed until the solution became colorless. At this point, the reaction mixture was warmed to room temperature and the remainder of the 1-chloroheptane (7.5 mL, 49 mmol) was added dropwise over 15 min. The solution was stirred at room temperature for 1 h and then the reaction mixture was transferred to a solution of amide **407** (4.00 g, 19.6 mmol) in anhydrous THF (20 mL) at 0 °C. The resulting solution was stirred for 12 h, quenched with 5 % HCl/ice-H_2O at 0 °C and extracted with 3x50 mL of ether. The combined organic layer was dried over Na_2SO_4, evaporated to a yellow oil and loaded onto a silica gel chromatography and eluted (10% ethyl acetate/hexanes) to give the desired ketone **405** (4.05 g, 90 %) as white solid. Spectral data for **405**: Mp 115-117 °C (ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.87 (t, 3 H, J = 6.9 Hz), 1.22-1.43 (m, 8 H), 1.73-1.81 (m, 2 H), 2.92 (t, 2 H, J = 7.4 Hz), 7.13 (ddd, 1 H, J = 8.0, 7.1, 1.1 Hz), 7.17-7.19 (m, 1 H), 7.32 (ddd, 1 H, J = 8.3, 7.3, 1.1 Hz), 7.41 (dt, 1 H, J = 8.4, 0.9 Hz), 7.69 (dd, 1 H, J = 7.9, 1.1 Hz), 9.10 (br, s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.03, 22.60, 25.19, 29.10, 29.37, 31.68, 38.39, 109.09, 112.24, 120.84, 122.96, 126.1, 127.58, 135.27, 137.27, 193.77; IR (CH_2Cl_2, cm^{-1}) 3316, 2928, 2857, 1653; mass spectrum (EI) m/z (% rel. intensity) 243 M^+ (31), 159 (100), 144 (70), 118

(20), 89 (47), 84 (58). Anal calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found C, 78.88; H, 8.37; N, 5.80.

Synthesis of 1-(3-bromo-1H-indol-2-yl)-octan-1-one (408)



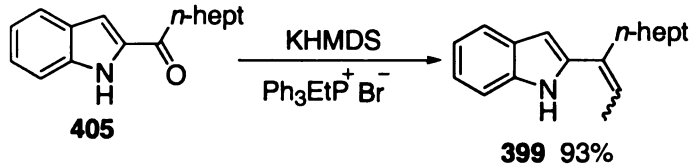
405 **408**, 71%

An ice-cooled solution of Br_2 (0.22l μL, 4.3 mmol) in DMF (10 mL) was added to the solution of **405** (400 mg, 1.7 mmol) and powdered KOH (58 mg, 12.9 mmol) in DMF (10 mL). After stirring at room temperature for 6 h, the mixture was poured into a solution of 28 % NH_4OH (25 mL) and $NaHSO_3$ (230 mg) in water (375 mL) to give a yellow precipitate. The precipitate separated by filtration and purified using silica gel chomatography (10 % ethylacetate/hexane) to give **408** (370 mg, 71 %) as light yellow solid. R_f (hexanes/ethylacetate 10:1) = 0.50.

Spectral data for **408**: Mp 125 - 127 °C (hexane/EtOAc); ^1H NMR (500MHz, $CDCl_3$): δ 0.88 (t, 3 H, J = 6.9 Hz), 1.23-1.46 (m, 8 H), 1.75-1.84 (m, 2 H), 3.17 (t, 2 H, J = 7.4 Hz), 7.20 (ddd, 1 H, J = 1.3, 6.7, 8.1 Hz), 7.34 - 7.42 (m, 2 H), 7.66 (qd, 1 H, J = 8.2, 0.9 Hz), 9.50 (br, s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.06, 22.62, 24.27, 29.14, 29.32, 31.71, 40.91, 97.4, 112.24, 121.51, 121.76, 127.15, 128.25, 132.11, 135.42, 192.97; mass spectrum (EI) *m/z* (% rel. intensity) 323 (17, ^{81}Br), 321 (19, ^{79}Br), 242 (23), 239 (94, ^{81}Br), 237 (100, ^{79}Br), 224 (64, ^{81}Br), 222 (61, ^{79}Br), 197 (17, ^{81}Br), 195 (19, ^{79}Br), 171 (28), 144 (21), 88 (31); IR

(CH_2Cl_2, cm^{-1}) 3304, 2922, 2855, 1642. Anal calcd for $C_{16}H_{20}BrNO$: C, 59.64; H, 6.26; N, 4.35. Found C, 59.60; H, 6.18; N, 4.36.

Synthesis of 2-(dec-2-en-3-yl)-1H-indole (399)



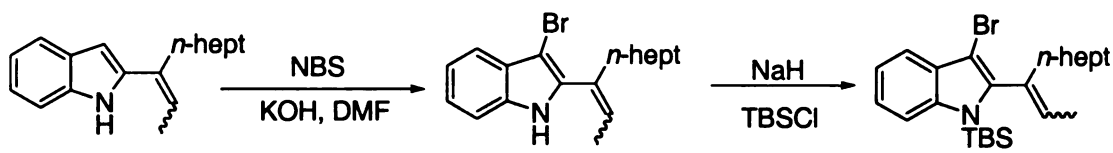
405 **399** 93%

E : *Z* = 1.0 : 0.84

To a stirred suspension of ethyltriphenylphosphonium bromide (78 g, 210 mmol) in toluene (210 mL) under N_2 at room temperature was added solid KHMDS (44 g, 210 mmol) over 30 min. The solution was stirred at room temperature for 1 h and then the solid ketone **405** (13 g, 42 mmol) was added. After stirring vigorously for 3 days at room temperature, the reaction mixture was quenched with 10 mL of H_2O at 0 °C. At this point the reaction mixture was filtered and washed with 3 x 150 mL of ether. The combined organic layers were evaporated and purified by silica gel chromatography (10 % EtOAc/hexanes) to give **399** (12.1 g, 93 %) as light pink oil and as a 1.0 : 0.8 ratio of E : Z isomers. These isomers were not separable and the following spectral data were collected on the mixture. The ^1H and ^{13}C spectral data of each isomer were determined with the aid of samples of **399** with different ratios of E : Z isomers. The stereochemical assignment was made based on the NOE data shown below. Spectral data of **399**: ^1H NMR (500 MHz, $CDCl_3$) (Z isomer) δ 0.87 (t, 3 H, J = 7.1 Hz), 1.18-1.60 (m, 10 H), 1.90 (dd, 3 H, J = 1.3, 7.1 Hz), 2.40 (td, 2 H, J = 7.6, 1.1 Hz), 5.68 (qd, 1 H, J = 7.1, 1.3 Hz), 6.42-6.48 (m, 1 H), 7.01-7.20 (m, 2 H), 7.32-7.36 (m, 1 H), 7.59 (dd, 1 H, J = 0.9, 7.7 Hz), 7.98 (br s, 1 H); (E isomer)

δ 0.87 (t, 3 H, J = 7.1 Hz), 1.18-1.40 (m, 8 H), 1.46-1.56 (m, 2 H), 1.83 (d, 3 H, J = 7.1 Hz), 2.48 (t, 2 H, J = 7.8 Hz), 5.88 (q, 1 H, J = 7.1 Hz), 6.38 (d, 1 H, J = 1.5 Hz), 7.04 (ddd, 1 H, J = 7.5, 7.1, 1.1 Hz), 7.11 (ddd, 1 H, J = 8.1, 7.1, 1.1 Hz), 7.27 (dd, 1 H, J = 8.8, 0.8 Hz), 7.53 (d, 1 H, J = 7.7 Hz), 8.02 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) (Z isomer) δ 14.05, 15.24, 22.62, 29.04, 29.09, 29.28, 31.82, 37.72, 102.29, 110.513, 119.758, 120.25, 121.66, 123.73, 128.50, 132.72, 135.62, 137.13; (E isomer) δ 13.71, 14.07, 22.65, 28.87, 29.20, 29.29, 29.76, 31.86, 99.49, 110.32, 119.75, 120.06, 120.28, 121.88, 129.08, 133.08, 136.26, 139.73; IR (CH_2Cl_2) 3422, 3057, 3032, 2930, 2855, 1651 cm^{-1}; mass spectrum (EI) *m/z* (% rel intensity) 255 M^+ (90), 240 (90), 171 (100), 130 (100), 117 (100). Anal calcd for $C_{18}H_{25}N$: C, 84.65; H 9.87; N 5.48. Found C, 84.24; H, 9.90; N, 5.43.

Synthesis of 1-(tert-butyldimethylsilyl)-3-bromo-2-(dec-2-en-3-yl)-1H-indole (410)



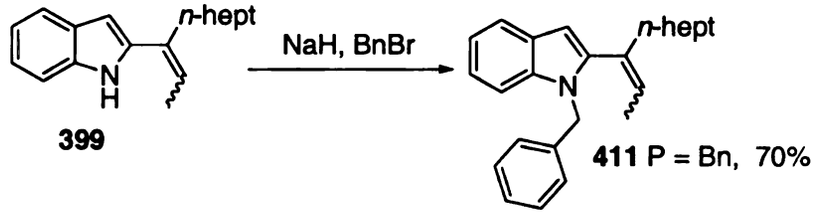
399 **409** **410**

45 % from **399**

To a solution of vinyl indole **399** (230 mg, 0.96 mmol) in 10 mL of DMF at room temperature was added crushed KOH (59 mg, 1.05 mmol). After stirring for 30 min at room temperature, NBS (187 mg, 1.05 mmol) was added, and the reaction mixture was again stirred for 1 h at room temperature. At this point the reaction mixture was diluted with CCl_4 and washed with 3x10 mL of brine and

2x10 mL of water. The organic extract was dried over $MgSO_4$ and evaporated to a brown residue. This residue containing **409** was then dissolved in 10 mL THF and transferred to a flame-dried round-bottomed flask containing a suspension of NaH (50 mg, 1.25 mmol, 60 % dispersion in mineral oil) in THF (5 mL). Then, a *tert*-butyldimethylsilyl chloride (173 mg, 1.15 mmol) solution in THF (5 mL) was added and the resulting solution was stirred for 6 h at room temperature. The reaction mixture was diluted with ether and washed with three portions of water and brine. The organic fraction was dried over $MgSO_4$, filtered and evaporated to give a brown residue. The residue was purified by column chromatography using ethyl acetate/hexanes (10 %) to give **410** (183 mg, 45 %) as light yellow oil. R_f (Hexanes/benzene 5:1) = 0.62.

Synthesis of 1-benzyl-2-(dec-2-en-3-yl)-1H-indole (411)

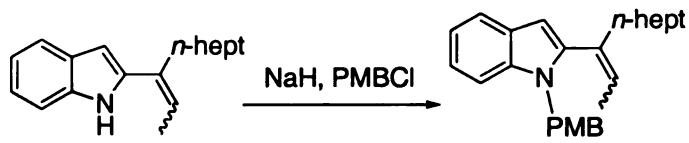


To a suspension of sodium hydride (132 mg, 1.5 mmol) in 11 mL of DMF at room temperature was added a solution of 2-vinyl indole **399** (562 mg, 2.2 mmol, E/Z ratio of 1:0.7) in 5 mL DMF. The reaction mixture was stirred for 30 min and then benzyl bromide (376 mg, 2.2 mmol) was added in small portions. After reaction mixture had stirred for 3 h at room temperature, it was carefully quenched with water and extracted with 3x20 mL of ethyl acetate. The combined organic extract was washed with 20 mL of brine and 20 mL of H_2O. The organic fraction was dried over $MgSO_4$, filtered, evaporated to a yellow oil, and purified

by silica gel chromatography (10 % EtOAc/hexane) to give 531 mg of **411** (70 %) as colorless oil and as a 1.0 : 0.5 ratio of E : Z isomers. These isomers were not separable and the following spectral data were collected on the mixture. The ^{1}H and ^{13}C spectral data of each isomer were determined with the aid of samples of **411** with different ratios of E : Z isomers.

Spectral data of **411**: ^{1}H NMR (500 MHz, $CDCl_3$) (Z isomer) δ 0.84 (t, 3 H, J = 7.1 Hz), 1.10-1.35 (m, 10 H), 1.48 (dt, 3 H, J = 6.8, 1.1 Hz), 2.13 (tt, 2 H, J = 1.1, 7.7 Hz), 5.2 (s, 2 H), 5.77 (qt, 1 H, J = 7.6, 1.2 Hz), 6.30 (d, 1 H, J = 0.8 Hz), 6.98 (d, 2 H, J = Hz), 7.06-7.11 (m, 2 H), 7.11-7.16 (m, 1 H), 7.16-7.25 (m, 3 H), 7.57-7.63 (m, 1 H); (E-isomer): δ 0.86 (t, 3 H, J = 7.1 Hz), 1.14-1.36 (m, 10 H), 1.76 (d, 3 H, J = 6.8 Hz), 2.35 (t, 2 H, J = 7.7 Hz), 5.31 (s, 2 H), 5.62 (q, 1 H, J = 6.8 Hz), 6.64 (s, 1 H), 7.00-7.04 (m, 2 H), 7.07-7.11 (m, 3 H), 7.18-7.29 (m, 3 H), 7.57-7.64 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) (Z isomer): δ 14.04, 15.20, 22.61, 28.28, 29.07, 29.14, 31.81, 38.56, 47.26, 101.42, 110.25, 119.51, 120.14, 120.98, 126.23, 127.00, 127.58, 128.44, 128.47, 133.543, 136.96, 138.15, 139.68; (E isomer) δ 13.09, 14.04, 22.61, 28.42, 29.11, 29.47, 31.31, 31.81, 47.68, 100.83, 110.30, 119.73, 120.147, 121.24, 125.97, 126.96, 127.30, 128.24,5, 128.57, 133.30, 137.59, 138.48, 143.95; IR (CH_2Cl_2) 3058, 3031, 2955, 2926, 2857 cm^{-1}; mass spectrum (EI) *m/z* (% rel intensity) 345 M^+ (65), 330 (23), 260 (47), 246 (31), 91 (100). Anal calcd for $C_{25}H_{31}N$: C, 86.90; H, 9.04; N, 4.05. Found C, 86.95; H, 8.84; N, 3.85.

Synthesis of 1-(4-methoxybenzyl)-2-(dec-2-en-3-yl)-1H-indole (412)

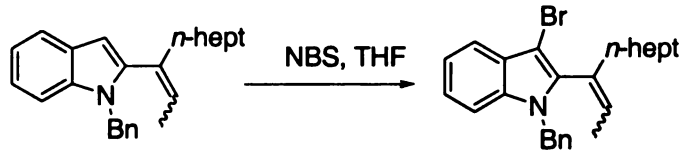


399 **412** P = PMB 70%

To a suspension of sodium hydride (95.6 mg, 2.39 mmol, 60 % dispersion in mineral oil) in 8 mL of DMF at room temperature was added a solution of vinyl indole **399** (554 mg, 2.17 mmol, E/ Z ratio of 1:0.6) in 5 mL DMF. The reaction mixture was stirred for 30 min and then PMBCl (357 mg, 2.46 mmol) was added in small portions. After the reaction mixture was stirred for 3 h at room temperature, it was carefully quenched with water and extracted with 3 x 10 mL of ethyl acetate. The combined organic extract was washed with 10 mL of brine and 10 mL of H_2O. The organic fraction was dried over $MgSO_4$, filtered, evaporated to a yellow oil, and purified by silica gel chromatography (10 % EtOAc/hexane) to give 586 mg of **412** (72 % yield) as a colorless oil and as a 1.0 : 0.5 ratio of E : Z isomers. These isomers were not separable and the following spectral data were collected on the mixture. Spectral data of **412**: ^{1}H NMR (300 MHz, $CDCl_3$): (E-isomer) δ 0.87 (t, 3 H, J = 6.6 Hz), 1.00-1.40 (m, 10 H), 1.78 (d, 3 H, J = 6.9 Hz), 2.36 (t, 2 H, J = 6.0 Hz), 3.76 (s, 3 H), 5.26 (s, 2 H), 5.64 (q, 1 H, J = 6.9 Hz), 6.41 (s, 1 H), 6.78-7.20 (m, 7 H), 7.58-7.64 (m, 1 H); (Z-isomer) δ 0.87 (t, 3 H, J = 6.6 Hz), 1.00-1.40 (m, 10 H), 1.50 (d, 3 H, J = 6.9 Hz), 2.17 (t, 2 H, J = 6.0 Hz), 3.76 (s, 3 H), 5.18 (s, 2 H), 5.80 (q, 1 H, J = 6.4 Hz), 6.31 (s, 1 H), 6.78-7.20 (m, 7 H), 7.58 -7.64 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.62, 15.24, 14.08, 13.94, 22.62, 28.26, 28.40, 29.10, 29.14, 29.47, 31.28, 31.81,

38.57, 55.16, 47.08, 46.67, 100.65, 101.25, 110.27, 110.32, 113.79, 113.90, 119.42, 119.65, 120.07, 120.87, 121.15, 127.08, 127.19, 127.40, 127.48, 128.15, 128.36, 130.14, 130.42, 133.13, 133.48, 136.79, 137.46, 139.60, 143.89, 158.48, 158.53, 5 aliphatic and 1 aryl carbons not located; IR (CH_2Cl_2) 3031, 2997, 2928, 2855, 1613, 1512, 1482, 1443 cm^{-1}; mass spectrum (EI) *m/z* (% rel intensity) 375 M^+ (80), 290 (27), 254 (29), 227 (86), 121 (100). Anal calcd for $C_{26}H_{33}NO$: C, 83.15; H, 8.86; N, 3.73. Found C, 82.78; H, 9.08; N, 3.66.

Synthesis of 1-benzyl-3-bromo-2-(dec-2-en-3-yl)-1H-indole (413)



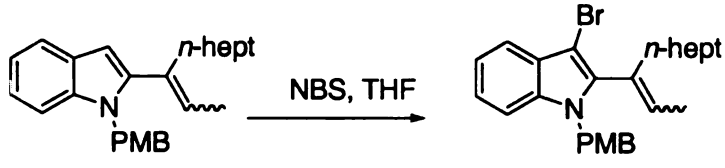
411 **413**, 90 %

To a stirred solution of **411** (1.00 g, 2.89 mmol, E/Z ratio of 1:0.5) in 20 mL of DMF under a N_2 atmosphere was added NBS (540 mg, 3.03 mmol). The reaction mixture was stirred for 15 min and quenched with water and diluted with ether. The water layer was extracted with 2x20 mL of ether. The combined organic extract was washed with 2x10 mL of brine, 2x10 mL of water and dried over $MgSO_4$. The solvent was evaporated to give a light green residue which was purified using silica gel chromatography (5 % EtOAc/hexanes) to give the desired compound **413** (1.09 g, 90 %) as a light green oil and as a 1.0 : 0.4 ratio of E : Z isomers. These isomers were not separable and the following spectral data were collected on the mixture.

Spectral data for **413**: ^1H NMR (500 MHz, $CDCl_3$) (E isomer) δ 0.86 (t, 3 H, J = 7.2 Hz), 1.10-1.41 (m, 10 H), 1.8 (d, 3 H, J = 7.1 Hz), 2.37 (t, 2 H, J = 7.5 Hz),

5.28 (s, 2 H), 5.69 (q, 1 H, J = 6.9 Hz), 6.92-7.32 (m, 8 H), 7.54-7.64 (m, 1 H); (Z isomer) δ 0.86 (t, 3 H, J = 7.1 Hz), 1.10-1.41 (m, 10 H), 1.48 (dt, 3 H, J = 6.9, 1.1 Hz), 2.15-2.25 (m, 2 H), 5.20 (d, 1 H, J = 6.8 Hz), 5.30 (d, 1 H, J = 6.8 Hz), 5.92 (qt, 1 H, J = 6.8, 1.3 Hz), 6.92-7.32 (m, 8 H), 7.54-7.64 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.91, 13.99, 15.13, 22.59, 28.10, 29.05, 29.07, 29.33, 29.63, 30.93, 31.81, 37.63, 48.08, 48.19, 90.32, 91.02, 110.38, 110.45, 119.05, 119.15, 120.28, 120.38, 122.36, 122.44, 125.99, 126.23, 127.23, 127.28, 127.54, 128.58, 128.63, 129.93, 131.18, 131.22, 131.58, 136.03, 136.33, 137.55, 137.61, 137.87, 140.91, 2 aliphatic and 3 aryl carbons not located; IR (CH_2Cl_2,) 3061, 3031, 2953, 2924, 2835, 1497, 1455 cm^{-1}; mass spectrum (EI) m/z (% rel intensity) 425 M^+ (52, ^{81}Br), 423 M^+ (45, ^{79}Br), 344 (24), 91 (100); HRMS (FAB^+) calcd for $C_{25}H_{30}BrN$ 423.1562 (^{79}Br) found 423.1560 (^{79}Br).

Synthesis of 1-(4-methoxybenzyl)-3-bromo-2-(dec-2-en-3-yl)-1H-indole (414)



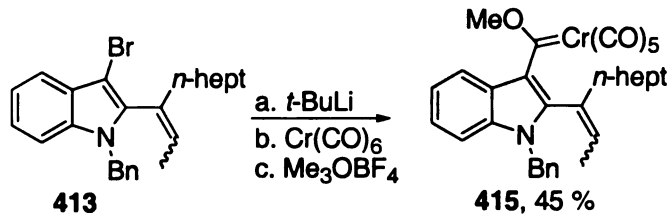
412 **414**, 89 %

To a stirred solution of **412** (1 g, 2.66 mmol, E/Z ratio of 1:0.6) in 20 mL of DMF under N_2 atmosphere added NBS (480 mg, 2.70 mmol). The reaction mixture was stirred for 30 min, quenched with water (20 mL) and diluted with ether. The water layer was extracted with 2x30 mL of ether. The combined organic extract was washed with 2x10 mL of brine, 2x10 mL of water and dried over $MgSO_4$. The solvent was evaporated to give a light green residue, which was purified using silica gel chromatography (5% EtOAc/hexanes) to give the

desired compound **414** (1.07 g, 89 %) as a light green oil and as a 1.0 : 0.5 ratio of E : Z isomers. These isomers were not separable and the following spectral data were collected on the mixture.

Spectral data of **414**: ^{1}H NMR (300 MHz, $CDCl_3$) (E-isomer) δ 0.88 (t, 3 H, J = 7.1 Hz), 1.10-1.44 (m, 10 H), 1.85 (d, 3 H, J = 7.0 Hz), 2.38 (t, 2 H, J = 7.5 Hz), 3.76 (s, 3 H), 5.23 (s, 2 H), 5.73 (q, 1 H, J = 6.9 Hz), 7.08-7.25 (m, 7 H), 7.58-7.65 (m, 1 H); (Z-isomer) δ 0.89 (t, 3 H, J = 7.1 Hz), 1.10-1.44 (m, 10 H), 1.51 (td, 3 H, J = 6.6, 1.1 Hz), 2.20-2.28 (m, 2 H), 3.77 (s, 3 H), 5.16 (d, 1 H, J = 6.4 Hz), 5.25 (d, 1 H, J = 6.4 Hz), 5.95 (qt, 1 H, J = 6.6, 1.3 Hz), 7.08-7.25 (m, 7 H), 7.58-7.65 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.95, 14.04, 15.18, 22.60, 28.07, 29.07, 29.09, 29.32, 29.61, 30.91, 31.81, 37.64, 47.52, 47.62,55.16, 90.12, 90.85, 110.41, 110.49, 113.95, 113.99, 118.95, 119.04, 120.17, 120.29, 122.25, 122.33, 127.14, 127.42, 129.57,129.80, 129.83, 131.12, 131.15, 131.48, 135.86, 136.15, 137.42, 140.81, 158.76, 158.81, 3 aliphatic and 4 aryl carbons not located; IR (CH_2Cl_2,) 2998, 2955, 2926, 2855, 1613, 1512 cm^{-1}; mass spectrum (EI) m/z (% rel intensity) 455 M^+ (36, ^{81}Br), 453 M^+ (33, ^{79}Br), 289 (5), 121 (100); HRMS (FAB^+) calcd for $C_{26}H_{32}BrNO$ m/z 453.1667 (^{79}Br), measd 453.1668 (^{79}Br).

Synthesis of (1-benzyl-2-(dec-2-en-3-yl)-1H-indol-3-yl)(methoxy)carbene pentacarbonyl chromium (0) (415)



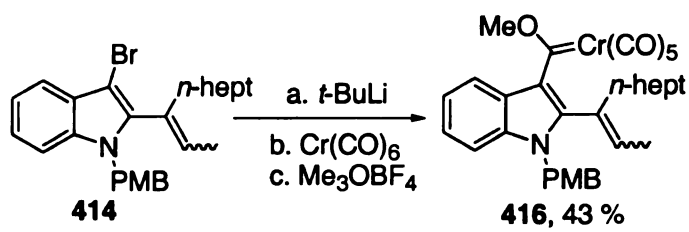
413 **415**, 45 %

To a flame-dried round-bottomed flask filled with Argon was added bromoindole **413** (1.23 g, 2.90 mmol, E:Z 1/0.58) in 20 mL of ether. The solution was cooled to -78 °C and t-butyl lithium (3.4 mL, 1.7 M in pentane, 5.80 mmol) was added drop wise. The resulting solution was stirred at -78 °C for 30 min, and then at 0 °C for 1h. This solution was then cooled to -78 °C and transferred by cannula into a side arm flask containing $Cr(CO)_6$ (702 mg, 3.19 mmol) and 15 mL of ether. The system was deoxygenated by freeze-thaw method (3 cycles) and then stirred at room temperature for 18 h. The reaction mixture was then cooled to 0 °C and Me_3OBF_4 (858 mg, 5.8 mmol) was added. After stirring for 30 min at 0 °C, the solvent was evaporated to give a red solid residue, which contained carbene complex **415** (E/Z 1:0.18) along with the reduced product **411** (E/Z 1:1.8). The ratio of **415**:**411** in the crude mixture was 1:0.18. The residue was purified by column chromatography using ethyl acetate/hexanes (3 : 97) to give 860 mg of a red oil that was a mixture of **415** and **411**. The ratio of **415** to **411** was determined to be 1.0 : 0.3 by integration of the 3-indole hydrogens of the E and Z-isomers of **415** versus the methoxy hydrogens of the E- and Z-isomers of **411**. This reveals that this reaction gave 730 mg (43 %) of carbene complex **415**

which was used is subsequent reactions without further purification. R_f of **415** (hexanes/EtOAc 10:1) = 0.60.

Spectral data for **415**: (E-isomer), 300 MHz ^{1}H NMR($CDCl_3$): δ 0.74-0.92 (m, 3 H), 1.00-1.80 (m, 13 H), 1.80-2.00 (m, 1 H), 2.06-2.25 (m, 1 H), 4.46 (s, 3 H), 5.24 (s, 2 H), 5.81 (q, 1 H, J = 7.4 Hz), 6.80-7.40 (m, 8 H), 8.12 (d, 1 H, J = 8.0 Hz). (Z isomer), 300 MHz ^{1}H NMR($CDCl_3$): δ 0.74-0.92 (m, 3 H), 1.00-1.80 (m, 13 H), 2.40-3.04 (m, 2 H), 4.55 (s, 3 H), 4.96 (q, 1 H, J = 6.2 Hz), 5.32 (d, 1 H, J = 17.0 Hz), 5.42 (d, 1 H, J = 17 Hz), 6.80-7.40 (m, 8 H), 7.86 (d, 1 H, J = 8.7 Hz).

Synthesis of (1-(4-methoxybenzyl)-2-(dec-2-en-3-yl)-1H-indol-3-yl)(methoxy) carbene pentacarbonyl chromium (0) (416)

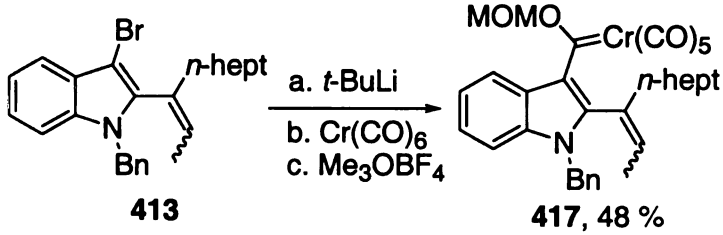


To a flame-dried round-bottomed flask filled with a Argon was added bromoindole **414** (1.07 g, 2.36 mmol, E/Z 1:0.5) in 20 mL of ether (deoxygenated by the freeze-thaw method). The solution was cooled to -78 °C and *tert*-butyllithium (2.8 mL, 1.7 M, 4.76 mmol) was added dropwise. The resulting solution was stirred at -78 °C for 30 min and then at 0 °C for 1 h. This solution was then cooled to -78 °C and transferred by cannula into a side arm flask containing $Cr(CO)_6$ (529 mg, 2.8 mmol) and 15 mL of ether. The system was deoxygenated by the freeze-thaw method (3 cycles) and then stirred at room temperature for 18 h. The reaction mixture was then cooled to 0 °C and Me_3OBF_4

(698 mg, 4.72 mmol) was added. After stirring for 30 min at 0 °C, the solvent was evaporated to give a red solid residue which contained carbene complex **416** (E/Z 1:0.24) along with the reduced product **412** (E/Z 1:2.00). The ratio of **416**:**412** in the crude mixture was 1:0.29. The reduced product could be separated by column chromatography using (3 % ethyl acetate/hexanes) to give compound **416** (618 mg, 43 %) as dark red oil.

Spectral data for **416**: (E isomer), 300 MHz ^{1}H NMR ($CDCl_3$): δ 0.83 (t, 3 H, J = 6.9 Hz), 1.05-1.80 (m, 13 H), 1.80-2.30 (m, 1 H), 2.06-2.26 (m, 1 H), 3.77 (s, 3 H), 4.57 (s, 3 H), 5.18 (s, 2 H), 5.82 (q, 1 H, J = 6.9 Hz), 6.76 (d, 2 H, J = 8.8 Hz), 6.86 (d, 2 H, J = 8.5 Hz), 7.10-7.30 (m, 3 H), 8.12 (d, 1 H, J = 8.0 Hz); (Z isomer), 300 MHz ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3 H, J = 7.2 Hz), 1.05-1.80 (m, 13 H), 2.48-2.64 (m, 1 H), 2.90-3.06 (m, 1 H), 3.76 (s, 3 H), 4.61 (s, 3 H), 4.96 (q, 1 H, J = 6.3 Hz), 5.25 (d, 1 H, J = 17.0 Hz), 5.36 (d, 1 H, J = 16.7 Hz), 6.82 (d, 2 H, J = 8.8 Hz), 6.97 (d, 2 H, J = 8.8 Hz), 7.80-7.32 (m, 3 H), 7.85 (d, 1 H, J = 5.8 Hz).

Synthesis of (1-benzyl-2-(dec-2-en-3-yl)-1H-indol-3-yl)(methoxymethoxy) carbene pentacarbonyl chromium (0) (417)



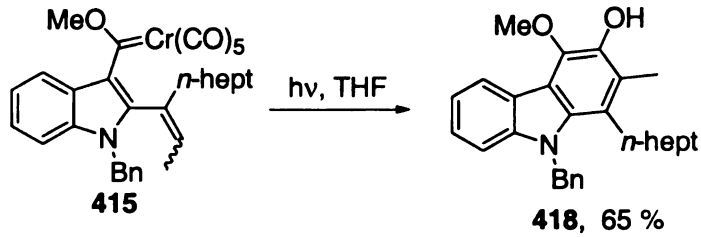
413 **417**, 48 %

To a flame-dried round-bottomed flask filled with argon was added bromoindole **413** (1.01 g, 2.38 mmol) in 20 mL of ether which had been

deoxygenated by the freeze-thaw method. The solution was cooled to -78 °C and *tert*-butyl lithium (2.8 mL, 1.7 M, 4.76 mmol) was added drop wise. The resulting solution was stirred at -78 °C for 30 min and then at 0 °C for 1 h. This solution was then cooled to -78 °C and transferred by cannula into a side-armed flask containing $Cr(CO)_6$ (529 mg, 2.85 mmol) and 15 mL of ether. The system was deoxygenated by the freeze-thaw method (3 cycles) and then stirred at room temperature for 20 h. The reaction mixture was then cooled to 0 °C and MOMCl (271 μL, 3.57 mmol) was added. After stirring for 30 min at 0 °C, the solvent was evaporated to give a red solid residue. The residue was purified by column chromatography using (10 % ethyl acetate/hexanes) to give a dark red oil which mainly consisted of desired carbene complex **417** (747 mg, 48 % yield) with trace amount of impurities. This compound was used in subsequent steps without further purification.

Spectral data for **417**: (E-isomer); 300 MHz ^{1}H NMR ($CDCl_3$): δ 0.68-0.90 (m, 3 H), 1.00-1.80 (m, 13 H), 1.80-2.24 (m, 2 H), 3.73 (s, 3 H), 4.45 (s, 2 H), 5.17 (s, 2 H), 5.81 (q, 1 H, J = 7.1 Hz), 6.64-7.32 (m, 8 H), 8.11 (d, 1 H, J = 7.8 Hz), (Z-isomer), 300 MHz ^{1}H NMR ($CDCl_3$): δ 0.68-0.90 (m, 3 H), 1.00-1.80 (m, 13 H), 2.48-2.64 (m, 1 H), 2.88-3.04 (m, 1 H), 3.76 (s, 3 H), 4.56 (s, 2 H), 4.96 (q, 1 H, J = 6.3 Hz), 5.26 (d, 1 H, J = 6.7 Hz), 5.34 (d, 1 H, J = 6.7 Hz), 6.82 (d, 2 H, J = 6.6 Hz), 6.97 (d, 2 H, J = 8.5 Hz), 7.10-7.28 (m, 4 H), 7.84 (dd, 1 H, J = 6.9, 1.1 Hz).

Synthesis of N-benzyl-1-heptyl-4-methoxy-2-methyl-9H-carbazol-3-ol (418)

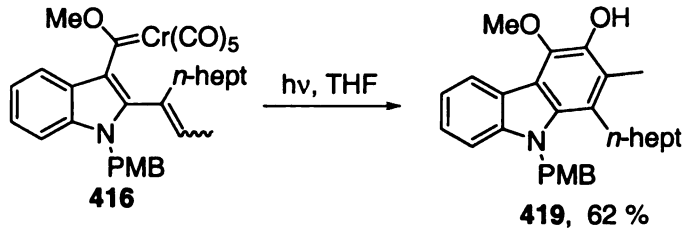


415 **418**, 65 %

A solution of carbene **415** (472 mg, 0.815 mmol) in 150 mL THF in a quartz photoreactor was purged with nitrogen for 15 min and then purged with carbon monoxide for another 15 min. The solution was irradiated with a 450 W medium pressure mercury lamp for 30 min at room temperature. The resulting solution was kept under a CO atmosphere for 12 h. The solvent was then evaporated to give red oily residue. The residue was purified by column chromatography (3 % ethyl acetate/hexanes) to give **418** (223 mg, 65 %) as a light brown solid.

Spectral data for **418**: Mp 102-104 °C (ethylacetate /hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, J = 6.9 Hz), 1.20-1.40 (m, 8H), 1.42 -1.64 (m, 2H), 2.38 (s, 3H), 2.74-2.84 (m, 2H), 4.06 (s, 3H), 5.65 (s, 1H), 5.66 (s, 2 H), 7.04 (d, 2H, J = 6.8 Hz), 7.19-7.30 (m, 5H), 7.34-7.40 (1H, m), 8.20 (dd, 1H, J = 7.8, 1.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.98, 14.06, 22.62, 28.18, 29.10, 29.78, 31.79, 31.85, 48.68, 60.53, 108.75, 114.71, 119.23, 121.02, 122.13, 122.98, 124.34, 125.41, 127.11, 128.82, 134.22, 138.66, 138.79, 140.62, 142.10, 1 aryl C not located; IR (CH_2Cl_2) 3544, 2959, 2928, 2857 cm^{-1}; mass spectrum (EI) m/z (% rel intensity) 415 (65), 330 (20), 240 (80), 91 (100). Anal calcd for $C_{28}H_{33}NO_2$: C, 80.93; H, 8.00; N, 3.37. Found C, 81.23; H, 7.84; N, 3.48.

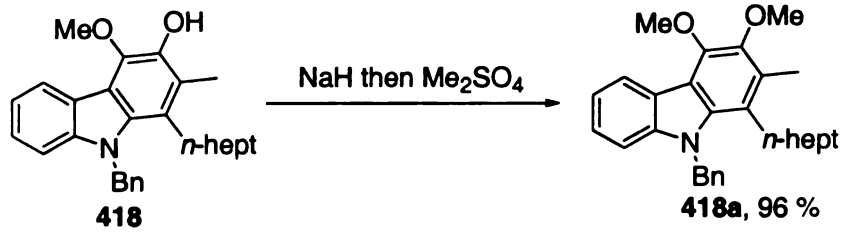
Synthesis of 9-(4-methoxybenzyl)-1-heptyl-4-methoxy-2-methyl-9H-carbazol-3-ol (419)



416 **419**, 62 %

The *ortho*-benzannulation of dienyl-chromium carbene complex **416** was performed following the procedure described above for complex **415.** The desired carbazole **419** was obtained after purification using column chromatography on silica gel (20 % ether/hexane) in 62 % yield as a white solid. Spectral data for **419**: Mp 108-110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (*t*, 3H, J = 6.9 Hz), 1.18-1.42 (m, 8 H), 1.44-1.62 (m, 2 H), 2.34 (s, 3 H), 2.68-2.82 (m, 2 H), 3.73 (s, 3 H), 4.03 (s, 3 H), 5.64 (s, 2 H), 5.60 (s, 1 H), 6.78 (d, 2 H, J = 8.7 Hz), 6.92 (d, 2 H, J = 9 Hz), 7.14-7.28 (m, 2 H), 7.30-7.42 (m, 1 H), 8.17 (d, 1 H, J = 7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.97, 14.08, 22.64, 28.18, 29.14, 29.81, 31.79, 31.86, 48.11, 55.21, 60.54, 108.78, 114.25, 114.67, 119.17, 120.98, 121.04, 122.11, 122.93, 125.32, 126.53, 130.65, 134.21, 138.76, 140.56, 142.07, 158.73; IR (CH_2Cl_2) 3544, 2959, 2928, 2857, 2255, 1512, 1458 cm^{-1}; mass spectrum (EI) m/z (% rel intensity) 445 M^+ (30), 240 (14), 121 (100). Anal calcd for $C_{29}H_{35}NO_3$: C, 78.17; H, 7.92; N, 3.14. Found C, 77.70; H, 8.07; N, 3.16.

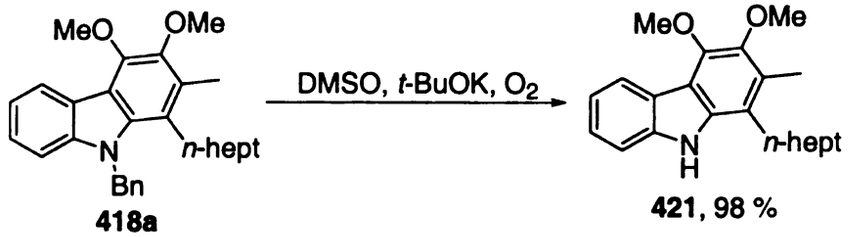
Synthesis of 9-benzyl-1-heptyl-3,4-dimethoxy-2-methyl-9H-carbazole (418a)



To a stirred suspension of NaH (57 mg, 1.420 mmol) in THF (3.5 mL) was added a solution of **418** (295 mg, 0.710 mmol, 60 % dispersion in mineral oil) in 1.5 mL of THF. After 15 min, Me_2SO_4 (336 μL, 3.550 mmol) was added. The reaction mixture was further stirred for 6 h, quenched with water and extracted with ether (2x20 mL). The organic exract was washed with 1x10 mL of brine and 1x10 mL of water, dried over $MgSO_4$ and evaporated to give an oily residue. The residue was purified using silica gel colum chromatography (5 % ethyl acetate/hexanes) to give 291 mg (96 % yield) of compound **418a** as colorless wax.

Spectral data for **418a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.0 Hz), 1.18-1.38 (m, 8 H), 1.52-1.62 (m, 2 H), 2.35 (s, 3 H), 2.70-2.78 (m, 2 H), 3.89 (s, 3 H), 4.12 (s, 3 H), 5.63 (s, 2 H), 7.02 (d, 2 H, J = 7.0 Hz), 7.16-7.30 (m, 5 H), 7.30-7.38 (m, 1 H), 8.32 (dd, 1 H, J = 8.1, 1.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.16, 14.07, 22.63, 28.43, 29.11, 29.82, 31.78, 31.86, 48.62, 60.24, 60.77, 108.56, 115.94, 119.42, 120.07, 122.15, 122.47, 125.26, 125.45, 127.11, 128.82, 129.47, 136.59, 138.65, 142.02, 144.38, 146.04; IR (CH_2Cl_2) 2960, 2928, 2855 cm^{-1}; mass spectrum (EI) *m/z* (% rel intensity) 429 M^+ (61), 414 (28), 344 (23), 254 (47), 91 (100). Anal calcd for $C_{29}H_{35}NO_2$: C, 81.08; H, 8.21; N, 3.26. Found C, 80.90; H, 8.27; N, 3.29.

Synthesis of 1-heptyl-3,4-dimethoxy-2-methyl-9H-carbazole (421)

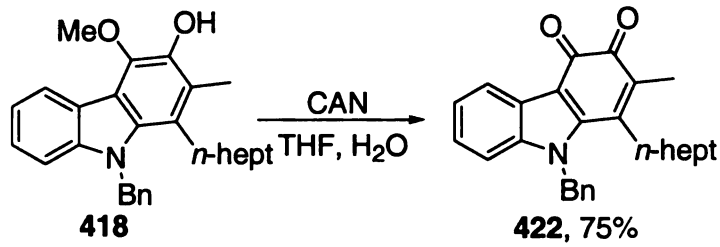


418a **421**, 98 %

To a stirred of **418a** (0.521 mmol, 224 mg) in 15 mL DMSO was added potassium *tert*-butoxide (6.63 mmol, 6.63 mL of 1 M of potassium *tert*-butoxide in THF) at room temperature. The reaction mixure was stirred for 5 min and O_2 was bubbled through the reaction mixture for 30 min. The reaction mixture was quenched with a saturated solution of NH_4Cl (10 mL) and extracted with 3x10 mL of ether. The organic extract was washed with 10 mL of water, dried over $MgSO_4$ and evaporated to give the an oily residue. This residue was purified using silica gel column chromatography (5 % ethyl acetate/hexanes) to give 173 mg of compound **421** (98 % yield) as white solid.

Spectral data for **421**: Mp 80-82 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 6.8 Hz), 1.20-1.40 (m, 6 H), 1.40-1.50 (m, 2 H), 1.55-1.70 (m, 2 H), 2.39 (s, 3 H), 2.82 (m, 2 H, J = 7.9 Hz), 3.90 (s, 3 H), 4.11 (s, 3 H), 7.21 (t, 1 H, J = 7.3 Hz), 7.30-7.45 (m, 2 H), 7.80 (s, 1 H), 8.23 (d, 1 H, J = 7.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.20, 14.07, 22.66, 28.64, 29.29, 29.52, 30.00, 31.85, 60.40, 60.92, 110.17, 114.64, 118.79, 119.39, 122.50, 122.87, 125.01, 128.35, 136.11, 139.33, 144.56, 146.03; IR (CH_2Cl_2) 3467, 3054, 2957, 2930, 2857 cm^{-1}; mass spectrum (EI) m/z (% rel intensity) 339 M^+ (84), 324 (100), 296 (12), 254 (72). Anal Calcd for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13. Found C, 77.81; H, 8.76; N, 4.04.

Synthesis of 9-benzyl-1-heptyl-2-methyl-9H-carbazole-3,4-dione 422

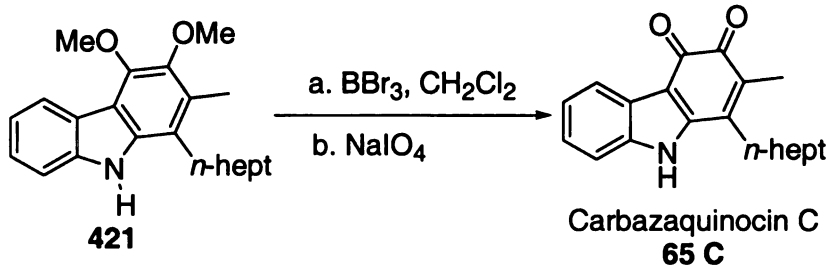


418 **422**, 75%

Carbazole derivative **418** (100 mg, 0.24 mmol) was dissolved in 10 mL of THF/H_2O (3:1). This solution was stirred for 5 min and CAN (394 mg, 0.72 mmol) was added. The mixture was stirred for 2 h, diluted with H_2O and extracted with three portions of ethyl acetate. The solvent was removed under vacuuo and residue was purified using flash chromatography on silica gel (hexanes:EtOAc = 5 : 1) to give **28** (72 mg, 75 %). R_f = 0.16 (hexanes/EtOAc = 9 : 2).

Spectral data for **28**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, 3 H, J = 6.6 Hz), 1.15-1.39 (m, 8 H), 1.48-1.62 (m, 2 H), 1.98 (s, 3 H), 2.47-2.54 (m, 2 H, J = 8.7 Hz), 5.57(s, 2 H), 6.94 (dd, 2 H, J = 7.5, 1.8 Hz), 7.19-7.39 (m, 6 H), 8.25 (dd, 1 H, J = 7.2, 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 14.0, 22.5, 28.8, 28.9, 29.4, 29.7, 31.7, 48.9, 110.8, 122.1, 125.0, 125.1, 125.7, 128.1, 129.33, 134.67, 135.7, 139.5, 142.4, 144.6, 174.0, 183.2, 2 aryl carbons not located.

Synthesis of carbazoquinocin-C (65C)



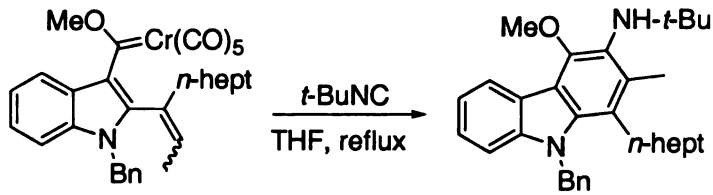
421

Carbazaquinocin C
65 C

To a stirred solution of **421** (0.074 mmol, 25 mg) in CH_2Cl_2 added BBr_3 221 μL, 221 mmol, 1 M in THF) at -78 ^{0}C. The reaction mixture was brought to room temperature over 30 min. After 30 min, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with 2x5 mL of water. To the organic extract was added excess $NaIO_4$ and the resulting solution was stirred for 20 min. At this point, the organic extract was filtered through a small pad of Celite. The resultant filtrate was evaporated to give the desired compound carbazoquinocin-C (17.6 mg) in 77 % yield which was clean by ^{1}H NMR and whose mp (226-228 ^{o}C) matches that in the literature (227-228 ^{o}C).[88a] The ^{1}H and ^{13}C NMR spectra matched the published spectra.[88a] This compound is dark green as a solid and is red in solution and is stable in air and at room temperature. The compound binds strongly to silica gel and is difficult to purify by chromatograph.

Spectral data for carbazoquinocin C: ^{1}H NMR (300 MHz, DMSO) δ 0.86 (t, 3 H, J = 6.4 Hz), 1.20-1.40 (m, 6 H), 1.40-1.62 (m, 4 H), 1.90 (s, 3 H), 2.66 (t, 2 H, J = 7.6 Hz), 7.20-7.30 (m, 2 H), 7.48-7.56 (m, 1 H), 7.82-7.92 (m, 1 H), 12.35 (brs, 1 H); ^{13}C NMR (125 MHz, DMSO), δ 11.41, 13.91, 22.02, 28.02, 28.48, 28.59, 28.96, 31.28, 110.98, 113.33, 120.21, 123.92, 124.15, 125.60, 133.06, 137.00, 142.09, 145.57, 172.68, 183.41; mass spectrum (FAB) *m/z* (% rel intensity) 311 (8), 310 $(M+1)^+$ (11), 231 (17), 215 (11), 117 (100), 95 (60), 81 (60), 69 (75), 55 (85), 57 (70), 55 (85); HRMS (FAB) calcd for $C_{20}H_{24}NO_2$ m/z 310.1807, measd 310.1808.

Synthesis of* N-tert-*butyl-9-benzyl-1-heptyl-4-methoxy-2-methyl-9*H-*carbazol-3-amine (424)



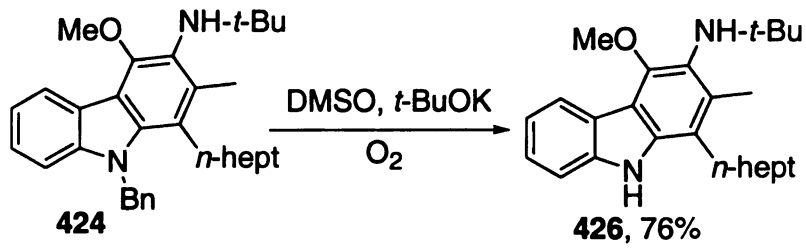
415 R = Me

424, 86 %

To a solution of **415** (710 mg, 1.23 mmol) in 1 mL THF was added *t*-BuNC (974 μL, 8.61 mmol). The reaction mixture was stirred at room temperature for 24 h. After 24 h, the reaction mixture was diluted with 2 mL of THF and heated to 75 °C for another 18 h. The reaction mixture was concentrated and the desired compound **424** was isolated in 86 % yield upon silica gel chromatography (5 %, ethyl acetate/hexanes) as a light yellow waxy liquid.

Spectral data for **424**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, 3 H, J = 7.0 Hz), 1.21 (s, 9 H), 1.24-1.42 (m, 8 H), 1.50-1.65 (m, 2 H), 2.47 (s, 3 H), 2.73-2.85 (m, 2 H), 2.95-3.20 (brs, 1 H), 3.98 (s, 3 H), 5.65 (s, 2 H), 7.09 (d, 2 H, J = 7.1 Hz), 7.23 (t, 3 H, J = 7.7 Hz), 7.26-7.32 (m, 2 H), 7.32-7.39 (m, 1 H), 8.26 (dd, 1 H, J = 8.6, 1.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.07, 16.41, 22.62, 14.07, 16.41, 22.62, 28.82, 29.12, 29.84, 30.38, 31.62, 31.87, 48.78, 55.40, 59.69, 108.59, 115.27, 119.40, 120.44, 121.72, 122.44, 125.08, 125.52, 127.07, 128.79, 130.38, 134.43, 137.43, 138.75, 142.01, 149.52; IR (CH_2Cl_2) 2959, 2928, 2859, 1453 cm^{-1}; mass spectrum (EI) m/z (% rel intensity) 472 (23), 470 (82), 455 (13), 414 (27), 413 (79), 399 (12), 239 (22), 149 (37), 130 (14), 91 (100), 57 (50). Anal calcd for $C_{32}H_{42}N_2O$: C, 81.66; H, 8.99; N, 5.95. Found C, 81.80; H, 9.12; N, 5.85.

Synthesis of N-tert-butyl-1-heptyl-4-methoxy-2-methyl-9H-carbazol-3-amine (426)

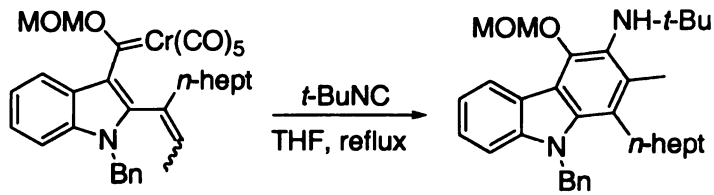


To a stirred of **424** (0.038 mmol, 17.8 mg) in 15 mL DMSO added potassium *tert*-butoxide (0.38 mmol, 380 μL, 1 M sol of potassium *tert*-butoxide in THF) at room temperature. The reaction mixure was stirred for 5 min and then O_2 was bubbled through the reaction mixture for 30 min. The reaction mixture was quenched with saturated solution of NH_4Cl (1x5 mL), extracted with 3x5 mL of ether. The organic extract was washed with 1x10 mL of water, dried over $MgSO_4$ and evaporated to give the oily residue. This residue was purified using silica gel column chromatography (20 %, Ethylacetate/hexanes) to give 173 mg of compound **426** (76 % yield) as light yellow viscous liquid.

Spectral data for **426**: ^1H NMR (300MHz, $CDCl_3$): δ 0.91 (t, 3 H, J = 6.6 Hz), 1.23 (s, 9 H), 1.26-1.56 (m, 8 H), 1.58-1.74 (m, 2 H), 2.50 (s, 3 H), 2.85 (t, 2 H, J = 7.8 Hz), 3.10 (brs, 1 H), 3.98 (s, 3 H), 7.16-7.28 (m, 1 H), 7.32-7.50 (m, 2 H), 7.84 (s, 1 H), 8.20 (d, 1 H, J = 7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.08, 16.34, 22.63, 29.04, 29.29, 30.00, 30.36, 31.85, 55.34, 59.78, 110.16, 113.90, 119.07, 119.34, 122.37, 122.50, 124.82, 130.19, 132.74, 136.77, 139.23, 149.24, one aliphatic C not located; IR (CH_2Cl_2) 3438 , 2926 , 2857, 1709, 1611, 1502, 1455 cm^{-1}; mass spectrum (EI) m/z (% rel intensity) 381 (21), 380 M^+ (90), 365 (16), 323 (47), 323 (100), 311 (12), 309 (62), 295 (10), 239 (24), 233 (14), 210 (15), 197 (18), 196

(26), 195 (17), 180 (8). Anal calcd for $C_{25}H_{36}N_2O$: C, 78.90; H, 9.53; N, 7.36. Found C, 78.88; H, 9.54; N, 7.08.

Synthesis of N-tert-butyl-9-benzyl-1-heptyl-4-(methoxymethoxy)-2-methyl-9H-carbazol-3-amine (425)



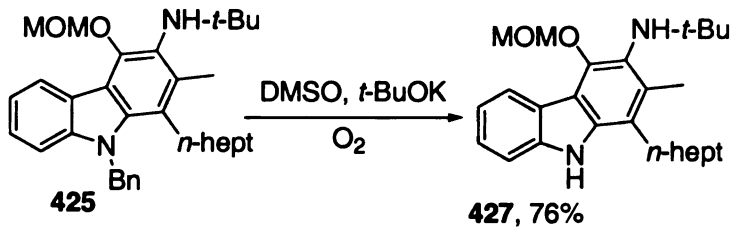
417 **425**, 72 %

To a solution of **417** (0.580 mg, 0.93 mmol) in 750 μL THF was added *t*-BuNC (974 μL, 8.61 mmol). The reaction mixture was stirred at room temperature for 24 h. After 24 h, the reaction mixture was diluted with 2 mL of THF and heated to 75 °C for another 18 h. The reaction mixture was concentrated and the desired compound **425** was isolated in 72 % yield as a yellow waxy solid after silica gel chromatography (5 % ethyl acetate/hexanes).

Spectral data for **425**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78-0.92 (m, 3 H), 1.17 (s, 9 H), 1.20-1.42 (m, 8 H), 1.46-1.64 (m, 2 H,), 2.47 (s, 3 H), 2.70-2.89 (m, 2 H), 3.59-3.63 (m, 3 H), 5.27 (s, 2 H), 5.63 (s, 2 H), 7.05 (d, 2 H, J = 7.7 Hz), 7.12-7.40 (m, 6 H), 8.15 (d, 2 H, J = 8.0 Hz); ^{13}C NMR (125 MHz $CDCl_3$) δ 14.06, 16.78, 22.61, 28.83, 29.11, 29.85, 30.19, 31.51, 31.87, 48.74, 55.37, 57.80, 100.00, 108.71, 115.05, 119.33, 120.93, 121.66, 121.71, 125.14, 125.51, 127.19, 128.80, 130.90, 134.75, 137.56, 138.68, 142.03, 147.46; IR (CH_2Cl_2) 3350, 3054, 2959, 2928, 1701, 1593, 1497, 1453 cm^{-1}; mass spectrum (EI) m/z (% rel intensity) 500 M^+ (19), 455 (8), 433 (7), 411 (8), 400 (19), 399 (72), 388 (15), 371

(8), 361 (7), 287 (12), 91 (100). Anal calcd for $C_{33}H_{44}N_2O_2$: C, 79.16; H, 8.86; N, 5.59. Found C, 79.06; H, 8.99; N, 5.23.

Synthesis of N-tert-*butyl-1-heptyl-4-(methoxymethoxy)-2-methyl-9H-carbazol-3-amine (427)*

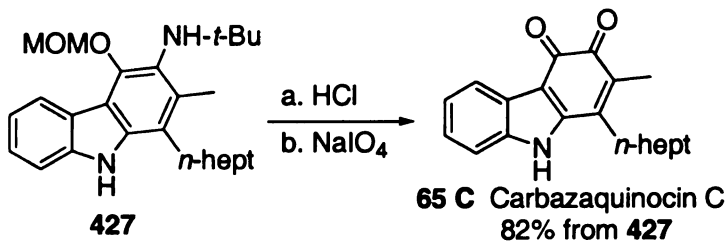


To a stirred of **425** (0.16 mmol, 82 mg) in 5 mL DMSO was added potassium *tert*-butoxide (1.6 mmol, 1.6 mL, 1 M potassium *tert*-butoxide in THF) at room temperature. The reaction mixure was stirred for 5 min and O_2 was bubbled through the reaction mixture for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with 3x5 mL of ether. The organic extract was washed with 10 mL of water, dried over $MgSO_4$ and evaporated to give the an oily residue. This residue was purified by silica gel column chromatography (20 % ethyl acetate/hexanes) to give 173 mg of compound **427** (72 % yield) as a light yellow viscous oil.

Spectral data for **427**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 7.0 Hz), 1.19 (s, 9 H), 1.22-1.50 (m, 8 H), 1.56-1.67 (m, 2 H), 2.49 (s, 3 H), 2.82 (t, 2 H, J = 8.1 Hz), 3.59 (s, 3 H), 5.82 (s, 2 H), 7.17-7.21 (m, 1 H), 7.32-7.39 (m, 1 H), 7.41 (d, 1 H, J = 8.2 Hz), 7.86 (s, 1 H), 8.08 (d, 1 H, J = 8.0 Hz), 1 NH proton not located; ^{13}C NMR (125 MHz, $CDCl_3$) 14.11, 16.67, 22.64, 29.06, 29.21, 29.29, 30.04, 30.16, 31.86, 55.39, 57.82, 99.84, 110.28, 113.66, 119.28, 119.55, 121.74,

122.27, 124.90, 130.59, 133.42, 136.88, 139.24, 147.27; IR (CH_2Cl_2) 3357, 3058, 2926, 2857, 1709, 1611, 1455, 1406 cm^{-1}; mass spectrum (EI) m/z (% rel intensity) 410 M^+ (18), 365 (6), 321 (11), 309 (100). Anal calcd for $C_{26}H_{38}N_2O_2$: C, 76.06; H, 9.33; N, 6.82. Found C, 76.54; H, 9.64; N, 6.64.

Synthesis of carbazoquinocin C (65C)



427

65 C Carbazaquinocin C
82% from **427**

To a stirred solution of **427** (12 mg, 0.03 mmol) in 1 mL of MeOH and 300 μL of H_2O was added 200 μL of conc. HCl. The reaction mixture was refluxed for 45 min. The resulting mixture was concentrated in vacuo and purified by silica gel column chromatography (30 % ethyl acetate/hexanes). The resulting compound was dissolved in 1 mL CH_2Cl_2 and 300 μL of H_2O. To this mixture was added excess $NaIO_4$ (200 mg) and the reaction mixture was stirred for 24 h at rt. After 24 h, the reaction mixture was diluted with 2 mL of CH_2Cl_2 and washed with 3x2 mL of water. The resulting organic layer was passed through Celite and washed with CH_2Cl_2. The organic solvent was then evaporated to give carbazoquinocin C as dark green solid in 82 % (7.5 mg) yield. This compound had spectral data identical to the compound obtained from **65C** as described above.

APPENDIX

Crystallographic Data of Selected Compounds

Figure A.1 ORTEP Diagram of Compound 184

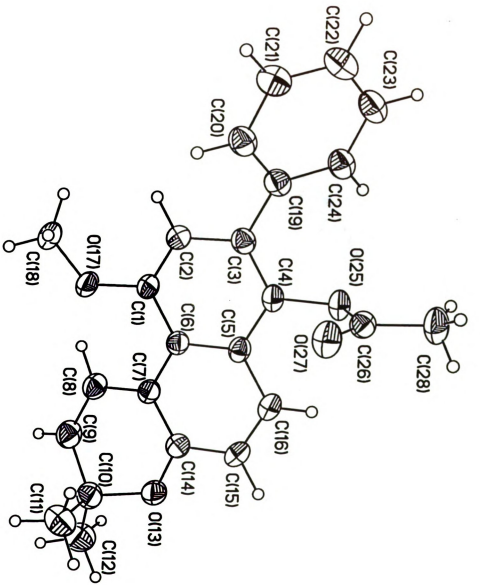


Table A.1.1. Crystal data and structure refinement for 184

Identification code	184
Empirical formula	C24 H22 O4
Formula weight	374.42
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 8.4101(17) A b = 9.858(2) A c = 12.214(2) A alpha = 81.35(3) deg. beta = 84.88(3) deg. gamma = 77.60(3) deg.
Volume	976.1(3) A^3
Z	2
Density (calculated)	1.274 Mg/m^3
Absorption coefficient	0.086 mm^-1
F(000)	396
Crystal size	0.6 x 0.2 x 0.15 mm
Theta range for data collection	1.69 to 28.29 deg.
Index ranges	-11<=h<=10, -13<=k<=12, -16<=l<=15
Reflections collected / unique	11763 / 4581 [R(int) = 0.0223]
Completeness to theta = 28.29	94.5%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4581 / 0 / 319
Goodness-of-fit on F^2	0.841
Final R indices [I>2sigma(I)]	R1 = 0.0402, wR2 = 0.1127
R indices (all data)	R1 = 0.0670, wR2 = 0.1282
Largest diff. peak and hole	0.217 and -0.202 e.A^-3

Table A.1.2. Atomic coordinates (x 10^4), equivalent isotropic displacement parameters (A^2 x 10^3), and occupancies for 184

	x	y	z	U(eq)	Occ.
C(1)	-1144(2)	9312(1)	3941(1)	28(1)	1
C(2)	-2028(2)	9618(2)	4905(1)	30(1)	1
C(3)	-2641(2)	8579(1)	5657(1)	28(1)	1
C(4)	-2366(2)	7256(1)	5357(1)	28(1)	1
C(5)	-1493(2)	6903(1)	4353(1)	27(1)	1
C(6)	-783(2)	7927(1)	3643(1)	26(1)	1
C(7)	156(2)	7552(1)	2651(1)	28(1)	1
C(8)	1243(2)	8371(2)	1967(1)	33(1)	1
C(9)	1822(2)	8026(2)	976(1)	38(1)	1
C(10)	1268(2)	6894(2)	503(1)	37(1)	1
C(11)	-324(2)	7457(2)	-67(2)	49(1)	1
C(12)	2579(2)	6137(2)	-265(2)	50(1)	1
O(13)	1009(1)	5799(1)	1417(1)	36(1)	1
C(14)	175(2)	6243(1)	2358(1)	29(1)	1
C(15)	-560(2)	5246(1)	3045(1)	33(1)	1
C(16)	-1343(2)	5552(1)	4033(1)	31(1)	1
O(17)	-601(1)	10310(1)	3183(1)	35(1)	1
C(18)	-1288(2)	11735(2)	3293(2)	43(1)	1
C(19)	-3583(2)	8991(2)	6689(1)	30(1)	1
C(20)	-4638(2)	10300(2)	6655(1)	34(1)	1
C(21)	-5529(2)	10725(2)	7601(1)	38(1)	1
C(22)	-5379(2)	9845(2)	8597(1)	42(1)	1
C(23)	-4320(2)	8549(2)	8653(1)	42(1)	1
C(24)	-3426(2)	8122(2)	7711(1)	36(1)	1
O(25)	-2876(1)	6153(1)	6080(1)	32(1)	1
C(26)	-4424(2)	5963(1)	6046(1)	30(1)	1
O(27)	-5368(1)	6654(1)	5396(1)	41(1)	1
C(28)	-4725(2)	4803(2)	6918(1)	43(1)	1

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table A.1.3. Bond lengths [A] and angles [deg] for 184

C(1)-O(17)	1.3699(15)
C(1)-C(2)	1.3723(19)
C(1)-C(6)	1.4282(18)
C(2)-C(3)	1.4211(19)
C(3)-C(4)	1.3737(19)
C(3)-C(19)	1.4900(19)
C(4)-O(25)	1.4107(15)
C(4)-C(5)	1.4223(18)
C(5)-C(16)	1.4203(18)
C(5)-C(6)	1.4244(18)
C(6)-C(7)	1.4382(18)
C(7)-C(14)	1.3861(18)
C(7)-C(8)	1.4714(19)
C(8)-C(9)	1.328(2)
C(9)-C(10)	1.504(2)
C(10)-O(13)	1.4669(17)
C(10)-C(11)	1.522(2)
C(10)-C(12)	1.525(2)
O(13)-C(14)	1.3706(16)
C(14)-C(15)	1.4048(19)
C(15)-C(16)	1.365(2)
O(17)-C(18)	1.4217(18)
C(19)-C(20)	1.397(2)
C(19)-C(24)	1.4034(19)
C(20)-C(21)	1.389(2)
C(21)-C(22)	1.383(2)
C(22)-C(23)	1.388(2)
C(23)-C(24)	1.387(2)
O(25)-C(26)	1.3599(16)
C(26)-O(27)	1.2011(17)
C(26)-C(28)	1.489(2)
O(17)-C(1)-C(2)	122.78(12)
O(17)-C(1)-C(6)	115.46(11)
C(2)-C(1)-C(6)	121.72(12)
C(1)-C(2)-C(3)	121.90(13)
C(4)-C(3)-C(2)	116.98(12)
C(4)-C(3)-C(19)	124.23(12)
C(2)-C(3)-C(19)	118.75(12)
C(3)-C(4)-O(25)	120.37(11)
C(3)-C(4)-C(5)	122.88(12)
O(25)-C(4)-C(5)	116.66(11)
C(16)-C(5)-C(4)	121.06(12)
C(16)-C(5)-C(6)	119.32(12)
C(4)-C(5)-C(6)	119.61(12)
C(5)-C(6)-C(1)	116.61(12)
C(5)-C(6)-C(7)	119.54(12)
C(1)-C(6)-C(7)	123.73(12)
C(14)-C(7)-C(6)	117.89(12)
C(14)-C(7)-C(8)	115.86(12)

C(6)-C(7)-C(8)	125.94(12)
C(9)-C(8)-C(7)	119.44(13)
C(8)-C(9)-C(10)	120.90(13)
O(13)-C(10)-C(9)	108.31(12)
O(13)-C(10)-C(11)	108.68(13)
C(9)-C(10)-C(11)	111.47(13)
O(13)-C(10)-C(12)	104.16(13)
C(9)-C(10)-C(12)	112.45(14)
C(11)-C(10)-C(12)	111.41(14)
C(14)-O(13)-C(10)	116.58(10)
O(13)-C(14)-C(7)	122.24(12)
O(13)-C(14)-C(15)	115.48(12)
C(7)-C(14)-C(15)	122.12(12)
C(16)-C(15)-C(14)	120.29(12)
C(15)-C(16)-C(5)	120.43(12)
C(1)-O(17)-C(18)	117.11(11)
C(20)-C(19)-C(24)	118.23(13)
C(20)-C(19)-C(3)	119.43(12)
C(24)-C(19)-C(3)	122.33(13)
C(21)-C(20)-C(19)	121.09(14)
C(22)-C(21)-C(20)	119.88(15)
C(21)-C(22)-C(23)	119.97(15)
C(24)-C(23)-C(22)	120.33(15)
C(23)-C(24)-C(19)	120.49(15)
C(26)-O(25)-C(4)	118.92(10)
O(27)-C(26)-O(25)	123.18(12)
O(27)-C(26)-C(28)	127.10(13)
O(25)-C(26)-C(28)	109.73(12)

Symmetry transformations used to generate equivalent atoms:

Table A.1.4. Anisotropic displacement parameters ($A^2 \times 10^3$) for 184

	U11	U22	U33	U23	U13	U12
C(1)	33(1)	26(1)	28(1)	-2(1)	-1(1)	-12(1)
C(2)	36(1)	28(1)	29(1)	-5(1)	-2(1)	-11(1)
C(3)	28(1)	32(1)	25(1)	-1(1)	-4(1)	-8(1)
C(4)	27(1)	28(1)	27(1)	4(1)	-4(1)	-10(1)
C(5)	26(1)	25(1)	29(1)	1(1)	-6(1)	-7(1)
C(6)	28(1)	26(1)	27(1)	-1(1)	-5(1)	-8(1)
C(7)	28(1)	26(1)	29(1)	-2(1)	-3(1)	-6(1)
C(8)	33(1)	31(1)	37(1)	-4(1)	2(1)	-10(1)
C(9)	39(1)	37(1)	38(1)	-4(1)	9(1)	-12(1)
C(10)	40(1)	35(1)	33(1)	-5(1)	5(1)	-7(1)
C(11)	51(1)	55(1)	38(1)	-5(1)	-6(1)	-7(1)
C(12)	53(1)	53(1)	44(1)	-17(1)	14(1)	-10(1)
O(13)	42(1)	30(1)	34(1)	-9(1)	4(1)	-6(1)
C(14)	28(1)	28(1)	31(1)	-4(1)	-2(1)	-4(1)
C(15)	37(1)	23(1)	40(1)	-5(1)	-3(1)	-7(1)
C(16)	33(1)	24(1)	36(1)	1(1)	-3(1)	-9(1)
O(17)	49(1)	24(1)	34(1)	-4(1)	10(1)	-14(1)
C(18)	64(1)	24(1)	39(1)	-2(1)	6(1)	-11(1)
C(19)	30(1)	36(1)	27(1)	-3(1)	-2(1)	-11(1)
C(20)	35(1)	39(1)	28(1)	-2(1)	-5(1)	-9(1)
C(21)	33(1)	45(1)	37(1)	-9(1)	-2(1)	-4(1)
C(22)	38(1)	58(1)	32(1)	-10(1)	2(1)	-11(1)
C(23)	46(1)	52(1)	27(1)	0(1)	-2(1)	-14(1)
C(24)	36(1)	40(1)	30(1)	-1(1)	-4(1)	-9(1)
O(25)	31(1)	32(1)	31(1)	6(1)	-3(1)	-11(1)
C(26)	29(1)	30(1)	31(1)	-4(1)	2(1)	-7(1)
O(27)	32(1)	41(1)	46(1)	5(1)	-8(1)	-8(1)
C(28)	43(1)	46(1)	41(1)	7(1)	-2(1)	-20(1)

The anisotropic displacement factor exponent takes the form:
$-2\ pi^2\ [\ h^2\ a^{*2}\ U11 + \ldots + 2\ h\ k\ a^*\ b^*\ U12\ ]$

Table A.1.5. Hydrogen coordinates (x 10^4), isotropic displacement parameters (A^2 x 10^3), and occupancies for 184

	x	y	z	U(eq)	Occ.
H(2)	-2241(18)	10577(17)	5101(12)	36	1
H(8)	1629(19)	9134(16)	2281(13)	40	1
H(9)	2620(20)	8450(17)	507(14)	46	1
H(11A)	-680(30)	6710(20)	-385(17)	73	1
H(11B)	-180(30)	8230(20)	-674(17)	73	1
H(11C)	-1230(30)	7880(20)	469(17)	73	1
H(12A)	2180(30)	5360(20)	-530(17)	75	1
H(12B)	3610(30)	5710(20)	160(18)	75	1
H(12C)	2910(30)	6740(20)	-902(18)	75	1
H(15)	-443(19)	4279(17)	2810(12)	40	1
H(16)	-1831(19)	4884(17)	4502(13)	37	1
H(18A)	-910(20)	12250(20)	2630(16)	64	1
H(18B)	-890(20)	12020(20)	3967(17)	64	1
H(18C)	-2490(30)	11930(20)	3284(16)	64	1
H(20)	-4775(19)	10926(17)	5971(13)	41	1
H(21)	-6260(20)	11652(18)	7532(13)	46	1
H(22)	-6000(20)	10135(18)	9285(14)	51	1
H(23)	-4220(20)	7910(18)	9382(15)	50	1
H(24)	-2670(20)	7216(18)	7756(13)	43	1
H(28A)	-4050(30)	4650(20)	7462(17)	65	1
H(28B)	-4420(20)	3950(20)	6632(16)	65	1
H(28C)	-5810(30)	4730(20)	7012(15)	65	1

Figure A.2 ORTEP Diagram of Compound 299

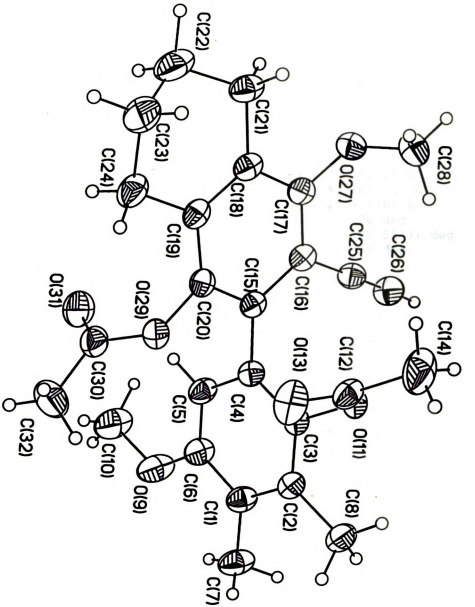


Table A.2.1 Crystal data and structure refinement for 299

Identification code	299
Empirical formula	C26 H28 O6
Formula weight	436.48
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 10.132(2) A b = 8.0145(16) A c = 28.714(6) A alpha = 90 deg. beta = 97.58(3) deg. gamma = 90 deg.
Volume	2311.4(8) A3
Z	4
Density (calculated)	1.254 Mg/m3
Absorption coefficient	0.089 mm-1
F(000)	928
Crystal size	0.4 x 0.4 x 0.3 mm
Theta range for data collection	1.43 to 28.29 deg.
Index ranges	-13<=h<=13, -10<=k<=10, -37<=l<=38
Reflections collected / unique	26866 / 5615 [R(int) = 0.0275]
Completeness to theta = 28.29	97.9%
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	5615 / 0 / 389
Goodness-of-fit on F2	1.004
Final R indices [I>2sigma(I)]	R1 = 0.0446, wR2 = 0.1315
R indices (all data)	R1 = 0.0640, wR2 = 0.1419
Largest diff. peak and hole	0.284 and -0.232 e.A-3

Table A.2.2 Atomic coordinates (x 10^4), equivalent isotropic displacement parameters (A^2 x 10^3), and occupancies for 299

	x	y	z	U(eq)	Occ.
C(1)	6995(1)	7033(2)	-11(1)	35(1)	1
C(2)	5837(1)	7216(2)	200(1)	30(1)	1
C(3)	5956(1)	7376(2)	690(1)	27(1)	1
C(4)	7174(1)	7429(2)	973(1)	28(1)	1
C(5)	8324(1)	7276(2)	759(1)	33(1)	1
C(6)	8227(1)	7069(2)	275(1)	36(1)	1
C(7)	6939(2)	6776(3)	-534(1)	47(1)	1
C(8)	4486(2)	7264(2)	-89(1)	40(1)	1
O(9)	9331(1)	6892(2)	45(1)	54(1)	1
C(10)	10595(2)	6986(4)	323(1)	65(1)	1
O(11)	4772(1)	7379(1)	899(1)	31(1)	1
C(12)	4385(1)	8837(2)	1075(1)	33(1)	1
O(13)	4983(1)	10113(1)	1052(1)	47(1)	1
C(14)	3147(2)	8609(3)	1297(1)	64(1)	1
C(15)	7309(1)	7713(2)	1492(1)	26(1)	1
C(16)	6951(1)	6496(2)	1806(1)	28(1)	1
C(17)	7135(1)	6840(2)	2288(1)	29(1)	1
C(18)	7742(1)	8315(2)	2470(1)	30(1)	1
C(19)	8107(1)	9521(2)	2160(1)	29(1)	1
C(20)	7849(1)	9194(2)	1679(1)	27(1)	1
C(21)	7982(2)	8575(2)	2998(1)	39(1)	1
C(22)	8965(2)	10006(2)	3137(1)	54(1)	1
C(23)	8631(2)	11526(2)	2837(1)	52(1)	1
C(24)	8759(2)	11157(2)	2329(1)	40(1)	1
C(25)	6435(1)	4909(2)	1636(1)	32(1)	1
C(26)	6034(2)	3589(2)	1491(1)	40(1)	1
O(27)	6742(1)	5670(1)	2596(1)	38(1)	1
C(28)	5341(2)	5715(3)	2620(1)	48(1)	1
O(29)	8013(1)	10496(1)	1363(1)	31(1)	1
C(30)	9240(1)	10822(2)	1249(1)	37(1)	1
O(31)	10217(1)	10041(2)	1396(1)	49(1)	1
C(32)	9159(2)	12269(3)	919(1)	64(1)	1

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table A.2.3. Bond lengths [A] and angles [deg] for 299

C(1)-C(2)	1.398(2)
C(1)-C(6)	1.401(2)
C(1)-C(7)	1.509(2)
C(2)-C(3)	1.4002(18)
C(2)-C(8)	1.5047(19)
C(3)-C(4)	1.3863(18)
C(3)-O(11)	1.4097(15)
C(4)-C(5)	1.3940(19)
C(4)-C(15)	1.4944(17)
C(5)-C(6)	1.3899(19)
C(6)-O(9)	1.3791(17)
O(9)-C(10)	1.419(2)
O(11)-C(12)	1.3522(16)
C(12)-O(13)	1.1952(18)
C(12)-C(14)	1.491(2)
C(15)-C(20)	1.3855(18)
C(15)-C(16)	1.4077(18)
C(16)-C(17)	1.4005(18)
C(16)-C(25)	1.4358(18)
C(17)-O(27)	1.3831(16)
C(17)-C(18)	1.4013(19)
C(18)-C(19)	1.3967(19)
C(18)-C(21)	1.5190(18)
C(19)-C(20)	1.3963(18)
C(19)-C(24)	1.5192(19)
C(20)-O(29)	1.4059(16)
C(21)-C(22)	1.537(2)
C(22)-C(23)	1.505(3)
C(23)-C(24)	1.512(2)
C(25)-C(26)	1.189(2)
O(27)-C(28)	1.431(2)
O(29)-C(30)	1.3526(17)
C(30)-O(31)	1.1999(19)
C(30)-C(32)	1.493(2)
C(2)-C(1)-C(6)	118.51(12)
C(2)-C(1)-C(7)	121.54(13)
C(6)-C(1)-C(7)	119.95(13)
C(1)-C(2)-C(3)	118.65(12)
C(1)-C(2)-C(8)	121.17(13)
C(3)-C(2)-C(8)	120.18(12)
C(4)-C(3)-C(2)	122.97(12)
C(4)-C(3)-O(11)	119.43(11)
C(2)-C(3)-O(11)	117.49(11)
C(3)-C(4)-C(5)	117.99(12)
C(3)-C(4)-C(15)	123.19(11)
C(5)-C(4)-C(15)	118.77(11)
C(6)-C(5)-C(4)	119.94(12)
O(9)-C(6)-C(5)	122.39(13)
O(9)-C(6)-C(1)	115.72(12)
C(5)-C(6)-C(1)	121.89(12)

C(6)-O(9)-C(10)	116.98(12)
C(12)-O(11)-C(3)	117.80(10)
O(13)-C(12)-O(11)	122.96(12)
O(13)-C(12)-C(14)	126.17(14)
O(11)-C(12)-C(14)	110.87(14)
C(20)-C(15)-C(16)	117.86(11)
C(20)-C(15)-C(4)	119.76(11)
C(16)-C(15)-C(4)	122.34(11)
C(17)-C(16)-C(15)	119.03(11)
C(17)-C(16)-C(25)	120.30(12)
C(15)-C(16)-C(25)	120.65(11)
O(27)-C(17)-C(16)	119.16(12)
O(27)-C(17)-C(18)	118.87(12)
C(16)-C(17)-C(18)	121.93(12)
C(19)-C(18)-C(17)	119.10(12)
C(19)-C(18)-C(21)	121.41(12)
C(17)-C(18)-C(21)	119.49(12)
C(18)-C(19)-C(20)	118.06(12)
C(18)-C(19)-C(24)	122.31(12)
C(20)-C(19)-C(24)	119.64(12)
C(15)-C(20)-C(19)	123.84(12)
C(15)-C(20)-O(29)	117.41(11)
C(19)-C(20)-O(29)	118.41(11)
C(18)-C(21)-C(22)	111.99(13)
C(23)-C(22)-C(21)	111.51(14)
C(22)-C(23)-C(24)	110.69(15)
C(23)-C(24)-C(19)	112.84(14)
C(26)-C(25)-C(16)	178.43(16)
C(17)-O(27)-C(28)	112.58(11)
C(30)-O(29)-C(20)	119.35(10)
O(31)-C(30)-O(29)	123.80(14)
O(31)-C(30)-C(32)	127.01(15)
O(29)-C(30)-C(32)	109.19(14)

Symmetry transformations used to generate equivalent atoms:

Table A.2.4. Anisotropic displacement parameters ($A^2 \times 10^3$) for 299

	U11	U22	U33	U23	U13	U12
C(1)	35(1)	41(1)	29(1)	-3(1)	2(1)	6(1)
C(2)	29(1)	29(1)	31(1)	-1(1)	1(1)	1(1)
C(3)	26(1)	24(1)	32(1)	-2(1)	6(1)	0(1)
C(4)	30(1)	26(1)	27(1)	-3(1)	4(1)	1(1)
C(5)	27(1)	42(1)	30(1)	-4(1)	2(1)	4(1)
C(6)	29(1)	51(1)	31(1)	-4(1)	7(1)	8(1)
C(7)	41(1)	72(1)	28(1)	-3(1)	2(1)	14(1)
C(8)	32(1)	52(1)	35(1)	0(1)	-2(1)	-1(1)
O(9)	31(1)	102(1)	31(1)	-6(1)	8(1)	14(1)
C(10)	30(1)	123(2)	43(1)	-3(1)	9(1)	12(1)
O(11)	27(1)	31(1)	35(1)	-1(1)	7(1)	-4(1)
C(12)	26(1)	41(1)	32(1)	-6(1)	1(1)	3(1)
O(13)	37(1)	32(1)	72(1)	-9(1)	9(1)	3(1)
C(14)	36(1)	98(2)	61(1)	-29(1)	21(1)	-12(1)
C(15)	23(1)	30(1)	27(1)	-3(1)	4(1)	3(1)
C(16)	26(1)	27(1)	30(1)	-2(1)	2(1)	3(1)
C(17)	26(1)	31(1)	30(1)	2(1)	4(1)	4(1)
C(18)	24(1)	35(1)	29(1)	-6(1)	2(1)	5(1)
C(19)	24(1)	31(1)	33(1)	-6(1)	2(1)	2(1)
C(20)	22(1)	28(1)	31(1)	-1(1)	4(1)	2(1)
C(21)	41(1)	49(1)	28(1)	-7(1)	2(1)	4(1)
C(22)	58(1)	63(1)	37(1)	-17(1)	-4(1)	-5(1)
C(23)	64(1)	50(1)	43(1)	-19(1)	8(1)	-13(1)
C(24)	41(1)	39(1)	40(1)	-11(1)	2(1)	-7(1)
C(25)	36(1)	30(1)	30(1)	1(1)	4(1)	2(1)
C(26)	50(1)	28(1)	39(1)	-2(1)	2(1)	-2(1)
O(27)	40(1)	41(1)	32(1)	8(1)	4(1)	-1(1)
C(28)	43(1)	60(1)	44(1)	6(1)	13(1)	-6(1)
O(29)	28(1)	29(1)	36(1)	1(1)	5(1)	-2(1)
C(30)	32(1)	46(1)	35(1)	-4(1)	8(1)	-7(1)
O(31)	29(1)	65(1)	54(1)	1(1)	10(1)	-1(1)
C(32)	54(1)	78(2)	59(1)	25(1)	12(1)	-14(1)

The anisotropic displacement factor exponent takes the form:
$-2\ pi^2\ [\ h^2\ a^{*2}\ U11 + \ldots + 2\ h\ k\ a^*\ b^*\ U12\ ]$

Table A.2.5. Hydrogen coordinates (x 10^4), isotropic displacement parameters (A^2 x 10^3), and occupancies for 299

	x	y	z	U(eq)	Occ.
H(5)	9182(17)	7298(19)	955(6)	37(4)	1
H(7A)	6520(30)	7580(40)	-681(10)	99(9)	1
H(7B)	7790(20)	6410(30)	-613(8)	73(6)	1
H(7C)	6250(30)	5950(40)	-664(10)	112(9)	1
H(8A)	4340(20)	8210(30)	-311(10)	93(8)	1
H(8B)	4400(20)	6370(30)	-317(9)	79(7)	1
H(8C)	3700(30)	7260(30)	86(10)	102(9)	1
H(10A)	11190(20)	6760(30)	112(8)	73(6)	1
H(10B)	10700(20)	8170(30)	412(8)	61(6)	1
H(10C)	10760(20)	6030(30)	588(9)	79(7)	1
H(14A)	2871	7464	1268	95	1
H(14B)	2456	9310	1141	95	1
H(14C)	3317	8907	1623	95	1
H(21A)	8330(17)	7500(20)	3148(6)	42(4)	1
H(21B)	7110(20)	8850(20)	3113(7)	58(5)	1
H(22A)	8920(20)	10240(30)	3495(7)	64(6)	1
H(22B)	9950(20)	9700(30)	3075(8)	76(7)	1
H(23A)	7620(20)	11810(30)	2882(8)	70(6)	1
H(23B)	9170(20)	12540(30)	2946(7)	63(6)	1
H(24A)	9712(19)	11130(20)	2287(6)	47(5)	1
H(24B)	8340(20)	12120(30)	2130(7)	58(5)	1
H(26)	5775(18)	2550(20)	1375(7)	48(5)	1
H(28A)	4820(20)	5640(30)	2290(9)	81(7)	1
H(28B)	5120(20)	4840(30)	2828(7)	61(6)	1
H(28C)	5100(30)	6740(40)	2738(11)	105(9)	1
H(32A)	9990(30)	12510(30)	833(9)	88(8)	1
H(32B)	8470(30)	12220(40)	686(12)	119(11)	1
H(32C)	8750(40)	13270(50)	1066(13)	142(13)	1

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